Medtronic

Clinical Investigation Plan

Clinical Investigation Plan	Evolut™ EXPAND TAVR I Feasibility Study
Study Product Name	Evolut PRO+ TAVR System
Sponsor/Local Sponsor	Global Sponsor Medtronic, Inc Coronary and Structural Heart Clinical 8200 Coral Sea St NE, MVS 66 Mounds View, MN 55112 United States Regional Sponsor: Europe and Israel Medtronic Bakken Research Center Coronary and Structural Heart Endepolsdomein 5 6229 GW Maastricht The Netherlands Regional Sponsor: Australia Medtronic Australasia Pty Ltd 2 Alma Road, Macquarie Park NSW 2113 Australia Regional Sponsor: New Zealand Medtronic New Zealand Limited Level 3, Bldg 5, 666 Great South Road Penrose, Auckland 1051 New Zealand Regional Sponsor: Canada Medtronic Canada ULC 99 Hereford St., Brampton ON, L6Y 0R3 Canada
Document Version	Revision D dated 09 Mar 2021
Document Reference Number	D00266108
Lead Principal Investigator(s)	Dr. Paul Sorajja Abbott Northwestern Hospital Minneapolis MN USA Dr. Josep Rodes-Cabau University Institute of Cardiology and Respirology of Quebec Quebec QC Canada

Table of Contents

Table of Contents **2**
1. Glossary **7**
2. Synopsis **11**
3. Introduction **13**
3.1 Background 13
3.2 Purpose 16
4. Objectives and Endpoints **17**
4.1 Primary Objectives 17
4.2 Endpoints and Outcome Measures 17
4.2.1 Safety Endpoints 17
4.2.2 Efficacy Endpoints 17
4.2.3 Additional Outcome Measures 18
5. Study Design **19**
5.1 Number of Subjects, Duration, and Number of Investigational Devices 20
5.2 Rationale 20
5.3 Centers for Medicare Services Considerations (United States Centers only) 20
5.4 Investigational Sites 21
5.5 Site Study Team Members 21
5.5.1 Site Principal Investigator 22
5.5.2 Heart Team 22
5.5.3 Echocardiographer 22
5.5.4 Cardiovascular Imaging Physician 22
5.5.5 Exercise Testing Physician 22
5.5.6 Study Coordinator 23
5.6 Clinical Investigational Agreement and Financial Disclosure 23
5.7 Curriculum Vitae 23
5.8 Study Site Training and Activation 23
5.9 Eligibility Review Committees 24
5.10 Echocardiography Core Lab 24
5.11 Clinical Events Committee 24

5.12 Data Safety Monitoring Board 24
5.13 Publication Committee 24
6. Methods 26
6.1 Study Population 26
6.2 Subject Selection Criteria 26
6.2.1 Inclusion Criteria 26
6.2.2 Exclusion Criteria 26
6.3 Informed Consent 28
6.4 Revisions in Patient Information and Informed Consent Form 28
6.5 Screening and Enrollment 29
6.6 Required Evaluations 31
6.7 Subject Disposition 34
6.8 Missed Follow-Up Visits 34
6.9 Unscheduled Follow-Up Visits 35
6.10 Protocol Deviations 35
6.11 Subject Withdrawal or Discontinuation 36
6.12 Study Materials and Study-Specific Equipment 37
6.13 Pre-TAVR Multi-Detector Computed Tomography (MDCT) 37
6.14 Clinical Assessment 37
6.15 Echocardiography 37
6.16 Exercise Tolerance Testing (ETT) 37
6.17 Cardiac Magnetic Resonance Imaging (CMR) 38
6.18 Six Minute Walk Test (6MWT) 38
6.19 TAVR Implant Procedure 38
6.20 Post-Implant Antithrombotic and Medical Therapy 38
7. Adverse Events and Device Deficiencies 39
7.1 Definitions 39
7.2 Evaluation and Documentation of Adverse Events and Device Deficiencies 40
7.3 Anticipated Adverse Events 42
7.4 Adverse Event Reporting Requirements for Clinical Sites 42
7.5 Documentation and Reporting of Device Deficiencies 44
7.6 Emergency Contact Details for Reporting SAE, SADE, UADE, and Device Deficiencies 44

7.7 Clinical Events Committee....44
7.8 Data Safety Monitoring Board....45
7.9 Product Complaint Reporting....45
8. Risks and Benefits....47
8.1 Potential Risks....47
8.2 Risk Analysis and Minimization....49
8.3 Potential Benefits....49
8.4 Risk-Benefit Rationale....50
9. Investigational Product Description....51
9.1 General....51
9.2 Medtronic Evolut PRO+ Transcatheter Aortic Valve (TAV) Prosthesis....52
9.3 Medtronic Evolut PRO+ Delivery Catheter System....52
9.4 Medtronic Evolut PRO+ Loading System....53
9.5 Packaging....53
9.6 Intended Population....53
9.7 Product Use....53
9.8 Product Training Requirements....54
9.9 Product Receipt, Tracking, Storage, and Accountability....54
9.10 Product Return....54
10. Statistical Design and Methods....56
10.1 General Aspects of Analysis....56
10.2 Analysis Execution....57
10.3 Interim Analysis....57
10.4 Safety Endpoints....57
10.5 Efficacy Endpoints....57
10.6 Additional Outcome Measures....58
10.7 Sample Size Determination....59
10.8 Minimization of Bias....59
11. Ethics and Regulatory Compliance....60
11.1 Statement(s) of Compliance....60
11.2 Institutional Review Boards and Ethics Committees....60
11.3 Regulatory Submission....61

12. Study Administration 62
12.1 Monitoring 62
12.2 Study Closure 62
12.3 Data Management 62
12.3.1 Time Windows for Completion and Submission of eCRFs 63
12.3.2 Data Review and Processing 63
12.3.3 Source Documents 63
12.3.4 Direct Access to Source Data/Documents 64
12.4 Confidentiality 64
12.5 Liability 65
12.6 CIP Amendments 65
12.7 Record Retention 65
12.8 Reporting Requirements 65
12.8.1 Investigator Reports 65
12.8.2 Sponsor Reports 69
12.9 Publication and Use of Information 74
12.10 Suspension or Early Termination 75
12.11 Role of Sponsor Representatives 75
12.12 Additional Contact Information 75
12.13 Consent Materials 75
12.14 Investigator's Brochure and Report of Prior Investigations 75
12.15 Contact Information: Other Institutions, Core Labs, and Committees 75
12.16 Institutional Review Board/Ethics Committee Information 76
13. Appendices 77
13.1 Appendix I: MDCT Procedures: Pre-TAVR Planning 77
13.2 Appendix II: Clinical Assessment 79
13.3 Appendix III: Echocardiography Procedures 81
13.3.1 Required Evaluations 81
13.3.2 General Procedures 81
13.3.3 Data Requirements 82
13.3.4 Acquisition of Key Variables 84
13.3.5 Echocardiography Core Lab Analysis 100

13.4 Appendix IV: Exercise Tolerance Testing Procedures 104
13.5 Appendix V: Cardiac Magnetic Resonance Imaging (CMR) Procedures 105
13.6 Appendix VI: Six Minute Walk Test (6MWT) Procedures 106
13.7 Appendix VII: TAVR Implant Procedure 108
13.8 Appendix VIII: Definitions of Endpoints and Outcome Measures 110
13.8.1 Safety Endpoint Definitions[70] 110
13.8.2 Other TAVR Related Complications[70] 113
13.8.3 Efficacy Endpoints 115
13.8.4 Classification of Causal Relationships 120
14. Version History 124
15. References 130

1. Glossary

Term	Definition
A	Atrial (late diastolic mitral inflow velocity with atrial contraction)
A’	A prime; mitral annular late diastolic velocity
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ADE	Adverse device effect
AE	Adverse event
AHA	American Heart Association
AKI	Acute kidney injury
AS	Aortic stenosis
AR	Aortic regurgitation
AV	Atrial ventricular
AVA	Aortic valve area
AVAI	Aortic valve area index
AVC	Aortic valve closure
BARC	Bleeding Academic Research Consortium
BMI	Body mass index
BSA	Body surface area
CABG	Coronary artery bypass grafting
EACTS	European Association of Cardio Thoracic Surgery
EQ-5D	European Quality of Life – 5 Dimensions
ESC	European Society of Cardiology
AVR	Aortic valve replacement
BAV	Balloon aortic valvuloplasty
BVD	Bioprosthetic valve dysfunction
BVF	Bioprosthetic valve failure
CEC	Clinical Events Committee
CD	Color Doppler
CIP	Clinical Investigational Plan
COPD	Chronic obstructive pulmonary disease
CW	Continuous wave
CWD	Continuous wave Doppler
CVA	Cerebral vascular accident
DCS	Delivery catheter system
DICOM	Digital Imaging and Communications in Medicine
DTL	Designated Task List
DSMB	Data Safety Monitoring Board
DVI	Doppler velocity index

Term	Definition
E	Early diastolic mitral inflow velocity
e’	E prime; mitral annular early diastolic velocity
E:A ratio	Ratio of early (E) to late (A) mitral inflow velocity
E:e’	Ratio of early (E) mitral inflow velocity to early (e’) mitral annular velocity
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EOAI	Effective orifice area index
ET	Ejection time
ETT	Exercise tolerance test
ERC	Eligibility Review Committee
ECL	Echocardiography Core Laboratory
HF	Heart failure
HREC	Human Research Ethics Committee
IB/RoPI	Investigator Brochure/Report of Prior Investigations
IDE	Investigational Device Exemption
IE	Infective endocarditis
IFU	Instructions for Use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV_1	Forced expiratory volume in one second
FS	Fractional shortening
F/U	Follow up
LGE	Late gadolinium enhancement
GCP	Good Clinical Practice
GI	Gastrointestinal
GCMT	Guideline compatible medical therapy
GLS	Global longitudinal strain
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HREC	Human Research Ethics Committee
ICH/GCP	International Harmonized Committee/Good Clinical Practice
IRB	Institutional Review Board
IRB/EC	Institutional Review Board/Ethics Committee
KCCQ	Kansas City Cardiomyopathy Quality of Life
Kg	Kilograms
LAVI	Left atrial volume index
LAX	Long axis
LS	Loading system
LV	Left ventricle
LVEDV	Left ventricular end-diastolic volume

Term	Definition
LVESV	Left ventricular end-systolic volume
LVEF	Left ventricular ejection fraction
LVIDD	Left ventricular internal dimension at end-diastole
LVIDS	Left ventricular internal dimension at end-systole
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVOT	Left ventricular outflow tract
m-mode	Motion mode
MDCT	Multi-detector computed tomography
MdT	Mitral E wave deceleration time
MG	Mean gradient
MI	Myocardial infarction
µg	microgram
MR	Mitral regurgitation
MRI	Magnetic resonance imaging
mRS	Modified Rankin Score
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
PAR	Paravalvular aortic regurgitation
PI	Principal investigator
PISA	Proximal isovelocity surface area
PPI	Permanent pacemaker implant
PPM	Patient-prosthesis mismatch
PW	Pulsed wave
QoL	Quality of Life
RA	Right atrium
REB	Research Ethics Board
ROI	Region of interest
RF	Regurgitant fraction
RDC	Remote data capture
RVol	Regurgitant volume
RV	Right ventricle
RVOT	Right ventricular outflow tract
RVSP	Right ventricular systolic pressure
SAE	Serious adverse event
SADE	Serious adverse device effect
SAVR	Surgical aortic valve replacement
SAX	Short axis
SOP	Standard operating procedure
SoV	Sinus of Valsalva

Term	Definition
STE	Speckle tracking echocardiography
TAPSE	Tricuspid annular plane systolic excursion
TAV	Transcatheter aortic valve
TAVR	Transcatheter aortic valve replacement
TDI	Tissue Doppler imaging
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
TR	Tricuspid regurgitation
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
WBC	White blood count
WHO	World Health Organization
vMax	Maximal velocity aortic valve
VARC-2	Valve Academic Research Consortium
VTI	Velocity time integral
Z_vA	Valvulo-arterial impedance
2-D	Two dimensional
6MWT	Six-minute walk test

2. Synopsis

Study Type	Prospective, interventional, premarket, feasibility
Study Design	Single arm, descriptive, multi-center
Global Sponsor	Medtronic, Inc. Coronary Structural Heart 8200 Coral Sea St NE Mounds View, MN 55112
Investigational Device	The Medtronic Evolut PRO+ TAVR System
Product Status	Investigational
Indication under investigation	Severe, asymptomatic aortic stenosis
Investigation Purpose	Obtain safety and efficacy data to inform pivotal studies to support indication expansion to patients with severe asymptomatic aortic stenosis
Primary Objectives	• Characterize the spectrum of cardiac function, degree of symptoms, and severity of aortic stenosis in the study population • Estimate event rates for potential study endpoints to be evaluated in pivotal studies for the proposed patient population, and • Evaluate the effect of TAVR on cardiac function, functional capacity, effort tolerance, and quality of life in the study population.
Key Study Endpoints	Safety • All-cause mortality at 30 days and 6 months • All stroke (disabling and non-disabling) at 30 days and 6 months • Valve-related dysfunction requiring repeat procedure at 30 days and 6 months • New permanent pacemaker implant (PPI) at 30 days and 6 months Efficacy • Cardiovascular and heart failure hospitalizations at 30 days and 6 months • Heart failure events at 30 days and 6 months • Change in KCCQ at 6 months • Change in 6MWT at 6 months • Change in cardiac function by echo (LVEF, Peak GLS, E:e') at 6 months
Number of Centers	Up to 25 centers in the United States, Canada, Europe, Israel, Australia, and New Zealand
Sample Size and Follow-up Duration	Up to 75 patients with severe asymptomatic AS followed for five years

Key Patient Selection Criteria	Key inclusion criteria:
	• Severe aortic stenosis, defined as:
	  ○ AVA $\leq$ 1.0 cm^2, or AVAI $\leq$ 0.6 cm^2/m^2, and
	  ○ Mean gradient > 40 mmHg or Vmax $\geq$ 4.0 m/sec
	• Subject denies symptoms attributable to aortic stenosis, including but not limited to:
	  ○ Dyspnea on rest or exertion
	  ○ Angina
	  ○ Syncope in the absence of another identifiable cause
	  ○ Fatigue

	• LVEF ≥50% Key exclusion criteria: • Age < 65 years • Class I indication for SAVR • Bicuspid, unicuspid, or quadricuspid aortic valve • In need and suitable for coronary revascularization

3. Introduction

3.1 Background

Calcific aortic stenosis (AS) is the most prevalent valvular heart disease in developed countries, and its burden is expected to increase dramatically over the next 20 years with the aging of the population.[1] In adults, AS is characterized by progressive thickening, calcification, and fibrosis of the valve leaflets leading to restricted leaflet motion and narrowing of the valve opening area, resulting in obstruction to left ventricular outflow. The consequent increase in pressure afterload leads to an adaptive hypertrophic response of the left ventricle to normalize wall stress and maintain cardiac output. In many patients, this compensatory mechanism cannot be maintained indefinitely, and ventricular function begins to decline, resulting in the development of symptoms, heart failure, and death because of inadequate cardiac output and elevated left ventricular filling pressure caused by diastolic dysfunction.[2,3,4] This transition of ventricular adaption (compensation) to decompensation is driven by progressive myocyte death and fibrosis. Therefore, it is important to consider AS a condition that affects both the valve and the myocardium.[5,6]

The classic symptoms of AS include dyspnea, exertional angina, and syncope. It is well accepted the onset of these symptoms is a marker of left ventricular decompensation, and once these symptoms develop, the cumulative mortality is high if AS is left untreated.[7,8] In their seminal 1968 paper, Ross and Braunwald reported the average survival following onset of symptoms was five years for angina, three years for syncope, and two years for dyspnea.[8]

Currently, there are no medications proven to attenuate or reverse the progression of AS, and aortic valve replacement (AVR), either surgical or transcatheter, is the only effective treatment for severe AS. Ideally, AVR should be performed when the risks of the disease process (heart failure, irreversible ventricular functional impairment) outweigh the risks of the intervention (complications of the implant procedure, long term device risks, and need for reintervention).[2] However, determining the optimal timing for intervention remains one of the most challenging and important decisions in the management of AS.[9,10]

Contemporary guidelines make a Class I recommendation for AVR when AS is deemed severe *and* there are either symptoms of AS *or* objective evidence of left ventricular systolic dysfunction, where severe aortic stenosis is defined as an aortic valve area (AVA) ≤ 1.0 cm^2 or a mean pressure gradient across the stenotic valve of > 40 mmHg, and left ventricular systolic dysfunction is defined by a left ventricular ejection fraction (LVEF) of < 50%.[11,12,13] However, current guidelines are hesitant to recommend AVR for patients with AS outside of these criteria.

The evaluation and treatment of AS has evolved considerably over the past decade in direct relationship to advancements in multimodality imaging,[14,15,16,17,18] enhanced understanding of the natural history of AS[19,20,21,22] and the transformative development of transcatheter aortic valve replacement (TAVR).[23,24,25,26,27,28,29,30] These rapid advances have fueled a growing interest for the indications for AVR to evolve beyond the current measures defining the hemodynamic burden of AS in order to identify and

treat patients with AS who are at risk for adverse outcomes, but outside the current indications for intervention. [10,19,31,32,33,34,35,36,37]

Severe Asymptomatic AS. The management of asymptomatic patients with severe AS, particularly the choice between early AVR and "watchful waiting", remains controversial.[32,33,36,38] Due to the high prevalence of AS in the elderly and ready access to echocardiography, severe AS is frequently diagnosed in asymptomatic patients. For asymptomatic patients with severe AS, the guidelines make a Class I recommendation for AVR when the LVEF is reduced to < 50%.[11,12]

Many patients with symptoms can remain undetected in clinical practice because they have unconsciously adapted by slowing their activity level to avoid symptoms. Further, they may not recognize what represents important symptoms, or underestimate their severity and only report when they become extremely limiting. Dyspnea, one of the most important prognostic symptoms in AS, may be particularly hard to detect, as patients may attribute their shortness of breath to poor stamina.[39]

Studies have shown that roughly 50% of patients with severe AS report no symptoms on initial diagnosis.[40,41,42] Among these patients, irreversible myocardial damage or sudden cardiac death can occur if symptoms are overlooked and treatment is deferred. Therefore, for asymptomatic patients with severe AS and LVEF≥ 50%, the guidelines recommend exercise tolerance testing (ETT) to unmask the presence of AS-related symptoms. If ETT reveals spontaneous symptoms clearly related to AS, the ESC/EACTS guidelines make a Class I recommendation for AVR, while the AHA/ACC guidelines make a Class IIa recommendation for AVR.[11,12] Although the guidelines recommend ETT in these patients, it's use is rather limited in routine practice, as a considerable number of elderly patients present with physical impairment that limit their ability to exercise.[43,44]

For severe asymptomatic patients without a Class I or IIa indication for AVR, the guidelines recommend close follow-up for reassessment of symptoms and TTE every 6 to 12 months, and deferral of AVR until symptoms or signs of left ventricular systolic dysfunction, defined as LVEF <50%, develop.[11,12] This strategy of "watchful waiting" is based on consensus opinion that the potential benefit of AVR to prevent sudden cardiac death may not be greater than the risk of dying during or within 30 days of the surgical AVR procedure. This is supported by observational studies estimating the annual risk of sudden cardiac death in patients with severe, asymptomatic AS to be approximately 1%.[45,46,47,48,49]

However, important issues have been identified regarding the strategy to "watch and wait" for symptoms or reduction in LVEF to <50% to determine the timing of intervention in these patients. A 2018 study by Wald et al[50] observed that life-threatening decompensation is not uncommon in patients with known AS. Among patients under watchful waiting who were admitted to the hospital for acute decompensated AS, 45% were in LV failure at the time of admission. Inpatient mortality was high in this group (19%), exposing a shortcoming of a watchful waiting strategy in some patients with severe AS.

Observational studies evaluating the outcomes of patients with severe asymptomatic aortic stenosis have been recently published. In 2016, Généreux et al[20] published a meta-analysis comparing a surgical AVR strategy to a conservative approach. Their pooled analysis of four retrospective observational studies

indicated that patients with severe asymptomatic AS have an unadjusted ~3.5-fold higher rate of all-cause death with a watchful-waiting strategy compared with AVR. This suggests that early AVR might improve outcomes in patients with asymptomatic severe AS, but the authors note their findings should be considered hypothesis-generating. In 2020, Pompeu et al[38] published a meta-analysis of seven studies comparing early AVR to clinical follow up. A principal finding was the overall hazard ratio for death showed a statistically significant difference in mortality between the two groups, with a lower risk of dying in the "early AVR" group.

Other studies have identified limitations of the LVEF <50% cut-point as the threshold for AVR in severe asymptomatic AS. In their 2018 report of study of outcomes of patients with severe asymptomatic patients followed in dedicated heart valve clinics, Lancellotti et al[51] noted that patients with LVEF between 50% and 59% had less favorable outcomes and more heart failure-related deaths than patients with an LVEF > 60%. In their 2018 report of a study evaluating the temporal course of LVEF in patients with severe AS, Ito et al[52] noted that 21% of patients had an LVEF < 50% at the time of initial diagnosis of severe AS. Notably, in patients with severe AS and LVEF < 50%, the LVEF began to deteriorate and gradually worsened before AS became severe or AVA became <1.0 cm^2. The authors suggest the normal LVEF appears to >60% in patients with AS. For patients with severe AS and LVEF <60%, mortality is worse even after AVR is performed. These studies raise the question if the current threshold for AVR of LVEF < 50% should be increased to <60% in these patients.

Potential of TAVR in Expanded Indications. The rapid evolution of TAVR over the last 10 years has completely changed the landscape for decision-making regarding valve intervention in severe AS patients. Randomized trials have demonstrated similar or better outcomes compared to surgical AVR (SAVR) in patients with severe, symptomatic AS deemed at increased risk for operative mortality.[23-28] Based on these studies, both the 2017 European and United States guidelines make a Class I indication for TAVR in patients with severe, symptomatic AS at high risk for SAVR, and a Class I or Class IIa for patients at intermediate risk for SAVR, respectively.[11,12]

Advanced imaging, technological advances in delivery catheter systems and prosthesis design, and growing operator experience have led to improved procedural safety and transcatheter valve performance. As a result, TAVR has recently been studied in patients with severe AS at low operative risk for SAVR. In 2019, two randomized trials comparing TAVR to SAVR were published (one involving the Edwards balloon-expandable Sapien 3 system,[29] and one involving the Medtronic Evolut R and PRO self-expanding systems.[30] In younger and low risk patients, both trials showed TAVR had an early safety benefit (lower rates of mortality, disabling stroke, acute kidney injury, life-threatening bleed and new-onset atrial fibrillation) over SAVR, significantly shorter length of hospital stay, faster recovery, and fewer rehospitalizations. Importantly, the Medtronic Evolut R and PRO transcatheter valves demonstrated more complete relief of aortic valve obstruction compared to surgical bioprostheses in the form of larger effective orifice areas, lower prosthetic gradients, and a significantly lower incidence of patient-prosthesis mismatch.[30]

The current state of TAVR, with its procedural safety and hemodynamic performance benefits over SAVR, offers the potential to change the thresholds for AVR and extend the benefits of AVR to patients with AS who are at risk for adverse cardiac events, but outside the current indications for AVR. When considering recent evidence on the prognosis of moderate symptomatic and severe asymptomatic AS, the need to reappraise the current indications for AVR becomes apparent. As a result, clinical trials are underway to investigate the use of TAVR in patients with severe, asymptomatic AS.

The EARLY TAVR (Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis, NCT030421040) is an ongoing randomized control trial to compare TAVR with "watchful waiting" in truly asymptomatic patients with severe AS.[53] The EVoLVeD (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients with Severe AS, NCT03094143) TAVR study is an ongoing randomized clinical trial in which subjects are assessed for increased heart muscle strain that could lead to scarring using cardiac magnetic resonance imaging. Subjects at risk for increased scarring are randomized to either routine clinical care or referral for AVR.[54]

Medtronic is sponsoring this feasibility study to evaluate the safety and efficacy of the Medtronic Evolut PRO+ TAVR system in patients with severe asymptomatic aortic AS. There are important differences in the inclusion/exclusion criteria for this study compared to the EARLY TAVR study. The EARLY TAVR study requires ETT to establish the absence of symptoms. While this is consistent with current guidelines, it is important to note that ETT is not feasible in a considerable number of elderly patients. Therefore, this study will allow patients irrespective of the ability to perform ETT, provided they have additional markers of LV dysfunction that may prove to be more sensitive than LVEF for identification of LV dysfunction attributable to AS.

3.2 Purpose

The purpose of this study is to evaluate the safety and efficacy of the Medtronic Evolut PRO+ TAVR system in patients with severe asymptomatic AS. Data will be used to inform the design of pivotal studies to support expansion of the current indication to include this patient population.

4. Objectives and Endpoints

4.1 Primary Objectives

The primary objectives of this feasibility study are as follows:

1. Characterize the spectrum of cardiac function, symptomology, and severity of aortic stenosis in the study population,
2. Estimate event rates for potential safety and effectiveness endpoints to be evaluated in pivotal studies for the proposed patient population, and
3. Evaluate the effect of TAVR on cardiac function, functional capacity, effort tolerance, and patient-reported quality of life in the study population.

4.2 Endpoints and Outcome Measures

4.2.1 Safety Endpoints

1. All-cause and cardiovascular mortality at 30 days and 6 months
2. All stroke (disabling and non-disabling) at 30 days and 6 months
3. Myocardial infarction (periprocedural and spontaneous) at 30 days and 6 months
4. Acute kidney injury at 30 days and 6 months
5. Major vascular complications at 30 days and 6 months
6. Life-threatening bleed at 30 days and 6 months
7. New permanent pacemaker implantation (PPI) at 30 days and 6 months
8. New intraventricular conduction delays at 30 days and 6 months
9. New-onset atrial fibrillation at 30 days and 6 months
10. Valve-related dysfunction requiring repeat procedure at 30 days and 6 months

4.2.2 Efficacy Endpoints

1. Device success (VARC-2)[63]
2. Cardiovascular and heart failure hospitalizations at 30 days and 6 months
3. Heart failure events at 30 days and 6 months
4. Hemodynamic performance metrics by Doppler echocardiography at discharge, 30 days, and 6 months
   - Mean aortic gradient
   - Effective orifice area
   - Degree of total, para, and transvalvular prosthetic regurgitation
   - Incidence of moderate and severe patient-prosthesis mismatch (PPM)
5. Change in New York Heart Association (NYHA) functional classification from baseline at 30 days and 6 months
6. Change in six-minute walk test (6MWT) from baseline at 6 months
7. Change in Kansas City Cardiomyopathy (KCCQ) from baseline at 30 days and 6 months

8. Change in left ventricular ejection fraction (LVEF) from baseline at 6 months
9. Change in peak global longitudinal strain (GLS) from baseline at 6 months
10. Change in left ventricular filling pressure (E:e') from baseline at 6 months
11. Change in stroke volume index (SVI) from baseline at 6 months
12. Change in NT-pro B-type natriuretic peptide (NT-proBNP) from baseline at 6 months

4.2.3 Additional Outcome Measures

The following outcome measures will be also be evaluated:

1. All-cause and cardiovascular mortality annually through 5 years
2. All stroke (disabling and non-disabling) annually through 5 years
3. Cardiovascular and heart failure hospitalizations at annually through 5 years
4. Heart failure events at annually through 5 years
5. New York Heart Association (NYHA) functional classification at 30 days, 6 months, and annually through 5 years
6. Change in New York Heart Association (NYHA) functional classification from baseline annually through 5 years
7. Kansas City Cardiomyopathy (KCCQ) annually through 5 years
8. Hemodynamic performance metrics by Doppler echocardiography
    - Mean aortic gradient annually through 5 years
    - Effective orifice area annually through 5 years
    - Degree of total, para, and transvalvular prosthetic regurgitation annually through 5 years
    - Incidence of moderate and severe patient-prosthesis mismatch (PPM) annually through 5 years
9. Prosthetic valve thrombosis 30 days, 6 months, and annually through 5 years
10. Prosthetic valve endocarditis at 30 days, 6 months, and annually through 5 years
11. Bioprosthetic valve dysfunction (BVD) at 30 days, 6 months, and annually through 5 years
12. Bioprosthetic valve failure (BVF) at 30 days, 6 months, and annually through 5 years
13. Valve-related dysfunction requiring repeat procedure annually through 5 years

Definitions of endpoints and outcome measures are provided in Section 13.8.

5. Study Design

This is a prospective, descriptive, interventional, multi-center, single-arm, pre-market, feasibility study. The study will involve up to 75 subjects with severe, asymptomatic AS implanted using the Medtronic Evolut PRO+ TAVR system among up to 25 centers in the United States, Canada, Europe, Israel, Australia, and New Zealand. An initial analysis is anticipated when 50 to 75 subjects have completed their 6 month follow up exam. The analysis will be descriptive; information on the data analyses are provided in Section 10. Study design and flow is outlined in Figure 1.

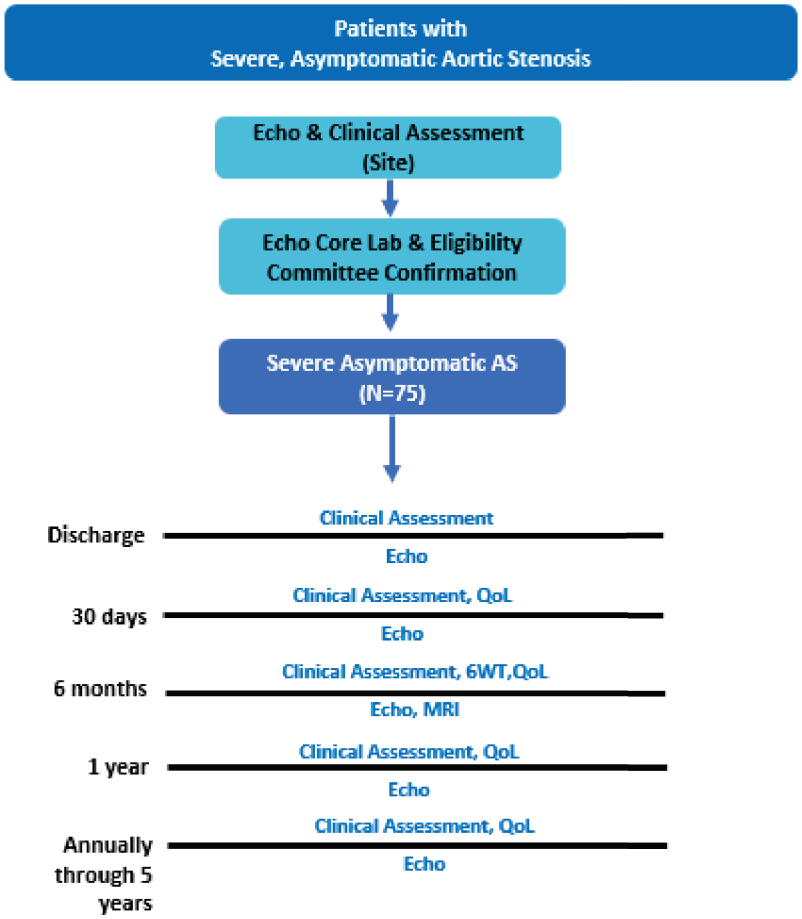


Figure 1: Study Design and Flow

5.1 Number of Subjects, Duration, and Number of Investigational Devices

This study will involve up to 75 subjects implanted with the study device among all active sites. As not all patients consented for evaluation will go forward to implantation, the number of subjects consented for the study is expected to be higher (up to 150). No site will implant more than 15 subjects without prior authorization from Medtronic in order to minimize bias.

Subjects will be consented for follow-up through five years following implantation, and all implanted subjects will be followed per protocol through five years following implantation. Subjects who exit from the study after implantation will not be replaced. The enrollment period is estimated to be between 9 and 20 months, and the estimated total study duration (first subject implanted to last subject completing his/her last follow-up exam) is estimated to be seven years.

The number of investigational TAVR systems involved in this study is estimated to be between 75 and 150 (inclusive of devices used during index implantation procedures, devices opened but not used, and devices shipped to sites as inventory for the study but not opened or used).

5.2 Rationale

The safety and effectiveness of the Medtronic self-expanding Evolut R and PRO TAVR systems have been established through rigorous clinical evaluation in patients with severe symptomatic AS. However, contemporary evidence from scientific literature indicates patients with a degree of AS outside of the current TAVR indications are also at risk for serious adverse effects of AS. The risk and benefits of TAVR in patients with severe asymptomatic AS has not been well studied in prospective clinical studies, although clinical trials have recently been initiated in AS patients using the balloon expandable TAVR system.

This feasibility study is intended to obtain initial procedural safety and efficacy data on the use of the Medtronic self-expanding Evolut PRO+ TAVR system in this group of AS patients. Data from this study will be used to inform the design of future pivotal studies to expand the current indications to include this population. Specifically, the study objectives and associated endpoints are intended to fully characterize the spectrum of AS severity, LV function, and symptomology, provide information on event rates for pivotal sample size estimations, and refine the entrance criteria for future pivotal studies. The single arm design and sample size of 75 subjects is consistent with the views and opinions of US FDA physicians regarding feasibility studies in the development of percutaneous heart valves[55] and will provide adequate information to inform a pivotal study. A comprehensive bench testing protocol has been completed on the Evolut PRO+ system and is generalizable to the study population. The clinical study endpoints are relevant and consistent with the study objectives. The design of this study is based on clinical evaluation and aligned with risk assessment results.

5.3 Centers for Medicare Services Considerations (United States Centers only)

This study protocol is designed to ensure all beneficiaries of the United States Centers for Medicare Services (CMS) are eligible for participation, and that the results are generalizable to all beneficiaries

with the degree of AS and symptomology under investigation. Specifically, the inclusion/exclusion criteria require that the subjects to be ≥ 65 years of age, anatomically suited for the study TAVR system, and have a degree of AS that places them at risk for adverse cardiac events from their AS.

An analysis of 2018 US claims data for claims with a diagnosis of nonrheumatic aortic stenosis found that 88% of patients were age 65 or older, and Medicare was the primary payer in 84% of the claims, and secondary payer in 88% of the claims.[56] Therefore, results from this study will be generalizable to the Medicare population. In addition, the inclusion and exclusion criteria ensure that traditionally underrepresented groups (e.g. minorities, women) will not be excluded from this study. Information on subject age, gender, and ethnicity will be collected in the study through electronic Case Report Forms (eCRFs).

In addition, investigational sites are expected to retain participation of all enrolled subjects through their routine processes for arranging follow-up visits and encouraging subjects to attend visits and continue his/her participation. Finally, the study report will include information (e.g. % of subjects by race, gender) on the level of representation of these traditionally underrepresented groups among the overall study population.

5.4 Investigational Sites

This study may be conducted at up to 25 sites in the United States, Canada, Europe, Israel, Australia, and New Zealand. Investigative sites will meet the following criteria:

1. The site will have extensive experience with TAVR and SAVR, including the following:
   - Interventional Cardiologist with ≥20 TAVR procedures in the prior year, or ≥ 40 TAVR procedures in the prior two years.
2. The site will have the presence or capacity of establishing an investigative team consisting of the following:
   - Interventional Cardiologist with expertise in transcatheter aortic valve replacement
   - Cardiothoracic Surgeon with expertise in aortic valve replacement
   - Echocardiographer with expertise in evaluation of aortic stenosis and speckle-tracking echocardiography (STE), dobutamine stress echocardiography, and prosthetic valve evaluation
   - Cardiovascular Imaging Specialist (either radiologist or cardiologist) with expertise in multi-detector computed tomography (MDCT) for pre-TAVR procedure planning and cardiac MRI
   - Exercise Testing physician with expertise in exercise tolerance testing
   - Study Coordinator with experience in regulated medical device studies

5.5 Site Study Team Members

The following is a description of the key personnel who will form the investigative team at each site.

5.5.1 Site Principal Investigator

Each site will have a Principal Investigator (PI) who is either an interventional cardiologist, cardiothoracic surgeon, or non-interventional cardiologist. The PI has overall responsibility for the conduct of the study at the site, including protecting the rights, safety, and welfare of the study subjects at their site, the integrity of the study data generated by their site, and for ensuring the study is conducted in compliance with the Clinical Investigation Plan, all relevant regulatory requirements, and the IRB/EC requirements. The site PI may also serve as a member of the Heart Team.

5.5.2 Heart Team

Each site will utilize a local multi-disciplinary Heart Team to assess and document eligibility of the prospective subject for the study. Local Heart Team members must be trained, delegated, and activated to participate in the clinical study. At a minimum, the local Heart Team should include the following four members:

1. A Cardiothoracic Surgeon
2. An Interventional Cardiologist
3. An Echocardiographer

5.5.3 Echocardiographer

Each site will have a designated cardiologist whose primary responsibilities are to confirm the prospective subjects meets the echocardiographic criteria for the study, to ensure the required echocardiograms are performed in accordance with the CIP, and reviewing and approving the site echocardiography eCRFs, if authorized by the PI. Protocol-driven exams should be performed by designated individuals delegated by the site PI. The designated echocardiographer shall also serve as a member of the local Heart Team.

5.5.4 Cardiovascular Imaging Physician

Each site will have a designated cardiovascular imaging specialist, whose responsibilities include ensuring the required pre-TAVR planning MDCT images are acquired per protocol, overseeing the acquisition of the protocol-required cardiac MRI images, analysis of the protocol-required MDCT and MRI exams, and reviewing and approving the site MDCT and MRI eCRFs, if authorized by the PI. The Cardiovascular Imaging Specialist is either a radiologist or cardiologist with expertise in MDCT and Cardiac MRI.

5.5.5 Exercise Testing Physician

Each site will have designated physician whose responsibilities include overseeing the administration, interpretation, and reporting of protocol-required exercise tolerance, and reviewing and approving the site exercise testing eCRFs, if authorized by the PI.

5.5.6 Study Coordinator

Each site will have a designated study coordinator whose responsibilities include coordination of study activities, follow-up evaluations, and maintaining the records defined in the CIP. The study coordinator may conduct follow-up clinical evaluations if qualified per their scope of practice and authorized by the PI.

5.6 Clinical Investigational Agreement and Financial Disclosure

Medtronic contracts with participating institutions/investigators through a clinical investigational agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.

A Clinical Investigational Agreement shall be signed by the participating investigation site and/or the principal investigator at each investigation center per local legal requirements and returned to Medtronic prior to study center activation. The investigator is required to indicate their approval of the CIP (and any subsequent amendments) by signing and dating the agreement. All investigators will be asked to complete financial disclosure statements provided by Medtronic prior to their participation in the study.

5.7 Curriculum Vitae

Current, signed and dated curriculum vitae shall be obtained for all site study personnel, including their current position at the investigation site. The signature on the curriculum vitae must be on or prior to the date of activation or delegation of any tasks.

5.8 Study Site Training and Activation

Prior to investigational center activation or subsequent involvement in study activities, Medtronic will provide training to the investigative team on the clinical investigation plan, relevant standards and regulations, informed consent, data collection and reporting tools, and the study methods, procedures, and requirements. Training may be conducted via site initiation visits, investigator meetings, and/or other media sessions. Medtronic will maintain documentation of these training sessions. If new members join the study team, they will receive training on the applicable study requirements relevant to their role before contributing to the study. Additionally, Medtronic representative(s) may be present at each site's implant procedures as part of the ongoing training process.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including but not limited to the following:

- IRB/EC approval (and voting list, as required by local law) of the current CIP and ICF
- Fully executed CTA
- Financial disclosure, as applicable
- CV of investigators and investigational site study team members as applicable
- Documentation of delegated tasks

- Documentation of study training
- Additional requirements per local regulations, IRB/EC as applicable

5.9 Eligibility Review Committees

An Eligibility Review Committee (ERC) will be used to ensure subject selection is appropriate and consistent among study sites. The role of the ERC will include the following:

- Confirmation that subjects have severe aortic stenosis per the relevant inclusion/exclusion criteria
- Confirmation that subjects symptoms have been adequately evaluated by the local Heart Team. For subjects unable to undergo ETT, the ERC will confirm if the subject is asymptomatic for AS
- Confirmation that subjects have tricuspid aortic valves and are anatomically suitable for transfemoral TAVR with the study device

The ERC may include representation from the following disciplines: interventional cardiology, cardiac surgery, echocardiography, and heart failure management. A charter that describes the roles, responsibilities, and processes of the ERC will be approved by Medtronic prior to the start of enrollment.

5.10 Echocardiography Core Lab

An Echocardiography Core Lab (ECL) will be used to ensure consistency of evaluation and interpretation of the echocardiographic exams among the study sites. The role of the ECL will include the following:

- Confirming all subjects meet echocardiographic criteria for severity of aortic stenosis and left ventricular function
- Evaluation of all protocol-driven echocardiograms
- Evaluation of unplanned echocardiograms as available

Details on the echocardiography procedures are provided in Section 13.3.

5.11 Clinical Events Committee

A Clinical Events Committee (CEC) will be used to ensure consistent evaluation and adjudication of adverse events and safety-related endpoints. Additional information on the composition, roles, and responsibilities of the CEC is provided in Section 7.7.

5.12 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be used to monitor accruing data from study in order to protect the safety of the study subjects. Additional information on the composition, roles, and responsibilities of the DSMB is provided in Section 7.8.

5.13 Publication Committee

A Publication Committee will provide direction and support in the development of clinical publications. The Publication Committee will consist of study investigators and Medtronic representatives. The Publication Committee will be responsible to:

- Define the publication plan

- Review, approve, and prioritize publication proposals
- Provide input on the scientific merit and clinical relevance of ancillary publications
- Identify the manuscript/abstract first author(s)/writer(s)/presenter(s)
- Review publications prior to submission

6. Methods

6.1 Study Population

The study population includes males and females ≥ 65 years of age with severe, asymptomatic AS. Selection criteria are described in Section 6.2.

6.2 Subject Selection Criteria

6.2.1 Inclusion Criteria

Prospective subjects must meet all of following inclusion criteria to be eligible for implantation:

1. Severe aortic stenosis, defined as:
   - AVA ≤ 1.0 cm^2, or AVAI ≤ 0.6 cm^2/m^2, **and**
   - Mean gradient ≥ 40 mmHg **or** Vmax ≥ 4.0 m/sec
2. NYHA I
3. Subject denies symptoms attributable to aortic stenosis, including but not limited to:
   - Dyspnea on rest or exertion
   - Angina
   - Syncope in the absence of another identifiable cause
   - Fatigue
4. LVEF $\geq$ 50%
5. Anatomically suitable for transfemoral TAVR using the Medtronic Evolut PRO+ system
6. The subject and treating physician agree the subject will return for all required follow-up visits

6.2.2 Exclusion Criteria

If any of the following exclusion criteria are present, the prospective subject is not eligible for implantation:

1. Age < 65 years
2. Class I indication for cardiac surgery
3. Very severe aortic stenosis, defined as Vmax $\geq$ 5m/sec, or mean gradient $\geq$ 60 mmHg
4. Bicuspid, unicuspid, or quadracuspid aortic valve
5. Contraindication for placement of a bioprosthetic valve
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)
   - Contrast media

7. Blood dyscrasias as defined: leukopenia (WBC < 1000 mm^3), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states
8. Ongoing sepsis, including active endocarditis
9. Any percutaneous coronary or peripheral interventional procedure within 30 days prior to date of qualifying echocardiogram
10. In need of and suitable for coronary revascularization per Heart Team
11. Chronic obstructive pulmonary disease (GOLD stage 3 or higher)[57]
12. Placement of cardiac resynchronization device within 90 days of qualifying echocardiogram
13. Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 70 days of qualifying echocardiogram
14. Heart failure event or hospitalization within 14 days prior to qualifying echocardiogram
15. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
16. Recent (within 60 days of qualifying echocardiogram) cerebrovascular accident (CVA) or transient ischemic attack (TIA)
17. Child-Pugh class C liver cirrhosis
18. Gastrointestinal (GI) bleeding that would preclude anticoagulation
19. Subject refuses a blood transfusion
20. Severe dementia (resulting in either inability to provide informed consent for the study/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits)
21. Estimated life expectancy of less than 24 months due to associated non-cardiac co-morbid conditions
22. 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
23. Currently participating in an investigational drug or another device trial or study (excluding registries)
24. Evidence of an acute myocardial infarction ≤ 30 days before date of qualifying echocardiogram[58]
25. Advanced renal impairment (defined as GFR <30 mL/min) or need for renal replacement therapy
26. Need for emergency surgery for any reason
27. Subject is pregnant or breast feeding
28. Subject is less than legal age of consent, unable to provide his/her own informed consent, legally incompetent, or otherwise vulnerable

Anatomical exclusion criteria:

29. Pre-existing prosthetic heart valve in any position
30. Severe mitral regurgitation
31. Severe tricuspid regurgitation
32. Moderate or severe mitral stenosis
33. Hypertrophic obstructive cardiomyopathy
34. Significant aortopathy requiring ascending aortic replacement

35. Severe aortic regurgitation

6.3 Informed Consent

Prior to enrolling in the study, patients should be fully informed of the details of study participation as required by applicable regulations, the site's IRB/EC, and by sponsor. Informed consent must be obtained from each patient prior to conducting any protocol-induced activities beyond standard of care, by using the informed consent form (ICF) approved by that site's IRB/EC, regulatory authorities as required and by Medtronic, Inc. The ICF must be signed and dated by the patient and by the person obtaining the consent. Any additional persons required by the site's IRB/EC to sign the informed consent form must also comply. In the event the subject cannot read and/or write, a witnessed (impartial third party) ICF will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF.

If applicable, independent witness must be present throughout the entire informed consent process, and the written informed consent form and any other information related to the study must be read aloud and explained to the prospective subject. If applicable, witness shall also sign and personally date the consent form to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given.

Prior to the patient signing the ICF, the investigator or delegate will fully explain to the patient the nature of the research, study procedures, anticipated benefits, and potential risks of participation in the study. The investigator or delegate will allow adequate time for the patient to read and review the consent form and to ask questions. Signing the ICF serves to document the written and verbal information that the investigator or delegate provides to the patient, the patient's understanding of the information, and his/her agreement to participate. The investigator or delegate must document in the patient's medical records that the patient was consented and the date on which the consent was obtained. The original signed consent form will be retained in the patient's study records and a copy of the informed consent will be provided to the patient. If consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

Patients unable to provide his/her own informed consent, legally incompetent, or otherwise vulnerable are not allowed in the study. Vulnerable subjects include individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

6.4 Revisions in Patient Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's continued participation in the study. The revised information will be sent to the

investigator for approval by the IRB/EC (as applicable). After approval by the IRB/EC, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated. The investigator or his/her authorized designee should inform the subject in a timely manner.

6.5 Screening and Enrollment

The process of patient screening and subject enrollment is as follows (Figure 2):

1. Patients identified by or presented to the study site with AS will be screened by the investigative team for the subject selection criteria using available medical records, including relevant imaging studies previously performed for diagnostic purposes.
2. If the patient is deemed a potential candidate, all aspects of the study will be explained to the patient. The patient will then be invited to participate in the study. If the patient agrees to participate, written informed consent will be obtained. The date informed consent is signed is considered the point of enrollment, and the subject will be assigned a Subject ID number.
3. The subject will undergo transthoracic echocardiography (TTE) to assess his/her degree of AS and cardiac function.
4. If the site investigative team determines the subject meets AS criteria for severe asymptomatic AS, the qualifying echocardiogram will be submitted to the ECL for confirmation of severity of AS and other echocardiographic criteria.
5. If the ECL confirms echocardiographic criteria are met[1], the subject will undergo the following evaluations:
   - Exercise tolerance testing (ETT), unless contra-indicated
   - Multi-detector computed tomography (MDCT)
   - Pulmonary function testing (simple spirometry with FEV_1)
   - Cardiac MRI
   - Coronary arteriography if there is uncertainty regarding the status of coronary artery disease
6. If the local Heart Team considers the subject suitable for implantation, the following information should be submitted to the ERC:
   - Clinical assessments including medical history, co-morbidities, and symptomology
   - TTE data on degree of AS and cardiac function
   - MDCT data on anatomical suitability
7. The ERC will review the submitted information and either confirm, disapprove, or defer eligibility for implantation. Subjects confirmed eligible for implantation should undergo TAVR within 90 days of ERC approval. Subjects disapproved should be exited from the study, and not be reconsidered for future participation without permission from Medtronic.

[1]If a subject has balloon aortic valvuloplasty after their qualifying TTE, they must have repeat TTE to confirm he/she meets criteria for aortic stenosis prior to submission to the ERC.

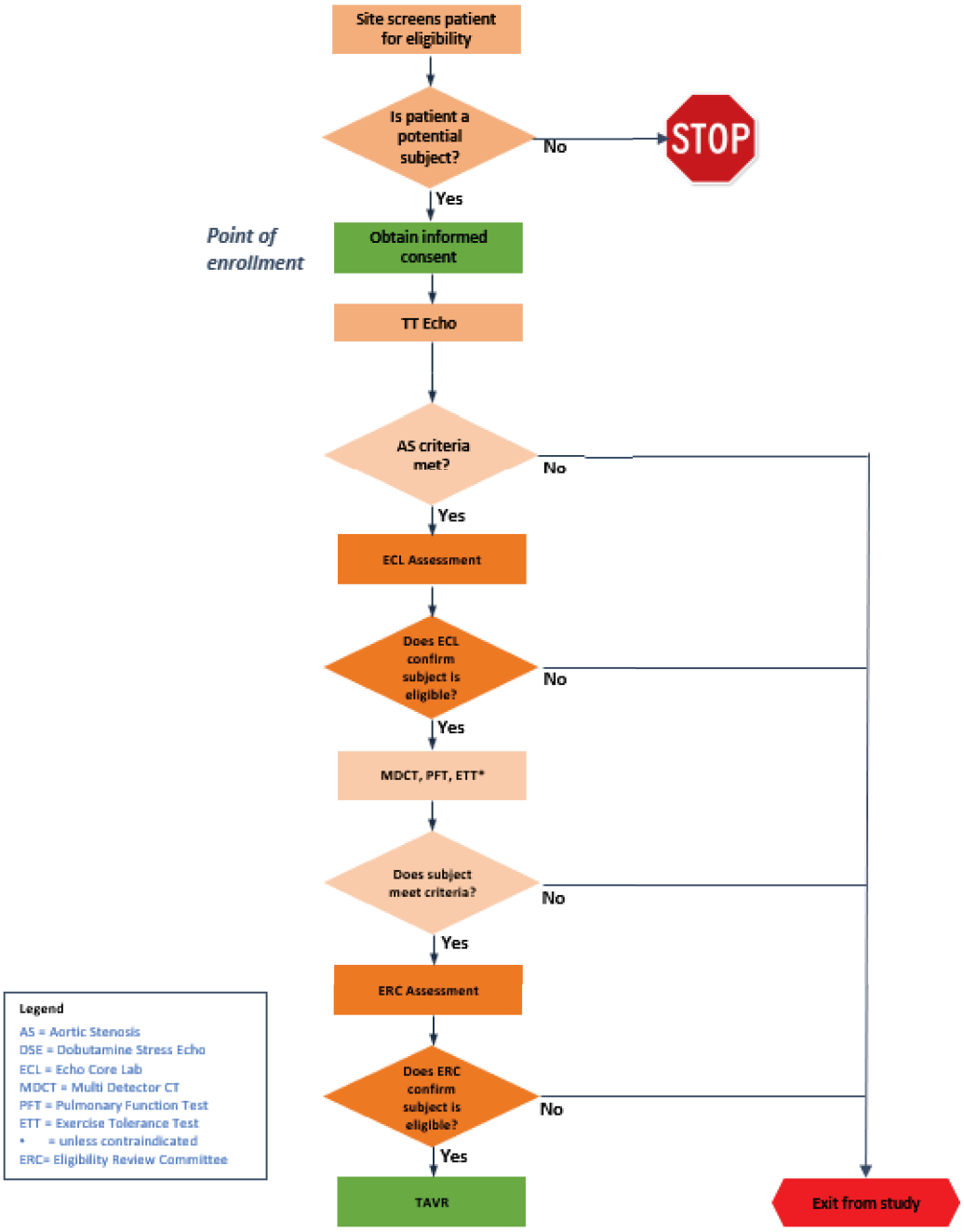


Figure 2. Flow diagram of the study entry process. Patients should give written consent before undergoing any protocol-required testing. However, if any of protocol-required baseline/screening evaluations (e.g. echocardiography, ETT, MDCT, lab work) have been performed for diagnostic purposes or standard of care prior to consenting, they can be used as the protocol-required exams, provided they are within the protocol-required time windows and contain the necessary information.

6.6 Required Evaluations

Protocol required evaluations should be performed at the study site. The protocol required evaluations are as follows and summarized in Table 1. Additional information on data collection requirements is provided in Section 6.13 through Section 6.18. As this is an interventional study, some or all of the required study procedures may be outside of standard of care for a given patient.

Baseline (within 12 weeks prior to submission to the Eligibility Review Committee[2])

- Clinical assessment and medical history, including NYHA classification
- Coronary arteriography (may be either selective or by computed tomography)
- Transthoracic echo (TTE)
- Exercise Tolerance Test (ETT)[3]
- Cardiac MRI
- Simple spirometry (timed vital capacity with FEV_1)
- MDCT (peripheral vasculature and aortic annulus)
- 12-lead ECG
- Complete blood count
- pro B-type natriuretic peptide (NT-proBNP)
- Heart Team assessment
- Six-minute walk test (6MWT)
- Modified Rankin Score
- Quality of Life Questionnaires:
    - Kansas City Cardiomyopathy Questionnaire (KCCQ)
    - European Quality of Life – 5 Dimensions (EQ-5D)
- Medications
- Adverse events

Implant Procedure

- Pre-deployment hemodynamics (LV and aortic pressures)
- Aortography (final result)
- Adverse events and device deficiencies

Discharge

- Clinical assessment (NYHA not assessed at discharge)
- 12 lead ECG
- Medications
- TTE[4]
- Adverse events and device deficiencies

30 days (between 30 to 45 days post implant)

[2] Pre-implant MDCT and coronary arteriography should be performed within 365 days of submission to the eligibility review committee
[3] Unless subject has contra-indication for ETT
[4] Discharge TTE should be performed ≥ 12 hours and ≤ 7 days post procedure

- Clinical assessment, including NYHA classification
- 12 lead ECG
- TTE
- Medications
- Adverse events and device deficiencies
- KCCQ

6 Months (between 183 to 210 days post implant)

- Clinical assessment, including NYHA classification
- 12 lead ECG
- TTE
- Medications
- pro B-type natriuretic peptide (NT-proBNP)
- Quality of Life Questionnaires:
    - Kansas City Cardiomyopathy Questionnaire (KCCQ)
    - European Quality of Life – 5 Dimensions (EQ-5D)
- Cardiac MRI
- Six-minute walk test (6MWT)
- Adverse events and device deficiencies

1 Year (between 365 to 395 days post implant)

- Clinical assessment, including NYHA classification
- TTE
- Medications
- KCCQ
- Adverse events and device deficiencies

2 Years (between 730 to 760 days post implant)

- Clinical assessment, including NYHA classification
- TTE
- Medications
- KCCQ
- Adverse events and device deficiencies

3 Years (between 1095 to 1125 days post implant)

- Clinical assessment, including NYHA classification
- TTE
- Medications
- KCCQ
- Adverse events and device deficiencies

4 Years (between 1460 to 1490 days post implant)

- Clinical assessment, including NYHA classification
- TTE
- Medications

- KCCQ
- Adverse events and device deficiencies

5 Years (between 1825 to 1855 days post implant)

- Clinical assessment, including NYHA classification
- TTE
- Medications
- KCCQ
- Adverse events and device deficiencies

Other Evaluations

- Suspected stroke events should be confirmed by neurology consult and neuroimaging per site's standard practice. A Modified Rankin Score assessment should be conducted at 1 and 3 months following any confirmed stroke event.
- The investigative team should follow their standard practices for assessment of suspected myocardial infarction, acute kidney injury, neurological events, prosthetic valve endocarditis, prosthetic valve thrombosis, etc.
- Non-protocol echocardiograms (e.g. performed for suspicion of prosthetic valve dysfunction) should be submitted to the ECL for evaluation.

Table 1. Summary of required evaluations and visit schedule

	Baseline	Implant	Discharge	30 Days	6 Months	Annual through 5 Years	1 month post stroke event	3 months post stroke event
Clinical assessment including NYHA	✓[5]		✓[1]	✓	✓	✓		
Transthoracic Echo	✓		✓[4]	✓	✓	✓		
Multi-detector CT	✓							
12-lead ECG	✓		✓	✓	✓			
Coronary arteriography	✓							
Exercise Tolerance Test (unless contraindicated)	✓							
Cardiac MRI	✓				✓			
6-Minute Walk Test	✓				✓			
Spirometry	✓							
Complete Blood Count	✓							
Pro B-type natriuretic peptide	✓				✓			

Heart Team Assessment	✓							
Aortography		✓						
Hemodynamics		✓						
Medications	✓		✓	✓	✓	✓		
KCCQ	✓			✓	✓	✓		
EQ-5D	✓				✓			
Modified Rankin Score	✓						✓	✓
Adverse Events and/or device deficiencies[2]	✓	✓	✓	✓	✓	✓		

Notes
1. NYHA not required at discharge
2. Adverse events should be assessed and captured at each follow-up visit after time of informed consent.
3. Discharge TTE used for "Device Success" should be performed > 12 hours and ≤ 7 days post implant
4. Clinical assessment and medical history required at baseline

Visit Windows

Baseline	Within 12 weeks prior to submission to ERC (except for MDCT and coronary arteriography)
Discharge	At the time of discharge from index TAVR procedure (at least 12 hours post-procedure) or within 7 days post implant, whichever comes first
30 Days	Between 30 and 45 days post implant
6 Months	Between 183 and 210 days post implant
1 Year	Between 365 and 395 days post implant
2 Years	Between 730 and 760 days post-implant
3 Years	Between 1095 to 1125 post-implant
4 Years	Between 1460 to 1490 days post-implant
5 Years	Between 1825 to 1855 days post-implant

6.7 Subject Disposition

Sites will maintain a log of subjects consented, the subject ID numbers assigned to them, and the dates of their implants (or attempted implants). Subjects who are consented but are not taken to the procedure room for implantation should be exited from the study and need not be followed beyond the date of study exit.

Subjects taken to the procedure room for implantation, and any of the following occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed, but do not receive a TAV for any reason should be followed for safety events for 30 days after the procedure or through the hospitalization, whichever is longer, and then exited from the study. Subjects that have their TAV explanted should be followed for safety events for 30 days after the explant procedure, or through resolution of related adverse events, whichever is longer, then exited from the study.

6.8 Missed Follow-Up Visits

Every effort should be made to ensure subjects return to the clinic for all protocol required follow-up visits, tests, and assessments. If the subject is unable to return for an in-person clinic visit, the

Investigator, or designee, should document in the subject record the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in Section 6.10.

The investigator should also make every effort to contact the subject within the visit window to collect the subject's vital status as well as information related to potential adverse events, safety data, and hospitalizations.

6.9 Unscheduled Follow-Up Visits

If a subject returns to the study site or is contacted via telephone between their scheduled follow-up visits for an event potentially related to a study endpoint, the visit or telephone call will be treated as an unscheduled follow-up, and the assessments completed at this visit will be conducted at the discretion of the investigator per local standards of care and/or institutional policies and procedures. Relevant unscheduled visit data should be reported and imaging should be provided to the sponsor as needed.

6.10 Protocol Deviations

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the study according to the CIP or the Clinical Investigational Agreement. Examples of CIP deviations include but are not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain IRB/EC approval before the start of the study
- Implanted subject did not meet inclusion/exclusion criteria[5]
- Required testing and/or measurements not done or incorrectly done
- Subject does not attend follow-up visit or follow-up visit outside window
- Unauthorized use of investigational devices
- Adverse events not reported in the required time frame as required by regulation or as specified in the CIP
- Control of study devices not maintained
- Source data permanently missing
- Enrollment of patients during lapse of IRB/EC approval
- Enrollment limits exceeded

Investigators should obtain prior approval from Medtronic before initiating any change or deviation from the CIP, except where necessary to protect the life or physical well-being of a subject in an emergency situation. Such approval shall be documented in writing and maintained in the Investigator Site File. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g. subject did not attend scheduled follow-up visit).

[5] Subjects must meet all inclusion/exclusion criteria to be eligible for implantation. However, it will not be considered a protocol deviation if study related testing (e.g. echo, MDCT, labs, coronary arteriography, Heart Team assessment, or ERC review) of a consented subject identifies implantation eligibility criteria that are not met.

Deviations will be reported to Medtronic regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Study deviations should be reported to Medtronic via the Study Deviation eCRF.

Investigators should report the following deviations to Medtronic, and if applicable their reviewing IRB/EC, within 5 working days (or earlier according to local requirements) of the occurrence of the deviations:

- Failure to obtain written informed consent
- Deviations to protect the life or physical well-being of a subject in an emergency

In addition, Investigators are required to adhere to applicable local regulations and IRB/EC procedures for reporting deviations. Sponsor and investigator will follow requirements for reporting and handling serious breaches in Australia. Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any corrective and/or preventive actions that may be warranted. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, which may include suspension of enrollment or the investigator's or site's participation in the study.

6.11 Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the study through the last follow-up visit at five years. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total study subjects. If a subject is discontinued from the study early, the reason for discontinuation should be documented in the subject file and a Study Exit eCRF must be completed.

The study site should make every effort to have all subjects complete the follow up visit schedule. When subjects are lost to follow-up the investigator will make efforts to confirm the vital status of the subject, as described in the informed consent. A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful. At a minimum, the efforts to obtain follow-up information must include 3 attempts to make contact via telephone and if contact via phone is not successful, a traceable letter from the investigator should be sent to the subject's last known address. The study site may also utilize a civil register for subject information, as applicable. Should both telephone and mail efforts to contact the subject be unsuccessful, the subject's primary physician should be contacted. Subjects will then be deemed lost to follow up. All contact efforts to obtain follow-up must be documented in both the subject's medical records and on the study eCRFs.

If a subject discontinues the study at any time, is withdrawn from the study early, or completes all protocol required follow-up they should continue to be followed by the implanting site according to their routine clinical practice for patients with prosthetic aortic valves. If for any reason this is not possible for a particular subject, or if a subject needs to change their follow-up site at any time point after conclusion of the study, investigators should refer subjects to a local site with appropriate training and experience in managing patients with prosthetic aortic valves. Study data will not be collected after a subject has ended their participation in the study.

6.12 Study Materials and Study-Specific Equipment

Medtronic will control the supply of investigational devices and study materials (e.g. Investigator Site File, eCRF access). Investigational devices will not be sent to the site until the site is activated. Medtronic will not provide any study specific equipment. Equipment used for assessing study variables (e.g. echocardiographic systems, laboratory equipment) should be maintained per the site's standard procedures.

6.13 Pre-TAVR Multi-Detector Computed Tomography (MDCT)

MDCT of the aortic root and peripheral vascular is required within 365 days of the qualifying echocardiogram to assess suitability for transfemoral TAVR with the study system. Information regarding the required MDCT variables are provided in Section 13.1.

6.14 Clinical Assessment

Clinical assessment is required at each study interval. Assessments should be performed at the study center by a member of the investigative team as delegated by the PI. If the subject is unable to attend a follow-up visit, the clinical assessment can be performed by telephone, and this should be indicated on the eCRF and documented in the subject's medical record at the site. Information regarding the required variables and assessment procedures are provided in Section 13.2.

6.15 Echocardiography

Comprehensive transthoracic echocardiography (TTE) including speckle tracking (STE) is required at baseline, discharge, 30 days, 6 months, and annually through five years. Protocol-required exams should be performed at the study center by designated members of the study team as delegated by the site PI. All protocol-required exams will be sent to the ECL for central assessment. In addition, unplanned echocardiograms (e.g. clinically indicated exams for change in symptoms or findings on physical exam) should be sent to the ECL if possible. A listing of the required variables and details regarding their acquisition is provided in Section 13.3.

6.16 Exercise Tolerance Testing (ETT)

Subjects confirmed by the ECL to meet severe asymptomatic AS criteria should undergo ETT unless contraindicated. Examples of contraindications include an established indication for AVR, uncontrolled hypertension, symptomatic or hemodynamically significant arrhythmias, and inability to perform the test such as orthopedic limitations or global disabilities.[59,60,61] The reason for not undergoing ETT should be documented in the study records.

A symptom-limited exercise test with the goal of reaching 80% to 85% of the age-predicted maximum heart rate is recommended. The recommended protocol is the modified-Bruce with treadmill, however the choice of the specific ETT protocol for each subject is per the clinical judgment of site study team.

Subjects who develop spontaneous AS-related symptoms or signs of AS (e.g. a drop or an insufficient rise in blood pressure, significant ventricular arrhythmias)[39] may continue in the study as follows: At maximum, up to 30 subjects with a positive ETT will be included in the study. Subjects with a positive ETT who are approved by the ERC may continue in the study until the 30-subject maximum is reached. Once the 30-subject maximum is reached, only subjects with a negative ETT may continue in the study. Details regarding the ETT methods and data requirements are provided in Section 13.4.

6.17 Cardiac Magnetic Resonance Imaging (CMR)

Subjects confirmed by the ECL to meet the severe asymptomatic AS criteria should undergo CMR unless contraindicated, and subjects implanted should have a CMR at the six-month follow-up. CMR exams will be sent to the CMR core lab for central analysis. Details on CMR methods and data requirements are provided in Section 13.5.

6.18 Six Minute Walk Test (6MWT)

Subjects confirmed by the ECL to meet the severe asymptomatic AS criteria should have a 6MWT unless contraindicated, and subjects implanted should have a 6MWT at the six-month follow-up. Details on 6MWT methods and data requirements are provided in Section 13.6.

6.19 TAVR Implant Procedure

The implantation procedure is performed according to the standard procedures of the implant team. For sites in the United States, the local heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of the TAVR procedure. Procedural aspects specific to the Medtronic TAVR system should be performed according to the Instructions for Use (IFU). Valve deployment in accordance with the cusp overlap technique[62] is recommended for TAVR implant for all study subjects, as appropriate. Transfemoral access is required for the TAVR implant. Information on TAVR implant data requirements is provided in Section 13.7.

6.20 Post-Implant Antithrombotic and Medical Therapy

Management of subject's anti-thrombotic regimen will be per the discretion of the investigative team.

7. Adverse Events and Device Deficiencies

7.1 Definitions

The definitions to be applied for the purposes of reporting adverse events are provided in Table 2.

Table 2. Adverse event definitions for reporting requirements

Event Type	Definition
Device Deficiency (ISO 14155:2020 3.19)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator
Adverse Event (AE) (ISO/FDIS 14155:2020 3.2)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other parties, whether or not related to the investigational medical device, and whether anticipated or unanticipated. *NOTE 1: This definition includes events related to the investigational medical device or the comparator.* *NOTE 2: This definition includes events related to the procedures involved.* *NOTE 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.*
Serious Adverse Event (SAE) (ISO/FDIS 14155:2020 3.45)	Adverse event that led to any of the following a) Death, b) Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function including chronic diseases, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment. *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*
Adverse Device Effect (ADE) or Device Related Adverse Event (ISO/FDIS 14155:2020 3.1)	Adverse event related to the use of an investigational medical device. *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device* *NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.* *NOTE 3: This includes 'comparator' if the comparator is a medical device.*
Serious Adverse Device Effect (SADE) (ISO/FDIS 14155:2020 3.44)	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Unanticipated Adverse Device Effect (UADE) (21 CFR 812.3)	Any serious adverse effect on health or safety of a patient, or any life-threatening problem or death caused by or associated with the device, if the effect, problem, or death has not been previously identified in nature, severity, or degree of incidence in the investigational plan or application, (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Serious Adverse Device Effect (USADE) (ISO/FDIS 14155:2020 3.51)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment *NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.*
Serious Health Threat (ISO 14155:2020 3.46)	A signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. *NOTE: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.*
Additional Event Types	**Definition**
Significant Safety Issue (SSI) (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016) (Australia ONLY)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial.
Urgent Safety Measure (USM) (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016) (Australia ONLY)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. Note: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions.

Notes:

- The interpretation of Seriousness will exclude certain interventions considered standard of care during hospitalization (e.g. IV hydration, certain medications delivered intravenously due to available intravenous access or NPO (nothing by mouth) status, and the delivery of electrolytes to maintain electrolyte balance or to address mild electrolyte depletion). Any nonoral medication or fluid delivery used to treat an acute physical decompensation/deterioration episode or to otherwise resuscitate a subject will be considered serious by definition in that it prevents a permanent impairment of a body structure or deterioration of the health of a subject.
- Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
- Hospitalization requires admission for at least 24 hours.
- Ballooning as needed during the implant procedure is standard practice and should not be considered a reintervention.

7.2 Evaluation and Documentation of Adverse Events and Device Deficiencies

Investigators are required to evaluate and document in the subject's medical records all adverse events (AE) and device deficiencies (per the definitions in Table 2) observed in study subjects from the time

they are enrolled until they are exited from the study. All AEs should be followed through their resolution.

All AEs that occur during the study need to be reported to Medtronic via the AE eCRF. Documented pre-existing conditions are not considered to be reportable unless there is a change in the nature or severity of the condition. Pre-existing events should be reported as AE in the situation where a new treatment has to be started or an existing treatment has to be changed to treat the adverse event and the event is accompanied with signs and symptoms. In addition, after the subject has completed his/her 6-month follow-up visit, only SAE, device-related AEs, and device deficiencies need to be reported to Medtronic.

Unavoidable events are conditions which do not fulfill the definition of an Adverse Event, meaning those medical occurrences, clinical signs (including toward abnormal laboratory findings), diseases or injuries that are not untoward in nature; specifically, those resulting from the intended injury such as the index TAVR procedure. The events listed in Table 3 are expected for patients undergoing TAVR, and do not need to be reported as AE, unless they occur outside of the stated timeframe, are otherwise considered to be an AE according to the treating investigator, or are suspected or confirmed to be device-related.

Table 3. Non-reportable medical occurrences associated with the index implant procedure

Event	Timeframe (hours) from the Index Procedure
Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure	0
Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (e.g. CT)	72
Dizziness and/or lightheadedness with or without treatment	24
Headache with or without treatment	72
Sleep problems or insomnia with or without treatment	120 (5 days)
Mild dyspnea or cough with or without treatment	72
Oxygen supply after extubation/"forced breathing therapy"	48
Diarrhea with or without treatment	48
Obstipation/Constipation with or without treatment	72
Anesthesia-related nausea and/or vomiting with or without treatment	24
Low-grade fever (<101.3°F or <38.5°C) without confirmed infection	48
Low body temperature	6
Pain (eg, back, shoulder) related to laying on the procedure table with or without treatment	72
Incisional pain (pain at access site) with or without standard treatment and patient not returning to clinic to have additional treatment	No time limit
Pain in throat and/or trachea due to intubation	72

Mild to moderate bruising or ecchymosis	168 (7 days)
Atelectasis/Pleural Effusion not requiring punctuation	168 (7 days)
Edema resulting in weight increase up to 4 kg/9lbs from baseline	168 (7 days)

For all reportable AEs, investigators should assess and document the following information on the Adverse Event eCRF:

- Date of onset and first observation/awareness of the event
- Description of the event
- Seriousness of the event
- Causal relationship of the event to the TAV
- Causal relationship of the event to the DCS or LS
- Causal relationship of the event to the TAVR implant procedure
- Treatment required
- Outcome or status of the event
- Date of resolution

For all deaths, investigators should assess and document the following information on the Death eCRF:

- Date of death
- Primary death category
- Causal relationship of the event to the TAV
- Causal relationship of the event to the DCS or LS
- Causal relationship of the event to the implant procedure

In addition, for all endpoint-related adverse events and deaths, sites should submit relevant, de-identified source documents to Medtronic for the Clinical Events Committee (CEC) members to use in their adjudication of the event. The CEC may request source documentation on additional events, at their discretion and according to the CEC Charter.

Definitions of safety endpoints and guidelines for accessing causal relationships are provided in Section 13.8.

7.3 Anticipated Adverse Events

Adverse events that are anticipated (foreseeable) for subjects participating in this study are described in Section 8.1 and in the Investigator's Brochure/ROPI.

7.4 Adverse Event Reporting Requirements for Clinical Sites

Adverse events and device deficiencies that occur during this study are required to be reported to Medtronic via the AE or device deficiency eCRF, as soon as possible after the event occurs, but no later than the timeframes listed in Table 4 or local requirements, whichever is more stringent.

Table 4. Required timeframes for adverse event reporting to Medtronic

Event Type	Timeframe for Reporting
Adverse Event (AE)	No later than 10 working days of the investigator's / site's first knowledge of the event
Serious Adverse Event (SAE)	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Adverse Device Effect (ADE) or Device Related Adverse Event	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Unanticipated Adverse Device Effect (UADE)	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Device Deficiency	No later than 72 hours of the investigator's / site's first knowledge of the event
Device Deficiency that might have led to a SADE	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Serious Health Threat	Immediately, but no later than 72 hours of the investigator's / site's first knowledge of the event
Additional Event Types	**Timeframe for Reporting**
Mandatory Problem Reporting Incident (Canada ONLY)	No later than 72 hours of the investigator's / site's first knowledge of the event, to Health Canada and Medtronic
All SAEs and DDs with potential SADE (Australia ONLY)	Without unjustified delay to Medtronic (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b)
Significant Safety Issues (Australia ONLY)	• Urgent Safety Measures (USMs): Within 24 hours to Medtronic (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.c) • All significant safety issues: Without undue delay and no later than 72 hours of the principal investigator becoming aware of the event to HREC and Institution (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)
Unanticipated Serious Adverse Device Effect (USADE) (Australia ONLY)	Report to their HREC and institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)

In addition, Investigators are obligated to report adverse events in accordance with the requirements of their reviewing IRB/EC and local regulations.

The Sponsor is obligated to report adverse events and device deficiencies that occur during this study to the Regulatory Authorities and IRB/EC as per local requirements. The applicable timeframes are described in the Safety Plan associated with this study.

7.5 Documentation and Reporting of Device Deficiencies

Device deficiency information will be collected throughout the study and reported to Medtronic. Device deficiencies that led to an AE are reported on the AE eCRF. Device deficiencies that did not lead to an AE should be reported on a Device Deficiency eCRF (one for each Device deficiency).

Device deficiencies that did not lead to an adverse event but might have led to a SADE if:

- a suitable action had not been taken, or
- an intervention had not been made, or
- circumstances had been less fortunate,

Device deficiency information should be reported to Medtronic via the Device Deficiency eCRF as soon as possible but no later than 72 hours after the investigator first learns of the event.

7.6 Emergency Contact Details for Reporting SAE, SADE, UADE, and Device Deficiencies

Investigators should contact their Medtronic clinical study manager or site manager if they have any questions regarding reportable AEs. Medtronic will provide and maintain a listing of current contact details for each site.

7.7 Clinical Events Committee

A Clinical Events Committee (CEC) will provide independent medical review and adjudication of adverse event data used in the safety assessment of the investigational device. The CEC will adjudicate, at minimum, all deaths and safety endpoint-related adverse events and TAVR related complications reported by the investigators, and may leverage core lab-reported data for events where echo imaging is used in the adjudication. The CEC will follow the VARC II[63] recommendations where relative for classifying adverse events related to clinical safety endpoints. The analysis of the study safety data will be based on CEC adjudicated events. Definitions of safety endpoints and other TAVR related complications are provided in Section 13.8.

The committee will consist of at least 3 independent experts (non-Medtronic employed physicians that are not participating investigators for the study) with expertise relevant to the study. This may include experience in the areas of:

- Interventional cardiology
- Cardiology
- Neurology
- Cardiac surgery

A CEC charter will be approved by Medtronic and the CEC prior to the first subject enrollment.

7.8 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will assess interim study data and provide recommendations to Medtronic regarding study conduct, should they identify any issues that may affect the safety of the study subjects. DSMB members will be free from bias towards the study and will be independent from both the study and investigators and Medtronic. The DSMB will consist of a minimum of 4 members:

- a non-interventional cardiologist with expertise in the management of aortic stenosis
- an interventional cardiologist with expertise in TAVR
- a cardiothoracic surgeon with expertise in aortic valve replacement
- a statistician

A DSMB charter will be approved by Medtronic and the DSMB members prior to the first subject enrollment. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for safety data review, chairman appointment, and guidelines for study recommendations. The DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all SAEs and deaths, and will meet more frequently when needed. Safety-related endpoints may also be reviewed at these meetings. DSMB meetings may consist of both open and closed sessions. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges.

Following each meeting, the DSMB will report to Medtronic in writing and may recommend changes in the conduct of the study. The DSMB recommendations may include recommendations on study status such as continuing the study without modifications, continuing the study with modifications, stopping or suspending enrollment, or recommendations regarding study conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical study within 5 working days after making that determination and no later than 15 working days after Medtronic first receives notice of the effect. All clinical sites will be notified of this action. The DSMB may call additional meetings if, at any time, there is concern about any aspect of the study. All data presented at the meetings will be considered confidential.

7.9 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the regulatory authorities as applicable for the following incidents immediately upon learning of them and is not limited to adverse events and device deficiencies only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
  - Life-threatening illness or injury
  - Permanent impairment of a body function or permanent damage to a body structure
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

8. Risks and Benefits

8.1 Potential Risks

As with any TAVR procedure, there are risks associated with participation in this study. However, the risks to a patient for participation in this study are not materially different than those a patient would incur if they underwent TAVR outside of this study.

TAVR has been associated with serious complications, including death. In addition, complications may occur at varying intervals necessitating re-intervention or surgical replacement of the TAV. Known (anticipated) complications that may result from TAVR include but are not limited to the following:

- Allergic reaction to anti-platelet agents, contrast medium, or anesthesia
- Anemia
- Bowel ischemia
- Cardiac arrest
- Cardiac tamponade
- Cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle myocardium, or valvular structure that may require intervention)
- Coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- Exposure to radiation through fluoroscopy and angiography
- Major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding)
- Mitral valve regurgitation or injury
- Myocardial infarction
- Myocardial ischemia
- Pericardial effusion
- Peripheral ischemia
- Pleural effusion
- Stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), encephalopathy, or other neurological deficits

Known complications that are associated with the TAV include but are not limited to the following:

- Ancillary device embolization
- Delivery catheter system malfunction resulting in the need for additional re-crossing of the aortic valve and prolonged procedural time
- Hemolysis
- Hypertension
- Prosthetic valve dysfunction, which could lead to urgent need for balloon valvuloplasty or Percutaneous Coronary Intervention (PCI), including but not limited to:
  - Fracture
  - Bending (out-of-round) configuration of the valve frame
  - Calcification
  - Pannus
  - Wear, tear, prolapse, or retraction in the valve leaflet

  - Poor valve coaptation
  - Suture breaks or disruption
  - Leak
  - Mal-sizing (prosthesis-patient mismatch)
  - Malposition (either too high or too low)
  - Valve regurgitation (paravalvular or transvalvular)
  - Valve stenosis
- Tissue erosion
- Valve migration/embolization

Known complications that could result from either the TAVR procedure or the TAV include but are not limited to the following:

- Abnormal lab values (including electrolyte imbalance)
- Angina
- Cardiac arrhythmias
- Disturbances in the electrical system of the heart that may result in the permanent placement of a device (pacemaker):
  - Atrio-ventricular node block
  - Bundle branch block
  - Asystole
- Dyspnea
- Fever
- Hypotension
- Individual organ, for example, cardiac, respiratory, or renal (including acute kidney failure), insufficiency or failure
- Infection (including septicemia or endocarditis)
- Inflammation
- Multi-organ failure or low cardiac output
- Pulmonary edema
- Permanent disability
- Syncope
- Thrombosis (including valve thrombosis)
- Valvular access site or access related complications including but not limited to:
  - Dissection
  - Perforation
  - Pain
  - Bleeding
  - Hematoma
  - Pseudoaneurysm
  - Irreversible nerve injury
  - Compartment syndrome
  - Arteriovenous fistula
  - Stenosis

Known risks associated with participation in this study include but are not limited to the following:

- Minor pain, bruising, presyncope, or syncope (fainting) during blood draws
- Excessive bleeding, infection, blood clots, or inflammation of the vein during blood draws
- Anxiety
- Skin irritation from ECG electrodes
- Chest pain
- Arrhythmia
- Dizziness
- Nausea
- Fatigue
- Allergic reaction to contrast medium
- Changes in taste
- Headache

Each of these complications has the potential to be life-threatening, and some could lead to the need for open heart surgery.

8.2 Risk Analysis and Minimization

Medtronic has determined this to be a significant risk clinical study. In the United States, Medtronic will obtain an Investigational Device Exemption (IDE) from the United States Food and Drug Administration. Medtronic will obtain approval from country-specific authorities in Canada, Europe, Israel, Australia, and New Zealand.

Risk Analysis procedures were completed in accordance with ISO 14971:2012, and the results are provided in the Investigator Brochure/Report of Prior Investigations.

The following measures will be implemented to minimize risks to the study subjects:

- Implanting physicians will have considerable experience with TAVR
- Study sites will have significant experience with surgical SAVR and TAVR
- Patients will undergo thorough imaging assessment during their pre-implant screening
- Patients will be rigorously followed over the course of the study
- An independent DSMB will review interim results in order to advise Medtronic regarding study conduct, should safety concerns be identified.

8.3 Potential Benefits

The primary potential benefit to subjects participating in the study is restored function of their aortic valve, specifically relief of obstruction of their stenotic aortic valve. In patients with severe, symptomatic aortic stenosis, TAVR has been demonstrated to improve symptoms and survival. However, the benefits with TAVR have not been confirmed in clinical trials for patients with severe, asymptomatic AS.

8.4 Risk-Benefit Rationale

Study subjects will be exposed to the procedural and device risks associated with TAVR, as well as the study specific risks listed in Section 8.1. However, evidence from the scientific literature indicates patients with the degree of AS in this study are also exposed to the serious risks associated with their disease, including heart failure, irreversible ventricular functional impairment, and death. Further, recent evidence indicates the risks of the disease for the subjects in this study are similar to those with for which TAVR has been shown to be effective in improving symptoms and survival.

The known benefits of TAVR in patients with severe symptomatic AS are expected to be conferred to the study subjects with severe asymptomatic AS, and it is believed that the benefits of the relief of obstruction will outweigh the risks of intervention. Therefore, the risk/benefit ratio for the study subjects is justified.

9. Investigational Product Description

9.1 General

The investigational device in this study is the Medtronic Evolut PRO+ System. The Medtronic Evolut PRO+ System (Figure 3) is a recapturable transcatheter aortic valve replacement (TAVR) implantation system comprised of the following three components:

1. Medtronic Evolut PRO+ TAV
2. Medtronic Evolut PRO+ DCS
3. Medtronic Evolut PRO+ LS

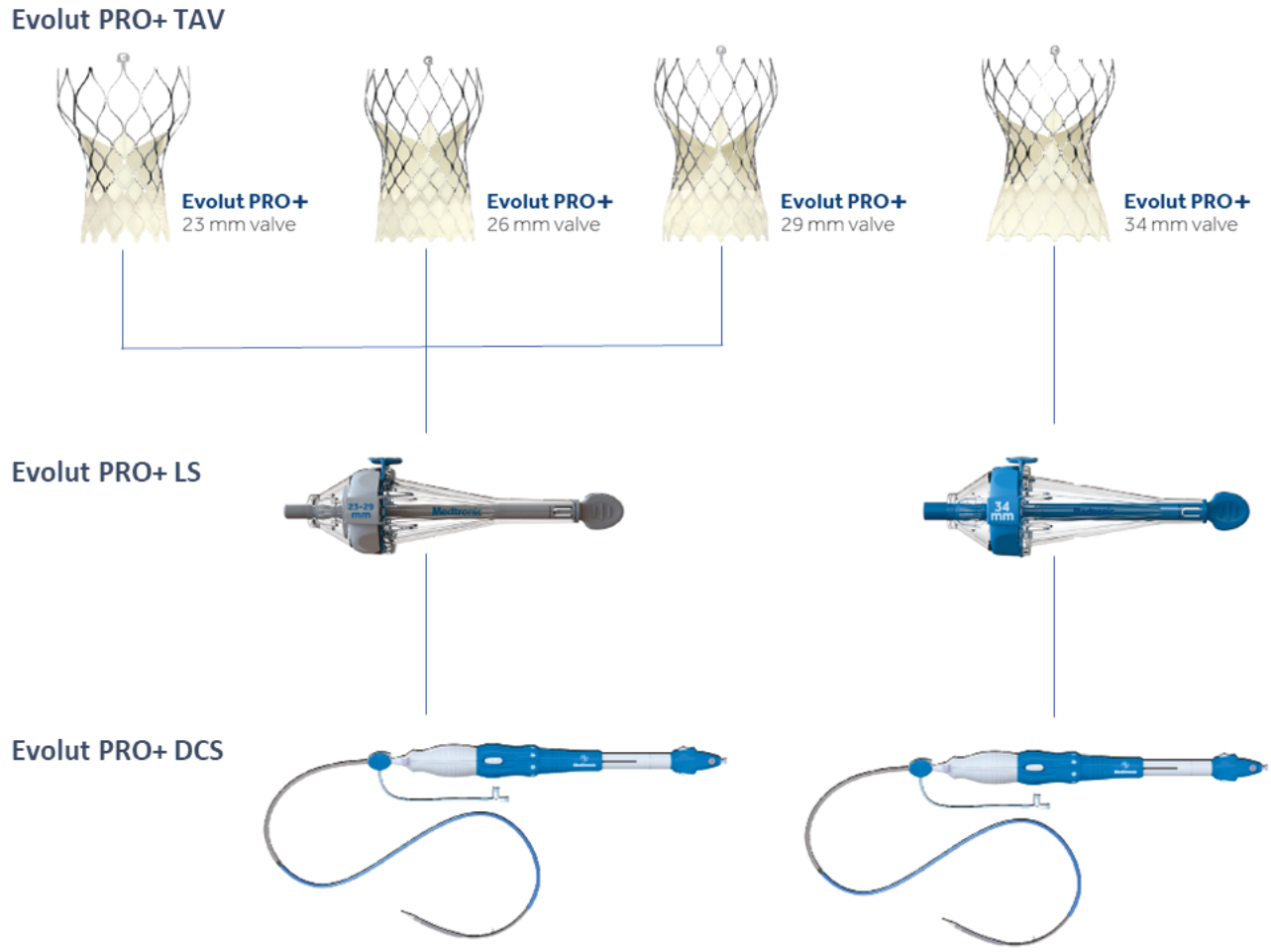


Figure 3. The Evolut PRO+ TAVR system; Evolut PRO+ Transcatheter Aortic Valve (top); Evolut PRO+ Loading System (middle); Evolut PRO+ Delivery Catheter System (bottom).

There are no anticipated changes to any of the system components during this investigation. A listing of the system components is provided in Table 5.

Table 5. Evolut PRO+ System Components

Component	US Model Number	OUS Model Number	Size (mm)	Aortic Annulus Diameter (mm)
Medtronic Evolut PRO+ TAV	EVPROPLUS-23US-C	EVPROPLUS-23-C	23	18 – 20
	EVPROPLUS-26US-C	EVPROPLUS-26-C	26	20 – 23
	EVPROPLUS-29US-C	EVPROPLUS-29-C	29	23 – 26
	EVPROPLUS-34US-C	EVPROPLUS-34-C	34	26 - 30
Medtronic Evolut PRO+ DCS	D-EVPROP2329US-C	D-EVPROP23-29GC	Used with 23, 26, and 29 mm TAVs	Not applicable
	D-EVPROP34US-C	D-EVPROP34GC	Used with 34mm TAV	Not applicable
Medtronic Evolut PRO+ LS	L-EVPROP2329US-C	L-EVPROP23-29GC	Used with 23,26, and 29 mm TAVs	Not applicable
	L-EVPROP34US-C	L-EVPROP34GC	Used with 34 mm TAV	Not applicable

9.2 Medtronic Evolut PRO+ Transcatheter Aortic Valve (TAV) Prosthesis

The Medtronic Evolut PRO+ TAV is available in 4 sizes (23, 26, 29, 34mm), covering an aortic annulus diameter of 18 to 30 mm. The TAV is comprised of 3 leaflets, a sealing skirt, and outer tissue wrap constructed from glutaraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame. The TAV is processed with an anti-mineralization treatment of AOA, a compound derived from oleic acid, a naturally occurring long-chain fatty acid.

9.3 Medtronic Evolut PRO+ Delivery Catheter System

The Evolut PRO+ catheter facilitates the placement of the bioprosthesis within the annulus of the aortic valve. The catheter assembly is flexible and compatible with a 0.035 in (0.889 mm) guidewire. The distal (deployment) end of the system features an atraumatic, radiopaque catheter tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The capsule includes a distal flare to enable the bioprosthesis to be partially or fully recaptured after partial deployment. A stability layer is fixed at the handle and extends down the outside of the catheter shaft. It provides a barrier between the retractable catheter and the introducer sheath and vessel walls, thus enabling the catheter to retract freely. A PRO+ InLine sheath is assembled over the stability layer, which functions as a hemostatic introducer sheath and minimizes the access site size to the capsule diameter. The catheter

is compatible with an 18 Fr (6.0 mm) introducer sheath for the 23, 26, and 29 mm TAVs and a 22 Fr (7.3 mm) introducer sheath for the 34 mm TAV.

The DCS consists of a catheter with an integrated handle to assist the user with accurate and controlled deployment. The handle is on the proximal end of the catheter and is used to load, deploy, recapture, and reposition the bioprosthesis. The handle features a gray front grip used to stabilize the system. The deployment knob turns to deploy the bioprosthesis. Arrows on the deployment knob indicate the direction of rotation required to deploy the bioprosthesis. If desired, the deployment knob can be turned in the opposite direction to partially or fully recapture the bioprosthesis if the radiopaque capsule marker band has not yet reached the distal end of the radiopaque paddle attachment. Once the radiopaque capsule marker band reaches the distal end of the radiopaque paddle attachment, it is at the point of no recapture. The deployment knob also features a trigger, which can be engaged to make macro adjustments to the capsule position. A blue hand rest connects to the deployment knob. The end of the handle features a tip-retrieval mechanism, which can be used to withdraw the catheter tip to meet the capsule after the device has been fully deployed.

The catheter packaging contains an integrated loading bath and a removable tray with 3 rinsing bowls for loading and rinsing the bioprosthesis. The integrated loading bath features a mirror, which aids in accurate placement of the bioprosthesis frame paddles during loading. In addition to these features, the device packaging is swiveled and secured to facilitate the bioprosthesis loading procedure.

9.4 Medtronic Evolut PRO+ Loading System

The Evolut PRO+ LS compresses the bioprosthesis into the catheter. Note: verify the correct delivery system and loading system are used for the Evolut PRO+ 34 mm valve. This loading system is designed for compatibility with this specific TAV and delivery system.

9.5 Packaging

Examples of the Instructions for Use (IFU) and package labeling (English versions) will be provided under separate cover. Devices will be labeled as investigational (i.e. “Exclusively for clinical investigation”). IFU and labeling will be provided in local languages. Labeling will be in accordance with country regulation in each geography.

9.6 Intended Population

The intended population for this study includes males and females ≥ than 65 years of age with severe, asymptomatic aortic stenosis.

9.7 Product Use

The Evolut PRO+ TAV treats aortic stenosis by displacing and functionally replacing the dysfunctional native valve with a bioprosthetic valve delivered on a catheter while the heart is still beating. Its intended performance is to relieve aortic valve stenosis without inducing significant regurgitation,

thereby restoring effective aortic valve function. The Evolut PRO+ device shall be used in compliance with applicable national regulations.

9.8 Product Training Requirements

There are no training requirements specific to this study. Study trained, delegated, and activated implanters will have experience with the TAVR procedure as noted in Section 5.4.

9.9 Product Receipt, Tracking, Storage, and Accountability

All components of the Evolut PRO+ TAVR system are not approved for use outside of patients in this study and therefore are considered investigational devices. As such, they should be stored as labeled and in a secure location. The method of storage should prevent the use of these investigational devices for applications other than mentioned in this CIP. The investigator shall maintain adequate records of the receipt and disposition of all investigational devices.

Centers are required to maintain investigational device records that contain the following information:

- Investigational device name
- TAV serial number
- Lot number (for delivery and loading systems only)
- Date of receipt of device
- Name of person receiving the device
- Name of person using the device
- Date of implant or use
- ID number of subject receiving or using the device
- Disposition (implanted, disposed of, or returned to Medtronic)

For devices that are returned to Medtronic or disposed of, centers are required to document the following information:

- The device serial numbers
- Lot numbers (for delivery systems only)
- The quantity and reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date of shipment back to Medtronic

At the study closeout visit, the investigator must return to Medtronic any unused devices and a copy of the completed device inventory. The investigator's copy of the device reconciliation records must document any unused devices that have been returned to Medtronic as well as all product usage including opened but non-implanted devices. Country specific regulations will also be followed.

9.10 Product Return

In the event of a device malfunction of the Evolut PRO+ system prior to implant, or in the event a TAV is explanted after implant (due to reintervention or autopsy), the TAV and/or affected components of the Evolut PRO+ system should be sent to Medtronic at the following address:

Medtronic, Inc.
Attn: Explant Lab [PCR#]
1851 E. Deere Avenue
Santa Ana, CA 92705-5720

Study sites shall notify the sponsor at the time of TAV explant. Additional details surrounding the device return process are contained within the Medtronic explant kit that will be provided upon notification of a device malfunction or explant. Explanted TAVs returned to Medtronic will be evaluated by a Pathology Core lab.

10. Statistical Design and Methods

10.1 General Aspects of Analysis

Data analysis will be performed by Medtronic clinical personnel per departmental SOP and according to the Statistical Analysis Plan developed for this study. As this is a descriptive study, there are no prospectively developed study hypotheses or powered clinical endpoints. There will be two analysis sets: 1) the Attempted Implant set, and 2) the Implanted set:

Attempted Implant. The attempted implant data set will include all subjects with an attempted implant, where an attempted implant is defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed. Day 0 is the date of first attempted procedure.

Implanted. The implanted data set includes of all subjects with an attempted implant where the study device is implanted, defined as when the TAV is fully released from the DCS. Day 0 is the date of first attempted procedure.

Information on the analysis data sets specific to the study endpoints and outcome measures are provided in Section 10.4. Data from all geographies and active centers will be included in the analyses; there are no planned poolability analyses (e.g. by gender, race, geography).

Baseline demographic and clinical variables will be summarized for attempted implant analysis set. The subjects' baseline characteristics will be summarized with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, first and third quartiles, minimums and maximums for continuous variables.

Subject disposition will be illustrated in a flow diagram. Subject visits will be tabulated and compliance to visit schedule and visit windows will be summarized, and attrition will be identified and summarized. Every effort will be undertaken to minimize missing data. Missing (accidentally, due to withdrawal, missing follow-up or loss to follow-up, etc.), unused and spurious data will remain identifiable in the database. Data from subjects that cannot be analyzed for a specific variable will be displayed as missing All analyses will be based on available data and missing data will not be imputed. Subgroup analyses may be performed (but are not limited to) include the following subject groups:

1. Baseline Peak GLS $\geq$ median value and < median value
2. Baseline NO-proBNP $\geq$ median value and < median value

Subgroup analyses will be performed at minimum for the following key study endpoints at 30 days and 6 months, where applicable: all-cause mortality, stroke, valve-related dysfunction requiring repeat procedure, new PPI, cardiovascular and heart failure hospitalizations, heart failure events, change in KCCQ, change in 6MWT, and change in cardiac function by echo.

10.2 Analysis Execution

Analyses are planned when all implanted subjects have completed his/her six-month follow-up, and when all implanted subjects have completed his/her five-year follow-up. A final report will be prepared once all implanted subjects have completed his/her five-year follow-up and all data collection has ended. See section 10.3 for additional analyses.

10.3 Interim Analysis

An initial analysis is planned when the first 50 implanted subjects have completed his/her six-month follow-up; however initial analyses may be performed earlier if enrollment is slower than expected Initial analyses will assess all safety and efficacy endpoints based on available data.

There are no formal interim analyses planned for purposes of "early-win" assessment, futility, or sample size confirmation.

10.4 Safety Endpoints

Safety endpoints include:

1. All-cause and cardiovascular mortality at 30 days and 6 months
2. All stroke (disabling and non-disabling) at 30 days and 6 months
3. Myocardial infarction (periprocedural and spontaneous) at 30 days and 6 months
4. Acute kidney injury at 30 days and 6 months
5. Major vascular complications at 30 days and 6 months
6. Life-threatening bleed at 30 days and 6 months
7. New permanent pacemaker implantation (PPI) at 30 days and 6 months
8. New intraventricular conduction delays at 30 days and 6 months
9. New-onset atrial fibrillation at 30 days and 6 months
10. Valve-related dysfunction requiring repeat procedure at 30 days and 6 months

Analysis for the safety endpoints will be based on the "Attempted Implant" data set. For each time-related event, Kaplan-Meier rates (cumulative incidence) and 95% two-sided confidence intervals at 30 days and 6 months will be calculated. Safety endpoints will be based on CEC adjudicated events.

10.5 Efficacy Endpoints

Efficacy endpoints include:

1. Device success (VARC-2)
2. Cardiovascular and heart failure hospitalizations at 30 days and 6 months
3. Heart failure events at 30 days and 6 months
4. Hemodynamic performance metrics by Doppler echocardiography at discharge, 30 days, and 6 months
   - Mean aortic gradient

- Effective orifice area
- Degree of total, para, and transvalvular prosthetic regurgitation
- Incidence of moderate and severe patient-prosthesis mismatch (PPM)

5. Change from baseline in New York Heart Association (NYHA) functional classification at 30 days and 6 months
6. Change in six-minute walk test (6MWT) from baseline at 6 months
7. Change in Kansas City Cardiomyopathy (KCCQ) from baseline at 30 days and 6 months
8. Change in left ventricular ejection fraction (LVEF) from baseline at 6 months
9. Change in peak global longitudinal strain (GLS) from baseline at 6 months
10. Change in left ventricular filling pressure (E:e') from baseline at 6 months
11. Change in stroke volume index (SVI) from baseline at 6 months
12. Change in NT-pro B-type natriuretic peptide (NT-proBNP) from baseline at 6 months

Analyses of the efficacy endpoints will be descriptive. The attempted implant set will be used for safety and quality of life outcomes. However, the efficacy endpoints involving echocardiographic variables will be analyzed for the implanted set. Continuous variables will be summarized as the number of subjects, mean, standard deviation, median, first and third quartiles, minimums, and maximums. Categorical variables will be summarized as counts and percentages. For each time-related event, Kaplan-Meier rates (cumulative incidence) and 95% two-sided confidence intervals will be calculated. Efficacy endpoints involving echocardiographic variables will be based on ECL reported data.

10.6 Additional Outcome Measures

The following outcome measures will be also be evaluated:

1. All-cause and cardiovascular mortality annually through 5 years
2. All stroke (disabling and non-disabling) annually through 5 years
3. Cardiovascular and heart failure hospitalizations at annually through 5 years
4. Heart failure events at annually through 5 years
5. New York Heart Association (NYHA) functional classification at 30 days, 6 months, and annually through 5 years
6. Change in New York Heart Association (NYHA) functional classification from baseline annually through 5 years
7. Kansas City Cardiomyopathy (KCCQ) annually through 5 years
8. Hemodynamic performance metrics by Doppler echocardiography
   - Mean aortic gradient annually through 5 years
   - Effective orifice area annually through 5 years
   - Degree of total, para, and transvalvular prosthetic regurgitation annually through 5 years
   - Incidence of moderate and severe patient-prosthesis mismatch (PPM) annually through 5 years
9. Prosthetic valve thrombosis 30 days, 6 months, and annually through 5 years
10. Prosthetic valve endocarditis at 30 days, 6 months, and annually through 5 years

11. Bioprosthetic valve dysfunction (BVD) at 30 days, 6 months, and annually through 5 years
12. Bioprosthetic valve failure (BVF) at 30 days, 6 months, and annually through 5 years
13. Valve-related dysfunction requiring repeat procedure annually through 5 years

Analyses of the additional outcome measures will be descriptive. The attempted implant set will be used for safety and quality of life outcomes. However, the outcomes involving echocardiographic variables will be analyzed for the implanted set. Continuous variables will be summarized as the number of subjects, mean, standard deviation, median, first and third quartiles, minimums, and maximums. Categorical variables will be summarized as counts and percentages. For each time-related event, Kaplan-Meier rates (cumulative incidence) and 95% two-sided confidence intervals will be calculated.

10.7 Sample Size Determination

As this is a descriptive study, the sample size of 75 subjects was not determined by statistical sample size methods. However, a sample size of 75 subjects is adequate to accomplish the study objectives and for an assessment of the procedural safety and efficacy of the study device in the study population.

10.8 Minimization of Bias

The study methods include the following measures to minimize potential sources of bias:

- An Eligibility Review Committee (ERC) will confirm each subject's eligibility for the study.
- An external, independent Clinical Events Committee (CEC) will adjudicate all deaths and safety-related endpoint events. Safety endpoint results will be based on CEC adjudications.
- Sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- Echocardiographic endpoint results will be based on Echocardiography Core Lab assessments.
- A statistical analysis plan (SAP) will be developed prior to analyzing data. The plan will document all pre-specified analyses and analysis methods.

In summary, potential sources of bias that may be encountered in this study have been considered and minimized by careful study design.

11. Ethics and Regulatory Compliance

11.1 Statement(s) of Compliance

The Evolut™ EXPAND TAVR I Feasibility Study will be conducted in compliance with the current version of the Declaration of Helsinki, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) R2 guidelines, the study protocol, the Sponsor's standard operating procedures and/or guidelines, and in accordance with federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted.

These include but are not limited to the following:

- In the United States, the study will be conducted under a US FDA Investigational Device Exemption (IDE) in compliance with 21 CFR Parts 11, 50, 54, 56 and 812, and ISO 14155:2020 (except for Adverse Event reporting after 6-month visit as noted in section 7.2)
- In the EMEA region the study will be conducted in compliance with ISO 14155:2020 (except for Adverse Event reporting after 6-month visit as noted in section 7.2). The laws and regulations of the countries in which the study is conducted, included data protection laws, must be followed.
- In Canada, SOR/98-282, Section 79-88 will be followed. The study will be conducted in compliance with ISO 14155:2020 (except for Adverse Event reporting after 6-month visit as noted in section 7.2
- In Australia, New Zealand the study will be conducted in compliance with local regulations and ISO 14155:2020 (except for Adverse Event reporting after 6-month visit as noted in section 7.2)

In addition, the study will be conducted in compliance with 21 CFR Part 11 and 54 in all participating geographies.

11.2 Institutional Review Boards and Ethics Committees

The study will be conducted in accordance with the requirements of local Institutional Review Boards and Ethics Committees. The responsible Institutional Review Board (IRB) or Ethics Committee (EC) at each investigational site must approve the study protocol and informed consent form. Study activities will not commence prior to receipt of documentation of IRB/EC approval by the site and Medtronic. The Investigator and study staff must comply with the requirements of their IRB/EC, including any additional requirements imposed by the IRB/EC after initial approval.

Prior to enrolling subjects, each investigation site's IRB/EC will be required to approve the current CIP, the Informed Consent form, and any other written information to be provided to the subjects. Study sites in the United States must also utilize IRB approved Health Insurance Portability and Accountability Act (HIPAA) Authorization.

IRB/EC approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. In addition, the approval letter

needs to be accompanied by an IRB/EC roster or letter of compliance, to allow verification that the investigator, other center study staff, and/or Medtronic personnel are not members of the IRB/EC. If they are members of the IRB/EC, written documentation is required stating that he/she did not participate in the approval process. Investigators must inform Medtronic of any change in status of IRB/EC approval once the investigation site has started enrollment. If any action is taken by an IRB/EC with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

11.3 Regulatory Submission

Each site must fulfill all local regulatory requirements prior to enrolling subjects. Each study site must have written documentation of site/investigator readiness, including but not limited to IRB/EC approval of the current version of the CIP, Informed Consent form, a signed Clinical Investigational Agreement, current investigator curriculum vitae, and documentation of training. The principal investigators and their institutions shall agree to this CIP and any amendments and indicate their approval by signing and dating the Clinical Investigational Agreement. Each center is required to have documented approval from their local Regulatory Authority prior to their first subject enrollment.

If a regulatory authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority.

Any revisions or amendments to the CIP, Investigator Brochure, Reports of Prior Investigations, Informed Consent documents or any other documents submitted to Regulatory Authorities will be notified to all affected Regulatory Authorities. A final report will be submitted to all Regulatory Authorities upon study closure.

12. Study Administration

12.1 Monitoring

Investigational sites will be monitored to ensure compliance with the study protocol, adherence to applicable regulations, and accuracy of study data. Monitoring visits may be conducted both on site and remotely, primarily to ensure the safety and well-being of the subjects is preserved, as well as to assess study site progress periodically, the investigator's adherence to the CIP, regulatory compliance, maintenance of records and reports, and review and verification of source documents against subject CRFs in accordance to the study-specific monitoring plan. Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of adverse events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring visits will also be used to verify that data submitted on case report forms are complete and accurate with respect to the subject clinical records and to verify device accountability. Sites should provide appropriate access to the source data. For countries where local law allows this should also include remote access to the EMR. Site personnel will complete eCRFs following each subject visit. Study data submitted will be reviewed against subject charts and other sources containing original records of subject data.

The progress of the study will be monitored by:

- On-site and remote review, as deemed appropriate by Medtronic and as described in the Monitoring Plan.
- Remote source data verification will be done where local country regulations allow
- Telephone communications between the site personnel (e.g., investigator, study coordinator) and study monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

Monitoring and monitoring oversight will be provided by the global sponsor (8200 Coral Sea St NE, Mounds View, MN 55112). Representatives of the global sponsor (contractors and designees) may also act as study monitors.

12.2 Study Closure

Upon completion of the study, Site Closeout Visits will be conducted, as outlined in the Monitoring Plan. After the study has been completed, medical care will be provided to the subjects upon the discretion of the treating physician.

12.3 Data Management

Study sites will assign a unique ID number to each subject. Records of the subject/subject ID relationship will be maintained by the study site. Individual subject medical information obtained as a result of this study will be considered confidential.

This study will utilize an internet based Remote Data Capture (RDC) system that is the property of Medtronic. Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegation Task List (DTL). Study personnel delegated for eCRF completion and/or approval per the DTL will be trained on the use of the RDC system and thereafter provided with a username and password to access the system. The eCRFs must be completed or updated to reflect the latest observations on the subjects participating in the study. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each eCRF.

Data from the echocardiography core lab will be entered into the RDC system by core lab personnel per their procedures established for the study. The echocardiography core lab cardiologist (or designee) will approve core lab eCRFs.

The RDC system maintains an audit trail of entries, changes, and corrections in eCRFs. If a person only authorized to complete eCRFs makes changes to an already signed eCRF, the investigator shall re-approve this eCRF.

All study-related documents must be retained until notified by Medtronic that retention is no longer required. Medtronic will inform the investigator/institution when these documents are no longer required to be retained.

No study document or image should be destroyed without prior written agreement between Medtronic and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

12.3.1 Time Windows for Completion and Submission of eCRFs

The Device Use Notification eCRF should be completed as soon as possible after device use. As a best practice, study sites should strive to complete and approve all other eCRFs within 2 weeks of the applicable follow-up visit.

12.3.2 Data Review and Processing

Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal SOPs and the Data Management Plan for this study. The study database will be developed and validated per the Data Management Plan and will employ validation programs (e.g. range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation. The study database will maintain an audit trail of all changes made to the eCRFs.

12.3.3 Source Documents

Entered data must be traceable to source documents. Source documentation is defined as the first time the data appear and may include all clinical records, hospital records, procedural reports, autopsy reports, and any other material that contains original information used for study data collection or

adverse event reporting. Identified discrepancies between source documents and the eCRFs will be resolved through the on-line query resolution process per the Data Management plan.

The eCRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g. echocardiography variables, MDCT variables, implant procedural variables, exercise testing variables, Heart Team assessment, Modified Rankin Score) may vary from center to center: the site may use technical worksheets if identified as source documents.

Source documents must be retained by the investigational site for a period of two years after study conclusion (or longer as required by local law) and made available for monitoring or auditing by the sponsor's representative or representatives of the US FDA and other applicable regulatory agencies or IRB/EC.

The Investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigation site team indicating they are a true reproduction of the original source document.

In addition, the medical records of study subjects should be marked or flagged in such a way to indicate their participation in the study.

12.3.4 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. Regulatory bodies, such as the US FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, IRB/ECs and regulatory bodies direct access to source data and documents during monitoring, audits and regulatory inspections.

12.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique subject ID number (SID) to each subject. The SID is to be recorded on all study documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any study document other than the informed consent form. In the event a subject's name is included for any reason, it will be masked as applicable. In the event of inability to mask the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Access to subject confidential information will be confined to authorized personnel only; specifically, members of the sponsor clinical study team, the ECL, and the CEC. The sponsor will maintain a list of all authorized personnel with access to subject confidential information.

12.5 Liability

Medtronic, Inc. (including all wholly owned subsidiaries) maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Study Insurance statement/certificate will be provided to the EC if required.

12.6 CIP Amendments

The investigator may propose any appropriate modification(s) of the CIP or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any amendment to the CIP, including a justification for the amendment, to all affected regulatory agencies and to the investigators to obtain approval from their IRB/EC. The investigator will only implement the amendment after approval of the IRB/EC, regulatory agencies, and Medtronic, as applicable. Furthermore, the Principal investigators shall sign any approved amendment for agreement.

12.7 Record Retention

The investigator must retain the Investigator Site File, source documents, and the records listed in Section 12.8 until informed by Medtronic they no longer need to be retained. At a minimum, the investigator must retain records for at least 2 years, or longer as in accordance with local law, after the last approval of a marketing application and until there are no pending or contemplated marketing applications, or at least two years have elapsed since the formal discontinuation of clinical development of the investigational devices. The investigator should take measures to prevent accidental or early destruction of the study related materials.

12.8 Reporting Requirements

12.8.1 Investigator Reports

The Investigator is responsible for the preparation, review, and signature (as applicable), and retention of the following records:

- All essential correspondence that pertains to the investigation
- Device use/disposition records
- Records of each subject's case history and exposure to the device. Case histories include the approved eCRFs and supporting data (source documentation), including, for example:
  - Signed and dated consent forms
  - Medical records, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurses' notes
  - All adverse event/device deficiency information

- A record of the exposure of each subject to the investigational device (e.g., date of implant procedure and follow-up assessment dates)

- Documentation of any deviation from the CIP, including the date and the rationale for such deviation
- Signed Clinical Investigational Agreement, signed and dated curriculum vitae of the PI, sub-investigator(s) and key members, signed Delegated Task List
- The approved CIP, Patient Information/Informed Consent Form, Investigator Brochure or Report of Prior Investigations, and any amendments
- Insurance certificate, where applicable
- IRB/EC Approval documentation and voting list
- Regulatory authority notification and approval documentation
- List of sponsor contacts and monitoring contact list
- List of investigation sites
- Training records
- Disclosure of conflict of interest
- Lab certificate/lab normal ranges
- Subject ID and enrollment log
- Sponsor's statistical analyses and clinical investigation report
- Shipping records of investigational devices
- Investigational device Product Accountability Log(s)
- Any other records that US FDA or local regulatory agencies require to be maintained

The Investigator may withdraw from responsibility to maintain records by transferring custody to another person, who will accept responsibility for record and report maintenance. The Investigator is responsible for the preparation, review, signature, and submission of the reports listed in Table 6 - Table 9 for their respective geographies. These are also subject to inspection by government agencies and must be retained. Reports will be submitted to regulatory authorities per local reporting requirements/regulations. Requirements for reporting Adverse Events to Medtronic are described in Table 4.

Table 6. Investigator records and reporting responsibilities applicable to the United States

Report	Submit To	Description/Constraints
Withdrawal of IRB approval (either suspension or termination)	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. *(21 CFR 812.150(a)(2)).*
Progress report	Sponsor and IRB	The investigator must submit this report to the sponsor and IRB at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (3)).*
Study deviations	Sponsor and IRB	Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. *(21 CFR 812.150(a)(4))*
Failure to obtain IC prior to investigational device use	Sponsor and IRBs	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final investigator report	Sponsor, IRB s and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	IRB and US FDA	An investigator shall, upon request by a reviewing IRB, US FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

Table 7. Investigator reports applicable to Europe and Israel

Report	Submit To	Description/Constraints
Withdrawal of EC approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing EC of the investigator's part of the investigation within 5 working days of the date of withdrawal. *(Medtronic Requirement)*
Progress Report	Sponsor and EC	Provide if required by local law or EC. (ISO/FDIS 14155:2020)
Study Deviations	Sponsor, EC and Relevant Authorities	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ECs, competent authorities or the appropriate regulatory bodies should be informed. (ISO/FDIS 14155:2020) Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. (*Medtronic Requirement)*
Final Report	EC and Relevant Authorities	This report must be submitted within 3 months of study completion or termination. *(Medtronic Requirement)*
Failure to obtain IC	Sponsor and Relevant Authorities	IC shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. (ISO/FDIS 14155:2020)

Table 8. Investigator reports applicable to Canada

Report	Submit To	Description/Constraints
Withdrawal of REB approval	Sponsor	The investigator must report a withdrawal of approval by the reviewing REB of the investigator's part of the investigation within 5 working days of the date of withdrawal. *(Medtronic Requirement)*
Study Deviations	Sponsor and REB	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. *(Medtronic Requirement)*
Final Report	REB, Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the investigator's part of the investigation. (*Medtronic Requirement)*
Mandatory Problem Reporting Incident	Health Canada, Sponsor, REB as applicable	Report the incident to Medtronic and Health Canada no later than 72 hours of the investigator's / site's first knowledge of the event. Submit to Ethics Board per local requirement.

Table 9. Investigator reports applicable to Australia and New Zealand

Report	Submit To	Description/Constraints
Study Deviation	Sponsor, EC, other relevant authorities	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days or earlier when required due to local requirements, after the emergency occurred. (Medtronic Requirement) Australia: Report any suspected breaches to the sponsor and confirmed serious breaches to their institution (research governance office) within 72 hours of being aware or notified of the same; provide any follow up information as required and work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions.
Withdrawal of EC approval	Sponsor and applicable authorities per local requirements	The investigator must report a withdrawal of approval by the reviewing EC of the investigator's part of the investigation within 5 working days of the date of withdrawal. (Medtronic Requirement)
USADEs for Australia and international / Annual Safety Report/ updated IB/ approved Product Information	HREC	Australia: Per EC requirements, but at least annually, the investigator must provide to HREC responsible for study; • Updated Investigator Brochure or IF, if appropriate ((NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.h) • Annual Safety Report including; - a summary of the evolving safety profile of the trial, a brief description and analysis of new/relevant findings, implications of safety data to the risk-benefit ratio for the trial, a description of any measures taken or proposed to minimize risks (NHMRC Safety Monitoring and Reporting in Clinical Trials involving Therapeutic Goods November 2016 section C.1.i)
Other information	HREC	Any additional reports required per local requirements and EC must be provided Australia: Upon request, supply Medtronic, with any additional information related to the safety reporting (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016, section C.2(f)

12.8.2 Sponsor Reports

The Sponsor will maintain the following records, including but not limited to:

- All essential correspondence related to the clinical study
- Signed Clinical Investigational Agreement
- Signed and dated current curriculum vitae for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Investigational Device Accountability Log(s)
- Adverse event and device deficiency information
- Device complaint documentation
- All data forms, prepared and signed by the Investigators, and received source documentation and core lab reports
- CIP, investigator brochure or report of prior investigations and subsequent amendments
- Site monitoring reports
- Financial disclosure information
- Study training records for site participants and internal study staff members
- Contact lists of all participating investigators/investigative sites, Ethics Board information, study monitors and Sponsor staff members; Sponsor will maintain these lists and provide updates to the necessary parties.
- Sample of device labeling attached to investigational device
- Insurance certificates
- Ethics Committee approval documentation and voting list
- Regulatory authority notification and approval documentation
- Lab certificates /Lab normal ranges
- Statistical analyses
- Clinical investigation report
- Any other records that US FDA or local regulatory agencies require to be maintained

The Sponsor is responsible for the preparation of, the accuracy of the data contained in, the review of and the submission of the reports listed in Table 10 - Table 13.

Table 10: Sponsor records and reporting responsibilities applicable to the United States

Report	Submit To	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, IRB, and Relevant authorities	Provide prompt notification of termination or suspension and reason(s). *(ISO/FDIS 14155:2020), (MHLW Ordinance 36, Article 32)*
Unanticipated Adverse Device Effect	Investigators, IRB, US FDA, and relevant authorities	Notification within ten working days after the sponsor first receives notice of the effect. *(21 CFR 812.150(b)(1))*
Withdrawal of IRB approval	Investigators, IRB, US FDA, and relevant authorities	Notification within five working days after receipt of the withdrawal of approval. *(21 CFR 812.150(b)(2))*
Withdrawal of US FDA approval	Investigators, IRB, and relevant authorities	Notification within five working days after receipt of notice of the withdrawal of approval. *(21 CFR 812.150(b)(3))*
Investigator List	US FDA	Submit at 6-month intervals, a current list of the names and addresses of all investigators participating in the investigation. *(21 CFR 812.150(b)(4))*
Progress Reports	IRB and US FDA	Progress reports will be submitted at least annually. *(21 CFR 812.150(b)(4)(5), 812.36(f)*
Recall and device disposition	Investigators, IRB, relevant authorities, and US FDA	Notification within 30 working days after the request is made and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. *(21 CFR 812.150(b)(6))*
Failure to obtain informed consent	US FDA	Investigator's report will be submitted to US FDA within five working days of notification. *(21 CFR 812.150(b)(8))*
Final Report	Investigators, IRB, Regulatory authorities upon request, and US FDA	Medtronic will notify US FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the US FDA, investigators, and IRBs within six months after completion or termination of this study. *(21 CFR 812.150(b)(7))*
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators quarterly. *(ISO/FDIS 14155:2020)*

Table 11: Sponsor records and reporting responsibilities applicable to Europe and Israel

Report	Submit To	Description/Constraints
Unanticipated Serious Adverse Device Effects (USADE)	EC, Investigators, Relevant Authorities	Medtronic will notify investigators and EC in all geographies as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. For reporting to Regulatory authorities, all UADEs are classified as SADEs and should follow the applicable reporting requirements. (ISO/FDIS 14155:2020) and Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 3.A.1). Reporting timeframe as per local Regulatory authority. (ISO/FDIS 14155:2020 3.42)
Serious Adverse Event (SAE)	EC, Relevant Authorities	Submit to EC per local reporting requirement. Submit to Regulatory Authorities per local reporting requirement. Reports will be in compliance with the laws and regulations of the countries in which the study is conducted, including data protection laws.
Serious Adverse Device Effects (SADE)	EC, Relevant Authorities	Submit to EC per local requirement (ISO/FDIS 14155:2020). Submit to regulatory authorities as per local requirements.
Device Deficiency that might have led to a SADE	EC, Relevant Authorities	Submit to EC per local requirement. Submit to regulatory authorities as per local requirements. (ISO/FDIS 14155:2020)
Premature termination or suspension of the clinical investigation	Investigators, EC, Relevant Authorities	Provide prompt notification of termination or suspension and reason(s). (ISO/FDIS 14155:2020)
Withdrawal of EC approval	Investigators, EC, Relevant Authorities	Investigators and ECs will be notified only if required by local laws or by the EC.
Withdrawal of Regulatory Authority approval	Investigators, EC, Relevant Authorities	Investigators and ECs will be notified only if required by local laws or by the EC.
Progress Reports	EC, Relevant Authorities	This will be submitted to the EC and/or Regulatory Authorities only if required.
Final Report	Investigators, EC, and Relevant Authorities (upon request)	The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The coordinating investigator shall sign the report (ISO/FDIS 14155:2020)
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically. (ISO/FDIS 14155:2020)
Significant new information	EC and Relevant Authorities	Ensure that the ECs and Regulatory Authorities are informed of significant new information about the clinical investigation (ISO/FDIS 14155:2020)

Table 12: Sponsor records and reporting responsibilities applicable to Canada

Report	Submit To	Description/Constraints
Unanticipated Serious Adverse Device Effects (USADE)	REB, Investigators, Health Canada	Medtronic will notify investigators and Ethics Boards in all geographies as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1) , 59(2), 60 (1))
Serious Adverse Device Effects (SADE)	REB, Health Canada	Submit to Ethics Boards per local requirement (ISO 14155:2020) Preliminary and final reporting to the Canadian Ministry of Health of events occurring inside (always) or outside Canada (in case of corrective actions) that is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or its directions for use and has led to the death or a serious deterioration in the state of health of a patient, user or other person or could do so were it to recur. Report a) within 10 days after awareness, if incident has led to death or a serious deterioration in the state of health of a patient, user or other person b) within 30 days, if incident has not led to death or a serious deterioration in the state of health of a patient, user or other person, but could do so were it to recur c) as soon as possible, if incident occurred outside of Canada and is related to a corrective action. (Canada Medical Device Regulations, SOR/98-282; Mandatory Problem Reporting 59(1) , 59(2), 60 (1))
Device Deficiency that might have led to a SADE	REB, Investigators, Health Canada	Submit to Ethics Board per local requirement. Submit to regulatory authority as per local requirement.
Premature termination or suspension of the clinical investigation	Investigators, REB, Health Canada	Provide prompt notification of termination or suspension and reason(s). (ISO/FDIS 14155:2020)
Recall and device disposition	Investigators, Head of Institution, REB, Health Canada	Notification within 30 working days of the request and will include the reasons for any request that an investigator return, repair, or otherwise dispose of any devices. (Medical Devices Regulation Mandatory Problem Reporting 63 – 65.1)
Final Report	Investigators, REB, and Health Canada	The investigator shall have the opportunity to review and comment on the final report. If a clinical investigator does not agree with the final report, his/her comments shall be communicated to the other investigator(s). The principal clinical investigator in each center shall sign the report. (ISO/FDIS 14155:2020)
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators quarterly. (ISO/FDIS 14155:2020)
Significant new information	REB and Health Canada	Ensure that the Ethics Boards and Regulatory Authorities are informed of significant new information about the clinical investigation (ISO/FDIS 14155:2020)

Table 13: Sponsor records and reporting responsibilities applicable to Australia and New Zealand

Report	Submit To	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, and relevant authorities	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2020) Australia: Temporary halt due to safety reasons along with its scope or an early termination of a trial for safety reasons must be notified to Therapeutic Goods Authority (TGA), HREC and investigators along with reasons, measures and further action planned without undue delay and no later than 15 calendar days of the sponsor's decision. (Safety Monitoring and reporting in clinical trials involving therapeutic goods by NHMRC Nov 2016, Table 1)
Notification of an amendment	Investigators, Ethics Committee, relevant authorities	Australia: Notification of an amendment due to SSI, without undue delay and no later than 15 calendar days Note: TGA should receive notification that a SSI has occurred but the amendment revising trial documentation should be submitted to the HREC only (Safety Monitoring and reporting in clinical trials involving therapeutic goods by NHMRC Nov 2016, Table 1)
Urgent Safety Measure(s)	Investigators, Ethics committee, relevant authorities	Australia: Urgent Safety Measure (USMs) be reported within 24 hours (where possible) and in any case, no later than 72 hours of the measure being taken to TGA, HREC and Australian investigators with reasons for the urgent safety measure, measures taken and further actions planned. (Safety Monitoring and reporting in clinical trials involving therapeutic goods by NHMRC Nov 2016, Table 1)
USADE	TGA, Australia	Fatal or life-threatening Australian USADE: No later than 7 calendar days after being made aware of the case with any follow up information within a further 8 calendar days to TGA Other Australian USADEs: No later than 15 calendar days after being made aware of the case to TGA (Safety Monitoring and reporting in clinical trials involving therapeutic goods by NHMRC Nov 2016, Table 1)
Recall and device disposition	Investigators, Ethics Committee, relevant authorities	Notification as per local requirements
Study deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to investigators periodically. (ISO 14155:2020) Australia: Reporting of serious breaches should be reported to the reviewing HREC and PI within 7 calendar days of confirming a serious breach has occurred and provide follow-up reports when required (NHMRC Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods 2018)
Action with respect to safety that has been taken by another country's regulatory agency	TGA, Australia	Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action (Australian clinical trial handbook version 2.3)

Report	Submit To	Description/Constraints
(relevant to an ongoing clinical trial in Australia)		
USADEs, Annual Safety Report/ updated IB/ approved PI	Investigator and HREC	Australia: Per EC requirements, but at least annually, the sponsor will ensure investigator will provide to HREC responsible for study; • an Annual Safety Report (including a summary of the evolving safety profile of the trial, a brief description and analysis of new/relevant findings, implications of safety data to the risk-benefit ratio for the trial, a description of any measures taken or proposed to minimize risks • an updated Investigator Brochure, or current, approved Product Information (PI), if appropriate (e.g. in a study for a product approved in Australia or where an Investigator Brochure is no longer maintained) (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.i)
Annual Safety Reports and other single adverse events reports	TGA, Australia	To be submitted upon request by TGA

12.9 Publication and Use of Information

Medtronic is committed to the dissemination of the study results. A Publication Plan will be implemented and followed. At the conclusion of the study, a multisite abstract reporting the primary results will be prepared by the Principal Investigators (in collaboration with others including but not limited to the echocardiography core lab physicians, and the CEC/DSMB). A multisite publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the study is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

Following analysis and presentation of the endpoint results, active participation of all participating investigators, CEC/DSMB committee members, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the study results requires approval by the Principal Investigators after review by the Publications Committee. A separate Publication Plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data.

The results of the study will be made public within 12 months of the study's primary completion point, defined as the date the final subject has completed his/her five-year follow-up. Final results will be reported in a publicly accessibly manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).

12.10 Suspension or Early Termination

Medtronic may decide to suspend or prematurely terminate the study (e.g. if information becomes available that the risk to study subjects is higher than initially indicated. If the study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators and regulatory authorities of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB/EC. Medtronic will, as soon as possible, provide a written statement to the investigators to enable prompt notification of the IRB/ECs. If study enrollment is terminated early, follow-up visits will continue for all enrolled subjects.

12.11 Role of Sponsor Representatives

Representatives from Medtronic may participate in confirmation of MDCT anatomical measurements prior to implant of each subject. In addition, representatives from Medtronic may provide technical support during the implant procedures to the implanting physicians and study site staff relative to the use of the investigational devices. A list of sponsor personnel (including monitors, safety representatives, and the medical expert) and their contact details will be maintained in a separate document and provided to the study centers.

12.12 Additional Contact Information

The following contact information will be provided to the clinical sites in a separate document:

- Additional relevant sponsor contact information, including email and telephone number
- The name, address, and telephone number of the monitor
- The name, title, address, and telephone numbers of the study Principal Investigators
- The name, title, address, and telephone number of the sponsor's medical expert for the study.

12.13 Consent Materials

A sample informed consent form for the study will be provided under separate cover.

12.14 Investigator's Brochure and Report of Prior Investigations

An Investigator Brochure/Report of Prior Investigations (IB/RoPI) will be provided under separate cover to the sites and regulatory agencies. Medtronic will update the IB/RoPI in accordance with ISO/FDIS 14155:2020; and provide those updates to sites and regulatory agencies. For geographies under ISO/FDIS 14155:2020, documentation of receipt of the IB/RoPI by each site's Ethics Board is required for all versions of the IB/RoPI.

12.15 Contact Information: Other Institutions, Core Labs, and Committees

Information and contact details for the ECL, CEC, DSMB, ERC, and Explant Core Lab each of will be maintained in a separate document and provided to the study sites. A definitive list of all participating parties will be provided in clinical reports. In addition, a list of the names and addresses of participating institutions will maintained and provided to the sites.

12.16 Institutional Review Board/Ethics Committee Information

Information on each participating Institutional Review Board/Ethics Committee will be maintained in a separate document. A definitive list of all participating IRB/ECs will be maintained and provided in clinical reports.

13. Appendices

13.1 Appendix I: MDCT Procedures: Pre-TAVR Planning

MDCT is required to confirm anatomical suitability for transfemoral TAVR with the Evolut PRO+ system. The MDCT exam should be performed at the study center, but exams performed for diagnostic purposes outside the study center and prior to consent can be used, provided they are within 365 days of the qualifying echocardiogram, and contain the protocol-required data as determined by a designated study Cardiovascular Imaging physician.

Technical Aspects. Technical aspects of the exam are per the site's standard routine for clinical TAVR cases; however, the following are recommended parameters:

- Detector collimation 0.4-0.625 mm.
- Slice thickness ≤ 1.0 mm.
- Coverage area from superior to the aortic arch to inferior to the cardiac apex.
- Slice overlap of 0.4 mm (will result in isotropic voxels with a 20 cm field of view)

Required Variables. The following variables are required to confirm anatomical suitability for implantation and TAV size selection (Figure 4).

- Annulus perimeter (measured at systole if retrospective gating is used)
- Sinus of Valsalva (SoV)diameters (measured at diastole)
  - Right coronary sinus diameter
  - Left coronary sinus diameter
  - Non coronary sinus diameter
  - Mean sinus diameter (mean of the three coronary sinus diameters)
- SoV heights (measured at diastole)
  - Right coronary SoV height
  - Left coronary SoV height
  - Non coronary SoV height
  - Mean SoV height (mean of the three SoV heights)
- Mean diameter of left iliofemoral artery
- Mean diameter of right iliofemoral artery

These variables should be documented in the MDCT report for the subject's medical record or on an alternative source document to be maintained in the subject's study files (e.g. a report from dedicated off-line cardiac image analysis system such as 3mensio, Vital Images, etc).

In addition, calcium volumes should be determined in the following 3 regions: 1) the basal annular plane to the top of the aortic valve leaflets, 2) the basal annular plane to 5 mm below the basal annular plane, and 3) 5 mm below the basal annular plane to 10 mm below the annular plane (Figure 5). These measurements are intended for exploratory analyses and are not required. If performed, patient-specific calcium threshold detection is recommended; however, determination of the calcium threshold detection should be per the site's standard practice.

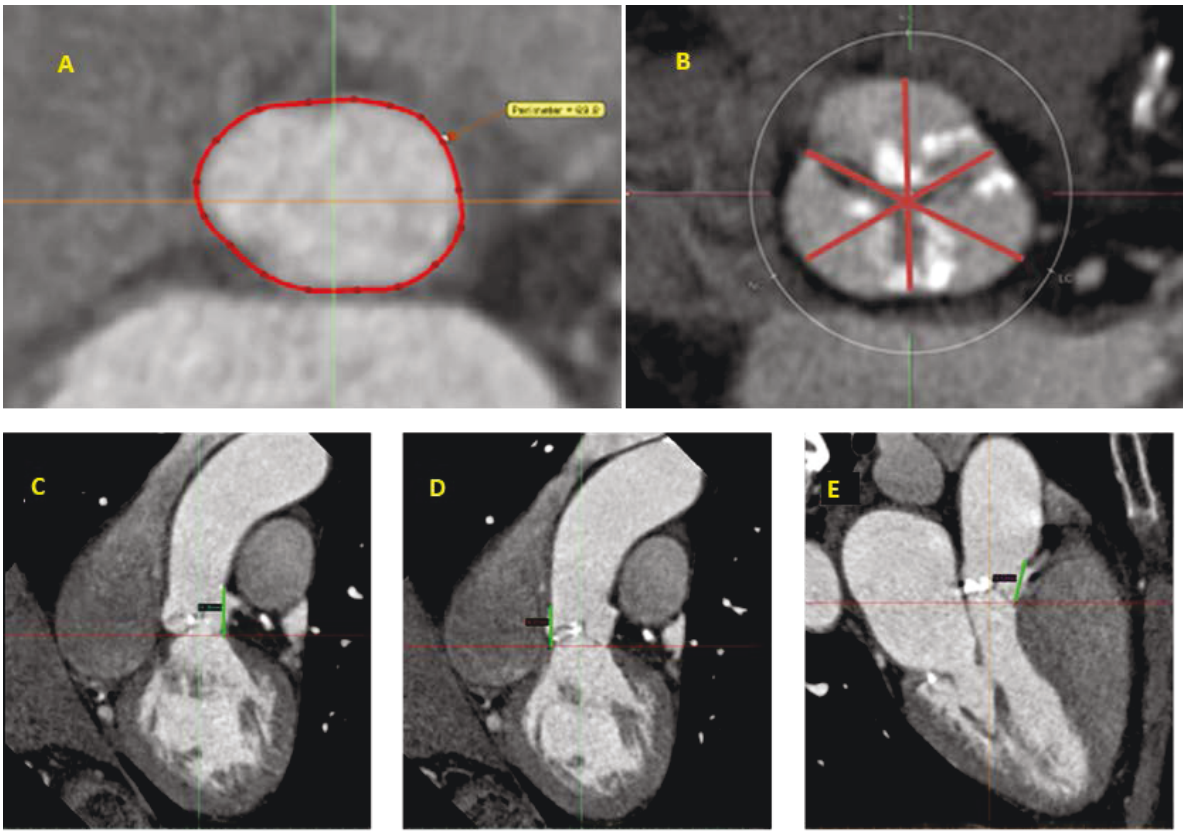
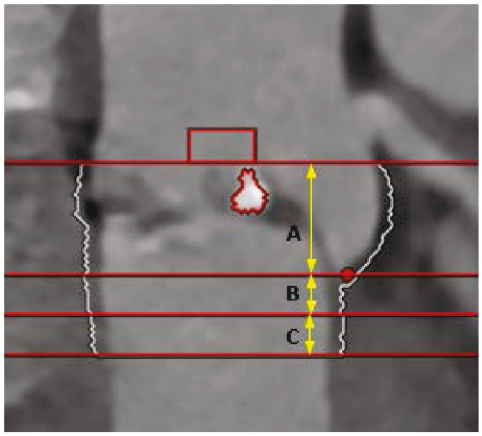


Figure 4. (A) Annular perimeter measured from a reformatted double-oblique axial image at aortic annulus level. Measurement is recommended at systole if retrospective gating was used, although measurement at diastole is also acceptable; **(B)** SoV diameter is measured at diastole from the double oblique axial image where the widest portion of the three sinuses is visible. A diameter from each commissure is measured through the site of the root to the opposite sinus. The mean of the three SoV diameters is reported on the eCRF; **(C, D, & E)** Measurement of the left, non, and right coronary SoV heights, respectively. SoV heights measured at diastole from double oblique axial image located at the level of the aortic annulus. For the left coronary and non-coronary heights, use the oblique coronal image. For the right coronary height, use the oblique sagittal image. SoV height is measured from the aortic annular plane to the sinotubular junction.



(A) Basal plane to top of aortic valve leaflets

(B) Basal plane to 5 mm below basal plane

(C) 5 mm to 10 mm below basal plane

Figure 5. Stretched view of the aortic root showing the 3 regions for calcium volume measurements.

13.2 Appendix II: Clinical Assessment

Clinical assessment by a delegated member of the study team is required at each study interval.

Baseline. The baseline clinical assessment can be conducted on an outpatient, clinic, or inpatient basis, and should include the following:

- History and physical, with special emphasis for symptoms of aortic stenosis, coronary heart disease, chronic obstructive lung disease, and cerebrovascular disease
- New York Heart Association Functional (NYHA) functional class assessment
- Modified Rankin Score assessment
- Complete blood count
- pro B-type natriuretic peptide (NT-proBNP)
- Simple spirometry (e.g. timed vital capacity and FEV_1)

Blood pressure should be taken with the subject sitting in a chair after resting for 5-10 minutes. The subject's weight and height can be taken with shoes off or on. The subject's height at baseline will be used for calculation of BSA and BMI at all subsequent follow-up exams, but weight must be taken at each visit. Findings of the baseline assessment must be documented in the subject's medical record or study records.

Post-Implant. Post-implant follow-up exams should also be conducted by a delegated member of the study team, and can be performed on either an outpatient, clinic, or inpatient basis. If the subject is unable to attend a visit, a telephone follow-up can be performed, but should be documented on the eCRF. Post-implant clinical evaluation should include the following:

- A physical exam (including blood pressure and weight) and interview, with special emphasis for symptoms of aortic stenosis, coronary heart disease, neurological events, and pulmonary symptoms. If suspicion of a neurological event is raised, a neurologist should be consulted to see if further evaluation for a stroke is warranted.
- NYHA functional class assessment (except at discharge)
- Assessment for any adverse events and device deficiencies since last follow-up, and follow-up of any unresolved adverse events previously identified.

The findings of post-implant clinical assessment must be documented in the subject's medical records or study records, and should include the presence or absence of any symptoms, NHYA functional class, prescribed medications, description of any new adverse events and device deficiencies since last follow-up (or absence of new adverse events), and follow up any unresolved adverse events previously identified.

Information and definitions for ACCF/AHA Heart Failure stages[64], NYHA functional classifications, and Modified Rankin Score[65] are provided in Table 14, Figure 6, Table 15, and Table 16.

Table 14. ACCF/AHA heart failure stages

Stage	Description
A	At high risk for HF but without structural heart disease or symptoms of HF
B	Structural heart disease but without signs or symptoms of HF
C	Structural heart disease with prior or current symptoms of HF
D	Refractory HF requiring specialized interventions

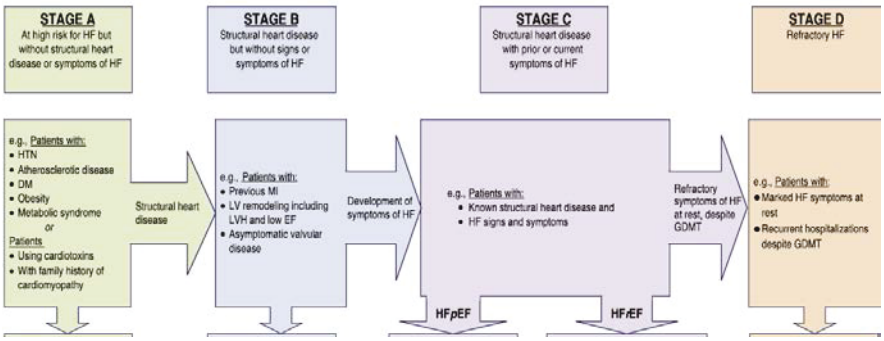


Figure 6. Stages in the development of heart failure. Adapted from Hunt et al.[64]

Table 15. NYHA classification

Class	Description
Class I	Patient is without limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, or dyspnea.
Class II	Patient has slight limitations of physical activity. Is comfortable at rest. Ordinary physical activity results in fatigue, palpitations, or dyspnea.
Class III	Patient has marked limitations of physical activity. Is comfortable at rest. Less than ordinary activity causes fatigue, palpitations, or dyspnea.
Class IV	Patient has inability to carry on any physical activity without discomfort. Heart failure symptoms are present even at rest or with minimal exertion.

Table 16. Modified Rankin score

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

13.3 Appendix III: Echocardiography Procedures

13.3.1 Required Evaluations

Comprehensive transthoracic echocardiography is required at the following intervals:

- Baseline
- Discharge
- 30 Days
- 6 Months
- Annually through 5 years

13.3.2 General Procedures

- Protocol-driven exams should be performed by designated individuals delegated by the site PI
- Subject's blood pressure and weight should be recorded at each visit. Blood pressure should be taken with the subject sitting in a chair after resting for 5-10 minutes. Subject's weight can be taken with shoes off or on.[6]
- The subject's ID number and exam interval should be annotated on the image.
- A simultaneous ECG with a clearly defined R-wave should be displayed on all clips
- Digital cine clips should be a minimum of two cardiac cycles
- To minimize inter-vendor and inter-software variation in GLS measurements, serial assessments should be performed using the same vendor's equipment and software to the extent practical.
- Color Doppler images for assessment of prosthetic regurgitation should be obtained at a minimum frame rate of 20 Hz through optimization of sector width and depth settings.
- Still frames of measured variables should be captured. In addition, still frames of spectral Doppler tracings without the measurements should be captured to facilitate analysis by the Echo Core Lab. Still frames of spectral and tissue Doppler tracings should contain a minimum of 3 cardiac cycles for subjects in sinus rhythm, and a minimum of 5 cardiac cycles for subjects in atrial fibrillation (two sequential frames per variable may be necessary).
- Spectral and tissue Doppler waveforms should be recorded at a minimum sweep speed of 50 mm/sec.
- Exams will be transmitted to the Echo Core Lab via web-based picture archiving and communication system. Details of the image transmission process for each site will be established during site initiation process.

[6] Weight can be taken from the clinical assessment exam. Blood pressure should be taken within 5-10 minutes before or after the echo exam.

13.3.3 Data Requirements

Sites should acquire the necessary views and Doppler recordings to assess the following variables. Procedures for acquiring key variables are described in Section 13.3.4.

- Height (cm) and weight (kg)
- Heart rate (HR)
- Blood pressure (BP)
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic or prosthetic valve velocity (vMax) by CW Doppler
- Aortic or prosthetic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic or prosthetic aortic valve (MG) by CW Doppler
- LVOT VTI by PW Doppler
- Systolic ejection time (ET)
- Aortic valve area (AVA) by continuity equation with VTI[7]
- Aortic valve area index (AVAI) by continuity equation with VTI
- Grade of native aortic regurgitation (baseline only)
- Grade of prosthetic paravalvular regurgitation (post-implant only)
- Grade of prosthetic transvalvular regurgitation (post-implant only)
- Grade of total prosthetic regurgitation (post-implant only)
- Right ventricular outflow tract (RVOT) diameter (post-implant; if AR > mild by visual estimate
- RVOT VTI (post-implant; if aortic regurgitation > mild by visual estimate)
- Grade of mitral regurgitation (MR)
- Grade of tricuspid regurgitation (TR)
- Max TR jet velocity (if TR is present)
- Left ventricular internal dimension at end diastole (LVIDD)
- Left ventricular internal dimension at end systole (LVIDS)
- Interventricular septal thickness at end diastole (IVS)
- Left ventricular posterior wall thickness at end diastole (LVPW)
- Left ventricular end diastolic volume by modified Simpson's rule (LVEDV)
- Left ventricular end systolic volume by modified Simpson's rule (LVESV)
- Left atrial volume at end systole by bi-plane Simpson's rule (LAV)
- Mitral inflow early (E) velocity
- Mitral inflow atrial (A) velocity
- Mitral inflow E wave deceleration time (MdT)
- Mitral annular early (e') diastolic velocity; lateral
- Mitral annular late (a') diastolic velocity; lateral
- Mitral annular early (e') diastolic velocity; medial
- Mitral annular late (a') diastolic velocity; medial

[7] AVA and AVAI should be based on the LVOT diameter, LVOT VTI, aortic valve VTI, height and weight reported on the eCRF

- Grade of diastolic dysfunction
- Pattern of LV geometry
- Peak average left ventricular global longitudinal strain (GLS) at end systole (aortic valve closure)
- Vendor, model, and software version of echocardiography system
- Tricuspid annular plane systolic excursion (TAPSE)
- Basal right ventricular linear dimension at end diastole (RVD)
- Right ventricular area at end diastole (RVAD)
- Right ventricular area at end systole (RVAS)

Information on variables that will be derived by the central database from these measurements is provided in Section 13.3.5.

13.3.4 Acquisition of Key Variables

13.3.4.1 LVOT Diameter

The LVOT diameter is measured in the parasternal long-axis view, with the optimal imaging plane through the long axis of the aorta (anterior and posterior walls of the aortic root parallel with the maximal aortic diameter).[66]

LVOT diameter is measured in mid-systole at the level of the aortic annulus at the base of the aortic valve cusps, with a line drown from where the anterior aortic cusp meets the ventricular septum to where the posterior aortic cusp meets the anterior mitral leaflet perpendicular to the anterior aortic wall (Figure 7, A and B).[67,68,69,70,71,72] Post-implant, LVOT diameter is measured in the parasternal long-axis view in mid-systole, from the outer edge to outer edge of the inflow aspect of the stent (Figure 7, C and D).[73,74]

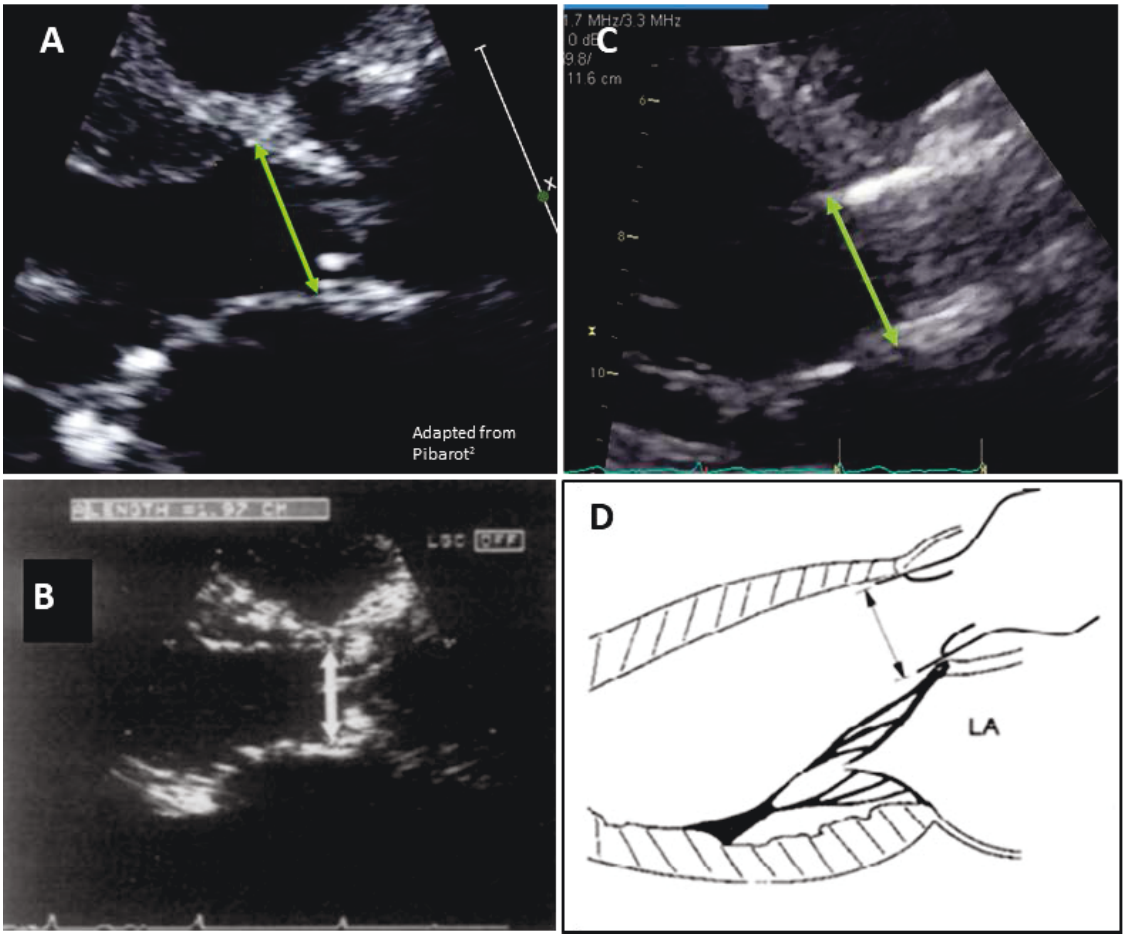


Figure 7. (A) and **(B)** Examples of measurement of pre-implant LVOT diameter. LVOT diameter is measured at the level of the aortic annulus, with a line drawn from where the anterior aortic cusp meets the ventricular septum to where the posterior aortic cusp meets the anterior mitral leaflet perpendicular to the anterior aortic wall; **(C)** and **(D)** Post TAV implantation, LVOT diameter measurement is from outer edge to outer edge of the inflow aspect of the stent.

13.3.4.2 LVOT Velocity

LVOT velocity is recorded with PW Doppler from the apical position, in either the apical long-axis view or the anteriorly angulated four-chamber view ("5-chamber view"). For pre-implant exams, the PW sample volume should be positioned just proximal to the aortic valve, with care to avoid the zone of pre-valve acceleration (usually 0.5 to 1.0 cm proximal to the cusps**,** (Figure 8, A and B).[75,76]The recommended procedure is to initially place the sample volume within the aortic valve leaflets, and then gradually move it apically until a clear spectral waveform is observed with a well-defined peak and minimal spectral broadening. Post TAVR, the sample volume should be placed proximal to the inflow aspect of the stent (Figure 8, C).[77,78.] The VTI is measured by tracing the modal velocity (middle of the dense signal).

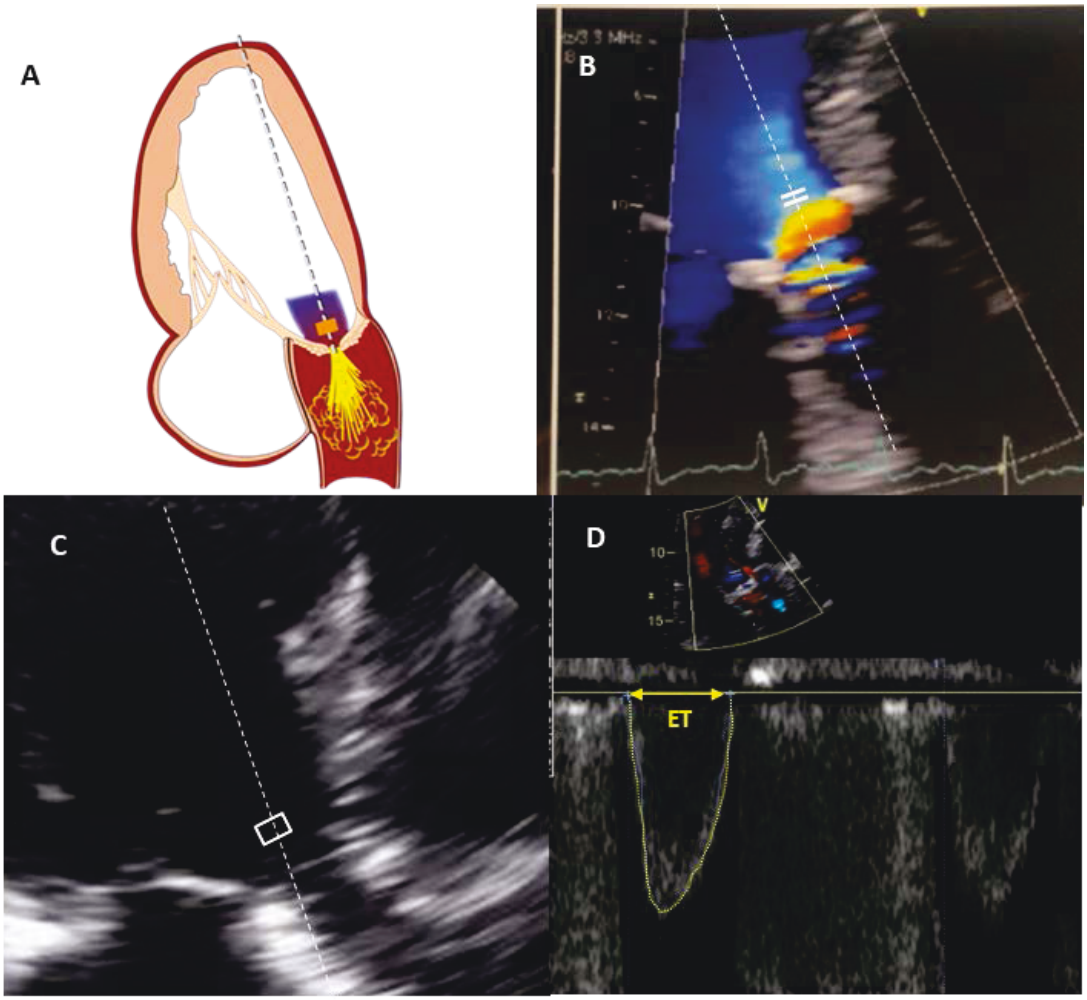


Figure 8. (A) Sample volume placement just proximal to zone of pre-valve acceleration (*illustration by Mayo Clinic);* **(B)** Example of pre-stenotic acceleration at the aortic annulus and LVOT near the annulus; **(C)** Correct sample volume placement just proximal to inflow of stent. Full-screen imaging of stent is helpful to verify positioning of sample volume proximal to the stent before switching to Doppler mode. **(D)** Measurement of LVOT VTI and ejection time.

13.3.4.3 Aortic Valve Velocities

To avoid underestimation of the aortic valve gradient (native or prosthetic), the aortic valve velocity should be interrogated with CW Doppler from the apical, suprasternal notch, right supraclavicular, and right parasternal windows.[79] The window that provides the highest velocity is used for measurements. A smooth velocity curve with a clear outer edge and maximal velocity should be recorded. The maximal velocity is measured at the outer edge of the dark signal; fine linear signals at the peak should not be included in measurements. The outer edge of the dark "envelope" of the velocity curve is traced to provide both the VTI for the continuity equation and the mean gradient (Figure 9).[76]

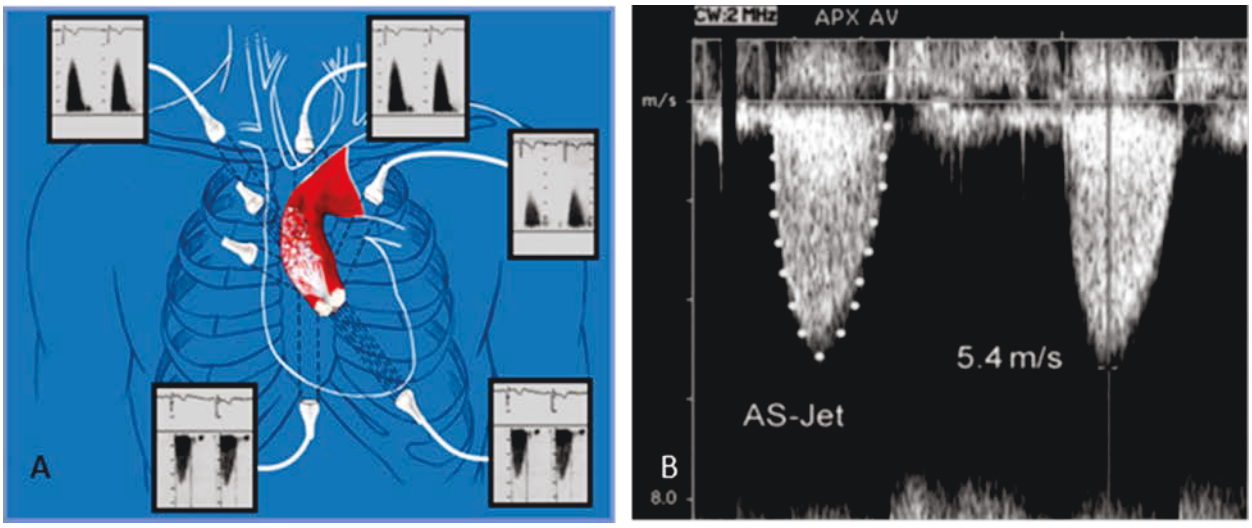


Figure 9. (A) Aortic valve velocities interrogated from multiple transducer positions *(illustration by Mayo Clinic);* **(B)** CW Doppler of severe aortic stenosis showing tracing of the velocity curve for mean gradient and VTI, and max velocity. American Society of Echocardiography 2017 30372-392DOI: (10.1016/j.echo.2017.02.009) Copyright © 2017 The Authors

13.3.4.4 Left-Ventricle and Left Atrium: Volumes, Ejection Fraction, and Dimensions

Left Ventricle. Standard 2-D views of the left ventricle should be obtained from parasternal and apical transducer positions for quantitative assessment of left ventricular volumes and ejection fraction, and visual assessment of regional wall motion.

Specifically, for LV volumes and ejection fraction, two orthogonal views (apical four-chamber and apical two-chamber) should be recording at equal depth settings for quantification using the modified Simpson's rule (biplane method of disks, (Figure 10, A). Image acquisition should aim to maximize LV areas, while avoiding foreshortening of the LV. Acquiring LV views at reduced depth to focus on the LV cavity can reduce likelihood of foreshortening and minimize errors in endocardial border tracings.[80] Use of contrast agents to improve endocardial delineation when segments are poorly visualized is per discretion of the study echocardiographer and institutional procedures. LV volumes should be traced at the actual endocardial border (between the compacted and non-compacted myocardium rather than at the blood-tissue interface). Trabeculations and papillary muscles should be included as part of the LV

cavity, not part of the LV wall.[72] At the mitral valve level, the contour is closed by connecting the two opposite sections of the mitral ring with a straight line. LV length is defined as the distance between the middle of this line and the most distant point of the LV contour.[80]

M-mode recordings of the LV should also be obtained. Dimensions of the left ventricle should be obtained by either 2-D linear measurements or 2-D guided m-mode in the parasternal long-axis view, perpendicular to the LV long axis, and measured at the level of the mitral valve leaflet tips Figure 10, B and C).

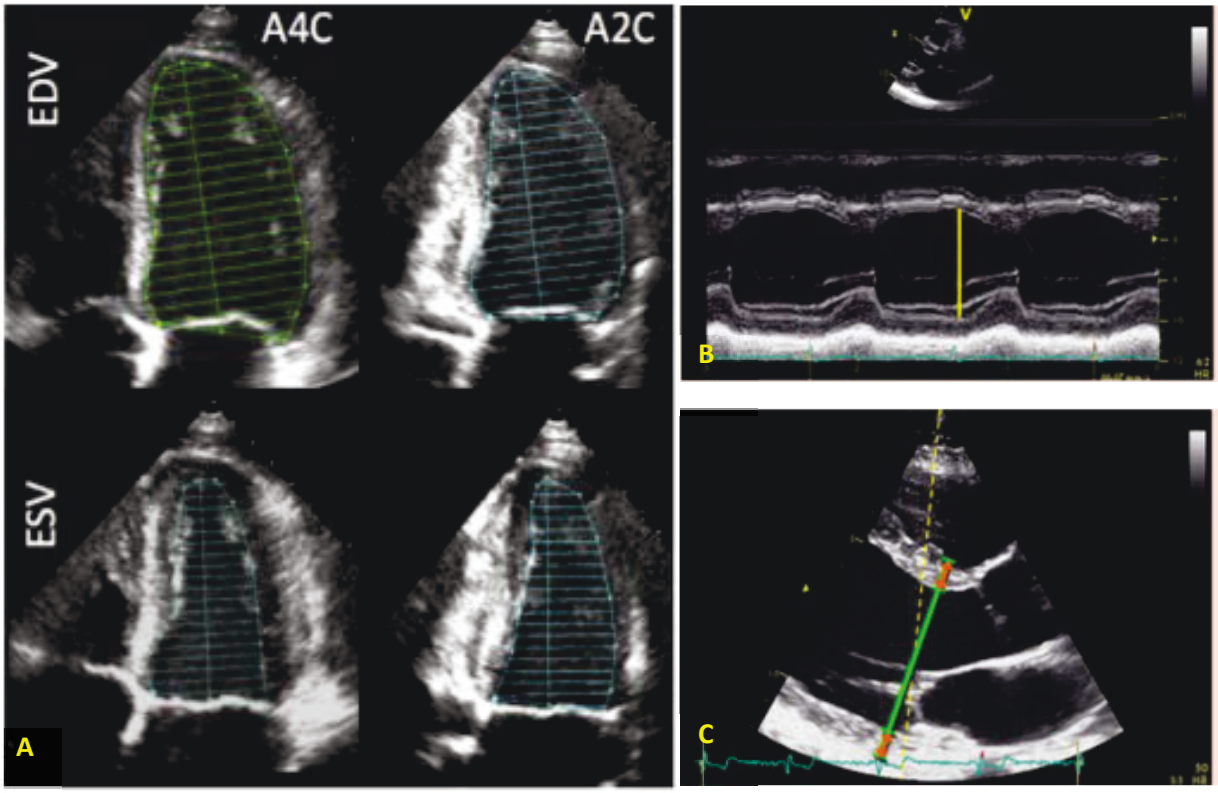


Figure 10. (A) Still frames of two orthogonal planes at end systole and diastole to calculate LV volumes and ejection fraction by modified Simpson; **(B)** measurement of LV end-diastolic diameter by 2-D guided m-mode; **(C)** Measurement of LV linear dimensions by 2-D, electronic calipers should be positioned on the interface between myocardial wall and cavity and the interface between wall and pericardium (orange arrow). [Journal of the American Society of Echocardiography 2015 281-39.e14DOI: (10.1016/j.echo.2014.10.003) Copyright © 2015 American Society of Echocardiography]

Left Atrium. Two-dimensional images should be obtained from the apical four-chamber and apical two-chamber views to enable quantification of left atrial volume by the bi-plane Simpson's method. The views should be adjusted to optimize left atrial size. Image optimization should include avoiding foreshortening and optimizing focus depth and gain.

Left atrial measurements are taken at ventricular end systole, with the left atrium at its maximal size just prior to mitral valve opening. The chamber area is traced at the blood tissue interface, starting at the lateral mitral annulus and finishing at the medial annulus. The length of the left atrium is measured parallel to the long axis of the left atrium (Figure 11 A). The left atrial appendage, pulmonary vein orifices, and any atrial septal aneurysm should be excluded from the area measurement.[80]

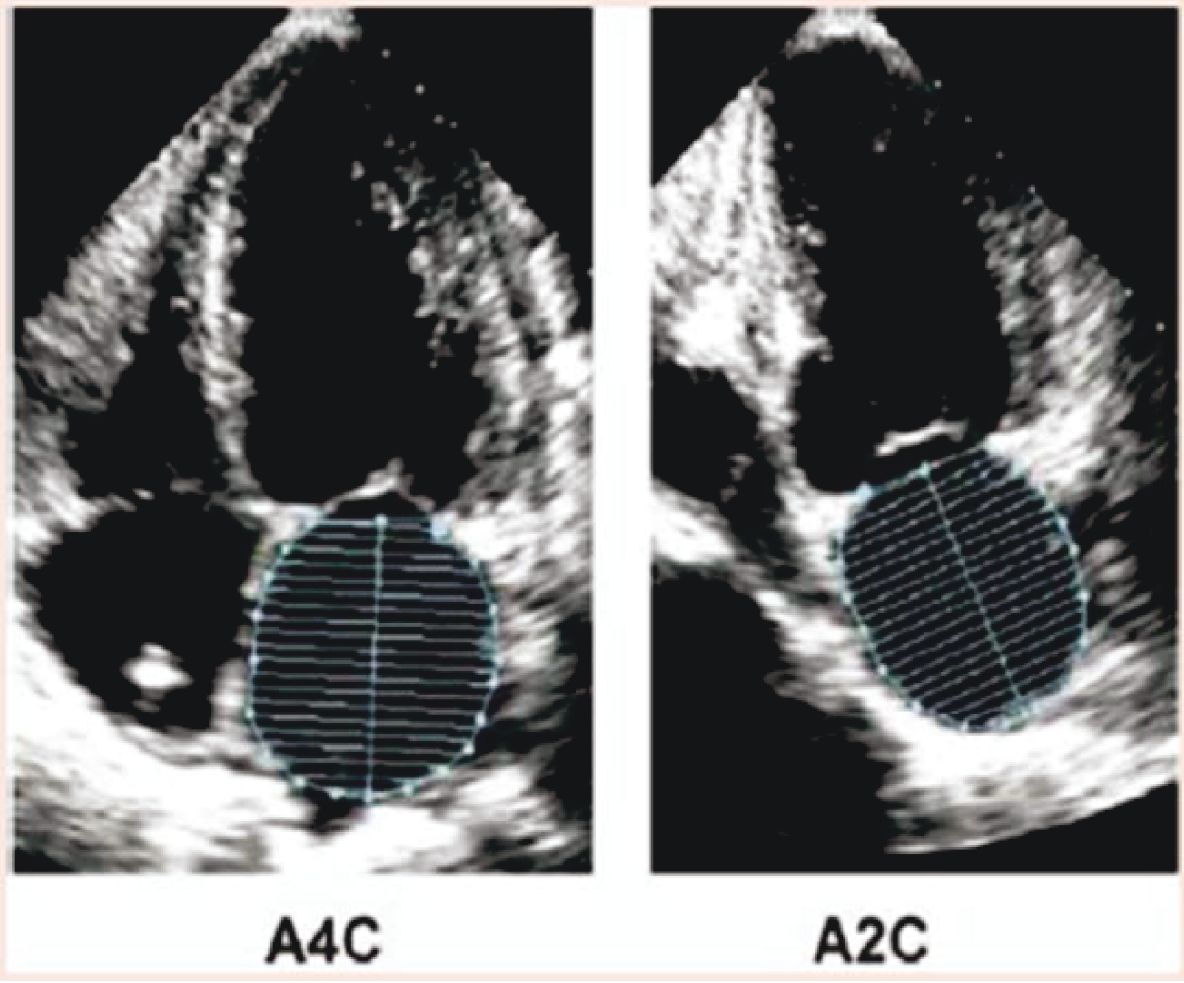


Figure 11. Still frame of apical 4 and 2 chamber views demonstrating bi-plane Simpson's method for quantification of LA volume. [Journal of the American Society of Echocardiography 2015 281-39.e14DOI: (10.1016/j.echo.2014.10.003) Copyright © 2015 American Society of Echocardiography]

13.3.4.5 Peak Left Ventricular Global Longitudinal Strain (GLS)

Speckle tracking echocardiography (STE) for measurement of peak left ventricular GLS should be performed at each study interval. Serial exams for each subject should be performed using the same vendor's equipment and software to the extent practical. The following is intended to provide a standardized approach for image acquisition and minimize sources of variability.

Optimal Image Acquisition (Figure 12)

- **Electrocardiographic (ECG) gating.** An optimal ECG signal with prominent P, R, and T waves and minimal heart rate variability should be present across 3 cardiac cycles in patients with normal sinus rhythm. Clips for GLS should include 3 cardiac cycles.
- **Frame rate.** Images for STE should be maintained at a frame rate of 40 to 90 frames per second through optimization of image depth and sector width. Images for GLS should be acquired at the same depth and section width.
- **Image quality.** Images should be acquired using optimal gain settings and breath-hold techniques to delineate endocardial and epicardial borders throughout the cardiac cycle and to avoid artifact related to excess noise, rib or lung movements, and translational motion of the heart. Images should be "on-axis", with image width and depth focused on the LV. It is essential to avoid foreshortening in the apical views. Also, there should be a space of at least 5 mm between the epicardium in diastole and the sector width.[72]
- **Required views.** The following views are required for GLS: 1) apical 2 chamber, 2) apical 3 chamber (apical LAX), and 3) apical 4 chamber. It is recommended the images for GLS analysis be acquired at the beginning or end of the apical section of the exam; this allows the operator to see the apical images in a row and facilitates selection of images with similar heart rates.

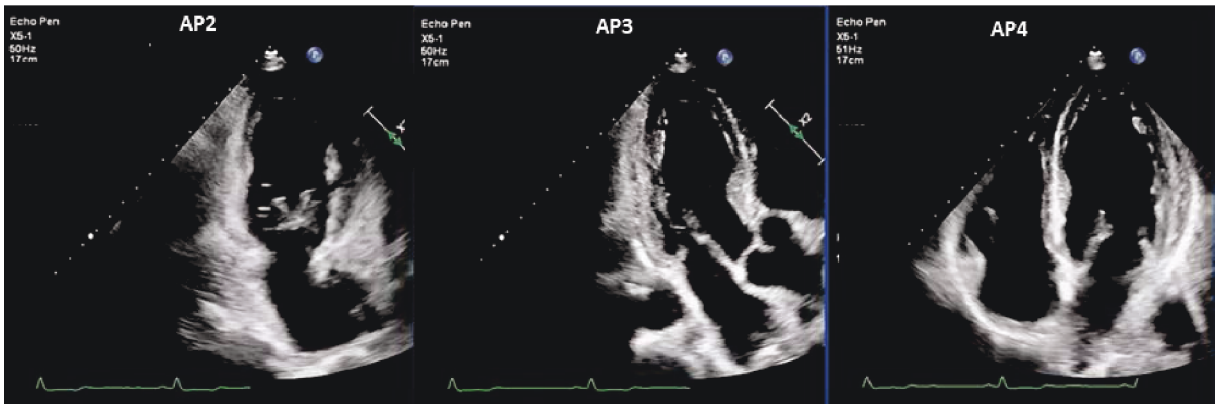


Figure 12. Example of optimal apical 2,3, and 4 chamber images for GLS analysis. Endocardial borders are visualized over the cardiac cycle, apex not foreshortened, frame rate is 50 fps, and depth and sector width the same in all three.

Image Analysis and Post-Processing

Contemporary echocardiography systems perform automated analysis of GLS once the required apical views have been selected, however the automated analysis for each of the views should be visually assessed for the following and corrected if indicated.

Region of interest (Figure 13). The auto-generated region of interest (ROI) for each view should be visually assessed for adequacy of tracking. The ROI should encompass the myocardium form the subendocardial border to the subepicardium border[81], and should be at least 85% to 90% of the thickness of the myocardium.[72] If the auto-generated ROI is inadequate, it should be adjusted manually or semi-automatically using the "3 point" method available on contemporary systems. The redrawn ROI should be visually assessed, and the endocardial borders and ROI width adjusted as needed. The ROI should include the endocardium and myocardium within the lines, excluding the pericardium, trabeculation, and papillary muscles.

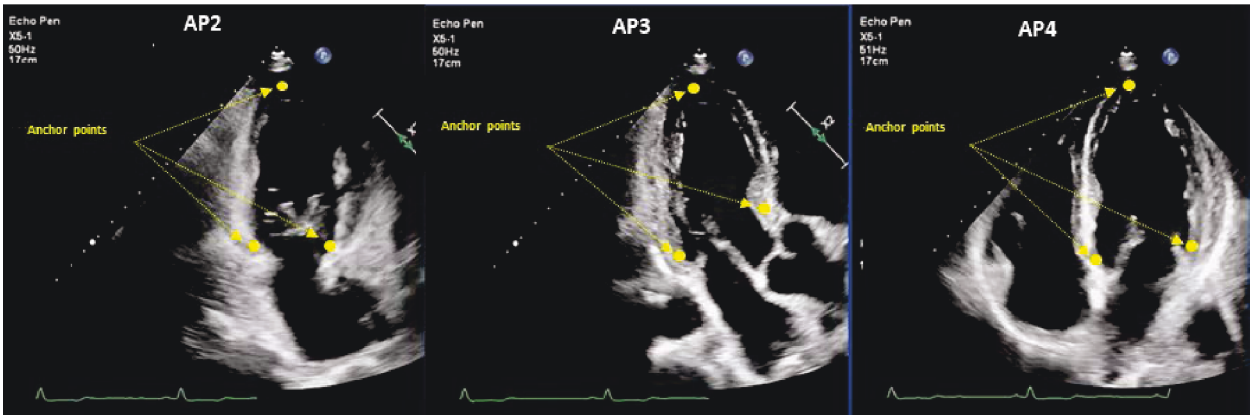


Figure 13. Three-point method for defining start and end points for ROI. For the apical 2-chamber view, the first point is on the basal posterior wall at the mitral annulus, the second point is at the basal anterior wall at the mitral annulus, and the third point is at the apex. For the apical 3-chamber view, one point is placed at the basal posterior wall at the mitral annulus (ventricular side), one point is placed at the apex, and one point is placed at the base of the anterior septum just proximal to the LVOT. For the apical 4-chamber view, the first point is placed on the basal inferoseptum at the mitral annulus (ventricular side), the second point is placed at the basal anterolateral wall at the mitral annulus (ventricular side), and the third point is at the apex.

Event timing. The apical 3 chamber view should be reviewed frame by frame to ensure the reference point for defining aortic valve closure (AVC) is correct. AVC should be corrected manually in indicated.

Review of Strain Curves. The resulting strain curves and bulls-eye plot should be reviewed by possible errors in tracking and the affected analyses corrected as indicated. The final peak average LV GLS should be reported on the eCRF.

13.3.4.6 Left Ventricular Diastolic Function

A spectral Doppler recording of mitral inflow should be obtained with PW Doppler in the apical 4-chamber view, using a 1 to 2 mm sample volume placed between the mitral leaflet tips (Figure 14, A). The following variables should be measured:

- Mitral inflow "A" velocity
- Mitral inflow "E" velocity
- Mitral inflow E-wave deceleration time (MdT)

Mitral annular velocities should be recorded from the lateral and medial (septal) aspects of the mitral annulus using tissue Doppler imaging (TDI) in the apical 4-chamber view (Figure 14, C). Minimal angulation (<20 degrees) should be present between the ultrasound beam and the plane of cardiac motion. The following variables should be measured:

- Mitral annular tissue Doppler early diastolic velocity (e'); medial and lateral
- Mitral annular tissue Doppler late diastolic velocity (a'); septal and lateral

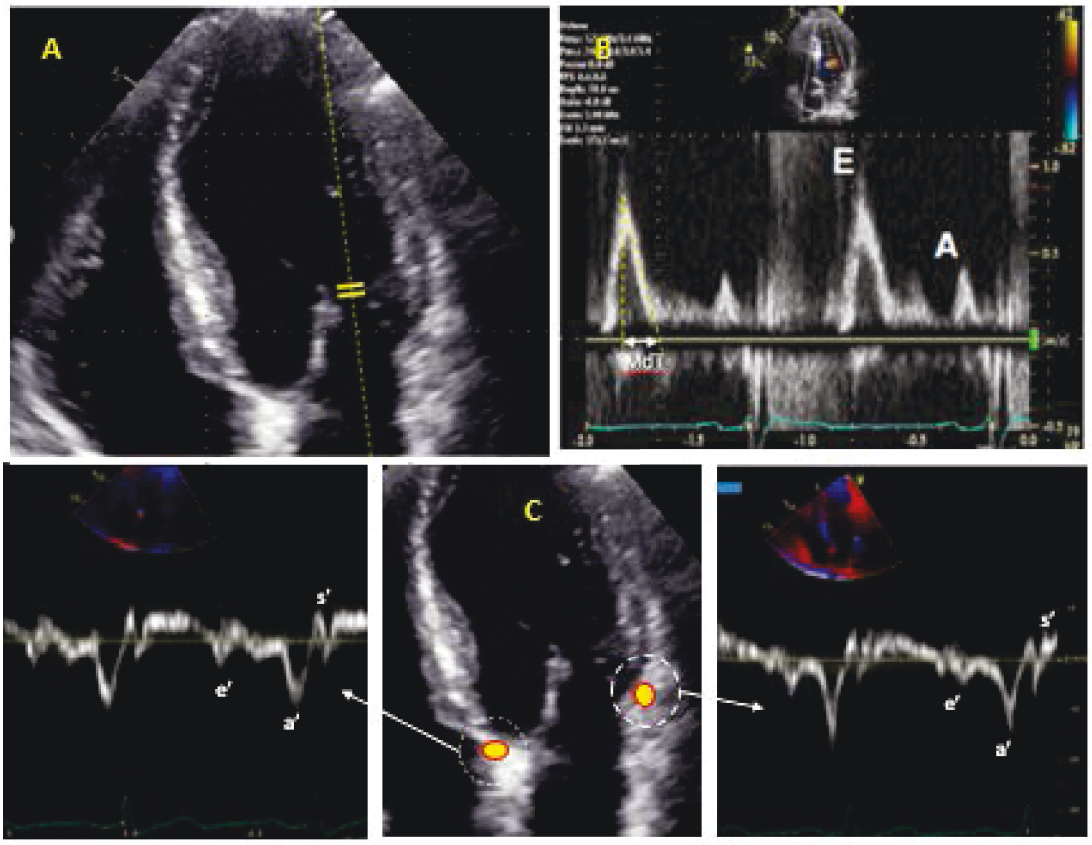


Figure 14. (A) Apical 4 chamber with sample volume placement between mitral leaflet tips during diastole; **(B)** Doppler gains and wall filters optimized to clearly show onset and cessation of mitral inflow; **(C)** A 2 to 5 mm sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary to cover the longitudinal excursion of the mitral annulus in both systole and diastole.

13.3.4.7 Prosthetic Aortic Regurgitation

An integrated approach using color flow, pulsed-wave (PW), and continuous-wave (CW) Doppler is used to assess the severity of transvalvular and paravalvular aortic regurgitation (AR). Color flow Doppler imaging should be performed from the parasternal long and short-axis views, and the apical 5-chamber and apical 3 chamber views (Figure 15). The entire valve should be scanned, from the aortic to the ventricular end of the TAV to identify the number, location, and direction of regurgitant jets, which can be multiple and eccentric. In the short axis view, color imaging should be performed at multiple planes (sweeping from level of the leaflets to below the skirt and frame to assess paravalvular regurgitation), and at the coaptation point of the leaflets for transvalvular (central) regurgitation (Figure 16).[82]

Figure 15. Standard views showing detection of paravalvular regurgitation. Color coding delineates the regions around the valve that can be visualized from the parasternal and apical views. With ultrasound plane rotation, tilting upwards or sideways, a more complete interrogation of the valve can be accomplished. Apical views are important in that some jets may not be detected in the parasternal views because of shadowing from the prosthesis. [Journal of the American Society of Echocardiography 2019 32431-475DOI: (10.1016/j.echo.2019.01.003, Copyright © 2019 American Society of Echocardiography]

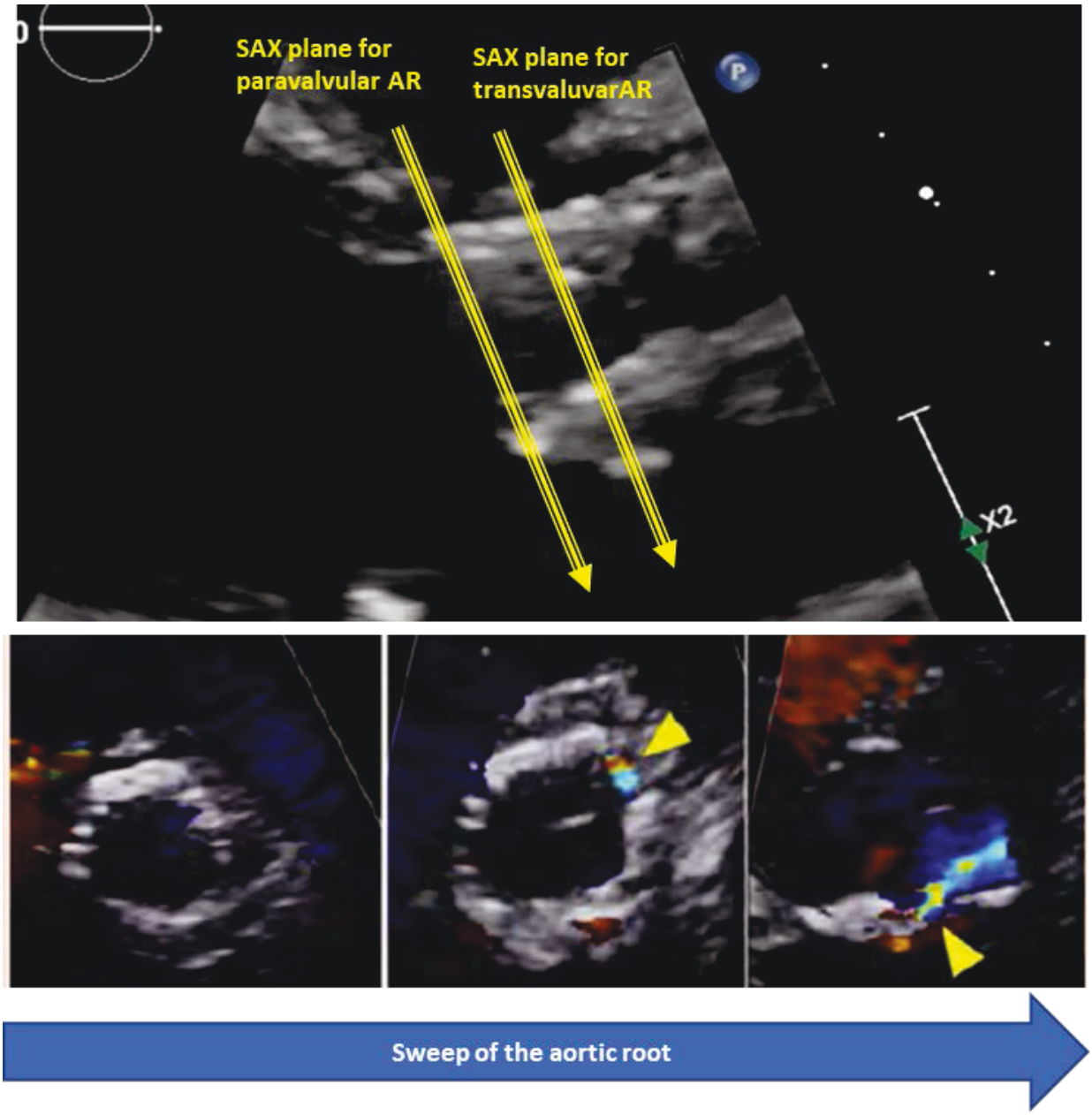


Figure 16. Imaging planes for detection for paravalvular and transvalvular regurgitation. Thorough imaging of the entire valve is needed to identify the origin and vena contracta of regurgitant jets, which may be multiple and not be all at the same level. A sweep of the aortic root from the parasternal SAX view is recommended. [Journal of the American Society of Echocardiography2019 32431-475DOI: (10.1016/j.echo.2019.01.003, Copyright © 2019 American Society of Echocardiography]

If prosthetic AR is seen by color Doppler, a CW spectral Doppler recording of the regurgitant signal should be obtained for measurement of pressure half-time and assessment of jet density (Figure 17, A). In addition, a PW spectral Doppler recording from the proximal descending or abdominal aorta should be recorded to assess the degree of flow reversal (Figure 17, B).

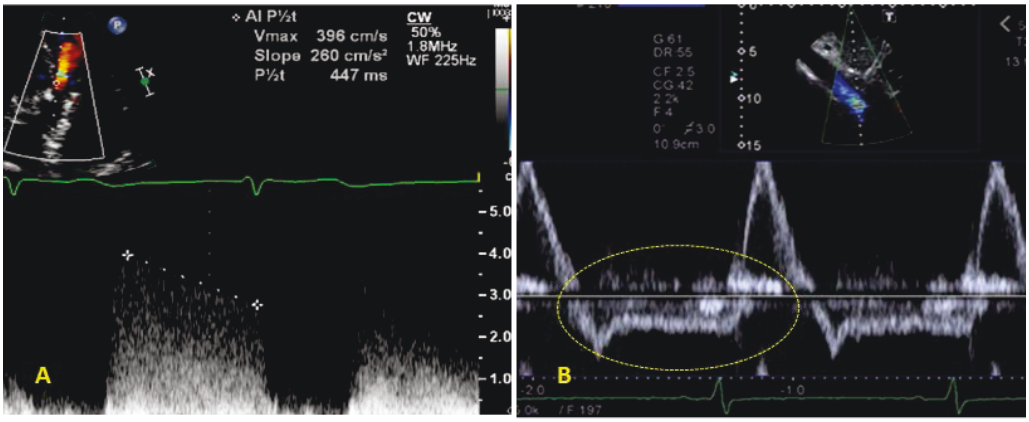


Figure 17. (A) CW Doppler spectral recording of AR regurgitant signal and measurement of pressure half-time; **(B)** PW Doppler spectral recording from abdominal aorta showing flow reversal.

If AR appears more than mild by visual assessment, and if image quality is technically adequate, the RVOT and LVOT diameters and VTIs can be measured to calculate regurgitant volume and fraction (Figure 18).

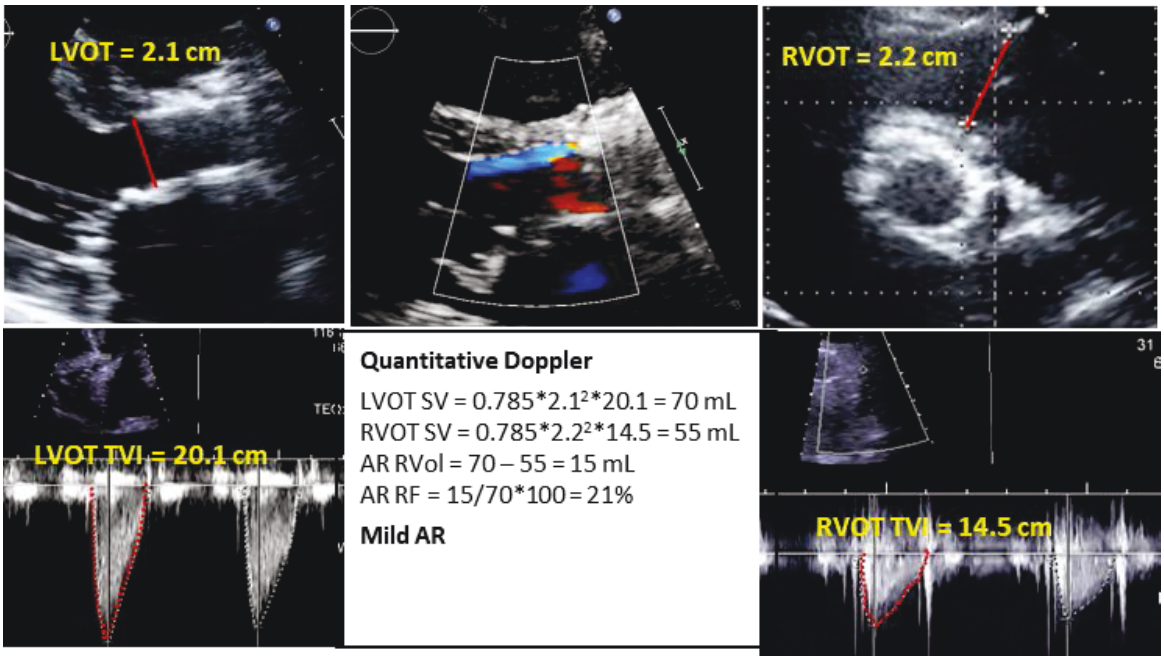


Figure 18. Example of quantification of aortic regurgitant fraction and volume to complement other assessments. Stroke volume is calculated at the RVOT and LVOT.

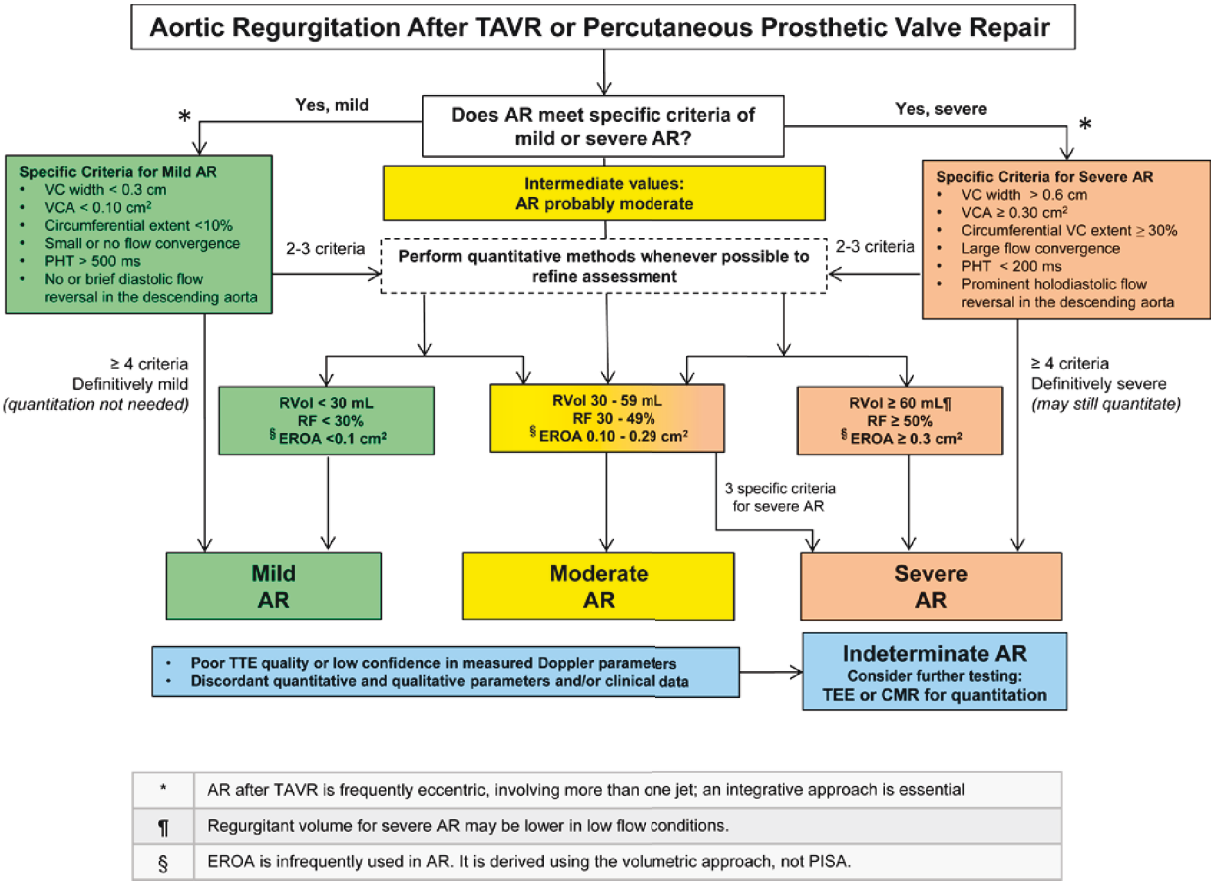
Grading of Prosthetic Regurgitation. The degree of transvalvular, paravalvular, and total (transvalvular plus paravalvular) AR should be graded as none, mild, moderate, or severe based on overall comprehensive evaluation the echocardiographic findings in Table 17, Figure 19.[82] The category of "trace" can be used if regurgitation is barely detectable. The following caveats are noted in the ASE 2019 Guidelines for the evaluation of valvular regurgitation after percutaneous valve replacement.

1. Central AR jets will occur at the level of leaflet coaptation whereas PVR will be seen at the proximal (ventricular) edge of the valve. The jet must enter the LV to be considered true regurgitation, thus imaging just below the edge of the stent will confirm the presence of true PVR; however, the vena contracta of the jet should be measured at its narrowest region.
2. Color flow around the TAV within the sinuses of Valsalva but above the annular valve skirt should not be mistaken for PVR. Flow in the sinuses has low velocity and does not connect with the LVOT in diastole. Scanning through the long axis of the valve is useful in distinguishing color flow in the sinuses from PVR.
3. Small jets of regurgitation are typically isolated to open stent cells and not at the "nodes" of the stent frame. It is important not to include the stented frame in the measurement of circumferential extent of the regurgitation but to integrate only the regurgitant jets when determining the circumferential extent.

Table 17. Evaluation of severity of prosthetic aortic regurgitation post TAVR

	Mild	Moderate	Severe
Structural Parameters			
Position of prosthesis	Usually normal	Variable	Frequently abnormal
Stent and leaflet morphology	Usually normal	Variable	Frequently abnormal
Doppler Parameters			
Proximal flow convergence (CD)	Absent	May be present	Often present
AR velocity waveform density (CWD)	Soft	Dense	Dense
Diastolic flow reversal in proximal aorta	Brief, early diastolic	May be holodiastolic	Holodiastolic (end-diastolic velocity ≥ 20 cm/sec)
Diastolic flow reversal in abdominal aorta	Absent	Absent	Present
Vena contracta width (cm) (CD)	< 0.3	0.3 – 0.6	> 0.6
Vena contracta area (cm^2) * (2D, CD)	< 0.10	0.10 – 0.29	≥ 0.30
Circumferential extent of PVR (%)[ŧ]	<10	10-29	≥ 30
Jet deceleration rate (PHT, ms)[#] (CWD)	Variable Usually > 500	Variable	Steep
Regurgitant volume (mL)	<30	30-59	>60
Regurgitant fraction (%)	<30	30-49	≥50
EROA (cm^2)[##]	<0.10	0.10 – 0.29	≥0.30

CD, Color Doppler; CWD, continuous wave Doppler; PVR, paravalvular regurgitation; PHT, pressure half-time
*Vena contracta area is measured by planimetry of the vena contracta of the jet(s) on the 2-D color Doppler images in the short-axis view
[ŧ]Circumferential extent of PVR best not to be used alone, but in combination with vena contracta width or area
[#]Influenced by LV and aortic compliance
[##]ERO is infrequently used in A



*	AR after TAVR is frequently eccentric, involving more than one jet; an integrative approach is essential
¶	Regurgitant volume for severe AR may be lower in low flow conditions.
§	EROA is infrequently used in AR. It is derived using the volumetric approach, not PISA.

Figure 19. Suggested algorithm to guide integration of multiple parameters of AR severity after TAVR. Good-quality echocardiography imaging and complete data acquistion are assumed. [Journal of the American Society of Echocardiography2019 32431-475DOI: (10.1016/j.echo.2019.01.003, Copyright © 2019 American Society of Echocardiography]

13.3.4.8 Mitral Regurgitation

Color flow Doppler imaging of the left atrium should be performed from the parasternal long-axis view, and from the apical 4, 2, and long axis views.

Mitral regurgitant (MR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the MR jet. If severity appears moderate or greater by visual assessment, pulmonary vein velocities should be recorded with PW Doppler to assess for the presence of systolic flow reversal. A spectral Doppler recording of mitral inflow should be recorded to assess the early filling velocity (E) and the A wave inflow pattern. If image quality is technically adequate, quantitative assessment of the mitral regurgitant orifice area using PISA, or derivation of regurgitant volume and regurgitant fraction (stroke volume method) can be performed. Grading of the severity of mitral regurgitation should be integrative using the parameters in Table 18.[83]

Table 18. Parameters for grading the severity of mitral regurgitation

Parameter	Mild	Moderate	Severe
Structural			
MV Morphology	None or mild leaflet abnormality (e.g., mild thickening, calcifications or prolapse, mild tenting	Moderate leaflet abnormality or moderate tenting	Severe valve lesions (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation
LA and LV Size†	Usually normal	Normal or mildly dilated	Dilated‡
Qualitative Doppler			
Color flow jet area§	Small, central, narrow, often	Variable	Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergencek	Not visible, transient or small	Intermediate in size and duration	Large throughout systole
CWD jet	Faint/partial/parabolic	Dense but partial or parabolic	Holosystolic/dense/triangular
Semi-quantitative			
Vena contracta width (cm)	<0.3	Intermediate	≥0.7 (>0.8 for biplane)
Pulmonary vein flow	Systolic dominance (may be blunted in LV dysfunction or AF)	Normal or systolic blunting	Minimal to no systolic flow systolic flow reversal
Mitral inflow	A-wave dominant	Variable	E-wave dominant (>1.2 m/sec)
Quantitative			
EROA, 2D PISA (cm^2)	<0.20	0.20-0.39	≥0.40 (may be lower in secondary MR with elliptical ROA)
RVol (mL)	< 30	30-44	≥ 60
RF (%)	< 30	30-49	≥ 50

EROA, Effective regurgitant orifice area; RVol, Regurgitant volume; RF, Regurgitant fraction; PISA, Proximal isovelocity surface area
Bolded qualitative and semiquantitative signs are considered specific for their MR grade.
†This pertains mostly to patients with primary MR.
‡LV and LA can be within the ''normal'' range for patients with acute severe MR or with chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR.
§With Nyquist limit 50-70 cm/sec.
K Small flow convergence is usually <0.3 cm, and large is ⩾ 1 cm at a Nyquist limit of 30-40 cm/sec.

13.3.4.9 Tricuspid Regurgitation and Estimated RVSP

Color flow imaging of the right atrium should be performed from the apical 4-chamber view, the parasternal long-axis view of the RVOT, and the parasternal short-axis view at the level of the aortic valve.

Tricuspid regurgitant (TR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the TR jet. If severity appears mild or greater by visual assessment, hepatic vein and tricuspid inflow velocities should be recorded with PW Doppler to assess systolic flow reversal and tricuspid inflow pattern, respectively. If image quality is technically adequate, quantitative assessment of the regurgitant orifice area using PISA, or derivation of regurgitant volume (stroke volume method) can be performed. Grading of the severity of tricuspid regurgitation should be integrative using the parameters in Table 19.[83]

Table 19. Parameters for grading the severity of tricuspid regurgitation

Parameter	Mild	Moderate	Severe
Structural			
TV Morphology	**Normal** or mildly abnormal leaflets	Moderately abnormal leaflets	**Severe valve lesions** (e.g., flail leaflet, severe retraction, large perforation
RV and RA Size†	Usually normal	Normal or mildly dilated	Usually dilated‡
Qualitative Doppler			
Color flow jet area	Small, narrow, central	Moderate central	**Large central jet** or eccentric wall-impinging jet of variable size
Flow convergence	Not visible, transient or small	Intermediate in size and duration	**Large throughout systole**
CWD jet	**Faint/partial**/parabolic	Dense, parabolic or triangular	Dense, often triangular
Semi-quantitative			
Color flow jet area (cm^2)†	Not defined	Not defined	> 10
Vena contracta width (cm)	<0.3	0.3-0.69	≥ 0.7
PISA radius (cm)‡	≤0.5	0.6-0.9	> 0.9
Hepatic vein flow§	Systolic dominance	Systolic blunting	**Systolic flow reversal**
Tricuspid inflow§	**A-wave dominant**	Variable	E-wave >1.0 m/sec
Quantitative			
EROA, 2D PISA (cm^2)	<0.20	0.20-0.39	≥ 0.40
RVol (mL)	<30	30-44	≥ 45

RA, Right atrium; RV, Right ventricle; EROA, Effective regurgitant orifice area; RVol, Regurgitant volume; PISA, Proximal isovelocity surface area
Bolded signs are considered specific for their TR grade.
*RV and RA size can be within the ''normal'' range in patients with acute severe TR
†With Nyquist limit >50-70 cm/sec.
‡With baseline Nyquist limit shift of 28 cm/sec.
§Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure).

13.3.4.10 Right Ventricular Function

The right ventricle (RV) should be imaged from the apical four-chamber, RV-focused apical 4-chamber, left parasternal long- and short-axis, left parasternal RV inflow, and subcostal views. In most cases, visualization of the entire RV free wall is better in the RV-focused view (transducer angled medially) than the standard 4-chamber view. Therefore, the RV-focused view is recommended for measurements.[80] The following measurements should be obtained to evaluate RV function (Figure 20):

- Basal RV internal dimension at end-diastole
- RV internal area at end-diastole
- RV internal area at end-systole
- Tricuspid annular plane systolic excursion (TAPSE)

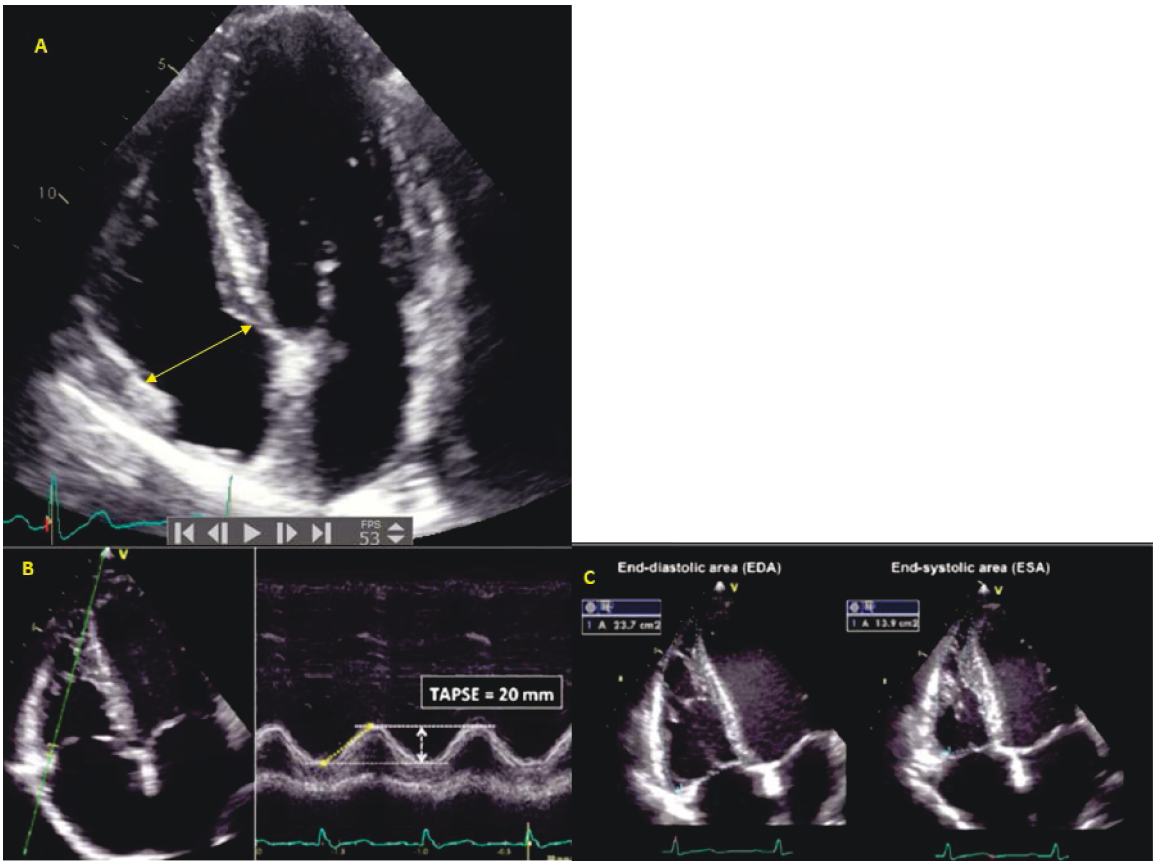


Figure 20. (A) Measurement of basal RV linear dimension; maximal transversal dimension in the basal 1/3 of RV inflow at end-diastole (RV-focused view); **(B)** TAPSE by m-mode, measured between end-diastole and peak systole. Proper alignment of m-mode cursor with the direction of RV longitudinal excursion should be achieved from the apical approach; **(C)** Example of measurement of RV areas: manual tracing of RV endocardial border from the lateral tricuspid annulus along the free wall to the apex and back to medial tricuspid annulus, along the interventricular septum at end-diastole and at end-systole. Trabeculations, papillary muscles and moderator band are included in the cavity area. [Journal of the American Society of Echocardiography 2015 281-39.e14DOI: (10.1016/j.echo.2014.10.003) Copyright © 2015 American Society of Echocardiography]

13.3.5 Echocardiography Core Lab Analysis

Protocol-required and endpoint or event related (as applicable) echocardiograms will be sent to the ECL for assessment: the data generated by the ECL will be the primary data used for analysis and reporting. Received echocardiograms will be logged in and analyzed by the ECL according to their procedures determined for this study. Qualitive assessment of valvular regurgitation and quantitative analysis of variables related to hemodynamic valve performance, cardiac function and cardiac dimensions will be performed according to the methods described in Section 13.3.2.

The ECL will report the following variables:

- Height (cm) and weight (kg)
- Heart rate (HR)
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic or prosthetic valve velocity (vMax) by CW Doppler
- Aortic or prosthetic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic or prosthetic aortic valve (MG) by CW Doppler
- LVOT VTI by PW Doppler
- Systolic ejection time (ET)
- Grade of native aortic regurgitation (baseline only)
- Grade of prosthetic paravalvular regurgitation (post-implant only)
- Grade of prosthetic transvalvular regurgitation (post-implant only)
- Right ventricular outflow tract (RVOT) diameter (post-implant; if AR > mild by visual estimate
- RVOT VTI (post-implant; if aortic regurgitation > mild by visual estimate)
- Grade of prosthetic total (transvalvular plus paravalvular) regurgitation (post-implant only)
- Grade of mitral regurgitation (MR)
- Grade of tricuspid regurgitation (TR)
- Max TR jet velocity (if TR is present)
- Left ventricular internal dimension at end diastole (LVIDD)
- Left ventricular internal dimension at end systole (LVIDS)
- Interventricular septal thickness at end diastole (IVS)
- Left ventricular posterior wall thickness at end diastole (LVPW)
- Left ventricular end diastolic volume by modified Simpson’s rule (LVEDV)
- Left ventricular end systolic volume by modified Simpson’s rule (LVESV)
- Left atrial volume at end systole by bi-plane Simpson’s rule (LAV)
- Left atrial internal linear dimension at end systole (LA)
- Mitral inflow early (E) velocity
- Mitral inflow atrial (A) velocity
- Mitral inflow E wave deceleration time (MdT)
- Mitral annular early (e’) diastolic velocity; lateral
- Mitral annular late (a’) diastolic velocity; lateral
- Mitral annular early (e’) diastolic velocity; medial

- Mitral annular late (a') diastolic velocity; medial
- Grade of diastolic dysfunction
- Pattern of LV geometry
- Peak average left ventricular global longitudinal strain (GLS) measured at end systole (aortic valve closure)
- Vendor, model, and software version of echocardiography system
- Tricuspid annular plane systolic excursion (TAPSE)
- Basal right ventricular linear dimension at end diastole (RVD)
- Right ventricular area at end diastole (RVAD)
- Right ventricular area at end systole (RVAS)

In addition, the following variables will be derived by the central database from the appropriate measurements reported by both the site and ECL.

- **Body Surface Area (BSA) in m^2**
  BSA = 0.007184 x height 0.725 x weight 0.425
  Where: BSA is the body surface area in cm^2, height is in cm, and weight is in kg[8]
- **Body Mass Index (BMI) in kg/cm**
  BMI =weight in kg/height in cm
- **Aortic Valve Area (AVA) in cm^2**
  AVA = LVOT diameter in cm^2 x 0.785 x (LVOT VTI/aortic valve VTI)
  Where: LVOT VTI is the velocity time integral of the left ventricular outflow tract in cm, and aortic valve VTI is the velocity time integral of the native aortic valve in cm
- **Aortic Valve Area Index (AVAI) in cm^2/m^2**
  AVAI = AVA/BSA
  Where: AVA is the native aortic valve area in cm^2, and BSA is the body surface area in m^2
- **Effective Orifice Area (EOA) in cm^2**
  EOA = LVOT $diameter^2$ x 0.785 x (LVOT VTI/Aortic valve VTI)
  Where: LVOT VTI is the velocity time integral of the left ventricular outflow tract in cm, and aortic valve VTI is the velocity time integral of the aortic prosthesis in cm
- **Effective Orifice Area Index (EOAI) in $cm^2/m2$**
  EOAI = EOA/BSA
  Where: EOA is the effective orifice area in cm^2, and BSA is the body surface area in m^2
- **Doppler Velocity Index (DVI)**
  DVI= LVOT VTI/Aortic valve VTI
  Where: LVOT VTI is the velocity time integral of the left ventricular outflow tract in cm, and aortic valve VTI is the time velocity integral of the prosthetic aortic valve in cm

[8] Height will be pulled from the site baseline eCRF, and weight will be pulled from the site eCRF for the visit

- **Estimated Right Ventricular Systolic Pressure (RVSP) in mmHg**
  RVSP = (4 x MVTR jet^2) + 10
  Where: MV TR jet is the max velocity of the tricuspid regurgitant jet, and 10 = the assumed mean right atrial pressure in mmHg
- **Cardiac Output (CO) in l/min**
  CO = (SV x HR)/1000
  Where: SV is the stroke volume in ml/beat, and HR is the heart rate in beats per minute
- **Cardiac Index (CI) in l/min/m^2**
  CI=CO/BSA
  Where CO is the cardiac output in l/min and BSA is Body Surface Area in cm^2
- **Stroke Volume (SV) in ml/beat**
  SV = LVOT diameter^2 x 0.785 x LVOT VTI
  Where: LVOT VTI is the velocity time integral from the left ventricular outflow tract in cm
- **Stroke Volume Index (SVI) in ml/beat/m^2**
  SVI=SV/BSA
  Where SV is stroke volume in ml/beat and BSA is Body Surface Area in m^2
- **Stroke Volume RVOT (SV RVOT) in ml/beat**
  SV RVOT = RVOT diameter x RVOT VTI
  Where RVOT diameter is the right ventricular outflow tract diameter in cm and RVOT VTI is the right ventricular velocity time integral
- **Aortic Regurgitant Volume (ARVol) in ml/beat**
  RV = SV – SV RVOT
  Where: SV = LVOT diameter^2 x 0.785 x LVOT VTI, and SV RVOT = RVOT diameter^2 x 0.785 x RVOT VTI
- **Aortic Regurgitant Fraction (ARF) in %**
  ARF = ARVol/SV
  Where ARVol is the aortic regurgitant volume in ml and SV is the stroke volume in ml
- **Left Atrial Volume Index (LAVI)**
  LAVI = LAV/BSA,
  Where LAV is left atrial volume (biplane Simpson's) at end systole in ml, and BSA is body surface area in m^2
- **Aortic transvalvular flow rate (AFR) in ml/second**
  AFR = SV/ET
  Where SV is the stroke volume in ml/beat and ET is systolic ejection time in milliseconds
- **Valvulo-arterial impedance (Z_{va})**
  Z_{va}=(MG + SAP)/SVI
  Where MG is mean aortic gradient in mmHg, SAP is systolic blood pressure in mmHg[9], and SVI is stroke volume index in ml/beat/m^2 body surface area

[9] Systolic blood pressure will be pulled from the site eCRF

- **E:e'**
  Mitral inflow early (E) velocity/(mitral annular early (e') diastolic velocity; lateral + mitral annular early (e') diastolic velocity; medial)/2
- **E:A Ratio**
  Mitral inflow early (E) velocity/ mitral inflow atrial (A) velocity
- **Left ventricular ejection fraction (LVEF) by modified-Simpson's rule**
  LVEF=[(LVEDV-LVESV)/LVEDV] x 100
  Where LVEDV is left ventricular end-diastolic volume in ml and LVESV is left ventricular end systolic volume
- **Fractional Shortening (FS) in %**
  FS = [(LVIDD - LVIDS)/LVIDD] x 100
  Where: LVIDD is left ventricular internal dimension at end diastole in cm, and LVIDS is left ventricular internal dimension at end systole in cm
- **Relative wall thickness (RWT)**
  RWT = (IVS + LVPW)/LVIDD
  Where IVS is interventricular septal thickness at end-diastole in cm, LVPW is left ventricular posterior wall thickness at end-diastole in cm, and LVIDD is left ventricular internal dimension at end-diastole in cm
- **Left Ventricular Mass (LVM) in grams**
  $LVM = 0.83 \times [(LVIDD + LVPW + IVS)^3 - (LVIDD)^3] + 0.6$
  Where: LVIDD is the left ventricular internal dimension at end diastole in cm, LVPW is the left ventricular posterior wall thickness at end diastole in cm, and IVS is the interventricular wall thickness at end diastole in cm.
- **Left Ventricular Mass Index (LVMI) in g/m^2 body surface area**
  LVMI = LVM/BSA
  Where: LVM is left ventricular mass in g, and BSA is body surface area in m^2
- **Right Ventricular Fractional Area Change (RVFAC) in %**
  RVFAC = [(RVAD-RAS)/RVAD} x 100
  Where RVAD is right ventricular area at end diastole and RVAS is right ventricular area at end-systole

13.4 Appendix IV: Exercise Tolerance Testing Procedures

Subjects confirmed by the ECL to meet the AS criteria should undergo ETT unless contraindicated. A symptom-limited exercise test with the goal of reaching 80% to 85% of the age-predicted maximum heart rate is recommended. The recommended protocol is the modified-Bruce with treadmill, however the choice of the specific ETT protocol for each subject is per the clinical judgment of site study team.

During the test, subjects should be questioned for symptoms every 2 min, and blood pressure and a 12-lead ECG are recorded at baseline, at the end of each stage, and at peak exercise. The test should be stopped prematurely for symptoms (significant breathlessness) or any chest constriction or dizziness), progressive ventricular ectopy >3 beats, new atrial fibrillation, a sustained fall in systolic blood pressure >10 mm Hg from the previous stage or more than 2 mm ST segment depression.[39] Significant breathlessness can be differentiated clinically from physiological breathlessness by the presence of distress, the inability to speak, facial pallor and sometimes associated ventricular ectopy or a fall in blood pressure.[84]

The following information should be recorded: reason(s) for stopping (symptom, fall in blood pressure, ventricular ectopy, ST segment depression and fatigue with physiological breathlessness), exercise time, exercise capacity in metabolic equivalents (METs), maximum rise in systolic blood pressure and maximum fall from peak and ST segment depression in millimeters, and percentage of target heart rate achieved.

METs should be calculated from the speed and gradient of the treadmill by the machine's software using the formula (METS=[(speed × 0.1)+(gradient/100×1.8×speed)+ 3.5]/3.5), where speed is measured in meters/minute and grade as a percentage. One MET is usually defined as the energy expended at rest, which is equal to a body oxygen consumption of nearly 3.5 mL per kilogram of body weight for an average adult.[85]

A positive ETT is defined by the development of significant symptoms, a sustained fall in systolic blood pressure >10 mm Hg below baseline or more than 2 mm ST segment depression, a sustained tachyarrhythmia, or test limiting dyspnea or fatigue before reaching 60% age and gender adjusted predicted MET capacity. At maximum, up to 30 subjects with a positive ETT will be included in the study. Subjects with a positive ETT may continue in the study until the 30-subject maximum is reached. Once the 30-subject maximum is reached, only subjects with a negative ETT may continue in the study.

13.5 Appendix V: Cardiac Magnetic Resonance Imaging (CMR) Procedures

Subjects confirmed by the ECL to meet the AS criteria should undergo CMR with late gadolinium enhancement (LGE) unless contraindicated, and subjects implanted should have a CMR at the six-month follow-up. CMR exams can be performed with either 1.5 Tesla or 3 Tesla. Details of the acquisition protocol will be provided under separate cover. CMR exams will be sent to a core CMR lab for centralized analysis. The following variables will be reported:

- Left ventricular end-diastolic volume
- Left ventricular end-systolic volume
- Left ventricular end-diastolic volume index
- Left ventricular end-systolic volume index
- Left ventricular ejection fraction
- Stroke volume
- Stroke volume index
- Left ventricular mass
- Left ventricular mass index
- Maximum left ventricular wall thickness
- Left ventricular mass/left ventricular volume
- Longitudinal systolic function
- Left atrial volume index
- Presence of infarct on LGE
- Infarct LGE mass
- Presence of midwall LGE
- Midwall LGE mass
- Aortic regurgitant volume (post implant only)
- Aortic regurgitant fraction (post implant only)

13.6 Appendix VI: Six Minute Walk Test (6MWT) Procedures

Subjects confirmed by the ECL to meet the AS criteria should have a 6MWT unless contraindicated, and subjects implanted should have a 6MWT at the six-month follow-up. The 6MWT test is administered per the site's standard procedure, although the following recommendations are intended to standard the test across sites and minimize sources of variability.[86]

Technical Aspects. The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course should be 30 meters in length, and the course marked every 3 meters. Turnaround points should be marked (e.g. with an orange traffic cone). A starting line, which marks the beginning and end of each 60-meter lap, should be marked on the floor using brightly colored tape. A stopwatch and means to record the number of laps should be in place (e.g. lap counter or worksheet).

Patient Preparation. Subjects should wear comfortable clothing and appropriate walking shoes; and should not have exercised vigorously within 2 hours of beginning the test. A light meal is acceptable before early morning or early afternoon tests. Patients should use their usual walking aids during the test (cane, walker, etc.

Test Procedures

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The subject should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.
4. Set the timer to 6 minutes and lap counter to zero (if used).
5. Instruct the patient as follows:

   "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.
6. Position the patient at the starting line. As soon as the subject starts to walk, start the timer. Do not walk with the subject.

   Use an even tone of voice when using standard phrases of encouragement. For example, after each minute tell the subject *"You are doing well and have X minutes to go".* Do not use other words of encouragement (or body language to speed up).

If the subject stops walking during the test and needs to rest, do not stop the timer. The subject should be told to rest, "*but continue walking whenever you feel able.*" If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), bring a chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, tell the subject *"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."* When the timer rings, mark the spot where they stopped walking.

7. Record the number of laps from the counter (or tick marks on the worksheet).
8. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record on the worksheet.

13.7 Appendix VII: TAVR Implant Procedure

The implantation procedure is performed according to the standard procedures of the implanting physicians. Valve deployment in accordance with the cusp overlap technique[62] is recommended for TAVR implant for all study subjects, as appropriate. Transfemoral access is required for the TAVR implant. For sites in the United States, the local heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of the TAVR procedure. Procedural aspects specific to the Medtronic TAVR system should be performed according to the Instructions for Use. TAV size selection should be based on MDCT measurements and the dimensional criteria shown in Figure 21.

Size	23 mm	26 mm	29 mm	34 mm
Annular perimeter	56.5 – 62.8 mm	62.8 – 72.3 mm	72.3 – 81.7 mm	81.7 – 94.2 mm
Annular diameter (mean)	18 – 20 mm	20 – 23 mm	23 – 26 mm	26 – 30 mm
Sinus of Valsalva diameter (mean)	≥ 25 mm	≥ 27 mm	≥ 29 mm	≥ 31 mm
Sinus of Valsalva height (mean)	≥ 15 mm	≥ 15 mm	≥ 15 mm	≥ 16 mm

Figure 21. TAV sizing matrix showing the anatomical dimensional criteria for each TAV size.

The following variables will be collected regarding the TAVR implantation procedure:

- Name of the primary operator
- Anesthesia type (general or local)
- Pre-implant pressures (LV systolic and end-diastolic, aortic systolic and diastolic)
- Pre-implant mean aortic gradient (simultaneous recording or LV and central aortic pressures)
- Pre-deployment BAV (yes/no)
- Use of rapid or controlled pacing during BAV and deployment (yes/no)

- Size of TAV implanted
- Post-implant dilation (yes/no)
- Implantation of TAV within the desired location (yes/no)
- Post-implant grade of prosthetic regurgitation by angiography (final result)
- More than one TAV implanted (yes/no)
- Patency of coronary arteries post-implant (yes/no)
- Occurrence of adverse events
- If TAV implantation not attempted, reason why

Criteria for grading prosthetic regurgitation by aortography[87]

Grade 1+, mild: A small amount of contrast material enters the left ventricle in diastole; it is essentially cleared with each beat and never fills the ventricular chamber.

Grade 2+, moderate: More contrast material enters with each diastole and faint opacification of the entire chamber occurs.

Grade 3+, moderately severe: The left ventricle chamber is well opacified and equal in density with the ascending aorta.

Grade 4+, severe: Complete, dense opacification of the left ventricle chamber in one beat and the left ventricle appears more densely opacified than the ascending aorta.

13.8 Appendix VIII: Definitions of Endpoints and Outcome Measures

Definitions of safety endpoints, TAVR related complications, and efficacy endpoints are provided in Sections 13.8.1, 13.8.2, and 13.8.3, respectively. The CEC will code safety endpoints according to these definitions.

13.8.1 Safety Endpoint Definitions[63]

Mortality

Cardiovascular: Any of the following:

1) Death due to proximate cardiac cause (eg, myocardial infarction, cardiac tamponade, worsening heart failure)
2) Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
3) All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
4) All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events
5) Sudden or unwitnessed death
6) Death of unknown cause

Non-cardiovascular: Any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide).

Myocardial Infarction

Periprocedural MI (≤72 h after the index procedure): New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least 2 contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least 1 sample post procedure with a peak value exceeding 15x as the upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% post procedure is required AND the peak value must exceed the previously stated limit.

Spontaneous MI (>72 h after the index procedure): Any of the following criteria:

1) Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least 1 of the following:
   - Symptoms of ischemia
   - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]
   - New pathological Q-waves in at least 2 contiguous leads
   - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
2) Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, OR new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
3) Pathological findings of an acute myocardial infarction

Stroke and TIA

Diagnostic Criteria: Acute episode of a focal or global neurological deficit with at least 1 of the following:

- change in the level of consciousness
- hemiplegia, hemiparesis
- numbness or sensory loss affecting 1 side of the body
- dysphasia or aphasia
- hemianopia
- amaurosis fugax

1. other neurological signs or symptoms consistent with stroke
   Stroke: duration of a focal or global neurological deficit ⩾24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; **OR** the neurological deficit results in death
   TIA: duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
2) No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist
3) Confirmation of the diagnosis by at least 1 of the following:
   - Neurologist or neurosurgical specialist, **OR**
   - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

Stroke Definitions

Disabling stroke: mRS of 2 or more at 90 days and an increase in at least 1 mRS category from an individual's pre-stroke baseline
Non-disabling stroke: mRS of <2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual's pre-stroke baseline

Stroke Classifications

Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

Undetermined: insufficient information to allow categorization as ischemic or hemorrhagic

Bleeding Complications

Life-threatening or disabling bleeding: Fatal bleeding *(BARC type 5)* **OR,** bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* **OR,** bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* **OR,** overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units[10] (BARC type 3b)[88]

Major Bleeding: Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, **OR** causing hospitalization or permanent injury, **OR** requiring surgery **AND** does not meet criteria of life-threatening or disabling bleeding.

Minor bleeding: Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major.

Acute Kidney Injury (up to 7 days post procedure)

Stage 1: Increase in serum creatinine to 150%-199% (1.5-1.99 x increase compared with baseline) **OR,** increase of ≥0.3 mg/dL (≥26.4 mmol/L) **OR,** Urine output <0.5 mL/kg/h for >6 but <12 h

Stage 2: Increase in serum creatinine to 200%-299% (2.0%-2.99% increase compared with baseline) **OR,** Urine output <0.5 mL/kg/h for ≥12 but <24 h

Stage 3: Increase in serum creatinine to ≥300% (>3 x increase compared with baseline) **OR,** serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) **OR,** urine output <0.3 ml/kg/h for ≥24 h **OR,** anuria for ≥12 h

[10] Given one unit of packed RBC typically will raise hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated. A bleeding complication has to be the result of overt bleeding and cannot be adjudicated based on blood transfusions alone.

Vascular Access Site and Access Related Complications

Major vascular complication:

1) Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm **OR,**
2) Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) *leading to* death, life-threatening or major bleeding, visceral ischemia, or neurological impairment **OR,**
3) Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage **OR,**
4) Use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment **OR,**
5) Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram **OR,**
6) Surgery for access site-related nerve injury **OR,**
7) Permanent access-site related nerve injury

Minor vascular complication

1) Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding[11], visceral ischemia, or neurological impairment **OR,**
2) Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage **OR,**
3) Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication **OR,**
4) Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft

Percutaneous closure device failure: Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

Valve Dysfunction Requiring Repeat Procedure: Any valve dysfunction that requires repeat procedure (e.g. balloon valvuloplasty, TAVR, snare repositioning, placement of vascular plug paravalvular leak, or surgical AVR)

[11] Refer to bleeding definitions

13.8.2 Other TAVR Related Complications[63]

Conversion to open surgery: Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications.

Unplanned use of cardiopulmonary bypass: Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure.

Coronary artery obstruction: Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the TAV prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure.

Ventricular septal perforation: Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure

Mitral valve apparatus damage or dysfunction: Angiographic or echocardiographic evidence of new damage (chordae, papillary muscle, or leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the TAV of the mitral valve during or after the TAVR procedure.

Cardiac tamponade: Evidence of new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure.

Prosthetic valve thrombosis:

1. Clinical: Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment which is associated with any of the following clinical sequelae:

- Thromboembolic complications including
  - Any ischemic stroke
  - Any peripheral embolic event
  - ST segment elevation or Non-ST elevation myocardial infarction
  - Hemodynamic impairment associated with a worsening of heart failure

Note: valve thrombus found at autopsy in a subject whose cause of death was not valve-related or found at operation for an unrelated indication should be reported as valve thrombosis

2. Sub-Clinical: Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path or interferes with valve function, without evident clinical sequelae, causing a hemodynamic impediment meeting the following criteria:

- Increase in aortic regurgitation to moderate to severe.
- An increase by more than 50% of discharge mean aortic valve gradient (with the post discharge mean gradient being $\geq$ 20 mmHg) or a decrease in the Doppler Velocity Index (DVI) by more than 50%

Valve migration: After initial correct positioning, any observed movement (upward or downward) of the TAV within the aortic annulus from its initial position, with or without consequences.

Valve embolization: The TAV moves during or after deployment such that it loses contact within the aortic annulus.

Ectopic valve deployment: Permanent deployment of the TAV in a location other than the aortic root.

TAV in TAV deployment: Additional valve prosthesis is implanted within a previously implanted TAV because of sub-optimal device position and/or function, during or after the index procedure.

Hemolysis: Red cell destruction confirmed by lab data; Minor hemolysis: No intervention required; Major hemolysis: Requires intervention (e.g. iron supplements, transfusion, invasive intervention).

Prosthetic Valve Endocarditis: Any of the following;

1) Fulfillment of the following Duke criteria for definite endocarditis:
   - Histologic and/or microbiologic evidence of infection at surgery or autopsy, or
   - 2 major criteria, or
   - 1 major criteria or 3 minor criteria, or
   - 5 minor criteria

   Major Criteria:
   - Blood cultures positive for Infective Endocarditis (IE)
     - Typical microorganisms consistent with IE isolated from two separate blood cultures, as noted below
       - Viridans streptococci, *Streptococcus bovis*, *Staphylcoccus aureus*, or HACEK group
       - Community-acquired enterococci in the presence of a primary focus
     - Microorganisms consistent with IE isolated from persistently positive blood cultures defined as:
       - At least two positive cultures or blood samples obtained >12 hours apart, or
       - All of three, or a majority of four or more separate cultures of blood, the first and last sample obtained > one hour apart
     - Single blood culture positive for Coxiella burnetti or an antiphase I IG antibody titer >1:800
   - Evidence of endocardial involvement
     - Positive results of echocardiography for IE defined as:
       - Oscillating intracardiac mass on a valve or supporting structures in the path of regurgitant jets or on implanted material in the absence of an anatomic explanation, or
       - Abscess, or
       - New partial dehiscence of a valvular prosthesis
     - New valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)

   Minor Criteria:
   - Predisposition: predisposing heart condition or intravenous drug use
   - Fever: temperature >38°C
   - Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
   - Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
   - Microbiological evidence: positive blood culture but does not meet a major criterion (as noted above) or serological evidence of active infection with organism consistent with infectious endocarditis.
   - Echocardiographic findings: consistent with IE but do not meet a major criterion as noted above

   If only 1 major and 1-2 minor criteria are fulfilled, or if only 3-4 minor criteria are fulfilled, the event will be coded as "possible endocarditis"

2) Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation

3) Findings of abscess, pus, or vegetation involving the TAV or surgical bioprosthesis at autopsy

13.8.3 Efficacy Endpoints

Cardiovascular Hospitalization: includes hospitalizations for heart failure, unstable angina, myocardial infarction, cardiogenic shock, conduction disturbances and arrythmias, or other hospitalizations directly related to complications of the implant procedure or device (Figure 22), defined as follows;

Heart Failure[89]

A hospitalization that meets **all** of the following criteria:

1. The patient is admitted to the hospital with a primary diagnosis of heart failure (HF)
2. The patient's length of stay extends for at least 24 hours (or a change in calendar date if hospital admission and discharge times are unavailable)
3. The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following:
   - Dyspnea
   - Decreased exercise tolerance
   - Fatigue
   - Other symptoms of worsened end-organ perfusion (decreased blood supply to the vital organs (kidney, liver, lungs, heart, and brain)) or volume overload (excessive accumulation of intravascular fluid resulting from compromised regulatory mechanisms)
4. The patient has evidence of new or worsening HF, consisting of at least two physical examination findings or one physical examination finding and at least one laboratory criterion, including:
   - Physical Examination findings, including new or worsening:
     - Peripheral edema
     - Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
     - Pulmonary rales/crackles/crepitations
     - Increased jugular venous pressure and/or hepatojugular reflux
     - S3 gallop
     - Clinically significant or rapid weight gain thought to be related to fluid retention
   - Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
     - Increased B-type natriuretic peptide (BNP) / N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
     - Radiological evidence of pulmonary congestion
     - Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: septal or lateral E/e' > 15 or > 12, respectively; D-dominant pulmonary venous inflow pattern; plethoric inferior vena cava with minimal collapse on inspiration; or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI]), **OR**
     - Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) $\geq$ 18 mmHg, central venous pressure $\geq$ 12 mmHg, or a cardiac index < 2.2 L/min/m2
5. The patient receives at least one of the following treatments specifically for HF:
   - Significant augmentation in oral diuretic therapy (e.g., doubling of loop diuretic dose, initiation of maintenance loop diuretic therapy, initiation of combination diuretic therapy)
   - Combination diuretic therapy could include a thiazide-type diuretic (e.g. hydrochlorothiazide, metolazone, chlorothiazide) plus a loop diuretic, or mineral-corticoid receptor antagonist (MRA) (e.g., spironolactone or eplerenone) plus a loop diuretic.
   - Initiation of intravenous diuretic (even a single dose) or vasoactive agent (e.g., inotrope, vasopressor, vasodilator)
   - Mechanical or surgical intervention, including:
     - Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
     - Mechanical fluid removal (e.g. ultrafiltration, hemofiltration, dialysis)

Unstable Angina[89]

1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring at rest, or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity, **AND**
2. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available), **AND**
3. At least one of the following:
   - New or worsening ST or T wave changes on resting ECG (in absence of confounders, such as LBBB or LVH)
     - Transient ST elevation (duration < 20 minutes)
     - New ST elevation at the J point in two contiguous leads with the cut-points:
     - 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.
     - ST depression and T-wave changes
     - New horizontal or down-sloping ST depression > 0.05 mV in two contiguous leads and/or new T-wave inversion > 0.3 mV in two contiguous leads with prominent R wave or R/S ratio > 1.
   - Definite evidence of inducible myocardial ischemia as demonstrated by:
     - an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets, **OR**
     - stress echocardiography (reversible wall motion abnormality) **OR,**
     - myocardial scintigraphy (reversible perfusion defect), **OR**
   - MRI (myocardial perfusion deficit under pharmacologic stress) **AND** believed to be responsible for the myocardial ischemic symptoms/signs.
   - Angiographic evidence of new or worse > 70% lesion (> 50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.
   - Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge **AND,**
4. Negative cardiac biomarkers and no evidence of acute MI

General Considerations

Escalation of pharmacotherapy for ischemia, such as IV nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient to support classification as hospitalization for unstable angina.

If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for MI should not be adjudicated as unstable angina.

Planned hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,

- Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.
- Rehospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina.
- A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.

Myocardial Infarction[89]

Hospitalization for primary diagnosis of myocardial infarction (MI); includes peri-procedural or spontaneous MI as defined in Section 13.8.1.

Cardiogenic Shock[89]

Sustained (>30 min) episode of hypoperfusion evidenced by systolic blood pressure <90 mm Hg and/or, if available, cardiac index <2.2 L/min per square meter determined to be secondary to cardiac dysfunction and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., IABP, extracorporeal circulation, VADs) to maintain blood pressure and cardiac index above those specified levels.

Note: Transient episodes of hypotension reversed with IV fluid or atropine do not constitute cardiogenic shock. The hemodynamic compromise (with or without extraordinary supportive therapy) must persist for at least 30 min.

Conduction Disturbances and Arrhythmias[89]

Hospitalization for new or worsening of any of the following new or worsening conduction disturbances or arrhythmias:

- First-degree atrioventricular (AV) block
- Second-degree AV block (Mobitz I or Mobitz II)
- Third-degree AV block
- Incomplete right bundle branch block
- Right bundle branch block
- Intraventricular conduction delay
- Left bundle branch block
- Left anterior or posterior fascicular block
- Atrial fibrillation (or flutter), defined as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG or at least 30 seconds on a rhythm strip

Other Procedural or Device Related

Includes any other hospitalization where the primary cause was directly related to complications of the implant procedure or device.

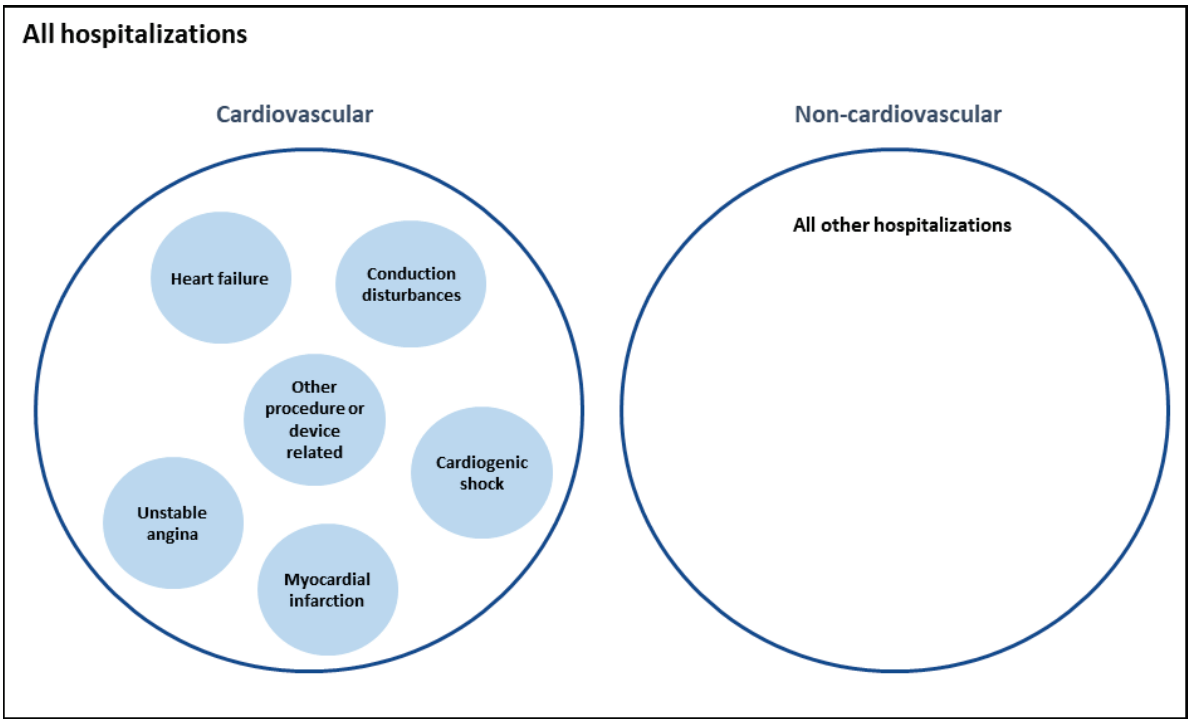


Figure 22. Diagram of categorization of hospitalizations.

Heart Failure Events[89]: Includes hospitalization for heart failure (per previous definition) **AND** urgent outpatient visits, defined as an event that meets **all** of the following criteria:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but does not meet the criteria for a HF hospitalization
2) The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following:
   - Dyspnea
   - Decreased exercise tolerance
   - Fatigue
   - Other symptoms of worsened end-organ perfusion (decreased blood supply to the vital organs (kidney, liver, lungs, heart, and brain)) or volume overload (excessive accumulation of intravascular fluid resulting from compromised regulatory mechanisms)
3) The patient has evidence of new or worsening HF, consisting of at least two physical examination findings or one physical examination finding and at least one laboratory criterion, including:
   - Physical Examination findings, including new or worsening:
     - Peripheral edema
     - Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
     - Pulmonary rales/crackles/crepitations
     - Increased jugular venous pressure and/or hepatojugular reflux
     - S3 gallop
     - Clinically significant or rapid weight gain thought to be related to fluid retention
   - Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
     - Increased B-type natriuretic peptide (BNP) / N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.
     - Radiological evidence of pulmonary congestion
     - Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: septal or lateral E/e' > 15 or > 12, respectively; D-dominant pulmonary venous inflow pattern; plethoric inferior vena cava with minimal collapse on inspiration; or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI])

     OR

   - Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) $\geq$ 18 mmHg, central venous pressure $\geq$ 12 mmHg, or a cardiac index < 2.2 L/min/m^2
4) The patient receives at least one of the following treatments specifically for HF:
   - Initiation of intravenous diuretic or vasoactive agent (e.g. inotrope, vasopressor, or vasodilator)

     Note that signification augmentation of oral diuretic therapy will not be sufficient to fulfill the urgent HF visit criteria
   - Mechanical or surgical intervention, including:
     - Mechanical circulatory support (e.g. intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart)
     - Mechanical fluid removal (e.g. ultrafiltration, hemofiltration, dialysis

*Note that clinic visits for scheduled administration of HF therapies or procedures (e.g. intravenous diuretics, intravenous vasoactive agents, or mechanical fluid removal) **do not** qualify as non-hospitalized HF events.*

Device Success[63]

All of the following:

- Absence of procedural mortality, **AND**
- Correct positioning of a single prosthetic heart valve into the proper anatomical location, **AND**
- Absence of patient prosthesis-mismatch and mean aortic valve gradient < 20 mmHg (or peak velocity < 3 m/sec), **AND**
- Absence of moderate or severe prosthetic valve regurgitation.

Bioprosthetic Valve Dysfunction (BVD)[63]: Any of the following

- **Stenosis: moderate/severe;** any of the following:
  - Peak aortic velocity > 4 m/s OR mean aortic gradient > 40 mmHg, AND EOA < 0.8 cm^2
  - Peak aortic velocity > 4 m/s OR mean aortic gradient > 40 mmHg, AND EOA ≥ 0.8 cm^2, **AND** DVI < 0.25
  - Peak aortic velocity ≤ 4 m/s and mean aortic gradient ≤ 40 mmHg, AND EOA < 0.8 cm^2, **AND** DVI < 0.25
- **Paravalvular regurgitation: moderate**
- **Paravalvular regurgitation: severe**
- **Transvalvular regurgitation: moderate**
- **Transvalvular regurgitation: severe**
- **Total regurgitation: moderate**
- **Total regurgitation: severe**

Notes:

1. For subjects with BSA < 1.6 m^2, the EOA criteria for significant (moderate or severe) stenosis is < 0.6 cm^2
2. For subjects with LVOT diameter > 2.5 cm, the DVI criteria for significant (moderate or severe) stenosis is < 0.2
3. Reporting of prosthetic valve dysfunction will be based on core lab results.
4. Bioprosthetic valve dysfunction events are not reported as adverse events, unless the dysfunction is accompanied with clinical sequelae at the time of event detection, and the clinical sequelae are chronologically and physiologically associated with the dysfunction. However, prosthetic dysfunctions that are associated with adverse events, and that meet the definition of a serious adverse event, should be reported as such.

Patient-Prosthesis Mismatch (PPM)[63]

For subjects with BMI < 30 kg/cm^2

- **Moderate PPM:** EOAI = 0.85 – 0.65
- **Severe PPM:** EOAI < 0.65

For subjects with BMI ≥ 30 kg/cm^2

- **Moderate PPM[12]:** EOAI = 0.70 – 0.60
- **Severe PPM:** EOAI < 0.60

Bioprosthetic Valve Failure (BVF)[90]: Any of the following:

- Autopsy findings of bioprosthetic valve dysfunction, likely related to the cause of death, or valve-related death (i.e. any death caused by bioprosthetic valve dysfunction or sudden unexplained death following diagnosis of bioprosthetic valve dysfunction)
- Repeat intervention (i.e. valve-in-valve TAVI, paravalvular leak closure or SAVR following confirmed diagnosis of bioprosthetic valve dysfunction)
- Severe bioprosthetic valve dysfunction

[12] Original VARC-2 definition lists 0.90-0.60 as moderate PPM range, this definition has been updated to reflect corrected range of 0.70-0.60 for moderate PPM

13.8.4 Classification of Causal Relationships

The following definitions are intended as guidelines for classifying causal relationships between the event and the TAV, the catheter delivery system, the loading system, and the TAVR implant procedure.

Causal relationships between event and the TAV

Not related to the TAV	The relationship to TAV can be excluded when: • the event is not a known side effect of the TAV or product category the device belongs to or of similar devices; • The event has no temporal relationship with the TAV • The event does not follow a known response pattern to the TAV and is biologically implausible; • The event involves a body-site or an organ not expected In order to establish non-relatedness, not all the criteria listed above might be met at the same time.
Unlikely to be related to the TAV	The relationship with the TAV seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related to the TAV	The relationship with the TAV is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably related to the TAV	The relationship with TAV seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Causal relationship "Related" to the TAV	The event is associated with the TAV beyond reasonable doubt when: • the event is a known side effect of the TAV or product category the device belongs to or of similar devices; • the event has a temporal relationship with investigational device use/application or procedures; • the event involves a body-site or organ that - the TAV is applied to; - the TAV of has an effect on; • the event follows a known response pattern to the TAV; • other possible causes (eg an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out • harm to the subject is due to error in use In order to establish relatedness, not all the criteria listed above might be met at the same time.

Timeframe for assessing implant procedure relationships begin when subject is being prepared for the TAVR or implant (or re-implant) procedure.

Causal relationships between event and the TAVR delivery system

Not related to the TAVR delivery system	The relationship with the TAVR delivery system can be excluded when: • the event is not a known side effect of the TAVR delivery system product category the device belongs to or of similar devices; • The event has no temporal relationship with the use of the TAVR delivery system • The event does not follow a known response pattern to the TAVR delivery system and is biologically implausible; • The event involves a body-site or an organ not expected In order to establish non-relatedness, not all the criteria listed above might be met at the same time
Unlikely to be related to the TAVR delivery system	The relationship with the TAVR delivery system seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related to the TAVR delivery system	The relationship with the TAVR delivery system is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably related to the TAVR delivery system	The relationship with the TAVR delivery system seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal relationship "Related" to the TAVR delivery system	The event is associated with the TAVR delivery system reasonable beyond doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices; • the event has a temporal relationship with the TAVR delivery system use/application; • the event involves a body-site or organ that - the TAVR delivery system is applied to; - the TAVR delivery system has an effect on; • the event follows a known response pattern to the TAVR delivery system; • other possible causes (eg an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out • harm to the subject is due to error in use In order to establish relatedness, not all the criteria listed above might be met at the same time.

Causal relationships between event and the loading system

Not related to the loading system	The relationship with the loading system can be excluded when: • the event is not a known side effect of the loading system product category the device belongs to or of similar devices; • The event has no temporal relationship with the use of the loading system • The event does not follow a known response pattern to the loading system and is biologically implausible; • The event involves a body-site or an organ not expected In order to establish non-relatedness, not all the criteria listed above might be met at the same time
Unlikely to be related to the loading system	The relationship with the system seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related to the loading system	The relationship with the loading system is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably related to the loading system	The relationship with the loading system seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal relationship "Related" to the loading system	The event is associated with the loading system reasonable beyond doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices; • the event has a temporal relationship with the Loading system use/application; • the event involves a body-site or organ that - the Loading system is applied to; - the Loading system has an effect on; • the event follows a known response pattern to the Loading system; • other possible causes (eg an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out • harm to the subject is due to error in use In order to establish relatedness, not all the criteria listed above might be met at the same time.

Causal relationships between event and the TAVR implant procedure

Not related to the TAVR implant procedure	The relationship with the TAVR or SAVR implant procedure can be excluded when: • the event is not a known side effect of the TAV implant procedure; • The event has no temporal relationship with the TAVR implant relationship • The event does not follow a known response pattern to the TAVR implant procedure and is biologically implausible; • The event involves a body-site or an organ not expected In order to establish non-relatedness, not all the criteria listed above might be met at the same time.
Unlikely to be related to the TAVR implant procedure	The relationship with the TAVR implant procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly related to the TAVR implant procedure	The relationship with the TAVR implant procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably related to the TAVR implant procedure	The relationship with TAVR implant procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal relationship "Related" to the TAVR implant procedure	The event is associated with the TAVR implant procedure beyond reasonable doubt when: • the event is a known side effect of the TAVR implant procedure; • the event has a temporal relationship with the TAVR implant procedure; • the event involves a body-site or organ that - the TAVR is applied to; - the TAVR implant procedure has an effect on; • the event follows a known response pattern to the TAVR implant procedure; • other possible causes (eg an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out • harm to the subject is due to error in use In order to establish relatedness, not all the criteria listed above might be met at the same time.

Note:
Procedure related events refers to the procedure related to the initial application of the investigational medical device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat (serious) adverse events.

14. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
Revision A	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	Charles Boldt Sr Clinical Program Mgr Maggie Haltvick Sr Clinical Research Specialist Leah Crocker Clinical Research Specialist Hang Nguyen Sr Clinical Research Mgr Bibi Waterval Associate Clinical Research Specialist
Revision B	Study name change to "Evolut™ EXPAND TAVR I Feasibility Study" (was previously Evolut™ System EXPAND I Feasibility Study). Administrative change only	N/A - Administrative Change only	N/A - Administrative Change only	Study name change to be updated in affected study documents, as applicable	Charles Boldt Sr Clinical Program Mgr Maggie Haltvick Sr Clinical Research Specialist Leah Crocker Clinical Research Specialist Hang Nguyen Sr Clinical Research Mgr Bibi Waterval Associate Clinical Research Specialist

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
Revision C	Study follow-up period extended through 5 years, and total study duration extended to 7 years Inclusion criteria #5 added to Cohort B to align with Cohort A inclusion criteria (anatomical suitability for transfemoral TAVR) Additional clarifying language regarding procedures for subjects lost to follow-up added to section 6.11 Removed requirement for CEC to adjudicate additional outcome measures from section 7.7 Clarified procedures for collecting calcium volume measurements in section 13.1 Removed requirement to document in eCRF whether shoes were on or off for height and weight measurements throughout Clerical changes throughout	Study duration updated based on FDA feedback Additional changes made to ensure alignment throughout the CIP and correction of clerical issues	Endpoints updated to reflect 5 year follow up	Updates to be reflected in applicable study documents	Charles Boldt Sr Clinical Program Mgr Maggie Haltvick Sr Clinical Research Specialist Leah Crocker Clinical Research Specialist Hang Nguyen Sr Clinical Research Mgr Bibi Waterval Associate Clinical Research Specialist

Revision D	Entire document updated throughout to reflect removal of Cohort A (Moderate Symptomatic AS) Sections 4.2.3 and 10.6: Clarified that incidence of PPM will also be evaluated annually through 5 years Section 5.3: Added clarification on plan for the retention and reporting of traditionally underrepresented populations in this study Sections 5.4, 5.5.2, and 6.20 Removal of Heart Failure Specialist Role (note that section 5.5.4 was removed entirely due to this change) Section 5.9: Noted confirmation of AS will be made per relevant inclusion/exclusion criteria Section 6.2.1: Added inclusion criteria #6 "The subject and treating physician agree the subject will return for all required follow-up visits" Section 6.7: Clarified that subjects who have their TAV explanted will be followed for 30 days post explant, **or through resolution of related adverse events**, whichever is	Removal of Cohort A (Moderate Symptomatic AS) agreed upon with internal stakeholders and applicable regulatory bodies Sections 4.2.3 and 10.6: Clarified that incidence of PPM will also be evaluated annual through 5 years, to align with all additional outcome measures Section 5.3: Language added clarifying retention and reporting of traditionally underrepresented patient populations based on CMS feedback Sections 5.4, 5.5.2, and 6.20 Removal of Heart Failure Specialist Role, as this role is not required following removal of Cohort A (Moderate Symptomatic AS) Section 5.9: Clarification provided to specify the criteria ERC will use to confirm AS diagnosis Section 6.2.1: Added inclusion criteria #6 "The subject and treating physician agree the subject will return for all required follow-up visits" to align inclusion	Removal of Cohort A: No negative impact on performance. Data will not be collected on Moderate, Symptomatic AS subjects to support safety, efficacy, or other endpoints. Sections 4.2.3 and 10.6: No negative impact on performance, effectiveness, safety, or endpoints. Section 5.3: No negative impact on performance, effectiveness, safety, or endpoints. Section 5.4, 5.5.2, and 6.20 (removal of Heart Failure Specialist): No negative impact on performance, effectiveness, safety, or endpoints. Section 5.9: No negative impact on performance, effectiveness, safety, or endpoints. Section 6.2.1: No negative impact on performance, effectiveness, safety, or endpoints. Section 6.7: No negative impact on	Updates to be reflected in applicable study documents.	Charles Boldt Sr Clinical Program Mgr Maggie Haltvick Sr Clinical Research Specialist Leah Crocker Clinical Research Specialist Hang Nguyen Sr Clinical Research Mgr Bibi Waterval Associate Clinical Research Specialist

	longest, then exited from the study. Section 6.9: Added entire section to clarify when and how unscheduled visits would occur and how data and imaging would be entered. Section 6.16: Clarified that up to 30 subjects with a positive ETT **who are approved by the ERC** may move forward in the study Section 7.1, Table 2: Clarified event definitions to align with ISO14155:2020. Further defined additional Australian safety definitions for SSI and USM Section 7.4, Tables 4, 9, and 13: Updated to further define Australian safety reporting requirements Section 7.7: Clarification provided on CEC membership and events adjudicated Section 10.1: Clarification provided on subgroup analysis Section 11.1 and Table 11: Updated EMEA compliance to reference applicable laws and regulations of the countries in which the study will be conducted. Clarified current version of Declaration	criteria between both study cohorts. Section 6.7: Following subjects who have their TAV explanted will be followed for 30 post explant, **or through resolution of related adverse events**, whichever is longest, will allow collection of relevant subject AE data to ensure adequate reporting prior to study exit. Section 6.9: Language added regarding unscheduled visit data will provide clarity around unscheduled visit procedures and data. Section 6.16: Additional language added to clarify how subjects with a positive ETT may move forward in the study. Section 7.1, Table 2 and Section 7.4 Tables 4, 9, and 13: Alignment with ISO14155:2020, Australian safety reporting requirements per NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016, and internal Medtronic documentation requirements.	performance, effectiveness, safety, or endpoints. Section 6.9: No negative impact on performance, effectiveness, safety, or endpoints. Unscheduled data collected following subject adverse events may provide additional clarity around endpoint-related events. Section 6.16: No negative impact on performance, effectiveness, safety, or endpoints. Section 7.1, Table 2 and Section 7.4, Table 4: No negative impact on performance, effectiveness, safety, or endpoints. Clarification of NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 requirements. Section 7.7: No negative impact on performance, effectiveness, safety, or endpoints Section 10.1: No negative impact on performance, effectiveness,		

	of Helsinki will be followed. Section 12.8.1, Table 9: Investigator reporting requirements updated Section 12.8.2, Table 13: Australia and New Zealand sponsor reporting requirements updated Section 13.3.5: Added language to clarify that endpoint and event-related echocardiograms will be sent to the echo core lab for assessment. Section 13.8.2: Updated definitions of Other TAVR Related Complications (ventricular septal perforation and prosthetic valve thrombosis) Clerical updates completed throughout document.	Section 7.7: Clarification provided on CEC membership and events adjudicated to align with current CIP template Section 10.1: Clarification on subgroup analysis provided to align with SAP and define subset of endpoints to focus. Section 11.1 and Table 11: Updated EMEA compliance to reference applicable laws and regulations of the countries in which the study will be conducted, to ensure compliance with local regulations. Clarified current version of Declaration of Helsinki will be followed. Section 12.8.1, Table 9: Investigator reporting requirements updated to align with current requirements Section 12.8.2, Table 13: Australia and New Zealand sponsor reporting requirements updated to align with current requirements Section 13.3.5: Language added will clarify that the echo	safety, or endpoints Section 11.1 and Table 11: No negative impact on performance, effectiveness, safety, or endpoints. Event reporting to occur per CIP and local laws and regulations. Section 12.8.1, Table 9: No negative impact on performance, effectiveness, safety, or endpoints. Reporting to occur per CIP and local laws and regulations Section 12.8.2, Table 13: No negative impact on performance, effectiveness, safety, or endpoints. Reporting to occur per CIP and local laws and regulations Section 13.3.5: No negative impact on performance, effectiveness, safety, or endpoints. Echo core lab assessment of event-related and endpoint echocardiograms may provide additional clarity around endpoint-related events.		

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/Title
		core lab will also assess endpoint and event-related echocardiograms. Section 13.8.2: Updated definitions of Other TAVR Related Complications (ventricular septal perforation and prosthetic valve thrombosis) for alignment with CEC charter and code list. Additional clerical changes made to ensure alignment throughout the CIP and correction of clerical issues	Section 13.8.2; No negative impact on performance, effectiveness, safety, or endpoints. Updated definitions of ventricular septal performance and prosthetic valve thrombosis will align with the CEC code list to provide consistency in adjudication of these events. Clerical changes throughout have no negative impact on performance, effectiveness, safety, or endpoints.		

Medtronic approvals are maintained in an electronic document control system.

15. References

[1] Lindman BR, Clavel MA, Mathieu P, et al. Calcific aortic stenosis. Nat Rev Dis Primers 2016;2: 16006.

[2] Marganti K, Rigolin V, Sarano M, Bonow B. Valvular heart disease: diagnosis and management. Mayo Clin Proc. May 2010; 85 (5):483 – 500.

[3] Everett R, Clavel MA, Pibarot P, Dweck M. Timing of intervention in aortic stenosis: a review of current and future strategies. Heart 2018;0:1-11.

[4] Ito S, Miranda W, Oh J. Assessment of aortic stenosis beyond the aortic valve area. Structural Heart 2019, Vol 3, No 4, 268-279.

[5] Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol. 2012; 60:1854–63. [PubMed: 23062541]

[6] Chin CW, Vassiliou V, Jenkins WS, Prasad SK, Newby DE, Dweck MR. Markers of left ventricular decompensation in aortic stenosis. Expert Rev Cardiovasc Ther. 2014; 12:901–12. [PubMed: 24866867]

[7] Schwarz F, Baumann P, Manthey J, et al. The effect of aortic valve replacement on survival. Circulation. 1982;66:1105–1110.

[8] Ross J Jr, Braunwald E. Aortic stenosis. Circulation. 1968;38(Suppl 1):61-7.

[9] Stewart A. Aortic stenosis is still very tricky, especially when it Is moderate. J Am Coll Cardiol 2017, Vol 69, No 19; 2393-6.

[10] Strange G, Stewart S, Celermaje D, Prior D, Scalia G, Marwick T, Ilton M, Joseph M, Codde J, Playford D. National echocardiography database of Australia contributing sites. Poor long-term survival in patients with moderate aortic stenosis. J Am Coll Cardiol. 2019;74(5):1851-1863.

[11] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Rodriguez Muñoz D, Rosenhek R, Sjögren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017 Sep 21; 38(36):2739-2791.

[12] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd and Thomas JD. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014;129:e521-643.

[13] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, III, Fleisher LA, et al. . 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol. (2017) 70:252–89. 10.1016/j.jacc.2017.03.011

[14] Chin C, Messika-Zeitoun Dm Shah A, Lefevre L4, Bailleul S, Yeung E, Koo M, Mirsadraee S, Mathieu T, Semple S, Mills N, Vahanian A, Newby D, Marc R. Dweck M. A clinical risk score of myocardial fibrosis predicts adverse outcomes in aortic stenosis. European Heart Journal (2016) 37, 713–723.

[15] Chin C, Pawade T, Newby D, Dweck M. Risk stratification in patients with aortic stenosis using novel imaging approaches. Circ Cardiovasc Imaging. 2015 August ; 8(8): e003421. doi:10.1161/CIRCIMAGING.115.003421.

[16] Ng A, Prihadi E, Antoni M, Bertini M, Ewe S, Marsan N, Leung D, Delgado V, Bax J. Left ventricular global longitudinal strain is predictive of all-cause mortality independent of aortic stenosis severity and ejection fraction. European Heart Journal - Cardiovascular Imaging (2017) 0, 1–9.

[17] Klaeboe L, Haland T, Leren I, MD, PhD, Bekke R, Brekke P, Røsjø H, MD, PhD, Omland T,Gullestad L, Aakhus S, Haugaa K, Edvardsen T. Prognostic value of left ventricular deformation parameters in patients with severe aortic stenosis: a pilot study of the usefulness of strain echocardiography. J Am Soc Echocardiogr 2017;30:727-35.

[18] Zhu D, Ito S, Miranda W, Nkomo V, MD, Pislaru S, Villarraga H, Pellikka P, Crusan D, Oh J. Left ventricular global longitudinal strain is associated with long-term outcomes in moderate aortic stenosis. Circ Cardiovasc Imaging. 2020;13:e009958. DOI: 10.1161/CIRCIMAGING.119.009958

[19] Ba¨rwolf C, Minners J, Jander N, Gerdts E, Wachtell K, Ray S, Pedersen T. Natural history of mild and of moderate aortic stenosis—new insights from large prospective European study. Curr Probl Cardiol 2013;38:365–409.

[20] Généreux P, Stone G, O'Gara P, Marquis-Gravel G, Redfors B, Giustino G, Pibarot P, Bax J, Bonow R, Leon M. Natural history, diagnostic approaches,and therapeutic strategies for patients with asymptomatic severe aortic stenosis. J Am Coll Cardiol 2016;67:2263–88.

[21] van Gils L, Clavel MA, Vollema E, Hahn R, Spitzer E, Delgado V, Nazif T,De Jaegere, Geleijnse M, Ben-Yehuda O, Bax J, Leon M, Pibarot P, Van Mieghem. Prognostic implications of moderate aortic stenosis in patients with left ventricular systolic dysfunction. J Am Coll Cardiol. 2017;69:2383-2392.

[22] Delesalle G, Bohbot Y, Rusinaru D, Delpierre Q, Marechaux S, Tribouilloy C. Characteristics and prognosis of patients with moderate aortic stenosis and preserved left ventricular ejection fraction. J Am Heart Assoc. 2019;8:e011036. DOI: 10.1161/JAHA.118.011036.)

[23] Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S and Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. The New England Journal of Medicine. 2010;363:1597-607.

[24] Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ. Transcatheter versus surgical aortic-valve replacement in high-risk patients. The New England Journal of Medicine. 2011;364:2187-98.

[25] Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, Hermiller J, Jr., Hughes GC, Harrison JK, Coselli J, Diez J, Kafi A, Schreiber T, Gleason TG, Conte J, Buchbinder M, Deeb GM, Carabello B, Serruys PW, Chenoweth S, Oh J. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol. 2014.

[26] Adams DH, Popma JJ and Reardon MJ. Transcatheter aortic-valve replacement with a self-expanding prosthesis. The New England Journal of Medicine. 2014;371:967-8.

[27] Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk Patients. N Engl J Med 2016;374:1609-20.

[28] Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, Adams DH, Deeb GM, Maini B, Gada H, Chetcuti S, Gleason T, Heiser J, Lange R, Merhi W, Oh JK, Olsen PS, Piazza N, Williams M, Windecker S, Yakubov SJ, Grube E, Makkar R, Lee JS, Conte J, Vang E, Nguyen H, Chang Y, Mugglin AS, Serruys PW, Kappetein AP, SURTAVI Investigators. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017 Apr 6; 376(14):1321-1331.

[29] Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR (2019) Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 380(18):1695–1705. https://doi. org/10.1056/NEJMoa1814052

[30] Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, Bajwa T, Heiser JC, Merhi W, Kleiman NS, Askew J, Sorajja P, Rovin J, Chetcuti SJ, Adams DH, Teirstein PS, Zorn GL 3rd, Forrest JK, Tchetche D, Resar J, Walton A, Piazza N, Ramlawi B, Robinson N, Petrossian G, Gleason TG, Oh JK, Boulware MJ, Qiao H, Mugglin AS, Reardon MJ (2019) Transcatheter aorticvalve replacement with a self-expanding valve in low-risk patients. N Engl J Med 8380(18):1706–1715. https://doi.org/10.1056/ NEJMoa1816885.

[31] Genereux P, Pibarot P, Redfors B, Mack M, Makkar R,Wael A, Jaber W, Svensson L, Kapadia S, Tuzcu EM, Thourani V, Babaliaros V, Herrmann H, Szeto W, Cohen D, Lindman B, McAndrew T, Alu M, Douglas P, Hahn R, Kodali S, Smith C, Miller DC, Webb J, Leon M. Staging classification of aortic stenosis based on the extent of cardiac damage. European Heart Journal. 2017;38:3351-3358.

[32] Zilberszac R, Gabriel H, Schemper M, Laufer G, Maurer G, Rosenhek R. Asymptomatic severe aortic stenosis in the elderly. J Am Coll Cardiol Img 2017;10:43–50.

[33] Chau K, Douglas P, Pibarot P, Hahn R, Khalique O, Jaber W, Cremer P, Weissman N, Asch F, Zhang, Zachary M, Gertz Z, Elmariah S, Clavel MA, Thourani V, Daubert M, Alu M, Leon M, Lindman B. Regression of left ventricular mass after transcatheter aortic valve replacement: The PARTNER trials and registries. J Am Coll Cardiol 2020;75:2446–58.

[34] Lindman B, Dweck M, Lancellotti P, Généreux P, Piérard L, O'Gara P, Bonow R. Management of asymptomatic severe aortic stenosis: evolving concepts in timing of valve replacement. J Am Coll Cardiol Img 2020;13:481–93).

[35] Kang K, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, Yun SC, Hong GR, Song JM, Chung CH, M.D., Ph.D., Song JK, Jae-Won Lee, M.D., Ph.D., and Seung-Woo Park, M.D., Ph.D. Early surgery or conservative care for asymptomatic aortic stenosis. N Engl J Med 382;2 nejm.org January 9, 2020.

[36] Lancellotti P, Vannan M, M. Timing of intervention in aortic stenosis. N Engl J Med 382;2 nejm.org January 9, 2020.

[37] Vannan M, Pibarot P, Lancellotti P. Aortic stenosis: the emperor's new clothes. J Am Coll Cardiol. VOL. 74, NO. 15, 2019; 1864 – 7

[38] Pompeu M, Rafael L, Cavalcanti P, Antônio C, Neto E, Perazzo A, Simonato M, Clavel MA, Pibarot P, Lima R.. Early aortic valve replacement versus watchful waiting in asymptomatic severe aortic stenosis: a study-level meta-analysis. Structural Heart 2019, Vol 3, No 6, 483-490. https://doi.org/10.1080/24748706.2019.1652946.

[39] Redfors B, Pibarot P, Gillam L, Burkhoff D, Bax J, Lindman B, Bonow R, O'Gara P, Leon M, Généreux P. Stress testing in asymptomatic aortic stenosis. Circulation. 2017;135:1956–1976. OI:10.1161/CIRCULATIONAHA.116.025457.

[40] Pellikka PA, Nishimura RA, Bailey KR, Tajik AJ. The natural history of adults with asymptomatic, hemodynamically significant aortic stenosis. J Am Coll Cardiol. 1990;15:1012–1017.

[41] Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation. 2005;111:3290–3295. doi: 10.1161/CIRCULATIONAHA. 104.495903.

[42] Pai RG, Kapoor N, Bansal RC, Varadarajan P. Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. Ann Thorac Surg. 2006;82:2116–2122. doi: 10.1016/j.athoracsur.2006.07.043.

[43] Otto C, Burwash I, Legget M et al. Prospective study of asymptomatic valvular stenosis. Clinical, echocardiographic, and exercise predictors of outcome. Circulation. 1997;95:2262-2270. Doi;10.1161/01.CIR.95.9.2262.

[44] Green P, Cohen D, Genereux P et al. Relation between six-minute walk test performance and outcomes after transcatheter aortic valve implantation (from the PARTNER trial). Am J Cardiol. 2013;112:700-706. Doi:10.1016/j.amcard.2013.04.06

[45] Bhattacharyya S, Hayward C, Pepper JR, et al. Risk stratification in asymptomatic severe aortic stenosis: a critical review. Eur Heart J 2012;33:2377–87. 4.

[46] Kelly TA, Rothbart RM, Cooper CM, Kaiser DL, Smucker ML, Gibson RS. Comparison of outcome of asymptomatic to symptomatic patients older than 20 years of age with valvular aortic stenosis. Am J Cardiol 1988;61: 123–30.

[47] Otto CM, Burwash IG, Legget ME, et al. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. Circulation 1997;95:2262-70.

[48] Pellikka PA, Sarano ME, Nishimura RA, et al. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111:3290-5.

[49] Carabello BA. Evaluation and management of patients with aortic stenosis. Circulation 2002;105:1746-50.

[50] Wald DS, Williams S, Bangash F, Bestwick JP. Watchful waiting in aortic stenosis: the problem of acute decompensation. *Am J Med*. 2018;131(2):173-177.

[51] Lancellotti P, Magne J, Dulgheru R, MD; Clavel MA, Donal E, Vannan M, Chambers J, Rosenhek R, Habib G, Lloyd G, Nistri S, Garbi M, Marchetta S, Fattouch K, Coisne A, Montaigne D, Modine T, Davin L, Gach O, Radermecker M, Liu S, Gillam L, Rossi A,

Galli E, Ilardi F, Tastet L, Capoulade R, Zilberszac R, Vollema M, Delgado V, Cosyns B, Lafitte S, Bernard A, Pierard L, Jeroen J. Bax J, Pibarot P, Oury C. Outcomes of patients with asymptomatic aortic stenosis followed up in heart valve clinics. JAMA Cardiol. 2018;3(11):1060-1068. doi:10.1001/jamacardio.2018.3152

[52] Ito S, Miranda W, Nkomo V, Connolly H, Pislaru S, Greason K, Pellikka P, Lewis B, Oh J. Reduced Left Ventricular Ejection Fraction in Patients With Aortic Stenosis. J Am Coll Cardiol 2018;71:1313–21.

[53] Evaluation of Transcatheter Aortic Valve Replacement Compared to SurveilLance for Patients with AsYmptomatic Severe Aortic Stenosis (EARLY TAVR). ClinicalTrials.gov posting: https://clinicaltrials.gov/ct2/show/NCT03042104?term=early+tavr&recrs=a&cond=aortic+stenosis&draw=2&rank=1

[54] Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS (EVoLVeD). ClinicalTrials.gov posting: https://clinicaltrials.gov/ct2/show/NCT03094143

[55] Zuckerman B, Sapirstein W, Swain J. The FDA role in the development of percutaneous heart valve technology. EuroIntervention Supplements (2006) 1 (Supplement A) A75-A78.

[56] IBM Watson IPView, 2018 claims query.

[57] Global Initiative for Chronic Obstructive Lung Disease. https://goldcopd.org

[58] Thygesen K, Alpert J, Jaffe A, Chaitman B, Bax J, Morrow D, White D The Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction Authors/Task Force Members/Chairpersons: Kristian Thygesen* (Denmark). ESC/ACC/AHA/WHF Expert Consenus Document. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018;138:e618–e651. DOI: 10.1161/CIR.0000000000000617

[59] Lancellotti P, Magne J, Piérard LA. The role of stress testing in evaluation of asymptomatic patients with aortic stenosis. Curr Opin Cardiol. 2013;28:531–539. doi: 10.1097/ HCO.0b013e3283632b41.

[60] Gibbons RJ, Balady GJ, Bricker JT, Chaitman BR, Fletcher GF, Froelicher VF, Mark DB, McCallister BD, Mooss AN, O'Reilly MG, Winters WL Jr. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the ACC/AHA Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). Circulation. 2002;106:1883–1892. doi: 10.1161/01.CIR.0000034670.06526.15.

[61] Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, Mark DB, Marwick TH, McCallister BD, Thompson PD, Winters WL Jr, Yanowitz FG, Ritchie JL, Cheitlin MD, Eagle KA, Gardner TJ, Garson A Jr, Lewis RP, O'Rourke RA, Ryan TJ. ACC/AHA guidelines for exercise testing: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation. 1997;96:345–354.

[62] Tang G, Zaid S, Michev I, Ahmad H, Kaple R, Undemir C,Cohen M, Lansman S. "Cusp-overlap" view simplifies fluoroscopy-guided implantation of self-expanding valve in transcatheter aortic valve replacement. J Am Coll Cardiol 2018;11(16):1658-67.

[63] Kappetein AP, Head S,Généreux P, Piazza N, van Mieghem N, Blackstone E, Brott T, Cohen D, Cutlip D, van Es, G, Hahn R, Kirtane A, Krucoff M, Kodali S, Mack M, Mehran R, Rodes-Cabau J, Vranckx P, Webb J, Windecker S, Serruys P, Leon M. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438-54.

[64] Hunt SA, Abraham WT, Chin MH, et al. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2009;53:e1–90.

[65] Broderick P, Adeoye O, Elm J, Evolution of the Modified Rankin Scale and Its Use in Future Stroke Trials. Stroke Volume 48, Issue 7, July 2017, Pages 2007-2012.

[66] Bednarz J, Krauss D, Lang R. An echocardiographic approach to the assessment of aortic stenosis. J Am Soc Echocardiogr, 1996;9:286-94.

[67] Oh JK, Taliercio CP, Holmes DR Jr., Reeder GS, Bailey KR, Seward JB, et al. Prediction of the severity of aortic stenosis by Doppler aortic valve area determination: prospective Doppler-catheterization correlation in 100 patients. J Am Coll Cardiol 1988;11:1227-34.

[68] Otto CM, Pearlman AS, Comess KA, Reamer RP, Janko CL, Huntsman LL. Determination of the stenotic aortic valve area in adults using Doppler echocardiography. J Am Coll Cardiol 1986;7:509-17.

[69] Pibarot, P, Annick Clavel MA. Left ventricular outflow tract geometry and dynamics in aortic stenosis: implications for the echocardiographic assessment of aortic valve area. J Am Soc Echocardiogr, Vol. 28, Issue 11, p 1267–1269

[70] LaBounty TM, Miyasaka R, Chetcuti S, Grossman PM, Deeb GM, Patel HJ, et al. Annulus instead of LVOT diameter improves agreement between echocardiography effective orifice area and invasive aortic valve area. JACC Cardiovasc Imaging 2014;7:1065-6.

[71] Hahn R, Pibarot P. Accurate measurement of left ventricular outflow tract diameter: comment on the updated recommendations for the echocardiographic assessment of aortic valve stenosis. J Am Soc Echocardiogr 2017;30:1038-41.

[72] Oh J, Kane G, Seward J, Tajik A. The Echo Manuel. Fourth Edition. Wolters Kluwer 2019.

[73] Clavel M-A, Rodes-Cabau J, Dumont E, Bagur R, Bergeron S, De Larochelliere R, Doyle D, Larose E, Dumesnil J, Pibarot P. Validation and characterization of the aortic valve effective orfice área measured by Doppler echocardiography. JACC: Cardiovascular Imaging 2011; 4:10:1053-62.

[74] Hahn R, MD, Leipsic J, Douglas P, Jaber W, Weissman N, Pibarot P, Blanke P, Oh J. Comprehensive echocardiographic assessment of normal transcatheter valve function. JACC 2019. Cardiovascular Imaging, Vol. 12, No. 1. 25 – 34

[75] Zogbi W, Chambers J, Dumesnil J, Foster E, Gottdiener J, Grayburn P, Khandheria B, Levine R, Marx GR, Miller F, Nakatani S, Quinones M, Rakowski H, Rodriguez L, Swaminathan M, Waggoner A, Weissman N. Recommendations for evaluation of prosthetic valves with echocardiography and Doppler ultrasound. J Am Soc Echocardiogr 2009; 22:9:975-1014.

[76] Baumgartner H, Hung J, Bermejo J, Chambers J, Evangelista A,Griffin B,Iung B, Otto C, Pellikka P, and Quiñones M. Echocardiographic assessment of valve stenosis; EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009; Volume 22, Number 1; 1-33

[77] Shames S, Koczo A, Hahn R, Jin Z, Picard M, Gillam L. Flow characteristics of the SAPIEN aortic valve: the importance of recognizing in-stent flow acceleration for the echocardiographic assessment of valve function. J Am Soc Echocardiogr 2012;25:603-9.

[78] Miller F. Echocardiography derived valve area of the Edwards SAPIEN aortic valve prosthesis; new methodology is required to comply with old hemodynamic principles. J Am Soc Echocardiogr 2012;25:610-612.

[79] Thaden J, Nkomo V, Lee KJ, Oh J. Doppler imaging in aortic stenosis: the importance of the nonapical imaging windows to determine severity in a contemporary cohort. J Am Soc Echocardiogr 2015;28:780-5.

[80] Lang R, Badano L, Mor-Avi V, VPhD, Afilalo J, Armstrong A, Ernande L, Flachskampf F, Foster E, MD, Goldstein S, Kuznetsova T, MD, Lancellotti P, Muraru D, Picard M, MD, Rietzschel E, Rudski L, Spencer K, Tsang W, MD, and Voigt JU MD. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.

[81] Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. European Heart Journal: Cardiovascular Imaging 2015 16 1–11.

[82] Zoghbi W, Asch F, Bruce C, Gillam L, Grayburn P, Hahn R, MD, Inglessis I, Ashequl I. Islam A, Lerakis S, Little S, Siegel R, Skubas N, MD, Slesnick T, Stewart W, MD, Thavendiranathan P, Weissman N, MD, Yasukochi S, Zimmerman K. Guidelines for the evaluation of valvular regurgitation after percutaneous valve Repair or replacement. J Am Soc Echocardiogr 2019 Volume 32 Issue 4 Pages 431-475.

[83] Zoghbi W, MD, Adams D, Bonow R, Enriquez-Sarano M, Foster E, Grayburn P, Hahn R, Han Y, Hung J, Lang R, Little S, Shah D, Shernan S, Thavendiranathan P, Thomas J, Weissman N., MD. Recommendations for non-invasive evaluation of native valvular regurgitation. J Am Soc Echocardiogr 2017, Volume 30 Issue 4 Pages 303-371.

[84] Saeed S, Rajani R, Parkin D & Chambers JB. Exercise testing in patients with asymptomatic moderate or severe aortic stenosis. Heart 2018 104 1836–1842. (https://doi.org/10.1136/heartjnl-2018-312939)

[85] Jetté M, Sidney K, Blümchen G. Metabolic equivalents (METS) in exercise testing, exercise prescription, and evaluation of functional capacity. Clin Cardiol 1990;13:555–65.

[86] Crapo R, Casaburi R, Coates A, Enright E, Macintyre N, Mckay R, et al on behalf of ATS Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS Statement: Guidelines for the Six-Minute Walk Test. Am J Respir Crit Care Med Vol 166. pp 111–117, 2002

[87] Baim D, Grossman W. Grossman's Cardiac catheterization, angiography and intervention. Lippincott Williams and Wilkins Seventh Edition, 2005.

[88] Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation. 2011 Jun 14;123(23):2736-47

[89] Karen A. Hicks K, Kenneth W. Mahaffey K, Mehran R, Nissen S. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137:961–972.

[90] Capodanno D, Petronio AS, Prendergast B, Eltchaninoff H, Vahanian A, Modine T, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. (2017) 38:3382–90. doi: 10.1093/eurheartj/ehx303.