National Heart, Lung, and Blood Institute

Protocol Title:

Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA) prospective investigation

Version History

2017-08-07 IDE application after NHLBI Branch Review
2017-10-03 NHLBI Scientific Review
2017-11-13 NHLBI IRB Stipulations
2018-03-09 Add site

Investigational Device Exemption (IDE)

G170201 Pending

NIH IRB Number NCT Number

18-H-N018 N CT03381989

IDE Sponsor-Investigator:

Robert J. Lederman, MD, Senior Investigator, NHLBI Division of Intramural Research

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* No subject enrollment

Estimated Duration of Study:

Participant duration: 1 year

Analysis 1: year after enrollment is complete

Total estimated study duration: 2 years

Estimated Completion Date of Study:

September 30, 2019

Subjects of study and sites:

Subjects	Sex	Age range	Sites
60 screened	Men & Women	≥21 years	Up to 6
30 enrolled			

DISCLOSURES

The non-NIH investigators have the following conflicts of interest:

DD is a consultant Edwards Lifesciences, Medtronic, Abbott, and W.L. Gore.

ABG serves as a proctor for Edwards Lifesciences and St Jude Medical.

VCB is a consultant for Edwards Lifesciences and for Abbott Vascular, and his employer has research contracts from Edwards Lifesciences, Abbott Vascular, Medtronic, St Jude Medical, and Boston Scientific.

ABBREVIATIONS

ADE	Adverse device effect
AR	Aortic valve regurgitation
AS	Aortic valve stenosis
CT	Computed tomography
BASILICA	Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction
iFR	Instantaneous wave-free Flow Reserve index
LAMPOON	Intentional Laceration of the Anterior Mitral leaflet to Prevent iatrogenic left ventricular Outflow tract ObstructiON after transcatheter mitral valve replacement
MACE	Major adverse clinical events
SADE	Serious adverse device effect
SAE	Serious adverse event
TAVR	Transcatheter aortic valve implantation
TEE	Transesophageal echocardiography
THV	Transcatheter heart valve
VARC	Valve academic research consortium (criteria)
UADE	Unanticipated adverse device effect
UP	Unanticipated problem
6MWT	Six minute walking test

KEYWORDS

Transcatheter aortic valve replacement

Valve-in-valve TAVR

Coronary artery obstruction

Bioprosthetic heart valve failure

PRÉCIS

Transcatheter aortic valve replacement (TAVR) is an option to treat aortic valve stenosis or failure of a surgically implanted tissue valve. Sometimes TAVR displaces the diseased aortic valve leaflets outwards, causing life-threatening obstruction of the coronary arteries that supply blood to the heart. This is more common in surgically implanted tissue valves that are designed to achieve the largest aortic valve orifice area. Despite attempts to protect the coronary arteries from obstruction in these patients using coronary stents, the mortality of TAVR-associated coronary artery obstruction remains prohibitively high.

The investigators have developed and tested a technique to tear the existing aortic valve leaflet and enable TAVR in such patients. The procedure is called Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA).

The purpose of this study is to perform BASILICA in patients who have no good options to prevent coronary artery obstruction during TAVR.

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1.0 Protocol Summary

Title:	Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA) prospective investigation
Précis:	Transcatheter aortic valve replacement (TAVR) is an option to treat aortic valve stenosis or failure of a surgically implanted tissue valve. Sometimes TAVR displaces the diseased aortic valve leaflets outwards, causing life-threatening obstruction of the coronary arteries that supply blood to the heart. This is more common in surgically implanted tissue valves that are designed to achieve the largest aortic valve orifice area. Despite attempts to protect the coronary arteries from obstruction in these patients using coronary stents, the mortality of TAVR-associated coronary artery obstruction remains prohibitively high. The investigators have developed and tested a technique to split the existing aortic valve leaflet and enable TAVR in such patients. The procedure is called Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA). The purpose of this study is to perform BASILICA in patients who have no good options to prevent coronary artery obstruction during TAVR.
Hypothesis:	BASILICA avoids life-threatening coronary artery obstruction in at-risk patients during TAVR
Specific Aims	Specific aim 1: To determine early multi-center feasibility of BASILICA Specific aim 2: To determine provisional feasibility of BASILICA (Freedom from MACE to hospital discharge and 30days)
Primary Safety Endpoint	Freedom from MACE (according to VARC-2) at 30 days
Primary Feasibility Endpoints	Procedure clinical success (defined below)
Study Population:	Patients with bioprosthetic aortic valve failure or native aortic valve stenosis at high risk of coronary artery obstruction from leaflet displacement during TAVR

Inclusion Criteria	Adults age ≥ 21 years High or extreme risk of surgical aortic valve replacement according to the local multidisciplinary heart team Undergoing TAVR for valve-in-valve failure or native aortic stenosis ("on-label" TAVR) Deemed likely to suffer coronary artery obstruction from TAVR according to multidisciplinary heart team Concurrence of the study eligibility committee
Exclusion Criteria	Does not consent to participate Excessive target aortic leaflet calcification or masses on baseline CT Survival despite successful procedure expected < 12 months Subjects unwilling to participate or unwilling to return for study follow-up activities. Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures
Phase:	Pilot
Study Procedure	NHLBI Data Coordinating Center NHLBI + Local Institutional Review Boards Sites are trained by national PIs and NHLBI investigators Subjects are identified by site investigators Baseline and follow-up CT and fluoroscopy are analyzed by core laboratory Subject eligibility is confirmed by local multidisciplinary heart team including cardiac surgery, and is confirmed by study eligibility committee Subjects are enrolled prospectively Primary analysis based on 30-day outcomes; Secondary analysis includes 12-month outcomes
Sample Size	30 subjects at up to 6 sites
Risk-benefit determination	These patients have few or no therapeutic alternatives and have the potential to benefit from this procedure
Number of Sites enrolling participants:	6
Study Duration:	Two years
Participant Duration:	One year

2.0 OBJECTIVE

The objective of this protocol is further to characterize the feasibility and safety of Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA), in patients at high risk of coronary artery obstruction complicating TAVR.

In this protocol, we use transcatheter heart valves (THV) according to their marketed indication, on-label.

3.0 BACKGROUND

Transcatheter aortic valve replacement (TAVR) is an effective alternative to surgical aortic valve replacement in intermediate and high-risk patients. TAVR is also an effective treatment for failure of bioprosthetic surgical aortic valves, a treatment known as valve-in-valve TAVR. Valve-in-valve TAVR is associated with low mortality, satisfactory hemodynamics, and good intermediate-term functional outcomes in selected high risk patients [1, 2]. Valve-in-valve TAVR commonly exacerbates valve under-sizing (a phenomenon known as patient-prosthetic mismatch), which increases one-year mortality [1, 2].

Coronary artery obstruction is a devastating complication of valve-in-valve TAVR with a greater than 50% mortality [3]. Coronary artery obstruction occurs when the transcatheter heart valve displaces the underlying surgical or native aortic valve leaflets outwards and obstructs the coronary artery ostia, usually by sealing the sinus of Valsalva at the sinotubular junction (Figure 1). Coronary artery obstruction occurs most commonly during TAVR for surgical bioprothesis designs intended to maximize effective aortic orifice area ("stented" bioprostheses that have externally mounted leaflets, and "stentless" surgical bioprostheses). Coronary artery obstruction can be predicted by pre-procedure morphology and CT.

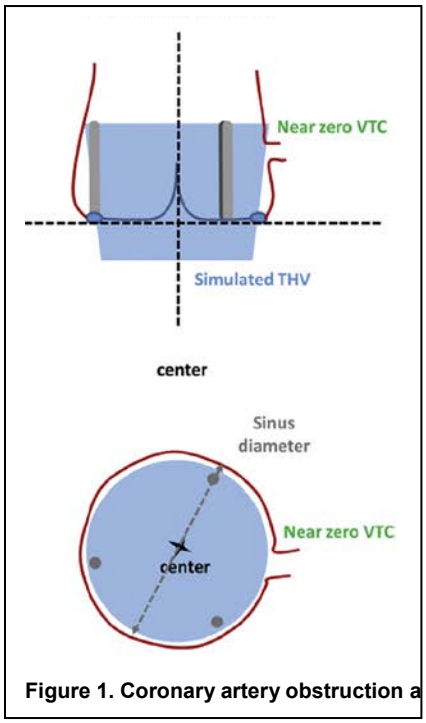


Figure 1. Coronary artery obstruction a

4.0 CLINICAL AND SCIENTIFIC JUSTIFICATION

We propose a solution based on our non-clinical [5] and initial clinical [6] LAMPOON procedure (intentional catheter-based traversal and laceration a mitral valve leaflet structure in order to prevent the complications of leaflet displacement after related transcatheter mitral valve implantation). In LAMPOON, we use catheter techniques to split the mitral valve leaflet to prevent obstruction of the left ventricular outflow tract.

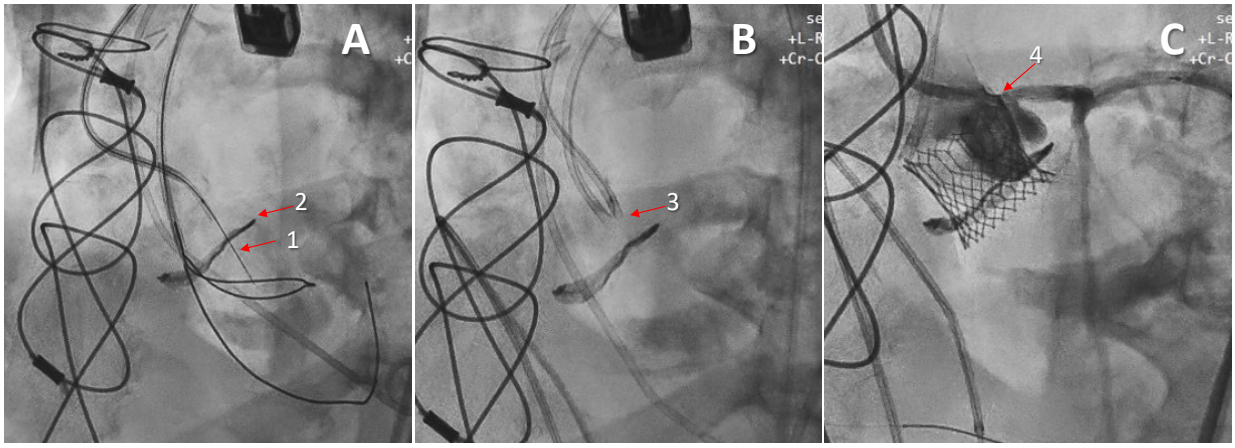


Figure 2. A represent BASILICA TAVR procedure. A: An electrified crossing wire (1) traverses the level of a bioprosthetic valve frame (2). B: The electrified shaft of the BASILICA guidewire is splitting the left coronary scallop of the intended aortic valve (3). C: After successful BASILICA, a Sapien 3 TAVR valve is implanted and coronary arteriography demonstrates patency of the left coronary artery ostium.

Using a simple modification of the LAMPOON technique, we have developed a technique to split an aortic valve leaflet, whether bioprosthetic or native, to prevent coronary artery obstruction after TAVR. The new technique is called Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction (BASILICA). Figure 2 shows a representative BASILICA TAVR procedure.

To date, seven patients have undergone compassionate BASILICA to enable TAVR. All survived to discharge without major adverse events.

4.1 Predictors of coronary artery obstruction after TAVR

Table 1 lists anatomic and artificial valve factors thought to contribute to the risk of coronary artery obstruction during TAVR. Many of these are continuous parameters and are thought to interact with each other, such as narrow and short sinuses of Valsalva. One of the most powerful predictors is thought to be a small "virtual tube to coronary artery distance (VTC)", especially when less than 3-4mm[3, 7]. However, the risk determination must integrate all of these factors, and must incorporate judgement.

Table 1. Predictors of coronary artery obstruction after TAVR, expanded from Dvir [7] and Riberio[3]

Anatomic factors	Narrow virtual transcatheter heart valve to coronary distance (VTC): <4mm* Low-lying coronary ostia Narrow sinotubular junction Low sinus of Valsalva height Narrow sinuses of Valsalva * Previous root repair (eg, root graft and coronary reimplantation)
Bioprosthetic valve factors	Internal stent frame with external leaflets (eg, Mitroflow, Trifecta)* No stent frame (homograft, stentless valves)* Long or thick or bulky bioprosthetic leaflets Supra-annular position

	Stent posts that extend beyond sinotubular junction Intended overexpansion/fracture of bioprosthetic valve frame during TAVR
Transcatheter valve factors	Extended sealing cuff High implantation

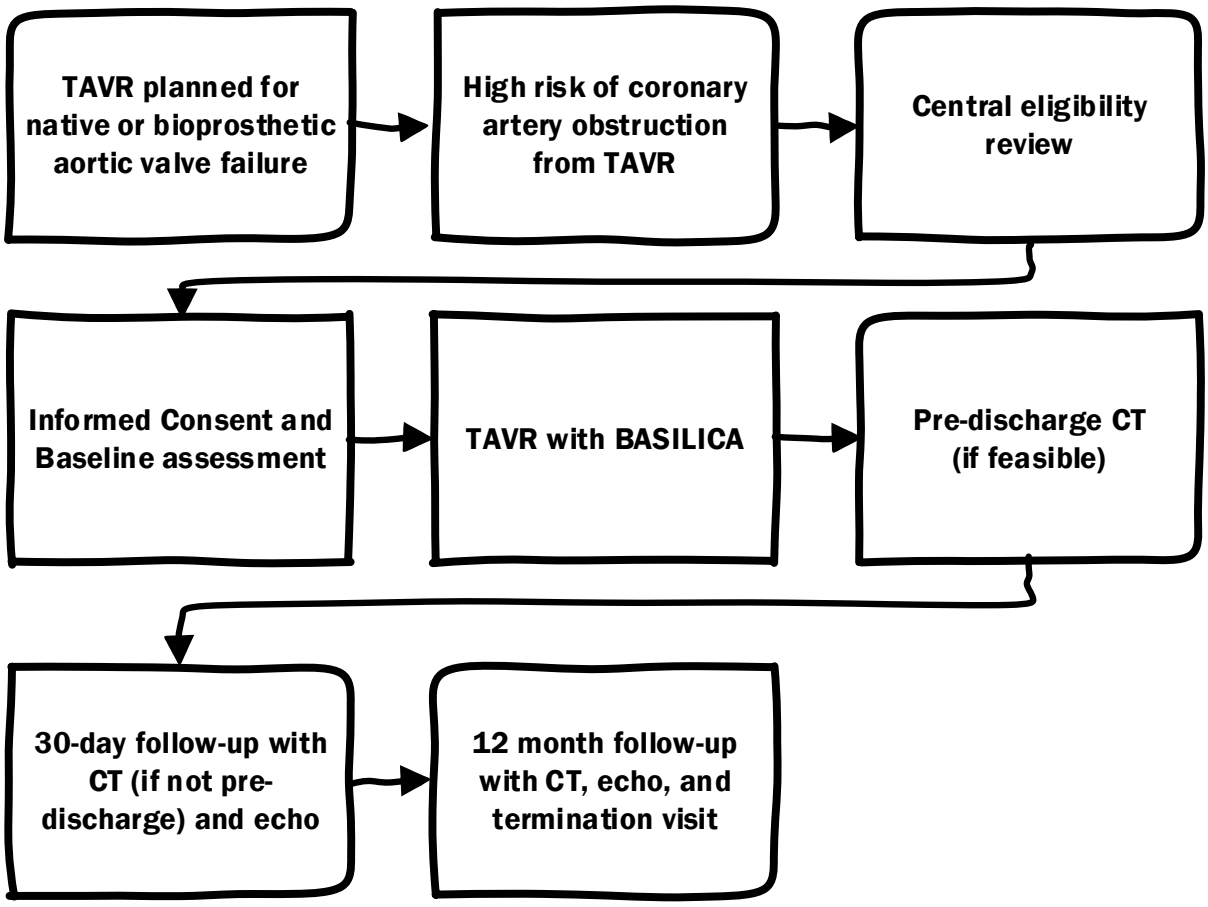
* Independent predictor of coronary obstruction in one retrospective registry [3]

5.0 TREATMENT OPTIONS

Candidates for TAVR with BASILICA have no good alternative treatment options. They are not eligible for definitive treatment using surgical aortic valve repair or replacement. Despite pre-positioning of bailout coronary stent delivery systems before TAVR, the outcome of TAVR-induced coronary artery obstruction is catastrophic with a mortality > 50% [3].

6.0 STUDY DESIGN

6.1 Schematic of Study Design



6.2 Overview of Study Design

This is a prospective, open-label, single-arm, multi-center, investigator-initiated, independently-adjudicated trial of BASILICA immediately before TAVR in subjects at high risk of coronary artery obstruction.

Candidates will be identified by the participating structural heart disease programs. In evaluation of aortic valve disease, candidates will undergo clinical evaluation, echocardiography, and contrast-enhanced gated cardiac CT. Eligibility will be reviewed and proposed by the local multidisciplinary heart teams. Candidates will then undergo central eligibility review by the sponsor and designated investigators. If deemed eligible, candidates will be offered participation in the study.

Once enrolled, subjects will undergo baseline assessment and blood tests.

Subjects will be admitted to the hospital and undergo TAVR with BASILICA. They will undergo endpoint assessment before discharge, after 30 days, and then 12 months.

6.3 Study Population

Subjects are undergoing planned TAVR because of high or prohibitive risk of surgical aortic valve replacement for bioprosthetic aortic valve failure or native aortic valve stenosis. The subjects are deemed to have excessive risk of TAVR-induced coronary artery obstruction based on features enumerated in Table 1 in section 4.1.

6.4 BASILICA TAVR Procedure

The BASILICA TAVR procedure is planned from a contrast-enhanced CT of the heart to select a suitable transcatheter heart valve size, predict suitability of the sub- and supra-annular landing zone, and predict post-TAVR coronary obstruction related leaflet encroachment on the sinotubular junction and coronary artery ostia. Knowledge of the aortic valve operative history is integrated into this assessment. These data are used to select a BASILICA traversal point, radiographic landmarks, and fluoroscopic projection angles.

The procedure is performed under general anesthesia or under moderate sedation at the discretion of the institutional heart team. The BASILICA procedure has three steps: (1) leaflet traversal with a guidewire, followed by (2) leaflet laceration, immediately followed by (3) TAVR. These are all guided by fluoroscopy and adjunctive echocardiography as needed.

Research study participation is defined as beginning the moment BASILICA traversal is attempted.

First catheter access is obtained typically via four arterial introducer sheaths (two for BASILICA, one for hemodynamics and angiography, and one for TAVR) and at least one venous introducer sheaths for temporary transvenous pacing. Anticoagulation with heparin or equivalent achieves an activated clotting time > 300s.

Hemodynamic and echocardiography measurements are recorded at baseline including gradients across the aortic valve, severity of valvular obstruction and severity of valvular regurgitation.

Two retrograde catheters are positioned, using a guidewire anchor as needed, in the LVOT and Aorta respectively. Care is taken to avoid entrapment of mitral valvular structures. A snare catheter is positioned in the LVOT. A coaxial traversal guiding catheter system (typically tandem catheters) directs electrosurgery devices (typically a rigid 0.014” guidewire inside a polymer jacket wire convertor) against the base of the coronary cusp targeted for laceration, using fluoroscopic and/or echocardiographic guidance.

Traversal is accomplished by transcatheter electrosurgery by connecting the back end of the 0.014” guidewire to an electrosurgery pencil during short bursts of “pure, cutting” radiofrequency energy at approximately 30W. The guidewire is repositioned as needed until it crosses the aortic leaflet and is snare-retrieved and externalized. Nonionic conductive flush (dextrose 5%) can be administered as needed via the guiding catheters to reduce guidewire char and thromboembolism.

Next the polymer jacket wire convertor is withdrawn, and the traversal wire is modified by the operator by (1) denuding a non-circumferential segment ~2mm in length, 90° arc and (2) kinking the denuded segment to enforce its position at the inner curvature of the intended guidewire lacerating surface. Next the polymer jacket radiopaque marker tip is locked adjacent to the kinked denuded shaft segment. Next the ensnared guidewire is externalized to position the lacerating surface across the base of the leaflet.

BASILICA may be performed on one or two valve leaflets that may threaten coronary artery obstruction.

Next, at operator discretion, the transcatheter heart valve may be positioned before or after the laceration step. If before, the operator assures no entrapment of the TAVR system with the laceration system of catheters.

At operator discretion, stroke prevention strategies may be employed, including external carotid artery compression and intravascular embolic protection devices.

Laceration is performed by positioning the laceration surface along the intended leaflet base, and applying tension on both free ends of the guidewire while simultaneously apply electrosurgery energy (typically 70W) in short bursts, until the laceration is complete and the guidewire is free.

Hemodynamics are recorded quickly after laceration before TAVR. Coronary artery stent systems are positioned prophylactically at the discretion of the operator. Predilatation, including intentional disruption of the bioprosthetic valve frame, is performed at operator discretion, before or after TAVR. Then TAVR is performed using established techniques typically during rapid ventricular pacing. The device size and inflation volumes are selected and applied at the discretion of the operator. Post-dilatation is performed at operator discretion to achieve an optimum TAVR result. Coronary artery patency is established using angiography and, if employed, using prepositioned pressure-tip guidewires. Coronary artery pressure (instantaneous wave-free ratio, *iFR*) may further be examined if possible at the discretion of the operator.

Completion hemodynamics and echocardiography are recorded. Finally, percutaneous femoral artery and vein vascular hemostasis is obtained and the subject convalesces in the appropriate inpatient recovery unit.

Before discharge, follow-up transthoracic echocardiography is recorded. A single contrast-enhanced CT of the heart is obtained before discharge if renal function allows, otherwise it is deferred as long as 30-days. Blood tests are recorded for research only as obtained for medical care.

Anticoagulation and antiplatelet therapy is prescribed after discharge at the physicians' discretion, and is recorded.

All subjects are to be enrolled in the TVT-Registry postmarketing TAVR registry.

6.5 Time and Events Schedule

	Screening	Baseline	Day 0	Inpatient	30 d (±14d) FU	12 mo (± 4 wk) (range) FU
Baseline informed consent:		X				
Multidisciplinary heart team eligibility determination		X				

	Screening	Baseline	Day 0	Inpatient	30 d (±14d) FU	12 mo (± 4 wk) (range) FU
Baseline clinical assessment		X				
NYHA Classification		X				X
Blood tests: CBC, Platelet, Haptoglobin, Liver panel, Chemistry Panel, Albumin, LDH, BNP/Pro-BNP, Troponin that are obtained for medical care are captured for research. Pregnancy test if applicable before day 0 and before research CT		X		X	X	X
Vital signs and in-person visit		X			X	X
Cardiac CT contrast-enhanced gated dynamic	Screening or baseline	Screening or baseline		Inpatient or 30D	Inpatient or 30D	
BASILICA assisted TAVR Enrollment begins once attempted			X			
Echocardiogram, surface or transesophageal	Screening or baseline	Screening or baseline	X		X	X
Adverse event assessment			X	X	X	X
Data capture from TVT-registry surveillance: KCCQ-12, baseline-only frailty		X			X	X

Subjects would receive continuing care from their primary physicians with consultant input as requested from the structural heart disease program.

For subjects who die, necropsy evaluation is requested to examine the heart at NIH.

6.6 Visit Schedule

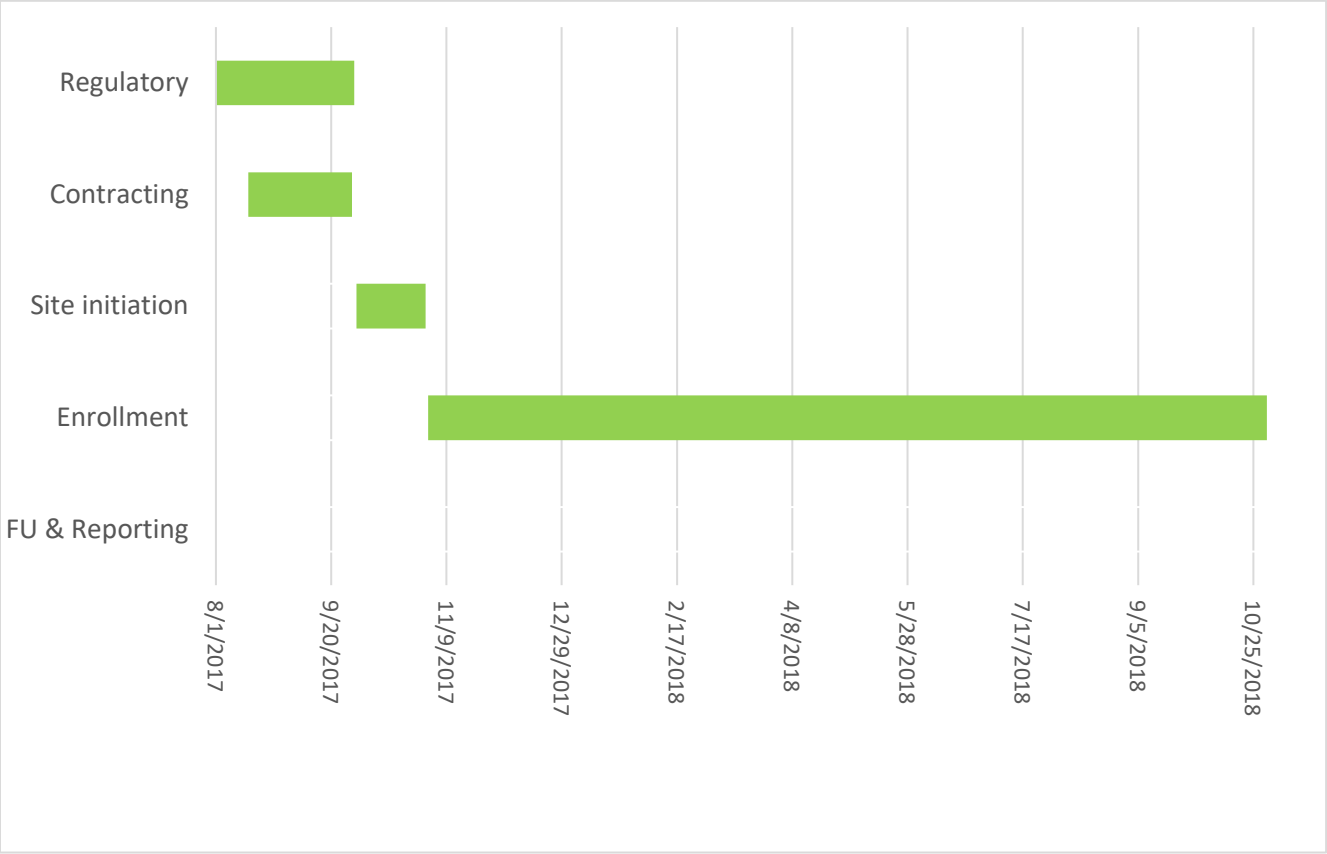
All activities except TAVR/BASILICA, Consent, KCCQ, and Adverse event assessment are performed for standard clinical care.

Timing	Event
Screening (any time)	Medical, Surgical and Interventional Assessment, determination and documentation that the subject has no other options for TAVR
Screening (any time)	Cardiac CT contrast enhanced, gated dynamic
Screening (any time)	Echocardiogram, transesophageal or surface
Screening (any time)	Multidisciplinary heart team eligibility determination and documentation
Baseline (within 30 days of procedure)	Research Informed Consent to include documented Inclusion and Exclusion criteria

Baseline (within 30 days of procedure)	Clinical Assessment to include: • Vital signs • Baseline symptoms • NYHA Classification • Other co-morbidities that could preclude the subject living the required 12 months post procedure • Surface echocardiogram-transthoracic and/or transesophageal • TVTRegistry quality surveillance data, including QOL, Frailty Clinical Blood tests if obtained are captured for research • CBC • Platelets • Haptoglobin • Liver Function panel • Chemistry panel • Troponin • Albumin • LDH • BNP/Pro-BNP • Pregnancy test if applicable
Day 0	TAVR with BASILICA procedure attempted, which marks enrollment. Subjects who do not proceed to BASILICA attempts are recorded as screen failures, and the reason is recorded.
Pre-discharge	Clinical Evaluation to include: • Cardiac CT scan contrast enhance, gated dynamic- if not clinically suitable then re-schedule for 30 Day follow up visit • Surface echocardiogram and/or transesophageal • Adverse Event Assessment Clinical Blood tests if obtained are captured for research • CBC • Platelets • Haptoglobin • Liver Function panel • Chemistry panel • Troponin • Albumin • LDH • BNP/Pro-BNP Pregnancy test if applicable

30-day (±14 days)	Clinic/office visit to update subject's vital status to include: • Vital signs • ECG • Medication Assessment • NYHA Classification • Surface Echocardiogram and/or transesophageal • Cardiac CT scan contrast enhanced, gated dynamic if not conducted pre-discharge for clinical reasons • Clinical blood work is captured for research including: CBC with platelets Haptoglobin Chemistry Panel PT INR BNP/Pro-BNP • TVTRegistry quality surveillance data, including QOL • Adverse Event Assessment
12 month (±30 days)	Clinic/office visit to update subject's vital status to include: • Vital signs • Medication Assessment • NYHA Classification • Surface Echocardiogram and/or transesophageal • Clinical blood work is captured for research including: CBC with platelets Haptoglobin Chemistry Panel PT INR BNP/Pro-BNP • TVTRegistry quality surveillance data, including QOL • Adverse Event Assessment

6.7 Milestones



This section is submitted to comply with recent NIH IRP initiatives. Should a milestone not be met, all milestones will be shifted in time until the protocol is complete within the predicted protocol completion timeline.

- Milestone one: Regulatory phase

Regulatory approval including scientific and ethics review, at NIH and at participating sites, and FDA review, is expected to be complete by October 1 2017.

- Milestone two: Contracting phase

NIH contracts for services including clinical events adjudication are expected to be complete by October 1 2017.

- Milestone three: Site initiation

Site selection, training, and initiation is expected to be complete before November 1 2017.

- Milestone four: Enrollment

First patient should be enrolled 30 days from the initiation of the first site. Should this not occur, then the 30 day period will be extended. Enrollment should be completed within 12 months. We expect the tempo of enrollment to increase over time as additional sites and experience accrue.

Continuing reviews to IRB, DSMB, and FDA will be performed during this period.

- Milestone five: Follow-up and reporting

After the last patient is enrolled, follow-up is performed for 12 months. The study phase is changed from recruitment to follow-up and to analysis, as appropriate. We expect the primary manuscript to be prepared based on data from 30 day follow-up. We expect the final analysis to be complete within 12 months after follow-up is complete.

7.0 ELIGIBILITY ASSESSMENT

7.1 Inclusion Criteria

- Adults age ≥ 21 years
- High or extreme risk of surgical aortic valve replacement according to the local multidisciplinary heart team
- Undergoing TAVR for valve-in-valve or native aortic valve failure ("on-label" TAVR)
- Deemed likely to suffer coronary artery obstruction from TAVR according to multidisciplinary heart team
- Concurrence of the study eligibility committee

7.2 Exclusion criteria

- Subjects unable to consent to participate, unless the subject has a legally authorized representative
- Excessive target aortic leaflet calcification or masses on baseline CT
- Survival despite successful procedure expected < 12 months
- Planned concurrent valve intervention in the same setting (such as transcatheter mitral valve therapy or paravalvular leak therapy)
- Subjects unwilling to participate or unwilling to return for study follow-up activities.
- Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures

7.3 Rationale for selection criteria

The selection criteria allow enrollment of the intended population with little anticipated selection bias. Instead of functional or geometric selection criteria, the study will enroll all subjects deemed otherwise suitable for TAVR yet at risk of the problem to be addressed by BASILICA, the investigational procedure.

There are no validated prediction models for coronary artery obstruction. Features predictive of coronary obstruction will be specifically outlined to the heart team and to the study eligibility committee and captured in the data collection form.

Subjects are eligible if BASILICA laceration is contemplated for one or for two threatened coronary arteries.

The inclusive selection criteria and geographic extent of enrolling sites are expected to allow recruitment of a diverse economic, ethnic, and racial mix of patients that reflects the incident disease.

Composition of the study eligibility committee is described in section 14.10.

8.0 Strategies for Recruitment

Subjects will be recruited from the Structural Heart Disease clinical programs of the participating hospitals.

The distribution of planned enrolling sites assures accessibility of the trial to ethnically, racially, and economically diverse populations. The study will track sex, age, ethnicity, and racial background of subjects.

Once recruited, subject retention rate is expected to be high because follow-up activities are not onerous and are timed to correspond with routine follow-up medical care, without prohibitively expensive follow-up testing.

During the early clinical development of the BASILICA procedure, 3 clinical patients were treated in one week at two centers, which suggests the recruitment objectives will be met.

9.0 SAMPLE COLLECTION, STORAGE AND TRACKING PLAN

Imaging data (from angiography, CT, and echocardiography) constitute the only specimens to be collected. CT examinations performed for clinical evaluation prior to signing informed consent may be used as the baseline scan.

CT and fluoroscopy data will be analyzed at the NHLBI DIR Core Laboratory. These data will be transmitted on electronic media such as a DVD via carrier or using secure file transfer mechanisms abiding FISMA, HIPAA and local institutional standards (such as SFTP or https://secureemail.nih.gov).

Imaging data are transmitted to a central facility (NHLBI) using secure HIPAA compliant methods and are stored in a secure Picture Archive Computer System (PACS), according to local institutional standards.

Necropsy specimens will be handled according to local institutional medical standards and will be disposed accordingly.

10.0 BIOSTATISTICAL AND ANALYTICAL CONSIDERATIONS

10.1 Sample Size

The sample size is not statistically derived. This is a safety and feasibility study that enables patient access to a novel medical procedure, when these patients have no other good medical options to treat symptomatic aortic valve failure.

Up to 60 subjects will be consented until 30 subjects undergo attempted BASILICA TAVR in this protocol.

10.2 Study Analysis

Clinical events are classified by the local site Principal Investigator and confirmed by the NIH Principal Investigator. The results of the study will be released within 12 months of study completion.

Primary and secondary analyses will be stratified according to the setting for TAVR, whether native or bioprosthetic, and whether the bioprosthetic valve will intentionally be over-expanded to achieve a greater than nominal orifice area.

The study will be analyzed using descriptive statistics, including a case-by-case narrative summary of major adverse events. Kaplan-Meier estimates will be used to estimate the overall survival and the event-free survival Afterwards, we will survey for parameters associated with an increased risk of major adverse events by exploratory subgroup analysis and regression models.

10.2.1 Primary efficacy endpoint

The primary endpoint is Clinical success (measured at exit from the catheterization laboratory). All of the following must be present:

- Successful BASILICA traversal and laceration of the intended aortic leaflet; and
- Absence of procedural mortality; and
- Successful access, delivery, and retrieval of the BASILICA device system; and
- Successful TAVR device implantation; and
- Absence of acute life-threatening ostial coronary artery obstruction (by immediate hemodynamics, by angiography, and by iFR <0.89 if obtained)
- Freedom from emergency cardiac surgery or reintervention related to the BASILICA TAVR procedure, including attempted implantation of coronary artery stents to treat TAVR-induced coronary artery obstruction.

Additional details about primary endpoint

Valve post-dilatation is not considered unplanned re-intervention. When pre-positioned coronary artery stents are not able to be retrieved, they may be implanted without impacting the primary endpoint.

10.2.2 Primary safety endpoint

The primary safety endpoint is freedom from major adverse clinical events (MACE) according to VARC-2 at 30days.

10.2.3 Secondary Endpoints

Secondary endpoints include

- Technical success, defined as clinical success irrespective of coronary artery stenting
- Clinical success without stroke, as determined by site physicians
- Technical success of BASILICA only (delivery and removal of BASILICA catheter equipment, traversal, and laceration of intended aortic leaflet)
- Coronary artery obstruction measured as instantaneous wave-free pressure ratio (iFR) or related measurements using a solid-state pressure-transducer guidewire, if measured
- Survival to discharge, to 30d, and to 12mo
- Neurological events as reported by the site clinicians
- Access and vascular complications
- Peri-procedural and spontaneous acute myocardial infarction
- Pericardial effusion or tamponade
- VARC-2 bleeding complications
- AKIN acute kidney injury
- Freedom from hemolytic anemia related to BASILICA TAVR
- BASILICA Device or Procedure related technical failure: acute embolism, mitral valve injury, traversal into left atrium, coronary artery injury induced by BASILICA, etc.
- Rotational orientation of transcatheter heart valve commissures with regard to coronary artery ostia

- Hemodynamic instability caused by BASILICA before TAVR
- TAVR thrombosis on CT or echocardiography during follow-up
- Endocarditis during follow-up
- Outcomes for laceration of native versus surgical aortic valves, for single versus double scallop laceration, and for procedures with versus without bioprosthesis intentional overexpansion

10.2.4 Rationale for primary endpoint

The main clinical objective of BASILICA is to allow TAVR without causing death from acute coronary artery obstruction in patients identified at baseline because of existing valve design and geometry. The primary endpoint is selected to provide a binary summary assessment of procedure success to help assess the clinical utility of the investigational procedure.

10.2.5 Independent Clinical Events Adjudication

An independent Clinical Events Adjudication Committee will review all of the following that occur in the first year:

- Deaths
- Primary endpoints
- Site-reported strokes

The CEAC will classify relatedness of the above events to the BASILICA procedure. The PI and the CEAC will agree on a charter, but only after the CEAC contract is awarded. CEAC adjudication prevails over PI classifications.

10.3 Stopping Rules and Data Safety Monitoring

A Data and Safety Monitoring Board (DSMB) appointed by the NHLBI Division of Intramural Research will monitor the safety of subjects in the study as described in the investigational plan. All members of the DSMB are unaffiliated to the study. The NHLBI DSMB will review the protocol progress report at six month intervals, or more frequently upon request of PI, IRB, and/or NHLBI Clinical Director. The DSMB may recommend early termination of the study for considerations of safety and efficacy. Unanticipated Adverse Device Effects (UADEs) will be submitted to the DSMB following the same timelines as the IRB (See section 9.2.4).

In the case of death or serious UADE, if the sponsor and the principal investigator determine that the event presents an unreasonable risk to the participating subjects, the clinical trial will be terminated within 5 working days after making that determination and not later than 15 working days after the sponsor first receives notice of the effect. [21 CFR 812.46]. All clinical sites will be notified of this action.

Each institutional IRB will review all Serious Adverse Events, Unanticipated Adverse Device Effects, and Unanticipated Problems, and may choose to suspend or terminate the protocol based on those findings. We believe this will protect subject safety.

We propose different stopping rules based on whether the operator elects intentionally to over-expand the bioprosthesis.

10.3.1 Anticipated mortality

There are few data available to guide mortality assumptions. In an international registry of valve-in-valve TAVR, the short-term (30-day) mortality of coronary obstruction complicating TAVR was 50%, despite coronary stenting {Ribeiro, 2017 #362183}. The long-term mortality is expected to be larger. There is no registry of subjects not offered valve-in-valve TAVR because of threatened coronary obstruction.

Absent data, we are forced to use judgement and experience to estimate clinically acceptable mortality for this group of patients with "no good options." We assume that intentional fracture of surgical bioprosthetic valve frames would confer incremental mortality, although there are no available data. To come to this determination, we polled our lead site investigators, who are selected for their high-volume experience and quality. The best estimate of clinically-acceptable 30-day mortality was 15% for standalone BASILICA and 20% for BASILICA with valve fracture.

10.3.2 Stopping Rules for no intentional overexpansion of bioprosthesis stratum

The study will be monitored to ensure that the mortality within 30-days after the procedure does not substantially exceed an anticipated rate. We anticipate the rate of 30-day mortality is 15% or less and determine the stopping rule by a Bayesian approach [8]. The stopping boundary is reached if the posterior probability that the 30-day mortality rate exceeds 15% is at least 90%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new study data, which gives the prior parameters a = 0.9, b =5.1. Hence when we make decisions about stopping the study, the data from the study will dominate over the prior opinion.

The following table summarizes the threshold numbers for the stop rule boundary, which would lead to a recommendation to stop the study due to the excess 30-day mortality.

Number of subjects in the stratum	Stop if the number of deaths within 30 days reaches
2	2
3-6	3
7-11	4
12-16	5
17-21	6
22-26	7
27-30	8

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 30 independent Bernoulli trials, each with a true certain 30-day mortality, and compared these outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies using the above stopping rule. The following table summarizes the performance of this stopping rule:

True 30-day mortality rate	10%	15%	20%	25%	30%	35%
Proportion of Stopped Studies	4.8%	17.3%	39%	62.3%	81.3%	92.2%
Average number of subjects	29.1	27	23.5	19.4	15.4	12.1
Average number of 30-day mortality	2.9	4	4.7	4.9	4.6	4.2

These simulation results suggest that our stopping rule has a low probability stopping a study when the true 30-day mortality rate is 15% or less, and the probability of stopping a study is high when the true 30-

day mortality rate exceeds 15%. There, we believe that our Bayesian stopping rule for 30-day mortality has satisfactory statistical properties.

10.3.3 Stopping Rules for intentional overexpansion of bioprosthesis stratum

The study will be monitored to ensure that the mortality within 30-days after the procedure does not substantially exceed an anticipated rate. We anticipate the rate of 30-day mortality is 20% or less and determine the stopping rule by a Bayesian approach [8]. The stopping boundary is reached if the posterior probability that the 30-day mortality rate exceeds 20% is at least 90%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new data. This gives the prior parameters a = 1.2, b =4.8. Hence when we make decisions about stopping the study, the data from the study will dominate over the prior opinion.

The following table summarizes the threshold numbers for the stop rule boundary, which would lead to a recommendation to stop the study due to the excess 30-day mortality.

Number of subjects in the ”overexpansion of bioprosthesis” stratum	Stop if the number of deaths within 30 days reaches
3-5	3
6-8	4
9-12	5
13-16	6
17-20	7
21-24	8
25-28	9
29-30	10

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 30 independent Bernoulli trials, each with a true certain 30-day mortality, and compared these outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies using the above stopping rule. The following table summarizes the performance of this stopping rule:

True 30-day mortality rate	10%	15%	20%	25%	30%	35%	40%
Proportion of Stopped Studies (%)	1.6%	6.9%	18.9%	38.3%	60.5%	78.5%	90.5%
Average number of subjects	29.6	28.7	26.7	23.6	19.7	16	12.7
Average number of 30-day mortality	3	4.3	5.3	5.9	5.9	5.6	5.1

These simulation results suggest that our stopping rule has a low probability stopping a study when the true 30-day mortality rate is 20% or less, and the probability of stopping a study is high when the true 30-day mortality rate exceeds 20%. There, we believe that our Bayesian stopping rule for 30-day mortality has satisfactory statistical properties.

10.4 Off study criteria

- Completion of the 12-month follow-up
- The subject voluntarily withdraws
- Significant subject non-compliance with follow-up visits
- Death

11.0 ADVERSE EVENT REPORTING

11.1 Definitions

Adverse events: Any untoward medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

This will include:

- Expected events related to the subject's disease process during active enrollment in the research protocol and do not directly result from use of the investigational device or study.
- Procedural events directly related to the cardiac catheterization procedure and recovery from the procedure and do not directly result from use of the investigational device.

Serious Adverse Event (SAE): A serious adverse event that results in any of the following and NOT directly related to the device. This includes any event that

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurs);
- results in in-patient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity;
- results in a congenital anomaly/birth defect (not relevant to this study); or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Adverse Device Effect (ADE): Any untoward or unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device or any event that is a result of user error.

During this clinical investigation, an event should be considered related to the device when it is the result of:

- BASILICA procedure
- Asahi-Intecc *Astato XS 20* guidewire

An event will be considered NOT related to the BASILICA procedure when it is the result of:

- A pre-existing medical condition
- Clearly attributable to TAVR but not BASILICA part of procedure (example: apical left ventricular perforation)

Anticipated Adverse Device Effects (ADEs): An ADE is an adverse event with a reasonable possibility that the device or procedure caused or contributed to the event. The following ADEs are considered anticipated based on previous human experience:

- BASILICA device procedure failure including failure to traverse, to lacerate, or to position catheters or guidewires
- BASILICA device mechanical failure including wire fracture, including causing embolization requiring retrieval

- Embolization of air, valve debris, atheroma, or thrombus to coronaries, brain, limbs, or viscera causing myocardial infarction, stroke, or limb ischemia
- Mitral valve injury such as chordal disruption causing deterioration in mitral valve function
- Hemodynamic instability during BASILICA caused by traction on the aortic valve leaflets, or after BASILICA caused by acute or acute-on-chronic aortic valve regurgitation
- Electrical coupling of traversal or laceration system and other conductive structures such as THV guidewire
- Other mechanical device failure
- Allergic reaction to anesthesia, contrast media, or device materials
- Valve malposition, reposition, dislocation, migration, or embolization or deployment in unintended location
- Prosthetic valve dysfunction, including stenosis, regurgitation and patient-prosthesis mismatch, causing symptoms or requiring unplanned re-intervention
- Transcameral shunt, for example, from aorta to left atrium
- Coronary artery injury
- Atrial-ventricular conduction defects to include bundle branch block and complete heart block requiring placement of a temporary or permanent pacemaker
- Cardiac arrhythmia including ventricular fibrillation
- Transient myocardial dysfunction attributed to rapid ventricular pacing required for aortic valve implantation, including brady-asystole or pulseless electrical activity, or requiring cardiopulmonary resuscitation
- Angina and myocardial ischemia or myocardial infarction
- Coronary artery obstruction or injury that may require intervention, which may represent a failure of BASILICA
- Congestive heart failure, elevated natriuretic peptides, or cardiogenic shock that may require intervention
- Infective endocarditis or other infective complications of TAVR
- Infection or sepsis including access sites, lung, urinary tract, or other system infection related to procedure or its complications
- Left ventricular, ventricular septal, or left atrial perforation or pseudoaneurysm
- Pericardial effusion or tamponade
- Hypertension
- Hypotension requiring fluid resuscitation, vasopressor support or mechanical circulatory support or chest compressions
- Stroke, transient ischemic attacks, or seizure
- Hemolysis (defined as anemia requiring transfusion with significant or dramatic schizocytes on peripheral blood examination and depressed haptoglobin)
- Low platelets or thrombocytopenia
- Mechanical injury to the myocardium, access vasculature, cardiac valves that may require intervention
- Bleeding leading to anemia and blood transfusions
- Aortic valve thrombosis
- Retroperitoneal bleed, hematoma, fistula, or other access site injury
- Contrast-induced nephropathy requiring temporary or permanent hemodialysis or medical treatment
- Volume overload, pleural effusion, or dyspnea from procedure-related volume perturbations
- Respiratory insufficiency failure requiring oxygen therapy, mechanical support or mechanical ventilation

- Pain including back pain, access site pain, and generalized pain
- Mechanical circulatory support including emergency cardiopulmonary bypass
- Emergency cardiac surgery
- Cardiac arrest
- Death

Serious Adverse Device Effect (SADE): An adverse effect that may have been or is attributed to the use of the device and produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not 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 (21 CFR 812.3(s)).

Unanticipated Problem (UP): An unanticipated problem is any incident, experience, or outcome that meets ALL of the following criteria:

- Unexpected in terms of nature, severity, or frequency in relation to:

a. the research risks that are described in the IRB-approved research protocol and informed consent document, Investigator's Brochure or other study documents, and

b. the characteristics of the subject population being studied, and

- Related or possibly related to participation in the research, and
- Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Protocol Deviation: A protocol deviation is any change, divergence, or departure from the study design or procedures of an IRB-approved research protocol.

Non-Compliance

Non-compliance is defined as failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

Non-compliance may be further characterized as:

1. Serious non-compliance: Non-compliance that:
    a. Increases risks, or causes harm, to participants.
    b. Decreases potential benefits to participants.
    c. Compromises the integrity of the NIH HRPP.
    d. Invalidates the study data.
2. Continuing non-compliance: Non-compliance that is recurring.
3. Minor (non-serious) non-compliance: Non-compliance that is neither serious nor continuing.

11.2 Adverse event management:

The following adverse event management guidelines are intended to ensure the safety of each subject while on the study. Adverse events and adverse device effects will be attributed to study procedure and graded by severity according to the following tables:

11.2.1 Grading of adverse events and adverse device effects

Category	Description
Mild	Awareness of symptom. Not expected to have a clinically significant effect on the subject's condition. Not surpassing the expected standard medical intervention.
Moderate	Condition creates a level of discomfort that interferes with the subject's usual activity or affects clinical status. May require medical intervention.
Severe	Incapacitating and significantly affects the subject's clinical status. Likely requires medical intervention and prolonged hospitalization.

11.2.2 Attribution of adverse events to the research protocol

The relatedness of adverse events will be classified as:

Classification	Description
Definite	The event is clearly related to the research protocol.
Probable	The event is likely related to the research protocol. The event has a reasonable temporal relationship to the research device or research procedure and alternative causes, such as underlying disease, concomitant medications, or concomitant treatment-can be excluded.
Possible	The event may be related to the research protocol. The event has a reasonable temporal relationship to the research device or research procedure, and attribution of the event to the device or procedure cannot be excluded. However, alternative causes—such as underlying disease, concomitant medications, or concomitant treatments—are presumably responsible.
Unlikely	It is doubtful the event is related to the research protocol. The event can reasonably be explained by other factures, including underlying disease, concomitant medications, or concomitant treatments.
Unrelated	The event is clearly not related to the research protocol. There either is no temporal association with the research device or procedure, or the event is readily explained by other factures, including underlying disease, concomitant medications, or concomitant treatments.

11.2.3 Adverse Event Reporting

Adverse event recording will start on Day (0) of the BASILICA TAVR procedure and will continue through the 12 month Follow Up. New events or conditions present at baseline that increase in severity will be recorded and evaluated and reported on the case report form. Once the subject has completed the 30 day follow up, only serious adverse events (SAE), serious adverse device effects (SADE), unanticipated device effects (UADE) and unanticipated problems (UP) will be reported to the Sponsor. It is the responsibility of the site investigator to report adverse events and adverse device effects to their respective IRBs or other regulatory bodies according to their reporting requirements. Monitoring visits will be conducted by the Sponsor to review source documentation, and accuracy and completion of the adverse event case report forms.

11.2.4 Adverse event reporting timeframes:

Serious Adverse Events (SAEs)

- All serious adverse events will be reported to the Sponsor immediately but not later than 3 working days from the event. The respective institutional IRB should be notified according to their requirements.
- The serious adverse event will be evaluated by the sponsor. If determined to be an unanticipated adverse device effect that increases the risk to the participating subjects, the sponsor will terminate the investigation within 5 days after making the determination, and not later than 15 working days after the sponsor was first notified of the event. [21 CFR 812.46]

Unanticipated Adverse Device Effects (UADE)

- Must be reported to the Sponsor and the institutional IRB immediately but no later than 10 working days after the investigator learns of the event. [21 CFR 812.150]
- Unanticipated Adverse Device Effects should be reported via telephone as well as on the adverse event section of the case report form.
- If the event is determined by the Sponsor to be a UADE, the Sponsor will report the event to all investigators to enable reporting to their respective IRB/regulatory bodies. The Sponsor will provide this notification to participating sites and to the FDA within 10 working days after they first receive notice of the effect. [21 CFR 812.150]
- All Unanticipated Adverse Device Effects will be reported by the Sponsor to the NHLBI IRB immediately upon notification but no later than 10 working days.

Deaths

- The investigator will notify the Sponsor immediately but within 3 working days of notification of a subject's death, whether the death is device related or clinical condition. Institutional IRB's will be notified according to the specific institutional regulatory requirements for reporting a death.
- The Sponsor will notify the NHLBI IRB of a subject's death within 7 days.
- A subject's death will be recorded on the Case Report Form.

12.0 HUMAN SUBJECT PROTECTION

12.1 Rationale for Subject Selection

12.1.1 Study population:

Subjects are selected for being adults who are determined otherwise likely to benefit from transcatheter aortic valve replacement yet are expected to suffer TAVR-related left coronary artery obstruction. The determination will be made by the local institutional multidisciplinary heart team. No patient will be excluded from participation based on gender, race or ethnicity.

Subjects who are unable to provide consent may be enrolled, if allowed by participating IRBs.

12.2 Risks and Discomforts

A formal risk analysis is provided in APPENDIX A.

Risks of TAVR will be considered separately from the risks of preparatory BASILICA before TAVR. Known risks of TAVR, which is a clinical procedure using approved medical devices as intended, include:

- Death
- Stroke/transient ischemic attack, clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- AV fistula or pseudoaneurysm
- Reoperation
- Ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia
- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope

- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever
- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Rotational mal-orientation of Sapien 3 THV such that commissural post obstructs coronary ostium despite successful BASILICA

Anticipated risks of preparatory BASILICA before TAVR include:

- Death
- Embolization of air, valve debris, atheroma, or thrombus to coronaries, brain, limbs, or viscera causing myocardial infarction, stroke, or limb ischemia
- Severe aortic regurgitation after laceration before TAVI, causing hypotension or cardiogenic shock including requiring cardiopulmonary resuscitation, chest compressions, vasoactive medications, and/or mechanical circulatory support
- Avulsion or other injury of the native or prosthetic aortic valve leaflet
- Inadvertent injury of the mitral valve apparatus
- Traversal into the left atrium or other non-target chamber
- Pericardial effusion or tamponade requiring drainage
- Electrical coupling of traversal guidewire and bioprosthetic valve frame
- Native coronary artery ostial injury from electrosurgery or BASILICA guide catheter mechanical disruption
- Vascular access site injury
- Hemolysis related to blood flow around the lacerated aortic leaflets
- Acute kidney injury related to BASILICA and to follow-up CT examination

The sponsor and investigators recognize these risks are high and reflect the underlying comorbidities, yet consider procedural hemorrhage overall to be an acceptable compromise to enable treatment of the underlying mitral valve failure in patients otherwise ineligible.

12.2.1 Risks Related to Radiation

In this research protocol, subjects will be exposed to radiation from 2 CT scans. The CT scans are performed for research surveillance of transcatheter heart valve dysfunction. It is estimated that the amount of research radiation that a subject will be exposed to during participation in this research protocol will be approximately 3-4 REM from the CT scans, and 72mSv[9] from approximately 60-100 minutes of research fluoroscopy during performance of BASILICA and TAVR. This is equivalent to 740 chest X-rays. We believe the total fluoroscopy exposure to be justifiable in this setting, given the seriousness of their cardiovascular disease and limited options. We estimate the benefit to the research subjects for these procedures to outweigh the risks.

12.2.2 Data collection from patients who have undergone BASILICA at participating sites before this protocol begins enrollment

As of the time of submission of this protocol for review, 3 patients are known to have undergone standalone TAVR with BASILICA. We wish to aggregate all available follow-up data on these patients to the extent possible, including patients who have died during the follow-up period. This number of patients analyzed retrospectively will not count against ("reduce") the number of prospectively enrolled patients.

Subjects must have undergone BASILICA TAVR before enrollment begins in this protocol, which is expected October 2017. Retrospective findings will be analyzed separately from the subjects in the main (prospective) investigational IDE arm.

12.2.3 Personal Identifiable Information

Clinical data from subjects participating in this trial will retain personally identifiable information. This includes CT scans, echocardiograms, and medical records.

Abstracted data will be coded and de-identified for transmission to participating subcontracting investigators, such as core imaging laboratories, clinical events adjudication committee, and statistician.

DICOM data will be stored in a secured NIH research PACS system for analysis, including personally identifiable information.

13.0 TEST ARTICLE

13.1 Asahi-Intecc Astato XS 20, 510(k) K103057

13.1.1 Indications For Use

The Astato 0.014" guidewire is used for transcatheter electrosurgery in two steps in this procedure. First it is used for leaflet traversal during electrification. This procedure is similar to the use of the Astato XS20 and an amputated Asahi Confienza Pro 12 in the transcaval IDE investigation recently published [10].

Second, the midshaft is focally denuded and electrified for the leaflet traversal step. This is described in the pre-clinical [5] and early clinical [6] LAMPOON manuscripts.

Neither of these procedures are addressed in the indications for use:

Asahi-Intec Astato XS 20: This product is intended to facilitate the placement and exchange of diagnostic and therapeutic devices during intravascular procedures. This device is intended for peripheral vascular use only.

13.1.2 In vitro testing of bedside modification

We performed a benchtop investigation of the tensile strength implications of intended ("conventional") and unintended ("undesirable") bedside modification of the Astato guidewire shaft. Using the available testing equipment, the BASILICA modification of the Astato guidewire left a fracture force exceeding 75N in all tests, compared with the ISO 11070-2014, part 8.6 limit (which is 5N) by over tenfold. See Appendix B. We believe this demonstrates the safety of the guidewire modification when following the prescribed technique.

14.0 INVESTIGATOR ADMINISTRATIVE REQUIREMENTS

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) E6 (Guideline for Good Clinical Practice), Title 21 of the Code of Federal Regulations, Parts 50 (Protection of Human Subjects), and 56 (Institutional Review Boards), and other appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the BASILICA TAVR technique as described in the protocol and the Investigational plan. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Regulatory files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 IRB Submissions

The IRB/IEC and other appropriate institutional regulatory bodies will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC and other appropriate institutional regulatory body approval have been obtained. The protocol, informed consent, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC and other appropriate institutional regulatory bodies by the Investigator.

14.3 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or his/her legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

Subjects who are unable to provide consent may be enrolled, if allowed by participating IRBs. Consent for these subjects must be obtained from a legally authorized representative. The process for obtaining this consent must conform to local human subjects protection policies and to state laws.

Waiver of consent is requested to collect de-identified clinical data into a retrospective registry arm of patients treated before IDE enrollment begins nationwide, on the grounds that the retrospective collection of de-identified clinical data imparts no increase over minimal risk and that informed consent is impractical in this population of extremely ill and elderly patients, many of whom have poor survival despite TAVI, and many of whom have severe disability.

14.4 Subject Confidentiality

In order to maintain subject privacy, all CRFs, accountability records, study reports, and communications will identify the subject by initials and the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority (ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.5 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor, and given approval/favorable opinion by the IRB/IEC and other appropriate institutional regulatory bodies. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC and other appropriate institutional regulatory body approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC and other appropriate institutional regulatory bodies. The Sponsor will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the CRF and source documentation.

14.6 Direct Access to Source Data

Monitoring and auditing procedures developed by the Sponsor will be followed, in order to comply with GCP guidelines.

Regulatory authorities, the IRB/IEC and other appropriate institutional regulatory bodies, and/or the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

14.7 Case Report Form Completion

CRFs will be completed for each study subject. It is the Principal Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Principal Investigator or designated representative, should complete the CRF screens as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure but no more than 5 days post procedure. An explanation should be given for all missing data.

The Principal Investigator must sign and date the Investigator's Statement at the end of the CRF to endorse the recorded data.

14.8 Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years following marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

The Sponsor has full rights over any invention, discovery, or innovation, patentable or not, that may occur when performing the study.

14.9 Publication and Presentation of Study Findings and Use of Information

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee comprised of Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee the publication and presentation of the study results, which will reflect the experience of all participating clinical sites. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Sponsor and the investigator and/or the investigator's institution.

14.10 Study Eligibility Committee

Clinical data for all research candidates are confirmed by the study eligibility committee before enrollment.

The study eligibility committee consists of the NHLBI investigators and the local site principal investigators. A quorum of the committee requires a local site investigator where the candidate is not to be enrolled, as well as at least two NHLBI investigators.

15.0 SPONSOR REGULATORY REQUIREMENTS

15.1 Role of Sponsor

As the study sponsor of this clinical study, Dr. Robert Lederman has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies.

15.2 General Duties

The Sponsor's general duties consist of submitting the appropriate regulatory applications, selecting investigators, obtaining their signed agreement, providing them with the information necessary to conduct the study, ensuring proper clinical site monitoring, and ensuring study subject informed consent is obtained.

15.3 Monitoring

The study will be monitored by the Sponsor designee, an independent contract research organization. Monitoring will be done by personal visits and will include on-site review of the informed consent documents and case report forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a

manner to ensure that subject confidentiality is maintained. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, e-mail, telephone, and fax).

15.4 Site Selection and Training

The sponsor or its designee (national co-principal investigator) will ensure appropriate training in the technique of caval-aortic access prior to enrollment at any participating institution.

15.4.1 Site selection:

Site selection will be based on

1. Physician expression of interest and need to apply this treatment approach to patients at the site.
2. Physician prior experience performing or proctoring 10 transcaval TAVR procedures to assure competence in transcatheter electrosurgery. Preference given to sites with prior experience with LAMPOON TMVR experience.
3. Site prior participation in IDE protocols evaluating a treatment of structural heart disease
4. Site ability to obtain CT examinations that are satisfactory for consideration of BASILICA TAVR.
5. Site investigators willing and able to comply with the requirements of this protocol.

A waiver for criterion 2 is specifically applied to Site #1, which was the first to perform BASILICA TAVR in patients. To compensate for limited transcaval experience, every research BASILICA procedure will be proctored by experienced transcaval operators until the criterion is met.

15.4.2 Site training:

Site training will consist of

- Principal investigator and/or sponsor didactic training about the technique, preclinical, and clinical experience to date.
- Proctored conduct of BASILICA TAVR procedures in patients at the local site, at the sole discretion of the Sponsor and/or Principal Investigator.
- Completion of training, and suitability for independent BASILICA TAVR enrollment, will be certified by the Principal Investigator and with the concurrence of the Sponsor.

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APPENDIX A: Risk Analysis

This is a patient-centered risk analysis[11] in accordance with 21 CFR 812.25(c). It considers probable and not possible risk. This risk analysis applies to candidates for TAVR with BASILICA, who have a fatal disease with few or no therapeutic options.

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
BASILICA	Insufficiently basal leaflet laceration	Failure to spare coronary ostium	4	2	8	Inadequate leaflet splaying causing inadequate coronary artery protection from bioprosthetic leaflet	Standard coronary artery protection, bailout Impella
	Mitral chordal laceration	Mitral valve regurgitation	4	2	8	Mitral valve regurgitation	Snare in LVOT, assess for chordal entrapment by TEE before laceration
	Traversal into left atrium	Puncture of aortic sinus or aorto-mitral curtain	2	3	6	Guidewire traversal into LA is probably clinically inconsequential; Requires withdrawal and repeat traversal	Guidewire positioning relative to bioprosthetic valve frame; CT-derived landmarks; Inability to snare if LA position; May require repeat traversal; Low energy and short burns to minimize collateral RF damage
	Rotational mal-orientation of Sapien 3 THV such that commissural post obstructs coronary ostium despite successful BASILICA	Failure to spare coronary ostium	4	3	12	Coronary obstruction by THV commissural posts subverts the objective of BASILICA which is to prevent coronary obstruction	Attempt rotational alignment with greature curvature of S3 THV delivery system; Model alignment on 3D-printed aorta; Use concomittant standard coronary stent protection methods
	Severe aortic regurgitation after laceration before TAVI	Cardiogenic shock	3	3	9	Hypoperfusion; accelerated TAVI implantation	Preposition TAVI Pigtail or THV; Tachypacing; Mechanical support devices as needed
	Electrical coupling of laceration system and THV guidewire	Likely dissipation of current. Possible endocardial injury.	2	1	2	Failed electrosurgery, or inadvertent electrosurgery via TAVI guidewire causing LV endocardial injury and failed laceration	THV Pigtail in LV during laceration to avoid electrical coupling

KEY LEVEL	**1**	**2**	**3**	**4**	**5**
Probability	Rare	Uncommon	Common	Normal	
Severity	Easy to correct, no anticipated harm to patient	Difficult to correct, no anticipated harm to patient	Potentially harmful to patient	Likely harmful, even with immediate correction	Life threatening
Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Tolerable but undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	Electrical coupling of traversal guidewire and bioprosthetic valve frame	Likely dissipation of current. Possible endocardial injury.	2	1	2	Failed electrosurgery, or inadvertent heating of surgical bioprosthetic valve frame	Direct traversal wire away from valve frame; Surrounding fibrotic tissue makes this interaction unlikely
	Native coronary artery ostial injury from electrosurgery or BASILICA guide catheter mechanical disruption	Left main coronary artery disruption	4	2	8	Require PCI with late sequelae	Left main coronary stent using bailout devices already in place
Electrosurgery	Ventricular fibrillation	Life-threatening but reversible	4	1	4	VF from electrosurgical stimulation of LVOT after successful bioprosthetic leaflet traversal	Prevent: Short bursts; Survey: Continuous ECG monitoring; Treat: Defibrillation and antiarrhythmics as needed.
	Difficult laceration	Potential procedure failure	2	2	4	Procedure failure precluding purported benefit of BASILICA	Focal denudation of guidewire; Focal kink of guidewire; Focus charge using Piggyback insulation; Focus charge using non-conductive dextrose injection during electrosurgery
	Thromboembolism	Electrosurgery may cause intravascular coagulation and char	2	1	2	Thromboembolism including stroke	Prevent: Anticoagulation; limit electrosurgery duration and energy; Consider analogy to LV endocardial radiofrequency ablation for EP
Percutaneous procedures	Vascular access site injury	Additional arterial access for BASILICA (two sheaths)	2	3	6	Vascular access site injury	Ipsilateral access for two BASILICA sheaths to avert carina injury

KEY LEVEL	**1**	**2**	**3**	**4**	**5**
Probability	Rare	Uncommon	Common	Normal	
Severity	Easy to correct, no anticipated harm to patient	Difficult to correct, no anticipated harm to patient	Potentially harmful to patient	Likely harmful, even with immediate correction	Life threatening
Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Tolerable but undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	ATN from procedural contrast and from follow-up contrast CT	Temporary or permanent hemodialysis	3	2	6	Temporary or permanent hemodialysis	Minimize contrast exposure. Request low-energy and low-contrast time-resolved CT to minimize contrast. Follow operator discretion about timing of contrast exposure

KEY LEVEL	**1**	**2**	**3**	**4**	**5**
Probability	Rare	Uncommon	Common	Normal	
Severity	Easy to correct, no anticipated harm to patient	Difficult to correct, no anticipated harm to patient	Potentially harmful to patient	Likely harmful, even with immediate correction	Life threatening
Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Tolerable but undesirable	Intolerable	

APPENDIX B: Tensile strength implications of bedside modification of Astato XS 20 guidewire

See attachment.