Novel transcatheter electrosurgical laceration of heart valve leaflets to prevent blood flow obstruction from transcatheter heart valve implantation

Khan, Jaffar

Awarding institution:
King's College London

Novel transcatheter electrosurgical laceration of heart valve leaflets to prevent blood flow obstruction from transcatheter heart valve implantation

A thesis submitted for the degree of Doctor of Philosophy

JAFFAR M. KHAN

BA Hons. MA Cantab. BM BCH MRCP (UK)

CARDIOVASCULAR INTERVENTIONAL PROGRAM, NATIONAL HEART LUNG AND BLOOD INSTITUTE, NATIONAL INSTITUTES OF HEALTH

CARDIOVASCULAR DIVISION, RAYNE INSTITUTE, KINGS COLLEGE LONDON

ABSTRACT

Transcatheter intervention for cardiac valve disease is an attractive alternative to open-heart surgery, avoiding a thoracotomy and cardiopulmonary bypass, and associated morbidity. A limitation of transcatheter intervention is the inability to cut tissue – the hallmark of surgery, and what makes it so versatile. During transcatheter valve implantation, native diseased valve tissue is displaced rather than resected. However, this displacement can occasionally cause fatal complications. In transcatheter mitral valve implantation, septal displacement of the anterior mitral valve leaflet can obstruct the left ventricular outflow tract. In transcatheter aortic valve implantation, displacement of the left or right coronary cusps may obstruct the flow to the coronary arteries.

This thesis explores the use of radiofrequency energy delivered through guidewires directed by catheters to enable closed-chest beating-heart valve leaflet laceration using marketed devices. We call this technique transcatheter electrosurgery. Two entirely novel procedures are developed that use transcatheter electrosurgery techniques to cut valve tissue prior to transcatheter valve implantation: LAMPOON (Laceration of the Anterior Mitral leaflet to Prevent left ventricular Outflow ObstructioN); and BASILICA (Bioprosthetic and native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction). Benchtop experiments, pre-clinical procedure development in swine, first-in-human “compassionate use” experience, and early feasibility clinical trials are described for each procedure.

STATEMENT OF ORIGINALITY

I declare that the work presented in this thesis was primarily carried out by me. My colleagues and I conceived the idea of the LAMPOON and BASILICA procedures. I personally devised the specific procedure steps, inventory and techniques. I performed all pre-clinical experiments, both benchtop and in swine. I planned and proctored all the first-in-human cases and participated as an operator in most. I was the lead clinical investigator and on the steering committee and for both the NHLBI LAMPOON trial and NHLBI BASILICA trial. RJL and I designed both trials, drafted the trial protocols, and drafted the case report forms.

I analysed the data presented here and prepared the enclosed manuscripts and figures. I personally consulted all the quoted references.

This thesis is submitted as a 'thesis incorporating publication' in accordance with the King's college guidelines. Permission to include reproduction of published manuscripts was granted by the publishers in accordance with United States Federal government work. I declare that this thesis has not been submitted elsewhere for a higher degree.

ACKNOWLEDGEMENTS

Thank you to Robert Lederman, who provided me with superb mentorship and enabled me to pursue this research with gusto. He created an environment of creativity and productivity at the NIH and established crucial clinical links to translate our pre-clinical work into patients. Thank you to Toby Rogers, who showed me the ropes at NIH and has been a constant source of guidance both clinically and academically. Thank you to Adam Greenbaum and Vasilis Babaliaros for their enthusiasm, creative drive, and for taking these procedures forward into patients who needed them. I am incredibly fortunate to be part of this inspirational and supportive team that has become my cardiology family. Thank you to Simon Redwood, Bernard Prendergast and Mike Marber for supporting me throughout my research degree. Thank you to the exceptional team at the cardiac interventional program at the NIH, and the catheter laboratory teams at Emory University and Henry Ford Hospitals. Thank you to Katrina, my wife, for her uplifting support. Finally, thank you to the patients that took part in this research.

Table of Contents

List of Figures

List of Videos

List of Tables

CHAPTER 1. THESIS OVERVIEW

This thesis is submitted as a 'thesis incorporating publication', in accordance with Kings College guidelines.

Summary of Chapters

This thesis explores the concept and background of transcatheter electrosurgery and describes two novel percutaneous cardiovascular interventions for valve disease from concept, to animal experiments, to first-in-human, to early feasibility prospective clinical trial.

Chapter 1 provides an overview and specific aims of this thesis.

Chapter 2 provides an overview of transcatheter electrosurgery with a literature review of current applications. Benchtop and simulation experiments exploring the technique are described.

Chapter 3 describes LAMPOON, a technique to lacerate the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve implantation. The chapter describes pre-clinical animal experiments, first-in-human findings, and the early feasibility clinical trial.

Chapter 4 describes BASILICA, a technique to lacerate the aortic valve leaflets to prevent coronary artery obstruction during transcatheter aortic valve implantation. The chapter describes benchtop and animal experiments, first-in-human findings, and the early feasibility clinical trial.

Chapter 5 explores future directions using this novel technology.

Chapter 6 concludes the thesis.

Background and Significance

Heart valve disease is a leading global health problem. The prevalence increases with age and, with an ageing population, the disease burden is increasing. Of people over the age of 75, 4.8% have moderate or severe aortic valve disease and 9.5% have moderate or severe mitral valve disease (1). Patients with heart valve disease suffer reduced functional capacity and increased mortality. Many are too frail to undergo open-heart surgery. Transcatheter valve implantation is a life-saving treatment for these people. Large multicentre randomized trials have demonstrated that transcatheter aortic valve implantation (TAVI) is comparable to or better than surgical valve replacement in patients at all levels of surgical risk(2-7). Transcatheter mitral valve implantation (TMVI) is significantly more challenging, as the mitral valve is a more complex structure in its shape, dynamic nature, and in its integral role as part of the left ventricle. Several devices are in early investigation(8).

The problem: During surgical valve replacement, the patient's existing valve is cut out and a new one sewn in. Transcatheter valves are implanted inside the patient's existing heart valve, displacing the failing valve leaflets. Occasionally, this displacement may fatally obstruct blood flow. This catastrophic complication is screened for during pre-procedure CT-image planning and patients at risk are excluded from treatment. For TMVI, over 40% of screened patients are excluded because of the risk of the displaced anterior mitral valve leaflet obstructing the left ventricular outflow tract (LVOT)(9). The incidence of LVOT obstruction after TMVI is 11%, with an 62% 30-day mortality(10). In TAVI, bulky aortic leaflets near the coronary ostia is an exclusion criterion for treatment. Fewer than 1% of all cases suffer coronary artery obstruction after TAVR, but with close to 50% mortality(11,12).

Scientific premise and rationale: The pathophysiology of obstruction in both TAVI and TMVI is the displaced native leaflet. There is currently no transcatheter technique or device that can resect existing valve leaflets. Electrosurgery is a technique used to cut or coagulate tissue using radiofrequency current through a blunt conducting implement. Interventional cardiologists have used this principle to direct current to the tip of a guidewire to cross blockages in vessels, between chambers of the heart, or between blood vessels(13-15). We propose to use radiofrequency energy to make a controlled cut in valve tissue, and thereby to prevent blood flow obstruction following TMVI and TAVI.

Limitations: Prevention relies on accurate prediction of obstruction, and there are limitations to the current prediction models for LVOT obstruction with TMVI (16) and coronary artery obstruction with TAVI (11).

Specific Aims

The proposed solution: Transcatheter resection of mitral and aortic leaflets may enable safe valve implantation and so increase the number of patients who can access this life-saving treatment. Transcatheter electrosurgery techniques, deploying electrical current directed through catheters and guidewires, have previously been limited to crossing lesions, occlusions or vessel walls. We propose that by simple modification of transcatheter electrosurgery techniques, a linear laceration can be achieved.

I hypothesize that the mitral and aortic valve leaflets can be precisely lacerated using transcatheter electrosurgery. I hypothesize that this controlled laceration will prevent blood flow obstruction following transcatheter valve implantation. My specific aims are to:

1. Determine if transcatheter laceration of the mitral valve leaflet prevents left ventricular outflow tract obstruction following TMVI

1A) We will develop a transcatheter procedure in anesthetized pigs to precisely lacerate the anterior mitral valve leaflet in line with the LVOT; and

1B) We will conduct an early feasibility phase 1 study of the procedure in 30 human subjects predicted on CT imaging to be at prohibitive risk of LVOT obstruction from TMVI and therefore excluded from available treatment.

2. Determine if transcatheter laceration of the aortic valve leaflets can prevent coronary artery obstruction following TAVI

2A) We will develop a transcatheter procedure in anesthetized pigs to precisely lacerate the left and right coronary cusps in line with the coronary arteries; and

2B) We will conduct an early feasibility phase 1 study of the procedure in 30 human subjects predicted on CT imaging to be at prohibitive risk of coronary artery obstruction from TAVI and therefore excluded from available treatment.

If positive, these studies will give patients currently ineligible for transcatheter valve implantation an option for treatment. These studies may trigger larger trials, potentially with dedicated devices. The ability to cut cardiac tissue in a closed chest and with a beating heart may allow other patient-specific interventional therapies in the future.

Research Design and Methods

AIM 1

To determine if transcatheter electrosurgical laceration of the anterior mitral valve leaflet prevents left ventricular outflow tract obstruction following TMVI, we will develop a novel procedure in animals and assess the impact on LVOT geometry. If successful, we will conduct a phase 1 early feasibility trial in patients.

Laceration of the anterior mitral leaflet to prevent outflow obstruction (LAMPOON) – developing a novel procedure

Procedures will be performed in anesthetized naïve pigs and guided by biplane X-ray fluoroscopy and intracardiac echocardiography, an established model for percutaneous cardiac structural intervention. A reproducible technique will be developed using transcatheter electrosurgery to cut the anterior mitral leaflet and create enough room in the LVOT for blood flow following TMVI.

Phase 1 clinical trial

The LAMPOON IDE trial will enroll patients with severe mitral valve disease and high risk of mortality with surgery and prohibitive risk of LVOT obstruction with TMVI. We aim to enroll 30 patients, typical in similar early device studies, with the primary endpoint assessed at 30 days.

AIM 2

To determine if transcatheter electrosurgical laceration of the aortic valve leaflets prevents coronary artery obstruction following TAVI, we will develop a novel procedure in animals and assess the impact on aortic leaflet geometry. If successful, we will conduct a phase 1 early feasibility trial in patients.

Bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction (BASILICA) – developing a novel procedure

Procedures will be performed in anesthetized naïve pigs and guided by biplane X-ray fluoroscopy and intracardiac echocardiography, an established model for percutaneous cardiac structural intervention. A reproducible technique will be developed using transcatheter electrosurgery to cut the left and right coronary cusps to create enough room for blood flow into the coronary arteries following TAVI.

Phase 1 clinical trial

The BASILICA IDE trial will enroll patients with severe aortic valve disease and high risk of mortality with surgery and high risk of coronary artery obstruction with TAVI. We aim to enroll

30 patients, typical in similar early device studies, with the primary endpoints assessed at 30 days.

References

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.
2. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
3. 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.
4. Adams DH, Popma JJ, Reardon MJ et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
5. Reardon MJ, Van Mieghem NM, Popma JJ et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2017;376:1321-1331.
6. Regueiro A, Granada JF, Dagenais F, Rodes-Cabau J. Transcatheter Mitral Valve Replacement: Insights From Early Clinical Experience and Future Challenges. J Am Coll Cardiol 2017;69:2175-2192.
7. Guerrero M, Urena M, Himbert D et al. 1-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Severe Mitral Annular Calcification. J Am Coll Cardiol 2018;71:1841-1853.
8. Ribeiro HB, Rodes-Cabau J, Blanke P et al. Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. Eur Heart J 2018;39:687-695.
9. Ribeiro HB, Webb JG, Makkar RR et al. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. J Am Coll Cardiol 2013;62:1552-62.
10. Greenbaum AB, Babaliaros VC, Chen MY et al. Transcaval Access and Closure for Transcatheter Aortic Valve Replacement: A Prospective Investigation. J Am Coll Cardiol 2017;69:511-521.
11. Justino H, Benson LN, Nykanen DG. Transcatheter creation of an atrial septal defect using radiofrequency perforation. Catheter Cardiovasc Interv 2001;54:83-7.

12. Nicholson W, Harvey J, Dhawan R. E-CART (ElectroCautery-Assisted Re-enTry) of an Aorto-Ostial Right Coronary Artery Chronic Total Occlusion: First-in-Man. JACC Cardiovasc Interv 2016;9:2356-2358.

13. Halabi M, Ratnayaka K, Faranesh AZ et al. Transthoracic delivery of large devices into the left ventricle through the right ventricle and interventricular septum: preclinical feasibility. J Cardiovasc Magn Reson 2013;15:10.

14. Blanke P, Naoum C, Dvir D et al. Predicting LVOT Obstruction in Transcatheter Mitral Valve Implantation: Concept of the Neo-LVOT. JACC Cardiovasc Imaging 2016:10.1016/j.jcmg.2016.01.005.

CHAPTER 2. TRANSCATHETER ELECTROSURGERY

State of the Art Review

Introduction

Transcatheter electrosurgery is a technique to traverse or cut tissue, typically within blood-filled spaces, using alternating current directed by guidewires and catheters. The technique has been applied to traverse occluded arterial and venous lesions, traverse between intact as well as atretic cardiac chambers, and, as part of the work developed in this thesis, to cut heart valve leaflets. Alternating current in the radiofrequency range (approximately 500KHz) is concentrated at the target tissue to heat and vaporize tissue, also called 'cutting' (1). Electro*surgery* should not be confused with electro*cautery*. Electro*surgery* relies on transfer of current to the target tissue where the increased current density generates heat and vaporization. Electro*cautery* relies on direct transfer of heat from a hot implement to tissue, typically to arrest bleeding. Furthermore, electrophysiological catheter ablation differs from transcatheter electrosurgery in that radiofrequency energy is used to form non-conductive lesions rather than to vaporize tissue.

Surgeons typically employ electrosurgery using an active electrode, the electrosurgery 'pencil', in a dry air-filled field and under direct operator vision. By contrast, transcatheter electrosurgery uses a long guidewire within conductive media (blood) and under fluoroscopic or echocardiographic guidance. This has important technical implications for charge concentration to achieve cutting, inadvertent charge dispersion that impedes cutting, electrode degradation through carbonization, and undesired blood coagulation.

This chapter explores the physics of transcatheter electrosurgery relevant to interventional applications. It concludes with a review of contemporary applications of the technique.

Basic physics of transcatheter electrosurgery

This section summarizes the principles of charge concentration to heat and vaporize target tissue using transcatheter tools. An understanding of these mechanisms will help enable the operator to use these techniques safely and effectively.

Tissue heating and dielectric properties

The goal of transcatheter electrosurgery is to cut tissue, whether to modify structures or allow device traversal.

Electrosurgery relies on tissue conducting alternating current between two electrodes. High frequency alternating currents (~500KHz, or 'radiofrequency') are used because they do not stimulate nerve and muscle tissue and thus avoid pain, muscle contraction, and myocardial fibrillation (2).

Current conducting through tissue causes resistive heating. Heat is generated by collision of ions and corresponds to the work done by charge carriers (ions or electrons) to travel to a lower potential. At a certain threshold, the delivered energy breaks down polar molecules (for example, water) to create mobile charge particles (for example, protons and hydroxide ions). This process, called dielectric breakdown, causes an exponential rise in ion collision and therefore in tissue heating.

The conductivity of tissue increases with its water content. Tissues with high water content include muscle, skin, kidney and liver. Tissues with intermediate water content include brain, lung and bone marrow. Tissues with low water content include fat and bone(1). Tissue permittivity and conductivity values are shown in Table 1. These values explain why calcified tissues are harder to vaporize using radiofrequency energy, as are synthetic non-conductive materials like certain sutures and graft materials.

Table 2 shows the behavior of tissues heated to different temperature thresholds at sea level (1,3). Irreversible tissue denaturization occurs at 60°C. Intracellular water boils at 100°C, causing the cells to rupture. In transcatheter electrosurgery, focal temperatures to 100°C will vaporize the tissue, effecting "cutting". Heating of adjacent tissue is generally undesirable.

Radiofrequency waveforms: cutting versus coagulation

Targeted tissue vaporization requires a rapid and focal increase in current density, and hence temperature rise. This is achieved using continuous alternating currents at high voltages over short treatment times (4). Interrupted waveforms, including all varieties of 'blended' waveforms, allow intercurrent cooling resulting in slower heating and are intended to cause coagulation (1) [Figure 1]. While coagulation may be desirable in surgical applications to stop bleeding, in the transcatheter endovascular setting blood coagulation may cause stroke and other thromboembolic events. Moreover, at slower temperature rises, tissues desiccate over wide distances, with loss of water content and reduced conductivity, making the tissue more difficult to vaporize. These properties are exploited in radiofrequency ablation for treating arrythmias(5). Steam pops, the audible sounds produced by intramyocardial tissue vaporization, are a complication of electrophysiological ablation and are avoided by controlling the temperature rise. Conversely, tissue vaporization is the goal of transcatheter electrosurgery.

Current Density

The rate of heating depends on current density in the tissue. The current density decreases exponentially with the contact area between the target tissue and the active electrode. This is the principle behind improved cutting with plasma arcs, discussed below. The current density also decreases exponentially with the distance between tissue and active electrode. This enables tissue adjacent to the active electrode to be vaporized while sparing deeper layers.

Plasma Arcs

Plasma arcs form when the medium between two electrodes ionizes due to a strong electric field. If ionized molecules bump into other molecules with enough energy, they ionize too, leading to avalanche multiplication, creating a plasma cloud. The impedance of the medium drops and current increases. Small area arcs concentrate current onto the tissue over an area a fraction of the area of the active electrode. Therefore, cutting with the electrosurgical knife in the plasma cloud at a short distance is more effective than when it touches tissue. At enough power, dramatic plasma arcs are created and

contribute to tissue vaporization. Some electrosurgery generators attempt to reduce power in response to sudden impedance drops, in order to suppress arcing.

Clinical applications

Prior to this thesis, there were two broad applications for transcatheter electrosurgery: radiofrequency perforation to recanalize occlusive lesions and radiofrequency perforation to traverse tissue between two cardiovascular chambers. Table 3 summarizes the evidence for the common clinical applications of this technology. A novel application, radiofrequency laceration to make linear cuts in tissue, will be explored in the body of this thesis.

Radiofrequency perforation to recanalize occlusive lesions

Pulmonary atresia

The first transcatheter use of radiofrequency energy was to perforate atretic pulmonary valves in patients with congenital heart disease and intact ventricular septum (6). Purpose built wires were connected to a radiofrequency generator and directed by catheters positioned below the atretic valve. The wire was electrified and advanced through the valve into the pulmonary artery and balloon dilatation performed.

Several groups have since published their experience with radiofrequency perforation and balloon dilation in pulmonary atresia demonstrating both immediate success and satisfactory long-term outcomes with and without downstream surgery (7-11). It is now an acceptable first line treatment for this uncommon application (12).

Vascular occlusion

Radiofrequency perforation using both off-the-shelf and dedicated devices (PowerWire RF, Baylis Medical Company, Burlington, MA) have been used to recanalize peripheral and central vascular occlusions following failed conventional antegrade and retrograde attempts. These include subclavian vein occlusion (4,13), non-malignant superior vena cava obstruction(14), occlusions of the anterior and posterior tibial arteries, common iliac vein, and superior vena cava (11), acquired chronic total occlusion of the left

pulmonary artery (15), acquired right pulmonary artery atresia (16), interrupted aortic coarctation (17), and re-entry for ostial right coronary artery chronic total occlusion (18). Transcatheter electrosurgery has been used to successfully restore flow following iatrogenic occlusion of the right pulmonary artery, by bioprosthetic bovine jugular vein material, after transcatheter pulmonary valve replacement with a Melody valve (Medtronic, Minneapolis, MN) (21).

The Safe Cross radiofrequency guidewire (DSM, Heerleen, Netherlands) combined optical coherence reflectometry and radiofrequency energy to tackle chronic totally occluded coronary lesions(19) and the PlasmaWire (RetroVascular, Asahi Intecc, Japan) uses bipolar radiofrequency guidewires either side of chronic totally occluded arteries(20). The former is no longer marketed, and the latter is not yet marketed.

Radiofrequency perforation of tissue planes between cardiovascular chambers

Atrial septal puncture

Atrial septal perforation using radiofrequency energy has been performed through a coaxial injectable catheter and radiofrequency wire (Nykanen Radiofrequency Perforation Catheter, Baylis Medical Company) (22). A randomized control trial comparing radiofrequency and needle transseptal access found reduced procedure time, reduced procedure failure, and reduced plastic particulate matter with the radiofrequency system (NRG Transseptal needle, Baylis) (23).

Atrial septal radiofrequency assisted perforation has been performed in newborns with hypoplastic left heart syndrome (24). Atrial septal puncture has also been achieved by electrifying a Brockenbrough needle (25-27), or a coronary guidewire advanced through a transseptal dilator and sheath (28).

Ventricular septal puncture

The ventricular septum has been perforated using radiofrequency energy to create a ventricular septal defect in a patient with double outflow right ventricle and restrictive ventricular septal defect (29). Radiofrequency perforation was used to access the left ventricular endocardium for a ventricular tachycardia ablation in a patient with

mechanical aortic and mitral valves (30). It has also been used to position an endocardial left ventricular lead for cardiac resynchronization therapy (31,32).

Transcatheter electrosurgery and valve repair

Pledget-assisted suture tricuspid annuloplasty (PASTA) uses off-the-shelf guidewires to traverse myocardial and annular tissue, and then exchange these guidewires for suture to effect transcatheter tricuspid annuloplasty resulting in a double orifice valve(33). The annulus is traversed with electrified guidewires at target sites on the septal and anterior wall. The guidewires are exchanged for sutures that are then plicated to create a double orifice valve. PASTA is especially interesting because suture exchange for electrified guidewires is an early step towards transcatheter surgery with suture delivery.

The Mitralign system (Mitralign Inc, Tewksbury, MA), which is not commercially available, uses an insulated radiofrequency crossing wire through the mitral or tricuspid annulus at adjacent positions to eventually cinch the annulus to reduce regurgitation (34).

Intervascular traversal and extra-anatomic bypass

Transcaval access

Transcaval access is an alternative large bore access route when femoral artery access is not suitable for TAVR or mechanical assist devices. A stiff coronary guidewire (Astato XS 20 or amputated Confianza, Asahi Intecc) is insulated in a polymer jacket (Piggyback, Teleflex, NC) or other microcatheter and connected to an electrosurgery pencil and generator. The wire is electrified at 50W briefly during advancement out of the vena cava into the abdominal aorta, where it is snared and exchanged for a stiff wire over which the large bore sheath is advanced. TAVR is performed as if it were via usual transfemoral access. Arterial extravasation, if any, spontaneously decompresses via the hole in the adjoining vena cava. On exit, the hole in the aorta is closed with a nitinol cardiac occluder at the end of the case (35,36) or with a dedicated occluder device (Transcaval Closure Device, Transmural Systems, Boston) (37). In the prospective 100 patient NHLBI Transcaval TAVR trial, transcaval access was successful in 99% (38). There were no late vascular complications out to 1 year(39). The experience was

independently validated in Europe (40). Transcaval access has also been used to percutaneously deliver large bore mechanical circulatory assist devices (5.0 Impella, Abiomed, Danvers, MA), averting surgical implantation (41).

Reverse Potts shunt

Transcatheter electrosurgery enables a non-surgical reverse Potts shunt to decompress severe (supra-systemic) pulmonary artery hypertension. A radiofrequency wire is advanced from the aorta into the left pulmonary artery, exchanged for a stiff wire and a covered stent allows a right-to-left shunt that bypasses the cerebral circulation (42).

Glenn shunt

Radiofrequency energy was used for guidewire traversal between superior vena cava and pulmonary artery to create a catheter-only, closed chest, large vessel anastomoses, equivalent to a bidirectional superior cavopulmonary anastomosis (Glenn shunt) (43-45). A purpose-built transcatheter Glenn shunt device is under development.

Transcatheter electrosurgery through synthetic material

Transcaval TAVR has been performed through a polyester aortic graft(46) and radiofrequency assisted transseptal puncture through an atrial septal patch repair(28). TEVAR fenestrations have been performed through polyester grafts (Valiant, Medtronic Vascular, Santa Rosa, CA; Zenith TX2, Cook Medical, Bloomington, IN) (47).

Tissue laceration using transcatheter electrosurgery

The applications described above all require pinhole perforation with the tip of an insulated guidewire. For tissue laceration, controlled targeted directional radiofrequency delivery is required, with greater care to avoid charring and coagulation during potentially longer and higher energy applications. The next section describes simulation and benchtop experiments to optimize transcatheter electrosurgery for tissue laceration. The chapters following describe two procedures developed using transcatheter electrosurgery for precise heart valve laceration.

Conclusions

Tissues vaporize when heated to 100 degrees Centigrade, which can be achieved by resistive heating using alternating current directed to the target tissue through guidewires and catheters. Sufficient charge concentration is required for tissue vaporization, while keeping charge focal to avoid collateral tissue denaturing or coagulation. Contemporary applications include recanalization of occluded vessels and traversal between cardiac chambers. There is potential to expand the use of transcatheter electrosurgery to further modify tissues, beginning with linear laceration.

TABLE 1. Known tissue dielectric properties.

The tissue dielectric parameters are computed according to the 4-Cole-Cole Model (48) at frequency = 10.00 MHz

Tissue	Electrical Permittivity (ε)	Electrical Conductivity (σ)
Blood	280	1.10
Bone Cancellous	71	0.12
Bone Cortical	37	0.04
Fat	14	0.03
Heart	293	0.50
Lung (Inflated)	124	0.23
Muscle (Parallel Fiber)	149	0.67
Muscle (Transverse Fiber)	171	0.62
Skin (Wet)	221	0.37

TABLE 2. Known tissue effects of heating(1,3)

Temperature	Tissue effect
49° C	Tissue coagulates
60° C	Protein denatures
70° C	Cells desiccate
100° C	Cells rupture from vaporization of intracellular water

TABLE 3: Representative clinical applications of transcatheter electrosurgery

Application	References	Study type	Total patients	Procedure success	Complications
Pulmonary valve atresia traversal in newborns	Veldtman 2004 (11)	Case series	136	87% successful in establishing antegrade flow	Procedural death (7%); Arrhythmia, RVOT perforation (16%)
Central chronic total venous occlusion traversal (subclavian vein, SVC)	Baerlocher 2006; Iafrati 2012; Foerst 2017 (4,13,14)	Case reports	6	100%	None reported
Coronary chronic total occlusion	Baim 2004 (19)	Prospective multicenter registry	116	54%	Perforation and tamponade (2.6%)
Transseptal puncture	Hsu 2013 (23)	Randomized control trial	36 RF; 36 conventional	100% RF; 72% conventional (with cross-over to RF and subsequent success)	Pericardial effusion (2.8%)
Interventricular septum puncture (for	Gamble 2018 (32)	Prospective single center	20	100% success in	Disabling stroke (5%)

LV lead placement)		single arm clinical trial		ventricular traversal	
Transcaval for large bore access for TAVR	Greenbaum 2017(38) Lederman 2019(39) Costa 2019(40)	Prospective multicenter single arm clinical trial Retrospective registry	150	99%	Life-threatening or disabling bleeding (4-12%) No late complications

References

1. Pearce JA. Electrosurgery. 1 ed. New York: Wiley Medical, 1986.
2. Benson LN, Nykanen D, Collison A. Radiofrequency perforation in the treatment of congenital heart disease. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2002;56:72-82.
3. Honig WM. The mechanism of cutting in electrosurgery. IEEE Trans Biomed Eng 1975;22:58-62.
4. Baerlocher MO, Asch MR, Myers A. Successful recanalization of a longstanding complete left subclavian vein occlusion by radiofrequency perforation with use of a radiofrequency guide wire. J Vasc Interv Radiol 2006;17:1703-6.
5. Calkins H, Hindricks G, Cappato R et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275-e444.
6. Rosenthal E, Qureshi SA, Chan KC et al. Radiofrequency-assisted balloon dilatation in patients with pulmonary valve atresia and an intact ventricular septum. Br Heart J 1993;69:347-51.
7. Justo RN, Nykanen DG, Williams WG, Freedom RM, Benson LN. Transcatheter perforation of the right ventricular outflow tract as initial therapy for pulmonary valve atresia and intact ventricular septum in the newborn. Catheterization and cardiovascular diagnosis 1997;40:408-13.
8. Hausdorf G, Schulze-Neick I, Lange PE. Radiofrequency-assisted "reconstruction" of the right ventricular outflow tract in muscular pulmonary atresia with ventricular septal defect. Br Heart J 1993;69:343-6.
9. Hijazi ZM, Patel H, Cao QL, Warner K. Transcatheter retrograde radio-frequency perforation of the pulmonic valve in pulmonary atresia with intact ventricular septum, using a 2 French catheter. Catheterization and cardiovascular diagnosis 1998;45:151-4.
10. Wang JK, Wu MH, Chang CI, Chen YS, Lue HC. Outcomes of transcatheter valvotomy in patients with pulmonary atresia and intact ventricular septum. Am J Cardiol 1999;84:1055-60.

11. Veldtman GR, Hartley A, Visram N, Benson LN. Radiofrequency applications in congenital heart disease. Expert Rev Cardiovasc Ther 2004;2:117-26.
12. Krasemann T. Radiofrequency perforation: the optimum treatment for pulmonary atresia? Heart 2009;95:1473-4.
13. Foerst JR, Kim D, May TP. Percutaneous electrosurgical technique for treatment of subclavian vein occlusion: Application of transcaval techniques. HeartRhythm Case Rep 2017;3:551-554.
14. Iafrati M, Maloney S, Halin N. Radiofrequency thermal wire is a useful adjunct to treat chronic central venous occlusions. J Vasc Surg 2012;55:603-6.
15. Fink C, Peuster M, Bertram H, Hausdorf G. Transcatheter recanalization of the left main pulmonary artery after four years of complete occlusion. Catheter Cardiovasc Interv 2001;53:81-4.
16. Pedra CA, Filho RM, Arrieta RS, Tellez R, Fontes VF. Recanalization of a discrete atretic right pulmonary artery segment with a new radiofrequency system. Catheter Cardiovasc Interv 2003;60:82-7.
17. Almashham Y, Dahdah N, Miro J. Use of radiofrequency then stent implantation for recanalization of complete aorta coarctation. Pediatr Cardiol 2008;29:207-9.
18. Nicholson W, Harvey J, Dhawan R. E-CART (ElectroCautery-Assisted Re-enTry) of an Aorto-Ostial Right Coronary Artery Chronic Total Occlusion: First-in-Man. JACC Cardiovasc Interv 2016;9:2356-2358.
19. Baim DS, Braden G, Heuser R et al. Utility of the Safe-Cross-guided radiofrequency total occlusion crossing system in chronic coronary total occlusions. The American journal of cardiology 2004;94:853-8.
20. Kanno D, Tsuchikane E, Nasu K et al. Initial results of a first-in-human study on the PlasmaWire System, a new radiofrequency wire for recanalization of chronic total occlusions. Catheter Cardiovasc Interv 2017.
21. Nageotte SJ, Lee JW, El-Said HG, Moore JW, Ratnakaya K. Transcatheter Electrosurgery Rescue: Jailed Pulmonary Artery Following Melody Pulmonary Valve Replacement. JACC Cardiovascular Interventions 2019;[In Press].
22. Justino H, Benson LN, Nykanen DG. Transcatheter creation of an atrial septal defect using radiofrequency perforation. Catheter Cardiovasc Interv 2001;54:83-7.

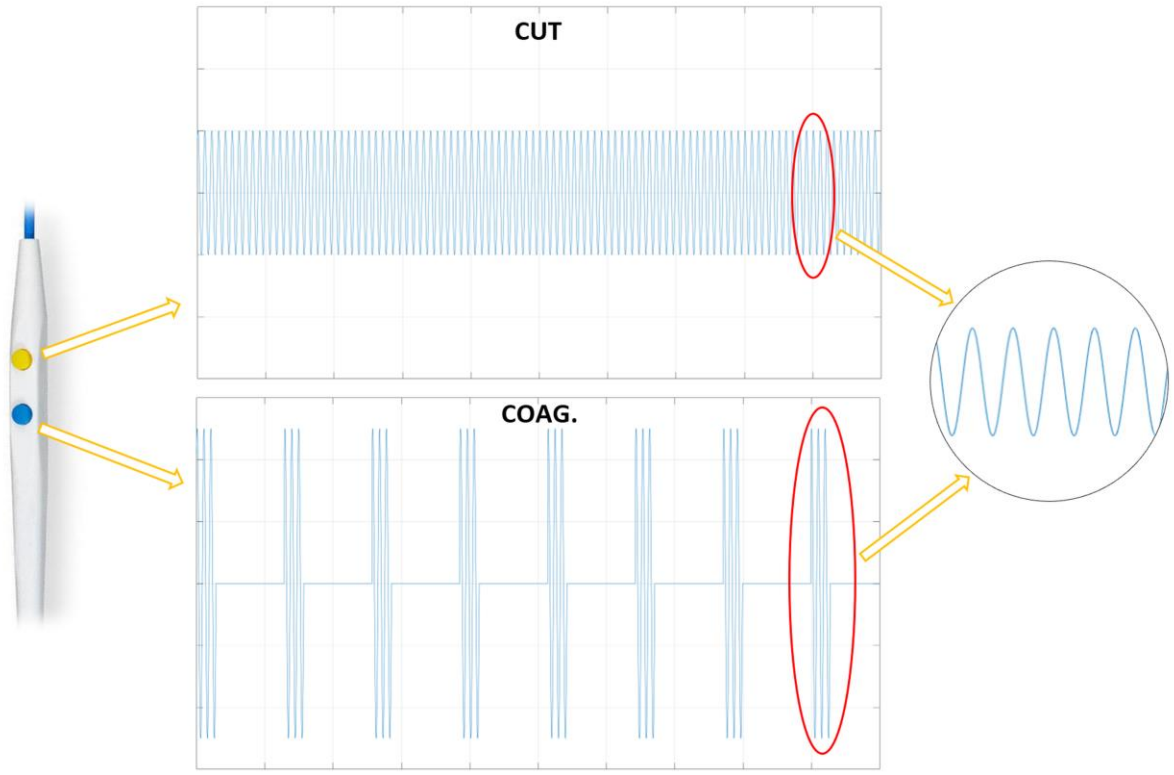
23. Hsu JC, Badhwar N, Gerstenfeld EP et al. Randomized trial of conventional transseptal needle versus radiofrequency energy needle puncture for left atrial access (the TRAVERSE-LA study). J Am Heart Assoc 2013;2:e000428.
24. Hill SL, Mizelle KM, Vellucci SM, Feltes TF, Cheatham JP. Radiofrequency perforation and cutting balloon septoplasty of intact atrial septum in a newborn with hypoplastic left heart syndrome using transesophageal ICE probe guidance. Catheter Cardiovasc Interv 2005;64:214-7.
25. Bidart C, Vaseghi M, Cesario DA et al. Radiofrequency current delivery via transseptal needle to facilitate septal puncture. Heart Rhythm 2007;4:1573-6.
26. Gordon BM, Levi DS, Shannon KM. Electrosurgical energy in combination with a transseptal needle: a novel method for the creation of an atrial communication in hypoplastic left heart syndrome with intact atrial septum. Catheter Cardiovasc Interv 2009;73:113-6.
27. Maisano F, La Canna G, Latib A et al. Transseptal access for MitraClip(R) procedures using surgical diathermy under echocardiographic guidance. EuroIntervention 2012;8:579-86.
28. Khan JM, Rogers T, Eng MH, Lederman RJ, Greenbaum AB. Guidewire electrosurgery-assisted trans-septal puncture. Catheter Cardiovasc Interv 2017.
29. Lin CH, Huddleston C, Balzer DT. Transcatheter ventricular septal defect (VSD) creation for restrictive VSD in double-outlet right ventricle. Pediatr Cardiol 2013;34:743-7.
30. Santangeli P, Shaw GC, Marchlinski FE. Radiofrequency Wire Facilitated Interventricular Septal Access for Catheter Ablation of Ventricular Tachycardia in a Patient With Aortic and Mitral Mechanical Valves. Circulation Arrhythmia and electrophysiology 2017;10.
31. Betts TR, Gamble JH, Khiani R, Bashir Y, Rajappan K. Development of a technique for left ventricular endocardial pacing via puncture of the interventricular septum. Circulation Arrhythmia and electrophysiology 2014;7:17-22.
32. Gamble JHP, Herring N, Ginks MR, Rajappan K, Bashir Y, Betts TR. Endocardial left ventricular pacing across the interventricular septum for cardiac resynchronization therapy: Clinical results of a pilot study. Heart Rhythm 2018;15:1017-1022.

33. Khan JM, Rogers T, Schenke WH et al. Transcatheter pledget-assisted suture tricuspid annuloplasty (PASTA) to create a double-orifice valve. Catheter Cardiovasc Interv 2018;92:E175-E184.
34. Nickenig G, Schueler R, Dager A et al. Treatment of Chronic Functional Mitral Valve Regurgitation With a Percutaneous Annuloplasty System. J Am Coll Cardiol 2016;67:2927-36.
35. Halabi M, Ratnayaka K, Faranesh AZ, Chen MY, Schenke WH, Lederman RJ. Aortic access from the vena cava for large caliber transcatheter cardiovascular interventions: pre-clinical validation. J Am Coll Cardiol 2013;61:1745-6.
36. Greenbaum AB, O'Neill WW, Paone G et al. Caval-aortic access to allow transcatheter aortic valve replacement in otherwise ineligible patients: initial human experience. J Am Coll Cardiol 2014;63:2795-804.
37. Rogers T, Greenbaum AB, Babaliaros VC et al. Dedicated closure device for transcaval access closure: from concept to first-in-human testing. JACC Cardiovasc Interven 2019;[In Press].
38. Greenbaum AB, Babaliaros VC, Chen MY et al. Transcaval Access and Closure for Transcatheter Aortic Valve Replacement: A Prospective Investigation. J Am Coll Cardiol 2017;69:511-521.
39. Lederman RJ, Babaliaros VC, Rogers T et al. The Fate of Transcaval Access Tracts: 12-Month Results of the Prospective NHLBI Transcaval Transcatheter Aortic Valve Replacement Study. JACC Cardiovasc Interv 2019;12:448-456.
40. Costa G, De Backer O, Pilgrim T et al. Initial European experience with transcaval transcatheter aortic valve implantation. EuroIntervention 2019.
41. Kamioka N, Patel A, Burke MA, Greenbaum A, Babaliaros V. Biventricular Impella placement via complete venous access. Catheter Cardiovasc Interv 2019;93:E343-E345.
42. Schranz D, Kerst G, Menges T et al. Transcatheter creation of a reverse Potts shunt in a patient with severe pulmonary arterial hypertension associated with Moyamoya syndrome. EuroIntervention 2015;11:121.
43. Ratnayaka K, Moore JW, Rios R, Lederman RJ, Hegde SR, El-Said HG. First-in-Human Closed-Chest Transcatheter Superior Cavopulmonary Anastomosis. J Am Coll Cardiol 2017;70:745-752.

44. Ratnayaka K, Rogers T, Schenke WH et al. Magnetic Resonance Imaging-Guided Transcatheter Cavopulmonary Shunt. JACC Cardiovasc Interv 2016;9:959-70.
45. Levi DS, Danon S, Gordon B et al. Creation of transcatheter aortopulmonary and cavopulmonary shunts using magnetic catheters: feasibility study in swine. Pediatr Cardiol 2009;30:397-403.
46. Lederman RJ, O'Neill WW, Greenbaum AB. Transcaval access for TAVR across a polyester aortic graft. Catheter Cardiovasc Interv 2015;85:1270-3.
47. Tse LW, Lindsay TF, Roche-Nagle G, Oreopoulos GD, Ouzounian M, Tan KT. Radiofrequency in situ fenestration for aortic arch vessels during thoracic endovascular repair. J Endovasc Ther 2015;22:116-21.
48. Gabriel C. Compilation of the dielectric properties of body tissues at RF and microwave frequencies. Brooks Airforce Base, Texas, 1996.

FIGURE 1 Cutting versus coagulation radiofrequency waveforms

Schematic diagram of typical radiofrequency (RF) waveforms in cutting mode, intended to vaporize tissue, compared with coagulation mode, intended to stop bleeding. Cutting mode is typically activated using a yellow-colored button on electrosurgical pencils and is associated with continuous-duty radiofrequency energy that constantly heats tissue until it vaporizes. Coagulation mode, activated typically using blue-colored buttons on electrosurgical pencils, applies interrupted-duty waveforms. The interrupted waveforms cause rapid heating-cooling cycles that allow blood to coagulate.



Simulation and Benchtop testing

The rate of heating depends on current density in the tissue. We performed simulations to demonstrate the key principals of charge concentration required for transcatheter electrosurgery, and to inform transcatheter electrosurgical techniques.

Comparative electrosurgical properties of commercial guidewires

Although electrosurgical equipment is commercially available from at least one vendor (Baylis Medical Company), we usually use other commercial off-the-shelf guidewires for transcatheter electrosurgery, off-label, because they provide mechanical features not available in approved products. We tested guidewires from different major manufacturers to determine suitability for transcatheter electrosurgery. Guidewires were categorized by core material (stainless steel versus nitinol), tip style (core-to-tip versus fused shaping ribbon), tip cover (bare spring coils versus spring coils covered in a polymer jacket), and hydrophilic tip coating to determine different total-guidewire conduction properties.

There are a variety of electrosurgical generators available. The experiments below were all performed with the Valleylab ForceFx generator (Medtronic, MN). Different power settings may be required with other commercial generators, many of which have adaptive circuitry to modulate power output in response to dynamic impedance changes.

Freshly explanted pig hearts were incompletely submerged in a saline bath. Guidewire tips were apposed to myocardial tissue and secured 5cm proximally. Guidewire distal shafts were manually denuded of insulating polymer coating and then clamped to an electrosurgery generator (Valleylab ForceFx). The guidewire shaft was suspended in air, resembling perfect insulation with only the tip in contact with saline and myocardial tissue. The minimal power required for instantaneous vaporization, judged by unimpeded rapid wire traversal, was noted [Table 1].

The results showed that guidewire polymer coating acts as electrical insulation. Guidewires with a polymer jacket coating the tip did not penetrate tissue even at 30W, whereas guidewires with uncoated bare spring coils penetrated tissue without hindrance at 7-13W. When the polymer jacket was excised with a scalpel to expose the

spring coils, the guidewires performed similarly to uncoated guidewires. Design parameters such as core material (steel versus nitinol), design (core-to-tip versus fused), and presence of shaping ribbon did not appear to influence electrosurgical performance because all tested metal systems appeared highly conductive. Guidewires with a high tip load appear more suitable for transcatheter electrosurgery as they are less likely to prolapse when attempting traversal.

Empirical experience suggests that a guidewire tip voltage of 70V or greater is required for tissue traversal (12). Voltages at the guidewire tip in a saline bath were measured by oscilloscope at a fixed power output. As expected, the voltage decreased exponentially with increased wire exposure in saline. To test properties of different guidewires, all guidewires were tested with 2mm of the tip exposed through an insulating polymer jacket (Piggyback Wire Converter, Teleflex, NC). Guidewires achieved 70V tip voltage when 5-13W power was applied, which corresponds with the traversal tests.

Current density simulation

Methods

The current density simulations were performed using the AC/DC module on Comsol Multiphysics (v5.2a, Comsol Inc. MA, USA) simulation software. The biological structures were represented as simplified geometries in the simulation setup to reduce the computational cost. A 60cm height and 25cm diameter cylinder was used as the blood pool. A 3mm height and 10cm diameter disk was placed at the bottom of the blood pool to be used as the ground path. The leaflet and the myocardial tissues were represented with a 2cm X 0.5cm X 5cm and a 3cm X 20cm X 20cm rectangular blocks, respectively. A 0.014” guidewire with 0.001” PTFE insulation (representing an Astato XS 20 guidewire, Asahi Intecc, Japan) was used as the energized wire. A 3Fr microcatheter was used over the energized wire. A 100W power source was used with 100V and 1A voltage and current outputs at 700kHz to simulate commercially available electrosurgery units. The relative permittivity and the conductivity values were used as 79 and 63 mS/cm for the blood, 61 and 49mS/cm for the leaflet and the myocardial tissues, respectively (6). The conductivity and the relative permittivity values of dextrose were extrapolated for

700kHz and set as 72 and 0.5mS/cm, respectively (7). The dielectric constant of PTFE coating was set as 2.1 (8).

Simulations were run for a comprehensive set of conditions to assess the effects of guidewire denudation length, the use of insulating microcatheters and the use of dextrose on the current density in blood and the myocardial tissue. First, the effect of the guidewire insulation length was studied for a unipolar electrode in blood and in contact with the myocardial tissue in blood. Then a pair of bipolar electrodes were simulated to compare the current density around and in between the guidewire electrodes between the unipolar and bipolar setups. Finally, leaflet laceration conditions were simulated on a kinked wire straddling the leaflet tissue. Kinked wire variations included intact insulation, insulation focally denuded from the inner surface of the kink, the impact of adjacent insulating microcatheters, and the impact of flooding the field with dextrose to displace conductive ions in solution. The current density values were plotted for each condition in arbitrary units.

Impact of different electrosurgical guidewire configurations

Extending an un-insulated electrosurgical guidewire beyond the tip of a catheter allows current to disperse and thereby reduces its ability to vaporize and traverse tissue. Figure 1 demonstrates that current density decreases exponentially as the guidewire electrode is extended beyond the insulating catheter tip. Current density also decreases exponentially with increased *distance* from the guidewire electrode. Therefore, both limiting the area of exposed guidewire electrode and close approximation with the target tissue are important for generating enough current density to vaporize tissue.

Exposing an electrosurgical guidewire to blood also reduces cutting efficiency. Figure 2 depicts a catheter delivering an electrified guidewire into tissue though blood, compared with the same catheter abutting tissue to deliver the electrified guidewire. As always, current follows the path of least resistance. The wire spans a medium with higher conductivity (blood) and a medium with lower conductivity (aortic valve leaflet), resulting in preferential current flow into the high conductivity medium (blood). In this case, there will be no current concentration, and therefore little resistive heating and

‘cutting’ of the target tissue. However, if the guidewire is insulated using a microcatheter, current will concentrate in and vaporize the target tissue.

All electrosurgery involves current flow between two electrodes. Figure 4 demonstrates current densities in unipolar and bipolar modes. In unipolar mode, current flows between an ‘active electrode’ at the target tissue and a broad ‘indifferent’ or ‘dispersive electrode’ at a remote site on the skin surface. In a bipolar setup, two active electrodes are in close proximity to each other. Bipolar modes generate a larger electric field and have traditionally been used for coagulation rather than vaporization, using lower energy between two closely positioned static electrodes (1,9). Using static active electrodes is undesirable in transcatheter electrosurgery because of electrode carbonization and collateral tissue heating and coagulation. Traditionally, unipolar modes have been used for tissue cutting, generating concentrated current at an active electrode tip as it moves through the target tissue. Precisely applied, unipolar radiofrequency can vaporize cells adjacent to the guidewire electrode and spare cells only a few layers deep as current decreases exponentially with the radial distance from the source (1,10). To date, few transcatheter electrosurgery applications employ bipolar mode.

Simulating transcatheter electrosurgery laceration

The above demonstrations describe electrosurgical *traversal* of tissue or valve leaflets using the tip of a guidewire. To slice or *lacerate* a valve leaflet is more challenging. We determined the simplest approach to electrosurgical leaflet laceration is to traverse the leaflet to straddle both sides and then apply traction during electrification. Traction causes the guidewire to bend at the “lacerating surface” where it contacts the leaflet edge being cut. We hypothesized that the lacerating surface is more effective if specially configured. Using the same parameters for current density simulations above, we tested different guidewire configurations for valve tissue laceration.

Figure 4 simulates current density using the kinked mid-shaft of a guidewire, the “Flying V”, which serves as the lacerating surface. Using an unmodified guidewire having intact PTFE coating, there is insufficient charge conducted from guidewire to tissue. After focally denuding the inner surface at the guidewire kink, charge density around the

lacerating surface increases but there is still charge dispersal along the guidewire shaft. With insulating microcatheters positioned on either side, charge dispersal along the guidewire shaft is reduced, but most of the charge still disperses in blood adjacent to the tissue. After displacing blood with 5% dextrose, a non-ionic fluid, alternative current paths are minimized and charge concentrates in tissue without heating the surrounding blood pool. This allows focal vaporization of target tissue at lower power outputs and minimizes char, coagulation, and possible thromboembolism in blood. Concentrating current on target tissue by displacing ionic solution with a non-ionic solution is not unique to transcatheter electrosurgery. For example, during transurethral electrosurgical resection of the prostate, the urethra is irrigated with sterile non-conductive solution (dextrose or glycerin) (11).

In vitro laceration testing

We tested the optimal configurations for the guidewire together with a variety of insulation strategies.

A benchtop model with freshly explanted pig aortas in a saline bath was used to test different insulating conditions for electrosurgical laceration (Figure 5A&B). The pulling force was maintained at 5N and 30W of “pure cut” radiofrequency energy was delivered for 2s and tested in triplicate. These parameters were chosen as they produced replicable cutting results *in vitro*. The laceration distance was measured and compared.

The results showed no significant cut when an unmodified guidewire was used, or when the midshaft was circumferentially denuded. With a partially denuded guidewire that was kinked to enforce the denuded segment onto the target tissue, a steady laceration was achieved. Additional insulation strategies with microcatheters (Piggyback, Teleflex, NC) and 5% dextrose flush demonstrated incremental benefit (Figure 5C).

This experiment emphasizes the importance of inner curvature charge concentration via selective denudation, and of robust insulation with both micro-catheters and non-ionic fluid, to concentrate charge for tissue laceration. These essential concepts underlie the clinical techniques employed for mitral and aortic leaflet laceration.

Conclusions

Charge concentration is required for target tissue vaporization. Using commercial equipment, this can be achieved using microcatheters, selective guidewire denudation, and displacement of blood with a non-ionic liquid such as 5% dextrose solution. Guidewires with uncoated spring coil tips and high tip load appear most suited to transcatheter electrosurgery applications.

TABLE 4: Observed power (Watts) required for commercial guidewires to traverse tissue under the described in vitro conditions.

Guidewires (0.014”) that require low traversal power and that have high tip loads appear best suited for transcatheter electrosurgery (highlighted in green). Guidewire models that failed to traverse even at the highest tested energy (30W) are indicated with an asterisk (*). These non-traversing models were tested again after manually stripping distal polymer insulation (highlighted in orange), at which point they successfully traversed the target tissue at acceptable power.

Required Power (W)	**Exposed (un-insulated) distal spring coil**	**Product Name**	**Manufacturer**	**Length (cm)**	**Distal tip coating**	**Tip load (g)**
Chronic total occlusion guidewires						
7	Yes	Confianza Pro-9	Asahi	300	hydrophilic except distal 1mm	9
7	Yes	Approach CTO-6	Cook	300	hydrophilic	6
8	Yes	Astato XS 20	Asahi	300	hydrophilic except ball tip	20
8	Yes	MIRACLEbros 6	Asahi	180	hydrophobic	6
8	Yes	ProVia 9	Medtronic	300	hydrophilic	9
8	Yes	Progress 200T	Abbott	190	hydrophobic	13
9	Yes	Samurai	Boston	190	hydrophilic	1.2
>30*	No	Pilot150	Abbott	190	hydrophilic	2.7
>30*	No	Shinobi Plus	Cordis	300	hydrophilic	4
Extra support guidewires						
8	Yes	Iron Man	Abbott	190	hydrophobic	1
8	Yes	Grand Slam	Asahi	180	hydrophobic	0.7
8	Yes	Platinum Plus	Boston	180	hydrophilic	7
12	Yes	Mailman	Boston	182	hydrophilic except distal 3cm	0.8

Workhorse guidewires						
9	Yes	Runthrough NS extra floppy	Terumo	180	hydrophilic	0.6
11	Yes	Balance Middle Weight	Abbott	190	hydrophilic	0.7
11	Yes	Kinetix	Boston	185	hydrophilic except distal 1.27cm	0.8
13	Yes	Choice Floppy	Boston	182	hydrophobic	0.8
>30*	No	Fielder	Asahi	180	hydrophilic	1
>30*	No	Whisper	Abbott	300	hydrophilic	1
Distal polymer manually stripped to expose conductive spring coils						
7	Yes	Fielder	Asahi	180	hydrophilic	1
8	Yes	Whisper	Abbott	300	hydrophilic	1
8	Yes	Pilot 150	Abbott	190	hydrophilic	2.7
8	Yes	Shinobi Plus	Cordis	300	hydrophilic	4

FIGURE 2 Insulating a guidewire shaft (with a catheter) concentrates charge at the tip and improves effectiveness.

Current density simulations were performed using the AC/DC module on Comsol Multiphysics simulation software using methods described in the manuscript. Figure 2 is a simulation depicting the electric field around a conductive guidewire as it progressively extends beyond an insulating catheter. The top row shows long-axis views and the bottom row shows the cross-sectional views of the field in arbitrary units. On the left, a guidewire is extending far beyond the tip of an insulating catheter, resulting in a modest electrical field around the guidewire tip. Moving towards the middle and right columns, the guidewire is extended only minimally beyond the tip of the insulating catheter, resulting in marked enhancement of the electrical field. This focused insulation significantly increases electrosurgical efficiency, for example, during tissue traversal.

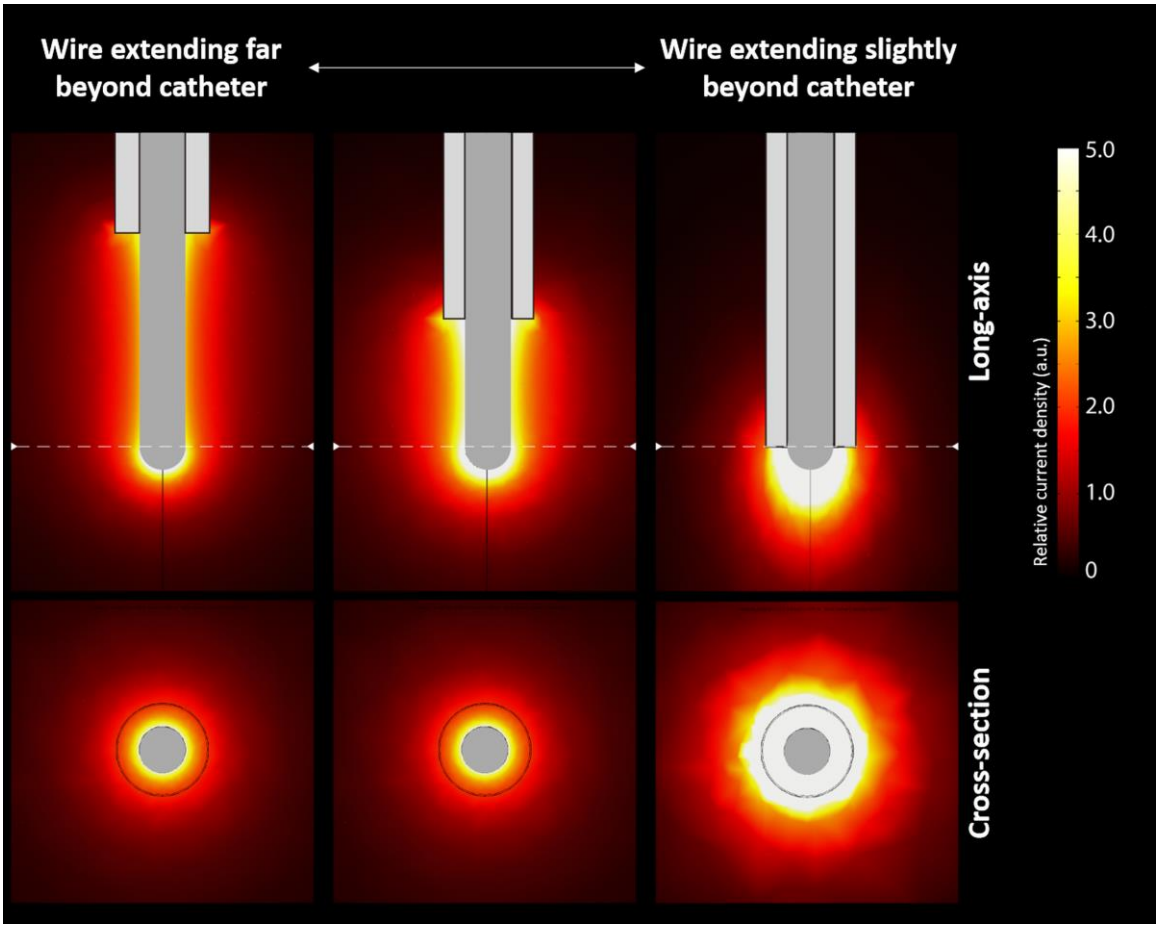


FIGURE 3 Electrosurgical guidewires should contact tissue directly; blood contact reduces effectiveness.

Simulation depicting a guidewire spanning blood and tissue. In the left column the guidewire is exposed in both blood and tissue, with most of the current following the path of least resistance and dispersing in blood. In the right column the guidewire is insulated from blood so current concentrates through tissue. The bottom rows show cross-sectional views at the level of blood and of tissue, respectively.

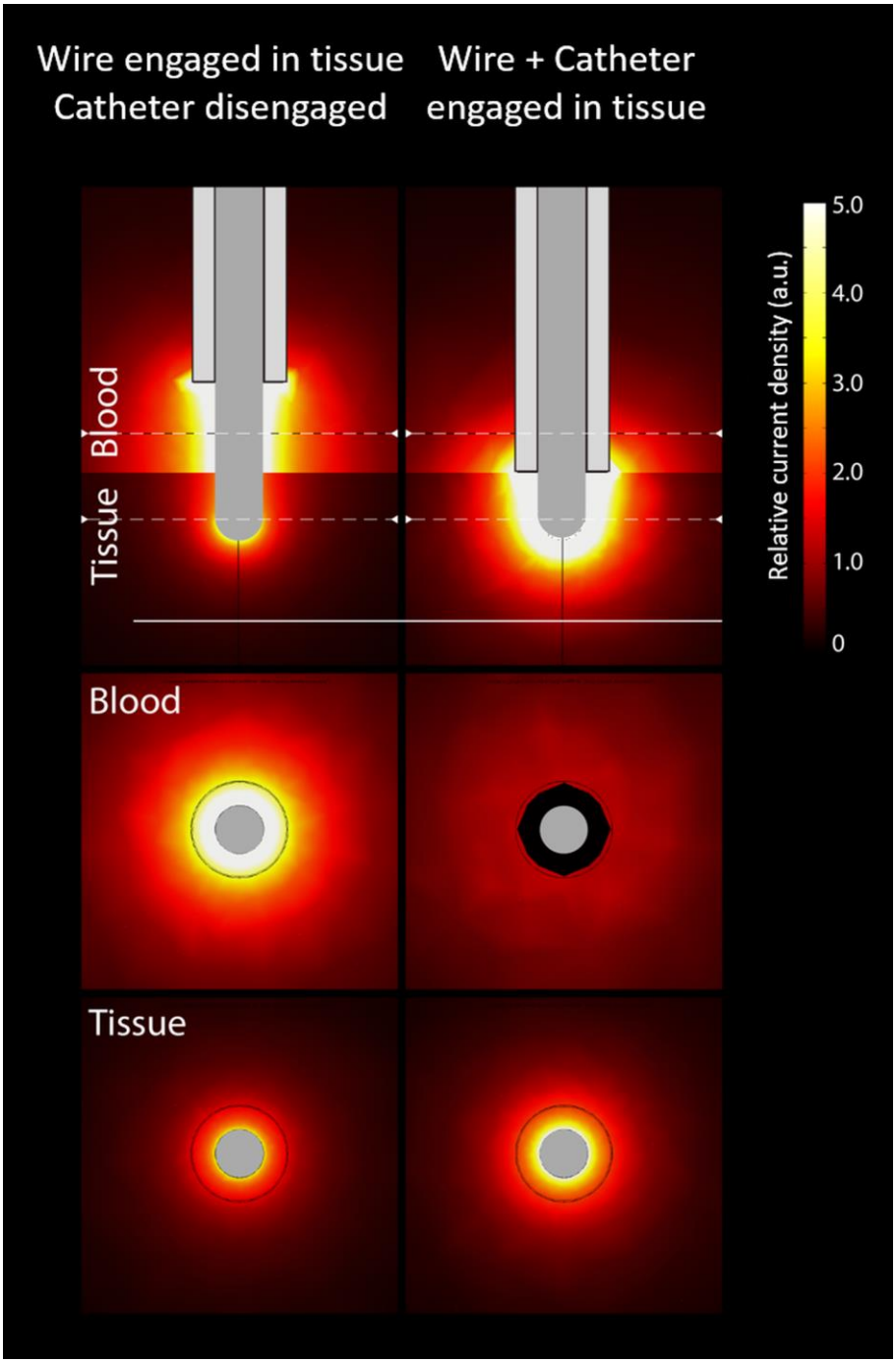


FIGURE 4 Unipolar versus Bipolar modes

Simulation comparing current density achieved with an exposed unipolar guidewire tip with two exposed bipolar guidewire tips, one black and one white, at progressively larger separation distances. Note the electrical field lines. Bipolar electrosurgery is less effective at-a-distance. The scale shows relative current density.

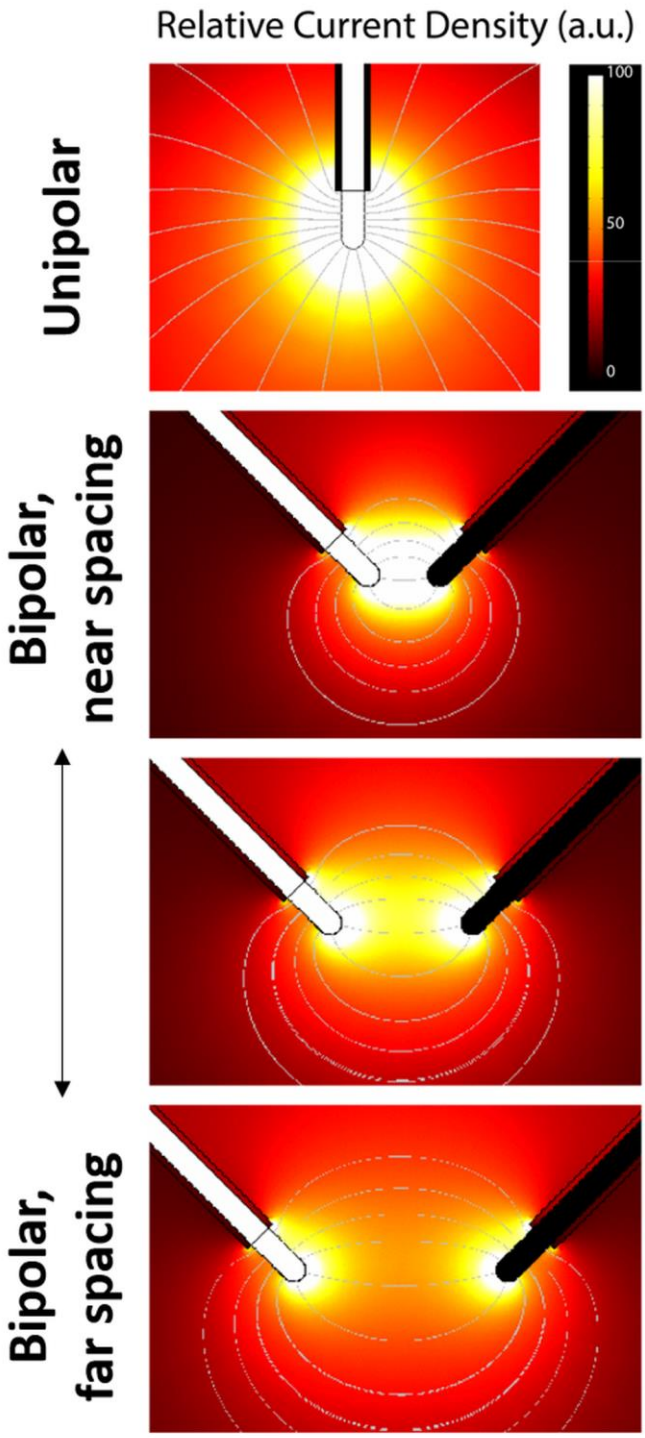


FIGURE 5 Charge density at the “Flying V” is highest when combining inner-surface denudation, insulating catheters, and dextrose flush

Impact of focally denuding a kinked guidewire used for electrosurgical laceration of leaflet tissue, depicted on electromagnetic simulations. (A) Schematic diagram of an electrified Flying V in position across a leaflet to be lacerated. (B) Charge is dispersed throughout the length of the guidewire straddling a leaflet. (C) Focally denuding the inner surface of the kinked wire increases charge on the inner lacerating surface. (D) Apposing two insulating microcatheters further enhances charge concentration on the inner lacerating surface. (E) Flooding the field with non-conductive dextrose displaces blood ions and further concentrates charge onto leaflet, contributing to more effective electrosurgical laceration.

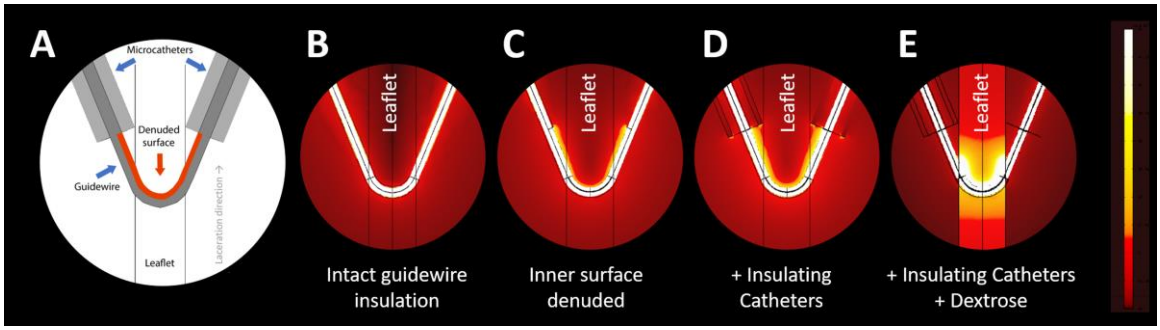
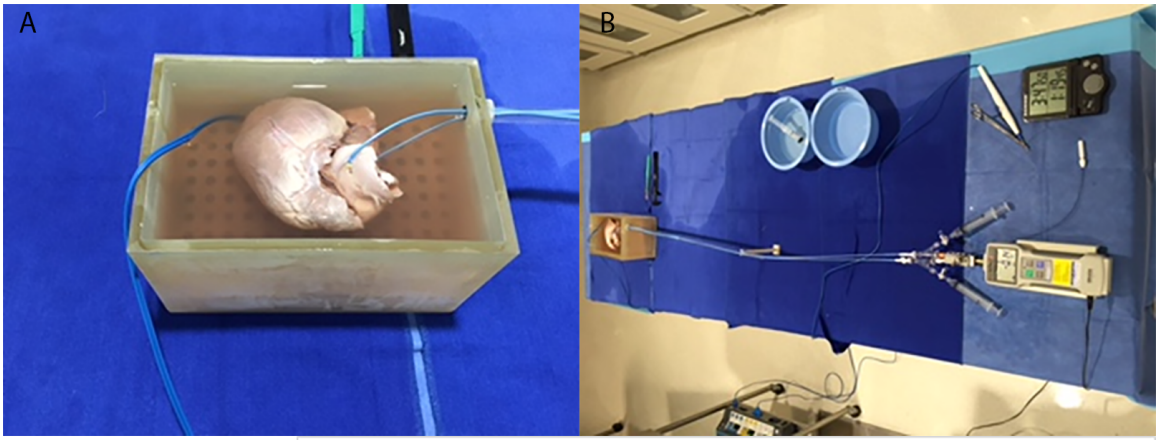


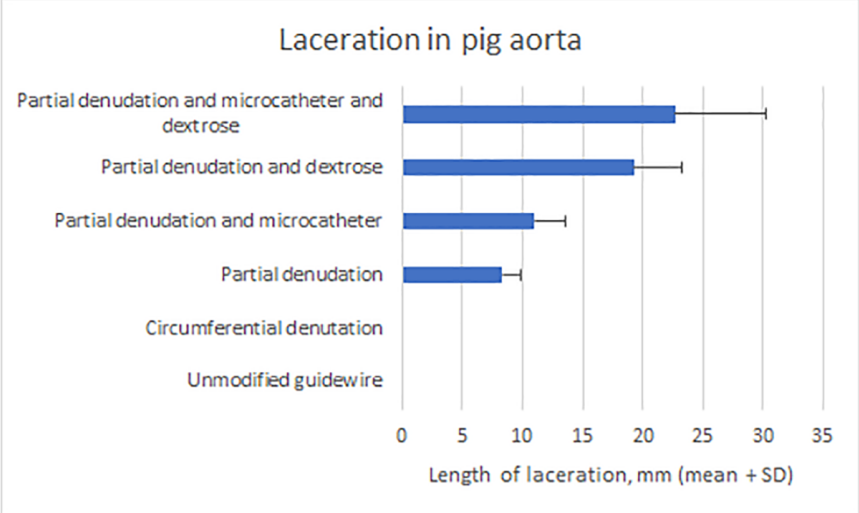
FIGURE 6 Optimizing charge density at the “Flying V”

Benchtop setup and results of testing different guidewire charge concentration strategies in pig hearts. (A) the pig hearts are submerged in saline and the traversal wire is positioned in a typical transcatheter electrosurgery configuration with suitable guiding catheters and microcatheters attached to a force meter (B). Panel (C) shows progressive electrosurgery strategies compared using the distance lacerated in a given time. More effective strategies traverse a greater distance, including inner-surface denudation, closely apposed microcatheters, and flooding the ionic fluid field with non-ionic dextrose.



C

Fixed conditions:
Force 5N;
Time 2s;
Power 30W.



CHAPTER 3. LAMPOON (incorporating three published manuscripts)

Introduction

The first specific aim of this thesis was *to determine if transcatheter laceration of the mitral leaflet prevents left ventricular outflow tract obstruction following TMVI.* The preceding chapters have summarized the current state of the art of transcatheter electrosurgery and explored the physics of transcatheter electrosurgery. This chapter describes the first of two novel techniques to lacerate valve tissue using transcatheter electrosurgery to prevent blood flow obstruction from transcatheter valve implantation. The chapter incorporates three published manuscripts, describing the procedure from pre-clinical development through to first-in-human experience and finally early feasibility investigation in a prospective clinical trial.

Transcatheter mitral valve implantation is an emerging treatment for patients with mitral valve disease who are not candidates for surgical mitral valve replacement or repair. Left ventricular outflow tract obstruction is a common and devastating complication of transcatheter mitral valve implantation, caused by septal displacement of the anterior mitral valve leaflet. During mitral valve replacement surgery, surgeons resect that anterior mitral leaflet to avoid left ventricular outflow tract obstruction. Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN (LAMPOON) is a transcatheter technique to cut the anterior mitral valve leaflet using an electrified guidewire. The preserved chords and the implanted mitral prosthesis splay the split leaflet away from the left ventricular outflow tract, mimicking surgical chord-sparing leaflet resection, preventing obstruction.

In line with the specific aims, we developed the novel LAMPOON transcatheter procedure in anesthetized pigs to precisely lacerate the anterior mitral valve leaflet in line with the LVOT. Also, in line with the specific aims, we conducted an early feasibility phase 1 study of the procedure in 30 human subjects predicted on CT imaging to be at prohibitive risk of LVOT obstruction from TMVI and therefore excluded from available treatment.

Role of transcatheter electrosurgery

Leaflets can be cut mechanically with sharp implements. However, the advantage of soft catheters and guidewires is that it allows atraumatic navigation through the vasculature. Transcatheter electrosurgery imparts temporary “sharpness” to the guidewire when need for traversal and laceration. It enables the LAMPOON procedure to be minimally invasive, with percutaneous femoral access, without cardiac arrest, guided by echocardiography and fluoroscopy. Transcatheter electrosurgery is required first to traverse then lacerate the anterior mitral leaflet, which would otherwise either not be lacerated, or avulsed unpredictably. The principals learnt from benchtop experiments and simulations are applied to concentrate current on the anterior mitral valve leaflet to enable laceration without collateral damage.

Intentional Laceration of the Anterior Mitral Valve Leaflet to Prevent Left Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement: Pre-Clinical Findings

An original research manuscript published in the journal *JACC: Cardiovascular Interventions* in 2016.

Candidate's contribution

My colleagues and I conceived of the idea for LAMPOON. I personally devised the specific procedure steps, techniques, and inventory. I established how to effectively direct current through the mid-shaft of a guidewire. I then established how to reproducibly use this to cut the anterior mitral valve leaflet using a transfemoral transcatheter approach. I personally performed the animal and benchtop experiments. I am first author on the enclosed pre-clinical manuscript, which I drafted, designed the figures, and consulted the references.

JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 17, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.06.020

TRANSLATIONAL

Intentional Laceration of the Anterior Mitral Valve Leaflet to Prevent Left Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement

Pre-Clinical Findings

Jaffar M. Khan, BM BCH,[a] Toby Rogers, BM BCH,[a] William H. Schenke, BS,[a] Jonathan R. Mazal, MS,[a] Anthony Z. Faranesh, PHD,[a] Adam B. Greenbaum, MD,[b] Vasilis C. Babaliaros, MD,[c] Marcus Y. Chen, MD,[a] Robert J. Lederman, MD[a]

ABSTRACT

OBJECTIVES The authors propose a novel transcatheter transection of the anterior mitral leaflet to prevent iatrogenic left ventricular outflow tract (LVOT) obstruction during transcatheter mitral valve replacement (TMVR).

BACKGROUND LVOT obstruction is a life-threatening complication of TMVR caused by septal displacement of the anterior mitral leaflet.

METHODS In vivo procedures in swine were guided by biplane x-ray fluoroscopy and intracardiac echocardiography. Retrograde transaortic 6-F guiding catheters straddled the anterior mitral leaflet. A stiff 0.014-inch guidewire with polymer jacket insulation was electrified and advanced from the LVOT, through the A2 leaflet base, into the left atrium. The wire was snared and externalized, forming a loop that was energized and withdrawn to lacerate the anterior mitral leaflet.

RESULTS The anterior mitral leaflet was successfully lacerated in 7 live and 1 post-mortem swine under heparinization. Lacerations extended to 89 ± 19% of leaflet length and were located within 0.5 ± 0.4 mm of leaflet centerline. The chordae were preserved and retracted the leaflet halves away from the LVOT. LVOT narrowing after benchtop TMVR was significantly reduced with intentional laceration of the anterior mitral leaflet to prevent LVOT obstruction than without (65 ± 10% vs. 31 ± 18% of pre-implantation diameter, $p < 0.01$). The technique caused mean blood pressure to fall (from 54 ± 6 mm Hg to 30 ± 4 mm Hg, $p < 0.01$), but blood pressure remained steady until planned euthanasia. No collateral tissue injury was identified on necropsy.

CONCLUSIONS Using simple catheter techniques, the anterior mitral valve leaflet was transected. Cautiously applied in patients, this strategy can prevent anterior mitral leaflet displacement and LVOT obstruction caused by TMVR.
(J Am Coll Cardiol Intv 2016;9:1835-43) © 2016 by the American College of Cardiology Foundation.

From the [a]Cardiovascular and Pulmonary Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; [b]Center for Structural Heart Disease, Division of Cardiology, Henry Ford Health System, Detroit, Michigan; and the [c]Structural Heart and Valve Center, Emory University Hospital, Atlanta, Georgia. This work was supported by the Division of Intramural Research (Z01-HL006040), National Heart, Lung, and Blood Institute, National Institutes of Health. Dr. Greenbaum serves as a proctor for Edwards Lifesciences and St. Jude Medical, which manufactures transcatheter

ABBREVIATIONS AND ACRONYMS

LAMPOON = laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction

LVOT = left ventricular outflow tract

TMVR = transcatheter mitral valve implantation

Transcatheter stent valves (both purpose-built and off-label) are implanted to relieve mitral valve failure—whether native, bioprosthetic, or after annuloplasty—when the risk for mitral valve surgery is prohibitive (1,2). These transcatheter mitral stent valves may cause acute left ventricular outflow tract (LVOT) obstruction by displacing the anterior mitral valve leaflet toward the septum. Formal criteria have not been established, but as in surgery (3,4), contributors to LVOT obstruction include angulated mitral and aortic annular planes, long or redundant anterior mitral leaflets, small ventricles, bulging septa, and narrow leaflet-to-septum distance (5–7). Preparatory or bailout transcoronary alcohol septal ablation can debulk the septum (8,9) but risks important myocardial and conduction system injury. Moreover, alcohol septal ablation is not feasible when septal thickness is normal and typically requires a delay of 4 to 6 weeks for remodeling before transcatheter mitral valve replacement (TMVR), in highly symptomatic patients. The anterior mitral leaflet can be resected during hybrid surgical TMVR but requires cardiopulmonary bypass (10). We propose a transcatheter alternative.

We describe a simple catheter technique to prevent LVOT obstruction by transecting the anterior mitral valve leaflet, called laceration of the anterior mitral leaflet to prevent LVOT obstruction (LAMPOON). The procedure uses an electrified guidewire that traverses the leaflet base, between 2 retrograde aortic catheters, and which then is pulled outward toward the leaflet tip (**Figures 1A and 1B**). The split anterior mitral leaflet no longer obstructs the LVOT after stent valve implantation and is displaced around the implant by intact chordae tendineae (**Figures 1C to 1F**). We developed and tested the technique in vivo and ex vivo in swine.

METHODS

LAMPOON TECHNIQUE. The technique has 2 steps: leaflet traversal followed by leaflet laceration (**Figure 2**). Traversal is intended to be performed before, and laceration after, positioning of the transcatheter mitral valve. This would allow rapid valve implantation during expected hemodynamic compromise from intended mitral leaflet laceration.

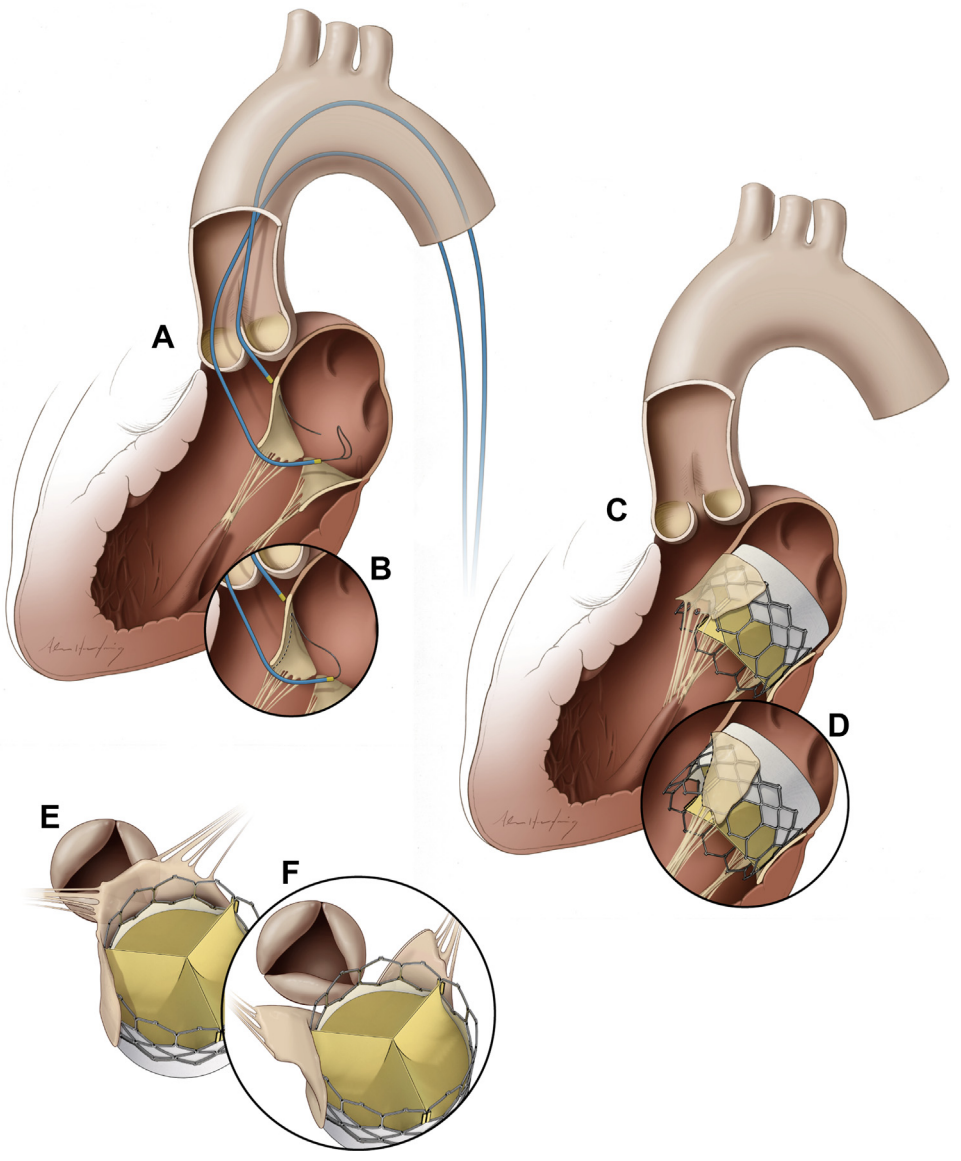
For leaflet traversal, dual retrograde 6-F guiding catheters (Vista Brite Tip, Cordis Corporation, Miami Lakes, Florida) were positioned using 0.035-inch guidewires, 1 into the left atrium, taking care to cross the main mitral orifice without chordal entanglement, and the other in the LVOT, abutting the aortomitral curtain. The LVOT catheter was positioned immediately below the hinge point of the aortomitral curtain, as confirmed by contrast angiography in a projection that corresponds to a 3-plane echocardiogram. Alignment along the center of the anterior leaflet, corresponding to the commissure between the left and noncoronary cusps of the aortic valve, was achieved using contrast angiography in a projection corresponding to a short-axis echocardiogram. Intracardiac echocardiography (AcuNav; Siemens Healthcare, Erlangen, Germany) confirmed this position. A closed-loop snare (10-mm Amplatz GooseNeck, Medtronic, Minneapolis, Minnesota) was positioned through the left atrial catheter behind the atrial base of the anterior mitral leaflet. Through the LVOT catheter, a stiff 0.014-inch guidewire (Astato XS 20, Asahi-Intecc, Nagoya, Japan) was extended through an electrically insulating 0.035-inch polymer jacket (Piggyback Wire Convertor 145 cm, Vascular Solutions, Minneapolis, Minnesota) and directed toward the snare. The proximal guidewire was connected via forceps to a monopolar electrosurgery pencil and diathermy generator (Valleylab Force FX, Medtronic, Minneapolis, Minnesota) set at 30-W continuous duty cycle (“cutting” mode). After traversal, the Piggyback polymer jacket was withdrawn, and the free end of the guidewire was externalized through the retrograde left atrial catheter, positioned to protect against inadvertent tissue injury. The result was a transcatheter guidewire loop around the anterior mitral valve leaflet. No traction was applied until the laceration procedure was initiated, to avoid causing or exacerbating mitral valve regurgitation. Correct traversal was confirmed by angiography through the LVOT catheter and by echocardiography.

Laceration entails traction on both ends of the guidewire that has crossed the leaflet base, during electrification. The intended result is longitudinal

heart valves. Dr. Babaliaros is a consultant for Edwards Lifesciences and Abbott Vascular; and his employer has research contracts for multicenter investigation of transcatheter aortic and mitral devices from Edwards Lifesciences, Abbott Vascular, Medtronic, St. Jude Medical, and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 23, 2016; revised manuscript received June 13, 2016, accepted June 13, 2016.

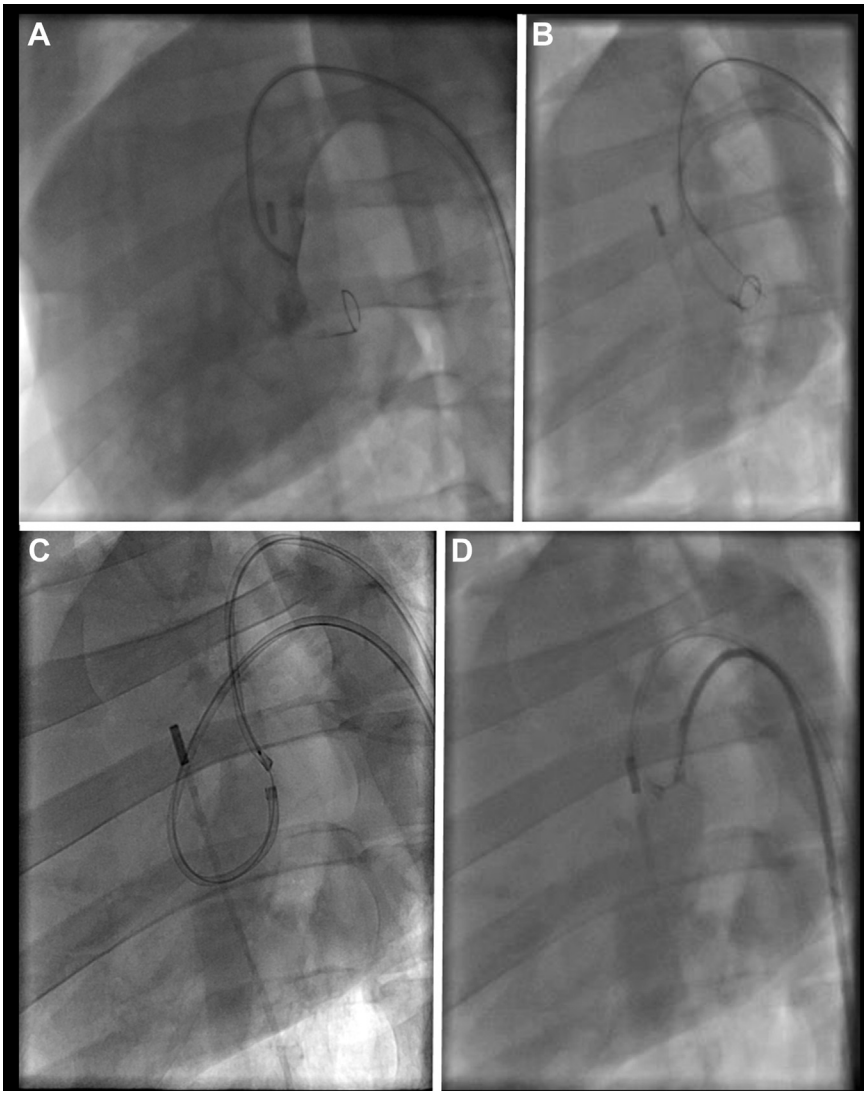
FIGURE 1 Illustrations of the Technique of Intentional Laceration of the Anterior Mitral Valve Leaflet to Prevent Left Ventricular Outflow Tract Obstruction



(A) Two Judkins left catheters are positioned on either side of the A2 mitral leaflet base. An energized guidewire is advanced from the left ventricular outflow tract (LVOT) catheter into the left atrial catheter snare. **(B)** The snared tip is externalized to form a guidewire loop around the A2 leaflet. This is energized and pulled outward to lacerate the leaflet lengthwise into 2 halves. **(C,E)** A transcatheter mitral valve implant tents the anterior mitral leaflet into the septum, obstructing the LVOT. **(D,F)** Splitting the leaflet by intentional laceration of the anterior mitral valve leaflet to prevent LVOT obstruction instead causes the 2 tethered halves to displace along either side of the transcatheter valve, preventing LVOT obstruction.

transection of the anterior mitral valve leaflet, so that 2 remaining flaps are displaced medially and laterally by the transcatheter mitral valve implant, without causing LVOT obstruction. To facilitate radiofrequency ablation energy delivery on the inner (cutting) side of the guidewire, a 5- to 10-mm section of the middle shaft of the 0.014-inch guidewire insulation was denuded by noncircumferential scalpel abrasion (Figure 3A) and then deliberately kinked to confine the denuded section to the inner curvature. The original insulating Piggyback is positioned to mark and abut 1 margin of the denuded

FIGURE 2 Fluoroscopy Demonstration of Intentional Laceration of the Anterior Mitral Valve Leaflet to Prevent Left Ventricular Outflow Tract Obstruction in a Left Oblique Projection

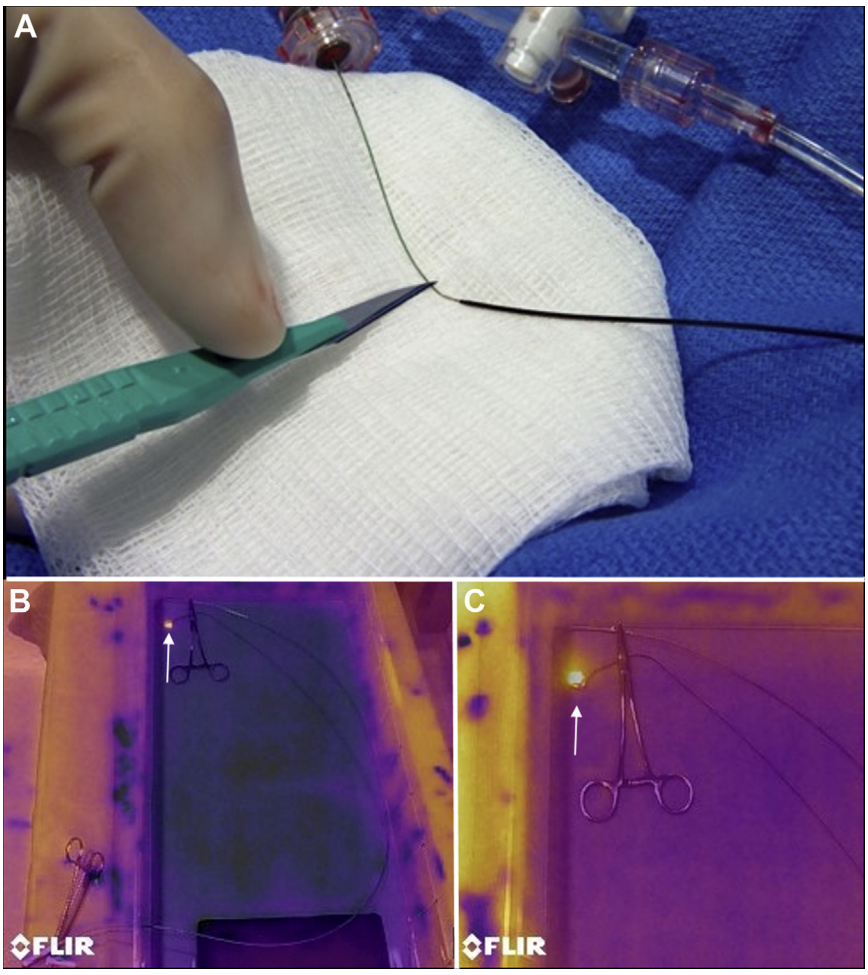


(A) Angiography through the left ventricular outflow tract (LVOT) catheter shows good positioning of this catheter at the base of the anterior leaflet, below the aortic valve, with a loop snare positioned through the left atrial (LA) catheter. **(B)** The electrified guidewire is advanced through the A2 mitral leaflet base into the LA snare. **(C)** A denuded kinked section of the guidewire, insulated and marked proximally with a polymer wire convertor further insulated by the 2 guiding catheters, is electrified while the LA catheter is pulled back into the LVOT (position D) during stage 1 of the 2-step electrosurgical laceration. **(D)** Stage 2 of the laceration. Both catheters are pulled in tandem during a burst application of radiofrequency energy, lacerating the leaflet completely and freeing the catheter-guidewire loop.

shaft, locked in place, and then the kinked denuded section is positioned at the intended laceration site. The guiding catheter tips are apposed within 2 to 5 mm to provide mechanical and electric protection during laceration. The guidewire-catheter relationships are locked using torque devices, and the guidewire is clamped to an electrosurgery pencil. To lacerate, both locked guiding catheters are retracted during brief 2-step electrification. Retraction force was measured using a force meter (ZP-11, Imada, Northbrook, Illinois). Afterward, the guiding catheters are further apposed, and 1 guidewire limb is pulled through to allow catheter removal.

ANIMAL PROCEDURES. Nonsurvival procedures on Yorkshire swine (mean weight, 51 ± 7 kg) were approved by the institutional animal care and use

FIGURE 3 Guidewire Electrosurgery



(A) A short midshaft section of the electrically insulating polytetrafluoroethylene coating of a 0.014-inch guidewire is stripped using a scalpel and then kinked, with a polymer jacket wire convertor locked alongside. **(B)** Infrared images of a saline bath with a denuded guidewire loop through 2 catheters, replicating in vivo intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction. The guidewire is clipped to an electrosurgery pencil and electrified, revealing a hot spot **(bright yellow, arrow)** only at the exposed guidewire loop. **(C)** A close-up of the guidewire loop reveals no heating around the nearby metallic hemostat, suggesting freedom from electric coupling.

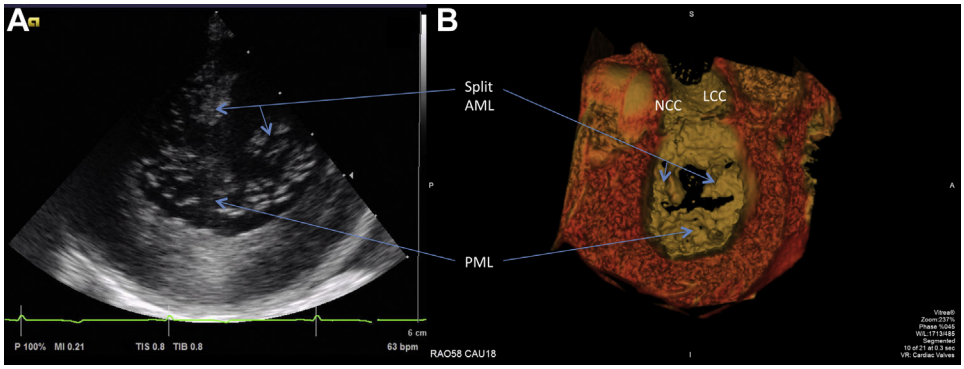
committee and conducted according to contemporary National Institutes of Health guidelines. Bilateral percutaneous femoral artery and vein introducer sheaths were placed during isoflurane anesthesia with mechanical ventilation, and animals received intravenous heparin (150 IU/kg) to achieve an activated clotting time >350 s. Biplane x-ray fluoroscopy (Artis Zee, Siemens Healthcare) and intracardiac echocardiography (AcuNav 8.5-F, Siemens) guided procedures. Euthanasia and necropsy were performed hours after the procedure.

To test the consequences of wrong crossing along the aortomitral curtain, an intentionally high traversal and laceration was performed. To test whether flowing blood would obscure thermal injury, the procedure was also performed in another animal under heparinization, immediately after euthanasia.

At the conclusion of these nonsurvival experiments, animals were euthanized. In all animals, the mitral and aortic structures were examined carefully for thermal or mechanical injury. The laceration positions and lengths were recorded.

TAVR was not performed in these naive animals, absent a suitable fixation mechanism, and instead was performed ex vivo. Native LVOT length (from aortic root to mitral annulus) and minimum LVOT

FIGURE 4 Images of the Lacerated Anterior Mitral Leaflet After Intentional Laceration of the Anterior Mitral Valve Leaflet to Prevent Left Ventricular Outflow Tract Obstruction



(A) Short-axis intraoperative intracardiac echocardiographic image of the mitral valve showing the anterior mitral leaflet (AML) split in 2 equal halves. **(B)** The corresponding post-procedural surface rendering of contrast-enhanced computed tomography also displaying split and splayed leaflets. See Online Video 1. AML = anterior mitral leaflet; LCC = left coronary cusp; NCC = noncoronary cusp; PML = posterior mitral leaflet.

anteroposterior diameter were measured in explanted hearts following in vivo LAMPOON. Transcatheter heart valves (23-mm SAPIEN 3, Edwards Lifesciences, Irvine, California) were implanted at the benchtop at a 70:30 ventricular position across the annulus, and LVOT geometry was measured with and without LAMPOON modification.

IN VITRO HEATING. We performed infrared photography (FLIR E40, FLIR, Portland, Oregon) to test focal midshaft heating during electrification of the insulation-stripped guidewire. A 2-catheter and guidewire crossing system was partially submerged in a saline bath including the electrosurgery indifferent electrode and held in place by a steel clamp to simulate potential electric coupling with a transcatheter mitral valve (Figure 3B).

IMAGING AND DATA ANALYSIS. Post-procedure contrast-enhanced CT was performed on a 320-row volume scanner (Aquilion One Vision, Toshiba, Tokyo, Japan). Surface renderings were generated on an image processing workstation (Vitrea version 6.7, Toshiba).

Data are expressed as mean ± SD. LVOT diameters were compared, before and after simulated TMVR with and without LAMPOON, using 1-way analysis of variance and a Student *t* test with Dunnett's correction for multiple comparisons (Prism version 6, GraphPad Software, La Jolla, California).

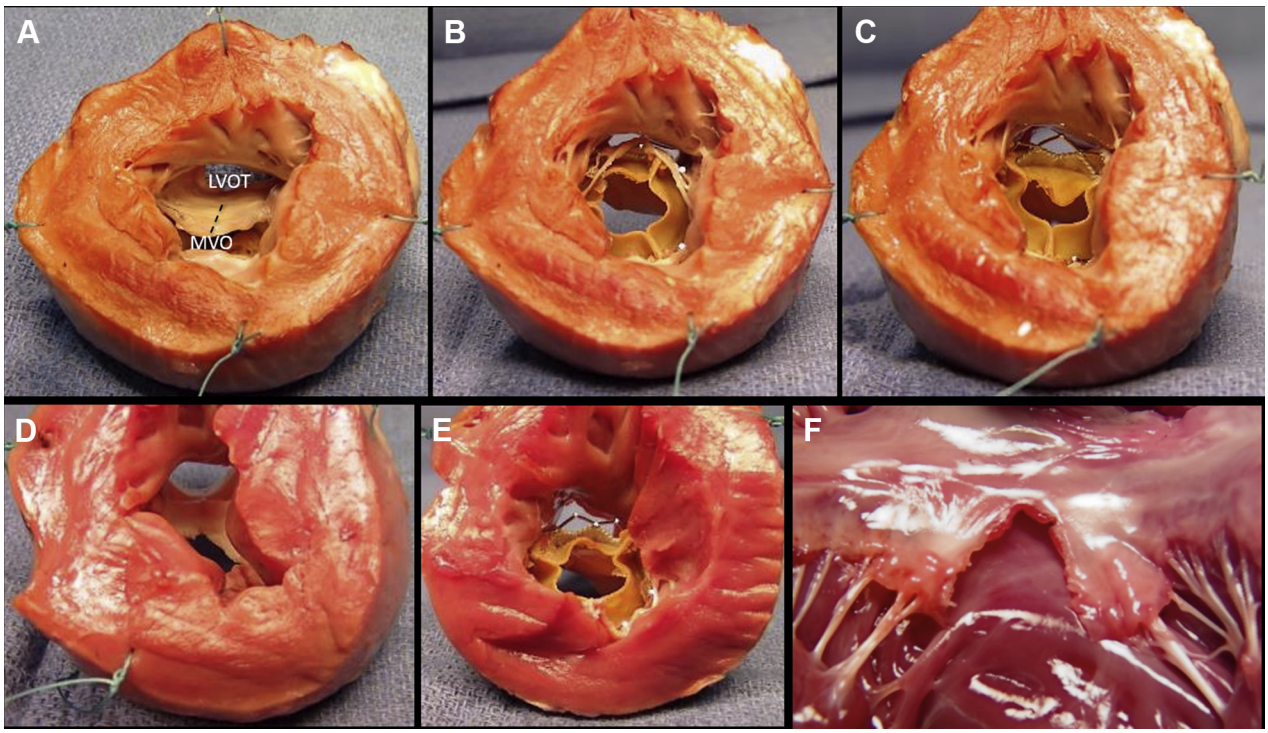
RESULTS

IN VIVO FINDINGS. The LAMPOON procedure was performed in 7 live animals and in 1 post-mortem animal under heparinization. A representative procedure is depicted in Figure 2. The procedure was successful in all animals. The mean procedure time was 55 ± 22 min, including imaging but excluding anesthesia and vascular access. LAMPOON caused mean blood pressure to fall by 44% (from 54 ± 6 mm Hg to 30 ± 4 mm Hg, $p < 0.01$), as expected, but blood pressure remained steady until planned euthanasia for approximately 4 hours. Retraction force was high (50 N, 5.1 kg) with an intact and electrified lacerating guidewire in vivo; retraction force was reduced (to 15 N, 1.5 kg) using a denuded cutting surface surrounded by an insulated polymer jacket.

In 1 animal, the traversal was intentionally performed "low" to simulate avoiding a calcified basal leaflet and traversed 52% of the length of the A2 leaflet. In another animal, the traversal was intentionally performed "high" or above the aortomitral curtain, across the transverse sinus, into the left atrium, to test a serious complication. This caused a small pericardial effusion without hemodynamic change, and the animal was excluded from further analysis. No other animal had pericardial effusion after 2 ± 1 h of survival.

Intracardiac echocardiography demonstrated cavitation microbubbles, as expected, during both the traversal and laceration steps of the procedure. Intracardiac echocardiography also demonstrated not only laceration but also splaying of the A2 mitral leaflet and acute mitral valve regurgitation, as expected, after LAMPOON (Figure 4A). Concomitantly, in vivo computed tomography demonstrated splitting and splaying of the A2 mitral valve leaflets (Figure 4B, Online Video 1).

FIGURE 5 Benchtop Assessment of Left Ventricular Outflow Tract Geometry Impact



The base of the left ventricle is viewed in cross section after the apex is cut away. **(A)** A naive heart with the anterior mitral leaflet intact. The trajectory of an intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction (LAMPOON) laceration is depicted by the dashed line. **(B)** Transcatheter mitral valve replacement (TMVR) with intact anterior leaflet showing reduced left ventricular outflow tract (LVOT) area. **(C)** LAMPOON modification made to the same heart, with the anterior leaflets displaced to the side by TMVR and reduced LVOT obstruction. Flow would be possible through uncovered stent struts. **(D)** Explant after in vivo LAMPOON heart showing lacerated anterior leaflet. **(E)** TMVR in the explanted heart after LAMPOON showing displacement of the anterior leaflet away from the LVOT. **(F)** Explanted heart after isolated in vivo LAMPOON viewed from the posterior wall, showing central laceration down the complete length of the anterior leaflet. The intact subvalvular apparatus displaces the leaflet tips away from the LVOT. LVOT = left ventricular outflow tract; MVO = mitral valve orifice.

POST MORTEM FINDINGS. Post mortem examination of leaflets revealed jagged transections of the A2 anterior mitral leaflet in all animals (Figure 5F). All transections were located between major chordal insertions, as intended. The transection lengths were 19 ± 3 mm in leaflets that were 21 ± 4 mm long (89 ± 19% of leaflet length). The average intercommissural distance was 32 ± 6 mm; the average position of the laceration was 0.5 ± 0.4 mm from the center of the anterior mitral leaflet, as intended. Leaflets were 0.9 ± 0.1 mm thick and showed no visible eschar.

There was no necropsy evidence of injury to the aortic root or aortic valve, nor disruption of the mitral subvalvular apparatus, on any animal whether LAMPOON was performed in vivo or post mortem in situ.

IN VITRO AND EX VIVO FINDINGS. Infrared photography demonstrated that heat during the application of radiofrequency ablation energy emanated from a single location, the denuded portion of the guidewire suspended between insulated guiding catheters (Figure 3B). A nearby stainless steel clamp, positioned to simulate a potentially conductive metallic transcatheter heart valve, did not exhibit heating, which would reflect radiofrequency coupling with the ablation guidewire.

IMPACT ON LVOT OBSTRUCTION. Figure 5 demonstrates LVOT obstruction after benchtop TMVR with and without preparatory LAMPOON. Figure 5F shows a typical post mortem result after in vivo LAMPOON. The 2 halves of the A2 leaflet are parted by the intact subvalvular apparatus. After benchtop TMVR, the LVOT anteroposterior diameters fell from 17 ± 3 to 5 ± 4 mm ($p < 0.01$) without LAMPOON and to 11 ± 2 mm ($p < 0.01$) with LAMPOON. This represented a 69 ± 18% reduction in LVOT diameter following TMVR compared with a 35 ± 10% reduction following LAMPOON ($p < 0.01$).

DISCUSSION

We demonstrate a new application for transcatheter electrosurgery to mitigate a life-threatening complication of TMVR. Using simple catheter techniques, we can split the anterior mitral valve leaflet, which otherwise would be displaced anteriorly by the mitral valve implant and cause LVOT obstruction. The split leaflet edges are displaced around the transcatheter valve by chordal structures.

The potential for LVOT obstruction is a key barrier to TMVR and remains a devastating complication of early and investigational TMVR for native and post-annuloplasty mitral valve failure (1,11,12). Imaging may predict risk for LVOT obstruction (5,6,9) but their sensitivity and specificity remain uncertain. Nevertheless, it is clear that many patients are excluded from clinical and investigational transcatheter mitral valve therapy out of concern for iatrogenic LVOT obstruction.

LAMPOON may be especially helpful applied prophylactically in patients deemed at high risk for LVOT obstruction: those with unfavorable left ventricular geometry, acute aortomitral plane angulation, long leaflets, and a prominent septal bulge (5,6,9). Without LAMPOON, operators may feel compelled to implant TMVR devices higher into the left atrium, which risks embolization. LAMPOON may allow lower implant position and more aggressive flaring of the implant, measures that otherwise would increase the risk for LVOT obstruction.

By comparison, intentional alcohol infarction to reduce interventricular septal thickness would best be performed in a separate procedure, is not suitable for patients with thin interventricular septa, and risks conduction injury and exacerbation of myocardial dysfunction (13).

The procedure sequence in patients would first be LAMPOON traversal and guidewire externalization, followed by pre-positioning of the TMVR device into the left atrium or unexpanded across the mitral valve, followed by LAMPOON laceration, followed by TMVR. Patients without baseline severe mitral valve regurgitation might be expected to experience severe hypotension between the laceration and implantation steps, which with proper planning could be achieved quickly.

STUDY LIMITATIONS. We use radiofrequency ablation to traverse and then lacerate the anterior mitral leaflet. Our traversal technique is the same as used to obtain transcaval access to the aorta (14,15) and relies on radiofrequency power concentration on the guidewire monopole tip, further insulated by the Piggyback polymer jacket. For laceration, we overcome the tendency of charge to concentrate on the outer curvature of the intentionally kinked guidewire shaft by selectively denuding the inner curvature. During laceration, we minimize the length of exposed denuded guidewire by closely approximating the 2 guiding catheters. Both in vitro and in vivo, we observed no evidence of electric coupling to nearby conductive structures, which might heat the transcatheter mitral valve frame or hinder electrosurgical laceration (16).

Many of the risks and limitations of LAMPOON are related to incorrect catheter placement and to electrosurgery. An eccentric or low crossing of the anterior leaflet would result in suboptimal parting of the leaflets. A high crossing may exit into the transverse sinus, risking pericardial effusion, but the guidewire can probably be withdrawn and the traversal repeated in the desired position. Entanglement with chordae could cause chordal injury or deleterious leaflet draping over the prosthetic valve and must be avoided by proper left atrial catheter positioning. We predict that 3-dimensional transesophageal echocardiography, of limited use in swine because of unfavorable anatomy, will be superior to 2-dimensional intracardiac echocardiography in guiding catheter position in patients. The risk for thrombus and gas embolism is mitigated by lower ablation energy and anticoagulation (17). Thrombus may form on the free edges of the lacerated leaflet, although we did not observe it, and may require post-procedural anticoagulation. There is a risk for bystander injury to the aortic valve, which is mitigated by proper insulation of the electrified guidewire. The role of LAMPOON is unclear for valve-in-valve TMVR, where chordal attachments are absent. Bailout LAMPOON is not an option in its current form, as the stent struts of the implanted valve prosthesis would prevent leaflet laceration.

This pre-clinical experience is limited to healthy juvenile swine, which unlike human patients have pristine noncalcified mitral leaflets and nontortuous aligned aortas and aortomitral structures. These structures may be more difficult to align and to lacerate in patients. Post mortem distortion of cardiac geometry probably confounds our ex vivo measurements of LVOT obstruction with and without LAMPOON. LAMPOON was not combined with TMVR in vivo in these animals, absent suitable valve devices. LAMPOON would appear better suited in combination with specific TMVR devices that do not rely on the intact anterior mitral leaflet for fixation. LAMPOON may induce hemodynamic compromise of different severity in human patients with pre-existing mitral valve disease and abnormal left atrial compliance.

CONCLUSIONS

LAMPOON has a promising role in therapy for patients ineligible for surgery and who have a risk for developing LVOT obstruction with TMVR. Serious risks can be mitigated by intraoperative echocardiographic guidance, adequate anticoagulation, and safe electrosurgical practice. Cautious application may be warranted in patients requiring TMVR expected to cause LVOT obstruction but who have no alternative options.

ACKNOWLEDGMENTS The authors thank Alan Hoofring of the National Institutes of Health Division of Medical Arts and Katherine Lucas, Shawn Koslov, and Joni Taylor from the National Heart, Lung, and Blood Institute's Animal Surgery and Resources Core.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Robert J. Lederman, Cardiovascular and Pulmonary Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room 2c713, MSC 1538, Bethesda, Maryland 20892-1538. E-mail: lederman@nih.gov.

PERSPECTIVES

WHAT IS KNOWN? TMVR risks life-threatening LVOT obstruction by displacing the anterior mitral leaflet.

WHAT IS NEW? LAMPOON is a catheter technique to transect the anterior mitral leaflet, to prevent iatrogenic LVOT obstruction.

WHAT IS NEXT? On the basis of this series of pre-clinical experiments, LAMPOON may be ready for cautious investigation in selected patients at high risk for LVOT obstruction.

REFERENCES

1. Eleid MF, Cabalka AK, Williams MR, et al. Percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. J Am Coll Cardiol Intv 2016;9:1161–74.

2. Sud K, Agarwal S, Parashar A, et al. Degenerative mitral stenosis: unmet need for percutaneous interventions. Circulation 2016;133:1594–604.

3. Lee KS, Stewart WJ, Lever HM, Underwood PL, Cosgrove DM. Mechanism of outflow tract obstruction causing failed mitral valve repair. Anterior displacement of leaflet coaptation. Circulation 1993;88:II24–9.

4. Mihaileanu S, Marino JP, Chauvaud S, et al. Left ventricular outflow obstruction after mitral valve repair (Carpentier's technique). Proposed mechanisms of disease. Circulation 1988;78:I78–84.

5. Blanke P, Naoum C, Dvir D, et al. Predicting LVOT obstruction in transcatheter mitral valve implantation: concept of the neo-LVOT. J Am Coll Cardiol Img. In press.

6. Wang DD, Eng M, Greenbaum A, et al. Predicting LVOT obstruction after TMVR. J Am Coll Cardiol Img. In press.

7. Maisano F, Alfieri O, Banai S, et al. The future of transcatheter mitral valve interventions: competitive or complementary role of repair vs. replacement? Eur Heart J 2015;36:1651–9.

8. Deharo P, Urena M, Himbert D, et al. Bail-out alcohol septal ablation for left ventricular outflow tract obstruction after transcatheter mitral valve replacement. J Am Coll Cardiol Intv 2016;9:e73–6.

9. Guerrero M, Urena M, Pursnani A, et al. Balloon expandable transcatheter heart valves for native mitral valve disease with severe mitral annular calcification. J Cardiovasc Surg 2016;57:401–9.

10. Guerrero M, Dvir D, Himbert D, et al. Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: results from the first multicenter global registry. J Am Coll Cardiol Intv 2016;9:1361–71.

11. Descoutures F, Himbert D, Maisano F, et al. Transcatheter valve-in-ring implantation after failure of surgical mitral repair. Eur J Cardiothorac Surg 2013;44:e8–15.

12. Bouleti C, Fassa AA, Himbert D, et al. Transfemoral implantation of transcatheter heart valves after deterioration of mitral bioprosthesis or previous ring annuloplasty. J Am Coll Cardiol Intv 2015;8:83–91.

13. Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. J Am Coll Cardiol 2011;58:2703–38.

14. Halabi M, Ratnayaka K, Faranesh AZ, Chen MY, Schenke WH, Lederman RJ. Aortic access from the vena cava for large caliber transcatheter cardiovascular interventions: pre-clinical validation. J Am Coll Cardiol 2013;61:1745–6.

15. Greenbaum AB, O'Neill WW, Paone G, et al. Caval-aortic access to allow transcatheter aortic valve replacement in otherwise ineligible patients: initial human experience. J Am Coll Cardiol 2014;63:2795–804.

16. Robinson TN, Barnes KS, Govekar HR, Stiegmann GV, Dunn CL, McGreevy FT. Antenna coupling—a novel mechanism of radiofrequency electrosurgery complication: practical implications. Ann Surg 2012;256:213–8.

17. Takami M, Lehmann HI, Parker KD, Welker KM, Johnson SB, Packer DL. Effect of left atrial ablation process and strategy on microemboli formation during irrigated radiofrequency catheter ablation in an in vivo model. Circ Arrhythm Electrophysiol 2016;9:e003226.

KEY WORDS left ventricular outflow tract obstruction, mitral valve, structural heart disease, subvalvular aortic stenosis, transcatheter mitral valve replacement, valvular heart disease

APPENDIX For a supplemental video, please see the online version of this article.

Intentional Percutaneous Laceration of the Anterior Mitral Leaflet to Prevent Outflow Obstruction During Transcatheter Mitral Valve Replacement: First-in-Human Experience

An original research manuscript published in the journal *JACC: Cardiovascular Interventions* in 2017.

Candidate's contribution

I am joint first author (third position) on the enclosed first-in-human manuscript. For this publication, I drafted the manuscript and figures, and planned and proctored the clinical cases. I designed the LAMPOON procedure steps for the first-in-human cases and prepared the contingency plans. My co-first authors recruited and screened the patients and performed the procedures as the primary operators.

JACC: CARDIOVASCULAR INTERVENTIONS
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN
COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 10, NO. 8, 2017
ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2017.01.035

STRUCTURAL

Intentional Percutaneous Laceration of the Anterior Mitral Leaflet to Prevent Outflow Obstruction During Transcatheter Mitral Valve Replacement

First-in-Human Experience

Vasilis C. Babaliaros, MD,[a] Adam B. Greenbaum, MD,[b] Jaffar M. Khan, BMBCH,[c] Toby Rogers, PHD, BMBCH,[c] Dee Dee Wang, MD,[b] Marvin H. Eng, MD,[b] William W. O'Neill, MD,[b] Gaetano Paone, MD,[b] Vinod H. Thourani, MD,[a] Stamatios Lerakis, MD,[a] Dennis W. Kim, MD, PHD,[a,d] Marcus Y. Chen, MD,[c] Robert J. Lederman, MD[c]

ABSTRACT

OBJECTIVES This study sought to use a new catheter technique to split the anterior mitral valve leaflet (AML) and prevent iatrogenic left ventricular outflow tract (LVOT) obstruction immediately before transcatheter mitral valve replacement (TMVR).

BACKGROUND LVOT obstruction is a life-threatening complication of TMVR, caused by septal displacement of the AML.

METHODS The procedure was used in patients with severe mitral valve disease and prohibitive surgical risk. Patients either had prior surgical mitral valve ring (n = 3) or band annuloplasty (n = 1) or mitral annular calcification with stenosis (n = 1). Iatrogenic LVOT obstruction or transcatheter heart valve dysfunction was predicted in all based on echocardiography and computed tomography. Transfemoral coronary guiding catheters directed an electrified guidewire across the center and base of the AML toward a snare in the left atrium. The externalized guidewire loop was then electrified to lacerate the AML along the centerline from base to tip, sparing chordae, immediately before transseptal TMVR.

RESULTS Five patients with prohibitive risk of LVOT obstruction or transcatheter heart valve dysfunction from TMVR successfully underwent LAMPOON, with longitudinal splitting of the A2 scallop of the AML, before valve implantation. Multiplane computed tomography modeling predicted hemodynamic collapse from TMVR assuming an intact AML. However, critical LVOT gradients were not seen following LAMPOON and TMVR. Doppler blood flow was seen across transcatheter heart valve struts that encroached the LVOT, because the AML was split. Transcatheter heart valve function was unimpeded.

CONCLUSIONS This novel catheter technique, which resembles surgical chord-sparing AML resection, may enable TMVR in patients with prohibitive risk of LVOT obstruction or transcatheter heart valve dysfunction.
(J Am Coll Cardiol Intv 2017;10:798–809) Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Structural Heart and Valve Center, Emory University Hospital, Atlanta, Georgia; [b]Center for Structural Heart Disease, Henry Ford Health System, Detroit, Michigan; [c]Cardiovascular and Pulmonary Branch, Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland; and the [d]Children's Healthcare of Atlanta, Emory University, Atlanta, Georgia. Supported without industry funding by the clinical programs of the Structural Heart and Valve Center, Emory University Hospital; the Center for Structural Heart Disease, Division of Cardiology, Henry Ford Health System; and the Division of Intramural Research (Z01-HL006040), National Heart Lung and Blood Institute, National Institutes of Health. Dr. Babaliaros is a consultant for Edwards Lifesciences and Abbott Vascular; and his employer has research contracts from Edwards Lifesciences, Abbott Vascular, Medtronic, St Jude Medical, and Boston Scientific. Dr. Greenbaum is a proctor for Edwards

The anterior mitral valve leaflet (AML) is a mobile structure that physically separates inflow and outflow zones of the left ventricle (1). Preserving the AML during surgical mitral valve replacement can cause left ventricular outflow tract (LVOT) obstruction, either when the prosthesis struts protrude into the LVOT or when a long redundant anterior leaflet prolapses into the LVOT (2,3). In a similar manner, implantation of a transcatheter heart valve (THV) inside the native or repaired mitral valve enforces an "open position" of the AML that may encroach on the LVOT (4–7). This septal displacement of the AML is exaggerated when the aortic and mitral annular planes are acutely angulated rather than parallel, when the interventricular septum bulges toward the LVOT, when the AML is elongated, and when the implant extends or flares into the left ventricle. In this setting transcatheter mitral valve replacement (TMVR) may cause life-threatening LVOT obstruction (**Figure 1A**). Moreover, after TMVR an excessively long AML may prolapse anteriorly into a narrowed LVOT as in hypertrophic cardiomyopathy, or it can prolapse posteriorly and interfere with bioprosthetic heart valve opening or closing by mechanical or Bernoulli effects after surgical (3) or transcatheter mitral replacement (8). Longer AMLs are more susceptible to these effects (9). Although few data are available to guide decision-making, one-half of TMVR candidates having an intact AML (Mayra Guerrero, personal communication February 24, 2017; NCT02370511) are excluded from an ongoing clinical investigation because of the perceived risk of life-threatening LVOT obstruction.

One approach to prevent or treat TMVR-related LVOT obstruction is pre-emptive transcoronary alcohol septal ablation (10,11), which sacrifices myocardium and risks conduction system injury and pacemaker-dependence in patients with cardiomyopathy, which is unsuitable in patients with thin interventricular septa, and which delays TMVR by 4 to 6 weeks to allow remodeling in highly symptomatic patients. Another option is surgical AML resection combined with TMVR during thoracotomy and cardiopulmonary bypass (12–14), with attendant risk and morbidity to patients already believed to be at high risk for cardiac surgery.

As an alternative, we have developed a transcatheter adjunct to TMVR using off-the-shelf equipment, and described its preclinical use (15). This technique resembles David's (16) surgical anterior resection with chordal sparing. We create a longitudinal split of the middle scallop (A2) of the AML, immediately before TMVR. As a result, chordal attachments displace the split AML away from the LVOT after the cylindrical THV is implanted, and blood flows unobstructed across the THV stent struts (**Figure 1B**).

We report the initial human experience with this intentional laceration of the AML to prevent left ventricular outflow tract obstruction (LAMPOON) procedure.

ABBREVIATIONS AND ACRONYMS

AML = anterior mitral valve leaflet

CT = computed tomography

LA = left atrium

LAMPOON = laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction

LVOT = left ventricular outflow tract

MAC = mitral annular calcification

TEE = transesophageal echocardiography

THV = transcatheter heart valve

TMVR = transcatheter mitral valve replacement

METHODS

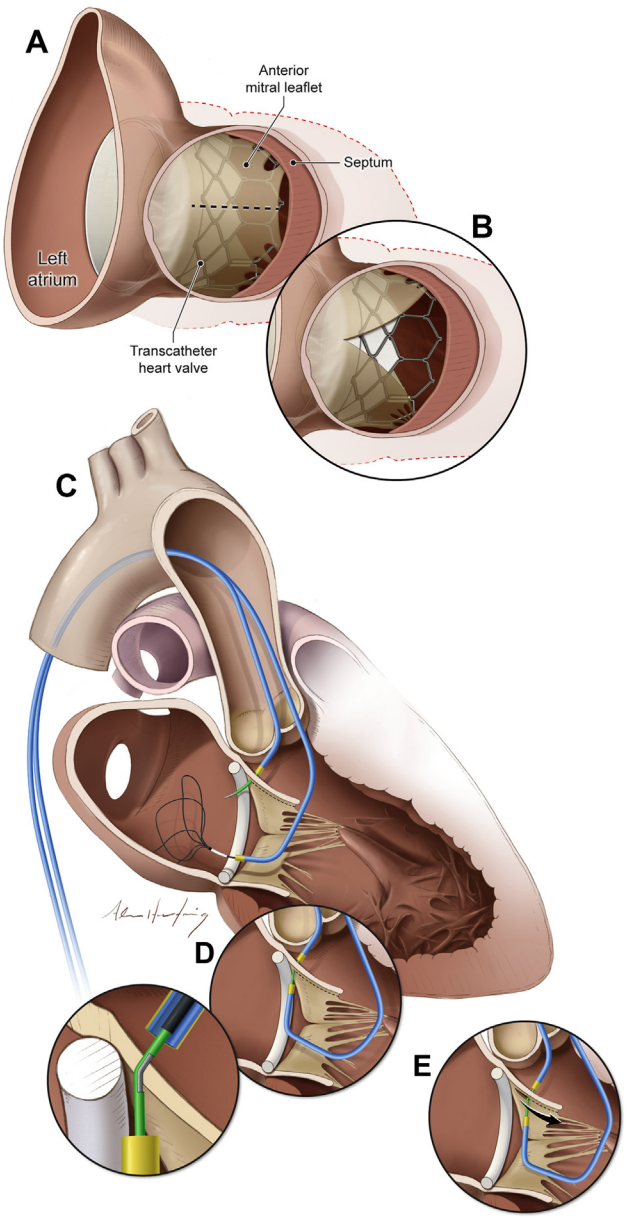
PATIENTS. TMVR with LAMPOON was performed at 2 medical centers, Emory University Hospital and Henry Ford Hospital. The institutional ethics review boards of both approved this communication. Five patients deemed inoperable and believed to have prohibitive risk of TMVR because of intact native mitral leaflets consented explicitly to this novel procedure, as clinical therapy, after consensus from the local multidisciplinary structural heart teams.

PROCEDURE PLANNING AND IMAGE GUIDANCE. Baseline electrocardiogram-gated contrast-enhanced 64-detector row cardiac computed tomography (CT) angiography was obtained to measure annular and/or annuloplasty dimensions to select a THV. Multiplanar reconstruction (Vitrea, Toshiba, Tustin, California) was performed to predict the following working projections: angle of TMVR deployment perpendicular to the prosthesis or annulus, a left anterior oblique caudal projection corresponding to a short-axis CT reconstruction to depict LAMPOON traversal position along the medial-lateral dimension, and an attainable right anterior oblique caudal projection corresponding to a 3-chamber CT reconstruction to depict LAMPOON traversal position along the leaflet base-to-tip dimension.

Lifesciences and St Jude Medical. Dr. O'Neill is a consultant for Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Vascular, and St. Jude Medical; and serves on the Board of Directors of Neovasc Inc. Dr. Thourani is a consultant for Edwards Lifesciences. Dr. Lerakis is a consultant for Edwards Lifesciences and Abbott Vascular. Dr. Kim is a consultant for Edwards Lifesciences; and a proctor for B. Braun. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Babaliaros, Greenbaum, and Khan contributed equally to this work.

Manuscript received December 23, 2016; revised manuscript received January 30, 2017, accepted January 31, 2017.

FIGURE 1 Views of the Anterior Mitral Valve Leaflet From the LVOT



(A) In this example, transcatheter mitral valve implantation displaces the native anterior mitral valve leaflet causing LVOT obstruction. **(B)** After LAMPOON, LVOT obstruction is reduced and blood flows across the unobstructed struts of the implanted transcatheter heart valve. **(C to E)** Illustration of the LAMPOON procedure. **(C)** In 2 retrograde guiding catheters are positioned across the aortic valve, 1 into the LVOT and another across the mitral valve into the left atrium. The LVOT catheter directs an electrified guidewire across the base of the anterior mitral valve leaflet under echocardiographic guidance into a snare positioned through the left atrial guiding catheter. **(D)** Once the guidewire traverses the mitral leaflet, it is ensnared and externalized. The **inset** depicts a denuded and kinked section of the guidewire shaft that directs electrosurgery energy to the leaflet. **(E)** The guidewire is electrified and the 2 guiding catheters withdraw it to lacerate the anterior mitral leaflet lengthwise. LAMPOON = laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction; LVOT = left ventricular outflow tract. Online Video 1 is depicted in this figure.

A predicted post-TMVR minimum LVOT area ("threatened neo-LVOT") area was obtained on a separate workstation (Mimics, Materialise, Leuven, Belgium). TMVR was simulated in systole using cylinders corresponding to the known external length and diameter of the planned THVs, implanted at the intended depth relative to the mitral annulus (80/20 left ventricle/left atrium [LA]), and the minimum projected area recorded assuming the AML would be obstructive only where it contacts the TMVR device.

AML lengths were measured on CT and transesophageal echocardiography (TEE). Long leaflet length (>30 mm, compared with nominal height 18.0 to 22.5 mm of Sapien 3, Edwards Lifesciences, Irvine, California) combined with acute aortomitral angle, was considered an independent risk factor for LVOT obstruction and THV dysfunction as part of the multidisciplinary heart team evaluation, accepting the difficulty modeling this based on static CT images. TMVR with LAMPOON was performed in a biplane angiography system at 1 site, and single plane in the other. All patients underwent general anesthesia and intraprocedural TEE.

LAMPOON TECHNIQUE. The LAMPOON procedure has 3 steps (Online Video 1): leaflet traversal with a guidewire, followed by leaflet laceration, immediately followed by TMVR. These are all guided by fluoroscopy combined with TEE.

For leaflet traversal, 2 6-F coronary guiding catheters (JL3.5) are advanced across the aortic valve (**Figure 1C**) through 2 femoral artery sheaths. One guiding catheter is positioned retrograde in the LVOT abutting the base of A2 to direct the traversal guidewire, and the other retrograde into the LA across the aortic and mitral valves.

In patients with mitral stenosis, we found it helpful to advance the retrograde LA catheter over a 0.014 wire rail into the transseptal catheter. The rail eases LA catheter repositioning should it prolapse into the left ventricle. The rail is formed by advancing a balloon tip catheter from a transseptal deflectable catheter (Agilis NxT medium curl, St. Jude Medical, St. Paul, Minnesota) in the LA through the main orifice of the mitral valve. The rail is a kink-resistant guidewire (Runthrough NS 0.014-inch, Terumo Interventional Systems, Somerset, New Jersey), and is externalized after snaring. Through the retrograde LA catheter, a multiloop snare (Atrieve 18/30, Argon Medical, Plano, Texas) is positioned alongside the rail and alongside the mitral coaptation surfaces.

The electrosurgical traversal technique is derived from the technique of transcaval crossing (17,18). The traversal guidewire is a 0.014-inch × 300 cm

guidewire (Astato XS 20, Asahi Intecc USA, Santa Ana, California) inside an insulating polymer jacket wire convertor (Piggyback, Teleflex Vascular Solutions, Minneapolis, Minnesota), inside the retrograde LVOT guiding catheter. The external back end of the guidewire is connected via hemostatic forceps to an electrosurgery pencil and generator (ValleyLabFX, Medtronic Covidien, Minneapolis, Minnesota), set to "pure" cutting mode at 50 W. The traversal guidewire is advanced from the LVOT catheter, penetrating the base of the A2 scallop, during brief (<1 s) electrification into the prepositioned left atrial snare (Figure 1D). The wire is captured and externalized through the retrograde LA catheter.

A short segment along the middle of the guidewire shaft is noncircumferentially denuded of its polymer insulation, and then kinked, using a scalpel. This minor modification focuses electrosurgery energy required for laceration on the "inner elbow" of the guidewire (Figure 1D, inset). The radiopaque tip of the Piggyback wire converter is locked behind the denuded kinked segment for added fluoroscopic visibility and electrical insulation. The kinked segment is positioned to straddle the AML.

For laceration, both free guidewire ends are firmly pulled during electrification in a series of brief (<1 s) steps. Pulling the guidewires helps to oppose the guiding catheters, to protect the aortic valve, and to initiate laceration at the base of the AML (Figure 1E). Further tension on the guidewires completes the splitting of the AML.

ANTEGRADE TRANSSEPTAL TMVR TECHNIQUE. TMVR was performed via an antegrade transseptal route using Edwards Sapien 3 devices. The rigid TMVR guidewire was delivered into the left ventricle after first crossing the major mitral orifice using a balloon wedge endhole catheter, and atrial septostomy performed using 12-to-16-mm balloon dilatation catheters to ensure transseptal THV delivery. Tension was applied to the LAMPOON catheter system under fluoroscopy to ensure the TMVR guidewire was not entrapped. The THV was positioned in the left atrium or partway across the mitral valve before LAMPOON laceration to facilitate rapid deployment in case of early hemodynamic compromise.

TMVR was performed immediately after LAMPOON, using rapid right ventricular pacing and slow balloon inflation. After the first inflation, the THV delivery balloon was advanced slightly forward and reinflated with at least 4 ml additional inflation volume to flare the ventricular aspect of the THV stent. At the conclusion of the procedure, the iatrogenic atrial septal defect was closed based on operator discretion.

TABLE 1 Baseline Clinical Characteristics (n = 5)

Age, yrs	64.8 ± 13.2
Female, %	40
Severe pulmonary disease, %	60
Prior stroke, %	40
Atrial fibrillation, %	60
eGFR ml/min/1.73 m^2	65.4 ± 11.4
NT-proBNP baseline	432.3 ± 346.9
STS PROM mitral valve replacement, %	8.2 ± 3.6
NYHA CHF functional class	3.8 ± 0.4
TMVR setting	TMVR-in-ring = 3 TMVR-in-band = 1 TMVR-in-MAC = 1
Primary lesion (valvular stenosis/regurgitation/mixed)	3/1/1
Ring or band nominal diameter, mm	30.0 ± 2.8
Left ventricular ejection fraction	0.48 ± 0.14
Right ventricular dysfunction, %	80
Echo septal thickness, mm	8.8 ± 1.1
Echo septal thickness amenable to alcohol septal ablation, %	0

Values are mean ± SD or %.

CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; MAC = mitral annular calcification; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; STS PROM = Society of Thoracic Surgeons predicted risk of mortality; TMVR = transcatheter mitral valve replacement.

POST-PROCEDURE IMAGE AND DATA ANALYSIS. Post-procedure invasive pressure and Doppler echocardiography gradients were recorded across the LVOT and THV, using peak-to-peak and peak-instantaneous measurements as suggested by Geske et al. (19) for hypertrophic cardiomyopathy. Post-procedure neo-LVOT was evaluated by echocardiography. TMVR encroachment on the LVOT was measured in B-mode to determine the retrospective "threatened" LVOT diameter as if LAMPOON had not been performed, and in color Doppler mode to visualize blood flow across the THV stent struts and determine the "actual" LVOT diameter. Similarly, post-procedure CT was evaluated to measure a "threatened" LVOT area as if LAMPOON had not been performed. Data were reported as mean ± SD or as median (range) as appropriate.

RESULTS

PATIENTS. Clinical characteristics of the 5 patients are shown in Table 1. All were believed to have prohibitive surgical risk and no therapeutic alternatives. None were considered suitable for preparatory alcohol septal ablation to debulk the LVOT.

The first 4 patients had undergone prior surgical mitral annuloplasty. The first had a rigid annuloplasty ring (primarily regurgitant lesion), the next 2 had semi-rigid rings (1 primarily stenotic and the other mixed regurgitant/stenotic), the fourth had a flexible posterior annuloplasty band (primarily stenotic), and

TABLE 2 Procedure Characteristics, Hemodynamics, and Imaging (n = 5)

TMVR size, Sapien 3, mm	26 (n = 2); 29 (n = 3)
Crossing power, W	50 ± 0
Lacerating power, W	58 ± 11
LVOT catheter Judkins left length, cm	3.9 ± 0.7
Left atrial retrograde catheter Judkins left length, cm	3.7 ± 0.3
Procedure time, min	214 ± 24
Time from catheter to valve, min	133 ± 19
Time from leaflet traversal to leaflet laceration, min	66 ± 10
Time from laceration to TMVR, min (range)	3.0 (1–38)
Fluoroscopy time, min	116 ± 39
Radiation dose-area product, Gy·cm^2	335 ± 319
Contrast volume, ml	68 ± 41
Iatrogenic atrial septal defect closed	4 of 5

Pressure, mm Hg	Before	After
Mitral valve gradient mean	9.2 ± 4.2	4.6 ± 4.0
LVOT gradient (range)	7.4 ± 0.5 (7–8)	17.6 ± 12.4 (8–39)
LA mean pressure	25.8 ± 9.2	18.2 ± 4.8
LA v-wave	50.2 ± 15.9	30.0 ± 6.4
PA systolic pressure	72.8 ± 10.9	58.2 ± 15.4

Computed Tomography Characteristics	
Aortomitral plane angle, degrees, n = 5	123 ± 10
Neo-LVOT* predicted, mm^2, n = 2	67 ± 4
Neo-LVOT* after TMVR, mm^2, n = 2, assuming LAMPOON had not been performed	50 ± 71

Echo Characteristics After TMVR	
LVOT max native dimension B-mode after TMVR, mm	17.6 ± 2.1
LVOT vena contracta after TMVR (includes stent-free), mm	11.8 ± 3.5
LVOT stent-free length after TMVR, mm	4.4 ± 4.5
LVOT obstruction threatened diameter,† %	76 ± 24
LVOT obstructed actual diameter, %	34 ± 15
LVOT gradient peak-instantaneous by echo, pre-discharge, mm Hg	26 ± 11
LVOT gradient peak-instantaneous by echo, 1 month, mm Hg	17 ± 10

Values are mean ± SD (range). *Neo-LVOT is the minimum cross-sectional area of the LVOT expected after implantation of the selected valve, based on 3-dimensional computed tomography analysis. These assume there is no flow across the struts of the implanted transcatheter heart valve. Neo-LVOT is reported on the 2 patients with predicted stent encroachment rather than excessive anterior mitral valve leaflet length. †Threatened diameter refers to the diameter obstruction of the LVOT assuming there would be no flow across the struts of the transcatheter heart valve.

LA = left atrium; LAMPOON = laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction; LVOT = left ventricular outflow tract; PA = pulmonary artery; other abbreviations as in Table 1.

the fifth had native mitral annular calcification (MAC) with stenosis.

Three (Patient #1, #2, and #4) were predicted to have prohibitive risk of LVOT obstruction or THV dysfunction from long redundant AMLs, with mean AML length 32 ± 2 mm and average peak-to-peak catheter resting LVOT gradient 7.4 ± 0.5 mm Hg. Two (Patient #3 and #5) were predicted to have life-threatening LVOT obstruction after TMVR with a predicted neo-LVOT of 67 ± 4 mm^2 on the basis of multiplanar CT modeling. One required intra-aortic balloon pump at baseline because of intractable heart failure. No others required mechanical circulatory support.

LAMPOON PROCEDURE. Procedure details are shown in Table 2. A representative procedure is depicted in Online Video 2. Preparatory LAMPOON successfully split the A2 scallop of the AML in all 5 patients. Figures 2 and 3 show representative radiograph, TEE, and CT images of a patient undergoing LAMPOON and TMVR after prior surgical mitral annuloplasty. Figure 4 shows radiograph and TEE sequences of a patient undergoing LAMPOON and TMVR for MAC causing mitral stenosis. Figure 5 shows the split mitral leaflet in the interval between LAMPOON and TMVR. Figure 6 shows CT images of a patient treated for mitral stenosis caused by MAC, causing pulmonary alveolar hemorrhage. After TMVR with LAMPOON, the THV is seen spanning the entire LVOT, and the pleural and pulmonary abnormalities are dramatically improved.

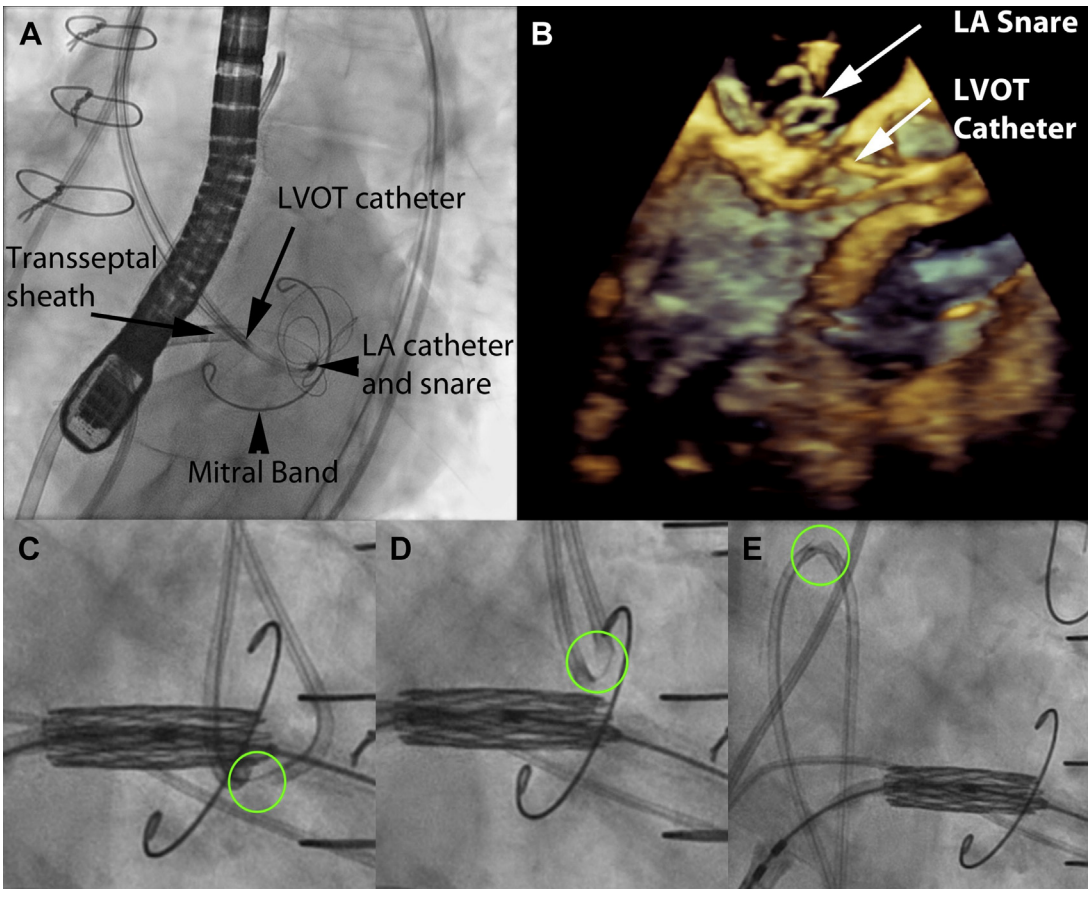
The blood pressure and heart rate did not decline in any patient during the 1-to-38-min interval between LAMPOON and TMVR. Hemodynamic details are shown in Table 2. The average post-procedure LVOT catheter gradient was 17.6 ± 12.4 mm Hg immediately after LAMPOON and TMVR in these patients otherwise expected to have intolerable LVOT obstruction or THV dysfunction.

X-plane TEE guided medial-lateral and base-to-tip positioning of the LVOT catheter before and during leaflet traversal and laceration, complemented by left anterior oblique caudal short-axis and right anterior oblique caudal pseudo-3-chamber fluoroscopic projections. A true 3-chamber extreme left anterior oblique cranial or extreme right anterior oblique caudal projection was not attainable in any patient.

POST-LAMPOON IMAGING. LAMPOON created a new jet of severe mitral regurgitation across the A2 scallop in all 5 cases (Figure 4F). After TMVR, blood flow across the THV struts was evident from the left ventricular inflow into the LVOT, which would not have been possible if the AML had not been disrupted (Figures 3A, 3C, 4G, and 4I). Echocardiography and CT details are summarized in Table 2.

SURVIVAL AND COMPLICATIONS. Four patients (80%) survived beyond 1 month (197 days [range 23 to 273 days] as of this report). Complications are described in Table 3. One patient died 23 days after TMVR with LAMPOON because of intractable right heart failure that did not improve after TMVR. There were no procedural strokes, clinically significant

FIGURE 2 LAMPOON to Enable Transcatheter Mitral Valve Replacement Inside a Flexible Mitral Annuloplasty Band



(A) Left anterior oblique caudal short-axis fluoroscopic projection showing 2 retrograde catheters positioned before anterior mitral valve leaflet traversal. The retrograde LVOT and LA catheters overlap in this view, as intended. The posterior mitral valve band provides a fluoroscopic marker to position the LVOT catheter along the base of the A2 scallop. The LA catheter is directing the multiloop snare and is supported by a transseptal rail through a transseptal sheath. **(B)** A 3-dimensional transesophageal echocardiograph of the same step, with a LVOT catheter positioned at the base of the A2 scallop, and the LA catheter pointing a multiloop snare at the other side of the A2 scallop. **(C)** Initiation of laceration. The kinked guidewire cutting edge is circled in **green**. The transcatheter heart valve is pre-positioned at the orifice of the mitral valve. The LAMPOON guidewire is pulled outward to apply tension. **(D)** The LAMPOON guidewire is electrified during further pulling to initiate laceration. **(E)** Completed laceration, with both retrograde catheters insulating the wire safely in the descending aorta. The kinked guidewire cutting edge, adjacent to the radiopaque piggyback tip marker, is seen sheathed in the catheter. LA = left atrium; other abbreviation as in **Figure 1**. Online Video 2 is depicted in this figure.

paravalvular leaks, or major bleeding or vascular complications of the LAMPOON and TMVR procedure.

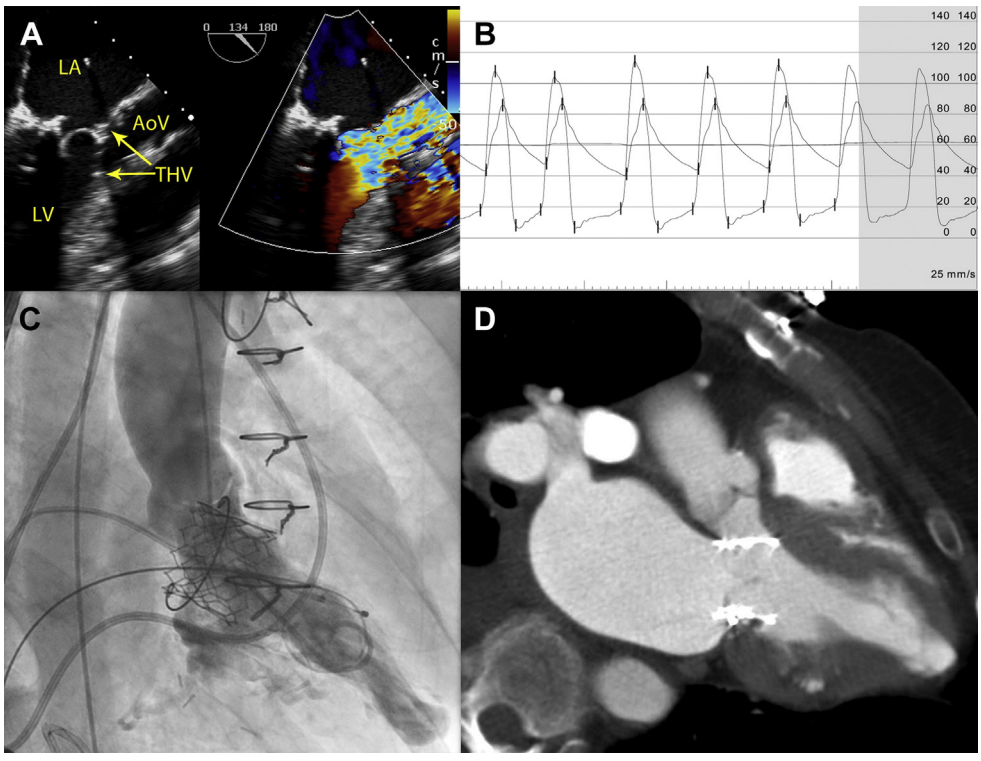
In the first patient, the THV embolized immediately into the left atrium. In retrospect it was significantly undersized for the rigid annuloplasty ring. After successful TMVR using a 29-mm Sapien 3 THV, the embolized valve was secured against the LA septum using a 35-mm Amplatzer septal occluder.

Patient #5 suffered mild hemolysis, evident from low haptoglobin and elevated lactate dehydrogenase levels, and not requiring treatment. Post-procedure anemia resolved but haptoglobin remained depressed 4 months later. We suspect this is caused by mechanical red blood cell injury (20) from flow across the THV struts, because there is no paravalvular leak.

DISCUSSION

We have successfully lacerated the AML using a straightforward percutaneous technique (LAMPOON) immediately before TMVR in 5 patients. The technique resembles chordal-sparing AML resection that has become a standard in surgical mitral valve replacement (16,21). The technique succeeded in a

FIGURE 3 Imaging Immediately After LAMPOON for TMVR-in-Band



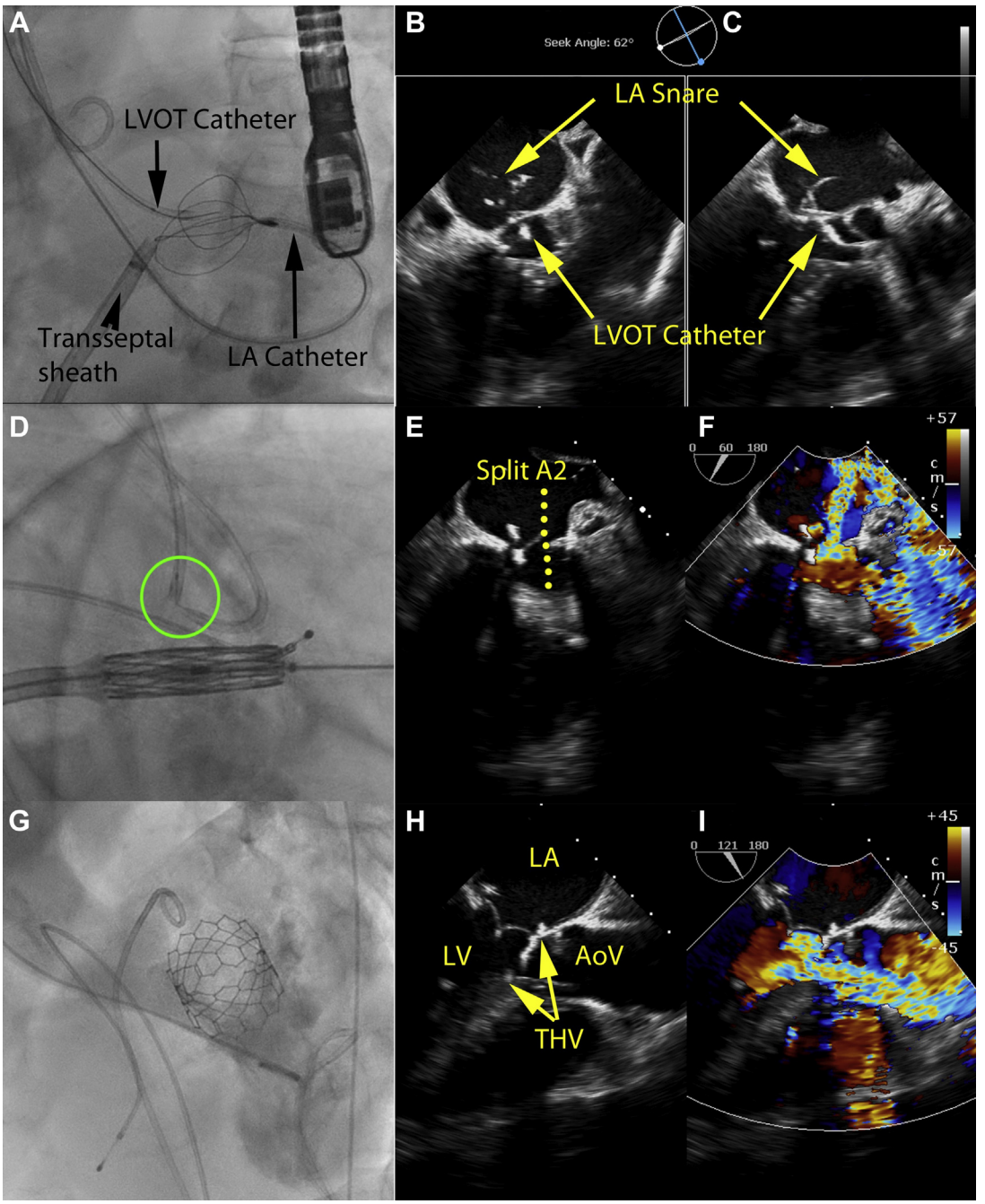
These images are from the same patient as in Figure 2. **(A)** B-mode and color Doppler transesophageal echocardiography after LAMPOON and TMVR shows the stent struts protruding into the LVOT, and blood flow across those struts indicating successful leaflet splitting. **(B)** Catheter pressure measurements across the LVOT show a tolerable gradient of 16 mm Hg. **(C)** Left ventriculography and **(D)** contrast computed tomography after TMVR shows the THV encroaches completely across the LVOT and would nearly completely obstruct it if not for LAMPOON. AoV = aortic valve; LV = left ventricle; THV = transcatheter heart valve; TMVR = transcatheter mitral valve replacement; other abbreviations as in Figures 1 and 2. Online Video 2 is depicted in this figure.

range of different TMVR settings: mitral valve rigid ring annuloplasty, mitral valve semi-rigid ring annuloplasty, mitral valve flexible posterior band annuloplasty, and native MAC. In patients deemed ineligible for TMVR because of predicted catastrophic LVOT obstruction or THV dysfunction, LAMPOON allowed TMVR without THV dysfunction and generated LVOT obstruction that was less than otherwise predicted.

The LAMPOON technique is important because 9% to 22% of patients selected to undergo TMVR in annuloplasty rings or native MAC experience critical LVOT obstruction (14,22,23). At present at least one-third of patients seem to be excluded from TMVR out of predicted risk of LVOT obstruction caused by the displaced AML. LAMPOON may allow TMVR in most, or perhaps all such excluded patients when using commercially available (uncovered) aortic THV devices off-label. Moreover, long or redundant native mitral leaflets have occasionally interfered with THV function either by direct mechanical interposition or by creating a low-pressure Bernoulli jet that impairs THV closure. Three of 5 patients had such long and redundant AMLs. The LAMPOON technique may prevent this THV dysfunction by displacing the split mitral leaflet. Finally, the LAMPOON strategy of splitting the AML, combined with TMVR devices that allow flow across uncovered stent struts, should inform development of future dedicated TMVR devices.

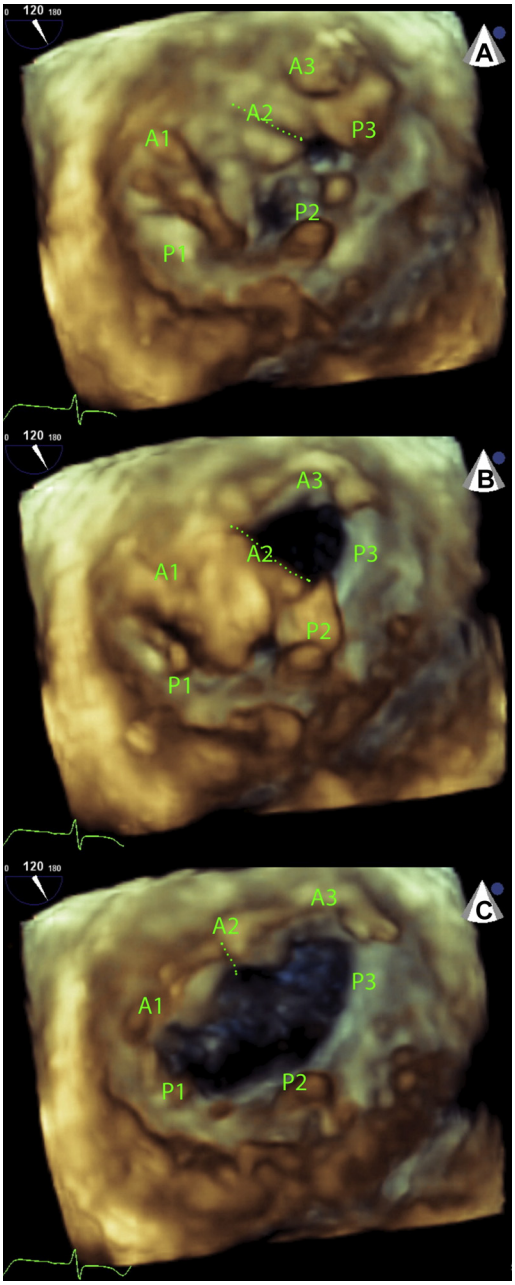
Remarkably, no patient exhibited a change in heart rate or blood pressure in the short time interval between LAMPOON mitral laceration and TMVR. In each case, echocardiography revealed acute exacerbation of mitral regurgitation. Acute mitral regurgitation caused by leaflet tethering is a recognized cause of hemodynamic deterioration in antegrade transvenous transseptal transcatheter aortic valve replacement (24), and unintentional guidewire laceration of the AML, in a tip-to-base fashion, is a

FIGURE 4 LAMPOON to Enable TMVR in Native Mitral Annular Calcification



(A to C) Leaflet traversal, **(D to F)** leaflet laceration, and **(G to I)** imaging after LAMPOON and TMVR. **(A)** Guidewire traversal across the base of the anterior mitral leaflet. Four catheters are in place. An antegrade transseptal sheath, used for TMVR, is currently connected via a guidewire rail to control the retrograde LA catheter, which is used to deliver the multiloop snare on the LA side of the anterior mitral leaflet. A retrograde catheter in the LVOT is directing the traversing guidewire. There also is a pigtail catheter in the ascending aorta. **(B, C)** X-plane TEE immediately after leaflet traversal shows the mid-basal A2 position of the traversal system. Also evident are the 2 catheters and the LA snare. **(D)** The traversing guidewire tip has been externalized. The guidewire shaft is denuded, kinked, and exposed between the 2 catheters **(green circle)**, and is electrified to slice the anterior mitral leaflet longitudinally. The THV is pre-positioned for immediate deployment. **(E, F)** B-mode and color Doppler TEE after LAMPOON but before TMVR shows severe acute mitral valve regurgitation across the split A2 leaflet scallop. **(G)** Left ventriculography after TMVR shows the THV encroaches nearly completely across the LVOT and would nearly completely obstruct it if not for LAMPOON. **(H, I)** B-mode and color Doppler TEE after LAMPOON and TMVR shows the stent struts protruding into the LVOT, and blood flow across those struts indicating successful leaflet splitting. TEE = transesophageal echocardiography; other abbreviations as in Figures 1 to 3.

FIGURE 5 LAMPOON-Induced Anterior Mitral Leaflet Split



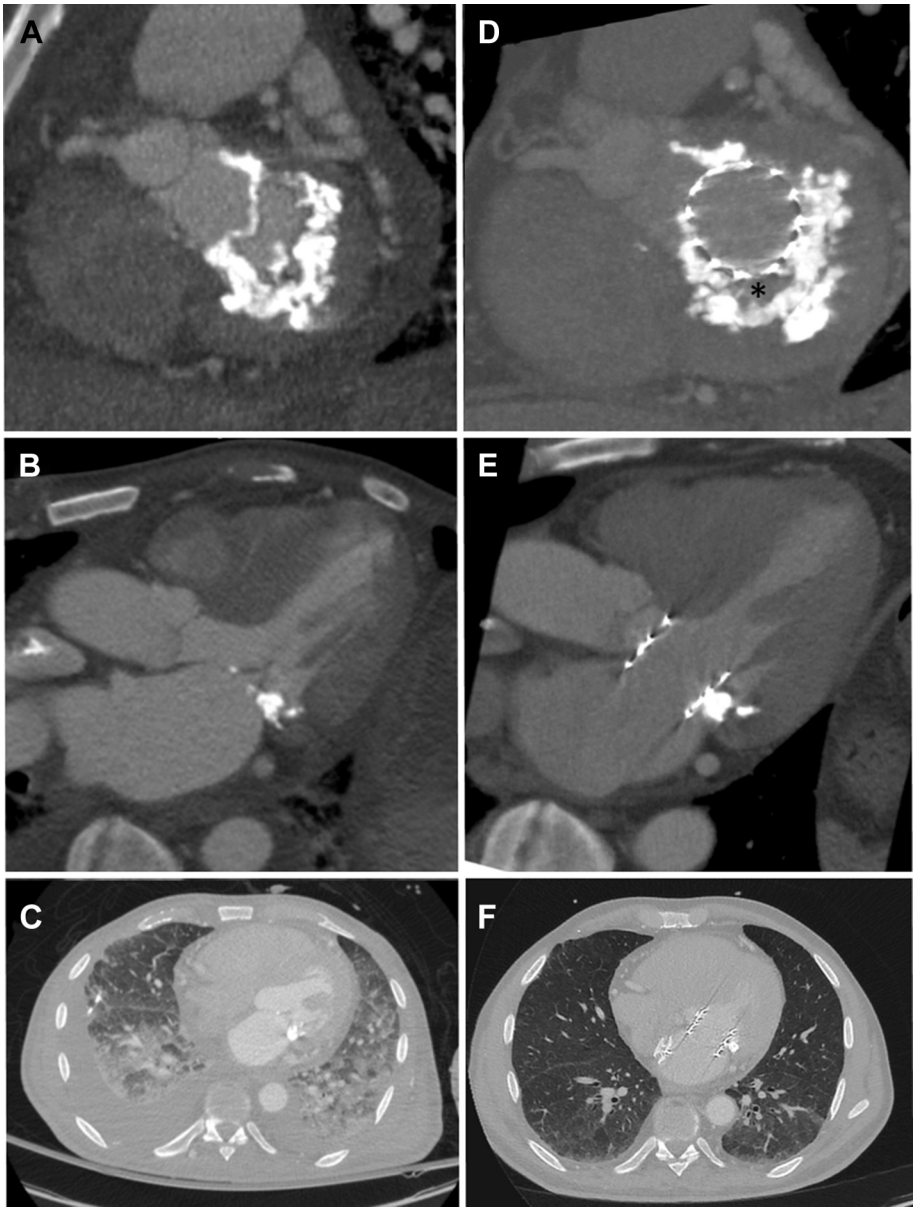
Three sequential diastolic frames of a 3-dimensional echocardiogram performed immediately after LAMPOON but before TMVR. The volume is rendered from a left-atrial "surgeons view." **(A)** A laceration cleft is evident **(dotted green line)** at the beginning of diastole in the A2 scallop of the anterior mitral leaflet. **(B)** The medial half of A2 and the whole of A3 open early in diastole and then **(C)** the lateral half of A2 along with the whole of A1 open a fraction later in diastole. A1 to A3 and P1 to P3 represent the lateral to medial scallops of the anterior and posterior mitral leaflets, respectively. Abbreviations as in Figures 1 and 3.

recognized lethal complication of this approach (25). After LAMPOON, however, we observe a "grace period" that may reflect adaptation to left atrial volume and pressure overload from longstanding mitral stenosis or mitral regurgitation. Nonetheless, in every case we had pre-positioned the TMVR device in the left atrium to allow immediate implantation.

We did not observe severe mechanical complications of the LAMPOON procedure. One theoretical complication is injury to the aorta or aortic valve; we mitigated this risk by protecting the laceration wire surface using rigid braided guiding catheters. Another is mitral leaflet laceration through a lateral orifice of the mitral valve, which might leave a residual chorda that could prevent the split mitral leaflet from draping around the TMVR device. Another theoretical risk is of insufficiently basal traversal and laceration of the AML that causes insufficient leaflet debulking. We do not believe LAMPOON reduced stability of the THV implant; THV embolization in the first case reflected our mistaken selection of an undersized initial device. We attribute the observed low-grade hemolysis in patient #5 to nonlaminar flow across the THV struts as it spans across the LVOT. This would be classified as a mild complication according to the Mitral Valve Academic Research Criteria (26). Guidewire electrification may cause thromboembolism including cerebral thromboembolism; we mitigated this risk by anticoagulation and by selecting ablative energies used in cardiac electrophysiology procedures (27).

STUDY LIMITATIONS. Limitations of our work include the lack of a control group. We do not know with certainty that LVOT obstruction would have been clinically important without LAMPOON. However, we have compelling circumstantial evidence, such as the finding that the THV straddled the full width of the LVOT cases #3 and #5. Based on available evidence, it does not seem reasonable to offer TMVR without leaflet or septal debulking in patients with a low predicted neo-LVOT. Additional limitations are that the nature and long-term implications of THV flow disruption caused by redundant AMLs is not understood; neither is flow following LAMPOON. Given the infancy of this field, we have few data to predict post-TMVR LVOT obstruction with confidence, whether based on LVOT geometry or on specific AML configurations (length, aortomitral angle, redundancy, laxity). Despite LAMPOON there was appreciable but tolerable residual LVOT geometric obstruction and gradient in most of our patients. Relying on flow across THV struts may predispose to

FIGURE 6 LAMPOON and TMVR in Mitral Annular Calcification



Computed tomography scans before **(A to C)** and after **(D to F)** TMVR with LAMPOON in a patient treated for mitral annular calcification causing mitral valve stenosis. Noncalcified fibrous valve tissue **(asterisk)** is interposed between the THV and the mitral annular calcification **(D)**. The transcatheter heart valve is shown to span across the LVOT **(E)**, suggesting there would have been complete LVOT obstruction had LAMPOON not been performed. Follow-up chest images **(F)** show near-resolution of pulmonary alveolar hemorrhage and pleural effusion. Abbreviations as in Figures 1 and 3.

mechanical hemolysis, as we observed in 1 patient. Although this procedure relies on off-the-shelf catheter devices, the transcatheter valves were not designed and are not indicated for implantation in the mitral position, and are used off-label. In the mitral position, these THV devices may not perform as well as they do in the aortic position and, for example, may be subject to premature degeneration or thrombosis. Finally, the LAMPOON technique adds to the procedural complexity of antegrade transseptal TMVR, and perhaps should be undertaken in coordination with more experienced operators.

TABLE 3 Complications and Clinical Outcomes

Complications (n = 5)	
Valve embolization	1 (20)
Paravalvular leak grade	None, n = 4 (80%) Mild, n = 1 (20%)
Stroke	0
Bleeding major	0
Vascular major	0
Left ventricular perforation or pseudoaneurysm	0
Hemolysis	1 (20)
Clinical outcomes (n = 5)	
Length of stay after TMVR, days	8.6 ± 5.6
Intensive care unit length of stay, days	3.2 ± 2.7
Survival to hospital discharge	5 (100)
Survival 30 days	4 (80)
Survival ascertainment, days	132 (23-208)

Values are n (%), n, mean ± SD, or median (range).
Abbreviation as in Table 1.

LAMPOON joins the family of transcatheter electrosurgery procedures. Originally limited to radiofrequency ablation of cardiac arrhythmias, transcatheter electrosurgery now includes atrial septal crossing by electrification of a Brockenbrough needle (28), and guidewire electrification for traversal of congenital cardiac lesions including pulmonic atresia (29) and complete aortic coarctation (30), transcaval transcatheter aortic valve replacement (17,31), and coronary CTO traversal (32), among others.

CONCLUSIONS

By splitting the AML without surgery, LAMPOON allowed successful TMVR in patients at risk of LVOT obstruction or THV dysfunction. Remarkably LAMPOON did not induce any short-term hemodynamic deterioration. Operators should use caution applying this new technique to patients. A clinical investigation of the procedure (NCT03015194) begins in 2017. The concept of disrupting the native anterior leaflet, to allow blood flow across THV struts, may inform further development of TMVR devices.

ACKNOWLEDGMENTS The authors thank Lauren Wheeler, Jonathan Mazal, Bill Schenke, Annette Stine, Adriana Byrnes, Sharon Howell, Ioannis Parastatidis, Frank Corrigan, Patricia Keegan, Amy Simone, Ateet Patel, Jessica Forcillo, Kelly Broxton, Neil Holtz, Deborah Dunn, Andrew Youmans, Benjamin Maples, James Lee, Nancy Sarpong, Ronnie Ramadan, Talal Alatassi, and Vicki Smith for patient care and data management; and Alan Hoofring of National Institutes of Health Division of Medical Arts.

ADDRESS FOR CORRESPONDENCE: Dr. Robert J. Lederman, Cardiovascular and Pulmonary Branch, Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health, Building 10, Room 2c713, MSC 1538, Bethesda, Maryland 20892-1538. E-mail: lederman@nih.gov.

PERSPECTIVES

WHAT IS KNOWN? TMVR risks life-threatening LVOT obstruction by displacing the native anterior mitral leaflet.

WHAT IS NEW? LAMPOON is a catheter technique to transect the anterior mitral leaflet, to prevent iatrogenic LVOT obstruction. In the 5 patients described, there was no immediate hemodynamic deterioration during the short interval between LAMPOON and TMVR. LAMPOON allowed TMVR without causing life-threatening LVOT obstruction or transcatheter heart valve dysfunction in patients believed otherwise ineligible for any treatment.

WHAT IS NEXT? We plan a cautious multicenter investigation of LAMPOON in a larger number of patients at high risk of LVOT obstruction and prosthetic heart valve dysfunction after TMVR.

REFERENCES

1. Anderson RH, Spicer DE, Hlavacek AM, Cook AC, Backer CL. Wilcox's Surgical Anatomy of the Heart. 4th edition. New York: Cambridge University Press, 2013.

2. Come PC, Riley MF, Weintraub RM, et al. Dynamic left ventricular outflow tract obstruction when the anterior leaflet is retained at prosthetic mitral valve replacement. Ann Thorac Surg 1987;43:561–3.

3. Esper E, Ferdinand FD, Aronson S, Karp RB. Prosthetic mitral valve replacement: late complications after native valve preservation. Ann Thorac Surg 1997;63:541–3.

4. Bapat V, Pirone F, Kapetanakis S, Rajani R, Niederer S. Factors influencing left ventricular outflow tract obstruction following a mitral valve-in-valve or valve-in-ring procedure, part 1. Catheter Cardiovasc Interv 2015;86:747–60.

5. Hamid NB, Khalique OK, Monaghan MJ, et al. Transcatheter valve implantation in failed surgically inserted bioprosthesis: review and practical guide to echocardiographic imaging in valve-in-valve procedures. J Am Coll Cardiol Img 2015;8:960–79.

6. Blanke P, Naoum C, Dvir D, et al. Predicting LVOT obstruction in transcatheter mitral valve implantation: concept of the Neo-LVOT. J Am Coll Cardiol Img 2017;10:482–5.

7. Wang DD, Eng M, Greenbaum A, et al. Predicting LVOT obstruction after TMVR. J Am Coll Cardiol Img 2016;9:1349–52.

8. Greenbaum AB, Condado JF, Eng MH, et al. Long or redundant leaflet complicating transcatheter mitral valve replacement: case vignettes that advocate for removal or reduction of the anterior mitral leaflet. Catheter Cardiovasc Interv 2016. In press.

9. He S, Hopmeyer J, Lefebvre XP, Schwammenthal E, Yoganathan AP, Levine RA. Importance of leaflet elongation in causing systolic anterior motion of the mitral valve. J Heart Valve Dis 1997;6:149–59.

10. Deharo P, Urena M, Himbert D, et al. Bail-out alcohol septal ablation for left ventricular outflow tract obstruction after transcatheter mitral valve replacement. J Am Coll Cardiol Intv 2016;9:e73–6.

11. Guerrero M, Wang DD, O'Neill W. Percutaneous alcohol septal ablation to acutely reduce left ventricular outflow tract obstruction induced by transcatheter mitral valve replacement. Catheter Cardiovasc Interv 2016;88:E191–7.

12. Murashita T, Suri RM, Daly RC. Sapien XT transcatheter mitral valve replacement under direct vision in the setting of significant mitral annular calcification. Ann Thorac Surg 2016;101:1171–4.

13. Dahle G, Rein KA, Fiane AE. Edwards SAPIEN XT in native stenotic mitral valve, open technique on cardiopulmonary bypass: an option, but safe? Innovations 2016;11:288–90.

14. Guerrero M, Dvir D, Himbert D, et al. Transcatheter mitral valve replacement in native mitral valve disease with severe mitral annular calcification: results from the first Multicenter Global Registry. J Am Coll Cardiol Intv 2016;9:1361–71.

15. Khan JM, Rogers T, Schenke WH, et al. Intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve replacement: pre-clinical findings. J Am Coll Cardiol Intv 2016;9:1835–43.

16. David TE. Mitral valve replacement with preservation of chordae tendinae: rationale and technical considerations. Ann Thorac Surg 1986;41:680–2.

17. Greenbaum AB, O'Neill WW, Paone G, et al. Caval-aortic access to allow transcatheter aortic valve replacement in otherwise ineligible patients: initial human experience. J Am Coll Cardiol 2014;63:2795–804.

18. Lederman RJ, Babaliaros VC, Greenbaum AB. How to perform transcaval access and closure for transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2015;86:1242–54.

19. Geske JB, Cullen MW, Sorajja P, Ommen SR, Nishimura RA. Assessment of left ventricular outflow gradient: hypertrophic cardiomyopathy versus aortic valvular stenosis. J Am Coll Cardiol Intv 2012;5:675–81.

20. Yeo TC, Freeman WK, Schaff HV, Orszulak TA. Mechanisms of hemolysis after mitral valve repair: assessment by serial echocardiography. J Am Coll Cardiol 1998;32:717–23.

21. Reardon MJ, David TE. Mitral valve replacement with preservation of the subvalvular apparatus. Curr Opin Cardiol 1999;14:104–10.

22. Descoutures F, Himbert D, Maisano F, et al. Transcatheter valve-in-ring implantation after failure of surgical mitral repair. Eur J Cardiothorac Surg 2013;44:e8–15.

23. Eleid MF, Cabalka AK, Williams MR, et al. Percutaneous transvenous transseptal transcatheter valve implantation in failed bioprosthetic mitral valves, ring annuloplasty, and severe mitral annular calcification. J Am Coll Cardiol Intv 2016;9:1161–74.

24. Cribier A, Eltchaninoff H, Tron C, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. J Am Coll Cardiol 2006;47:1214–23.

25. Hanzel GS, Harrity PJ, Schreiber TL, O'Neill WW. Retrograde percutaneous aortic valve implantation for critical aortic stenosis. Catheter Cardiovasc Interv 2005;64:322–6.

26. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement. Part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308–21.

27. Takami M, Lehmann HI, Parker KD, Welker KM, Johnson SB, Packer DL. Effect of left atrial ablation process and strategy on microemboli formation during irrigated radiofrequency catheter ablation in an in vivo model. Circ Arrhythm Electrophysiol 2016;9:e003226.

28. Bidart C, Vaseghi M, Cesario DA, et al. Radiofrequency current delivery via transseptal needle to facilitate septal puncture. Heart Rhythm 2007;4:1573–6.

29. Rosenthal E, Qureshi SA, Chan KC, et al. Radiofrequency-assisted balloon dilatation in patients with pulmonary valve atresia and an intact ventricular septum. Br Heart J 1993;69:347–51.

30. Almashham Y, Dahdah N, Miro J. Use of radiofrequency then stent implantation for recanalization of complete aorta coarctation. Pediatr Cardiol 2008;29:207–9.

31. Halabi M, Ratnayaka K, Faranesh AZ, Chen MY, Schenke WH, Lederman RJ. Aortic access from the vena cava for large caliber transcatheter cardiovascular interventions: preclinical validation. J Am Coll Cardiol 2013;61:1745–6.

32. Nicholson W, Harvey J, Dhawan R. E-CART (ElectroCautery-Assisted Re-enTry) of an aorto-ostial right coronary artery chronic total occlusion: first-in-man. J Am Coll Cardiol Intv 2016;9:2356–8.

KEY WORDS left ventricular outflow tract obstruction, mitral valve, structural heart disease, transcatheter mitral valve replacement, valvular heart disease

APPENDIX For supplemental videos and their legends, please see the online version of this article.

Anterior Leaflet Laceration to Prevent Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement

An original research manuscript published in the *Journal of the American College of Cardiology* in 2019.

Candidate's contribution

I am the first author on the enclosed clinical trial paper. I drafted the manuscript and figures. I, together with RJL, designed the NHLBI LAMPOON trial, prepared the trial protocol and drafted the case report forms. I was the Clinical Lead for the trial and member of the steering committee. I planned and proctored all the cases performed.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN
COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 73, NO. 20, 2019

Anterior Leaflet Laceration to Prevent Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement

Jaffar M. Khan, BM, BCH,[a,*] Vasilis C. Babaliaros, MD,[b,*] Adam B. Greenbaum, MD,[b,c] Jason R. Foerst, MD,[d] Shahram Yazdani, MD,[e] James M. McCabe, MD,[f] Gaetano Paone, MD,[c] Marvin H. Eng, MD,[c] Bradley G. Leshnower, MD,[b] Patrick T. Gleason, MD,[b] Marcus Y. Chen, MD,[a] Dee Dee Wang, MD,[c] Xin Tian, PHD,[g] Annette M. Stine, RN,[a] Toby Rogers, BM, BCH, PHD,[a,h] Robert J. Lederman, MD[a]

ABSTRACT

BACKGROUND Left ventricular outflow tract (LVOT) obstruction is a leading cause of mortality and exclusion from transcatheter mitral valve replacement (TMVR). Intentional laceration of the anterior mitral valve leaflet to prevent LVOT obstruction (LAMPOON) is a transcatheter mimic of surgical chord-sparing leaflet resection.

OBJECTIVES The purpose of this prospective multicenter trial was to study LAMPOON with transseptal (Edwards Lifesciences, Irvine, California) TMVR in annuloplasty rings or native mitral annular calcification (MAC).

METHODS Subjects at high or extreme surgical risk and prohibitive risk of LVOT obstruction from TMVR were included. Eligibility was modified midtrial to exclude subjects with threatened LVOT obstruction from a Sapien 3 valve fabric skirt. The primary endpoint was procedure survival with successful LAMPOON, with successful TMVR, without reintervention, and with LVOT gradient <30 mm Hg ("optimal") or <50 mm Hg ("acceptable"). Secondary endpoints included 30-day mortality and major adverse cardiovascular events. There was universal source-data verification and independent monitoring. All endpoints were independently adjudicated. Central laboratories analyzed echocardiogram and CT images.

RESULTS Between June 2017 and June 2018, 30 subjects were enrolled equally between the MAC and ring arms. LAMPOON traversal and midline laceration was successful in 100%. Procedure survival was 100%, and 30-day survival was 93%. Primary success was achieved in 73%, driven by additional procedures for paravalvular leak (10%) and high-skirt neo-LVOT gradients observed before a protocol amendment. There were no strokes.

CONCLUSIONS LAMPOON was feasible in native and annuloplasty ring anatomies in patients who were otherwise ineligible for treatment, with acceptable safety. LAMPOON was effective in preventing LVOT obstruction from TMVR. Despite LAMPOON, TMVR using Sapien 3 in annuloplasty rings and MAC still exhibits important limitations. (NHLBI DIR LAMPOON Study: Intentional Laceration of the Anterior Mitral Leaflet to Prevent Left Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Implantation; NCT03015194) (J Am Coll Cardiol 2019;73:2521–34) Published by Elsevier on behalf of the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Cardiovascular Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; [b]Structural Heart and Valve Center, Emory University Hospital, Atlanta, Georgia; [c]Center for Structural Heart Disease, Division of Cardiology, and Division of Cardiac Surgery, Henry Ford Health System, Detroit, Michigan; [d]Carilion Roanoke Memorial Hospital, Roanoke, Virginia; [e]Inova Fairfax Hospital, Fairfax, Virginia; [f]University of Washington, Seattle, Washington; [g]Office of Biostatistics Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and the [h]Medstar Washington Hospital Center, Washington, DC. *Drs. Khan and Babaliaros contributed equally to this work. This work was supported by the Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health (Z01-HL006040-7), and by the intramural programs of the participating centers. The National Heart, Lung, and Blood Institute and Edwards Lifesciences have a collaborative research and development agreement on transcatheter modification of mitral valve leaflets, including joint financial support of this study. Drs. Khan, Rogers, and Lederman are co-inventors on patents, assigned to the National Institutes of Health, on catheter devices to lacerate valve leaflets. Dr. Babaliaros has served as a consultant for Edwards Lifesciences and Abbott Vascular; and his employer has research contracts for clinical investigation of transcatheter aortic and mitral devices from Edwards Lifesciences, Abbott Vascular, Medtronic, St. Jude Medical,

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.02.076

ABBREVIATIONS AND ACRONYMS

LAMPOON = intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow obstruction

LVOT = left ventricular outflow tract

MAC = mitral annular calcification

NHLBI = National Heart Lung and Blood Institute

PVL = paravalvular leak

TMVR = transcatheter mitral valve replacement

Transcatheter mitral valve replacement (TMVR) is an option for patients with mitral stenosis or regurgitation who are not suitable candidates for open surgical mitral repair or replacement (1). Pending commercial development of dedicated TMVR devices, transcatheter aortic valves have been implanted in the mitral position in bioprosthetic mitral valves (valve-in-valve), mitral annuloplasty rings or bands (valve-in-ring), and in native mitral annular calcification (MAC) (valve-in-MAC) (2,3). Left ventricular outflow tract (LVOT) obstruction is a dreaded complication of TMVR, occurring in up to 40% of valve-in-MAC, 5% of valve-in-ring, and 2% of valve-in-valve cases (2), and with 62% in-hospital mortality (3). Fear of LVOT obstruction is a leading cause for treatment exclusion, with 49% of screened patients for valve-in-MAC and 6% for valve-in-ring excluded in the MITRAL (Mitral Implantation of Transcatheter Valves) trial for predicted risk of LVOT obstruction (4,5).

SEE PAGE 2535

TMVR-induced LVOT obstruction has 2 mechanisms. *Fixed obstruction* occurs when the anterior mitral valve leaflet is pushed toward the interventricular septum by the mitral valve prosthesis, creating a narrowed and elongated "neo-LVOT" (6). Predicting the neo-LVOT area on pre-procedural time-resolved computed tomography (CT) integrates multiple risk factors for LVOT obstruction, including acute angulation of the aortic and mitral annular planes, a small left ventricle, a prominent septal bulge, and ventricular deployment of the transcatheter valve (6,7). Observational registries suggest a simulated neo-LVOT area of under 170 to 190 mm^2 predicts high risk of LVOT obstruction (8,9). *Dynamic obstruction* occurs when the narrowed neo-LVOT generates Bernoulli forces that draw the anterior mitral leaflet toward the interventricular septum during systole (10). A long anterior mitral leaflet with redundant chordae is a risk factor (11). A long anterior mitral leaflet may also prolapse back into the transcatheter heart valve, interfering with valve closure and causing acute valve failure (12).

Preventive strategies include either surgical transatrial leaflet resection, which involves cardiopulmonary bypass, associated morbidity, and reported 30-day mortality of 27% (13), or prophylactic alcohol septal ablation (14,15), which causes septal infarction, sacrifices myocardium and conduction tissue, may not be anatomically feasible or effective in all patients, and delays TMVR by 4 to 6 weeks. Current expert opinion recommends that TMVR should probably be contraindicated in most of these patients who are at high risk of LVOT obstruction (16).

Contemporary surgical mitral valve replacement includes resection of the anterior mitral leaflet to prevent LVOT obstruction and sparing of the subvalvular apparatus to preserve left ventricular function (17). Laceration of the anterior mitral valve leaflet to prevent outflow obstruction (LAMPOON) is a percutaneous transcatheter mimic of the surgical standard. Animal studies (18) and early compassionate use in humans (19) demonstrated that LAMPOON and TMVR may be feasible in these "contraindicated" patients. The split anterior mitral leaflet parts away from the LVOT and blood flow is maintained through the open cells of the transcatheter heart valve despite threatened obstruction were the anterior mitral leaflet intact.

METHODS

TRIAL DESIGN AND OVERSIGHT. The LAMPOON IDE trial (NCT03015194) was a prospective, single-arm, multicenter study of the LAMPOON procedure with transseptal Sapien 3 valve (Edwards Lifesciences, Irvine, California) TMVR in annuloplasty ring or band, or native MAC. The U.S. Food and Drug Administration granted Investigational Device Exemption (IDE) for the study. The institutional review board at each site and at National Heart, Lung, and Blood Institute (NHLBI) approved the study protocol. The NHLBI Data Safety Monitoring Board provided study oversight. The NHLBI was the data coordinating center. All subjects consented in writing.

The trial was designed by the investigators and sponsored by the senior author (R.J.L.) on behalf of the NHLBI. Edwards Lifesciences provided arms-length financial support for the study as part of a

and Boston Scientific. Dr. Greenbaum has served as a proctor for Edwards Lifesciences, Medtronic, and Abbott Vascular; and has served as a consultant and a scientific advisor for and is an equity holder in Transmural Systems. Drs. Foerst and Rogers have served as consultants/proctors for Edwards Lifesciences and Medtronic. Dr. Yazdani, Paone, and Eng have served as proctors for Edwards Lifesciences. Dr. Leshnower has served on the Speakers Bureau for Medtronic. Dr. Wang has served as a consultant for Edwards Lifesciences, Boston Scientific, and Materialise. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 12, 2019; revised manuscript received February 22, 2019, accepted February 25, 2019.

Collaborative Research and Development Agreement with NHLBI on transcatheter modification of the mitral valve. Edwards Lifesciences was not involved in study design or analysis, and did not review this report before submission. The study investigators have custody of all data and are responsible for the findings.

To ensure data integrity, all case report forms were independently verified with source data on-site, clinical events were independently monitored, and all echocardiography and computed tomography (CT) images were analyzed by central laboratories. An independent Clinical Event Adjudication Committee classified the primary and all clinical endpoints including death and stroke, and determined relatedness to the LAMPOON procedure and to TMVR.

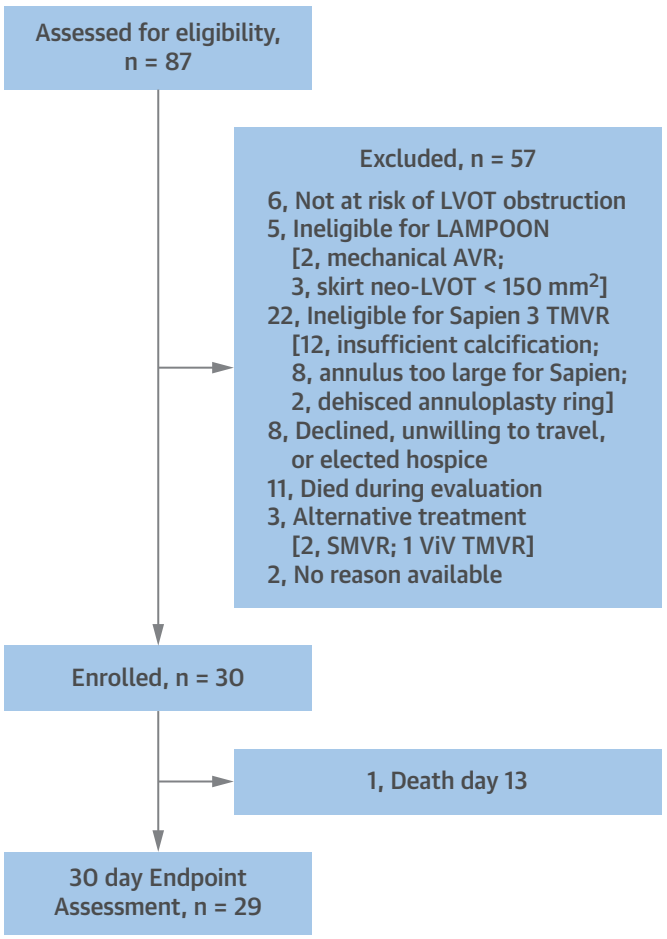
SUBJECTS. Between June 2017 and June 2018, 30 adult subjects with severe mitral stenosis or regurgitation and high or extreme risk for surgical mitral valve replacement were enrolled at 5 centers in the United States (Online Appendix). Reasons for exclusion are shown in **Figure 1**. No subject was excluded for excessive leaflet calcification. A central eligibility committee confirmed eligibility for transseptal Sapien 3 valve in ring or band, or native MAC, based on CT annular measurements for suitable anchoring. Only candidates with prohibitive risk of LVOT obstruction from TMVR were enrolled, based on neo-LVOT area <200 mm^2, or long redundant anterior mitral leaflet. The complete selection criteria are listed in the Online Appendix.

The study was amended after the first 5 subjects were enrolled, after LVOT obstruction was observed despite anterior leaflet laceration requiring rescue alcohol septal ablation. These were attributed to obstruction from the covered fabric skirt at the base of the Sapien 3 valve (20). The selection criteria were therefore changed to exclude candidates with a "skirt neo-LVOT" <150 mm^2 on baseline CT. All enrolled subjects were included in the final analysis.

LAMPOON TECHNIQUE. The LAMPOON technique has been described previously (18,19). Briefly, 2 transfemoral guide catheters are advanced retrograde through the aortic valve and positioned in the LVOT and left atrium, respectively, on either side of the middle-scallop (A2) of the anterior mitral leaflet (**Figure 2A**). The left atrial guide catheter is stabilized using a transseptal rail. A stiff 0.014-inch guidewire (Astato XS 20, Asahi, Japan) is sheathed in an insulating polymer jacket (Piggyback Wire Convertor, Teleflex, North Carolina), and advanced from the LVOT to perforate through the center and base of the anterior mitral leaflet using a short pulse of radiofrequency energy. The guidewire tip is snare-retrieved from the left atrium to form a guidewire loop through the base of the anterior mitral leaflet, with both guidewire limbs exiting femoral arteries and insulated in catheters (**Figure 2B**). Tension is applied to the guidewire loop during further radiofrequency energy application, lacerating the anterior mitral leaflet from base to tip (Online Video 1). Using a retrograde guide catheter trajectory, the laceration aligns in front of the LVOT and down the midline of the anterior leaflet. The anterior mitral leaflet splays in diastole and coapts in systole (**Figure 3A**, Online Video 2), in part because the chordae are preserved.

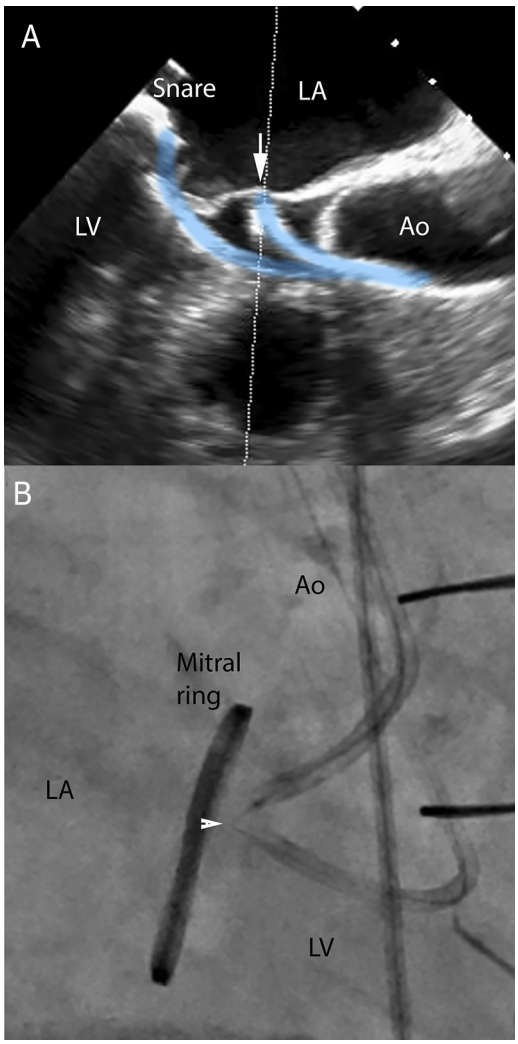
Immediately after laceration, transseptal TMVR is performed using a Sapien 3 balloon-expandable

FIGURE 1 Study Flow Chart



A total of 87 subjects were screened and 30 were enrolled. Reasons for exclusion are listed. AVR = aortic valve repair; LAMPOON = intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow obstruction; LVOT = left ventricular outflow tract; SMVR = surgical mitral valve replacement; TMVR = transcatheter mitral valve replacement; ViV = valve-in-valve.

FIGURE 2 LAMPOON Procedure



(A) Transesophageal echocardiography visualization of retrograde LVOT catheter contacting the middle of the anterior mitral leaflet **(arrow)** and pointed toward a snare positioned by a second retrograde catheter in the left atrium. **(B)** The focally denuded lacerating guidewire straddles the anterior mitral leaflet **(arrowhead)** during electrification to achieve laceration (Online Video 1). Ao = Aorta; LA = left atrium; LV = left ventricle.

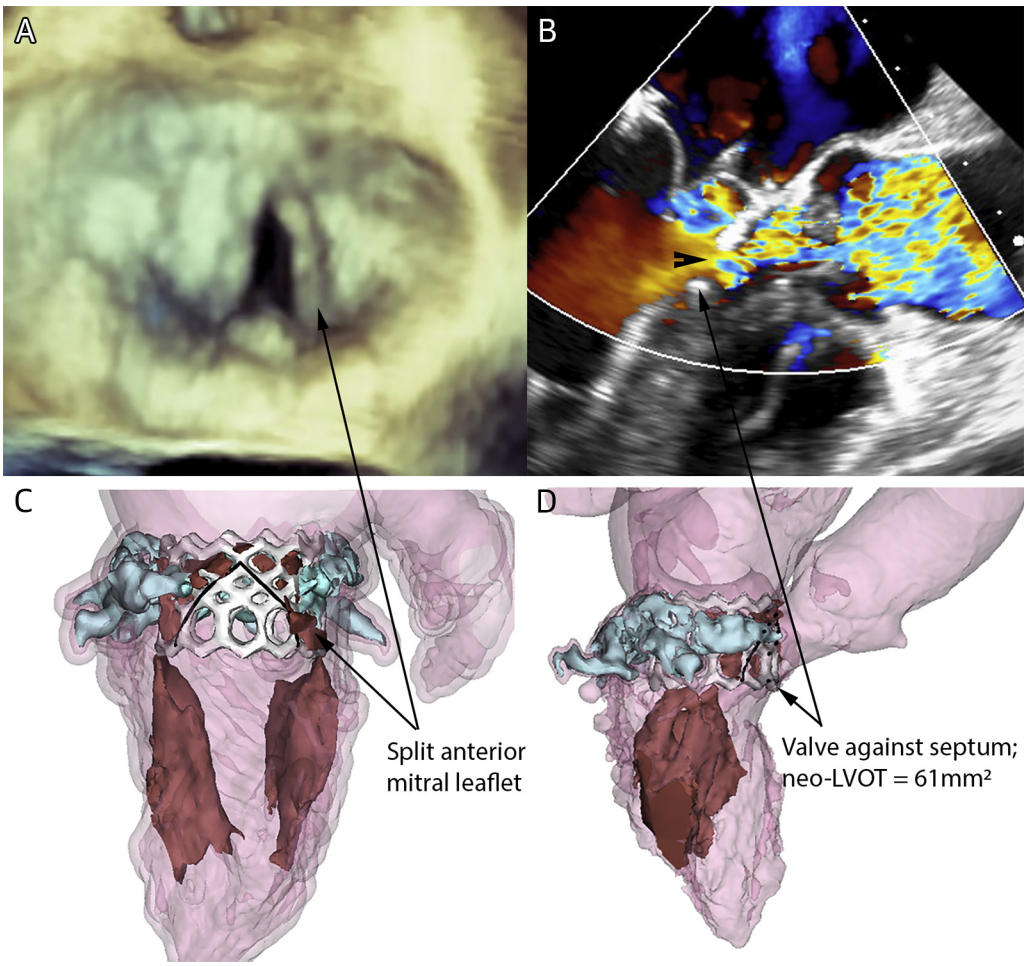
valve. During valve inflation, the 2 halves of the split anterior mitral leaflet parted to either side of the LVOT. Blood flows through the open cells of the Sapien 3 valve frame in the LVOT, which would have otherwise been obstructed by the anterior mitral leaflet (**Figure 3**). At completion, we recommended but did not require closure of the iatrogenic atrial septal defect.

STUDY ENDPOINTS. Primary and key secondary endpoints were independently adjudicated. The primary endpoint was technical success on exit from the catheter laboratory for both LAMPOON and TMVR, which was defined as successful LAMPOON traversal and laceration, successful deployment and correct positioning of the first intended transcatheter heart valve, final LVOT gradient <30 mm Hg, freedom from emergency surgery or reintervention, and absence of procedural mortality.

Exploratory endpoints included in-hospital or 30-day death, stroke, life-threatening bleeding, major vascular complications, major cardiac structural complications, stage 2 or 3 acute kidney injury, myocardial infarction requiring intervention, severe hypotension requiring vasopressors or unplanned mechanical assist devices, ventilation ≥48 h, repeat surgery or intervention, proper device placement, device delivery failure, device structural failure, major atrial septal defect, coronary obstruction, tamponade, valve fracture, damage to native mitral structures, LVOT gradient ≥10 mm Hg from baseline, valve thrombosis, endocarditis, hemolysis, residual mitral regurgitation, mitral valve gradient ≥5 mm Hg, and paravalvular leak (PVL). Mitral Valve Academic Research Consortium definitions (21) were used to determine endpoint success. The complete list of endpoints is provided in the Online Appendix.

IMAGING. Baseline and post-procedure contrast-enhanced, time-resolved CT used retrospective electrocardiogram-gated acquisitions. Images were reconstructed at 5% to 10% intervals with <1.0-mm slice thickness. Baseline and follow-up neo-LVOT and skirt neo-LVOT area measurements were performed using dedicated mitral valve CT analysis software (3mensio, PIE Medical, the Netherlands). The neo-LVOT area was measured in the last systolic phase with the aortic valve fully open (typically 30% phase). This was not the phase that gave the smallest neo-LVOT area (typically 40% to 50% phase), used in some observational studies (8,9). We noted that at these later phases, the aortic valve is partially or completely closed and the earlier phase selected for this study would better represent gradient across the LVOT after TMVR. A virtual valve with dimensions of the intended Sapien 3 implant was simulated in a 70:30 ventricle to atrium position across the mitral annulus. The smallest resulting cross-sectional area along the axis of the LVOT, circumscribed by the virtual valve and the interventricular septum, was measured to predict the neo-LVOT area (**Figures 4A and 4B**). The same was repeated by simulating only the fabric covered portion of the Sapien 3 valve for the "skirt" neo-LVOT, and excluding the ventricular open cells as described previously (20) (**Figures 4C and 4D**). This simulates the neo-LVOT that would result

FIGURE 3 LAMPOON Outcomes



(A) Successful laceration of the anterior mitral leaflet before TMVR depicted on 3-dimensional transesophageal echocardiography (Online Video 2). **(B)** Color-flow across open cells of the Sapien 3 valve frame that without leaflet laceration would have completely obstructed the LVOT. The **arrowhead** shows the vena contracta, indicating the "leaflet lampooned" diameter; the **arrow** points to the edge of the valve abutting septum, indicating "leaflet intact" diameter. **(C)** A 3-dimensional computed tomography volume rendering after TMVR showing the split anterior mitral leaflet **(black-outlined brown)** splayed by the Sapien 3 valve frame **(white)** in the context of annular calcification **(blue).** **(D)** A 3-chamber perspective shows the valve frame contacted the interventricular septum across the LVOT (Online Video 3). Abbreviations as in **Figure 1**.

after TMVR and complete partition, or surgical excision, of the anterior mitral leaflet. Leaflet thrombosis was defined as leaflet thickening with reduced motion on follow-up CT or echocardiography.

Transthoracic or transesophageal echocardiograms were performed at baseline, intraprocedure, discharge, and 30 days. The neo-LVOT diameter on echocardiography was measured as the distance between the Sapien 3 stent frame and the interventricular septum in a 3-chamber view. This was called the "leaflet intact" LVOT diameter and approximated the neo-LVOT diameter assuming the anterior leaflet covered the Sapien 3 frame and ended at the valve edge. On color Doppler, the vena contracta through the neo-LVOT was measured in the same 3-chamber view (**Figure 3B**). This was called the "leaflet lampooned" LVOT diameter and approximated the physiological neo-LVOT diameter after LAMPOON. Echocardiograms and CT images were analyzed at central laboratories.

STATISTICAL ANALYSIS. The sample size of 30 subjects was not statistically derived. Baseline subject and procedural characteristics were summarized as mean ± SD or median and interquartile range for continuous variables and counts and percentages for categorical variables. Wilcoxon signed-rank tests

FIGURE 4 Neo-LVOT and Skirt Neo-LVOT Areas

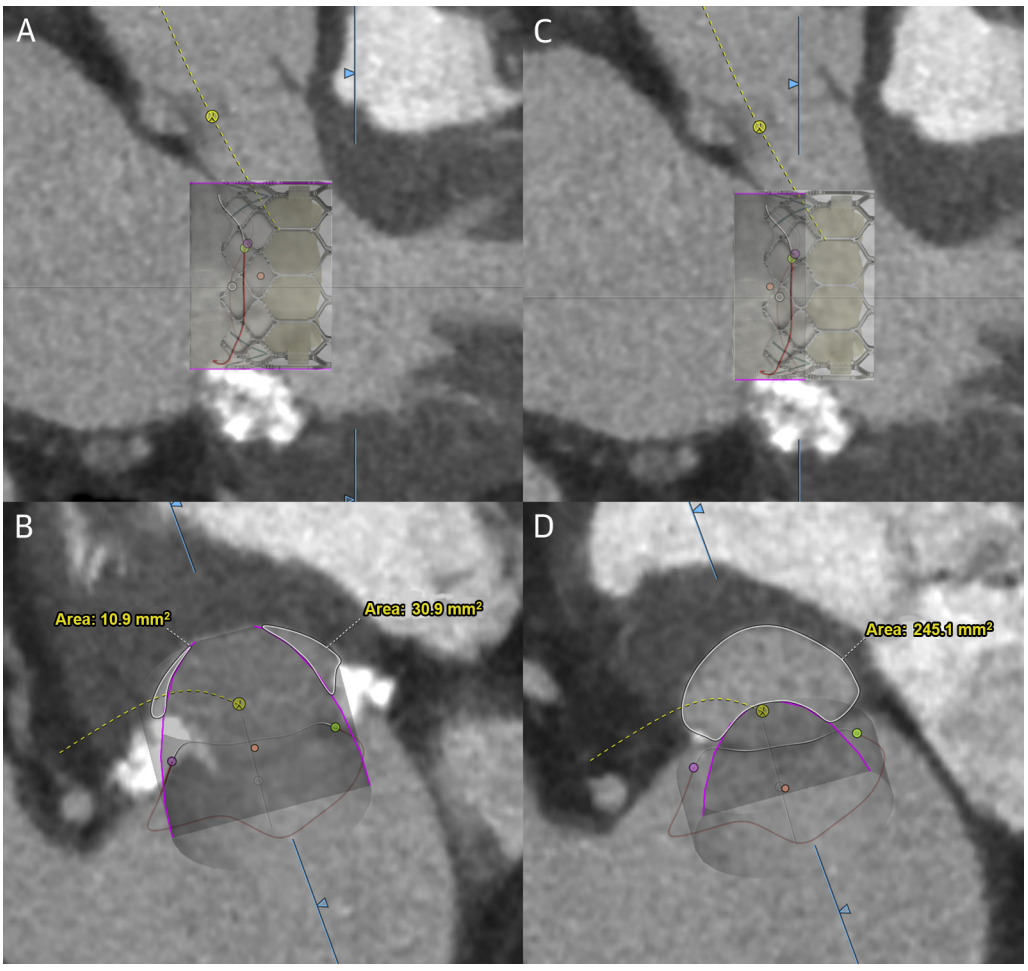


Illustration of computed tomography-based prediction of neo-LVOT **(A and B)** and skirt neo-LVOT **(C and D)** area using 3-chamber projections **(top)** and LVOT short-axis projections **(bottom)** and a simulated valve **(purple outline)**. A Sapien 3 valve is superimposed, illustrating covered and uncovered sections of the valve frame. LVOT = left ventricular outflow tract.

were used to assess the difference in the observed neo-LVOT areas before and after LAMPOON, and the differences in New York Heart Association functional class, 6-min walk distance, and Kansas City Cardiomyopathy Questionnaire quality-of-life summary scores between baseline and 30-day visits. Spearman rank tests assessed relationships between predicted neo-LVOT and skirt neo-LVOT and residual gradients.

Statistical analyses were performed using R statistical software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

SUBJECT AND PROCEDURE CHARACTERISTICS. Baseline subject characteristics are shown in Table 1. The majority were women and presenting late in their disease process, with end-organ failure and multiple comorbidities. All were at high or extreme risk for surgery. There were an equal number of subjects with mitral annuloplasty rings or bands and native MAC. The 29-mm Sapien 3 valves were implanted in 20 patients (67%), 26-mm in 7 (23%), and 23-mm in 3 (10%).

Table 2 details the LVOT obstruction risk for enrolled subjects. A total of 25 (83%) were at risk of *fixed* LVOT obstruction, defined as having a predicted neo-LVOT area <200 mm^2 (mean 81 mm^2). The majority (88%) had extremely small predicted neo-LVOT area (<150 mm^2). A total of 5 (17%) subjects were at risk of *dynamic* LVOT obstruction, with anterior mitral leaflet length >24 mm (mean 28 mm). One

TABLE 1 Baseline Subject Characteristics (n = 30)

Age, yrs	76 (47-89)
Female	22 (73)
BSA, m^2	1.8 ± 0.2
End-organ failure	
Severe pulmonary disease	8 (27)
Severe pulmonary hypertension	16 (55)
Home oxygen	6 (20)
Severe RV dilation or dysfunction	4 (13)
End-stage kidney disease on dialysis	4 (13)
Liver cirrhosis	4 (13)
Comorbidities	
Diabetes	17 (57)
Hypertension	28 (93)
Peripheral artery disease	4 (13)
Coronary artery disease	21 (70)
Prior myocardial infarction	6 (20)
Prior stroke or TIA	5 (17)
Atrial fibrillation	16 (53)
Prior endocarditis	4 (13)
Prior rheumatic fever	1 (3)
Pacemaker or ICD	9 (30)
≥2 prior cardiac surgery	9 (30)
NYHA functional class III or IV	27 (90)
Frail	14 (47)
STS predicted risk of mortality, %	10.2 ± 6.2
HAS-BLED score	2.8 ± 0.9
NT-proBNP, pg/ml	515 [282-850]
Medication	
Dual antiplatelet baseline	11 (37)
Dual antiplatelet discharge	2 (7)
Oral anticoagulant agent baseline	10 (33)
Oral anticoagulant agent discharge	26 (93)
TMVR setting	
Complete ring	13 (43)
Incomplete ring/band	2 (7)
MAC	15 (50)
Primarily mitral stenosis	20 (67)
Primarily mitral regurgitation	10 (33)
Mean mitral valve gradient, mm Hg	9.6 ± 4.3
Severe mitral regurgitation (ASE guideline integrated analysis)	11 (37)
CT annular measurements	
Annular area	551.3 ± 141.2
Antero-posterior distance	30.3 ± 3.9
Intercommissural distance	21.5 ± 3.6

Values are median (range), n (%), mean ± SD, or median [interquartile range].

ASE = American Society of Echocardiography; BSA = body surface area; CT = computed tomography; ICD = implantable cardioverter-defibrillator; MAC = mitral annular calcification; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack; TMVR = transcatheter mitral valve replacement.

TABLE 2 LVOT Obstruction Risk

Aorto-mitral angle, °	117.3 ± 9.8
Septal thickness, mm	12.9 ± 3.6
Fixed LVOT obstruction subset	25
Predicted neo-LVOT, mm^2	81 ± 51
Neo-LVOT <200 mm^2	25 (100)
Neo-LVOT <150 mm^2	22 (88)
Neo-LVOT <100 mm^2	15 (60)
Neo-LVOT <50 mm^2	7 (28)
Predicted skirt neo-LVOT, mm^2	230 ± 56
Skirt neo-LVOT <200 mm^2	7 (28)
Skirt neo-LVOT <150 mm^2	2 (8)
Skirt neo-LVOT <100 mm^2	0 (0)
Dynamic LVOT obstruction subset	5
Anterior mitral leaflet length on CT, mm	28 ± 3.1
Systolic anterior motion at baseline	1 (20)

Values are mean ± SD, n, or n (%).

CT = computed tomography; LVOT = left ventricular outflow tract.

subject had prior prophylactic alcohol septal ablation, but still had a predicted neo-LVOT area of 25 mm^2 and was enrolled in the study.

PROCEDURE OUTCOMES. Table 3 shows the adjudicated primary and key secondary endpoints. The LAMPOON traversal and laceration was successful in all 30 (100%) subjects, including in subjects with heavily calcified anterior mitral leaflets, and where laceration trajectory was through a complete anterior calcium bridge. Full leaflet laceration was not achieved in 1 subject due to insufficiently basal traversal. All (100%) survived the immediate procedure and 28 (93%) survived to discharge and 30 days (100% for valve-in-ring; 87% for valve-in-MAC). The LVOT gradient immediately after TMVR was <30 mm Hg in 27 patients (90%), and on exit from the catheter laboratory was <30 mm Hg in 29 patients (97%; "optimal") and <50 mm Hg in 30 patients (100%; "acceptable"). A total of 8 patients (27%) required further intervention before exiting the catheter laboratory: 4 had alcohol septal ablation to decrease LVOT gradients; 2 had second valve implantations for PVL and displacement during interatrial septum traversal, respectively; 1 had on-table conversion to surgery for severe PVL; and 1 had percutaneous closure for PVL through a dehisced mitral ring. The primary endpoint of success was met in the remaining 22 (73%) subjects.

There were 2 post-procedural deaths. One was attributed to clostridium difficile colitis and toxic megacolon following clindamycin for dental extraction, despite a technically successful procedure. The other was a failed TMVR despite successful LAMPOON, requiring surgical conversion for PVL, with a stormy post-operative course, and death on day 38.

There were no strokes. Cerebral protection (Sentinel, Claret Medical, Santa Rosa, California) was used in 1 subject who had left atrial appendage thrombus at baseline; no debris was retrieved.

TABLE 3 Adjudicated Clinical Outcomes

Primary endpoint (exit from catheter laboratory)	30
Successful LAMPOON traversal and laceration	30 (100)
Successful access, delivery, and retrieval of LAMPOON device system	30 (100)
Successful deployment of first TMVR valve	27 (90)
LVOT gradient <30 mm Hg ("optimal")	29 (97)
LVOT gradient <50 mm Hg ("acceptable")	30 (100)
Freedom from emergency surgery or reintervention related to LAMPOON or TMVR	22 (73)
Procedure survival	30 (100)
Procedure success (all of the above)	22 (73)
Secondary endpoints (30 days)	30
All death	2 (7)
Related to LAMPOON	0 (0)
Related to TMVR but not LAMPOON	1 (3)
Not related to TMVR or LAMPOON	1 (3)
All stroke	0 (0)
Life-threatening bleeding	3 (10)
Major vascular complication	6 (20)
Major structural complication	0 (0)
AKI stage 2/3	3 (10)
Myocardial infarction requiring PCI or CABG	0 (0)
Surgery or repeat intervention	8 (27)
Hypotension requiring increase in vasopressors or mechanical support	12 (40)
Respiratory failure requiring prolonged (>48 h) intubation	1 (3)
Valve position failure	1 (3)
Valve structural failure	0 (0)
Major ASD	0 (0)
Coronary obstruction	0 (0)
Cardiac tamponade or pericardial drainage	1 (3)
Damage to native mitral apparatus	0 (0)
LVOT ≥10 mm Hg from baseline	2 (7)
Aortic regurgitation 2+ or more	0 (0)
Valve thrombosis	4 (13)
Endocarditis	0 (0)
Hemolysis	12 (40)
MR more than mild	1 (3)
MVG ≥5 mm Hg	18 (60)
PVL more than mild	7 (23)

Values are n or n (%).

AKI = acute kidney injury; ASD = atrial septal defect; CABG = coronary artery bypass graft; LAMPOON = intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow obstruction; LVOT = left ventricular outflow tract; MR = mitral regurgitation; MVG = mitral valve gradient; PCI = percutaneous coronary intervention; PVL = paravalvular leak; TMVR = transcatheter mitral valve replacement.

Planned intra-aortic balloon pump support was used in 43%, when the transcatheter valve was not pre-positioned in the left atrium. Table 4 shows echocardiogram and invasive hemodynamic changes with LAMPOON-TMVR. Hypotension requiring increase in vasopressor support during the procedure and recovery was common (n = 12; 40%), but only 6 subjects (20%) had hypotension during LAMPOON catheter manipulation and laceration. Unplanned mechanical support was required in 1 subject (3%) after the Sapien 3 skirt caused LVOT obstruction. Per-subject procedural hemodynamics are reported in Online Figure 1.

LVOT OBSTRUCTION PREDICTION AND OUTCOMES. The predicted neo-LVOT simulated on pre-procedural CT correlated well with the observed neo-LVOT measured on post-procedural CT (Pearson r = 0.95) (Online Figure 2).

Among subjects who were at high predicted risk of LVOT obstruction with standalone TMVR, 29 (97%) exited the catheter laboratory with an LVOT gradient <30 mm Hg, and 28 (93%) had an LVOT gradient of within 10 mm Hg of their baseline on 30-day echocardiography follow-up. Both subjects who failed to meet these endpoints had a skirt neo-LVOT area <150 mm^2 and were enrolled before the protocol was amended to require an adequate skirt neo-LVOT.

A total of 3 of the first 5 subjects had LVOT obstruction (gradient ≥30 mm Hg) immediately after TMVR and underwent alcohol septal ablation. Of these, 2 had a skirt neo-LVOT <150 mm^2, and 1 had a heavily calcified anterior leaflet patch after prior repair for subacute endocarditis combined with a skirt neo-LVOT of 183 mm^2. Thereafter, the protocol was amended to exclude subjects with a skirt neo-LVOT <150 mm^2, with no further cases of LVOT obstruction. A fourth subject had an insufficiently basal anterior mitral leaflet laceration, likely limiting leaflet splay after laceration, with an LVOT gradient of 29 mm Hg; she also underwent alcohol septal ablation.

Figure 5 shows post-TMVR LVOT gradient by catheterization in relation to predicted neo-LVOT area and to predicted skirt neo-LVOT area. The majority had a predicted neo-LVOT area of <150 mm^2 but did not develop LVOT obstruction after LAMPOON TMVR. There was a nonsignificant trend toward high LVOT gradient among subjects with lowest neo-LVOT and with lowest skirt neo-LVOT.

LAMPOON increased the observed neo-LVOT area. The "leaflet intact" LVOT diameter on echocardiography at discharge was 0.4 ± 0.3 cm, whereas the "leaflet lampooned" LVOT diameter was 0.8 ± 0.3 cm ($p < 0.01$). On post-procedural CT, the skirt neo-LVOT was 150 mm^2 greater than the neo-LVOT ($p < 0.001$). There was no systolic anterior motion or leaflet infolding causing TMVR dysfunction in the subjects with long anterior mitral leaflet.

PARAVALVULAR LEAK AND HEMOLYSIS. A total of 7 subjects (23%) developed greater-than-mild paravalvular leak after first valve deployment (3 valve-in-MAC; 4 valve-in-ring). Details and treatment are provided in Table 5. One subject (4%) had greater-than-mild PVL at 30 days.

In total, 12 subjects (40%) developed hemolysis, 7 (23%) clinical requiring blood transfusion and 5 (17%) subclinical. Hemolysis was associated with trace (n = 4), mild (n = 7), and moderate (n = 1) paravalvular leak. No subject developed hemolysis in the absence of paravalvular leak.

OTHER CLINICAL ENDPOINTS. Subjects improved in New York Heart Association functional class and Kansas City Cardiomyopathy Questionnaire (22) Clinical and Overall Summary scores, but not 6-min walking distance (**Figure 6**). N-terminal pro-B-type natriuretic peptide did not improve from baseline to 30 days (515 pg/ml [first and third quartiles: 282 to 850 pg/ml] to 736 pg/ml [first and third quartiles: 318 to 1,427 pg/ml]). A total of 18 subjects (60%) had mean mitral valve gradient ≥5 mm Hg, of whom 1 (4%) had a mitral gradient ≥10 mm Hg on 30-day echocardiography. Leaflet thrombosis was seen in 4 subjects (13%) and resolved with anticoagulation. A total of 6 subjects (20%) had major vascular complications: 5 with groin hematomas and 1 with retroperitoneal hematoma. Iatrogenic atrial septal defects were electively closed during the index procedure in 25 (83%). All subjects had general anesthesia, and 22 (73%) were extubated in the catheter laboratory. Total procedure-to-hemostasis time was 195 ± 77 min; LAMPOON-to-TMVR time was 22 ± 27 min; fluoroscopy time was 120 ± 53 min; and contrast volume used was 47 ± 48 ml. Baseline and procedure characteristics and outcomes are stratified by subjects with mitral stenosis and mitral regurgitation in Online Tables 1 and 2.

TABLE 4 Hemodynamics

Echocardiography	Baseline	Pre-Discharge	30-Day
Left ventricular end-diastolic volume, ml	65.8 ± 29.6	65.0 ± 27.6	68.8 ± 32.4
Left ventricular end-systolic volume, ml	26.5 ± 15.9	28.8 ± 19.8	33.6 ± 25.7
LVEF, %	60.8 ± 9.7	56.6 ± 14.8	55.0 ± 15.2
Left atrium volume index	53.0 ± 16.5	53.4 ± 25.2	52.2 ± 18.1
LVOT peak velocity, m/s	1.1 ± 0.3	1.5 ± 0.5	1.4 ± 0.6
LVOT peak gradient, mm Hg	5.7 ± 4.8	9.8 ± 7.2	9.2 ± 7.3
LVOT mean gradient. Mm Hg	2.4 ± 1.4	4.8 ± 4.0	4.4 ± 3.9
LVOT VTI, m	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
Mean transmitral gradient, mm Hg	9.6 ± 4.3	5.6 ± 2.1	6.6 ± 2.3
Mitral regurgitation severity			
None	0 (0)	5 (17)	5 (19)
Trace	6 (21)	10 (34)	8 (30)
Mild	6 (21)	13 (45)	12 (44)
Moderate	6 (21)	1 (3)	0 (0)
Severe	11 (38)	0 (0)	2 (7)
Perivalvular regurgitation			
None	–	16 (59)	17 (63)
Trace	–	3 (11)	4 (15)
Mild	–	8 (30)	5 (19)
Moderate	–	0 (0)	0 (0)
Severe	–	0 (0)	1 (4)

Cath Hemodynamics	Baseline	Post-LAMPOON	Post-TMVR
Heart rate, beats/min	69.6 ± 10.8	76.4 ± 15.5	73.4 ± 10.5
Systolic arterial pressure, mm Hg	123.4 ± 22.4	96.2 ± 20.5	123.3 ± 19.0
Diastolic arterial pressure, mm Hg	61.5 ± 12.0	51.4 ± 11.6	57.4 ± 15.6
Mean arterial pressure, mm Hg	85.0 ± 14.7	65.8 ± 14.7	82.7 ± 14.3
Right atrial pressure, mm Hg	13.9 ± 6.1	–	13.1 ± 6.3
Systolic pulmonary artery pressure, mm Hg	56.8 ± 18.5	–	52.8 ± 17.0
Diastolic pulmonary artery pressure, mm Hg	24.8 ± 8.3	–	22.6 ± 6.8
Mean pulmonary artery pressure, mm Hg	38.7 ± 11.2	–	34.4 ± 9.2
Mean left atrial pressure, mm Hg	26.7 ± 11.0	–	18.1 ± 4.7
Left atrial v-wave, mm Hg	45.2 ± 16.8	–	25.4 ± 8.6
Mean transmitral gradient, mm Hg	8.2 ± 4.8	–	2.8 ± 1.6
Cardiac output, l/min	5.1 ± 1.7	–	5.4 ± 1.5
Left ventricular end-diastolic pressure, mm Hg	18.3 ± 6.0	–	17.9 ± 5.0
LVOT peak-to-peak gradient, mm Hg	7.6 ± 6.0	17.7 ± 23.4	10.7 ± 9.3
Calculated mitral valve area, cm^2	1.5 ± 0.7	–	2.8 ± 0.9

Values are mean ± SD or n (%).
LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; VTI = velocity time integral.

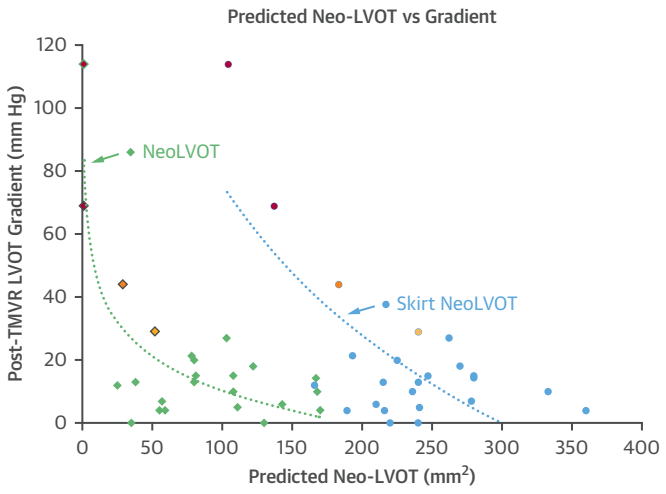
DISCUSSION

The LAMPOON IDE study enrolled 30 subjects at prohibitive risk of LVOT obstruction equally between valve-in-ring and valve-in-MAC arms. None were eligible for standalone TMVR and most were deemed ineligible for any other therapy. Most would have been excluded from contemporaneous cohort and registry reports of TMVR for valve-in-ring and valve-in-MAC because of the baseline risk of LVOT obstruction (3,4,23,24). The main findings were that LAMPOON was feasible in 100% of subjects across a variety of native and annuloplasty ring anatomies and calcium patterns. There was 100% procedure survival and 93% in-hospital and 30-day survival (100% valve-in-ring, 87% valve-in-MAC) in a very sick cohort, many presenting with end-organ failure, in whom outcomes have historically been very poor. There were no neurological events (**Central Illustration**).

THE LAMPOON TECHNIQUE. The LAMPOON technique, although technically challenging, was successfully performed in all sites with proctorship and without roll-in procedures for new sites. The technique cannot be used with the transfemoral approach in subjects with mechanical aortic valves. Furthermore, LAMPOON, or other anterior leaflet modification or resection strategies, is unlikely to prevent LVOT obstruction when there is a small predicted skirt neo-LVOT area. Extent and pattern of anterior mitral leaflet calcification was not a contraindication to LAMPOON. There was no collateral damage to adjacent structures, particularly the aortic valve, from LAMPOON.

One safety consideration raised by this study is LVOT obstruction despite LAMPOON. The 3 cases of

FIGURE 5 Predicted Neo-LVOT, Skirt Neo-LVOT, and Observed Gradients



LVOT catheter gradient after TMVR is compared with predicted neo-LVOT area **(diamonds)** and predicted skirt neo-LVOT area **(circles)**. **Red, orange, and yellow symbols** indicate subjects who underwent bailout alcohol septal ablation. **Red** indicates subjects with inadequate skirt neo-LVOT. **Orange** indicates a subject with calcific anterior mitral leaflet patch and inadequate skirt neo-LVOT. **Yellow** indicates a subject with insufficiently basal LAMPOON. Abbreviations as in Figure 1.

high LVOT gradients after TMVR highlight the value of appropriate screening, especially for skirt neo-LVOT area in extremely small ventricles.

A second safety consideration is transient procedural hypotension. Leaflet manipulation and laceration was associated with increased vasopressor support in 20% of subjects. There was a high rate of planned intra-aortic balloon pump use as, with increasing comfort with the technique, operators stopped pre-positioning the Sapien 3 valve before laceration, increasing time from laceration to valve deployment. Emergency mechanical support was required in only 1 subject to relieve severe LVOT obstruction. Reasons for the relative hemodynamic stability observed with LAMPOON procedures may be that the lacerated anterior leaflet still coapts in systole, and that patients with chronic mitral disease may tolerate a further acute exacerbation in the short period between LAMPOON and TMVR.

TABLE 5 Paravalvular Leak

PVL Mechanism	MAC	Ring or Band
High deployment	1 (severe), converted to surgery	2, repeat TMVR-in-TMVR (1 immediate, 1 day 3)
Ring dehiscence	—	2, exacerbated from baseline, treated percutaneously with occluders
Malapposition	2 (moderate), treated conservatively	0

Abbreviations as in Tables 1 and 3.

TRANSCATHETER MITRAL VALVE REPLACEMENT. TMVR in the setting of annuloplasty rings and in native MAC has previously been demonstrated to be feasible but with problems, particularly LVOT obstruction and PVL. The 30-day survival in carefully selected patients screened out for LVOT obstruction in the MITRAL trial was 93% for valve-in-ring and 81% for valve-in-MAC (4,5). The 30-day survival in the TMVR Registry was 90% for valve-in-ring and 65% for valve-in-MAC (2). In patients who developed LVOT obstruction, who likely represent the cohort enrolled in this study, 30-day survival was only 48% and 1-year survival was 15% (3).

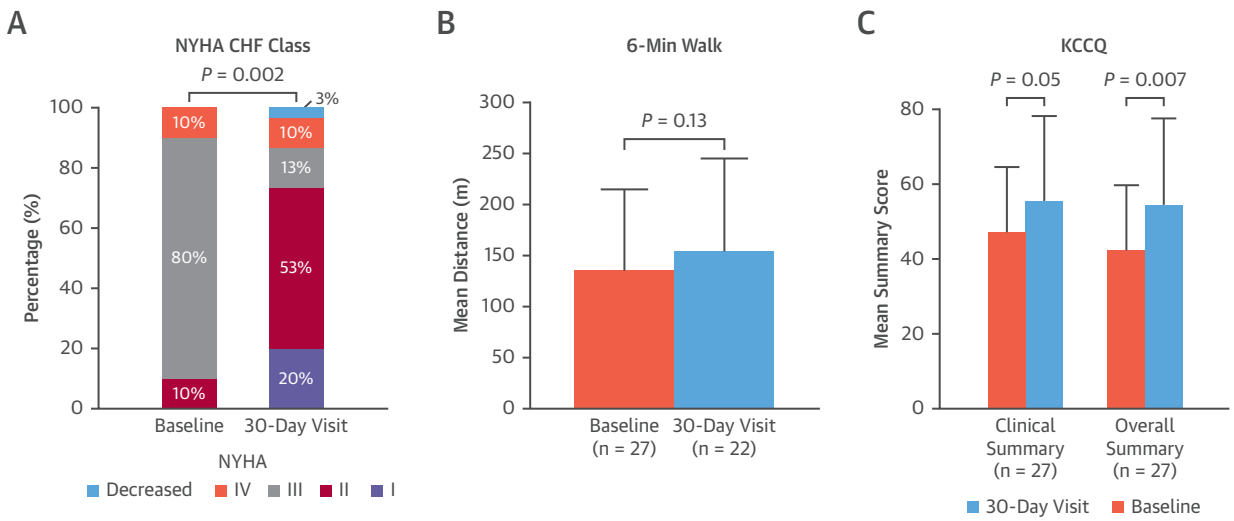
Although LAMPOON was largely technically successful, there were important safety considerations for TMVR not related to LAMPOON, namely clinically significant PVL and hemolysis, and high residual transmitral gradients. Large annuli (9% screen failure rate) and insufficient mitral calcification (14% screen failure rate) remain important exclusion criteria for TMVR using aortic valves.

Moderate or severe PVL occurred in 23% after first valve deployment, and the majority required further intervention. Even trace PVL was associated with hemolysis. It is possible that blood flow through the open valve cells in the LVOT caused additional hemolysis, but no patient developed hemolysis in the absence of PVL, and so we were unable to test this hypothesis.

High transmitral valve gradients were seen in this study. Other groups reporting similar rates (82.4% [24]) have used a threshold of mean mitral valve gradient <10 mm Hg when assessing success of mitral valve-in-valve, valve-in-ring, and valve-in-MAC (23,24) based on American College of Echocardiography guidelines (25) and guidelines for transcatheter aortic valve failure (26). In a study comparing surgical mitral valve replacement with TMVR, mean mitral valve gradients at 30 days were similar (6.5 ± 2.5 mm Hg surgery vs. 7.1 ± 2.5 mm Hg TMVR; p = 0.42) (27), and compares with mean gradients in this study (6.6 ± 2.3 mm Hg). However, studies with dedicated TMVR devices have reported lower transmitral gradients (28,29), reflecting a shortcoming of using transcatheter aortic valve devices in the mitral position.

Rates of leaflet thrombosis were similar to reported case series (30), suggesting the value of anticoagulation in these patients and the heightened risk of thrombosis in transcatheter mitral valve replacement (31).

FIGURE 6 Quality of Life and Function



Changes before and 30 days after LAMPOON TMVR in New York Heart Association (NYHA) functional class ($p = 0.004$), 6-min walk test (nonsignificant $p = 0.15$ based on $n = 20$ nonmissing pairs), and Kansas City Cardiomyopathy Questionnaire (Kansas City Cardiomyopathy Questionnaire)-15 Overall ($p = 0.007$) and Clinical Summary ($p = 0.050$) scores. Abbreviations as in Figure 1.

STUDY LIMITATIONS. CT-predicted neo-LVOT area measurements are not standardized, and there is variation between centers in choice of cardiac phase, virtual valve depth, and orientation. Observational registries support a neo-LVOT cut-off of 170 mm^2 when a later cardiac phase is used (9) and 190 mm^2 when a more ventricular implantation depth is used (8). The confidence intervals around these measurements remain broad. Therefore, using the methodology in this study, 200 mm^2 appears to be an acceptable cut-off for high risk of LVOT obstruction. The CT-predicted neo-LVOT area, although an advance over previous linear measurements, remains a 2-dimensional assessment of a 3-dimensional structure that varies during the cardiac cycle. Computational fluid dynamics models accounting for this time-varying structure as well as variations in flow and behavior of the anterior mitral leaflet will help better predict risk of LVOT obstruction (32-34). The 5 subjects enrolled were deemed at high risk of LVOT obstruction from an excessively long anterior mitral leaflet, but it is possible that these subjects may not have developed systolic anterior motion of the mitral leaflet after TMVR. The problem of the long anterior mitral leaflet needs to be further studied, both in causing LVOT obstruction as well as in-folding interfering with transcatheter heart valve function (10,12).

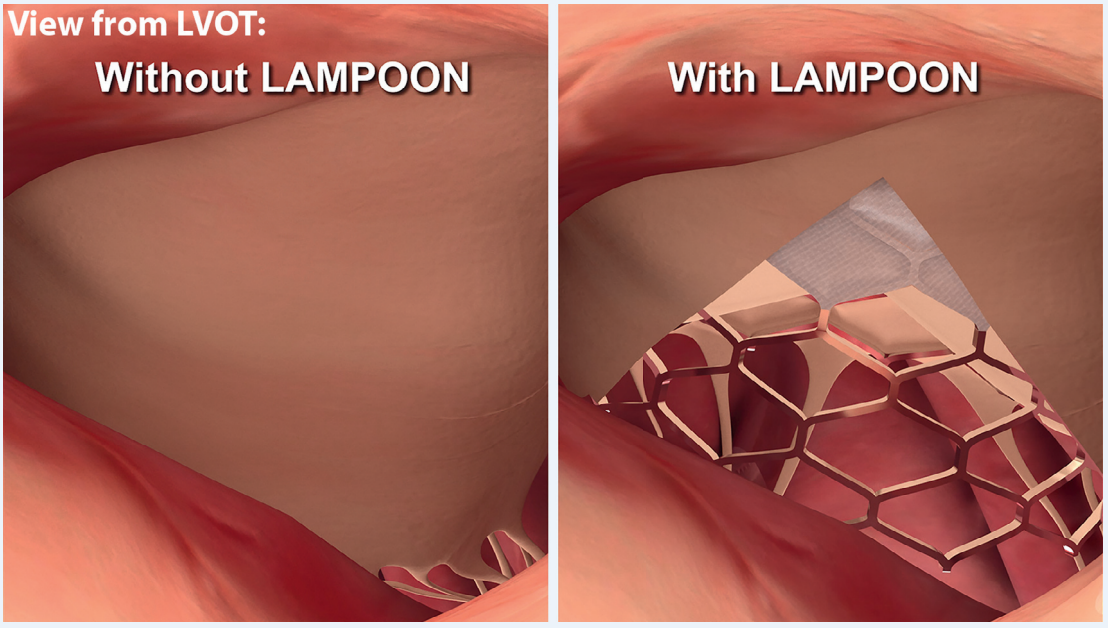
Given the small sample size, no meaningful comparisons could be made between several procedure parameters and their effect on LVOT gradient, particularly nonbasal or eccentric lacerations, surgically implanted neo-chordae, anterior mitral leaflet calcium volume and pattern, and degree of anteroposterior valve oversizing. The merits of closing the atrial septal defect were not tested in this study.

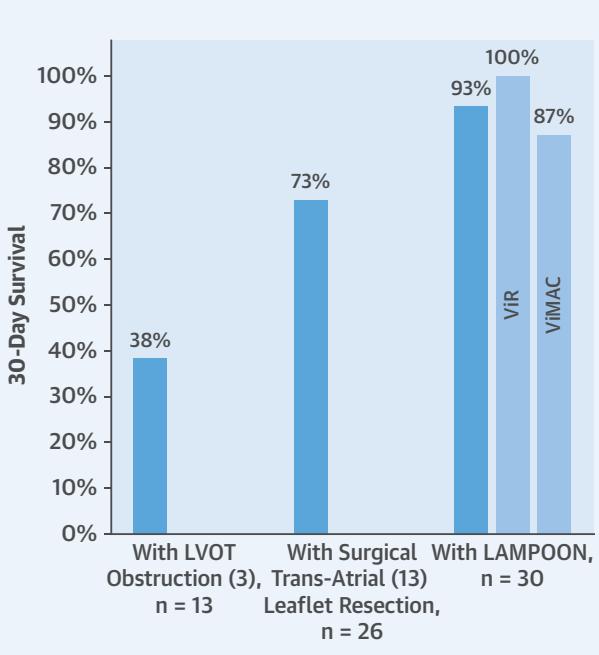
There was no control group in this study because the subjects enrolled were not eligible for standalone TMVR due to risk of life-threatening LVOT obstruction. No subject had severe left ventricular dysfunction, perhaps reflecting the low likelihood of these patients developing LVOT obstruction from TMVR due to increased ventricular size, and so the safety of LAMPOON in this cohort was not tested.

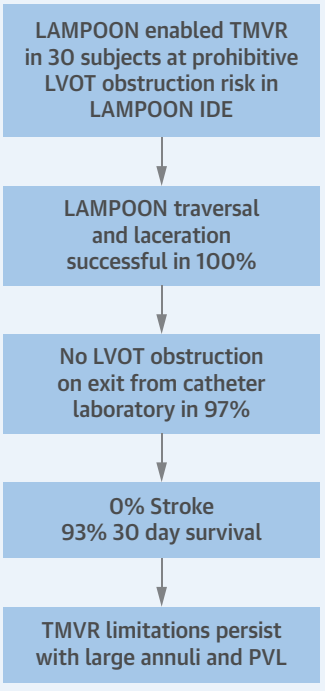
We await 1-year outcomes to assess long-term safety. Successful patient outcomes depended on both successful LAMPOON and successful transseptal TMVR using an aortic transcatheter valve off-label. The results of this study should be applied with caution when combining LAMPOON with other transcatheter valves. The lessons learned on cautions and contraindications to LAMPOON and to TMVR are summarized in Online Table 3.

FUTURE DIRECTIONS. Dedicated TMVR devices have attempted several valve designs to reduce the risk of

CENTRAL ILLUSTRATION **Anterior Leaflet Laceration to Prevent Ventricular Outflow Tract Obstruction During Transcatheter Mitral Valve Replacement**







Khan, J.M. et al. J Am Coll Cardiol. 2019;73(20):2521-34.

(Top) View from left ventricular outflow tract with and without intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow obstruction. **(Bottom)** Summary trial results. LAMPOON = intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow obstruction; LVOT = left ventricular outflow tract; PVL = paravalvular leak; TMVR = transcatheter mitral valve replacement.

LVOT obstruction (1). However, LVOT obstruction remains a leading reason to exclude candidates for investigational TMVR devices to treat severe native mitral regurgitation (22% excluded for LVOT obstruction in the Intrepid TMVR device early feasibility study [29]; 21% excluded for anatomical reasons in general in the Tendyne TMVR device early feasibility study [35]). LAMPOON has been successfully used with a Tendyne valve (Abbott, Chicago, Illinois) (11) at risk of *dynamic* LVOT obstruction from a long anterior leaflet and acute aortomitral angulation. The utility of LAMPOON with other novel TMVR devices remains to be tested. LAMPOON has also been used to treat LVOT obstruction from systolic anterior motion of the native mitral valve leaflet after TMVR (10). Dedicated devices for LAMPOON, TMVR, and increased experience should elevate this procedure to an acceptable therapy for high-risk patients with mitral valve dysfunction.

LAMPOON is an entirely percutaneous technique and is the first endovascular procedure to our knowledge to create a controlled cut in cardiac tissue. The technique can be adapted and has been used in other settings, such as to free the anterior mitral leaflet from an Alfieri stitch prior to TMVR (36) and to prevent coronary obstruction from transcatheter aortic valve replacement (bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction) (37).

The LAMPOON IDE study corroborates findings from the first-in-human series (19), and provides further support for percutaneous leaflet laceration enabling TMVR in very sick patients at risk of LVOT obstruction. Longer-term follow-up and future larger studies will be further helpful in assessing safety and efficacy in the long term.

CONCLUSIONS

In selected cases, LAMPOON overcomes the most common contraindication to TMVR for valve-in-ring or valve-in-MAC, which is risk of LVOT obstruction. This cohort study demonstrates that LAMPOON is technically feasible in a variety of native and annuloplasty ring morphologies. LAMPOON enabled TMVR in patients deemed otherwise ineligible for therapy. Candidates with a low skirt neo-LVOT do not benefit from LAMPOON and remain contraindicated. LAMPOON exhibits an acceptable safety profile and did not cause death or stroke.

TMVR in annuloplasty rings and MAC remains challenging, with high complication rates, especially related to large mitral annuli and residual paravalvular leak. Efficacy and functional improvement with TMVR in these subgroups needs to be assessed with longer-term follow-up, in larger studies, and in less critically ill subjects.

ADDRESS FOR CORRESPONDENCE: Dr. Robert J. Lederman, Cardiovascular Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room 2c713, MSC 1538, Bethesda, Maryland 20892-1538. E-mail: lederman@nih.gov. Twitter: @nih_nhlbi.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: LVOT obstruction is a common complication of mitral valve replacement that is associated with a high risk of fatality. Similar to chord-sparing leaflet resection in patients undergoing mitral valve surgery, deliberate laceration of the anterior mitral leaflet achieved with the LAMPOON technique can prevent LVOT obstruction and improve clinical outcomes in patients undergoing TMVR.

TRANSLATIONAL OUTLOOK: Larger studies with longer-term follow-up are necessary to confirm the safety and efficacy of the LAMPOON approach in patients undergoing TMVR.

REFERENCES

1. Regueiro A, Granada JF, Dagenais F, Rodes-Cabau J. Transcatheter mitral valve replacement: insights from early clinical experience and future challenges. J Am Coll Cardiol 2017;69:2175–92.

2. Yoon SH, Whisenant BK, Bleiziffer S, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J 2019;40:441–51.

3. Guerrero M, Urena M, Himbert D, et al. 1-year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. J Am Coll Cardiol 2018;71:1841–53.

4. Guerrero ME. MITRAL (Mitral Implantation of Transcatheter Valves): 30-day outcomes of transcatheter mitral valve replacement in patients with severe mitral valve disease secondary to mitral annular calcification or failed annuloplasty rings. Paper presented at: Transcatheter Therapeutics; Denver, Colorado; November 1, 2017.

5. Guerrero ME. Mitral Implantation of TRAnscatheter vaLves (MITRAL). 2015. Available at: https://clinicaltrials.gov/ct2/show/NCT02370511. Accessed April 13, 2019.

6. Blanke P, Naoum C, Dvir D, et al. Predicting LVOT obstruction in transcatheter mitral valve implantation: concept of the neo-LVOT. J Am Coll Cardiol Img 2017;10:482–5.

7. Bapat V, Pirone F, Kapetanakis S, Rajani R, Niederer S. Factors influencing left ventricular outflow tract obstruction following a mitral valve-in-valve or valve-in-ring procedure, part 1. Catheter Cardiovasc Interv 2015;86:747–60.

8. Wang DD, Eng MH, Greenbaum AB, et al. Validating a prediction modeling tool for left ventricular outflow tract (LVOT) obstruction after transcatheter mitral valve replacement (TMVR). Catheter Cardiovasc Interv 2018;92:379–87.

9. Yoon SH, Bleiziffer S, Latib A, et al. Predictors of left ventricular outflow tract obstruction after transcatheter mitral valve replacement. J Am Coll Cardiol Intv 2019;12:182–93.

10. Khan JM, Trivedi U, Gomes A, Lederman RJ, Hildick-Smith D. 'Rescue' LAMPOON to treat transcatheter mitral valve replacement-associated left ventricular outflow tract obstruction. J Am Coll Cardiol Intv 2019 Feb 7 [E-pub ahead of print].

11. Khan JM, Lederman RJ, Devireddy CM, et al. LAMPOON to facilitate Tendyne transcatheter mitral valve replacement. J Am Coll Cardiol Intv 2018;11:2014–7.

12. Greenbaum AB, Condado JF, Eng M, et al. Long or redundant leaflet complicating transcatheter mitral valve replacement: case vignettes that advocate for removal or reduction of the anterior mitral leaflet. Catheter Cardiovasc Interv 2018;92:627–32.

13. Praz F, Khalique OK, Lee R, et al. Transatrial implantation of a transcatheter heart valve for severe mitral annular calcification. J Thorac Cardiovasc Surg 2018;156:132–42.

14. Deharo P, Urena M, Himbert D, et al. Bail-out alcohol septal ablation for left ventricular outflow tract obstruction after transcatheter mitral valve replacement. J Am Coll Cardiol Intv 2016;9:e73–6.

15. Guerrero M, Wang DD, O'Neill W. Percutaneous alcohol septal ablation to acutely reduce left ventricular outflow tract obstruction induced by transcatheter mitral valve replacement. Catheter Cardiovasc Interv 2016;88:E191–7.

16. Urena M, Himbert D, Brochet E, et al. Transseptal transcatheter mitral valve replacement using balloon-expandable transcatheter heart valves: a step-by-step approach. J Am Coll Cardiol Intv 2017;10:1905–19.

17. David TE. Mitral valve replacement with preservation of chordae tendinae: rationale and technical considerations. Ann Thorac Surg 1986;41:680–2.

18. Khan JM, Rogers T, Schenke WH, et al. Intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve replacement: pre-clinical findings. J Am Coll Cardiol Intv 2016;9:1835–43.

19. Babaliaros VC, Greenbaum AB, Khan JM, et al. Intentional percutaneous laceration of the anterior mitral leaflet to prevent outflow obstruction during transcatheter mitral valve replacement: first-in-human experience. J Am Coll Cardiol Intv 2017;10:798–809.

20. Khan JM, Rogers T, Babaliaros VC, Fusari M, Greenbaum AB, Lederman RJ. Predicting left ventricular outflow tract obstruction despite anterior mitral leaflet resection: the "Skirt Neo-LVOT". J Am Coll Cardiol Img 2018;11:1356–9.

21. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308–21.

22. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000;35:1245–55.

23. Yoon SH, Whisenant BK, Bleiziffer S, et al. Transcatheter mitral valve replacement for degenerated bioprosthetic valves and failed annuloplasty rings. J Am Coll Cardiol 2017;70:1121–31.

24. Urena M, Brochet E, Lecomte M, et al. Clinical and haemodynamic outcomes of balloon-expandable transcatheter mitral valve implantation: a 7-year experience. Eur Heart J 2018;39:2679–89.

25. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr 2009;22:975–1014, quiz 1082–4.

26. Capodanno D, Petronio AS, Prendergast B, 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.

27. Kamioka N, Babaliaros V, Morse MA, et al. Comparison of clinical and echocardiographic outcomes after surgical redo mitral valve replacement and transcatheter mitral valve-in-valve therapy. J Am Coll Cardiol Intv 2018;11:1131–8.

28. Muller DWM, Farivar RS, Jansz P, et al. Transcatheter mitral valve replacement for patients with symptomatic mitral regurgitation: a global feasibility trial. J Am Coll Cardiol 2017;69:381–91.

29. Bapat V, Rajagopal V, Meduri C, et al. Early experience with new transcatheter mitral valve replacement. J Am Coll Cardiol 2018;71:12–21.

30. Eng MH, Greenbaum A, Wang DD, et al. Thrombotic valvular dysfunction with transcatheter mitral interventions for postsurgical failures. Catheter Cardiovasc Interv 2017;90:321–8.

31. Khan JM, Lederman RJ. Unnatural milieu: thrombus after transcatheter mitral valve replacement. Catheter Cardiovasc Interv 2017;90:329–30.

32. Khan JM, Lederman RJ. Adventures across the second dimension: predicting left ventricular outflow tract obstruction following transcatheter mitral valve replacement. Catheter Cardiovasc Interv 2018;92:388–9.

33. Kohli K, Wei ZA, Yoganathan AP, Oshinski JN, Leipsic J, Blanke P. Transcatheter mitral valve planning and the neo-LVOT: utilization of virtual simulation models and 3D printing. Curr Treat Options Cardiovasc Med 2018;20:99.

34. De Vecchi A, Marlevi D, Nordsletten DA, et al. Left ventricular outflow obstruction predicts increase in systolic pressure gradients and blood residence time after transcatheter mitral valve replacement. Sci Rep 2018;8:15540.

35. Urena M, Vahanian A, Sondergaard L. Patient selection for transcatheter mitral valve implantation: why is it so hard to find patients? EuroIntervention 2018;14:AB83–90.

36. Khan JM, Lederman RJ, Sanon S, et al. Transcatheter mitral valve replacement after transcatheter electrosurgical laceration of Alfieri STItCh (ELASTIC): first-in-human report. J Am Coll Cardiol Intv 2018;11:808–11.

37. Khan JM, Dvir D, Greenbaum AB, et al. Transcatheter laceration of aortic leaflets to prevent coronary obstruction during transcatheter aortic valve replacement: concept to first-in-human. J Am Coll Cardiol Intv 2018;11:677–89.

KEY WORDS mitral annular calcification, structural heart disease, transcatheter electrosurgery, transcatheter mitral valve replacement, transseptal interventions, valve-in-ring

APPENDIX For an expanded Methods section as well as supplemental tables, figures, and videos, please see the online version of this paper.

Supplement

LAMPOON to prevent LVOT Obstruction during Transcatheter Mitral Valve Replacement (TMVR): Prospective Multicenter Trial Results

Participating Sites

Site	**City, State**	**Principal Investigator**	**Subjects enrolled**
Emory University Hospital	Atlanta, GA	Vasilis Babaliaros	15 subjects
Henry Ford Hospital	Detroit, MI	Adam Greenbaum Marvin Eng	8 subjects
Carilion Roanoke Memorial Hospital	Roanoke, VA	Jason Foerst	4 subjects
Inova Fairfax Hospital	Fairfax, VA	Shahram Yazdani	2 subjects
University of Washington	Seattle, WA	James McCabe	1 subject

Participating Personnel

Emory University Hospital, Atlanta GA: Vasilis Babaliaros; Adam Greenbaum; Bradley Leshnower; Madeline Kohrumel; Lisa Warren; Afua Harris; Neil Holtz; Patrick Gleason; Frank Corrigan; Norihiko Kamioka; Stamatios Lerakis; Chandan Devireddy; James Stewart; Altayyeb Yousef; Anurag Sahu; Sharon Howell; Mary Mungai; Jennifer James; Patricia Keegan; James Lee; Kelby Parsons; Vicki Smith; Lauren Wheeler Roberts. **Henry Ford Hospital,** Detroit MI**:** Adam Greenbaum; Marvin Eng; Dee Dee Wang; Tongwa Aka; Rewaa Yas; Marianne Rollet; Ashish Solanki. **Carilion Roanoke Memorial Hospital,** Roanoke VA**:** Joseph Rowe; Vivian Wilson. **Inova Fairfax Hospital**, Fairfax VA: Shahram Shawn Yazdani; Eric Sarin; Nadim Geloo; Anna Villagomez. **University of Washington**, Seattle WA**:** James McCabe; Gabriel Aldea; Claire Schwaegler.

Study Management: Annette Stine (Study Manager); Adriana Byrnes.

Independent Data Monitors: Artur Karapetyan; Valeriy Matveev; Olha Katynska.

Data Manager: Sergei Avdiushko.

Clinical Events Adjudication Committee (Medstar Heart and Vascular Institute): Hector Garcia-Garcia (Chair); Eugene McFadden; Alexandre Kajita; Yuichi Ozaki; Petros Okubagzi

NHLBI Data Safety Monitoring Board: Jamison Bourque (Chair); Thomas Aversano; Dean Follmann; David Malenka; Mary Marshall; Gregg Stone

Central CT Laboratory (NHLBI): Marcus Chen

Central Echo Laboratory (Henry Ford): Dee Dee Wang

Statistical Analysis (NHLBI Office of Biostatistics Research): Xin Tian

Study Selection criteria

Inclusion Criteria

- Adults age ≥ 21 years
- Severe symptomatic native mitral valve failure after mitral annuloplasty repair or related to mitral annular calcification.
- Unacceptably high or prohibitive risk for surgical mitral valve replacement and indicated for transcatheter mitral valve replacement (TMVR) as determined by the multidisciplinary institutional heart team, including at least one cardiovascular surgeon who has examined the patient
- High or prohibitive risk of LVOT obstruction (predicted neo-LVOT less than 200 mm2) or transcatheter heart valve dysfunction from long/redundant anterior mitral valve leaflet, as determined by the multidisciplinary institutional heart team.
- Anatomic eligibility for LAMPOON based on core lab assessment of the baseline CT and echocardiogram.
- Concordance of the study selection committee

Exclusion criteria

- Subjects unable to consent to participate, unless the subject has a legally authorized representative
- Subjects unwilling to participate or unwilling to return for study follow-up activities.
- Predicted neo-LVOT created by the Sapien 3 skirt, after LAMPOON, less than 150 mm2
- TAVR within 6 weeks
- Intended concurrent structural heart procedure, such as aortic or tricuspid valve implantation
- Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures

Trial endpoints

Primary endpoint

The primary endpoint is “Technical success ACCEPTABLE” (measured at exit from the catheterization laboratory). All the following must be present:

- Successful LAMPOON traversal and laceration; and
- Peak LVOT gradient < 50 mm Hg; and
- Absence of procedural mortality; and
- Successful access, delivery, and retrieval of the LAMPOON device system; and
- Successful deployment and correct positioning of the first intended device; and
- Freedom from emergency surgery or reintervention related to the device or access procedure.

The first two factors are modifications of the MVARC (mitral valve academic research consortium) consensus endpoint (GW Stone GW, *et al*, Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308-21.), specific for LAMPOON procedure.

Co-Primary endpoint

Based on feedback from the FDA, the co-primary endpoint is Technical Success OPTIMAL (measured at exit from the catheterization laboratory). This differs from 0 only in the magnitude of the peak LVOT gradient.

All the following must be present:

- Successful LAMPOON traversal and laceration; and
- Peak LVOT gradient < 30 mm Hg; and
- Absence of procedural mortality; and
- Successful access, delivery, and retrieval of the LAMPOON device system; and
- Successful deployment and correct positioning of the first intended device; and
- Freedom from emergency surgery or reintervention related to the device or access procedure.

Exploratory Endpoints

Exploratory endpoints include

- LVOT obstruction measured as a pressure gradient on catheterization and echocardiography

- Incidence of LVOT obstruction > 20 mm Hg before discharge and at 30 days, including as an alternative LVOT gradient threshold to the primary endpoint
- Predicted neo-LVOT area based on THV frame had LAMPOON not been performed
- MVARC 30-day Device Success
- MVARC 30-day Procedure Success
- MVARC 1-year Patient Success
- Mortality, all-cause, cardiovascular vs non-cardiovascular, peri- vs non-periprocedural, LAMPOON and TMVR relatedness)
- Neurological events as reported by the site clinicians only
- Pre-discharge stroke, alone, and in combination with the primary endpoint
- Myocardial infarction
- Access and vascular complications
- MVARC bleeding complications
- AKIN acute kidney injury
- Arrhythmia and conduction disturbances
- Freedom from infection related to the TMVR at each time point
- Freedom from hemolytic anemia related to TMVR/LAMPOON
- Device related technical failure: Device Failure, Paravalvular Leak, Pericardial effusion, Conversion to open surgery, Device mal-positioning or migration or detachment, Device fracture, Unintended damage to native mitral valve apparatus
- Aortic valve regurgitation change
- Device thrombosis

Supplement Table 1. Baseline characteristics stratified by mitral regurgitation and mitral stenosis

Baseline patient characteristics n==30	Mitral Regurgitation (n=10)	Mitral Stenosis (n=20)
Age, years (median and range)	73.5 (47 - 84)	81.5 (49 - 89)
Female	6 (60%)	16 (80%)
BSA, m^2	1.8 ± 0.1	1.8 ± 0.2
TMVR SETTING		
Complete ring	6 (60%)	7 (35%)
Incomplete ring/band	2 (20%)	0 (0%)
MAC	2 (20%)	13 (65%)
Mean mitral valve gradient (mmHg)	6.3±3.4	11 ± 4.0
CT ANNULAR MEASUREMENTS		
Annular area	523.2 ± 137.2	565.4±144.51
Antero-posterior distance	21.7 ± 4.0	21.4 ± 3.5
Inter-commissural distance	29.3 ± 2.7	30.9 ± 4.3
LVOT obstruction risk		
Aorto-mitral angle, º	118.1 ± 14.8	116.9 ± 6.6
Septal thickness, mm	11.1 ± 2.9	13.9 ± 3.6
Fixed LVOT obstruction subset, n==25	(n=6)	(n=19)
Predicted neo-LVOT, mm^2	118.8 ± 45.1	68.8 ± 47.8
Predicted skirt neo-LVOT, mm^2	250.5 ± 49.7	224.1 ± 57.1
Dynamic LVOT obstruction subset, n==5	(n=4)	(n=1)
Anterior mitral leaflet length on CT, mm	26.9 + 2.7	31.5

Supplement Table 2. Outcomes stratified by mitral regurgitation and mitral stenosis

	Mitral Regurgitation (n=10)			Mitral Stenosis (n=20)		
ECHOCARDIOGRAPHY	**Baseline**	**Pre-Discharge**	**30-Day**	**Baseline**	**Pre-Discharge**	**30-Day**
Left ventricle end diastolic volume, ml	87.3±25.9	74.8±35	90.3±34.8	56.7±26.7	59.6±21.8	56.1±23.8
Left ventricle end systolic volume, ml	36.2±18.7	39.3±26.8	39.3±26.8	22.5±13	22.9±11.8	22±12.7
LVEF, %	60±13	49.3±17.2	43.8±16.2	61.2±8.4	60.6±11.9	61.6±10.2
Left atrium volume index	59±17.9	59.8±32.3	58.7±17.8	50.3±15.7	49.1±19.2	47.6±17.5
LVOT peak velocity, m/s	1±0.3	1.3±0.4	1.2±0.6	1.1±0.3	1.6±0.6	1.5±0.6
LVOT peak gradient, mmHg	7.5±8.4	6.9±4.4	7.2±7	5.1±2.7	11.3±8	10.3±7.5
LVOT mean gradient. mmHg	1.9±0.9	3.3±2	3.5±3.7	2.6±1.5	5.6±4.6	4.9±4
LVOT VTI, cm	0.2±0.1	0.2±0.1	0.3±0.2	0.2±0.1	0.3±0.1	0.3±0.1
Mean transmitral gradient, mmHg	6.3±3.4	5.1±1.2	6.3±2.1	11±4	5.9±2.5	6.8±2.5
Mitral regurgitation severity						
None	0 (0%)	1(10%)	2 (20%)	0(0%)	4 (21%)	3(18%)
Trace	0 (0%)	4 (40%)	4 (40%)	6 (30%)	6 (32%)	4(24%)
Mild	0 (0%)	4 (40%)	4 (40%)	6 (30%)	9 (47%)	8 (47%)
Moderate	2 (22%)	1 (40%)	0 (0%)	4 (20%)	0 (0%)	0 (0%)
Severe	7 (78%)	0 (0%)	0 (0%)	4 (20%)	0 (0%)	2 (12%)
Peri-prosthetic regurgitation						
None	——	5 (50%)	9 (90%)	——	11 (65%)	8 (47%)

Trace	——	2 (20%)	1 (10%)	——	1 (6%)	3 (18%)
Mild	——	3 (30%)	0 (0%)	——	5 (29%)	5 (29%)
Moderate	——	0 (0%)	0 (0%)	——	0 (0%)	0 (0%)
Severe	——	0 (0%)	0 (0%)	——	0 (0%)	1 (6%)
CATH HEMODYNAMICS	**Baseline**	**Post-LAMPOON**	**Post TMVR**	**Baseline**	**Post-LAMPOON**	**Post TMVR**
Heart rate, bpm	70.2±13.1	74.3±21	74.9±12.9	69.2±9.8	77.5±12.3	72.7±9.6
Systolic arterial pressure, mmHg	112.6±18	92.3±14.5	128.2±16.3	128.8±22.8	98.2±23.2	120.9±20.1
Diastolic arterial pressure, mmHg	59.1±10.7	50.7±6	55.8±16.7	62.6±12.7	51.8±13.8	58.2±15.5
Mean arterial pressure, mmHg	80.4±13.3	62.9±7	86.7±13.7	87.3±14.8	67.4±17.4	80.8±14.6
Right atrial pressure, mmHg	16.0±5.9	NA	14.6±6.3	12.8±6.1	NA	12.4±6.4
Systolic pulmonary artery pressure, mmHg	52.3±14.5	NA	52.4±17.2	59.1±20.2	NA	53.1±17.5
Diastolic pulmonary artery pressure, mmHg	23.5±7.4	NA	22.4±5.6	25.5±8.9	NA	22.7±7.4
Mean pulmonary artery pressure, mmHg	35.9±9.3	NA	33.7±8.4	40.1±12.1	NA	34.8±9.8
Mean left atrial pressure, mmHg	29.7±16.2	NA	18.3±4.4	25.1±6.9	NA	18.1±4.9
Left atrial v-wave, mmHg	52.1±20.6	NA	24.3±8.4	41.2±13.2	NA	26.0±9.0
Mean transmitral gradient, mmHg	4.3±3.5	NA	2.7±1.7	10.0±4.3	NA	2.9±1.6

Cardiac Output, L/min	4.9±1.8	NA	5.7±1.4	5.2±1.8	NA	5.3±1.6
Left ventricle end diastolic pressure, mmHg	18.8±6.6	NA	15.9±5.0	18.1±5.8	NA	18.9±4.9
LVOT peak-to-peak gradient, mmHg	4.0±3.5	7.1±7.3	7.1±7.3	9.5±6.2	22.9±26.8	12.6±9.8
Calculated mitral valve area, cm2	2.2±1.1	NA	2.0±NA	1.2±0.2	NA	3.0±1.0

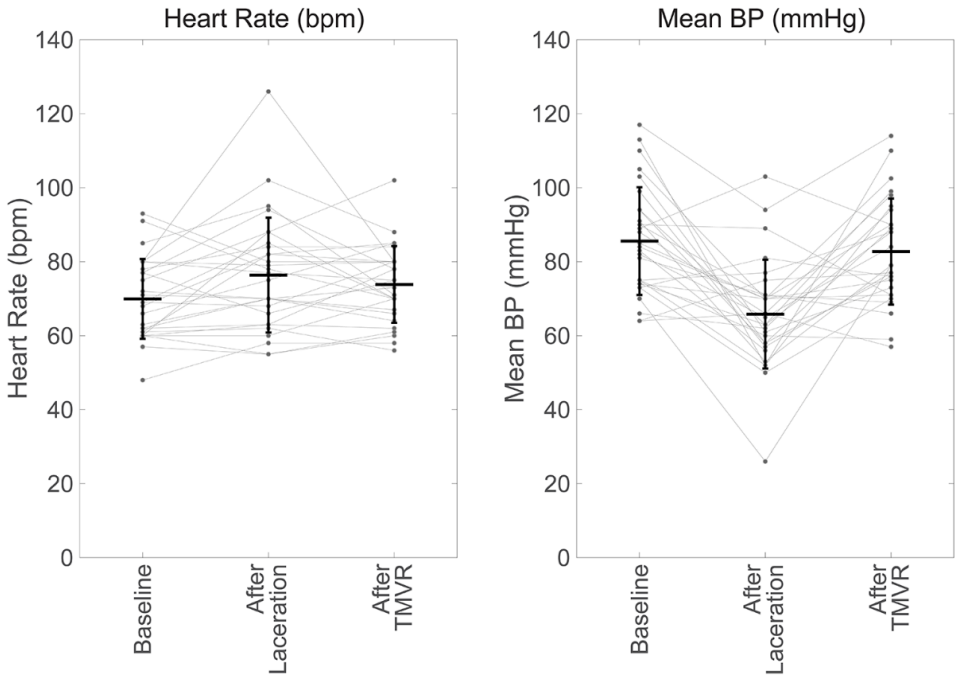
Supplement Table 3. Cautions and contra-indications to LAMPOON and TMVR

Step	**Caution or Contra-indication**	**Comments**
LAMPOON	Mechanical AVR (for conventional retrograde transaortic LAMPOON)	Alternative access routes for LAMPOON are under development
	Skirt neoLVOT <150mm^2	Causes life-threatening LVOT gradients
	No calcium free traversal target on anterior mitral leaflet	Once a leaflet is traversed, even if heavily calcified, in our experience it can be lacerated through electrosurgery and possibly fracture
TMVR	LVOT obstruction	Avoiding this complication is the rationale for procedures such as LAMPOON and transcoronary alcohol septal ablation
	Large annulus • Intercommissural distance >34mm • Area >850 mm^2	TMVR using the largest-available marketed Sapien 3 29mm valve risks life-threatening paravalvular leak and embolization. Off-label solutions are under development
	Insufficient calcium for anchoring	Objective criteria are missing, but most operators there must be opposed regions of heavy calcification to allow the TMVR to anchor
	Bulky protruding calcium mass in the annulus	We have observed TMVR "kick-back" during deployment, and zones of PVL, attributable to such rigid and bulky masses

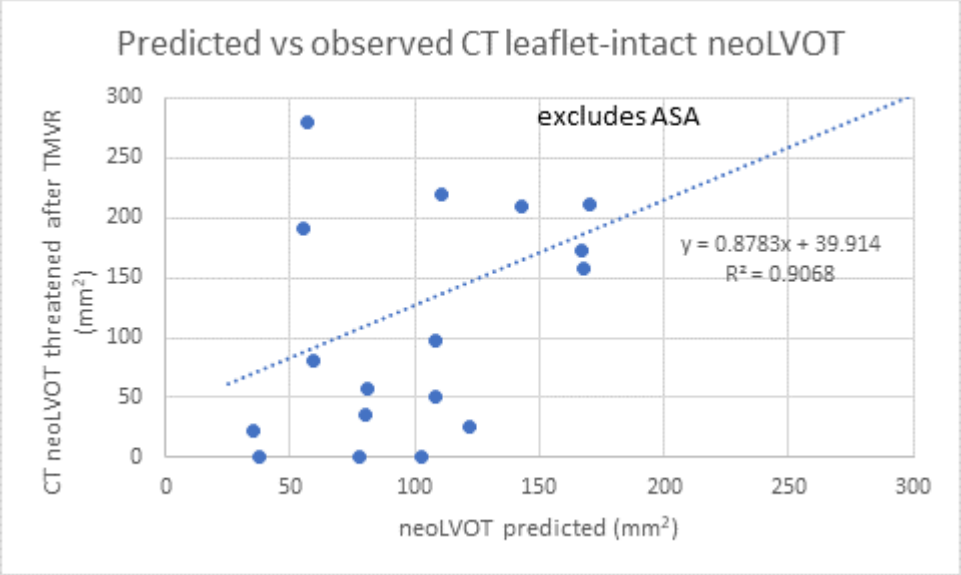
	Calcium pattern suggesting caseous necrosis	Caseous necrosis of the mitral annular calcification remodels during TMVR and can cause paravalvular leak
	Very eccentric rigid ring	Eccentric annuloplasty rings can distort the TMVR device, can create zones of paravalvular leak, and can contribute to or exaggerate annuloplasty ring dehiscence during TMVR
	Dehisced bioprosthetic ring	As above
	Futility	Irreversible pulmonary hypertension and end-stage cardiomyopathy are not amenable to TMVR

Supplement Figure 1. Procedure Hemodynamics

Heart rate and mean arterial pressure is shown for all subjects at three procedure stages: immediately before and after LAMPOON laceration and after transcatheter mitral valve replacement.



Supplement Figure 2. Correlation between predicted and observed neo-LVOT by CT



Chapter Summary

LAMPOON is a technique to lacerate the anterior mitral valve leaflet using transcatheter electrosurgery. First, charge is concentrated at the centre (A2 scallop) and base of the anterior mitral valve leaflet via the tip of a guidewire insulated by a polymer jacketed microcatheter. During radiofrequency energy application, the focused current density causes tissue vaporization and permits guidewire traversal through the leaflet. The guidewire tip is snared and externalized, and the kinked and denuded inner surface of the guidewire mid-shaft is positioned through the perforated base of A2. Both limbs of the guidewire are insulated in guiding catheters that are flushed with non-ionic 5% dextrose during guidewire electrification. These modifications focus charge on the anterior mitral valve leaflet at the lacerating edge of the guidewire. The guidewire and catheters are gently pulled, guiding the guidewire loop down the centreline of the anterior mitral leaflet as the tissue adjacent to the lacerating edge is vaporized.

The procedure was tested in seven anesthetized pigs and in one heparinised post-mortem pig. The results showed controlled centreline laceration of the anterior mitral valve leaflet is feasible using transcatheter electrosurgery. Precise traversal at the base of A2, guided by echocardiography and cineangiography, and a chord-free trajectory of the catheters was necessary for optimal splitting and splaying of the anterior mitral valve leaflet.

The procedure was then performed on a compassionate basis in five patients with mitral valve failure in the setting of native mitral annular calcification or previous mitral valve annuloplasty suitable for anchoring a transcatheter aortic valve. All patients were considered inoperable by the heart team and had prohibitive risk of LVOT obstruction as predicted on pre-procedure cardiac CT. LAMPOON traversal and laceration was successfully performed in all five patients. Following TMVR, no patient developed severe LVOT obstruction despite the high predicted risk. One patient developed haemolysis, possibly due to red blood cell shearing against the open stent cells of the transcatheter valve protruding into the LVOT. All patients survived to discharge and one patient died within 30 days from intractable right ventricular failure. The differences in procedure in humans compared to in swine

were that 3-D transoesophageal echocardiography provided superior procedure guidance in patients compared with 2-D intracardiac echocardiography in swine, a transseptal veno-arterial rail was required to position the left atrial snare catheter and ensure a chord free trajectory, and TMVR was performed after LAMPOON in patients. Unlike in naïve pigs, no patient developed hemodynamic compromise after LAMPOON. This could be because the leaflets coapted in systole after the linear laceration, and that patients had physiologically compensated for chronically elevated left atrial pressures and the acute exacerbation was tolerated in the brief time between LAMPOON and TMVR.

LAMPOON was investigated in a prospective single-arm multicentre clinical trial with independent end-point adjudication and core laboratory analysis of images. 30 subjects at high or prohibitive surgical risk and high risk of LVOT obstruction from TMVR were enrolled. LAMPOON traversal and laceration was successful in all patients. Four patients required alcohol septal ablation after TMVR due to increased LVOT gradients. Three of these patients had a small “skirt neo-LVOT”, an important concept realized during this trial and subsequently adopted as an exclusion criterion for enrolment. The fourth patient had insufficiently basal leaflet laceration. Seven subjects had moderate or severe paravalvular leak, all remote from the site of leaflet laceration, with five requiring further procedures to treat the paravalvular leak. At 30 days, there were no strokes and 93% survival.

In developing this novel procedure and investigating it in a carefully designed clinical trial, the hypothesis that mitral valve leaflets can be precisely lacerated using transcatheter electrosurgery, and that controlled laceration may prevent blood flow obstruction following transcatheter valve implantation has been demonstrated. Accordingly, the first specific aim of this thesis has been addressed.

CHAPTER 4. BASILICA (incorporating two published manuscripts)

Introduction

The second specific aim of this thesis was *to determine if transcatheter laceration of aortic leaflets prevents coronary artery obstruction following TAVI.* This chapter describes the second of two novel procedures to lacerate valve tissue using transcatheter electrosurgery to prevent blood flow obstruction from transcatheter valve implantation. The chapter incorporates two published manuscripts, describing the pre-clinical and first-in-human experience, and the early feasibility prospective clinical trial.

Transcatheter aortic valve implantation (TAVI) is an effective treatment for aortic stenosis. Rarely, the diseased aortic valve leaflets, whether native or from a failed bioprosthetic valve, obstruct the coronary arteries when displaced, which can be fatal. Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Coronary Artery obstruction (BASILICA) is a transcatheter technique that uses an electrified guidewire to lacerate the aortic valve leaflet prior to TAVI to prevent coronary artery obstruction. Using procedure steps similar to those described for the LAMPOON procedure, the target aortic leaflet is lacerated in line with the coronary ostium and splays after valve implantation.

In line with the specific aims, we developed the novel BASILICA transcatheter procedure in anesthetized pigs to precisely lacerate the aortic valve leaflets in line with the coronary ostia. Also, in line with the specific aims, we conducted an early feasibility phase 1 study of the procedure in 30 human subjects predicted on CT imaging to be at prohibitive risk of coronary artery obstruction from TAVI and therefore excluded from available treatment.

Role of transcatheter electrosurgery

The transcatheter electrosurgery techniques in BASILICA are like those used in LAMPOON. They enable the procedure to be done percutaneously. A guidewire is directed by a catheter to the target at the base of the aortic leaflet. The guidewire is insulated in a polymer jacketed microcatheter with only the tip exposed to minimize

the surface area of the active electrode for charge concentration at the leaflet base. During brief electrification, the guidewire traverses the base of the leaflet. The guidewire is snared and retrieved and the Flying V lacerating surface created and positioned at the basal perforation site. Insulation around this lacerating edge is provided by 5% dextrose infusion through catheters which sheath both limbs of the guidewire. Gentle tension is applied to the catheters and guidewires, directing the lacerating edge from the base of the aortic leaflet to the tip, vaporizing the leaflet down the centreline. Careful transcatheter electrosurgery techniques are required to create a controlled laceration without unpredictable leaflet avulsion or collateral injury.

Transcatheter Laceration of Aortic Leaflets to Prevent Coronary Obstruction During Transcatheter Aortic Valve Replacement: Concept to First-in-Human

An original research manuscript published in the journal *JACC: Cardiovascular Interventions* in 2018

Candidate's contribution

My colleagues and I conceived of the idea for BASILICA. I personally devised the specific procedure steps, techniques, and inventory list. I established how to reproducibly use transcatheter electrosurgery to cut both left and right coronary cusps of the aortic valve using a transfemoral approach. I designed and performed all the animal experiments. I planned all clinical cases, including all procedure steps and contingency plans, and proctored or performed all cases. I drafted, designed the figures, and consulted all the references for this pre-clinical and first-in-human manuscript, on which I am first author.

JACC: CARDIOVASCULAR INTERVENTIONS
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN
COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 11, NO. 7, 2018

STRUCTURAL

Transcatheter Laceration of Aortic Leaflets to Prevent Coronary Obstruction During Transcatheter Aortic Valve Replacement

Concept to First-in-Human

Jaffar M. Khan, BM BCH,[a] Danny Dvir, MD,[b] Adam B. Greenbaum, MD,[c] Vasilis C. Babaliaros, MD,[d] Toby Rogers, PHD, BM BCH,[a] Gabriel Aldea, MD,[b] Mark Reisman, MD,[b] G. Burkhard Mackensen, MD,[b] Marvin H.K. Eng, MD,[c] Gaetano Paone, MD,[c] Dee Dee Wang, MD,[c] Robert A. Guyton, MD,[d] Chandan M. Devireddy, MD,[d] William H. Schenke, BS,[a] Robert J. Lederman, MD[a]

ABSTRACT

OBJECTIVES This study sought to develop a novel technique called bioprosthetic or native aortic scallop intentional laceration to prevent coronary artery obstruction (BASILICA).

BACKGROUND Coronary artery obstruction is a rare but fatal complication of transcatheter aortic valve replacement (TAVR).

METHODS We lacerated pericardial leaflets in vitro using catheter electrosurgery, and tested leaflet splaying after benchtop TAVR. The procedure was tested in swine. BASILICA was then offered to patients at high risk of coronary obstruction from TAVR and ineligible for surgical aortic valve replacement. BASILICA used marketed devices. Catheters directed an electrified guidewire to traverse and lacerate the aortic leaflet down the center line. TAVR was performed as usual.

RESULTS TAVR splayed lacerated bovine pericardial leaflets. BASILICA was successful in pigs, both to left and right cusps. Necropsy revealed full length lacerations with no collateral thermal injury. Seven patients underwent BASILICA on a compassionate basis. Six had failed bioprosthetic valves, both stented and stent-less. Two had severe aortic stenosis, including 1 patient with native disease, 3 had severe aortic regurgitation, and 2 had mixed aortic valve disease. One patient required laceration of both left and right coronary cusps. There was no hemodynamic compromise in any patient following BASILICA. All patients had successful TAVR, with no coronary obstruction, stroke, or any major complications. All patients survived to 30 days.

CONCLUSIONS BASILICA may durably prevent coronary obstruction from TAVR. The procedure was successful across a range of presentations, and requires further evaluation in a prospective trial. Its role in treatment of degenerated TAVR devices remains untested. (J Am Coll Cardiol Intv 2018;11:677–89) Published by Elsevier on behalf of the American College of Cardiology Foundation.

From the [a]Cardiovascular Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; [b]University of Washington, Seattle, Washington; [c]Center for Structural Heart Disease, Division of Cardiology, and Division of Cardiac Surgery, Henry Ford Health System, Detroit, Michigan; and the [d]Structural Heart and Valve Center, Emory University Hospital, Atlanta, Georgia. Supported by the National Heart, Lung, and Blood Institute, National Institutes of Health (Z01-HL006040-7), and by the intramural programs of the participating centers. National Heart, Lung, and Blood Institute has a collaborative research and development agreement with Edwards Lifesciences on transcatheter modification

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2018.01.247

ABBREVIATIONS AND ACRONYMS

BASILICA = bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction

CT = computed tomography

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) is an effective alternative to surgical aortic valve replacement in intermediate- and high-risk patients with native aortic stenosis (1,2). TAVR is also an effective treatment for failure of bioprosthetic surgical aortic valves, a treatment known as valve-in-valve TAVR (3,4). Coronary artery obstruction is a devastating complication of TAVR, with a >50% mortality (5). Coronary artery obstruction occurs when the transcatheter heart valve displaces the underlying surgical or native aortic valve leaflets outward and obstructs the coronary artery ostia, either by sealing the sinus of Valsalva at the sinotubular junction or by the leaflet itself covering the coronary ostia because of low-lying coronary ostia and inadequate sinus width (**Figure 1**). Coronary artery obstruction is 4 times as common during valve-in-valve TAVR as during TAVR for native aortic stenosis (6),

SEE PAGE 690

likely because most surgical prostheses are supra-annular in design, lowering coronary heights relative to the valve leaflets, and because valve suturing draws the coronaries closer, decreasing sinus width. The risk of coronary obstruction is highest during TAVR for surgical bioprothesis designs intended to maximize effective aortic orifice area ("stented" bioprostheses that have externally mounted leaflets, and "stent-less" surgical bioprostheses) (5). Treatment requires bail-out percutaneous coronary intervention, which may not be possible with a valve leaflet obstructing the coronary artery, or emergency bypass surgery. Pre-emptive coronary protection with a guidewire, with or without a coronary balloon or stent prepositioned down the coronary artery, is variably successful (7,8) in the short and intermediate term. One-third of coronary obstruction events may manifest after the TAVR is concluded (5).

We propose a solution based on the LAMPOON procedure (9,10), which uses catheters to split the mitral valve leaflet and prevent obstruction of the left ventricular outflow tract during transcatheter mitral valve replacement. Here we report a technique to split aortic valve leaflets, whether bioprosthetic or native, to prevent coronary artery obstruction after TAVR. The new technique is called bioprosthetic or native aortic scallop intentional laceration to prevent coronary artery obstruction (BASILICA).

We developed the technique in vitro and in animals, and then offered the procedure to patients experiencing aortic valve failure who were ineligible for conventional surgical aortic valve replacement, and high or prohibitive risk of coronary artery obstruction from TAVR.

METHODS

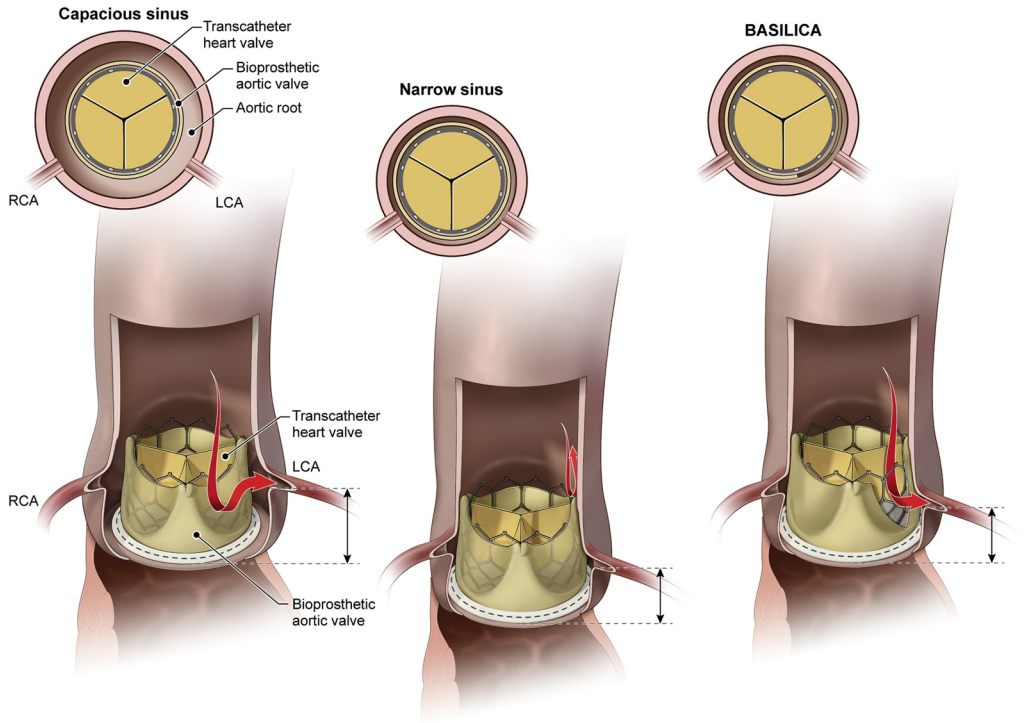
We set out to demonstrate several key technical principles. First, that an aortic leaflet scallop can be traversed in situ by an electrified guidewire between the sinus of Valsalva and the left ventricular outflow tract. Second, that the traversed leaflet, whether native or bioprosthetic, can be lacerated in situ by the mid-shaft of an electrified guidewire. Third, that the lacerated leaflets splay after TAVR to allow blood flow across them toward otherwise obstructed coronary ostia. Fourth, whether partial (mid-scallop vs. basal leaflet) lacerations extend lengthwise when stretched by an implanted valve, which may influence the required spatial precision of the procedure. Fifth, that both left and right coronary cusps can be lacerated simultaneously in vivo.

IN VITRO. We tested radiofrequency-assisted transcatheter perforation and laceration of exterior-mounted bovine pericardial leaflets on a representative bioprosthetic heart valve (19-mm Trifecta valve, Abbott St. Jude Medical, St. Paul, Minnesota) submerged in a 0.9% saline bath with a remote dispersive electrode (Online Figure 1). Two lacerations were attempted on the bioprosthetic heart valve. One leaflet was lacerated from base to tip and the second from

of the mitral valve. Dr. Dvir is a consultant for Edwards Lifesciences, Medtronic, and St. Jude Medical. Dr. Greenbaum is a proctor for Edwards Lifesciences and Abbott St. Jude Medical. Dr. Babaliaros is a consultant for Edwards Lifesciences and Abbott Vascular; and his employer has research contracts for clinical investigation of transcatheter aortic and mitral devices from Edwards Lifesciences, Abbott Vascular, Medtronic, St. Jude Medical, and Boston Scientific. Dr. Eng is a proctor for Edwards Lifesciences. Dr. Paone is a proctor for Edwards Lifesciences. Dr. Wang is a consultant for Edwards Lifesciences. Dr. Guyton's employer has research contracts for clinical investigation of aortic and mitral devices from Edwards Lifesciences, Abbott Vascular, Medtronic, and Boston Scientific. Dr. Devireddy is a consultant for Medtronic; and his employer has research contracts for clinical investigation of transcatheter aortic and mitral devices from Edwards Lifesciences, Abbott Vascular, Medtronic, St. Jude Medical, and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Khan and Dvir contributed equally to this work.

Manuscript received October 20, 2017; revised manuscript received December 19, 2017, accepted January 1, 2018.

FIGURE 1 Illustrations of Coronary Obstruction and Prevention by BASILICA



In normal transcatheter aortic valve replacement performed in a capacious aortic root, blood flows unrestricted around valve leaflets into coronary arteries. In patients with a crowded sinus and low-lying coronary arteries, coronary blood flow is obstructed by the bioprosthetic valve leaflets after transcatheter aortic valve replacement. After BASILICA, blood flows through the open cells of the transcatheter heart valve unimpeded into the coronary artery. BASILICA = bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction; LCA = left coronary artery; RCA = right coronary artery.

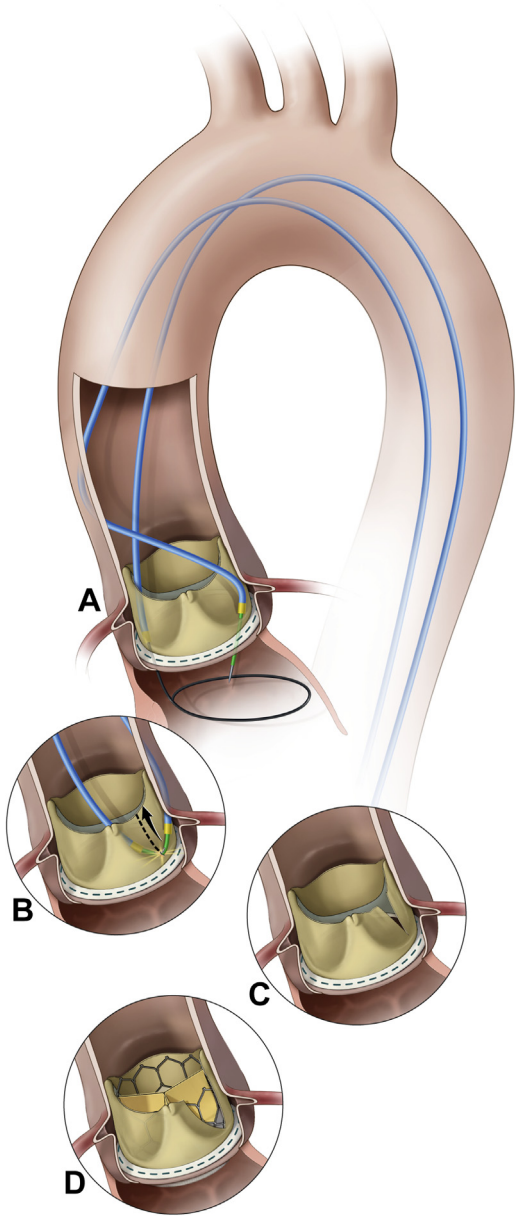
mid-point to tip. A third scallop was left intact and served as a control.

Balloon expandable (20-mm Sapien 3, Edwards Lifesciences, Irvine, California) and self-expanding valves (23-mm Evolut Pro, Medtronic, Minneapolis, Minnesota) were deployed in the bioprosthetic valve to test splaying of split leaflet around the open cells of the transcatheter heart valve and propagation of the split in the leaflet. A second valve (25-mm Mitroflow, Sorin Livanova, London, England) was cut with a scalpel and leaflet splaying was also tested with appropriately sized balloon expanding and self-expanding valves.

ANIMALS. Animal experiments on naive Yorkshire and Yucatan pigs were approved by the institutional animal care and use committee and conducted per contemporary National Institutes of Health guidelines. Anesthesia was induced and maintained with mechanical ventilation and inhaled isoflurane, 2 femoral arterial sheaths of 6-F catheter and a 9-F catheter femoral venous sheath were placed percutaneously, and heparin and amiodarone were administered. The BASILICA procedure without TAVR was performed using catheters directed under biplane x-ray fluoroscopy and intracardiac echocardiography guidance. Pre-procedural cardiac magnetic resonance imaging was performed at 1.5-T (Aera, Siemens, Erlangen, Germany) to plan fluoroscopy projection angles. Hemodynamics were recorded for 1 h after laceration until euthanasia. The length of scallop laceration relative to the overall length of the scallop was measured using calipers at necropsy. The heart was carefully inspected for evidence of bystander electrical or mechanical injury.

CLINICAL. Patients. Patients with high or prohibitive risk for surgical aortic valve replacement and high risk of coronary artery obstruction with TAVR underwent TAVR with BASILICA at 3 medical centers (University of Washington, Henry Ford, and Emory University Hospitals). All consented to clinical treatment on a compassionate basis, despite explicitly high risk, after consensus from the local

FIGURE 2 Illustration of the BASILICA Procedure



A catheter directs an electrified guidewire through the base of the left aortic cusp into a snare in the left ventricular outflow tract **(A)**. After snare retrieval **(B)**, the mid-shaft of the guidewire is electrified to lacerate the leaflet **(C)**. The leaflet splays after transcatheter aortic valve replacement permitting coronary flow **(D)**. Abbreviation as in Figure 1.

multidisciplinary heart teams. The institutional ethics review boards of all participating institutions approved this retrospective report.

The local heart teams determined coronary obstruction risk based on manufacturer-described geometry of the specific implanted bioprosthetic valve; and computed tomography (CT) and angiographic measurements of the coronary ostia heights, sinus of Valsalva width, presence and type of bioprosthetic valve, and virtual transcatheter heart valve to coronary distance (Figure 1) (5).

BASILICA procedure. The procedure was planned using electrocardiogram-gated contrast-enhanced CT, performed under general anesthesia, and guided by fluoroscopy and transesophageal echocardiography. Catheter access was obtained typically via 3 femoral arterial (2 typically ipsilateral for BASILICA, and 1 for TAVR) and at least 1 venous (for temporary transvenous pacing) introducer sheaths. Heparin anticoagulation achieved an activated clotting time >300 s.

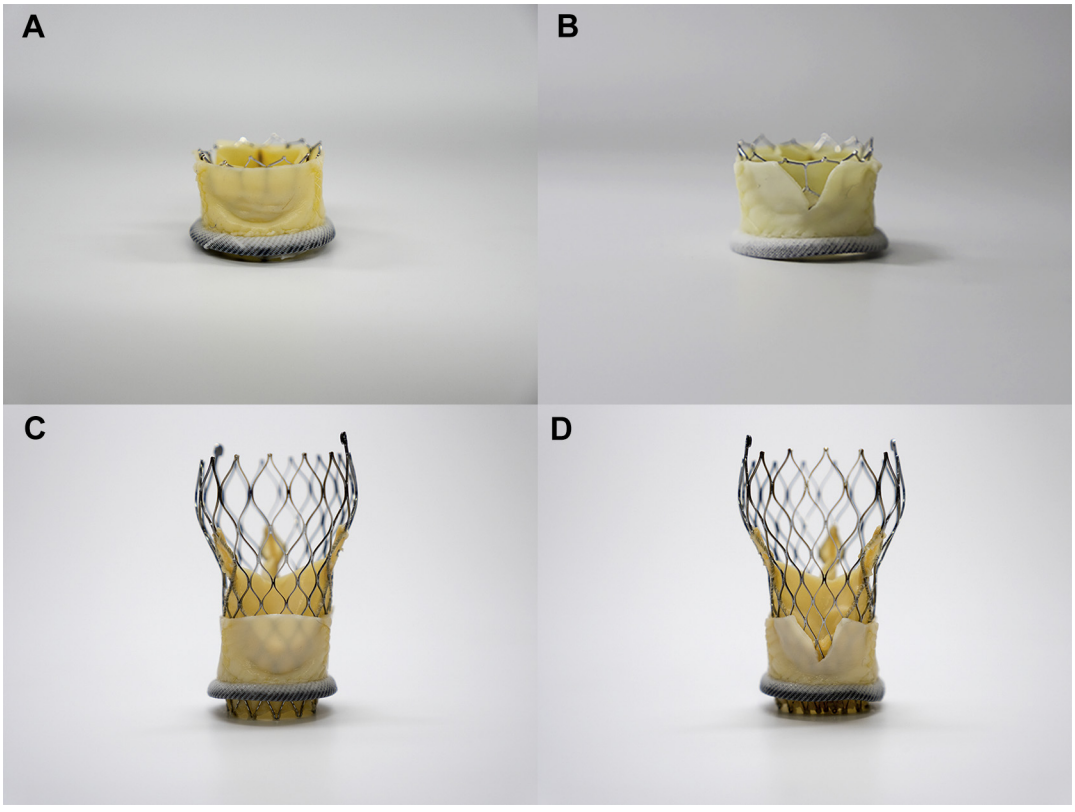
A pair of coaxial catheters (typically a 5-F mammary diagnostic catheter inside a 6-F extra backup shape-guiding catheter) was positioned in the targeted aortic leaflet scallop to direct a guidewire across it, near the scallop hinge point, by echocardiographic and angiographic guidance. These aimed at a snare positioned immediately below the leaflet using a separate retrograde catheter (Figure 2, Online Video 1).

To traverse the aortic leaflet scallop, a 0.014-inch guidewire (Astato XS 20, Asahi-Intecc, Santa Ana, California) sheathed in an insulated polymer jacket (Piggyback Wire Convertor, Vascular Solutions Teleflex, Minneapolis, Minnesota) was electrified, advanced, and snare-retrieved. The wire was electrified using a short burst of "cutting" radiofrequency energy (~30 W) by clamping to an electrosurgery pencil (Valleylab FX, Covidien Medtronic, Minneapolis, Minnesota).

After externalization of the free guidewire end, the guidewire straddles across the leaflet scallop between 2 catheters. The scallop was lacerated by applying radiofrequency energy at approximately 70 W while tensioning both free ends of the guidewire. A pigtail catheter was pre-positioned in the left ventricle to allow TAVR to be performed immediately afterward.

TAVR was performed using established techniques. Coronary artery stent systems were positioned prophylactically at the discretion of the operator. Cracking of a failed bioprosthetic heart valve frame, using a high-pressure balloon (11), was performed at operator discretion to achieve an optimum hemodynamic result. Coronary artery patency was assessed using angiography and post-TAVR CT. Antiplatelet and anticoagulation therapy were prescribed at operator discretion. Complications were assessed according to the Valve Academic Research Consortium-2 Consensus Document (12).

FIGURE 3 Benchtop Simulation of BASILICA



Two different transcatheter heart valves (23-mm Sapien 3, **A, B**; 26-mm Evolut Pro, **C, D**) implanted in 25-mm Mitroflow before **(A, C)** and after **(B, D)** the leaflet is cut with a scalpel.

print & web 4C/FPO

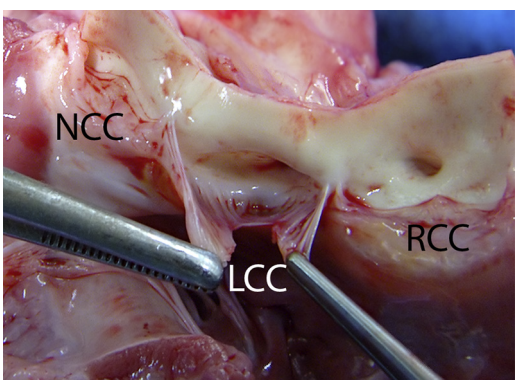
STATISTICAL ANALYSIS. In this small clinical series, we express continuous variables as median and interquartile range. We express categorical variables as counts and percentages. We made no statistical comparisons because of the small sample size.

RESULTS

IN VITRO. A guidewire (Astato XS 20, Asahi) perforated a bioprosthetic bovine pericardial valve leaflet (Trifecta, Abbott St. Jude Medical) using a <1-s burst of radiofrequency energy at 20 W in a saline bath. Laceration with a continuous nonionic (5% dextrose) flush through 2 guiding catheters required 5 s (half leaflet) and 18 s (full leaflet) of radiofrequency energy at 20 W. Laceration using mechanical force without electrification was not possible in this valve.

A 20-mm Sapien 3 valve (Edwards Lifesciences) was deployed on the benchtop inside the lacerated Trifecta valve. The laceration mid-way down the

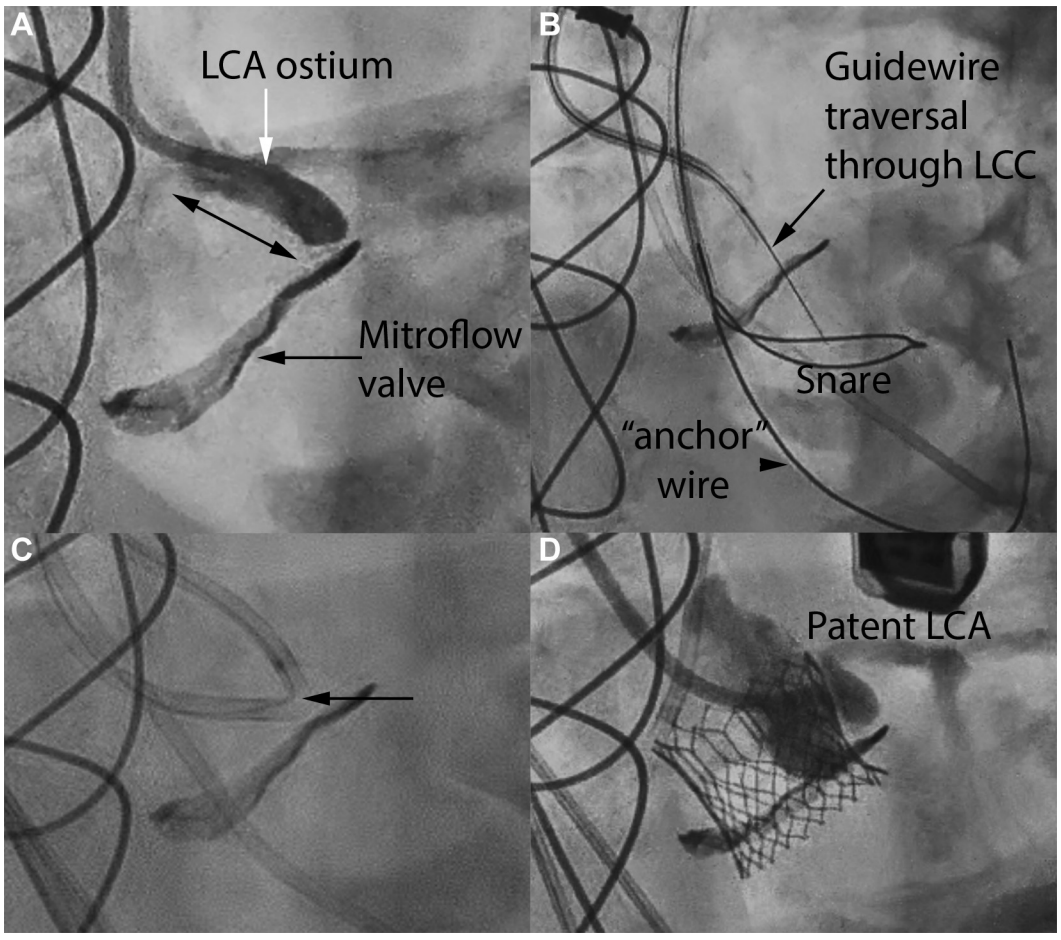
FIGURE 4 Necropsy After BASILICA in an Animal



Animal necropsy viewed from the aorta showing a split left coronary cusp in line with the left coronary artery ostium. LCC = left coronary cusp; NCC = noncoronary cusp; RCC = right coronary cusp.

print & web 4C/FPO

FIGURE 5 BASILICA for Transcatheter Aortic Valve Replacement With Sapien 3 in Failed Mitroflow Valve



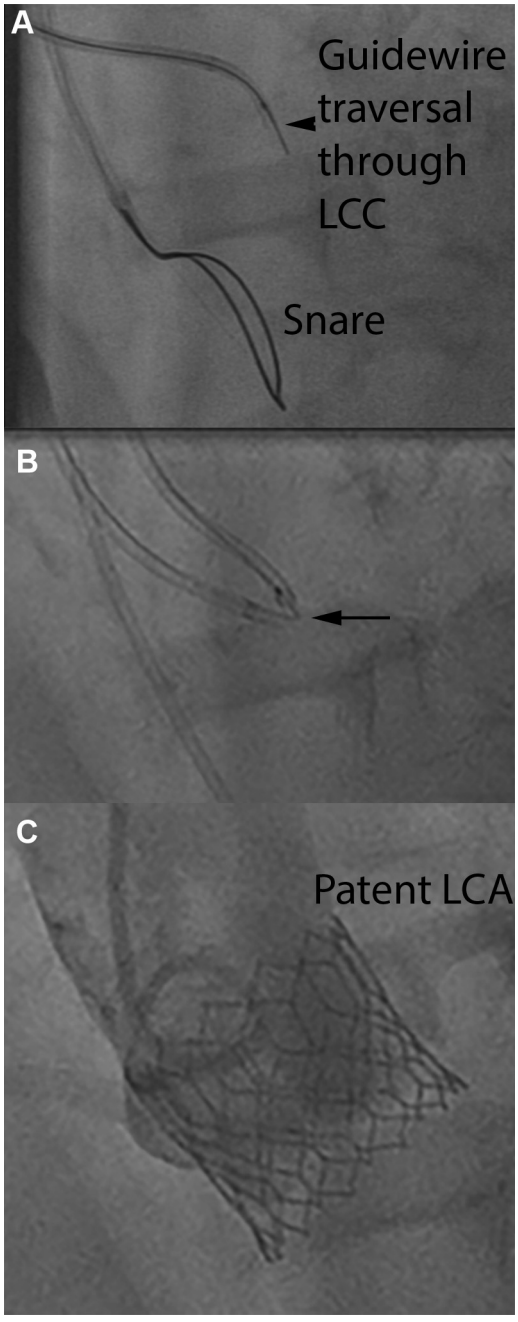
(A) Left coronary injection demonstrates a high risk of left coronary obstruction from the Mitroflow leaflet **(double headed arrow)**. **(B)** Coaxial catheters direct an electrified guidewire through the left coronary leaflet of the Mitroflow valve into the left ventricular outflow tract snare. **(C)** Laceration with radiofrequency concentrated at the kinked mid-shaft of the Astato guidewire **(arrow)**. **(D)** Left cusp injection with flow through split leaflet and patent left coronary artery that would otherwise have been obstructed. Abbreviations as in Figures 1 and 4.

bioprosthetic scallop did not propagate, nor did it result in satisfactory parting of the leaflet. The full-length laceration did not propagate further and resulted in satisfactory parting of the leaflet. The intact leaflet completely draped the Sapien 3 stent cells. The results with the cut Mitroflow valve were similar (Figure 3). Flaring of the bioprosthetic stent posts increased splaying of the split leaflet.

ANIMALS. Five consecutive pigs (38 to 47 kg) underwent attempted BASILICA, 3 on the left coronary cusp and 2 on both left and right coronary cusps (Online Table S1). The procedure time reduced with further experience, despite the increased complexity of double BASILICA. BASILICA resulted in severe aortic regurgitation with a reduction in diastolic blood pressure in all pigs. Two pigs required euthanasia before 1 h was complete because of poor hemodynamics, the first after inadvertent mitral chordal laceration, and the other following double BASILICA.

Guidewire traversal required <1 s of radiofrequency energy at 20 to 30 W for all 5 animals. Guidewire laceration required 2 to 3 s of radiofrequency energy at 30 W and <1 s at 70 W. Minimal subjective mechanical force was required for both traversal and laceration. Laceration was central and extended from base to tip in all animals (mean laceration length was 12 mm and mean cusp length 14 mm for the left, and 12 mm and 12.5 mm, respectively, for the right) (Figure 4).

FIGURE 6 BASILICA and Transcatheter Aortic Valve Replacement With Sapien 3 for Native Aortic Stenosis



(A) An electrified guidewire traverses native left coronary cusp leaflet into the left ventricular outflow tract snare. **(B)** Leaflet laceration through exposed kinked guidewire shaft **(arrow)**. **(C)** Aortic root angiography showing coronary flow in a low-lying coronary artery that may have been obstructed without BASILICA. Abbreviations as in Figures 1 and 4.

Major complications occurred in the first attempted animal BASILICA for left and right coronary cusps, respectively. These included mitral chord entrapment and laceration resulting in severe mitral regurgitation; misdirected wire traversal into the left atrium or interventricular septum, the latter causing ventricular fibrillation requiring defibrillation; and partial annular laceration without pericardial effusion from annulus rather than leaflet traversal. Thereafter we refined the BASILICA technique (assiduous positioning of the traversal wire and of the snare catheter in the distal left ventricular outflow tract) and observed no important complications. There was no macroscopic evidence of collateral thermal damage in benchtop or in vivo necropsy specimens.

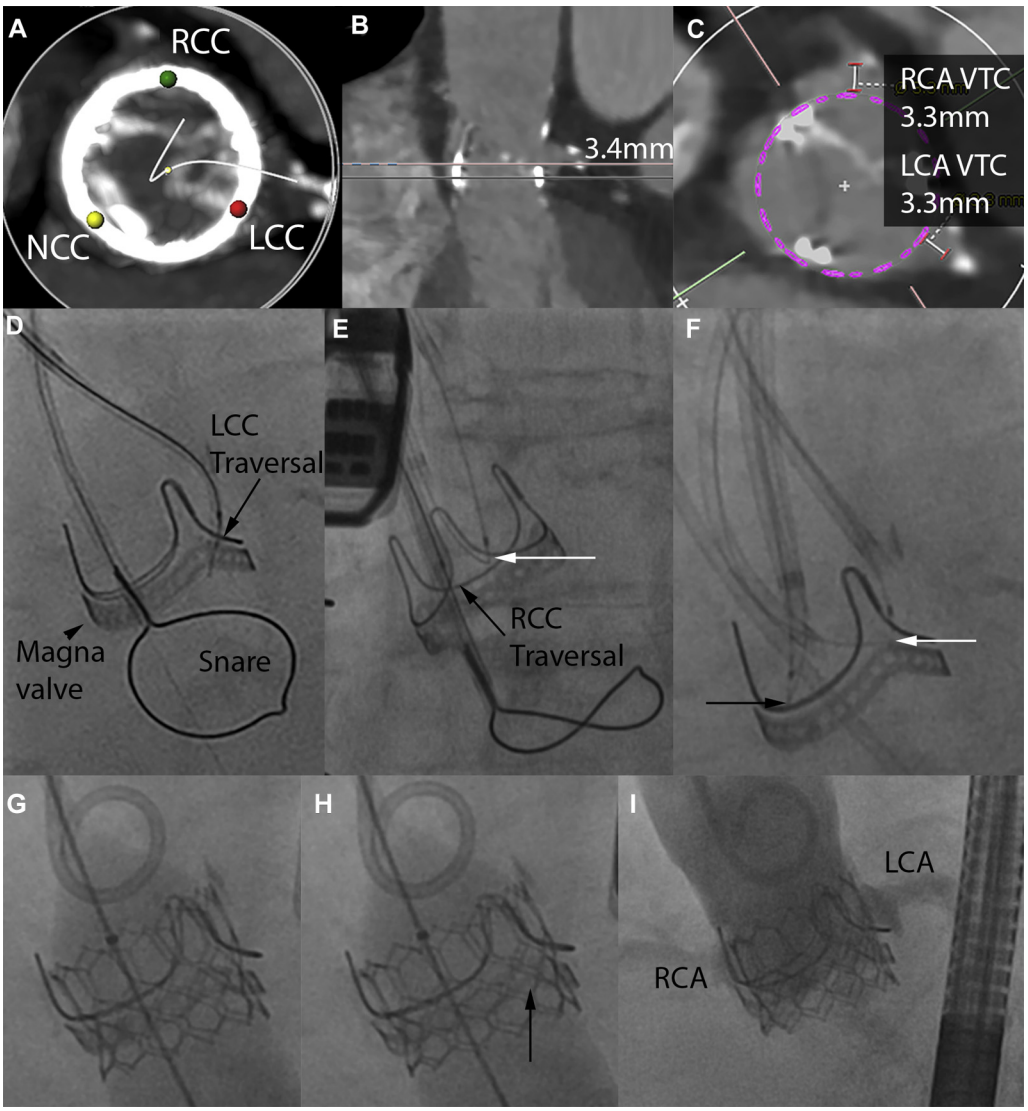
CLINICAL. Seven patients underwent TAVR with BASILICA (Figures 5 to 9). There were a range of diseased aortic valve substrates: 1 had a porcine aortic stent-less bioprosthetic valve, 1 had a stent-less bovine pericardial valve, 4 had stented bovine pericardial valves, and 1 had native aortic valve stenosis. One of the 7 required laceration of 2 aortic leaflet scallops and the rest of only the left.

Table 1 shows their clinical characteristics. All were believed to be unsuitable for surgery by the multidisciplinary heart teams. Five had prior coronary artery bypass grafts that were believed not to protect threatened vessels. Six had failed bioprosthetic aortic valves and 1 had native aortic stenosis. All were believed to be at high risk of left coronary obstruction with median coronary height of 6.8 mm, left sinus of Valsalva width of 24.3 mm, and virtual transcatheter valve to coronary distance of 2.8 mm (Online Figure 2). One patient also had a threatened right coronary artery (Online Table S2).

Table 2 details the procedure. All attempted leaflets were successfully traversed and lacerated. The laceration was central and along most of the leaflet length as depicted on transesophageal echocardiography (Figure 8B). All patients had severe aortic regurgitation after laceration. Heart rate and systolic blood pressures were unchanged in all cases, and no patient required pharmacologic or mechanical hemodynamic support in the 8 to 30 min between laceration and valve deployment, nor afterward.

No patient had coronary obstruction evident on coronary and aortic root angiography, nor echocardiographic regional wall motion assessment. One of the pre-positioned stents was entrapped by the transcatheter heart valve and so was deployed in the left main coronary artery in the absence of coronary obstruction, otherwise all others were removed from

FIGURE 7 Double BASILICA and Transcatheter Aortic Valve Replacement With Sapien 3 for Failed Magna Valve

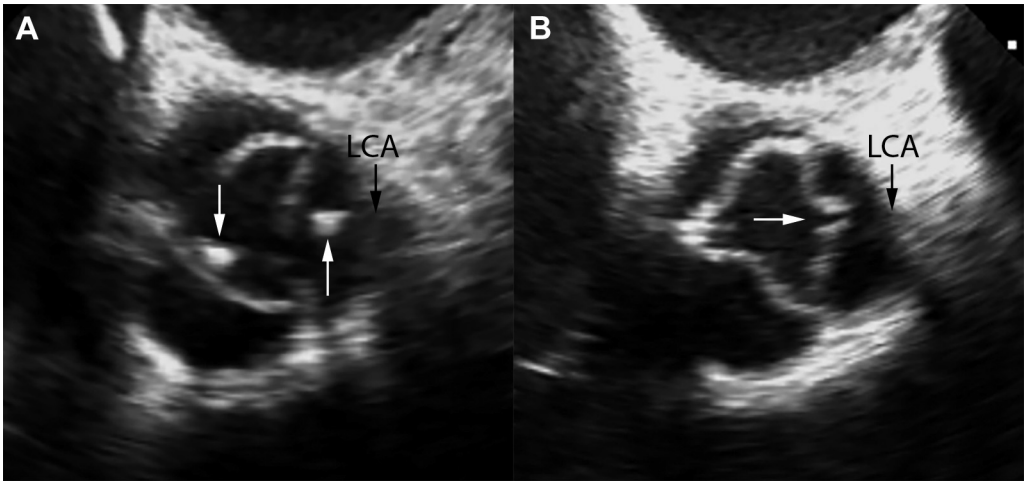


(A) Heavily calcified leaflets, especially the left coronary cusp. **(B)** Left coronary height is low at 3.4 mm. **(C)** Both left and right VTC are low at 3.3 mm. **(D)** An electrified guidewire traverses the left coronary leaflet of a Magna valve. **(E)** The left coronary leaflet guidewire has been externalized to form a loop and a second electrified guidewire traverses the right coronary leaflet. **(F)** Loops formed around both left **(white arrow)** and right **(black arrow)** coronary cusps, ready for sequential laceration. **(G)** After transcatheter aortic valve replacement a high-pressure balloon is inflated to crack the bioprosthetic valve to improve hemodynamics. **(H)** The bioprosthetic valve has been fractured at the site of the **black arrow**. **(I)** Angiography demonstrates good flow to both coronary arteries that may otherwise have been completely obstructed. VTC = virtual transcatheter valve to coronary distance; other abbreviations as in Figures 1 and 4.

the body undeployed. Procedural hemodynamics confirmed satisfactory valve gradients and no patient with more than mild paravalvular leak. Three patients had follow-up CT scans confirming good flow in the coronary arteries.

Clinical outcomes and standardized TAVR endpoints are shown in **Table 3 and** Online Table S3 (12). One patient had transient sinus bradycardia requiring temporary transvenous pacing. There were no other complications. Four patients underwent precautionary intensive care unit observation overnight; the remainder were transferred directly to ward beds. The median length of stay was 4 days. All patients survived beyond 30 days.

FIGURE 8 Transesophageal Echocardiography During BASILICA and Transcatheter Aortic Valve Replacement With Sapien 3 for Failed Sorin Solo Freedom Valve



(A) Echocardiography view showing the traversal catheter is aligned at the base of the left coronary cusp **(upward white arrow)**. A snare catheter is positioned across the valve **(downward white arrow)**. **(B)** The laceration in the left coronary cusp is seen **(white arrow)**, adjacent to the left coronary artery ostium. Abbreviation as in Figure 1.

DISCUSSION

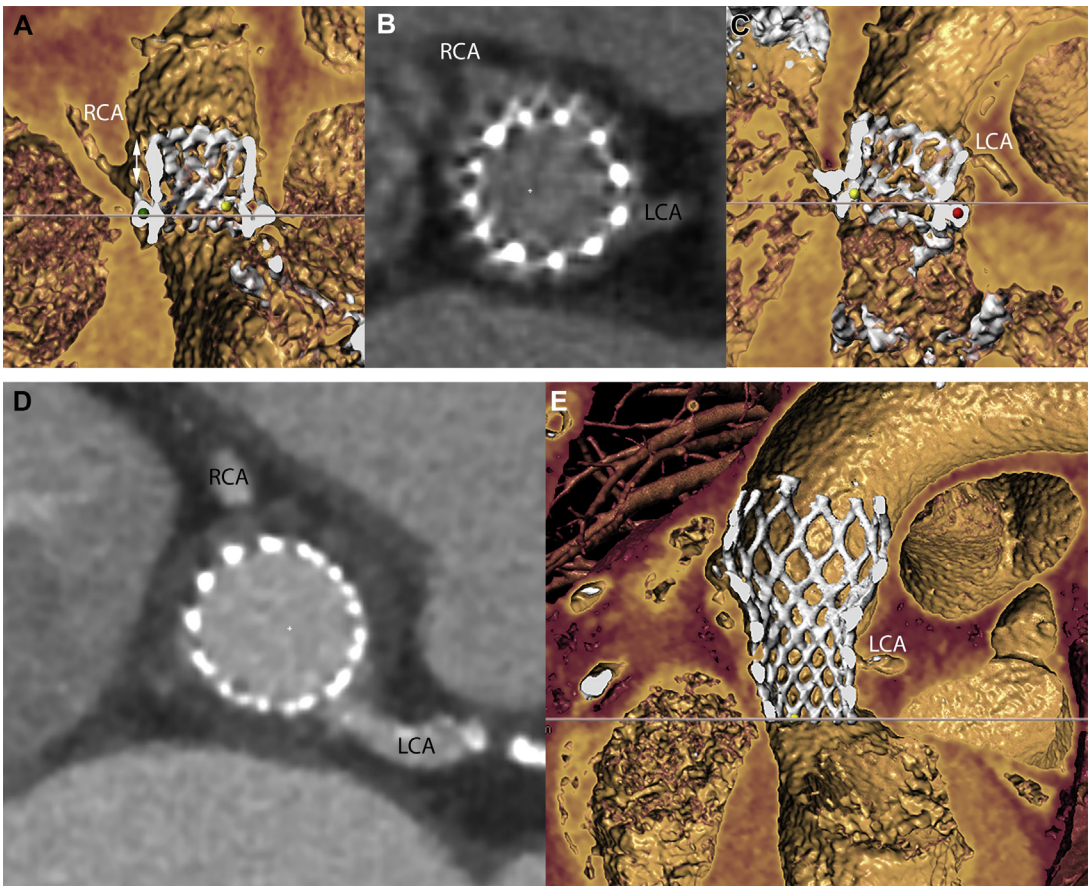
We describe a new technique that allows transcatheter heart valve treatment in patients otherwise ineligible for any therapy because of a high risk of valve leaflet-induced coronary artery obstruction. We have demonstrated through benchtop testing, animal experiments, and experience from 7 patients that: 1) BASILICA seems technically feasible in all valve types and valve conditions, including single and double leaflet laceration, porcine and bovine pericardial bioprostheses, stented and stent-less bioprostheses, and in 1 case of native aortic leaflet disease; 2) there was no hemodynamic collapse after laceration regardless of baseline aortic regurgitation (n = 5) or aortic stenosis (n = 2); and 3) there was uniform success in preserving coronary blood flow.

The current strategy of ad hoc percutaneous intervention or up-front coronary protection using a pre-positioned wire, with or without balloon or stent, is problematic. Coronary obstruction may be delayed despite normal flow at the end of the TAVR procedure (13). There are few data to support the longevity of a "chimney" coronary stent extending beyond the coronary ostium with a valve leaflet draped across it. The ostial left main stent is at risk of fatal restenosis and thrombosis (14). Re-engaging a coronary artery is challenging after TAVR, and becomes almost impossible with an ostial "chimney" stent (14,15). As seen in Patient #7, the stent can be entrapped and then requires unnecessary deployment. Applying caution in this initial human experience, the threatened coronaries were still protected by wiring and placing a stent mid-vessel after BASILICA. Although the 1 entrapped stent confirmed the preprocedural concern for coronary obstruction and need for intervention to allow safe TAVR, the inability to remove the stent necessitated deployment despite otherwise successful BASILICA. It is difficult to know at this early stage whether pre-positioning a stent after successful BASILICA is mandated or whether the harm outweighs the benefits. As experience with BASILICA and its success increases, we would predict a transition to no prophylactic coronary stent protection.

One application of BASILICA not yet performed but worth considering is to treat failed TAVR devices, which are likely to become more common as TAVR is applied to lower-risk patients who are expected to live longer. The risk of coronary obstruction in patients with previous TAVR may be elevated in patients with high implantation and supra-annular TAVR devices engineered to have longer leaflets (such as Medtronic Corevalve). Several transcatheter heart valves are implanted with the top of the valve at the sinotubular junction where coronary filling is dependent on diastolic valve-leaflet closure. We speculate that BASILICA may be helpful in this setting.

In this small series, we observed that split leaflets continued to appose during diastole, and caused incremental but not catastrophic aortic regurgitation.

FIGURE 9 Computed Tomography Images Following BASILICA and Transcatheter Aortic Valve Replacement With Sapien 3 and Evolut Pro



(Top) Sapien 3; **(Bottom)** Corevalve Evolut Pro. **(A and B)** A narrow neosinus **(double-headed arrow)** maintains flow to the right coronary artery but the left sinus **(B and C)** is completely effaced. **(D and E)** The left coronary artery was at risk of occlusion but there is adequate filling following BASILICA. Abbreviations as in Figure 1.

Patients did not require pharmacologic or mechanical support during the short period before TAVR.

STUDY LIMITATIONS. Our experience remains limited, and confined to the specific bioprosthetic devices and single native valve described. The leaflets may splay variably depending on the type of bioprosthetic and transcatheter heart valve combination used, as may flow through the open cells of the transcatheter heart valve. Despite successful BASILICA, TAVR device commissures may limit flow to the coronary arteries by accidentally unfavorable rotational orientation.

We observed no hemodynamic deterioration between BASILICA laceration and TAVR in this small series. Our patients had relatively preserved left ventricular systolic function (Table 1). Although 2 of 7 had primarily stenotic lesions and 3 of 7 primarily mixed stenotic and regurgitant, the applicability to patients with more profound ventricular dysfunction requires further investigation. Likewise, despite operator precautions, BASILICA may injure mitral valvular structures.

The role of BASILICA combined with intentional balloon fracture to expand the valve frame (11), remains uncertain. Double-leaflet BASILICA poses extra challenges particularly with vascular access. Heavily calcified leaflets are probably unsuited to BASILICA, as evidenced by the prolonged procedure time because of difficulty traversing in Patient #4.

Although there were no evident strokes in this initial series, lacerating a heavily calcified leaflet may generate embolic debris that cause stroke and in this setting, judicious use of cerebral embolic protection

TABLE 1 Clinical Characteristics

		Patient #						
	All	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Age, yrs	74 (70–76)	87	74	74	67	78	68	71
Female, %	86	1	1	1	0	1	1	1
STS PROM aortic replacement, %	12.7 (6.3–14.1)	13.4	4.6	19.5	2.0	12.7	8.0	14.7
Frailty, %	67	1	1	1	0	1	0	NA
Coronary artery disease, binary, %	71	1	1	0	1	0	1	1
Prior CABG, %	71	1	1	0	1	0	1	1
Prior stroke, %	14	0	0	0	0	0	0	1
Atrial fibrillation, %	57	1	0	1	0	1	0	1
eGFR, ml/min/1.73 m^2	53 (41–61)	60	31	12	62	51	65	53
NT-proBNP baseline, pg/ml	517 (289–709)	701	332	712	2,145	262	275	NA
NYHA CHF functional class	3 (3–4)	4	3	4	3	3	3	3
Severe pulmonary disease, %	29	0	0	0	0	1	1	0
LV ejection fraction, %	0.58 (0.45–0.60)	65	58	45	45	60	60	40
RV dysfunction, %	14	0	0	0	0	1	0	0
Porcelain aorta, %	14	0	0	0	0	0	1	0
TAVR setting (native or valve-in-valve)	Valve-in-valve, 86%	Valve-in-valve	Valve-in-valve	Valve-in-valve	Valve-in-valve	Native	Valve-in-valve	Valve-in-valve
Bioprosthetic valve nominal diameter, mm	21 (21–23)	19	21	21	23	NA	21	23
Bioprosthetic valve type		Trifecta	Toronto SPV	Mitroflow	Mitroflow	NA	Magna	Sorin Solo Freedom SMT
Bioprosthetic implant age, yrs	5 (3–11)	6	14	4	3	NA	13	2
Primary lesion	Regurgitation, 3; stenosis, 2; mixed, 2	Regurgitation	Regurgitation	Mixed	Mixed	Stenosis	Stenosis	Regurgitation
Suitability for cardiac surgery		Inoperable because of advanced age, marked frailty, and prospect of repeat cardiac surgery	Inoperable because of grafts threatened by repeat surgery, marked frailty, and renal dysfunction	Inoperable because of functional class IV symptoms, prospect of combined mitral and aortic surgery after prior AVR, worsening kidney disease with creatinine >300 μmol/L, recent cardiopulmonary arrest	Prolonged recovery after prior MVR/AVR/CABG believed by surgical team better treated by catheter; patient declined repeat surgery	Inoperable because of very poor functional status and ongoing radiation therapy for thoracic malignancy Long aortic leaflets obstruct coronaries during test balloon inflation and aortography	Prohibitively high operative risk with porcelain aorta, mitral annular calcification, prospect of ascending and root aorta repair along with AVR and MVR	Inoperable because of NYHA functional class IV symptoms, radiotherapy for malignancy, moderate left ventricular dysfunction, prior stroke, prior AVR + MVR + atrial ablation + LAA ligation

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CHF = congestive heart failure; eGFR = estimated glomerular filtration rate; LAA = left atrial appendage; LV = left ventricle; MVR = mitral valve replacement; NA = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; RV = right ventricle; STS PROM = Society of Thoracic Surgery predicted risk of mortality; TAVR = transcatheter aortic valve replacement.

strategies, and brain magnetic resonance imaging, may be appropriate. Protracted radiofrequency ablation is widely used in the left atrium and left ventricle with a low risk of coronary and cerebral thromboembolism. By comparison we use shorter bursts of vaporizing high duty-cycle "cutting mode" electrosurgery, also with full anticoagulation. Human cadaver experiments may shed light on the potential for embolization during bioprosthetic and native aortic valve manipulation.

Coronary flow was assessed angiographically by assessing echocardiographic left ventricular wall motion but a pressure wire or other intracoronary imaging was not used.

TABLE 2 Procedure Characteristics and Hemodynamics

	All	Patient # 1	2	3	4	5	6	7
Transcatheter heart valve	Sapien 3, 6; Evolut Pro, 1	Sapien 3	Evolut Pro	Sapien 3	Sapien 3	Sapien 3	Sapien 3	Sapien 3
Transcatheter heart valve size, mm	23 (22–23)	20	23	23	23	26	20	23
Transcatheter heart valve post-dilatation	14%	0	0	0	0	0	1	0
Invasive hemodynamics baseline								
Aortic regurgitation severity (0 = none, 1 = trace, 2 = mild, 3 = moderate, 4 = severe)	4 (3–4)	4	4	4	3	2	2	4
Aortic valve peak-to-peak gradient, mm Hg	43 (14–64)	12	8	43	72	56	135	15
HR	75 (71–80)	84	72	67	77	69	83	75
SBP	126 (96–148)	151	126	93	95	166	145	97
DBP	44 (39–50)	32	47	35	53	73	42	44
LVEDP	31 (22–34)	23	21	35	36	31	32	16
Invasive hemodynamics completion								
Aortic regurgitation severity (0 = none, 1 = trace, 2 = mild, 3 = moderate, 4 = severe)	0 (0–1)	0	0	1	0	0	1	2
Aortic valve peak-to-peak gradient, mm Hg	1 (1–7)	1	10	1	12	0	0	3
HR	81 (79–84)	80	82	85	79	62	87	40 (sinus brady, paced at 80)
SBP	175 (151–179)	177	151	175	120	181	197	150
DBP	68 (64–72)	64	63	79	68	72	57	71
LVEDP	27 (26–30)	34	28	26	26	27	18	31
Echocardiography, baseline								
Aortic regurgitation severity (0 = none, 1 = trace, 2 = mild, 3 = moderate, 4 = severe)	4 (3–4)	4	4	3.5	4	3	2	4
Aortic valve peak velocity, m/s	3.4 (3.2–4.6)	3.3	3.1	5.6	4.1	3.4	5.0	1.6
Aortic valve mean gradient, mm Hg	24 (22–48)	24.0	22.0	67.0	22.6	45.4	51.0	4.8
Indexed effective orifice area, m^2/m^2	0.62 (0.49–1.00)	1.0	1.6	0.48	0.31	0.49	0.62	1.0
LVEF, %	58 (45–60)	65	58	45	45	60	60	35
Echocardiography, pre-discharge								
Aortic regurgitation severity (0 = none, 1 = trace, 2 = mild, 3 = moderate, 4 = severe)	0 (0–0)	0	0	1	0	0	0	0
Aortic valve peak velocity, m/s	2.9 (2.7–3.2)	3.3	2.7	3.6	2.6	3.1	2.9	1.6
Aortic valve mean gradient, mm Hg	18 (17–21)	17.0	16.0	28.2	17.6	21.0	20.0	4.8
LVEF, %	61 (56–65)	71	64	61	51	60	65	35

DBP = diastolic blood pressure; HR = heart rate; LVEDP = left ventricular end diastolic pressure; LVEF = left ventricular ejection fraction; SBP = systolic blood pressure.

TABLE 3 Clinical Outcomes

	All	Patient # 1	2	3	4	5	6	7
Length of stay after TAVR, days	4 (4–5)	4	4	6	1	5	5	3
ICU stay, days	1 (0–2)	2	2	0	0	1	1	0
Survival to hospital discharge	100%	1	1	1	1	1	1	1
Survival 30 days	100%	1	1	1	1	1	1	1
Survival ascertainment, days	116 (109–153)	154	154	151	116	109	109	95
NYHA functional class at latest follow-up	2.0 (1.5–2.0)	2	2	1	2	1	2	2

Values are median (interquartile range) or %. ICU = intensive care unit; other abbreviations as in Table 1.

Finally, there was no comparator and so coronary artery obstruction was not certain but predicted using prevailing standards, which have their limitations. The potential risk and benefit of BASILICA should be weighed before applying it to any patient, including the risk of embolization and, in patients with severe ventricular dysfunction, the risk of acute severe aortic regurgitation.

We believe technical descriptions are no substitute for live observation, and we recommend BASILICA only be undertaken with appropriate training.

CONCLUSIONS

Bioprosthetic and native aortic leaflet laceration seems feasible and may reduce the risk of coronary artery obstruction following TAVR in patients at high risk. No patient had a drop in blood pressure following BASILICA. The technique offers a promising alternative to "chimney" stenting to provide durable prevention against coronary obstruction from TAVR. BASILICA needs careful prospective investigation, which begins with a Food and Drug Administration-approved trial in early 2018.

ACKNOWLEDGMENTS The authors thank Alan Hoofring for medical illustrations; Katherine Lucas for animal care; Daniel Herzka, Merdim Sonmez, and Dmitri Levin for technical assistance; Norihiko Kamioka, Lauren Wheeler, and Patricia Keegan for data assistance; and Elena Grant and James McCabe for thoughtful advice. They thank Richard Olson of Abbott for supplying a sample Trifecta valve in anticipation of helping the first patient.

ADDRESS FOR CORRESPONDENCE: Dr. Robert J. Lederman, Cardiovascular Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room 2c713, MSC 1538, Bethesda, Maryland 20892-1538. E-mail: lederman@nih.gov.

PERSPECTIVES

WHAT IS KNOWN? Coronary obstruction following TAVR carries up to 50% mortality, and CT-predicted coronary obstruction may deprive patients of TAVR as a therapeutic option. Current methods of pre-emptive or bail-out coronary stenting are suboptimal.

WHAT IS NEW? We describe a catheter technique (BASILICA) to lacerate aortic leaflets that otherwise threaten to obstruct a coronary artery during TAVR. After TAVR, which is performed immediately after BASILICA, blood is able to flow across the lacerated aortic leaflets into the coronary arteries.

WHAT IS NEXT? BASILICA may have value in the future as more patients have bioprosthetic surgical and even transcatheter aortic valves likely to degenerate. BASILICA warrants further prospective evaluation in a larger number of patients.

REFERENCES

1. 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.

2. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017;376:1321–31.

3. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA 2014;312:162–70.

4. Webb JG, Mack MJ, White JM, et al. Transcatheter aortic valve implantation within degenerated aortic surgical bioprostheses: PARTNER 2 Valve-in-Valve Registry. J Am Coll Cardiol 2017;69:2253–62.

5. Ribeiro HB, Rodés-Cabau J, Blanke P, et al. Incidence, predictors and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID Registry. Eur Heart J 2018;39:687–95.

6. Ribeiro HB, Webb JG, Makkar RR, et al. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. J Am Coll Cardiol 2013;62:1552–62.

7. Yamamoto M, Shimura T, Kano S, et al. Impact of preparatory coronary protection in patients at high anatomical risk of acute coronary obstruction during transcatheter aortic valve implantation. Int J Cardiol 2016;217:58–63.

8. Abramowitz Y, Chakravarty T, Jilaihawi H, et al. Clinical impact of coronary protection during transcatheter aortic valve implantation: first reported series of patients. EuroIntervention 2015;11:572–81.

9. Khan JM, Rogers T, Schenke WH, et al. Intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve replacement: pre-clinical findings. J Am Coll Cardiol Intv 2016;9:1835–43.

10. Babaliaros VC, Greenbaum AB, Khan JM, et al. Intentional percutaneous laceration of the anterior mitral leaflet to prevent outflow obstruction during transcatheter mitral valve replacement: first-in-human experience. J Am Coll Cardiol Intv 2017;10:798–809.

11. Chhatriwalla AK, Allen KB, Saxon JT, et al. Bioprosthetic valve fracture improves the hemodynamic results of valve-in-valve transcatheter aortic valve replacement. Circ Cardiovasc Interv 2017;10.

12. Kappetein AP, Head SJ, Genereux P, et al. 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.

13. Dvir D, Webb J, Brecker S, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation 2012;126:2335–44.

14. Dvir D. Transcatheter aortic valve-in-valve implantations: lessons from bench to bedside [oral presentation]. Presented at: Transcatheter Valve Therapies; June 14 to 17, 2017; Chicago, IL.

15. Valsecchi O, Vassileva A. The chimney technique during valve in valve TAVR in stentless freestyle [oral presentation]. Presented at: Joint Interventional Meeting Milan (JIM); February 9 to 11, 2017; Milan, Italy.

KEY WORDS bioprosthetic heart valve failure, coronary artery obstruction, structural heart disease, transcatheter aortic valve replacement, transcatheter electrosurgery

APPENDIX For supplemental tables, figures, and a video, please see the online version of this paper.

Supplement

Transcatheter laceration of aortic leaflets to prevent coronary obstruction during transcatheter aortic valve implantation: concept to first-in-human

Methods

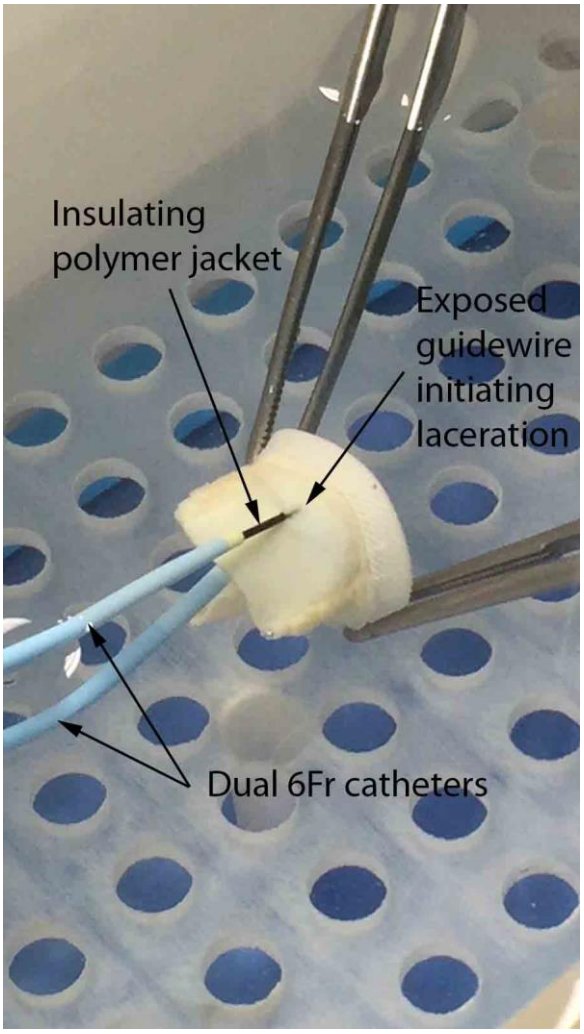
Details about BASILICA Technique

Radiofrequency energy was confined to the guidewire-leaflet contact point by four maneuvers. First, the guidewire was kinked in mid-shaft, to assure proper positioning and close tissue contact. Second, the guidewire was focally denuded at the inner curvature of the kink, by the operator at the tableside, to concentrate charge at the target. Third, the insulating polymer jacket was positioned close to the kink. Fourth, during radiofrequency energy application, non-ionic flush (5% dextrose) displaced blood, concentrated current at the lacerating surface, and suppressed guidewire carbonization and blood coagulation.

Findings

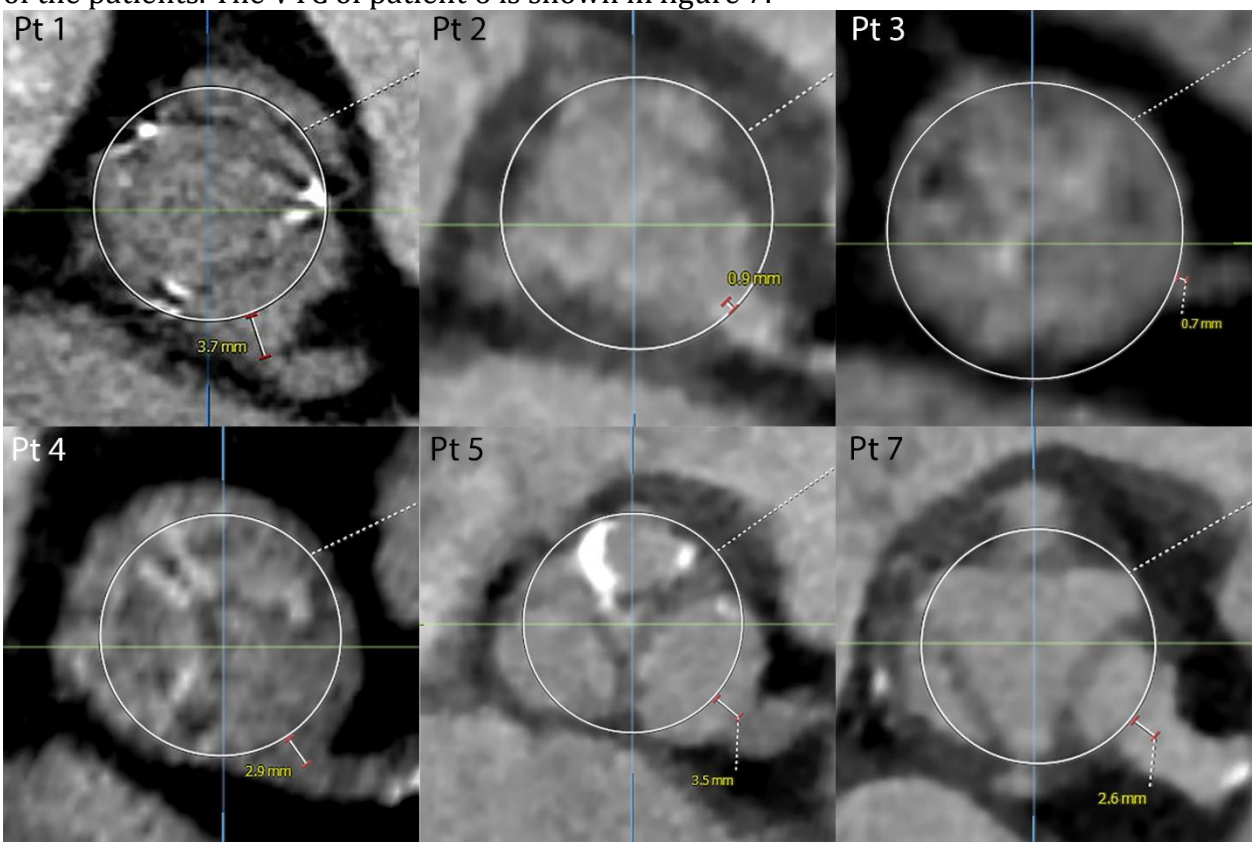
Supplement Figure 3: In vitro laceration of a bovine bioprosthetic heart valve

The shaft of an Astato XS20 guidewire, sheathed in a polymer wire-convertor and guiding catheter, was positioned against a bovine bioprosthetic heart valve (Trifecta, Abbott St Jude Medical) and perforated the bioprosthetic leaflet using a <1s burst of radiofrequency energy at 20W. Next, we tested laceration, during continuous 5% dextrose flush through two guiding catheters. Laceration at 20W required 5s to traverse a half-leaflet (shown in the figure below) and 18s to traverse a full leaflet. Mechanical laceration without electrification was not possible in this valve.


Insulating
polymer jacket
Exposed
guidewire
initiating
laceration
Dual 6Fr catheters

Supplement Figure 4: VTC distance

The figure depicts the virtual transcatheter valve to coronary (VTC) distance in six of the patients. The VTC of patient 6 is shown in figure 7.



Supplement Table 4: Animal Findings

Basilica pre-clinical	PIG1	PIG2	PIG3	PIG4	PIG5
Weight (kg)	41	40	47	38	49
LCC attempted	Yes	Yes	Yes	Yes	Yes
RCC attempted	No	No	No	Yes	Yes
Procedure time (mins)	205	35	11	70	58
Survival time (mins)	5	>60	>60	>60	10
Complications					
Left false crossing	X (4)	X (1)			
Right false crossing				X (2)	
Ventricular fibrillation				X	
Mitral chord rupture	X				
Annulus laceration				X	
Cusp hematoma	X	X			
Hemodynamics					
Systolic BP pre	61	74	78	70	74
Diastolic BP pre	35	48	44	50	45
Heart rate pre	63	71	82	88	59
Systolic BP post	30	63	75	80	57
Diastolic BP post	17	29	29	30	21
Heart rate post	41	68	104	107	65
Necropsy measurements					
LCC length (mm)	14	15	15	12	16
LCC tear (mm)	10	13	11	12	10
RCC length (mm)				10	15
RCC tear (mm)				10	14

LCC= left coronary cusp; RCC = right coronary cusp; BP = blood pressure

Supplement Table 5: Additional clinical and CT findings and procedure details

Patient number	**ALL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Height, cm	160 (151-165)	147	150	152	178	165	165	160
Weight, kg	79.6 (73.3-92.3)	43	69.5	77	97.5	112	79.6	87
L-VTC on CT for selected valve, mm	2.9 (1.7-3.6)	3.7	-0.9	0.7	2.9	3.5	3.3	2.6

R-VTC on CT for selected valve, mm	3.5 (3.-3.7)	3.7	-0.9	3.6	NA	2.9	3.3	4.4
L-coronary height on CT	5.8 (4.5-7.9)	6.9	5.8	5.5	8.9	9.3	3.4	2
R-coronary height on CT	13.2 (9.5-13.4)	13.2	7	11.9	15	13.3	6.7	13.5
L-sinus width on CT	24.3 (21.1-27.8)	20.8	21.3	20.7	29.3	30.8	24.3	26.2
R-sinus width on CT	24.2 (23.6-26.8)	23.5	21.2	24.2	27.1	26.4	23.7	29
CT annulus average diameter, mm	19.8 (18.3-21.1)	16.2	18.2	18.4	21.1	23.8	19.8	21
CT annulus area, mm^2	307.6 (258.3-367.4)	206.3	247.4	269.2	354.8	453.7	307.6	380
CT sinus height, average, mm	14.6 (13.2-17.3)	12.5	14.6	13.1	18.6	19.7	13.3	16
CT leaflet calcification (0=None, 1=mild, 2=moderate, 3=severe)	None,3; Mild, 1; Moderate, 2; Severe, 1	0	0	1	2	2	3	0
Procedure Time, min	195 (162-213)	195	145	173	264	201	225	150
Time to traverse leaflet (both if applicable), min	33 (28-82)	43	23	32	140	33	121	23
Time from traversal to laceration (both if applicable), min	46 (32-52)	54	46	50	28	59	33	30
Time from laceration to TAVI, min	19 (15-22)	12	8	25	30	19	19	18
Fluoroscopy Time, min	74 (68-91)	82	62	68	114	74	100	68

Fluoroscopy Dose-Area Product (Gy·cm2)	345 (270-435)	398	471	154	327	651	345	213
Contrast volume (mL)	102 (90-170)	37	115	102	225	90	285	90
LCA prophylactic stent or balloon positioned	None, 1; Balloon, 1; Stent, 5	Stent	Stent	Stent	Stent	Balloon	None	Stent
LCA stent deployed	14%	0	0	0	0	0	0	1
RCA prophylactic stent positioned	29%	0	0	1	1	0	0	0
RCA stent deployed	0%	0	0	0	0	0	0	0
Neuroprotection	None, 3; External carotid compression, 4	None	None	External carotid compression	External carotid compression	None	External carotid compression	External carotid compression
Intentional balloon rupture of bioprosthetic frame to increase orifice	Successful 1; Not attempted, 6	Not attempted	Not attempted	Not attempted	Not attempted	NA	Successful	Not attempted
General anaesthesia	100%	1	1	1	1	1	1	1
Transoesophageal echocardiography	100%	1	1	1	1	1	1	1

Supplement Table 6: Clinical complications classified according to VARC-2

Patient number	**ALL**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Mortality	0%	0	0	0	0	0	0	0
Myocardial infarction	0%	0	0	0	0	0	0	0
Stroke or transient ischemic attack	0%	0	0	0	0	0	0	0
Life threatening or major bleeding	0%	0	0	0	0	0	0	0
Acute kidney injury	0%	0	0	0	0	0	0	0
Vascular major complications	0%	0	0	0	0	0	0	0
Conduction disturbances or arrhythmias	0%	0	0	0	0	0	0	Transient sinus bradycardia
Conversion to open surgery	0%	0	0	0	0	0	0	0
Unplanned cardiopulmonary bypass or mechanical hemodynamic support	0%	0	0	0	0	0	0	0
Coronary obstruction	0%	0	0	0	0	0	0	0
Ventricular septal defect	0%	0	0	0	0	0	0	0
Mitral valve apparatus damage or dysfunction	0%	0	0	0	0	0	0	0
Cardiac tamponade	0%	0	0	0	0	0	0	0
Endocarditis	0%	0	0	0	0	0	0	0
Valve thrombosis	0%	0	0	0	0	0	0	0
Valve mal-positioning (including migration and embolization)	0%	0	0	0	0	0	0	0
Additional valve-in-valve deployment	0%	0	0	0	0	0	0	0

VARC-2 = Valve Academic Research Consortium-2 Consensus Document (Kappetein, et al, 2012, reference #13).

The BASILICA Trial Prospective Multicenter Investigation of Intentional Leaflet Laceration to Prevent TAVR Coronary Obstruction

An original research manuscript published in the journal *JACC: Cardiovascular Interventions* in 2019.

Candidate's contribution

I am first author on the enclosed clinical trial manuscript, which I drafted, designed the figures, and consulted the references. I, together with RJL, designed the NHLBI BASILICA trial, prepared the trial protocol and drafted the case report forms. I was the Clinical Lead for the trial and member of the steering committee. I planned and proctored all the cases performed.

JACC: CARDIOVASCULAR INTERVENTIONS
PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN
COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 12, NO. 13, 2019

The BASILICA Trial

Prospective Multicenter Investigation of Intentional Leaflet Laceration to Prevent TAVR Coronary Obstruction

Jaffar M. Khan, BM BCh,[a] Adam B. Greenbaum, MD,[b,c] Vasilis C. Babaliaros, MD,[c] Toby Rogers, BM BCh, PhD,[a,d] Marvin H. Eng, MD,[b] Gaetano Paone, MD,[b] Bradley G. Leshnower, MD,[c] Mark Reisman, MD,[e] Lowell Satler, MD,[d] Ron Waksman, MD,[d] Marcus Y. Chen, MD,[a] Annette M. Stine, RN,[a] Xin Tian, PhD,[a] Danny Dvir, MD,[e] Robert J. Lederman, MD[a]

ABSTRACT

OBJECTIVES The BASILICA (Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction during TAVR) investigational device exemption trial was a prospective, multicenter, single-arm safety and feasibility study.

BACKGROUND Coronary artery obstruction is a rare but devastating complication of transcatheter aortic valve replacement (TAVR). Current stent-based preventative strategies are suboptimal. Bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction during TAVR (BASILICA) is a novel transcatheter technique performed immediately before TAVR to prevent coronary artery obstruction.

METHODS Subjects with severe native or bioprosthetic aortic valve disease at high or extreme risk for surgery, and at high risk of coronary artery obstruction, were included. The primary success endpoint was successful BASILICA and TAVR without coronary obstruction or reintervention. The primary safety endpoint was freedom from major adverse cardiovascular events. Data were independently monitored. Endpoints were independently adjudicated. A core laboratory analyzed computed tomography images.

RESULTS Between February 2018 and July 2018, 30 subjects were enrolled. Primary success was met in 28 (93%) subjects. BASILICA traversal and laceration was successful in 35 of 37 (95%) attempted leaflets. There was 100% freedom from coronary obstruction and reintervention. Primary safety was met in 21 (70%), driven by 6 (20%) major vascular complications related to TAVR but not BASILICA. There was 1 death at 30 days. There was 1 (3%) disabling stroke and 2 (7%) nondisabling strokes. Transient hemodynamic compromise was rare (7%) and resolved promptly with TAVR.

CONCLUSIONS BASILICA was feasible in both native and bioprosthetic valves. Hemodynamic compromise was uncommon. Safety was acceptable and needs confirmation in larger studies. BASILICA appears effective in preventing coronary artery obstruction from TAVR in subjects at high risk. (J Am Coll Cardiol Intv 2019;12:1240–52) Published by Elsevier on behalf of the American College of Cardiology Foundation.

Transcatheter aortic valve replacement (TAVR) is an effective treatment for patients with severe aortic stenosis or failing bioprosthetic valves (1-3). Coronary artery obstruction is a rare but devastating complication of TAVR, with an overall incidence of 0.7% but 30-day mortality of 41% (4). The incidence is higher (2.3%) in bioprosthetic surgical valves (5), and does not account for patients excluded from TAVR for concern of this complication. Coronary obstruction occurs when

From the [a]Cardiovascular Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; [b]Center for Structural Heart Disease, Division of Cardiology, and Division of Cardiac Surgery, Henry Ford Health System, Detroit, Michigan; [c]Structural Heart and Valve Center, Emory University Hospital, Atlanta, Georgia; [d]Medstar Washington Hospital Center, Washington, DC; and the [e]University of Washington, Seattle, Washington. This work was supported by the Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health (Z01-HL006040-7), and by the intramural programs of the participating centers. Dr. Greenbaum has served as a proctor for Edwards Lifesciences, Medtronic, and Abbott Vascular; and a consultant for Transmural Systems. Dr. Babaliaros has served as a consultant for Edwards Lifesciences and Abbott Vascular; and his employer has research contracts for clinical investigation of transcatheter aortic and mitral devices from Edwards Lifesciences, Abbott Vascular, Medtronic, St. Jude Medical, and Boston Scientific.

ISSN 1936-8798/$36.00 https://doi.org/10.1016/j.jcin.2019.03.035

unresected diseased leaflets are displaced toward the coronary artery ostia or sinotubular junction during transcatheter valve deployment.

Predicting coronary obstruction is imprecise. From the available data, those at highest risk are female, with coronary ostial height of <10 mm, sinus of Valsalva width of <30 mm, and those with previous aortic bioprostheses, particularly with externally mounted leaflets or stentless surgical valves, and with virtual transcatheter heart valve to coronary distance (VTC) of <4 mm (4,5).

SEE PAGE 1253

Preventive strategies have to date involved prepositioning a guidewire or stent in the threatened coronary artery and, after TAVR, deploying the stent in the ostium and "snorkeling" it alongside the TAVR valve into the aorta (6). This may be a suboptimal solution, as these stents are prone to extrinsic compression, deformation, and thrombosis, causing delayed thrombotic coronary occlusion with often challenging percutaneous bailout (7).

Bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction during TAVR (BASILICA) is a transcatheter procedure performed immediately before TAVR. The target aortic leaflet is split using focused radiofrequency energy directed by catheters and guidewires. The BASILICA technique is derived from the earlier LAMPOON (Intentional Laceration of the Anterior Mitral leaflet to Prevent left ventricular Outflow ObstructioN during transcatheter mitral valve implantation) technique (8,9). Early in vitro, animal, and clinical BASILICA experience in 7 patients (10) showed that the split leaflets splay away from the coronary ostia during TAVR and that flow is maintained through the open cells of the TAVR valve. The purpose of this study was to systematically assess the early safety and efficacy of the BASILICA procedure.

METHODS

TRIAL DESIGN AND OVERSIGHT. The BASILICA (Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction during TAVR) investigational device exemption (IDE) trial (NCT03381989) was a prospective, single-arm, multicenter study of the BASILICA procedure, with independent on-site source-data verification and data monitoring, independent endpoint adjudication, and central core laboratory analysis of baseline and post-procedure images. The trial was designed by the investigators and sponsored by the senior author (R.J.L.) on behalf of the National Heart, Lung, and Blood Institute (NHLBI). Sites were not reimbursed for research activities. The U.S. Food and Drug Administration granted IDE for the study under the Early Feasibility pathway. The Institutional Review Board at each site and at the NHLBI approved the study protocol. The NHLBI Data Safety Monitoring Board provided study oversight. The NHLBI was the data-coordinating center. A Clinical Event Committee independently adjudicated the primary endpoints, all strokes, and all deaths, and determined relatedness to the BASILICA procedure and to TAVR. The authors have full custody of the data and the senior author had final responsibility for the decision to submit for publication.

SUBJECTS. Between February 15, 2018, and July 31, 2018, 30 subjects with symptomatic severe aortic stenosis or bioprosthetic aortic valve failure were enrolled at 4 centers in the United States (see **Figure 1** and the Online Appendix for study enrollment details). Adult patients were included if they were considered to be at high or prohibitive risk for surgical aortic valve replacement on the basis of clinical assessments by the institutional multidisciplinary heart team and considered at high risk of developing coronary artery obstruction from TAVR as determined by a central eligibility committee (see **Figure 1**). Coronary artery height, sinus width, VTC, sinotubular junction height and diameter, leaflet length and thickness, bioprosthetic valve type, prior coronary

ABBREVIATIONS AND ACRONYMS

BASILICA = bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction during TAVR

HALT = hypoattenuated leaflet thickening

IDE = investigational device exemption

KCCQ = Kansas City Cardiomyopathy Questionnaire

NHLBI = National Heart, Lung, and Blood Institute

NYHA = New York Heart Association

TAVR = transcatheter aortic valve replacement

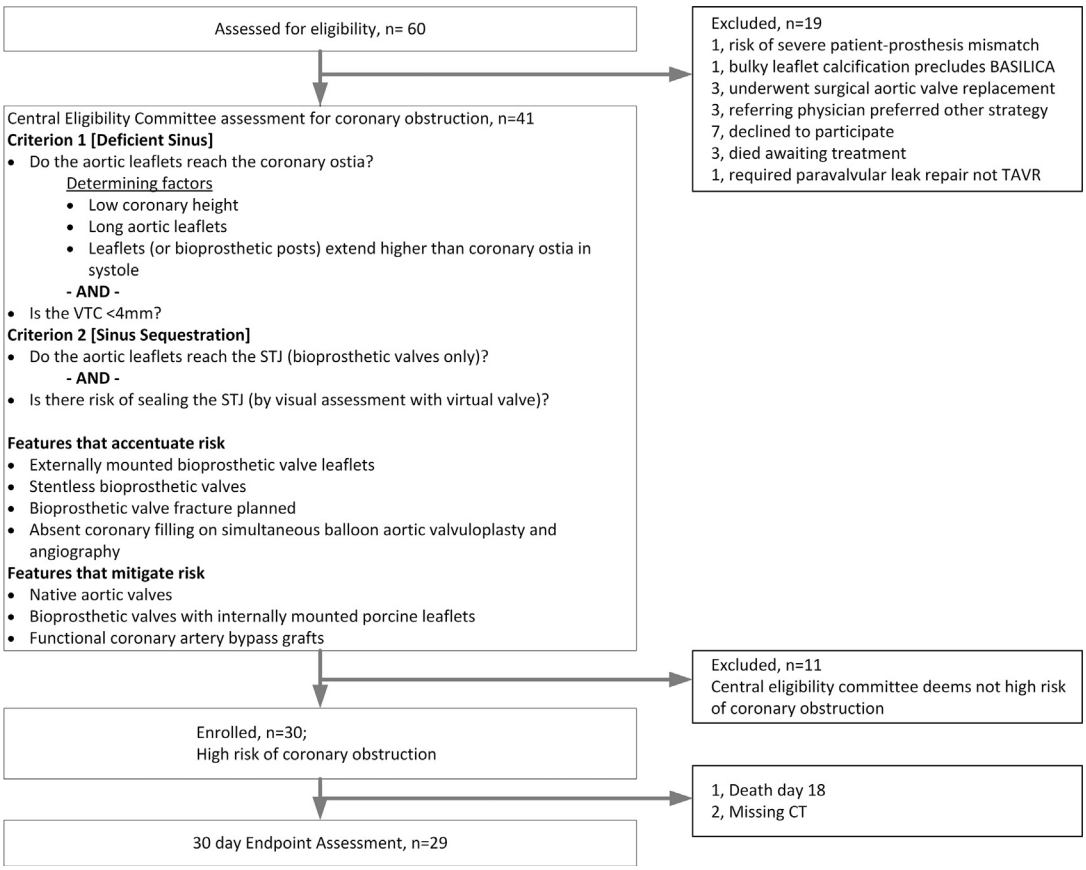
VARC = Valve Academic Research Consortium

VTC = virtual transcatheter valve to coronary distance

Dr. Rogers has served as a consultant for Medtronic; and a physician proctor for Edwards Lifesciences and Medtronic. Drs. Eng and Paone have served as proctors for Edwards Lifesciences. Dr. Leshnower has served on the Medtronic Speakers Bureau. Dr. Waksman has served on the advisory board for Abbott Vascular, Amgen, Boston Scientific, Cardioset, Cardiovascular Systems, Medtronic, Philips Volcano, and Pi-Cardia; has served as a consultant for Abbott Vascular, Amgen, Boston Scientific, Biotronik, Biosensors, Cardioset, Cardiovascular Systems, Philips Volcano, Pi-Cardia, and Medtronic; has received grant support from Abbott Vascular, AstraZeneca, Boston Scientific, and Chiesi; has served on the Speakers Bureau for AstraZeneca and Chiesi; and is an investor in MedAlliance. Dr. Dvir has served as a consultant for Edwards Lifesciences, Medtronic, and Abbott Vascular. Drs. Khan, Rogers, and Lederman are co-inventors on patents, assigned to the National Institutes of Health, on catheter devices to lacerate valve leaflets. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Lars Soendergaard, MD, served as the Guest Editor for this paper.

Manuscript received January 22, 2019; revised manuscript received February 20, 2019, accepted March 11, 2019.

FIGURE 1 Trial Enrollment

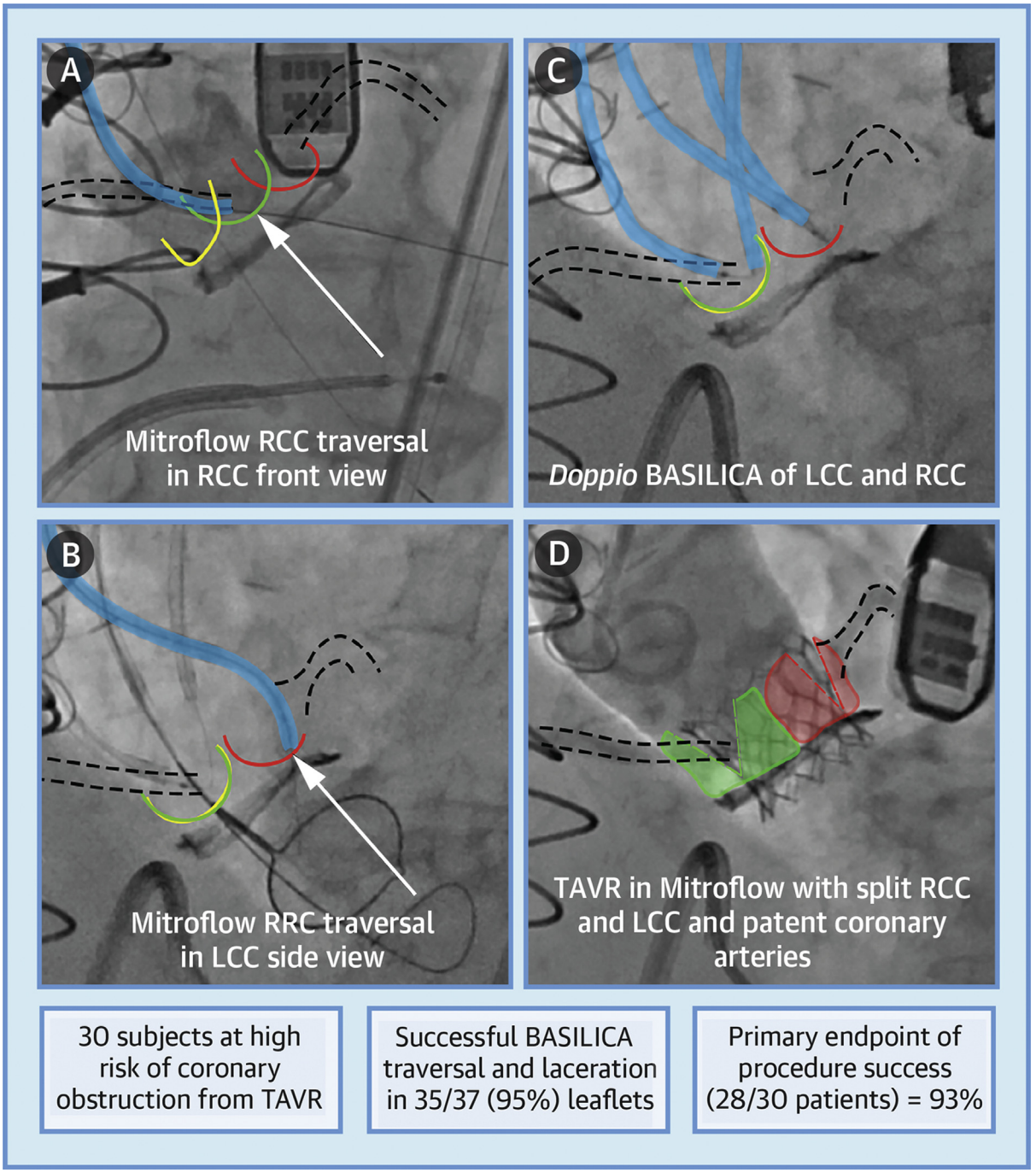


Sixty patients were screened and 30 were enrolled. All patients completed follow-up. One patient declined 30-day computed tomography (CT) and 1 died before 30 days. BASILICA = bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction during TAVR; STJ = sinotubular junction; TAVR = transcatheter aortic valve replacement; VTC = virtual transcatheter heart valve to coronary distance.

artery bypass grafts, and balloon valvuloplasty with simultaneous aortography were all considered, where appropriate, to determine coronary obstruction risk. Patients with severe calcified masses on the target aortic leaflets and those not expected to survive beyond 12 months despite TAVR were excluded. The complete list of inclusion and exclusion criteria is provided in the Online Appendix. All subjects consented to participate in writing.

BASILICA TECHNIQUE. The technique is described elsewhere (10,11) and is demonstrated in the **Central Illustration** and Online Video 1. Briefly, the BASILICA target leaflet or leaflets are chosen depending on the coronary artery at risk of obstruction. Fluoroscopic projection angles for the target aortic leaflets are planned on cardiac computed tomography (CT). The BASILICA procedure is performed under general anesthesia or moderate sedation. The procedure uses standard cardiovascular catheterization equipment. Two guiding catheters are used per target leaflet. For single leaflet or solo BASILICA, no additional vascular access is required beyond the 2 sheaths required for TAVR deployment and angiography. For double leaflet or doppio BASILICA, the sheath used for angiography is upsized to 12- to 14-F to house 2 side-by-side 6- to 8-F catheters. The guiding catheters are positioned on either side of the aortic leaflet, with a traversal guidewire (Astato XS 20, Asahi, Japan) in the aortic root and snare (Amplatz Gooseneck, AGA Medical Corporation, Minneapolis, Minnesota) in the left ventricular outflow tract, respectively. The guidewire is insulated in a microcatheter (Piggyback Wire Convertor, Teleflex, Wayne, Pennsylvania) to confine the electrical current to the tip, and electrified using a radiofrequency generator (ForceFx Valleylab, Minneapolis, Minnesota) to perforate the base

CENTRAL ILLUSTRATION **BASILICA Representative Example and Trial Results**



Khan, J.M. et al. J Am Coll Cardiol Intv. 2019;12(13):1240–52.

A representative subject with failed Mitroflow valve and at high risk of coronary obstruction who underwent doppio bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction during TAVR (BASILICA) and transcatheter aortic valve replacement (TAVR) (Online Video 1). **(A)** The guidewire traverses the right coronary cusp (RCC). **(B)** The guidewire traverses the left coronary cusp (LCC) into a snare in the left ventricular outflow tract. **(C)** BASILICA guidewire loops are formed through the base of both right and left cusps, ready for radiofrequency-assisted laceration. **(D)** Aortic root angiography demonstrates flow to both coronaries through the split Mitroflow leaflets after TAVR with a SAPIEN 3 valve. The RCC is highlighted in **green**, LCC highlighted in **red**, noncoronary cusp highlighted in **yellow**, BASILICA catheters highlighted in **blue**, coronary arteries outlined by **dashed lines**, and **arrow points** indicate traversal target.

TABLE 1 Baseline Characteristics (n = 30)

Age, yrs	76 (69-82)
Female	24 (80)
Comorbidities	
Prior stroke	7 (23)
Prior myocardial infarction	5 (17)
Coronary artery disease	19 (63)
Peripheral artery disease	7 (23)
Diabetes	12 (40)
End-stage kidney disease on dialysis	3 (10)
Severe pulmonary disease	12 (40)
Liver cirrhosis	2 (7)
Hypertension	26 (87)
Atrial fibrillation	11 (37)
Prior endocarditis	0 (0)
Prior rheumatic fever	1 (3)
Prior percutaneous revascularization	11 (37)
Prior coronary artery bypass surgery	7 (23)
≥2 prior cardiac surgeries	4 (13)
Pacemaker or ICD	6 (20)
NYHA functional class III or IV	26 (87)
Aspirin or $P2Y_{12}$ inhibitor	23 (77)
Oral anticoagulant	8 (27)
Frail	14 (47)
STS predicted risk of mortality	6 (3-15)
KCCQ-12 summary score	23 (16-40)
TAVR setting	
Native	13 (43)
Bioprosthetic	17 (57)
Aortic valve dysfunction	
Aortic stenosis	24 (80)
Aortic regurgitation	1 (3)
Mixed	5 (17)
LVEF <30%	4 (13)
AV peak velocity, m/s	4 (4-5)
AV mean gradient, mm Hg	43 (37-53)
AVA, cm^2	0.7 (0.6-0.8)

Values are median (interquartile range) or n (%).

AV = aortic valve; AVA = aortic valve area; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

TABLE 2 Procedure Characteristics

Valve type	
SAPIEN 3	16 (53)
Evolut R	11 (37)
Evolut Pro	3 (10)
Valve nominal size	
20 mm	4 (13)
23 mm	17 (57)
26 mm	6 (20)
29 mm	3 (10)
Access for TAVR	
Transfemoral	23 (77)
Transcaval	6 (20)
Percutaneous axillary	1 (3)
Target cusp	
Left solo	18 (60)
Right solo	5 (17)
Doppio	7 (23)
Sentinel cerebral protection	13 (43)
Balloon pre-dilation	5 (17)
Balloon post-dilation	7 (23)
Bioprosthetic valve fracture	3 (10)
General anesthesia	27 (90)
Moderate sedation	3 (10)
Total procedure time (access to hemostasis), min	113 (98-162)
BASILICA time, solo (catheter introduction to laceration), min	73 (58-88)
BASILICA time, doppio (catheter introduction to laceration), min	123 (106-137)
Time from BASILICA to TAVR, min	9 (7-16)
Fluoroscopy time, min	75 (57-111)
Contrast volume, ml	143 (101-226)

Values are n (%) or median (interquartile range)

BASILICA = bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction during TAVR; TAVR = transcatheter aortic valve replacement.

of the target leaflet. The guidewire is snared in the left ventricular outflow tract and externalized to form a loop through the leaflet, between the 2 guiding catheters. The guidewire shaft is shaped to confine electrical contact with leaflet tissue, and then further electrified under tension to lacerate the leaflet down the centerline. The split leaflet typically splays in systole and coapts in diastole. The BASILICA system is disconnected and removed from the body, and then TAVR is performed as usual. The TAVR valve displaces the leaflets outwards but the split leaflets splay away from the coronary ostia, maintaining coronary flow.

STUDY ENDPOINTS. The prespecified primary endpoint was procedure success, measured at exit from the catheterization laboratory, and required all the following: successful BASILICA traversal and laceration of the intended leaflet(s); successful access, delivery, and retrieval of the BASILICA device system; successful TAVR device implantation; absence of procedural mortality; absence of coronary artery obstruction; and freedom from emergency cardiac surgery or reintervention related to the BASILICA TAVR procedure, including attempted implantation of coronary stents to treat TAVR-induced coronary artery obstruction. The prespecified primary safety endpoint was freedom from major adverse clinical events according to Valve Academic Research Consortium (VARC)-2 early safety at 30 days, which is a composite of all-cause mortality, all stroke, life-threatening bleeding, acute kidney

TABLE 3 Coronary Obstruction Risk

Risk Prediction	Total Coronary Leaflets (N = 60)		Native (N = 26)		Bioprosthetic (N = 34)	
	BASILICA Leaflet (n = 37)	Non-BASILICA Control Leaflet (n = 23)	BASILICA Leaflet (n = 14)	Non-BASILICA Control Leaflet (n = 12)	BASILICA Leaflet (n = 23)	Non-BASILICA Control Leaflet (n = 11)
Coronary height, mm	7.2 (5.2–9.7)	10.4 (6.2–12.1)	9.8 (7.9–11.8)	11.7 (10.4–12.4)	6.3 (3.8–8.4)	5.6 (4.6–10.7)
Coronary height <10 mm	28 (76)	9 (24)	7 (50)	1 (8)	21 (91)	8 (73)
Sinus width, mm	25.9 (24.8–29.0)	27.9 (24.8–31.4)	26.5 (24.7–29.6)	28.4 (24.8–31.1)	25.5 (24.9–28.6)	27.9 (25.5–32.1)
Leaflet above coronary ostium	34 (92)	13 (57)	12 (86)	4 (33)	22 (96)	9 (82)
Leaflet above STJ	18 (49)	6 (26)	0 (0)	0 (0)	18 (78)	6 (55)
Calcium volume, mm^3	94 (33–298)	127 (85–228)	57 (29–96)	118 (91–190)	136 (60–395)	164 (75–230)
VTC, mm	3.3 (2.7–4.0)	4.3 (3.4–5.2)	2.9 (2.4–3.7)	4.2 (3.4–4.8)	3.7 (2.9–4.1)	4.6 (3.6–5.3)
VTC <4 mm	27 (73)	9 (39)	13 (93)	5 (42)	14 (61)	4 (36)
VTC <3 mm	14 (38)	3 (13)	7 (50)	2 (17)	7 (30)	1 (9)
THV to STJ, mm	2.2 (0.5–3.1)	2.6 (1.1–4.0)	1.2 (0.1–2.2)	2.0 (0.5–2.8)	2.6 (1.6–3.4)	3.5 (2.5–5.8)
THV to STJ <3 mm	27 (73)	15 (65)	13 (93)	10 (83)	14 (61)	5 (46)
Post-procedure risk assessment						
VTC, mm	3.3 (1.7–4.5)	3.6 (2.8–4.7)	2.3 (0.6–3.7)	3.2 (2.6–3.8)	3.6 (3.0–4.6)	4.7 (3.9–6.0)
VTC <4 mm	24 (69)	12 (57)	13 (93)	9 (75)	11 (52)	3 (33)
VTC <3 mm	14 (40)	7 (33)	9 (64)	6 (50)	5 (24)	1 (11)
THV to STJ, mm	1.4 (0–2.2)	1.3 (0–2.2)	0 (0–0.7)	0.4 (0–1.1)	1.8 (0.9–2.7)	2.1 (1.6–2.9)
THV to STJ <3 mm	28 (90)	16 (89)	11 (100)	10 (100)	17 (85)	6 (75)

Values are median (interquartile range) or n (%).

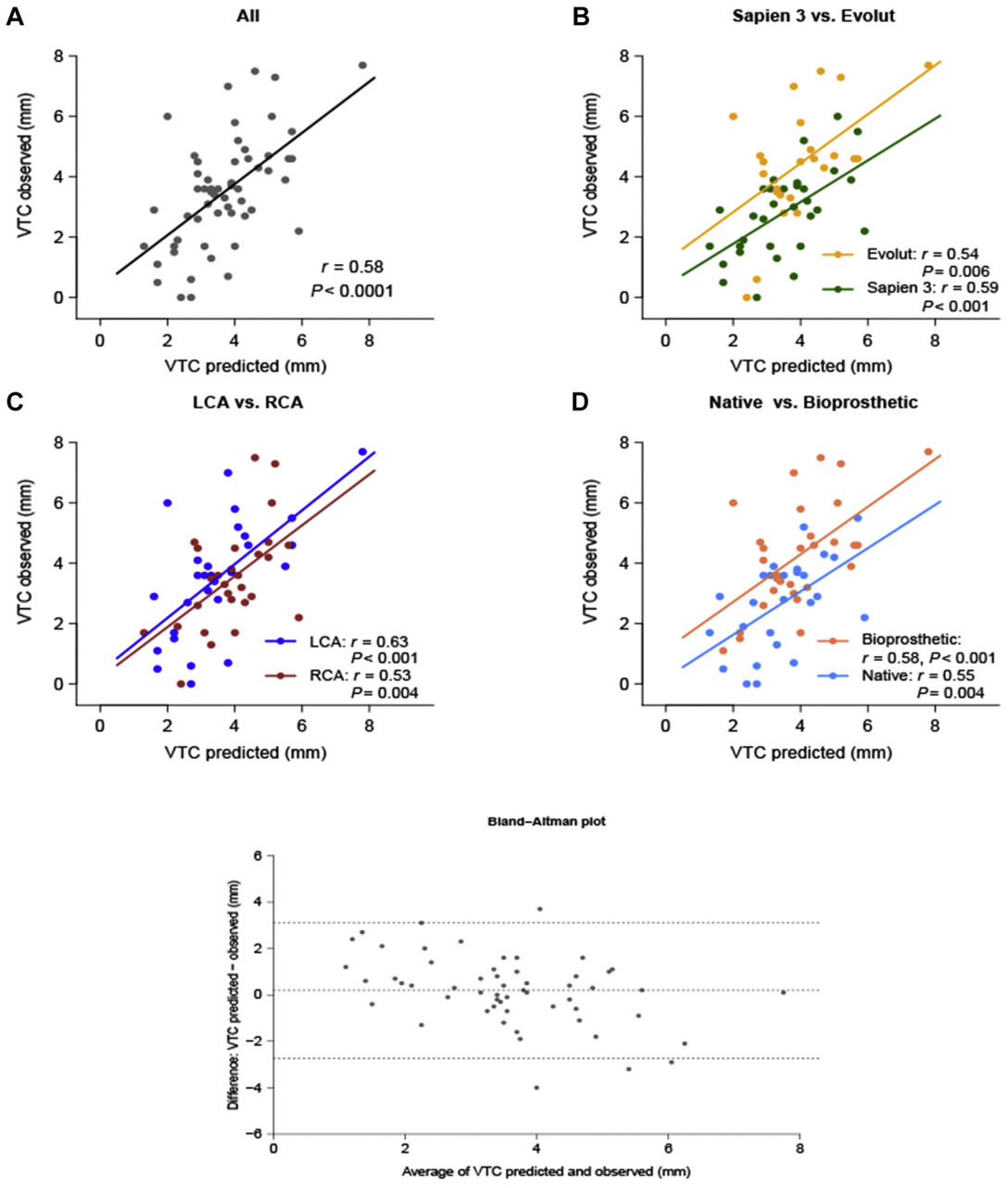
BASILICA = bioprosthetic or native aortic scallop intentional laceration to prevent iatrogenic coronary artery obstruction during TAVR; STJ = sinotubular junction; THV = transcatheter heart valve; VTC = virtual transcatheter heart valve to coronary distance.

injury (stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complications, and valve-related dysfunction requiring repeat procedure. Secondary endpoints included hemodynamic instability caused by BASILICA before TAVR, TAVR thrombosis on follow-up CT or echocardiography, hemolytic anemia, and BASILICA-related technical failure, including embolism, mitral valve injury, off-target traversal, and coronary artery injury. The complete list of endpoints is provided in the Online Appendix.

IMAGING. Transesophageal or transthoracic echocardiograms were performed at baseline, intra-procedure, discharge, and 30-days. Contrast-enhanced electrocardiogram-gated multislice CT scans were performed at baseline and post-procedure. Images were analyzed by the NHLBI core laboratory using dedicated 4-dimensional CT software, 3mensio version 9.1 (Pie Medical, Maastricht, the Netherlands). The VTC was measured using the Vancouver method (12). A virtual valve cylinder with a diameter of the selected valve being implanted was simulated in position and the distance to the coronary ostia measured in the short and long axes. For SAPIEN valves (Edwards Lifesciences, Irvine, California), the nominal valve diameter was used for the virtual valve (a 23 SAPIEN 3 valve was simulated with a valve with diameter 23 mm). For Evolut R/Pro valves (Medtronic, Minneapolis, Minnesota), a "constrained" diameter was used as follows: 20 mm, 23 mm, and 26 mm for 23, 26, and 29 Evolut valves, respectively. Follow-up CT was performed to measure observed valve to coronary artery distances; and to evaluate coronary patency; hypoattenuated leaflet thickening (HALT), defined as an area of hypodensity on TAVR valve leaflets on CT; and hypoattenuation affecting motion, defined as reduced leaflet motion in the presence of HALT (13). Leaflet calcium volumes were measured on contrast CT using dedicated software (3mensio) after performing automation-assisted segmentation of the aortic valve leaflets, using established methodology (14).

STATISTICAL ANALYSIS. All analyses were based on the intention-to-treat principle with data from all enrolled patients. The sample size of 30 subjects was not derived statistically. Baseline subject and procedural characteristics were summarized as median and interquartile range for continuous variables and count and proportion for categorical variables. McNemar's test and paired *t* test were used to assess the difference in the proportion of New York Heart Association (NYHA) functional class and Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life

FIGURE 2 Correlation Between Predicted and Observed Valve-to-Coronary Distance



(A) The overall correlation coefficient was 0.58, with **(C)** good correlation across left and right cusps. Observed virtual transcatheter heart valve to coronary distance (VTC) was smaller than predicted **(B)** for SAPIEN 3 valves and **(D)** in native aortic stenosis. **(B, D)** There were few outliers when using Evolut valves in surgical bioprostheses in which prediction underestimated VTC. The Bland-Altman plot demonstrates no systematic difference (bias) between predicted and observed VTC. LCA = left coronary artery; RCA = right coronary artery.

measure between baseline and 30-day visits, respectively. Pearson's correlation and Bland-Altman plot were used to assess the correlation and agreement between predicted VTC on pre-procedure CT and observed measurements on post-procedure CT. Statistical analyses were performed using R statistical software 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

SUBJECT AND PROCEDURE DETAILS. Baseline subject characteristics are shown in Table 1. Subjects were typically elderly, with high surgical risk and comorbidity, and in NYHA functional class III or IV. Of note, 80% were women, and 23% had a prior stroke. 43% had native aortic stenosis and 57% had bioprosthetic aortic valve failure. Procedure characteristics are shown in Table 2. SAPIEN 3 valves were used in 53% and Evolut R/Pro in 47%. TAVR access was transfemoral in 77%, transcaval 20%, and percutaneous axillary in 3%. The bioprosthetic valve frame was intentionally fractured (15) with high-pressure balloon inflation in 10%. A Sentinel device (Claret Medical, Santa Rosa, California) was used for cerebral protection in 43% and embolic debris was recovered in 46% of those cases, though no systematic inspection technique was mandated. General anesthesia and transesophageal echocardiography were used in 90% and moderate sedation without transesophageal echocardiography in 10%.

CORONARY OBSTRUCTION RISK. The target BASILICA leaflet was solo in 77% of subjects (left only in 60%, right only in 17%) and doppio (both leaflets) in 23%. The risk profile of the target leaflets and associated coronary arteries compared with the nontarget control leaflets is shown in Table 3. Individual risk for each patient is presented in Online Table 1. A total of 95% of target leaflets fit at least 2 of 3 best-available CT risk criteria for coronary obstruction—namely coronary height <10 mm, sinus width <30 mm, and VTC <4 mm (4,5). The predicted VTC on pre-procedure CT and observed transcatheter heart valve-to-coronary ostia measurements on post-procedure CT correlated well overall (Figure 2). Observed valve-to-coronary distance tended to be smaller than predicted VTC in SAPIEN 3 valves and in native annuli.

PROCEDURE OUTCOMES. The adjudicated endpoints are shown in Table 4. The primary endpoint of procedure success was met in 93% of subjects. Leaflet traversal was successful in 35 of 37 (95%) of target leaflets. Laceration was successful in all leaflets traversed. All subjects survived their procedure with successful implantation of the first TAVR device. There were no cases of coronary obstruction. There were no cases requiring reintervention or surgery. In the 2 cases in which leaflet traversal was not successful, coronary stents were pre-positioned, of which 1 was deployed after TAVR and the other removed due to low probability of obstruction on angiographic assessment after TAVR. We attribute the 2 traversal failures to confluent leaflet calcification at the crossing target at the nadir of the leaflet.

TABLE 4 Clinical Outcomes

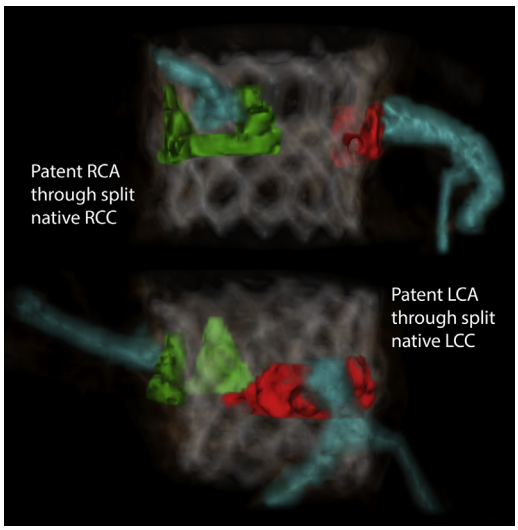
Primary efficacy endpoint (exit from catheter laboratory)*	(n = 30)
Successful BASILICA traversal and laceration	28 (93)
Immediate survival	30 (100)
Successful first TAVR device implantation	30 (100)
Coronary obstruction	0 (0)
Freedom from emergency surgery or reintervention related to BASILICA or TAVR	30 (100)
Technical success (all of above)	28 (93)
Primary safety endpoint (30 days)*	(n = 30)
All death	1 (3)
Cardiovascular	1 (3)
Noncardiovascular	0
All stroke	3 (10)
Disabling	1 (3)
Nondisabling	2 (7)
Life threatening bleeding	2 (7)
Clearly related to BASILICA	0
Potentially related to BASILICA	0
Not related to BASILICA	2 (7)
Major vascular complication	6 (20)
Clearly related to BASILICA	0
Potentially related to BASILICA	0
Not related to BASILICA	6 (20)
AKI stage 2/3	1 (3)
Coronary artery obstruction	0 (0)
Valve-related dysfunction requiring repeat procedure	0 (0)
VARC-2 early safety (all of above)	21 (70)
Secondary endpoints (30 days)	(n = 30)
Secondary myocardial infarction	1 (3)
Major cardiac structural complication	0 (0)
Hemolytic anemia	0 (0)
Endocarditis	0 (0)
New pacemaker	2 (7)
Need for second valve	0 (0)
PVL > mild	0 (0)
Cardiac tamponade	0 (0)
Nontarget BASILICA traversal (left atrial entry)	1 (3)
Hemodynamic instability from laceration requiring vasopressors	2 (7)
Embolic debris recovered if cerebral protection used	6/13 (46)
Coronaries obstructed on follow-up CT	0/28 (0)
30-day mean gradient >20 mm Hg	9/28 (32)
HALT on follow-up CT	3/28 (11)
HAM on follow-up CT	1/28 (4)

Values are n (%) or n/N (%). *Clinical Event Committee adjudicated.

AKI = acute kidney injury; ICA = bioprosthetic or native aortic scallop intentional laceration; CT = computed tomography; HALT = hypoattenuated leaflet thickening; HAM = hypoattenuation affecting motion; PVL = paravalvular leak; VARC = Valve Academic Research Consortium.

Figure 3 and Online Video 2 show a manually segmented post-procedure CT of a typical subject, demonstrating split native leaflets parting away from otherwise threatened left and right coronary ostia.

FIGURE 3 Three-dimensional CT Reconstruction After Doppio Native BASILICA



Native leaflets (LCC in **red**, RCC in **green**) and coronary arteries **(blue)** are manually segmented and colorized on a CT acquired after BASILICA and TAVR. Both left and right coronary leaflets are seen split and parted away from the coronary ostia. (Online Video 2) The leaflet configuration suggests that both coronary ostia would have obstructed without BASILICA. Abbreviations as in **Figures 1 and 2**.

The primary endpoint of early safety was met in 70% of subjects at 30 days (**Table 4**). This was mostly driven by 6 TAVR-related major vascular complications: 1 retroperitoneal bleed from femoral access; 1 transcaval bleed requiring covered stent placement, both of which qualified as VARC-2 life-threatening bleeds; 2 groin hematomas; 1 groin bleed without hematoma; and 1 ischemic limb requiring femoral artery thromboendarterectomy.

There was 1 death in a subject who developed a severe inflammatory response at induction of anesthesia despite a technically successful procedure, leading to multiple organ failure on a background of multiple brain metastases. Care was withdrawn and the subject died on post-procedure day 18.

There was 1 (3%) disabling stroke and 2 (7%) nondisabling strokes, detailed in **Table 5**. Two of the 3 subjects had baseline central neurological pathology, including the subject that died, making the clinical and radiological diagnosis ambiguous. Cerebral protection was used in 1 and no debris was recovered.

OTHER CLINICAL ENDPOINTS. Mean arterial pressures for each subject at baseline, before and after BASILICA, and after TAVR are shown in Online Figure 1. Transient hypotension after laceration was seen in 2 subjects. This resolved promptly with TAVR. There was 1 off-target guidewire traversal into the left atrium. The guidewire was withdrawn and traversal reattempted without clinical sequelae. One subject went into ventricular fibrillation after left leaflet guidewire traversal requiring cardioversion. No subject had greater than mild paravalvular leak. Two subjects had permanent pacemaker implantation. Mean aortic valve gradient fell from 44 ± 16 mm Hg to 18 ± 7 mm Hg at 30 days. Gradients were similar between bioprosthetic and native valve TAVR subjects. A total of 29% had severe patient-prosthesis mismatch (indexed effective orifice area <0.65 cm^2/m^2), and 38% had moderate prosthesis-patient mismatch (indexed effective orifice area 0.65 to 0.85 cm^2/m^2).

There was improvement in subject NYHA functional class and KCCQ quality of life scores (16) (**Figure 4**). At 30-day visit, the median KCCQ summary score was 52.9 (interquartile range: 42.5 to 76.8) with 14% subjects in NYHA functional class III to IV, compared with a median KCCQ of 23.4 (interquartile range: 15.6 to 39.6) and 87% subjects in NYHA functional class III to IV at baseline (both $p < 0.0001$). HALT was seen in 3 (11%) subjects on follow-up CT, all in SAPIEN 3 valves, and on the noncoronary leaflet in all. One of these subjects had hypoattenuation affecting motion. No HALT was seen on TAVR leaflets adjacent to leaflets split by BASILICA.

DISCUSSION

The purpose of this IDE trial was to determine feasibility, early safety, and efficacy of TAVR with BASILICA in subjects who might obstruct their coronary arteries with stand-alone TAVR. BASILICA-TAVR met the composite primary endpoint of procedure success in 93%. Crucially, despite the high predicted risk, 100% of subjects were free of coronary artery obstruction after TAVR, with no evidence of coronary obstruction on angiography, CT, electrocardiogram, or echocardiogram, or clinically at 30 days.

Guidewire traversal failed in 2 leaflets. These cases demonstrate that confluent heavy leaflet calcification at the nadir of the target aortic leaflets may be an obstacle to leaflet traversal using radiofrequency energy. This is similar to the experience using guidewire electrification in transcaval access for TAVR (17,18). In all cases where leaflet traversal was successful, laceration was able to be performed.

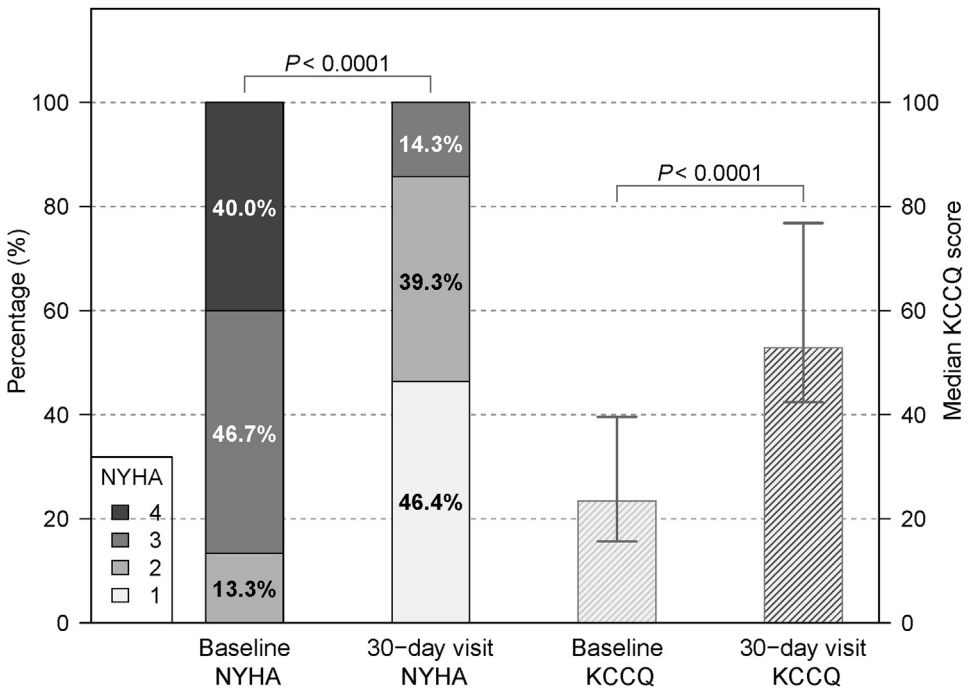
TABLE 5 Procedural Stroke

	Subject 1	Subject 2	Subject 3
Neurological symptoms and sequelae	Mild bilateral hand weakness, resolved at 30 days	Confounded by baseline central and peripheral neuropathy; subjective left leg weakness, resolved at 30 days	Confounded by acute encephalopathy from anesthesia-related hypotension; fluctuating neurology with right hand weakness
Disability (by modified Rankin score)	Nondisabling	Nondisabling	Disabling
MRI	MRI-DWI multiple small bilateral foci of diffusion restriction	MRI-DWI multiple small bilateral foci of diffusion restriction	MRI-DWI confounded by multiple brain metastases and global ischemia
Setting	Mitroflow stenosis, doppio BASILICA L+R	Native aortic stenosis, solo BASILICA L	Mitroflow stenosis, solo BASILICA L
TAVR valve	SAPIEN 3	SAPIEN 3	Evolut R
Pre-dilatation/post-dilatation	No/no	Yes/yes	No/yes
Calcium volume of BASILICA leaflet	LCC 182, RCC 215	LCC 95	LCC 93
Sentinel cerebral protection used; debris retrieved	No; N/A	Yes; no debris	No; N/A
HALT on CT	No	Yes	No

DWI = diffusion-weighted imaging; L = left; LCC = left coronary cusp; MRI = magnetic resonance imaging; N/A = not applicable; R = right; RCC = right coronary cusp; other abbreviations as in Table 4.

Three (10%) subjects had neurological events (3% disabling stroke). The neurological event rate from TAVR in contemporary adjudicated trials in intermediate-risk subjects was 6.4% (3.2% disabling stroke) in the PARTNER 2 (Placement of Aortic Transcatheter Valves) trial (1) and 4.5% (1.2% disabling stroke) in SURTAVI (Surgical Replacement and Transcatheter Aortic Valve Implantation) trial

FIGURE 4 Symptom and Quality of Life Improvement



There was an improvement in New York Heart Association (NYHA) functional class and Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 30 days compared with baseline. **Error bars** represent the interquartile range.

(2), and in high-risk subjects in the SENTINEL (Cerebral Protection in Transcatheter Aortic Valve Replacement) trial was 5.6% with cerebral protection and 9.1% without (19). Whether there is an excess risk of stroke from BASILICA cannot be determined from this small sample size of high- and extreme-risk subjects, 23% of whom had a previous stroke and 23% of whom had severe vascular disease requiring alternative TAVR access. Two of the 3 subjects experiencing stroke had ambiguous findings related to baseline neurological comorbidity including a central demyelinating syndrome and metastatic brain cancer. Embolic stroke from BASILICA may theoretically be caused by multiple catheter manipulations and leaflet laceration releasing calcific debris. Stroke risk for BASILICA-TAVR needs to be assessed in larger prospective trials and registries.

Hemodynamic instability was uncommon but tolerated after BASILICA (7%) and resolved promptly with TAVR. Another concern is the VARC-2 major vascular complication rate (20%), which was higher than seen in contemporary registries—4.1% in for SAPIEN 3 in the SOURCE 3 trial (20) and 6.5% for Evolut R in the FORWARD trial (21). This may reflect the smaller anatomies in patients at risk of coronary obstruction, with increased the risk of vascular complications. All were independently adjudicated as related to TAVR and not related to BASILICA. Small anatomies are also reflected in the high post-procedural gradients and higher rates of severe and moderate prosthesis-patient mismatch compared with those recently reported from the TVT (Transcatheter Valve Therapy) registry (12% and 25%, respectively) (22) but similar to those seen in the Valve-in-Valve registry (23). Overall, the results of this early feasibility study suggest an acceptable early safety profile for BASILICA in high-risk subjects.

Subclinical leaflet thrombosis rates (11%) were similar to those in observational registries (13% in the RESOLVE (Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment With Anticoagulation) and SAVORY (Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed With 4D CT) registries (24) and clinical trials (14% in Low Risk TAVR trial) (3). Interestingly, no HALT was seen in TAVR leaflets adjacent to lacerated aortic leaflets. This generates a testable hypothesis that BASILICA might reduce subclinical leaflet thrombosis by promoting sinus washout and reducing stasis (25).

There is an unmet clinical need for high surgical risk patients at risk of coronary obstruction from TAVR. Coronary protection with pre-positioned guidewires and coronary stents is potentially hazardous (7). "Snorkel" stents, implanted to create a channel between TAVR valve and coronary sinus, are at risk of deformation and thrombosis due to constant mechanical pressures from the TAVR valve and poor blood flow in the obstructed neosinus. Future coronary access may be compromised, and patients are committed to long-term thromboprophylaxis and potential late bleeding complications. Furthermore, absence of coronary obstruction while a guidewire is down the coronary artery may be falsely reassuring, and the coronary artery may obstruct once the leaflet is unpinned after guidewire withdrawal. Additionally, coronary obstruction may occur remotely from the index procedure (7).

PROCEDURE LIMITATIONS. High-quality CT image acquisition is required to assess for a calcium-free target at the base of the leaflet for guidewire traversal. If there appears to be confluent leaflet calcium, there may be a low likelihood of success, and if BASILICA is attempted, we recommend it is only tried briefly and by an experienced operator.

Careful procedure planning and image-guided execution is required to align the laceration in front of the coronary artery ostium. If the laceration is not aligned, obstruction may occur from a portion of the leaflet.

The poor correlation between predicted and post hoc observed VTC probably reflects unpredictable TAVR implantation characteristics (e.g., device selection, implantation depth, canting angle, and device flaring), as well as variable surgical bioprosthesis characteristics (leaflet material, frame geometry, and frame expansion after TAVR).

STUDY LIMITATIONS. Further study is required to enhance the specificity of coronary obstruction risk prediction. Coronary obstruction is a rare complication and it is possible that some of the subjects undergoing BASILICA may not have obstructed their coronary arteries with standalone TAVR. Indeed, 1 subject did not obstruct their coronary artery after failed BASILICA. Acknowledging these limitations, all subjects were at high risk of coronary obstruction from TAVR by currently available criteria, as determined by the central eligibility committee based on pre-procedural CT imaging including simulation of the transcatheter heart valve and assessing the relation to the coronary arteries and aortic sinuses. Indeed, the predicted risk correlated well with observed measurements on follow-up CT. In this study, the coronary obstruction

risk appeared to be underestimated in SAPIEN 3 valves and native annuli. In a few cases of Evolut valves implanted into bioprostheses, expansion of the valve was less than predicted.

No control arm was possible in this study as TAVR-related coronary obstruction has a high mortality and these subjects had no suitable alternatives that could provide clinical equipoise for a randomized comparison.

This study was designed to test early feasibility. Whether there are excess cardiovascular events related to BASILICA need to be addressed in larger studies.

FUTURE DIRECTIONS. Further registry data are required to increase the sensitivity and specificity of coronary artery obstruction risk prediction, including analysis of high-quality pre- and post-procedure CT. This trial should inform further study. We do not believe that we have equipoise to compare BASILICA against alternatives such as snorkel stenting. One possible investigation might be a comparison of BASILICA and TAVR against surgical aortic valve replacement among patients at high or extreme surgical risk.

Dedicated catheter tools may make BASILICA into a relatively easy and swift adjunct to TAVR. At present, the BASILICA procedure is a novel technique and should be limited to high-volume centers and be performed with appropriate education and proctoring.

The method may be used to lacerate bicuspid aortic leaflets (Bi-SILiCA [Bicuspid Scallop Intentional Laceration to Circularize the Annulus]) and may enhance transcatheter heart valve circularity and improve TAVR outcomes in this difficult cohort of patients. We have reported this technique previously (26) and it needs to be evaluated in a prospective trial.

CONCLUSIONS

In subjects at high risk of coronary artery obstruction from TAVR, BASILICA demonstrated feasibility in both native and surgical bioprosthetic valves in a prospective, independently adjudicated, IDE early feasibility trial. Hemodynamic compromise was rare, and resolved with TAVR. Safety was acceptable and needs to be confirmed in larger studies. BASILICA appears effective in preventing coronary obstruction from TAVR in subjects at high risk.

ACKNOWLEDGMENTS The authors thank clinical and research staff at University of Washington (Christopher Rumer, Data Manager; Ikki Komatsu, MD; Gabriel Aldea, MD; G. Burkhard Mackensen, MD, PhD; James M. McCabe, MD); Emory University (Lauren Wheeler; James Lee, RN; Patricia Keegan, DNP; Elizabeth Charles, Research Coordinator; Kristy Pitts, Research Coordinator; Kimberly McWhorter, Research Coordinator; Hima Patel, Research Coordinator; Jennifer James, Research Coordinator); Medstar Washington Hospital Center (Petros Okubagzi, Clinical Research Director; Dorion Hoffmeister, Research Coordinator); Henry Ford Hospital (Ashish Solanki, Research Coordinator); and independent Data Monitors (Olha Katynska; Valeriy Matveev; Artur Karapetyan). We thank the Medstar Clinical Events Adjudication Committee (Hector Garcia-Garcia, Soloman Beyene, Kayode Kuku, and Viana Azizi); and the National Heart, Lung, and Blood Institute Computed Tomography Core Laboratory.

ADDRESS FOR CORRESPONDENCE: Dr. Robert J. Lederman, Cardiovascular Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, Building 10, Room 2c713, MSC 1538, Bethesda, Maryland 20892-1538. E-mail: lederman@nih.gov.

PERSPECTIVES

WHAT IS KNOWN? Coronary artery obstruction from the residual diseased aortic leaflets is a rare and devastating complication of TAVR. BASILICA is a transcatheter technique that slices the aortic valve leaflets to prevent coronary obstruction, with proof of principal demonstrated in animal and first-in-human studies.

WHAT IS NEW? The BASILICA IDE clinical trial demonstrated feasibility in native and bioprosthetic aortic valves, with an acceptable safety profile, and appeared effective in preventing coronary artery obstruction in subjects at high risk.

WHAT IS NEXT? This early feasibility study should instigate larger prospective studies to further assess the safety of BASILICA as an adjunct to TAVR. BASILICA may be offered to enable TAVR in patients at risk of coronary artery obstruction at experienced centers.

REFERENCES

1. 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.

2. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017; 376:1321–31.

3. Waksman R, Rogers T, Torguson R, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis. J Am Coll Cardiol 2018;72:2095–105.

4. Ribeiro HB, Webb JG, Makkar RR, et al. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. J Am Coll Cardiol 2013;62:1552–62.

5. Ribeiro HB, Rodes-Cabau J, Blanke P, et al. Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. Eur Heart J 2018;39:687–95.

6. Abramowitz Y, Chakravarty T, Jilaihawi H, et al. Clinical impact of coronary protection during transcatheter aortic valve implantation: first reported series of patients. EuroIntervention 2015; 11:572–81.

7. Jabbour RJ, Tanaka A, Finkelstein A, et al. Delayed coronary obstruction after transcatheter aortic valve replacement. J Am Coll Cardiol 2018; 71:1513–24.

8. Khan JM, Rogers T, Schenke WH, et al. Intentional laceration of the anterior mitral valve leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve replacement: pre-clinical findings. J Am Coll Cardiol Intv 2016;9:1835–43.

9. Babaliaros VC, Greenbaum AB, Khan JM, et al. Intentional percutaneous laceration of the anterior mitral leaflet to prevent outflow obstruction during transcatheter mitral valve replacement: first-in-human experience. J Am Coll Cardiol Intv 2017;10:798–809.

10. Khan JM, Dvir D, Greenbaum AB, et al. Transcatheter laceration of aortic leaflets to prevent coronary obstruction during transcatheter aortic valve replacement: concept to first-in-human. J Am Coll Cardiol Intv 2018;11:677–89.

11. Lederman RJ, Babaliaros VC, Rogers T, et al. Preventing coronary obstruction during TAVR: From CT to BASILICA. J Am Coll Cardiol Intv 2019; 12:1197–216.

12. Blanke P, Soon J, Dvir D, et al. Computed tomography assessment for transcatheter aortic valve in valve implantation: the vancouver approach to predict anatomical risk for coronary obstruction and other considerations. Journal of cardiovascular computed tomography 2016;10: 491–9.

13. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373: 2015–24.

14. Khalique OK, Hahn RT, Gada H, et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. J Am Coll Cardiol Intv 2014;7: 885–94.

15. Chhatriwalla AK, Allen KB, Saxon JT, et al. Bioprosthetic valve fracture improves the hemodynamic results of valve-in-valve transcatheter aortic valve replacement. Circ Cardiovasc Interv 2017;10:e005216.

16. Spertus JA, Jones PG. Development and validation of a short version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes 2015;8:469–76.

17. Greenbaum AB, Babaliaros VC, Chen MY, et al. Transcaval access and closure for transcatheter aortic valve replacement: a prospective investigation. J Am Coll Cardiol 2017;69:511–21.

18. Lederman RJ, Greenbaum AB, Rogers T, Khan JM, Fusari M, Chen MY. Anatomic suitability for transcaval access based on computed tomography. J Am Coll Cardiol Intv 2017;10:1–10.

19. Kapadia SR, Kodali S, Makkar R, et al. Protection against cerebral embolism during transcatheter aortic valve replacement. J Am Coll Cardiol 2017;69:367–77.

20. Wendler O, Schymik G, Treede H, et al. SOURCE 3 registry: design and 30-day results of the european postapproval registry of the latest generation of the SAPIEN 3 transcatheter heart valve. Circulation 2017;135: 1123–32.

21. Grube E, Van Mieghem NM, Bleiziffer S, et al. Clinical outcomes with a repositionable self-expanding transcatheter aortic valve prosthesis: the international FORWARD study. J Am Coll Cardiol 2017;70:845–53.

22. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-patient mismatch in patients undergoing transcatheter aortic valve replacement: from the STS/ACC TVT registry. J Am Coll Cardiol 2018;72:2701–11.

23. Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA: the journal of the American Medical Association 2014;312:162–70.

24. Chakravarty T, Sondergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389: 2383–92.

25. Midha PA, Raghav V, Sharma R, et al. The fluid mechanics of transcatheter heart valve leaflet thrombosis in the neosinus. Circulation 2017;136: 1598–609.

26. Kamioka N, Lederman RJ, Khan JM, et al. BI-SILICA during transcatheter aortic valve replacement for noncalcific aortic insufficiency: initial human experience. J Am Coll Cardiol Intv 2018;11:2237–9.

KEY WORDS bioprosthetic heart valve failure, coronary artery obstruction, structural heart disease, transcatheter aortic valve replacement, transcatheter electrosurgery

APPENDIX For a supplemental figure, table, videos, selection criteria, trial endpoints, and enrolling sites, please see the online version of this paper.

Supplement

The BASILICA Trial: A prospective multi-centre cohort study of intentional leaflet laceration before transcatheter aortic valve implantation (TAVI) to prevent coronary obstruction

Study selection criteria

Inclusion Criteria

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

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

Trial endpoints

Primary efficacy endpoint

The **primary efficacy endpoint** is procedure 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 TAVI 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 TAVI procedure, including attempted implantation of coronary artery stents to treat TAVI-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.

Primary safety endpoint

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

- All-cause mortality
- All stroke (disabling and non-disabling)
- Life-threatening bleeding
- Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)
- Coronary artery obstruction requiring intervention
- Major vascular complication
- Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)

Additional endpoints

- 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
- Acute kidney injury
- Freedom from hemolytic anemia related to BASILICA TAVI
- 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 TAVI
- TAVI 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

Enrolling Sites

Site	City	Principal Investigator	Subjects enrolled
Emory University Hospital	Atlanta	Vasilis Babaliaros	10 Subjects
University of Washington	Seattle	Danny Dvir	10 Subjects
Henry Ford Hospital Systems	Detroit	Adam Greenbaum and Marvin Eng	7 subjects
Medstar Washington Hospital Center	Washington DC	Toby Rogers	3 subjects

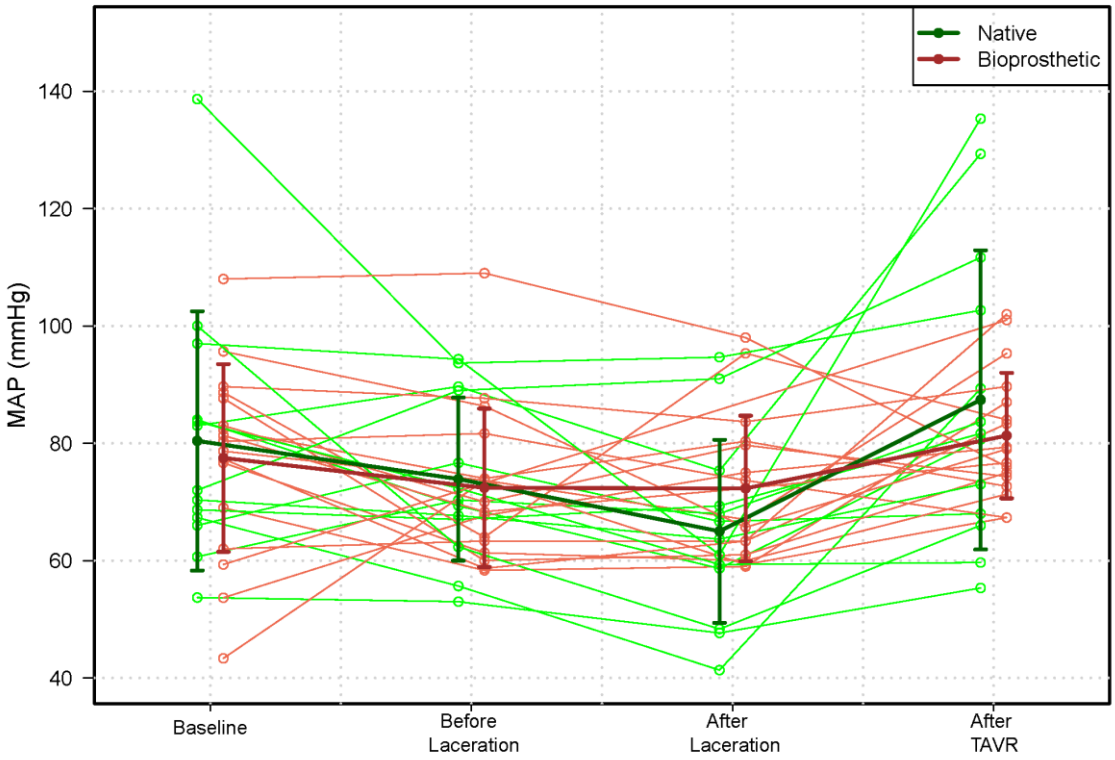
Supplement Table 6 Coronary obstruction risk factors and BASILICA technical success for 30 subjects

Age	Sex	TAVI setting	High risk features of bioprosthesis	Aortic valve mean gradient	Aortic regurg. severity	Annulus area (mm^2)	LCA height (mm)	RCA height (mm)	Left SOV width (mm)	Right SOV width (mm)	LCA VTC (mm)	RCA VTC (mm)	TAVI access	THV implanted	Valve size (mm)	# of leaflet targets	1st leaflet attempted	1st leaflet successful traversal	1st leaflet successful laceration	2nd leaflet attempted	2nd leaflet successful traversal	2nd leaflet successful laceration
83	F	Magna		51	Mild	260	9.7	15.7	30.3	27.7	7.8	5.0	Femoral	Evolut R	23	2	Right	Yes	Yes	Left	Yes	Yes
75	F	Magna		61	Mild	262	3.7	0.0	24.4	25.3	2.0	3.7	Transcaval	Evolut R	23	2	Right	Yes	Yes	Left	Yes	Yes
67	M	Magna Ease		41	None	265	5.2	6.4	25.5	24.9	4.4	4.0	Femoral	Evolut Pro	23	2	Right	Yes	Yes	Left	Yes	Yes
82	F	Magna Ease		43	None	268	6.3	8.9	24.6	23.9	2.2	4.0	Femoral	Sapien 3	23	2	Right	Yes	Yes	Left	Yes	Yes
92	F	Mitroflow	Ext. leaflets	33	Moderate	259	8.9	6.6	26.2	23.2	2.2	2.9	Femoral	Sapien 3	20	2	Right	Yes	Yes	Left	Yes	Yes
77	F	Mitroflow	Ext. leaflets	56	None	290	5.4	8.7	25.2	25.1	1.7	3.8	Femoral	Sapien 3	20	2	Right	No	N/A	Left	Yes	Yes
79	F	Mitroflow	Ext. leaflets	81	None	305	5.7	9.7	28.8	33.3	5.5	3.2	Transcaval	Evolut R	23	1	Left	Yes	Yes			
67	F	Trifecta	Ext. leaflets	43	Mild	277	4.1	5.6	25.9	24.2	3.4	3.9	Femoral	Evolut R	23	1	Left	Yes	Yes			

82	F	Trifecta	Ext. leaflets	76	None	226	2.0	4.9	24.3	21.8	4.0	2.8	Axillary	Evolut R	23	1	Left	Yes	Yes			
69	F	Trifecta	Ext. leaflets	73	Moderate	260	2.7	5.3	25.1	22.9	5.7	3.3	Femoral	Evolut R	23	1	Left	No	N/A			
62	M	Freestyle	Stentless	17	Moderate	393	7.2	12.1	31.1	39.2	3.3	4.6	Femoral	Evolut Pro	29	1	Left	Yes	Yes			
69	M	Toronto SPV	Stentless	9	Severe	477	3.9	4.2	30.0	31.6	3.8	5.2	Femoral	Evolut R	29	1	Left	Yes	Yes			
83	F	Magna		43	Moderate	262	12.3	11.7	26.4	27.2	2.9	5.6	Femoral	Evolut R	23	1	Left	Yes	Yes			
76	F	Magna		42	None	243	2.5	4.3	29.0	28.1	3.0	7.2	Femoral	Evolut R	23	1	Left	Yes	Yes			
74	M	Magna		37	Mild	489	3.3	6.9	28.6	27.9	3.2	5.1	Femoral	Sapien 3	26	1	Left	Yes	Yes			
73	F	Magna Ease		38	None	259	1.7	8.2	26.9	24.8	4.3	2.9	Femoral	Evolut R	23	1	Right	Yes	Yes			
81	M	Mosaic		45	None	293	13.7	6.7	32.6	28.7	5.5	4.2	Transaval	Sapien 3	23	1	Right	Yes	Yes			
74	F	Native		45	Mild	307	6.5	8.1	27.2	25.9	3.8	3.9	Transaval	Sapien 3	23	2	Right	Yes	Yes	Left	Yes	Yes
59	F	Native		39	Mild	227	12.2	11.3	20.8	20.5	3.5	2.4	Femoral	Evolut R	23	1	Right	Yes	Yes			
82	F	Native		43	Mild	306	11.4	12.4	26.0	25.8	5.7	2.3	Femoral	Sapien 3	20	1	Right	Yes	Yes			
62	F	Native		59	Mild	366	12.7	9.6	27.3	22.2	2.9	3.3	Femoral	Sapien 3	23	1	Right	Yes	Yes			
85	M	Native		45	Moderate	585	10.1	10.4	33.9	33.2	3.9	5.0	Femoral	Sapien 3	29	1	Left	Yes	Yes			
76	F	Native		34	Mild	471	13.2	11.4	31.8	31.0	4.1	5.9	Femoral	Sapien 3	26	1	Left	Yes	Yes			
76	F	Native		26	None	536	12.0	12.0	29.0	32.6	2.6	3.1	Transaval	Sapien 3	26	1	Left	Yes	Yes			
61	F	Native		53	Mild	234	10.9	10.1	20.7	20.3	1.6	1.3	Transaval	Sapien 3	20	1	Left	Yes	Yes			
75	F	Native		19	None	379	7.8	10.3	25.9	25.3	2.7	4.5	Femoral	Sapien 3	23	1	Left	Yes	Yes			
52	F	Native		48	Moderate	522	5.8	7.8	29.8	29.5	3.1	3.5	Femoral	Sapien 3	26	1	Left	Yes	Yes			
77	F	Native		46	Mild	274	13.3	13.8	24.3	23.1	2.7	4.7	Femoral	Evolut Pro	23	1	Left	Yes	Yes			
79	F	Native		22	None	446	8.8	13.8	29.0	29.7	1.7	4.3	Femoral	Sapien 3	26	1	Left	Yes	Yes			
82	F	Native		53	None	450	4.6	12.3	30.9	31.2	3.2	4.1	Femoral	Sapien 3	26	1	Left	Yes	Yes			

Supplement Figure 5 Procedure Hemodynamics

Mean arterial pressures for each patient is shown at baseline, before and after (*solo* or *doppio*) laceration, and after TAVI for native and bioprosthetic valves. Small decrements in mean arterial pressures were seen more often in native aortic valves. Only two subjects required transient increase in vasopressor support prior to TAVI.



Chapter Summary

BASILICA is a technique developed using transcatheter electrosurgery tools. Using guidewires, microcatheters, guiding catheters and non-ionic 5% dextrose infusion, charge is concentrated to first perforate the base of the aortic valve leaflet then lacerate the leaflet from base to tip. The split leaflet splays away from the coronary artery ostium when a transcatheter valve is implanted, maintaining flow to the coronary arteries.

Benchtop tests were performed on bioprosthetic aortic valves with bovine pericardial leaflets. The valves were submerged in a saline bath and traversed and cut with an electrified guidewire, demonstrating feasibility of transcatheter electrosurgery in these valves, and confirming leaflet splay after transcatheter valve implantation within the bioprosthetic valves. The procedure was tested in five anaesthetized pigs demonstrating central base to tip laceration in all animals. An important lesson about snaring high in the LVOT to prevent inadvertent mitral chordae laceration was learnt, as well as careful guidewire positioning for traversal. BASILCA was performed on a compassionate basis in seven patients with aortic valve failure in either native or bioprosthetic valves who were at prohibitive surgical risk. All had prohibitive risk of coronary artery obstruction from TAVI as predicted on pre-procedure CT. All patients had successful leaflet traversal and laceration, with no resulting coronary artery obstruction or stroke. No patient had hemodynamic compromise from BASILICA. In this early experience, back-up stents were pre-positioned in the coronary artery in case of obstruction. None were required for coronary obstruction, but one was deployed as it could not be retrieved past the transcatheter valve.

The procedure was then investigated in the prospective single arm NHLBI BASILICA IDE trial, with independent end point adjudication and core laboratory analysis of images. 30 subjects at high or prohibitive risk for surgical aortic valve replacement and high risk of coronary artery obstruction from TAVR were enrolled. BASILICA traversal and laceration was successful in 28 out of 30 patients. No patient had coronary artery obstruction of required re-intervention. There was one death and one disabling stroke at 30 days.

In developing this novel procedure and investigating it in a carefully designed clinical trial, the hypothesis that aortic valve leaflets can be precisely lacerated using transcatheter electrosurgery, and that controlled laceration may prevent blood flow obstruction following transcatheter valve implantation has been demonstrated. Accordingly, the second specific aim of this thesis has been addressed.

CHAPTER 5. FUTURE DIRECTIONS

LAMPOON has been demonstrated when using a transcatheter aortic valve (Sapien 3, Edwards Lifesciences) in the mitral position, anchored in native annular calcification or a surgical bioprostheses. Its compatibility with dedicated mitral devices remains untested. Many dedicated transcatheter mitral valves in their current iteration have a complete outer fabric covering which would not allow blood flow despite anterior mitral leaflet laceration. However, dynamic left ventricular outflow tract obstruction from systolic anterior motion of the mitral valve leaflet may be prevented by LAMPOON.

LAMPOON has been demonstrated in an anaesthetized pig predicted to have LVOT obstruction following Tendyne valve implantation(104). The Tendyne bioprosthetic mitral valve system is a tri-leaflet pericardial valve mounted in a coaxial dual-frame covered stent, fixed using an adjustable apical tether. The naïve pig had SAM after initial Tendyne valve implantation with an LVOT gradient of 26mmHg. Following retrieval of the Tendyne valve, LAMPOON was performed and the valve re-implanted. There was no SAM and the LVOT gradient reduced to 3mmHg [Figure 39].

LAMPOON with Tendyne valve implantation was performed in a patient on compassionate basis(104). The patient had risk factors for developing SAM and LVOT obstruction following Tendyne valve implantation based on his long anterior mitral valve leaflet, redundant chordae and acute aorto-mitral angulation. LAMPOON was performed and the Tendyne valve implanted without SAM or LVOT obstruction [Figure 39].

Like splitting a sail, splitting the anterior leaflet may prevent Bernoulli forces from dragging the leaflet towards the septum, which in turn could obstruct outflow and impair prosthetic sealing. However, LAMPOON can only alleviate LVOT obstruction from a reduced neo-LVOT, caused by valves that protrude towards the septum, in transcatheter valves with uncovered stent cells across the LVOT.

BASILICA has been performed in native valves and in bioprosthetic surgical valves. The effectiveness of BASILICA in failed transcatheter heart valves, where there is

excess leaflet material and an enclosing cage, remains untested. It is possible more extensive leaflet excision is required in these cases. Benchtop experiments with some common transcatheter heart valves demonstrate variability in leaflet splay, partly due to the external cage restricting leaflet splay and partly due to increased leaflet redundancy in second generation valve designs [Figure 40].

LAMPOON and BASILICA are performed using marketed devices off-label. Dedicated catheters and guidewires should simplify the procedure. Dedicated electrosurgery equipment may also reduce the variability in current losses in the present set-up. In its current form, transcatheter electrosurgery has been used to make simple linear cuts. Dedicated cutting and capture devices, and improved imaging, may enable more complex percutaneous resections and manipulations.

One relatively simple application is to enable TMVI after mitral valve repair. Edge-to-edge mitral valve repair with an Alfieri Stitch or MitraClip device may prohibit future transcatheter mitral valve replacement. Cutting the Alfieri stitch or MitraClip away from its anterior leaflet attachment has been demonstrated to create a single orifice where TMVI can be performed(121). The clip or stitch may be accessed antegrade via a transseptal approach or retrograde from the femoral arteries. Catheters are positioned in each mitral valve orifice and guidewire is passed from one and snared from the other. The Flying V is positioned along the anterior mitral valve leaflet edge of the clip or stitch, which is lacerated during 1-5s of radiofrequency energy application at 70W with a continuous dextrose infusion. The clip or stitch remains on the posterior mitral valve leaflet and TMVR is performed, pinning the liberated device to the posterior ventricular wall.

Finally, data on both LAMPOON and BASILICA are now being collected as part of the STS/ACC TVT Registry in the United States, which will provide real world data on a larger number of patients.

FIGURE 39 LAMPOON in Tendyne

A) Transthoracic echocardiogram of Tendyne implantation without LAMPOON in a pig demonstrating SAM causing LVOT obstruction and anterior PVL. B) Following LAMPOON, SAM, LVOT obstruction, and PVL are abolished. Transthoracic (C) and transesophageal (D) echocardiogram following LAMPOON and Tendyne valve implantation in a patient showing a split anterior leaflet and no SAM. E) CT with motion artefact in diastole with long anterior mitral leaflet with close approximation to the interventricular septum and acute aorto-mitral angulation. F) Post procedure CT in systole with no evidence of LVOT obstruction. LV=Left Ventricle; LA=Left Atrium; Ao=Aorta

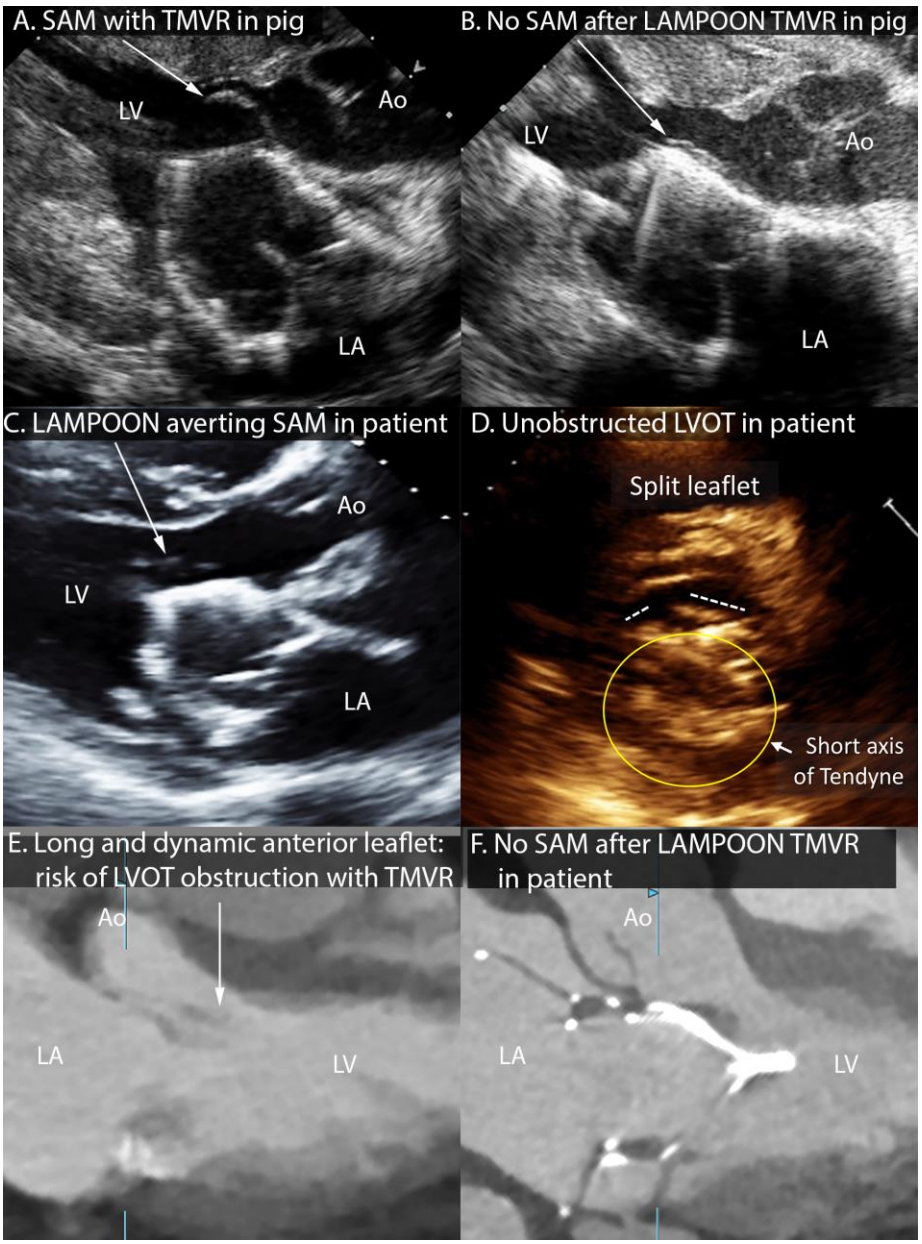
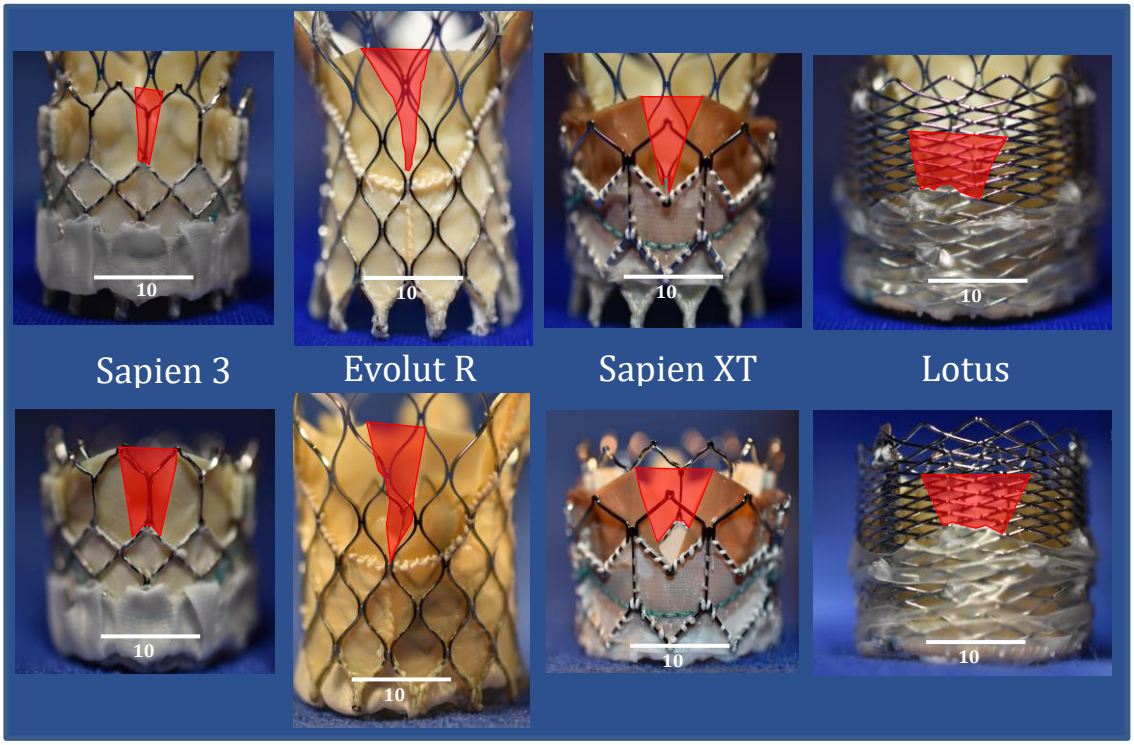


FIGURE 40 Splay characteristics after benchtop BASILICA and TAVR-in-TAVR in four common TAVR devices

The orifices created by BASILICA-splayed leaflets are depicted in red. The figure shows that early-generation TAVR devices (Sapien XT and Lotus) exhibited wider splay angles (50±11 vs 17±5 degrees, Student *t*-test p<0.01) and slit width (9±2 vs 5±2, p=0.05) after BASILICA *in vitro* than newer-generation TAVR devices (Sapien 3 and Evolut R).



CHAPTER 6. SUMMARY AND CONCLUSIONS

This thesis has attempted to achieve the specific aims set out. It demonstrates that the mitral and aortic valve leaflets can be precisely lacerated using transcatheter electrosurgery in animals and subsequently in patients. This laceration prevented obstruction in the left ventricular outflow tract in the case of LAMPOON and coronary artery obstruction in the case of BASILICA in patients predicted to be at high risk of obstruction.

Previous applications of transcatheter electrosurgery were limited to making pinhole perforations with the tip of an insulated guidewire. For more extensive tissue laceration, controlled targeted directional radiofrequency delivery is required, with greater care to avoid charring and coagulation during longer and higher energy applications. Simulation and benchtop experiments for transcatheter electrosurgery tissue laceration demonstrated feasibility of this technique. Selective denudation of the kinked inner surface of a guidewire with catheter insulation and blood displacement with non-ionic flush was demonstrated to be optimal for charge concentration for cutting.

For the development of two novel procedures, the technique was investigated in anesthetised pigs. Reproducible midline laceration was demonstrated in these experiments, in line with the left ventricular outflow tract in the case of LAMPOON and coronary artery ostia in the case of BASILICA.

Both procedures were translated into clinical care in selected high-risk patients with no other options on a compassionate basis.

Both procedures were studied prospectively in patients in FDA approved 30 patient early feasibility clinical trials.

In the LAMPOON trial, eligible patients were suitable for transcatheter mitral valve replacement except for prohibitive risk LVOT obstruction as predicted by CT. LAMPOON traversal and laceration was successful in all patients. LVOT obstruction was seen in three patients who were at risk from LVOT obstruction from the transcatheter heart valve skirt, which is an important exclusion criterion, and one

patient with a mid-leaflet laceration. The other patients did not demonstrate LVOT obstruction despite the high predicted risk without LAMPOON.

In the BASILICA trial, eligible patients were suitable for transcatheter aortic valve implantation except for the prohibitive risk of coronary artery obstruction as predicted by CT. BASILICA traversal and laceration was successful in 93% of patients. No patient developed coronary artery obstruction despite the high predicted risk without BASILICA.

These techniques enabled transcatheter valve replacement in otherwise ineligible patients. These patients all high risk of mortality with valve replacement surgery and so had no other options for treatment. LAMPOON and BASILICA have been included in the STS/ACC TVT Registry in the United States, which will provide valuable data in a large number of patients in the real-world setting.

Transcatheter electrosurgery takes us one step closer to bespoke “transcatheter surgery” for patients.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005-11.
2. Smith CR, Leon MB, Mack MJ et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
3. 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.
4. Adams DH, Popma JJ, Reardon MJ et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
5. Reardon MJ, Van Mieghem NM, Popma JJ et al. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2017;376:1321-1331.
6. Mack MJ, Leon MB, Thourani VH et al. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med 2019.
7. Popma JJ, Deeb GM, Yakubov SJ et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med 2019.
8. Regueiro A, Granada JF, Dagenais F, Rodes-Cabau J. Transcatheter Mitral Valve Replacement: Insights From Early Clinical Experience and Future Challenges. J Am Coll Cardiol 2017;69:2175-2192.
9. Guerrero ME. MITRAL (Mitral implantation of transcatheter valves): 30-Day Outcomes of Transcatheter Mitral Valve Replacement in Pa1ents With Severe Mitral Valve Disease Secondary to Mitral Annular Calcification or Failed Annuloplasty Rings. Transcatheter Therapeutics. Denver, Colorado, 2017.
10. Guerrero M, Urena M, Himbert D et al. 1-Year Outcomes of Transcatheter Mitral Valve Replacement in Patients With Severe Mitral Annular Calcification. J Am Coll Cardiol 2018;71:1841-1853.

11. Ribeiro HB, Rodes-Cabau J, Blanke P et al. Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. Eur Heart J 2018;39:687-695.
12. Ribeiro HB, Webb JG, Makkar RR et al. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. J Am Coll Cardiol 2013;62:1552-62.
13. Greenbaum AB, Babaliaros VC, Chen MY et al. Transcaval Access and Closure for Transcatheter Aortic Valve Replacement: A Prospective Investigation. J Am Coll Cardiol 2017;69:511-521.
14. Justino H, Benson LN, Nykanen DG. Transcatheter creation of an atrial septal defect using radiofrequency perforation. Catheter Cardiovasc Interv 2001;54:83-7.
15. Nicholson W, Harvey J, Dhawan R. E-CART (ElectroCautery-Assisted Re-enTry) of an Aorto-Ostial Right Coronary Artery Chronic Total Occlusion: First-in-Man. JACC Cardiovasc Interv 2016;9:2356-2358.
16. Blanke P, Naoum C, Dvir D et al. Predicting LVOT Obstruction in Transcatheter Mitral Valve Implantation: Concept of the Neo-LVOT. JACC Cardiovasc Imaging 2016:10.1016/j.jcmg.2016.01.005.
17. Pearce JA. Electrosurgery. 1 ed. New York: Wiley Medical, 1986.
18. Benson LN, Nykanen D, Collison A. Radiofrequency perforation in the treatment of congenital heart disease. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2002;56:72-82.
19. Honig WM. The mechanism of cutting in electrosurgery. IEEE Trans Biomed Eng 1975;22:58-62.
20. Baerlocher MO, Asch MR, Myers A. Successful recanalization of a longstanding complete left subclavian vein occlusion by radiofrequency perforation with use of a radiofrequency guide wire. J Vasc Interv Radiol 2006;17:1703-6.
21. Calkins H, Hindricks G, Cappato R et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on

catheter and surgical ablation of atrial fibrillation. Heart Rhythm 2017;14:e275-e444.

22. Duck FA. Chapter 6 - Electrical Properties of Tissue. In: Duck FA, editor Physical Properties of Tissues. London: Academic Press, 1990:167-223.
23. Yoon G. Dielectric properties of glucose in bulk aqueous solutions: Influence of electrode polarization and modeling. Biosens Bioelectron 2011;26:2347-53.
24. Ebnesajjad S. 12 - Electrical and Electronic Applications of Expanded PTFE. In: Ebnesajjad S, editor Expanded PTFE Applications Handbook. Oxford: William Andrew Publishing, 2017:253-258.
25. Khan JM, Lederman RJ. Transcatheter electrosurgery in bipolar or monopolar modes. Catheter Cardiovasc Interv 2018;91:1052-1053.
26. Haines DE, Watson DD. Tissue heating during radiofrequency catheter ablation: a thermodynamic model and observations in isolated perfused and superfused canine right ventricular free wall. Pacing Clin Electrophysiol 1989;12:962-76.
27. Kelly HAW, Grant E. Electrosurgery. 1st edition ed: W.B. Saunders Co, 1932.
28. Shimko N, Savard P, Shah K. Radio frequency perforation of cardiac tissue: modelling and experimental results. Med Biol Eng Comput 2000;38:575-82.
29. Rosenthal E, Qureshi SA, Chan KC et al. Radiofrequency-assisted balloon dilatation in patients with pulmonary valve atresia and an intact ventricular septum. Br Heart J 1993;69:347-51.
30. Justo RN, Nykanen DG, Williams WG, Freedom RM, Benson LN. Transcatheter perforation of the right ventricular outflow tract as initial therapy for pulmonary valve atresia and intact ventricular septum in the newborn. Catheterization and cardiovascular diagnosis 1997;40:408-13.
31. Hausdorf G, Schulze-Neick I, Lange PE. Radiofrequency-assisted "reconstruction" of the right ventricular outflow tract in muscular pulmonary atresia with ventricular septal defect. Br Heart J 1993;69:343-6.

32. Hijazi ZM, Patel H, Cao QL, Warner K. Transcatheter retrograde radio-frequency perforation of the pulmonic valve in pulmonary atresia with intact ventricular septum, using a 2 French catheter. Catheterization and cardiovascular diagnosis 1998;45:151-4.
33. Wang JK, Wu MH, Chang CI, Chen YS, Lue HC. Outcomes of transcatheter valvotomy in patients with pulmonary atresia and intact ventricular septum. Am J Cardiol 1999;84:1055-60.
34. Veldtman GR, Hartley A, Visram N, Benson LN. Radiofrequency applications in congenital heart disease. Expert Rev Cardiovasc Ther 2004;2:117-26.
35. Krasemann T. Radiofrequency perforation: the optimum treatment for pulmonary atresia? Heart 2009;95:1473-4.
36. Foerst JR, Kim D, May TP. Percutaneous electrosurgical technique for treatment of subclavian vein occlusion: Application of transcaval techniques. HeartRhythm Case Rep 2017;3:551-554.
37. Iafrati M, Maloney S, Halin N. Radiofrequency thermal wire is a useful adjunct to treat chronic central venous occlusions. J Vasc Surg 2012;55:603-6.
38. Fink C, Peuster M, Bertram H, Hausdorf G. Transcatheter recanalization of the left main pulmonary artery after four years of complete occlusion. Catheter Cardiovasc Interv 2001;53:81-4.
39. Pedra CA, Filho RM, Arrieta RS, Tellez R, Fontes VF. Recanalization of a discrete atretic right pulmonary artery segment with a new radiofrequency system. Catheter Cardiovasc Interv 2003;60:82-7.
40. Almashham Y, Dahdah N, Miro J. Use of radiofrequency then stent implantation for recanalization of complete aorta coarctation. Pediatr Cardiol 2008;29:207-9.
41. Baim DS, Braden G, Heuser R et al. Utility of the Safe-Cross-guided radiofrequency total occlusion crossing system in chronic coronary total occlusions. The American journal of cardiology 2004;94:853-8.
42. Kanno D, Tsuchikane E, Nasu K et al. Initial results of a first-in-human study on the PlasmaWire System, a new radiofrequency wire for

recanalization of chronic total occlusions. Catheter Cardiovasc Interv 2017.

43. Nageotte SJ, Lee JW, El-Said HG, Moore JW, Ratnakaya K. Transcatheter Electrosurgery Rescue: Jailed Pulmonary Artery Following Melody Pulmonary Valve Replacement. JACC Cardiovascular Interventions 2019;[In Press].
44. Hsu JC, Badhwar N, Gerstenfeld EP et al. Randomized trial of conventional transseptal needle versus radiofrequency energy needle puncture for left atrial access (the TRAVERSE-LA study). J Am Heart Assoc 2013;2:e000428.
45. Hill SL, Mizelle KM, Vellucci SM, Feltes TF, Cheatham JP. Radiofrequency perforation and cutting balloon septoplasty of intact atrial septum in a newborn with hypoplastic left heart syndrome using transesophageal ICE probe guidance. Catheter Cardiovasc Interv 2005;64:214-7.
46. Bidart C, Vaseghi M, Cesario DA et al. Radiofrequency current delivery via transseptal needle to facilitate septal puncture. Heart Rhythm 2007;4:1573-6.
47. Gordon BM, Levi DS, Shannon KM. Electrosurgical energy in combination with a transseptal needle: a novel method for the creation of an atrial communication in hypoplastic left heart syndrome with intact atrial septum. Catheter Cardiovasc Interv 2009;73:113-6.
48. Maisano F, La Canna G, Latib A et al. Transseptal access for MitraClip(R) procedures using surgical diathermy under echocardiographic guidance. EuroIntervention 2012;8:579-86.
49. Khan JM, Rogers T, Eng MH, Lederman RJ, Greenbaum AB. Guidewire electrosurgery-assisted trans-septal puncture. Catheter Cardiovasc Interv 2017.
50. Lin CH, Huddleston C, Balzer DT. Transcatheter ventricular septal defect (VSD) creation for restrictive VSD in double-outlet right ventricle. Pediatr Cardiol 2013;34:743-7.
51. Santangeli P, Shaw GC, Marchlinski FE. Radiofrequency Wire Facilitated Interventricular Septal Access for Catheter Ablation of Ventricular

Tachycardia in a Patient With Aortic and Mitral Mechanical Valves. Circulation Arrhythmia and electrophysiology 2017;10.

52. Betts TR, Gamble JH, Khiani R, Bashir Y, Rajappan K. Development of a technique for left ventricular endocardial pacing via puncture of the interventricular septum. Circulation Arrhythmia and electrophysiology 2014;7:17-22.
53. Gamble JHP, Herring N, Ginks MR, Rajappan K, Bashir Y, Betts TR. Endocardial left ventricular pacing across the interventricular septum for cardiac resynchronization therapy: Clinical results of a pilot study. Heart Rhythm 2018;15:1017-1022.
54. Khan JM, Rogers T, Schenke WH et al. Transcatheter pledget-assisted suture tricuspid annuloplasty (PASTA) to create a double-orifice valve. Catheter Cardiovasc Interv 2018;92:E175-E184.
55. Nickenig G, Schueler R, Dager A et al. Treatment of Chronic Functional Mitral Valve Regurgitation With a Percutaneous Annuloplasty System. J Am Coll Cardiol 2016;67:2927-36.
56. Halabi M, Ratnayaka K, Faranesh AZ, Chen MY, Schenke WH, Lederman RJ. Aortic access from the vena cava for large caliber transcatheter cardiovascular interventions: pre-clinical validation. J Am Coll Cardiol 2013;61:1745-6.
57. Greenbaum AB, O'Neill WW, Paone G et al. Caval-aortic access to allow transcatheter aortic valve replacement in otherwise ineligible patients: initial human experience. J Am Coll Cardiol 2014;63:2795-804.
58. Rogers T, Greenbaum AB, Babaliaros VC et al. Dedicated closure device for transcaval access closure: from concept to first-in-human testing. JACC Cardiovasc Interven 2019;[In Press].
59. Lederman RJ, Babaliaros VC, Rogers T et al. The Fate of Transcaval Access Tracts: 12-Month Results of the Prospective NHLBI Transcaval Transcatheter Aortic Valve Replacement Study. JACC Cardiovasc Interv 2019;12:448-456.
60. Costa G, De Backer O, Pilgrim T et al. Initial European experience with transcaval transcatheter aortic valve implantation. EuroIntervention 2019.

61. Kamioka N, Patel A, Burke MA, Greenbaum A, Babaliaros V. Biventricular Impella placement via complete venous access. Catheter Cardiovasc Interv 2019;93:E343-E345.
62. Schranz D, Kerst G, Menges T et al. Transcatheter creation of a reverse Potts shunt in a patient with severe pulmonary arterial hypertension associated with Moyamoya syndrome. EuroIntervention 2015;11:121.
63. Ratnayaka K, Moore JW, Rios R, Lederman RJ, Hegde SR, El-Said HG. First-in-Human Closed-Chest Transcatheter Superior Cavopulmonary Anastomosis. J Am Coll Cardiol 2017;70:745-752.
64. Ratnayaka K, Rogers T, Schenke WH et al. Magnetic Resonance Imaging-Guided Transcatheter Cavopulmonary Shunt. JACC Cardiovasc Interv 2016;9:959-70.
65. Levi DS, Danon S, Gordon B et al. Creation of transcatheter aortopulmonary and cavopulmonary shunts using magnetic catheters: feasibility study in swine. Pediatr Cardiol 2009;30:397-403.
66. Lederman RJ, O'Neill WW, Greenbaum AB. Transcaval access for TAVR across a polyester aortic graft. Catheter Cardiovasc Interv 2015;85:1270-3.
67. Tse LW, Lindsay TF, Roche-Nagle G, Oreopoulos GD, Ouzounian M, Tan KT. Radiofrequency in situ fenestration for aortic arch vessels during thoracic endovascular repair. J Endovasc Ther 2015;22:116-21.
68. Gabriel C. Compilation of the dielectric properties of body tissues at RF and microwave frequencies. Brooks Airforce Base, Texas, 1996.
69. Eleid MF, Cabalka AK, Williams MR et al. Percutaneous Transvenous Transseptal Transcatheter Valve Implantation in Failed Bioprosthetic Mitral Valves, Ring Annuloplasty, and Severe Mitral Annular Calcification. JACC Cardiovasc Interv 2016:10.1016/j.jcin.2016.02.041.
70. Sud K, Agarwal S, Parashar A et al. Degenerative Mitral Stenosis: Unmet Need for Percutaneous Interventions. Circulation 2016;133:1594-604.
71. Lee KS, Stewart WJ, Lever HM, Underwood PL, Cosgrove DM. Mechanism of outflow tract obstruction causing failed mitral valve repair. Anterior displacement of leaflet coaptation. Circulation 1993;88:II24-9.

72. Mihaileanu S, Marino JP, Chauvaud S et al. Left ventricular outflow obstruction after mitral valve repair (Carpentier's technique). Proposed mechanisms of disease. Circulation 1988;78:I78-84.
73. Wang DD, Eng M, Greenbaum A et al. Predicting LVOT Obstruction After TMVR. JACC Cardiovascular imaging 2016;10.1016/j.jcmg.2016.01.017.
74. Maisano F, Alfieri O, Banai S et al. The future of transcatheter mitral valve interventions: competitive or complementary role of repair vs. replacement? Eur Heart J 2015;36:1651-9.
75. Deharo P, Urena M, Himbert D et al. Bail-Out Alcohol Septal Ablation for Left Ventricular Outflow Tract Obstruction After Transcatheter Mitral Valve Replacement. JACC Cardiovasc Interv 2016;9:e73-6.
76. Guerrero M, Urena M, Pursnani A et al. Balloon expandable transcatheter heart valves for native mitral valve disease with severe mitral annular calcification. The Journal of cardiovascular surgery 2016;57:401-9.
77. Descoutures F, Himbert D, Maisano F et al. Transcatheter valve-in-ring implantation after failure of surgical mitral repair. Eur J Cardiothorac Surg 2013;44:e8-15.
78. Bouleti C, Fassa AA, Himbert D et al. Transfemoral implantation of transcatheter heart valves after deterioration of mitral bioprosthesis or previous ring annuloplasty. JACC Cardiovasc Interv 2015;8:83-91.
79. Gersh BJ, Maron BJ, Bonow RO et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy. J Am Coll Cardiol 2011;58:2703-38.
80. Robinson TN, Barnes KS, Govekar HR, Stiegmann GV, Dunn CL, McGreevy FT. Antenna coupling--a novel mechanism of radiofrequency electrosurgery complication: practical implications. Ann Surg 2012;256:213-8.
81. Takami M, Lehmann HI, Parker KD, Welker KM, Johnson SB, Packer DL. Effect of Left Atrial Ablation Process and Strategy on Microemboli Formation During Irrigated Radiofrequency Catheter Ablation in an In Vivo Model. Circulation Arrhythmia and electrophysiology 2016;9:e003226.

82. Anderson RH, Spicer DE, Hlavacek AM, Cook AC, Backer CL. Wilcox's Surgical Anatomy of the Heart. 4/e ed: Cambridge University Press, 2013.
83. Come PC, Riley MF, Weintraub RM et al. Dynamic left ventricular outflow tract obstruction when the anterior leaflet is retained at prosthetic mitral valve replacement. Ann Thorac Surg 1987;43:561-3.
84. Esper E, Ferdinand FD, Aronson S, Karp RB. Prosthetic mitral valve replacement: late complications after native valve preservation. Ann Thorac Surg 1997;63:541-3.
85. Bapat V, Pirone F, Kapetanakis S, Rajani R, Niederer S. Factors influencing left ventricular outflow tract obstruction following a mitral valve-in-valve or valve-in-ring procedure, part 1. Catheter Cardiovasc Interv 2015;86:747-60.
86. Hamid NB, Khalique OK, Monaghan MJ et al. Transcatheter Valve Implantation in Failed Surgically Inserted Bioprosthesis: Review and Practical Guide to Echocardiographic Imaging in Valve-in-Valve Procedures. JACC Cardiovascular imaging 2015;8:960-79.
87. Greenbaum AB, Condado JF, Eng MH et al. Long or redundant leaflet complicating transcatheter mitral valve replacement: case vignettes that advocate for removal or reduction of the anterior mitral leaflet. [Under Review] 2016.
88. He S, Hopmeyer J, Lefebvre XP, Schwammenthal E, Yoganathan AP, Levine RA. Importance of leaflet elongation in causing systolic anterior motion of the mitral valve. J Heart Valve Dis 1997;6:149-59.
89. Guerrero M, Wang DD, O'Neill W. Percutaneous alcohol septal ablation to acutely reduce left ventricular outflow tract obstruction induced by transcatheter mitral valve replacement. Catheter Cardiovasc Interv 2016.
90. Murashita T, Suri RM, Daly RC. Sapien XT Transcatheter Mitral Valve Replacement Under Direct Vision in the Setting of Significant Mitral Annular Calcification. Ann Thorac Surg 2016;101:1171-4.
91. Dahle G, Rein KA, Fiane AE. Edwards SAPIEN XT in Native Stenotic Mitral Valve, Open Technique on Cardiopulmonary Bypass: An Option, But Safe? Innovations 2016.

92. Guerrero M, Dvir D, Himbert D et al. Transcatheter Mitral Valve Replacement in Native Mitral Valve Disease With Severe Mitral Annular Calcification: Results From the First Multicenter Global Registry. JACC Cardiovasc Interv 2016;9:1361-71.
93. David TE. Mitral valve replacement with preservation of chordae tendinae: rationale and technical considerations. Ann Thorac Surg 1986;41:680-2.
94. Lederman RJ, Babaliaros VC, Greenbaum AB. How to perform transcaval access and closure for transcatheter aortic valve implantation. Catheter Cardiovasc Interv 2015;86:1242-54.
95. Geske JB, Cullen MW, Sorajja P, Ommen SR, Nishimura RA. Assessment of left ventricular outflow gradient: hypertrophic cardiomyopathy versus aortic valvular stenosis. JACC Cardiovasc Interv 2012;5:675-81.
96. Yeo TC, Freeman WK, Schaff HV, Orszulak TA. Mechanisms of hemolysis after mitral valve repair: assessment by serial echocardiography. J Am Coll Cardiol 1998;32:717-23.
97. Reardon MJ, David TE. Mitral valve replacement with preservation of the subvalvular apparatus. Curr Opin Cardiol 1999;14:104-10.
98. Cribier A, Eltchaninoff H, Tron C et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. J Am Coll Cardiol 2006;47:1214-23.
99. Hanzel GS, Harrity PJ, Schreiber TL, O'Neill WW. Retrograde percutaneous aortic valve implantation for critical aortic stenosis. Catheter Cardiovasc Interv 2005;64:322-6.
100. Yoon SH, Whisenant BK, Bleiziffer S et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J 2018.
101. Wang DD, Eng MH, Greenbaum AB et al. Validating a prediction modeling tool for left ventricular outflow tract (LVOT) obstruction after transcatheter mitral valve replacement (TMVR). Catheter Cardiovasc Interv 2018;92:379-387.

102. Bapat V, Rajagopal V, Meduri C et al. Early Experience With New Transcatheter Mitral Valve Replacement. J Am Coll Cardiol 2018;71:12-21.
103. Urena M, Vahanian A, Sondergaard L. Patient selection for transcatheter mitral valve implantation: why is it so hard to find patients? EuroIntervention 2018;14:AB83-AB90.
104. Khan JM, Lederman RJ, Devireddy CM et al. LAMPOON to Facilitate Tendyne Transcatheter Mitral Valve Replacement. JACC Cardiovasc Interv 2018;11:2014-2017.
105. Praz F, Khalique OK, Lee R et al. Transatrial implantation of a transcatheter heart valve for severe mitral annular calcification. J Thorac Cardiovasc Surg 2018;156:132-142.
106. Urena M, Himbert D, Brochet E et al. Transseptal Transcatheter Mitral Valve Replacement Using Balloon-Expandable Transcatheter Heart Valves: A Step-by-Step Approach. JACC Cardiovasc Interv 2017;10:1905-1919.
107. Babaliaros VC, Greenbaum AB, Khan JM et al. Intentional Percutaneous Laceration of the Anterior Mitral Leaflet to Prevent Outflow Obstruction During Transcatheter Mitral Valve Replacement: First-in-Human Experience. JACC Cardiovasc Interv 2017;10:798-809.
108. Khan JM, Rogers T, Babaliaros VC, Fusari M, Greenbaum AB, Lederman RJ. Predicting Left Ventricular Outflow Tract Obstruction Despite Anterior Mitral Leaflet Resection: The "Skirt NeoLVOT". JACC Cardiovasc Imaging 2018;11:1356-1359.
109. Stone GW, Adams DH, Abraham WT et al. Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document From the Mitral Valve Academic Research Consortium. J Am Coll Cardiol 2015;66:308-21.
110. Urena M, Brochet E, Lecomte M et al. Clinical and haemodynamic outcomes of balloon-expandable transcatheter mitral valve implantation: a 7-year experience. Eur Heart J 2018;39:2679-2689.

111. Yoon SH, Whisenant BK, Bleiziffer S et al. Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings. J Am Coll Cardiol 2017;70:1121-1131.
112. Zoghbi WA, Chambers JB, Dumesnil JG et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound. J Am Soc Echocardiogr 2009;22:975-1014.
113. Capodanno D, Petronio AS, Prendergast B 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;38:3382-3390.
114. Kamioka N, Babaliaros V, Morse MA et al. Comparison of Clinical and Echocardiographic Outcomes After Surgical Redo Mitral Valve Replacement and Transcatheter Mitral Valve-in-Valve Therapy. JACC Cardiovasc Interv 2018;11:1131-1138.
115. Muller DWM, Farivar RS, Jansz P et al. Transcatheter Mitral Valve Replacement for Patients With Symptomatic Mitral Regurgitation: A Global Feasibility Trial. J Am Coll Cardiol 2017;69:381-391.
116. Eng MH, Greenbaum A, Wang DD et al. Thrombotic valvular dysfunction with transcatheter mitral interventions for postsurgical failures. Catheter Cardiovasc Interv 2017;90:321-328.
117. Khan JM, Lederman RJ. Unnatural milieu: Thrombus after transcatheter mitral valve replacement. Catheter Cardiovasc Interv 2017;90:329-330.
118. Khan JM, Lederman RJ. Adventures across the second dimension: Predicting left ventricular outflow tract obstruction following transcatheter mitral valve replacement. Catheter Cardiovasc Interv 2018;92:388-389.
119. Kohli K, Wei ZA, Yoganathan AP, Oshinski JN, Leipsic J, Blanke P. Transcatheter Mitral Valve Planning and the Neo-LVOT: Utilization of Virtual Simulation Models and 3D Printing. Curr Treat Options Cardiovasc Med 2018;20:99.

120. De Vecchi A, Marlevi D, Nordsletten DA et al. Left ventricular outflow obstruction predicts increase in systolic pressure gradients and blood residence time after transcatheter mitral valve replacement. Sci Rep 2018;8:15540.
121. Khan JM, Lederman RJ, Sanon S et al. Transcatheter Mitral Valve Replacement After Transcatheter Electrosurgical Laceration of Alfieri STItCh (ELASTIC): First-in-Human Report. JACC Cardiovasc Interv 2018;11:808-811.
122. Khan JM, Dvir D, Greenbaum AB et al. Transcatheter Laceration of Aortic Leaflets to Prevent Coronary Obstruction During Transcatheter Aortic Valve Replacement: Concept to First-in-Human. JACC Cardiovasc Interv 2018;11:677-689.
123. Dvir D, Webb JG, Bleiziffer S et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA : the journal of the American Medical Association 2014;312:162-70.
124. Webb JG, Mack MJ, White JM et al. Transcatheter Aortic Valve Implantation Within Degenerated Aortic Surgical Bioprostheses: PARTNER 2 Valve-in-Valve Registry. J Am Coll Cardiol 2017;69:2253-2262.
125. Ribeiro HB, Rodés-Cabau J, Blanke P et al. Incidence, Predictors and Clinical Outcomes of Coronary Obstruction Following Transcatheter Aortic Valve Replacement for Degenerative Bioprosthetic Surgical Valves: Insights from the VIVID Registry [In Press]. Eur Heart J 2017.
126. Yamamoto M, Shimura T, Kano S et al. Impact of preparatory coronary protection in patients at high anatomical risk of acute coronary obstruction during transcatheter aortic valve implantation. International journal of cardiology 2016;217:58-63.
127. Abramowitz Y, Chakravarty T, Jilaihawi H et al. Clinical impact of coronary protection during transcatheter aortic valve implantation: first reported series of patients. EuroIntervention 2015;11:572-81.
128. Ribeiro HB, Rodés-Cabau J, Blanke P et al. Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic

valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. Eur Heart J 2017.

129. Chhatriwalla AK, Allen KB, Saxon JT et al. Bioprosthetic Valve Fracture Improves the Hemodynamic Results of Valve-in-Valve Transcatheter Aortic Valve Replacement. Circ Cardiovasc Interv 2017;10.
130. Kappetein AP, Head SJ, Genereux P et al. 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.
131. Dvir D, Webb J, Brecker S et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation 2012;126:2335-44.
132. Dvir D. Transcatheter Aortic Valve-in-Valve Implantations: Lessons From Bench to Bedside [Oral presentation]. Transcatheter valve therapies. Chicago, IL, 2017.
133. Valsecchi O, Vassileva A. The chimney technique during valve in valve TAVR in stentless Freestyle [Oral presentation]. Joint Interventional Meeting Milan (JIM) Milan, 2017.
134. Waksman R, Rogers T, Torguson R et al. Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic Severe Aortic Stenosis. J Am Coll Cardiol 2018.
135. Jabbour RJ, Tanaka A, Finkelstein A et al. Delayed Coronary Obstruction After Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2018;71:1513-1524.
136. Lederman RJ, Babaliaros VC, Rogers T et al. State of the Art. How to prevent coronary obstruction during TAVR: from CT to BASILICA. [Under review, JACC Cardiovascular Interventions] 2019.
137. Blanke P, Soon J, Dvir D et al. Computed tomography assessment for transcatheter aortic valve in valve implantation: The vancouver approach to predict anatomical risk for coronary obstruction and other considerations. Journal of cardiovascular computed tomography 2016;10:491-499.

138. Makkar RR, Fontana G, Jilaihawi H et al. Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves. The New England journal of medicine 2015;373:2015-24.
139. Khalique OK, Hahn RT, Gada H et al. Quantity and location of aortic valve complex calcification predicts severity and location of paravalvular regurgitation and frequency of post-dilation after balloon-expandable transcatheter aortic valve replacement. JACC Cardiovasc Interv 2014;7:885-94.
140. Spertus JA, Jones PG. Development and Validation of a Short Version of the Kansas City Cardiomyopathy Questionnaire. Circ Cardiovasc Qual Outcomes 2015;8:469-76.
141. Lederman RJ, Greenbaum AB, Rogers T, Khan JM, Fusari M, Chen MY. Anatomic Suitability for Transcaval Access Based on Computed Tomography. JACC Cardiovasc Interv 2017;10:1-10.
142. Kapadia SR, Kodali S, Makkar R et al. Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement. J Am Coll Cardiol 2017;69:367-377.
143. Wendler O, Schymik G, Treede H et al. SOURCE 3 Registry: Design and 30-Day Results of the European Postapproval Registry of the Latest Generation of the SAPIEN 3 Transcatheter Heart Valve. Circulation 2017;135:1123-1132.
144. Grube E, Van Mieghem NM, Bleiziffer S et al. Clinical Outcomes With a Repositionable Self-Expanding Transcatheter Aortic Valve Prosthesis: The International FORWARD Study. J Am Coll Cardiol 2017;70:845-853.
145. Herrmann HC, Daneshvar SA, Fonarow GC et al. Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement: From the STS/ACC TVT Registry. J Am Coll Cardiol 2018;72:2701-2711.
146. Chakravarty T, Sondergaard L, Friedman J et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383-2392.

147. Midha PA, Raghav V, Sharma R et al. The Fluid Mechanics of Transcatheter Heart Valve Leaflet Thrombosis in the Neosinus. Circulation 2017;136:1598-1609.
148. Kamioka N, Lederman RJ, Khan JM et al. BI-SILICA During Transcatheter Aortic Valve Replacement for Noncalcific Aortic Insufficiency: Initial Human Experience. JACC Cardiovasc Interv 2018;11:2237-2239.