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Optimal timing of TEVAR in Uncomplicated Type B Aortic Dissection:

Implications from clinical outcomes, and biomechanical and histological analysis of acute versus chronic aortic dissection flaps

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By Xiaoying Lou

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Optimal medical therapy(OMT) is the standard-of-care in the management of uncomplicated-type-B-aortic-dissection(TBAD) with operative intervention indicated if complications arise in the chronic-phase. However, growing evidence suggests that thoracic endovascular aortic repair(TEVAR) more effectively remodels the dissected aorta in the acute-phase. This thesis examined the impact of TEVAR on short-and long-term survival in uncomplicated TBAD patients(Aim 1). Additionally, we characterized changes in biomechanics and microstructure between acute-vs-chronic dissection flaps that may underlie aortic-remodeling(Aim 2).

Methods:

Aim 1:A review of our institutional database from 2000-2016 identified 398 patients diagnosed with TBAD. At index hospitalization, complicated patients underwent TEVAR(aTEVAR,n=80) and uncomplicated patients received OMT(n=318). Uncomplicated patients were divided into subgroups based upon final treatment received:1)TEVAR(cTEVAR);2)open aortic replacement(OPEN);and 3)OMT.

Aim 2:Dissection flaps were obtained from patients presenting for open aortic replacement to treat acute type A(ACUTE) or chronic type B(CHRONIC) aortic dissection(n=10 each). Tissues were subjected to biaxial testing circumferentially and longitudinally with stiffness quantified by the tangent modulus(TM) in the low and high linear-regions of the biaxial response curves. Qualitative histological analyses of elastin and collagen organization were also conducted.

Results:

Among uncomplicated TBAD patients, 146(45.9%) failed OMT and underwent open(n=59) or endovascular(n=87) repair in the chronic phase. There was a trend towards improved long-term survival in complicated TBAD patients(complicated 84.1% vs uncomplicated 58.9%,p=0.17). Intervention-free survival at 5 and 10 years for all uncomplicated patients was 49.4% and 30.9%.

On biaxial testing, while stiffness between ACUTE and CHRONIC was similar circumferentially(chronic vs acute ratio:TM_{low}1.36,p=0.656, and TM_{high}0.42,p=0.067), in the longitudinal direction, CHRONIC was over 3-fold stiffer than ACUTE(chronic vs acute ratio:TM_{low}3.45,p=0.011 and TM_{high}3.76,p=0.016). Histology corroborated these findings, demonstrating increased fibrosis and loss of collagen fiber organization in CHRONIC.

Conclusions:

Despite being the highest-risk subgroup of TBAD patients, complicated TBAD patients receiving TEVAR in the acute-phase had improved survival compared to uncomplicated patients receiving any intervention in the chronic-phase. The loss of anisotropy, increased fibrosis and stiffness as a dissection flap transitions from the acute- to chronic-phase may explain the worse aortic-remodeling outcomes after TEVAR in chronic TBAD. TEVAR at index hospitalization may serve as optimal therapy for uncomplicated TBAD.

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Despite being the highest-risk subgroup of TBAD patients, complicated TBAD patients receiving TEVAR in the acute-phase had improved survival compared to uncomplicated patients receiving any intervention in the chronic-phase. The loss of anisotropy, increased fibrosis and stiffness as a dissection flap transitions from the acute- to chronic-phase may explain the worse aortic-remodeling outcomes after TEVAR in chronic TBAD. TEVAR at index hospitalization may serve as optimal therapy for uncomplicated TBAD.

INTRODUCTION

Thoracic aortic dissections are associated with high morbidity and mortality, accounting for nearly 14,000 deaths in the United States each year (1). While 90% of type A dissections are treated with open surgery upon initial presentation, the standard of care for type B aortic dissections (**TBADs**), entry site tear occurs distal to the left subclavian artery, depends on whether the patient presents with *complications* such as malperfusion or rupture (Figure 1).

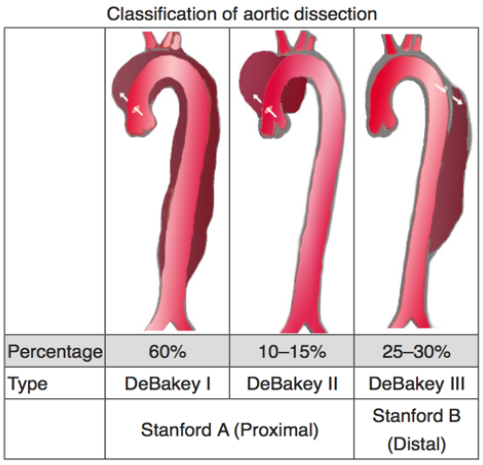

Figure 1. Classification of aortic dissection

In recent years, thoracic endovascular aortic repair (**TEVAR**) has been established as the treatment of choice for acute ***complicated*** TBADs (Figure 2). In contrast, the management of acute ***uncomplicated*** TBADs remains controversial. Traditionally, these patients are treated medically with intervention (open surgery or TEVAR) indicated in the chronic phase when complications arise.

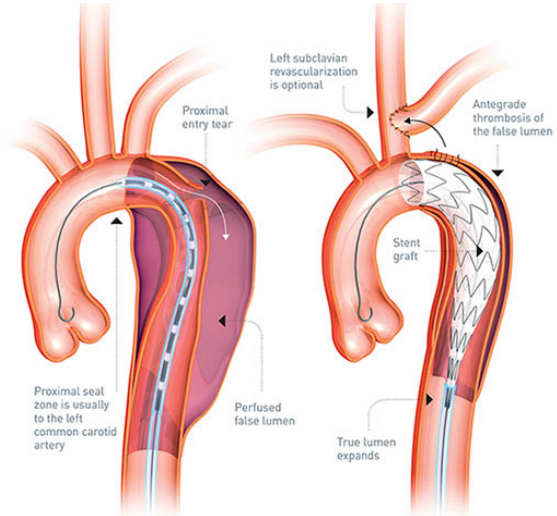

Figure 2. Principles of TEVAR

However, <u>there is a high incidence of failure with this approach, and the optimal therapy and timing of intervention remain unknown.</u> The disappointing long-term results with optimal medical therapy (**OMT**) combined with emerging data regarding the efficacy

of TEVAR in remodeling the dissected aorta have led to the investigation of the use of TEVAR for uncomplicated TBAD (2-4). Proponents of this strategy argue that TEVAR is highly effective in remodeling the aorta in the acute phase of TBAD (within 2 weeks of dissection onset), thereby reducing the incidence of long-term false lumen aneurysm formation and aortic-related mortality. However, the efficacy of aortic remodeling with TEVAR in the chronic phase (>2 weeks after dissection onset) is variable due to a reduction in compliance of the dissection flap and retrograde false lumen perfusion from distal uncovered fenestrations. The primary disadvantages of "prophylactic" TEVAR in uncomplicated TBAD are the high cost of the procedure, the risk of retrograde type A dissection, and the risk of stroke and spinal cord ischemia in patients who may never require intervention with OMT alone.

Acute flaps are thought to be more freely mobile and flexible so that intervention may enable complete or near complete re-expansion of the true lumen while obliterating the false lumen and preventing further aneurysmal degeneration, thereby promoting "favorable aortic remodeling". The elasticity and mobility of the dissection flap tend to decrease over time through fibrosis and gradually increasing wall stiffness and decreased compliance. However, these changes have not been well-characterized and have not been studied in human aortic tissue.

Therefore, this thesis addressed the gap in our understanding of the natural history of uncomplicated TBAD and its management - with implications for the optimal timing of endovascular intervention. First, we conducted a retrospective review of consecutive TBAD patients presenting to Emory Healthcare over a 16-year span and analyzed their postoperative and long-term survival outcomes. Second, we quantified the biomechanical

and histological differences between acute and chronic aortic dissection flaps using explanted human aortic tissue samples. Ultimately, the insights gained will serve as a basis for understanding the mechanisms and pathobiology of aortic enlargement and remodeling, which will optimize timing, intervention, and follow-up for patients presenting with TBADs.

BACKGROUND

Despite a heightened awareness, novel technology, and improved medical therapy, TBAD remains a lethal disease with poor long-term survival. The current treatment algorithm of TBADs depends on whether a patient presents with complications such as malperfusion or rupture. Complicated TBADs are now uniformly treated with TEVAR at index hospitalization. In contrast, uncomplicated TBADs have traditionally been treated with OMT with intervention indicated in the chronic phase when complications arise. The optimal management of acute *uncomplicated* TBADs remains unclear. While short-term outcomes of OMT are excellent with in-hospital mortality of 2.6-6.4%, the reported intervention-free and overall survival are only 60% and 75% at 5 years, respectively (2-3,5-7). The disappointing long-term results with OMT combined with emerging data regarding the efficacy of TEVAR in remodeling the dissected aorta have led to the investigation of the use of TEVAR for uncomplicated TBAD (8-10).

Earlier intervention during the acute phase of TBAD is potentially advantageous as the acute dissection flap is more pliable, providing the best chance of complete remodeling. This advantage must be balanced with an increased risk of peri-procedural complications such as retrograde dissection, neurological complications, and kidney injury in the acute period (11).

The basis for these clinical findings may be related to intrinsic differences between acute and chronic dissection flaps and their ability to remodel (12-13). Acute flaps are thought to be more freely mobile and flexible so that intervention may enable complete or near complete re-expansion of the true lumen while obliterating the false lumen and

preventing further aneurysmal degeneration, thereby promoting “favorable aortic remodeling”. The elasticity and mobility of the dissection flap tend to decrease over time through fibrosis and gradually increasing wall stiffness and decreased compliance. However, these changes have not been well-characterized, and the mechanics of this process have not been well-defined.

Natural history data demonstrate that rapid changes in aortic diameter occurs early post-dissection, stabilizing after 25 days (during the subacute phase) and plateauing after 88 days (during the chronic phase). Dissection flap mobility and thickness obtained from imaging analysis similarly show high rates of change acutely with stabilization reached after 83 days (14). However, the temporal changes in tissue architecture and biomechanical properties that underlie these findings have not been well-characterized.

A review of cadaveric TBAD samples by the Yale group showed significant increases in elastin fragmentation and media fibrosis (14), but the interplay of factors contributing to these features is still under investigation. Prior tissue architecture and biomechanics work has been performed primarily on healthy aortas and aneurysmal tissue (15-17). Layer-specific uniaxial tensile testing of healthy aortas shows that each layer behaves differently with the intima layer weaker and stiffer than those of the media and adventitia. Additionally, studies have demonstrated a lower delamination strength of ascending aortic aneurysms compared to controls and reduced strength among bicuspid versus tricuspid valve aortopathies (18). Protocols for histological analysis and biomechanical testing of aortic tissue have only recently been standardized. Previously, the Sun lab examined the mechanical and microstructural properties of Marfan aneurysmal thoracic aortic tissue using two-photon microscopy and uniaxial and biaxial strength

testing. These techniques have laid the groundwork for the methodology utilized in the present thesis (19).

In one of the few reports in the literature to examine aortic dissection tissue, Pasta et al. conducted delamination tests on explanted human thoracic aortic samples by creating an intimal tear and showed a difference in dissection strength between the circumferential and longitudinal directions (20). The direction of collagen fibers may also play a role in dissection propagation (21). Despite this progress, the biomechanics underlying aortic dissection remain unclear, and the properties of acute versus chronic dissection flaps that may underlie aortic remodeling have not been extensively studied.

METHODS

Aim 1: Exploratory/hypothesis-generating.

- Estimate the intervention-free survival of uncomplicated type B aortic dissection (TBAD) patients undergoing optimal medical therapy (OMT) alone
- Compare long-term survival among TBAD patients receiving TEVAR in the acute (**<2 weeks of diagnosis**) vs chronic (**>2 weeks after diagnosis**) phase

Study Design

Patients and Methods

This aim was conducted with the approval of the Institutional Review Board at Emory University in compliance with HIPAA regulations and the Declaration of Helsinki. The Institutional Review Board waived the need for individual patient consent. The Emory Data Warehouse was queried from 2000-2016 using the International Classification of Diseases Ninth and Tenth Revision codes for aortic dissection. After a detailed review of the electronic medical record, 172 patients with TBAD who received OMT alone were identified. A retrospective review of the Emory Aortic Surgery Database identified 226 patients who were diagnosed with TBAD and underwent open or endovascular surgery within the Emory Healthcare system from 2000-2016.

The electronic medical record was reviewed to collect demographics, the date of the initial diagnosis of TBAD, comorbidities, procedure specific details, re-interventions, and complications. All complicated TBAD patients were treated with TEVAR at the index hospitalization (**aTEVAR**, n=80). The remainder were uncomplicated (n=318) and

initially treated with OMT and surveillance imaging. During the chronic phase, 146 (45.9%) patients failed OMT and were treated with either open aortic replacement (**OPEN**, n=59) or endovascular therapy (**cTEVAR**, n=87). The indications for surgical or endovascular intervention were aortic growth with a maximum aneurysm size of ≥5.5cm, rapid aortic growth (≥5mm/year), rupture, malperfusion, or intractable pain despite adequate blood pressure control. The remaining patients were continued on OMT (n=172). Residual distal aortic dissections following proximal aortic repair for type A aortic dissection and all other acute aortic syndromes involving the descending thoracic aorta were excluded from this analysis.

Operative Details

TEVAR

All TEVAR procedures were performed using transfemoral access, intravascular ultrasound (**IVUS**) and transesophageal echocardiogram. IVUS was used to confirm true lumen wire access, identify the location of the primary intimal tear and assist in graft sizing. Following endograft deployment, IVUS was routinely performed to rule out retrograde type A aortic dissection and ensure adequate true lumen expansion in the stented and non-stented aortic segments. In patients undergoing TEVAR in both the acute or chronic phases, the length of aortic coverage was extended over the course of the series. The patients undergoing TEVAR in the latter 3 years of the study routinely received aortic coverage from the left subclavian artery to the celiac artery.

Open Repair

Open surgical replacement of the descending (n=32) or thoracoabdominal aorta (n=27) was performed with either left heart bypass (n=34) or hypothermic circulatory arrest (n=25) depending upon the degree of aneurysmal dilatation of the distal aortic arch. All patients underwent placement of a lumbar drain for cerebrospinal fluid drainage to mitigate the risk of spinal cord ischemia. Neuro-monitoring of motor and somatosensory evoked potentials was used routinely in all open repairs.

Follow-up

Follow-up data was obtained via office visits, telephone calls, queries of the social security death index or internet obituary searches. Follow-up within the last 12 months was complete in 86% (69/80) of the aTEVAR patients, 92% (54/59) in the OPEN patients, 86% (75/87) of the cTEVAR patients, and in 84% (145/171) of the OMT patients. The remainder of the follow-up was based upon their last visit >12 months from December 2016. Patients underwent contrast-enhanced computed tomographic or magnetic resonance angiograms at presentation and upon follow-up. Aortic centerline analysis was performed using a TeraRecon Aquarius iNtuition three-dimensional workstation (TeraRecon Inc, San Mateo, CA), and descending thoracic aortic diameters were measured as the maximum diameters orthogonal to the aortic centerline. Imaging analysis was complete in 85% (271/318) of the uncomplicated TBAD patients at presentation.

Analytic Plan

Categorical variables were summarized using frequencies and percentages. Continuous variables were analyzed with means and standard deviations (SD) if normally distributed; otherwise medians with interquartile ranges (IQR) were used. Comparisons among groups were performed using chi-squared analysis for qualitative variables and ANOVA for continuous variables. When the frequency of any nominal variable was ≤5, a Fischer exact test was used. Patient survival and re-intervention rates were estimated using Kaplan-Meier methodology and compared between groups using the log-rank test.

Aim 2: Pilot study. Quantify the biomechanical and histological differences between ACUTE and CHRONIC human aortic dissection flaps.

- Determine the biaxial stress-strain response curves of ACUTE vs CHRONIC aortic dissection flaps
- Estimate the association in stiffness between ACUTE and CHRONIC, as measured by the tangent modulus (TM) in the circumferential and longitudinal directions
- Qualitatively compare collagen and elastin fiber organization and cellular composition in ACUTE vs CHRONIC on histological analysis

Hypothesis: Chronic dissection flaps are stiffer, and exhibit decreased mobility and increased fibrosis, compared to acute dissection flaps.

Study Design

Thoracic aortic samples were obtained from consented patients presenting to Emory Healthcare for open repair of acute type A aortic dissection or chronic TBAD from

a start date of January 1, 2017. Demographic data was obtained from the electronic medical record. Institutional review board approval was obtained for aortic outcomes research as well as the use of human tissues for histological and biomechanical analysis. Chronicity of collected samples was determined from onset of symptoms and characterized as acute (**ACUTE**, ≤2 weeks of initial diagnosis) or chronic (**CHRONIC**, >2 weeks) in accordance with current European Society of Cardiology guidelines (22). Patients with connective tissue diseases and bicuspid valve aortopathies were excluded. Additionally, patients with documented atherosclerotic changes within the aneurysm wall by either gross inspection or histologic examination were excluded to eliminate patients in whom the inflammatory infiltrate associated with an atherosclerotic plaque could be a component of disease pathogenesis.

Collection of Samples

Human aortic dissection tissue can only be obtained fresh at time of operative repair during open surgery. As outlined previously, the majority (90%) of type A dissections are repaired with open surgery in the acute phase. In contrast, complicated TBADs are now uniformly treated endovascularly in the acute phase (during which no dissection flap tissue can be obtained). Uncomplicated TBADs undergo repair with TEVAR or open surgery when complications arise in the chronic phase. Thus, acute (n=10) dissection tissue were obtained from patients presenting for open repair of type A aortic dissections and chronic dissection tissue from patients presenting for open repair of type B dissections (n=10). Samples were matched based on potential confounding co-morbidities. It is important to note that there are no previous relatable data to carry out a power calculation in this study.

Thus, it represents a pilot study to evaluate differences at a tissue level that may help inform our clinical observation that acute and chronic aortic dissection flaps remodel differently after repair.

Tissue Cryopreservation Methods

Aortic dissection tissue samples were obtained fresh from the operating room. Samples were excised from the middle anterior and posterior regions of the ascending or descending aorta proximal to and including the dissection flap itself (**Figure 3**). Excised samples were cryopreserved in accordance to previously published laboratory protocols (23). When ready to test, the tissue was thawed and serially diluted with 0.9% saline at 4°C until a 2.5% DMSO solution was obtained.

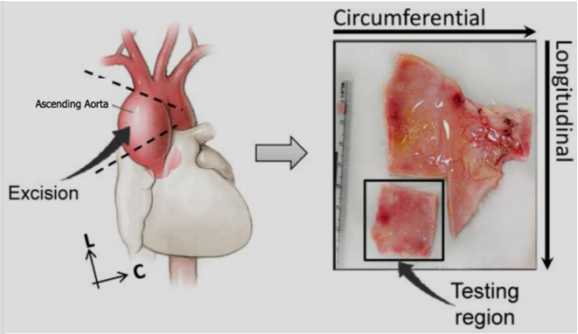

Figure 3. Collection of aortic dissection tissue samples and labeling of axes

Biomechanical Analysis: Biaxial Testing

Planar biaxial tensile testing was conducted according to the methods described by Sacks and Sun (24). Briefly, a square section of the aortic sample was cut such that the X_1 axis corresponds with the circumferential direction and X_2 with the longitudinal (**Figure 4, A.**).

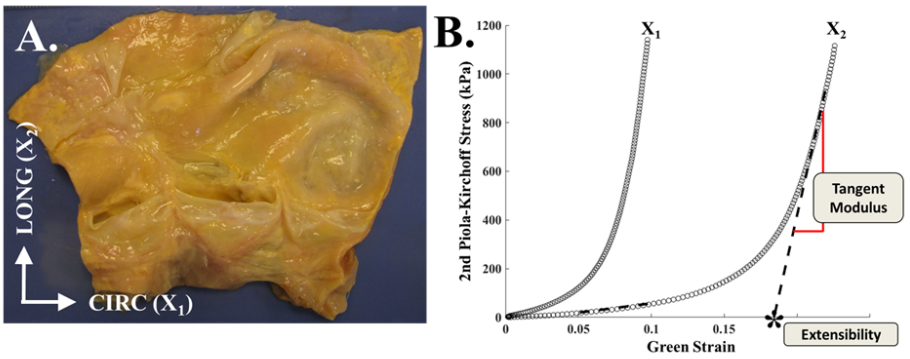

Figure 4.
A. Representative human aortic tissue sample depicting circumferential and longitudinal directions.

B. Representative equibiaxial response, showing calculations for the tangent modulus and extensibility.

Sample thickness was measured and averaged in three distinct locations throughout the testing region using a Mitutoyo 7301 rotating thickness gage (Aurora, IL, ±0.01 mm resolution).

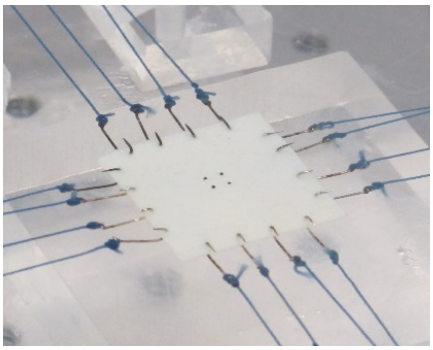

Figure 5. Mounting of tissue for testing

A square region was delimited by 16 suture hooks, four per side (**Figure 5**). Four graphite markers were fixed to the center of the tissue for strain tracking. The sample was then mounted onto a testing machine in a trampoline-like fashion, submerged in a 0.9% saline solution maintained at 37° Celsius for the duration of the test, and subjected to a stress-controlled testing protocol. Samples were subjected to a minimum of 30 equibiaxial preconditioning cycles to minimize hysteretic effects and ensure repeatability of the mechanical response (**Figure 4, B.**).

All biaxial plots show Green Strain, calculated as $\boldsymbol{E} = \frac{1}{2}(\boldsymbol{F}^T\boldsymbol{F} - \boldsymbol{I})$, and Second Piola-Kirchoff Stress, calculated as $\boldsymbol{S} = \boldsymbol{F}^{-1}\frac{\boldsymbol{f}}{hL}$, where $\boldsymbol{F}$ is the deformation gradient, $\boldsymbol{f}$ is the current force value in the circumferential and longitudinal directions, h and L are the initial unloaded thickness and length, respectively.

From the biaxial tensile testing data, stiffness was quantified with the tangent modulus (TM) in both the low and high linear regions of the equibiaxial response curve (**Figure 4, B.**). The data points within each region were fitted in the least-square sense with a custom MATLAB code (MathWorks, Natick, MA). TM was calculated from the slope of the fitted line, and extensibility was defined as the intersection of the fitted line from the high linear region with the x-axis.

Histological Analysis

Histological analysis was conducted in accordance with established laboratory protocols (19,23). Aortic tissue was rinsed with ice-cold phosphate buffered saline and sections of tissue were immersion-fixed in 10% formalin for >24 hours, processed, and embedded in paraffin. Samples were sectioned into 7 μm-thick slices and subjected to Verhoeff Van-Gieson (**VVG**) and PicroSirius Red stains to analyze elastin and collagen content, respectively. Additionally, Hematoxylin and Eosin (**H&E**) staining was used to analyze cellular composition.

Analytic Plan

Biomechanical Analysis: Biaxial Testing

Differences between groups were assessed with unpaired student's t-tests for normally distributed results. Non-normally distributed outcomes were log-transformed, and linear regression analysis was used to quantify the association of stiffness between groups.

Histological Analysis

A collection of images of acute and chronic samples were taken at various levels of magnification (5x, 10x, 20x, and 40x) using the Zeiss Axio Scope and processed with Zeiss Zen imaging software. Images were visually compared between groups qualitatively.

RESULTS

Aim 1.

Table 1 lists the baseline characteristics of patients presenting with complicated and uncomplicated TBAD at the time of initial diagnosis. The mean age of all patients was 57±12 years, and 67% were male. The uncomplicated TBAD patients were older (uncomplicated 58±12 years vs complicated 54±13 years, p=0.009), and had a higher incidence of hypertension, diabetes mellitus, and preoperative beta-blocker utilization. Debakey IIIb dissections were more common in the complicated group compared to the uncomplicated group (complicated 85% vs uncomplicated 72.6%, p=0.022). The maximum diameter of the descending aorta at the time of TBAD diagnosis was significantly larger in the uncomplicated group (uncomplicated 4.7±1.1cm vs. complicated 4.0±0.6cm, p=0.004).

In the chronic phase of TBAD, 146/318 (45.9%) uncomplicated patients developed complications that required either open (OPEN n=59) or endovascular (cTEVAR n=87) therapy. The remaining 172 patients continued to be treated with OMT alone as definitive therapy. Table 2 lists the baseline characteristics of the three treatment groups of uncomplicated TBAD at their initial diagnosis. End stage renal disease was more common in the OMT group compared to OPEN or cTEVAR groups in the chronic phase. OPEN patients were younger and had a significantly higher incidence of Marfan syndrome, preoperative beta-blocker usage, and active tobacco usage compared to the other two cohorts. The most common indications for intervention in the chronic phase were aneurysmal degeneration (75.3%) or intractable pain (9.5%) (Table 3).

In the 87 cTEVAR patients, the mean time between the initial diagnosis of TBAD and intervention was 2.4±3.0 years, and the maximum diameter of the descending aorta was 5.8±1.0 cm. Extended aortic endografting of ≥20 cm was performed in 56.3% (49/87) of cTEVAR patients. The maximum diameter of the descending aorta in the OMT group was 4.2±0.9 cm at presentation and 4.6±0.9 cm at last follow-up with a mean duration between scans of 2.3±2.6 years.

At the index hospitalization, the in-hospital mortality was equivalent between complicated and uncomplicated TBAD patients (complicated 5.0% vs uncomplicated 5.3%, p=0.55). In the group of uncomplicated TBAD patients who required intervention in the chronic phase, the in-hospital mortality was significantly higher in patients undergoing open repair compared to endovascular therapy (OPEN 16.9% vs cTEVAR 2.3%, p=0.003). All in-hospital mortalities for patients receiving interventions are listed in Table 4. An analysis of major postoperative adverse outcomes demonstrated that the stroke rate was higher in the aTEVAR patients compared to the OPEN or cTEVAR groups (aTEVAR 7.5% vs OPEN 1.7% vs cTEVAR 0%, p=0.009). The incidence of new onset paraparesis/paraplegia was low and equivalent among the three groups, and there was a trend towards a higher incidence of renal failure requiring dialysis in the OPEN patients (Table 5).

Although equivocal mortality was observed at the index hospitalization between complicated and uncomplicated TBAD patients, there was a trend towards improved long-term survival in the complicated group at 10 years (complicated 84.1% vs uncomplicated 58.9%, p=0.172, Figure 6). Long-term survival was also examined between the four treatment groups (Figure 7). Kaplan-Meier survival estimates at 1, 5 and 10 years were

highest for aTEVAR patients compared to any of the other sub-groups. When the OMT group was excluded, and only patients who required intervention were examined, there was a significant difference in survival between the aTEVAR group and the OPEN and cTEVAR groups (log rank p=0.018, Figure 8). The intervention-free survival for all uncomplicated TBAD patients treated with OMT at the initial diagnosis was 49.4% at 5 years, and 30.9% at 10 years (Figure 9).

Aim 2.

After matching for potential confounding co-morbidities, there were no differences in co-morbidities, maximum aortic diameter, and wall thickness between groups (Table 6). The mean age of ACUTE and CHRONIC flaps was 3.4±3.4 days and 1868.7±1354.0 days, respectively.

ACUTE exhibited an anisotropic stress-strain response with increased extensibility longitudinally than circumferentially (0.18 vs 0.09, p=0.022) while CHRONIC demonstrated loss of anisotropy with similar extensibility in either direction (0.11 vs 0.12, p=0.606) (Table 7 and Figure 10). While stiffness between groups was similar circumferentially (chronic vs acute ratio: TM_{low}1.36, p=0.656, and TM_{high} 0.42, p=0.067), in the longitudinal direction, CHRONIC was over 3-fold stiffer than ACUTE (chronic vs acute ratio (TM_{low}3.45, p=0.011 and TM_{high}3.76, p=0.016) (Table 8).

PicroSirius Red staining demonstrated a predominance of older (red/yellow) collagen content in ACUTE and more densely packed concentration of younger (green) collagen in CHRONIC. Additionally, there was evidence of increase fibrosis and loss of collagen fiber crimping and organization in CHRONIC (Figure 11).

Figure 12 shows representative VVG images at the media for ACUTE and CHRONIC samples. ACUTE samples exhibited preserved density and crimping of elastin fibers. Compared to ACUTE, CHRONIC demonstrated more extensive elastin fiber degradation as well as straightening of fibers.

Finally, H&E stain demonstrated that while there was a predominance of inflammatory cells in ACUTE at the level of the intima, this region of the sample was predominantly acellular (i.e. dead tissue) in CHRONIC (Figure 13). However, CHRONIC did exhibit extensive inflammatory cell composition at the level of the media.

DISCUSSION/CONCLUSIONS

The current dilemma in the treatment of TBAD is whether endovascular therapy should replace OMT as the primary therapy for acute uncomplicated TBAD patients to improve long-term survival. It has been well documented that OMT provides excellent in-hospital mortality for uncomplicated TBAD ranging from 2.6%-6.4% (3,5). However, the metrics for success of OMT must also include the prevention of complications requiring surgical intervention and long-term survival. Historical and contemporary data have demonstrated a 25-30% incidence of open surgical intervention for medically managed patients with TBAD (25-27). Furthermore, recent natural history TBAD data have demonstrated long-term survival rates of 48-59% with OMT and overall intervention-free survival rates of <50% (5-7). These poor outcomes argue for a paradigm change in the treatment of the disease.

The introduction of endovascular therapy for the treatment of TBAD has radically transformed the overall treatment algorithm. Approximately 30% of TBAD patients present with ischemia or rupture and represent the highest risk subgroup with an in-hospital mortality risk of 31% (28-30). TEVAR has improved survival rates to >90% in patients with complicated TBAD and has become the unequivocal treatment of choice for these patients, with superior in-hospital outcomes compared to open surgery or OMT (31-33).

The efficacy of TEVAR in the treatment of uncomplicated TBAD is currently unclear, as there is minimal data on its use in this challenging group of patients. The ADSORB trial is the only prospective randomized trial that has compared OMT to TEVAR for patients with uncomplicated acute TBAD. The early results of this trial demonstrated

improved aortic remodeling, but no difference in mortality with TEVAR at 1 year (9). The INSTEAD trial compared TEVAR to OMT in patients with subacute and chronic uncomplicated TBAD (2-52 weeks after the initial diagnosis of TBAD). The early results of this trial demonstrated improved aortic remodeling with TEVAR but no difference in mortality. However, the 5-year follow up data demonstrated that TEVAR significantly reduced the incidence of aneurysm formation, and aortic-related mortality compared to OMT (8). A recent large multi-institutional retrospective study from China confirmed the feasibility of TEVAR in uncomplicated TBAD compared to OMT. These authors demonstrated equivalent short-term mortality, but a reduction in adverse aortic-related events and 5-year mortality with the use of TEVAR (10).

The "natural history" data from Aim 1 add to the growing body of literature demonstrating poor long-term outcomes of patients with uncomplicated TBAD who are treated with OMT. In the current study, 46% of patients required either open or endovascular intervention at a mean of 2.7 years following their initial diagnosis of TBAD. It should be noted that these patients had significant aneurysmal degeneration of the descending thoracic aorta at the time of their initial diagnosis of TBAD (OPEN 5.3cm, cTEVAR 5.2cm), and clearly represent a "high-risk" category of uncomplicated patients that has been described in previous studies (3-4). It is also not surprising that following the development of complications, these patients had higher long-term mortality compared to the aTEVAR or definitive OMT groups (Figure 2). The poor outcomes of OMT are best expressed by the 49.4% and 30.9% 5-and 10-year intervention-free survival outcomes (Figure 4).

A major concern for implementing a more aggressive strategy of TEVAR for uncomplicated TBAD patients are the perioperative risks of TEVAR. In the current analysis, there was no increase in mortality compared to OMT when TEVAR is performed in the acute setting. The incidence of retrograde type A intramural hematoma or aortic dissection was low (3.7%) in the aTEVAR group and could be attributable to technical errors related to inexperience early in the series that resulted in wire injuries to the ascending aorta. The incidence of spinal cord ischemia and renal failure were 2.5% and 1.3%, respectively in the aTEVAR patients. The major morbidity that was observed in this study with TEVAR in the acute phase was stroke, which occurred in 6 patients early in the series. Stroke represents the most significant risk of prophylactic TEVAR for uncomplicated TBAD (Table 5).

The main limitations in the analysis of Aim 1 are the lack of complete follow-up and the inability to determine aortic-related mortality in the uncomplicated TBAD group. Follow-up in all groups was ≥ 84%; however, the lack of complete data could have significantly impacted the results. Moreover, our understanding of the natural history of TBAD treated with OMT would be enhanced with aortic-related mortality data. Unfortunately, these data were unattainable, as many people changed addresses and/or phone numbers or died outside of our hospital system.

Perhaps the most important finding of Aim 1 was that despite having the highest mortality risk at the time of diagnosis, patients who were treated with TEVAR for complicated TBAD had equivalent short-term mortality (complicated TBAD 5.0% vs uncomplicated TBAD 5.0% p=0.55) and a trend towards improved long-term survival compared to the uncomplicated cohort treated with OMT (complicated TBAD 84.1% vs

uncomplicated TBAD 58.9%, p=0.172, Figure 1). TEVAR was less effective in reducing long-term mortality in the uncomplicated patients once they developed complications in the chronic phase (10-year survival: aTEVAR 84.2% vs cTEVAR 46.8%, p=0.018).

The discrepancy in results between TEVAR in the acute vs chronic phase has been hypothesized to be due to differences in the material properties of the dissection flap. TEVAR is highly effective in remodeling the aorta in the acute phase of TBAD because the thin, compliant dissection flap can be effectively reapproximated to the outer tissue layer (media/adventitia) of the false lumen by the radial force of the stent graft. This results in a high incidence of false lumen obliteration or thrombosis throughout the entire thoracic aorta, and prevents false lumen aneurysm formation, thereby reducing aortic-related mortality (12). TEVAR is thought to be less effective in in the chronic phase because the dissection flap has become fibrotic and rigid over time. Therefore, it is more difficult for the stent graft to move the thick septum, thereby reducing its efficacy in promoting false lumen thrombosis and stabilizing or reducing the aneurysm sac size.

These clinical observations formed the hypothesis-generating basis for Aim 2. In this pilot analysis, we investigated the mechanical and structural properties of acute versus chronic aortic dissection flaps explanted from patients at the time of operative intervention.

Normal aortic tissue typically exhibits an anisotropic response with increased stiffness circumferentially compared to longitudinally. In general, the lower linear portion of the stress-strain bi-axial response curve (as reflected by TM_{low}) correlates with the stretch of elastin fibers and the higher linear portion of the stress-strain curve (as reflected by TM_{high}) correlates with the engagement of stiffer collagen fibers.

Compared to ACUTE, we found that CHRONIC samples were over three-fold higher in stiffness, particularly in the longitudinal direction (Table 8). Moreover, this increase in stiffness was evident at TM_{low} and TM_{high}, perhaps reflecting the lower density of medial elastin fibers and increased elastin fragmentation in CHRONIC. The relative loss of elastin contribution to the dissection flap leads to earlier engagement of collagen fibers and transition of the biomechanical response. The clinical significance of why CHRONIC was significantly stiffer than ACUTE longitudinally but not circumferentially is unclear, and further study is necessary. However, it may reflect that ACUTE tissue behaves more similarly to normal aortic tissue, which is naturally stiffer in the circumferential direction, roughly correlating with the organization of collagen fibers distributed circumferentially.

Similar to normal aortic tissue, ACUTE exhibited an anisotropic response demonstrating increased stiffness circumferentially compared to longitudinally (Figure 10); however, histologic analysis demonstrated a high degree of elastin fragmentation and inflammation, consistent with what would be expected in the acute phase of aortic dissection. Therefore, the difference in stiffness between ACUTE and CHRONIC may be less pronounced circumferentially than longitudinally.

Indeed, CHRONIC exhibited loss of anisotropy with similar stiffness in both the circumferential and longitudinal directions (Figure 10). This bi-axial biomechanical response was reflected in the histological analysis, which demonstrated loss of organization and directionality of the collagen fibers as well as increased collagen deposition. Moreover, the collagen was predominantly newly synthesized (green on PicroSirius stain), perhaps mediated by the persistent presence of inflammatory cells and fibroblasts at the level of the media in CHRONIC. As a whole, these observations suggest that aortic remodeling is

ongoing in the CHRONIC phase of aortic dissection. However, it appears to be disorganized, contributing to the increased fibrosis and decreased compliance of chronic dissection flaps.

There are a few important limitations to the current analysis. First, acute type A dissection flaps were used as a surrogate for acute type B dissection flaps. This is a limitation of any study utilizing explanted human aortic tissue, given that they can only be obtained fresh at time of operative repair during open surgery. The current established treatment of acute complicated TBAD patients with TEVAR precluded use of their aortic tissues for analysis. However, prior studies have demonstrated similar biomechanical responses of aortic tissue regardless of whether they are extracted from the ascending or descending positions (35-36). Secondly, this pilot analysis presents data from a single center with a small sample size. A larger sample size would provide higher statistical power to detect differences in biomechanical properties. To respond to this limitation, ACUTE and CHRONIC samples were matched based on potential confounding co-morbidities. Ongoing analysis of prospectively collected aortic dissection flaps will increase our sample size moving forward. Finally, the histological analyses presented in this thesis represent qualitative comparisons only, and a quantitative microstructural analysis may provide additional support for the presented findings.

In summary, our data from Aim 1 demonstrates that medical management alone is a suboptimal treatment for patients with uncomplicated TBAD that results in a high incidence of late complications and poor long-term survival. Endovascular therapy at the initial hospitalization for the highest risk subgroup of TBAD patients (complicated) did not increase short-term mortality and improved long-term survival compared to the

uncomplicated patients receiving any type of intervention in the chronic phase. Through our pilot analysis in Aim 2, we demonstrate that an acute dissection flap is more compliant and less stiff than a chronic flap. This transition from the acute to chronic phase of aortic dissection may be facilitated by disordered collagen synthesis by persistent inflammatory cells at the level of the aortic media leading to increased fibrosis of the dissection flap. Our pilot analysis thus corroborates our clinical outcomes data and offers biomechanical and histological support for endovascular intervention in the acute phase of uncomplicated TBAD when aortic remodeling is more favorable. Taken as a whole, the data presented in this thesis support a more aggressive strategy of TEVAR at the index hospitalization in the treatment of uncomplicated TBAD, which would represent a paradigm shift in the field. Future work will focus on establishing a timeline for when the transition in dissection flap properties occurs to further optimize the timing of intervention in patients presenting with TBAD.

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TABLES/FIGURES (in order of reference in the text)

Table 1. Baseline characteristics of aTBAD patients at the time of initial diagnosis

Variable	Complicated (N = 80)	Uncomplicated (N = 318)	P-value
Age, yrs	53.7 ± 12.9	57.7 ± 12.0	0.009
Male	63.8% (51/80)	67.3% (214/318)	0.548
Hypertension	86.3% (69/80)	93.1% (295/317)	0.049
Diabetes	3.8% (3/79)	17.1% (50/292)	0.003
End stage renal disease	3.8% (3/79)	9.8% (31/316)	0.115
History of stroke	7.6% (6/79)	8.2% (26/318)	0.854
COPD	6.3% (5/79)	10.4% (33/318)	0.274
Marfan syndrome	2.5% (2/80)	1.6% (5/318)	0.632
Beta blocker status (yes)	28.9% (22/76)	55.2% (155/281)	<0.001
Active or recent tobacco use	38.7% (29/75)	26.8% (77/287)	0.045
Acute Debakey III Aortic Dissection			0.022
IIIA	15.0% (12/80)	27.4% (87/318)	
IIIB	85.0% (68/80)	72.6% (231/318)	
Aortic diameter at presentation (cm)	4.0 ± 0.6	4.7 ± 1.1	0.004

Data represented as mean ± SD or % (number/total). COPD, chronic obstructive pulmonary disease; Aortic diameter at presentation refers to maximum aortic diameter of descending aorta.

Table 2. Baseline characteristics of uncomplicated aTBAD patients at the time of initial diagnosis

Variable	OPEN (N = 59)	cTEVAR (N = 87)	OMT (N = 172)	P-value
Age, yrs	53.4 ± 10.9	59.5 ± 11.8	58.3 ± 12.1	0.006
Male	76.3% (45/59)	67.8% (59/87)	64.0% (110/172)	0.218
Hypertension	98.3% (58/59)	92.0% (80/87)	91.8% (157/171)	0.213
Diabetes	8.8% (5/57)	20.0% (13/65)	18.8% (32/170)	0.172
End stage renal disease	5.1% (3/59)	4.7% (4/86)	14.0% (24/171)	0.023
History of stroke	8.5% (5/59)	9.2% (8/87)	7.6% (13/172)	0.898
COPD	11.9% (7/59)	12.6% (11/87)	8.7% (15/172)	0.569
Marfans	6.8% (4/59)	0.0% (0/87)	0.6% (1/172)	0.002
Beta blocker status (yes)	76.8% (43/56)	66.7% (52/78)	40.8% (60/147)	<0.001
Active or recent tobacco use	44.1% (26/59)	33.9% (19/56)	18.6% (32/172)	<0.001
Acute Debakey III Aortic Dissection				<0.001
IIIA	52.5% (31/59)	21.8% (19/87)	21.5% (37/172)	
IIIB	47.5% (28/59)	78.2% (68/87)	78.5% (135/172)	
Aortic diameter at presentation (cm)	5.3 ± 1.2	5.2 ± 1.1	4.2 ± 0.9	<0.001

Data represented as mean ± SD or % (number/total). COPD, chronic obstructive pulmonary disease; Aortic diameter at presentation refers to maximum aortic diameter of descending aorta.

Table 3. Presentation and indications for intervention in the chronic phase

	OPEN (N = 59)	cTEVAR (N = 87)
Presenting symptom		
Aymptomatic/incidental	13.6% (8/59)	11.5% (10/87)
Chest/back/abdominal pain	78.0% (46/59)	70.1% (61/87)
Hypertensive emergency	0.0% (0/59)	3.4% (3/87)
Unknown/none of the above	8.5% (5/59)	14.9% (13/87)
Indications for intervention		
Aneurysmal degeneration	83.1% (49/59)	70.1% (61/87)
Rapid rate of expansion	11.9% (7/59)	2.3% (2/87)
Intractactable pain	3.4% (2/59)	13.8% (12/87)
Malperfusion	1.7% (1/59)	6.9% (6/87)
Unknown/none of the above	0.0% (0/59)	6.9% (6/87)

Data represented as % (number/total).

Table 4. In-hospital mortality: cause of death

	aTEVAR (N = 4)	OPEN (N = 10)	cTEVAR (N = 2)
Intra-operative cardiopulmonary failure	0	3	0
Retrograde Type A	0	2	1
Presented with aortic rupture	0	2	0
Delayed aortic rupture	2	0	0
Post-operative cardiac arrest	0	1	0
Mesenteric ischemia	2	0	0
Multi-system organ failure/shock	0	2	1

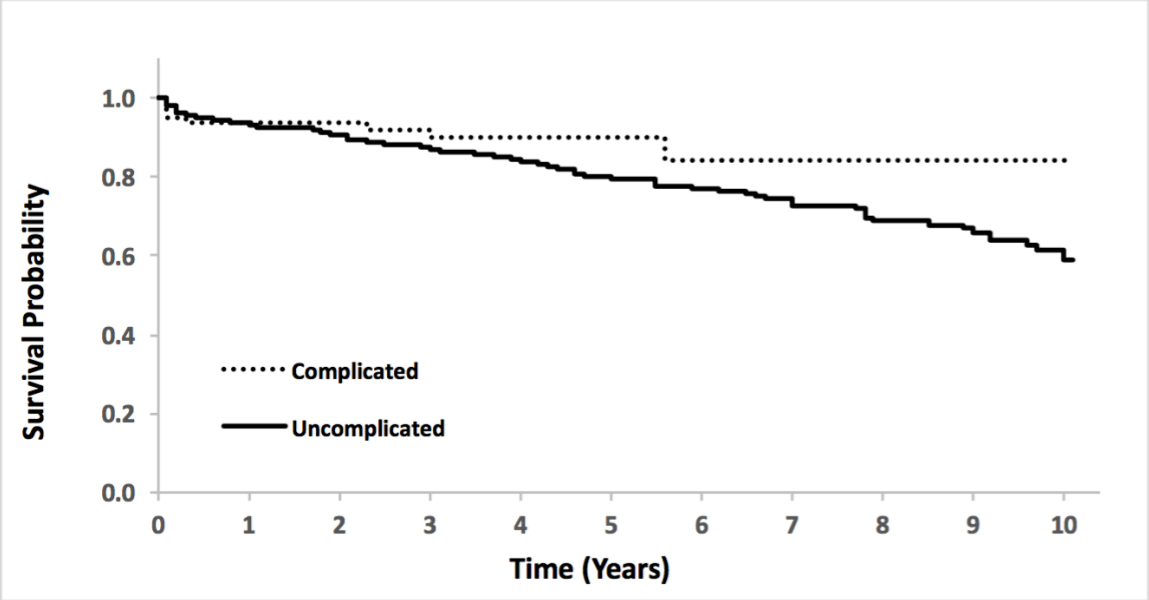
Data represented as counts.

Table 5. In-hospital mortality and adverse events

	aTEVAR (N = 80)	OPEN (N = 59)	cTEVAR (N = 87)	P-value
In-hospital mortality	5.0% (4/80)	16.9% (10/59)	2.3% (2/87)	0.003
Paraplegia	0.0% (0/80)	3.4% (2/59)	2.3% (2/87)	0.308
Paraparesis	2.5% (2/80)	1.7% (1/59)	1.1% (1/87)	0.833
Stroke	7.5% (6/80)	1.7% (1/59)	0.0% (0/87)	0.009
*Renal failure	1.3% (1/80)	10.2% (6/59)	4.6% (4/87)	0.054

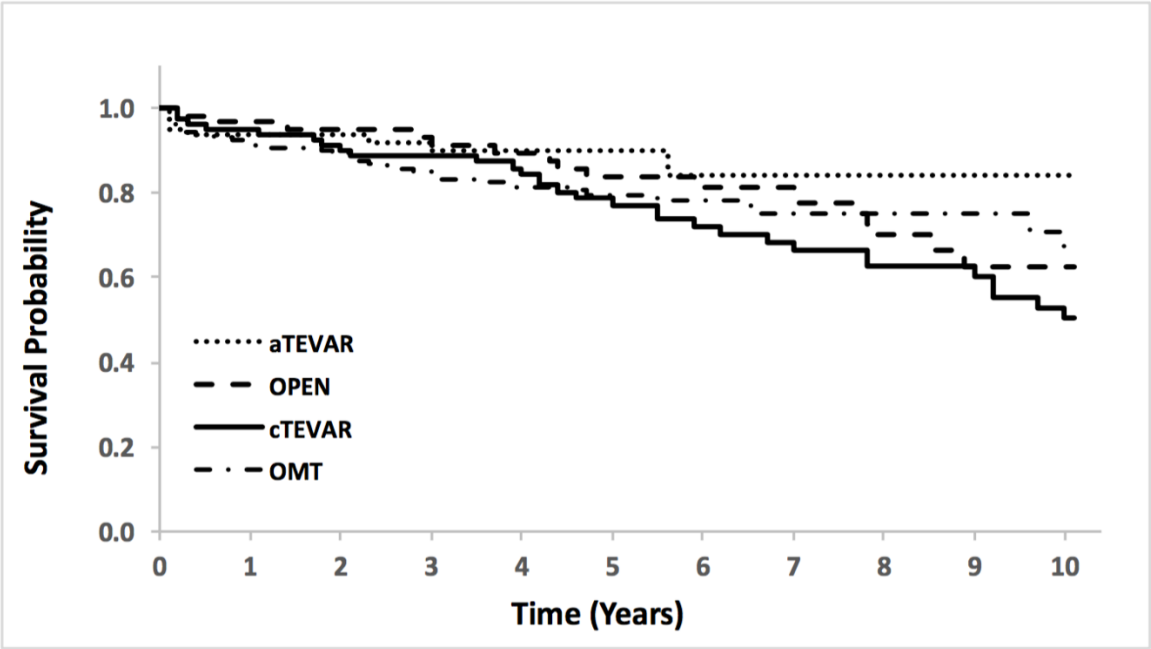
Data represented as % (number/total). *Renal failure requiring initiation of renal replacement therapy.

Figure 6. Kaplan Meier long-term survival curve comparing complicated and uncomplicated acute type B aortic dissection patients.



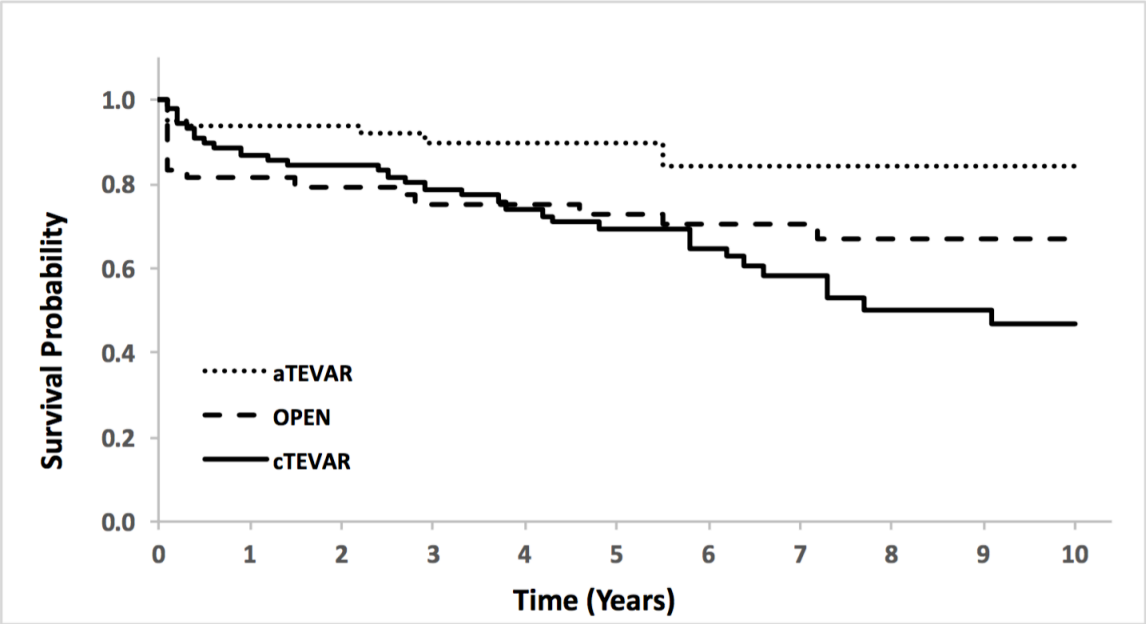
		1 Year	3 Years	5 Years	8 Years	10 Years
Survival (%)	Complicated (N = 80)	93.6 (68)	89.7 (43)	89.7 (18)	84.1 (5)	84.1 (2)
	Uncomplicated (N = 318)	93.3 (283)	86.7 (227)	79.3 (173)	68.7 (88)	58.9 (53)
p-value (by log-rank test)		0.936	0.508	0.209	0.204	0.172

Figure 7. Kaplan Meier survival curve of all patients presenting with acute type B aortic dissection based upon treatment strategy.



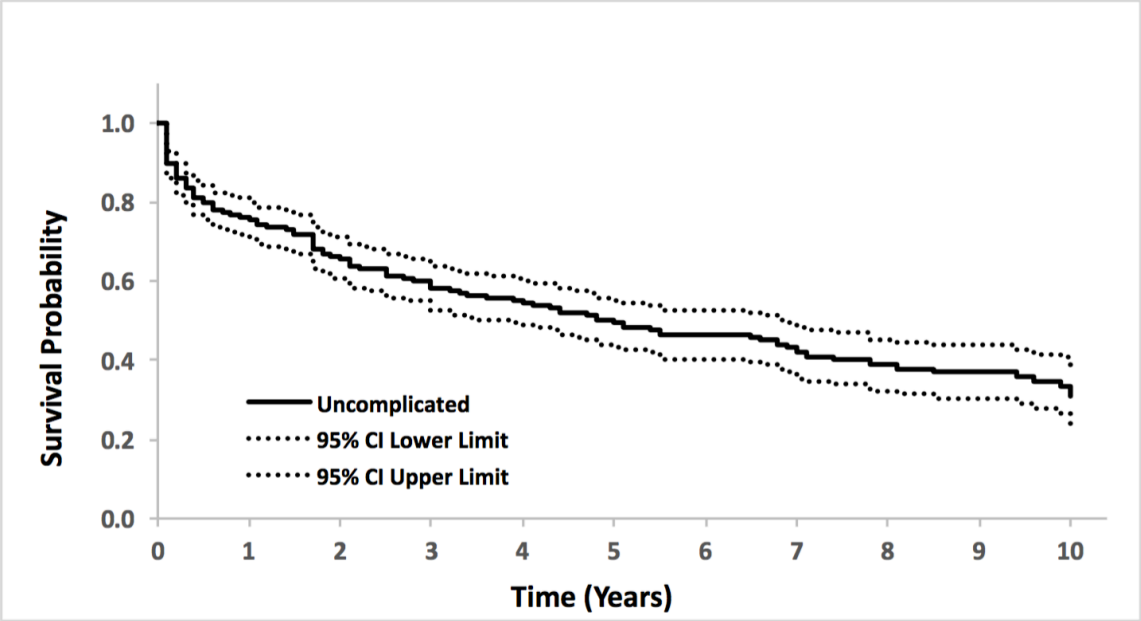
		1 Year	3 Years	5 Years	8 Years	10 Years
Survival (%)	aTEVAR (N = 80)	93.6 (68)	89.7 (43)	89.7 (18)	84.1 (5)	84.1 (2)
	OPEN (N = 59)	96.6 (55)	91.2 (51)	83.5 (43)	69.8 (27)	62.5 (15)
	cTEVAR (N = 87)	95.2 (78)	88.7 (65)	77.2 (52)	62.5 (30)	50.4 (22)
	OMT (N = 172)	91.2 (150)	84.0 (111)	79.5 (78)	75.1 (31)	66.4 (16)
p-value (by log-rank test)		0.446	0.421	0.466	0.421	0.302

Figure 8. Kaplan Meier survival curves of type B patients who required intervention.



		1 Year	3 Years	5 Years	8 Years	10 Years
Survival (%)	aTEVAR (N = 80)	93.6 (68)	89.8 (42)	89.8 (18)	84.2 (5)	84.2 (2)
	OPEN (N = 59)	81.4 (46)	75.3 (36)	73.0 (31)	67.0 (13)	67.0 (6)
	cTEVAR (N = 87)	87.1 (71)	78.7 (54)	69.1 (38)	50.3 (18)	46.8 (12)
p-value (by log-rank test)		**0.090**	**0.069**	**0.036**	**0.021**	**0.018**

Figure 9. Kaplan-Meier intervention-free survival curve of uncomplicated TBAD patients.



	1 Year	3 Years	5 Years	8 Years	10 Years
Uncomplicated (N = 318)	75.4 (234)	58.4 (160)	49.4 (108)	38.9 (46)	30.9 (27)

Table 6. Baseline co-morbidities between ACUTE and CHRONIC aortic dissection flaps

	ACUTE (n=10)	CHRONIC (n=10)	
Age (years)	52.6±15.1	49.9±10.6	
Gender (male)	7	7	
Hypertension	10	10	
Hyperlipidemia	4	5	
Diabetes mellitus	3	0	
COPD	1	0	
End-stage-renal-disease	3	2	
Active smoker	5	2	
Maximum aortic diameter (cm)	5.1±0.2	6.1±1.1	

Data represented as counts or mean±SD.

Table 7. Biomechanical properties between ACUTE and CHRONIC aortic dissection flaps

	ACUTE (n=10)	CHRONIC (n=10)	P-value
Flap thickness (mm)	1.7±0.5	1.8±0.5	0.519
Age of flap (days)	3.4±3.4	1868.7±1354.0	0.011
TM_{low} Circumferential (kPa)	2651.97	964.18	0.133
TM_{high} Circumferential (kPa)	8874.37	1961.37	0.185
TM_{low} Longitudinal (kPa)	254.95	1094.65	0.009
TM_{high} Longitudinal (kPa)	937.25	10636.82	0.133
Extensibility Circumferential	0.09	0.12	0.836
Extensibility Longitudinal	0.18	0.11	0.150

Data represented as mean±SD.

TMs and extensibilities reflect calculations from the compiled biaxial response curves for each group.

Table 8. Linear regression analysis quantifying stiffnes of CHRONIC vs ACUTE aortic dissection flaps

	CHRONIC vs ACUTE (ratio)	95% CI	P-value
TM_{low} Circumferential (kPa)	1.36	0.35, 5.21	0.656
TM_{high} Circumferential (kPa)	0.42	0.16, 1.1	0.067
TM_{low} Longitudinal (kPa)	3.45	1.34, 8.91	0.011
TM_{high} Longitudinal (kPa)	3.76	1.28, 11.06	0.016

Figure 10. Compiled equibiaxial response curves in the circumferential (left) and longitudinal (right) directions comparing stress-strain responses of type A (ACUTE) vs type B (CHRONIC) aortic dissection flaps.

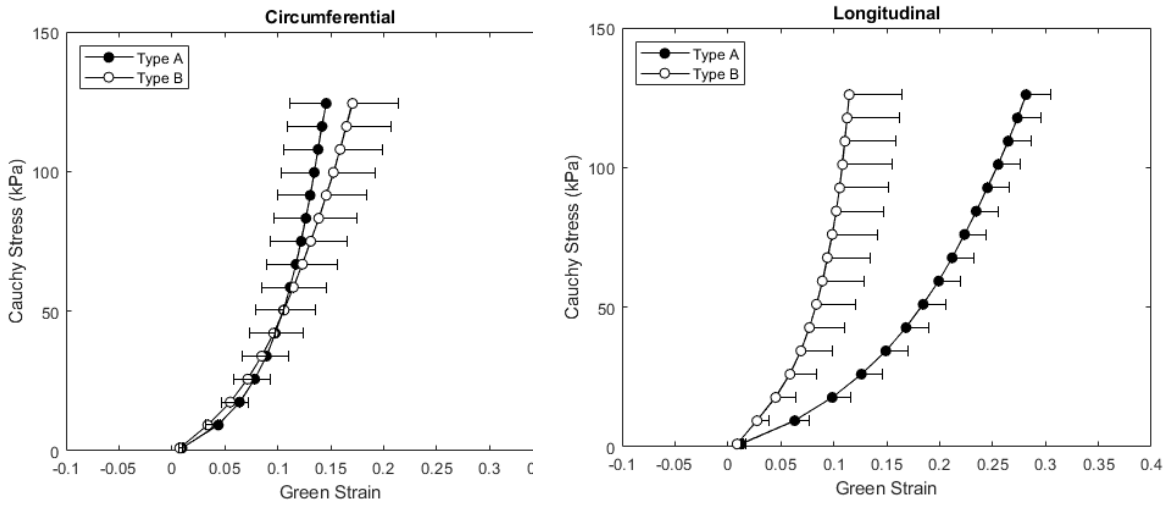


Figure 11. Representative PicroSirius Red stains along the circumferential and longitudinal directions comparing ACUTE vs CHRONIC aortic dissection flaps. Newly synthesized collagen is shown as green, while older collagen is shown as yellow/orange-red.

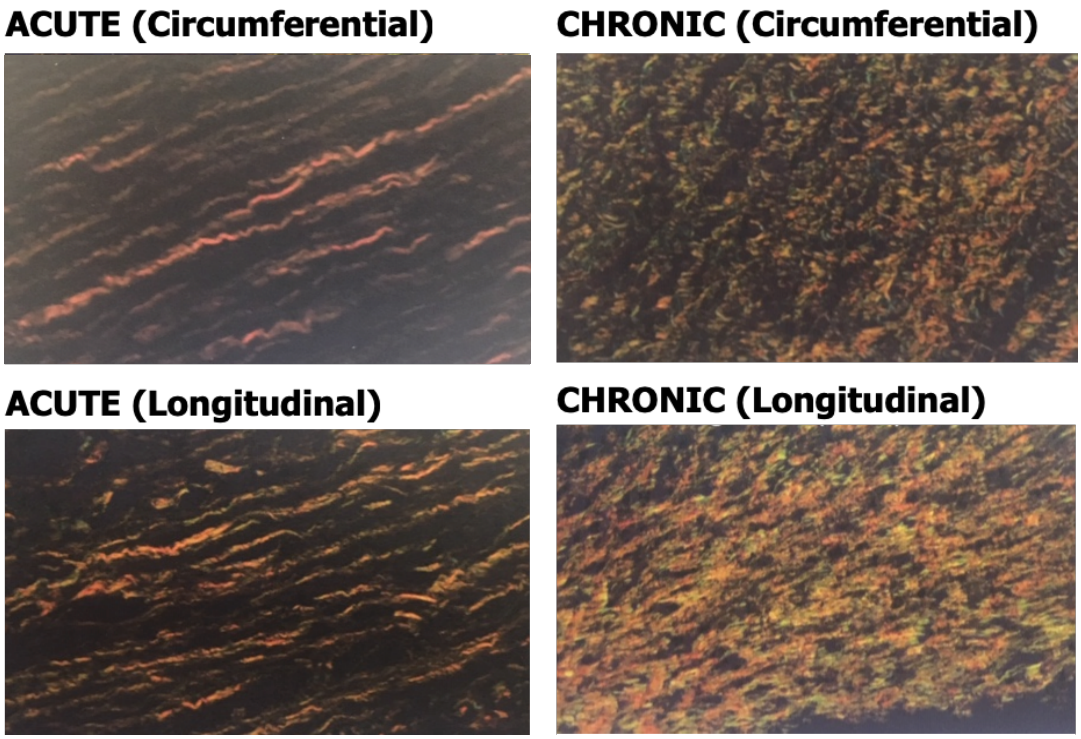


Figure 12. Representative Verhoeff-Van Gieson (VVG) stains at the level of the intima and media of ACUTE vs CHRONIC aortic dissection flaps. Elastic fibers are shown in black.

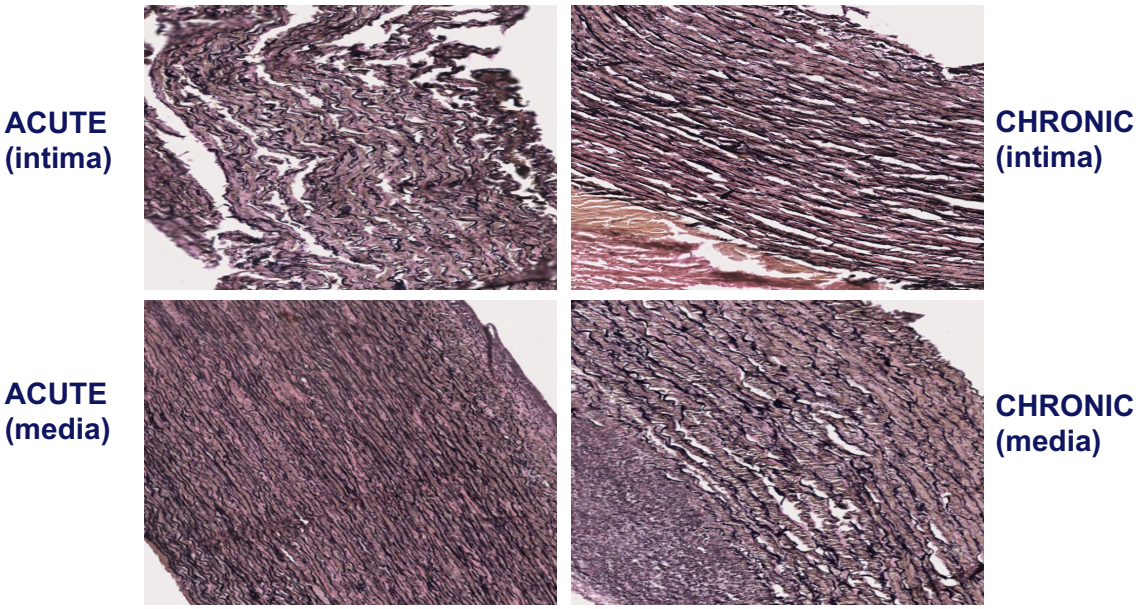


Figure 13. Representative Hematoxylin and Eosin (H&E) stains at the level of the intima and media of ACUTE vs CHRONIC aortic dissection flaps. The hematoxylin stains cells nuclei blue and extracellular matrix and cytoplasm pink.