The Learning Curve and Annual Procedure Volume Standards for Optimum Outcomes of Transcatheter Aortic Valve Replacement: Findings from an International Registry

by

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Institute of Medical Science

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Abstract

Transcatheter aortic valve replacement (TAVR) is a technically complex procedure. Despite increasing use of TAVR across institutions, incomplete knowledge exists to describe the learning curve and minimum annual volumes for this procedure. We hypothesize that TAVR has a prolonged learning curve, as well as a high minimal annual volume to maintain competency. In this study, we analyzed data from 16 international centers comprising 3403 patients from the inception of their TAVR programs. The study identified an important learning curve, with higher mortality for the first 225 cases compared to those performed after > 300 case volume, and higher combined major complications up until a 300-case volume. In addition, the 30-day mortality was higher for centers performing < 50 procedures per year, compared to those performing > 100 TAVR procedures per year. These findings highlight the importance of operator training and institutional annual TAVR volumes to optimize patient outcomes.
Acknowledgements

I would like to acknowledge and thank my family, who have supported me and encouraged me through all endeavours in my life. Thank you.

I would like to express my gratitude to all of those who have taught me throughout my long training, especially those at St. Michael’s Hospital, where this project was completed and where the latter part of my clinical training took place. I would not have accomplished what I have done without their training and guidance.
# Table of Contents

**Acknowledgements** .................................................................................................................... iii

**Table of Contents** .......................................................................................................................... iv

**Abbreviations:** ............................................................................................................................. viii

**List of Figures:** ............................................................................................................................ x

**List of Tables:** .............................................................................................................................. xii

**Chapter 1** ..................................................................................................................................... 1

## Aortic Stenosis – Diagnosis, Evaluation, Surgical and Transcatheter Management Strategies .......................................................................................................................... 1

1.1 Aortic Stenosis ............................................................................................................................ 1
   1.1.1 Background .......................................................................................................................... 1
   1.1.2 Pathophysiology of Aortic Stenosis ...................................................................................... 2
   1.1.3 Epidemiology of Aortic Stenosis .......................................................................................... 5
   1.1.4 Clinical Findings of Aortic Stenosis .................................................................................... 6
   1.1.5 Echocardiography, Cardiac Catheterization, and Ancillary testing in Aortic Stenosis .......... 7
   1.1.6 Physiology of Severe Aortic Stenosis .................................................................................. 11
   1.1.7 Prognosis of Severe Aortic Stenosis .................................................................................... 11

1.2 Surgical Management of Severe Aortic Stenosis ....................................................................... 13
   1.2.1 Background ....................................................................................................................... 13
   1.2.2 Medical Management ......................................................................................................... 13
   1.2.3 Surgical Management of Severe Aortic Stenosis ................................................................ 14

1.3 Limitation of Surgical Aortic Valve Replacement and the Aging Population ......................... 16
   1.3.1 Limitations of Surgical Aortic Valve Replacement .............................................................. 16
   1.3.2 Untreated Patient Population Prior to Transcatheter Aortic Valve Replacement ................ 18

1.4 Transcatheter Aortic Valve Replacement (TAVR) .................................................................. 18
   1.4.1 History of TAVR ................................................................................................................ 19
   1.4.2 Types of Transcatheter Aortic Valves ................................................................................ 19
   1.4.3 Pre-procedure Planning ..................................................................................................... 20
1.4.4 The TAVR Procedure ................................................................. 21
1.4.5 Pivotal Randomized Controlled Trials for TAVR .......................... 24
1.4.6 Current Societal Guidelines TAVR ........................................... 29
1.4.7 Measures of Outcomes in TAVR .............................................. 30
1.4.8 Outcomes and Complications of TAVR ..................................... 31
1.4.9 Growth of TAVR/Growing Aging Population ............................... 32

Chapter 2 .......................................................................................... 34

2 Learning Curve Characteristics and Relationship of Procedural Volumes with Clinical Outcomes for Transcatheter Aortic Valve Replacement (TAVR) ........................................ 34

2.1 Learning Curve in Transcatheter Aortic Valve Replacement (TAVR) ................. 35
2.1.1 General Principles for Learning Curve Analysis ................................ 35
2.1.2 Learning Curve Phenomenon in Clinical Medicine .......................... 36
2.1.3 Learning Curve for Transcatheter Aortic Valve Replacement (TAVR): Measures of Process ........ 36
2.1.4 Learning Curve for Transcatheter Aortic Valve Replacement (TAVR): Measures of Clinical Outcomes 37

2.2 Procedural Volume and Outcome Relationship for Transcatheter Aortic Valve Replacement 44
2.2.1 Procedural Volume and Outcomes in Clinical Medicine ...................... 44
2.2.2 Procedural Volume and Outcomes Relationship for TAVR .................. 45

2.3 Implications for Clinical Practice ..................................................... 49

2.4 Conclusions ................................................................................ 50

Chapter 3 .......................................................................................... 52

3 Research Aims and Hypotheses ....................................................... 52

Chapter 4 .......................................................................................... 55

4 Institutional Experience and Outcomes of Transcatheter Aortic Valve Replacement ..... 55

4.1 Introduction ................................................................................ 55

4.2 Methods ..................................................................................... 56
4.2.1 Population ................................................................................ 56
4.2.2 Design ..................................................................................... 58
4.2.3 Statistical Analysis ................................................................... 58
Chapter 6

4.3 Results .............................................................................................................................. 59
  4.3.1 Clinical Outcomes ........................................................................................................... 59
  4.3.2 Procedural Parameters ................................................................................................. 60
  4.3.3 Multivariate Analysis..................................................................................................... 60

Chapter 5 .................................................................................................................................... 67

5 The Learning Curve and Annual Procedure Volume Standards for Optimum Outcomes of
 Transcatheter Aortic Valve Replacement: Findings from an International Registry.............. 67

5.1 Introduction ........................................................................................................................ 68

5.2 Methods ............................................................................................................................ 69
  5.2.1 Population ..................................................................................................................... 69
  5.2.2 Study Design ................................................................................................................ 69
  5.2.3 Data Definitions .......................................................................................................... 70
  5.2.4 Statistical Analysis ..................................................................................................... 70

5.3 Results ................................................................................................................................ 71
  5.3.1 TAVR Learning Curve Analysis - Baseline Characteristics ........................................... 71
  5.3.2 TAVR Learning Curve Analysis - Clinical Outcomes ................................................... 73
  5.3.3 TAVR Learning Curve Analysis - Procedural Outcomes .............................................. 73
  5.3.4 TAVR Learning Curve Analysis - Multivariate Analysis ............................................. 78
  5.3.5 TAVR Annual Volume Analysis - Patient Population .................................................... 81
  5.3.6 TAVR Annual Volume Analysis - Clinical Outcomes ................................................... 85
  5.3.7 TAVR Annual Volume Analysis - Procedural Outcomes .............................................. 85
  5.3.8 TAVR Annual Volume Analysis – Multivariate Analysis ............................................. 88

Chapter 6 .................................................................................................................................... 90

6 Discussion .............................................................................................................................. 90

6.1 Preamble ........................................................................................................................... 90

6.2 Summary of Principle Findings ....................................................................................... 91
  6.2.1 TAVR Institutional Experience and Outcomes ............................................................. 91
  6.2.2 TAVR Learning Curve Study ...................................................................................... 91
  6.2.3 TAVR Annual Institutional Volumes and Outcomes Study ........................................... 92

6.3 Clinical Significance and Novelty of findings ................................................................... 92
  6.3.1 TAVR Institutional Experience and Learning Curves for TAVR .................................... 92
6.3.2 Annual Institutional Volumes for TAVR ................................................................. 94

6.4 Limitations .................................................................................................................. 96

Chapter 7 .......................................................................................................................... 97

7 Conclusions ...................................................................................................................... 97

Chapter 8 ............................................................................................................................ 98

8 Future Directions ............................................................................................................ 98

References ......................................................................................................................... 101

Appendix A: Contributions ............................................................................................... 122

Appendix B: Copyright Acknowledgements .................................................................... 124
### Abbreviations:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA</td>
<td>American College of Cardiology/American Heart Association</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin converting enzyme</td>
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<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
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<td>AI</td>
<td>Aortic Insufficiency</td>
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<td>AKI</td>
<td>Acute kidney injury</td>
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<td>AR</td>
<td>Aortic regurgitation</td>
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<td>AS</td>
<td>Aortic stenosis</td>
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<tr>
<td>AV</td>
<td>Aortic valve</td>
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<tr>
<td>AVA</td>
<td>Aortic valve area</td>
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<tr>
<td>AVAi</td>
<td>Aortic valve area indexed</td>
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<tr>
<td>AVR</td>
<td>Aortic valve replacement</td>
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<td>BAV</td>
<td>Balloon aortic valvuloplasty</td>
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<tr>
<td>BP</td>
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<td>BSA</td>
<td>Body surface area</td>
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<td>CABG</td>
<td>Coronary Artery Bypass Grafting</td>
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<td>CAD</td>
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<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
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<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<td>EuroSCORE</td>
<td>European System for Cardiac Operative Risk Evaluation</td>
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<td>HR</td>
<td>Hazard Ratio</td>
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<td>IL-1B</td>
<td>Interleukin 1B</td>
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<td>Low density lipoprotein</td>
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<tr>
<td>LOS</td>
<td>Length of stay</td>
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<td>Left ventricular outflow tract</td>
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<td>Full Form</td>
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<td>Major adverse events</td>
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<tr>
<td>MMP</td>
<td>Matrix metalloproteinase</td>
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<tr>
<td>NOTION trial</td>
<td>Nordic Aortic Valve Intervention trial</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>PARTNER trial</td>
<td>Placement of Aortic Transcatheter Valves trial</td>
</tr>
<tr>
<td>Q</td>
<td>Quantile</td>
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<tr>
<td>SAVR</td>
<td>Surgical aortic valve replacement</td>
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<tr>
<td>SE THV</td>
<td>Self-expanding transcatheter heart valve</td>
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<tr>
<td>SURTAVI trial</td>
<td>Surgical Replacement and Transcatheter Aortic Valve Implantation trial</td>
</tr>
<tr>
<td>STS-PROM</td>
<td>Society of Thoracic Surgeons Predicted Risk of Mortality</td>
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<tr>
<td>STS/ACC TVT</td>
<td>Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry</td>
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<tr>
<td>TA</td>
<td>Transapical</td>
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<td>Tao</td>
<td>Transaortic</td>
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<td>TEE</td>
<td>Transesophageal echocardiography</td>
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<tr>
<td>TF</td>
<td>Transfemoral</td>
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<tr>
<td>TAVR</td>
<td>Transcatheter aortic valve replacement</td>
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<tr>
<td>TGF-1B</td>
<td>Transforming growth factor 1B</td>
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<tr>
<td>TTE</td>
<td>Transthoracic echocardiography</td>
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<td>VARC-2</td>
<td>Valve Academic Research Consortium</td>
</tr>
</tbody>
</table>
List of Figures:

Chapter 1:
Figure 1: Gross specimen of normal and calcific degenerative aortic valve. Adapted from (Freeman and Otto 2005)
Figure 2. Pathological Mechanisms for Aortic Stenosis. Adapted from (Freeman and Otto 2005)
Figure 3. The prevalence of Aortic Stenosis as a Function of Age. Adapted from (Lindman, Clavel et al. 2016)
Figure 4. The natural history of aortic stenosis. Adapted from (Ross and Braunwald 1968)
Figure 5. 2014 ACC/AHA Guidelines for the Management of Aortic Stenosis Adapted from (Nishimura, Otto et al. 2014)
Figure 6. In Hospital Mortality after Aortic Valve Replacement as a Function of Age. Adapted from (Astor, Kaczmarek et al. 2000)
Figure 7 (A-C). Commonly Used Transcatheter Heart Valves. Adapted from (Webb and Wood 2012)
Figure 8. Schematic Diagram of Access for TAVR. Adapted from (Jones, Krishnaswamy et al. 2017)
Figure 9. 2017 ACC/AHA Recommendations for the Management of Severe Symptomatic Aortic Stenosis. Adapted from (Nishimura, Otto et al. 2017)
Figure 10. Growth in the number of TAVR sites and procedures performed in the United States. Adapted from (Grover, Vemulapalli et al. 2017)

Chapter 2:
Figure 11. Procedural Sequence Number association with Complications. Adapted from (Carroll, Vemulapalli et al. 2017)

Chapter 4:
Figures in this section have been previously published, and are adapted from (Wassef, Alnasser et al. 2017)
Figure 12. (A and B): Patient population of the institutional experience study divided into the chronological quantiles.
Chapter 5:
Figures in this section have been previously published, and are adapted from (Wassef, Rodes-Cabau et al. 2018)

Figure 16. Unadjusted Clinical and Procedural Outcomes Learning Curve Analysis
Figure 17. Relationship between TAVR procedural volume and odds of mortality
Figure 18. A and B: Multivariate Analysis of Mortality and Early Safety Endpoint Learning Curve Analysis.
Figure 19. Annual institutional TAVR volume 2008-2013
Figure 20. Unadjusted Clinical and Procedural Outcomes for the Annual Volume Analysis
Figure 21. A and B: Multivariate Analysis of Mortality and Composite Early Safety Endpoint for Annual Volume Analysis.
List of Tables:

Chapter 1:
Table 1. American College of Cardiology/American Heart Association Stages of Valvular AS. Adapted from the 2014 ACC/AHA guidelines (Nishimura, Otto et al. 2014)
Table 2. Randomized Controlled Trials of TAVR

Chapter 2:
Tables in this section have been submitted for publication in “Transcatheter Aortic Valve Implantation: Clinical, Interventional, and Surgical Perspectives”.
Table 3. Summary of studies examining the learning curve for transcatheter aortic valve implantation.
Table 4. Summary of studies examining the volume outcome relationship for transcatheter aortic valve replacement.

Chapter 4:
Figures in this section have been previously published, and are adapted from (Wassef, Alnasser et al. 2017)
Table 5. Baseline characteristics of the institutional experience study divided by chronological quantile.
Table 6. Procedural characteristics of patients the institutional experience study, divided by chronological quantile.
Table 7. Clinical and procedural outcomes for the institutional experience study divided into patient quantiles.

Chapter 5:
Figures in this section have been submitted for publication, and are adapted from Wassef et al. JACC 2018
Table 9. Unadjusted Clinical and Procedural Outcomes for Learning Curve Analysis

Table 11. Unadjusted Clinical and Procedural outcomes for Annual Volume-Outcome Analysis
Chapter 1

1 Aortic Stenosis – Diagnosis, Evaluation, Surgical and Transcatheter Management Strategies

In Chapter 1 of this thesis, as an introduction to the learning curve and minimal annual procedural volume analysis for transcatheter aortic valve replacement (TAVR), an in-depth review the disease of aortic stenosis (AS) will be undertaken. In this chapter, four major points will be covered. We will review of aortic stenosis regarding its pathophysiology, diagnosis, and prognosis. Then a discussion regarding the conventional management of severe symptomatic AS with surgical aortic valve replacement (SAVR). Following this, limitations for SAVR will be discussed. Finally, an in-depth discussion with regards to transcatheter aortic valve replacement (TAVR), especially with regards to the indications, patient selection, techniques as well as complications, and the profound increase in its use with the expected large increase in volumes of TAVR.

1.1 Aortic Stenosis

In the first section of this chapter, a comprehensive review of the pathophysiology, diagnosis and prognosis of aortic stenosis will be undertaken.

1.1.1 Background

The aortic valve (AV), one of two left sided heart valves, regulates the anterograde flow of blood in the heart. Cardiac valves, in a healthy state, function one-way doors to allow blood to move forward in one direction. The aortic valve lies between the left ventricle (LV), the main pump chamber of the heart pumping oxygen rich blood into the systemic circulation, and the aorta which is the largest artery in the body (Nishimura 2002). The aortic valve is composed of three cusps which should align in the central axis of the left ventricular outflow tract (LVOT) and aorta. During systole, the contraction of the left ventricle causes the valve cusps to open, and when the valve is healthy, there is no impedance to blood flow leaving the LV. Conversely, during diastole, the relaxation of the LV causes a sharp drop in LV pressure, resulting in the
closure of the AV, preventing the previous cardiac contraction’s blood to regurgitate, and allowing the left ventricle to fill with oxygenated blood from the left atrium (Nishimura 2002).

Narrowing of the aortic valve leading to impedance of blood leaving the left ventricle during systole is referred to as aortic stenosis (AS), while an incompetent AV leading to blood flowing back into the left ventricle during diastole is referred to as aortic regurgitation (AR); AS will be the major focus of this thesis.

1.1.2 Pathophysiology of Aortic Stenosis

Aortic stenosis is the pathological narrowing of the aortic valve during systole. The most common causes of aortic stenosis are bicuspid AS, caused by various phenotypes resulting in two functional leaflets instead of three, rheumatic AS, caused by damage and fusion of the leaflets during one or more episodes of rheumatic fever, and calcific degenerative AS, occurring due to aging. Calcific degenerative aortic stenosis will be the major focus of this discussion.

Bicuspid aortic valve disease is a relatively common cardiac anomaly affecting 0.5% - 2% of the population (Braverman, Guven et al. 2005). In this condition, patients are born with either two true AV cusps (as opposed to three) or having fusion of two of the three AV cusps (Sievers and Schmidtke 2007). There is a bimodal age distribution with higher rates of complications in patients aged 30-40 and those > 50 years old, and there is a strong 2-3:1 male to female ratio (Michelena, Desjardins et al. 2008). In a recent review and metaanalysis of 13 studies assessing complications of bicuspid aortic valve disease (Masri, Svensson et al. 2017), the incidence of significant complications include severe AR with a prevalence of 13-30%, moderate to severe AS with a prevalence of 12-37%, infective endocarditis as well as aortic dilation. Aortic stenosis tended to occur later than that of aortic regurgitation, with a peak in the 5th to 6th decade.

Rheumatic heart disease, including rheumatic AS, results from abnormal autoimmune response to group A streptococcal infections in susceptible patients (Kaplan, Bolande et al. 1964). Acute rheumatic fever occurs typically 3 weeks after group A streptococcus pharyngitis, which affects multiple organs, including causing inflammation of the valvular endocardium. Rheumatic heart disease occurs after one or repeated episodes of rheumatic fever, and symptomatic valvular disease may be diagnosed decades later (Marijon, Ou et al. 2007). The most common valvular disease associated with rheumatic heart disease is mitral stenosis, however aortic valve disease, including aortic stenosis may occur. This disease is mainly present
in developing nations and has nearly disappeared from developed nations (Carapetis, Steer et al. 2005).

Calcific aortic stenosis (figure 1) is by far the most common cause of aortic stenosis, especially in the elderly population who receive transcatheter aortic valve replacement (TAVR) in western nations. Valve sclerosis is prevalent in approximately 25% of patients over the age of 65 years (Freeman and Otto 2005). The pathophysiology of calcific aortic stenosis may be conceptualized as first an initiation phase followed by a sclerosis phase (figure 2).

**Figure 1: Gross specimen of normal and calcific degenerative aortic valve**

Right represents normal tricuspid aortic valve, left figure demonstrates calcific degenerative aortic valve. Arrow points to lipocalcific changes on aortic side of valve cusps (arrow), with sparing of commissures. Adapted from Rosario V. Freeman, and Catherine M. Otto Circulation. 2005;111:3316-3326 (Freeman and Otto 2005)

The initiation phase of aortic stenosis begins with mechanical shear stresses causing focal legions on the aortic side of the leaflets, with similarities to that of atherosclerotic vascular disease (Stewart, Siscovick et al. 1997). Extracellular lipid accumulation is seen in the subendocardial regions (Otto, Kuusisto et al. 1994). Apolipoproteins as well as oxidized phospholipids have been found in these legions (Olsson, Thyberg et al. 1999). These are then taken up by macrophages to create foam cells. Inflammation follows, via lymphocytes and
proinflammatory cytokines, which contribute to extracellular matrix deposition and local calcification (Wallby, Janerot-Sjoberg et al. 2002). Angiotensin converting enzyme has been implicated in the pathogenesis of AV sclerosis (O’Brien, Shavelle et al. 2002).

In the propagation phase, leaflet calcification is a major factor in developing aortic stenosis. Oxidized phospholipids stimulate myofibroblasts which results in calcific nodules, and as the disease progresses, osteoblast like cells release pro-calcific mediators associated with skeletal bone formation (Rajamannan, Subramaniam et al. 2003). Dystrophic calcification is found in the majority of aortic valves removed for aortic valve replacement (Mohler, Gannon et al. 2001).

**Figure 2. Pathological Mechanisms for Calcific Aortic Stenosis**

Schematic diagram for the pathogenesis of aortic calcification and stenosis. IL-1B – interleukin 1B, TGF-1B – transforming growth factor 1B, LDL – low density lipoprotein, MMP – matrix metalloproteinase, ACE – angiotensin converting enzyme. *Adapted from Rosario V. Freeman, and Catherine M. Otto Circulation. 2005;111:3316-3326 (Freeman and Otto 2005).*
1.1.3 Epidemiology of Aortic Stenosis

Aortic stenosis increases in prevalence with age. Figure 3 demonstrates the exponential rise in the rates of aortic stenosis with increasing age from 5 large studies. In the study from a large population of 11,911 adults in Olmsted county, USA (Nkomo, Gardin et al. 2006), the incidence of aortic stenosis increased from 0.6% ages 55-64, 1.4% ages 65-74, increasing to 4.6% ages >75 years of age. A similar finding was found in 5201 subjects in the Cardiovascular Health Study (Stewart, Siscovick et al. 1997) with the burden of aortic stenosis being 1.3% ages 65-74, increasing to 4% for those >85 years of age. Because of the increase in age of the population, AS has become the most prevalent heart valve disease in western countries (Lindroos, Kupari et al. 1993).

As above, much of the pathophysiology of aortic stenosis is shared with that of coronary artery disease (CAD). In the same study by Steward (Stewart, Siscovick et al. 1997), after multivariate correction, increased age (OR 2.18), male gender (OR 2.03), history of hypertension (OR 1.23), smoking (OR 1.35) and elevated low-density lipoprotein (LDL) (OR 1.12) were found to be clinical factors associated with aortic stenosis or sclerosis. In the multiethnic study of atherosclerosis of 6700 participants, a higher prevalence of aortic valve sclerosis was found amongst diabetics compared to non-diabetic patients (Katz, Wong et al. 2006).
The prevalence of Aortic Stenosis as a Function of Age

The increase in aortic stenosis prevalence with age from 5 large studies. Adapted by Lindman, B. R. *et al.* (2016) Calcific aortic stenosis *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.6 (Lindman, Clavel *et al.* 2016)

1.1.4 Clinical Findings of Aortic Stenosis

Aortic stenosis is a disease with a prolonged asymptomatic phase. The classical symptoms on presentation are exertional angina, exertional dizziness (presyncope) or frank syncope followed by progressive symptoms of congestive heart failure (CHF) including decreased exercise capacity, dyspnea, orthopnea and frank pulmonary edema (Ross and Braunwald 1968, Lindman, Clavel *et al.* 2016). Angina can occur due to increased LV mass due to hypertrophy, increased LV filling pressures as well as concomitant coronary artery disease (Julius, Spillmann *et al.* 1997). Presyncope occurs due to exercise induced vasodilation in the setting of fixed cardiac output resulting in hypotension. Finally, dyspnea is due to diastolic or systolic dysfunction resulting in increased left atrial pressures and pulmonary edema.

The physical examination for aortic stenosis has been well described and correlates well with the severity of aortic stenosis, although no physical examination maneuvers are both sensitive and specific (Etchells, Bell *et al.* 1997). The carotid pulse (as well as other central pulses) demonstrates a low volume, slow rising characters (pulsus parvus et tardus) in severe aortic stenosis, which is highly specific (Etchells, Bell *et al.* 1997). There may be a palpable thrill
over the carotid as well as a delay between the apical impulse and the carotid. Precordial exam can infrequently reveal a thrill over the right base of the heart or the suprasternal notch (Henn, Percival et al. 2017).

Auscultation of the heart in severe aortic stenosis reveals a second heart sound that is soft and often the aortic component is absent (Munt, Legget et al. 1999). The murmur in aortic stenosis is an ejection murmur – a crescendo, decrescendo murmur best heard at the right upper sternal border, radiating to the carotids and clavicles. The timing of the peak of the murmur predicts severity with a late peaking murmur being specific for aortic stenosis (Etchells, Bell et al. 1997). The murmur may also radiate to the apex with a more musical quality – the Gallavardin phenomenon. In patients with bicuspid aortic stenosis, an ejection click may be heard before the first heart sound (Lindman, Clavel et al. 2016).

1.1.5 Echocardiography, Cardiac Catheterization, and Ancillary testing in Aortic Stenosis

Aortic stenosis is usually suspected based on physical examination, demonstrating the classical murmur with physical exam findings as described in the previous section, associated with the symptoms of angina, syncope or heart failure.

Confirmation of the diagnosis is most commonly made with transthoracic echocardiography (TTE) and have been described extensively elsewhere (Baumgartner, Hung et al. 2009). TTE describes valve anatomy, severity of aortic stenosis including hemodynamics, as well as consequences of aortic stenosis on the left ventricle. Concomitant valvular disease as well as aortic enlargement may also be appreciated. The typical findings on two-dimensional echocardiography include thickening and immobility of the aortic valve leaflets with a small orifice area. Doppler echocardiography allows the assessment of transvalvular aortic gradients. From this, an aortic valve area (AVA) may be estimated. The left ventricle is often hypertrophied, and systolic dysfunction may also occur. As described in table 1, the diagnosis of classic severe aortic stenosis requires an aortic velocity (Vmax) >4 m/s, a valve gradient of > 40 mmHg, and an estimated AVA < 1.0 mm2.

Electrocardiography in aortic stenosis very frequently demonstrates left ventricular hypertrophy, although the major purpose is to assess AV nodal conduction as well as assess for arrhythmia.
Cardiac catheterization is not routinely required unless to assess for aortic valve gradient when there is non-diagnostic non-invasive testing (Nishimura and Carabello 2012). This technique however is associated with increased risk of cerebral embolism (Omran, Schmidt et al. 2003). Coronary angiography is indicated in patients who are deemed to require an intervention (SAVR or TAVR as described below) in order to determine coronary anatomy and revascularization options prior to any intervention.

Patients with sedentary life styles and no symptoms, but echocardiographically severe disease, are recommended to undergo stress testing to determine their exercise capacity and if symptoms develop should be considered for treatment (Nishimura, Otto et al. 2017). Patients who have equivocal symptoms may be assessed with measurement of natriuretic peptide, as elevated levels suggest symptoms may be due to AS (Gerber, Stewart et al. 2003).

The majority of patients with severe symptomatic aortic stenosis have high gradients (mean AV gradient > 40 mmHg), however a subset may have stage D2 – low flow low gradient AS due to underlying LV dysfunction (Nishimura, Otto et al. 2014). In this situation, it can be difficult to determine if the patient has true severe AS vs pseudo-severe AS (caused by insufficient stroke volume to open the aortic valve). In such patients, low dose dobutamine echocardiography is indicated to assess for true vs pseudo severe AS, and to assess for contractile reserve. This has been reviewed extensively elsewhere (Monin, Monchi et al. 2001, Burwash 2007) and is beyond the scope of this thesis. An entity exists of severely restricted aortic valve opening, gradients <40 mmHg and LVEF >50% with a computed aortic valve area <1.0 cm2. This entity has been referred to as paradoxical low flow low gradient aortic stenosis, with the diagnosis and management of this having been reviewed extensively elsewhere (Magne and Mohty 2015).
Table 1. American College of Cardiology/American Heart Association stages of valvular aortic stenosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| A     | At risk of AS | • Bicuspid aortic valve (or other congenital valve anomaly)  
• Aortic valve sclerosis | • Aortic $V_{\text{max}} < 2$ m/s | • None | • None |
| B     | Progressive AS | • Mild-to-moderate leaflet calcification of a bicuspid or trileaflet valve with some reduction in systolic motion or  
• Rheumatic valve changes with commissural fusion | • Mild AS:  
Aortic $V_{\text{max}}$ 2.0–2.9 m/s or mean $\Delta P < 20$ mm Hg  
• Moderate AS:  
Aortic $V_{\text{max}}$ 3.0–3.9 m/s or mean $\Delta P$ 20–39 mm Hg | • Early LV diastolic dysfunction may be present  
• Normal LVEF | • None |
| C: Asymptomatic severe AS | | | | | |
| C1    | Asymptomatic severe AS | • Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening | • Aortic $V_{\text{max}} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg  
• AVA typically is $\leq 1.0$ cm$^2$ (or AVAi $\leq 0.6$ cm$^2$/m$^2$)  
• Very severe AS is an aortic $V_{\text{max}} \geq 5$ m/s or mean $\Delta P \geq 60$ mm Hg | • LV diastolic dysfunction  
• Mild LV hypertrophy  
• Normal LVEF | • None: Exercise testing is reasonable to confirm symptom status |
| C2    | Asymptomatic severe AS with LV dysfunction | • Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening | • Aortic $V_{\text{max}} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg  
• AVA typically $\leq 1.0$ cm$^2$ (or AVAi $\leq 0.6$ cm$^2$/m$^2$) | • LVEF <50% | • None |
<p>| D: Symptomatic severe AS | | | | | |</p>
<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Valve Anatomy</th>
<th>Valve Hemodynamics</th>
<th>Hemodynamic Consequences</th>
<th>Symptoms</th>
</tr>
</thead>
</table>
| D1    | Symptomatic severe high-gradient AS | • Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening | • Aortic $V_{\text{max}} \geq 4$ m/s or mean $\Delta P \geq 40$ mm Hg  
• AVA typically $\leq 1.0$ cm$^2$ (or AVAi $\leq 0.6$ cm$^2$/m$^2$) but may be larger with mixed AS/AR | • LV diastolic dysfunction  
• LV hypertrophy  
• Pulmonary hypertension may be present | • Exertional dyspnea, angina, syncope or presyncope |
| D2    | Symptomatic severe low-flow/low-gradient AS with reduced LVEF | • Severe leaflet calcification with severely reduced leaflet motion | • AVA $\leq 1.0$ cm$^2$ with resting aortic $V_{\text{max}} < 4$ m/s or mean $\Delta P < 40$ mm Hg  
• Dobutamine stress echocardiography shows AVA $\leq 1.0$ cm$^2$ with $V_{\text{max}} \geq 4$ m/s at any flow rate | • LV diastolic dysfunction  
• LV hypertrophy  
• LVEF $<50\%$ | • CHF  
• Angina  
• Syncope or presyncope |
| D3    | Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS | • Severe leaflet calcification with severely reduced leaflet motion | • AVA $\leq 1.0$ cm$^2$ with aortic $V_{\text{max}} < 4$ m/s or mean $\Delta P < 40$ mm Hg  
• Indexed AVA $\leq 0.6$ cm$^2$/m$^2$  
• Stroke volume index $<35$ mL/m$^2$  
• Measured when patient is normotensive (systolic BP $<140$ mm Hg) | • Increased LV relative wall thickness  
• Small LV chamber with low stroke volume  
• Restrictive diastolic filling  
• LVEF $\geq 50\%$ | • CHF  
• Angina  
• Syncope or presyncope |

Stages of valvular AS. Adapted from the 2014 ACC/AHA guidelines (Nishimura, Otto et al. 2014). AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; BP, blood pressure; CHF, congestive heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; $\Delta P$, pressure gradient; and $V_{\text{max}}$, maximum aortic velocity.
1.1.6 Physiology of Severe Aortic Stenosis

The symptoms of severe aortic stenosis occur primarily due to increased afterload on the left ventricle caused by fixed outflow obstruction, beyond the compensatory mechanisms of the heart. The increase in left ventricular systolic pressure results in compensatory LV hypertrophy which in turn increases LV wall thickness to restore normal LV wall stress (Lorell and Carabello 2000). Increased hypertrophy results from an increase LV myocardium, as well as an increase in connective tissue/fibrosis which in turn worsens LV diastolic function (Lorell and Carabello 2000, Lindman, Clavel et al. 2016). The patterns of LV hypertrophy can vary from concentric remodelling where mass is normal but the LV cavity is reduced, concentric hypertrophy where ventricular mass is increased but the cavity is normal and for eccentric remodelling where wall thickness is normal or slightly increased and the left ventricular cavity is enlarged (Lindman, Clavel et al. 2016).

Angina develops due to increased LV hypertrophy that is out of proportion to the coronary blood supply with microcirculatory dysfunction demonstrated by reduced coronary vasodilator reserve (Rajappan, Rimoldi et al. 2002). Additionally, increased wall stress results in decreased coronary perfusion pressure. Dyspnea results from increased LV filling pressures due to increased wall thickness/fibrosis resulting in increased pulmonary filling pressures secondary to left atrial hypertension which is associated with poorer prognosis (Mutlak, Aronson et al. 2012). The majority of patients will retain normal LV systolic function until late in the disease, however a subset will develop LV systolic dysfunction (Lindman, Clavel et al. 2016).

1.1.7 Prognosis of Severe Aortic Stenosis

Early aortic stenosis has a long asymptomatic latent phase, followed by rapid progression and a poor prognosis once symptoms arise. Patients with severe AS with no symptoms have a low rate of sudden cardiac death, approximately 1% per year, however once AS becomes severe and symptomatic, the incidence of sudden cardiac death increase exponentially, to 8-34% per year (Chizner, Pearle et al. 1980, Sorgato, Faggiano et al. 1998). Patients with mild to moderate aortic stenosis may be monitored clinically until they develop severe symptomatic aortic stenosis as the rates of sudden cardiac death are low, with serial echocardiography every 3-5 years for mild, 1-2 year for moderate and 6-12 months for severe aortic stenosis (Nishimura, Otto et al. 2017). In a study by the university of Vienna studying the natural history of moderate aortic
stenosis, event free survival (freedom from death or valve surgery) was 67% at one year, 56% at two years and 33% at three years (Rosenhek, Binder et al. 2000). From the university of Washington, aortic jet velocity increased by 0.32±0.34 m/sec per year and the valve area decreased by 0.12±0.19 cm²/year (Otto, Burwash et al. 1997).

The prognosis of symptomatic severe aortic stenosis has been well known for 50 years. In the classic paper by Ross and Braunwald in 1968 (figure 4) assessing autopsy data from 7 prior studies (Ross and Braunwald 1968) the onset of symptoms occurred in the 6th decade followed by a rapid deterioration with average survival being 5 years for patients with the onset of angina, 3 years with the onset of syncope, and 2 years with the onset of CHF (Ross and Braunwald 1968).

**Figure 4. The natural history of aortic stenosis**

Survival during asymptomatic and symptomatic phases of aortic stenosis. Adapted from Ross and Braunwald Circulation 1968 (Ross and Braunwald 1968)
More contemporary studies have been published that have validated the poor prognosis found with patients with severe aortic stenosis. In the study at Georgetown University Hospital with non-operatively managed severe aortic stenosis, the 1, 2 and 3 year mortalities were 26%, 48% and 57% respectively (Chizner, Pearle et al. 1980). From the PARTNER trial, the medically managed severe symptomatic aortic stenosis group had a 50.7% mortality (Leon, Smith et al. 2010).

1.2 Surgical Management of Severe Aortic Stenosis

1.2.1 Background

As presented in the previous section, aortic stenosis is an indolent disease with a long asymptomatic phase, followed by rapid progression once symptoms have developed. While asymptomatic aortic stenosis may be managed with careful observation with serial clinical and echocardiographic assessments, once severe symptomatic aortic stenosis has developed, intervention is required. In this section, as an introduction to later sections discussing TAVR, the conventional surgical management of AS, SAVR will be discussed.

1.2.2 Medical Management

Medical management (including percutaneous balloon aortic valvuloplasty) has no role in the management of severe, symptomatic aortic stenosis who are candidates for AVR, whether surgical or transcatheter (Lindman, Clavel et al. 2016, Nishimura, Otto et al. 2017) due to poor survival compared to valve replacement. In a study of 252 patients who underwent AVR and 47 unoperated patients, the 3 year mortality survival for unoperated patients was 21% (Schwarz, Baumann et al. 1982). Percutaneous balloon aortic valvuloplasty, the dilation of the aortic valve with a balloon in order to increase valve area and decrease aortic gradient (in the absence of insertion of a transcatheter valve), was previously performed. However, long term event free survival without aortic valve replacement was poor, resembling the natural history of aortic stenosis (Lieberman, Bashore et al. 1995). Statins have been tried with regards to delaying the progression of severe symptomatic aortic stenosis, however the results were not positive (Cowell, Newby et al. 2005). The exception where medical therapy has utility is for patients with severe
aortic stenosis with reduced ejection fraction and heart failure with shock. In this high-risk population, the use of nitroprusside has been shown to improve survival to valve replacement (Khot, Novaro et al. 2003).

1.2.3 Surgical Management of Severe Aortic Stenosis

Surgical replacement of the aortic valve (SAVR) in severe symptomatic aortic stenosis was the only treatment that improves survival in aortic stenosis prior to TAVR. SAVR improved survival in severe symptomatic AS to nearly the same life expectancy as those without aortic valve disease(Ross and Braunwald 1968, Schwarz, Baumann et al. 1982, Nishimura, Otto et al. 2017). This compared to mortality rates > 50% in those who are not operated on in the first two years with severe symptomatic AS, translating to a mortality rate of 2% per month that surgery is delayed(Schwarz, Baumann et al. 1982). Since the first SAVR was performed in 1960(Harken, Soroff et al. 1960), SAVR has become the second most common cardiac surgery in the United States(Lee, Li et al. 2011).

The choice of SAVR prosthesis is beyond the scope of this thesis, however this topic has been published on extensively (David 2013). Mechanical prosthetic valves are durable, however require lifelong anticoagulation with warfarin, whereas bioprosthetic heart valves do not require anticoagulation, but have higher incidence of structural valve deterioration. Bioprosthetic valves are ideal choices for older patients and patients with higher bleeding risk of long term anticoagulation, whereas mechanical prosthesis are preferred for patients under the age of 50 years, and those with other indications for anticoagulation, and low bleeding risk (David 2013).

The indications for aortic valve surgery have been well established, as described by the 2014 American Heart Association/American College of Cardiology guidelines for the management of patients with valvular heart disease(Nishimura, Otto et al. 2014) describe in detail the indications for aortic valve replacement. For symptomatic patients, there is a class I indication for aortic valve replacement for patients with stage D1 (symptomatic severe AS (Vmax > 4m/s, gradient > 40 mmHg)), and class IIa recommendations for patients with patients with true low flow low gradient severe AS (stage D2) with augmentation for gradient with DSE (Tribouilloy, Levy et al. 2009), paradoxical low flow low gradient AS (stage D3) as confirmed by a recent metanalysis of eighteen studies (Dayan, Vignolo et al. 2015).

For symptomatic patients, there is a class I indication for stage C2 (severe AS with an LVEF<50%), and severe AS for other cardiac surgery. Multiple class IIa recommendations exist
including patients with asymptomatic AS but very severe AS (Vmax > 5 m/s), asymptomatic patients with abnormal stress tests, as well as moderate AS (stage B) awaiting other cardiac surgery.

**Figure 5: 2014 ACC/AHA Guidelines for Management of Aortic Stenosis**

Indications for aortic valve replacement adapted from the 2014 ACC/AHA guidelines for the management of valvular heart disease (Nishimura, Otto et al. 2014)
1.3 Limitation of Surgical Aortic Valve Replacement and the Aging Population

Transcatheter aortic valve replacement has emerged as a treatment option for patients with severe symptomatic aortic stenosis due to the limitations of surgical aortic valve replacement. In this section, these limitations will be discussed.

1.3.1 Limitations of Surgical Aortic Valve Replacement

Surgical aortic valve replacement has been the standard of care for the treatment of symptomatic severe aortic stenosis for decades (Schwarz, Baumann et al. 1982). However, there are many clinical factors that increase the risk of SAVR for patients who would otherwise be indicated for surgery, including to levels that would make operative mortality prohibitive. These factors included increase patient age, severe systemic comorbidities, as well as procedure specific variables (Lindman, Clavel et al. 2016).

The most important risk factor for increased surgical risk is patient age (Astor, Kaczmarek et al. 2000, Ashikhmina, Schaff et al. 2011, Agarwal, Garg et al. 2015). In a large sample of 46,397 inpatient SAVR performed in 1994 (Astor, Kaczmarek et al. 2000), for every 10 year increase in patient age, risk of 30 day mortality increases by an adjusted odds ratio (OR) of 1.29, with a surgical risk of approximately 5% in patients under 70 years of age, to a surgical risk of mortality > 10% for those > 85 years. In another study from the mayo clinic of 2890 patients >70 years of age, having an age 75-80, 80-84 and >85 years conferred an adjusted hazard ratio of 1.26, 1.86 and 2.87 respectively for late death as compared to patients 70-75 years of age (Ashikhmina, Schaff et al. 2011).
Figure 6. In Hospital Mortality after Aortic Valve Replacement as a Function of Age

Estimated in-hospital Mortality after SVAR, adapted from a large 1994 inpatient sample (Astor, Kaczmarek et al. 2000)

Clinical as well as procedural factors also impact the surgical risk for SAVR. From the large inpatient sample above (Astor, Kaczmarek et al. 2000), female gender - OR 1.33 (1.16-1.43), multiple valve surgery - OR 1.75 (1.12-1.59), replacement of previous SAVR - OR 2.26 (1.63-3.14), urgent surgery - OR 1.92 (1.53-2.41), CHF – OR 1.62 (1.28-2.05), cerebrovascular disease – OR 2.26 (1.70-3.00) as well as chronic renal failure - OR 2.57 (1.61-4.10) all predicted greater adjusted odds for in hospital mortality (Astor, Kaczmarek et al. 2000). Similarly, from a large Mayo Clinic registry (Ashikhmina, Schaff et al. 2011), as above age, reduced LVEF, diabetes, renal failure, prior stroke, prior myocardial infarction, prior CABG, New York Heart Association (NYHA) III -IV, and immunosuppression were found to be risk factors for late death.

Other risk factors associated with increased surgical risk include prior chest wall radiation (Chang, Smedira et al. 2007), porcelain aorta, pulmonary hypertension (Lai, Lai et al. 2007) as well as liver cirrhosis (Jacob, Hjortnaes et al. 2015). It is essential to consider patient frailty, defined as diminished reserve and inability to tolerate physiological stressors, prior to determining risk for surgery (Mack 2013).
With regards to measurements of surgical risk for SAVR, several risk scores have been developed including the commonly uses society of thoracic surgery (STS) risk calculator (http://riskcalc.sts.org) as well as the EuroSCORE calculator (http://www.euroscore.org). Use of these risk scores are critical in the evaluation of patients for surgical vs transcatheter aortic valves.

1.3.2 Untreated Patient Population Prior to Transcatheter Aortic Valve Replacement

Prior to the advent of TAVR, a significant population of patients were not offered SAVR, largely due to patient age and other comorbidities. In a European heart survey on valvular heart disease of 216 patients age > 75 years of age with an indication to perform SAVR, a decision not to operate was made in 33% of patients (Lung, Baron et al. 2003). In multivariable analysis, older age and LV dysfunction were the most striking characteristics for patients not offered surgery. Similarly, in a study of 3 large tertiary care institutions in Michigan, one third of patients with severe symptomatic AS did not undergo AVR (Bach, Siao et al. 2009). A US study of 124 patients at two large US centres (Charlson, Legedza et al. 2006) found that only 39.5% were offered AVR despite having severe AS, and those who were offered surgery had large reductions in mortality. Age < 80 was strongly associated with being offered surgery.

1.4 Transcatheter Aortic Valve Replacement (TAVR)

As clearly demonstrated, symptomatic severe aortic stenosis carries a grave prognosis, with aortic valve replacement being the only treatment that has proven to improve survival. Despite the clear benefit of SAVR in patients who have severe symptomatic AS, a substantial proportion of patients are deemed non-operative due to age or comorbidities, with a large cohort at elevated risk for operative death and complications due to advanced age. Thus, TAVR emerged as a solution to this significant health problem. In this section, the TAVR procedure itself will be discussed, the evidence base that has been used to guide societal guidelines, as well as the growth of TAVR as an introduction to the study of its learning curve and minimal annual procedural volume.
1.4.1 History of TAVR

Percutaneous balloon aortic valvuloplasty (Lababidi, Wu et al. 1984) was an initial treatment for patients with non-operable severe AS. Unfortunately, results were not durable with high recurrence of severe AS. The first balloon mounted stented valve was implanted in a pig in 1989 (Andersen, Knudsen et al. 1992). The first transcatheter valve implanted was in a right ventricle to pulmonary artery conduit in 2000 (Bonhoeffer, Boudjemline et al. 2000). TAVR was first performed in 2002 by Dr. Cribier and used a bioprosthetic valve mounted on a stainless-steel stent performed via an antegrade technique (transeptal access from right atrium to left atrium into the left ventricle and then deployed in the aortic position (Cribier, Eltchaninoff et al. 2002).

The first retrograde approach (approach most commonly used via the femoral artery) was reported by Dr Webb in 2006 (Webb, Chandavimol et al. 2006) and the first transapical approach was reported by Lichtenstein (Lichtenstein, Cheung et al. 2006) the same year. Following this single centre and multicenter registries demonstrated the feasibility of transcather aortic valve replacement, setting the stage for larger clinical trials (Webb, Pasupati et al. 2007).

1.4.2 Types of Transcatheter Aortic Valves

The most common transcatheter valve in North America is the balloon expandable valve by Edwards Lifesciences™ (Grover, Vemulapalli et al. 2017), demonstrated figure 7 A and B. Details of this valve have been published prior (Webb and Wood 2012, Lasala and Rogers 2014), briefly the valve is a trileaflet, bovine pericardial valve that is mounted initially on a stainless-steel frame, with later iterations being mounted on a cobalt-chromium frame. This valve is pretreated to reduce valve calcification. This valve may be inserted either retrograde through the femoral (most common), axillary or direct aortic route, or antegrade through the LV apex. The valve has gone through multiple iterations from the original Edwards Sapien™, to the Sapien XT™ valve to the Sapien 3™ valve, with each iteration resulting in reducing the cross-sectional area of the delivery catheter thus reducing the vascular complications, and a sealing skirt in the Sapien 3™ valve reducing paravalvular regurgitation. The valves come in 20mm, 23mm, 26mm and 29mm sizes, and are mounted on a 30-mm balloon catheter sized appropriately to the valve size. A crimping tool is used to manually compress and mount the valve onto the delivery
balloon/catheter. A 25mm delivery sheath is employed to guide the valve/delivery catheter through the vasculature into the abdominal aorta. A transapical delivery sheath is shorter.

The second most common valve is the CoreValve™ ReValving System by Medtronic™, demonstrated figure 7 C. The details of this have been published previously (Webb and Wood 2012, Lasala and Rogers 2014). This is a transcatheter heart valve that is inserted retrogradely only (transfemoral, axillary or direct aortic) with no transapical option. The valve consists of a self-expanding nitinol support frame, within which a trileaflet porcine valve. The lower portion of the frame sits within the annulus with high radial strength to secure the valve. The middle portion supports a supra-annular valve. The top portion orients the valve in the aorta.

Figure 7. Commonly Used Transcatheter Heart Valves


1.4.3 Pre-procedure Planning

Prior to the procedure, patients should be risk stratified as to their surgical risk, including a complete review of patient history, physical examination and investigations (Jones, Krishnaswamy et al. 2017). A surgical risk assessment tool, which factor patients age and body habitus, comorbidities and procedural details should be completed. The most frequently used STS score or the EuroSCORE, (Jones, Krishnaswamy et al. 2017). Using the definitions from major randomized controlled trials (RCT), patients were considered prohibitive risk if 30 day
mortality predicted is greater than 15% or permanent morbidity was felt to be >50% (Leon, Smith et al. 2010), high risk if predicted mortality is greater than 8-10%(Smith, Leon et al. 2011, Popma, Adams et al. 2014), and intermediate risk if predicted mortality is greater than 3-4%(Leon, Smith et al. 2016, Reardon, Van Mieghem et al. 2017). These risk tools do not include specific issues including hostile chest, calcification of the aorta (porcelain aorta), or patient frailty(Mack 2013). Clinical judgement is crucial, and a “heart team” approach is mandatory, being given a class I recommendation in the literature, (Nishimura, Otto et al. 2017).

In terms of evaluation, an echocardiogram is required to confirm the diagnosis, establish ventricular function and rule out additional valve pathology(Zamorano, Badano et al. 2011). A left heart catheterization is required to establish coronary anatomy, which may need to be treated prior to any procedure. There is controversy about the best management of concomitant coronary disease; this has been reviewed elsewhere(Mahmood and Muir 2017). Consideration of crossing the valve should be undertaken if there is a question of the diagnosis(Nishimura and Carabello 2012).

For all patients with acceptable renal function, a contrast enhanced, ECG gated CT scan with illeofemoral run off will need to be performed and reviewed by a qualified radiologist. The 3D reformatted CT scan will establish the size of the aortic annulus at the nadir of the leaflet cusps(Schoenhagen, Hausleiter et al. 2011). Based on annular area or perimeter, the valve size will be chosen corresponding to 0-15% oversizing. Furthermore, reformatting of the CT will be able to determine a coaxial plane of the annulus to assist in valve deployment. The heights of the coronary arteries will be determined off of the CT; lower coronary height above the annulus increases risk of coronary obstruction(Ribeiro, Webb et al. 2013). The CT aorta/iliac/femoral run off is performed for vascular access screening. Reformatted images determine vessel tortuosity, calcification, and the minimal luminal diameter of the femoral arteries; with minimal diameter of femoral artery being specific to prosthesis type and size(Lasala and Rogers 2014). If adequate the illeofemoral system is adequate, then transfemoral approach is used, otherwise if inadequate then alternative access is employed(Jones, Krishnaswamy et al. 2017).

1.4.4 The TAVR Procedure

The details of the TAVR procedure have been published previously and will be reviewed briefly(Webb and Wood 2012, Lasala and Rogers 2014, Lauck, Wood et al. 2016, Jones, Krishnaswamy et al. 2017). TAVR is performed in either a hybrid operating room or a cardiac
catheterization lab where there is suitable equipment including fluoroscopy, a cardiopulmonary bypass machine as well as equipment and expertise to treat iatrogenic vascular complications or coronary obstruction (Bavaria JE 2017). The procedure may be done under general anaesthesia if TEE required, however more recently conscious sedation has emerged as the preferred option due to decreased length of stay and faster procedure times (Lauck, Wood et al. 2016).

The approach for TAVR depends on multiple factors (Lindman, Clavel et al. 2016). The default approach is transfemoral. This is the least invasive approach however does require minimal femoral/iliac artery diameter of 6.0-6.5 mm. Transapical is an approach when femoral is not feasible and involves deployment of the valve via a thoracotomy on the left chest. This is more invasive and is associated with more respiratory complications. Transaortic and transaxillary approaches have also been performed successfully.

Vascular access is obtained on the contralateral side for aortic root injection, as well as venous access for rapid ventricular pacing. Femoral vascular access is generally performed via percutaneous access, although a cut down may be required (Lauck, Wood et al. 2016). Preclosure of the arteriotomy is performed. Periprocedural antibiotics and periprocedural ASA and clopidogrel are given. Aortic angiography should be performed to determine the optimal deployment angle where all aortic cusps are in line and parallel. Once the optimal deployment angle is obtained, the valve is crossed with a straight wire and exchanged for an extra-stiff wire. Over this wire, the sheath is inserted from the femoral artery into the aorta, after serial dilation. Balloon aortic valvuloplasty may then be performed to allow the valve to pass more easily. Through the femoral sheath, the valve prosthesis on the delivery catheter is inserted and advanced into the abdominal aorta. The patient is then systemically anticoagulated. For the balloon expandable Edwards™ system, the valve will be loaded onto the balloon. The valve/delivery catheter is then advanced over the stiff wire, across the aortic arch into the ascending aorta and across the stenotic native valve. For the Edwards™ system, once the valve is satisfactorily aligned across the annulus, the heart is rapidly paced to reduce cardiac output. Aortography is performed to ensure valve is adequately positioned. The balloon is then inflated to deploy the valve. Once the valve has been deployed, final aortography is performed to ensure the valve is correctly positioned with minimal paravalvular regurgitation. If paravalvular regurgitation is present, repeat dilation of the stent valve should be performed. The balloon delivery catheter and the sheath are then removed, and hemostasis is performed, usually through closure of the previously deployed perclose devices.
Transapical valve deployment is an alternative for patients without adequate femoral artery access. Femoral arterial and venous access is obtained for aortography and ventricular pacing. A lateral thoracotomy is performed to expose the LV apex and purse string sutures are placed in the apical lateral wall. The patient is anticoagulated, and the apex is punctured, and a stiff wire is advanced antegrade through the aortic valve into the aorta. The transapical sheath is inserted a few centimetres into the LV apex and balloon valvuloplasty is performed. The valve, loaded on the transapical delivery catheter is then inserted through the sheath, into the correct position across the stenotic aortic valve. As with transfemoral TAVR, under rapid ventricular pacing, and after aortography to ensure the valve is correctly positioned, the balloon is inflated, deploying the valve in place. Finally, the deployment balloon catheter and sheath are removed, and the puncture site is repaired using the pursestring sutures.

Figure 8. Schematic Diagram of Access for TAVR

Access balloon expandable TAVR valve via retrograde (transfemoral, transcaval, transaortic, or subclavian) vs transapical access. Adapted from Nat. Rev. Cardiol.
doi:10.1038/nrcardio.2017.82(Jones, Krishnaswamy et al. 2017)
1.4.5 Pivotal Randomized Controlled Trials for TAVR

Over the last decade, multiple large international randomized clinical trials have demonstrated superiority for TAVR compared to medical management for patients with prohibitive surgical risk, and equivalence or superiority for TAVR compared to SAVR for high, and intermediate risk patients, with trials ongoing for low risk patients ongoing. A summary of the largest randomized controlled trials to date are found in Table 2.

**Prohibitive Surgical Risk**

The PATNER 1B trial published in 2010 (Leon, Smith et al. 2010) studied a total of 358 patients deemed inoperable (predicted mortality > 15% or predicted mortality and morbidity > 50% by heart team) who were randomized to either TAVR or optimal medical therapy, including balloon aortic valvuloplasty. At 1 year, the rate of death was 30.7% with TAVR, significantly lower than the 50.7% with standard therapy (p<0.001). The composite of death or repeat hospitalization was 42.5% with TAVI, lower than the 71.6% with standard therapy (p<0.001). The rate of NYHA class III or IV heart failure among survivors was lower among patients who had undergone TAVI than among those who had received standard therapy (25.2% vs. 58.0%, P<0.001). TAVI had a higher rate of major strokes (5.0% vs. 1.1%, P=0.06) and major vascular complications (16.2% vs. 1.1%, P<0.001).

**High Surgical Risk**

The PARTNER IA trial published in 2011 randomly assigned 699 patients with severe aortic stenosis who were deemed high risk for surgery (predicted mortality > 10%). At 30 days, there was a non-significant trend to lower death from any cause (3.4% vs 6.5%, p=0.07), which became equivalent at 1 year (24.2% vs 26.8%, p=0.44). Furthermore, death and stroke were equal at 1 year, 26.5% vs 28%, p=0.7. Major vascular complications were greater with TAVR (11.0% vs. 3.2%, P<0.001); however major bleeding (9.3% vs. 19.5%, P<0.001) and new-onset atrial fibrillation (8.6% vs. 16.0%, P = 0.006) were more frequent after SAVR.

In 2014 the US CoreValve Clinical Investigators published the pivotal trial for high and prohibitive surgical risk patients (Adams, Popma et al. 2014) wherein 795 patients were randomized to TAVR or SAVR. In this trial, high surgical risk was defined as predicted mortality of > 15% or mortality and irreversible morbidity of > 50%. The rate of death from any cause was death from any cause at 1 year was significantly lower in the TAVR vs SAVR (14.2%
vs. 19.1%, p<0.001). The rates of any stroke were 4.9% vs 6.2% in the TAVR vs SAVR groups at 30 days (P = 0.46). Major vascular complications (5.9% vs 1.7%, p=0.003) and permanent pacemaker implantation (19.8% vs 7.1%, P<0.001) were higher with TAVR, however major bleeding (28.1% vs 34.5%, p=0.05) and acute kidney injury (6.0% vs 34.5%, p<0.001) were lower with TAVR.

**Intermediate Surgical Risk**

The PARTNER 2 trial published in 2016(Leon, Smith et al. 2016) randomly assigned 2032 patients with intermediate-risk severe aortic stenosis (STS predicted rate of death 4-8%). The rate of death from any cause was equal at two years between TAVR and SAVR (16.7 vs 18.0, p=0.45), death from any cause or disabling stroke (19.3 vs 21.1, p=0.33), death from any cause or hospitalization (30.5% vs 29.6%, p=6.07) with higher rates of vascular complications with TAVR but lower rates of life threatening bleeding, acute kidney injury, new onset atrial fibrillation.

In the SURTAVI trial published in 2017(Reardon, Van Mieghem et al. 2017), 1746 patients with STS risk of death of 3% to 15% with SAVR were randomized to TAVR with the CoreValve or conventional SAVR. The results of this study demonstrated that as compared to SAVR, TAVR had equivalent rates of 2-year mortality or disabling stroke 12.6% vs 14.0% (non-inferior), 2-year rates of death from any cause 11.4% vs 11.6%, and 2-year rates of stroke 2.6% vs 4.5%. The rates of major vascular complications were higher with TAVR and the rates of atrial fibrillation were higher with SAVR.

**Low Risk Patients**

At the time of writing, major multicenter randomized trials are ongoing for patients with lower predicted mortality comparing TAVR with SAVR. However, a smaller 3 center study form Denmark and Sweden, the NOTION trial(Sondergaard, Steinbruchel et al. 2016), compared TAVR with SAVR in 280 patients at lower risk (mean STS score of 3.0%) with the Medtronic CoreValve being used. Two-year results have been published demonstrating that in this small population there was no significant difference in 2-year mortality, stroke or MI (15.8% vs 18.8%, p=0.43), 2 years mortality (8.0% vs 9.8%, p=0.45). New onset atrial fibrillation (AF) however was lower with TAVR (22.7% vs 60.2%, p<0.001) but the need for permanent pacemaker (PPM) insertion was higher with TAVR (41.3% vs 4.2%, p<0.001).
## Table 2. Randomized Controlled Trials of TAVR

<table>
<thead>
<tr>
<th>Study</th>
<th>Valve Used</th>
<th>Patients Enrolled</th>
<th>Surgical Risk</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prohibitive Surgical Risk</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| PARTNER 1B (Leon, Smith et al. 2010) | TAVR (Edwards Sapien) vs Medical Management (Including BAV) | 358               | Ineligible for surgery | • 1-year mortality: 30.7% vs 50.7%, p<0.001  
• 1-year mortality or hospitalization: 42.5% vs 71.6%, p<0.001  
• NYHA II-III CHF: 25.2% vs 58.0%, P<0.001  
• TAVI had a higher rate of major strokes (5.0% vs. 1.1%, P=0.06) and major vascular complications (16.2% vs. 1.1%, P<0.001) |
| **High Surgical Risk**       |                              |                   |               |                                                                                                                                                                                                           |
| PARTNER IA (Smith, Leon et al. 2011) | TAVR (Edwards Sapien) vs SAVR | 669               | High Surgical Risk | • 1-year mortality: 24.2% vs 26.8%, p=0.44  
• 1-year mortality or major stroke: |
<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>n</th>
<th>Patient Risk</th>
<th>1-year of death</th>
<th>Stroke</th>
<th>Major vascular complications</th>
<th>Major bleeding</th>
<th>Acute kidney injury</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoreValve (Adams, Popma et al. 2014)</td>
<td>TAVR (CoreValve) vs SAVR</td>
<td>795</td>
<td>High Surgical Risk</td>
<td>14.2% vs 19.1%, p&lt;0.001</td>
<td>4.9% vs 6.2%, p = 0.46</td>
<td>(5.9% vs 1.7%, p=0.003)</td>
<td>(28.1% vs 34.5%, p=0.05)</td>
<td>(6.0% vs 34.5%, p&lt;0.001)</td>
<td>0.003</td>
</tr>
<tr>
<td>PARTNER IIA (Leon, Smith et al. 2016)</td>
<td>TAVR (Sapien XT) vs SAVR</td>
<td>2032</td>
<td>Intermediate Surgical Risk</td>
<td>19.3% vs 21.1%, p=0.25</td>
<td>30.5% vs 29.6%, p=0.67</td>
<td></td>
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</tr>
</tbody>
</table>
|                       | TAVR (CoreValve) vs SAVR | 1746 | Intermediate Surgical Risk | • 2-year mortality or disabling stroke 12.6% vs 14.0%  
• 2-year death from any cause 11.4% vs 11.6%  
• 2 Year Stroke 2.6% vs 4.5% |
<table>
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<tbody>
<tr>
<td><strong>Low Surgical Risk</strong></td>
<td></td>
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</tr>
</tbody>
</table>
| NOTION (Sondergaard, Steinbruchel et al. 2016) | TAVR (CoreValve) vs. SAVR | 280  | Low Surgical Risk | • 2-year mortality, stroke or MI 15.8% vs 18.8%, p=0.43  
• 2 years mortality 8.0% vs 9.8%, p=0.45  
• AF 22.7% vs 60.2%, p<0.001  
• PPM 41.3% vs 4.2%, p<0.001 |

Randomized controlled trials of TAVR compared to SAVR for high, intermediate and low risk surgical candidates, and TAVR compared to medical therapy for prohibitive surgical risk patients. TAVR – transcatheter aortic valve replacement, SAVR – surgical aortic valve replacement, PARTNER - Placement of Aortic Transcatheter Valves, SURTAVI - Surgical Replacement and Transcatheter Aortic Valve Implantation, NOTION - Nordic Aortic Valve Intervention.
1.4.6 Current Societal Guidelines TAVR

TAVR has been incorporated in the most recent 2017 ACC/AHA guidelines for the management of valvular heart disease (Nishimura, Otto et al. 2017). The guidelines give a Class I, level of evidence (LOE) C recommendation for patients for whom TAVR of high-risk SAVR is being considered, a heart valve team approach using healthcare professionals with expertise in aortic stenosis, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery should collaborate to provide optimal patient care.

In terms of patient populations to be served with each approach, the guidelines have been summarized in figure 9. Prohibitive surgical risk patients are recommended to be considered for TAVR when life expectancy post TAVR is greater than 1 year (Class I, LOE A). For patients who are deemed high surgical risk, the guidelines give both TAVR and SAVR a class I, LOE A recommendation depending on patient-specific risks, values and preferences. For Intermediate risk patients, the guidelines diverge with SAVR being given a Class I recommendation and TAVR being given a Class IIa recommendation. For low risk patients, because of the paucity of RCT data, SAVR remains the only recommended therapy at this time.

Figure 9. 2017 ACC/AHA Recommendations for the Management of Severe Symptomatic Aortic Stenosis

1.4.7 Measures of Outcomes in TAVR

The definitions for outcomes in TAVR have been established by the Valve Academic Research Consortium-2 (VARC-2) consensus document (Kappetein, Head et al. 2012). They will be reviewed in detail here as they will be used extensively in the studies to follow. The purpose of this document is to provide standardized definitions for clinically relevant endpoints in trials of TAVR including mortality, stroke, myocardial infarction, bleeding complications, acute kidney injury, vascular complications, conduction disturbances and arrhythmias. While most of the clinically relevant endpoints are self-explanatory, for the purpose of this thesis, the most important points that will be described in detail include the definition of (passages take from the VARC-2 consensus document) (Kappetein, Head et al. 2012):

1. Major vascular complications:
   - Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR
   - Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR
   - Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
   - The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR
   - Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
   - Surgery for access site-related nerve injury OR
   - Permanent access site-related nerve injury
2. Major bleeding – Overt bleeding either associated with a drop in hemoglobin level of at least 3.0 g/dl or requiring transfusion of 2-3 units of red blood cells, or requiring hospitalization or surgery.

For the two studies performed in this thesis, two major combined endpoints were assessed. They are defined by the VARC-2 guidelines (passages taken from the VARC-2 consensus document, (Kappetein, Head et al. 2012)):

1. Device success:
   - Absence of procedural mortality AND
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
   - Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation)

2. Early Safety/Major Adverse Cardiac Events (MACE):
   - All-cause mortality
   - All stroke (disabling and non-disabling)
   - Life-threatening bleeding
   - Acute kidney injury
   - Coronary artery obstruction requiring intervention
   - Major vascular complication
   - Valve-related dysfunction requiring repeat procedure (balloon aortic valvuloplasty, TAVR, or SAVR)

1.4.8 Outcomes and Complications of TAVR

1. Mortality – The mortality rates for TAVR have been falling with progressive studies, likely due to the decreasing morbidity in patients enrolled in lower risk trials, as well as possibly due to improved device and procedural techniques. The mortality rate for TAVR was 5% at 30 days and 30.7% at 1 year in the PARTNER 1B trial (Leon, Smith et al. 2010), dropping to a 3.9% at 30 days and 2-year mortality of 19.3% in the PARTNER IIa trial (Leon, Smith et al.
2016), and 2.2% at 30 days and 12.6% at 2-year in the SURTAVI trial (Reardon, Van Mieghem et al. 2017). From the most recent STS/ACC TVT annual report, the 30-day mortality rate is reported at 4.6% (Grover, Vemulapalli et al. 2017). Characteristics post TAVR independently associated with increased mortality from the STS/ACC TVT registry include advanced age, male sex, end-stage renal disease, severe chronic obstructive pulmonary disease, non-transfemoral access, STS PROM score greater than 15% vs less than 8, and preoperative atrial fibrillation/flutter (Holmes, Brennan et al. 2015).

2. Stroke and cerebral embolism occurred at rates of 4-5% in the early TAVR trials (Smith, Leon et al. 2011, Adams, Popma et al. 2014). In a study from the PARTNER trial, risk factors for stroke in transfemoral TAVR included higher pre-TAVR AV gradient, and for transapical TAVR included more post dilation as well as lower LVEF and presence of AF (Kapadia, Agarwal et al. 2016). From the most recent STS report, the 30 rates of stroke were 2.1% (Grover, Vemulapalli et al. 2017).

3. The rate of major bleeding was 16.8% at 30 days in the Partner Ib trial (Leon, Smith et al. 2010), falling to 10.4% at 30 days in the PARTNER IIa trial (Leon, Smith et al. 2016). The rate of bleeding has been falling in the STS report, decreasing from 5.4% in 2012, to 4.2% in 2014 to 3.9% in 2015 (Grover, Vemulapalli et al. 2017).

4. Similarly, the rates of major vascular complications were high in the early trials, with the rate being 5.9% in both the CoreValve extreme risk trial (Adams, Popma et al. 2014) and the SURTAVI trials (Reardon, Van Mieghem et al. 2017), but being reported as lower, 1.3%, in the STS registry (Grover, Vemulapalli et al. 2017)

1.4.9 Growth of TAVR/Growing Aging Population

With the advent of TAVR, a new option for treatment of severe AS has arrived, with proven efficacy in patients with inoperable, high, intermediate, and now even lower surgical risk. With these results, there has been considerable growth in the volume of TAVR being performed across the world, as well as an increase in the number of centers performing TAVR. From the GARY registry in Germany, the number of TAVR procedures increased from 144 in 2007 to 9147 in 2013 (Reinöhl, Kaier et al. 2015). In the most recent STS/ACC TVT registry (Grover, Vemulapalli et al. 2017), the number of sites performing TAVR has more than doubled in 4 years on a stepwise increase, form 198 in 2012, to 414 in 2015. Concomitant with this, the
The number of procedures has demonstrated over a fourfold increase in the number of procedures performed, from 4427 annually in 2012 to 24808 in 2015 (Figure 10).

The future trends for TAVR are likely to see ongoing significant growth in the number of patients who will be treated with TAVR. This will likely be driven by increasing indications for the procedure as the indication drops to lower risk patients, the growth of the elderly population, as well as the increase in the incidence of comorbidities that increase surgical risk. In terms of increasing age, the United States Census Bureau 2012 estimates(Ortman 2014) have the population of the United States of the age 65-84 increasing from 37 million in 2012 to 64 million in 2030, and the population >85 years of age increasing from 6 million in 2012 to 9 million in 2030 and then to 18 million in 2050. In a separate report by the US Census Bureau, the world population over the age of 65 is expected to grow from approximately 600 million currently to 1.6 Billion in 2050(Wan He 2016). With the increase in the elderly population, a concomitant increase in the prevalence of AS will almost certainly occur.

**Figure 10. Growth in the number of TAVR sites and procedures performed in the United States**

Over a four-year period, a greater than two fold increase in TAVR centers and a greater than fourfold increase in TAVR volume in the United States. Adapted from the STS/ACC TVT registry(Grover, Vemulapalli et al. 2017)
Chapter 2

2 Learning Curve Characteristics and Relationship of Procedural Volumes with Clinical Outcomes for Transcatheter Aortic Valve Replacement (TAVR)

Dr Anthony Wassef, MD and Dr Asim Cheema, MD, Ph.D.

Chapter has been submitted for publication, publication pending.

Transcatheter aortic valve replacement (TAVR) has experienced marked growth in utilization after the successful outcomes of large randomized trials confirming clinical utility of TAVR for patients at high (Leon, Smith et al. 2010, Smith, Leon et al. 2011, Adams, Popma et al. 2014) and intermediate risk for surgical aortic valve replacement (SAVR) (Leon, Smith et al. 2016, Reardon, Van Mieghem et al. 2017). This success has further stimulated enthusiasm and the results of studies investigating safety and efficacy of TAVR among low surgical risk patients with aortic stenosis are anxiously awaited (Thyregod, Steinbruchel et al. 2015). With the expanding indications for TAVR (Nishimura, Otto et al. 2017), there has been a significant increase in the number of centers performing TAVR as well as the number of procedures being performed at each center. Compared to 2012, when 4627 procedures were performed at 198 centers in the United States, greater than 24000 procedures were performed at more than 400 centers in 2015 (Grover, Vemulapalli et al. 2017). An increasing proportion of elderly population in the Western society over the next decades (Stewart, Siscovick et al. 1997, Wan He 2016) will require a greater demand for TAVR procedures with a concomitant increase in the need of new operators and centers (Osnabrugge, Mylotte et al. 2013). However, TAVR is a technically challenging procedure requiring a unique skill set that is distinct from conventional learning in interventional cardiology and cardiac surgery (Tommaso, Bolman et al. 2012). Therefore,
ongoing quality assurance is highly desirable to optimize clinical outcomes and maintain excellence for operators and sites performing TAVR.

The phenomenon of procedural learning curve has been well described for technically difficult or complex procedures (Sanchez, Harrell et al. 2001, Ball, Sharieff et al. 2011). In addition, the effects of operator and institutional volumes on procedural success rates and patient outcomes are well documented in the surgical literature (Hannan, Racz et al. 1997). However, limited information is available regarding the learning curve and annual volume relationship with clinical outcome for TAVR procedures.

In this chapter, we will review the general principles associated with the learning curve phenomenon and the relationship between institutional or operator volumes with clinical outcomes. In addition, we will discuss the evidence for TAVR learning curve and data examining the effect of annual institutional volumes on patient outcomes as well as identify areas that require further research to answer outstanding questions.

2.1 Learning Curve in Transcatheter Aortic Valve Replacement (TAVR)

2.1.1 General Principles for Learning Curve Analysis

The concept of the learning curve was first introduced in aircraft manufacturing in 1936, where Wright described how the cost of aircraft manufacturing decreased with increasing time and experience (Wright 1936). This has since been applied to other industries including the medical profession supporting the principle that people and organizations would become better at performing specific tasks with increasing exposure and experience (Craig, Dieppe et al. 2008). In contrast to pharmacological treatments, both surgical and interventional procedures including TAVR are difficult to investigate due to their complex and multifaceted nature including need for specific training and continued experience for satisfactory results (Subramonian and Muir 2004, Hopper, Jamison et al. 2007, Craig, Dieppe et al. 2008). Cook et al. (Cook, Ramsay et al. 2004) described a conceptual approach to learning curve analysis where incremental improvement in outcomes finally reaches a plateau. It is important to note, that “surgical skill” is not a quantity or variable that can be measured directly; instead the two quantities that are
assessed in the learning curve analysis include measures of process (operative time, contrast volume, etc.) and measures of clinical outcome (e.g. death, stroke, bleeding, etc.) (Subramonian and Muir 2004).

2.1.2 Learning Curve Phenomenon in Clinical Medicine

The learning curve has been assessed in multiple studies, primarily related to surgical specialties and medical education (Hopper, Jamison et al. 2007). In terms of clinical implications, the most notable case is related to the excessive rates of death among pediatric patients undergoing cardiac surgery in Bristol, UK when the poor outcomes were identified to be related to the limited experience of the surgeon (Smith 1998). In cardiovascular medicine, the presence of a learning curve has been documented for both interventional and cardiac surgery procedures. For coronary artery bypass grafting (CABG), Bridgewater et al. showed that patient mortality rates consistently declined from 2.2% for surgeons in the first year of practice after completion of residency training to 1.2% for the fourth year of practice post training (Bridgewater, Grayson et al. 2004). Similarly, operative time for CABG has been shown to decrease by over 17 minutes when comparing new with experienced surgeons (Maruthappu, Duclos et al. 2015). In interventional cardiology, the phenomenon of learning curve has been demonstrated for transradial cardiac catheterization and coronary interventions (PCI). Ball et al. (Ball, Sharieff et al. 2011) studied 1672 patients undergoing transradial PCI by 28 operators and found that failure rates and contrast use were significantly higher for the first 50 cases compared to experienced radial operators and the odds of radial failure reduced by 32% for every 50 case increase in the operator experience. Similar results were reported from the much larger CathPCI registry confirming that a minimum of 50 case volume was required to achieve technical proficiency for transradial PCI (Hess, Peterson et al. 2014).

2.1.3 Learning Curve for Transcatheter Aortic Valve Replacement (TAVR):

Measures of Process

Multiple studies have demonstrated that with increasing procedural experience, measures of process for TAVR including procedure time, fluoroscopy time and contrast use will improve (table 1). Early single center trials focusing on transapical TAVR (TA-TAVR) (Kempfert,
Rastan et al. 2011) showed that fluoroscopy time (7.1 min vs 6.2 min) and contrast volume (104 mL vs 93 mL) significantly decreased after the initial 150 cases. Similarly, D’Ancona et al. (D’Ancona, Pasic et al. 2014) showed a 5% decrease in operative time and 15% lowering of radiation exposure for every 100 TAVR procedures performed. A similar analysis from the PARTNER trial was reported by Suri et al. and included 1100 patients undergoing TA-TAVR showing significant reductions in fluoroscopy time (14 to 12 minutes) and contrast volume (114 to 90 ml) after the initial 60 cases (Suri, Minha et al. 2016). A similar trend for transfemoral TAVR (TF-TAVR) cohort from PARTNER study (n=1521) was reported with a decrease in procedure time from 154 to 85 minutes, and reduced fluoroscopy time from 28 to 20 minutes over the course of the study duration (Alli, Rihal et al. 2016).

We have previously examined the learning curve phenomenon in a large cohort of patients from an international TAVR registry comprising 1953 patients (Wassef, Alnasser et al. 2017). Data for all TAVR cases was collected from the start of the respective TAVR programs and stratified into chronological quantiles. We observed a consistent decrease in procedure time with increasing case volume. The TAVR performed in the fourth quantile (>243 procedures) showed a procedures times >120 minutes for only 2.3% of cases compared to 13.3% in the first quantile (<62 procedures). Similarly, <5% of cases in the fourth quantile utilized contrast volume of >100 ml compared to 15% of cases in the first quantile. These findings were later confirmed in a publication from the TVT registry from the United States for 42,988 TAVR patients also showing a comparable decrease in contrast use, air kerma radiation dose and fluoroscopy time with increasing experience (Carroll, Vemulapalli et al. 2017).

2.1.4 Learning Curve for Transcatheter Aortic Valve Replacement (TAVR):
Measures of Clinical Outcomes

As with measures of process examining procedural outcomes, multiple studies have studied and reported an improvement in clinical outcomes for TAVR with increasing procedural experience (table 3). The initial report of a learning curve from the Vancouver group (Gurvitch, Tay et al. 2011) divided their initial 270 cases into first and second half and showed improved 30-day mortality that decreased from 13.3% among the first half to 5.9% among the second half of procedures. A three-center study from France and Japan examined early learning curve for TA- and TF-TAVR (Arai, Lefevre et al. 2016). The authors observed that 1-year mortality
significantly improved after the initial 86 cases for the Sapien valve (34% vs 21%) and after the
initial 40 cases for the CoreValve (38% to 14%) for TF-TAVR. However, there was no
significant difference in mortality with higher volume for TA-TAVR, though life-threatening
bleeding (9% vs 1%), stroke (5% vs 0%) and acute kidney injury (16% vs 6%) decreased only
after the first 128 cases.

Three large multicenter studies have examined relationship of procedural volumes with
clinical outcomes among TAVR populations. Minha et al. (Minha, Waksman et al. 2016) used
data from 1521 patients undergoing TF-TAVR from the PARTNER trial and found that 80%
device success was achieved by 22 cases, major vascular complications fell below 5% after 70
cases and major bleeding was <10% after the 25-case volume. Wassef et al. (Wassef, Alnasser et
al. 2017) used data from an international TAVR registry from nine centres with 1953 patients
and stratified all cases in chronological case quantiles (Q1≤ 62 cases, Q2 63-133, Q3 134-233,
Q4 ≥ 234). The authors reported a significant increase in device success (78% for Q1 to 89% for
Q4), decreased incidence of moderate to severe paravalvular leak (19% for Q1 to 11% for Q4)
and lower rates of valve embolization (3.8% for Q1 to 0.2% for Q4) with greater TAVR volume.
The overall rate of the early safety endpoint improved from 19% for patients in Q1 to 10% for
patients in Q4, with a significant decrease from Q1 to Q 4 for the rate of major vascular
complications (9% vs 4%), major bleeding (4.4% vs 1.6%) and all-cause mortality (8.3% vs
3.7%). Multivariate correction for baseline and procedural variables demonstrated that Q2 (OR
2.18), Q3 (OR 3.82) and Q4 (OR 13.5) were independently associated with higher device success
while Q3 (OR 0.67) and Q4 (OR 0.41) were associated with higher early safety end point. Q4
was also independently associated with a lower mortality (OR 0.36). Using data from the TVT
registry, Carrol et al. also demonstrated a similar learning curve (figure 11) (Carroll, Vemulapalli
et al. 2017). In their analysis of 42,988 TAVR procedures at 395 hospitals in the US performed
between 2011-2015, the modeled rates of mortality, vascular complications and bleeding
complications for the first case versus the 400th case reduced from 3.6% vs 2.6%, 6.1% vs 4.2%,
and 9.6% vs 5.1% respectively. The differences in outcomes were most pronounced for the first
100 cases.
Table 3. Summary of studies examining the learning curve for transcatheter aortic valve implantation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Source</th>
<th>Data/ Population</th>
<th>N</th>
<th>Access</th>
<th>Principle Comparison / Analysis</th>
<th>Principle Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gurvitch et al. (Gurvitch, Tay et al. 2011)</td>
<td>Single center</td>
<td>270</td>
<td>TF and TA</td>
<td>First half (135) vs second half (135)</td>
<td>Significant increase in overall procedural success (92.6% vs 97.8%), significant decrease in overall mortality (13.3% vs 5.9%)</td>
<td></td>
</tr>
<tr>
<td>Kempfert et al. (Kempfert, Rastan et al. 2011)</td>
<td>Single center</td>
<td>299</td>
<td>TA</td>
<td>First half (150) vs second half (149)</td>
<td>Significantly reduced contrast load (104 mL vs 93 mL), balloon re-dilation and reduced 30-day mortality (11.3% to 6.0%)</td>
<td></td>
</tr>
<tr>
<td>Alli et al. (Alli, Booker et al. 2012)</td>
<td>Single center</td>
<td>44</td>
<td>TF and TA</td>
<td>1st to 3rd tertile</td>
<td>Significant decrease in median contrast volume (180 to 160 to 130 ml), valvuloplasty to valve time, fluoroscopy time (26.1 to 17.2 to 14.3 min) and radiation dose</td>
<td></td>
</tr>
<tr>
<td>D’Ancon et al. (D'Ancona, Pasic et al. 2014)</td>
<td>Single Center</td>
<td>500</td>
<td>TA</td>
<td>Linear and non-parametric correlation</td>
<td>5% reduction in operating time and 15% reduction in contrast dose per 100 cases performed.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Center Type</td>
<td>Sample Size</td>
<td>Technique</td>
<td>Primary Endpoint</td>
<td>Description</td>
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<tr>
<td>Lunardi et al. (2016)</td>
<td>Single center</td>
<td>177</td>
<td>TF</td>
<td>Cumulative Sum</td>
<td>54 cases for plateau of primary composite endpoint of major complications; 32 cases for plateau of device success.</td>
<td></td>
</tr>
<tr>
<td>Arai et al. (2016)</td>
<td>3 Centers</td>
<td>312</td>
<td>TF</td>
<td>Cumulative Sum</td>
<td>Edwards valve: 30-day mortality (17% to 7%) and 1 year mortality (34% to 21%) improved. CoreValve: 30-day mortality (20% to 6%) and 1 year mortality (38% to 15%) improved.</td>
<td></td>
</tr>
<tr>
<td>Arai et al. (2016)</td>
<td>3 Centers</td>
<td>257</td>
<td>TAo</td>
<td>Cumulative Sum</td>
<td>30-day mortality was not significantly different, the incidence of life-threatening bleeding (9% vs 1%), stroke (5% vs 0%), and AKI (16% vs 6%) decreased in the late phase group.</td>
<td></td>
</tr>
<tr>
<td>Suri et al. (2016)</td>
<td>Multicenter PARTNER</td>
<td>1100</td>
<td>TA</td>
<td>Non-linear mixed modeling</td>
<td>30 cases: Procedure time decreased from 131 to 116 minutes; 45 cases: Device success increased to 90%.</td>
<td></td>
</tr>
<tr>
<td>Study Authors</td>
<td>Setting</td>
<td>N</td>
<td>Technique</td>
<td>Plateau of Effect</td>
<td>Plateau of Effect Details</td>
<td></td>
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<tr>
<td>Minha et al.</td>
<td>Multicenter - PARTNER</td>
<td>1521</td>
<td>TF</td>
<td>Clinical</td>
<td>22 cases: 80% device success; 70 cases: major bleeding below 10%; 25 cases: major vascular complications below 5%; 28 cases: consistently low 30-day mortality.</td>
<td></td>
</tr>
<tr>
<td>Alli et al.</td>
<td>Multicenter - PARTNER</td>
<td>1521</td>
<td>TF</td>
<td>Technical</td>
<td>Procedure time decreased from 154 to 85 minutes; fluoroscopy time from 28 to 20 minutes. Plateau achieved at 25 cases for centers entering late</td>
<td></td>
</tr>
<tr>
<td>D’Anconna et al.</td>
<td>Single Center</td>
<td>133</td>
<td>TF</td>
<td>Early learning</td>
<td>Statistically significant reduction in catheterization time after first 20 cases</td>
<td></td>
</tr>
<tr>
<td>Henn et al.</td>
<td>Single Center</td>
<td>400</td>
<td>TF, TA and TAo</td>
<td>Case sequence</td>
<td>Technical proficiency begins to develop by the 25th case, and achieved by 50th case</td>
<td></td>
</tr>
<tr>
<td>Gurevitch et al.</td>
<td>Single Center – recent</td>
<td>269</td>
<td>TF and alternative</td>
<td>Mentorship</td>
<td>After 1 year and 50 cases: No difference in outcomes (procedural safety, procedure times, length of stay) between experienced center and novice center</td>
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<tr>
<td></td>
<td>initiation with mentorship</td>
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<td>novice center</td>
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<tr>
<td>Study</td>
<td>Registry</td>
<td>N</td>
<td>TF and alternative</td>
<td>Case sequence quartiles</td>
<td>Q4 vs Q1: All-cause mortality decrease (4% vs 8%), improved device success (89% vs 78%), reduced combined safety endpoint (10% vs 19%)</td>
<td></td>
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<tr>
<td>Carrol et al. (Carroll, Vemulapalli et al. 2017)</td>
<td>STS/TVT Registry</td>
<td>42998</td>
<td>TF and alternative</td>
<td>Case sequence quartiles, linear and non-linear modeling</td>
<td></td>
<td></td>
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</table>

TF = transfemoral; TA=transapical; TAo= transaortic; AKI – acute kidney injury; STS/TVT – society of thoracic surgeons/transcatheter valve therapy.
Figure 11. Procedural Sequence Number association with Complications.

Association of A) Mortality, B) Vascular complications C) Bleeding and D) Stroke with procedure sequence number, with the most marked improvement in outcomes being in the first 100 cases. Adapted with permission from Carrol et al. 2017.(Carroll, Vemulapalli et al. 2017)
2.2 Procedural Volume and Outcome Relationship for Transcatheter Aortic Valve Replacement

2.2.1 Procedural Volume and Outcomes in Clinical Medicine

The relationship between and hospital and operator volumes and adverse outcomes for surgical procedures has been well described, with the first large report published by Luft et al. in 1979 reporting improved mortality for a variety of surgical procedures in high volume compared to low volume hospitals (Luft, Bunker et al. 1979). Factors that may influence improved surgical outcome in higher volume hospital include more skilled surgeons, referral bias to surgeons with better outcomes, increased familiarity with and ability to anticipate and manage post-operative complications, greater resources to manage complex patients and better communication between the health care team (Luft, Bunker et al. 1979, Gonzalez, Dimick et al. 2014). The role of post-operative management and “failure to rescue” from a complication has also been identified as another important factor for adverse outcomes seen among low volume centres. Results from a series of >100,000 US Medicare patients undergoing cardiovascular surgery procedures showed that there was a 12% higher rate of major complications but 57% were more likely to die from the complications when procedures were performed at centers in the lowest compared to the highest annual volume quintile (Gonzalez, Dimick et al. 2014). Although, studies which have examined volume outcome relationships for both individual operators and institutions, a recent systematic review suggests that institutional volumes are more predictive of adverse outcomes for complex procedures, while operator volumes are reasonable predictor for outcomes of less complex procedures (McAteer, LaRiviere et al. 2013). Birkmeyer et al. reported from a large series of nearly half a million patients undergoing a variety of common surgical procedures showing a strong relationship between hospital surgical volume and adjusted operative mortality for CABG, (5.5% for >162 procedures/yr vs 3.5% for <101 procedures/year), aortic valve replacement (10% for >42 procedures/year vs 6% for <22 procedures/year), and repair of abdominal aortic aneurysm (6% for >18% procedures/year vs 4% for <8 procedures/year) (Birkmeyer, Stukel et al. 2003). In interventional cardiology, several studies have reported on the important relationship between annual procedure volume and clinical outcomes. A widely known study by Hannan et al. analyzed data from the New York PCI registry and found a significantly higher rate of mortality (0.96% vs 0.90%) and same stay CABG (3.9% vs 3.4%) for hospitals.
performing <600 procedures and operators performing <75 PCI procedures per year (Hannan, Racz et al. 1997). With the multitude of studies and meta analyses demonstrating improved outcomes with higher operator and hospital volumes, a public initiative is suggested to limit complex surgical procedures to specific operators and institutions (Urbach 2015).

2.2.2 Procedural Volume and Outcomes Relationship for TAVR

TAVR is a complex procedure that requires involvement of specialists from multiple specialties including interventional cardiology, cardiovascular surgery, cardiac imaging and anesthesia for appropriate patient selection, procedure performance and post-operative management. In view of the heart team approach for TAVR, examination of operator volume and clinical outcome relationship has limited application and most investigators have focused on delineating the influence of hospital volumes on clinical outcome of TAVR as summarized in Table 2. Recognizing the importance of hospital volumes on clinical excellence in a variety of medical procedures, the Centers for Medicare and Medicaid Services in the US requires a hospital to perform at least 50 SAVR, employ 2 or more cardiac surgeons, perform ≥1000 coronary angiograms and ≥400 PCI prior to be approved as a TAVR site.

With regards to clinical endpoints of interest, Kim et al. (Kim, Minutello et al. 2015) using the US National Inpatient Sample (256 hospitals, 7660 patients) found a correlation between clinical outcome and hospital volumes. Low volume TF-TAVR centers (<20 TAVR/year) had higher rates of all cause death (OR 1.55), bleeding (OR 1.53), pacemaker implantation (OR 1.39) with no significant difference in stroke when compared to high volume centers (>20 TAVR/year). Similarly, low volume TA-TAVR centers (<10 TAVR/year) had higher rates of death (OR 3.1), pacemaker implantation (OR 6.0) and myocardial infarction (OR 5.4) compared to high volume TA-TAVR (>20 TAVR/year) centers. Similarly, Badheka et al. (Badheka, Patel et al. 2015) using the US National Inpatient Sample (n=1481) divided the population into hospital volume quartiles (<5 TAVR/year for lowest and >20 TAVR/year for highest) and found in-hospital mortality rates decreased with increasing hospital volume with 6.4% (first quartile), 5.9% (second quartile), 5.2% (third quartile), and 2.8% (fourth quartile). In addition, length of stay and index hospital costs were significantly lower for the fourth quartile hospitals. However, contrary to the above findings, de Baisi et al. (de Biasi, Paul et al. 2016) also used the US National Inpatient Sample, did not find a linear inverse relationship between hospital volume and mortality for TAVR, with comparable mortality at both very high and very
low volume centers. Khera et al. (Khera, Kolte et al. 2017) reported from the 2014 Nationwide Readmissions Database representing 49% of all US hospitalizations and found a significant inverse relationship between hospital TAVR volume and rates of readmission after the index procedures. The 30 day readmission rates were lowest in high volume (≥100 procedures/year) compared with medium (50-100 procedures/year) (OR 0.76) and low volume (≤50 procedures/year) (OR 0.75) hospitals. These observations suggest that technical excellence and possibly superior post procedure care may be large contributors to the differences in clinical outcomes. It is interesting to note that the volume-outcome relation for TAVR may also be applicable for TAVR quality measures. A recent study by Verma et al. (Verma, Pershad et al. 2016) examined CT reports performed at multiple institutions and reported that CT performed at high volume sites (>75 TAVR/year) had excellent correlation with independent reporting of annular size and transcatheter valve size (r=0.96), a finding that was not reproduced for lower annual volumes centres.
Table 4. Summary of studies examining the volume outcome relationship for transcatheter aortic valve replacement.

<table>
<thead>
<tr>
<th>Study</th>
<th>Source Data/Population</th>
<th>N</th>
<th>Access</th>
<th>Principle Comparison</th>
<th>Principle Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim (Kim, Minutello et al. 2015) et al</td>
<td>USA: National Inpatient Sample</td>
<td>7660 in 256 Hospitals</td>
<td>TF and TA</td>
<td>Low vs High volume (TF – 20 cases/yr, TA – 10 cases/year)</td>
<td>TF: Significantly higher mortality, renal failure, vascular complications, pacemaker implantation at low volume centers. TA: Significantly higher mortality (3.6% vs 2.3%), renal failure, pacemaker implantation low volume center</td>
</tr>
<tr>
<td>Badheka et al. (Badheka, Patel et al. 2015)</td>
<td>USA: National Inpatient Sample</td>
<td>1418</td>
<td>TF and alternative</td>
<td>Annual volume quartiles first (&lt;5/year), second (6-10/year), third (11-20/year), and fourth (&gt;20/year)</td>
<td>With multivariate analysis, statistically significantly lower risk of death (2.4% lowest vs 6.4% highest quartile), death and morbidity, hospital stay &gt; 6 days in hospitals with the highest volume quartile</td>
</tr>
<tr>
<td>De Biasi et al (de Biasi,</td>
<td>USA: National</td>
<td>7,635</td>
<td>TF and alternative</td>
<td>TAVR distributed</td>
<td>Hospital volume did not predict in hospital</td>
</tr>
<tr>
<td>Study</td>
<td>Sample</td>
<td>Size/Location</td>
<td>Site Reporting</td>
<td>Correlation</td>
<td>Results</td>
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<tr>
<td>Paul et al. (2016)</td>
<td>Inpatient Sample</td>
<td>&lt;20, 20-40, 40-60, &gt;60</td>
<td>morbidity and mortality.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verma et al. (Verma, Pershad et al. 2016)</td>
<td>USA: 3 Center</td>
<td>3 Hospitals, 181 Cases</td>
<td>NR</td>
<td>Correlation of CT site reported annulus sizing to independent review; Higher rate of correlation between site reported annulus size to re-reviewed annulus size in high volume center; mismatch predicted higher composite endpoint.</td>
<td></td>
</tr>
<tr>
<td>Khera et al. (Khera, Kolte et al. 2017)</td>
<td>USA: National Readmissions Database</td>
<td>129 hospitals, 16252 TAVR</td>
<td>TF and alternative</td>
<td>Hospitals were classified as low (&lt;50), medium (≥50 to &lt;100), and high (≥100) volume</td>
<td>Significantly lower rates of readmission in the high-volume hospitals, with no difference in index length of stay, procedural cost</td>
</tr>
<tr>
<td>Bestehorn et al. (Bestehorn, Eggebrecht et al. 2017)</td>
<td>Germany</td>
<td>87 Hospitals, 9924 patients</td>
<td>TF and alternative</td>
<td>Continuous decrease in mortality with increasing Hospital volume, statistically higher mortality in Hospitals performing &lt; 50 TAVR vs &gt; 200 TAVR/year</td>
<td></td>
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</table>

TF= transfemoral, TA= transapical
2.3 Implications for Clinical Practice

TAVR is a complex procedure with cognitive and technical aspects that are unique, and different than those of cardiac surgery and interventional cardiology (Tommaso, Bolman et al. 2012). These include understanding of the underlying pathophysiology, comprehension and analysis of diagnostic work up including cardiac hemodynamics, non-invasive imaging as well as technical expertise including large bore access, implantation of the prosthesis and management of potential operative and post-operative complications with appropriate clinical follow up schedule. With this complexity, there is little doubt that experience gained from prior similar procedures (i.e., learning curve) will further improve procedural success, and concentration of services in high volume centers will result in superior outcomes. The available data consistently shows that both a learning curve phenomenon and a volume outcome relationship exist for TAVR procedures.

However, there are important limitations with regards to methodology used and patient population studied. In addition, TAVR is an advancing field with major modification in available devices with significant decrease in size of catheters, improved valve designs and incorporation of features (retrievability) that allow bail out in case of procedural challenges. Furthermore, improved clinical knowledge with incorporation of CT findings, better anticipation of potential complications and advances in care algorithm (percutaneous access, conscious sedation) greatly impact the procedural success rates and clinical outcomes. Defining learning curve thresholds and institutional volume criteria is inherently difficult for any evolving field including TAVR. In addition, most published studies were done at early adopting centers that used first and second-generation devices. Whether recent improvement is TAVR technology translate into a shorter learning curve remains uncertain. In addition, the role of a formal mentorship arrangement is poorly understood. In a recent study, a formal mentorship agreement between a new program and an established program in Minnesota, USA, greatly improved technical proficiency as measured by procedural time, device success and safety with comparable results demonstrated for the new and the established program after 50 cases and at 1 year (Gurevich, John et al. 2017). Another approach has been adopted by the province of British Columbia in Canada that has enacted a regionalization policy for TAVR programs with a central medical director with a TF-TAVR as the default strategy for all sites. All non-TF-TAVR, valve in valve, and non-aortic valve intervention can only be performed at a center of excellence (Stub, Lauck et
al. 2015). In the most recent 2017 AATS/ACC/SCAI/STS Expert Consensus Systems of Care document specific recommendations have been made for new TAVR programs (Bavaria JE 2017). These include interventional cardiologist to have ≥100 TAVR experience with 50 as a primary operator, the surgeon with ≥100 SAVR career cases or 25 SAVR during the prior year or 50 SAVR over the last 2 years, along with the hospital performing ≥ 300 PCI and ≥40 SAVR per year.

There are important implications for the learning curve threshold as well as annual procedural volume criteria for maintaining necessary skill set, hospital credentialing as well as for the medico-legal area. Furthermore, it is increasingly important to rationally allocate resources in the era of constantly rising health care costs. TAVR is a pioneering procedure for transcatheter structural heart intervention and the lessons learned are likely applicable to future similar systems of care in this field.

Finally, as TAVR transitions to the main stream interventional cardiology, a robust understanding of the learning curve thresholds and procedural volume-outcome relationship is needed for the development of competency-based training programs for structural interventional fellowship to produce the next generation of TAVR operators.

2.4 Conclusions

Transcatheter aortic valve replacement is a maturing technology with a marked increase in the number of procedures performed and centers offering TAVR. TAVR is also a technically complex procedure, with a characteristic learning curve and clinically important relationship between institutional volume and patient outcomes. The operator excellence in TAVR procedures continues to improve for a case volume >240 procedures. In addition, available evidence suggests improved clinical outcomes for institutions with an annual TAVR volume >50 procedures.

However, it is important to note that these thresholds are devised by data form early adopting centers that included first and second generation TAVR devices. It remains unclear whether new centres implanting contemporary TAVR devices with formal mentorship arrangements can achieve proficiency with a shorter learning curve and achieve comparable clinical outcomes to high volume centres. Further research will be required to refine the above
thresholds as advances in technology, formal physician training, and evolving indications change the landscape of TAVR.
Chapter 3

3 Research Aims and Hypotheses

Severe symptomatic aortic stenosis is a disease with a grave prognosis, with a median life expectancy of 5 years at the onset of angina, 3 years after the onset of syncope and only 2 years after signs of congestive heart failure have developed (Ross and Braunwald 1968). Aortic stenosis can be successfully treated in patients who are good surgical candidates by aortic valve replacement (Schwarz, Baumann et al. 1982), however there is a substantial population who are at elevated surgical risk (Astor, Kaczmarek et al. 2000, Ashikhmina, Schaff et al. 2011). With the introduction of transcatheter aortic valve replacement (Cribier, Eltchaninoff et al. 2002), patients who are inoperable (Leon, Smith et al. 2010), are at high surgical risk (Smith, Leon et al. 2011, Adams, Popma et al. 2014), intermediate surgical risk (Leon, Smith et al. 2016, Reardon, Van Mieghem et al. 2017), and now even lower (Sondergaard, Steinbruchel et al. 2016) surgical risk have a treatment option that has similar, if not improved outcomes compared with surgical aortic valve replacement.

With the increase in indications for TAVR, and with its increasing uptake in the population, there has been a marked, greater than fourfold, increase in the number of TAVR procedures been performed and a doubling of the number of centers offering TAVR over a four-year period (Grover, Vemulapalli et al. 2017). Furthermore, there is expected to be a marked increase in the population of patient’s who will be eligible for TAVR (Ortman 2014, Wan He 2016). Two important questions arise with regards in situations where a large expansion of a procedure or technology:

1. The learning curve of TAVR requires a more comprehensive description. As described in chapter 2, a learning curve is a phenomenon where incremental improvements occur with increasing experience until a plateau occurs (Cook, Ramsay et al. 2004). This phenomenon has been described in multiple procedures including coronary artery bypass grafting (Bridgewater, Grayson et al. 2004) as well as percutaneous coronary intervention in the setting of acute myocardial infarction (Ball, Sharieff et al. 2011). This phenomenon has been explored in TAVR, however the current literature is limited. First, the majority of studies in
this field have been small (Kempfert, Rastan et al. 2011, Alli, Booker et al. 2012, D'Ancona, Pasic et al. 2014, Arai, Lefevre et al. 2016, Gurevich, John et al. 2017, Henn, Percival et al. 2017) with a limited number of centers inputting data. Furthermore, other studies have been learning curves from large randomized controlled trials and may not represent real world data (Alli, Rihal et al. 2016, Minha, Waksman et al. 2016, Suri, Minha et al. 2016).

2. The minimal annual procedural volumes to optimize outcomes in TAVR requires further description. Minimal annual volumes in surgery has been an area that has been extensively researched, with a demonstration of worse adverse outcomes lower volume centers (Birkmeyer, Stukel et al. 2003, McAteer, LaRiviere et al. 2013). This has been demonstrated for cardiac procedures including CABG, aortic valve replacement and abdominal aortic aneurism repair, as well as for percutaneous coronary artery intervention (Hannan, Racz et al. 1997). The currently published literature has only 5 adequately sized studies assessing the questions, with one study suggesting no relationship (de Biasi, Paul et al. 2016), two suggesting a threshold of 20 cases per year (Badheka, Patel et al. 2015, Kim, Minutello et al. 2015) and two suggesting that 50 cases per year are required (Bestehorn, Eggebrecht et al. 2017, Khera, Kolte et al. 2017)

Accurate and meaningful descriptions of the learning curve and minimal annual procedural volumes in TAVR are of significant importance to this field, and to the delivery of TAVR. TAVR has had a marked proliferation in the number of procedures performed as well as the number of centers performing it. The debate in medicine between equitable access vs. centers of excellence has been ongoing in the literature. With the large body of data demonstrating that many complex surgeries have learning curves, and minimal annual procedural volumes, it is imperative to accurately describe this for TAVR in order to inform regulatory authorities with regards to site requirements to optimize outcomes. Furthermore, accurate descriptive data is important in that higher thresholds for TAVR would potentially have the consequence of fewer centers performing this procedure. Despite any potential improvement in patient outcomes with these centers of excellence, there may be an unanticipated decline in access to the procedure. Finally, a long learning curve would necessitate increased supervision of early initiation sites, with associated costs. With all of these considerations, having high quality data to describe the learning curve, and minimal annual procedural volumes is of great importance to society.
In the two studies that will be presented in this thesis, our group of investigators used an international multicenter registry of TAVR, containing consecutive TAVR cases from each program’s inception to answer the above questions about the learning curve, and minimal annual procedural volumes associated with improved outcomes in TAVR. We have three major hypotheses based on the current literature which will be demonstrated in the trials in chapters 4 and 5:

1. A learning curve phenomenon exists with regards to transcatheter aortic valve replacement with regards to clinical outcomes, including mortality, major bleeding and vascular complications as well as combined clinical endpoints, as well measures of process, including procedure time and hospital stay. In chapter 4 of this thesis, we will demonstrate that with increasing institutional experience with TAVR procedures, clinical outcomes improve, and complications are reduced.

2. The current literature has underestimated the duration of the learning curve and we hypothesize that there is a prolonged learning curve consisting of hundreds of cases that must be complete before optimal clinical and procedural outcomes are achieved. In chapter 5 of this thesis, we will demonstrate that there is higher mortality for the first 225 cases compared to those performed after > 300 case volume, with higher combined major complications up until a 300-case volume.

3. We hypothesize that a minimal annual volume is required for transcatheter aortic valve replacement in order to achieve optimal clinical and procedural outcomes. In chapter 5 of this thesis, we will demonstrate higher rates of mortality and higher combined major complications for centers performing less than 50 TAVR procedures in a calendar year, as compared to centers performing greater than 100 TAVR procedures in a calendar year.
Chapter 4

Institutional Experience and Outcomes of Transcatheter Aortic Valve Replacement

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4.1 Introduction

Transcatheter Aortic Valve Replacement (TAVR) has revolutionized the management of symptomatic aortic stenosis. Compared to medical therapy, TAVR is associated with a substantial reduction in cardiac mortality, hospitalization for heart failure and symptomatic benefit for non-operable patients(Leon, Smith et al. 2010), and comparable outcomes to surgical aortic valve replacement in high-risk patients(Smith, Leon et al. 2011). However, TAVR is a technically complex procedure that requires a unique skill set distinct from other coronary and
endovascular interventions. The positive relationship between experience and outcomes is well described for complex procedures such as coronary artery bypass surgery (Bridgewater, Grayson et al. 2004), mitral valvuloplasty (Sanchez, Harrell et al. 2001) and transradial coronary interventions (Ball, Sharieff et al. 2011). In addition, temporal trends in TAVR outcomes have shown improvement in multiple registries (Holmes, Nishimura et al. 2015). However, the relationship between institutional TAVR experience with procedural and clinical outcomes is unclear. In the present study, we investigated the effects of institutional experience on procedural and clinical outcomes in the international multicentre TAVR registry.

4.2 Methods

4.2.1 Population

All consecutive patients who underwent TAVR at eight international sites in North America, South America and Europe since the initiation of the respective centre's TAVR program were included in this study. All centres employed a heart-team model of multidisciplinary decision making for patient selection, procedural planning and performance (Holmes, Mack et al. 2012). Choice of TAVR device, valve size, approach, post procedure care and antithrombotic management were at the discretion of treating centre's heart team. A total of 1960 patients underwent TAVR during the study period with complete data were available for 1953 (99.6%) patients comprising the study population (Fig. 12 A and B).
Figure 12 (A and B): Patient population of the institutional experience study divided into the chronological quantiles.

TAVR Implants, N=1960

Incomplete data, N=7

Quantile 1
N = 496
Procedure 1 to 62

Quantile 2
N = 483
Procedure 63 to 133

Quantile 3
N = 489
Procedure 134 to 233

Quantile 4
N = 485
Procedure ≥ 234

Figure A representing allocation of total patient population into quartiles and figure B representing distribution of individual centers contributing data. Adapted from (Wassef, Alnasser et al. 2017)
4.2.2 Design

Baseline, procedural, echocardiographic and outcome data were collected in a prospective manner and patients from each centre were chronologically ordered and divided into quantiles. To allocate equal volume quantiles, first quantile (Q1) represented chronologically ordered patients number 1 to 62, second quantile (Q2) represented patient number 63 to 133, third quantile (Q3) represented patient number 134 to 242, and fourth quantile (Q4) represented patient number 243 to 476. All procedural and clinical outcomes were defined according to VARC-2 criteria (Kappetein, Head et al. 2012). Briefly, device success was defined as successful access, delivery, deployment in the correct position and anatomical location with aortic valve area > 1.2 cm² and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe aortic insufficiency. The early safety endpoint was defined as the composite of death, stroke, major bleeding, vascular complications and surgical conversion.

4.2.3 Statistical Analysis

Categorical variables were reported as frequency and percentages and continuous variables as mean ± standard deviation. Baseline patient characteristics, procedural variables and clinical outcomes were compared among quantiles using Kruskal Wallis one-way analysis of variance, chi-square test or Fisher exact test as appropriate. The TAVR centres from Q1 were rank ordered to determine relationship between time taken to complete first 62 cases and clinical outcomes. Q1 was chosen for this analysis due to contribution of cases from all participating centres. Kendall's tau rank correlation coefficient was performed to determine association of rank order centres with outcomes of device success, early safety endpoint and all-cause mortality. A repeated measures logistic regression was performed to determine association between quantile allocation and all-cause mortality. The variables included in the model included baseline characteristics (age, body surface area (BSA), Society of Thoracic Surgeons (STS) mortality score, sex, New York heart association (NYHA) class, prior coronary artery bypass grafting (CABG), chronic kidney disease (CKD) as well as procedural variables (approach and prosthesis type). Results of the multivariate analysis were expressed as odds ratio with 95% confidence interval. All analysis were performed with SAS software (SAS institute Inc., Cary, NC) and a p value < 0.05 defined statistical significance.
4.3 Results

A total of 1953 patients from 8 sites (Fig. 12 A and B) comprised the study population. The baseline clinical and echocardiographic parameters are shown in table 5. The mean age of the population was 81 ± 7 years and was similar across quantiles. The mean STS score gradually decreased over time and was significantly different among quantiles (10.7 ± 9.7 for Q1, 10.5 ± 8.9 for Q2, 8.6 ± 5.5 for Q3 and 7.6 ± 4.2 for Q4, p = 0.001). The number of patients undergoing transfemoral TAVR was higher in each quantile compared to other TAVR approaches and Edwards Sapien™ prosthesis was the predominant valve used in all quantiles with comparable rates of valve in valve procedures, table 6.

4.3.1 Clinical Outcomes

The overall device success as defined by VARC2 criteria was 82% (table 6). There was a statistically significant increase in device success (figure 14) among quantiles (78% for Q1 to 89% for Q4, p = 0.001). The major component of VARC-2 defined device failure was moderate to severe paravalvular leak, that decreased from 19% Q1 to 11% in Q4, p = 0.01. The incidence of valve embolization also significantly decreased from 3.8% in Q1 to 0.2% in Q4, p = 0.002 (figure 15). The overall rate of the early safety endpoint during the study period was 15% with a significant improvement observed from 19% in Q1 to 10% in Q4 (p < 0.001). There was a statistically significant decrease from Q1 to Q 4 for the rate of major vascular complications (9.1% vs 4.3%, p = 0.04), major bleeding (4.4% vs 1.6%, p = 0.04) and valve embolization (3.8% vs 0.2%, p = 0.002). However, the rates of surgical conversion for TAVR were similar across quantiles (1.4% vs 1.6% for Q1 and Q4 respectively, p = 0.28). Both the rates of pacemaker implantation (14.1% and 8.6% for Q1 and Q4 respectively, p = 0.04) and moderate to severe paravalvular aortic insufficiency (19.1% and 10.5% for Q1 and Q4 respectively, p = 0.01) significantly decreased from Q1 to Q4. The length of stay of < 5 days was achieved in 16.3% of Q1 patients compared to 26.2% of Q4 patients, p < 0.001 (table 7). There was no significant difference in the rate of myocardial infarction, acute kidney injury and stroke between different quantiles, Table 7. However, there was a significant decrease in mortality for patients undergoing TAVR in Q4 compared to Q1 (3.7% vs 8.3%, p = 0.011), Fig. 13. When centres were ranked for the time needed to complete Q1 cases, no significant relationship was noted for the time to
4.3.2 Procedural Parameters

The detail of procedural parameters is described in Table 7. 13.3% of Q1 patients had a procedure time > 120 min compared to only 2.3% in Q4 (p < 0.001). The median contrast used was 45 ml (IQR 20–123). A contrast volume of > 100 ml was used in 14.9% of patients in Q1 compare to only 4.7% of Q4 patients, p < 0.001.

4.3.3 Multivariate Analysis

The results of repeated measures logistic regression analysis adjusting for baseline and procedural variables showed that Q2 (OR 2.18, 95% CI 1.08–4.38, p = 0.03), Q3 (OR 3.82, 95% CI 1.62–8.97, p = 0.002) and Q4 (OR 13.5, 95% CI 4.18–43.5, p < 0.001) were independently associated with higher device success. Both Q3 (OR 0.67, 95% CI 0.47–0.96, p = 0.030) and Q4 (OR 0.41, 95% CI 0.27–0.63, p < 0.0001) were associated with better early safety. Q3 (OR 0.45, 95% CI 0.24–0.85, p = 0.01) and Q4 (OR 0.26, 95% CI 0.12–0.59, p = 0.001) were independently associated with lower risk of major bleeding while Q4 was independently associated with a lower mortality (OR 0.36, 95% CI 0.19–0.70, p = 0.002).
Table 5. Baseline characteristics of the institutional experience study divided by chronological quantile.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>80.6 ± 7.4</td>
<td>80.9 ± 7.1</td>
<td>80.7 ± 6.8</td>
<td>80.5 ± 7.1</td>
<td>80.4 ± 8.5</td>
<td>0.741</td>
</tr>
<tr>
<td>Female, %</td>
<td>991 (50.7)</td>
<td>266 (53.6)</td>
<td>236 (48.9)</td>
<td>266 (54.4)</td>
<td>223 (46.0)</td>
<td>0.025</td>
</tr>
<tr>
<td>BMI</td>
<td>26.9 ± 5.3</td>
<td>26.3 ± 4.8</td>
<td>27.0 ± 5.1</td>
<td>27.2 ± 5.3</td>
<td>27.1 ± 5.8</td>
<td>0.06</td>
</tr>
<tr>
<td>BSA</td>
<td>1.8 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>1593 (81.6)</td>
<td>399 (80.4)</td>
<td>400 (82.8)</td>
<td>395 (80.8)</td>
<td>399 (82.3)</td>
<td>0.734</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>621 (31.8)</td>
<td>148 (29.8)</td>
<td>153 (31.7)</td>
<td>156 (31.9)</td>
<td>164 (33.8)</td>
<td>0.616</td>
</tr>
<tr>
<td>History of CHF, %</td>
<td>1461 (74.8)</td>
<td>361 (72.8)</td>
<td>373 (77.2)</td>
<td>354 (72.4)</td>
<td>373 (76.9)</td>
<td>0.156</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>478 (24.5)</td>
<td>99 (20.0)</td>
<td>118 (24.4)</td>
<td>115 (23.5)</td>
<td>146 (30.1)</td>
<td>0.023</td>
</tr>
<tr>
<td>Lung disease, %</td>
<td>618 (31.6)</td>
<td>170 (34.3)</td>
<td>140 (29.0)</td>
<td>173 (35.4)</td>
<td>135 (27.8)</td>
<td>0.015</td>
</tr>
<tr>
<td>CKD, %</td>
<td>1103 (56.5)</td>
<td>270 (54.4)</td>
<td>289 (59.8)</td>
<td>282 (57.7)</td>
<td>262 (54.0)</td>
<td>0.21</td>
</tr>
<tr>
<td>STS Score</td>
<td>9.4 ± 7.6</td>
<td>10.7 ± 9.7</td>
<td>10.5 ± 8.9</td>
<td>8.6 ± 5.5</td>
<td>7.6 ± 4.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean AV gradient</td>
<td>46.4 ± 16.7</td>
<td>49.6 ± 17.4</td>
<td>47.4 ± 16.7</td>
<td>45.8 ± 15.4</td>
<td>42.6 ± 16.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aortic valve area</td>
<td>0.7 ± 0.4</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.7</td>
<td>0.7 ± 0.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Normal LV function, %</td>
<td>1414 (72.4)</td>
<td>362 (73.0)</td>
<td>351 (72.7)</td>
<td>345 (70.6)</td>
<td>356 (73.4)</td>
<td>0.757</td>
</tr>
</tbody>
</table>

All values are mean±SD unless noted otherwise. Q-quantile, BMI–body mass index, BSA–body surface area, CHF-congestive heart failure, CABG-coronary artery bypass surgery, CKD-chronic kidney disease, STS-society of thoracic surgeons
Table 6. Procedural characteristics of patients the institutional experience study, divided by chronological quantile.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1953</td>
<td>N=496</td>
<td>N=483</td>
<td>N=489</td>
<td>N=485</td>
<td></td>
</tr>
<tr>
<td>Approach</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trans femoral</td>
<td>1389 (71.1)</td>
<td>377 (76.0)</td>
<td>333 (68.9)</td>
<td>355 (72.6)</td>
<td>324 (66.8)</td>
<td></td>
</tr>
<tr>
<td>Trans apical</td>
<td>478 (24.5)</td>
<td>113 (22.8)</td>
<td>126 (26.1)</td>
<td>117 (23.9)</td>
<td>122 (25.2)</td>
<td></td>
</tr>
<tr>
<td>Trans aortic</td>
<td>42 (2.2)</td>
<td>1 (0.2)</td>
<td>7 (1.4)</td>
<td>4 (0.8)</td>
<td>30 (6.2)</td>
<td></td>
</tr>
<tr>
<td>Trans subclavian</td>
<td>44 (2.3)</td>
<td>5 (1.0)</td>
<td>17 (3.5)</td>
<td>13 (2.7)</td>
<td>9 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Prosthesis type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Edward Sapien</td>
<td>1148 (59)</td>
<td>252 (50)</td>
<td>259 (53)</td>
<td>264 (54)</td>
<td>373 (77)</td>
<td></td>
</tr>
<tr>
<td>Medtronic CoreValve</td>
<td>789 (40)</td>
<td>244 (49)</td>
<td>224 (46)</td>
<td>221 (45)</td>
<td>100 (21)</td>
<td></td>
</tr>
<tr>
<td>St. Jude Portico</td>
<td>7 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (0.8)</td>
<td>3 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (0.5)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>9 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Valve-in-valve</td>
<td>64 (3.3)</td>
<td>11 (2.2)</td>
<td>18 (3.7)</td>
<td>18 (3.7)</td>
<td>17 (3.5)</td>
<td>0.486</td>
</tr>
</tbody>
</table>

All values are %, Q-quantile
Table 7: Clinical and procedural outcomes for the institutional experience study divided into patient quantiles.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1953</td>
<td>N=496</td>
<td>N=483</td>
<td>N=489</td>
<td>N=485</td>
<td></td>
</tr>
<tr>
<td>Device Success</td>
<td>1604 (82.1)</td>
<td>387 (78.0)</td>
<td>378 (78.3)</td>
<td>409 (83.6)</td>
<td>430 (88.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Early Safety Endpoint</td>
<td>294 (15.1)</td>
<td>93 (18.8)</td>
<td>86 (17.8)</td>
<td>66 (13.5)</td>
<td>49 (10.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Death</td>
<td>135 (6.9)</td>
<td>41 (8.3)</td>
<td>40 (8.3)</td>
<td>36 (7.4)</td>
<td>18 (3.7)</td>
<td>0.011</td>
</tr>
<tr>
<td>Stroke</td>
<td>63 (3.2)</td>
<td>12 (2.4)</td>
<td>20 (4.1)</td>
<td>20 (4.1)</td>
<td>11 (2.3)</td>
<td>0.178</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>22 (1.1)</td>
<td>5 (1.0)</td>
<td>5 (1.0)</td>
<td>5 (1.0)</td>
<td>7 (1.4)</td>
<td>0.9</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>94 (4.8)</td>
<td>23 (4.6)</td>
<td>27 (5.6)</td>
<td>20 (4.1)</td>
<td>24 (5.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Major Vascular Complication</td>
<td>139 (7.1)</td>
<td>45 (9.1)</td>
<td>36 (7.5)</td>
<td>37 (7.6)</td>
<td>21 (4.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>85 (4.4)</td>
<td>34 (6.9)</td>
<td>26 (5.4)</td>
<td>17 (3.5)</td>
<td>8 (1.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Valve Embolization</td>
<td>40 (2.0)</td>
<td>19 (3.8)</td>
<td>11 (2.3)</td>
<td>9 (1.8)</td>
<td>1 (0.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgery Conversion</td>
<td>21 (1.1)</td>
<td>7 (1.4)</td>
<td>3 (0.6)</td>
<td>3 (0.6)</td>
<td>8 (1.6)</td>
<td>0.276</td>
</tr>
<tr>
<td>Mod-Severe AI post TAVR</td>
<td>254 (13)</td>
<td>95 (19.1)</td>
<td>56 (11.5)</td>
<td>52 (10.6)</td>
<td>51 (10.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pacemaker implantation</td>
<td>231 (11.8)</td>
<td>70 (14.1)</td>
<td>65 (13.4)</td>
<td>54 (11.0)</td>
<td>42 (8.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Procedure time &gt;120 min</td>
<td>139 (7.1)</td>
<td>66 (13.3)</td>
<td>52 (10.8)</td>
<td>10 (2.0)</td>
<td>11 (2.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Contrast volume &gt;100 ml</td>
<td>183 (9.4)</td>
<td>74 (14.9)</td>
<td>59 (12.2)</td>
<td>27 (5.5)</td>
<td>23 (4.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Length of stay &lt; 5 days</td>
<td>436 (22.3)</td>
<td>81 (16.3)</td>
<td>94 (19.5)</td>
<td>134 (27.4)</td>
<td>127 (26.2)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

All values are %, Q-quantile, AI-aortic insufficiency, TAVR-transcatheter aortic valve replacement
Figure 13. Rates of Death and Stroke in the Institutional Experience Study

Statistically lower rates of death but not stroke associated with increased procedural experience.

Q - quantile
Figure 14. Rates of procedural success and major adverse events (MACE), institutional experience study

The highest rates of procedural success and lowest rates of MACE with highest procedural experience. MACE - death/stroke/bleeding/vascular complications/surgical conversion. Q - quantile
The highest quantile demonstrated the lowest rates of major vascular complications, major bleeding or valve embolization. Q - quantile
Chapter 5

5 The Learning Curve and Annual Procedure Volume Standards for Optimum Outcomes of Transcatheter Aortic Valve Replacement: Findings from an International Registry

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5.1 Introduction

Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of severe symptomatic aortic stenosis (AS), with several randomized trials demonstrating equivalence or superiority to conventional surgical aortic valve replacement for inoperable (Leon, Smith et al. 2010), high risks (Smith, Leon et al. 2011, Adams, Popma et al. 2014) and intermediate risk patients (Leon, Smith et al. 2016, Reardon, Van Mieghem et al. 2017). Concomitantly, there has been a large increase in the number of procedures being performed and the number of centers performing the procedure in North America as well as internationally (Mylotte, Osnabrugge et al. 2013, Grover, Vemulapalli et al. 2017). This trend is likely to continue as there is expected to be a large increase in the number of elderly patients with aortic valve disease (Nkomo, Gardin et al. 2006), as well as an increase in the utilization of this technology in lower risk patients (Thyregod, Steinbruchel et al. 2015).

A learning curve phenomenon, defined as an improvement in outcome with increasing experience has been demonstrated for multiple cardiac (Sanchez, Harrell et al. 2001, Ball, Sharieff et al. 2011) as well as non-cardiac (Hopper, Jamison et al. 2007) procedures. In addition, maintaining minimal annual procedural volumes are associated with improved clinical outcomes (Hannan, Racz et al. 1997). Although improved procedural results with greater TAVR experience have been described (Alli, Booker et al. 2011, Gurvitch, Tay et al. 2011, Minha, Waksman et al. 2016, Suri, Minha et al. 2016), adequate understanding of the TAVR learning curve and the minimal annual procedural volume required to achieve competence is lacking. In the present study, we characterize the procedure learning curve and investigate the relationship between annual institutional volume and clinical outcomes from the international multicenter TAVR registry.
5.2 Methods

5.2.1 Population

All consecutive patients who underwent TAVR at 16 large, urban international academic teaching sites in North and South America and Europe since the initiation of the respective center’s TAVR program were included in this study. All centers employed a heart-team model of multi-disciplinary decision making for patient selection, procedural planning and performance (Grover, Vemulapalli et al. 2017). Choice of TAVR device, valve size, approach, post procedure care and antithrombotic management were at the discretion of treating center’s heart team, and participation in clinical trials as well as investigational devices were included in this analysis. A total of 3468 patients underwent TAVR during the study period with complete data were available for 3403 (98.1%) patients comprising the study population. Patients with incomplete data, totaling under 2% of the population were excluded. Baseline, procedural, echocardiographic and outcome data were collected in a prospective manner at each center. Each center was responsible for collection of baseline demographic and procedural details, as well as relevant 30-day outcomes. Events were adjudicated at each site, with no central adjudication. The first patient included had their procedure performed January 6, 2005, and the last patient included had their procedure January 29, 2016.

5.2.2 Study Design

Patients from each center were chronologically ordered from the initiation of the TAVR program for the learning curve analysis. To determine the procedural learning curve characteristics, TAVR cases from each center were chronological grouped into initial (1 to 75), early (76 to 150), intermediate (151 to 225), high (226-300) and very-high (>300) experience groups, to determine the effect of increasing procedural experience on procedural and clinical outcomes. To determine the minimum annual institutional TAVR volume for optimum clinical outcomes, each individual center’s TAVR volume per calendar year (January 1st to December 31st) was determined, and grouped into low (1 to 50), intermediate (51 to 100) and high (> 100) TAVR volume groups. Centers may contribute to different volume groups depending only on their annual volume per calendar year. For this analysis, all TAVR performed in the first and last calendar year from each center were excluded from analysis as the completeness of annual
volume data could not be assured. Complete data available for 2205 (64.8%) patients from 16 institutions.

5.2.3 Data Definitions

All procedural and clinical outcomes were defined per VARC-2 criteria (Kappetein, Head et al. 2012) and determined at 30 days. Briefly, device success was defined as successful access, delivery, deployment in the correct position and anatomical location with aortic valve area > 1.2 cm² and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe aortic insufficiency. Early safety endpoint was defined as the composite of death, stroke, major bleeding, vascular complications, surgical conversion and renal failure.

5.2.4 Statistical Analysis

Categorical variables were reported as frequency and percentages and continuous variables as mean ± standard deviation. For the learning curve analysis, the very-high experience group was used as a reference and baseline characteristics, procedural variables and clinical outcomes for each experience group (initial, early, intermediate and experienced) were compared with the very-high experience group using paired wise comparisons with a t-test, a Mann-Whitney U or a Chi-square test as appropriate, with Dunnet’s test to control for multiple comparisons. A logistic regression was performed to determine association between experience and annual volume group allocation and all-cause mortality and composite early safety endpoint. Covariate adjustment with logistic regression has been demonstrated to compare well to propensity adjustment methods for clinical trials (Elze, Gregson et al. 2017). Variables chosen for the model were included if there were significant baseline differences between the groups, and if they had previously been demonstrated to predict worse outcomes in TAVR (Holmes, Brennan et al. 2015). The variables included in the logistic regression for the learning curve analysis included baseline characteristics age, body surface area (BSA), gender, New York heart association (NYHA) class, prior coronary artery bypass grafting (CABG), prior coronary artery disease (CAD), chronic kidney disease (CKD) as well as continent of the participating institution (Europe, South America, North America), procedural variables (transfemoral vs transapical vs other) and prosthesis generation for the Sapien platform (Sapien, Sapien XT, Sapien 3) to account for the geographical differences in clinical practice and technological changes which
may impact vascular access complications and paravalvular leak rates. The logistic regression analysis was performed first using procedural volume as a continuous variable and then repeated using the procedural volume categories as defined earlier. Results of the multivariate analysis were expressed as odds ratio with 95% confidence interval. All analyses were performed with SAS software (SAS institute Inc., Cary, NC) and a p value <0.05 defined statistical significance.

5.3 Results

5.3.1 TAVR Learning Curve Analysis - Baseline Characteristics

Among the 3403 patients enrolled at 16 international sites, 1141 (33.5%) cases were performed by initial, 780 (22.9%) cases performed by early, 549 (16.1%) cases performed by intermediate, 354 (10.4%) cases performed by high experience groups and 579 (17.0%) cases were performed by very-high experience operators, table 8. Furthermore, of the 16 centers included, 16 centers contributed performed sufficient cases to be included in the initial cohort, 13 centers to early, 8 centers to intermediate, 6 centers to the high and 4 centers to the very-high cohort. The mean age of the study population was 82±8 years, and a balloon expandable valve used 59% of patients, with higher use in the high-experience group (p<0.001). In total, 77% underwent TAVR via the transfemoral route, with a stepwise drop in the rate of transfemoral route (81.9% initial experience, 78.3% early experience, 77.6% moderate experience, 72% high experience, and 68.2% in the very-high experience group.)

There were statistically significant intergroup differences in age (p<.001) between the groups. Mean aortic valve gradient dropped from early experience (46.3±16.9 mmHg) to very-high experience group (41.3±17.0), (p<0.001). There was a statistically significant drop in the surgical risk as assessed by the STS score, with a drop from 8.2±6.4 to 7.0±4.5, p<0.001. The components of the STS score that had significant intergroup differences included the body mass index (BMI) (p<0.001), NYHA class IV (dropping from 16% in the initial experience group down to 8.8% in the very-high experience group (p<0.001)), CAD (increasing from 54.5% in the initial experience group to 64.4% in the very-high experience group (p<0.001)).

<table>
<thead>
<tr>
<th>Variables</th>
<th>All (n=3403)</th>
<th>Initial experience (n=1141)</th>
<th>Early experience (n=780)</th>
<th>Moderate experience (n=549)</th>
<th>High experience (n=354)</th>
<th>Very-high experience (n=579)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>81.5±7.7</td>
<td>81.8±7.2</td>
<td>81.6±7.2</td>
<td>81.1±7.6</td>
<td>82.5±7.6</td>
<td>80.5±9.1</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>1652 (48.6)</td>
<td>576 (50.6)</td>
<td>384 (49.2)</td>
<td>271 (49.4)</td>
<td>170 (48)</td>
<td>251 (43.7)</td>
</tr>
<tr>
<td>Mean gradient, mmHg</td>
<td>46.3±16.9</td>
<td>49.0±16.8</td>
<td>47.1±16.9</td>
<td>45.7±15.9</td>
<td>44.4±16.0</td>
<td>41.3±17.0</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
<td>0.6±0.2</td>
<td>0.6±0.3</td>
</tr>
<tr>
<td>BMI</td>
<td>26.8±5.2</td>
<td>26.3±4.9</td>
<td>26.9±5.1</td>
<td>26.7±5.2</td>
<td>27.1±5.0</td>
<td>27.4±6.0</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.5±14.1</td>
<td>55.2±14.1</td>
<td>55.3±13.7</td>
<td>53.3±14.7</td>
<td>53.9±13.9</td>
<td>53.7±14.1</td>
</tr>
<tr>
<td>STS PROM</td>
<td>8.2±6.4</td>
<td>9.1±7.4</td>
<td>7.7±5.9</td>
<td>8.7±7.2</td>
<td>7.4±5.0</td>
<td>7.0±4.5</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>2676 (78.6)</td>
<td>855 (74.9)</td>
<td>598 (76.7)</td>
<td>446 (81.2)</td>
<td>294 (83.1)</td>
<td>483 (83.4)</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>1017 (29.9)</td>
<td>328 (28.7)</td>
<td>222 (28.5)</td>
<td>151 (27.5)</td>
<td>113 (31.9)</td>
<td>203 (35.1)</td>
</tr>
<tr>
<td>NYHA IV, n (%)</td>
<td>504 (14.8)</td>
<td>183 (16)</td>
<td>115 (14.7)</td>
<td>92 (16.8)</td>
<td>63 (17.8)</td>
<td>51 (8.8)</td>
</tr>
<tr>
<td>AF, n (%)</td>
<td>1033 (30.4)</td>
<td>299 (26.2)</td>
<td>244 (31.3)</td>
<td>184 (33.5)</td>
<td>113 (31.9)</td>
<td>193 (33.3)</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>1900 (55.8)</td>
<td>622 (54.5)</td>
<td>390 (50)</td>
<td>306 (55.7)</td>
<td>209 (59)</td>
<td>373 (64.4)</td>
</tr>
<tr>
<td>Prior CABG, n (%)</td>
<td>769 (22.6)</td>
<td>249 (21.9)</td>
<td>158 (20.3)</td>
<td>114 (20.8)</td>
<td>86 (24.3)</td>
<td>162 (28.1)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>907 (26.7)</td>
<td>297 (26)</td>
<td>199 (25.5)</td>
<td>154 (28.1)</td>
<td>101 (28.5)</td>
<td>156 (26.9)</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>1707 (50.2)</td>
<td>597 (52.3)</td>
<td>355 (45.5)</td>
<td>255 (46.4)</td>
<td>198 (55.9)</td>
<td>302 (52.2)</td>
</tr>
<tr>
<td>Prior MI, n (%)</td>
<td>491 (14.4)</td>
<td>146 (12.8)</td>
<td>121 (15.5)</td>
<td>56 (10.2)</td>
<td>49 (13.8)</td>
<td>119 (20.6)</td>
</tr>
<tr>
<td>TF approach, n (%)</td>
<td>2622 (77)</td>
<td>935 (81.9)</td>
<td>611 (78.3)</td>
<td>426 (77.6)</td>
<td>255 (72)</td>
<td>395 (68.2)</td>
</tr>
<tr>
<td>SE THV, n (%)</td>
<td>1397 (41.1)</td>
<td>593 (52)</td>
<td>332 (42.6)</td>
<td>214 (39)</td>
<td>159 (44.9)</td>
<td>99 (17.1)</td>
</tr>
</tbody>
</table>

5.3.2 TAVR Learning Curve Analysis - Clinical Outcomes

Clinical outcomes are detailed in table 9 as well as figure 16. There was a consistent decrease in all cause death with increasing TAVR experience and was significantly higher for the initial (9.6%, p<0.001) and early experience (7.9%, p=0.002) groups compared to the very-high experience (3.3%) operators. Similarly, the composite early safety endpoint decreased with increasing procedural experience from 27.5% for the initial experience, 28.5% for the early experience to 14.9% for very-high experience operators (p<0.001 for both groups.)

This was driven by reductions in major bleeding, which dropped from 11.3% in the initial experience and 8.1% in the early experience, down to 5.2% in the very-high experience group (p<0.001 for both groups.) Major vascular complications also demonstrated a statistically significant drop, from 10.6% in the initial experience and 11.2% in the early experience, down to 5.4% in the very high experience group (p<0.001 for both groups).

There were no significant changes in the rates of myocardial infarction between the initial experiences group (1.8%, p=NS), and the very high experience group (1.9%) indicating no learning curve. Similarly, the rate of stroke did not demonstrate a learning curve phenomenon, with the rates of stroke between the initial experience (3.1%, p=NS) and early experience (p=3.5%) not statistically significantly different than that of the very-high experience group (2.1%). Finally, while there was a numerical decrease in the rates of new dialysis initiation between the initial experience group (1.8%, p=NS) and the early experience group (1.4%, p=NS) and the moderate (0.2%) and high experience (0.3%), the very high experience group’s new dialysis initiation rate was 0.9%. This did not demonstrate a clear stepwise drop and thus did not demonstrate a learning curve phenomenon.

The rate of new pacemaker insertion was higher in the initial experience group (15.1%, p=0.007), and in the early experience group (13.6%, p=0.085), compared to the very-high experience group (9.7%) however this was not a stepwise progressive improvement as would be expected with a learning curve type change. The rate of pacemaker insertion was 15.1%

5.3.3 TAVR Learning Curve Analysis - Procedural Outcomes

The procedural time was statistically significantly longer in the initial experience group (135±80, p<0.001) compared to the very high experience group (83±38.2), however the early, moderate and high experience groups did not demonstrate such a step wise drop. The contrast
volume administered was also high in the initial (143±95, p<0.001) and early experience groups (139±124, p<0.001) compared to very-high experience operators (78±51). The rate of device success did not change with increasing experience with a device success of 76.5% in the initial experience group (p=NS), 81.2% in the early experience group (p=NS), 86.2% in the moderate experience group (borderline statistical significance of p=0.032), 83.6% in the high experience group (p=NS) compared to 80.3% in the very-high experience group. The rates of surgical conversion remained low, with a rate of 1.8% in the initial experience group and 2.4% in the very-high experience group, with no statistically significant change with increasing procedural experience.
Study population divided into chronological groups for learning curve analysis, with pairwise comparison with very-high experience group used as a reference group.
Table 9: Unadjusted Clinical and Procedural Outcomes for Learning Curve Analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial experience (n=1141)</th>
<th>p value</th>
<th>Early experience (n=780)</th>
<th>p value</th>
<th>Moderate experience (n=549)</th>
<th>p value</th>
<th>High experience (n=354)</th>
<th>p value</th>
<th>Very-high experience (n=579)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedural outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Device success</td>
<td>873 (76.5)</td>
<td>0.22</td>
<td>633 (81.2)</td>
<td>0.985</td>
<td>473 (86.2)</td>
<td>&lt;0.001</td>
<td>296 (83.6)</td>
<td>0.523</td>
<td>465 (80.3)</td>
</tr>
<tr>
<td>Procedure time (min)</td>
<td>135±80</td>
<td>0.001</td>
<td>78±77</td>
<td>0.805</td>
<td>47±45</td>
<td>&lt;0.001</td>
<td>79±53</td>
<td>0.940</td>
<td>83±38.2</td>
</tr>
<tr>
<td>Contrast volume (ml)</td>
<td>143±95</td>
<td>0.001</td>
<td>139±124</td>
<td>&lt;0.001</td>
<td>77±44</td>
<td>1.000</td>
<td>56±32</td>
<td>0.101</td>
<td>78±51</td>
</tr>
<tr>
<td>Surgical conversion</td>
<td>21 (1.8)</td>
<td>0.860</td>
<td>9 (1.2)</td>
<td>0.255</td>
<td>5 (0.9)</td>
<td>0.192</td>
<td>7 (2)</td>
<td>0.982</td>
<td>14 (2.4)</td>
</tr>
<tr>
<td><strong>Clinical outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>109 (9.6)</td>
<td>&lt;0.001</td>
<td>62 (7.9)</td>
<td>0.002</td>
<td>32 (5.8)</td>
<td>0.115</td>
<td>17 (4.8)</td>
<td>0.525</td>
<td>19 (3.3)</td>
</tr>
<tr>
<td>Early safety endpoint</td>
<td>314 (27.5)</td>
<td>&lt;0.001</td>
<td>222 (28.5)</td>
<td>&lt;0.001</td>
<td>143 (26)</td>
<td>0.032</td>
<td>80 (22.6)</td>
<td>0.098</td>
<td>86 (14.9)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>129 (11.3)</td>
<td>&lt;0.001</td>
<td>63 (8.1)</td>
<td>0.111</td>
<td>35 (6.4)</td>
<td>0.767</td>
<td>26 (7.3)</td>
<td>0.429</td>
<td>30 (5.2)</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>121 (10.6)</td>
<td>0.001</td>
<td>87 (11.2)</td>
<td>0.001</td>
<td>70 (12.8)</td>
<td>&lt;0.001</td>
<td>34 (9.6)</td>
<td>0.043</td>
<td>31 (5.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>35 (3.1)</td>
<td>0.532</td>
<td>27 (3.5)</td>
<td>0.336</td>
<td>19 (3.5)</td>
<td>0.387</td>
<td>9 (2.5)</td>
<td>0.963</td>
<td>12 (2.1)</td>
</tr>
<tr>
<td>Condition</td>
<td>Value1</td>
<td>Value2</td>
<td>Value3</td>
<td>Value4</td>
<td>Value5</td>
<td>Value6</td>
<td>Value7</td>
<td>Value8</td>
<td></td>
</tr>
<tr>
<td>------------------------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>21 (1.8)</td>
<td>1.00</td>
<td>5 (0.6)</td>
<td>0.145</td>
<td>8 (1.5)</td>
<td>0.953</td>
<td>2 (0.6)</td>
<td>0.342</td>
<td>11 (1.9)</td>
</tr>
<tr>
<td>New dialysis</td>
<td>20 (1.8)</td>
<td>0.429</td>
<td>11 (1.4)</td>
<td>0.780</td>
<td>1(0.2)</td>
<td>0.430</td>
<td>1(0.3)</td>
<td>0.708</td>
<td>5(0.9)</td>
</tr>
<tr>
<td>New PPM</td>
<td>172 (15.1)</td>
<td>0.007</td>
<td>106 (13.6)</td>
<td>0.085</td>
<td>64 (11.7)</td>
<td>0.612</td>
<td>72 (20.3)</td>
<td>&lt;0.00</td>
<td>56 (9.7)</td>
</tr>
<tr>
<td>Mod-severe AI</td>
<td>59 (5.8)</td>
<td>0.914</td>
<td>20 (3.1)</td>
<td>0.974</td>
<td>5 (1.1)</td>
<td>0.891</td>
<td>15 (4.2)</td>
<td>1.000</td>
<td>42 (8.1)</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>15.4±37.4</td>
<td>0.001</td>
<td>12.2±13.8</td>
<td>0.117</td>
<td>11.1±22.2</td>
<td>0.452</td>
<td>9±8</td>
<td>0.988</td>
<td>9±18</td>
</tr>
</tbody>
</table>

Very high experience (>300 procedures) group used as a reference group for pair wise comparison. All values are n (%) except as noted. PPM - permanent pacemaker; AI - aortic insufficiency, LOS – length of stay post TAVR
5.3.4 TAVR Learning Curve Analysis - Multivariate Analysis

A logistic regression plot of the odds of mortality plotted against the TAVR procedural volume revealed no significant early inflection point indicating a likely prolonged learning curve phenomenon (figure 17). The results of logistic multivariate analysis (figure 18 A and B) showed that TAVR performed by the initial (OR 3.83, 95% CI 1.93-7.60, p<0.001), early (OR 2.41, 95% CI 1.51-5.03, p=0.020) and intermediate (OR 2.53, 95% CI 1.19-5.40, p=0.016) experience groups were independently associated with higher mortality compared to the very-high experience operators. In addition, the early safety endpoint was significantly higher for initial (OR 2.02, 95%CI 1.41-2.89, p<0.001), early (OR 1.74, 95% CI 1.19-2.56, p=0.005), intermediate (OR 2.07, 95% CI 1.40-3.07, p<0.01) and high (OR1.70, 95% CI 1.14-2.59, p=0.009) experience groups compared to the very-high experience operators. Higher STS score (OR 1.84, 95% CI 1.20-2.82, p=0.005) and TA access (OR 1.84, 95% CI 1.20-2.82, p=0.005) were also independent predictor of increased mortality, while LVEF, gender, NYHA class, prior CABG, CKD, COPD status, balloon expandable vs self-expanding valves did not demonstrate a significant association with increased mortality or early safety endpoint (data not shown.)
Figure 17: Relationship between TAVR procedural volume and odds of mortality

Logistic regression analysis using TAVR procedural volume as a continuous variable
Figure 18 A and B: Multivariate Analysis of Mortality and Early Safety Endpoint Learning Curve Analysis.

**Death**

<table>
<thead>
<tr>
<th>Procedure Range</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-75 vs &gt;300</td>
<td>3.83</td>
<td>1.93-7.60</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>76-150 vs &gt;300</td>
<td>2.41</td>
<td>1.51-5.03</td>
<td>0.020</td>
</tr>
<tr>
<td>151-225 vs &gt;300</td>
<td>2.53</td>
<td>1.19-5.40</td>
<td>0.016</td>
</tr>
<tr>
<td>226-300 vs &gt;300</td>
<td>1.83</td>
<td>0.84-3.99</td>
<td>0.131</td>
</tr>
</tbody>
</table>

**Early Safety Endpoint**

<table>
<thead>
<tr>
<th>Procedure Range</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-75 vs &gt;300</td>
<td>2.02</td>
<td>1.41-2.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>76-150 vs &gt;300</td>
<td>1.74</td>
<td>1.19-2.56</td>
<td>0.005</td>
</tr>
<tr>
<td>151-225 vs &gt;300</td>
<td>2.07</td>
<td>1.40-3.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>226-300 vs &gt;300</td>
<td>1.70</td>
<td>1.14-2.59</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Pairwise comparison with very high experience (>300 procedure) group used as a reference group.
5.3.5 TAVR Annual Volume Analysis - Patient Population

A total of 2205 of 3403 (64.8%) patients were included in this analysis with 569 (25.8%) cases performed at low, 1121 (50.84%) cases performed at intermediate and 515 (23.36) cases performed at high annual volume centres. Figure 19 demonstrates procedural volume at each site per calendar year. All 16 centres included in this study contributed data, with the first and last calendar year removed, with the year 2008 being the first calendar year included, and 2013 being the last. There were 69 calendar/years of data included, with 2 centres having 2 calendar/years, 1 centre having 3 calendar/years, 4 centres having 4 calendar/years, 6 centres having 5 calendar years, and 1 centre having 6 calendar years.

Table 10 describes baseline patient characteristics in each volume group. There were significant differences in the proportion of females (p=0.018), mean BMI (p=0.001), LVEF (p=0.001), mean STS PROM (p=0.001), prior CAD (p=0.001), prior CABG (p<0.001) and chronic kidney disease (p=0.001), and rates of atrial fibrillation (p=0.001) among the three groups. The rates of diabetes mellitus, hypertension and COPD did not differ significantly between the groups, and the rates of NYHA IV heart failure did not differ significantly. The mean AV gradient was highest in the low volume group (48.6±16.2 mmHg) and lowest in the high-volume group (41.3±17.5 mmHg, p<0.001). The use of TF approach (p<0.001) and self-expanding valve (p<0.001) was highest at low compared to high annual volume centres.
Figure 19. Annual institutional TAVR volume 2008-2013

Annual institutional TAVR volume 2008-2013, n=16

Annual (calendar year) procedural volume (y axis) plotted against calendar year (x axis)
Table 10: Baseline Unadjusted Clinical and Procedural Characteristics for Annual Volume-Outcome Analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low volume (1-50)</th>
<th>Intermediate volume (51-100)</th>
<th>High volume (&gt;100)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=569 (25.8%)</td>
<td>N=1121 (50.84%)</td>
<td>N=515 (23.36%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>81.5±7.2</td>
<td>81.6±7.2</td>
<td>80.7±9.7</td>
<td>0.09</td>
</tr>
<tr>
<td>Female</td>
<td>263 (46.3)</td>
<td>571 (50.9)</td>
<td>224 (43.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean AV gradient, mmHg</td>
<td>48.6±16.2</td>
<td>45.7±16.4</td>
<td>41.3±17.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AV Area, cm²</td>
<td>0.7±0.2</td>
<td>0.6±0.2</td>
<td>0.6±0.3</td>
<td>0.05</td>
</tr>
<tr>
<td>BMI</td>
<td>26.4±4.9</td>
<td>27.4±5.3</td>
<td>26.5±5.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>54.8±14.1</td>
<td>55.1±13.8</td>
<td>52.2±14.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>STS PROM</td>
<td>8.7±7.6</td>
<td>6.9±5.6</td>
<td>8.1±5.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>314 (55.2)</td>
<td>579 (51.7)</td>
<td>324 (62.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>300 (52.7)</td>
<td>504 (45)</td>
<td>280 (54.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>144 (25.3)</td>
<td>303 (27)</td>
<td>141 (27.4)</td>
<td>0.68</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>168 (29.5)</td>
<td>345 (30.8)</td>
<td>170 (33)</td>
<td>0.45</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>448 (78.7)</td>
<td>890 (79.4)</td>
<td>409 (79.4)</td>
<td>0.94</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter, n (%)</td>
<td>137 (24.1)</td>
<td>326 (29.1)</td>
<td>184 (35.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>NYHA class IV, n (%)</td>
<td>83 (14.6)</td>
<td>155 (13.8)</td>
<td>59 (11.5)</td>
<td>0.28</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>121 (21.3)</td>
<td>235 (21)</td>
<td>152 (29.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Transfemoral approach, n (%)</td>
<td>470(82.6)</td>
<td>905(80.7)</td>
<td>342(66.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CoreValve, n (%)</td>
<td>945 (42.9)</td>
<td>312 (54.8)</td>
<td>568 (50.7)</td>
<td></td>
</tr>
<tr>
<td>Edwards Sapien, n (%)</td>
<td>430 (19.5)</td>
<td>90 (15.8)</td>
<td>277 (24.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Edwards Sapien XT/3, n (%)</td>
<td>830 (37.6)</td>
<td>178 (29.4)</td>
<td>283 (24.6)</td>
<td></td>
</tr>
</tbody>
</table>

High volume (>100 procedures/year) group used as a reference group for pair wise comparison. AV – aortic valve; BMI – body mass index; LVEF – left ventricular ejection fraction; STS PROM – Society of Thoracic Surgeons predicted risk of mortality; NYHA – New York Heart
Association; CAD – coronary artery disease; CABG – coronary artery bypass grafting; COPD – chronic obstructive pulmonary disease
5.3.6 TAVR Annual Volume Analysis - Clinical Outcomes

All-cause mortality was significantly higher in the low volume centres compared to the high (8.8 vs 3.9%, p=0.003) volume centres, but was statistically similar between intermediate (5.7%, p=0.22) and high-volume centers (table 11 and figure 20). The early safety endpoint was statistically significantly higher the lower annual volume vs the higher annual volume groups (34.3% vs 26.4%, p=0.01) but was not statistically different between the intermediate volume group (27.9%, p=0.73). Major bleeding similarly was significantly higher in the lower annual volume group vs the higher annual volume group (11.1%, vs 4.9%, p=0.037), with a trend to higher bleeding in intermediate volume groups that did not reach significance (7.3%, p=0.24).

Major vascular complications were 8.6% (p=0.87%) in the low annual volume, 9.1% (p=0.98) in the intermediate and 9.3% in the high annual volume group. The rates of stroke were similar between the low (3.7%), intermediate (3.1%) and high (2.3%) annual volume groups which was not statistically significant. The rate of surgical conversion was similar between low (1.4%), intermediate (1.4%) and high (1.9%) annual volume groups. New permanent pacemaker rates (PPM) did not differ significantly between low (13.2%), intermediate (14.8%) and high (11.5%). Similarly, the rates of severe aortic insufficiency did not differ significantly.

5.3.7 TAVR Annual Volume Analysis - Procedural Outcomes

The procedure time (184.3±101.6 vs 84.8±36.3 min, p<0.001), and contrast volume (219.8±92.4 vs 74.8±45.5 mL, p<0.001) were higher in low compared to high volume centers. Device success did not demonstrate a significant difference between low annual volume (78%, p=0.88), intermediate volume (83.2%, p=0.07) and high volume (79%) groups. There was a higher length of stay (LOS) post TAVR in the low annual volume group (15.0±21.0, p<0.001) (data expressed as mean +/- standard deviation), and a non-statistically significant trend to higher LOS in the intermediate volume group (11.0±23.1, p=0.1) compared to the high-volume group (8.9±7.7).
Table 11: Unadjusted Clinical and Procedural outcomes for Annual Volume-Outcome Analysis

<table>
<thead>
<tr>
<th></th>
<th>Low volume (1-50) N=569 (26%)</th>
<th>P value*</th>
<th>Intermediate volume (51-100) N=1121 (51%)</th>
<th>P value*</th>
<th>High volume (&gt;100) N=515 (23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>50 (8.8)</td>
<td>p=0.003</td>
<td>64 (5.7)</td>
<td>p=0.22</td>
<td>20 (3.9)</td>
</tr>
<tr>
<td>Device Success, n (%)</td>
<td>444 (78)</td>
<td>p=0.88</td>
<td>933 (83.2)</td>
<td>p=0.07</td>
<td>407 (79)</td>
</tr>
<tr>
<td>Early safety endpoint, n (%)</td>
<td>195 (34.3)</td>
<td>p=0.01</td>
<td>313 (27.9)</td>
<td>p=0.73</td>
<td>136 (26.4)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>21 (3.7)</td>
<td>p=0.30</td>
<td>35 (3.1)</td>
<td>p=0.54</td>
<td>12 (2.3)</td>
</tr>
<tr>
<td>Major bleeding, n (%)</td>
<td>63 (11.1)</td>
<td>p=0.03</td>
<td>82 (7.3)</td>
<td>p=0.24</td>
<td>25 (4.9)</td>
</tr>
<tr>
<td>Major vascular complication, n (%)</td>
<td>49 (8.6)</td>
<td>p=0.87</td>
<td>102 (9.1)</td>
<td>p=0.98</td>
<td>48 (9.3)</td>
</tr>
<tr>
<td>Surgical conversion, n (%)</td>
<td>16 (1.4)</td>
<td>p=0.86</td>
<td>16 (1.4)</td>
<td>p=0.65</td>
<td>10 (1.9)</td>
</tr>
<tr>
<td>New PPM, n (%)</td>
<td>75 (13.2)</td>
<td>p=0.57</td>
<td>166 (14.8)</td>
<td>p=0.11</td>
<td>59 (11.5)</td>
</tr>
<tr>
<td>Aortic insufficiency (&gt;2+), n (%)</td>
<td>22 (4.2)</td>
<td>p=0.92</td>
<td>33 (3.4)</td>
<td>p=0.29</td>
<td>34 (7.4)</td>
</tr>
<tr>
<td>LOS post TAVR (days), mean±SD</td>
<td>15.0±21.0</td>
<td>p&lt;0.001</td>
<td>11.0±23.1</td>
<td>p=0.1</td>
<td>8.9±7.7</td>
</tr>
</tbody>
</table>

High volume (>100 procedures/year) group used as a reference group for pair wise comparison. PPM – permanent pacemaker, LOS – length of stay, TAVR – transcatheter aortic valve replacement.
Study population divided into annual volume groups for analysis, with pairwise comparison with high volume (>100 procedures/year) group used as a reference group.
5.3.8 TAVR Annual Volume Analysis – Multivariate Analysis

The results of logistic multivariate analysis (figure 21 A and B) showed that low annual volume group was independently associated with increased mortality (OR 2.70, 95% CI 1.44-5.07, p=0.002), but annual volumes in the intermediate range were not associated with increased mortality (OR 1.63, CI 0.89-2.99, p=0.11). Similarly, after multivariate analysis, annual volumes in the low group were associated with higher rates of the early safety endpoint (OR 1.60, CI 1.17-2.17, p=0.003), while annual volumes in the intermediate range were not independently associated with higher rates of the early safety endpoint (OR 1.01, CI 0.76-1.33, p=0.959).

Device success was not statistically significantly worse in low annual volume groups compared with high annual volume groups (OR 1.16, CI 0.82-1.63, p=0.41). As with the learning group analysis, approach (transapical vs transfemoral) was strongly associated with worse rates of death (OR 1.88, CI 1.04-3.32, p=0.038) and the early safety endpoint (OR 1.69, CI 1.25-2.20, p=0.001.)
Figure 21 A and B: Multivariate Analysis of Mortality and Composite Early Safety Endpoint for Annual Volume Analysis.

**Death**

- Annual Volume 0-50 vs >100: 2.70 (1.44-5.07) \( P=0.002 \)
- Annual Volume 50-100 vs >100: 1.63 (0.89-2.99) \( P=0.111 \)

**Early Safety Endpoint**

- Annual Volume 0-50 vs >100: 1.60 (1.17-2.17) \( P=0.003 \)
- Annual Volume 50-100 vs >100: 1.01 (0.76-1.33) \( P=0.959 \)

Pairwise comparison with high volume group used as a reference group.
Chapter 6

6 Discussion

6.1 Preamble

The number of TAVR procedures being performed has increased markedly as the indications have expanded from inoperable (Leon, Smith et al. 2010), to high (Smith, Leon et al. 2011, Adams, Popma et al. 2014) and intermediate risk patients (Leon, Smith et al. 2016, Reardon, Van Mieghem et al. 2017). There is likely to be a further increase in TAVR utilization in view of demographic changes (Holmes, Nishimura et al. 2015) and potential confirmation of safety and efficacy in lower risk patients (Mylotte, Osnabrugge et al. 2013). However, TAVR remains a technically challenging procedure requiring a high level of skill and prior experience with percutaneous and endovascular procedures. In addition to a comprehensive pre-procedural patient assessment by a dedicated heart team, the TAVR requires a unique skillset and expertise for implantation and expeditiously manage unexpected complications. Therefore, adequate training and experience play a critical role in improving procedural safety and clinical success. In addition, similar to other procedural skills, it is likely that a minimum annual procedural volume is required to provide optimum results.

The two major components of clinical proficiency include measures of process such as procedural time, contrast use and radiation exposure (Ball, Sharieff et al. 2011, Hess, Peterson et al. 2014) and measures of outcome such as complication rates and clinical success (Sanchez, Harrell et al. 2001, Bridgewater, Grayson et al. 2004). Despite the increasing use of TAVR across institutions, there is limited data for the effect of experience on measures of procedural and clinical success. In the studies presented here in this thesis, we used an international multicenter TAVR registry from the initiation of the TAVR program of 16 sites to establish the optimal
6.2 Summary of Principle Findings

6.2.1 TAVR Institutional Experience and Outcomes

Our hypothesis that a learning curve exists for TAVR was demonstrated in the institutional experiences and outcomes study that was presented in chapter 4. In this study of 1953 patients from 8 sites in North America and Europe (chapter 4), we divided the population in equal chronological quantiles of each institution’s TAVR experience. In this study, we found that TAVR patients in Q4 (>243 procedures) was independently associated with a lower mortality. Q2 (procedures 63 to 133), Q3 (procedures 134 to 242 and Q4 were independently associated with higher device success. Both Q3 and Q4 were associated with better early safety. Q3 and Q4 were independently associated with lower risk of major bleeding. In this study, the chronological sequence was divided into equal quantiles, which demonstrated improved outcomes as procedural experience accumulated. Given the arbitrary nature of cut off points derived from equal quantiles, a threshold of procedural experience could not be determined.

6.2.2 TAVR Learning Curve Study

While the institutional experience study of chapter 4 strongly suggested a learning curve was present, the arbitrary cut off points from a quantile approach limited determination of a minimal institutional procedural experience to optimize outcomes. In the section of chapter 5 dealing with the learning curve to optimize outcomes in TAVR, the main findings from this study of 3403 patients from 16 international centers are: 1) an important learning curve exist with incremental improvement in clinical outcomes for increasing TAVR experience. 2) A TAVR experience of at least 225 procedures is associated with reduced TAVR mortality while the early safety endpoint, the composite of death, stroke, major bleeding, vascular complications, surgical conversion and renal failure, continued to improve beyond the 225 case volume. In addition to this, markers of procedural efficiency such as length of stay and procedure time were high in the initial experience, as well as the contrast dose. The rates of stroke, myocardial infarction, new dialysis, severe aortic regurgitation, and surgical conversion also were similar throughout the group suggesting that there was no significant learning curve phenomenon with these outcomes.
This section expands upon the findings of the institutional experience and outcomes study. In this study, clear cut off points are established, and minimal experience to optimize outcomes is established. These findings of a prolonged learning curve are in keeping with our second hypothesis.

6.2.3 TAVR Annual Institutional Volumes and Outcomes Study

In the second part of chapter 5, the annual institutional volume and clinical outcomes study, a total of 2205 of 3403 (64.8%) patients were included in this analysis with 569 (25.8%) cases performed at low, 1121 (50.8%) cases performed at intermediate and 515 (23.36) cases performed at high annual volume centres. The results of logistic multivariate analysis showed that low annual volume group (<50 cases per year) was independently associated with increased mortality and high rate of composite early safety endpoint, the composite of death, stroke, major bleeding, vascular complications, surgical conversion and renal failure. Measures of process including procedure time and contrast volume were worse in lower volume centers. The device success rates and risk of post procedural myocardial infarction, stroke, surgical conversion, new pacemaker or aortic regurgitation were similar for the three volume groups.

6.3 Clinical Significance and Novelty of findings

6.3.1 TAVR Institutional Experience and Learning Curves for TAVR

The two important components of any procedural learning curve include measures of clinical outcome including patient survival or procedural success and process efficiency including procedural time and resource utilization(Subramonian and Muir 2004). For cardiovascular procedures, prior learning curve studies have demonstrated important relationship for increasing experience with both outcome measures as well as process efficiency (Le Morvan and Stock 2005, Hopper, Jamison et al. 2007). Four years’ experience post training has shown to decrease mortality for coronary artery bypass surgery (Bridgewater, Grayson et al. 2004) and > 150 cases required to optimize outcomes of percutaneous balloon mitral valvuloplasty (Sanchez, Harrell et al. 2001). Similarly, minimum procedural volume criteria for optimizing procedural efficiency has been described for radial PCI (Ball, Sharieff et al. 2011, Hess, Peterson et al. 2014).
In the present study, we examined 30-day mortality and composite early safety endpoint as measures of clinical outcome and procedural time and contrast media usage as measures of procedural efficiency. In addition, the “very-high experience group” was defined for operators with >300 case volume as the reference group to assess the learning curve of the all operators and effect on outcome measures with increasing procedural volumes. The patients undergoing TAVR by the very-high experience operators in the present study showed a mortality rate of 3.3% which is lower than that reported for the TVT registry (Grover, Vemulapalli et al. 2017) and similar to sites with the most TAVR experience in the US (Carroll, Vemulapalli et al. 2017). TAVR learning curve analysis from the PARTNER I trial (Minha, Waksman et al. 2016, Suri, Minha et al. 2016) showed an excess mortality and procedural failure only for initial TAVR experience but the findings are limited by a small sample size as well as being clinical trial data as opposed to real world data. The results of the present study are consistent with recently published data from the TVT registry showing lower major adverse events with increasing TAVR experience (Carroll, Vemulapalli et al. 2017). Carroll et al. (Carroll, Vemulapalli et al. 2017) observed a reduction in vascular and bleeding complications most noted in the first 100 cases, and a reduction in mortality that became statistically insignificant after adjustment. When used as a continuous variable, the present study identified procedural volume to be independently associated with 30-day mortality (figure 2A), major bleeding and MACE and the odds of mortality continued to decrease with increasing procedural experience. On comparing procedural experience as a categorical variable in multivariate regression analysis, the 30-day mortality showed a consistent decrease for up to 225 case volume (figure 2B). For the early safety endpoint up, we observed improvement beyond the 225 case volume (figure 2C), a finding consistent with earlier reports (Carroll, Vemulapalli et al. 2017). The rates of stroke, paravalvular aortic regurgitation, and dialysis requirement did not change with increasing experience. The measures of procedural efficiency such as procedure time, contrast volume also improved with increasing experience, but no significant difference was observed after initial and early experience when compared to the very-high experience operators.

Our study adds unique contributions to previous studies on the subject of the learning curve for TAVR. The initial studies in the field were small single center studies, or small studies of up to 3 centers (Alli, Booker et al. 2011, Gurvitch, Tay et al. 2011, Kempfert, Rastan et al. 2011, Arai, Lefevre et al. 2016, Arai, Romano et al. 2016) as compared to ours involving 3403 patients in 16 international centers. A series of 3 studies examining patients from the PARTNER...
studies demonstrated a plateau of clinical and technical proficiency in 22-30 cases experience (Alli, Rihal et al. 2016, Minha, Waksman et al. 2016, Suri, Minha et al. 2016). While these studies suggest mastery of the procedure with a short learning curve, the generalizability of these studies is likely lower given this data is taken form a clinical trial as opposed to real world data. In the aforementioned paper by Carroll et al., mortality decreased with procedural experience which in their trial seemed to continue to drop even after hundreds of cases has been performed. However, in his study thresholds for this were not established. Our study would seem to back up this finding that the learning curve for this procedure is likely greater than the previously described studies and continues until at least > 200 cases have been completed, perhaps even longer.

Our study would seem to agree with the most recent 2017 AATS/ACC/SCAI/STS Expert Consensus Systems of Care document (Bavaria JE 2017), with specific recommendations have been made for new TAVR programs which suggests to include interventional cardiologist with a ≥100 TAVR experience, as opposed to the lower threshold set from the PARTNER studies on learning curve (Alli, Rihal et al. 2016, Minha, Waksman et al. 2016, Suri, Minha et al. 2016).

Our study has important implications for hospital credentialing in the current medico-legal environment. Furthermore, our study is important in that there has been an increase in other structural heart procedures (Grover, Vemulapalli et al. 2017), with these also likely to have a separate learning curve.

6.3.2 Annual Institutional Volumes for TAVR

The present study showed that low volume (<50 cases per year) centers experienced a 30-day mortality of 8.8%, which is significantly higher than 5.7% for intermediate volume (51-100 cases per year) and 3.9% for high volume (51-100 cases per year) centers, figure 3. The mortality rates for high volume centers in the present study are lower than those reported for contemporary TAVR experience (Auffret, Lefevre et al. 2017, Carroll, Vemulapalli et al. 2017, Grover, Vemulapalli et al. 2017) confirming that high-annual volume is an important contributor to improved clinical outcomes. Similarly, the early safety endpoint was also significantly worse among the low volume group and low volume group was an independent predictor of worse 30-day mortality and the early safety endpoint, figure 4. There is limited data for the relationship between annual institutional TAVR volume and clinical outcomes. A recent study by Khera et al. (Khera, Kolte et al. 2017) showed that low volume centers identified as performing <50 TAVR
cases per year have a significantly higher 30-day readmission rates compared to high volume centers performing >100 cases per year. This threshold has been identified in another German study (Bestehorn, Eggebrecht et al. 2017) as being associated with reduced mortality. Our study would add to this growing body of evidence.

As in the previous section, there are important implications for our finding. As described in chapter 2, there has been a considerable amount of research and publications in the field of surgery about the deleterious effect of low volume surgery (Luft, Bunker et al. 1979, Gonzalez, Dimick et al. 2014). Despite the large increase in the number of TAVR procedures being performed at greater number of institutions, many hospitals perform a relatively small number of procedures. There are many low volume centers performing <50 procedures a year both in the United States and internationally. This trend is likely to continue with potential utilization of this technology in lower risk patients (Thyregod, Steinbruchel et al. 2015). The findings from the present study suggest a minimum annual volume threshold to provide the best clinical outcomes for patients undergoing TAVR procedures and can serve as a guide for optimal distribution of resources and technology. In the 2017 AATS/ACC/SCAI/STS Expert Consensus Systems of Care document specific recommendations have been made for new TAVR programs, a threshold has been set for a minimum of 50 TAVR/year or 100 TAVR over two years. Our study would agree with this recommendation.

There is a clear need for high quality data to define minimal annual procedural volumes. While the implications of having low volume centers performing technically complex procedures are self-evident in terms of higher complications, there are consequences for setting high annual thresholds. Setting high thresholds would necessitate closing low volume centers, with many of these centers in rural or underserviced areas. This would have the consequence of reducing access. This is an important implication of our research, and one that must be considered by regulatory authorities who use our data, or similar data to determine site specific minimal thresholds. We feel that, in spite of the reduction in access with high minimal annual threshold for TAVR, the improvement in outcomes for patients outweighs this.
6.4 Limitations

There are important limitations to the present study. First, there were significant differences in baseline demographic and procedural characteristics between the chronological and volume groups in the learning curve and annual volume analysis that may have confounded the outcomes of interest. Although, multivariate regression analysis was performed to adjust for these differences; other unmeasured confounders may still remain. Multivariate regression has compared well as a means to account for confounding compared to propensity scores or other methods (Elze, Gregson et al. 2017).

Secondly, this study was only able to assess the center learning curve and center annual volume, not of individual operators. However, the current guidelines recommend a heart team approach to decision making and most centers require a two-member TAVR team for procedures making individual operator data less relevant. Prior data from coronary interventions have shown center volume to be a more robust predictor of outcome compared to individual operator volume. (Hannan, Racz et al. 1997, McGrath, Wennberg et al. 2000) However, the interaction between low volume TAVR operators and high annual volume centers and vice versa could not be assessed in the present analysis as all operators performed TAVR procedures at a single institution.

Our analysis only included 16 centers, thus while this study had a large population of 3403 patients, the limited number of centers may impact results. While our study represents one of the largest yet done to assess the learning curve, consideration for repeating this study with more centers to better assess the learning curve should be considered.

One of the most important limitations of our study is that we were unable to accurately account for frailty. Frailty is an important consideration for patient selection for TAVR vs SAVR and has been reviewed extensively elsewhere (Afilalo, Lauck et al. 2017, Forcillo, Condado et al. 2017). Due to the variable definitions and measures for frailty, including variable documentation of patient frailty, we were unable to accurately measure this across centres, and thus unable to control for this used multivariate analysis.

Finally, many of the centers that were included in this study began their TAVR experience early; whether the learning curve may be abbreviated in the current environment with more centers performing the procedure, with newer technology and more educational opportunities is not known.
Chapter 7

7 Conclusions

In this thesis, we examined the learning curve and minimal institutional volumes associated with optimal outcomes for transcatheter aortic valve implantation (TAVR). We hypothesized that, as TAVR is a complex procedure with a unique skill set, there exists a prolonged learning curve, and one that is longer than what has been published in the literature. Furthermore, we also hypothesized that TAVR requires a relatively high minimal annual institutional volume to optimize outcomes.

Our principle findings in the institutional outcomes study was that incremental improvements occurred with increasing procedural experience in terms of measures of process with decreased contrast use and procedure time, as well as improved measures of outcome including lower mortality, and major complications. In order to expand this further, we conducted a learning curve study with a larger patient population. In this study, we found that performing > 225 TAVR was independently associated with lower complication rates and performing > 300 procedures was associated with lower combined major adverse outcomes. Using a subset of this data, we conducted an annual institutional volumes and outcomes study. Our group found that centers performing < 50 TAVR / year were independently associated with increased rates of death and combined major adverse outcomes.

The findings of our study will inform policy makers in defining minimal training requirements as well as minimal institutional volumes to optimize outcomes in transcatheter aortic valve replacement.
Chapter 8

8 Future Directions

With regards to the learning curve of TAVR, our study, as with the previous studies, used older first and second generation TAVR devices. Newer generation devices have since come on the market with multiple improvements. The Edwards Sapien 3 device™ (Binder, Rodes-Cabau et al. 2013) is designed to have a lower crimped profile reducing the femoral sheath size, which may potentially result in easier deployment with fewer major bleeding or major vascular injury episodes. Furthermore, the valve is designed with a cuff at the inflow to reduce the rate of paravalvular regurgitation which is associated with increased mortality (Abdel-Wahab, Zahn et al. 2011). Similarly, the Medtronic CoreValve Evolut R™ (Schulz, Jabs et al. 2016) is designed to have a lower profile for insertion, a design allowing repositioning and a sealing skirt to reduce paravalvular regurgitation. Other valve designs will be coming onto market with similar improvements over the initial designs (Wiegerinck, Van Kesteren et al. 2016). Technological advancement in TAVR is both intended to reduce the rates of complications, but also may have the benefit of making the implantation process easier and thus reducing the learning curve. As such, future operators and centers using newer generation of TAVR devices may require a shorted learning curve in order achieve optimal outcomes. In order to assess whether the learning curve of operators beginning to use newer lower profile TAVR devices is shortened, a study similar to ours would need to be undertaken where “valve generation” would be stratified. The learning curve for implantation of earlier generations of valves would be compared to the learning curve of later generation of valves.

The second major limitation of our research was that many of the centers in this study were early in the development of the technology, and thus were not in a position to have benefitted from the knowledge of the wider TAVR implant community. Now that the technology has matured, the ability to provide proctorship, the supervised initiation of a TAVR implant program, is available. With regards to this point, a group from Japan (OCEAN registry) has published a recent review of their proctorship experience (Yamawaki, Iwasaki et al. 2018). In this study, there was a period of required proctorship for the first 25 cases, followed by independent implantation at each site. This study demonstrated that the composite early safety
endpoint was lower in the independent practice period, as well as the lower rates of major bleeding for TA-TAVR and lower procedure times for TF-TAVR. A future direction of this research to incorporate the concept of proctorship would be to compare the learning curve for centers which started their program with no proctorship (the early adopting centers where this was not feasible) to the later adopting centers who had the ability to have proctorship. This may be done via identifying centers who have had proctorship from the device manufacturers.

While our study described in detail the learning curve and minimal annual procedural volume associated with optimal outcomes in TAVR, by nature of a retrospective study it is unable to determine to mechanism of the learning curve or minimal annual procedural volume. As described in chapter 3, some of the contributors to this include better patient selection, more skilled operators, referral bias to operators with better outcomes, increased familiarity with and ability to anticipate and manage post-operative complications, greater resources to manage complex patients and better communication between the health care team (Luft, Bunker et al. 1979, Gonzalez, Dimick et al. 2014). The role of post-operative management and “failure to rescue” from a complication has also been identified as another important factor for adverse outcomes seen among low volume centres(Gonzalez, Dimick et al. 2014). Future studies should examine the contributors to minimal annual volumes and the learning curve, which would inform future training and societal guidelines. One approach would be to undertake a qualitative study of centers at various stages of the learning curve and various annual volumes to generate data on causes of patient morbidity and mortality, and interventions that these centers have taken to reduce these.

Finally, like any advance in medicine, once the early adopting centers have achieved a level of familiarity and comfort with the procedure, a training program opens in this field. There now exists a number of structural heart disease and TAVR training programs. No literature yet exists about the learning curve for new operators with structural heart disease fellowships. One limitation to studying the outcomes would be that TAVR in general has multiple members of the team performing the procedure and thus isolating the outcome of one of the members of the team is difficult. The literature in this field including this study so far has only assessed learning curve of institutions, not the learning curve of individual operators. A future research project would involve documenting the operators in the procedure at each center, determining each operator’s training, and assessing outcomes based on training level.
In determining a minimal annual threshold of 50 TAVR per year, our study, like all other studies in this field assessed the institution annual volume not the operator volume. In order to assess if operator annual volume interacts with institution volume, carefully documenting the case experience of each operator would be required. This study may need to be undertaken if regulatory agencies begin to question annual procedural volumes per operator, similar to what is recommended in the United States with PCI volumes.
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Appendix A: Contributions

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Appendix B: Copyright Acknowledgements

Figure 1 and 2. Gross specimen of normal and calcific degenerative aortic valve. Adapted from Rosario V. Freeman, and Catherine M. Otto Circulation. 2005;111:3316-3326

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Figure 3 - Adapted by Lindman, B. R. et al. (2016) Calcific aortic stenosis Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.6

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Figure 5 and Table 1. 2014 ACC/AHA Guidelines for the Management of Aortic Stenosis
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Figure 6. In Hospital Mortality after Aortic Valve Replacement as a Function of Age. Adaptefrom (Astor, Kaczmarek et al. 2000)
Figure 7 (A-C). Commonly Used Transcatheter Heart Valves. Adapted from (Webb and Wood 2012)
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Figure 9. 2017 ACC/AHA Recommendations for the Management of Severe Symptomatic Aortic Stenosis
Adapted from (Nishimura, Otto et al. 2017)
Figure 10. Growth in the number of TAVR sites and procedures performed in the United States

Adapted from the STS/ACC TVT registry (Grover, Vemulapalli et al. 2017)

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Figure 11. Procedural Sequence Number association with Complications. Adapted from (Carroll, Vemulapalli et al. 2017)

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The text of this chapter, including all tables and figures has been published in modified format in the Journal of the American College of Cardiology: Cardiovascular Interventions. (Wassef, Rodes-Cabau et al. 2018)

Title: The Learning Curve and Annual Procedure Volume Standards for Optimum Outcomes of Transcatheter Aortic Valve Replacement Findings From an International Registry


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Chapter 2

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