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# **DOCTORAL THESIS**

**ACQUIRED VON WILLEBRAND FACTOR  
ALTERATION AT PATIENT-PROSTHESIS  
MISMATCH AFTER AORTIC VALVE  
REPLACEMENT PROCEDURE**

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## TABLE OF CONTENTS

LIST OF PUBLISHED SCIENTIFIC PAPERS .....	VI
LIST OF ABBREVIATIONS AND SYMBOLS.....	VII
LIST OF FIGURES .....	IX
LIST OF TABLES.....	X
INTRODUCTION .....	XI
<b>1. GENERAL PART .....</b>	<b>1</b>
<b>1.1. AORTIC VALVE REPLACEMENT ESSENTIALS.....</b>	<b>1</b>
1.1.1. Aortic valve disease.....	1
1.1.2. Aortic valve replacement procedure .....	4
1.1.3. Patient-Prosthesis Mismatch .....	10
<b>1.2. VON WILLEBRAND FACTOR .....</b>	<b>15</b>
1.2.1. Von Willebrand Factor: Structure and Function.....	15
1.2.2. Von Willebrand Disease: Congenital and Acquired Forms.....	17
1.2.3. Shear Stress-induced von Willebrand Disease.....	17
<b>1.3. VON WILLEBRAND FACTOR IN AORTIC ALTERATIONS AND HEMODYNAMIC CHANGES .....</b>	<b>21</b>
1.3.1. Aortic Aneurysms and von willebrand factor.....	21
1.3.1.1. Thoracic Aortic Aneurysms.....	21
1.3.1.2. Abdominal Aortic Aneurysms.....	23
1.3.2. Aortic Dissection and von willebrand factor .....	24
1.3.2.1. Acute Aortic Dissection.....	24
1.3.2.2. Chronic Aortic Dissection.....	25
1.3.3. Penetrating Aortic Ulcers and von willebrand factor .....	26
1.3.4. Endovascular Interventions and von willebrand factor.....	27
1.3.5. Heyde's Syndrome.....	29

<b>2. SPECIAL PART .....</b>	<b>31</b>
<b>2.1. AIMS AND OBJECTIVES.....</b>	<b>31</b>
<b>2.2. STUDY I. ACQUIRED VON WILLEBRAND FACTOR ALTERATION – LITERATURE REVIEW .....</b>	<b>34</b>
2.2.1. <i>Data acquisition .....</i>	34
2.2.2. <i>The prevalence of PPM and how to avoid it .....</i>	35
2.2.3. <i>Diagnostic approach on von willebrand factor alteration .....</i>	40
2.2.4. <i>Shear-stress induced von Willebrand factor disease.....</i>	43
2.2.5. <i>Conclusions .....</i>	49
<b>2.3. STUDY II. BIOLOGICAL AND MECHANICAL FACTORS THAT INDUCE PATIENT-PROSTHESIS MISMATCH, ONE OF THE MAIN ELEMENT IN GENERATING VON WILLEBRAND FACTOR MODIFICATIONS .....</b>	<b>51</b>
2.3.1. <i>"Long-Term Results (up to 20 Years) of 19 mm or Smaller Prostheses in the Aortic Position. Does Size Matter? A Propensity-Matched Survival Analysis"</i>	52
2.3.2. <i>"Patient-Prosthesis Mismatch in Contemporary Small-Size Mechanical Prostheses Does Not Impact Survival at 10 Years".....</i>	56
2.3.3. <i>"Successful Interventional Endovascular Management of Ruptured Penetrating Aortic Ulcer with Associated Enormous Right Pleural False Aneurysm" .....</i>	59
<b>2.4. STUDY III. "VON WILLEBRAND FACTOR DYNAMICS IN PATIENTS WITH AORTIC STENOSIS UNDERGOING SURGICAL AND TRANSCATHETER VALVE REPLACEMENT".....</b>	<b>62</b>
2.4.1. <i>Materials and methods.....</i>	62
2.4.3. <i>Results.....</i>	70
2.4.4. <i>Discussion.....</i>	85
2.4.5. <i>Conclusions .....</i>	87
2.4.6. <i>Limitations.....</i>	88
<b>2.5. STUDY IV. PATIENT-PROSTHESIS MISMATCH AND ITS INFLUENCE ON IMMEDIATE POSTOPERATIVE VON WILLEBRAND FACTOR LEVELS .....</b>	<b>90</b>
2.5.1. <i>Introduction and Objectives .....</i>	90
2.5.2. <i>Materials and Methods.....</i>	91
2.5.3. <i>Results.....</i>	91
2.5.4. <i>Discussion.....</i>	92

## IV

2.5.5. Conclusion .....	92
3. CONCLUSIONS AND ORIGINAL CONTRIBUTIONS .....	93
4. BIBLIOGRAPHY .....	97
5. PUBLISHED ARTICLES IN EXTENSO .....	108

## **ABSTRACT**

### **INTRODUCTION**

Aortic valve replacement (AVR) is a life-saving procedure for patients with severe aortic valve disease, especially aortic stenosis (AS). Despite advances in surgical techniques and prosthetic valve design, patient-prosthesis mismatch (PPM) remains a significant complication after AVR. PPM occurs when the effective orifice area (EOA) of the implanted valve is too small for the patient's body size and hemodynamic needs, leading to persistent high gradients.

Recent studies suggest a link between PPM and acquired von Willebrand factor alteration (AVWFA), a bleeding disorder characterized by loss of high molecular weight multimers of von Willebrand factor (VWF). VWF is crucial for primary hemostasis and its alteration increases bleeding risk.

This thesis aims to investigate the relationship between PPM and AVWFA in AVR patients. By examining the incidence, severity, and mechanisms of AVWFA in PPM, it seeks to improve understanding of this complex phenomenon and its impact on patient outcomes. It will also explore implications for diagnosis, management and prevention of AVWFA in PPM after AVR.

## **AIMS AND OBJECTIVES**

The main aims of the thesis are:

1. To provide a comprehensive analysis of current literature on the correlation between VWF and PPM through selection, interpretation and synthesis of recent data. This will establish a theoretical framework for understanding the PPM-AVWFA relationship.
2. To study how biological and mechanical factors that induce PPM contribute to VWF level alteration, recognizing PPM as one of main elements of VWF alterations.
3. To directly investigate VWF level dynamics in AVR procedures, elucidating how surgical vs transcatheter approaches affect VWF behavior. Original research will compare VWF changes in SAVR and TAVR.
4. To assess the influence of PPM severity on postoperative VWF levels in SAVR patients through prospective analysis.

Patient-prosthesis mismatch is a multifactorial phenomenon influenced by biological factors like vessel wall degeneration, and mechanical factors like valve size-requirement mismatch. All instances of PPM significantly alter VWF production and catabolism. A comprehensive study of VWF alterations is essential to elucidate how different factors affect this critical hemostatic protein.

## **STUDY I. ACQUIRED VON WILLEBRAND FACTOR ALTERATION – LITERATURE REVIEW**

A thorough review of databases like PubMed, Google Scholar, MDPI and Springer, without date restrictions, was performed using terms like "aortic stenosis", "patient-prosthesis mismatch", "acquired von Willebrand deficiency", and "aortic valve replacement". 35 sources directly addressing AVWFA in PPM after AVR were identified.

Data was extracted on research design, patient characteristics, AVR specifics, AVWFA diagnosis, and patient outcomes. Synthesis revealed:

- Prevalence of moderate PPM is 20-70% and severe PPM 2-10% after AVR
- Factors increasing PPM risk include small aortic roots (especially in females), large body surface area, and bioprosthetic valves
- Strategies to avoid PPM include accurate annulus measurement, selecting prosthesis by target indexed EOA, root enlargement, and stentless bioprostheses
- Long-term survival impact of PPM remains debated
- AVWFA diagnosis involves lab testing (VWF levels, activity, FVIII), bleeding history, and physical exam; classification is based on quantitative (Types 1, 3) or qualitative (Type 2) VWF modifications
- High shear stress forces from PPM could induce VWF structural changes and proteolysis, similar to in native aortic stenosis, possibly causing acquired von Willebrand factor alterations

In summary, the review established a clear association between PPM and AVWFA warranting further original investigation.

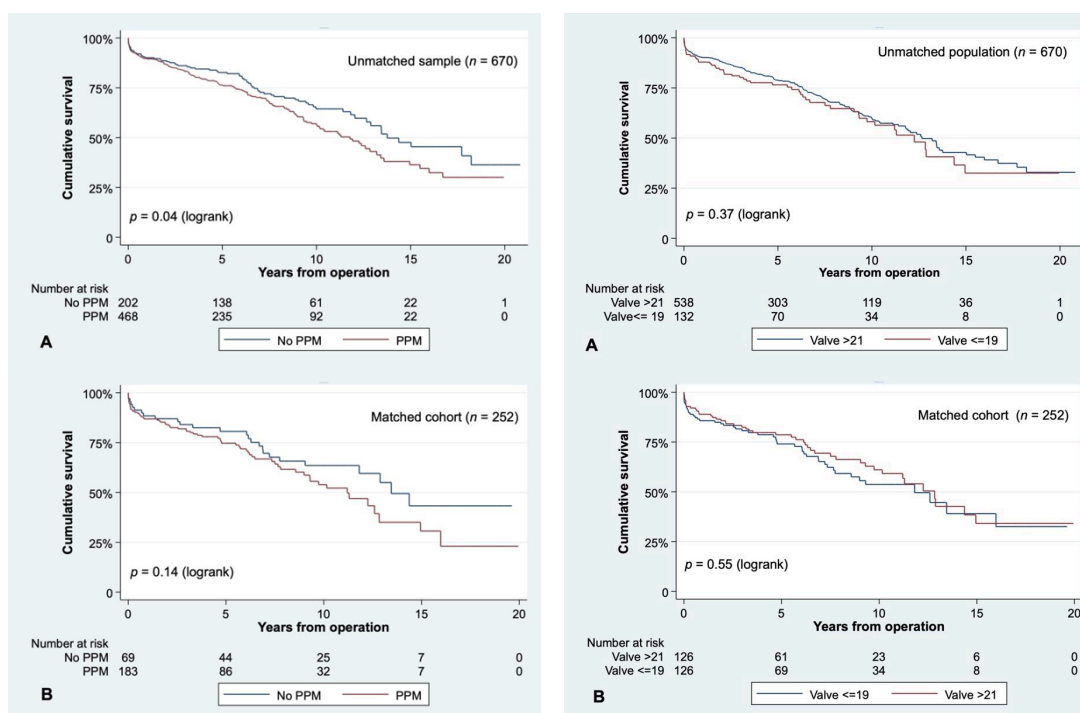
## **STUDY II. BIOLOGICAL AND MECHANICAL FACTORS THAT INDUCE PATIENT-PROSTHESIS MISMATCH, ONE OF THE MAIN ELEMENT IN GENERATING VON WILLEBRAND FACTOR MODIFICATIONS**

This study encompassed analysis of how biological factors like vessel wall degeneration and mechanical factors like valve size-requirement mismatch contribute to PPM as a driver of VWF alterations.

Two published articles examined the impact of small ( $\leq 21\text{mm}$ ) prostheses on long-term survival, PPM incidence, and the influence of PPM on outcomes:

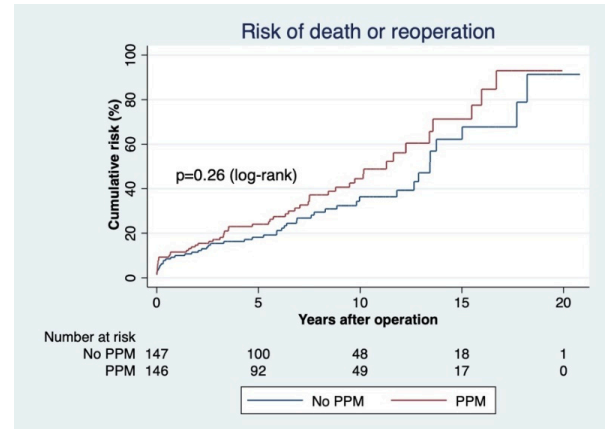
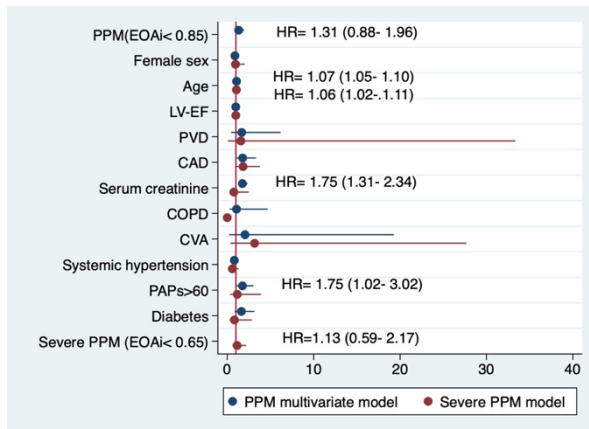
1. "Long-Term Results (up to 20 Years) of 19mm or Smaller Prostheses in the Aortic Position. Does Size Matter? A Propensity-Matched Survival Analysis"
  - Retrospective analysis of 670 patients receiving  $\leq 21\text{mm}$  valves from 2000-2018
  - Propensity matching created balanced groups of 19mm (n=126) vs 21mm (n=126) valves
  - 10yr survival was comparable: 58.69% for  $\leq 19\text{mm}$  vs 53.60% for 21mm (p=0.55)
  - $\leq 19\text{mm}$  valves had significantly higher PPM incidence (87.30% vs 57.94%, p<0.01)
  - PPM affected 10yr mortality in unmatched (52.66% vs 64.38%, p=0.04) but not matched analysis (51.82% vs 63.12%, p=0.14)





- Conclusion: Modern 19mm prostheses do not reduce 10year survival despite higher PPM rates. Other factors beyond valve size influence outcomes.
2. "Patient–Prosthesis Mismatch in Contemporary Small-Size Mechanical Prostheses Does Not Impact Survival at 10 Years"
- Retrospective review of 416 patients receiving  $\leq 21$ mm mechanical valves from 2000–2011
  - Propensity matching compared PPM (n=147) vs no PPM (n=147), and severe PPM (n=61) vs no severe PPM (n=61)
  - 10year survival was 64.51% with PPM vs 69.37% without ( $p=0.28$ )
  - 10year survival was 61.76% with severe PPM vs 67.50% without ( $p=0.49$ )
  - Independent mortality predictors were age, creatinine, and pulmonary hypertension

X



- Conclusion: Moderate to severe PPM in contemporary mechanical valves does not significantly impact 10year all-cause mortality when matching for other variables

Additionally, a case report illustrated the complex interactions between prosthetic valves and surrounding cardiovascular structures. While the primary focus was on the endovascular intervention, the case also raises interesting considerations about the potential role of von Willebrand factor in such acute aortic pathologies:

3. "Successful Interventional Endovascular Management of Ruptured Penetrating Aortic Ulcer with Associated Enormous Right Pleural False Aneurysm"
  - 66M presented with hemoptysis; CT showed penetrating aortic ulcer ruptured and 12x9cm right pleural false aneurysm
  - Successful endovascular repair with stent graft to seal aortic rupture
  - Discharged after 5 days; 3 month follow-up showed no signs of recurrent leak or infection

- While VWF was not specifically addressed in this patient's management, the case opens up discussions about the potential role of coagulation factors in acute aortic syndromes.

In summary, this study elucidated how both biological vessel degeneration and valve size-requirement mismatch mechanically induce PPM, one of the main elements of VWF alterations.

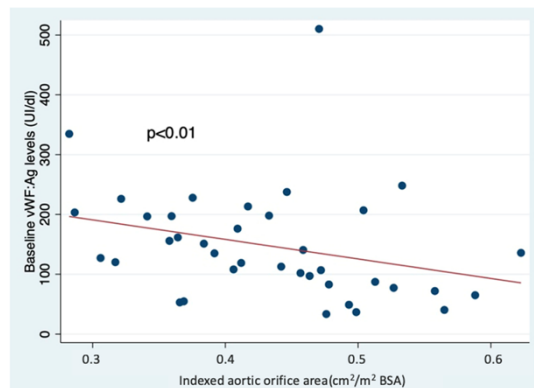
### STUDY III. VON WILLEBRAND FACTOR DYNAMICS IN PATIENTS WITH AORTIC STENOSIS UNDERGOING SURGICAL AND TRANSCATHETER VALVE REPLACEMENT

This prospective study directly investigated how aortic valve replacement(AVR) affects VWF levels, comparing the impact of surgical(SAVR) vs transcatheter(TAVR) approaches.

39 consecutive severe AS patients undergoing aortic valve replacement(AVR) procedure were enrolled. Comprehensive preoperative, intraoperative, and postoperative data was collected, including demographics, comorbidities, echocardiographic parameters, valve type and size, and lab values. VWF antigen (VWF:Ag), activity (VWF:RCo), and factor VIII were measured pre-procedural and on day 7 post-procedural.

Key findings:

- VWF:Ag increased from 145.94 IU/dL pre-procedural to 289.26 IU/dL post-procedural ( $p<0.01$ )
- VWF:Ag inversely correlated with indexed valve area pre-procedural ( $r=-0.41$ ,  $p<0.01$ ) but not post-procedural
- VWF:RCo increased from 80.34% to 191.20% ( $p<0.01$ ); FVIII was unchanged
- VWF:Ag increase was significantly lower in TAVR than SAVR ( $p<0.01$ )
- PPM did not significantly influence post-procedural VWF:Ag, VWF:RCo or FVIII



This study demonstrated a marked increase in VWF:Ag after AVR, indicating hemostatic function improvement. The lower VWF increase after TAVR vs SAVR suggests less hemostatic activation in the less invasive approach. Short-term VWF dynamics were not significantly impacted by PPM.

#### **STUDY IV. PATIENT-PROSTHESIS MISMATCH INFLUENCE ON IMMEDIATE POST SURGICAL AORTIC VALVE REPLACEMENT VON WILLEBRAND FACTOR LEVELS**

This original prospective study built upon Study III by specifically examining PPM impact on VWF dynamics in the first week after surgical AVR.

The data presented here, though unpublished, represent a step in our ongoing exploration of VWF dynamics, and are useful for comprehending the final conclusions drawn in this thesis.

31 consecutive severe AS patients undergoing SAVR were analyzed. PPM was graded by indexed EOA as moderate (0.65-0.85cm<sup>2</sup>/m<sup>2</sup>) or severe (<0.65cm<sup>2</sup>/m<sup>2</sup>). VWF:Ag, VWF:RCo and FVIII were measured pre-SAVR and on day 7 post-SAVR.

Key findings:

- 61.29% of patients had PPM (45.16% moderate, 16.13% severe)
- VWF:Ag rose from 131.37 to 311.01 IU/dL post-SAVR (p<0.01)
- VWF:RCo also significantly increased from baseline
- PPM did not significantly influence on short-term postoperative VWF:Ag, VWF:RCo or FVIII

Although PPM was common, it did not significantly affect immediate post-SAVR VWF levels or activity.

This final stage, consisting of long-term evaluation of the effect, is ongoing, with patients initially investigated after the aortic valve replacement procedure being under observation for the next years.

## **CONCLUSIONS AND PERSONAL CONTRIBUTIONS**

### **PRIMARY CONCLUSIONS**

1. As a first conclusion of our study, aortic valve replacement led to normalization of VWF, regardless of PPM severity.
2. Secondly, the type of procedure used for aortic valve replacement (TAVR vs. SAVR) significantly influenced the level of VWF restoration, but in both cases, it entered normalization limits.
3. The aortic valve replacement procedure has proven to be an effective long-term procedure, and long-term survival was not influenced by the degree of mismatch.

### **ORIGINAL CONTRIBUTIONS**

We can highlight the following original contributions of our study:

- a. Our work is the first attempt at the national level to identify a connection between patient-prosthesis mismatch and von Willebrand factor level alteration.
- b. It is the first national study on the association between patient-prosthesis mismatch and survival rate.
- c. We discovered for the first time at the national level the differences between transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR) procedures in von Willebrand factor level alteration. Specifically, we found a significant increase in VWF levels in SAVR compared to TAVR procedures.