ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

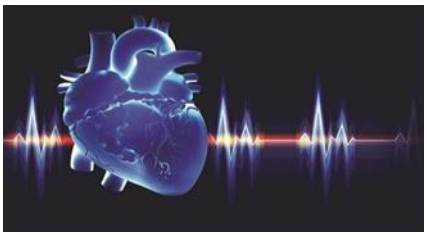
ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

«ΚΑΡΔΙΑΚΗ ΑΝΕΠΑΡΚΕΙΑ - ΚΑΡΔΙΟ-ΟΓΚΟΛΟΓΙΑ - ΚΑΡΔΙΑΓΓΕΙΑΚΗΑΠΟΚΑΤΑΣΤΑΣΗ»

(MSc in Heart Failure - Cardio-oncology - Cardiac Rehabilitation)



Διαδερμική επιδιόρθωση μιτροειδούς βαλβίδας σε ασθενείς με σοβαρή δευτεροπαθή ανεπάρκεια με τη χρήση τέταρτης γενιάς MitraClip.

Transcatheter mitral valve repair in patients with severe secondary regurgitation with the use of fourth generation MitraClip.

ΑΝΔΡΕΑΣ ΙΩΑΝΝΙΔΗΣ, ΕΙΔΙΚΟΣ ΚΑΡΔΙΟΛΟΓΟΣ

ΛΑΡΙΣΑ, 2024

«Βεβαιώνω ότι η παρούσα διπλωματική εργασία είναι αποτέλεσμα δικής μου δουλειάς και δεν αποτελεί προϊόν αντιγραφής. Στις δημοσιευμένες ή μη δημοσιευμένες πηγές έχω χρησιμοποιήσει εισαγωγικά και όπου απαιτείται έχω παραθέσει τις πηγές τους στο τμήμα της βιβλιογραφίας».

Υπογραφή:

ΑΝΔΡΕΑΣ ΙΩΑΝΝΙΔΗΣ

ΑΝΔΡΕΑΣ ΙΩΑΝΝΙΔΗΣ

Πανεπιστήμιο Θεσσαλίας, Σχολή Επιστημών Υγείας, Τμήμα Ιατρικής, 2024

ΔΙΕΥΘΥΝΤΗΣ ΤΟΥ ΠΡΟΓΡΑΜΜΑΤΟΣ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ

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“Transcatheter mitral valve repair in patients with severe secondary regurgitation with the use of fourth generation MitraClip.”

Θα ήθελα να εκφράσω τις θερμές μου ευχαριστίες προς όλους τους Καθηγητές μου και σε καθέναν ξεχωριστά γιατί υπήρξαν φωτεινοί φάροι σε αυτό το συναρπαστικό επιστημονικό ταξίδι.

Ιδιαιτέρως θα ήθελα να ευχαριστήσω τον επιβλέποντα Καθηγητή μου, κο Γρηγόριο Γιαμούζη, Αν. Καθηγητή Καρδιολογίας Πανεπιστημίου Θεσσαλίας, για την πολύτιμη βοήθεια και καθοδήγηση που μου παρείχε, με μεγάλη γενναιοδωρία, καθ' όλη τη διάρκεια της εκπόνησης της εργασίας αυτής.

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Δεν θα μπορούσα να μην ευχαριστήσω τον επί χρόνια συνεργάτη και συνοδοιπόρο, επιστήθιο φίλο και Διευθυντή μου στη Β' Καρδιολογική Κλινική του Ιατρικού Διαβαλκανικού Θεσσαλονίκης, κο Βλάση Νινιό, για την αδιάλειπτη και ανιδιοτελή στήριξή του όλα αυτά τα χρόνια.

Η εργασία αυτή αφιερώνεται σε όλους αυτούς τους ασθενείς, οι οποίοι καθημερινά, μέσα από τα σοβαρά προβλήματα υγείας που αντιμετωπίζουν , επιμένουν να δείχνουν έμπρακτα την εμπιστοσύνη τους στην Ιατρική Επιστήμη και στους λειτουργούς της.

Αφιερώνεται επίσης στην σύζυγό μου Μαρία και τα παιδιά μου Χριστόφορο και Νίκη για την συνεχή ενθάρρυνση και τη στήριξη.

Ανδρέας Ιωαννίδης

Curriculum Vitae

PERSONAL DETAILS

Name	Dr Ioannidis Andreas
Date of Birth	20/3/1969
Family status	Married, two children
	Bachelor Degree, Medical School, 'Victor Babes' University, Timisoara, Romania, Grade 8,65 (EXCELLENT), 10/1996
Languages:	English, Romanian, German, Turkish

PROFESSIONAL EXPERIENCE

Specialty training

General Medicine, Hospital for Communicative and Infectious disease, Thessaloniki, Greece. (2000-2002)

Specialist Registrar for Cardiology, 'Panagia' General Hospital, Thessaloniki, Greece. (2004-2008)

Completion of specialty Training in Cardiology (2008)

Specialist Appointment

Consultant Cardiologist, Director of Department of Clinical Cardiology, St. Luke's Hospital, Thessaloniki, Greece (2009-20019)

Consultant Cardiologist, Director of Clinical Cardiology, 2nd Department of Cardiology, Interbalkan Medical Center, Thessaloniki, Greece. (2019- current post)

CLINICAL EXPERIENCE

- Proficient in clinical Cardiology, management of emergency Cardiac cases, of patients in the Coronary Care unit and Patient Ward.
- Postgraduate student in Cardio-oncology, Heart Failure and Rehabilitation (University of Thessalia).
- Cardiopulmonary exercise testing (Ergo spirometry) in National and Kapodistrian University of Athens.
- Expertised in "Quality systems in Health" in National and Kapodistrian University of Athens.
- Advanced Life Support Provider (European Resuscitation Council).
- Large Experience in management of patients following Cardiac Surgery

- Regular outpatient clinic of average 150 patients per month
- Proficient in Transthoracic ECHO studies (TTE)
- Proficient in 4D ECHO

CLINICAL TRIALS

Member of the investigator's team, as a Heart Failure Specialist, in the following clinical trials on medical devices and drugs:

- ANTHEM HFrEF
- RESHAPE II
- ALIVE
- AFIRE
- CARILLON
- EMPOWER
- APD418-201
- LANDMARK
- ALTAVALVE
- VICTOR
- HERMES
- ZEUS
- CORCINCH - HF

MEDICAL LICENCE NUMBER: 4880 – 11.05.1999

Abstract

Background: This study centres on the one-year outcomes of patients treated with the Mitraclip G4 system, reflecting real-world applications in treating secondary mitral regurgitation (SMR).

Objectives: The primary goal was to assess the safety and performance of the Mitraclip G4 system over one year, focusing on subjects with SMR in a real-world setting.

Methods: This was a prospective, single-arm, single - center, open-label, non-randomized, all-comers, post-market observational study. Patients were selected based on regional guidelines and underwent transcatheter edge-to-edge repair (TEER) with the Mitraclip G4. The study emphasized acute procedural success, major adverse events (MAEs) within 30 days, and evaluations of mitral regurgitation (MR) severity, functional capacity, and quality of life. Echocardiographic and clinical assessments were conducted at multiple stages, and statistical analysis was performed using various tests, adhering to the intention-to-treat principle.

Results: The study enrolled 83 patients, with a median follow-up of 15.08 months. The majority were male, with a mean age of 74.85 years, and had significant comorbidities. Echocardiographically, patients exhibited moderate to severe left ventricular dysfunction and significant MR. Hemodynamic data supported these findings. Procedural outcomes showed a high rate of acute procedural success, with a minimal number of clips needed per patient (1.36). Echocardiographic outcomes post-procedure indicated favourable reduction in MR with > 97% of the patients having Grade 1 or trace residual MR at 30 days and one year. Clinically, there was a significant improvement in NYHA classification and a low rate of all-cause mortality (8.4%) and heart failure hospitalization (11.8%) at one year. Safety profiles remained consistent throughout the follow-up, with minimal major adverse events.

Conclusions: The Mitra clip G4 system demonstrated high procedural success and effectiveness in reducing MR severity, along with a favourable safety profile in a real-world cohort with SMR. The findings suggest that the Mitraclip G4 is a viable option for patients with secondary mitral regurgitation, offering significant improvements in functional capacity and quality of life with minimal adverse events.

Key words: Heart Failure, Mitra clip, Mitral Regurgitation, TEER, Mitral Valve

CONTENTS

GENERAL PART

Introduction

The Mitraclip's development began in the late 1990s at Evalve Inc. in California (1). Acquired by Abbott in 2009, the team focused on a catheter-based approach for mitral valve repair in a beating heart. The idea originated from a suggestion by Ottavio Alfieri to Dr. Mehmet Oz in 1996 (2) about repairing the mitral valve with a single suture. The Mitraclip's development transitioned from a suture-based to a clip-based design. Cardiologist Dr. Fred St. Goar played a crucial role in its initial design, drafting the first sketches of the catheter-based device. The first Mitraclip implantation occurred successfully in 2003 in Caracas, Venezuela, successfully reducing patient's mitral regurgitation without needing open-heart surgery (3). The device received CE marking in Europe in 2008 and FDA approval in the U.S. in 2013 (4). The Mitraclip, used for mitral valve transcatheter edge-to-edge repair (M-TEER), has become an essential non-surgical treatment for patients with severe and symptomatic mitral regurgitation (MR). It is now included in European and American treatment guidelines for these patients (5). The FDA first approved the Mitraclip in 2013 (4) for patients with significant primary mitral regurgitation and heart failure symptoms who were at high risk for surgery. In 2019, the FDA expanded its approval to include patients with normal mitral valves who develop heart failure symptoms and moderate-to-severe or severe secondary mitral regurgitation, even with optimal medical therapy.

CHAPTER 1. Important clinical trials

1.1 The **EVEREST II** trial (6) was a pivotal study in evaluating the Mitraclip device for mitral regurgitation (MR) treatment. This multicentre, randomized controlled trial compared the safety and efficacy of percutaneous mitral repair using the Mitraclip with conventional surgical repair or replacement. The trial's design involved assigning patients in a 2:1 ratio to Mitraclip repair versus conventional surgery. The study focused on patients with severe MR (grade 3 to 4+). Key findings of the EVEREST II trial include **Short-term Results:** In the first year, the Mitraclip group required more valve surgery compared to those initially treated with surgery. This indicated a higher immediate intervention need for patients treated with Mitraclip. **Primary Composite End Point:** Surgical treatment was superior for the primary composite endpoint, which included freedom from death, surgery for mitral valve dysfunction, and from severe MR at 12 months. This highlighted surgery's effectiveness in reducing MR and avoiding additional interventions in the first year. **Long-term Results:** Over a 5-year period, the trial showed similar mortality rates for both treatment groups. However, there was a higher rate of reintervention in the Mitraclip group, attributed to more frequent mitral valve dysfunction. The **conclusion** drawn from the EVEREST II trial was that while the Mitraclip demonstrated significant safety and was effective for patients at prohibitive surgical risk, conventional surgery remained superior in terms of reducing MR and avoiding additional interventions in the first year. In the long term, although mortality rates were similar between the two groups, the Mitraclip group had a higher need for reintervention.

1.2 The **MITRA-FR** trial (7), focused on the effectiveness of the Mitraclip device in treating severe functional or secondary mitral regurgitation. The trial's main objective was to evaluate the efficacy of the Mitraclip device for percutaneous mitral valve repair compared to medical therapy in patients with severe functional mitral regurgitation. Enrolment and Methodology: A randomized controlled trial with 304 patients, split equally between the Mitraclip group and the medical therapy group. The study primarily targeted patients with severe secondary mitral regurgitation. The primary Outcome measured as a combination of death or hospitalization for heart failure, showing 54.6% in the Mitraclip group versus 51.3% in the medical therapy group, with no significant statistical difference. The secondary outcomes showed similar rates of death and hospitalization for heart failure in both groups. Death rates were 24.3% for the Mitraclip group and 22.4% for medical therapy, while hospitalization rates

were 48.7% and 47.4%, respectively. In conclusion, despite a significant reduction in mitral regurgitation in 92% of Mitraclip patients, the trial concluded that the device did not significantly reduce the combined risk of death or hospitalization for heart failure, largely due to the severe underlying cardiomyopathy in patients.

1.3 The **COAPT** trial (8), was a multicentre, randomized trial evaluating the efficacy of the Mitraclip device for heart failure (HF) patients with secondary mitral regurgitation (MR). The trial aimed to compare the safety and efficacy of transcatheter mitral valve repair (TMVr) using the Mitraclip with guideline-directed medical therapy (GDMT) alone in patients with HF and secondary MR. It was. Enrolled were 614 patients with HF and severe MR (grade 3-4+), symptomatic despite maximally tolerated GDMT. These patients had either ischemic or nonischaemic cardiomyopathy, left ventricular ejection fraction (LVEF) between 20%-50%, and were in NYHA functional class II-IVa. HF hospitalization at 24 months was significantly lower in the Mitraclip plus GDMT group (35.8%) compared to the GDMT alone group (67.9%). The primary safety endpoint was a high freedom from device-related complications at 12 months (96.6%) in the Mitraclip group. Moreover, the Mitraclip group showed improved outcomes in all-cause mortality, death or HF hospitalization, cardiovascular death, stroke, LV assist device (LVAD) or heart transplant, and changes in LV end-diastolic volume and MR severity, compared to GDMT alone. h Additionally, a Cost-effectiveness Analysis demonstrated the mean cost for the TMVr procedure was substantial, but despite higher initial costs, the Mitraclip led to reduced follow-up medical care costs. The incremental cost-effectiveness ratio (ICER) for Mitraclip versus GDMT was $55,600 per quality-adjusted life-year (QALY), indicating a balance between cost and quality of life benefits.

Moreover, **the five-year outcomes of the COAPT trial** (9) revealed a considerable reduction in the annualized rate of HF hospitalization (33.1% in the Mitraclip group vs. 57.2% in the medical therapy group) and all-cause mortality (hazard ratio of 0.72), thus demonstrating the Mitraclip’s lasting efficacy over five years. Device-specific safety events were minimal, occurring in only 1.4% of patients confirming the safety of the intervention. However, despite the benefits, the five-year mortality rate remained high in both the device (57.3%) and control (67.2%) arms, reflecting the progressive nature of HF and highlighting the importance of long-term follow-up. Importantly, after two years, 21% of patients in the control arm received Mitraclip, which might have influenced the trial's results. In summary, the five-year data from the COAPT trial affirmed the long-term benefits of Mitraclip in improving survival and

reducing hospitalizations for patients with systolic HF and significant MR The COAPT trial's findings were pivotal in demonstrating the clinical benefits of the Mitraclip in treating HF patients with significant secondary MR. It provided strong evidence for the MitraClip's role in reducing hospitalizations and improving survival rates.

1.4 The evolution of the Mitraclip device across its **four generations** showcases significant improvements in design and functionality for treating mitral regurgitation (MR): **The first - generation Mitraclip** was aimed to mimic the surgical Alfieri stitch. It initially used nitinol arms for leaflet contact but later switched to Elgiloy® arms for better stability and healing. This generation allowed for precise grasping and release of leaflets without puncturing them, enabling customization of repair to optimize MR reduction and the mitral valve (MV) gradient. Following that the **Second-Generation Mitraclip (NT)**, introduced in 2016, featured an improved nitinol gripper design for enhanced leaflet capture and steering capabilities. The **Third-Generation Mitraclip (NTR/XTR)** that was Launched in 2018, addressed challenges associated with larger leaflet gaps and longer redundant leaflets. It introduced a new longer-arm Clip size (XTR) and enhancements in delivery catheter shaft stability. This generation showed improved postprocedural MR severity and reduced procedure times, as evidenced in the EXPAND study. Currently the **Fourth Generation Mitraclip (G4)** introduced wider arm Clip sizes (NTW and XTW), was better suited for treating wide regurgitant jets and challenging valve pathologies. It featured Controlled Gripper Actuation (CGA) for improved and independent leaflet capture, automatic gripper line detachment to simplify the deployment process, and demonstrated significant MR reduction, minimal risk of mitral stenosis, and low adverse event rates in the EXPAND G4 study. Overall, each generation of the Mitraclip has built upon the last, enhancing the system's effectiveness and ease of use in the treatment of mitral regurgitation.

1.5 The EXPAND G4 study, led by Bardeleben et al. (10), evaluated the one-year outcomes of patients treated with the fourth generation Mitraclip transcatheter edge-to-edge repair (M-TEER) device, providing insights into its performance in a real-world setting. The study demonstrated that the fourth-generation M-TEER device was safe and effective over a one-year period, significantly reducing the severity of mitral regurgitation (MR) to ≤1+ in over 90% of the patients. Beyond the reduction in MR severity, the study observed improvements in the functional status and quality of life of patients, highlighting the device's impact on both physical and overall well-being. The study is particularly significant as it provides the first real-world evidence of the effectiveness and safety of the Mitraclip G4 System. With a cohort of over 1,000 patients, the study offers a substantial data set for analysis.

SPECIAL PART

CHAPTER 2. Study design and subject cohort

This study was designed to evaluate the one-year outcomes of subjects treated with the Mitraclip G4 system, focusing on a contemporary, real-world cohort. The study was structured as follows:

2.1 Objectives: The primary aim was to assess the 1-year outcomes in subjects who underwent treatment with the Mitraclip G4 system, particularly looking at its safety and performance in a real-world context.

Study Design: The research was set up as an ongoing, prospective, single-arm, single-centre, open-label, non-randomized, all-comers, post-market observational study. Its focus was on subjects with secondary (functional) mitral regurgitation (SMR). The study's design allowed for a thorough evaluation of the fourth-generation system's safety and performance.

Inclusion and Procedure: All subjects met the inclusion and exclusion criteria based on regional guidelines and patient selection standards. The transcatheter edge-to-edge repair (TEER) procedure was attempted on all eligible and enrolled patients, with the choice of clip size and number left to the discretion of the operator.

Follow-up and Ethics: Follow-up visits were scheduled at discharge, 30 days, and one year. Additionally, subjects will continue clinical follow-up with in-hospital visits annually for five years. This study received approval from local ethics committees.

2.2 Key Outcomes: The study primarily focused on three outcomes:

- Acute procedural success, which was defined in the study's criteria.
- The occurrence of major adverse events (MAE) at 30 days.
- Evaluations of MR severity, functional capacity, and quality of life at 30 days. These endpoints were in line with the Mitra Valve Academic Research Consortium criteria and recommendations for mitral valve trial design.

Overall, this study aimed to provide comprehensive data on the effectiveness and safety of the Mitraclip G4 system in treating SMR, contributing valuable insights into its real-world application.

2.3 Safety and Performance Assessment

The study rigorously assessed the safety of the Mitraclip device by monitoring all major adverse events (MAE) within the first 30 days and throughout the follow-up period. These included critical incidents such as all-cause death, myocardial infarction, stroke, or any nonelective cardiovascular (CV) surgeries necessitated by device-related complications. The performance of the device was evaluated based on its ability to reduce mitral regurgitation (MR) severity to ≤2+ within 30 days.

2.4 Acute Procedural Outcomes

The study focused on several key aspects of the acute procedural outcomes:

Acute Procedural Success: Defined as successful implantation of the Mitraclip device with a resultant MR severity of <2+ at discharge.

Acute Device Success: This involved successful implantation without any device-related complications.

Procedure and Device Times: The duration of both the device implantation and the overall procedure was tracked.

Device-Related Complications: This included monitoring for complications such as mitral stenosis, single-leaflet device attachment (SLDA), device embolization, myocardial perforation, and the necessity for surgical mitral valve (MV) replacement due to issues arising from the Mitraclip procedure.

2.5 Echocardiographic Assessment

Echocardiographic evaluations were conducted at baseline, discharge, at the 30-day mark and at one year (or as indicated), focusing on:

- MR severity grade.
- Effective regurgitant orifice area, using the proximal isovelocity surface area method (at baseline).
- Coaptation measures including depth and length (at baseline).
- Anatomy of the grasping area, measuring any significant cleft or scallop.
- Assessment of chordal support (at baseline).
- Location and quantity of regurgitant jets (at baseline).
- Severity of tricuspid regurgitation (TR), categorized as none, mild, moderate, or severe.

2.5 Clinical Outcomes

Clinical outcomes were measured at discharge and after 30 days, encompassing:

- All-cause mortality.
- Functional status, assessed via the New York Heart Association (NYHA) functional classification and 6-minute walk test.
- For the evaluation of Quality of Life, the KCCQ was used.

2.6 Statistical Analysis Overview

The study employed a comprehensive statistical analysis approach to evaluate the data collected. The methods used for analysis were chosen based on the nature of the data (categorical or continuous) and its distribution. The primary statistical analyses included:

Categorical Variables Analysis: For comparing categorical variables, the Fisher exact test was utilized. This test is particularly effective for analysing small sample sizes and determining if there are non-random associations between two categorical variables.

Paired Nominal Data: The Bowker test was applied to paired nominal data. This test is useful for comparing responses or observations that are categorized nominally and are paired.

Continuous Variables Analysis: For continuous variables, the Student's t-test was used in cases where the data followed a normal distribution. In instances where the data were not normally distributed, the Wilcoxon rank sum test was employed. These tests help in comparing the means or medians of two groups, respectively.

Intention-to-Treat Analysis: All analyses adhered to the intention-to-treat principle, which includes all participants initially allocated to each treatment arm in the analysis, regardless of whether they completed the treatment as per the protocol.

Statistical Significance: A 2-sided P value of less than 0.05 was set as the threshold for statistical significance. This criterion helps in determining whether the observed differences or associations in the study are unlikely to have occurred by chance.

CHAPTER 3. Results

3.1 Study population: The study enrolled 83 patients, beginning on February 3, 2021, and spanning until November 11, 2023. Within this period, every participant crossed the threshold of discharge and was observed until the 30-day post-discharge mark. Reflecting on the duration of surveillance, the median follow-up period reached 15.08 months, allowing a substantial window into the patients' post-procedural course. Notably, the longest follow-up stretched to 33.8 months, providing a deep insight into the long-term outcomes. Furthermore, a significant number of these patients, 48 in total which represents 56.47% of the cohort, have successfully completed a 12-month follow-up, marking a year of progress and recovery.

3.2 Baseline characteristics: In the studied patient population, males constituted 65.85%, and the mean age was approximately 74.85+/- 10.4 years. A notable 67.24% of these patients had been hospitalized prior to the study, while prior myocardial infarction was reported in 36.21% of the cases. Atrial fibrillation was quite common, affecting 64.63% of the patients. More than half of the patients, specifically 54.88%, suffered from severe chronic renal failure. Chronic obstructive pulmonary disease was present in 36.59% of the population, and diabetes mellitus was observed in 17.07%. A quarter of the patients, at 25.61%, had either an implantable cardioverter-defibrillator or a cardiac resynchronization therapy defibrillator. Most patients were classified as NYHA IV, which represented 71.95%, followed by 26.83% at NYHA III, and a small 1.22% at NYHA II, with none falling into NYHA I. The mean pro-BNP was 4903.65 +/- 6984.31 pg/ml in keeping with severe Heart Failure. The Society of Thoracic Surgeons' (STS) risk score averaged at 8.2 for repair procedures, and 7.2 for replacement procedures while the EUROSCORE II, used to estimate the risk of mortality after cardiac surgery, was 9.1 +/- 6% with reflecting an overall high-risk patient profile for surgical intervention. These data are summarised in **table 1.**

3.3 Echocardiographic assessment: The Left Ventricular Ejection Fraction (EF) stands at 39%+/- 9.85%, indicating moderate to severe dysfunction in many patients. The Left Ventricular End-Diastolic Dimensions (LVDD), average 6.05 +/- 0.65 cm, suggesting at least a moderate degree of cardiac enlargement. The Effective Regurgitant Orifice (ERO) area, was measured at 45.27 mm^2, and the Vena Contracta (VC), was noted at 7.31 mm. These measurements point towards a significant presence of mitral valve regurgitation within the

cohort. Pulmonary Arterial Pressure (PAP), both by echocardiographic estimation and hemodynamic measurement, was elevated with an echo-derived systolic pressure of 53.75 mm Hg. Hemodynamic measurements returned a mean systolic/diastolic pressure of 55.39/21.92 mm Hg, further supporting these findings. The severity of Mitral Regurgitation (MR), graded on a scale of severity, averaged at a high 3.9, with a significant majority of 87.95% of patients categorized with severe MR (grade 4+), while 12.05% were considered to have moderate MR (grade 3+). This high prevalence of severe MR is concerning and underscores the potential impact on patient outcomes. The echocardiographic Parameters are summarised on **Table 2.**

3.4 Hemodynamic data: All patients underwent Right Heart Catheterization per protocol. The mean Pulmonary Artery (PA) pressure was observed to be at 33.11 mm Hg. The Pulmonary Wedge Pressure (PWP) showed a V wave average of 36.90 +/- 11.8 mm Hg, and a mean pressure of 24.75 +/- 9.71 mm Hg. These values are in accordance with the presence mitral valve disease and/or left ventricular diastolic dysfunction. Right Atrial (RA) pressure had a mean value of 10.89 mm Hg, with a peak V wave pressure reaching 13.86 mm Hg. The Transpulmonary Gradient (TPG), which is the difference between the mean PA pressure and the mean PWP, was calculated to be 8.36 +/- 9.71 mm Hg. This variation could be due to a mix of pre- and post-capillary pulmonary hypertension. The Cardiac Index was found to be 1.98 +/- 0.48 lt/min/m^2, which indicate reduced cardiac output. The Pulmonary Vascular Resistance Indexed to Body Surface Area (PVRI), was 4.22+/- 5.01 Wood units·m^2. This broad range in values suggests that there may be significant variability among patients in the resistance within the pulmonary vasculature, which could have implications for the severity of pulmonary hypertension and the response to treatment. Hemodynamic data is summarized in **table 3.**

3.5 Procedural outcomes Mitraclip G4 use: Of the 83 patients who underwent the Mitraclip procedure the total number of Mitraclips used was 113 and the average Mitraclip usage per patient was 1.36. A breakdown of the number of clips implanted reveals that the majority, approximately 68.7%, received a single clip. A significant subset, 27.7% of the patients, required two clips for optimal treatment results. A small fraction, 2.4% and 1.2% necessitated the use of three and four clips respectively. The data reflects a trend towards minimal intervention, with a single clip sufficing in most cases, thereby potentially reducing procedural risk and complexity and are summarized in **Figure 1** In total, 10 different Mitraclip G4 device combinations were used in the treatment of patients within the study population. However, two specific types predominantly dominate: XTW and NTW. The use of a single

XTW clip is the most frequently used, constituting 50.60% of the cases followed by a single NTW clip usage accounting for 15.66% of the cases. Other notable combination include XTW/ XT, used in 10.84% of cases, while less common used combinations are: 2 XTW, NT/NTW or 2NTW. In total 'wide' clips were used widely, while 'narrow' clips alone or in combination were only used in a minority of cases (4.81%) **Figure 2** summarizes these data.

Regarding the modes of grasping, independent Grasp Alone (42.3%) where each arm of the Mitraclip is grasping the leaflets independently, was the most common approach, followed by Simultaneous Grasp Alone (33.1%), independent Grasping Followed by Confirmation of Leaflet Optimization (8.6%), Simultaneous Grasp Followed by Confirm Leaflet Optimization (11.5%) and finally Simultaneous Grasp Followed by Independent Grasping (4.5%). This is summarized in **Figure 3.** 82% of patients undergoing this procedure achieved the desired result after the very first grasping attempt while 12% of the patients needed a second attempt to achieve the optimal outcome. A smaller fraction of patients, accounting for 3%, required three attempts and lastly, another 3% of patients presented significant challenges, requiring more than three attempts (**Figure 4**).

Both implantation success rate and device success rate were 100% for the study population. On average, the device time was 26 minutes, and the procedure time 55 minutes, indicating a swift and consistent application of the procedure across cases.

The average length of stay post-procedure was short, at approximately 2.86 +/- 0.60 days, demonstrating a quick recovery and discharge process. Remarkably, every patient was discharged home, which underscores the procedure's success and the patients' ability to return to their usual environment without the need for extended postoperative care (**Table 4**)

3.6 Echocardiographic outcomes In terms of treatment efficacy, the distribution of Residual Mitral Regurgitation (MR) after the procedure is highly favorable. 62.65% of the patients, were left with Trace MR while 34.94% of patients improved to Grade 1 MR, which is considered mild. Only a small fraction, 2.41%, had residual moderate MR at Grade 2. Additionally, 11.76% of patients underwent concomitant Triclip procedures, due to presence of significant Tricuspid Regurgitation, with favorable outcomes: 50% of patients had Grade 1 and another 50% Grade 2 residual TR.

The paired analysis is highly significant for the improvement of Mitral Regurgitation grade from baseline to discharge ($p<0.00001$). This performance is maintained throughout the 30- day landmark analysis and up to one year. Notably 97.59% of the patients had < grade 2 MR (59.04% trace) at 30 days, and 97.92% had < grade 2 MR at one year (43.75% trace). Results are summarized on **Figure 5**

3.7 Clinical outcomes All-cause mortality and Heart failure Hospitalization. The median follow-up duration for patients was 15.08 months, with the longest follow-up being 33.8 months. More than half of the patients (56.5%) completed a 12-month follow-up. The median survival time for the patient group was approximately 418 days. The one-year all-cause mortality rate among these patients was 8.4%. The rate of hospitalization within one year was 11.8%. Survival, Mortality and Hospitalization curves are depicted in **Figure 6.**

Prior to undergoing the Mitraclip procedure, the majority of patients were severely symptomatic being classified in NYHA class III and IV mostly (NYHA Mean: 3.71+/-0.4).

A remarkable improvement in the NYHA classification is observed at 30 days and out to one year after the procedure. The mean NYHA class at 30 days is 1.70 +/- 0.6 ($p<0.0001$) and at one year, 1.59 +/- 0.5 ($p<0.0001$) indicating significant improvement in patient symptoms. NYA Class distribution is illustrated in **Figure 7**

3.9 Safety events and adverse effects

During the initial hospitalization and the first 30 days post-procedure, major adverse events (MAEs) were minimal. Notably, there were no instances of death, stroke, myocardial infarction, major bleeding, acute renal injury requiring extended hospitalization, leaflet detachment, leaflet damage, or the need for emergency surgery. There was one case where a patient required percutaneous closure of an iatrogenic atrial septal defect (ASD) due to a right-to-left shunt that caused oxygen desaturation. Throughout the one-year follow-up period, the safety profile remained consistent, with no additional incidents related to leaflet detachment or the necessity for surgical intervention. **Table 5** summarizes the MAE profile.

CHAPTER 4. Discussion

This study provides a comprehensive analysis of the outcomes following the Mitraclip procedure in a cohort of 83 consecutive real-life patients. The results are significant in terms of both procedural success and long-term patient outcomes.

The study's robust follow-up period, averaging 15.08 months and extending up to 33.8 months for some, underscores its reliability in assessing long-term outcomes.

A significant portion (56.47%) of the patients reached the one-year follow-up milestone, which is critical for evaluating sustained procedural benefits.

The patient profile, predominantly male with an average age of about 75 years, reflects a high-risk group with various comorbidities, including previous hospitalizations, myocardial infarctions, atrial fibrillation, and chronic diseases.

The severity of heart failure in the cohort is evident, with a majority in NYHA Class IV, and high mean pro-BNP levels indicating advanced disease.

Echocardiographic data revealed moderate to severe left ventricular dysfunction and significant mitral regurgitation, which are key indicators of the severity of the underlying cardiac pathology. Hemodynamic measurements further validated the presence of heart conditions like pulmonary hypertension and reduced cardiac output.

The use of Mitraclip G4 devices, predominantly single clips, suggests a trend towards minimal intervention with successful outcomes. The high success rate (100%) of implantation and device application, coupled with the short average procedural and hospital stay, highlights the procedure's safety and efficiency.

The procedural efficacy is further corroborated by the statistical significance of MR grade sustained improvement from baseline to discharge, 30 days, and up to one year. In this study, it was observed that over 97% of patients achieved a mitral regurgitation (MR) of grade 1 or lower. Specifically, 62% of patients exhibited only trace levels of MR, and just over 2% experienced grade 2 regurgitation. These outcomes were consistent over time, persisting for at least one year during follow-up assessments. When compared to similar studies, such as the EVEREST II trial (6) in the REALISM study (11) and the COAPT trial (8), this current iteration of the device demonstrated a more significant reduction in MR to grade 1 or lower. In these

previous studies, the proportion of patients achieving this level of reduction ranged from 37% to 69%.

The EXPAND G4 study (10) recently demonstrated notable advancements in reducing residual mitral regurgitation (MR), with 92.6% of the treated population achieving MR ≤1. These findings align closely with our own data. The introduction of wider 'W' size devices and the enhanced capability for independent leaflet grasping may have contributed to these improved technical outcomes.

Furthermore, this cohort exhibited lower one-year mortality (8.4%) and heart failure hospitalization rates (11.8%) compared to previous studies. In the COAPT trial (8), the one-year mortality rate was recorded at 19.1%, and in the EVEREST II trial (6), it was 22.8%. Contrastingly, the EXPAND G4 study (10) reported a reduced annual mortality rate of 14.2% in the cohort with functional Mitral regurgitation. This improvement may be attributable to the enhanced technical performance of the fourth - generation Mitraclip and possibly reflects advancements in medical therapy for this patient group. Additionally, improvements in the functional class observed in this cohort are consistent with these outcomes.

Clinical outcomes are promising, with an improvement in NYHA classification observed at 30 days and maintained up to one year, indicating enhanced patient quality of life.

The safety profile of the Mitraclip procedure is noteworthy, with minimal major adverse events during the initial hospitalization and the first-year post-procedure.

The absence of serious procedural complications like stroke, major bleeding, or the need for emergency surgery underscores the procedure's safety.

CHAPTER 5. Conclusion

The study provides robust evidence of the Mitraclip procedure's effectiveness and safety in a high-risk real-life, all-comers, heart failure population. Significant improvements in NYHA classification, MR grade, and a low incidence of adverse events post-procedure highlight its potential as a transformative approach in managing severe mitral regurgitation and associated heart failure symptoms. Contemporary use of Mitraclip G4 with wide variety of sizes and the ability to independently customize leaflet capture, further enhances procedure efficacy. The results affirm the procedure's role in improving the quality of life for patients with severe heart conditions while maintaining an excellent safety profile.

Emerging evidence suggests the enhanced efficacy of the Mitra Clip G4 device in reducing mitral regurgitation among patients with secondary mitral regurgitation and heart failure. Concurrently, the evolution of medical therapy, incorporating novel medications, has raised questions about the comparative effectiveness of these advanced treatments. This scenario underscores the need for new randomized studies in a modern clinical setting, aimed at evaluating whether the current and improved therapeutic strategies offer congruent benefits. Current patient selection criteria for these studies are predominantly based on regional guidelines, heavily influenced by COAPT study findings. However, with the high efficacy and safety profiles of existing therapies, there is a critical need to investigate the potential expansion of MitraClip therapy to broader patient groups, including those with atrial functional mitral regurgitation. This expansion necessitates further research to validate the broader applicability and benefits of such therapies in diverse patient populations.

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Table 1: Demographics and Comorbidities

Demographics and Comorbidities	Value
Male	65.85%
Mean age	74.85 years +/- 10.4 years
Prior hospitalisation	67.24%
Prior MI	36.21%
AF	64.63%
Severe CRF (chronic renal failure)	54.88%
COPD	36.59%
DM	17.07%
ICD or CRT-D	25.61%
NYHA IV	71.95%
NYHA III	26.83%
NYHA II	1.22%
NYHA I	0%
STS score for repair	8.2 +/- 8.3
STS score for replacement	7.2 +/- 9.3
EUROSCORE II	9.1 +/- 6.0%
pro-BNP	4903.65 +/- 6984.31 pg/ml

Table 2: Echocardiographic Variables I

Echocardiographic Variables	Value
EF	39 +/- 9.85%
LVDD	6.05 +/- 0.65 cm
ERO	45.27 mm^2
VC	7.31 mm
PAP SYSTOLIC (ECHO)	53.75 +/- 9.84 mm Hg
PAP hemodynamic	55.39/21.92 mm Hg
Mean MR grade	3.9
MR grade moderate 3+	12.05%
MR grade severe 4+	87.95%

Table 3: Echocardiographic Variables II

Echocardiographic Variables	Value
Mean PA pressure	33.11 mm Hg
PWP V wave	36.90 +/- 11.79 mm Hg
PWP mean	24.75 +/- 9.71 mm Hg
RA pressure mean	10.89 mm Hg
RA pressure V wave	13.86 mm Hg
TPG	8.36 +/- 9.71 mm Hg
Cardiac Index	1.98 +/- 0.48 lt/min/m²
PVRI	4.22 +/- 5.01 WU*m²

Table 4: Procedure outcomes

Procedure outcomes	
Acute procedural success	100%
Implantation rate	100%
Device time	26+/- 8 min
Procedure time	55+/- 11 min
Length of stay	2.86+/- 0.6
Discharged Home	100%

Table 5: Major Adverse Events (MAE) In-Hospital and 30 days

Major Adverse Events (MAE) In-Hospital and 30 days	
Death	0%
Stroke	0%
Myocardial Infarction	0%
Major bleeding	0%
Acute renal injury	0%
SLDA- leaflet damage	0%
Need for surgery	0%
ASD closure	1.18% (1 patient due to right to left shunt)

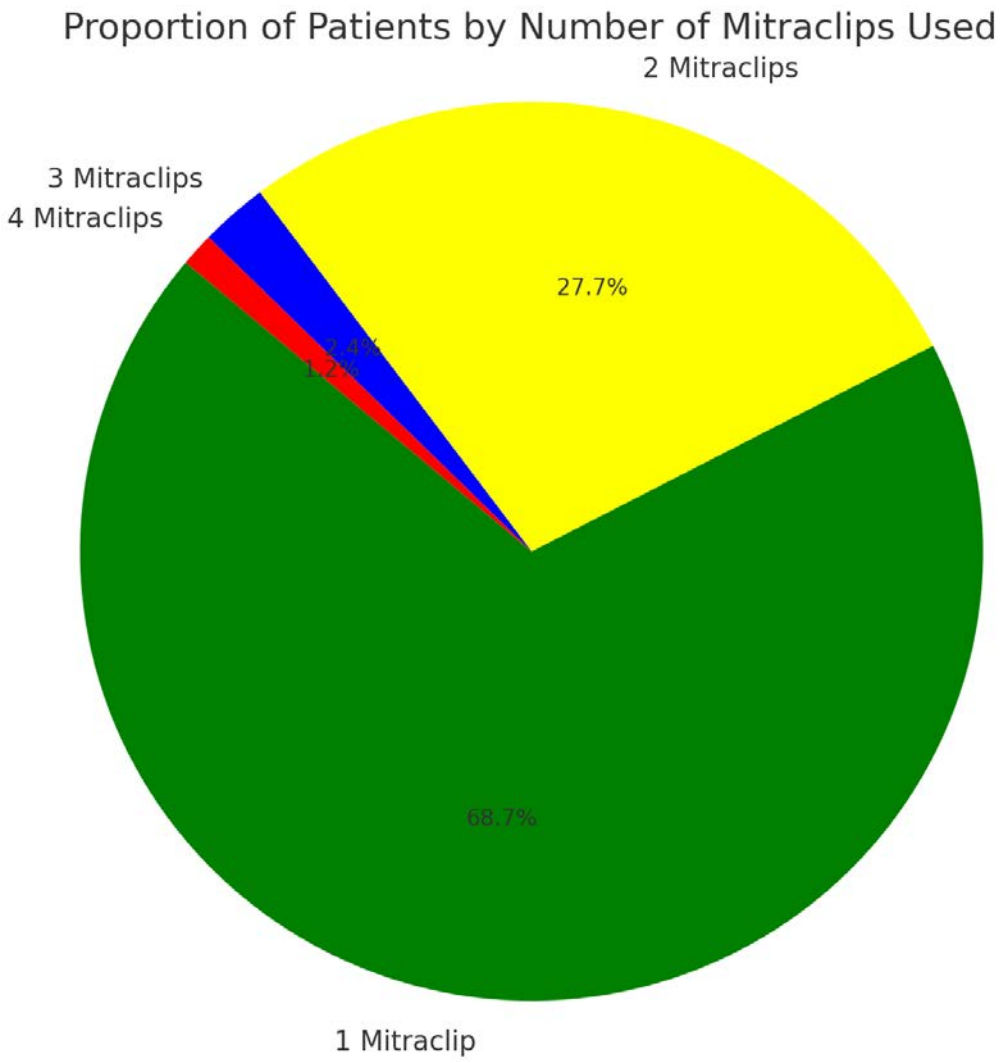

Figure 1: Prorortion of Patients by Number of Mitraclips Used

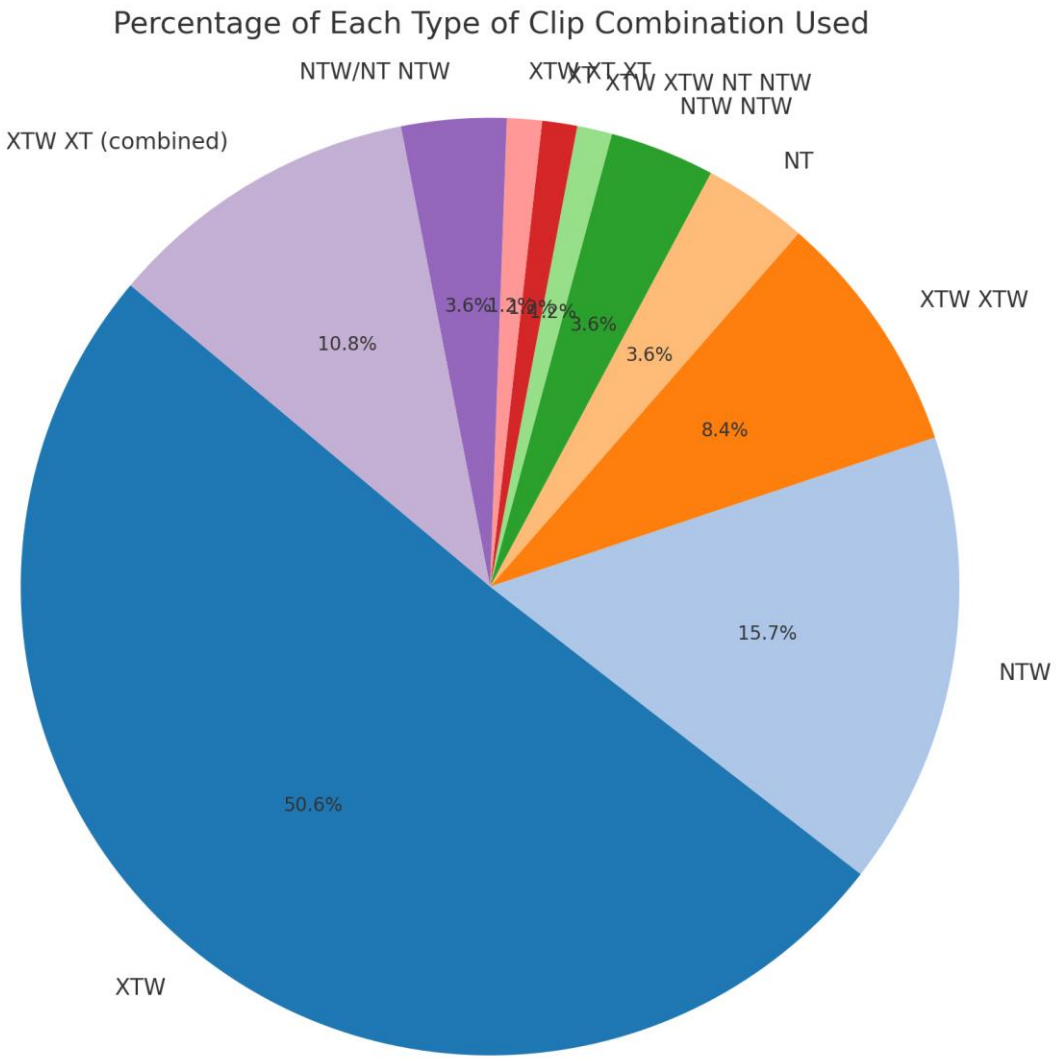

Figure 2: Percentage of Each Type of Clip Combination Used

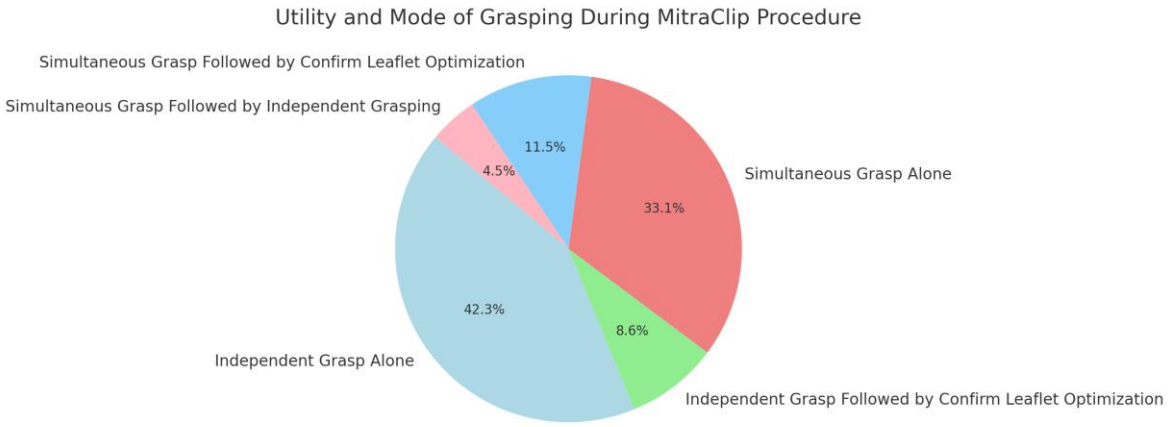

Figure 3: Utility and Mode of Grasping During MitraClip Procedure

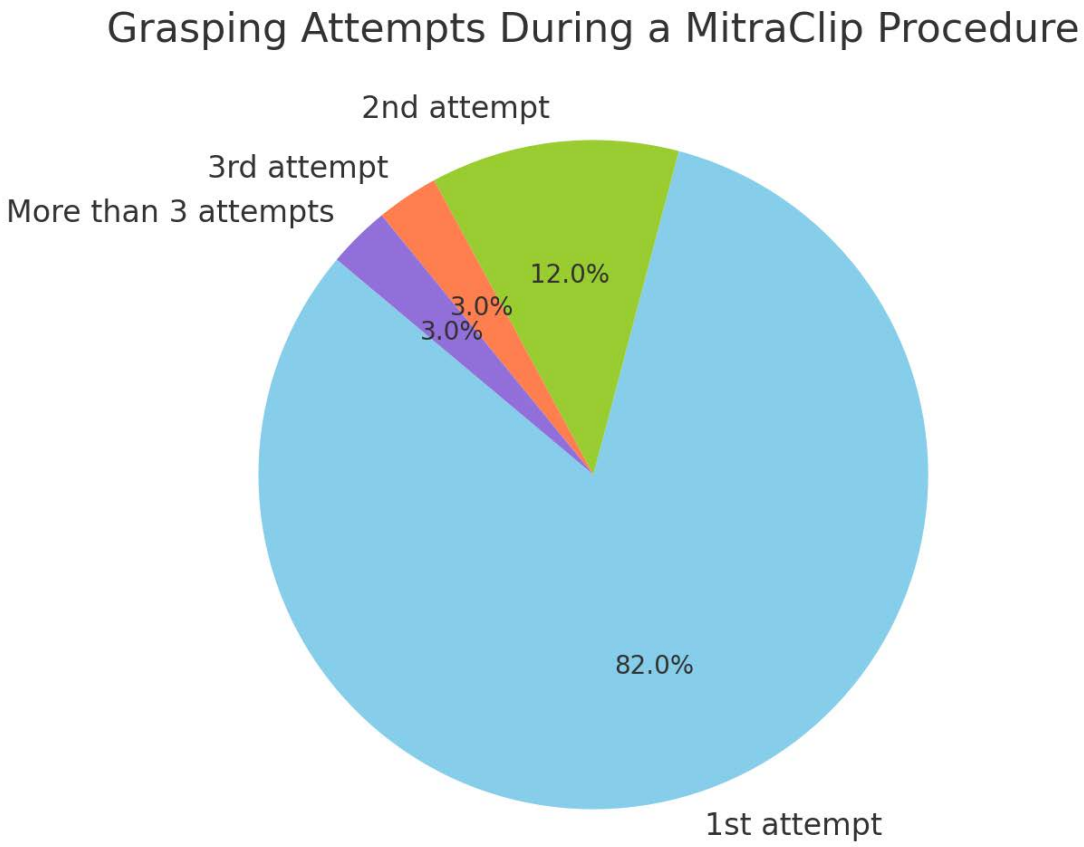

Figure 4: Grasping Attempts During a MitraClip Procedure

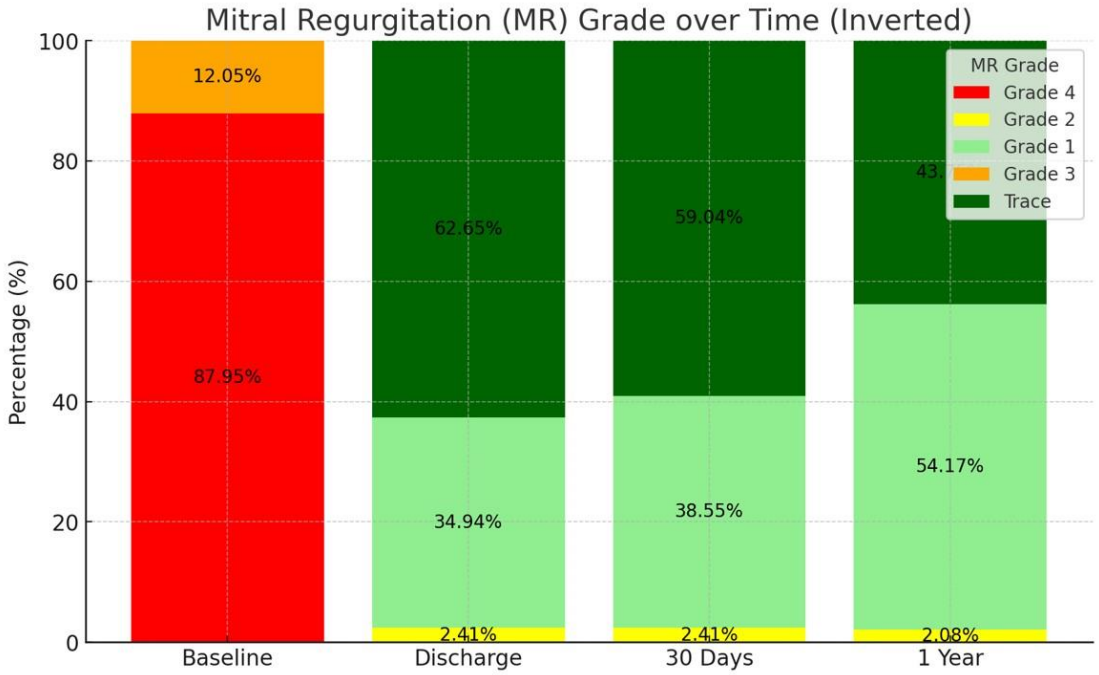

Figure 5: Mitral Regurgitation (MR) Grade over Time (Interted)

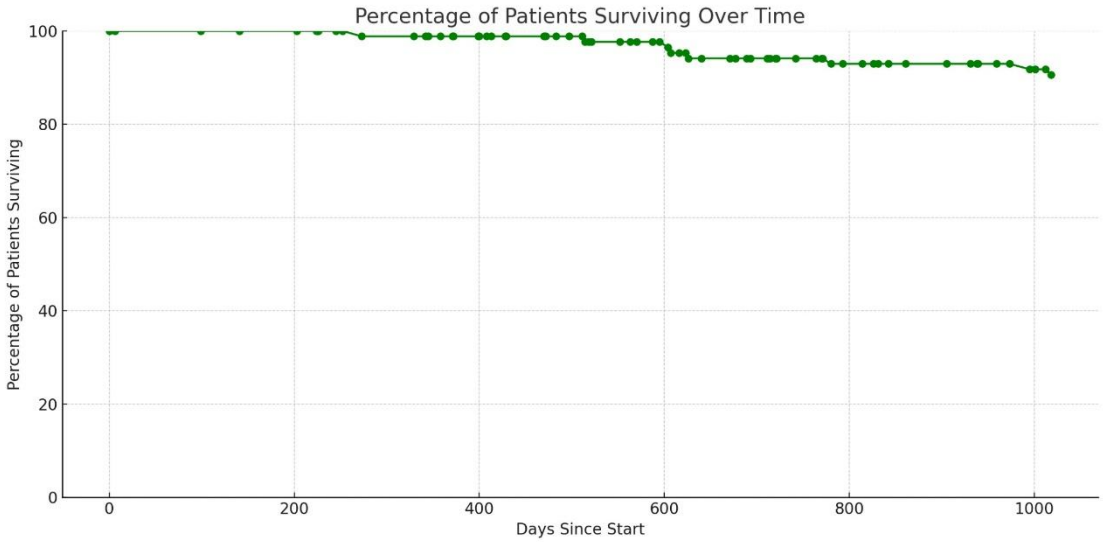

Figure 6: Percentage of Patients Surviving Over Time

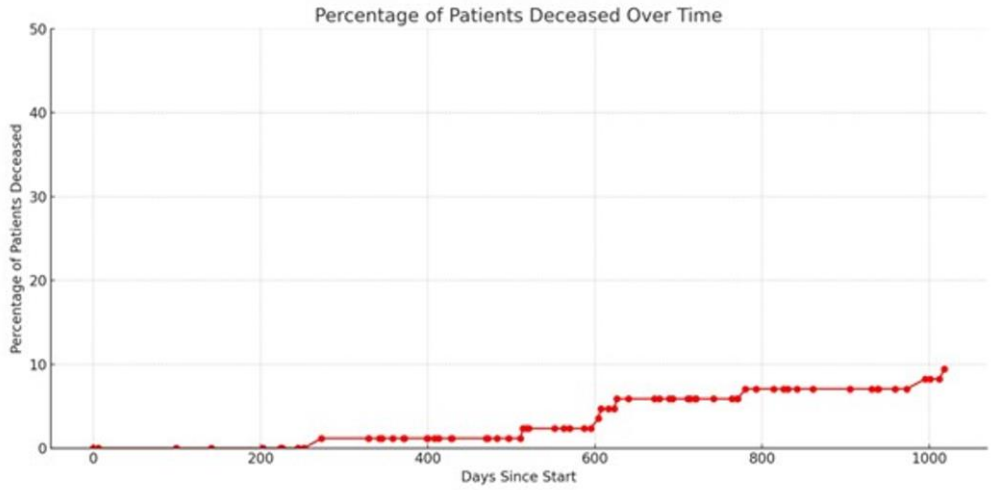

Figure 7: Percentage of Patients Deceased Over Time

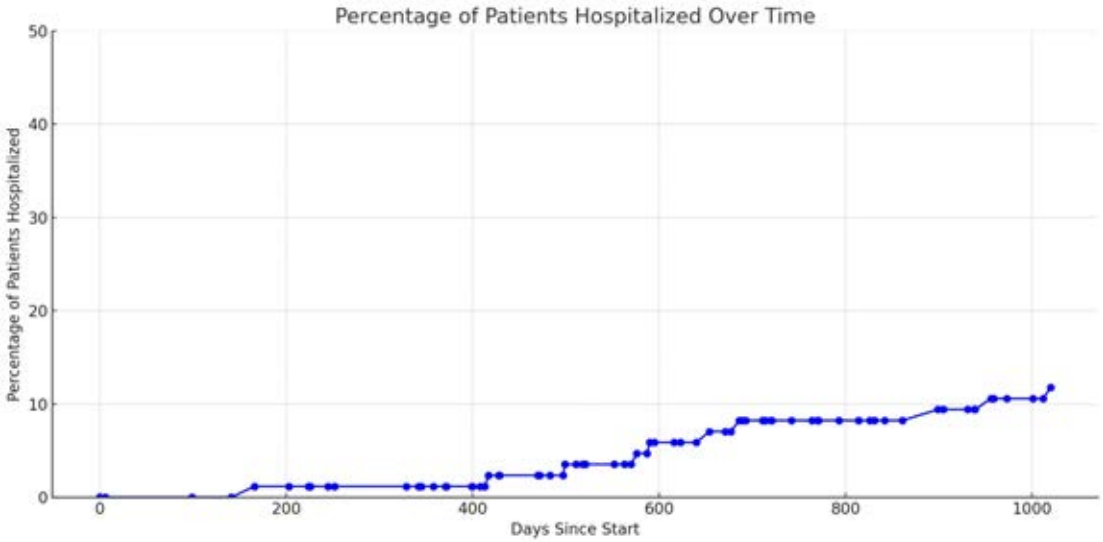

Figure 8: Percentage of Patients Hospitalized Over Time

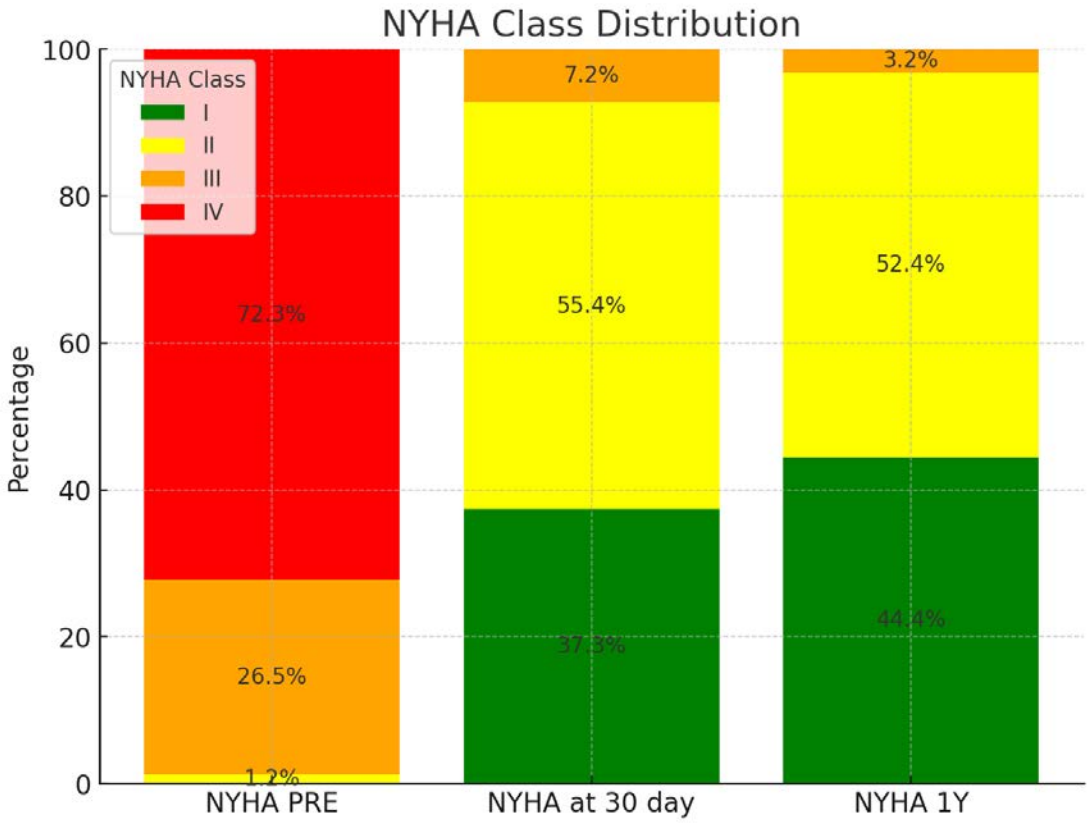

Figure 9: NYHA Class Distribution