HEALTH TECHNOLOGY ASSESSMENT FOR MITRACLIP SYSTEM

HEALTH TECHNOLOGY ASSESSMENT FOR MITRACLIP SYSTEM IN PATIENTS WITH MITRAL REGURGITATION

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Lay Abstract

Mitral regurgitation is an abnormal leakage of blood back into the left heart chambers. About 2% of the population who have chronic mitral regurgitation are elderly and are at high risk for surgery. For such patients, a treatment has been proposed that involves a catheter puncturing the skin of the groin and travelling all the way to the affected valve to deploy a device that clips and repairs the valve leaflets (a mitral valve clip). This thesis sought to compare the safety, effectiveness and cost-effectiveness of mitral valve clips with current standards of care in patients at high risk for surgery. To address this question, we searched, critically appraised, and collated existing research evidence. We found that this new treatment was not harmful and may provide a survival advantage. In addition, the approach may be cost-effective when compared to current stand of care in patients at high risk for surgery.

Abstract

Approximately 2% of the population have mitral regurgitation (MR) and many may be not tolerant for mitral valve surgery. The objective of this thesis was to investigate the comparative safety, effectiveness, and cost-effectiveness of percutaneous mitral valve repair using MitraClip System for patients with severe MR. Articles in MEDLINE, Embase, CNKI, and the Cochrane Library published from 1997 to February 2017 were searched for evidence of safety and effectiveness. A systematic review was conducted to address the uncertainty in the safety and effectiveness of MitraClip system in patients with MR. A cost-effectiveness analysis and cost-utility analysis in U.S. settings was conducted to address the uncertainty in health economic evaluation for the MitraClip system. One randomized trial and seven observational studies were included in the systematic review. The pooled data show that 30-day, one-year and two-year survival are similar in MitraClip arm and surgery arm. Residual MR occurs more frequently after MitraClip therapy than surgery, especially in younger patients, functional MR patients, and patients whose LVEF<50%. The risk of 30-day major adverse event from lower odds ratio appeared to be lower in older patients and patients whose LVEF≥50%.For economic evaluation, the base case incremental costs per LY and per QALY were $ 28,217.18 and $27,344.38 US dollars, respectively. Results were most sensitive to alternative assumptions regarding time horizon and long-term survival. Therefore, low quality of evidence due to lack of conclusive RCT data suggested that MitraClip system may provide improvements in MR, patients' quality of life and survival advantage. It is cost-effective as threshold of $50,000 U.S. dollars per QALY gained for high surgical risk

patients. Future RCT designed to reduce confounding and lessen participant attrition, which have adequate sample size, consistent reporting of outcomes, and adequate length of follow-up period will better evaluate the clinical benefits of the MitraClip System.

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List of Abbreviations

Abbreviation	Description
CC	comorbidity/complication
CDS	clip delivery system
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CUA	cost-utility analysis
DRG	Diagnosis-related group
EVEREST	Endovascular Valve Edge-to-Edge Repair Study
GI	gastrointestinal
HRR	High Risk Registry
HRS	High Risk Study
ICER	incremental cost-effectiveness ratio
ITT	intent-to-treat
LV	left ventricular
LY	life year
MAE	major adverse event
MCC	major comorbidity/complication
MI	myocardial infarction
MR	mitral regurgitation
MVR	mitral valve repair
NOS	Newcastle-Ottawa Scale
NYHA	New York Heart Association
OR	odds ratio
PP	per protocol
QALY	quality adjusted life year
QoL	quality-of-life

RCT	randomized controlled trial
RevMan	Review Manager software
SGC	steerable guide catheter
SOC	standard of care
STS	Society of Thoracic Surgeons
U.S.	United States

Declaration of Academic Achievement

Chapter 2: Under the supervision of Dr. Shamir Mehta, I was responsible for the design of the systematic review as well as the data analysis and interpretation, and write-up of the findings. Yu Chen, my wife, assisted with literature review and data extraction.

Chapter 3: Under the supervision of Dr. Shamir Mehta, I was responsible for the design of the health economic analysis as well as the data analysis and interpretation, and write-up of the findings. Prof Xie, the committee member, also a faculty member in the Department of Health Research Methods, Evidence, and Impact, assisted with Markov Model establishment.

Chapter One: Pathophysiology and Epidemiology of Mitral Regurgitation and Introduction of MitraClip System

Pathophysiology and Epidemiology of Mitral Regurgitation

Mitral regurgitation (MR), also known as mitral insufficiency, is a common form of valvular heart disease that is increasing in prevalence. Significant MR has a prevalence of approximately 2% of the population, affecting males and females equally [1]. It is one of the two most common valvular heart diseases in the elderly and is present in more than 10% of this population in North America [2]. MR is caused by incompetence of the mitral valve leading to regurgitation of blood from the left ventricle into the left atrium, instead of into the aorta, during systole. The two main causes for MR are degenerative (also called primary MR) or functional (also called secondary MR). Degenerative MR is due to degenerative changes affecting the mitral valve leaflets themselves (e.g. leaflet prolapse). Functional MR is secondary to ischemia or non-ischemic remodeling of structures adjacent to the mitral valve, including the left ventricle, left atrium and subvalvular apparatus. Some patients may have elements of both degenerative and functional MR. Patients with chronic MR usually remain asymptomatic for many years. However, over time the left atrial pressure steadily increases with dilatation of the left atrium resulting in elevated pulmonary arterial pressure. The increased volume in the left ventricle triggers compensatory mechanisms, including left ventricle dilatation or remodeling, which maintains the cardiac output for a period of time. However, remodeling of the left

ventricle eventually results in displacement of the papillary muscles, annular dilatation, and leaflet tethering. This leads to a vicious cycle of further increasing the severity of MR. When not treated, MR ultimately leads to symptoms of left and eventually right-sided heart failure which eventually become refractory to medical management. Simultaneously, the decrease in forward stroke volume leads to symptoms associated with a low output state such as profound fatigue and ultimately death.

MR is graded on a scale of mild (1+) to severe (4+). Medical management is the cornerstone of the treatment for most patients with mild or moderate MR (1+ or 2+). Medical management is primarily instituted to mitigate preload, afterload, and treat hypertension. However, medical therapy is palliative at best. Mitral valve surgery (repair or replacement) is another effective treatment for the reduction of MR and is the second leading valvular surgery performed.

Although surgery is effective in reducing MR, there is significant morbidity and mortality associated with mitral valve surgery. Patients with MR who are symptomatic despite optimal medical treatment and who are deemed too high risk to undergo mitral valve surgery currently have few options to improve morbidity and mortality. Without surgery to repair or replace the mitral valve, heart failure progresses and heart transplant or ventricular assist devices may be considered. Most patients unable to have surgery can only be managed medically.

Introduciton of MitraClip System

The MitraClip System (Abbott Vascular, Menlo Park, CA, USA) was developed as a percutaneous technology to provide an option for treatment of patients with significant MR. The MitraClip System consists of the Clip Delivery System (CDS) and Steerable Guide Catheter (SGC). The CDS is introduced transvenously through the SGC that includes a dilator. Both the CDS and SGC are actuated by control knobs, levers and fasteners located on the handles. The MitraClip Device can be repeatedly opened, closed and repositioned on the mitral valve leaflets in order to optimize leaflet insertion and MR reduction. The operator may choose to place 1 or more MitraClip devices to achieve final MR reduction. Percutaneous repair of a mitral valve using MitraClip System is shown in Figure 1 [3]. Additionally, the MitraClip procedure preserves the option for future percutaneous intervention or surgical procedures should the patients risk status improve or emergent procedures be warranted.

A number of studies have been completed or are ongoing and data have been generated:

EVEREST I Study

The EVEREST I study [4] enrolled 55 patients in the US from July 2003 to February 2006 and five year follow up was completed in October 2011. The study affirmed feasibility of the percutaneous approach to MR reduction with the MitraClip System. The majority pf patients (89%) had the device successfully implanted with successful reduction of MR to 2+ or less achieved in 70.9% of patients at discharge.

In addition, low rates of adverse events supported the overall safety of the device. In patients with follow-up to five years, MR reduction to ≤ 2+was durable and was accompanied by reverse left ventricular remodeling and clinically meaningful improvements in New York Heart Association (NYHA) Functional Class.

EVEREST II Trial

The EVEREST II randomized controlled trial (RCT) [5,6,7] randomized 279 patients (27% functional MR and 73% degenerative MR, 184 MitraClip and 95 surgical control) in North America. The primary safety endpoint was a 30-day major adverse event (MAE) composite. The proportion of patients experiencing the MAE composite in the MitraClip arm was compared to that in the surgical Control group using pre-specified margins of superior safety of 2% and 6% for the Intent-To-Treat (ITT) and Per Protocol (PP) populations, respectively. In the ITT analysis, the MAE rate at 30 days was 15.0% for the MitraClip arm and 47.9% for the surgical Control arm, an observed difference of 32.9% (97.5% UCB = 20.7%, $p<0.0001$). In the PP analysis, the MAE rate at 30 days was 9.6% for the MitraClip arm and 57.0% for the surgical Control arm, an observed difference of 47.4% (97.5% UCB = 34.4%, $p<0.0001$). The safety endpoint was met by a significant margin. The EVEREST II RCT primary effectiveness endpoint was clinical success defined as freedom from surgery or re-operation, death, and MR>2+ at one year. In the ITT analysis, the clinical success rate was 67.4% for the MitraClip arm and 73.0% for the surgical Control arm. The results of the EVEREST II RCT through 2 years demonstrated that 78% of patients in the MitraClip arm were free from surgery at two years with similar clinical benefit

compared to surgery. There was no incidence of mitral stenosis, device embolization or device migration in the EVEREST II RCT. Sustained reduction in the MR was observed, although not quite to the extent of surgery as measured by a core laboratory with established echocardiographic techniques. Continued reduction in left ventricular (LV) volumes and dimensions were observed in both MitraClip and surgery group, although diastolic volumes were reduced to a greater degree postsurgery. Symptomatic benefit, as evidenced by improvements in NYHA Functional Class and Quality of Life measures for patients in the MitraClip device arm, was at least as good as surgery. The authors concluded that although percutaneous repair was less effective at reducing MR than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes. The authors also concluded the data demonstrated a place for the MitraClip device as a therapeutic option for selected patients with MR.

EVEREST II High Risk Registry (HRR)

Another separate registry study following EVEREST II trial, the EVEREST II HRR [8] enrolled 78 high surgical risk patients of advanced age (mean = 77 years) with a high rate of baseline co-morbidities such as prior myocardial infarction (MI), prior stroke, and moderate-to-severe renal disease. The primary objective of the EVEREST II HRR was to assess procedural safety in high surgical risk patients (a predicted surgical mortality risk of 12%, based on either the Society of Thoracic Surgeons [STS] risk calculator or surgeon co-investigator estimated mortality risk following prespecified protocol criteria). Potentially qualifying criteria included high-risk patients with

porcelain aorta, mobile ascending aorta atheroma, post-mediastinal radiation, functional MR with left ventricular ejection fraction (LVEF) < 40%, age older than 75 years with LVEF <40%, previous median sternotomy with patent bypass graft(s), >2 previous chest surgeries, hepatic cirrhosis, or ≥ 3 of the following STS high-risk criteria: creatinine level > 2.5 mg/dl, previous chest surgery, age older than 75 years or LVEF <35%[8]). A secondary objective of the EVEREST II HRR was to assess major effectiveness measures, including changes in left ventricular volumes and dimensions, NYHA Functional Class, SF-36 quality of life score, and rate of heart failure hospitalization at one year compared to baseline. The observed procedural mortality rate a 30 days was 7.7% (95.472% UCB = 14.8%) and compared favorably (p=0.006) to average predicted surgical mortality of 18.2%. The observed procedural mortality rate was also lower when compared to the average STS mortality risk (14.2). Significant improvements were observed in left ventricular volumes and dimensions, coupled with reduction in heart failure hospitalizations, improvement in NYHA Functional Class and improvement in quality of life.

EVEREST II High Risk Study (HRS)

After the EVEREST HRR, a matched comparator group of patients (N=32) with MR severity of ≥ 3+ and a predicted surgical mortality rate of 12% who were retrospectively identified and screened for enrollment in the HRS but did not enroll or were not anatomically eligible for MitraClip device placement were retrospectively identified. This comparator group of patients were treated by standard of care (86% managed medically and 14% underwent MV surgery) and

were consented to compare survival in patients treated with MitrClip System. The 30-day procedure-related mortality rate was 7.7% in the HRR and 8.3% in the comparator group. The 12-month survival rate was 76% in the HRR and 55% in the concurrent comparator group (p = 0.047). In surviving patients with matched baseline and 12-month data, 78% had an MR grade of ≤ 2+. Left ventricular end-diastolic volume improved from 172 ml to 140 ml and end-systolic volume improved from 82 ml to 73 ml (both p=0.001). NYHA Functional Class improved from III/IV at baseline in 89% to class I/II in 74% (p<0.0001). Quality of life was improved (Short Form-36 physical component score increased from 32.1 to 36.1 [p=0.014] and the mental component score from 45.5 to 48.7 [p=0.065]) at 12 months. The annual rate of hospitalization for congestive heart failure in surviving patients with matched data decreased from 0.59 to 0.32 (p = 0.034). The authors concluded that the MitraClip device reduced MR in a majority of patients deemed at high risk of surgery, resulting in improvement in clinical symptoms and significant left ventricular reverse remodeling over 12 months [9].

In summary, multiple clinical studies in a large number of patients provide scientific data on the safety and effectiveness of the MitraClip System. The results of these studies provide evidence for significant clinical benefit with relatively low risk of excessive peri-procedural or long-term mortality. This thesis is to further investigate the safety and effectiveness of the MitraClip System in the treatment for patients with severe MR, as compared to conventional surgery and current standard of care.

Chapter Two: Safety and Effectiveness of MitraClip system versus Surgery for Patients with Severe Mitral Regurgitation: A Systematic Review and Meta-analysis

Introduction

Background

Mitral regurgitation (MR), the second most common valvular heart disease after aortic stenosis, is a serious condition with significant morbidity and mortality[10]. Patients with severe symptomatic MR have a poor prognosis, with an annual mortality rate without surgical procedure being about 6% and is reported to be as high as 60% within five years[11,12]. Conservative medical options are limited and show no prolonged survival[4]. Surgical mitral valve repair (MVR) is generally considered the standard treatment for MR; however, randomized studies documenting the outcomes and long-term follow-up are still lacking[13-15].

Since a significant number of patients with severe MR (49%) are not treated due to age, reduced left ventricular (LV) function, co-morbidities, or other contraindications to open mitral valve surgery[16], less invasive percutaneous transcatheter MVR procedures have been developed. The MitraClip system (Abbott Vascular-Structural Heart, Menlo Park, CA, USA) is an approved system in Europe and North America for transcatheter MVR. With this technique, both mitral valve leaflets are attached with one or more clips, resulting in a so-called “doubleorifice mitral valve.” However, there are only a limited number of patients studied. The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) I trial, first conducted in 2004, demonstrated the safety, feasibility and significant hemodynamic

improvement of the MitraClip[17]. Following the success of EVEREST I, EVEREST II, a randomised controlled trial (EVEREST II RCT) of 279 surgical candidates with grade 3+ or 4+ MR, randomised in a 2:1 design to the MitraClip system (n=184) or MV surgery (n=95), was conducted[5]. The 12 month per protocol success rate was 72% in the device group and 88% in the surgery group, and New York Heart Association (NYHA) functional class I and II were seen in 98% of the device group and 87% of the surgical group. Although major adverse events were significantly lower in the device group (15% vs 48%), this difference was almost entirely attributable to the inclusion of transfusion ≥ 2 units of blood as an adverse event. The efficacy of MitraClip and surgery was similar, with 21% of MitraClip patients and 20% of surgery patients still suffering from grade 3+ or 4+ MR at 12 months. However, there was a significant difference in the rate of MV surgery/reoperation in favour of the surgical group (2% vs 20%). Subsequently, EVEREST II High Risk Study (HRS) was continued and revealed that MitraClip system significantly reduced MR in a majority of patients deemed at high risk of surgery, improved clinical symptoms, and decreased LV dimensions at 12 months in this high-surgical-risk cohort[9].

Currently, the evidence does not support the superiority of MitraClip implantation over surgical MV repair or replacement in terms of efficacy, especially in patients with low surgical risk. MitraClip implantation, however, can be seen as a viable option in patients with severe MR who are denied surgery. Therefore, this systematic review and meta-analysis is to find and update sufficient evidence to compare the safety, clinical efficacy, and survival outcomes of MitraClip

implantation versus surgical correction of severe MR.

Research Question

Amongst the patients with severe MR (3+ or 4+), does treatment using MitraClip system as compared to conventional mitral valve surgery, provide a lower 30-day mortality, a lower one-year mortality, a lower residual MR rate, a lower post-procedure major adverse event (MAE) rate?

Population: Symptomatic patients with severe MR (3+ or 4+) of degenerative etiology or chronic functional.

Intervention: MitraClip system treatment / percutaneous transcatheter MVR/mitral valve clip treatment.

Comparator: Conventional surgery (surgical mitral valve repair or replacement).

Outcome:

Primary Outcome: one-year mortality.

Secondary Outcomes: 30-day mortality, two-year mortality, residual MR, post-procedure major adverse events

Objectives

1) To determine, if the MitraClip system is associated to a lower mortality, a lower serious adverse event rate, a lower readmission rate, a shorter length of hospital stay, or a high quality of life compared to current standard surgical mitral valve repair or replacement or conservative medical treatment.

2) To determine, if there are any biological covariates or potential sources of heterogeneity can affect the clinical outcomes and the results of meta-analysis.

Methods

Criteria for Selecting Studies

Types of studies

All eligible randomized controlled trials (EVEREST II RCTs) and observational studies (prospective and retrospective) (no language restriction) comparing the safety and efficacy of MitraClip system to conventional surgery for patients with severe MR were included.

Types of participants

All symptomatic patients (NYHA class III or IV) with severe MR (3+ or 4+) of chronic functional or degenerative etiology who were at high or prohibitive risk for surgical mitral valve repair or replacement (i.e., those who had a high risk based on The Society of Thoracic Surgeons (STS) score, or elderly with patients who have undergone previous cardiac surgery). Populations with rheumatic heart disease, malignant tumour, NYHA class I or II symptoms and acute MR were not considered to be included in the analysis.

Types of intervention

Studies involving MitraClip system treatment/percutaneous transcatheter MVR/mitral valve clip treatment.

Types of comparator

Studies involving conventional surgery (surgical mitral valve repair or replacement).

Types of outcome measures

Studies reporting the following outcomes:

Primary Outcome: one-year mortality.

Secondary Outcomes: 30-day mortality, two-year mortality, residual MR, post-procedure major adverse events. 30-day myocardial infarction, stroke, renal failure, cardiac perforation, gastrointestinal complication requiring surgery, sepsis, blood transfusion and mechanical ventilation requirement.

Search Methods for Identification of Studies

Search Strategy

Studies in any language were identified using MEDLINE (January 2000 - present), EMBASE (January 2000 – present), Cochrane Central Register of Controlled Trials (until April 2016), CINAHL (January 2000 – present) and CNKI database (Chinese, 2000-present). All of the above listed databases (except CNKI) were searched using separate comprehensive search strategies developed in consultation with a research librarian experienced in conducting systematic reviews. In order to enhance sensitivity, methodology filters were used in the search strategies. Subsequently, an additional search of PubMed was done to identify articles electronically published prior to print publication within 6 months of the search, and therefore not yet be indexed in other databases. The clinical trials databases clinicaltrials.gov and controlled-trials.com and the National Institutes of Health database of funded studies were searched for unpublished data. Relevant review articles and systematic reviews were reviewed manually. Conference, which occurred from 2000 to present were searched using the Web of Science and BIOSIS databases (http://ipscience.thomsonreuters.com/) and review of the grey literature database OpenGrey (http://www.opengrey.eu/) were done. Potential sources of

unpublished data were searched through the National Institute of Health database of funded studies from 2000 through to present. There were no language restrictions.

Search Terms

Mitral Regurgitation, transcatheter mitral repair, transcatheter mitral repair, percutaneous transcatheter mitral repair, MitraClip, mitral valve surgery, mitral valve repair (see Appendix 1).

Data Collection and Analysis

Study selection and data abstraction

Two independent reviewers screened the titles and abstracts of all eligible studies. In the case of any disagreement between the two reviewers, the full articles were reviewed by both reviewers. In case of persistent disagreement, a third reviewer settled eligibility. A kappa statistic was calculated to determine inter-rater agreement between the two reviewers.

Relevant information from eligible studies was retrieved through data collection forms. Those collected all the important information on details of the study and information relevant to the methodological quality of each study. Both reviewers independently extracted the data. Disagreements were resolved by consensus or by the third author if no agreement could be reached. Study authors were consulted for additional or missing information of required.

Bias Assessment

The methodological qualities of eligible EVEREST II RCT were evaluated independently by each reviewer using the Cochrane Collaboration's Risk of Bias tool

based on the following parameters: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The risk of bias of observational studies was assessed by using the Newcastle-Ottawa Scale (NOS). This tool includes eights items which evaluate the selection of the cohort, comparability and the outcome. The overall quality of evidence for outcomes was assessed using the GRADE criteria (GRADEpro/GDT online), which assesses for risk of bias, inconsistency, indirectness, imprecision and publication bias. Both independent reviewers applied the GRADE criteria for each outcome to summarize an overall quality of the summary statistic. Publication bias were determined by using funnel-plot.

Data Analysis

A meta-analysis of the studies was done for each outcome using a random effects model. Dichotomous variables were summarized in odds ratio (OR), 95% confidence intervals were provided for all estimates. Statistical analysis was performed using Review Manager Software (RevMan 5.2) and 95% confidence intervals (95%CI) were provided for all estimates. Statistical heterogeneity was determined by using the Cochrane's Q statistic. Quantification of the degree of heterogeneity was performed by the I^2 statistic where I^2 values ≤ 25% was considered as low, 26-50% as moderate and > 50% as high. Additional subgroup analyses were performed when significant heterogeneity exists.

Planned Subgroup analyses: The following sources of heterogeneity were

anticipated based on known differences.

1) Age: Young patients (<70 yrs) vs. old patients (≥70 yrs).

2) MR etiology: Functional MR vs. degenerative MR.

3) Left ventricular ejection fraction: <50% vs. ≥50%.

Planned sensitivity analysis: Sensitivity analysis to subtotal the plots by EVEREST II RCTs versus observational studies was conducted to explore whether or not there are significant differences of OR between EVEREST II RCT and observational studies. Also, sensitivity analyses were carried out based on studies with outlying results and methodological rigor of included studies to demonstrate that the findings were robust to the decision made to include these studies. A sensitivity analysis based on the type of analysis (fixed versus random-effects) was also applied.

Results

Description of studies

Results of the search

Using the OVID interface (literature search strategy can be found in Appendix 1) to perform electronic searches in MEDLINE and EMBASE (n=907), and the Cochrane Central Register of Controlled Trials (n=51), and the EBSCOhost interface to perform the electronic search in CINAHL (n=17), and CNKI database (n=34), 1009 results were obtained. After elimination of duplicate papers, 867 pertinent papers were screened for relevance, based on their titles and abstracts. Of these, 27 were selected for full text review, and eight ultimately met the inclusion criteria and were

included in this review. See Appendix 2 for study flow diagram.

Included studies

All eight publications comparing MitraClip with surgical MV repair or replacement were published in peer-reviewed journals (Feldman 2011, Taramasso 2012, Conradi 2013, Paranskaya 2013, Swaans 2014, Buzzatti 2015, De Bonis 2016, Ondrus 2016). These studies provided data on 1082 participants who had severe MR (3+ or 4+). Only one study was a RCT the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II trial [5], whereas the others [18-24] were observational comparative studies. One study [22] only included > 80-year patients. One study [22] only enrolled patients with degenerative MR and four studies [18,19,23,24] only included those with functional MR, whereas 3 studies [5,20,22] enrolled both those with functional MR and those with degenerative MR. The characteristics of included studies can be found in Table 1.

Excluded studies

After full text review, 19 studies were excluded. They were excluded because of ineligible population, ineligible comparator or extended follow-up of included studies.

Risk of bias in included studies

The EVEREST II RCT (Feldman 2011) [5] was judged to be at high risk of bias for confounding because some patients who underwent the MitraClip procedure later had additional surgical repair (21%) were counted in the intervention group. There was no blinding of outcome assessment, and it could be a potential source of bias. See Table 2.

Three of seven observational studies were at high risk of bias due to concerns regarding attrition/selection bias or confounding factors (Taramasso 2012, Paranskaya 2013, Conradi 2013). The remaining four observational studies have an unclear risk of bias due to selection and outcome reporting issues (Swaans 2014, Buzzatti 2015, De Bonis 2016, Ondrus 2016). Risk-of-bias assessment for observational studies is reported in Table 3. No studies had any conflicts of interest with regards to industry funding.

Agreement statistics

The level agreement between reviewers based on the unweighted kappa for title/abstract screening was 0.98 (95% CI 0.94-1.00). The unweighted kappa for full text eligibility was 1.00 (95% CI 1.00, 1.00).

Outcomes

Mortality

All studies reported postoperative 30-day mortality, and seven reported one-year mortality and six reported two-year mortality, so the data were allowed for meta-analysis. For 30-day mortality, the resulting sample was comprised of eight studies including 594 participants who received the MitraClip therapy and 488 who had surgery. The forest plot (Appendix 3) of the resulting meta-analysis shows that the pooled OR of 30-day mortality was 0.51 (95% CI: 0.22 to 1.19, P=0.18), and there was no obvious heterogeneity (I^2=0%, P=0.49). For one-year mortality, the resulting sample was comprised of seven studies including 500 participants who received the MitraClip therapy and 407 who had surgery. The forest plot (Appendix 4) of the resulting meta-analysis shows that the pooled OR of one-year mortality

was 1.11 (95% CI: 0.69 to 1.789, P=0.67), and there was no obvious heterogeneity (I^2=0%, P=0.92). For two-year mortality, the resulting sample was comprised of six studies including 476 participants who received the MitraClip therapy and 381 who had surgery. The forest plot (Appendix 4) of the resulting meta-analysis shows that the pooled OR of two-year mortality was 1.05 (95% CI: 0.71 to 1.56, P=0.81), and there was no obvious heterogeneity (I^2=0%, P=0.83). Planned subgroup analyses and sensitivity analysis are shown in Appendix 4.

Residual MR

Six studies reported residual MR (patients in one study [Ondrus 2016] did not have residual MR) so the data were allowed for meta-analysis. The resulting sample was comprised of the six studies including 453 participants who received the MitraClip therapy and 421 who had surgery in meta-analysis of residual MR. The forest plot (Appendix 5) of the resulting meta-analysis shows that the pooled OR was 6.47 (95% CI: 2.71 to 15.41, P<0.0001) and there was no obvious heterogeneity (I^2=5%, P=0.38). Planned subgroup analyses and sensitivity analyses are shown in Appendix 6. Recurrent MR other than 30-day time point was summarized in Table 5.

30-day Major Adverse Events

A number of 30-day major adverse events (MAE) were reported in six studies. Meta-analyses were also conducted to explore the effect of MitraClip therapy and surgery on the incidence of composite of 30-day MAEs. The resulting sample was comprised of the six studies including 430 participants who received the MitraClip therapy and 400 who had surgery in meta-analysis of 30-day MAE. The forest plot (Appendix 7) of the resulting meta-analysis shows that the pooled OR was 0.54 (95%

CI: 0.25 to 1.17, P=0.12) and but there was a strong heterogeneity (I^2=73%, P=0.002). The significant degree of heterogeneity was explored using sensitivity analysis and a number of pre-specified subgroup analyses, the forest plots are showed in Appendix 8. Sensitivity analysis shows that heterogeneity decreased (OR=0.73, 95% CI: 0.42 to 1.26, P=0.26; I^2=26%, P=0.25) by eliminating the EVEREST II RCT. Among the observational studies, subgroup analysis by patient age shows that there was no obvious heterogeneity in patients under 70 (OR=0.73, 95% CI: 0.42 to 1.26, P=0.26; I^2=0%, P=0.57) and moderate heterogeneity in patients who are 70 or older (OR=0.48, 95% CI: 0.23 to 1.03, P=0.26; I^2=32%, P=0.23).

Other outcomes

There are some outcomes reported in these studies but the data are not feasible to be synthesized. They are summarized in Table 4.

Sensitivity analysis

Research method

There is only one RCT (EVEREST II trial) included in this systematic review. This RCT was removed from the analysis to gauge the effects of research method on the summary estimate. No result change was observed in the sensitivity analysis. However, the heterogeneity reduced after eliminating the RCT in the meta-analysis of 30-day MAE (Appendix 8).

Methodological quality

The observational study by Conradi 2013 was judged to have the lowest methodological quality (3 stars) because of attrition/selection bias, confounding factors and no important primary endpoints or secondary endpoints reported. This

observational study was removed from the analysis to gauge the effects of methodological quality on the summary estimate. This analysis changed the result of subgroup analysis of 30-MAE in older patient (≥70 yrs) which showed such patients had lower 30-MAE rate after MitraClip therapy than surgery (OR: 0.38, 95%CI: 0.17 to 0.87, P=0.02). (Appendix 9).

Fixed vs. random model

There was no result of meta-analysis changed when using fixed effects model instead of random effects model.

Publication bias

No obvious publication bias was detected in all analyses, funnel plots in analyses of mortality, residual MR and 30-day MAE were provided in Appendix 10.

Discussion

Major findings

Amongst patients with severe MR, the MitraClip therapy achieves similar survival to conventional surgery (MV repair or replacement). Residual MR, however, occurs more frequently (6.46-fold) after MitraClip therapy than conventional surgery. Surgery may be more effective to reduce MR severity in the early post procedure period and the true advantage (effectiveness) of MitraClip therapy may be greater in older patients (≥70) and patients with degenerative MR and those with LVEF≥50%. In addition, MitraClip may be able to provide more benefits (safety) to older patients (≥70) and patients whose LVEF<50%.

Survival and composite of end points

The major findings show non-inferiority of the MitraClip as a treatment for severe MR compared to conventional surgery (MV repair or replacement), however, they should be interpreted with caution due to the high risk profile (older patients, lower EF, higher predicted mortality) in the MitraClip group than surgery group. Similar survival despite higher risk profiles indicates that the MitraClip therapy may not achieves at least worse survival than conventional surgery. The EVEREST II RCT reported similar early (30-day and one-year) and late (five-year) survival between MitraClip and surgery [5].Heterogeneity of the treatment effect, however, is observed on patient sex, age, MR pathology, and EF. The rate of the primary efficacy end point (freedom from death, from mitral-valve surgery, and from grade 3+ or 4+ mitral regurgitation) was higher in surgery group than in MitraClip therapy group in the subgroups of men (73% vs. 55%), younger patients (<70) (82% vs. 51%), patients with degenerative MR (82% vs. 56%) and those with EF of ≥60% (82% vs. 58%), which indicates that conventional surgery provides more benefits in such patients. Although the EVEREST II RCT shows better results after conventional surgery for denegerative MR, both of the procedures showed similar survival in patients with functional MR in the study by Swaans et al [21].

Residual MR after treatments

Although survival is similar between MitraClip therapy and conventional surgery in this study, residual MR is more frequent after MitraClip therapy than surgery. Residual MR after MitraClip repair may be associated with impaired outcomes. Lim and colleagues [25] reported that 12-month survival was similar (p=0.61) between

patients who were discharged with MR severity of 2+ and those with MR ≤1+ at discharge. On the other hand, patients with either MR ≤1+ or MR 2+ at discharge had better 12-month survival compared to those discharged with either MR 3+ or MR 4+ [25]. Multivariate analysis reported by Puls and colleages [26] also identified failure of acute procedural success defined as persisting MR grade 3+ or 4+ as a significant independent predictor of all-cause mortality. Futhermore, in a study by Sürder et al [27], the proportion of the clinical efficacy endpoint composite (combination of absence of post-implant congestive heart failure, freedom from MV surgery survival, persistent MR ≤ 2+ at 6 months follow-up, and survival) was significantly higher among patients with an MR grade of 1+ at discharge compared with the patients with MR 2+ [27]. In Sürder et al's study, a high MR grade at discharge was identified as a predictor of mortality, patients with MR grade 2+ at discharge had a worse prognosis compared to patients with an MR grade of 1+ or more at discharge, highlighting the importance of the initial procedural result [27]. Furthermore, multivariate analyses in the study by Paranskaya 2013 [20] demonstrated that the degree of residual MR immediately after MitraClip therapy was an important predictor for the combined endpoint of re-intervention, cardiac re-hospitalization, major cerebro-vascular and cardiac events, and mortality. Nevertheless, the negative prognostic effect of persisting MR could not be demonstrated within the surgical patients, which is possibly due to the lower postoperative MR incidence within surgical patients, and studies with larger sample size and a longer follow-up period are necessary to establish whether the higher

efficacy of surgery will transfer to a survival benefit compared with MitraClip therapy [23]. The presence of a concomitant annuloplasty might be the reason for lower residual MR rate in the MitraClip therapy group [23,28]. In the future, percutaneousmitral annuloplasty techniques might overcome this limitation [23].

MAEs following treatments

In the present systematic review, strong heterogeneity (I^2=73%, P=0.002) was observed in the meta-analysis of post-procedure major adverse events (MAEs). In the sensitivity analysis by eliminating the EVEREST II RCT, the heterogeneity decreased (I^2=26, P=25%), and the 30-day MAE rate is significantly lower in MitraClip group than surgery group (15% vs. 48%) in the EVEREST II RCT, indicating the result might be sensitive to the research methodology. In the subgroup analysis, the results showed that the OR of MAE was lower in older patients (≥70) compared to those under 70 years (0.48 vs. 0.93) among observational studies. Moreover, the sensitivity analysis by eliminating the study with the lowest methodological quality changed the result of subgroup analysis of 30-MAE in older patient (≥70 yrs) which showed such patients had lower 30-MAE rate after MitraClip therapy than surgery (OR: 0.38, 95%CI: 0.17 to 0.87, P=0.02). All these evidence indicates that MitraClip therapy might be able to provide more benefits (safety) to the patients over 70, which is consistent with the EVEREST II RCT [5].

In addition, The ACCESS-EU study was designed to provide further evidence of the safety and effectiveness of the MitraClip system in a real-world setting through a snapshot of the current practice in Europe. The one-year findings have recently

been published showing that patients in the real-world undergoing the MitraClip therapy are high-risk, elderly and mainly affected by functional MR. This represents a significant shift from the population originally studied in the EVEREST II RCT trial. As aforementioned, clinical outcomes from surgical intervention was not superior compared to the MitraClip in these groups (elderly and functional MR) in the exploratory intention-to-treat analysis of the EVEREST II trial. This is reaffirmed by the results of the ACCESS-EU study which found that the MitraClip in high risk patients with functional MR was safe with low rates of hospital mortality and adverse events. Meaningful clinical improvement was observed, with objective improvement of quality of life and functional status reported [29].

Furthermore, LVEF is associated with MR etiology among the included studies. Patients with functional MR have a relatively lower LVEF while those with degenerative MR have a higher LVEF. If MitraClip therapy can provide more benefits to patients with functional MR, then in terms of health economics, percutaneous approach may involve a higher medical cost for short-term MAE management, but it will improve mortality in mid-term and long-term period, particularly in patients with higher age, functional MR and/or lower LVEF, and whose who are not tolerant to conventional surgery.

Quality of evidence

Quality of evidence assessment was performed using GRADEpro/GDT. The evidences for mortality, residual MR and 30-day MAE were downgraded for risk of bias and inconsistency because four studies had loss to follow-up and they have

different composite of 30-day MAEs. See Table 6.

Generalizability of findings

The findings of this review are generalizable to the care of patients in developed countries. Studies included both male and female patients ranging in age from <64 to >84 years who presented to a surgical or percutaneous care setting. The eight studies included patients with functional MR and degenerative MR. Thus, the results of mortality of this review are applicable to adult patients with severe MR regardless of the etiology.

Limitations

1) Only one RCT and seven observational studies were included in this systematic review, and only a few studies were used in the subgroup analyses, the patients enrolled in these studies may not representative of patients typically seen in real-world clinical practice. The included EVEREST II RCT has a profound confounding factor which is 21% patients received MitraClip therapy needed subsequent surgery.

2) Included studies have different composite of 30-day MAEs make it infeasible to demonstrate whether or not the patients received MitraClip therapy would have comparable MAE rate to conventional surgery. Furthermore, included studies have different length of follow-up period and different time point of death report, result in missing data when synthesizing the data of mortality.

3) No subgroup of meta-analysis of degenerative MR could be conducted due to a lack of reporting. Only the EVEREST II RCT provided a subgroup comparison

between the MitraClip therapy and conventional surgery in the subgroups functional MR and degenerative MR.

4) Another major weakness is the absence of RCTs in evaluation the efficacy of the MitraClip System. RCTs balance both known and unknown confounders across treatment groups, is the least vulnerable to bias. While patients enrolled in RCTs might not be representative of patients typically seen in real-world clinical practice, clinicians need to know whether an intervention is beneficial in the most unbiased way. Therefore, potential biases must be greater for non-randomized studies than for RCTs. Non-randomized observational studies retain a large potential for biases which could confound the results. One important potential confounder is selection bias by which the investigators consciously or non-consciously choose patients whom they think will more benefit from the MitraClip procedure. So, the safety and effectiveness of MitraClip System could be inferior to (or not superior to) the results of this systematic review in real clinical practice. Another potential for bias is the choice of outcomes and the method of outcome adjudication. Therefore, the results should be always interpreted with caution when non-randomized studies have been evaluated in meta-analyses.

Conclusions

1. MitraClip procedure achieves apparently short-term (safety) and long-term (effectiveness) survival to surgical MV repair despite MR pathology or higher risk profiles (older patients, lower LVEF).
2. Residual MR appears to occur more frequently after MitraClip therapy than

surgery, especially in younger patients (<70 yrs, 11.74-fold vs. 6.47-fold), functional MR patients (5.7-fold vs. 6.47 fold), and patients whose LVEF<50%. That is, surgery is more effective to reduce MR severity in the early post procedure period and the true advantage (effectiveness) of MitraClip therapy may be greater in older patients and patients with degenerative MR and those with LVEF≥50%.

3. The odds ratio of 30-day major adverse event is lower in older patients and patients whose LVEF≥50%, indicating that MitraClip may be able to provide more benefits (safety) to older patients and patients whose LVEF⩾50%.
4. The generalizability and implication of this systematic review must be regarded with caution as observational studies can have biases and confounders which could not be minimized in the analysis. Because investigators consciously or non-consciously chose patients in the intervention arm whom they thought would more benefit from the MitraClip procedure in the included non-randomized observational studies, the safety and effectiveness of MitraClip System could be inferior to (or not superior to) the results of this systematic review in clinical practice. Future well designed randomized controlled trials with more consistent reporting of outcomes and adequate sample size and length of follow-up period will better evaluate the clinical benefits of the MitraClip System.

Chapter Three: Cost-effectiveness Analysis of MitraClip System in High Surgical Risk Patients with Significant Mitral Regurgitation in U.S. Settings

Introduction.

Mitral regurgitation (MR), the second most common valvular heart disease after aortic stenosis, is a serious condition with significant morbidity and mortality[10]. Patients with severe symptomatic MR have a poor prognosis, with an annual mortality rate without surgical procedure being about 6% and is reported to be as high as 60% within five years[11,30]. Conservative medical options are limited and show no prolonged survival[4]. Surgical mitral valve repair (MVR) is generally considered the standard treatment for MR; however, randomized studies documenting the outcomes and long-term follow-up are still lacking[31-33].

Since a significant number of patients with severe MR (49%) are not treated due to age, reduced left ventricular (LV) function, co-morbidities, or other contraindications to open mitral valve surgery[34], less invasive percutaneous transcatheter MVR procedures have been developed. The MitraClip system (Abbott Vascular-Structural Heart, Menlo Park, CA, USA) is an approved system in Europe and North America for transcatheter MVR. With this technique, both mitral valve leaflets are attached with one or more clips, resulting in a so-called “doubleorifice mitral valve.” However, there are only a limited number of patients studied. The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) I trial, first conducted in 2004, demonstrated the safety, feasibility and significant hemodynamic improvement of the MitraClip[17]. Following the success of EVEREST I, EVEREST II, a

randomised controlled trial (RCT) of 279 surgical candidates with grade 3+ or 4+ MR, randomised in a 2:1 design to the MitraClip system (n=184) or MV surgery (n=95), was conducted[3]. The 30 day mortality in MitraClip arm and conventional surgery arm were 1% and 2%, respectively. Patients were then followed up for 12 month mortality and clinical outcomes. The 12 month mortality in MitraClip arm and conventional surgery arm were 3% and 7%, respectively. The New York Heart Association (NYHA) functional class I and II were seen in 98% of the device group and 87% of the surgical group at 12 month endpoint. Although major adverse events were significantly lower in the device group (15% vs 48%), this difference was almost entirely attributable to the inclusion of transfusion ≥ 2 units of blood as an adverse event. The efficacy of MitraClip and surgery was similar, with 21% of MitraClip patients and 20% of surgery patients still suffering from grade 3+ or 4+ MR at 12 months. Other than that, many observational studies report similar feasibility, efficacy, and safety results using the MitraClip device in patients with severe MR[6,25,29, 35-52].

A recent meta-analysis[53] analyzing the safety, clinical effectiveness, and survival outcomes of MitraClip system compared with MV surgery in patients with severe MR highlighted the need for safer alternatives in patients at high risk for mitral valve surgery and supported the indication for MitraClip therapy in these patients. This systematic review indicated that treatment with the MitraClip system in patients with severe MR was associated with similar mortality and symptomatic improvement as MV surgery and was a potential treatment option for up to half of

all patients with severe symptomatic MR who are not tolerant to surgery.

Even though the MitraClip system is a potential alternative for high surgical risk patients with severe MR, it is an expensive procedure compared to current standard of care (SOC, surgery and medical management). Therefore, despite promising clinical results, the costs, cost-effectiveness and cost-utility of MitraClip system therapy must be evaluated to support decisions regarding the efficient allocation of healthcare resources in the United States. The objective of this study is to conduct a cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) from the perspective of the American payers to compare the costs and benefits of MitraClip system treatment to current standard of care in high surgical risk patients with severe MR.

Methods

Microsoft Excel was used to construct the decision analytic model to estimate the long-term benefits, costs, cost effectiveness and cost utility of MitraClip system therapy compared to current standard of care (SOC, All SOC patients were treated according to standard of care over the 12-month period, with 86% managed medically and 14% undergoing MV surgery) for high surgical risk patients with severe MR. The analysis was performed for a five-year time horizon from the perspective of the American healthcare payers. Treatment-specific overall mortality, risk of clinical adverse events, and quality-of-life data for the CEA and CUA were obtained from the EVEREST II HRS[9]. The analysis included direct medical costs borne by the American payers. All the disease and treatment-related cost were obtained

from the U.S. Medicare Diagnosis-related group (DRG). Health utility estimates and unit costs (expressed in 2017 U.S. dollars) were taken from the U.S. cost databases and published literatures. Costs were discounted at a rate of 5% per year (It can be converted to monthly discounting rate 0.41% which was used in the monthly cycle calculation). Final outputs of the analysis included the incremental cost per life year (LY) gained and the incremental cost per quality adjusted life year (QALY) gained for MitraClip system treatment compared to current SOC. The impact of alternative assumptions was tested in one-way sensitivity analyses. A probabilistic sensitivity analysis was performed to characterize uncertainty in the model parameters

Model Description

In the Markov health state transition model (Appendix 11), all patients started the model in the "alive" health state, where patients in the MitraClip arm of the model received the MitraClip procedure and patients in the current SOC arm of the model took conventional mitral valve repair surgery or treated with medication. In each model cycle, patients either stayed in the "alive' health state or transitioned to the "dead" health state. Transition probabilities representing movement from "alive" to "dead" were calculated from treatment-specific mortality from the EVEREST II HRS. The analysis was carried out using a monthly cycle length in order to capture the timing of all relevant outcomes/hospitalization and costs associated with the MitraClip system treatment and current SOC treatment.

Patients in the "alive" states were stratified by NYHA functional class so that health-related quality-of-life (QoL) and health utility associated with disease

severity could be taken into consideration in the CUA[54]. Health utility decrements from the literature were applied to the MitraClip procedure and current SOC. Patients in MitraClip arm and current SOC arm were also at risk of major comorbidity/complication (MCC) or comorbidity/complication (CC) during hospitalization, such as major vascular complication, major bleeding complication, and major adverse events (e.g., myocardial infarction, stroke, renal failure, etc.) were taken from the EVEREST II HRS. For the MitraClip group, resource utilization and costs associated with the MitraClip procedure, periprocedural MCC/CC were included in the analysis according to the DRG billing system. For the current SOC group, resource utilization and costs associated with mitral valve surgery (14%) / medical management (86%), in-hospital MCC/CC were included in the analysis according to the DRG billing system. There were 26.9% of patients had MCC during initial hospitalization in the MitraClip arm. In the SOC arm, there were 48% of patients had MCC in the MV surgery group and 41% of patients who were managed medically had MCC. As EVEREST II HRS only reported MCC rate in each group, a 50% incidence of CC was applied within non-MCC patients in the base case analysis. Sensitivity analysis was also used to determine the impact of the uncertainty. Cost for CHF hospitalization, MV surgery and MitraClip reoperation from EVEREST II HRS was applied in the analysis. The 12-month post-procedure annual CHF-related hospitalization rate of 0.36 was used in the model for the MitraClip treatment group. The annual rate of CHF-related hospitalization was not reported for the current SOC group included in the EVEREST II HRS. Thus, the annual rate of CHF-related

hospitalization for MitraClip patients reported for the 12 months prior to the MitraClip procedure (0.65), assumed to be a reasonable estimate of the rate of CHF hospitalization in the current SOC group, was utilized in the base case analysis. The CHF hospitalization rate was applied for the duration of the analysis. The 1-year probability of MV surgery (including mitral valve repair or replacement surgery) was also taken from the EVEREST II HRS and was 0% for the MitraClip arm and 14% for the current SOC arm. The 1-year probability of MV surgery was applied in the first cycle of the model only. EVEREST II HRS reported that one patient (1.28%) experienced MitraClip device attachment to a single leaflet during the procedure and underwent a successful second MitraClip procedure 6 weeks later for placement of a second device. The MitraClip reoperation rate was applied in the first 12 month analysis only.

Overall survival

Monthly transitions that informed the proportion of patients that remained in the "alive" health state and the proportion of patients that transitioned to "all-cause mortality" were informed directly by 30 day and 12 month mortality data from the EVEREST II HRS. The published results of the EVEREST II HRS provided 30-day and 12-month survival data for the MitraClip and current SOC groups[9]. As the EVEREST II HRS only provided Kaplan-Meier survival curves in the first twelve months following the initial procedure/hospitalization, Weibull function was applied to extrapolate the overall survival from the clinical trial to five-year time horizon. The cumulative survival estimates were extrapolated into the future and used to

derive monthly transition probabilities. The study reported that there were 6 patients out of 78 (7.7%) and 19 patients out of 78 (24.4%) died at 30 day endpoint and 12 month endpoint respectively in the MitraClip arm, and 3 out of 36 patients (8.3%) and 16 out of 36 patients (44.4%) died at 30 day endpoint and 12 month endpoint respectively in the current SOC arm. The monthly death rate was evaluated using Weibull regression calculated using 30 day endpoint and 12 month endpoint mortality. The assumption of 0% of mortality after the first year following initial treatment was applied in the base case analysis. The modelled survival extrapolated using Weibull function was applied in the sensitivity analysis.

Clinical outcomes

During the initial hospitalization, MitraClip and SOC patients were at risk of MCC such as myocardial infarction (MI), major stroke, renal failure, mechanical ventilation >48 hours, gastrointestinal (GI) complication requiring surgery, sepsis, and blood transfusion requiring 2 units of blood. The probabilities for these MCCs were reported in the EVEREST II HRS for the 30-day periprocedural period following the MitraClip procedure or MV surgery or initial hospitalization. The probability of MCC was applied in hospitalization cost using the 30-day periprocedural adverse event rate.

NYHA functional class

The NYHA functional classification characterizes the extent of heart failure by placing patients in one of four categories based on the degree of limitation during daily physical activities and experience of symptoms of cardiac insufficiency. The

limitations/symptoms are in regards to fatigue, shortness of breath, angina pain, and palpitations. NYHA class I is representative of patients with cardiac disease, but no symptoms and no limitation in ordinary physical activity (e.g., shortness of breath when walking, climbing stairs, etc.). NYHA class II is representative of patients with mild symptoms (e.g., mild shortness of breath and/or angina) and slight limitation during ordinary activity. NHYA III characterizes patients with marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g., walking short distances of 20-100 metres), and NYHA IV is associated with severe limitations and symptoms even while at rest. NYHA class was used in the model to assign health utility to patients during each cycle. NYHA class for patients in the MitraClip and current SOC group was reported as four categories, which were NYHA I, II, III and IV, in the EVEREST II HRS. In the MitraClip arm, 0% of the patients were NYHA class I, 11% were NYHA class II, 59% were NYHA class III and 30% were NYHA class IV at baseline. In the current SOC arm, 3% of patients were NYHA class I, 13% were NYHA class II, 65% were NYHA class III, and 19% were NYHA class IV at baseline. After 12 month follow-up period, there were 33% of MitraClip patients were NYHA class I, 41% were NYHA class II, 24% were NYHA class III and 2% were NYHA class IV. In the current SOC arm, the NYHA class was assumed to be constant.

The percentage breakdown of patients by NYHA functional class was assumed to remain the same (monthly transition rate was equal) until 12^{th} month in the analysis. After 12 month, the proportion of NYHA class sustained in the two arms since both groups showed an improvement in NYHA functional class from baseline

to 12 months, which was sustained at 4 years[6]. Therefore, the monthly transition probabilities in MitraClip arm and SOC arm were cycle number power of 1.013 and cycle number power of 1 for the first 12 month, respectively, and remained the same after.

Quality-of-life and health utility

Patients in the "alive" state were assigned health utility based on NYHA class. For the base case analysis, health state utilities for NYHA functional class were taken from a heart failure population reported by Gohler et al[55]. The authors reported a health utility of 0.90 for NYHA class I, 0.83 for NYHA class II, 0.74 for NHYA class III, and 0.598 for NYHA class IV. The utility estimates from Gohler et al. were selected as the most appropriate set of values for the base case analysis, as this study was recent and included a large number of American patients (n=6,232), included a population of patients that were most similar to the patients enrolled in the EVEREST II HRS (i.e., heart failure patients), and provided a complete set of health utility estimates (i.e., a utility estimate for each of the NYHA classes).

Resource use and unit costs

The CEA and CUA incorporated all resource utilization and costs associated with the MitraClip procedure or MV surgery or medical management and in-hospital MCC/CC management according to U.S. MS DRG billing system (Table 7). No indirect costs such as out of pocket costs borne by the patient and/or caregiver or productivity losses were included in the analysis. Resource utilization was calculated based on the EVEREST II HRS following the MitraClip procedure or MV

surgery or medical management, post-procedural/operative complications and adverse events. All Costs associated with the in-hospital payment for MitraClip procedure, MV surgery and medical management for CHF are summarized in Table 7.

Sensitivity analyses

One-way deterministic sensitivity analyses were performed to test the impact of alternative assumptions regarding the time horizon, discount rate and mortality after the first year. A probabilistic sensitivity analysis was performed to determine the impact of uncertainty using the variability around point estimates used in model parameter (proportion of patients with CC in each group) in five-year time horizon. Results were presented using a scatter plot of 1,000 runs.

Results

Base case analysis

The survival curve under the assumption that 0% of mortality after the first year following initial treatment in presented in Figure 2A. The modelled survival extrapolated using Weibull function is presented in Figure 2B. The detailed results of the base-case analysis are shown in Table 8. Overall, MitraClip therapy resulted in greater life years (LYs), QALYs, and costs compared to current SOC. In a five-year time horizon, the total costs for MitraClip therapy and SOC are US $58,280.43 and $31,756.28, respectively; and costs for CHF hospitalization after MitraClip therapy and SOC are $7,065.86 and $15,590.21, respectively. Compared to patients in the current SOC group, MitraClip therapy patients gained on average 0.94 life years (LYs)

(half cycle correction was applied in the calculations) and 0.97 QALYs in a five-year tome horizon, but incurred additional costs ($26,524.15) for an incremental cost-effectiveness ratio (ICER) of $28,217.18 per life year gained, and $27,344.48 per QALY gained. The analysis was primarily driven by improved survival and health utility in the MitraClip group.

Deterministic sensitivity analyses

The results of the one-way sensitivity analysis scenarios are shown in Table 9. Overall, the model was sensitive to time horizon and long-term survival. Alternative assumptions regarding time horizon led to a large impact on the ICER. In the base case analysis, alternative time horizons demonstrated the sensitivity of the model to duration of the analysis, with shorter time horizons increasing the ICER. Time horizons of 2 and 10 years led to ICERs of $96,531.25 and $10,070.05 per QALY, respectively.

The ICER increased to $29,992.54 when modelled survival using Weibull function applied in the sensitivity analysis, indicating that the ICER will be higher if mortality is higher in the SOC arm than MitraClip after the first year following the initial treatment.

Discount rates had slight impact on the ICER. Annual discount rate of 0% and 3% led to ICERs of $26,847.36 and $27,098.13 per QALY, respectively.

The probabilistic sensitivity analysis determining the impact of uncertainty (proportion of patients with CC in each group) using the distribution for each parameter in five-year time horizon showed that all of the cases were located in the

area in which the ICER is between $22,000 and $31,000 and the incremental QALY gained is between 0.7 and 1.3 year (Figure 3A). The cost-effectiveness acceptability curve (CEAC) is presented in Figure 3B. If the willingness-to-pay threshold is below $20,000, the probability of MitraClip being cost effective is zero (meaning SOC is a cost effective treatment for this patient population). If the threshold is set at typical $50,000 or above, then the probability of MitraClip being cost-effective increased to 1.0 [56].

Discussion

Major Findings

This study represents the first American CEA and CUA of mitral valve repair with the MitraClip system versus current SOC in high surgical risk patients with severe MR. In the base-case analysis the incremental cost per QALY gained and the incremental cost per LY gained were U.S. $27,344.48 and $28,217.18, respectively. The analysis was driven by a statistically significant advantage in overall survival and improvement of quality of life for patients receiving the MitraClip therapy compared to patients receiving SOC. Over a five-year time horizon, treatment with the MitraClip system resulted in a gain of 0.94 years of life and 0.97 quality-adjusted life years compared with current SOC.

One-way sensitivity analyses confirmed the sensitivity of the model to time horizon. Given that the costs for treatment with the MitraClip system are incurred within the first 30 days, while the health benefits accrue over the remaining time of the time horizon of the patient, a sensitivity analysis that utilized a shorter time

horizon of 2 years also resulted in a higher incremental cost per QALY gained for MitraClip therapy compared with current SOC ($96,531.25) and a longer time horizon of 10 years resulted in a lower incremental cost per QALY gained for MitraClip therapy compared with current SOC ($10,070.05). It seems that MitraClip therapy is getting more cost-effective as the patients live longer after treatment. However, because most of the patients in EVEREST II HRS were over 65 years old, MitraClip therapy is not feasible to be less cost and more effective in real life if other variables are constant. In addition, a subgroup analysis in EVEREST II HRS indicated that MitraClip therapy led to lower CHF hospitalization rate (as compared to SOC) in patients under 70 years old compared to those over 70. Therefore, MitraClip therapy might be more cost-effective in younger high surgical risk patients since the cost for CHF hospitalization would be reduced after treatment.

Furthermore, the results of CEA are not very sensitive to the annual discount rate. Lower annual discount rate led to lower ICERs of $26,847.36 (for 0%) and $27,098.13 (for 3%) per QALY, respectively.

Another CEA[57] from the perspective of UK payers showed that the MitraClip therapy was cost-effective in comparison to SOC with an ICER of £22,200/QALY (approx. 27,545.76 U.S. dollars) over a five-year time horizon, which is similar with the results of this analysis. However, this study also revealed that the results were most sensitive to the age of the patient and the presence of severe functional MR at baseline, which was not feasible to analyze in this study.

Limitations

The primary limitation of the CEA is that it used aggregate data from a relatively small sample size of MitraClip patients enrolled in the EVEREST II HRS (n=78), and a smaller number of retrospectively identified non-propensity matched patients in the current SOC group (n=36)[9]. Therefore, a group of data from a large randomized controlled trial that compare the safety and effectiveness of MitraClip system to current SOC (MV surgery and medical management) for high surgical risk patients with severe MR is necessary to improve this CEA and CUA.

In addition, in order to evaluate the cost-effectiveness of MitraClip system therapy compared with standard of care, Weibull regression analysis was required to extrapolate overall survival beyond the duration of the clinical study. Extrapolation of survival data is imprecise, and may result in under- or over-estimation of the true effectiveness of a given therapy.

Conclusions

Using the clinical data available from the EVEREST II HRS, this American CEA and CUA demonstrated that mitral valve repair with the MitraClip system was cost-effective vs current SOC in high surgical risk patients with severe MR. In the base-case analysis the incremental cost per QALY gained and the incremental cost per life year gained were $27,344.48 and $28,217.18, respectively. The cost per QALY falls below the typical threshold of $50,000 U.S. dollars per QALY gained which is often cited as representing good value for money in the United States [56]. However, the probability of MitraClip being cost effective is zero (meaning SOC is a cost effective treatment for this patient population) if the willingness-to-pay threshold is

below $20,000. The results from clinical trials indicate that the MitraClip device can reduce the severity of MR and improve quality-of-life in patients who are not considered as suitable candidates for MV surgery. The results of this analysis demonstrate that MitraClip therapy also offers a cost-effective option for these patients.

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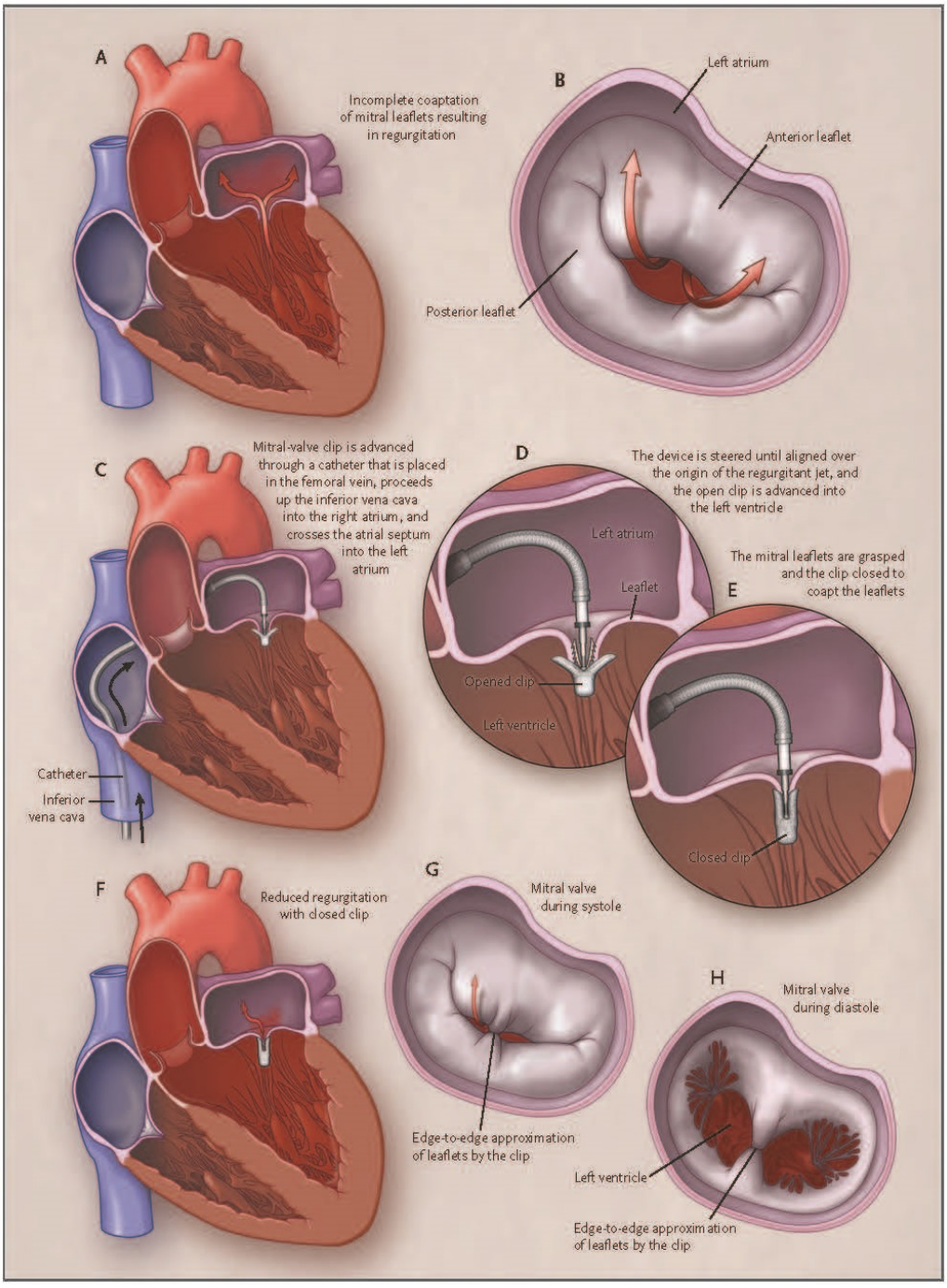
Figures, Tables and Appendice

Figure 1: Percutaneous Repair of Mitral Valve [3].



N ENGL J MED 364;15 NEJM.ORG APRIL 14, 2011

In patients with mitral regurgitation resulting from incomplete leaflet coaptation (Panels A and B), percutaneous mitral-valve repair is performed by means of femoral venous and transseptal access to the left atrium to steer the device toward the origin of the regurgitant jet (Panel C). A mitral clip is passed through the mitral orifice from the left atrium to the left ventricle and pulled back to grasp the leaflet edges (Panels D and E). If reduction of the mitral regurgitation is satisfactory, the device can be locked and then released (Panel F). A double orifice is created in conjunction with reduction in mitral regurgitation (Panels G and H) [3]. The animation of the MitraClip procedure is also available at http://mitraclip.com/the_mitraclip_procedure

Appendix 1: Literature Search Strategy

Embase 1974 to 2017 February 17, Database Info Icon OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. (Mitraclip* or Mitralclip* or (mitra adj clip*) or (mitral adj clip*)).tw. (1954)
2. "Endovascular Valve Edge-to-Edge Repair".tw. (56)
3. ("edge-to-edge" and (endovascular* or percutaneous*)).tw. (532)
4. (Alfieri and (technique? or surger* or surgical* or repair*)).tw. (207)
5. 1 or 2 or 3 or 4 (2291)
6. Mitral Valve/su [Surgery] (14718)
7. Mitral Valve Insufficiency/su, th [Surgery, Therapy] (14397)
8. Mitral Valve Prolapse/su, th [Surgery, Therapy] (1925)
9. Mitral Valve Annuloplasty/ (2511)
10. ((mitral adj2 (valv* or insufficien* or incompeten* or prolaps* or regurgitat*)) and (surger* or surgical* or repair* or angioplast* or annuloplast* or catheter* or prothes?s or prosthetic* or plication*)).tw. (47952)
11. 6 or 7 or 8 or 9 or 10 (61707)
12. Surgical Instruments/ (38010)
13. (clip* or clamp*).tw. (235823)
14. Surgical Procedures, Minimally Invasive/is, mt [Instrumentation, Methods] (11081)
15. Heart Valve Prosthesis Implantation/is, mt [Instrumentation, Methods] (8325)
16. Cardiac Catheterization/is, mt [Instrumentation, Methods] (10354)
17. exp Endovascular Procedures/is, mt [Instrumentation, Methods] (37475)
18. exp Angioplasty/is, mt [Instrumentation, Methods] (18796)
19. Mitral Valve Annuloplasty/is, mt (522)
20. exp Suture Techniques/is, mt [Instrumentation, Methods] (4761)
21. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 (336132)
22. 11 and 21 (5532)
23. 5 or 22 (6971)
24. exp Animals/ not (exp Animals/ and Humans/) (15924458)
25. 23 not 24 (4928)
26. limit 25 to systematic reviews [Limit not valid in Embase; records were retained] 973
27. meta analysis.pt. (74673)
28. exp meta-analysis as topic/ (53801)
29. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (254243)
30. (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (299090)
31. exp Technology assessment, biomedical/ (21801)
32. (cochrane or health technology assessment or evidence report).jw. (31899)

33. 27 or 28 or 29 or 30 or 31 or 32 (539745)
34. 25 and 33 (70)
35. 26 or 34 (992)
36. (comment or editorial or interview or letter or news).pt. (3253766)
37. 35 not 36 (970)
38. implantable clip/ (1144)
39. (Mitraclip? or Mitralclip? or (mitra adj clip?) or (mitral adj clip?)).tw. (1901)
40. (Alfieri and (technique? or surger* or surgical* or repair*)).tw. (207)
41. "Endovascular Valve Edge-to-Edge Repair".tw. (56)
42. ("edge-to-edge" and (endovascular* or percutaneous*)).tw. (532)
43. 38 or 39 or 40 or 41 or 42 (2494)
44. mitral valve/su [Surgery] (14718)
45. mitral valve regurgitation/su, th [Surgery, Therapy] (19100)
46. mitral valve prolapse/su, th [Surgery, Therapy] (1925)
47. mitral annuloplasty/ (2753)
48. ((mitral adj2 (valv* or insufficien* or incompeten* or prolaps* or regurgitat*)) and (surger* or surgical* or repair* or angioplast* or annuloplast* or catheter* or prothes?s or prosthetic* or plication*)).tw. (47952)
49. 44 or 45 or 46 or 47 or 48 (63491)
50. exp clip/ (40504)
51. (clip* or clamp*).tw. (235823)
52. suturing method/ (29742)
53. (sutur* adj3 (method* or technique*)).tw. (16328)
54. 50 or 51 or 52 or 53 (299795)
55. 49 and 54 (3928)
56. 43 or 55 (5088)
57. exp animals/ or exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (45254137)
58. exp humans/ or exp human experimentation/ or exp human experiment/ (34987334)
59. 57 not 58 (10268431)
60. 56 not 59 (4950)
61. limit 60 to "reviews (maximizes specificity)" (59)
62. meta-analysis/ (233492)
63. "systematic review"/ (155057)
64. "meta analysis (topic)"/ (38308)
65. (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw. (254243)
66. (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or "review of reviews" or technology assessment* or HTA or HTAs).tw. (299090)
67. biomedical technology assessment/ (20693)
68. (cochrane or health technology assessment or evidence report).jw. (31899)

69. 62 or 63 or 64 or 65 or 66 or 67 or 68 (588079)
70. 60 and 69 (113)
71. 61 or 70 (114)
72. 37 or 71 (1039)
73. limit 72 to last 20 years (907)
74. remove duplicates from 73 (867)

Appendix 2: Study Flow Diagram

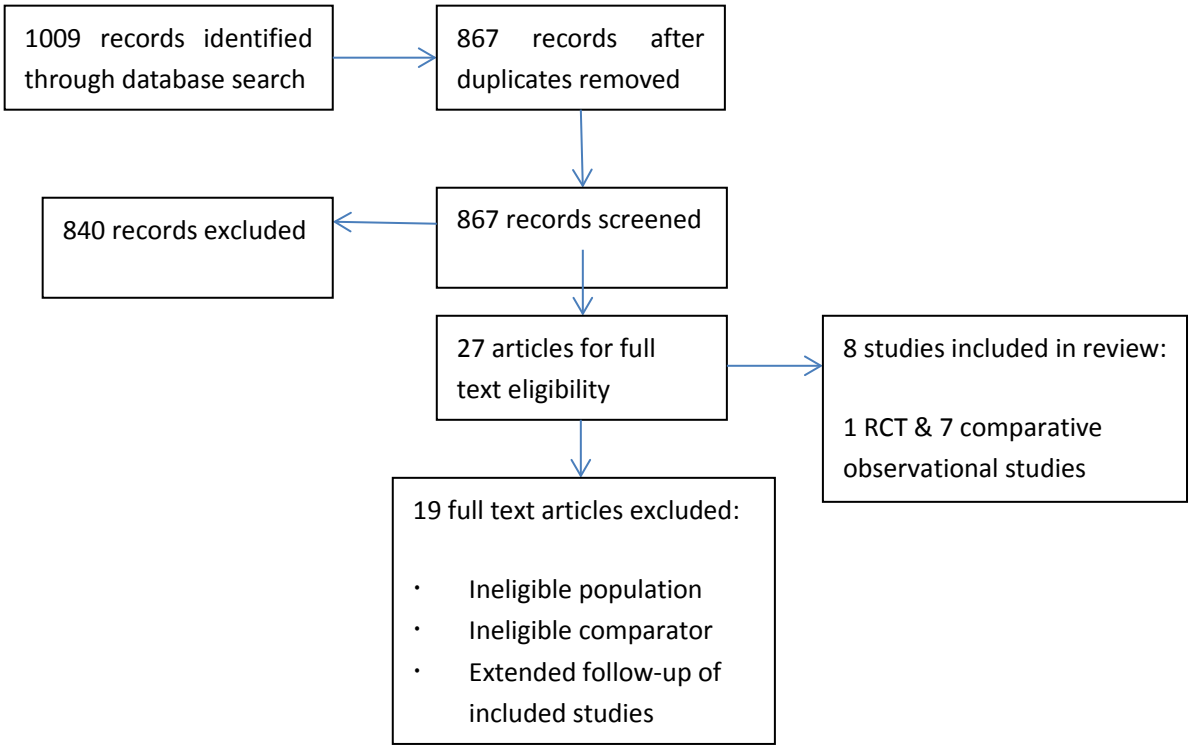


Table 1: characteristics of included studies.

Study	Study Design	Number of Patients		Age (years)		Male %		Mitral Valve Pathology (%)				MR Grade≥3 (%)		LVEF %	
								MitraClip		Surgery					
		MitraClip	Surgery	MitraClip	Surgery	MitraClip	Surgery	FMR	DMR	FMR	DMR	MitraClip	Surgery	MitraClip	Surgery
Feldman 2011 [9]	RCT	184	95	67.3±12.8	65.7±12.9	63	66	27	73	27	73	96	93	60.0±10.1	60.6±11.0
Taramasso 2012 [11]	Ret Cohort	52	91	68.4±9.2	64.9±9.8	83	77	100	0	100	0	-	-	27.7±10.0	38.6±11.3
Conradi 2013 [12]	Ret Cohort	95	76	72.4±8.1	64.5±11.4	64	45	100	0	100	0	100	99	36.2±12.5	42.1±16.2
Paranskaya 2013 [13]	Ret Cohort	24	26	80±5	63±12	42	65	33	67	27	73	100	100	57.9±6.9	58.8±8.2
Swaans 2014 [14]	Ret Cohort	139	53	74.6±9.4	70.2±9.5	68	51	79.5	20.5	63.2	26.8	100	100	36.8±15.3	43.9±14.4
Buzzatti 2015 [15]	Ret Cohort	25	35	84.5±3.2	81.9±2.0	-	-	0	100	0	100	-	-	59.8±9.9	61.6±8.0
De Bonis 2016 [16]	Ret Cohort	55	65	68.3±9.2	63.2±10.1	83.6	69.2	100	0	100	0	-	-	27.9±9.8	29.3±6.7
Ondrus 2016 [17]	Ret Cohort	24	48	75±9	76±4	75	56	100	0	100	0	-	-	31±9	30±7

Age and LVEF are expressed using mean ± standard deviation.
Ret Cohort: retrospective cohort study.

Table 2: Risk of bias assessment for RCT

Study	Overall Assessment of Study Risk of Bias						
	Sequence generation	Concealed allocation	Blinding Participants & Personnel	Blinding Outcomes	Incomplete outcome data	Selective reporting	Other bias (Confounding)
Feldman 2011	Low	Low	Low	Low[a]	Low	Low	High[b]

a: No blinding of outcome assessment, it could be a potential source of bias.

b: Some patients who underwent the MitraClip procedure later had additional surgical repair (21%) were counted in the intervention group.

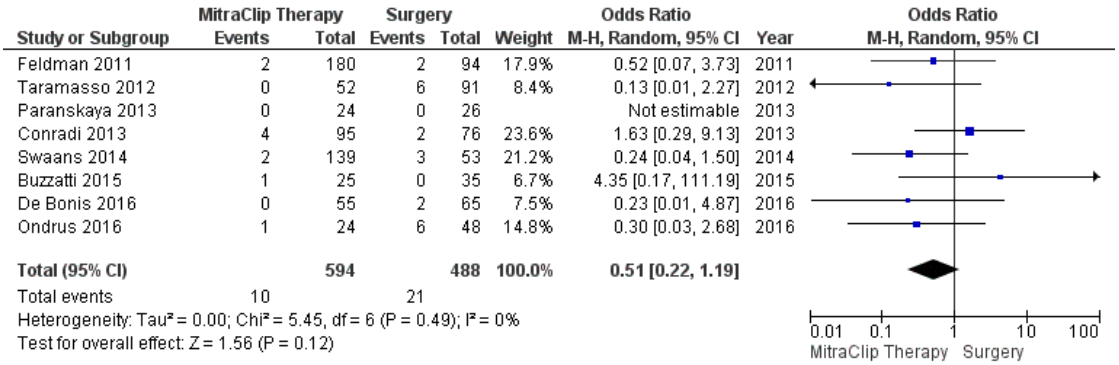
Table 3: Risk of bias assessment for observational studies.

Study	Overall Assessment of Study Risk of Bias							
	Selection				Comparability	Outcome		
	a	b	c	d	e	f	g	h
Taramasso 2012			★		★	★	★	★
Conradi 2013			★		★			
Paranskaya 2013			★		★	★	★	
Swaans 2014	★		★	★	★	★	★	
Buzzatti 2015			★		★		★	★
De Bonis 2016			★		★	★	★	★
Ondrus 2016			★		★		★	

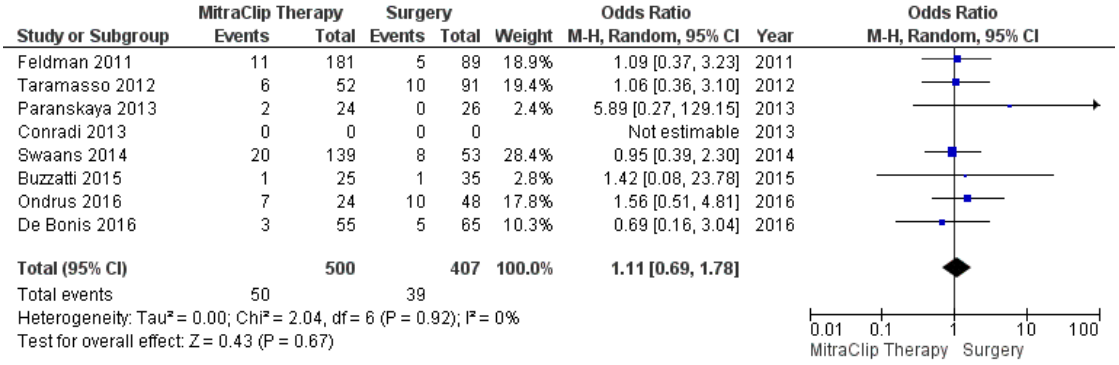
Low Risk	Unclear risk	High risk

Selection:
a: Representativeness of the exposed cohort;
b: Selection of the non-exposed cohort;
c: Ascertainment of exposure;
d: Demonstration that outcome of interest was not present at start of study.
Comparability:
e: Comparability of cohorts on the basis of the design or analysis.
Outcome:
f: Assessment of outcome;
g: Was follow-up long enough for outcomes to occur;
h: Adequacy of follow up of cohorts.

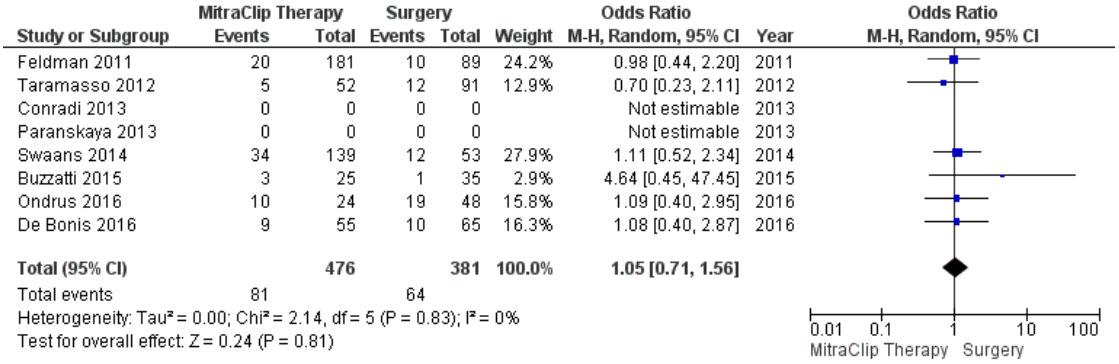
Appendix 3: Forest plots of mortality



Forest plot of the 30-day mortality (data is depicted using OR with 95% CI)

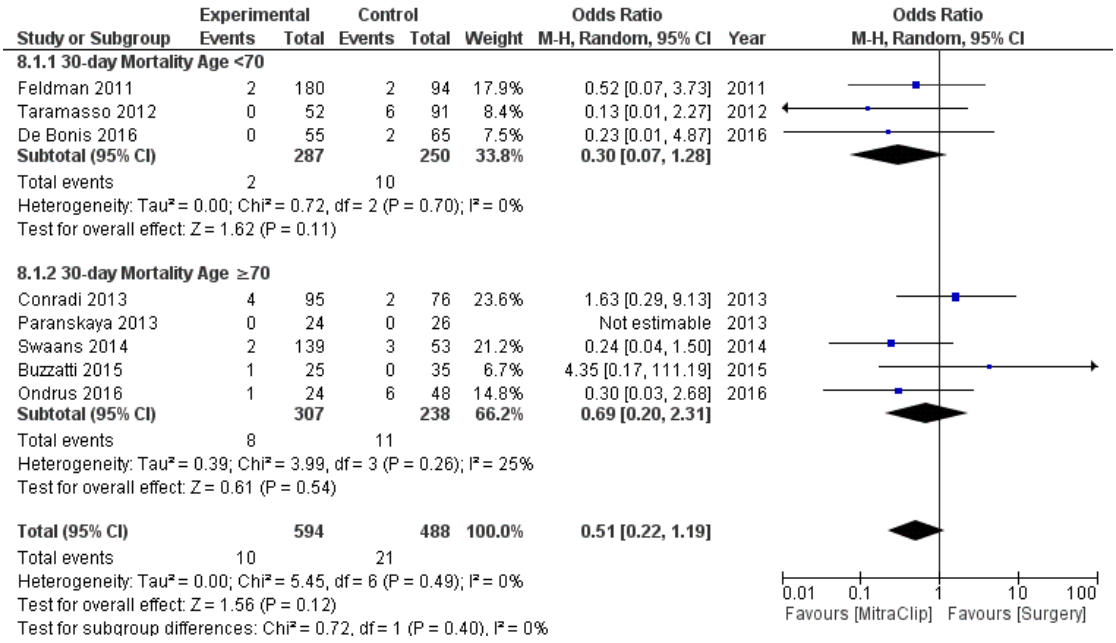


Forest plot of the one-year mortality (data is depicted using OR with 95% CI)

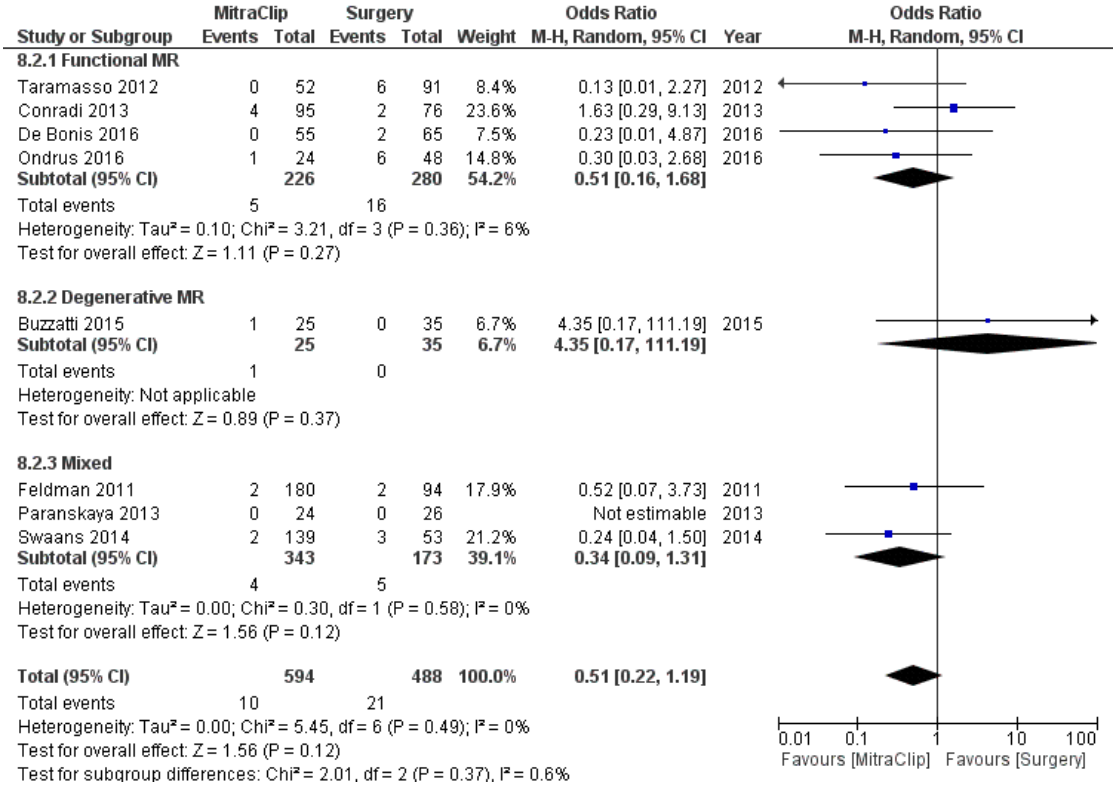


Forest plot of the two-year mortality (data is depicted using OR with 95% CI)

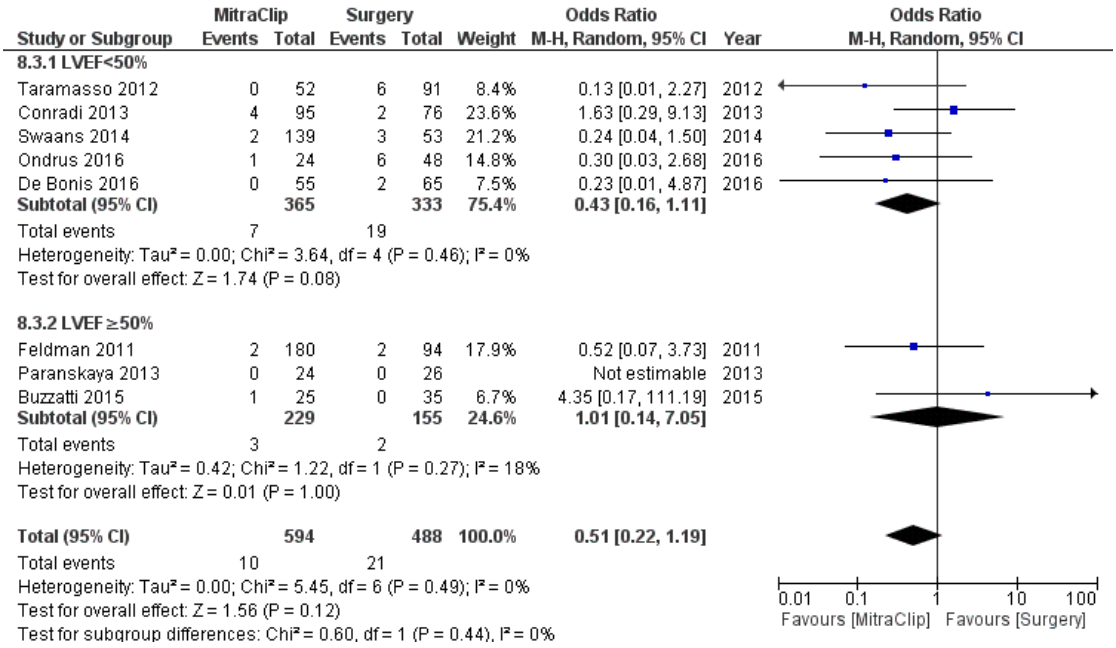
Appendix 4: Subgroup analysis of mortality



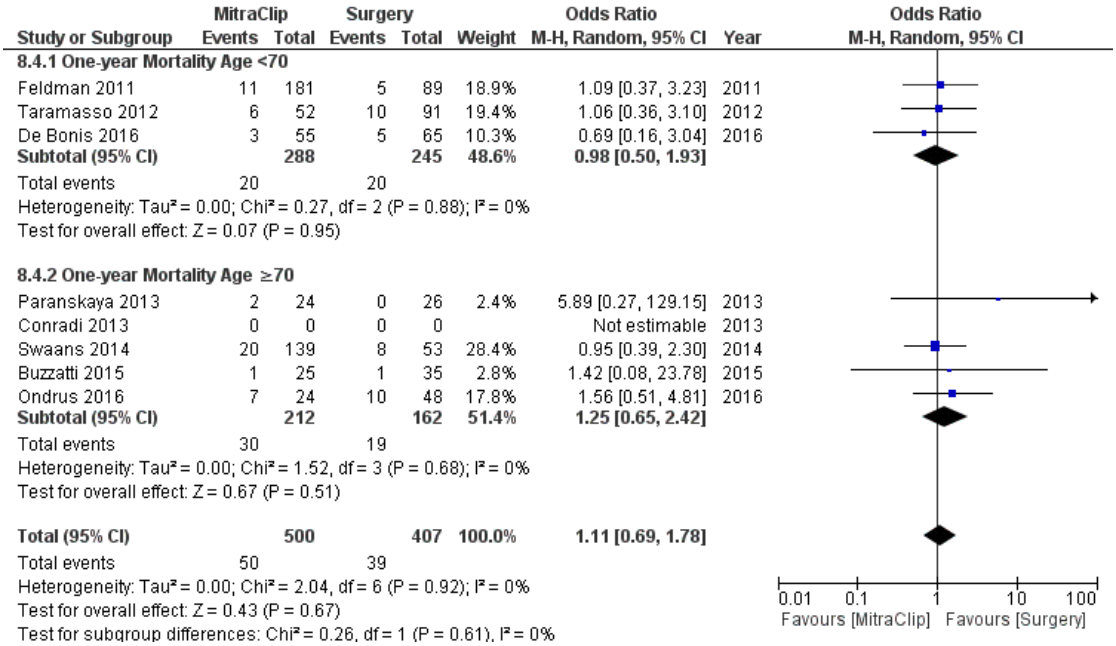
Subgroup analysis of 30-day mortality by patient's age (<70 yrs vs. ≥70 yrs).



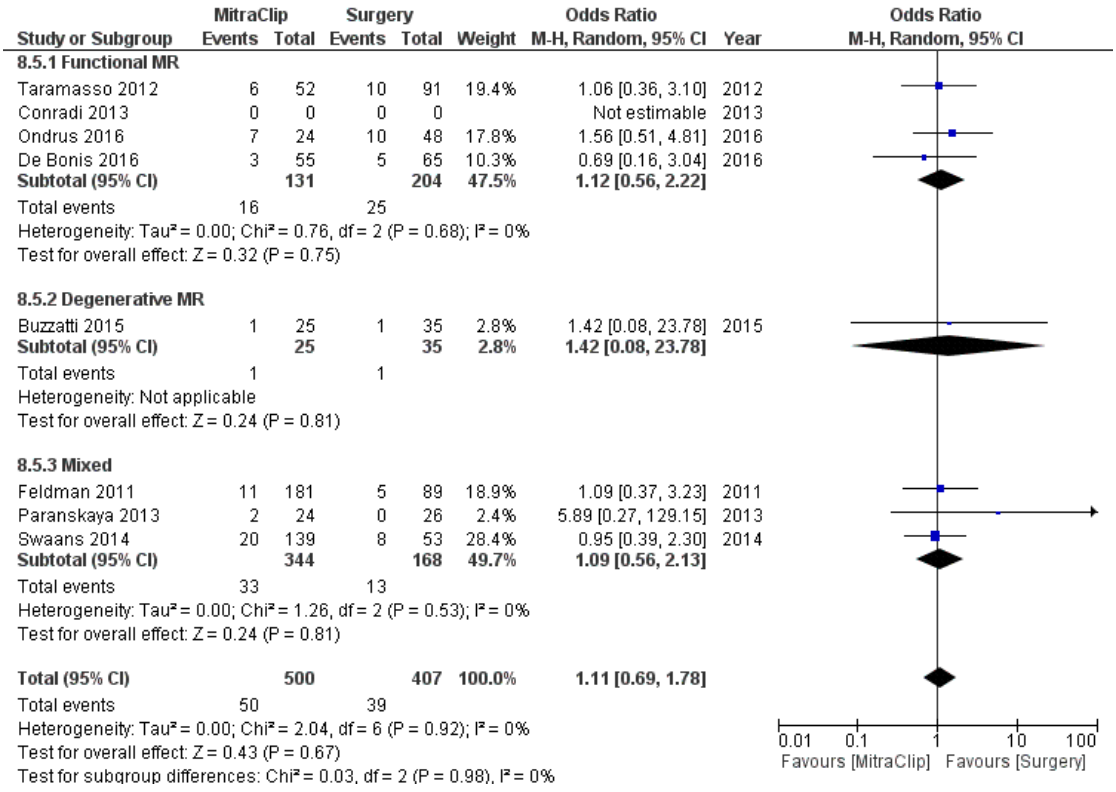
Subgroup analysis of 30-day mortality by MR pathology (functional MR vs. degenerative MR vs. mixed etiology).



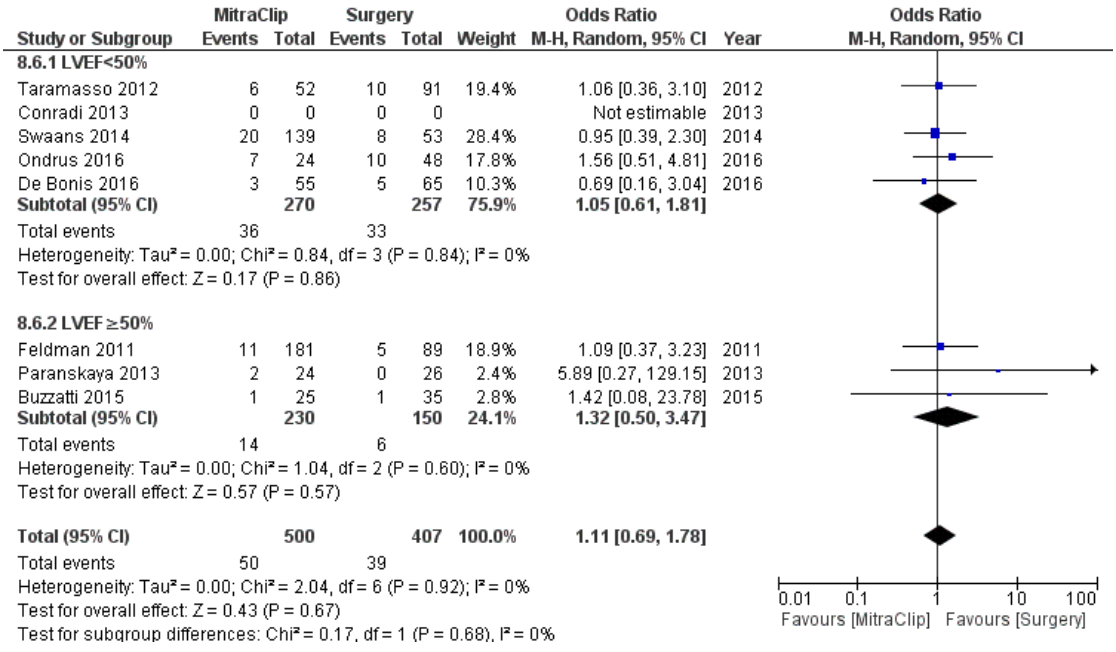
Subgroup analysis of 30-day mortality by LVEF (<50% vs. ≥50%).



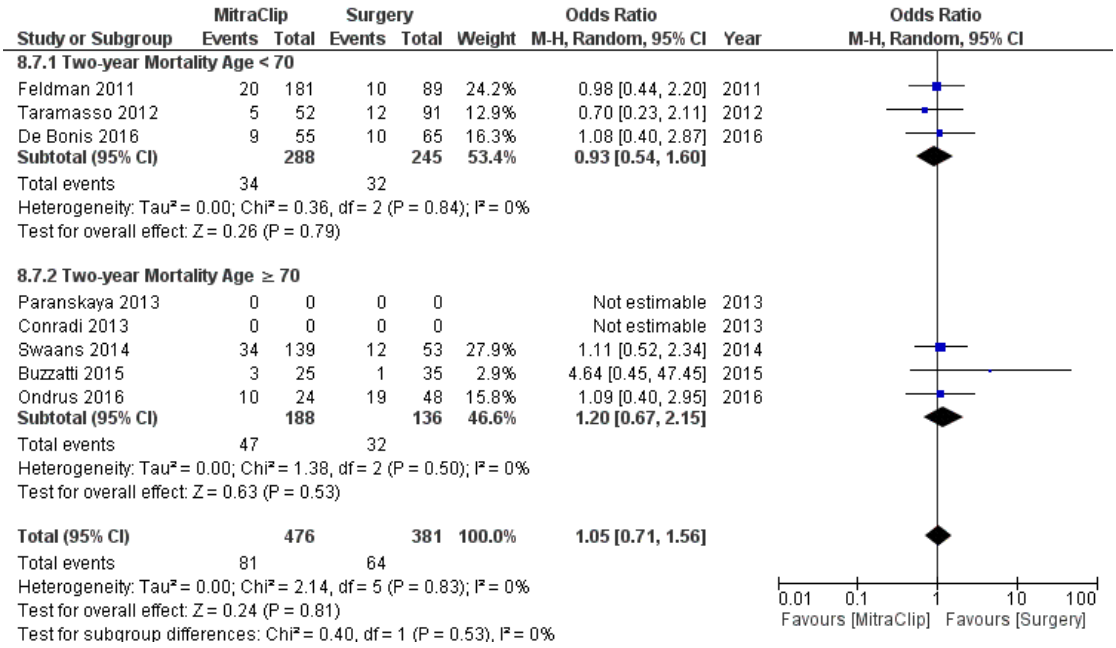
Subgroup analysis of one-year mortality by patient's age (<70 yrs vs. ≥70 yrs).



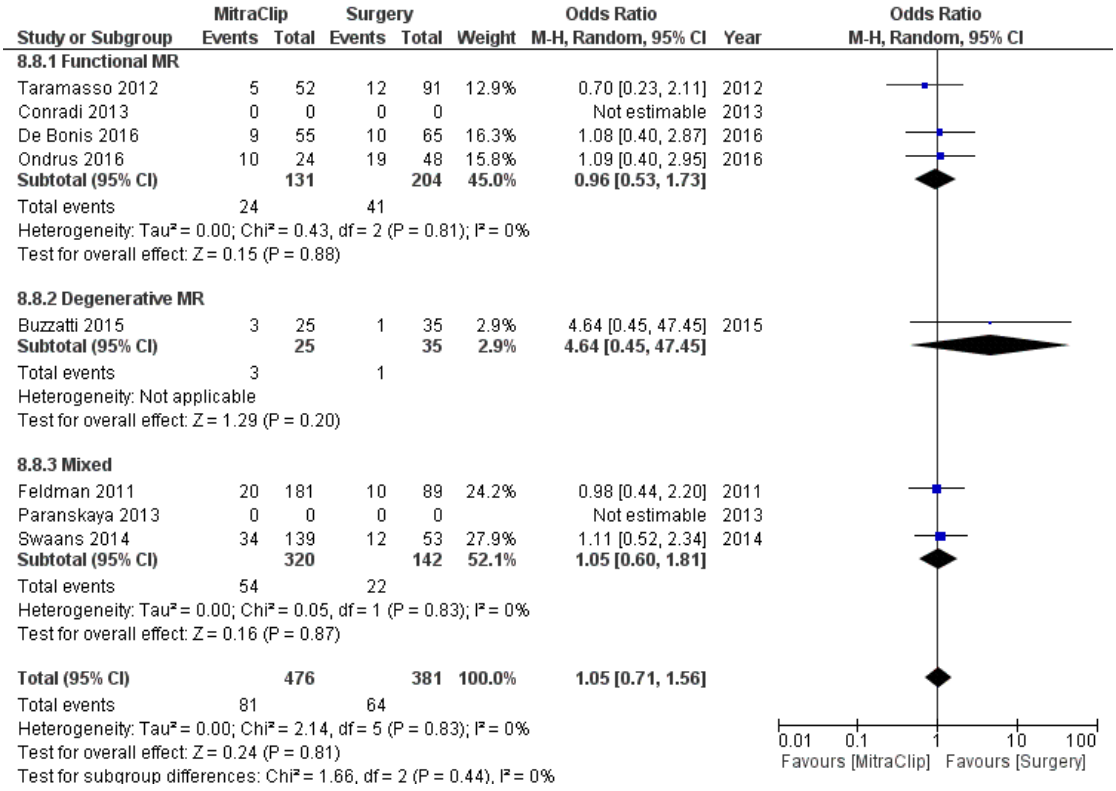
Subgroup analysis of one-year mortality by MR pathology (functional MR vs. degenerative MR vs. mixed etiology).



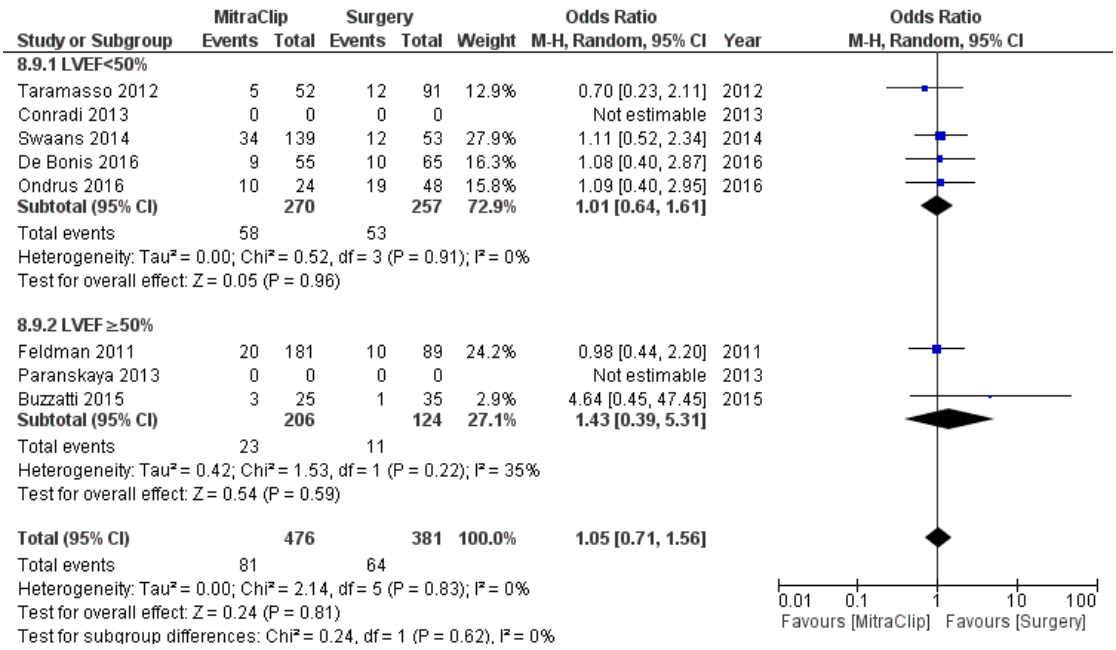
Subgroup analysis of one-year mortality by LVEF (<50% vs. ≥50%).



Subgroup analysis of two-year mortality by patient's age (<70 yrs vs. ≥70 yrs).



Subgroup analysis of two-year mortality by MR pathology (functional MR vs. degenerative MR vs. mixed etiology).

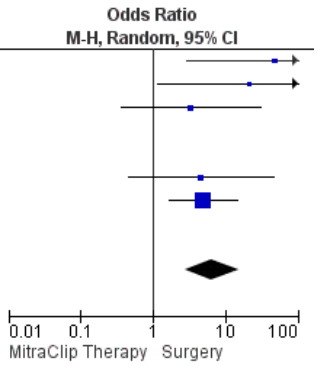


Subgroup analysis of two-year mortality by LVEF (<50% vs. ≥50%).

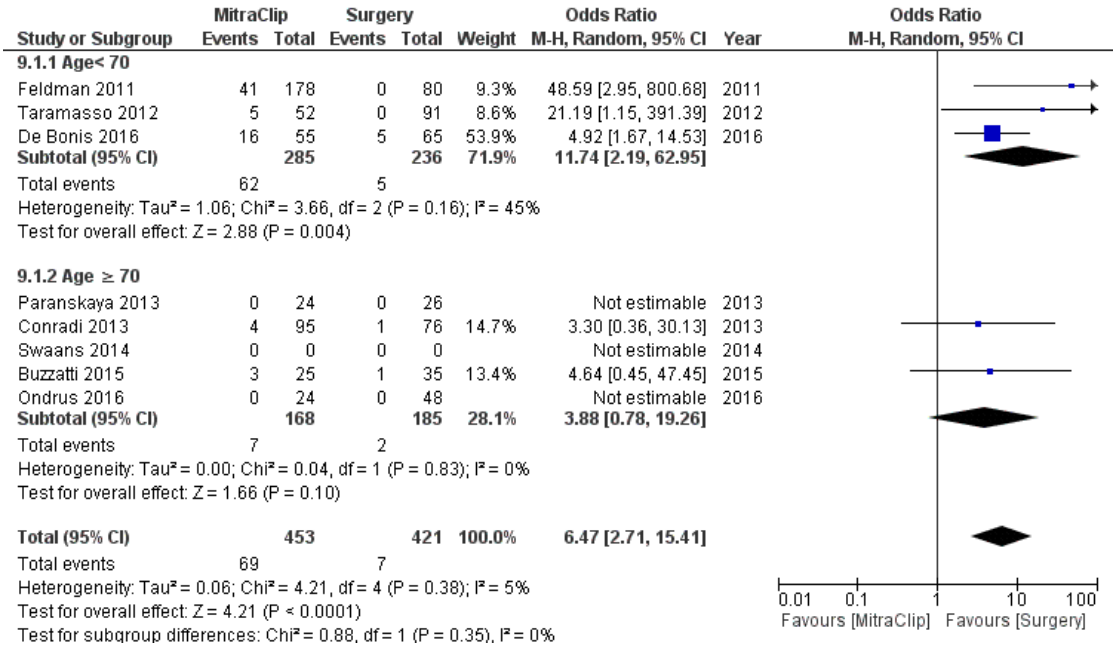
Appendix 5: Forest plot of the residual MR (data is depicted using OR with 95% CI)

Study or Subgroup	MitraClip Therapy Events	Total	Surgery Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Feldman 2011	41	178	0	80	9.3%	48.59 [2.95, 800.68]	2011
Taramasso 2012	5	52	0	91	8.6%	21.19 [1.15, 391.39]	2012
Conradi 2013	4	95	1	76	14.7%	3.30 [0.36, 30.13]	2013
Paranskaya 2013	0	24	0	26		Not estimable	2013
Swaans 2014	0	0	0	0		Not estimable	2014
Buzzatti 2015	3	25	1	35	13.4%	4.64 [0.45, 47.45]	2015
De Bonis 2016	16	55	5	65	53.9%	4.92 [1.67, 14.53]	2016
Ondrus 2016	0	24	0	48		Not estimable	2016
Total (95% CI)		**453**		**421**	**100.0%**	**6.47 [2.71, 15.41]**	
Total events	69		7				

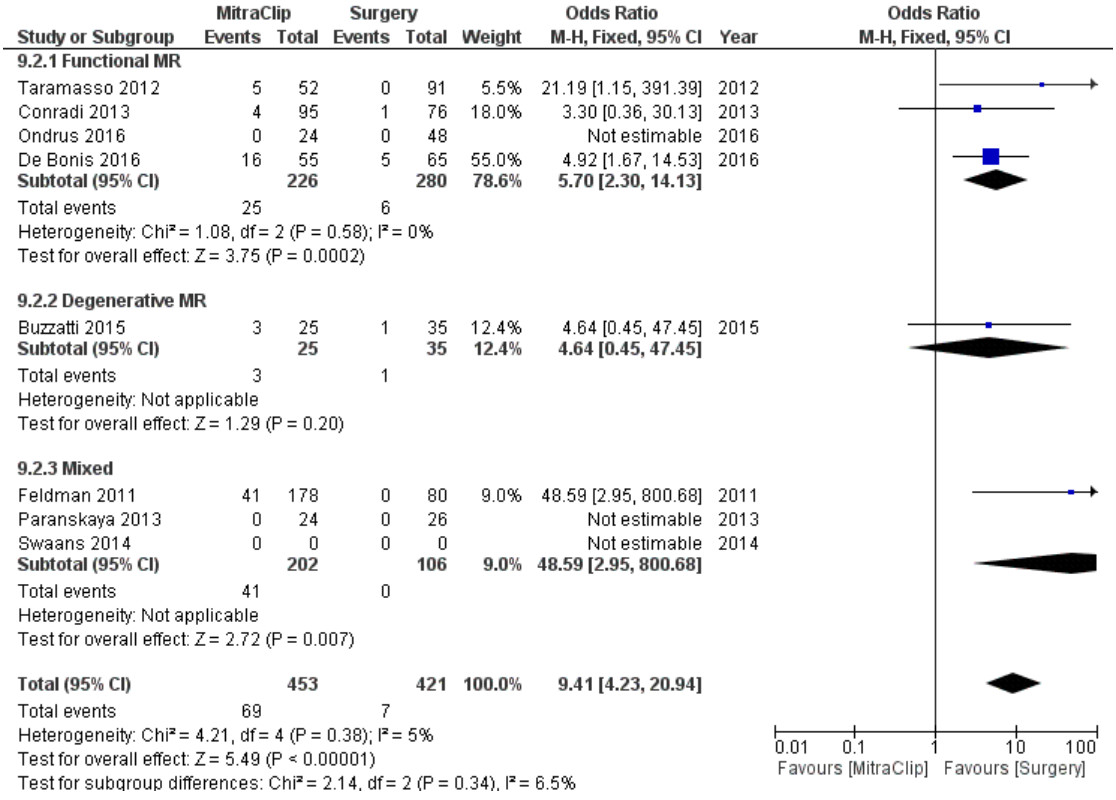
Heterogeneity: Tau² = 0.06; Chi² = 4.21, df = 4 (P = 0.38); I² = 5%
Test for overall effect: Z = 4.21 (P < 0.0001)



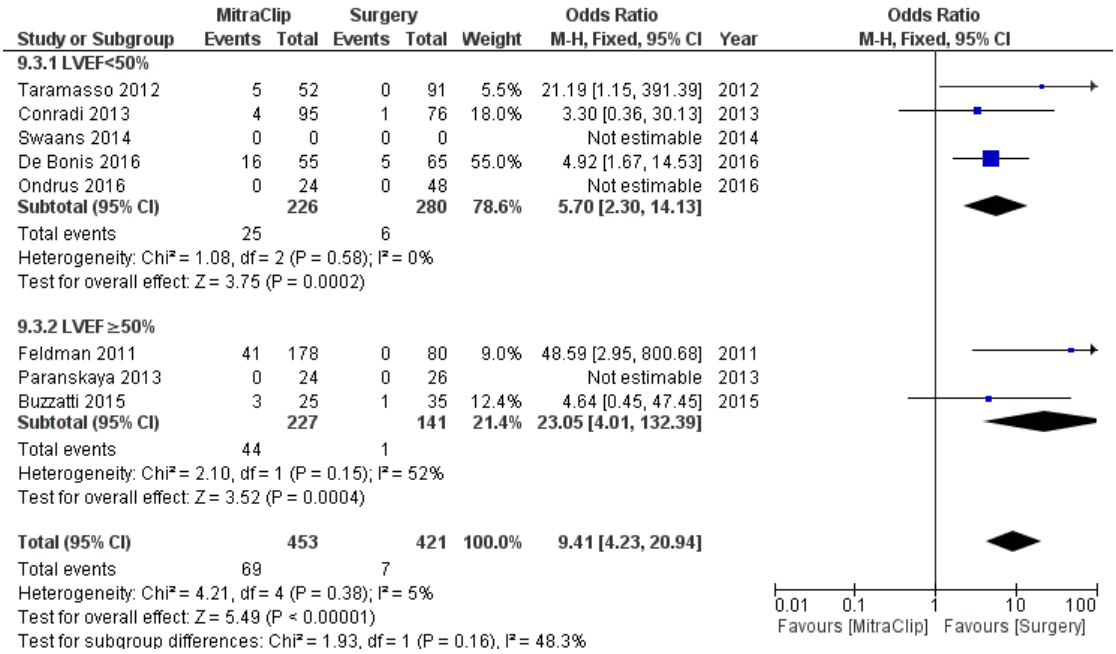
Appendix 6: Subgroup analysis and sensitivity analysis of residual MR.



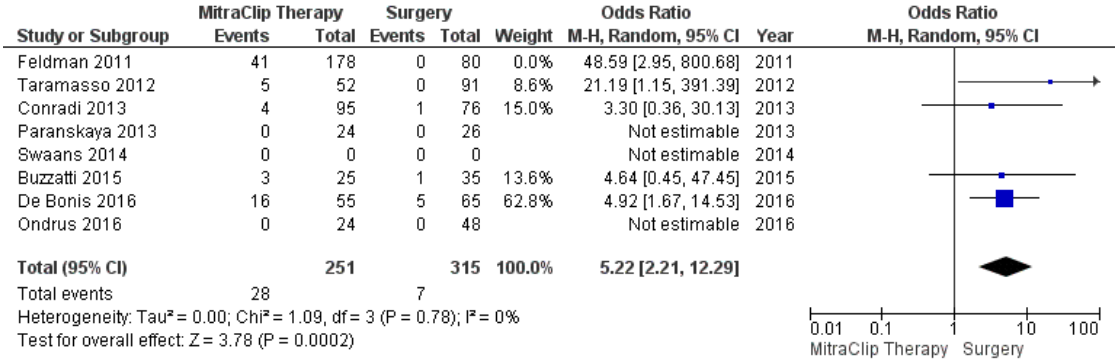
Subgroup analysis of residual MR by patient's age (<70 yrs vs. ≥70 yrs).



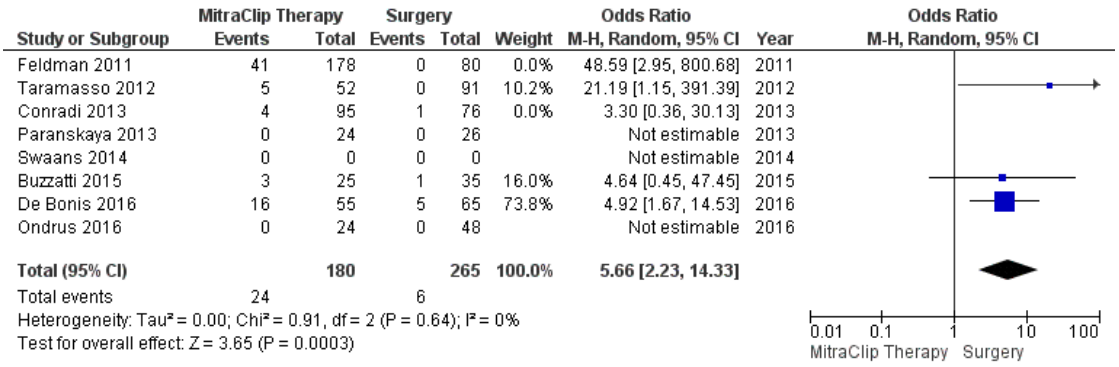
Subgroup analysis of residual MR by MR pathology (functional MR vs. degenerative MR vs. mixed etiology).



Subgroup analysis of residual MR by LVEF (<50% vs. ≥50%).



Sensitivity analysis of residual MR by eliminating the RCT

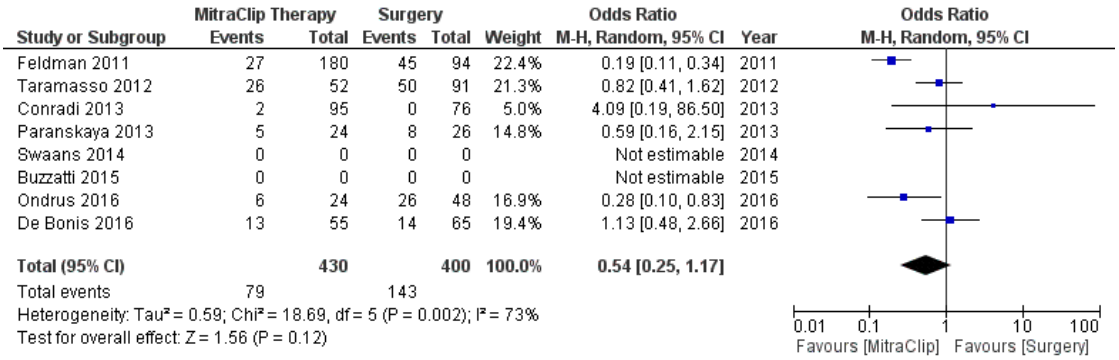


Sensitivity analysis of residual MR by eliminating the study with the lowest methodological quality (Conradi 2013) among observational studies.

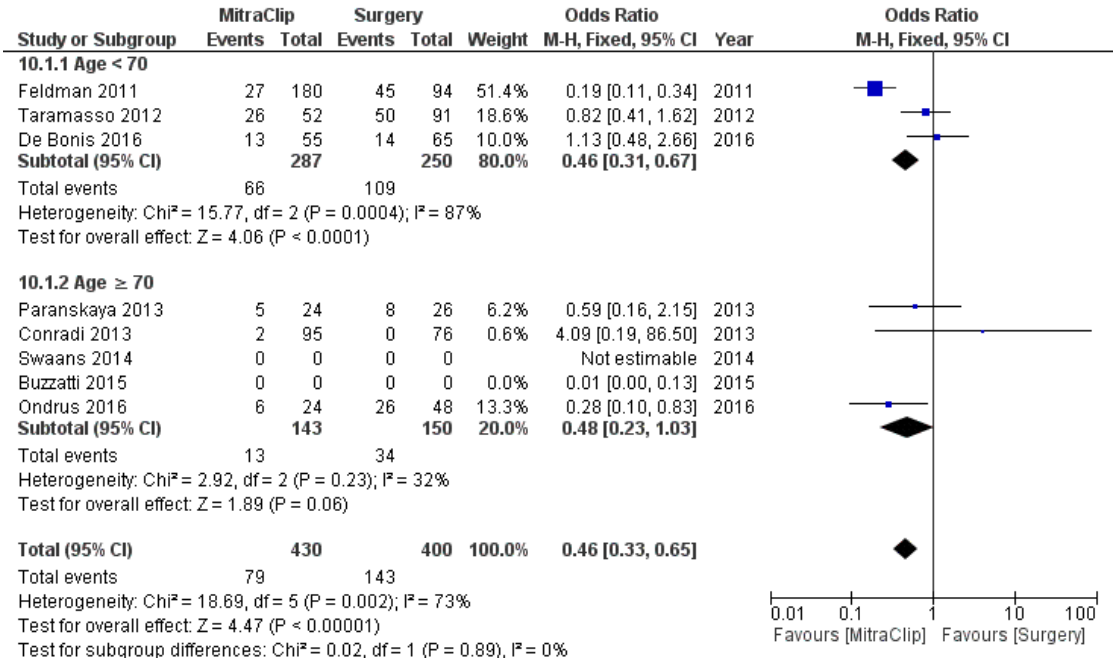
Table 4: Freedom of one-year and three-year recurrent MR.

Study	Recurrent MR > 2+			
	Freedom rate (%)			
	One-year		Three-year	
	MitraClip	Surgery	MitraClip	Surgery
Feldman 2011	82.1	100	78.3 (4 year)	75.3 (4 year)
Taramasso 2012	79.1	94	79.1 (2 year)	94 (2 year)
Conradi 2013	88 (6 months)	97 (6 months)	N/A	N/A
Paranskaya 2013	100	96.2	N/A	N/A
Swaans 2014	N/A	N/A	N/A	N/A
Buzzatti 2015	77.9	100	52.5	100
De Bonis 2016	N/A	N/A	81.4	96.5
Ondrus 2016	N/A	N/A	N/A	N/A

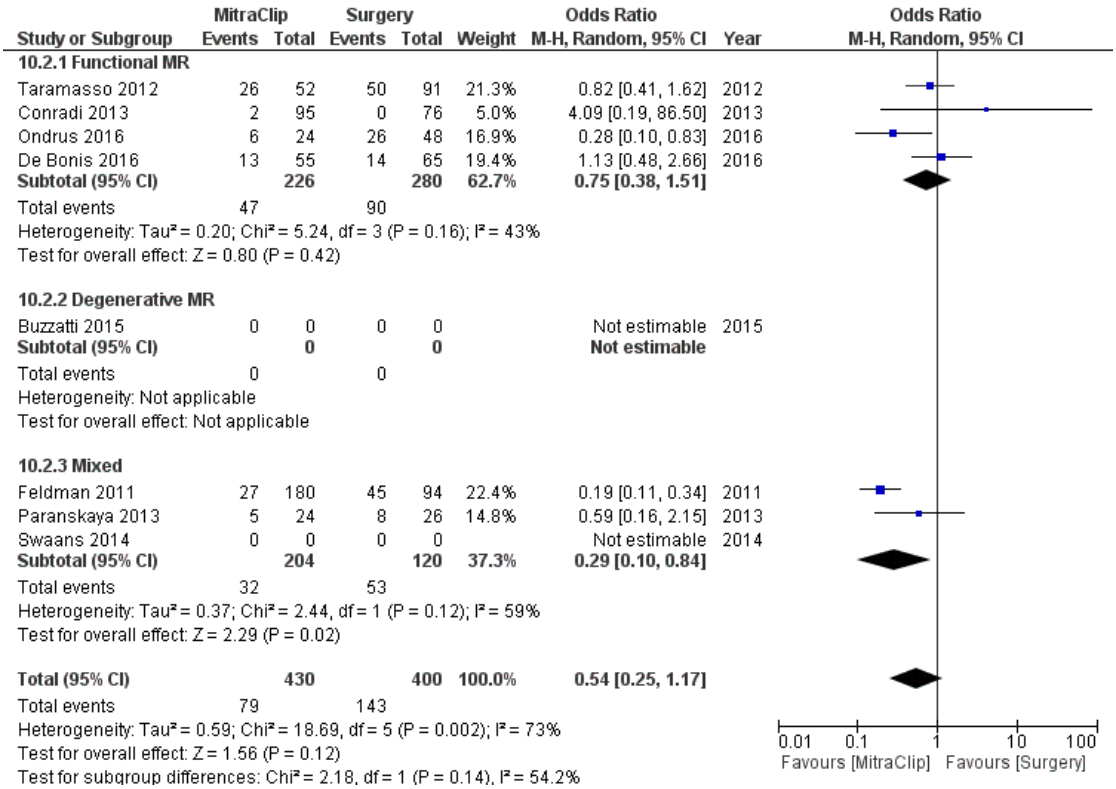
Appendix 7: Forest plot of the 30-day MAE (data is depicted using OR with 95% CI)



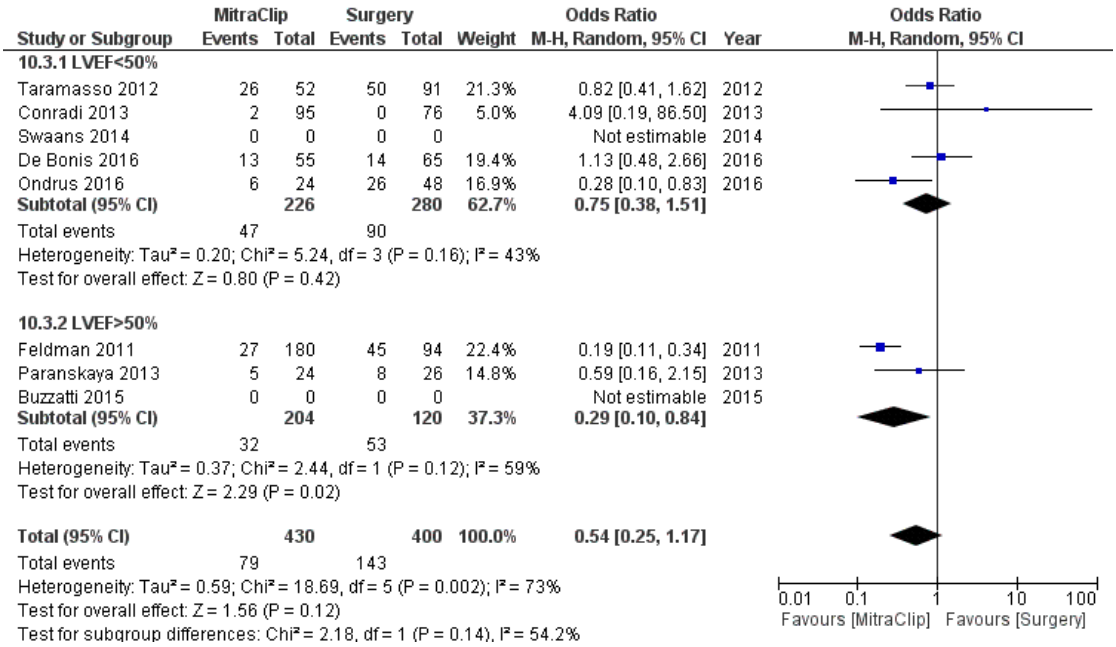
Appendix 8: Subgroup analysis and sensitivity analysis of 30-day MAE.



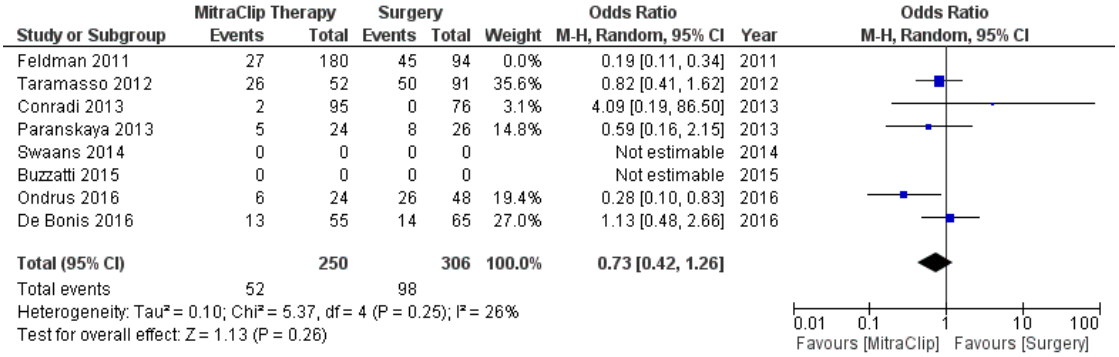
Subgroup analysis of 30-day MAE by patient's age (<70 yrs vs. ≥70 yrs).



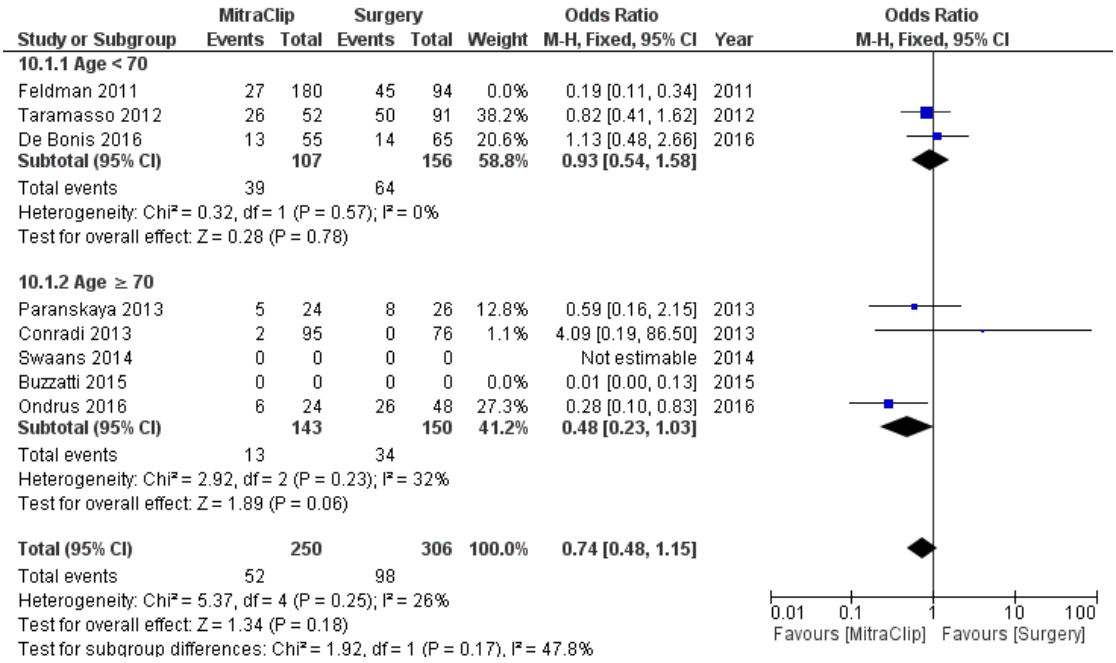
Subgroup analysis of 30-day MAE by MR pathology (functional MR vs. degenerative MR vs. mixed etiology).



Subgroup analysis of 30-day MAE by LVEF (<50% vs. ≥50%).



Sensitivity analysis of 30-day MAE by eliminating the RCT

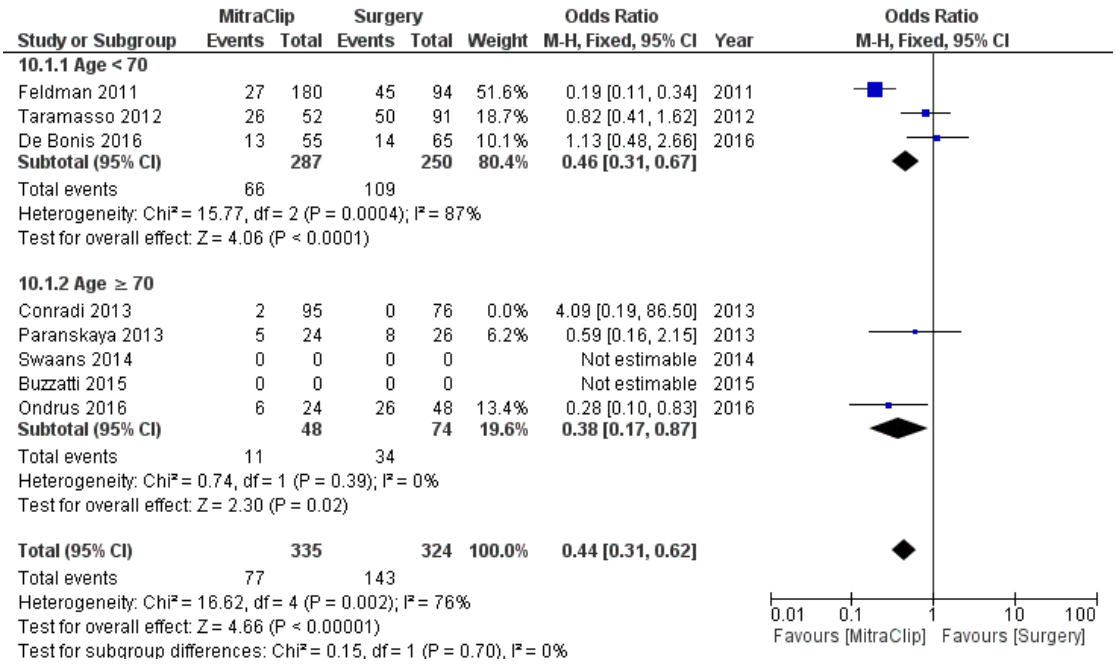


Subgroup analysis of 30-day MAE by patient's age (<70 yrs vs. ≥70 yrs) in observational studies

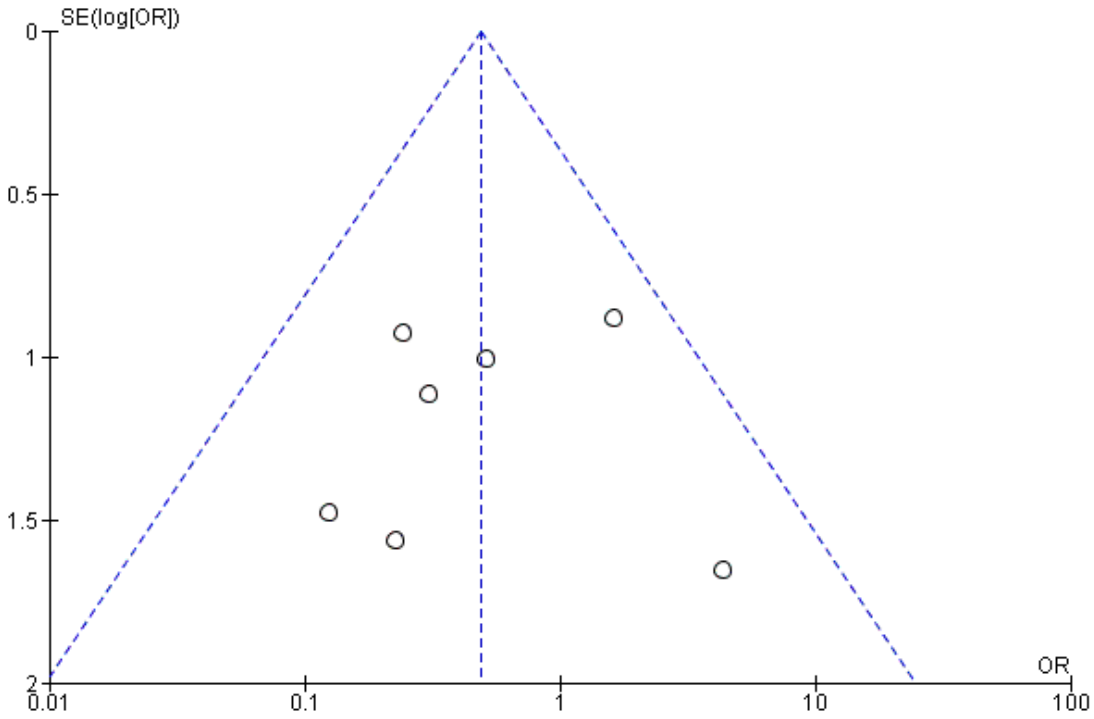
Table 5: Other outcomes.

Study	Reoperation for failed MV repair or replacement %		Stroke %		MI %		Renal failure %		Transfusion ≥ 2 units %		Neurological events %		Length of hospital stay, days	
	MitraClip	Surgery	MC	SR	MC	SR	MC	SR	MC	SR	MC	SR	MC	SR
Feldman 2011	0	1	1	2	0	0	0.55	0	13	45	1	2	N/A	N/A
Taramasso 2012	2	N/A	0	2.2	0	0	30.8	30.8	N/A	N/A	0	2	5 (IQR: 4–9)	11 (IQR: 7–19)
Conradi 2013	3	N/A	1.1	0	1.1	0	N/A	N/A	N/A	N/A	1	0	13.4 ± 12.4	9.2 ± 3.8
Paranskaya 2013	8	4	0	3.8	0[#]	3.8[#]	4.2	7.7	4	8	0	4	8.6 ± 6.5	10.6 ± 1.7
Swaans 2014	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Buzzatti 2015	N/A	N/A	0	0	N/A	N/A	12	51	12	48	0	9	4.9±1.8	10.6±6.9 (post surg)
De Bonis 2016	N/A	N/A	0	1.5	0	0	5.4	3	N/A	N/A	N/A	N/A	5 (IQR: 3.9–7.8)	10 (IQR: 8–13)
Ondrus 2016	0	2	0	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	12 (IQR: 6–22)	14 (IQR: 10–30)

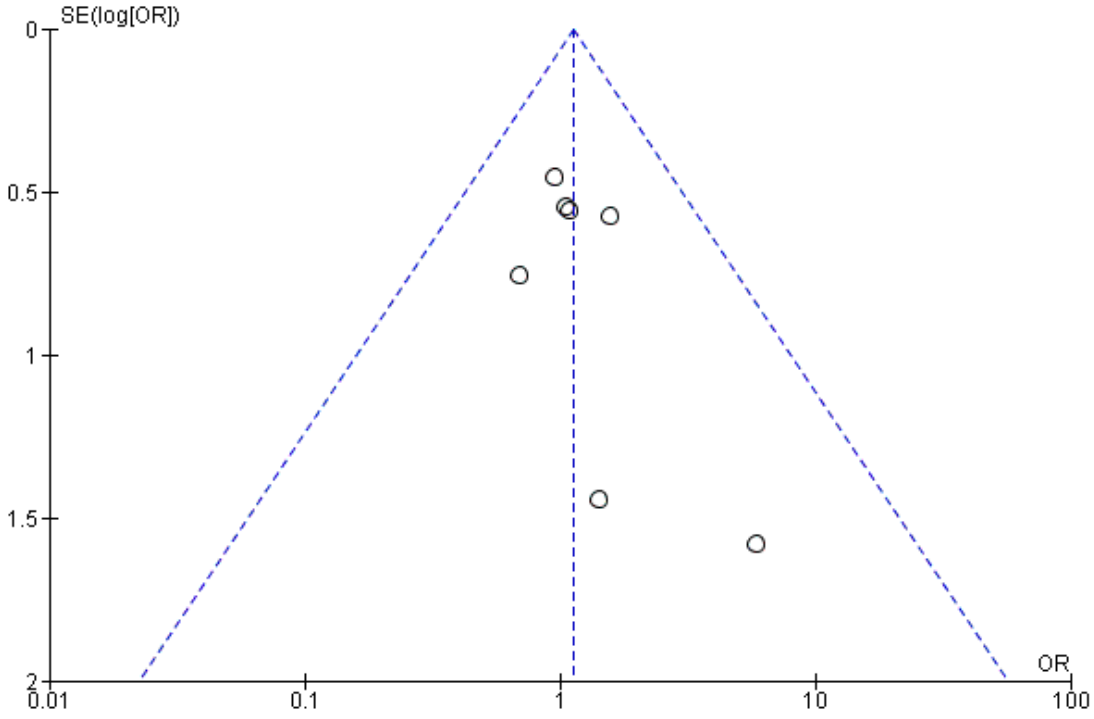
Appendix 9: Sensitivity analysis by eliminating Conradi 2013 in meta-analysis of 30-day MAE



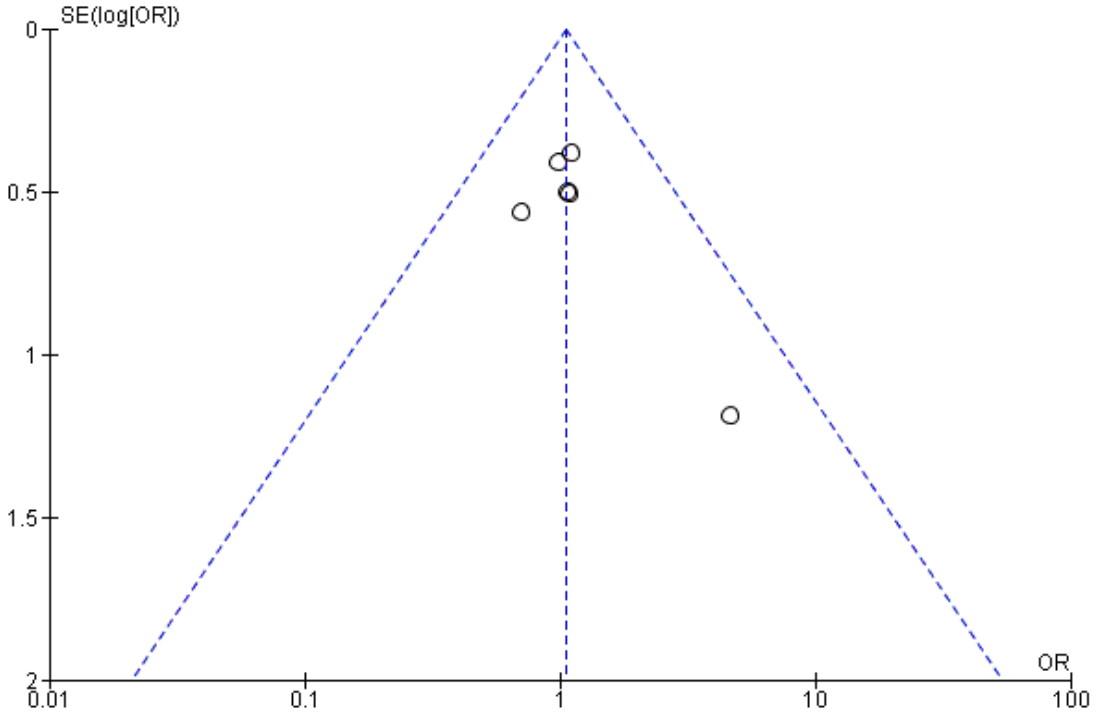
Appendix 10: Funnel plots in analyses of mortality, residual MR and 30-day MAE.



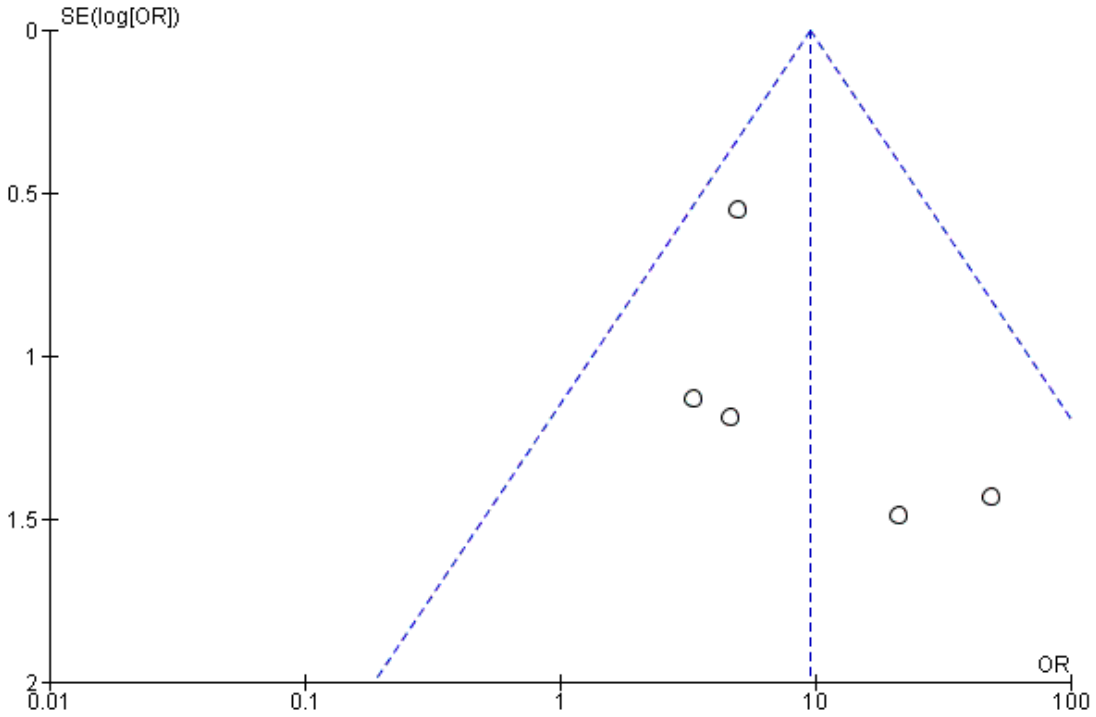
Funnel plot in the analysis of 30-day mortality.



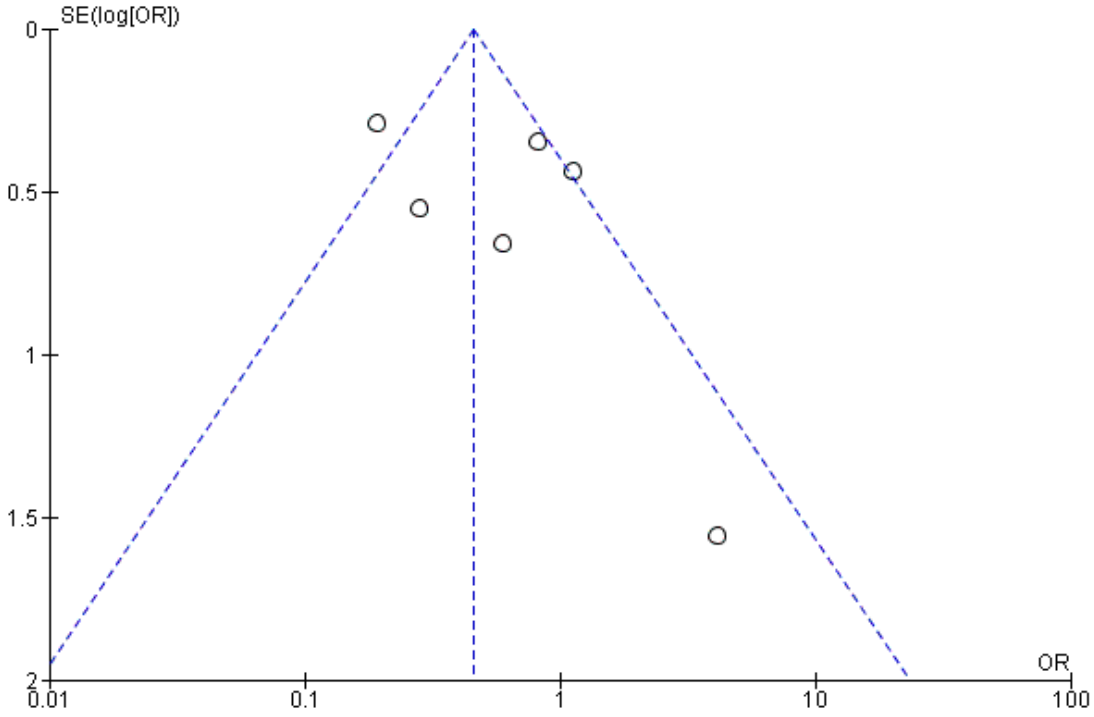
Funnel plot in the analysis of one-year mortality.



Funnel plot in the analysis of two-year mortality.



Funnel plot in the analysis of residual MR.



Funnel plot in the analysis of 30-day MAE.

Table 6: Quality of Evidence Assessment

Summary of findings: Mortality

MitraClip therapy compared to Surgery in treatment for patients with severe mitral regurgitation

Patient or population: treatment for patients with severe mitral regurgitation
Setting:
Intervention: MitraClip therapy
Comparison: Surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Surgery	Risk with MitraClip therapy				
30-day Mortality	43 per 1,000	22 per 1,000 (10 to 51)	OR 0.51 (0.22 to 1.19)	1082 (1 RCT & 7 observational studies) [a]	⊕◯◯◯ VERY LOW [b,c,d,e]	
One-year Mortality	96 per 1,000	105 per 1,000 (68 to 159)	OR 1.11 (0.69 to 1.78)	907 (1 RCT & 7 observational studies) [a]	⊕◯◯◯ VERY LOW [b,c,d,f,g]	
Two-year Mortality	168 per 1,000	175 per 1,000 (125 to 240)	OR 1.05 (0.71 to 1.56)	857 1 RCT & 7 observational studies) [a]	⊕◯◯◯ VERY LOW [b,d,e,f]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. One RCT and seven retrospective cohort studies.
b. Relatively good surgical candidates in the RCT.
c. Low applicability because of good surgical candidates in the RCT. Components of Functional MR and degenerative MR were different among the included studies.
d. Unclear surgical risk—mixed of functional and degenerative MR (MR3+/4+ NR).
e. Wide CI and few events in the studies.
f. High risk of bias—loss to follow up. Confounding by co-intervention as 21% of patients with mitral valve clip had subsequent surgery in the RCT. Prognostic imbalance and variable duration of patient follow-up in Paranskaya 2013.
g. Wide CI and optimal information size criteria not met.

References

Summary of findings: Residual MR

MitraClip therapy compared to Surgery in Treatment for Patients with Severe Mitral Regurgitation

Patient or population: Treatment for Patients with Severe Mitral Regurgitation
Setting:
Intervention: MitraClip therapy
Comparison: Surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Surgery	Risk with MitraClip therapy				
Residual MR severity>2	17 per 1,000	99 per 1,000 (44 to 207)	OR 6.47 (2.71 to 15.41)	874 (1 RCT & 7 observational studies) [a]	⊕◯◯◯ VERY LOW [b,c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. One RCT and seven retrospective cohort studies.
b. RCT: Relatively good candidates in surgery group. Observational studies: Mixed functional and degenerative MR patients were included in the studies.
c. Baseline MR>2+ does not equal in each study.
References

Summary of findings: 30-day MAE

MitraClip therapy compared to Surgery in Treatment for Patients with Severe Mitral Regurgitation

Patient or population: Treatment for Patients with Severe Mitral Regurgitation
Setting:
Intervention: MitraClip therapy
Comparison: Surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Surgery	Risk with MitraClip therapy				
Postoperative serious adverse events	358 per 1,000	231 per 1,000 (122 to 394)	OR 0.54 (0.25 to 1.17)	830 (1 RCT & 7 observational studies) [a]	⨁◯◯◯ VERY LOW [b,c]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; OR: Odds ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

a. One RCT and seven retrospective cohort studies
b. Different composites of MAE were reported.
c. Relatively good surgical candidates; comparator is surgery or conservative medical management; Mixed functional and degenerative MR

References

Appendix 11: Markov Health State Transition Model

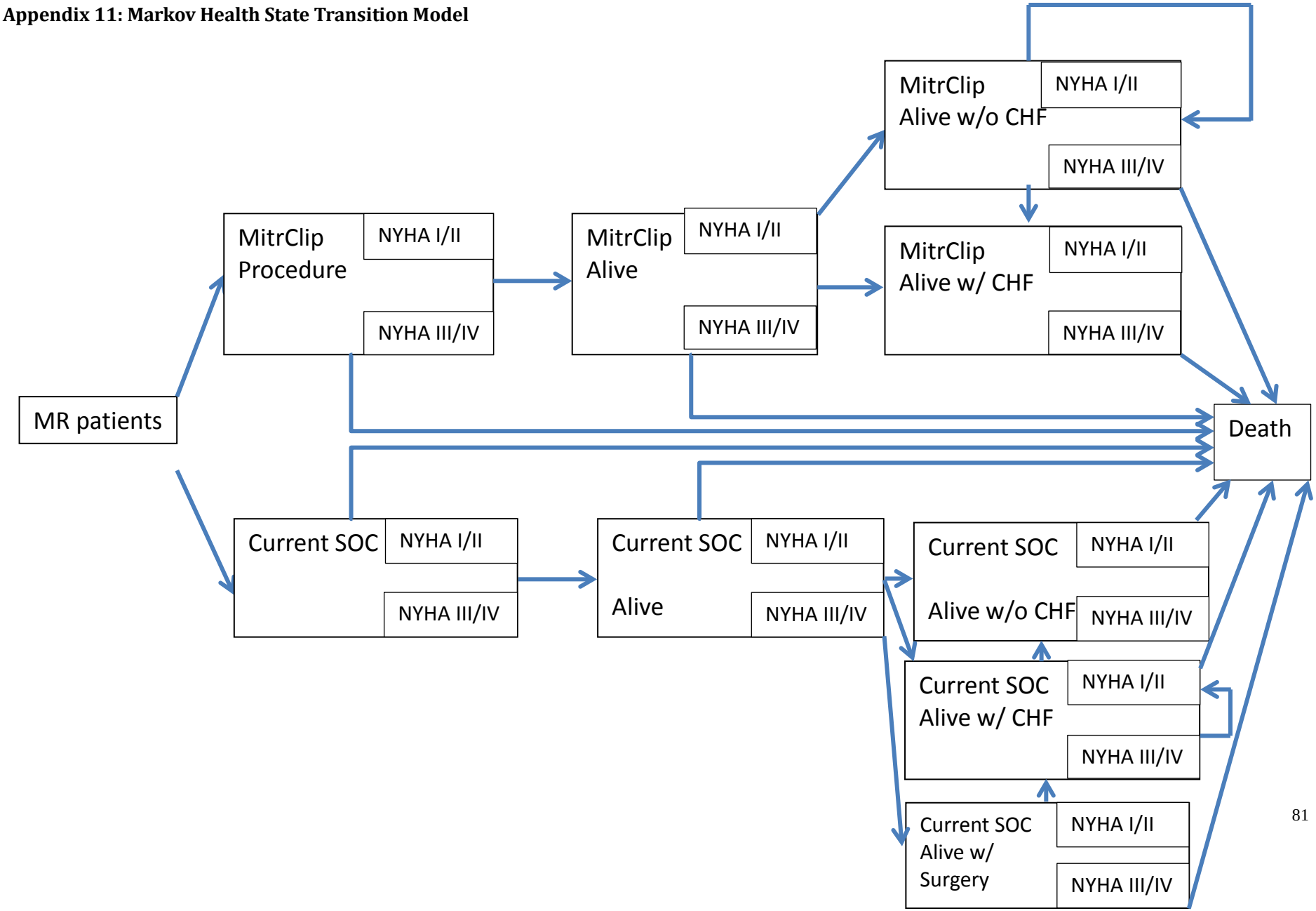


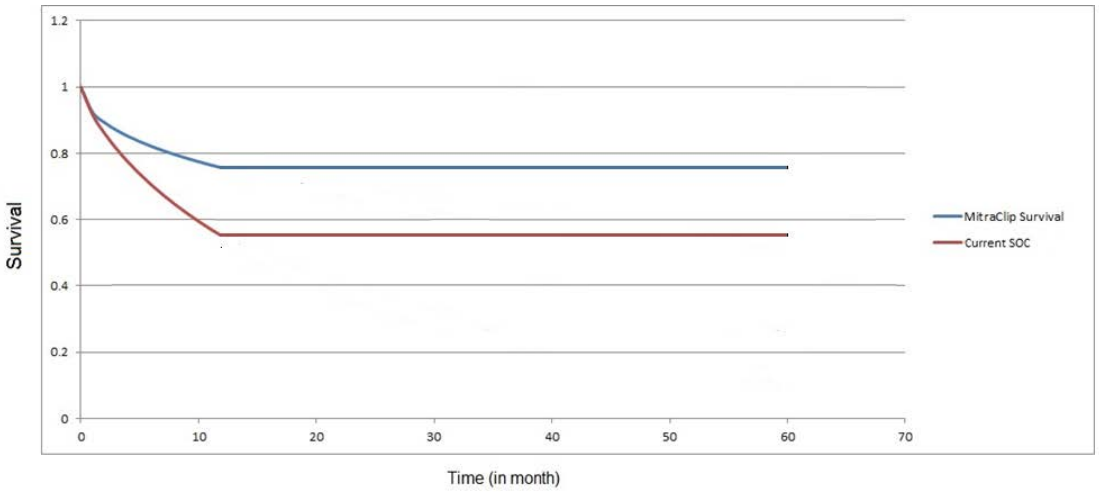
Table 7: In-patient payment according to the U.S. MS-DRG classification system.

MS-DRG & Code		ICD-10-PCS Code	Payment (USD)	Description
Repair Mitral Valve, Percutaneous Approach	216	02QG3ZZ	57,511.42	W CARD CATH W MCC
	217		37,687.75	W CARD CATH W CC
	218		33,800.18	W CARD CATH W/O CC/MCC
Repair Mitral Valve, Open Approach	219	02QG0ZZ	45,985.28	W/O CARD CATH W MCC
	220		30,743.92	W/O CARD CATH W CC
	221		27,494.44	W/O CARD CATH W/O CC/MCC
Replacement of Mitral Valve , Open Approach	219	02RG07Z 02RG08Z 02RG0JZ 02RG0KZ	45,985.28	W/O CARD CATH W MCC
	220		30,743.92	W/O CARD CATH W CC
	221		27,494.44	W/O CARD CATH W/O CC/MCC
Nonrheumatic mitral (valve) insufficiency	306	I34.0	8,577.81	CARDIAC CONGENITAL & VALVULAR DISORDERS W MCC
	307		4,856.03	CARDIAC CONGENITAL & VALVULAR DISORDERS W/O MCC
Unspecified systolic (congestive) heart failure	291	I50.20	8,823.51	HEART FAILURE & SHOCK W MCC
	292		5,709.40	HEART FAILURE & SHOCK W CC
	293		3,946.60	HEART FAILURE & SHOCK W/O CC/MCC

Data updated as of Feb 23, 2017

Figure 2. Survival Curves

A: The survival curve under the assumption that 0% of mortality after the first year following initial treatment.



B: Modelled overall survival using Weibull function.

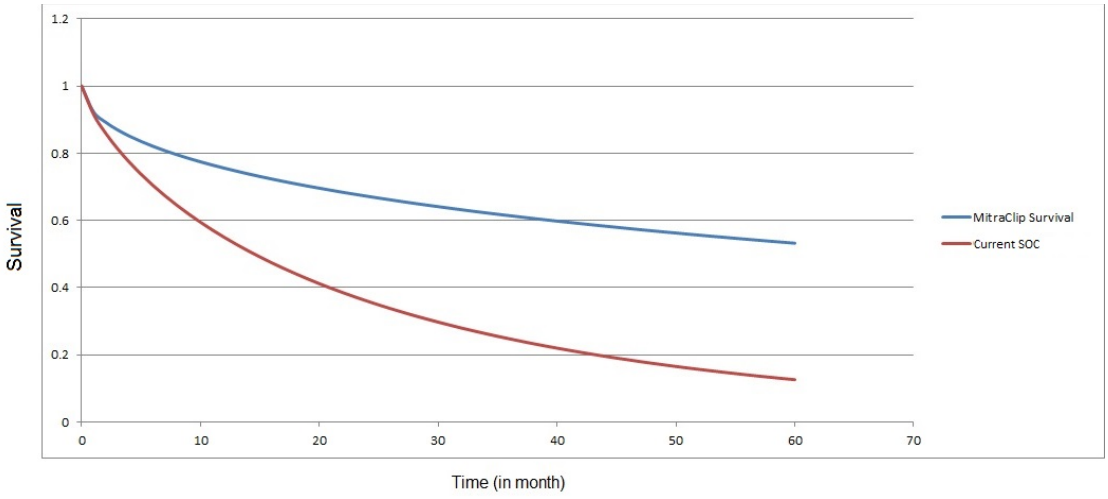


Table 8. Base Case Analysis.

Outcome	MitraClip	SOC	Incremental difference[a]
Total LYs per patient	3.86	2.92	0.94
Total QALYs per patient	3.20	2.23	0.97
Procedure cost	51,214.57	16,166.07	35,048.50
CHF hospitalization cost	7,065.86	15,590.21	-8,524.35
Total costs per patient ($US)	58,280.43	31,756.28	26,524.15
Incremental cost per LY gained[b]	N/A	N/A	28,217.18
Incremental cost per QALY gained[c]	N/A	N/A	27,344.48

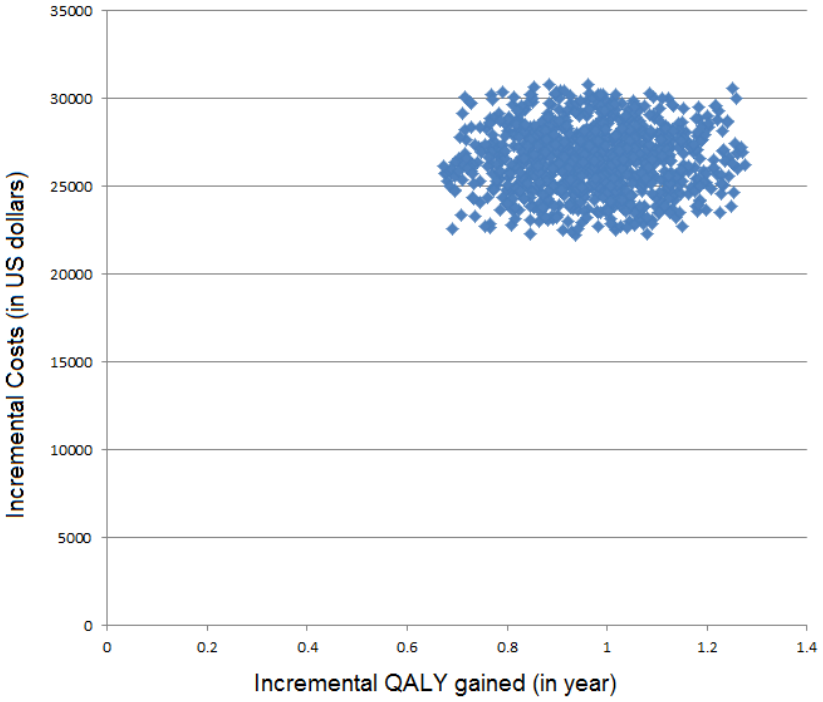
Time horizon: five years
Yearly discounting rate: 5%
Half cycle correction was applied in the calculations. a: Calculated as MitraClip therapy minus SOC. b: Calculated as the difference in costs divided by the difference in LYs. c: Calculated as the difference in costs divided by the difference in QALYs

Table 9. Results for the one-way deterministic sensitivity analyses.

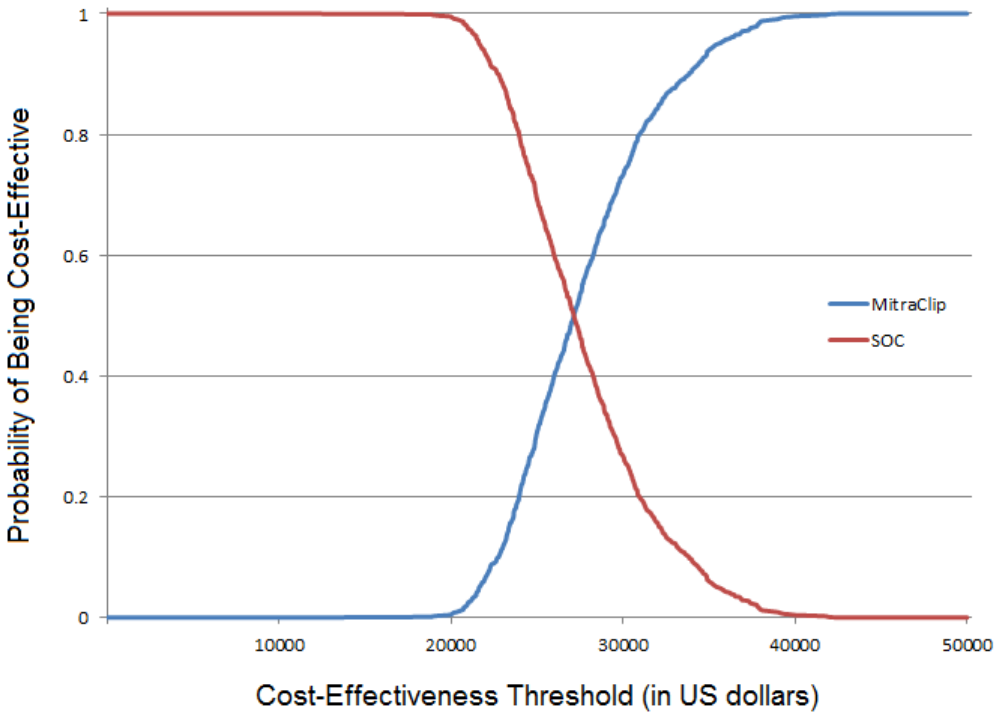
Analysis	Low value	Low value ICER ($USD/QALY)	High value	High value ICER ($USD/QALY)
Time horizon (years)	2	96,531.25	10	10,070.05
Discounting for costs (%)	0	26,847.36	3	27,098.13
Long-term survival	N/A	N/A	Modelled survival	29,992.54

Figure 3. Probabilistic sensitivity analysis.

3A: Probabilistic sensitivity analysis according to proportion of patients with CC.



3B



Cost-effectiveness acceptability curve (CEAC). In 100% of the runs, MitraClip therapy was cost-effective versus standard of care at a threshold of $50,000 per QALY gained. If the willingness-to-pay threshold is below $20,000, the probability of MitraClip being cost effective is zero.