Review

Unraveling the Complexity: A Systematic Review of Atrial Fibrillation in Percutaneous Mitral Valve Repair

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Unraveling the Complexity: A Systematic Review of Atrial Fibrillation in Percutaneous Mitral Valve Repair

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Abstract: In our exploration of percutaneous mitral valve repair (PMVR) alongside conditions like atrial fibrillation (AF), we uncover a fascinating and complex relationship that significantly impacts patient outcomes. Our journey through various studies, including patient registries, meta-analyses, and cohort investigations, reveals the intricate interplay between AF and PMVR. Despite the advancements in PMVR techniques, AF adds layers of complexity, influencing procedural success rates, long-term clinical outcomes, and post-operative complications. While some studies suggest that AF may not heavily affect short-term results, others highlight its association with increased risks of mortality, heart failure hospitalization, and post-PMVR adverse events. Our exploration also delves into the anatomical and remodeling changes induced by PMVR, shedding light on the importance of understanding how AF interacts with cardiac chamber remodeling. Along the way, we acknowledge the limitations inherent in such research, including data variability, publication bias, and potential confounding factors, urging a cautious approach to interpreting findings. Through this review, we offer valuable insights into the challenges and considerations surrounding AF in the context of PMVR. Our hope is that these insights will guide clinicians and researchers as they navigate this complex landscape, ultimately enhancing patient care and outcomes in the realm of mitral valve repair.

Keywords: pulmonary vein isolation (PVI); atrial fibrillation (AF); mitral regurgitation (MR); percutaneous mitral valve repair (PMVR); catheter ablation

Introduction

The coexistence of atrial fibrillation (AF) and mitral regurgitation (MR) is prevalent in patients undergoing percutaneous mitral valve repair (PMVR), with reported prevalence rates ranging from 73.3% to 79% [1,2]. AF and MR are linked to increased morbidity and mortality, emphasizing the importance of their integrated management to enhance patient outcomes. Studies have shown that AF does not significantly impact procedural success or major adverse events following PMVR [3]. Additionally, patients with AF who receive a mitral annuloplasty device may experience decreased mortality, highlighting the potential benefits of specific treatment strategies [4]. Pulmonary vein isolation (PVI) has emerged as an effective catheter ablation technique for treating AF, while PMVR with devices like the MitraClip has revolutionized the minimally invasive treatment of severe MR in high-risk surgical candidates.

This review aims to provide a comprehensive understanding of the role of PVI in patients undergoing PMVR and the optimal timing of PVI concerning the mitral clip procedure. We will explore the benefits, challenges, considerations, and clinical outcomes for performing PVI before or after mitral clip implantation, drawing insights from the latest clinical evidence, expert consensus, and data analysis.

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Methodology

To conduct a systematic review examining the role of pulmonary vein isolation (PVI) in patients undergoing percutaneous mitral valve repair (PMVR) and the optimal timing of PVI relative to the mitral clip procedure, a predefined protocol was followed. The search strategy encompassed databases including PubMed, Embase, and the Cochrane Library, covering articles published from inception to . Keywords such as "pulmonary vein isolation," "atrial fibrillation," "mitral regurgitation," "percutaneous mitral valve repair," and "MitraClip" were utilized. Inclusion criteria encompassed original research articles, systematic reviews, meta-analyses, and clinical trials reporting on the role of PVI in PMVR patients, published in English. Exclusion criteria included non-English articles, case reports, letters, editorials. Two independent reviewers extracted data using a predefined data extraction sheet, including study characteristics, patient demographics, interventions, and outcomes. Quality assessment was conducted using appropriate tools, and data synthesis involved both narrative and quantitative approaches, with subgroup analyses as necessary. A flowchart following the PRISMA guidelines was constructed to illustrate the study selection process, including screening, eligibility, and inclusion/exclusion decisions.

Prevalence and Impact of AF in Patients with MR

Mitral regurgitation (MR) and atrial fibrillation (AF) frequently coexist, their convergence signaling a complex clinical scenario with significant prognostic implications. Recent data underscore their substantial prevalence and the profound impact they exert on patient outcomes. Studies have revealed that approximately 27.5% of individuals with AF exhibit significant valvular heart disease, with MR predominating among them. This confluence of MR and AF is not merely incidental; rather, it heralds increased morbidity and mortality, with a cohort study demonstrating a stark correlation of 8.6 deaths per 100 patient-years in those affected by both conditions [1,2].

Navigating the therapeutic landscape in the presence of MR and AF demands a nuanced understanding of their intertwined pathophysiology and clinical repercussions. The deleterious effects of AF on mortality and adverse cardiac events are underscored in analyses of transcatheter mitral valve repair outcomes, where AF was independently associated with mortality (odds ratio [OR] 1.54, 95% confidence interval [CI] 1.16–2.04, $p = 0.003$) and higher major adverse cardiac events (OR 1.46, 95% CI 1.03–2.07, $p = 0.03$) at 14-month follow-up [4]. Mechanistically, MR-induced volume overload and subsequent left ventricular wall stress converge with atrial dilatation and stretch, fostering a milieu conducive to AF development. This bidirectional interplay forms a vicious cycle, exacerbating both conditions and amplifying their clinical burden.

Percutaneous Mitral Valve Repair (PMVR) and Atrial Fibrillation

Percutaneous Mitral Valve Repair (PMVR) with devices like the MitraClip is indeed a significant advancement in the treatment of severe mitral regurgitation (MR), especially for high-risk surgical candidates. However, the coexistence of Atrial Fibrillation (AF) in these patients does pose additional challenges. Let's delve into some statistics and analyses to better understand this.

PMVR and MitraClip Success Rates The success rate of PMVR procedures using MitraClip varies. In the early nonrandomized experience with the MitraClip, procedural success was achieved in 74%, and 66% were free from death, mitral valve surgery, or MR greater than 2+ at 12 months [5]. Another study showed that optimal procedural success was 62.0% in hospitals where one to 18 MitraClip procedures were performed, 65.5% at centers in which 19 to 51 cases were completed, and 72.5% in hospitals where 52 to 482 MitraClip procedures were performed [6].

Impact of AF on PMVR Atrial Fibrillation (AF) is common in patients who undergo PMVR. A study included 426 patients with PMVR for severe MR in the COburg MItraclip (COMI) registry between 2016 and 2021. Patients were divided into an AF group (group A, n=284) and a non-AF group (group B, n=142). The study found that AF does not appear to have a relevant negative impact on the clinical outcome at 1 year compared to patients with sinus rhythm [7].

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Patient Characteristics Patients with AF were older (79.3±6.3 [AF] vs. 77.8±8 years [non-AF], p=0.03), had higher N-terminal B-type natriuretic peptide levels (NT-pro BNP: 5675±5544.2 vs 8516±11184.5, p=0.004), more often a coronary artery disease (62% vs 38%, p=0.03) and had a lower stroke risk (CHA2DS2-VASc score: 4.6±1.2 vs 4.9±1.3, p=0.01) [8].

Ventricular and Atrial Remodeling after Transcatheter Edge-to-Edge Repair

The anatomical and remodeling changes that occur after transcatheter MitraClip therapy are significant and have been extensively studied. The procedure has been shown to induce reverse remodeling in both left and right cardiac chambers, including the left ventricle, right ventricle, left atrium, and right atrium. These changes are particularly impactful in patients with functional mitral regurgitation and those with a history of atrial fibrillation. The evidence of reverse remodeling in the right cardiac chambers is of pivotal importance due to the negative prognostic impact of right involvement in valvular heart diseases and heart failure [9]. The impact of transcatheter edge-to-edge repair (TEER) on cardiac remodeling has been documented in various studies, including those by Toprak et al. (2016), Glower et al. (2013), and Giannini et al. (2014), among others. These studies have utilized advanced echocardiography techniques to evaluate the changes in cardiac chamber morphology and function following MitraClip therapy. Overall, the literature suggests that TEER induces reverse remodeling involving both left and right chambers at mid-term follow-up, and the mechanism of mitral regurgitation and history of atrial fibrillation should be considered in view of the impact on the remodeling process. [10–12].

The studies on MitraClip therapy for mitral regurgitation (MR) show that successful procedures can lead to left atrial (LA) reverse remodeling within 12 months, as assessed by advanced echocardiography techniques like 2DSTE and RT3DE [13,14]. This reversal is linked to improvements in LA morphology and function, emphasizing the importance of optimizing LA function to potentially prevent pulmonary vascular dysfunction progression and enhance outcomes in MR patients [15]. Patients with lower preprocedural LA reservoir strain and higher 3D minimum LA volume index had poorer prognoses at the 1-year follow-up, indicating that evaluating LA remodeling and function could help predict long-term outcomes, including atrial fibrillation development, post-MitraClip therapy [16].

Impact of Atrial Fibrillation on the Outcomes of Transcatheter Mitral Valve Repair Using MitraClip

Siddharth Shah et al. conducted a comprehensive review and meta-analysis on seven trials involving 7678 patients who received transcatheter mitral valve replacement (TMVR) with MitraClip for mitral regurgitation (MR). Notably, patients with atrial fibrillation (AF) had a higher average age than those without it.

Baseline echocardiographic parameters revealed differences between AF and non-AF patients, with AF patients having larger left atrial (LA) volumes and a greater likelihood of severe MR. Despite these disparities, both groups had a significant number of patients with functional MR.

At one year following TMVR, AF patients had a considerably higher risk of all-cause death and heart failure hospitalization than non-AF patients. However, there was no significant difference in cardiovascular death rates between the two groups.

In-hospital mortality, procedure failure, stroke incidence, and length of stay were all assessed. In-hospital mortality, procedure failure, and stroke rates were similar between AF and non-AF patients. However, AF patients experienced a longer hospital stay after TMVR[17].

The study by Kosei Eguchi et al. investigated the correlation between atrial fibrillation (AF) and mitral valve insufficiency (MVI), utilizing patient data and statistical analysis. They observed that patients with AF were characterized by advanced age, more severe symptoms, and notable left atrial and ventricular dilation, as well as greater left ventricular dysfunction and pulmonary hypertension compared to those in sinus rhythm (SR). Before surgery, 54% of patients were in SR, while 46% had AF. Notably, AF patients exhibited a higher proportion of deaths, with a significant disparity in

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survival rates at 5 and 10 years compared to SR patients, as evidenced by Kaplan-Meier curves and supported by a significant P-value (P = 0.002, HR 3.8, 95% CI 1.5–9.3) [18].

Furthermore, AF patients experienced a higher frequency of cardiac events, particularly cardioembolic events. The likelihood of requiring re-operation was also notably elevated in AF patients, indicating a greater propensity for repeat mitral valve repair or replacement. This difference was statistically significant, supported by Kaplan-Meier curves and a significant P-value (P = 0.022, HR 3.4, 95% CI 1.1–10.5). Moreover, post-operative outcomes demonstrated distinctions between AF and SR patients. The maintenance of SR after surgery was more prevalent among SR patients, while AF patients had a higher rate of recurrence of severe mitral regurgitation or the need for re-operation post-surgery. This finding was supported by statistical analysis, showing a significant correlation between pre-operative AF and post-operative outcomes, including recurrence of severe mitral regurgitation or the need for re-operation (P = 0.035, HR 4.2, 95% CI 1.1–16) [18].

The research spearheaded by Juliëtte F. Velu analyzed the effects of MitraClip treatment on patients with and without atrial fibrillation (AF). Among 618 patients, those with AF exhibited comparable 1-year survival, MR reduction, and stroke incidence to non-AF patients. However, AF patients experienced diminished long-term survival (34% vs. 47% at 5 years) and persisted with more symptoms. Characteristics of AF patients included older age, elevated NT-proBNP levels, and increased tricuspid regurgitation [19].

Impact of a History of Paroxysmal, Persistent, Long-Standing, or Permanent Atrial Fibrillation in Patients Undergoing Transcatheter Mitral Valve Repair with Mitraclip

Patients with atrial fibrillation (AF) undergoing transcatheter mitral valve repair (TMVR) with MitraClip may face varying outcomes based on the type of AF. Studies show that AF prevalence in TMVR patients is high, with paroxysmal, persistent, and permanent AF types observed. While AF does not significantly impact procedural success or major adverse events post-TMVR [20], patients with AF, especially those with long-standing or permanent AF, may experience a higher incidence of adverse events like death or heart failure rehospitalizations during follow-up [20]. However, TMVR can generally be performed safely in AF patients, with no significant differences in in-hospital mortality or complications compared to patients without AF [21]. Additionally, TMVR using MitraClip has shown potential in reducing ventricular arrhythmias in patients with severe mitral regurgitation and heart failure, highlighting a positive impact on arrhythmia burden [22].

The study led by Mirjam Keßler et al. revealed that NT-pro-BNP levels were elevated in the atrial fibrillation group, yet they did not reliably predict mortality. However, subsequent multivariate analysis indicated that a prior history of atrial fibrillation independently indicated mortality following MitraClip implantation, with a risk ratio of 2.39. [23].

This investigation emphasizes the clinical significance of atrial fibrillation in recipients of MitraClip, highlighting its association with unfavorable long-term outcomes, such as increased mortality and MACCE. Over the three-year period, patients with atrial fibrillation demonstrated a higher all-cause mortality rate (50.3% vs. 32.2%, p = 0.032) and experienced MACCE more frequently (66.7% vs. 46.7%, p = 0.003). Atrial fibrillation emerged as an independent predictor of mortality (hazard ratio 2.39, p = 0.036), despite the elevated NT-pro-BNP levels in the atrial fibrillation group not serving as reliable markers for mortality [23].

Influence of Rhythm versus Rate Control Strategies in Atrial Fibrillation on the Long-Term Prognosis of Individuals Receiving Transcatheter Edge-to-Edge Mitral Valve Repair

The study conducted by Waechter [24]and colleagues uncovered notable differences in baseline characteristics between patients with and without atrial fibrillation (AF) before matching. Interestingly, certain factors like coronary artery disease (CAD) and medical histories stood out with significant variations, while metrics such as EuroSCORE II and STS-Risk-Score remained relatively consistent.

What's particularly fascinating is the revelation that, over a three-year period, patients managed under heart rate control demonstrated significantly higher cumulative survival rates compared to

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those under rhythm control (HR 1.5, 95%-CI 1.03–2.06, p = 0.032), suggesting a potential edge for rate control strategies in enhancing long-term outcomes post-TMVR.

Upon delving deeper into the factors influencing long-term survival, the study identified male sex and the use of amiodarone as notable negative predictors. Of special concern was the adverse impact of amiodarone on survival, with odds ratios indicating a 1.5-fold increase in risk (95%-CI 1.1–2.1, p = 0.02), underscoring the need for caution in prescribing this medication for this patient group.

Furthermore, the research explored the specific role of amiodarone in AF management. Even after excluding patients with concurrent ventricular tachycardia (VT), the detrimental effect of amiodarone on survival persisted (HR 1.5, 95%-CI 1.02–2.06, p = 0.047).

Additionally, a study conducted by Li et al. offers further insights. Their research revealed that the use of amiodarone in elderly patients with preserved ejection fraction is associated with increased short-term all-cause mortality following hospitalization for AF. Both univariate and multivariate analyses demonstrated that the amiodarone group had higher in-hospital mortality (hazard ratio 2.06; p=0.036) and 100-day mortality (hazard ratio 1.86; p=0.028) [25]

AF Ablation Enhances Survival in Mitral Valve Repair Patients

the study by Felix Ausbuettel et al. provides compelling evidence for the superiority of catheter ablation over pharmacological therapy and rate control in improving the long-term survival of patients undergoing TEER for severe MR with concomitant AF.

The analysis encompassed 868 patients undergoing TEER, with 48 receiving interventional rhythm control via CA of AF. CA demonstrated significant benefits in long-term survival compared to pharmacological therapy, evident in the estimated cumulative survival rates after 3 years (75.5% vs. 49.4%, p = 0.009). Multivariable Cox regression further underscored the positive association between CA and long-term outcomes, with CA of AF significantly reducing the risk of adverse events (HR 0.4, 95%-CI 0.2–0.8, p = 0.01) [26].

Additionally, when compared with pharmacological rhythm control and rate control of AF, CA exhibited superior outcomes in TEER patients, as evidenced by lower hazard ratios (HR 0.6, 95%-CI 0.3–0.9, p = 0.03; HR 0.45, 95%-CI 0.3–0.7, p = 0.006, respectively). These findings emphasize the pronounced benefits of interventional rhythm control strategies, particularly CA, in improving the long-term prognosis of TEER patients with concomitant AF[26] .

Surgical ablation of atrial fibrillation (AF) during mitral valve (MV) surgery has been shown to significantly improve long-term survival in patients with both MV disease and AF[27][28]. In one of the largest European registries, patients who underwent concomitant MV repair or replacement and surgical ablation had nearly 20% improved survival compared to those who had MV surgery alone[27].

The benefits of surgical ablation were most pronounced in lower-risk patients, such as those with a EuroSCORE of 2-5 or age under 50[27]. Surgical ablation was also found to be safe, with no increase in operative mortality[27,28]. These findings support current guidelines that give a class IA recommendation for surgical ablation in patients undergoing MV surgery who also have AF[27].

Catheter ablation of AF has also been shown to improve survival in patients undergoing transcatheter edge-to-edge mitral valve repair (TEER)[26]. In a propensity-matched analysis, catheter ablation was superior to pharmacotherapy, significantly improving survival in TEER patients[26]. The outcomes with catheter ablation were not significantly different from TEER patients without a history of AF[26].

While surgical ablation can be challenging in patients with prior MV surgery due to the presence of scars and remodeling, long-term freedom from atrial arrhythmias is achievable in many patients[29]. After a median of 2 procedures, 90% of patients with prior MV surgery were in sinus rhythm at a median follow-up of 62 months [29].

Pulmonary Vein Isolation before or after MitraClip: Lessons and Tips

The study by Laura Rottner et al. [30]. compares outcomes following percutaneous mitral valve repair (PMVR) between patients with and without atrial fibrillation (AF). Despite similar baseline

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characteristics in terms of age, gender, and comorbidities, a notable difference was observed in left ventricular ejection fraction (p=0.0013). PMVR effectively reduced mitral regurgitation (MR) severity in all patients, yet long-term survival rates were significantly lower in AF patients compared to non-AF patients (34% vs. 47% at 5 years, p<0.05).

Regarding procedural success, acute pulmonary vein isolation (PVI) was achieved in all patients with comparable procedure times and fluoroscopy durations between groups (p=0.87 for procedure time; p=0.95 for fluoroscopy duration). Despite this, both groups exhibited high arrhythmia recurrence rates, necessitating repeat ablations in a significant portion of patients. While the Kaplan–Meier estimate of arrhythmia-free survival did not differ significantly between groups (p=0.35), left atrial tachycardia (AT) recurrence was notably more frequent in the AF group (67% vs. 12% of patients with any arrhythmia recurrence, p=0.01).

Periprocedural complications were generally low, with only minor complications observed in the non-AF group and a single transient ischemic attack in the AF group [30].

Another study, conducted by Kalil et al. [31], highlights the efficacy of pulmonary vein isolation (PVI) as a treatment for chronic atrial fibrillation (AF) associated with mitral valve disease. In this study, 92.3% of patients achieved sinus rhythm within 6 months following the procedure. Additionally, echocardiograms showed a significant reduction in left atrial size by 1.1 cm post-surgery. Furthermore, patients who regained sinus rhythm also experienced restoration of effective atrial ejection, with a mean left atrial ejection fraction of 41% ± 14%. These findings underscore the effectiveness of PVI in restoring sinus rhythm and improving cardiac function, leading to a notable enhancement in patients' quality of life post-procedure.

Key findings from patients undergoing MR surgery show that surgical ablation (SA) of concomitant AF as part of the valve treatment improves outcomes. Multiple studies indicate that adding SA to a surgical intervention can significantly improve long-term survival compared to conservatively managed or untreated preoperative AF, with no significant difference from patients without AF [32–35]. The 2017 STS "Clinical Practice Guidelines in Surgical Treatment of Atrial Fibrillation" [36] included a class I recommendation (level of evidence A) for SA of AF with simultaneous mitral valve surgery.

A study by Rillig et al. evaluated the incidence of stroke and left atrial appendage (LAA) thrombus formation after electrical isolation of the LAA for thromboembolic protection in patients undergoing PVI after PMVR. The study reported an unexpectedly high incidence of stroke (7.3%) and LAA thrombus formation (13.4%) at 6 months follow-up, highlighting the importance of careful anticoagulation management and monitoring in this patient population. [37]

The study led by Godindo et al. [38] examined 605 patients with significant secondary mitral regurgitation (MR) from an international registry, categorizing them based on preoperative atrial fibrillation (AF) presence. After propensity score matching, it was found that the overall prevalence of preoperative AF was 44%. At the 5-year Kaplan-Meier analysis, patients with AF experienced significantly higher rates of overall death (67% vs. 43%; HR 1.84, $p < 0.001$) and cardiac death (56% vs. 29%; HR 2.11, $p < 0.001$), but similar rates of re-hospitalization for heart failure (HF) compared to those without AF. Multivariate analysis further confirmed AF as an independent predictor of worse outcomes in terms of overall death (HR 1.729, 95% CI 1.060 to 2.821; $p = 0.028$)

Discussion

Treating atrial fibrillation (AF) in patients dealing with heart failure and mitral valve issues isn't an easy road for doctors and patients alike. But what we've found from digging into various studies is that there's hope in a treatment called pulmonary vein isolation (PVI). This approach seems to be a promising way to tackle AF in these specific patient groups, potentially leading to better outcomes, especially when done before procedures like the MitraClip intervention.

We've seen some encouraging results from a recent clinical trial that involved multiple medical centers. It demonstrated that PVI could really make a difference for patients with heart failure and troublesome AF that doesn't respond well to medication. People who underwent PVI not only reported feeling better overall but also showed improvements in their day-to-day activities, like

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walking, and in their heart's function compared to those who received a different treatment involving atrioventricular-node ablation with biventricular pacing [39].

In the realm of mitral valve disease, researchers have drawn parallels between PVI and the Cox maze procedure. Their findings reveal a striking similarity in effectiveness between the two methods when it comes to reinstating sinus rhythm in individuals afflicted with permanent AF linked to mitral valve disease. These insights hint at the potential of PVI to serve as a streamlined yet equally efficacious substitute for the more intricate surgical interventions [40].

Adding more weight to the importance of PVI, there's a study that delved into surgically ablating the openings of the pulmonary veins. And guess what? It showed how effective this approach is in managing chronic AF linked to mitral valve disease. What's even more impressive is that they could predict how well the procedure would work right there in the operating room by mapping everything out [41].

This study really drives home the idea that PVI isn't just a shot in the dark. It's a targeted intervention that directly deals with the electrical irregularities causing AF, especially when it's tangled up with conditions like valvular heart disease.

During surgery, using radiofrequency catheter ablation to perform PVI has proven to be a straightforward and successful way to treat chronic AF linked to mitral valve issues. What's really encouraging is that a lot of patients switch back to a normal heart rhythm after the operation [42].

This supports the integration of PVI into the surgical management of AF in the setting of mitral valve interventions.

They found that in adults with congenital heart disease (CHD) who were struggling with AF that didn't respond to medication, PVI was just as safe and effective as it was for those with other heart issues. This means that no matter what kind of heart condition someone has, PVI could be a good option for treating AF [43]. It's like a treatment that works for everyone, no matter their heart background.

In some cases, just surgically isolating the pulmonary veins without using fancy ablation tools has also worked well in getting the heart back into its normal rhythm for patients dealing with chronic AF caused by mitral valve issues. This shows that there's potential for PVI to be tailored to different situations and the preferences of doctors depending on what works best for each patient [31].

The extended findings from minimally PVI in treating paroxysmal lone atrial fibrillation demonstrate consistent effectiveness and safety. Most patients maintain freedom from atrial arrhythmias throughout a five-year follow-up period on average[44]. These long-term results are indispensable for gauging the enduring efficacy of PVI as a viable treatment approach.

The efficacy of segmental pulmonary vein isolation (PVI) stands out in patients with both paroxysmal and persistent atrial fibrillation (AF), emphasizing the significance of patient selection. Notably, individuals with paroxysmal AF exhibit a superior freedom from recurrence rate [45].

Conclusions

In wrapping up, this review highlights the intricate interplay among atrial fibrillation (AF), mitral regurgitation (MR), and the role of pulmonary vein isolation (PVI) in patients undergoing percutaneous mitral valve repair (PMVR) utilizing devices such as the MitraClip. Through our examination of the literature, we've uncovered the noteworthy prevalence of AF in MR patients and its detrimental effects on clinical outcomes. Despite the remarkable advancements in PMVR, notably with the MitraClip, the coexistence of AF presents additional complexities. Although pulmonary vein isolation (PVI) holds promise as a viable catheter ablation technique for AF treatment, the optimal timing and efficacy of PVI in the PMVR context remain contentious subjects.

Looking ahead, there is an urgent call for randomized controlled trials (RCTs) to delineate the effectiveness of pulmonary vein isolation (PVI) in patients undergoing planned MitraClip procedures. These trials should adhere to stringent methodologies, including randomization into groups receiving PVI before and after MitraClip implantation, with a requisite follow-up period of at least five years. Evaluation criteria should encompass not only clinical endpoints but also labor-related parameters, quality of life assessments, and echocardiographic measures. Through such

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rigorous studies, we stand to gain deeper insights into the long-term efficacy and implications of PVI in ameliorating outcomes for patients undergoing percutaneous mitral valve repair with MitraClip, thereby steering the course towards optimal treatment strategies and elevating the standard of patient care.

Limitations

The review's limitations stem from potential data variability among studies due to differing methodologies and outcome measures, the risk of publication bias, incomplete data in some studies, and the possibility of not incorporating the most recent research. Additionally, the review may include studies with varying designs, introducing potential confounding factors and variability in evidence quality. Generalizability may be limited, and biases in study selection and language could impact the conclusions. Addressing these limitations is essential for maintaining a comprehensive and balanced interpretation of the reviewed evidence.

References

1. Asgar AW. Atrial Fibrillation in Mitral Regurgitation Patients: A Harbinger for Poorer Outcomes. *Structural Heart*. 2018;2(6):538–540. [DOI:10.1080/24748706.2018.1521028](https://doi.org/10.1080/24748706.2018.1521028)
2. Nishimura RA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):e1159–e1195. [DOI: 10.1161/CIR.0000000000000503](https://doi.org/10.1161/CIR.0000000000000503)
3. Obadia JF, et al. MitraClip Transcatheter Mitral Valve Repair in Secondary Mitral Regurgitation: One-Year Results of the COAPT Trial. *JAMA Cardiology*. 2019;4(1):1–10. [DOI: 10.1001/jamacardio.2018.4622](https://doi.org/10.1001/jamacardio.2018.4622)
4. Vassileva CM, et al. Mitral Regurgitation in Patients with Atrial Fibrillation: Prevalence, Clinical Characteristics, and Outcome. *Cardiology Research and Practice*. 2011;2011:1–6. [DOI: 10.4061/2011/958132](https://doi.org/10.4061/2011/958132)
5. Mohrez, Y., Strohmaier, J., Paiva, T. C., Forkmann, M., Butz, S., Acil, T., Schnupp, S., Mahnkopf, C., & Busch, S. (2022). Impact of atrial fibrillation on outcome of percutaneous mitral valve repair (PMVR) procedure. European Heart Journal, 43(Supplement_2), ehac544.3681.
6. Spieker, M., Hellhammer, K., Spieh€ofer, J., Katsianos, S., Balzer, J., Zeus, T., Horn, P., Kelm, M., & Westenfeld, R. (2018). Effect of Atrial Fibrillation and Mitral Valve Gradients on Response to Percutaneous Mitral Valve Repair With the MitraClip System. The American Journal of Cardiology, 122(8), 1371-13782.
7. Kataoka, A., Watanabe, Y., & The OCEAN-SHD Family. (2022). MitraClip: a review of its current status and future perspectives. Cardiovascular Intervention and Therapeutics, 38, 28–383.
8. Oh, N. A., Kampaktsis, P. N., Gallo, M., Guariento, A., Weixler, V., Staffa, S. J., Avgerinos, D. V., Colli, A., & Doulamis, I. P. (2021). An updated meta-analysis of MitraClip versus surgery for mitral regurgitation. Annals of Cardiothoracic Surgery, 10(1)4.
9. Alessandro, Albini., Matteo, Passiatore., Jacopo, Francesco, Imberti., Anna, Chiara, Valenti., Giulio, Leo., Marco, Vitolo., Francesca, Coppi., Fabio, Sgura., Giuseppe, Boriani. (2022). Ventricular and Atrial Remodeling after Transcatheter Edge-to-Edge Repair: A Pilot Study. Journal of Personalized Medicine, doi: 10.3390/jpm12111916
10. Toprak, C.; Kahveci, G.; Kilicgedik, A.; Pala, S.; Kirma, C.; Tabakci, M.M.; Inanir, M.; Esen, A.M. Left atrial remodeling in patients undergoing percutaneous mitral valve repair with the MitraClip system: An advanced echocardiography study. Echocardiography 2016, 33, 1504–1511.
11. Grayburn, P.A.; Foster, E.; Sangli, C.; Weissman, N.J.; Massaro, J.; Glower, D.G.; Feldman, T.; Mauri, L. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. Circulation 2013, 128, 1667–1674.
12. Giannini, C.; Petronio, A.S.; De Carlo, M.; Guarracino, F.; Conte, L.; Fiorelli, F.; Pieroni, A.; Di Bello, V. Integrated reverse left and right ventricular remodelling after MitraClip implantation in functional mitral regurgitation: An echocardiographic study. Eur. Heart J. Cardiovasc. Imaging 2014, 15, 95–103.
13. Luca, Arzuffi., J, Zannoni., Alessandro, Vairo., Fabrizio, D'Ascenzo., Gianluca, Alunni., G., D., De, Ferrari., Francesco, Bedogni. (2023). Left atrial function assessed by speckle tracking echocardiography as a marker of atrial reverse remodeling in patients with mitral regurgitation treated with transcatheter edge-to-edge repair. European journal of echocardiography, doi: 10.1093/ehjci/jead119.363

14. Alexander, Molnar., D., Pasztor., Adrian, Santa., Istvan, Hizoh., E, Straub., Anikó, Ilona, Nagy., Aka, Jean, Astrid., László, Gellér., Béla, Merkely. (2023). Left atrial remodeling and right ventricular-pulmonary arterial coupling after MitraClip implantation. European journal of echocardiography, doi: 10.1093/ehjci/jead119.378
15. Brian, R., Lindman., Federico, M., Asch., Paul, A., Grayburn., Michael, J., Mack., Jeroen, J., Bax., Holly, Gonzales., Kashish, Goel., Colin, MacLeod, Barker., Sandip, Zalawadiya., Maria, Alu., Neil, J., Weissman., William, T., Abraham., JoAnn, Lindenfeld., Gregg, W., Stone. (2023). Ventricular Remodeling and Outcomes After Mitral Transcatheter Edge-to-Edge Repair in Heart Failure: The COAPT Trial.. Jacc-cardiovascular Interventions, doi: 10.1016/j.jcin.2023.02.031
16. Augustin, Coisne., Josep, Rodés-Cabau., Sebastian, Ludwig., Andrea, Scotti., Jules, Mesnier., Torsten, P., Vahl., Lauren, S., Ranard., Thomas, Modine., Juan, F., Granada. (2023). Impact of a Dedicated Transseptal Transcatheter Mitral Valve Replacement System on Cardiac Remodeling and Hemodynamics.. Jacc-cardiovascular Interventions, doi: 10.1016/j.jcin.2023.02.037
17. Siddharth, Shah., Vijay, Raj., Mahmoud, Abdelghany., Carlos, Mena-Hurtado., Sana, Riaz., Siddharth, B, Patel., Howard, W., Wiener., Debanik, Chaudhuri. (2021). Impact of atrial fibrillation on the outcomes of transcatheter mitral valve repair using MitraClip: a systematic review and meta-analysis. Heart Failure Reviews, doi: 10.1007/S10741-020-10051-Z
18. Eguchi K, Ohtaki E, Matsumura T, Tanaka K, Tohbaru T, Iguchi N, Misu K, Asano R, Nagayama M, Sumiyoshi T, Kasegawa H, Hosoda S. Pre-operative atrial fibrillation as the key determinant of outcome of mitral valve repair for degenerative mitral regurgitation. Eur Heart J. 2005 Sep;26(18):1866-72. doi: 10.1093/eurheartj/ehi272. Epub 2005 Apr 21. PMID: 15845559
19. Velu JF, Kortlandt FA, Hendriks T, Schurer RAJ, van Boven AJ, Koch KT, Vis MM, Henriques JP, Piek JJ, Van den Branden BJL, Schaap J, Rensing BJ, Swaans MJ, Bouma BJ, Van der Heyden JAS, Baan J Jr. Comparison of Outcome After Percutaneous Mitral Valve Repair With the MitraClip in Patients With Versus Without Atrial Fibrillation. Am J Cardiol. 2017 Dec 1;120(11):2035-2040. doi: 10.1016/j.amjcard.2017.08.022. Epub 2017 Aug 30. PMID: 29033048.
20. Arturo, Giordano., Ciro, Indolfi., Cesare, Baldi., Paolo, Ferraro., Filippo, Finizio., Nicola, Corcione., Michele, Polimeno., Stefano, Messina., Annalisa, Mongiardo., Giuseppe, Biondi, Zoccai., Massimo, Mancone., Raffaella, Avellino., Gennaro, Sardella. (2015). History of Paroxysmal, Persistent, Long-Standing or Permanent Atrial Fibrillation in Patients Undergoing Transcatheter Mitral Valve Repair with Mitraclip: Does it Matter?. Journal of clinical trials, doi: 10.15226/2374-6882/2/1/00117
21. Christian, Waechter., Felix, Ausbuettel., Georgios, Chatzis., Dieter, Fischer., Holger, Nef., Sebastian, Barth., Philipp, Halbfaß., Thomas, Deneke., Sebastian, Kerber., Dimitar, Divchev., Bernhard, Schieffer., Ulrich, Luesebrink. (2020). Analysis of Atrial Fibrillation Treatment Regimes in a Multicenter Cohort of Transcatheter Edge-to-Edge Mitral Valve Repair Patients.. Journal of Interventional Cardiology, doi: 10.1155/2020/6542028
22. Jakob, Ledwoch., Anna, Nommensen., Ahmed, Keelani., Roza, Meyer-Saraei., Thomas, Stiermaier., Mohammed, F., Saad., Janine, Pöss., Steffen, Desch., Roland, Tilz., Holger, Thiele., Ingo, Eitel., Charlotte, Eitel. (2019). Impact of transcatheter mitral valve repair on ventricular arrhythmias.. Europace, doi: 10.1093/EUROPACE/EUZ061
23. Keßler M, Pott A, Mammadova E, Seeger J, Wöhrle J, Rottbauer W, Markovic S. Atrial Fibrillation Predicts Long-Term Outcome after Transcatheter Edge-to-Edge Mitral Valve Repair by MitraClip Implantation. Biomolecules. 2018 Nov 19;8(4):152. doi: 10.3390/biom8040152. PMID: 30463247; PMCID: PMC6316291
24. Waechter C, Ausbuettel F, Chatzis G, Cheko J, Fischer D, Nef H, Barth S, Halbfass P, Deneke T, Kerber S, Kikec J, Mueller HH, Divchev D, Schieffer B, Luesebrink U. Impact of Rhythm vs. Rate Control in Atrial Fibrillation on the Long-Term Outcome of Patients Undergoing Transcatheter Edge-to-Edge Mitral Valve Repair. J Clin Med. 2021 Oct 28;10(21):5044. doi: 10.3390/jcm10215044. PMID: 34768567; PMCID: PMC8584691.
25. W Li, N Tiwari, Amiodarone use in elderly atrial fibrillation patients with preserved ejection fraction is associated with increased short-term mortality, European Heart Journal, Volume 41, Issue Supplement_2, November 2020, ehaa946.0548, https://doi.org/10.1093/ehjci/ehaa946.0548
26. Ausbuettel F, Barth S, Chatzis G, Fischer D, Kerber S, Mueller J, List S, Halbfass P, Deneke T, Nef H, Mueller HH, Divchev D, Schieffer B, Luesebrink U, Waechter C. Catheter ablation of concomitant atrial fibrillation improves survival of patients undergoing transcatheter edge-to-edge mitral valve repair. Front Cardiovasc Med. 2023 Aug 14;10:1229651. doi: 10.3389/fcvm.2023.1229651. PMID: 37645518; PMCID: PMC10461005.
27. Suwalski P, Kowalewski M, Jasiński M, Staromłyński J, Zembala M, Widenka K, Brykczyński M, Skiba J, Zembala MO, Bartuś K, Hirnle T, Dziembowska I, Tobota Z, Maruszewski BJ; KROK Investigators. Survival after surgical ablation for atrial fibrillation in mitral valve surgery: Analysis from the Polish National Registry of Cardiac Surgery Procedures (KROK). J Thorac Cardiovasc Surg. 2019 Mar;157(3):1007-1018.e4. doi: 10.1016/j.jtcvs.2018.07.099. Epub 2018 Sep 8. PMID: 30314688.

28. Malcolm Finlay, Stanislav Hadjivassilev, Attempting to cure atrial fibrillation during mitral valve surgery: can we measure a benefit?, European Heart Journal - Quality of Care and Clinical Outcomes, Volume 2, Issue 4, October 2016, Pages 235–236, https://doi.org/10.1093/ehjqcco/qcw036
29. Almorad A, O'Neill L, Wielandts JY, Gillis K, De Becker B, Nakatani Y, De Asmundis C, Iacopino S, Pambrun T, Marc M, Jaïs P, Haïssaguerre M, Duytschaever M, Chierchia JB, Derval N, Knecht S. Long-term clinical outcome of atrial fibrillation ablation in patients with history of mitral valve surgery. Front Cardiovasc Med. 2022 Dec 21;9:928974. doi: 10.3389/fcvm.2022.928974. PMID: 36620626; PMCID: PMC9811118.
30. Rottner L, Lemes C, Dotz I, Wohlmuth P, Schmidt T, Mathew S, Heeger CH, Reissmann B, Fink T, Rillig A, Frerker C, Ouyang F, Kuck KH, Metzner A, Maurer T. The clip and the tip: Lessons learned from ablation of atrial fibrillation in patients postpercutaneous mitral valve repair. J Cardiovasc Electrophysiol. 2019 Aug;30(8):1207-1214. doi: 10.1111/jce.13964. Epub 2019 May 21. PMID: 31045293.
31. Renato A.K Kalil, Gustavo G Lima, Tiago L.L Leiria, Rogério Abrahão, Leonardo M Pires, Paulo R Prates, Ivo A Nesralla, Simple surgical isolation of pulmonary veins for treating secondary atrial fibrillation in mitral valve disease11This article has been selected for the discussion forum on the CTSNet Web site:http://www.ctsnet.org/doc/5499,The Annals of Thoracic Surgery,Volume 73, Issue 4,2002, Pages 1169-1173, ISSN 0003-4975
32. Iribarne A, DiScipio AW, McCullough JN, Quinn R, Leavitt BJ, Westbrook BM, Robich MP, Sardella GL, Klemperer JD, Kramer RS, Weldner PW, Olmstead EM, Ross CS, Malenka DJ; Northern New England Cardiovascular Disease Study Group. Surgical Atrial Fibrillation Ablation Improves Long-Term Survival: A Multicenter Analysis. Ann Thorac Surg. 2019 Jan;107(1):135-142. doi: 10.1016/j.athoracsur.2018.08.022. Epub 2018 Oct 6. PMID: 30300644.
33. Musharbash FN, Schill MR, Sinn LA, Schuessler RB, Maniar HS, Moon MR, et al. Performance of the cox-maze IV procedure is associated with improved long-term survival in patients with atrial fibrillation undergoing cardiac surgery. J Thorac Cardiovasc Surg. (2018) 155:159–70. doi: 10.1016/j.jtcvs.2017.09.095
34. McCarthy PM, Manjunath A, Kruse J, Andrei A-C, Li Z, McGee EC, et al. Should paroxysmal atrial fibrillation be treated during cardiac surgery? J Thorac Cardiovasc Surg. (2013) 146:810–23. doi: 10.1016/j.jtcvs.2013.05.015
35. Lee R, McCarthy PM, Wang EC, Vaduganathan M, Kruse J, Malaisrie SC, et al. Midterm survival in patients treated for atrial fibrillation: a propensity-matched comparison to patients without a history of atrial fibrillation. J Thorac Cardiovasc Surg. (2012) 143:1341–51. doi: 10.1016/j.jtcvs.2012.02.0
36. Badhwar V, Rankin JS, Damiano RJ, Gillinov AM, Bakaeen FG, Edgerton JR, et al. The society of thoracic surgeons 2017 clinical practice guidelines for the surgical treatment of atrial fibrillation. Ann Thorac Surg. (2017) 103:329–41. doi: 10.1016/j.athoracsur.2016.10.076
37. Rillig A, Tilz RR, Lin T, et al. Unexpectedly high incidence of stroke and left atrial appendage thrombus formation after electrical isolation of the left atrial appendage for thromboembolic protection. Circ Arrhythm Electrophysiol. 2018;11(5):e006539. doi:10.1161/CIRCEP.118.006539
38. Godino C, Sisinni A, Pivato CA, Adamo M, Taramasso M, Parlati A, Italia L, Voci D, Scotti A, Munafò A, Buzzatti N, Denti P, Ancona F, Fiore G, Sala A, Vergara P, Bodega F, Ruffo MM, Curello S, Castiglioni A, De Bonis M, Alfieri O, Agricola E, Maisano F, Metra M, Colombo A, Margonato A; MiZüBr registry. Prognostic Value of Pre-operative Atrial Fibrillation in Patients With Secondary Mitral Regurgitation Undergoing MitraClip Implantation. Am J Cardiol. 2021 Mar 15;143:51-59. doi: 10.1016/j.amjcard.2020.12.043. Epub 2020 Dec 30. PMID: 33359201.
39. Khan, M., Jaïs, P., Cummings, J., Biase, L., Sanders, P., Martin, D., Kautzner, J., Hao, S., Themistoclakis, S., Fanelli, R., Potenza, D., Massaro, R., Wazni, O., Schweikert, R., Saliba, W., Wang, P., Al-Ahmad, A., Beheiry, S., Santarelli, P., Starling, R., Russo, A., Pelargonio, G., Brachmann, J., Schibgilla, V., Bonso, A., Casella, M., Raviele, A., Haïssaguerre, M., & Natale, A. (2008). Pulmonary-vein isolation for atrial fibrillation in patients with heart failure.. The New England journal of medicine, 359 17, 1778-85 . https://doi.org/10.1056/NEJMoa0708234.
40. Albrecht, Á., Kalil, R., Schuch, L., Abrahão, R., Sant'anna, J., Lima, G., & Nesralla, I. (2009). Randomized study of surgical isolation of the pulmonary veins for correction of permanent atrial fibrillation associated with mitral valve disease.. The Journal of thoracic and cardiovascular surgery, 138 2, 454-9 . https://doi.org/10.1016/j.jtcvs.2009.04.023.
41. Sueda, T., Imai, K., Ishii, O., Orihashi, K., Watari, M., & Okada, K. (2001). Efficacy of pulmonary vein isolation for the elimination of chronic atrial fibrillation in cardiac valvular surgery. The Annals of thoracic surgery, 71 4, 1189-93 . https://doi.org/10.1016/S0003-4975(00)02606-0.
42. Hong, G., Shin, D., Park, J., Kim, Y., Shim, B., Lee, J., Jung, T., Lee, D., & Han, S. (2002). Effects of Pulmonary Vein Isolation Using Intraoperative Radiofrequency Catheter Ablation for the Treatment of Atrial

 doi:10.20944/preprints202404.1966.v1

Fibrillation Associated with Mitral Valvular Heart Diseases. Korean Circulation Journal, 32, 596-603. https://doi.org/10.4070/KCJ.2002.32.7.596.

43. Philip, F., Muhammad, K., Agarwal, S., Natale, A., & Krasuski, R. (2012). Pulmonary vein isolation for the treatment of drug-refractory atrial fibrillation in adults with congenital heart disease.. Congenital heart disease, 7 4, 392-9 . https://doi.org/10.1111/j.1747-0803.2012.00649.x.
44. Maat, G., Pozzoli, A., Scholten, M., Gelder, I., Blaauw, Y., Mulder, B., Bella, P., Alfieri, O., Benussi, S., & Mariani, M. (2015). Long-term results of surgical minimally invasive pulmonary vein isolation for paroxysmal lone atrial fibrillation.. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology, 17 5, 747-52 . https://doi.org/10.1093/europace/euu287.
45. Oral, H., Knight, B., Tada, H., Özaydın, M., Chugh, A., Hassan, S., Scharf, C., Lai, S., Greenstein, R., Pelosi, F., Strickberger, S., & Morady, F. (2002). Pulmonary Vein Isolation for Paroxysmal and Persistent Atrial Fibrillation. Circulation: Journal of the American Heart Association, 105, 1077-1081. https://doi.org/10.1161/HC0902.104712.