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# Abstract: Review

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# Atrial Fibrillation and Poor Outcomes in Critically Ill COVID-19 Patients: A Systematic Review

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**Background:** Atrial fibrillation (AF) is one of the most frequent cardiovascular problem encountered in critically ill COVID-19 patients. Increasing evidence suggests that COVID-19 infection is associated with myocardial injury and arrhythmic complications, thus increasing the susceptibility to AF. In critically ill COVID-19 patients, atrial tachyarrhythmia is related with higher mortality. Furthermore, AF has been linked to poorer clinical outcomes in individuals with sepsis. Despite the fact that numerous research suggest the association between severe COVID-19 and cardiovascular events, the link between AF and poor outcomes in critically ill COVID-19 patients remains unexplained. This study aims to systematically review the increasing evidence related to atrial fibrillation and it's correlation with poor outcomes in critically ill COVID-19 patients.
**Methods:** A systematic review was performed according to the PRISMA guidelines in search of relevant studies in the online databases PUBMED and ScienceDirect. Included studies are the ones focusing on critically ill COVID-19 patients with AF, both new onset and history of AF. The Newcastle-Ottawa Scale was used to evaluate the risk of bias.
**Results:** Three retrospective studies were included in this review. All of the studies showed that AF patients have higher ICU mortality. AF patients also have higher baseline risk that may act as a confounding factor. The correlation between AF and poor outcomes in critically ill COVID-19 patients is prominent, although the exact mechanism needs further research.
**Conclusions:** AF can be considered as a risk factor for increased mortality in severe COVID-19 patients, although it may not be the only contributing risk factor. As a result of its strong predictive value, the assessment of cardiac involvement, particularly AF, in COVID-19 infection is crucial.

**Keywords:** Atrial Fibrillation, COVID-19, Critical Care

**Table 1.** Characteristics of Included Studies

| Author, publication date | Setting | Inclusion Time | Participants | Results | AF Patients Characteristics | Conclusion |
|---|---|---|---|---|---|---|
| **Abdulrahman et al.** | Bahrain | April 2020 to November 2020 | 492 patients with severe COVID-19 in the ICU<br><br>30 patients had NOAF | AF had an **odds ratio of 3.96 (95% CI: 1.05-14.98; p = 0.042) for the primary outcome** (requirement of mechanical ventilation or death). | • Older mean age<br>• Higher prevalence of baseline comorbidities (diabetes, hypertension, CAD and HF)<br>• Significantly higher rise in biochemical parameteres (CKMB, BNP, D-Dimer, CRP)<br>• Lower mean eGFR,<br>• Significantly lower SBP,<br>• Higher BUN and serum creatinine<br>• Higher percentage of inotrope use | NOAF increases risk of mechanical ventilation requirement and mortality in patients admitted with severe COVID-19 in the ICU. |
| **Ip, Randy J et al.** | Michigan, USA | 15 March 2020 to 30 April 2020 | 171 patients with COVID-19 admitted to the ICU<br><br>23 patients had NOAF<br>27 patients had prior AF history | The presence of AF led to a **2.38 times greater risk of mortality** compared to normal sinus rhythm. **(95% CI, 1.52-3.71; p < 0.001)** A multivariable logistic regression analysis identified the presence or history of AF **(OR 4.8, p=0.004)** as a **significant cardiovascular attribute that contributed to increased mortality**. | • Older age<br>• Higher propensity to be intubated during ICU stay<br>• Higher maximum troponin value | This study suggests a relationship between AF and increased mortality from COVID-19. While AF may not be the sole driver, findings from this study suggest that it can be considered a risk factor for increased mortality. |
| **Ergün et al.** | Turkey | March 2020 to January 2021 | 248 of 301 patients with COVID-19 admitted to the ICU included in the study<br><br>37 patients had NOAF | **Hospital mortality was higher in the NOAF group (87% vs 67%, respectively, P = 0.019).** However, in multivariate analysis, NOAF was **not an independent risk factor for hospital mortality (OR 1.42, 95% CI 0.40- 5.09, P = 0.582).** | • Older age<br>• Higher CCI median score<br>• Higher BNP level, median level for HS troponin I and BUN<br>• Lower PaO2/FiO2 ratio<br>• Higher pulmonary embolism rate<br>• Significantly higher incidence of secondary bacterial infection<br>• More frequent incidence of AKI and VAP | Hospital mortality was higher in the NOAF group. However, NOAF was not an independent risk factor for hospital mortality in patients with COVID-19. |

**NOAF** = New Onset Atrial Fibrillation, **CAD** = Coronary Artery Disease, **HF** = Heart Failure, **CKMB** = Creatine Kinase-MB, **BNP** = B-type natriuretic peptide, **SBP** = Systolic Blood Pressure, **BUN** = Blood Urea Nitrogen, **CCI** = Charlson Comorbidity Index, **AKI** = Acute Kidney Injury, **VAP** = Ventilator-associated pneumonia

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# Comparison of efficacy between Catheter Ablation and Anti-arrhythmic Drugs to Treat Episodes of Atrial Fibrillation: A Systematic Review and Meta-analysis

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**Background:** Atrial Fibrillation (AF) is the most common arrhythmia in clinical practice. Patients with AF have an increased longterm risk of stroke, heart failure, and all-cause mortality. The primary treatment of patients with AF is the relief of symptoms measured by reducing the frequency and episodes of AF. Catheter ablation has become an alternative therapy for AF. Several recent studies have compared antiarrhythmic drug therapy with catheter ablation. This study was conducted to compare the efficacy between catheter ablation and anti-arrhythmic drugs in treating episodes of atrial fibrillation.
**Methods:** We searched PubMed, ScienceDirect, and Google Scholar for Randomised Controlled Trials (RCTs) of catheter ablation and anti-arrhythmic drugs for the treatment atrial Fibrillation. RCTs were screened with our eligibility criteria and the quality was assessed using the Cochrane Risk Index of Bias tools. The primary outcome analyzed is free episode of atrial fibrillation measured as standardized mean differences (SMDs) with 95% confidence intervals (CIs). Heterogenecity was assessed using the $I^2$ test, and publication bias was evaluated using a funnel plot. All analysis were performed using Review Manager 5.4.
**Results:** Six RCTs involving 1118 patients (of whom 601 underwent catheter ablation) met the inclusion criteria. Our pooled analysis showed that compared to drug group, catheter ablation had significant effect in improving episodes of AF (SMD 1.57, 95% CI 1.21, 2.02, p=0.00001, $I^2$=84%). The funnel plot appeared symmetrical.

**Conclusion:** Our study revealed that catheter ablation is more beneficial in treating atrial fibrillation. However, it is still the patient preference whether to do catheter ablation or not according to the current guideline.

**Keywords:** Atrial fibrillation, Catheter ablation, Anti-arrhythmic drugs

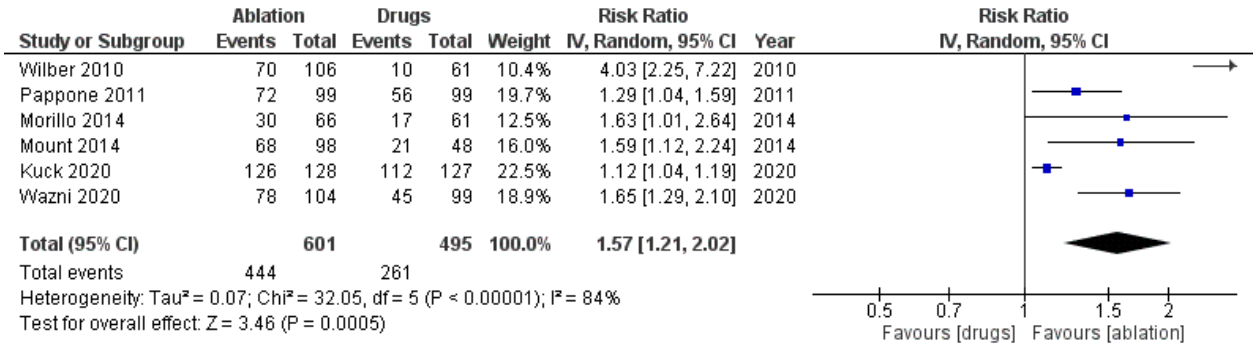


**Figure 1**. Forest plot of Comparison between catheter ablation and anti-arrhythmic drugs

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# The Role of Dexmedetomidine to Reduce New-Onset Atrial Fibrillation in Patients Who Undergo Invasive Cardiac Treatment: A Systematic Review

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**Background:** One of common consequences of cardiac surgery or invasive cardiac treatment is atrial fibrillation (AF) incidence. Activation of the sympathetic nervous system and provocation of systemic inflammatory responses after cardiac surgery reportedly contributes to the new-onset AF. Dexmedetomidine (DEX), an exceptionally selective α2-adrenergic receptor (α2-AR) agonist, depresses sinus nodes and ventricular nodal function. That makes DEX considered for having the effect of reducing new-onset AF, thus a reasonable prophylactic drug of choice to lower the incidence of atrial fibrillation after invasive treatment. In this systematic review, we aimed to know the role of a dexmedetomidine (DEX) to reduce new-onset AF in patients who undergo cardiac surgery or invasive cardiac treatment.
**Methods:** A systematic review of interventional studies was performed. Four scientific databases (PubMed, EbscoHost, ClinicalKey, and ScienceDirect) were included in the literature searching strategy. Selected papers then explored by two independent authors regarding the clinical use of dexmedetomidine. Relevance studies further reviewed using the Centre for Evidence-based Medicine (CEBM) critical appraisal tool.
**Results:** Three studies that included in the review were published within five years between 2016 to 2021. One of the three studies suggest that dexmedetomidine infusions were more likely to have less incidence of postoperative atrial fibrillation (POAF). In contrast, the other two articles concluded that did not decrease postoperative atrial arrhythmias or delirium. In patients recovering from cardiac surgery, DEX may impair sinus and AV nodal function, however, it may not reduce the AF inducibility.
**Conclusion:** Atrial fibrillation still becomes one of the risks after invasive cardiac treatment. The administration of DEX is still untimely to become the solution to prevent arrhythmic complications. Further data needed to give a better understanding.

**Keywords:** Atrial Fibrillation; Cardiac Surgery; Dexmedetomidine.

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# Left Atrial Strain as The Predictor of New-Onset Atrial Fibrillation: A Meta-analysis

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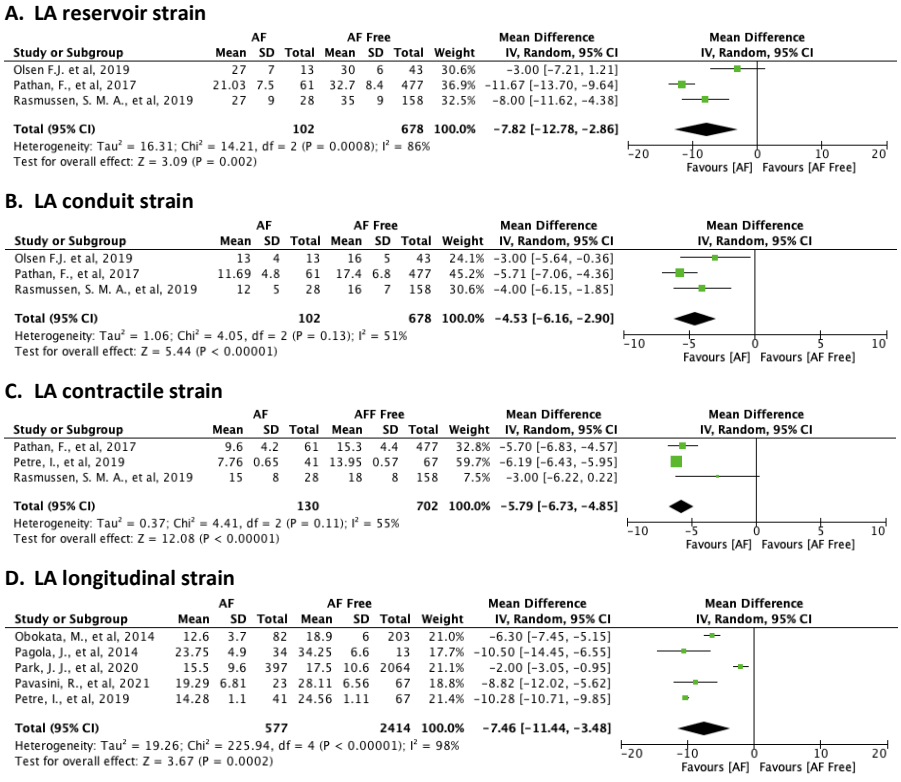
**Background:** Atrial fibrillation (AF) is the most common arrhythmia in daily clinical practice. Predictors of the AF incidence are important to be explored to anticipate thromboembolic events. Left atrial (LA) strain is considered a predictor of the incidence of AF, but the relationship remains unclear. This study aims to investigate the ability of the LA strain in predicting now onset AF.
**Method:** A meta-analysis was conducted in September 2021. The relevant articles reporting the correlation between LA strain and new-onset AF were collected from the electronic scientific database such as PubMed, ScienceDirect, and Google Scholar. The pooled effects were determined using mean difference (MD). We also estimated the 95% confidence interval (CI).
**Results:** A total of 8 studies including 679 and 3092 patients with sinus rhythm in baseline in AF and AF free groups were involved in this meta-analysis. Patients who suffered from AF during follow-up period had a lower LA reservoir strain (MD = -7.82 %; 95% CI = -12.78 to -286; $p < 0.01$), LA conduit strain (MD = -4.53 %; 95% CI = -6.16 to -2.90; $p < 0.01$), LA contractile strain (MD = -5.79 %; 95% CI = -6.73 to -4.85; $p < 0.01$) and LA longitudinal strain (MD = -7.46 %; 95% CI = -11.44 to -3.48; $p < 0.01$).
**Conclusion:** LA strain could be the predictor for new-onset AF. LA strain parameters for predicting the new-onset AF include LA reservoir strain, LA conduit strain, LA contraction strain, and LA longitudinal strain.

**Keywords**: left atrial strain, new-onset atrial fibrillation, predictors




Forest plot comparing the: (A) LA reservoir strain; (B) LA conduit strain; (C) LA contractile strain; and (D) LA longitudinal strain between AF and AF free group. CI = confidence interval; M-H = Mantel-Haenszel; and LA = left atrial.

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# The Antiarrhythmic Properties of Angiotensin Receptor-Neprilysin Inhibitor (ARNi) in Preventing Cardiac Arrhythmias in Heart Failure with Reduced Ejection Fraction Patients: A Systematic Review and Meta Analysis

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**Background:** Angiotensin receptor-neprilysin inhibitor (ARNi) is a medicine resulting from the combination of sacubitril and valsartan, which is known to improve the LVEF and lower mortality in patients with HFrEF. Several clinical trials suggest that ARNi was highly effective in modulating the risks of atrial and ventricular arrhythmias by reversing disadvantageous cardiac remodelling, thereby indirectly targeting the arrhythmogenic substrate, and reducing the proarrhythmogenic sarcoplasmic reticulum $Ca^{2+}$ leak, subsequently reducing the arrhythmic burden. This meta analytic study aims to summarize the possible antiarrhythmic properties and beneficial roles of ARNi against cardiac arrhythmia in patients with heart dissases with reduced LVEF.
**Methods:** Systematic search and meta-analysis were conducted with literatures from Elsevier, SpringerLink, Oxford Academic, and ProQuest according to PRISMA Guidelines for interventional trials regarding antiarrhythmic properties and benefits of angiotensin receptor-neprilysin inhibitor against all-type cardiac arrhythmias in patients with heart failure with reduced ejection fraction, using ARNi, cardiac arrhythmia, HFrEF, and antiarrhythmic properties as keywords.
**Results:** A sum of 7 literatures were analysed, consisting of 655 adult patients with reduced ejection fraction with or without ICD or CRT device implanted. The subjects were treated with sacubitril/valsartan in comparison to conventional angiotensin inhibitions with ACEi or ARBs, in either a single group with consecutive therapies or two group interventional trials in a period of 6 months – 1 year. Most of these trials exhibit beneficial antiarrhythmic effects of sacubitril/valsartan, significantly reducing the number of patients experiencing sustained VT (0.83% vs. 6.66%, $P<0.03$) and NSVT (37.5% vs. 59.1%, $P<0.0001$); reducing the mean episodes count (5.4 vs. 15, $P<0.002$) and duration (5.4s vs. 8s, $P<0.001$) of NSVT, and reducing mean PVC count per hour (33/hour vs. 78/hour, $P<0.001$) in the intervention group. Also less total shocks (6 shocks/patient vs. 20 shocks/patient, $P<0.007$), both appropriate and inappropriate, recorded in patients with ICD. One study reported superior outcome regarding recurring atrial fibrillation, with 35 patients (87.5%) experiencing zero relapse after 1 year therapy with ARNi, compared to the control group with 22 patients (55%) ($P=0.001$).
**Conclusion:** ARNi showed beneficial antiarrhythmic effects in patients with reduced LVEF based on evidences exhibited. Further research is necessary to accurately explain the antiarrhythmic mechanisms of ARNi.
**Keywords:** ARNi, cardiac arrhythmia, HFrEF, antiarrhythmic properties.

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# Holistic Approach of Ablation Versus Antiarrhythmic Drugs for Efficacy, Safety, and Quality of Life Improvement in Rhythm Control of Atrial Fibrillation: A Meta-Analysis of Randomized Trials

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**Background:** Recent studies have shown that catheter ablation (CA) is more superior compared to the usage of the antiarrhythmic drug (AAD) regarding its efficacy in decreasing the incidence of persistent and chronic atrial fibrillation (AF). However, choosing the right rhythm control strategy to provide holistic care for the patients should be individualized on each patients' condition. In this meta-analysis, the author will compare both CA and AAD regarding their efficacy, safety, and their effect on the quality of life of AF patients.
**Methods:** The authors systematically searched the relevant journals throughout PubMed, Medline, and the Cochrane Library, with a range of publications from 2010 to 2021. The primary outcomes were AF recurrence, quality of life score, and adverse events. Secondary outcomes were the rehospitalization rate and all-cause mortality. Analysis was performed using a random-effects model with the Mantel-Haenszel method, and results are presented as 95% CIs.
**Results**: A total of 23 RCTs consisted of 10,316 patients were included. Although some adverse events (pericarditis, pleural effusions, and cardiac tamponade) were found in 2.8% population of the CA group (RR: 4.15; 95% CI:1.65,10.41; p=0.002), the CA group was found superior in suppressing the rate of AF recurrence (RR: 0.56; 95% CI:0.48,0.65; p<0.00001). Regarding the SF-36 Mental (p<0.00001) and Physical Assessment (p<0.0001), both CA and AAD showed increased quality of life post treatment compared with baseline level (pre-treatment) for each therapy. Following the interventions, the CA group significantly showed a lower rehospitalization rate (RR: 0.82; 95% Ci:0.70,0.97; p=0.02) and also showed a lessened mortality trend (6.84%) compared to the AAD group (9.01%) even though not statistically significant.
**Conclusion**: Statistically, there is no difference for both groups in their capability of reducing the mortality rate. However, CA was found to be more superior in efficacy and reducing the number of rehospitalizations. Quality of life also significantly improve same as AAD, which further might be provide a holistic outcome of rhytm control.

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# Is Leadless Pacemakers Associated with Higher Incidence of Lead dislodgement and Post-procedural Hematoma?

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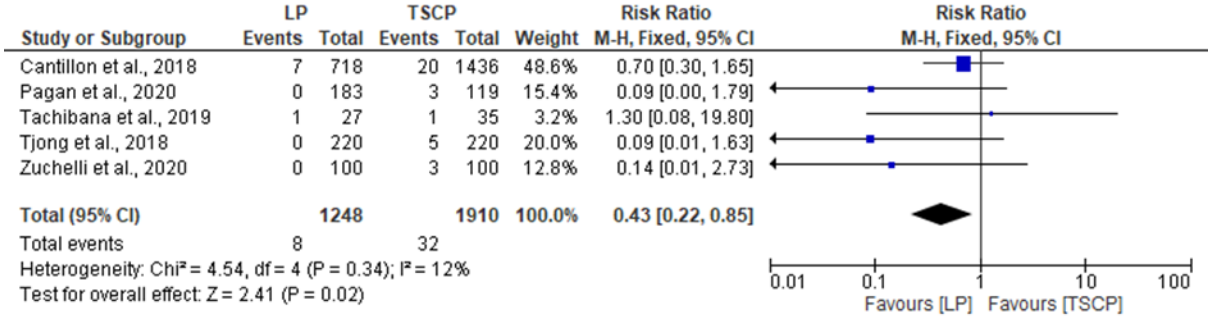
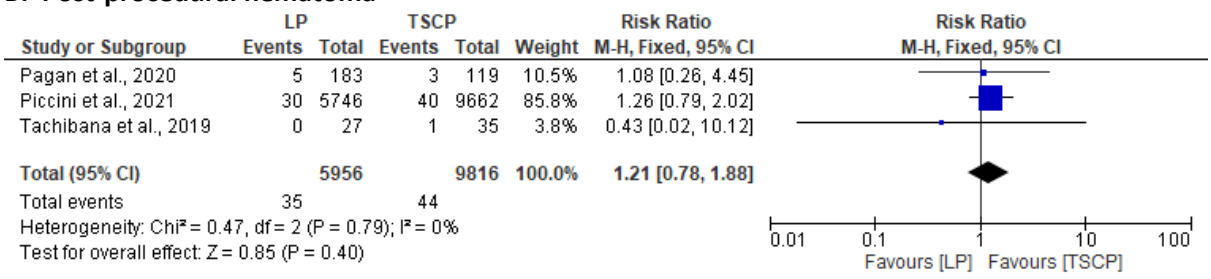
**Background:** Leadless pacemakers and transvenous single-chamber pacemakers have been widely used for bradycardia treatment. However, it is still necessary to assess the safety of both procedures. We performed a meta-analysis to investigate the complication of leadless pacemakers and transvenous single-chamber pacemaker procedures.
**Methods:** Relevant articles reporting complications after pacemaker insertion published from 2018 to 2021 were collected from PubMed, ScienceDirect, and Cochrane Library. The overall effects were determined using risk ratio (RR) and 95% confidence interval (CI).
**Results:** A total of 7 studies, including 7021 and 11607 patients with the leadless pacemaker and transvenous single-chamber pacemaker procedures, respectively, were involved in this meta-analysis. Patients with leadless pacemaker had a lower risk in lead dislodgement than patients with transvenous single-chamber pacemaker (RR = 0.43; 95% CI = 0.22 to 0.85; $p$ = 0.02). There was no difference in the post-procedural hematoma complication between leadless pacemaker and transvenous single-chamber pacemaker patients (RR = 1.21; 95% CI = 0.78 to 1.88; $p$ = 0.40).
**Conclusion:** Leadless pacemaker procedure has a lower incidence of dislodgement than a transvenous single-chamber pacemaker. However, compared to the transvenous single-chamber pacemaker, the leadless pacemaker failed to reduce post-procedural hematoma.

**Keywords:** leadless pacemaker, transvenous single-chamber pacemaker, complications.

**A. Lead dislodgement**




**B. Post-procedural hematoma**




Forest plot comparing the: (A). lead dislodgement and (B). post-procedural hematoma between leadless pacemaker and transvenous single-chamber pacemaker. CI = confidence interval; M-H = Mantel-Haenszel; LP = leadless pacemaker; and TSCP = transvenous single-chamber pacemaker.

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# Exercise capacity measured by peak oxygen consumption in atrial fibrillation patients undergoing various treatment: A systematic review

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**Background:** The most prevalent cardiac arrhythmia in adults is atrial fibrillation (AF), which affects between 2% and 4% of the population worldwide. Two main therapeutic techniques for addressing AF patients at the moment are rate control and rhythm control. If suitable therapies are not provided, the disease's progression will have an impact on the patients' quality of life (QoL) due to deteriorated physical abilities. Recent studies have demonstrated that rhythm control is preferable to rate control in sustaining the QoL of AF patients. However, the direct influence of different treatment approaches to exercise capacity is still unclear. Thus, further research into this area is required. This study aims to systematically review the available evidence of atrial fibrillation treatments' impact on exercise capacity as measured by peak oxygen consumption ($VO_2$).
**Methods:** A comprehensive search for relevant literatures was conducted using predefined keywords in the online databases PUBMED, COCHRANE, and SCOPUS. Studies published in the last ten years that reported exercise capacity using $VO_2$ measurements in individuals with atrial fibrillation before and after treatment were considered. Duplicated articles were removed. The Newcastle-Ottawa Scale was used to evaluate the risk of bias.
**Results**: Seven studies were retained for the final review, which consisted of three randomized controlled trials (RCTs), two prospective cohorts, one retrospective cohort, and one cross-sectional study. Overall, rhythm control by catheter ablation (CA) has been shown to increase exercise capacity in different forms of AF when compared to pharmaceutical rate controls. Additionally, one study suggests that adding cardiac rehabilitation after CA could improve exercise capacity without increasing the risk of AF recurrence.
**Conclusion**: Individuals with atrial fibrillation are more likely to have improved exercise capacity when treated with a rhythm control strategy, whereas rate control had not shown a positive effect on exercise capacity. Larger long-term studies are needed to confirm these findings and determine the consistency over a long period.

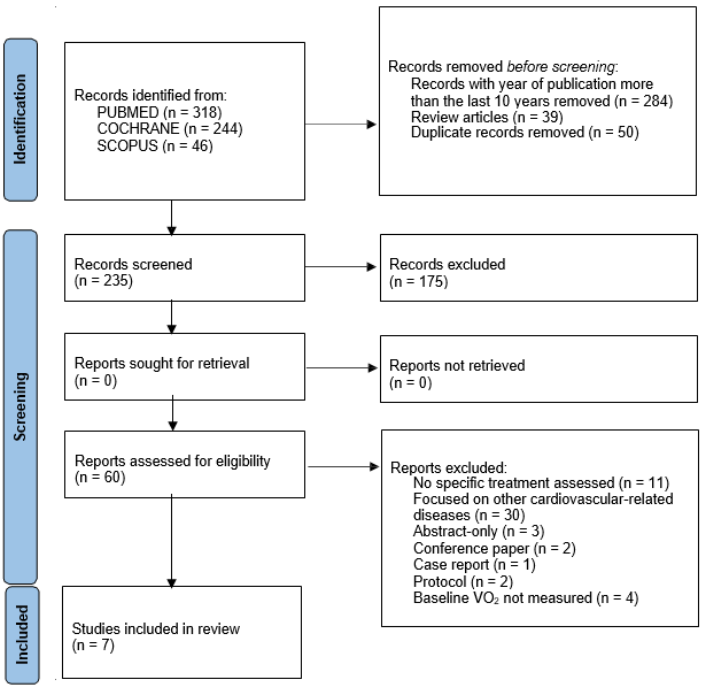


**Figure 1.** PRISMA Flow Diagram

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# Cardiac Resynchronization Therapy vs Pharmacological Therapy, Which One is Superior for Atrial Fibrillation? A Systematic Review and Meta-Analysis

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**Background:** Atrial fibrillation is the most common cardiac arrhythmia in clinical practice and has significant mortality and morbidity. It is widely accepted that the onset of atrial fibrillation (AF) in patients with heart failure (HF) indicates a poor prognosis. In the management of AF with HF, cardiac resynchronization therapy (CRT) and pharmacological therapy may become an option. However, it is yet unknown whether CRT has any advantages over conventional pharmacological therapy. The primary purpose of this study was to comprehensively evaluate the impact of CRT on the hospitalization in atrial fibrillation (AF) patients compared to pharmacological therapy
**Methods:** This was a systematic review and meta-analysis study. The article search was conducted using PubMed, SpringerLink, ProQuest, and EBSCOHost. The articles were collected using the PRISMA diagram, critically appraised using PICO analysis, then the data were analyzed using Review Manager 5.4.1 with Random Effect Model (REM). The results were effect size, heterogeneity, and study model. Data were expressed as odds ratio (OR).
**Results:** Four articles consisted of three randomized controlled trials and one cohort with a total of 571 patients reported the role of CRT and pharmacological therapy as treatment of AF with HF. Based on the analysis, there was high heterogeneity between samples ($I^2$ = 75%; p = 0.007) thus the REM was used. CRT did not significantly affect the hospitalization in AF patients compared to pharmacological therapy (OR=1.67; 95% CI 0.59-4.71; p=0.33).
**Conclusion:** CRT and pharmacological therapy showed similar effects in treating AF with HF in terms of reducing the risk of HF hospitalization, thus CRT was not superior. However, since there is only a limited amount of study available to date, further studies to compare other outcomes of CRT vs pharmacological therapy in treating AF are needed.

**Keywords:** Atrial Fibrillation, Cardiac Resynchronization Therapy, Meta-Analysis, Pharmacological Therapy

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# Safety Comparison Between Edoxaban and Warfarin in Non-Valvular Atrial Fibrillation Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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**Background:** Atrial fibrillation (AF) as the most common cardiac rhythm abnormality, is increasing in prevalence as the population ages. Morbidity and mortality are highly associated in AF, whereas it is also a strong independent risk factor for stroke. Studies have shown that the risk of bleeding with anticoagulant or antiplatelet therapy is higher in Asians than in Western patients. Previous studies have also shown that anti-coagulation with vitamin K antagonists (VKAs) is the most effective way to reduce the risk of stroke, but it turns out that about half of all eligible patients do not receive anticoagulation therapy due to several factors including the risk of bleeding. Direct factor Xa (FXa) inhibitors as the new approaches to anticoagulation for stroke prevention in patients with non-valvular AF are being studied. This study was conducted to compare the safety between edoxaban and warfarin (RFA) in non-valvular Atrial Fibrillation.
**Methods:** We searched through PubMed, Science Direct, and Google Scholar for randomized controlled trials (RCTs) of edoxaban and warfarin for non-valvular atrial fibrillation. RCTs were screened with our eligibility criteria and the quality was evaluated using the Cochrane Risk Index of Bias tools. The primary outcome analyzed in this study were the safety depicted by the outcome of bleeding and and adverse events occurred in patients, respectively measured as risk ratio (RR) with 95% confidence intervals (CIs). Heterogeneity was assessed using the $I^2$ test. All statistical analysis were performed using Review Manager 5.4.
**Results:** Four RCTs involving 3537 patients (of whom 1983 received Edoxaban) met the inclusion criteria. Our pooled analysis showed that the safety of Edoxaban group was not significantly better than warfarin group with lower bleeding risk in warfarin (RR 1.01, 95% CI 0.82, 1.25, p=0.90, $I^2$= 43%), while the adverse event of both group were also not significantly different (RR 0.96, 95% CI 0.87, 1.06, p=0.43, $I^2$= 24%).
**Conclusion:** Our study revealed that there was no significant difference for safety aspect in both treatment groups, shown by non-significant difference in the occurrence of bleeding outcome and adverse events post-treatment

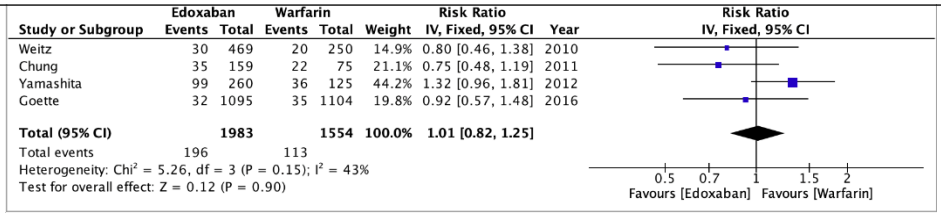


Figure 1. Forest Plot of comparative safety shown by the bleeding outcome post Edoxaban and Warfarin treatment in patients with atrial fibrillation

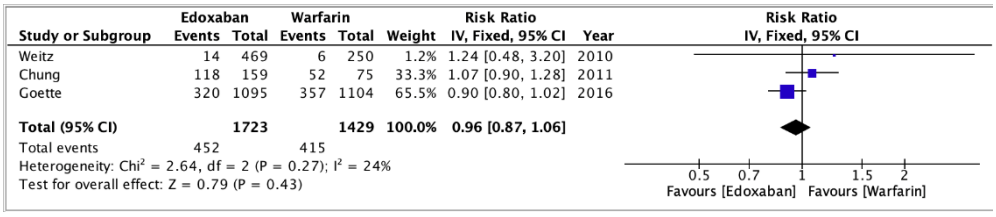


Figure 2. Forest Plot of comparative safety shown by the occurrence of adverse events post Edoxaban and Warfarin treatment in patients with atrial fibrillation

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# Investigation of QT-prolonging Drugs in the Treatment Outcome of COVID-19 Patients: A Systematic Review Incorporating Network Meta-Analysis

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**Background:** The Coronavirus disease 2019 continues to affect the world severely. In search of a cure, many drugs have been repurposed off-label to treat COVID-19, such as hydroxychloroquine, azithromycin, and lopinavir/ritonavir. These drugs are known to increase the risk of QTc prolongation and subsequently, arrhythmias. Despite the fact, these drugs are commonly used as empiric therapy for COVID-19 patients. The aim of this systematic review and network meta-analysis is to evaluate the incidence of all-cause mortality, QTc prolongation and arrhythmias in COVID-19 patients receiving hydroxychloroquine, azithromycin, lopinavir/ritonavir, and a combination of two or three of these regiments to assess their comparative effectiveness and safety.
**Methods:** This systematic review and network meta-analysis was conducted based on PRISMA updated 2020 checklists, and has been registered in the International Prospective Register for Systematic Reviews database with registration no. CRD42021272462. Network geometry was constructed based on collections of pairwise comparison of direct treatment data. Three different networks would be constructed for assessment of treatment outcomes of QT-prolonging drugs in COVID-19 patients in terms of risk of mortality, QTc interval > 450 ms, and incidence of arrhythmia.
**Results:** No significant difference (p>0.05 or I2>50%) of all-cause mortality risk among treatment outcomes. Combination treatment of hydroxychloroquine and azithromycin would increase risk of arrhythmia (RR = 1.92, 95% CI 1.28-2.88, p=0.002) compared to that of only azithromycin. Combination treatment of azithromycin and lopinavir/ritonavir compared to only lopinavir/ritonavir dramatically increases the risk of QTc prolongation (RR=2.17, 95% CI 1.29-3.65, p=0.003). Risk of QTc prolongation is further precipitated when given only hydroxychloroquine compared to the control or only azithromycin group. There is a lower chance of developing arrhythmia when given combination treatment of hydroxychloroquine, azithromycin, and lopinavir/ritonavir.
**Conclusion:** No direct association was found between risk of QT prolongation and arrhythmias caused by the treatment regimens with mortality in COVID-19 patients. Thus, a conclusive relationship between each treatment arm and the respective outcomes cannot be reached. More research on the combination of these drugs should be considered in the future.

**Keywords:** COVID-19, QTc prolongation, mortality, hydroxychloroquine, azithromycin, lopinavir/ritonavir

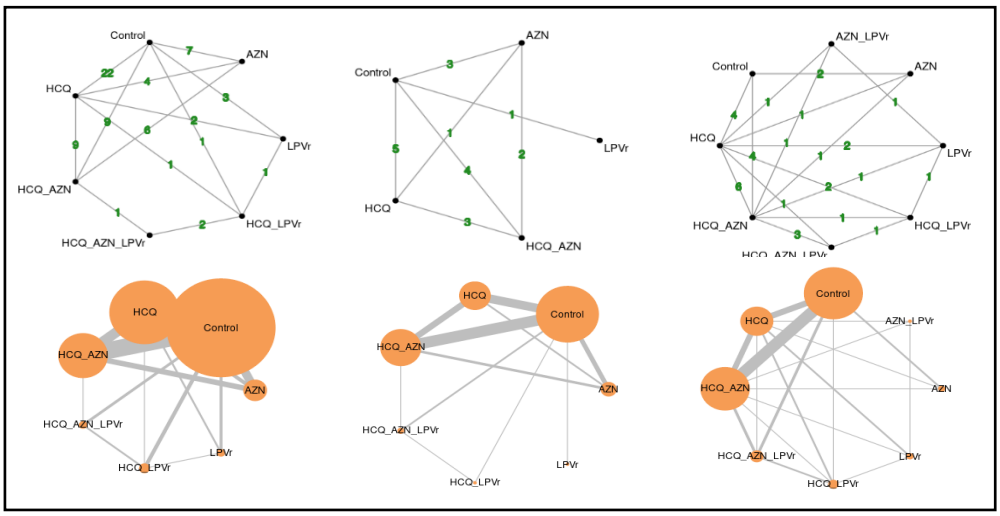


**Figure 1.** Network A: mortality; network B: arrhythmia; network C: QT prolongation.

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# Comparison Between His-Bundle Pacing and Biventricular Pacing as Cardiac Resynchronization Therapy for Heart Failure Patients: A Systematic Review and Meta- Analysis

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**Background:** Cardiac resynchronization therapy (CRT) has demonstrated significant improvements in cardiovascular outcomes of selected heart failure patients. However, conventional biventricular CRT implantation can be challenging due to unfavorable coronary sinus anatomy, leads to lead instability, poor capture, and insufficient cardiac resynchronization. His-bundle pacing has gained interest as alternative strategy for patients underwent biventricular CRT implantation when coronary sinus lead implantation is unsuccesful or in non-responder cases. This study aims to compare the efficacy of his-bundle pacing and biventricular pacing in improving electrocardiographic, echocardiographic, and clinical parameters of heart failure patients that required resynchronization therapy.

**Methods:** A search for eligible studies was conducted until August 2021 on three databases (PubMed, ScienceDirect, ProQuest). Included studies were evaluated for risk of bias. Our primary outcomes of interest were mean difference in QRS duration, left ventricular ejection fraction (LVEF), and change in systolic blood pressure (SBP). We also investigated left ventricular activation time, left ventricular dyssynchrony index, left ventricular end-systolic volume (LVESV), New York Heart Association (NYHA) functional class, 6-minute walk test, quality of life, heart failure hospitalization and cardiovascular or all cause death. Review Manager (RevMan) 5.4 was utilized to compute mean differences.

**Results:** We identified five studies from 2010 to 2019, involving 95 heart failure patients underwent CRT implantation. Pooled analysis showed that his-bundle pacing resulted in significant narrowing of QRS duration compared to biventricular pacing [Mean Difference -23.17 ms (95% CI -36.10, -10.24; p=0.0004; $I^2$=0.63)]. Left ventricular activation time and left ventricular dyssynchrony index were significantly improved in his bundle pacing. There were no significant differences of changes in LVEF, LVESV, and SBP. Clinical parameters such as NYHA functional class, 6-minute walk test, and quality of life were significantly improved in both pacing modality. No significant difference in heart failure hospitalization and cardiovascular or all cause mortality.

**Conclusion:** His-bundle pacing delivers better decrease of QRS duration, also reduction in left ventricular activation time and left ventricular dyssynchrony index compared to biventricular pacing. These suggests that his-bundle pacing is a reasonable alternative option for cardiac resynchronization therapy.

**Keywords**: His-bundle pacing, biventricular pacing, cardiac resynchronization therapy, heart failure

**Table 1.** Characteristics of studies.

| Author | Years | Design | HBP | BiVP | Follow-up | Outcome |
|---|---|---|---|---|---|---|
| Lustgarten et al | 2010 | Prospective Crossover Cohort Study | 10 | 10 | N/A | Mean QRS duration |
| Lustgarten et al | 2015 | Prospective Crossover Cohort Study | 12 | 12 | 6 months | Mean QRS duration<br>Mean LVEF<br>Mean NYHA FC<br>Mean 6MWT<br>Mean QOL (MUHFQ) |
| Sohaib et al | 2015 | Prospective Crossover Cohort Study | 12 | 13 | N/A | QRS duration<br>Mean change in SBP |
| Arnold et al | 2018 | Prospective Crossover Cohort Study | 17 | 17 | N/A | Mean QRS duration<br>Mean change in LVAT<br>Mean change in LVDI<br>Mean change in SBP |
| Upadhyay et al | 2019 | Single Blind Randomized Control trial | 16 | 24 | 6 months | QRS duration<br>Mean LVEF<br>Mean change in LVEF<br>Mean change in LVESV<br>Mean NYHA FC<br>Mean QOL (KCCQ)<br>CV hospitalisation and death |

6-MWT: Minute walk test; CV: Cardiovascular; KCCQ: Kansas City Cardiomyopathy Questionnare; LVAT: Left ventricular activation time; LVDI: Left ventricular dyssynchrony index; LVEF: Left ventricular ejection fraction; MLHFQ: Minnesota Living with Heart Failure Questionnare; NYHA FC: New York Heart Association functional class; QOL: Quality of life

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# Initial Response Comparison of Standard Valsalva Maneuver and Carotid Sinus Massage in Terminating Supraventricular Tachycardia: A Meta-analysis of Randomized Control Trials

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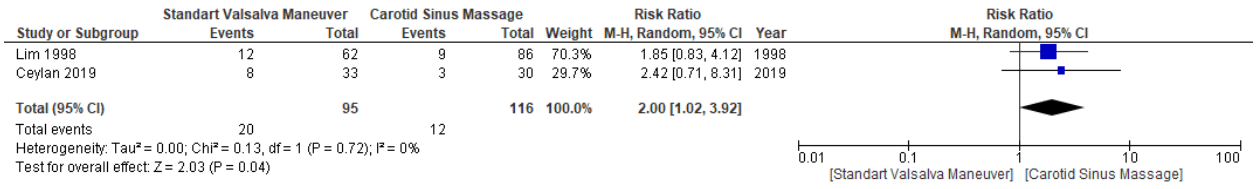
**Background:** Supraventricular tachycardia (SVT) is an arrhythmia frequently encountered in the emergency department. Treatment options for SVT include vagal maneuvers, pharmacologic therapy, and synchronized cardioversion. Vagal maneuvers such as standard valsalva maneuver and carotid sinus massage, are safe and efficacious first-line treatment options for patients with hemodynamically stable SVT. Thus, this study aimed to compare the standard valsalva maneuver to carotid sinus massage success rate in terminating SVT.
**Methods:** A comprehensive literature searching was conducted through four electronic databases (PubMed, Cochrane Library, Proquest, and Ebscohost) from inception to September 30th, 2021 for randomized control trials that compared the standard valsalva maneuver to the carotid sinus massage in SVT. The primary outcome was the termination of SVT at first response. Data were analysed using a random-effects model with RevMan version 5.4.
**Results:** Two randomized control trials with a total of 246 patients were finally included for meta-analysis. Sinus rhythm was achieved 2 times more in the standard valsalva maneuver group compared to the carotid sinus massage group (pooled risk ratio, RR=2.00 95% CI [1.02, 3.92]; p=0.04). This study reported that there were no major complications found among the patients receiving standard valsalva maneuver.
**Conclusion:** Standard valsalva maneuver is more safe and effective than carotid sinus massage at converting SVT into sinus rhythm. More high-quality studies are needed to confirm this finding.
**Keywords**: standard valsalva maneuver, carotid sinus massage, supraventricular tachycardia




Forest plot of comparison: valsalva maneuver vs carotid sinus massage for terminating SVT, outcome: rhythm converted.