

EVIDENCE-BASED CASE REPORT

Pharmacologic Rhythm Control versus Rate Control in Heart Failure and Atrial Fibrillation

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Abstract

Heart failure (HF) with atrial fibrillation (AF) is correlated with worse prognosis requiring special approach. Rate control has been the first line of treatment in cases of HF and AF. On the other hand, rhythm control has been proven to be effective in returning sinus rhythm resulting in better prognosis for patients with HF but not HF. Its role in cocurring cases of HF and AF is not fully understood. Thus, this study aims to analyse whether pharmacologic rhythm control can be applied to cases of HF and AF to reduce mortality. A search was conducted via PubMed, Medline, ProQuest, and Cochrane Database on January 2016. One study was selected after filtering process by inclusion and exclusion criteria and critical appraisal was performed. It was found that there was rhythm control and rate control do no have favouring effect towards mortality shown by RR 1.03 (95% CI 0.90-1.17, $p=0.69$). Rate control has protective effect towards hospitalizations by RR of 0.92 (95% CI 0.86 – 0.98, $p=0.008$, NNT=19). To conclude, rhythm control is not superior to rate control in reducing mortality and rate control should be still be considered as first line treatment of HF and AF.

Keywords: heart failure; pharmacologic rhythm control; rate control; atrial fibrillation

Farmakologis Rhythm Control Dibandingkan dengan Rate Control pada Kasus Gagal Jantung dan Atrial Fibrilasi

Abstrak

Gagal jantung dengan atrial fibrilasi berhubungan dengan prognosis yang lebih buruk dan membutuhkan penanganan khusus. Saat ini strategi rate control merupakan terapi lini pertama pada kasus gagal jantung dan atrial fibrilasi. Rhythm control memberikan prognosis yang lebih baik pada pasien gagal jantung dengan mengembalikan sinus ritme. Kegunaan rhythm control pada kasus gagal jantung dan atrial fibrilasi sampai saat ini belum sepenuhnya dimengerti. Tujuan studi ini adalah menelaah apakah terapi farmakologis rhythm control dapat menurunkan mortalitas gagal jantung dan atrial fibrilasi. Pencarian data dilakukan di PubMed, Medline, ProQuest, dan Cochrane Database pada Januari 2016. Setelah penyaringan dengan kriteria inklusi dan eksklusi, didapatkan satu studi dan dilakukan telaah kritis terhadap studi tersebut. Didapatkan hasil bahwa rhythm control tidak menurunkan mortalitas dibandingkan rate control dengan RR 1,03 (95% CI 0,90-1,17 $p=0,69$). Rate control dapat menurunkan kejadian rawat inap dengan RR of 0,92 (95% CI 0,86 – 0,98, $p=0,008$, NNT=19). Disimpulkan bahwa rhythm control tidak superior dibandingkan dengan rate control dalam menurunkan mortalitas dan rate control sebaiknya tetap digunakan sebagai lini pertama penanganan gagal jantung dan atrial fibrilasi.

Kata kunci: gagal jantung; atrial fibrilasi; pharmacologic rhythm control; rate control; atrial fibrilasi

Introduction

As number of HF cases is increasing it is highly important to be able to treat this condition comprehensively. Statistics from American Heart Association mentioned that in the US one in nine people died due to HF showing the magnitude of the problem.¹ Every year in the US it is the main cause of hospital visits and hospitalizations thus causing huge social and economic burden.² It is estimated that every year \$33 billion was spent on HF cases.³ AF is the most commonly found arrhythmia in clinical settings and estimated to be doubled in number by 2050.⁴ Framingham Heart Study showed that 26% participants enrolled in the study between 1948 to 1995 had both AF and HF.⁵ It is one of the comorbidities often found along with HF and is associated to worse outcome.⁶ A study also showed that as the severity of HF is increasing, so is the number of AF found. In patients with mild HF, 5% was proven to have AF while in moderate HF 10% to 26% of these patients had AF while in severe HF, 50% of the patients suffered from AF.⁷

Currently there are options in treating AF. Rhythm control is used to restore the sinus rhythm while rate control is used to reduce ventricular response rate. Guideline of management in the cases of HF and AF recommend the use of rate control using agents such as beta blockers, digoxin, or calcium channel blockers.⁸ However, in cases of AF alone, especially when symptomatic, the use of rhythm control is more preferred compared to rate control.⁸

It is essential to understand the advantages and disadvantages of a treatment before giving it to the patients. As the number of cases with HF and AF is ever increasing, we would like to find out whether treatment with pharmacologic rhythm control can reduce mortality rate in HF patients with AF in comparison with rate control.

Case Illustration

A 46 year old female patient came with the chief complaint of shortness of breath worsening since three days before admission. Shortness of breath occurred during mild exertion such as walking for

five meters and relieved at rest. Shortness of breath often kept patient awake during the night and she had to use three pillows. Patient's legs were also swollen since the past 3 days. Before the onset of shortness of breath, patient recalled having chest pain occurred on the left side and radiating to the right side up until her back. Pain accompanied by cold sweat and present. Previously patient had been diagnosed with heart failure (HF) for 1 year and was also diagnosed with valvular heart disease since 7 years earlier. Patient had no history of hypertension and diabetes mellitus. From physical examination, it was found that patient had tachypnea with the respiratory rate of 26 times per minute, tachycardia with heart rate of 110 times per minute, enlarged heart borders, systolic murmur at the apex with the grade of 3/6 and mid-diastolic murmur with the grade of 4/6 at the tricuspid valve, rales at the base of the lungs, and edema on both legs. From ECG, it was found that patient had atrial fibrillation (AF) with heart rate of 110x per minute. From chest x-ray, patient had cardiothoracic ratio (CTR) of 70%.

Clinical Question

Is pharmacologic rhythm control more effective in reducing mortality compared to rate control in patients with HF and AF?

Methods

A comprehensive search via Pubmed®, Proquest®, Medline®, and Cochrane® databases were conducted using search term "HF AND AF AND pharmacologic rhythm control AND rate control AND mortality" on January 31st, 2016. Results were narrowed based upon inclusion criterias, such as clinical study, clinical trial, journal article, meta-analysis, and systematic reviews, within 10 years of publication, and studies conducted on human. Afterwards, screening of titles and abstracts were performed to exclude studies which are not suitable for our clinical questions which were invasive procedures. Full text analysis were done to analyse which studies could be used for our purpose. Flowchart of each database search is as presented in Figure 1.

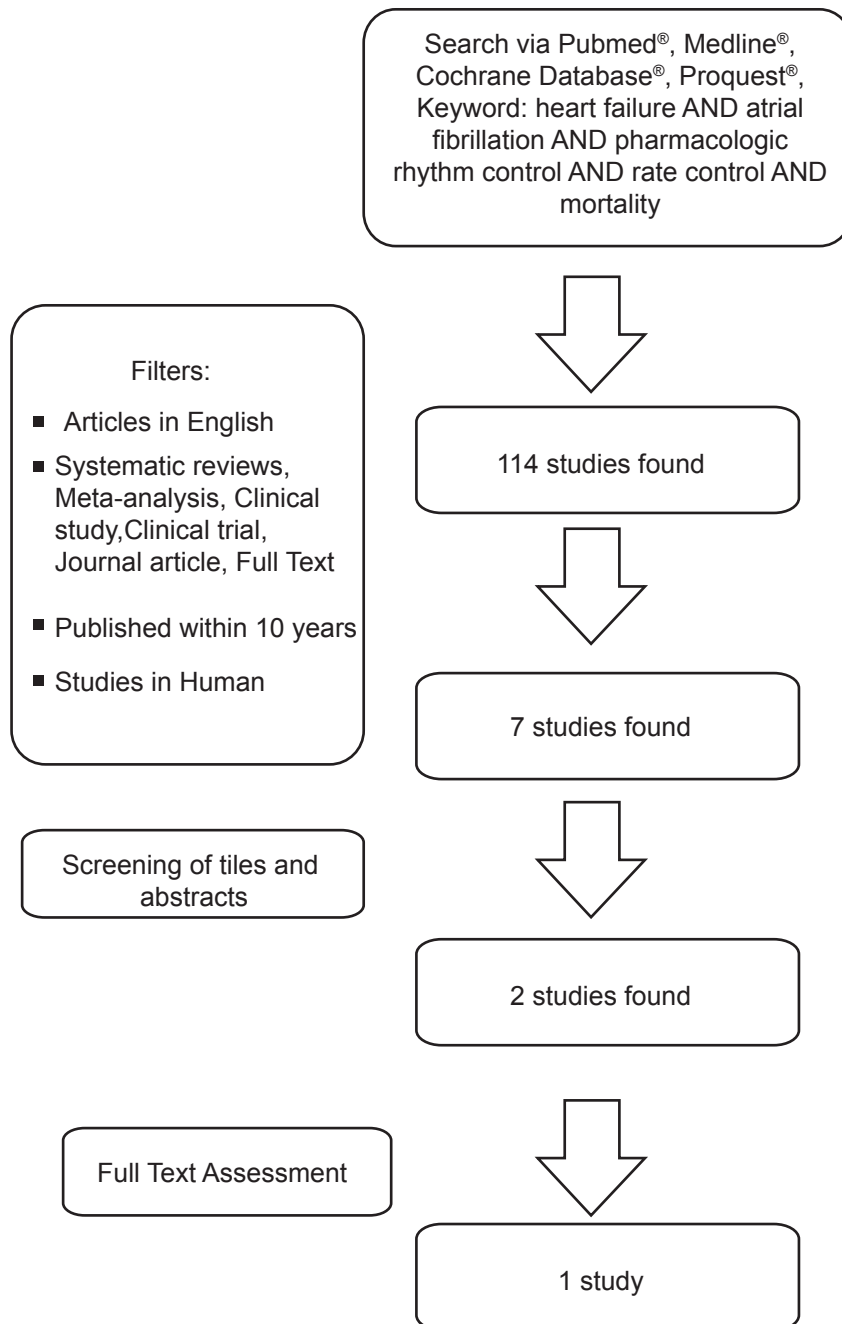


Figure 1. Flowchart of Search Process Conducted on January 31st, 2016

The studies were then appraised using appraisal tools from the Center of Evidence-Based Medicine, University of Oxford for therapy and meta – analysis studies.⁹

Results

This study focuses on the effectiveness of rhythm control in reducing mortality compared to rate control in patients with HF and AF. The primary endpoint of the study was all-cause mortality.

After a thorough searching method through few databases of Pubmed®, Cochrane®, ProQuest®, and Medline®, two studies were found to be in theme with the clinical question. These studies were Caldera, *et al.*¹⁰ and Chatterjee, *et al.*¹¹ However, after further reading, study by Chatterjee, *et al.* was excluded because the studies involved in the meta-analysis involved patients with AF alone without presence of HF. The study by Caldeira, *et al.*¹⁰ was reviewed for its validity and relevance as shown in Table 1 and is summarized in Table 2.

Table 1. Validity and Relevance Assessment of The Study Included¹⁰

Year	PICO	Validity			Heterogeneity	Level of Evidence
		Appropriate Searching	Relevant Study Included	Quality Assessment of Trials		
2011	+	+	+	+	+	1

+ present in the study
 - not present in the study
 ? not stated in the study

The study by Caldeira et al¹⁰ was a meta-analysis published in 2011 and involved 4 randomised controlled trials (RCT) with the total of 2486 patients with HF and AF. The study compared pharmacological rhythm control and rate control in such patients. The authors then searched for studies relevant to their studies via CENTRAL and MEDLINE databases using proper search terms.¹⁰ Inclusion criteria included RCT, pharmacological management of rhythm and rate control, HF patients with minimum New York Heart Association (NYHA) class of 2 or ejection fraction of less than 50%. Any studies with invasive methods of rhythm control including catheter ablation technique were not included to the analysis.¹⁰

The studies found were then assessed for PEDro score for its quality which all scored 6 to 7 out of 11 points showing fair qualities of the studies.¹² The score featured eligibility criteria, random allocation, allocation, concealment, similar baseline characteristics, blinding of subjects, blinding of therapists, blinding of outcome assessors, crossover rate of less than 15%, intention-to-treat analysis, statistical comparisons between groups, and measures of variability. Studies were then analysed using revman version 5.0.23 in which

relative risk (RR) was found. Results were written in 95% confidence intervals (CI) and assessed for its heterogeneity using I² test which revealed that the studies used were homogenous by I² of 0%.¹⁰

The primary endpoint of the study was mortality while other complications such as hospitalisations, stroke or thromboembolic complications were also assessed. For mortality, RR did not differ significantly between two treatments as it was 1.03 (95% CI 0.90-1.17, p=0.69).¹⁰ There are four studies included in the analysis and they showed mostly consistent results.¹⁰

For hospitalization, the result was supportive towards rate control with RR of 0.92 (95% CI 0.86 – 0.98, p=0.008).¹⁰ For clinical importance, number needed to treat (NNT) calculation was performed and it was found that NNT was 19. For stroke or thromboembolic complications, RR was 1.09 (95% CI 0.61 – 1.96, p=0.77).¹⁰

The study showed importance of the pharmacologic rhythm control and rate control in managing HF and AF. These results can be applied in the patient with both HF and AF. This would be beneficial in determining treatment for our patient as treatment may help reducing hospitalisation but not mortality.

Table 2. Summary of Study Used All-Cause Mortality as the Endpoint¹⁰

Results	Summary
Pharmacologic rhythm control does not reduce mortality rate when compared to rate control RR 1.03 (95% CI 0.90-1.17, p=0.69)	
Hospitalization is reduced in rate control patients compared to patients with pharmacologic rhythm control RR 0.92 (95% CI 0.86-0.98, p=0.008, NNT=19)	Rate control strategy reduces hospitalizations in patients with HF and AF. Neither strategy showed favouring effects towards mortality and stroke or thromboembolic complications.
There is no reduction in stroke or thromboembolic complications RR 1.09 (95% CI 0.61-1.96, p=0.77).	

Discussion

In cases of HF, there are few hypotheses on how AF develops. One of the pathophysiological pathways is from the neurohormonal imbalance and activation of the renin-angiotensin-aldosterone system (RAAS).¹³ This results in left atrial stretch and fibrosis thus the impairment of conduction.⁶ Impaired calcium handling and calcium overload in HF also contributes to the development of AF.¹³

Current guideline published by American Heart Association supports the use of rate control agents in cases of HF and atrial HF. Rate control preferred in these cases are beta blockers or non dihydropyridine calcium channel blocker which can be used in conjunction with digoxin.⁸ Previous studies have shown that beta blockers could reduce mortality, hospitalization, and cardiovascular (CV) death when compared with the use of placebo. A meta – analysis showed that when compared to placebo, beta blockers could reduce the all – cause mortality to 0.73 (95% CI 0.67 – 0.80) in cases of sinus rhythm.¹⁴ While in presence of AF, beta blockers could reduce the risk ratio was 0.97 (95% CI 0.83 – 1.14).¹⁴ Beta blockers are used due to their high sympathetic and negative inotropic effects. Other preferred agent of rate control is digoxin which belongs to the class of cardiac glycosides. Currently, the prescription of digoxin has not been proven to reduce mortality, especially as digoxin itself has risk of toxicity. A study by the af follow-up investigation of rhythm management (AFFIRM) study found an association of increased mortality with the use of digoxin with or without presence of HF.¹⁵ Non – dihydropyridine calcium channel blockers are also an option because their negative inotropic effects and reduction of risk of re-infarction and cardiac death to 1.41 (95% CI 1.01-1.96).¹⁶

Approaches to control heart rate should mind the optimal heart rate of these patients. A study conducted in 33 centers in the Netherlands followed up patients for 12 months, lenient rate control, in which the goal of resting heart rate was below 110, was proven to have hazard ratio of 0.79 (90% CI 0.38 – 1.65) in comparison to strict rate control, which had goal of resting heart rate of below 80 beats per minute.¹⁷ Difference of mortality in groups attributed to lenient rate control and strict rate control was significant ($p < 0.0001$).¹⁷ Thus it may be wiser to be less aggressive in reducing the heart rate in patients with HF and AF.

Rhythm control, on the other hand, aims on the reversing to sinus rhythm. This could be achieved via: cardioversion, antiarrhythmic drugs, and catheter

ablation. Cardioversion should be used in cases where haemodynamic disturbances are found. Antiarrhythmic drugs approved for the usage in HF and AF are only dofetilide and amiodarone.¹³ These drugs should also be used in caution as they are toxic. Amiodarone has been proven to be effective in preventing the recurrence of AF with odds ratio of 0.15 (95% 0.10 – 0.22) and had better results when compared to sotalol (OR 0.47, 95% CI 0.36 – 0.69) and dronedarone (OR 0.42, 95% CI 0.29 – 0.60).¹⁸

The question remains whether reversing to sinus rhythm is essential in reducing mortality of patients with both HF and AF. It has been widely studied that presence of HF with concurring AF yields poorer prognosis and HF with sinus rhythm has better outcome especially in terms of mortality, hospitalizations, and other complications. In patients with HF and AF, a study showed that when the rhythm has returned to sinus, the patients had significant improvement of left ventricular ejection fraction with the mean difference of 11.1% (95% CI 7.1 – 15.2, $p < 0.001$).¹⁹

According to Canadian Cardiovascular Society, there are few indicators in determining the proper management in cases of AF and HF. For those with: persistent AF, less symptoms, age above 65 years old, hypertension, no history of HF, previous failure of antiarrhythmic drugs, rate control is more favorable. On the other hand, those with paroxysmal AF or newly detected AF, symptomatic patients, age below 65 years old, no history of hypertension, exacerbation of HF by AF, no history of failure when treated by antiarrhythmic drugs, have more benefits when treated with rhythm control. However, patient preferences should always be taken into account when determining which treatment is used.

The result of the study we found stated that there was no difference of mortality in patients treated with rhythm control when compared to rate control (RR 1.03 95%CI 0.90 – 1.17, $p = 0.69$). However, it was found that hospitalization rate was significantly lower in group of rate control with the NNT of 19 ($p = 0.008$). This result is in conjunction with another meta-analysis studying the outcome of beta blockers use in patients with HF and AF showing that there is also no reduction of mortality in patients with AF and HF treated with beta blockers. However, the reduction of hospitalization was not seen in patients in this study. The heterogeneity of sample population is also shown in I^2 which was 0% indicating that the heterogeneity of the population was minimal. However, there was no information regarding baseline characteristics of the patients

sampled in the study. This could be a suggestion to improve the quality of study by Caldeira et al¹⁰ as baseline characteristics may play role in determining the prognosis of the patient. Women had higher mortality in comparison to men with both HF and AF (HR 2.7, 95% CI 2.0 – 3.6 vs HR 1.6, 95% CI 1.2 – 2.1).⁵ Presence of other risk factors such as coronary heart disease, chronic kidney disease, and the functional class of the HF also determine prognosis of HF.²⁰

A review done by Kotecha and Piccini in 2015 summarized priorities in treatment of HF and AF.¹³ In patients with HF, the top 3 priorities are euvoemia, diminish RAAS disturbances, and managing non – cardiovascular comorbidity.¹³ While in patients with AF, preventing complications such as stroke and embolism, controlling rapid heart rate, and managing non – cardiovascular comorbidity are the priorities.¹³ In patients with AF and HF, restoring sinus rhythm via pharmacologic management is not the priority.¹³ There has been few hypotheses on why pharmacological rhythm control is superior in reducing mortality in patients with AF only but not in patients with HF and AF.¹³ Limited efficacy, side effects, irreversibility of damage caused by AF, and difficulties of maintaining the rhythm name a few of the hypotheses.¹³ In patients undergo rhythm control in AF and congestive HF (AF-CHF) trial, 58% of these patients had at least one episode of AF during follow up period proving that achieving and maintaining sinus rhythm may be a challenge needed.²¹

This should be our consideration in determining therapeutic goals of our patients. The use of rate control would not reduce mortality in patients with HF and AF. However, it may be beneficial in reducing hospitalization eventhough there is still inconsistent results. Returning to sinus rhythm has not been proven to be effective in reducing mortality and there is also risk of returning to AF. There is also no proof that it would be beneficial in reducing hospitalizations but there is still evidence of reduction in symptoms of HF. Weighing risk and benefit ratio the use of rate control with the first choice of beta blockers can be current option in management of AF and HF. The use of rhythm control should be considered when rate control fails to ameliorate symptoms of AF in these population of patients.

Conclusion

Pharmacologic rhythm control does not reduce mortality of patient with HF and AF when compared to rate control. Patients given rate control are proven to have less hospitalization when compared

to patients given rhythm control ($p=0.008$). A critical appraisal has been done to study done by Caldeira et al¹⁰ and it has been concluded that the study was valid, important, and applicable to cases met in daily clinical practice.

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