



Comparative efficacy of ivabradine versus beta-blockers in patients with mitral stenosis in sinus rhythm: systematic review and meta-analysis

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Abstract

Background Patients with mitral valve stenosis have increased heart rate. HR reduction is known as an important treatment and therapy strategy for patients with mitral valve stenosis. **Aim of the review** The aim of this systematic review and meta-analysis was to compare the efficacy of ivabradine versus beta-blockers in patients with mitral stenosis in sinus rhythm. **Methods** Randomized controlled trials were searched in Cochrane Library, PubMed, Web of Science, CRD, Scopus, and Google Scholar with no start time limitation and ending June 2018. Risk of bias across was assessed by the Cochrane Risk of Bias Assessment tool. Fixed effects models were used to combine the results and the mean difference with a 95% confidence interval. This meta-analysis was performed using Meta Package in R software. **Results** Five studies entered meta-analysis. The total number of patients treated with ivabradine and beta-blockers was 178 and 178 respectively. The results showed that the mean of maximum HR and HR at rest was lower at about 5.03 units and upper 4.32 units respectively with use of ivabradine compared with the use of beta-blockers. These values were statistically significant. **Conclusion** It seems that the efficacy of ivabradine is good in comparison with betablockers, but it still requires more clinical trials.

Keywords Heart rate · Ivabradine · Meta-analysis · Mitral stenosis

Impacts on practice

- The use of beta-blockers for patients with mitral valve stenosis, does not improve exercise tolerance.
- Ivabradine has no effect on cardiac systole and seems to be safer than beta-blockers.
- Ivabradine has positive effect on the maximum heart rate and also on the heart rate at rest, and therefore seems a suitable drug to treat mitral stenosis in sinus rhythm.

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Background

Increased heart rate (HR) is seen in many cardiovascular disorders [1, 2]. In mitral stenosis, low cardiac output state leads to increased HR. With exercise, HR increases substantially which results in shorter diastolic periods. Consequently, blood flow through stenosed valve in such short diastolic periods are compromised [3–7]. For this reason, HR reduction is known as an important treatment and therapy strategy for patients with mitral valve stenosis [8]. Treatment for stenosis of the mitral valve is usually done by balloon or surgery [7]. To date, the most important drugs used to lower heart rate are beta-blockers such as metoprolol, propranolol, carvedilol or bisoprolol and

non-DHP calcium channel blockers such as verapamil or diltiazem [7]. These drugs are widely used in controlling heart rate, angina, heart failure, and arrhythmias [9, 10]. On the other hand, they can reduce the contraction power of the myocardium, and this complication may prevent the use of medication [11, 12].

Recently a new drug called ivabradine has entered the field of drug technology. Ivabradine is a negative chronotropic drug that acts concurrently on the sinusoidal node and has no effect on myocardial drainage [13]. Ivabradine directly inhibits the sinoatrial node depolarization without altering and ventricle conduction, thus reducing the dose-dependent heart rate [14]. Ivabradine reduces hyperpolarization-activated cyclic nucleotide-gated (HCN) pacemaker spontaneous activity and reduces heart rate by inhibiting a specific funnel generated by the HCN channel [15–17] This is useful for reducing heart rate in patients with heart failure because a rapid heart rate is associated with an increase in mortality in patients with heart failure [15]. In patients with heart failure, ivabradine reduces the risk of hospitalization [18]. It is prescribed for patients with symptoms of stable heart failure (normal heart rate of at least 70 beats per minute) and mitral valve stenosis [19].

There are several randomized clinical trials (RCT) on the efficacy of ivabradine. There are other articles that show contradictory results [20–23]. Evidence from ivabradine's study suggests that atenolol increases the duration of exercise and controls heart rate in patients with mild mitral stenosis [24]. In another study, no significant difference was found between the two drugs, ivabradine and atenolol in patients [22]. According to the different results from articles that have examined the efficacy of ivabradine, the strength of the drug in protecting patients with mitral valve stenosis is unclear.

Aim of the review

The present study aimed to evaluate the efficacy of ivabradine in comparison with beta-blockers through meta-analysis of RCTs. This study was aimed at performing a meta-analysis using existing RCTs to evaluate the efficacy of ivabradine in comparison with beta-blockers.

Method

This was a meta-analysis study that utilized RCTs to evaluate the efficacy of ivabradine in comparison with Beta-blockers in patients with mitral stenosis in sinus rhythm, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [25].

Data sources and literature searches

In order to access RCTs, a systematic search was done in the databases including PubMed, Cochrane Library, Scopus, Center for Review and Dissemination (CRD), and Google Scholar. The keywords “ivabradine”, “ β -blockers”, “randomized controlled trials”, “RCTs”, “rate control”, “heart rate”, “mild to moderate mitral stenosis” and “exercise” combined by using OR and AND operators, with no start time limitation and ending June 2018 were searched. The reference list of the selected studies, unpublished studies (grey literature) and studies presented at conferences were also searched. The complete search strategy is presented in Appendices table S1.

Inclusion and exclusion criteria

After removing duplicate studies, to select the full text of appropriate articles, we include all randomized clinical trials, clinical trial studies in the treatment group with ivabradine and the group of beta-blockers and patients with mitral valve stenosis.

We exclude review articles, studies other than RCT that were published in languages other than English, and studies of incomplete information about the mean and standard deviation of the intended outcomes, as well as summaries of conferences that were not published (we did not have full access to them), were excluded from this meta-analysis.

Data extraction and quality assessment

Articles were retrieved from databases using mentioned keywords. Selection of articles was done in 3 steps. The Endnote X5 Resources Management Software was used to organize, study titles and abstracts, and identify duplicates. After removing duplicates, the titles of all articles reviewed and articles that didn't match with inclusion criteria were removed. For the next step, the abstract and the full text of the articles were studied and checked based on inclusion criteria and study objectives. The study selection and quality assessment were done by two researchers independently, and in case of disagreement, the subject was referred to a third person. Information extracted from articles was summarized in the extraction form. Extracted information includes first author, year of publication, country of study, type of intervention, sample size, the average age of patients, mean heart rate, exercise time average, total exercise time, maximum and minimum heart rate with Holter monitor before and after the intervention with their standard deviation.

Statistical analysis

Changes in outcomes of patients were measured after intervention. Finally, using Meta-analysis, the mean difference between the two groups was used and the efficacy of ivabradine was compared with beta-blockers in the treatment of mitral valve stenosis. The heterogeneity of the studies was examined by Cochran (Q) and I^2 statistics, which expresses the percentage of variations between studies. For $I^2 < 25\%$ indicates low heterogeneity, $25\% < I^2 < 50\%$ of average heterogeneity and $I^2 > 75\%$, heterogeneity was considered high [26]. In case of heterogeneity, random effect model was used to calculate the overall effect size. The funnel plot was used to examine the publication bias. We performed the analysis using the CMA v.2.0 software and P value ≤ 0.05 was considered as statistically significant.

Results

Study characteristics

In the systematic search of all databases, 791 ivabradine related articles were identified. After removing duplicates, 668 papers remained. By reviewing the full text of these articles and considering the inclusion and exclusion criteria, 5 articles were entered into the meta-analysis (see Fig. 1). These 5 studies had 356 patients in total. These studies were published between 2012 and 2016. The patient characteristics are shown in Table 1.

Risk of bias in the selected studies

All the five included articles had open-label design, in which there was no possibility of blinding. Thus, this design caused selection, performance and detection bias (See Fig. 2).

Fig. 1 PRISMA flow diagram for clinical trials

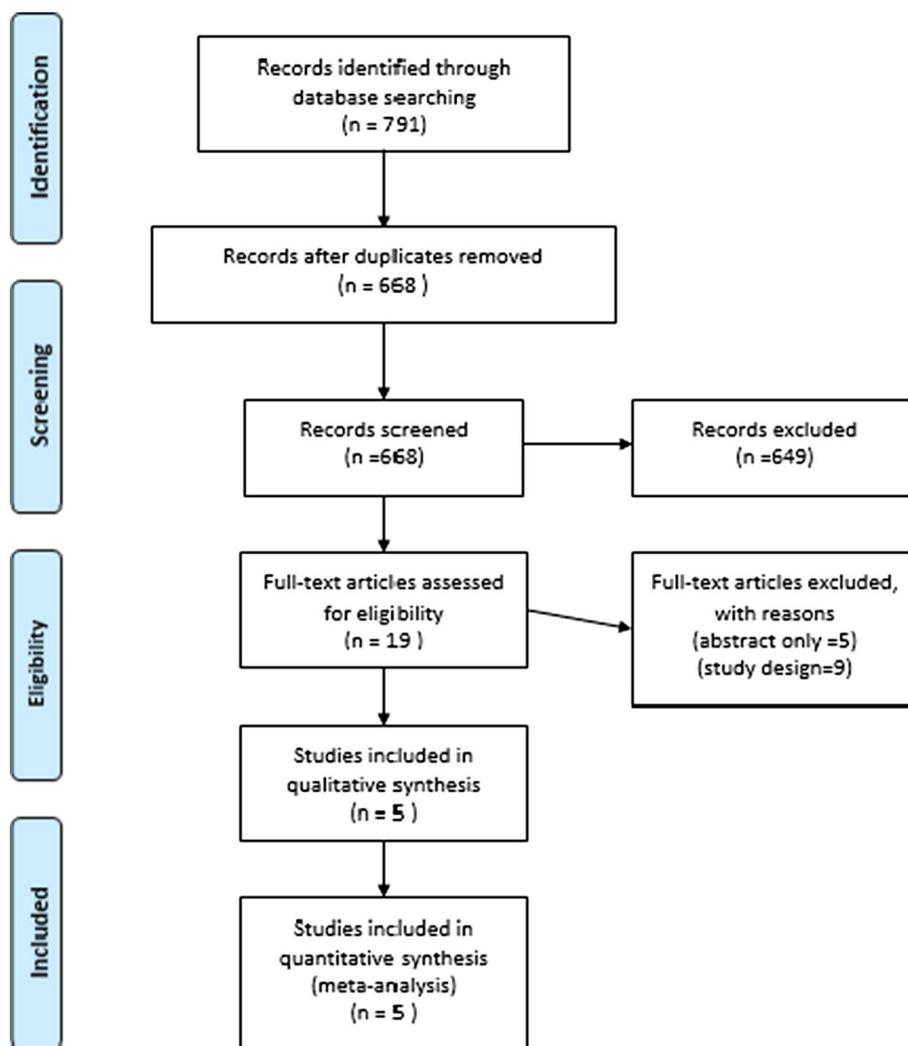


Table 1 Characteristics of included studies in meta-analysis

Author	Year	Study type	Type of drug	Sample size	P value	age
Agrawal	2016	Interventional, randomized, open label, non-cross over study	IVA 5 mg or 7.5 mg	Metoprolol 50 mg or 100 mg	97 patients	0.783
Saggu	2015	Prospective, open-label crossover double-blind trial	IVA 5 mg or 7.5 mg	Metoprolol 50 mg or 100 mg	34	28.9 ± 6.6
MUHAMMAD	2016	Prospective, open-label	IVA 5 mg or 7.5 mg	Atenolol 50 mg or 100 mg	50	28.9 ± 6.6
PARAKH	2012	Randomized, open-label, crossover trial	IVA 5 mg	Atenolol 50 mg	50	30.9 (7.9)
Rajesh	2016	Randomized, open-label, parallel group trial cross-over	IVA 5 mg	Atenolol 50 mg	82	38

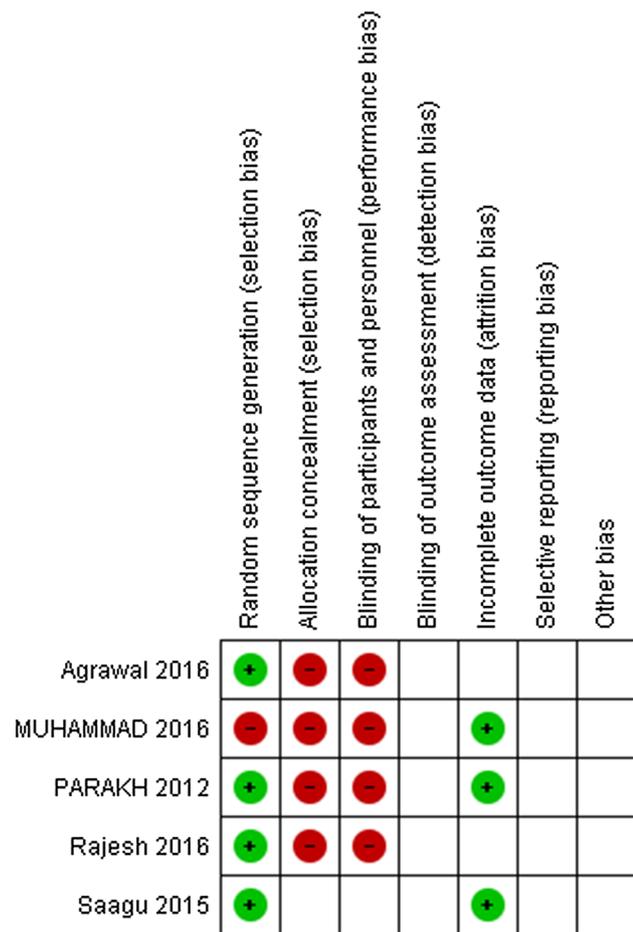


Fig. 2 Quality of included trials mitral

Meta-analysis

Finally, five articles included in this meta-analysis. The total number of subjects studied was 356, of whom 178 were treated with ivabradine and 178 were treated with beta-blockers. From the four variables of the selected response, two variables of maximum heart rate and heart rate at rest were possible for meta-analysis.

The mean (standard deviation) for max Exercise HR, mean total exercise time (s), maximum HR on holter, mean HR on holter and minimum HR on holter was 170.26 (14.19), 121.18 (72.00), 115.66 (19.96), 84.30 (2.81) and 57.65 (1.45) respectively.

At the maximum heart rate, heterogeneity was not significant between studies ($I^2 = 0.000$, Q -Value = 3.70, P Value = 0.448). The fixed effects model was used to combine the results. The meta-analysis of results showed that the mean maximum heart rate in the treatment of mitral valve stenosis by ivabradine was 5.03 units less than beta-blockers. (Pooled Estimate[Iva-BB] (SD) = -5.03(1.37), 95%CI = (-7.71; -2.35), $Z = -3.67$, P Value < 0.001).

Also, the analysis in subgroups was based on the type of drug in the beta-blocker group. Meta-analysis results in subgroups are shown in Table 2. In Fig. 3, the forest plots are shown in the meta-analysis of the maximum heart rate.

The three studies had data on heart rate at rest. Heterogeneity was not significant among studies. The fixed effects model was used to combine the results. Meta-analysis results showed that heart rate at rest was higher with ivabradine 4.32 units in comparison with beta-blockers in

Table 2 The result of subgroups in the comparative efficacy of ivabradine versus beta blockers

Groups	Number studies	Effect size and 95% confidence interval				Test of null (2-tail)		Heterogeneity			
		Point estimate	SE	Lower limit	Upper limit	Z-value	P value	Q-value	df (Q)	P value	I-squared
Atenolol	3	-2.63	2.32	-7.19	1.92	-1.13	0.257	0.88	2	0.643	0.000
Metoprolol	2	-6.31	1.70	-9.63	-2.98	-3.72	0.000	1.19	1	0.276	15.874
Overall	5	-5.03	1.37	-7.71	-2.35	-3.67	0.000	3.70	4	0.448	0.000

HR at Maximal Exercise(min)

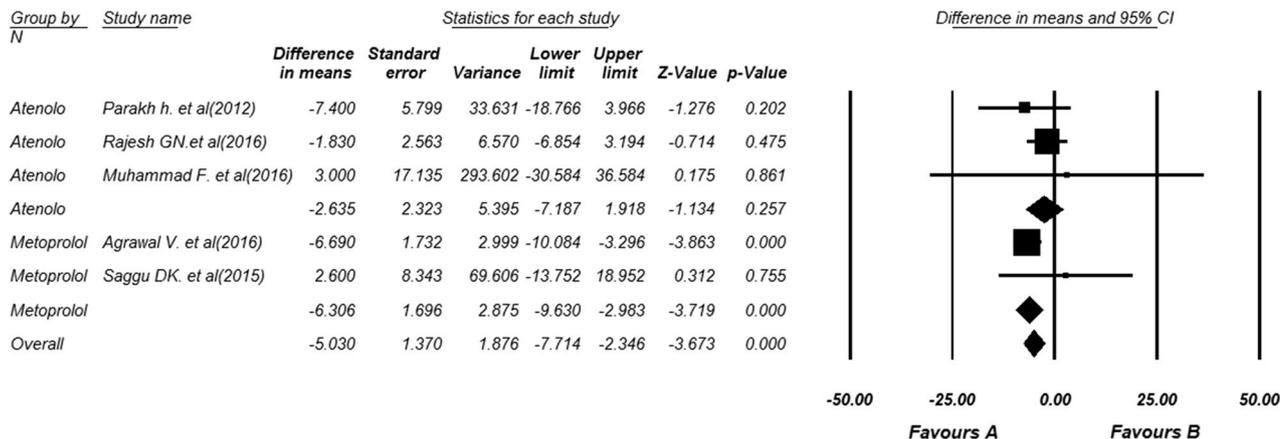


Fig. 3 Forest plot of maximum heart rate comparing ivabradine with beta-blockers

order to treat mitral valve stenosis. (Pooled Estimate[Iva-BB] (SD)=4.32(1.49), 95%CI= (1.40–7.25, Z=2.901, P Value =0.004). Figure 4 shows the forest plot of the heart rate at rest.

Evaluation of publication bias

Figure 5 is the funnel plot to explore publication bias. Based on the regression test Egger, there was no statistically significant difference between publication biases. (t=0.995; P value =0.392).

Discussion

The stenosis of the mitral valve restricts the flow of blood from the left atrium to the left ventricle. This can lead to heart failure, rapid, slow, or irregular heartbeat (arrhythmia) [27]. Ivabradine and beta-blockers can both reduce heart rate in rest and activity. However, several studies have shown that beta-blockers and calcium channel blockers can be useful in tachycardia and prevent pulmonary capillary wedge pressure. Due to the negative effects on the myocardium, it seems that patients with mitral valve stenosis do not have much effect [11, 12, 28]. Previous studies have shown that with the use of beta-blockers, in the sinus rhythm of patients with mitral valve stenosis, no improvement in duration of exercise tolerance test as assessed by mean exercise time to dyspnea is achieved. Compared with beta-blockers and

HR at Rest(min)

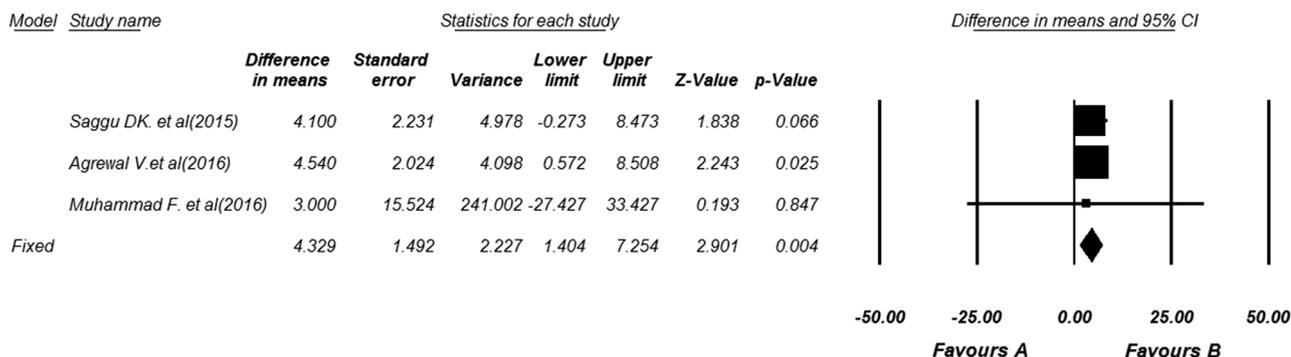
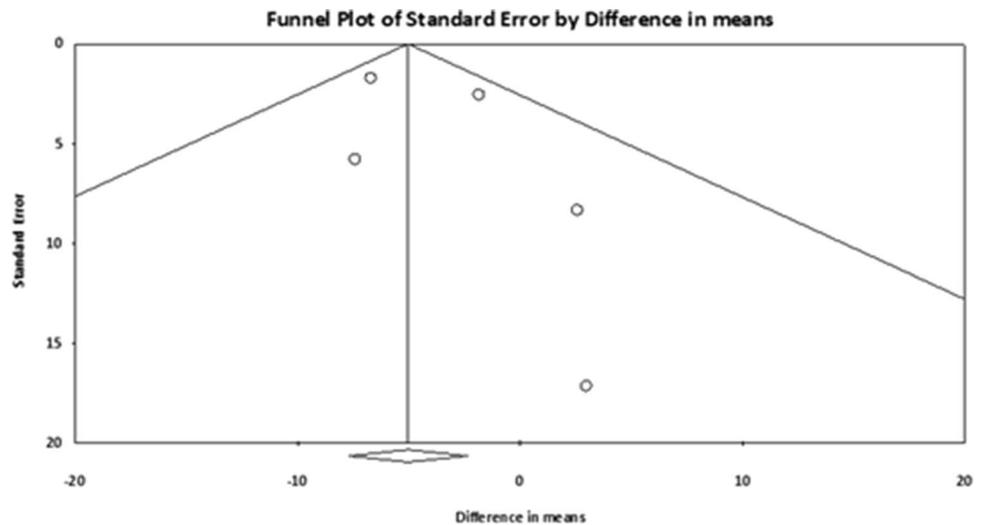


Fig. 4 Forest plot of heart rate comparing Ivabradine with beta-blockers

Fig. 5 Egger's publication bias plot. Ivabradine versus beta blockers in patients with mitral stenosis in sinus rhythm



calcium channel blockers, ivabradine has been taken into consideration, because it has no effect on cardiac systole and it is safer [20, 29].

This systematic review and meta-analysis aimed to evaluate the efficacy of ivabradine in comparison with beta-blockers in patients with mitral valve stenosis. Five RCTs with 356 patients included in this study [20–24]. Two outcomes of HR at maximal exercise (min) and HR at rest (min) were analyzed in this study. In the current meta-analysis study, the mean maximum heart rate in ivabradine was 5.03 units lower than beta-blockers. In the outcome of the heart rate at rest, for the treatment of mitral valve stenosis, ivabradine was 4.32 units more than beta-blockers. Regarding these results, it can be argued that ivabradine, in comparison with beta-blockers, controls better heart rate in exercise, but has less effect on reducing heart rate at rest. This benefit of ivabradine alongside with its other benefits like having no negative effect on cardiac conduction, contractility, relaxation or repolarization, or blood pressure, this drug is a very good option.

In the study of Pasceri et al. [30] has been shown that ivabradine in patients with mitral valve stenosis reduces sinus rhythm. Parakh et al. [24] showed that ivabradine 5 mg twice daily, compared to Atenolol 50 mg per day reduced the increased heart rate in patients with mitral valve stenosis.

The studies on the positive effect of ivabradine on reducing sinus rhythm as well as reducing the heart rate in patients with mitral valve stenosis can confirm our results. In other studies, about the efficacy of ivabradine, in reducing heart rate at rest and during exercise has been shown to be in line with the results of this study [31–33].

In general, the present meta-analysis revealed a significant reduction in the outcome HR at maximal exercise (min) and HR at Rest (min). While meta-analysis Ye et al. concluded that ivabradine had no effect on peak heart rate and

heart rate in resting mode compared to placebo and beta-blockers. Of course, this meta-analysis was done in patients with angina and the difference in the results of the study is probably because of the difference between the type of heart disease or the larger sample size in the Ye et al. study [34].

Limitations

This study had several limitations. First, based on five articles, there is a need for more studies to validate the meta-analysis. For this reason, the analysis of all the implications studied in various articles, as well as comparisons of ivabradine with the various drugs commonly used in the treatment of mitral stenosis was not possible. Only two therapeutic indexes were analyzed and other items were not identified. And other types of beta-blockers were considered, which may not have the same effect. Comparison of ivabradine with various of beta-blockers was not applicable. Another limitation is that data from these papers were not enough to assess differences in functional capacity and patient satisfaction, so only heart rate as a surrogate marker was evaluated. We didn't examine the cost of ivabradine, as this medication is an expensive medication and cost will be a large part in clinical application.

Conclusion

According to studies on the effects of ivabradine, it seems that this drug has the potential to be effective in the treatment of mitral valve stenosis. The decision to prescribe ivabradine in the treatment of mitral valve stenosis, however, still requires clinical trials with conventional control groups for treating the disease with longer follow-up periods.

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Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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