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Systematic review and meta-analysis of the efficacy of olprinone and *MEFV* gene in treating heart failure

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ABSTRACT

Cardiovascular failure is the main cause of death in industrialized societies. The results of recent studies have shown that some mutations in the *MEFV* gene are common in heart failure patients. For this reason, the study of mutations and genetic factors has been of great help in the treatment of this disease, but despite this, due to the heterogeneity of clinical symptoms, multiple pathophysiological processes, and environmental genetic factors, the complete understanding of the genetic causes of this disease is very complicated. As the new generation of phosphodiesterase (PDE) III inhibitor, olprinone, the inhibition of human heart PDE III by olprinone is highly selective. It is suitable for the treatment of acute heart failure (HF) and acute cardiac insufficiency after cardiac surgery. In this study Olprinone, milrinone, PDE inhibitors, cardiac failure, and HF were selected as the search terms to retrieve articles published between January 1999 and March 2022. RevMan5.3 and Stata were employed to analyze and evaluate the risk bias of the included articles. Besides, the Q test and heterogeneity were utilized to evaluate the heterogeneity between articles. The results of this research showed No heterogeneity was found between each research group. The sensitivity (Sen) and specificity (Spe) of the two methods were compared. Olprinone showed more significant therapeutic effects than other PDE inhibitors. Besides, the therapeutic effect on the patients with HF in the two groups was obvious. The incidence of postoperative adverse reactions among the patients without relieving HF was low. The influences on urine flow of the two group's demonstrated heterogeneity, and its effect revealed no statistical meaning. The meta-analysis confirmed that the Spe and Sen of olprinone treatment were higher than those of other PDE inhibitors. In terms of hemodynamics, there was little difference between various treatment methods.

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Introduction

Vascular diseases have been proposed as the most important cause of death in developing countries, and the rate of death and death related to them is equal to the rate of death and death related to cancer. The incidence rate of coronary heart disease is approximately one-third of all vascular patients. Genetic and environmental factors or the interaction between them play an important role in the occurrence of coronary artery disease. One of the genes involved in causing heart failure is the MEFV gene (NM_000243), which is located on chromosome number 16 (16p13.3). This gene was identified in 1997 and has 10 exons (1-2). Marenostrin and pyrin are two proteins encoded by the MEFV gene. These proteins are expressed in neutrophils and are involved in apoptosis, pyroptosis, and necroptosis and are effective as a negative regulator in inflammatory reactions of the body, response to bacterial infections, and heart failure (1-2).

Heart failure (HF) is the terminal stage of the development of various cardiovascular diseases. It is featured complex diseases and poor prognosis, which seriously endanger human life and health. In recent years, patients with HF become an essential component of clinical diseases with the growth of the morbidity of cardiovascular diseases year by year. Epidemiological data show that the number of current patients with HF in China reaches as high as 29.97 million, accounting for about 1/3 of the total number of patients with HF worldwide. Great progress has been made in the prevention and treatment of HF and the prevalence of HF in some regions declines in recent years. However, the prevalence of HF in developing countries still shows an apparent rising trend, which may be related to hypertension, diabetes, obesity, smoking, and other bad life habits (3-4). Although rapid progress has been made in the therapy of HF and a large number of new treatment methods are introduced, the prevalence of HF is increasing worldwide. What's more, most patients with HF are still increasing continuously, which is even higher than that for most malignant tumors. The 1-year and 3-year mortality of patients with HF in Japan are 11.3% and 29.2%, respectively. In contrast, the 1-year mortality of patients with HF in the USA is higher, and the situation in Europe is not better. The 4-year survival rate of patients with heart disease in Europe reaches only 50%. Patients admitted to the hospital due to HF may be hospitalized for treatment again or die in the same year. Although there is no exact data on the annual mortality of HF in China, the retros-

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pective investigation lasting 3 years demonstrates that the mortality among hospitalized patients amounts to 8.9%, which is higher than the total mortality of cardiovascular patients hospitalized in the same period. The mean age of the patients dying of HF was only 66.4. Given the high morbidity and mortality of HF, which is also likely to further enhance, the treatment of anti-HF becomes a hot research topic (5-7).

There is great progress in the research into anti-HF drugs recently. Phosphodiesterase (PDE) III inhibitor is a new anti-HF drug developed in the past more than 20 years. It can selectively inhibit and degrade PDE3 of cyclic adenosine monophosphate (cAMP) to block the degradation of cAMP into 5'-AMP. Besides, PDE III inhibitor increases the content of cAMP in cardiac muscle and vascular smooth muscle to promote the influx and uptake of ceftazidime (Caz+), enhance myocardial systolic and diastolic abilities, and improve the working efficiency of the heart. the cAMP also can result in the relaxation of vascular smooth muscle and reduce cardiac load. Hence, PDE III inhibitor plays a role in treating HF by enhancing myocardial contractility and reducing the cardiac load (8-10). Besides, the existing studies reveal that PDE III inhibitors can inhibit cytokines and inflammatory factors. HF is a process of chronic inflammation, and the inhibition of cytokines and inflammatory factors can delay the further progression of HF lesions. Representative milrinone is widely applied in clinical practice and shows good effects. In addition, considerable clinical experiments also confirm the clinical efficacy of milrinone (11-12).

Olprinone is a new generation of PDE III inhibitor recently developed for the therapy of acute HF. The inhibition of the human heart PDE III by olprinone is highly selective. The drug was produced and marketed in Japan in 1996. Relevant studies suggested that olprinone improves the mechanical effect of the left ventricle more significantly than dobutamine does. With the improvement of cardiac function, the relative changes in blood pressure, heart rate, and myocardial oxygen consumption are not obvious. Olprinone shows advantages compared with other PDE III inhibitors and catecholamine drugs. During short-term treatment, olprinone can replace catecholamine drugs and is suitable for the treatment of acute HF and acute cardiac insufficiency after cardiac surgery (13-14). The drug is still in the clinical trial stage in China. Olprinone possesses multiple properties. Firstly, olprinone shows positive inotropic and vasodilatation effects and enhances myocardial mechanical efficiency. Secondly, olprinone increases cerebral blood flow through the direct vasodilatation of cerebral arteries. The reactivity of cerebral vascularity of patients with impaired cerebral circulation to olprinone is very obvious. Thirdly, olprinone selectively improves the dilation of the carotid artery due to the variety of arterial structural components or the reactivity of smooth muscle cells to olprinone. Fourthly, olprinone can ameliorate the redistribution deficiency of cerebral perfusion and prevent abnormal cerebral metabolism during HF (15-16).

The research on the treatment of HF by PDE inhibitor olprinone was innovatively included. The therapeutic effects of olprinone and other PDE inhibitors on HF were systematically evaluated using meta-analysis to investigate the efficacy and safety of the treatment of HF by olprinone, which provided the basis for clinical medication.

Materials and Methods

Article retrieval

The Cochrane Library, PubMed, MEDLINE, EBSCO, Science Direct, and China National Knowledge Infrastructure (CNKI) databases were searched by computers. Internationally published articles on the treatment of HF by PDE inhibitor olprinone were searched. Olprinone, milrinone, PDE inhibitors, cardiac failure, and HF were set as the search terms to retrieve the relevant articles published between January 1999 and March 2022. Those terms were randomly combined to retrieve all databases and they have adjusted appropriately according to specific databases. All retrieval strategies were determined after multiple pre-retrievals. Besides, professional journals were retrieved manually to avoid omission. All research objects in the retrieved articles must be humans.

During the retrieval process, subject words were combined with free words for multiple retrievals to harvest the needed articles. The search engine was then utilized to trace each one. RevMan5.3 (Cochrane collaboration network) was employed to assess the quality of included articles.

Inclusion and exclusion criteria

Inclusion criteria:

A. The articles on the therapy of HF by PDE inhibitor
B. The articles with the diagnosis and therapy of HF as the gold standard
C. The articles with humans as the research objects
D. The articles whose true positive, false positive, false negative, and true negative values of the treatment could be acquired
E. The articles with subjects of more than 10 cases

Exclusion criteria:

A. Reports, overviews, conferences, periodicals, and reviews.
B. The articles were duplicated in literature or data.
C. The articles involved treatment methods other than PDE inhibitors.
D. The articles didn't include sufficient data that determined the treatment indexes.

Data retrieval

Uniform Microsoft Excel (Microsoft, USA) was utilized by two professionals to screen articles, extract data, and cross-check the results. Should there be disagreement, they needed to consult with each other to settle it down. The extracted data included the general included data and information (title, the first author, and publication year), the basic features of research objects (case number, age, and gender), interventional measures (name of drugs and disease course), the key factors of bias risk evaluation (methods for randomness, whether blind method was carried out, and allocation concealment), and the effective rate of the focused outcome indexes and outcome measurement data, the incidence of adverse reactions, as well as hemodynamic indexes.

Article evaluation criteria

Article quality was assessed using the QUADAS standard recommended by Cochrane (USA). Each article was rated as satisfied, dissatisfied, or uncertain regarding the quality of the included original articles determined by each evaluation index.

Statistical methodologies

RevMan5.3 (Cochrane, USA) and Stata (Stata Corp, USA) were adopted. The odds ratio (OD) of the dichotomous variable was used as the effective index, and the mean difference (MD) of the continuous variable was used as the effective index. The point estimate and the 95% confidence interval (CI) of each effect index were offered. The heterogeneity was determined by the X2 test (test level α=0.1). The size of heterogeneity was quantitatively assessed combined with I2. If no statistical difference was revealed by the heterogeneity between the result of each article, the fixed effect model (FEM) was adopted. If the differences in heterogeneity demonstrated statistical meaning, a randomized effect model (REM) was utilized. Besides, subgroup analysis was employed to investigate the possible source of heterogeneity. The test level α=0.05 was set for meta-analysis. Forest plots, summary receiver operating characteristic (SROC) curves, and funnel plot asymmetrical linear regression were drawn. The funnel plots with various treatment indexes were used to detect potential publication bias and implement the analysis of sensitivity(Sen).

For gene analysis, first, the MEFV gene sequence was obtained from the NCBI database. Then the exact location of this gene was determined using the UCSC database. Analyses related to the Reactome site were used to investigate autophagy mechanisms and to identify their specific targets, and UCSC and GeneCards sites were used to investigate MEFV gene exons and related mutations. Then the cellular comparison of the MEFV gene was analyzed by the Human Protein Atlas OMIM database.

Results

Mechanisms of autophagy in the MEFV gene

Autophagy mechanisms act as a platform for the assembly of Beclin, ULK1, ATG16L1, and ATG8 family members and identify specific autophagy targets (17). The MEFV gene has a positive effect on the inflammatory pathway and acts as an innate immune sensor and coordinates the initiation of autophagy by identifying the targets and assembling the autophagy apparatus. Also, the MEFV gene prevents excessive inflammation caused by IL1B and IL18 by destroying several inflammatory components including NLRP1, CASP1, and NLRP3. Exons 2 and 10 are called HOTSPOT points due to multiple mutations. In exon number 10, four major mutations occur. Codons 680 (18) and 694 (19) are called HOTSPOT codons. In exon number 2, 2 major mutations in codon 148 have been detected. The presence of multiple mutations in these exons has important effects on the function of the MEFV gene (19).

Molecular cellular functions and biological activity of the MEFV gene

Molecular functions related to the MEFV gene include membrane-associated actin binding, protein amino acid binding, glycoprotein binding, zinc binding, isoform-specific homophilic binding, and protein homopolymerization. Biological activities of the MEFV gene include the immune system process, inflammatory response, positive regulation of autophagy, negative regulation of interleukin-1 beta production, negative regulation of interleukin-12 production, response to interferon-gamma, innate immune response, negative regulation of inflammatory response, negative regulation of macrophage inflammatory protein 1 alpha production, negative regulation of cytokine production involved in the inflammatory response, negative regulation of NLRP3 inflammasome complex assembly and positive regulation of cysteine-type endopeptidase activity (20).

Article retrieval results and basic information

262 articles were harvested by database retrieval. Firstly, 46 duplicated articles and 73 disqualified articles were removed. After 38 articles were eliminated for other reasons, there were 105 remaining. Regarding abstracts and titles, 37 articles were eliminated and 68 were kept. 29 research reports and overviews were eliminated, and 39 were kept. Through full-text reading, 7 articles with undesired research types and 14 with incomplete or inaccessible treatment results were eliminated. There were 11 articles with the research objects not being humans. Finally, 7 articles were utilized for meta-analysis. Figure 1 showed the retrieval process.

Among the seven articles (21-27), the sample size of the articles with olprinone treatment was 1,287, and the sample size of the articles with other PDE inhibitors for treatment was 1,287. Additionally, the sample size of 7 included articles ranged from 10 to 951. In the 7 articles, the process of the treatment of HF by PDE inhibitors was described in detail, the changes in each index of the patients before and after treatment were recorded, and different PDE inhibitors and olprinone were compared. According to the evaluation results, 4 articles were rated level A (57.14%), 2 level B (28.6%), and 1 level C (14.3%). Tables 1 and 2 displayed the basic features of these articles. Figures 2 and 3 showed the risk bias evaluation and summary of the articles plotted by Rev-

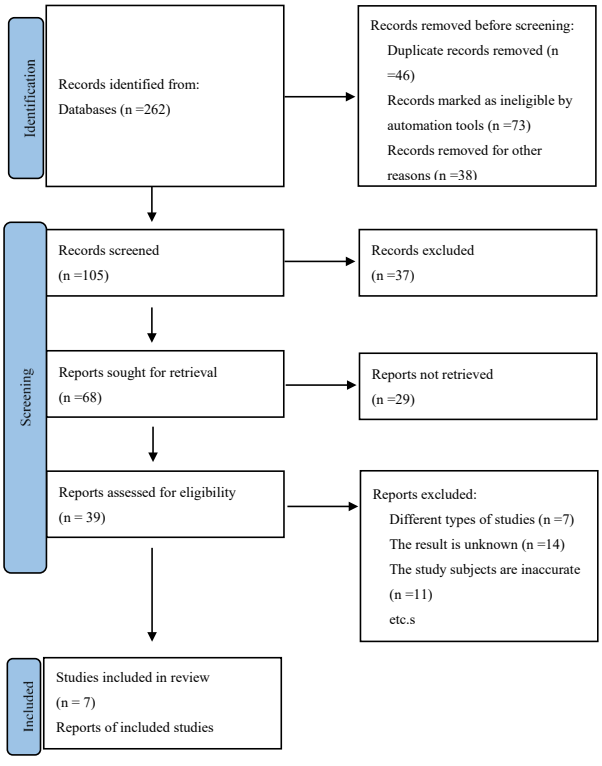

Figure 1. Process of article retrieval.

Table 1. Basic data on olprinone of the included articles.

Author	Year	Cases	Treatment methods
Arai(15)	2006	22	Olprinone
Cuffe(16)	2002	951	Olprinone
Hoffman(17)	2003	227	olprinone
Kanda(18)	1999	12	Olprinone
Kurokana(19)	2013	50	Olprinone
Mizushige(20)	2010	15	Olprinone
Momoi(21)	2000	10	Olprinone

Table 2. Basic data on other treatment methods of the included articles.

Author	Year	Cases	Treatment methods
Arai(15)	2006	22	Other treatment methods
Cuffe(16)	2002	951	Other treatment methods
Hoffman(17)	2003	227	Other treatment methods
Kanda(18)	1999	12	Other treatment methods
Kurokana(19)	2013	50	Other treatment methods
Mizushige(20)	2010	15	Other treatment methods
Momoi(21)	2000	10	Other treatment methods

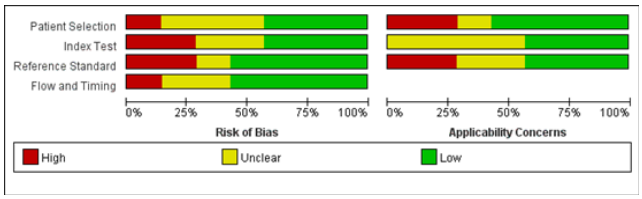

Figure 2. Evaluation of article risk bias.

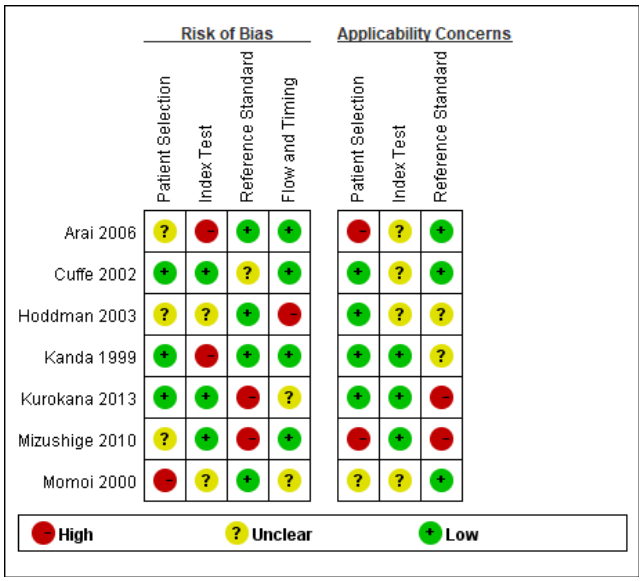

Figure 3. Summary of article risk bias. Note: "+" represented a low risk, "-" denoted high risk, and "?" referred to unclear.

Man5.3.

Results of heterogeneity evaluation

The heterogeneity results of olprinone treatment showed that the Sen and specificity (Spe) between each article showed no heterogeneity (I2=0.00%, 0.00%). Regarding the heterogeneity of the treatment by other PDE inhibitors, Sen and Spe between each article demonstrated heterogeneity (I2=79.79%. 74.83%). To verify whether the data of the two methods were heterogeneous and compare the indexes of different treatment methods, REM was employed for summary analysis and SROC curve fitting.

Meta-analysis of olprinone treatment

The treatment of patients with HF by olprinone was analyzed in the seven articles. Figure 4 presented the forest plots of the Sen and Spe of a single study and a summary study on the olprinone treatment of patients with HF below. The Sen of 7 articles on olprinone treatment was performed with a heterogeneity test. Q=0.95, df (degree of freedom)=6.00, I2=0.00%, and P=0.99, suggestingno heterogeneity between each research group. Combined Sen was 0.88 and 95%CI was (0.86,0.91). The lowest Sen was 0.75 and the lowest 95%CI was (0.19,0.99). The highest Sen was 0.90 and the highest 95%CI was (0.55,0.99). Besides, the Spe of 7 articles on olprinone treatment was performed with a heterogeneity test. Q=3.87, df=6.00, I2=0.00%, and P=0.69, demonstrating no heterogeneity between each research group. Combined Spe was 0.90 and 95%CI was (0.88,0.92). The lowest Sen was 0.83 and the

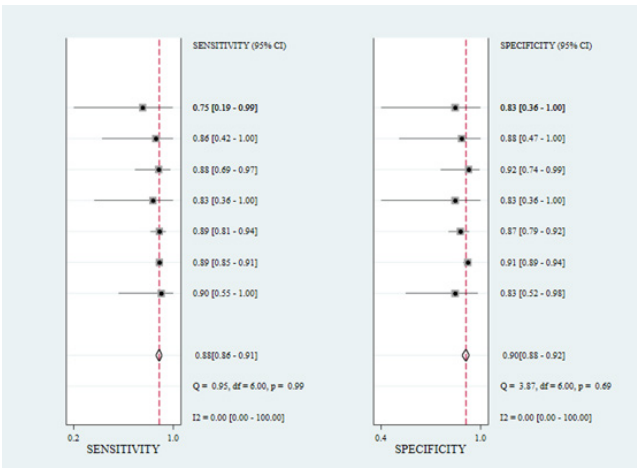

Figure 4. Forest maps of Sen and Spe of single study and summary study on olprinone treatment. CI represented confidence interval and df denoted degree of freedom.

lowest 95%CI was (0.36,0.99). The highest Sen was 0.92 and the highest 95%CI was (0.74,0.99).

In terms of hemodynamic indexes, the meta-analysis results of fixed effect models of 7 articles on olprinone treatment were shown in Figure 5 (Deek's funnel plot). Olprinone showed a stable effect in treating patients with HF. No statistical difference was detected in the same treatment method (OR= 3.84, 95%CI (2.86, 5.16), P = 0.58). Olprinone treatment couldn't reduce the incidence of postoperative adverse reactions among the patients with HF (OR=0.24, 95% CI(0.18, 0.33), P = 0.84), and no drastic difference was suggested in the same treatment method. A heterogeneity test was performed on the Sen of the hemodynamic index of olprinone treatment. Q=4.74, df(degree of freedom)=6.00, I2=0.00%, and P=0.58 showed no heterogeneity between each research group. Combined Sen was 0.81 and 95%CI was (0.75,0.86). The Spe of the hemodynamic index of olprinone treatment was performed with a heterogeneity test. Q=2.78, df=6.00, I2=0.00%, and P=0.84 suggested no heterogeneity between each research group. Combined Sen was 0.79 and 95%CI was (0.72,0.84).

In terms of urine flow, olprinone treatment could increase the urine flow of patients. There was a statistical difference in the same treatment method (OR= 4.00, 95%CI(2.86, 5.61), and P<0.01). The probability that olprinone treatment couldn't increase urine flow was 44% (OR=0.44, 95% CI(0.31, 0.62), and P<0.01), which indicated considerable differences. Sen of the hemodynamic index of olprinone treatment was assessed using a heterogeneity test. Q=31.64, df =6.00, I2=67.71%, and P<0.01 indicated certain heterogeneity between each research group. Spe of the hemodynamic index of olprinone treatment was performed with a heterogeneity test. Q=99.56, df=6.00, I2=93.97%, and P<0.01, revealing substantial differences in heterogeneity between each research group.

To further observe the therapeutic effects, the treatment was analyzed comprehensively. Figure 6 was a Galbraith meta-analysis diagram. The assessment of the heterogeneity and potential abnormal values between each article suggested that the difference in heterogeneity between each article was very little with high accuracy (ACC). Figure 7 was a bivariate boxplot in which the evaluation of therapeutic effects could be obtained. The method demonstrated good Spe and Sen in treatment. Figure 8 presented SROC curves of olprinone treatment. The proximity of SROC curves to the top left corner of the plot indicated the larger area under the SROC curve and higher therapeutic Acc. Figure 9 displayed a likelihood matrix analysis. Positive likelihood ratio and negative likelihood ratio could be observed. The proportions of false negatives and false positives

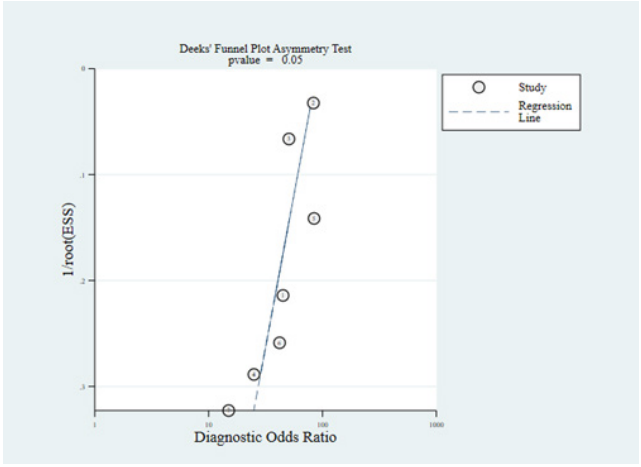

Figure 5. Deek's funnel plot of the effects of olprinone treatment.

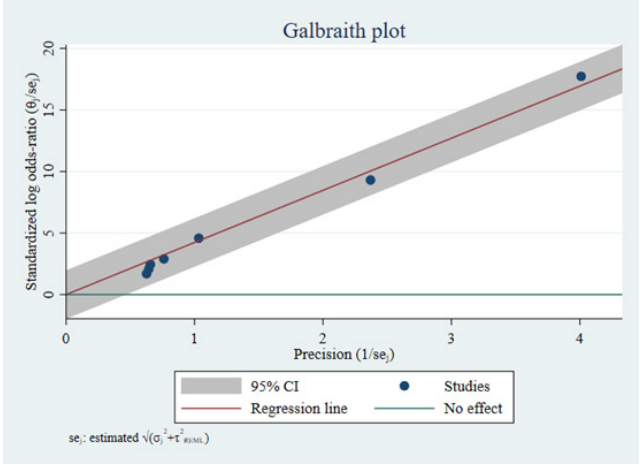

Figure 6. Galbraith meta-analysis of olprinone treatment.

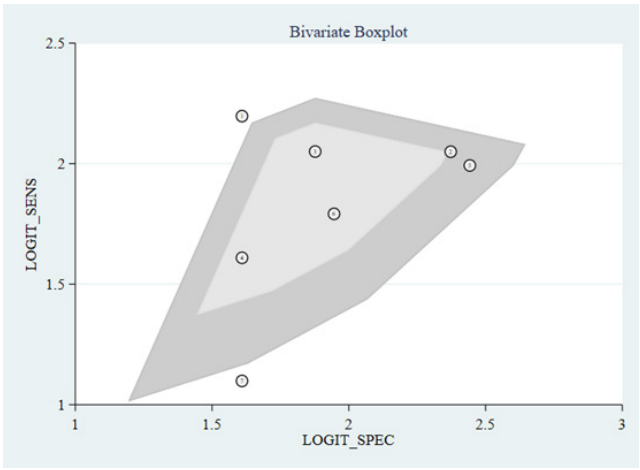

Figure 7. Bivariate boxplot of olprinone treatment.

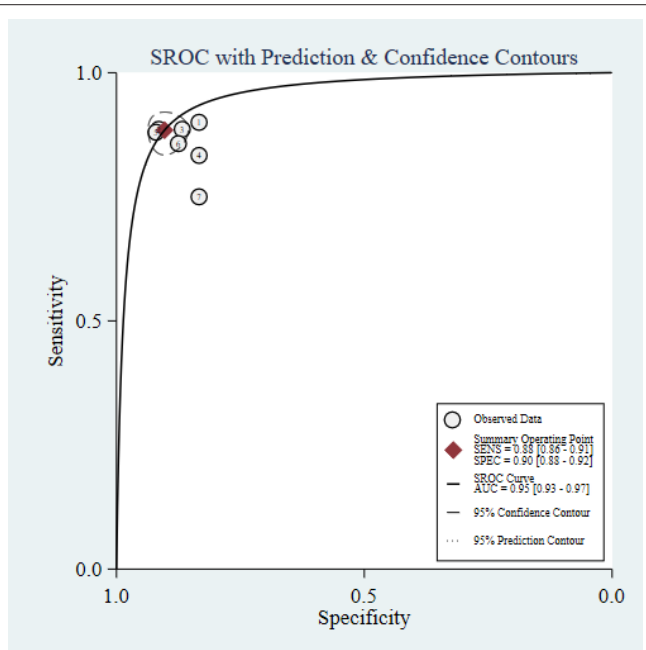

Figure 8. SROC curve of olprinone treatment. SROC referred to summary receiver operating characteristic, AUC denoted area under the curve, SENS represented Sen, and SPEC indicated Sen.

were low, while therapeutic Acc was high. All articles were detected by Western blotting. Spe of olprinone treatment was high and olprinone could better improve the hemodynamic index. Figure 10 showed funnel asymmetrical linear regression analysis. The random effect was utilized to further detect the therapeutic effect. It was found that the difference in heterogeneity between each article was little with high Acc.

Meta-analysis of the treatment by other PDE inhibitors

In 7 included articles, the results of the treatment of patients with HF by other PDE inhibitors were analyzed. Figure 11 were the forest plots of the Sen and Spe of a single study and summary study on the treatment of patients with HF by other PDE inhibitors below. The Sen of 7 articles on the treatment by other PDE inhibitors was performed with a heterogeneity test. Q=0.29.68,df=6.00, I2=79.79%, and P<0.01 suggested high heterogeneity between each research group. Combined Sen was 0.69 and 95%CI was (0.59,0.78). The lowest Sen was 0.60 and 95%CI was (0.15,0.95). The highest Sen was 0.81 and 95%CI was (0.77,0.84). Besides, the Spe of 7 articles on the treatment by other PDE inhibitors was evaluated by heterogeneity test. Q=23.84, df=6.00, I2=74.83%, and P<0.01 showed no heterogeneity between each research group. Combined Sen was 0.69 and 95%CI was (0.60,0.76). The lowest Sen was 0.57 and 95%CI was (0.18,0.90). The highest Sen was 0.78 and 95%CI was (0.74,0.82).

In terms of hemodynamic index, the meta-analysis results of fixed effect models of 7 articles on the treatment by other PDE inhibitors were illustrated in Figure 12 (Deek's funnel plot) below. According to Figure 12, other PDE inhibitors showed a stable effect in treating patients with HF, and no statistical difference was detected in the same treatment method (OR= 3.61, 95%CI (2.75, 4.74), and P = 0.77). The treatment by other PDE inhibitors couldn't reduce the incidence of postoperative adverse reactions among the patients with HF (OR=0.27, 95%CI(0.21,0.35), and P = 0.97). No remarkable difference was indicated in the same treatment method. Sen of the hemodynamic index of the treatment by other PDE inhibitors was performed with a heterogeneity test. Q=3.29,df=6.00, I2=0.00%, and P=0.77 indicated that no heterogeneity was detected between each research group. Combined Sen was 0.79 and 95%CI was (0.73,0.84). The heterogeneity test was performed on the Spe of the hemodynamic index of the treatment by other PDE inhibitors. Q=1.37, df=6.00, I2=0.00%, and P=0.97 suggested no heterogeneity between each research group. Combined Spe was 0.78 and 95%CI was (0.72,0.83).

In terms of urine flow index, olprinone could enhance patients' urine flow. There was a statistical difference in the same treatment method (OR= 2.56, 95%CI(1.99, 3.29), and P<0.01). The probability that the treatment by other PDE inhibitors couldn't increase urine flow was 34% (OR=0.34, 95%CI(0.24, 0.49), and P<0.01), which showed significant

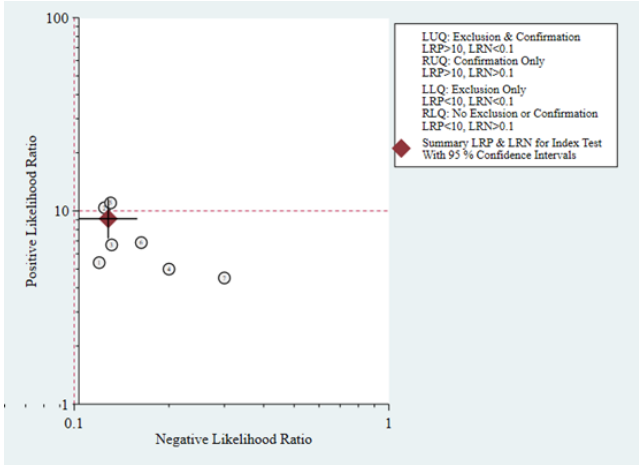

Figure 9. Likelihood matrix analysis of olprinone treatment.

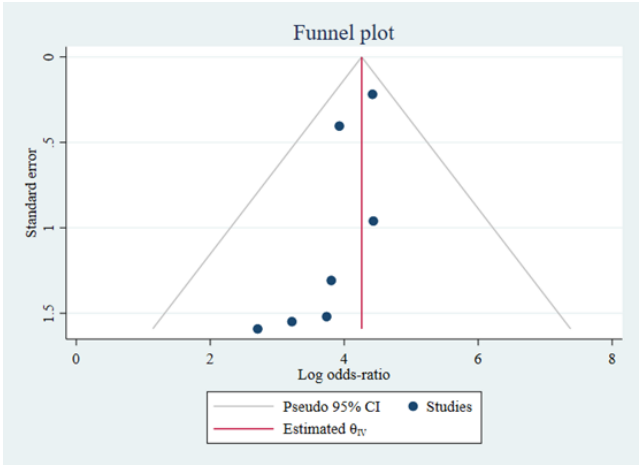

Figure 10. Funnel plot of olprinone treatment.

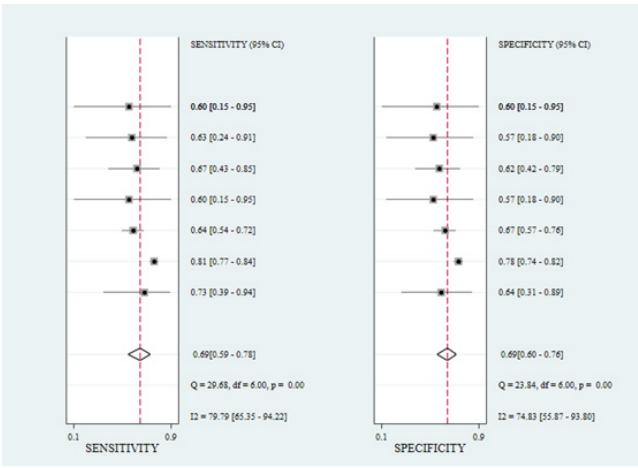

Figure 11. Forest maps of Sen and Spe of a single study and summary study on the treatment of HF by other PDE inhibitors. CI referred to a confidence interval and df denoted the degree of freedom.

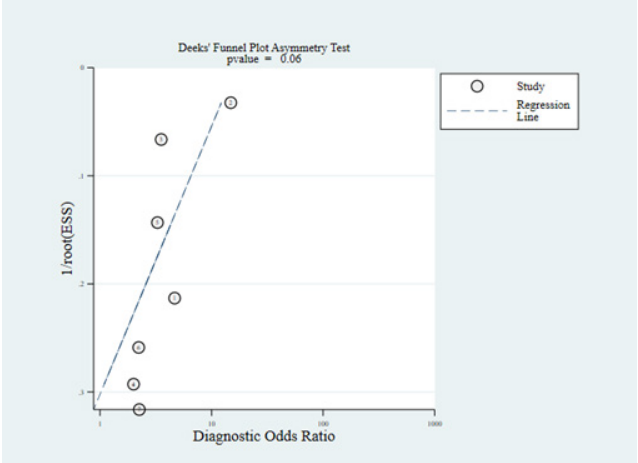

Figure 12. Deek's funnel plot of therapeutic effects of other PDE inhibitors.

differences. The heterogeneity test on the Sen of the hemodynamic index of the treatment by other PDE inhibitors showed that Q=20.71, df =6.00, I2=48.47%, and P<0.01, indicating heterogeneity between each research group. The Spe of the hemodynamic index of the treatment by other PDE inhibitors was performed with a heterogeneity test. Q=33.97, df=6.00, I2=82.34%, and P<0.01 suggested that the difference in heterogeneity between each research group was remarkable.

To further observe the therapeutic effects, the treatment was analyzed comprehensively. Figure 13 was a Galbraith meta-analysis diagram. The assessment of the heterogeneity and potential abnormal values between each article suggested that the difference in heterogeneity between each article was very little with high Acc. Figure 14 was a bivariate boxplot in which the evaluation of therapeutic effects could be obtained. The method demonstrated good Spe and Sen in treatment. Figure 15 presented SROC curves of the treatment by other PDE inhibitors. The proximity of SROC curves to the top left corner of the image indicated the larger area under the SROC curve and higher therapeutic Acc. Figure 16 displayed a likelihood matrix analysis. The positive likelihood ratio and negative likelihood ratio of the data could be observed. The proportions of false negative and false positive were scattered and the therapeutic Acc was uncertain. All articles were detected by Western blotting. The Spe and Sen of the treatment by other PDE inhibitors were lower than those of olprinone treatment. No notable difference in the improvement of the hemodynamic index was revealed between the treatment by other PDE inhibitors and olprinone treatment. Figure 17 showed funnel asymmetrical linear regression analysis. The random effect was utilized to further detect the therapeutic effect. It was found that the difference in heterogeneity between each article was little with high Acc.

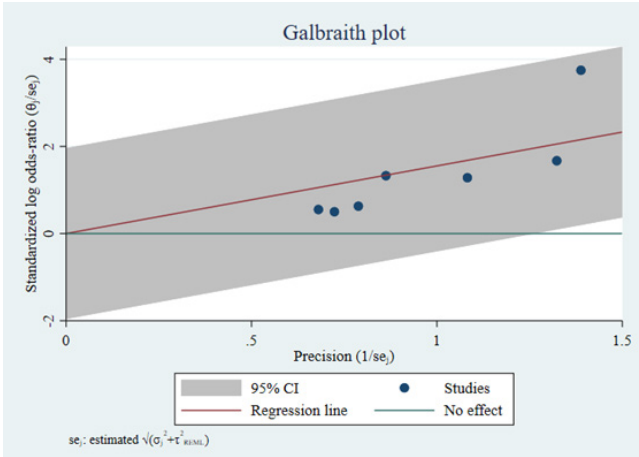

Figure 13. Galbraith meta-analysis of the treatment by other PDE inhibitors.

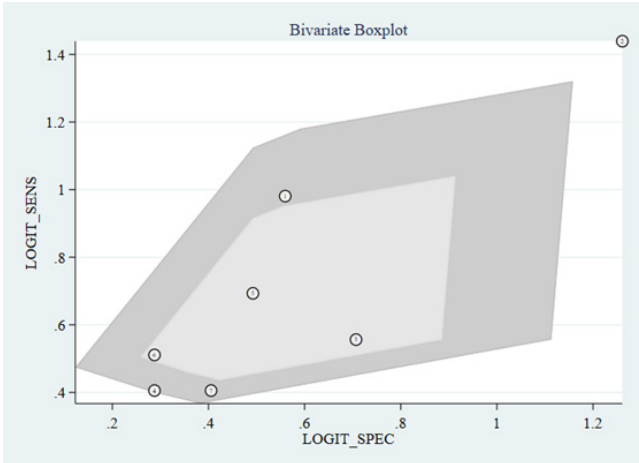

Figure 14. Bivariate boxplot of the treatment by other PDE inhibitors.

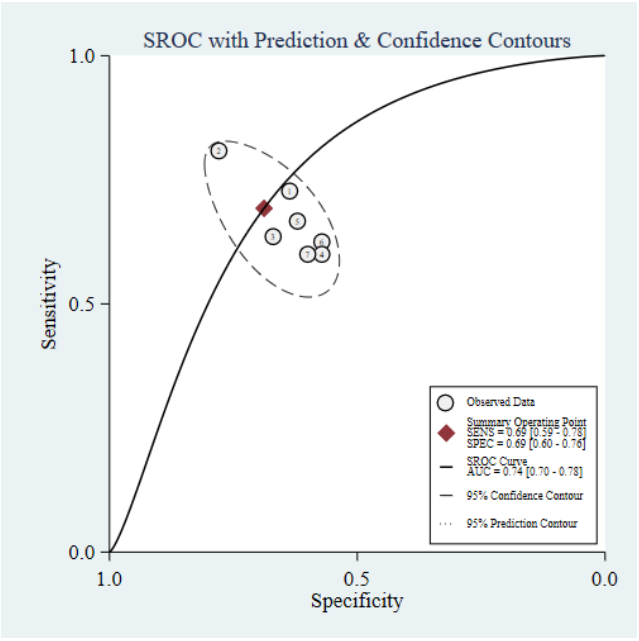

Figure 15. SROC curve of the treatment by other PDE inhibitors. SROC denoted summary receiver operating characteristic, AUC referred to the area under the curve, SENS represented Sen, and SPEC indicated Sen.

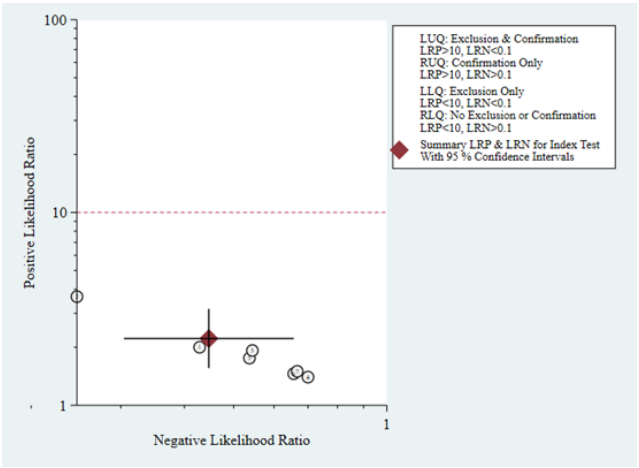

Figure 16. Likelihood matrix analysis of the treatment by other PDE inhibitors.

Reliability analysis

The Sen was analyzed by changing analysis models. Meta-analysis showed that the summary of results with various analysis models revealed no great changes, which indicated that all involved articles demonstrated high stability. The model analysis, such as funnel asymmetrical linear regression analysis also suggested that the verification by Spe and Sen was consistent.

Discussion

Chronic HF refers to the symptom of the reduction in

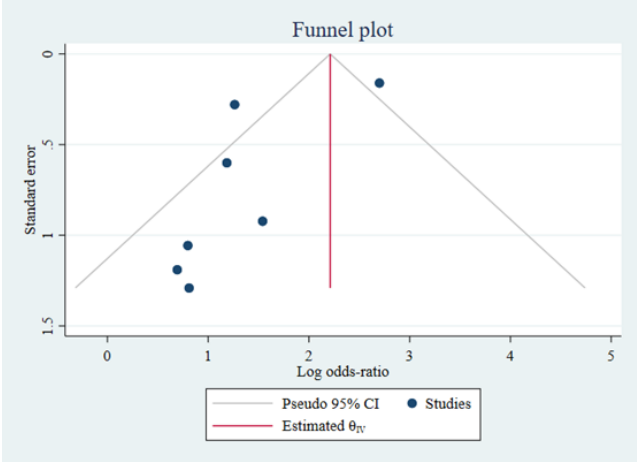

Figure 17. Funnel plot of the treatment by other PDE inhibitors.

tissue blood perfusion or the congestion of the body circulation system caused by the decreased cardiac output, which results from the obvious weakening of myocardial systolic (or diastolic) function due to multiple causes of disease (28). Because of the lack of supply and demand, the body's role in regulating the improvement of the work of the myocardium is initialized, such as the accelerated heart rate caused by sympathetic excitation and vasoconstriction as well as cardiovascular remodeling resulting from the renin-angiotensin-aldosterone system (RAAS). These regulatory functions can improve the work of the myocardium within a certain range. However, the long-term effects of various regulatory mechanisms lead to increased systolic or diastolic function due to the change in cardiac structure, and the decline in cardiac function further promotes the role of body regulatory mechanisms, which is a vicious circle (29-30). The studies on anti-HF in recent years focus on interrupting the vicious cycle at each step to prevent the further deterioration of cardiac function. The increase in myocardial systolic (or diastolic) function as well as the reduction of the workload of the heart can significantly increase the pumping of blood by the heart, reduce the deficiency in blood supply, and inhibit the role of body regulatory mechanisms. Consequently, the vicious cycle is broken down fundamentally. Cardiac function is improved and further deterioration of cardiac function is inhibited. Therefore, the drugs that play the two roles have good effects in the treatment of anti-HF (31).

PDE inhibitor is a new anti-HF drug developed in the past more than 20 years. Its action process is different from that of traditional digitalis and catecholamine drugs. It is reported that 11 PDE gene families are discovered and each family includes multiple subfamilies. PDEs are distributed in several tissues and their inhibitors show extensive physiological effects. PDE III is distributed mainly in cardiac muscle cells, vascular smooth muscle cells, and most immunoinflammatory cells in tracheal smooth muscle. PDE III inhibitors can selectively inhibit and degrade PDE III of cAMP to block the degradation of cAMP into 5'-AMP and increase the content of cAMP in the myocardium and vascular smooth muscle (32). cAMP can promote the influx and uptake of Ca2+ to increase myocardial systolic and diastolic abilities and enhance the efficiency of cardiac work. Increased cAMP can cause the vasodilation of vascular smooth muscle and reduce cardiac load. The clinical application proves that PDE III inhibitors can increase cardiac output, reduce cardiac load as well as myocardial oxygen consumption, and relieve congestive HF. Besides, PDE III inhibitors can delay the further development of HF by inhibiting cytokines and inflammatory factors (33).

At present, several venous dilators with the properties of cardiotonic and vasodilator can be employed to treat HF. Among various regulators that can be administered intravenously, milrinone, olprinone, anagrelide (PDE III inhibitors), and oxymuriate (an adenylate cyclase activator) are approved for clinical application in Japan (34). Because of the role of their vasodilators, these drugs possess greater potential in improving left ventricular function and hemodynamics than strict cardiotonic drugs. They are also superior to catecholamine in terms of working efficiency and the influences on myocardial oxygen supply and demand. In addition, their immunomodulators can significantly improve rapidly deteriorated hemodynamics among patients with chronic HF caused by the downregulation of a-adrenergic receptor without involving a-adrenergic receptor as a cardiac reinforcing agent. Immune inoculant is expected to benefit the patients without catecholamine response. Some scholars research dobutamine administered to milrinone or patients with HF and compare the abilities of the two drugs to improve cardiac function. Blood norepinephrine level (no increase in left ventricular dP/dt) of dobutamine-resistant patients is remarkably higher than that of dobutamine-sensitive patients (increased left ventricular dP/dt). However, it is found that there is no significant difference in blood norepinephrine levels between milrinone-sensitive patients and milrinone-resistant patients (35). Although the influences of single therapy and the combination therapy of dobutamine and PDE III inhibitors on heart rate and mean aortic pressure demonstrate no notable differences, the combination therapy increases cardiac index as well as the amount of stroke and reduces pulmonary artery and pulmonary wedge pressure. Hence, PDE III inhibitors are very effective in improving the hemodynamics of patients without response to or resistance to catecholamine.

A total of 7 articles involving 1,287 patients were used for meta-analysis. The Sen of 7 included articles on the therapy of patients with HF by olprinone was assessed with a heterogeneity test. Q=0.95, df (degree of freedom)=6.00, I2=0.00%, and P=0.99 indicated no heterogeneity between each research group. Combined Sen was 0.88 and 95%CI was (0.86,0.91). The lowest Sen was 0.75 and 95%CI was (0.19,0.99). The highest Sen was 0.90 and 95%CI was (0.55,0.99). The Spe of 7 included articles on the therapy of patients with HF by olprinone was performed with heterogeneity test. Q=3.87, df=6.00, I2=0.00%, and P=0.69 indicated no heterogeneity between each research group. Combined Spe was 0.90 and 95%CI was (0.88,0.92). The lowest Spe was 0.83 and 95%CI was (0.36,0.99). The highest Sen was 0.92 and 95%CI was (0.74,0.99). In 7 included articles,

In 7 included articles, the Sen of the therapy of patients with HF by other PDE inhibitors was performed with heterogeneity test. Q=0.29.68, df (degree of freedom)=6.00, I2=79.79%, and P<0.01 indicated great heterogeneity between each research group. Combined Sen was 0.69 and 95%CI was (0.59,0.78). The lowest Sen was 0.60 and 95%CI was (0.15,0.95). The highest Sen was 0.81 and 95%CI was (0.77,0.84). The Spe of 7 articles on the therapy of patients with HF by other PDE inhibitors was performed with heterogeneity test. Q=23.84, df=6.00,

I2=74.83%, and P<0.01 showed that no heterogeneity existed between each research group. Combined Spe was 0.69 and 95%CI was (0.60,0.76). The lowest Sen was 0.57 and 95%CI was (0.18,0.90). The highest Sen was 0.78 and 95%CI was (0.74,0.82).

The comparison of the influence of two treatment methods on hemodynamics revealed that the Sen and Spe of each article in the olprinone group demonstrated no heterogeneity (Q=4.74, df=6.00, I2=0.00%, and P=0.58; Q=2.78, df=6.00, I2=0.00%, and P=0.84). The therapeutic effect on patients with HF was stable and good (OR= 3.84, 95%CI(2.86,5.16), and P = 0.58). The incidence of postoperative adverse reactions among the patients without reducing HF was low (OR=0.24, 95% CI(0.18,0.33), and P = 0.84). The difference in the effect of other PDE inhibitors and olprinone was not significant, and its Sen and Spe showed no heterogeneity (Q=3.29, df=6.00, I2=0.00%, and P=0.77; Q=1.37, df=6.00, I2=0.00%, and P=0.97). Its therapeutic effect was also stable (OR= 3.61, 95%CI(2.75,4.74), and P = 0.77). The incidence of postoperative adverse reactions among the patients without reducing HF was low (OR=0.27, 95% CI(0.21,0.35), and P = 0.97). The influences of the two treatment methods on urine flow revealed heterogeneity and its effect had no statistical meaning.

To sum up, the therapeutic effects of olprinone and other PDE inhibitors on HF were synthesized and assessed to provide evidence-based recommendations for clinical practice guidelines. In clinical studies, different medication methods were adopted to exert medicinal values according to different situations of patients. More indexes will be collected to compare the differences between different drugs in detail in subsequent studies, which provides a more accurate reference for clinical treatment.

So far, more than 80 multiple mutations have been identified in the MEFV gene, the most important of which are E148Q, V726A, M694V, M680I, and M694I. More than 80% of these mutations occur in exon numbers 2 and 10. In 2014, Baster et al showed that a group of patients with heart failure (coronary arteries) had at least one mutant allele of the MEFV gene (36). The results of the analysis of exon number 10 in the MEFV gene by Bagheri et al. in 2018 showed that M680I, K695R, A744S, and V726A mutations are very common in this exon. Grimaldi et al., 2006, after examining 121 patients with acute myocardial infarction, showed that M694V mutation (heterozygous) was present in 12% of the studied population (37). The collection of these findings can be effective in choosing treatment methods, patient management, and diagnosis methods (38,39). Also, it seems that conducting screening tests to track people who are carriers will help to prevent the occurrence of heart failure and reduce treatment costs in the future. Therefore, it is recommended to determine the treatment protocols for patients with heart failure and their families and to check all the exons related to heart failure in suspected patients.

Conclusion

Articles related to the therapeutic effects of olprinone and other PDE inhibitors on HF were selected and used in meta-analysis to investigate the effects of olprinone and other PDE inhibitors on hemodynamics, urine flow, and clinical treatment. The results confirmed that the Spe and Sen of olprinone therapy were higher than those of the therapy by other PDE inhibitors with better therapeutic effects on patients with HF. In terms of hemodynamics, the differences between different treatment methods were not significant. Nonetheless, heterogeneity existed between different articles in terms of urine flow. More samples and high-quality articles were needed to provide a more accurate and effective basis for clinical practice.

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