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REVIEW ARTICLE

Early Administration of Apelin Could Prevent Heart Failure Following Myocardial Injury; A Systematic Review and Meta-Analysis

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Abstract: **Introduction:** Heart failure (HF) is a prevalent and advancing cardiovascular disorder that impacts 1-2% of the worldwide population, particularly the elderly. Studies indicate that the intravenous administration of apelin may yield advantageous effects in preventing heart failure subsequent to myocardial injury. This meta-analysis aimed to assess the effects of exogenous apelin administration on heart failure in animal models, in light of the lack of a definitive consensus on the matter. **Methods:** An extensive search was performed in the Medline (via PubMed), Web of Science, Embase, and Scopus databases till the end of January 2024. Two independent reviewers screened and summarized the relevant articles. Outcomes related to cardiac function, including ejection fraction (EF), maximum and minimum rate of left ventricle systolic pressure (+dp/dt and –dp/dt, respectively), heart rate, left ventricular end-diastolic pressure (LVEDP), and left ventricular systolic pressure (LVSP) were assessed. Findings were reported as a pooled standardized mean difference (SMD) with a 95% confidence interval (95% CI). **Results:** 12 studies were included. Pooled analysis demonstrated that early treatment with apelin following myocardial injury significantly increases +dp/dt (SMD = 2.36; 95% CI: 1.58 to 3.15; $p < 0.001$) and decreases -dp/dt (SMD = -3.31; 95% CI: -4.46 to -2.17; $p < 0.001$). Furthermore, the administration of apelin resulted in a significant increase in EF (SMD = 0.79; 95% CI: 0.15 to 1.44; $p = 0.02$) and LVSP (SMD = 2.09; 95% CI: 0.82 to 3.36; $p < 0.001$), while it led to a decrease in LVEDP in the animals (SMD = -1.85; 95% CI: -2.81 to -0.88; $p < 0.001$). Noteworthy, apelin treatment was shown to have no significant influence on the heart rate of the animals (SMD = -0.12; 95% CI: -0.82 to -0.58; $p = 0.73$). **Conclusions:** The current study demonstrated that the early administration of apelin has the potential to improve cardiac function and mitigate the onset of heart failure subsequent to myocardial injury. Further, in vivo research is essential to lay the groundwork for the integration of apelin into clinical practice.

Keywords: Apelin; Myocardial Ischemia reperfusion injury; Myocardial infarction, Heart Failure

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1. Introduction

Heart failure (HF) is a prevalent, chronic, and progressive cardiovascular condition characterized by dynamic pathological changes in the structure and function of cardiomyocytes. Epidemiological studies estimate that HF affects 1–2% of the global population, with annual expenditures exceeding $30 billion in the United States alone (1-3). The incidence of HF is notably higher among the elderly, with a prevalence of over 10% in individuals over 70 years old. Despite ongoing efforts to decrease the morbidity and mortality associated with HF, the burden of the disease remains substantial, with mortality rates surpassing those of certain types of cancer (4). While the precise mechanisms of HF progression are comprehended, many patients experience declining cardiac function, necessitating heart transplantation as the only available therapeutic option, which is limited by factors such as donor scarcity and allograft rejection (3, 5).

Early prevention and timely treatment of HF are crucial for a more favorable patient prognosis, and there is a growing research interest in identifying new preventive and therapeutic agents for addressing HF. In recent years, researchers have focused on the Apelin-APJ system as a novel neu-

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roendocrine pathway implicated in the pathogenesis of HF. Apelin, discovered as an endogenous ligand for APJ, a G protein-coupled receptor of Apelin, is produced through the C-terminal cleavage of 77 amino acids of pre-proapelin, encoded by a gene on chromosome X (6).

Pre-proapelin is enzymatically cleaved to form various apelin fragments, with the most active fragment being apelin-13 (7-12). The widely dispersed apelin-APJ system in cardiac tissue plays a crucial role in maintaining cardiovascular homeostasis. Apelin, upon binding to its receptor, induces vasodilation and enhances cardiac contractility in a manner dependent on nitric oxide (NO) and endothelium (5, 13, 14). Apelin-induced vasodilation reduces ventricular preload, afterload, and cardiac workload while increasing coronary blood flow. Simultaneously, it increases the contractility of the cardiac muscle, thereby elevating cardiac output (CO) (15, 16).

It seems that modulation of the apelin-APJ pathways may yield desirable therapeutic effects on HF. Chen et al. showed that apelin levels depend on the severity and stage of HF, so that in the early stages of HF, plasma levels of apelin were higher, but in patients with severe disease, they reduced significantly compared to normal subjects (17). They also reported that in patients with ventricular assist device implantation who later undergo heart transplantation, apelin plays an important role in reversing heart failure (17). It has also been reported that serum levels of apelin decreased in patients with an unfavorable prognosis compared with patients with a favorable prognosis. There was a significant positive correlation between serum levels of apelin and left ventricular systolic function. In addition, there was a significant negative correlation with heart rate and the dimensions of the left and right ventricles (2).

Chen et al. have established a correlation between apelin levels and the severity and progression of heart failure (HF). Their research suggests that plasma apelin levels are elevated in the early stages of HF but decrease significantly in patients with advanced disease compared to individuals without heart failure. Furthermore, diminished serum apelin levels were linked to an unfavorable prognosis, while higher levels were associated with a favorable prognosis. Studies on apelin-null mice indicated decreased cardiac systolic functions at rest and reduced exercise capacity (5, 17). Additionally, apelin administration was found to reverse multiple heart failure phenotypes, inhibit cardiac hypertrophy, and improve myocardial contraction (18, 19). In a rat model of HF induced by chronic systemic hypoxia, elevated levels of apelin-36 and oxidative stress were observed. Hence, it can be inferred that apelin-36, in conjunction with oxidative stress, likely functions as a biomarker of HF (20).

Several studies have been undertaken on the administration of apelin as a preventive or therapeutic measure for heart failure. However, their results have been inconsistent. For instance, Sato et al. reported an increase in heart rate in response to 2-weeks of apelin-13 administration in mice after transverse aortic constriction compared to the vehicle group (21). At the same time, a study by Jia showed a decrease in heart rate among isoproterenol-induced heart failure rats after 5 days of daily treatment with apelin (22). Therefore, there is no consensus on the protective effect of apelin on heart failure. The objective of this meta-analysis was to evaluate the effects of administering exogenous apelin on heart failure in animal models.

2. Methods

2.1. Study design and setting

The present meta-analysis was designed to evaluate the effectiveness of apelin administration in rodent models of heart failure. We investigated the cardiac effects of apelin administered as a therapeutic or preventive measure. Concordantly, we sought studies employing apelin in rodent models of established heart failure or at risk of progressing to heart failure following myocardial injury.

We evaluated the cardiac effect of apelin administration irrespective of dose and route of administration with regard to functional parameters including ejection fraction (EF), fractional shortening (FS), cardiac output (CO), maximum and minimum rate of left ventricle systolic pressure (+dp/dt and –dp/dt, respectively), heart rate (HR), left ventricular end diastolic pressure (LVEDP), and left ventricular systolic pressure (LVSP).

2.2. Selection criteria

In this investigation, all in vivo experimental studies examining the preventive or therapeutic effect of apelin administration on heart failure were considered. Rat and mouse populations were predominantly studied, and as such, they were included in our analysis without limitations based on gender or race. Exclusion criteria encompassed studies lacking a control group, those involving animals other than rodents, studies on heart diseases other than heart failure, and studies that did not report any of our desired specified outcomes. Additionally, duplicate studies, review articles, and in-vitro studies were also excluded.

2.3. Search strategy

A comprehensive search was carried out across four main electronic databases, including Medline (via PubMed), Embase, Scopus, and Web of Science, from their inception up to January 2024. The search strategy utilized all pertinent keywords concerning heart failure and apelin, chosen to encompass a wide range of relevant studies. As online databases do not consistently discriminate between animal and human studies, we did not employ an animal studies filter. The selection of keywords was informed by reviewing MeSH terms and Emtree terms and supplemented by consultation with experts in the field. To catch all possible relevant studies, the systematic search was complemented by a manual search in Google and Google Scholar search engines as well as a bibliography of the included articles. The detailed search string

employed for each database is provided in appendix 1.

2.4. Data gathering

The records obtained were imported into the Endnote X9.0 software and subjected to de-duplication. Initial screening was conducted independently by two reviewers who assessed the titles and abstracts of all records, selecting potentially relevant studies for full-text review.

Subsequently, two independent reviewers comprehensively evaluated all full texts and extracted data from eligible articles using a checklist aligned with the PRISMA statement guidelines. Any discrepancies between reviewers were resolved through discussion or consultation with a third author. The extracted data included the first author's name, publication year, animal species, breed, age or weight, method of heart failure induction, number of animals per group, apelin administration protocol (single or multiple doses), route of administration (intravenous or intraperitoneal), heart rate, +/- dp/dt, ejection fraction, LVSP, LVEDP, and follow-up duration. As most animal studies present data graphically, information was extracted using Plot Digitizer software.

2.5. Risk of bias assessment

Articles underwent quality control based on the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) risk of bias tool for animal studies' recommended guidelines (23). Disagreements were resolved through discussions with a third researcher.

2.6. Statistical analysis

For statistical analysis, the mean and standard deviation of the evaluated outcomes, as well as the number of samples in each group, were recorded in the STATA 17.0 statistical program (Stata Corporation, College Station, TX). Next, we calculated a standardized mean difference (SMD) for each individual study using the "meta" command, ensuring a 95% confidence interval (95% CI) by fitting a random effect model.

Finally, we pooled the study results to provide an overall SMD. Statistical heterogeneity between studies was evaluated using the I2 test and Cochran's Q test. A funnel plot was used to visually inspect publication bias, and the modified Egger's test proposed by Doleman et al. was applied to statistically assess it (24).

3. Results

3.1. Characteristics of imported studies

Upon conducting a search of the databases, 722 unique records were retrieved. Following the screening of article titles and abstracts, 33 articles were subjected to a detailed examination. Subsequently, data from 12 studies was incorporated into the present study (15, 25-35) (Figure 1). Notably, 8 of the studies involved rats, 3 involved mice, and 1 involved rabbits. In the apelin-treated and control groups across 8 studies, there were 95 and 89 animals, respectively. Apelin-13 was the agent utilized in 8 studies, while apelin-12 or 13 was used in one study, apelin-16 in another, apelin-36 in a separate study, and one study did not specify the type of apelin. Moreover, apelin was administered intraperitoneally in 8 studies and intravenously in 4 studies.

In the examination of heart failure models across various studies, the inducement methods included left anterior descending artery (LAD) ligation in seven studies, isoproterenol administration in two studies, one kidney artery ligation in one study, transverse aortic constriction (TAC) in one study, and continuous infusion sodium phenobarbital in another. The studies were categorized into two groups based on the timing of the heart failure induction model and the initial administration of apelin. In the treatment group, apelin was administered after the onset of cardiac function impairment and established heart failure to evaluate its therapeutic effect, comprising three studies. Conversely, the pre-treatment group encompassed studies where apelin administration began before the development of heart failure to assess its preventive effect, totaling nine studies.

3.2. Pre-treatment Effect of Apelin on cardiac function

Based on our research, apelin's potential to prevent heart failure has been assessed in nine studies. Among these, six studies administered apelin after inducing myocardial ischemia-reperfusion injury through ligation of the left anterior descending artery (LAD). Two studies utilized isoproterenol injection, while one study used transverse aortic constriction to evaluate the efficacy of apelin in preventing subsequent heart failure.

In comparison to non-treated animals, pre-treatment with apelin significantly increases +dp/dt (SMD = 2.36; 95% CI: 1.58 to 3.15; $p < 0.001$; I2 = 69.87%) and decreases -dp/dt (SMD = -3.31; 95% CI: -4.46 to -2.17; $p < 0.001$; I2 = 77.89%). Furthermore, the administration of apelin resulted in a significant increase in ejection fraction (SMD = 0.79; 95% CI: 0.15 to 1.44; $p = 0.02$; I2 = 73.90%) and left ventricular systolic pressure (SMD = 2.09; 95% CI: 0.82 to 3.36; $p < 0.001$; I2 = 90.33%), while it led to a decrease in left ventricular end-diastolic pressure (LVEDP) (SMD = -1.85; 95% CI: -2.81 to -0.88; $p < 0.001$; I2 = 84.19%). Noteworthy, apelin pre-treatment was shown to have no significant influence on the heart rate of the animals (SMD = -0.12; 95% CI: -0.82 to -0.58; $p = 0.73$; I2 = 70.22%). Due to the scarcity of included studies, we could not perform any subgroup analysis or sensitivity analysis.

3.3. Treatment effect of apelin on heart failure

We identified three studies investigating the impact of apelin after confirming heart failure. Due to a significant variation among administration doses and different follow-up durations, we were unable to pool the data and perform a meta-

analysis.

Berry et al. conducted a study involving male adult rats 6 weeks after the induction of heart failure by LAD ligation. The rats received an intravenous infusion of apelin 16 at a rate of 0.01 ug per minute for 20 minutes. Hemodynamic measurements were taken at 5-minute intervals until 15 minutes after the infusion was stopped. The results indicated a rapid increase in +dp/dt, -dp/dt, EF, and LVSP, along with a decrease in heart rate within five minutes. The authors concluded that the administration of apelin has a positive inotropic effect on failing hearts.

In a study by Pang et al., 6-week-old male rats were subjected to left renal artery clipping, leading to the development of heart failure 17 weeks later. This was followed by the administration of apelin 13 intravenously at doses of 0.1, 1, and 10 ug at 10-minute intervals. Hemodynamic measurements were taken 10 minutes before the first injection and 30 minutes after the last injection. Following the first apelin injection, there was an observed increase in +dp/dt and -dp/dt, along with a decrease in heart rate, LVEDP, and LVSP 10 minutes after administration. The study suggests that hypertensive heart failure model animals may derive benefits from exogenous apelin due to endogenous downregulation of APJ.

In their study, Li et al. investigated the effects of apelin 13 on adult male rabbits with induced heart failure through sodium pentobarbital administration. The rabbits were intravenously administered 10 ug/kg/h of apelin 13 for 3 hours, during which hemodynamic measurements were recorded. The findings revealed that the apelin group exhibited significant increases in +dp/dt, -dp/dt, heart rate, and LVSP while displaying decreased LVEDP within five minutes. The authors suggested that apelin's intervention may mitigate cardiac dysfunction induced by AHF through the regulation of the APJ/Akt/ERS signaling pathway.

3.4. Publication bias assessment

Publication bias assessment in the present study showed that there was no evidence of publication bias (Figure 9) in the relationship between apelin administration with +dp/dt (p = 0.205), -dp/dt (p = 0.400), heart rate (p = 0.235), EF (p = 0.476), LVSP (p = 0.927) and LVEDP (p = 0.765).

3.5. Risk of bias assessment

The results of the risk of bias assessment also revealed that there was a high risk of bias in the domains of allocation concealment, random housing, blinding of caregivers, and random outcome assessment across most studies. Meanwhile, there were two studies gauged as low risk regarding the blinding of observers, six studies in the sequence generation, and ten in the incomplete outcome data (Table 2). Accordingly, the overall risk of bias was judged to be high.

4. Discussion

The findings of this study demonstrate that the administration of apelin resulted in an increase in +dp/dt, LVSP, and EF and a decrease in LVEDP and -dp/dt, with no significant impact on heart rate. All the studies included in the analysis investigated the effects of apelin on cardiac function during the progression of heart failure. Apelin was administered in multiple doses, with a follow-up period of 12 hours or more.

The introduction of exogenous apelin positively impacts heart function by enhancing contractility and reducing the extent of left ventricular hypertrophy (36). Recent findings indicate that the activation of apelin receptors has positive effects that go beyond the known benefits for heart failure and provide protection for the heart following injury to the myocardium. Cardiac apelin expression was increased in response to hypoxia and ischemia (37-39). The process includes triggering the activity of the reperfusion injury salvage kinase pathway, which could include PI3K-protein kinase B or ERK. It also leads to a reduction in apoptosis and reactive oxygen species formation, as well as an increase in NO production (39).

The underlying processes through which apelin induces inotropic effects remain inadequately comprehended. It appears that apelin triggers the activation of sodium-hydrogen exchangers (NHEs) in cardiac muscle cells, leading to an elevation in intracellular pH and heightened sensitivity of contractile myofilaments to intracellular calcium. Concurrently, the augmented activity of sodium-hydrogen exchangers indirectly raises intracellular calcium levels, producing the same effect on myocardial contractility (14, 19, 40, 41). Statistical analysis following the administration of apelin revealed an increase in the rate of change of pressure over time (+dp/dt). Apelin appears to enhance +dp/dt by modulating sodium-hydrogen exchangers and augmenting the sensitivity of myofilaments to calcium.

Statistical analysis revealed that apelin administration led to a decrease in -dp/dt, a measure of myocardial relaxation, or lusitropy. Apelin is known to increase myocardial contractility, and therefore, an increase in both -dp/dt and +dp/dt is anticipated, which ultimately enhances the heart's capacity to distribute blood throughout the body by boosting myocardial contraction and relaxation. An improvement in ±dp/dt during heart failure treatment signifies enhanced heart efficiency. In essence, a single-dose administration can yield short-term favorable effects by binding to receptors (APJ), while adhering to a multi-dose administration regimen in the long term could activate signaling pathways that induce advantageous structural alterations and enhance cardiac function.

Apelin has been discovered to possess a vasodilatory impact on peripheral blood arteries. Apelin induces vasodilation by activating endothelial nitric oxide synthase (eNOS) activity. Additionally, it triggers the phosphorylation of the myosin light chain, leading to the contraction of vascular smooth muscles and vasoconstriction. The observations indicate that apelin can directly stimulate contraction in vascular smooth muscle by binding to APJ receptors. However, when the endothelium is healthy, this impact is counteracted

by the activation of local nitric oxide generation through endothelial APJ receptors (14). Rapid response After a single dose of apelin results in a reduction in blood pressure, which, in certain studies, prompts reflex tachycardia by modulating the vasomotor centers in the medulla oblongata and pons. Furthermore, when apelin is introduced into the central nervous system, it has been observed to elevate both arterial blood pressure and heart rate (42).

In the majority of studies, the impact on heart rate was also examined. Statistical analysis revealed that the administration of apelin did not yield a significant effect on heart rate in animals. Various studies have presented conflicting findings regarding the influence of apelin on heart rate; some have documented an increase in heart rate following apelin administration, while others have observed a decrease. This disparity may be attributed to the method of apelin administration, the animal species involved in the studies, the type and dosage of apelin, the frequency of apelin administration, and the duration of the apelin treatment (14, 18, 43, 44).

Administering apelin through intravenous bolus injection decreases the average circulatory filling pressure, which is a reliable indicator of systemic venous tone. This suggests that apelin has the ability to dilate both arteries and veins. The changes in vascular tone are accompanied by comparable adjustments in ventricular loading circumstances. The administration of apelin reduces the left ventricular end-diastolic area and left ventricular end-systolic pressure in an acute manner (14, 18). In our study, LVSP increased while LVEDP decreased.

All the included studies in our meta-analysis consisted of multiple doses of apelin administered during the progression of heart failure, Therefore, we specifically investigated the impact of apelin on LVSP and LVEDP in a chronic context. One possible explanation is that the positive ionotropic effect of apelin outweighed its vasodilator effect.

In our analysis, we considered echocardiographic parameters associated with heart failure and cardiac function, such as fractional shortening (FS), systolic and diastolic dimensions, cardiac output, and other cardiovascular function indicators across the studies. However, due to the varying examination protocols in these studies, we could not include all indicators in our analysis. Therefore, parameters such as -dp/dt, heart rate, EF, LVEDP, and LVSP, which are essential for evaluating heart performance and improving heart failure, were utilized in this study.

4.1. Limitations

Nevertheless, there were some limitations to this study. First, the studies employed various apelin administration protocols, and the heterogeneity among types of apelin, routes of administration, doses, and durations could impact the genuine effect size calculation. Also, we couldn't pool the data from all 12 studies retrieved at first because three of the studies evaluated the short-term treatment effect of apelin on heart failure models. Secondly, in most of the studies, we didn't have access to the study protocols, which prevented us from accurately estimating the risk of bias. Finally, as a pre-plan strategy, we decided to conduct subgroup analyses and sensitivity analyses based on methodological diversity among the included studies. However, due to the scarce number of included articles, these ancillary analyses were not performed.

5. Conclusion

Based on the present meta-analysis of experimental evidence, it has been demonstrated that the administration of apelin leads to improvements in +dp/dt, -dp/dt, LVEDP, LVSP, and EF. Notably, apelin administration does not appear to significantly impact heart rate. It is recommended that additional translational studies be conducted on large animal models to ascertain the efficacy of apelin across various species. This approach will enable the accumulation of substantial evidence to facilitate the design of potential further clinical trials. Given apelin's capacity to rapidly enhance cardiac function, it may be deemed a promising candidate for the early management of patients with heart failure in emergency care settings.

6. Declarations

6.1. Acknowledgments

None.

6.2. Ethical consideration

This study was approved by the Ethics Committee of the Iran University of Medical Sciences (Code: IR.IUMS.REC.1398.1404).

6.3. Funding

This study was supported by the Iran University of Medical Sciences.

6.4. Conflict of interest

None.

6.5. Author contributions

All authors contributed equally in all stages of the development of the paper and had the authorship criteria of the International Committee of Medical Journal Editors (ICMJE).

6.6. Using artificial intelligence chatbots

None.

References

1. Garg R, Packer M, Pitt B, Yusuf S. Heart failure in the 1990s: evolution of a major public health problem in cardiovascular medicine. J Am Coll Cardiol. 1993;22(4 Suppl A):3a-5a.

2. El Amrousy D, El-Mahdy H. Prognostic Value of Serum Apelin Level in Children with Heart Failure Secondary to Congenital Heart Disease. Pediatr Cardiol. 2018;39(6):1188-93.
3. Aalbers J. New ESC heart failure guidelines with South African expert comment. Cardiovasc J Afr. 2012;23(5):295-6.
4. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. Am Heart J. 1999;137(2):352-60.
5. Parikh VN, Liu J, Shang C, Woods C, Chang AC, Zhao M, et al. Apelin and APJ orchestrate complex tissue-specific control of cardiomyocyte hypertrophy and contractility in the hypertrophy-heart failure transition. Am J Physiol Heart Circ Physiol. 2018;315(2):H348-h56.
6. Cox CM, D'Agostino SL, Miller MK, Heimark RL, Krieg PA. Apelin, the ligand for the endothelial G-protein-coupled receptor, APJ, is a potent angiogenic factor required for normal vascular development of the frog embryo. Dev Biol. 2006;296(1):177-89.
7. Ma Y, Yue Y, Ma Y, Zhang Q, Zhou Q, Song Y, et al. Structural Basis for Apelin Control of the Human Apelin Receptor. Structure. 2017;25(6):858-66.e4.
8. Mohr-Sasson A, Chayo J, Bart Y, Meyer R, Sivan E, Mazaki-Tovi S, et al. Laboratory characteristics of pregnant compared to non-pregnant women infected with SARS-CoV-2. Archives of Gynecology and Obstetrics. 2020;302(3):629-34.
9. Chen L, Li Q, Zheng D, Jiang H, Wei Y, Zou L, et al. Clinical characteristics of pregnant women with Covid-19 in Wuhan, China. New England Journal of Medicine. 2020;382(25):e100.
10. Wang Z, Wang Z, Xiong G. Clinical characteristics and laboratory results of pregnant women with COVID-19 in Wuhan, China. International Journal of Gynecology & Obstetrics. 2020;150(3):312-7.
11. Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine. 2020;382(18):1708-20.
12. Kleinz MJ, Baxter GFJRp. Apelin reduces myocardial reperfusion injury independently of PI3K/Akt and P70S6 kinase. 2008;146(1-3):271-7.
13. Goidescu CM, Vida-Simiti LA. The Apelin-APJ System in the Evolution of Heart Failure. Clujul Med. 2015;88(1):3-8.
14. Japp AG, Newby DE. The apelin-APJ system in heart failure: pathophysiologic relevance and therapeutic potential. Biochem Pharmacol. 2008;75(10):1882-92.
15. Ouyang Q, You T, Guo J, Xu R, Guo Q, Lin J, et al. Effects of Apelin on Left Ventricular-Arterial Coupling and Mechanical Efficiency in Rats with Ischemic Heart Failure. Dis Markers. 2019;2019:4823156.
16. Folino A, Montarolo PG, Samaja M, Rastaldo R. Effects of apelin on the cardiovascular system. Heart Fail Rev. 2015;20(4):505-18.
17. Chen MM, Ashley EA, Deng DX, Tsalenko A, Deng A, Tabibiazar R, et al. Novel role for the potent endogenous inotrope apelin in human cardiac dysfunction. Circulation. 2003;108(12):1432-9.
18. Ashley EA, Powers J, Chen M, Kundu R, Finsterbach T, Caffarelli A, et al. The endogenous peptide apelin potently improves cardiac contractility and reduces cardiac loading in vivo. Cardiovasc Res. 2005;65(1):73-82.
19. Farkasfalvi K, Stagg MA, Coppen SR, Siedlecka U, Lee J, Soppa GK, et al. Direct effects of apelin on cardiomyocyte contractility and electrophysiology. Biochem Biophys Res Commun. 2007;357(4):889-95.
20. Ferdinal F, Limanan D, Rini RD, Alexsandro R, Helmi R. Elevated Levels of Apelin-36 in Heart Failure Due to Chronic Systemic Hypoxia. Int J Angiol. 2019;28(3):194-9.
21. Sato T, Suzuki T, Watanabe H, Kadowaki A, Fukamizu A, Liu PP, et al. Apelin is a positive regulator of ACE2 in failing hearts. 2013;123(12):5203-11.
22. Jia Y-X, Pan C-S, Zhang J, Geng B, Zhao J, Gerns H, et al. Apelin protects myocardial injury induced by isoproterenol in rats. 2006;133(1-3):147-54.
23. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol. 2014;14:43.
24. Doleman B, Freeman SC, Lund JN, Williams JP, Sutton AJJRSM. Funnel plots may show asymmetry in the absence of publication bias with continuous outcomes dependent on baseline risk: presentation of a new publication bias test. 2020;11(4):522-34.
25. Berry MF, Pirolli TJ, Jayasankar V, Burdick J, Morine KJ, Gardner TJ, et al. Apelin has in vivo inotropic effects on normal and failing hearts. Circulation. 2004;110(11 Suppl 1):Ii187-93.
26. Jia YX, Pan CS, Zhang J, Geng B, Zhao J, Gerns H, et al. Apelin protects myocardial injury induced by isoproterenol in rats. Regul Pept. 2006;133(1-3):147-54.
27. Pang H, Han B, Yu T, Zong Z. Effect of apelin on the cardiac hemodynamics in hypertensive rats with heart failure. Int J Mol Med. 2014;34(3):756-64.
28. Li L, Zeng H, Chen JX. Apelin-13 increases myocardial progenitor cells and improves repair postmyocardial infarction. Am J Physiol Heart Circ Physiol. 2012;303(5):H605-18.
29. Li Y, Lu H, Xu W, Shang Y, Zhao C, Wang Y, et al. Apelin ameliorated acute heart failure via inhibiting endoplasmic reticulum stress in rabbits. Amino Acids. 2021;53(3):417-27.
30. Sato T, Suzuki T, Watanabe H, Kadowaki A, Fukamizu A, Liu PP, et al. Apelin is a positive regulator of ACE2 in failing hearts. J Clin Invest. 2013;123(12):5203-11.
31. Soltani Hekmat A, Javanmardi K, Tavassoli A, Gholampour Y. Angiotensin (1-7) and Apelin co-therapy: New

strategy for heart failure treatment of rats. Anatol J Cardiol. 2020;23(4):209-17.
32. Zhang X, Hu W, Feng F, Xu J, Wu F. Apelin-13 protects against myocardial infarction-induced myocardial fibrosis. Mol Med Rep. 2016;13(6):5262-8.
33. Zhong S, Guo H, Wang H, Xing D, Lu T, Yang J, et al. Apelin-13 alleviated cardiac fibrosis via inhibiting the PI3K/Akt pathway to attenuate oxidative stress in rats with myocardial infarction-induced heart failure. Biosci Rep. 2020;40(4).
34. Chung WJ, Cho A, Byun K, Moon J, Ge X, Seo HS, et al. Apelin-13 infusion salvages the peri-infarct region to preserve cardiac function after severe myocardial injury. Int J Cardiol. 2016;222:361-7.
35. Azizi Y, Faghihi M, Imani A, Roghani M, Zekri A, Mobasheri MB, et al. Post-infarct treatment with [Pyr(1)]apelin-13 improves myocardial function by increasing neovascularization and overexpression of angiogenic growth factors in rats. Eur J Pharmacol. 2015;761:101-8.
36. Foussal C, Lairez O, Calise D, Pathak A, Guilbeau-Frugier C, Valet P, et al. Activation of catalase by apelin prevents oxidative stress-linked cardiac hypertrophy. FEBS Lett. 2010;584(11):2363-70.
37. Ronkainen VP, Ronkainen JJ, Hänninen SL, Leskinen H, Ruas JL, Pereira T, et al. Hypoxia inducible factor regulates the cardiac expression and secretion of apelin. Faseb j. 2007;21(8):1821-30.
38. Kleinz MJ, Baxter GF. Apelin reduces myocardial reperfusion injury independently of PI3K/Akt and P70S6 kinase. Regul Pept. 2008;146(1-3):271-7.
39. Yang P, Maguire JJ, Davenport AP. Apelin, Elabela/Toddler, and biased agonists as novel therapeutic agents in the cardiovascular system. Trends Pharmacol Sci. 2015;36(9):560-7.
40. Dai T, Ramirez-Correa G, Gao WD. Apelin increases contractility in failing cardiac muscle. Eur J Pharmacol. 2006;553(1-3):222-8.
41. Atluri P, Morine KJ, Liao GP, Panlilio CM, Berry MF, Hsu VM, et al. Ischemic heart failure enhances endogenous myocardial apelin and APJ receptor expression. Cell Mol Biol Lett. 2007;12(1):127-38.
42. Rozwadowski J, Borodzicz-Jażdżyk S, Czarzasta K, Cudnoch-Jędrzejewska A. A Review of the Roles of Apelin and ELABELA Peptide Ligands in Cardiovascular Disease, Including Heart Failure and Hypertension. Med Sci Monit. 2022;28:e938112.
43. Yao F, Modgil A, Zhang Q, Pingili A, Singh N, O'Rourke ST, et al. Pressor effect of apelin-13 in the rostral ventrolateral medulla: role of NAD(P)H oxidase-derived superoxide. J Pharmacol Exp Ther. 2011;336(2):372-80.
44. Cheng X, Cheng XS, Pang CC. Venous dilator effect of apelin, an endogenous peptide ligand for the orphan APJ receptor, in conscious rats. Eur J Pharmacol. 2003;470(3):171-5.

Table 1: Characteristics of included studies

Author; Year	Gender; Race; Species	Dose (g/kg)	Type of apelin	Rout*	Type**	Model of HF induction	Follow up duration	NO. control	NO. treated	Outcome
Pre-treatment Azizi; 2015	Male; Wistar; Rat	16.6	13	IP	Multi-dose	LAD ligation	14 days	12	12	dp/dt; -dp/dt; LVSP; LVEDP
Chung; 2016	Male; F VB/N; Mice	500	13	IV	Multi-dose	LAD ligation	7, 14, 21, 28, 63 days	7	8	Heart rate, EF, LVEDP, LVSP
Jia; 2005	Male; Wistar; Rat	21, 42, 84	36	IP	Multi-dose	ISO injection	0.5 day	6	6	dp/dt, -dp/dt, heart rate
Li; 2012	Male; C57 BL/6J; Mice	1000	13	IP	Multi-dose	LAD ligation	14 days	6	6	Heart rate, EF, dp/dt; -dp/dt; LVSP; LVEDP
Ouyang; 2019	Male; Wistar; Rat	200	13	IP	Multi-dose	LAD ligation	84 days	12	12	dp/dt, -dp/dt, heart rate
Sato; 2013	Male; Wild type littermate; Mice	1000	12 or 13	IV	Multi-dose	TAC	14 days	3	5	Heart rate, EF
Soltani Hekmat; 2020	Male; Sprague-dawley; Rat	20		IP	Multi-dose	ISO injection	10 days	7	7	dp/dt, -dp/dt, heart rate;LVEDP;LVSP
Zhang; 2016	Male; Sprague-dawley; Rat	200	13	IP	Multi-dose	LAD ligation	28 days	6	6	dp/dt; -dp/dt; LVSP; LVEDP
Zhong; 2020	Male; Sprague-dawley; Rat	15.5	13	IP	Multi-dose	LAD ligation	28 days	8	8	dp/dt; LVEDP; LVSP Treatment
Berry; 2004	Male; Lewis; Rat	0.8	16	IV	Single dose	LAD ligation	0, 5, 10, 15, 20, 25, 30, 35 min	11	11	dp/dt, -dp/dt, heart rate
Pang; 2014	Male; SD; Rat	0.5, 5.5, 55.5	13	IP	Single dose	One kidney artery ligation	0, 10, 20, 30, 40, 50 min	8	8	dp/dt, -dp/dt, heart rate
Li;2021	Male; newsland; white rabbit	82.5	13	IV	Single dose	Sodium phenobarbital continuous infusion	0;5;15;30;60; 120;180 min	6	6	dp/dt; -dp/dt; LVSP;LVEDP;

HF: Heart failure, IV: Intravenous, IP: Intraperitoneal, ISO: Isoproterenol, LAD: Left anterior descending artery, NO: Number of animals, and SD: Sprague Dawley. *: Rute of administration; **: Type of administration.

Table 2: Risk of bias assessment among the studies based on SYRCLE's tool

Domain	Sequence generation	Baseline characteristics	Allocation concealment	Random housing	Blinding of caregivers	Random outcome assessment	Blinding of observers	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Berry; 2004	High	Low	High	High	High	High	High	Low	ND	High
Jia; 2005	High	Low	High	High	High	High	High	High	ND	High
Ouyang; 2019	High	Low	High	High	High	High	High	Low	ND	Low
Pang; 2014	High	Low	High	High	High	High	Low	Low	ND	Low
Azizi; 2015	High	Low	High	High	High	High	Low	Low	ND	Low
Chung; 2016	Low	Low	High	High	High	High	High	High	ND	High
Li;2012	High	Low	High	High	High	High	High	Low	ND	High
Sato;2013	Low	Low	High	High	High	High	High	Low	ND	Low
Zhang;2016	High	Low	High	High	High	High	High	Low	ND	High
Zohng 2020	Low	Low	High	High	High	High	High	Low	ND	Low
Hekmat;2020	Low	Low	High	High	High	High	High	Low	ND	Low
Li;2021	Low	Low	High	High	High	High	High	Low	ND	Low

ND: Not determined.

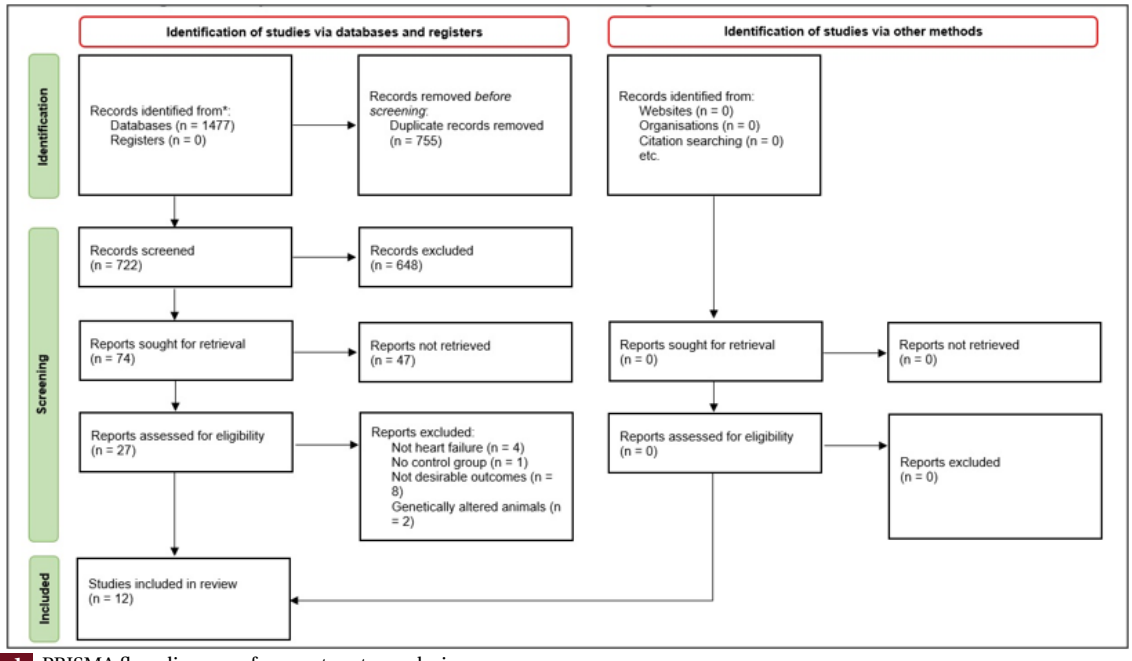

Figure 1: PRISMA flow diagram of present meta-analysis.

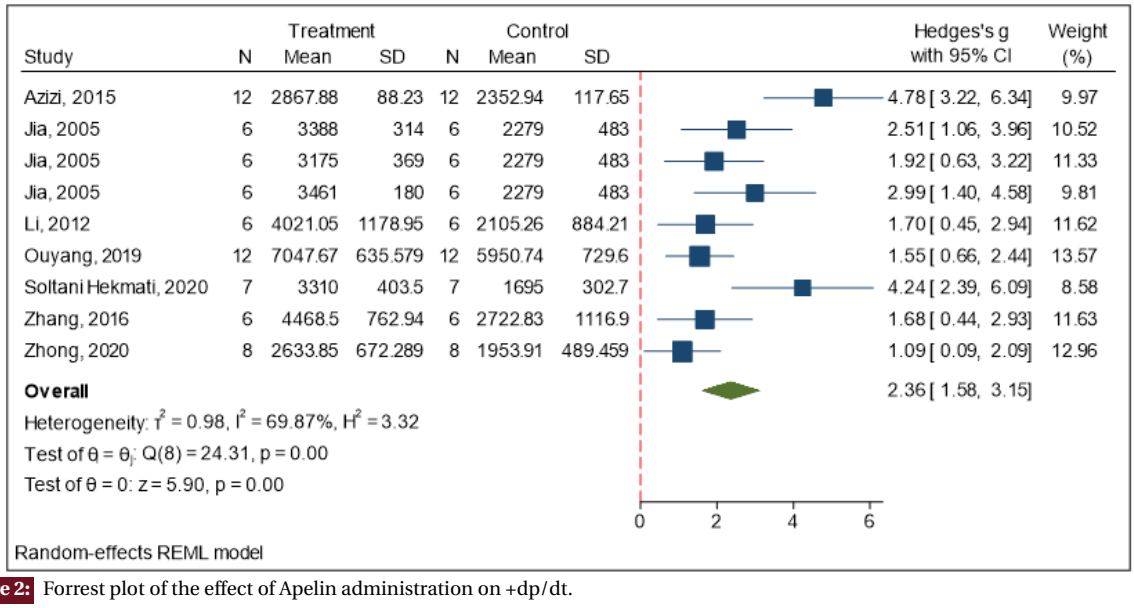

Figure 2: Forrest plot of the effect of Apelin administration on +dp/dt.

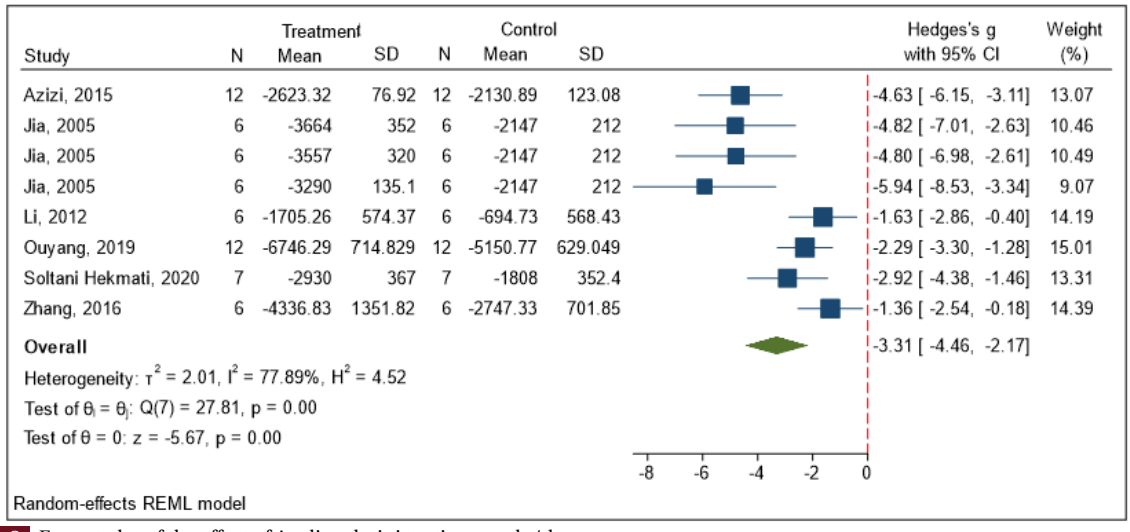

Figure 3: Forrest plot of the effect of Apelin administration on -dp/dt.

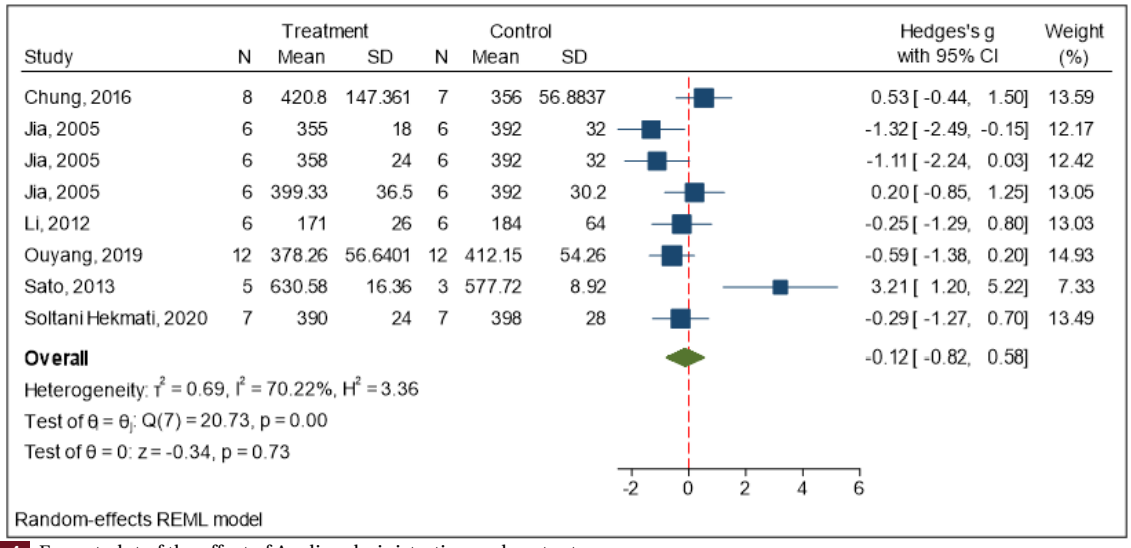

Figure 4: Forrest plot of the effect of Apelin administration on heart rate.

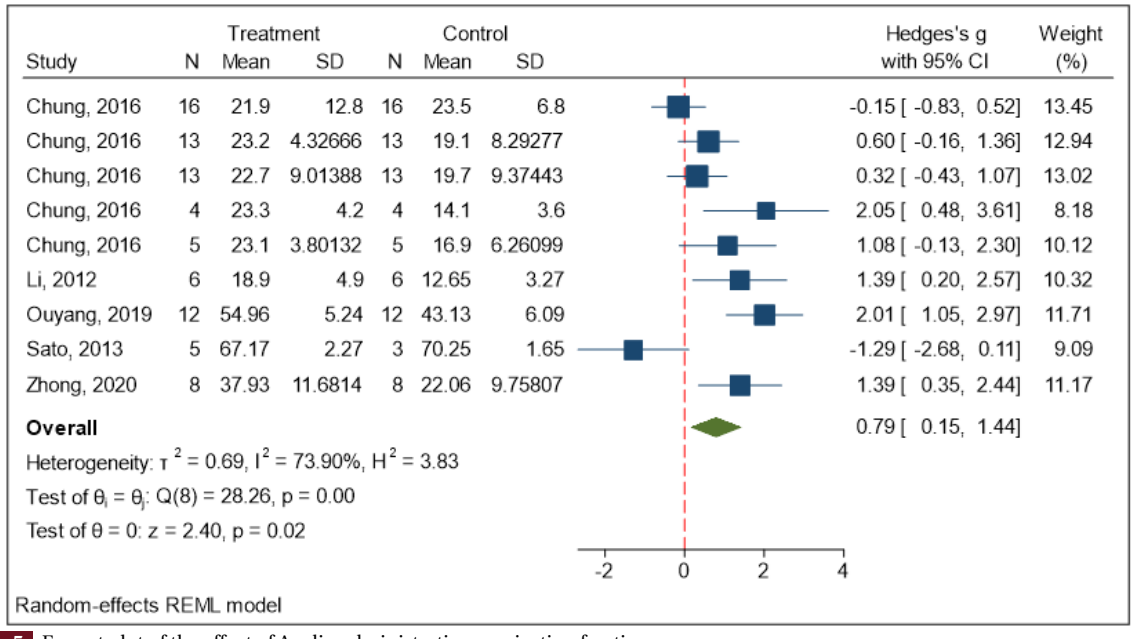

Figure 5: Forrest plot of the effect of Apelin administration on ejection fraction.

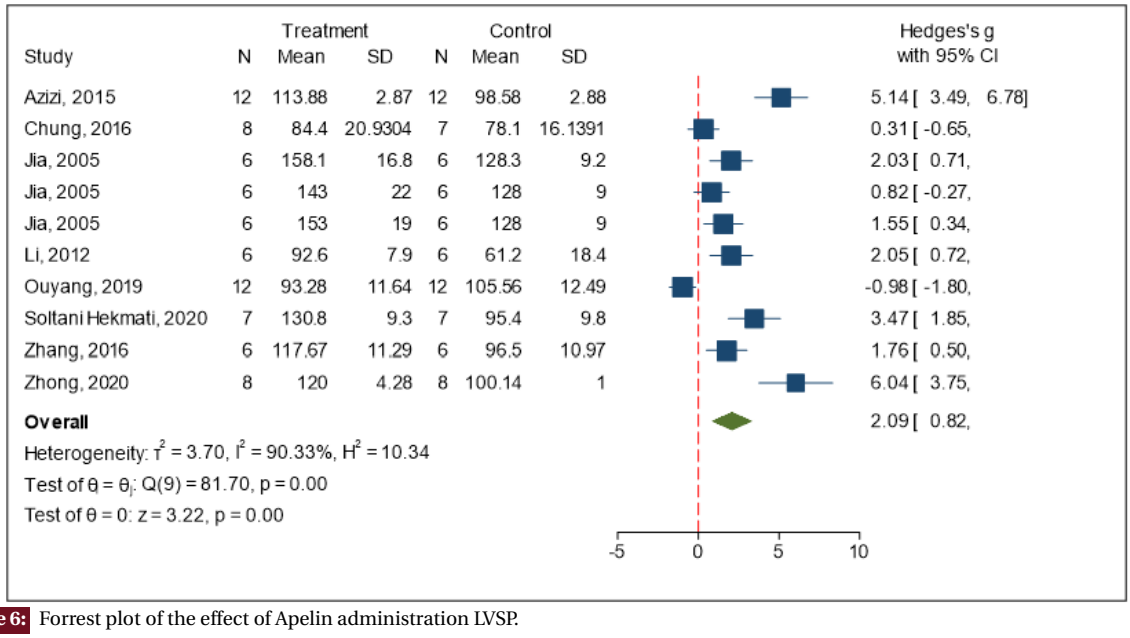

Figure 6: Forrest plot of the effect of Apelin administration LVSP.

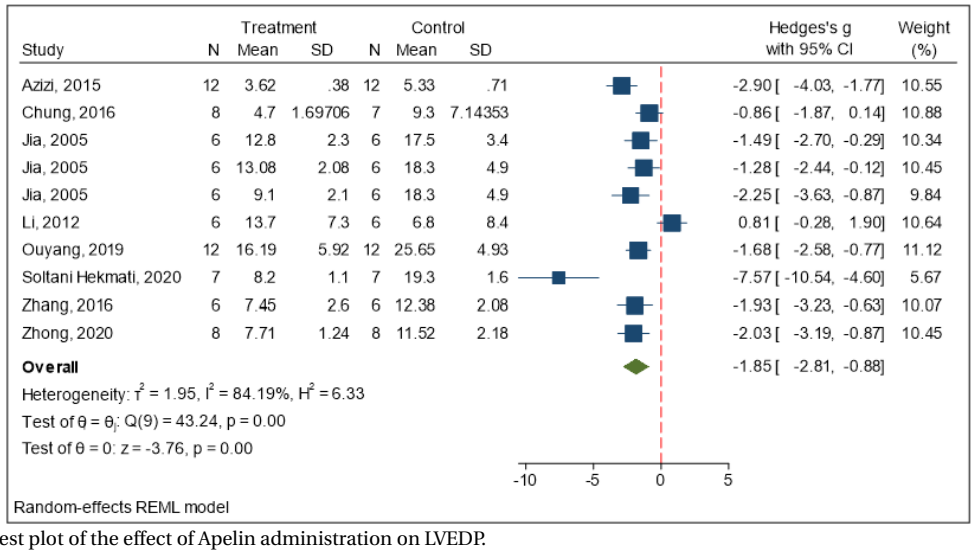

Figure 7: Forrest plot of the effect of Apelin administration on LVEDP.

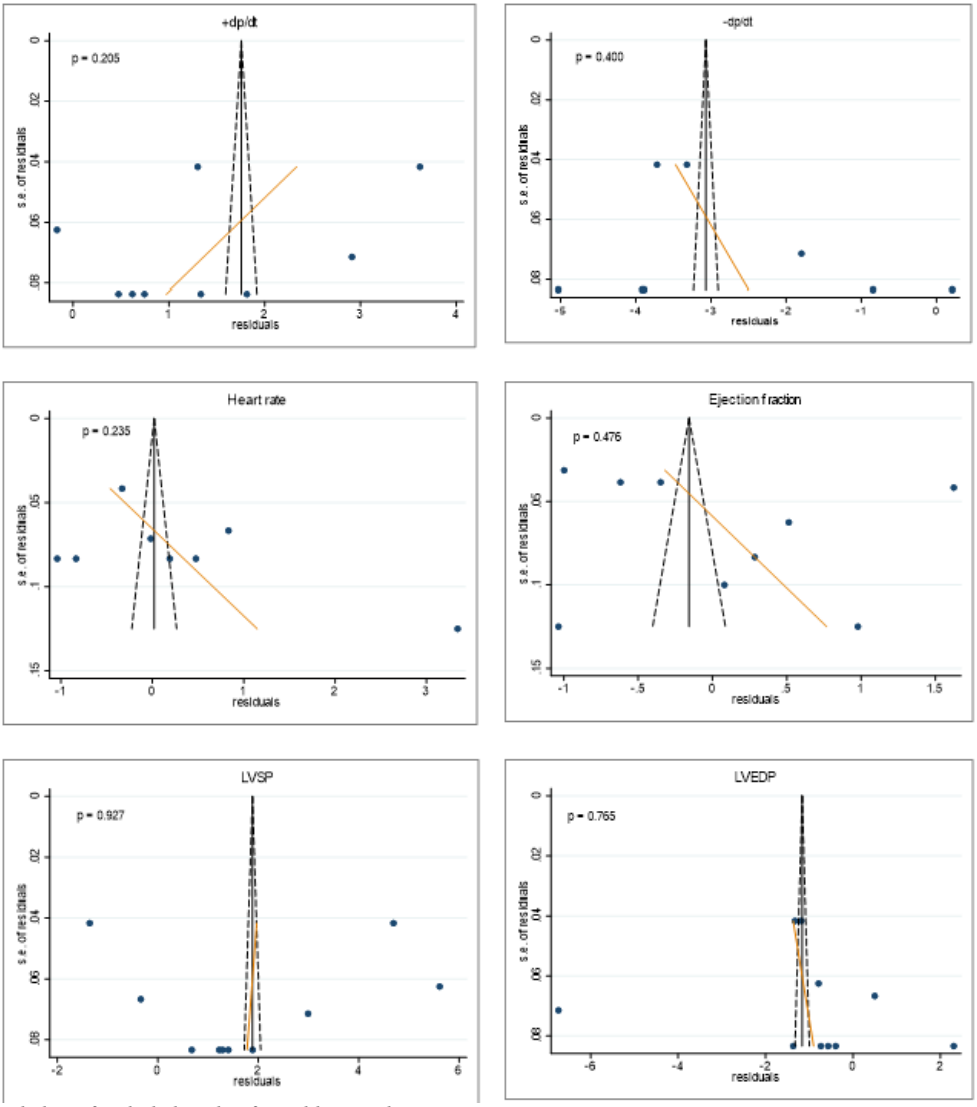

Figure 8: Funnel plots of included studies for publication bias assessment.

Appendix 1: Search strategy which was used in different databases

PubMed
1. "Apelin"[mh] OR "Apelin Receptors"[mh] OR APJ endogenous ligand[tiab] OR Apelin Receptor[tiab] OR Receptor, Apelin[tiab] OR Angiotensin Receptor-Like 1 Protein[tiab] OR Angiotensin Receptor Like 1 Protein[tiab] OR Receptors, Apelin[tiab] OR APLNR[tiab] OR AGTRL1 protein[tiab] OR angiotensin II receptor like 1[tiab] OR angiotensin receptor like 1[tiab] OR apelin receptors[tiab] OR APJ receptor[tiab] OR G protein coupled receptor APJ[tiab] OR orphan receptor APJ[tiab] OR protein AGTRL1[tiab] OR receptor APJ[tiab] OR Apelin [tiab] OR Apelin Receptors[tiab] OR apelin receptor[tiab] 2. "Heart Failure"[mh] OR "Heart Failure, Diastolic"[mh] OR "Heart Failure, Systolic"[mh] OR acute heart failure[tiab] OR cardiogenic shock[tiab] OR cardiopulmonary insufficiency[tiab] OR cardiorenal syndrome[tiab] OR congestive heart failure[tiab] OR diastolic dysfunction[tiab] OR experimental heart failure[tiab] OR forward heart failure[tiab] OR heart arrest[tiab] OR heart outflow tract obstruction[tiab] OR heart ventricle failure[tiab] OR heart ventricle overload[tiab] OR high output heart failure[tiab] OR propofol infusion syndrome[tiab] OR systolic dysfunction[tiab] OR Cardiac Failure[tiab] OR Heart Decompensation[tiab] OR Decompensation, Heart[tiab] OR Heart Failure, Right-Sided[tiab] OR Heart Failure, Right Sided[tiab] OR Right-Sided Heart Failure[tiab] OR Right Sided Heart Failure[tiab] OR Myocardial Failure[tiab] OR Congestive Heart Failure[tiab] OR Heart Failure, Congestive[tiab] OR Heart Failure, Left-Sided[tiab] OR Heart Failure, Left Sided[tiab] OR Left-Sided Heart Failure[tiab] OR Left Sided Heart Failure[tiab] OR Diastolic Heart Failures[tiab] OR Heart Failures, Diastolic[tiab] OR Diastolic Heart Failure[tiab] OR Heart Failures, Systolic[tiab] OR Systolic Heart Failures[tiab] OR Systolic Heart Failure[tiab] OR Heart Failure[tiab] OR Heart Failure, Diastolic[tiab] OR Heart Failure, Systolic[tiab] OR [tiab] OR [tiab] OR backward failure, heart[tiab] OR cardiac backward failure[tiab] OR cardiac decompensation[tiab] OR cardiac failure[tiab] OR cardiac incompetence[tiab] OR cardiac insufficiency[tiab] OR cardiac stand still[tiab] OR cardial decompensation[tiab] OR cardial insufficiency[tiab] OR chronic heart failure[tiab] OR chronic heart insufficiency[tiab] OR decompensatio cordis[tiab] OR decompensation, heart[tiab] OR heart backward failure[tiab] OR heart decompensation[tiab] OR heart incompetence[tiab] OR heart insufficiency[tiab] OR insufficientia cardis[tiab] OR myocardial failure[tiab] OR myocardial insufficiency[tiab] 3. #1 AND #2
Embase
1- 'apelin'/exp OR 'apelin' OR 'apelin receptor'/exp OR 'apelin receptor' OR 'apelin 13'/exp OR 'apelin 13' OR 'apelin 36'/exp OR 'apelin 36' OR 'apelin 12'/exp OR 'apelin 12' OR 'apelin 13 peptide'/exp OR 'apelin 13 peptide' OR 'apelin 17'/exp OR 'apelin 17' OR 'apelin gene'/exp OR 'apelin gene' OR 'apelin blood level'/exp OR 'apelin blood level' 2- 'heart failure'/exp OR 'heart failure' OR 'congestive heart failure'/exp OR 'congestive heart failure' OR 'acute heart failure'/exp OR 'acute heart failure' OR 'systolic heart failure'/exp OR 'systolic heart failure' OR 'diastolic heart failure'/exp OR 'diastolic heart failure' OR 'heart failure with preserved ejection fraction'/exp OR 'heart failure with preserved ejection fraction' OR 'heart failure with reduced ejection fraction'/exp OR 'heart failure with reduced ejection fraction' OR 'high output heart failure'/exp OR 'high output heart failure' OR 'heart failure congestive therapy'/exp OR 'heart failure congestive therapy' 3- #1 AND #2
Scopus
1. TITLE-ABS-KEY ("apelin" OR "apelin receptors" OR "apj endogenous ligand " OR "apelin receptor" OR "receptor, apelin" OR "angiotensin receptor-like 1 protein" OR "angiotensin receptor like 1 protein" OR "receptors, apelin" OR "aplnr" OR "agtrl1 protein" OR " angiotensin ii receptor like 1" OR " angiotensin receptor like 1" OR " apelin receptors" OR " apj receptor" OR " g protein coupled receptor apj" OR " orphan receptor apj" OR " protein agtrl1" OR " receptor apj" OR "apelin " OR "apelin receptors" OR "apelin receptor") 2. TITLE-ABS-KEY ("heart failure" OR "heart failure, diastolic" OR "heart failure, systolic" OR "acute heart failure" OR "cardiogenic shock" OR "cardiopulmonary insufficiency" OR "cardiorenal syndrome" OR "congestive heart failure" OR "diastolic dysfunction" OR "experimental heart failure" OR "forward heart failure" OR "heart arrest" OR "heart outflow tract obstruction" OR "heart ventricle failure" OR "heart ventricle overload" OR "high output heart failure" OR "propofol infusion syndrome" OR "systolic dysfunction" OR "cardiac failure" OR " heart decompensation" OR "decompensation, heart" OR "heart failure, right-sided" OR "heart failure, right sided" OR "right-sided heart failure" OR "right sided heart failure" OR "myocardial failure" OR "congestive heart failure" OR "heart failure, congestive" OR "heart failure, left-sided" OR "heart failure, left sided" OR "left-sided heart failure" OR "left sided heart failure" OR "diastolic heart failures" OR "heart failures, diastolic" OR "diastolic heart failure" OR "heart failures, systolic" OR "systolic heart failures" OR "systolic heart failure" OR "backward failure, heart" OR "cardiac backward failure" OR " cardiac decompensation" OR " cardiac failure" OR " cardiac incompetence" OR " cardiac insufficiency" OR " cardiac stand still" OR " cardial decompensation" OR " cardial insufficiency" OR " chronic heart failure" OR " chronic heart insufficiency" OR " decompensatio cordis" OR " decompensation, heart" OR " heart backward failure" OR " heart decompensation" OR " heart incompetence" OR " heart insufficiency" OR " insufficientia cardis" OR " myocardial failure" OR " myocardial insufficiency" OR "heart failure" OR "heart failure, diastolic" OR "heart failure, systolic") 3. #1 AND #2

Appendix 1: Search strategy which was used in different databases (continue)

Web of Sciences
1. TS=(“apelin” OR “apelin receptors” OR “apj endogenous ligand “ OR “apelin receptor” OR “receptor, apelin” OR “angiotensin receptor-like 1 protein” OR “angiotensin receptor like 1 protein” OR “receptors, apelin” OR “aplnr” OR “agtrl1 protein” OR “ angiotensin ii receptor like 1” OR “ angiotensin receptor like 1” OR “ apelin receptors” OR “ apj receptor” OR “ g protein coupled receptor apj” OR “ orphan receptor apj” OR “ protein agtrl1” OR “ receptor apj” OR “apelin “ OR “apelin receptors” OR “apelin receptor”)
2. TS=(“heart failure” OR “heart failure, diastolic” OR “heart failure, systolic” OR “acute heart failure” OR “cardiogenic shock” OR “cardiopulmonary insufficiency” OR “cardiorenal syndrome” OR “congestive heart failure” OR “diastolic dysfunction” OR “experimental heart failure” OR “forward heart failure” OR “heart arrest” OR “heart outflow tract obstruction” OR “heart ventricle failure” OR “heart ventricle overload” OR “high output heart failure” OR “propofol infusion syndrome” OR “systolic dysfunction” OR “cardiac failure” OR “ heart decompensation” OR “decompensation, heart” OR “heart failure, right-sided” OR “heart failure, right sided” OR “right-sided heart failure” OR “right sided heart failure” OR “myocardial failure” OR “congestive heart failure” OR “heart failure, congestive” OR “heart failure, left-sided” OR “heart failure, left sided” OR “left-sided heart failure” OR “left sided heart failure” OR “diastolic heart failures” OR “heart failures, diastolic” OR “diastolic heart failure” OR “heart failures, systolic” OR “systolic heart failures” OR “systolic heart failure” OR “backward failure, heart” OR “cardiac backward failure” OR “ cardiac decompensation” OR “ cardiac failure” OR “ cardiac incompetence” OR “ cardiac insufficiency” OR “ cardiac stand still” OR “ cardial decompensation” OR “ cardial insufficiency” OR “ chronic heart failure” OR “ chronic heart insufficiency” OR “ decompensatio cordis” OR “ decompensation, heart” OR “ heart backward failure” OR “ heart decompensation” OR “ heart incompetence” OR “ heart insufficiency” OR “ insufficientia cardis” OR “ myocardial failure” OR “ myocardial insufficiency” OR “heart failure” OR “heart failure, diastolic” OR “heart failure, systolic”)
3. #1 AND #2