



Systematic Review

Thiamine Supplementation and its Impact on Ejection Fraction: A Systematic Review and Meta-analysis of Clinical Trials

Mohammad Hossein Sharifi¹ , Maryam Jalali² , Sorour Sarihi³ , Parisa Keshani^{4*} , Firoozeh Abtahi⁵ , Samane Nematollahi⁶

¹Non-Communicable Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

²Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

³Department of Human Nutrition and Hospitality Management, College of Human Environmental Sciences, The University of Alabama, Tuscaloosa, AL, USA

⁴Health Policy Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran

⁵Department of Echocardiography, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

⁶Non-Communicable Diseases Research Center, Bam University of Medical Sciences, Bam, Iran

Abstract

Background and aims: Heart failure (HF) is a serious cardiovascular condition with a high mortality rate. In the last decade, there have been concerns about the use of thiamine as a potential factor for enhancing ejection fraction in people with HF. Accordingly, this study aimed at investigating whether thiamine supplementation affects ejection fraction.

Methods: The PubMed, Scopus, and Web of Science databases were systematically searched, and a systematic review and meta-analysis was conducted on the clinical trials performed on thiamine supplementation in patients with HF. Six of the eleven studies included in this systematic review were considered suitable for the meta-analysis (randomized controlled trial and cross-over designs) and 4 within-group designs. The total sample sizes for the systematic review and meta-analysis were 545 and 319. Heterogeneity among the primary studies was assessed using Cochran's Q test and the I² index. The analyses were conducted with Comprehensive Meta-Analysis software. Eventually, the trim-and-fill method was utilized to verify the validity of the findings.

Results: The analysis of the seven eligible studies for meta-analysis (six studies and seven reports) revealed that thiamin had no significant effect on left ventricular ejection fraction (LVEF; $P=0.05$, 95% CI: -0.003 to 0.46). The results of the subgroup meta-analysis were not significant. Notably, the results of the five within-group comparisons for meta-analysis (four studies and five reports) revealed the considerable effect of thiamin on LVEF ($P<0.001$, 95% CI: 0.57 to 1.88).

Conclusion: Thiamine supplementation might improve ejection fraction in patients with HF. More information on the role of thiamine in HF would help establish a greater degree of accuracy on this matter.

Keywords: Heart failure, Ejection fraction, Thiamine, Meta-analysis

*Corresponding Author:

Parisa Keshani,

Email: parisa.keshani@gmail.com

Received: August 19, 2024

Revised: April 5, 2025

Accepted: April 6, 2025

ePublished: June 7, 2025



Introduction

Heart failure (HF) is considered a severe cardiovascular disease that has a high rate of mortality.^{1,2} The progress of the disease can lead to complications, such as hospitalization, fatal arrhythmia, and death.³ Various pharmaceutical and non-pharmacological interventions, including thiamin, Coenzyme Q10, and omega-3 supplementation, aim to mitigate underlying cardiac diseases and improve the quality of life.^{4,5}

Thiamine, a generally safe dietary supplement, has raised concerns regarding its potential to improve ejection fraction in HF patients.^{6,7} Definitions of HF vary, with HF with reduced left ventricular ejection fraction (HFrEF)

defined as LVEF < 40% and HF with preserved EF (HFpEF) as LVEF ≥ 50%. The prevalence of HF in developed countries ranges from 1% to 2%.^{8,9} Research suggests that interventions raising ejection fraction enhance the quality of life while alleviating HF symptoms.^{10,11} Despite guidelines for HF management, dietary supplements, such as thiamine, have received less attention.

Thiamine, a water-soluble vitamin B1, is essential for cellular energy synthesis.¹² Thiamine deficiency (TD) is notably higher in both developed and developing nations due to factors such as poor diet, long-term alcohol use, and aging.¹² Marginal TD can cause symptoms such as anorexia, weight loss, and exhaustion.⁷ Studies indicate that TD is 2.5

times more prevalent in HF patients than in controls,¹³ with higher rates in hospitalized patients (3–27%) compared to ambulatory patients (5%–95%)¹⁴. DiNicolantonio et al conducted the first meta-analysis in 2013, supporting thiamine's benefits for cardiac ejection fraction.⁵ However, subsequent meta-analyses in 2022 and 2023 revealed insufficient evidence to conclusively support thiamine's benefits in HF patients despite promising indications for cardiac function.^{14–16} Conflicting findings exist regarding thiamine's effect on ejection fraction.^{5,6,17}

HF poses significant public health challenges. While clinicians emphasize thiamine's potential benefits on ejection fraction and symptoms,^{13,15,18} this meta-analysis aims to clarify thiamine's impact on ejection fraction in HF patients.

Materials and Methods

Search Strategy

The articles of interest were chosen after a systematic search in PubMed, Scopus, and Web of Science databases, and the Google Scholar search engine was used to ensure a comprehensive literature search. Keywords were selected based on related MeSH terms and the content of selected articles. The study syntax comprised three main keywords combined with the “AND” operator. The first keyword,

thiamine, and the related synonyms were searched using the “OR” operator. The second keyword covered the ejection fraction-related terms.

It should be noted that no time limitation was considered in database searches. The supplementary document, including the search strategy (until June 2024), is presented in [Table S1](#). Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed for data analysis.

Study Selection

The search phase and screening stage (K. P. and Sh. M.), selection (K. P. and Sh. M.), quality assessment (J. M., S. S., and Sh. M.), and data extraction (J. M. and S. S.) were conducted independently. Any disagreement was resolved by consensus, and a third expert's opinion was sought if the dispute was not resolved. The population, outcome, location, indicator, and study design criteria used to perform the systematic review are provided in [Table S2](#) (see [Supplementary file 1](#)). Any disagreement was resolved by consensus, and no disagreement remained unsolved.

Inclusion and Exclusion Criteria

This systematic review and meta-analysis was performed on clinical trials, pre-post studies, and case series of

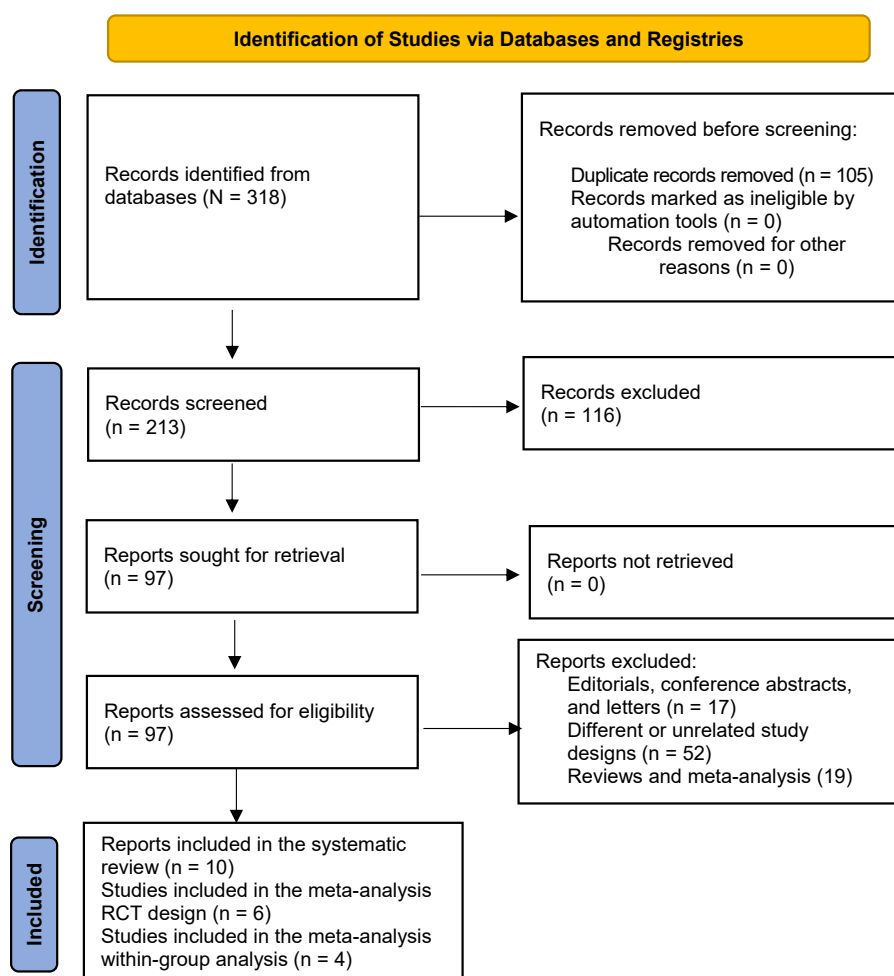


Figure 1. Flow Diagram of the Systematic Review and Searches for the Effect of Thiamine Supplementation on Ejection Fraction. *Note.* RCT: Randomized controlled trial

thiamine supplementation in patients with HF. Letters, editorials, conference abstracts, grey literature, and non-English papers were excluded from the investigation. Figure 1 depicts the exclusion process of unrelated articles in each category.

Article Screening and Data Extraction

In the primary screening, the titles and abstracts of the studies collected from the search phase were independently reviewed by two authors (K. P. and Sh. M.) based on the inclusion and exclusion criteria. Studies that did not meet the eligibility criteria were excluded at this stage. In the secondary screening, the full texts of these articles were reviewed regarding the inclusion criteria. Then, the data of the included studies were extracted, as briefly presented in Tables 1 and 2.

Quality Assessment

Two reviewers (J. M. and S. S.) independently assessed the quality of the included studies, and disagreements were resolved through consensus. The corresponding author (Sh. M.) was also consulted whenever necessary. The Cochrane checklist was used to assess the quality of the studies. Each randomized controlled trial (RCT) was assessed for selection bias, performance bias, attrition bias, detection bias, reporting bias, and other biases. The bias of each article was assessed as good, fair, and unclear.²⁹ Accordingly, the articles were considered to be of good quality when all the criteria were met, fair when one criterion was not met (i.e., high risk of bias for one domain) or two criteria were unclear, or poor when two or more criteria showed a high or unclear risk of bias

(Table S3, Supplementary file 1).

Statistical Analysis

The mean and standard deviation (SD) of LVEF for thiamin and control groups at baseline and after the intervention were utilized to calculate the study effect size, which was the mean difference (MD) in this meta-analysis. It should be noted that all the included studies reported the means and SDs for the intervention and control groups. The SD and LVEF change from pre- to post-intervention reported by Iqbal et al²⁰ was used to estimate the correlation coefficient in the present study ($r=0.8$). In addition, the random effects model was employed for study variations when computing the effect size. I^2 and Cochran's Q tests were also applied to assess between-study heterogeneities. Moreover, funnel plots, Egger's regression asymmetry test, and Begg's test were utilized to check the publication bias. The trim-and-fill method was used to confirm the validity and reliability of the results. Furthermore, sensitivity analysis was applied to determine whether the inferences depend on a particular study. All statistical analyses were performed using the Comprehensive Meta-Analysis software (version 2.0), and P values less than 0.05 were considered statistically significant.

Results

This study investigated whether thiamine supplementation affected ejection fraction. A total of 318 studies were obtained from the literature search, and the duplicates were eliminated from the analysis. Then, the full texts were assessed for eligibility according to the inclusion and exclusion criteria. Among the remaining studies, 54 were

Table 1. Descriptive Characteristics of the Included Studies in the Systematic Review and Meta-analysis

First Author and Reference	Country	Study Population	Sample Size (Case-Control)	Gender	Treatment (Mean Age+SD)	Control (Mean Age+SD)	Type of the Study	Setting of the Study
Seligmann ¹⁹	Israel	Congestive HF	6 (6-0)	M/F	70	69	Within-group comparison	Hospitalized
Iqbal ²⁰	India	Chronic HF	50 (25-25)	M/F	62.4±8	61.4±7.1	Double-blind placebo-controlled	Hospitalized
Iqbal ²⁰	India	Chronic HF	50 (25-25)	M/F	62.4±8	61.4±7.1	Double-blind placebo-controlled	Hospitalized
Mousavi ²¹	Iran	Systolic HF	52 (26-26)	M/F	61.92±10.73	60.96±12.94	Double-blind placebo-controlled	Hospitalized
Schoenenberger ²²	Switzerland	Chronic HF	18 (9-9)	M/F	56.7±9.2	56.7±9.2	Double-blind placebo-controlled cross-over	Outpatient
Keith ²³	Canada	Chronic HF	64 (31-33)	M/F	64±11	63±11	Double-blind placebo-controlled	Outpatient
Shimon ²⁴	Israel	Chronic HF	29 (15-14)	M/F	67±12	72±9	Double-blind placebo-controlled	Outpatient
Shimon ²⁴	Israel	Chronic HF	27 (27-0)	M/F	67±12	72±9	Within-group comparison	Hospitalized
Lomivorotov ²⁵	Russia	Patients undergoing combined valvular and coronary artery bypass surgery	50 (25-25)	M/F	61.92	60.96	Randomized, placebo-controlled, pilot feasibility trial	Hospitalized
Smithline ²⁶	United States	Acute HF	119 (63-55)	M/F	72.64	73.25	Stratified block randomized double-blinded placebo-controlled study	Hospitalized
Wong ²⁷	Hamilton, Canada	Symptomatic HF	24 (12-12)	M/F	72.6±7.0	74.1±8.0	Double-blinded randomized placebo-controlled 2-period cross-over feasibility study	Hospitalized
Jikrona ²⁸	Surabaya	NYHA II HF	24 (14-14)	M/F	35-75	35-75	Within-group comparison	Hospitalized

Note. SD: Standard deviation; HF: Heart failure.

Table 2. Intervention Characteristics and the Results of the Included Studies in the Systematic Review and Meta-analysis

First Author and Reference	Inclusion Criteria	Comorbidities	Use of Diuretics	TD	Dose mg/Day/ Time	Duration	Results
Seligmann ¹⁹	Patients with chronic HF receiving furosemide and 16 age-matched control patients without HF and not taking diuretics. The duration of furosemide therapy was 3–14 months.	None	Yes, furosemide	Yes	100/IV/2	1 week	LVEF increased 13 ± 2.7% in four out of five patients studied by echocardiography and remained unchanged in one.
Iqbal ²⁰	Chronic HF and New York Heart Association (NYHA) functional class 2–4 due to (i) chronic ischemic heart disease, (ii) idiopathic dilated cardiomyopathy, (iii) valvular heart disease, and (iv) atrial fibrillation. These patients were admitted to the cardiology department from June 2010 onward.	Not reported	Yes, furosemide	Yes	100/IV/2	1 week	After one week of treatment, the thiamine group's LVEF percentage change was significantly improved compared to the placebo group's.
Iqbal ²⁰	The same study as above.	Not reported	Yes, furosemide	Yes	200/Oral/1	6 weeks	After 6 weeks of oral thiamine, the thiamine and placebo groups' LVEF increased non-significantly.
Mousavi ²¹	The absence of any change in the patient's clinical signs and symptoms or drug regimen in the past 3 months was attributed to aggravated symptoms or the optimization of dosage for survival benefit according to the present guidelines.	Not reported	Yes, furosemide	No	300/Oral/1	1 month	The ejection fraction was not influenced by thiamine supplementation.
Schoenenberger ²²	All outpatients at the Lucerne Hospital who were treated with diuretics for symptomatic chronic HF were eligible for this study. Congestive HF was defined as LVEF below 40% and the presence of at least one of the following four criteria: (a) shortness of breath or orthopnea, (b) positive hepatojugular reflex, (c) interstitial transudation on chest radiography, or (d) elevated brain natriuretic peptide (BNP) (C39 ng/L).	Coronary artery disease = 6 Hypertensive heart disease = 1 Excess alcohol consumption = 1	Yes, furosemide	No	300/Oral/1	28 days	The LVEF increased significantly more than the LVEF in the placebo group.
Keith ²³	Consecutive patients with a primary diagnosis of ischemic, dilated, idiopathic, or valvular HF, LVEF < 40% (by echocardiography or radionuclide ventriculography), and NYHA class II–III symptoms	Hypertension Hyperlipidemia Stroke	Yes, furosemide Spironolactone Metolazone	No	200/Oral/1	6 months	Oral thiamin supplementation failed to improve LVEF.
Shimon ²⁴	All patients with chronic HF and NYHA functional class 2 to 4 (due to chronic ischemic heart disease or idiopathic dilated cardiomyopathy) were considered eligible for the study if they were prescribed daily doses of 80 mg furosemide or more for at least 3 months. The patients also received various other drugs, including digoxin, nitrates, and angiotensin-converting enzyme inhibitors.	Previous myocardial infarction (one person)	Yes, furosemide	No	200/IV/1	1 week	LVEF was significantly higher in the thiamin group than in the placebo group.
Shimon ²⁴	The same study as above.	Previous myocardial infarction	Yes, furosemide	No	200/Oral /1	6 weeks	There was no comparison between groups. There was an intragroup comparison for the thiamin group.
Lomivorotov ²⁵	> 18 years of age undergoing combined valvular and coronary artery bypass graft surgery with CPB.	Hypertension: control: 80%, thiamin 78% diabetics: control 30%, thiamin 26%	No	No	600 mg on the day of surgery and 400 mg/day on postoperative days 1, 2, and 3	5 months	Not reported.
Smithline ²⁶	History of HF on a loop diuretic, worsening dyspnea over the past 24 hours, dyspnea at time of enrollment, radiographic cephalization of vessels, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP; > 450 pg/ml), age > 18 years, and a primary admitting diagnosis of acute HF.	Diabetes	No	No	100 mg in the evenings of their first and second days	2 days	Not reported.
Wong ²⁷	Included adults aged 60 years with symptomatic HF (NYHA class II–IV), LVEF 45%, and either of the following: (i) An HF-related hospitalization in the past 12 months or (ii) an NT-proBNP level of 600 ng/L within 60 days of screening. Due to challenges with recruiting stable patients with recent HF-related hospitalization, we added the option of using the NT-proBNP level as an alternative to requiring a recent hospitalization, similar to the approach used in other recent HF trials. ^{11,12} Patients also were optimized medically on guideline-directed medical therapy ¹⁰ and were stable on medications without hospitalization in the month immediately preceding enrollment.	Diabetes and Hypertension	No	No	500/Oral/1	90 days, and were switched to the opposite treatment for 90 days after a 6-week washout period.	With thiamine, nonsignificant improvements occurred in LVEF and NT-proBNP levels. Seven patients experienced 13 serious adverse events; none were related to the study drug.
Jikrona ²⁸	Male patients with NYHA II HF who received furosemide Therapy.	None	Yes, furosemide	No	300/Oral/1	28 days	This study concluded that thiamine supplement therapy of 300 mg/day could increase the ejection fraction rate in patients with stage II HF.

Note. TD: Thiamine deficiency; HF: Heart failure; CPB: Cardiopulmonary bypass.

excluded due to irrelevancy, and 17 were removed because they were conference abstracts, editorials, and letters. Finally, the systematic review included eleven studies, six considered suitable for the meta-analysis (RCT and cross-over), and 4 within-group analyses (Figure 1).

The total sample sizes for the systematic review and meta-analysis were 545 and 319, respectively. The sample size was 406 in RCT studies and 89 in experimental studies. According to the results (Tables 1 and 2), the population under investigation consisted of patients with chronic,^{20,22-24,27,28} congestive,¹⁹ systolic,²¹ and acute HF²⁶ and those undergoing combined vascular and coronary artery bypass surgery.²⁵ All the studies, except for two, used furosemide.^{25,26} Additionally, three studies recruited patients with TD.^{19,20} Moreover, seven studies were conducted on hospitalized patients, and three studies were performed on outpatients.²¹⁻²³ Furthermore, four studies were randomized placebo-controlled clinical trials, two were cross-over research,^{22,27} and four were within-group studies.^{19,24,28,30} Some studies had two reports in different study designs (Table 1).

Meta-analysis

Based on the analysis of the seven eligible studies for meta-analysis (six studies and seven reports),²⁰⁻²⁴ thiamin had no significant impact on LVEF ($P=0.05$, MD=0.23 mg/d, 95% confidence interval [CI]: -0.003 – 0.46, $I^2=0$, and $P>0.05$, Figure 2).

After carefully evaluating the selected studies, some subgroup analyses were performed to find the sources of heterogeneity. The dose of thiamin, duration of thiamine prescription, and treatment method were considered subgroups. There were two dose categories for thiamin (≤ 200 mg and >200 mg), two durations for thiamin prescription (one week and more than one week), and two methods of thiamin supplementation (oral and

intravenous), the details of which are listed in Table 3.

Intravenous

The results of the subgroup meta-analysis for dose indicated that the difference in means was insignificant in the two categories (Figure S1). Subgroup meta-analysis for the type of intervention (Figure S2) and prescription duration (Figure S3) also showed no significant results. Figure 3 depicts Begg's funnel plot of MD versus standard error (SE) for the studies reporting the effect of thiamin on the mean of LVEF. The analysis of the five within-group comparison studies for meta-analysis (four studies and five reports) revealed the significant impact of thiamin on LVEF ($P<0.001$, MD=1.22 mg/day, 95% CI: 0.57 to 1.88, $I^2=0$, and $P>0.05$ Figure 4). Figure 5 displays Begg's funnel plot in MD versus SE for the studies reporting the effect of thiamin on the mean of LVEF in the within-group studies.

Six articles were evaluated using the Cochrane checklist to assess the quality of studies. Three were categorized as high-quality, and three were placed in the medium-quality category. Two researchers verified the quality scores. Notably, none of the articles were of low quality, and all were included in the meta-analysis.

Publication Bias

The publication bias was assessed by applying a funnel plot, which showed the MDs of LVEF against their SE, considering a measure of precision. There was no evidence

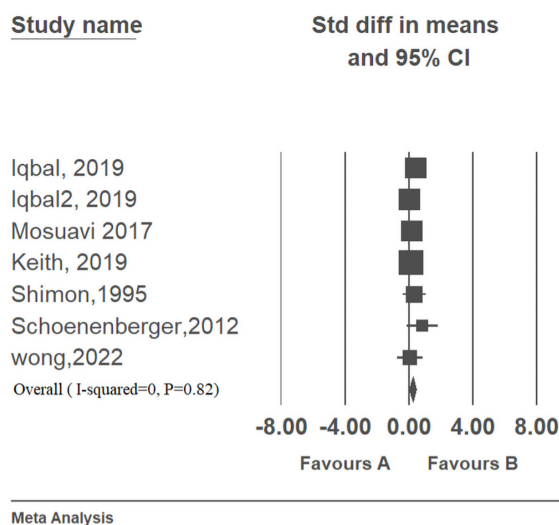


Figure 2. Forest Plot Illustrating the Weighted Mean Difference in LVEF Change Between Treatment and Control Groups. Note. Std diff: Standard error of the mean; CI: Confidence interval; LVEF: Left ventricular ejection fraction. B and A stand for treatment and control, respectively

Table 3. Subgroup Variables

First Author and Reference	Thiamin Dose (≤ 200 mg or >200 mg)	Intervention Type (Oral or IV)	Intervention Duration (One Week or More)
Iqbal et al ²⁰	200	IV	One week
Iqbal et al ²⁰	200	Oral	More than one week
Mousavi et al ²¹	300	Oral	More than one week
Keith et al ²³	200	Oral	More than one week
Shimon et al ²⁴	200	IV	One week
Schoenenberger et al ²²	300	Oral	More than one week
Wong et al ²⁷	500	Oral	More than one week

Note. IV: Intravenous.

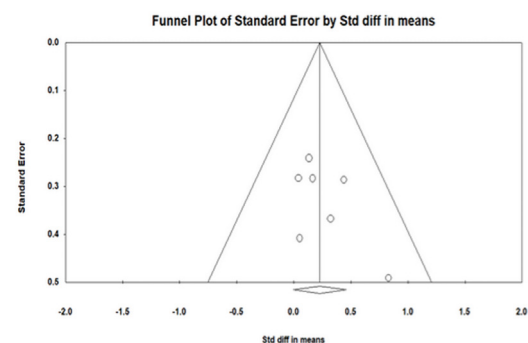


Figure 3. Begg's Funnel Plot in MD Versus SE for Studies Reporting the Effect of Thiamin on the Mean of LVEF. Note. Std diff: Standard error of the mean; CI: Confidence interval; MD: Mean difference; SE: Standard error; LVEF: Left ventricular ejection fraction

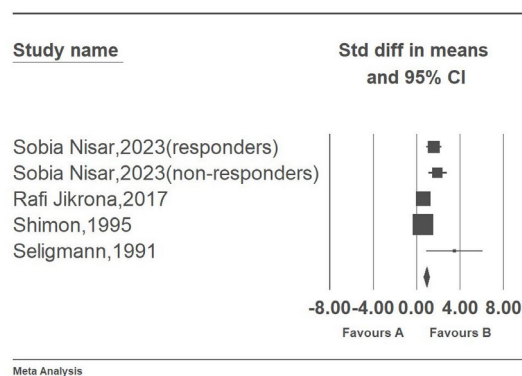


Figure 4. Forest Plot Illustrating the Weighted Mean Difference in LVEF Change Between the Baseline and Post-Treatment (Within-Group Analysis). Note. Std diff: Standard error of the mean; CI: Confidence interval; LVEF: Left ventricular ejection fraction

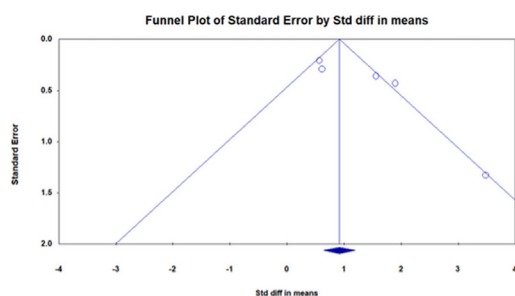


Figure 5. Begg's Funnel Plot in MD Versus SE for Studies Reporting the Effect of Thiamin on the Mean of LVEF (Within-Group Design). Note. Std diff: Standard error of the mean; CI: Confidence interval; MD: Mean difference; SE: Standard error; LVEF: Left ventricular ejection fraction

of publication bias based on the asymmetry tests (Begg's test, $P=0.26$, Egger's test, $P=0.30$, Figure 3). A trim-and-fill analysis revealed no missing articles, suggesting no significant publication bias in our dataset (Figure 6).

Sensitivity Analysis

The sensitivity analysis was conducted by excluding one study at a time. The results indicated that the pooled estimate remained robust (Figure 7).

Discussion

HF is a public health concern that affects the healthcare system. However, the existing data on the effect of thiamine supplementation on ejection fraction is unclear. The current meta-analysis demonstrated that although thiamine did not significantly impact LVEF. Conversely, the within-group comparative reports revealed the significant effect of thiamine supplementation on LVEF. Nonetheless, there was no significant difference in thiamine supplementation dose (200 mg and 300 mg), type of intervention (oral and intravenous), and duration (one week or more than one week). Based on the asymmetry test, there was no evidence of publication bias.

There are two main types of HF. The predominant clinical characteristic of HFrEF is a decrease in LVEF.³¹ Life-threatening irregular heartbeats can occur due to a reduced ejection fraction, leading to sudden cardiac arrest/death.³² Furthermore, reduced ejection fraction

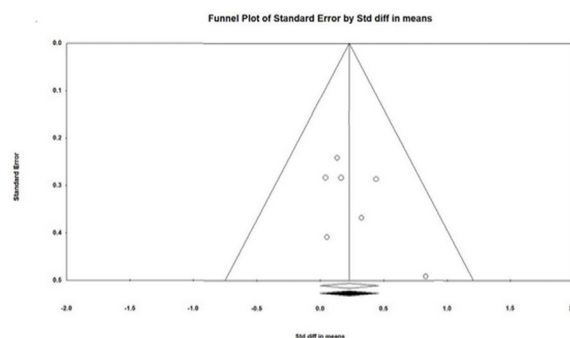


Figure 6. Begg's Funnel Plot in MD Versus SE for Studies Reporting the Effect of Thiamin on the Mean of LVEF After Trim-and-Fill Analysis. Note. Std diff: Standard error of the mean; MD: Mean difference; SE: Standard error; LVEF: Left ventricular ejection fraction

Model	Study name	Std diff in means (95% CI) with study removed				
		-8.00	-4.00	0.00	4.00	8.00
Fixed	Iqbal, 2019			+		
	Iqbal2, 2019			+		
	Mossavi, 2017			+		
	Keith, 2019			+		
	Shimon, 1995			+		
	Schoenenberger, 2012			+		
	wong, 2022			+		

Figure 7. Sensitivity Analysis for Studies Reporting the Effect of Thiamin on the Mean of LVEF by the Removal of Each Study. Note. Std diff: Standard error of the mean; CI: Confidence interval; LVEF: Left ventricular ejection fraction

has been associated with a shorter life expectancy in males and females, worse quality of life, and psychological and physical disabilities.^{33,34} Despite the availability of various treatments, such as medications and treatment with an implantable cardioverter defibrillator or cardiac resynchronization therapy, the need for adjuvant therapy, including nutrient supplementation, to improve the management of HF signs and symptoms appears unavoidable. Although TD is more common in HF patients than in healthy people, the detailed pathophysiology of TD remains unclear.⁵ Patients with or without HF may develop TD due to a variety of causes.⁵ Nutrition deficiencies, feeling full before eating, a restricted high-sodium diet, excessive alcohol consumption, malabsorption syndromes, medications (e.g., diuretics, phenytoin, penicillin, cephalosporin, and aminoglycosides), infections, surgery, fever, trauma, persistent diarrhea, and vomiting are some of these factors.⁵ The possible benefits of thiamine supplementation in enhancing ejection fraction and HF therapy have been discussed throughout the past decade.^{5,12,14,16,30} In a 2013 systematic review and meta-analysis, DiNicolantonio et al demonstrated that supplementing with thiamine helped increase ejection fraction in patients with systolic HF.⁵ Two meta-analyses that followed were released in 2022 and 2023.^{14,16} The results of a meta-analysis of eight studies by Xu et al revealed that, despite the constraints of prior research, there was not enough evidence to establish clear conclusions regarding the effects of thiamine supplementation in HF patients. However, thiamine status and symptoms associated with HF may improve.¹⁴ Additionally, Syed et al concluded that thiamine supplementation did not affect the ejection

fraction of patients with HF, except for heart rate.¹⁶ It is noteworthy that the outcomes and study limitations of these meta-analyses were different. Therefore, future meta-analyses will be beneficial in this regard. Based on six high-quality clinical trials, the findings of the current meta-analysis confirmed that thiamine supplementation had no significant effect on LVEF in patients with HF. Notably, the five within-group comparison reports demonstrated the substantial impact of thiamin on LVEF. Even though the results of the current meta-analysis and those of two previous meta-analyses suggested that thiamin supplementation had no significant effect on LVEF, a within-group comparison revealed that thiamin supplementation had a substantial impact on LVEF. A possible explanation/mechanism is the effect of thiamine, an essential water-soluble vitamin required for cellular energy generation, on the energy breakdown of cardiomyocytes.¹⁷ In this regard, TD may contribute to the progression of HF. Hence, in clinical practice, it is critical to understand TD's pathophysiology and consider it one of the differentials in patients with new-onset HF with an unknown etiology and appropriate risk factors.¹⁷ Notably, in the present study, there was no significant difference in the period (one week or more than one week), form of intervention (oral and intravenous), or dosage (200 mg and 300 mg) of thiamine supplementation. According to the asymmetry test, there was no indication of publishing bias.

Although thiamine supplementation is not recommended in the current congestive HF guidelines, clinical experience and some data have shown promising outcomes when it comes to the use of thiamine therapy in patients with renal disease and HF.^{35,36} Moreover, at high daily doses (300–900 mg), thiamine is a relatively safe prescription with no notable adverse effects.³⁷ In this regard, thiamine may be added to chronic HF guidelines as an adjuvant therapy to help with HF symptoms and signs. Nonetheless, a large, multi-center study should be conducted to confirm the advantages of thiamine in systolic HF and ameliorate the symptoms.

The strength of the present study was the utilization of many databases for searching and high-quality RCTs for analysis. On the other hand, the limitations of the current investigation were the lack of information on comorbidities, a comprehensive prescription list, and the usage of supplements, such as Coenzyme Q10 and Omega-3. Furthermore, hospitalization, death, dyspnea, heart rate, and diastolic hypertension could not be analyzed due to the heterogeneity of the studies. It is noteworthy that a future meta-analysis seems necessary because only six papers were reviewed in the current investigation.

Conclusion

The results of the current investigation on how thiamine affects the ejection fraction in HF patients revealed that thiamine supplementation might benefit patients with systolic HF. It was found that thiamine is a reasonably safe

prescription with no significant side effects at high doses (300–900 mg/d). Considering the prevalence of TD in patients with HF and those using loop diuretics, thiamine supplementation may be a sensible suggestion to enhance the clinical condition, promote quality of life, and reduce symptoms and signs in patients with HF. However, further data on the function of thiamine in HF would contribute to the development of a higher level of accuracy in this area.

Acknowledgements

The authors would like to express their gratitude to Shiraz University of Medical Sciences, Shiraz, Iran, as well as to the Center for Development of Clinical Research at Nemazee Hospital and Dr. Nasrin Shokrpour, for their editorial assistance.

Authors' Contribution

Conceptualization: Mohammad Hossein Sharifi, Firoozeh Abtahi.

Data curation: Maryam Jalali, Sorour Sarihi, Parisa Keshani.

Formal analysis: Maryam Jalali, Parisa Keshani, Samane Nematollahi.

Investigation: Mohammad Hossein Sharif, Parisa Keshani.

Methodology: Mohammad Hossein Sharif, Parisa Keshani.

Project administration: Mohammad Hossein Sharif, Parisa Keshani.

Supervision: Mohammad Hossein Sharif, Parisa Keshani.

Validation: Mohammad Hossein Sharifi, Maryam Jalali, Firoozeh Abtahi.

Visualization: Mohammad Hossein Sharifi, Maryam Jalali, Parisa Keshani.

Writing-original draft: Mohammad Hossein Sharifi, Maryam Jalali, Parisa Keshani.

Writing-review and editing: Mohammad Hossein Sharifi, Maryam Jalali, Sorour Sarihi, Parisa Keshani, Firoozeh Abtahi.

Competing Interests

There are no competing interests to disclose.

Ethical Approval

Not applicable.

Funding

There is no funding to report for this study.

Supplementary Files

Supplementary file 1 contains Tables S1-S3 and Figures S1-S3.

References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail.* 2020;22(8):1342-56. doi: [10.1002/ejhf.1858](https://doi.org/10.1002/ejhf.1858).
2. Lippi G, Sanchis-Gomar F. Global epidemiology and future trends of heart failure. *AME Med J.* 2020;5:15. doi: [10.21037/amj.2020.03.03](https://doi.org/10.21037/amj.2020.03.03).
3. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GM, Coats AJ. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res.* 2023;118(17):3272-87. doi: [10.1093/cvr/cvac013](https://doi.org/10.1093/cvr/cvac013).
4. Truby LK, Rogers JG. Advanced heart failure: epidemiology, diagnosis, and therapeutic approaches. *JACC Heart Fail.* 2020;8(7):523-36. doi: [10.1016/j.jchf.2020.01.014](https://doi.org/10.1016/j.jchf.2020.01.014).
5. DiNicolantonio JJ, Lavie CJ, Niazi AK, O'Keefe JH, Hu T. Effects of thiamine on cardiac function in patients with systolic heart failure: systematic review and metaanalysis of randomized, double-blind, placebo-controlled trials. *Ochsner J.* 2013;13(4):495-9.
6. Helali J, Park S, Ziaeiian B, Han JK, Lankarani-Fard A. Thiamine and heart failure: challenging cases of modern-day cardiac beriberi. *Mayo Clin Proc Innov Qual Outcomes.*

- 2019;3(2):221-5. doi: [10.1016/j.mayocpiqo.2019.03.003](https://doi.org/10.1016/j.mayocpiqo.2019.03.003).
7. Kattoor AJ, Goel A, Mehta JL. Thiamine therapy for heart failure: a promise or fiction? *Cardiovasc Drugs Ther*. 2018;32(4):313-7. doi: [10.1007/s10557-018-6808-8](https://doi.org/10.1007/s10557-018-6808-8).
8. Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *J Card Fail*. 2021;27(4):387-413. doi: [10.1016/j.cardfail.2021.01.022](https://doi.org/10.1016/j.cardfail.2021.01.022).
9. Choi HM, Park MS, Youn JC. Update on heart failure management and future directions. *Korean J Intern Med*. 2019;34(1):11-43. doi: [10.3904/kjim.2018.428](https://doi.org/10.3904/kjim.2018.428).
10. Fukuta H, Goto T, Wakami K, Kamiya T, Ohte N. Effects of exercise training on cardiac function, exercise capacity, and quality of life in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. *Heart Fail Rev*. 2019;24(4):535-47. doi: [10.1007/s10741-019-09774-5](https://doi.org/10.1007/s10741-019-09774-5).
11. Salmani M, Alipoor E, Navid H, Farahbakhsh P, Yaseri M, Imani H. Effect of L-arginine on cardiac reverse remodeling and quality of life in patients with heart failure. *Clin Nutr*. 2021;40(5):3037-44. doi: [10.1016/j.clnu.2021.01.044](https://doi.org/10.1016/j.clnu.2021.01.044).
12. He S, Wang S, Xu T, Wang S, Qi M, Chen Q, et al. Role of thiamine supplementation in the treatment of chronic heart failure: an updated meta-analysis of randomized controlled trials. *Clin Cardiol*. 2024;47(7):e24309. doi: [10.1002/clc.24309](https://doi.org/10.1002/clc.24309).
13. Jain A, Mehta R, Al-Ani M, Hill JA, Winchester DE. Determining the role of thiamine deficiency in systolic heart failure: a meta-analysis and systematic review. *J Card Fail*. 2015;21(12):1000-7. doi: [10.1016/j.cardfail.2015.10.005](https://doi.org/10.1016/j.cardfail.2015.10.005).
14. Xu M, Ji J, Lu Q, Gong J, Luo Z, Zhu L. The effects of thiamine supplementation on patients with heart failure: a systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med*. 2022;70:102853. doi: [10.1016/j.ctim.2022.102853](https://doi.org/10.1016/j.ctim.2022.102853).
15. Ahmed M, Azizi-Namini P, Yan AT, Keith M. Thiamin deficiency and heart failure: the current knowledge and gaps in literature. *Heart Fail Rev*. 2015;20(1):1-11. doi: [10.1007/s10741-014-9432-0](https://doi.org/10.1007/s10741-014-9432-0).
16. Syed AR, Syed AA, Akram A, Azam MS, Muzammil MA, Deepak, et al. Does thiamine supplementation affect heart failure? A systematic review and meta-analysis of randomized control trials. *Heart Lung*. 2023;61:37-45. doi: [10.1016/j.hrtlng.2023.04.011](https://doi.org/10.1016/j.hrtlng.2023.04.011).
17. DiNicolantonio JJ, Liu J, O'Keefe JH. Thiamine and cardiovascular disease: a literature review. *Prog Cardiovasc Dis*. 2018;61(1):27-32. doi: [10.1016/j.pcad.2018.01.009](https://doi.org/10.1016/j.pcad.2018.01.009).
18. Goel A, Kattoor AJ, Mehta JL. Thiamin therapy for chronic heart failure: is there any future for this vitamin? *Am J Clin Nutr*. 2019;110(6):1270-1. doi: [10.1093/ajcn/nqz246](https://doi.org/10.1093/ajcn/nqz246).
19. Seligmann H, Halkin H, Rauchfleisch S, Kaufmann N, Motro M, Vered Z, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. *Am J Med*. 1991;91(2):151-5. doi: [10.1016/0002-9343\(91\)90007-k](https://doi.org/10.1016/0002-9343(91)90007-k).
20. Iqbal S, Rashid A, Bhat I, Rashid J, Hafeez I, Lone A, et al. Role of thiamine supplementation in the treatment of patients with heart failure: a double-blind randomized controlled trial. *Heart India*. 2019;7(2):68-73. doi: [10.4103/heartindia.heartindia_7_19](https://doi.org/10.4103/heartindia.heartindia_7_19).
21. Mousavi M, Namazi S, Avadi M, Amirahmadi M, Salehifar D. Thiamine supplementation in patients with chronic heart failure receiving optimum medical treatment. *J Cardiol Curr Res*. 2017;9(2):00316. doi: [10.15406/jccr.2017.09.00316](https://doi.org/10.15406/jccr.2017.09.00316).
22. Schoenenberger AW, Schoenenberger-Berzins R, der Maur CA, Suter PM, Vergopoulos A, Erne P. Thiamine supplementation in symptomatic chronic heart failure: a randomized, double-blind, placebo-controlled, cross-over pilot study. *Clin Res Cardiol*. 2012;101(3):159-64. doi: [10.1007/s00392-011-0376-2](https://doi.org/10.1007/s00392-011-0376-2).
23. Keith M, Quach S, Ahmed M, Azizi-Namini P, Al-Hesayen A, Azevedo E, et al. Thiamin supplementation does not improve left ventricular ejection fraction in ambulatory heart failure patients: a randomized controlled trial. *Am J Clin Nutr*. 2019;110(6):1287-95. doi: [10.1093/ajcn/nqz192](https://doi.org/10.1093/ajcn/nqz192).
24. Shimon I, Almog S, Vered Z, Seligmann H, Shefi M, Peleg E, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. *Am J Med*. 1995;98(5):485-90. doi: [10.1016/s0002-9343\(99\)80349-0](https://doi.org/10.1016/s0002-9343(99)80349-0).
25. Lomivorotov VV, Moroz G, Ismoilov S, Shmyrev V, Efremov S, Abubakirov M, et al. Sustained high-dose thiamine supplementation in high-risk cardiac patients undergoing cardiopulmonary bypass: a pilot feasibility study (the APPLY trial). *J Cardiothorac Vasc Anesth*. 2020;34(3):594-600. doi: [10.1053/j.jvca.2019.08.044](https://doi.org/10.1053/j.jvca.2019.08.044).
26. Smithline HA, Donnino M, Blank FS, Barus R, Coute RA, Knee AB, et al. Supplemental thiamine for the treatment of acute heart failure syndrome: a randomized controlled trial. *BMC Complement Altern Med*. 2019;19(1):96. doi: [10.1186/s12906-019-2506-8](https://doi.org/10.1186/s12906-019-2506-8).
27. Wong EK, Lee JY, Chow J, Power P, Jin L, Leong DP, et al. High-dose thiamine supplementation in older patients with heart failure: a pilot randomized controlled crossover trial (THIAMINE-HF). *CJC Open*. 2022;4(6):532-9. doi: [10.1016/j.cjco.2022.02.007](https://doi.org/10.1016/j.cjco.2022.02.007).
28. Jikrona R, Suharjono S, Ahmad A. Thiamine supplement therapy improves ejection fraction value in stage ii heart failure patients. *Folia Med Indones*. 2017;53(2):139-43.
29. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med*. 2015;8(1):2-10. doi: [10.1111/jebm.12141](https://doi.org/10.1111/jebm.12141).
30. Nisar S, Mohi-U-Din K, Tak SI, Andrabi SM, Tanvir M, Muzaffer U, et al. Thiamine responsive high output heart failure of adults: an under-recognized entity. *Eur J Clin Nutr*. 2023;77(7):757-60. doi: [10.1038/s41430-023-01279-7](https://doi.org/10.1038/s41430-023-01279-7).
31. Chong PF, Torio M, Fujii F, Hirata Y, Matsuoka W, Sonoda Y, et al. Critical vitamin deficiencies in autism spectrum disorder: reversible and irreversible outcomes. *Eur J Clin Nutr*. 2022;76(11):1618-21. doi: [10.1038/s41430-022-01170-x](https://doi.org/10.1038/s41430-022-01170-x).
32. Kotecha D, Chudasama R, Lane DA, Kirchhof P, Lip GY. Atrial fibrillation and heart failure due to reduced versus preserved ejection fraction: a systematic review and meta-analysis of death and adverse outcomes. *Int J Cardiol*. 2016;203:660-6. doi: [10.1016/j.ijcard.2015.10.220](https://doi.org/10.1016/j.ijcard.2015.10.220).
33. Dewan P, Rørth R, Jhund PS, Shen L, Raparelli V, Petrie MC, et al. Differential impact of heart failure with reduced ejection fraction on men and women. *J Am Coll Cardiol*. 2019;73(1):29-40. doi: [10.1016/j.jacc.2018.09.081](https://doi.org/10.1016/j.jacc.2018.09.081).
34. Okuhara Y, Asakura M, Orihara Y, Morisawa D, Matsumoto Y, Naito Y, et al. Reduction in left ventricular ejection fraction is associated with subsequent cardiac events in outpatients with chronic heart failure. *Sci Rep*. 2019;9(1):17271. doi: [10.1038/s41598-019-53697-y](https://doi.org/10.1038/s41598-019-53697-y).
35. Kędzierska-Kapuza K, Szczuko U, Stolińska H, Bakaloudi DR, Wierzbza W, Szczuko M. Demand for water-soluble vitamins in a group of patients with CKD versus interventions and supplementation-a systematic review. *Nutrients*. 2023;15(4):860. doi: [10.3390/nu15040860](https://doi.org/10.3390/nu15040860).
36. Dkhillon D, Samogulova A, Kolobov B. B vitamins as adjunctive treatment for chronic heart failure. *Cardiovasc Hematol Disord Drug Targets*. 2023;23(1):64-71. doi: [10.2174/1871529x23666230719090419](https://doi.org/10.2174/1871529x23666230719090419).
37. Alemanno F. Thiamine (vitamin B1). In: Alemanno F, ed. *Biochemistry for Anesthesiologists and Intensivists*. Cham: Springer; 2020. p. 1-10. doi: [10.1007/978-3-030-26721-6_12](https://doi.org/10.1007/978-3-030-26721-6_12).