Effectiveness of Thiamine Supplementation Plus Optimal Medical Therapy as an Adjunct Treatment in Improving Cardiac Function Among Patients With Heart Failure With Reduced Ejection Fraction: A Meta-analysis

Oliver T. Rances, MD | Jeffrey P. Mendoza, MD | Rafael A. Tagayuna, MD
Cardinal Santos Medical Center, San Juan City, Metro Manila, Philippines

Abstract

BACKGROUND: Thiamine plays a crucial role for normal cardiac function, as severe vitamin B_1 (thiamine) deficiency leads to congestive heart failure. Thus, patients undergoing diuretic treatment might have compromised heart function. Several small-scale studies were conducted with conflicting results".

OBJECTIVE: The aim of this study was to determine the effects of thiamine supplementation on cardiac function among patients with heart failure with reduced ejection fraction receiving optimal medical therapy versus optimum medical therapy alone.

DESIGN: This was a meta-analysis of randomized, double-blind, placebo-controlled trials.

METHODS: Studies for inclusion were searched using PubMed, Google Scholar, Cochrane, EMBASE, and other databases. Gray literature was also explored. Review Manager version 5.3 was used to analyze data. The mean difference and 95% confidence interval were estimated using random-effects model. χ^2 and I^2 were computed to assess heterogeneity.

RESULTS: After the analysis of the combined effects of five studies with 218 subjects, the pooled results showed no significant effect on the left ventricular ejection fraction in heart failure patients when given thiamine supplementation with a *P* value of 0.04.

CONCLUSION: Based on this limited group of studies, there is insufficient information to suggest that thiamine supplementation has a positive effect on left ventricular ejection fraction in heart failure patients. Further large-scale clinical trials are needed to determine the optimum dose, duration, and route of thiamine in patients with heart failure.

KEYWORDS: thiamine supplementation, vitamin B, heart failure, HFrEF, reduced ejection fraction

INTRODUCTION

Heart failure is a clinical syndrome characterized by distinct symptoms and signs, which is caused by structural and/or functional cardiac abnormalities.[1–3] It is a global pandemic affecting at least 26 million people worldwide and is increasing in prevalence. Heart failure health expenditures are considerable and will increase dramatically with an aging population. Despite the significant advances in therapies and prevention, mortality and morbidity are still high, and quality of life is poor.[4] In the Philippines, hospitalization for heart failure was reported to be 1648 cases for every 100,000 patient claims in 2014.[5]

In the treatment of congestive heart failure, the recommended pharmacological therapy includes the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, β-blockers, diuretics, and aldosterone antagonists.[6] Diuretic drugs have become a firm cornerstone of therapy. Up to 50% of patients with congestive heart failure in industrialized nations will undergo long-term diuretic treatment. Diuretic therapy has been shown to be associated with loss of water-soluble vitamins, including vitamin B_1 (thiamine).[7]

Thiamine is a water-soluble vitamin that plays an important role in the energy metabolism in the human body. It is required for macronutrient oxidation as well as for the production of adenosine triphosphate that fuels myocardial contraction.[8] Reductions in adenosine triphosphate production may limit the energy available for myocyte contraction, thereby contributing to myocardial dysfunction and a low cardiac output.[9] Deficiency in thiamine can lead to neurological and cardiovascular abnormalities, known as dry beriberi and wet beriberi, respectively.[10]

According to a study done by Seligmann et al,[11] the prevalence of thiamine deficiency in patients with heart failure undergoing diuretic treatment is 91%. Thiamine deficiency in patients with heart failure is multifactorial.[12] The primary factors associated with thiamine deficiency in patients with heart failure are use of diuretics, malnutrition, preserved renal function, severe heart failure, and advanced age.[13,14]

Currently, several small scale randomized controlled trials have been conducted to investigate the effectiveness of thiamine supplementation in improving cardiac function among patients with heart failure.[15–19] Some studies showed statistically significant improvement in cardiac function after thiamine therapy. These include improvement in left ventricular ejection fraction (LVEF) as well as improved functional capacity[15–17] Another study showed otherwise compared to placebo.[18] For this reason, a systematic, quantitative review of available studies to determine the overall effect of thiamine supplementation on LVEF as an adjuvant therapy in the treatment of heart failure is needed.

Because of the presence of several small-scale studies and conflicting results on the effect of thiamine supplementation, a systematic, quantitative review of available studies to determine the overall effect of thiamine supplementation on cardiac function among patients with heart failure is needed to increase the power and provide more precise estimates of the effects of thiamine than those derived from the individual studies included within the review.[11,15–19]

If proven to have substantial effect, thiamine may be a cost-effective, easily available adjuvant therapy especially in developing countries (Figure 1).

RESEARCH QUESTION

Does thiamine supplementation plus optimal medical therapy help improve cardiac function among patients with heart failure with reduced ejection fraction?

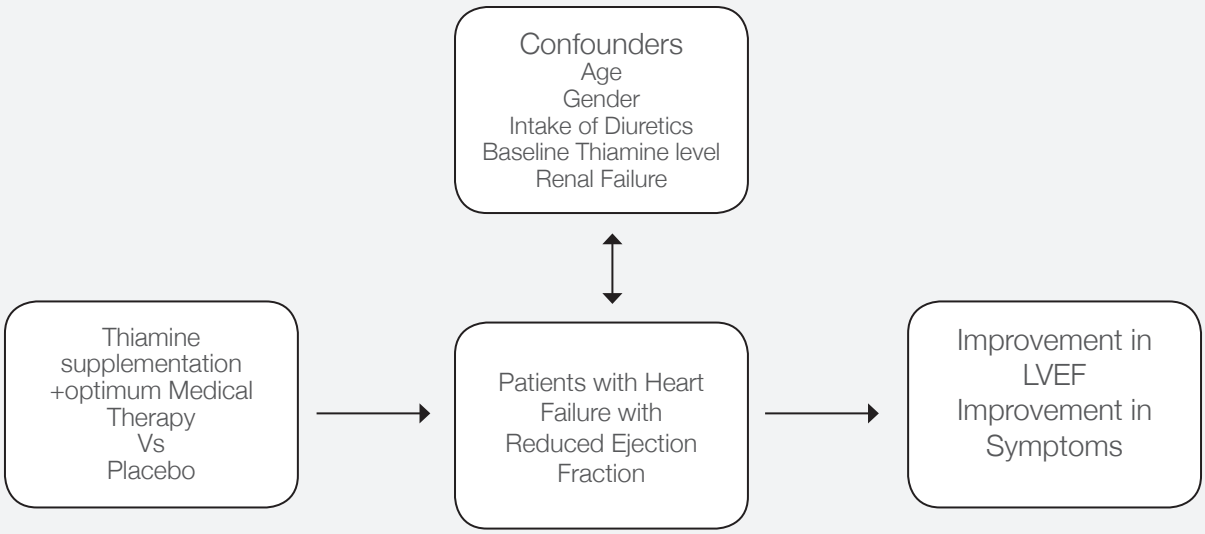

FIGURE 1. Conceptual framework

OBJECTIVES

General Objective

To determine the effects of thiamine supplementation on cardiac function among patients with heart failure with reduced ejection fraction (HFrEF) receiving optimal medical therapy versus optimal medical therapy alone.

Specific Objective

(1) To compare the LVEF of HFrEF patients who had thiamine supplementation as an adjunct to standard treatment versus optimal medical therapy alone.
(2) To compare the functional capacity of HFrEF patients who had thiamine supplementation as an adjunct to standard treatment versus optimal medical therapy alone.

METHODS

Search Strategy

The search was performed for literature published up to 2017. The databases PubMed, Google Scholar, Cochrane Library, EMBASE, BioMedCentral, PLoS (Public Library of Science), Free Medical Journals, HighWirePress, and Herdin were systematically searched. In the MeSH search engine, the following search terms were used *heart failure, thiamine supplementation, vitamin B supplementation, HFrEF,* and *reduced ejection fraction* and a combination of all these terms. Both indexing and text terms were used, and languages were restricted to English. Gray Literature such as books and journal articles, unpublished completed studies or ongoing studies, national and international trial register (ClinicalTrials.gov), pharmaceutical industry trials register, colleagues, and formal letters of request for information were also explored.

Selection of Studies

The studies' population comprised patients with heart failure with reduced ejection fraction. The intervention used was thiamine supplementation plus optimal medical therapy versus placebo plus optimal medical treatment.

Measurement of Outcome

The following outcome measure was extracted from each study:

- Increase in LVEF
- Improvement in functional capacity

Study Design

This study is a meta-analysis that includes published and unpublished studies that meet the specified inclusion criteria.

Inclusion Criteria

Studies were considered acceptable for inclusion in the meta-analysis if it met the following criteria: (1) the study was a randomized, double-blind, placebo-controlled intervention trial in which the supplemented and control groups were enrolled concurrently; (2) participants include patients diagnosed with HFrEF (baseline ejection fraction <40%) documented by two-dimensional echocardiography of any etiology; and (3) patients under New York Heart Association (NYHA) class II or greater.

Exclusion Criteria

The studies were excluded if they included (1) patients with identifiable causes of thiamine deficiency, for example, alcoholism, malnutrition, and malabsorption or (2) patients with acute myocardial infarction and acute heart failure and (3) if they were not randomized, placebo-controlled studies.

Information Sources

Published and unpublished papers from PubMed, Google Scholar, Cochrane, EMBASE, Clinicaltrials.gov, and references from journals were sources for information.

Data Extraction

Two independent reviewers assessed the suitability of each study. Once the final set of studies for inclusion in the analyses was established, the authors evaluated the study quality in terms of randomization, concealment, intention to treat, equality of baseline characteristics, and complete follow-up. Data extraction was done independently. Any conflicts were resolved by a third party. The outcome measure was combined and analyzed using a random-effects model in Review Manager version 5.3. Mean difference and its corresponding 95% confidence interval were computed. Review Manager version 5.3 was utilized for the analysis. Heterogeneity was interpreted as a total variation between studies that is attributable to heterogeneity rather than to chance. I^2 was used to assess the degree of heterogeneity wherein greater than 50% suggests significant degree of heterogeneity (Figure 2).

RESULTS

A total of five studies were included (Table 1). The literature search strategy was outlined in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart. No evidence of publication bias was observed in the funnel plot. Across all five studies, different improvements of symptoms were associated with the use of thiamine supplementation in patients with heart failure. Two studies showed improvement in myocardial function and functional class. In the study by Shimon et al,[16] mean NYHA class decreased from 2.6 ± 0.6 at baseline to 2.2 ± 0.7 ($P < 0.01$) in all 27 patients who completed the full 7-week intervention. Likewise, in the study by Iqbal et al,[19] there was significant improvement in NYHA class from 2.2 to 1.6 in the thiamine group, whereas no significant change occurred in the placebo group.[16,19] Moreover, the studies by Schoenenberger et al[15] and Sofi et al[17] both showed improvement of functional capacity as measured by the 6-minute walking test.[15,17] The effect of thiamine on functional capacity is shown in Table 2. Adverse effects of thiamine were not discussed in the articles.

The pooled analysis on the effect of thiamine supplementation in LVEF among patients with heart failure showed a mean difference of 1.90 (95% confidence interval, 0.12–3.68) with

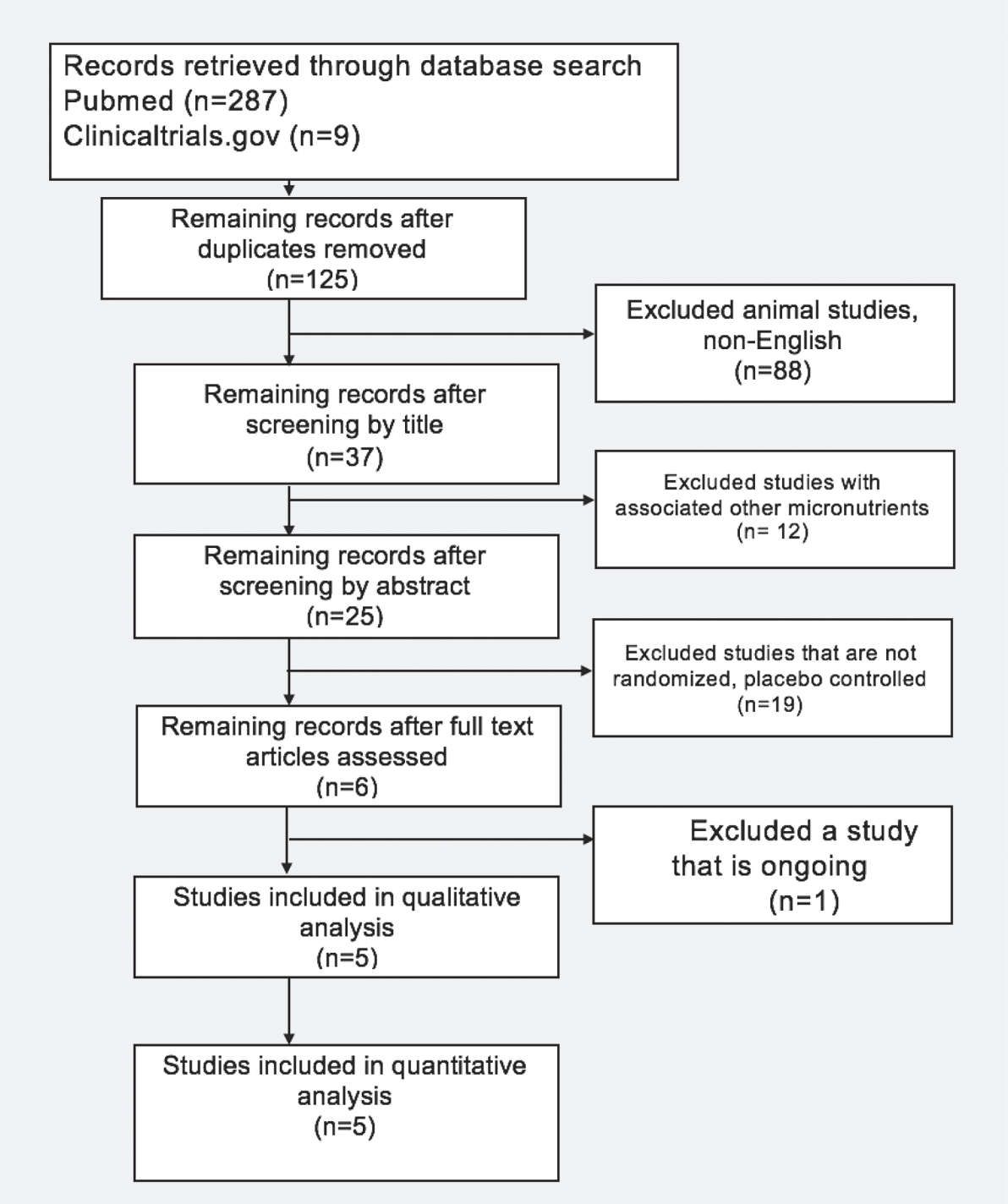

FIGURE 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart

TABLE 1. Description of Characteristic Studies

Study	Method	Intervention Group	N	Baseline EF%	Thiamine Dose	Duration of Intervention	Outcome
Shimon et al,[16] 1995	Randomized, double-blind, placebo-controlled trial	Thiamine supplementation+ optimal medical therapy	27	26 ± 9	200 mg/d IV for 1 wk 200 mg/d oral for 6 wk	49 d	Improved EF
Schoenenberger et al,[15] 2012	Randomized, double-blind, placebo-controlled trial	Thiamine supplementation+ optimal medical therapy	9	29.5 ± 2.4	300 mg/d oral	28 d	Improved EF Improved functional capacity
Sofi et al,[17] 2015	Randomized, double-blind, placebo-controlled trial	Thiamine supplementation+ optimal medical therapy	40	32.81 ± 9.26	100 mg/d oral	30 d	Improved EF Improved functional capacity
Mousavi et al,[18] 2017	Randomized, double-blind, placebo-controlled trial	Thiamine supplementation+ optimal medical therapy	52	32.79 ± 5.26	300 mg/d oral	30 d	No significant change in EF
Iqbal et al,[19] 2019	Randomized, double-blind, placebo-controlled trial	Thiamine supplementation+ optimal medical therapy	50	28.1 ± 6.7	100 mg/d IV for 1 wk 100 mg/d BID for 1 mo	49 d	Improved EF

BID=twice a day; EF=ejection fraction; IV=intravenous.

TABLE 2. Effect of Thiamine on Functional Capacity

Studies	Initial Functional Class (Thiamine)	End-of-Treatment Functional Class (Thiamine)
Shimon et al[16]	NYHA 2.6 ± 0.6	2.2 ± 0.7
Mousavi et al[18]	NYHA 2	2
Iqbal et al[19]	NYHA 2.2 ± 0.4	1.6 ± 0.5
Schoenenberger et al[15]	6MWT 549 ± 31 m	6MWT 624 ± 28 m
Sofi et al[17]	6MWT 263.13 ± 61.49 m	6MWT 318.48 ± 73.23 m

6MWT=6-minute walk test; NYHA=New York Heart Association.

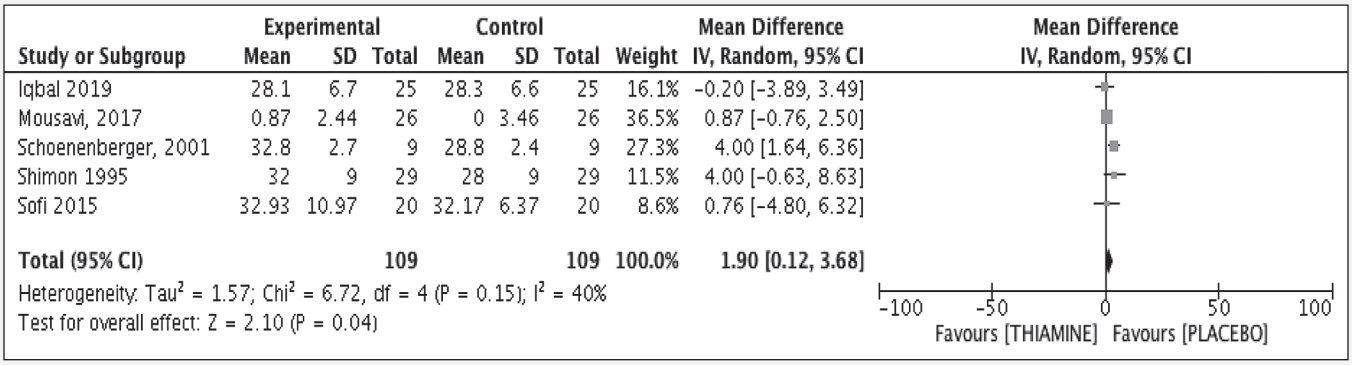

FIGURE 3. Forest plot on the effect of thiamine on left ventricular ejection fraction

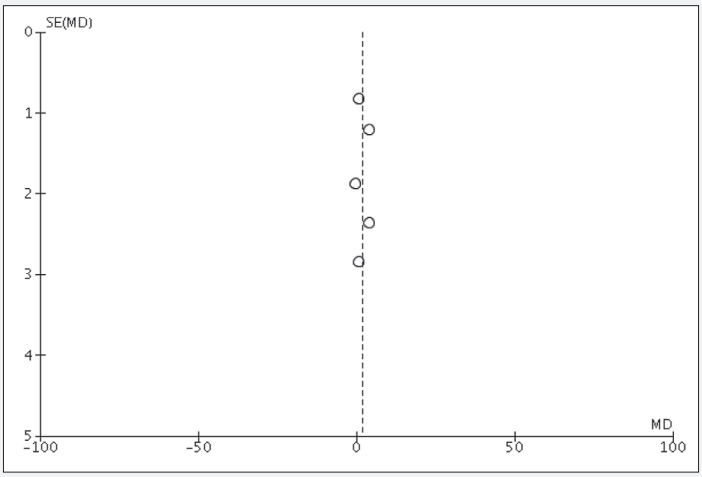

FIGURE 4. Funnel plot

a $P = 0.04$, which is considered statistically significant. The I^2 is 40%, which means that 40% of the variability is due to heterogeneity of studies.

Forest plot on the effect of thiamine supplementation on improvement of LVEF is shown in Figure 3.

DISCUSSION

Thiamine intake is less in heart failure patients because of early satiety due to splanchnic congestion and cardiac cachexia.[20] Some dietary thiamine sources may also be high in sodium content and thus are generally avoided by heart failure patients.[21] In addition, heart failure patients have increased thiamine requirements as a result of the chronic diuretic use, which may promote renal wasting[22,23] (Figure 4).

After the analysis of the combined effects of three studies with 218 subjects, the pooled results showed no significant effect on the LVEF in heart failure patients when given thiamine supplementation with a $P = 0.04$.

This study is limited by a number of factors. The studies were relatively small-scale, with a participant, averaging only to 25 subjects. The administration of thiamine was also varied. In the study by Iqbal et al[19] and Shimon et al,[16] thiamine was given through intravenous route first prior to shifting to oral route, whereas the other studies used only the oral route.[15,16,18,19] The duration of treatment among the studies were also of various range.

CONCLUSION

Based on this limited group of studies, there is insufficient information to suggest that thiamine supplementation has a positive effect on LVEF in heart failure patients. Further large-scale clinical trials are needed to determine the optimum dose, duration, and route of thiamine in patients with heart failure.

RECOMMENDATION

Large-scale, multicenter randomized, placebo-controlled clinical trials should be conducted to obtain stronger statistically significant evidence in the efficacy of thiamine in patients with heart failure. The optimum dose, duration, and route for thiamine to be effective should also be determined.

DEFINITION OF TERMS

Heart failure: a complex clinical syndrome resulting from structural and functional impairment of ventricular filling or ejection of blood.[24]

Heart failure with reduced ejection fraction: baseline ejection fraction less than 40%.[24]

Ejection fraction: the fraction of the end-diastolic volume that is ejected with each beat; that is, it is stroke volume divided by end-diastolic volume.[25]

End-diastolic volume: the volume of blood within a ventricle at the end of diastole is the end-diastolic volume.[25]

End-systolic volume: the volume of blood left in a ventricle at the end of systole (contraction).[25]

Stroke volume: The difference between end-diastolic volume and end-systolic volume.[25]

6MWT: measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. It assesses the submaximal level of functional capacity. Its strongest indication is for measuring the response to medical intervention with moderate to severe heart disease.[17]

Increased left ventricular ejection fraction: increased maximal systolic velocity of myocardial tissue of septal and lateral walls, which correlates well with left ventricular ejection fraction.[18]

Functional Capacity

Functional Capacity	Objective Assessment
Class I. Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	A. No objective evidence of cardiovascular disease
Class II. Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	B. Objective evidence of minimal cardiovascular disease
Class III. Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	C. Objective evidence of moderately severe cardiovascular disease
Class IV. Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	D. Objective evidence of severe cardiovascular disease

Optimal medical therapy: the recommended pharmacologic therapy includes the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, β-blockers, and aldosterone antagonists.[17]

Thiamine supplementation: therapy with oral or intravenous thiamine of at least 100 mg/d.[19]

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