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Effects of Thiamine on Cardiac Function in Patients With Systolic Heart Failure: Systematic Review and Metaanalysis of Randomized, Double-Blind, Placebo-Controlled Trials

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ABSTRACT

Background: Thiamine is an important micronutrient, and thiamine deficiency is prevalent in patients with congestive heart failure.

Methods: Using Ovid MEDLINE, PubMed, and Excepta Medica (Embase), we conducted a systematic review and metaanalysis of randomized, double-blind, placebo-controlled trials of thiamine supplementation in patients with congestive heart failure.

Results: Compared with placebo (2 trials, n=38), thiamine supplementation resulted in a significantly improved net change in left ventricular ejection fraction (LVEF) (3.28%, 95% confidence interval [CI]: 0.64%, 5.93%).

Conclusion: Compared against placebo, thiamine supplementation in 2 randomized, double-blind trials resulted in a significant improvement in net change in LVEF. While further trials are required to establish thiamine's role in patients with systolic heart failure, thiamine may help to improve LVEF in these patients.

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INTRODUCTION

Congestive heart failure (CHF) is a serious public health concern. Approximately 5 million people in the United States have CHF, and more than 550,000 people are diagnosed with this condition each year.[1,2] Although therapies for CHF—including angiotensin-converting enzyme inhibitors, beta-blockers, loop diuretics, and omega-3 fatty acids—have improved morbidity and mortality, mortality rates in patients with CHF remain high.[3]

Loop diuretics have caused thiamine deficiency in animal and human trials, and the prevalence of thiamine deficiency in patients with CHF is 21%-98%.[4-8] A 1995 trial indicated that thiamine supplementation in patients with CHF significantly improved left ventricular ejection fraction (LVEF); resulted in trends for improving left ventricular end-systolic volume (LVESV); and significantly improved New York Heart Association (NYHA) functional class, diuresis, and urinary sodium excretion.[9] Thus, we sought to determine the effects of thiamine in patients with CHF by performing a systematic review and metaanalysis of available studies.

METHODS

We reviewed the available literature according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for conducting systematic reviews of intervention studies.[10]

Data Sources and Searches

We identified studies through searches of the following sources: Ovid MEDLINE (1997-2011), PubMed (1966-2012), and Embase (1997-2011). To identify further potentially relevant studies missed by

Table 1. Characteristics of Trials Included in the Metaanalysis

	Shimon et al[9] 1995	Schoenenberger et al[11] 2012
Patients (n)	29[a]	9
Inclusion Criteria	1. Chronic CHF 2. NYHA class 2 to 4 3. Use of 80 mg/d furosemide for at least 3 months	1. Symptomatic CHF 2. Use of diuretics
Protocol	Random allocation to 1 week of twice daily IV placebo (saline) or 100 mg thiamine HCl. Patients were evaluated at the end of 1 week. After this 1-week intervention, patients in both groups were given 200 mg/d oral thiamine.	Random allocation to 300 mg/d thiamine or placebo for 28 days. Intervention period was followed by a 6-week washout. After the washout, the patients were crossed over to the other group (ie, placebo to thiamine and thiamine to placebo).
Baseline and Ending Blood Pressure (mmHg)	**Baseline placebo:** 121 ± 14/ 73 ± 8 **Baseline thiamine:** 119 ± 26/ 75 ± 15 **Ending:** Unchanged (exact values not specified)	**Baseline for group 1:** 122 ± 18 **Baseline for group 2:** 74 ± 12 **Ending:** Not specified
Baseline and Ending Heart Rate (bpm)	No change between baseline and ending heart rate (exact values not specified)	**Baseline:** 74 ± 14 **Ending:** Not specified
Baseline and Ending Thiamine-Pyrophosphate Effect (%)	**Baseline placebo:** 14.0 ± 10.0 **Baseline thiamine:** 11.7 ± 6.5 **Ending placebo:** No change (exact value not specified) **Ending thiamine:** 5.4 ± 3.2	Did not measure
Baseline and Ending Ejection Fraction (%)	**Baseline placebo:** 26 ± 9 **Baseline thiamine:** 28 ± 11 **Ending placebo:** 28 ± 9 **Ending thiamine:** 32 ± 9	**Baseline placebo:** 29.5 ± 2.5 **Baseline thiamine:** 29.5 ± 2.4 **Ending placebo:** 28.8 ± 2.4 **Ending thiamine:** 32.8 ± 2.7
Follow-up	Patients were evaluated at 1 week after IV intervention and then after 3 and 6 weeks of oral thiamine supplementation.	Patients were evaluated on days 1, 8, 15, and 29 of each treatment period.
HF Etiology	HF due to chronic ischemic heart disease or idiopathic dilated cardiomyopathy	HF due to coronary artery disease, valvular heart disease, hypertensive heart disease, or dilated cardiomyopathy

[a]Thirty patients were randomized in the Shimon et al study, but 29 completed the trial.
CHF, congestive heart failure; IV, intravenous; NYHA, New York Heart Association.

the electronic database search, we manually screened reference lists from identified trials and review articles. Searches were restricted to articles written in the English language and were updated using automated weekly email alerts until December 2012.

Study Selection

We selected studies for inclusion on the basis of the following criteria:

- Study design: Randomized, double-blind, placebo-controlled
- Types of participants: Systolic HF (LVEF <45%)
- Intervention: Thiamine
- Comparator: Placebo
- Outcomes: LVEF

We excluded studies that did not report LVEF. Two reviewers (JJD and TH) independently screened the titles and abstracts of studies identified by the search strategy and discarded clearly irrelevant studies.

Data Extraction

The following data elements were extracted from each study: the number of patients per arm; the nature of the intervention; patient inclusion criteria, baseline and follow-up blood pressure, heart rate,

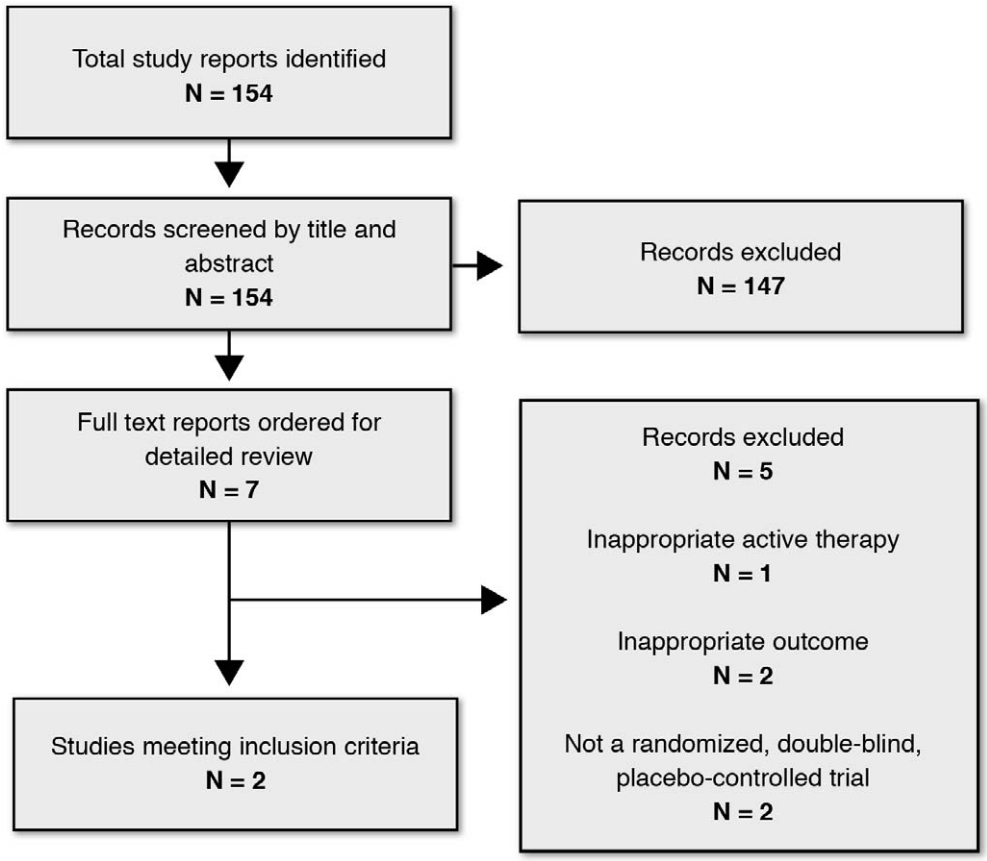

Figure 1. Process for selecting trials included in this metaanalysis.

thiamine-pyrophosphate effect, and LVEF; details of follow-up, and HF etiology (Table 1).

Data Synthesis and Analysis

The mean net change in LVEF was calculated by subtracting the mean change in the placebo group from the mean change in the thiamine group. Statistical heterogeneity across trials was estimated using Q test and I^2 statistic.[12] Specifically, $P<0.05$ in Q test indicates the presence of heterogeneity; $I^2<30\%$ denotes low heterogeneity, $I^2=30$-50% represents moderate heterogeneity, and $I^2>50\%$ denotes substantial heterogeneity.[13] Analyses were conducted using Stata, version 10 (StataCorp LP, College Station, TX).

RESULTS

Identification and Selection of Studies

The literature search yielded 154 titles, and we reviewed 7 of the 154 on the basis of the inclusion criteria (Figure 1). Of these 7, 2 studies were deemed eligible for inclusion.[9,11] Table 1 summarizes the characteristics of the included studies, and Table 2 lists the excluded studies and the reasons for their exclusion.

Characteristics of Included Studies

The included trials were randomized double-blind studies of thiamine supplementation compared to placebo in systolic HF patients. The trials enrolled a mean of 19 patients with a mean follow-up of 6 weeks.

Study Outcomes

In the study by Schoenenberger and colleagues (n=9), patients who took thiamine had 3.30% (95% confidence interval [CI]: 0.63%, 5.97%) greater LVEF compared to those on placebo.[11] Likewise, Shimon et al reported that thiamine resulted in 2.20% greater LVEF than the placebo group (n=29), although the extra improvement was not significant (95% CI: −18.97, 23.37%).[9] In our metaanalysis, thiamine supplementation resulted in a significantly improved net change in LVEF (3.28%, 95% CI: 0.64%, 5.93%) compared with placebo (2 trials; n=38; Figure 2). There was no heterogeneity in the results ($P=0.92$; $I^2=0.0\%$).

Table 2. Details of Studies Excluded From the Metaanalysis

Reason for Exclusion	Study Citation
Inappropriate Active Therapy	Witte KK, Nikitin NP, Parker AC, et al. The effect of micronutrient supplementation on quality-of-life and left ventricular function in elderly patients with chronic heart failure. *Eur Heart J*. 2005 Nov;26(21):2238-2244.
Inappropriate Outcome	Freye E, Hartung E. The potential use of thiamine in patients with cardiac insufficiency. *Acta Vitaminol Enzymol*. 1982;4(4):285-290.
	Smithline HA. Thiamine for the treatment of acute decompensated heart failure. *Am J Emerg Med*. 2007 Jan;25(1):124-126.
Not a Randomized, Double-Blind, Placebo-Controlled Trial	Mendoza CE, Rodriguez F, Rosenberg DG. Reversal of refractory congestive heart failure after thiamine supplementation: report of a case and review of literature. *J Cardiovasc Pharmacol Ther*. 2003 Dec;8(4):313-316.
	Seligmann H, Halkin H, Rauchfleisch S, et al. Thiamine deficiency in patients with congestive heart failure receiving long-term furosemide therapy: a pilot study. *Am J Med*. 1991 Aug;91(2):151-155.

DISCUSSION

The preferential improvement in LVEF with thiamine supplementation in patients with systolic HF may be a result of thiamine's direct action on cardiomyocytes (improved energy production and thus improved cardiac function) or may be attributable to a diuretic effect.[9,14] A deterioration of LVEF is a powerful predictor of worsening CHF and death.[15] Thus, it is possible that thiamine may even confer a reduction in all-cause mortality in patients with systolic HF through an improvement in LVEF.[5,9,11] Mortality events were low in the study by Shimon et al: 0 deaths in the thiamine group vs 1 death in the placebo group (ie, 1-week treatment groups).[9] Moreover, the Shimon et al study showed improvement in NYHA functional class, LVESV, diuresis, and urinary sodium excretion with the use of thiamine supplementation compared to placebo.[9]

The findings of this metaanalysis suggest that thiamine supplementation may benefit patients with systolic HF who are also receiving loop diuretics. Although current CHF guidelines do not recommend thiamine supplementation, the evidence discussed above seems to indicate that a large, multicenter trial should be performed to verify the benefit of thiamine in systolic HF patients.[5,9,11,16,17]

The prevalence of thiamine deficiency in HF patients ranges from 21%-98%.[18] Several risk factors can contribute to thiamine deficiency in patients with and without heart failure such as inadequate dietary intake, excess alcohol ingestion, malabsorption syndromes, and medications (such as diuretics, phenytoin, penicillins, cephalosporins, aminoglycosides, tetracyclines, fluoroquinolones, sulfonamides, and trimethoprim).[19] Comorbid conditions such as infection, trauma, surgery, cancer, fever, and persistent diarrhea and vomiting can also contribute to thiamine deficiency.[19]

Benefits of thiamine supplementation in patients with HF include improvements in end-systolic volume and NYHA functional class.[9] Even patients with mild to moderate HF have shown significant improvements in LVEF and right ventricular area.[11] Additionally, thiamine supplementation in HF patients has been shown to improve blood pressure, urine output, and functional capacity along with the LVEF improvement.[5] Thus, thiamine supplementation may offer benefits beyond improvements in LVEF in patients with HF.

Some important potential study limitations should be considered. First, although the trials included in

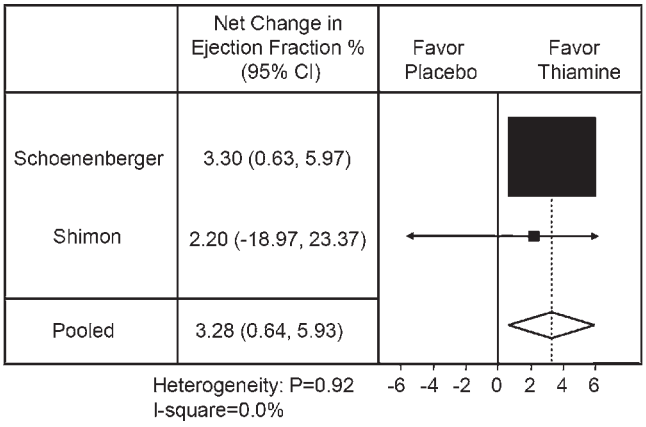

Figure 2. Forest plot of net change in ejection fraction: thiamine vs placebo. CI, confidence interval.

our metaanalysis were randomized, double blind, and placebo controlled, they included a small number of patients. However, comparing LVEF between thiamine and placebo showed no heterogeneity between trials (I^2=0%). Also, as in most such metaanalyses, various dosages (200-300 mg/d) and formulations (intravenous and by mouth) were used, as typically occurs in clinical situations.

Despite these potential study limitations, we believe that the overall results of this metaanalysis support the use of thiamine in select systolic HF patients, especially those who are on loop diuretics (higher risk of thiamine deficiency) or who are symptomatic despite optimal medical therapy. Certainly, a larger, randomized, double-blind, placebo-controlled trial should be performed to confirm the results of this metaanalysis, as well as to assess thiamine's potential impact on major cardiovascular events, including mortality, in patients with systolic HF.

CONCLUSION

Compared against placebo, thiamine supplementation in 2 randomized, double-blind, placebo-controlled trials resulted in a significantly improved net change in LVEF. Further trials are required to establish thiamine's role in patients with systolic HF.

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