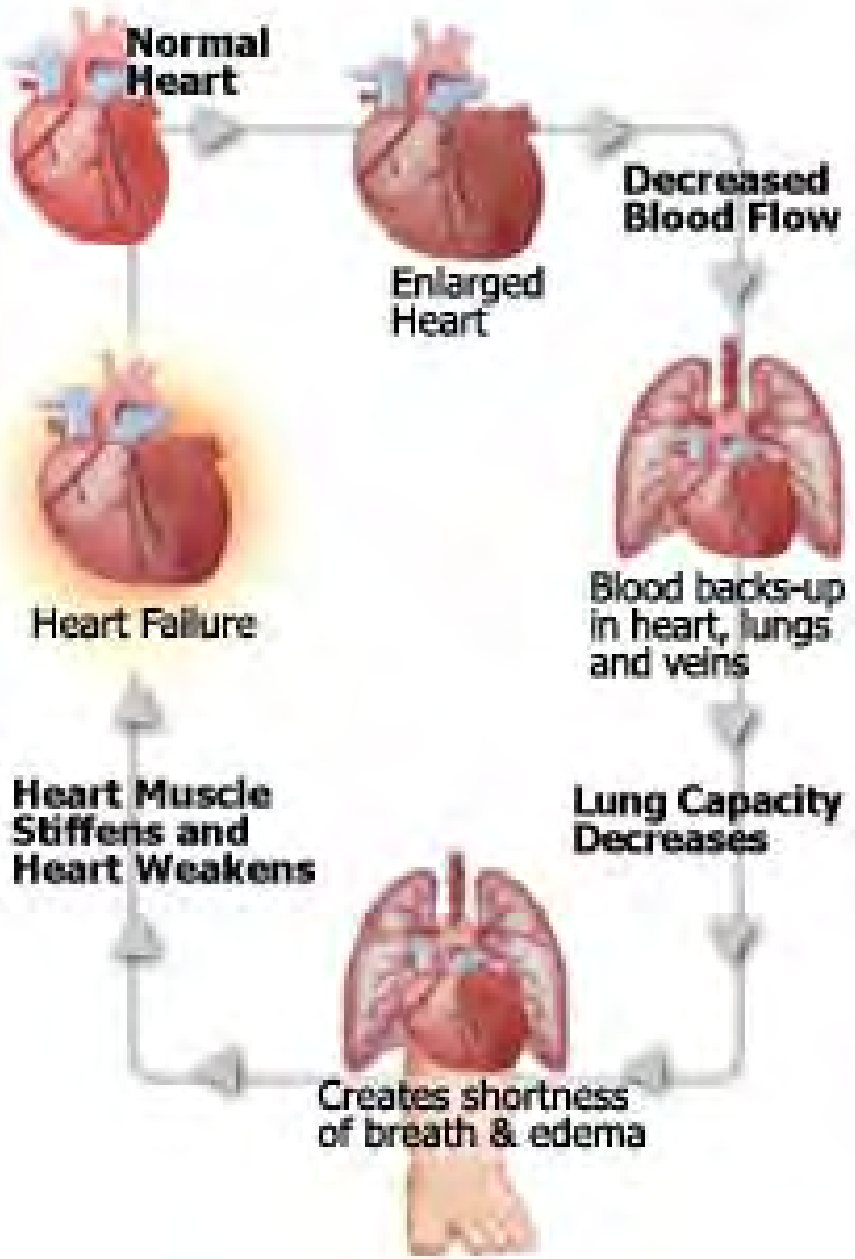
Leading with Innovation
Serving with Compassion

ST. MICHAEL'S HOSPITAL
A teaching hospital affiliated with the University of Toronto

PREVALENCE OF THIAMIN DEFICIENCY IN HOSPITALIZED PATIENTS WITH CONGESTIVE HEART FAILURE

Divisions of Cardiology, Cardiovascular Surgery and Nutrition, St. Michael's Hospital, The University Health Network, and Department of Nutritional Sciences, University of Toronto, Toronto, Ontario

Congestive Heart Failure



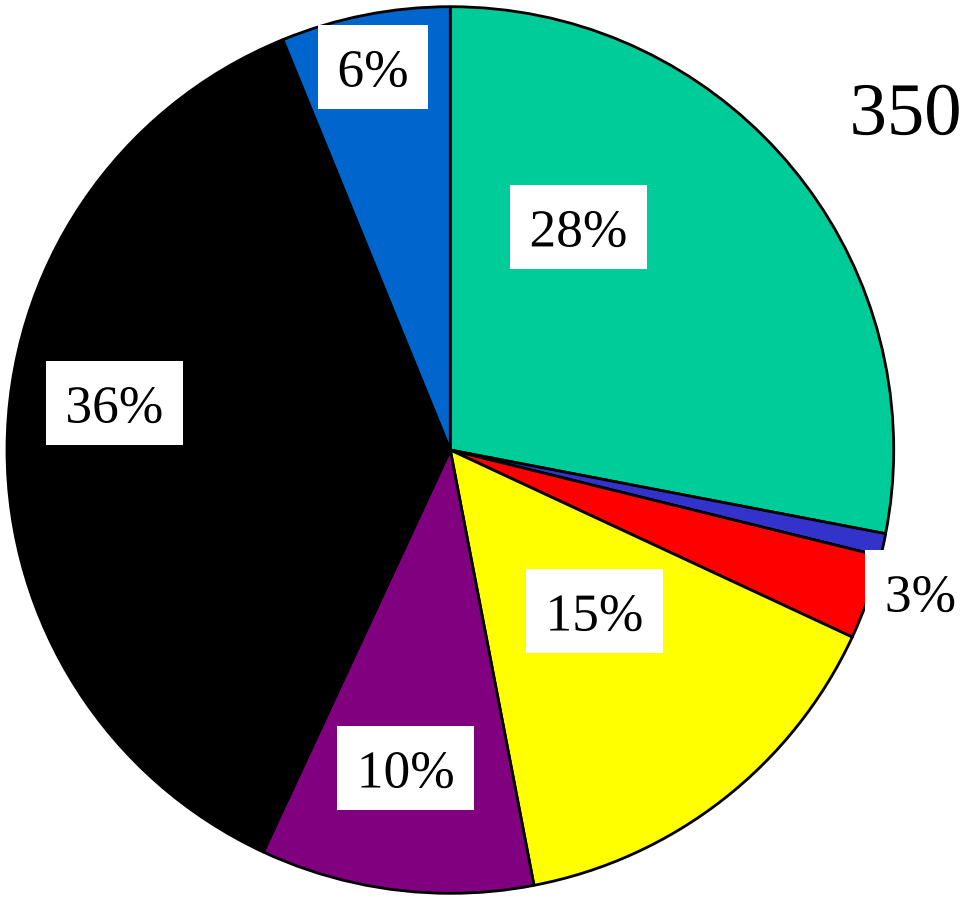
What are the Main Causes of Heart Failure?

- A viral infection of the heart
- Myocardial infarction (heart attack)
- Chronic high blood pressure
- A heart valve that is not working properly
- Alcohol abuse or other drugs
- Congenital defects

Symptoms of Heart Failure

- Salt and water retention
- Shortness of breath – reduced capacity
- Swelling of the ankles
- Weight gain
- Fatigue
- Loss of appetite – bloated feeling
- Nausea/ vomiting

Health Burden of Heart Failure



350,000 Canadians

- **cancer**
- **diabetes**
- **respiratory**
- **accidents/violence**
- **infectious disease**
- **other**
- **cardiovascular**

Heart and Stroke Foundation of Canada, 2003

Management of Heart Failure

- Pharmacologic

Beta blockade, ACE inhibitors, inotropes, calcium channel blockers, statins and DIURETICS

- Nutritional

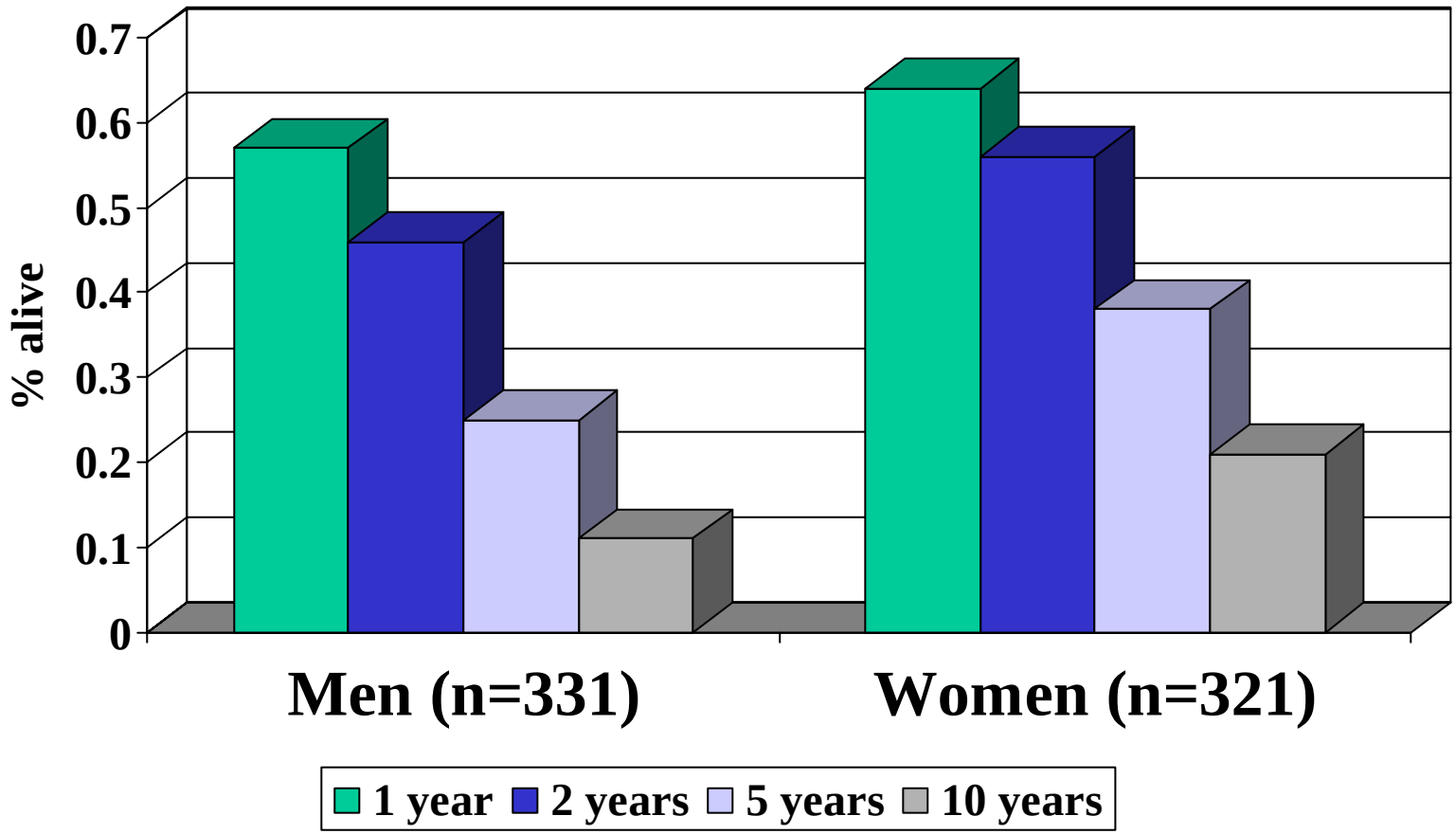
Sodium and fluid restriction, potassium balance, cholesterol reduction and heart healthy eating

- Lifestyle

Smoking and exercise

- Dismal Prognosis

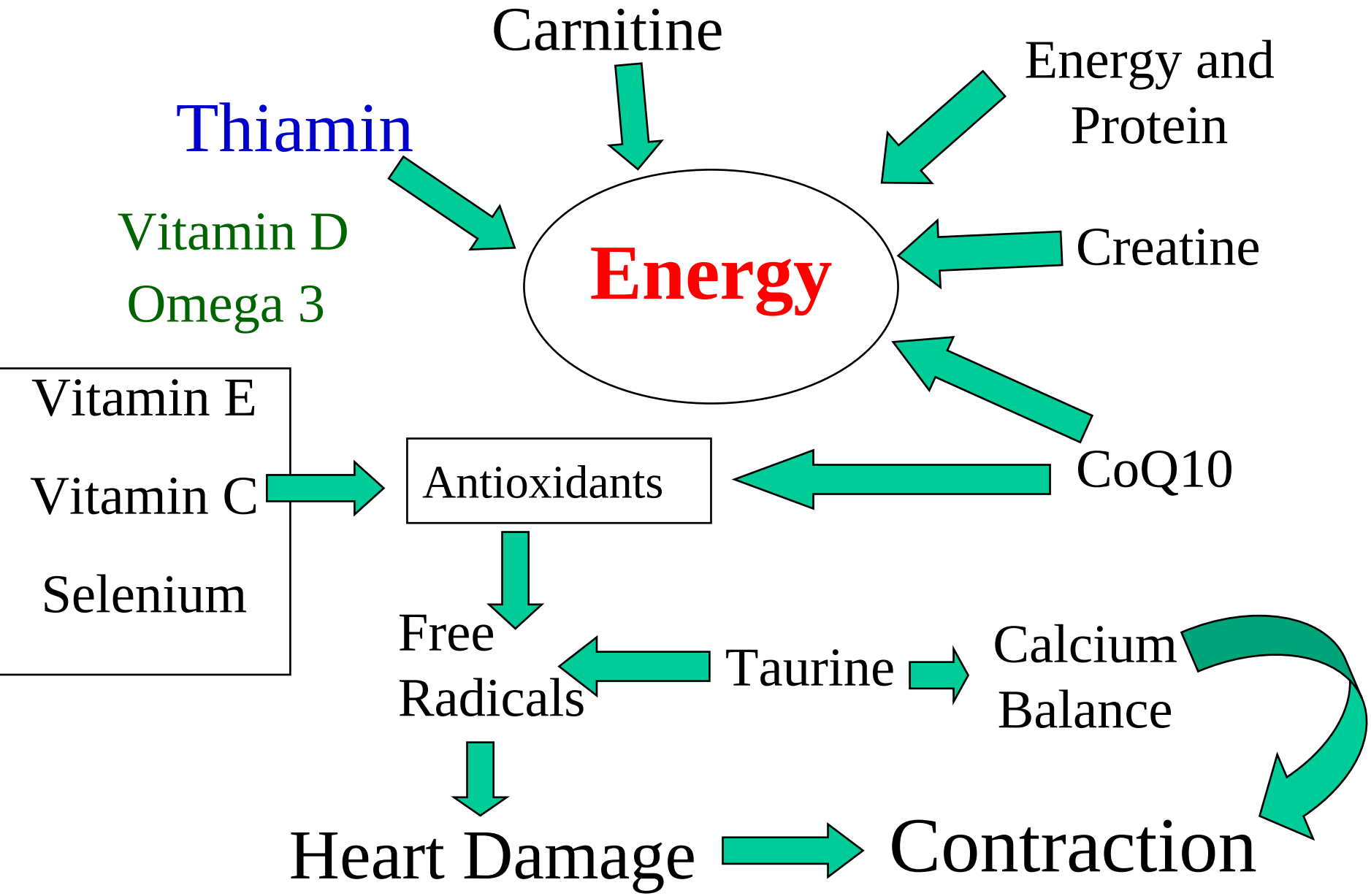
Overall Survival after CHF as Estimated using Kaplan-Meier Methods



Ho et al. JACC 1993

The race continues for new, alternative and complementary strategies

New Paradigm of Nutritional Care



Thiamin Background

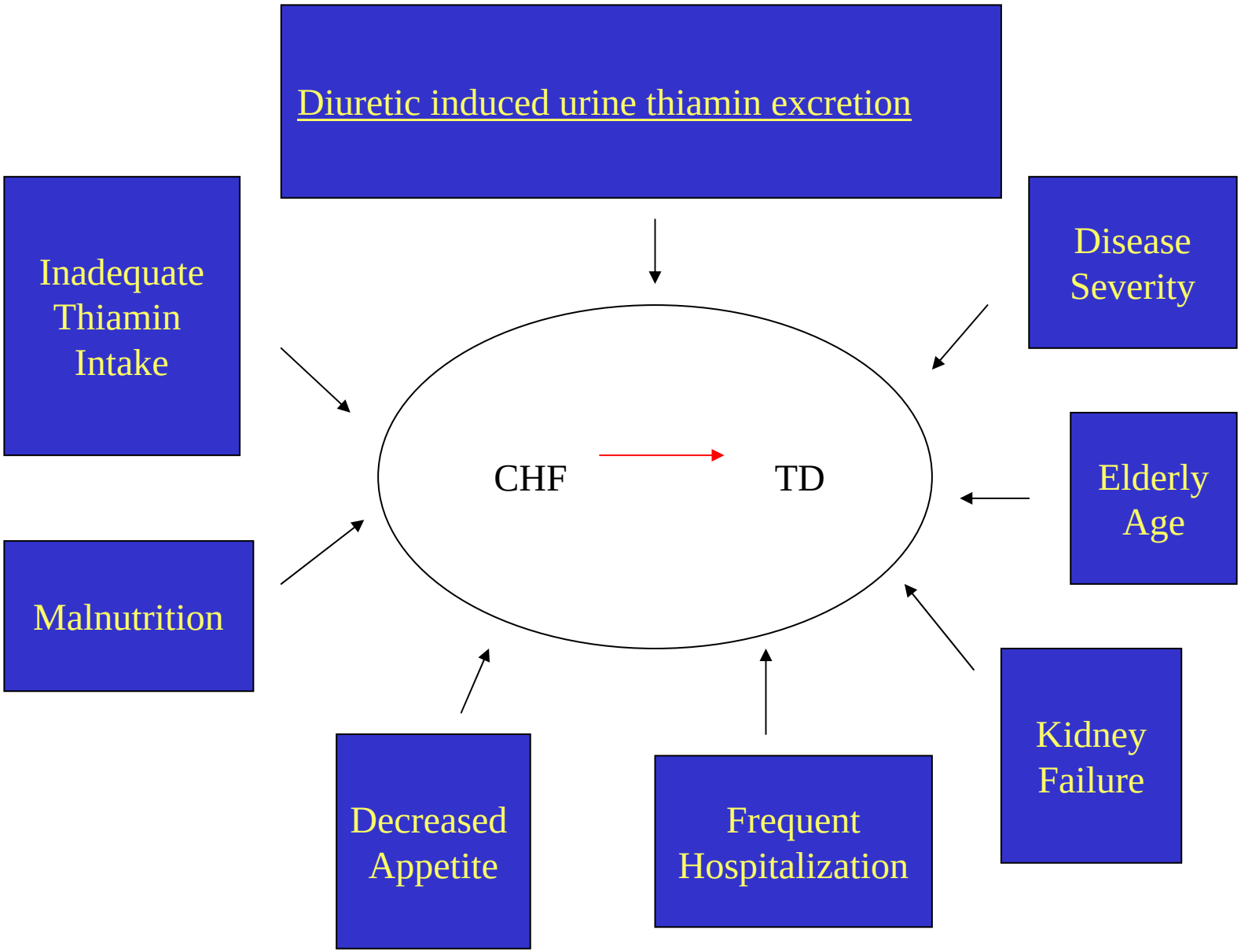
- Thiamin is a water soluble vitamin – B vitamin.

  It is not stored in the body and is excreted in the urine.

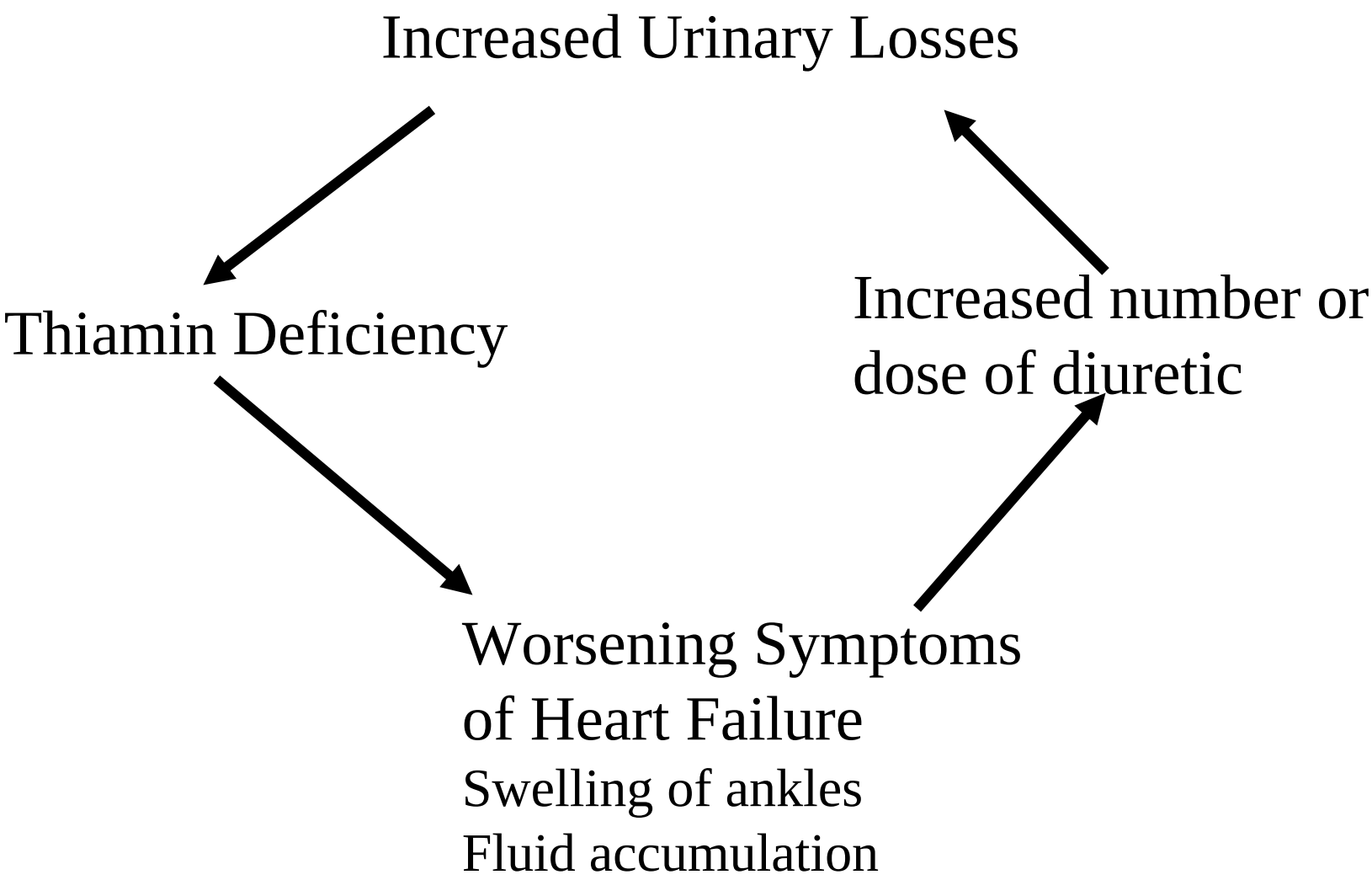
- Thiamin (TPP) is a coenzyme in carbohydrate metabolism - production of ATP for cellular energy.

- Thiamin deficiency manifests as symptoms of CHF (wet beri-beri).

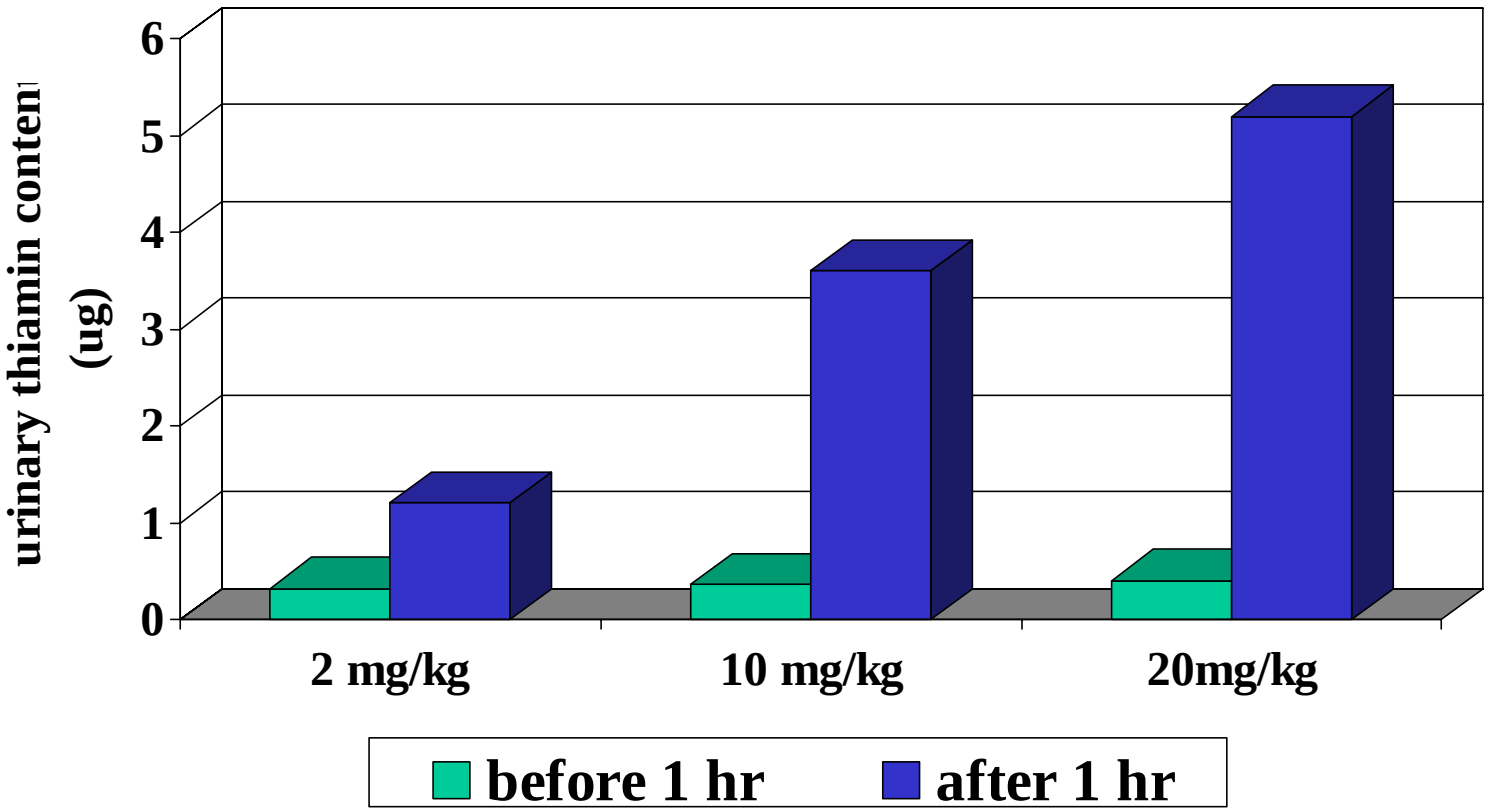
Thiamin Deficiency in Heart Failure



Proposed Vicious Cycle of Deficiency



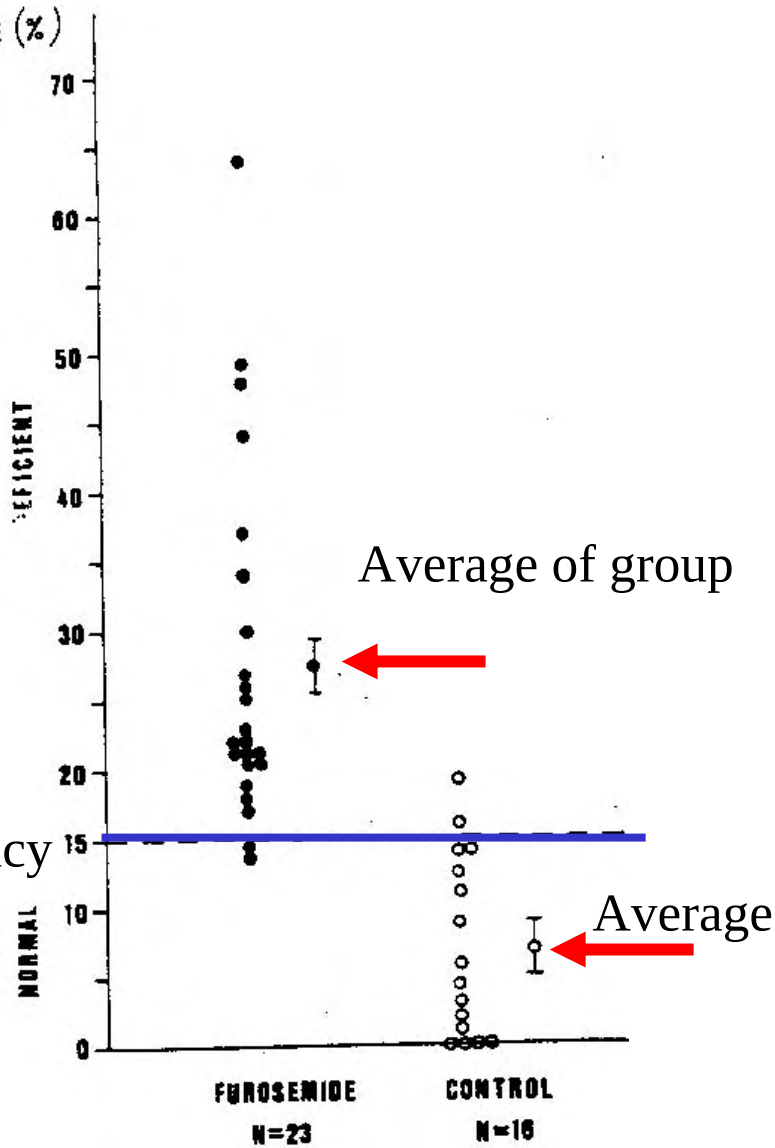
Changes in Urinary Thiamin Content before and after treatment with Furosemide



Yui et al. Cardiovasc Res 1980

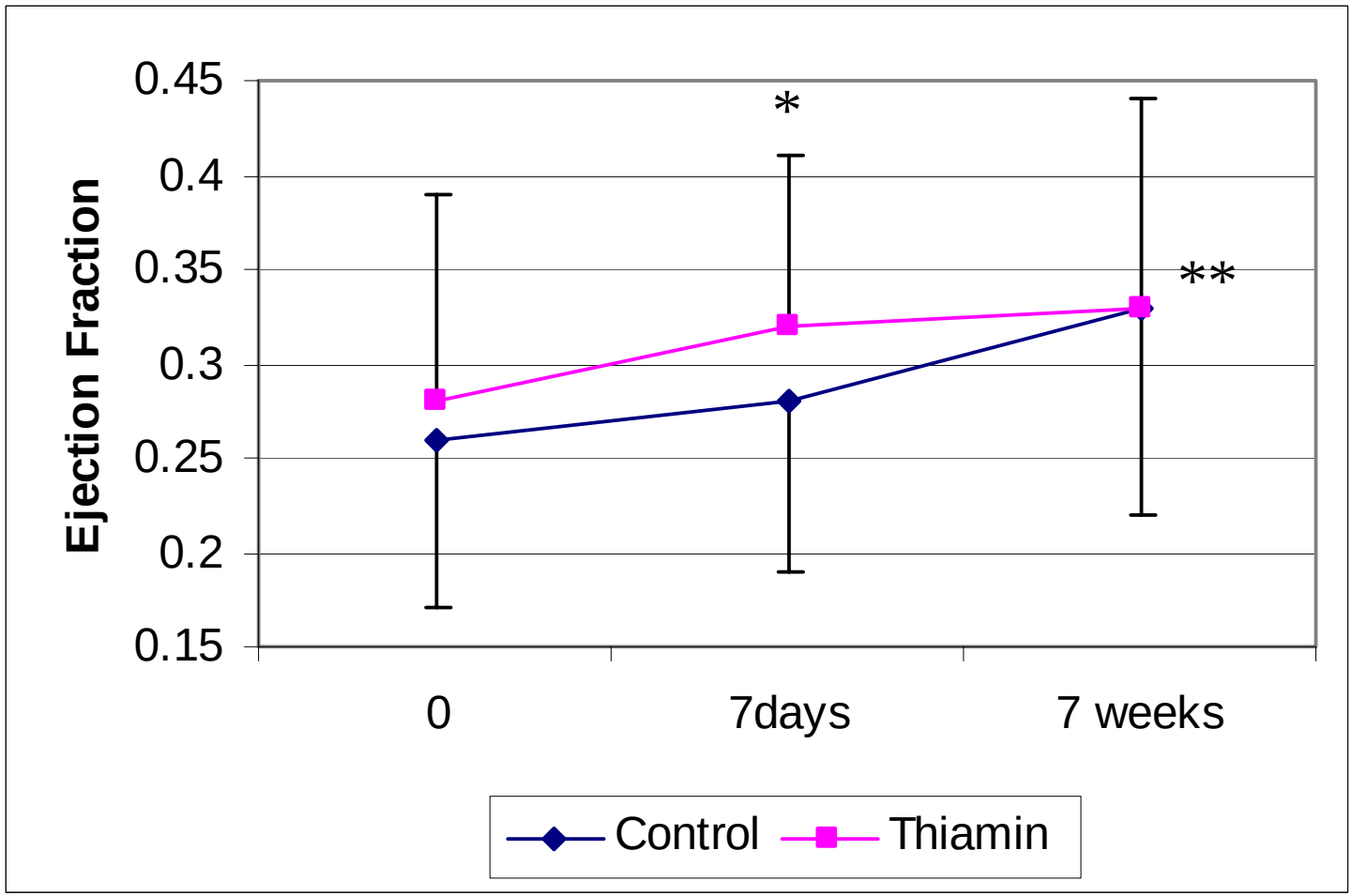
Thiamine Status of Patients with Heart Failure

21/23 deficient



Seligmann Am J Medicine 1991

The Effect of Thiamin Supplementation on Heart Function



* p<0.05 vs baseline
** p< 0.01 vs baseline

Shimon et al 1994 Am J Med

OBJECTIVES

1. To determine the prevalence of TD in a large cross-section of hospitalized CHF patients.

2. To investigate the influence of age, sex, diuretics, urinary thiamin excretion, CHF disease severity, hospitalization, thiamin intake, appetite, malnutrition, decreased renal function, and diabetes on the development of TD.

METHODS: CHF PATIENTS

- 100 CHF patients admitted to St. Michael's Hospital (April 2001-June 2002).
- 50 age and sex matched healthy control subjects.
- TD was defined as erythrocyte TPP < 78 ng/mL packed cells.
- Approval for this study was obtained from SMH Research Ethics Board.

Patients—Selection Criteria

Inclusion Criteria:

Patients admitted to the cardiology ward or coronary care unit at SMH with a primary diagnosis of CHF

Patients– Exclusion Criteria

- Exclusion Criteria:
  - High-dose thiamin supplementation (200mg/day) for alcohol abuse
  - Experimental medication
  - Inability to give informed consent (because of dementia or inability to speak English)
  - Short anticipated hospital stay

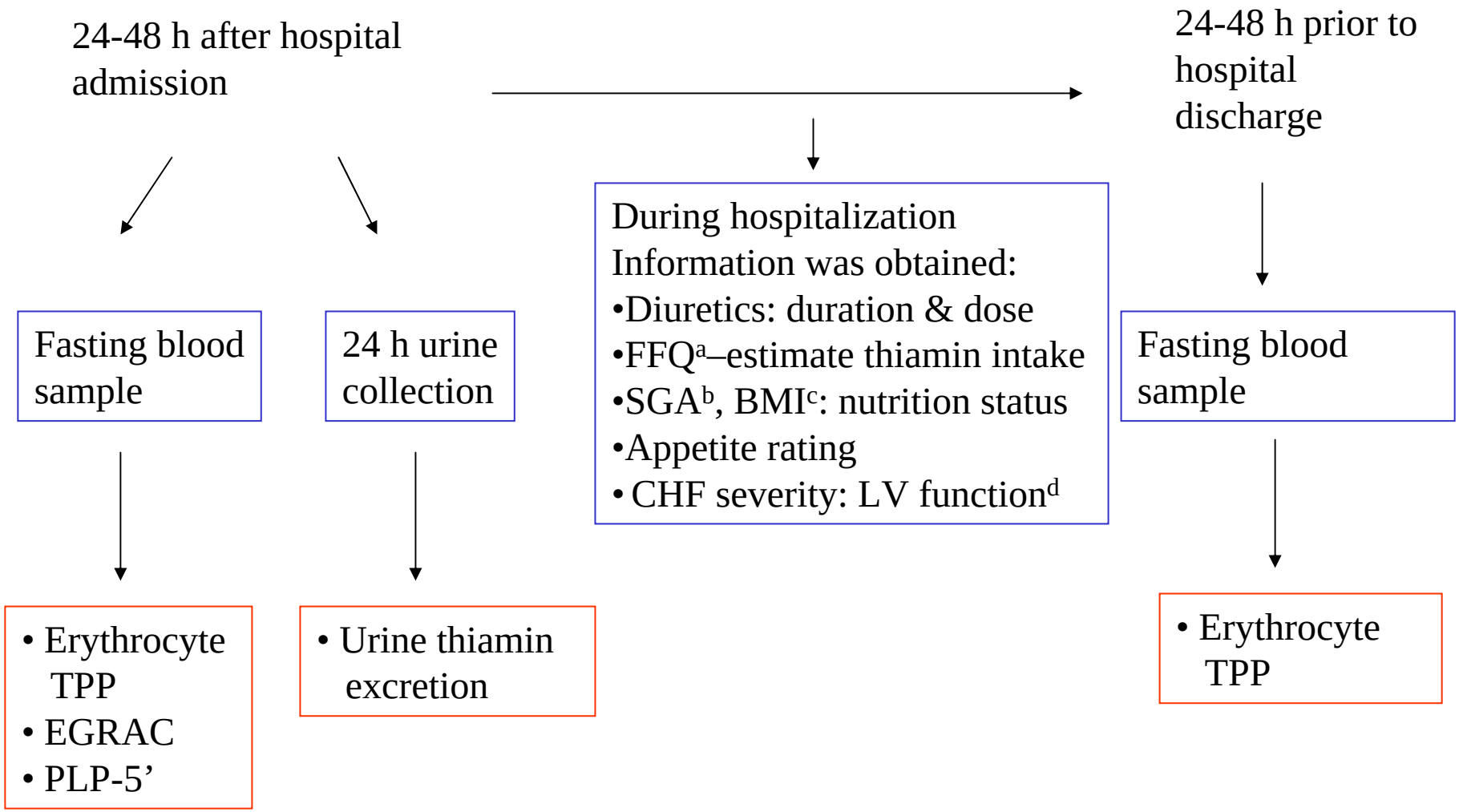
Healthy Controls

- Inclusion Criteria:
  - Age-matched to patients within 5 years

- Exclusion Criteria:
  - Any known conditions affecting thiamin status
  - Use of thiamin-containing supplements.

Spouses, staff members, patients undergoing elective cardiac procedures, cardiac rehab patients

STUDY PROCEDURES FOR CHF PATIENTS



[a] FFQ, food frequency questionnaire. [b]SGA, subjective global assessment. [c]BMI, body mass index.
[d]LV, left ventricle function.
Study procedures for control subjects included age and sex matching to CHF patients and obtaining a fasting blood sample for determination of erythrocyte TPP concentration.

Characteristics of CHF patients and control subjects

Characteristics	CHF (n = 100)	Control (n = 50)	P Value
Gender Male/Female	58 (58%) / 42 (42%)	24 (48%) / 26 (52%)	0.246[a]
Age [mean(SD)]	67.1 (10.1) y	61.1 (11.1) y	**0.001[b]**
BMI [mean(SD)]	27.3 (5.5) kg/m^2	27.2 (4.7) kg/m^2	0.762[b]
Thiamin-containing Supplement use	21 (21%)	NA	
Other supplement use	41 (41%)	9 (18%)	**0.001[c]**

[a] Pearson Chi-Square, [b] Mann- Whitney, [c] Fisher's Exact

Cardiac disease characteristics of CHF patients

Characteristics	n	Characteristics	n
CHF Etiology		**NYHA Classification**	
Coronary artery disease	40	Class I	6
Valve disease	18	Class II	18
Hypertension	3	Class III	43
CAD & Valve	11	Class IV	32
Cardiomyopathy	28		
Left Ventricle Function		**Diuretic Use at Admission**	
Grade I	21	Furosemide	80
Grade II	26	Spironolactone	16
Grade III	27	Metolazone	7
Grade IV	26	Multiple Diuretics	26

Prevalence of TD in CHF patients and control subjects

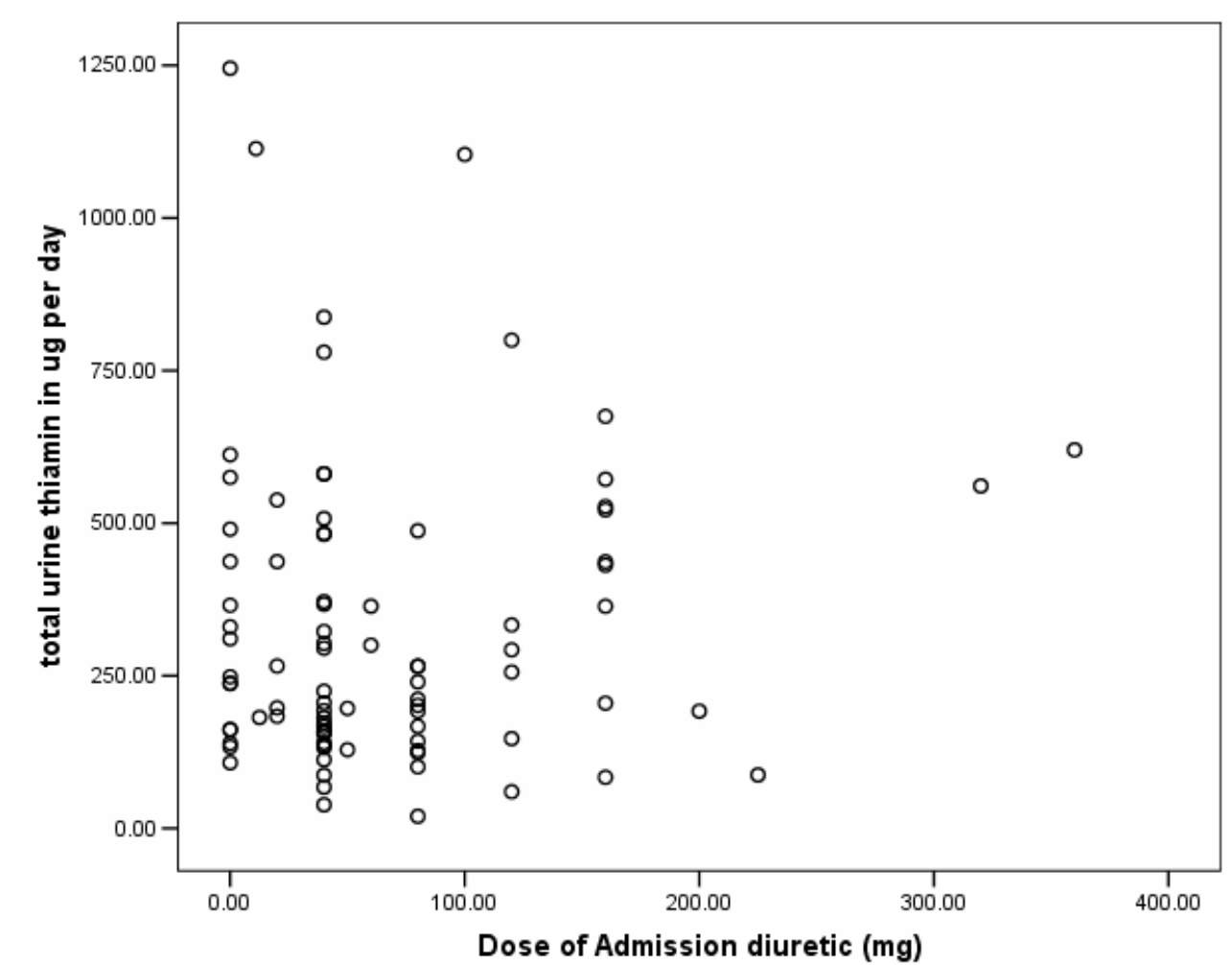
CHF (n = 100)	Control (n = 49)	P[a]
33.0 %	12.2 %	**0.007***

[a] Pearson Chi-Square, * Significant at P < 0.05

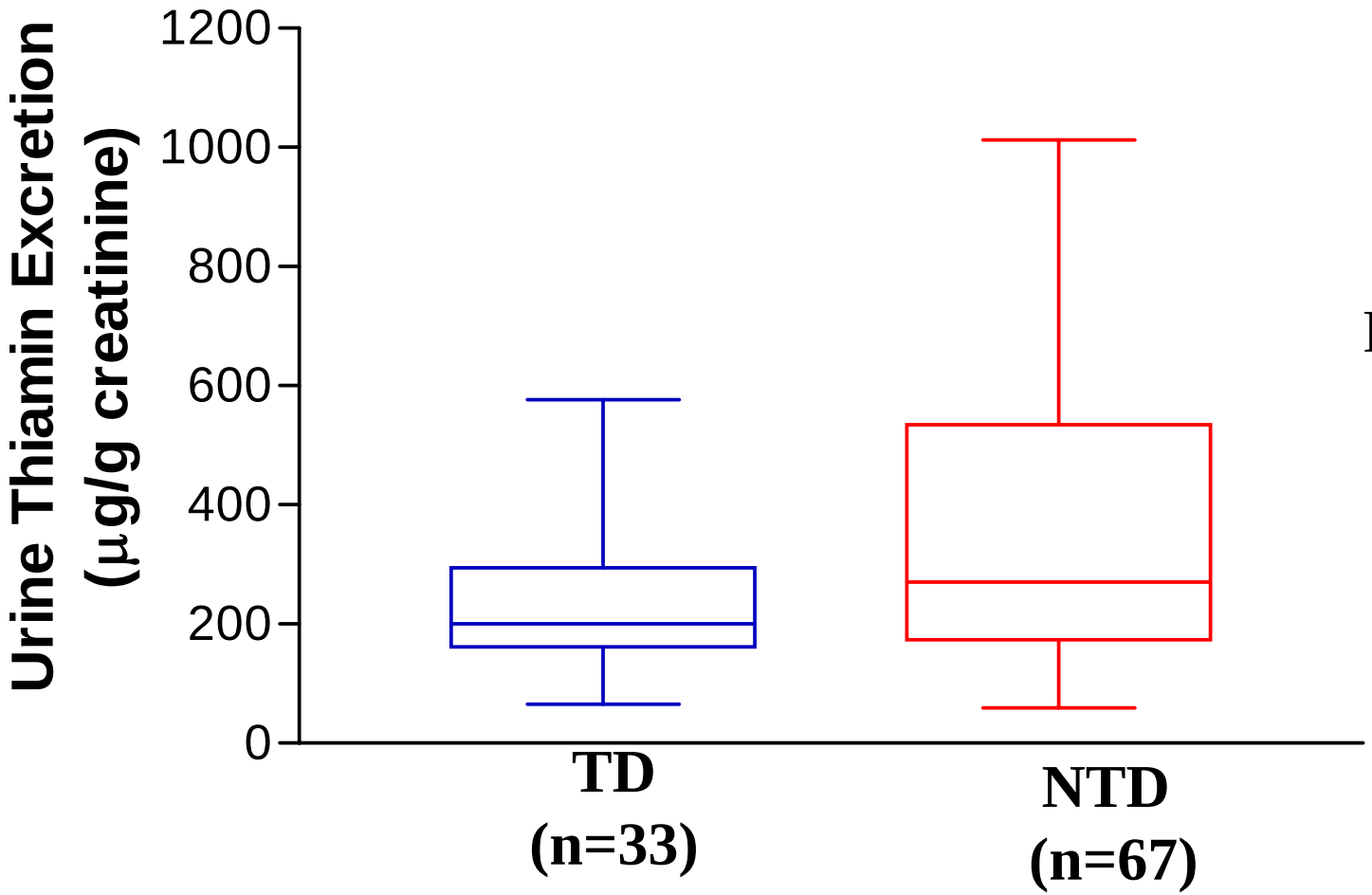
Factors Related to the Presence of Thiamin Deficiency

Which are predictive of those at risk?

Relationship Between Diuretic Dose and Urine Thiamin Loss

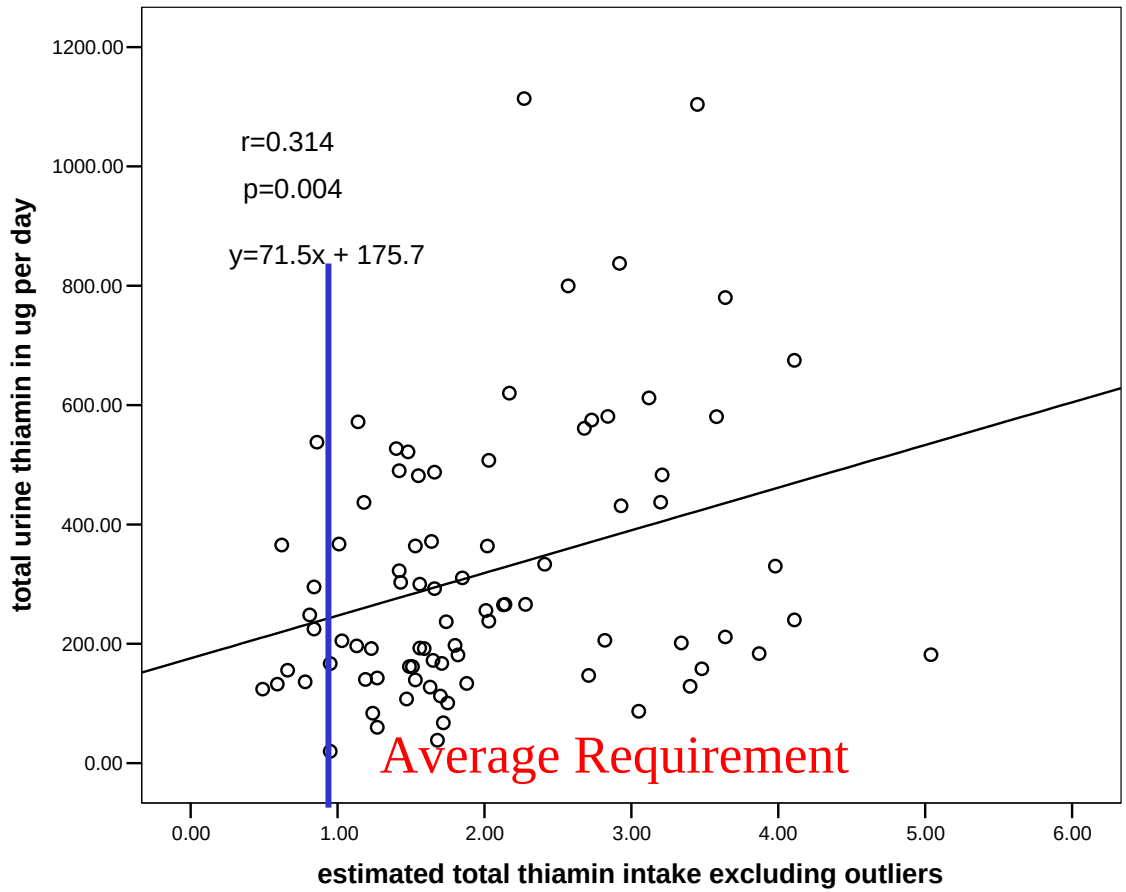


Relationship between TD and urine thiamin excretion in CHF patients

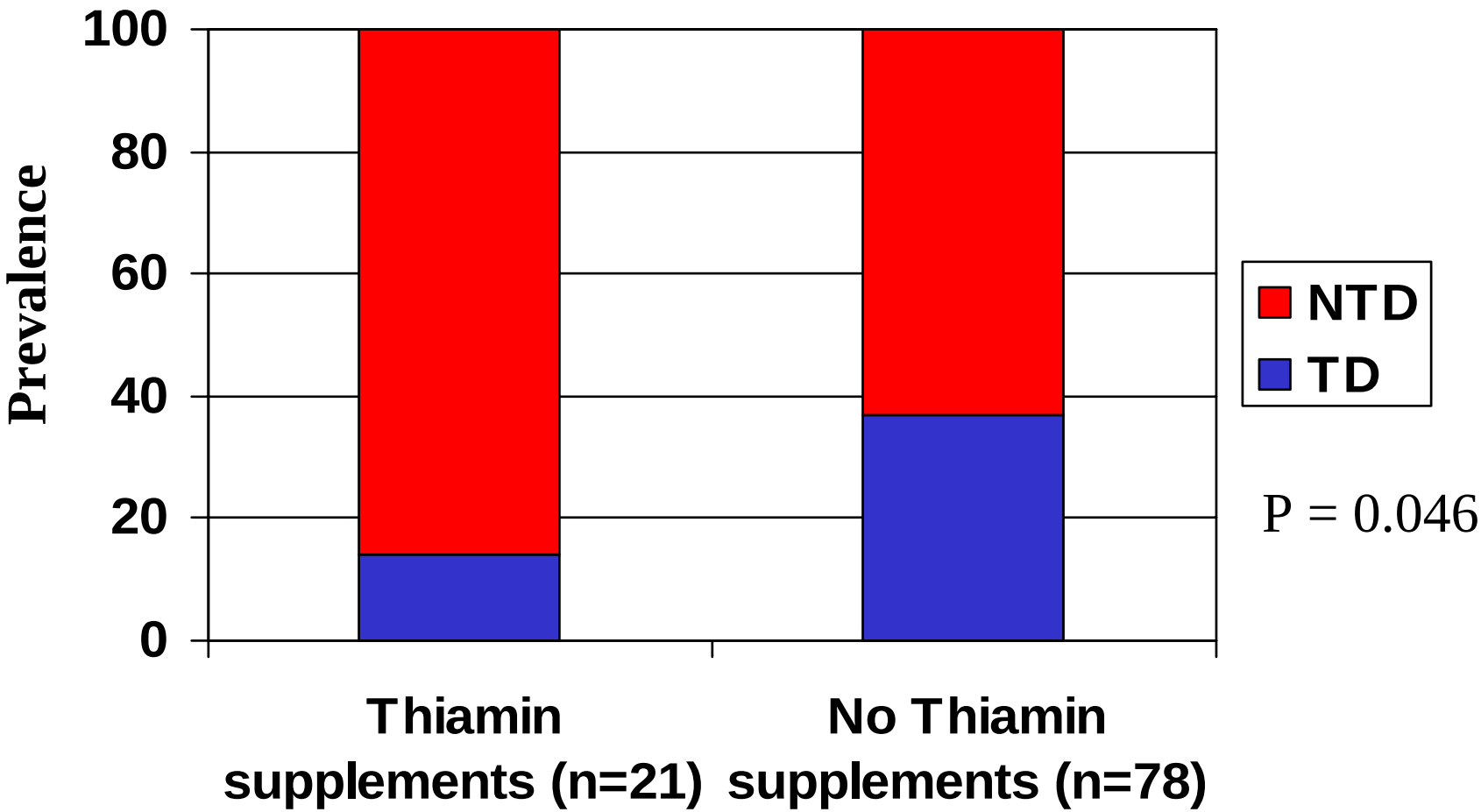


Mann-Whitney Test

Relationship between Thiamin Intake and Loss



Relationship between TD and thiamin supplement use in CHF patients



Pearson Chi-Square Test

Factors not associated with Thiamin Deficiency in CHF patients

- Age
- Gender
- Hospitalization
- Diabetes
- Furosemide use
- Metolazone use
- multiple diuretics

Factors associated with thiamin deficiency

- Having low urinary thiamin losses
- Not using thiamin containing supplements
- Having good kidney function
- Worsening heart failure
- Having a poor appetite
- Having a thiamin intake that is less than the average requirement
- Having mild or moderate malnutrition

CHF and B Vitamins

- We have demonstrated that 33% of CHF patients at SMH were thiamin deficient (*Hanninen et al, 2005*).

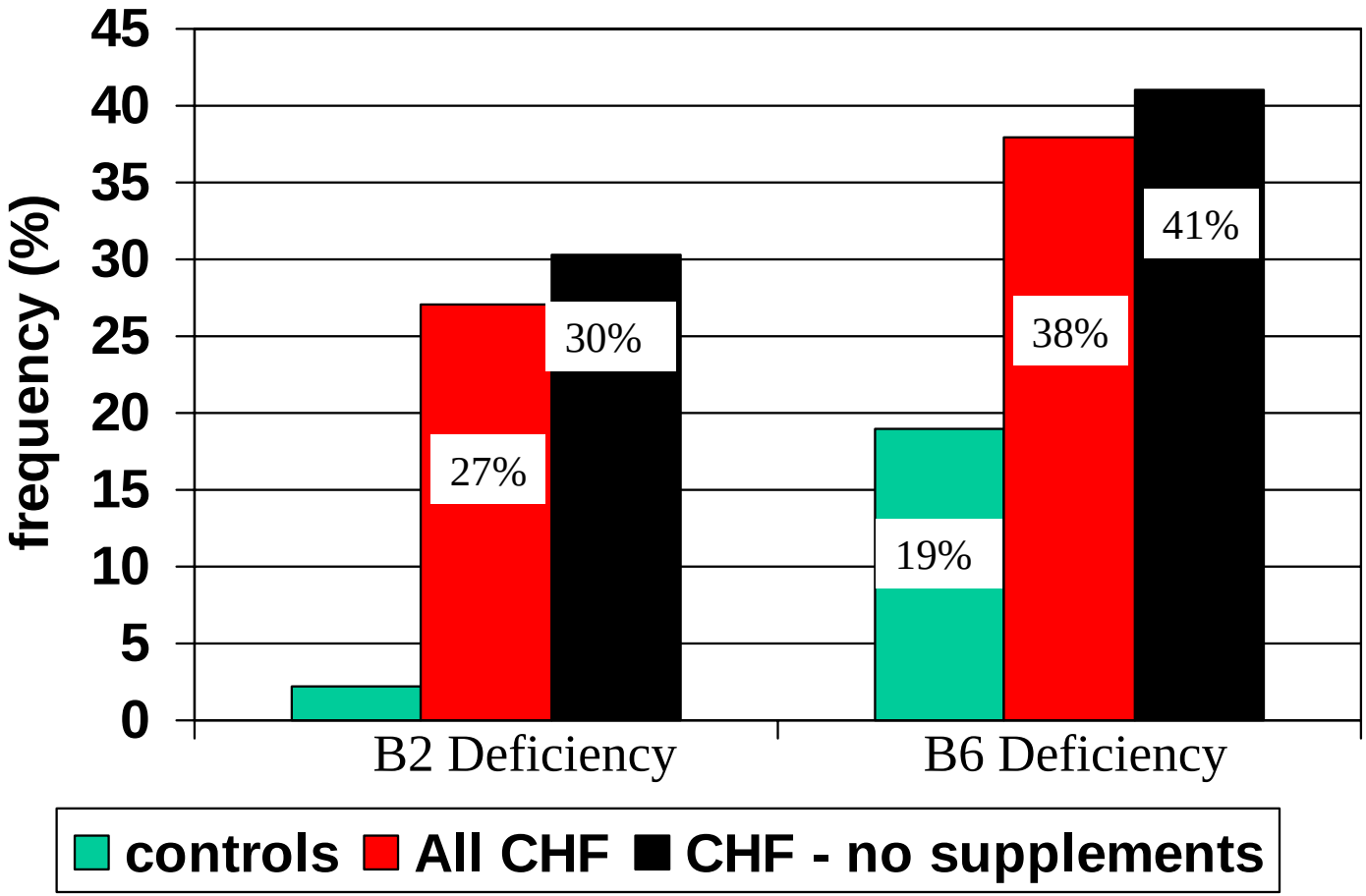
- Riboflavin and vitamin B6 are water-soluble with no appreciable tissue storage.

- Therefore, as an adjunct study, we investigated the status of riboflavin and vitamin B6 in the same CHF patients

Role of Riboflavin (B2) and B6 in Metabolism

- Important factor in fatty acid oxidation and glucose metabolism.
- B2 and B6 participate in the production of energy
- B2 required to form active B6
- B6 is needed for red blood cell formation (heme) and plays a role in homocysteine metabolism

The Prevalence of B6 and B2 Deficiency in CHF Patients and Controls



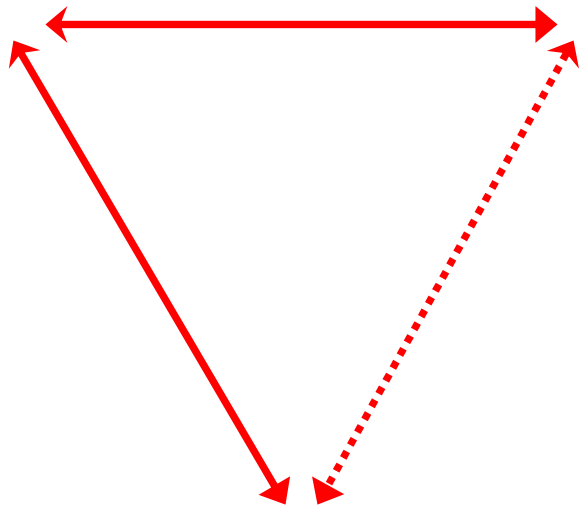
Discussion: Inter-relationships Between B Vitamin Deficiencies

•B6 deficiency significantly related to riboflavin deficiency

•plasma B6 significantly correlated with total riboflavin intake

Riboflavin

Vitamin B6



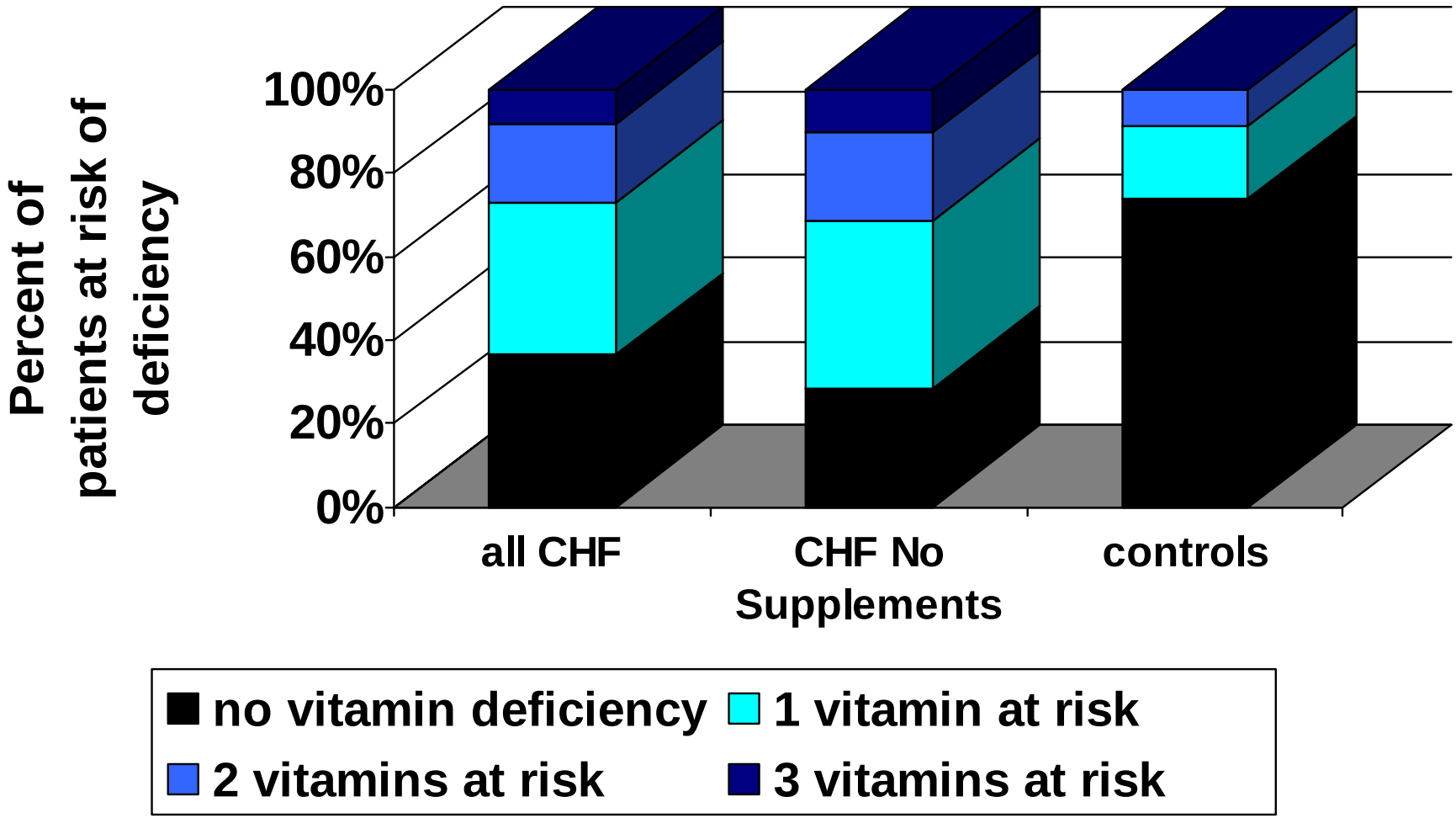
Thiamin

•riboflavin deficiency was significantly related to thiamin deficiency

•EGRAC correlated significantly with thiamin intake even when supplement users excluded

•no relationship between B6 deficiency and thiamin deficiency

The Overall Prevalence of B vitamin Deficiency in CHF Patients



CONCLUSIONS

- The prevalence of B vitamin deficiency in our hospitalized CHF patients is high (71%).

- Development of deficiency is complex – not simply related to the dose or duration of furosemide (diuretic) use

- Dietary intake meeting requirement for healthy population yet deficient - Conditional Nutrient Deficiency? Paucity of data – NIH call

Our Research Team

Stacy Douglas-Hanninen

Mary Keith

Pauline Darling

Michael Sole

Aiala Barr

CFDR funds allowed the completion of the biochemical analysis of B vitamin status

Study Methodology

- Same population as B1 study
- Plasma riboflavin was assessed by enzymatic activity assay (*Sauberlich, 1999*)
- Deficiency was defined as erythrocyte glutathione reductase activity coefficient (EGRAC) > 1.2
- Vitamin B6 concentrations were determined by radioimmunoassay (RIA) measures PLP-5’
- Deficiency was defined as < 20 nmol/L plasma

Implications for Practice
What about routine supplementation?

- Thiamin status was significantly improved in those taking a multi-vitamin (low dose B1 – 1.5 mg/day) or B complex supplement
- B6 status was also improved ($p=0.09$) in those taking a multi-vitamin or B complex supplement
- Evidence of benefit difficult to obtain – do the potentials benefit outweigh the risks?
- How can we measure success?

Micronutrient Supplementation in Elderly Patients with CHF

- 32 patients with age >70 years
- Stable – reduced heart function
- Quality of Life, cytokines, six minute walk test and cardiac magnetic resonance imaging
- Randomized, double blind study
- Multi-micronutrients – 9 months

Witte et al. European Heart Journal, 2005

Multi-Nutrient Supplement for Heart Failure

Table 1 Doses of micronutrients, RDI, and upper safe daily intakes

Nutrient	Daily dose (four capsules)	RDI	Upper safe limit for total daily intake
Calcium	250 mg	800 mg	2500 mg
Magnesium	150 mg[a]	300 mg	700 mg
Zinc	15 mg	15 mg	30 mg
Copper	1.2 mg	1.2 mg	9 mg
Selenium	50 μg	65 μg	450 μg
Vitamin A	800 μg	800 μg	3300 μg
Thiamine	200 mg[a]	1.4 mg	No limit
Riboflavin	2 mg	1.5 mg	No limit
Vitamin B_6	200 mg[a]	2 mg	300 mg
Folate	5 mg[a]	200 μg	No limit
Vitamin B_{12}	200 μg	1 μg	No limit
Vitamin C	500 mg[a]	60 mg	2000 mg
Vitamin E	400 mg[a]	10 mg	900 mg
Vitamin D	10 μg[a]	5 μg	25 μg
Co-enzyme Q10	150 mg[a]	15 mg	No limit

[a]Doses taken from previous work[8] or RDI.

Clinical Outcomes Following Micro-Nutrient Supplementation

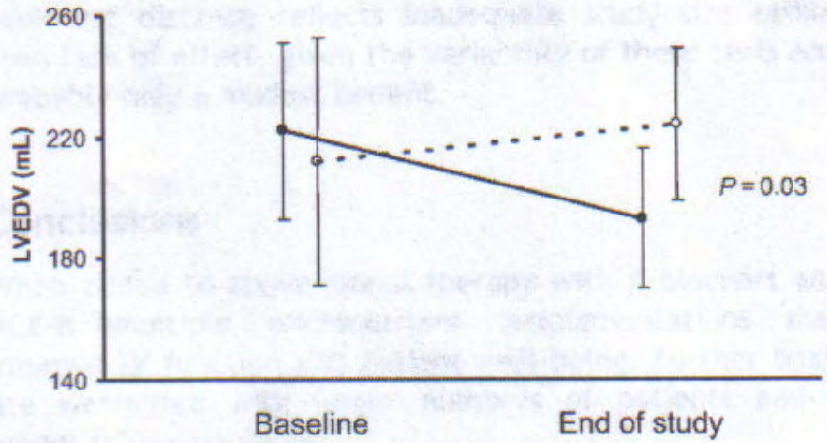


Figure 1 Change in left ventricular end-diastolic volume with placebo (unfilled circles and dashed line) and micronutrient supplementation (filled circles and solid line), (error bars are SD).

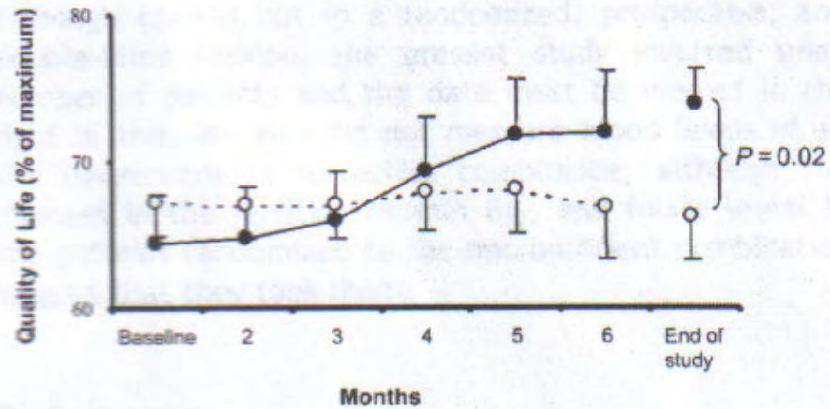
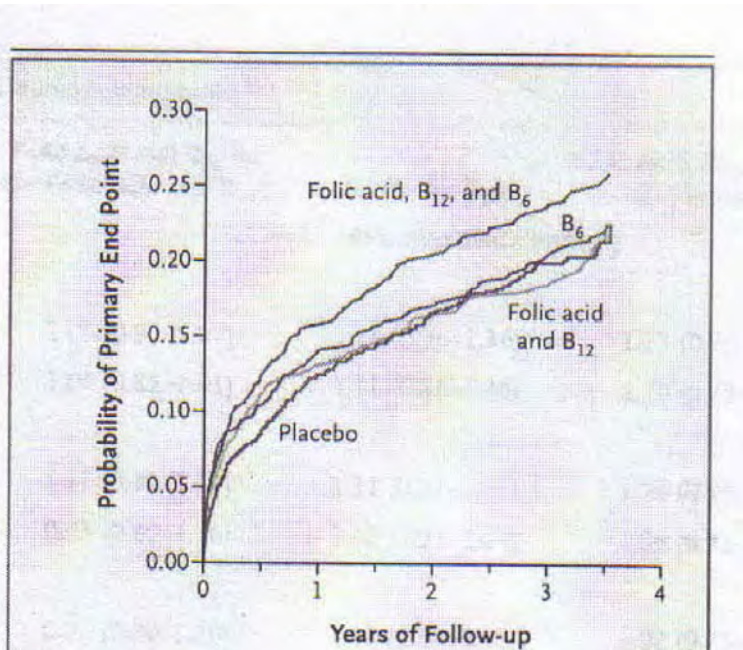


Figure 2 Quality of life score (percentage of maximum) during study period for patients taking placebo (unfilled circles and dashed line) or micronutrient supplementation (filled circles and solid line), (error bars are SD).

NORVIT Study

- Large trial post MI - 3749 patients
- Gave 0.8mg folic acid, 0.4 mg B12, 40mg B6
- Looked at homocysteine lowering and cardiovascular risk over 4 years
- Composite endpoint – fatal MI and non-fatal MI, stroke and sudden death due to heart disease.

Bonna et al. NEJM 2006



No. at Risk				
Folic acid, B_{12}, and B_6	937	795	745	517
Folic acid and B_{12}	935	812	764	518
B_6	934	805	766	511
Placebo	943	823	771	523

Figure 1. Kaplan–Meier Estimates of the Probability of Reaching the Primary End Point during Follow-up.

The primary end point was a composite of fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and sudden death attributed to coronary heart disease.

N=3749

0.8 mg folic acid
0.4 mg B12
40 mg B6

Bonna et al. NEJM 2006

Implications for Practice

- NIH call recognizing paucity of data
- Routine supplementation of B1 appears safe and justifiable
- Supplementation with B6 requires additional investigation to determine:

the impact of deficiency status

the impact of dose (high or low)

Continue to investigate the impact of specific disease states on nutritional requirements