ORIGINAL RESEARCH

Reduction in the Frequency of Arrhythmic Episodes in Patients with Paroxysmal Atrial Arrhythmia with a Vitamin/Essential Nutrient Supplementation Program

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ABSTRACT

Chronic deficiency of vitamins and other essential nutrients impairs cellular bio-energy production and can lead to disturbances in the generation and conduction of electrical impulses in the myocardium. We investigated the effect of long-term supplementation with a combination of vitamins and other essential nutrients on the number of clinically apparent episodes in patients with paroxysmal atrial arrhythmia. A randomized, double-blind, placebo-controlled, multi-center study in Germany was undertaken on 131 patients (ITT), aged 18 to 70 years, diagnosed with paroxysmal atrial arrhythmia, who were receiving anti-arrhythmic medication for at least three months, and who reported at least one paroxysmal cardiac episode per month. Study participants were advised to continue their prescribed medication and were treated with either an essential nutrient formulation or placebo during the 24-week study. Analysis of data demonstrated a significant decrease in the frequency of clinically apparent arrhythmic episodes with vitamin/essential nutrient supplementation (ITT analysis: p=0.0221; PP analysis: p=0.0160) that improved with time (45.5% of the supplemented group experienced frequent arrhythmic episodes at three months, in contrast to only 27.3% at six months). By addressing the underlying cause of arrhythmia, a deficiency in nutrients that generate bio-energy in the heart muscle cells, a vitamin/essential nutrient supplementation program provides a safe and effective reduction of arrhythmic episodes.

Key Words: atrial paroxysmal arrhythmia, nutrient synergy, carnitine, coenzyme Q10, bioenergy, lysine, vitamin C, B vitamins

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INTRODUCTION

Chronic deficiency of vitamins and other essential nutrients impairs cellular bio-energy production, and can lead to disturbances in the generation and conduction of electrical impulses in the myocardium. This disturbance of electrical impulses due to chronic vitamin and nutrient deficiency can be an underlying cause of the majority of arrhythmic episodes of unknown origins, according to the Rath concept.[1,2] There is an accumulating body of evidence supporting the beneficial effects of optimal levels of vitamins and other essential nutrients on the metabolic, nutritional and functional status of the myocardium.[3] Our previous study on the synergistic effect of a combined vita-

min/essential nutrient formula on progression of coronary artery calcification in patients with documented coronary artery disease, using Ultrafast CT, observed a decrease from a 44% calcification rate prior to intervention to 15% after the course of one year of nutritional supplementation.[4]

To generate electricity, the "electrical cells" of the heart need large amounts of bio-energy. Therefore, they need a constant supply of nutrients that facilitate the conversion of food into cellular energy. The most critical among them are: coenzyme Q10, carnitine, the B vitamins, lysine, and vitamin C, together with magnesium, calcium and potassium.[2,4] McCarty suggests the use of meaningful doses of the mitochondrial megavitamins as protection from cardiovascular disease.[5]

Carnitine, an often deficient non-essential amino acid, is essential for cardiac energy production. It is produced from lysine, an essential amino acid, with the participation of vitamin C. Since both lysine and vitamin C are not produced in the human body, their deficiency is likely to impair endogenous carnitine levels. The carnitine molecule is necessary to translocate fatty acids through the outer mitochondrial membrane for conversion to ATP in order to sustain heart function. A hospital-based, double-blind clinical study of patients admitted after myocardial infarction demonstrated that intake of 2 grams of carnitine per day for four weeks cut the number of complications from arrhythmia, angina and heart failure in half.[6]

Like carnitine, coenzyme Q10 is essential for ATP production by the mitochondria. Low levels of coenzyme Q10 have been reported to be associated with increased severity of heart failure.[7] Three months of adjunctive treatment of congestive heart patients with coenzyme Q10 resulted in reduction of arrhythmias in 62% of the treatment group in contrast to the placebo group.[8] Furthermore, a one-month coenzyme Q10 treatment of patients with acute myocardial infarction, reduced angina pectoris and total arrhythmias, and improved ventricular function.[9]

In addition to carnitine and coenzyme Q10, other nutrients such as magnesium, the B vitamins, vitamin C and vitamin E help optimize the pumping performance of the heart.[10,11] These nutrients optimize the function of the heart's electrical cells, as well as the myocardial smooth muscle cells of the blood vessel walls, supporting regular heart contractions. A deficiency of these nutrients leads to an imbalance in cellular energy that can cause irregular heartbeat. Many studies have been done on the therapeutic effect of individual nutrients on cardiovascular health. However, for optimal biological effect, these nutrients must complement and support each other in synergy.

The objective of this Phase II clinical study was to investigate whether long-term administration of a combination of vitamins, amino acids and other essential nutrients, individually shown to be effective in improving cardiac health, in addition to conventional basic therapy, could lead to a reduction in the number of clinically apparent episodes in patients with paroxysmal atrial arrhythmia.

MATERIALS AND METHODS

A randomized, double-blind, placebo-controlled multicenter study was undertaken to evaluate the effect of vitamin/essential nutrient supplementation on arrhythmia. Internists and general practitioners at 35 clinics in Germany conducted this multi-center study on 131 patients diagnosed with paroxysmal atrial arrhythmia. Of these, 90 patients (44 in the supplemented group and 46 in the placebo group) strictly adhered to the study protocol and completed the six-month study. (See Figure 1–STARD diagram.) Although the number of patients in the ITT (n=131) and the PP (n=90) populations differed, the results from both groups shared the same trend.

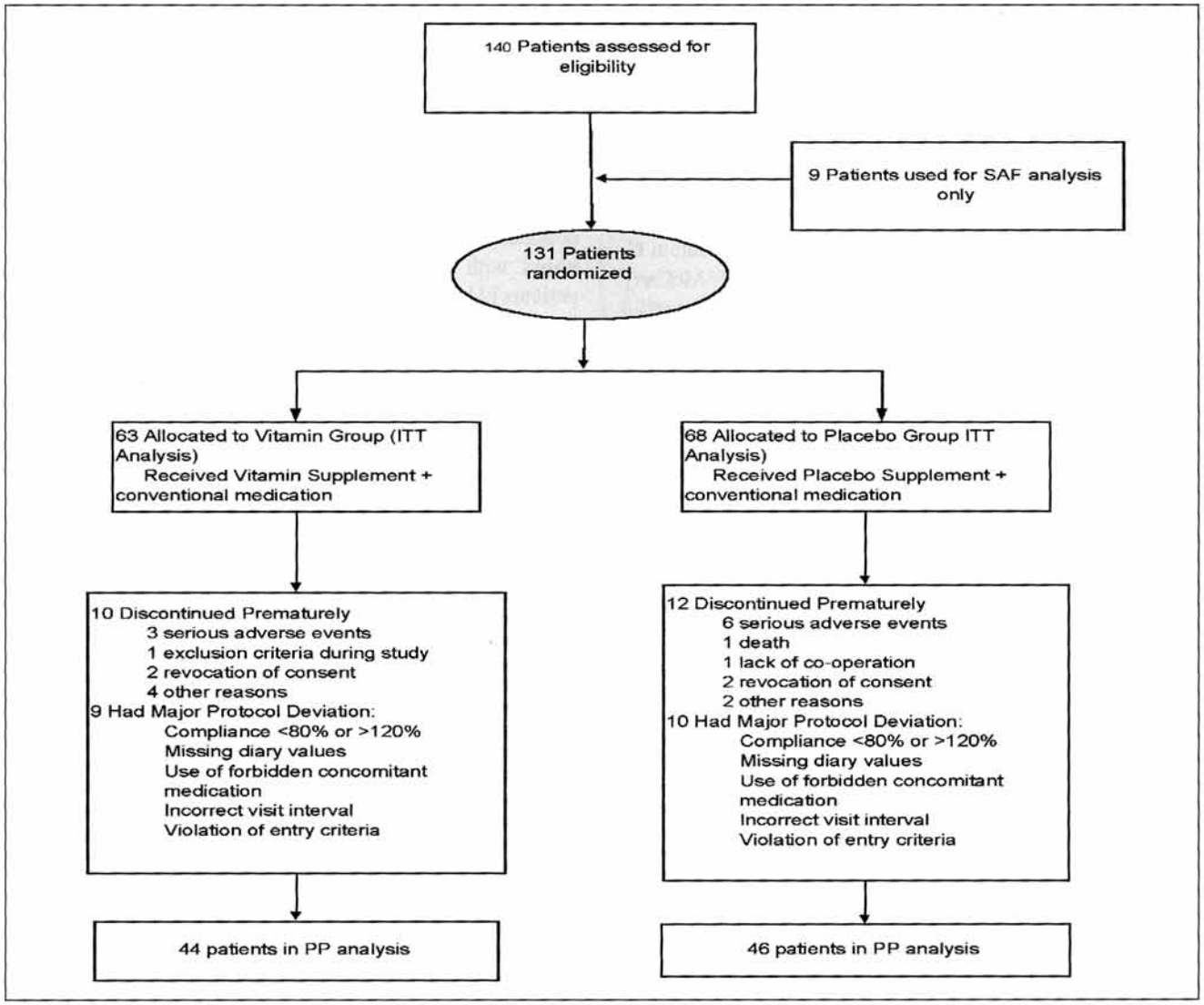
Inclusion criteria for selection were: males/females from 18 to 70 years of age, and patients with paroxysmal atrial arrhythmia receiving anti-arrhythmic treatment for at least three months and reporting at least one paroxysmal cardiac episode per month. All participants met the entrance criteria and were diagnosed with long-lasting or chronic arrhythmia. There was no statistical difference in the distribution of males and females in each group, and the average age in the supplemented group was 58 years and in the placebo group, 56 years. (See Table 1 for baseline demographics and characteristics.)

The study was conducted according to the recommendations of the Declaration of Helsinki as amended in South Africa and Edinburgh, Scotland (1996 and 2000), and AMG, particularly sections 40 and 41 of the Tenth Amendment to the Drugs Act, the Principles of Proper Implementation of Clinical Studies and the ICH-GCP Note for Guidance.

Table I. Baseline Patient Demographics and Treatment Characteristics.

	Supplemented Group 63 patients	Placebo Group 68 patients
Age (mean)	57.7years	55.9 years
Females	37.7%	42.3%
Males	62.3%	57.7%
Race —Caucasian	100%	100%
Body Weight	78 kg/171.83 lbs	76 kg/167.43 lbs
Body Height (cm)	169.4	168.8
Treated with Beta-blockers	64%	66%
Treated with Calcium channel blockers	20%	20%
Cardiac Therapy	20%	21%

Figure 1. STARD Flow Diagram



Methods of determining efficacy

The primary target parameter was defined as the number of clinically symptomatic episodes in six months compared to the placebo group. Since the patient's clinical benefit was the most important therapeutic aspect, participants were instructed to document, in a diary, all clinical arrhythmic symptoms (rapid heart rate, palpitations, chest pain, dyspnea, dizziness, weakness, tiredness, and perspiration outbreaks), time of occurrence, episode duration, and episode severity, and return for monthly follow-up. Since this study was designed as a first "proof of concept," sophisticated technologies such as remote EKG telephonic transmission were not used.

Statistical Methods/Issues

For confirmatory analysis of the main target parameter, with $\alpha = 0.05$, the Mantel-Haenszel test was used. Patient classification for this purpose was: no episodes, 1-3, 4-6, 7-10, and over 10 episodes during the period. Analysis of the secondary parameters was done in an exploratory sense with $\alpha = 0.05$ without α-adjustment. The secondary parameters, related to episode frequency, were analyzed analogously to the main target parameter, with class boundary adjustment. The time to first episode after the fifth week was statistically compared for the groups using Kaplan-Meier analysis and a log-rank test. No interim analysis was performed.

Intervention

All patients were advised to continue taking their prescribed conventional medications during the study period, and were provided conventional standard treatment for paroxysmal atrial arrhythmia. (Approximately 60% of the patients in both treatment groups were being treated with beta-blockers and 20% by calcium blockers.) In addition, patients allocated to the supplement group were each provided with blister packages containing vitamin/essential nutrients labeled with a lot # (to ensure the double-blind

character of the study) and the appropriate week. (See Table 3 for the nutrient composition.) The placebo group patients received identical blister packs of placebo tablets containing material of no medical significance such as cellulose, fructose, etc., but physically indistinguishable from the two types of nutrient tablets. Patients were instructed to take the prescribed nutrient/placebo tablets provided for 24 weeks.

Efficacy Parameters

Frequency of symptomatic episodes of arrhythmia was the primary target parameter for determining efficacy of treatment. Secondary parameters included: the number of clinically apparent episodes in each group during study months 1-3 and during months 4-6, time elapse before first occurrence of clinically apparent arrhythmic symptoms, pre-and post-study 24-hour Holter monitoring for assessment of arrhythmia-specific changes, and pre-and post-treatment scores on the SF–36 (Short Form 36 Healthy Survey,[12] a standard Quality of Life Questionnaire) to evaluate how vitamin intake affected the patients' perceived general well-being and quality of life. The questionnaire evaluated 36 parameters describing physical functions, role functions from the emotional perspective, social functionality, level of pain, psychological status, vitality, and perception of general health and other aspects.

RESULTS

For the primary efficacy parameter (clinically apparent arrhythmic episodes during months 1-6), a statistically significant effect of vitamin supplementation on the reduction of clinically apparent arrhythmic episodes was observed in both analysis sets (p=0.0221 for ITT analysis set, p=0.0160 for PP analysis set) (Figure 2). Only 47.8% of the supplemented patients reported seven or more arrhythmic episodes during the treatment study, in contrast to 73.9% reported in the placebo group (PP analysis). The number of patients with less than seven episodes in the supplemented group (52.7%) was almost twice that in the placebo group (26.1%). Furthermore, the number of patients with more than ten episodes was significantly less in the supplemented group (45.5%) than in the placebo group (69.6%). In addition, the elapse of time prior to the first arrhythmic episode was shorter in the placebo group than in the supplemented group (Log Rank Test: p=0.3797 for ITT analysis set and p=0.0332 for PP analysis set).

The data was also analysed to determine the effect of supplementation on arrhythmic episodes with time at three months vs. six months. At three months, 45% of the supplemented patients experienced seven or more arrhythmia attacks in contrast to 27.3% at six months (Figure 3). Approximately 22.7% of the supplemented patients reported no arrhythmic episodes at three months in contrast to 43.2% at six months (Figure 4).

For all dimensions of the SF-36, the differences between the post-and pre-study values of the supplemented group demonstrated a stronger perceived quality of life than did those of the placebo group (Table 2). Baseline values were comparable between treatment groups. This questionnaire evaluates 36 different parameters that relate to the physical functioning of patients, including pain, emotional

Table 2. Effect of Supplementation on General Well-Being of Patients
SF-36 -Changes from baseline values
(ITT Analysis Set: Supplemented n=63, Placebo n=68)

Scores on SF-36	Mean - Supplemented Group	Mean - Placebo Group
General Health	+ 4.0	- 0.3
Vitality	+ 9.5	+ 2.8
Mental Health	+ 7.4	- 1.6
Physical Functioning	+ 5.9	+ 4.3
Bodily Pain	+ 11.4	+ 7.7
Social Functioning	+ 10.4	+ 2.3
Role – Physical Functioning	+ 22.5	+ 18.0
Role – Emotional Functioning	+ 16.7	+ 13.5
Total Score	+ 90	+ 47

Two-sided Wilcoxon Rank Sum Test (Normal Approximation): p=0.0118

Table 3. Nutrient Composition
Bottle 1A (Serving size - three tablets)

Vitamin A (from 7.5% Betatene (Henkel))	1665 IU
Vitamin C (as Ascorbic Acid, Ascorbyl Palmitate, Calcium Ascorbate, Magnesium Ascorbate)	600 mg
Vitamin D3 (as Cholecalciferol)	130 IU
Vitamin E (Mixed Covitol)	130 IU
Vitamin B1 (from Thiamine Mononitrate	7 mg
Vitamin B2 (as Riboflavin)	7 mg
Niacin (as from Niacinamide)	45 mg
Vitamin B6 (from Pyridoxine HCl)	10 mcg
Folic Acid	90 mcg
Vitamin B12 (as Cyanocobalamin)	20mcg
Biotin	65 mcg
Pantothenic Acid (from D-Calcium Pantothenate)	40mcg
Calcium (from Glycinate, Ascorbate)	35 mg
Phosphorus (from Dicalcium Phosphate)	15 mg
Magnesium (from Magnesium Glycinate, Magnesium Ascorbate)	40 mg
Zinc (from Zinc Glycinate)	7 mg
Selenium (from L-Selenomethionine)	20mcg
Copper (from Copper Glycinate)	330 mcg
Manganese (from Amino Acid Chelate)	1.3 mg
Chromium (from Chromium Glycanate)	10 mcg
Molybdenum (from Molybdenum Glycinate)	4 mcg
Potassium (from Potassium Proteinate)	20 mg
L-Lysine (from L-Lysine HCl)	110 mg
L-Proline	110 mg
Citrus Fruit Peel Bioflavanoids	100 mg
L-Arginine (from L-Arginine HCl)	40 mg
L-Cysteine (from L-Cysteine Monohydrate HCl)	35 mg
Inositol	35 mg
L-Carnitine (from L-Carnitine Tartrate	35 mg
CoEnzyme Q10	7 mg
Pycnogenol	7mg

Bottle 1B (Serving size - 2 tablets)

Vitamin C (from Calcium Ascorbate, Magnesium Ascorbate)	700 mg
Vitamin E (as d-Alpha Tocopheryl Succinate)	70 IU
Vitamin B1 (from Thiamine Mononitrate)	15 mg
Vitamin B2 (as Riboflavin)	15 mg
Niacin (as Niacinamide)	30 mg
Vitamin B6 (from Pyridoxine HCl)	4 mg
Vitamin B12 (as Cyanocobalamin)	7 mcg
Biotin	130 mcg
Pantothenic Acid (from Calcium D-Pantothenate)	40mcg
Calcium (from Calcium Ascorbate)	13 mg
Taurine	200 mg
L-Carnitine (from L-Carnitine Tartrate)	160 mg
CoEnzyme Q10	20 mg

Figure 2. Arrhythmic episode frequency over six-month study of nutrient supplemented (n=44) and placebo (n=46) patients (PP analysis set) Exact Mantel-Haenszel Chi-Square Test: **p=0.0160**.

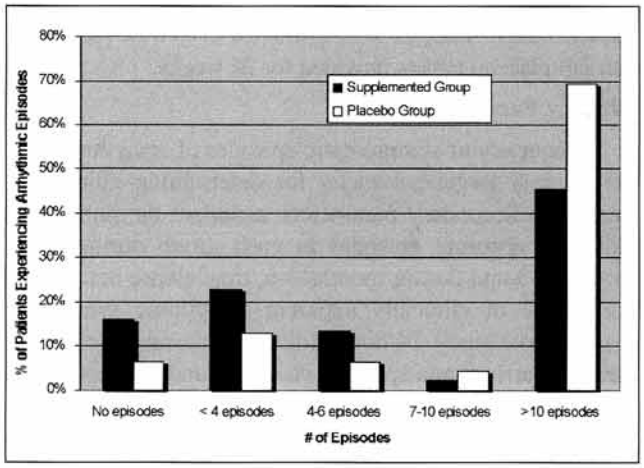


Figure 3. Percentage of supplemented (n=44) patients experiencing frequent (>7) arrhythmic episodes during treatment intervals 1-3 months and 4-6 months.

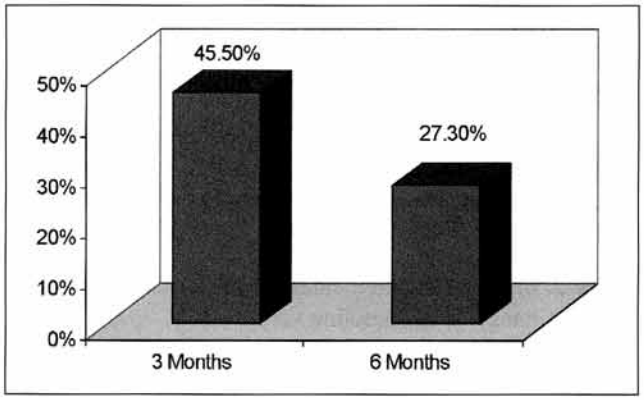
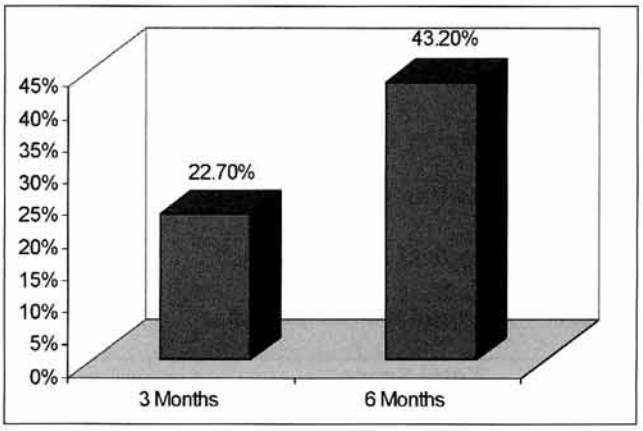


Figure 4. Percentage of supplemented (n=44) patients experiencing no arrhythmic episodes during treatment intervals 1-3 months and 4-6 months (PP analysis set).



status, vitality, general health perception, and other aspects of health. Evaluation of the "mental health" measure results, for example, showed an improvement of 7.4 in the supplemented group and a decrease of –1.6 in the placebo group (Two-sided Wilcoxon rank sum test was statistically significant for ITT analysis: p=0.0118). For PP analysis, statistical significance was almost achieved (two-sided Wilcoxon rank sum test p=0.0506).

DISCUSSION

Overall, the results of this randomized double-blind, placebo-controlled trial conclusively documented the effectiveness of supplementation using a combined vitamin/essential nutrient supplementation program in controlling arrhythmia, a condition for which conventional medicine does not provide a solution, and instead attempts to control symptomatically. Active treatment with the multivitamin/essential nutrient combination over a six-month period was significantly more effective in reducing clinically apparent symptoms of arrhythmia in patients than standard drug regimens alone. Furthermore, the reduction in arrhythmic episodes was more pronounced at six months than at three months of supplementation, suggesting increased benefits with a longer duration of supplementation. Thus, with the adjunctive use of the vitamin/essential nutrient supplement, the likelihood of being free from arrhythmia doubled (15.9% in the supplemented group vs. 6.5% in the placebo group).

These health benefits were achieved by addressing the underlying cause of arrhythmia, the deficiency of bio-energy-generating nutrients. The electrical cell cluster that triggers the heartbeat sends electrical impulses approximately once every 830 milliseconds. To generate electricity, these electrical cells of the heart need large amounts of bio-energy. Therefore, they need a constant supply of nutrients that facilitate the conversion of food into cellular energy. The most critical among them are coenzyme Q10, carnitine, the B vitamins, lysine and vitamin C, together with magnesium, calcium and potassium. For optimal biological effect, these nutrients must complement and support each other in synergy. These nutrients optimize the function of the heart's electrical cells, as well as the cells building the heart muscle, blood vessels and other organs. When these nutrients are lacking, the heart cells fail to generate electrical energy and electrical impulses are sent in a chaotic manner.

This study sheds a new light on conventional medicine's approach to arrhythmia, which has relied on mechanical regulation of the heart rhythm using catherization, or drugs such as beta-blockers and calcium channel blockers which can have severe side effects, the most important of these being the generation of even more irregular heartbeats and not infrequently, sudden cardiac death. Large clinical trials have revealed that anti-arrhythmic drugs, which are used by more than 1.5 million Americans and many more people in European and other countries, do not offer health benefits and increase the risk of serious complications, including death. In 1989, a study using anti-arrhythmic drugs in patients who had experienced heart attacks was prematurely stopped when preliminary results showed the risk of death was two-and-a-half times (2.5) greater in patients taking drugs.[13] In 2002, two large studies, one conducted in Canada and the other in the Netherlands, provided similar evidence.[14] The six-year study, conducted with more than 4,000 patients, showed higher death and hospitalization rates among patients on anti-arrhythmic drugs. These drugs included those that affect heart rate, such as dioxin, beta-blockers, and calcium channel blockers. The European study came to the same conclusion, and also found that women taking anti-arrhythmic medications faced a higher risk of heart failure, stroke and other medical events than men.

Of significance, the results of this study indicate that combining conventional drug treatment with a vitamin/nutrient supplement program to treat arrhythmia is an effective, safe, therapeutic approach that provides enhanced improvement with long-term use. Due to the synergistic effect of specific vitamin/essential nutrients, therapeutic effect is achieved with moderate levels of these nutrients in contrast to single nutrient megadose approaches. In addition to improvement in arrhythmic episode frequency, the vitamin/essential nutrient program used by the supplemented group significantly improved their perceived quality of life, especially in the area of mental health. This is an important benefit of supplementation, as arrhythmia patients not only suffer from depression and fear of experiencing heart dysfunction, but also from deteriorating health and a gradual diminishing of their quality of life. To a large extent, these adverse mental and emotional consequences are associated with drug side effects and the belief that a cure for paroxysmal atrial arrhythmia is not available.

SUMMARY

Although further clinical studies are warranted to better determine its effectiveness for treatment of arrhythmia, this nutrient combination offers great potential as an adjunctive treatment for arrhythmia patients and as a preventative measure for patients with a predisposition for developing arrhythmia.

ACKNOWLEDGMENTS

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