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Research Article

Prophylaxis of Atrial Fibrillation After Isolated On-pump Coronary Artery Bypass Surgery with Postoperative Intravenous Magnesium Sulfate Supplementation

Elona Dado[1], Edvin Dado[2], Juliana Karanxha[3], Cory Greguske[4], Elizana Zaimi Petrela[5], Efrosina Kajo[6], Mrunal Teja Chinthapalli M[7], Edlira Horjeti[8], Fjolla Hyseni[9], Sepideh Jahanian[10], Blina Abdullahu[11], Mohammad Abubaker SIDDIQUE[12] and Juna Musa[13]*

[1]*Cardiologist, Hygea Hospital Tirana, Albania*

[2]*Cardiologist, Faculty of Medicine, UMT, /"UHC " Mother Teresa", Tirana, Albania*

[3]*Cardiologist, American Hospital 3. Tirana, Albania*

[4]*Department of Cardiology St Elizabeth"s Medical Center Boston, USA*

[5]*Professor of Medicine, UMT, Faculty of Medicine/ UHC "Mother TERESA" Tirana, Albania*

[6]*Professor of Medicine, Institution (Current Position): UMT, Faculty of Medicine, Tirana, Albania*

[7]*Department of Endocrinology Diabetes and Nutrition Mayo Clinic Rochester Minnesota, USA*

[8]*Research Fellow Department of Urology Mayo Clinic Rochester Minnesota, USA*

[9]*PhD Candidate NYU Langone Medical Center New York City, USA*

[10]*Department of Anesthesiology Mayo Clinic Rochester Minnesota, USA*

[11]*Mother Teresa Hospital Tirane, Albania*

[12]*Northeast Medical College and Hospital Sylhet, Bangladesh*

[13]*Department of Endocrinology Diabetes and Nutrition Mayo Clinic Rochester Minnesota, USA*

***Corresponding Author:** Juna Musa, Department of Endocrinology Diabetes and Nutrition, Mayo Clinic Rochester, Minnesota, USA.

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Abstract

Objective: Atrial fibrillation (AF) is the most common arrhythmia complicating cardiac surgery and carries a high risk for significant morbidity and mortality in short and long term. Its prophylaxis remains crucial to improve outcomes. The role of magnesium administration in preventing the occurrence of AF after isolated bypass surgery is not well established. Variations of dose, timing and mode of administration have been proposed. The purpose of this study was to investigate the efficacy of 4-day postoperative intravenous magnesium supplementation on the incidence of postoperative AF.

Methods: We performed a prospective, randomized, placebo-controlled clinical study on 200 consecutive patients who underwent initial, elective, isolated on-pump coronary artery bypass surgery, to assess the role of magnesium sulfate administration for postoperative AF prevention. Patients in the treatment group received 10.3 mmol of magnesium sulfate in 100 mL of saline solution infused intravenously over 2 hours once daily for 4 consecutive days, starting immediately after surgery. There were no significant differences in the preoperative characteristics of patients.

Results: The incidence of postoperative AF was 18% in the magnesium-treated group compared with 35% in the control group (p 0.006). Absence of magnesium administration, magnesium serum levels less 2 mg/dl, age over 65, decreased ejection fraction, increased aortic cross clamping and cardiopulmonary bypass time were identified as independent risk factors for the development of AF on the multivariate logistic regression analysis. The duration of AF in the magnesium treated patients was longer than in the control group. There was a significantly higher presence of risk factors in the magnesium treated patients who developed AF compared with those who developed AF in the control group.

Conclusion: Our study indicates that postoperative 4-day supplementation of magnesium sulfate is helpful in reducing the incidence of AF after coronary surgery. For older patients, patients with reduced EF, patients with longer cardiopulmonary bypass and aortic cross clamping times, magnesium supplementation alone is inadequate for the prophylaxis of postoperative AF.

The longer duration of AF and the increased presence of risk factors in the magnesium treated patients who developed AF, supports the rationale that magnesium therapy is efficacious in the prevention of the subset of postoperative AF that is transitory and self-limited. Important advantages of magnesium therapy include the high safety profile and utility in identifying patients with the subset of AF that carries a higher risk of morbidity and mortality.

Keywords: Atrial Fibrillation (AF); Coronary Artery Bypass Grafting Surgery (CABG); Postoperative Atrial Fibrillation (POAF)

Introduction

Atrial fibrillation (AF) is the most common arrhythmia complicating cardiac surgery. It remains a common complication after coronary artery bypass grafting surgery (CABG) despite substantial improvements in surgical techniques and perioperative management. The reported incidence is between 20% and 50% [3-5].

Postoperative atrial fibrillation (POAF) typically develops within the first week after surgery. The usual onset is between 24 and 96 hours after cardiac surgery, with a peak incidence on the second to third postoperative days [3-5].

Based on increasing evidence, it is almost universally accepted that patients who develop AF following cardiac surgery are at increased risk of stroke, congestive heart failure, hemodynamic instability, renal and respiratory failure. This leads to prolonged hospitalization, increased length of stay (LOS) in the intensive care unit (ICU), [1,6] and increased risk of early and late morbidity and mortality [1-7,9].

POAF has also been shown to be an independent predictor of postoperative delirium and neurocognitive decline [7,8].

POAF after isolated CABG is multifactorial and as such, several clinical and biochemical factors have been implicated as risk factors. The most pronounced risk factors are advanced age, prior history of AF, congestive heart failure, left atrial enlargement, decreased left ventricular function, postoperative withdrawal of β-adrenergic blockade, chronic obstructive pulmonary disease, thyroid dysfunction, longer aortic cross clamping (AXC) and cardiopulmonary bypass (CBP) time, myocardial ischemia and reperfusion, postoperative myocardial infarction, right coronary artery disease, local inflammatory reaction, metabolic disorder, excessive catecholamines, and electrolyte imbalance [2-5]. Hypomagnesemia, in particular, has also been identified as a possible independent predictor of POAF [10].

In most studies B-blockers [11] and amiodarone [12,13] have been shown to decrease the incidence of POAF.

There is conflicting evidence regarding the role of short term intravenous magnesium administration in patients undergoing isolated CABG [10,14-24].

There is existing evidence that supports the role of magnesium in stabilizing the cellular transmembrane potential and overall cellular function by suppressing excessive cellular calcium influx, energy demands, preserving myocardial metabolites, and reducing the severity of reperfusion injuries [28].

It has been demonstrated that hypomagnesemia is common following cardiac surgery and that correction of ionized plasma magnesium during cardiopulmonary bypass reduces the risk of postoperative cardiac arrhythmias [25,26]. Three main factors contributing to magnesium deficiency are found to be hemodilution, elevated catecholamine levels, and increased urinary loss [27].

Although there is a lack of consistency in magnesium supplementation's role in the prophylaxis of POAF, several studies have demonstrated that magnesium infusion significantly reduced the incidence of POAF [14-19,24].

Considering the role of magnesium in stabilizing the cellular transmembrane potential, the depletion demonstrated after CABG may predispose to unstable cellular activity.

This study aimed to prospectively investigate the efficacy of postoperative magnesium sulfate administration for the prophylaxis of AF after on-pump CABG and discuss the available evidence, guidelines, and recommendations.

Patients and Methods

Study population

200 consecutive patients, who underwent elective and initial isolated on-pump CABG operations in University Hospital Centre Mother Tereza were enrolled in this prospective, randomized, placebo-controlled study.

Exclusion criteria included: history of AF, preoperative heart rate of less than 50 beats/min, concomitant valve surgery, redo coronary artery surgery, systolic blood pressure of less than 100 mm Hg, history of renal failure (serum creatinine level greater than 2.0 mg/dL), type II respiratory failure, EF<30%, implanted permanent pacemaker, postoperative myocardial infarction, and severe hemodynamic disorder requiring postoperative cardiopulmonary support.

Candidates that met the criteria were continuously enrolled. All the patients were in sinus rhythm preoperatively.

Perioperative clinical outcomes of these patients were compared between groups with and without magnesium treatment and between patients who did and did not experience AF postoperatively.

EuroSCORE was used for preoperative risk scoring. There was no significant difference between the two groups (p = 0.46).

There was no difference between the 2 groups in terms of preoperative use of a beta-blocker (p = 0.61), calcium-channel blocker (p = 0.63), or angiotensin-converting enzyme inhibitor (p = 0.77).

Beta-Blocker withdrawal, a well-known significant risk factor for the development of AF, was avoided.

Beta-Blockers were initiated as early as possible in the postoperative period, unless contraindicated.

The preoperative characteristics of two groups are summarized in table 1.

Variables	Mg, n = 100	C, n = 100	P-value
Age	67.8 ± 5.5	65.9 ± 7.8	0.37
Pts>65	66%	68%	0.76
Male sex	76%	78%	0.74
Past history			
Previous myocardial infarction	62%	58%	0.56
*Recent MI	30%	27%	0.64
Hypertension	69%	72%	0.64
Diabetes mellitus	47%	45%	0.77
CHF	11%	9%	0.64
Hypercholesterol-emia	52%	55%	0.67
*COPD	12%	10%	0.65
Preoperative LVEF			
> = 50	38%	40%	0.77
>40-<50	33%	35%	0.76
< = 40	29%	25%	0.52
*Moderate PHT	35%	33%	0.76
*Severe PHT	11%	13%	0.66
*RV dysfunction	32%	28%	0.54
*LA enlargement	48%	44%	0.57
Number of diseased vessels			
Single	12%	11%	0.82
Double	24%	26%	0.74
Triple	63%	60%	0.66
LMT disease	22%	19%	0.60
RCA disease	73%	71%	0.75

Table 1: Preoperative characteristics of patients.

Values are presented as mean ± standard deviation or percent of patients; C - Non Treated (control) Group; CHF - Congestive Heart Failure; COPD - Chronic Obstructive Pulmonary Disease; LMT - Left Main Trunk; LA - Left atrium, LVEF - left ventricular ejection fraction as calculated mainly by transthoracic echocardiography or cineangiography; Mg - Magnesium-Treated Group; MI - Myocardial Infarction; Pts - Patients; RCA - Right Coronary Artery, RV - Right Ventricle.

*Recent MI - Within 90 days before operation; *COPD - Long term use of corticosteroids and bronchodilators, *Moderate PHT - PA pressure 31-55 mmHg *Severe PHT - PA Pressure 56 mmHg and above

*RV dysfunction - Tricuspid annular plane excursion (TAPSE) < 17 mm and/or peak systolic velocity of lateral tricuspid annulus in tissue Doppler imaging (PSV) < 9.5 cm/sec. *LA enlargement > 34 ml/cm^2.

Magnesium administration

Timing and dosage of magnesium sulfate administration was based on evidence from the literature and clinical experience. Hypomagnesemia is generally observed in patients who undergo cardiopulmonary bypass. Magnesium levels reach a nadir on the first postoperative day and usually do not return to normal levels before the fourth postoperative day.

Patients in the treatment group received 10.3 mmol of magnesium sulfate (2.5 g of $MgSO_4$/10 ml, 1 ampule) in 100 mL of saline solution infused intravenously over 2 hours once daily for 4 consecutive days starting immediately after surgery.

Serum potassium and calcium concentrations were adjusted to maintain the potassium levels 4 mmol/L or more and calcium levels within the normal physiologic range.

Intraoperative and postoperative characteristics of both groups are summarized in table 2.

Variables	Mg (N = 100)	C (N = 100)	P-value ł
Number of distal anastomoses	3.0 ± 1.02	2.95 ± 0.95	0.368*
Operation time (min)			
CPB	78.5 ± 13.2	79.05 ± 12.4	0.970*
Aortic cross-clamping	59.9 ± 10.5	59.65 ± 10.3	0.431*
Blood transfusion	35.0%	42.0%	0.307
Extubation time (h)	3.76 ± 1.29	3.9 ± 1.1	0.414*
Incidence of postoperative AF	18.0%	35.0%	0.006
Initial AF (hours after surgery)	40.8 ± 14.8	42.4 ± 15.2	0.717
Hospital stay (days after surgery)	7.2 ± 0.8	7.28 ± 0.92	0.626*
Hospital stay in pts with AFib	7.36 ± 0.6	7.27 ± 0.9	0.704*
LOS in ICU stay (hours after surgery)	47.9 ± 4.7	48.9 ± 6.6	0.220*
LOS in ICU in pts with Afib	53.9 ± 8.5	52.1 ± 6.7	0.402*
Symptoms due to AF ESS 3-4	1 (5.5%)	12 (34.0%)	0 .021
Duration of atrial fibrillation (hours)	24.5 ± 9.4	14.8 ± 11.4	0.003*
HR during AF	70.7 ± 4.04	80.0 ± 6.95	0.001*

Table 2: Intraoperative and postoperative characteristics of both groups.

ł Chi-square test, *t-test.

A fib - Atrial Fibrillation; HR - Heart Rate; CPB - Cardiopulmonary Bypass; ESS - EHRA Symptom Scale; ICU - Intensive Care Unit; LOS - Length of Stay.

Anesthetic management

All patients received premedication with midazolam and scopolamine. For the maintenance of anesthesia, we used mainly intravenous administration of fentanyl, sufentanil or remifentanil and propofol sometimes in combination with inhaled agents such as sevoflurane.

Operative procedures

During cardiopulmonary bypass, aortic and right atrial 2-staged cannulation, systemic hypothermia (32°C), anterograde repeated cardioplegia, a membrane oxygenator and roller pump were used. Blood flow rate and systemic perfusion pressure were kept at greater than 2.5 L x m^2 x min and 50 mmHg, respectively.

Perioperative measurements

After completion of the surgical procedure, patients were taken to the ICU and then transferred to the wards when their hemodynamic and respiratory functions were stable.

Continuous EKG and hemodynamic monitoring were performed throughout the operation and during the intensive care stay.

After discharge from the intensive care unit, for an average of 7 days, a routine 12-lead electrocardiogram was obtained daily for all patients. Additional 12-lead ECG was obtained each time clinical observation suggested arrhythmias or if non-invasive EKG monitoring detected tachycardia or other arrhythmias.

Serum magnesium concentration was measured before surgery, immediately after surgery, and every morning for 4 days postoperatively. Our laboratory's normal reference range for serum magnesium concentration is from 1.7 mg/dl to 2.6 mg/dl.

Close monitoring of serum potassium and calcium levels was performed as well to scrupulously avoid any imbalances. Potassium serum levels were kept ≥ 4 mmol/L.

The primary endpoint of the study was postoperative development of AF.

The secondary endpoints were ventricular rate at the onset of AF, day of onset of AF, duration of AF, ICU and hospital LOS.

Atrial fibrillation diagnosis was established according to the criteria of American Association for Thoracic Surgery (AATS) as well as European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines [29,30].

Onset of AF, persisting for greater than 15 minutes or in shorter duration but with clinical symptoms and hemodynamic deterioration, was considered as sufficient criteria for the initiation of treatment. The treatment consisted of amiodarone or an additional dosage of beta-blocker along with 10.3 mmol $MgSO_4$ intravenous administration in patients not prophylactically treated with Mg therapy. Magnesium therapy was utilized even if serum levels were within normal limits. In all patients, sinus rhythm was restored in less than 48 hours.

Statistical analysis

The continuous quantitative variables are presented as mean ± standard deviation. Discrete variables are presented in absolute numbers and percentages. Pearson chi-square test was used to compare the proportions. Student's t-test was used to compare the means between two groups.

The independent contribution of the potential factors involved in the development of POAF was determined by using logistic regression analysis. Odds ratio and confidence interval (CI) 95% were calculated for each variable.

A p-value less than 5% was considered significant. The statistical analysis was performed using SPSS 25.0.

Results

The incidence of postoperative AF was 18% (18 patients) in the magnesium-treated group and 35% (35 patients) in the control group ($p = 0.006$).

Mean serum Magnesium concentration in the treatment and control groups were as follows:

- **Preoperative:** Treatment group: 1.96 ± 0.38 mg/dl vs Control group: 1.98 ± 0.42 mg/dL ($p = 0.73$).
- **Immediately after surgery, and before Mg supplementation:** Treatment group 1.74 ± 0.28 vs Control group 1.73 ± 0.24 ($p = 0.78$).
- **First postoperative day:** Treatment group 2.0 ± 0.22 mg/dL vs Control group 1.8 ± 0.32 mg/dL ($p < 0.05$).
- **Second postoperative day:** Treatment group 2.1 ± 0.19 mg/dL vs Control group 1.88 ± 0.29 mg/dL ($p < 0.05$).
- **Third postoperative day:** Treatment group 2.2 ± 0.15 mg/dL vs 2.1 ± 0.25 mg/dL ($p < 0.05$).
- **Fourth postoperative day:** Treatment group 2.2 ± 0.25 mg/dl vs 2.1 ± 0.22 mg/dl ($p < 0.05$).

There was no statistically significant difference in the mean serum magnesium concentration between the two groups preoperatively and immediately after surgery. In both groups immediately after surgery, a decrease of magnesium serum levels to the lowest limit of the normal range was observed. Magnesium serum concentration increased significantly in the magnesium treatment group during the first postoperative day and remained significantly higher in the treatment group for the next three consecutive postoperative days.

Magnesium administration did not induce severe bradycardia, hypotension, or respiratory depression in any of the treated patients.

As shown in Table 1, there is no significant difference in preoperative characteristics between the two groups.

No statistically significant difference was found between the two groups and between the two subgroups of patients who developed POAF regarding the time of AF onset, length of ICU stay, and the duration of postoperative hospital stay. There was a significant difference in ventricular rate during AF between the two groups, with rates significantly lower in the treated group. Significantly less patients in the treated group experienced grade 3-4 EHRA scale symptoms during AF when compared to the control group (Table 2).

A statistically significant difference was found between the two groups regarding the duration of AF, being longer in the treated group (Table 2).

Comparison of all patients with and without AF to identify risk factors for POAF was performed. Although there was no significant difference in ICU stay between the treated and the control group, a significant increase in ICU stay was found in the patients who developed POAF compared with those who didn't, with no significant difference in hospital LOS (Table 3).

Variables	AF (pos), n = 53 (%)	AF (neg), n = 147 (%)	P-value ƚ
Age	69.9 ± 4.6	64.9 ± 3.2	0.001*
Pts>65y/o	45 (84.9)	89 (60.5)	0.001
Male sex	45 (84.9)	109 (74.1)	0.116
Past history			
Previous myocardial infarction	35 (66.0)	85 (57.8)	0.290
Recent MI	21 (39.6)	36 (24.5)	0.030
Hypertension	42 (79.2)	99 (67.3)	0.114
Diabetes mellitus	30 (56.6)	62 (42.1)	0.072
CHF	9 (16.9)	11 (7.5)	0.089
Hypercholesterolemia	33 (62.3)	74 (50.0)	0.133
COPD	10 (18.9)	12 (8.0)	0.032
Preoperative Echo			
EF value	0.46 ± 0.086	0.52 ± 0.08	0.001*
≤40%	23 (43.4)	31 (21.0)	0.002
Moderate PHT	25 (47.0)	43 (29.2)	0.018
Severe PHT	11 (20.0)	13 (8.8)	0.027
RV dysfunction	22 (41.5)	38 (25.8)	0.031
La enlargement	32 (60.3)	60 (40.8)	0.014
Number of diseased vessels			
Single	7 (13.0)	16 (11.0)	0.652
Double	15 (28.3)	35 (23.8)	0.531
Triple	30 (56.6)	93 (63.2)	0.412

LMT disease	10 (18.9)	31 (21.0)	0.731
RCA disease	40 (75.4)	104 (70.7)	0.503
Number of distal anastomoses	3.0 ± 0.9	2.9 ± 1.07	0.540*
Operation time (min)			
CPB	80.1 ± 13.5	72.5 ± 12.4	0.002*
Aortic cross-clamping	63.1 ± 9.05	53.9 ± 7.8	0.001*
Blood transfusion	30 (56.6)	47 (31.9)	0.001
Mg therapy	18 (33.9)	82 (55.8)	0.006
Mg blood level <2mg/dl	32 (60.4)	58 (39.5)	0.008
Hospital stay	7.3 ± 0.9	7.25 ± 0.8	0.705*
ICU stay	52.7 ± 7.4	43.6 ± 4.1	0.001*

Table 3: Comparison of All Patients With and Without Atrial Fibrillation.

ǂ Chi-square test, *t-test.

Abbreviations correspond to those in Tables 1 and 2.

The independent contribution of the potential factors involved in the development of POAF was determined by using logistic regression analysis. Odds ratio and CI 95% were calculated for each variable (Table 4).

Variables	OD	CI95%	P-value
Age	1.21	1.000-2.133	0.063
Pts > 65yo	3.665	2.64-4.89	0.001
EF ≤ 40%	2.868	1.99-6.32	0.011
CPB time(min)	1.791	1.001-4.99	0.023
Aortic cross-clamping time (min)	1.11	1.001-2.99	0.048
Blood transfusion	0.277	0.12-1.78	0.238
Mg therapy	0.407	0.11-0.64	0.003
Mg blood level <2 mg/dl	2.338	1.99-4.83	0.001

Table 4: Results of binary logistic regression analysis. Correlation between Afib and independent variables.

OD- Odds Ratio, CI 95%-Confidence Interval 95%.

Binary logistic regression analysis resulted in a statistically significant correlation between the postoperative development of AF and the age over 65 (p = 0.001), EF ≤ 40% (p = 0.011), duration of CPB (p = 0.023), duration of aortic cross-clamping (p = 0.048), Mg therapy (p = 0.003) and the Mg blood serum level < 2 (p = 0.001).

So it can be concluded that according to our findings: Patients over age 65 are 3.7 times more likely than those 65 or younger to develop POAF (OD:3.67, CI95%: 2.64 - 4.89).

Patients with EF 40% or less are 2.9 times more likely to develop POAF than those with EF over 40% (OD:2.87, CI95%: 1.99-6.32). For every minute increase of AXC and CPB time there is a respective 11% (OD:1.11, CI95%: 1.001-2.99) and 79% (OD:1.79, CI95%: 1.001-4.99) increased risk for POAF.

Magnesium treated patients are 2.5 times less likely to develop POAF than untreated patients (OD:0.41, CI95%: 0.11-0.64). Patients with Magnesium serum levels less than 2 mg/dl are 2.3 times more likely to develop POAF than those with Mg serum levels equal to or above 2 mg/dl (OD:2.33, CI95%: 1.99-4.83).

Age over 65 years, absence of magnesium administration, magnesium levels less than 2 mg/dl, EF ≤ 40%, longer AXC and CPB time were identified as independent risk factors for the development of POAF.

The statistically significant difference in AF duration between two groups revealed possible differences in the burden of the risk factors for POAF development in each group. Comparison between the two groups of patients who developed POAF with and without magnesium therapy to identify the differences in the presence of risk factors was performed (Table 5).

Variables	Afib Mg n = 18(%)	Afib C n = 35(%)	P-value ɫ
Age	72.8 ± 3.07	68.5 ± 1.67	0.001*
Male sex	15 (83.3)	30 (85.7)	0.465
Past history			
Previous myocardial infarction	13 (72.2)	22 (62.8)	0.495
Recent MI	9 (50.0)	12 (34.3)	0.267
Hypertension	16 (88.8)	26 (74.3)	0.214
Diabetes mellitus	14 (77.7)	16 (45.7)	0.026
CHF	4 (22.2)	5 (14.2)	0.466
Hypercholesterolemia	12 (66.6)	21 (60.0)	0.635
COPD	6 (33.3)	4 (11.4)	0.053
Preoperative Echo			
EF value	0.42 ± 0.08	0.47 ± 0.08	0.029*
EF < = 40	12 (66.6)	11(31.4)	0.014
Moderate PHT	10 (55.5)	15 (42.9)	0.380
Severe PHT	7 (38.8)	4 (11.4)	0.019
RV dysfunction	9 (50.0)	13 (37.1)	0.368
La enlargement	15 (83.3)	17 (48.5)	0.014
RCA disease	15 (83.3)	25 (71.4)	0.340
Operation time (min)			
CPB	83.6 ± 9.9	78.3 ± 6.97	0.028*
Aortic cross-clamping	65.8 ± 8.95	61.6 ± 5.62	0.041*
Blood transfusion	14 (77.7)	6 (45.7)	0.026

Table 5: Comparison of All Patients who developed POAF with and without Mg therapy.

ɫ Chi-square test, *t-test.

Abbreviations correspond to those in Tables 1 and 2.

Age, EF, CBP and AXC time were identified in this study through multivariate analysis as independent contributors for POAF development (Table 4). These variables were also those that showed a significant correlation with the occurrence of AF ($p < 0.05$) in univariate analysis (Table 3). Additionally these variables have well-known clinical relevance.

Patients who developed POAF in the Mg treatment group were older, had lower EF, longer CBP, longer aortic cross clamp duration, higher rates of blood transfusion, higher prevalence of severe PHT, diabetes and LA enlargement. These findings can explain the significantly higher AF duration in the magnesium treated group. This remained significant even after patients that reverted in sinus rhythm within one hour in the control group were excluded from the analysis (24.5 ± 9.4 vs 16.96 ± 10.7, p = 0.016).

Discussion

New onset atrial fibrillation after isolated CABG is the most common arrhythmia observed postoperatively. The reported incidences of AF after CABG, in prior studies ranged from 10% to 50% [3-5].

In a recent systematic review and meta-analysis, the reported incidence of new onset atrial fibrillation (NOAF) after isolated CABG surgery ranged from 15% to 36% [31].

The traditional consideration is to consider POAF after cardiac surgery as a separate clinical entity from conventional non valvular AF that is benign, self-limited and transitory. However, increasing evidence shows that POAF carries a high risk for significant morbidity and mortality. POAF was demonstrated to be associated with two to four times: increased risk of postoperative stroke in short and long-term, increased morbidity and hospital stay, increase in all-cause 30-day and 6-month mortality, increased long term cardiovascular mortality and all-cause mortality [1,31,32]. Patients with POAF after cardiac surgery have a 5-fold increased risk of permanent AF and increased risk for long-term newly developed AF [33,34].

An association between POAF, death, and ischemic stroke persisting up to 10 years after surgical intervention is reported in two recent systematic reviews [35,36].

Early recognition and management of POAF as well as its prophylaxis could improve clinical outcomes.

POAF is multifactorial, with several risk factors being implicated, including low magnesium sulfate levels [2-5,10,27].

POAF incidence is not low after off-pump CABG operations. Consequently, cardiopulmonary bypass is not the only procedure related risk factor for the development of POAF.

Additional substantial risk factors for POAF related to intervention include: electrolyte imbalances, metabolic changes, anesthetic agents, body temperature, increased sympathetic activity, local surgical trauma, local pericardial inflammation, pericardial dissection [3,21,27].

Meanwhile, during on-pump CABG, cardioplegic perfusion is intermittently discontinued for distal anastomosis construction. This leads to myocardial ischemic injury and ischemic reperfusion injury-induced atrial/ventricular arrhythmias. Cardioplegia content and its pattern of administration, duration of cardiopulmonary bypass, duration of aortic cross clamping, and insufficient right atrial protection with consecutive atrial infarction are added risk factors related to CPB [37].

A wide variety of prophylactic strategies have been evaluated, including perioperative magnesium administration. Our findings demonstrate a beneficial role of magnesium in preventing AF after CABG.

A significant reduction in the incidence of POAF was found in the 100 consecutive patients treated with the 4-day magnesium administration (18%) compared with the 100 consecutive patients who did not receive the prophylactic treatment (35%; p 0.006).

Well established evidence demonstrates that withdrawal of preoperative beta-blockers in the postoperative period doubles the risk of AF after CABG [29,38]. In our practice, routine preoperative use and early postoperative initiation of beta-blockers to antagonize increased sympathetic activation is considered a standard approach to reduce the risk of POAF after CABG. In our study, magnesium supplementation was administered in addition to standard conventional use of beta-blockers.

Magnesium supplementation in addition to Cordarone or a beta-blocker was also applied in patients with POAF not previously treated with magnesium even in the presence of normal magnesium serum levels.

The explanation for the beneficial effects of magnesium supplementation in prophylaxis of POAF is based on the reports that hypomagnesemia increases the risk of atrial and ventricular arrhythmias [39]. Meanwhile it is demonstrated that myocardial magnesium depletion and hypomagnesemia in the immediate postoperative period, is common after cardiac surgery [10,25,26]. This is the period that POAF predominantly occurs in.

Interestingly, studies have shown that serum magnesium levels do not correlate with myocardial tissue magnesium levels [40]. Therefore, postoperative magnesium supplementation might make sense even if the serum magnesium level is normal.

Multiple randomized clinical trials have evaluated the role of prophylactic magnesium supplementation for prevention of POAF after cardiac surgery. The results are conflicting, ranging from a very significant reduction of POAF in one study (2% in the Magnesium group vs 21% in the control group; $p < 0.001$) [24] to an increased risk of POAF with higher magnesium levels in a more recent study. In this study, patients with POAF had higher magnesium than those without POAF (2.33 versus 2.16 mg/dL, $p < 0.001$) and magnesium level was shown as an independent predictor of POAF (odds ratio 4.26, $p < 0.001$) [23]. The inconsistency of results has impacted guidelines over time.

Reference	No of included RCTs	Type of cardiac surgery	Recommendation for Mg administration regimens
Shiga., *et al.* 2004	17 RCTs with 2069 pts	Not specified	No recommendation
Miller., *et al.* 2005	20 RCTs with 2490 pts	CABG or valve surgery	No recommendation
Alghamdi., *et al.* 2005	8 RCTs	Isolated CABG surgery	No recommendation
Burgess at al 2006	22 RCT with 2896 pts	Not specified	No recommendation
Henyan., *et al.* 2005	7 RCTs 1234 pts	Not specified	No recommendation
Gu., *et al.* 2012	7 RCTs 1,028 pts	Isolated CABG surgery	No recommendation
Arsenault KA., *et al.* 2013	21 RCT s 2988 pts	Not specified	No recommendation
Fairley JL., *et al.* 2017	35 RCTs	Not specified	No recommendation
Chaudhary R., *et al.* 2019	20 RCTs 2,430 pts	on -pump CABG surgery	Postoperative administration. No dosage and therapy duration specification

Table 6: Summary of meta-analyses that demonstrate a beneficial role of magnesium supplementation in POAF prophylaxis.

The European Association for Cardiothoracic Surgery in 2006 supports a Grade A recommendation for the prophylactic use of IV magnesium as an effective strategy to minimize the incidence of AF for patients undergoing cardiac surgery that may safely be given in addition to other strategies to reduce the incidence of Afib [41]. The recommendation was mainly based on 3 meta-analyses that addressed this issue as well as 20 RCTs also reviewed. The proposed magnesium regimen is a 6 mmol magnesium sulfate infusion preoperatively, just after cardiopulmonary bypass, and once daily for 4 days after surgery. This dosage suggestion is based on an individual level 1b study [24].

The first meta-analysis included in these guidelines, was performed by Shiga., *et al.* 2004 [42]. It summarized 17 RCTs with 2069 patients that utilized magnesium alone as prophylaxis of POAF after cardiac surgery and compared it to placebo treatment. There was a significant reduction of reported supraventricular tachyarrhythmias in the magnesium group compared with the placebo group (23% vs 31% RR = 0.77; 95% CI: 0.63 to 0.93; $p = 0.002$). They found a significant reduction in the incidence of ventricular tachyarrhythmias as well (RR = 0.52; 95% CI: 0.31 to 0.87; $p < 0.0001$). The number-needed-to-treat (NNT) to prevent one episode of SVT and one episode of VT was 13 patients and

14 patients respectively. Different magnesium administration regimens showed similar efficacy. Consequently, although magnesium therapy has proven efficacious, no specific prophylactic regimen has been suggested.

The second included meta-analysis, published in 2005, by Miller., *et al.* [43] summarized 20 studies with 2490 patients aiming primary prevention of postoperative AF in CABG or valve surgery. The publication dates spanned from 1982 to 2003. Patient enrollment in single studies ranged from 20 to 400 patients. They found that the incidence of POAF in the Magnesium treated patients was reduced from 28% to 18% (OR 0.54, 95% CI 0.38—0.75).

Again, due to disparities in the administration regimens with no superiority in efficacy, no specific prophylactic regimen was suggested.

The third included meta-analysis published in 2005, Alghamdi., *et al.* summarized only eight RCTs that compared magnesium with placebo in patients undergoing CABG surgery [44]. They also found a highly significant reduction in relative risk with the addition of magnesium (RR 0.64, 95% CI: 0.47— 0.87).

Shortly after EACS guidelines were published, another meta-analysis by Burgess., *et al.* reported beneficial effects of magnesium administration for the prophylaxis of POAF [45]. Twenty-two trials with 2896 patients evaluated magnesium supplementation for the prevention of POAF after cardiac surgery. An overall reduction in AF (OR 0.57, 95% CI 0.42–0.77) was reported, but there was significant heterogeneity between trials. Some of this heterogeneity was explained by the concomitant use of a beta-blocker. The largest effect of magnesium was in the two trials with no use of BB (OR 0.05, 95% CI 0.02–0.16). Again, these trials varied greatly in dose and timing of magnesium delivery.

The Canadian Cardiovascular Society in 2010 suggested that patients who have a contraindication to beta–blockers and amiodarone therapy before or after cardiac surgery be considered for prophylactic therapy to prevent postoperative AF with intravenous magnesium (Conditional Recommendation, Moderate-Quality Evidence) [38]. The evidence for this recommendation is mainly a meta-analysis published by Henyan., *et al.* in 2005. The meta-analysis consisted of 7 randomized controlled trials involving 1234 patients between 1999 and 2004 which evaluated intravenous magnesium therapy for the prevention of postoperative AF after cardiac surgery [46]. It was reported that intravenous magnesium therapy was associated with a reduction in the incidence of postoperative AF from 26.7% to 20.0% (OR 0.66, 95% CI 0.51-0.87, p = 0.003). A reduction of the postoperative length of hospital stay was reported as well (95% CI 0.05-0.54 days, p = 0.02) The greatest reduction of POAF occurrence was achieved with lower doses of intravenous magnesium and therapy initiation in the preoperative period.

Most intravenous magnesium trials reported no adverse effects of magnesium therapy in properly selected patients. There is moderate evidence behind these guidelines that lower-dose magnesium therapy initiated before cardiac surgery will reduce the postoperative incidence of AF after cardiac surgery [21,46]. The major advantage of this approach was that the therapy has a very low probability of being associated with adverse effects in patients without renal dysfunction. The proposed prophylactic IV magnesium dosage in this guideline is the same as the EACS 2006 guidelines based on the same study [24].

Three more recent reviews and meta-analyses reported beneficial effects of prophylactic magnesium therapy for the prevention of POAF.

The first one by Gu., *et al.* published in 2012 included seven double-blind placebo-controlled randomized clinical trials consisting of 1,028 individuals [47]. They reported that intravenous magnesium significantly reduced the incidence of POAF after CABG by 36% (RR 0.64; 95% CI 0.50-0.83; P = 0.001); with no statistical heterogeneity between trials (heterogeneity P = 0.8, I 2 = 0%). Four of the randomized controlled trials were also included in the previous meta-analysis by Alghamdi., *et al.* [44]. The remaining three were published more recently in 2007, 2008. Again, this meta-analysis shows diversity between trials in the dosing, timing, duration of magnesium administration, and in follow up time. Meanwhile, studies with modest samples were included.

The second one by Arsenault KA., *et al.* published in 2013 which investigated all interventions for preventing POAF in patients undergoing heart surgery included 21 RCTs that enrolled 2988 participants between 1991 and 2008 [48]. Dosing regimens varied between studies, but all administration of magnesium was done intravenously. In 12 (57.1%) of these studies, magnesium was first administered intraoperatively. This analysis demonstrated a significant reduction in POAF in the treatment group (16.5%) compared to the control group (26.2%) (OR 0.55; 95% CI 0.41 to 0.73; I 2 = 51%;).

The third one by Fairley JL published in 2017, included 35 RCTs between 1975 and 2015 with significant methodological heterogeneity [49]. Magnesium reduced the incidence of POAF after cardiac surgery (RR 0.69, 95%CI 0.56-0.86, p = 0.002) particularly if administered postoperatively for longer than 24 hours, with maximal benefit achieved with bolus doses up to 60 mmol.

The most recent meta-analyses and the first one in the setting of on-pump CABG surgery that studied the role of prophylactic magnesium for POAF prevention in patients undergoing on-pump CABG was published on 2019 by Chaudhary R., *et al.* [50]. It was aimed at determining the role of prophylactic Mg in the prevention of POAF in 3 different settings: intraoperative, postoperative, and intraoperative plus postoperative. 20 randomized placebo-controlled trials were included, with a total of 2,430 participants. Significant reduction in POAF was observed with postoperative Mg supplementation (RR 0.76; 95% CI, 0.58- 0.99; p = 0.04; I^2 = 17.6%) but not with intraoperative (RR 0.77; 95% CI, 0.49-1.22; p = 0.27; I^2 = 49%) or intraoperative plus postoperative Mg supplementation (RR 0.92; 95% CI, 0.68-1.24; p = 0.58; I^2 = 51.8%, respectively). The exact explanation for this finding was considered uncertain. No significant difference was observed between the two groups for length of stay, perioperative myocardial infarction, perioperative mortality, aortic cross-clamping time, and duration of CPB. The long-time span of trials included in this study from 1991 to 2009, the lack of specification in majority of trials of the concomitant use of beta-blockers and the diverse dosing regimens, mode of supplementation and follow-up time were considered the limitations of this study. No significant heterogeneity was observed for POAF reduction in the postoperative Mg supplementation group. Ultimately, it was concluded that Magnesium supplementation in the postoperative period is an effective strategy in reducing POAF following CABG.

Finally, ESC recommends perioperative amiodarone or beta blocker therapy for the prevention of postoperative AF after cardiac surgery [29].

Data for Magnesium administration along with other interventions such as statins, sotalol, colchicine, posterior pericardiotomy, (bi)atrial pacing and corticosteroids are not robust.

Interestingly the guidelines give a Class IIb recommendation for the consideration of long term oral anticoagulation in the population of patients that develop AF after cardiac surgery, without excluding a careful screening of patients who are at increased risk of stroke. The explanation for this approach is the presence of transitory risk factors for the development of POAF mainly related to intervention in addition to permanent intrinsic risk factors.

Our study showed a significant benefit of 4-day intravenous magnesium administration in the postoperative period in preventing POAF after on-pump CABG surgery.

Interestingly the duration of fibrillation in the magnesium treatment group was significantly higher than in the control group. No patient with AF in the treatment group reverted spontaneously to sinus rhythm while 5 patients (14%) with AF in the control group reverted in less than 1 hour with the remaining patients still having a significantly shorter duration of AF compared with patients in the treatment group.

One explanation would be the propensity of intrinsic or surgery related risk factors like: older age, EF, duration of CPB, or need for blood transfusion, in the magnesium treatment group that developed POAF where magnesium supplementation as a prophylactic tool and treatment alternative in addition to conventional POAF treatment is already consumed. That was the rationale for the comparison of risk factors between two groups of patients who developed POAF with and without magnesium. It was shown that patients who developed POAF in the magnesium treatment group had a significantly higher presence of risk factors compared with patients who developed POAF in the control group.

This leads to the rational assumption that magnesium administration might prevent that percentage of POAF that tends to be transitory, self-limited, and of shorter duration. In such cases, magnesium administration might be considered a helpful tool in identifying patients with POAF that have an increased risk for permanent AF in the future. These patients do not respond to magnesium therapy alone due to higher risk factor burden and need more aggressive and extended therapy, more frequent reevaluation and careful periodic reconsideration for the need of continuation of therapy, especially anticoagulation.

In conclusion, postoperative 4-day supplementation of magnesium sulfate is helpful in reducing the incidence of AF after CABG. In older patients, patients with reduced EF, and patients with longer CPB and Aortic cross clamping times, magnesium supplementation alone is inadequate for the prevention of postoperative AF. The higher duration of AF and the increased presence of risk factors in the patients who developed AF in the magnesium treatment group, argues for magnesium therapy's effectiveness in the prevention of a more benign form of POAF. In our view, an important advantage of magnesium therapy is helping to identify patients who develop POAF with a higher risk of morbidity and mortality.

Identification of patients with risk factors, efforts in optimizing surgery duration, techniques to improve myocardial protection and adjunctive prophylactic interventions are required to further decrease the incidence of POAF after isolated on-pump CABG surgery.

Due to the heterogeneity, long time span, and studies with limited number of patients, there is a need for further examination of the role of magnesium therapy. Large prospective randomized controlled trials, preferably multicenter studies, are required to clarify and unify the approach towards this simple, safe, and cost-effective therapeutic tool.

Bibliography

1. Greenberg JW., *et al*. "Postoperative atrial fibrillation following cardiac surgery: a persistent complication". *European Journal of Cardio-Thoracic Surgery* 52.4 (2017): 665-672.

2. Melby S J., *et al*. "A time-related parametric risk factor analysis for postoperative atrial fibrillation after heart surgery". *The Journal of Thoracic and Cardiovascular Surgery* 149 (2015): 886-892.

3. Aranki SF., *et al*. "Predictors of atrial fibrillation after coronary artery surgery: current trends and impacts on hospital resources". *Circulation* 94 (1996): 390-397.

4. Funk M., *et al*. "Incidence, timing, symptoms, and risk factors for atrial fibrillation after cardiac surgery". *American Journal of Critical Care* 12 (2003): 424-433.

5. Kalman JM., *et al*. "Atrial fibrillation after coronary artery bypass grafting is associated with sympathetic activation". *The Annals of Thoracic Surgery* 60 (1995): 1709-1715.

6. Reed G III., *et al*. "Stroke following coronary-artery bypass surgery. A case-control estimate of the risk from carotid bruits". *The New England Journal of Medicine* 319 (1988): 1246-1250.

7. Roach GW., *et al*. "Adverse cerebral outcomes after coronary bypass surgery". *The New England Journal of Medicine* 335 (1996): 1857-1863.

8. Bucerius J., *et al*. "Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery". *The Journal of Thoracic and Cardiovascular Surgery* 127 (2004): 57-64.

9. Saxena A., *et al*. "Usefulness of postoperative atrial fibrillation as an independent predictor for worse early and late outcomes after isolated coronary artery bypass grafting (multicenter Australian study of 19,497 patients)". *American Journal of Cardiology* 109 (2012): 219-225.

10. Kaplan M., *et al*. "Intravenous magnesium sulfate prophylaxis for atrial fibrillation after coronary artery bypass surgery". *The Journal of Thoracic and Cardiovascular Surgery* 125 (2003): 344-352.

11. O'Neal JB., *et al*. "Effect of preoperative beta-blocker use on outcomes following cardiac surgery". *American Journal of Cardiology* 120 (2017): 12931297.

12. Daoud EG., *et al*. "Preoperative amiodarone as prophylaxis against atrial fibrillation after heart surgery". *The New England Journal of Medicine* 337.25 (1997): 1785-1791.

13. Buckley MS., *et al*. "Amiodarone prophylaxis for atrial fibrillation after cardiac surgery: meta analysis of dose response and timing of initiation". *Pharmacotherapy* 27 (2007): 360-368.

14. Fanning WJ., *et al*. "Prophylaxis of atrial fibrillation with magnesium sulfate after coronary artery bypass grafting". *The Annals of Thoracic Surgery* 52.3 (1991): 529-533.

15. Colquhoun IW., *et al*. "Arrhythmia prophylaxis after coronary artery surgery. A randomised controlled trial of intravenous magnesium chloride". *European Journal of Cardio-Thoracic Surgery* 7.10 (1993): 520-523.

16. Parikka H., *et al*. "The influence of intravenous magnesium sulphate on the occurrence of atrial fibrillation after coronary artery by-pass operation". *European Heart Journal* 14.2 (1993): 251-258.

17. Speziale G., *et al*. "Arrhythmia prophylaxis after coronary artery bypass grafting: regimens of magnesium sulfate administration". *Thoracic and Cardiovascular Surgery* 48 (2000): 22-26.

18. Shakerinia T., *et al*. "Magnesium in cardioplegia: is it necessary?". *Canadian Journal of Surgery* 39.5 (1996): 397-400.

19. Jensen BM., *et al*. "Magnesium substitution and postoperative arrhythmias in patients undergoing coronary artery bypass grafting". *Scandinavian Cardiovascular Journal* 31.5 (1997): 265-269.

20. Treggiari-Venzi MM., *et al*. "Intravenous amiodarone or magnesium sulphate is not cost-beneficial prophylaxis for atrial fibrillation after coronary artery bypass surgery". *British Journal of Anaesthesia* 85.5 (2000): 690-695 JO.

21. Solomon AJ., *et al*. "The combination of propranolol and magnesium does not prevent postoperative atrial fibrillation". *The Annals of Thoracic Surgery* 69.1 (2000): 126-129.

22. Hazelrigg SR., *et al*. "The efficacy of supplemental magnesium in reducing atrial fibrillation after coronary artery bypass grafting". *The Annals of Thoracic Surgery* 77.3 (2004): 824-830.

23. Lancaster TS., *et al*. "Potassium and Magnesium Supplementation Do Not Protect Against Atrial Fibrillation After Cardiac Operation: A Time-Matched Analysis". *The Annals of Thoracic Surgery* 102 (2016): 1181-1189.

24. Toraman F., *et al*. "Magnesium infusion dramatically decreases the incidence of atrial fibrillation after coronary artery bypass grafting". *The Annals of Thoracic Surgery* 72 (2001): 1256-1261.

25. Aglio LS., *et al*. "Hypomagnesemia is common following cardiac surgery". *The Journal of Cardiothoracic and Vascular Anesthesia* 5 (1991): 201-208.

26. Wilkes NJ., *et al*. "Correction of ionized plasma magnesium during cardiopulmonary bypass reduces the risk of postoperative cardiac arrhythmia". *Anesthesia and Analgesia* 95 (2002): 828-834.

27. Satur CMR., *et al*. "Magnesium flux caused by coronary artery bypass operation: three patterns of deficiency". *The Annals of Thoracic Surgery* 58 (1994): 1674-1678.

28. Yang Q., *et al*. "Protective effect of magnesium on the endothelial function mediated by endothelium-derived hyperpolarizing factor in coronary arteries during cardioplegic arrest in a porcine model". *The Journal of Thoracic and Cardiovascular Surgery* 124 (2002): 361-370.

29. Hindricks G., *et al*. "2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS):)". *European Heart Journal* 42 (2020): 373-498.

30. Frendl G., *et al*. "2014 AATS guidelines for the prevention and management of perioperative atrial fibrillation and flutter for thoracic surgical procedures". *The Journal of Thoracic and Cardiovascular Surgery* 148 (2014): e153-e193.

31. Kerwin M., *et al*. "New-onset atrial fibrillation and outcomes following isolated coronary artery bypass surgery: A systematic review and metaanalysis". *Clinical Cardiology* 43 (2020): 928-934.

32. Benedetto U., *et al*. "Postoperative Atrial Fibrillation and Long-Term Risk of Stroke After Isolated Coronary Artery Bypass Graft Surgery". *Circulation* 142 (2020): 1320-1329.

33. Lee SH., *et al*. "New-onset atrial fibrillation predicts long-term newly developed atrial fibrillation after coronary artery bypass graft". *American Heart Journal* 167 (2014): 593-600. e591.

34. Lin MH., *et al*. "Perioperative/postoperative atrial fibrillation and risk of subsequent stroke and/or mortality". *Stroke* 50 (2019): 1364-1371.

35. Phan K., *et al*. "Newonset atrial fibrillation following coronary bypass surgery predicts long-term mortality: a systematic review and meta analysis". *European Journal of Cardio-Thoracic Surgery* 48 (2015): 817-824.

36. Kaw R., *et al*. "Short-and long-term mortality associated with new-onset atrial fibrillation after coronary artery bypass grafting: a systematic review and meta-analysis". *The Journal of Thoracic and Cardiovascular Surgery* 141 (2011): 1305-1312.

37. Saatvedt K., *et al*. "Is atrial fibrillation caused by extracorporeal circulation?". *The Annals of Thoracic Surgery* 68 (1999): 931-933.

38. Mitchell BL and the CCS Atrial Fibrillation Guidelines Committee Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010. "Prevention and Treatment of Atrial Fibrillation Following Cardiac Surgery". *Canadian Journal of Cardiology* 27 (2011): 91-97.

39. Klevay LM and Milne DB. "Low dietary magnesium increases supraventricular ectopy". *American Journal of Clinical Nutrition* 75.3 (2002): 550-554.

40. Millane TA., *et al*. "Myocardial magnesium depletion associated with prolonged hypomagnesemia: a longitudinal study in heart transplant recipients". *Journal of the American College of Cardiology* 20.4 (1992): 806-812.

41. Dunning J., *et al*. "Guidelines on the prevention and management of de novo atrial fibrillation after cardiac and thoracic surgery". *European Journal of Cardio-thoracic Surgery* 30 (2006): 852-872.

42. Shiga T., *et al*. "Magnesium prophylaxis for arrhythmia after cardiac surgery: a meta-analysis of randomised controlled trials". *American Journal of Medicine* 117 (2004): 325-333.

43. Miller S., *et al*. "Effects of Magnesium on atrial fibrillation after cardiac surgery: a meta-analysis". *Heart* 91 (2005): 618-623.

44. Alghamdi AA., *et al*. "Intravenous magnesium for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and meta-analysis". *Journal of Cardiac Surgery* 20 (2005): 293-299.

45. Burgess D C., *et al*. "Interventions for prevention of post-operative atrial fibrillation and its complications after cardiac surgery: a meta-analysis". *European Heart Journal* 27 (2006): 2846-2857.

46. Henyan NH., *et al*. "Impact of intravenous magnesium on post-cardiothoracic surgery atrial fibrillation and length of hospital stay: a meta-analysis". *The Annals of Thoracic Surgery* 80 (2005): 2402-2406.

47. Gu., *et al*. "Intravenous magnesium prevents atrial fibrillation after coronary artery bypass grafting: a metaanalysis of 7 double-blind, placebo-controlled, randomized clinical trials". Gu et al. Trials (2012).

48. Arsenault KA., *et al*. "Interventions for preventing post-operative atrial fibrillation in patients undergoing heart surgery". *Cochrane Database System Review* (2013): CD003611.

49. Fairley JL., *et al*. "Magnesium status and magnesium therapy in cardiac surgery: a systematic review and meta-analysis focusing on arrhythmia prevention". *Journal of Critical Care* 42 (2017): 69-77.

50. Chaudhary R., *et al*. "Role of Prophylactic Magnesium Supplementation in Prevention of Postoperative Atrial Fibrillation in Patients Undergoing Coronary Artery Bypass Grafting: a Systematic Review and Meta-Analysis of 20 Randomized Controlled Trials". *Journal of Atrial Fibrillation* 12.1 (2019).