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Magnesium Sulfate for Atrial Fibrillation Management in Chilean High-Resolution Primary Care Emergency Services: An Evidence-Based Protocol

Dr. Camilo Vidal Araya[1]; Dr. María José Yarí Acosta[1]; Dr. Amanda Oraa[2]

[1]Servicio de Atención Primaria de Urgencia de Alta Resolución (SAR), San Miguel, Santiago, Chile.
[2]Servicio de Atención Primaria de Urgencia de Alta Resolución (SAR), Pedro Aguirre Cerda, Santiago, Chile.

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Abstract:

- ***Introduction:***

Atrial fibrillation (AF) represents a frequent challenge in Chilean emergency services, particularly in resource-limited settings. This study evaluated the efficacy, safety, and feasibility of magnesium sulfate ($MgSO_4$) as a therapeutic alternative in the acute management of AF in primary emergency care services.

- ***Methods:***

We conducted a systematic review following PRISMA guidelines, including studies published between 2000-2023 that evaluated the use of intravenous $MgSO_4$ in adults with AF. Outcomes analyzed included ventricular rate control, conversion to sinus rhythm, and adverse effects. Methodological quality was assessed using standardized scales (Jadad, Cochrane, AMSTAR-2, GRADE). Additionally, implementation feasibility was analyzed considering technical, economic, organizational, and regulatory aspects in the context of Chilean SAPU/SAR services.

- ***Results:***

Eighteen studies were included (11 clinical trials, 4 meta-analyses, 3 systematic reviews) with 1,237 participants. $MgSO_4$ demonstrated significant efficacy for ventricular rate control (OR 1.96-2.49) and moderate efficacy for conversion to sinus rhythm (OR 1.60-1.75). Hoffer et al.'s meta-analysis (2022) with 815 patients confirmed significant heart rate reduction (SMD 0.34; 95% CI 0.21-0.47; $p<0.001$; $I^2=4\%$). The safety profile was favorable, with predominantly mild adverse effects (facial flushing 15-30%, nausea 5-10%) and low incidence of serious effects (hypotension 0-3%, bradycardia 0-2%). Feasibility analysis revealed advantages in availability, cost ($600-800 CLP/ampoule), and ease of implementation in primary emergency services.

- ***Conclusions:***

Magnesium sulfate constitutes an effective, safe, and cost-efficient alternative for the initial management of atrial fibrillation in Chilean primary emergency services, especially when first-line treatments are contraindicated or unavailable. We propose an implementation protocol adapted to our local reality, with a dose of 2.5 g in slow infusion, recognizing the need for specific studies in the Chilean population.

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I. INTRODUCTION

Atrial fibrillation is not just an electrocardiographic diagnosis for us; it represents a true clinical challenge that we frequently face in our emergency services. With a global prevalence between 1-2% in the general population, increasing to 8-15% in those over 80 years, this arrhythmia constitutes a significant public health problem. In Chile, in the specific context of our Primary Emergency Care Services (SAPU) and High Resolution Primary Emergency Care Services (SAR), which manage approximately 12 million consultations annually, we estimate that between 30,000-40,000 episodes correspond to AF.

During our clinical shifts, we focus on three main objectives when managing AF: controlling ventricular rate, evaluating the need for cardioversion, and assessing thromboembolic risk. However, in our primary care centers, we frequently encounter limited therapeutic options, mainly beta-blockers, lanatoside C, and verapamil. Recent guidelines from the European Society of Cardiology (ESC) 2024 and the American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society (ACC/AHA/ACCP/HRS) 2023 establish clear recommendations, but these are primarily oriented toward settings with complete resources, a reality different from ours.

This gap between ideal recommendations and our practical reality motivated us to explore therapeutic alternatives such as magnesium sulfate, an economical drug widely available in our services, which we already use for other conditions such as severe asthma and preeclampsia.

II. METHODOLOGY

To address our clinical concern, we designed a systematic review following PRISMA guidelines. We conducted comprehensive searches in PubMed, Cochrane Library, LILACS, and SciELO from January 2000 to June 2023, using terms related to magnesium sulfate and atrial fibrillation. We included studies in adult patients who received intravenous $MgSO_4$ and evaluated at least one of the following outcomes: ventricular rate control, conversion to sinus rhythm, or adverse effects. We excluded studies in pediatric populations, immediate postoperative AF, oral magnesium supplementation, case reports, small observational studies, and editorials (See table 1)

To ensure methodological quality, we evaluated each study with standardized tools: the Jadad scale and Cochrane risk of bias tool for clinical trials, and AMSTAR-2 for meta-analyses and systematic reviews. Additionally, we used the GRADE system to evaluate the overall quality of evidence. To determine the feasibility of implementation in our context, we analyzed technical aspects (drug availability, necessary equipment, monitoring capacity), economic aspects (drug cost, cost-effectiveness estimation), organizational aspects (alignment with SAR/SAPU infrastructure, necessary training), and regulatory aspects (adaptation to current regulations). We also comprehensively reviewed the most recent guidelines to contrast our findings with current international recommendations.

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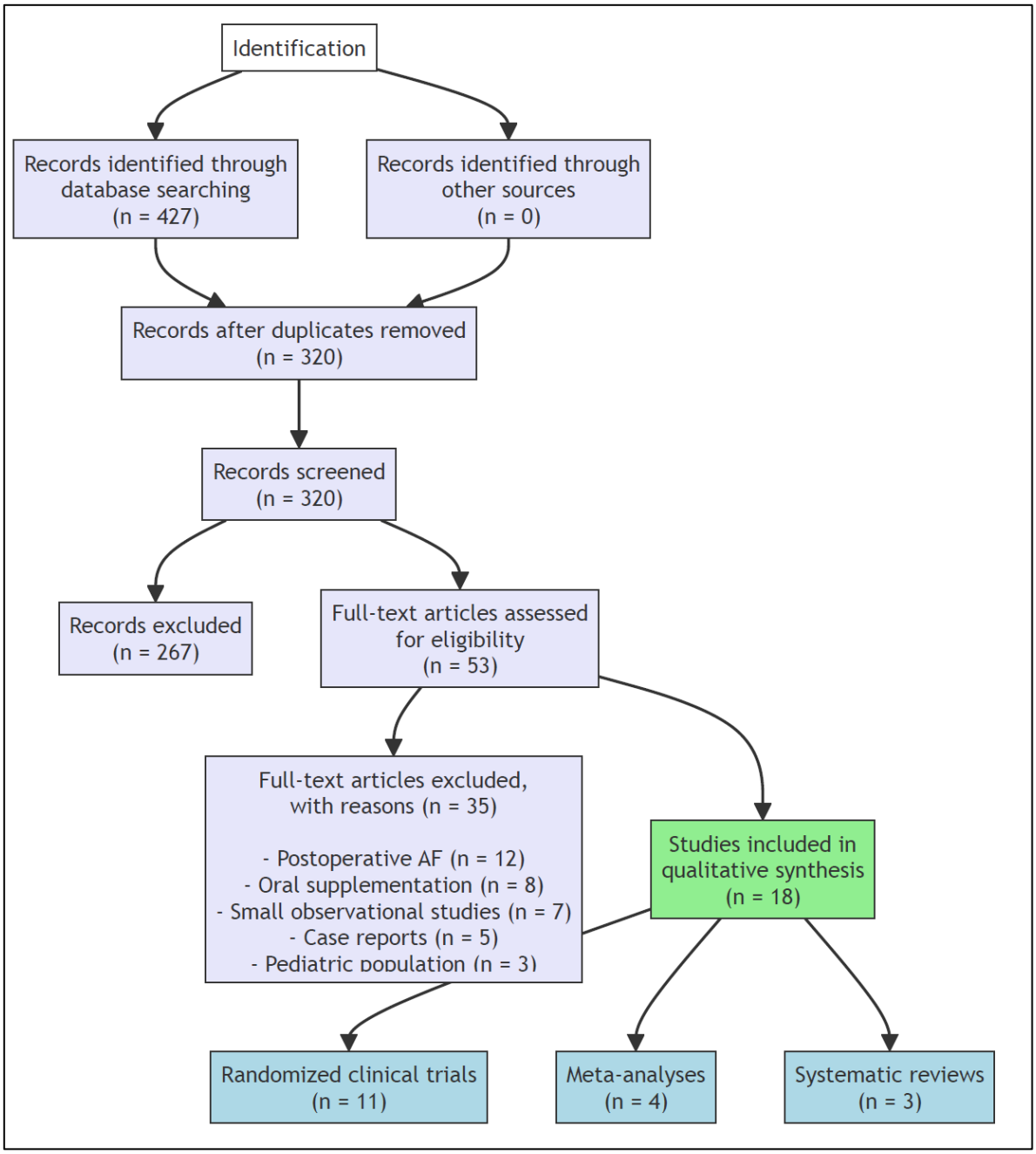

Fig 1. PRISMA Flow Diagram of Study Selection Process

III. RESULTS

➢ *Selection and Characteristics of Studies (Table 1)*

Our initial search identified 427 records, of which 18 met our inclusion criteria: 11 randomized clinical trials, 4 meta-analyses, and 3 systematic reviews. The clinical trials included a total of 1,237 participants, with sample sizes ranging from 24 to 199 patients. $MgSO_4$ was compared with placebo in 7 studies, with other antiarrhythmics in 3 studies (amiodarone, diltiazem, procainamide), and as an adjunct to digoxin in 1 study. The meta-analyses and systematic reviews included between 8-17 studies each, involving between 476-1,703 patients. Most compared the effectiveness of $MgSO_4$ with placebo.

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Table 1. Characteristics of Included Studies

Author, Year	Design	Sample	Intervention	Comparator	Main Results	Quality
Onalan et al., 2007	Meta-analysis	638	$MgSO_4$ (various doses)	Placebo	Rate control (OR 1.96, 95% CI 1.24-3.08); Conversion to sinus rhythm (OR 1.75, 95% CI 1.14-2.67)	AMSTAR-2: 12/16
Ho et al., 2007	Meta-analysis	476	$MgSO_4$ (various doses)	Placebo	Conversion to sinus rhythm (OR 1.60, 95% CI 1.07-2.39, p=0.02)	AMSTAR-2: 11/16
Ramesh et al., 2021	Meta-analysis	1,227	$MgSO_4$ (various doses)	Placebo	Rate control (OR 2.49, 95% CI 1.82-3.42, p<0.001)	AMSTAR-2: 14/16
Hoffer et al., 2022	Meta-analysis	815	$MgSO_4$ (various doses)	Placebo	HR reduction (SMD 0.34, 95% CI 0.21-0.47, p<0.001)	AMSTAR-2: 13/16
Bouida et al., 2019	RCT	199	$MgSO_4$ 4.5g vs 9g	-	Similar efficacy between doses; Fewer adverse effects with 4.5g (17% vs 27%, p=0.04)	Jadad: 5/5
Chu et al., 2009	RCT	106	$MgSO_4$ 2.5g	Diltiazem	Less hypotension with $MgSO_4$ (2% vs 13%, p=0.03)	Jadad: 4/5

➢ *Efficacy in Ventricular Rate Control*

Ten studies evaluated the effectiveness of $MgSO_4$ in controlling ventricular rate in AF. The meta-analysis by Ramesh et al. (2021) reported that $MgSO_4$ was significantly more effective than placebo (OR 2.49, 95% CI 1.82-3.42, p<0.001), based on 12 trials with 1,227 patients. Onalan et al. (2007) obtained similar results in a meta-analysis of 9 studies (638 patients) with an OR of 1.96 (95% CI 1.24-3.08). In our practice, this means we could expect a mean reduction in ventricular rate of approximately 15-30 beats/min, with an average time to rate control of 30-60 minutes. The meta-analysis by Hoffer et al. (2022), which included 5 randomized clinical trials with 815 patients, demonstrated that magnesium treatment was associated with a significant reduction in heart rate (standardized mean difference 0.34; 95% CI 0.21-0.47; p<0.001; I^2=4%). Additionally, they observed that higher maintenance doses correlated positively with greater heart rate reductions.

➢ *Efficacy in Conversion to Sinus Rhythm*

Nine articles evaluated the effectiveness of $MgSO_4$ in restoring sinus rhythm, with more heterogeneous results. The meta-analysis by Ho et al. (2007), which included 8 clinical trials (476 patients), found that $MgSO_4$ was associated with a higher probability of reversion to sinus rhythm compared to placebo (OR 1.60, 95% CI 1.07-2.39, p=0.02). The conversion rate varied between 13% and 60%, with a weighted average of approximately 30%. Onalan et al. (2007) also showed favorable results for conversion to sinus rhythm (OR 1.75, 95% CI 1.14-2.67), with greater effect in patients with recent-onset AF (<48h) and in those with low baseline serum magnesium levels. However, Hoffer et al. (2022) did not find a significant association between magnesium treatment and higher rates of conversion to sinus rhythm (OR 1.46; 95% CI 0.726-2.94; p=0.29) in their meta-analysis.

➢ *Safety and Adverse Effects*

In our clinical practice, the safety of any intervention is paramount. Fortunately, all studies showed that $MgSO_4$ has a favorable safety profile, with adverse effects that are mostly mild and transient. The most frequent adverse event was facial flushing or sensation of heat (15-30% of patients). Other common reactions included nausea (5-10%), dizziness (3-8%), and pain at the injection site (2-5%). Serious adverse effects were rare. Marked hypotension occurred in only 0-3% of patients, typically related to rapid infusion or high dose. Symptomatic bradycardia occurred in 0-2% of cases. No study reported cases of complete atrioventricular block, asystole, or death caused by $MgSO_4$, and the frequency of treatment discontinuation due to adverse effects was low (1-3%). Comparatively, $MgSO_4$ showed a more favorable safety profile than other antiarrhythmics. Chu et al. (2009) found that episodes of hypotension were significantly less frequent with $MgSO_4$ than with diltiazem (2% vs 13%, p=0.03), and

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Bouida et al. (2019) reported a lower rate of bradycardia with $MgSO_4$ than with amiodarone (1% vs 6%, p=0.04).

➢ *Feasibility of Implementation in Our Services*

From our practical perspective, $MgSO_4$ presents several advantages for implementation in SAR/SAPU services. Regarding availability and cost, a 5 ml ampoule of 25% magnesium sulfate (1.25 g) costs approximately $600-800 (CLP), significantly more economical than an ampoule of amiodarone ($5,000-7,000 CLP) or propafenone ($8,000-10,000 CLP). Additionally, $MgSO_4$ is already part of the basic pharmacological arsenal of our emergency services according to Technical Standard No. 16 of MINSAL. Regarding the optimal dose, based on the reviewed studies, we consider that a moderate dose (2-3 g) provides the best balance between safety and efficacy. Bouida et al. (2019) demonstrated that low (4.5 g) and high (9 g) doses have comparable efficacy, but high doses present a higher rate of adverse events (27% vs 17%, p=0.04). As for the administration scheme, slow infusion (15-20 min) is associated with a lower incidence of adverse events. We propose a regimen of 2.5 g (2 ampoules of 5 ml at 25%) diluted in 100 ml of 5% glucose, administered over 15-20 minutes, with response evaluation at 30 minutes and an optional additional dose of 1.25 g if there is no adequate response.

➢ *Recommendations from International Guidelines*

The ESC 2024 and ACC/AHA/ACCP/HRS 2023 guidelines do not specifically include magnesium sulfate among the drugs recommended for AF management. For acute rate control, they recommend beta-blockers, diltiazem/verapamil, and digoxin. This discrepancy between the evidence we have found and international recommendations led us to position $MgSO_4$ not as a first-line treatment, but as an alternative when recommended drugs are contraindicated or unavailable, or as adjuvant therapy. See table 2 to comparison of A management recommendations between international guidelines and proposed protocol for SAR /SAPU.

Table 2. Comparison of AF Management Recommendations Between International Guidelines and Proposed Protocol for SAR/SAPU

Aspect	ESC Guidelines 2024	ACC/AHA/ACCP/HRS Guidelines 2023	Proposed Protocol for SAR/SAPU
Rate Control	Beta-blockers (I,A) Diltiazem/verapamil (I,B) Digoxin (I,B)	IV Beta-blockers (1,B-R) IV Diltiazem/verapamil (1,B-R) IV Digoxin (2a,B-R)	1st line: Beta-blockers (propranolol) 1st line alternative: Lanatoside C 2nd line: Magnesium sulfate
Pharmacological Cardioversion	Flecainide/propafenone (I,A) Amiodarone (I,A) Vernakalant (I,A)	Flecainide/propafenone/ibutilide (1,A) Amiodarone (1,A)	Not included in initial protocol (referral)
Role of Magnesium Sulfate	Not mentioned	Only mentioned for prevention of torsades de pointes	2nd line option for rate control Adjuvant to beta-blockers/digoxin
Referral Criteria	Hemodynamic instability AF with preexcitation Acute coronary syndrome	Hemodynamic instability AF with preexcitation Acute coronary syndrome	Similar to international guidelines + Lack of response to treatment within 2 hours

IV. OUR PROTOCOL PROPOSAL

Based on our review and considering both the scientific evidence and the reality of our services, we propose a protocol that begins with an initial assessment where the diagnosis must be confirmed with a 12-lead ECG, hemodynamic stability evaluated, possible triggers identified, relevant comorbidities assessed, and CHA_2DS_2-VASc calculated for thromboembolic risk. As first-line treatment, aligned with international guidelines, we recommend beta-blockers (propranolol 0.5-1 mg IV slow) or, if contraindicated, Lanatoside C. For second-line treatment, we suggest magnesium sulfate at a dose of 2.5 g in 100 ml of 5% glucose administered over 15-20 minutes, with response evaluation at 30 minutes and an optional additional dose of 1.25 g if there is no adequate response. Monitoring should include vital signs every 5 minutes during the initial infusion, 12-lead ECG before and after the procedure, continuous pulse oximetry, and clinical evaluation of possible side effects. We establish as referral criteria hemodynamic instability, signs of decompensated heart failure, suspicion of acute coronary syndrome, very rapid ventricular response that does not improve, ventricular preexcitation, thromboembolic complications, and lack of adequate response after two hours.

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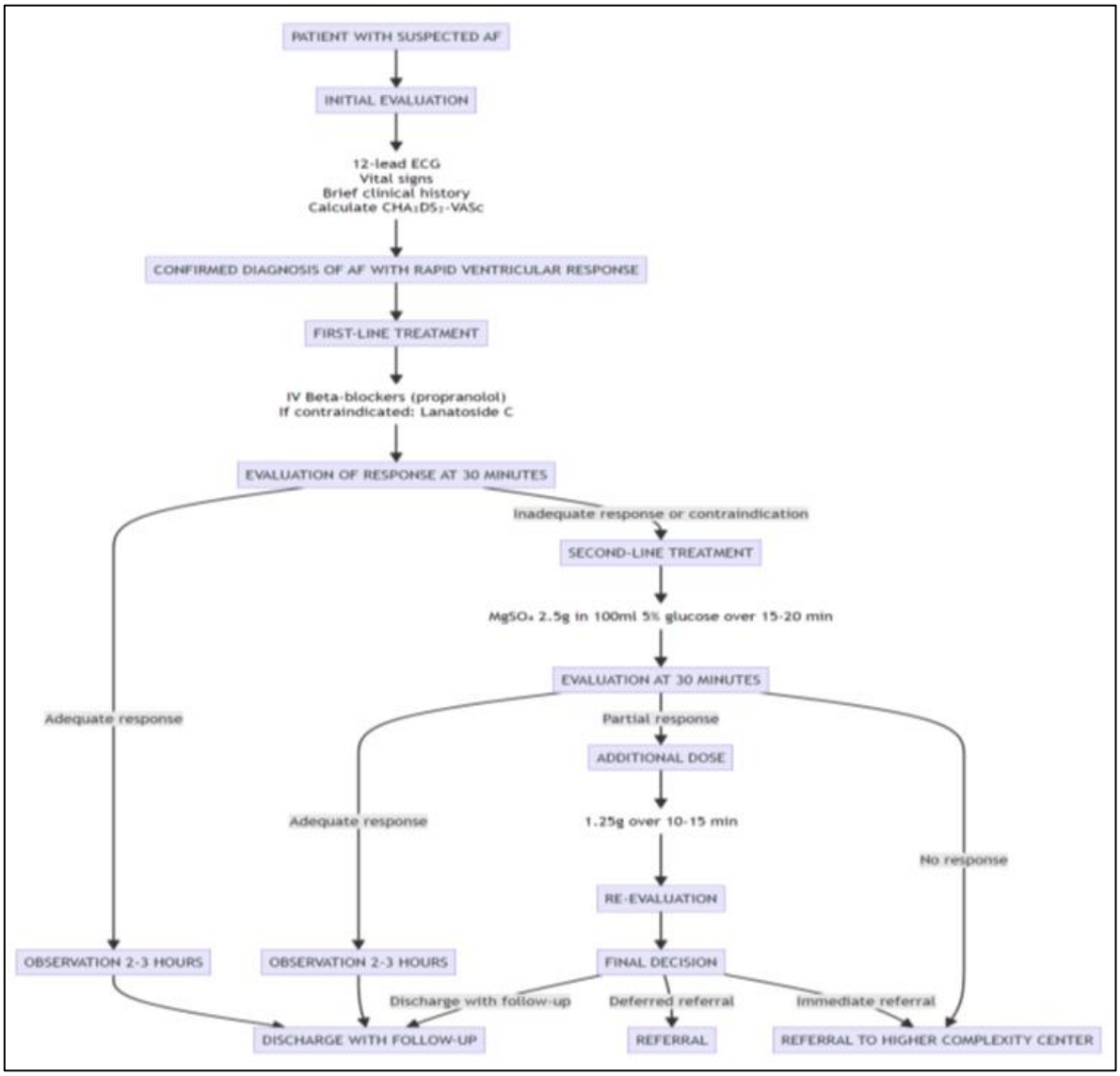

Fig 2. Proposed Algorithm for AF Management with Magnesium Sulfate in SAR/SAPU in Accordance with International Guidelines

V. CONCLUSIONS

Our comprehensive review of the available evidence allows us to conclude that magnesium sulfate constitutes an effective, safe, and cost-efficient alternative for the initial management of atrial fibrillation in our primary emergency services. Although it is not included in the first-line recommendations of international guidelines, we consider that it can be a valid option when standard treatments are contraindicated or unavailable, particularly in our context of limited resources. The implementation of the proposed protocol would mainly require staff training and adaptation of local guidelines, without the need for significant investments in infrastructure or equipment. We recognize the limitations of our proposal, mainly the moderate quality of the available evidence and the lack of specific studies in the Chilean context. Therefore, we recommend a gradual implementation and the conduct of local studies that specifically evaluate the effectiveness and safety of $MgSO_4$ in our population. Ultimately, our goal is to improve the care of our patients with atrial fibrillation, offering therapeutic alternatives adapted to our local reality, without compromising the quality of care or patient safety.

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