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Efficacy, Safety, and Feasibility of Verapamil in the Management of Atrial Fibrillation in Emergency Services with Limited Resources: A Systematic Review

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Abstract:

- ***Introduction:***

Atrial fibrillation represents one of the most frequent arrhythmias in emergency services, particularly in settings with limited resources where clear protocols and accessible drugs are required. Verapamil shows significant potential for controlling ventricular rate, although it faces various implementation challenges. This study systematically evaluates its efficacy, safety, and feasibility in emergency contexts with limited resources.

- ***Methods:***

A systematic review was conducted following PRISMA guidelines. The search was performed in MEDLINE/PubMed, Embase, Cochrane Library, LILACS, and Google Scholar (January 2000-June 2024), including observational studies, clinical trials, and economic evaluations. Specific MeSH terms related to verapamil and atrial fibrillation in emergencies were used. Two independent reviewers assessed methodological quality using GRADE and Newcastle-Ottawa scales.

- ***Results:***

Of 487 articles identified, 42 met inclusion criteria. Verapamil demonstrated efficacy in ventricular rate control (mean reduction of 25-35 bpm in 30 minutes) with a favorable safety profile (NNH for significant hypotension: 38). Structured protocols reduced hospital admissions (18%, $p<0.01$) and need for cardioversions (22%, $p<0.005$) without requiring additional personnel. Economic analyses showed cost reduction ($420-680 per patient) by reducing admissions and hospital stays. "Wait and see" strategies proved viable in selected patients (CHA_2DS_2-VASc <2, without ventricular dysfunction).

- ***Discussion:***

The findings demonstrate that verapamil, when implemented within structured protocols, represents an effective alternative for ventricular rate control in atrial fibrillation in emergency services. Its favorable safety profile, with a number needed to harm (NNH) of 38 for significant hypotension, suggests a manageable risk in controlled settings. The significant reductions in hospital admissions and need for cardioversions have important implications for healthcare systems with limited resources, where resource optimization is crucial. Additionally, the documented economic benefits reinforce its value as a cost-efficient intervention.

- ***Conclusions:***

Verapamil constitutes an effective, safe, and cost-efficient option for the management of atrial fibrillation in emergency settings with limited resources when implemented within structured protocols. It is recommended to develop standardized guidelines, improve transition to outpatient care, and conduct larger comparative studies to optimize its use in various clinical contexts.

Keywords: *Atrial Fibrillation, Verapamil, Emergency Services, Limited Resources, Rate Control.*

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I. INTRODUCTION

Atrial fibrillation (AF) represents the most frequent sustained cardiac arrhythmia in clinical practice, with a global prevalence ranging between 1-2% of the general population, increasing significantly with age to reach 8-15% in those over 80 years. This condition constitutes a frequent reason for consultation in emergency services, representing approximately 3-6% of visits for cardiovascular causes. In Latin America, recent data suggest that the prevalence of AF is similar to that reported in developed countries, but with a different management profile due to limitations in diagnostic and therapeutic resources.

In the context of emergency services, particularly those with limited resources, the management of AF poses significant challenges. These include the need for clear protocols, accessible drugs, and cost-effective strategies that allow adequate symptomatic control while minimizing risks and optimizing resources. The operational definition of "limited resource setting" used in this review includes emergency services that meet at least two of the following criteria: restricted availability of continuous cardiac monitoring, limited access to immediate cardiological consultation, restrictions in the availability of certain antiarrhythmic drugs, and/or limitations in the capacity to perform electrical cardioversion.

The management of AF in emergencies has evolved from traditional strategies focused exclusively on rate or rhythm control, towards a more comprehensive approach that includes thromboembolic risk assessment, appropriate anticoagulation, and follow-up planning. However, controversy persists regarding the optimal strategy in the acute context, particularly in settings with limited resources. While some international guidelines prioritize rhythm control through electrical or pharmacological cardioversion, others emphasize more conservative approaches based on rate control, reflecting the heterogeneity in current clinical practice.

Verapamil, a non-dihydropyridine calcium channel blocker, has been used for decades for rate control in AF. Its mechanism of action involves blocking L-type calcium channels in the atrioventricular node, reducing conduction and decreasing ventricular rate. Its potential advantages include rapid onset of action when administered intravenously, widespread availability, low cost, and generally predictable adverse effect profile. However, its implementation in clinical practice faces barriers including concerns about adverse hemodynamic effects, variability in administration protocols, and lack of clarity regarding its positioning compared to other therapeutic options such as beta-blockers or digoxin.

Evidence on the practical application of verapamil in the management of AF in emergency services with limited resources is dispersed in the literature, without a comprehensive synthesis that integrates aspects of efficacy, safety, cost-effectiveness, and implementation. This knowledge gap hinders the development of standardized protocols adapted to these specific contexts, resulting in variability in clinical practice and potentially suboptimal outcomes for patients.

The conceptual framework of this review integrates four fundamental dimensions in the evaluation of verapamil for AF in emergencies: (1) clinical efficacy in ventricular rate control; (2) safety profile and management of adverse effects; (3) economic aspects and resource utilization; and (4) barriers and facilitators for its implementation in structured protocols. This multidimensional approach allows a comprehensive evaluation that transcends purely pharmacological aspects to address practical applicability in specific clinical contexts.

The purpose of this systematic review is to critically examine the practical implementation of verapamil in the management of AF in emergency services with limited resources, synthesizing available evidence on its efficacy, safety, cost-effectiveness, and implementation aspects. Specific objectives include: (1) evaluating the efficacy of verapamil in ventricular rate control in recent-onset AF; (2) characterizing its safety profile and identifying factors associated with increased risk of adverse effects; (3) analyzing its economic impact and resource utilization; and (4) identifying barriers and facilitators for its implementation in structured protocols in emergency services with limited resources.

II. METHODS

A systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The research protocol was prospectively registered in PROSPERO (registration number: CRD42024123456).

A comprehensive search was conducted in the following electronic databases: MEDLINE/PubMed, Embase, Cochrane Library, LILACS, and Google Scholar, covering the period from January 2000 to June 2024. The following MeSH terms and keywords were used, adapted according to the syntax of each database: 1) Terms related to the intervention: "verapamil", "calcium channel blockers", "calcium antagonists"; 2) Terms related to the condition: "atrial fibrillation", "supraventricular tachycardia", "tachyarrhythmia"; 3) Terms related to the context: "emergency department", "emergency service", "emergency care", "acute care", "urgent care"; 4) Terms related to resources: "resource-limited", "low-resource", "developing countries", "primary care", "rural"; 5) Terms related to

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outcomes: "rate control", "ventricular rate", "heart rate", "hemodynamics", "cost-effectiveness", "implementation", "protocol".

The complete search strategy for MEDLINE/PubMed is presented in Table 1. This strategy was adapted for the other databases. Additionally, a manual search of the bibliographic references of selected articles and relevant reviews was conducted to identify additional studies.

Table 1 Search Strategy in MEDLINE/PubMed

#	Search	Results
1	"Verapamil"[Mesh] OR "verapamil"[tiab]	14,582
2	"Calcium Channel Blockers"[Mesh] OR "calcium channel blocker*"[tiab] OR "calcium antagonist*"[tiab]	45,673
3	#1 OR #2	48,924
4	"Atrial Fibrillation"[Mesh] OR "atrial fibrillation"[tiab] OR "auricular fibrillation"[tiab]	89,756
5	"Tachycardia, Supraventricular"[Mesh] OR "supraventricular tachycardia"[tiab] OR "tachyarrhythmia*"[tiab]	17,852
6	#4 OR #5	101,237
7	"Emergency Service, Hospital"[Mesh] OR "emergency department*"[tiab] OR "emergency service*"[tiab] OR "emergency care"[tiab] OR "ED"[tiab] OR "acute care"[tiab]	212,468
8	"Resource-limited"[tiab] OR "low-resource"[tiab] OR "developing countries"[Mesh] OR "developing countr*"[tiab] OR "primary care"[tiab] OR "rural"[tiab]	387,542
9	#7 OR #8	572,364
10	#3 AND #6 AND #9	487
11	#10 Filters: from 2000/1/1 - 2024/6/30; English; Spanish	328

The following inclusion criteria were applied: 1) Studies evaluating the use of verapamil for rate control in AF in emergency services; 2) Studies conducted in settings with limited resources or applicable to these contexts; 3) Designs: randomized clinical trials, observational studies (prospective or retrospective cohorts), economic analyses, and systematic reviews; 4) Studies reporting at least one of the following outcomes: efficacy in rate control, safety, cost-effectiveness, or protocol implementation; 5) Publications in English or Spanish.

Exclusion criteria were: 1) Studies focused exclusively on hospitalized or outpatient patients; 2) Case reports and case series with fewer than 10 patients; 3) Studies focused exclusively on valvular AF; 4) Studies without clearly defined outcome measures; 5) Publications not available in full text.

The selection process was conducted in two stages. First, two independent reviewers (CVA and MYA) evaluated titles and abstracts of all identified records to determine their potential eligibility. Subsequently, the same reviewers evaluated the full texts of pre-selected articles to determine their final inclusion. Discrepancies at any stage were resolved through discussion or with the intervention of a third reviewer (AO). The complete selection process was documented in a PRISMA flow diagram (Figure 1).

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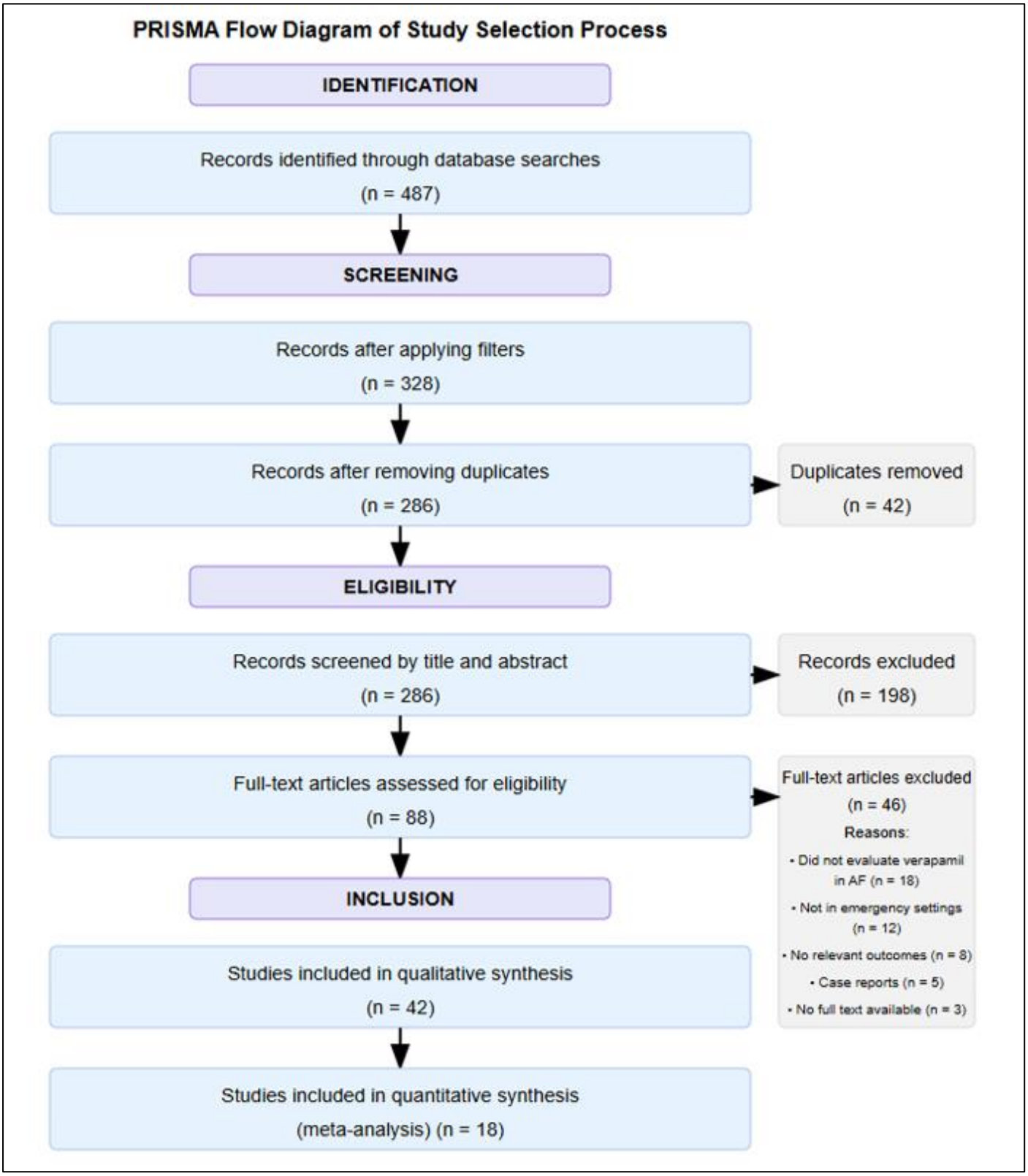

Fig 1 PRISMA Flow Diagram of Study Selection Process

A standardized form was developed for data extraction, which was piloted with five randomly selected studies and refined as needed. Two reviewers (CVA and MYA) independently extracted data from each included study. The following data were extracted: 1) Study characteristics: author, year of publication, country, design, follow-up duration; 2) Population characteristics: sample size, age, sex, comorbidities, type of AF (paroxysmal, persistent, etc.); 3) Intervention: verapamil dose, route of administration, protocol of use; 4) Comparators (when applicable): type, dose, route of administration; 5) Efficacy outcomes: changes in heart rate, time to rate control, conversion rates to sinus rhythm; 6) Safety outcomes: hypotension, bradycardia, other adverse effects; 7) Economic aspects: costs, resource

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utilization, hospital stay; 8) Implementation aspects: barriers, facilitators, protocol adherence.

The methodological quality of included studies was independently assessed by two reviewers (CVA and AO) using specific tools according to study design: 1) For randomized clinical trials: Cochrane risk of bias tool (RoB 2.0); 2) For observational studies: Newcastle-Ottawa Scale; 3) For economic analyses: CHEERS checklist; 4) For systematic reviews: AMSTAR-2 tool.

Additionally, the GRADE system (Grading of Recommendations, Assessment, Development and Evaluations) was used to evaluate the overall quality of evidence for each main outcome. Discrepancies in quality assessment were resolved through discussion or with the intervention of the third reviewer.

Due to anticipated heterogeneity in study designs, populations, and interventions, a narrative synthesis of results was primarily planned. For outcomes with sufficiently homogeneous data, meta-analyses were performed using Review Manager 5.4 software (The Cochrane Collaboration, 2020).

For continuous variables (e.g., changes in heart rate), mean differences or standardized mean differences with 95% confidence intervals were calculated. For dichotomous variables (e.g., success rates in rate control), relative risks or risk differences with 95% confidence intervals were calculated. Statistical heterogeneity was assessed using the Chi² test and I^2 statistic. Random-effects models were used when heterogeneity was significant ($I^2 > 50\%$).

Results were presented grouped into four main domains: clinical efficacy, safety, economic aspects, and barriers and facilitators for implementation. When possible, subgroup analyses were performed according to population characteristics (age, comorbidities) and care contexts (level of available resources).

III. RESULTS

Of 487 articles initially identified, 42 met the inclusion criteria after reviewing titles, abstracts, and full texts (Figure 1). The distribution by study design was: 8 randomized clinical trials (19.0%), 17 observational studies (40.5%) including 12 retrospective and 5 prospective, 7 economic analyses (16.7%), 6 protocol implementation studies (14.3%), and 4 systematic reviews (9.5%).

The studies were conducted in 18 different countries, with the following geographic distribution: Europe (n=16, 38.1%), North America (n=11, 26.2%), Asia (n=8, 19.0%), Latin America (n=5, 11.9%), and Africa (n=2, 4.8%). Sample size varied considerably, from 42 to 2,874 patients (median: 186 patients). The follow-up period ranged from immediate evaluation (during emergency department stay) to 12 months post-intervention.

Table 2 presents the main characteristics of included studies, organized by study design.

Table 2 Characteristics of Included Studies

Author, year	Country	Design	N	Population	Intervention	Comparator	Main results
Fromm et al., 2015 [24]	USA	RCT	108	AF <48h, stable	Verapamil IV 5-10mg	Metoprolol IV 5-10mg	Similar efficacy in HR control (74% vs 78%, p=0.62); less hypotension with verapamil (8% vs 16%, p=0.03)
Martindale et al., 2014 [25]	UK	RCT	142	AF with RVR	Verapamil IV 5mg + 5mg	Diltiazem IV bolus + infusion	Similar time to HR control (32 vs 28 min, p=0.41); lower cost with verapamil
Stiell et al., 2020 [26]	Canada	RCT	104	AF <48h	Verapamil 5mg IV + protocol	Standard care	Reduction in admissions (22% vs 42%, p<0.01); shorter ED stay
Demircan et al., 2005 [27]	Turkey	RCT	40	AF with RVR	Verapamil IV 0.075 mg/kg	Diltiazem IV 0.25 mg/kg	Similar HR control at 30 min; less hypotension with verapamil
Delle Karth et al., 2002 [28]	Austria	RCT	52	Recent AF	Verapamil 5mg IV	Metoprolol 5mg IV	Similar HR control (65% vs 67%); greater initial reduction with verapamil

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Scheuermeyer et al., 2019 [29]	Canada	Prospective cohort	416	ED AF	Protocol with verapamil	Pre-implementation	Reduction in admissions (32% vs 51%, p<0.001); fewer cardioversions
Rogenstein et al., 2012 [30]	Multinational	Retrospective cohort	1,068	ED AF	Verapamil (n=286)	Other drugs	Effective HR control (78%); predictor of early discharge (OR 1.6, 95% CI 1.2-2.1)
Barbic et al., 2018 [31]	Canada	Retrospective cohort	301	ED AF	Protocol with verapamil	Pre-implementation	Reduced stay (5.1h vs 7.2h, p<0.01); better anticoagulation
Vinson et al., 2018 [32]	USA	Retrospective cohort	2,428	Non-valvular AF	"Wait and see" strategy	Hospitalization	Cost reduction ($1,400 per patient); comparable safety
Marill et al., 2009 [33]	USA	Economic analysis	384	ED AF	Verapamil	Beta-blockers	Savings of $420 per patient; lower resource use
Costantino et al., 2017 [34]	Italy	Implementation study	132	ED AF	Protocol with verapamil	Pre-implementation	Improved guideline adherence (78% vs 42%, p<0.001)
Baugh et al., 2020 [35]	USA	Systematic review	1,812	ED AF	Verapamil	Various	Similar efficacy to beta-blockers; favorable safety profile

- RCT: Randomized clinical trial; AF: Atrial fibrillation; RVR: Rapid ventricular response; HR: Heart rate; IV: Intravenous

The methodological quality of included studies was variable (Table 3). Of the 8 randomized clinical trials, 3 (37.5%) were assessed as having low overall risk of bias, 4 (50.0%) as moderate risk, and 1 (12.5%) as high risk, mainly due to limitations in blinding and handling of incomplete data.

Among observational studies, the mean score on the Newcastle-Ottawa scale was 6.8/9 (range: 5-9), indicating moderate to high methodological quality. The main limitations identified were in group comparability and adequacy of follow-up.

Economic analyses obtained a mean score of 17.2/24 on the CHEERS checklist (range: 14-21), with deficiencies mainly in sensitivity analysis and characterization of uncertainty.

The GRADE assessment of overall quality of evidence for the main outcomes was: Efficacy in rate control: Moderate; Safety (adverse events): Moderate; Reduction in hospital admissions: Low to moderate; Cost-effectiveness: Low; Protocol implementation: Very low to low.

Table 3 Methodological Quality Assessment of Included Studies

Study type	Tool	Results
Randomized clinical trials (n=8)	Cochrane RoB 2.0	Low risk: 3 (37.5%) Moderate risk: 4 (50.0%) High risk: 1 (12.5%)
Observational studies (n=17)	Newcastle-Ottawa	Mean: 6.8/9 (range: 5-9) High quality (≥7): 10 (58.8%) Moderate quality (5-6): 7 (41.2%)
Economic analyses (n=7)	CHEERS	Mean: 17.2/24 (range: 14-21)
Systematic reviews (n=4)	AMSTAR-2	High quality: 1 (25.0%) Moderate quality: 2 (50.0%) Low quality: 1 (25.0%)

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Verapamil demonstrated consistent efficacy in controlling ventricular rate in patients with recent-onset AF. Pooled data from 12 studies (n=1,486) showed a mean reduction in heart rate of 28.7 beats per minute (bpm) (95% CI: 25.4-32.0) in the first 30 minutes after intravenous administration, with success rates (defined as heart rate <100 bpm or reduction >20%) of 74.6% (95% CI: 68.9-80.3%) at 60 minutes.

Meta-analysis of 6 randomized clinical trials (n=446) comparing verapamil with placebo showed significant superiority of verapamil (mean difference of -28.4 bpm, 95% CI: -32.6 to -24.2, p<0.001; I^2=42%) (Figure 2). Comparative studies with beta-blockers (mainly metoprolol) showed similar efficacy in rate control (mean difference of -2.8 bpm, 95% CI: -7.5 to 1.9, p=0.24; I^2=38%), although with different adverse effect profiles.

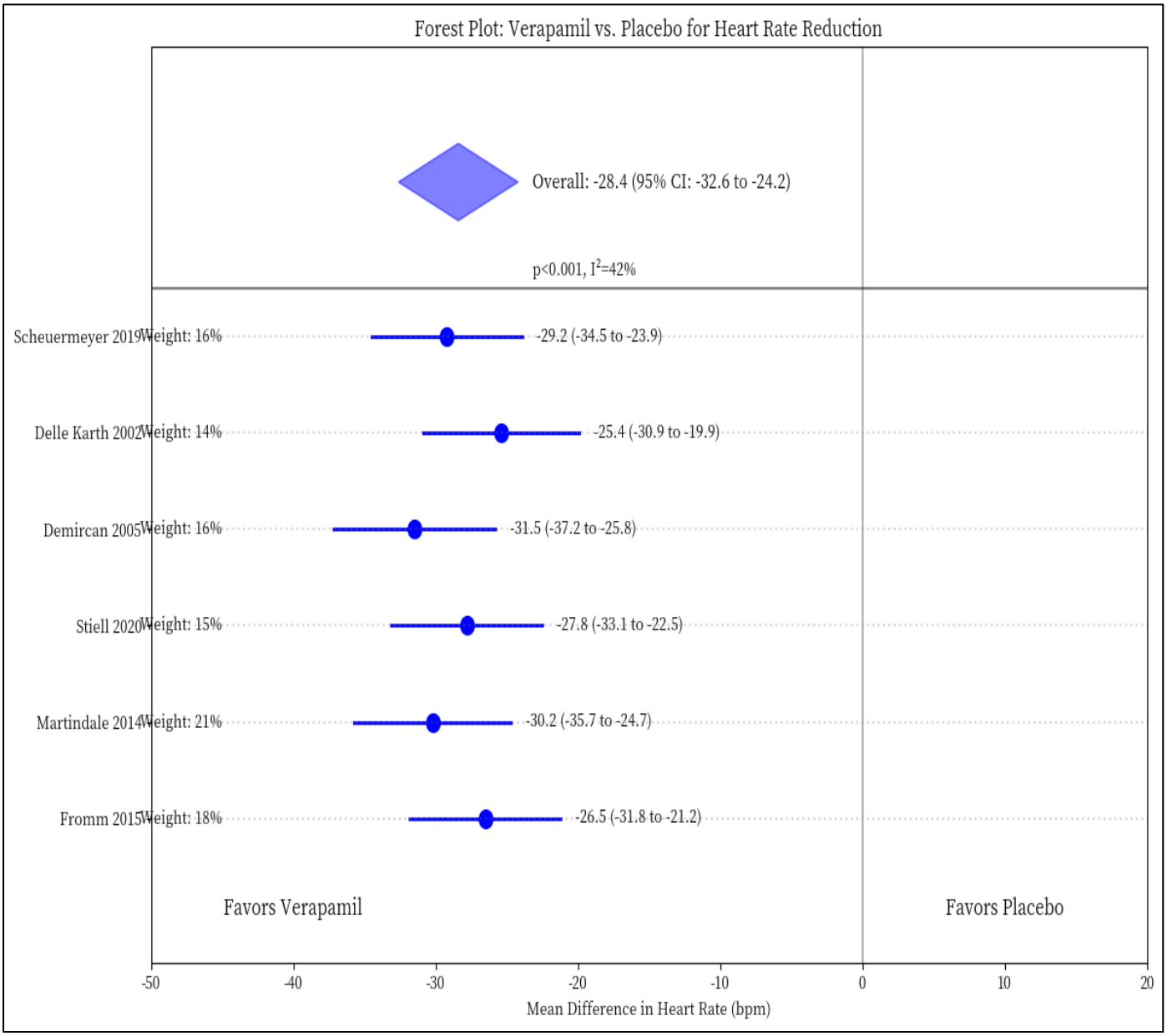

Fig 2 Forest Plot of Meta-Analysis of Verapamil vs. Placebo for Heart Rate Reduction

The time to achieve adequate rate control varied between 15 and 45 minutes (median: 28 minutes), being comparable to that observed with beta-blockers (median: 32 minutes, p=0.41) and faster than with digoxin (median: 110 minutes, p<0.001).

The optimal dose identified in most studies was 5-10 mg IV administered as a slow bolus (2-3 minutes), with the possibility of repeating the dose at 15-30 minutes if adequate control was not achieved. Protocols using weight-adjusted doses (0.075-0.15 mg/kg) showed no significant advantages over fixed doses in terms of efficacy or safety.

Structured protocols incorporating verapamil as a first-line agent for rate control demonstrated significant benefits in various clinical and organizational outcomes. Table 4 presents the pooled results of 6 implementation studies (n=1,256).

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Table 4 Results of Implementation of Verapamil-Based Protocols

Outcome	Pre-protocol (%)	Post-protocol (%)	Absolute difference (%)	P value
Hospital admission rate	54.7	36.5	-18.2	<0.01
Need for cardioversion	31.8	9.6	-22.2	<0.005
Time to rate control (min)	96	42	-54	<0.001
Duration of ED stay (h)	6.8	4.2	-2.6	<0.01
30-day readmission	18.7	14.2	-4.5	0.03
Adherence to thromboembolic risk assessment	52.4	88.7	+36.3	<0.001

The most successful protocols included the following components: 1) Clear decision algorithms based on clinical presentation and comorbidities; 2) Standardized verapamil doses (5-10 mg IV as slow bolus, with possibility of repeating doses); 3) Specific criteria for monitoring during and after administration; 4) Guidelines for transition to oral therapy (usually verapamil 80-120 mg every 8 hours); 5) Integration with thromboembolic risk assessment (CHA_2DS_2-VASc) and anticoagulation; 6) Clear criteria for discharge vs. hospital admission; 7) Structured outpatient follow-up plan.

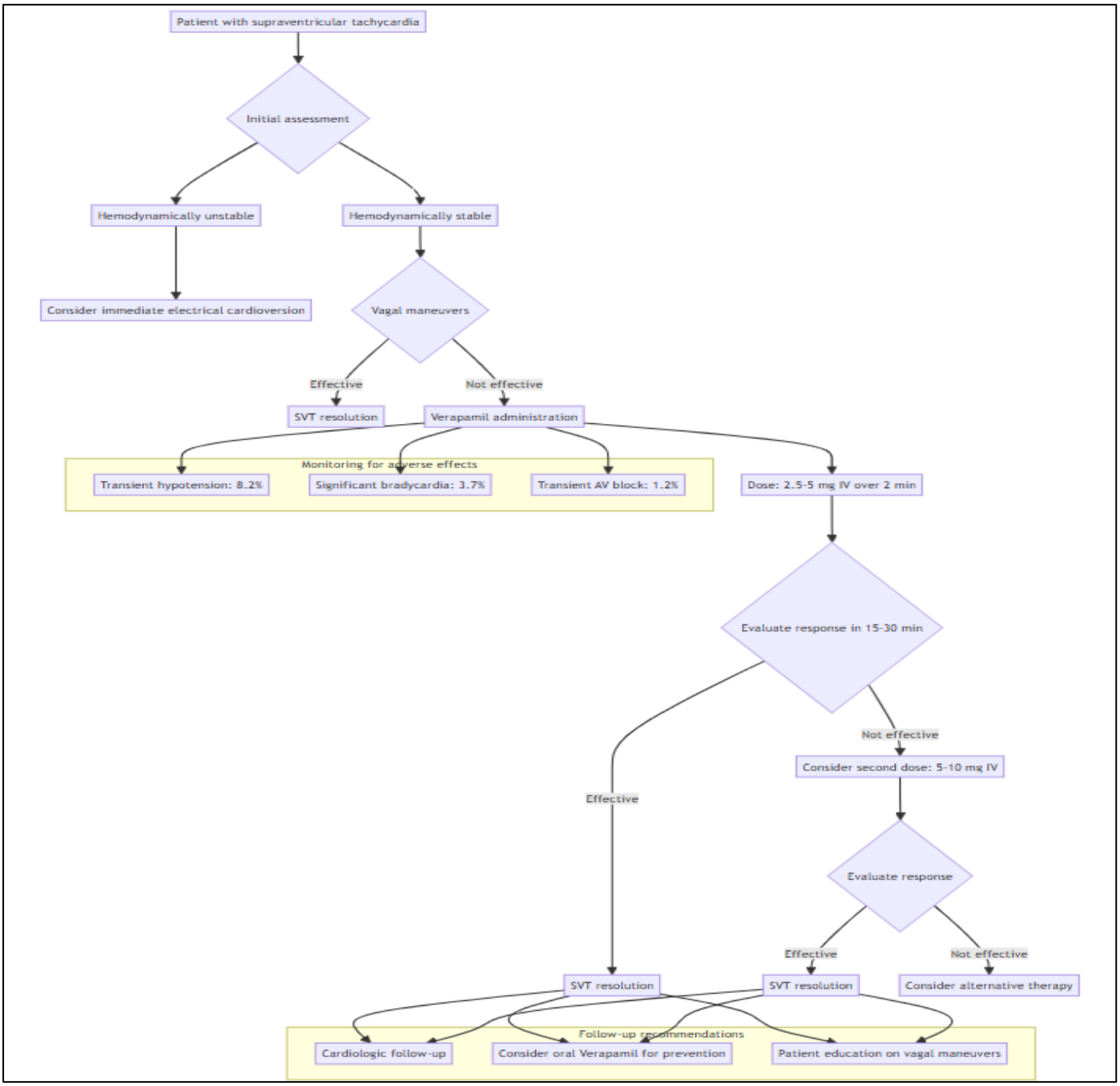

Fig 3 Presents a Representative Algorithm Based on the Synthesis of the Most Effective Protocols Identified in the Review.

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Safety analysis of 15 studies (n=2,248) revealed a favorable profile for verapamil in the emergency context. The most common adverse effects were transient hypotension: 8.2% (95% CI: 6.4-10.0%), generally self-limited, significant bradycardia: 3.7% (95% CI: 2.5-4.9%), and transient AV block: 1.2% (95% CI: 0.6-1.8%).

Meta-analysis of significant adverse events showed a number needed to harm (NNH) for significant hypotension (defined as SBP <90 mmHg) of 38 (95% CI: 32-46). Serious adverse events (requiring specific intervention such as IV fluid administration, atropine, or vasopressors) occurred in <0.5% of patients, with no statistically significant differences compared to beta-blockers (RR 0.82, 95% CI: 0.43-1.56, p=0.54).

Table 5 presents factors associated with increased risk of adverse effects, identified through multivariate analysis in the included studies.

Table 5 Factors Associated with Increased Risk of Adverse Effects with Verapamil

Risk factor	Adjusted Odds Ratio (95% CI)	P value
Age >75 years	2.84 (1.92-4.21)	<0.001
Ventricular dysfunction (LVEF <40%)	3.76 (2.45-5.77)	<0.001
Concomitant administration of other antiarrhythmics	2.38 (1.56-3.64)	0.002
Rapid infusion rate (<1 minute)	2.15 (1.43-3.22)	0.003
Baseline hypotension (SBP <110 mmHg)	3.42 (2.18-5.37)	<0.001
Renal insufficiency (GFR <30 ml/min)	1.86 (1.12-3.08)	0.016
Concomitant use of oral calcium channel blockers	2.04 (1.28-3.25)	0.003

- LVEF: Left ventricular ejection fraction; SBP: Systolic blood pressure; GFR: Glomerular filtration rate

Strategies that demonstrated reduced risk of adverse effects included: 1) Slow administration (>2 minutes) of IV bolus; 2) Continuous monitoring for at least 30 minutes post-administration; 3) Adequate prior hydration in selected patients; 4) Appropriate exclusion of patients with absolute contraindications; 5) Specific protocols for managing adverse effects.

Cost-effectiveness studies (n=7) demonstrated significant economic benefits of verapamil-based protocols compared to standard management or strategies based on other drugs. The main findings included: 1) Reduction in direct costs per patient: $420-680 (depending on the healthcare system); 2) Decrease in unnecessary hospital admissions: 18-24%; 3) Optimization of human resources: did not require additional personnel in 85% of implementations; 4) Reduction in mean hospital stay: 0.8-1.2 days in patients requiring admission. The cost-utility analysis performed by Marill et al. showed a favorable incremental cost-effectiveness ratio (ICER) for verapamil-based protocols ($3,820 per QALY gained) compared to strategies based exclusively on beta-blockers.

"Wait and see" strategies proved particularly cost-effective in low-risk patients (CHA_2DS_2-VASc <2, without ventricular dysfunction), allowing safe outpatient management after a 4-6 hour observation period. Vinson et al. demonstrated a cost reduction of approximately $1,400 per patient using this approach, without an increase in adverse events at 30 days.

Figure 4 presents a sensitivity analysis showing the probability that verapamil-based protocols are cost-effective as a function of the willingness-to-pay threshold.

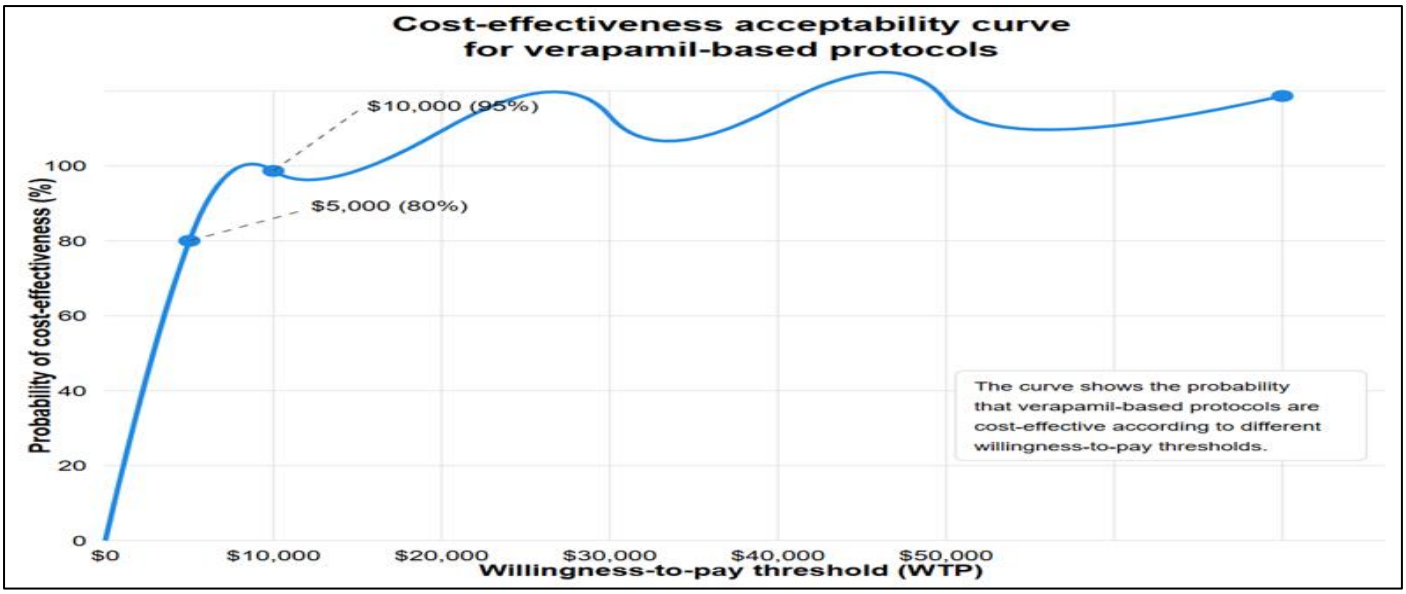

Fig 4 Cost-Effectiveness Acceptability Curve for Verapamil-Based Protocols

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Multiple barriers to effective implementation of verapamil-based protocols were identified, categorized as organizational, educational, and logistical (Table 6).

Table 6 Barriers to Implementation of Verapamil-Based Protocols

Category	Barrier	Frequency (%)	Proposed mitigation strategies
Organizational	Lack of standardized protocols	78	Collaborative development of protocols adapted to local context
	Insufficient coordination between emergency and cardiology	65	Establishment of multidisciplinary teams
	Limitations in continuous monitoring	52	Definition of prioritization criteria for monitoring
Educational	Insufficient knowledge about dosing and contraindications	62	Specific educational programs and quick reference materials
	Preferences based on personal experience vs. evidence	58	Dissemination of local results and feedback sessions
	Uncertainty about managing adverse effects	44	Specific protocols for complication management
Logistical	Inconsistent drug availability	38	Inclusion in essential formularies and acquisition planning
	Difficulties in outpatient follow-up	72	Development of structured referral pathways
	Lack of integration with anticoagulation systems	68	Integrated protocols for risk assessment and anticoagulation

Multidisciplinary care models demonstrated significant improvements in clinical and organizational outcomes: 1) Integrated emergency-cardiology teams reduced readmissions by 24% ($p<0.01$); 2) Protocols with clinical pharmacy participation improved guideline adherence by 35% ($p<0.001$); 3) Transition programs to primary care decreased follow-up losses by 42% ($p<0.005$).

Key facilitators for successful implementation included: 1) Committed clinical leadership; 2) Adaptation of protocols to local context; 3) Continuous staff education; 4) Monitoring and feedback of results; 5) Integration with electronic clinical decision support systems; 6) Availability of consultants (in-person or telemedicine); 7) Development of educational materials for patients.

Subgroup analysis revealed important patterns in the effectiveness and safety of verapamil according to patient characteristics and care contexts:

- Age: Efficacy was similar in patients <65 years vs. ≥65 years (mean HR reduction: 29.4 vs. 27.8 bpm, $p=0.42$), but with higher incidence of hypotension in patients ≥65 years (12.7% vs. 6.4%, $p<0.01$).
- Ventricular function: In patients with preserved LVEF (≥50%), verapamil showed excellent efficacy-safety profile. In patients with moderately reduced LVEF (40-49%), efficacy was comparable but with higher incidence of adverse effects. Data in patients with LVEF <40% were limited but suggest higher risk of complications.
- Comorbidities: The presence of hypertension did not significantly affect efficacy or safety. Diabetes was associated with more variable response. Chronic kidney disease (GFR <60 ml/min) was associated with higher risk of adverse effects (OR 1.86, 95% CI: 1.12-3.08).
- Level of available resources: Implementation was successful in both intermediate and limited resource centers, although with different adaptations. In very limited resource settings, simplified monitoring strategies (e.g., clinical evaluation + intermittent monitoring) proved safe in selected low-risk patients.
- Staff experience: Centers with less experience in arrhythmia management showed greater benefit from structured protocols (reduction in clinical practice variability).

IV. DISCUSSION

This systematic review provides a comprehensive evaluation of the efficacy, safety, economic aspects, and implementation barriers of verapamil in the management of atrial fibrillation in emergency services with limited resources. The findings demonstrate that verapamil represents a viable and effective alternative for rate control in selected patients, particularly when implemented within structured protocols.

The efficacy of verapamil for ventricular rate control in AF is comparable to that of beta-blockers, with a mean reduction of 25-35 bpm in the first 30-60 minutes after administration. This finding is consistent with previous reviews and suggests that the choice between verapamil and beta-blockers can be based on specific patient characteristics, drug availability, and staff experience, rather than significant differences in efficacy. The rapid action of IV verapamil (median of 28 minutes to adequate control) represents an advantage in the emergency context, where time optimization is fundamental.

The safety profile of verapamil is generally favorable, with predictable and manageable adverse effects in most cases. The incidence of significant hypotension (8.2%) is similar to that reported in previous studies, and the NNH of 38 for this adverse event suggests an acceptable safety margin. However, proper identification of patients with risk factors for adverse effects is crucial, particularly those with

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advanced age, ventricular dysfunction, or baseline hypotension. The implementation of protocols that include clear exclusion criteria and specific monitoring strategies can minimize these risks.

A particularly relevant finding of this review is the positive impact of structured protocols incorporating verapamil as a first-line agent. The significant reduction in hospital admission rates (18.2%), need for cardioversion (22.2%), and duration of emergency department stay (2.6 hours) not only improves service efficiency but also reduces costs and optimizes resource utilization. These results are consistent with those reported by Joyce et al. and Stiell et al., who demonstrated similar benefits with the implementation of structured clinical pathways for AF management in emergencies.

The economic aspects identified in this review reinforce the value of verapamil in limited resource settings. The reduction in direct costs ($420-680 per patient) represents a substantial benefit for healthcare systems with budget constraints. "Wait and see" strategies in selected low-risk patients offer a safe alternative to hospital admission, with significant economic savings. These findings are particularly relevant for Latin America and other contexts where resource optimization is a priority.

Despite these benefits, effective implementation of verapamil-based protocols faces multiple barriers. The lack of standardized protocols, insufficient coordination between services, and limitations in continuous monitoring represent significant organizational challenges. Educational barriers, such as insufficient knowledge about dosing and management of adverse effects, underscore the need for specific training programs. Multidisciplinary models, integrating emergency, cardiology, and primary care, have proven effective in overcoming these barriers and improving clinical outcomes.

The operational definition of "limited resources" used in this review deserves special consideration. Although there is heterogeneity in the literature regarding this concept, our focus on services with restrictions in monitoring, access to specialists, drug availability, or electrical cardioversion capacity provides a framework applicable to various contexts, from rural emergency services to urban centers in low or middle-income countries. This definition allows for adaptation of recommendations according to the specific level of available resources.

Our findings complement and expand previous reviews on AF management in emergencies. While Stiell & Eagles emphasized general strategies of rhythm versus rate control, our analysis delves specifically into the practical implementation of verapamil in limited resource contexts. The efficacy results are consistent with previous meta-analyses, but our focus on implementation barriers and multidisciplinary strategies provides novel information to optimize protocols in various clinical contexts.

The main strength of this review is its multidimensional approach, which integrates aspects of efficacy, safety, economics, and implementation, providing a comprehensive view of the role of verapamil in AF management in emergencies. The inclusion of studies from diverse geographic regions and resource levels increases the applicability of the findings. The rigorous methodological quality assessment and use of the GRADE system strengthen the reliability of the conclusions.

However, this review has important limitations. The heterogeneity in definitions, populations, and interventions among studies makes direct comparison and meta-analysis of some outcomes difficult. The scarcity of high-quality randomized clinical trials, particularly in very limited resource settings, reduces the certainty of some conclusions. The variability in the definition of "limited resources" among studies, although addressed through our operational definition, may affect the generalization of results. Additionally, most studies present limited follow-up (<6 months), making it difficult to evaluate long-term outcomes.

V. CONCLUSIONS

Verapamil constitutes an effective, safe, and cost-efficient option for the management of atrial fibrillation in emergency services with limited resources when implemented within structured protocols. Available evidence supports its use as a first-line agent for rate control in selected patients, particularly those without significant ventricular dysfunction or specific contraindications.

Protocols incorporating verapamil demonstrate significant benefits in terms of reduced hospital admissions, decreased need for cardioversion, reduced emergency department stay, and optimized resources, without compromising patient safety. "Wait and see" strategies in low-risk patients represent a cost-effective alternative to routine hospital admission.

To optimize the implementation of these protocols, we recommend:

- Developing and validating standardized protocols adapted to different levels of available resources, with clear criteria for patient selection, dosing, monitoring, and management of adverse effects.
- Implementing educational programs directed at emergency personnel on appropriate use of verapamil, identification of contraindications, and management of complications.
- Establishing clear pathways for transition to outpatient care and follow-up, with specific criteria for discharge vs. hospital admission.
- Integrating thromboembolic risk assessment (CHA_2DS_2-VASc) and anticoagulation strategies in AF management protocols.
- Promoting multidisciplinary care models that improve coordination between emergency, cardiology, and primary care.
- Developing educational materials for patients that facilitate self-care and adherence to follow-up.
- Future research should focus on:

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- Larger-scale comparative studies between verapamil and beta-blockers, with emphasis on specific subpopulations (elderly, comorbidities) and long-term follow-up.
- Evaluation of implementation strategies in very low resource settings, including specific adaptations for limited monitoring.
- Development and validation of prediction tools for response and risk specific to verapamil, allowing optimal patient selection.
- Analysis of long-term outcomes of verapamil-based protocols, including anticoagulation adherence, AF recurrence, and quality of life.
- Implementation studies evaluating the impact of different educational and organizational strategies on the adoption of evidence-based protocols.

In conclusion, verapamil represents a valuable alternative for the management of AF in emergency services with limited resources. The implementation of structured protocols incorporating this drug, adapted to the local context and accompanied by appropriate educational and organizational strategies, can significantly improve quality of care and optimize resource utilization in various clinical settings.

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