REVIEW ARTICLE

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Efficacy and safety of intravenous vernakalant for the rapid conversion of recent-onset atrial fibrillation: A meta-analysis

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Background: Atrial fibrillation is a common cardiac arrhythmia with increasing prevalence in the aging population. It is a major cause of emergency department visits worldwide. Vernakalant, a relatively new antiarrhythmic drug with selectively preferential effects on the atrial tissue is currently used in many European countries for the termination of recent-onset atrial fibrillation. Presently, the drug is still not approved by the United States Food and Drug Administration due to safety concerns. We evaluate the efficacy and safety of vernakalant for the conversion of recent-onset atrial fibrillation or atrial flutter into normal sinus rhythm (NSR).

Methods: PubMed/MEDLINE (1993–2017), the Cochrane Central Register of Controlled Trials (2000–2017), and reference lists of relevant articles were searched for randomized controlled trials (RCTs) comparing vernakalant to a control drug and extracted subsequently.

Results: Nine RCTs were identified and included in the meta-analysis. Pooled analysis of events extracted for a total of 1421 patients with recent-onset atrial fibrillation showed a statistically significant increase in cardioversion within 90 minutes from drug infusion (Relative Risk [RR], 6.61; 95% Confidence Interval [CI], 2.78 – 15.71; $p < .00001$). In terms of adverse events, vernakalant was considered safe in comparison to control drugs (RR, 0.80; 95% CI, 0.61–1.05; $p = .11$).

Conclusion: Vernakalant is effective for rapid conversion of recent-onset atrial fibrillation into NSR. However, although it showed a safe profile in terms of side effects in this analysis, we are still hesitant about this conclusion and few safety issues should be addressed within specific patients' subgroups.

KEYWORDS
atrial fibrillation/atrial arrhythmias, cardioversion, pharmacokinetics/dynamics, pharmacology

1 | INTRODUCTION

Atrial fibrillation is a common cardiac dysrhythmia with increasing prevalence in the aging population. It remains one of the strongest risk factors for stroke and a major cause of cardiovascular morbidity worldwide (January et al., 2014; Kirchhof et al., 2016). Moreover, this arrhythmia is a frequent cause of hospital presentations and admissions, and is commonly encountered on daily basis especially in the emergency departments (Go et al., 2001; Friberg, Buch, Scharling, Gadsbøll, & Jensen, 2003). Conversion of recent onset atrial fibrillation into normal sinus rhythm (NSR) is essentially important for reducing the risk of hemodynamic instability, atrial remodeling, and the rate of hospitalizations (Conde & Baranchuk, 2014). Conversion into NSR can be achieved either pharmacologically or by direct-current (DC) electrical
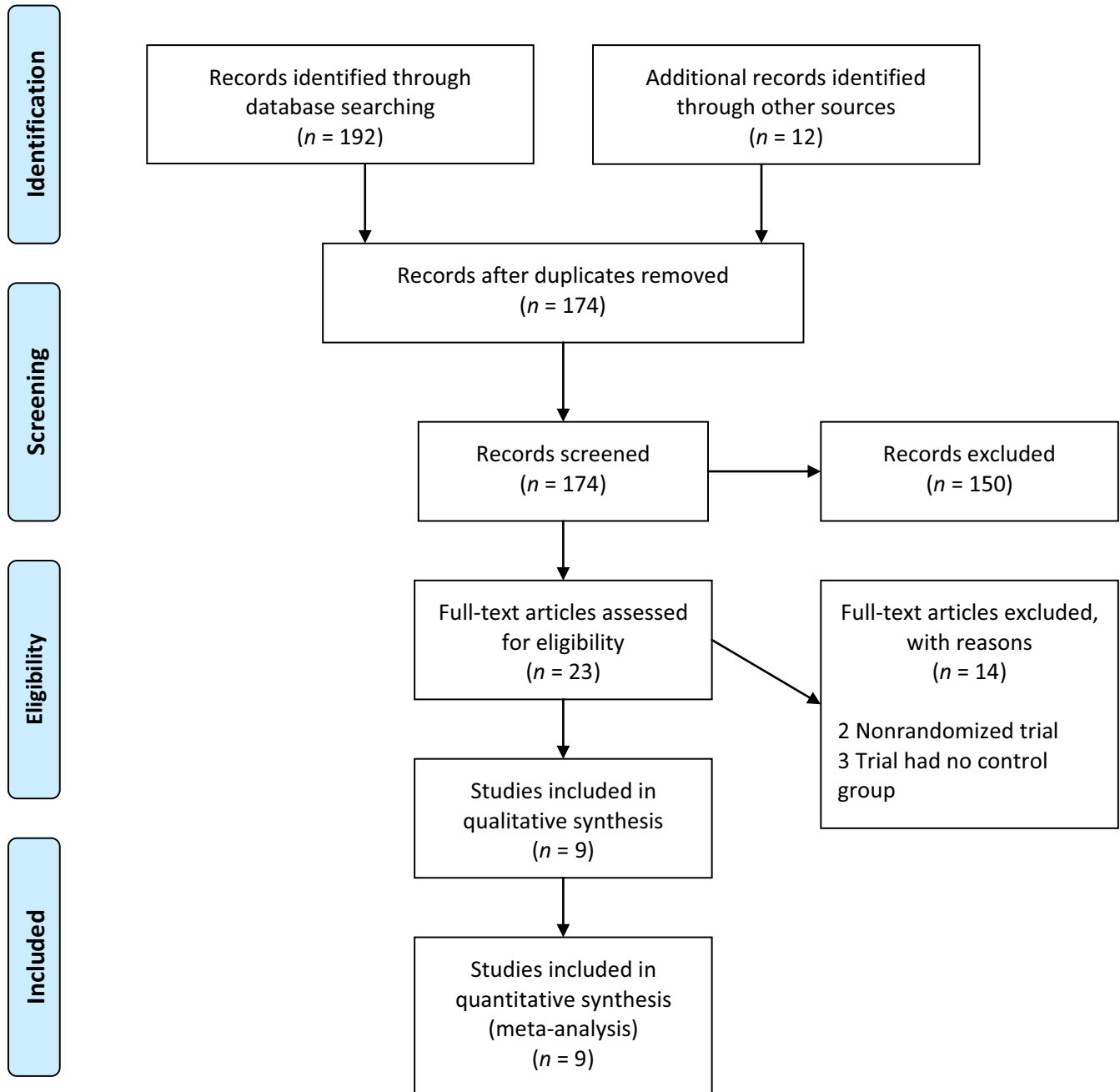
FIGURE 1 PRISMA 2009 flow diagram

cardioversion. While DC electrical cardioversion is more effective and restores NSR instantaneously, it necessitates the use of general anesthesia. Also, it can be associated with psychological stress for the patient along with multiple adverse events such as skin burns, heart block, and pacemaker malfunction (if present) Hanley, Robinson, & Kowey, 2016; Van Gelder, Tuinenburg, Schoonderwoerd, Tieleman, & Crijns, 1999; Conde, Lalor, Rodriguez, Elissamburu, & Marcelo, 2013).

Although antiarrhythmic drug therapy is a cornerstone in the treatment of cardiac arrhythmias, the development of new antiarrhythmics has remained slow despite substantial efforts given. This is most likely due to our limited understanding of the complex interplay between various ionic currents and their definitive role in arrhythmogenesis (Hanley et al., 2016;

Kumar & Zimetbaum, 2013). Currently available antiarrhythmic drugs are limited by incomplete efficacy for maintaining NSR along with their extensive side effects profiles such as life-threatening ventricular arrhythmias and extracardiac toxicities (Camm, 2012; Tsuji & Dobrev, 2013).

Vernakalant is the first antiarrhythmic drug with selectively preferential effects on the atrial tissue. This atrial-selectivity causes a prolongation in the effective refractory period of the atria with minimal effects on the ventricles (Tsuji & Dobrev, 2013; Dorian et al., 2007; Dobrev, Hamad, & Kirkpatrick, 2010). Vernakalant is hepatically metabolized by cytochrome P450 (CYP 2D6) with a half-life of approximately 3 hr, and can reach up to 8.5 hr in poor metabolizers (Savelieva, Graydon, & Camm, 2014; Mao, Wheeler, Clohs, Beatch, & Keirns,

TABLE 1 Characteristics of the included trials

	CRAFT	ACT I	ACT II	ACT III	AVRO	Scene II	Simon et al.	Beatch and Mangal	Asia-Pacific trial
Year	2004	2008	2009	2010	2011	2012	2016	2016	2016
Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, double-blind, active-controlled	Randomized, double-blind, placebo-controlled	Randomized, controlled	Randomized, placebo controlled	Randomized, double-blind, placebo-controlled
No. of patients	56	336	161	262	232	54	100	197	111
AF duration	3–72 hr	3 hr–45 days	3–72 hr	3 hr–45 days	3–48 hr	3–48 hr (atrial flutter)	No longer than 48 hr	3 hr–7 days	3 hr–7 days
Primary endpoint	Proportion of patients who converted to NSR within 30 min	Proportion of patients who converted to NSR within 90 min	Proportion of patients who converted to NSR within 90 min	Proportion of patients who converted to NSR within 90 min	Proportion of patients who converted to NSR within 90 min	Proportion of patients who converted to NSR within 90 min	Time to conversion of atrial fibrillation to NSR	Proportion of patients who converted to NSR within 90 min	Proportion of patients who converted to NSR within 90 min
Age, mean (SD), y	64	62 (13)	68 (7)	62 (11)	63 (11)	68 (11)	57 (15)	62 (13)	60 (13)
Gender, male/female	34/22	234/336	121/40	178/84	146/86	36/16	68/32	121/76	67/44
No. CAD (%)	NR	68 (20)	129 (80)	31 (12)	52 (22)	NR	7 (7)	30 (15)	11 (10)
No. CHF (%)	Excluded	50 (15)	51 (32)	52 (20)	46 (20)	NR	99 (99)	Excluded	8 (7)
Independent clinical events committee	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes

2009). The mean plasma concentration of vernakalant peaks at the end of its ten-minutes infusion and decreases abruptly afterwards. No dose adjustment for age, gender, or renal function is required. Moreover, it is unlikely for vernakalant to cause any major drug-drug interactions given its rapid distribution, short half-life and lack of significant effect on CYP3A4 (Savelieva et al., 2014; Mao et al., 2009).

2 | METHODS

2.1 | Search strategy

In this meta-analysis, all prospective randomized controlled trials (RCTs) testing the efficacy and safety of vernakalant versus a control drug for conversion of recent-onset atrial fibrillation or atrial flutter into NSR were identified. An online database search using Cochrane Central Register of Controlled Trials and PubMed/MEDLINE for all relevant trials published since 1993 onward till the date of last search: July 1, 2017 was conducted. English language restriction was applied to the search. Keywords and MeSH terms used included: "atrial fibrillation," "atrial flutter," "vernakalant," "RSD1235," "clinical trials," and "randomized controlled trials." Meeting abstracts or other gray literature weren't included. In addition, a manual search of secondary sources which included reference lists of initially reviewed articles was performed.

2.2 | Study selection

Abstracts of trials meeting the following inclusion criteria were considered for review: (i) randomized controlled trial; (ii) studies that compared vernakalant versus a control drug; (iii) patient population with atrial fibrillation or atrial flutter. In addition, full-text articles of abstracts that were unclear with respect to meeting the inclusion criteria were retrieved for further analysis. A PRISMA (Moher, Liberati, Tetzlaff, & Altman, 2009) flow diagram of the trials' selection is illustrated in Figure 1. Nine prospective randomized controlled trials were included in this meta-analysis: The CRAFT trial (Roy et al., 2004); the ACT I trial (Roy et al., 2008); the ACT II trial (Kowey et al., 2009); the ACT III trial (Pratt et al., 2010); the AVRO trial (Camm et al., 2011); the Scene II trial (Camm et al., 2012); Simon et al. trial (Simon et al., 2016); Beatch and Mangal trial (Beatch & Mangal, 2016); and the Asia-Pacific trial (Beatch, Bhirangi, Juul-Moller, & Rustige, 2016).

2.3 | Data abstraction

Dichotomous data type was extracted, i.e. the number of events and participants in the experimental and the control groups were identified. Relevant baseline characteristics of patients were extracted and presented in Table 1.

2.4 | Study outcome

The primary outcome of interest in this meta-analysis was the proportion of patients who converted to NSR within 90 minutes following drug infusion, i.e. testing the efficacy of rapid conversion from atrial fibrillation or atrial flutter into NSR. Secondary outcomes
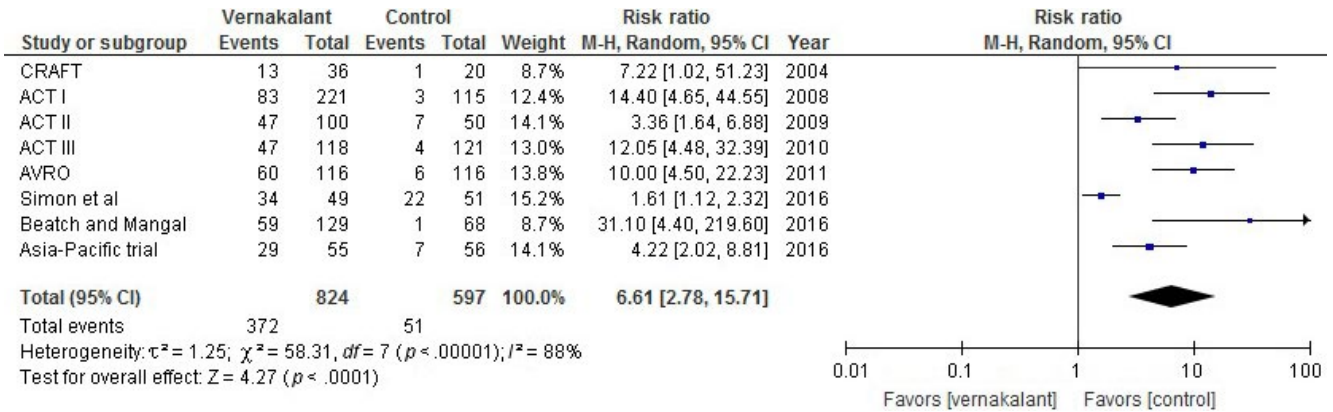
Study or subgroup	Vernakalant Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
CRAFT	13	36	1	20	8.7%	7.22 [1.02, 51.23]	2004	
ACT I	83	221	3	115	12.4%	14.40 [4.65, 44.55]	2008	
ACT II	47	100	7	50	14.1%	3.36 [1.64, 6.88]	2009	
ACT III	47	118	4	121	13.0%	12.05 [4.48, 32.39]	2010	
AVRO	60	116	6	116	13.8%	10.00 [4.50, 22.23]	2011	
Simon et al	34	49	22	51	15.2%	1.61 [1.12, 2.32]	2016	
Beatch and Mangal	59	129	1	68	8.7%	31.10 [4.40, 219.60]	2016	
Asia-Pacific trial	29	55	7	56	14.1%	4.22 [2.02, 8.81]	2016	
Total (95% CI)		**824**		**597**	**100.0%**	**6.61 [2.78, 15.71]**		
Total events	372		51					

Heterogeneity: $\tau^2 = 1.25$; $\chi^2 = 58.31$, $df = 7$ ($p < .00001$); $I^2 = 88\%$
Test for overall effect: $Z = 4.27$ ($p < .0001$)

FIGURE 2 Conversion into NSR within 90 min in patients with atrial fibrillation treated with vernakalant versus control

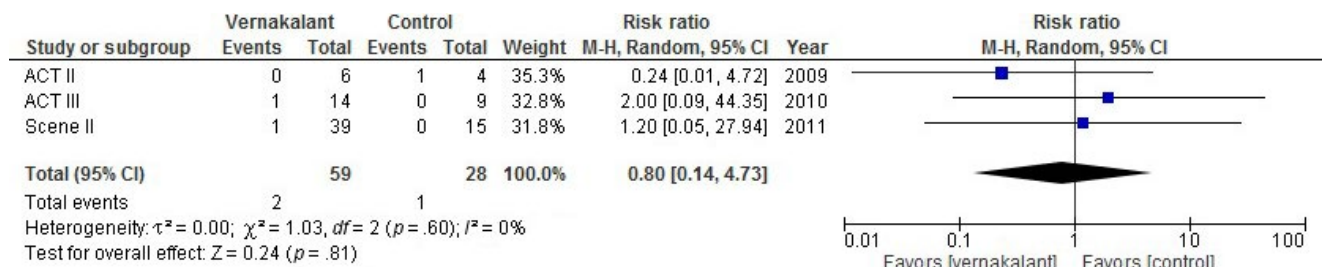| Study or subgroup	Vernakalant Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
ACT II	0	6	1	4	35.3%	0.24 [0.01, 4.72]	2009	
ACT III	1	14	0	9	32.8%	2.00 [0.09, 44.35]	2010	
Scene II	1	39	0	15	31.8%	1.20 [0.05, 27.94]	2011	
Total (95% CI)		**59**		**28**	**100.0%**	**0.80 [0.14, 4.73]**		
Total events	2		1					

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.03$, $df = 2$ ($p = .60$); $I^2 = 0\%$
Test for overall effect: $Z = 0.24$ ($p = .81$)

FIGURE 3 Conversion into NSR within 90 min in patients with atrial flutter treated with vernakalant versus control

Study or subgroup	Vernakalant Events	Total	Control Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
CRAFT	1	36	4	20	1.7%	0.14 [0.02, 1.16]	2004	
ACT I	29	221	21	115	28.9%	0.72 [0.43, 1.20]	2008	
ACT II	10	107	6	54	8.3%	0.84 [0.32, 2.19]	2009	
ACT III	14	134	17	131	17.3%	0.81 [0.41, 1.57]	2010	
Scene II	7	39	4	15	6.6%	0.67 [0.23, 1.97]	2011	
AVRO	5	116	2	116	2.9%	2.50 [0.49, 12.63]	2011	
Asia-Pacific trial	6	55	6	56	6.7%	1.02 [0.35, 2.96]	2016	
Simon et al	13	49	18	51	21.5%	0.75 [0.41, 1.36]	2016	
Beatch and Mangal	10	129	4	68	6.1%	1.32 [0.43, 4.05]	2016	
Total (95% CI)		**886**		**626**	**100.0%**	**0.80 [0.61, 1.05]**		
Total events	95		82					

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 5.80$, $df = 8$ ($p = .67$); $I^2 = 0\%$
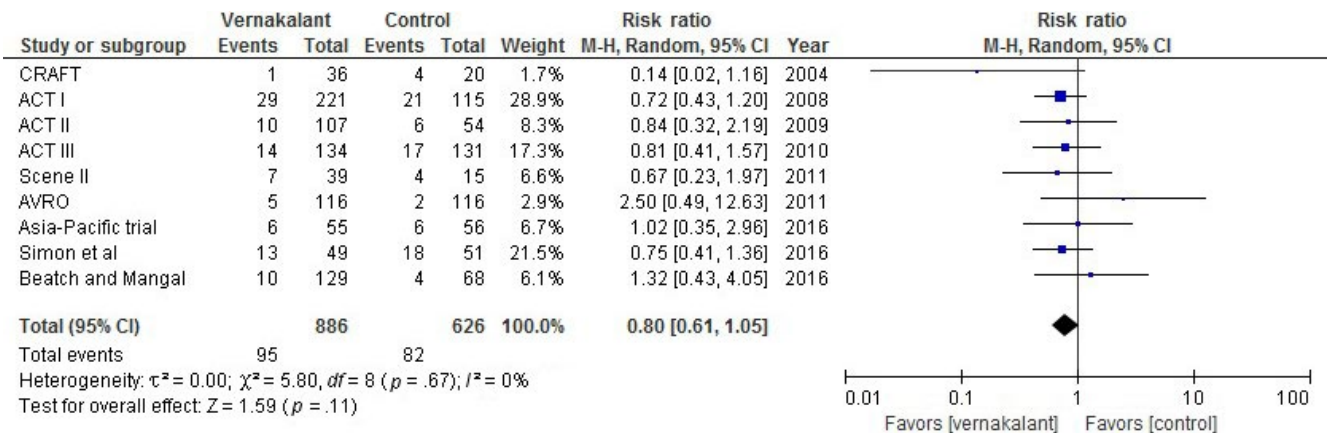Test for overall effect: $Z = 1.59$ ($p = .11$)

FIGURE 4 Adverse events in patients treated with vernakalant versus control

of this meta-analysis included vernakalant safety in patients, which is characterized by the proportion of patients who developed adverse events, hypotension, nonsustained ventricular tachycardia, or death. Adverse events of interest included events prespecified in each trial as a safety endpoint and are considered serious enough or treatment-emergent warranting immediate medical attention or drug discontinuation.

2.5 | Data synthesis and analysis

A meta-analysis was conducted from the extracted data using Review Manager (RevMan, version 5.4; Cochrane). Pooled risk ratios (RRs) were generated along with their 95% confidence intervals (CIs). To account for between-studies heterogeneity, the random effects model was used. A p value of <.05 was predefined to indicate statistical significance. Moreover, heterogeneity was assessed using chi-square test and the I^2 test, with considerable heterogeneity defined as $I^2 > 50\%$.

3 | RESULTS

As summarized in Figure 1, and after removing duplicates, the search yielded 174 potentially pertinent articles. Of them, 9 prospective randomized controlled trials were identified and included in the meta-analysis;
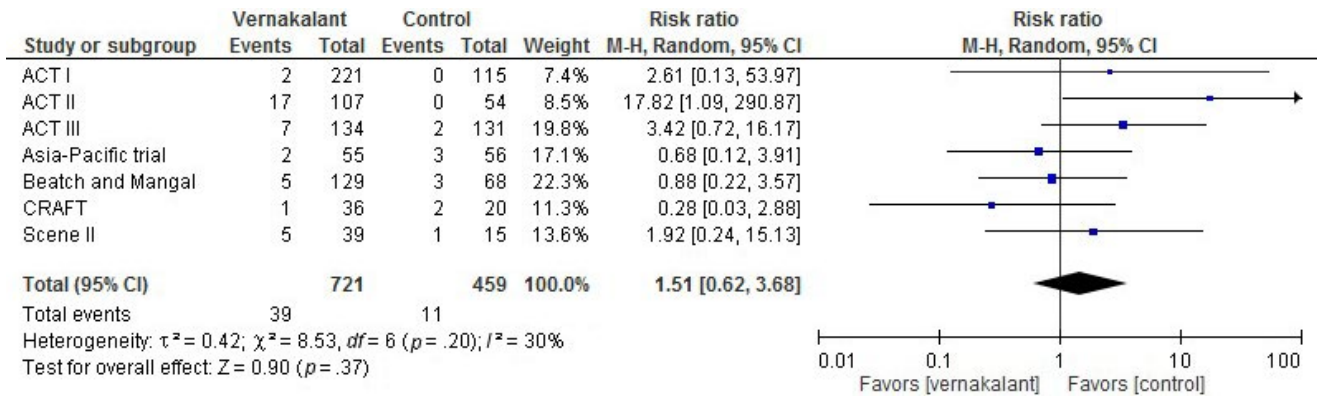
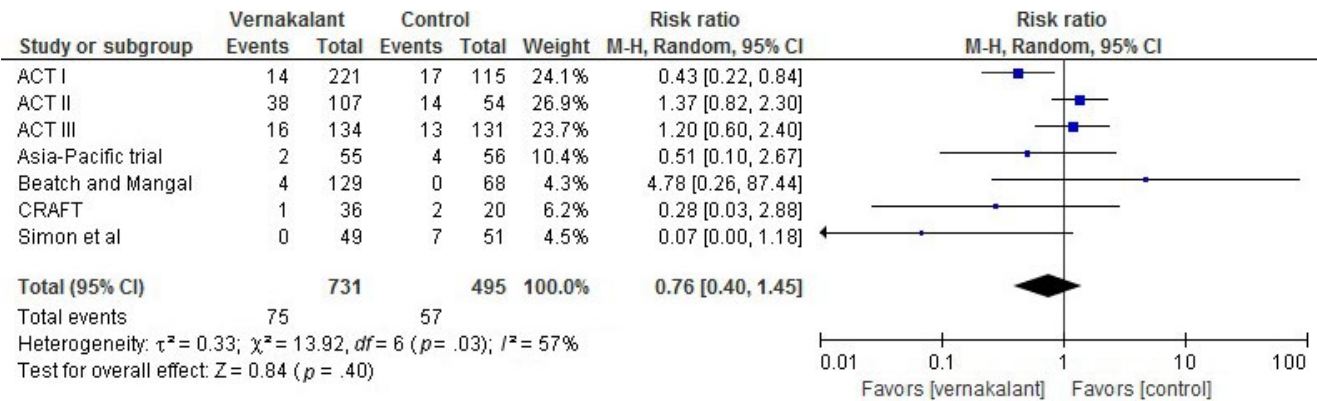**FIGURE 5** Hypotension events in patients treated with vernakalant versus control

FIGURE 6 Episodes of nonsustained ventricular tachycardia in patients treated with vernakalant versus control

FIGURE 7 Death events in patients treated with vernakalant versus control

Table 1. A total of 1,421 patients with recent-onset atrial fibrillation were included. Of them, 824 received vernakalant and 597 received control drug. In the vernakalant arm 372 patients converted into NSR within 90 min from drug infusion while only 51 patients who received the control drug converted into NSR. Pooled analysis of events extracted showed a statistically significant result in favor of vernakalant (RR, 6.61; 95% CI, 2.78–15.71; $p < .00001$); Figure 2. For patients with recent-onset atrial flutter, only three trials studied the effect of vernakalant in comparison to control drug with 87 patients included. Of them, 39 received vernakalant and 28 received a control drug; only two patients from the vernakalant arm and one patient from the control arm converted into NSR. Pooled analysis of events extracted for the 87 patients did not yield a statistically significant result (RR, 0.80; 95% CI, 0.14–4.73; $p = .81$); Figure 3.

In terms of adverse events, vernakalant was considered safe in comparison to control drugs (RR, 0.80; 95% CI, 0.61–1.05; $p = .11$); Figure 4. Hypotensive events were also analyzed in each group and showed no difference among them (RR, 1.51; 95% CI, 0.62–3.68; $p = .37$); Figure 5. For episodes of nonsustained ventricular tachycardia, there was no difference between the two groups (RR, 0.76; 95% CI, 0.40–1.45; $p = .11$); Figure 6. Likewise, death events were not statistically significant between the two groups (RR, 2.05; 95% CI, 0.53–7.97; $p = .3$); Figure 7.

4 | DISCUSSION

Vernakalant is a relatively new antiarrhythmic agent with predominant properties on atrial electrophysiology. It has been used in many European countries for pharmacological cardioversion of new-onset atrial fibrillation. At physiological heart rates, the block of atrial sodium (Na^+) channels by vernakalant is relatively weak due to rapid unbinding kinetics from the channel. While at higher heart rates, its affinity for activated Na^+ channels becomes greater (Tsuji & Dobrev, 2013; Savelieva et al., 2014; Fedida, 2007). Hence, effects on Na^+ channels are rate and voltage dependent, i.e. it will likely exert an enhanced inhibitory effect at rapid rates and depolarized potentials as in the fibrillating atria (Conde & Baranchuk, 2014). Moreover, vernakalant inhibits the early activating potassium (K^+) channels I_{Kur} and $I_{K,ACh}$. These currents are specific to the atrium and are the ones responsible for prolongation of the atrial refractory period (Fedida, 2007; Fedida et al., 2005; Camm, 2014) Consequently, this atrial selectivity along with the minimal effects on the ventricles explain the low proarrhythmic risk for torsades de pointes (TdP) arrhythmia with vernakalant use (Dobrev et al., 2010; Dorian et al., 2007). At present, vernakalant is only available as intravenous formulation. Oral formulation of vernakalant was initially developed and evaluated in one randomized placebo-controlled trial for the prevention of atrial fibrillation recurrence after cardioversion. (Torp-Pedersen et al., 2011) In this trial, patients were randomized to receive 150, 300, or 500 mg of vernakalant vs placebo twice daily for up to 90 days. Only vernakalant 500 mg twice daily was effective and safe for prevention of atrial fibrillation after electrical cardioversion with a median time to first recurrence of >90 days versus 29 days for placebo (p = .0275). Afterwards, the sponsor of vernakalant decided that reluctance from the Food and Drug Administration (FDA) to license the intravenous form of vernakalant rendered further development of the oral form unattractive (Camm, 2014).

According to this meta-analysis, vernakalant was effective in patients with recent-onset atrial fibrillation. However, for atrial flutter patients it wasn't. The explanation for its lack of effect is unclear yet. It is possible that more selective and potent blockade of the potassium current, especially I_{Kr}, as seen with ibutilide or dofetilide, is required for effective conversion of atrial flutter into NSR (Camm et al., 2012). Moreover, this lack of effect could be related to the lower atrial rate with atrial flutter compared to atrial fibrillation. It is also interesting to observe that atrial flutter has been reported after vernakalant infusion. Although most of the reported cases where self-limited, some required electrical cardioversion (Roy et al., 2004; Simon et al., 2016; Beatch & Mangal, 2016; Cosin-Sales et al., 2016; Roy et al., 2008). Nevertheless, there are few described cases of atrial flutter with 1:1 atrioventricular (AV) conduction after administration of vernakalant for atrial fibrillation (Franzini, Muller-Burri, & Shah, 2014; de Riva-Silva et al., 2012). The mechanism behind this is also uncertain. It is possible that slowing of atrial conduction due to Na^+ channels blocking could have favored the conversion into atrial flutter.

With respect to safety issues, vernakalant has been mainly evaluated within hours to days from drug administration. The most common adverse events were mild to moderate in nature and included dysgeusia, sneezing, and paresthesia, which are probably secondary to Na^+ channel blockade in the central nervous system (Savelieva et al., 2014). Currently, the drug is still not approved for use in the United States as the FDA continues to have further questions about the safety of the drug (Camm, 2014). The FDA had concerns about drug-induced hypotension as well as safety issues in patients with heart failure and acute coronary syndromes. Furthermore, the FDA requested another large trial to be conducted in 2008 to address the drug's safety. The ACT 5 trial was designed for this purpose; however, it was terminated early after a case of cardiogenic shock in a patient who received vernakalant (Camm, 2014).

In the included trials of this meta-analysis, the reported adverse events were not homogenous across the studies. Moreover, not all the trials specified exactly the adverse events of interest. In addition, none of the included trials specified whether there are certain subgroups of patients who are at higher risk for developing adverse events. For example, it was unclear whether the adverse events happened mainly in heart failure patients or not, especially events of hypotension. Thus, more safety data needs to be collected while taking into consideration the variable comorbidity profiles in the population.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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