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Review Article

Efficacy and Safety of Ibutilide for the Cardioversion of Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Abstract

Background: Ibutilide has been approved for cardioversion of Atrial Fibrillation (AF), but its side-effects include a high risk of torsade de pointes, besides, one recent meta-analysis showed ibutilide was inferior to vernakalant for conversion (AF<7 days). Hence, the aim of this study is to evaluate the efficacy and safety of ibutilide for the cardioversion of AF within 90 days.

Methods: The Embase, PubMed, Web of Science, Cochrane Central databases and clinical trials.gov were comprehensively searched for relevant studies from January 1991 to May 2020 using the keywords "ibutilide" and "atrial fibrillation". Only Randomized Controlled Trials (RCTs) comparing ibutilide with placebo or other Anti-Arrhythmic Drugs (AADs) for the termination of AF (duration of AF ≤90 days) were included. The primary outcome was successful cardioversion in response to ibutilide versus placebo or other AADs within 4h. Related adverse events were defined as secondary outcomes.

Results: A total of 1712 patients in 13 RCTs met the eligibility criteria. Four trials compared ibutilide to placebo; nine trials compared ibutilide to other active drugs. The results revealed that ibutilide had a higher success rate for the termination of recent-onset atrial fibrillation compared to placebo within 4h [Risk Ratio (RR), 4.64; 95% Confidence Interval (CI), 1.30-16.56, P=0.006]; and ibutilide also showed superiority to DL-sotalol, Propafenone, Procainamide for successful termination of recent-onset AF within 4h. As compared to other active drugs, Ibutilide was associated with a lower risk of hypotension (RR 0.23, 95% CI 0.09-0.57, P=0.002); but significantly increased the incidence of Polymorphic ventricular tachycardia (RR 3.78, 95% CI 1.08-13.23, P=0.04).

Conclusion: Intravenous ibutilide could be an accessible choice for the cardioversion of recent-onset AF patients without contraindications, but under strict monitored condition is needed for at least 6 hours.

Keywords: Atrial fibrillation; Cardioversion; Ibutilide; Meta-analysis

Abbreviations

AF: Atrial Fibrillation; AADS: Anti-Arrhythmic Drugs; RR: Risk Ratio; CI: Confidence Interval; RCTs: Randomized Controlled Trials

Introduction

Atrial Fibrillation (AF) is the most prevalent cardiac arrhythmia, occurring in 1-2 % of the general population. Patients with AF have an increased risk of death, hospitalizations, and a lower quality of life [1]. Sinus restoration can relieve rhythm-related symptoms and attenuate functional impairment [2-4]. As such, early chemical or electrical conversion is the preferred choice for the treatment of AF, but electro cardioversion requires sedation or anesthesia [5], which limits its use. Pharmacological treatment is therefore more appealing for the conversion of recent-onset AF.

Ibutilide is a class III intravenous anti-arrhythmic agent that blocks the rapid component of the cardiac delayed rectifier potassium current and activates a late inward sodium current [6]. Ibutilide has been approved for the termination of recent-onset atrial fibrillation and atrial flutter [7]. However, given the limited sample size in previous trials [8-10], the superiority of ibutilide over other Anti-Arrhythmic Drugs (AADs) remains undefined. The aim of this review was to investigate the effectiveness and safety of ibutilide for the conversion of recent-onset AF compared with placebo and other AADs.

Methods

This meta-analysis was performed according to the Cochrane Handbook for Systematic Reviews of Interventions [11] and presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA Guidelines) [12].

Search strategy

Two researchers (Gong C, and Tang Y) independently performed a comprehensive literature search. Trials comparing ibutilide with placebo or other AADs for the termination of recent-onset AF (duration of AF ≤90 days) were retrieved from PubMed, Embase, Web of Science, the Cochrane Library and Clinical Trials.gov until

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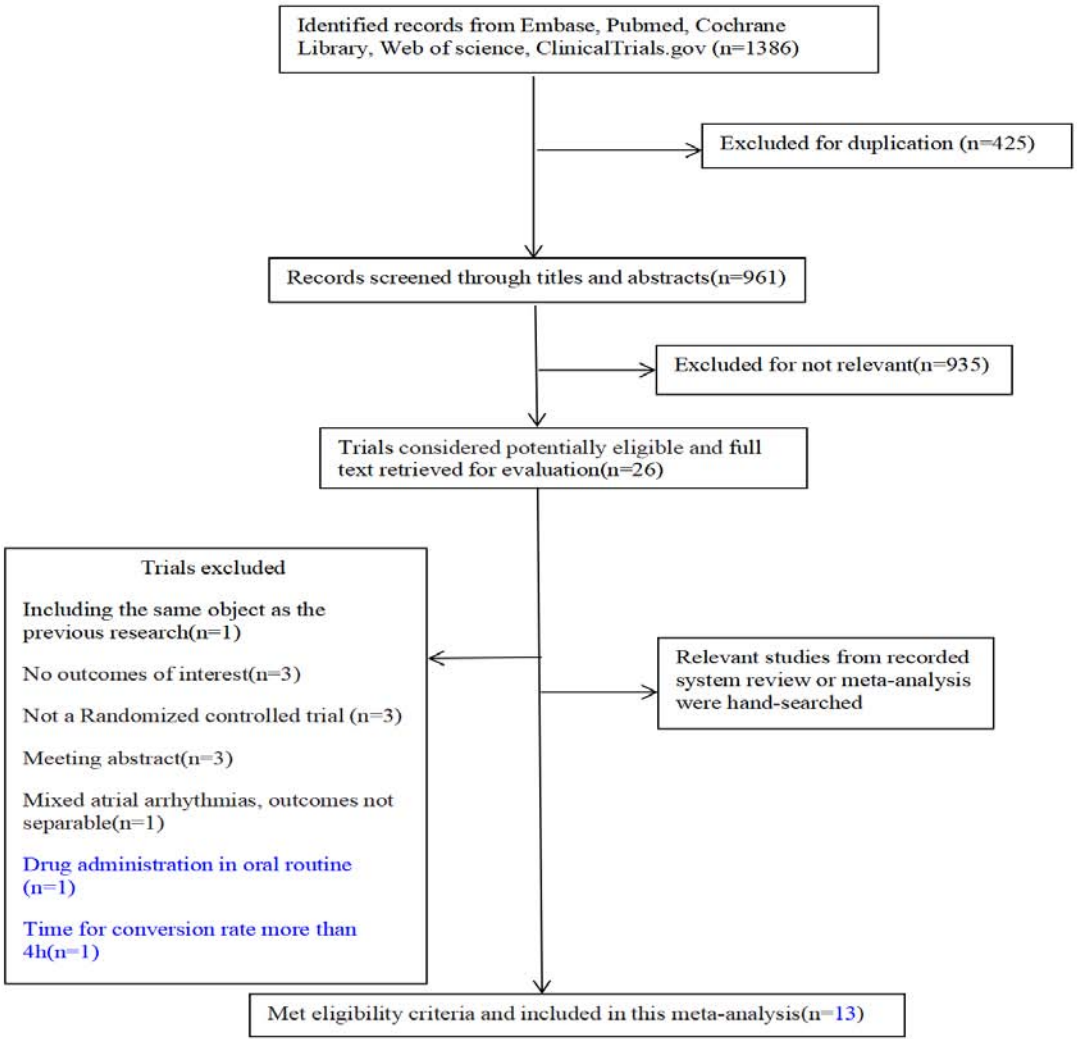

Figure 1: The flow diagram of study selection.

May, 2020. A basic search was carried out using the key words as follows: ("atrial fibrilation" or "atrial arrhythmia") and ("ibutilide" or "ibutilide fumarate"). No language limitation was applied for the selection of articles.

Eligibility criteria

Trials were selected based on the following inclusion criteria: (1) Adult patients; (2) Ibutilide versus placebo or other AADs for treatment of recent-onset AF (duration of AF ≤90 days); (3) Randomized controlled trials.

Quality assessment

The methodological quality for the included studies was evaluated separately by two researchers(Gong C and Tang Y) using the Cochrane risk of bias criteria [11] and each quality item was graded as low risk, high risk, or unclear risk. We defined other bias as trials in which baseline characteristics were significant variation between different treatment groups. The included trials were graded as low quality, high quality or moderate quality based on the criteria in the following: (1) trials were evaluated as low quality if either randomization or allocation concealment was assessed as a high risk of bias, without taking the risk of other items into consideration; (2) trials were considered as high quality when both randomization and allocation concealment were assessed as a low risk, along with all other items assessed as low or unclear risk of bias in a trial; (3) trials were considered as moderate quality if they did not meet criteria for high or low quality [13].

Data extraction

The following information from each trial was extracted independently by two researchers (Fang H and Huang Y): first author, year of publication, country of origin, sample size, treatment strategies, the duration of AF, the time point for evaluating conversion efficacy, the length of follow-up and patient population. Disagreements on data extraction and quality assessment between the 2 reviewers were resolved by consensus (Liu X).

Outcomes

The primary outcome was the success conversion rate of AF within 4h, secondary outcomes were as follows: the incidence of

Polymorphic ventricular tachycardia and hypotension.

Statistical analysis

Risk Ratio (RR) with 95% Confidence Interval (CI) were calculated for dichotomous data. Analyses were performed using Review Manager 5.3 (Revman: The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). We assessed the heterogeneity among studies using Cochran's Q-test (P<0.05 for statistical significance) and the I2 index (I2>50% for substantial heterogeneity). The random-effect model was chosen to pool the data.

Results

Selection of studies

Following the database search, a total of 1386 studies were identified. After the removal of duplications, 961 studies were screened according to titles and abstracts. Then, full texts of 26 potentially eligible trials were assessed based on predefined eligibility criteria. A total of 13 eligible trials were finally included in the meta-analysis (Figure1).

Description of the included RCTs

Four RCTs [14-17] depicted the efficacy and safety of ibutilide *vs.* Placebo, the cardioversion efficacy in all these trials was evaluated within 90min. A further nine studies [8-10,18-23] compared ibutilide with other AADs (including DL-sotalol, Amiodarone, Propafenone, Flecainide, Vernakalant, Procainamide), of which, the cardioversion efficacy in seven trials [8-10,18-21] was observed within 90min, while in other trials [22,23] was observed at more than 90 min and even up to 4 h. In addition, three studies [15,17,20] were designed to clarify that the treatment effects of ibutilide were dose-dependent. Detailed information of the patient characteristics. The outcomes of quality assessments were that two trials were of high quality, ten trials were of moderate quality, and one trials were of low quality.

Outcomes of the pooled studies

ibutilide versus placebo: A meta-analysis of 4 RCTs (total of 614 patients, Figure 2) demonstrated that ibutilide was superior to placebo for termination of recent-onset atrial fibrillation within 4h (RR 4.64, 95% CI 1.30-16.56, P=0.02). In addition, there were no significant difference between ibutilide and placebo for the incidence of Polymorphic ventricular tachycardia and hypotension events (Figure 4,5).

ibutilide versus other anti-arrhythmic drugs: A pool of 9 studies showed that no significant difference in the conversion rate was observed between the ibutilide and the active drugs (Figure 3, RR 1.18, 95% CI 0.91-1.51, P=0.21), also there existed substantial heterogeneity (I2=74%), which might caused by different comparator drugs and drug dosing. Then we did a subgroup analysis based on different control drugs, and we found ibutilide was more effective than DL-sotalol, Propafenone and Procainamide.

Pooled data from the 9 trials showed that ibutilide led to a higher risk of Polymorphic ventricular tachycardia (Figure 4 RR 3.78, 95% CI 1.08-13.23, P=0.04). But upon comparison with AADs, ibutilide retained a lower risk of hypotension (Figure 5, RR 0.23, 95% CI 0.09-0.57, P=0.002).

Discussion

This analysis suggested that ibutilide could be an accessible choice for the cardioversion of recent-onset AF patients, which had minimal effects on blood pressure. However, ibutilide had a relatively much higher risk of ventricular tachycardia than other AADs.

Ibutilide is a class III antiarrhythmic agent that exerts its function by markedly prolonging the effective refractory period and monophasic action potential duration in the atrium [24-26]. Our meta-analysis showed that ibutilide was superior to DL-sotalol, Propafenone, Procainamide for rapidly successful termination of recent-onset AF, which was in coincidence with ibutilide function. However, the included trials showed that vernakalant and flecainide exhibited higher conversion rate than ibutilide, further to dig out the data, it seemed that these two active drugs had higher efficacy for conversion with the same shorter AF duration (<48h). This needs to be verified through relevant clinical trials. Besides, although Vernakalant is promoted as much less proarrhythmic along with a higher conversion rate, it is more expensive and not available in the US. Moreover, Intravenous flecainide are mainly available in many European countries, meanwhile, drug contraindications are also vital, which needs taking into consideration when drug selection.

What's more, significant heterogeneity of the data on cardioversion rate in the trials were observed, this substantial heterogeneity may be due to the changes in the dose of ibutilide, the duration of atrial fibrillation. A random-effect model was therefore employed for the meta-analysis to reduce the false positive outcomes.

Moreover, we found that ibutilide was associated with a lower incidence of hypotension compared with other AADs. Previous studies also indicated that ibutilide was available for conversion of patients with hemodynamically unstable arrhythmia [27,28]. These results were in accordance with our data. For example, in the Varriale, et al. Trial [27], 27 of 34 ibutilide treated patients with

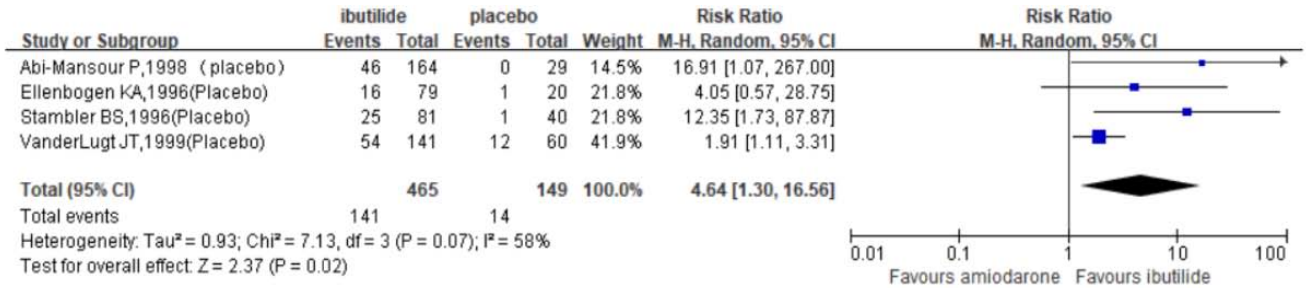

Figure 2: Relative risks of the conversion rate in trials comparing ibutilide to placebo within 4h.

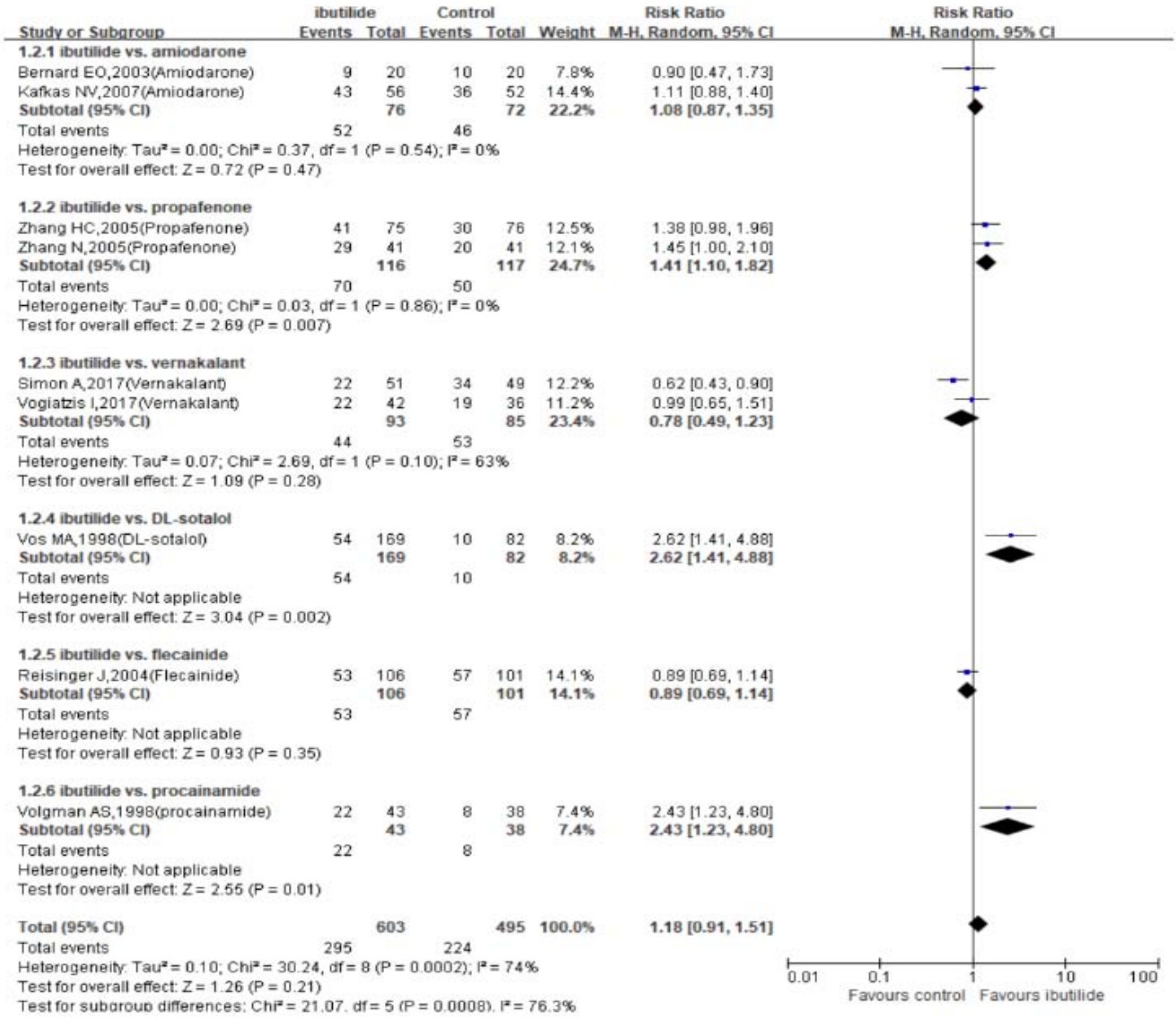

Figure 3: Relative risks of the conversion rate in trials comparing ibutilide to other active drugs within 4h: subgrouped based on different active drugs in control group.

symptomatic and/or hemodynamically unstable disorders reversed into sinus rhythm, with few cases of serious adverse events. Similarly, a recent study [28] showed that ibutilide was effective for refractory ventricular tachycardia in patients with hemodynamic instability.

In addition, pooled data from clinical trials showed that ibutilide was associated with a relatively much higher risk of polymorphic ventricular tachycardia compared with other active drugs, which occurred in 2.0% (30/1491) of participants. But in general, rapidly resolved following discontinuation [8-10,18-23]. Furthermore, one unscripted real-world clinical practice [29] reported that ibutilide-induced ventricular tachycardia was uncommon [0.6% (2/361)] and only one case of polymorphic ventricular tachycardia occurred for mild hypokalemia. Ibutilide is therefore a safe antiarrhythmic agent when patients are monitored through close electrocardiograph assessments and are administered magnesium or potassium to maintain electrolyte balance as well as avoidance combination with drugs of prolongation QT intervals [20,23].

There were several limitations in this study. Firstly, the sample size of many of the included trials were relatively small, affecting the quality of the review. Secondly, some RCTs were of low quality, including randomization or allocation concealment that was of high risk. Thirdly, the dose of ibutilide was variable and was difficult to stratify with relevant efficacy and safety data; meantime,patients in our included trials with different atrial fibrillation duration. Finally, few trials did cost effectiveness comparation, one of important factors affecting doctor to make drug selection.

Conclusion

In this meta-analysis of 13 RCTs, ibutilide was an accessible choice for the cardioversion of recent-onset atrial fibrillation when

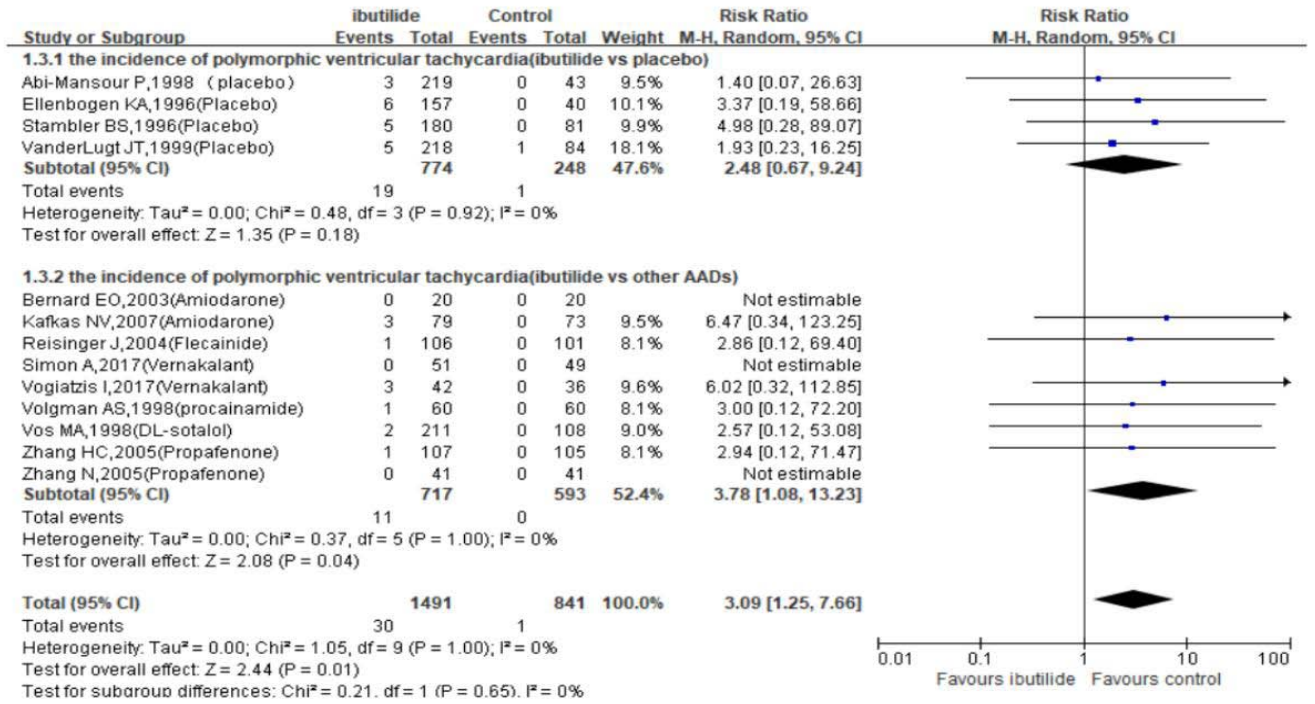

Figure 4: Relative risks of the polymorphic ventricular tachycardia events in trials comparing ibutilide to comparators: subgrouped based on whether the control group received placebo or active drugs.

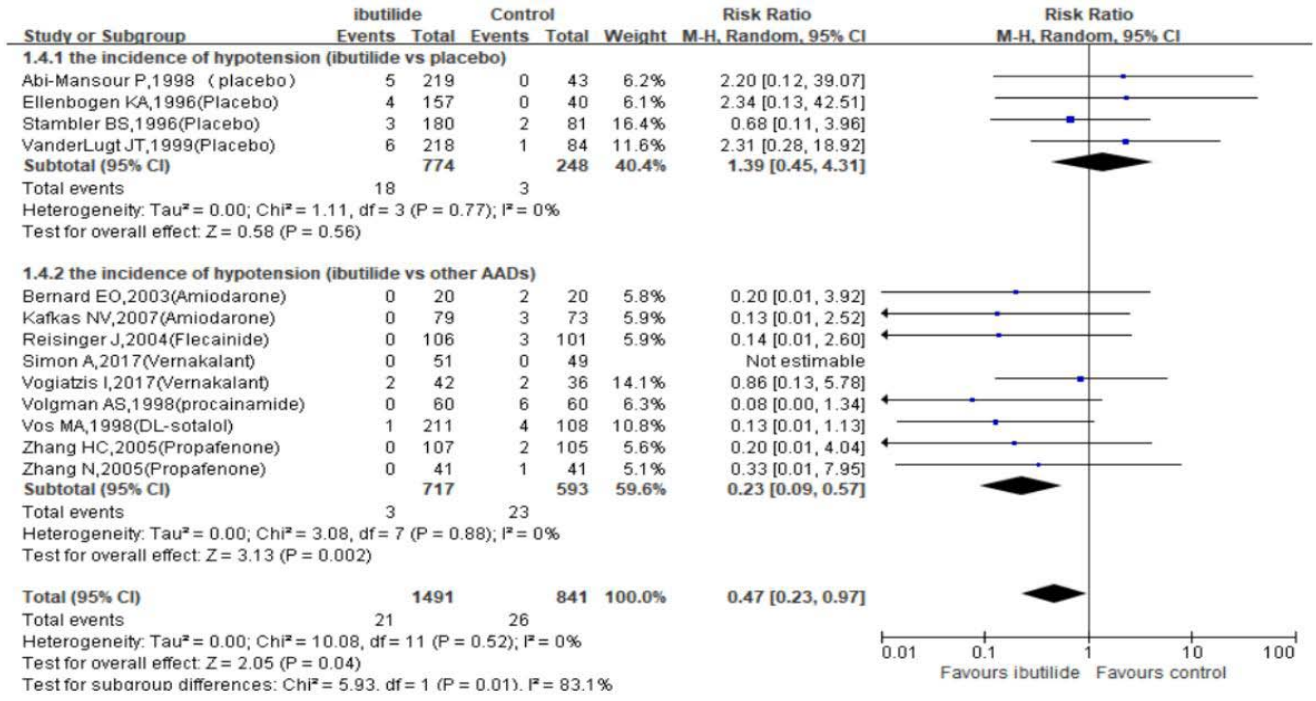

Figure 5: Relative risks of the hypotension events in trials comparing ibutilide to comparators: subgrouped based on whether the control group received placebo or active drugs.

patients were closely monitored.

Acknowledgment

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