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Intravenous diltiazem versus metoprolol for atrial fibrillation with rapid ventricular rate: A meta-analysis

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ABSTRACT

Background: Intravenous diltiazem and metoprolol are both commonly used to treat atrial fibrillation (AF) with rapid ventricular rate (RVR) in the emergency department (ED), but the advantages and disadvantages of these drugs cannot be verified. This meta-analysis aimed to assess the efficacy and safety of intravenous diltiazem versus metoprolol for AF with RVR.

Method: We systematically searched PubMed, Web of Science, Embase, Cochrane library, the China National Knowledge Infrastructure (CNKI), Wanfang, China Biology Medicine disc (CBM) and the WeiPu (VIP). Meta-analysis was performed using weighted mean difference (WMD), relative risk (RR) and 95% confidence interval (CI). Statistical analysis was performed using Review Manager 5.4.1.

Results: Seventeen studies involving 1214 patients in nine randomized controlled trials (RCTs) and eight cohort studies were included in meta-analysis, including 643 patients in the intravenous diltiazem group and 571 patients group in the intravenous metoprolol. The results of the meta-analysis showed that compared with intravenous metoprolol, intravenous diltiazem was found higher efficacy (RR =1.11; 95% CI = 1.06 to 1.16, $p < 0.00001$), shorter average onset time (RR = −1.13; 95% CI = −1.97 to −0.28, $p = 0.009$), lower ventricular rate (RR = −9.48; 95% CI = −12.13 to −6.82, $p<0.00001$), less impact on systolic blood pressure (WMD = 3.76; 95% CI: 0.20 to 7.33, $P = 0.04$), and no significant difference in adverse events (RR = 0.80, 95% CI = 0.55 to 1.14, $P = 0.22$) and diastolic blood pressure (WMD = −1.20; 95% CI: −3.43 to 1.04, $P = 0.29$) was found between intravenous diltiazem and metoprolol.

Conclusion: Intravenous diltiazem has higher efficacy, shorter average onset time, lower ventricular rate, less impact on blood pressure, and with no increase in adverse events compared to intravenous metoprolol.

1. Introduction

Atrial fibrillation(AF) is the most common arrhythmia [1], and it is also the most commonly encountered cardiac dysrhythmia in emergency department (ED) [2]. With the aging of the population and the improvement of average age, the incidence rate of AF is increasing year by year. The incidence rate of AF has increased three times in the past 50 years [3]. The prevalence of AF in China in 2018 is 0.71%, and the incidence rate of elderly people over 75-year-old is 2.35% [4]. Nowadays the high incidence of AF is rising markedly, which has brought heavy financial burden to the world.

AF can cause asymptomatic or present with a wide spectrum of symptoms, including fatigue, palpitations, dyspnea, hypotension, and syncope, the most serious complication is stroke [5]. AF with rapid ventricular response (RVR) is defined as heart rate ≥ 120 beats per minute (bpm), and the use of drugs for rate or rhythm control is the option for management of AF in ED if patients who are hemodynamic stability [6]. Recommended by the plenty of guides, intravenous beta blockers or non-dihydropyridine calcium channel blocker can slow ventricular heart rate in the acute setting in patients without pre-excitation [7,8], however, there is no preference between them. Therefore, the main purpose of this meta-analysis was to provide evidence-based medicine for choosing the most appropriate drug to terminate the attack when patients with AF with RVR present to the ED.

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2. Materials and methods

2.1. Search strategy

PubMed, Embase, Web of Science, Cochrane library, the China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), Wanfang, and the WeiPu (VIP) were systematically searched before June 2021. The main search terms were "Atrial Fibrillation", "Atrial Fibrillation*", "Fibrillation*, Atrial", "Auricular Fibrillation*", "Fibrillation*, Auricular", "Persistent Atrial Fibrillation", "Atrial Fibrillation*, Persistent", "Fibrillation*, Persistent Atrial", "Persistent Atrial Fibrillation*", "Familial Atrial Fibrillation", "Atrial Fibrillation*, Familial", "Familial Atrial Fibrillation*", "Fibrillation*, Familial Atrial", "Paroxysmal Atrial Fibrillation*", "Atrial Fibrillation*, Paroxysmal", "Fibrillation*, Paroxysmal Atrial", "Diltiazem", "Cardil","Cardizem", "CRD-401", "CRD 401", "CRD401", "Tiazac", "Dilacor XR", "Dilren", "Diltiazem Hydrochloride", "Diltiazem Malate", "Dilzem", "Aldizem", "Dilacor", "Metoprolol", "Toprol", "Betaloc", "Betaloc-Astra", "Betaloc Astra", "Betalok", "CGP-2175", "CGP 2175", "CGP2175", "H 93–26", "H 93 26", "H 932", "Metoprolol Tartrate", "Seloken", "Spesicor", "Spesikor", "Metoprolol Succinate", "Metoprolol CR-XL", "Metoprolol CR XL", "Toprol-XL", "Toprol XL", "Beloc-Duriles", "Beloc Duriles" and "Lopressor". We used these terms alone or in combination for literature search. The languages, publication type, and regions were not limited. We also checked the articles' reference lists to identify additional relevant publications. Two investigators reviewed each title and abstract screening and full-text review. A third investigator adjudicated any disagreements.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: ① Participants: Patients with AF were definitely diagnosed according to electrocardiogram, RVR was defined as heart rate ≥ 120 bpm, and aged 18 years old or above; ② Intervention: The experimental group was treated with intravenous diltiazem; The control group was treated with intravenous metoprolol; ③ Outcome measures: efficacy, average onset time, ventricular rate, impact on blood pressure, and adverse events; ④ Study type: randomized controlled trials (RCTs) or non-randomized controlled trials (non-RCTs).

The exclusion criteria were as follows: ① duplicated publications; ② systematic reviews and/or meta-analysis, expert commentaries or review articles, and case reports; ③ Incomplete or wrong data.

2.3. Data extraction and quality assessment

The data extracted include: (1) Basic information of the reviewed studies: author, year of publication and sample size; (2) Research objects: patient age, gender, number of male patients; (3) Intervention measures: the treatment method of experimental group and control group; (4) Outcomes: efficacy, average onset time, ventricular rate, impact on blood pressure, and adverse events. Two investigators independently evaluated the included studies, assessed the quality of the articles, a third party when disagreement occurred until consensus was reached, and cross checked the results finally. The Oxford quality scoring system (Jadad scale) was used to evaluate the quality of literature for RCTs. All RCTs were evaluated on the basis of five items: patient randomization, appropriateness of generating a randomized sequence, adequacy of double-blind procedure, description of double-blinding method, details of patient's exclusion and drop-out. The quality score ranged between 0 and 5. Studies with Jadad score ≥ 3 were regarded to be of high-quality with a low risk of bias, while studies with Jadad score ≤ 2 were regarded to be of low-quality with a high risk of bias, and the Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the quality of the included non-RCTs, which consists of three domains: selection, comparability and outcomes. Scores ranging from 0 to 9, Studies that received a score of six or higher were considered high-quality studies. Related table was shown in Table 1.

2.4. Statistical analysis

The results were presented as relative risks (RR) with 95% confidence interval (CI) for dichotomous outcomes, weighted mean difference (WMD) with 95% CI for continuous outcomes. All effect indicators were evaluated for heterogeneity. We used a fixed-effects model in the absence of heterogeneity ($I^2 < 50\%$). Otherwise, a random-effects model was used. $P < 0.05$ was considered statistically significant. Subgroup and sensitivity analysis were performed to explore sources of potential heterogeneity between studies and to explore other potentially confounding factors. Statistical analyses were performed using Review Manager, version 5.4.1 (RevMan, The Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Search results and reviewed literature

A total of 315 studies were retrieved according to the inclusion and exclusion criteria, and a total of seventeen articles [9-25] were included in the meta-analysis. There are 10 high-quality and 7 low-quality studies. Fig. 1 is the flow chart demonstrating the detailed selection process and identification.

3.2. Study characteristics

A total of seventeen studies were included, which involved a total of 1214 patients. Among them, there were 643 cases in the diltiazem group and 571 cases in the metoprolol group. Table 1 summarizes the characteristics of included studies.

3.3. Meta-analysis results

3.3.1. Efficacy

Thirteen studies [9,11-15,17-23] including 869 patients reported the efficacy. We conducted a subgroup analysis according to time, however, we found obvious heterogeneity in 5-min efficacy, 10-min efficacy, and 30-min efficacy, then we conducted sensitivity analysis and found that Fromm [9] was the source of heterogeneity. After the Fromm 2015 study was removed, no significant heterogeneity was observed among the studies ($I^2 = 0\%$, $P = 0.96$), thus we applied the fixed-effect model for further investigation. The pooled results showed that intravenous diltiazem was superior to intravenous metoprolol (RR: 1.11, 95% CI: 1.06 to 1.16, $P<0.00001$), and the results showed that intravenous diltiazem was better than intravenous metoprolol in the efficacy at 30 min (RR: 1.13, 95% CI: 1.03 to 1.24, $P = 0.007$), 60 min (RR: 1.11, 95% CI: 1.01to 1.23, $P = 0.03$). No statistically significant difference was found between two groups at 5 min (RR: 1.13, 95% CI: 0.96 to 1.32, $P = 0.14$), 10 min (RR: 1.09, 95% CI: 0.96 to 1.22, $P = 0.17$), 90 min (RR: 1.09, 95% CI: 1.00 to 1.18, $P = 0.05$), 120 min (RR: 1.10, 95% CI: 0.99 to 1.22, $P = 0.06$, Fig. 2).

3.3.2. Average onset time

Seven studies [10,17-21,25] including 411 patients reported the average onset time. No significant heterogeneity was observed among the studies ($I^2 = 39\%$, $P = 0.15$), thus the fixed-effect model was used for further investigation. The results showed that the average onset time of intravenous diltiazem was significantly shorter than that of

Table 1

Author	Year	Scale	Score	Number(T/C)	Diltiazem	Metoprolol	Gender (male/female)	Age
Demircan	2005	Jadad	5	20/20	0.25 mg/kg (maximum 25 mg)	0.15 mg/kg (maximum 10 mg)	22/18	NA
Ye Xianhua	2007	Jadad	2	37/35	10 mg (maximum 30 mg)	5 mg (maximum 15 mg)	46/26	71.3 ± 10.6/72.1 ± 10.1
Lin Bin	2007	Jadad	2	35/39	15 mg	5 mg (maximum 10-15 mg)	NA	NA
Kong Xianmei	2008	Jadad	2	20/20	0.25 mg/kg (maximum 20 mg)	0.15 mg/kg (maximum 10 mg)	22/18	61 ± 18
Diao Hongying	2009	NOS	7	24/24	10 mg	5 mg	22/26	57 ± 11/58 ± 12
Zhang Renhan	2009	NOS	5	38/21	0.25 mg/kg	5 mg (maximum 20 mg)	NA	NA
Zhong Sigan	2010	Jadad	2	40/40	0.25 mg/kg	5 mg (maximum 15 mg)	45/35	70.1 ± 7.7
Fan Shuxiong	2012	NOS	7	24/24	10-15 mg	5 mg	24/24	NA
Han Jian	2013	Jadad	2	34/34	10 mg	5 mg (maximum 10 mg)	41/27	68.9 ± 2.7/69.5 ± 2.3
Gao Yi	2013	Jadad	2	40/40	NA	NA	45/35	69 ± 3
Fromm	2015	Jadad	5	24/28	0.25 mg/kg (maximum 30 mg)	0.15 mg/kg (maximum 10 mg)	26/26	66.2 ± 13.4/69.5 ± 14.8
Hines	2016	NOS	8	55/45	NA	NA	51/49	64.2 ± 12.0/64.2 ± 12.0
Hirschy	2019	NOS	8	34/14	NA	NA	31/17	67.7 ± 18.6/64.9 ± 20.6[a]
Nuñez	2020	NOS	7	80/80	NA	NA	83/77	65.9 ± 18.1/66.7 ± 16.6[a]
Nicholson	2020	NOS	7	63/45	10 mg(maximum 25 mg)	2.5(maximum 5 mg)	55/43	64 ± 11/68 ± 13
Sun Junhua	2012	Jadad	4	43/43	0.25 mg/kg(maximum 30 mg)	5 mg	57/29	69.25 ± 6.38/69.30 ± 6.25
Hargrove	2021	NOS	8	32/19	NA	NA	21/30	62.2 ± 13.9/62.9 ± 13.2

[a] The original study only provided the Median and Inter-Quartile Range. After numerical conversion according to the method of Hozo etc. [26], the Mean ± Standard Deviation was obtained.

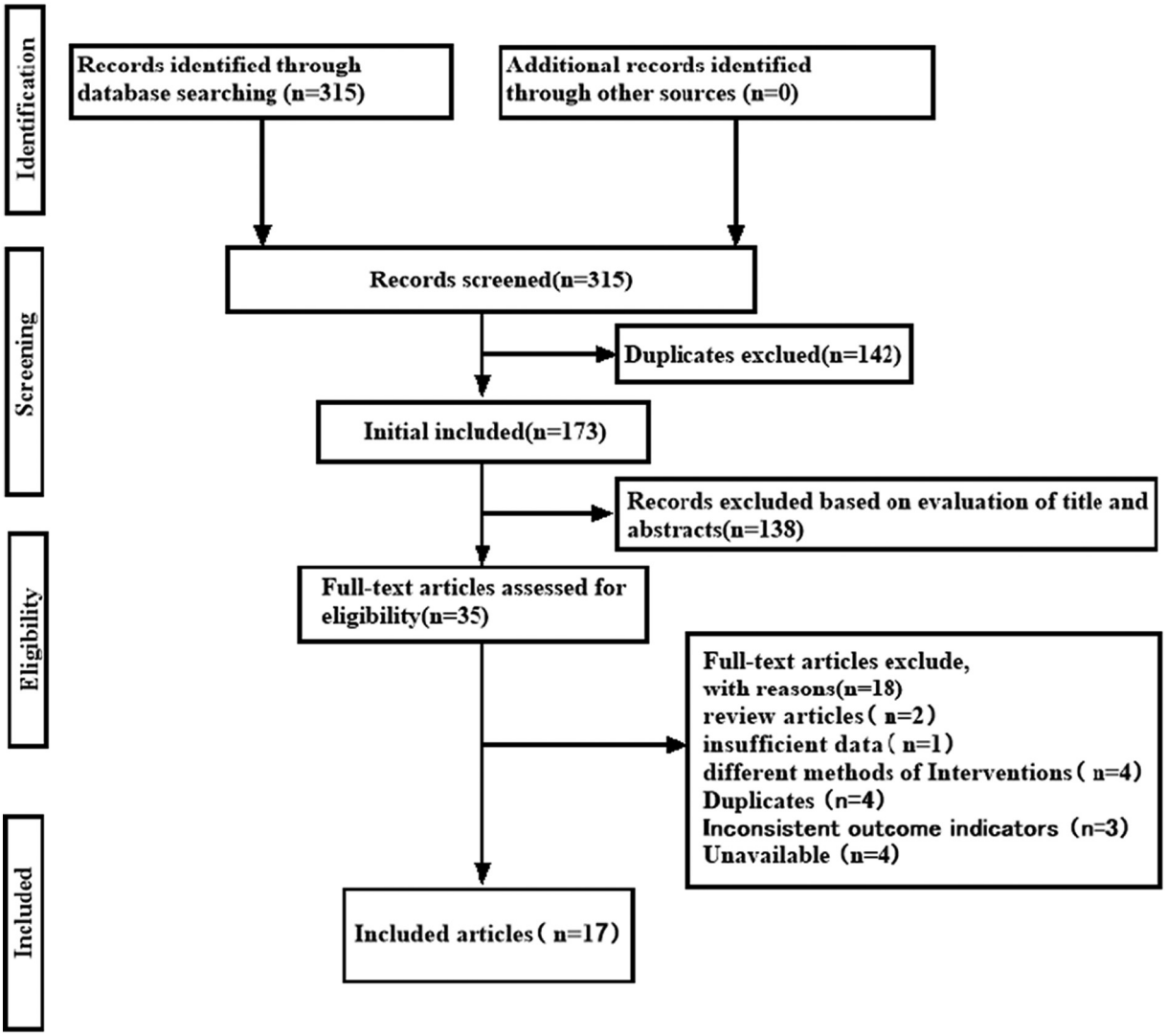

Fig. 1. Flow diagram of study searching and selection process.

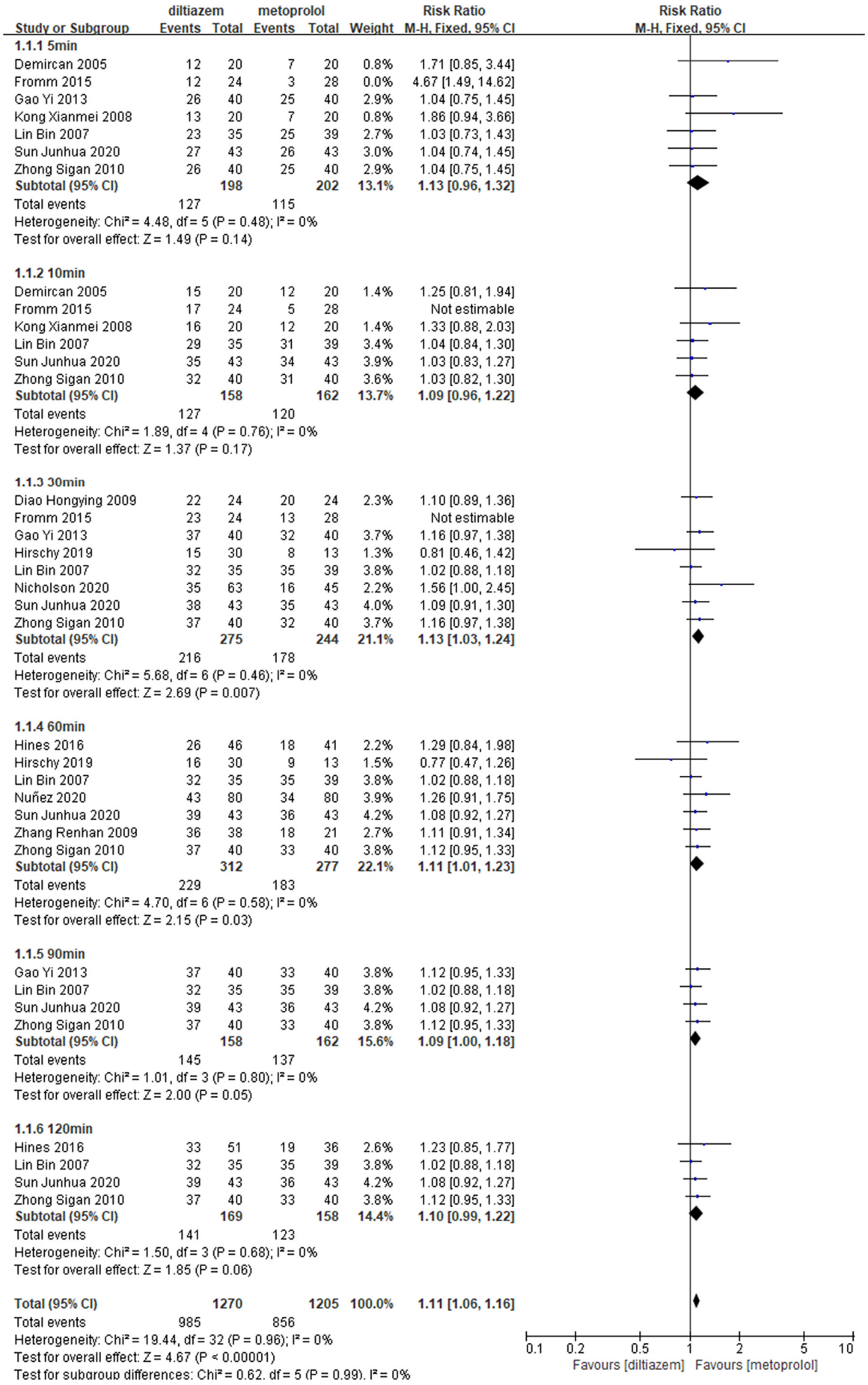

Fig. 2. Forest plot for the meta-analysis of efficacy.

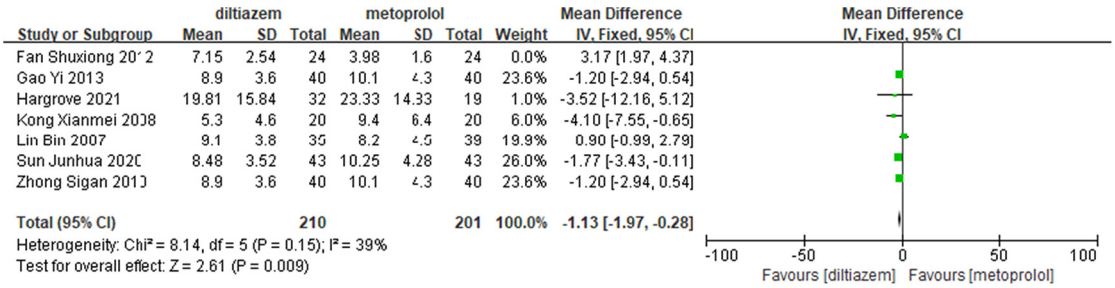

Fig. 3. Forest plot for the meta-analysis of average onset time.

intravenous metoprolol (WMD: −1.13; 95% CI: −1.97 to −0.28, P = 0.009, Fig. 3).

3.3.3. Decrease in ventricular rate

Twelve studies [9-11,15,16,18-24] including 755 patients reported decrease in ventricular rate. There was obvious heterogeneity in all subgroups ($I^2 > 50\%$), thus the random-effect model was selected for further investigation. The pooled results showed that intravenous diltiazem was superior to intravenous metoprolol (WMD = −9.48; 95% CI: −12.13 to −6.82, $P < 0.00001$). The results showed that intravenous diltiazem was better than intravenous metoprolol in decrease in ventricular rate at 5 min (WMD = −10.15; 95% CI: −19.49 to −0.81, P = 0.03), 10 min (WMD = −13.98; 95% CI: −20.47 to −7.50, $P < 0.0001$), 15 min (WMD = −9.63; 95% CI: −16.77 to −2.48, P = 0.008), 30 min (WMD = −11.56; 95% CI: −17.05 to −6.07, $P < 0.0001$), 60 min (WMD = −7.97; 95% CI: −14.36 to −1.58, P = 0.01), 90 min (WMD = −6.90; 95% CI: −11.95 to −1.84, P = 0.008) . However, no statistically significant difference was found between two treatments at 120 min (WMD = −5.31; 95% CI: −11.48 to 0.86, P = 0.09, Fig. 4).

3.3.4. Systolic blood pressure

Three studies [11,16,22] including 160 patients reported systolic blood pressure. There was no obvious heterogeneity in all subgroups (I^2 = 19%, P = 0.26), thus the fixed-effect model was selected for further investigation. The results showed that two treatments were not statistically significant in terms of systolic blood pressure at 5 min (WMD = 6.63; 95% CI: −1.59 to 14.84, P = 0.11), 10 min (WMD = 6.43; 95% CI: −1.53 to 14.38, P = 0.11), 30 min (WMD = −1.72; 95% CI: −7.32 to 3.87, P = 0.55). However, intravenous metoprol can decrease the systolic blood pressure at 15 min compared to intravenous diltiazem (WMD = 9.42; 95% CI: 1.53 to 17.32, P = 0.02, Fig. 5).

3.3.5. Diastolic blood pressure

Three studies [11,16,22] including 160 patients reported diastolic blood pressure. There was no obvious heterogeneity in all subgroups (I^2 = 0%, P = 0.56), thus the fixed-effect model was selected for further investigation. The results showed that two treatments were no statistical significance in terms of diastolic blood pressure at 5 min (WMD = −0.84; 95% CI: −5.23 to 3.54, P = 0.71), 10 min (WMD = −1.45; 95% CI: −5.75 to 2.85, P = 0.51), 15 min (WMD = 0.61; 95% CI: −3.64 to 4.85, P = 0.78) and 30 min (WMD = −3.94; 95% CI: −9.07 to 1.18, P = 0.13, Fig. 6).

3.3.6. Adverse events

Fifteen studies [9-12,14-23,25] including 411 patients reported adverse events, there was no significant heterogeneity among the studies (I^2 = 0%, P = 0.86), thus the fixed-effect model was selected for further investigation. No difference was found for incidence of adverse events (RR = 0.80,95% CI:0.55 to 1.14, P = 0.22, Fig. 7).

4. Discussion

Our meta-analysis showed that intravenous diltiazem was more effective than intravenous metoprolol in controlling ventricular rate in patients with AF with RVR. The advantage of intravenous diltiazem was gradually revealed at 30 min, and no significant difference was found at 90 and 120 min after intravenous injection. In terms of the decrease in ventricular rate, we observed that intravenous diltiazem was more effective, which reflected that the ventricular rate was slowed down more obviously and the onset time of diltiazem was shorter. There was no significant difference in diastolic blood pressure and adverse events between intravenous diltiazem and metoprolol, but we found that intravenous metoprolol may reduce systolic blood pressure. Therefore, for emergency doctors, intravenous diltiazem can control the ventricular rate in patients with AF with RVR well in ED, intravenous diltiazem has more benefits and less adverse events.

The joint American Heart Association and American College of Cardiology guidelines recommend the initial bolus dose of intravenous diltiazem is 0.25 mg/kg actual body weight, while the intravenous dose of metoprolol is 2.5–5.0 mg [7]. Diltiazem is a non-dihydropyridine calcium channel blocker and belongs to class IV antiarrhythmic drugs. Reported half-lives for the elimination phase of diltiazem in healthy volunteers have ranged from 2 to 7 h (average about 4.5 h), however, its potent vasodilatory activity often lead to decreases in peripheral resistance and blood pressure, the main adverse events of diltiazem were as follows: vasodilatation (resulting in headache or flushing, and occasional hypotension) and depression of at nodal conduction, but adverse events occur in only 2% to 10% and are generally minor in nature [27]. Metoprolol is selective β1 receptor blockers, belonging to class II antiarrhythmic drugs, it can control ventricular rate in patients with AF by reducing sympathetic activity, its half-lives in healthy have ranged from 2 to 6 h [28]. Both metoprolol and diltiazem can slow atrioventricular nodal conduction, however, our results showed that the onset time of intravenous diltiazem was shorter than that of intravenous metoprolol.

The limitations of this study include: ① The sample size of the included studies are relatively small, which makes the statistical power relatively low that may affect the accuracy of the results; ② Some of the included studies did not explicitly mention the random sampling method, some studies did not mention the allocation concealment scheme, therefore, there might be selective bias and implementation bias in the trial design. ③ We observed significant heterogeneity across the studies, which decreases the robustness of the conclusions despite the use of the random-effects model. ④ Some of the included studies had retrospective designs, therefore, selection bias, recall bias, and other biases should be considered. ⑤ The difference of drug dosage between different studies.

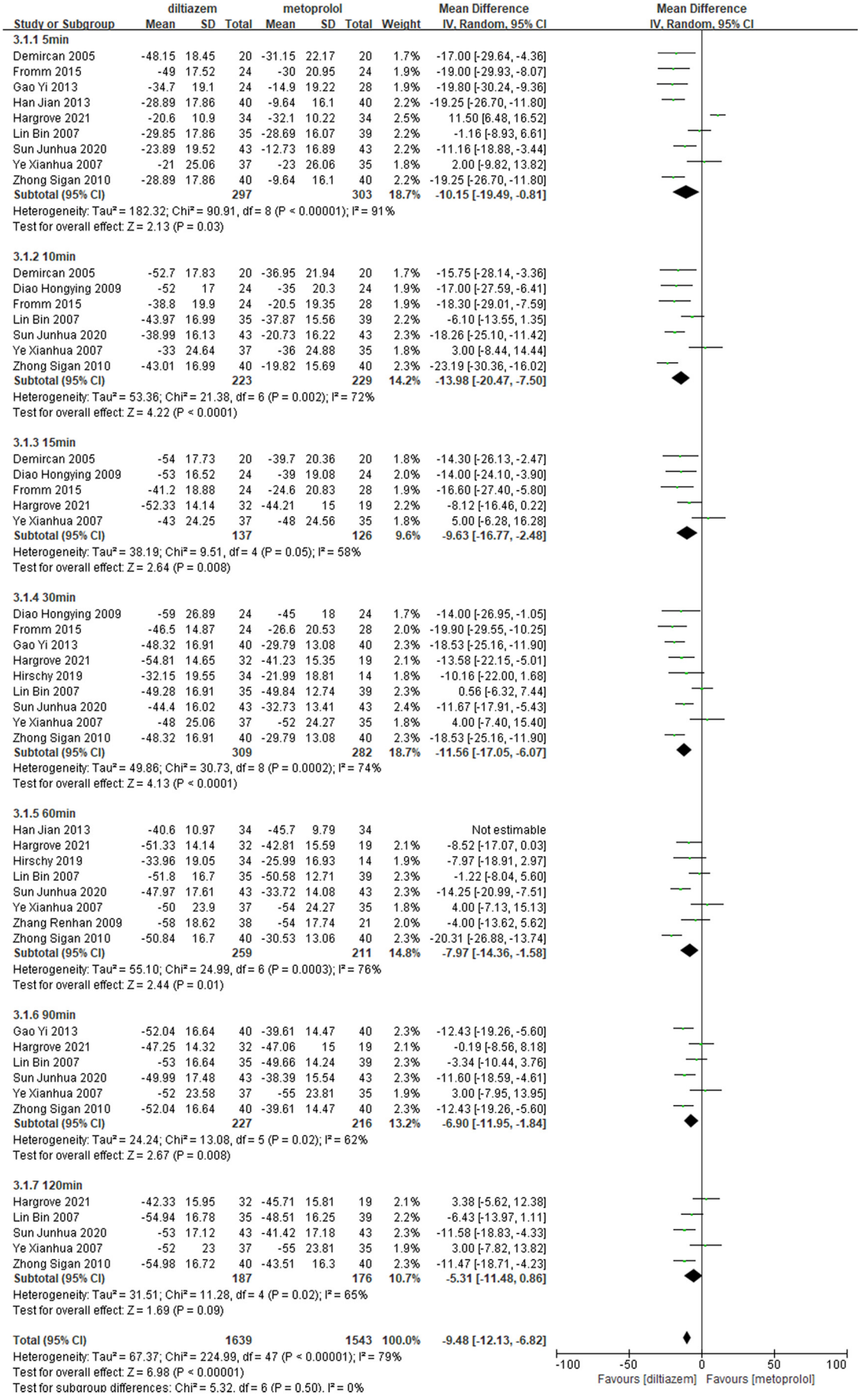

Fig. 4. Forest plot for the meta-analysis of decrease in ventricular rate.

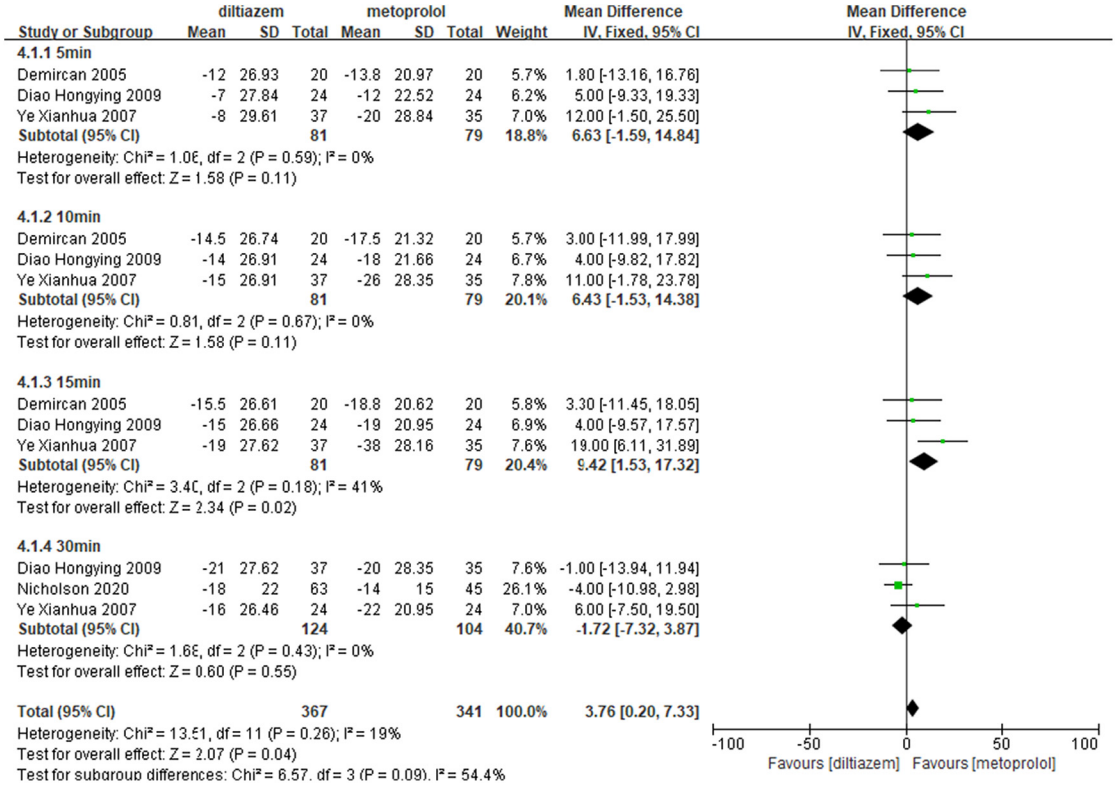

Fig. 5. Forest plot for the meta-analysis of systolic blood pressure.

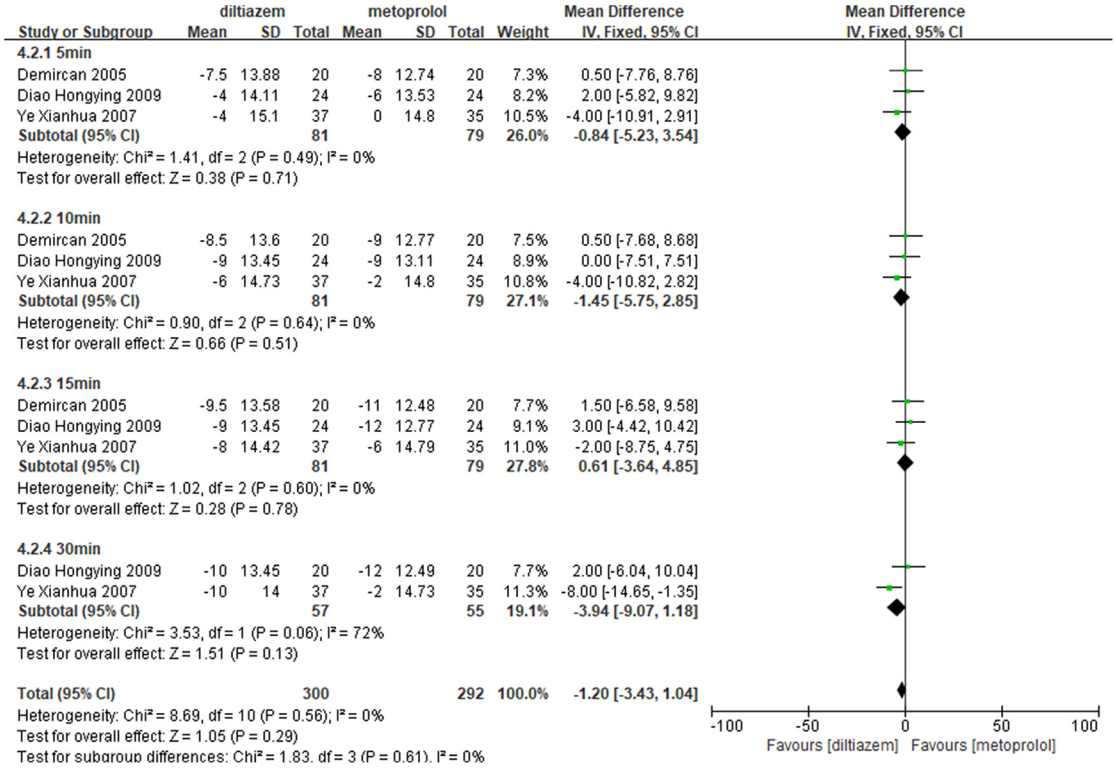

Fig. 6. Forest plot for the meta-analysis of diastolic blood pressure.

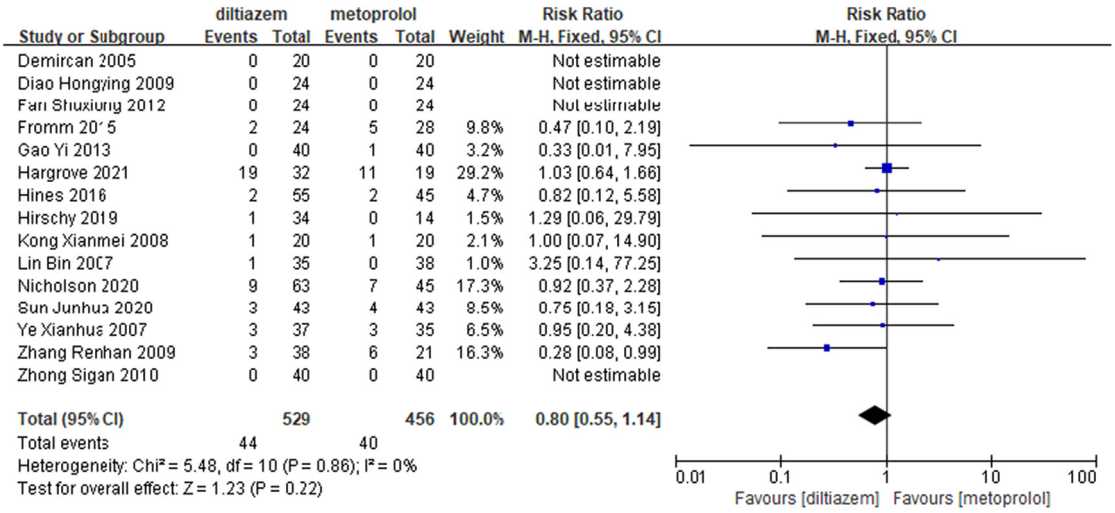

Fig. 7. Forest plot for the meta-analysis of adverse events.

5. Conclusion

Compared with intravenous metoprolol, intravenous diltiazem for AF with RVR has higher efficacy, shorter average onset time, lower ventricular rate, less impact on blood pressure, and no significant increase in adverse events.

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Contributors

LQS and WFC conceived the research and set standards; LQS and WFC performed the research; LQS, WFC, and HB performed the statistical analysis; LQS and WFC wrote the manuscript; YYL and HB provided professional knowledge of treatment and made a final revision of the manuscript; all authors read and approved the final manuscript. LQS and WFC are the first authors of this paper.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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None.

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