

# The effects of antithrombotic drugs on the recurrence and mortality in patients with chronic subdural hematoma

## A meta-analysis

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### Abstract

**Objectives:** Chronic subdural hematoma (cSDH) is a common neurological disorder in elderly and the immediate outcome of surgery is satisfied. The high reoperation rate hinders the long-term effect of surgery and the risk factor is still unclear. Some researchers reported that high recurrence rate is related to the antithrombotic (AT) drugs, which is commonly used to prevent diseases in elderly patients. In this article, we conducted a meta-analysis to determine whether AT agents increase the risk of recurrence and mortality in patients with cSDH.

**Methods:** The human case-control or randomized controlled trial (RCT) studies regarding the association of cSDH and AT were systematically identified through online databases (PubMed, Cochrane, Web of Science, Elsevier Science Direct, and Springer Link). Inclusion and exclusion criteria were defined for the eligible studies. The fixed-effects model was performed when homogeneity was indicated.

**Results:** This meta-analysis included 24 studies. AT drugs significantly increased the risk of recurrence in patients with cSDH (odds ratio (OR) of 1.30, 95% confidence interval (CI), 1.11–1.52,  $P = .001$ ). Further analysis demonstrated that both anticoagulation (OR of 1.41, 95% CI, 1.10–1.81,  $P = .006$ ) and antiplatelet (OR of 1.23, 95% CI, 1.01–1.49,  $P = .03$ ) had higher risk of recurrence, but no difference was found between them (OR of 0.80, 95% CI, 0.58–1.09,  $P = .16$ ). However AT drugs did not increase the risk of mortality for patients with cSDH (OR of 1.08, 95% CI, 0.61–1.92,  $P = .78$ ).

**Conclusion:** AT treatment is an important risk factor of recurrence in patients with cSDH in spite of similar mortality rate. When and how to resume AT drugs is still unclear, more well-designed prospective researches are needed on this issue.

**Core tip:** High recurrence is an important factor against the long-term outcome of surgery in patients with cSDH, the use of AT drugs is a potential risk factor. In this study we found that the use of AT drugs increased the risk of recurrence rather than mortality. Anticoagulation and antiplatelet showed no difference in causing cSDH recurrence.

**Abbreviations:** AT = antithrombotic, CI = confidence interval, cSDH = Chronic subdural hematoma, NOS = Newcastle–Ottawa Scale, OR = odds ratio, RCT = randomized controlled trial.

**Keywords:** anticoagulation, antiplatelet, antithrombotic drugs, chronic subdural hematoma, meta-analysis, mortality, recurrence, surgery

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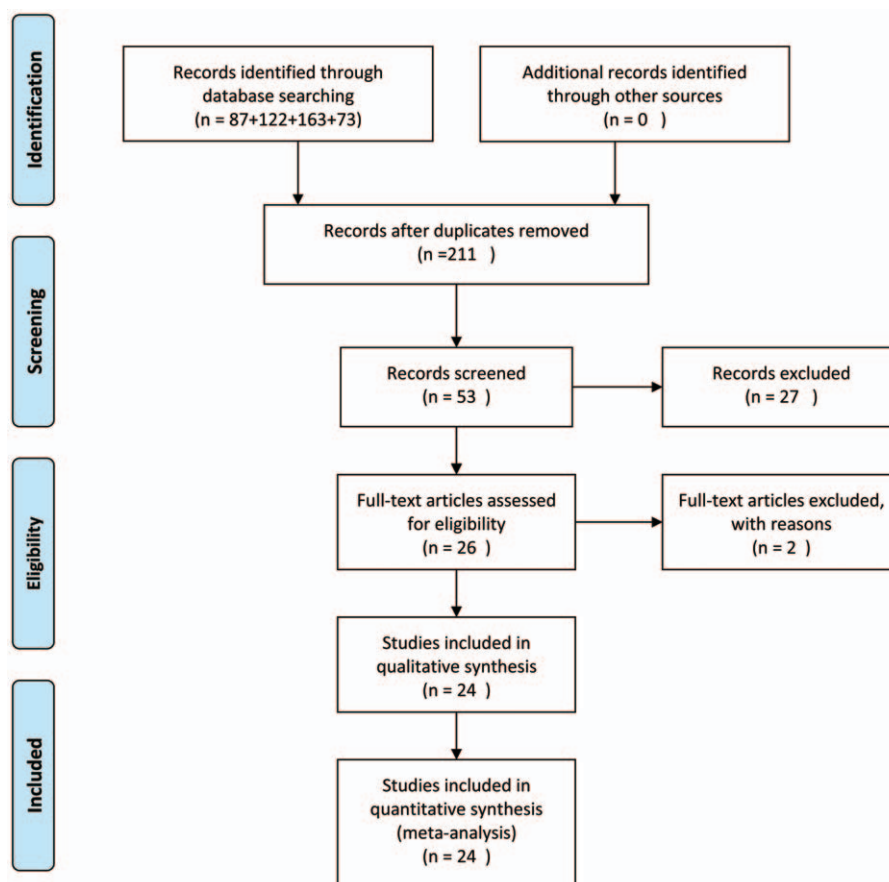


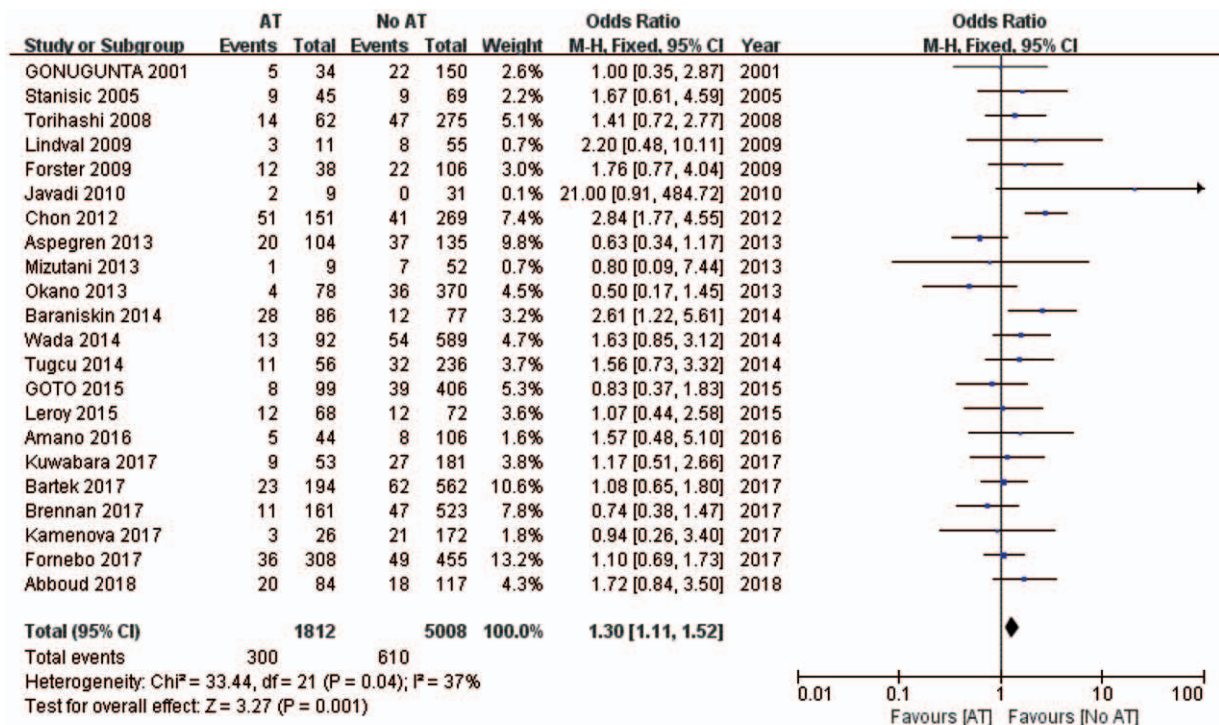
Figure 1. A flow diagram of the selection process for antithrombotic drugs on patients with chronic subdural hematoma.

Table 1

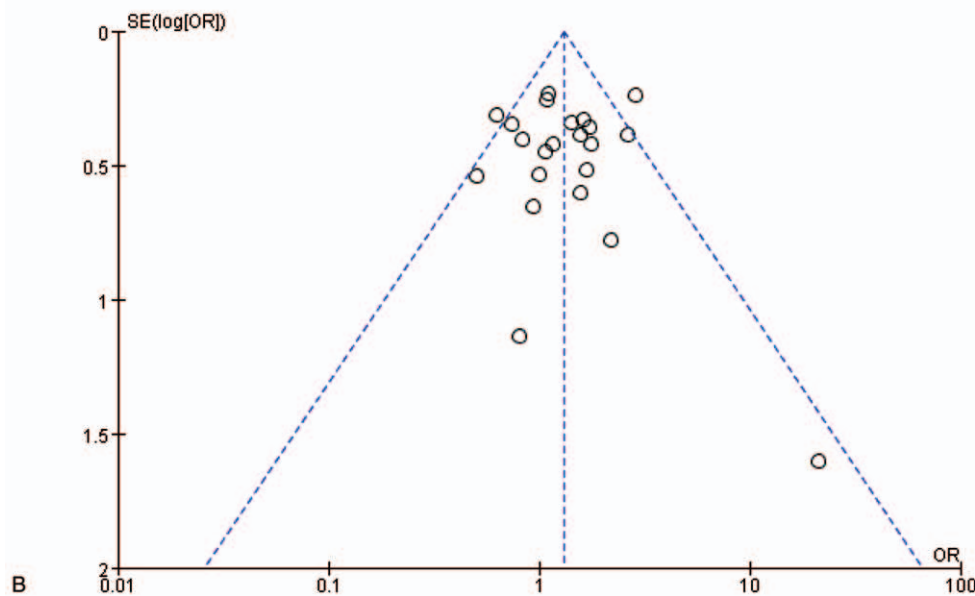
Main characteristics of studies included in this meta-analysis.

First Author	Year	Country	NOS								
			Selection			Comparability		Exposure		Score	
Gonugunta	2001	UK	*	*	*	*	*	*	*	*	8
Stanisic	2005	Norway	*	*	*	*	*	*	*	*	7
Torihashi	2008	Japan	*	*	*	*	*	*	*	*	7
Forster	2009	Germany	*	*	*	*	*	*	*	*	8
Lindvall	2009	Sweden	*	*	*	*	*	*	*	*	7
Chon	2012	Republic of Korea	*	*	*	*	*	*	*	*	7
Okano	2013	Japan	*	*	*	*	*	*	*	*	7
Mizutani	2013	Japan	*	*	*	*	*	*	*	*	7
Aspegren	2013	Denmark	*	*	*	*	*	*	*	*	7
Ohba	2013	Japan	*	*	*	*	*	*	*	*	7
Baraniskin	2014	Germany	*	*	*	*	*	*	*	*	7
Tugcu	2014	Turkey	*	*	*	*	*	*	*	*	6
Wada	2014	Japan	*	*	*	*	*	*	*	*	8
Goto	2015	Japan	*	*	*	*	*	*	*	*	7
Leroy	2015	France	*	*	*	*	*	*	*	*	7
Amano	2016	Japan	*	*	*	*	*	*	*	*	7
Fornebo	2017	Norway	*	*	*	*	*	*	*	*	7
Bartek	2017	Sweden	*	*	*	*	*	*	*	*	7
Kuwabara	2017	Japan	*	*	*	*	*	*	*	*	7
Lemenova	2017	Switzerland	*	*	*	*	*	*	*	*	7
Brennan	2017	UK	*	*	*	*	*	*	*	*	8
Abboud	2018	Germany	*	*	*	*	*	*	*	*	8
Bonis	2018	Italy	*	*	*	*	*	*	*	*	7
			Modified Jadad Score								
			Randomization		Concealment of allocation		Double blinding		Withdrawals and dropouts		Score
Javadi	2010	Iran	2		1		1		1		5

NOS = Newcastle–Ottawa Scale.



A



B

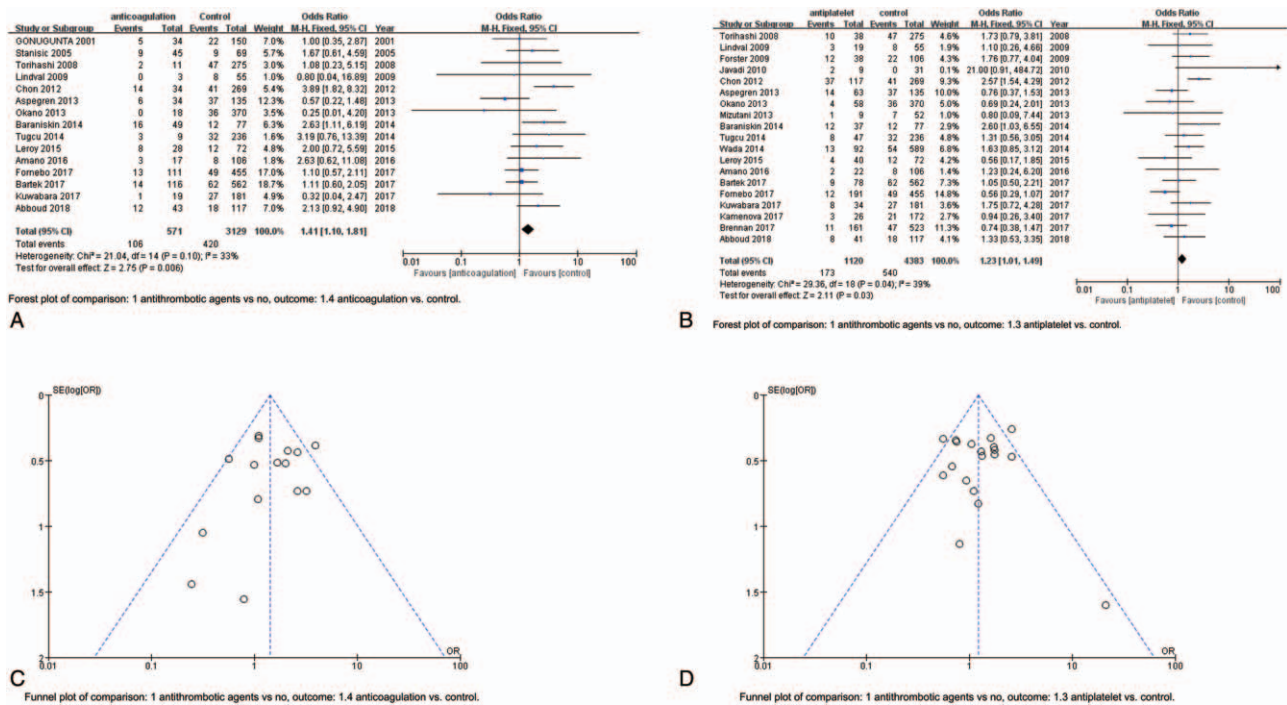
**Figure 2.** Comparison for recurrence between AT and no AT treatment. (A) Forest plot demonstrated that AT drugs increased the risk of chronic subdural hematoma recurrence. (B) Funnel plot showed that no publication bias was found. AT = antithrombotic.

### 1. Introduction

Chronic subdural hematoma (cSDH) is a pretty common neurological disorder especially in elderly population<sup>[1]</sup>; its pathophysiology is adequately studied; repeated absorption and rehemorrhage in the cavity of hematoma are the most widely accepted points of view<sup>[2]</sup>; surgery is often recommended to symptomatic patients. Although ideal surgery remains controversial, burr-hole craniostomy with or without a closed drainage system is the most popular procedure which is used to evacuate

the hematoma. Usually the immediate outcome of surgery is satisfied, but the reoperation rate reaches up to 33%.<sup>[3]</sup>

Although many risk factors for recurrence have been investigated in previous studies, antithrombotic (AT) agents, which are widely used in the elderly to treat the comorbidities, are frequently discussed besides age.<sup>[4-6]</sup> Several studies have focused on the relationship between the use of AT agents and cSDH recurrence, but the results are not consistent.<sup>[6-8]</sup> Fornebo et al found that preoperative AT agents' use did not increase the recurrence rate,<sup>[6]</sup> Chon et al reported that anticoagulant therapy



**Figure 3.** Sub-group analysis. (A and B) Forest plot demonstrated that both anticoagulation and antiplatelet increased the risk of chronic subdural hematoma recurrence. (C and D) Funnel plot showed that no publication bias was found.

was an independent risk of the recurrence.<sup>[7]</sup> AT agents' use increases with the growth of age in elderly people; therefore, it is reasonable to expound the interrelation between antithrombosis including antiplatelets and anticoagulation and cSDH recurrence.

Here, we conducted a meta-analysis to analyze the recurrence rate and mortality by comparing patients with cSDH who underwent surgery with AT agents against those without them: further we compared the data of different AT agents to explore whether they have different influences on cSDH recurrence.

## 2. Materials and methods

### 2.1. Ethical review

The clinical ethics committee of the Second Affiliated Hospital of Zhejiang University School of Medicine approved the study (Chairman of the committee is MS. Zhao Xiaoying).

### 2.2. Literature search and study identification

We comprehensively searched eligible studies through several electronic databases, including PubMed, Cochrane, Web of Science, Elsevier Science Direct, and Springer Link. The search term used were “chronic subdural hematoma,” “surgery,” “antithrombotic or antiplatelet or anticoagulation,” and “recurrence or reoperation.” All English papers published before June 2018 were included. Two authors (KHL, XLX) independently evaluated the search results by reading the titles, and other 2 reviewing authors (MBZ, FG) independently reviewed the abstracts of the initially screened papers, with disagreement settled by senior author (CQ and HZ).

### 2.3. Inclusion and exclusion criteria

Our criteria for inclusion were as follows: patients had cSDH and received surgery; randomized controlled trials (RCTs), prospective

controlled cohort studies, and retrospective case-controlled studies; quality score >5 on the Newcastle–Ottawa Scale (NOS)<sup>[9]</sup> or >3 on modified Jadad Score.<sup>[10]</sup> The exclusion criteria were as follows: a system review or case report; the study wasn't written in English; only the abstract of a study was available.

### 2.4. Data extraction

Two reviewers (CQ, HW), respectively, extracted data using a uniform standardized form until an agreement was reached. The primary outcome was recurrent cSDH for which another operation is recommended in the follow-up period (more than 3 months). The secondary outcome was mortality after surgery. Other related factors, such as population characteristics, were also extracted.

### 2.5. Statistical analysis

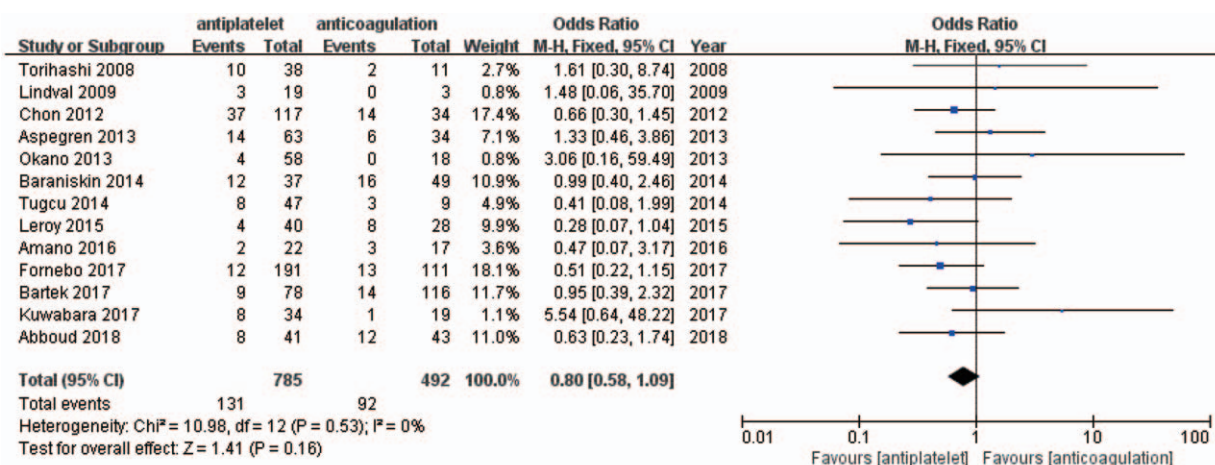
Data were performed by Review Manager version 5.3. Dichotomous variables were presented as an odds ratio (OR) with a 95% confidence interval (CI). Heterogeneity was accessed by  $I^2$  and interpreted as follow:  $I^2=0$ , no heterogeneity;  $0 < I^2 < 40\%$ , mild heterogeneity;  $30\% < I^2 < 60\%$ , moderate heterogeneity;  $50\% < I^2 < 90\%$ , substantial heterogeneity;  $75\% < I^2 < 100\%$ , considerable heterogeneity. A fixed-effect model was used when  $I^2 < 50\%$ , otherwise a random effect model was adopted. In addition, funnel plots were also conducted to find a potential publication bias.

## 3. Results

### 3.1. Study selection and characteristics

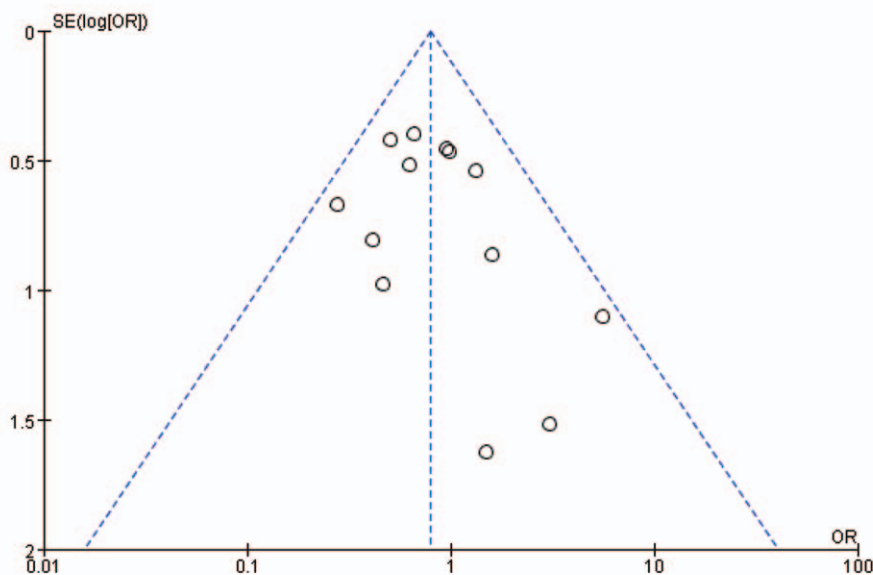
The details of searching are presented in the flow chart (Fig. 1). A total of 211 records remained after duplicate removal, and after





Forest plot of comparison: 2 antiplatelet vs anticoagulation, outcome: 2.1 New Outcome.

A



B Funnel plot of comparison: 2 antiplatelet vs anticoagulation, outcome: 2.1 New Outcome.

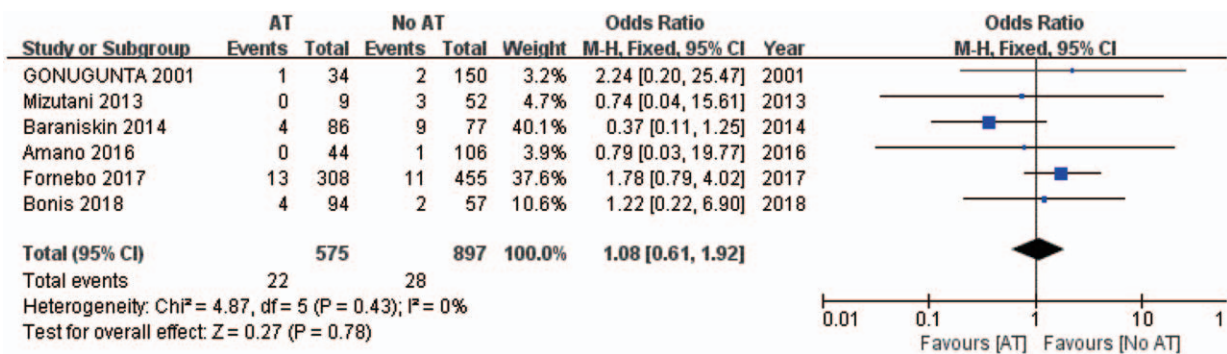
**Figure 4.** Comparison for recurrence between anticoagulation and antiplatelet. (A) Forest plot demonstrated that there were no difference between anticoagulation and antiplatelet. (B) Funnel plot showed that no publication bias was found.

screening the title and abstract of 26 studies for which full-text are available were kept for further analysis. Two articles were excluded due to no relevant data. At last 24 studies were included in this meta-analysis and only 1 was RCT<sup>[4-8,11-29]</sup>; all of the included studies demonstrated high methodological quality (Table 1). A total of 6820 cases in 22 articles were compared the influence of AT agents on the recurrence of cSDH. For subgroup analysis, 3700 patients from 15 studies were compared the influence on recurrence between anticoagulation and control, 5503 patients from 19 studies were compared the effect on reoperation between antiplatelet and control, and 13 studies involving 1277 patients were analyzed to explain whether antiplatelet and anticoagulation may lead to different reoperation rate, 6 studies including 1473 patients compared the effect of AT

agents on mortality of cSDH. For all analyses pertaining to efficacy and acceptability, no heterogeneity was detected.

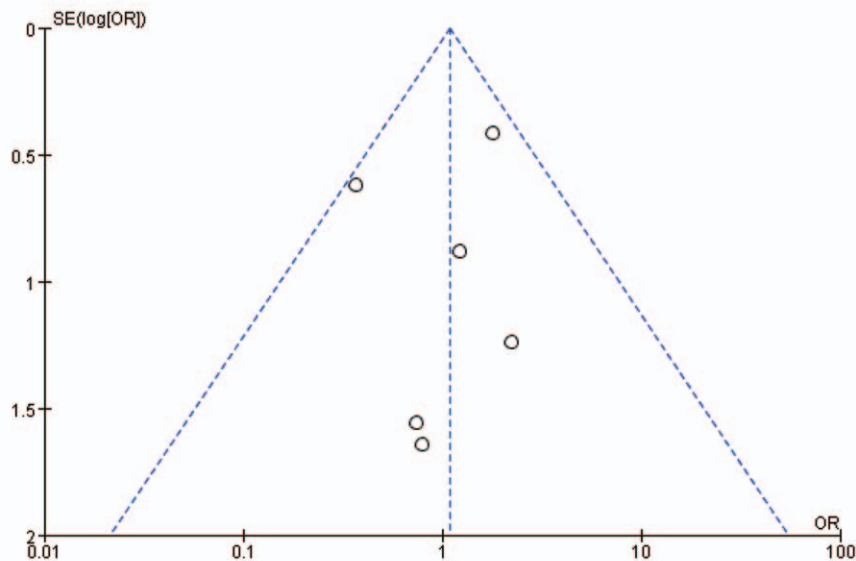
### 3.2. The effect of AT agents on the recurrence in patients with cSDH

A total of 6820 patients from 23 studies were included (1812 patients took AT drugs preoperatively with respect to 5008 unused patients). According to the data, patients who used AT drugs including both antiplatelets and anticoagulation had higher risk of the recurrence of cSDH for which another operation was recommended (OR of 1.30, 95% CI, 1.11–1.52, P = .001, I<sup>2</sup> = 37%) (Fig. 2A), and no publication bias was found in the funnel plot (Fig. 2B). In the subgroup analysis, anticoagulation was



Forest plot of comparison: 1 antithrombotic agents vs no, outcome: 1.2 mortality.

A



B

Funnel plot of comparison: 1 antithrombotic agents vs no, outcome: 1.2 mortality.

**Figure 5.** Comparison for mortality between AT and no AT treatment. (A) Forest plot demonstrated that AT drugs did not increase the mortality of chronic subdural hematoma. (B) Funnel plot showed that no publication bias was found. AT=antithrombotic.

found to increase the risk of recurrence in patients with cSDH compared to unused patients (OR of 1.41, 95% CI, 1.10–1.81,  $P = .006$ ,  $I^2 = 33\%$ ) and antiplatelet showed the similar effect (OR of 1.23, 95% CI, 1.01–1.49,  $P = .03$ ,  $I^2 = 39\%$ ) (Fig. 3A and B), no publication bias was found in the funnel plot (Fig. 3C and D). We also compared the effect of different AT drugs (antiplatelet vs anticoagulation) on the recurrence of cSDH, 13 studies involving 1277 patients were included for comparative analysis finally. Although antiplatelet tended to have lower reoperation rate of cSDH, no significant difference was found (OR of 0.80, 95% CI, 0.58–1.09,  $P = .16$ ,  $I^2 = 0\%$ ) (Fig. 4A), and no publication bias was found in the funnel plot (Fig. 4B).

### 3.3. The effect of AT agents on the mortality in patients with cSDH

Fourteen-hundred seventy-three patients from 6 studies were analyzed (575 patients took AT drugs preoperatively and 897 patients did not take them, respectively). AT drugs didn't increase the risk of mortality in patients with cSDH (OR of 1.08, 95% CI,

0.61–1.92,  $P = .78$ ,  $I^2 = 0\%$ ) (Fig. 5A). No publication bias was found in the funnel plot (Fig. 5B).

## 4. Discussion

The reoperation rate of cSDH varies from 2.3% to 38.7%, which is related with patient's outcome.<sup>[30]</sup> The recurrence increases with the growth of age, one potential factor is that the elderly usually suffer from various chronic diseases which is treated by AT drugs.<sup>[17,31]</sup> Of the 23 included studies, only 2 studies from Chon et al and Baraniskin et al supported the viewpoint that AT drugs can increase the chance of reoperation, respectively<sup>[7,18]</sup>, the combined analysis demonstrated that AT drugs is a risk factor of recurrence in patients with cSDH. Pathophysiologically the main reason of cSDH enlargement was the continuous absorption and rehemorrhage from the envelop.<sup>[2]</sup> Although new vessels on the envelop help the absorption of hematoma, they also increase the risk of micro-bleeding.<sup>[32]</sup> AT drugs raise the possibility of micro-bleeding and may accelerate the growth of hematoma; our findings supported this hypothesis.

The different mechanism of antiplatelet and anticoagulation may have different risk on micro-bleeding; hence, we compared their effects on the recurrence of cSDH separately in subgroup analysis. Although the value of OR was different, both of them were risk factors on the recurrence of cSDH. We also compared the difference between anticoagulation and antiplatelet directly, but the data from 13 studies demonstrated no difference despite the value of OR was 0.8. On the other hand, AT drugs are beneficial for the cardiac and cerebral vascular events, so when and how to use AT drugs has become a thorny problem for these patients. Some researchers believed that early resumption of AT agents may have more beneficial for the elderly with cSDH than late resumption because of similar recurrence rate and lower thromboembolic frequency,<sup>[6,33]</sup> but no adequate evidence supports this point of view and prospective RCTs are needed.

Fortunately, our analysis about the influence of AT agents on the mortality of patients with cSDH demonstrated that AT treatment did not increase the risk of mortality. This result may support the standpoint of early resumption of AT drugs, but we considered this evidence is not sufficient to guide the clinical use of AT drugs for patients with cSDH, after all only 1472 patients from 6 non-RCT studies were included for analysis.

Several limitations in this analysis should be noted. First, only one RCT was available and most of other studies in this meta-analysis were retrospective, so heterogeneity was a potential but inevitable confound factor, and more strictly designed studies are urgently needed. Second, only a few studies used clear inclusion and exclusion criteria, and different objectives were conducted in each study. Then differences in the diagnostic criteria and technique between the different hospitals of each study we analyzed might have led to inconsistent results. In addition, detailed data on AT drugs were insufficient, and thus an advanced analysis could not be conducted.

In conclusion, AT drugs increased the risk of reoperation rate in patients with cSDH, but they did not increase the risk of death. Although anticoagulation and antiplatelet has different AT mechanism, they were not different from each other in the role of cSDH recurrence. When and how to resume AT drugs is still unclear, well-designed prospective researches are needed.

## Author contributions

**Data curation:** Han Wang, Meibiao Zhang, He Zheng, Xiaolong Xia, Kehui Luo, Feng Guo.

**Formal analysis:** Xiaolong Xia.

**Investigation:** Feng Guo, Cong Qian.

**Methodology:** Han Wang, Meibiao Zhang, Xiaolong Xia.

**Project administration:** Cong Qian.

**Resources:** Han Wang, Meibiao Zhang, He Zheng, Kehui Luo, Feng Guo.

**Software:** Xiaolong Xia.

**Supervision:** Cong Qian.

**Writing – original draft:** Meibiao Zhang, Xiaolong Xia.

**Writing – review & editing:** Xiaolong Xia, Cong Qian.

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