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Outcome reporting from clinical trials of non-valvular atrial fibrillation treated with traditional Chinese medicine or Western medicine: a systematic review

Ruijin Qiu,[1] Jiayuan Hu,[1] Ya Huang,[1] Songjie Han,[1] Changming Zhong,[1] Min Li,[1] Tianmai He,[1] Yiyi Lin,[1] Manke Guan,[1] Jing Chen,[2] Hongcai Shang[1,3]

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RQ and JH contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Jing Chen; cjshcsyc@126.com

Hongcai Shang; shanghongcai@foxmail.com

ABSTRACT

Objectives To examine variation in outcomes, outcome measurement instruments (OMIs) and measurement times in clinical trials of non-valvular atrial fibrillation (NVAF) and to identify outcomes for prioritisation in developing a core outcome set (COS) in this field.

Design This study was a systematic review.

Data sources Clinical trials published between January 2015 and March 2019 were obtained from PubMed, the Cochrane Library, Web of Science, Wanfang Database, the China National Knowledge Infrastructure and SinoMed.

Eligibility criteria Randomised controlled trials (RCTs) and observational studies were considered. Interventions included traditional Chinese medicine and Western medicine. The required treatment duration or follow-up time was ≥4 weeks. The required sample size was ≥30 and≥50 in each group in RCTs and observational studies, respectively. We excluded trials that aimed to investigate the outcome of complications of NVAF, to assess the mechanisms or pharmacokinetics, or for which full text could not be acquired.

Data extraction and synthesis The general information and outcomes, OMIs and measurement times were extracted. The methodological and outcome reporting quality were assessed. The results were analysed by descriptive analysis.

Results A total of 218 articles were included from 25 255 articles. For clinical trials of antiarrhythmic therapy, 69 outcomes from 16 outcome domains were reported, and 28 (31.82%, 28/88) outcomes were reported only once; the most frequently reported outcome was ultrasonic cardiogram. Thirty-one outcomes (44.93%, 31/69) were provided definitions or OMIs; the outcome measurement times ranged from 1 to 20 with a median of 3. For clinical trials of anticoagulation therapy, 82 outcomes from 18 outcome domains were reported; 38 (29.23%, 38/130) outcomes were reported only once. The most frequently reported outcome was ischaemic stroke. Forty (48.78%, 40/82) outcomes were provided OMIs or definitions; and the outcome measurement times ranged from 1 to 27 with a median of 8.

Conclusion Outcome reporting in NVAF is inconsistent. Thus, developing a COS that can be used in clinical trials is necessary.

Strengths and limitations of this study

- This systematic review is the first to describe variation in outcomes, outcome measurement instruments and outcome measurement time reporting in clinical trials for non-valvular atrial fibrillation (NVAF).
- The methodology is reproducible and transparent and has been assessed during a peer-review process.
- English and Chinese databases were searched, and randomised controlled trials and observational studies were considered.
- The aim of this review was to provide a list of outcomes for clinical trials of NVAF in traditional Chinese medicine, which is focused on Chinese herbal medicine therapy. Thus, clinical trials of surgery were not considered.

INTRODUCTION

According to a systematic review, atrial fibrillation (AF) is the main contributor to many diseases, such as ischaemic heart disease, stroke, renal disease and peripheral arterial disease. In addition, AF usually results in major cardiovascular events, cardiovascular and all-cause mortality, and sudden cardiac death.[1] Thus, treating AF is important.

There are different kinds of classifications for AF. According to the aetiology, AF can be classified as isolated AF, valvular AF, non-valvular AF (NVAF) and so on. NVAF refers to AF occurring without rheumatic mitral stenosis, mechanical/bioprosthetic or mitral valve repair.[2] According to the characteristics and timing of AF onset, AF can be classified as first diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF.[3]

Current evidence has shown that catheter ablation and drug therapy are beneficial for controlling heart rhythm, maintaining ventricular rate, and preventing thrombosis and stroke. However, the arrhythmogenic

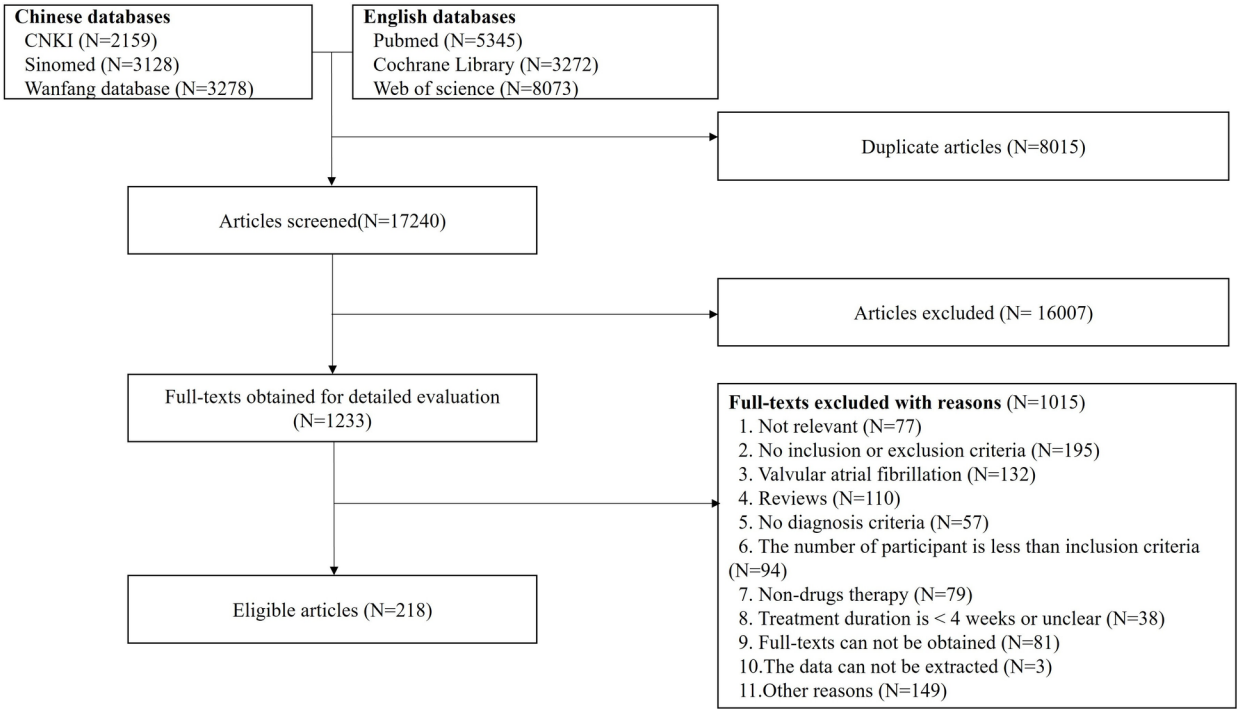

Figure 1 The flowchart of the systematic review.

effects and risk of death after taking antiarrhythmic drugs cannot be ignored. With the increasing number of traditional Chinese medicine (TCM) clinical trials in treating AF, the efficacy and safety of TCM have been proven.[4] However, there are some problems in these TCM clinical trials; for example, similar clinical trials reported different outcomes. Therefore, some trials cannot be included in systematic reviews/meta-analyses because of outcome reporting heterogeneity. In TCM clinical trials, the long-term outcomes, patient-reported outcomes and safety outcome reporting are limited; thus, these trials cannot provide appropriate evidence for TCM in treating AF. Developing a core outcome set (COS) may resolve these problems.

A COS is a minimum set that should be measured and reported in all clinical trials for a specific condition.[5] According to the characteristics and advantages of TCM, we intend to develop a COS for TCM clinical trials for NVAF, with registered[6] and published[7] protocols.

According to the study protocol, conducting a systematic review is the first step in the development of a COS for NVAF to develop a long list of outcomes. In this research, we will report the results of the systematic review, including assessing the quality of outcome reporting and the quality of trials, as well as examining the variation in outcome reporting, outcome measurement instrument (OMI) reporting and measurement time point reporting.

METHODS

Search strategy

In clinical trials and clinical practice, TCM, especially Chinese herbal medicine therapy is often used as an adjuvant therapy in internal medicine treatment; thus, obtaining a comprehensive list of outcomes for TCM clinical trials is difficult. In this systematic review, we focused on clinical trials of TCM, integrated medicine and Western medicine in internal medicine. The literature database included PubMed, the Cochrane Library, Web of Science, Wanfang database, the China National Knowledge Infrastructure and SinoMed. A literature search was conducted two times. The first search was conducted from January 2015 to June 2017, and the second search was conducted from May 2017 to March 2019. The search strategy for English databases is shown in online supplementary additional file 1.

Inclusion criteria

According to the protocol, both randomised controlled trials (RCTs) and observational studies were considered. Patients with NVAF who accepted interventions including TCM or Western medicines were eligible. The required treatment duration or follow-up time was ≥4 weeks. For RCTs, the required number of participants was ≥30 in each group. For observational studies, the required number of participants was ≥50.

Exclusion criteria

We excluded clinical trials that aimed to investigate the outcome of complications of NVAF, to assess the mechanism of drug action or pharmacokinetics, or for which full text could not be acquired.

Methodological quality has little influence on developing a long list of outcomes in the development of a COS. However, we excluded some studies with serious problems, such as a Jadad score of 0 for RCTs, contradictions

Table 1 The characteristics of included articles

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Kang[17]	RCT	China	98	1 Year	/	2	2/5	Triple antithrombotic therapy+CT	Dual antithrombotic therapy+CT
Guo *et al*[18]	RCT	China	62	/	1 Year	2	2/5	Atorvastatin+CT	CT
Li *et al*[19]	RCT	China	76	8–10 Days	6 Months	0	2/5	Amiodarone+dabigatran	Warfarin
Bu *et al*[20]	RCT	China	192	/	1 Year	2	3/5	Low-dose warfarin	Normal-dose warfarin
Pan and Liu[21]	RCT	China	90	6 Months	/	0	3/5	Candesartan+rosuvastatin	CT+candesartan
LI[22]	RCT	China	80	4 Weeks	1 Year	2	2/5	Dabigatran+CT	Warfarin+CT
Chen *et al*[23]	RCT	China	80	/	1 Year	2	2/5	Warfarin+CT	Aspirin+CT
Sang *et al*[24]	RCT	China	80	/	1 Year	2	2/5	Valsartan+rosuvastatin+CT	CT
Guo[25]	RCT	China	60	1 Month	6 Months	2	2/5	Amiodarone+irbesartan	Amiodarone
Zuo *et al*[26]	RCT	China	180	/	3 Months	2	3/5	Dabigatran	Warfarin
Liu, *et al* [27]	RCT	China	140	/	1 Year	0	2/5	Dabigatran	Warfarin
Yang [28]	RCT	China	120	/	1 Year	0	2/5	Amlodipine+amiodarone	Candesartan+amiodarone
Li *et al*[29]	RCT	China	60	3 Months	/	0	2/5	Candesartan+amiodarone	Amiodarone
Yang *et al*[30]	RCT	China	88	2 Months	/	0	3/5	Sotalol+irbesartan	Sotalol
Li *et al* [31]	CoS	China	74	4 Weeks	/	0	5/9	Valsartan	Hydrochlorothiazide
Lin *et al*[32]	RCT	China	120	6 Months	6 Months	2	2/5	Rosuvastatin+CT	CT
Qin *et al*[33]	RCT	China	360	/	2 Years	0	2/5	Warfarin	Aspirin
Qin *et al*[34]	RCT	China	360	/	2 Years	0	2/5	Low-dose warfarin	High-dose warfarin; aspirin
Chen *et al*[35]	RCT	China	77	1 Year	/	0	2/5	Dabigatran+clopidogrel	Warfarin
Wang *et al*[36]	RCT	China	150	/	1 Year	3	2/5	Aspirin+warfarin	Aspirin; warfarin
Liu and Zhang[37]	RCT	China	150	3 Months–1 year	/	0	2/5	Low-dose warfarin	High-dos-e warfarin; aspirin
Zhang[38]	RCT	China	118	/	1 Year	0	2/5	Irbesartan+CT	Irbesartan
Zhang[39]	RCT	China	120	/	30 Days	0	2/5	Amiodarone	Propafenone
Huang *et al*[40]	RCT	China	76	1 Year	/	2	2/5	Irbesartan+amiodarone+CT	Amiodarone+CT
Xu *et al*[41]	RCT	China	234	/	2 Years	0	2/5	Aspirin	Low-dose warfarin; high-dose warfarin
Lin[42]	RCT	China	158	/	10 Months	0	2/5	Candesartan+amiodarone+CT	Amiodarone+CT
Zhang and Zong[43]	RCT	China	62	/	3 Months	0	2/5	High-dose warfarin	Normal-dose warfarin
Guo[44]	RCT	China	100	1 Year	/	0	2/5	Amiodarone+irbesartan	Amiodarone+metoprolol
Zhang[45]	RCT	China	160	1 Year	/	0	3/5	Indapamide+valsartan+CT	Valsartan+CT
Yang and Yao[46]	RCT	China	150	3 Months	/	0	3/5	Methimazole+bisoprol+CT	Bisoprol+CT

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Zhang and Gu [47]	RCT	China	70	/	3 Months	0	2/5	Amiodarone +CT	Amiodarone+deacetyl glucoside
Hou and Liu[48]	RCT	China	136	1 Year	/	0	2/5	Amiodarone+irbesartan	Amiodarone
Jiang and Xu[49]	RCT	China	70	4 Weeks	11 Months	0	2/5	Valsartan+amiodarone+CT	Amiodarone+CT
Song *et al*[50]	RCT	China	120	1 Year	/	0	3/5	Amiodarone+fosinopril	Amiodarone
Wang and Yuan[51]	RCT	China	76	4 Weeks	/	0	2/5	Bisoprol+CT	Amiodarone+CT
Yan et al[52]	RCT	China	96	/	2 Years	0	2/5	Propafenone+CT	Amiodarone+CT
Zhang and Yin[53]	RCT	China	92	1 Year	/	2	2/5	Irbesartan+amiodarone	Amlodipine+amiodarone
Jian[54]	RCT	China	68	/	3 Months	0	2/5	Warfarin	Aspirin
Huang and Qin6[55]	RCT	China	60	/	2 Years	0	2/5	Dabigatran	Warfarin
Yang[56]	RCT	China	180	1 Year	/	2	3/5	Rosuvastatin+amiodarone+CT	Amiodarone+CT
Liu *et al*[57]	RCT	China	91	/	2 Years	2	2/5	Moderate-dose warfarin	Low-dose warfarin
Zhou *et al*[58]	RCT	China	120	6 Months	/	0	3/5	High-dose atorvastatin	Low-dose atorvastatin
Chen[59]	RCT	China	96	6 Months	/	0	3/5	Enalapril+amiodarone	Amiodarone
Wang and Jin[60]	RCT	China	176	6 Months	/	0	3/5	High-dos-e rosuvastatin	Normal-dose rosuvastatin
Ou *et al*[61]	RCT	China	88	/	6 Months	0	2/5	Atorvastatin+CT	CT
Geng *et al*[62]	RCT	China	198	/	10–20 mMonths	0	2/5	Aspirin+dipyridamole	Aspirin
Chu[63]	RCT	China	90	1 Year	/	0	2/5	Amiodarone+benapril	Amiodarone
Zhu[64]	RCT	China	86	3 Months	/	0	2/5	Candesartan+amiodarone	Amiodarone
Lin[65]	RCT	China	90	1 Year	/	0	3/5	Amiodarone+telmisartan	Amiodarone
Duan *et al*[66]	RCT	China	80	/	1 Year	0	2/5	Amiodarone+spironolactone	Amiodarone
Lu *et al*[67]	RCT	China	64	/	2 Months	0	3/5	Dabigatran	Warfarin
Wei and Li[68]	RCT	China	120	6 Months	/	2	2/5	High-dose dabigatran +warfarin	Low-dose dabigatran+warfarin
Su *et al*[69]	RCT	China	74	/	6 Months	0	3/5	Amiodarone	Cedilanid
Yu[70]	RCT	China	82	12 Weels	/	2	3/5	Irbesartan+amiodarone	Amiodarone
Li *et al*[71]	RCT	China	108	1 Year	/	2	2/5	Perindopril+amiodarone+CT	CT
Wen[72]	RCT	China	80	/	2 Years	0	2/5	Low-dose aspirin	High-dose aspirin
Chen[73]	RCT	China	200	/	1 Year	2	2/5	Low-dose warfarin	High-dose warfarin

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Xu *et al*[74]	RCT	China	200	/	1 Year	0	2/5	Metoprolol; metoprolol+spironolactone; metoprolol+valsartan	No treatment
Huang *et al*[75]	RCT	China	153	1 Year	/	2	3/5	Rosuvastatin+amiodarone + CT	Amiodarone+CT
Zhao and Dong[76]	RCT	China	98	1 Year	/	0	3/5	Atorvastatin+CT	CT
Feng *et al*[77]	RCT	China	64	4 Weeks	/	0	2/5	Maixuekang+warfarin+CT	CT+warfarin
Bo *et al*[78]	RCT	China	160	1 Month	6 Months	2	2/5	Amiodarone+wenxin granule	Amiodarone
Zhang and Peng[79]	RCT	China	80	30 Days	/	2	3/5	CT+modified Buuyang huanwu decoction	CT
Chen *et al*[80]	RCT	China	60	3 Months	/	2	2/5	Jianxin pinglv pill+warfarin+metoprolol	Warfarin+metoprolol
Cao *et al*[81]	RCT	China	220	4 Weeks	/	2	3/5	CT+shensong yangxin capsule	CT
Chang and Zhou[82]	RCT	China	88	8 Weeks	/	2	3/5	Atorvastatin+wenxin granule+CT	CT+amiodarone
Fan[83]	RCT	China	112	6 Months	/	0	1/5	Losartan+amiodarone +shensong yangxin capsule	Losartan+amiodarone
Ye[84]	RCT	China	80	4 Weeks	/	0	2/5	Wenxin granule+propafenone	Propafenone
Wang[85]	RCT	China	60	3 Months	/	0	2/5	Taoren honghua decoction+warfarin	Warfarin
Cheng *et al*[86]	RCT	China	200	180 Days	/	0	3/5	Yangxin guicao decoction+CT	CT
Han et al[87]	RCT	China	60	4 Weeks	/	2	3/5	Xifeng Zhiji decoction+metoprolol	Metoprolol
Peng[88]	RCT	China	96	1 Year	/	0	2/5	CT+Amiodarone+shexiang baoxin pill	CT+amiodarone
Zhang[89]	RCT	China	180	12 Weeks	/	2	2/5	Wenxin granule+CT	CT
Pan *et al*[90]	RCT	China	65	3 Months	/	0	2/5	Amiodarone+jianxin pinglv pill	Amiodarone
Huang[91]	RCT	China	120	1 Year	/	0	2/5	CT+valsartan+dabuyuan decoction	CT+valsartan
Li *et al*[92]	RCT	China	90	1 Month	/	0	3/5	Shensong yangxin capsule+Amiodarone + CT	Amiodarone+CT
Wang and Wang[93]	RCT	China	72	3 Months	/	0	3/5	Wenxin granule+CT	CT
Cui[94]	RCT	China	80	8 Weeks	/	2	2/5	Zhigancao decoction+metoprolol	Metoprolol
Bi[95]	RCT	China	70	8 Weeks	/	0	3/5	Dingxin granule	Amiodarone

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Zhang[96]	RCT	China	116	24 Weeks	/	0	3/5	Shensong yangxin capsule+CT	CT
Chen *et al*[97]	RCT	China	60	4 Weeks	/	2	3/5	Zhigancao decoction+amiodarone	Amiodarone
Liu *et al*[98]	RCT	China	68	4 Weeks	/	2	2/5	Dingxin granule+metoprolol	Metoprolol
Zhang[99]	RCT	China	84	6 Months	/	0	1/5	CT+amiodarone+wenxin granule	CT+amiodarone
Granger *et al*[100]	RCT	International	13397	1–4 Years	/	4	3/5	Apixaban	Warfarin
Held *et al*[101]	RCT	International	18201	1–4 Years	/	4	3/5	Apixaban	Warfarin
Jaspers et al[102]	RCT	International	18201	1–4 Years	30 Months*	5	3/5	Apixaban	Warfarin
Bahit *et al*[103]	RCT	International	18140	1–4 Years	/	2	3/5	Edoxaban	Warfarin
Alexander *et al*[104]	RCT	International	17370	1–4 Years	1.8 Years†	2	3/5	Higher-dose edoxaban; lower-dose edoxaban	Warfarin
Hu *et al*[105]	RCT	International	18 201	1–4 Years	1 Year	4	3/5	Aapixaban	Warfarin
Pengo *et al*[106]	RCT	Italy	180	/	≥30 Days	2	3/5	Pharmacogenetic warfarin dosing	Standard warfarin dosing
Steffel *et al*[107]	RCT	International	2492	907 Days†	2.8 Years†	1	5/5	Edoxaban	Warfarin
Yamashita *et al*[108]	RCT	International	1943	907 Days†	2.8 Years†	6	5/5	Warfarin	Edoxaban
Kato *et al*[109]	RCT	International	21105	907 Days†	2.8 Years†	4	5/5	Higher-dose edoxaban; lower-dose edoxaban	Warfarin
Meng *et al*[110]	RCT	China	180	/	12 Months	3	3/5	Wenxin granule	Sotalol
Wang *et al*[111]	RCT	China	151	1 Year	1 Year	4	3/5	Aspirin+naoxintong capsule	Warfarin
Brambatti *et al*[112]	RCT	USA	18113	/	2 Years	3	5/5	Dabigatran	Warfarin
Verdecchia *et al*[113]	RCT	USA	10372	/	2 Years	3	5/5	Dabigatran	Warfarin
Tan *et al*[114]	RCT	China	126	/	2 Years	2	5/5	Fluvastati	Placebo
Shah *et al*[115]	RCT	International	5205	1 Year	668 Days†	2	3/5	Aspirin	Rivaroxaban
Sun *et al*[116]	RCT	International	14236	1 Year	668 Days†	2	3/5	Rivaroxaban	Warfarin
Yao *et al*[117]	RCT	China	92	1 Year	/	0	3/5	Fluvastatin+benazepril	Fluvastatin
Goette *et al*[118]	RCT.	International	2199	28 Days	30 Days	4	3/5	Edoxaban	Enoxaparin-warfarin
Magnani *et al*[119]	RCT	International	14071	907 Days	2.8 Years	5	5/5	Edoxaban	Warfarin
Senoo *et al*[120]	RCT	UK	4556	/	11.6 Months	3	3/5	SR34006	Warfarin or acenocoumarol
Hijazi *et al*[121]	RCT	International	16 869	1 Year	/	4	3/5	Apixaban	Warfarin
Cadrin *et al*[122]	RCT	Canada	1376	/	37 Months†	3	4/5	Rhythm control	Rate control therapy

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Maciag *et al*[123]	RCT	Poland	74	/	/	5	4/5	Antazoline	Control
Ng *et al* [124]	RCT	International	5599	/	1.1 Years	4	4/5	Apixaban	Acetylsalicylic acid
Inoue *et al*[125]	RCT	Japan	127	2 Weeks	/	5	3/5	5 mg fixed dose β-Blockers	10 mg dose-escalation group; 20 mg dose-escalation group
Dong *et al*[126]	RCT	China	79	/	19.84 Months†	2	2/5	Intravenous ibutilide	Intravenous amiodarone+Intravenous ibutilide
Hong *et al*[127]	RCT	South Korea	183	4 Weeks	7 Days	4	5/5	Rivaroxaban	Warfarin sodium
Tan *et al*[128]	RCT	China	118	2 Years	/	2	2/5	Fluvastatin+CT	CT
Zhang *et al*[129]	RCT	China	120	1 Year	/	0	2/5	CT+low-dose rosuvastatin; CT+high-dose rosuvastatin	CT
Zhou *et al*[130]	RCT	China	186	6 Months	/	2	3/5	Telmisartan	Non-ARB and non-ACEI
Qian *et al*[131]	RCT	China	85	4 Weeks	/	0	3/5	TCM+CT	CT
Di *et al*[132]	RCT	China	50	6 Months	/	3	2/5	Telmisartan+amiodarone	Amiodarone
Liu [133]	RCT	China	200	2 Months	/	0	3/5	Valsartan	Nifedipine
Yu *et al*[134]	RCT	China	146	/	1 Year	2	2/5	Amiodarone +rosuvastatin+valsartan	Amiodarone+valsartan
Zhang and Jiao[135]	RCT	China	158	/	1–2 Years	2	2/5	Warfarin+CGA	Warfarin
Li *et al*[136]	RCT	China	120	1 Year	/	0	1/5	Telmisartan+CT	Amlodipine+CT
Pang *et al*[137]	RCT	China	60	6 Months	/	2	2/5	Valsartan	Amlodipine
Wang [138]	RCT	China	126	12 Weeks	/	2	3/5	Atorvastatin+irbesartan+CT	Irbesartan+CT
Yan *et al*[139]	RCT	China	124	1 Year	/	0	3/5	Benapril+amiodarone+CT	Amiodarone+CT
Huang *et al*[140]	RCT	China	125	6 Months	/	2	2/5	Valsartan+CT	Nifedipine+CT
Yuan and Liu[141]	RCT	China	92	1 Year	/	2	2/5	Candesartan+CT	CT
Chen *et al*[142]	RCT	China	102	/	1 Year	2	2/5	Rivaroxaban	Warfarin
Tu[143]	RCT	China	124	/	1 Year	0	2/5	Warfarin	Aspirin
Bassand *et al*[144]	CoS	International	17 162	/	2 Years	0	7/9	Antithrombotic treatment	
Haas *et al*[145]	CoS	International	9934	/	1 Year	0	7/9	VKAs	
Chan *et al*[146]	CoS	China	571	/	2.6 Years*	4	5/9	Dabigatran	Warfarin
Chan *et al*[147]	CoS	China	2153	/	4.2 Years*	4	6/9	Dabigatran	Warfarin
Xie *et al*[148]	CoS	USA	127 068	/	30 days	2	7/9	Apixaban	Warfarin
Bengtson *et al*[149]	CoS	USA	61 648	/	15 Months†	4	5/9	Dabigatran; rivaroxaban	Warfarin

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Chan *et al*2016[150]	CS	China	115	/	4 Weeks	4	14/20	Warfarin; aspirin; or dabigatran	
Hohnloser *et al*[151]	CoS	Germany	35013	/	218–280 Days	4	5/9	Phenprocoumon; anticoagulants	
Saji *et al*[152]	CoS	Japan	235	/	30 Days	2	7/9	NOACs	Warfarin
Korenstra *et al*[153]	CoS	Netherlands	920	/	2 Years	5	8/9	Dabigatran	Acenocoumarol
Naganuma *et al*[154]	CoS	Japan	362	/	1.3 Years	3	8/9	Dabigatran	Warfarin
Sunbul *et al*[155]	CoS	Turkey	171	/	1 Year	2	7/9	Coumadin; dabigatran;rivaroxaban	
Yao *et al*[156]	CoS	USA	76354	/	0.5–0.7 Year*	3	4/9	Dabigatran; rivaroxaban; apixaban	Warfarin
Ezekowitz *et al*[157]	RCT	USA	5851	/	4.6 Years†	3	5/5	Dabigatran 150 mg	Dabigatran 110 mg
Camm *et al*[158]	CS	UK	6785	/	1 Year	5	17/20	Rivaroxaban	
Marquez-Contreras *et al*[159]	CS	Spain	412	/	1 Year	2	14/20	Rivaroxaban	
Tepper *et al*[160]	CoS	USA	45338	/	1.1 Years†	1	9/9	Warfarin	
Li *et al*[161]	CoS	USA	76940	/	1 Year	2	8/9	Warfarin	Apixaban
Marquez *et al*[162]	CS	Spain	412	/	1 Year	2	14/20	Rivaroxaban	
Larsen *et al*[163]	CoS	Denmark	61 678	/	2.5 Years	2	6/9	Non-vitamin K antagonist oral anticoagulants	Warfarin
Kilickiran *et al*[164]	CoS	Turkey	294	280–336 days	/	3	6/9	Dabigatran	Rivaroxaban
Inoue *et al*[165]	CoS	Japan	6148	/	2 Years	2	4/9	Dabigatran	
Chan *et al*[166]	CoS	China	5426	/	3.6 Years*	2	5/9	Warfarin	Aspirin; no therapy
Laliberte *et al*[167]	CoS	Canada	13049	/	114 and 123.7 Days*	3	4/9	Rivaroxaban	Warfarin
Lee *et al*[168]	CoS	Korea	321	/	2.3 Months*	3	6/9	VKAs	
Lau *et al*[169]	CoS	China	8152	/	501 Days*	0	6/9	Dabigatran	Warfarin
Ho *et al*[170]	CoS	China	8754	/	3 Years*	4	5/9	Aspirin	Dabigatran; warfarin
Chan *et al*[171]	CoS	China	9727	/	2Yyears	2	7/9	Warfarin	Aspirin
Chao *et al*[172]	CoS	China	101243	/	4.9 Years*	0	7/9	Betablockers	Calcium channel blockers; digoxin

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Pastori *et al*[173]	CoS	Italy	815	/	33.2 Months†	2	6/9	Digoxin	
Chen *et al*[174]	CoS	China	10384	/	3.2 Years	2	6/9	Anticoagulation and antiplatelet therapy	
Engelberger *et al*[175]	CoS	Switzerland	537	/	3 Months	4	5/9	Rivaroxaban	
Li *et al*[176]	RCT	China	137	/	1 Year	0	2/5	Low-dose warfarin	Unclear
Tung *et al*[177]	CS	Canada	148 446	/	5 Years	1	10/20	Warfarin	
Wu *et al*[178]	CoS	China	4638	/	2.4 Years†	4	8/9	Statin	Non-statin
Kodani *et al*[179]	CoS	Japan	6616	/	5 Years	1	6/9	Warfarin; NOACs	No anticoagulation therapy
Yamashita *et al*[180]	CoS	Japan	6404	/	2 Years	0	7/9	Warfarin	
Kumagai *et al*[181]	CoS	Japan	6404	/	2 Years	0	7/9	Warfarin+statin	Warfarin alone
Blin *et al*[182]	CoS	France	8894	/	28–29 Months	2	8/9	VKAs:	
Piccini *et al*[183]	CoS	USA	10135	/	2.3Years†	0	5/9	Unclear	
Allen *et al*[184]	CoS	USA	9619	/	22 Months*	3	7/9	Digoxin	
Genovesi *et al*[185]	CoS	Italy	290	/	2 Years	0	7/9	Warfarin	
Qin *et al*[186]	CoS	USA	5952	/	26.1 Months	4	7/9	Antiarrhythmic drugs	
Purmah *et al*[187]	CoS	International	3119	/	1 Year	2	7/9	Rate control	Rhythm control
Pasca *et al*[188]	CS	Italy	143	/	1 Year	2	15/20	Oral anticoagulant therapy	No oral anticoagulant therapy
Nielsen *et al*[189]	CoS	Denmark	55644	/	2.3 Years*	1	8/9	NOACs	Warfarin
Bo *et al*[190]	CoS	Italy	452	/	300.5 Days*	2	7/9	Oral anticoagulant therapy	No oral anticoagulant therapy
Jacobs *et al*[191]	CoS	USA	5254	/	243 Days*	2	7/9	DOACs	Warfarin
Lip *et al*[192]	CoS	International	29338	/	90–127 Days	2	8/9	Warfarin	Apixaban, dabigatran or rivaroxaban.
Hanon *et al*[193]	CS	France	405	/	6 Months	4	14/20	Rivaroxaban	
Patti *et al*[194]	CoS	International	6412	/	1 Year	2	8/9	Antithrombotic therapies	
Graham *et al*[195]	CoS	USA	118891	/	108 and 111 Days*	4	6/9	Dabigatran	Rivaroxaban
Tampieri *et al*[196]	CS	Italy	218	/	30 Days	1	15/20	Anticoagulation	
Lee *et al*[197]	CoS	South Korea	754	/	3.2–3.5 years*	2	7/9	VKAs	No vitamin K antagonist
Stolk *et al*[198]	CoS	Netherlands	30 146	/	1–3 Years	2	5/9	DOACs; VKAs; low-dose aspirin or mixed users	
Boriani *et al*[199]	CoS	International	2589	/	1 Year	2	7/9	According to AF type	

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Eisen *et al*[200]	RCT	International	21 105	907 Days#	2.8 Years#	3	7/9	Digoxin	No Digoxin
Wan and Deng[201]	RCT	China	292	3 Months	3 Months	0	2/5	Dabigatran+clopidogrel	Clopidogrel
Jian [202]	RCT	China	128	3 Months	/	0	2/5	Dabigatran+CT	Warfarin+CT
Gao [203]	RCT	China	71	/	1 Year	0	3/5	Low-dose warfarin	Normal-dose warfarin
Wang [204]	RCT	China	84	/	1 Year	0	3/5	Warfarin	Warfarin
DM Zhang and HM Zhang [205]	RCT	China	81	/	1 Year	0	2/5	Warfarin	Warfarin
Haqingaowa *et al*[206]	RCT	China	146	6 Months	/	2	3/5	Rivaroxaban+CT	Warfarin+CT
Chen *et al*[207]	RCT	China	86	1 Year	/	2	3/5	Rivaroxaban+CT	Warfarin+CT
Chen *et al*[208]	RCT	China	160	/	6 Months	2	1/5	Maixuekang capsule	Aspirin
Li and Yue[209]	RCT	China	76	4 Weeks	/	0	3/5	TCM+dabigatran+aspirin	Dabigatran+aspirin
Yu [210]	RCT	China	80	4 Weeks	/	0	2/5	Xuefu Zhuyu decoction+dabigatran	Dabigatran
RR *et al*[211]	RCT	International	245	/	1 Year	5	5/5	Targeted therapy+CT	CT
Ezekowitz *et al*[212]	RCT	International	1500	/	30 and 90 Days*	2	3/5	Apixaban	Heparin/VKA
Li X *et al*[213]	RCT	China	66	/	6 Months	1	2/5	Genotype-based anticoagulant therapy with warfarin	Routine warfarin therapy
Yamashita *et al*[214]	RCT	Japan	220	4 weeks	/	4	2/5	Bisoprolol transdermal patch	Bisoprolol fumarate oral formulation
Bartlett *et al*[215]	CoS	USA	286	12.4 months†	16.5 Months†	6	7/9	Rivaroxaban with concomitant diltiazem	Rivaroxaban
Andersson *et al*[216]	CoS	Denmark	9212	/	1 Year	2	8/9	Dabigatran	Warfarin
Deitelzweig *et al*[217]	CoS	USA	25 857	/	5–6 Months†	1	8/9	Apixaban	Rivaroxaban, dabigatran, warfarin
Friberg and Oldgren[218]	CoS	Sweden	68 056	/	0.71 and 1.74 Years†	3	8/9	NOAC	Warfarin
Hernandez *et al*[219]	CoS	USA	41 336	/	185–294 Days*	5	8/9	Apixaban;dabigatran; rivaroxaban; warfarin	Never used oral anticoagulation
Pohjantahti *et al*[220]	CoS	Finland	200	/	1 Year	6	7/9	Vernakalant	Flecainide
Koretsune *et al*[221]	CoS	Japan	18 261	/	1 Year	5	8/9	Dabigatran	Warfarin

Continued

Table 1 Continued

Study ID	Study type	Country	Patients recruited	Course of treatment	Follow-up duration	Quality of outcome reporting	Quality of study	Interventions	Comparisons
Lai *et al*[222]	CoS	China	2592	/	3.86–4.95 Years*	3	8/9	Amiodarone; amiodarone+digoxin	Digoxin
Li WH *et al*[223]	CoS	China	2099	/	21.7 Months*	6	8/9	Warfarin	Rivaroxaban; dabigatran
Link *et al*[224]	CoS	International	21 099	907 Days*	1022 Days†	5	7/9	Warfarin	High-dose edoxaban; low-dose edoxaban
Lip *et al*[225]	CoS	Denmark	14 020	/	2.6 Years*	3	8/9	Apixaban; dabigatran; rivaroxaban	Warfarin
Noseworthy *et al*[226]	CoS	USA	107 373	/	3 Years	2	8/9	Warfarin	Apixaban; dabigatran; rivaroxaban
Lip *et al*[227]	CoS	USA	321 182	/	1 Year	4	8/9	Apixaban; warfarin; dabigatran; rivaroxaban	
Martinez *et al*[228]	CoS	The USA	6836	/	1.4 Years†	3	8/9	Rivaroxaban	Warfarin
Gieling *et al*[229]	CoS	The UK	31 497	/	0.95–2.94 Years*	6	8/9	NOACs; VKA; aspirin; mixed	
Go *et al*[230]	CoS	The USA	50 578	66 Days†	102–123 Days*	3	8/9	Dabigatran	Warfarin
Forslund *et al*[231]	CoS	Sweden	22 198	/	1.07 and 1.61 Years*	6	8/9	Dabigatran; rivaroxaban; apixaban	Warfarin
Sjalander *et al*[232]	CoS	Sweden	64 382	208–407 Days*	/	3	8/9	Dabigatran; rivaroxaban; apixaban	Warfarin
Corbalan *et al*[233]	CoS	International	21 105	/	2.8 Years	5	8/9	Edoxaban	Warfarin
Bae *et al*[234]	CS	Korea	1350	/	3 Years	3	16/20	Non-VKA	VKA

*Mean follow-up.
†Median follow-up.
ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonist; CGA, comprehensive geriatric assessment; CS, case series; CT, conventional therapy; CoS, cohort study; DOACs, direct oral anticoagulants; NOACs, non-vitamin K antagonist oral anticoagulants; TCM, traditional Chinese medicine; VKAs, vitamin K antagonists.

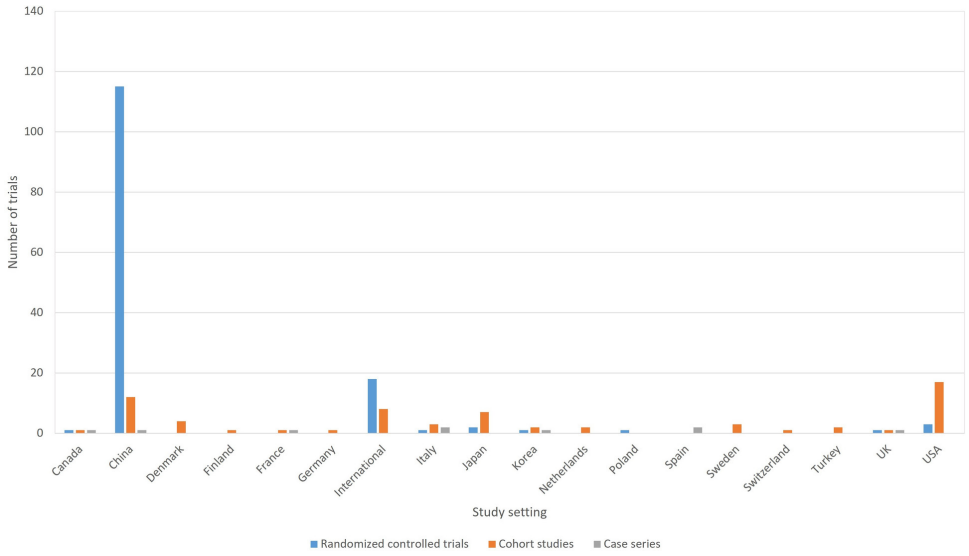

Figure 2 The type and distribution of clinical trials.

in the research or the authors are in the institutions who do not have the ability to conduct RCTs in China.

Study identification

Two reviewers (RQ and SH) independently assessed the titles and abstracts from searches. Then, the full texts of the potential articles were retrieved and assessed for further identification. Any disagreement was resolved by discussion or consulting the third investigator (HS).

Data extraction

Two reviewers (RQ and JH) independently extracted information. The information included the first author's name, publication time, number of participants, country of authors (if the authors are from different countries, it was stated as 'international'), interventions, comparisons, course of treatment, follow-up duration, outcomes, the definition of outcomes, OMIs and measurement time (intervention duration or follow-up time). Any disagreement was resolved by discussion or consulting the third investigator (HS).

In addition, we assessed the quality of outcome reporting according to the method used in other studies.[8 9] There were six items; if the information of eligible studies completely meet the items, then 1 point was awarded. If this information did not meet or fully meet the items, then 0 point was awarded. If the outcome was objective, then the definition is unnecessary.

The items include the following:

1. Is the primary outcome clearly stated?
2. Is the primary outcome clearly defined so that another researcher would be able to reproduce its measurement? Where appropriate, this outcome should include a clear description of time points, the person measuring the outcome, how the outcome was measured (for example, tools and methods used) and where the outcome was measured.

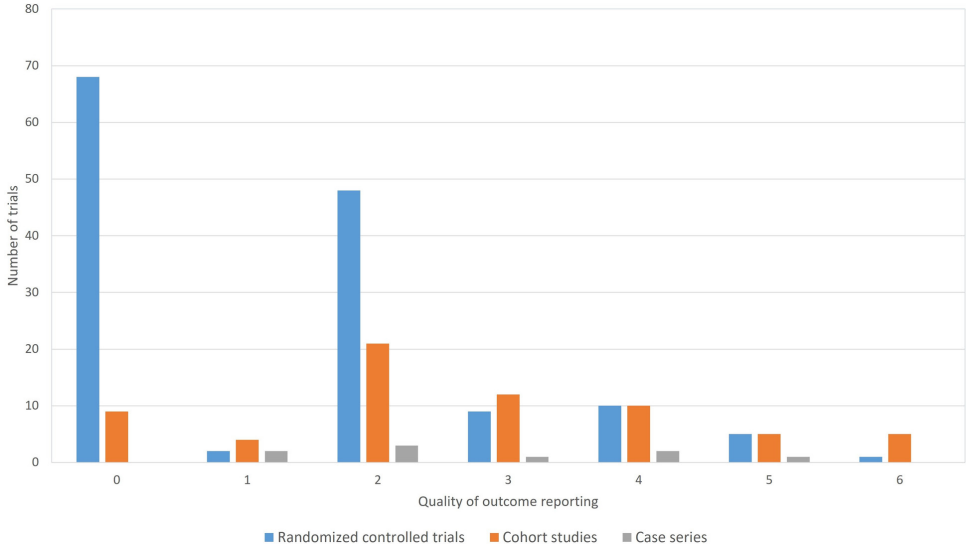

Figure 3 The quality of outcome reporting in different types of clinical trials.

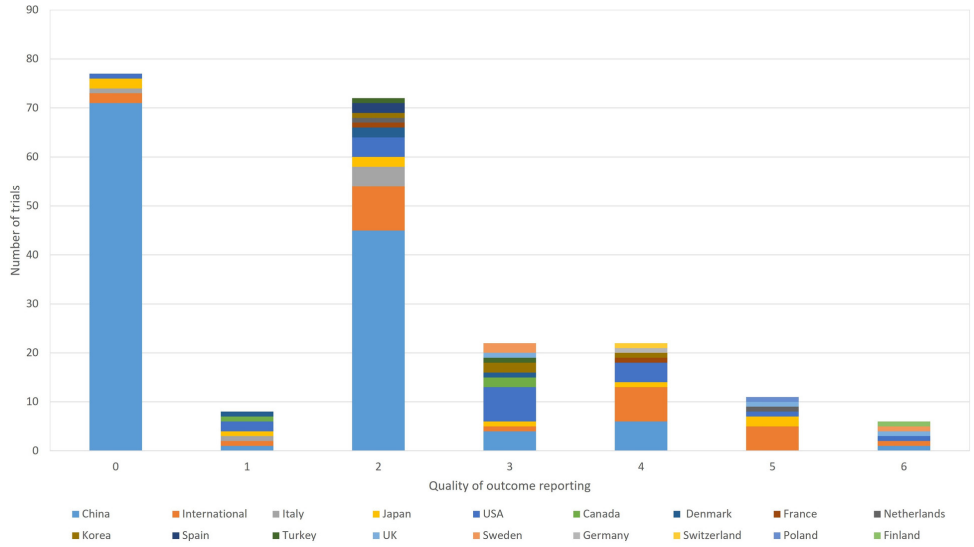

Figure 4 The quality of outcome reporting in different countries.

3. Are the secondary outcomes clearly stated?
4. Are the secondary outcomes clearly defined?
5. Do the authors explain the use of the outcomes they have selected?
6. Are methods used to enhance the quality of outcome measurement (for example, repeated measurement, training) if appropriate?

The methodological quality was assessed according to the type of study. The Jadad score was used to assess the quality of RCTs,[10] and the Newcastle-Ottawa Scale was used to assess the quality of cohort studies (CoSs).[11] The tool developed by Canadian Institute of Health Economics can be used to assess the quality of case series studies.[12]

Two reviewers (RQ and JH) independently assessed the quality of outcome reporting and the methodological quality. Any disagreement was resolved by discussion or consulting the third investigator (HS).

Merging outcomes and grouping under outcome domains

Two researchers (RQ and CZ) merged the overlapping outcomes according to the definition of outcomes independently. If no definition was provided, they discussed and achieved consensus if necessary. For example, death, death from any cause, mortality, overall mortality, total mortality, all causes of death and all causes of mortality were aggregated as 'all-cause mortality'.

The original list of outcomes from systematic review is usually very long and unwieldy,[13] so researchers developed a taxonomy for outcome classification[14] that included 38 outcome domains. Two researchers (RQ and CZ) grouped individual outcomes into the appropriate outcome domain together and achieved consensus.

Statistical analysis

The results were analysed by descriptive analysis.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study. Patients will be involved in the larger study to develop the COS. Informed consent will be obtained from patients who will participate in the later research.

RESULTS

Characteristics of literature

In this systematic review, a total of 25 255 articles from Chinese and English databases were retrieved. After removing duplicates, there were 17 240 articles. By reading the titles and abstracts, ineligible articles were removed, and full texts for 1233 potential eligible articles were retrieved. A total of 1015 articles were removed for various reasons, and 218 articles were finally included. The flowchart of this systematic review is shown in figure 1.

In the included studies, 88 studies were for antiarrhythmic therapy, and 130 studies were for anticoagulant therapy. A total of 110 articles were in Chinese, and 108 articles were in English. Thirty articles were TCM clinical trials, and 188 were Western medicine clinical trials. Seventy-five articles were observational studies (including 66 CoS and 9 case series), while 143 articles were RCTs. The general characteristics of the included articles are shown in table 1.

The majority of RCTs were conducted in China. The USA had more CoSs than other countries did (figure 2). Because of the limited information provided in the articles, 35.32% (77/218) of the studies received 0 points for the quality of outcome reporting, and the majority were RCTs (figure 3). Compared with other countries, China had a much lower quality of outcome reporting (figure 4). The majority of RCTs were poor quality, while the majority of observational studies were high quality.

The list of outcomes

There are two main types of therapy for NVAF: antiarrhythmic treatment and anticoagulation treatment. Some differences exist in the outcome reporting between these

Table 2 The outcomes reporting for clinical trials of antiarrhythmic treatment (N=88)

Domains/outcomes	Outcomes reporting (n)	OMIs/ definitions (n)	Measurement time point (n)
Mortality/survival			
All-cause mortality	11	0	8
Cardiovascular death	5	0	3
Vascular outcomes			
Non-central nervous system embolism	6	0	2
Cardiac outcomes			
ECG outcomes	18	2	14
Time to conversion	7	1	5
Mean sinus rhythm maintenance time	1	1	6
Time to first AF recurrence	4	1	3
Conversion to sinus rhythm	26	1	12
Sinus rhythm maintenance	15	3	6
AF recurrence	36	2	2
AF progression	6	2	3
AF controlling rate	2	0	2
AF persistence	11	2	5
Number of electrical cardioversion	1	0	1
Number of taking antiarrhythmic drugs	1	0	1
Number of undertaking ablation	1	0	1
Ultrasonic cardiogram	39	1	10
Heart rate	21	2	14
NYHA classification grading of cardiac function	3	1	2
Myocardial infarction	2	0	2
Bradycardia	1	0	0
Ventricular arrhythmia	2	1	1
Heart failure	2	0	2
Blood pressure	20	0	6
NT-proBNP	3	0	3
Blood and lymphatic system outcomes			
D-dimer	2	0	2
APTT	1	0	1
TT	1	0	1
PT	1	0	1
FIB	3	1	3
Nervous system outcomes			
Haemorrhagic stroke	11	0	6
Ischaemic stroke	6	0	4
Immune system outcomes			
IFN-γ	1	0	1
IL-10	1	0	1
IL-4	1	0	1
IL-6	10	1	4
TNF-α	9	1	4
MMP2	4	1	3
Solubility P-selectin	1	1	1
Connective tissue growth factor	1	1	1
TIMP2	1	1	1
Endocrine outcomes			
Aldosterone	1	0	1
ANP	1	1	1
TSH	2	0	1
Renin, AngII	4	1	1
Adiponectin	1	1	1
Hepatobiliary outcomes			
ALT	1	0	3
AST	1	0	3
Renal and urinary outcomes			
BUN	6	1	3
Serum creatinine	1	0	3
Urine sodium	1	0	1
Metabolism and nutrition outcomes			
HDL-C	3	0	4
LDL-C	7	1	4
TC	6	0	4
TG	5	0	4
Serum homocysteine	3	1	3
General outcomes			
Body mass index	1	0	1
Mean drug onset time	1	0	1
Symptoms	9	2	7
CRP	6	1	5
hs-CRP	12	2	4

Table 2 Continued

Domains/outcomes	Outcomes reporting (n)	OMIs/ definitions (n)	Measurement time point (n)
Adherence/compliance			
Therapeutic compliance	1	0	5
Withdrawal from treatment			
Withdrawal from treatment	1	0	1
Physical functioning			
6 Min walk test	1	1	1
Adverse events/effects			
Adverse events/ side effects	26	0	8
Resource use: Hospital			
All-cause hospitalisation	5	0	3
Cardiovascular hospitalisations	6	1	4
Hospital length of stay	1	0	0
Readmission rates	1	0	1

ALT, alanine aminotransferase; ANP, atrial natriuretic peptide;APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C reactive protein; ECG, electrocardiogram; FIB, fibrinogen; HDL-C, High density lipoprotein cholesterol; IFN-γ, interferon-γ; IL, interleukin; LDL-C, low-density lipoprotein cholesterol; MMP2, matrix metalloproteinase-2; NT-proBNP, N terminal pro B type natriuretic peptide; NYHA, New York Heart Association; PT, prothrombin time; TC, total cholesterol; TG, total triglyceride; TIMP2, tissue inhibitor of metalloproteinase 2; TNF-α, tumour necrosis factor-α; TSH, thyroid stimulating hormone; TT, thrombin time.

therapies. This review shows the outcomes according to the type of interventions in the original study.

For clinical trials of antiarrhythmic therapy, 69 outcomes from 16 outcome domains were reported (table 2). Twenty-eight (31.82%, 28/88) outcomes were reported only once; the most frequently reported outcome was ultrasonic cardiogram, which was reported 39 times (44.32%, 39/88). None of the outcomes were reported more than 50 times. In the 16 outcome domains, 5 outcome domains (vascular outcomes, adherence/compliance, adverse events/effects; physical functioning; withdrawal from treatment) consisted of only one outcome. These outcomes were reported between 1 and 26 times, and the median outcome reporting time was 1. Cardiac outcomes consisted of the largest number of outcomes, including 22 outcomes. In cardiac outcomes, ultrasonic cardiogram (39 times), AF recurrence (36 times), conversion to sinus rhythm (26 times), heart rate (21 times) and blood pressure (20 times) were reported much more often than other outcomes.

Table 3 The outcomes reporting for clinical trials of anticoagulant treatment (N=130)

Domains/outcomes	Outcomes reporting (n)	OMIs/ definitions (n)	Measurement time point (n)
Mortality/survival			
All-cause mortality	52	2	40
Cardiovascular death	26	2	13
Death from ischaemic events	3	0	1
Death from stroke	1	1	1
Death from bleeding	1	0	1
Non-cardiovascular death	1	0	1
Vascular outcomes			
Non-central nervous system embolism	73	1	31
Major bleeding	75	10	42
Time to first major bleeding event	2	0	3
Minor bleeding	21	2	8
Clinically relevant non-major bleeding	15	4	5
Time to first clinically relevant non-major bleeding event	1	0	2
Time to the first SEE	2	0	1
Cardiac outcomes			
Acute coronary syndrome	31	0	27
Ultrasonic cardiogram	1	1	1
Blood pressure	1	0	1
Heart failure	1	0	1
NT-proBNP	2	1	3
Blood and lymphatic system outcomes			
INR	17	1	7
Prothrombin time	8	1	5
APTT	8	1	5
PT	10	2	6
TT	5	1	5
FIB	4	1	3
Thrombin time	5	1	4
Time spent in the therapeutic range	5	0	3
PLT	2	0	2
RBC	1	0	1
HGB	1	0	1
D-dimer	3	0	3
Haemorheology	1	1	1
Thromboelastogram	1	1	1

Continued

Table 3 Continued

Domains/outcomes	Outcomes reporting (n)	OMIs/ definitions (n)	Measurement time point (n)
Plasma P selectin	1	1	1
TXB2	1	1	1
Nervous system outcomes			
Ischaemic stroke	105	2	56
Haemorrhagic stroke	75	2	39
Transient ischaemic attack	18	0	10
Intracranial bleeding	14	2	11
Time to the first stroke	3	0	2
Score standard of neural function deficient degree	1	1	1
Dementia	1	0	1
Hepatobiliary outcomes			
ALT	2	0	2
AST	2	0	2
TBIL	1	0	1
Renal and urinary outcomes			
Serum creatinine	1	1	1
Glomerular filtration rate	1	0	1
BUN	1	1	1
Creatinine clearance	1	0	1
Carbamide	1	0	1
β_2-microglobulin	1	1	1
Musculoskeletal and connective tissue outcomes			
Hip fracture	2	0	1
Pelvic fracture	1	0	1
Vertebral fracture	1	0	1
General outcomes			
Symptoms	3	0	3
Warfarin dosage	2	0	1
INR variance growth rate	1	1	1
Time to stable anticoagulation	1	0	1
Weight	1	0	1
Traditional Chinese medicine syndrome	2	1	2
CRP	1	0	1
CGA score	1	1	2
Physical functioning			
Modified Rankin Scale score	1	1	1
Disability	1	0	1
Satisfaction/patient preference			
Patient satisfaction	3	3	4
Adherence/compliance			
Therapeutic compliance	11	0	9
Anticoagulation discontinuation	3	1	8
Withdrawal from treatment			
Withdrawal from treatment	1	1	2
Global quality of life			
Quality of life	4	5	4
Economic			
Index hospitalisation costs	1	1	1
Resource use: Hospital			
Admission for cerebrovascular event	7	3	5
All-cause hospitalisation	4	0	2
Cardiovascular hospitalisation	4	0	1
Hospital length of stay	3	1	1
Bleeding-cause hospitalisation	2	0	3
Healthcare resource utilisation	2	1	1
Emergency room visits	1	0	10
Readmission rates	2	1	11
Need for further intervention			
The difference between the predicted and the actual warfarin maintenance dose	1	0	1
The number of warfarin dose changes needed	1	0	1
First catheter ablation	1	0	1
First AV node/His bundle ablation	1	0	1
Adverse events/effects			
Adverse events/ effects	16	0	7

ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; AV, atrioventricular; BUN, blood urea nitrogen; CGA, comprehensive geriatric assessment; CRP, C reactive protein; FIB, fibrinogen; HGB, haemoglobin; INR, international normalised ratio; NT-proBNP, N terminal pro B type natriuretic peptide; PLT, platelet; PT, prothrombin time; RBC, red blood cell; SEE, systemic embolic event; TBIL, total bilirubin; TT, thrombin time; TXB2, thromboxane B2.

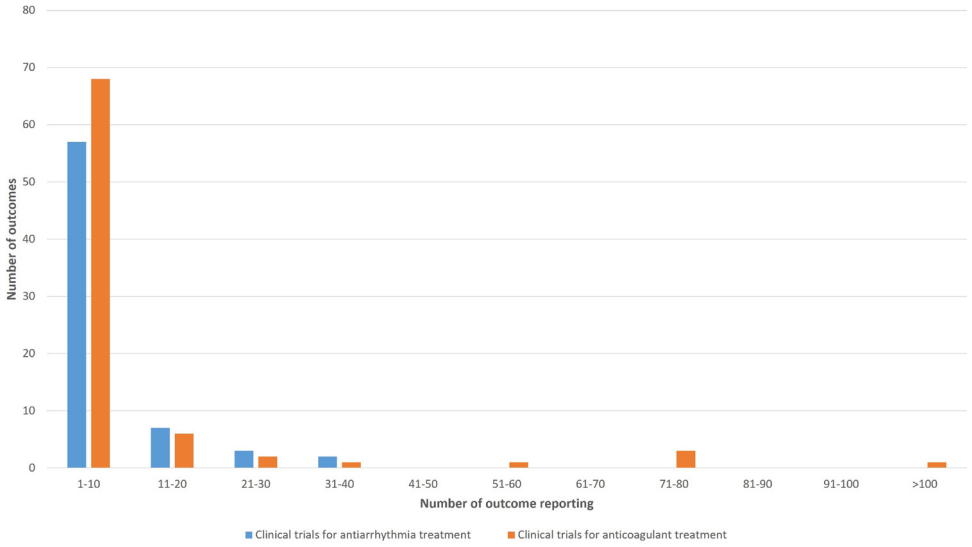

Figure 5 The summary of outcome reporting times.

For clinical trials of anticoagulation therapy, there were 82 outcomes from 18 outcome domains in the studies of anticoagulation therapy (table 3). Thirty-eight (29.23%, 38/130) outcomes were reported only once; the most frequently reported outcome was ischaemic stroke, which was reported 105 times (80.77%, 105/130). Only 5 (3.85%, 5/130) outcomes were reported more than 50 times. In the 18 outcome domains of anticoagulation therapy studies, 5 outcome domains (satisfaction/patient preference, withdrawal from treatment, global quality of life, economic and adverse events/effects) consisted of only one outcome. These outcomes were reported between 1 and 16 times, and the median outcome reporting time was 3. Blood and lymphatic system outcomes included the largest number of outcomes, which was 14 outcomes; the international normalised ratio (INR) was reported more frequently than other outcomes.

There were 24 duplicated outcomes between antiarrhythmic therapy and anticoagulation therapy. After removing duplicates, there were 127 outcomes. Figure 5 shows a summary of outcomes reporting times. Figure 6 shows the number of outcomes in different outcome domains in antiarrhythmic treatment trials. Figure 7 shows the number of outcomes in different outcome domains in anticoagulation treatment trials.

A large number of clinical trials did not provide definitions or OMIs. In the outcomes of antiarrhythmic treatment trials, 31 outcomes (44.93%, 31/69) were provided definitions or OMIs. Twenty-three (33.33%, 23/69) outcomes were provided one OMI or definition, seven (10.14%, 7/69) outcomes were provided two OMIs or definitions and one (1.45%, 1/69) outcome was provided three OMIs or definitions. Sinus rhythm maintenance had three different OMIs or definitions, which was higher than that of other outcomes. In the outcomes of anticoagulant therapy trials, 40 (48.78%, 40/82) were provided OMIs or definitions. Twenty-eight (35.37%, 28/82) outcomes were provided one OMI or definition, seven (8.54%, 7/82) outcomes were provided two OMIs or definitions and five (6.10%, 5/82) outcomes were provided

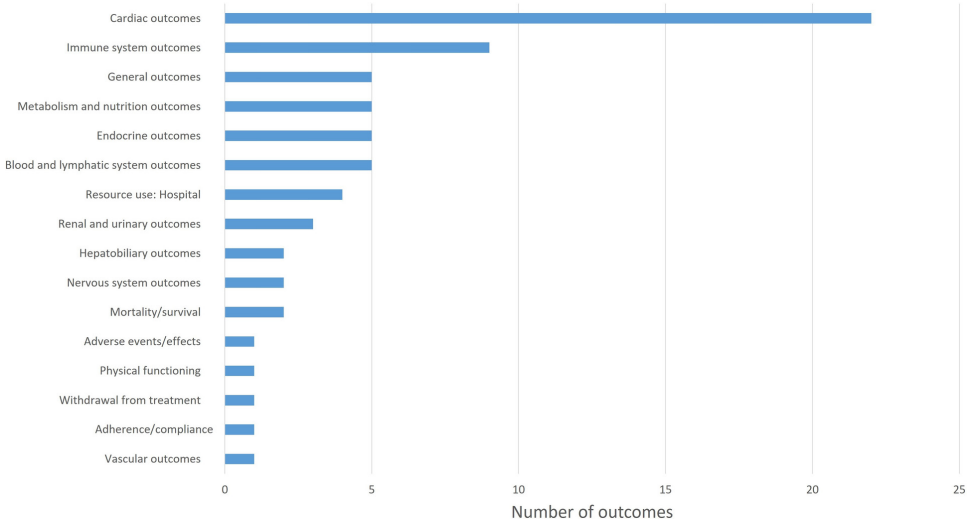

Figure 6 The number of outcomes in different outcome domains in antiarrhythmic treatment trials.

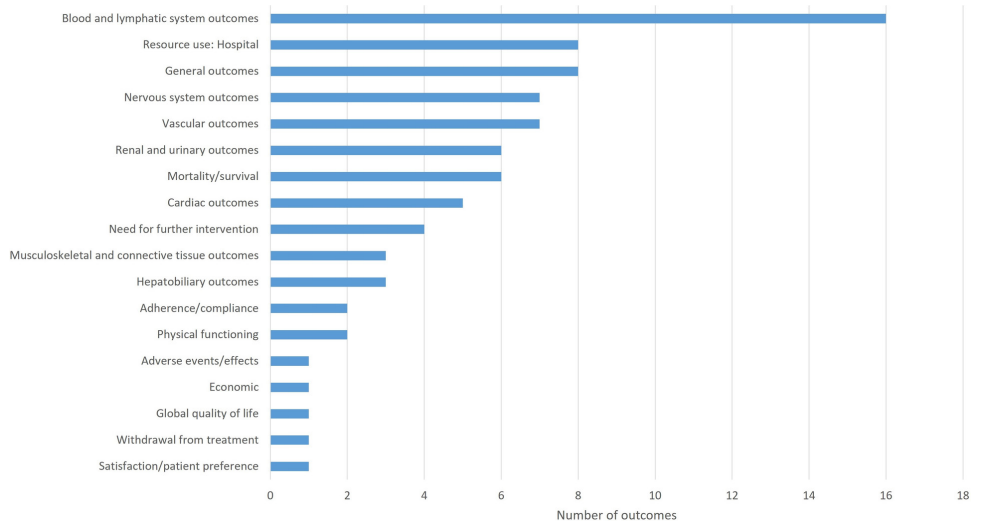

Figure 7 The number of outcomes in different outcome domains in anticoagulant treatment trials.

three or more OMIs or definitions. Major bleeding had more definitions than other outcomes did.

In addition, there were many different measurement times for the same outcome. In the clinical trials of antiarrhythmic treatment, the outcome measurement times ranged from 1 to -14 times, and the median time was 3.Forty-three outcomes (62.32%, 43/69) had two or more measurement times. Heart rate and ECG outcomes had more measurement times than other outcomes did. In clinical trials of anticoagulant therapy, the outcome measurement times ranged from 1 to 56, with a median of 1.5; among these outcomes 41(50.00%, 41/82) had two or more measurement times. In addition, ischaemic stroke had more measurement times than other outcomes did.

DISCUSSION

This systematic review is the first to evaluate the quality of outcome reporting of clinical trials of TCM and western medicine for treating NVAF. The results showed variations in the outcome reporting, OMIs/outcome definitions and outcome measurement time reporting in different clinical trials. These problems may result in the exclusion of some studies from systematic reviews/meta-analyses due to the heterogeneity of outcomes or outcome measurements; thus, these studies cannot provide a higher level of evidence for clinical practice.

In clinical trials for NVAF, investment wastes also exist because approximately 1/3 of outcomes were reported only once in included trials of anticoagulation therapy and antiarrhythmic therapy. For example, conversion to sinus rhythm, which is important to the results of clinical trials of antiarrhythmic therapy, was reported by 29.55% (26/88) of articles. Some long-term outcomes, such as all-cause mortality and cardiovascular deaths, were reported in 12.50% (11/88) and 5.68% (5/88) of articles, respectively.

In addition, adverse events/effects were inadequately reported. In clinical trials of anticoagulant therapy, safety outcomes such as haemorrhage were grouped under vascular outcomes according to the degree of bleeding (such as major bleeding, clinically relevant non-major bleeding and minor bleeding). Then, only 12.31% (16/130) of the included articles reported other kinds of adverse events/effects. For clinical trials of antiarrhythmic therapy, only 29.55% (26/88) of the included articles reported adverse events/effects.

For all of the outcomes in the list, patient' perspectives could not be identified sufficiently. For example, among all of the included 88 articles for antiarrhythmic therapy, none of them reported quality of life, while in all of the included 130 articles for anticoagulant therapy, only 4 of them reported quality of life.

There were 30 articles for clinical trials of TCM. TCM syndrome, which could reflect the characteristics of TCM, was reported only two times. A few other articles reported symptoms related to TCM syndrome. This phenomenon cannot reflect the characteristics and advantages of TCM.

After assessing the quality of outcome reporting and studies, the results showed that the majority of included trials had poor quality. Although the poor quality of studies may not influence the result of developing a long list of outcomes, the poor quality of outcome reporting made it difficult to extract sufficient information from the articles. The reasons for poor quality of studies and outcome reporting may be because most studies in China do not follow the Consolidated Standards of Reporting Trials (CONSORT) statement or observational studies reporting items. Moreover, the majority of journals in Chinese do not require studies to follow the CONSORT statement; thus, some studies provided limited information on key methodological issues. In addition, Chinese researchers prefer to report comprehensive outcomes rather than individual outcomes, and studies have reported only primary outcomes.

Only a small number of included studies provided OMIs or definitions, which made it difficult to assess

the quality of outcome measures. Additionally, the variation in OMIs or definitions can make it impossible to conduct meta-analyses. In addition, selecting OMIs with good measurement properties is very important after developing a COS[15] to ensure that reliability, validity and ethical standards are achieved.

The measurement time was much shorter in Chinese journals than in English journals. In general, long-term outcomes were usually reported in observational studies, while short-term outcomes were usually reported in RCTs. It is a challenge for a single trial to measure all of these outcomes in a meaningful way, especially an outcome such as mortality, which requires longer follow-up and a larger sample size.[16] Therefore, recommending measurement times for different outcomes is important.

Developing a COS for NVAF may reduce the heterogeneity of outcome reporting in different clinical trials, so that clinical trials can be included in systematic reviews/meta-analyses to provide a higher quality of evidence for clinical practice. Moreover, if the majority of clinical trials can be included in systematic review, it may help reduce investment wastes. Reviewers can easily determine if publication bias is present when a COS is used. For TCM clinical trials, a COS may help improve the quality of studies if researchers report consensus outcomes, which may help improve the development of TCM.

Author affiliations
[1]Key Laboratory of Chinese Internal Medicine of Ministry of Education and Beijing, Dongzhimen Hospital, Beijing University of Chinese Medicine, Beijing, China
[2]Baokang Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China
[3]Evidence-based Medicine Center, Jiangxi University of Chinese Medicine, Nanchang, China

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