Review Article

Optimized stratification of risk factors in and beyond the CHA_2DS_2-VASc score to differentiate the real thromboembolic risk in mainland China: a systematic review and meta-analysis

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Abstract: Recent studies have demonstrated the limitations of the CHA_2DS_2-VASc score [congestive heart failure, hypertension, age (>65 years=1 point; >75 years=2 points), diabetes, and previous stroke/transient ischemic attack (2 points), vascular disease] which lacks many of less common risk factors for stroke. Moreover, only two risk factors, gender and age, are assigned with different points according to the stratification in the CHA_2DS_2-VASc score. Thus, this meta-analysis was aimed to optimize the stratification of risk factors in and beyond the CHA_2DS_2-VASc score for patients in mainland China. PubMed, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Chinese Science and Technology Journal Database (VIP) were searched from their inception to January 2020 for articles assessing risk factors of nonvalvular atrial fibrillation (NVAF) with ischemic stroke in mainland China. Odd risks (ORs) with 95% confidence intervals (CIs) were applied for dichotomous variable, and the weighed mean differences (WMDs) with standard deviations (SDs) were used for continuous variables. The meta-analysis included 20 eligible studies involving 14,675 patients. Compared with the non-stroke group [systolic blood pressure (SBP): 132.99 mmHg, 95% CI: 131.86–134.12; diastolic blood pressure (DBP): 80.08 mmHg, 95% CI: 78.63–81.53], the ischemic stroke group (SBP:144.07 mmHg, 95% CI: 140.74–147.40; DBP: 84.41 mmHg, 95% CI: 82.39–86.43) showed increased levels of SBP (WMD 10.98 mmHg, 95% CI: 7.80–14.17, P<0.00001) and DBP (WMD 4.46 mmHg, 95% CI: 2.57–6.35, P<0.00001). In addition, the ischemic stroke group demonstrated significantly lower levels of left ventricular ejection fractions (LVEFs) (WMD 3.05% 95% CI: –5.96 to –0.14, P=0.04), and significantly higher levels of total cholesterol (TC) (WMD 0.32 mmol/L, 95% CI: 0.04–0.61, P=0.02) and low density lipoprotein cholesterol (LDL-C) (WMD 0.14 mmol/L, 95% CI: 0.02–0.26, P=0.02), as compared with the non-stroke group. The optimized stratification and the addition of risk factors in and beyond the CHA_2DS_2-VASc score may improve the predictive performance, thus helping to differentiate patients with the real thromboembolic risk.

Keywords: Nonvalvular atrial fibrillation; ischemic stroke; heart failure; optimized stratification; mainland China

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Introduction

Atrial fibrillation (AF) is a dominant cause of morbidity and mortality worldwide, frequently leading to systemic thromboembolism and ischemic stroke (1,2). Strokes associated with AF are related to higher mortality and greater disability when compared with those from other causes (3). Moreover, the prevalence of AF among adults aged ≥40 years in mainland China was up to 2.31%, which was higher than the reported global scale (4). Thus, stroke prevention is central to the management of AF, regardless of rhythm control strategies (2).

The CHA_2DS_2-VASc score is currently considered as the cornerstone for the thromboembolic risk assessment and the anticoagulation therapy (5). Previous evidence suggested that the CHA_2DS_2-VASc score may be more excellent than other scoring systems in discriminating the risk of embolization (6,7). However, several limitations of the CHA_2DS_2-VASc score are observed gradually. Recent work has showed that the score may not be validated in an ethnically diverse population (8). Moreover, many of the less common stroke risk factors, beyond the CHA_2DS_2-VASc score, should be included in the score (9). Only two risk factors, gender and age, are currently assigned with different points according to each stratification in the CHA_2DS_2-VASc score. It would be simplistic to regard that all risk factors carry equal weight (9). The weight of each risk factor should be appropriately modified according to the different stratification. No previous study has investigated the stratification of risk factors in the score. Thus, the aim of this meta-analysis was to optimize the stratification of risk factors in and beyond the CHA_2DS_2-VASc score.

We present the following article/case in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/apm-20-297).

Methods

Search strategy, inclusion and exclusion criteria, data extraction, outcomes of interest, quality assessment and statistical methods in the present meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISRM) guidelines.

Search strategy

PubMed, Embase, Web of Science, Cochrane Library, Chinese National Knowledge Infrastructure (CNKI), and Chinese Science and Technology Journal Database (VIP) were systematically searched from their inception to January 2020 for all studies regarding risk factors of nonvalvular atrial fibrillation (NVAF) with ischemic stroke in mainland China. The following terms were used in [Tittle/abstract]: "nonvalvular atrial fibrillation OR ischemic stroke AND risk factors AND mainland China". To expand the search scope, we used the function of related articles and performed the manual search to get all reference lists of retrieved studies and conference abstracts. The most complete or recent literature was included if multiple literatures with the same population were found.

Inclusion and exclusion criteria

Independent reviewers (Wenjie Li and Lingling Xu, Tao Wang and Xiaojun Zeng) performed the literature screening according to selection criteria, titles, abstracts, and full-texts. Any discrepancies were resolved by discussion with the third reviewer (Bi-hui Luo).

All available prospective and retrospective trials that evaluated risk factors of NVAF with ischemic stroke in and beyond the CHA_2DS_2-VASc score, that were performed in mainland China and had at least three of the outcomes of interest mentioned in the next part of this article, were included. Studies that enrolled patients with valvular atrial fibrillation (including moderate to severe mitral stenosis or mechanical heart valve), animal experimental literatures, case reports and review articles were excluded.

Data extraction and outcomes of interest

By using the EndNote X9.3 system, two reviewers (Wenjie Li and Xiaojun Zeng) screened all identified documents and extracted information as follows: (I) title, author, study design, study site, year of publication, (II) sample size, mean age, follow-up duration, and (III) related items for outcomes of interest. If the outcome data were not available in the studies, we contacted the corresponding authors by email, with a reminder after one week.

The outcomes of interest were risk factors in the CHA_2DS_2-VASc score (age, female, hypertension, stroke/transient ischemic attack, diabetes mellitus, congestive heart failure, coronary heart disease and vascular disease), and risk factors beyond the score, including body mass index (BMI), smoking, drinking, use of anticoagulant drugs, total cholesterol (TC), triglyceride (TG), low/high density

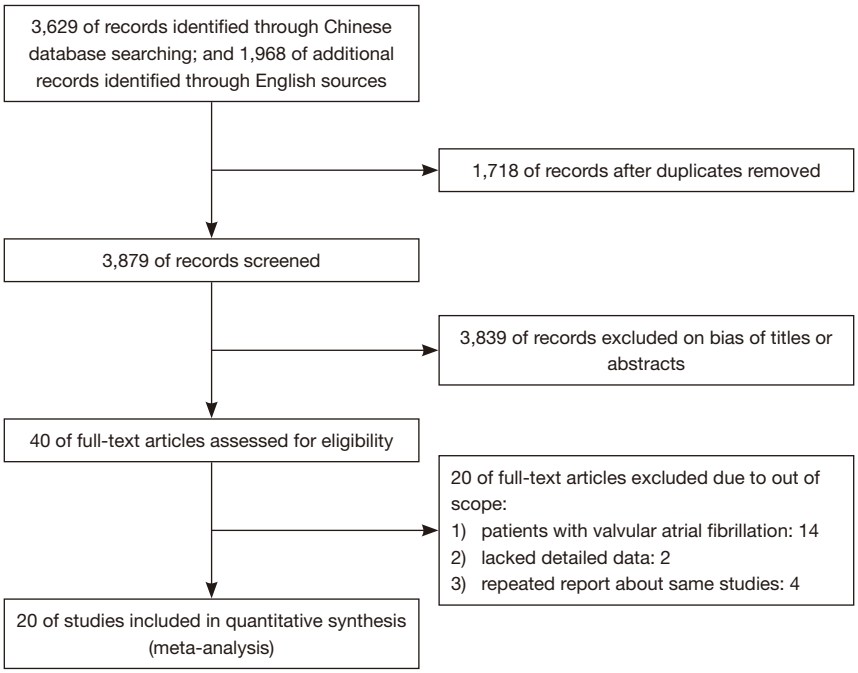

Figure 1 Search flowchart. NVAF, nonvalvular atrial fibrillation; OR, odd ratio; MD, mean difference.

lipoprotein cholesterol (LDL-C/HDL-C), systolic blood pressure (SBP), diastolic blood pressure (DBP) and left ventricular ejection fractions (LVEF).

Quality assessment

The methodological quality of the included studies was accessed by using the Newcastle-Ottawa Scale (NOS), which included eight items (10). Each included study was scored out of a maximum of 8 scores. Studies with scores ≥7 were of high quality. Moderate-quality was judged if the scores were 4 to 6, and studies with scores <4 were of low quality.

Statistical analysis

All statistical analyses were performed by using RevMan 5.3 and Stata 15.0. Because of the large variety of patient characteristics, the odds ratios (ORs), weighted mean differences (WMDs) with standard deviations (SDs) and 95% confidence intervals (CIs) were obtained by using random-effects models even in case no heterogeneity was found. Single-arm analyses were conducted to evaluate the mean of SBP, DBP and LVEF, and the double-arm analyses were performed to evaluate the ORs and WMDs. Statistical heterogeneity was assessed by Cochrane Q test and I^2 statistic. For Q test, P<0.1 (two-sided) was statistically significant. Heterogeneity was considered to be low if I^2 was <50%; otherwise, it was high. Sensitivity analyses were conducted to assess the robustness of results by removing each included study individually. Potential publication bias was estimated by a funnel plot.

Results

Study selection

The database search yielded 3,629 Chinese articles and 1,968 English articles. Initial screening of these articles yielded 3,876 potentially qualified studies following the removal of 1,718 duplicates. After reviewing titles and abstracts, 40 articles were identified for full-text review, with 20 articles meeting full criteria (*Figure 1*).

Study characteristics and quality assessment

Table 1 outlines the characteristics of all the 20 observational studies. All publications were full-text literatures. These studies sourced from 14 regions in mainland China and included a total of 14,675 patients. Sample sizes ranged from 44 patients to 8,143 patients. All patients underwent

Table 1 Study characteristics and quality assessment

Study	Sample size	Number		Mean age		Study design	Use of antithrombotic agents	Risk factor*	Origin zone	Study period	NOS Score
		Non-stroke group	Stroke group	Non-stroke group	Stroke group						
Shanjiao Huang, 2019	314	239	75	72.20±7.10	74.10±8.10	Case-control study	No	A, B, D, E, F, G, H, J, K, L, M, N, O, P, Q, R	Fujian	2013–2017	7
Yichen Qu, 2018	44	25	19	75.6±0.29	80.53±6.16	Case-control study	Yes	A, B, D, E, G, H, J, L, N, O, P, Q, R	Fujian	2016–2017	7
Haohui He, 2018	400	266	134	68.02±12.03	73.70±10.77	Case-control study	No	A, D, E, F, G, H, I, J, K, L, M, O, P, R	Guangdong	2010–2017	7
Bang He, 2018	903	845	58	71.70±9.40	79.40±10.10	Case-control study	Yes	A, B, C, D, E, F, G, H, Q, R	Sichuan	2014–2016	7
Hongli Cui, 2017	122	85	37	–	–	Case-control study	NA	A, D, E, G, J, K, N, O, P	Xinjiang	2013–2016	5
Yijie Guo, 2017	901	862	39	77.64±7.26	67.50±13.22	Case-control study	Yes	A, D, E, F, G, H, I, R	Hainan	2009–2011	5
Xiaoli Liu, 2016	365	167	188	68.67±11.16	62.35±10.24	Case-control study	NA	A, B, D, E, F, J, K, L, M, N, R	Hubei	2011–2014	6
Shan Zeng, 2016	2,442	2,159	283	70.60±11.30		Case-control study	Yes	D, E, F, G, H, I	Jiangxi	2011-2013	7
Danlin Yao, 2015	229	132	97	66.6±14.00	71.90±12.80	Case-control study	NA	A, D, E, F, H, R	Beijing	2008–2014	6
Yangjian Zheng, 2015	426	356	70	72.61±9.24		Case-control study	Yes	A, D, E, G	Zhejiang	2013-2014	5
Jiangang Wang, 2015	180	60	120	74.10±7.80	76.90±7.10	Case-control study	Yes	A, B, J, K, L, N, R	Shanxi	2010–2014	5
Yongqi Fu, 2015	230	190	40	64.84±10.92	70.65±9.72	Case-control study	NA	A, B, C, J, K, L, R	Hebei	2012–2013	5
Shuying Xu, 2014	975	721	254	66.85±12.55	69.39±11.23	Case-control study	Yes	A, B, J, K, L, M, N, Q, R	Guangxi	2009–2013	7
Yan Liu, 2013	111	53	58	74.58±12.06	74.34±9.23	Case-control study	Yes	A, B, C, D, E, F, J, K, L, M, N, R	Shanghai	2009–2012	7
Na Li, 2012	1,064	924	140	–	–	Case-control study	Yes	A, B, C, D, E, N, Q	Xinjiang	2002–2009	6

Table 1 (*continued*)

Table 1 (*continued*)

Study	Sample size	Number		Mean age		Study design	Use of antithrombotic agents	Risk factor*	Origin zone	Study period	NOS Score
		Non-stroke group	Stroke group	Non-stroke group	Stroke group						
Naping Lin, 2014	322	171	151	67.8±12.3	73.56±10.1	Case-control study	NA	A, D, E, F, G, H, I, J, K, R	Fujian	2014.3–2014.10	6
Jing Zhou, 2015	551	432	119	62.5±10.7	70.7±10.3	Case-control study	NA	J, L, U	Shanbei	2010–2012	5
Xianhui Zhou, 2017	4,490	3,653	837	–	–	Case-control study	Yes	A, B, C, D, E, G	Xinjiang	2013–2014	5
Lecheng Wu, 2015	168	122	46	67.8±9.27	74.10±9.10	Case-control study	NA	A, D, E, F, J, K, O, P, R	Zhejiang	2010–2014	6
Liying Mu, 2006	438	279	159	69.4±10.15	71.65±8.54	Case-control study	Yes	D, E, F, J, K, O, P, R	Beijing	2002–2003	5

*Risk factors: A = Female; B = Smoking; C = Alcohol intake; D = Diabetes; E = Hypertension; F = Heart failure; G = Coronary heart disease; H = Vascular disease; I = History of ischemic stroke; J = TC; K = TG; L = LDL-C; M = HDL-C; N = left ventricular ejection fraction; O = systolic blood pressure; P = diastolic blood pressure; Q = BMI; R = age. NA, not available.

antihypertensive therapy. The quality assessment demonstrated that no study was less than four scores. Six studies were of high-quality (11-16) and fourteen studies were of moderate-quality (17-30) by using the NOS.

Results of meta-analysis

The assessment of all the outcomes is presented in Table S1. Most risk factors in the CHA_2DS_2-VASc score were significantly associated with ischemic stroke (hypertension: OR 2.06, 95% CI: 1.54–2.27, P<0.00001; age: OR 3.88, 95% CI: 2.20–5.56, P<0.00001; diabetes mellitus: OR 1.60, 95% CI: 1.30–1.98, P<0.0001; vascular disease: OR: 2.56, 95% CI: 1.19–5.48, P=0.02). However, female and congestive heart failure showed no statistical significance. Eight studies provided detailed data regarding the use of anticoagulant agents and showed a greater risk of stroke (OR 0.97, 95% CI: 0.86 to 1.10), but the difference did not reach statistical significance (P=0.65).

The mean SBP and DBP at baseline between the ischemic stroke group (SBP: 144.07 mmHg, 95% CI: 140.74–147.40; DBP: 84.41 mmHg, 95% CI: 82.39–86.43) and the non-stroke group (SBP: 132.99 mmHg, 95% CI: 131.86–134.12; DBP: 80.08 mmHg, 95% CI: 78.63–81.53) are shown in Figures S1-S4. Notably, the double-arm analysis demonstrated that compared with the non-stroke group, patients with the higher blood pressure (BP) level at baseline were significantly related to a higher incidence of ischemic stroke (SBP: WMD 10.98 mmHg, 95% CI: 7.80–14.17, P<0.00001; and DBP: WMD 4.46 mmHg, 95% CI: 2.57–6.35, P<0.00001) in the ischemic stroke group (*Figures 2,3*).

The single-arm analysis showed that the mean LVEF was 55.37% (95% CI: 52.40–58.33) in the stroke group and 58.41% (95% CI: 57.11–59.71) in the non-stroke group (Figures S5,S6). LVEF in the ischemic stroke group was 3.05% lower than that in the non-stroke group (95% CI: -5.96 to -0.14, P=0.02) (*Figure 4*). Moreover, risk factors beyond the CHA_2DS_2-VASc score also demonstrated the statistical significance. The levels of TC (WMD 0.32, 95% CI: 0.04–0.61, P=0.02) and LDL-C (WMD 0.14, 95% CI: 0.02–0.26, P=0.02) in the ischemic stroke group were significantly higher than those in the non-stroke group (Figures S7,S8).

Sensitivity analysis and publication bias

Sensitivity analysis showed that none of the outcomes

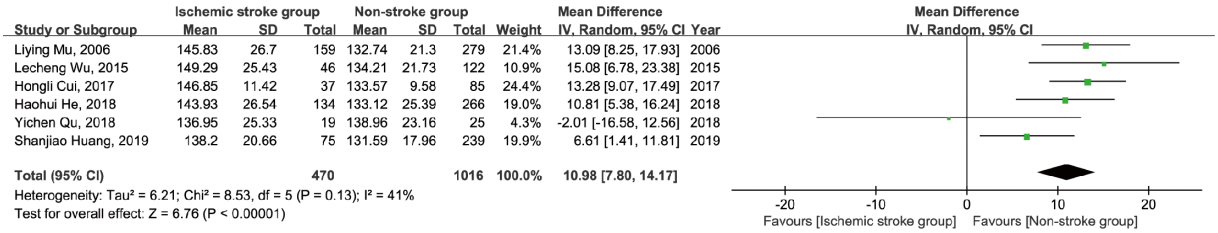

Figure 2 Forest plot of mean difference in systolic blood pressure (SBP) between the ischemic stroke group and the non-stroke group. Weights were from random effects analysis. SD, standard deviation; IV, inverse variance; CI, confidence interval.

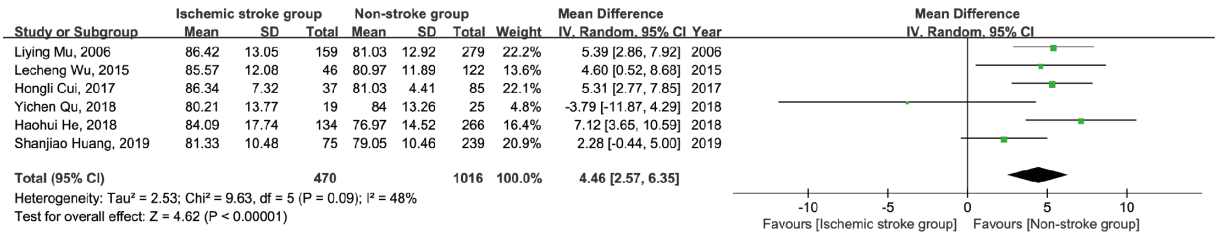

Figure 3 Forest plot of mean difference in diastolic blood pressure (DBP) between the ischemic stroke group and the non-stroke group. Weights were from random effects analysis. SD, standard deviation; IV, inverse variance; CI, confidence interval.

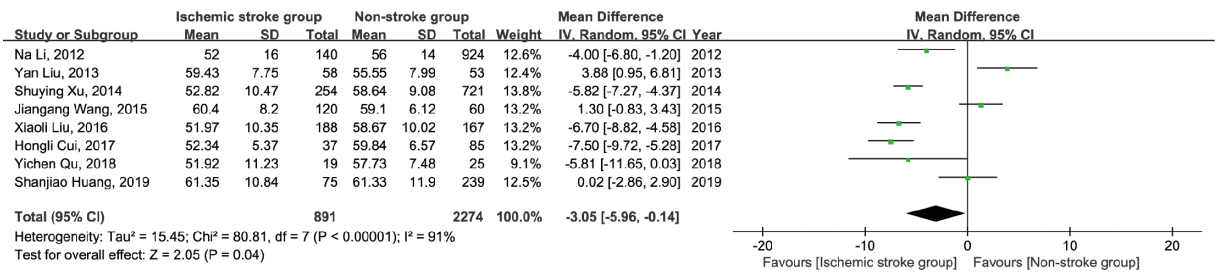

Figure 4 Forest plot of mean difference in left ventricular ejection fractions (LVEF) between the ischemic stroke group and the non-stroke group. Weights were from random effects analysis. SD, standard deviation; IV, inverse variance; CI, confidence interval.

changed significantly and that the degree of heterogeneity decreased slightly. No obvious publication bias was found in the funnel plot of the studies that evaluated LVEF (Figures S9).

Discussion

The value of the CHA_2DS_2-VASc score for stroke risk prediction has been well documented (6,7). However, patients with NVAF might be of higher risks for left atrial thrombus (LAT) despite a low CHA_2DS_2-VASc score. The optimized weight of risk factors in and beyond the CHA_2DS_2-VASc score according to the stratification is relatively new (9,31). To the best of our knowledge, this is the first systematic review to optimize the stratification of risk factors in and beyond the CHA_2DS_2-VASc score. The major findings were as follows: (I) Patients with higher BP levels at baseline were significantly associated with a higher incidence of ischemic stroke. (II) HFpEF subgroup could be subdivided into heart failure with lower preserved ejection fraction (HFLpEF) and with higher preserved ejection fraction (HFHpEF), which represented different thromboembolic risks. (III) The addition of risk factors beyond the CHA_2DS_2-VASc score, TC and LDL-C, may improve the predictive performance of the score. 4) Female might not be an independent risk factor of thromboembolism for NVAF patients in mainland China. This finding was consistent with the latest data from China-

AF study and the contemporary Japanese-AF guideline, which did not include female sex as an independent risk factor for anticoagulant treatment (32,33).

Hypertension is the most common risk factor for the development of AF worldwide (34). However, it remains unclear whether SBP and DBP levels are related to the risk of stroke in AF patients (35). In the present meta-analysis, the ischemic stroke group showed significantly higher BP levels and a greater risk of ischemic stroke than the non-stroke group. These results corroborated the finding of the previous trial (36) and suggested that AF patients with higher BP above the median values experienced a higher risk of stroke. Moreover, the Stroke Prevention in Atrial Fibrillation (SPAF) trial suggested that SBP ≥160 mmHg was independently related to the increased risk of stroke (37). Another analysis showed that the cutoff was elevated SBP ≥140 mmHg (38). The present study indicated that the mean SBP 144.07 mmHg (95% CI: 140.74–147.40) was at a significantly higher risk of ischemic stroke, with the elevated mean DBP 84.41 mmHg (95% CI: 82.39–86.43). This conceivably reflected a negative correlation between the elevated BP and the risk of ischemic stroke in NVAF patients. The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guideline put forward a stricter definition of hypertension (SBP ≥130 mmHg or DBP ≥80 mmHg), inconsistent with the previous definition in the CHA_2DS_2-VASc score (39). The guideline also recommended treating SBP/DBP to <130/80 mmHg for AF patients (39). However, few studies have validated this recommendation and the predictive abilities of recalculated risk scores for ischemic stroke (40). In this meta-analysis, the mean SBP and DBP in the non-stroke group were 132.99 mmHg (95% CI: 131.86–134.12) and 80.08 mmHg (95% CI: 78.63–81.53), which may have implications guiding the target of antihypertensive therapy for ischemic stroke prevention and support anticoagulation recommendations. Of note, low BP reducing to <110/60 mmHg would lead to more adverse events (41). Based on the mean SBP and DBP, we produced some evidence on new BP cut-off values to predict ischemic stroke in patients with NVAF. Weigh of "H" in the CHA_2DS_2-VASc score could be optimized according to the stratification of SBP and DBP, not simply history of hypertension or uncontrolled BP.

In the present study, patients with congestive heart failure showed a greater risk of ischemic stroke, but the difference did not reach statistical significance. This may be attributed to the insufficient number of events. As recommended in the guideline, the diagnosis of heart failure mainly included symptoms, a clinical examination, NT-proBNP and transthoracic echocardiography to detect LVEF (42). Heart failure is currently defined as 'with reduced ejection fraction (HFrEF)'and 'with normal or preserved ejection fraction (HFnEF or HFpEF)' (43). Of note, the definition of HFpEF is difficult, which can be defined by various classifications or inclusive criteria of clinical researches (ranging from ≥40% to ≥55%) (44,45). The unclear definition resulted in the heterogeneity of HFpEF patients in many researches. In addition, it is puzzling to note that HFpEF is a special group, featuring the highest CHA_2DS_2-VASc scores but the lowest risk of thromboembolic events (46). Such difficulties in classification influenced our study to some extent, but the present findings still added important insights into highlighting HFpEF definition for the modified CHA_2DS_2-VASc score. Based on our data, LVEF ranged from 50% to 60% in the majority of patients with HFpEF. Further analysis demonstrated that LVEF in the ischemic stroke group was lower than that in the non-stroke group. Given that, we hypothesized that HEpEF (LVEF: 50–60%) could be subdivided into lower preserved ejection fraction (HFLpEF) and higher preserved ejection fraction (HFHpEF). The risk of thromboembolism will be significantly great when LVEF reaches certain value between 50% and 60%. That is, HEpEF patients with HFLpEF and HFHpEF may identify quite distinct populations, which differ appreciably in terms of the thromboembolic risk (46). Although a body of researches are required to validate the best critical value, congestive heart failure in the CHA_2DS_2-VASc score is necessary to be modified according to the stratification of LVEF.

Interestingly, in the light of our data, indicators beyond the CHA_2DS_2-VASc score could also refine the scoring system. This was consistent with recent evidence which demonstrated that TC and LDL-C were independent predictors of NVAF with ischemic stroke (47,48). The underlying mechanism may be that cholesterol depletion resulted in impairment in cardiomyocyte contractility by deregulating adrenergic signaling, calcium handling and the myofibrillar architecture (49). More large-scale trials are required to investigate the best cut-off values of TC and LDL-C to predict ischemic stroke in patients with NVAF.

This study has potential limitations that must be emphasized. First, inclusion of observational studies may share an intrinsic risk for selection bias. However, it must be highlighted that there were no available randomized trials in this respect. Second, the studies included in the current

meta-analysis comprised of a wider population in terms of regions, making the heterogeneity observed in the current meta-analysis. Third, the present systematic review was unable to offer specific cut-off values of the stratification due to a lack of data at the individual level. More researches are needed in the future.

Conclusion

This paper firstly proposed a framework for the optimized stratification of risk factors in and beyond the CHA_2DS_2-VASc score. The weight of risk factors in the CHA_2DS_2-VASc score, especially for hypertension and congestive heart failure, could be modified according to the stratification. In addition, TC and LDL-C may be independent predictors of NVAF with ischemic stroke. The addition of risk factors beyond the score could improve the predictive performance. These findings might be of great importance in differentiating patients who are potentially at high risks for ischemic stroke and LAT.

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Footnote

Reporting Checklist: The authors have completed the PRISRM reporting checklist. Available at http://dx.doi.org/10.21037/apm-20-297

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/apm-20-297). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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