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Increased risk of ischemic stroke associated with new-onset atrial fibrillation complicating acute coronary syndrome: A systematic review and meta-analysis

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ABSTRACT

Background: Atrial fibrillation has been established as a major risk factor of ischemic stroke, however, the influence of new-onset atrial fibrillation (NOAF) complicating acute coronary syndrome (ACS) on ischemic stroke remains controversial. This meta-analysis aimed to validate the association between NOAF complicating ACS and ischemic stroke.

Methods: We identified randomized controlled trials and cohort studies comparing the ischemic stroke risk between patients with NOAF and sinus rhythm after ACS by searching MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials databases. We included studies reporting the number of ischemic stroke events or their risk estimates at the longest follow-up. We pooled risk ratios (RRs) using a random-effects model. This meta-analysis is registered in PROSPERO (CRD42017079858).

Results: In the 14 included studies ($n = 292{,}774$, 5 randomized controlled trials and 9 cohort studies), NOAF was associated with an increased risk of ischemic stroke (RR: 2.84, 95% confidence interval [CI]: 1.91–4.23; 6 studies), especially for patients with ST-segment elevation myocardial infarction (RR: 4.01, 95% CI: 2.61–6.18; 3 studies). In addition, the detrimental impact persisted in patients with transient NOAF (RR: 3.05, 95% CI: 1.63–5.70; 3 studies). The pooled result from a sensitivity analysis in which all individual components in the CHA_2DS_2-VASc score (heart failure, hypertension, age, diabetes, previous stroke, vascular disease and female sex) had been adjusted further validated the association between NOAF and ischemic stroke (RR: 2.32, 95% CI: 1.53–3.52; 4 studies).

Conclusions: NOAF is significantly associated with ischemic stroke events in patients with ACS, even after adjustment for several important ischemic stroke risk factors.

1. Introduction

Stroke is a rare but devastating clinical event after acute coronary syndrome (ACS) and has been validated as a strong predictor for subsequent mortality [1–3]. During the past decades, the incidence of stroke after ACS is gradually falling, which may be attributable to the rigorous secondary prevention of atherosclerotic diseases [4,5], as well as the decreased incidence of hemorrhagic stroke due to the shift in reperfusion strategies from fibrinolysis to percutaneous coronary intervention [6]. Until now, ischemic stroke has increasingly been perceived as the leading cause of stroke after ACS [2].

Atrial fibrillation (AF) has been established as a major risk factor for ischemic stroke [7]. In fact, AF is a common finding in patients with ACS as the result of their similar risk factors and can be categorized as pre-existing and new-onset AF (NOAF) based on their temporal relationships with ACS. In a previous meta-analysis, Jabre et al. showed both AF types were significantly associated with increased mortality and suggested more attention should be paid to their management [8]. Unlike the confirmed ischemic stroke susceptibility of pre-existing AF [9], it is still controversial whether the NOAF complicating ACS is also associated with an increased risk of ischemic stroke [10–15]. Hence, we aimed to perform a systematic review and meta-analysis to quantify the risk of ischemic stroke associated with post-ACS NOAF.

2. Methods

2.1. Literature search and selection criteria

The present meta-analysis was performed following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline [16] and was registered in the International Prospective Register for Systematic Reviews (PROSPERO: CRD42017079858). We searched Ovid MEDLINE, Ovid EMBASE and Cochrane Central Register of Controlled Trials databases from their inception to October 2017, using the combination of medical subjects heading terms and keywords: "acute coronary syndrome", "myocardial infarction", "coronary thrombosis", "atrial fibrillation", "cerebrovascular disorders", "cerebrovascular accident",

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"ischemic stroke", "brain infarction", without any language limitation. The reference lists of retrieved studies and prior reviews were also screened for other eligible studies.

Studies considered in our study were randomized controlled trials (RCTs) and cohort studies comparing the ischemic stroke risk between patients with NOAF and sinus rhythm (SR) after index ACS. We excluded studies that did not report the number of stroke events or their risk estimates and those in which no distinction could be made between hemorrhagic and ischemic stroke. In addition, "reviews", "editorials", "letters", "case reports", "conference abstracts", and "case-control studies" were also excluded.

We classified NOAF as transient NOAF, persisting NOAF or any NOAF. NOAF was defined as AF occurring for the first time after the ACS with no history of AF in medical records. Transient NOAF was defined as NOAF occurring during hospitalization with SR at discharge. Persisting NOAF was defined as NOAF occurring during hospitalization with AF at discharge. If no distinction about the status of NOAF at discharge was made, NOAF was classified as any NOAF.

2.2. Data extraction

Four reviewers working independently and using a standardized form extracted data from all eligible studies, including baseline characteristics of studies and patients and the number of ischemic stroke events or their risk estimates. If several risk estimates were available in the same study, the most fully adjusted result corresponding to the longest follow-up duration was extracted. We further tried to contact corresponding authors of studies for missing data through E-mail. Discrepancies were resolved by consensus.

2.3. Quality evaluation

For the purpose of our study, we dealt with all eligible RCTs as cohort studies, with the population being treated as a whole without considering the randomization process. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of studies. A quality score was calculated according to three major components: selection (0–4 points), comparability (0–2 points) and outcome (0–3 points) [17]. Notably, whether the individual components in the CHA_2DS_2-VASc score had been adjusted was used for comparability assessment. The age was chosen as the major risk factor, and other risk factors were heart failure, hypertension, diabetes, previous stroke/transient ischemic attack (TIA), vascular disease and female sex (Table S1 [supplements]). Good comparability was considered if one or two stars were obtained. A total score of seven or more was considered as a high-quality study.

2.4. Outcomes and subgroup analyses

The primary study endpoint was the ischemic stroke. TIA would be an alternative when ischemic stroke was not reported. Subgroup analyses were performed to compare the outcomes according to study type, sample size, geographic location, comparability, and publication date. In addition, we explored the risk of ischemic stroke in patients with either ST-segment elevation myocardial infarction (STEMI) or transient NOAF.

2.5. Sensitivity analyses

To confirm the robustness of our analyses, several sensitivity analyses were performed including: 1) statistical models (fixed- and random-effects); 2) limited to studies with large sample (≥10,000), with all components in the CHA_2DS_2-VASc score being adjusted, conducted in multiple centers, or in which ischemic stroke events were measured after discharge; 3) exclusion of studies with the largest sample or the most outlier result, with atrial flutter being included, or in which coronary artery bypass grafting surgery was performed.

2.6. Statistical analysis

Descriptive analyses were demonstrated as frequencies for categorical variables and standardized means (standard deviations) or median (interquartile) for continuous variables. We used random-effects model described by DerSimonian and Laird to calculate pooled risk ratios (RR) and 95% confidence intervals (CI) [18]. Heterogeneity was evaluated with the χ^2 based-Q-statistic test, and I^2 was used to quantify the inconsistency. I^2 < 25%, 25%–50% and >50% suggested low, moderate and high heterogeneity, respectively. Univariate meta-regression models were used to determine the interactions between subgroups. Publication bias was evaluated using Egger's test [19]. A value of $p < 0.05$ (2 sided) was considered statistically significant. All analyses were performed using Stata software version 14 (StataCorp, College Station, Texas).

3. Results

3.1. Characteristics of the included studies

As demonstrated in Fig. 1, our initial literature search identified 1198 studies. After title and abstract screening, 1153 studies were excluded and full-text review retrieved 45 studies; 31 studies were further excluded according to exclusion criteria and 14 studies including 5 retrospectives from RCTs [20–24] and 9 cohort studies [12–15,25–29] were available for the final analysis. Atrial flutter and fibrillation were treated as a whole in 4 studies [15,23,24,29] and 6 studies only included STEMI patients [12,20,21,23,24,27]. Most of NOAF events were evaluated during hospitalization except for 3 studies in which on-admission NOAF were included [15,25,26]. All studies had reported the ischemic stroke except for one in which only TIA was available [24]. Table 1 showed the details of included studies.

3.2. Characteristics of the included patients

The incidence of NOAF was 7.4% (95% CI: 5.8%–9.0%). Patients with NOAF were older (70.1 ± 3.4 years vs 61.9 ± 2.8 years), more likely to be women (31.8 ± 4.2% vs 24.5 ± 4.5%) and had more baseline coexisting conditions (e.g., hypertension, diabetes, myocardial infarction, etc.) than those with SR. In addition, the CHA_2DS_2-VASc score was significantly higher in patients with NOAF (4.2 ± 0.1 vs 3.1 ± 0.2). Furthermore, patients with NOAF were more likely to receive oral anticoagulants (17.0% vs 4.0%) and less likely to receive aspirin (84.8% vs 87.3%) or $P2Y_{12}$ inhibitors (41.6% vs 49.0%) at discharge. Details of patients' characteristics were demonstrated in Table 2.

3.3. Quality evaluation

Quality evaluation by NOS revealed a median score of 7 (range, 4–9). Furthermore, six studies with good comparability demonstrated an excellent quality (median 8, range 7–9), whereas the other 8 studies only had a median score of 6 (range, 4–6) (Table S2 [supplements]).

Accounting for the high heterogeneity from the pooled result of all eligible studies, and the origins of which could not be determined by performing subgroup analyses and meta-regression analyses (Table S3 [supplements]), we decided to report only stroke risk estimates from 6 studies that with good comparability and high quality [13,21,23,27–29].

3.4. Ischemic stroke associated with NOAF complicating ACS

The incidence of ischemic stroke after ACS was 1.6% (95% CI: 0.5%–2.8%), and ischemic stroke rates at three periods: in-hospital, 1 month to 1 year and ≥1 year were 0.9%, 1.2%, and 3.7%, respectively. Post-ACS NOAF was associated with an increased risk of ischemic stroke compared with those in SR (RR: 2.84; 95% CI: 1.91–4.23; $p < 0.01$) (Fig. 2A). After removing the GRACE registry [29], only a low heterogeneity was observed and the significance of the pooled result remained (RR: 3.21; 95% CI: 2.36–4.37; $p < 0.01$) (Fig. 2B). Of note, in the GRACE registry, only in-hospital ischemic stroke events were evaluated. No risk of publication bias was showed by the Egger's test ($p = 0.15$).

3.5. Subgroup and sensitivity analyses

In a subgroup analysis of patients with STEMI [21,23,27], NOAF was significantly associated with an increased risk of ischemic stroke (RR: 4.01; 95% CI: 2.61–6.18; $p < 0.01$) (Fig. S1A [supplements]). When subgroup analysis was performed with respect to transient NOAF [13,27,28], the RR of ischemic stroke was 3.05 (95% CI: 1.63–5.70; $p < 0.01$) (Fig. S1B [supplements]).

We conducted a sensitivity analysis pooling studies in which all components in the CHA_2DS_2-VASc score had been adjusted [13,21,28,29], the detrimental impact of post-ACS NOAF was still of great significance (RR: 2.32, 95% CI: 1.53–3.52; $p < 0.01$). Details of sensitivity analyses were demonstrated in Fig. S2 (supplements).

4. Discussion

4.1. Main findings

The current meta-analysis demonstrates the mean incidence of ischemic stroke after ACS is 1.6%. NOAF complicating ACS is significantly

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