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RISK OF CEREBRAL MICROBLEEDS AND ICH IN STROKE ISCHEMIC AND TIA PATIENTS ASSOCIATED WITH THE USE OF ANTIPLATELET MEDICATIONS: A SYSTEMATIC REVIEW

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Abstract

Stroke is conventionally described as a neurological dysfunction linked with acute focal central nervous system (CNS) injury resulting from vascular sources. Ischemic stroke is a neurological impairment resulting from arterial blockage. Ischemic strokes are the most prevalent type of stroke. Antiplatelet therapy is essential to the treatment of noncardioembolic ischemic stroke and transient ischemic attack (TIA) in order to alleviate the severity of this burden. The evidence supports aspirin, aspirin-dipyridamole, clopidogrel, and ticagrelor, four antiplatelet medicines. These antiplatelets were selected as the most effective since they have been the subject of decisive clinical trials and are the most frequently referenced in clinical practice guidelines. The low incidence of intracranial hemorrhage (ICH) could be attributed to the fact that the majority of patients took aspirin instead of oral anticoagulants. The incidence of ICH was equivalent to that seen in trials that included antiplatelet drug participants. The study was unable to rule out the potential that the presence of microbleeds in patients on oral anticoagulants suggests an increased risk of ICH. The use of antiplatelet medicines enhanced the risk of strictly lobar MBs and the rate of intracerebral hemorrhage in CMB patients.

Keyword: *Antiplatelet; Cerebral Microbleeds; ICH; Stroke Ischemic; TIA*

INTRODUCTION

In 2019, globally, stroke is the second leading cause of death and the third largest cause of death and disability combined. Platelets are triggered by collagen, ADP, and the thromboxane A2 metabolite of arachnoid acid.[1] Activated platelets cause platelet aggregation and blood clot formation, which results in acute ischemic stroke (AIS) or transient ischaemic attack (TIA).[2] Antiplatelet medicines minimize the risk of AIS or TIA by inhibiting platelet aggregation. Antiplatelet medications such as aspirin, clopidogrel, dipyridamole/aspirin, cilostazol, and ticagrelor are routinely prescribed.[3]

Numerous randomized controlled trials (RCTs), Cochrane systematic reviews, and meta-analyses have assessed the efficacy and safety of antiplatelet treatment for secondary stroke prevention in recent years. Due to the intricacy of the etiology of stroke and the diversity of antiplatelet drugs' actions. In clinical practice, it is crucial to choose the most appropriate antiplatelet therapy. In this review, we sought to emphasize the existing data and recommendations for antiplatelet medication for secondary stroke prevention.[4–8]

The purpose of this paper is to analyze previous research on the risk of cerebral microbleeds and ICH in stroke ischemic and TIA patients associated with the use of antiplatelet medications.

METHODS Protocol

To ensure that this study was carried out in accordance with the standards cited, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 recommendations were followed. These steps were required to ensure that the findings of this study were reliable.

Criteria for Eligibility

By assessing and analyzing the results of earlier research on the topic, the purpose of this review of the literature is to study about risk of cerebral microbleeds and ICH in stroke ischemic and TIA patients associated with the use of antiplatelet medications. The ongoing probe has uncovered a substantial concern about the situation. Participation in research projects requires that they fulfill all of the following criteria: 1) In order for a publication to be taken into consideration for publishing, it must be written in English and the primary focus of the publication must be on the link about risk of cerebral microbleeds and ICH in stroke ischemic and TIA patients associated with the use of antiplatelet medications. 2) The scope of this evaluation was expanded to include articles that were published after 2013 but before the time period that was the focus of this systematic review. Examples include editorials, submissions that do not have a DOI, review articles that have been previously published, and entries that are substantially identical to those that have been previously published in a journal.

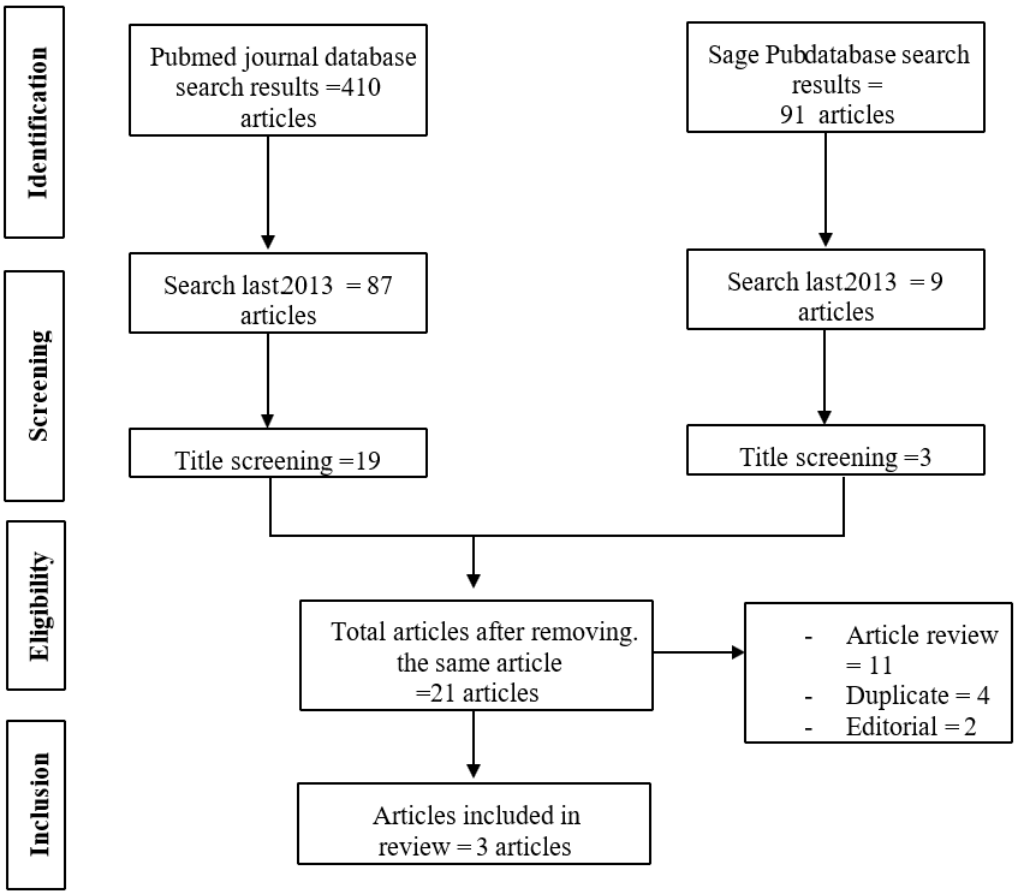

Figure 1. Article search flowchart

Search Strategy

The search for studies to be included in the systematic review was carried out from February, 6th 2023 using the PubMed and SagePub databases by inputting the words: "microbleeds"; "ICH", "stroke ischemic"; "TIA"; and "antiplatelet". *(("microbleed"[All Fields] OR "microbleeds"[All Fields]) AND "ICH"[All Fields] AND ("ischemic stroke"[MeSH Terms] OR ("ischemic"[All Fields] AND "stroke"[All Fields]) OR "ischemic stroke"[All Fields] OR ("stroke"[All Fields] AND "ischemic"[All Fields]) OR "stroke ischemic"[All Fields]) AND "TIA"[All Fields] AND ("antiplatelet"[All Fields] OR "antiplatelets"[All Fields])) AND ((y_10[Filter]) AND (clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter]))* is used as search keywords.

Data retrieval

The author decided to change the inclusion criteria after reviewing the titles and abstracts of previous studies. The details of the revised criteria can be found in the study's additional materials. This clarified the scope of the problem as well as its numerous dimensions, both of which necessitate further investigation. The author arrived at this conclusion after conducting a thorough examination of a number of comparable studies. Only studies that met all of the inclusion criteria were considered for the systematic reviews. This limited the scope of the search to only relevant material.

Our staff rejected those research proposals that did not meet our requirements. This ensured that the research was completed completely. Many pieces of information were discovered during this examination, including names, authors, publication dates, locations, study activities, and parameters. The following is a list of the various product categories available for purchase. It is possible to develop these skills through repeated practice. It's possible that the source of this information will influence how it's displayed.

Quality Assessment and Data Synthesis

Before selecting which studies to investigate further, each author conducted their own analysis of a distinct piece of research offered in the titles and abstracts of the articles. Then, we will read all of the papers that meet the inclusion criteria and are consequently eligible for inclusion in the systematic review. Then, we'll choose which papers to include in the review based on the findings we've identified. These selection criteria were applied to select the pieces of writing that will be evaluated. In order to simplify as much as possible, the approach for selecting papers for review. Which previous investigations have been conducted, and what elements of those research allow for their inclusion in the review?

RESULT

First study showed after being discharged, no patient presented with symptoms of having a brain hemorrhage. Patients who experienced cerebral microbleeds exhibited a greater prevalence of hypertension (92% as opposed to 74%) and suffered from more severe leukoaraiosis (3.0 ± 1.7 vs 1.3 ± 1.4 points on the Fazekas scale). The severity of leukoaraiosis was found to have a correlation (r = 0.42) with the number of cerebral microbleeds.[9]

Table 1. The litelature include in this study.

Author	Origin	Method	Sample Size	Period	Result
Meng, 2020[9]	China	Retrospective cohort study	184 ischemic stroke patients	2015 to 2018	Post-discharge cerebral hemorrhage was absent. Cerebral microbleed patients experienced more severe leukoaraiosis (3.0 ± 1.7 vs 1.3 ± 1.4 points on the Fazekas scale) and hypertension (92% versus 74%). Leukoaraiosis scores linked with cerebral microbleeds (r = 0.42).
Kwa, 2013[10]	Netherland	Prospective cohort study	397 patients with newly diagnosed TIA or minor ischaemic stroke	June 2000 to January 2010	A symptomatic ICH occurred in five patients (1%). One ICH occurred in a patient with baseline microbleeds (adjusted HR [aHR] = 2.6, 95% CI 0.3-27). The incidence of all strokes was higher in patients with microbleeds than in those without (aHR 2.3, 95% CI 1.0-5.3), with a dose-response relationship. In patients with microbleeds, the rates of ischaemic stroke, vascular death, nonvascular death, and death from any cause were higher, but not. statistically significant.
Jung, 2022[11]	public of Korea	Retrospectiv ecohort study	202 patients	January 2011 and December 2020	Compared with patients in the noAPT resumption group, those in the APT resumption group were more likely to have hyperlipidemia (p < 0.001) and a previous ischemic stroke event (p = 0.026). Recurrent ICH and ischemic vascular events occurred in 14 and 15 patients, respectively. Univariate analysis demonstrated that the risk factors for recurrent ICH were older age, renal dysfunction, and no APT resumption; however, only renal. dysfunction significantly increased the risk of re-bleeding in multivariate analysis (HR, 4.631; 95 % CI 1.432–14.977; p = 0.010). Moreover, previous cerebral ischemia and atrial fibrillation were positively associated with ischemic events in univariate analysis; however, only atrial fibrillation. demonstrated a significant correlation in multivariate analysis (HR, 4.309. 95 % CI 1.383–13.426; p = 0.012). APT resumption had a significant prevention effect on recurrent ICH (HR, 0.180; 95 % CI 0.055–0.586; p = 0.004) and ischemic vascular events (HR, 0.240; 95 % CI 0.077–0.750; p = 0.014).

Kwa, et al (2013)[10] study showed one percent patient showed signs and symptoms of having an ICH. At baseline, there was one patient who developed intracerebral hemorrhage (ICH; adjusted HR [aHR]: 2.6; 95% confidence interval [CI]: 0.3-27). With a dose–response relationship, the incidence of all strokes during follow-up was greater in patients who had microbleeds as compared to those who did not have microbleeds (aHR 2.3, 95% CI 1.0-5.3). Although there was a higher incidence of ischemic stroke, vascular death, non-vascular death, and mortality from all causes in individuals with microbleeds, these differences did not reach statistical significance.

Jung, et al (2022)[11] showed patients in the no-APT resumption group, those in the APT resumption group were more likely to have hyperlipidemia ($p < 0.001$) and a previous ischemic stroke event ($p = 0.026$). Recurrent ICH and ischemic vascular events occurred in 14 and 15 patients, respectively. Univariate analysis demonstrated that the risk factors for recurrent ICH were older age, renal dysfunction, and no APT resumption; however, only renal dysfunction significantly increased the risk of re-bleeding in multivariate analysis (HR = 4.631; 95% CI = 1.432–14.977; $p = 0.010$).
Moreover, previous cerebral ischemia and atrial fibrillation were positively associated with ischemic events in univariate analysis; however, only atrial fibrillation demonstrated a significant correlation in multivariate analysis (HR = 4.309; 95% CI = 1.383-13.426; $p = 0.012$). APT resumption had a significant prevention effect on recurrent ICH (HR = 0.180; 95% CI = 0.055–0.586; $p = 0.004$) and ischemic vascular events (HR
= 0.240; 95% CI = 0.077–0.750; $p = 0.014$).[11]

DISCUSSION

Stroke is classically defined as a condition in which a person has a neurological deficit that is associated with acute focal central nervous system (CNS) injury by vascular causes. Ischemic stroke is a neurological deficit caused by arterial occlusion. Ischemic strokes make up the majority of stroke cases.[12] In every region of the world, stroke is the top cause of death and disability. Initial manifestations of acute cerebral ischemia, such as ischemic stroke and transient ischemic attack (TIA), are frequently followed by recurrent vascular events, including recurrent stroke. This is because TIA and ischemic stroke are both forms of the same condition: acute cerebral ischemia.[13,14.]

Ischemic stroke patients lose approximately 190,0000 brain cells every minute, of which 14,000,000,000 nerve connections are damaged every minute and 12 km (7.5 miles) of nerve pathways are lost every minute. The 3.6-year-old brain is deprived of blood supply for every hour. There are two treatment modalities available for the treatment of acute ischemic stroke. Intravenous thrombolysis and mechanical thrombectomy. The management after a clinical diagnosis of acute stroke is made, including stabilizing the patient, evaluating the causes of reversible neurological symptoms, determining the nature of the stroke (ischemic or hemorrhagic), and stroke treatment.[15]

Antiplatelet therapy is a crucial component in the treatment of noncardioembolic ischemic stroke and TIA in order to lessen the severity of this burden. The evidence for these four antiplatelet medications, aspirin, aspirin-dipyridamole, clopidogrel, and ticagrelor. These were chosen as the most effective antiplatelets because they have been the focus of conclusive clinical trials and are the ones that are most frequently referenced in clinical practice guidelines.[13,14] In patients who had mild-to-moderate acute noncardioembolic ischemic stroke, dual antiplatelet therapy with aspirin and clopidogrel was related with a lower risk of vascular events at 3 months compared with aspirin alone. This was the case when comparing the two treatments to each other.[16]

Study showed TIA / IS patients with 5 microbleeds on antiplatelet medicines had a 3-fold greater risk of recurrent ischemic stroke and a 13-fold increased risk of ICH compared to patients with no microbleeds. The relative risk of ischemic vs hemorrhagic episodes was time dependent, with a 3-fold excess in risk of recurrent ischemic stroke versus ICH in the first year (9.5% versus 3.7%) and an increasing relative risk of ICH thereafter. In addition, the disability caused by ICH was considerably greater than that caused by recurrent ischemic stroke. Our relative risk estimates for ICH in relation to microbleed burden were comparable to the pooled estimates from prior meta-analyses, however our relative risk estimates for recurrent ischemic stroke were lower.[17]

Antithrombotic medication use is hypothesized to be a predictor of CMBs. Meng et al. (2020)[9] found that antiplatelet medication may be safe for patients with CMB and ischemic stroke. Despite taking antiplatelet medication, patients exhibited a substantial risk of cerebral infarction recurrence in the early phase after stroke. Patients with CMB benefited from dual antiplatelet therapy after endovascular intervention, according to one study.[18] CMB did not raise the incidence of cerebral hemorrhage in ischemic stroke patients receiving antiplatelet medications, according to another study.[10]

Even for people who have more than four CMBs, antiplatelet treatment should be taken for the first year after an ischemic stroke. For those who have CMB or who have had an ischemic stroke, the potential benefits of antiplatelet medicine may be greater than the potential risks. As a consequence of this, the presence of CMB should not influence the decision of whether or not to administer antiplatelet medication when there is insufficient evidence from other sources.[19]

The fact that the majority patients took aspirin rather than oral anticoagulants could be taken as an explanation for the low incidence of ICH. The incidence of ICH was comparable to that which was observed in studies including patients who were on antiplatelet medications. Study unable to rule out the possibility that the existence of microbleeds indicates an increased risk of ICH in the few patients who are using oral anticoagulants. Additional research is currently being conducted using patient cohorts from Europe to investigate the use of anticoagulants in the presence of microbleeds.[10]

The biological rationale for the low incidence of ICH is that the effects of microangiopathy in a white European population are different from those in an Eastern population.[18] This is one explanation for why there are so few cases of ICH. The occurrence of ICH is approximately two times more common in Asian populations than it is in white Westerners.[20] Patients from Asia and the West have very different responses to the same genetic variations when they are exposed to the same

environmental factors. For example, Asian carriers of the APOE genotype ε2 and ε4 have almost twice as large a risk of future ICH compared with European carriers.[21]

An association between the use of antiplatelets and the presence of brain microbleeds (BMBs) was found in a group of ICH patients with an odds ratio of 2.418, but this association was not found in a group of IS patients. This finding supported a recently published systematic review that analyzed data from European cohorts and Asian cohorts. It was found in that review that antiplatelet users had a significantly higher odds of having BMBs associated with ICH than nonusers did (OR 1.7), although an analysis that involved patient classification based on antiplatelet medications was not carried.
out.22,23

In addition, the association was largely driven by the findings of a Japanese cohort, which seemed to strongly support the importance of conducting a detailed analysis of the association between antiplatelet use and BMBs in bleeding-prone ethnic groups in order to determine the safe use of antiplatelet agents. This analysis is necessary in order to determine whether or not antiplatelet agents can be safely used. According to the findings of a meta-analysis, using aspirin significantly raises the risk of developing ICH while simultaneously lowering the risk of developing IS. It is possible that paying special attention to patients with a BMB positive status is required in order to ensure the safe use of aspirin and prevent antiplatelet-associated ICH.[22,23.]

On the other hand, comparable relationships could not be found for the medications clopidogrel, cilostazol, or ticlopidine.[24] ICH risks with the secondary prevention of IS were discovered to be considerably lower in patients receiving cilostazol than in those taking aspirin in the Japanese Cilostazol Stroke Prevention Study 2, and Cilostazol has been licensed as an agent for the prevention of IS in Japan (CSPS2). The results of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial showed no statistical difference for intracranial hemorrhage between the clopidogrel group and the aspirin group.[24–26]

The results of a comparison of patients treated with 75 mg once daily or 50 mg once daily of clopidogrel that was recently performed with a Japanese cohort showed low ICH occurrence rates (0.20% per year) in both groups The presence of BMBs may not be a risk factor for ICH in patients who are only taking one antiplatelet medication, and the results of the aspirin use group may reflect the effects of dual administration rather than the effects of the use of aspirin alone. This is due to the fact that the majority of ICH patients who were receiving dual antiplatelet therapy were also taking aspirin.[22,23.]

It is possible that the sample size was insufficient to verify the clinical issue, and it is also feasible that the results were created by accident. Both of these possibilities are worth considering. In order to verify the correlations, further research with substantial sample sizes is required. The possibility of an association between the use of dual antiplatelet therapy and the occurrence of brain microbleeds was not investigated in this study. This is despite the fact that dual antiplatelet therapy has been linked to an increased risk of ICHs, also known as intracranial hemorrhages.[22,23.]

The rationale for this was because if the groups had been divided according to the combinations of antiplatelet medicines, there would have been an extremely low number of patients in each group, making it impossible to conduct a statistical analysis on the data. Concerns over dual antiplatelet therapy are growing as a direct result of the rise in atherothrombosis, which is caused by the progression of atherosclerosis. In addition, the usage of multiple antiplatelet drugs, as well as treatments that act on both antiplatelets and anticoagulants, is becoming an increasingly concerning trend.[23]

Also noted was a correlation between the duration of aspirin medication (>10 years vs. 10 years) and deep or infratentorial microbleeds, but this result became nonsignificant after adjusting for hypertension and other variables. Aspirin use for >5 years did not increase the risk of CMBs in older patients.[27,28] In addition, a study revealed that bleeding events tend to cluster around therapeutic changes, however the present study did not cover patients who switched therapies. In addition, the present study did not assess aspirin or clopidogrel resistance.[29]

To confirm whether the length of antiplatelet medication impacts the risk of CMBs, additional research is required. Platelet reactivity, pharmacometabolomics, and microRNAs should also be studied as resistance markers.[29] Patients who have suffered an ischemic stroke and have CMB may benefit from antiplatelet medication. Before stopping antiplatelet treatment, it is important to conduct a thorough analysis of the risk-benefit ratio. It is recommended that additional prospective studies be carried out in order to verify these early findings.[30]

CONCLUSION

The use of antiplatelet medications was associated with an elevated risk of strictly lobar MBs and increased the incidence of intracerebral hemorrhage in CMB patients.

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