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# Anticoagulants versus Antiplatelet agents for acute Ischemic Stroke: Systematic Review and Meta-analysis

**Abdulelah Mohammed Alghamdi[1], Bader Mosfer Ali Alshomrani[2], Abeer Mustafa Gusti[3], Abdullah Hommadi[4], Abdulrahman Thabet Mohammad Alawi[5], Ahmed Hassan Alsameti[6], Emad Mohammed Noor Kamreegh[6], Nasser Hamed Alsayali[6], Hashim Kassim Eissa[6], Adnan Hameed Al Harbi[6], Akrm Saad Al Harbi[6], Haitham Mohammed Ahmed Yanbauei[6]**

1. *Pharmacist, Azizia Children's Hospital*
2. *X-ray tecntion, Azizia Children's Hospital*
3. *Pharmacist, Azizia Children's Hospital*
4. *Pharmacy Technician, Azizia Children's Hospital*
5. *Health Administration Senior Specialist, Eradah Complex and Mental Health - Eradah Services*
6. *Health Licensing Management.*

**ABSTRACT**
**Background:** Acute ischemic stroke is a primary etiology of mortality and morbidity globally, and prompt treatment with antiplatelet or anticoagulants medications is essential for enhancing results.
**Aim:** This meta-analysis aimed to evaluate the safety & efficacy of anticoagulants compared to antiplatelet medicines in the managing of acute ischemic stroke.
**Methods:** A search of PubMed, Embase, Cochrane Library, and Google Scholar identified studies with key words as: Anticoagulants, acute ischemic stroke, Antiplatelet agents, venous thromboembolism and recurrent ischemic stroke. Additional searches were done on ClinicalTrials.gov and relevant references were reviewed.
**Results:** The meta-analysis, including three research with a total of 6,242 participants, found insignificant differences between anticoagulants and antiplatelet agents in preventing venous thromboembolism (RR 0.58, ninety-five percent confidence interval 0.05–6.95, p = 0.6), hypertension (RR 0.98, ninety-five percent confidence interval 0.88–1.09, p = 0.7), or recurrent ischemic stroke within fourteen days (RR 1.1, ninety-five percent confidence interval 0.69–1.75, p = 0.6). Mortality rates were comparable (RR 1.19, ninety-five percent confidence interval 0.76–1.86, p = 0.4), as was long-term death or dependency (RR 1.02, ninety-five percent confidence interval 0.98–1.06, p = 0.3). Subgroup analysis suggested that the combination of small-dose unfractionated heparin and aspirin may provide net advantages compared to aspirin only.
**Conclusion:** The meta-analysis study found no clear advantage among antiplatelet and anticoagulants agents in preventing venous thromboembolism, hypertension, frequent ischemic stroke, mortality, or long-term death in acute ischemic stroke cases.
**Keywords:** Anticoagulants, Antiplatelet agents, acute ischemic stroke, venous thromboembolism and recurrent ischemic stroke.

## Introduction:

Acute stroke is the sudden emergence of focal neurological impairments within a vascular region impacting the retina, spinal cord, or brain, because of causal cerebrovascular disorders **(1)**. Stroke is common throughout populations as well as can significantly lead to mortality and morbidity. Strokes are classified into hemorrhagic as well as ischemic types **(2)**.
The cause of ischemic stroke involves a embolic or thrombotic event that obstructs blood flow to a specific brain region. A thrombotic event occurs when the flow of blood to brain is hindered by a thrombus (clot) within the blood vessel, typically resulting from arterial dissection, atherosclerotic disease, inflammatory disorders, or fibromuscular dysplasia. An

embolic event occurs when debris from another part of the body obstructs the flow of blood in the affected vessel **(3, 4)**.

Emboli may originate from the proximal artery, like an atherosclerotic plaque in the internal carotid artery, resulting in a distal artery-to-artery embolic stroke, frequently stemming from heart. Sometimes, the origin could be from the right side of circulation, traversing a right-to-left shunt, like a patent foramen ovale, into the cerebral artery system. The cause of stroke influences both consequences and prognosis **(5)**.

Prompt antithrombotic intervention using antiplatelet or anticoagulant medications might diminish the extent of infarcted cerebral tissue, therefore lowering the possibility of neurological impairments, disability, or mortality. Moreover, it could decrease the incidence of early venous thromboembolism and repeated ischemic stroke. Nonetheless, antithrombotic medicines may elevate the risk of cerebral or extracranial hemorrhage, thereby offsetting any advantages **(6)**.

This meta-analysis and systematic review aimed to compare the efficacy and safety of anticoagulants versus antiplatelet agents in the controlling of acute ischemic stroke. By addressing critical outcomes and evaluating statistical heterogeneity, this study seeks to provide evidence-based guidance for clinical decision-making in controlling of acute stroke.

**Patients and methods:**

**Search strategy:** The authors performed a thorough search across various databases to uncover research comparing antiplatelet and anticoagulants medications in cases that had acute ischemic stroke. The search initially yielded 319 articles, and after removing duplicates, 120 articles remained. Full-text screening led to the inclusion of three studies in the final meta-analysis.

**Inclusion criteria:** (1): Randomized controlled trials (RCTs) comparing anticoagulants (e.g., low molecular weight heparin [LMWH], unfractionated heparin [UFH]) with antiplatelet agents (e.g., aspirin) in cases diagnosed with acute ischemic stroke. (2): Adult patients (>18 years old) are diagnosed with acute ischemic stroke, involving both transient ischemic attack (TIA) and ischemic stroke cases. (3): Research that evaluated the use of anticoagulants (LMWH, UFH) or antiplatelet agents (aspirin) either as monotherapy or in combination therapies. (4):Trials that reported outcomes including venous thromboembolism, hypertension, recurrent ischemic stroke (within 14 days), mortality (from ischemic stroke), and long-term death or dependency.

**Exclusion criteria:** (1): studies focusing on pediatric populations, patients with conditions other than acute ischemic stroke (e.g., hemorrhagic stroke, trauma), or those with severe comorbidities that may confound the treatment effects. (2): studies that evaluated treatments not related to anticoagulants or antiplatelet agents, such as thrombolytic therapy or alternative medical therapies. (3): trials that did not report on the specified outcomes (venous thromboembolism, hypertension, recurrent ischemic stroke, mortality, or long-term death/dependency).

**Data Extraction and Analysis:** Data on baseline characteristics, outcomes, and risk of bias were extracted from the research involved. Statistical analysis included estimating relative risks (RR) with ninety five percent confidence intervals for various outcomes, such as venous thromboembolism, hypertension, recurrent ischemic stroke, mortality, and long-term death or dependency.

**Risk of Bias Evaluation:** The risk of bias in the research involved has been evaluated utilizing the ROB1 tool, which evaluates biases across various domains (such as performance bias, selection bias, detection bias, etc.).

**Results:**

**Figure 1** represents PRISMA flow chart for research selection process.

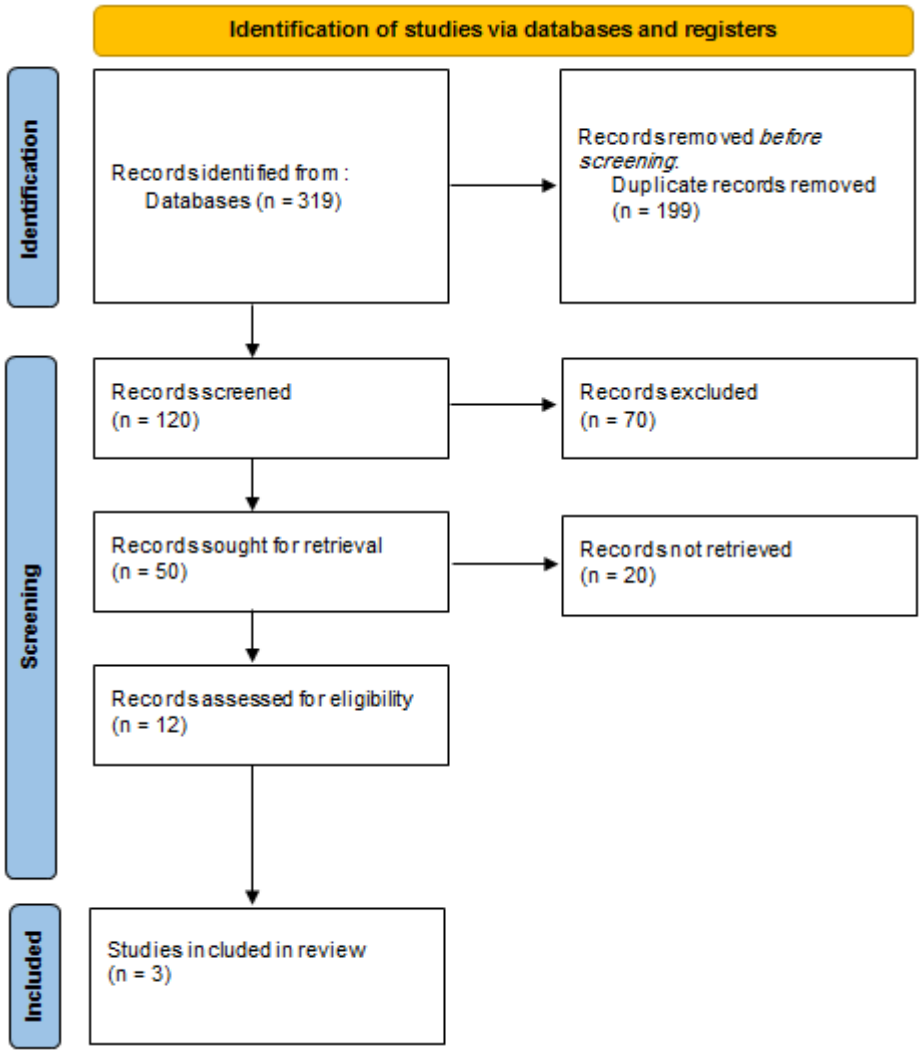


**Figure 1:** PRISMA flow diagram.

## 2. baseline characteristics of included population:

Our meta-analysis and systematic review involved 3 research totaling 3,118 cases and 3,124 controls with mean age >18 years old detailed description of baseline characteristics for our included population is represented in Table 1.

| Study ID | Intervention | sample size | Age | Male or Female | Smoking | Stroke or TIA |
|---|---|---|---|---|---|---|
| Berge2000 | LMWH (Dalteparin) | 224 | 80 (55–96) | 111F (50%) | 46 (21%) | 51 (23%) |
| | Aspirin | 225 | 80 (44–98 | 137F (61%) | 36 (16%) | 57 (25% |
| IST 1997 | UFH | 2407 | >18 | NR | NR | NR |
| | Aspirin | 2408 | >18 | NR | NR | NR |
| Bath 2001 | LMWH (Tinzaparin) | 487 | 74 | 260 M | 120 | 79 |
| | Aspirin | 491 | 74 | 265 M | 124 | 79 |

LMWH: low molecular weight heparin.
UFH: unfractionated heparin.
**Table 1:** baseline features of study population.

## 3. Risk of bias assessment:

Our included three trials were assessed using ROB1 tool our studies showed low risk regarding all domains and unclear risk regarding attrition bias and unclear. Figure 2 and Table 2 represents the risk of bias graph and summary.

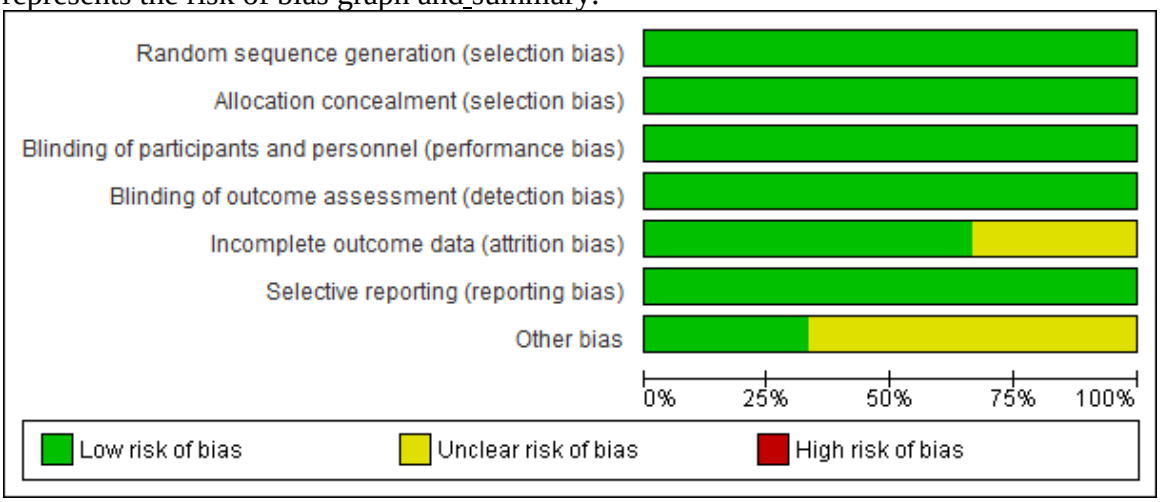


**Figure 2:** Risk of bias graph.


**Table 2**: Risk of bias summary.

**4. Outcomes:**

*Venous Thromboembolism*:

Regarding Venous Thromboembolism there was insignificant variance among cases who had anticoagulants and patients who had antiplatelet with RR and 95% CI ;0.58 [0.05, 6.95], p-value 0.6 major heterogeneity was detected among our pooled studies so we applied random effect model in our analysis yielding chi-p 0.004 and $I^2$ 88%. Figure 3: illustrations forest plot for this comparison.

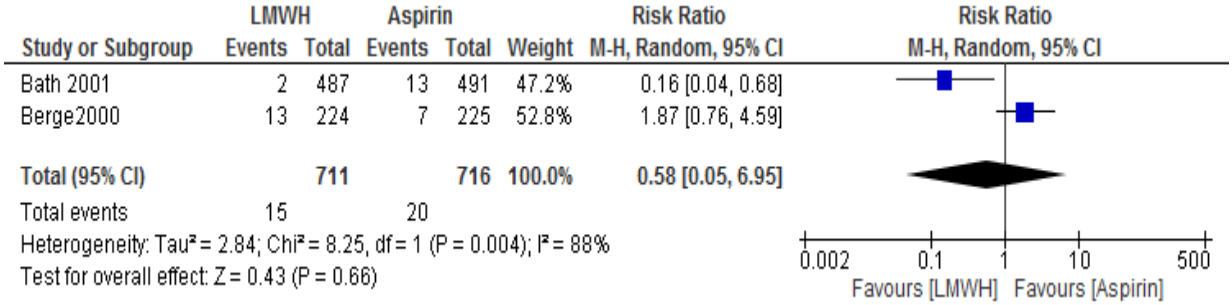


**Figure 3**: forest plot for Venous Thromboembolism.

*Hypertension*:

Regarding Hypertension there was insignificant variance among cases who had anticoagulants and patients who had antiplatelet with RR and ninety-five percent confidence interval;0.98 [0.88, 1.09] p-value 0.7, no heterogeneity was detected among our pooled studies with chi-p 0.7, $I^2$ 0%. Figure 4: shows forest plot for this comparison.

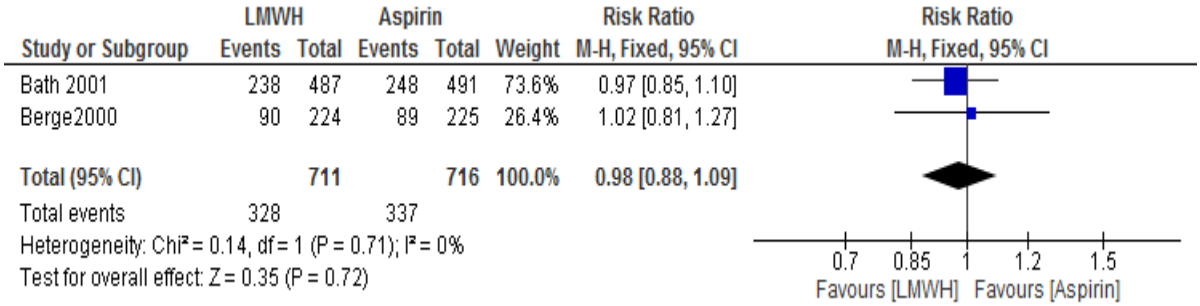


**Figure 4**: forest plot for Hypertension.

*Frequency of recurrent Ischemic stroke during 14 days*:
The major objective was to evaluate whether therapy with low molecular weight heparin is superior than aspirin in preventing recurrent stroke throughout the initial 14 days. Our pooled meta-analysis indicated there was insignificant distinction among the two, with a relative risk and ninety-five percent confidence interval; 1.1 [0.69, 1.75], p-value 0.6. Our aggregated research for this outcome exhibited homogeneity, with a chi-squared p-value of 0.9 and an $I^2$ of zero percent. Figure 5: illustrates the forest plot depicting the frequency of recurrent ischemic strokes over a period of fourteen days.

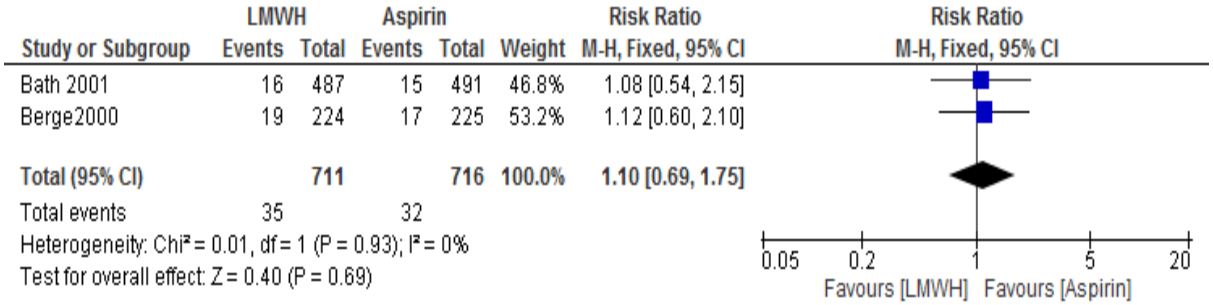


**Figure 5**: Frequency of recurrent Ischemic stroke for fourteen days.

*Death:*

Medication with Low molecular weight heparins, is not superior than aspirin for the prevention of death, our pooled meta-analysis showed RR and ninety-five percent confidence interval; 1.19 [0.76, 1.86], p-value 0.4 . our pooled studies for this outcome were homogenous with chi-p 0.6, $I^2$ 0%. Figure 6: shows forest plot for death from ischemic stroke.


**Figure 6**: shows forest plot for death from Ischemic stroke.

*Death or dependency at long term:*

Our pooled meta-analysis exhibited that insignificant distinction among Aspirin and Heparin regarding Death or dependency at long term with RR and ninety five percent confidence interval; 1.02 [0.98, 1.06], p-value 0.3. Our pooled studies for this outcome were

homogenous so fixed effect model was applied with chi-p 0.6, $I^2$ 0%. Figure 7: shows forest plot for dependency or death at long term.

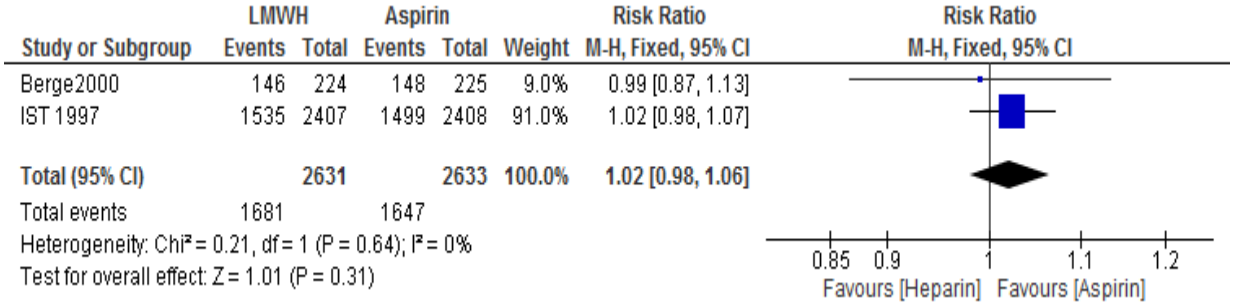


**Figure 7**: shows forest plot for Death or dependency at long term.

**Discussion:**

Thrombosis significantly contributes to the pathophysiology of ischemic stroke; therefore, platelet anti-aggregants and anticoagulants, which interrupt formation of clots and hemostasis, are frequently utilized in the treatment of cerebrovascular disorders **(7,8)**.

This meta-analysis assessed the safety and efficiency of anticoagulants versus antiplatelet medicines in cases that had acute ischemic stroke. A statistically insignificant variations have been found in the prevention of venous thromboembolism (relative risk 0.58, ninety-five percent confidence interval 0.05–6.95, p-value equal 0.6), hypertension (relative risk 0.98, ninety-five percent confidence interval 0.88–1.09, p-value equal 0.7), or recurrent ischemic stroke within 14 days (relative risk 1.1, ninety-five percent confidence interval 0.69–1.75, p-value equal 0.6) across the included studies **(9-11)**. The rates of death were similar in both groups (relative risk 1.19, ninety-five percent confidence interval 0.76–1.86, p-value equal 0.4, $I^2 = 0\%$). Ultimately, long-term mortality or reliance exhibited insignificant difference (relative risk 1.02, ninety-five percent confidence interval 0.98–1.06, $p = 0.3$, $I^2 = 0\%$).

These results were identical with those of **Berge E et al. (12)**, who evaluated the efficacy of anticoagulants relative to antiplatelet drugs in acute ischemic stroke and investigated whether incorporation of anticoagulants with antiplatelet medicine provides any net benefit compared with antiplatelet drugs only. Research indicated that anticoagulants provided no overall benefits compared to antiplatelet medicines in cases of acute ischemic stroke. A subgroup analysis indicated that the combination of small-dose unfractionated heparin (UFH) with aspirin could provide net benefits compared to aspirin only underscoring the need for additional research of specific case subgroups and combination therapy.

Additionally, our findings have been corroborated by **Coull BM et al. (13)**, who investigated the impact of antiplatelet and anticoagulants agents on morbidity, death and rates of recurrence in acute ischemic stroke, along with the correlated advantages and risks of these therapies concerning deep vein thrombosis, pulmonary embolism, and cardiovascular complications. The marginal, advantageous impact of aspirin in acute ischemic stroke seems unaffected by the subtype of the stroke. No compelling data exists to support the efficiency of anticoagulants for any specific subtype of stroke.

In a previous investigation conducted by **Wang X et al. (14)**, the efficacy and safety of early anticoagulation (administered during the initial fourteen-day period of onset) for cases with acute probable or confirmed ischemic stroke were evaluated. They established that anticoagulant therapy diminished the incidence of recurrent stroke, deep vein thrombosis, & pulmonary embolism, while elevating the risk of hemorrhage.

Furthermore, **Kamarova M et al. (15)** indicated that antiplatelet medications are among the most effective and thoroughly investigated secondary preventative strategies for stroke management.

According to a combined analysis of existing research by **Chen Z et al. (13)**, aspirin (160 or 325 milligrams daily) yields a small although statistically significant decrease in mortality and disability when administered within forty-eight hours following an ischemic stroke. Furthermore, UFH, Abciximab, heparinoids, and LMWH haven't demonstrated a reduction in death or stroke-related morbidity when administered within forty-eight hours of onset in cases had acute ischemic stroke. Abciximab, LMWH, unfractionated heparin, and heparinoids haven't demonstrated a reduction in mortality or stroke-correlated morbidity when administered within forty-eight hours of onset in cases having acute ischemic stroke **(13)**.

**Conclusion:**

This meta-analysis suggests that there are insignificant variances among anticoagulants and antiplatelet agents in the stoppage of venous thromboembolism, hypertension, recurrent ischemic stroke, mortality, or long-term death or dependency in cases with acute ischemic stroke.

Despite the low risk of bias and rigorous statistical analysis, the restricted number of involved studies and the heterogeneity observed in some outcomes suggest that further high-quality research with larger sample sizes is required to draw definitive conclusions. Clinicians should consider individual patient characteristics and risks when choosing between anticoagulant and antiplatelet therapy in acute ischemic stroke management.

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