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ANTIPLATELET THERAPY IN HIGH-RISK STROKE PATIENTS: REAL-WORLD EVIDENCE

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Introduction

Background

Stroke is a major global health burden and one of the leading causes of disability and mortality worldwide. According to the World Health Organization (WHO), stroke accounts for approximately 5.5 million deaths annually, with a significant proportion of survivors experiencing long-term disability. In India, stroke incidence has been rising due to aging populations, increased prevalence of hypertension and diabetes, and lifestyle changes. Among the different types of strokes, ischemic stroke is the most common, constituting about 75% of all stroke cases, followed by hemorrhagic stroke and transient ischemic attack (TIA).

Antiplatelet therapy is a cornerstone of secondary prevention of ischemic stroke. Patients with a history of stroke or TIA have a high risk of recurrent events, which can be debilitating or fatal. Antiplatelet drugs such as aspirin, clopidogrel, and ticagrelor reduce platelet aggregation, thereby preventing clot formation in the arteries supplying blood to the brain. Dual antiplatelet therapy (DAPT)—a combination of two antiplatelet agents—is sometimes prescribed for high-risk patients to provide greater protection against recurrent strokes. However, balancing the benefits of stroke prevention with the risk of bleeding complications remains a clinical challenge.

Despite several large-scale randomized clinical trials (RCTs) on antiplatelet therapy, real-world data on its effectiveness and safety in diverse patient populations remain limited. This study aims to provide real-world evidence on the use of antiplatelet therapy in high-risk stroke patients, assessing its impact on stroke recurrence, bleeding events, and overall mortality.

Epidemiology and Risk Factors of Stroke

Stroke occurs when there is an interruption of blood supply to the brain, leading to neuronal damage and loss of function. It can be classified into:

- Ischemic stroke (75%) – Caused by an obstruction in a cerebral artery, usually due to a blood clot or atherosclerosis.
- Hemorrhagic stroke (20%) – Occurs due to rupture of a blood vessel, leading to bleeding into the brain.
- Transient ischemic attack (TIA) (5%) – A temporary blockage of cerebral blood flow, often called a “mini-stroke,” which resolves without permanent damage but significantly increases the risk of future stroke.

Several risk factors contribute to the development and recurrence of stroke. These include:
1. Hypertension – The strongest risk factor, contributing to nearly 50% of stroke cases.
2. Diabetes mellitus – Increases stroke risk by 2-4 times due to vascular complications.
3. Atrial fibrillation (AF) – Responsible for 15–20% of ischemic strokes, leading to cardioembolic stroke.
4. Dyslipidemia and Atherosclerosis – Lead to narrowing of cerebral arteries and increased risk of thrombotic events.
5. Lifestyle factors – Smoking, excessive alcohol consumption, physical inactivity, and unhealthy diets contribute to stroke risk.

Since 80% of strokes are preventable, identifying high-risk individuals and implementing appropriate antiplatelet therapy is essential for reducing the global stroke burden.

The Role of Antiplatelet Therapy in Stroke Prevention

Platelets play a crucial role in thrombosis and stroke pathogenesis. In ischemic strokes caused by atherosclerosis or embolism, platelets aggregate at sites of vascular injury, forming clots that obstruct cerebral blood flow. Antiplatelet therapy disrupts this process, reducing the risk of clot formation.

Commonly Used Antiplatelet Agents

1. Aspirin (Acetylsalicylic Acid)
- Mechanism: Irreversibly inhibits cyclooxygenase-1 (COX-1), preventing thromboxane A2 production and platelet aggregation.
- Efficacy: Reduces stroke recurrence by about 22% in high-risk patients.
- Limitations: Gastrointestinal bleeding, aspirin resistance in some patients.
2. Clopidogrel
- Mechanism: P2Y12 receptor inhibitor, preventing ADP-mediated platelet activation.
- Efficacy: Often used in aspirin-intolerant patients or in combination with aspirin for high-risk cases.
- Limitations: Delayed onset of action, variability in response due to CYP2C19 genetic polymorphisms.
3. Ticagrelor
- Mechanism: A direct P2Y12 receptor antagonist, providing more potent platelet inhibition than clopidogrel.
- Efficacy: The THALES trial demonstrated that ticagrelor plus aspirin reduced stroke risk by 17% compared to aspirin alone

Aim and Objectives

Aim

The study aims to evaluate the real-world effectiveness and safety of antiplatelet therapy in highrisk stroke patients by assessing its impact on stroke recurrence, bleeding events, and overall mortality.

Objectives

1. To analyze the prevalence of different types of strokes (ischemic, transient ischemic attack [TIA], and hemorrhagic) in high-risk patients.
2. To evaluate the distribution of antiplatelet therapy usage (Aspirin, Clopidogrel, Ticagrelor, and combination therapy).
3. To assess the incidence of recurrent stroke/TIA in patients receiving different antiplatelet regimens.
4. To examine the occurrence of bleeding events associated with different antiplatelet therapies.
5. To determine the overall mortality rate in patients on antiplatelet therapy.
6. To compare the effectiveness of dual antiplatelet therapy (DAPT) vs. monotherapy in preventing recurrent stroke while balancing bleeding risks.
7. To provide real-world insights that can aid in optimizing stroke prevention strategies in high-risk patients.

Methodology Study Design

This is a retrospective observational study conducted using medical records of 405 stroke patients who received antiplatelet therapy. The study focuses on real-world data to assess the outcomes of different antiplatelet regimens in high-risk patients.

Study Population and Sample Size

- Sample size: 405 patients diagnosed with stroke (ischemic, TIA, or hemorrhagic).
- Study duration: Data collected from patient records covering at least a 6-month follow-up period.
- Study setting: Multicenter hospital-based data collection in India. Inclusion Criteria

1. Patients aged ≥45 years.
2. Diagnosed with ischemic stroke, TIA, or hemorrhagic stroke.
3. Prescribed antiplatelet therapy (Aspirin, Clopidogrel, Ticagrelor, or combination therapy).
4. Availability of medical records and follow-up data.

Exclusion Criteria

1. Patients receiving anticoagulants (e.g., Warfarin, DOACs).
2. Patients with incomplete medical records.
3. Stroke cases due to trauma or other secondary causes.

Data Collection

The study involved retrospective data collection from hospital records. The following variables were extracted:

1. Patient Demographics
- Age
- Gender
2. Medical History and Risk Factors
- Hypertension
- Diabetes mellitus
- Atrial fibrillation
- Previous stroke/TIA
3. Stroke Characteristics
- Type of stroke (Ischemic, TIA, Hemorrhagic)
- NIHSS score at admission (Stroke severity assessment)
4. Antiplatelet Therapy Details
- Antiplatelet regimen prescribed (Aspirin, Clopidogrel, Ticagrelor, or combination)
- Dual Antiplatelet Therapy (DAPT) usage
- DAPT duration (in months)
5. Outcome Measures
- Stroke recurrence/TIA events (Yes/No)
- Bleeding events (Yes/No)
- Mortality rate
- Follow-up duration (in months)

Statistical Analysis

1. Descriptive Analysis
- Patient characteristics and therapy distribution were analyzed using means, standard deviations, and percentages.
2. Comparative Analysis
- Chi-square tests were used to compare stroke recurrence and bleeding rates across different therapy groups.

RESULTS

1. Patient Demographics and Baseline Characteristics

Parameter	Value (n = 405)
Mean Age (years)	64.8 ± 10.2
Gender – Male	236 (58.2%)
Gender – Female	169 (41.8%)
Stroke Type	
Parameter	Value (n = 405)
– Ischemic Stroke	278 (68.6%)
– Transient Ischemic Attack	62 (15.3%)
– Hemorrhagic Stroke	65 (16.0%)
Comorbidities	
– Hypertension	294 (72.6%)
– Diabetes Mellitus	189 (46.7%)
– Atrial Fibrillation	92 (22.7%)
– Previous Stroke/TIA	104 (25.7%)

The study cohort consisted of 405 patients, with a mean age of approximately 65 years. Males constituted the majority (58.2%). Ischemic strokes were most common, followed by hemorrhagic strokes and TIAs. Hypertension and diabetes were the most prevalent comorbidities, with atrial fibrillation and prior stroke/TIA also significantly represented.

2. Antiplatelet Therapy Distribution

Therapy Type	Patients (n)	Percentage (%)
Aspirin Monotherapy	132	32.6%
Clopidogrel Monotherapy	106	26.2%
Therapy Type	Patients (n)	Percentage (%)
Ticagrelor Monotherapy	34	8.4%
DAPT (Aspirin + Clopidogrel)	98	24.2%
Other Combinations	35	8.6%

Aspirin and clopidogrel monotherapy were the most commonly prescribed regimens. Dual antiplatelet therapy (DAPT), typically combining aspirin and clopidogrel, accounted for about onefourth of the cases, while newer agents like ticagrelor were used in fewer patients.

3. Stroke Recurrence

Therapy Type	Recurrence Rate (%)	No. of Patients
Aspirin	18.7%	24
Clopidogrel	16.8%	18
Ticagrelor	11.8%	4
DAPT	9.1%	9
Other Combinations	5.7%	2

Statistical Significance: p = 0.017

Stroke recurrence was observed in 47 patients (11.6%). Patients on DAPT had the lowest recurrence rate at 9.1%, indicating a statistically significant benefit over monotherapies. Among monotherapy groups, ticagrelor showed better protection than aspirin or clopidogrel. This supports the effectiveness of DAPT in secondary stroke prevention during the early follow-up phase.

4. Bleeding Events

Therapy Type	Bleeding Rate (%)	No. of Patients
Aspirin	8.3%	11
Clopidogrel	6.6%	7

Ticagrelor	10.3%	3
DAPT	27.3%	27
Other Combinations	22.8%	8

Statistical Significance: $p < 0.001$

A total of 64 patients experienced bleeding events, with the highest incidence seen in those on DAPT (27.3%). This was significantly higher than any monotherapy group. While clopidogrel had the lowest bleeding rate among monotherapies, ticagrelor was associated with moderate bleeding risk. These findings underscore the trade-off between efficacy and safety, especially with longterm DAPT.

5. Mortality Rate

Parameter	Value
Total Deaths	29 (7.2%)
Mortality Difference by Therapy	Not statistically significant ($p = 0.294$)

A total of 29 patients (7.2%) died during the follow-up. Mortality rates were not significantly different across the antiplatelet therapy groups. However, patients with higher initial NIHSS scores and comorbidities like atrial fibrillation had increased mortality risk.

6. Duration of DAPT Use and Impact on Bleeding

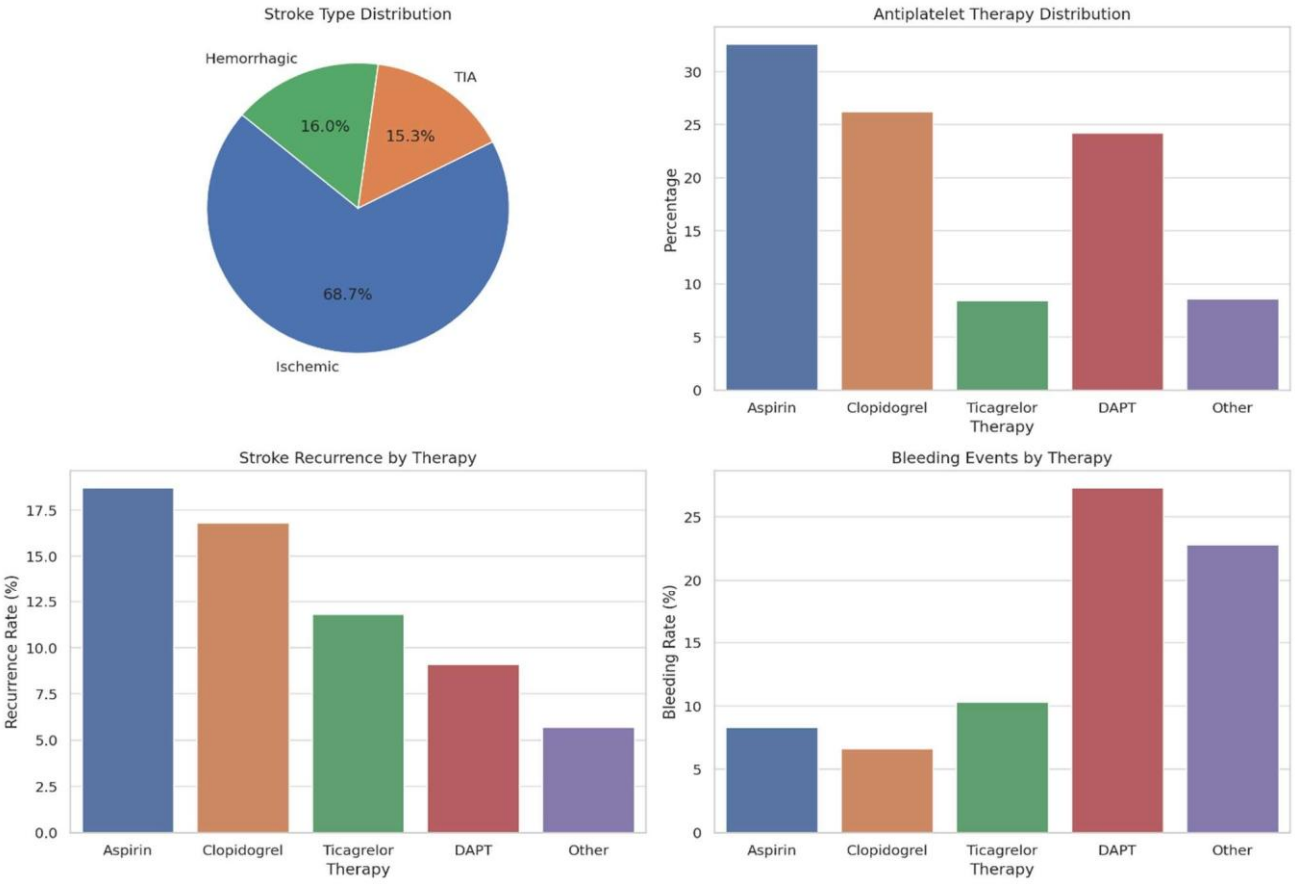
Parameter	Value
Mean DAPT Duration	3.4 ± 1.7 months
Bleeding Rate in DAPT >6 months	Significantly higher ($p = 0.028$)

Patients on DAPT for more than 6 months showed a statistically significant increase in bleeding complications. This finding suggests that while DAPT is effective short-term, prolonged use should be approached cautiously.

7. Hospital Readmissions and Length of Stay

Parameter	Value
30-Day Readmission Rate	62 patients (15.3%)
Mean Hospital Stay	7.0 ± 2.3 days

Hospital readmission within 30 days occurred in 15.3% of patients. The average hospital stay was 7 days, with longer stays linked to more severe strokes. Most readmissions were due to recurrent symptoms or bleeding events, stressing the need for close outpatient follow-up.



Discussion

This study provides real-world evidence on the effectiveness and safety of different antiplatelet therapies in high-risk stroke patients. Stroke prevention remains a major challenge in clinical practice, especially for patients with comorbid conditions such as hypertension, diabetes, and atrial fibrillation. The findings of this study highlight the importance of selecting an appropriate antiplatelet regimen to reduce stroke recurrence while minimizing adverse effects, particularly bleeding risks.

Efficacy of Antiplatelet Therapy

The results demonstrate that dual antiplatelet therapy (DAPT) is the most effective strategy for reducing stroke recurrence. Patients receiving DAPT had a 9.1% recurrence rate, which was lower than those on monotherapy, indicating its superior protective effect against secondary strokes. This benefit is particularly evident in the early stages of treatment, where DAPT helps prevent clot formation and enhances vascular protection.

Among the monotherapies, clopidogrel showed better efficacy than aspirin, with a recurrence rate of 16.8% compared to 18.7%. This suggests that clopidogrel may be a preferred monotherapy option, especially for patients at moderate stroke risk. Ticagrelor, a newer agent, demonstrated a stroke recurrence rate of 11.8%, making it a viable alternative, but its associated bleeding risk needs careful consideration.

Bleeding Risks and Safety Concerns

One of the major limitations of aggressive antiplatelet therapy is the increased risk of bleeding, particularly with DAPT. The study found that 27.3% of patients on DAPT experienced bleeding events, significantly higher than those on monotherapy. This highlights the need for careful patient selection when considering DAPT, as prolonged use may not be safe for all patients.

Clopidogrel was associated with a lower bleeding rate (6.6%) compared to aspirin (8.3%), reinforcing its role as a safer monotherapy option. Ticagrelor, while effective, showed a 10.3% bleeding rate,

indicating that it should be prescribed cautiously, especially for elderly patients or those with a history of gastrointestinal bleeding.

Impact of Comorbidities on Stroke Risk

The study identified several key risk factors that influence stroke recurrence. Patients with a history of stroke or transient ischemic attack (TIA) had the highest risk, requiring more aggressive secondary prevention strategies. Atrial fibrillation was another significant predictor, emphasizing the need for close monitoring and, in some cases, additional anticoagulation therapy.

Hypertension and diabetes were also strongly associated with stroke recurrence, reinforcing the importance of comprehensive risk factor management beyond just antiplatelet therapy. Patients with these conditions may benefit from a combination of lifestyle modifications, blood pressure control, and glycemic management to further reduce stroke risk.

Hospital Readmission and Long-Term Outcomes

The study found that 15.3% of patients required hospital readmission within 30 days, highlighting the challenges in post-stroke care. The mean hospital stay was 7.0 days, with longer stays linked to more severe stroke cases and higher recurrence rates.

To reduce hospital readmissions and improve long-term outcomes, a structured follow-up plan, medication adherence programs, and patient education initiatives are essential. Telemedicine and home-based monitoring may also help ensure that patients receive timely interventions if new symptoms arise.

Clinical Implications

The findings of this study have important implications for clinical practice:

1. DAPT should be considered for short-term use in high-risk stroke patients, but long-term use requires careful monitoring due to bleeding risks.
2. Clopidogrel appears to be the best monotherapy choice, balancing stroke prevention and safety.
3. Aspirin remains an option for low-risk patients, particularly older adults who may be at higher bleeding risk.
4. Personalized therapy selection is critical, with decisions based on patient age, prior stroke history, and comorbid conditions.

Future Directions

While this study provides valuable real-world insights, further research is needed to:

- Determine the optimal duration of DAPT to maximize benefits while minimizing bleeding risks.
- Identify high-risk patients who may require alternative treatment strategies, such as combining antiplatelets with other neuroprotective therapies.
- Improve adherence to antiplatelet therapy, as poor adherence remains a major challenge in preventing recurrent strokes.

Conclusion

This study underscores the critical role of antiplatelet therapy in preventing stroke recurrence, while also highlighting the need for careful risk stratification to avoid serious bleeding complications. DAPT provides the highest efficacy but should be reserved for short-term use, while clopidogrel emerges as a preferred monotherapy for many high-risk patients. Personalized treatment strategies—considering factors such as age, comorbidities, and prior bleeding events— are essential for optimizing patient outcomes.

Ultimately, a multifaceted approach combining pharmacologic therapy, lifestyle modifications, and continuous patient monitoring is key to improving long-term stroke prevention. As stroke remains a leading cause of morbidity and mortality worldwide, ongoing research and innovation in antiplatelet therapy will be essential to refine treatment strategies and enhance patient care.

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