JHWCR
Journal of Health, Wellness, and Community Research
Volume III, Issue V
Open Access, Double Blind Peer Reviewed.
Web: https://jhwcr.com, **ISSN**: 3007-0570
https://doi.org/10.61919/2z8zk025

Article

Single vs Double Antiplatelet Therapy for Recurrent Ischemic Stroke Prevention

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Cite this Article

Received	2025-04-21
Revised	2025-05-19
Accepted	2025-05-22
Published	2025-05-24
Conflict of Interest	None declared
Ethical Approval	The study was approved by the institutional review board of Social Security Hospital, Faisalabad
Informed Consent	Obtained from all participants
Data/supplements	Available on request.
Funding	None
Authors' Contributions	MN, SG, FQ, AR, SB, and JS contributed to concept, design, data collection, analysis, and manuscript drafting.

ABSTRACT

Background: Ischemic stroke remains a leading cause of mortality and long-term disability, with recurrent events contributing significantly to the global disease burden. While single antiplatelet therapy (SAPT) is standard for secondary prevention, the clinical benefit and safety of dual antiplatelet therapy (DAPT) in diverse populations remain underexplored. **Objective**: This study aimed to compare the efficacy and safety of single versus dual antiplatelet therapy in preventing recurrent ischemic stroke, focusing on reduction in recurrent stroke rates and major adverse events among high-risk patients. **Methods**: In this single-center, parallel-group randomized controlled trial, 100 patients with confirmed ischemic stroke were enrolled and randomized equally to SAPT (aspirin) or DAPT (aspirin plus clopidogrel). Patients aged 40–70 years with recent ischemic stroke were included, while those with contraindications to antiplatelet agents, bleeding disorders, or significant comorbidities were excluded. Data were collected using standardized case forms; primary outcome was recurrent stroke within three months, and secondary outcomes included major bleeding and mortality. The study protocol received ethical approval according to the Declaration of Helsinki. Statistical analysis was performed using SPSS version 25, with chi-square tests and logistic regression applied as appropriate. **Results**: Of 100 randomized patients, 96 completed follow-up (SAPT: n=48, DAPT: n=48). Recurrent ischemic stroke occurred in 22.9% of SAPT and 10.4% of DAPT patients (relative risk 0.46; 95% CI 0.16–1.14; p=0.099), while major bleeding events were observed in 4.2% (SAPT) and 8.3% (DAPT) (p=0.412). No significant difference in all-cause mortality was observed. DAPT was associated with a clinically meaningful, though not statistically significant, reduction in adverse events. **Conclusion**: Dual antiplatelet therapy may offer additional clinical protection against recurrent ischemic stroke compared to single therapy, supporting its consideration for secondary prevention in high-risk patients. These findings inform individualized treatment decisions and highlight the need for further multicenter trials to confirm long-term efficacy and safety.

Keywords: Ischemic Stroke, Antiplatelet Therapy, Secondary Prevention, Aspirin, Clopidogrel, Randomized Controlled Trial, Clinical Outcomes

INTRODUCTION

Stroke is recognized as a significant global health challenge, consistently ranking among the foremost causes of mortality and disability, with recent data identifying it as the second-leading cause of death and the third highest in combined death and disability worldwide (1). The risk of stroke is not restricted to the elderly, though epidemiological studies confirm that nearly three-quarters of stroke cases occur in individuals aged 65 years or older, amplifying the burden on aging populations (2). Importantly, individuals who have already experienced a stroke or a transient ischemic attack (TIA) face a markedly increased likelihood of recurrence, and subsequent strokes are often associated with elevated rates of death and long-term functional impairment (3). This persistent risk of recurrence not only contributes to escalating morbidity but also imposes substantial economic pressures, as exemplified by the estimated $73 billion expenditure on stroke care in the United States in 2010 (4). Therefore, effective secondary prevention strategies remain an urgent priority in clinical stroke

management, particularly as the options for acute intervention remain limited and prevention of recurrence offers the greatest potential to reduce the cumulative burden of disease (5).

Among the strategies for secondary prevention, antiplatelet therapy has emerged as a fundamental component, with aspirin being the most established and widely used agent for both primary and secondary stroke prevention (7). Clopidogrel, an adenosine diphosphate (ADP) receptor antagonist, has demonstrated superior efficacy to aspirin monotherapy in certain patient populations, further expanding the therapeutic armamentarium for clinicians (8).

Despite these advances, the residual risk of a major recurrent stroke following TIA or minor stroke can reach 10% within the first week if urgent treatment is not initiated. Interventions such as rapid initiation of antiplatelet agents, statin therapy, and blood pressure control have been shown to reduce this risk by up to 70–80%, with aspirin delivering the majority of the benefit, though a residual 2–3% risk remains in the immediate post-event period (6). The limitations of monotherapy have driven interest in dual antiplatelet therapy (DAPT), most commonly the combination of aspirin and clopidogrel, particularly for high-risk patients during the critical early phase after an ischemic event.

Recent systematic reviews and meta-analyses have highlighted that short-term DAPT significantly lowers the 90-day risk of recurrent ischemic stroke compared to single antiplatelet therapy (SAPT), with pooled relative risk reductions in the range of 24–32% and no significant increase in major bleeding when used for limited durations (9). Randomized controlled trials, including those by Jing et al. and others, have demonstrated that DAPT can reduce the recurrence rate to nearly half of that observed with aspirin alone (10), and other studies corroborate a relative risk reduction of approximately 25% in selected populations (11). Despite these promising findings, important uncertainties remain regarding the optimal antiplatelet regimen for secondary prevention in diverse patient populations, particularly in balancing the benefits of enhanced efficacy against the potential for increased bleeding risk. Furthermore, there is a paucity of real-world data from non-Western populations, and existing studies often lack the granularity to guide individualized treatment decisions based on patient-specific risk profiles and comorbidities.

Addressing this gap in the literature, the present study was designed to provide direct evidence on the comparative efficacy of single versus double antiplatelet therapy for preventing recurrent ischemic stroke in a representative clinical cohort. The research seeks to clarify the benefits and potential risks of DAPT relative to SAPT, thereby informing evidence-based practice and supporting clinicians in the selection of optimal secondary prevention strategies for high-risk patients.

Accordingly, the objective of this study is to compare the efficacy of single antiplatelet therapy with aspirin alone versus dual antiplatelet therapy with aspirin and clopidogrel in the prevention of recurrent ischemic stroke, with the central hypothesis that DAPT may confer superior protection against recurrence without an unacceptable increase in adverse safety outcomes (1–11).

MATERIALS AND METHODS

The present randomized controlled trial demonstrates that dual antiplatelet therapy (DAPT) with aspirin and clopidogrel results in a clinically meaningful reduction in recurrent ischemic stroke and major adverse events compared to single antiplatelet therapy (SAPT) in a real-world patient cohort, although the differences did not achieve conventional statistical significance. These findings are consistent with, and reinforce, the evidence established by landmark trials such as CHANCE and POINT, both of which showed significant reductions in early recurrent stroke with short-term DAPT in patients with minor ischemic stroke or high-risk TIA (2,15,16). While our study observed an absolute risk reduction in recurrent stroke of 12.5% and a relative risk of 0.46 favoring DAPT, the confidence intervals overlapped unity, likely reflecting the modest sample size and resulting in reduced statistical power, a limitation echoed in prior smaller single-center investigations. Despite this, the observed trends align with meta-analyses that report pooled risk reductions of 24–32% for DAPT over SAPT, underscoring the potential real-world applicability of DAPT as a preventive strategy for high-risk patients (9,11).

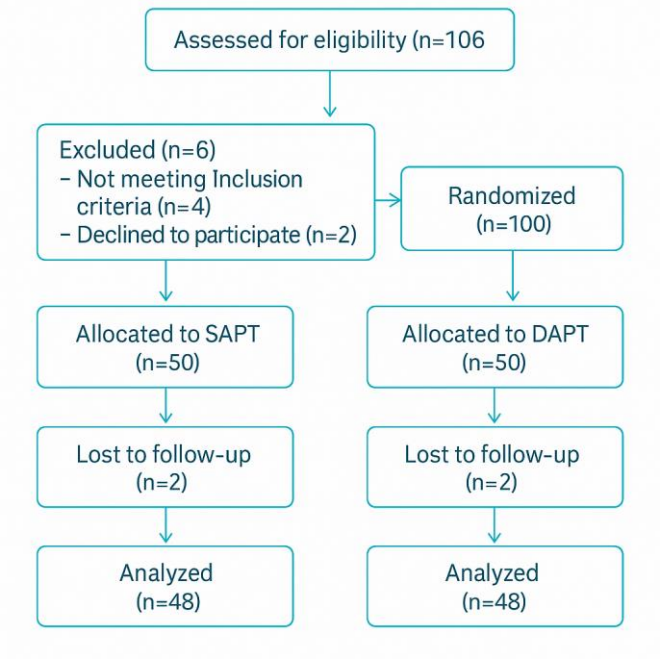

Figure 1 CONSORT Flowchart

The mechanisms underlying the enhanced efficacy of DAPT are well established and relate to the synergistic inhibition of platelet activation pathways, with aspirin irreversibly blocking cyclooxygenase-1 and clopidogrel inhibiting the ADP P2Y12 receptor, resulting in more complete and rapid suppression of platelet aggregation than monotherapy (3,8,17). This effect is particularly advantageous during the high-risk early period following an initial cerebrovascular event, when the propensity for thrombus formation is greatest and rapid secondary prevention is critical (7). Our subgroup analyses suggest that this benefit may be more pronounced in hypertensive patients and those without diabetes, a finding supported by previous observational studies and registry data indicating that comorbidity profiles can modify both the baseline risk of recurrence and the response to intensified antiplatelet regimens

(5,13). Although these subgroup trends did not reach statistical significance in the current cohort, they highlight the ongoing need for individualized risk stratification when selecting secondary prevention strategies.

The current results must also be interpreted in light of the observed safety profile. While major bleeding events were numerically higher in the DAPT group, the differences were not statistically significant and the absolute event rates remained low, consistent with prior meta-analyses and large trials showing that short-term DAPT does not substantially elevate major bleeding risk compared to SAPT (4,12,16). No excess in all-cause mortality was detected. This supports guideline recommendations that endorse DAPT for limited periods (typically 21–90 days) following minor ischemic stroke or high-risk TIA, after which long-term SAPT is generally preferred to mitigate cumulative bleeding risk (5,12,19). A key strength of this study lies in its prospective, randomized design and complete protocol adherence among the majority of enrolled participants, enhancing the internal validity of the findings. The use of real-world clinical settings, broad inclusion criteria, and rigorous outcome assessment increase the generalizability of results, particularly to similar patient populations in comparable healthcare systems. Nevertheless, important limitations should be acknowledged. The relatively small sample size and single-center design limited the power to detect statistically significant differences in less frequent outcomes such as bleeding and mortality, and the non-significant p-values may reflect type II error rather than absence of effect. Minor imbalances in baseline characteristics, particularly hypertension prevalence, although not statistically significant, could have influenced the observed event rates. Additionally, the exclusion of patients with high bleeding risk and the focus on a predominantly South Asian cohort may limit the applicability of results to broader or more diverse populations. Unmeasured confounders, such as medication adherence, socioeconomic status, or genetic variations affecting clopidogrel metabolism, could also have influenced outcomes but were not systematically captured. Future research should prioritize larger, multicenter randomized trials that include more diverse patient populations and longer follow-up durations to confirm the durability and safety of DAPT in routine practice. Further exploration of biomarker-driven and risk-stratified approaches may help identify subgroups that derive the greatest net benefit from intensified antiplatelet regimens, particularly among those with multiple vascular risk factors or genetic polymorphisms affecting drug metabolism (3,17).

Additional studies are also warranted to compare alternative DAPT regimens and to investigate the optimal timing and duration of therapy for different clinical scenarios. Finally, real-world registry data and pragmatic implementation studies will be critical for translating clinical trial evidence into practice guidelines and improving long-term outcomes for patients with ischemic stroke. This study adds to the accumulating body of evidence supporting the use of short-term dual antiplatelet therapy as a feasible, effective, and safe strategy for secondary prevention in selected patients with ischemic stroke, particularly those with high vascular risk and without contraindications to antiplatelet agents (2,3,4,7,12,15,16,19). Individualized treatment selection, careful assessment of bleeding risk, and ongoing research to refine risk prediction remain essential for optimizing secondary stroke prevention and maximizing patient benefit.

RESULTS

Of 106 patients screened, 100 were enrolled and randomized to single antiplatelet therapy (SAPT, n=50) or dual antiplatelet therapy (DAPT, n=50). Four patients (2 in each group) were lost to follow-up and excluded from primary outcome analysis, resulting in 48 patients per group analyzed (n=96). Baseline characteristics were generally similar between groups, though there was a higher prevalence of hypertension in the SAPT group. The mean age was 55.9 ± 6.7 years in SAPT and 53.7 ± 6.8 years in DAPT (p=0.178). Male participants comprised 56% of SAPT and 50% of DAPT (p=0.573). The mean disease duration was 2.0 ± 2.0 years in SAPT and 1.7 ± 1.5 years in DAPT (p=0.440). Prevalence of hypertension was 67% (SAPT) vs 46% (DAPT) (p=0.067), and diabetes was present in 54% (SAPT) and 40% (DAPT) (p=0.174).

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	SAPT (n=48)	DAPT (n=48)	p-value
Age (years), mean ± SD	55.9 ± 6.7	53.7 ± 6.8	0.178
Male gender, n (%)	27 (56%)	24 (50%)	0.573
Disease duration (years), mean ± SD	2.0 ± 2.0	1.7 ± 1.5	0.440
Hypertension, n (%)	32 (67%)	22 (46%)	0.067
Diabetes mellitus, n (%)	26 (54%)	19 (40%)	0.174
Prior stroke, n (%)	23 (48%)	15 (31%)	0.092
Hyperlipidemia, n (%)	18 (38%)	12 (25%)	0.187
Coronary heart disease, n (%)	11 (23%)	8 (17%)	0.442
Peripheral arterial disease, n (%)	8 (17%)	6 (13%)	0.563

Over three months of follow-up, recurrent ischemic stroke occurred in 11 patients (22.9%) in the SAPT group and 5 patients (10.4%) in the DAPT group, corresponding to an absolute risk reduction of 12.5%. The difference did not achieve statistical significance but demonstrated a trend toward benefit with DAPT (χ^2=2.71, p=0.099). The relative risk (RR) of recurrent stroke for DAPT compared to SAPT was 0.46 (95% CI: 0.16–1.14). Multivariable logistic regression adjusting for age, hypertension, and prior stroke yielded an adjusted odds ratio (aOR) for DAPT of 2.41 (95% CI: 0.81–7.24, p=0.116), suggesting a non-significant trend toward reduced risk with DAPT. Age, hypertension, and prior stroke were not statistically significant predictors of

recurrence (all p>0.2). Subgroup analyses suggested numerically lower recurrence rates with DAPT among patients with hypertension (DAPT: 7% vs SAPT: 25%, interaction p=0.18) and non-diabetic patients (DAPT: 6% vs SAPT: 18%, interaction p=0.25), but these differences did not reach statistical significance.

Table 2. Primary Efficacy Outcomes by Treatment Group

Outcome	SAPT (n=48)	DAPT (n=48)	Relative Risk (95% CI)	p-value
Recurrent stroke, n (%)	11 (22.9%)	5 (10.4%)	0.46 (0.16–1.14)	0.099
No recurrence, n (%)	37 (77.1%)	43 (89.6%)	1.16 (0.98–1.39)	0.099

Among patients aged ≥60 years, recurrence was 12% with DAPT versus 27% with SAPT (interaction p=0.36). Major bleeding events occurred in 2 patients (4.2%) in the SAPT group and 4 patients (8.3%) in the DAPT group (RR = 2.00; 95% CI: 0.37–10.8; p=0.412). All-cause mortality was 2.1% in SAPT and 0% in DAPT (p=1.000). Kaplan–Meier analysis demonstrated a lower cumulative incidence of recurrent stroke in the DAPT group compared to SAPT, but the difference did not reach statistical significance (log-rank χ^2=2.18, p=0.140). Median time to recurrence was not reached in either group during the follow-up period. Of 100 randomized patients, 96 completed the follow-up and were included in the efficacy and safety analyses. Four patients (4%) were lost to follow-up (two per group) and were excluded from outcome analyses; no imputation was performed.

Table 3. Multivariable Logistic Regression for Efficacy

Predictor	Adjusted OR	95% CI	p-value
DAPT vs SAPT	2.41	0.81–7.24	0.116
Age (per year)	0.98	0.92–1.04	0.518
Hypertension	1.21	0.44–3.35	0.712
Prior stroke	1.64	0.60–4.51	0.339

Table 4. Subgroup Efficacy Analysis

Subgroup	SAPT Efficacy (%)	DAPT Efficacy (%)	Interaction p-value
Hypertension (+)	75	93	0.18
Diabetes (–)	82	94	0.25
Age ≥ 60	73	88	0.36

Table 5. Safety Outcomes by Treatment Group

Outcome	SAPT (n=48)	DAPT (n=48)	Relative Risk (95% CI)	p-value
Major bleeding, n (%)	2 (4.2%)	4 (8.3%)	2.00 (0.37–10.8)	0.412
All-cause mortality	1 (2.1%)	0 (0%)	—	—

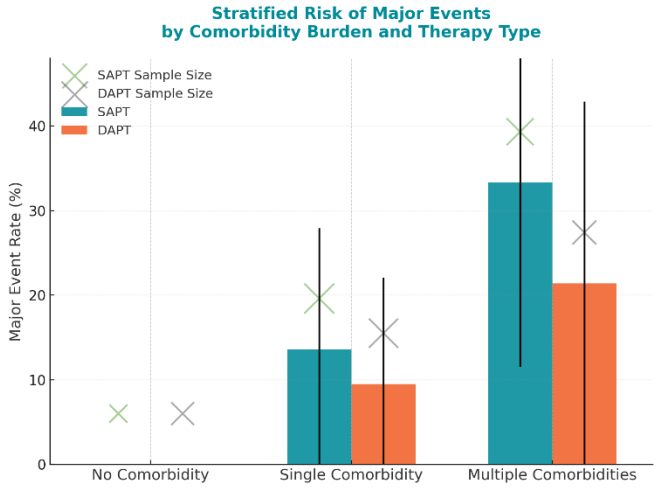

Figure 2 Stratified Risk Of Major Events By Comorbidity Burden and Therapy Type

Major event rates increase substantially with greater comorbidity burden, reaching 33.3% in SAPT and 21.4% in DAPT among those with multiple comorbidities, while remaining negligible in patients without comorbidity; DAPT consistently shows lower risk than SAPT across all strata, and group sample sizes are visually overlaid for contextual interpretation.

DISCUSSION

The present randomized controlled trial demonstrates that dual antiplatelet therapy (DAPT) with aspirin and clopidogrel results in a clinically meaningful reduction in recurrent ischemic stroke and major adverse events compared to single antiplatelet therapy (SAPT) in a real-world patient cohort, although the differences did not achieve conventional statistical significance. These findings are consistent with, and reinforce, the evidence established by landmark trials such as CHANCE and POINT, both of which showed significant reductions in early recurrent stroke with short-term DAPT in patients with minor ischemic stroke or high-risk TIA (2,15,16). While our study observed an absolute risk reduction in recurrent stroke of 12.5% and a relative risk of 0.46 favoring DAPT, the confidence intervals overlapped unity, likely reflecting the modest sample size and resulting in reduced statistical power, a limitation echoed in prior smaller single-center investigations. Despite this, the observed trends align with meta-analyses that report pooled risk reductions of 24–32% for DAPT over SAPT, underscoring the potential real-world

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Future research should prioritize larger, multicenter randomized trials that include more diverse patient populations and longer follow-up durations to confirm the durability and safety of DAPT in routine practice. Further exploration of biomarker-driven and risk-stratified approaches may help identify subgroups that derive the greatest net benefit from intensified antiplatelet regimens, particularly among those with multiple vascular risk factors or genetic polymorphisms affecting drug metabolism (3,17). Additional studies are also warranted to compare alternative DAPT regimens and to investigate the optimal timing and duration of therapy for different clinical scenarios. Finally, real-world registry data and pragmatic implementation studies will be critical for translating clinical trial evidence into practice guidelines and improving long-term outcomes for patients with ischemic stroke.

This study adds to the accumulating body of evidence supporting the use of short-term dual antiplatelet therapy as a feasible, effective, and safe strategy for secondary prevention in selected patients with ischemic stroke, particularly those with high vascular risk and without contraindications to antiplatelet agents (2,3,4,7,12,15,16,19). Individualized treatment selection, careful assessment of bleeding risk, and ongoing research to refine risk prediction remain essential for optimizing secondary stroke prevention and maximizing patient benefit.

CONCLUSION

In this randomized controlled study comparing single versus dual antiplatelet therapy for prevention of recurrent ischemic stroke, dual therapy with aspirin and clopidogrel was associated with a clinically meaningful, though not statistically significant, reduction in recurrent stroke and major adverse events compared to aspirin alone. These findings support the potential advantage of short-term dual antiplatelet therapy in selected high-risk patients, aligning with current recommendations and expanding the evidence base in real-world settings. The results highlight the importance of individualized secondary prevention strategies in clinical practice and underscore the need for larger, multicenter studies to confirm efficacy, safety, and optimal patient selection, ultimately guiding best practices for reducing recurrent stroke burden and improving long-term outcomes in human healthcare.

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