LITERATURE REVIEW : COMBINATION OF DUAL THERAPY USING ASPIRIN AND CLOPIDOGREL TO PREVENT STROKE

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ABSTRAK

Terapi antiplatelet ganda dengan aspirin dan clopidogrel (DAPT-AC) sering digunakan untuk mencegah stroke berulang, terutama pada tahap awal pencegahan sekunder. Tinjauan literature ini menganalisis 10 studi yang diterbitkan antara tahun 2022 dan 2024 untuk mengevaluasi tentang efektivitas, keamanan, dan durasi optimal penggunaan DAPT-AC (kombinasi terapi ganda penggunaan aspirin dan clopidogrel). Hasil penelitian menunjukkan bahwa penggunaan DAPT-AC dalam jangka pendek (< 3 bulan) secara efektif mengurangi risiko stroke berulang dengan komplikasi yang lebih sedikit, sesuai dengan pedoman saat ini. Namun, penggunaan jangka panjang dapat menyebabkan peningkatan risiko cedera saluran cerna (gastrointestinal) dan pendarahan, sehingga perlu diterapkan secara hati-hati, terutama pada pasien dengan risiko tinggi. Fakta yang terjadi menunjukkan bahwa penggunaan DAPT-AC semakin meningkat, bahkan pada pasien yang tidak memenuhi kriteria uji klinis. Selain itu, kombinasi ticagrelor-aspirin dapat menjadi pilihan lain bagi pasien yang tidak merespons clopidogrel, sehingga penting untuk menyesuaikan pengobatan berdasarkan kondisi masing-masing pasien. Temuan ini menegaskan bahwa durasi penggunaan DAPT-AC harus seimbang antara manfaat dan risiko. Penelitian lebih lanjut diperlukan untuk melihat keuntungan pengobatan ganda jangka panjang, menyempurnakan pengobatan, mengeksplorasi alternatif baru, dan mengatasi perbedaan praktik medis. Secara keseluruhan, DAPT-AC tetap menjadi pilihan utama dalam pencegahan stroke, terutama jika digunakan dengan mempertimbangkan kondisi pasien secara individu.

Kata kunci : aspirin, clopidogrel, kombinasi, stroke

ABSTRACT

Dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) is often used to prevent recurrent stroke, especially in the early stages of secondary prevention. This literature review analyses 10 studies published between 2022 and 2024 to evaluate the effectiveness, safety, and optimal duration of use of DAPT-AC (combined dual therapy using aspirin and clopidogrel). The results show that short-term use of DAPT-AC (<3 months) effectively reduces the risk of recurrent stroke with fewer complications, in accordance with current guidelines. However, long-term use is associated with an increased risk of gastrointestinal injury and bleeding, so it needs to be applied with caution, especially in high-risk patients. The facts show that the use of DAPT-AC is increasing, even in patients who do not meet the clinical trial criteria. In addition, the ticagrelor-aspirin combination may be another option for patients who do not respond to clopidogrel, so it is important to adjust treatment based on the condition of each patient. These findings confirm that the duration of DAPT-AC use must balance benefits and risks. Further research is needed to look at the benefits of long-term dual therapy, improve treatment, explore new alternatives, and address differences in medical practice. Overall, DAPT-AC remains the first choice in stroke prevention, especially when used with individual patient conditions in mind.

Keywords *: combination, aspirin, clopidogrel, stroke*

INTRODUCTION

Stroke remains a global health challenge, characterized by its severe impact on mortality and long-term disability. Stroke is a syndrome, clinically defined as an acute focal

neurological deficit caused by vascular injury to the central nervous system, including cerebral infarction and hemorrhage. The vast majority (85%) of strokes are ischemic strokes, which are mainly caused by atherosclerosis in small vessels, cardioembolism, and atherothromboembolism in large arteries (Murphy & Werring, 2023). According to the World Health Organization (WHO), around 15 million people worldwide suffer a stroke every year. Of these, 5 million die and another 5 million become permanently disabled, placing a huge burden on families and communities (World Health Organization, 2024).

The burden of stroke in the world is very high, especially in developing countries. Several countries in Asia have a high incidence of stroke, such as in Indonesia and China. Meanwhile, Singapore has succeeded in reducing the death rate through improved health facilities, early detection, and public education about risk factors. Differences in stroke rates between countries indicate the need for appropriate prevention strategies. Awareness, early detection, and better access to health services can reduce the global impact of stroke (Venketasubramanian et al., 2017). The use of antiplatelet therapy such as aspirin has become the main strategy in the prevention of recurrent stroke (secondary stroke). However, some recent studies show that a combination of dual antiplatelet therapy (DAPT), especially aspirin and clopidogrel, can provide additional benefits in certain conditions, such as in patients with transient ischemic attacks (TIAs) or minor strokes. Several large clinical trials have examined the effectiveness of combination therapy of aspirin and clopidogrel (DAPT therapy) in preventing recurrent stroke. The results of the CHANCE and POINT studies show that the short-term use of a combination of aspirin and clopidogrel (21 to 30 days) can significantly reduce the risk of recurrent stroke compared to aspirin monotherapy (using aspirin alone). However, it is necessary to consider the increased risk of bleeding if used in the long term (Chan et al., 2024).

The short-term benefits of using DAPT-AC have been proven effective in reducing the risk of recurrent ischemic stroke. The CHANCE clinical trial (2013) in China showed that the combination of clopidogrel and aspirin is more effective than aspirin alone in preventing recurrent stroke in the first 90 days without increasing the risk of bleeding (Wang et al., 2013), CHANCE Trial, 2013. Similarly, the POINT clinical trial (2018) found that this combination therapy reduces the risk of recurrent stroke in patients with mild ischemic stroke or high-risk TIA, despite an increased risk of major bleeding (Pan et al., 2019). The SAMMPRIS clinical trial (2011) examined the DAPT-AC combination in patients with severe intracranial stenosis (severe narrowing of the blood vessels in the brain), the results showed that aggressive medical therapy, including DAPT-AC, was more effective than stenting in preventing recurrent vascular events (Chimowitz et al., 2011). Overall, DAPT-AC has an important role in the secondary prevention of ischemic stroke, especially in short-term use, but the individual patient's condition must be considered before determining the duration of DAPT-AC therapy in the secondary prevention of ischemic stroke (Dawson et al., 2021).

Despite clinical success, DAPT-AC has significant limitations. The increased risk of bleeding with long-term use is still a concern in some studies. In addition, there are still inconsistencies in clinical practice, as evidenced by more than 40% of non-minor stroke patients who received DAPT-AC outside the main clinical trial criteria such as CHANCE and POINT (Xian et al., 2022). This shows a difference between research results and practice in the field, especially for patients who are not included in clinical trials. This situation also raises questions about whether the current use of DAPT-AC is in accordance with existing guidelines.

This study aims to evaluate the effectiveness, safety, and optimal duration of use of DAPT-AC (combination of dual therapy of aspirin and clopidogrel) in stroke prevention.

METHODS

This literature search was conducted in November 2024, and review was conducted in adherence to the Preferred Reporting Items for Literature Reviews and Meta-Analyses (PRISMA) guidelines. PRISMA was selected as it provides a robust and transparent framework for conducting systematic reviews, ensuring replicability, rigor, and clarity in reporting. Its structured approach allowed for the comprehensive identification, evaluation, and synthesis of relevant literature, making it highly suitable for this study, which aimed to assess the impact of dual antiplatelet therapy (aspirin and clopidogrel) on ischemic stroke. The identification phase involved a systematic search of two primary databases, Google Scholar and PubMed, chosen for their extensive coverage of scientific and biomedical literature. A Boolean search query, “combination” and “aspirin” and “clopidogrel” and “ischemic stroke” and “antiplatelets” -"hemorrhagic stroke," was employed to capture studies relevant to the research objectives. The search was restricted to articles published between 2022 and 2024 to ensure the inclusion of the most recent advancements in the field. This initial search yielded 592 articles. To enhance the credibility and relevance of the review, only studies published in Scopus-indexed Q1 and Q2 journals were selected, resulting in 207 articles after the removal of duplicate records.

In the screening phase, the titles and abstracts of these 207 articles were reviewed to determine their relevance to the research objectives. Articles were included if they were empirical studies published in peer-reviewed journals, focused on the effects of dual antiplatelet therapy on ischemic stroke, and were written in English. Conversely, articles were excluded if they were literature reviews, addressed hemorrhagic stroke or unrelated topics, or lacked empirical data. This screening process excluded 190 articles, leaving 17 studies for full-text assessment. The eligibility phase involved a detailed review of the full-text articles to ensure alignment with the study objectives and methodological rigor.

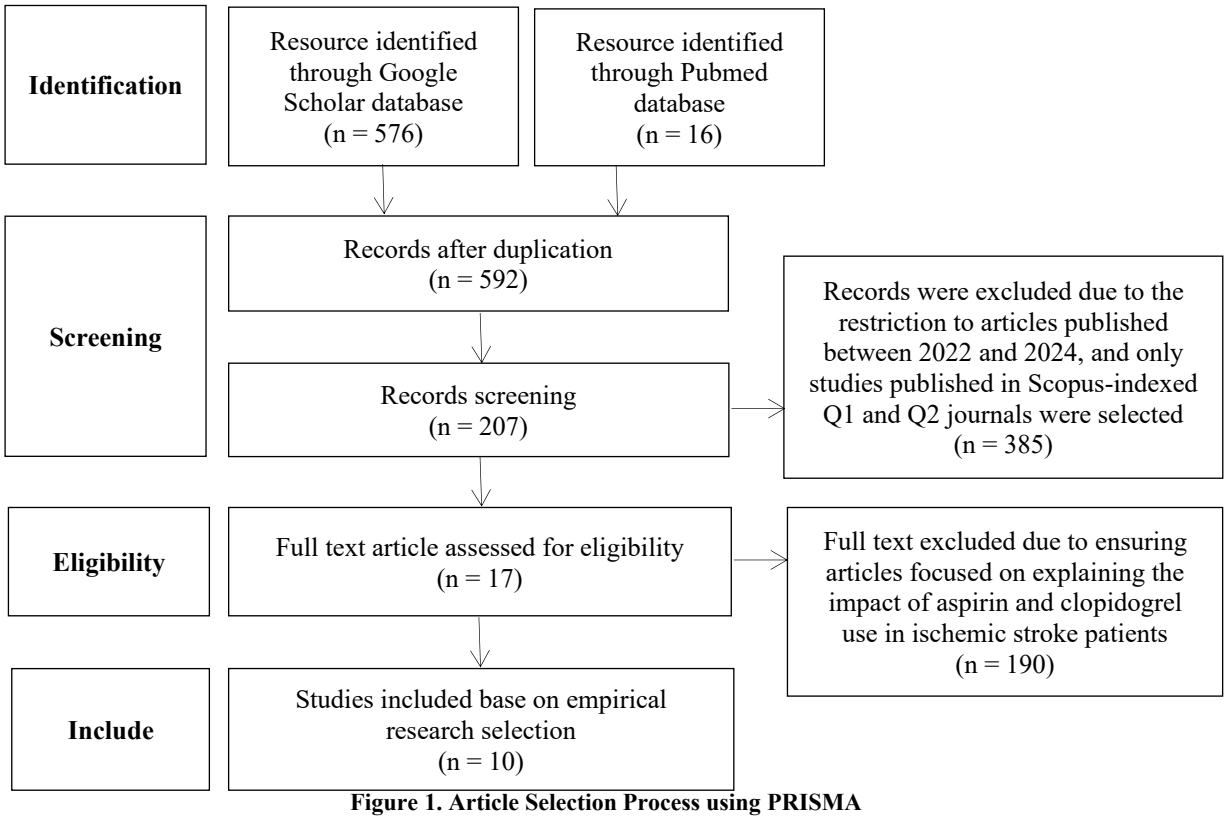

Figure 1. Article Selection Process using PRISMA

Articles were excluded at this stage if they lacked detailed methodological descriptions or were categorized as literature reviews. Seven articles were excluded for being literature reviews, resulting in a final selection of 10 empirical studies that met all inclusion criteria. This systematic selection process was meticulously documented, and the PRISMA flow diagram (figure 1) provides a visual representation of the study selection process. Data extraction was carried out systematically using a predefined template to ensure accuracy and uniformity. Key information was extracted from each study, including the study design, sample size and characteristics, methodological approaches, outcomes related to dual antiplatelet therapy, and the main findings. A thematic analysis was conducted to synthesize the data and identify recurring patterns or themes. The analysis focused on understanding the effects of dual antiplatelet therapy on ischemic stroke outcomes and exploring related factors such as adverse events and treatment efficacy. Key themes were identified through systematic coding of the findings from the selected studies, ensuring that the synthesis captured the core insights across the literature. Studies were grouped based on their methodologies, findings, and contributions to the research objectives. This synthesis highlighted the key themes related to dual antiplatelet therapy and its impact on ischemic stroke while identifying existing knowledge gaps. The narrative synthesis ensured that the findings were clearly articulated and directly addressed the research questions, providing valuable insights for future research and clinical practice.

RESULT

This part begins by presenting key results from recent real-world evidence studies that clarify the current concept of antiplatelet medication in the management of ischemic stroke. These studies are essential in augmenting randomized clinical trials (RCTs) by illustrating the actual implementation of dual antiplatelet treatment with aspirin and clopidogrel (DAPT-AC) and other regimens in various clinical contexts and demographics. The collected data provides important insights into comparative efficacy, safety profiles, and diversity in treatment procedures.

Table 1 highlights the characteristics of 10 included real-world evidence studies, emphasizing their designs, comparators, and geographic locations. These studies provide a worldwide view on the use of antiplatelet medication by analyzing data from areas including Asia, Europe, and North America. They investigate several therapy strategies, including monotherapies and alternate dual regimens, highlighting the need of contextualizing results according to local healthcare practices, patient demographics, and clinical requirements. This table provides a basis for the comprehensive analysis and synthesis in the next sections, where results are rigorously assessed to respond to the primary research questions.

Tabel 1. The Study Designs and Methodologies

No.	Author	Design	Comparison	Country
1	(He et al., 2023)	Multi randomized	Aspirin alone. Clopidogrel alone.	China
2	(Barrios et al., 2022)	Observational and cross-sectional study	Aspirin + ticagrelor. Aspirin + prasugrel.	Spain
3	(Farooqui et al., 2023)	Multicenter study	Aspirin/Clopidogrel. Aspirin + ticagrelor. Kombinasi 4 (inhibitor or cangrelor).	15 hospitals in the USA and one in Spain
4	(Huang et al., 2023)	Retrospective cohort	Cilostazol + Aspirin.	Taiwan

5	(Han et al., 2023)	Prospective randomized trial	Sarpogrelate 300 mg and aspirin 100 mg once daily.	South Korea
6	(Oh et al., 2024)	Kaplan-Meier estimation and Cox proportional hazards regression	Short-term Dual Antiplatelet Therapy (Aspirin + Clopidogrel). Long-term Dual Antiplatelet Therapy (Aspirin + Clopidogrel).	South Korea
7	(Pracoń et al., 2022)	Prospective registry of Left Atrial Appendage Closure (LAAC)	Only using dual antiplatelet therapy (DAPT) but were differences in the treatment groups. Study group included patients with oral anticoagulation (OAC) failure. Control group with oral anticoagulation (OAC) contradiction.	Poland
8	(Liu et al., 2023)	Double-blind CHANCE-2 trial	Ticagleror + aspirin. Clopidogrel + aspirin.	China
9	(Kim et al., 2024)	Analysis of a prospective, multicenter	51,6% Patient received DAPT-AC, and 45.2% received other antiplatelet regimens; aspirin alone (37.1%), clopidogrel alone (2.9%), or other antiplatelet treatment (5.2%), such as cilostazol, ticlopidine, or triflusal, either alone or in combination with aspirin or clopidogrel.	South Korea
10	(Woodhouse et al., 2023)	International multicentre prospective randomised open-label blinded-end-point (PROBE)	Clopidogrel (300 mg loading followed by 75 mg daily). Aspitom (300 mg loading followed by 50-150 mg daily, typically 75 mg) Dipyridamole (200 mg twice daily modified release). Randomised to guideline antiplatelet therapy received either clopidogrel alone or combined aspirin and dipyridamole, using the same doses above.	Denmark, Georgia, New Zealand, UK.

The findings presented in table 1 offer a comprehensive overview of the current perspectives on antiplatelet therapy, particularly the use of dual antiplatelet therapy combining aspirin and clopidogrel (DAPT-AC), in the management of ischemic stroke. The studies incorporate various methodological designs, including multicenter randomized trials, retrospective cohort analyses, and prospective registries, thereby providing a solid evidence base that integrates the rigor of clinical trials with the applicability of real-world settings. A number of investigations have specifically addressed the comparative efficacy of DAPT-AC in relation to other antiplatelet regimens. One study compared aspirin monotherapy, clopidogrel monotherapy, and DAPT-AC within a multicenter randomized setting in China

and highlighted the respective benefits and risks of each approach (He et al., 2023). Another study explored the effectiveness of ticagrelor-aspirin versus clopidogrel-aspirin in the CHANCE-2 trial, with a particular focus on clopidogrel resistance among East Asian patients (Liu et al., 2023). These comparative analyses are crucial in identifying the most effective and safest regimens for specific populations, especially in areas with distinct genetic predispositions or clinical profiles.

The duration of DAPT-AC also emerged as a significant consideration. A study evaluating short-term versus long-term DAPT-AC found that shorter therapy durations led to optimal outcomes by reducing ischemic recurrence while limiting the risk of bleeding (Oh et al., 2024). This supports current guidelines that recommend short-term use of DAPT-AC during the early stages of secondary prevention, particularly within the first 21 to 90 days following an ischemic event. The increased bleeding risk observed with prolonged use underscores the need for careful evaluation of therapy duration. Beyond the standard DAPT-AC regimen, several studies examined alternative antiplatelet combinations. Cilostazol-aspirin was evaluated in a Taiwanese retrospective cohort (Huang et al., 2023). While sarpogrelate-aspirin was assessed in a South Korean population (Han et al., 2023). These investigations reflect an emerging interest in customizing antiplatelet therapy based on regional needs and healthcare system capacities, especially in settings where clopidogrel resistance or other barriers may compromise standard treatment efficacy.

Real-world data also revealed substantial discrepancies in clinical practice. Over 50% of stroke patients in South Korea were reported to have received DAPT-AC, despite differences in patient eligibility and inconsistent adherence to clinical guidelines (Kim et al., 2024). These gaps between clinical research and real-world practice highlight the need for standardized treatment protocols that align with real-world healthcare environments. Regional variations in antiplatelet therapy use further emphasize the necessity for tailored treatment strategies. Research conducted in Asia has underlined the influence of genetic factors on treatment selection, including clopidogrel resistance (Liu et al., 2023; He et al., 2023). In contrast, European studies have explored alternative combinations such as aspirin-ticagrelor and aspirin-prasugrel, reflecting different therapeutic innovations and preferences (Barrios et al., 2022; Pracoń et al., 2022). The complexity of antiplatelet strategies in the United States and Spain has been demonstrated through investigations of newer agents like cangrelor in addition to conventional DAPT-AC regimens (Farooqui et al., 2023).

The findings summarized in Table 1 offer a broad overview of the study designs and methodologies underpinning recent research on dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) as well as alternative antiplatelet regimens. By integrating evidence from diverse regions and healthcare systems, these studies underscore the variability in clinical practices and the ongoing advancements aimed at optimizing therapeutic strategies for ischemic stroke management. The studies highlight the importance of factors such as treatment duration, population-specific considerations, and the comparative effectiveness of DAPT-AC relative to other therapeutic approaches. This foundational analysis of study designs and contexts paves the way for a deeper exploration of how these therapies impact patient outcomes.

In this context, table 2 shifts the focus from a methodological perspective to an analysis centered on patient characteristics and clinical outcomes associated with the use of clopidogrel and aspirin combinations. This transition provides critical views into the real-world application of DAPT-AC by examining variables such as patient demographics, comorbidities, and specific therapeutic results. The detailed patient-level data captured in diverse populations. This patient-centered analysis is essential for addressing key research questions about the role of DAPT-AC in preventing recurrent ischemic stroke and ensuring its applicability in varied clinical scenarios.

Table 2. Patient Characteristics and Combination of Clopidogrel + Aspirin Result of Collected Studies

No.	Author	Sample	Aim	Characteristic	Result
1	(He et al., 2023)	394 patients	The purpose of this study was to assess the association of aspirin, clopidogrel, and their combination with gastrointestinal injury progression among patients without high bleeding risk after PCI	The patients with a mean age of 56.9 years. Clinical Conditions: stable coronary artery disease or acute coronary syndromes (without ST-segment elevation) after PCI; low gastrointestinal bleeding (GIB) risk (no history of ulcers or bleeding in the past 24 months). Comorbidities: hypertension (57.6%–65.4%), diabetes (20.0%–30.3%), hyperlipidemia (5.3%–10.8%), prior myocardial infarction (6.1%–9.1%), prior stroke (10.6%–12.1%), and smoking (10.0%–15.2% former smokers, 35.4%–40.2% current smokers).	Combination of clopidogrel + aspirin increased the risk of gastrointestinal injury progression, with 53.1% of patients experiencing gastric injury and 54.6% experiencing small-intestinal injury. Compared to aspirin alone, clopidogrel + aspirin showed a higher risk of gastric injury progression (RR 0.70; 95% CI, 0.49–0.99; P = .009).
2	(Barrios et al., 2022)	1089 patients	The purpose of this study was to ascertain the clinical profile and management of patients with ischemic heart disease (IHD) and/or peripheral artery disease (PAD).	The patients with a mean age of 68.9 years, mean BMI: 27.9 kg/m², and mean blood pressure: 132/76 mmHg. Co morbidities: hypertension (72.3%), dyslipidemia (78.8%), diabetes (38.7%), prior myocardial infarction (57.9%), sedentary lifestyle (33.1%), and smoking (16.1% current smokers, 55.4% former smokers).	In this study, this combination was the most commonly used dual antiplatelet therapy (58.1%), demonstrating significant benefits in reducing major adverse cardiovascular events (MACE).
3	(Farooqui et al., 2023)	595 patients	The purpose of this study was to compare the safety of different anti-platelet regimens in patients presenting	The patients with a mean age of 67 years. Comorbidities: hypertension (73%), hyperlipidemia	There was a significant increase in the odds of successful

			with TL undergoing acute CAS treatment during EVT	(46.3%), diabetes mellitus (27.9%), atrial fibrillation (13.9%), and smoking history (46.7%).	reperfusion (mTICI 2b/3: dual aspirin + clopidogrel: aOR 5.85, CI 2.12–16.14, p = 0.001) and excellent reperfusion (mTICI 2c/3: dual aspirin + clopidogrel: aOR 1.87, CI 1.07–3.29, p = 0.028) in patients receiving dual oral loading therapy.
4	(Huang et al., 2023)	3403 patients	The purpose of this study was to compare the effectiveness, safety, and mortality risks between cilostazol plus aspirin and clopidogrel plus aspirin treatment for patients with acute minor ischemic stroke or transient ischemic attack (TIA).	The patients in this study were predominantly older adults, with a mean age of 67–69 years. 84% of patients used Clopidogrel + Aspirin Comorbidities: hypertension, diabetes, dyslipidemia	Clopidogrel + Aspirin effectively reduced the risk of recurrent ischemic stroke with an incidence rate of 44.89 per 1,000 person-years. It had a lower risk of intracranial hemorrhage (HR: 1.65; 95% CI: 1.05-2.60) compared to Cilostazol + Aspirin.
5	(Han et al., 2023)	272 patients, Randomized	The purpose of this study was to evaluate whether sarpogrelate plus aspirin was non-inferior for preventing early restenosis after femoropopliteal (FP) EVT compared to clopidogrel plus aspirin.	Significant atherosclerotic steno-occlusive lesion (>50% diameter stenosis on angiography) of the FP artery.	Patient characteristics and EVT patterns were similar. The sarpogrelate group showed a tendency of less restenosis at 6 months than the clopidogrel group (13.0% vs. 19.1%) Secondary endpoints related to safety outcomes were rare in both groups. Risks of target lesion restenosis of the

					two intervention arm were uniform across most major subgroups except for those with coronary artery disease.
6	(Oh et al., 2024)	1215 patients	The purpose of this study was to assess the clinical outcome of patients discharged after successful transfemoral TAVR in real-world practice	Net adverse clinical events (NACEs), all-cause death, myocardial infarction, stroke, any coronary and peripheral revascularization, systemic thromboembolism, and bleeding events, at 1 year	The rate of net adverse clinical events (NACE), including all-cause death, ischemic events, and bleeding, showed no significant difference between the short-term and long-term DAPT groups.
7	(Pracoń et al., 2022)	195 patients	The purpose of this study was to report outcomes of LAAC in patients with prior OAC failure and low bleeding risk (study group) compared to classic indications of long-term OAC unsuitability (i.e. high-bleeding risk) (control group), utilizing se-rial postprocedural left atrial imaging for DRT detection.	Study group with patient oral anticoagulation (OAC) failure defined as stroke/TIA/PE/LAA thrombus Control group with oral anticoagulation (OAC) contradiction	Patients after LAAC for OAC failure and unremarkable prior bleeding history presented with high residual stroke and low bleeding risks.
8	(Liu et al., 2023)	4168 patients	The purpose of this study was to compare the risk of stroke recurrence and the responses to dual antiplatelets with ticagrelor-aspirin versus clopidogrel-aspirin between patients with posterior circulation infarct (PCI) and those with anterior circulation infarct (ACI) after minor stroke or transient ischemic attack.	Patients with positive diffusion-weighted imaging were included and classified into PCI and ACI groups according to the hyperintense lesions on diffusion-weighted imaging	Ticagrelor-aspirin was superior to clopidogrel-aspirin in reducing the risk of stroke within 90 days in both posterior circulation infarct (PCI) and anterior circulation infarct (ACI) patients.
9	(Kim et al.,	32.118	The purpose of this	Patients with medical	The use of

	2024)	patients	study was to evaluate trends in the use of dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) and its outcomes in patients with ischemic stroke who are not eligible for the POINT/CHANCE trials	history such as TIA, stroke, PAD, CAD, Hypertension, Diabetes, and dyslipidemia	DAPT-AC increased significantly from 33% in 2008 to 78% in 2022 among patients with nonminor strokes or late presentation DAPT-AC was associated with significant reductions in recurrent stroke in some subgroups, such as those with undetermined ischemic stroke causes.
10	(Woodhouse et al., 2023)	3096	The purpose of this study was to compare the effects of intensive antiplatelet therapy (aspirin, clopidogrel, dipyridamole) versus guideline-recommended antiplatelet therapy in patients with acute ischemic stroke or transient ischemic attack (TIA).	Adult patients aged ≥50 years were suitable for inclusion if they were at risk of a recurrent ischaemic stroke and had either a non-cardioembolic ischaemic stroke	The primary results showed that intensive antiplatelet therapy did not significantly reduce the risk of recurrent stroke or TIA compared with standard therapy. On the other hand, this therapy increased the risk of bleeding, especially in patients with certain characteristics such as older age and a history of previous bleeding.

DISCUSSION

The findings presented in table 2 provide a comprehensive overview of patient characteristics and clinical outcomes linked to the use of dual antiplatelet therapy combining clopidogrel and aspirin (DAPT-AC). Across various studies, participant demographics were diverse, with sample sizes ranging from 195 to more than 32,000 individuals, indicating the broad applicability of this therapy. The average patient age varied, with the youngest cohort reported as 56.9 years and over 50 years in other studies (He et al., 2023; Woodhouse et al.,

2023). Comorbid conditions including hypertension, diabetes, dyslipidemia, and smoking history were consistently observed. These variations highlight the heterogeneity of real-world populations and reinforce the need to personalize antiplatelet therapy according to individual patient characteristics.

Several studies reported meaningful therapeutic benefits from DAPT-AC. Improved reperfusion outcomes were noted in patients receiving this therapy, with statistically significant odds ratios for both successful and excellent reperfusion (Farooqui et al., 2023). Likewise, the risk of recurrent ischemic stroke was effectively reduced, with an incidence rate of 44.89 per 1,000 person-years (Huang et al., 2023). These outcomes affirm the clinical value of DAPT-AC, particularly among high-risk populations. Nevertheless, discrepancies in study results suggest that careful patient selection remains crucial in maximizing therapeutic effectiveness.

Regarding safety, DAPT-AC has been associated with a higher risk of adverse events, particularly bleeding and gastrointestinal complications. Patients receiving DAPT-AC experienced a greater incidence of gastrointestinal injury compared to those treated with aspirin alone, with significant relative risks for gastric injury progression (He et al., 2023). An increased risk of bleeding was also observed, especially among elderly individuals and those with a history of bleeding (Woodhouse et al., 2023). These findings underscore the need to balance ischemic benefits against bleeding risks when prescribing DAPT-AC. Comparative studies have assessed the effectiveness of DAPT-AC relative to alternative regimens. For instance, ticagrelor-aspirin was shown to be more effective than clopidogrel-aspirin in reducing stroke recurrence in patients with posterior and anterior circulation infarcts (Liu et al., 2023). In contrast, no significant difference in net adverse clinical events (NACEs) was observed between short-term and long-term DAPT groups, indicating that treatment duration should be individualized based on patient risk profiles (Oh et al., 2024). These results highlight the ongoing evolution of antiplatelet therapy strategies.

Increasing trends in the use of DAPT-AC in clinical practice have been documented. Between 2008 and 2022, utilization rose from 33% to 78% among patients with nonminor strokes or late presentations (Kim et al., 2024). This upward trend signals broader acceptance of the therapy but also raises concerns regarding its use in populations not traditionally included in clinical trials. These dynamics point to the need for further real-world evidence to support clinical decision-making. The use of DAPT-AC in special populations presents additional complexity. Patients who underwent left atrial appendage closure due to oral anticoagulant failure or contraindications exhibited high residual stroke risk but lower rates of bleeding (Pracoń et al., 2022). Likewise, alternative regimens demonstrated a reduction in restenosis after six months when compared to DAPT-AC (Han et al., 2023). These outcomes emphasize the necessity of tailoring treatment according to individual clinical scenarios and patient-specific risk factors.

Efficacy of Dual Antiplatelet Therapy (DAPT-AC) in Stroke Management

Dual antiplatelet therapy combining aspirin and clopidogrel (DAPT-AC) has become a cornerstone in the prevention and management of ischemic stroke, especially in high-risk populations. The combination targets platelet aggregation through complementary mechanisms, forming the basis of its efficacy in reducing ischemic events. Recent studies have provided strong clinical evidence supporting its role in improving stroke outcomes and lowering recurrence rates (Farooqui et al., 2023; Huang et al., 2023; Barrios et al., 2022; Kim et al., 2024). In patients undergoing endovascular treatment for ischemic stroke with tandem lesions, DAPT-AC has been shown to significantly improve reperfusion outcomes. Adjusted odds ratios indicated substantial increases in successful reperfusion (aOR: 5.85; 95% CI: 2.12–16.14; $p = 0.001$) and excellent reperfusion (aOR: 1.87; 95% CI: 1.07–3.29; $p = 0.028$).

Moreover, the therapy did not elevate the risk of symptomatic intracranial hemorrhage or mortality, confirming its safety and effectiveness in acute procedural settings (Farooqui et al., 2023).

For recurrent stroke prevention, DAPT-AC significantly reduced the incidence of ischemic events, particularly in patients with acute minor strokes or transient ischemic attacks (TIA). The incidence rate in the DAPT-AC group was 44.89 per 1,000 person-years, reflecting a notable advantage over alternative therapies such as cilostazol or aspirin. Furthermore, the combination therapy exhibited a favorable safety profile with a lower risk of intracranial hemorrhage (HR: 1.65; 95% CI: 1.05–2.60) (Huang et al., 2023). DAPT-AC has also seen widespread use among high-risk cardiovascular patients, emerging as the most commonly used dual antiplatelet regimen (58.1%). It effectively reduced major adverse cardiovascular events (MACE), and although the study primarily focused on cardiovascular conditions, its relevance extends to stroke management due to the overlap in risk factors and treatment strategies (Barrios et al., 2022).

Long-term data also supports the role of DAPT-AC in secondary stroke prevention. Over a 14-year period, its use increased significantly, particularly after the publication of the CHANCE trial in 2013, which validated its efficacy. During this period, vascular events declined steadily, with an annual relative risk reduction (HR: 0.98; 95% CI: 0.97–1.01), suggesting meaningful impact in real-world clinical practice (Kim et al., 2024). Collectively, these findings underscore the strong efficacy of DAPT-AC in stroke management. Whether during acute interventions like endovascular reperfusion or in long-term prevention of recurrent events, DAPT-AC consistently demonstrates benefits in reducing ischemic risk. Nevertheless, its effectiveness must be carefully weighed against potential bleeding risks, especially in vulnerable populations. Ongoing research should continue refining patient selection criteria to optimize the risk-benefit balance of this therapeutic approach.

Safety Concerns and Adverse Events Associated with DAPT-AC

Although dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) effectively reduces the risk of ischemic stroke, it carries important safety concerns that must not be overlooked. Research consistently highlights a delicate balance between the benefits of ischemic event prevention and the potential for adverse outcomes, especially bleeding and gastrointestinal complications. These safety risks highlight the importance of proper patient selection and continuous monitoring to achieve optimal treatment results (He et al., 2023; Woodhouse et al., 2023; Oh et al., 2024; Pracoń et al., 2022; Barrios et al., 2022; Huang et al., 2023). Gastrointestinal injury is among the most commonly reported complications associated with DAPT-AC. Compared to aspirin monotherapy, patients receiving the combination therapy showed significantly higher rates of gastric and small-intestinal injuries. In a recent study, 53.1% of patients experienced gastric injury and 54.6% had small-intestinal damage, with a relative risk of 0.70 (95% CI: 0.49–0.99, $p = 0.009$) for the progression of gastric injury, indicating a need for alternative therapies or gastroprotective strategies like proton pump inhibitors in patients with a history of gastrointestinal disorders (He et al., 2023).

Bleeding risk remains a major concern with DAPT-AC, especially when therapy is intensified. One study found that major or fatal bleeding occurred more frequently with intensive antiplatelet therapy (2.5%) compared to guideline-directed therapy (1.4%), with a hazard ratio of 2.21 (95% CI: 1.24–3.93). The risk was higher among older individuals, women, those with a history of major bleeding, and those with delayed treatment initiation, indicating the need for a cautious approach in high-risk patients (Woodhouse et al., 2023). Supporting this, an investigation into short- versus long-term DAPT-AC in patients undergoing transcatheter aortic valve replacement (TAVR) found that bleeding events were

more frequent in the long-term DAPT group (4.4%) than in the short-term group (2.2%, p = 0.072). These results lend support to current clinical guidelines that recommend limiting the duration of DAPT-AC to reduce bleeding risks without compromising efficacy (Oh et al., 2024).

Certain high-risk populations may be especially vulnerable to the adverse effects of DAPT-AC. In patients undergoing left atrial appendage closure (LAAC) after failing oral anticoagulant therapy, DAPT-AC resulted in a similar rate of device-related thrombosis (13.2%) but showed a lower incidence of major bleeding (0% compared to 5.1%, p = 0.361), suggesting it may be a safer alternative to full anticoagulation in select patients. Nevertheless, the residual risk of stroke remained high, requiring ongoing evaluation of long-term treatment strategies (Pracoń et al., 2022).

Collectively, these studies emphasize the critical need to balance ischemic benefits with bleeding risks when using DAPT-AC. Although the therapy significantly reduces major adverse cardiovascular events (MACE), its application must be carefully considered to avoid serious complications (Barrios et al., 2022). Even though DAPT-AC has been shown to reduce ischemic stroke recurrence with a relatively safe profile compared to other regimens, close monitoring is necessary to manage and prevent adverse effects (Huang et al., 2023). Therefore, tailoring DAPT-AC therapy to individual patient risk profiles is essential. Those with a history of gastrointestinal issues or bleeding may benefit from alternative antiplatelet options, shorter therapy durations, or concurrent protective treatments. Moreover, utilizing clinical tools such as the HAS-BLED or ATRIA scores can aid clinicians in evaluating bleeding risk and making informed decisions to ensure that the benefits of DAPT-AC outweigh its potential harms.

Duration of DAPT-AC and Its Clinical Implications

The duration of dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) plays a crucial role in balancing its efficacy in preventing ischemic events and its associated safety risks. Evidence from recent studies underscores the importance of optimizing therapy duration to maximize benefits while minimizing complications, particularly bleeding and other adverse events. Several studies have explored the comparative outcomes of short-term (≤3 months) versus long-term (>3 months) use of DAPT-AC. One such study involved 1,215 matched patients undergoing transcatheter aortic valve replacement (TAVR), showing no significant difference in net adverse clinical events (NACEs) between short and long durations (9.6% vs. 11.6%), although long-term use resulted in more ischemic events (4.5% vs. 1.4%) and bleeding (4.4% vs. 2.2%) (Oh et al., 2024). These findings suggest that short-term DAPT-AC may offer a safer yet equally effective alternative for many patients.

The upward trend in the use of DAPT-AC among stroke patients from 2008 to 2022 has also been marked by a transition toward shorter therapy periods, reflecting clinical adoption of evidence from pivotal trials like CHANCE (Kim et al., 2024). This shift underscores the growing consensus around the benefits of limiting DAPT-AC duration to reduce complications without sacrificing efficacy. In line with these findings, research has shown that DAPT-AC reduces the rate of stroke recurrence particularly in the early post-event period in patients with minor strokes or transient ischemic attacks (TIA), making short-term therapy a favorable approach (Huang et al., 2023). Prolonging therapy beyond this phase has been associated with a heightened risk of bleeding, which may offset its benefits.

Further supporting this, prolonged use of DAPT-AC beyond established guideline timelines was shown to substantially increase the incidence of major or life-threatening bleeding, particularly among elderly patients and those with a bleeding history (Woodhouse et al., 2023). These results affirm the importance of strict adherence to evidence-based duration recommendations unless specific high-risk conditions warrant extended treatment.

Additionally, individual characteristics such as comorbidities and genetic variations can influence both response and risk during therapy. A study evaluating the effect of infarct location and CYP2C19 loss-of-function alleles found that ticagrelor combined with aspirin outperformed clopidogrel-aspirin, especially in early secondary prevention stages and among patients with specific stroke types (Liu et al., 2023). These data reinforce the importance of personalizing therapy duration based on clinical and genetic profiles. Taken together, this body of evidence confirms that therapy duration is a major determinant of DAPT-AC's benefit-risk profile. For most patients, short-term therapy is sufficient to prevent ischemic events effectively while minimizing harm. In contrast, longer treatment durations may be reserved for select groups, including those with conditions such as symptomatic intracranial stenosis or individuals undergoing procedures like left atrial appendage closure (Pracoń et al., 2022).

These insights into duration-specific outcomes provide valuable guidance for both clinical decision-making and future updates to treatment protocols. For the majority of stroke patients, short-term DAPT-AC should remain the preferred strategy. At the same time, clinicians are encouraged to assess extension of therapy on a case-by-case basis, taking into account patient-specific risks including age, comorbidities, and genetic susceptibility. Moreover, the observed trends in clinical practice highlight the ongoing need for education and consistent dissemination of updated guidelines to promote evidence-based use of DAPT-AC across different care settings (Kim et al., 2024).

Future Research Agenda

The findings from this study emphasize several key areas for future research to further refine and optimize dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) in ischemic stroke management. These areas include personalizing therapy duration, evaluating alternative regimens, addressing safety concerns, evaluating real-world application, integrating precision medicine, and expanding research on long-term therapy. Each of these domains offers opportunities to address current knowledge gaps and improve patient outcomes.

Personalizing Therapy Duration

While evidence supports short-term DAPT-AC for most ischemic stroke patients, questions remain about the optimal duration for specific subgroups, such as those with intracranial stenosis or undergoing high-risk interventions. Future studies should investigate intermediate therapy durations, such as 4–6 months, to bridge the gap between short-term and long-term strategies. Additionally, large-scale, multicenter trials are needed to validate real-world findings on short-term DAPT-AC efficacy and safety. Predictive models incorporating biomarkers, genetic factors like CYP2C19 alleles, and advanced imaging data could help tailor therapy duration to individual patient needs, reducing risks while maintaining efficacy.

Exploring Alternative Antiplatelet Regimens

Emerging alternatives to DAPT-AC, such as ticagrelor-aspirin or sarpogrelate-aspirin, highlight the potential for more effective and safer therapies. Future research should prioritize randomized controlled trials comparing DAPT-AC with these newer combinations in diverse populations, particularly in those with high rates of clopidogrel resistance. The long-term safety and efficacy of these alternative regimens also warrant further investigation, as does their cost-effectiveness in various healthcare settings. This research will be crucial in identifying the most suitable antiplatelet strategies for different patient groups.

Addressing Safety Concerns in High-Risk Populations

High-risk populations, such as patients with prior bleeding events, advanced age, or gastrointestinal conditions, present unique challenges in the use of DAPT-AC. Research should focus on the role of adjunctive therapies, such as proton pump inhibitors, in mitigating gastrointestinal risks. The development and validation of bleeding risk stratification tools specifically for DAPT-AC in ischemic stroke patients could guide safer prescribing practices. Additionally, advances in wearable technology and artificial intelligence (AI) could enable real-time monitoring for early detection of bleeding complications, improving safety outcomes for these vulnerable groups.

Integrating Precision Medicine Into Stroke Management

The integration of precision medicine into antiplatelet therapy remains underexplored but holds significant potential. Future research should investigate the role of genetic testing, such as CYP2C19 polymorphism screening, in guiding antiplatelet therapy decisions. Imaging biomarkers could further refine treatment strategies by identifying patients most likely to benefit from DAPT-AC. Additionally, AI-driven predictive models could analyze patient-specific data, including comorbidities and demographics, to provide real-time, tailored recommendations for clinicians. These innovations could pave the way for highly personalized, effective stroke management strategies.

Expanding Research on Long-Term Therapy

While short-term DAPT-AC is the standard of care for most patients, certain high-risk populations may benefit from prolonged therapy. Focused trials are needed to evaluate long-term DAPT-AC in patients with severe intracranial stenosis, left atrial appendage closure (LAAC), or recurrent strokes despite monotherapy. These studies should assess the risk-benefit profile of prolonged therapy, particularly in balancing stroke prevention with the increased risk of adverse events. Additionally, exploring the combination of DAPT-AC with novel anticoagulants could offer new solutions for managing complex, high-risk cases.

These future research agendas identify critical areas for advancing the understanding and application of DAPT-AC in ischemic stroke management. By addressing these gaps—personalizing therapy duration, exploring alternatives, improving safety for high-risk populations, evaluating real-world practices, integrating precision medicine, and expanding research on long-term therapy—future studies can refine clinical guidelines, enhance therapeutic outcomes, and ensure safer, more effective treatment for diverse patient populations.

CONCLUSION

This literature review synthesizes recent findings on dual antiplatelet therapy with aspirin and clopidogrel (DAPT-AC) in ischemic stroke management, focusing on its efficacy, safety, and clinical implications. The results highlight the effectiveness of DAPT-AC in reducing recurrent ischemic events, particularly during the early stages of secondary prevention. Short-term therapy has consistently demonstrated a favorable balance between efficacy and safety, aligning with current clinical guidelines and reinforcing its role as the standard of care for most ischemic stroke patients. However, the benefits of DAPT-AC must be weighed against its potential risks, including gastrointestinal complications and bleeding, which are more pronounced in long-term use and high-risk populations.

The review also underscores the importance of optimizing therapy duration, with evidence supporting short-term use for most patients and prolonged therapy only in select high-risk cases. Emerging alternative antiplatelet regimens, such as ticagrelor-aspirin, show promise in certain populations, particularly those with clopidogrel resistance, but require

further investigation to establish their long-term efficacy and safety. The variability in real-world application of DAPT-AC, as well as gaps between clinical trial evidence and practice, highlight the need for continued research and updated guidelines to ensure evidence-based decision-making.

Future research should focus on addressing the unresolved questions identified in this review. These include personalizing therapy duration using genetic and clinical biomarkers, exploring the efficacy and safety of alternative regimens, and refining strategies to mitigate risks in high-risk populations. In conclusion, DAPT-AC remains a cornerstone in ischemic stroke management, providing substantial benefits when used judiciously. Continued efforts to refine its application and explore innovative approaches will be crucial in enhancing patient outcomes while minimizing risks. By addressing the gaps and challenges identified in this review, future studies can further optimize antiplatelet therapy and contribute to the development of more personalized, effective, and safe stroke prevention strategies.

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