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Case report

Efficacy of triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) in cerebral infarction presenting with hemiplegia: A case report and critical appraisal of current evidence

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Abstract. Cerebral infarction, a type of stroke, occurs when blood vessels in the brain become occluded. Triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol) has been used to prevent recurrent episodes in patients with cerebral infarction; however, it carries a risk of bleeding. In this case report, we demonstrated the effectiveness of triple antiplatelet therapy in a patient with cerebral infarction and hemiplegic motor deficits. A 38-year-old man presented with paralysis of the right side of his body and slurred speech after resting for 14 hours before hospital admission. He denied prior head trauma, fever, headache, nausea, or loss of consciousness. There was no history of hypertension, diabetes mellitus, or heart disease, but the patient reported smoking 24 cigarettes daily. A head CT scan revealed an infarction in the external capsule and left corona radiata. Cerebral angiography showed occlusion of the left lenticulostriate artery, a branch of the middle cerebral artery (MCA) at the M1 segment. The patient was treated with citicoline, mecobalamin, atorvastatin, and ranitidine, in addition to triple antiplatelet therapy (aspirin, clopidogrel, and cilostazol). After eight days of treatment, the motor strength in the right upper and lower extremities showed significant improvement. The use of triple antiplatelet therapy in cerebral infarction remains a controversial topic due to the associated risk of major bleeding. However, in this case, the administration of triple antiplatelet therapy, guided by the TARDIS study, resulted in a favourable clinical outcome. (www.actabiomedica.it)

Key words: cerebral infarction, triple antiplatelet therapy, bleeding intracranial, hemiplegic motor deficit

Introduction

Cerebral infarction is a type of stroke caused by blockage of blood vessels in the brain. This obstruction can occur as a result of a thrombus growing in a blood vessel, disrupting blood flow to the brain; therefore, steps to prevent recurrence episodes are critical in the management of cerebral infarction (1,2). The components of triple antiplatelet therapy (TAT) are used to prevent thrombus formation in blood vessels. Aspirin works by inhibiting the action of thromboxane A2 (TXA2), which aids in thrombus formation. Clopidogrel works by inhibiting the activity of adenosine diphosphate (ADP), and cilostazol works by inhibiting phosphodiesterase type 3, also helping in thrombus formation (3-5). However, meta-analyses

suggest that concurrent TAT may increase the risk of bleeding; thus, the risks and benefits must be carefully considered before administering this therapy to a patient (6). This case report presents a 38-year-old man with cerebral infarction and hemiplegic motor deficits, emphasizing the diagnostic evaluation, management with triple antiplatelet therapy (TAT), and clinical outcomes in this critical condition.

Case presentation

A 38-year-old man was referred to Wahidin Sudirohusodo Hospital for sudden right-sided hemiplegia (motor strength 0) and slurred speech for 14 hours. He had no significant past medical history, including trauma, fever, hypertension, diabetes, or cardiac disease but was a longtime smoker, starting who started smoking 24 cigarettes a day from high school. Symptoms began with a headache and without vomiting. His blood pressure was 130/80 mmHg, and his consciousness was intact. His vital signs were stable, and his neurological examination was consistent with upper motor neuron hemiplegia. Sensory and autonomic function was intact. Electrocardiogram (ECG) was unremarkable; laboratory studies revealed leucocytosis, normal LDL and triglycerides. Non contrast CT performed 14 hours after the onset demonstrated infarction of the external capsule and left corona radiata (Figure 1). Cerebral angiography demonstrated left lenticulostriate artery occlusion at the MCA M1 segment with collateral flow from the left anterior and posterior cerebral arteries (Figure 2). Diagnosis of cerebral infarction was made based on the clinical and diagnostic findings. Citicoline was given for neuronal function improvement due to phosphatidylcholine synthesis and therefore acetylcholine production augmentation (7). Mecobalamin further facilitated myelin sheath repair (8), whereas atorvastatin enhanced angiogenesis and functional recovery through VEGF, BDNF, cGMP and synaptic protein upregulation (9). Ranitidine, a competitive inhibitor of the H2 receptor, also decreased gastric acid secretion (10). Triple antiplatelet therapy (aspirin, clopidogrel, cilostazol)

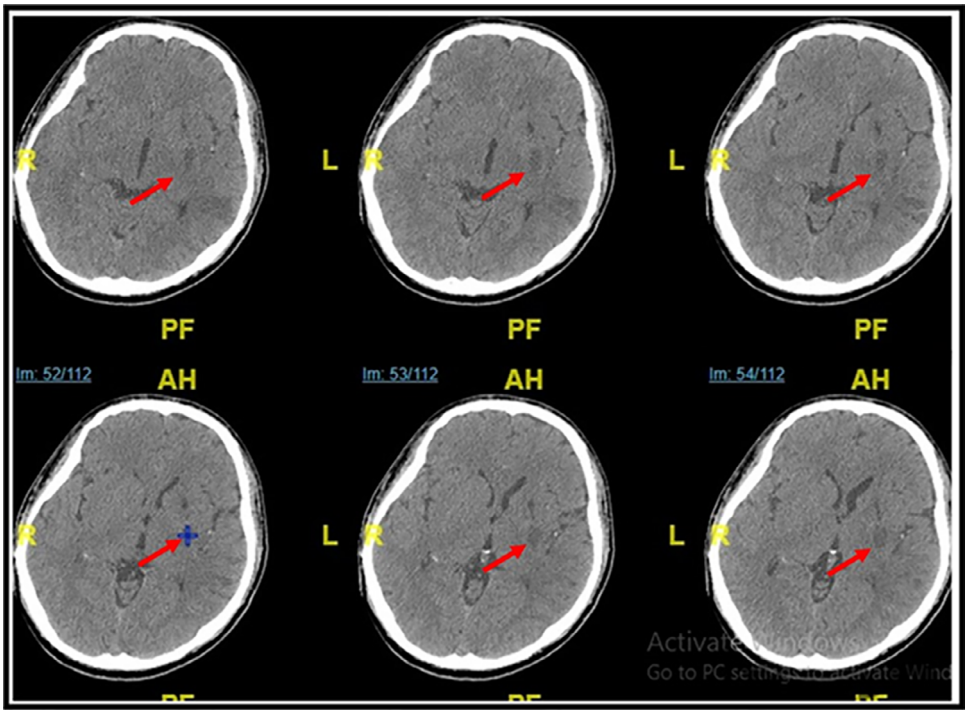

Figure 1. Head CT-Scan examination without contrast. Onset 14 hours before admission to the hospital. There was an infarction in the external capsule and left corona radiata (showed by red arrow).

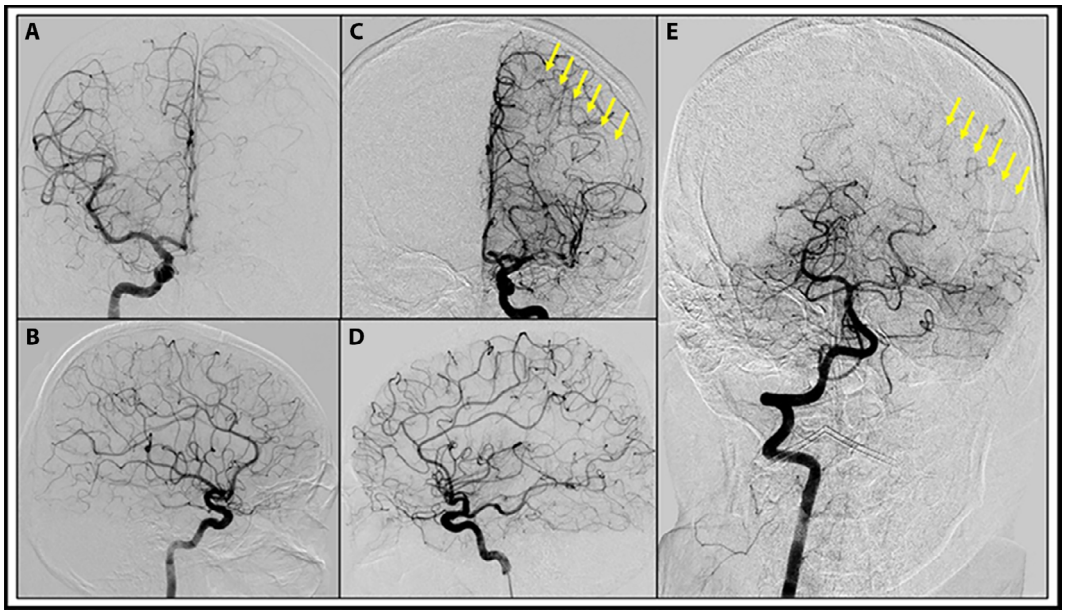

Figure 2. Cerebral angiography examination. **A.** Contrast injection from the right internal carotid artery anterior posterior view; **B.** Contrast injection of the right internal carotid artery lateral view; **C.** Contrast injection from the left internal carotid artery anterior posterior view, showed occlusion of the left lenticulostriate artery branch of the middle cerebral artery of the M1 segment and left arterial collaterals from the left anterior cerebral artery branch (yellow arrows); **D.** Contrast injection of the left internal carotid artery lateral view; **E.** Contrast injection of the right vertebral artery reveals Townes position and branches of the left posterior cerebral artery were also visible (yellow arrows).

was provided to prevent the recurrence through action on different pathways on platelet aggregation. On day 2 of hospitalization, motor strength started to improve progressively over the next 8 d before returning to baseline levels. On day eight, strength was 3 in the right upper and 4+ in the right lower extremity. The patient had no fever, headache, dizziness, or vomiting, and there was no bleeding complications from triple therapy.

Discussion

Cerebral infarction, or ischemic stroke, results from reduced cerebral blood flow, leading to hypoxia and ischemia. Clinical presentations range from asymptomatic cases and transient vertigo to limb paralysis, sudden coma, or death in severe cases. Risk factors include hyperlipidaemia, heart disease, hypertension, smoking, and alcohol consumption (11). The primary goal of cerebral infarction treatment is to salvage ischemic brain tissue by recanalizing blocked arteries and restoring perfusion to the ischemic penumbra. The penumbra, a hyperperfused yet viable region surrounding irreversibly damaged tissue, is temporarily sustained by leptomeningeal collaterals (12). For non-cardioembolic infarctions, antiplatelets reduce stroke recurrence and mortality both acutely and long-term. Aspirin, clopidogrel, and dipyridamole, widely used worldwide, have strong evidence supporting stroke prevention (13). Antiplatelets are classified by mechanism of action: (1) platelet aggregation inhibitors, including (a) aspirin and cyclooxygenase inhibitors, and (b) oral thienopyridines (clopidogrel, ticagrelor, ticlopidine, prasugrel); (2) glycoprotein inhibitors (abciximab, eptifibatide, tirofiban); (3) protease-activated receptor-1 antagonists (vorapaxar); (4) others, such as dipyridamole and cilostazol, which inhibit phosphodiesterase type 3 (PDE3) (14). Aspirin, the most widely used, irreversibly inhibits cyclooxygenase

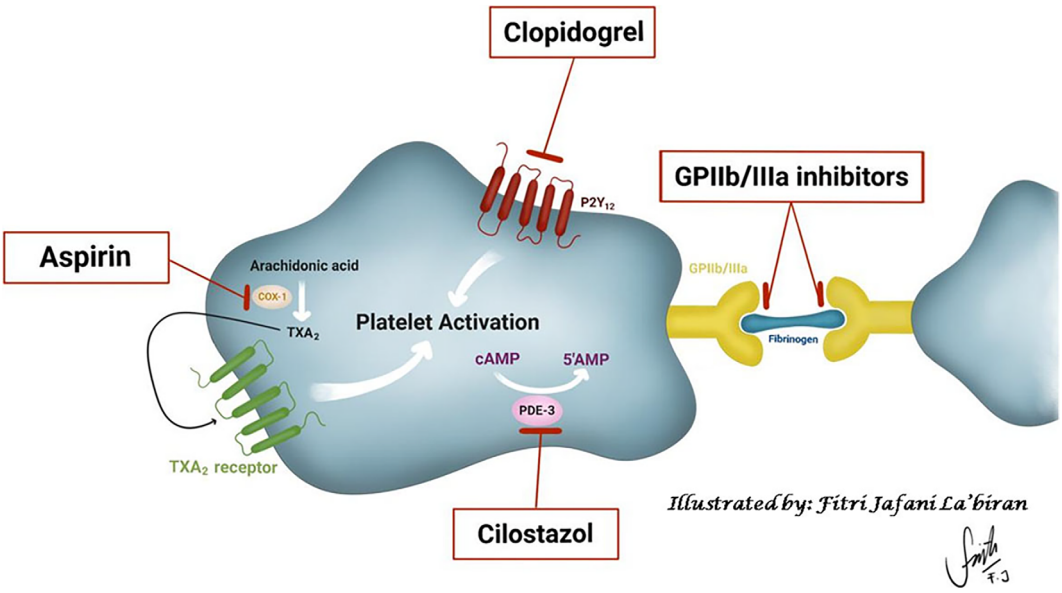

Figure 3. Mechanisms of Action for Triple Antiplatelet Therapy in Illustration. Synergistic Effects of Aspirin, Clopidogrel, and Cilostazol in Inhibiting Platelet Aggregation.

(COX), blocking thromboxane A2 (TXA2) synthesis and reducing platelet aggregation. Low doses (75–150 mg) inhibit COX-1, preventing TXA2 production, while higher doses affect COX-2. Thienopyridines inhibit ADP-induced platelet aggregation by irreversibly blocking the P2Y12 receptor via hepatic CYP450 metabolism. Prasugrel is the most effective, acting faster than clopidogrel in coronary stenting, while ticlopidine is less favoured due to bone marrow toxicity. Cangrelor, a reversible intravenous P2Y12 inhibitor, provides rapid platelet inhibition. Glycoprotein inhibitors block the GpIIb/IIIa receptor, reducing platelet aggregation, and are primarily used intravenously in acute coronary syndrome (ACS). Dipyridamole, with antiplatelet and vasodilatory effects, inhibits cyclic nucleotide phosphodiesterase, increasing intra-platelet cyclic AMP and preventing platelet aggregation. Cilostazol exhibits vasodilatory, antiplatelet, and antiproliferative effects, reducing smooth muscle hyperproliferation and intimal hyperplasia after endothelial injury (14). The mechanisms of triple therapy (aspirin, clopidogrel, cilostazol) are illustrated in Figure 3.

The use of more than one antiplatelet, triple antiplatelet, is expected to provide better effectiveness, but the use of triple antiplatelet therapy for cerebral infarction is a controversial issue. Studies by Willmot and Sprigg showed that triple antiplatelet therapy may be effective in preventing recurrent stroke, but it also significantly increased the risk of major bleeding associated with this treatment (15,16). In 2015, Krishnan reported a TARDIS trial comparing intensive antiplatelet therapy with standard therapy claiming greater efficacy in non-cardioembolic events. Triple therapy might oppose the tolerance to clopidogrel or aspirin monotherapy. The study also confirmed that dual therapy was more effective at preventing recurrence than monotherapy, and thus, if recurrence risk is high and bleeding is controlled, triple therapy (aspirin + clopidogrel + dipyridamole) is supported. In vitro studies conducted since the year 2000 have demonstrated triple anti-platelet therapy to be most effective in terms of inhibiting platelet aggregation, platelet-leukocyte conjugation, and leukocyte activation. Phase I and II multiway crossover trials consistently showed either mono, dual, or triple therapy with aspirin and clopidogrel with or without dipyridamole had ex vivo antiplatelet activity greater than each component alone in healthy volunteers and stroke/TIA patients.

A parallel-group trial confirmed the feasibility of 24 months of triple therapy (17). Geeganage performed a systematic review and meta-analysis of randomized trials for triple antiplatelet therapy for the prevention of vascular events. Intravenous GP IIb /IIIa inhibitors were more effective in reduction of vascular events in acute coronary syndrome than aspirin based dual therapy as found in the study. However, the data are limited in patients with previous ischemic stroke or peripheral vascular disease (18). In this case, triple antiplatelet therapy with aspirin, clopidogrel, and cilostazol was selected based on the 2015 study by Krishnan, with cilostazol used as an alternative to dipyridamole, both being PDE inhibitors. No bleeding complications occurred during short-term administration in the high-care unit; however, long-term safety remains uncertain, necessitating careful risk-benefit evaluation. The patient exhibited motor improvement on the right side, though causality with triple therapy remains unproven. Favourable clinical outcomes may also be attributed to robust collateral circulation from the anterior and posterior cerebral arteries, particularly leptomeningeal collaterals from the left ACA and PCA, which helped maintain perfusion despite arterial blockage (19–21). Since there is no direct causality in this case, it is not possible to determine if recovery occurred due to triple therapy or some other factors. In addition, as observational data requires longer times, short-term results do not allow to evaluate long-term safety, and the single-case nature of the findings restricts generalization. Outcome may have been influenced by confounding factors such as baseline condition and supportive care. The lack of follow-up neuroimaging also limits objective assessment. More research surrounding triple antiplatelet therapy in acute ischemic stroke is still required. Table 1 summarizes several cases or studies based on clinical presentations, approaches to triple antiplatelet therapy (TAT), and associated outcomes.

Conclusion

The efficacy of triple antiplatelet therapy in cerebral infarction is still controversial. Studies have shown its role in preventing recurrent strokes; however, an exploratory analysis by Krishnan of the 2015 TARDIS trial suggests its main benefit of intensive antiplatelet therapy lies in non-cardioembolic events but that it markedly increases bleeding risk. Furthermore, acute ischemic stroke patients with good collateral circulation may also have good outcomes. A careful patient selection is necessary and additional studies may be needed to further define exactly how to maximize benefit and minimize harm.

Abbreviations

TAT: Triple antiplatelet therapy
TXA2: Thromboxane A2
ADP: Adenosine diphosphate
ECG: Electrocardiography
LDL: Low density lipoprotein
TG: Triglycerides
CT: Computerized tomography
MCA: Middle cerebral artery
ACA: Anterior cerebral artery
PCA: Posterior cerebral artery
ACS: Acute coronary syndrome
VEGF: Vascular endothelial growth factor
BDNF: Brain-derived neurotrophic factor
PDE3: Phosphodiesterase type 3
COX: Cyclooxygenase
PGH2: Prostaglandin
ADP: Adenosine diphosphate
GpIIb-IIIa: Glycoprotein IIb/IIIa
AMP: Adenosine monophosphate

Authors' Contribution: MYA: conceptualization, investigation, writing-original draft, writing-review, editing and supervision, MAY: conceptualization, investigation, writing-review and editing; MFH, FJL, SGAG, IH: investigation, writing – review, editing. All authors read and approved the final manuscript.

Availability of Data and Materials: All data generated or analysed during this study are included in this published article.

Ethics Approval: Ethics approval and consent to participate according to national regulations, no ethical approval was required as this is merely a case report and review. Written informed consent was obtained from the patient for publication.

Table 1. Summary of Clinical Presentations, Triple Antiplatelet Therapy Approaches, and Outcomes in Reported Cases and Studies

Authors	Year	Patient Demography	Clinical Presentation	Treatment	Outcome	Recommendation
Bath PM, et al (22).	2018	3,096 patients aged >50 years with acute non-cardioembolic ischemic stroke or TIA within 48 hours of onset. Geographic representation: UK, Denmark, Georgia, New Zealand.	Acute non-cardioembolic ischemic stroke or TIA.	Triple therapy (Aspirin + Clopidogrel + Dipyridamole) vs. Guideline therapy (Aspirin + Dipyridamole or Clopidogrel alone).	No significant reduction in recurrent stroke/ TIA or severity. Increased major bleeding observed with triple therapy (HR 2.23).	Triple therapy is not recommended due to increased bleeding risk without added benefit. Future trials should assess personalized approaches for antiplatelet therapy.
Kim TJ, Lee JS, Yoon JS, et al (23).	2023	9,284 patients with acute non-cardioembolic ischemic stroke, treated with SAPT prior to stroke. Age: 68.2 ± 10.9 years, 58.2% male. Inclusion: ischemic stroke within 7 days of onset, non-cardioembolic origin, SAPT pre-stroke. Study conducted in South Korea.	Acute non-cardioembolic ischemic stroke while on SAPT.	SAPT (n=5,565), DAPT (n=3,638), TAPT (n=81). Follow-up at 1 year.	Multiple antiplatelet therapy (DAPT/TAPT) did not reduce stroke recurrence or composite vascular outcomes but increased major bleeding, particularly with TAPT.	SAPT should be continued for patients already on it; DAPT and TAPT are not recommended for long-term prevention due to increased bleeding risks without added benefit.
Wu Z, Liu AF, Zhou J, et al (24).	2019	183 patients (110 in TAT group, 73 in DAT group) with extracranial and/or intracranial atherosclerotic stenosis resistant to aspirin and/or clopidogrel. Study conducted in China.	Undergoing stenting for extracranial and/or intracranial artery stenosis.	TAT (Aspirin, Clopidogrel, Cilostazol) under TEG guidance vs. DAT (Aspirin, Clopidogrel).	TAT significantly reduced thromboembolic events (0.9% in TAT vs. 8.2% in DAT, P=0.017) without increasing major bleeding or stent thrombosis.	TAT under TEG guidance is safe and effective for reducing thromboembolic events in patients undergoing stenting for artery stenosis. Advocate using PFT for guidance.
Woodhouse LJ, et al (25).	2023	3,096 patients with acute non-cardioembolic ischemic stroke or TIA. Inclusion: ischemic stroke or TIA within 48 hours, randomization within 48 hours (24 hours post-thrombolysis). Locations: UK, Denmark, Georgia, and New Zealand.	Acute ischemic stroke or TIA.	Intensive therapy: Aspirin, Clopidogrel, Dipyridamole vs. Guideline therapy: Aspirin + Dipyridamole or Clopidogrel alone.	Intensive therapy resulted in higher fatal/major bleeding (2.5% vs. 1.4% with guideline therapy, p=0.007) without reducing stroke or TIA recurrence.	Intensive triple antiplatelet therapy should be avoided due to increased bleeding risk and lack of benefit, especially within 24–48 hours post-thrombolysis.

Sprigg N, Gray LJ, England T, et al (16).	2008	17 patients enrolled (9 in triple therapy group, 8 in aspirin group). Location: Nottingham, UK. Inclusion: Adults with ischemic stroke or TIA within 5 years. Exclusion: Prior cerebral haemorrhage, severe anaemia, or hypersensitivity to antiplatelet agents.	Ischemic stroke or TIA with a mean time to randomization of 12 months post-event.	Triple therapy (Aspirin, Clopidogrel, Dipyridamole) vs. Aspirin monotherapy.	Triple therapy showed significantly higher adverse events and bleeding rates. Treatment discontinuation was higher in triple therapy (44%) compared to aspirin (0%).	Long-term triple antiplatelet therapy is not recommended due to increased bleeding risk. Future trials should focus on short-term use in high-risk patients or those failing dual therapy.
Jonas S, Grieco G (26).	2003	Meta-analysis of multiple secondary stroke prevention trials. Geographic representation includes international studies like CAPRIE, ESPS, and others. Patient demographics varied across trials, but the focus was on non-cardiac ischemic stroke or transient ischemic attack patients.	Non-cardiac ischemic stroke or TIA.	Comparative analysis of Aspirin (ASA), Dipyridamole (DP), Clopidogrel, and their combinations, with a projection for triple therapy (ASA + DP + Clopidogrel).	Triple therapy projected a potential relative risk reduction (RRR) of up to 45% against placebo, compared to 35% with DP + ASA, but increases bleeding risk.	A clinical trial is recommended to confirm the potential benefit of triple therapy (ASA + DP + Clopidogrel) over DP + ASA. Dual therapy with DP + ASA remains the standard.
Antithrombotic Trialists' Collaboration (27).	2002	Meta-analysis of 195 trials with 135,640 high-risk patients, including those with a history of myocardial infarction, stroke, or peripheral arterial disease. Geographic representation included international data.	Patients at high risk of vascular events, including myocardial infarction, stroke, or transient ischemic attacks.	Aspirin, Clopidogrel, Dipyridamole, and combinations such as Aspirin + Dipyridamole or Clopidogrel vs. Aspirin.	Antiplatelet therapy reduced vascular events by ~25%, non-fatal myocardial infarction by ~33%, and stroke by ~25%. Aspirin at 75-150 mg daily was effective for long-term use. Major extracranial bleeding risk increased by ~1.6 times.	Antiplatelet therapy is recommended for high-risk patients. Aspirin (75-150 mg daily) is effective for long-term use. Combining antiplatelet agents offers additional benefits in select cases but requires further research.

Table 1 (*continued*)

Authors	Year	Patient Demography	Clinical Presentation	Treatment	Outcome	Recommendation
Wang MT, et al (28).	2018	5,585 patients with cerebral infarction after first acute myocardial infarction (AMI). Geographic representation: Taiwan. Inclusion: Stroke post-AMI and antiplatelet therapy use.	Patients with cerebral infarction after AMI.	Dipyridamole added to DAPT (aspirin + clopidogrel) compared to DAPT alone.	No survival benefit for dipyridamole-DAPT. Increased intracerebral haemorrhage (ICH) risk. DAPT superior in long-term outcomes after one year.	Dipyridamole addition to DAPT is not recommended due to lack of survival benefit and increased ICH risk. DAPT remains the preferred treatment strategy.
Liu L, et al (29).	2018	14 observational studies with 11,697 patients undergoing coronary stenting and diagnosed with atrial fibrillation (AF). 4,266 received triple therapy (TT), and 7,431 received dual antiplatelet therapy (DAPT). Studies included patients from multiple countries.	Atrial fibrillation with coronary stenting.	Triple therapy (TT: warfarin, clopidogrel, aspirin) vs. dual antiplatelet therapy (DAPT: clopidogrel, aspirin).	TT reduced ischemic stroke (26%) and stent thrombosis (60%) compared to DAPT but increased major bleeding risk (55%). No difference in MACE, mortality, or MI outcomes.	TT can be considered for AF patients after stenting to prevent stroke and thrombosis but requires careful risk-benefit assessment due to bleeding risks. Further randomized trials are needed.
Gwyn JCV, et al (30).	2017	Patients undergoing PCI with atrial fibrillation requiring oral anticoagulation. Approx. 5–10% of PCI patients also have AF. Geographic representation: International studies.	Atrial fibrillation with PCI requiring combined antithrombotic therapy.	Triple therapy (oral anticoagulant + aspirin + clopidogrel) vs. dual therapy (oral anticoagulant + clopidogrel).	Triple therapy increases bleeding risks without significantly reducing cardiovascular events. Dual therapy reduces bleeding and may be sufficient for many patients.	Use dual therapy (oral anticoagulant + P2Y12 inhibitor) as the preferred approach. Prolonged triple therapy should be restricted to high-risk patients. Further trials are needed.

Abbreviations: TIA: Transient Ischemic Attack; TT: Triple Therapy; SAPT: ingle Antiplatelet Therapy; DAPT: Double Antiplatelet Therapy; TAPT: Triple Antiplatelet Therapy; TEG: Thromboelastographic; RRR: Relative Risk Reduction; AF: Atrial Fibrillation; PCI: Percutaneous Coronary Intervention.

Declaration of Patient Consent: The patient in this case report have provided written informed consent regarding the writing and publication of the report.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article

Use of Artificial Intelligence (AI)-Assisted Technology for Manuscript Preparation: The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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