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Dual antiplatelet Tx for stroke prevention: Worth the risk?

Here's what the evidence tells us about the use of 2 regimens—clopidogrel + aspirin and ER dipyridamole + aspirin—to prevent secondary ischemic stroke.

PRACTICE RECOMMENDATIONS

› *Initiate combined clopidogrel plus aspirin within 24 hours of a minor stroke or TIA and continue for no longer than 1 month; then switch patients to aspirin or clopidogrel monotherapy.* (A)

› *Do not use combined clopidogrel plus aspirin for long-term secondary stroke prevention.* (A)

› *Limit use of aspirin plus extended-release dipyridamole as a first choice for secondary stroke prevention because of limitations in efficacy and poor tolerability.* (B)

Strength of recommendation (SOR)

- (A) Good-quality patient-oriented evidence
- (B) Inconsistent or limited-quality patient-oriented evidence
- (C) Consensus, usual practice, opinion, disease-oriented evidence, case series

The incidence of ischemic stroke in the United States is estimated to be more than 795,000 events each year.¹ After an initial stroke, the rate of recurrence is 5% to 20% within the first year, with the greatest prevalence in the first 90 days following an event.²⁻⁵ Although dual antiplatelet therapy, often with aspirin and a P2Y₁₂ inhibitor such as clopidogrel, reduces the risk for recurrent cardiovascular events, cerebrovascular events, and death following acute coronary syndromes and percutaneous intervention, the role of combination antiplatelet therapy for secondary prevention of ischemic stroke continues to be debated.⁶ Reconciling currently available data can be challenging, as many studies vary considerably in both the time to antiplatelet initiation and duration of therapy.

For many years, aspirin alone was the drug of choice for secondary prevention of noncardioembolic ischemic stroke.⁷ Efficacy is similar at dosages anywhere between 50 and 1500 mg/d; higher doses incur a greater risk for gastrointestinal hemorrhage.⁷ Current secondary prevention guidelines recommend a dosage of aspirin somewhere between 50 and 325 mg/d.⁷

Alternative agents have also been evaluated for secondary stroke prevention, but only clopidogrel is currently considered an acceptable alternative for monotherapy based on a subgroup analysis of the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial.^{7,8} Other alternatives, including cilostazol, ticlopidine, and ticagrelor, are limited by a lack of data, adverse drug reactions, or unproven efficacy and are not recommended in current guidelines.^{7,9} The ongoing THALES (Acute Stroke or Transient Ischaemic Attack Treated with Ticagrelor and Aspirin for Prevention of Stroke and Death) trial, assessing combination ticagrelor and aspirin, may identify an additional option for antiplatelet therapy following acute stroke.¹⁰

The current guidelines from the American Heart Asso-

ciation/American Stroke Association (AHA/ASA) support the combination of aspirin and extended-release dipyridamole (ASA-ERDP) as a long-term alternative to aspirin monotherapy.^{7,11} Additionally, the combination of clopidogrel and aspirin (CLO-ASA) is now recommended for limited duration in the early management of ischemic stroke.¹¹

This review will explore the role of dual antiplatelet therapy for secondary prevention of noncardioembolic ischemic stroke or transient ischemic attack (TIA), with particular focus on acute use of CLO-ASA.

Clopidogrel and aspirin: When to initiate, when to stop

The combined use of clopidogrel and aspirin has been well-studied for secondary prevention of ischemic stroke and TIA. However, interpreting and applying the results of these trials can be challenging given key differences in both time to treatment initiation and the duration of combination therapy. Highlights of the major randomized controlled trials (RCTs) evaluating the safety and efficacy of CLO-ASA are detailed in TABLE 1.^{4,5,12-15}

■ **Initial trials evaluating CLO-ASA** for secondary stroke prevention, including the MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients),¹² SPS3 (Secondary Prevention of Small Subcortical Strokes),¹³ and CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management and Avoidance)¹⁴ trials assessed the long-term benefits of combination therapy, with most patients initiating treatment a month or more following an initial stroke and continuing therapy for at least 18 months.¹²⁻¹⁴ Results from these trials indicate that long-term use (> 18 months) of CLO-ASA does not reduce recurrent events but increases rates of clinically significant bleeding.¹²⁻¹⁴

■ **A look at Tx timing.** Since these initial attempts failed to show a long-term benefit with CLO-ASA, subsequent trials attempted to establish an appropriate balance between the optimal time to initiate CLO-ASA and the optimal duration of therapy. The FASTER (Fast Assessment of Stroke and Transient ischaemic attack to prevent Early Recurrence)

trial was a small pilot study of 392 patients randomized to CLO-ASA or aspirin *within 24 hours* of stroke or TIA onset and continued for only 3 months.¹⁵ While this trial did not find a significant reduction in ischemic or hemorrhagic stroke with combination therapy, there was a large numerical difference in event rates between the 2 groups (7.1% CLO-ASA vs 10.8% aspirin).¹⁵ An underpowered sample size (due to difficulty recruiting participants) is likely responsible for the lack of statistical significance.¹⁵ Despite the trial's failure to show a benefit with acute use of CLO-ASA, it suggested a possible benefit that led to further investigation in the CHANCE (Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events)⁵ and POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke)⁴ trials.

The CHANCE trial conducted in China included more than 5000 patients with acute minor ischemic stroke (National Institutes of Health Stroke Scale [NIHSS] score ≤ 3) or high-risk TIA (ABCD2 [a scale that assesses the risk of stroke on the basis of age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes] score ≥ 4).⁵ Similar to FASTER, patients were randomized within 24 hours of symptom onset to CLO-ASA or aspirin. However, CHANCE utilized combination therapy for only 21 days, after which the patients were continued on clopidogrel monotherapy for up to 90 days; the aspirin monotherapy group continued aspirin for 90 days.

After 90 days, patients initially using combination therapy had significantly lower rates of ischemic or hemorrhagic stroke vs those assigned to aspirin monotherapy. This result was driven heavily by the reduction in ischemic stroke (7.9% CLO-ASA vs 11.4% aspirin; $P < .001$). Additionally, there was no significant difference in moderate or severe bleeding events between the 2 groups.⁵ Efficacy and safety results were similar among a subgroup of patients who were randomized to treatment within 12 hours rather than 24 hours from symptom onset.¹⁶ The CHANCE trial was the first major study to demonstrate a clinical benefit of CLO-ASA to prevent recurrent stroke. Accordingly, the 2018 AHA/ASA guidelines included a new recommen-



Patients who are best suited to benefit from clopidogrel + aspirin are those who have had minor noncardioembolic ischemic strokes or high-risk TIAs.

TABLE 1

Clopidogrel and aspirin for recurrent stroke: A summary of RCTs

Trial	Intervention	Time to treatment onset	Outcomes/results	Notes
MATCH ¹² (2004)	CLO 75 mg + ASA 75 mg vs CLO 75 mg Treatment/study duration: 18 mo	Mean time: 26 d	Primary efficacy endpoint ^a 16% vs 17% (<i>P</i> = NS) Life-threatening bleeding 3% vs 1% (<i>P</i> < .0001) Major bleeding 2% vs 1% (<i>P</i> < .0001)	NNH (life-threatening bleed) = 50
FASTER ¹⁵ (2007)	CLO 75 mg + ASA 81 mg vs ASA 81 mg Treatment/study duration: 90 d	Mean time: 8.2 - 9.1 hr	Primary efficacy endpoint ^b 7.1% vs 10.8% (<i>P</i> = NS) Symptomatic bleeding 3% vs 0% (<i>P</i> = .03)	CLO loading dose: 300 mg Stopped early due to lack of recruitment in a statin arm substudy NNH = 34
CHARISMA substudy ¹⁴ (2011)	CLO 75 mg + ASA 75-162 mg vs ASA 75-162 mg Treatment/study duration (median): 25 mo	31% randomized within 30 d 69% randomized after 30 d	Primary efficacy endpoint ^c 4.9% vs 6.1% (<i>P</i> = NS) Severe bleeding 1.9% vs 1.7% (<i>P</i> = NS)	
SPS3 ¹³ (2012)	CLO 75 mg + ASA 325 mg vs ASA 325 mg Treatment/study duration (mean): 3.4 y (range 0 - 8.2 y)	Mean time: 62 d	Primary efficacy endpoint ^c 2.5%/y vs 2.7%/y (<i>P</i> = NS) Major bleeding 2.1% vs 1.1% (<i>P</i> < .001)	Only lacunar strokes included All-cause mortality: 2.1%/y vs 1.4%/y (<i>P</i> = .004) NNH = 100

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dation regarding secondary prevention for the use of CLO-ASA initiated within 24 hours and continued for 21 days following a minor stroke or TIA.¹¹

A drawback of the CHANCE trial was its narrow patient population of only Chinese patients, which may limit applicability in clinical practice. There are known genetic variations in cytochrome P450 2C19 (*CYP2C19*) that may affect clopidogrel metabolism. *CYP2C19* is responsible for the conversion of clopidogrel into its activated form *in vivo*. Carriers of a *CYP2C19* loss-of-function allele may have reduced clopidogrel activation and subsequent reduced antiplatelet activity. Such loss-of-function alleles are more common in Asian populations vs non-Asian populations.¹⁷

A substudy of CHANCE found that CLO-ASA's efficacy benefit was preserved in

noncarrier patients; however, patients with the *CYP2C19* loss-of-function allele did not benefit from combination therapy.¹⁸ Interestingly, these genetic differences did not affect bleeding outcomes. Given that approximately 60% of patients in the CHANCE substudy were loss-of-function allele carriers and that the overall study results still showed benefit with combination therapy, application of CHANCE's findings to broader populations may not be a concern after all.¹⁸

In efforts to gain insight on CLO-ASA's use in a more diverse patient population, the POINT trial included almost 5000 patients, with 82% from the United States, who were randomized *within 12 hours* of symptom onset to CLO-ASA or aspirin monotherapy for 90 days.⁴ Similar to the CHANCE study, the POINT study included patients with mild ischemic strokes (NIHSS ≤ 3) or high-risk

TABLE 1

Clopidogrel and aspirin for recurrent stroke: A summary of RCTs (cont'd)

Trial	Intervention	Time to treatment onset	Outcomes/results	Notes
CHANCE ⁵ (2013)	CLO 75 mg + ASA 75 mg vs ASA 75 mg for 21 d Treatment/study duration: 90 d (0 - 21 d CLO-ASA vs ASA; 22 - 90 d CLO vs ASA)	Mean time: 13 hr	Primary efficacy endpoint ^b 8.2% vs 11.7% ($P < .001$) Moderate-to-severe bleeding 0.3% vs 0.3% ($P = NS$)	Included only minor strokes (72%) and high-risk TIA (28%) Randomized within 24 hr of index event CLO loading dose: 300 mg Exclusively within Chinese centers NNT = 29
POINT ⁴ (2018)	CLO 75 mg + ASA 81 mg vs ASA 81 mg Treatment/study duration: 90 d	Mean time: 7 hr	Primary efficacy endpoint ^d 5% vs 6.5% ($P = .02$) Major bleeding 0.9% vs 0.4% ($P = .02$)	Included only minor strokes (57%) and high-risk TIA (43%) Randomized within 12 hr of index event CLO loading dose: 600 mg Stopped early due to increased hemorrhage with 83.6% of anticipated patients enrolled NNT = 67 NNH = 200

ASA, aspirin; CLO, clopidogrel; NNH, number needed to harm; NNT, number needed to treat; NS, not significant; RCTs, randomized controlled trials; TIA, transient ischemic attack.

^aFatal or nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, other vascular death, rehospitalization for acute ischemic event.

^bAny stroke (ischemic or hemorrhagic) within 90 days.

^cAny stroke (ischemic or hemorrhagic).

^dIschemic stroke, myocardial infarction, or death from ischemic vascular causes.

TIA (ABCD2 ≥ 4). Combination therapy significantly reduced the primary endpoint of ischemic stroke, myocardial infarction (MI), or death from an ischemic event. Contrary to CHANCE, there was a significant increase in major bleeding in those assigned to combination therapy, which resulted in the trial being stopped early.⁴

■ A closer look at safety differences. CHANCE and POINT were the first major trials to show a benefit of CLO-ASA for secondary prevention of stroke, yet their differences in safety outcomes, specifically major hemorrhage, argued for a deeper reconciliation of their results.^{4,5} While both trials initiated secondary prevention within 24 hours of symptom onset, the difference in duration of combination therapy (21 days in CHANCE vs

90 days in POINT) likely impacted the rates of hemorrhage. When results from POINT were stratified by time period, particularly within the first 30 days of therapy (similar to the 21-day treatment duration of CHANCE), combination therapy significantly reduced the primary endpoint of ischemic stroke, MI, or death from an ischemic event (3.9% CLO-ASA vs 5.8% aspirin; $P = .02$) without an increased risk for major hemorrhage. Between 30 and 90 days, this efficacy benefit disappeared. However, bleeding rates between groups continued to separate throughout the 90-day course. In this light, the 30-day outcomes of POINT are largely similar to CHANCE and support the short-term use of CLO-ASA for secondary prevention without an associated increase in major bleeding.^{4,5}

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Initiate clopidogrel + aspirin therapy within 24 hours of symptom onset and continue for no longer than 1 month; then switch to monotherapy with aspirin or clopidogrel.

■ **Antiplatelet dosing** in POINT and CHANCE may also play a role in the contrasting safety results between the trials.^{4,5} While both studies utilized clopidogrel loading doses, POINT used 600 mg while CHANCE used 300 mg. Clopidogrel maintenance dosing was the same at 75 mg/d. In CHANCE, aspirin dosing was protocolized to 75 mg/d; however, in POINT, 31% of patients used > 100 mg/d aspirin.^{4,5} It is possible that the higher doses of both aspirin and clopidogrel in the POINT trial contributed to the difference in the occurrence of major hemorrhage between the treatment groups in these trials.

■ **The takeaway.** Based on currently available data, patients who are best suited to benefit from CLO-ASA are those who have had minor noncardioembolic ischemic strokes or high-risk TIAs.^{4,5,11} Clopidogrel should be given as a 300-mg loading dose followed by 75 mg/d given concomitantly with aspirin at a dose no higher than 100 mg/d. CLO-ASA therapy should be initiated within 24 hours of symptom onset and be continued for no longer than 1 month, after which chronic preventive therapy with either aspirin or clopidogrel monotherapy should be started.^{4,5,11}

Dipyridamole and aspirin: A controversial option

Since the approval of the combination product ASA-ERDP, there has been considerable controversy about using this combination over other therapies, such as aspirin or clopidogrel, for recurrent ischemic stroke prevention. Much of this controversy arises from limitations in the trial designs.

The first trial to show benefit with ASA-ERDP was ESPS2 (European Stroke Prevention Study 2), which demonstrated superiority of the combination over placebo in reducing recurrent stroke when treatment was added within 3 months of an index stroke.¹⁹ A few studies have evaluated ASA-ERDP compared to aspirin monotherapy; however, most of these studies were small and did not show any difference in outcomes.²⁰ Only ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial)²¹ carried significant weight

in a 2013 meta-analysis, which showed a significant reduction in recurrent events with the combination product compared to aspirin monotherapy.²⁰

Both the ESPS2 and ESPRIT trials had significant limitations.^{19,21} Patients in both studies had vascular comorbidities including atherosclerotic cardiovascular disease (ASCVD); however, pharmacotherapies designated to treat these diseases were not mentioned in the demographic data, nor were these medications taken into consideration to limit potential bias.^{19,21} Retrospectively, a significant proportion of aspirin doses utilized as a control in ESPRIT were inferior to the guideline-recommended dosing with 42% to 46% of patients receiving 30 mg/d.²¹ Despite these controversies, ASA-ERDP is still considered an alternative to aspirin monotherapy in the guidelines.⁷

■ **The timing of ASA-ERDP initiation** appears to be inversely related to the efficacy of the combination over therapeutic alternatives. Studies in which the therapy was initiated 3 to 6 months from the index stroke indicated favorable outcomes for the combination when compared to ASA or ERDP monotherapy.^{19,21} Studies utilizing early initiation (ie, within 24 or 48 hours of the index event) or even within 3 weeks showed no difference in outcomes; however, this may be due in part to the use of clopidogrel or other combination antiplatelet therapy as active comparators.²²⁻²⁴

Early initiation of ASA-ERDP also demonstrated a higher risk of major and intracranial bleeding compared to clopidogrel.²² Additionally, use of triple therapy with ASA-ERDP plus clopidogrel increased bleeding events without improving efficacy.²⁴ More recent studies of ASA-ERDP are focusing on earlier initiation of therapy; it is unknown whether the benefits of late initiation will be confirmed in future studies. Highlights of the major RCTs evaluating the safety and efficacy of ASA-ERDP are detailed in **TABLE 2**^{19,21-24}.

■ **The takeaway.** Methodological issues and potential confounding factors in many of the key trials for ASA-ERDP make it challenging to fully discern the role that ASA-ERDP may play in the secondary prevention

TABLE 2

Aspirin and extended-release dipyridamole for recurrent stroke: A summary of RCTs

Trial	Intervention	Time to treatment onset	Outcomes/results	Notes
ESPS2 ¹⁹ (1996)	ASA-ERDP 25/200 mg twice daily or ASA 25 mg twice daily or ERDP 200 mg twice daily vs placebo Treatment/study duration: 2 y	Treatment within 3 mo of index event	<i>Primary:</i> For ASA-ERDP vs placebo Stroke (OR = 0.59; 95% CI, 0.48-0.73) Death (OR = 0.90; 95% CI 0.73-1.12; <i>P</i> = NS) Stroke and/or death (OR = 0.71; 95% CI, 0.59-0.84)	Stroke NNT = 18 Stroke and/or death NNT = 18 ASA and ERDP monotherapy also significantly reduced stroke and stroke and/or death endpoints Included patients with atrial fibrillation (approximately 6.5% in each group)
ESPRIT ²¹ (2006)	ASA-ERDP 25/200 mg twice daily vs ASA (dosing varied) Treatment/study duration: Mean 3.5 yr (SD 2 yr)	Treatment within 6 mo of index event	<i>Primary:</i> Composite death from vascular cause, nonfatal stroke, nonfatal MI, major bleeding complication HR = 0.8 (95% CI, 0.66-0.98) ^a <i>Secondary:</i> Death from all vascular causes and nonfatal stroke HR = 0.78 (95% CI, 0.62-0.97) ^a Death from vascular causes, nonfatal stroke, nonfatal MI HR = 0.78 (95% CI, 0.62-0.97) ^a	Primary outcome NNT = 34 66%-69% of patients randomized 1-6 mo from event 42%-46% of patients were on 30 mg/d ASA
PROFESS ²² (2008)	ASA-ERDP 25/200 mg twice daily vs CLO 75 mg/d Treatment/study duration: mean 2.5 y (range 1.4-4.4 y)	Within 90 d of index event Median time: 15 d	<i>Primary:</i> Recurrent stroke of any type HR = 1.01 (95% CI, 0.92-1.11; <i>P</i> = NS) <i>Secondary:</i> Composite stroke, MI, or death from vascular causes HR = 0.99 (95% CI, 0.92-1.07; <i>P</i> = NS) <i>Tertiary:</i> Major bleeding, HR = 1.15 (95% CI, 1-1.22) Intracranial bleeding, HR = 1.42 (95% CI, 1.11-1.83)	Major bleed NNH = 193 Intracranial bleed NNH = 233 Underpowered 10% received CLO + ASA for 8 mo before switching to CLO monotherapy

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of stroke. Further evidence utilizing appropriate controls, timing, and assessment of confounders is needed. Additionally, ASA-ERDP is plagued by tolerability issues such as headache, nausea, and vomiting, leading to higher rates of discontinuation than its comparators in clinical trials. Accordingly, the maintenance use of ASA-ERDP for sec-

ondary stroke prevention may be considered less preferred than other recommended alternatives such as aspirin or clopidogrel monotherapies. **JFP**

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TABLE 2

Aspirin and extended-release dipyridamole for recurrent stroke:
A summary of RCTs (cont'd)

Trial	Intervention	Time to treatment onset	Outcomes/results	Notes
EARLY ²³ (2010)	Day 1-7: ASA-ERDP 25/200 mg twice daily vs ASA 100 mg/d Day 8-90: ASA-ERDP 25/200 mg twice daily, both groups Treatment/study duration: 90 d	Within 24 hr of index event	Primary: Functionality change at Day 90 -2 vs -2 (P = NS) Secondary: Composite safety and efficacy HR = 0.73 (95% CI, 0.44-1.19; P = NS)	Mean NIHSS score < 4 at baseline indicated low-severity strokes Results represent early vs late initiation of ASA-ERDP (< 7 d vs > 7 d)
TARDIS ²⁴ (2018)	ASA-ERDP + CLO vs CLO or ASA-ERDP (guideline dosing) Treatment/study duration: 90 d	Within 48 hr of index event	Primary: Incidence and severity of recurrent stroke/TIA up to 90 d HR = 0.9 (95% CI, 0.67-1.20; P = NS) Safety: All bleeding events 20% vs 9% (P < .0001) Fatal bleed 1% vs < 1% (P = NS) Minor bleed 16% vs 7%	All bleeding NNH = 10 Thrombolysis allowed, randomization delayed 24 hr after administration Loading doses given

ASA, aspirin; CLO, clopidogrel; ERDP, extended-release dipyridamole; HR, hazard ratio; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale; NNH, number needed to harm; NNT, number needed to treat; NS, nonsignificant; RCTs, randomized controlled trials; SD, standard deviation; TIA, transient ischemic attack.

^aHR for intention-to-treat arm.

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