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Dual Antiplatelet Therapy after Noncardioembolic Ischemic Stroke or Transient Ischemic Attack: Pros and Cons

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Dual antiplatelet therapy simultaneously blocks different platelet activation pathways and might thus be more potent at inhibiting platelet activation and more effective at reducing major ischemic vascular events compared to antiplatelet monotherapy. Aspirin plus clopidogrel dual therapy is now the standard therapy for patients with acute coronary syndrome and for those undergoing percutaneous coronary intervention. However, dual antiplatelet therapy carries an increased risk of bleeding. Patients with ischemic stroke or transient ischemic attack (TIA) are generally older and likely to have a fragile cerebrovascular bed, which further increases the risk of systemic major bleeding events and intracranial hemorrhage. Clinical trials and meta-analyses suggest that in comparison to antiplatelet monotherapy, dual antiplatelet therapy initiated early after noncardioembolic ischemic stroke or TIA further reduces the rate of recurrent stroke and major vascular events without significantly increasing the rate of major bleeding events. In contrast, studies of long-term therapy in patients with noncardioembolic ischemic stroke or TIA have yielded inconsistent data regarding the benefit of dual antiplatelet therapy over monotherapy. However, the harm associated with major bleeding events, including intracranial hemorrhage, which is generally more disabling and more fatal than ischemic stroke, is likely to increase with dual antiplatelet therapy. Physicians should carefully assess the benefits and risks of dual antiplatelet therapy versus antiplatelet monotherapy when managing patients with ischemic stroke or TIA.
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Key Words ischemic stroke, TIA, dual antiplatelet therapy.

Introduction

More than 100000 Korean people experience a new or recurrent stroke each year.[1] Ischemic stroke accounts for more than 75% of all strokes, and one in five ischemic strokes is a recurrent stroke.[1,2] The introduction of therapies with proven efficacy into clinical practice has resulted in a substantial decline in the rates of recurrent stroke and major vascular events over the last 5 decades, and antiplatelet therapy has contributed to the significant decline in vascular event rates in patients with ischemic stroke or transient ischemic attack (TIA).[3,4]

Currently five antiplatelet agents, or combinations thereof, have been formally endorsed by the Korean stroke guidelines for secondary stroke prevention: aspirin, clopidogrel, cilostazol, triflusal, and extended-release dipyridamole plus aspirin (ERDP-ASA).[5] These individual antiplatelet agents operate via different mechanisms to inhibit the platelet-activation process: aspirin and triflusal inhibit cyclooxygenase, clopidogrel irreversibly blocks the P2Y12 subtype of the adenosine diphosphate receptor, dipyridamole inhibits phosphodiesterase (PDE), and cilostazol selectively inhibits PDE-3. Antiplatelet monotherapy is generally recommended and widely used in patients with noncardioembolic ischemic stroke or TIA, but the magnitude of its preventive effect is modest.[3]

Since platelet activation resulting in arterial occlusion occurs via multiple mechanisms, dual antiplatelet therapy that simultaneously blocks different platelet-activation pathways may more potently inhibit platelet activation and more effectively reduce the rate of major ischemic vascular events compared to antiplatelet monotherapy. In coronary heart disease (CHD), dual antiplatelet therapy with aspirin plus clopidogrel

is the standard therapy for acute coronary syndrome (ACS) and for percutaneous coronary intervention (PCI). However, dual antiplatelet therapy carries an increased risk of bleeding. Patients with ischemic stroke or TIA are more likely to be older and to have a fragile cerebrovascular bed compared to those with ischemic events in other vascular beds, and might thereby be particularly prone to intracranial hemorrhage as well as other major bleeding events. The risk of recurrent stroke is highest during the early period after ischemic stroke or TIA; as such, the balance of benefit and harm of dual antiplatelet therapy over monotherapy might depend upon the disease period (acute vs. chronic stage) and the duration of therapy (short term vs. long term). This article reviews the pros and cons of dual antiplatelet therapy for patients with ischemic stroke or TIA.

Dual Antiplatelet Therapy in CHD

The benefit of dual therapy with clopidogrel plus aspirin in patients with ACS and those undergoing PCI has been well established in multiple large clinical trials.[6-11] Compared to aspirin monotherapy, clopidogrel (300 mg loading followed by 75 mg once daily in all except for one of the trials) plus aspirin has been shown to reduce the risk of the composite of vascular events [absolute risk reduction (ARR)=0.9−6.7%; relative risk reduction (RRR)=8.9−41.9%] at the cost of more major bleeding events [absolute risk increase (ARI)=-0.6% to 2.1%; relative risk increase=-54.5% to 37.0%] over variable periods from 8 days to 12 months. It should be noted that these trials exclusively included the following types of patients who were in the high-risk period: patients experiencing ST-elevation myocardial infarction (STEMI), ACS with non-STEMI, or suspected acute myocardial infarction (MI) within 12 or 24 hours of onset, or patients with symptomatic CHD who were highly likely to undergo elective PCI. In addition, the duration of dual antiplatelet therapy was ≤12 months. Therefore, the benefit and harm of dual antiplatelet therapy observed in patients with ACS or those undergoing PCI are not directly applicable to long-term dual antiplatelet therapy for patients with ischemic stroke or TIA.

Short-Term Dual Antiplatelet Therapy for Patients with Acute Ischemic Stroke and TIA

Dipyridamole plus aspirin in acute ischemic stroke and TIA

The early treatment with ERDP-ASA for TIA or ischemic stroke (EARLY) trial, which was a prospective, randomized, open-label, blinded-end-point evaluation (PROBE) study enrolling 543 patients acute ischemic stroke or TIA within 24 hours of onset, compared clinical outcomes in patients treated with early initiation of ERDP-ASA (200 mg of ERDP plus 25 mg of aspirin twice daily) versus late initiation after 7 days of aspirin monotherapy (100 mg once daily).[12] The primary endpoint, a 90-day modified Rankin Scale (mRS) score of 0 or 1 [56.4% in the ERDP-ASA group vs. 52.4% in the aspirin monotherapy group, absolute difference=4.1%, 95% confidence interval (CI)=-4.5 to 12.6, p=0.45], and the overall mRS score distribution [odds ratio=1.07, 95% CI=0.78 to 1.46, p=0.68] did not differ significantly between the two groups. The early-dual-therapy-initiation group appeared to have a lower rate of the composite endpoint of nonfatal stroke, TIA, nonfatal MI, major bleeding complications, and mortality than the late initiation group, but the difference was not statistically significant [10% vs. 15%; hazard ratio (HR)=0.73, 95% CI=0.44 to 1.19, p=0.20]. The two groups had comparable and very low rates of major bleeding (<0.4% for both). The results of the EARLY trial suggest that the early initiation of ERDP-ASA therapy is a safe option, but is no more efficacious than late initiation after aspirin monotherapy during the acute stage of ischemic stroke.

Clopidogrel plus aspirin in acute ischemic stroke and TIA

In two small trials [Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) and Clopidogrel plus Aspirin for Infarction Reduction in Acute Stroke or Transient Ischemic Attack Patients with Large Artery Stenosis and Microembolic Signals (CLAIR)], clopidogrel (300 mg loading followed by 75 mg once daily) plus aspirin (75−160 mg once daily) was found to be more effective than aspirin monotherapy for preventing the asymptomatic microembolic signals detected by transcranial Doppler ultrasound. The CARESS trial enrolled 107 patients with recent (within 3 months) symptomatic extracranial carotid stenosis,[13] and the CLAIR trial enrolled 100 patients with recent (within 7 days) symptomatic internal carotid or middle cerebral artery stenosis (intracranial stenosis in 93%).[14] However, these two trials were proof-of-concept studies using surrogate markers, and thus did not have adequate statistical power to demonstrate the clinical efficacy of reducing stroke or TIA with clopidogrel plus aspirin dual therapy.

The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial compared the efficacy of clopidogrel (300 mg loading followed by 75 mg once daily) plus aspirin [162 mg loading dose (for aspirin-naïve patients only) followed by 81 mg once daily] versus aspirin monotherapy in preventing recurrent stroke within 90 days in 392 patients with minor stroke or TIA within 7 days.[15]

Although there was no significant difference in the rate of 90-day recurrent stroke between the dual therapy and monotherapy groups (7.1% vs. 10.8%; risk ratio=0.7, 95% CI=0.3 to 1.2, p=0.19), dual therapy was associated with a significant increase in symptomatic bleeding compared to aspirin monotherapy (3.0% vs. 0%, p=0.03): there were seven less recurrent strokes, but six more symptomatic bleeding events (including two more intracranial hemorrhage). The original enrollment plan of the FASTER trial was to recruit 500 patients to test the trial feasibility and then to proceed to enroll 7500 patients for the main trial to detect a 2% ARR of recurrent stroke with the dual therapy versus aspirin monotherapy.[16] However, due to a slow recruitment rate, the trial was terminated after enrolling only 392 patients; it was therefore a substantially underpowered study.

The largest trial was the Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial, which compared clopidogrel (300 mg loading followed by 75 mg once daily for 90 days) plus aspirin (75 mg once daily for the first 21 days) versus aspirin monotherapy (75 mg once daily for 90 days) in 5170 patients with minor ischemic stroke [National Institutes of Health Stroke Scale (NIHSS) score <4] or high-risk TIA [Age, Blood pressure, Clinical features, Duration, and Diabetes ($ABCD^2$) score ≥4] within 24 hours of symptom onset.[17] The rate of the primary endpoint of a recurrent stroke within 90 days was significantly lower for dual therapy than for aspirin monotherapy (8.2% vs. 11.7%; HR=0.68, 95% CI=0.57−0.81, p<0.001). The rate of composite events including stroke, MI, or vascular death was also lower with dual therapy than with aspirin monotherapy (8.4% vs. 11.9%; HR=0.69, 95% CI=0.58−0.82, p<0.001). A particularly notable finding was that the rate of moderate or severe bleeding did not differ between the two groups (0.3% vs. 0.3%, p=0.73).

Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Event was a pivotal trial for the following reasons: 1) it was the first large trial of dual therapy focusing on patients with TIA and minor ischemic stroke who are at high risk of recurrent ischemic stroke and at low risk of intracranial bleeding, 2) it tested a short course of dual antiplatelet therapy, thereby maximizing the efficacy and minimizing the risk, and 3) it demonstrated a substantial treatment effect with a number-needed-to-treat of 29 for preventing one recurrent stroke. However, the limitations of this trial should also be noted. The trial was performed in China where the risk of stroke is much higher than in other countries. Moreover, the risk-factor control for secondary stroke prevention was insufficient, as reflected by the low rates of treatment with antihypertensive agents (35%), lipid-lowering agents (42%), and antidiabetic drugs (13%), but a high rate of using traditional Chinese drugs (25%) during the follow-up. Therefore, the generalizability of the findings of the CHANCE trial to other populations is questionable. Currently, a similar North-American trial called the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial is ongoing (ClinicalTrials.gov number, NCT00991029), which will enroll 4150 patients with minor stroke (NIHSS score <4) or high-risk TIA ($ABCD^2$ score ≥4) within a narrower time window of 12 hours from the onset, and will use a higher clopidogrel loading dose of 600 mg.[18] However, it should be noted that the results of both the CHANCE and POINT trials will be directly applicable to patients with minor stroke or high-risk TIA presenting within 12 or 24 hours.

Meta-analyses comparing dual antiplatelet therapy versus antiplatelet monotherapy in acute ischemic stroke or TIA

A meta-analysis of 12 trials involving 3766 patients with acute noncardioembolic stroke or TIA within 3 days of onset showed that compared to monotherapy with aspirin, clopidogrel, or dipyridamole, dual antiplatelet therapy with dipyridamole plus aspirin (DP-ASA) or clopidogrel plus aspirin led to lower risks of recurrent stroke (3.3% vs. 5.0%; risk ratio=0.67, 95% CI=0.49−0.93), major vascular events including stroke, MI, and vascular death (4.4% vs. 6.0%; risk ratio=0.75, 95% CI=0.56−0.99), and the composite of stroke, TIA, ACS, and all-cause deaths (6.6% vs. 9.1%; risk ratio=0.71, 95% CI=0.56−0.91), but no significant difference in major bleeding events (0.9% vs. 0.4%; risk ratio=2.09, 95% CI=0.86−5.06).[19]

After publication of the CHANCE trial, an updated meta-analysis of 14 trials (the CHANCE and a Japanese single-center trials were added to the previous 12 trials) was conducted, which involved 9012 patients within 3 days of acute noncardioembolic stroke or TIA.[20] The comparison arms were clopidogrel plus aspirin versus aspirin in 5 trials (5901 patients), clopidogrel plus aspirin versus clopidogrel in 1 trial (491 patients), DP-ASA versus aspirin in 5 trials (964 patients), DP-ASA versus dipyridamole in 2 trials (220 patients), DP-ASA versus clopidogrel in 1 trial (1360 patients), and cilostazol plus aspirin versus aspirin in 1 trial (76 patients). Dual therapy compared to monotherapy significantly reduced recurrent stroke (6.2% vs. 9.0%; risk ratio=0.69, 95% CI=0.60−0.80, p<0.001) and the composite of stroke, TIA, ACS, and all-cause deaths (8.6% vs. 12.1%; risk ratio=0.71, 95% CI=0.63−0.81, p<0.001) during variable follow-up durations ranging from 7 days to >18 months. Major bleeding events appeared to be slightly increased with dual therapy, but the increase was not statistically significant (0.5% vs. 0.4%; risk ratio=1.35, 95% CI=0.70−2.59, p=0.37). However, a major limitation of both of these meta-analyses is that they pooled trials

that varied widely with respect to the enrolled patients, antiplatelet therapy, interval from onset to enrollment, and treatment duration. In addition, the results of the second meta-analysis might have been largely driven by the CHANCE population, which accounted for 57% of the patients included in the study.[20] However, the direction and magnitude of the treatment effect were generally comparable when the CHANCE population was not included.[19]

Long-term dual antiplatelet therapy for patients with ischemic stroke and TIA

Long-term DP-ASA therapy in patients with ischemic stroke or TIA

Two small trials performed during the late 1970s and early 1980s failed to show the superiority of DP-ASA dual therapy over aspirin monotherapy.[21,22] Four subsequent large randomized trials have tested the efficacy of DP-ASA in patients with stroke or TIA.

The European Stroke Prevention Study (ESPS), the first large trial enrolling 2500 patients with TIA, reversible ischemic neurologic deficit, or stroke within 3 months of onset, showed that after 2 years, the DP-ASA group (75 mg of immediate-release dipyridamole plus 325 mg of aspirin three times daily) had lower rates of the primary endpoint of stroke or death (15.2% vs. 22.6%; RRR=33%, $p<0.001$), recurrent stroke (9.1% vs. 14.7%; RRR=35%, $p<0.001$), and mortality (8.6% vs. 12.5%, $p<0.01$) compared to the placebo group.[23]

The second large trial was the ESPS-2 study, which randomly assigned 6602 patients with TIA or ischemic stroke within 3 months of onset to one of four groups: ERDP-ASA dual therapy (200 mg of ERDP plus 25 mg of aspirin twice daily), ERDP monotherapy (200 mg twice daily), aspirin monotherapy (25 mg twice daily), and placebo. ERDP-ASA dual therapy reduced recurrent stroke with RRRs of 23.1% ($p=0.006$), 24.7% ($p=0.002$), and 37.0% ($p<0.001$) compared with aspirin, ERDP, and placebo, respectively. For the composite endpoint of stroke or all-cause deaths, the dual therapy was superior to placebo (RRR=24.4%, $p<0.001$), and trended toward a reduction compared to aspirin (RRR=12.9%, $p=0.056$) and ERDP (RRR=10.7%, $p=0.073$). The rates of recurrent stroke and the composite endpoint were reduced for both the aspirin and ERDP monotherapies compared to placebo. Bleeding from any site (from mild to fatal bleeding) occurred in 4.5%, 4.7%, 8.2%, and 8.7% of subjects in the placebo, ERDP monotherapy group, aspirin monotherapy, and ERDP-ASA groups, respectively, suggesting that aspirin is associated with an increased bleeding risk whereas ERDP is not.[24] Headache resulting in discontinuation of study medication was more frequent with ERDP monotherapy (8.0%) and ERDP-ASA (8.1%) than with aspirin monotherapy (1.9%) or placebo (2.4%; treatment groups overall comparison, $p<0.001$). However, even after the ESPS-2 study, the benefit of DP-ASA dual therapy over aspirin monotherapy was not widely accepted because 1) it was demonstrated by only one trial, 2) the ESPS-2 trial used a relatively low dose of aspirin (25 mg twice daily), 3) there was no reduction in the risks of MI and vascular death despite the more potent antiplatelet activity of dual therapy, and 4) in a meta-analysis of 11 trials, DP-ASA dual therapy was associated with a marginal reduction of vascular events compared to aspirin monotherapy, a finding that was largely driven by the ESPS-2 data [relative risk (RR)=0.90, 95% CI=0.80−1.00] and was not associated with a reduction in the rate of vascular death (RR=1.03, 95% CI=0.87−1.22).[25]

The uncertainty about the superior efficacy of the dual therapy with dipyridamole plus aspirin over aspirin monotherapy led to a third large trial, the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), which used a PROBE design, in which DP-ASA [fixed-dose combination of 200 mg of ERPD plus 25 mg of aspirin twice daily or as a free combination of 200 mg of dipyridamole twice daily plus aspirin (30−325 mg/day)] was compared with aspirin monotherapy (30−325 mg/day) in 2763 patients with ischemic stroke or TIA of presumed arterial origin within 6 months of onset. The primary endpoint of the composite of vascular death, nonfatal stroke, nonfatal MI, or major bleeding complication was significantly reduced with dual therapy versus aspirin monotherapy (13% vs. 16%; HR=0.80, 95% CI=0.66−0.98; ARR=1.0%/year, 95% CI=0.1−1.8). The rates of the major vascular events of vascular death, nonfatal stroke, and nonfatal MI (excluding major bleeding events) were also significantly lower with dual therapy (HR=0.78, 95% CI=0.63−0.97). Dual therapy was associated with a trend toward a reduction in ischemic stroke (HR=0.84, 95% CI=0.64−1.10) and major ischemic events including nonhemorrhagic vascular death, nonfatal ischemic stroke, and nonfatal MI (HR=0.81, 95% CI=0.65−1.01). The dual therapy group more frequently discontinued the trial medication compared to the aspirin monotherapy group, and at least 25% of the discontinuations were attributed to headache. An accompanying updated meta-analysis found that DP-ASA dual therapy versus aspirin monotherapy was more effective for preventing the major vascular events of vascular death, nonfatal stroke, and nonfatal MI (HR=0.82, 95% CI=0.74−0.91).[26]

The ESPRIT results have been the subject of some debate. First, some of the findings cannot be explained by dual-therapy-enhanced antiplatelet activity. The dual therapy group had fewer major bleeding events compared to the monotherapy group, and the difference was more prominent for on-treatment analysis (statistically significant) than for intention-to-

treat analysis (statistically nonsignificant). According to the Kaplan-Meier curves for the composite ischemic vascular events, there was no difference in the first 2.5 years, but a difference emerged thereafter. If the benefit of dual therapy was related to an enhanced antiplatelet effect, the Kaplan-Meier curves would have diverged earlier. Second, the ESPRIT used a PROBE design, which carries a risk of event reporting bias. In addition, the ESPRIT investigators did not provide information on risk factor control during the follow-up, which is particularly important for an unblinded study.

Since earlier trials and a network meta-analysis suggested that DP-ASA dual therapy had a greater vascular protection effect than did clopidogrel monotherapy and both regimens were more effective than aspirin monotherapy,[26-29] the Prevention Regimen for Effectively Avoiding Second Strokes study was conducted to compare ERDP-ASA dual therapy (200 mg of ERDP plus 25 mg of aspirin twice daily) and clopidogrel monotherapy (75 mg once daily) among 20332 patients with ischemic stroke within 3 months of onset with a mean follow-up of 2.5 years.[30] At its inception, the trial aimed to compare ERDP-ASA and clopidogrel plus aspirin, but after the results of the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent TIA or Ischemic Stroke (MATCH) trial,[31] the design was modified to compare ERDP-ASA and clopidogrel monotherapy after enrolling 2027 patients. In addition, the planned statistical analysis was changed from a superiority test to a noninferiority test because of lower-than-expected event rates observed during the trial. The primary endpoint of recurrent stroke did not differ between the ERDP-ASA and clopidogrel groups (9.0% vs. 8.8%; HR=1.01, 95% CI=0.92−1.11), but the trial failed to demonstrate the noninferiority of ERDP-ASA to clopidogrel monotherapy because the upper limit of the confidence interval crossed the predetermined noninferiority margin of 1.075 (indicating a 7.5% noninferiority difference). The ERDP-ASA group appeared to have fewer ischemic strokes, although the difference was not statistically significant (7.7% vs. 7.9%; HR=0.97, 95% CI=0.88−1.07), but had significantly more intracranial hemorrhages (1.4% vs. 1.0%; HR=1.42, 95% CI=1.11−1.83). The rates of major vascular events including stroke, MI, and vascular death did not differ between the two groups (13.1% vs. 13.1%; HR=0.99, 95% CI=0.92−1.07), but the ERDP-ASA group had a higher rate of major bleeding events (4.1% vs. 3.6%; HR=1.15, 95% CI=1.00−1.32). However, the rate of treatment adherence was lower for patients receiving ERDP-ASA than for those receiving clopidogrel, which was due to more frequent discontinuation of the study drug, largely due to headache and gastrointestinal adverse effects, and lower medication compliance (defined as taking the study medication for >75% of the time). The imbalanced adherence to treatment might have affected the trial results. Whatever the reasons, clopidogrel monotherapy and ERDP-ASA dual therapy were found to be equally efficacious for secondary stroke prevention.

Long-term clopidogrel plus aspirin therapy in patients with ischemic stroke or TIA

The first large trial was the MATCH study, which was a randomized, double-blind, placebo-controlled trial to compare clopidogrel (75 mg once daily) plus aspirin (75 mg once daily) versus clopidogrel monotherapy in patients who had an ischemic stroke or TIA, within 3 months of onset, and had one or more risk factors of previous ischemic stroke, previous MI, angina pectoris, diabetes mellitus, or symptomatic peripheral arterial disease (PAD). The MATCH trial enrolled 7599 patients, and the mean follow-up was 18 months. The clopidogrel plus aspirin group and the clopidogrel monotherapy group had similar rates for the primary efficacy endpoint of the composite of ischemic stroke, MI, vascular death, or hospitalization for TIA, angina pectoris, or worsening of PAD (15.7% vs. 16.7%; RRR=6.4%, 95% CI=-4.6 to 16.3, p=0.244) as well as for secondary efficacy endpoints of major vascular events of stroke, MI, or vascular death (11.7% vs. 12.4%; RRR=5.9%, 95% CI=-7.1 to 17.3, p=0.360) and recurrent ischemic stroke (10.6% vs. 11.3%; RRR=6.6%, 95% CI=-7.0 to 18.5, p=0.324). However, the dual therapy group had significantly more life-threatening bleeding events compared to the clopidogrel monotherapy group (2.6% vs. 1.3%; ARI=1.26%, 95% CI=0.64−1.88, p<0.0001), and more major bleeding events (1.9% vs. 0.6%; ARI=1.36%, 95% CI=0.86−1.86, p<0.0001).[31] Therefore, adding aspirin to clopidogrel provided no further benefit, while increasing the harm.

There are several criticisms of the MATCH trial. First, less than 20% of patients were enrolled within 7 days from stroke onset, and more than 30% were enrolled after 30 days. Therefore, the trial largely missed the period when the risk is high and the treatment effect would be greatest. Second, more than 50% of the patients had an etiologic mechanism of small-vessel occlusion, which has a lower risk of recurrent stroke but a higher risk of subsequent intracerebral hemorrhage than other ischemic stroke subtypes, and thereby increases the risk of major bleeding and decreases the benefit of clopidogrel and aspirin dual therapy.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial was another large randomized, double-blind, placebo-controlled trial, which compared clopidogrel (75 mg once daily) plus aspirin (75−162 mg once daily) versus aspirin monotherapy in 15603 patients with established cardiovascular disease or with multiple risk factors. The trial revealed no significant benefit of

adding clopidogrel to aspirin during the 28-month follow-up for preventing the composite of vascular events in this broad population of patients at high risk for atherothrombotic events.[32]

When analyzing the data of 9478 patients with established cardiovascular disease (prior MI, stroke, or symptomatic PAD), dual therapy significantly reduced the composite of MI, stroke, or vascular death (7.3% vs. 8.8%; HR=0.83, 95% CI=0.72−0.96, p=0.01) compared to aspirin monotherapy, without increasing the rate of severe bleeding events (1.7% vs. 1.5%; HR=1.12, 95% CI=0.81−1.53, p=0.50).[33] However, moderate bleeding events were more frequent with dual therapy in this subgroup of patients (2.0% vs. 1.3%; HR=1.60, 95% CI=1.16−2.20, p=0.004). Another subgroup analysis of 4320 patients with prior ischemic stroke or TIA found that dual therapy tended to reduce the composite of stroke, MI, or vascular death (8.1% vs. 9.6%; HR=0.84, 95% CI=0.69−1.03) and recurrent stroke (4.9% vs. 6.1%; HR=0.80, 95% CI=0.62−1.03) without significantly increasing the rate of severe bleeding events (1.9% vs. 1.7%; HR=1.11, 95% CI=0.71−1.73), but again significantly increased that of moderate bleeding events (2.4% vs. 1.1%; HR=2.15, 95% CI=1.32−3.49).[34] However, post-hoc subgroup analysis is associated with high risk of bias related to multiple testing and selective reporting, and thereby should be considered as hypothesis-generating only.

The most recent trial was the Secondary Prevention of Small Subcortical Strokes (SPS3) trial, which was a randomized, double-blind, placebo-controlled trial that compared clopidogrel (75 mg once daily) plus aspirin (325 mg once daily) versus aspirin monotherapy in 3020 patients who had a symptomatic lacunar infarction confirmed by magnetic resonance imaging within 6 months of onset, with a mean follow-up of 3.4 years. The rate of primary endpoint of recurrent stroke (ischemic or hemorrhagic stroke) did not differ between the clopidogrel plus aspirin group and the aspirin monotherapy groups (2.5%/year vs. 2.7%/year; HR=0.92, 95% CI=0.72−1.16, p=0.48). There were no differences between dual therapy and aspirin monotherapy in the rate of ischemic stroke (2.0%/year vs. 2.4%/year; HR=0.82, 95% CI=0.63−1.09, p=0.13) or disabling or fatal stroke (0.84%/year vs. 0.78%/year; HR=1.06, 95% CI=0.69−1.64, p=0.79). However, the dual therapy group had a higher major bleeding rate than the aspirin monotherapy group (2.1%/year vs. 1.1%/year; HR=1.97, 95% CI=1.41−2.71, p<0.001) and had numerically more cases of intracranial hemorrhage (0.42%/year vs. 0.25%/year; HR=1.65, 95% CI 0.83−3.31, p=0.15). The rate of all-cause deaths was higher in the dual therapy group than the monotherapy group (2.1%/year vs. 1.4%/year; HR=1.52, 95% CI=1.14−2.04, p=0.004); these deaths were largely attributed to the increase in definite and probable vascular deaths.[35] The SPS3 trial clearly showed that the addition of clopidogrel to aspirin for long-term therapy should be contraindicated in patients with lacunar infarction.

Meta-analysis of long-term dual therapy in patients with ischemic stroke or TIA

A recent meta-analysis of 7 trials involving 39574 patients with ischemic stroke or TIA compared long-term (range=1.3−3.5 years) dual antiplatelet therapy and antiplatelet monotherapy for risk of intracranial hemorrhage and benefit of preventing recurrent stroke: 2 trials with clopidogrel plus aspirin versus aspirin, 1 trial with clopidogrel plus aspirin versus clopidogrel, 2 trials with DP-ASA versus aspirin, 1 trial with DP-ASA versus clopidogrel, and 1 trial with ticlopidine plus aspirin versus ticlopidine. Dual antiplatelet therapy was associated with a trend toward a reduction in recurrent stroke risk compared to aspirin monotherapy (RR=0.89, 95% CI=0.78 to 1.01), but had no increase in the intracranial hemorrhage risk (RR=0.99, 95% CI=0.70 to 1.42). Compared to clopidogrel monotherapy, dual therapy had a comparable risk reduction for recurrent stroke (RR=1.01, 95% CI=0.93−1.08), but incurred a higher risk of intracranial hemorrhage (RR=1.46, 95% CI=1.17−1.82), resulting in an average of 4 more intracranial hemorrhages per 1000 patients treated (95% CI=1−7).[36] The magnitude of the risk increase was not substantial. However, given that dual therapy conferred no further benefit with respect to preventing recurrent stroke, and the greater disabling and fatal health impacts of intracranial hemorrhage compared with ischemic stroke, dual therapy cannot be recommended over clopidogrel monotherapy as a long-term therapy.

In summary, dual antiplatelet therapy initiated early after ischemic stroke or TIA might further reduce recurrent stroke and major vascular events compared to antiplatelet monotherapy, with no significant increase in major bleeding events. In contrast, for the long-term therapy usually administered after a high-risk period, dual antiplatelet therapy is likely to increase the harm caused by major bleeding, including intracranial hemorrhage, and its benefit of further preventing recurrent stroke as well as major ischemic events remains controversial. The risk of recurrent stroke is highest during the early period after ischemic stroke or TIA, but this risk decreases with time. Accordingly, the benefit of dual antiplatelet therapy more potently blocking platelet activation pathways might outweigh the bleeding risk for short-term use, but might be outweighed by the bleeding risk for long-term use. Further research is therefore needed to establish the best candidates for dual antiplatelet therapy. Currently, Korean, American, and European stroke guidelines are not recommending long-term dual antiplatelet therapy except for ERDP-ASA dual therapy.[37-39]

Conflicts of Interest

The author has no financial conflicts of interest.

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REFERENCES

1. Hong KS, Bang OY, Kang DW, Yu KH, Bae HJ, Lee JS, et al. Stroke Statistics in Korea: Part I. Epidemiology and Risk Factors: A Report from the Korean Stroke Society and Clinical Research Center for Stroke. *J Stroke* 2013;15:2-20.
2. Jung KH, Lee SH, Kim BJ, Yu KH, Hong KS, Lee BC, et al. Secular trends in ischemic stroke characteristics in a rapidly developed country: results from the Korean Stroke Registry Study (secular trends in Korean stroke). *Circ Cardiovasc Qual Outcomes* 2012;5:327-334.
3. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;324:71-86.
4. Hong KS, Yegiaian S, Lee M, Lee J, Saver JL. Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. *Circulation* 2011;123:2111-2119.
5. Park TH, Kim MK, Oh HG, Oh MS, Yu KH, Hong KS, et al. Antiplatelet Therapy for Secondary Stroke Prevention: 2012 Focused Update of Korean Clinical Practice Guidelines for Stroke. *Korean J Stroke* 2012;14:1-5.
6. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001; 345:494-502.
7. Chen ZM, Jiang LX, Chen YP, Xie JX, Pan HC, Peto R, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet* 2005;366:1607-1621.
8. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179-1189.
9. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001;358:527-533.
10. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288:2411-2420.
11. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA* 2005;294:1224-1232.
12. Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T, et al. Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol* 2010;9:159-166.
13. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation* 2005;111:2233-2240.
14. Wong KS, Chen C, Fu J, Chang HM, Suwanwela NC, Huang YN, et al. Clopidogrel plus aspirin versus aspirin alone for reducing embolisation in patients with acute symptomatic cerebral or carotid artery stenosis (CLAIR study): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol* 2010;9:489-497.
15. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM, et al. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol* 2007;6:961-969.
16. Kennedy J, Eliasziw M, Hill MD, Buchan AM. The fast assessment of stroke and transient ischemic attack to prevent early recurrence (FASTER) trial. Proceedings of the 2006 International Stroke Conference; 2006 Feb 15-18; Orlando, FL. Dallas, TX: American Heart Association; 2006.
17. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369:11-19.
18. Johnston SC, Easton JD, Farrant M, Barsan W, Battenhouse H, Conwit R, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. *Int J Stroke* 2013;8:479-483.
19. Geeganage CM, Diener HC, Algra A, Chen C, Topol EJ, Dengler R, et al. Dual or mono antiplatelet therapy for patients with acute ischemic stroke or transient ischemic attack: systematic review and meta-analysis of randomized controlled trials. *Stroke* 2012;43:1058-1066.
20. Wong KS, Wang Y, Leng X, Mao C, Tang J, Bath PM, et al. Early dual versus mono antiplatelet therapy for acute non-cardioembolic ischemic stroke or transient ischemic attack: an updated systematic review and meta-analysis. *Circulation* 2013;128:1656-1666.
21. Bousser MG, Eschwege E, Haguenau M, Lefaucconnier JM, Thibult N, Touboul D, et al. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. *Stroke* 1983;14:5-14.
22. Persantine Aspirin Trial in cerebral ischemia. Part II: Endpoint results. The American-Canadian Co-Operative Study group. *Stroke* 1985;16: 406-415.
23. The European Stroke Prevention Study (ESPS). Principal end-points. The ESPS Group. *Lancet* 1987;2:1351-1354.
24. European Stroke Prevention Study 2: efficacy and safety data. 8. Safety. *J Neurol Sci* 1997;151(Suppl):S41-S51.
25. De Schryver EL, Algra A, van Gijn J. Cochrane review: dipyridamole for preventing major vascular events in patients with vascular disease. *Stroke* 2003;34:2072-2080.
26. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* 2006;367:1665-1673.
27. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet* 1996;348:1329-1339.
28. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
29. Thijs V, Lemmens R, Fieuws S. Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. *Eur Heart J* 2008;29:1086-1092.
30. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;359:1238-1251.
31. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet* 2004;364:331-337.
32. Bhatt DL, Fox KA, Hacke W, Berger PB, Black HR, Boden WE, et al.

Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-1717.
33. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol* 2007;49:1982-1988.
34. Hankey GJ, Johnston SC, Easton JD, Hacke W, Mas JL, Brennan D, et al. Effect of clopidogrel plus ASA vs. ASA early after TIA and ischaemic stroke: a substudy of the CHARISMA trial. *Int J Stroke* 2011; 6:3-9.
35. SPS3 Investigators, Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012;367:817-825.
36. Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbiagele B. Risk-benefit profile of long-term dual- versus single-antiplatelet therapy among patients with ischemic stroke: a systematic review and meta-analysis. *Ann Intern Med* 2013;159:463-470.
37. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the american heart association/american stroke association. *Stroke* 2011;42:227-276.
38. European Stroke Organisation (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;25:457-507.
39. Clinical Research Center for Stroke (KR). *Clinical Practice Guideline for Stroke*. Rev. ed. Seoul: Clinical Research Center for Stroke, 2013.