共識聲明

Dual Antiplatelet Therapy in the Management of Acute Minor Ischemic Stroke and High-Risk Transient Ischemic Attack: An Expert Consensus Statement from Taiwan Stroke Society and Taiwan Society of Emergency Medicine

Po-Lin Chen[1], Ying-Ju Chen[2], Chih-Ping Chung[3], Chen-June Seak[4], Jiann-Shing Jeng[5], Ming-Ju Hsieh[6], Li-Ming Lien[7], Jiann-Hwa Chen[8], Yu-Wei Chen[9], Te-Fa Chiu[10], Jiunn-Tay Lee[11*], Chip-Jin Ng[12*]

[1]Division of Neurology, Neurological Institute, Taichung Veterans General Hospital, Taichung, Taiwan.
[2]Department of Emergency Medicine, Taipei Veterans General Hospital, Taiwan.
[3]Department of Neurology, Neurological Institute, Taipei Veterans General Hospital, Taipei, Taiwan.
[4]Department of Emergency Medicine, New Taipei Municipal Tucheng Hospital, New Taipei City and College of Medicine, Chang Gung University, Taoyuan, Taiwan.
[5]Department of Neurology and Stroke Center, National Taiwan University Hospital, Taipei, Taiwan.
[6]Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan.
[7]Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.
[8]Department of Emergency Medicine, Cathay General Hospital, Taipei, Taiwan.
[9]Department of Neurology, Landseed International Hospital, Taoyuan, Taiwan.
[10]Department of Emergency Medicine, China Medical University Hospital, Taichung, Taiwan.
[11]Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Neihu, Taipei, Taiwan.
[12]Department of Emergency Medicine, Chang Gung Memorial Hospital, Linkou and College of Medicine, Chang Gung University, Tao-Yuan, Taiwan.

ABSTRACT

The aim of this review is to achieve a consensus between Taiwan Stroke Society (TSS) and Taiwan Society of Emergency Medicine (TSEM) to manage acute non-cardioembolic minor ischemic stroke (MIS) and high-risk transient ischemic attack (TIA). The methodology is to review the recent findings from clinical trials of dual antiplatelet therapy (DAPT) from 2010 to 2021 and updates in clinical practice guidelines from 2018 to 2022 for non-cardioembolic MIS/TIA management at the acute stage. Four leading clinical studies, CHANCE, POINT, THALES, and CHANCE-2 along with other relevant studies introducing DAPT, are discussed in this review. The risk-benefit profile between stroke recurrence reduction and major bleeding increase is also elucidated. TSS and TSEM concluded that for patients presenting with non-cardioembolic MIS or high-risk TIA who did not receive intravenous alteplase, initiation of DAPT within 24 hours after stroke onset and continued up to 21 days, followed by antiplatelet monotherapy, is effective in reducing recurrent ischemic stroke for a period of up to 90 days.

Keywords: acute minor ischemic stroke, consensus statement, dual antiplatelet therapy, transient ischemic attack.

*, Corresponding author: Dr. Jiunn-Tay Lee, Department of Neurology, Tri-Service General Hospital, Taipei, Taiwan.
Dr. Chip-Jin Ng, Department of Emergency Medicine, Chang Gung Memorial Hospital, Taoyuan, Taiwan.
E-mail: jiunntay@gmail.com ; ngowl@ms3.hinet.net
DOI: 10.6318/FJS.202206_4(2).0002

Introduction

Stroke is a primary driver of disability and morbidity; it is also the second leading cause of mortality worldwide and third in Taiwan.[1] Ischemic stroke, including minor ischemic stroke (MIS) or transient ischemic attack (TIA), accounts for 70-90% of strokes.[2] Patients who have had an acute MIS/TIA have a 3-15% risk of having a recurrent ischemic stroke in the first three months post-index event,[3] of which 75-80% occur within the first two weeks.[4] In a survey from 2000 to 2005 in Taiwan, stroke prevalence was found to increase each year in older adults. This resulted in the prolonged hospital stay with more intensive long-term care.[5] The consequence of disease burden and financial costs highlight an unmet need in the management of MIS/TIA. Historically, various antiplatelet agents, including aspirin (acetylsalicylic acid, ASA), dipyridamole, cilostazol, and clopidogrel, have been used individually for the prevention of recurrent stroke or TIA.[6] However, the concomitant use of two agents, known as dual antiplatelet therapy (DAPT), has emerged recently as a promising intervention for reducing the risk of ischemic stroke recurrence while balancing the risk of hemorrhage at the earlier, acute stage.[1, 6]

To date, several large-scale pivotal randomized controlled trials (CHANCE, POINT, THALES, and CHANCE-2) on the use of DAPT in MIS/TIA have emerged with positive outcomes. In the CHANCE trial, clopidogrel and aspirin given dually within 24 hours after a MIS or high-risk TIA were superior to aspirin alone for reducing the risk of stroke in the first 90 days without increasing the risk of major hemorrhage.[4] In the POINT trial, clopidogrel and aspirin given within 12 hours after MIS/TIA onset resulted in a lower risk of major ischemic events but a higher risk of major hemorrhage at 90 days than those who received aspirin monotherapy.[3] The THALES trial, which included slightly more involved patients with mild-to-moderate acute noncardioembolic ischemic stroke or TIA, found that the risk of the composite of stroke or death within 30 days was lower with ticagrelor–aspirin than with aspirin alone. However, the incidence of severe bleeding was higher with ticagrelor.[7, 8] The combination of ticagrelor and aspirin was further tested in the CHANCE-2 trial which included acute noncardioembolic MIS/high-risk TIA populations who carried CYP2C19 loss-of-function (LOF) alleles.[9] The CHANCE-2 trial concludes that ticagrelor plus aspirin is more effective than clopidogrel plus aspirin in reducing the risk of stroke at 90 days in this population. The risk of severe or moderate bleeding did not differ between the two treatment groups. Recently, the administration of DAPT in patients with MIS/high-risk TIA has gained increasing acceptance and is now supported by many leading stroke clinical practice guidelines globally.[10-17] It is recommended that administration shall be in the early phase of onset (within 24 hours) for a short duration (≤ 21 days).[18, 19]

The purpose of this scientific statement is to establish an up-to-date treatment consensus between the Taiwan Stroke Society (TSS) and the Taiwan Society of Emergency Medicine (TSEM). The primary aim is to review clinical data relevant to the use of antiplatelet therapy in patients with noncardioembolic MIS and high-risk TIA. The secondary objective is to examine the risk-benefit profile of DAPT in the reduction of recurrent strokes during the acute phase (≤ 30 days) and the potential risk of bleeding events in the subacute and chronic phases.[20]

Methods

Joint Expert Meeting Objectives

The joint expert meeting between TSS and TSEM was held in April 2021. The panel performed a review of pertinent DAPT clinical trials and current international guidelines from 2018 to 2021 for MIS/high-risk TIA, along with case sharing of real-world practice in Taiwan. The purpose was to critically evaluate recent stroke management updates and relevant guidelines to optimize clinical stroke pathways in Taiwan. The meeting gathered insights on challenges of guideline implementation in post-stroke patients (in-hospital & post-discharge) across different hospitals and explored initiatives to address existing barriers to improve the stroke pathway.

Voting System

The goal is to reach a joint TSS/TSEM consensus regarding the role of DAPT in the management of MIS and high-risk TIA. As a two-thirds vote from 12 experts was needed to reach a consensus, the scientific statement was amended after the first round of voting and discussion, with unanimous agreement subsequently achieved in the second casting of votes.

Results

Review of Pivotal Clinical Trials

Consensus was achieved through the analysis and comparison of four pivotal clinical trials—CHANCE, POINT, THALES and CHANCE-2—along with other relevant DAPT studies including TARDIS, PROFESS, ADS, CSPS.com and Lee (Table 1).[3, 7, 9, 21-27] DAPT with clopidogrel and aspirin was used in most studies, and combinations of ticagrelor and dipyridamole with aspirin were also investigated in THALES, CHANCE-2 and PROFESS trials. DAPT was administered within 12 to 48 hours and followed for 90 days in most studies. The efficacy and safety endpoints were event rates of stroke recurrence and hemorrhage, respectively.

Results from CHANCE, POINT and THALES all demonstrated a significant reduction of stroke recurrence risk in the DAPT group compared to the single antiplatelet therapy (SAPT) group.[10, 28] Of note, the risk of severe hemorrhage was higher in the THALES trial. In the rest of trials, TARDIS, PROFESS, ADS, CSPS.com and Lee, no significant differences in the efficacy and safety parameters between DAPT and SAPT groups were found.

CHANCE and POINT subgroup analyses stratified by different clinical variables were also examined. The treatment time course was evaluated in a secondary analysis of both trials, which revealed that the benefit of DAPT in reducing stroke recurrence without increasing the risk of major hemorrhage in MIS/high-risk TIA patients was predominantly in the first three weeks.[29, 30] Additionally, infarct patterns were evaluated in a CHANCE subgroup analysis, which concluded that infarct patterns could serve as a predictor of stroke recurrence within three months post-index event. Patients with multiple acute infarctions (MAIs) showed a higher risk of recurrent stroke and gained the most prominent benefit from DAPT without increasing the risk of severe bleeding.[19] The relationship between the presence of carotid stenosis and the risk of MIS/TIA was investigated in the POINT trial. It was found that the presence of carotid stenosis (defined by ≥ 50% narrowing) was associated with an increase in ischemic stroke,

Table 1. Comparison of study design and efficacy/safety outcomes of representative DAPT clinical trials.[3, 7, 9, 21, 27]

Trial	DAPT*	Initiation window	Dosing regimen	Follow-up	Risk of ischemic stroke recurrence	Risk of bleeding
CHANCE	Clo + ASA	24 hours	DAPT group: Day 1: Clo 300 mg (LD) + ASA 75−300 mg Days 2−21: Clo 75 mg + ASA 75 mg Days 22−90: Clo 75 mg SAPT group (ASA): Day 1: ASA 75−300 mg Days 2−90: ASA 75 mg	90 days	DAPT 7.9% vs ASA 11.4%; HR 0.67, p < 0.001	Severe bleeding: DAPT 0.2% vs ASA 0.2%; HR 0.94, p = 0.94
POINT	Clo + ASA	12 hours	DAPT group: Day 1: Clo 600 mg (LD) + ASA 50−325 mg Days 2−90: Clo 75 mg + ASA 50−325 mg SAPT group (ASA): Days 1−90: ASA 50−325 mg	90 days	DAPT 4.6% vs ASA 6.3%; HR 0.72, p = 0.01	Major bleeding: DAPT 0.9% vs ASA 0.4%; HR 2.32, p = 0.02
THALES	Tic + ASA	24 hours	DAPT group: Day 1: Tic 180 mg (LD) + ASA 300−325 mg Days 2−30: Tic 90 mg (BID) + ASA 75−100 mg SAPT group (ASA): Day 1: ASA 300−325 mg Days 2−30: ASA: 75−100 mg	30 days	DAPT 5.0% vs ASA 6.3%; HR 0.79, p = 0.004	Severe hemorrhage: DAPT 0.5% vs ASA 0.1%; HR 3.99, p = 0.001
CHANCE-2	Tic + ASA Clo + ASA	24 hours	DAPT group 1: Day 1: Tic 180 mg (LD) + ASA 75−300 mg Days 2−21: Tic 90 mg (BID) + ASA 75 mg Days 22−90: Tic 90 mg (BID) DAPT group 2: Day 1: Clo 300 mg (LD) + ASA 75−300 mg Days 2−21: Clo 75 mg + ASA 75 mg Days 22−90: Clo 75 mg	90 days	Tic + ASA 6.0% vs Clo + ASA 7.6%; HR 0.77, p = 0.008	Severe or moderate bleeding: Tic + ASA 0.3% vs Clo + ASA 0.3%; HR 0.82, p = 0.66

Table 1. Comparison of study design and efficacy/safety outcomes of representative DAPT clinical trials.[3, 7, 9, 21, 27] (continued)

Trial	DAPT*	Initiation window	Dosing regimen	Follow-up	Risk of ischemic stroke recurrence	Risk of bleeding
PROFESS	Dip + ASA	72 hours	DAPT group: Days 1−90: Dip 200 mg (BID) + ASA 25 mg (BID) SAPT group (Clo): Days 1−90: Clo 75 mg	90 days	DAPT 7.7% vs SAPT 7.9%; HR 0.97, p = ns	Major bleeding: DAPT 4.1% vs SAPT 3.6%; HR 1.15, p < 0.05
ADS	Cilo + ASA	48 hours	DAPT group: Days 1−14: Cilo 200 mg + ASA 81−200 mg Days 15−90: Cilo 200 mg SAPT group (ASA and Cilo): Days 1−14: ASA 81−200 mg Days 15−90: Cilo 200 mg	90 days	DAPT 1% vs SAPT 1%; p = 0.789	ICH: 0.2% in both groups; p = 0.999 SAH: DAPT 0.2% vs SAPT 0%; p = 0.499 Serious extracranial hemorrhage: DAPT 0.3% vs SAPT 0.2%; p = 0.624
CSPS.com	Cilo + ASA	8 days to 6 months	DAPT group: Cilo 100 mg (BID) + ASA 81 or 100 mg / Clo 50 or 75 mg SAPT group (ASA or Clo): ASA 81 or 100 mg (QD) or Clo 50 or 75 mg (QD)	3.5 years (median 1.4 years)	DAPT 3% vs SAPT 7%; HR 0.49, p = 0.001	Severe hemorrhage: DAPT 1% vs SAPT 1%; HR 0.66, p = 0.35
Lee	Clo + ASA	24 hours	DAPT group: Clo + ASA† SAPT group (ASA): ASA†	90 days	Ischemic stroke: DAPT 14.1% vs SAPT 15.1%; p = 0.044	Hemorrhagic stroke: DAPT 0.38% vs SAPT 0.23%; 0 = 0.148

*The dosing regimen is based on local guidelines.
†The dosing regimen is based on Korean clinical practice (2011−2018).
Abbreviations: ASA, acetylsalicylic acid; BID, twice-daily; Clo, clopidogrel; Cilo, cilostazol; DAPT, dual antiplatelet therapy; Dip, dipyridamole; HR, hazard ratio; ICH, Intracerebral hemorrhage; LD, loading dose; ns, nonsignificant; OR, odds ratio; QD, once-daily; SAH, subarachnoid hemorrhage; SAPT, single antiplatelet therapy; TAPT, triple antiplatelet therapy; Tic, ticagrelor.

whereas no significant difference was observed between patients with and without carotid stenosis when DAPT was administered.[31]

Furthermore, the incidence of major hemorrhage and non-intracranial hemorrhage (ICH) was explored in POINT and CHANCE trials, respectively. The secondary POINT analysis revealed that the most common location of major hemorrhage was in the gastrointestinal tract. After DAPT or aspirin alone, the risk of major hemorrhage was low but was still elevated from 0.2% to 0.9% in the DAPT group.[32] All hemorrhagic events were further analyzed in the CHANCE trial including ICH and non-ICH. In the post hoc analysis, higher non-ICH hemorrhagic rates were confirmed in the MIS population with DAPT.[33]

Although the efficacy of DAPT with clopidogrel and aspirin is considered effective in reducing stroke in MIS/high-risk TIA patients, its effectiveness in the population who carries CYP2C19 LOF alleles is doubted. A CHANCE substudy estimated the association between CYP2C19 LOF allele status and efficacy of DAPT with clopidogrel and aspirin.[34] After 90 days of follow-up, compared with SAPT, DAPT with clopidogrel and aspirin significantly reduced the rate of new stroke in the noncarriers but not in the carriers of the LOF alleles. The CHANCE-2 trial evaluated the DAPT regimens with either ticagrelor-aspirin or clopidogrel-aspirin in reducing stroke in MIS/high-risk TIA patients with CYP2C19 LOF alleles.[9] In the CHANCE-2 trial, patients were assigned within 24 hours after stroke onset to receive ticagrelor (180 mg on day 1 followed by 90 mg twice daily on days 2 through 90) or to receive clopidogrel (300 mg on day 1 followed by 75 mg once daily on days 2 through 90); both groups received aspirin for 21 days. At 90 days, new stroke was significantly less in the ticagrelor group (6.0%) than in the clopidogrel group (7.6%). Although any bleeding occurred more often in the ticagrelor group (5.3%) than in the clopidogrel group (2.5%), severe or moderate bleeding was similar between both groups (0.3%).

Review of Guideline Updates

Leading international clinical practice guidelines on stroke management were evaluated for pertinent updates. Current recommendations from the American Heart Association/American Stroke Association (AHA/ASA), European Stroke Organisation (ESO), Australian Stroke Foundation, Taiwan, and Canadian Stroke Best Practices were compared and summarized in Table 2. To summarize, early initiation of DAPT for short durations (≤ 21 days) has been adopted globally as standard clinical practice for the management of MIS/high-risk TIA.[10-13, 15-17]

Discussion

Risk and Benefit of DAPT

Results from clinical trials thus far demonstrate that the benefit of DAPT in reducing the incidence of recurrent strokes is greater than the potential risk of bleeding associated with DAPT in patients with MIS/high-risk TIA at the acute stage. However, the different study designs may contribute to diverse outcomes in efficacy and safety; particularly, a higher risk of hemorrhage was associated with increased duration of DAPT use.[28]

In the CHANCE study, DAPT with clopidogrel and aspirin reduced the risk of ischemic stroke in the first two weeks. However, an increased rate of bleeding events of any kind was observed after the 10th day of DAPT.[30] In

Table 2. Recommendations for DAPT for acute minor ischemic stroke and high-risk transient ischemic attack in international stroke guidelines.[10-15, 17]

Guidelines	Initiation window	Recommendations and treatment duration	Dosing regimen
American Heart Association/American Stroke Association (2021)	24 hours	Recommendation of COR I, LOE A: DAPT (clopidogrel and aspirin) for 21 to 90 days followed by SAPT Recommendation of COR IIb, LOE B-R: DAPT (ticagrelor and aspirin) for 30 days	Initiation: DAPT with clopidogrel and aspirin Maintenance: SAPT Initiation: DAPT with ticagrelor and aspirin
European Stroke Organisation (2021)	24 hours	Strong recommendation: DAPT (clopidogrel and aspirin) for 21 days followed by SAPT Weak recommendation: DAPT (ticagrelor and aspirin) for 30 days	Initiation: DAPT with clopidogrel and aspirin* Maintenance: SAPT Initiation: DAPT with ticagrelor and aspirin
Australian Stroke Foundation (2021)	24 hours	Strong recommendation: DAPT (clopidogrel and aspirin) for 21 days followed by SAPT Weak recommendation: DAPT (ticagrelor and aspirin) for 30 days	Initiation: DAPT with clopidogrel and aspirin† Maintenance: SAPT Initiation: DAPT with ticagrelor and aspirin
Taiwan Stroke Society (2022)	24 hours	Recommendation of COR I, LOE A: DAPT (clopidogrel and aspirin) for 21 days followed by SAPT Recommendation of Class IIb, LOE BR: DAPT (ticagrelor and aspirin) for 30 days	Initiation: DAPT with clopidogrel and aspirin Maintenance: SAPT Initiation: DAPT with ticagrelor and aspirin
Canadian Stroke Best Practices (2018)	24 hours	Recommendation of LOE A DAPT (clopidogrel and aspirin) for 21 to 30 days followed by SAPT	Initiation: DAPT with clopidogrel and aspirin‡ Maintenance: SAPT

* ESO guideline recommends a single loading dose of 300 mg clopidogrel in patients not already taking the relevant medication.

† Australian guideline recommends a loading dose of 300 mg aspirin and 300−600 mg clopidogrel followed by 100−150 mg aspirin and 75 mg clopidogrel daily for 21 days.

‡ Canadian guideline recommends a loading dose of 300−600 mg of clopidogrel and 160 mg of aspirin at the start of treatment.

Abbreviations: COR, class of recommendation; DAPT, dual antiplatelet therapy; LOE, level of evidence; SAPT, single antiplatelet therapy.

a modeled analysis of the POINT study, the clopidogrel–aspirin combination demonstrated a reduction in ischemic strokes when it was administered within 72 hours from symptom onset.[29] The advantage was maintained in the first three weeks across a total treatment duration of 90 days, while the risk of major hemorrhage remained low. Unlike CHANCE and POINT trials, THALES enrolled patients with a mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS score ≤ 5) or TIA ($ABCD^2 \geq 6$) and treated them with a DAPT regimen of ticagrelor–aspirin combination for 30 days. Consistent with findings from CHANCE and POINT studies, the THALES trial revealed a reduction in stroke recurrence rate when DAPT was initiated within 24 hours, and treatment duration was maintained for 30 days.[7]

In addition to these three pivotal studies,

the risk and benefit of DAPT in secondary stroke prevention are further elucidated by several systemic reviews and meta-analyses. In 2021, three short-duration and two long-duration randomized controlled trials were analyzed.[32] Between the short- and long-duration trials, DAPT is superior to SAPT for preventing secondary ischemic stroke when administered early after stroke symptom onset in MIS/high-risk TIA patients. The benefit still prevails within a treatment duration of 90 days.[35] A meta-analysis of 27,358 patients from 17 clinical trials concludes that compared with SAPT, DAPT treated for less than 30 days reduces the risk of stroke recurrence. After excluding the combination of aspirin plus ticagrelor, the risk of major hemorrhage was not increased in the DAPT group.[36] Efficacy of multiple antiplatelet agents was compared to that of a single antiplatelet agent on early stroke recurrence in another meta-analysis of 17,091 participants from 15 clinical trials.[32] When DAPT treatment was initiated early and continued for one month, there was a significantly lower risk of stroke recurrence compared to SAPT. In addition, the benefit seemed to outweigh the increased risk of hemorrhage.[37]

Current evidence on the optimal time course supports that early initiation and short-term administration of DAPT provides the most prominent benefit of reducing ischemic stroke recurrence and hemorrhage in MIS/high-risk TIA patients.

In addition to differences in initiation window and duration of treatment, loading doses of clopidogrel also varied between CHANCE and POINT trials. A loading dose of 300 mg of clopidogrel was administered in CHANCE on day 1, followed by 75 mg/day on days 2–90, plus aspirin at 75 mg/day on days 2–21. POINT used a loading dose of 600 mg of clopidogrel on day 1, followed by 75 mg plus 50–325 mg of aspirin daily. In the Canadian Stroke Best Practices, a minimum loading dose of clopidogrel 300 mg, but up to 600 mg as appropriate, along with 160 mg of aspirin is recommended early on in patients with high-risk TIA (ABCD2 score > 4) or minor noncardioembolic stroke (NIHSS ≤ 3). To date, no unified loading dose has been established, and differences persist based on various considerations across treatment guidelines worldwide.

Variability in Stroke Subtypes/ Subgroups

Among numerous post hoc analyses performed on CHANCE and POINT, different infarction patterns were also investigated to identify their potential correlation with DAPT on the reduction of ischemic strokes. In the CHANCE sub-analysis, patients with MAIs demonstrated the most prominent benefit of DAPT without increasing the risk of severe bleeding; however, the risk of stroke recurrence in the MAI population still remained similar as the single acute infarction group and higher than the no acute infarction group.[19] The presence and degree of carotid stenosis is also an image marker for stroke diagnosis. The relationship between nonsignificant (< 50%) vs. significant (≥ 50%) cervical internal carotid stenosis and the risk of MIS/TIA during the follow-up period was investigated in the POINT trial. Stroke recurrence was more remarkable in the latter population, while no recurrent ischemic stroke risk reduction by clopidogrel was observed in this population.[31] The comparison between patients with (≥ 50%) and without (< 50%) intracranial arterial stenosis (ICAS) in the CHANCE study indicated that higher stroke recurrence was associated with ICAS, but no significant difference can be

concluded in response to DAPT.[38] DAPT as a secondary prevention regimen was evaluated in POINT trial patients with ipsilateral nonstenotic carotid disease (1–49% stenosis), a contributor to ischemic stroke. The analysis demonstrated a higher risk of recurrent stroke was associated with patients with ipsilateral nonstenotic carotid disease than patients without carotid disease. DAPT showed a non-statistically significant reduction in recurrent ischemic stroke without increased risk of bleeding in patients with ipsilateral nonstenotic carotid disease.[39] The heterogeneity in infarction subtypes may in part explain the lack of statistical significance in efficacy and safety outcomes. In addition to infarction subtypes, it is noteworthy to mention the population with CYP2C19 LOF alleles which are more prevalent in Asia than in other areas worldwide.[40] The CHANCE substudy demonstrated the unsatisfied efficacy of DAPT with clopidogrel and aspirin in the population with CYP2C19 LOF alleles.[34] In addition to the CHANCE-2 trial, which provided clinical evidence of the DAPT regimen of ticagrelor and aspirin in reducing stroke in this population, the PRINCE study compared high platelet reactivity between DAPT groups with ticagrelor-aspirin (280 patients) or clopidogrel-aspirin (290 patients) in the MIS/high-risk TIA population.[41] The PRINCE study showed that the ticagrelor-aspirin group had a significantly lower frequency of high platelet reactivity (12.5%) than the clopidogrel-aspirin group (29.7%). Furthermore, in patients carrying CYP2C19 LOF alleles, the ticagrelor-aspirin group also had less frequency of high platelet reactivity (10.8%) than the clopidogrel-aspirin group (35.4%). However, the stroke occurrence within 90 days was similar between these two DAPT groups. Despite the beneficial effects of ticagrelor-aspirin DAPT in MIS/high-risk TIA patients carrying CYP2C19 LOF alleles, it should be mentioned that the point-of-care genotyping system adopted in the CHANCE-2 trial is not widely available at present. Therefore, using ticagrelor-aspirin DAPT within 24 hours in MIS/high-risk TIA patients with CYP2C19 LOF alleles is hard to implement in clinical practices.

Variability in Definitions of MIS snd High-Risk TIA

More than 20,000 patients with MIS or high-risk TIA were investigated in CHANCE, POINT, and THALES. There were distinct differences in the inclusion criteria between these studies. Patients in CHANCE experienced acute MIS with NIHSS ≤ 3 or high-risk TIA (defined as focal brain ischemia) with an $ABCD^2$ score ≥ 4. The POINT trial adopted the same NIHSS and $ABCD^2$ profile. The THALES trial, however, departed from these definitions of MIS and high-risk TIA and included more severe patient populations with NIHSS ≤ 5 and $ABCD^2$ score ≥ 6.[3, 7, 21]

TIA was originally defined as focal neurological symptoms of presumed vascular origin lasting less than 24 hours. The definition later evolved into a tissue-based perspective as various locations of focal brain ischemia were identified. This new definition has been adopted worldwide.[6] $ABCD^2$ stroke risk score is the evaluator of TIA, composed of age, blood pressure, clinical features, duration of TIA, and presence of diabetes mellitus. On the other hand, no consensus was concluded for MIS. Cutoff of NIHSS ≤ 3 to 5 have been used and proposed nowadays. Nevertheless, TIA and MIS are accepted as the mild end of the severity spectrum.[6]

Guideline Comparison

In the summary of updated guidelines

worldwide (Table 2), there is consensus on early initiation (within 24 hours) of DAPT with clopidogrel and aspirin and maintenance for at least 21 days, followed by SAPT of either aspirin or clopidogrel. However, variance persists among international recommendations on treatment duration and loading dose due to different study protocols and methodologies employed in clinical trials. Among the guidelines, the DAPT regimen in CHANCE and POINT studies has been universally adopted, while the THALES regimen is suggested by AHA/ASA, ESO, Taiwan, and the Australian Stroke Foundation. Besides, treatment duration from 21 to 90 days is recommended by the AHA/ASA due to prominent outcomes associated with a 90–day treatment period in the POINT parent trials, their respective subanalyses involving different stroke subtypes, and the SAMMPRIS study with analysis of severe major intracranial artery stenosis.[10] A treatment period of 21 days is suggested by ESO, Australian Stroke Foundation and Taiwan guidelines. In Canadian Stroke Best Practices, the treatment period is confined to 30 days due to higher major hemorrhages identified from 31–90 days in the POINT study. The ESO guideline recommended the loading dose of 300 mg clopidogrel in patients not already taking the relevant medication. Australian Stroke Foundation recommends a loading dose of 300 mg aspirin and 300–600 mg clopidogrel. Canadian Stroke Best Practices recommends a loading dose of 300–600 mg of clopidogrel and 160 mg of aspirin at the start of treatment. In the population with CYP2C19 LOF alleles, the recently updated Taiwan guideline moderately recommends the reasonable use of DAPT regiment with ticagrelor-aspirin.[17]

TSS/TSEM Scientific Statement

After careful review of the currently available evidence, the TSS and TSEM unanimously established a joint scientific statement on the role of DAPT: “For patients presenting with non-cardioembolic minor ischemic stroke or high-risk TIA who did not receive intravenous alteplase, treatment with DAPT started ideally within 24 hours of symptom onset and continued up to 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days with subsequent transition to antiplatelet monotherapy (such as clopidogrel or aspirin alone).”

Future Considerations

The benefit of DAPT on MIS/high-risk TIA patients in reducing stroke recurrence and major hemorrhage is demonstrated in these pivotal trials and confirmed in the updated guidelines worldwide; however, some clinical gaps still need to be clarified in future research. Firstly, the optimal treatment duration and antiplatelet combination have yet to be determined. Secondly, the risk of any form of hemorrhage in different subgroups of stroke patients has not been fully elucidated. Thirdly, evidence for the benefit of switching antiplatelet agents in patients who were already receiving one medication at the time of stroke onset is lacking. Therefore, future research to address these three unanswered questions is warranted.

Acknowledgments

The expert panel thanks Sanofi Taiwan Co. Ltd for supporting the organization of the meeting. The meeting during which this scientific statement was formulated was funded by an unrestricted educational grant from Sanofi Taiwan Co. Ltd. The funder had no role in determining the content of the scientific statement.

The writing/editorial assistance of the manuscript was supported by EMD Asia Scientific Communication (Taiwan branch) Co., Ltd.

References

1. Kaufman BG, Shah S, Hellkamp AS, *et al*. Disease burden following non-cardioembolic minor ischemic stroke or high-risk TIA: A GWTG-Stroke study. *J Stroke Cerebrovasc Dis* 2020;29:105399. doi: 10.1016/j.jstrokecerebrovasdis.2020.105399.
2. Vališ M, Klímová B, Novotný M, Herzig R. Antiplatelet therapy in the secondary prevention of non-cardioembolic ischemic stroke and transient ischemic attack: a mini-review. *Front Neurol* 2021;12:626106. doi: 10.3389/fneur.2021.626106.
3. Johnston SC, Easton JD, Farrant M, *et al*. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018;379:215-225. doi: 10.1056/NEJMoa1800410.
4. Wang Y, Johnston SC, Bath PM, *et al*. Acute dual antiplatelet therapy for minor ischaemic stroke or transient ischaemic attack. *BMJ* 2019;364:l895. doi: 10.1136/bmj.l895.
5. Chen CY, Huang YB, Lee CTC. Epidemiology and disease burden of ischemic stroke in Taiwan. *Int J Neurosci* 2013;123:724-731. doi: 10.3109/00207454.2013.796552.
6. Tse D, Hill MD, Coutts SB. Early secondary prevention in transient ischemic attack (TIA) and minor stroke. *Curr Neurol Neurosci Rep* 2019;19:34. doi: 10.1007/s11910-019-0950-y.
7. Johnston SC, Amarenco P, Denison H, *et al*. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med* 2020;383:207-217. doi: 10.1056/NEJMoa1916870.
8. Wang Y, Pan Y, Li H, *et al*. Efficacy and safety of ticagrelor and aspirin in patients with moderate ischemic stroke: an exploratory analysis of the THALES randomized clinical trial. *JAMA Neurol* 2021;78:1091-1098. doi: 10.1001/jamaneurol.2021.2440.
9. Wang Y, Meng X, Wang A, *et al*. Ticagrelor versus clopidogrel in CYP2C19 loss-of-function carriers with stroke or TIA. *N Engl J Med* 2021;385:2520-2530. doi: 10.1056/NEJMoa2111749.
10. Kleindorfer DO, Towfighi A, Chaturvedi S, *et al*. 2021 Guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. *Stroke* 2021;52:e364-e467. doi: 10.1161/str.0000000000000375.
11. Fonseca AC, Merwick A, Dennis M, *et al*. European Stroke Organisation (ESO) guidelines on management of transient ischaemic attack. *Eur Stroke J* 2021;6:CLXIII-CLXXXVI. doi: 10.1177/2396987321992905.
12. Dawson J, Merwick Á, Webb A, Dennis M, Ferrari J, Fonseca AC. European Stroke Organisation expedited recommendation for the use of short-term dual antiplatelet therapy early after minor stroke and high-risk TIA. *Eur Stroke J* 2021;6:VI. doi: 10.1177/23969873211027006.
13. Australian Clinical Guidelines for Stroke Management. Chapter 3 of 8: Acute medical and surgical management v.10.1. 2021.
14. Australian Clinical Guidelines for Stroke Management. Chapter 4 of 8: Acute medical and surgical management v.8.10. 2022.
15. Boulanger JM, Lindsay MP, Gubitz G, *et al*. Canadian stroke best practice recommendations

for acute stroke management: prehospital, emergency department, and acute inpatient stroke care, 6th Edition, Update 2018. *Int J Stroke* 2018;13:949-984. doi: 10.1177/1747493018786616.

16. Chen PL, Chen CH, Tang SC, *et al*. 2020 Taiwan Stroke Society guideline on antiplatelet therapy for noncardioembolic ischemic stroke. *Formos J Stroke* 2020;2:5-34. doi: 10.6318/FJS.202003_2(1).0001.
17. Tang SC, Chung CP, Chen PL, *et al*. Taiwan Stroke Society guideline consensus group. Focus Update of the 2020 Taiwan Stroke Society guideline on antiplatelet therapy for noncardioembolic acute ischemic stroke. *Formos J Stroke* 2022; In press.
18. Moussouttas M, Papamitsakis NIH. Critique on the use of early short-term dual antiplatelet therapy following minor acute cerebral ischemic events. *Cerebrovasc Dis* 2020;49:237-243. doi: 10.1159/000508026.
19. Jing J, Meng X, Zhao X, *et al*. Dual antiplatelet therapy in transient ischemic attack and minor stroke with different infarction patterns: subgroup analysis of the CHANCE randomized clinical trial. *JAMA Neurol* 2018;75:711-719. doi: 10.1001/jamaneurol.2018.0247.
20. Leng X, Leung TW, Wong KSL. Antiplatelet therapy after stroke: should it differ in the acute and chronic phase after stroke. *Curr Opin Neurol* 2018;31:14-22. doi: 10.1097/wco.0000000000000509.
21. Wang Y, Wang Y, Zhao X, *et al*. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369:11-19. doi: 10.1056/NEJMoa1215340.
22. Bath PM, Woodhouse LJ, Appleton JP, *et al*. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. *Lancet* 2018;391:850-859. doi: 10.1016/s0140-6736(17)32849-0.
23. Sacco RL, Diener HC, Yusuf S, *et al*. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008;359:1238-1251. doi: 10.1056/NEJMoa0805002.
24. Aoki J, Iguchi Y, Urabe T, *et al*. Acute aspirin plus cilostazol dual therapy for noncardioembolic stroke patients within 48 hours of symptom onset. *J Am Heart Assoc* 2019;8:e012652. doi: 10.1161/jaha.119.012652.
25. Toyoda K, Uchiyama S, Yamaguchi T, *et al*. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: a multicentre, open-label, randomised controlled trial. *Lancet Neurol* 2019;18:539-548. doi: 10.1016/s1474-4422(19)30148-6.
26. Lee HL, Kim JT, Lee JS, *et al*. Comparative effectiveness of dual antiplatelet therapy with aspirin and clopidogrel versus aspirin monotherapy in mild-to-moderate acute ischemic stroke according to the risk of recurrent stroke: an analysis of 15000 patients from a nationwide, multicenter registry. *Circ Cardiovasc Qual Outcomes* 2020;13:e006474. doi: 10.1161/CIRCOUTCOMES.119.006474.
27. Benavente OR, Hart RG, McClure LA, Szychowski JM, Coffey CS, Pearce LA. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012;367:817-825. doi: 10.1056/NEJMoa1204133.
28. Pan Y, Elm JJ, Li H, *et al*. Outcomes associated with clopidogrel-aspirin use in minor stroke or

transient ischemic attack: A Pooled Analysis of Clopidogrel in High-Risk Patients With Acute Non-Disabling Cerebrovascular Events (CHANCE) and Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trials. *JAMA Neurol* 2019;76:1466-1473. doi: 10.1001/jamaneurol.2019.2531.

29. Johnston SC, Elm JJ, Easton JD, *et al*. Time Course for benefit and risk of clopidogrel and aspirin after acute transient ischemic attack and minor ischemic stroke. *Circulation* 2019;140:658-664. doi: 10.1161/circulationaha.119.040713.
30. Pan Y, Jing J, Chen W, *et al*. Risks and benefits of clopidogrel-aspirin in minor stroke or TIA: Time course analysis of CHANCE. *Neurology* 2017;88:1906-1911. doi: 10.1212/wnl.0000000000003941.
31. Yaghi S, de Havenon A, Rostanski S, *et al*. Carotid stenosis and recurrent ischemic stroke: a post-hoc analysis of the POINT trial. *Stroke* 2021;52:2414-2417. doi: 10.1161/strokeaha.121.034089.
32. Tillman H, Johnston SC, Farrant M, *et al*. Risk for major hemorrhages in patients receiving clopidogrel and aspirin compared with aspirin alone after transient ischemic attack or minor ischemic stroke: a secondary analysis of the POINT randomized clinical trial. *JAMA Neurol* 2019;76:774-782. doi: 10.1001/jamaneurol.2019.0932.
33. Wang D, Gui L, Dong Y, *et al*. Dual antiplatelet therapy may increase the risk of non-intracranial haemorrhage in patients with minor strokes: a subgroup analysis of the CHANCE trial. *Stroke Vasc Neurol* 2016;1:29-36. doi: 10.1136/svn-2016-000008.
34. Wang Y, Zhao X, Lin J, *et al*. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA* 2016;316:70-78. doi: 10.1001/jama.2016.8662.
35. Brown DL, Levine DA, Albright K, *et al*. Benefits and risks of dual versus single antiplatelet therapy for secondary stroke prevention: a systematic review for the 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack. *Stroke* 2021;52:e468-e479. doi: 10.1161/str.0000000000000377.
36. Trifan G, Gorelick PB,Testai FD. Efficacy and safety of using dual versus monotherapy antiplatelet agents in secondary stroke prevention: systematic review and meta-analysis of randomized controlled clinical trials. *Circulation* 2021;143:2441-2453. doi: 10.1161/circulationaha.121.053782.
37. Naqvi IA, Kamal AK, Rehman H. Multiple versus fewer antiplatelet agents for preventing early recurrence after ischaemic stroke or transient ischaemic attack. *Cochrane Database Syst Rev* 2020;8:Cd009716. doi: 10.1002/14651858.CD009716.pub2.
38. Liu L, Wong KS, Leng X, *et al*. Dual antiplatelet therapy in stroke and ICAS: Subgroup analysis of CHANCE. *Neurology* 2015;85:1154-1162. doi: 10.1212/wnl.0000000000001972.
39. Bulwa Z, Saleh Velez FG, Brorson JR,Pinto CB. Ipsilateral nonstenotic carotid disease in minor ischemic stroke: an exploratory analysis of the POINT randomized clinical trial. *J Stroke Cerebrovasc Dis* 2020;29:105115. doi: 10.1016/j.jstrokecerebrovasdis.2020.105115.
40. Klein MD, Williams AK, Lee CR,Stouffer GA. Clinical utility of CYP2C19 genotyping to guide antiplatelet therapy in patients with

an acute coronary syndrome or undergoing percutaneous coronary intervention. *Arterioscler Thromb Vasc Biol* 2019;39:647-652. doi: 10.1161/ATVBAHA.118.311963.

41. Wang Y, Chen W, Lin Y, *et al*. Ticagrelor plus aspirin versus clopidogrel plus aspirin for platelet reactivity in patients with minor stroke or transient ischaemic attack: open label, blinded endpoint, randomised controlled phase II trial. *BMJ* 2019;365:l2211. doi: 10.1136/bmj.l2211.

急性輕微缺血性腦中風及高風險暫時性腦缺血處置的雙抗血小板藥物治療：台灣腦中風學會與台灣急診醫學會的共識聲明

陳柏霖[1]、 陳盈如[2]、鍾芷萍[3]、薛承君[4]、鄭建興[5]、謝明儒[6]、連立明[7]、陳健驊[8]、陳右緯[9]、邱德發[10]、李俊泰[11*]、黃集仁[12*]

[1]台中榮民總醫院神經醫學中心腦中風中心
[2]台北榮民總醫院急診部
[3]台北榮民總醫院神經醫學中心神經內科
[4]新北市立土城醫院急診醫學科
[5]台大醫院神經部暨腦中風中心
[6]台大醫院急診醫學部
[7]新光吳火獅紀念醫院神經科
[8]國泰綜合醫院急診醫學部
[9]聯新國際醫院中風醫療中心
[10]中國醫藥大學附設醫院急診部
[11]三軍總醫院神經科部
[12]林口長庚紀念醫院急診醫學科

摘　要

本綜述乃根據台灣腦中風學會與台灣急診醫學會所舉行之專家會議所撰寫，該專家會議完整檢視「急性非心因性輕微缺血性腦中風及高風險暫時性腦缺血」抗血小板治療的科學證據，並討論其臨床意義及影響。兩會專家依據討論結果，達成「急性非心因性輕微缺血性腦中風及高風險暫時性腦缺血」的治療共識。會議檢視自2010年至2021年間以「急性非心因性輕微缺血性腦中風及高風險暫時性腦缺血」病人為研究對象的雙(或多重)抗血小板藥物治療的臨床試驗及研究，並參考各國於2018年至2022年間針對「急性非心因性輕微缺血性腦中風及高風險暫時性腦缺血」的治療指引及建議。本綜述討論了四項大型隨機臨床試驗，包括CHANCE、POINT、THALES和CHANCE-2，並參酌其他雙(或多重)抗血小板藥物治療的研究文獻，分析雙(或多重)抗血小板藥物治療於「急性非心因性輕微缺血性腦中風及高風險暫時性腦缺血」的風險與效益，提出預防腦中風復發且不增加嚴重出血風險的治療策略。台灣腦中風學會與台灣急診醫學會專家會議的共識聲明如下：對於未接受靜脈血栓溶解治療的「急性非心因性輕微缺血性腦中風及高風險暫時性腦缺血」的病人，於發作24小時內開始使用雙抗血小板藥物治療至21天，並轉換至單一抗血小板藥物治療，例如clopidogrel或aspirin至90天，可有效減少缺血性腦中風復發風險。

關鍵詞：急性輕微缺血性腦中風，共識聲明，雙抗血小板藥物治療，暫時性腦缺血

*, 共同通訊作者：李俊泰醫師　三軍總醫院神經科部；黃集仁醫師　林口長庚紀念醫院急診醫學科
E-mail: jiunntay@gmail.com；ngowl@ms3.hinet.net