ANALYSIS

Acute dual antiplatelet therapy for minor ischaemic stroke or transient ischaemic attack

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Yongjun Wang and colleagues discuss recent evidence for using dual antiplatelet therapy to reduce recurrence of stroke or transient ischaemic attack

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Key messages

Recent research on antiplatelet therapy has advanced the knowledge of early, intensive treatment for recurrent stroke in minor ischaemic stroke or transient ischaemic attack

In patients with high risk, non-disabling ischaemic cerebrovascular events, including minor stroke and transient ischaemic attack, short term dual antiplatelet therapy should be given within 24 hours after the onset of symptoms and as early as possible

Further studies are needed to evaluate antiplatelet strategies, explore whether dual antiplatelet therapy could benefit broader patient population, and improve adherence of the recommended antiplatelet therapy

The risk of recurrent stroke and other vascular events is high in the first few weeks after index minor ischaemic stroke and high risk transient ischaemic attack (5-11.7%).[1 2] Dual antiplatelet therapy (DAPT), comprising clopidogrel and aspirin, is an effective strategy for reducing recurrence.[1] An expert panel from the MAGIC group (http://magicproject.org/) recently produced a strong rapid recommendation in *The BMJ* for starting DAPT within 24 hours of symptom onset and continuing for 10-21 days in patients with minor stroke or transient ischaemic attack.[3] The evidence for this came from a systematic review and meta-analysis of published clinical trials.[4] Most current international guidelines,[5-8] but not all,[9] recommend early (within 24 hours) and short term (a duration of 21 days or 21-30 days) DAPT in patients with minor stroke or transient ischaemic attack (table 1).

Questions remain regarding choice of antiplatelet strategy, possibility of safe expansion of DAPT to a broader patient population, and adherence of patients to recommended antiplatelet therapy in clinical practice.

Recent trials

In the past five years, trials on acute antiplatelet treatment have focused on evaluating the efficacy and safety of more intensive treatment to prevent recurrent stroke after minor ischaemic stroke or high risk transient ischaemic attack. These include dual therapy versus monotherapy,[1 2] triple versus dual antiplatelet treatment,[10] and a potentially more potent agent (ticagrelor)

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compared with aspirin alone (table 2).[11-13] The findings of these studies have greatly advanced the antiplatelet strategy for secondary prevention of stroke in patients with minor ischaemic stroke or transient ischaemic attack.

Treatment population for DAPT

Patients who have a minor stroke or a transient ischaemic attack are at high risk of developing thrombosis and having ischaemic brain damage that could increase their risk of bleeding.[1 2 14] More intensive antiplatelet therapy could be effective and safe in these patients. The CHANCE and POINT trials compared the efficacy and safety of DAPT with clopidogrel plus aspirin against aspirin alone in patients with minor stroke (National Institutes of Health Stroke Scale (NIHSS) ≤3) or high risk transient ischaemic attack (ABCD2 score ≥4). The primary results from CHANCE[1] and secondary analysis from POINT[15] show that up to 21 days of dual antiplatelet therapy were both effective and safe (table 2), indicating that patients with minor stroke or high risk transient ischaemic attack are suitable for dual antiplatelet therapy with clopidogrel plus aspirin.

Time window of starting antiplatelet therapy

Approximately 75-80% of recurrent strokes occur in the first two weeks after onset of the index stroke or transient ischaemic attack.[1 2] Almost all guidelines recommend that antiplatelet therapy be given as soon as possible after the diagnosis of an ischaemic event. Five of the recent trials included patients that started treatment within 24 hours (table 2).[1 2 11-13] Exploratory analysis of the TARDIS trial showed that intensive triple antiplatelet therapy could significantly reduce recurrence after mild stroke or transient ischaemic attack, or minor stroke alone, if started within 24 hours, but not if started after 24 hours (PM Bath, personal communication). This further supports the consensus that antiplatelet therapy should be given as soon as possible within 24 hours.

Duration of dual antiplatelet therapy

Risk of bleeding is the main harm of intensive dual or triple antiplatelet therapy. The CHANCE and POINT trials showed similar efficacy of DAPT with up to ~30% reduction of recurrent stroke (table 2), but the POINT trial also showed a 2.3-fold increase in the risk of major haemorrhage in the DAPT group compared with aspirin alone (P=0.02), whereas the CHANCE trial did not (P=0.73).[1 2] This discrepancy is not completely understood, but a longer duration of DAPT (90 days in the POINT trial versus 21 days in the CHANCE trial) may be the explanation.[16] A secondary time course analysis of the POINT trial provided further supportive evidence for the recent rapid recommendation.[3 15] But more systematic studies are needed to determine how to choose the duration of DAPT more precisely—between 10 and 21 days in clinical practice.

Future research

Although DAPT with clopidogrel and aspirin is an effective strategy for secondary stroke prevention, some patients fail to respond. DAPT is not effective in patients with lacunar strokes,[17] but is potent in patients with multiple acute infarctions or ipsilateral atherosclerotic stenosis.[18 19] Further studies are needed to thoroughly examine the effects of antiplatelet treatment on minor stroke or transient ischaemic attack with different causes and to identify those who will respond well.

Pharmacogenetics may also play an important role. A few genetic polymorphisms have been identified that might influence the metabolism of clopidogrel, which is a pro-drug that requires biotransformation to become an active metabolite and exert its effect.[20] Carriers of the *CYP2C19* loss of function alleles are less likely to benefit from clopidogrel.[20] Although not recommended in current clinical practice, genetic testing may be considered to personalise antiplatelet therapy, especially in Asian populations, which have high prevalence of the *CYP2C19* loss of function allele. Escalation of clopidogrel dosages or considering new antiplatelet agents (such as ticagrelor) could be alternatives for those carriers with *CYP2C19* loss of function alleles. The efficacy, feasibility, and cost effectiveness of treatment for patients with minor stroke or transient ischaemic attack based on genetic testing requires further evaluation through randomised controlled trials.

The CHANCE trial and secondary data of POINT have shown that short term usage of dual antiplatelet therapy further reduced up to ~30% of recurrent stroke without increased major bleeding compared with aspirin alone. Clinicians and researchers are eager to know whether dual antiplatelet therapy can benefit a broader population of patients who are at high risk of new stroke. The SOCRATES trial implied that the patient population at slightly more severe risk (NIHSS ≤5) also benefited from ticagrelor compared with aspirin in reducing recurrent stroke as the secondary efficacy outcome (table 2).[11] A recent meta-analysis indicated that DAPT was associated with reduced stroke recurrence among patients with acute non-cardioembolic ischaemic stroke or TIA when started within three days of ictus.[21] DAPT might also be effective with acceptable safety in broader patient populations, such as those with more severe stroke (NIHSS 4-5) or in an expanded time window (within 72 hours of symptom onset). These matters need further evaluation in randomised controlled trials.

Whether a treatment is effective will eventually be influenced by patients' adherence. Although short term DAPT was shown to be safe in patients with minor stroke or high risk transient ischaemic attack, concerns still exist for bleeding risk in clinical practice. Secondary analysis of the CHANCE trial showed that DAPT may increase the risk of non-intracranial haemorrhage in patients with minor strokes.[22] Mild bleeding, such as skin bruises and gum bleeding, could influence physicians' decisions and patients' adherence to antiplatelet therapy. Further research is needed to improve adherence.

In summary, DAPT should be started as soon as possible within 24 hours of minor ischaemic stroke or high risk transient ischaemic attack and should be continued up to 21 days. The 21st day is the possible trade-off point to balance treatment effect and bleeding risk. Further studies are needed to evaluate novel and more precise antiplatelet therapy after minor ischaemic stroke and transient ischaemic attack.

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Tables

Table 1| Current recommendations on antiplatelet therapy for patients with minor stroke or TIA

Guideline	Antiplatelet to be used	Recommendations
AHA/ASA, 2018[5]	Aspirin plus clopidogrel	In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset. (Class IIa recommendation, evidence level B, based on randomised data)
Canadian Stroke Best Practice Guideline, 2018[6]	Aspirin plus clopidogrel	In very high risk TIA patients (ABCD2 score ≥4) or minor stroke (NIHSS 0-3), a combination of clopidogrel and aspirin should be given for 21-30 days followed by antiplatelet monotherapy (such as aspirin or clopidogrel alone). (Evidence level A)
Australian Clinical Guidelines for Stroke Management, 2017[7]	Aspirin plus clopidogrel	For high risk patients with minor ischaemic stroke or TIA, aspirin plus clopidogrel may be used in the short term (first three weeks) to prevent stroke recurrence.
		The combination of aspirin plus clopidogrel should not be used for the long term secondary prevention of cerebrovascular disease in people who do not have acute coronary disease or recent coronary stent
Royal college of Physicians guideline 2016[9]	Clopidogrel	Patients with non-disabling stroke or TIA should receive clopidogrel 300 mg loading dose followed by 75 mg daily.
		The combination of aspirin and clopidogrel is not recommended unless there is another indication—eg, acute coronary syndrome, recent coronary stent
Chinese Guidelines 2014[8]	Aspirin Clopidogrel Aspirin plus clopidogrel	Using a combination of aspirin and clopidogrel for 21 days is recommended to patients with minor stroke (NIHSS 0-3) or high risk TIA (ABCD2 ≥4) within 24 h of onset (Grade I recommendation, class-A evidence). After 21 days, either aspirin or clopidogrel can be continued for long term use (Grade I recommendation, class-A evidence)
BMJ Rapid Recommendation[3]	Aspirin plus clopidogrel	In patients with high risk TIA and minor ischaemic stroke, we recommend starting dual antiplatelet therapy using aspirin and clopidogrel within 24 hours of the index event (strong recommendation).
		In patients with high risk TIA and minor ischaemic stroke, we recommend giving dual antiplatelet therapy for 10-21 days after the index event rather than continuing for longer than 21 days (strong recommendation)

AHA/ASA=American Heart Association/American Stroke Association. TIA=transient ischaemic attack.

Table 2| Recent trials in antiplatelet therapy for stroke

	CHANCE[1]	POINT[2]	TARDIS[10]	SOCRATES[11]	PRINCE[12]	THALES[13]
Published year	2013	2018	2018	2016	Recently completed	Ongoing
Study design	Randomised, double blind, placebo controlled	Randomised, double blind, placebo controlled	Randomised, open label, blinded endpoint	randomised, double blind, parallel group	Randomised, open label, blinded endpoint	Randomised, double blind, placebo controlled
Sample size	5170	4881	3096	13 199	675	Estimated 13 000
Study population:						
Ethnicity	100% Asian	3% Asian 75% white 20.4% black 1.5% other	2% Asian 94.9% white 2.0% black 1.1% other	29.6% Asian 66.6% white 1.8% black 2% other	100% Asian	Multiethnic
Patients	TIA*: 27.9% Minor stroke‡: 72.1%	TIA*: 43.2% Minor stroke‡: 56.8%	TIA* or crescendo TIA: 27% Ischaemic stroke: 72%	TIA* or ipsilateral large vessel stenosis:26.8% Minor stroke (NIHSS ≤5):73.2%	TIA*: 16.4%; Minor stroke‡: 83.6%	High risk TIA†, ipsilateral large vessel stenosis ≥50%, or minor stroke (NIHSS ≤5)
Time from onset to randomisation	≤24 h	≤12 h	≤48 h	≤24 h	≤24 h	≤24 h
Interventions:						
Clopidogrel	Day 1: 300 mg Days 2-90: 75mg	Day 1: 600 mg Days 2-90: 75 mg	Day 1: 300 mg Days 2-30: 75 mg			
Aspirin	Day 1: 75-300 mg Days 2-21: 75 mg	Days 1-90: 50-325 mg	Day 1: 300 mg Days 2-30: 75 mg		Days 1-21: 100 mg	Day 1: 300-325 mg Days 2-30: 75-100 mg
Dipyridamol			Days 1-30: either 200 mg twice daily or 150 mg three times a day			
Ticagrelor				Day 1: 180 mg Days 2-90: 180 mg	Day 1-90: 180 mg	Day 1-30: 180 mg
Controls:	Aspirin: Day 1: 75-300 mg Days 2-21: 75 mg	Aspirin: Days 1-90: 50-325 mg	Guideline antiplatelet therapy (aspirin + dipyridamol, or clopidogrel alone)	Aspirin: Day 1: 300 mg Days 2-90: 100 mg	Clopidogrel: Day 1: 300 mg Days 2-90: 75 mg Aspirin: Days 1-21: 100 mg/day;	Aspirin: Day 1: 300-325 mg Days 2-30: 75-100 mg
Time of outcome	Day 90	Day 90	Day 90	Day 90	Day 90	Day 30
Primary efficacy outcome (intervention *v* control)	Stroke: 8.2% *v* 11.7% HR: 0.68 (0.57 to 0.81), P<0.001	Stroke + MI + CV death: 5% *v* 6.5% HR: 0.75 (0.59 to 0.95), P=0.02	Ordinal stroke/TIA: 7% *v* 6%; cOR: 0.90 (0.67 to 1.20), P=0.47	Stroke + MI + death: 6.7% *v* 7.5%; HR: 0.89 (0.78 to 1.01), P=0.07	High platelet reactivity: 12.5% *v* 29.7%; OR:0.34 (0.22 to 0.52), P<0.001	Stroke + death
Secondary efficacy outcome	Stroke + M I +CV death: 8.4% *v* 11.9% HR: 0.69 (0.58 to 0.82), P<0.001	Stroke: 4.8% *v* 6.4% HR: 0.74 (0.58 to 0.94), P=0.01	Stroke: 4% *v* 4% HR: 1.05 (0.73 to 1.51), P=0.79	Stroke: 5.9% *v* 6.8% HR: 0.86 (0.75 to 0.99), P=0.03	Stroke: 6.3% *v* 8.8% HR:0.70 (0.40 to 1.22), P=0.20	Stroke
Primary safety outcome	Moderate to severe bleeding: 0.4% *v* 0.3% HR: 0.84 (0.30 to 2.31), P=0.73	Major haemorrhage: 0.9% *v* 0.4% HR: 2.32 (1.10 to 4.87), P=0.02	Ordinal bleeding: 20% *v* 9% cOR: 2.45 (2.05 to 3.16), P<0.001	Major bleeding: 0.5% *v* 0.6% HR: 0.83 (0.52 to 1.34), P=0.45	Major or minor bleeding: 4.8% *v* 3.5%; HR:1.36 (0.64 to 2.88), P=0.42	Bleeding

* ABCD2 score ≥4. †ABCD2 score ≥6. ‡NIHSS ≤3. MI=myocardial infarction. HR=hazard ratio. cOR=common odds ratio. TIA=transient ischaemic attack. NIHSS=National Institutes of Health Stroke Scale.