

# Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke: a clinical practice guideline

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This *BMJ* Rapid Recommendation article is one of a series that provides clinicians with trustworthy recommendations for potentially practice changing evidence. *BMJ* Rapid Recommendations represent a collaborative effort between the MAGIC group (<http://magicproject.org/>) and *The BMJ*. A summary is offered here and the full version including decision aids is on the MAGICapp (<https://app.magicapp.org/>), for all devices in multilayered formats. Those reading and using these recommendations should consider individual patient circumstances, and their values and preferences and may want to use consultation decision aids in MAGICapp to facilitate shared decision making with patients. We encourage adaptation and contextualisation of our recommendations to local or other contexts. Those considering use or adaptation of content may go to MAGICapp to link or extract its content or contact *The BMJ* for permission to reuse content in this article.

What is the role of dual antiplatelet therapy after high risk transient ischaemic attack or minor stroke? Specifically, does dual antiplatelet therapy with a combination of aspirin and clopidogrel lead to a greater reduction in recurrent stroke and death over the use of aspirin alone when given in the first 24 hours after a high risk transient ischaemic attack or minor ischaemic stroke? An expert panel produced a strong recommendation for initiating dual antiplatelet therapy within 24 hours of the onset of symptoms, and for continuing it for 10-21 days. Current practice is typically to use a single drug.

The recommendations in this clinical practice guideline are based on a linked systematic review<sup>1</sup> triggered by a randomised controlled trial published in the *New England Journal of Medicine* in August 2018.<sup>2</sup> This trial and the linked review found that dual antiplatelet therapy (DAPT) with clopidogrel and aspirin (acetylsalicylic acid) during the first 21 days after the index event reduced the risk of recurrent major ischaemic events compared with aspirin monotherapy.

This Rapid Recommendation aims to quickly and transparently translate evidence for working clinicians

and their patients in adherence with standards for trustworthy guidelines and the GRADE system.<sup>3-5</sup> A panel free of financial conflicts of interest, and including patients, drafted the recommendations. We have managed intellectual interests.

Box 1 shows all of the articles and evidence linked in this Rapid Recommendation package. The core infographic provides an overview of the absolute benefits and harms for DAPT compared with aspirin monotherapy.

## Current practice

Single antiplatelet therapy with aspirin or clopidogrel is an effective intervention for both short and long term secondary prevention of stroke and transient ischaemic attack after an index event. Clinicians sometimes use alternatives of cilostazole or a combination of dipyridamole and aspirin, both referred to for this recommendation as single agent therapy.<sup>6-9</sup>

Aspirin and clopidogrel have synergistic action to inhibit platelet aggregation. So it is plausible that the two

## WHAT YOU NEED TO KNOW

- People with high risk transient ischaemic attack or minor ischaemic stroke are at an increased risk of recurrent stroke and death
- Aspirin and clopidogrel decrease this risk, even more so when used in combination
- We make a strong recommendation for dual antiplatelet therapy (DAPT) with clopidogrel and aspirin to be started within 24 hours in patients who have had a high risk transient ischaemic attack or minor stroke
- We make a strong recommendation for DAPT to be continued for 10-21 days, at which point patients should continue with single antiplatelet therapy
- DAPT is not to be used for major stroke because of the increased risk of intracranial bleeding in these patients


## Box 1 | Linked articles in this *BMJ* Rapid Recommendations cluster

- Prasad K, Siemieniuk R, Hao Q, et al. Dual antiplatelet therapy with aspirin and clopidogrel for acute high risk transient ischaemic attack and minor ischaemic stroke: a clinical practice guideline. *BMJ* 2018;**363**:j656:k5130. doi:10.1136/bmj.k5130
  - Summary of the results from the Rapid Recommendation process
- Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RAC, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ* 2018;**363**:k5108. doi:10.1136/bmj.k5108
  - Review of all available randomised trials that assessed dual antiplatelet therapy (clopidogrel and aspirin) versus aspirin monotherapy after a high risk transient ischaemic attack or minor stroke
- MAGICapp ([www.magicapp.org](http://www.magicapp.org))
  - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

## Recommendation 1: Dual vs single antiplatelet therapy

### Population

Patients that have experienced:




**High risk transient ischaemic attack (TIA)**

A score of 4 or more on the ABCD2 scale, which estimates the risk of recurrent stroke after a TIA

0 ————— 7

OR



**Minor ischaemic stroke**

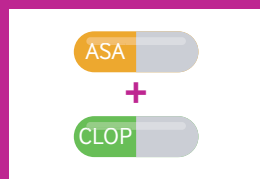
A score of 3 or less on the National Institutes of Health Stroke Scale (NIHSS), and no persistent disabling neurological deficit

0 ————— 42

### Interventions compared

#### Dual antiplatelet therapy

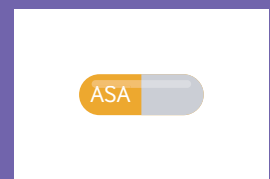
Aspirin and clopidogrel



OR

#### Single agent therapy

All identified trials compared with aspirin alone



### Recommendation

Strong

Weak

Weak

Strong

We recommend dual antiplatelet therapy over single agent therapy. Start as soon as possible after index event.

### Comparison of benefits and harms

	Favours dual antiplatelets	No important difference	Favours single agent	Evidence quality
<b>Within 90 days</b>	<b>Events per 1000 people</b>			
Non-fatal recurrent stroke	44	19 fewer	63	★★★★ High
All cause mortality	6	No important difference	5	★★★★ Moderate
Functional disability	128	14 fewer	142	★★★★ Moderate
Poor quality of life	55	13 fewer	68	★★★★ Moderate
Recurrent TIA	36	No important difference	40	★★★★ Moderate
Moderate or major bleeding	5	2 fewer	3	★★★★ Moderate
Minor bleeding	13	7 fewer	6	★★★★ High

## Recommendation 1: Dual vs single antiplatelet therapy (continued)

### Key practical issues

#### Dual antiplatelets

Two different tablets taken once daily at same time

#### Single agent

A single aspirin tablet once daily

Aspirin tablet should be swallowed whole, but clopidogrel tablet can be crushed or split

### Dosing

Although dosing varied slightly in the included trials, for clopidogrel, most physicians and patients would probably prefer a loading dose of 300 mg rather than a higher dose. For aspirin, a daily dose between 75 mg and 81 mg represents a reasonable choice.

### Values and preferences

The panel believes almost all patients place a high value on avoiding a recurrent stroke and a lower value on avoiding moderate or major bleeding.

## Recommendation 2: Duration of dual antiplatelet therapy

### Population



Patients initiating dual antiplatelet therapy after TIA or minor ischaemic stroke

### Interventions compared

#### Shorter duration

Dual antiplatelet therapy for 10-21 days after TIA or minor stroke



or

#### Longer duration

Dual antiplatelet therapy for 22-90 days after TIA or minor stroke



### Recommendation

Strong

Weak

Weak

Strong

We recommend administering dual antiplatelet therapy for 10-21 days after the index event

#### Comparison of benefits and harms



#### Key practical issues

##### All people taking dual antiplatelets

Most patients should probably remain on single antiplatelet therapy indefinitely

Switch to anticoagulation instead of antiplatelet therapy when stroke workup reveals an indication (such as atrial fibrillation or patent foramen ovale without plans for closure)

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**Table 1 | Current recommendations for antiplatelet therapy for secondary prevention of stroke**

Guideline	Antiplatelet to be used	Statement
AHA/ASA 2018 <sup>6</sup>	<ul style="list-style-type: none"> <li>Aspirin</li> <li>DAPT</li> </ul>	Aspirin (50 to 325 mg) monotherapy, combination of aspirin and extended-release dipyridamole, and clopidogrel monotherapy are all acceptable options for initial therapy for patients with non-cardioembolic stroke or TIA. For patients with minor stroke, treatment for 21 days with DAPT begun within 24 hours can be beneficial for early secondary stroke prevention for up to 90 days from symptom onset
Canadian Stroke Best Practice guideline 2017 <sup>7</sup>	<ul style="list-style-type: none"> <li>Aspirin</li> <li>Combined aspirin and dipyridamole</li> <li>Clopidogrel</li> </ul>	Aspirin 80-325 mg daily, combined aspirin 25 mg and extended-release dipyridamole 200 mg twice daily, or clopidogrel 75 mg daily are appropriate options and selection should depend on clinical circumstances
Australian Clinical Guidelines for Stroke Management 2017 <sup>12</sup>	<ul style="list-style-type: none"> <li>Low dose aspirin</li> <li>Clopidogrel</li> <li>Combined low dose aspirin and modified release dipyridamole</li> <li>DAPT</li> </ul>	Long term antiplatelet therapy (low dose aspirin, clopidogrel, or combined low dose aspirin and modified release dipyridamole) should be prescribed to all people with ischaemic stroke or transient ischaemic attack who are not prescribed anticoagulation therapy, taking into consideration patient comorbidities. For high risk patients with minor ischaemic stroke or transient ischaemic attack, DAPT may be used in the first three weeks to prevent stroke recurrence. DAPT should not be used for long term secondary prevention of cerebrovascular disease in people who do not have acute coronary disease or recent coronary stent
NICE 2016 <sup>13</sup>	<ul style="list-style-type: none"> <li>Clopidogrel</li> <li>Aspirin with modified release dipyridamole</li> <li>Modified release dipyridamole</li> </ul>	For long term vascular prevention in people with ischaemic stroke or transient ischaemic attack without paroxysmal or permanent atrial fibrillation, clopidogrel 75 mg daily should be standard antithrombotic treatment. Aspirin 75 mg daily with modified-release dipyridamole 200 mg twice daily should be used for those who are unable to tolerate clopidogrel. Aspirin 75 mg daily should be used if both clopidogrel and modified release dipyridamole are contraindicated or not tolerated. Modified release dipyridamole 200 mg twice daily should be used if both clopidogrel and aspirin are contraindicated or not tolerated. The combination of aspirin and clopidogrel is not recommended unless there is another indication (such as acute coronary syndrome, recent coronary stent)

AHA/ASA = American Heart Association/American Stroke Association. NICE = National Institute for Health and Care Excellence. DAPT = dual antiplatelet therapy of clopidogrel plus aspirin.

drugs together may provide better secondary prevention of stroke than one. However, they are not in widespread use for various reasons:

- *They are not useful in the long term after stroke*—Several large randomised controlled trials (RCTs) have examined if DAPT (aspirin and clopidogrel) is better at preventing recurrent stroke than single agent antiplatelet therapy. However, DAPT was no better than single agent therapy.<sup>10 11</sup>
- *They are considered too risky after major stroke*—Major strokes, as opposed to minor ones, are treated with single agent only because of the higher risk of haemorrhagic transformation.

- *The balance of benefit and harm is uncertain for short term use after minor stroke or high risk transient ischaemic attack*—In the days and weeks after such an event there is an increased risk of a second ischaemic event. This uncertainty in the setting of acute transient ischaemic attacks and minor stroke could have been reduced by the recent RCT.

Table 1 outlines how international guidelines vary. A minority make a weak recommendation or suggestion for short term DAPT. It also shows some international variation in the single agents that are recommended in the long term. The NICE guideline favours clopidogrel over others, and combined aspirin and dipyridamole over aspirin, whereas most guidelines consider all three as equivalent options.

The ABCD2 score and NIHSS score are typically used to help assess the severity of a transient ischaemic attack or stroke and can help to guide future care. Around 1 in 10 people go on to have a stroke after high risk transient ischaemic attack (box 2). The chance of a further stroke soon after minor stroke is less clear but is likely to be around 10-12% range.

**The evidence**

The linked systematic review<sup>1</sup> found three RCTs examining DAPT versus aspirin alone reporting on a total of 10 447 patients.<sup>2-16</sup> Figure 2 provides an overview of the RCTs and RCT participants. Overall, patients included in these trials were similar to those seen in everyday practice. Mean age varied from 62 to 68.1 years. In the FASTER trial 1/6 of the patients were older than 81 years; in CHANCE 1/4 of patients were over 72; and in POINT 1/4 were over 85. Just over half of participants (52.8-66.2%) were male.

- Compared with single antiplatelet therapy, DAPT decreased all (ischaemic and haemorrhagic) non-fatal recurrent stroke (risk ratio 0.70 (95% confidence interval 0.61 to 0.80), high certainty)

**Box 2 | Assessment of severity of transient ischaemic attack and minor stroke and subsequent risk of stroke**

**Transient ischaemic attack**

- Severity assessed by ABCD2 score:
  - Age—1 point if ≥60 years
  - Blood pressure—1 point if ≥140/90 mm Hg
  - Clinically—1 point if speech disturbance only, 2 points if unilateral weakness
  - Duration—1 point if 10 minutes to 1 hour, 2 points if ≥1 hour
  - Diabetes—1 point if present
- Subsequent risk of stroke based on ABCD2 score:
  - Score 1-3 (low)=1.2% at 7 days
  - Score 4-5 (moderate)=5.9% at 7 days
  - Score 6-7 (high)=11.7% at 7 days

**Minor stroke**

- Severity defined as NIHSS score ≤3
- Subsequent risk of stroke not well characterised but likely equal to that of a high risk transient ischaemic attack

NIHSS = National Institute of Health Stroke Scale.<sup>14</sup> Scale ranges from 0 to 42, based on assessment of 15 measures of motor and sensory function, language and speech production, vision, level of consciousness and attention, and neglect. The elements are summed to provide an overall assessment of stroke severity. A score of 0 to 3 or 4 indicates mild stroke, 5-14 moderate, 15-24 moderately severe, and ≥25 severe.

DATA SOURCES

Use this information to gauge how similar your patients' conditions are to those of people studied in the trials

NUMBER OF TRIALS

3

NUMBER OF PATIENTS

10 447

TRIAL CHARACTERISTICS

Treatment within

24 hours

2

5566

12 hours

1

4881

Loading dose clopidogrel

300 mg

2

5566

600 mg

1

4881

Duration of treatment

21 days

1

5170

90 days

2

5277

Location

North America

1

396

China

1

5170

10 countries, 269 sites

1

4881

Minor stroke defined as

NIH Stroke Scale score of  $\leq 3$

3

10 447

High-risk TIAs defined as

ABCD<sup>2</sup> score of  $\geq 4$

2

10 051

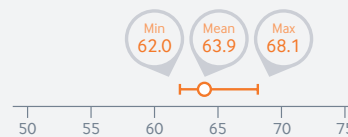
Not defined

1

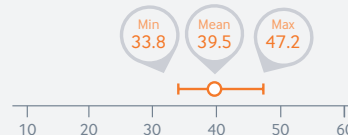
396

PATIENT CHARACTERISTICS

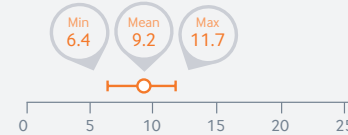
MEAN AGE at baseline



SEX % women



CONTROL GROUP Recurrent stroke %



2 trials had industry sponsorship



All trials were publicly preregistered



No trials reported patient involvement

Fig 2 | Characteristics of patients and trials included in systematic review of the use of DAPT (clopidogrel plus aspirin) versus aspirin monotherapy given within 12-24 hours of symptom onset in patients with high risk transient ischaemic attack or minor stroke

- DAPT led to small improvements in functional disability (moderate certainty) and quality of life (moderate certainty)
- DAPT led to a small, possibly important increase in moderate or major extracranial bleeding (moderate certainty) (see main infographic).

The RCTs varied from 396 participants to 5170; the two largest trials contributed 10 051 patients. One trial was conducted in China,<sup>15</sup> one in North America,<sup>16</sup> and one, the POINT trial,<sup>2</sup> in 269 study sites from 10 countries worldwide. The POINT trial<sup>2</sup> included a diverse population and may therefore be more generalisable than the CHANCE trial, which included only Chinese patients.<sup>15</sup> All trials defined minor stroke as a National Institutes of Health Stroke Scale (NIHSS) score of  $\leq 3$  at the time of ran-

domisation (scores range from 0 to 42, with higher scores indicating greater deficits). The two large trials defined high risk transient ischaemic attacks as an ABCD<sup>2</sup> score of  $\geq 4$  (see box 2 for details) at the time of randomisation.<sup>17</sup> In all trials, patients had undergone computed tomography (CT) scan or magnetic resonance imaging (MRI) to exclude the presence of cerebral haemorrhage or alternative explanations for their symptoms. Enrolment had to take place within 12-24 hours of onset of symptoms.

Understanding the recommendation

Absolute benefits and harms

The infographic provides an overview of the recommendation, the benefits and harms, and our certainty in the evidence. Estimates of baseline risk are generated

**Table 2 | Definitions of the modified Rankin scale**

Score	Disability
0	No symptoms
1	No significant disability
2	Slight disability
3	Moderate disability, can walk unassisted
4	Moderately severe disability, needs help with activities of daily living and walking
5	Severe disability, requires constant nursing
6	Dead

from the control arm of the POINT trial because it was a multinational study and so the population was more diverse.

Overall, the panel was confident that DAPT, when started within 24 hours of symptom onset and used for 10-21 days:

- Reduces non-fatal recurrent stroke (ischaemic and haemorrhagic) in the first 90 days by 1.9% (high quality evidence)
- Reduces the incidence of moderate or severe functional disability by 1.4% (moderate quality evidence)
- Reduces the incidence of poor quality of life by 1.3% (moderate quality evidence).

However, DAPT has little or no impact on:

- All-cause mortality (moderate quality evidence).
- Incidence of myocardial infarction or recurrent transient ischaemic attack (moderate quality evidence).

Furthermore, DAPT also has some harms:

- A small (0.2%), possibly important increase in moderate to major extracranial bleeding events (moderate quality evidence)
- A small increase in the risk of minor extracranial bleeding events by 0.7% (high quality evidence).

Patient-important functional disability was defined as modified Rankin scale score of  $\geq 2$  as defined by the panel (see table 2).

**Duration of DAPT with clopidogrel and aspirin**

The panel was confident that DAPT given for 10-21 days compared with 22-90 days results in:

- Absolute risk decrease of 0.4% in recurrent ischaemic stroke (moderate quality evidence of no benefit on stroke reduction with prolonged clopidogrel)
  - Absolute risk decrease of 0.3% in moderate to major bleeding events (high quality evidence).
- The maximum benefit occurred in the first 10 days.

**Values and preferences**

The panel discussed how patients might weigh the benefit of reduced stroke with DAPT against its harm of increased bleeding. The panel believed that most patients would consider a stroke considerably worse than a bleed and so would choose DAPT over single agent therapy. There was no published evidence to support this from patients considering DAPT, but this view is consistent with a systematic review of values and preferences in decision making for antithrombotic therapy.<sup>18</sup> In that scenario patients

considered non-fatal stroke (thrombotic or haemorrhagic) to be two to three times worse than serious gastrointestinal bleeding.

The panel believed that all or almost all patients would choose 10-21 days of therapy rather than 22-90 days as shorter therapy is associated with equivalent benefit and less harm.

**Practical issues**

Figure 3 outlines the key practical considerations.

*When should patients begin their DAPT?*

If brain imaging is done within 24 hours of onset of symptoms, patients should begin DAPT as soon as the imaging results exclude intracranial haemorrhage or stroke-mimicking lesions. If a delay of 24 hours or more in imaging is suspected, then patients should begin DAPT as soon as a clinician makes a diagnosis of minor ischaemic stroke or transient ischaemic attack, be the clinician a primary care doctor or stroke neurologist, and be the setting inpatient or outpatient. Such patients should have imaging as soon as possible.

*How should patients respond if experiencing adverse effects of DAPT?*

We are most confident of the stroke reduction with clopidogrel in the first seven days after commencement. If adverse effects are minor, patients may be well advised to continue until at least seven days.

*Dosing of antiplatelets*

There were no head to head comparisons in the studies to give clear guidance on what loading and maintenance dose to offer. However, the following considerations may be useful:

- *For clopidogrel*—A loading dose of 300 mg and a dose of 75 mg thereafter seem reasonable because bleeding was marginally greater in the POINT trial,<sup>2</sup> which used a higher loading dose (table 3)
- *For aspirin*—A dose between 75 mg and 345 mg seems reasonable. The results of the trials do not offer particular insights. Some clinicians may prefer to prescribe at the low end of this range to minimise harm. However, other clinicians may wish to take into account recent evidence of dosing based on weight from studies in primary prevention of cardiovascular events and long term secondary prevention of stroke.<sup>19</sup>



The addition of a second agent, likely clopidogrel, adds to the immediate cost of treatment. This drug is, however, widely available and relatively inexpensive, and the duration of use is short. Moreover, the cost savings related to stroke reduction are likely to be as much or more than the costs of clopidogrel administration.

**Uncertainties**

The following remains uncertain for clinicians and patients:

- What is the optimal starting dose of clopidogrel or aspirin? What is the optimal maintenance dose of both agents?

Fig 3 | Practical issues about use of DAPT (clopidogrel plus aspirin) versus aspirin monotherapy for patients with high risk transient ischaemic attack or minor stroke

PRACTICAL ISSUES	
Dual anti-platelet therapy (Clopidogrel and Aspirin)	
 MEDICATION ROUTINE	Two different tablets taken once daily at same time, important to take them regularly Aspirin tablet should be swallowed whole, clopidogrel tablet can be crushed or split
 TEST & VISIT	Not necessary to take regular blood samples due to medication
 RECOVERY & ADAPTATION	Follow-up necessary from family physician/GP after discharge from hospital
 ADVERSE EFFECTS, INTERACTIONS & ANTIDOTE	Gastrointestinal symptoms such as diarrhoea, dyspepsia, and bleeding Clopidogrel should not be used with proton pump inhibitors
 PHYSICAL WELL-BEING	Clopidogrel contains lactose
 EMOTIONAL WELL-BEING	Emotional stress related to starting new medication
 PREGNANCY & NURSING	Clopidogrel cannot be used during pregnancy and nursing
 COSTS & ACCESS	Cost depends on health policy and health insurance
 FOOD & DRINKS	Clopidogrel can be taken with or without food and aspirin should be taken without food Moderation in alcohol consumption is advised
 EXERCISE & ACTIVITIES	Participation in high risk activities may increase risk of bleeding
 WORK & EDUCATION	Participation in high risk activities and work may increase risk of bleeding
 TRAVEL TIME & DRIVING	Does not affect ability to drive



**Table 3 | Clopidogrel and aspirin doses used in intervention arms of the trials included in the systematic review<sup>1</sup>**

Trial	Clopidogrel dose	Aspirin dose
FASTER <sup>16</sup>	300 mg load followed by 75 mg daily	162 mg load followed by 81 mg daily
CHANCE <sup>15</sup>	300 mg load followed by 75 mg daily	75-300 mg load to be decided by physician, followed by 75 mg daily
POINT <sup>2</sup>	600 mg load followed by 75 mg daily	50-325 mg daily, suggested 162 mg aspirin for 5 days followed by 81 mg daily

**Table 4 | New evidence which has emerged after initial publication**

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article.				

- What are the benefits and risks of DAPT with clopidogrel and aspirin in patients with low risk transient ischaemic attack compared with aspirin alone?
- What are the risks and benefits of DAPT in patients with moderate strokes (NIHSS score 3-10) with or without thrombolysis treatment?
- What are the benefits and risks of DAPT with clopidogrel and aspirin compared with clopidogrel alone in this population?

**Updates to this article**

Table 4 shows evidence that has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

**EDUCATION INTO PRACTICE**

- For prevention of recurrent stroke in patients with recent transient ischaemic attacks or minor stroke, which antiplatelet or combination of antiplatelets do you prescribe?
- How do you identify patients with transient ischaemic attacks as high risk or low risk?
- How do you classify stroke as minor or major?
- Based on this article, how do you think your personal practice might change? Is there anything that you would do differently for patients with high risk transient ischaemic attack or minor stroke?

**HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE**



Three people with lived experience of stroke, and one person with lived experience as a carer for a patient with stroke, were full panel members. They identified and rated outcomes, and led the discussion on values and preferences. The patient partners rated all included outcomes as important to them. Although these values may not be shared by all patients for all outcomes considered, the panel expected little variation in how much importance other patients would place on the critical outcomes of recurrent non-fatal stroke, moderate to major bleeding events, all-cause mortality, functional disability and quality of life.

Patients and carers were instrumental to this guideline in weighing the benefits and harms of DAPT. They clearly articulated the consistent view that avoiding recurrent stroke is paramount in those with transient ischaemic attack and minor stroke and that most would be willing to risk extracranial bleeding to achieve this.

We thank them for their time and valuable input.

**Contributors:** All panel members participated in the teleconferences and email discussions and met all authorship criteria.

**Competing interests:** All authors have completed the *BMJ* Rapid Recommendations interests disclosure form, and a description of all disclosures is reported in appendix 1 on [bmj.com](http://www.bmj.com). As with all *BMJ* Rapid Recommendations, the executive team and *The BMJ* judged that no panel member had any financial conflict of interest. Professional and academic interests are minimised as much as possible, while maintaining necessary expertise on the panel to make fully informed decisions.

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**Transparency:** K Prasad affirms that the manuscript is an honest, accurate, and transparent account of the recommendation being reported; that no important aspects of the recommendation have been omitted; and that any discrepancies from the recommendation as planned (and, if relevant, registered) have been explained.

**Provenance and peer review:** Commissioned; externally peer reviewed

- 1 Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RAC, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ* 2018;363:k5108. 10.1136/bmj.k5108.
- 2 Johnston SC, Easton JD, Farrant M, et al. Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med* 2018;379:215-25. 10.1056/NEJMoa1800410 pmid:29766750.
- 3 Guidelines IoMCoSfDCP. *Clinical practice guidelines we can trust*. Washington DC: National Academies Press, 2011.
- 4 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. 10.1136/bmj.39489.470347.AD pmid:18436948.
- 5 Qaseem A, Forland F, Macbeth F, Ollenschläger G, Phillips S, van der Wees P. Board of Trustees of the Guidelines International Network. Guidelines International Network: toward international standards for clinical practice guidelines. *Ann Intern Med* 2012;156:525-31. 10.7326/0003-4819-156-7-201204030-00009 pmid:22473437.

**HOW THIS RECOMMENDATION WAS CREATED**

This guideline was triggered by a randomised controlled trial that compared dual antiplatelet therapy (DAPT, clopidogrel plus aspirin) with aspirin monotherapy given within 12-24 hours of symptom onset in patients with high-risk transient ischaemic attack or minor stroke.<sup>2</sup> This added to a previous DAPT trial published in 2013.<sup>15</sup> The Rapid Recommendations team thought that the results had the potential to change practice.

The scope of the recommendation and the patient-important outcomes were defined by an international guideline panel consisting of three patients with lived experience of stroke, one adult who cared for someone with a stroke, five stroke neurologists, one vascular surgeon, one health research methodologist, five general internists (four who are also methodologists), one nurse, one physiotherapist, and one critical care physician (who is also a methodologist) (see appendix 1 on [bmj.com](http://www.bmj.com) for details of panel members). The panel judged death, non-fatal stroke, major extracranial bleeding, functional ability, and quality of life as critical outcomes. Myocardial infarction, recurrent transient ischaemic attack, and minor extracranial bleeding were judged less important.

The panel requested a systematic review and meta-analysis of RCTs examining the benefits and harms of DAPT versus single agent antiplatelet in order to inform the recommendation. The panel then met online to discuss the evidence and to formulate recommendations. In our judgment no panel member had relevant financial conflicts of interest; intellectual and professional conflicts were minimised and transparently described (see appendix 1 on [bmj.com](http://www.bmj.com)).

The panel followed the *BMJ* Rapid Recommendations procedures for creating a trustworthy recommendation,<sup>20,21</sup> including using the GRADE approach to critically appraise the evidence and translate it to recommendations (see appendix 2 on [bmj.com](http://www.bmj.com)).<sup>4</sup> The panel considered the benefits, harms and burdens of DAPT versus single antiplatelet therapy, the quality (certainty) of the evidence for each outcome, variations in patient values and preferences, as well as acceptability and feasibility.<sup>22</sup> Following the GRADE based approach, recommendations can be strong or weak for or against a specific course of action.<sup>23</sup> The recommendations take a patient-centred perspective that de-emphasises public health, societal, and health payer points of view. Healthcare systems can adapt these recommendations by including costs and other key issues of relevance, contextualised to national and local circumstances.

- 6 Powers WJ, Rabinstein AA, Ackerson T, et al. American Heart Association Stroke Council. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;49:e46-110. 10.1161/STR.000000000000158 PMID:29367334.
- 7 Wein T, Lindsay MP, Côté R, et al. Heart and Stroke Foundation Canadian Stroke Best Practice Committees. Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017. *Int J Stroke* 2018;13:420-43. 10.1177/1747493017743062 PMID:29171361.
- 8 Australian Clinical Practice Guidelines. *Clinical guidelines for stroke management 2017*. 2017. www.clinicalguidelines.gov.au/portal/2585/clinical-guidelines-stroke-management-2017.
- 9 Royal College of Physicians. National clinical guideline for stroke 2016. 2016. www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines.
- 10 Diener HC, Bogousslavsky J, Brass LM, et al. MATCH investigators. 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;364:331-7. 10.1016/S0140-6736(04)16721-4 PMID:15276392.
- 11 Bhatt DL, Fox KA, Hacke W, et al. CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med* 2006;354:1706-17. 10.1056/NEJMoa060989 PMID:16531616.
- 12 Stroke Foundation. *Clinical guidelines for stroke management 2017*. 2017. https://informme.org.au/en/Guidelines/Clinical-Guidelines-for-Stroke-Management-2017.
- 13 National Institute for Health and Care Excellence. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (clinical guideline CG68). 2017. www.nice.org.uk/guidance/cg68.
- 14 Kasner SE, Chalela JA, Luciano JM, et al. Reliability and validity of estimating the NIH stroke scale score from medical records. *Stroke* 1999;30:1534-7. 10.1161/01.STR.30.8.1534 PMID:10436096.
- 15 Wang Y, Wang Y, Zhao X, et al. CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med* 2013;369:11-9. 10.1056/NEJMoa1215340 PMID:23803136.
- 16 Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol* 2007;6:961-9. 10.1016/S1474-4422(07)70250-8 PMID:17931979.
- 17 Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. *Lancet* 2007;369:283-92. 10.1016/S0140-6736(07)60150-0 PMID:17258668.
- 18 MacLean S, Mulla S, Akl EA, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012;141(Suppl):e1S-23S. 10.1378/chest.11-2290 PMID:22315262.
- 19 Rothwell PM, Cook NR, Gaziano JM, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. *Lancet* 2018;392:387-99. 10.1016/S0140-6736(18)31133-4 PMID:30017552.
- 20 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. 10.1136/bmj.i5191 PMID:27680768.
- 21 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. 10.1136/bmj.i5085 PMID:27680583.
- 22 Andrews JC, Schünemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation—determinants of a recommendation’s direction and strength. *J Clin Epidemiol* 2013;66:726-35. PMID:23570745.
- 23 Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008;336:1049-51. 10.1136/bmj.39493.646875.AE PMID:18467413.

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