

Transient ischaemic attack: clopidogrel

Evidence summary

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[nice.org.uk/guidance/esuom23](https://www.nice.org.uk/guidance/esuom23)

Key points from the evidence

The content of this evidence summary was up-to-date in December 2013. See [summaries of product characteristics \(SPCs\)](#), [British national formulary \(BNF\)](#) or the [MHRA](#) or [NICE](#) websites for up-to-date information.

Summary

No relevant [randomised controlled trials \(RCTs\)](#) were identified that assessed clopidogrel monotherapy in people who have had a transient ischaemic attack (TIA). In addition, no high quality observational data were identified on the efficacy of clopidogrel monotherapy in people with TIA. Limited RCT evidence was identified for the use of clopidogrel in combination with aspirin for TIA.

Regulatory status: off-label

This topic of transient ischaemic attack: clopidogrel was chosen for an evidence summary as there were a high volume of requests from the NHS for information on this topic and potential for variation in practice.

<p>Effectiveness</p> <ul style="list-style-type: none"> • No relevant evidence was identified on the use of clopidogrel monotherapy in TIA. • Two RCTs were identified that compare clopidogrel plus aspirin with aspirin alone, initiated within 24 hours of TIA or minor ischaemic stroke. Primary outcome of both studies was any new stroke event (ischaemic or haemorrhagic) at 90 days. • One of the 2 RCTs found a statistically significant reduction in risk of any new stroke event at 90 days with clopidogrel plus aspirin for 21 days followed by clopidogrel alone. However this trial was carried out in a Chinese population; it has limitations and the results may not be generalisable to the UK. 	<p>Safety</p> <ul style="list-style-type: none"> • The summary of product characteristics for clopidogrel lists haematoma, epistaxis, gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia, bruising and bleeding at puncture sites as common adverse effects (occurring in between 1 in 10 and 1 in 100 people). No relevant safety data were identified that compared clopidogrel monotherapy with alternative treatment in a population with TIA.
<p>Patient factors</p> <ul style="list-style-type: none"> • Additional antiplatelet therapy may add to the burden of polypharmacy. 	<p>Resource implications</p> <ul style="list-style-type: none"> • Cost of £1.71 for 28 days' supply of generic clopidogrel 75 mg daily. • Cost of £33.26 for 28 days' supply of branded clopidogrel (Plavix) 75 mg daily.

Key points

Clopidogrel is licensed for the prevention of atherothrombotic events in people who have had an ischaemic stroke (from 7 days until less than 6 months) but it is not licensed for use in people who have had a TIA. NICE has issued guidance on [clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events](#) which recommends that modified-release dipyridamole in

combination with aspirin is an option to prevent occlusive vascular events for people who have had a TIA.

No RCTs were identified that assessed clopidogrel monotherapy in people with TIA for either the acute phase or long-term treatment. In addition, no high quality observational data were identified on the efficacy of clopidogrel monotherapy in people with TIA.

Two RCTs ([CHANCE](#) and [FASTER](#)) were identified that compared clopidogrel plus aspirin with aspirin alone for 90 days in people with acute TIA or minor ischaemic stroke ([NIHSS](#) score ≤ 3) in the past 24 hours.

The [CHANCE](#) trial compared clopidogrel plus aspirin for 21 days followed by clopidogrel alone for a total of 90 days with aspirin alone for 90 days. The [CHANCE](#) trial only included people with TIA at a higher risk of early stroke ([ABCD²](#) score ≥ 4). The [CHANCE](#) trial (n=5170) found a statistically significant reduction in the primary outcome of risk of new stroke events (ischaemic or haemorrhagic) at 90 days with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with aspirin alone (8.2% compared with 11.7%; hazard ratio [HR] 0.68, 95% [confidence interval](#) [CI] 0.57 to 0.81; $p < 0.001$). The [CHANCE](#) trial found no statistically significant reduction in all-cause mortality or death from cardiovascular causes with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with aspirin alone.

The [FASTER](#) trial (n=392) compared clopidogrel plus aspirin with aspirin alone for 90 days. It found no statistically significant difference between clopidogrel plus aspirin and aspirin alone for the same primary outcome (7.1% compared with 10.8%; [risk ratio](#) [RR] 0.7; 95% CI 0.3 to 1.2; $p = 0.19$). However, it may have been underpowered to detect an effect.

The [CHANCE](#) trial, which was conducted in China, has a number of substantial limitations. In particular, the results may not be generalisable to the UK population because of differences between the Chinese and western populations in aetiology of stroke and background use of preventive interventions to reduce cardiovascular risk. An ongoing trial in the USA and worldwide (the [POINT](#) trial) is assessing the effects of clopidogrel plus aspirin started within 12 hours of high-risk TIA or minor ischaemic stroke with follow-up for 90 days. The results from this trial may be more applicable to a western population.

The [CHANCE](#) trial found no statistically significant difference in moderate or severe bleeding events between clopidogrel plus aspirin for 21 days followed by clopidogrel alone and aspirin alone (0.3% in both groups, $p = 0.73$). The [FASTER](#) trial found a statistically significant increase in symptomatic bleeding events (3.0% compared with 0%; [risk difference](#) [RD] 3.0%, 95% CI 0.6% to

5.4%; $p=0.03$) and asymptomatic bleeding events (30.8% compared with 13.9%; RD 16.9%, 95% CI 8.8% to 25.0%; $p=0.0001$) with clopidogrel plus aspirin compared with aspirin alone.

The CHANCE and FASTER trials both lasted for 90 days and results, particularly safety results, may not apply to longer-term treatment.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Clopidogrel is an irreversible adenosine diphosphate-receptor antagonist with antiplatelet properties.

Regulatory status of clopidogrel

All of the generic preparations of clopidogrel and the Plavix branded preparation are licensed for the prevention of atherothrombotic events in patients with myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. Not all versions of clopidogrel are licensed for acute coronary syndrome in combination with aspirin, and this is also the case for use in combination with aspirin in adults with atrial fibrillation who have at least one risk factor for vascular events, for whom vitamin K antagonists are not suitable and who have a low bleeding risk. No version of clopidogrel is licensed for use in people with transient ischaemic attack (TIA), so this use is off-label.

In line with the [guidance from the General Medical Council \(GMC\)](#), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using clopidogrel outside its authorised indications.

Evidence statements

- No [randomised controlled trials](#) (RCTs) were identified that compared clopidogrel monotherapy with an alternative treatment in people who have experienced a TIA. No high quality observational data on the efficacy of clopidogrel monotherapy in TIA were identified.
- Two RCTs ([CHANCE](#) and [FASTER](#)) were identified that compared clopidogrel plus aspirin with aspirin alone in people with acute TIA or minor ischaemic stroke started within 24 hours of the event. Follow-up was continued for 90 days. In both trials, clopidogrel was given as a loading dose of 300 mg on day 1, followed by 75 mg daily. In the CHANCE trial, aspirin was only given concomitantly for the first 21 days and the trial only included people with high-risk TIA ([ABCD²](#) score ≥ 4).
- The [CHANCE](#) trial included 5170 patients in China. It found that clopidogrel plus aspirin for 21 days followed by clopidogrel alone reduced the risk of a new stroke event (ischaemic or haemorrhagic) over 90 days' follow-up (8.2% compared with 11.7%; hazard ratio [HR] 0.68, 95% [confidence interval](#) [CI] 0.57 to 0.81; $p < 0.001$) compared with aspirin alone. The [FASTER](#) pilot trial included 392 patients in Canada and the USA. This found no statistically significant difference between clopidogrel plus aspirin and aspirin alone for the same primary outcome (7.1% compared with 10.8%; [risk ratio](#) [RR] 0.7, 95% CI 0.3 to 1.2; $p = 0.19$). However, the trial may have been underpowered.
- The [CHANCE](#) trial found no statistically significant reduction in all-cause mortality (HR 0.97, 95% CI 0.40 to 2.33) or death from cardiovascular causes (HR 1.16, 95% CI 0.35 to 3.79) with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with aspirin alone.
- There are substantial limitations to the [CHANCE](#) trial. Its results may not be generalisable to the wider population of people with acute high-risk TIA and minor stroke because of differences between the Chinese and western populations in aetiology of stroke and background use of preventive interventions to reduce cardiovascular risk.
- An ongoing trial in the USA and worldwide (the [POINT](#) trial) is assessing the effects of clopidogrel plus aspirin started within 12 hours of TIA or minor ischaemic stroke and continued for 90 days. The results from this trial may be more applicable to a western population.

- The [CHANCE](#) trial found no statistically significant differences in moderate or severe bleeding events between clopidogrel plus aspirin for 21 days followed by clopidogrel alone and aspirin alone (0.3% in both groups, $p=0.73$). The [FASTER](#) trial found a statistically significant increase in symptomatic bleeding events (3% compared with 0%; risk difference [RD] 3.0%, 95% CI 0.6% to 5.4%; $p=0.03$) and asymptomatic bleeding events (30.8% compared with 13.9%; RD 16.9%, 95% CI 8.8% to 25.0%; $p=0.0001$) with clopidogrel plus aspirin.
- The CHANCE and FASTER trials both lasted for 90 days after minor ischaemic stroke or TIA and results, particularly safety results, may not apply to longer-term treatment. A pre-specified subgroup analysis from the [MATCH](#) trial of people who had had a TIA in the past 3 months ($n=1605$) found no statistically significant difference between clopidogrel plus aspirin and clopidogrel alone for first occurrence of an event in the composite of ischaemic stroke, myocardial infarction, vascular death or rehospitalisation for an acute ischaemic event over an 18-month period (14.7% compared with 15.6%; p value not reported).

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the [Evidence review](#) section.

Efficacy

Clopidogrel monotherapy

No relevant RCTs that compared clopidogrel monotherapy with an alternative treatment in people with TIA were identified. Therefore no RCTs were identified comparing:

- an initial loading dose of clopidogrel monotherapy with high-dose aspirin immediately after a patient presents with suspected acute TIA
- clopidogrel monotherapy for long-term antiplatelet treatment with alternative treatment for people who have had a TIA.

In addition, no high quality observational data on the efficacy of clopidogrel monotherapy in people with TIA were identified.

Clopidogrel as dual therapy

Two RCTs ([CHANCE](#) and [FASTER](#)) were identified that compared clopidogrel plus aspirin with aspirin alone in people with acute TIA or minor ischaemic stroke in the past 24 hours; follow-up was

for 90 days. The [CHANCE](#) trial compared clopidogrel plus aspirin for 21 days followed by clopidogrel alone for a total of 90 days with aspirin alone for 90 days. The [FASTER](#) trial compared clopidogrel plus aspirin with aspirin alone for 90 days. Both trials defined minor stroke as a National Institutes of Health Stroke Scale ([NIHSS](#)) score of 3 or lower.

The [CHANCE](#) trial (n=5170), which was conducted in China, found a statistically significant reduction in the risk of new stroke events (ischaemic or haemorrhagic) at 90 days with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with aspirin alone (8.2% compared with 11.7%; HR 0.68, 95% CI 0.57 to 0.81; $p < 0.001$). In a pre-specified subgroup of people with TIA (n=1445) there remained a statistically significant reduction in the risk of new stroke events with clopidogrel plus aspirin for 21 days followed by clopidogrel alone. However, this trial has a number of limitations. The results may not be generalisable to other populations because of differences between Chinese and western populations in aetiology of stroke and background use of preventive interventions to reduce cardiovascular risk. The trial also only included people with TIA at a high risk of recurrence ([ABCD²](#) score ≥ 4) (see [Evidence strengths and limitations](#)).

The [FASTER](#) trial (n=392) found no statistically significant difference between clopidogrel plus aspirin and aspirin alone in the risk of any new stroke at 90 days (7.1% compared with 10.8%; RR 0.7; 95% CI 0.3 to 1.2; $p=0.19$). However, this trial was stopped early and may have been underpowered to detect an effect.

An ongoing trial in the USA and worldwide (the [POINT](#) trial) is assessing the effects of clopidogrel plus aspirin started within 12 hours of high-risk TIA or minor ischaemic stroke and continued for 90 days. Its results may be more generalisable to a western population.

A pre-specified subgroup analysis from the [MATCH](#) trial of people who had had a TIA in the previous 3 months (n=1605) found no statistically significant difference between clopidogrel plus aspirin and clopidogrel alone in first occurrence of an event in the composite of ischaemic stroke, myocardial infarction, vascular death or rehospitalisation for an acute ischaemic event over an 18-month period (14.7% compared with 15.6%; no p value reported).

Safety

The most common side effect associated with use of clopidogrel is bleeding. The summary of product characteristics ([Plavix](#)) notes that the most common adverse effects (occurring in between 1 in 10 and 1 in 100 people) are haematoma, epistaxis, gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia, bruising and bleeding at puncture sites.

The safety results from the [CHANCE](#) and [FASTER](#) trials are for clopidogrel plus aspirin compared with aspirin alone with a follow-up period limited to 90 days. In the CHANCE trial, clopidogrel plus aspirin was only given for the first 21 days; in the FASTER trial clopidogrel plus aspirin was given for 90 days. The CHANCE trial found no statistically significant difference between clopidogrel plus aspirin for 21 days followed by clopidogrel alone and aspirin alone in moderate or severe bleeding events (0.3% in both groups; $p=0.73$). The FASTER trial found a statistically significant increase in symptomatic bleeding events (3.0% compared with 0%; RD 3.0%, 95% CI 0.6% to 5.4%; $p=0.03$) and asymptomatic bleeding events (30.8% compared with 13.9%; RD 16.9%, 95% CI 8.8% to 25.0%; $p=0.0001$) with clopidogrel plus aspirin compared with aspirin alone. There were 6 symptomatic bleeding events in the FASTER trial, all of which occurred in the clopidogrel plus aspirin group (2 intracranial haemorrhages, 1 severe extracranial haemorrhage, 2 moderate extracranial haemorrhages and 1 mild extracranial haemorrhage). When symptomatic bleeding events were split into intracranial and extracranial haemorrhages, with the latter divided by severity, there were no statistically significant differences between the 2 groups. This may be because of the small number of events reducing power in these analyses.

Cost effectiveness and cost

No cost-effectiveness analyses for clopidogrel use in people with TIA or acute suspected TIA and minor stroke only were identified.

[NHS electronic drug tariff](#) (October 2013) data indicate that the cost of the branded form of clopidogrel (Plavix, Sanofi) is £142.54 for 30 tablets of 300 mg. The cost of generic clopidogrel 75 mg tablets is £1.71 for 28 tablets. The cost of the branded form of clopidogrel 75 mg tablets (Plavix, Sanofi) is £35.64 for 30 tablets ([MIMS](#); November 2013).

Relevance to NICE guidance programmes

This use of clopidogrel in people with transient ischaemic attack (TIA) is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued guidance on [clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events](#) (NICE technology appraisal guidance 210), but no recommendations are made regarding clopidogrel in people with TIA because this use is off-label.

In [NICE technology appraisal guidance 210](#), clopidogrel is recommended as an option to prevent occlusive vascular events:

- for people who have had an ischaemic stroke or who have peripheral arterial disease or multivascular disease or
- for people who have had a myocardial infarction only if aspirin is contraindicated or not tolerated.

NICE guidance also exists for the other licensed indications for clopidogrel and for managing bleeding in people taking clopidogrel:

- [Clopidogrel in the treatment of non-ST-segment-elevation acute coronary syndrome](#) (NICE technology appraisal guidance 80)
- [Unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction](#) (NICE clinical guideline 94)
- [MI – secondary prevention: Secondary prevention in primary and secondary care for patients following a myocardial infarction](#) (NICE clinical guideline 172)
- [Acute upper gastrointestinal bleeding: management](#) (NICE clinical guideline 141) provides guidance on the control of bleeding and prevention of re-bleeding in patients on clopidogrel. It recommends discussing the risks and benefits of continuing clopidogrel in patients with upper gastrointestinal bleeding with the appropriate specialist (for example, a cardiologist or a stroke specialist) and with the patient.
- [Atrial fibrillation: the management of atrial fibrillation](#) (NICE clinical guideline 36; this guideline is [currently being updated](#) and is due to be published in June 2014) recommends that bleeding risk should be part of the clinical assessment of patients before starting anticoagulant therapy, with particular attention paid to specified groups of patients, including those taking antiplatelet drugs such as clopidogrel.

NICE has also produced guidance on the [diagnosis and initial management of acute stroke and transient ischaemic attack](#) (NICE clinical guideline 68).

Intervention and alternatives

Clopidogrel is an irreversible adenosine diphosphate-receptor antagonist with antiplatelet properties. According to the summary of product characteristics ([Plavix](#)) it is a prodrug, 1 of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel is metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. [NICE technology appraisal guidance 210](#) reports that clopidogrel is available as branded and generic preparations and has marketing authorisation for 'the prevention of atherothrombotic events in patients suffering from

myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease'. It is not licensed for use to prevent occlusive vascular events in people with transient ischaemic attack (TIA), so this use is off-label.

Condition

TIA is a form of occlusive vascular event. Occlusive vascular events include ischaemic stroke, TIA and myocardial infarction. They occur when blood flow is impeded because an artery is blocked or restricted because of atherosclerosis and atherothrombosis. In the UK each year between 46,000 and 65,000 people are estimated to have a TIA. People who have had an occlusive vascular event are at increased risk of another event.

Symptoms and signs of stroke and TIA develop rapidly, are usually focal (although they can be global), and include numbness, weakness or paralysis, slurred speech and visual disturbances (characteristically a sudden visual loss in one-half of the visual field, or visual loss in one-quarter of the visual field, or visual loss in 1 eye). Headache is not a typical feature of ischaemic stroke or TIA. With stroke, the symptoms and signs persist beyond 24 hours or cause death within 24 hours. With TIA, the symptoms and signs resolve within 24 hours ([NICE Clinical Knowledge Summaries](#)). NICE guidance on the [diagnosis and initial management of acute stroke and transient ischaemic attack \(TIA\)](#) states that the symptoms of a TIA usually resolve within minutes or a few hours at most, and anyone with continuing neurological signs when first assessed should be assumed to have had a stroke (rather than a TIA).

People who have a TIA are at increased risk of a stroke, particularly in the 2 days after the event ([Wang et al. 2013](#)). [NICE guidance](#) recommends that people who have had a suspected TIA (that is, they have no neurological symptoms at the time of assessment [within 24 hours]) should be assessed as soon as possible for their risk of subsequent stroke using a validated scoring system such as ABCD². ABCD² assigns a score based on age, blood pressure at presentation, clinical features, duration of TIA symptoms and presence or absence of diabetes. People with a score of 4 or more are regarded as being at a higher risk of early stroke.

Current [NICE guidance](#) on TIA and stroke recommends that:

People with suspected TIA and at high risk of stroke (ABCD² score ≥ 4 , or those with 2 or more TIAs in a week [crescendo TIA] with any ABCD² score) should have:

- aspirin (300 mg daily) started immediately
- specialist assessment and investigation within 24 hours of onset of symptoms

- measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

People who have had a suspected TIA who are at lower risk of stroke (an [ABCD²](#) score ≤ 3 and who do not have crescendo TIA, or who present >1 week after resolution of their last symptom) should have:

- aspirin (300 mg daily) started immediately
- specialist assessment and investigation as soon as possible, but definitely within 1 week of onset of symptoms (for those not presenting later than this)
- measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

Alternative treatment options

Aspirin and modified-release dipyridamole (with or without aspirin) are both licensed for prevention of occlusive vascular events in people who have had a TIA.

NICE guidance on the [diagnosis and initial management of acute stroke and transient ischaemic attack \(TIA\)](#) recommends that people with suspected TIA should have aspirin (300 mg daily) started immediately. Measures for secondary prevention should be introduced as soon as the diagnosis is confirmed, including discussion of individual risk factors.

For long-term antiplatelet treatment, [NICE technology appraisal guidance 210](#) recommends that modified-release dipyridamole in combination with aspirin is an option to prevent occlusive vascular events for people who have had a TIA. Modified-release dipyridamole alone is recommended as an option to prevent occlusive vascular events in TIA only if aspirin is contraindicated or not tolerated.

Evidence review: efficacy

Clopidogrel as monotherapy

No [randomised controlled trials](#) (RCTs) that compared clopidogrel monotherapy with an alternative treatment (such as aspirin or aspirin plus modified-release dipyridamole) in people with transient ischemic attack (TIA) were identified. Therefore, no RCTs were identified comparing:

- an initial loading dose of clopidogrel monotherapy with high-dose aspirin immediately after a patient presents with suspected acute TIA
- clopidogrel monotherapy for long-term antiplatelet treatment with aspirin or alternative treatment for people who have had a TIA.

In addition, no high quality observational data on the efficacy of clopidogrel monotherapy in people with TIA were identified.

Clopidogrel as dual therapy

Two completed RCTs comparing clopidogrel plus aspirin with aspirin alone in people with suspected acute TIA or minor ischaemic stroke in the past 24 hours, the [CHANCE](#) trial and the [FASTER](#) trial, were identified. They both defined minor stroke as a National Institutes of Health Stroke Scale ([NIHSS](#)) score of 3 or lower (the NIHSS score scale ranges from 0 to 42, with higher scores indicating greater deficits). They both had a primary efficacy outcome of new stroke event (ischaemic or haemorrhagic) at 90 days. Another RCT ([MATCH](#)) compared clopidogrel plus aspirin with clopidogrel alone over an 18-month period in high-risk patients who had had an ischaemic stroke or a TIA within the previous 3 months. A pre-specified subgroup analysis from the [MATCH](#) trial of people who had had a TIA (n=1605) found no statistically significant difference between clopidogrel plus aspirin and clopidogrel alone for first occurrence of an event in the composite of ischaemic stroke, myocardial infarction, vascular death or rehospitalisation for an acute ischaemic event over an 18-month period (14.7% compared with 15.6%; p value not reported). However, because clopidogrel was in both treatment arms its efficacy cannot be determined.

Clopidogrel plus aspirin compared with aspirin alone

The [CHANCE](#) trial was carried out at 114 centres in China. It included adults (mean age 62 years; 66.2% male) who had experienced high-risk TIA ([ABCD](#)² score ≥ 4) or minor ischaemic stroke in the past 24 hours. Of the 41,561 people screened, 5170 (12.4%) met inclusion criteria but not exclusion criteria and were randomised in approximately equal numbers using an automated system. All participants received open-label aspirin at a dose of 75 mg to 300 mg on day 1. Those in the clopidogrel plus aspirin group received clopidogrel 300 mg on day 1 and clopidogrel 75 mg daily from day 2 to day 90 plus aspirin 75 mg daily from day 2 to day 21 and placebo from day 22 to day 90. Those in the aspirin group received aspirin 75 mg daily from day 2 to day 90 and placebo from day 1 to day 90. There was a statistically significant reduction in the primary outcome of any new stroke event at 90 days with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with aspirin alone (8.2% compared with 11.7%; hazard ratio [HR] 0.68, 95% [confidence interval](#) [CI] 0.57 to 0.81; $p < 0.001$). In a pre-specified subgroup of participants who had had a TIA

(n=1445) there was a statistically significant reduction in any new stroke event with clopidogrel plus aspirin for 21 days followed by clopidogrel alone (HR 0.65, 95% CI 0.45 to 0.93). There was no statistically significant difference between clopidogrel plus aspirin for 21 days followed by clopidogrel alone and aspirin alone for all-cause mortality (HR 0.97, 95% CI 0.40 to 2.33) or death from cardiovascular causes (HR 1.16, 95% CI 0.35 to 3.79). However, there are substantial limitations to this trial that limit its generalisability to practice in the UK (see [Evidence strengths and limitations](#)).

The [FASTER](#) pilot trial was carried out at 18 centres in the USA and Canada. It enrolled adults aged 40 or older with TIA or minor stroke within 24 hours of symptom onset. Patients needed to have had weakness or speech disturbance, dysarthria or dysphasia for more than 5 minutes to be eligible for inclusion. The trial had a 2×2 factorial design, with participants randomised to either clopidogrel or placebo, and also to either simvastatin or placebo. All participants received aspirin 81 mg daily during the trial, with a loading dose of 162 mg if they were not taking aspirin before enrolment. Clopidogrel was given as a loading dose of 300 mg immediately, followed by 75 mg daily. Of the 3101 people screened, 87.2% did not meet inclusion criteria. The trial had a target of recruiting 500 people, but it was stopped early because of slow recruitment, which was attributed to the more widespread use of statins (current use of a statin was an exclusion criterion). A total of 396 people were randomised, with 4 withdrawing consent within 24 hours of randomisation. Therefore 392 participants (average age 68 years; 47% female) were included in the trial's intention-to-treat analysis. There was no statistically significant difference between clopidogrel plus aspirin (with or without simvastatin) and aspirin alone (with or without simvastatin) for the primary outcome of any stroke at 90 days (7.1% compared with 10.8%; [risk ratio \[RR\]](#) 0.7; 95% CI 0.3 to 1.2; p=0.19).

One ongoing trial (the [POINT](#) trial) comparing clopidogrel plus aspirin with aspirin alone in people with TIA or minor ischaemic stroke was also identified. The POINT trial is enrolling adults aged 18 years and over with high-risk TIA ([ABCD²](#) score ≥4) or minor ischaemic stroke (NIHSS score ≤3) within 12 hours of symptom onset. This multicentre trial is being conducted in the USA and worldwide. The trial is comparing clopidogrel plus aspirin with aspirin plus placebo. The primary efficacy outcome of the trial is a composite of new ischaemic vascular events (ischaemic stroke, myocardial infarction or ischaemic vascular death) up to day 90. The primary safety outcome is major haemorrhage.

The trial (ClinicalTrials.gov identifier [NCT00991029](#)) started in October 2009, and is estimated to be completed in September 2016, with the final collection of the primary outcome data in June 2016.

Evidence review: safety

The contraindications for clopidogrel reported in the summary of product characteristics ([Plavix](#)) are severe hepatic impairment, active pathological bleeding such as peptic ulcer or intracranial haemorrhage, or hypersensitivity to clopidogrel or the excipients in the tablets. The summary of product characteristics notes that clopidogrel has been assessed for safety in 44,000 people in clinical studies of various indications, including more than 12,000 people treated for 1 year or longer. The most common adverse effect reported in the trials and since marketing has been bleeding. The listed common adverse effects (occurring in between 1 in 10 and 1 in 100 people) are haematoma, epistaxis, gastrointestinal haemorrhage, diarrhoea, abdominal pain, dyspepsia, bruising, and bleeding at puncture sites.

The summary of product characteristics ([Plavix](#)) suggests that clopidogrel is used with caution in patients who may be at risk of increased bleeding from trauma, surgery, pathological conditions, or because of the use of aspirin, heparin, glycoprotein IIb/IIIa inhibitors or non-steroidal anti-inflammatory drugs, including Cox-2 inhibitors. Using clopidogrel with oral anticoagulants is not recommended because it may increase bleeding intensity.

The summary of product characteristics ([Plavix](#)) recommends that:

- patients should be followed carefully for any signs of bleeding including occult bleeding, especially during the first weeks of treatment and/or after invasive cardiac procedures or surgery
- blood cell count and/or other appropriate testing should be considered promptly if clinical symptoms suggestive of bleeding arise during treatment.

Clopidogrel is metabolised into its active form partly by the cytochrome P450 2C19 enzyme (CYP2C19). In people who are poor CYP2C19 metabolisers, the recommended doses of clopidogrel will have a smaller effect on platelet function.

Clopidogrel plus aspirin

The safety data described below from the [CHANCE](#) and [FASTER](#) trials compares the safety of clopidogrel plus aspirin with aspirin alone over a period of 90 days. The clopidogrel plus aspirin group in the CHANCE trial only received combined treatment with clopidogrel plus aspirin for the first 21 days.

CHANCE trial (Wang et al. 2013)

The primary safety outcome in the CHANCE trial was moderate-to-severe bleeding events. Severe haemorrhage was defined as fatal or intracranial haemorrhage or other haemorrhage causing haemodynamic compromise that needed blood or fluid replacement, inotropic support, or surgical intervention. Moderate haemorrhage was defined as bleeding that needed transfusion of blood but that did not lead to haemodynamic compromise requiring intervention.

In intention-to-treat analyses, there was no statistically significant difference in moderate or severe bleeding events between clopidogrel plus aspirin for 21 days followed by clopidogrel alone and aspirin alone (moderate or severe bleeding events: 0.3% in both groups, $p=0.73$; moderate bleeding events: 0.1% with clopidogrel plus aspirin compared with 0.2% with aspirin alone; hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.16 to 3.26, $p=0.68$; severe bleeding events: 0.2% in both groups; HR 0.94, 95% CI 0.24 to 3.79, $p=0.94$).

There was no statistically significant difference between clopidogrel plus aspirin for 21 days followed by clopidogrel alone and aspirin alone for mild bleeding events (1.2% compared with 0.7%; HR 1.57; 95% CI 0.88 to 2.79, $p=0.12$) or any bleeding event (2.3% compared with 1.6%; HR 1.41; 95% CI 0.95 to 2.10, $p=0.09$). The sum of 'severe' plus 'moderate' plus 'mild' bleeding event rates was lower than the 'any bleeding' event rate; the nature of the additional bleeding events was not clear.

The proportion of participants with adverse events or serious adverse events were reported as similar, with no statistical comparisons presented (adverse events: 5.8% with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with 5.0% with aspirin alone; serious adverse events: 1.0% with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with 0.8% with aspirin alone; p values not reported). There were 10 deaths (0.4%) in both groups.

Similar proportions of people in both groups discontinued treatment because of adverse events (2.4% with clopidogrel plus aspirin for 21 days followed by clopidogrel alone compared with 2.2% with aspirin alone; significance not reported).

FASTER pilot trial (Kennedy et al. 2007)

In the FASTER trial, participants were randomised to clopidogrel and simvastatin in a factorial design, and all participants received aspirin. The safety results described here are for clopidogrel plus aspirin (with or without simvastatin) compared with aspirin alone (with or without simvastatin).

There were statistically significantly more symptomatic haemorrhages with clopidogrel plus aspirin compared with aspirin alone (3.0% compared with 0%; risk difference [RD] 3.0%; 95% CI 0.6% to 5.4%; $p=0.03$). There were also statistically significantly more asymptomatic bleeding events (consisting of increased bruising only) with clopidogrel plus aspirin compared with aspirin alone (30.8% compared with 13.9%; RD 16.9%, 95% CI 8.8% to 25.0%; $p=0.0001$).

When split into intracranial and extracranial haemorrhages, with the latter divided by severity, there were no statistically significant differences between the groups. This may be because the small number of events reduced power in these analyses, with only 6 symptomatic bleeding events occurring in the 90 days of the trial. There were no symptomatic bleeding events in the aspirin alone group, whereas rates of bleeding events with clopidogrel plus aspirin were:

- intracranial haemorrhage: 1.0% (2/198; RD 1.0%, 95% CI -0.4% to 2.4%; $p=0.5$)
- severe extracranial haemorrhage: 0.5% (1/198; RD 0.5%, 95% CI -0.5% to 1.5%; $p=1.0$) (defined as bleeding that is life threatening, resulting in haemodynamic compromise or hypovolaemic shock, needing support to maintain cardiac output, needing transfusion of >2 units of packed red blood cells, or associated with a fall in haemoglobin ≥ 5 g/litre)
- moderate extracranial haemorrhage: 1.0% (2/198; RD 1.0%, 95% CI -0.4% to 2.4%; $p=0.5$) (defined as bleeding that did not meet criteria for being defined as severe, but needing transfusion of ≤ 2 units of packed red blood cells, or associated with a fall in haemoglobin <5 g/litre)
- mild extracranial haemorrhage: 0.5% (1/198; RD 0.5%, 95% CI -0.5% to 1.5%; $p=1.0$) (defined as not needing transfusion or causing haemodynamic compromise, usually including haematoma, subcutaneous bleeding, oozing from puncture sites, and possibly needing a modification of drug regimen).

A separate assessment of the data from the FASTER trial found that all of the symptomatic bleeds that occurred in the clopidogrel plus aspirin group occurred in participants who were not taking aspirin before study enrolment (6/104 in 'aspirin-naïve' participants compared with 0/94 in 'prior-aspirin' participants ; $p=0.03$) ([Geraghty et al. 2010](#)).

The rate of any bleeding events (symptomatic and asymptomatic) was higher in the FASTER trial than in the [CHANCE](#) trial (13.9% in the aspirin alone group in the FASTER trial compared with 1.6% in the CHANCE trial). The reasons for this are not clear, but may relate to the types of events considered or to differences between the trial populations in bleeding risks. The CHANCE trial may not have included asymptomatic bruising as a bleeding event.

There was no significant difference between groups in discontinuation because of adverse events (8.6% with clopidogrel plus aspirin compared with 10.3% with aspirin alone; $p=0.56$). This analysis for adverse events included efficacy outcomes such as stroke, and no separate analysis excluding these outcomes was reported.

Evidence review: economic issues

Cost effectiveness

We identified no cost-effectiveness studies of clopidogrel in transient ischaemic attack (TIA) or TIA and minor stroke specifically.

NICE guidance on [clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events](#) included an assessment of the cost effectiveness of clopidogrel for secondary prevention in people with ischaemic stroke.

The Assessment Group's effectiveness analysis carried out for [this guidance](#) considered the TIA and ischaemic stroke populations to be equivalent in risk and outcomes and so they were modelled together. When the generic price for clopidogrel was used, the optimal treatment strategy was generic clopidogrel followed by modified-release dipyridamole plus aspirin and then aspirin alone, which had an incremental cost-effectiveness ratio (ICER) of £13,558 per quality-adjusted life year (QALY) gained compared with the next best strategy of clopidogrel, followed by aspirin, followed by modified-release dipyridamole plus aspirin.

The Appraisal Committee recognised that recommendations could not be made for the use of clopidogrel for people who have had a TIA because it is not licensed for this indication. For people who have had a TIA, treatment with modified-release dipyridamole plus aspirin followed by aspirin had an ICER of £9100 per QALY gained compared with treatment with aspirin alone.

Cost

According to the [NHS Electronic Drug Tariff](#) (October 2013), the cost of the branded form of clopidogrel (Plavix) is £142.54 for 30 tablets of 300 mg. The cost of generic clopidogrel 75 mg tablets is £1.71 for 28 tablets. An oral solution of clopidogrel 75 mg/5 ml is available at £73.06 for up-to 150 ml and £0.49 for every additional millilitre. An oral suspension of clopidogrel 75 mg/5 ml is also available at £260.94 for up-to 100 ml and £0.75 for every additional millilitre. Both of these liquid formulations are specials. The cost of the branded form of clopidogrel 75 mg tablets (Plavix) is £35.64 for 30 tablets ([MIMS](#); November 2013).

Current drug usage

There were 5.39 million prescription items of clopidogrel dispensed in England in the community in 2012 according to the [Prescription Cost Analysis](#) report, at a cost of £13.4 million. The most commonly prescribed form was generic clopidogrel 75 mg tablets, which accounted for 5.35 million prescription items and a cost of £11.3 million. The Prescription Cost Analysis report does not include data on the indications for which the drugs are prescribed.

Evidence strengths and limitations

No [randomised controlled trials](#) (RCTs) that compared clopidogrel monotherapy with an alternative treatment (such as aspirin) in people with transient ischemic attack (TIA) were identified. In addition, no high quality observational data on the efficacy of clopidogrel monotherapy in people with TIA were identified.

The [CHANCE](#) trial was large and of good quality. However, it has a number of substantial limitations that limit its applicability to practice in the UK. Its main limitation is its generalisability to other populations with TIA. The trial was funded by the Ministry of Science and Technology of the People's Republic of China.

The population included in the [CHANCE](#) trial was at high risk of a recurrent ischaemic event and at low risk of haemorrhage. Many of the people assessed for inclusion in the trial were not eligible (87.6%), with the most common reason being presentation more than 24 hours after the onset of symptoms (26.4%). The trial did not include people with TIA at lower risk of recurrence.

The trial was carried out in China, where the rate of death from stroke was reported to be approximately 150 to 250 per 100,000 people per year, 5 times the rate in the USA. Diagnostic measures and therapies available in Europe and the USA are available in China, but some people cannot afford this care, and secondary prevention measures are not used as widely. For example, rates of treatment for hypertension (35.1%), diabetes (12.7%) and hyperlipidaemia (42.0%) in the trial population were reported to be low. The absolute benefits of clopidogrel plus aspirin for 21 days followed by clopidogrel alone seen in the trial may not be achievable in people or populations at lower absolute risk for recurrent stroke, such as those with a low prevalence of risk factors for recurrent stroke and those with access to effective secondary stroke prevention. The authors also noted that the distribution of stroke subtypes in China differs from that in western countries; China has a higher rate of large artery intracranial atherosclerosis and a higher prevalence of genetic polymorphisms that affect metabolism of clopidogrel. As a result of these considerations, the authors suggest that their findings may not apply to other populations with ischaemic events.

The ongoing [POINT](#) trial is comparing clopidogrel plus aspirin with aspirin alone started within 12 hours of TIA or minor ischaemic stroke and continued for 90 days. It is being conducted in the USA and worldwide, and the results when available may be more generalisable to western settings.

The [FASTER](#) trial was a small pilot trial. It did not include a power calculation, and may have lacked power to detect a difference between groups, particularly because it was stopped before meeting its recruitment target of 500 people. Allocation was concealed and the trial was double blinded, with central adjudication of outcomes in a blinded fashion.

As with the [CHANCE](#) trial, a large number of the patients screened for the [FASTER](#) trial did not qualify for entry (87.2%). The most common reason was being on a statin, an antiplatelet drug other than aspirin, anticoagulation or long-term non-steroidal anti-inflammatory drugs (27.4%). The trial was terminated early because of slow recruitment, which was attributed to more widespread use of statins.

Participants in the [CHANCE](#) trial had a median age of 62 years and the average age of participants in the [FASTER](#) trial was 68 years; the results may not be generalisable to older people.

The [CHANCE](#) and [FASTER](#) trials both only lasted for 90 days after ischaemic stroke or TIA, and results, particularly safety results, may not apply to longer term treatment.

Summary for patients

A [summary written for patients](#) is available on the NICE website

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Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The [integrated process statement](#) sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments

Google:allintitle: clopidogrel filetype:pdf. TRIP:Clopidogrel in title, limited by publication type guidance

Medline (via Ovid)

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search strategy:

1. (Clopidogrel or plavix).af. (8979)
2. Ischemic Attack, Transient/ (17465)
3. (transient ischaemic attack or TIA or mini stroke or mild stroke).ab,ti. (6008)
4. 2 or 3 (20965)
5. 1 and 4 (271)
6. limit 5 to English language (234)

Embase (via Ovid)

Embase <1988 to 2013 July 26>

Search strategy:

1. clopidogrel/ (33294)
2. (Clopidogrel or plavix).af. (34239)
3. 1 or 2 (34239)
4. Ischemic Attack, Transient/ (19215)

5. (transient ischaemic attack or TIA or mini stroke or mild stroke).ab,ti. (9203)
6. 4 or 5 (23530)
7. 3 and 6 (2001)
8. limit 7 to (English language and exclude Medline journals) (203)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 Clopidogrel or plavix:ti (Word variations have been searched)

#2 transient ischaemic attack or TIA or mini stroke or mild stroke

#3 MeSH descriptor: [Ischemic Attack, Transient] this term only

#2 or #3

#1 and #4

CRD HTA, DARE and EED database

TIA or transient ischaemic attack AND Plavix or Clopidogrel

Grey literature and ongoing trials

- [NICE Evidence](#)
- [Health Canada – Clinical Trial Search](#)
- [ClinicalTrials.gov](#)

Manufacturers' websites

- [Sanofi](#)

Potentially relevant additional studies cited in relevant articles were also assessed for inclusion.

Evidence selection

For the assessment of the efficacy, randomised controlled trials (RCTs) of clopidogrel for prevention of occlusive vascular events in people with transient ischaemic attack (TIA) were

sought. No RCTs solely in people with TIA were identified; therefore trials in TIA and minor stroke were included. Within the first 24 hours of symptom onset it may be difficult to differentiate what will be a TIA and what will be a minor stroke, therefore including both of these populations when looking at treatments given acutely is clinically appropriate.

For assessment of efficacy outcomes, studies were excluded if they:

- were not in people with TIA or TIA and minor stroke (for example studies including people with stroke of any severity or stroke with severity not described were excluded)
- were solely in people with stenosis
- did not allow assessment of the effect of clopidogrel (for example provided clopidogrel in both groups being compared, or compared clopidogrel plus another drug without providing this other drug in the control group)
- assessed only non-clinical outcomes (for example microembolic signals, measures of platelet aggregation, pharmacokinetics or pharmacodynamics).

For safety outcomes, as well as the RCTs, observational studies of safety were included if they were in people with TIA/minor stroke.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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