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HEALTH TECHNOLOGY BRIEFING AUGUST 2019

Ticagrelor in addition to acetylsalicylic acid for prevention of stroke in patients with acute ischaemic stroke or transient ischaemic attack

NIHRIO ID	20615	**NICE ID**	10145
Developer/Company	AstraZeneca UK Ltd	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III clinical trial

SUMMARY

Ticagrelor in addition to acetylsalicylic acid (ASA) is in development for the prevention of new stroke in patients with acute ischaemic stroke or high-risk transient ischaemic attack. A stroke is a serious life-threatening medical condition that happens when the blood supply to part of the brain is cut off. There are three different types of stroke; ischaemic strokes, haemorrhagic strokes and transient ischaemic attacks. The aim of stroke therapy is to restore optimal blood flow to the brain, reduce any damage caused to the brain tissues, modulate any factors that may exacerbate this damage and if possible, repair the damage. Early treatment is critical to rescue potentially salvageable brain tissue.

Both ticagrelor and ASA work in different but complementary ways to inhibit platelet activation. This dual antiplatelet action may be more effective in prevention of new stroke in patients with acute ischaemic stroke or high-risk transient ischaemic attack (TIA) compared with aspirin alone. If licensed, ticagrelor co-administered with ASA may offer an additional treatment option for preventing stroke or death in patients with non-severe, non-cardioembolic ischaemic stroke or high-risk transient ischaemic attack.

PROPOSED INDICATION

Prevention of stroke in patients with acute ischaemic stroke or high-risk transient ischaemic attack (TIA).[1,2]

TECHNOLOGY

DESCRIPTION

Ticagrelor (Brilique, AZD6140) is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding $P2Y_{12}$ receptor antagonist that prevents ADP-mediated $P2Y_{12}$ dependent platelet activation and aggregation. Ticagrelor does not prevent ADP binding but when bound to the $P2Y_{12}$ receptor prevents ADP-induced signal transduction. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function has been shown to reduce the risk of cardiovascular events such as death, myocardial infarction (MI) or stroke.[3]

Acetylsalicylic acid (ASA) inhibits platelet activation: blocking the platelet cyclooxygenase by acetylation, it inhibits thromboxane A2 synthesis, a physiological activating substance released by the platelets and which would play a role in the complications of the atheromatous lesions.[4]

Ticagrelor in addition to ASA is currently in clinical development for the prevention of new stroke in patients with acute ischaemic stroke or high-risk TIA. In the phase III clinical trial (NCT03354429; THALES), patients receive either ticagrelor 180 mg loading dose on day 1, then 90 mg twice daily during the study treatment period or matching placebo, in addition to receiving standard-of-care open-label ASA 300–325 mg on day 1, then 75–100 mg once daily during the study treatment period.[1]

INNOVATION AND/OR ADVANTAGES

The SOCRATES trial (NCT01994720) investigated whether ticagrelor was superior to aspirin, when initiated within 24 hours after symptom onset in patients with acute cerebral ischemia and the promising results prompted several secondary analyses to guide the design of the study THALES.[1]

In another subgroup analysis, the treatment effect of ticagrelor was more pronounced in patients who received aspirin within 7 days before randomisation. Since the antiplatelet effect of aspirin persisted into the first week of the trial, short-term dual antiplatelet therapy (DAPT) could account for the greater benefit of ticagrelor in patients taking aspirin prior to randomisation. This observation is in line with other studies suggesting that DAPT with clopidogrel and aspirin may be more effective in reducing the high risk of stroke after an acute ischaemic stroke or TIA compared with aspirin alone, including studies of microembolisation from atherosclerotic cerebral arteries in patients with acute cerebral ischaemic events and in trials of patients with minor stroke or TIA.[1]

This is a new indication for ticagrelor in addition to aspirin and is a new combination of drugs for the prevention of new stroke.[1]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Currently, ticagrelor co-administered with ASA is licensed in the EU/UK for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event. The most commonly reported adverse reactions in patients treated with ticagrelor were bleeding and dyspnoea.[3]

PATIENT GROUP

DISEASE BACKGROUND

Stroke is a serious life-threatening medical condition that occurs when the blood supply to part of the brain is cut off.[6] An acute stroke refers to the first 24-hour-period of a stroke event.[7] There are two main types of stroke: ischaemic strokes, caused by blockages which cut off the blood supply to parts of the brain, and haemorrhagic strokes, which are caused when a blood vessel bursts within or on the surface of the brain. Approximately 85% of all strokes are ischaemic and 15% are haemorrhagic.[8] There is also a related condition known as transient ischaemic attack (TIA), where the blood supply to the brain is temporarily interrupted.[6]

Stroke is most commonly manifested by focal neurological deficits such as numbness or weakness of the face, arm or leg on one side of the body, and often problems with speech and swallowing.[9,10] Certain conditions increase the risk of having a stroke including high blood pressure (hypertension), high cholesterol, atrial fibrillation, and diabetes.[6] Other risk factors may include smoking, age and gender, race and ethnicity, a personal or family history of stroke or TIA, and brain aneurysms or arteriovenous malformations.[11] As of 2017, the average age of stroke in England, Wales and Northern Ireland was 72 years for men and 78 years for women.[8,12]

With improvements in health care, more people survive stroke but many have to cope with the physical, psychological, social and functional sequelae, resulting in increased personal and public costs. Stroke causes a significant deterioration of the patient's functioning and worsening of her/his quality of life. Long-term disability caused by stroke is a common problem in all countries and its incidence increases markedly with advancing age.[13]

CLINICAL NEED AND BURDEN OF DISEASE

There are more than 100,000 strokes in the UK each year. This figure may be higher, as available data relies on hospital admission and does not include deaths before reaching hospital, or those who were not treated in hospital.[8]

Approximately 1 in 6 men and 1 in 5 women will have a stroke in their life.[8,14] There are over 1.2 million stroke survivors in the UK.[8] Stroke survivors are at greatest risk of having another stroke in the first 30 days following the initial occurrence.[8,15] Approximately 1 in 4 stroke survivors will experience another stroke within five years.[8]

In 2017-2018, there were 89,878 admissions (of which 584 were day case) for primary diagnosis of cerebral infarction and Transient cerebral ischaemic attack, unspecified (ICD-10 codes I63 and G45.9) in England, which resulted in 169,035 finished consultant episodes (FCE) and 1,348,590 FCE bed days.[16]

In 2015, the average societal cost of stroke per person was £45,409 in the first 12 months after stroke (cost of incident stroke), plus £24,778 in subsequent years (cost of prevalent stroke). It is projected that the overall costs of stroke in the UK for those aged 45 years and over will rise from £26 billion in 2015 to £43 billion in 2025 and £75 billion in 2035, an increase of 194% over 20 years. [17]

Stroke is a leading cause of death and disability in the UK. In 2016 there were a total of 32,627 deaths from stroke in England and Wales.[8]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The primary aim of stroke therapy is to restore blood flow to the brain in a manner that does not exacerbate the damage already caused by depriving the tissue of oxygen and nutrients. The secondary aim is to modulate any factors that may exacerbate this damage and if possible, repair the damage.[18] Early treatment is critical to rescue potentially salvageable tissue.[19]

The specific treatments depends on whether a stroke was caused by a blood clot obstructing the flow of blood to the brain (ischaemic stroke) or by bleeding in or around the brain (haemorrhagic stroke). Treatment usually involves taking one or more different medications, although some people may also need surgery.[20]

CURRENT TREATMENT OPTIONS

Treating ischaemic strokes involve a combination of medications to treat the condition and prevent it happening again. Some of these medications need to be taken immediately and only for a short time, while others may only be started once the stroke has been treated and may need to be taken long term.[20]

Pharmacological treatments for people with acute stroke include:[20,21]

- **Thrombolysis**
  Treatment with alteplase should be started as soon as possible within 4.5 hours of onset of stroke symptoms and intracranial haemorrhage has been excluded by appropriate imaging techniques.

- **Antiplatelets and anticoagulant treatment**
  Anticoagulant treatment should be offered as soon as possible within 24 hours, to everyone presenting with acute stroke who has had a diagnosis of intracerebral haemorrhage excluded by brain imaging. Most people will be offered a regular dose of aspirin. In addition to aspirin, other antiplatelet medicines are also available, such as clopidogrel and dipyridamole.
  Some people may be offered an anticoagulant to help reduce their risk of developing further blood clots in the future. Warfarin, apixaban, dabigatran, edoxaban and rivaroxaban are examples of anticoagulants for long-term use. Heparins should only be given by injection and are used short term.

PLACE OF TECHNOLOGY

If licensed, ticagrelor in addition to ASA will offer an additional treatment option for preventing new stroke in patients with acute ischaemic stroke or high-risk TIA.

CLINICAL TRIAL INFORMATION

Trial	THALES, NCT03354429, D5134C00003, EudraCT 2016-004232-37; aged ≥40; ticagrelor vs placebo; phase III
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry;[2,22] Journal article[1]
Location	EU countries (not the UK), Canada and other countries
Design	Randomised, placebo-controlled, quadruple-blind
Participants	n=11,000 (planned); aged 40 to 130 years old and acute onset of cerebral ischaemia.
Schedule	Patients will be randomised within 24 hr of onset of acute ischaemic symptoms. Study treatments are ticagrelor 180 mg loading dose on day 1, then 90 mg twice daily on days 2–30, or matching placebo. All patients will also receive open-label aspirin 300–325 mg on day 1, then 75–100 mg once daily on days 2–30.
Follow-up	30 days
Primary Outcomes	Time from randomisation to first subsequent stroke or death [Time frame: day1 to 30]
Secondary Outcomes	• Time from randomisation to first subsequent ischaemic stroke [Time frame: day1 to 30] • The modified Rankin Scale (mRS) score >1 at visit 3 [Time frame: day 30]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date in December 2019.

ESTIMATED COST

Ticagrelor is already marketed in the UK. The NHS indicative price for ticagrelor is:[23]

- Tablets:
  - A pack of 56 x 60 mg tablets costs £54.60
  - A pack of 56 x 90 mg tablets costs £54.60

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guidance in development. Dabigatran etexilate for the secondary prevention of stroke after an embolic stroke of undetermined source (ID1417). Expected publication date: TBC.
- NICE clinical guidance. Stroke and transient ischaemic attack in over 16s: diagnosis and initial management (NG128). May 2019.
- NICE quality standard. Stroke in adults (QS2). April 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Service Specifications: Specialised Vascular Services (Adults). 170004/S.

OTHER GUIDANCE

- Wein T, Lindsay MP, Cote R, et al. Canadian stroke best practice recommendations: Secondary prevention of stroke, sixth edition practice guidelines, update 2017. November 2018.[24]
- American Heart Association/American Stroke Association. 2018 Guidelines for the early management of patients with acute ischaemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. March 2018.[25]
- Royal College of Physicians. National clinical guideline for stroke: 5th edition. 2016.[26]
- American Heart Association/American Stroke Association. Guidelines for the Prevention of Stroke in Patients with Stroke or Transient Ischaemic Attack. May 2014.[27]
- Scottish Intercollegiate Guidelines Network (SIGN). Management of patients with stroke: Rehabilitation, prevention and management of complications, and discharge planning. A national clinical guideline (SIGN 118). June 2010.[28]

ADDITIONAL INFORMATION

AstraZeneca UK Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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