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Ticagrelor for prevention of cardiovascular events in patients with type 2 diabetes mellitus who have coronary artery disease

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LAY SUMMARY

Type 2 diabetes is a lifelong medical condition that causes the level of glucose in the blood to become too high due to problems with the hormone insulin. Type 2 diabetes can increase the risk of getting serious problems with the heart such as coronary artery disease (CAD). This is because having the condition increases the chance of having contributing risk factors for developing CAD such as high blood pressure, high levels of cholesterol, obesity and being physically inactive. CAD occurs when the heart's blood supply is blocked or interrupted by a build-up of fatty substances in the coronary arteries. It is one of the main causes of death and disability in the UK. More than half of type 2 diabetes patients will exhibit signs of CAD complications at diagnosis.

Ticagrelor is an oral blood thinning medicine used together with aspirin to prevent problems caused by blood clots and hardening of the arteries that leads to heart attacks or strokes. Ticagrelor is in a class of medications called antiplatelet medications that help prevent blood clots from forming. It is used in adults with acute coronary syndrome, a group of conditions in which blood flow in the vessels supplying the heart is blocked so heart tissue cannot work properly or dies, and which includes heart attack and chest pain. If licensed, ticagrelor will offer an additional antiplatelet therapy for the prevention of CAD in patients with type 2 diabetes.

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TARGET GROUP

Prevention of cardiovascular death, myocardial infarction (MI) or stroke in patients with type 2 diabetes mellitus who have coronary artery disease (CAD), but without a previous history of MI or stroke

TECHNOLOGY

DESCRIPTION

Ticagrelor (Brilique) is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is an oral, direct acting, selective and reversibly binding P2Y12 receptor antagonist that prevents adenosine diphosphate (ADP) - mediated P2Y12 dependent platelet activation and aggregation. It does not prevent ADP binding but when bound to the P2Y12 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 (CV) events such as death, myocardial infarction (MI) or stroke. Ticagrelor also increases local endogenous adenosine levels by inhibiting the equilibrative nucleoside transporter-1 (ENT-1).[1]

In the phase III clinical trial in patients with type 2 diabetes mellitus (THEMIS; NCT01991795), ticagrelor is administered orally at 60mg twice daily. Treatment duration was reported as time to first occurrence of any event from the composite of CV death, MI or stroke (up to 58 months).[2]

Brilique is used together with aspirin (acetylsalicylic acid) to prevent atherothrombotic events (problems caused by blood clots and hardening of the arteries) such as heart attacks or strokes. It is used in adults with acute coronary syndrome, a group of conditions in which blood flow in the vessels supplying the heart is blocked so heart tissue cannot work properly or dies, and which includes heart attack and unstable angina (a severe type of chest pain).[3] Very common adverse effects (≥10%) include blood disorder bleedings, hyperuricaemia and dyspnoea.[4]

INNOVATION and/or ADVANTAGES

Ticagrelor is an antiplatelet therapy that is used in conjunction with aspirin for primary and secondary prevention in patients with risks of cardiovascular events. Studies have demonstrated its efficacy and safety when compared active treatments (clopidogrel) or placebo.[5,6] Patients with type 2 diabetes mellitus who have CAD are at high risks of cardiovascular events, hence, if licenced, ticagrelor will offer an additional primary prevention therapy option for this patient population.

DEVELOPER

AstraZeneca

PATIENT GROUP

BACKGROUND

Diabetes is a lifelong condition that causes a person's blood sugar level to become too high. There are two main types of diabetes: type 1 diabetes, where the body's immune system attacks and destroys the cells that produce insulin and; type 2 diabetes, the more common type affecting over 90% of adults in the United Kingdom (UK), where the body does not produce enough insulin, or the cells of the body do not react to insulin.[7] Insulin is a hormone produced in the pancreas and is responsible for moving glucose (a type of sugar) from the bloodstream and into the cells of the body for energy.[8] Symptoms of diabetes include feeling thirsty, urinating more frequently than usual, feeling very tired, weight loss and loss of muscle bulk, itching around penis or vagina, or frequent episodes thrush, cuts or wounds that heal slowly and blurred vision.[7]

Coronary artery disease (CAD), also known as coronary heart disease happens when fatty material called atheroma build up inside the walls of arteries that supply the heart with oxygen-rich blood causing them to become so narrow that they cannot deliver enough oxygen-rich blood to heart. There are several factors that can increase the risk of developing CAD including smoking, high blood pressure, high blood cholesterol, diabetes, being physically inactive, being overweight or obese, family history of heart disease, being older, men and ethnic minority.[9] Symptoms of CAD include angina (chest pain), heart attacks and heart failure.[10]

People with diabetes have a greater risk of developing CAD. High levels of glucose in the blood can damage the walls of the arteries and make them more likely to develop atheroma which can lead to heart attack or stroke.[8] People with type 2 diabetes often have higher levels of triglyceride (a fatty substance in the blood) and lower levels of high density lipoprotein cholesterol (the protective type of cholesterol). This can increase the risk of atheroma developing. Diabetes can also affect the heart muscles, making it less impossible to pump effectively.[11]

CLINICAL NEED and BURDEN OF DISEASE

The number of people diagnosed with diabetes in the UK has more than doubled in the last twenty years. An estimated 3.7 million people have been diagnosed with the condition, an increase from 1.9 million in 1998. Almost 90% of people diagnosed with diabetes have type 2, and it is estimated that there are nearly 1 million people currently living with the condition remain undiagnosed. Counting this undiagnosed population, the total number of people living with diabetes reaches 4.6 million.[12]

In England in 2016/2017 there were 22,969 hospital admissions for patients with non-insulin-dependent diabetes mellitus (ICD-10 code E11) resulting in 178,270 bed days and 2,435 day cases.[13]

More than 50% of type 2 diabetes patients will exhibit signs of cardiovascular disease complications at diagnosis and are more likely to be at risk from heart attacks, strokes and high blood pressure. CAD is recognized to be the cause of death for 80% of people with diabetes.[14]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Rivaroxaban for preventing major cardiovascular events in people with coronary or peripheral artery disease (ID1397) [GID-TA10347]. Expected date of issue to be confirmed.
- NICE technology appraisal. Ticagrelor for preventing atherothrombotic events after myocardial infarction (TA420). December 2016.
- NICE technology appraisal. Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (TA210). December 2010.
- NICE technology appraisal. Ticagrelor for the treatment of acute coronary syndromes (TA236). October 2011.
- NICE technology appraisal. Drug-eluting stents for the treatment of coronary artery disease (TA152). July 2008.
- NICE clinical guideline. Peripheral arterial disease: diagnosis and management (CG147). February 2018.
- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). September 2016.
- NICE clinical guideline. Myocardial infarction: cardiac rehabilitation and prevention of further cardiovascular disease (CG172). November 2013.
- NICE quality standard. Cardiovascular risk assessment and lipid modification (QS100). September 2015
- NICE quality standard. Secondary prevention after a myocardial infarction (QS99). September 2015.
- NICE public health guidance. Cardiovascular disease prevention (PH25). June 2010.
- NICE public health guidance. Cardiovascular disease: identifying and supporting people most at risk of dying early (PH15). September 2008.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for cardiology: inherited cardiac conditions (All Ages) A09/S/c
- NHS England. 2013/14 NHS Standard Contract for Specialised Vascular Services (Adults). A04/S/a.

OTHER GUIDANCE

- Risk estimation and the prevention of cardiovascular disease (SIGN 149).[15]
- Stable Coronary Artery Disease (Management of): ESC Clinical Practice Guidelines. 2013[16]

CURRENT TREATMENT OPTIONS

Guidelines recommend a range of individualised multifactorial interventions for the prevention of cardiovascular events in patients with diabetes mellitus that target areas such[17]:

- Lifestyle modification (diet, physical activity, smoking)
- Glucose control

- Blood pressure
- Dyslipidaemia
- Platelet function

NICE guidelines recommends identifying and assessing cardiovascular disease (CVD) risks in patients with type 2 diabetes and the use of lipid modification therapy for primary and secondary prevention of CVD. It recommends the use of statins (atorvastatin) for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD.[17]

NICE guidelines recommends that patients with type 2 diabetes without cardiovascular disease should not be offered antiplatelet therapy (aspirin or clopidogrel).[18]

EFFICACY and SAFETY

Trial	THEMIS, NCT01991795, D513BC00001; adults aged ≥ 50 years; ticagrelor vs placebo; phase III
Sponsor	AstraZeneca
Status	Ongoing
Source of Information	Trial registry[2]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised
Participants	N=19,349; aged 50-130 years; type 2 diabetes mellitus; coronary artery occlusive disease; treatment with a glucose lowering medication since at least 6 months
Schedule	Randomised to 90mg initially then reduced to 60mg tablets twice daily; or placebo as 90mg initially then 60mg tablets twice daily
Follow-up	Not reported
Primary Outcomes	Time from randomisation to first occurrence of any event from the composite of CV death, MI or stroke [time frame: up to 58 months]
Secondary Outcomes	• Prevention of cardiovascular (CV) death. The efficacy variable is time from randomisation to death of CV cause • Prevention of myocardial infarction (MI). The efficacy variable is time from randomisation to first occurrence of MI • Prevention of ischaemic stroke. The efficacy variable is time from randomisation to first occurrence of ischaemic stroke • Prevention of all-cause death. The efficacy variable is time from randomisation to death of any cause [time frame: up to 58 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	November 2018

Trial	PLATO, NCT00391872, D5130C05262; adults aged ≥ 18 years; ticagrelor vs clopidogrel; phase III
Sponsor	AstraZeneca
Status	Completed
Source of Information	Publication,[19] trial registry[20]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised
Participants	N=18,624; aged ≥ 18 years; hospitalised for chest pain and potential ACS
Schedule	Randomised to ticagrelor 90mg twice daily; or clopidogrel 75mg once daily
Follow-up	Not reported
Primary Outcomes	• Participants with any event from the composite of death from vascular causes, myocardial infarction (MI), and stroke [time frame: randomization up to 12 months] • Participants with any major bleeding event [time frame: first dosing up to 12 months]
Secondary Outcomes	[Time frame: randomization up to 12 months] • Participants with any event from the composite of death from vascular causes, mi, and stroke for the subgroup of patients with intent for invasive management at randomization • Participants with any event from the composite of all-cause mortality, MI, and stroke • Participants with any event from the composite of death from vascular causes, MI (including silent), stroke, recurrent ischemia, transient ischemic attack (TIA) and other arterial thrombotic events • Participants with MI event • Participants with death from vascular causes • Participants with stroke • Participants with death from any cause [Time frame: first dosing up to 12 months] • Participants with Non-CABG (Coronary Artery Bypass Graft) related major bleeding • Participants with major or minor bleeding • Participants with non-procedural major bleeding • Participants with coronary artery bypass graft (CABG) major bleeding • Participants with coronary artery bypass graft (CABG) major fatal/life-threatening bleeding [Time Frame: 1-week period following randomization] • Participants with ventricular pauses of greater than or equal to 3 seconds in patients monitored by Holter 24-hour ECG recorders • Participants with ventricular pauses of greater than or equal to 3 seconds in patients monitored by Holter 24 hour ECG recorders for 1 week at 1 month following randomization
Key Results	Efficacy:

	• The primary end point occurred significantly less often in the ticagrelor group than in the clopidogrel group (in 9.8% of patients vs. 11.7% at 12 months; hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001) • The hierarchical testing of secondary end points showed significant reductions in the ticagrelor group, as compared with the clopidogrel group, with respect to the rates of the composite end point of death from any cause, myocardial infarction, or stroke (10.2% vs. 12.3%, P<0.001) • The composite end point of death from vascular causes, myocardial infarction, stroke, severe recurrent ischemia, recurrent ischemia, transient ischemic attack, or other arterial thrombotic events (14.6% vs. 16.7%, P<0.001); myocardial infarction alone (5.8% vs. 6.9%, P=0.005); and death due to vascular causes (4.0% vs. 5.1%, P=0.001) • The rate of stroke did not differ significantly between the two treatment groups, although there were more hemorrhagic strokes with ticagrelor than with clopidogrel (23 [0.2%] vs. 13 [0.1%], nominal P=0.10) • Among patients who received a stent during the study, the rate of definite stent thrombosis was lower in the ticagrelor group than in the clopidogrel group (1.3% vs. 1.9%, P=0.009) <u>Bleeding:</u> • The ticagrelor and clopidogrel groups did not differ significantly with regard to the rates of major bleeding as defined in the trial (11.6% and 11.2%, respectively; P=0.43) • There was also no significant difference in the rates of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) criteria (7.9% with ticagrelor and 7.7% with clopidogrel, P=0.57) or fatal or life-threatening bleeding (5.8% in both groups, P=0.70). • The two treatment groups did not differ significantly in the rates of CABG-related major bleeding or bleeding requiring transfusion of red cells. However, in the ticagrelor group, there was a higher rate of non–CABG-related major bleeding according to the study criteria (4.5% vs. 3.8%, P=0.03) and the TIMI criteria (2.8% vs. 2.2%, P=0.03) • With ticagrelor as compared with clopidogrel, there were more episodes of intracranial bleeding (26 [0.3%] vs. 14 [0.2%], P=0.06), including fatal intracranial bleeding (11 [0.1%] vs. 1 [0.01%], P=0.02) • There were fewer episodes of other types of fatal bleeding in the ticagrelor group (9 [0.1%], vs. 21 [0.3%] in the clopidogrel group; P=0.03)
Adverse effects (AEs)	• Dyspnea was more common in the ticagrelor group than in the clopidogrel group (in 13.8% of patients vs. 7.8%) • Discontinuation of the study drug due to adverse events occurred more frequently with ticagrelor than with clopidogrel (in 7.4% of patients vs. 6.0%, P<0.001)

Trial	PEGASUS-TIMI 54, 2009-017242-30 (EudraCT Number) ; adults aged ≥ 50 years; ticagrelor vs placebo-controlled; phase III
Sponsor	AstraZeneca
Status	Completed
Source of Information	Publication,[21] trial registry[22]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised
Participants	N=21,162; aged ≥ 50 years; person who had a heart attack within 1 - 3 years ago and at least: age ≥ 65 years old, diabetes requiring medication, 2nd prior MI (>1 year ago), multivessel CAD and CrCl <60 mL/min; tolerating ASA and able to be dosed at 75-150 mg/d
Schedule	Randomised to either ticagrelor 90mg twice daily; or ticagrelor 60mg twice daily or ticagrelor placebo twice daily
Follow-up	Not reported
Primary Outcomes	• Kaplan-Meier estimate of the percentage of patients who experienced cardiovascular death (CV death), myocardial infarction (MI) or stroke within 3 years from randomization [time frame: randomization up to 47 months] • Kaplan-Meier estimate of the percentage of patients who experienced a thrombolysis in myocardial infarction (TIMI) major bleeding within 3 years from first dose of study drug units: percentage of patients [time frame: first dosing up to 48 months]
Secondary Outcomes	• Kaplan-Meier estimate of the percentage of patients who experienced cardiovascular death (CV death) within 3 years from randomization [time frame: randomization up to 47 months] • Kaplan-Meier estimate of the percentage of patients who died from any cause within 3 years from randomization [time frame: randomization up to 47 months]
Key Results	• Kaplan-Meier estimates for CV death The two ticagrelor doses each significantly reduced, as compared with placebo, the rate of the primary composite end point of CV death, myocardial infarction, or stroke. Kaplan–Meier rates at 3 years were 7.8% in the group that received 90 mg of ticagrelor twice daily, 7.8% in the group that received 60 mg of ticagrelor twice daily, and 9% in the placebo group (hazard ratio for 90 mg of ticagrelor vs. placebo, 0.85; 95% confidence interval [CI], 0.75 to 0.96; P=0.008; hazard ratio for 60 mg of ticagrelor vs. placebo, 0.84; 95% CI, 0.74 to 0.95; P=0.004) • Kaplan-Meier estimates for TIMI The rate of the primary safety end point of TIMI major bleeding was higher with the two ticagrelor doses than with placebo. Kaplan–Meier rates at 3 years were 2.6% in the group that received 90 mg of ticagrelor twice daily, 2.3% in the group that received 60 mg of ticagrelor twice daily, and 1.1% in the placebo group (hazard ratio for 90 mg of ticagrelor vs. placebo, 2.69; 95% CI, 1.96 to 3.7; P<0.001; hazard ratio for 60 mg of ticagrelor vs. placebo, 2.32; 95% CI, 1.68 to 3.21; P<0.001)

Adverse effects (AEs)	• Bleeding which led to discontinuation was more prevalent in the groups that received 90mg (6.5%) and 60mg (5.1%) of ticagrelor compared to the placebo (1.2%)group • The rates of discontinuation due to dyspnea were also more frequent with the two ticagrelor doses, 6.2% for the 90mg group and 4.3% for 60mg group compared with 0.7% for the placebo group • The rates of discontinuation due to arrhythmia was lower in the 90mg group (1.1%) and fairly similar in the 60mg group (1.5%) and the placebo group (1.4%)

ESTIMATED COST and IMPACT

COST

Ticagrelor is already marketed in the UK for the treatment of peripheral vascular disease and ACS; a pack of 56 x 60mg tablets costs £55; a pack of 56 x 90mg tablets costs £55.[23]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

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