

# Therapeutic Advances

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Ticagrelor▼: a therapeutic advance



## **Prescriber**

A *Prescriber* supplement commissioned by AstraZeneca (see back page)  
Prescribing information appears on the back page

# Introduction

The Scottish Medicines Consortium (SMC) has approved the use of ticagrelor, a novel antiplatelet drug, for use by the NHS in Scotland.<sup>1</sup> The National Institute for Health and Clinical Excellence (NICE) has also recently approved the drug's use.

Ticagrelor is co-administered with aspirin for the prevention of

atherothrombotic events in adult patients with acute coronary syndromes (ACS) – unstable angina, non-ST elevation myocardial infarction or ST elevation myocardial infarction. It is indicated for patients managed medically, and those who are undergoing a percutaneous coronary intervention or coronary artery bypass grafting.<sup>2</sup>

This Prescriber Therapeutic Advances supplement gives an overview of antiplatelet therapies, and describes ticagrelor in terms of efficacy, safety and tolerability, and risk management. The supplement gives details of the SMC's recommendation and mentions the latest technology appraisal from NICE about the drug.

### Author

**Dr Alan Begg**, GP; Honorary Senior Lecturer, University of Dundee; member of the Scottish Intercollegiate Guidelines Network Steering Group on Acute Coronary Syndrome and on the Steering Group for Heart Disease Clinical Standards in Scotland

### Declaration of interests

Alan Begg has received fees from AstraZeneca for advisory and consultancy work related to ticagrelor.

# Ticagrelor: a therapeutic advance

The antiplatelet agent ticagrelor prevents adenosine diphosphate (ADP)-mediated platelet activation and aggregation. It has recently been recommended for use in patients with ACS by the NHS in Scotland.

## Oral antiplatelet therapy (single therapy)

Maintenance-dose aspirin, which, after an initial loading dose, is the foundation of antiplatelet therapy in ACS, acts by inhibiting the activity of the cyclo-oxygenase-1 (COX-1) enzyme, a platelet agonist that is involved in the pathological formation of thrombi. A collaborative meta-analysis of randomised trials showed that its use in patients with ACS significantly reduces the risk of any serious vascular event, subsequent myocardial infarction (MI) and vascular mortality, without an adverse effect on other deaths.<sup>3</sup> Alternative antiplatelet therapies include the ADP receptor antagonists that bind to and inhibit the activation of the P2Y<sub>12</sub> receptor on the platelet. Until recently, clopidogrel and prasugrel were the only agents used in clinical practice in the UK. The role of a single antiplatelet therapy as an alternative to aspirin has only been tested for clopidogrel; it has not been tested for prasugrel.

## Dual antiplatelet therapy

The CURE (Clopidogrel in unstable angina to prevent recurrent events) study demonstrated clinical benefit for the use of a combination of aspirin and clopidogrel for one year after an episode of non-ST elevation ACS.<sup>4</sup> Results from the COMMIT/ACS trial (Clopidogrel and metoprolol in myocardial infarction trial) suggest that patients with ST elevation ACS benefit from a combi-

nation of aspirin and clopidogrel for up to four weeks.<sup>5</sup> Prasugrel is a newer thienopyridine that is metabolised more effectively, and exhibits faster and more consistent platelet inhibition than clopidogrel.<sup>6</sup> Given orally, this inhibition of platelet aggregation is via its active metabolite, which binds irreversibly to the P2Y<sub>12</sub> ADP receptor on platelets.<sup>7</sup>

In the TRITON-TIMI study (Trial to assess improvement in therapeutic outcomes by optimising platelet inhibition with prasugrel thrombolysis in myocardial infarction), patients with unstable angina, non-ST elevation MI and ST elevation MI who were scheduled to receive a percutaneous coronary intervention were randomised to receive either clopidogrel or prasugrel in addition to aspirin.<sup>6</sup> The primary efficacy endpoint (death from cardiovascular causes, non-fatal MI, or non-fatal stroke) occurred in 12.1% and 9.9% of patients receiving clopidogrel and prasugrel, respectively (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.73–0.90;  $p < 0.001$ ). The prasugrel group had better outcomes compared with the clopidogrel group in terms of rate reduction of MI (7.4% versus 9.7%;  $p < 0.001$ ), urgent target vessel revascularisation (2.5% versus 3.7%;  $p < 0.001$ ) and stent thrombosis (1.1% versus 2.4%;  $p < 0.001$ ). Differences, respectively, between death rates from cardiovascular causes (2.1% versus 2.4%) and non-fatal stroke (1% versus 1%) were not statistically significant. The increased clinical benefit seen in this trial was, however, associated with increased rates of bleeding in the prasugrel group. A total of 146 patients (2.4%) treated with prasugrel had

at least one thrombolysis in MI major haemorrhage not related to coronary artery bypass graft (CABG), compared to 111 patients (1.8%) in the clopidogrel group (HR 1.32, 95% CI 1.03–1.68;  $p = 0.03$ ). Life-threatening bleeding occurred in 1.4% of the prasugrel group compared with 0.9% in the clopidogrel group (HR 1.52, 95% CI 1.08–2.13;  $p = 0.01$ ), and fatal bleeding occurred in 0.4% of those in the prasugrel group and 0.1% of those in the clopidogrel group (HR 4.19, 95% CI 1.58–11.11;  $p = 0.002$ ).

## Limitations of present therapies

Clopidogrel is a prodrug that requires a two-step metabolism for conversion to its active metabolite, which then irreversibly binds to the platelet ADP P2Y<sub>12</sub> receptor. Due to this metabolic activation, clopidogrel's onset of effect is relatively slow, with steady-state platelet inhibition only achieved two to four hours after a loading dose of 600mg.<sup>8</sup> There is considerable inter-individual variation in levels of inhibition of platelet aggregation due to variable metabolic conversion to the active metabolite.<sup>9</sup> The irreversible binding of clopidogrel results in a gradual recovery of platelet function after drug withdrawal, due to the generation of fresh platelets.<sup>10</sup> It is for this reason, to avoid serious bleeding, that patients undergoing CABG require clopidogrel to be discontinued up to seven days prior to surgery.<sup>10</sup>

Despite the effective use of current therapies in patients with ACS, there remains a residual risk of death and future events. Studies have also suggested that genetic polymorphisms of the cytochrome P450 enzymes can modulate

individual response to clopidogrel,<sup>10</sup> which can be a determinant of prognosis, although these issues remain to be fully resolved.

#### Ticagrelor

Ticagrelor is the first reversibly binding oral P2Y<sub>12</sub> receptor antagonist and, not being a prodrug, does not require metabolic activation to inhibit the P2Y<sub>12</sub> receptor. It is a member of a distinct chemical class, the cyclopentyltriazolopyrimidines, acting on the P2Y<sub>12</sub> ADP receptor to prevent ADP-mediated platelet activation and aggregation.<sup>11</sup> It does not directly interact with the ADP binding site, but interacts with the platelet P2Y<sub>12</sub> ADP receptor to prevent signal transduction. There is rapid peaking of plasma levels one and a half to three hours after dosage, with a rapid onset of antiplatelet effect, usually within two hours.<sup>2</sup> The variability between individuals is low, with a half-life of seven to eight hours and little antiplatelet effect 48 hours after the last dose.<sup>11</sup> The drug is given with an initial single loading dose of 180mg, consisting of two 90mg tablets, and then continued with a dose of 90mg twice daily.<sup>2</sup>

Patients should be advised that lapses in treatment should be avoided. If a patient misses a dose of ticagrelor, they should take only one 90mg tablet at its next scheduled time.<sup>2</sup>

Switching from ticagrelor to clopidogrel results in a decrease in absolute inhibition of platelet aggregation (IPA) of 24.5%, whereas switching from clopidogrel to ticagrelor results in an absolute IPA increase of 26.4%. Patients can be switched from clopidogrel to ticagrelor without any interruption of antiplatelet effect. Ticagrelor is given concurrently with aspirin in a maintenance dose, usually in the range of 75–150mg, with combination

therapy recommended to be continued for up to 12 months.<sup>2</sup>

#### PLATO study

The 18 000-patient study, PLATO (Platelet inhibition and patient outcomes), was designed to test whether ticagrelor plus aspirin was superior to clopidogrel plus aspirin for the prevention of vascular events. The primary endpoint was death from vascular causes, MI or stroke in patients with ACS, with or without non-ST elevation ACS and ST elevation ACS.<sup>11,12</sup> The phase 3, multicentre, double-blind, double-dummy, parallel-group, event-driven international trial randomised patients to receive ticagrelor or clopidogrel in a one-to-one ratio using a randomisation schedule. Ticagrelor was given as a loading dose of 180mg, followed by a dose of 90mg twice daily. Patients in the clopidogrel group who had not received an open-label loading dose and had not been taking clopidogrel for at least five days before randomisation received a 300mg loading dose, followed by a dose of 75mg daily. Otherwise they continued to receive a maintenance dose of 75mg daily. For those undergoing CABG, the study drug was withheld for five days with clopidogrel and one to three days with ticagrelor. All patients received aspirin at a dose of 75–100mg daily, unless they were unable to tolerate the drug. For those who had not previously been receiving aspirin, 325mg was the preferred loading dose, although 325mg was also allowed as the daily dose for six months after stent replacement.<sup>12</sup>

#### PLATO results

The primary endpoint, a composite of cardiovascular death, non-fatal MI and non-fatal stroke, occurred significantly less often in the ticagrelor group than in the clopidogrel

group (9.8% versus 11.7%) on an intention-to-treat analysis (HR 0.84, 95% CI 0.77–0.92;  $p < 0.001$ ) at 12 months.<sup>12</sup> After a median treatment duration of 277 days, there was a significantly lower incidence of the primary composite endpoint in the ticagrelor group due to a lower incidence of both death from vascular causes and MI.<sup>12</sup> The incidence of stroke was numerically higher in the ticagrelor group, but the difference was not statistically significant.

The beneficial effect of ticagrelor was evident at 30 days (primary endpoint 4.8% ticagrelor versus 5.4% clopidogrel; HR 0.88;  $p = 0.045$ ),<sup>12</sup> maintained until the end of the study, and seen in patients with and without ST segment elevation on the electrocardiogram. An important secondary endpoint was the primary composite endpoint analysed in the subgroup of patients planned for invasive management, which comprised 72% of the overall study population (13 408 patients). The endpoint was significantly better for ticagrelor (8.9% versus 10.6%; HR 0.84, 95% CI 0.75–0.94;  $p = 0.003$ ). Death from any cause was another secondary endpoint that showed a benefit for ticagrelor-treated patients (4.5% compared to 5.9%, corresponding to an HR of 0.78 [95% CI 0.69–0.89; nominal  $p < 0.001$ ]).<sup>12</sup> Table 1 depicts the outcome events in PLATO.

Analysis of subgroups of the study population, whether treated medically or by revascularisation, including those with diabetes and impaired renal function, showed a similar clinical benefit with similar bleeding risk.

#### Bleeding

Although not significantly different, the incidence of major bleeding was numerically slightly higher in the ticagrelor group as defined by

	Ticagrelor (% of patients with event) n=9333	Clopidogrel (% of patients with event) n=9291	Absolute risk reduction (%/year)	Relative risk reduction (%) (95% CI)	p-value (* denotes nominal p-value)
Cardiovascular death, MI (excluding silent MI) or stroke	9.3	10.9	1.9	16 (8, 23)	0.0003
Invasive intent	8.5	10.0	1.7	16 (6, 25)	0.0025
Medical intent	11.3	13.2	2.3	15 (0.3, 27)	0.0444*
Cardiovascular death	3.8	4.8	1.1	21 (9, 31)	0.0013
MI (excluding silent MI)	5.4	6.4	1.1	16 (5, 25)	0.0045
Stroke	1.3	1.1	-0.2	-17 (-52, 9)	0.2249
All-cause mortality, MI (excluding silent MI) or stroke	9.7	11.5	2.1	16 (8, 23)	0.0001
Cardiovascular death, total MI, stroke, serious recurrent and recurrent ischaemia, recurrent transient ischaemic attack, or other arterial thrombotic event	13.8	15.7	2.1	12 (5, 19)	0.0006
All-cause mortality	4.3	5.4	1.4	22 (11, 31)	0.0003*
Definite stent thrombosis	1.2	1.7	0.6	32 (8, 49)	0.0123*

**Table 1.** Outcome events in PLATO. MI, myocardial infarction<sup>2</sup>

the trial (11.6% versus 11.2%;  $p=0.43$ ). In the ticagrelor group, there was a higher rate of non-CABG-related major bleeding based on the study criteria (4.5% versus 3.8%;  $p=0.03$ ). Intracranial bleeding was numerically more common in the ticagrelor group than in the clopidogrel group and fatal intracranial bleeding was significantly more common. However, fatal non-intracranial bleeding was significantly more common in the clopidogrel group. Table 2 illus-

trates the bleeding rates per treatment group.

The summary of product characteristics states that ticagrelor is contraindicated if there is active pathological bleeding or a history of intracranial haemorrhage.<sup>2</sup> Precautions should be exercised in patients with a propensity to bleed, such as recent trauma, recent surgery or coagulation disorders. In those with concomitant administration of drugs, such as nonsteroidal anti-inflammatory drugs, oral antico-

agulants and/or thrombolytics that increase the risk of bleeding, additional care should be taken and the clinical benefit of the drug balanced against the perceived bleeding risk.

### Side-effects

Drug discontinuation due to adverse events occurred more frequently with ticagrelor than clopidogrel (7.4% versus 6.0%;  $p<0.001$ ).<sup>12</sup>

A Holter monitoring subset of the PLATO study included nearly 3000 patients to study the

	Ticagrelor (%/year) n=9235	Clopidogrel (%/year) n=9186	p-value
PLATO total major	11.6	11.2	0.4336
PLATO major fatal/ life-threatening	5.8	5.8	0.6988
Non-CABG PLATO major	4.5	3.8	0.0264
Non-procedural PLATO major	3.1	2.3	0.0058
PLATO total major+minor	16.1	14.6	0.0084
Non-procedural PLATO major+minor	5.9	4.3	<0.0001
TIMI-defined major	7.9	7.7	0.5669
TIMI-defined major+ minor	11.4	10.9	0.3272

CABG, coronary artery bypass graft; TIMI, thrombolysis in myocardial infarction. Bleeding category definitions are as follows. Major fatal/life-threatening bleed: clinically apparent with >50g/l decrease in haemoglobin or four or more red cell units transfused; or fatal; or intracranial; or intrapericardial with cardiac tamponade; or with hypovolaemic shock or severe hypotension requiring pressors or surgery. Major other: clinically apparent with 30–50g/l decrease in haemoglobin or two to three red cell units transfused; or significantly disabling. Minor bleed: requires medical intervention to stop or treat bleeding. TIMI major bleed: clinically apparent with >50g/l decrease in haemoglobin or intracranial haemorrhage. TIMI minor bleed: clinically apparent with 30–50g/l decrease in haemoglobin.

**Table 2.** Kaplan-Meier estimates of bleeding rates per treatment group in PLATO<sup>2</sup>

occurrence of arrhythmic episodes, especially ventricular pauses of three or more seconds (84 in the ticagrelor group versus 51 in the clopidogrel group in the first week;  $p \geq 0.01$ ).<sup>12</sup> This increase in ventricular pauses in the acute phase of ACS was more pronounced if there was a history of congestive heart failure, but it was rarely associated with symptoms, and with no significant difference in the incidence of syncope or pacemaker insertion.<sup>2</sup>

### Other side-effects

Dyspnoea was reported by 13.8% of patients treated with ticagrelor in

the PLATO study and by 7.8% of patients treated with clopidogrel.<sup>12</sup> However, only 2.2% of patients were considered to have developed dyspnoea directly related to treatment with ticagrelor (0.6% for clopidogrel).<sup>2</sup> The shortness of breath was usually mild to moderate in intensity and resolved without the need for treatment discontinuation (0.9% in PLATO).<sup>2</sup> Patients with asthma or chronic obstructive pulmonary disease may be at increased risk of experiencing dyspnoea with ticagrelor, so it should be used with caution in these patients.

An increase in creatinine was noted during treatment with ticagrelor compared to clopidogrel in the PLATO trial.<sup>12</sup> Renal function should therefore be checked after one month and thereafter according to routine medical practice. Special attention should be paid to patients aged 75 years and older; those with moderate or severe renal impairment, and those receiving concomitant treatment with an angiotensin receptor blocker.<sup>2</sup>

As a rise in blood urate levels is possible, care should be taken in patients with a history of raised urate or previous gouty arthritis, and ticagrelor should not be used in patients with uric acid nephropathy.<sup>2</sup>

### Interactions and metabolism

Ticagrelor is metabolised by the cytochrome P3A4 enzyme and is eliminated via hepatic metabolism. Co-administration with strong cytochrome P3A4 inhibitors such as ketoconazole, clarithromycin and nefazodone is contraindicated as it may lead to a substantial increase in antiplatelet effect.<sup>2</sup> Co-administration with strong cytochrome P3A4 inducers, such as rifampicin, dexamethasone, phenytoin, carbamazepine and phenobarbital, may lead to a substantial decrease in drug levels of ticagrelor, and may lead to a decrease in efficacy. Co-administration with statins metabolised by cytochrome P3A4, such as simvastatin and atorvastatin, leads to increased concentrations of these drugs. This is particularly true of doses above 40mg for simvastatin, which may cause an increased risk of side-effects, such as myopathy.

### Use with proton pump inhibitors

Proton pump inhibitors (PPIs) are widely used for possible gastric

protection and management of non-ulcer dyspepsia in patients on antiplatelet therapy. PPIs competitively inhibit the cytochrome 2C19 isoenzyme, preventing the conversion of clopidogrel into its active enzyme; this is not associated with ticagrelor use.<sup>2</sup> In the PLATO study, ticagrelor was commonly administered with PPIs, and no evidence of clinically significant interactions between the drugs was observed.<sup>2</sup> Aspirin bioavailability and subsequent reduction of platelet inhibition may be reduced with the use of PPIs. There is an association of increased risk of cardiovascular events in patients treated with aspirin and a PPI after a first MI.<sup>13</sup> In studies involving ticagrelor, nausea, vomiting, dyspepsia and gastritis were classified as uncommon adverse reactions.<sup>2</sup>

### Use in practice

Despite the proven clinical benefit and the approval of the SMC for its use within the NHS in Scotland, the introduction of ticagrelor is likely to be gradual, with cardiologists initially identifying those

patients at highest risk with most to gain. Ticagrelor is accepted by the SMC to be cost effective.<sup>1</sup> When compared with clopidogrel, the base cost per quality-adjusted life year (QALY) is £3966 based on a QALY gain of 0.095 and incremental costs of £375. According to an estimation supplied by AstraZeneca, but reviewed and supported by the SMC, within five years, about 50% of patients with ACS will be treated with ticagrelor in preference to clopidogrel.

There is currently significant variation in the advice on the use of antiplatelet therapy in both national and international guidelines. Local protocols have also recently started to reflect published trials suggesting a different dosage regimen (for clopidogrel) for those undergoing revascularisation with percutaneous coronary intervention.<sup>14</sup> Treatment with ticagrelor is recommended for up to 12 months unless discontinuation is clinically indicated. The risk of stent thrombosis, as well as higher residual risk, increases with the premature discontinuation of antiplatelet therapy, and registry

data have now demonstrated adverse mortality outcomes for those not continuing on dual antiplatelet therapy for up to 12 months after an ACS event.<sup>15</sup> Future guideline updates are likely to reflect the SMC's advice on the use and benefits of ticagrelor in patients with ACS.

### NICE guidance

In October 2011, NICE published technology appraisal guidance 236 on ticagrelor for the treatment of ACS, recommending the use of the drug.<sup>16</sup> Ticagrelor plus low-dose aspirin is a treatment option for up to 12 months in adults with ACS, on the basis that the incremental cost-effectiveness ratio produced in the economic analysis was within the range normally considered to be a cost-effective use of NHS resources. It did, however, additionally specify that before ticagrelor is continued beyond initial treatment, a diagnosis of unstable angina should be confirmed, ideally by a cardiologist.<sup>16</sup> Now that ticagrelor has been recommended for use by NICE, funding will be provided for its use within the NHS, not only in Scotland, but also in England and Wales.

### References

1. Scottish Medicines Consortium guidance on the use of Brilique. ([www.scottishmedicines.org.uk/SMC\\_Advice/Advice/699\\_11\\_ticagrelor\\_Brilique/ticagrelor\\_Brilique](http://www.scottishmedicines.org.uk/SMC_Advice/Advice/699_11_ticagrelor_Brilique/ticagrelor_Brilique); accessed 26 January 2012).
2. AstraZeneca UK Ltd. Brilique 90mg film-coated tablets Summary of Product Characteristics ([www.medicines.org.uk/EMC/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/](http://www.medicines.org.uk/EMC/medicine/23935/SPC/Brilique+90+mg+film+coated+tablets/); accessed 26 January 2012).
3. Antithrombotic Trialists' Collaboration. *Br Med J* 2002;324:71–86.
4. Fox KA, *et al.* *Circulation* 2004; 110:1202–8.
5. COMMIT (Clopidogrel and metoprolol in myocardial infarction trial collaborative group. *Lancet* 2005; 366:1607–21.
6. Wiviott SD, *et al.* *N Engl J Med* 2007; 357:2001–15.
7. Eli Lilly. Eficent 5mg & 10mg film-coated tablets Summary of Product Characteristics ([www.medicines.org.uk/EMC/medicine/21504/SPC/Eficent+5+mg+%26+10mg+filmcoated+tablets+%28Eli+Lilly+and+Company+Ltd+Daiichi+Sankyo+UK+Limited%29/](http://www.medicines.org.uk/EMC/medicine/21504/SPC/Eficent+5+mg+%26+10mg+filmcoated+tablets+%28Eli+Lilly+and+Company+Ltd+Daiichi+Sankyo+UK+Limited%29/); accessed 26 January 2012).
8. Wallentin L, *et al.* *Eur Heart J* 2008;29:21–30.
9. Brandt JT, *et al.* *J Thromb Haemost* 2007;5:2429–36.
10. Sandoz. Clopidogrel 75mg Summary of Product Characteristics. ([www.medicines.org.uk/EMC/medicine/22755/SPC/Clopidogrel+75+mg+Filmcoated+Tablets/](http://www.medicines.org.uk/EMC/medicine/22755/SPC/Clopidogrel+75+mg+Filmcoated+Tablets/); accessed 26 January 2012).
11. James S, *et al.* *Am Heart J* 2009; 157:599–605.
12. Wallentin L, *et al.* *N Engl J Med* 2009;361:1045–57.
13. Charlot M, *et al.* *Br Med J* 2011; 342:d2690.
14. Mehta SR, *et al.* *Lancet* 2010;376: 1233–43.
15. Boggon R, *et al.* *Eur Heart J* 2011; 32:2376–86.
16. NICE. Ticagrelor for the treatment of acute coronary syndromes. Technology Appraisal guidance 236. (<http://guidance.nice.org.uk/TA236/Guidance/pdf/English>; accessed 26 January 2012).

**BRILIQUE™ 90MG FILM-COATED TABLETS (ticagrelor)**  
**PRESCRIBING INFORMATION. Consult Summary of Product**

**Characteristics before prescribing.**

**Use:** Adults aged 18 years and older, co-administered with 75-150mg acetylsalicylic acid (ASA) daily: for the prevention of atherothrombotic events in patients with acute coronary syndromes (unstable angina, non-ST-segment elevation myocardial infarction [NSTEMI] or ST-segment elevation myocardial infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

**Presentation:** 90mg ticagrelor film-coated tablets. **Dosage and administration:** Treatment should be initiated with a single 180mg loading dose (two tablets of 90mg) and then continued at 90mg twice daily. Treatment is recommended for up to 12 months unless discontinuation is clinically indicated. Premature discontinuation of treatment or lapses in therapy should be avoided. Patients treated with clopidogrel can be directly switched to Brilique. For oral use.

**Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active pathological bleeding. History of intracranial haemorrhage. Moderate-to-severe hepatic impairment. Co-administration with strong CYP3A4 inhibitors (e.g. ketoconazole). **Precautions:** Due to the increased risk of non-fatal or non-life threatening bleeding, use with caution in patients at an increased risk for bleeding (e.g. recent trauma or surgery, bleeding disorders or recent gastrointestinal bleeding) or those on concomitant medication that may increase bleeding risk (e.g. NSAIDs, anticoagulants) within 24 hours of taking Brilique. Brilique should be stopped 7 days prior to elective surgery if the antiplatelet effect is not desired. Use with caution in patients with an increased risk of bradycardic events (e.g. patients on digoxin), as

asymptomatic ventricular pauses have been observed with Brilique, a history of asthma and/or COPD, a history of hyperuricaemia or gouty arthritis. Creatinine levels may increase during treatment with Brilique. Renal function should be checked after one month and thereafter according to routine medical practice, paying special attention to patients  $\geq$  75 years, patients with moderate-to-severe renal impairment and those receiving concomitant treatment with an ARB. Co-administration of Brilique is not recommended with a high maintenance dose of ASA ( $>$  300mg) or with doses of simvastatin  $>$  40mg. Co-administration of ticagrelor with strong CYP3A4 inducers is discouraged, as this may lead to a decrease in exposure and efficacy of ticagrelor. Brilique is not recommended during pregnancy and breastfeeding. **Undesirable events:** Common side effects include dyspnoea, epistaxis, gastrointestinal haemorrhage, subcutaneous or dermal bleeding, bruising and procedural site haemorrhage. Other adverse events include intracranial bleeding, elevations of serum creatinine and uric acid levels. **Consult SmPC for a full list of adverse events.**

**Legal category:** POM. **Marketing authorisation number:** EU/1/10/655/004. **Basic NHS cost:** Brilique 90mg film-coated tablets 56: £54.60. **Further information is available from:** AstraZeneca UK Ltd., 600 Capability Green, Luton, LU1 3LU.

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11/2010  
CV 10 0118

Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to AstraZeneca on 0800 783 0033

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