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GUIDANCE ON THE PRESCRIBING OF ASPIRIN, CLOPIDOGREL, PRASUGREL AND TICAGRELOR FOR THE PREVENTION OF ATHEROTHROMBOTIC EVENTS IN PATIENTS WITH ACUTE CORONARY SYNDROMES

Key Point Summary

- **The new oral anti-platelet agents, ticagrelor (*Brilique*) and prasugrel (*Efient*), offer distinct advantages over clopidogrel in terms of both rapid onset of action and reduction in the number of low or non-responders when used for the prevention of atherosclerotic events in patients with acute coronary syndromes. This *Bulletin* provides prescribing guidance and treatment algorithms relating to the use of these new agents in ST segment elevation MI (STEMI), non STEMI and unstable angina.**
- **Specifically, in STEMI, prasugrel or ticagrelor therapy is advocated prior to and for 12 months following primary percutaneous coronary intervention (PPCI). This should be in combination with low dose aspirin which should be life-long.**
- **NSTEMI intervention is not as time critical as STEMI as the artery is not fully blocked. Patients are risk stratified with high risk patients referred to a cardiologist for in-patient coronary angiograms and possible PCI (not primary PCI). Ticagrelor has a wider range of licensed indications and is advocated rather than prasugrel for this indication.**
- **All patients on prasugrel or ticagrelor should be reviewed at 12 months with a view to stopping this component of therapy unless the patient has been identified as exceptional by their cardiologist. Good compliance with antiplatelet therapy is absolutely crucial to ensure maximum patient benefit.**

CONTENTS

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SUMMARY OF PACEF DECISIONS

Drug	Indication(s)	Traffic Light Status
Prasugrel tablets 5mg and 10mg (*Efient*)	Licensed in conjunction with aspirin for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention (PCI)	AMBER without shared care For initiation by consultant cardiologists only. Approved for Joint Formulary.
Ticagrelor 90mg tablets (*Brilique*)	Licensed in combination with aspirin for the prevention of atherothrombotic events in acute coronary syndromes, including patients managed medically with PCI or with coronary artery bypass graft (CABG).	AMBER without shared care. For initiation by consultant cardiologists only. Approved for Joint Formulary.

Introduction

It is the purpose of this special edition of the *PACE Bulletin* to detail the place in therapy of two new and NICE approved antiplatelet drugs, prasugrel (*Efient*) and ticagrelor (*Brilique*), for the prevention of atherothrombotic events in patients with acute coronary syndrome. The *Bulletin* has been produced to coincide with the opening of the new cardiac catheter laboratory at Lincoln County Hospital and has been co-authored by Dr David O'Brien, a Consultant Interventional Cardiologist and Clinical Lead for the Primary Percutaneous Coronary Intervention (PPCI) Project at United Lincolnshire Hospitals Trust.

Historically, dual anti-platelet therapy (DAPT) with aspirin and clopidogrel has been recommended for the management of patients with acute coronary syndrome (ACS) either when managed medically or with coronary intervention. ACS can be defined collectively as ST segment elevation myocardial infarction (STEMI), non- ST segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). However, concerns exist with regard to the speed of onset of action of clopidogrel and with the recognised fact that a significant proportion of patients are low or non-responders to its platelet inhibition (estimated to be up to 30% of the population). Speed of onset of action is of particular concern for patients presenting with acute ST segment elevation myocardial infarction (STEMI) and requiring Primary Percutaneous Coronary Intervention (PPCI). Even the use of high loading doses of clopidogrel (e.g. 600 mg) still requires 2 to 4 hours before desirable levels of platelet inhibition are achieved. This is due to the fact that clopidogrel is a pro-drug that requires hepatic conversion before reaching its active form. New oral anti-platelet agents offer a distinct advantage in terms of both rapid onset of action and reduction in the number of low or non-responders. Both ticagrelor and prasugrel are rapidly bioavailable and cause therapeutic platelet inhibition after around 30 minutes. Ticagrelor is a reversible, direct acting P2Y12 inhibitor requiring twice daily dosage. Prasugrel inhibits platelet aggregation through the irreversible blockade of the P2Y12 receptor; it is a pro-drug, like clopidogrel, but has a quicker onset of action and a more consistent inhibitory effect on platelet aggregation; it is given once daily. Both drugs are marketed for use in patients with ACS. As detailed below, NICE have approved both drugs for use in patients with ACS.

Prescribing Guidance: *ST segment elevation myocardial infarction*

When a patient presents with cardiac sounding chest pain, an ECG is performed immediately. If the ECG demonstrates ST segment elevation (ST elevation MI or STEMI), this infers that there is a complete obstruction of a coronary artery. This obstruction is often as a result of a blood clot forming over a ruptured atherosclerotic plaque. As the artery is occluded, then any myocardium it supplies begins to infarct very quickly. Nearly half of potentially salvageable myocardium is lost within 1 hour of the coronary artery being occluded; two-thirds are lost within 3 hours. Hence, there is a time critical period within which the coronary artery can be unblocked and coronary flow and myocardial perfusion can be restored.

Previously the treatment of choice for these patients would have been thrombolysis as a means to achieve restoration of coronary flow. This is partially effective depending on the fibrinolytic agent used, the severity of the underlying stenosis and the clot burden. However, thrombolysis does not affect the underlying coronary stenosis and is associated with a risk of stroke secondary to intra-cerebral haemorrhage.

The recommended treatment of choice is now to open the artery mechanically with a balloon procedure (Percutaneous Coronary Intervention (PCI)). This is significantly more successful in restoring coronary blood flow and has the additional benefits of reducing mortality of MI, dealing with the underlying stenosis and reducing stroke risk in comparison to thrombolysis. It also reduced the length of hospital stay. If this procedure is performed as the first treatment for STEMI it is known as Primary PCI or PPCI for short.

Assuming a STEMI is confirmed on ECG the following pathway is followed:

(1) A 300mg loading dose of aspirin should be given followed by a 75mg aspirin dispersible tablet once daily thereafter. Aspirin therapy should be life-long.

(2) If the primary percutaneous coronary intervention (PPCI) pathway is activated, either prasugrel or ticagrelor should be added to the aspirin therapy. A loading dose of either prasugrel (60mg) or ticagrelor (180mg) should be given without delay. Agent selection will be made by the initiating cardiologist based on marketing authorisations, NICE guidance, cautions and contra-indications (see below).

Onset of action

Speed of onset of action is crucial for patients presenting with acute STEMI and requiring PPCI. Clopidogrel is a pro-drug requiring hepatic conversion; a 600mg loading dose requires 2 to 4 hours before desirable levels of platelet inhibition are achieved. Both prasugrel and ticagrelor are rapidly bioavailable producing therapeutic platelet inhibition after about 30 minutes. In addition, up to 30% of the population are known to be low or non-responders to the platelet inhibition effects of clopidogrel.

(3) After the initial loading dose, prasugrel will be continued at a dose of 10mg daily or ticagrelor at a dose of 90mg twice daily. Whichever agent is chosen should be prescribed concurrently with aspirin dispersible 75mg once daily.

Twice Daily Ticagrelor

Ticagrelor is a twice daily treatment with some concerns raised around the potential for poor compliance associated with more frequent dosage regimes. Both prasugrel

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and ticagrelor are ADP P2Y12 receptor blockers, but they have a significant difference: ticagrelor blockade is reversible while prasugrel blockade is irreversible. In practice this means that the antiplatelet effect of ticagrelor is likely to wear off more quickly than that of prasugrel, particularly if patient compliance is sporadic or poor. Ultimately, reversible blockade has both advantages and disadvantages; for example the reversibility of ticagrelor means that stopping therapy rapidly enables bleeding problems to be brought under control or the patient to be prepared for emergency surgical intervention; conversely, poor compliance with ticagrelor can leave the patient exposed to thrombotic problems should they miss a dose. Good compliance with antiplatelet therapy is absolutely crucial to ensure maximum patient benefit.

(4) Duration of prasugrel or ticagrelor therapy will normally be for no longer than 12 months. This will be clearly documented to both the patient and the GP on discharge. Where a longer duration of therapy is indicated this will be specified on discharge. All patients initiated on prasugrel or ticagrelor will need to be reviewed at 12 months with the intention of stopping therapy unless otherwise advised by a cardiologist. Aspirin therapy will need to continue long-term.

<u>Duration of Therapy</u>
The necessity for review and stop of prasugrel or ticagrelor at 12 months reflects the duration of the relevant clinical trials: PLATO in the case of ticagrelor (12 months) and TRITON TIMI 38 in the case of prasugrel (6 to 15 months). Twelve month review and stop should be firmly in place in all practices for both prasugrel and ticagrelor to prevent inappropriate use beyond the 12 month treatment period. Practical strategies that could be used to ensure 12 month review and stop include: (1) printing a stop date on the dosage instructions printed on the label; (2) putting a block on repeat issues after 12 months; (3) ensuring that a stop date is printed on the repeat slip; or (4) providing reminders through a computer screen message.

(5) If for any reason the patient is not accepted for PPCI, clopidogrel and aspirin combination therapy should be given. After a 300mg loading dose, clopidogrel is continued at a dose of 75mg daily for one month. After review and discontinuation of the clopidogrel, aspirin monotherapy should be life-long.

<u>Prasugrel and Ticagrelor as Alternatives to Clopidogrel</u>
Patients developing stent thrombosis whilst taking DAPT (aspirin and clopidogrel) are potentially low or non-responders to the platelet inhibition effects of clopidogrel and should be considered for substitution of clopidogrel with either prasugrel or ticagrelor. Patients with coronary stents in situ who develop an allergic reaction or intolerance to clopidogrel will also need to be considered for alternative antiplatelet cover by substituting with either prasugrel or ticagrelor in addition to aspirin.

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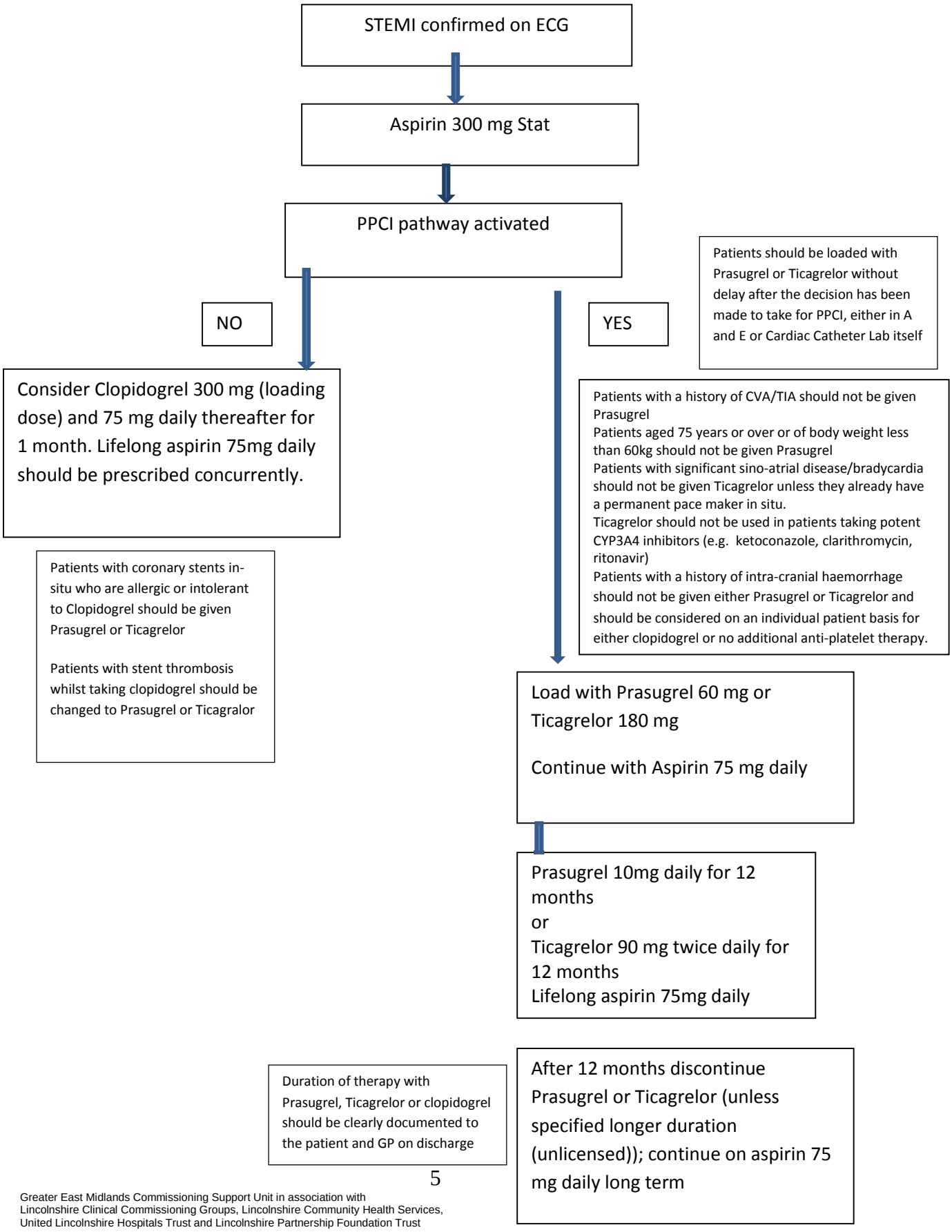
Treatment Algorithm: ST segment Elevation Myocardial Infarction (STEMI)



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Prescribing Guidance: ***Admission with Non ST segment Elevation Myocardial Infarction (NSTEMI) or unstable angina***

If there is no ST segment elevation seen on the presenting ECG, but the patient has cardiac sounding chest pain and subsequent confirmatory markers of myocardial injury (e.g. positive cardiac troponin), this is known as a non ST segment elevation MI or NSTEMI. NSTEMIs usually occur secondary to a plaque rupture with the same underlying pathophysiology as detailed above with adherent platelet aggregation/ activation and distal embolisation, this time resulting in incomplete occlusion of the coronary vessel. As a result of this, NSTEMI intervention is often not as time critical as STEMI as the artery is not fully blocked. Treatment involves aggressive anti-platelet therapy, anti-thrombotic therapy and anti-ischaemic therapy. Patients are risk stratified with high risk patients referred to a cardiologist for in-patient coronary angiograms and possible PCI (not primary PCI).

Elevated cardiac troponin is reflective of cardiac damage and myocyte necrosis, although the diagnosis of NSTEMI needs to be confirmed by the cardiology team to exclude other potential causes for raised troponin (e.g. chemotherapy, pulmonary embolus, arrhythmia and myocarditis). Diagnosis of NSTEMI will result in the patient being evaluated for suitability for an invasive management strategy usually including coronary angiography. Patients with NSTEMI are at high risk of a subsequent MI within the next thirty days. If the patient has coronary artery disease that is not obstructive, the decision may be taken to continue with aggressive medical therapy (i.e. dual antiplatelet therapy, statin etc). Similarly, patients with significant co-morbities (e.g. dementia) may be considered unsuitable for an invasive procedure and may be managed medically. However, severe narrowing of one or two arteries may necessitate balloon angioplasty and stenting or coronary artery bypass graft (CABG) surgery. Ticagrelor in combination with aspirin has been shown to significantly reduce the absolute risk of MI, stroke and death from vascular causes compared to clopidogrel and aspirin combination therapy in patients with ACS (see below).

If cardiac troponin levels are not elevated a diagnosis of unstable angina will be considered. Subject to confirmation of the diagnosis of UA by the cardiology team, NICE have endorsed ticagrelor as an option in patients who:

- are aged 60 years or older or;
- have had a previous myocardial infarction or previous coronary artery bypass grafting (CABG) or;
- have coronary artery disease with stenosis of 50% or more in at least two vessels or;
- have had a previous ischaemic stroke or;
- have had a previous transient ischaemic attack or,
- have carotid stenosis of at least 50%, or cerebral revascularisation or;
- have diabetes mellitus or;
- have peripheral arterial disease or;
- have chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml per minute per 1.73 m^2 of body-surface area.

Assuming NSTEMI is diagnosed, the following pathway is followed:

(1) A 300mg loading dose of aspirin should be given followed by a 75mg aspirin dispersible tablet once daily thereafter. Aspirin therapy should be life-long.
(2) A 300mg loading dose of clopidogrel should also be given.
(3) If the cardiology team confirm a diagnosis of acute coronary syndrome, clopidogrel should be stopped and ticagrelor added to the aspirin therapy. A loading dose of ticagrelor (180mg) should be given.

Clopidogrel vs Ticagrelor in ACS

NICE evaluated the PLATO study (see below) which concluded that ticagrelor 90mg twice daily plus aspirin 75mg to 100mg daily was superior to combination clopidogrel and aspirin therapy over 12 months in people with ACS whose symptoms began up to 24 hours before hospital admission. Combination ticagrelor/aspirin therapy reduced the absolute risk of experiencing MI, stroke or death from vascular causes (composite primary end point) by 11.7% compared to 9.8% with clopidogrel/aspirin (Absolute Risk Reduction 1.9%). No significant difference in major bleeding (the primary safety variable) was found between groups (ticagrelor 11.6%; clopidogrel 11.2%). Where ticagrelor therapy is poorly tolerated or contra-indicated, at this stage of the pathway, clopidogrel will be considered as a possible alternative.

(4) After the initial loading dose, ticagrelor will be continued at a dose of 90mg twice daily prescribed concurrently with aspirin dispersible 75mg once daily.

(5) Duration of ticagrelor therapy will normally be for no longer than 12 months. This will be clearly documented to both the patient and the GP on discharge. Where a longer duration of therapy is indicated this will be specified on discharge. All patients initiated on ticagrelor will need to be reviewed at 12 months with the intention of stopping therapy unless otherwise advised by a cardiologist. Aspirin therapy will need to continue long-term.

Duration of Therapy

The necessity for review and stop of ticagrelor at 12 months reflects the duration of the PLATO study. Practices will need to have 12 month review and stop firmly in place for ticagrelor to prevent inappropriate use of NHS resources beyond the 12 month treatment period. Practical strategies that could be used to ensure 12 month review and stop include: (1) printing a stop date on the dosage instructions printed on the label; (2) putting a block on repeat issues after 12 months; (3) ensuring that a stop date is printed on the repeat slip; or (4) providing reminders through a computer screen message. Patients who have extensive stenting in critical arteries (e.g. left main stem) or those with proven stent thrombosis after stopping DAPT or those unable to take aspirin after stent implantation may need to continue therapy beyond 12 months on the advice of their cardiologist. Exceptions are few and far between with an expectation that most patients will be appropriate to stop after 12 months.

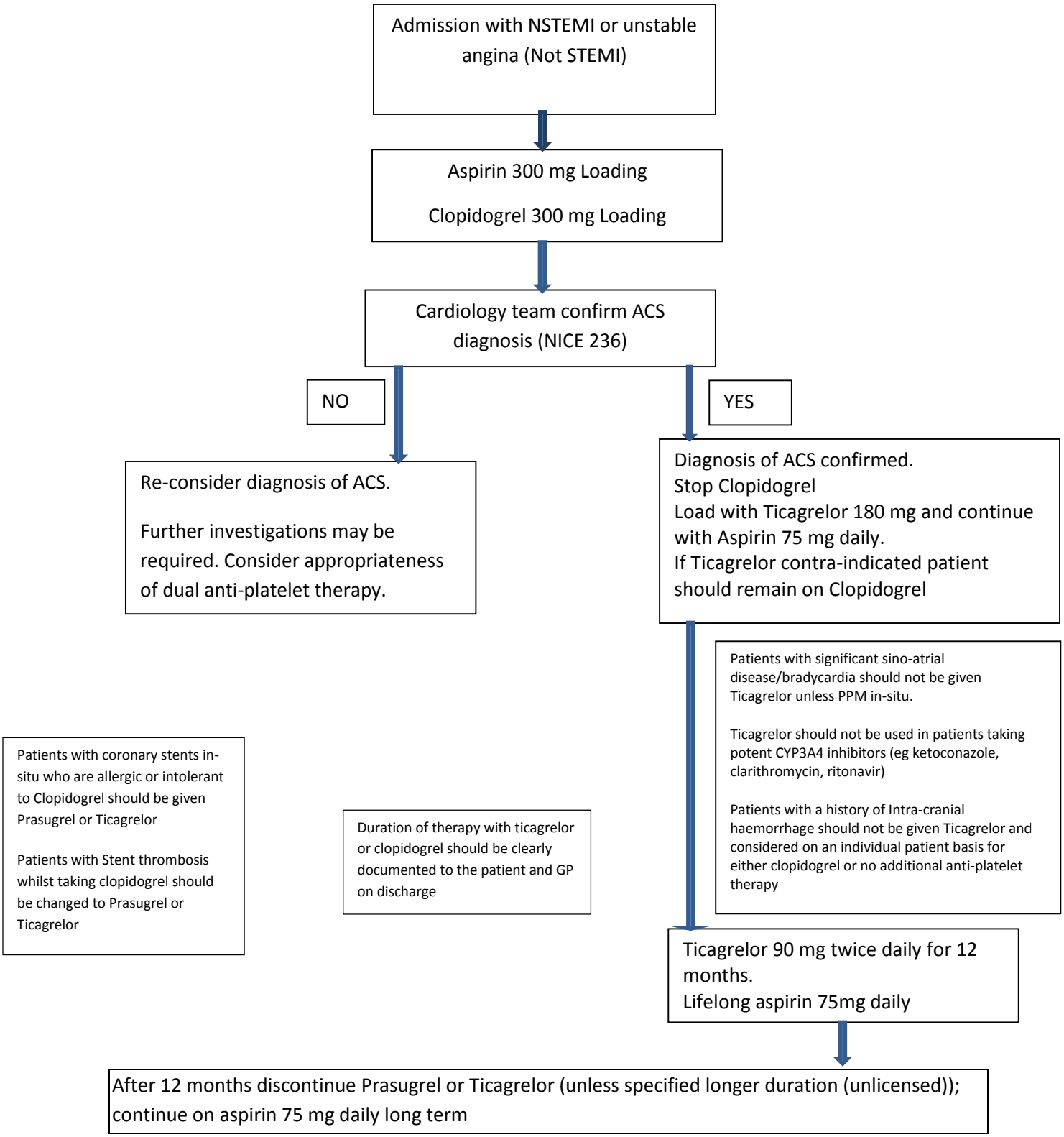
(6) If the patient is not confirmed as having ACS the diagnosis should be reviewed and an alternative diagnosis sought before deciding on whether dual anti platelet therapy is indicated or should be discontinued.

(7) After review and eventual discontinuation of the clopidogrel, aspirin monotherapy should be life-long.

Prasugrel and Ticagrelor as Alternatives to Clopidogrel

Patients developing stent thrombosis whilst taking DAPT with aspirin and clopidogrel are potentially low or non-responders to the platelet inhibition effects of clopidogrel and should be considered for substitution of clopidogrel with either prasugrel or ticagrelor. Patients with coronary stents in situ who develop an allergic reaction or intolerance to clopidogrel will also need to be considered for alternative antiplatelet cover by substituting prasugrel or ticagrelor in addition to aspirin.

Treatment Algorithm: *Admission with Non ST segment Elevation Myocardial Infarction (NSTEMI) or unstable angina*



Supporting Information

Clopidogrel, Prasugrel and Ticagrelor: *Summary of Marketing Authorisations*

Clopidogrel	Prasugrel	Ticagrelor
Clopidogrel (Plavix) co-administered with aspirin, is indicated for the prevention of atherothrombotic events in patients with acute coronary syndromes (ACS) (i.e. unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation MI (STEMI)) including patients undergoing a stent replacement following percutaneous coronary intervention (PCI) and those managed medically. Clopidogrel (Plavix) is also indicated in patients suffering from MI (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease. Clopidogrel (Plavix), co-administered with aspirin, is also indicated for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation in patients with at least once risk factor for vascular events who are not suitable for treatment with a vitamin K antagonist and who have a low bleeding risk.	Prasugrel (*Efient*), co-administered with aspirin, is indicated for the prevention of atherothrombotic events in patients with acute coronary syndromes (ACS) (i.e. unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation MI (STEMI)) undergoing primary or delayed percutaneous coronary intervention (PCI).	Ticagrelor(Brilique), co-administered with aspirin, is indicated for the prevention of atherosclerotic events in adult patients with acute coronary syndromes (ACS) (i.e. unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI) or ST segment elevation MI (STEMI); including patients managed medically and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG)

Prasugrel and Ticagrelor: *Summary of Cautions and Contra-indications*

	Prasugrel	**Ticagrelor**
Patient over 75 years	Not recommended (greater sensitivity to bleeding). A reduced dose of 5mg once daily is required if prasugrel is used in this patient group.	**No dosage adjustment required in the elderly. Ticagrelor preferred.**
Patient under 60kg	Not recommended (greater sensitivity to bleeding). A reduced dose of 5mg once daily is required if prasugrel is used in this patient group.	**No dose adjustment necessary. Ticagrelor preferred.**
Renal impairment	No dose adjustment necessary.	No dose adjustment necessary.
Hepatic impairment	No dose adjustment necessary in mild to moderate hepatic impairment; contra-indicated in severe hepatic impairment.	No dose adjustment necessary in mild hepatic impairment; contra-indicated in moderate to severe hepatic impairment.
Patient with a history of stroke or transient ischaemic attack (TIA)	Contra-indicated	**Ticagrelor preferred.**

Patient with active pathological bleeding	Contra-indicated	Contra-indicated
Patient with history of intracranial haemorrhage	Contra-indicated. Consider on an individual patient basis for either clopidogrel or no additional antiplatelet therapy.	Contra-indicated Consider on an individual patient basis for either clopidogrel or no additional antiplatelet therapy.
Patient taking concomitant medication that may increase the risk of bleeding (e.g. oral anticoagulants, clopidogrel, NSAIDs, fibrinolytics)	Only consider when the benefit of prevention of ischaemic events outweighs the risk of serious bleeding.	Only consider when the benefit of prevention of ischaemic events outweighs the risk of serious bleeding.
Patients taking strong CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, ritonavir)	**Prasugrel preferred.**	Contra-indicated
Patients with significant sino-atrial disease/bradycardia without a PPM in situ.	**Prasugrel preferred**.	Contra-indicated

Prasugrel vs Ticagrelor

The table above illustrates that both prasugrel and ticagrelor are preferred in different patient groups. As a result of this, both agents are approved for use and included on the Joint Formulary. Prasugrel (*Efient*) should only be initiated by a cardiologist; it is designated AMBER without shared care within licensed indications and NICE criteria. Similarly, ticagrelor (Brilique) should only be initiated by a cardiologist; it is designated AMBER without shared care within licensed indications and NICE criteria.

NICE Technology Appraisal 182: *Prasugrel for the treatment of acute coronary syndromes with percutaneous coronary intervention* (October 2009)

NICE have recommended prasugrel in combination with aspirin as an option for preventing atherothrombotic events in people with **acute coronary syndromes having percutaneous coronary intervention** only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction (STEMI) is necessary or
- stent thrombosis has occurred during clopidogrel treatment or
- the patient has diabetes mellitus.

This guidance is based on a NICE evaluation of the TRITON-TIMI 38 study. TRITON-TIMI 38 compared prasugrel with clopidogrel and revealed increased effectiveness, reduction in non-fatal MI and reduction in the incidence of stent thrombosis in the prasugrel group. In terms of safety, an increased rate of major bleeds (including fatal bleeds) occurred with prasugrel compared with clopidogrel. Overall, all-cause mortality, CV death and non-fatal stroke did not differ significantly between the two groups. NICE conclude that prasugrel and clopidogrel are broadly equivalent in terms of clinical effectiveness at 15 months for patients with ACS having PCI. In terms of cost-effectiveness, NICE conclude that prasugrel is only cost-effective in the sub-groups identified above.

NICE Technology Appraisal 236: *Ticagrelor for the treatment of acute coronary syndromes* (October 2011)

NICE have recommended ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with acute coronary syndromes (ACS) that is, people:

- with **ST-segment-elevation myocardial infarction (STEMI)** – defined as ST elevation or new left bundle branch block on electrocardiogram – **that cardiologists intend to treat with primary percutaneous coronary intervention (PCI)** or:
- with **non-ST-segment-elevation myocardial infarction (NSTEMI)** or:

- admitted to hospital with **unstable angina** – defined as ST or T wave changes on electrocardiogram suggestive of ischaemia plus one of the characteristics defined below. **Before ticagrelor is continued beyond the initial treatment, the diagnosis of unstable angina should first be confirmed, ideally by a cardiologist.**

For the purposes of this guidance, characteristics to be used in defining treatment with ticagrelor for unstable angina are:

- age 60 years or older; or
- previous myocardial infarction or previous coronary artery bypass grafting (CABG); or
- coronary artery disease with stenosis of 50% or more in at least two vessels; or
- previous ischaemic stroke; or
- previous transient ischaemic attack, or
- carotid stenosis of at least 50%, or cerebral revascularisation; or
- diabetes mellitus; or
- peripheral arterial disease; or
- chronic renal dysfunction, defined as a creatinine clearance of less than 60 ml per minute per 1.73 m^2 of body-surface area.

Platelet Inhibition and Patient Outcomes Study (PLATO)

NICE reviewed the Platelet Inhibition and Patient Outcomes Study (PLATO) as the only trial relevant to this decision problem. PLATO evaluated the efficacy and safety of ticagrelor plus aspirin compared to clopidogrel plus aspirin over 12 months in people with ACS whose symptoms began up to 24 hours before hospital admission. 18,624 adult patients with ACS with or without ST segment elevation were randomised to either:

- ticagrelor 180mg loading dose followed by 90mg twice daily or
- clopidogrel 300 to 600mg loading dose then 75mg daily thereafter.

All patients were also taking aspirin 75 to 100mg daily.

The primary end point was time to first event (composite of MI, stroke or death from vascular causes). The secondary end points were: MI, stroke, death from vascular causes, death from any cause, composite of MI, stroke and death from any cause, composite of MI, stroke, severe recurrent cardiac ischaemia, TIA, other arterial thrombotic events and death from vascular causes.

Randomisation to ticagrelor plus aspirin reduced the absolute risk of experiencing the primary end point from 11.7% to 9.8% (Absolute Risk Reduction 1.9%) compared with clopidogrel plus aspirin (the Number Needed to Treat is 53 over 12 months (i.e 53 patients with ACS would have to be treated with ticagrelor rather than clopidogrel for 12 months in order to prevent one additional event)).

No significant difference in major bleeding (the primary safety variable) was found between groups (ticagrelor 11.6%; clopidogrel 11.2%). However, ticagrelor was associated with a significantly increased risk of major bleeding not related to CABG (4.5% vs 3.8%; Number Needed to Harm 143); patients randomised to ticagrelor also experienced more major and minor bleeding overall (including intracranial bleeding). Patients treated with ticagrelor also experienced more dyspnoea, ventricular pauses (of 3 seconds or longer) and increases in serum creatinine and uric acid than clopidogrel (renal function should be checked a month after treatment initiation); a patient randomised to ticagrelor was nine times more likely to discontinue treatment due to dyspnoea than a patient randomised to clopidogrel. Breathlessness occurs in up to 10% of patients; this sometimes resolves with treatment but may persist until ticagrelor is discontinued. This needs to be kept in mind by prescribers for

all patients treated with DAPT using ticagrelor as premature discontinuation may result in excess stent thrombosis with associated mortality and morbidity if ticagrelor is discontinued and not substituted with an alternative agent (in combination with aspirin).

For patients with recent PCI and coronary stent insertion, premature interruption or discontinuation of DAPT for any reason (e.g. side effects, requirement of non-cardiac surgery etc) may also result in acute stent thrombosis with fatal consequences; such patients should ALWAYS be discussed with Cardiology prior to changing therapy with the exception of life threatening haemorrhage.

Cost Comparison: *Clopidogrel vs Prasugrel vs Ticagrelor*

Since the NICE TA was published the cost differential between clopidogrel, prasugrel and ticagrelor has widened markedly:

Drug	Daily dose	28 day cost
Clopidogrel 75mg tablets (generic)	75mg daily	£1.88
Prasugrel 5mg tablets (*Efient*)	5mg daily	£47.56
Prasugrel 10mg tablets (*Efient*)	10mg daily	£47.56
Ticagrelor 90mg tablets (*Brilique*)	90mg twice daily	£54.60

In terms of cost-effectiveness, NICE have concluded that prasugrel and ticagrelor are cost-effective in the sub-groups identified above.

Acknowledgements

Many thanks to Dr David O'Brien, Consultant Interventional Cardiologist and Clinical Lead for the PPCI Project at United Lincolnshire Hospitals Trust for co-authoring this edition of the *PACE Bulletin* with me.

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Summary of Product Characteristics, *Brilique 90mg film coated tablets* (AstraZeneca) (November 2012)
Summary of Product Characteristics, *Efient 5mg and 10mg film-coated tablets* (Lilly) (October 2012)
Summary of Product Characteristics, *Plavix 75mg tablets* (Sanofi) (June 2011)

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