

**NATIONAL INSTITUTE FOR HEALTH AND CARE  
EXCELLENCE**

**Appraisal consultation document**

**Ticagrelor for preventing atherothrombotic  
events after myocardial infarction**

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ticagrelor in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

**This document has been prepared for consultation with the consultees.**

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

**Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.**

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination (FAD).
- Subject to any appeal by consultees, the FAD may be used as the basis for NICE's guidance on using ticagrelor in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

**The key dates for this appraisal are:**

Closing date for comments: 5pm, Monday 5 September 2016

Second appraisal committee meeting: Wednesday 14 September 2016

Details of membership of the appraisal committee are given in section 7.

# 1 Recommendations

1.1 Ticagrelor 60 mg, in combination with aspirin, is recommended as an option as a continuation therapy for preventing atherothrombotic events in people who have a history of myocardial infarction and a high risk of developing atherothrombotic events, only if:

- they have had a myocardial infarction at least a year ago and have already taken ticagrelor 90 mg in combination with aspirin for 1 year and
- ticagrelor 60 mg in combination with aspirin is continued without interruption and
- treatment with ticagrelor 60 mg in combination with aspirin is stopped when clinically indicated or after a maximum of 3 years.

1.2 This guidance is not intended to affect the position of patients whose treatment with ticagrelor 60 mg, in combination with aspirin as a continuation therapy, was started within the NHS before this guidance was published. Treatment of those patients may continue without change to whatever funding arrangements were in place for them before this guidance was published until they and their NHS clinician consider it appropriate to stop.

## 2 The technology

<b>Description of the technology</b>	Ticagrelor (Brilique, AstraZeneca) is an oral antagonist of the P2Y <sub>12</sub> adenosine diphosphate receptor that inhibits platelet aggregation and thrombus formation in atherosclerotic disease.
<b>Marketing authorisation</b>	<p>Ticagrelor co-administered with aspirin (acetylsalicylic acid), has a marketing authorisation for 'the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) or a history of myocardial infarction and a high risk of developing an atherothrombotic event'.</p> <p>The marketing authorisation for ticagrelor for the 'prevention of atherothrombotic events in adult patients with a history of myocardial infarction and a high risk of developing an atherothrombotic event' was granted in February 2016. This marketing authorisation relates to ticagrelor 60 mg as a continuation therapy.</p> <p>NICE has appraised ticagrelor 90 mg and aspirin for the prevention of atherothrombotic events in ticagrelor for the treatment of acute coronary syndromes,  <a href="https://www.nice.org.uk/Guidance/TA236">https://www.nice.org.uk/Guidance/TA236</a>.</p>
<b>Adverse reactions</b>	Ticagrelor is contraindicated in patients with active pathological bleeding, a history of intracranial haemorrhage, or moderate-to-severe hepatic impairment. Co-administration of ticagrelor with a strong CYP3A4 inhibitor (for example, ketoconazole, clarithromycin, nefazodone, ritonavir or atazanavir) is also contraindicated. The most commonly reported adverse effects include dyspnoea, epistaxis, gastrointestinal haemorrhage, subcutaneous or dermal bleeding, and bruising. For full details of adverse reactions and contraindications, see the summary of product characteristics.
<b>Recommended dose and schedule</b>	<p>The summary of product characteristics states that treatment with ticagrelor 90 mg is recommended for 12 months in patients with ACS unless discontinuation is clinically indicated.</p> <p>Ticagrelor 60 mg twice daily is the recommended dose when an extended treatment is needed for patients with a history of myocardial infarction of at least 1 year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial 1-year treatment with ticagrelor 90 mg or other adenosine</p>

	<p>diphosphate (ADP) receptor inhibitor therapy in patients with ACS and with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the myocardial infarction, or within 1 year after stopping previous ADP receptor inhibitor treatment.</p> <p>Unless contraindicated, ticagrelor should always be given with a daily low maintenance dose of aspirin 75 mg to 150 mg.</p> <p>There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.</p>
<b>Price</b>	<p>Ticagrelor 60 mg costs £56.40 for 56-pack (28-day supply). Costs may vary in different settings because of negotiated procurement discounts.</p>

### 3 Evidence

The appraisal committee (section 7) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

### 4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of continuation therapy with ticagrelor, having considered evidence on the nature of prevention of atherothrombotic events in people with a history of myocardial infarction, and who are at high risk of developing an atherothrombotic event, and the value placed on the benefits of the continuation therapy by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

#### Nature of the treatment and patient perspective

4.1 The committee heard from the clinical expert that a history of a myocardial infarction causes considerable anxiety, particularly a fear of further myocardial infarctions or other cardiovascular events such as a stroke. It was also highlighted that people have concerns about the risks of

bleeding associated with antiplatelet therapy, and in particular with any extension to treatment length, and that the fear of a bleed increases over time and can have a negative impact on the quality of life of the person and their family. The clinical and patient experts stated that people also fear a recurrent myocardial infarction or other cardiovascular event. The committee concluded that an additional antiplatelet agent to reduce the risk of further cardiovascular events would be useful, but that any additional bleeding risk associated with extending the treatment length should be taken into account for any individual when considering continuation of antiplatelet treatment.

### **Clinical management**

4.2 The committee discussed the clinical management of myocardial infarction and the prevention of atherothrombotic events in England. It was aware that there are 2 types of myocardial infarction; ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). It was also aware of NICE's technology appraisal guidance on [ticagrelor for the treatment of acute coronary syndromes](#) and [prasugrel with percutaneous coronary intervention for treating acute coronary syndromes](#), as well as the NICE guidelines on [myocardial infarction with ST-segment-elevation: acute management](#) and [unstable angina and NSTEMI: early management](#). The committee understood that treatment options for STEMI include percutaneous coronary intervention followed by dual antiplatelet therapy prasugrel in combination with aspirin (for people who have had percutaneous coronary intervention or in whom it is planned), ticagrelor in combination with low-dose aspirin, or clopidogrel in combination with low-dose aspirin. It also understood that people in England with NSTEMI are offered different treatment options depending on their Global Registry of Acute Coronary Events (GRACE) or TIMI score. Medical management using aspirin is an option for people at the lowest risk of future adverse cardiovascular events, whereas people at higher risk are offered percutaneous coronary intervention along with

either ticagrelor, or clopidogrel and subsequent dual antiplatelet therapy with clopidogrel and aspirin. The committee was aware that ticagrelor and prasugrel have potential advantages over clopidogrel because of their faster antiplatelet action, although they are also associated with higher bleeding risk. The committee heard from the clinical experts that clopidogrel is used less in clinical practice as uptake of newer agents such as prasugrel and ticagrelor increases. The clinical experts explained that most centres in England use ticagrelor as first-line management in NSTEMI rather than the previous standard therapy of clopidogrel and either ticagrelor or prasugrel as first-line therapy for primary percutaneous coronary intervention, which is the usual strategy for managing STEMI. Most centres also recommend 12-months' treatment with ticagrelor or prasugrel after the myocardial infarction, in addition to long-term aspirin.

- 4.3 The committee considered how extended treatment with ticagrelor would fit into the current clinical pathway for myocardial infarction (see 4.2). The committee heard from the clinical experts that despite effective secondary prevention therapy for myocardial infarctions and other cardiovascular events such as stroke with the current available antiplatelet agents, there is still a high rate of recurrence of these events (approximately 1 in 5 people who are event-free in the first year after a myocardial infarction go on to experience a further myocardial infarction, stroke or within the subsequent 3 years). The committee was aware that patients enrolled into PEGASUS-TIMI 54, the trial which formed the basis of the company submission, had a history of myocardial infarction of at least 12 to 36 months, at least 1 additional risk factor for subsequent atherothrombotic events, and that their treatment with a previous antiplatelet agent could have been stopped anytime before being randomised to the treatment arms in the trial. The clinical experts explained that in clinical practice clinicians would not restart dual antiplatelet therapy unless people present with another myocardial infarction and the decision for standard or extended treatment length

would be made while the patient was an inpatient in hospital for their myocardial infarction. Therefore ticagrelor 60 mg in combination with aspirin would be used without interruption as a continuation therapy after the initial 1-year treatment with dual antiplatelet therapy. The clinical experts further explained that although most patients enrolled into the PEGASUS-TIMI 54 trial (84% in the 60 mg treatment arm and 84% in the placebo treatment arm) had clopidogrel as their previous antiplatelet agent, in clinical practice in England ticagrelor 60 mg in combination with aspirin would only be offered as continuation therapy to people who have already had ticagrelor for 1 year following a myocardial infarction. This is because clinicians would not switch a person's treatment to a different antiplatelet agent such as clopidogrel or ticagrelor because of the different mechanisms of action of the treatments and their different adverse effect profiles. The committee recognised that ticagrelor 60 mg with aspirin may be a useful additional treatment option for some patients and noted that in the trial it was started after interruption of a dual antiplatelet therapy, however it acknowledged that ticagrelor 60 mg with aspirin in clinical practice in England would be as a continuation therapy following ticagrelor 90 mg.

### **Decision problem**

- 4.4 The committee discussed the population in the company's decision problem in relation to ticagrelor's marketing authorisation and the final scope issued by NICE. The committee was aware that the population in the company's decision problem, and therefore the focus of the company's submission, was adults who had a myocardial infarction between 1 and 2 years ago and who are at increased risk of atherothrombotic events (referred to by the company as its base case population). The committee noted that the company had defined its population to be narrower than that specified in NICE's scope, that is adults who have had a myocardial infarction and are at increased risk of atherothrombotic events. The committee was aware that the company's



rationale for narrowing the population was that the marketing authorisation focusses eligibility on those patients for whom the side effects were most favourable in the PEGASUS-TIMI 54 study and allows it to be used for patients who had a myocardial infarction less than 2 years ago or within 1 year since the last antiplatelet agent. The marketing authorisation allows ticagrelor 60 mg to be started in patients who were beyond 2 years from an myocardial infarction but within 1 year of treatment with a previous antiplatelet agent. Based on clinical practice in England, the company was of the opinion that there are very few such patients, and therefore it was appropriate for it to focus solely on patients who experienced a myocardial infarction less than 2 years ago. The committee noted that the clinical experts indicated that when clinicians were considering prolonged antiplatelet therapy in patients with a high risk of atherothrombotic events, ticagrelor 60 mg would be used as continuation therapy following an initial one-year treatment with an antiplatelet agent, which reflects one of the treatment options in the summary of product characteristics (see section 4.3) The committee therefore concluded that it was appropriate for it to focus its decision making on the patient group who had a myocardial infarction between 1 and 2 years ago.

- 4.5 The committee discussed the comparator in the company's decision problem in relation to the final scope issued by NICE. It noted that the final scope specified clopidogrel in combination with aspirin and aspirin alone as comparators and that the company considered only aspirin to be the appropriate comparator. The committee understood that the company did not consider clopidogrel in combination with aspirin to be an appropriate comparator because it doesn't have a marketing authorisation for use more than 12 months after a myocardial infarction and is not considered established clinical practice at that point in the treatment pathway. The committee recognised that although the company did not consider clopidogrel in combination with aspirin to be an appropriate comparator, it had considered undertaking an indirect comparison of ticagrelor with

clopidogrel in combination with aspirin as there were no trials directly comparing the 2 treatments, but considered it inappropriate to undertake it (as did the ERG) because of differences in the trial designs and patient populations in the trials which would be included in the indirect comparison. The committee understood from the clinical experts that clopidogrel was sometimes used as an initial antiplatelet agent for up to 12-months following a myocardial infarction but was not used in clinical practice when an extended treatment is needed for patients with a history of myocardial infarction and a high risk of an atherothrombotic event, that is clopidogrel is not used in the same position in the treatment pathway as the summary of product characteristics recommends for ticagrelor 60 mg (see section 4.3). The committee concluded that clopidogrel in combination with aspirin was not an appropriate comparator and that the most appropriate comparison for its decision-making was ticagrelor 60 mg in combination with aspirin compared with aspirin.

### ***Clinical effectiveness***

#### **PEGASUS-TIMI 54**

4.6 The company presented clinical-effectiveness results for the PEGASUS-TIMI 54 trial whole population who had ticagrelor 60 mg plus aspirin compared with placebo plus aspirin (ticagrelor 60 mg n= 7,045, placebo n=7,067) and on which the marketing authorisation for ticagrelor as a continuation therapy was based, and results of a prespecified subgroup analysis of patients who had a myocardial infarction 1 to 2 years previously (ticagrelor 60 mg n= 4,331, placebo n=4,333). The committee noted that this prespecified subgroup (referred to as the 'base-case' population by the company) provided efficacy results that tended to be more favourable to ticagrelor than the results from the overall ticagrelor 60 mg population. The committee acknowledged that PEGASUS-TIMI 54 was not statistically powered to detect a difference in outcomes in the company's base-case population, but agreed that because of the size of

the subgroup, and the baseline characteristics being sufficiently similar to the overall ticagrelor 60 mg group, it was appropriate for it to focus on this subgroup analysis in its decision-making regarding the clinical effectiveness of ticagrelor.

- 4.7 The Committee considered the effectiveness of ticagrelor in combination with aspirin compared with aspirin plus placebo in the subgroup of patients from PEGASUS-TIMI 54 with a history of myocardial infarction between 1 and 2 years ago. The committee noted that ticagrelor 60 mg in combination with aspirin reduced the composite risk of myocardial infarction, stroke and death from cardiovascular causes by 23% compared with aspirin plus placebo. The committee considered which of the components of the composite outcome was the key driver of the reduction in the composite risk of myocardial infarction stroke and death from cardiovascular causes (results are considered academic in confidence and therefore cannot be reported here).
- 4.8 The committee concluded that although there was uncertainty due to the small number of events, extended ticagrelor 60mg with aspirin was clinically effective for people with a history of myocardial infarction and a high risk of developing an atherothrombotic event.
- 4.9 The committee heard contrasting views from the clinical and patient experts on the length of extended therapy with ticagrelor. On the one hand the disease process underpinning atherothrombotic events is enduring and progressive, on that basis, in theory, continued therapy may be justified. However, the committee was persuaded by the opposing view that the risk of bleeding was substantial and that prescribing should be informed by the evidence. The committee understood that the mean length of treatment in the PEGASUS-TIMI 54 trial was 25.3 months, and that the marketing authorisation for ticagrelor states that there are limited data on its efficacy and safety beyond 3 years of extended treatment. The committee concluded that there was limited evidence for the efficacy of

ticagrelor 60mg as a continuation therapy beyond 3 years of extended treatment and that any positive recommendation should therefore be for a maximum of 3 years.

### ***Cost effectiveness***

4.10 The committee considered the cost effectiveness of ticagrelor 60mg in combination with aspirin as a continuation therapy for preventing atherothrombotic events after myocardial infarction. It discussed the following concerns with the company's model:

- The use of 3 different approaches to cost effectiveness modelling (2 deterministic approaches and 1 probabilistic approach).
- A small number of amendments made to the company base case.

4.11 The committee discussed the application of a composite outcome measure of cardiovascular death, myocardial infarction or stroke in the PEGASUS-TIMI 54 trial. The committee was persuaded that this was common practice in cardiovascular studies. It noted that the cost-effectiveness model was based on data for separate components of that composite outcome, for the intention-to-treat population in most cases, and used a competing risk approach. The committee considered whether the PEGASUS-TIMI 54 trial was underpowered for these data to be used. The committee was persuaded by the clinical and health economic experts that this method was acceptable given that the population was large; consequently, the numbers of patients upon which the secondary outcomes were based were likely to generate reasonable estimates. The ERG confirmed the company's assertion that using the intention-to-treat population to calculate the risk equations was likely to be 'conservative' and would, therefore, be unfavourable to ticagrelor. The committee accepted that the ICERs presented by the company were likely to be overestimates because the parameters applied to derive them were for

the intention-to-treat population and therefore likely to underestimate the effect of ticagrelor 60mg with aspirin treatment.

4.12 The company modelled 2 deterministic base-case scenarios: the first generated by passing patient's data through the model 1 at a time, and the second by passing an 'average' patient through the model multiple times. These produced differing ICERs (£20,098 and £24,070 respectively) because of non-linearity of variables. In order to generate a probabilistic sensitivity analysis, the company selected a 'representative' patient whose profile resulted in an ICER closest to the complete analysis. The committee criticised this approach, and the method used in the probabilistic sensitivity analysis in particular. The use of a 'representative' patient was justified by the company on the grounds that to use individual patient data would have required excessive computation. The committee considered a number of small amendments to the base case suggested by the ERG. It heard that limitations and simplifications in the model had generally acted to inflate the company ICERs. The ERG presented a number of alternative analyses which demonstrated that the ICER was relatively robust when these issues were addressed. Only 1 scenario resulted in an ICER above £30,000. This scenario was considered to be implausible because it held treatment efficacy constant while assuming that all patients who did not die or have a non-fatal event incurred 3-year treatment costs, whereas the actual time on treatment for patients in the study who did not experience death or non-fatal event was less than 3 years. Ultimately the committee concluded that although the model did not account for all uncertainties, further refinements were unlikely to alter its decision.

4.13 The committee recognised that all the cost-effectiveness evidence it had considered had assumed a maximum treatment length of 3 years. It understood that there was a possibility that some clinicians and patients may want to continue treatment indefinitely, but that the costs and clinical benefits of doing so had not been presented for its consideration. The

committee therefore concluded that any positive recommendation should only be for the length of time for which evidence had been presented, specifically 3 years.

4.14 The committee considered the most plausible ICER on which to base its decision. Although it would have preferred a probabilistic estimate, it recognised that on this occasion the individual patient approach could be used as a starting point for its discussion, alongside the probabilistic analyses presented by the ERG using average-patient characteristics (see section 4.16). Using this approach, the ICER for ticagrelor in combination with aspirin compared with aspirin alone was £20,636 per quality-adjusted life year (QALY) gained (incremental costs £1,432, incremental QALYs 0.069). The ERG's probabilistic ICER was £24,711. The committee understood that the ERG's average-patient method was likely to be unfavourable to ticagrelor because of non-linearities in the model. It also understood that attempting to address these uncertainties was unlikely to increase the ICER to such an extent that ticagrelor would not be cost effective (see section 4.12). The committee recognised that all the estimates were within a range usually considered a cost effective use of NHS resources (£20,000 to £30,000 per QALY gained), but considered that the evidence had only been presented to support a positive recommendation for ticagrelor 60 mg, in combination with aspirin, as a continuation therapy for preventing atherothrombotic events in people who have a history of myocardial infarction and a high risk of developing atherothrombotic events, if:

- they have had a myocardial infarction at least a year ago and have already taken ticagrelor 90 mg and aspirin for 1 year and
- ticagrelor 60 mg and aspirin is continued without interruption and
- treatment with ticagrelor 60 mg and aspirin is stopped when clinically indicated or after a maximum of 3 years.

Given these conditions, the committee concluded that ticagrelor 60 mg, in combination with aspirin, is recommended as an option as a continuation therapy for preventing atherothrombotic events in people at a high risk of developing such events,

**Pharmaceutical Price Regulation Scheme (PPRS) 2014**

4.15 The committee was aware of NICE’s position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion ‘that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines’. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

**Summary of appraisal committee’s key conclusions**

TA	Appraisal title: Ticagrelor for preventing atherothrombotic events after myocardial infarction	Section
<b>Key conclusion</b>		
Ticagrelor 60 mg, in combination with aspirin, is recommended as an option as a continuation therapy for preventing atherothrombotic events in people who have a history of myocardial infarction and a high risk of developing atherothrombotic events, only if <ul style="list-style-type: none"> <li>• they have had a myocardial infarction at least a year ago and have already taken ticagrelor 90 mg in combination with aspirin for 1 year and</li> <li>• ticagrelor 60 mg in combination with aspirin is continued without</li> </ul>		1.1





<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The clinical experts explained that most centres in England use ticagrelor 90 mg or prasugrel in combination with aspirin, as first-line management in myocardial infarction rather than the previous standard therapy of clopidogrel in combination with aspirin. Most centres also recommend 12-months' treatment with ticagrelor 90 mg or prasugrel after the myocardial infarction, in addition to long-term aspirin monotherapy.</p> <p>The committee was aware the morbidity burden for post myocardial infarction patients continues beyond 12 months following the initial myocardial infarction with approximately 1 in 5 patients who are event-free in the first year after an myocardial infarction going on to experience a myocardial infarction, stroke or cardiovascular death within the subsequent 3 years. There is an unmet clinical need for prevention therapy because few agents can be used beyond 12 months for patients with a history of myocardial infarction .</p>	<p>4.2, 4.3</p>
<p><b>The technology</b></p>		

<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The committee was aware that ticagrelor has potential advantages over clopidogrel in preventing atherothrombotic events after MI because of their faster antiplatelet action, although it is also associated with higher bleeding risk.</p> <p>There is an unmet clinical need for prevention therapy because few agents can be used beyond 12 months for patients with a history of myocardial infarction.</p>	<p>4.2, 4.3</p>
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<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>Ticagrelor 90 mg or prasugrel in combination with aspirin is used as first-line management in myocardial infarction rather than the previous standard therapy of clopidogrel in combination with aspirin. Most centres also recommend 12-months' treatment with ticagrelor 90 mg or prasugrel after the myocardial infarction, in addition to long-term aspirin monotherapy.</p> <p>Despite effective secondary prevention therapy for myocardial infarctions and other cardiovascular events such as stroke with the current available antiplatelet agents, there is still a high rate of recurrence of these events. The committee heard from the clinical experts that ticagrelor 60 mg in combination with aspirin would be used without interruption as a continuation therapy after the initial 1-year treatment with ticagrelor 90 mg in combination with aspirin.</p>	<p>4.2, 4.3</p>
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Adverse reactions	Ticagrelor is contraindicated in patients with active pathological bleeding, a history of intracranial haemorrhage, or moderate-to-severe hepatic impairment. The most commonly reported adverse effects include dyspnoea, epistaxis, gastrointestinal haemorrhage, subcutaneous or dermal bleeding, and bruising.	2
<b>Evidence for clinical effectiveness</b>		
Availability, nature and quality of evidence	The committee considered the results from a randomised controlled trial (PEGASUS-TIMI 54), which compared ticagrelor 60 mg and aspirin with placebo and aspirin. The committee noted that the company presented clinical-effectiveness results for the whole population who had ticagrelor 60 mg plus aspirin compared with placebo plus aspirin (ticagrelor 60 mg n= 7,045, placebo n=7,067) and on which the marketing authorisation for ticagrelor as a continuation therapy was based, and results of a prespecified subgroup analysis of patients who had a myocardial infarction 1 to 2 years previously (ticagrelor 60 mg n= 4,331, placebo n=4,333).	4.6

<p>Relevance to general clinical practice in the NHS</p>	<p>The committee noted that people enrolled in the PEGASUS-TIMI 54 could have had their previous treatment with an antiplatelet agent stopped anytime before being randomised to the treatment arms in the trial. In practice clinicians do not seek out people post-event to restart or redefine treatment durations. Most patients enrolled into the PEGASUS-TIMI 54 trial (84% in the 60 mg treatment arm and 84% in the placebo treatment arm) had clopidogrel as their previous treatment with an adenosine diphosphate (ADP) receptor inhibitor. Consequently the trial did not reflect current clinical practice because but in clinical practice most people would have ticagrelor or prasugrel. The clinical experts stated that in clinical practice, ticagrelor would only be offered as continuation therapy to people who have had ticagrelor for 1 year following a myocardial infarction.</p>	<p>4.3</p>
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<p>Uncertainties generated by the evidence</p>	<p>The committee noted that this prespecified subgroups (referred to as the ‘base-case’ and the ‘label’ population by the company) were used by the company in clinical and cost-effectiveness analyses. The committee acknowledged that PEGASUS-TIMI 54 was not statistically powered to detect a difference in outcomes in the company’s base-case population, but agreed that because of the size of the subgroups, and the baseline characteristics being sufficiently similar to the overall ticagrelor 60 mg group, it was appropriate for it to focus on this subgroup analysis in its decision-making regarding the clinical effectiveness of ticagrelor.</p>	<p>4.6</p>
<p>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</p>	<p>The committee was aware that the population in the company’s decision problem, and therefore the focus of the company’s submission, was adults who had a myocardial infarction between 1 and 2 years ago and who are at increased risk of atherothrombotic events (referred to by the company as its base case population). The committee concluded that it was appropriate for it to focus its decision making on this patient subgroup.</p>	<p>4.4</p>

<p>Estimate of the size of the clinical effectiveness including strength of supporting evidence</p>	<p>Data from PEGASUS-TIMI 54 demonstrated that ticagrelor 60 mg in combination with aspirin was effective in people who had a myocardial infarction less than 2 years previously. The committee also understood that ticagrelor 60 mg in combination with aspirin reduced the composite outcome of cardiovascular death, myocardial infarction and stroke relative to placebo in the overall study population relative to placebo (HR 0.84, 95% CI 0.74 to 0.95) and also in the subgroup with a history of myocardial infarction between 1 and 2 years ago (HR 0.77, 95% CI 0.66 to 0.90).</p>	<p>4.6, 4.7</p>
<p><b>Evidence for cost effectiveness</b></p>		
<p>Availability and nature of evidence</p>	<p>The committee considered cost-effectiveness modelling which compared ticagrelor 60 mg and aspirin with placebo and aspirin.</p>	<p>4.10</p>

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The committee discussed:</p> <ul style="list-style-type: none"> <li>• the use of 3 different approaches to cost effectiveness modelling evaluate the most plausible ICER (2 deterministic approaches and 1 probabilistic approach)</li> <li>• the application of a composite outcome measure of cardiovascular death, myocardial infarction or stroke in the PEGASUS-TIMI 54 trial.</li> </ul> <p>The committee concluded that although the model did not account for all uncertainties, further refinements were unlikely to alter its decision on cost effectiveness.</p>	<p>4.10- 4.12.</p>
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<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>No concerns were raised by the committee.</p>	<p>-</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The population in the company's cost-effectiveness analyses were for a subgroup of people who had a myocardial infarction less than 2 years previously. No further subgroups were considered by the committee.</p>	<p>4.4, 4.6, 4.10</p>
<p>What are the key drivers of cost effectiveness?</p>	<p>The use of 3 different approaches to cost effectiveness modelling (2 deterministic approaches and 1 probabilistic approach).</p>	<p>4.10</p>

<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>Although it would have preferred a probabilistic estimate, it recognised that on this occasion the individual patient approach could be used as a starting point for its discussion, alongside the probabilistic analyses presented by the ERG using average-patient characteristics (see section 4.16). Using this approach, the ICER for ticagrelor in combination with aspirin compared with aspirin alone was £20,636 per quality-adjusted life year (QALY) gained (incremental costs £1,432, incremental QALYs 0.069). The ERG's probabilistic ICER was £24,711.</p>	<p>4.14</p>
<p><b>Additional factors taken into account</b></p>		
<p>Patient access schemes (PPRS)</p>	<p>Not applicable</p>	
<p>End-of-life considerations</p>	<p>Not applicable</p>	

<p>Equalities considerations and social value judgements</p>	<p>A consultee commented that the PEGASUS-TIMI 54 trial excluded people with a previous stroke,gastrointestinal bleed or who needed anticoagulation therapy.The consultee further commented that this is not representative of practice and that if these people presented with a further ischaemic event they would still require treatment. The inclusion criteria of clinical trials cannot be addressed in a technology appraisal; however, the committee was aware that the ticagrelor summary of product characteristics advises caution if ticagrelor is clinically indicated in such circumstances.</p>	<p>SmPC section 4.4</p>
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## 5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 The Welsh Assembly Minister for Health and Social Services has issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 3 months of the guidance being published.

5.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a person has a history of myocardial infarction of at least a year and a high risk of developing atherothrombotic events, who has had an MI at least a year ago, and has already taken ticagrelor 90 mg and aspirin for 1 year without interruption and the doctor responsible for their care thinks that ticagrelor 60mg in combination with aspirin is the right treatment, it should be available for use, in line with NICE's recommendations.

## **6 Proposed date for review of guidance**

6.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Eugene Milne  
Chair, appraisal committee  
August 2016

## **7 Appraisal committee members and NICE project team**

### ***Appraisal committee members***

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C [https://www.nice.org.uk/get-](https://www.nice.org.uk/get-involved/meetings-in-public/technology-appraisal-committee/committee-c-members)

[involved/meetings-in-public/technology-appraisal-committee/committee-c-members](https://www.nice.org.uk/get-involved/meetings-in-public/technology-appraisal-committee/committee-c-members)

The technology appraisal committees are standing advisory committees of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

### ***NICE project team***

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

#### **Wendy Gidman**

Technical Lead

#### **Nicola Hay, Joanne Holden**

Technical Advisers

#### **Stephanie Yates**

Project Manager

ISBN: [to be added at publication]