Ticagrelor for preventing atherothrombotic events after myocardial infarction

Technology appraisal guidance
Published: 14 December 2016
nice.org.uk/guidance/ta420
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 **Recommendations**

1.1 Ticagrelor, in combination with aspirin, is recommended within its marketing authorisation as an option for preventing atherothrombotic events in adults who had a myocardial infarction and who are at high risk of a further event.

Treatment should be stopped when clinically indicated or at a maximum of 3 years.
## 2 The technology

<table>
<thead>
<tr>
<th>Description of the technology</th>
<th>Ticagrelor (Brilique, AstraZeneca) is an oral antagonist of the P2Y12 adenosine diphosphate receptor that inhibits platelet aggregation and thrombus formation in atherosclerotic disease.</th>
</tr>
</thead>
</table>
| Marketing authorisation       | Ticagrelor 60 mg twice daily, co-administered with aspirin (acetylsalicylic acid), has a marketing authorisation for ‘the prevention of atherothrombotic events in adult patients with a history of myocardial infarction of at least 1 year and a high risk of developing an atherothrombotic event’.  
The marketing authorisation for preventing atherothrombotic events in adults with a history of myocardial infarction and a high risk of an atherothrombotic event was granted in February 2016.  
NICE’s technology appraisal guidance on ticagrelor for the treatment of acute coronary syndromes covers ticagrelor 90 mg and aspirin for preventing atherothrombotic events. |
| Adverse reactions             | Ticagrelor is contraindicated in patients with active pathological bleeding, a history of intracranial haemorrhage, or 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. |
| Recommended dose and schedule | Ticagrelor 60 mg twice daily is the recommended dose when 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 (continuation therapy) after the initial 1-year treatment with ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in patients with acute coronary syndromes and with a high risk of an atherothrombotic event. Treatment can also be started up to 2 years from the myocardial infarction, or within 1 year after stopping previous ADP receptor inhibitor treatment.  
Unless contraindicated, ticagrelor should always be given with a daily low maintenance dose of aspirin 75 mg to 150 mg.  
There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment. |

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| **Price** | Ticagrelor costs £54.60 for a 56-tablet pack (28 days' supply). Costs may vary in different settings because of negotiated procurement discounts. |

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3 Evidence

The appraisal committee (section 6) considered evidence submitted by AstraZeneca and a review of this submission by the evidence review group. 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 extended therapy with ticagrelor 60 mg twice daily plus aspirin (hereafter referred to as ticagrelor), having considered evidence on the nature of preventing atherothrombotic events in people with a history of myocardial infarction and at high risk of atherothrombotic events, and the value placed on the benefits of ticagrelor 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 and patient experts that a history of a myocardial infarction causes considerable anxiety, particularly about having further myocardial infarctions or other cardiovascular events such as a stroke. People also have concerns about the risk of bleeding associated with antiplatelet therapy, particularly with extended treatment. 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 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 extended treatment should be taken into account when deciding whether to continue a person's antiplatelet treatment.

Clinical management

4.2 The committee understood that ticagrelor is a therapy to prevent further atherothrombotic events after treatment of the acute coronary syndrome has stopped. It therefore briefly discussed the clinical management of acute coronary syndromes. It was 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 clinical experts explained that practice varies across the NHS and although clopidogrel plus aspirin has been the most commonly used treatment for acute coronary syndromes, the use of newer therapies such as prasugrel and ticagrelor (each as dual antiplatelet therapy with aspirin) is increasing.
4.3 The committee considered how treatment with ticagrelor would fit into the clinical pathway for preventing a myocardial infarction. 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 occurring between 12 and 36 months before entry. Patients also had at least 1 additional risk factor for subsequent atherothrombotic events, listed in the summary of product characteristics as age 65 or over, diabetes mellitus needing medication, a second prior myocardial infarction, evidence of multivessel coronary artery disease, or chronic non-end-stage renal dysfunction. In the trial, treatment with a previous adenosine diphosphate (ADP) receptor could have been stopped any time before randomisation to the treatment arms. The committee was also aware that 84% of patients in each treatment arm received clopidogrel plus aspirin as their previous antiplatelet therapy and, therefore, had switched from clopidogrel (as their first-line therapy) to ticagrelor. The committee heard from clinical experts that switching between treatments occurs in clinical practice and is not as much of a concern as having a gap between treatments. The clinical experts clarified that when there is a gap in therapy, the risk of an atherothrombotic event increases, particularly in people at high risk. Therefore any gap in therapy should be minimised whenever possible. The committee considered whether ticagrelor would only be used as continuation therapy, but noted from consultation comments that this would not always be possible if, for example, a person had stopped their first-line therapy because of an adverse reaction within 1 year of their myocardial infarction (that is, before ticagrelor 60 mg is indicated). Based on comments from clinical experts and those received during consultation, the committee concluded that patients and clinicians would value ticagrelor either as continuation therapy after their first year of treatment, or when first-line dual antiplatelet therapy has been used but stopped for less than 1 year.

**Decision problem: population**

4.4 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 who are at increased risk of an atherothrombotic event (referred to by the company as its base-case population). The committee noted that the company had defined a narrower population than that 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 the narrower population was that the marketing authorisation focuses on those patients for whom the adverse effect profile was most favourable in PEGASUS-TIMI 54. The marketing authorisation allows ticagrelor to be started in patients 1 to 2 years after a myocardial infarction or within 1 year of stopping treatment with a previous antiplatelet therapy. Based on clinical practice in England, the company suggested that few patients would have stopped antiplatelet therapy within 1 year. However, the committee noted comments received during consultation that the full population covered by the marketing authorisation should be included in the committee’s discussions; that is, not only people who had a myocardial infarction 1 to 2 years ago, but also people who had a myocardial infarction more than 2 years ago and stopped taking antiplatelet therapy no more than 1 year ago. The committee considered that because this latter group is covered by the marketing authorisation, and given comments that ticagrelor would be valued as an option for these people, it should include this group. The committee further concluded that although there may be only a minority of patients in this position, it was not appropriate to exclude these people in decision-making.

**Decision problem: comparator**

4.5 The committee noted that the final scope specified clopidogrel plus aspirin and aspirin alone as comparators and that the company considered aspirin alone to be the appropriate comparator. The committee understood that the company did not consider clopidogrel plus aspirin to be an appropriate comparator because it does not 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 plus aspirin to be an appropriate comparator, it had considered doing an indirect comparison of ticagrelor with clopidogrel plus aspirin because there were no trials directly comparing the 2 treatments. But the company considered this inappropriate (as did the evidence review group; ERG) because of differences in the design of the trials and the patient populations included in the indirect comparison. The committee understood from the clinical experts that clopidogrel plus aspirin was commonly used as an initial antiplatelet agent for up to 12 months after a myocardial infarction. However it is not used in clinical practice when continued treatment is needed for patients with a history of
myocardial infarction and a high risk of an atherothrombotic event, that is, at the same point in the treatment pathway where the summary of product characteristics recommends ticagrelor (see section 4.3). The committee concluded that clopidogrel plus aspirin was not an appropriate comparator and that the most appropriate comparison for its decision-making was ticagrelor compared with aspirin alone.

**Clinical effectiveness**

**PEGASUS-TIMI 54**

4.6 The company presented clinical effectiveness results for the PEGASUS-TIMI 54 trial whole population who had ticagrelor compared with placebo (ticagrelor n=7,045, placebo n=7,067). The marketing authorisation for ticagrelor as an extended therapy was based on prespecified subgroup analyses. The committee noted that the company presented a prespecified subgroup analysis of patients who had a myocardial infarction 1 to 2 years previously (ticagrelor n=4,331, placebo n=4,333). The committee also noted that these results (referred to as the ‘base-case’ population by the company) tended to be more favourable to ticagrelor than the results from the overall ticagrelor 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 group, it was appropriate for it to focus on this subgroup analysis in its decision-making about the clinical effectiveness of ticagrelor.

4.7 The committee considered the effectiveness of ticagrelor compared with placebo in the subgroup of patients from PEGASUS-TIMI 54 who had a myocardial infarction between 1 and 2 years ago. The committee noted that ticagrelor reduced the risk of myocardial infarction, stroke or death from cardiovascular causes by 23% compared with placebo. The committee concluded that treatment with ticagrelor is clinically effective for people with a history of myocardial infarction and a high risk of an atherothrombotic event.

4.8 The committee heard contrasting views from the clinical and patient experts on the length of treatment with ticagrelor. Based on the progressive disease process that causes an atherothrombotic event, continued therapy may be
justified. However, the committee was persuaded 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 PEGASUS-TIMI 54 was 25.3 months, and that the ticagrelor marketing authorisation states that there are limited data on its efficacy and safety beyond 3 years of treatment with ticagrelor. The committee concluded that it could only consider a maximum duration of treatment of up to 3 years, in line with the evidence presented for ticagrelor.

Cost effectiveness

4.9 The committee considered the cost effectiveness of ticagrelor for preventing atherothrombotic events after myocardial infarction. It noted that the company's economic model was based on data for secondary efficacy outcomes in PEGASUS-TIMI 54, including first and subsequent events, hospitalisations, dyspnoea, bleeds, EQ-5D responses and treatment discontinuations. The committee considered whether PEGASUS-TIMI 54 was underpowered to analyse these data. It was persuaded by the clinical and health economic experts that using these outcomes was acceptable because the population was large, so the numbers of patients on whom the secondary outcomes were based were likely to generate reasonable estimates. In addition, the committee understood that the model used equations to calculate the risk of an event occurring and that the company had used the intention-to-treat population for calculating these. The ERG confirmed the company’s view that the risk equations were likely to be conservative and would, therefore, be unfavourable to ticagrelor. The committee concluded that the company's incremental cost-effectiveness ratios (ICERs) were likely to be overestimates because the parameters used to derive them were for the intention-to-treat population and therefore likely to underestimate the effect of ticagrelor.

4.10 The committee considered the most plausible ICER on which to base its decision. It considered the company’s deterministic base-case estimate of £20,636, which incorporated some minor amendments suggested by the ERG. It also considered the ERG’s exploratory preferred base case of £24,711, which incorporated small changes to parameters including the cost and disutility associated with gout, adjusted health care costs, uncertainty around NHS reference costs and disutility for major bleeds. The committee was further reassured that when the ERG conducted scenario analysis, only one scenario
resulted in an ICER above £30,000 per quality-adjusted life year (QALY) gained. 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 die or have a non-fatal event was less than 3 years. The committee concluded that all the estimates were within a range considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained) and that it could recommend treatment with ticagrelor in line with its marketing authorisation. The committee agreed that, although the ICERs presented did not include the people at high risk who had a myocardial infarction more than 2 years ago and whose antiplatelet therapy had been stopped less than 1 year ago, the recommendation should cover this group.

4.11 The committee recognised that all the cost-effectiveness evidence assumed a maximum treatment length of 3 years. It understood 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. The committee therefore concluded that the positive recommendation should only be for the length of time for which evidence had been presented, specifically 3 years.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.12 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

<table>
<thead>
<tr>
<th>TA420</th>
<th>Appraisal title: Ticagrelor for preventing atherothrombotic events after myocardial infarction</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key conclusion</td>
<td></td>
<td></td>
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</tbody>
</table>
Ticagrelor, in combination with aspirin, is recommended within its marketing authorisation as an option for preventing atherothrombotic events in adults who have had a myocardial infarction and who are at high risk of a further event. Treatment should be stopped when clinically indicated or at a maximum of 3 years.

### Current practice

<table>
<thead>
<tr>
<th>Clinical need of patients, including the availability of alternative treatments</th>
<th>The clinical experts explained that practice varies across the NHS. Although clopidogrel has been the most commonly used treatment for acute coronary syndromes, the use of newer therapies such as prasugrel and ticagrelor (each as dual antiplatelet therapy with aspirin) is increasing.</th>
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</table>

### The technology

<table>
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<tr>
<th>Proposed benefits of the technology</th>
<th>The committee was aware that ticagrelor has potential advantages over clopidogrel in preventing atherothrombotic events after myocardial infarction because of their faster antiplatelet action, although it is also associated with higher bleeding risk.</th>
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<tr>
<th>What is the position of the treatment in the pathway of care for the condition?</th>
<th>Ticagrelor would fit in the current treatment pathway either as continuation therapy after the first year of treatment, or when first-line dual antiplatelet therapy has been used but stopped for less than 1 year.</th>
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</thead>
<tbody>
<tr>
<td><strong>Adverse reactions</strong></td>
<td>Ticagrelor is contraindicated in patients with active pathological bleeding, a history of intracranial haemorrhage, or severe hepatic impairment. The most commonly reported adverse effects include dyspnoea, epistaxis, gastrointestinal haemorrhage, subcutaneous or dermal bleeding, and bruising.</td>
</tr>
<tr>
<td><strong>Evidence for clinical effectiveness</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Availability, nature and quality of evidence</strong></td>
<td>The company presented clinical effectiveness results for the PEGASUS-TIMI 54 trial whole population who had ticagrelor compared with placebo (ticagrelor n=7,045, placebo n=7,067) and a prespecified subgroup analysis of patients who had a myocardial infarction 1 to 2 years previously (ticagrelor n=4,331, placebo n=4,333). The marketing authorisation for ticagrelor was based on the prespecified subgroup analysis.</td>
</tr>
<tr>
<td><strong>Relevance to general clinical practice in the NHS</strong></td>
<td>In the trial, treatment with a previous antiplatelet agent could have been stopped any time before randomisation to the treatment arms and 84% of patients in each treatment arm received clopidogrel plus aspirin as their previous antiplatelet therapy and, therefore, had switched from clopidogrel (as their first-line therapy) to ticagrelor. The committee heard from clinical experts that switching between treatments occurs in clinical practice and is not as much of a concern as having a gap between treatments. The clinical experts clarified that when there is a gap in therapy, the risk of an atherothrombotic event increases, particularly in people at high risk. Therefore, the gap should be minimised whenever possible.</td>
</tr>
<tr>
<td><strong>Uncertainties generated by the evidence</strong></td>
<td>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 group, it was appropriate for it to focus on this subgroup analysis in its decision-making about the clinical effectiveness of ticagrelor.</td>
</tr>
</tbody>
</table>
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?

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.

Estimate of the size of the clinical effectiveness including strength of supporting evidence

Data from PEGASUS-TIMI 54 demonstrated that ticagrelor was effective in people with history of myocardial infarction between 1 and 2 years previously. The committee also understood that ticagrelor reduced the risk of myocardial infarction, stroke and death from cardiovascular causes by 23% compared with placebo.

### Evidence for cost effectiveness

<table>
<thead>
<tr>
<th>Availability and nature of evidence</th>
<th>The committee considered cost-effectiveness modelling, which compared ticagrelor with placebo.</th>
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</table>
| Uncertainties around and plausibility of assumptions and inputs in the economic model | The committee discussed:  
- the use of 3 different approaches to cost effectiveness modelling  
- evaluate the most plausible ICER (2 deterministic approaches and 1 probabilistic approach)  
- the application of a composite outcome measure of cardiovascular death, myocardial infarction or stroke in the PEGASUS-TIMI 54 trial.  

The committee concluded that although the model did not account for all uncertainties, further refinements were unlikely to alter its decision on cost effectiveness. |
| Incorporation of health-related quality-of-life benefits and utility values | The committee did not raise any concerns. | - |
| Are there specific groups of people for whom the technology is particularly cost effective? | Not applicable. | - |
| What are the key drivers of cost effectiveness? | The use of 3 different approaches to cost effectiveness modelling (2 deterministic approaches and 1 probabilistic approach). | 4.9 |
### Most likely cost-effectiveness estimate (given as an ICER)

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. Using this approach, the ICER for ticagrelor compared with placebo 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.

<table>
<thead>
<tr>
<th>Additional factors taken into account</th>
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<tr>
<td><strong>Patient access schemes (PPRS)</strong></td>
<td>Not applicable.</td>
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<tr>
<td><strong>End-of-life considerations</strong></td>
<td>Not applicable.</td>
</tr>
<tr>
<td><strong>Equalities considerations and social value judgements</strong></td>
<td>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 need 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.</td>
</tr>
</tbody>
</table>
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 and a high risk of an atherothrombotic event and the doctor responsible for their care thinks that ticagrelor 60 mg plus aspirin is the right treatment, it should be available for use, in line with NICE’s recommendations.
6 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.

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.

Irina Voicechoskovskaja
Technical lead

Nicola Hay, Joanne Holden
Technical advisers

Stephanie Yates
Project manager

Accreditation

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