Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

Single Technology Appraisal

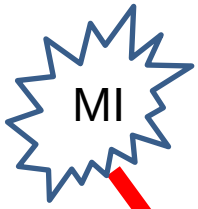
1st Appraisal Committee meeting: 13th July

2nd Appraisal Committee meeting: 14th September

Committee C

For public

Pathway



Exercise
Dietary Changes
STOP smoking

Aspirin (Clopidogrel if ASA CI)
Second Antiplatelet Agent – for 12 months
(Clopidogrel (TA210): Ticagrelor (TA236): Prasugrel (TA317)
Beta-Blocker
Statin

NICE CG
CG 172- MI-2ndry prevention
CG 167- Acute MI Mx
CG 94 - Angina/NSTEMI

Aspirin+Beta-Blocker+Statin

Ticagrelor – for up to three years

Ticagrelor

- Marketing authorisation: Co-administered with acetylsalicylic acid (ASA) for the prevention of atherothrombotic events in adult patients with acute coronary syndromes (ACS) **or a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event**
- SmPC states:
  - Ticagrelor 90 mg twice daily for 12 months for ACS unless discontinuation is clinically indicated
  - Ticagrelor 60 mg twice daily recommended when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event
  - Treatment can also be initiated up to 2 years from the MI, or within 1 year after stopping previous ADP receptor inhibitor treatment
  - Limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment
  - Risk factors for atherothrombosis described in PEGASUS-TIMI 54 as: age ≥ 65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel coronary artery disease, or chronic non-end-stage renal dysfunction

Ticagrelor (continuation)

- The remit of this appraisal and the focus of the company's submission is the use of ticagrelor for the prevention of atherothrombotic events in adults who have had a prior myocardial infarction and are at a high risk of developing atherothrombotic events (i.e. 60 mg twice daily dose of ticagrelor)

- TA 236 recommends ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with ACS

- Mode of administration: oral

NICE final scope and decision problem

	Final scope issued by NICE	Decision problem addressed in company submission	Decision problem same as NICE scope
Pop.	Adults who have had a myocardial infarction and are at increased risk of atherothrombotic events	Adults who have had a myocardial infarction between 1 and 2 years ago and are at increased risk of atherothrombotic events	×
Int.	Ticagrelor co-administered with aspirin	Ticagrelor co-administered with aspirin	✓
Com.	• Aspirin • Clopidogrel in combination with aspirin	Aspirin	×

NICE final scope and decision problem

	Final scope issued by NICE	Decision problem addressed in company submission	Decision problem same as NICE scope
Out.	• non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation • bleeding events • mortality • adverse effects of treatment • health-related quality of life	• non-fatal myocardial infarction (STEMI and NSTEMI) • non-fatal stroke • urgent coronary revascularisation • bleeding events • mortality • adverse effects of treatment • health-related quality of life	✓

Company's rationale for population in decision problem

- Marketing authorisation focusses on those patients for whom the benefit:harm profile most favourable in PEGASUS-TIMI 54
  - allows it to be used in MI ≤2 years or ≤12 months since last ADP inhibitor treatment (see slide 28)

- Very few patients in UK clinical practice who are beyond 2 years from MI but within 1 year of treatment with a previous ADP receptor inhibitor

- More relevant to focus solely on patients who experienced a MI <2 years ago

Company definition of populations

Term	Definition	Used
Full analysis (or study) population (n=21162)	All patients who were randomised to study drug were included irrespective of their protocol adherence and continued participation in the study. All patients had experienced an MI 1-3 years prior to study entry.	Clinical effectiveness
'label' population (n=10779)	Post-hoc subgroup of patients within PEGASUS-TIMI 54 who conform to the population defined in the marketing authorisation from EMA: i.e. experienced an MI <2 years previously or within 1 year of previous ADP inhibitor treatment	Cost effectiveness
base case (n=8664)	Patients within the PEGASUS-TIMI 54 study who experienced an MI <2 years previously. These patients are: pre-specified and stratified subgroup of the full analysis population and within the limits of the label population	Clinical effectiveness and cost effectiveness

Company: clinical Evidence
PEGASUS-TIMI 54

- Eligibility criteria
  - experienced MI 1-3 years before enrolment
  - at least 1 additional atherothrombosis risk factor
  - ADP receptor inhibitor therapy may have been stopped anytime before randomisation (84% had received clopidogrel)
- Randomised in 1:1:1 ratio to either ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily, placebo
- All receive 75 mg – 150 mg aspirin
- 33 month median follow-up
- Endpoints
  - Primary efficacy: Composite of CV death, MI or stroke
  - Safety endpoints: TIMI defined Major bleeding

PEGASUS-TIMI 54 full analysis set (ITT) - primary efficacy endpoint and individual components

Outcome	Ticagrelor 60 mg (n=7,045)	Placebo (n=7,067)	HR (95%, CI)	p value
Primary endpoint				
Composite of CV death, MI or stroke (%)	487 (6.9)	578 (8.2)	0.84 (0.74,0.95)	0.0043
Secondary endpoint				
CV death (%)	174 (2.5)	210 (3.0)	0.83 (0.68, 0.95)	0.0676
MI (%)	285 (4.0)	338 (4.8)	0.84 (0.72, 0.98)	0.0314
Stroke (%)	91 (1.3)	122 (1.7)	0.75 (0.68, 1.01)	0.0337

Source: Company's original submission Table 25

PEGASUS-TIMI 54 subgroup analysis (ITT) - Company's base case (MI<2 years ago) vs. MI> 2-3 years

	MI<2 years			MI>2-3 years		
	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo
	(n=4,331)	(n=4,333)	HR (95% CI)	n=NR*	n=NR	HR (95% CI) (n=5,428)
	Patients with events n (%)			Patients with events n (%)		
Primary endpoint						
Composite endpoint	NR	NR	0.77 (0.66, 0.90)	NR	NR	0.96 (0.79, 1.17)
Secondary endpoint						
CV death	XX (X.X)	XXX (X.X)	X.XX (X.XX, X.XX)	NR	NR	X.XX (X.XX, X.XX)
MI	XXX (X.X)	XXX (X.X)	X.XX (X.XX, X.XX)	NR	NR	X.XX (X.XX, X.XX)
Stroke	XX (X.X)	XX (X.X)	X.XX (X.XX, X.XX)	NR	NR	X.XX (X.XX, X.XX)

*NR = not reported

Company: PEGASUS-TIMI 54 bleeding events (ITT): full analysis set vs. Company's base case (MI<2 years)

	Full analysis set			MI< 2 years		
	Ticagrelor 60 mg, n=7,045	Placebo n=7,067	Ticagrelor vs. placebo	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo
	Patients with events n (%)		HR (95% CI)	Patients with events n (%)		HR (95% CI)
TIMI Major	138 (2.0)	78 (1.1)	1.78 (1.35, 2.35)	82 (1.9)	55 (1.3)	1.50 (1.06, 2.11)
Fatal	13 (0.2)	15 (0.2)	0.87 (0.41,1.82)	10 (0.2)	10 (0.2)	1.00 (0.42, 2.40)
IH	35 (0.5)	33 (0.5)	1.06 (0.66,1.71)	20 (0.5)	22 (0.5)	0.91 (0.50, 1.67)
Other Major	98 (1.4)	39 (0.6)	2.53 (1.74, 3.66)	59 (1.4)	27 (0.6)	2.19 (1.39, 3.46)
TIMI Major/Minor	201 (2.9)	106 (1.5)	1.91 (1.51, 2.42)	129 (3.0)	75 (1.7)	1.73 (1.30, 2.30)

Company's economic modelling

- The modelled population corresponds to the "MI < 2 years" subgroup of PEGASUS-TIMI 54, although most parameters use ITT values and some label population
- Model compares ticagrelor 60mg twice daily + 75mg aspirin (£178.06 per cycle) to 75mg aspirin (£2.64 per cycle). No evaluation with clopidogrel plus aspirin
- The company used 2 modelling approaches for the deterministic analyses
  - **Individual patient** modelling (using 8664 of the10,779 'label population' patients. Those without an MI <2 years were excluded)
  - '**Average patient**' analysis (selecting the average parameter values from the 8664 patients)
- For PSA, a single **representative patient** with an ICER closest to the mean ICER from the individual patient model was selected

Company's base case results (original submission)

Treatment	Total values		Incremental values		ICER (£)
	Costs (£)	QALYs	Cost (£)	QALYs	
Deterministic results: People with MI< 2 years (n=8664) – Base case					
ASA	13,019	9.203			
T+ ASA	14,443	12.336	1434	0.071	20,098
Deterministic results: 'Average Patient' analysis					
ASA					
T + ASA			1425	0.059	24,070
Probabilistic results: One representative patient whose ICER was 19,436					
ASA					
T + ASA			1289	0.067	19,275

- The 'average patient' analysis has a greater ICER than that associated with MI<2 years. The company claim this is due to non-linearities within the model.
- Some doubt if representative patient is the one with the ICER closest to £20,098

Source: ERG report p126 and p132

Company's cost effectiveness results
revised model (clarification stage)

Treatment	Total values		Incremental values		ICER (£)
	Costs (£)	QALYs	Cost (£)	QALYs	
Deterministic results – Base case (8664 patients)					
ASA	13,086	9.195			
T + ASA	14,518	9.264	1432	0.069	20,636

Source: ERG report p129

ERG's exploratory base case using the average patient (probabilistic results)

Treatment	Total values		Incremental values		ICER (£)
	Costs (£)	QALYs	Cost (£)	QALYs	
Probabilistic results: 'Average Patient'					
ASA	12,674	9.709			
T + ASA	14,113	9.768	1439	0.058	24,711

Source: ERG report p142

ACD: preliminary recommendations

- 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

ACD: Treatment pathway considerations

- Used without interruption as a continuation therapy after the initial 1-year treatment with dual antiplatelet therapy:
  - clinicians would not restart dual antiplatelet therapy unless people present with another MI. The decision for standard or extended treatment length would be made while the patient was an inpatient in hospital for their MI
- Used as a continuation therapy following ticagrelor 90 mg:
  - in clinical practice clinicians would not switch a person's treatment from a different antiplatelet agent such as clopidogrel or prasugrel because of the different mechanisms of action of the treatments and their different adverse effect profiles

ACD: Clinical effectiveness considerations

- Appropriate for committee to focus on the patient group who had a MI **between 1 and 2 years** ago and who are at increased risk of atherothrombotic events i.e. the company's 'base case' population:
  - Marketing authorisation allows ticagrelor 60 mg to be started in patients who are *beyond 2 years* from a myocardial infarction *but within 1 year of treatment with a previous antiplatelet agent.* Company is of the opinion that there are very few such patients. Therefore it has focussed its submission on patients who experienced a myocardial infarction less than 2 years ago
  - Clinical experts: when clinicians are considering prolonged antiplatelet therapy in patients with a high risk of atherothrombotic events, ticagrelor 60 mg twice daily 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

ACD: Clinical effectiveness considerations (continuation)

- The committee concluded that although there was uncertainty because of the small number of events, extended ticagrelor 60 mg with aspirin was clinically effective for people with a history of myocardial infarction and a high risk of developing an atherothrombotic event.
  - The committee noted that ticagrelor 60 mg in combination with aspirin reduced the composite risk of myocardial infarction, stroke and death from cardiovascular caused by 23% compared with aspirin plus placebo

ACD: Cost effectiveness considerations

- 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.
- The use of 3 different approaches to cost effectiveness modelling (2 deterministic approaches and 1 probabilistic approach) – is the key cost-effectiveness driver.
- Although the committee would have preferred a probabilistic estimate, it recognised that on this occasion the individual patient approach could be used as a starting point for discussion, alongside the probabilistic analyses presented by the ERG using average-patient characteristics.
- Using this approach, the ICER for ticagrelor in combination with aspirin compared with aspirin alone was £20,636/QALY gained. The ERG's probabilistic ICER was £24,711.

Consultation comments

- Comments received from:
  - Consultees:
    - Company: AstraZeneca
    - Professional organisation: British Society of Cardiology (BSC)
  - Web Comments x 1

Comments on ACD: AstraZeneca

- Overall supportive of the recommendation
- The recommendation should include a definition of 'high risk' of developing atherothrombotic events. Company proposes the following based on the CV risk used in PEGASUS-TIMI 54:

  'the presence of at least 1 of the following 5 risk factors:

  - Age ≥65 years or
  - Diabetes mellitus requiring medication or
  - A 2nd prior MI or
  - Evidence of multivessel coronary artery disease or
  - Chronic non-end stage renal dysfunction (creatinine clearance <60ml/min)'
- Use of the term 'continuation therapy' may be ambiguous in clinical practice

Comments on ACD: AstraZeneca
(continued)

- The final bullet point in the recommendation should be amended to clarify that the maximum treatment duration of 3 years applies to ticagrelor 60 mg twice daily only and not to low-dose aspirin

- Highlighted typographical errors in the ACD

Comments on ACD: Web comment

- The wording in the recommendation ‘ticagrelor 60 mg in combination with aspirin is continued without interruption’ should be amended to clarify whether patients who had a MI more than 1 year ago, but less than 3 years, who have had their ticagrelor 90 mg stopped should be re-started on ticagrelor 60 mg

Comments on ACD: BSC
Subgroup analysis vs. whole population analysis

- Based on PEGASUS-TIMI 54, ticagrelor 60 mg may be of potential clinical benefit to patients who have had a prior myocardial infarction and who are at increased risk of further cardiovascular events
- The statistical grounds for the group on which the committee decided to base its decision on (subgroup of patients who had a MI<2 years and at increased risk of atherothrombotic events rather than whole trial population) are not clear
  - Supplementary figures in the on-line appendix to the PEGASUS-TIMI 54 publication in the NEJM showed no significant interaction between:
    - Time from MI and primary efficacy endpoint (P=0.09)
    - Time from MI and the rates of TIMI major bleeding (P=0.23)
  - This subgroup is selective (results favour ticagrelor) and may overestimate the clinical efficacy and underestimate the side effects of ticagrelor. This would have contributed to a more favourable cost effectiveness estimate

Comments on ACD: BSC (continued)
Wording of recommendation

- The following should be specified in the recommendation:
  - Timing of initiation of ticagrelor i.e. between 1 or 2 years from MI
  - Dosing regimen is 60mg **twice daily**
  - Definition of high risk patients
  - Exclusion from ticagrelor use for people who are at high risk of bleeding
- Inappropriate restriction of ticagrelor to patients who received ticagrelor in the first 12 months after MI:
  - No clinical reason to exclude patients who have been treated with a different ADP antagonist in the 1st year after MI
  - Switching anti-platelet agents is not complicated; quiet common not least because ticagrelor is often poorly tolerated in the first year post MI
  - 84% of patients in PEGASUS-TIMI 54 received antiplatelet other than ticagrelor
  - Draft recommendation not consistent with the trial evidence and makes little clinical sense

PEGASUS-TIMI 54 primary efficacy and safety endpoints: full analysis set, subgroups by time since MI and by time from ADP inhibitor withdrawal

	Composite primary efficacy endpoint: CV death, MI or stroke (ITT analysis)		Primary safety endpoint: TIMI major bleeding (on treatment [OT] analysis)	
	HR (95% CI)	P value	HR (95% CI)	P value
PEGASUS-TIMI54 full analysis set	0.84 (0.74-0.95)	0.0043	2.32 (1.68-3.21)	<0.001
Subgroups within the marketing authorisation				
MI <2 years ago (company's base case)	0.77 (0.66-0.90)	0.001	2.05 (1.38-3.03)	0.0004
<30 days since ADP inhibitor withdrawal	0.76 (0.62-0.93)	0.0075	3.37 (1.85-6.16)	<0.0001
30 days – 1 year since ADP inhibitor withdrawal	0.81 (0.65-1.01)	0.0584	2.92 (1.65-5.19)	0.0003
Subgroups outside the marketing authorisation				
MI ≥2 years ago	0.96 (0.79-1.17)	0.6945	3.17 (1.76-5.70)	0.0001
>1 year since ADP inhibitor withdrawal	1.08 (0.82-1.42)	0.5726	2.12 (1.05-4.25)	0.0355

Source: Adapted from company submission p. 22, table 3

Key issues

- Is it appropriate to base the recommendation on the subgroup of patients who had a MI<2 years and at increased risk of atherothrombotic events rather than the whole trial population?
- Should the wording of the recommendation be amended?
  - Include:
    - Timing of initiation of ticagrelor i.e. between 1 or 2 years from MI
    - Definition of ‘high risk’ patients
    - Exclusion from ticagrelor use for people who are at high risk of bleeds
  - Remove restriction to patients who received ticagrelor in the first 12 months
- How should ‘high risk’ patients be defined?
- Would clinicians only consider extended treatment with ticagrelor 60 mg twice daily to those people who had ticagrelor 90 mg twice daily for their MI?