Lead team presentation for public observer

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

1st Appraisal Committee meeting: 13th July

Background and Clinical Effectiveness

Lead team: Nigel Langford, David Chandler

ERG: Kleijnen Systematic Reviews

Background

- 2012/13-141,000 IP episodes for myocardial infarction

- Post-MI patients remain at risk of further event

Pathway

Exercise
Dietary Changes
STOP smoking

Aspirin (Clopidogrel if ASA CI)
Second Antiplatelet Agent-for 12 months
(Clopidogrel (210): Ticagrelor (236): Prasugrel (317)
Beta-Blocker
Statin

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

Aspirin+Beta-Blocker+Statin

Ticagrelor – for up to three years

Post-MI Prognosis

- Clot-bound thrombin remains activated and causes progression of the thrombus
- This process can persist beyond the acute phase and can occur in patients up to 6 months following unstable angina or a MI
- Following an MI there is a risk of recurrent atherothrombotic events with risk remaining high for over a year
- Main risk factors for recurrent atherothrombotic events include; diabetes mellitus, recurrent MI, multi-vessel coronary artery disease, chronic non-end stage renal disease and older age

NICE Technology Appraisals

- **TA 335** 'Rivaroxaban for the prevention of adverse outcomes in patients after the acute management of acute coronary syndrome' (2015). Review Proposal Date Feb 2018.
- **TA 317** 'Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes (review of technology appraisal guidance 182)' (2014). Review Proposal Date June 2017.
- **TA 236** 'Ticagrelor for the treatment of acute coronary syndromes' (2011). Guidance has been incorporated into Clinical Guideline 167 and Clinical Guideline 172.
- **TA 210** 'Clopidogrel and modified-release dipyridamole for the prevention of occlusive vascular events (review of technology appraisal guidance 90) (2010). On static list.

NICE Guidelines

- NICE clinical guidelines
  - CG 172 ‘Secondary prevention in primary and secondary care for patients following a myocardial infarction (2013).
  - CG 167 ‘Myocardial infarction with ST-segment elevation: The acute management of myocardial infarction with ST-segment elevation (2013).
  - CG 95 ‘Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin (2010).
  - CG 94 ‘Unstable angina and NSTEMI: the early management of unstable angina and non-ST-segment-elevation myocardial infarction (2010).
- Public Health Guidelines
  - PHG 25 ‘Prevention of cardiovascular disease (2010). Review date December 2015.

Relevant NICE guidance

- NICE clinical guideline 236 ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes.
- NICE clinical guideline 172 clopidogrel is recommended as a treatment option instead of aspirin in patients who have other cardiovascular disease and have either: had a myocardial infarction and stopped dual antiplatelet therapy, or had a myocardial infarction more than 12 months ago.

Ticagrelor (1)

- 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 recommends:
  - Ticagrelor 90 mg 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

Ticagrelor (2)

- TA 236 recommends ticagrelor in combination with low-dose aspirin for up to 12 months as a treatment option in adults with ACS
- The remit of this appraisal and therefore 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)
- Mode of administration: oral

Impact on patients and carers (1)
Life after myocardial infarction

- The shock can be profound
- Often having to re-evaluate their whole life
- Some find it difficult adjusting to lifestyle changes
- General emotions following MI can include
  - sadness, worried, stressed, angry, lonely or guilty
- Often not taken seriously by other people
- Some people no longer enjoy the things they used to
  - worry about further attacks
  - returning to work
  - driving
  - living a normal life

Source: NHS Choices and British Heart Foundation

Impact on patients and carers (2)
Treatments

Important to patients

- Easy to take (prefer tablets)
- Do not have any adverse events
- No negative impact on quality of life
- Works at reducing risk

View of ticagrelor

- Taken twice a day
- Increased risk of bleeding
  - *“If the patient is aware... it does have psychological effect and may effect the patient and carer’s quality of life”**

**Pumping Marvellous Organisation’s submission*

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 clinical Evidence: PEGASUS-TIMI 54

- 21,162 patients treated 1-3 years post MI
- 1:1:1 randomised to:
  - ticagrelor 90 mg
  - ticagrelor 60mg
  - placebo
- All patients have 75 mg aspirin
- 33 month median follow-up
- Primary end-point: composite of cardiovascular death, myocardial infarction or stroke
- Secondary endpoints include: event rate of CV death, all-cause mortality, composite of CV death, non-fatal MI, non-fatal stroke or urgent coronary revascularisation
- Safety endpoints include: Thrombolysis in myocardial infarction (TIMI) Major bleeding event, TIMI Major or Minor bleeding, discontinuation of study drug due to any bleeding event

Company definition of populations

Term	Definition	Use
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 license 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

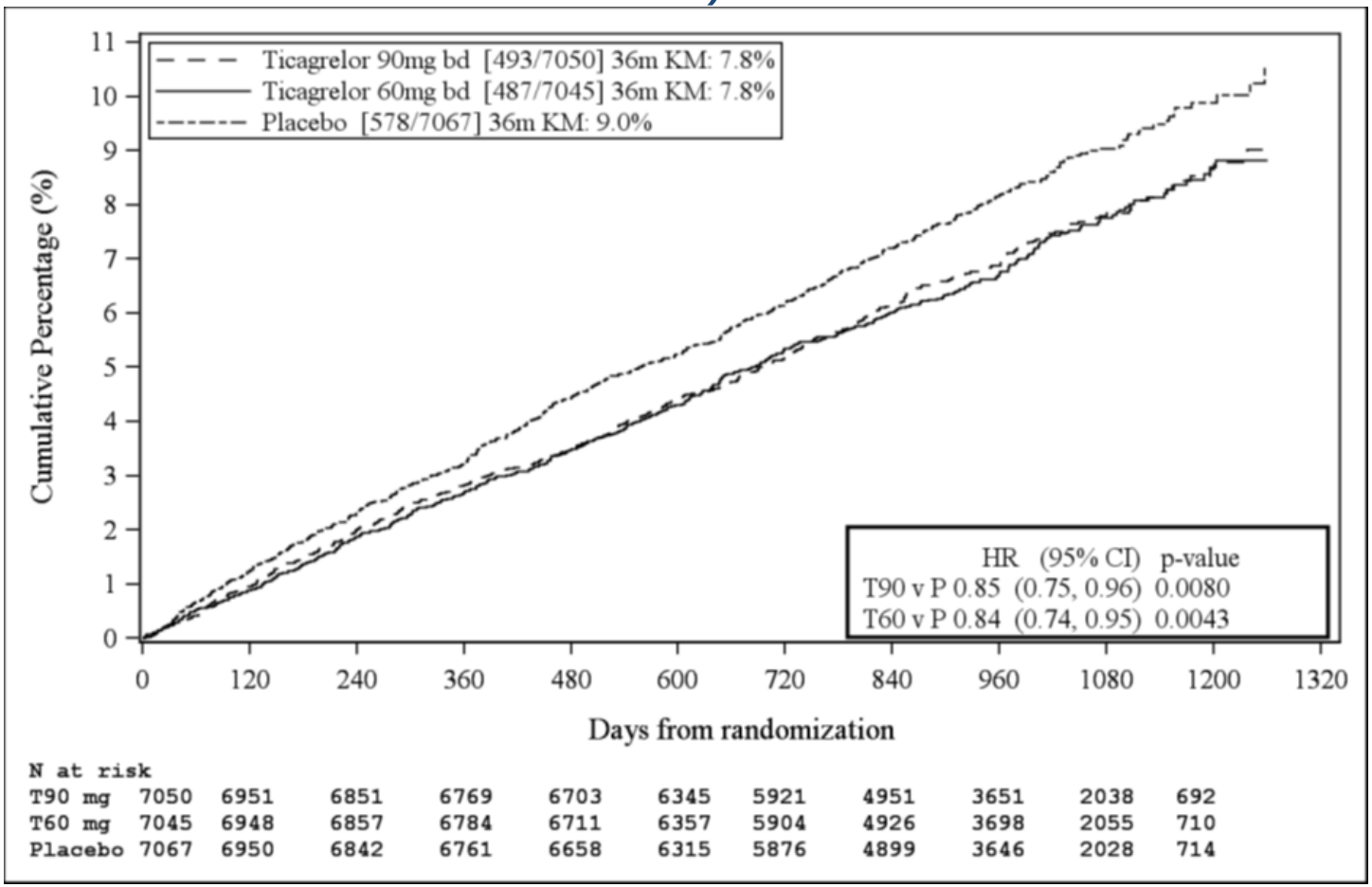
Company patient Base-line characteristics

Baseline characteristic	Study population		Company's Base Case population: MI < 2 years	
	Ticagrelor 60 mg (n=7,045)	Placebo (n=7,067)	Ticagrelor 60 mg (n=4331)	Placebo (n=4333)
Age – years (±SD)	65.2 ± 6.4	65.4 ± 8.3	65.2 ± 8.5	65.4 ± 8.3
Weight – kg (±SD)	82.0 ± 17.0	81.8 ± 16.6	82 ± 16.9	81.4 ± 16.5
Hypertension – n (%)	5,461 (77.5%)	5,484 (77.6%)	3354 (77.4%)	3346 (77.2%)
Hypercholesterolemia – n (%)	5,380 (76.4%)	5,451 (77.1%)	3265 (75.4%)	3332 (76.9%)
DM – n (%)	2,308 (32.8%)	2,257 (31.9%)	1419 (32.8%)	1322 (30.5%)
Multi-vessel CAD – n/total n (%)	4,190 (59.5%)	4,213 (59.6%)	2601 (60.1%)	2586 (59.7%)
History of PCI – n/total n (%)	5,879 (83.5%)	5,837 (82.6%)	3638 (84.0%)	3623 (83.6%)
>1 prior MI – n (%)	1,168 (16.6%)	1,188 (16.8%)	709 (16.4%)	699 (16.1%)
Median years since MI (IQR)	1.7 (1.2-2.3)	1.7 (1.2-2.3)	16 (3-24)	16 (2-24)
STEMI	3,757 (53.4%)	3,809 (54.0%)	2309 (53.3%)	2370 (54.7%)
NSTEMI	2,842 (40.4%)	2,843 (40.3%)	1770 (40.9%)	1759 (40.6%)
Unknown type	436 (6.2%)	405 (5.7%)	252 (5.8%)	204 (4.7%)

Company 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, 1.01)	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 (0.57, 0.98)	0.0337
Source: Company submission Table 25				

Company Kaplan-Meier rates of CV death, MI and stroke over three years, according to study group (full analysis set)

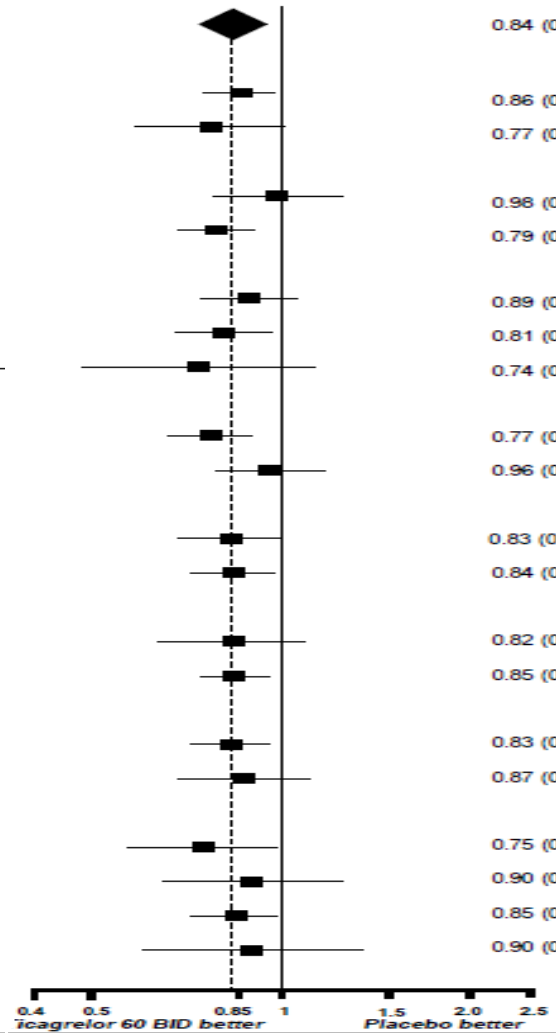


Abbreviations: CI confidence interval; HR hazard ratio; KM: Kaplan Meier; m month; P placebo; Ticagrelor
Source: company submission Figure 8

Company primary efficacy endpoint across subgroups

Supplemental Figure S2

Subgroup	Patients	Ticagrelor 60 mg 3 Year KM (%)	Placebo 3 Year KM (%)	HR (95% CI) Ticagrelor 60 mg BID vs Placebo	Interaction P-value
All Patients	21,162	7.77	9.04	0.84 (0.74 - 0.95)	
Age at Randomization					0.50
Age < 75	18,079	7.23	8.27	0.86 (0.75 - 0.98)	
Age ≥ 75	3,083	11.02	13.50	0.77 (0.59 - 1.01)	
Sex					0.12
Female	5,060	9.03	9.15	0.98 (0.78 - 1.24)	
Male	16,102	7.37	8.99	0.79 (0.69 - 0.91)	
Qualifying Myocardial Infarction					0.67
NSTEMI	8,583	9.32	10.14	0.89 (0.74 - 1.06)	
STEMI	11,329	6.43	7.83	0.81 (0.68 - 0.97)	
Unknown	1,223	9.46	12.34	0.74 (0.48 - 1.13)	
Time from Qualifying Myocardial Infarction					0.09
< 2 years	12,980	7.79	9.74	0.77 (0.66 - 0.90)	
≥ 2 years	8,155	7.76	7.94	0.96 (0.79 - 1.17)	
History of Diabetes					0.96
Diabetes	6,806	10.00	11.60	0.83 (0.69 – 1.00)	
No Diabetes	14,355	6.68	7.83	0.84 (0.72 - 0.98)	
Aspirin Dose					0.80
≤ 75 mg	4,182	7.73	9.23	0.82 (0.63 - 1.07)	
> 75 mg	16,950	7.79	8.93	0.85 (0.74 - 0.97)	
History of PCI					0.72
Prior PCI	17,568	6.87	8.09	0.83 (0.72 - 0.96)	
No Prior PCI	3,591	12.06	13.44	0.87 (0.69 - 1.11)	
Region					0.83
North America	3,907	7.79	9.77	0.75 (0.57 - 0.99)	
South America	2,458	9.94	9.75	0.90 (0.65 - 1.24)	
Europe	12,428	7.54	8.96	0.85 (0.72 - 0.99)	
Asia	2,369	7.11	6.86	0.90 (0.60 - 1.34)	



Source: Figure 17 company submission (modified from Bonaca et al 2015)

Company 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	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]
MI	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]
Stroke	[redacted]	[redacted]	[redacted]	NR	NR	[redacted]
Source : Based on Table 4.11 ERG report						

Company - subgroup analysis (ITT): Company's base case (MI<2 years ago) with and without diabetes

	Diabetes			**Without diabetes**		
	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo
	n=1419	n=1322	HR (95% CI)	n=2912	n=3011	HR (95% CI)
	Patients with events n (%)			Patients with events n (%)		
Primary endpoint						
Composite endpoint	128 (9.0)	144 (10.9)	0.82 (0.64, 1.04)	165 (5.7)	231 (7.7)	0.73 (0.60, 0.89)
Secondary endpoint						
CV death	47 (3.3)	64 (4.8)	0.68 (0.47, 0.99)	47 (1.6)	73 (2.4)	0.66 (0.46, 0.96)
MI	79 (5.6)	76 (5.7)	0.96 (0.70, 1.32)	101 (3.5)	145 (4.8)	0.72 (0.55, 0.92)
Stroke	21 (1.5)	33 (2.5)	0.59 (0.34, 1.02)	36 (1.2)	46 (1.5)	0.81 (0.52, 1.25)
Source : Table 35 of company submission						

Company subgroup analysis (ITT): Company's base case (MI<2 years ago) with and without a history of PCI

	With history of PCI			Without history of PCI		
	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo
	n=3638	n=3623	HR (95% CI)	n=692	n=709	HR (95% CI)
	Patients with events n (%)			Patients with events n (%)		
Primary endpoint						
Composite endpoint	218 (6.0)	277 (7.6)	0.78 (0.65, 0.93)	75 (10.8)	98 (13.8)	0.76 (0.56, 1.02)
Secondary endpoint						
CV death	51 (1.4)	81 (2.2)	0.63 (0.44, 0.89)	43 (6.2)	56 (7.9)	0.77 (0.52, 1.14)
MI	148 (4.1)	182 (5.0)	0.81 (0.65, 1.00)	32 (4.6)	39 (5.5)	0.82 (0.51, 1.31)
Stroke	44 (1.2)	54 (1.5)	0.81 (0.55, 1.21)	13 (1.9)	25 (3.5)	0.51 (0.26, 1.00)
Source : Table 36 of company submission						

Company adverse events: full analysis set

Adverse Event (AE)	Ticagrelor 60 mg	Placebo
	n (%)	n (%)
On treatment patient population	**(n=6,958)**	**(n=6,996)**
Any AE (serious and non-serious)	5,311 (76.3)	4,899 (70.0)
Leading to discontinuation of study drug	1,139 (16.4)	621 (8.9)
Most common AEs leading to discontinuation		
• Bleeding	354 (5.1)	86 (1.2)
• Dyspnoea	297 (4.3)	51 (0.7)
• Arrhythmia	103 (1.5)	96 (1.4)
Any serious AE	1,650 (23.7)	1,676 (24.0)
Leading to discontinuation of study drug	273 (3.9)	231 (3.3)
ITT population	**(n=7,045)**	**(n=7,067)**
All-cause mortality	299 (4.2)	336 (4.8)
Source Table 45 company submission		

Company safety endpoints as 3 Year Kaplan-Meier estimates – ITT analysis

	Full analysis set			MI< 2 years		
	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo
	n=7,045	n=7,067	HR (95% CI)	n=4,331	n=4,333	HR (95% CI)
	Patients with events n (%)			Patients with events n (%)		
Dyspnoea	1,019 (14.5%)	418 (5.9%)	2.60 (2.32, 2.91)	593 (13.7%)	259 (6.0%)	2.41 (2.09, 2.79)
Event leading to study drug discont.	297 (4.2%)	51 (0.7%)	5.95 (4.42, 8.01)	176 (4.1%)	29 (0.7%)	6.18 (4.17, 9.15)
Serious AE	27 (0.4%)	13 (0.2%)	2.08 (1.07, 4.02)	19 (0.4%)	7 (0.2%)	2.71 (1.14, 6.46)
Gout	114 (1.6%)	86 (1.2%)	1.33 (1.01, 1.76)	67 (1.5%)	54 (1.2)	1.24 (0.87, 1.78)

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

	Full analysis set			MI< 2 years		
	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo	Ticagrelor 60 mg	placebo	Ticagrelor vs. placebo
	n=7,045	n=7,067	HR (95% CI)	n=4,331	n=4,333	HR (95% CI)
	Patients with events n (%)			Patients with events n (%)		
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 or 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)

Summary of effectiveness issues

- After an MI there is an increased risk of another event due to underlying disease.
- Ticagrelor has a rapid onset of anti-platelet effect, low variability and reversibility that results in a faster onset of action compared with thienopyridines as well as a faster offset of action with more rapid recovery of platelet function.
- Ticagrelor with Aspirin is an option currently recommended for secondary prevention 12 months after an MI.
- The company focussed its clinical effectiveness submission on ticagrelor 60 mg in the population who had experienced a prior MI between 1 and 2 years ago who also had 1 or more additional atherothrombotic risk factors based on a post hoc subgroup analysis of PEGASUS-TIMI 54 on the basis of a composite endpoint of CV death/MI/stroke. (8665/21,162, 41% of the total trial population). The study was not powered for this subgroup analysis.
- The UK clinical pharmacy association question how generalisable the company results are to clinical practice in England.
- The External Review Group commented that NICE clinical guideline 172 recommendation indicates that clopidogrel may be used beyond 12 months post-myocardial infarction in some circumstances.
- However it was not possible to compare the clinical effectiveness of ticagrelor with clopidogrel with existing evidence.

Evidence Review Group's critique (1)

- The study population may not be generalisable to the usual post MI population.
  - The study differs from routine practice so implementation may be problematic because :
    - anticoagulant treatment is not restarted or initiated a year post-event.
    - Patients at high risk of atherothrombotic events are not selected out from the post MI population.

Evidence Review Group's critique (2)

- The primary outcome in PEGASUS-TIMI 54 was time to first occurrence after randomisation of any event from the composite of cardiovascular (CV) death, MI or stroke. The company presented results for the individual components of the composite primary outcome. This analysis may be underpowered.

- Results from PEGASUS-TIMI 54 were based on small numbers of events for each outcome and should therefore be interpreted with a degree of caution.

Key issues for consideration

KEY CLINICAL ISSUES	
Generalisability	How generalisable are the results from PEGASUS-TIMI to UK clinical practice?
Comparators	The comparators listed in the final scope issued by NICE were aspirin monotherapy or clopidogrel in combination with aspirin. The company submission only included aspirin monotherapy as a comparator. Should clopidogrel in combination with aspirin be included as a comparator?
Analysis	The company presented data from post hoc analyses of subgroups of subpopulations. How robust is the data?

Lead team presentation – for public observer

Ticagrelor for secondary prevention of atherothrombotic events after myocardial infarction

1st Appraisal Committee meeting

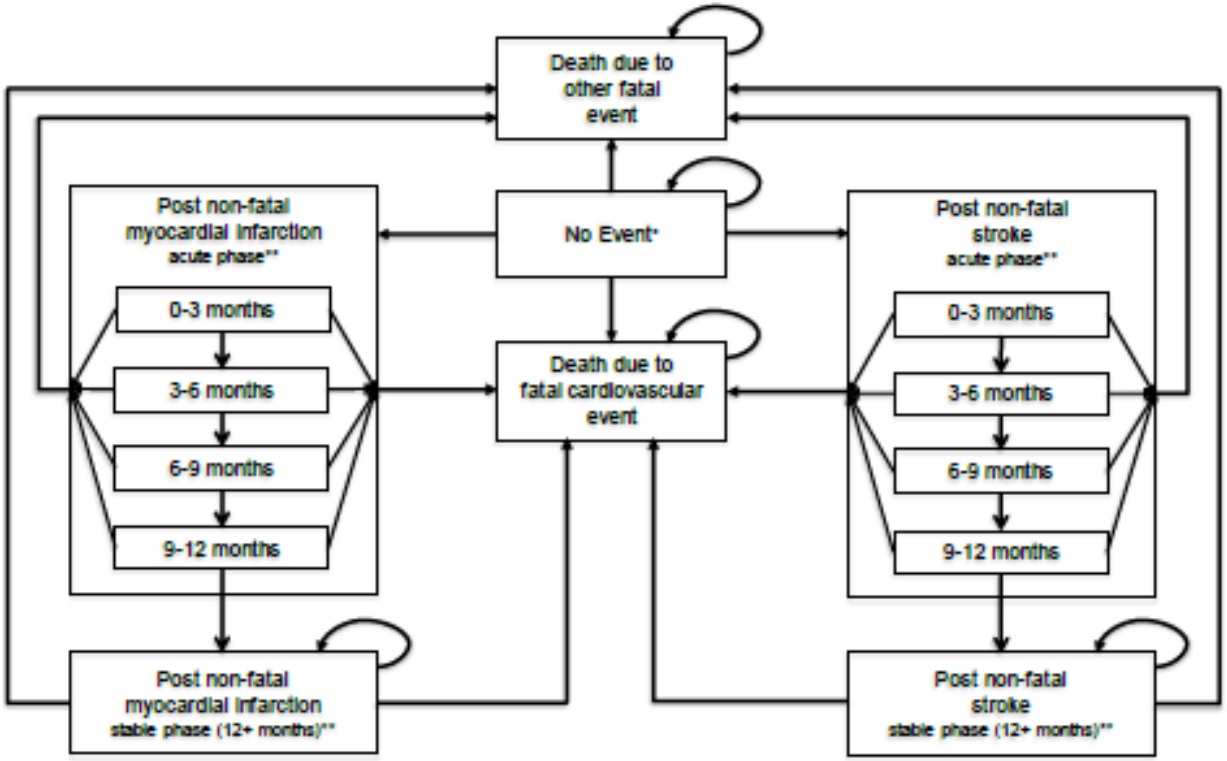
Cost Effectiveness

Lead team: Matt Stevenson

ERG: Kleijnen Systematic Reviews

13th July 2016

Model Structure – ERG report p95



* Patients in the no event health state can experience adverse events (major and minor bleeding and major and minor dyspnoea). The risk is dependent on treatment and disutility and costs are incurred for the duration of one cycle (3 months).

** Patients in the post non-fatal myocardial infarction and the post non-fatal stroke states can experience adverse events (major and minor bleeding and major and minor dyspnoea) and subsequent non-fatal myocardial infarction and stroke. These risks are dependent on treatment and disutility and costs are incurred for the duration of one cycle (3 months).

Time horizon: 40 years; Cycle Length 3 months; Half-cycle corrected; Perspective: NHS and PSSRU; Discount rate: 3.5% per annum

Assumptions and clinical inputs

- 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 BID + 75mg ASA (£178.06 per cycle) to 75mg ASA (£2.64 per cycle). No evaluation cf clopidogrel + ASA
- A competing risks model was used incorporating multiple parametric time-to-event models.
  - Time to: non-fatal MI; non-fatal stroke; fatal CV; treatment discontinuation; grade 1-2 dyspnoea; grade 3-4 dyspnoea; major bleeding and minor bleeding sourced from PEGASUS-TIMI 54
  - Other mortality sourced from UK life tables excluding CV related deaths

Assumptions and clinical inputs

- Following the cessation of ticagrelor (max 3 years of treatment) the transition probabilities immediately become that for ASA

- Time to subsequent events are assumed independent of initial treatment. The risk of subsequent non-fatal stroke was the only subsequent event dependent on 1st event.

- Hospitalisation rates estimated from a Poisson regression model. Cost of hospitalisation from 'No Event' state assumed to equal that of a fatal event (£2498)

Assumptions and clinical inputs

- Potential simplifications / limitations:
  - Non-explicit modelling of subsequent events and adverse events
  - Not differentiating between non-fatal strokes that were disabling and non-disabling

Both assumptions are likely unfavourable to ticagrelor and the ICER ⬇ if these were amended

Costs, utilities and hospitalisations

Event	One-off costs or *Ongoing costs* (Lit Review; Ref Costs) (£)	Trial estimated utility decrement from Age / Sex Norm	Hosp rate per cycle (%)
No event	*160*	0	1.6
Non-fatal MI	4593	0.0474	100.0
Non-fatal stroke	3240	0.0934	100.0
Post MI	*721 /540 /360 /180 /160*	0.0342	↑4.4
Post stroke	*2001/ 1715 /1143 /857 /690*	0.0665	↑4.4
Dyspnoea grade 3-4	733	0.0481	100.0 / ↑2.0
Dyspnoea grade 1-2	0	0.0154	1.6
TIMI major bleed	2825	0.0466	100.0
TIMI minor bleed	942	0.0129	100.0
Gout	22	0.0154	1.6
Fatal CV	2498	N/A	2.5
Non-CV fatal event	2498	N/A	9.7

Company's modelling methodology – deterministic analyses

- The company used 2 modelling approaches.
  - 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)

Company's modelling methodology – probabilistic analyses

- 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 results – revised model

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

Company's base case results – Deterministic Sensitivity Analyses

- The company undertook DSA based on the 'average patient' using the original model. These results are reported on p302 of the CS.

- Salient changes that increased the ICER > £25k were:
  - Fitting a Weibull distribution to the 1st non-fatal MI
  - Fitting a Gompertz distribution to 'other death'
  - Fitting a Gompertz distribution to CVD death
  - Fitting a Weibull distribution to CVD death

Company's deterministic scenario analyses Original model: Base case (n = 8664)

Scenario Analysis	Range in ICER (£)
CS base case	20,098
Adding initiation cost	20,098 – 21,810
Cost and utilities from TA335	20,366 – 21,524
Utility data from a systematic review	19,889
PEGASUS-TIMI 54 mortality	14,544
Subsequent treatment effects	18,817
'No event' maintenance cost = 'post non-fatal MI' maintenance cost	21,442 – 28,586
Changing starting age	22,000 – ≈ 30,000

Source: ERG report p133

Company's deterministic scenario analyses Original model: Base case (n = 8664)

Scenario Analysis	ICER (£)
CS base case	20,098
Ticagrelor 60mg treatment 12 months after subsequent MI	20,202
Ticagrelor 90mg treatment 1-12 months after subsequent MI	20,585
Excluding treatment effect variable for 'non-fatal stroke'	24,533
Baseline utilities (PEGASUS-TIMI 54) ≤ 1	19,253
Baseline utilities (PEGASUS-TIMI 54)	19,253
Baseline utilities (PEGASUS-TIMI 54) Gamma model	19,749
Tunnel state costs as per original submission	20,680
NHS Ref costs: lower quartile for CV events, upper quartile for AEs	20,860

Source: ERG report p135

Company's base case results – subgroup analysis. PSA results. Original submission

T + ASA cf ASA	Incremental values		ICER (£)
	Cost (£)	QALYs	
ADP < 30 days	1589	0.074	21,476
Diabetes (Yes)	1491	0.103	14,433
Diabetes (No)	1443	0.058	24,813
History of PCI (Yes)	1437	0.064	22,488
History of PCI (No)	1126	0.102	11,026

A single representative patient with an ICER closest to the mean ICER for the subgroup from the individual patient model was selected.

Source: ERG report p133

ERG comments

- Simplifications made in the model structure likely to be unfavourable to ticagrelor
- Time to subsequent events inappropriately modelled with an exponential distribution in the stable phase.
- ‘Unusual’ parameterisation of the log-logistic function
- Method to derive utility decrements not appropriate
- Data from ITT population used within the model may not be appropriate.
- The ‘average patient’ model may overestimate the ICER due to non-linearities in the model.

ERG exploratory analyses for the base case

1. Corrected parameterisation of the log-logistic model
2. Include the HRQoL and costs of gout
3. Choose the choice of distribution for AEs based on the AIC
4. Use adjusted health care costs
5. Add in the uncertainty associated with NHS reference costs
6. Using a greater disutility for major bleeds
7. Using alternative inpatient costs for the ‘no event’ state

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

Individual impact of each component of the ERG's exploratory base case – Probabilistic analyses. 'Average patient'

T + ASA cf ASA	Incremental values		ICER (£)
	Cost (£)	QALYs	
Company base case*	1425	0.059	24,072
Amending log-logistic parameterisation	1424	0.060	23,826
Including gout	1431	0.058	24,639
AE distribution based on AIC	1424	0.059	23,983
Adjusting health care costs	1433	0.059	24,108
Uncertainty in NHS Ref costs	1424	0.059	24,022
Greater disutility for major bleeds	1424	0.059	24,231
Alternative inpatient costs for 'no event'	1431	0.059	24,193
ERG exploratory base case	1439	0.058	24,711

* Calculated by the ERG

Source: ERG report p146

Further ERG exploratory analyses

1. ‘No Event’ hospitalisation probabilities were made treatment dependent
2. The time to non-CV fatality (as first event) was made treatment dependent
3. Treatment duration assumed to be 3 years unless a non-fatal events or death occurred. No change in efficacy assumed.
4. More unfavourable utility decrements were used (if available) – see p118 of the ERG submission

Further ERG exploratory analyses – Probabilistic results. 'Average patient'

T + ASA cf ASA	Incremental values		ICER (£)
	Cost (£)	QALYs	
ERG base case	1439	0.058	24,711
Treatment dependent hospitalisation probability in 'no event' state	1499	0.058	25,834
Time to non-CV death (as first event) made treatment dependent	1437	0.058	24,989
Treatment duration of 3 years unless a non-fatal event or death occurred. (No change in efficacy)	1929	0.057	33,676
More unfavourable utility decrements	1440	0.057	25,091

Source: ERG report p147

End of life criteria

- The company do not make a claim for the ‘End of Life’ criteria to be applied.

Potential equality issues

- The UKCPA commented that the trial excludes those patients with a previous stroke, GI bleed or need for anticoagulation - this is not representative of practice - should these patients present with a further ischaemic event they would still require treatment.

- Are there any (other) potential equality issues?

Innovation

- Ticagrelor has a rapid onset of anti-platelet effect, low variability and reversibility that results in a faster onset of action compared with thienopyridines as well as a faster offset of action with more rapid recovery of platelet function.
- The company stated that the technology is not expected to produce substantial health-related benefits not already included in the QALY calculation.
- The UKCPA considered the application of the technology innovative and thought it offered health benefits.

Key issues for consideration

KEY COST EFFECTIVENESS ISSUES	
Comparators	Should clopidogrel and low dose aspirin be included in the economic model?
Analysis	Is it appropriate to populate the model with component endpoints for which the study was not powered?
	On which population from PEGASUS-TIMI 54 should the time-to-event parameters be based?
	Which probabilistic sensitivity analysis is more appropriate?
Appraisal decision	What is the most plausible ICER for ticagrelor?
Equality	Are there any potential equality issues?
Innovation	Does the committee have any comments about Innovation?
PPRS	Has the Committee heard anything that would change the conclusion in the NICE position statement on the PPRS?