

Ticagrelor: analysis of predicted versus actual utilisation

Drug utilisation sub-committee (DUSC)

February 2016

Abstract

Purpose

To review the predicted versus actual use of ticagrelor for acute coronary syndrome, as requested by DUSC at its October 2015 meeting.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Ticagrelor was first listed on the PBS on 1 August 2012 for acute coronary syndrome.

Data Source / methodology

Prescription data were extracted from the Department of Human Services (DHS) prescription database for the period August 2012 to July 2015, inclusive. The analyses completed include the number of prescriptions and patients over time and the length of time patients are receiving treatment with ticagrelor.

Key Findings

- Since listing, 32,268 patients have been treated with ticagrelor. In 2014:
 - 19,770 patients were dispensed at least one prescription of ticagrelor;
 - 12,684 of these patients were starting treatment with ticagrelor for the first time.
- The length of treatment analysis suggests that although some patients remain on treatment for more than two years, the majority have stopped taking ticagrelor one year after initiation.

Purpose of analysis

To review the predicted versus actual use of ticagrelor for acute coronary syndrome, as requested by DUSC at its October 2015 meeting.

Background

Pharmacology

Ticagrelor belongs to a group of medicines called anti-platelet medicines. Platelets are very small cells in your blood that help to stop bleeding. When a blood vessel is damaged, they clump together to help form a blood clot. This stops bleeding. However, clots can also form inside a damaged blood vessel. This can be very dangerous because:

- the clot can cut off the blood supply completely - this can cause a heart attack (myocardial infarction) or stroke.
- the clot can partly block the blood vessels to the heart - this reduces the blood flow to the heart. This can cause chest pain which comes and goes (called 'unstable angina').

Ticagrelor helps stop the clumping of platelets. This reduces the chance of a blood clot forming that can block a blood vessel. This means that ticagrelor reduces the chance of you having another heart attack, chest pain or stroke.¹

Therapeutic Goods Administration (TGA) approved indications

Ticagrelor, in combination with aspirin, is indicated for the prevention of atherothrombotic events (cardiovascular death, myocardial infarction and stroke) in adult patients with acute coronary syndromes (unstable angina [UA], non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).²

Dosage and administration

Ticagrelor treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily.

For oral use. Ticagrelor can be taken with or without food. Patients taking ticagrelor should take aspirin daily unless specifically contraindicated. Following an initial dose of aspirin, ticagrelor should be used with a recommended maintenance dose of aspirin 100 mg daily.

¹ Brilinta® (ticagrelor), Australian Approved Consumer Medicine Information. North Ryde NSW: AstraZeneca Pty Ltd. July 2015, accessed 26 October 2015. Available from

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-CMI-02826-3>

² Brilinta® (ticagrelor), Australian Approved Product Information. North Ryde NSW: AstraZeneca Pty Ltd. Approved 21 June 2011, updated 25 July 2015, accessed 26 October 2015. Available from

<https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2011-PI-02824-3&d=2015102616114622412>

If required, the aspirin maintenance dose may vary from 75-150 mg according to clinical need.

Lapses in therapy should be avoided. A patient who misses a dose of ticagrelor should take one 90 mg tablet (their next dose) at its scheduled time.

Physicians who desire to switch patients from clopidogrel to ticagrelor should administer the first 90 mg dose of ticagrelor 24 hours following the last dose of clopidogrel. Switching from prasugrel to ticagrelor has not been investigated.

Treatment is recommended for at least 12 months unless discontinuation of ticagrelor is clinically indicated. In patients with acute coronary syndrome, premature discontinuation with any antiplatelet therapy, including ticagrelor, could result in an increased risk of cardiovascular death, or myocardial infarction due to the patient's underlying disease.²

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from the TGA (Product Information) and the TGA (Consumer Medicines Information).

Clinical situation

Acute coronary syndrome is a term used to describe the symptoms of coronary artery disease, which include unstable angina, non-ST elevation MI and ST-elevation MI. Acute coronary syndrome is associated with atherosclerosis (build-up of cholesterol-laden plaques) and is usually precipitated by acute thrombosis, induced by a ruptured or eroded atherosclerotic plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in coronary blood flow.

Platelets play a central role in the pathogenesis of atherothrombosis and the formation of thrombi following percutaneous coronary intervention (with or without stenting). Activated platelets are recruited to sites of coronary plaque rupture and intra-arterial stenting, thereby forming aggregates that may lead to platelet-rich thrombi, vascular occlusion, tissue ischemia, and MI.³

PBS listing details (current as at October 2015)

Table 1: PBS listing of ticagrelor

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
1418P	Ticagrelor Tablet 90 mg, 56	1	5	\$140.04	Brilinta® AstraZeneca Pty Ltd

Source: the PBS website.

³ Brillinta® (ticagrelor) [Public Summary Document](#), July 2011.

Restriction

Ticagrelor is PBS listed for treatment of acute coronary syndrome (myocardial infarction or unstable angina) in combination with aspirin.

For details of the current PBS listing refer to the PBS website.

Date of listing on PBS

Ticagrelor was first listed on the PBS on 1 August 2012.

Changes to listing

There have been no significant changes to the listing since ticagrelor was first PBS listed.

Current PBS listing details are available from the PBS website.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC recommended the listing of ticagrelor 90 mg as an Authority Required (Streamlined) benefit for the treatment of acute coronary syndrome (myocardial infarction or unstable angina) in combination with aspirin on the basis of acceptable cost-effectiveness compared with clopidogrel in combination with aspirin.

Given that the submission was based on clinical efficacy data up to 12 months and the fact that clinical guidelines recommend therapy for up to 12 months in the treatment of acute coronary syndrome, the PBAC considered whether it would be appropriate for the restriction to limit treatment up to a maximum of 12 months duration. However, the PBAC considered that length of treatment should be determined by the treating clinician and noted that the restrictions for similar drugs, clopidogrel and prasugrel, do not define treatment duration despite the listing of these drugs also being based on trials that limited treatment duration.

The PBAC considered the submission's estimates on ticagrelor PBS usage and financial implications to be uncertain due to the high potential for ticagrelor to be used in non-ACS conditions by clinicians. On the other hand, the Committee considered that its use may be less than predicted due to adverse events associated with ticagrelor (e.g. increased non-CABG bleeding) and potentially lower compliance arising from a twice daily dosing schedule compared to clopidogrel's once daily dosing. The high potential for ticagrelor to be prescribed for non-ACS conditions was of particular concern to the PBAC as use in such conditions has the potential to result in high costs to the PBS. To address the issue of ticagrelor's potential use outside any PBS restriction, the PBAC recommended that the Department enter into a risk share agreement with the sponsor.

For further details refer to the Public Summary Document from the July 2011 PBAC meeting.

Approach taken to estimate utilisation

The ticagrelor submission used a market share approach to estimate use. Following a positive recommendation from the PBAC, the Department re-estimated use using an epidemiological approach. [REDACTED]

[REDACTED] This was because clopidogrel had the majority of use in clinical practice and had the same restriction as that requested for ticagrelor. Prasugrel was only available to a sub group of patients with acute coronary syndrome managed by percutaneous coronary intervention.

For further details refer to the Public Summary Document from the July 2011 PBAC meeting.

Previous reviews by the DUSC

Ticagrelor has not been previously reviewed by DUSC.

Methods

Prescription data for ticagrelor were extracted from the Department of Human Services (DHS) prescription database for the supply period August 2012 to July 2015, inclusive. This database contains data on PBS prescriptions submitted to DHS for payment of a PBS/RPBS (R/PBS) subsidy by the Government.

All data were extracted based on the date of supply to the patient. The data differs from that available from the DHS (Medicare) PBS statistics website which is based on the date of processing and is only for subsidised R/PBS prescriptions (under patient co-payment not included).⁴

An analysis of the number of incident and prevalent patients was undertaken using the DHS prescription data. Patient counts were based on de-identified unique patient identification numbers (PINs) from the prescription data. New (initiating) patients were defined as those with no prior prescription for ticagrelor. Patients were identified as being on treatment (prevalent) if they had received at least one dispensing of ticagrelor in the specified period.

Length of treatment analysis was performed using DHS prescription data using the methodology described in Appendix A.

For the analysis of changes to other drugs, prescription data were extracted using the PBS item codes relating to acute coronary syndrome for the supply period February 2009 to July 2015, inclusive. The first listing for acute coronary syndrome was added to an existing PBS item code of clopidogrel on 1 February 2009. Streamlined codes were used to analyse use by indication from December 2011.

⁴ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

These data include under patient co-payment prescription data from 1 April 2012. As the price of clopidogrel was reduced to a price lower than the general patient copayment on 1 September 2013, capture of all patients is possible for these medicines.

Analyses were undertaken in SAS.

Results

Analysis of drug utilisation

Overall utilisation

The number of ticagrelor prescriptions supplied by month, between 1 August 2012 and 31 July 2015, is shown below.

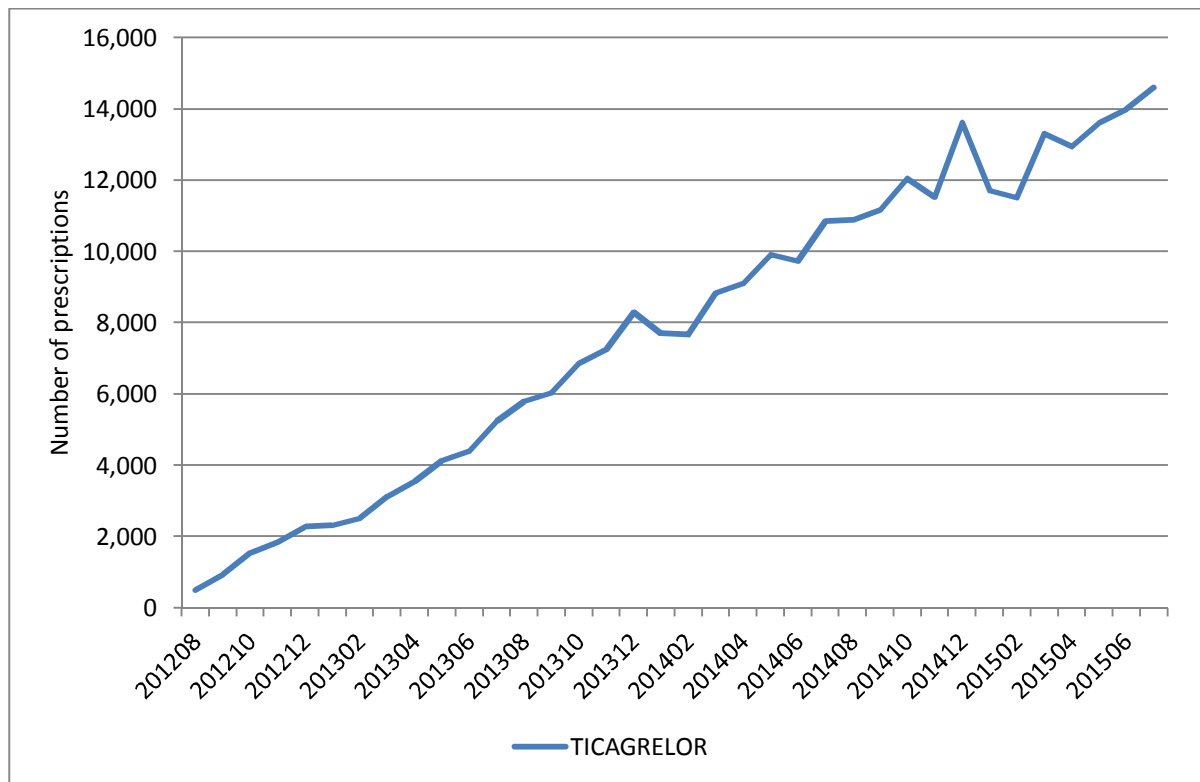


Figure 1: Number of ticagrelor prescriptions supplied since listing

The figure above shows the uptake of ticagrelor has been fairly steady since listing, with some peaks and troughs around the end and beginning of calendar years, likely due to PBS Safety Net eligible patients stockpiling extra prescriptions.

Overall in the first year of listing, 32,318 prescriptions of ticagrelor were supplied.

The number of initiating and treated unique patients each month is shown below.

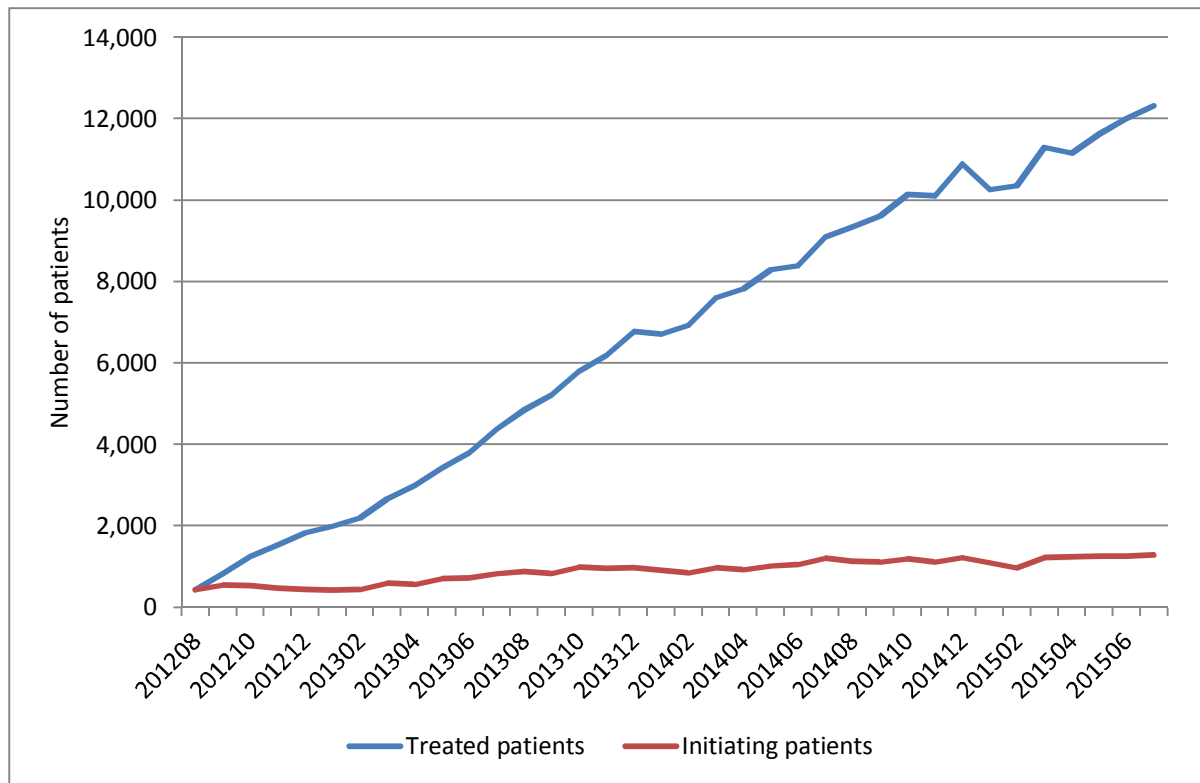


Figure 2: Number of initiating and treated patients by month

The increasing difference between initiating and treated patients suggests some patients may be remaining on therapy.

Utilisation by relevant sub-populations/regions or patient level analysis

An analysis of the length of treatment of ticagrelor by year of initiation is shown below. At the time of recommendation, the PBAC considered whether it would be appropriate for the restriction to limit treatment up to a maximum of 12 months duration. However, the PBAC considered that length of treatment should be determined by the treating clinician.

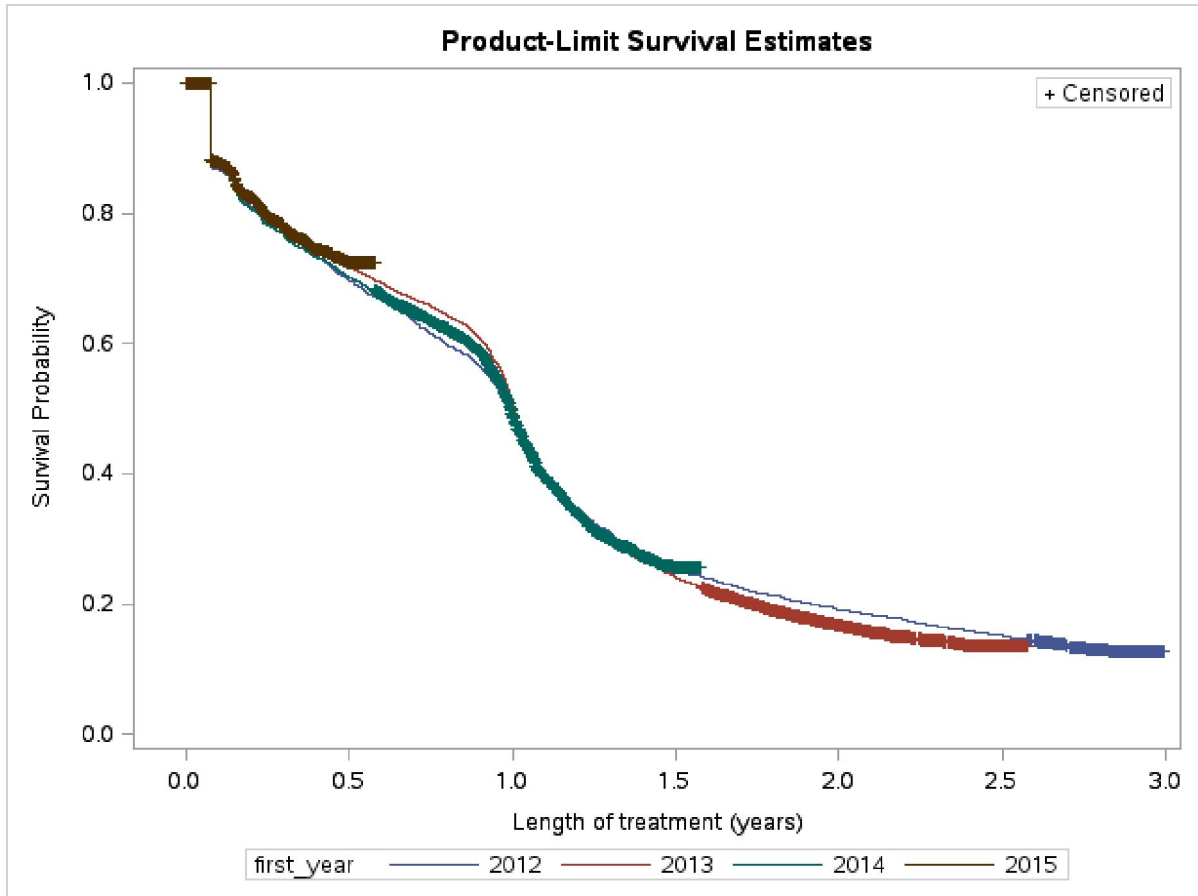


Figure 3: Kaplan-Meier analysis of the length of treatment by year of initiation

The length of treatment analysis shows that approximately 10% of patients do not refill their prescription after their initial supply. There is another noticeable decrease in the number of treated patients, by about 20%, around one year after initiation. Only 20% of patients are remaining on treatment for two years or more.

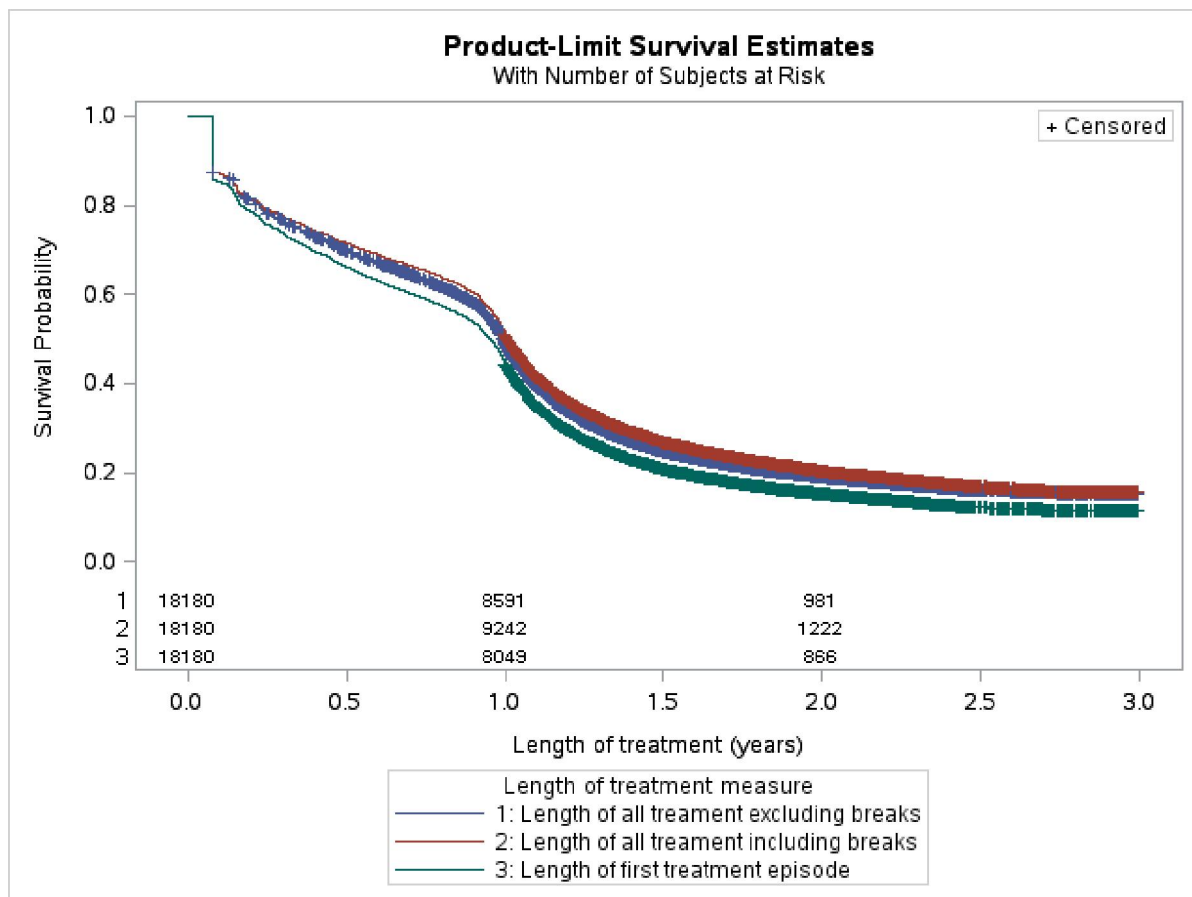


Figure 4: Kaplan Meier analysis of length of treatment using different approaches to managing breaks in therapy

A further analysis was undertaken to investigate whether breaks in therapy affect the length of treatment. Figure 4 above shows the length of treatment is similar whether breaks in therapy are included, excluded, or only the first episode of therapy is included. This analysis excluded patients who initiated therapy after July 2014.

Changes in the use of other drugs

The use of clopidogrel, prasugrel and the combination item clopidogrel plus aspirin are graphed below. As ticagrelor is taken with aspirin this should represent the drugs that could decrease in use with the listing of ticagrelor.

The dosage of these medicines is different; clopidogrel, prasugrel and clopidogrel with aspirin are once daily while ticagrelor is taken twice daily. However the maximum quantities (28, 28, 30 and 56 respectively) account for this.

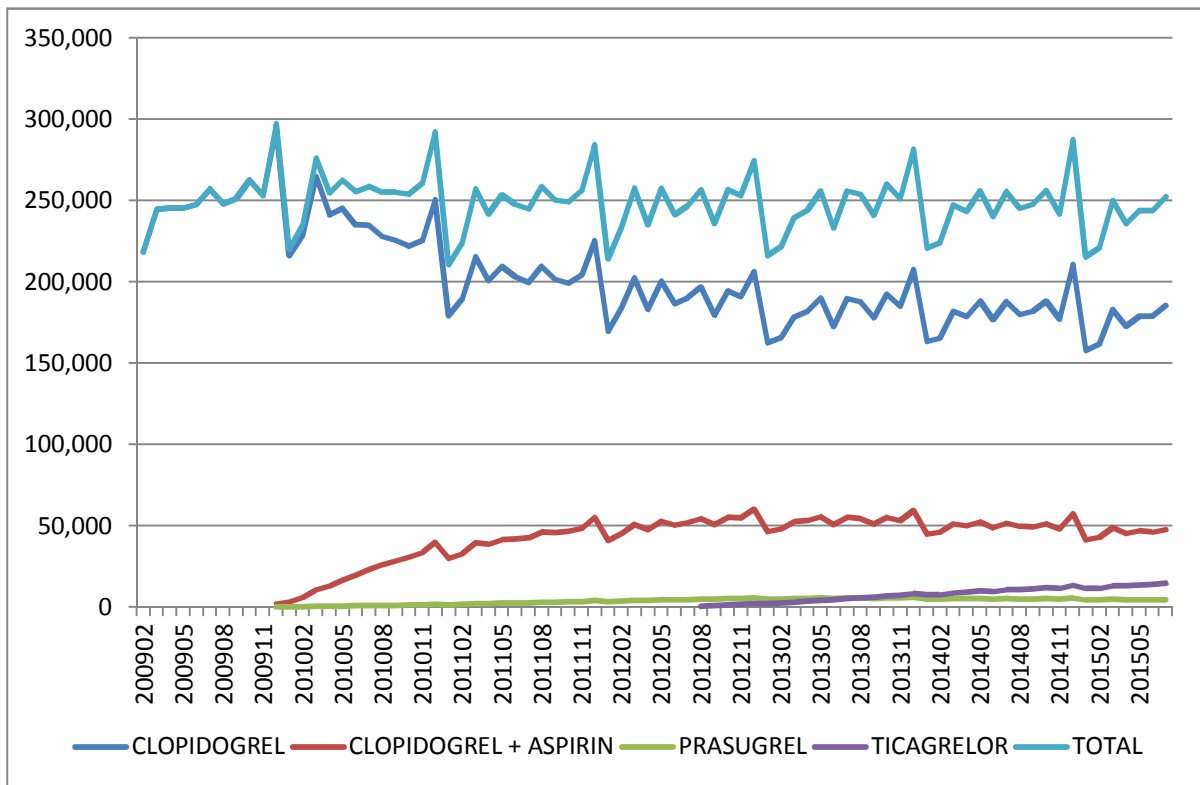


Figure 5: Use of clopidogrel, clopidogrel plus aspirin, prasugrel and ticagrelor

Figure 5 shows the use of these drugs using PBS item codes which include an indication for acute coronary syndrome. As noted in the methods, the original listing of clopidogrel for acute coronary syndrome was added to an existing PBS item code on 1 February 2009. The item codes for clopidogrel and clopidogrel plus aspirin that include acute coronary syndrome also include use for prevention of recurrence of ischaemic stroke or transient cerebral ischaemic events and prevention of recurrence of myocardial infarction or unstable angina in patients contraindicated to aspirin. The PBS item codes for use in patients pre- and post-angioplasty have been excluded from this analysis. For a complete list of the PBS item codes used in this analysis please see Appendix A.

Figure 6 below shows the use of these drugs by indication using streamlined authority code from December 2011. Any missing or invalid codes (a zero, three digit code, or a code relating to indications these medicines are not PBS listed for) have been excluded from this analysis. In December 2011 approximately 25% of the restrictions for these medicines were not recorded. From July 2012 onwards, approximately 1% of prescriptions did not have a code recorded, and less than 0.1% of prescriptions had an invalid code recorded.

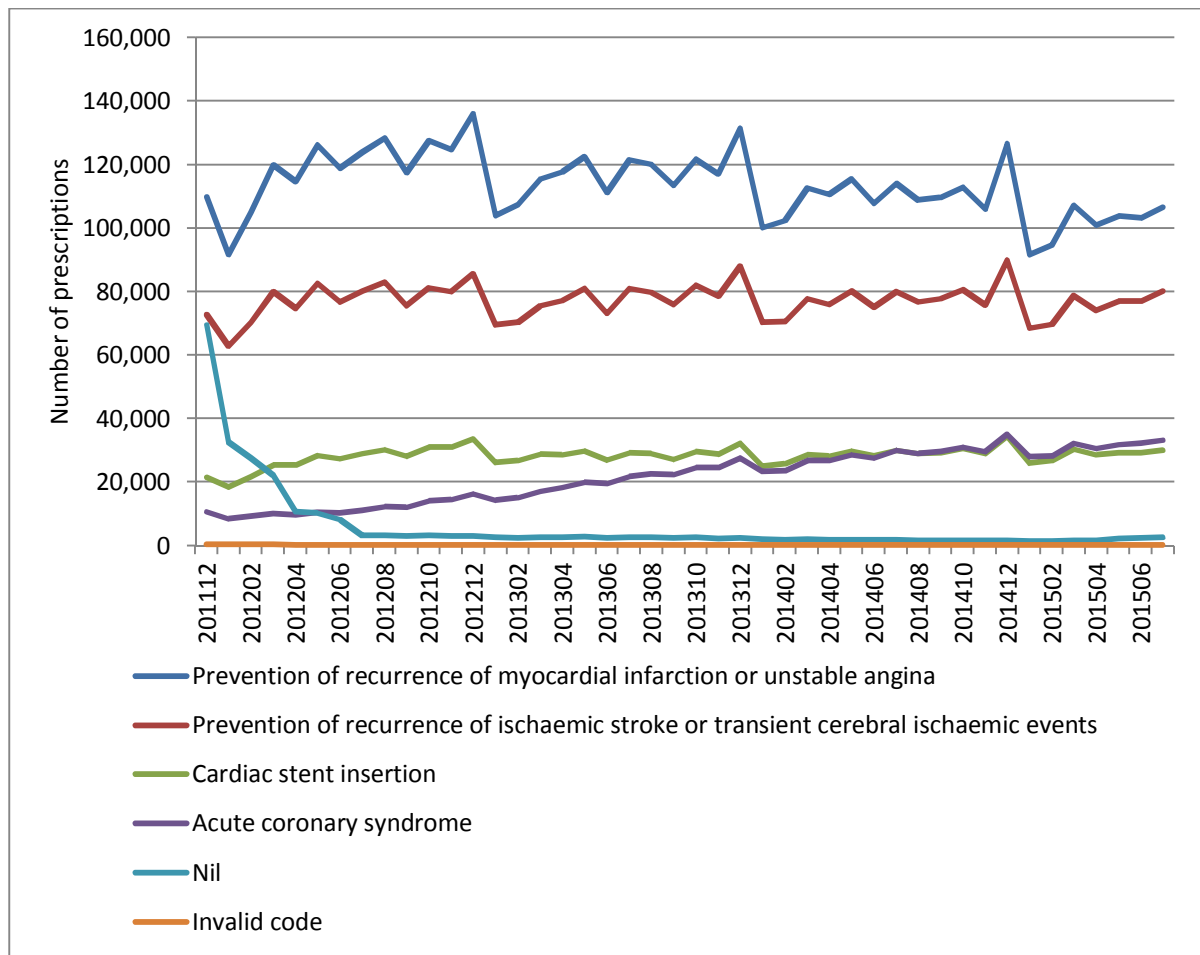


Figure 6: Use of clopidogrel, clopidogrel plus aspirin, prasugrel and ticagrelor by indication

The proportion of use for acute coronary syndrome across all these medicines has increased from 7% at the beginning of 2013 to 13% in July 2015. Over the same time period, other indications have remained steady; cardiac stent insertion at 12% and prevention of recurrence of ischaemic stroke or transient cerebral ischaemic events at 32%. However, prevention of recurrence of myocardial infarction or unstable angina where the patient has a history of symptomatic cardiac ischaemic events while on therapy with low-dose aspirin has decreased from 50% to 43%.

Figure 7 below shows the use of these drugs for acute coronary syndrome using streamlined authority code from December 2011.

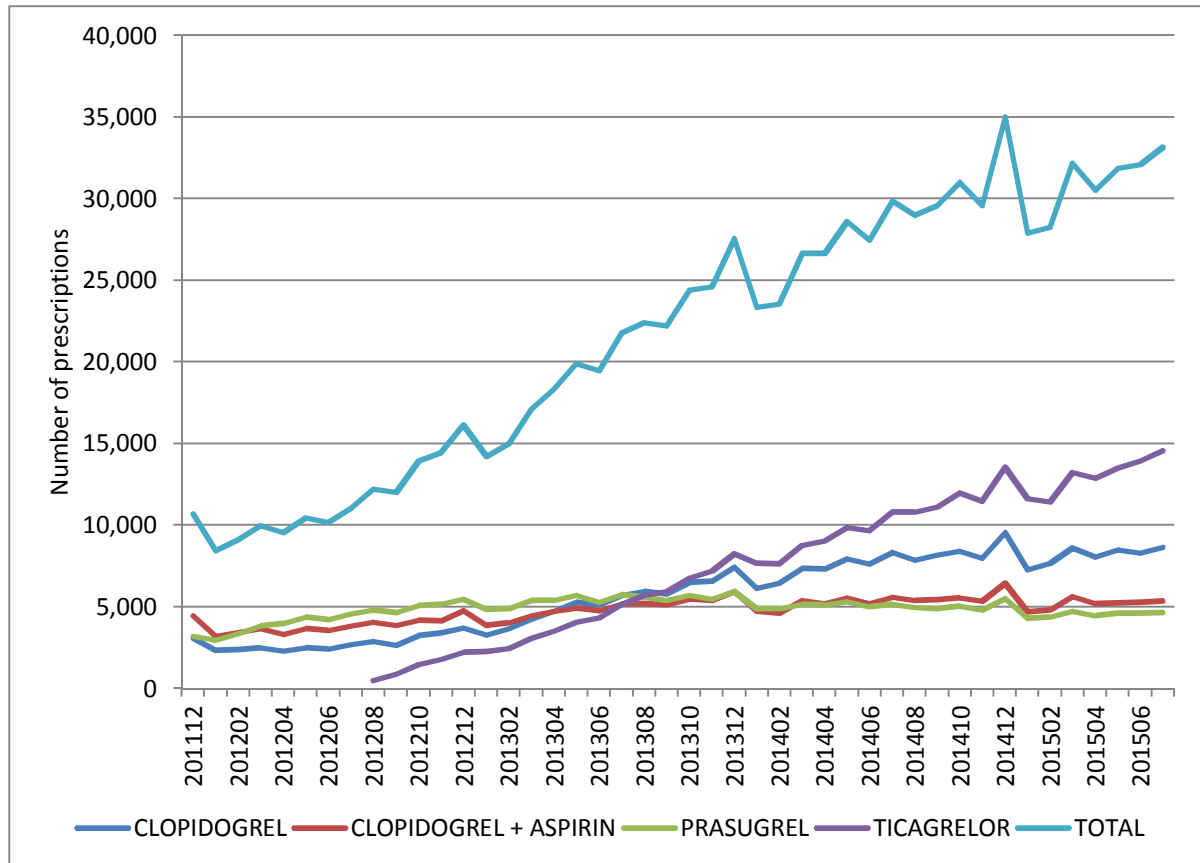


Figure 7: Use of medicines for acute coronary syndrome

Together Figure 5 and 7 show that although ticagrelor has taken a small proportion of the market of clopidogrel and clopidogrel with aspirin, it is now the most commonly used medicine for acute coronary syndrome.

Table 2: Prescriptions of medicines for acute coronary syndrome since December 2011

	CLOPIDOGREL	CLOPIDOGREL + ASPIRIN	PRASUGREL	TICAGRELOR	TOTAL
2011 (December only)	3,078	4,446	3,171	-	10,695
2012	32,789	45,517	52,347	6,850	137,503
2013	64,130	58,899	65,279	58,592	246,900
2014	93,041	64,385	60,570	122,202	340,198
2015 (YTD to July)	56,993	36,125	31,678	91,139	215,935

Analysis of expenditure

The table below summarises Commonwealth Expenditure on ticagrelor by calendar year since listing. Clopidogrel and clopidogrel with aspirin are not included in this analysis because they have been subject to several price reductions over the last few years.

Table 3: Government expenditure on ticagrelor by calendar year since listing

Year	Government expenditure on ticagrelor
2012	\$921,544
2013	\$7,735,143
2014	\$16,010,427
2015*	\$11,696,154

Note: *2015 includes 7 months of data.

It should be noted this analysis is based on date of supply. There may be small differences between these results and those obtained from publicly available Medicare Australia date of processing data. Further, the figures are based on the published price of ticagrelor. Ticagrelor has a special pricing arrangement and government expenditure may be less than presented in Table 3.

Analysis of actual versus predicted utilisation

This analysis compares the estimates of utilisation agreed between the Sponsor and the Department prior to listing. The actual numbers reflect all patients and prescriptions for ticagrelor, regardless of whether a valid streamlined authority code was recorded.

Table 4: Predicted versus actual numbers of patients and prescriptions

		2012	2013	2014	2015*
Patients	Predicted	■	■	■	■
	Actual	2,420	10,704	19,770	19,784
	Difference	■	■	■	■
Prescriptions	Predicted	■	■	■	■
	Actual	7,077	59,483	123,030	91,684
	Difference	■	■	■	■

Note: *2015 includes 7 months of data

The analysis of predicted versus actual use is based on calendar years as the final agreed estimates were based on calendar years. In the first two years of treatment it appears the number of patients were underestimated but these patients were supplied fewer prescriptions than estimated. In 2014 the number of patients and prescriptions were both underestimated. This suggests the uptake was underestimated in the first years of listing, but overestimated in later years.

Discussion

The use of ticagrelor is growing, which is demonstrated by the increasing number of prescriptions and treated patients each year. However, it is not growing as quickly as expected. In the first two years of PBS listing, two to three times more patients accessed ticagrelor than expected, but in 2014 less than half of the expected number of patients were prescribed ticagrelor. The difference between the predicted and actual numbers of prescriptions has always been lower than the patients, perhaps due to some patients filling fewer prescriptions than expected.

Issues that may be affecting the lower than expected use of ticagrelor include:

- Twice daily ticagrelor may be less convenient than its once daily alternatives such as clopidogrel and prasugrel.
- Ticagrelor is not as effective for patients who need higher doses of aspirin compared to clopidogrel.
- Adverse events are more common, in particular strokes, intracranial bleeds and minor bleeds.⁵

The length of treatment analysis shows there is relatively low use of ticagrelor beyond 12 months after initiation. The PBAC did not recommend the treatment duration be limited by the PBS restriction, although the submission was based on clinical efficacy data up to 12 months and clinical guidelines at the time recommended therapy for acute coronary syndrome be given for up to 12 months.³

When the total market of medicines for acute coronary syndrome is considered (Figure 5), it appears the PBS listing of ticagrelor has not had a large impact on the use of clopidogrel, clopidogrel plus aspirin or prasugrel.

Prior to the PBS listing of ticagrelor, the use of existing medicines specifically for acute coronary syndrome cannot be fully quantified. The streamlined authority codes of other medicines used for acute coronary syndrome, such as clopidogrel and prasugrel, began to be collected from December 2011. It took until July 2012 for there to be an appropriate streamlined code recorded for approximately 99% of prescriptions.

Since the PBS listing of ticagrelor, in August 2012, the monthly utilisation of prasugrel has remained relatively unchanged (Figure 7) and the use of clopidogrel has continued to grow. Clopidogrel has the same restriction as ticagrelor but prasugrel is only available to a sub group of patients with acute coronary syndrome managed by percutaneous coronary intervention.

Although the use of medicines for acute coronary syndrome appears to be growing (Figures 6 and 7), the use for prevention of recurrence of myocardial infarction or unstable angina has been decreasing over time. This suggests that some of the increase in the use of medicines for acute coronary syndrome (myocardial infarction or unstable

⁵ NPS MedicineWise, NSW Australia, available from <<http://www.nps.org.au/publications/health-professional/nps-radar/2011/december-2011/ticagrelor>>.

angina) may be due to all prescribing of ticagrelor being recorded for acute coronary syndrome where corresponding use of clopidogrel may have been recorded as for prevention of recurrence of myocardial infarction or unstable angina.

DUSC consideration

The uptake of ticagrelor has been rising in a steady manner since listing, with some peaks and troughs around the end and beginning of calendar years, likely due to PBS Safety Net eligible patients stockpiling extra prescriptions. Overall in the first year of listing, 32,318 prescriptions of ticagrelor were supplied.

The length of treatment analysis showed that approximately 10% of patients do not refill their prescription after their initial supply. DUSC agreed there is another noticeable decrease in the number of treated patients, by about 20%, around one year after initiation. Only 20% of patients remain on treatment for two years or more. DUSC noted the length of treatment analysis suggests there is a conscious decision to stop treatment in some patients. DUSC noted the response from the sponsor suggested that in some patients, continued use may be appropriate because of their underlying disease and that the PBAC considered that treatment beyond 12 months represents acceptable cost effectiveness⁶.

Ticagrelor has taken a small proportion of the market of clopidogrel, clopidogrel with aspirin, and prasugrel. (It was noted these medicines are PBS listed for several other indications). However, ticagrelor is now the most commonly used medicine for acute coronary syndrome (ACS), as identified by indications associated with specific PBS item codes.

DUSC noted the analysis of predicted versus actual use found the uptake was underestimated in the early years of listing but overestimated in later years. DUSC suggested the sponsor may have anticipated that initiation of prescribing of ticagrelor would move to general practitioners, however noting the context of its use for ACS, it is still being initiated by cardiologists. DUSC considered this may have affected the rate of uptake of ticagrelor. DUSC noted the response from the sponsor suggested the lower than expected use of ticagrelor may mean ACS patients in Australia are not treated as per clinical guidelines⁷, which could be a quality use of medicines issue.

DUSC actions

DUSC requested that the report be provided to the PBAC.

⁶ Ticagrelor Public Summary Document, July 2011

⁷ 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation; European heart Journal (2016) 37, 367-315

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsors' comments

AstraZeneca: The sponsor has no comment.

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

To the extent provided by law, DoH makes no warranties or representations as to accuracy or completeness of information contained in this report.

To the fullest extent permitted by law, neither the DoH nor any DoH employee is liable for any liability, loss, claim, damage, expense, injury or personal injury (including death), whether direct or indirect (including consequential loss and loss of profits) and however incurred (including in tort), caused or contributed to by any person's use or misuse of the information available from this report or contained on any third party website referred to in this report.

Appendix A

Detailed methodology for Kaplan Meier length of treatment analyses

A break in treatment is defined as a gap of $2 \times$ Standard Coverage Days (SCD) in drug coverage which is equivalent to $3 \times$ SCDs between script supply. An episode is defined as the time from the first script to the last script before a break plus one SCD (ie. the coverage of the last script). The script after a break in treatment is defined as the first script of the next episode. The SCDs are equal to the median time to re-supply of scripts, which for ticagrelor was calculated to be 28 days.

The data period used in the length of treatment analysis was from August 2012 (the listing of ticagrelor) and July 2015 inclusive. A patient was deemed to be continuing treatment (ie. censored for the purposes of the KM analysis) at the end of the data period if the supply of their last script was within $3 \times$ SCDs (which is equivalent to the item coverage end date being within $2 \times$ SCDs) of the end of the data period (ie. 31 July 2015). Patients initiating between August 2014 and July 2015 inclusive are excluded as they have minimal follow-up time. Three lengths of treatment were calculated, ie. the length of:

- the first episode of treatment (ie. up to the first break in treatment);
- all treatment excluding breaks (ie. the sum of all episodes); and
- all treatment including breaks (ie. the time from the first script of the first episode to the last script of the last episode plus one SCD (ie. the coverage of the last script).

PBS item codes used to analyse complete market

Medicine	PBS item codes
Clopidogrel	2275R 8358X 9317J
Clopidogrel plus aspirin	9296G
Prasugrel	9496T 9495R