

Novel Oral Anticoagulants: Predicted vs actual analysis

Drug utilisation sub-committee (DUSC)

June 2016

Abstract

Purpose

To review the predicted versus actual use of the novel oral anticoagulants (NOACs), including apixaban, dabigatran and rivaroxaban, for prevention of stroke or systemic embolism in non-valvular atrial fibrillation (NVAf).

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Rivaroxaban: 1 August 2013

Apixaban: 1 September 2013

Dabigatran: 1 September 2013

Data Source / methodology

Data were extracted from the DUSC and Department of Human Services (DHS) prescription databases from the earliest available data and continuing to December 2015. The DHS database was used for patient level analyses, including age, location, prescriber type, prior prescription, and time to refill.

Key Findings

- Based on the volume of prescriptions dispensed:
 - NOACs contributed to a growth in the anticoagulant market since their listing on the PBS for NVAf.
 - The use of warfarin has declined since the listing of NOACs on the PBS for NVAf.
- In calendar year 2015 for NOAC use in NVAf:
 - There were 1,604,242 PBS-subsidised prescriptions supplied for 188,130 patients.
 - For 72,484 patients, this was their first NOAC prescription.
- People starting anticoagulant therapy for the first time in 2014 and 2015 were more likely to commence on a NOAC than on warfarin.
- In 2015, the proportion of people initiating anticoagulant therapy with warfarin was greater in remote areas compared with metropolitan areas.
- In 2015, approximately 40% of prescriptions initiating anticoagulant therapy written by GPs were for warfarin compared to approximately 5% by cardiologists.

Purpose of analysis

To review the predicted versus actual use of the novel oral anticoagulants (NOACs), including apixaban, dabigatran and rivaroxaban, for prevention of stroke or systemic embolism in non-valvular atrial fibrillation (NVAF). DUSC requested that the NOACs be reviewed after 24 months of data are available. DUSC considered location, age and dose should be analysed. DUSC considered coadministration with aspirin would not be informative because data on over the counter purchase of these items is not available.

Background

Pharmacology

Rivaroxaban and apixaban are selective inhibitors of the coagulation Factor Xa.^{1,2}

Dabigatran is a competitive and reversible direct thrombin inhibitor. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.³

Therapeutic Goods Administration (TGA) approved indications

Rivaroxaban, dabigatran and apixaban are TGA approved for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke. Additionally, these NOACs are indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement); the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.

In February 2013, the TGA published information for health professionals regarding dabigatran and the increased risk of bleeding. In May 2013, it was updated to include details of:

- two safety reviews that were completed
- a new contraindication for concomitant use of dronedarone and dabigatran
- advice regarding repackaging dabigatran capsules
- advice that dabigatran may have an effect on some pathology tests

¹ Xarelto (rivaroxaban). Australian Approved Product Information. Sydney: Bayer Australia Ltd. Approved 24 November 2008, most recent amendment 15 January 2015. Available from <www.ebs.tga.gov.au>.

² Eliquis (apixaban). Australian Approved Product Information. Sydney: Pfizer Australia Pty Ltd. Approved 21 July 2011, most recent amendment 16 June 2014. Available from <www.ebs.tga.gov.au>.

³ Pradaxa (dabigatran). Australian Approved Product Information. Sydney: Boehringer Ingelheim Pty Limited. Approved 24 November 2008, most recent amendment 20 June 2014. Available from <www.ebs.tga.gov.au>.

- updated adverse event report numbers.⁴

In September 2013, the TGA released a warning to consumers that if they are taking apixaban, dabigatran or rivaroxaban:

- Do not stop taking it suddenly or change the dose without consulting your doctor. Stopping these medicines suddenly can increase your risk of stroke or may increase the risk of developing a blood clot.
- See your doctor immediately if you notice bleeding, red or brown urine, or red or black bowel motions.
- Remember to tell all doctors, dentists and pharmacists who are treating you that you are taking apixaban, dabigatran or rivaroxaban. Similarly, tell them what other medicines you are taking - especially aspirin, anti-inflammatory medicines and other medicines used to prevent blood clots, such as clopidogrel and warfarin - including any that you get without a prescription from a pharmacy, supermarket or health food store.⁵

Also in September 2013 the TGA released this warning for health professionals:

Clinical trials and post-marketing experience have shown that major bleeding events, including those leading to death, have occurred with all of these products and with other anticoagulants. At this time, there is no specific antidote available for these medicines, and there are no current recommendations for the routine monitoring of anticoagulant activity once they are administered. The TGA recommends referring to Product Information for these products when prescribing these agents.⁶

In June 2015, the TGA released this statement:

Consumers and health professionals are advised that a recently completed TGA review has found that based on the current information there is no evidence to support a recommendation for routine blood monitoring to improve the safety of the NOACs. The TGA undertook the review following recent publication of articles in the medical literature which suggested that the safety of these medicines could be improved if routine blood monitoring was undertaken.⁷

⁴ Therapeutic Goods Administration May 2013. Available at: <https://www.tga.gov.au/alert/dabigatran-pradaxa-and-risk-bleeding-information-health-professionals>

⁵ Therapeutic Goods Administration, Information for Consumers September 2013. Available at: <https://www.tga.gov.au/alert/apixaban-eliquis-dabigatran-pradaxa-and-rivaroxaban-xarelto-information-consumers>

⁶ Therapeutic Goods Association, Information for Health Professionals September 2013. Available at: <https://www.tga.gov.au/alert/apixaban-eliquis-dabigatran-pradaxa-and-rivaroxaban-xarelto-information-health-professionals>

⁷ Therapeutic Goods Administration June 2015. Available at: <https://www.tga.gov.au/alert/new-oral-anticoagulants-apixaban-eliquis-dabigatran-pradaxa-and-rivaroxaban-xarelto>

Dosage and administration

Table 1: Dosage and administration of NOACs for use in NVAF

Brand name and sponsor	Product	Dose and frequency of administration
Xarelto® Bayer Australia Ltd	Rivaroxaban	The recommended dose is 20 mg once daily. For patients with moderate renal impairment (Creatinine clearance: 30 – 49 mL/min), one 15 mg tablet of Xarelto® should be taken once daily. Therapy with Xarelto® should be continued long term provided the benefit of prevention of stroke and systemic embolism outweighs the risk of bleeding.
Pradaxa® Boehringer Ingelheim Pty Ltd	Dabigatran	The recommended daily dose is 300 mg taken orally as one 150 mg capsule twice daily. In patients with moderate renal impairment (30–50 mL/min CrCL) a reduced dose of 220 mg given as one 110 mg capsule twice daily may be considered. Patients aged 75 years and above should be treated with a daily dose of 220 mg taken orally as one 110 mg capsule twice daily. For patients with a potentially higher risk of major bleeding, a reduced dose of 220 mg given as 110 mg twice daily may be considered. Treatment should be continued life-long.
Eliquis® Bristol-Myers Squibb Australia Pty Ltd	Apixaban	The recommended dose is 5 mg taken twice daily. The recommended dose is 2.5 mg taken twice daily in patients with at least two of the following characteristics: ≥80 years; body weight ≤60 kg; serum creatinine ≥133 µmol/L.

Source: Product Information accessed on TGA website⁸

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

Clinical situation

Atrial fibrillation (AF) is the most common type of arrhythmia in adults and becomes more common with increased age. Individuals with AF have an increased risk of thromboembolic events (e.g. stroke, deep venous thrombosis, pulmonary embolism). The risk of stroke is about four to five times greater than for people of the same age who are in sinus rhythm, and it is estimated that about 15% to 20% of all strokes are caused by AF.⁹ Management of people with AF is aimed at reducing symptoms and preventing severe thromboembolic complications. Prevention of the latter relies on adequate antithrombotic therapy such as with warfarin or a NOAC. Both therapies carry risks, such as an increased risk of major bleeding.⁹

⁸ Xarelto®, Pradaxa® and Eliquis® Product Information. Available from <https://www.ebs.tga.gov.au>, Accessed 9 March 2016.

⁹ Slot B and Berge E. Factor Xa inhibitors versus vitamin K antagonists for preventing cerebral or systemic embolism in patients with atrial fibrillation (Review). Cochrane Database of Systematic Reviews 2013; 8: Article CD008980.

Warfarin has a narrow therapeutic window, variable dose response between patients and multiple interactions with other drugs, some foods and concurrent illnesses. Contraindications to warfarin are disease states where bleeding is active or a high risk, and alcoholism. Caution must be advised in prescribing warfarin where compliance is likely to be poor or there is protein C or S deficiency.¹⁰ Oral or injectable vitamin K can be administered to reverse the effects of warfarin, if necessary.¹¹

There is a need for frequent laboratory monitoring of dose–effect¹² via a blood test referred to as the International Normalised Ratio (INR). Maintaining an INR in the target range of 2.0 to 3.0 has been shown to reduce the risk of stroke by about two-thirds in patients with AF.⁹ Point-of-care testing of the INR can be done in general practice, in other locations such as pharmacies, or by the patients themselves (known as self-monitoring). These approaches are more convenient for patients than visits to an anticoagulation clinic in a pathology practice or in a hospital, particularly if a patient lives in a rural or remote area. The convenience of self-monitoring can be extended further to a model of self-management. Patients use algorithms to determine any necessary dose adjustments following INR measurement. Evidence supports the practice of self-monitoring, with or without self-management, but an essential prerequisite is the ability of the patient to correctly, competently and safely use the testing devices¹³. The starting dose of 5 mg represents a large loading dose for a patient who requires a maintenance dose of only 1-2 mg, and can lead to marked over-anticoagulation in a few days if INRs are not monitored¹³.

The NOACs differ to warfarin in that the recommended dose is universal, blood tests do not need to be conducted and there are fewer drug and food interactions. Conversely, bleeding risk assessment is especially important in patients taking a NOAC because there is no universal method of measuring or reversing the activity of the NOACs. In April 2016, the TGA approved an antidote to dabigatran, idarucizumab, for an implementation date of 1 June 2016. This antidote has no effect on the other NOACs.¹⁴ There is an antidote for apixaban and rivaroxaban being trialled overseas; however it is currently unavailable in Australia.¹⁵ Recent publications have reported variable findings regarding the risk of major bleeding with NOACs. In 2015, a retrospective cohort study suggested that NVAf patients who were newly initiated on apixaban had a reduced risk of major bleeding compared to those newly initiated on warfarin, dabigatran or rivaroxaban.¹⁶ Also in 2015, results were published from an international prospective study of rivaroxaban. The data suggested that

¹⁰ Australian Medicines Handbook 2016. Available at <https://amhonline.amh.net.au/>

¹¹ Baker R et al. Warfarin reversal: consensus guidelines on behalf of the Australasian Society of Thrombosis and Haemostasis. Medical Journal of Australia 2004; 181(9): 492-497.

¹² Gallus A. New oral anticoagulants – clinical applications. Aust Presc 2010;33 (42-7).

¹³ Tideman et al. How to manage warfarin therapy. Aust Presc 2015;38(2): 44-48.

¹⁴ Therapeutics Goods Administration, Reasons for scheduling delegate’s final decisions April 2016. Available at: <https://www.tga.gov.au/book-page/16-idarucizumab>

¹⁵ Connors JM. Antidote for factor Xa anticoagulants. N Engl J Med 2015; 373: 2471-2472.

¹⁶ Kamble et al. Anti-thrombotic therapy and associated haemorrhage. American Heart Association 2015; 132:Article 18465.

the risk of major bleeding was low and generally consistent with that seen in the initial trials.¹⁷

Medication adherence is important with the NOACs due to the shorter half-life than warfarin; the risk of stroke is greater if a dose is missed. Renal function should be assessed before starting NOAC treatment and at least annually thereafter (more frequently in people with renal impairment). Furthermore, hepatic function must be assessed before starting dabigatran¹⁸.

Dabigatran was the first NOAC to be TGA registered (April 2011). In June 2011, the sponsor of dabigatran introduced a nationwide Product Familiarisation Program (PFP) that had approximately 25,000 patients enrolled¹⁹. In May 2012, the sponsor for rivaroxaban commenced their own PFP¹⁹ (with approximately 3,000 patients enrolled)²⁰ after becoming TGA registered in April 2012. These programs meant that there was a population primed for the uptake of the NOACs at the time they were listed on the PBS.

PBS listing details (as at 1 May 2016)

Table 2: PBS listing of the NOACs for use in NVAF

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
2268J [†]	Rivaroxaban 20mg tablet, 28	1	5	\$86.50	Xarelto [®] Bayer Australia Ltd
2691P [†]	Rivaroxaban 15mg tablet, 28	1	5	\$86.50	Xarelto [®] Bayer Australia Ltd
2753X [†]	Dabigatran etexilate 110mg capsule, 60	1	5	\$87.71	Pradaxa [®] Boehringer Ingelheim Pty Ltd
2769R [†]	Dabigatran etexilate 150mg capsule, 60	1	5	\$87.71	Pradaxa [®] Boehringer Ingelheim Pty Ltd
2735Y [†]	Apixaban 5mg tablet, 60	1	5	\$96.57	Eliquis [®] Bristol-Myers Squibb Australia Pty Ltd
2744K [†]	Apixaban 2.5mg tablet, 60	1	5	\$96.58	Eliquis [®] Bristol-Myers Squibb Australia Pty Ltd

Source: the [PBS website](#).

[†]Special Pricing Arrangements apply.

PBS item codes with listings for use in stroke prevention or systemic embolism in NVAF only.

¹⁷ Camm J et al. XANTUS: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 2015. Available at: <http://dx.doi.org/10.1093/eurheartj/ehv466>

¹⁸ Brill D and Colyer S. Second free anticoagulant scheme to launch. Australian Doctor 24 April 2012. Available at: <http://www.australiandoctor.com.au/news/latest-news/second-free-anticoagulant-scheme-to-launch>

¹⁹ Colyer S. Free dabigatran scheme extended. Australian Doctor 26 April 2012. Available at: <http://www.australiandoctor.com.au/news/latest-news/free-dabigatran-scheme-extended>

²⁰ Therapeutic Goods Administration, AusPAR for rivaroxaban October 2013. Available at: <https://www.tga.gov.au/browse-auspars-product-name>

Restriction

For details of the current PBS listing refer to the [PBS website](#).

Date of listing on PBS

The dates of PBS listing for the prevention of stroke or systemic embolism in NVAF were:

Rivaroxaban: 1 August 2013

Apixaban: 1 September 2013

Dabigatran: 1 September 2013

Additionally, these NOACs are PBS-listed for the prevention of VTE events in adult patients who have undergone major orthopaedic surgery of the lower limb (elective total hip or knee replacement); the treatment of DVT and PE, and for the prevention of recurrent DVT and PE in adults. These listings commenced between August 2009 and January 2012. Refer to Appendix A for details.

Warfarin has been listed on the PBS as an anticoagulant since 1964.

Changes to listing

Please refer to Appendix A for details of changes to listing for NOACs. Current PBS listing details are available from the [PBS website](#).

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

The PBAC considered several submissions and a review report for the NOACs. Further details on the PBAC consideration of the submissions²¹ and the Review²² are available.

In March 2013, the PBAC noted the findings of the Review of Anticoagulation Therapies in Atrial Fibrillation, which presented an updated consideration of all NOACs trials (dabigatran, rivaroxaban and apixaban) and an assessment of new information concerning comparative safety as well as consideration of management of warfarin therapy in the Australian context. Revised multivariate sensitivity analyses were provided by the three sponsors of the NOACs in response to the PBAC's request of December 2012 for new analyses²³.

At the March 2013 meeting, the PBAC recommended the listing of rivaroxaban as an Authority Required (Streamlined) benefit for the prevention of stroke in patients with NVAF who meet certain criteria, at the price proposed in the submission on a cost-effectiveness

²¹ PBS Public Summary Documents by Product. Available at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product>

²² PBS Reviews. Available at: <https://www.pbs.gov.au/info/browse/reviews>

²³ Rivaroxaban SPAF Public Summary Document March 2013. Accessed on 15 April 2016. Available at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2013-03/rivaroxaban-spaaf>

basis in comparison with warfarin for the two outcomes, intracranial bleeding and haemorrhagic stroke, identified by the Review as being of most significance.

The PBAC considered that, given the substantial size of the potential patient population and the corresponding number of telephone Authority applications to the Department of Human Services, it did not consider an Authority Required listing to be practically implementable. The PBAC therefore recommended that rivaroxaban be listed as an Authority Required (Streamlined) listing.

The PBAC advised that the calculations of the total cost to government should be based on the advice provided by the DUSC to the PBAC following the DUSC's extraordinary meeting of 6 March 2013.

To manage the total costs of this therapeutic area to the PBS, the PBAC advised that the listing should be subject to a risk sharing arrangement between the sponsor and the government with 100% of expenditure above the agreed estimates to be rebated to the government.

The PBAC made a new recommendation for dabigatran which varied its initial recommendation of March 2011: The PBAC recommended the listing of dabigatran on the PBS on a cost-minimisation basis to rivaroxaban for the prevention of stroke in patients with non-valvular atrial fibrillation, with the equi-effective dose based on average doses in the trials, and subject to the same risk-sharing arrangement and PBS restriction.

The PBAC recommended the listing of apixaban on the PBS for the prevention of stroke in patients with non-valvular atrial fibrillation on a cost-minimisation basis to rivaroxaban with the equi-effective dose based on doses in the trials, and subject to the same risk-sharing arrangement and PBS restriction.

Details on the PBAC Outcomes from the March 2013 Meeting are available²⁴.

Previous reviews by the DUSC

There have been no previous reviews of NOACs for stroke prevention in NVAf.

In October 2014, the DUSC considered a utilisation analysis of NOACs for the treatment of deep vein thrombosis (DVT), the prevention of venous thromboembolism (VTE), treatment of pulmonary embolism (PE) and for the prevention of recurrent venous thromboembolism (outside the scope of the current analysis). The DUSC noted that although each indication had a separate streamlined code, there was some small use of the AF streamlined code for dabigatran and apixaban against PBS item codes for prevention of VTE in hip and knee

²⁴ PBS PBAC Positive Recommendations. Available at: <http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/2013-03/positive-recommendations>

replacements. This suggested miscoding of indications in the data²⁵. This finding has informed the assumptions underlying the methods for the current analysis.

Approach taken to estimate utilisation

All three minor submissions for the March 2013 PBAC meeting used epidemiological approaches; however, these approaches differed. DUSC provided advice to the PBAC on financial estimates for the total market.

[REDACTED]

[REDACTED]

[REDACTED]

²⁵ DUSC utilisation analysis Public Summary Document. Novel oral anticoagulants for non-atrial fibrillation indications October 2014. Available at: <http://www.pbs.gov.au/info/industry/listing/participants/public-release-docs/novel-oral-anticoagulants-10-2014>

Table 3: Assumptions for the DUSC estimates

Population	Age stratified population, aged ≥40	ABS 3222.0 Series B
AF prevalence	40-49 1%	Sturm et al. (2002)
	50-59 1.5%	
	60-69 4.2%	
	70-79 10.9%	
	≥80 14.8%	
NVAF prevalence	90.2%	Ang et al. (1998)
Stroke risk distribution in NVAF	CHADS ₂ =0 12.9%	Rietbrock et al. (2008) (Table 1)
	CHADS ₂ =1 30.3%	
	CHADS ₂ ≥2 56.8%	
Uptake rates	35% - 75% over 5 years	DUSC estimate

A table of the DUSC estimates of patients per year for NOACs is available in Appendix B. The DUSC noted that the three submissions had each taken a different approach in estimating the likely uptake of NOACs, resulting in a range of estimated use. The DUSC took account of the three submissions' estimates and additional sources of information, and considered that the best estimate of overall uptake for the NOACs is 35% of the total eligible population in Year 1 increasing to 75% in Year 5. In coming to these estimates, the DUSC triangulated submission estimates with publically available information. [REDACTED]

[REDACTED] DUSC considered that a high rate of compliance could be expected, especially for patients switching from warfarin. DUSC considered 90% to be a reasonable estimate of compliance in the eligible population.

Methods

The analyses used data from the DUSC database and the Department of Human Services (DHS) supplied prescriptions database.

The DUSC database combines data on PBS prescriptions submitted to the DHS for payment of a R/PBS subsidy by the Government with an estimate of under patient co-payment prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012. This was replaced by actual under patient co-payment prescription data from 1 April 2012. The DUSC database includes an estimate of private prescriptions based on dispensing data from a sample of pharmacies to the end of August 2012. An estimate of

private prescriptions is not included from 1 September 2012. The DUSC database was used for analyses of prescriptions and R/PBS benefits. The data were supplemented with information from the DHS supplied prescriptions database to limit prescriptions and benefits for NOACs to those supplied with streamlined code 4269 for prevention of stroke or systemic embolism in NVAF.

The DHS supplied prescriptions database includes data submitted to DHS for payment of a R/PBS subsidy by the Government. This database includes actual under co-payment prescription data from 1 April 2012. This database includes a de-identified patient identifier number that identifies prescriptions supplied to a single patient. This allows for patients to be classified as new patients and to identify prior treatments. The DHS database was used for patient level analyses, including age, location, prescriber type, prior prescription, and time to refill.

For NOACs, the relevant streamlined authority code for prevention of stroke or systemic embolism in NVAF is 4269. A patient may not consistently have the same code assigned to their original prescriptions over their treatment duration for a variety of reasons including, but not limited to, multiple prescribers, errors made or genuine changes in indication. For the purpose of limiting the patient level analyses to people supplied NOACs for NVAF, the most commonly assigned streamlined code on original prescriptions between August 2013 and December 2015 has been deemed to be the most accurate assumption for a correct indication. Only original prescriptions have been counted as the repeat prescriptions associated with an original prescription will carry the same streamlined code. This cohort was used for patient level analyses where indicated in the figure legend.

For the patient level analyses, patients initiating to a medicine or group of medicines were defined as those who have not been supplied that medicine or group of medicines since January 2010. Age was assigned based on the first supply in the time period. A small number of patients that had prescriptions with a code registering as blank or zero have been excluded.

The location analysis used the Australian Bureau of Statistics (ABS) Quarterly Population Estimates (ERP), by State/Territory, Sex and Age database in September 2015. The rate of people supplied anticoagulant therapy standardised per 100,000 population in each state and territory was calculated based on the ABS data and the DHS database.

A prior prescription analysis was conducted for patients in the NVAF cohort to determine if they had been supplied warfarin in the three years prior to their first NOAC prescription. This analysis included concessional only patients as warfarin is under the co-payment and under co-payment data were not available for the entire three year look-back period. A patient's status as a concessional or general patient was based on all NOAC and warfarin prescriptions from January 2010 to December 2015. A sensitivity analysis was performed with a one year look-back for all (i.e. concessional and general) patients.

For the time to refill prescription analysis, any form and strength of a drug could be resupplied in any form and strength of the same drug. All the data from January 2010 to December 2015 was used; however, prescriptions within three median days to resupply

(specific to that drug) of the end of the data period were excluded to avoid a bias towards shorter time to resupply. These were only excluded as resupplied prescriptions but they were still used for the purpose of determining the days to resupply of the previous prescription. Warfarin has not been included in this analysis as it is supplied in bottles of 50 tablets and in different strengths to accommodate the variable doses.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Department of Human Services (DHS) Medicare date of processing data.²⁶ The publicly available DHS Medicare data only includes subsidised R/PBS prescriptions with prescriptions under the patient co-payment not included.

Limitations of the data

For a NOAC prescription to be valid on the PBS, the prescriber must nominate the patient's treatment indication using an authority streamlined code. Although each indication has a separate streamlined code, in the data from August 2013 to December 2015, this field is blank or zero against a small number of patients.

Utilisation of NOACs for the treatment of DVT, the prevention of VTE, treatment of PE and for the prevention of recurrent VTE is out of scope of this review. Dabigatran has separate item codes for NVAF; rivaroxaban 15mg has a separate Item code yet the 20mg does not; and apixaban does not have specific item codes for NVAF (Appendix C). Therefore some item codes contain multiple indications, each with a different streamlined authority code. This may lead to miscoding of items by prescribers or dispensers.

Warfarin has an unrestricted listing on the PBS therefore the indication for the use of this anticoagulant cannot be deduced from PBS prescription data. Care must be taken when interpreting the data for this reason.

²⁶ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

Results

Analysis of drug utilisation

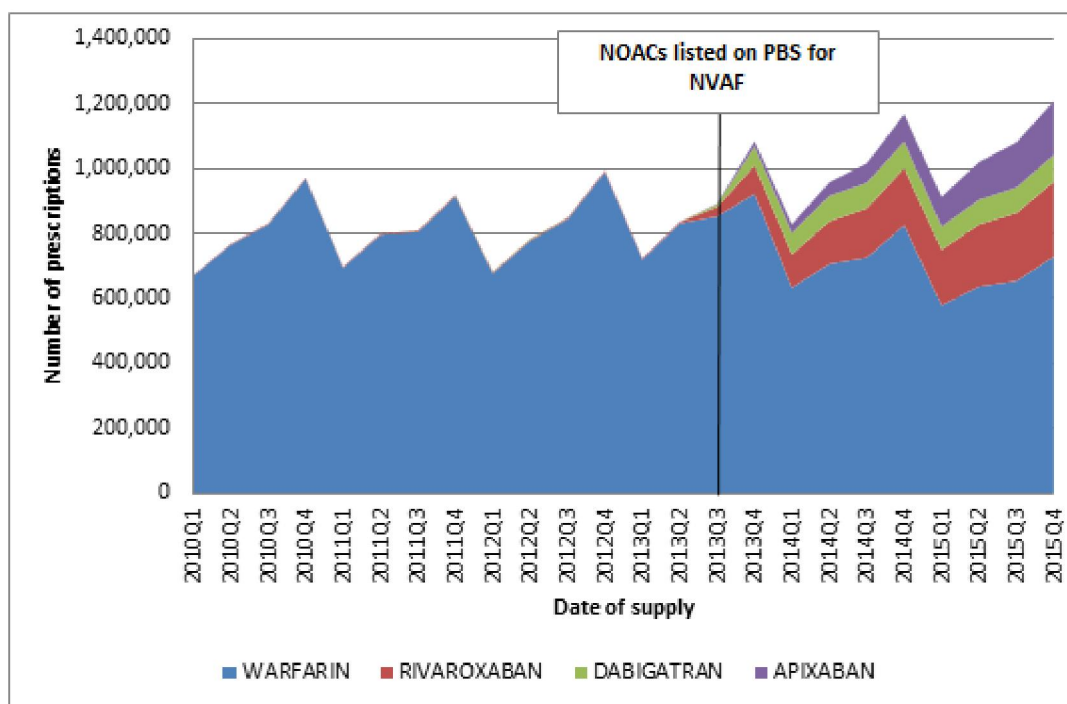


Figure 1: Number of anticoagulant prescriptions supplied from 2010 to 2015

Source: DUSC and DHS supplied prescriptions databases accessed March 2016. Includes private estimate, under co-payment estimate and actual. Only streamlined authority code 4269 for NVAF and blank codes have been included for NOACs.

Figure 1 illustrates the use of warfarin and NOACs for the NVAF indication since 2010. The use of warfarin has declined since the listing of the NOACs on the PBS for NVAF however it still remains the most used anticoagulant by prescription volume. The listing of the NOACs appears to have increased the total anticoagulant market. It should be noted that warfarin can be supplied in three different strengths and patients adjust their dose based on their INR. Therefore patients may have all three strengths, i.e. three separate prescriptions, dispensed at any one time. Furthermore, the fluctuations in supply seen in Figure 1 may be due to the safety net effect taking place in December each year.

Table 4: Total number of PBS subsidised NOAC prescriptions supplied for NVAF indication

Year	Number of prescriptions
2013 [†]	183,474
2014	1,061,580
2015	1,604,242

Source: DHS supplied prescriptions database accessed March 2016. Only streamlined authority code 4269 has been selected.

[†] NOACs first listed on PBS in August and September 2013 therefore data is part-year

Utilisation by individual NOACs

The first NOAC listing on the PBS for use in NVAF was in August 2013. Figure 2 depicts the number of NOAC prescriptions supplied by strength over a two year period from the first PBS listing.

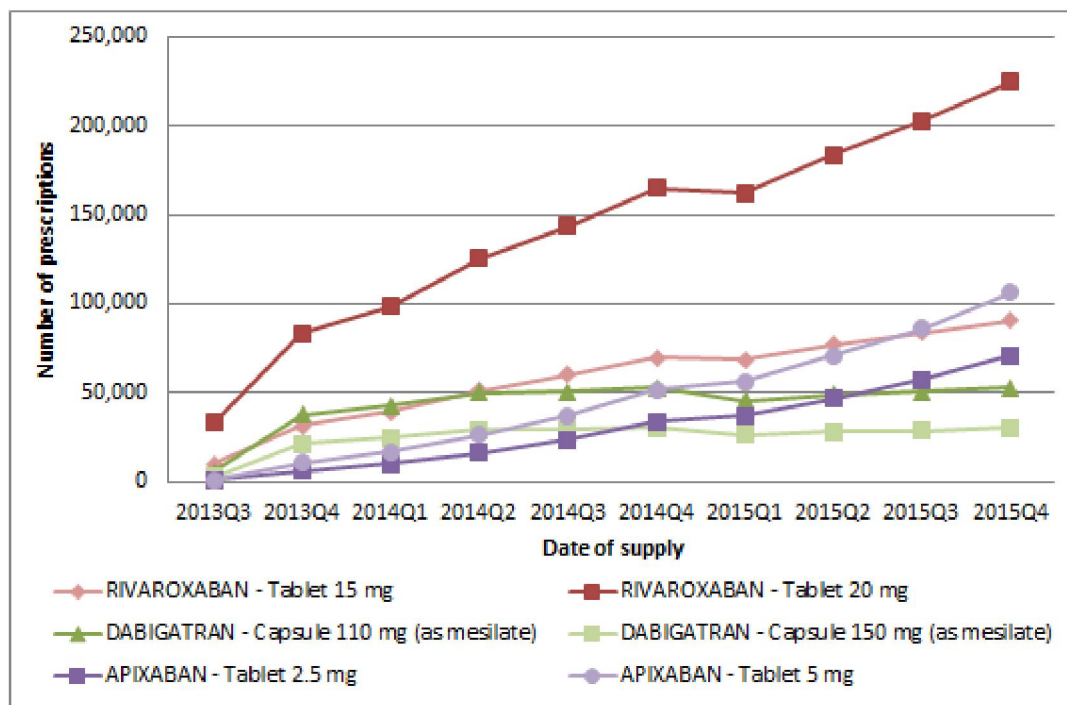


Figure 2: Number of NOAC prescriptions supplied by drug and strength from August 2013 to December 2015 for NVAF indication

Source: DUSC and DHS supplied prescriptions databases accessed March 2016. Prescriptions by date of supply. Only streamlined authority code 4269 has been selected.

The most commonly supplied NOAC by drug and strength was rivaroxaban 20mg. Use of apixaban is increasing rapidly.

Table 5 indicates the number of prescriptions supplied for the NOACs based on the strength of the drug since being listed on the PBS for NVAF. Both apixaban and rivaroxaban had the higher doses supplied the most, while for dabigatran the lower dose was supplied more often.

Table 5: NOAC prescriptions supplied by drug and strength from August 2013 to December 2015 for NVAF indication

	Apixaban		Dabigatran		Rivaroxaban	
	2.5mg	5mg	110mg	150mg	15mg	20mg
Prescriptions and % use for that drug	279,728 (38%)	453,145 (62%)	420,434 (63%)	247,071 (37%)	536,011 (37%)	913,024 (63%)

Source: DHS supplied prescription database accessed March 2016. Only streamlined authority code 4269 has been selected.

Figure 3 illustrates the number of people supplied a NOAC by calendar year (prevalent) and, of these people, the number for whom this was their first NOAC supply (initiating).

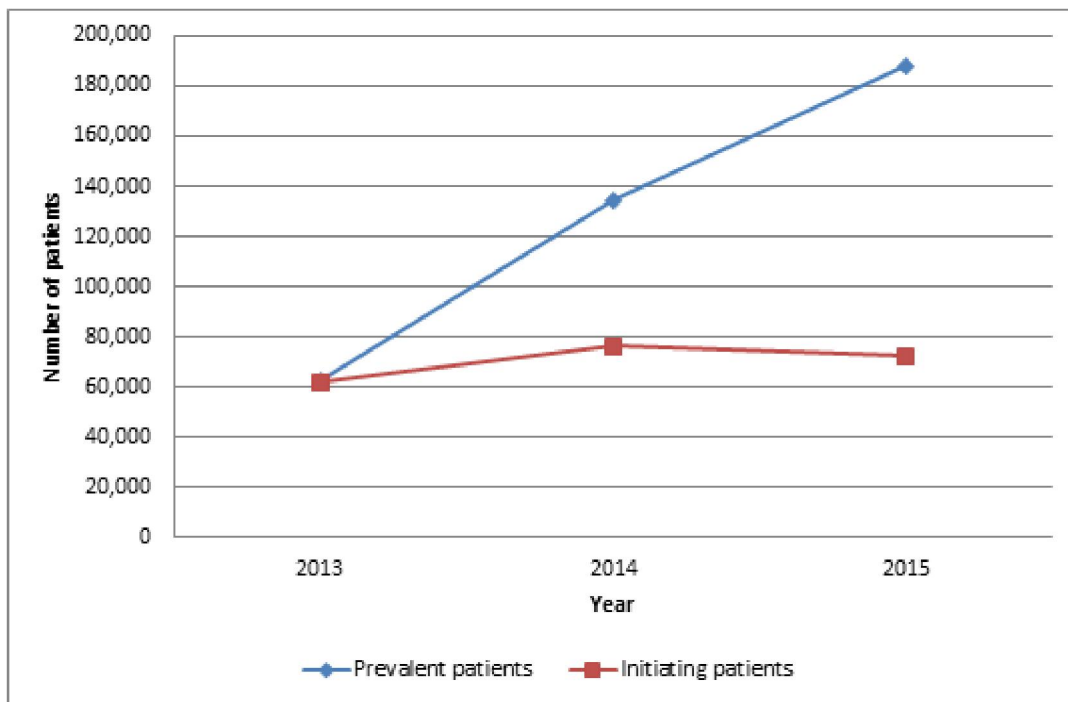


Figure 3: Number of patients initiating and prevalent to NOACs for NVAF by year

Source: DHS supplied prescription database accessed May 2016. Initiating patients are defined as those who have not been supplied a NOAC prescription since January 2010. NOACs are for NVAF cohort (refer to Method).

The number of initiating patients by calendar year has remained stable; however, 2013 is a part-year as the first NOAC was listed in August 2013. The overall number of patients supplied a NOAC prescription has increased steadily. In 2015, there were 188,130 patients supplied a NOAC prescription and, of these, 72,484 patients were supplied their first PBS-subsidised NOAC prescription.

It was expected that some patients with NVAF who commenced therapy with NOACs for the prevention of stroke or systemic embolism would have received prior therapy with warfarin, while other patients would be new to anticoagulant therapy. Figure 4 and Table 6 illustrate the proportion of patients initiating NOACs for use in NVAF who were supplied warfarin prior to their first NOAC supply.

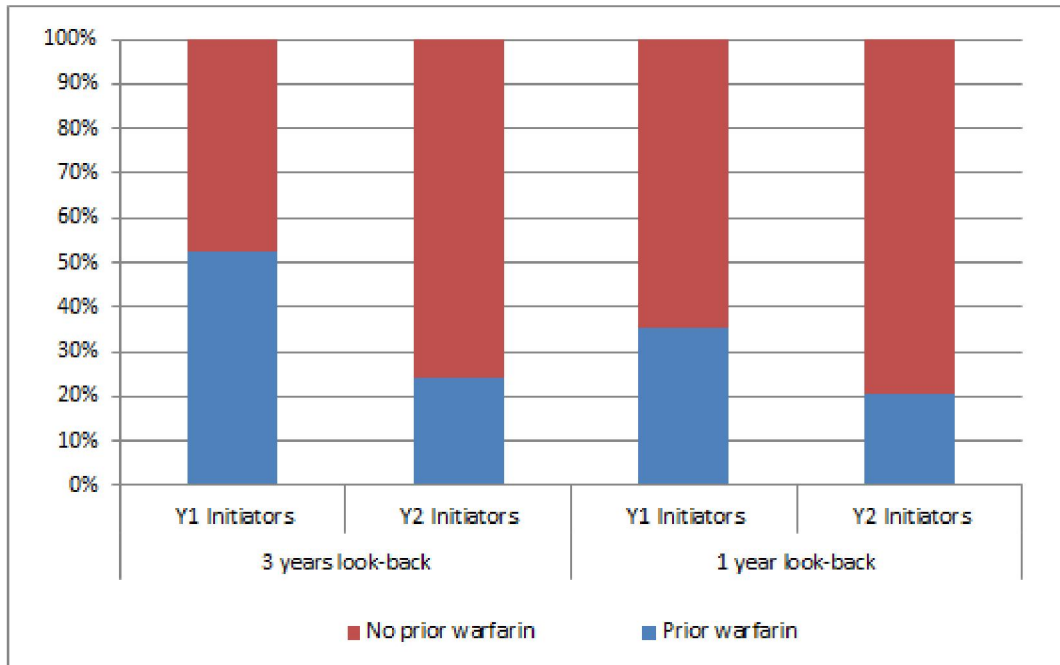


Figure 4: Proportion of patients initiating NOACs for NVAF indication supplied prior warfarin

Source: DHS supplied prescriptions database accessed April 2016. Patients were concessional only for the period. Y1 (year one) is the time period August 2013-July 2014 and Y2 (year two) is the time period August 2014-July 2015.

Table 6: Proportion of patients initiating NOACs for NVAF indication supplied prior warfarin

Look-back period	Cohort	Prior warfarin	No prior warfarin	Total
3 years look-back	Y1 Initiators	41,705 (53%)	37,629 (47%)	79,334
	Y2 Initiators	12,224 (24%)	38,328 (76%)	50,552
1 year look-back	Y1 Initiators	28,257 (36%)	51,077 (64%)	79,334
	Y2 Initiators	10,467 (21%)	40,085 (79%)	50,552

Source: DHS supplied prescriptions database accessed April 2016. Only concession patients have been included. Y1 (year one) is the time period August 2013-July 2014 and Y2 (year two) is the time period August 2014-July 2015.

Of concession only patients who initiated NOACs for NVAF in the first year of PBS-listing (August 2013 – July 2014), 47% had no prior warfarin supply in the three years before their initial NOAC prescription. In the following year (August 2014 – July 2015), this increased to 76%. This indicates that the proportion of initiating patients who switched from warfarin was lower in year two than in year one.

The first Product Familiarisation Program (PFP) for NOACs began in 2011¹⁹. A three year look-back period includes warfarin patients who may have stopped taking warfarin prior to initiating their NOAC on the PBS due to involvement in PFPs. A one year look-back was done as a sensitivity analysis. A benefit of a one year look-back is that it allowed an analysis to be performed with concessional and general patients as under co-payment data was

available for this period. The analysis combining general and concessional patients (not presented), had very similar results to those presented for the one year look-back in concessional only patients in Figure 4 and Table 6.

In 2013, it is likely that some patients who appear as new to PBS-subsidised anticoagulant therapy may have received NOACs previously through PFPs or other means. As anticoagulants are required to be taken in an ongoing manner, it is expected that these patients would have received their first PBS-subsidised NOAC in 2013, soon after listing. As such, by 2014 it is more likely that patients who appear in the data as new to PBS-subsidised anticoagulant therapy are true initiators. For NVAF patients new to PBS-subsidised anticoagulant therapy in 2014 or 2015, the choice of anticoagulant is shown in Figure 5.

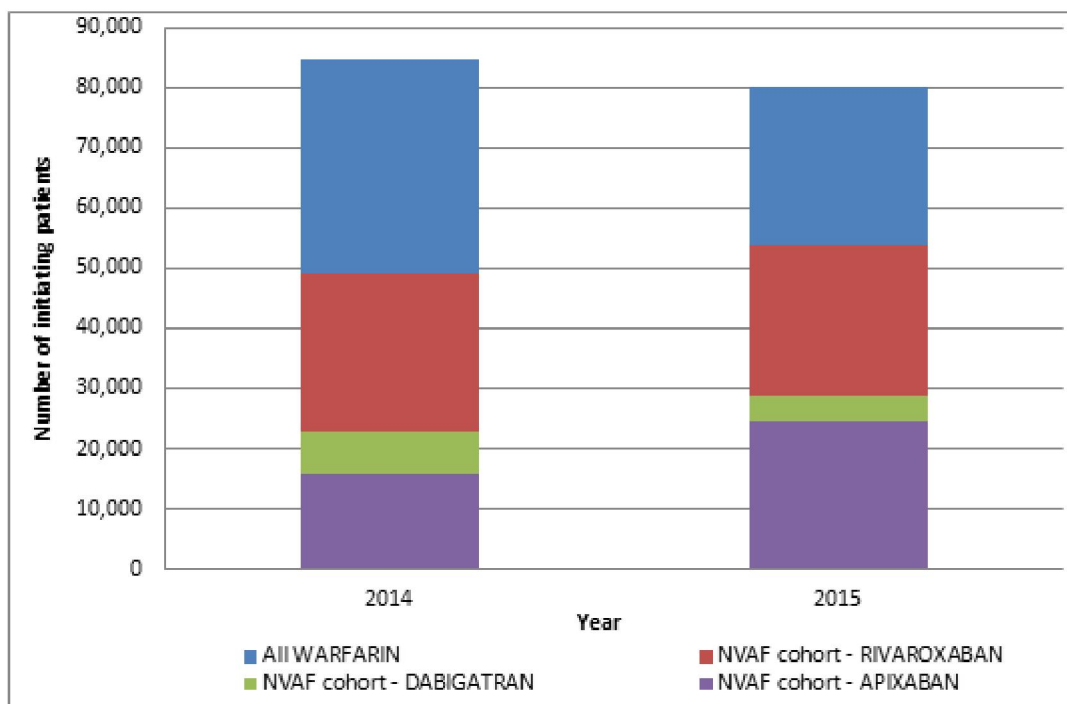


Figure 5: Number of patients initiating to anticoagulant therapy by initial therapy in 2014 and 2015

Source: DHS supplied prescriptions database accessed May 2016. Patients initiating to anticoagulant therapy are defined as those who have not been supplied a NOAC or warfarin since January 2010. All warfarin patients are included; NOACs are for NVAF cohort (refer to Method).

For patients new to anticoagulant therapy in 2014 and 2015, more patients commenced anticoagulant therapy with NOACs than with warfarin. Further, the number of people who started anticoagulant therapy on warfarin declined between 2014 and 2015.

In 2014, rivaroxaban had the greatest market share in patients starting anticoagulant therapy with a NOAC, while in 2015, rivaroxaban and apixaban had similar market share. In both 2014 and 2015 dabigatran use was substantially lower than that of rivaroxaban and apixaban.

The age distribution of people supplied their first anticoagulant therapy in 2015 is shown in Figure 6.

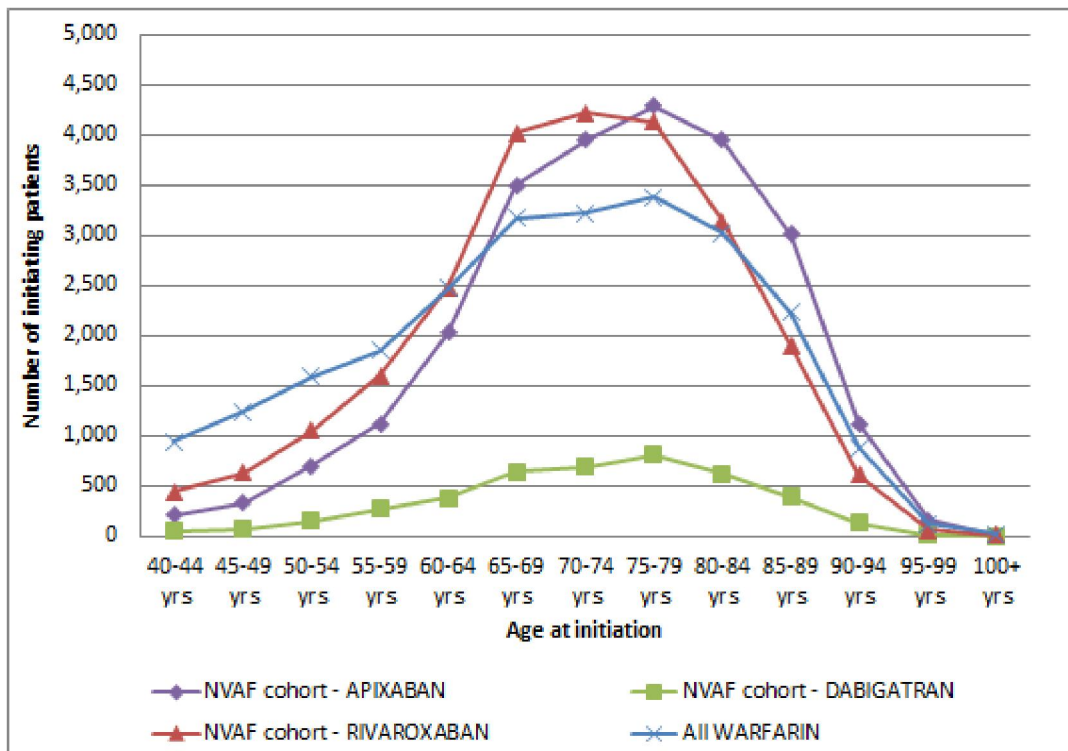


Figure 6: Number of patients initiating anticoagulant therapy in 2015 by age at initiation and first anticoagulant supplied

Source: DHS supplied prescriptions database accessed May 2016. Initiating patients are defined as those who have not been supplied a prescription for warfarin or a NOAC since January 2010. All warfarin patients are included; NOACs are for NVAf cohort (refer to Method).

The age distribution for people commencing their first anticoagulant therapy does not differ greatly by the medicine first supplied; that is, the data do not show a tendency for different anticoagulant choice on the basis of age.

For NVAf patients supplied their first NOAC, Figure 7 depicts the NOAC a patient was initiated on by their age, the drug form and the strength.

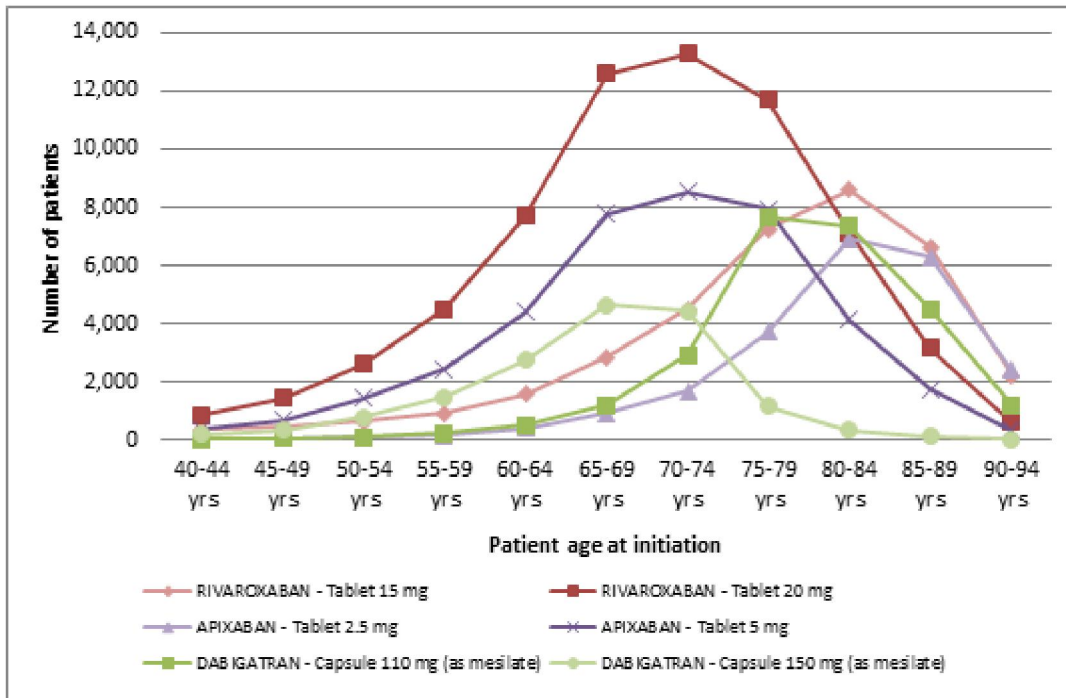


Figure 7: Number of patients initiating to a NOAC from August 2013 to December 2015 by age and NOAC drug and strength

Source: DHS supplied prescriptions database accessed April 2016. Initiating patients are defined as those who have not been supplied a prescription for their first NOAC since January 2010. NOACs are for NVAf cohort (refer to Method).

Of note is the trend for the lower strengths of NOACs to be prescribed in the older populations. This is in accordance with the clinical recommendation that lower doses be used in patients with impaired renal function, which typically presents in older populations.

Time to refilling prescription analysis

Figure 8 depicts the frequency of refill of prescriptions for the NOACs used in NVAF where the date of supply was on or after August 2013.

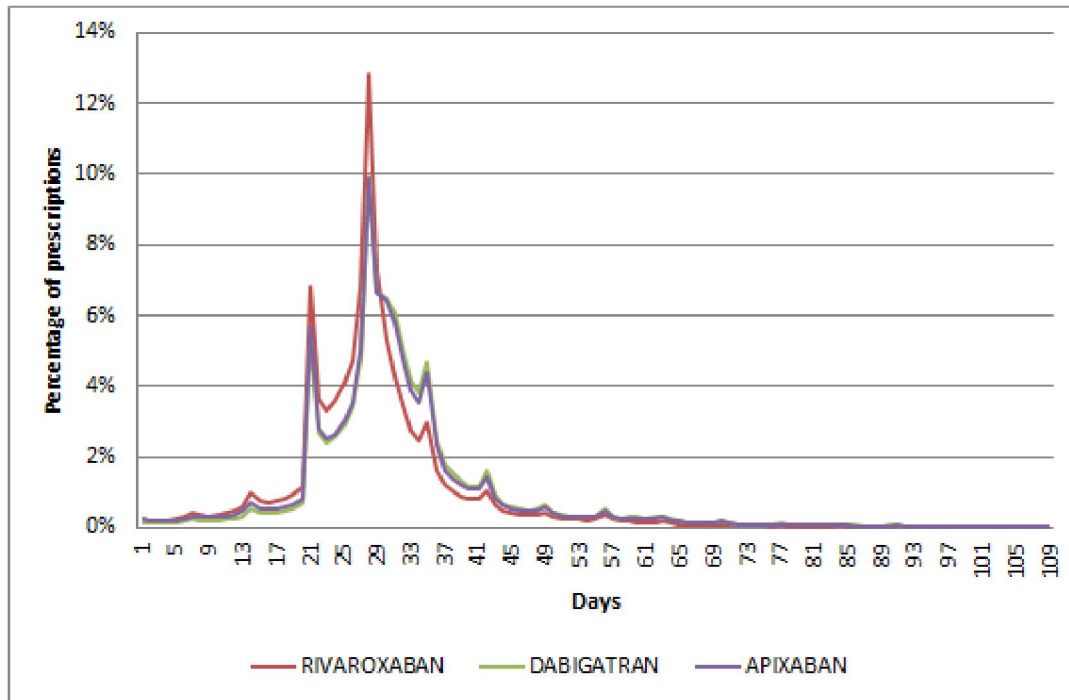


Figure 8: Percentage frequency of days to resupply of NOACs for NVAF indication

Source: DHS supplied prescriptions database accessed April 2016. NOACs are for NVAF cohort (refer to Method).

Patients who take rivaroxaban as prescribed will have a 28 day supply in each box therefore resupply at around 28 days may indicate that patients are compliant with their therapy. The peaks that can be seen at the 21 day mark may be due to resupply of a prescription by patients adhering to the 20 day PBS rule. Apixaban and dabigatran come in boxes of 60, with twice daily dosing. Due to the higher number of tablets or capsules in a box, patients taking either of these two medications have more capacity to delay their resupply for longer than rivaroxaban, if they are non-compliant.

Analysis by location

Figure 9 illustrates the rate of people supplied anticoagulant therapy age standardised per 1,000 population in each state and territory.

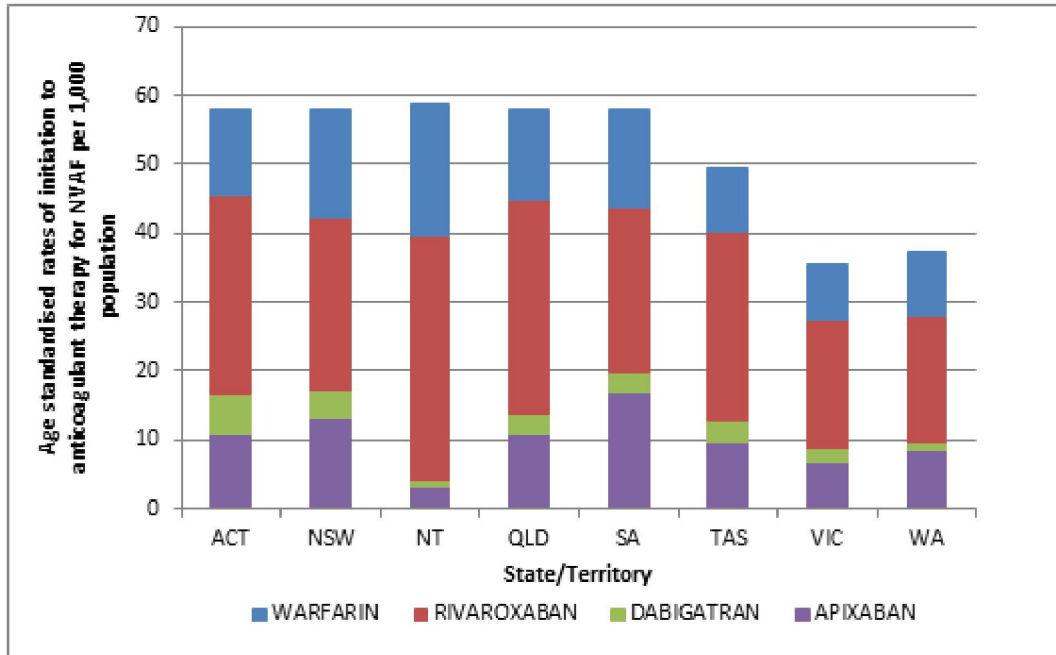


Figure 9: Choice of drug for patients initiating anticoagulant therapy in NVAF by state and territory in 2015

Source: DHS Medicare database and ABS Quarterly Population Estimates (ERP), by State/Territory, Sex and Age database in September 2015; accessed May 2016. Initiating patients are defined as those who have not been supplied an anticoagulant therapy since January 2010. NOACs are for NVAF cohort (refer to Method).

The proportion of new patients commencing on each NOAC varies across these areas. The supply of dabigatran as an initiating anticoagulant therapy was low in 2015 for all states and territories.

Figure 10 illustrates the choice of drug for patients initiating anticoagulant therapy for NVAF in 2015 by the regional or metropolitan area in which it was supplied.

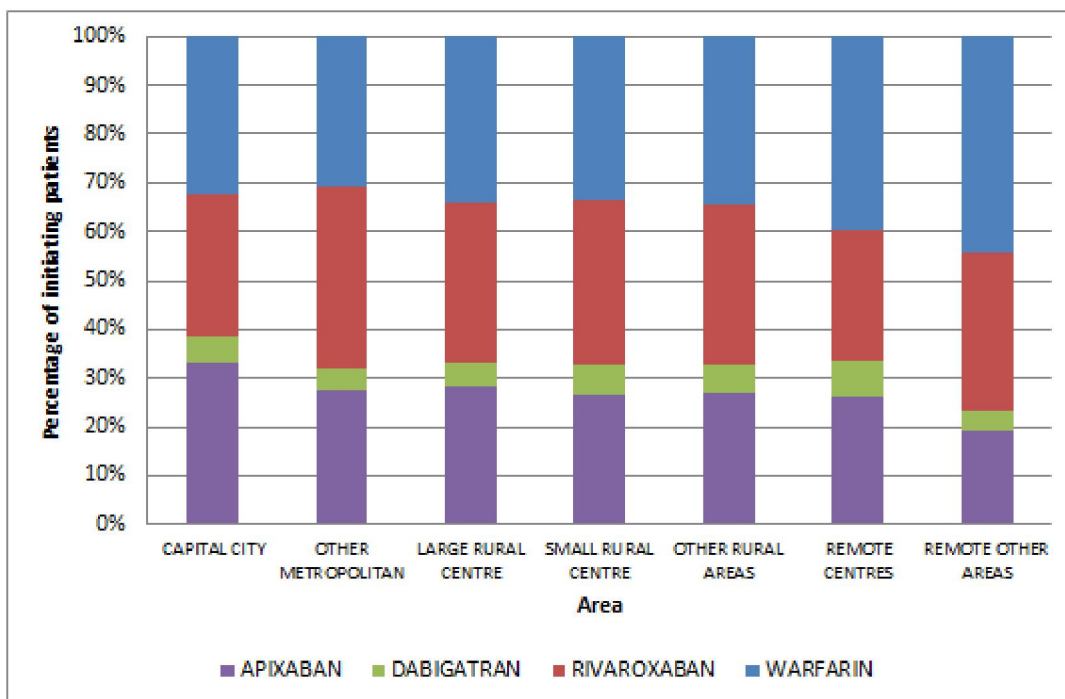


Figure 10: Choice of drug for patients initiating anticoagulant therapy in NVAF based on regional or metropolitan area in 2015

Source: DHS Medicare database accessed May 2016. Initiating patients are defined as those who have not been supplied an anticoagulant therapy since January 2010. NOACs are for NVAF cohort (refer to Method).

In 2015, more patients initiating anticoagulant therapy were supplied NOACs compared with warfarin regardless of the region in which they were supplied. A greater percentage of initiating prescriptions were for warfarin in the remote areas compared to the metropolitan areas.

Analysis by prescriber type

In 2015, more patients had their anticoagulant prescription written by GPs than cardiologists (approximately 1:8). In patients initiating therapy, while more patients had their prescriptions written by GPs, there was a higher proportion of prescriptions written by cardiologists compared with the prevalent population (approximately 1:3). GPs were more likely to initiate warfarin compared to cardiologists and other specialists. Approximately 40% of initiating anticoagulant therapy prescriptions written by GPs were for warfarin compared to approximately 5% by cardiologists.

Analysis of expenditure

The table below summarises R/PBS benefits paid for NOACs by listing year since the first NOAC was listed on the PBS for use in NVAF in August 2013.

Table 7: R/PBS benefits paid for NOACs by calendar year since PBS-listing

Year	Apixaban	Dabigatran	Rivaroxaban	Total
2013 [†]	\$2,463,170	\$5,945,285	\$13,461,414	\$21,869,868
2014	\$19,777,452	\$26,803,720	\$64,016,781	\$110,597,953
2015	\$46,954,994	\$26,247,949	\$89,563,876	\$162,766,819

Source: DUSC database accessed April 2016. Special pricing arrangements apply.

[†] NOACs first listed on PBS in August and September 2013 therefore data is part year

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. As special pricing arrangements apply to the three NOACs, the R/PBS benefits paid does not reflect the true cost to Government.

Analysis of actual versus predicted utilisation

This analysis compares the estimates of utilisation agreed between the Sponsor and the Department prior to listing. The analysis of predicted versus actual use is based on listing years from when the NOACs were first listed on the PBS for prevention of stroke or systemic embolism in NVAF (August 2013).

Table 8: Predicted versus actual numbers of patients and prescriptions for NOACs used in NVAF

		August 2013 – July 2014	August 2014 – July 2015
Patients	Predicted	129,964	171,705
	Actual	109,441	165,196
	Difference	-16%	-4%
Prescriptions	Predicted	1,217,366	1,608,357
	Actual	714,517	1,380,974
	Difference	-41%	-14%

Source: DHS supplied prescriptions database accessed April 2016. Prescriptions by date of supply. Patients are for NVAF cohort only (refer to Method). Only prescriptions with streamlined authority code of 4269 for NVAF are included. Predicted values are from the final agreed estimates based on the DUSC advice.

Table 9: Number of prescriptions for each NOAC supplied for NVAF indication

Number of prescriptions	August 2013-July 2014 (% market share in that year)	August 2014-July 2015 (% market share in that year)
Apixaban	101,998 (14%)	376,208 (27%)
Dabigatran	230,005 (32%)	304,045 (22%)
Rivaroxaban	382,514 (53%)	700,721 (50%)

Source: DHS supplied prescriptions database accessed April 2016. Prescriptions by date of supply. Only prescriptions with streamlined authority code of 4269 for NVAF are included.

In the first year of listing the predicted numbers of patients and prescriptions were overestimated. The predicted patient numbers were closer to actual than the predicted prescription numbers. The predicted numbers of patients and prescriptions in the second year of listing were slightly overestimated, with the actual patient numbers in the second year being just 4% different from actual.

Discussion

The ageing population in Australia means that more people will reach an age where AF will be diagnosed more often. Figure 1 shows that the number of anticoagulant prescriptions has increased since 2010. In particular, the use of NOACs has contributed to a growth in the anticoagulant market since their listing on the PBS for NVAF in August and September 2013. This Figure also shows a small reduction in warfarin use with listing of the NOACs; however, warfarin still remained the highest supplied anticoagulant for stroke prevention by number of prescriptions from 2010 to 2015. Warfarin can be supplied in three different strengths for patients to adjust their dose based on their INR results. This may contribute to the high volume of warfarin prescriptions. Furthermore, warfarin has an unrestricted PBS-listing therefore this Figure presents all PBS warfarin regardless of indication.

Figure 2 and Table 5 illustrate the number of NOAC prescriptions supplied by drug and strength. Rivaroxaban 20mg had the highest number of prescriptions supplied from August 2013 to December 2015 for the NVAF streamlined authority code. Table 5 shows that the higher strength was supplied more than the lower strength for both apixaban and rivaroxaban; while the converse is true for dabigatran.

For patients new to anticoagulant therapy in 2014 and 2015, more patients commenced anticoagulant therapy with NOACs than with warfarin (Figure 5). Further, the number of people who started anticoagulant therapy on warfarin declined between 2014 and 2015. In 2015, rivaroxaban and apixaban had similar market share in patients starting anticoagulant therapy with a NOAC. Dabigatran use was substantially lower. The PBS market may have been primed for dabigatran uptake from the Product Familiarisation Program that ended when the therapy was PBS-listed for the NVAF indication in September 2013. In February 2013, the TGA published updated safety information advising that dabigatran capsules be stored in the manufacturer's original packaging to protect from moisture.^{4,8} Due to the higher prevalence of AF in older people where the use of dose administration aids is common, this safety precaution may have contributed to the reduction in the supply of dabigatran to initiating patients. Many other factors may also affect the choice of NOAC,

such as safety profiles and dosing regimens. Recent publications have reported variable findings regarding the risk of major bleeding with NOACs.^{16,17}

The set daily doses for the NOACs are uniform across patients (with lower doses recommended in certain patient populations), which may be easier for some patients to manage compared to warfarin where individualised dose adjustment is required. Figure 5 illustrates a reduction in both the number and proportion of patients initiating their anticoagulant therapy with warfarin in 2015 compared to 2014. The dosing schedule and fewer monitoring requirements are factors that might influence the choice of NOAC over warfarin.

As warfarin has been PBS-listed for a longer period of time than the NOACs, there was a patient population already using warfarin for prevention of stroke or systemic embolism in NVAF (as well as other indications). The prior prescription analysis (Figure 4 and Table 6) showed that of concession only patients who initiated NOACs for NVAF in the first year of PBS-listing, 47% had no prior warfarin supply in the three years before their initial NOAC prescription. This percentage increased to 76% in the following year. This may suggest a trend as prescribers become increasingly familiar with use of NOACs in this indication. It should be noted that only 24 months of data is currently available and trends cannot be fully established at present.

Warfarin requires INR blood tests to be conducted regularly, which may be considered a barrier to initiating warfarin. Patients can self-monitor their blood coagulation levels, with handheld portable devices, if the prescriber and patient are comfortable with this arrangement.¹³ This may be an option for some patients as vitamin K can be supplied for use in emergency situations.¹¹ Conversely, regular monitoring is not required with NOACs; however, antidotes are not yet readily available in Australia,¹¹ and patients and prescribers might be mindful of this when considering initiation to NOAC therapy.

The age distribution for people commencing their first anticoagulant therapy does not differ greatly by the medicine first supplied; that is, the data do not show a tendency for different anticoagulant choice on the basis of age (Figure 6). Lower doses of each NOAC therapy were prescribed in the older populations initiating NOAC therapy (Figure 7). This is in line with the clinical guidelines for the NOACs as impaired renal function can typically present in older populations.

There was a general trend for most patients to refill their prescriptions within the expected timeframe assuming standard dosing schedules (Figure 8). There is some evidence of a small proportion of patients being supplied therapy outside of the timeframe expected for standard NOAC dosing.

The choice of anticoagulant therapy for initiating patients varied by the state or territory in which the prescription was supplied. Figure 9 shows the rate of people supplied anticoagulant therapy age standardised per 1,000 population in each state and territory in 2015. Being serious cardiovascular conditions, AF and stroke risk are often treated in a hospital environment. One of the potential factors that may influence the choice of anticoagulant therapy is the medicines that are listed on a public hospital's formulary. Most

of the states and territories have their own region-wide public hospital formularies with variations in operational procedures between them. For example, in Queensland and the Northern Territory all public hospital formularies list just rivaroxaban for use in AF. In South Australia all public hospitals have apixaban and rivaroxaban listed; however, rivaroxaban has restrictions on its use such as when apixaban is not appropriate as per the PBS criteria.

The choice of initial anticoagulant therapy for NVAf varied slightly depending on whether the prescription was supplied in a regional or metropolitan area (Figure 10). More patients initiating anticoagulant therapy in 2015 were supplied NOACs compared with warfarin regardless of the region in which they were supplied. A greater percentage of initiating prescriptions were for warfarin in the remote areas compared to the metropolitan areas.

In 2015, cardiologists wrote a greater proportion of prescriptions for patients initiating anticoagulant therapy than for ongoing anticoagulant prescriptions. Cardiologists were less inclined to prescribe warfarin to initiating patients compared to GPs. GPs wrote a far greater proportion of prescriptions for anticoagulant therapy than cardiologists for both initiating and ongoing prescriptions.

Table 8 outlines the analysis of actual versus predicted utilisation of NOACs for prevention of stroke or systemic embolism in NVAf. In the first year of listing the predicted numbers of patients and prescriptions were overestimated. The predicted patient numbers were closer to actual than the predicted prescription numbers. The predicted numbers of patients and prescriptions in the second year of listing were slightly overestimated, with the actual patient numbers in the second year being just 4% different from actual.

DUSC consideration

DUSC noted the growth in the anticoagulant market since the listing of NOACs for use in NVAf. DUSC also noted that warfarin has an unrestricted PBS-listing therefore all PBS warfarin was presented regardless of indication.

DUSC noted that for patients new to therapy in 2014 and 2015, dabigatran use was substantially lower than that of apixaban and rivaroxaban. Further, the number of people initiating NOAC therapy on dabigatran declined in 2015 compared to 2014. DUSC considered that the effect of the dabigatran Product Familiarisation Program, which ended when the therapy was PBS-listed for use in NVAf in September 2013, may have dissipated.

DUSC noted the sensitivity analysis which indicated that the observed trends in prior warfarin use were similar for concessional and general beneficiaries.

DUSC noted that whilst the warfarin antidote, vitamin K, is readily available in emergency situations, there are no readily available antidotes for NOACs in Australia as of yet.¹¹ DUSC noted that a reversal agent for dabigatran, idarucizumab, was registered on the Australian Register of Therapeutic Goods (ARTG) effective 11 May 2016 for use in emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding. DUSC also noted that idarucizumab has been available in some hospitals in the ACT in the past year,

which may have contributed to the higher use of dabigatran in the ACT compared with other states and territories in 2015. DUSC acknowledged the report provided by the Council of Australian Therapeutics Advisory Groups (CATAG) and discussed how the hospital formularies appear to have a considerable effect on the choice of initiating anticoagulant therapy for patients in that state or territory.

DUSC noted that the lower strengths of NOACs were used in older populations, possibly due to renal impairment, which is clinically appropriate. DUSC noted a recent study which found variation in the recommended NOAC dose depending on which kidney function tests and clinical guidelines were used; DUSC considered this may have implications for NOAC prescribing.²⁷ DUSC noted that rivaroxaban 20mg had the highest number of prescriptions supplied from August 2013 to December 2015 for the NVAF streamlined code. DUSC also noted the pre-subcommittee response from a sponsor that highlighted an Australian study which found inappropriate NOAC doses were used in up to a third of patients in the study, irrespective of renal impairment.²⁸

DUSC noted that there was no apparent difference in time to supply for NOACs that have twice daily or once daily dosing. DUSC recalled its predicted NOAC compliance estimate of 90% from its advice to the March 2013 PBAC meeting.

DUSC acknowledged that for the predicted versus actual analysis, the actual usage numbers were very similar to the predicted.

DUSC noted that there are currently no up to date national guidelines for stroke prevention in NVAF. DUSC considered that continued prescriber education is important to encourage quality use of NOACs as prescribers increase their familiarity with these medicines.

DUSC actions

DUSC requested that the report, sponsor responses, DUSC minutes and the advice obtained from CATAG be provided to the PBAC.

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.

²⁷ Jordan M et al. Use with caution in renal impairment: implications for drug dosing in the general practice setting. National Medicines Symposium 2016: Poster Abstracts (pp. 167-167). Australia: NPS.

²⁸ Pattullo et al. New oral anticoagulants (NOACs) – appropriateness of prescribing in real-world setting. Internal Medicine Journal May 2016. DOI: 10.1111/imj.13118

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

Bayer Australia Ltd: nil comment received.

Boehringer Ingelheim Pty Ltd: nil comment received.

Bristol-Myers Squibb Australia Pty Ltd: nil comment received.

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.

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Appendix A: Changes to listings of NOACs

Drug	Indication	Date
Rivaroxaban	Listed for prevention of VTE in hip replacements (out of scope)	1 August 2009
Rivaroxaban	Listed for prevention of VTE in knee replacements (out of scope)	1 August 2009
Dabigatran	Listed for prevention of VTE in hip replacements (out of scope)	1 April 2010
Dabigatran	Listed for prevention of VTE in knee replacements (out of scope)	1 April 2010
Apixaban	Listed for prevention of VTE in hip replacements (out of scope)	1 January 2012
Apixaban	Listed for prevention of VTE in knee replacements (out of scope)	1 January 2012
Rivaroxaban, dabigatran and apixaban	Restrictions changed to specify whether patient requires 10, 15 or 30 days of treatment and if this is required to complete a course of therapy (out of scope)	1 July 2012
Rivaroxaban	Listed for acute symptomatic deep vein thrombosis (out of scope)	1 December 2012
Rivaroxaban	Listed for prevention of recurrent venous thromboembolism. Patient must not have symptomatic pulmonary embolism (out of scope)	1 December 2012
Rivaroxaban	Listed for pulmonary embolism (out of scope)	1 August 2013
Rivaroxaban	Listed for prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation	1 August 2013
Apixaban	Listed for prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation	1 September 2013
Dabigatran	Listed for prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation	1 September 2013
Rivaroxaban, dabigatran and apixaban	Rivaroxaban, dabigatran and apixaban for prevention of VTE in patients undergoing total hip or knee replacements changed from an Authority Required listing to an Authority Required (STREAMLINED) listing (out of scope)	1 January 2014

Appendix B: DUSC estimate of patients/year for NOACs

	Year 1	Year 2	Year 3	Year 4	Year 5
Age bracket ¹ (AF prevalence) ²					
40-49 (1%)	31,998	32,184	32,378	32,593	32,786
50-59 (1.5%)	44,850	45,306	45,608	45,871	46,138
60-69 (4.2%)	101,562	104,107	106,668	107,753	109,432
70-79 (10.9%)	157,078	164,005	171,078	181,684	190,900
≥80 (14.8%)	137,150	140,072	143,613	147,510	151,501
Total population with AF	472,638	485,675	499,345	515,411	530,758
Total population with NVAF (90.2%) ³	426,320	438,079	450,410	464,901	478,743
Stroke risk distribution (prevalence in NVAF) ⁴					
Population with CHADS ₂ =0 (12.9%)	54,995	56,512	58,103	59,972	61,758
Population with CHADS ₂ =1 (30.3%)	129,175	132,738	136,474	140,865	145,059
Population with CHADS ₂ ≥2 (56.8%)	242,150	248,829	255,833	264,063	271,926
Total	426,320	438,079	450,410	464,901	478,743
Eligible patients (CHADS₂ ≥1)	371,324	381,567	392,307	404,928	416,985
Eligible patients (CHADS₂ ≥2)	242,150	248,829	255,833	264,063	271,926
Uptake rates ⁵	35%	45%	55%	65%	75%
Patients treated with NOAC					
Patients treated CHADS₂ ≥1	129,964	171,705	215,769	263,203	312,739
Patients treated CHADS₂ ≥2	84,752	111,973	140,708	171,641	203,945

¹ ABS 3222.0 Series B

² Sturm et al. (2002)

³ Ang et al. (1998)

⁴ Rietbrock et al. (2008) (Table 1)

⁵ DUSC estimate

Appendix C: PBS listing details for all NOACs and indications (as at May 2016)

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
2160Q	RIVAROXABAN rivaroxaban 15 mg tablet, 42	1	0	\$124.54	Xarelto® Bayer Australia Ltd
2268J	RIVAROXABAN rivaroxaban 20 mg tablet, 28	1	5	\$86.50	
9465E	RIVAROXABAN rivaroxaban 10 mg tablet, 10	1	1	\$37.59	
9466F	RIVAROXABAN rivaroxaban 10 mg tablet, 15	1	1	\$51.18	
9467G	RIVAROXABAN rivaroxaban 10 mg tablet, 30	1	0	\$91.93	
9468H	RIVAROXABAN rivaroxaban 10 mg tablet, 30	1	0	\$37.59	
9469J	RIVAROXABAN rivaroxaban 10 mg tablet, 15	1	0	\$51.18	
9318K	DABIGATRAN dabigatran etexilate 75 mg capsule, 10	2	1	\$43.33	Pradaxa® Boehringer Ingelheim Pty Ltd
9319L	DABIGATRAN dabigatran etexilate 110 mg capsule, 10	2	1	\$36.19	
9320M	DABIGATRAN dabigatran etexilate 75 mg capsule, 60	1	0	\$109.12	
9321N	DABIGATRAN dabigatran etexilate 110 mg capsule, 60	1	0	\$87.71	
9322P	DABIGATRAN dabigatran etexilate 75 mg capsule, 10	2	0	\$43.33	
9323Q	DABIGATRAN dabigatran etexilate 110 mg capsule, 10	2	0	\$36.19	
5054B	APIXABAN apixaban 2.5 mg tablet, 30	1	0	\$53.50	Eliquis® Bristol-Myers Squibb Australia Pty Ltd
5061J	APIXABAN apixaban 2.5 mg tablet, 60	1	0	\$96.58	
5500L	APIXABAN apixaban 2.5 mg tablet, 20	1	0	\$39.14	

Source: www.pbs.gov.au