The University of Auckland;
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PHARMAC

National Picture Of Dabigatran Persistence

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Background

Atrial fibrillation is a common cardiac arrhythmia that predominantly affects the elderly population. It is a risk factor for ischemic stroke and the internationally overall prevalence is around 1% (9).

Dabigatran, a direct thrombin inhibitor, in New Zealand has had funding by PHARMAC since 1 July 2011, indicated for stroke prevention in patients with atrial fibrillation, it is considered a long term therapy (1, 2, 4). There are two doses available for dabigatran 110mg and 150mg, at 110mg its therapeutic efficacy is the same as warfarin and superior for the latter (1).

The advantage of dabigatran is it has fewer drug interactions and potential for adverse events compared with warfarin (5, 7, 8). The most commonly cited side effect being dyspepsia and bleeding (1, 2, 3). It also does not require the frequency of laboratory testing that warfarin does, due to dabigatran's predictable pharmacokinetics (8).

However, this means that the mechanism to check the therapeutic efficacy and patients' adherence of the drug is removed. The potential consequence of non-adherence is increased risks of thromboembolic event with associated morbidity and mortality (5). Studies have reported continuous medication persistence in chronic conditions, including cardiovascular disease, may be half or less than expected (5, 13).

A criticism of data obtained in clinical trials is that they do not always apply to patients in real-world settings, including for dabigatran (1,7). In the study by Thorne et. al. (1), the discontinuation rate of dabigatran rate during clinical practice was 30% for a median period of 8 months use, being twice the rate in the pivotal RE-LY clinical trial (11).

Aim

The primary aim of the study is to quantify persistence (the duration of time from initiation to discontinuation of therapy) with dabigatran therapy.
The secondary aim is to determine the basic characteristics of dabigatran patients and compare and contrast the characteristic of those that discontinued versus those that stayed on dabigatran therapy continuously.

Method (5,6)

This is a retrospective population study of dabigatran patients from 1 July 2011 to 30 June 2014. This descriptive study uses administrative pharmacy claims from PHARMAC's (Pharmaceutical Management Agency) Pharmaceutical Collection data mart, which is a national data repository for subsidised dispensing (15).

Patients were identified by those dispensed dabigatran, and data extracted included dispensing dates. Demographic covariates included age, gender, ethnicity and district health board of domicile. Treatment covariates comprised warfarin and aspirin dispensings for the same patients during the same time period.

The primary outcome measures included dabigatran persistence, defined as "the duration of time from initiation to discontinuation of therapy" (12). Discontinuation was defined as a period of three months without a dabigatran dispensing, and included both 1) patients where the period between the final dispensing date and June 2014 was greater than three months and 2) intermittent users that had at least a three month break in dispensing but then restarted dabigatran dispensings. Pre-determined endpoints included death, discontinuation and end of study period and patients were right-censored if their first dispensing occurred between April and June 2014.

In patients non-persistent with (ie discontinuing) dabigatran therapy, the median time to discontinuation was calculated. The final status of patients that discontinued dabigatran was determined as at 1 July 2014 and included proportion of patients switching to warfarin or aspirin after discontinuation.

Patients were considered persistent on dabigatran therapy if they did not have a break in dabigatran dispensing of more than three months up from the time they entered the study till the end of the study period, patients that exited the study because they died were also classified in this group.

A comparison was undertaken between patients who discontinued and those who persisted with dabigatran treatment, stratified by demographic variables. In order to classify patients according to their treatment prior to dabigatran, dispensing claims data for warfarin and aspirin were obtained for patients from the twelve months prior to July 2011 and patients had to have more than one dispensing of warfarin or aspirin, otherwise they were classed as dabigatran.

Age standardisation (to account for differences in underlying populations' age structures) directly standardised against the NZ 2013 census age distributions. Patients' results were further disaggregated by major ethnicity classes and district health board of domicile populations. Population denominators derived from the 2013 New Zealand Census supplied by Statistics NZ (17).

Statistical significance for distribution was by way of X^2 test. All analyses were performed using SAS 9.3 Software

Results

Results are presented in the following tables and graphs. This shows 30205 patients dispensed dabigatran at any time during the 3-years, 60% being male, and the peak number of patients being in the 80-84 age group (median 71 years) One quarter of patients are aged 80- years and over.

Demographic profile of dabigatran patients

Gender	Number of patients
Female	12211 (40%)
Male	17994 (60%)
Grand Total	**30205**

Table 1: Number of patients dispensed dabigatran July 2011 – June 2014, by gender. – *Aspirin dispensation*

Age band	Number of patients
0-49	1328
50-54	1255
55-59	1881
60-64	3060
65-69	4495
70-74	5228
75-79	5346
80-84	4651
85-89	2349
90-94	569
95-99	39
100-104	4
Grand Total	**30205**

Age band	Patient numbers
0-69	12019 (40%)
70-79	10574 (35%)
80+	7612 (25%)
Total	30205

Mean age: 71.2 years
Median age: 73 years

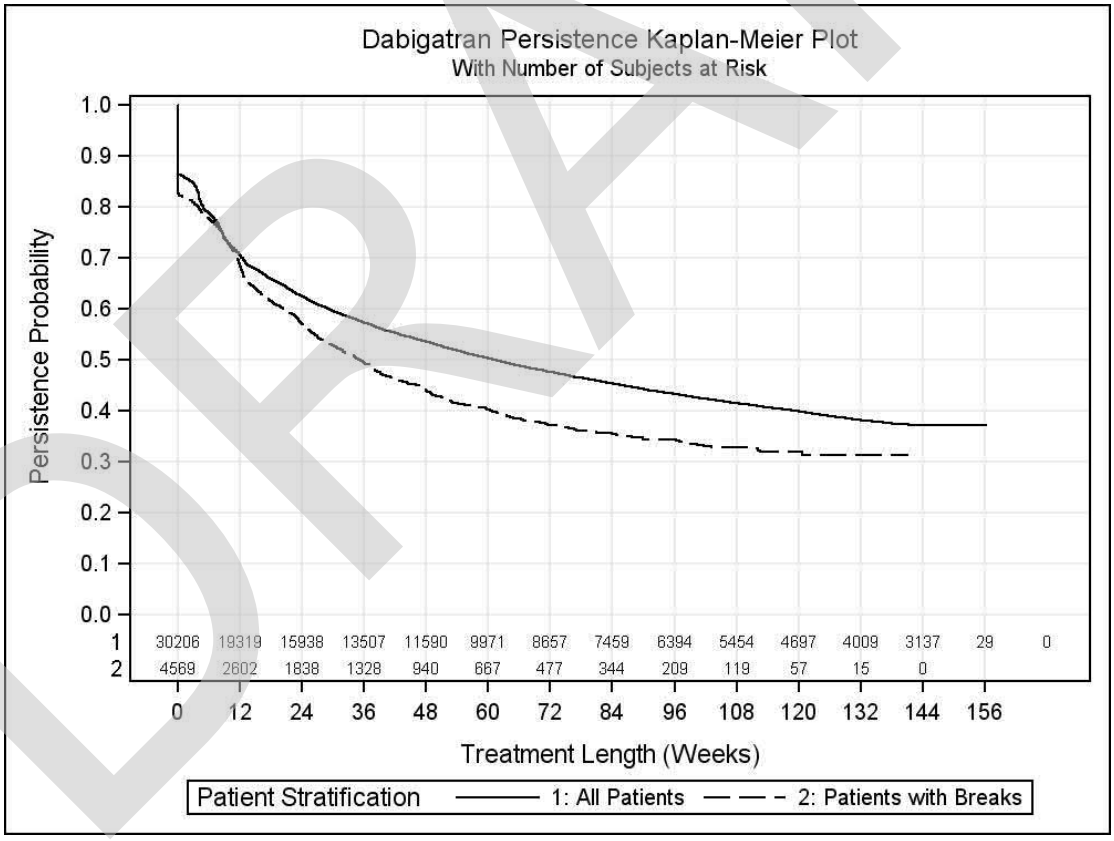
Table 2: Number of dabigatran patients by 5 year age band – *age band*

Ethnicity	Numbers	Proportion
European	24078	80 (74%)
Maori	3527	12 (15%)
Pacific Island	825	3 (7%)
Asian	554	2 (12%)
Other	1221	3
Total	30234	100

Note: Figures in brackets are population proportions from the 2013 NZ census.

Table 3: Number of patients by ethnicity. – *dabigatran patient analysis*

This table shows the variations seen in proportions by ethnicity between dabigatran patients and underlying 2013 Census populations, with ethnic patients other than European having lower-than-expected proportions



Dabigatran Persistence Kaplan-Meier Plot

The LIFETEST Procedure

Test of Equality over Strata			
Test	Chi-Square	DF	Pr > Chi-Square
Log-Rank	89.7628	1	<.0001
Wilcoxon	63.9078	1	<.0001
-2Log(LR)	546.7923	1	<.0001

Figure 1: Kaplan-Meier graph of dabigatran persistence – *KM graph*

This figure shows 15% of all patients are likely to discontinue dabigatran after one dispensing, with a median discontinuation time of 61 weeks. Patients who discontinued dabigatran before re-dispensing had higher chances of discontinuing and were significantly more likely to remain on the medication for a shorter period, with a median discontinuation time of 35 weeks.

Discontinued patients

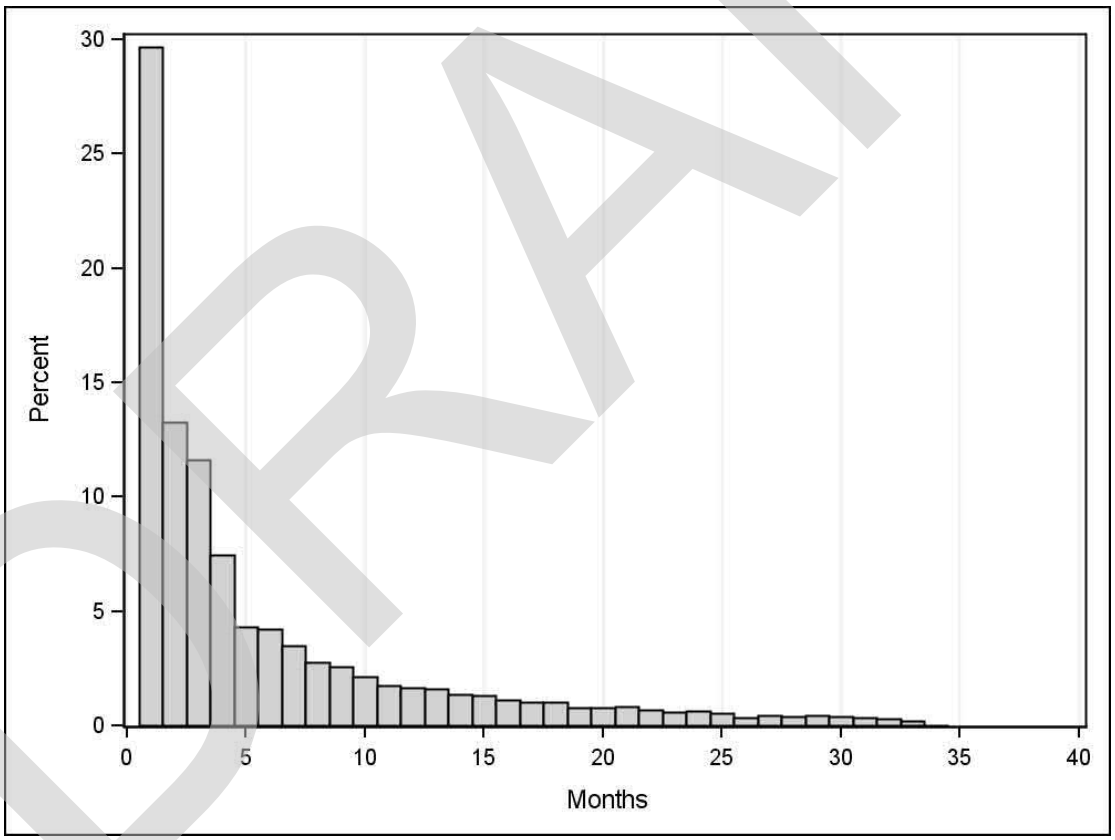


Figure 2: - This figure shows that for discontinued patients, majority of patients stayed on dabigatran for less than four months. (and t-test) - *histo*

	Proportion	Median Period
Dabigatran discontinued	15456 (51%)	3.3 months
Dabigatran stayed on	14749 (49%)	22.3 months*
Total Dabigatran Patients	30205 (100%)	15.3 months

*Maximum study period of 3 years.

Table 4: Median period of persistence for patients who discontinued and stayed on. – *dabigatran patient analysis*

This table stratified the two patient groups, those that continuously stayed on dabigatran and those that discontinued. It shows that around half each of patients discontinue or stay on treatment, and that where dabigatran has been discontinued, the median period that patients stay on the medication is 3.3 months, compared with those that remained on therapy, which has a median period of 22.3 months instead.

Number of breaks (of at least three months)	Number of patients
0	30205
1	4569 (15%)
2	1406
3	557
4	259
5	97
6	42
7	12
8	4

Table 5: Dabigatran discontinuation in patients with breaks (intermittent patients) – *dabigatran adherence*

This table shows that of the 30205 dabigatran patients, 4569 patients take at least one break period from dabigatran dispensing for a minimum of 3 months and may or may not restart dabigatran dispensing. Of those, 1406 would take at least two break periods and so they would restart dabigatran therapy but then take another break again and so forth.

Patient characteristics

Gender distributions of patients who persisted with (stayed on) dabigatran and those who discontinued were not significantly different.

Age distributions of patients who persisted with (stayed on) dabigatran and those who discontinued were not significantly different.

The ethnic distributions of patients who persisted with dabigatran and those who discontinued were very similar.

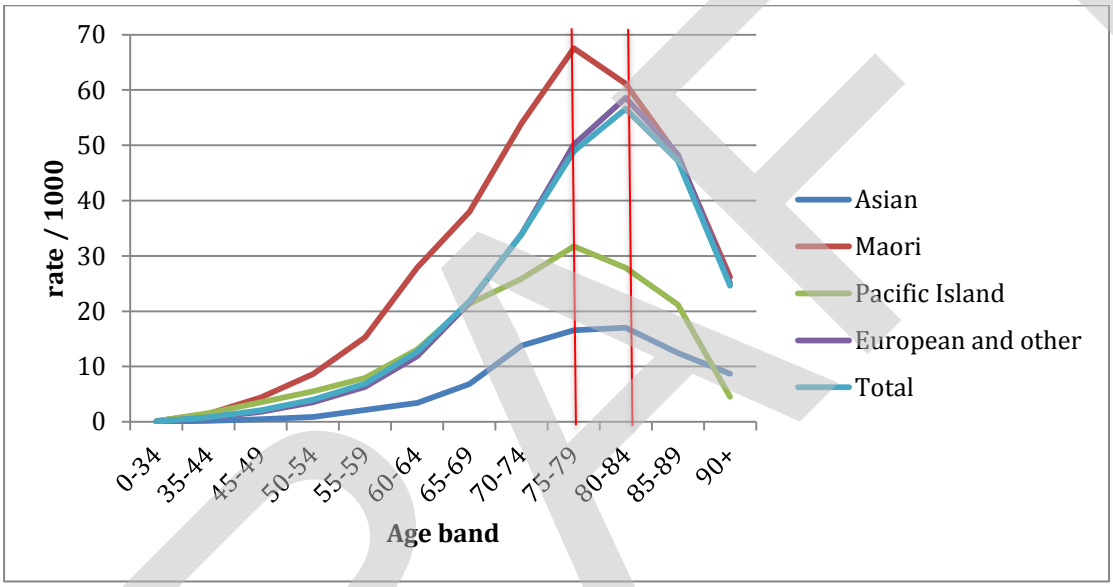


Figure 3: Age-specific three year cumulative incidence of patients dispensed dabigatran by ethnicity. – *AL age band*

This figure indicates that, for maori and pacific patients cumulatively dispensed dabigatran their peak incidence rates occurs in the 75-79 year age band. This is younger than European and Asians, whose incidence rates peak at the 80-84 years age band.

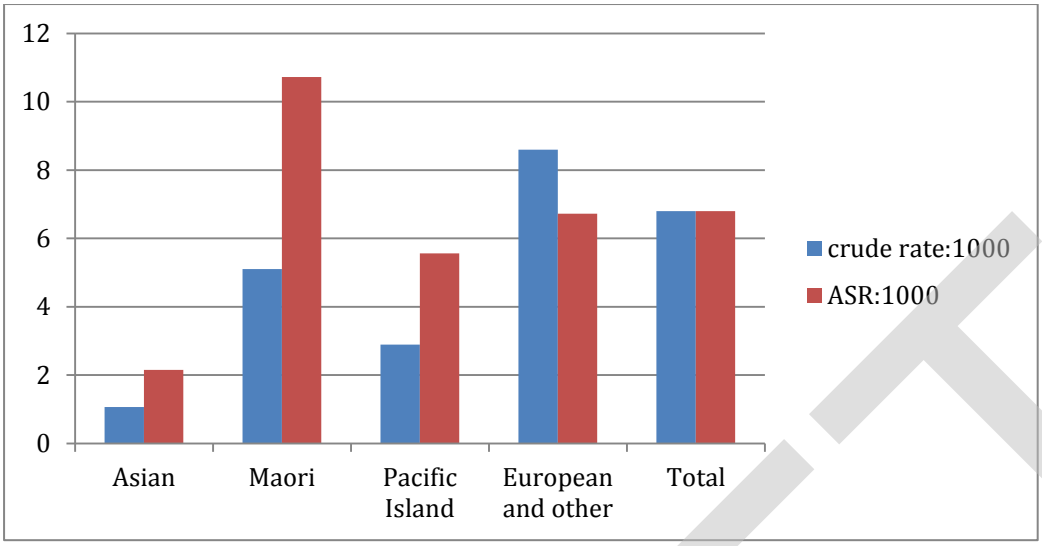


Figure 4: Crude and age-standardised cumulative incidence of patients dispensed dabigatran by ethnicity *–AL age band*

This figure demonstrates the effect of underlying population age distributions on the overall cumulative incidence across different ethnic groups of patients dispensed dabigatran. It indicates that when the overall rates are age standardised, the incidence of Maori receiving dabigatran is around twice (2.1) that of their crude rate. The effect of changing the cumulative incidence of dabigatran use amongst Maori to being less than Europeans/others (crude rates) to become higher than Europeans/others (after age standardising). Higher age-standardised rates than crude rates were seen with Pacific (1.92) and Asian (2.03) groups, although their cumulative rates remained less than European/others despite age-standardisation. Age-standardised, Maori had the highest cumulative incidence (rate ratio 10.7/6.7 = 1.6 compared with European/others), followed by European/others. Pacific people's cumulative incidence of dibigatran use was 5/6 that of European (RR 5.6/6.7 = 0.83, and lower still for Asian (RR 2.2/6.7 = 0.32) at 1/3 or European's.

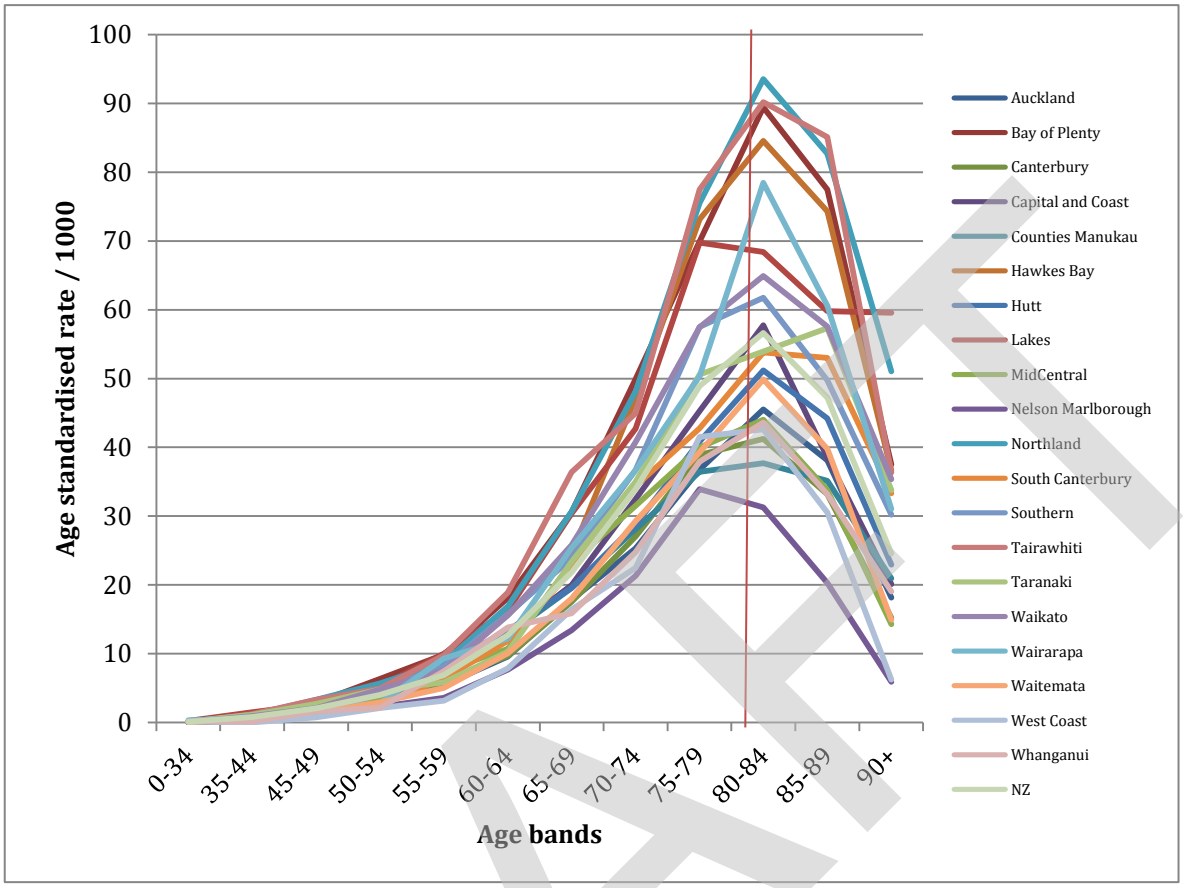
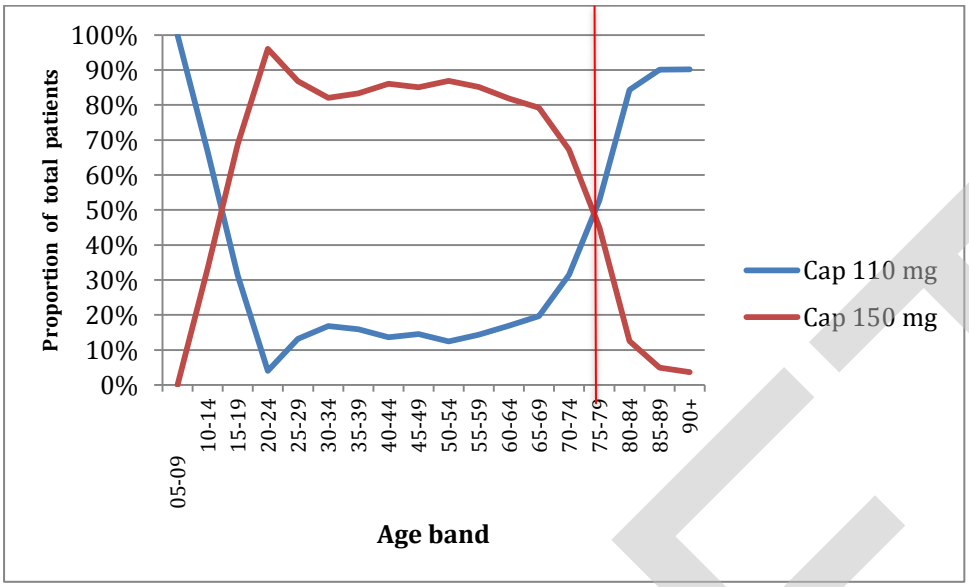


Figure 5: Age-specific three year cumulative incidence of patients dispensed dabigatran by DHBs –*AL age band*

This figure shows that the peak age band that dabigatran was dispensed at was at the 80-84 years of age for majority of DHBs. It also showed that have accounted for different age structures between DHBs, there is still marked variation between DHBs. With the top DHB's rates of 93.5 patients/1000 compared to the bottom DHB's rates of 31.3 patients/1000 at that age band, which is a threefold difference.

Patients dispensed dabigatran aged 80 years and over



Dosage	80-84	85-89	90+
110mg	84.35%	90.12%	90.16%
150mg	12.54%	4.92%	3.64%

Figure 6: Dabigatran dosage distribution – *dabigatran patient analysis*

This figure shows the distribution of dabigatran dosage across different age bands with majority of those over the age of 80 being prescribed the lower dose of 110mg.

Age band	Cap 110mg	Cap 150mg
0-70	14.0%	63.6%
71-79	41.4%	35.3%
80+	44.6%	1.1%

Table 6: Dabigatran prescriptions stratified by age band – *dabigatran data2*

This table shows that 1% of those over the age of 80 are receiving the higher dose of 150mg.

Discontinued patients

Of the 15,456 patients who have discontinued from dabigatran as at July 2014, 23% had aspirin dispensed subsequently, 24% had warfarin dispensed subsequently, 9% did not have any ongoing anticoagulant medication dispensed, 21% restarted dabigatran dispensing, and 23% had died.

	Discontinued patients		**Total patients**	
First Treatment	Patient number	Proportion	Patient number	Proportion
Aspirin	6071	39%	13018	43%
Dabigatran	4503	29%	8715	29%
Warfarin sodium	4882	32%	8472	28%

Table 7: This table shows that regardless of whether patients discontinued dabigatran or not, about 40% of patients had aspirin prior, about 30% had warfarin prior and about 30% were new anticoagulant patients. – *first status*

The distributions by type of DHB (by rurality) for patients who persisted with dabigatran and those who discontinued were very similar.

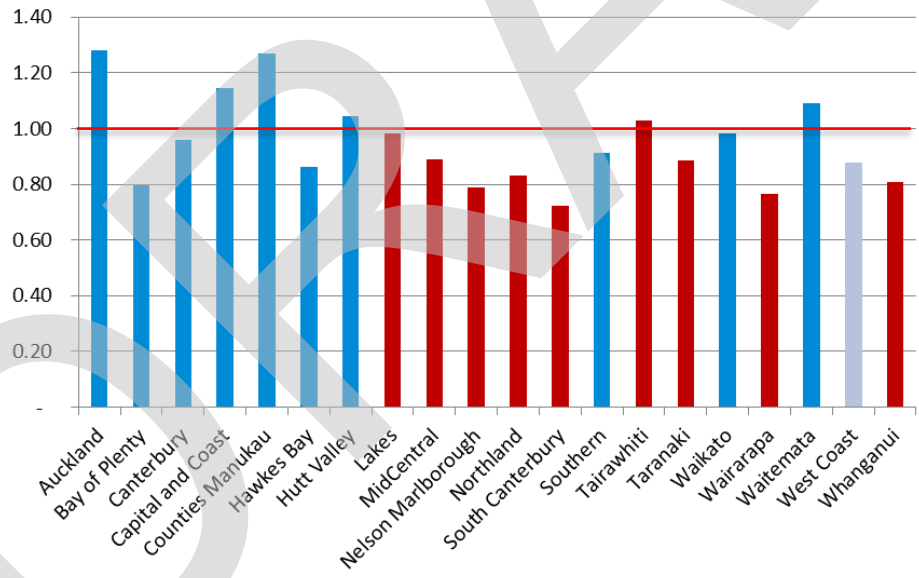


Figure 7: Ratio of age-standardised rates over crude rates of patients dispensed dabigatran by district health boards colour coded for rural (red) / city (blue) split –*AL age band*

This figure demonstrates the effect of underlying population age distributions on the overall cumulative incidence across different district health boards of domicile for patients that were dispensed dabigatran and the variation between DHBs.

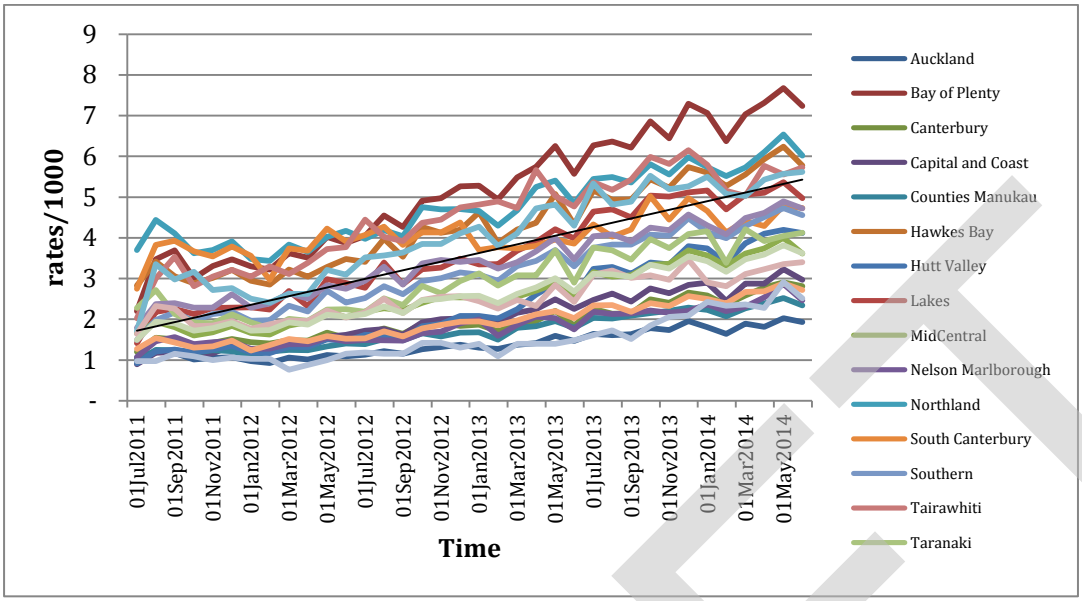


Figure 8: Number of monthly prescriptions of dabigatran, segregated by the 20 District health boards and adjusted for population numbers – *dabigatran prescription*

This figure shows that since funding was introduced in July 2011, the trend is dispensing has increased from July 2011, 2 patients /1000 to 5 patients /1000 in three years.

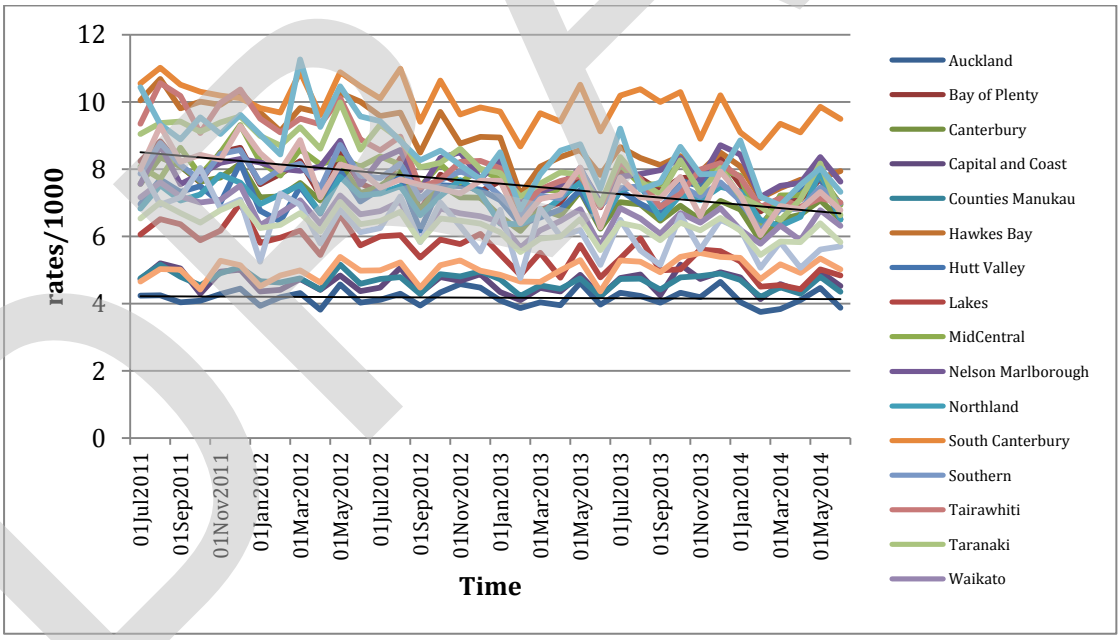


Figure 9: Number of monthly prescriptions of warfarin, segregated by the 20 District health boards and adjusted for population numbers. – *warfarin prescription*

This figure shows that during the period of July 2011 to July 2014, the number of warfarin patients went from 8 patients /1000 to 6 patients /1000 in three years.

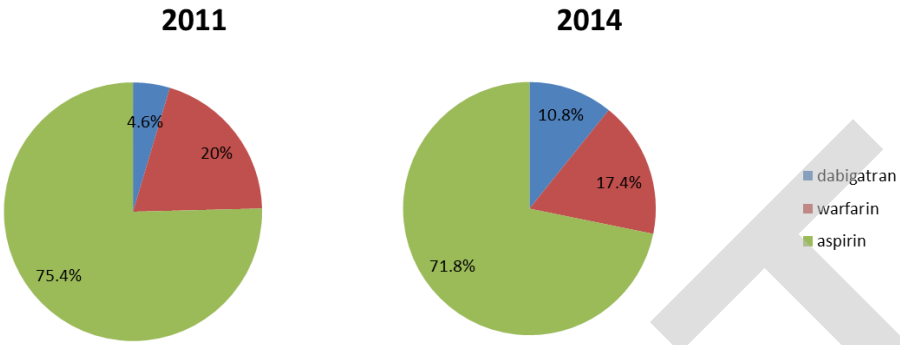


Figure 10: Prescription patterns for Dabigatran, Warfarin and Aspirin – *dabigatran prescriptions*

This figure shows that as at July 2011, Dabigatran was 4.6%, Warfarin was 20% Aspirin was 75.4% of the anticoagulant market. As at July 2014, Dabigatran was 10.8%, Warfarin was 17.4% Aspirin was 71.8%. The total number of monthly prescriptions grew from 144561 as at July 2011 to 148842 as at July 2014.

Discussion

In this New Zealand national dataset, we showed that for the three year study period there were 30205 dabigatran patients identified. Several studies have questioned the external validity and applicability of clinical trials such as the RE-LY trials to patients in the normal clinical environment (7, 14). Our study showed that the basic demographic characteristics of our patients are similar to the RE-LY trial, whereby 60% of dabigatran patients are male and the mean age is 71 years of age (11).

However, there was a marked difference between the rates of discontinuation in the RE-LY trial of 21% based on a two year follow up compared to our study (11). Whereby, at the end of three years, 51% of our patients had discontinued dabigatran and of those, the median period they were on dabigatran was 3.3 months. The 51% of discontinued patients included the 15% that were intermittent patients. Grey et al.

similarly showed that 33% of patients discontinued statin (preventative cardiovascular drug) after a two year follow up (18).

The 2.5 fold difference in rates of discontinuation in our study compared to the RE-LY trial highlights that clinical trials tend to not reflect real-world patient adherence. Clinical trials tend to have higher adherence rates as there is usually more frequent follow ups that may motivate better patient behaviour as well as the exclusion of patients with severe adverse effects (7).

As at July 2014, 47% of discontinued patients were being dispensed either Aspirin or Warfarin, which is suggestive that at least half of the patients were not tolerating dabigatran as a treatment. However, it also highlights options for anticoagulant therapy is not optimal as 71% of dabigatran patients were patients that had previously had either more than one dispensing of aspirin or warfarin.

A basic comparison of patients that persisted and those that discontinued found no significant difference between patients' gender, ethnicity or age bracket. This is supported by Vermeire et al., who found demographic variables poorly correlates with medication adherence (19). Rather, poor communication, patient-doctor relationships and patient beliefs are more commonly cited reasons for non-adherence (19).

Another key finding from our study is the ethnic disparity that was present in Maori and Pacific patients but particularly so in Asian patients. Whereby, the proportion of the respective ethnic patients was lower than the underlying 2013 census populations' proportion. This was most acutely seen with Asian only comprising of 2% of the dabigatran patients but make up 12% of the New Zealand population.

Even though higher age-standardised rates than crude rates were seen with Maori, Pacific and Asian, Asians' cumulative rates remained the lowest, with relative ratio one third of Europeans. Only Maori's age standardised cumulative incidence of dabigatran patients ends up higher than Europeans/others with a relative ratio of 1.6.

However, this is further compounded for ethnic patients when considering studies have shown greater incidence rates of ischemic stroke in non-European populations (Maori/Pacific RR 1.7 and Asian RR 1.3) compared to European population (16). In addition the mean age of stroke for Maori, Pacific and Asian is 62 years old, which is at least 10 years earlier than European. However, the peak age band of dabigatran dispensing for patients, regardless of ethnicity, was between the ages of 75-85 years. (16). This clearly highlights the current unmet need for ethnic patients, especially for the Asian population.

The marked ethnic inequalities in stroke prevention for ethnic minorities, particularly in Asians may be due to cultural and/or language barriers that results in poor access and/or less than ideal health behaviours (18).

From our study, we also found that consistent with age being a risk factor for atrial fibrillation and stroke (9, 16), 60% of dabigatran patients were over the age of 70 and 25% were over the age of 80 and as mentioned the peak age band for patients dispensing dabigatran is 80-84 years old.

Multiple studies have showed that increased plasma dabigatran concentration, is dependent on decreased renal function, which is strongly correlated with increased age (20). Patients have a higher risk of suffering from a major bleeding episode with an increased dabigatran concentration (20). BPAC has also cautioned dabigatran should be used carefully in the elderly and recommends the 110mg dose for patients over the age of 80 (21).

Our study showed that, for the 150mg dose, only 1% of the patients are over the age of 80. However, for patients within the age band of 80-84 years old, 13% of these patients were still on the 150mg dose. Overall, this is a positive result indicating clinicians are complying with the BPAC guidelines.

Lastly, from our age-specific three year cumulative incidence of patients dispensed dabigatran by DHBs, we can see there is still marked variation between DHBs. With the top DHB's rates of 93.5 patients/1000 compared to the bottom DHB's rates of 31.3 patients/1000 at that peak age band, which is a threefold difference. However, the data does not allow us to infer what the appropriate prescription rates should be and whether the variation is a result of variable prescribing patterns or due to access of pharmaceuticals. Even though, in NZ a 3-month prescription of dabigatran cost NZD$5 (heavily subsidized by PHARMAC), this can still be a cost barrier for certain socioeconomic group.

Conclusions

Our study has shown that the long term preventative use of dabigatran is suboptimal, with half of dabigatran patients discontinuing treatment and of those, the majority have only been on the drug for less than four months. We also highlighted the ethnic disparity in the current unmet need for Maori, Pacific Islander and most significantly for Asians. PHARMAC therefore needs to shift their focus to not only ensure drugs are funded but address the issue of adherence and access to medication as well to achieve the best health outcome for all New Zealanders.

Limitation

There are several limitations present in the study based on the data we have used. Limitation includes, the assumption that dabigatran being dispensed is a proxy for patient's adherence and that they are actually taking the medication every day, twice daily.

As dabigatran is able to be prescribed without special authority and indications for dabigatran prescription as well as clinical information are not able to be ascertained, the 30205 patients may include patients using dabigatran for VTE prevention. Even though clinically this is expected to be only a very small proportion of the dabigatran patients, we were unable to confirm that.

Indications for patients that discontinued dabigatran was also unable to be ascertained and could be for a range of reasons including side effects, contraindications, patients choice, cost and many more.

The three months period used as the cut-off for dabigatran persistence is arbitrary and some may argue that it is too strict while others may argue that it is too lenient. However, as dabigatran is a monthly dispensing, it is more likely to reflect a "real world" situation compared to clinical trials.

Intermittent patients who have discontinued at some point of their treatment and restarted dabigatran were also considered in the group of patients that have discontinued rather than analysed as a separate subgroup. Even if these patients could have been hospitalised and would have continued taking dabigatran but would not have their dabigatran dispensed from their community pharmacy.

Patients that has been classified as switching to either dabigatran, warfarin or aspirin was based on the assumption that it was the final status these patients were on at the end of the study period and also does not account for any other prescribing pattern before or after this snapshot.

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