Factors influencing warfarin control in Australia and Singapore

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ABSTRACT

INTRODUCTION

Warfarin is widely used for patients with non-valvular atrial fibrillation (NVAF). Variations in warfarin control, as measured by time in therapeutic range (TTR), have been reported across different regions and ethnicities, particularly between Western and Asian countries. However there is limited data on comparative factors influencing warfarin control in Caucasian and Asian patients. Therefore, the aim of this study was to determine warfarin control and potential factors influencing this in patients with NVAF in Australia and Singapore.

METHODS

Retrospective data was collected for patients receiving warfarin for January to June 2014 in Australia and Singapore. TTR was calculated for individuals with mean patient TTR used for analysis. Possible influential factors on TTR were analysed including age, gender, concurrent co-morbidities, and concurrent medication.

RESULTS

The mean TTR was significantly higher in Australia (82%) than Singapore (58%). At both sites, chronic kidney disease significantly lowered this TTR. Further factors influencing control were anaemia and age<60 years in Australia, and vascular disease, CHA₂DS₂-VASc score of 6, and concurrent platelet inhibitor therapy in Singapore.

DISCUSSION

Warfarin control was significantly higher in Australia compared to Singapore, however chronic kidney disease reduced control at both sites. The different levels of control in these two countries, together with patient factors further reducing control may impact on anticoagulant choice in these countries with better outcomes from warfarin in Australia compared to Singapore.

Key words: warfarin, atrial fibrillation, international normalised ratio

INTRODUCTION

Warfarin is widely used to prevent embolic stroke in patients with atrial fibrillation(AF).(1) The anticoagulant activity of warfarin is influenced by a number of genetic and environmental factors leading to large inter-individual and inter-ethnic differences in warfarin response.(2) This variability in response necessitates close monitoring of warfarin using the International normalised Ratio(INR).(3) Maintaining a patient within therapeutic INR range is associated with improved outcomes and time in therapeutic range(TTR) may be used to assess the quality of warfarin management.(4) Increasing the TTR can improve the safety and efficacy of warfarin, with target goals of 70% suggested to enhance patient outcomes.(5) However, Mearns et al(6) reported AF patients worldwide spend only 61% TTR but found differences reported between practice settings and according to geographical region. Similarly, Baker et al(7) reported only 55% TTR in patients with AF but, further to this, found only about 48% of patients with AF eligible for anticoagulation actually receive warfarin. Concerns regarding under treatment and ineffective management with warfarin have led to the development of new oral anticoagulants(NOACs).(8)

Comparative trials of warfarin to the NOACs in patients with non-valvular AF (NVAf) have demonstrated the NOACs to be non-inferior(9) or slightly superior(10) to warfarin in terms of stroke and systemic embolism, and associated with lower intracranial haemorrhage rates.(9, 10) However, Gomez-Outes et al(9) demonstrated differences in outcomes according to warfarin TTR and suggested a trend towards superiority of the NOACs in centres with TTR<65%. Subsequent sub-analyses have demonstrated large variations in warfarin TTR according to geographical region with the highest in Western Europe(11, 12) and lowest in India(11) and East Asia(12). Similar to this, Chiang et al(13) demonstrated consistently lower TTRs in Asians compared to non-Asians, and suggested difficulty in optimising warfarin use led to potential benefits of NOACs in Asian populations.

Amerena et al(14) found significant regional differences in treatment strategies and clinical cardiovascular outcomes in AF patients across Asia-Pacific countries. Chen et al(15) reported more than 70% of physicians in Australia and Singapore prescribe oral anticoagulants for stroke prevention but found suboptimal warfarin control to be a larger problem in Asia than other regions. Sub-analyses of the large comparative trials have demonstrated warfarin control of around 75% TTR in Australia and 65% TTR in Singapore.(12, 16) Outside of these trials, the limited data on warfarin control in these countries have reported similar results with TTRs between 55%(17) and 81%(18) in Australia, and between 58%(19) and 65%(20) in Singapore. Wang et al(21) suggested the differential effects in warfarin control seen between Asians and non-Asians may be influenced by genetic polymorphisms, but also affected by demographic differences including body weight and renal function. However, to our knowledge, there are no real-world studies comparing the influence of clinical characteristics on warfarin control in both Caucasian and Asian populations. Therefore, the aim of this study was to determine the level of warfarin control in patients with NVAF in Australia and Singapore and identify potential factors influencing this control including demographic and clinical characteristics.

METHODS

Ethics approval was obtained from Griffith University (PHM/09/14/HREC and PHM/08/15/HREC) and SingHealth Centralised Institutional Review Board (CIRB 2015/2435). Retrospective data was collected for patients receiving warfarin for AF for the period of January 2014 to June 2014 in Australia and Singapore. The Australian site was Sullivan Nicolaides Pathology, Queensland, and included patients enrolled in their warfarin management program. The Singapore site was The National Heart Centre Singapore, and included patients seen at the outpatient warfarin clinic and dispensed warfarin. To identify patients with NVAF, patients with mitral stenosis, valve replacement and/or valve repair were excluded from the study. Data collected included age, gender, co-morbidities, concurrent medications, warfarin dose and dose changes during the study period.

Further information included INR test date and result, and target range. Individual TTR was calculated using Rosendaal's linear interpolation algorithm (22) with software downloaded from INR Pro©. Patient exclusions were insufficient tests to calculate TTR (ie less than 2 tests) and a time of treatment of less than 30 days.

Statistical analysis was performed using GraphPad InStat Version 3 with patient characteristics reported as number and percentage for categorical data, mean±standard deviation for continuous data, and median and interquartile ranges for risk scores and warfarin doses. Mean data was used for analysis and comparison between sites for warfarin control and doses. Mean TTR was used to identify possible influential factors on TTR at each site including age, gender, concurrent co-morbidities, and concurrent medication. Patients with specific factors present (e.g.hypertension) were identified and the mean TTR of this group compared to the mean TTR for the site. Patients at each site were also categorised according to TTR above or below 65% for comparison within that site. Comparisons were made using ordinary analysis of variance through non-parametric methods, including Mann-Whitney test for univariate analysis and Dunn's multiple comparisons test for bivariate analysis. Significance was defined as* $p<0.05$, ** $p<0.01$, and *** $p<0.001$, and graphing performed with GraphPad Prism 6.

RESULTS

Of the 5554 patients being treated with warfarin for NVAf, a total of 4366 were included in the study. There were 3196 patients at the Australian site following exclusions for valvular AF (276), insufficient tests to calculate TTR (4), treatment time of less than 30 days (40), and incomplete warfarin dose information (3), and there were 1170 patients at the Singapore site following these exclusions (605, 195, 64 and 1 patient respectively). The majority of patients were male comprising 52.3% of patients in Australia and 60.3% in Singapore(Table 1). Mean age of patients was 77.2 ± 9.1 years in Australia and 69.7 ± 10.0 years in Singapore which was statistically different ($p<0.0001$). The

most common medical condition at both sites was hypertension (37.0% Australia, 59.6% Singapore). The prevalence of other co-morbidities differed but diabetes (17.6% Australia, 30.0% Singapore), dyslipidaemia (14.7% Australia, 51.9% Singapore), and vascular disease (11.2% Australia, 23.8% Singapore) were amongst the most common. Both sites had a median CHA₂DS₂-VASc score of 3 and a median HASBLED score of 1 at the start of the study period. Concurrent treatment with beta-blockers was most common at both sites (62.4% Australia, 77.9% Singapore), followed by statins (55.2% Australia, 72.8% Singapore).

<Insert Table 1>

During the study period there were a total of 35898 INR tests in Australia and 6588 in Singapore (Table 2). The mean TTR was 82.3±15.6% in Australia and 57.6±34.2% in Singapore which was statistically different ($p<0.0001$). The mean percentage of tests in range was statistically different between Australia and Singapore (78.9±19.1% versus 54.2 ± 30.5%, $p<0.0001$) as was the mean time between testing (16.9±8.1 versus 29.3±15.2 days, $p<0.0001$). The median weekly warfarin dose was 24.3 mg (IQR 3.5-94.5) in Australia and 16.5 mg (IQR 3.5-63) in Singapore, with a median of 2 (IQR 0-18) dose changes in Australia and 0 (IQR 0-9) in Singapore.

<Insert Table 2>

Comparison of patients according to TTR less than or greater than 65%, found a TTR>65% in 86% of patients in Australia and 46% of patients in Singapore (Table 3). There was a significantly reduced frequency of testing and number of dose changes in the patients with TTR>65% in both Australia and Singapore.

<Insert Table 3>

Univariate analysis of the mean TTR at each site to demographic and clinical factors found significant differences with three factors in Australia and four factors in Singapore (Figure 1). Chronic kidney disease was associated with a statistically lower TTR in Australia (77.2±16.8%, $p=0.002$) and

Singapore ($50.9 \pm 32.9\%$, $p=0.0165$). In Australia, anaemia and age less than 60 years were associated with significantly lower TTR. In Singapore, vascular disease, CHA₂DS₂-VASc score of 6, and concurrent platelet inhibitor therapy were associated with significantly lower TTR.

<Insert Figure 1 >

DISCUSSION

Warfarin has been used for decades in patients with AF but suboptimal use can lead to poor patient outcomes.(23) Alternative anticoagulants are now available for patients with NVAF, but the comparative benefits of these agents over warfarin appears dependent on the quality of warfarin control.(9) Regional differences in warfarin control have been reported with higher TTRs in Western countries and lower TTRs in Asian countries.(12) Suboptimal control in Asians has been suggested to be due to genetic polymorphisms and demographic differences(21), with the ethnic differences in risk profiles favouring NOACs in Asian patients with AF. However, despite the fact that the selection of warfarin or a NOAC appears dependent on TTR and influenced by patient factors(24), there is limited data on comparative factors influencing warfarin control in Caucasian and Asian patients. Therefore, the aim of this study was to determine warfarin control and potential factors influencing this in patients with NVAF in Australia and Singapore. This study found significant differences between Australia and Singapore in the mean warfarin TTR (82% and 58% respectively) and frequency of testing (17 and 29 days respectively). A higher proportion of patients in Australia achieved a TTR>65% compared to Singapore (86.0% and 46.4% respectively). In both Australia and Singapore, a lower TTR was associated with chronic kidney disease. Other factors influencing TTR were anaemia and age<60 years in Australia, and vascular disease, CHA₂DS₂-VASc score of 6, and concurrent platelet inhibitor therapy in Singapore.

AF is the most common sustained cardiac arrhythmia with a higher prevalence in men and an incidence that increases with age.(25) Chiang et al(26) found patients in the Asia-Pacific region to

have similar disease profiles to those in the rest of the world, with hypertension the most prevalent risk factor but a higher prevalence of valvular heart disease in Asia.(26) Consistent with this, in both Australia and Singapore, our study included a higher percentage of males and hypertension was the most common co-morbidity. The most common concurrent treatment at both sites was with beta-blockers which is also consistent with Amerena et al(14) who concluded that clinicians in the Asia-Pacific region prefer rate-control strategies. However there were several differences between the two populations. Consistent with Hori et al(27), the mean age of patients with AF in our Asian population was younger. Similarly, as described by Frank et al (28), there were higher rates of dyslipidaemia and vascular disease in our Asian population. Higher rates of statin and platelet inhibitors were also seen in our Asian population. Chen et al (15) reported higher proportions of Asian patients on antiplatelet therapy and, further to this, revealed overuse of anticoagulant therapy in low risk ($\text{CHA}_2\text{DS}_2\text{-VASc} = 0$) patients in many countries. Similar to this, our warfarin study included patients with $\text{CHA}_2\text{DS}_2\text{-VASc}$ scores of 0 however further investigation is required to determine the rationale for warfarin therapy in these patients.

Suarez et al(29) found vast differences in anticoagulant use in the Asia Pacific region with Australia having the highest adjusted rate of warfarin use. Australia had amongst the highest warfarin control in sub-analyses of the large comparative trials of warfarin to the NOACs with almost 75% TTR, whilst the TTR in Singapore was around 65%.(12, 16) Real-world data of warfarin control in patients with AF reported similar results with a TTR of 81% in Australia(18) and 58% in Singapore(19). Our study reported similar TTRs in Australia (82%) and Singapore (58%) and found a TTR>65% in 86% of Australian patients but only 46% of patients in Singapore. Further to this, our study found significant differences between these countries in frequency of testing and dose changes but also significant differences in these parameters for patients with TTR above and below 65% at both sites. The testing interval of 17 days in Australia and 29 days in Singapore was similar to results from Oh et al(30) who reported a median interval of testing of 14 days in other world regions compared to 28 days in Asia. Carrier et al(31) concluded that patients with 9 or more INR tests and 3 or more dose

changes in a six month period were more likely to have a TTR<65%. In contrast, our Australian population with an average of 10 tests and a mean 2.5 dose changes in the six month study had a high TTR of 82%. However, in the Australian patients with a TTR<65%, the number of INR tests in the six month period was a higher 16 and they had 6 dose changes. Similar to this result, Schaefer et al(32) associated poor control with long intervals between tests defining this as an interval >14 days. However, in our Singapore population with a TTR<65% the testing interval was 24 days. Ansell et al(33) reported a median monitoring interval of 20-21 days across five countries but reported that structured clinics achieve greater TTR due to differences in the frequency of consultations and response to non-therapeutic INRs. Previously, Lip et al(34) suggested the poorer TTRs in Asians may be attributed to the lack of structured anticoagulation services. Chua et al(20) describe improved outcomes with anticoagulation clinics in Singapore but note that the increased frequency of consultations can substantially increase a patient's out-of-pocket expenses. Whilst the more frequent testing in Australia resulted in significantly better control than Singapore, in both these populations, patients with poor control as defined by TTR<65% had more frequent testing suggesting simply testing more frequently cannot improve control. Therefore, further investigation is needed to determine the most suitable interval of testing and the optimal follow-up of out of range INRs to maintain cost-effectiveness and achieve high warfarin TTR.

No significant influence between TTR and warfarin dose was found in either Australia or Singapore. Previously, poorer warfarin control has been associated with higher warfarin doses by Okumura et al(35) and, in contrast, with lower doses by Palaretti et al(36). There were significant differences in the weekly warfarin doses in Australia and Singapore (26 mg and 18 mg respectively). Jonas et al(38) suggested that whilst age, race, and medications all influence dose requirements, it is genetic polymorphisms in enzymes important in warfarin pharmacology that account for about 40% of warfarin dose variations. Further to this, Dang et al(39) found that when adjusted for confounding factors, warfarin dose requirements varied across ethnic groups with Asians requiring lower doses than Caucasians. Consistent with Dang et al(39) we found higher doses in Australia compared to

Singapore, although the mean weekly doses in their study of 36 mg for Caucasians and 24 mg for Asians were higher than our study (26 mg and 18 mg respectively). Further investigation is needed to determine if further adjustment in warfarin dose could result in improvement of TTR, particularly if guided by dosing algorithms incorporating both genetic and clinical factors.

The clinical factor associated with significantly decreased TTR in both Australia and Singapore was chronic kidney disease. Previous studies(40-42) have also associated chronic kidney disease with worse INR control and substantially lower TTR. Poorer control has been associated with moderate to severe kidney disease(43) with a proposed mechanism being altered warfarin disposition due to reduced hepatic cytochrome metabolism from cytokines and uremic toxins.(44) Pokorney et al(45) found patients with renal dysfunction had lower median TTRs, but also associated younger age and a high CHA₂DS₂-VASc score of ≥ 5 with decreased TTR. Similar to this, we found age less than 60 to be associated with decreased TTR in Australia and a CHA₂DS₂-VASc score of 6 associated with decreased TTR in Singapore. In contrast, Putnam et al(46) found no correlation with warfarin control and CHADS₂ score, whilst Gallagher et al(47) found no substantial variation in TTR according CHA₂DS₂-VASc score or age. In our study, age was only associated with poor control in Australia and not Singapore, with a reduced TTR in patients <60 years plus a younger age was found in patients with a TTR<65%. Interestingly, age has been found to have variable effects on TTR with reports of no influence on TTR(48), TTR increasing with age(49), and poorer anticoagulation control associated with younger age as defined by <45 years(50) or <60 years(51). In addition to age, Dlott et al(50) and Apostolakis et al(51) associated female gender to influence warfarin control. In contrast to these authors, we found gender did not influence TTR in either Australia or Singapore. This finding corresponds to those of Gallagher et al(47) and Okumura et al(35) who also demonstrated no gender influences on TTR.

Further influences on TTR in our study included anaemia in Australia and vascular disease in Singapore. Lip et al(52) reported haemoglobin ≤ 13.5 g/dl to be associated with lower mean TTR and,

whilst they did not find an association with TTR and coronary artery disease or peripheral artery disease, these authors suggested warfarin control is related to a patient's overall clinical status. Further to this, Apostolakis et al(51) associated multiple co-morbidities with poorer warfarin control and also demonstrated the influence of interacting drugs such as amiodarone. Although our study did not investigate the influence of multiple co-morbidities on TTR, we found amiodarone both alone and in combination with beta-blockers did not influence warfarin control. This may be due to the well-documented interaction between warfarin and amiodarone and awareness by clinicians regarding potential influences on warfarin TTR. In the same way, the majority of medications were found to have no effect on warfarin control, with the exception of platelet inhibitors in Singapore. This is in contrast to Okumura et al(35) who found no differences in TTR with co-administration of anti-platelet agents and Mueller et al(48) who found no differences in TTR and concurrent aspirin therapy. However, concomitant use of warfarin and drugs with pharmacodynamic interactions do not usually result in INR changes but may increase the risk of bleeding.(53) Guo et al (54) describe higher risks of major bleeding and intracranial haemorrhage in Asian patients with AF. Thus, the reduced TTR with anti-platelets only seen in the Singapore population may reflect concerns regarding bleeding in this population. The retrospective nature of the study limits the ability to test this and other hypotheses, so further prospective studies would be required for conclusions to be made.

Patient demographics, co-morbidities, plus stroke and bleed risk are all strong determining factors in a patient's suitability for anticoagulant therapy.(60) In global studies of warfarin, Singer et al(12) concluded that patient clinical factors were modest determinants of TTR but the strongest determinants were geographic region and medical care practices. This study found significant differences in terms of warfarin control between Australia and Singapore (TTR 82% and 58% respectively). This is consistent with previous findings suggesting suboptimal warfarin control is a bigger problem in Asia than other regions.(15, 61) There are now alternate anticoagulant options to warfarin and the benefit of these NOACs over warfarin has been demonstrated in centres with

TTR<65%.(9) The percentage of patients with a TTR>65% was 86% in Australia and 46% in Singapore. Based on these results and the mean TTR at our two study sites, for the majority of patients, warfarin would remain favourable in Australia whilst the NOACs would be preferred in Singapore. Complicating this recommendation is the fact that chronic kidney disease significantly decreased TTR at both sites. Renal impairment impacts dosing and safety of the NOACs(62) and thus this population of patients with NVAf present a particular challenge.

In conclusion, this study in patients with NVAf found a high level of warfarin control in Australia with a TTR of 82%, but poorer control of 58% in a Singapore population. Patient factors influencing this control were chronic kidney disease at both sites, in addition to anaemia and age<60 years in Australia, and vascular disease, CHA₂DS₂-VAsC score of 6, and concurrent platelet inhibitor therapy in Singapore. These influences on warfarin control, together with the differing levels of control seen across the Asia-Pacific region, may impact on anticoagulant choice in these countries with better outcomes from warfarin in Australia compared to Singapore.

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TABLES AND FIGURES

Table 1 – Patient demographics at the study sites in Australia and Singapore. Data shown is number and percentage. Mean and standard deviation is also shown for age, and median and interquartile range for risk scores.

	Australia (n=3196)	Singapore (n=1170)
Gender		
Male	1671 (52.3%)	706 (60.3%)
Female	1525 (47.7%)	464 (39.7%)
Age - mean (SD)	77.2 (9.1)	69.7 (10.0)
Age <60 years	138 (4.3%)	176 (15.0%)
Age 60-69 years	458 (14.3%)	370 (31.6%)
Age 70-79 years	1185 (37.1%)	437 (37.4%)
Age ≥80 years	1415 (44.3%)	187 (16.0%)
Past Medical History		
Hypertension	1184 (37.0%)	697 (59.6%)
Diabetes	562 (17.6%)	351 (30.0%)
Heart Failure	278 (8.7%)	88 (7.5%)
Vascular Disease	357 (11.2%)	279 (23.8%)
Chronic Kidney Disease	149 (4.7%)	163 (13.9%)
Abnormal liver function	11 (0.3%)	6 (0.5%)
History of stroke or TIA	487 (15.2%)	46 (3.9%)
History of bleeds	18 (0.6%)	0 (0%)
History of cancer	277 (8.7%)	42 (3.6%)
Anaemia	50 (1.6%)	64 (5.5%)
Cardiomyopathy	136 (4.3%)	107 (9.1%)
Dyslipidaemia	470 (14.7%)	607 (51.9%)
Risk Model Scores		
CHA ₂ DS ₂ -VASc score 0	101 (3.2%)	93 (7.9%)
CHA ₂ DS ₂ -VASc score 1	374 (11.7%)	170 (14.5%)
CHA ₂ DS ₂ -VASc score 2	717 (22.4%)	266 (22.7%)
CHA ₂ DS ₂ -VASc score 3	869 (27.2%)	294 (25.2%)
CHA ₂ DS ₂ -VASc score 4	581 (18.2%)	197 (16.8%)
CHA ₂ DS ₂ -VASc score 5	346 (10.8%)	106 (9.1%)
CHA ₂ DS ₂ -VASc score 6	165 (5.1%)	35 (3.0%)
CHA ₂ DS ₂ -VASc score 7	35 (1.1%)	9 (0.8%)
CHA ₂ DS ₂ -VASc score 8	8 (0.3%)	
CHA ₂ DS ₂ -VASc score, median (IQR)	3 (0-8)	3 (0-7)
HAS-BLED score, median (IQR)	1 (0-5)	1 (0-4)
Concurrent treatment		
Amiodarone	215 (6.7%)	76 (6.5%)
Beta-blockers	1995 (62.4%)	912 (77.9%)
Amiodarone & Betablocker	117 (3.7%)	54 (4.6%)
Digoxin	1082 (33.9%)	331 (28.3%)
Angiotensin Converting Enzyme Inhibitor	1116 (34.9%)	338 (28.9%)
Angioreceptor Blocker	887 (27.7%)	320 (27.4%)

Calcium channel blocker	823 (25.8%)	386 (33.0%)
Statin	1765 (55.2%)	852 (72.8%)
Platelet Inhibitor	287 (9.0%)	300 (25.6%)
Diuretic	1291 (40.4%)	420 (35.9%)
Proton Pump Inhibitor	1163 (36.4%)	520 (44.4%)

Table 2 – Warfarin control at the study sites in Australia and Singapore. Data shown is mean (standard deviation) for warfarin control with median (interquartile range) shown for warfarin dose information.

	Australia	Singapore	P Value
Warfarin Control			
Total number of tests	35898	6588	
Time in therapeutic range	82.4 (15.6)	57.6 (34.2)	P<0.0001
Percentage tests in range	78.9 (19.1)	54.2 (30.5)	P<0.0001
Frequency of testing	16.9 (8.1)	29.3 (15.2)	P<0.0001
Weekly warfarin dose	26.2 (12.0)	18.4 (8.3)	P<0.0001
Weekly warfarin dose median (IQR)	24.3 (3.5-94.5)	16.5 (3.5-63)	P<0.0001
Number of dose changes	2.5 (2.7)	1.0 (1.5)	P<0.0001
Number of dose changes median (IQR)	2 (0-18)	0 (0-9)	P<0.0001

Table 3 – Warfarin control at the study sites in Australia and Singapore according to time in therapeutic range (TTR) both above and below 65%. Data shown is mean (standard deviation) for warfarin control with median (interquartile range) also shown for warfarin dose information.

	Australia (n=3196)			Singapore (n=1170)		
	TTR<65%	TTR>65%	P value	TTR<65%	TTR>65%	P value
Total	446 (14.0%)	2750 (86.0%)		627 (53.6%)	543 (46.4%)	
Male	245 (54.9%)	1426 (51.8%)		366 (58.4%)	340 (62.6%)	
Female	201 (45.1%)	1324 (48.1%)		261 (41.6%)	203 (37.4%)	
Age	75.9 (10.3)	77.4 (8.9)	P=0.0154	69.9 (9.9)	69.4 (10.2)	
Warfarin Control						
Total number of tests	7202	28696		4431	2157	
Percentage tests in range	54.3 (11.9)	82.9 (17.0)	P<0.0001	34.5 (19.7)	76.9 (24.2)	P<0.0001
Frequency of testing	11.3 (4.7)	17.8 (8.2)	P<0.0001	24.1 (14.5)	35.2 (13.8)	P<0.0001
Weekly warfarin dose	26.4 (13.3)	26.2 (11.8)		18.4 (8.6)	18.4 (7.9)	
Weekly warfarin dose median (IQR)	23.9 (3.5-86.5)	24.5 (4.5-94.5)		16.8 (3.5-63)	16.5 (5.5-61.5)	
Number of dose changes	6.4 (3.4)	1.9 (2.0)	P<0.0001	1.6 (1.7)	0.4 (0.7)	P<0.0001
Number of dose changes median (IQR)	6 (0-18)	1 (0-10)		1 (0-9)	0 (0-5)	

AUSTRALIA

SINGAPORE

Figure 1 – Comparison of mean TTR in Australia and Singapore to demographic and clinical characteristics. Individual data plotted represents mean and standard deviation with the solid vertical line representing the mean TTR at the site. Significance is represented as* $p<0.05$, ** $p<0.01$, and *** $p<0.001$