



**Predictors of Warfarin Control in Patients with Atrial Fibrillation in
South-East Queensland and Singapore**

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Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

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Acknowledgement of Papers included in Thesis

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Included in this thesis are nine peer-reviewed and published papers in Chapters 3, 4, 5, and 6 which are co-authored with other researchers. My contribution to each co-authored paper is outlined at the front of the relevant chapter. Appropriate acknowledgements of those who contributed to the research but did not qualify as authors are included in each paper. The bibliographic details for the nine peer-reviewed and published papers including all authors are:

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List of Abbreviations

AF	Atrial Fibrillation
ANOVA	Analysis of Variance
ASA	Acetyl Salicylic Acid (aspirin)
CAD	Coronary Artery Disease
BMI	Body Mass Index
CHADS ₂	Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, Stroke history
CHA ₂ DS ₂ -VA	Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, Stroke history, Vascular disease, Age 65 - 74 years
CHA ₂ DS ₂ -VASc	Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, Stroke history, Vascular disease, Age 65 - 74 years, Sex category
CIRB	Centralised Institutional Review Board
CKD	Chronic Kidney Disease
COPD	Chronic Obstructive Pulmonary Disease
COX-2	Cyclo-Oxygenase 2
CrCl	Creatinine Clearance
CYP	Cytochrome p450
DVT	Deep Vein Thrombosis
EXIT-A	Exit Warfarin Care for Apixaban
EXIT-D	Exit Warfarin Care for Dabigatran
EXIT-R	Exit Warfarin Care for Rivaroxaban
GORD	Gastro-Oesophageal Reflux Disease
GP	General Practitioner
GU	Griffith University
HAS-BLED	Hypertension, Abnormal renal/liver dysfunction, Stroke history, Bleed history, Labile international normalised ratio, Elderly, Drugs/alcohol
HREC	Human Research Ethics Committee

HTN	Hypertension
IHD	Ischaemic Heart Disease
INR	International Normalised Ratio
IQR	Interquartile Range
ISI	International Sensitivity Index
mg	Milligrams
mL	Millilitres
N	Number of patients
N/A	Not Available
NHCS	National Heart Centre Singapore
NOAC	Non-vitamin K Oral Anticoagulant
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NVAF	Non-Valvular Atrial Fibrillation
NYHA	New York Heart Association
OAC GUI	Oral AntiCoagulant Graphical User Interface
OAS	Outpatient Administrative System
PBS	Pharmaceutical Benefits Scheme
PE	Pulmonary Embolism
P-gp	P-glycoprotein
PROSPER	Pneumonia, Renal dysfunction, Oozing blood, Stay in hospital ≥ 7 days, Pain medication, no Enhanced anticoagulation care, pRescription of antibiotic
PT	Prothrombin Time
PE	Pulmonary Embolism
SAMe-TT ₂ R ₂	Sex - female, Age < 60 years, Medical history - more than two of hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, renal or hepatic disease, Treatment with interacting drugs, Tobacco use, Race = non-Caucasian
SCM	Sunrise Clinical Manager

SD	Standard Deviation
SNP	Sullivan Nicolaides Pathology
TIA	Transient Ischaemic Attack
TTR	Time in Therapeutic Range
VKA	Vitamin K Antagonists
VKOR	Vitamin K 2,3 epoxide Reductase
VKORC1	Vitamin K epoxide Reductase Complex subunit 1
VTE	Venous Thromboembolism
WARFARIN	Warfarin management program available, Atrial fibrillation valvular, Renal Function normal, Age > 60 years, Race = Caucasian, Intolerance to non-vitamin K oral anticoagulant therapy, Non- steroidal anti-inflammatory drugs or aspirin not concurrently used
WCP	Warfarin Care Program

Abstract

Background

Warfarin is an oral anticoagulant widely prescribed for several thromboembolic indications including stroke associated with atrial fibrillation (AF). Warfarin control is influenced by a number of genetic and environmental factors which, combined with a narrow therapeutic index, results in a need for close monitoring using the International Normalised Ratio (INR). Maintaining INR values within the therapeutic range can reduce adverse effects such as bleeding and stroke, with time in therapeutic range (TTR) commonly used as a measure of the quality of anticoagulation with warfarin. Increased TTR directly correlates to the efficacy and safety of warfarin and improved patient outcomes.

Many patients with AF are either ineffectively managed with warfarin or not candidates for warfarin therapy. This led to the development of alternate non-vitamin K oral anticoagulants (NOACs) which were compared to warfarin in patients with AF through large randomised controlled trials. Meta-analyses of these trials demonstrated the NOACs to be either non-inferior or slightly superior to warfarin in terms of stroke and associated with a lower risk of intracranial haemorrhage. However, sub-analyses of these trials highlighted concerns regarding the mean warfarin TTR in these trials and the differences in TTR according to geographical location and management systems. Variation in warfarin TTR impacts the clinical outcomes of warfarin therapy including the comparative outcomes with NOACs. The choice between anticoagulants requires consideration of likely warfarin control which may be influenced by patient demographics and clinical characteristics together with health care management systems. In Australia, this prompted the Australian Government to commission a review of anticoagulant therapies in AF. This review identified a need for

national guidelines for AF and therapeutic management algorithms for individual anticoagulants including warfarin. However, this review also identified a barrier to producing these management algorithms was the lack of information regarding the quality of warfarin management in Australia and factors which may influence TTR including patient variables and management systems.

Aims

The overall aim of this study was to determine predictors of warfarin control in patients with AF in South-East Queensland and Singapore. Singapore was chosen as a comparator site in the Asia-Pacific region to assist with applicability of results across the multi-cultural population of Australia given potential factors influencing warfarin TTR include patient demographics, ethnicity and management systems. Specific objectives of the study were to: (1) establish the prescribing of warfarin in AF since the introduction of the NOACs (2) determine the quality of warfarin control in Queensland achieved by different warfarin management systems; (3) identify factors influencing warfarin TTR in patients with AF in Queensland as compared to Singapore; and (4) establish the efficacy of risk models recommended in AF guidelines to predict warfarin control.

Methods

Ethics approval was granted (PHM/09/14HREC,2015/863 and 2015/2435). A retrospective observational study was conducted of patients receiving warfarin for AF at two study sites, Sullivan Nicolaides Pathology (SNP) in Queensland and the National Heart Centre Singapore (NHCS). PBS data was utilised to establish prescribing rates of oral anticoagulants since the introduction of the NOACs,

Data was collected as of 30 September 2014 at SNP and between 1 January and 30 June 2014 at the NHCS. Data collected was INR test results, together with patient demographics such as age, gender, co-morbidities and concurrent medications. Warfarin control for individuals was determined by calculation of percentage of INR tests within target range and TTR via a linear interpolation method. Patients were excluded if TTR could not be calculated, that is less than two INR tests, or if less than thirty days of treatment. Patient data categorised patients according to specific factors, including gender, age, concurrent co-morbidities and medication, bleed and stroke risk scores, and a predictor score for warfarin control. Mean patient data was used for analysis and comparison between groups with analysis of specific factors on TTR conducted using chi-squared, Tukey-Kramer, or a one-way analysis of variance tests via nonparametric methods including Kruskal-Wallis test and Dunn's multiple comparisons test with GraphPad Instat Version 3. Significance was defined at $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***), and $p < 0.0001$ (****).

Results

Warfarin prescribing decreased since introduction of the NOACs but it remains widely prescribed with almost 1.5 million units prescribed in Australia (2017/8 financial year), of which 250,478 units were prescribed in Queensland. In Queensland, the number of patients with AF managed by SNP decreased from 10,806 patients in July 2012 to 5524 patients in July 2017. During this time, 3036 patients exited the warfarin program to commence NOAC therapy but almost 5% (n=141) reverted to warfarin. In these patients, no significant difference in mean TTR was found before or after NOAC treatment but significantly more frequent testing and lower doses were required to obtain this level of control.

In Queensland, warfarin control in patients with AF was above recommended minimum targets of 65% with a mean TTR of $68.5 \pm 16.2\%$ by general practitioner (GP) and $81.5 \pm 9.1\%$ by SNP with significant differences ($p < 0.0001$) in frequency of testing between management systems. Warfarin control in Singapore was significantly lower than Queensland (mean TTR $82.3 \pm 15.6\%$ vs $57.6 \pm 34.2\%$, $p < 0.0001$). There were significant differences ($p < 0.0001$) in mean frequency of testing between Queensland and Singapore (16.9 vs 29.3 days). Patients with chronic kidney disease in both Queensland and Singapore had significantly lower TTR ($77.2 \pm 16.8\%$, $p < 0.01$ and $50.9 \pm 32.9\%$, $p < 0.05$ respectively). Age less than 60 years ($p < 0.05$) in Queensland and use of a platelet inhibitor in Singapore ($p < 0.01$) also significantly reduced TTR. After excluding interacting drugs with warfarin, a significantly reduced TTR ($p < 0.05$) was found in Queensland for patients taking concurrent non-steroidal inflammatory drugs (NSAIDs) and aspirin. In Singapore, a predictor score could identify poor warfarin control as patients with a score > 2 had significantly lower TTR than other patients ($55.8 \pm 34.1\%$ vs $63.2 \pm 34.1\%$, $p < 0.001$).

Discussion and conclusion

Warfarin requires regular monitoring to maintain INR levels within range and minimum targets of 65% TTR are recommended to optimise benefits from warfarin therapy. This study demonstrated that warfarin is well controlled in Queensland with TTR levels above this minimum by both GP and dedicated warfarin management systems but, in contrast, Singapore has poor control. Frequency of INR testing strongly contributed to warfarin control with increased warfarin monitoring leading to improved control in Queensland compared to Singapore but also by the dedicated warfarin management system compared to GP management in Queensland.

In this study, patient factors which consistently influenced warfarin TTR in both Queensland and Singapore were chronic kidney disease and the concurrent administration of NSAIDs and aspirin, whilst age < 60 years also influenced TTR in Queensland. Based on these factors, prescribing guidelines have been proposed which highlight these subsets of patients as being at risk of poor warfarin control and who may benefit from the additional intervention of a dedicated warfarin management system to optimise control. In addition, a risk model combining these factors into the mnemonic WARFARIN (Warfarin management program available, AF valvular, Renal Function normal, Age > 60 years, Race = Caucasian, Intolerance to NOAC, NSAIDs or aspirin not concurrently used) has been proposed as a method of identifying patients likely to obtain good warfarin control and best suited to warfarin therapy.

In conclusion, despite the introduction of the NOACs, warfarin remains widely prescribed and is currently the only anticoagulant option available for patients with valvular AF. Dedicated warfarin management programs can improve warfarin control and use of proposed algorithms or guidelines can identify subsets of patients at risk of reduced control who may benefit from additional intervention to improve warfarin TTR. This addresses recommendations from an Australian government report and may help optimise anticoagulant therapy for patients with AF.

Chapter One - Introduction

1. Warfarin - Background

Warfarin is widely prescribed for the treatment and prophylaxis of venous thromboembolism including stroke associated with atrial fibrillation (AF), pulmonary embolism (PE), and deep vein thrombosis (DVT) [1]. Clinical use of warfarin was first described in the 1950s, approximately ten years after synthesis of the chemical compound [2]. The chemical structure of warfarin or 3-(α acetonylbenzyl)-4-hydroxycoumarin [3] consists of an aromatic ring fused to a condensed lactone ring [4] as per Figure 1. The asymmetric centre results in two enantiomeric forms of warfarin, R-warfarin and S-warfarin [5]. Warfarin is available as a racemic mixture of the two enantiomers with R- and S- warfarin differing considerably in both potency and metabolism and thus impacting the clinical action of warfarin [6].

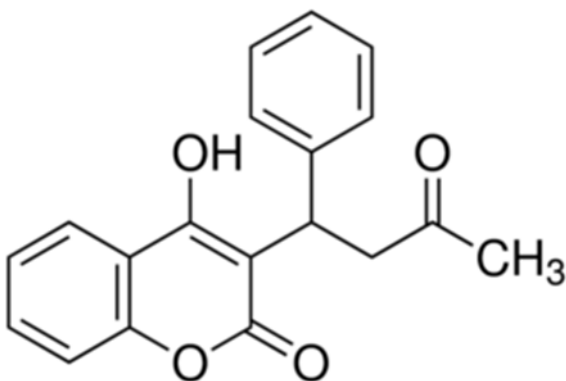


Figure 1 - Chemical structure of warfarin – adapted from Goodman & Gilman's [7].

1.1 Mechanism of action of warfarin

Warfarin exerts an anticoagulant effect by acting as a vitamin K antagonist [8]. Vitamin K is essential for the formation of prothrombin (Factor II) and the coagulant proteins Factors VII, IX, and X [9]. Warfarin binds to the vitamin K 2,3-epoxide reductase (VKOR) enzyme and interferes with the cyclical interconversion of vitamin K [10] as per Figure 2. The resultant depletion of the reduced form of vitamin K limits the γ -carboxylation of the vitamin K dependent proteins and the carboxylation of regulatory proteins C and S thus impairing the anticoagulant function of Factor II, VII, IX and X [11]. The onset of action of warfarin is therefore delayed until removal of pre-existing clotting factors from the circulation and production of defective clotting factors by the liver [12].

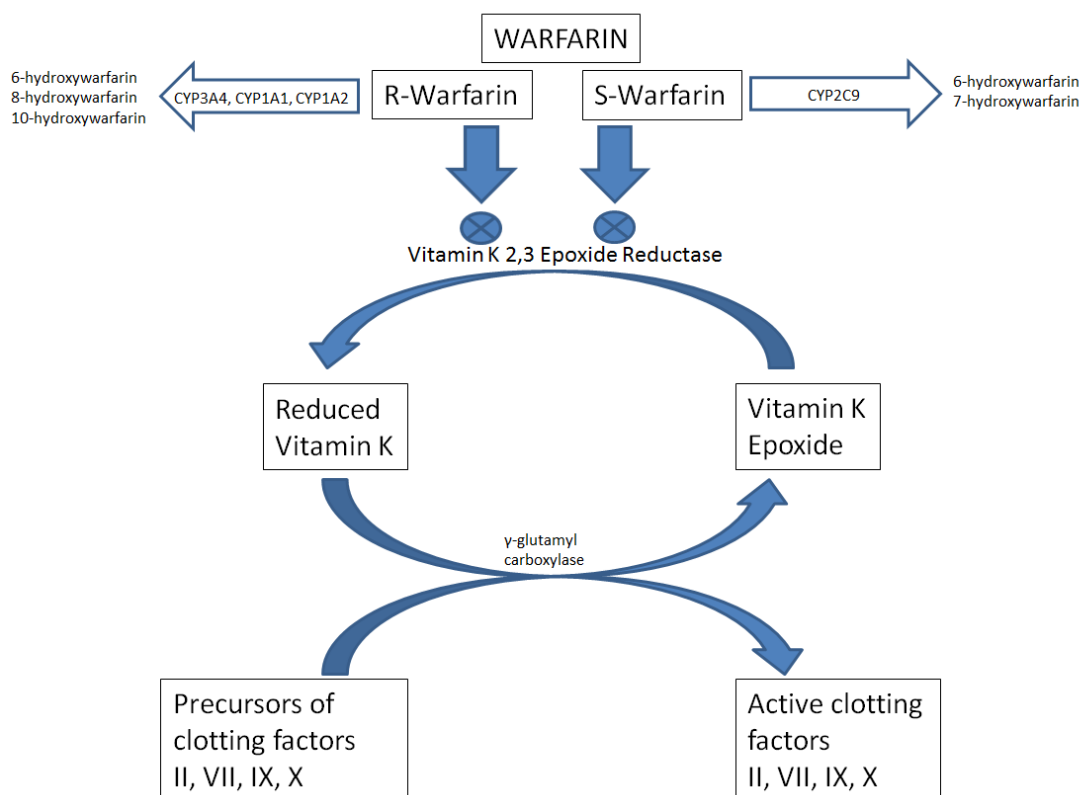


Figure 2 - Mechanism of action of warfarin and metabolism of the two enantiomers of warfarin - adapted from Schwarz & Stein [13].

1.2 Indications for warfarin therapy

Major indications for warfarin therapy include management of venous thromboembolism including DVT and PE, and prevention of ischaemic stroke in patients with AF [14]. Authors including O'Keefe et al [15] and Virji et al [16] have found that the majority of warfarin prescribed is for the indication of AF. AF is the most common sustained cardiac arrhythmia [17-20] with an estimated prevalence in Western countries ranging from 0.5 to 2% [21]. The prevalence of AF increases with age [17] with a higher incidence associated with male gender [20]. Further to this, Chugh et al [22] reported a higher incidence in developed nations and in Caucasian populations. Global estimates predict a doubling of AF cases by 2050 with an associated increase in hospitalisations and health care expenditure due to AF [20]. Ball et al [23] predicted that the number of Australians with AF among people aged over 55 years would more than double over the next fifteen years to 600,000, whilst Sansom [24] predicted there would be 750,000 Australians with AF by 2030.

AF is characterised by erratic transmission of atrial impulses and altered ventricular contractions which is associated with atrial blood stasis and subsequent potential for thrombus and embolism formation which increases the risk of stroke [25]. AF also results in endothelial dysfunction, activation of haemostatic factors, and induction of a hypercoagulable state which may further increase the risk of stroke [26]. Chiang et al [27] estimated that patients with AF are at a five-fold higher risk of stroke and a two-fold higher risk of mortality. AF management involves control of symptoms through rhythm or rate control together with assessment and reduction of stroke risk with antiplatelet agents or anticoagulants [28]. Antiplatelet agents such as aspirin and

anticoagulants such as warfarin may reduce stroke risk by 22 - 62% [29]. However, comparative trials of warfarin to aspirin found adjusted-dose warfarin to be approximately 40% more effective than aspirin with a relative reduction in all-cause mortality of 26% [30].

1.3 Genetic influences on warfarin action and metabolism

The action of warfarin is highly dependent on the vitamin K dependent γ -carboxylase system which includes the warfarin sensitive enzyme VKOR [31]. Warfarin inhibits the VKOR enzyme complex with the S-enantiomer estimated to be approximately five times more potent than the R-enantiomer at this inhibition [32]. The VKOR enzyme is encoded by the vitamin K epoxide reductase complex subunit 1 (VKORC1) gene found on chromosome 16p11.2 [33]. Genetic polymorphisms in VKORC1 leads to large inter-individual and inter-ethnic differences in warfarin dose requirements and significantly alter warfarin pharmacodynamics [34]. These VKORC1 polymorphisms have been found to vary greatest according to ethnicity [35]. Yuan et al [36] reported that more than 85% of the Caucasian population had high VKOR activity and thus required higher warfarin doses than Asian populations. Compared to the Caucasian population, Asians required lower maintenance warfarin doses whilst higher doses were required by Africans [13, 37] (Figure 3). Furthermore, differences in warfarin dose requirements have been reported between African and European Americans, and between different Asian ethnic groups with lower maintenance doses required by Chinese and Malay patients compared to Indians [38].

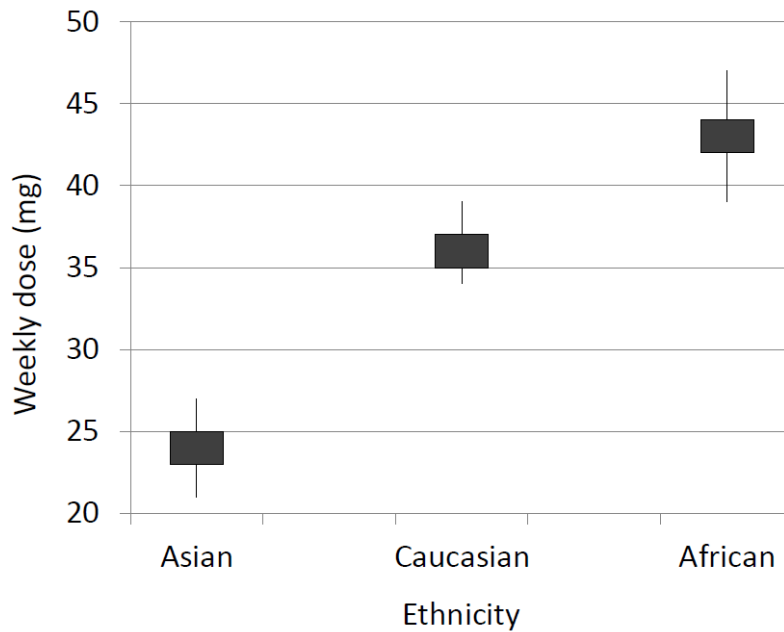


Figure 3 - Mean weekly warfarin doses among different ethnic groups - adapted from Dang et al [37].

Genetic polymorphisms are known to influence both the pharmacodynamics and pharmacokinetics of warfarin. Warfarin is rapidly and extensively absorbed, highly protein bound, and almost completely metabolised in specific pathways depending on the enantiomeric form [39]. R-warfarin is hydroxylated into its inactive form by three enzymes cytochrome p450 (CYP) 3A4, 1A1, and 1A2, whilst S-warfarin is largely hydroxylated by CYP2C9 [13] as shown in Figure 2. Polymorphisms exist for both CYP1A1 and CYP2C9 enzymes however the CYP1A1 variants do not appear to metabolise R-warfarin at different rates [40]. In contrast, CYP2C9 polymorphisms have a pronounced effect on warfarin response due to the altered metabolism of the more potent S-warfarin [41]. Many polymorphisms of CYP2C9 exist with CYP2C9*2 and CYP2C9*3 variants most associated with altered warfarin dose requirements [42]. Patients with variant CYP2C9 genotypes have a confirmed sensitivity to warfarin and require lower maintenance doses [43]. As shown in Table 1, the frequency of these

CYP2C9 variants differs amongst ethnic populations with higher rates in the Caucasian population and thus a greater impact on dose in Caucasians [44]. D’Andrea et al [45] state that CYP2C9 polymorphisms account for 5 - 22% of the inter-individual variability in warfarin response while VKORC1 polymorphisms account for 6 - 37% of this response.

Table 1 - Ethnic differences in genetic allele frequencies - adapted from Johnson [44].

Variant	Caucasian	African	Asian
CYP2C9*2	8-18%	Rare	Rare
CYP2C9*3	5-13%	1-2%	2-5%
VKORC1	35-45%	8-10%	90-95%

Genotype information for CYP2C9 and VKORC1 has been incorporated into the United States Food and Drug Administration initial dosing for warfarin[46]. Dosing algorithms based on theCYP2C9 and VKORC1 genotypes have been developed to estimate initial and maintenance warfarin dosing [47]. Proposed benefits of genetic testing and dosing algorithms include reduced time to therapeutic effect and reduced over- and under-dosing in the initial treatment period [48]. However, Lee and Klein [49] proposed that existing published algorithms explain only about 80% of variations in warfarin dosing. Individual dose requirements for warfarin are impacted by other patient factors with pharmacogenetic guidance of dosing unable to eliminate the need for clinical follow-up [50]. Therefore, despite potential benefit in predicting warfarin doses, uptake of pharmacogenetic guided warfarin dosing in clinical practice has been low and remains to be shown cost-effective [47, 50, 51].

1.4 Interactions with warfarin

CYP2C9 and VKORC1 contribute significantly to variability in dose requirements, however other individual and environmental factors also affect warfarin therapy [52]. Warfarin response is influenced by numerous factors including diet, alcohol, and concomitant medications [53]. A diet containing large amounts of foods rich in vitamin K such as kale, broccoli, green tea and soybean products, may antagonise response to warfarin [54]. However, whilst warfarin is antagonised by a high intake of vitamin K rich foods, inconsistent intake of these foods produces an unstable response [55]. Alcohol consumption has also been reported to produce variations in the levels of warfarin response [56]. Excessive warfarin activity results from acute alcohol ingestion through inhibition of warfarin metabolism, but in contrast chronic alcohol consumption activates cytochrome p450 metabolism of warfarin thus requiring higher doses for anticoagulant effect [57].

The anticoagulant action of warfarin is also influenced by concomitant medications that interfere with the metabolic clearance pathways, particularly CYP2C9 metabolising the more potent S-warfarin [58]. Inducers of CYP2C9 such as rifampicin will reduce the effect of warfarin necessitating a higher warfarin dose, while CYP2C9 inhibitors such as amiodarone will do the opposite [59]. According to Jonas and McLeod [32], patients receiving warfarin concurrently with amiodarone were estimated to require 29% to 33% lower warfarin doses. Warfarin doses may also be influenced by drug interactions with herbal medicines such as St John's Wort and ginseng [60]. In 2011, Hines et al [61] reported 231 listed interactions between warfarin and various drugs and drug classes. Drug interactions with warfarin may be

either pharmacokinetic involving warfarin metabolism or pharmacodynamic resulting in a synergistic effect [62] as outlined in Table 2. An increase in bleeding with warfarin has been reported with numerous medications that potentiate bleeding on their own including antiplatelets and non-steroidal anti-inflammatory drugs (NSAIDs) [63]. Data quantifying the bleeding risks with some of the medicines reported to increase bleeding with warfarin remains conflicting but the prevalence of these interactions is high [64]. Wittkowsky et al [65] reported almost 82% of patients on warfarin were co-prescribed at least one potentially interacting drug. Similar to this, Rikala et al [66] reported almost 75% of warfarin patients were co-prescribed potentially interacting drugs. The high frequency of prescribing interacting drugs with warfarin contributes to the need for ongoing follow-up and monitoring [67].

Table 2 - Major drug interactions with warfarin - adapted from Australian Medicines Handbook [68].

Drugs increasing warfarin effect	Drugs decreasing warfarin effect	Drugs increasing risk of bleeding with warfarin
Amiodarone	Aprepitant	Aspirin
Azole antifungals	Azathioprine	Non-steroidal Anti-inflammatorys
Cimetidine	Carbamazepine	
Ciprofloxacin	Carbimazole	Salicylates
Corticosteroids	Cholestyramine	Selective Serotonin Reuptake Inhibitors
Danazol	Dicloxacillin	
Disulfiram	Griseofulvin	
Fibrates	Mercaptopurine	
Fluorouracil	Phenobarbitone	
Fluvoxamine	Phenytoin	
Macrolides	Propylthiouracil	
Metronidazole	Raloxifene	
Tamoxifen	Rifampicin	
Tetracyclines	Ritonavir	
Tramadol	St John's Wort	
Trimethoprim-Sulfamethoxazole	Sucralfate	

1.5 Warfarin monitoring and adverse events

The numerous factors influencing warfarin response necessitates close monitoring with the International Normalised Ratio (INR) routinely used [69]. The INR is calculated by determining a ratio of the patient's prothrombin time (PT) to the mean of normal PT as calibrated to an international sensitivity index (ISI) and hence $INR = \left[\frac{PT_{patient}}{PT_{reference}} \right]^{ISI}$ [70]. The World Health Organisation adopted the INR in 1983 as a universal measure of warfarin therapy effectiveness enabling the development of target ranges for various clinical conditions and the ability to measure success of warfarin management [71]. An INR target of 2.0 to 3.0 is used for the majority of clinical conditions including prevention of stroke in AF [72, 73]. On initiation of warfarin it may take 5 - 10 days for therapeutic range of INR to be obtained due to the slow onset of action [74].

Therapy with warfarin is monitored for target INR ranges, and variability in INR is associated with outcomes and adverse events including stroke and bleeding [75]. Oake et al [76] found almost half of all adverse events occurred when INR levels were outside of range with a significantly greater proportion of thromboembolic events occurring when time spent below range increased. In addition, Go et al [77] found nearly two thirds of patients who sustained an ischaemic stroke while on warfarin had an INR of less than 2.0. However, whilst an INR of 2.0 or above is required to reduce the risk of thromboembolic events and obtain the full anticoagulant efficacy of warfarin [78], an INR over 3 increases the risk of bleeding with bleed risk becoming much higher with an INR above 4.5 [79] as per Figure 4. Recently McDowell et al [80] suggested that an INR between 2.0 and 2.5 provided the lowest estimated event rate for both ischaemic stroke and intracranial haemorrhage, with this risk only slightly

increased between INR 1.8 and 3.0. Intracranial haemorrhage is the most severe bleed event with warfarin therapy with other bleeds ranging from minor to major [81]. Major bleeds may be defined as bleeding in critical organs or those reducing haemoglobin levels and requiring blood transfusions [82]. Minor bleeds include epistaxis, excessive bleeding after minor injury or bruising, and are less clinically significant [83]. Bleed events whilst on warfarin can occur at therapeutic INRs but there is a direct relationship with increasing bleeds and increasing INR values [84]. Lowering of INR is principally achieved by withholding warfarin and/or administration of vitamin K [70]. This combination can manage minor bleeding but major bleeding may require emergency anticoagulation reversal with fresh frozen plasma or prothrombin complex concentrate [73]. Emergency use of prothrombin complex concentrate is associated with a more rapid normalisation of the INR and better therapeutic outcomes than use of fresh frozen plasma [85].

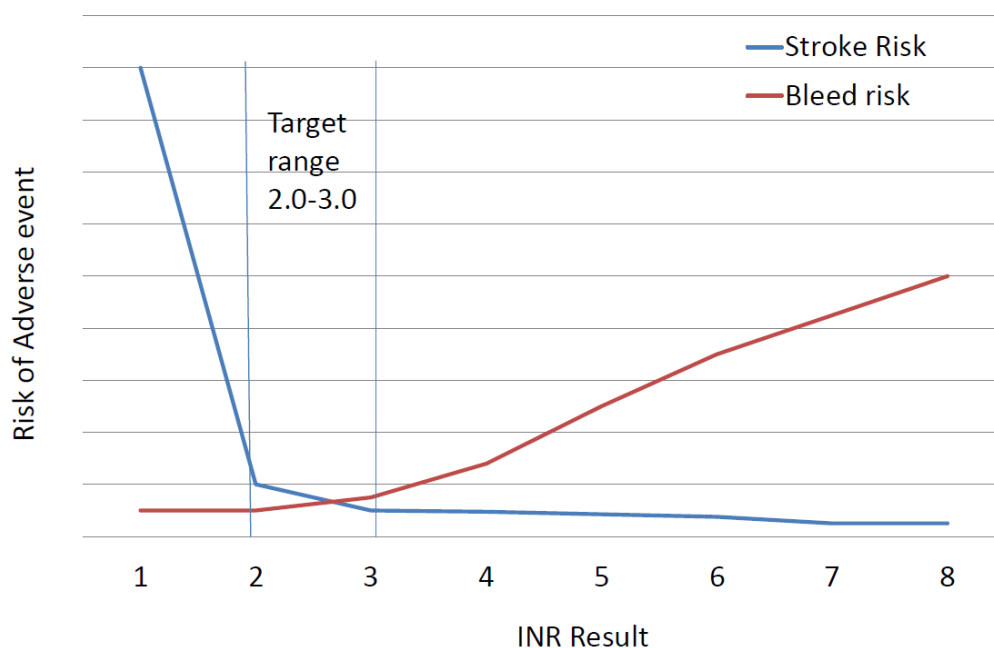


Figure 4 - Relationship of adverse effects specifically stroke and bleeding to INR with therapeutic range of 2-3 indicated - adapted from Fuster and Chinitz [86].

1.6 Warfarin time in therapeutic range

Improved therapeutic outcomes and reduced risk of adverse events is associated with maintaining INR values in therapeutic range [87]. However, numerous factors result in INR fluctuations and long-term stability can be difficult to achieve [88]. Bungard et al [89] reported that on admission to hospital, only 36.5% of patients with AF were in therapeutic range for warfarin whilst nearly half of the patients had sub-therapeutic INRs. Further to this, Mearns et al [90] in a pooled analysis of AF studies between January 1990 and June 2013 found only 56% of measured INRs to be in range, with individual reports ranging from 34 - 71% of INRs in therapeutic range. In clinical practice, the percentage of INR measurements in range is simple and easy to calculate, but there is limited data regarding utilising this as a measure for quality of warfarin control [91]. A more commonly used surrogate marker for the quality of warfarin control is time in therapeutic range or TTR [92]. TTR does not capture the short-term risks associated with highly variable periods or periods characterized by extreme deviations in INR but acts as a summary measure of anticoagulation intensity over time [93]. TTR is most frequently calculated using the Rosendaal linear interpolation technique [94]. The Rosendaal method assumes a linear relationship between INR measurements to calculate a percentage of time within the specified target range [95]. The Rosendaal method has limitations in that the linear assumption may not be accurate and INR extremes can bias overall results, however it remains the most commonly used and preferred method to assess warfarin management and potential outcomes [92].

TTR is considered to be an independent predictor for clinically relevant events whilst taking warfarin including systemic embolism and bleeding [96]. A strong correlation has been demonstrated between TTR and both bleeds and thromboembolic events [97] with rates of these events considerably higher in patients with TTR values below 50% - 55% [98, 99]. Similar to this, White et al [100] reported higher incidences of events and mortality in patients with poor control but defined this as $TTR < 60\%$. Liu et al [101] reported higher risk of stroke, major bleeding, and all-cause mortality with poor warfarin control but defined this as a $TTR < 65\%$, whilst eSilva et al [102] also reported higher incidences of major bleeds with a $TTR < 65\%$. Further to this, Razouki et al [103] reported that the highest percentage of ischaemic and bleeding events occurred with poor levels of warfarin control as defined by $TTR < 50\%$, whereas the lowest percentage of events occurred with high levels of control as defined by $TTR > 70\%$. Likewise, both Morgan et al [104] and Gallagher et al [105] found that patients with greater than 70% TTR had considerably lower risks of stroke. Comparable to this, Pastori et al [106] associated an increased incidence of cardiovascular events with a $TTR < 70\%$ but demonstrated that patients with consistently suboptimal control had similar event risks to patients with temporal worsening TTR, that is initially above 70% to below 70% at annual follow-up. Lehto et al [107] demonstrated that outcomes continue to improve with increasing TTR values up to a $TTR \geq 80\%$ and similarly, Raatikainen et al [108] reported well-managed warfarin as defined by a $TTR > 80\%$ was critical not only for prevention of stroke but also for improving cardiovascular outcomes for of patients. Wan et al [109] reported a TTR improvement of 6.9% to be associated with a reduction of one major haemorrhagic event per 100 patient years and an 11.9% TTR improvement to be associated with a reduction of one

thromboembolic event per 100 patient years. Therefore whilst minimum recommended targets of 60 – 70% TTR are commonly suggested, increased TTR values can reduce risk of stroke, bleeding, and mortality with warfarin [107].

1.7 Management of warfarin influencing time in therapeutic range

Increasing mean TTR with warfarin has been associated with a decreased rate of both systemic embolism and major bleeding and thus improved efficacy and safety [110]. Improving warfarin TTR can enhance long-term outcomes with variations in management practices impacting overall control [111]. Management models which utilise a systematic and co-ordinated approach to management are recommended to optimise warfarin therapy [112]. Current models for monitoring warfarin therapy include care by the patient's physician, anticoagulation monitoring clinics, and patient self-monitoring with point-of-care testing [113]. Important advantages have been demonstrated by both co-ordinated anticoagulant clinics and self-management systems over usual care in terms of warfarin safety and efficacy [114]. Numerous studies [115-123] have demonstrated improved warfarin control by anticoagulant clinics over standard physician care. In addition to more INR values in range, patients managed by anticoagulation clinics as compared to usual care are reported to have less high risk INR values of greater than 5 [119-121], reduced rates of adverse events [115, 116, 118, 124], reduced hospitalisations [121, 122, 124, 125] and mortality [121]. Rose et al [126] correlated prompt repeat INR testing following out-of-range results to be associated with better warfarin control. Several studies [115, 116, 127] found anticoagulant clinics had significantly reduced time between testing following extreme INR values compared to usual care. Similarly, Chamberlain et al [128] attributed the

more rigorous follow-up care and more regular INR testing demonstrated by anticoagulant clinics to be associated with their improved outcomes. Further rationale for better outcomes with anticoagulant clinics include improved patient education [129], increased patient satisfaction with their care [117, 129], and confidence in the skills and experience of the clinicians managing their warfarin [117].

A systematic review by van Walraven et al [130] showed time spent outside of range was lower in studies from anticoagulation clinics and randomised trials compared to studies with patients managed by their community based physicians. The improvement in TTR demonstrated by anticoagulant clinics is variable with the review by Van Walraven et al [130] finding a mean 6% improvement in TTR whilst two other meta-analyses [131, 132] reported a higher 11% improvement of TTR. The meta-analysis by Baker et al [131] included only patients with AF on warfarin managed in the United States with the rationale of results being more applicable to the United States population, whilst both Van Walraven et al [130] and Dolan et al [132] included studies regardless of geographical location. Ansell et al [133] compared anticoagulation management across five different countries and concluded that whilst anticoagulant clinic care provided better TTR than routine medical care, there remained large variation across countries in terms of warfarin control and INR monitoring practices.

Specialised anticoagulant clinics offer improved management of warfarin therapy but they have also been associated with greater inconvenience to patients due to an increased burden of testing and associated time depending on location of the monitoring centre [134]. Strain and distress on the patient due to the imposition of frequent attendance at appointments has been shown to be reduced by self-

monitoring of INR and full patient self-management, that is INR monitoring and dosing [135]. A systematic review of self-care by Sharma et al [136] reported that both self-management and self-testing were comparable to usual care in terms of bleed events, but self-management was associated with fewer thromboembolic events and reduced all-cause mortality whilst self-testing was associated with a modest 4% increase in TTR. In contrast, a more recent review by Heneghan et al [137] reported a reduction in thromboembolic events for both self-monitoring and self-management but no significant effects on either major haemorrhage or mortality. In comparison to anticoagulant clinics, self-management of anticoagulant therapy has been reported to result in similar control as measured by TTR [138-140]. Ebell [141] identified a distinguishing feature of both anticoagulant clinics and self-management to be the systematic, protocol driven approach to patient monitoring and adjustment of warfarin doses. Consistent with this idea, Rose et al [142] demonstrated that protocol driven warfarin management improved warfarin TTR and highlighted that a standardised patient assessment was a proactive tool beneficial to identifying medical and medication changes. The identification of patient-specific and practice specific factors is important as both contribute to variability in warfarin TTR and outcomes [143].

1.8 Patient factors influencing warfarin time in therapeutic range

Numerous patient-specific factors such as pharmacogenetics and clinical factors including co-morbid illness and concomitant medications confound the ability to achieve a high warfarin TTR [144]. Genetic factors influencing the various cytochromes involved in metabolism of warfarin (Figure 2) can influence control as can the

numerous drugs interacting with warfarin through these cytochromes (Table 2) [59, 60].

1.8.1 Concurrent medication

Patients receiving interacting medications have been shown to have lower TTR [145] and polypharmacy has been suggested as a predictor of poor control [146]. Van Walraven et al [147] found patients taking warfarin with two or more interacting drugs had significantly decreased proportion of days in therapeutic range, whereas Farsad et al [148] found poor control when the number of medications the patient was receiving was above four. Both Razouki et al [149] and Rose et al [150] associated lower TTR with patients taking 16 or more medications. Lobos-Bejarano et al [151] associated TTR with the number of tablets taken for chronic conditions and found a lower TTR with an intake of more than seven tablets per day besides warfarin. In contrast, Rouaud et al [152] found no association with warfarin control and the number of concomitant medications, but found patients with low quality TTR (that is less than 25%) more frequently took serotonin reuptake inhibitors, proton pump inhibitors, or antifungals. However, these authors [152] found no association with these specific medication groups and poor control in a subsequent multivariate analysis and highlighted the need to assess control with individual drugs rather than drug classes due to the potential for differing effects on cytochromes and subsequently INR.

One individual drug which has been frequently associated with decreased TTR is amiodarone [151, 153-155]. Amiodarone can alter the clearance of both R- and S-warfarin [156, 157] in a dose-dependent fashion [158] and using amiodarone as the

heart rhythm control strategy is considered a potential predictor of poor warfarin control [159]. Interestingly, Williams et al [160] concluded that the two strongest predictors for poor anticoagulant control were concurrent use of any antiarrhythmic and aspirin with an anticipated reduction of TTR of 5.0% and 5.2% respectively. Similar to this, both Proietti et al [161] and Szummer et al [162] have demonstrated reduced TTR with concomitant use of aspirin. In contrast, Okumura et al [163] showed no effect on TTR with co-administration of anti-platelet drugs, whilst Barta et al [98] found aspirin only modified the relationship between TTR and bleed events. Aspirin is proposed to interact with warfarin through a pharmacodynamic interaction [60] as high dose aspirin has a direct hypo-prothrombinemic effect whilst all NSAIDs inhibit platelet function and prolong bleeding [164].

1.8.2 Burden of disease

Bleeding history has been associated with low TTR in multiple studies [151, 165, 166]. In addition to a history of major bleeding, Plichart et al [165] associated poorer warfarin control (TTR < 50% vs \geq 50%) with antibiotic use and hospitalisation. Several studies [147, 149, 152, 167] have associated hospitalisations with poorer TTR. Rose et al [150] found TTR to be 7.3% lower for patients with two or more hospitalisations over a two year period compared to non-hospitalised patients and 9.4% lower with four or more hospitalisations over two years. The direction of the association between hospitalisation and TTR remains unclear. Poor warfarin control may result in hospitalisation due to active bleeding [147, 152] or be indicative of patients with a high burden of disease [149] or acute illness impacting warfarin control [147]. Alternatively

hospitalisation can result in poor warfarin control due to change in health status and changes to diet or medication in hospital [150, 152]. Van Walraven et al [147] suggested reduced warfarin TTR with hospitalisations may be due to ceasing of warfarin for procedures during the hospital stay. Similar to this, Hallinen et al [168] found TTR to be 9.3% higher in patients using warfarin continuously (that is no temporary hold) while Cryder et al [169] found a strong correlation to sub-therapeutic control following intentional withholding of warfarin therapy and after a change in medical status such as development of hepatic or thyroid dysfunction. In the same way, Lobos-Bejarano et al [151] found patients with three or more co-morbidities were more likely to have poorer warfarin control. Further to this, both Bertomeu-González et al [170] and Rouaud et al [152] found a high burden of co-morbidities to be associated with poorer warfarin TTR as expressed by the Charlson co-morbidity index of three or more. The Charlson index takes into account the number and seriousness of co-morbidities on mortality with individual conditions weighted differently [171] and individual co-morbidities have also been found to have differing potential to impact warfarin TTR.

1.8.3 Co-morbidities

Reduced warfarin TTR has been associated with the presence of diabetes [161, 162, 172-176] and chronic kidney disease (CKD) [147, 152, 161, 174, 177-182]. Reduced TTR in renal disease has been associated with both glomerular filtration rate strata [162] and high creatinine levels [175]. Inoue et al [183] demonstrated lower TTR values in patients with lower creatinine clearance (CrCl) and found a CrCl of less than

30 mL/minute independently associated with a TTR < 65%. In contrast, a study by Çelik et al [184] found patients with CKD had higher TTR levels than other patients but the mean TTR in both these population groups was 53% and 49% respectively. Odashiro et al [185] found contributing factors to low TTR in patients were both CrCl and liver dysfunction as measured by levels of transaminases and albumin. Lafarge et al [186] also found significant associations with the liver function measures aspartate transaminase and alkaline phosphatase and associated high values with poor warfarin control. Similarly, Efird et al [187] associated liver disease with reduced warfarin control whilst other studies [149, 150, 160, 188] have linked alcohol abuse with reduced TTR.

Reduced warfarin control has been associated with a number of cardiovascular conditions including ischaemic heart disease [154], coronary disease [162, 184, 189], and heart failure [153, 162, 172, 178, 179, 182, 184, 190-192]. Lip et al [193] associated higher TTR with New York Heart Association (NYHA) Class I heart failure but lower TTR with NYHA Class IV. Lee et al [167] showed that NYHA Class III/IV was associated with decreased likelihood of achieving high TTR, and likewise Beton et al [174] found NYHA Class III and IV to be independent predictors of poor control together with right ventricular dysfunction. In contrast, Ather et al [194] found the presence of left ventricular dysfunction in patients had no effect on risk of over anticoagulation (INR > 4) or warfarin TTR. Conflicting evidence was also found regarding hypertension and warfarin TTR. Beton et al [174] and Çelik et al [184] associated hypertension with poor warfarin control, whereas McAlister et al [176] found hypertension did not influence TTR. In contrast, Zubaid et al [195] found

patients with no history of hypertension were more likely to have poor control as defined by a TTR < 58%.

Other cardiovascular co-morbidities associated with poor warfarin control include a history of stroke [172, 174, 188, 189] and prior myocardial infarction [196]. Additional co-morbidities also associated with poor warfarin TTR include bipolar disorder [150], cancer [150, 197], anaemia [160] and a history of pulmonary disease [160, 173, 174, 196]. Being a current smoker is also a predictor of low TTR [152, 154, 159, 173, 174, 184, 196, 198] with Gateman et al [198] identifying a trend for current smokers to be at a five-fold increased risk of being below a TTR of 60%. Another modifiable patient lifestyle factor associated with affecting potential warfarin control is body mass index (BMI). Ciurus et al [155] linked obesity to decreased warfarin control but other studies [173, 175, 199] have found the opposite. In fact, Senoo and Lip [199] and Macedo et al [173] found a trend for increasing TTR with increasing BMI and that underweight patients were most at risk for poor warfarin control. Senoo and Lip [199] suggested that this association with low BMI and poor TTR may provide one possible explanation as to why certain patient populations, for example Asians, have a tendency towards poorer warfarin control.

1.8.4 Genetics

Wypasek et al [189] found patients with good control did not differ to those with poor control with regards to cardiovascular risk factors and concomitant disease but the CYP2C9*2 allele affected TTR. Similarly, Palareti et al [200] associated CYP2C9 variants with poor TTR. Further to this, two studies by Park et al [201, 202] related poor

warfarin control to VKORC1 genotypes and found the prevalence of allelic variants in CYP2C9 and VKORC1 influenced TTR and contributed to the variation in TTR between racial and ethnic groups. Anderson et al [203] genotyped patients for CYP2C9 and VKORC1 variants and reported no difference in TTR for patients dosed with pharmacogenetic guidance compared to patients dosed according to empirical protocol. However, Pirmohamed et al [204] demonstrated an improved TTR in patients with genotype-guided dosing of warfarin, whereas Kimmel et al [205] showed no difference in TTR for patients dosed with genotype guidance.

Numerous studies [150, 153, 193, 206, 207] have correlated highest TTR with White race and lowest TTR with Black patients. Specifically, Australian Indigenous people [208] and non-White race in the United States [149, 178, 181, 209] have been associated with less likelihood to achieve good warfarin control. Both Razouki et al [149] and Golwala et al [209] compared warfarin control in White, Hispanic and Black patients and found TTR lower in Hispanics compared to Whites (1.6% and 6% lower respectively) and lowest in Blacks compared to Whites (3.3% and 9% lower respectively).

1.8.5 Age and gender

Ethnicity, age and gender are all non-modifiable patient factors potentially affecting warfarin TTR but there remains conflicting data regarding the influence on TTR by both age and gender. The majority of studies [111, 149-151, 153, 162, 172, 173, 175, 180, 190, 191, 193, 195, 210-213] have identified poorer TTR in females with one study by Proietti et al [161] associating male gender with greater likelihood to achieve good

warfarin control as defined by a TTR > 70%. However, other studies [148, 163, 184, 185, 189, 192, 208, 214-217] have found TTR is not affected by gender. Equally conflicting data can be found regarding the impact of age on TTR. Several studies found no difference in TTR according to age [148, 152, 184, 189, 192, 214, 216, 217]. However, some studies [150, 173, 178, 213, 218-220] have identified younger age as a risk for lower TTR and Sawicka-Powierza et al [215] correlated individuals up to 60 years of age with worse control. Similarly, both Limdi et al [181] and Marcatto et al [221] associated higher TTR with patients aged 65 years and older, whilst Okumura et al [163] associated higher TTR with age \geq 70 years. Further to this, some studies [176, 180, 212, 222] have demonstrated an increasing TTR with age and Abohelaika et al [212] found this increasing TTR peaks at 70 - 75 years and then declines. Comparably, Atas et al [182] found patients aged > 75 years had lower TTR. Biteker et al [223] found poorer quality warfarin control in patients aged 80 and above compared to younger patients, and Szummer et al [162] found age over 85 years to be weakly associated with lower TTR. In contrast to these studies, Melamed et al [191] associated advancing age with poor warfarin control and Van Spall et al [153] correlated each year increase in age with a decrease of 0.07% TTR. Waterman et al [224] found age younger than 65 years and greater than 80 years was predictive of warfarin non-adherence. Poor adherence to warfarin therapy is common [225, 226] and influenced not only by age [224, 227] and gender [227, 228] but numerous other factors including dietary restrictions and inconvenience of INR testing [227, 229]. Adherence to any prescribed medication correlates to outcomes of therapy and warfarin endpoints are particularly vulnerable to patient adherence [230]. Numerous studies [224, 231-237] have demonstrated the association with poor

adherence and reduced warfarin control. Thus, whilst the correlation with adherence and warfarin TTR appears clear, the influence of other patient factors on warfarin control is more conflicting and may be confounded by the presence of numerous influencing factors in individual patients including age, gender, ethnicity, concurrent diseases and medications.

1.9 Predictor models for warfarin time in therapeutic range

The various patient factors influencing warfarin control may contribute to the likelihood of a patient achieving satisfactory TTR and being a suitable candidate for warfarin therapy [238]. Clinical predictor models combining multiple parameters and the relative impact they may have on patient management have been suggested to assist in medical decision-making [239]. In 2010, Rose et al [150] developed a TTR calculator incorporating 18 variables which determined an individual's projected control at the time of warfarin initiation (Table 3). This calculator assumes a mean overall population TTR of 58% but allows input of different mean population TTR if known, and calculates estimated TTR for both the first six months of therapy and for months 7 - 18 [150]. However, Rose et al [150] described the lack of external validation in different populations to be a limitation to this calculator. Furthermore, Proietti and Lip [240] cautioned that complex formulae derived from multivariate models using cohorts of specific patient populations do not work in clinical practice as clinicians need simple tools to aid decision making. Subsequently, in 2013, Apostolakis et al [159] proposed a predictor model to identify patients likely to achieve high TTR with warfarin known as SAME-TT₂R₂ (Table 4). The SAME-TT₂R₂ score rates patients as

either likely to do well on warfarin (score = 0 - 1) or as requiring additional intervention to achieve acceptable control (score ≥ 2).

Table 3 - The warfarin time in therapeutic range calculator proposed by Rose et al [150].

Characteristic		Response*	Months 0-6	Months 7-18
Female				
Age pick one	< 55 years			
	55 - 59 years			
	60 - 69 years			
	≥ 70 years			
Indication pick one	Atrial fibrillation			
	Venous thromboembolism			
	Other			
Health condition pick all that apply	Cancer (diagnosed < 1 year ago)			
	Chronic kidney disease			
	Chronic lung disease			
	Cirrhosis			
	Coronary artery disease			
	Diabetes			
	Epilepsy			
	Heart failure			
	Peripheral artery disease			
	Alcohol abuse			
	Bipolar disorder			
	Dementia			
	Major depression			
	Substance abuse (non-alcohol)			
Number of chronic medication in past year pick one	0 - 7			
	8 - 11			
	12 - 15			
	≥ 16			
Number of hospitalisations in past year pick one	0			
	1			
	≥ 2			
Mean TTR of your population (0.XX)				
PREDICTED TTR			0.524	0.632

* Response should be 1 when variable present or otherwise left blank. Calculation assumes a mean overall population TTR of 58% but if population has different TTR this may be entered. NB - Original calculator is spreadsheet with input enabling calculation of TTR.

Table 4 - The SAME-TT₂R₂ score components proposed by Apostolakis et al [159].

Acronym	Clinical characteristic	Allocated Point(s)
S	Sex – female	1
A	Age < 60 years	1
Me	Medical history - more than two of hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral artery disease, congestive heart failure, previous stroke, pulmonary disease, renal or hepatic disease	1
T	Treatment with interacting drugs e.g. amiodarone	1
T₂	Tobacco use (within two years)	2
R₂	Race = non-Caucasian	2
	Likely to do well on Vitamin K antagonist	Total = 0 - 1
	Intervention(s) required to achieve acceptable control	Total ≥ 2

Apostolakis et al [159] derived the SAME-TT₂R₂ model from participants enrolled in a study comparing rate and rhythm control strategies in patients with AF in the United States and externally validated the model in a cohort of patients with AF from the United Kingdom. In 2014, Poli et al [241] described the first independent validation of the model and found a score > 2 to be a good predictor of poor control, that is TTR < 70%. Later that year, Gallego et al [242] also associated a high SAME-TT₂R₂ score with poorer TTR. However, in this study the TTR remained above 70% with a score ≥ 3 and it was suggested that the study setting, that is an anticoagulation clinic without any prevalence of differing ethnicity, was a possible explanation for the reduced discriminatory value. Subsequently, Abumuaileq et al [243] validated the score in patients with poorer overall control (mean TTR 58%) plus Chan et al [244] demonstrated good correlation with the SAME-TT₂R₂ score and TTR in an Asian population with poor overall control (mean TTR 38%). After this time, numerous studies [151, 202, 245-254] have investigated application of the SAME-TT₂R₂ score in a variety of cohorts utilising differing approaches to assess predictive ability of the

model. In 2018, van Miert et al [255] published a meta-analysis of 16 studies investigating SAME-TT₂R₂ and found that the model predicted low TTR with cut-off scores of ≥ 2 and ≥ 3 . A later review by Zulkifly et al [256] included 18 studies and concluded that the SAME-TT₂R₂ score adequately predicted good or poor warfarin control in patients with AF. Fauchier et al [257] suggested that the SAME-TT₂R₂ model can inform clinicians regarding potential warfarin control but highlighted that some factors, particularly tobacco use and non-White race, may be over-represented depending on the setting. In support of this, Lee et al [258] found the SAME-TT₂R₂ score failed to have a linear relationship with control in a Korean population, but demonstrated good prediction of TTR with a modified score which included removal of race and tobacco as contributing factors. In addition to this, Skov et al [259] demonstrated the score was not predictive of TTR in a specialised anticoagulant clinic achieving high-quality control, that is a mean TTR 76%. However, Pastori et al [260] associated an increase in SAME-TT₂R₂ score with reduced number of patients with TTR < 70% but found after adjustment for this score the greatest predictor of TTR was actually the quality of warfarin management. Further to this, Esteve-Pastor et al [261] highlighted that the SAME-TT₂R₂ score identified patients that would benefit from additional strategies to improve warfarin control and thus interventions including educational programs or monitoring by anticoagulation clinics may still impact potential TTR in individual patients.

A lack of participation in a dedicated warfarin management service was one factor included in a more recently proposed predictor model for warfarin control by Lin et al [166]. Developed in 2017, this predictor model originally included a geriatric TTR score

with 42 variables and was subsequently simplified to 7 variables with the abbreviation PROSPER (Table 5) [166]. A PROSPER score > 2 is predictive of poor TTR, that is a TTR < 70%, and categorisation of total scores may indicate low (0 - 2), moderate (3 - 6), or high (≥ 7) risk of having poor TTR [166]. Lin et al [166] validated the PROSPER model and found it outperformed the SAME-TT₂R₂ score in patients aged ≥ 65 years in predicting TTR and may help choose the most suitable candidates for therapy with vitamin K antagonists.

Table 5 - The PROSPER score components proposed by Lin et al [166].

Acronym	Clinical characteristic	Allocated Point(s)
P	Pneumonia	1
R	Renal dysfunction, i.e. acute kidney injury, chronic kidney disease, or end stage kidney disease in the prior 180 days	2
O	Oozing blood (bleeding history)	1
S	Staying in hospital ≥ 7 days	1
P	Pain medications	1
E	no Enhanced anticoagulation care, i.e. lack of participation (no access or plan) in a dedicated anticoagulation management service when initiating a Vitamin K antagonist	4
R	Rx for antibiotics	1
	Predictive of having poor control as defined by TTR < 70%	Total > 2

Another predictor model for warfarin control was proposed by Williams et al [160] in 2017 which includes 15 variables in the final model and estimates TTR by subtracting coefficients for individual factors from the overall model intercept, that is TTR 69.5% (Table 6). In this model, the presence of four or more factors is said to result in a predicted TTR < 60% whilst the presence of seven or more factors results in a TTR < 50%. Williams et al [160] validated their model against SAME-TT₂R₂ and found it to have stronger predictive ability but acknowledged that this model still only explained a

modest amount of variation in TTR and was generated from data in a single health care system serving a predominantly White population.

Table 6 - The warfarin time in therapeutic range calculator proposed by Williams et al [160].

	Classification of variables in proposed model					
	Very low	Low	Low-normal	High-normal	High	Very high
Continuous variable						
Age, years	≤ 56	57 to 65	66 to 73	74 to 80	81 to 85	> 85
	- 6.5*					
Systolic blood pressure, mm Hg	≤ 100	> 100 to 118	> 118 to 132	> 132 to 148	> 148 to 164	> 164
	- 5.5*					- 4.2*
Body Mass Index, kg/m ²	≤ 23	> 23 to 26	> 26 to 30	> 30 to 35	> 35 to 41	>41
	- 3.7*	- 4.6*				
Albumin, g/L	≤ 3.2	> 3.2 to 3.6	> 3.6 to 4.0	> 4.0 to 4.3	> 4.3 to 4.6	> 4.6
	- 8.2*	- 5.8*				
Neutrophil, %	≤ 52	> 52 to 59	> 59 to 66	> 66 to 74	> 74 to 81	> 81
						- 4.9*
Red blood cell count, x10 ⁶ /mcl	≤ 3.5	> 3.5 to 3.9	> 3.9 to 4.4	> 4.4 to 4.8	> 4.8 to 5.1	> 5.1
	- 9.7*	- 5.4*	- 3.3*			
Red blood cell distribution width, %	≤ 12.8	> 12.8 to 13.3	> 13.3. to 14.1	> 14.1 to 15.4	> 15.4 to 16.9	> 16.9
					- 4.8*	- 6.8*
Binary variables	YES	NO				
Alcohol problem	- 5.9*					
Anaemia	- 5.0*					
Lung disease	- 4.0*					
Stroke haemorrhagic	- 9.2*					
Thrombocytopenia	- 5.4*					
Venous thromboembolism	- 5.4*					
Any arrhythmic	- 5.0*					
Aspirin	- 5.2*					

* Estimated time in therapeutic range (TTR) is calculated by subtracting applicable model variables from the intercept term. Intercept term is 69.5% TTR or mean site TTR if known.

The model by Williams et al [160] has the benefit of calculating an actual estimated TTR for an individual patient but it requires input of an extended list of variables including laboratory tests making the calculation more complex. To date, the tools suggested by both Williams et al [160] and Lin et al [166] still require application in different cohorts of patients to further validate their suitability in daily practice. In contrast, the SAME-TT₂R₂ model has been incorporated into several guidelines for AF [262-264] and as such is the currently recommended tool to predict potential warfarin control and assess the likelihood of achieving good TTR and benefit from warfarin prior to commencing therapy.

1.10 Predictor models for risk of bleed and thromboembolism

The potential benefit of warfarin therapy requires consideration of the potential TTR for an individual patient, but also the potential for bleed and thromboembolic events [265]. Adverse events have a clear association with warfarin TTR and this is known to be influenced by numerous patient clinical factors [266]. However, these clinical factors can also independently contribute to the risk of adverse events, particularly bleeding with warfarin [266]. Bleeding with warfarin is known to be influenced by factors including co-morbid conditions [72, 79, 267-271], concomitant drugs [64, 270, 272-276] and advancing age [79, 81, 270, 272, 276-280]. Gender has also been reported to influence bleeding with warfarin but there are some conflicting reports with no differences [79, 81, 276, 280], an increased frequency in males [272] and increased frequency in females reported [281-284]. Analysis of patient dependent factors associated with an increased risk of bleeding has resulted in the development of prediction tools for bleed risk with oral anticoagulant therapy [285]. In 2010, Pisters

et al [286] utilised consistent risk factors for major bleeding found in a systematic review together with additional risk factors determined from the prospective Euro Heart Survey on AF to developed a bleed risk score known as HAS-BLED (Table 7). HAS-BLED assesses the individual one year risk of major bleeding [286] with a score ≥ 3 indicating a patient is at high risk of bleeding and requires caution and regular review with anticoagulant therapy [287]. Several bleed risk scores have been developed for patients with AF which assess characteristics associated with bleeding and categorise patients into a low-, intermediate-, or high-risk group [288]. Studies [289-291] have raised concern regarding the poor predictive abilities of these bleed risk scores but generally the HAS-BLED score has demonstrated superior predictive value [292-294] and simplicity of application [292, 293, 295] compared to other schemes. As such, numerous AF guidelines [263, 264, 296-300] recommend the use of HAS-BLED to assess bleed risk prior to the commencement of oral anticoagulant therapy.

Table 7 - The HAS-BLED score components proposed by Pisters et al [286].

Acronym	Clinical characteristic	Allocated Point(s)
H	Hypertension, i.e. uncontrolled, >160mmHg systolic	1
A	Abnormal renal/liver function – one point for presence of renal impairment (i.e. chronic dialysis, renal transplant, or serum creatinine $\geq 200 \mu\text{mol/L}$) and/or liver impairment (i.e. cirrhosis or bilirubin > 2 times the upper limit)	1 or 2
S	Stroke, i.e prior history	1
B	Bleeding history or predisposition, i.e. previous bleeding requiring hospitalisation or causing a decrease in haemoglobin > 2 g/L and/or requiring blood transfusion, or predisposition such as bleeding diathesis or anaemia	1
L	Labile International Normalised Ratio , i.e. time in therapeutic range <60%	1
E	Elderly > 65 years	1
D	Drugs/alcohol concomitantly, one point for drugs (i.e. antiplatelet agents, non-steroidal anti-inflammatory drugs) and/or one point for alcohol excess (i.e. > 20U/week)	1 or 2
	Low risk of bleeding	Total = 0-1
	Intermediate risk of bleeding	Total = 2
	High risk of bleeding - requires caution and regular review	Total ≥ 3

In addition to the assessment of bleed risk, patients with AF also require assessment of stroke risk to assist in determining the potential benefit of oral anticoagulant therapy [287]. Stroke and bleed risk need to be considered together to determine the risk-benefit of anticoagulant therapy and hence assist in the decision to prescribe anticoagulant therapy for stroke prevention in AF for an individual [86]. A systematic review by the Stroke Risk in AF Working Group [301] identified four independent risk factors for stroke in patients with AF to be prior stroke or transient ischaemic attack, advancing age, hypertension and diabetes. These four clinical predictors of stroke are utilised in nearly all of the twelve stroke risk schemes available with other factors contributing to the overall scores in different schemes and subsequent classification of patients [302]. Whilst studies have identified similar discriminatory performance amongst various risk stratification schemes used to predict AF-related thromboembolisms [303, 304], the most widely accepted and used schemes are the CHADS₂ and CHA₂DS₂-VASc scores [305] (Table 8).

Gage et al [306] originally proposed the CHADS₂ scheme in 2001 to identify patients at low versus high risk of stroke. Subsequently in 2010, Lip et al [307] incorporated further risk factors into the scheme to improve the predictive value by producing the CHA₂DS₂-VASc acronym. The annual risk of stroke for patients assessed as low risk, that is a score of 0, is lower using the CHA₂DS₂-VASc model compared to CHADS₂ [307]. Hence, whilst both schemes have good predictive value for stroke and systemic embolism [308-311] the CHA₂DS₂-VASc score is more effective than the CHADS₂ in identifying very low risk stroke patients [295, 307, 308, 311-313]. Patients at low risk of stroke may not be candidates for anticoagulant therapy and evaluating patients

according to the CHA₂DS₂-VASc score instead of CHADS₂ can reclassify patients as warranting anticoagulant therapy and expand anticoagulation use in patients that may benefit from anticoagulation [314-316]. International AF guidelines recommend a formal assessment of stroke risk prior to anticoagulant therapy with most recommending CHA₂DS₂-VASc [262-264, 297, 300, 317] but others only CHADS₂ [299, 318], either CHADS₂ or CHA₂DS₂-VASc [296], or both [298]. Australian 2018 AF guidelines [319] recommend use of the CHA₂DS₂-VASc score without the gender variable, i.e. CHA₂DS₂-VA, with oral anticoagulation recommended for all patients with no contraindications and a score of ≥ 2 , and consideration of oral anticoagulation therapy in patients with a score of 1.

Table 8 - The CHADS₂ score components proposed by Gage et al [306] and the CHA₂DS₂VASc score components proposed by Lip et al [307].

Clinical characteristic	CHADS ₂		CHA ₂ DS ₂ VASc	
	Acronym	Allocated Point(s)	Acronym	Allocated Point(s)
Congestive heart failure or left ventricular systolic dysfunction	C	1	C	1
Hypertension, i.e. treated hypertension or blood pressure consistently above 140/90 mm Hg	H	1	H	1
Age > 75 years	A	1	A₂	2
Diabetes mellitus	D	1	D	1
Stroke history or history of transient ischaemic attack or thromboembolism	S₂	2	S₂	2
Vascular disease e.g. peripheral artery disease, myocardial infarction, aortic plaque			V	1
Age 65 - 74 years			A	1
Sex category, i.e. female gender			S_c	1
Low risk for ischaemic stroke - patient may not require anticoagulation	Total = 0		Total = 0	
Moderate risk for ischaemic stroke – consider anticoagulation	Total = 1 - 2		Total = 1	
High risk for ischaemic stroke – consider anticoagulation	Total ≥ 3		Total ≥ 2	

1.11 Bleed and thromboembolism risk models predicting time in therapeutic range

The bleed and thromboembolism risk models assess a number of individual patient variables including age, gender, and co-morbid conditions which are reported to influence warfarin TTR. As such, the relationship between warfarin TTR and these risk scores has also been investigated with several studies demonstrating no correlation with warfarin TTR and CHADS₂, CHA₂DS₂-VASc and HAS-BLED scores [193, 201, 214]. In contrast, both Lobos-Bejarano et al [151] and Rivera-Caravaca et al [320] found lower TTR for high risk scores of CHADS₂, CHA₂DS₂-VASc and HAS-BLED. Hellyer et al [321] correlated a decreasing proportion of patients with a TTR > 65% across increasing CHA₂DS₂-VASc and HAS-BLED strata. Similarly, Hong et al [175] associated a TTR < 60% with a high CHADS₂ and high CHA₂DS₂-VASc score. Other studies have linked poorer warfarin control with higher CHA₂DS₂-VASc scores [155, 178, 322] and higher CHADS₂ scores [172, 185, 216]. In addition, McAlister et al [176] found patients with a CHADS₂ score ≥ 2 were less likely to have a TTR > 65%. In contrast, Okumura et al [163] found patients with a CHADS₂ score ≥ 1 had significantly lower TTR than patients with a CHADS₂ ≥ 2 but found CHADS₂ was not an independent predictor of TTR. Kiliç et al [180] associated increased TTR with high CHA₂DS₂-VASc score but found decreased TTR with high HAS-BLED scores. In terms of bleed risk scores associated with TTR, both Bertomeu-González et al [170] and Mueller et al [323] associated high HAS-BLED scores with poorer warfarin control. Comparably, Pokorney et al [178] found lower TTR in patients with higher scores for risk of bleeds but these authors used a different risk model for bleeding than HAS-BLED.

HAS-BLED includes poor anticoagulation control in the bleeding assessment by assigning one point to labile INR and thus considers warfarin TTR in evaluating the risk of bleed events [324]. Importantly, a high risk of bleeding does not preclude patients from warfarin treatment but highlights the need for close monitoring and adjustment of any modifiable influencing factors [262-264, 298, 300, 319]. Patient dependent factors influence the risk of bleed complications and the quality of warfarin control, but achieving high TTR will result in reduced bleed risk and improved outcomes [285]. Several studies have reported a relationship between warfarin control and thromboembolic risk in patients with AF [26, 100, 104, 325]. Further to this, O'Donnell et al [326] have associated therapeutic warfarin with reduced severity of ischaemic stroke and reduced disability or death in patients with AF. However, despite the potential benefit of warfarin in patients with AF there is prevalent underutilisation [327]. Treatment with warfarin in patients with AF eligible for anticoagulation has been reported by Ogilvie et al [328] as under 60% whilst Connolly et al [329] also suggest 50 - 60% of eligible patients with AF are not treated with warfarin. Given that many patients with AF are undertreated, either through not receiving warfarin or not obtaining adequate TTR, other classes of oral anticoagulants were developed [330].

2. Non-vitamin K oral antagonists (NOACs)

Non-vitamin K oral anticoagulants (NOACs) have been developed that act as either direct thrombin inhibitors, for example dabigatran, or Factor Xa inhibitors, for example rivaroxaban, apixaban, and edoxaban [331] as shown in Figure 5. Dabigatran is orally administered as the etexilate prodrug which is rapidly absorbed and converted to the active dabigatran which specifically and reversibly inhibits thrombin [332]. Dabigatran

etexilate is a substrate for P-glycoprotein (P-gp) so strong inhibitors and inducers may alter bioavailability and plasma concentrations [333]. Bioavailability of dabigatran etexilate is low (~ 6.5%) and elimination occurs predominantly via the renal pathway with a half-life of 14 - 17 hours after multiple dosing [334]. The Factor Xa inhibitors share similar terminal half-lives, that is rivaroxaban 5 - 13 hours, apixaban 8 - 15 hours, and edoxaban 6 - 11 hours, with their elimination pathways including metabolism mainly by CYP3A4 as well as biliary and renal elimination [335]. The Factor Xa inhibitors are all substrates for P-gp so potent inhibitors of P-gp and CYP3A4 may result in clinically significant drug interactions and altered bioavailability which is approximately 62% for edoxaban, 50% for apixaban, and ranges for rivaroxaban from 80 - 100% according to dose and co-administration with food [336].

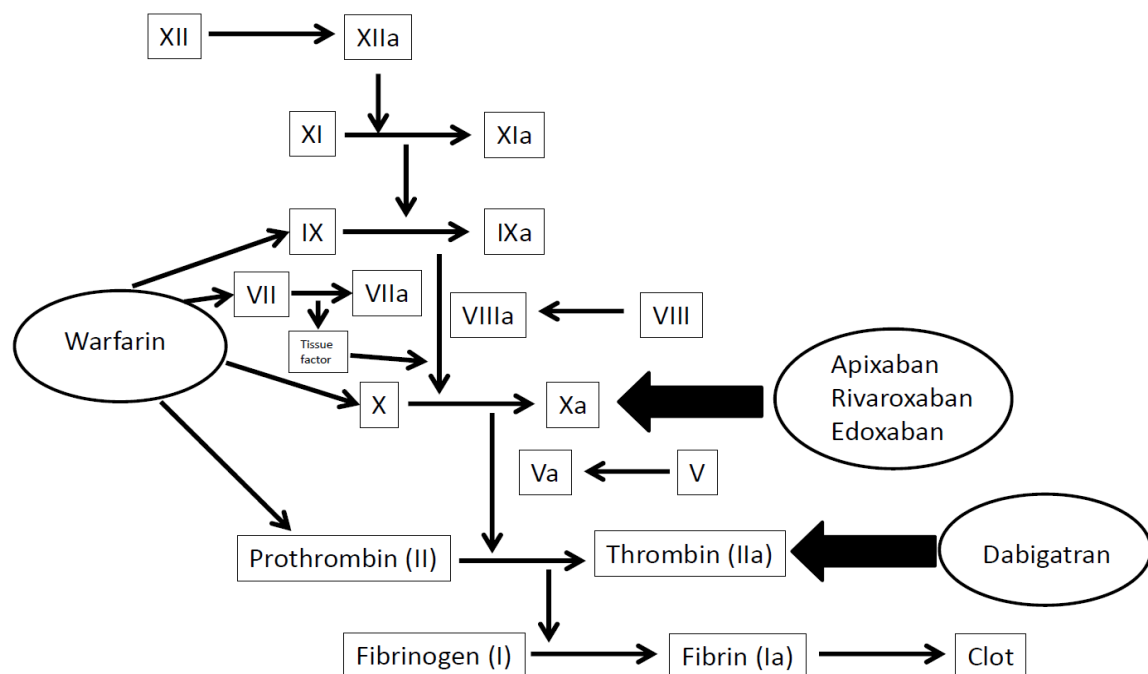


Figure 5 - Coagulation cascade with sites of inhibition of oral anticoagulants - adapted from Scaglione [39].

The NOACs exhibit fixed dosing according to indication with rivaroxaban and dabigatran dosed once or twice daily depending on indication whereas apixaban is always dosed twice daily and edoxaban once daily [337]. All the NOACs require reduced dosing according to degree of renal impairment with recommendations to avoid use at differing creatinine levels and in moderate-severe hepatic impairment depending on agent [338]. Routine monitoring of NOACs is not required to assess efficacy, however it may be of assistance in situations of urgent surgery, overdose, extremes of body weight, or during complications such as bleed or thrombotic events [339]. In the event of bleeding with the NOACs the short half-lives assist in decline of anticoagulant effect on withdrawal of the drug [340]. Specific reversal of the anticoagulant effect of dabigatran may be achieved with idarucizumab [341], however in the absence of licensed reversal agents for the other NOACs prothrombin complex concentrates may be used to manage life-threatening bleeding [342].

3. Treatment with warfarin versus NOACs in patients with AF

Large randomised controlled trials have compared the use of warfarin to the individual NOACs in patients with non-valvular AF (NVAF). NVAF is the absence of rheumatic mitral stenosis, mitral valve repair or mechanical heart valves in patients with AF [317]. As compared to warfarin, dabigatran at doses of 150 mg was associated with lower rates of stroke and systemic embolism but similar rates of major haemorrhage, while doses of 110 mg were associated with similar rates of stroke and systemic embolism but lower rates of major haemorrhage [343]. Rivaroxaban was non-inferior to warfarin for preventing stroke and systemic embolism with no difference in major bleed risk, although intracranial and fatal bleeding was less frequent with rivaroxaban [344].

Apixaban was superior to warfarin in preventing stroke or systemic embolism and caused less bleeding and mortality [345]. Edoxaban was non-inferior to warfarin in the prevention of stroke and systemic embolism and associated with significantly lower bleeding and mortality [346]. Meta-analyses of the dabigatran, rivaroxaban and apixaban comparative trials to warfarin have demonstrated these NOACs to be either non-inferior [347] or slightly superior [348, 349] to warfarin in stroke and systemic embolism rates, and associated with a lower risk of intracranial haemorrhage compared to warfarin [347, 348]. Similar to this, meta-analyses of the trials involving all four individual NOACs to warfarin found the NOACs to result in significant reductions in stroke and systemic embolism rates [350-354], intracranial haemorrhage [350, 351, 353-355] and mortality [350-353, 356]. However, Kumana et al [357] found NOACs and warfarin to be comparable in major bleeds and Ruff et al [350] found the NOACs had similar rates of major bleeding compared to warfarin with increased gastrointestinal bleeds. Likewise, López-López et al [353] found the risk of gastrointestinal bleeds with some NOACs higher than with warfarin, whilst Biondi-Zoccai et al [352] found NOACs to have a favourable trend towards bleeding but found estimates regarding major bleeding statistically inconsistent. Monaco et al [358] performed an analysis of the World Health Organisation database on adverse drug reactions and found a reduced risk of intracranial haemorrhage but increased risk of gastrointestinal haemorrhage with the NOACs compared to warfarin. In addition, Almutairi et al [359] performed a systematic review and meta-analyses of 13 randomised control trials and 27 observational studies comparing warfarin and NOACs, and concluded that the efficacy and safety of the NOACs were comparable or superior to warfarin but identified notable inconsistencies in major bleeding for rivaroxaban

and also in risk of stroke for dabigatran and rivaroxaban. In addition, a meta-analysis by Morimoto et al [360] found the efficacy of the individual NOACs was similar across each agent but found differences in the study designs, particularly the open label design with dabigatran affecting some endpoints and the varied definitions of major bleeding amongst the studies, could overestimate safety and efficacy with the NOACs.

Another major issue identified as potentially influencing the comparative efficacy and safety of warfarin to the NOACs was warfarin TTR. The mean TTR of warfarin in the large randomised comparative trials with dabigatran, rivaroxaban, apixaban and edoxaban was 64.4% [343], 55.2% [344], 62.2% [345] and 64.9% [346] respectively and thus below the 70% TTR targets which optimise outcomes with warfarin [103-106]. In addition, Mitchell et al [349] highlighted that the warfarin control varied across the studies from a TTR of 43.7% (INR 2.0 to 3.0) to 83.5% (INR 2.0 to 3.5) which could impact on the comparative efficacy and safety outcomes. Further to this, Gomez-Outes et al [347] found comparisons were difficult across the studies due to variable warfarin TTR but found the net benefit of NOACs was better in situations where the quality of warfarin control was poor (TTR < 65%). Li et al [361] demonstrated benefit of dabigatran and rivaroxaban was comparable to warfarin when TTR was > 65% in a Chinese population. Similarly, Ruff et al [350] demonstrated a greater reduction in major bleeding with NOACs compared to warfarin with a TTR < 66%, whilst Carmo et al [362] demonstrated that superiority in efficacy of NOAC compared to warfarin for stroke prevention was lost above a warfarin TTR of approximately 70%. Burn and Pirmohamed [363] suggest that when age profiles and adherence are factored in, the NOACs are likely to be inferior to warfarin in centres with warfarin TTR > 70%.

However, in an analysis only involving rivaroxaban, Piccini et al [364] found no overall relationship between warfarin TTR and relative effect compared to the NOAC but acknowledged this study had insufficient power to specifically examine centres achieving warfarin TTR > 70%. Bedeir et al [365] reported no difference in outcomes in the rivaroxaban comparative trial with warfarin at a warfarin TTR of 67%, supporting that TTR values could impact the relative efficacy and safety profiles of the drugs. Similar to this, Wallentin et al [366] showed significant interactions between warfarin control and the effects of warfarin versus both doses of dabigatran in relation to the composite of all cardiovascular events and mortality with reduced event rates at low warfarin control (defined as TTR < 57.1%) and similar rates at high control (defined as TTR > 72.6%). Likewise, Sjölander et al [367] found no difference in stroke prevention between high quality warfarin control (TTR > 70%) and the NOACs although fewer bleed events were seen with both apixaban and dabigatran compared to warfarin. Another study by Wallentin et al [368] demonstrated the benefits of apixaban over warfarin was comparable across all levels of warfarin control in preventing stroke or systemic embolism, and reducing both mortality and bleeds.

In comparing outcomes with warfarin and NOACs, Amin et al [369] found a significant negative correlation between warfarin TTR and rates of stroke and systemic embolism but not major bleedings. However Amin et al [369] found variations in TTR impacted the economic comparison of warfarin versus individual NOACs and specifically determined apixaban to be cost-effective across a warfarin TTR of 30 - 90%, whilst rivaroxaban and dabigatran may be associated with cost-reductions unless warfarin TTR reached above 65% and 70% respectively. Coyle et al [370] suggested dabigatran

150 mg would be optimal at centres with a warfarin TTR less than 66%, whilst apixaban would be optimal at centres with a warfarin TTR above 66%. Likewise, Janzic and Kos [371] suggested cost-effectiveness of NOACs was sensitive to warfarin control with NOACs cost-effective alternatives at warfarin control levels up to 65% TTR but found warfarin was preferred at levels of warfarin TTR above 65%. Further to this, Hospodar et al [372] found warfarin was more effective and less expensive than all NOACs when warfarin TTR was 75%. However, You [373] highlighted that acceptance of NOAC as cost-effective was dependent on not only warfarin control but also drug cost and anticoagulation service cost. Illustrating this, Jegathisawaran et al [374] performed a systematic review of 22 studies addressing cost and outcomes of dabigatran and vitamin K antagonists and found conflicting results ranging from no difference according to warfarin TTR to dabigatran not cost effective at high warfarin control. However, the review found the definition of high warfarin control required for warfarin to be cost-effective varied from 65 – 99% TTR and this was dependent on the economic model involved which was different across the countries and settings involved, particularly with regards to costs of hospitalisations, monitoring and drugs [374]. In the same way, Kasmeridis et al [375] concluded that NOACs are cost-effective compared to warfarin depending on both the price of the NOAC and the warfarin control achieved by local clinical practices.

4. International variation in warfarin control

An analysis by Singer et al [376] of the rivaroxaban versus warfarin trial involving multiple international sites found a dominant determinant of warfarin TTR variation was regional location of medical care and this was independent of patient clinical

features. This sub-analysis of the rivaroxaban versus warfarin trial found large variation of warfarin TTR across geographic regions ranging from 36% in India, to 53% in Eastern Europe and East Asia, to the highest TTRs in Canada/United States and Western Europe of 63% and 64% respectively [376]. Another sub-analysis by Singer et al [377] found poorer regional warfarin control was associated with longer INR inter-test intervals with the shortest interval of 14.9 days in Canada/United States and the longest of 23.7 days in East Asia. Asian patients were found to have a mean TTR which was 8% lower than White patients, but variation also occurred within Asian countries with the lowest TTR of 38% in Taiwan and a higher 64% TTR in Singapore [376]. Similarly, in an analysis of the dabigatran versus warfarin comparative study, Van Spall et al [153] found a mean warfarin TTR of around 54% in both South-East and Eastern Asia but a higher 62.6% in Western Asia. In addition, North America and Western Europe were amongst the highest warfarin control of 66.9% and 68.0% TTR respectively, however Australia was higher still with a 74.0% mean TTR [153]. Further to this, Wallentin et al [368] analysed the apixaban comparative trial with warfarin and found the highest levels of warfarin control in Sweden, followed by Norway then Australia. All these three sub-analyses determined that Australia was amongst the countries with the highest level of warfarin control with TTR values around 74.0% [153, 368, 376].

5. Australian data on warfarin control

Australia has demonstrated high levels of warfarin control with TTR values of 73% [376], 74% [366] and 76% [368] reported in the large comparative studies of warfarin to rivaroxaban, dabigatran and apixaban respectively. Previously, Connolly et al [378] also reported an Australian mean warfarin TTR of 74.5% in a post-hoc analysis of warfarin versus aspirin and clopidogrel. However, these reports were all in controlled prospective clinical trial conditions and not real-world clinical practice. Caldeira et al [210] reported slightly lower warfarin control in retrospective studies than those achieved in the randomised controlled trials in a Portuguese population. In contrast, when compared with the randomised trials of warfarin treatment, higher warfarin TTRs were reported by Hallinen et al [168] among Finnish patients and by Wieloch et al [222] in Sweden using structured anticoagulation programs. Australian data outside of trial conditions, that is real-world, has shown conflicting results in regard to warfarin control and these sporadic published reports are further complicated by variation in study setting and location (Table 9).

An early 2004 study by Jackson et al [379] investigated anticoagulant control in patients discharged on warfarin from one Tasmanian hospital and reported that 67% of patients were in therapeutic INR with home monitoring and 41% with usual care at day eight post-discharge. Similar to this, in 2009, Bubner et al [380] studied the introduction of point of care testing in general practice for 4968 patients across three states in Australia and found the percentage of tests in range to be 55.8% with point of care compared to 57.6% with usual pathology laboratory testing.

Table 9 – Published studies on warfarin control in Australia

Study	Study design	Study location	Study Participants	Warfarin monitoring	Warfarin Control reported
Jackson et al 2004 ³⁷⁹	Open-label randomised controlled trial	Public hospital in Southern Tasmania	128 Any indication (AF 71%)	Home monitoring with POCT and usual care	Therapeutic INR at discharge for 42% home monitoring & 45% usual care with therapeutic INR at day 8 for 67% home monitoring & 41% usual care
Pickering & Thomas 2007 ²¹⁹	Retrospective audit	Urban Aboriginal community controlled health service	26 Any indication (NVAF 50%)	Pathology laboratory results	Mean TTR 44.9% NVAF mean TTR 50.4% & other subgroup 39.4%
Bubner et al 2009 ³⁸⁰	Multicentre, cluster randomised control trial	53 general practices in urban, rural, remote areas across 3 states	4968 total with 944 taking OACs for any indication	POCT device	INR in target range 57.0% intervention & 61.5% control
Stafford et al 2011 ³⁸¹	Prospective non-randomised controlled cohort study	8 hospitals across 5 metropolitan, rural and remote regions of Australia	268 Any indication (AF 51%)	Usual care and post-discharge service	TTR 55.2% usual care & 55.6% post-discharge service
Bereznicki et al 2013 ³⁸²	Observational study	Southern Tasmania	1137 Indications N/A	Pathology laboratory results	Mean TTR 69.1% TTR>70% in 52.5% of patients
Bereznicki et al 2016 ³⁸³	Retrospective cohort study	Australia – Department of Veteran’s Affairs database	321 Any indication	Pathology laboratory results	Mean TTR 64.0% (27.3%)
Mueller et al 2016 ³²³	Retrospective cohort analysis	Queensland private pathology laboratory	533 Deep vein thrombosis	Warfarin management program	Mean TTR 78.3% (12.7)
Dennis et al 2017 ²⁰⁸	Retrospective cohort analysis	Northern Territory in outer regional to very remote	167 Any indication (AF 67%)	Laboratory testing and two POCT devices	Mean TTR 55.4% and average time in therapeutic range 52.3%

AF = Atrial Fibrillation, INR = International Normalised Ratio, N/A = Not Available, NVAF = Non-valvular Atrial Fibrillation, OAC = Oral Anticoagulant, POCT = Point of Care Testing, TTR = Time in Therapeutic Range,

The first report of warfarin TTR from Australian studies was in 2007 by Pickering and Thomas [219] who reported a TTR of 44.9% for patients in an Aboriginal community in Darwin in the Northern Territory, however this study included only 26 patients. Subsequently, in 2011, Stafford et al [381] conducted a prospective three-month study of 268 patients discharged on warfarin from eight hospitals across three Australian states and found a TTR of 55% regardless of whether patients were receiving usual care or a post discharge service. In 2013, Bereznicki et al [382] reported a TTR of 69.1% in a retrospective observational study of 1137 Tasmanian patients receiving monitoring for warfarin therapy. Three years later, Bereznicki et al [383] reported a lower 64.0% in 321 Australian war veterans and also found veterans living in outer regional and remote areas had significantly poorer warfarin control than those in major cities and inner regional areas. Dennis et al [208] reported an average TTR of 55.4% in patients living in areas classified as outer regional, remote or very remote within the top end of the Northern Territory in 2017. In contrast, Mueller et al [323] reported a high mean TTR of 78.3% in patients receiving warfarin for DVT at an anticoagulant clinic in Queensland. In Australia, approaches for managing warfarin therapy include usual care by the GP, anticoagulant clinics, and patient self-monitoring [384]. This data (Table 9) demonstrating differences in warfarin TTR from 44.9% [219] to 78.3% [323] suggests that the management systems together with other factors including study population and geographical location may impact the differences in warfarin control achieved across Australia.

6. International variation in oral anticoagulant recommendations for AF

The variation in TTRs among regions and centres has created difficulty in translating results from the warfarin versus NOACs comparative trials into clinical practice [385]. Gomez-Outes et al [347] suggested that the net benefit of NOACs may be of a lesser magnitude in Europe due to the quality of warfarin control achieved there. In contrast, Chiang et al [386] suggested potential benefits of NOACs in Asians compared to non-Asian populations due to the lower TTR in the Asian population, but recommended consideration to differences in Chinese, South and East Asian populations. This differential effect seen between Asians and non-Asians may be influenced by genetic polymorphisms, but also affected by other demographic differences including body weight and renal function [387]. The potential benefit of NOACs over warfarin in Asians is reflected in guidelines for NVAf from some Asian countries, with Japanese guidelines [299] stating NOACs are the preferred oral anticoagulants and Taiwan guidelines [264] also recommending NOACs over warfarin due to difficulty in achieving warfarin TTR of > 65%. Further to this, Korean guidelines [300] recommend use of NOACs or warfarin but warfarin TTR should be at least 60% when this anticoagulant is used. Similarly, the recommendation from the Asia Pacific Heart Rhythm Society [263] is that NOACs are preferred but warfarin would remain viable in certain scenarios, including those likely to have good control. These Asia-Pacific guidelines [263] may be utilised in Singapore, but as there are no specific national AF guidelines in Singapore clinicians may also be guided by recommendations from other continents including Europe [262] and the United States [317].

Conflicting recommendations regarding oral anticoagulant therapy in NVAf are found in other continents. The European Primary Care Cardiovascular Society [298] recommends either warfarin or NOACs in patients with NVAf but a preference for NOAC if not obtaining a warfarin TTR above 65%. However, other European guidelines [262, 388] state a preference for NOACs over warfarin and likewise Canadian guidelines [318] suggest patients should receive NOACs in preference to warfarin. American guidelines [296, 317] recommend either warfarin or NOACs depending on patient factors or preference, but NOACs are recommended in patients unable to maintain therapeutic INR levels with warfarin [317]. Similarly, the United Kingdom's National Institute for Health and Care Excellence [297] recommends either NOACs or warfarin based on clinical features and preference but endorses calculation of TTR at patient visits and over a maintenance period of six months, with reassessment of warfarin therapy if TTR < 65%. Despite these variations in international guidelines regarding the preferred anticoagulant therapy in AF, common to all these guidelines is the recommendation to optimise TTR if warfarin is used as the oral anticoagulant.

7. Australian guidelines on anticoagulation in AF

In Australia, current recommendations vary with regards to oral anticoagulant therapy in AF. The Australian AF guidelines [319] updated in August 2018 recommend NOACs in preference to warfarin in patients with NVAf. However, the current Australian Cardiovascular Therapeutic Guidelines [389] recommend NOACs or warfarin in these patients and suggest that the suitability of warfarin requires reassessment in patients with persistently high or labile INR. The Australasian Society of Thrombosis and Haemostasis recommends that patients who should not be on NOACs include patients

stably anticoagulated on warfarin as defined by TTR > 65% over a three-month period [390]. Despite variations in these Australian guidelines, each of them highlight specific patient groups that may be more suited to warfarin, e.g. patients with renal impairment, and recommend warfarin in patients with valvular AF, that is mechanical heart valves or moderate to severe mitral stenosis [319, 389, 390].

8. Changing patterns of oral anticoagulant use

Concerns regarding NOAC use in specific patient populations (for example renal dysfunction and extremes in bodyweight) and their higher drug costs compared to warfarin have been reported as factors affecting their uptake in health systems [391]. In the United States, Desai et al [392] demonstrated rapid adoption of NOACs into clinical practice particularly in lower-risk patients with AF, but associated the 62% of new NOAC prescriptions with 98% of anticoagulant-related medication costs. Another study from the United States by Marzec et al [393] found the introduction of the NOACs improved rates of oral anticoagulant use by 8.3%, particularly in patients at lower risk of stroke and with fewer co-morbidities. In addition, Huisman et al [394] found that NOACs have become more frequently prescribed than warfarin in North America and Europe. In contrast, a report from Canada by Weitz et al [395] revealed an increase in overall oral anticoagulant prescribing but found warfarin still represented the majority of prescriptions despite a decreasing trend in warfarin use. Albert [396] suggested the introduction of NOACs addressed some of the challenges associated with warfarin and anticipated that the NOACs would promote prescribing of oral anticoagulant therapy in patients with AF and address the underuse of warfarin.

However, the global study by Huisman et al [394] reported that in Asia, many patients remain undertreated with anticoagulants, quoting 27.5% of patients received warfarin, 27.7% NOACs, with the remainder receiving either antiplatelets or no treatment. Wee et al [397] investigated patients with NVAf in Singapore and found 30% were treated with warfarin, 20% NOAC, and the remainder antiplatelets or no treatment. Tagaya et al [398] analysed patients receiving oral anticoagulant therapy in Japan and found a higher 40% of patients were treated with NOAC and 60% with warfarin. Further to this, Ko et al [399] demonstrated an increase in NOAC prescribing in Korea from 36.2% to 60.8% in 2015 to 2016, but related this increase to a change in health insurance coverage policy. Likewise, Lee [400] reported affordability and access to drugs as an issue for patients under health care systems not providing subsidy for these oral anticoagulants. Similar to this, Leung et al [401] found cost, interpretation of clinical trials, prescriber beliefs and practice settings have all demonstrated to impact selection of NOACs or warfarin therapy in patients with AF.

9. Australian patterns of oral anticoagulant use

Numerous Australian studies have investigated prescribing of oral anticoagulants in patients with AF. Bellinge et al [402] found that in rural Western Australia 31% of patients with AF and an indication for oral anticoagulant therapy received no therapy. In addition, living location influenced choice of anticoagulant with warfarin more frequently prescribed for patients in metropolitan areas and less frequently for patients living more remotely where access to health care services required for warfarin monitoring would be more limited [402]. At a South Australian hospital, Wong et al [403] determined that Indigenous Australians were more likely to be under

prescribed anticoagulant therapy compared to non-Indigenous Australians when at high risk according to CHADS₂ or CHA₂DS₂-VASc scores despite the availability of both warfarin and the NOACs. Two studies from New South Wales by Baker et al [404] and Pandya et al [405] found that warfarin was more likely than NOACs to be prescribed to patients with poorer renal function and higher scores of HAS-BLED and CHA₂DS₂-VASc. Similar to this, a Tasmanian study by Alemneh et al [406] reported patients prescribed NOACs had significantly lower predicted bleed and stroke risk scores compared to warfarin users but overall found decreased prescribing of warfarin and increased prescribing of NOACs. Another Tasmanian study by Admassie et al [407] found that in the post-NOAC era, prescribing to high-risk patients improved from 52.5% to 60.7% but identified aging and previous bleeding as inversely associated with oral anticoagulant prescribing. However, to date, no studies specific to prescribing of warfarin and NOACs to patients with AF in Queensland have been published.

Australia-wide Pharmaceutical Benefit Scheme (PBS) prescribing data was analysed by Simons et al [408] who found persistence with warfarin improved with advancing age but also found warfarin treated patients were 2.5 times more likely to discontinue treatment over 12 months compared to patients on NOACs. However, these authors [408] found similar rates of new users of warfarin and NOACs which is in contrast to Pratt et al [409] who found a much higher number of new NOAC users compared to warfarin. Specifically, Pratt et al [409] analysed Australian Government Veterans' Affairs data and found those initiated on NOACs were younger and more likely to be men and have fewer co-morbidities. These authors [409] concluded that NOACs increased prescribing of oral anticoagulants and this may be reflective of prescribing to

patients considered unsuitable for warfarin. In June 2016, the Drug Utilisation Sub-Committee investigated PBS data specific to NVAF and found that NOACs contributed to a growth in the total Australian anticoagulant market [410]. However the use of individual NOACs varied across states and areas, with people new to anticoagulant therapy more likely to commence a NOAC than warfarin except in remote areas where warfarin was more commonly used [410].

Australian PBS statistics [411] for all indications indicate that warfarin prescribing by total items exceeded that of the NOACs until 2016/7, but the NOACs are being increasingly prescribed, with rivaroxaban and apixaban more widely used than dabigatran (Table 10). The PBS statistics [411] also show a higher acquisition cost of these agents and the expenditure for each NOAC has now exceeded that of warfarin (Table 11).

Table 10 - Pharmaceutical Benefits Scheme statistics [411] for total items of individual anticoagulants processed per financial year for all indications

	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/7	2017/8
Warfarin	2,695,331	2,644,243	2,721,898	2,677,017	2,366,331	2,075,514	1,730,011	1,489,857
Dabigatran	42	444	600	183,055	321,908	326,861	370,962	445,860
Rivaroxaban	11,888	14,305	24,965	424,441	953,974	1,289,051	1,502,294	1,694,596
Apixaban	0	119	914	70,909	345,520	721,733	1,125,671	1,547,862

Table 11 - Pharmaceutical Benefits Scheme statistics [411] for total benefits cost in Australian dollars (\$AUD) of individual anticoagulants processed per financial year for all indications

	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/7	2017/18
Warfarin	24,166,701	23,384,169	24,161,105	23,849,831	21,380,779	24,105,040	19,788,882	17,692,301
Dabigatran	4958	82,385	80,976	15,959,204	28,087,858	26,766,812	28,919,239	34,747,461
Rivaroxaban	2,083,258	2,473,596	2,548,356	35,101,682	79,513,715	100,739,502	112,145,785	126,662,948
Apixaban	0	20,807	155,965	7,215,923	31,673,518	62,509,860	95,787,439	127,042,376

On the PBS, NOACs have specific item codes listed for use in prevention of stroke or systemic embolism in patients with NVAf. These item codes for rivaroxaban (2268J, 2691P), dabigatran (2753X, 2769R), apixaban (2735Y, 2744K) also show increasing use (Table 12). Numerous studies [328, 329, 412-414] have demonstrated underuse of anticoagulation in eligible patients, particularly warfarin. The increased number of prescriptions processed for all anticoagulants suggests the total number of patients receiving anticoagulant treatment has increased since the introduction of the NOACs and supports this hypothesis that warfarin has been underutilised. Information specific to warfarin use in patients with AF is not available due to its unrestricted listing on the PBS. However, recently Pol et al [415] calculated that from September 2013 to May 2017, total monthly prescriptions of combined NOACs had increased by over 2900% (9,499 to 281,217) whilst for the same months warfarin prescriptions decreased by almost 30% (196,696 to 137,976).

Table 12 - Pharmaceutical Benefits Scheme statistics [411] for total items of individual non-vitamin K anticoagulants processed per financial year for codes with indications for atrial fibrillation, namely rivaroxaban (2268J, 2691P), dabigatran (2753X, 2769R), apixaban (2735Y, 2744K).

	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/7	2017/18
Dabigatran	0	0	0	180,125	318,536	324,064	366,580	439,839
Rivaroxaban	0	0	9,011	398,878	914,960	1,243,178	1,453,626	1,646,002
Apixaban	0	0	0	69,000	340,469	710,675	1,106,484	1,521,005

10. The Sansom report

Dabigatran was the first NOAC released in Australia and in 2011 it was considered for inclusion in the government subsidised PBS. Following this on 30 September 2011, the Australian Government commissioned Emeritus Professor Lloyd Sansom to lead a Review of Anticoagulation Therapies in Atrial Fibrillation, hereafter referred to as the

Sansom report [24]. The review aimed to consider the current and future management options for anticoagulation in patients with AF and determine the potential benefit of the NOACs compared to warfarin in the Australian context. However, the Sansom report [24] identified a lack of information in a number of areas specific to Australian clinical practice leading to uncertainty in determining the comparative benefits of NOACs and warfarin in Australia as opposed to outcomes demonstrated in the pivotal clinical trials. These included but were not limited to the quality of warfarin management, switching patterns, and the ability to monitor warfarin response in patients receiving multiple medications for various co-morbidities [24]. It was found that addressing barriers to the use of warfarin and improving the quality of warfarin control were key requirements to drive an improvement in health outcomes [24]. Further to this, it was determined that specific patient algorithms were required to assist in decision making between anticoagulants but to develop these, there required further understanding of patient factors influencing choice, management, and outcomes with individual anticoagulants including warfarin [24]. A total of fifteen recommendations were made in the Sansom report [24]. These recommendations aimed to improve the management of stroke prevention in patients with AF by considering the burden of disease and the need for improved guidance and management to ensure optimal cost-effectiveness of anticoagulant therapies in Australian clinical practice. Recommendations specific to anticoagulant therapies were:

- Recommendation 3 – Develop national guidelines which include a systematic approach to risk assessment through algorithms like CHADS₂, CHA₂DS₂-VASc

and HAS-BLED and provide consideration of co-morbid conditions and concomitant medications in addressing barriers to the optimisation of anticoagulant use;

- Recommendation 8 – Optimisation of warfarin TTR and identification of factors that influence TTR for individual patients;
- Recommendation 9 – Government support of warfarin management options that incorporate a timely, systematic and co-ordinated approach of INR testing, dosing, communication and follow-up to patients;
- Recommendation 12 – Funding of formalised anticoagulation programs such as programs offered by laboratory programs in Queensland and Victoria;
- Recommendation 15 – Determine the clinical and cost-effectiveness benefit of NOACs over warfarin in clinical practice with consideration to the impact should use be restricted to patients unable to tolerate warfarin or obtain satisfactory INR control, noting definition of satisfactory warfarin control was required.

Overall the Sansom report [24] found there was a need to determine satisfactory warfarin control and identify methods of optimising warfarin TTR including determination of factors influencing intra-patient variability so that the quality of warfarin use in Australia could be optimised. These findings and the specific recommendations in the Sansom report [24] led directly to the aims of this project.

11. Rationale and aims

The Minister for Health and Ageing In Australia commissioned a Review of Anticoagulation Therapies in Atrial Fibrillation after the first application was made for a NOAC to be subsidised under the PBS in 2011 [24]. This report identified a lack of available information as a barrier in determining the comparative benefits of warfarin and the NOACs in the Australian context, and it was specifically identified that more information was required regarding warfarin control in Australia including identification of factors influencing TTR to ensure optimisation of warfarin use [24]. This study aims to investigate current levels of warfarin control and determine factors influencing TTR, and thus directly address recommendations resulting from the Australian Government commissioned report. Further to this, given potential factors influencing warfarin TTR include patient demographics, ethnicity, and management systems, a comparator site in the Asia-Pacific region, namely Singapore, was selected to assist with applicability across the multi-cultural population of Australia. Identifying subsets of patients who could particularly benefit or experience adverse outcomes from warfarin could provide clinicians with an evidence-based approach to prescribing of warfarin. This would particularly benefit patients with valvular AF where warfarin remains the only available anticoagulant option. Furthermore, for patients with NVAf, this data could contribute to guidelines which assist in decision-making between available anticoagulants and ensure warfarin is tailored to the most suitable candidates. Improving the quality of warfarin control could potentially reduce the hospitalisation costs associated with poorly controlled warfarin in addition to having a follow on effect of potentially reducing use of the more expensive NOACs with accompanying savings to the federal budget.

The overall aim of this study was to determine predictors of warfarin control in patients with AF in South-East Queensland and Singapore and thus inform prescribing and management of warfarin to patients with AF. Specific objectives of the study were to:

Specific Objective 1: Establish the prescribing of warfarin in patients with AF in Queensland since the introduction of the NOACs and determine the potential impact on warfarin control for patients transitioning between anticoagulants.

Specific Objective 2: Determine the quality of warfarin control in patients with AF in South-East Queensland achieved by different warfarin management systems and identify factors contributing to the levels of warfarin control.

Specific Objective 3: Identify the factors influencing time in therapeutic range of warfarin in patients with AF in South-East Queensland and compare this to influencing factors in Singapore.

Specific Objective 4: Establish the efficacy of risk models recommended in AF guidelines to predict warfarin control in patients with AF in South-East Queensland and Singapore.

12. Overview of this thesis

The following chapter outlines the methods by which the aims and objectives of this thesis will be achieved. Chapter three establishes the prescribing of warfarin since the introduction of the NOACs with PBS prescribing data and prescribing data specific to a Queensland warfarin management program. The impact on transitioning between

anticoagulants on warfarin control is addressed in the form of a published article to complete specific objective one. Chapter four contains two published articles to determine warfarin control by different management systems in South-East Queensland and factors contributing to the levels of warfarin control achieved to address specific objective two. Likewise, chapter five addresses specific objective three of factors influencing TTR in South-East Queensland compared to Singapore through three published articles. Chapter six also utilises three published articles to determine the ability of risk models, namely SAME-TT₂R₂, CHADS₂, CHA₂DS₂-VASc and HAS-BLED, to predict suitability of warfarin and addresses specific objective four. Chapter seven provides discussion on the findings of the thesis and also considers limitations and future directions.

Chapter Two - Methods

2.1. Study design

A retrospective observational study was conducted on patients receiving warfarin for atrial fibrillation at two study sites, one in Queensland and one in Singapore. PBS data was utilised to establish prescribing rates of oral anticoagulants in Queensland since the introduction of the NOACs.

2.1.1 Queensland study site

The Queensland study site was Sullivan Nicolaides Pathology (SNP), a private pathology laboratory that offers a warfarin management program named Warfarin Care.

Warfarin Care is available on referral from a general practitioner (GP) to any patient initialised on warfarin in Queensland and northern New South Wales. The service offered to patients by this program includes blood collection, laboratory testing with interpretation of results by pathologists and specialist GPs, ongoing dose instruction and information on timing of next blood test communicated via the patient's preferred method, for example telephone call or text message. Prior to each blood test patients complete a short questionnaire (Figure 6) regarding recent compliance, events, medication changes, and planned surgery or holidays to assist with result interpretation and to identify any potential areas for follow-up, for example compliance. Data at this site was determined to be suitable to address all aims and objectives, however it was identified that information regarding race was not available. Similarly, information regarding some social factors, specifically alcohol use and smoking status, was variable with details only available for some patients.

<input type="checkbox"/> Yes <input type="checkbox"/> No Are you taking the warfarin dose recommended by SNP? If 'No', what dose are you taking and who prescribed it? <hr/> <input type="checkbox"/> Yes <input type="checkbox"/> No Have you missed any doses in the last week? If 'Yes', list date(s): <hr/> <input type="checkbox"/> Yes <input type="checkbox"/> No Since your last test have you had a recent illness, bleeding, clot, or hospital admission? If 'Yes', please describe: <hr/> <input type="checkbox"/> Yes <input type="checkbox"/> No Do you intend to have a medical procedure (e.g. surgery, dental extraction)? If 'Yes', please describe: <hr/> Date of procedure: / / Expected discharge date: / / <input type="checkbox"/> Yes <input type="checkbox"/> No Are you planning holidays soon? If 'Yes', please describe: <hr/> Date of departure: / / Expected return date: / / 	Please list your current medications: <hr/> Medication changes (include vitamins, supplements, herbal)* <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="text-align: left; border-bottom: 1px solid black;">Medication</th> <th style="text-align: left; border-bottom: 1px solid black;">Start date</th> <th style="text-align: left; border-bottom: 1px solid black;">Stopped date</th> <th style="text-align: left; border-bottom: 1px solid black;">Changed dose and date</th> </tr> </thead> <tbody> <tr><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td></tr> <tr><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td></tr> <tr><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td><td style="border-bottom: 1px solid black;"> </td></tr> </tbody> </table> <hr/> Patient authority I hereby authorise Sullivan Nicolaides Pathology to obtain from my medical records all clinical information relevant to my warfarin management. Completed by: <input type="checkbox"/> Patient <input type="checkbox"/> Collection staff <input type="checkbox"/> Agent** details: Name: _____ Signature: _____ Date: / / 	Medication	Start date	Stopped date	Changed dose and date												
Medication	Start date	Stopped date	Changed dose and date														
<small>* IMPORTANT! Please also advise your doctor of any clinical or medication changes.</small>	<small>** If Agent, please provide relationship to patient (e.g. carer, family member, doctor, nurse).</small>																

Figure 6 - Patient questionnaire used by Sullivan Nicolaides Pathology to be completed by patients enrolled in Warfarin Care program at the time of each blood test to check International Normalised Ratio.

2.1.2 Singapore study site

The Singapore study site was the National Heart Centre Singapore (NHCS). This provided an overseas comparator site in the Asia-Pacific region. The NHCS is a national and regional referral centre for cardiovascular medicine in Singapore. Patients receiving warfarin therapy are monitored at the NHCS through regular appointments at the outpatient clinics. At these appointments, patients are consulted by clinicians with questions during consultation including any recent adverse events or issues with regards to warfarin dosing. Blood results are then interpreted to determine a warfarin dose for ongoing treatment and a subsequent appointment made for follow-up review. Singapore is a mix of predominantly Chinese, Malay and Indian populations so it was identified that data from the NHCS would provide specific information on warfarin control in differing Asian populations. Available information on race and

certain social factors such as alcohol consumption and tobacco use was particularly pertinent to apply the SAME-TT₂R₂ model as this data was not available from SNP.

2.2. Ethics

Human research ethics approval was granted by Griffith University for the research to be conducted at SNP (GU Ref No PHM/09/14HREC) following signing of a data licence agreement between SNP and Griffith University. Ethics approval was granted at NHCS by SingHealth Centralised Institutional Review Board (CIRB Ref 2015/2435) and via prior approval through Griffith University (GU Ref No 2015/863). Appendix 1 contains ethics approval letters from both study sites.

2.3. Data collection

2.3.1 PBS prescribing

PBS data was extracted for Queensland prescribing of warfarin and each individual NOAC for the period 2012 to 2018. Specific item codes related to the use of NOACs in the prevention of stroke or systemic embolism in patients with NVAf was used for rivaroxaban (2268J, 2691P), dabigatran (2753X, 2769R) and apixaban (2735Y, 2744K). Information related to warfarin prescribing specific to AF was not available due to the unrestricted PBS listing for warfarin so general item codes were used (2843P, 2209G, 2844Q, 2211J). Total items dispensed per financial year in Queensland were collated for each anticoagulant, that is warfarin, dabigatran, rivaroxaban, and apixaban.

2.3.2 Queensland study site - SNP

At SNP, data extraction identified patients enrolled in the Warfarin Care program as of September 2014 with the primary indication of AF. The Oral AntiCoagulant Graphical User Interface (OAC GUI) program was accessed for data collection. INR test dates and results were collected for all patients receiving warfarin for AF together with the recommended INR target range for that patient. Patient demographic data collected included date of birth, gender and postcode of residential location. Clinical parameters collected included medical conditions, current medications and any changes to medication including any short-term medication, and any adverse events and/or hospitalisations reported. The start date of warfarin and the date of enrolment in Warfarin Care were recorded. The patient data was also screened to determine if INR results were available prior to enrolment in Warfarin Care, that is whilst managed by their GP and, if so, all the INR tests (date and result) were recorded for the time prior to enrolment in Warfarin Care. Data was collected for the entire time a patient was enrolled in Warfarin Care however the OAC GUI system had been implemented at SNP in November 2007 so this was the earliest date recorded for enrolment in the program. Patient data, for example medical conditions and medications, for patients enrolled prior to this date had transferred to this system so were available for collection from November 2007 onwards.

Another data extraction at SNP identified patients recorded as exiting and/or reactivating the Warfarin Care program for a NOAC for the period of January 2012 to November 2017. SNP had utilised an internal code for patients exiting the warfarin program to commence a NOAC of EXIT-A, EXIT-D, and EXIT-R for apixaban, dabigatran and rivaroxaban respectively and this was utilised for data extraction. Data collected

for these patients included date of birth, gender, main indication of therapy, start date of warfarin, date of exit or reactivation in the program, and any documented reason for the change in therapy. For patients reverting to warfarin therapy after another oral anticoagulant, INR results were collected together with warfarin doses for the treatment both before and after NOAC therapy.

2.3.2.1 Inclusion and exclusion criteria

Patients enrolled at Warfarin Care and taking warfarin for the primary indication of AF were eligible for inclusion in the study but inclusion and exclusion criteria differed according to the specific objectives. Objective one was to determine patterns of switching anticoagulants included all patients for the period of January 2012 to November 2017 who were coded as exiting the program for a NOAC, that is 3036 patients. The potential impact on warfarin control included only patients who had returned to warfarin therapy, that is 142 patients, and exclusion criteria included insufficient INR tests to calculate warfarin control, that is less than 30 days treatment before or after NOAC therapy (Figure 7).

Objective two was to determine warfarin control at SNP included all patients with AF enrolled in Warfarin Care, that is 3954 patients, unless they had insufficient tests to calculate INR control or a target range which was not INR 2.0 to 3.0 (Figure 8). To address differences in warfarin control between management systems, INR results for a minimum of six months whilst managed by the patient's GP were required. Patients were excluded if they had been with Warfarin Care since commencement of the current database in November 2007 as no prior INR results were available. To ensure a minimum of six months of INR results were available for calculation of TTR, patients

were also excluded if they had enrolled in Warfarin Care less than six months after commencing warfarin or if dates of commencing warfarin or enrolment in the program was missing. Patients were also excluded if enrolled in Warfarin Care before October 2008 as six months of INR results whilst managed by both GP and SNP would not be available with the current database implemented November 2007. INR results of all remaining patients were screened to determine if at least six months of continuous INR results were available for the time prior to enrolment in Warfarin Care and these patients included in the study.

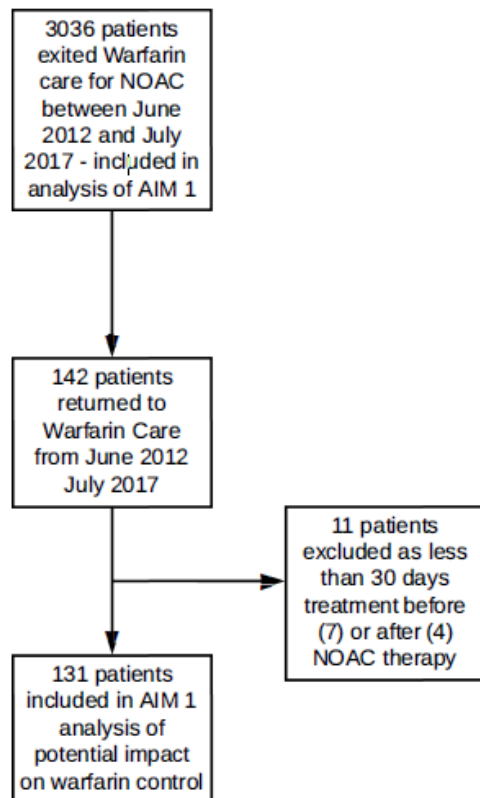


Figure 7 - Inclusion and exclusion criteria to address aim one at Queensland study site.
NOAC = non-vitamin K oral antagonist

Objective three and four required a comparison to the Singapore study site which had ethics approval for patients with NVAf receiving warfarin between January 2014 and June 2014. Therefore, for analysis of this objective, patients with a classification of

valvular AF, that is presence of mitral stenosis, valve replacement or valve repair were excluded from analysis as were any patients who had warfarin dose information missing (Figure 8).

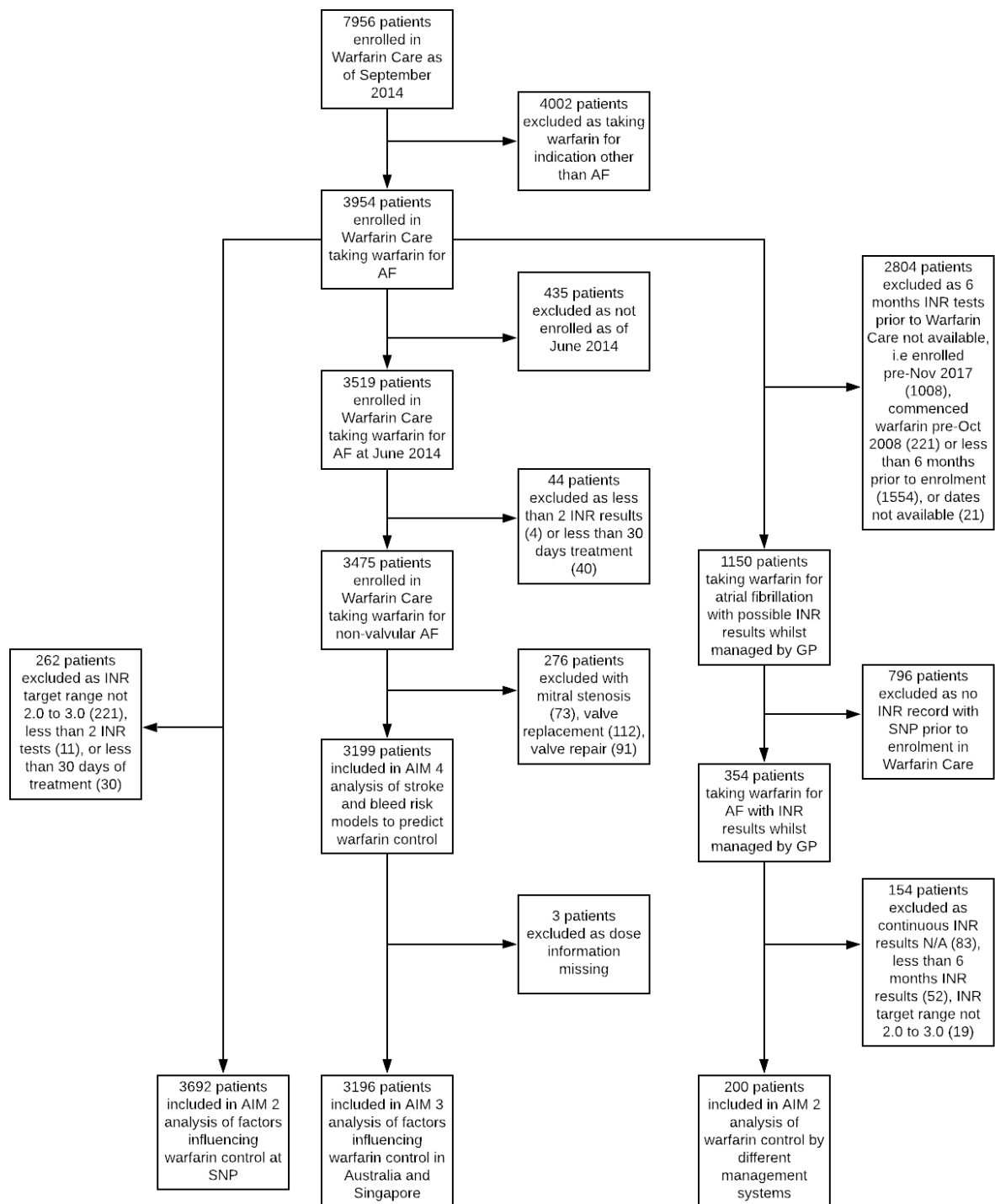


Figure 8 - Inclusion and exclusion criteria to address aim two, three and four at Queensland study site.
 AF = atrial fibrillation, GP = general practitioner, INR = International Normalised Ratio, N/A = not available, SNP = Sullivan Nicolaides Pathology

2.3.3 Singapore study site - NHCS

At the NHCS, data extraction identified all patients dispensed warfarin via the Outpatient Administrative System (OAS) from January 2014 to June 2014, that is 3122 patients. The Sunrise Clinical Manager (SCM) program was accessed for data collection. Patient data was screened to identify patients receiving warfarin for the indication of AF, that is 2035 patients, and patients with mitral stenosis, valve replacement, or valve repair were excluded to investigate only patients with AF classified as non-valvular, that is 1430 patients. INR test dates and results were collected for all patients receiving warfarin for NVAf together with the warfarin dose prescribed at each INR test date. Patient demographic data collected included age, gender, race, and social history including height, weight, smoking status and alcohol consumption. Clinical parameters collected from SCM included medical conditions, current medications and any changes to medication including any short-term medication, together with any adverse events or hospitalisations during the study period.

2.3.3.1 Inclusion and exclusion criteria

All patients receiving warfarin for the treatment of NVAf during the study period of January to June 2014 were eligible for inclusion in the study, that is 1430 patients (Figure 9). Patients were excluded if they had less than 2 INR tests or less than 30 days treatment, that is insufficient INR tests to calculate warfarin control. Objective four with analysis of bleed and risk scores included all remaining patients whilst the comparison with the Australian site required dose information and thus missing dose information was a further exclusion for aim three. The NHCS data had all variables

available for application of the SAME-TT₂R₂ model to complete objective four. Patients of non-Asian race were excluded from this analysis to specifically determine the suitability of the SAME-TT₂R₂ score in an Asian population.

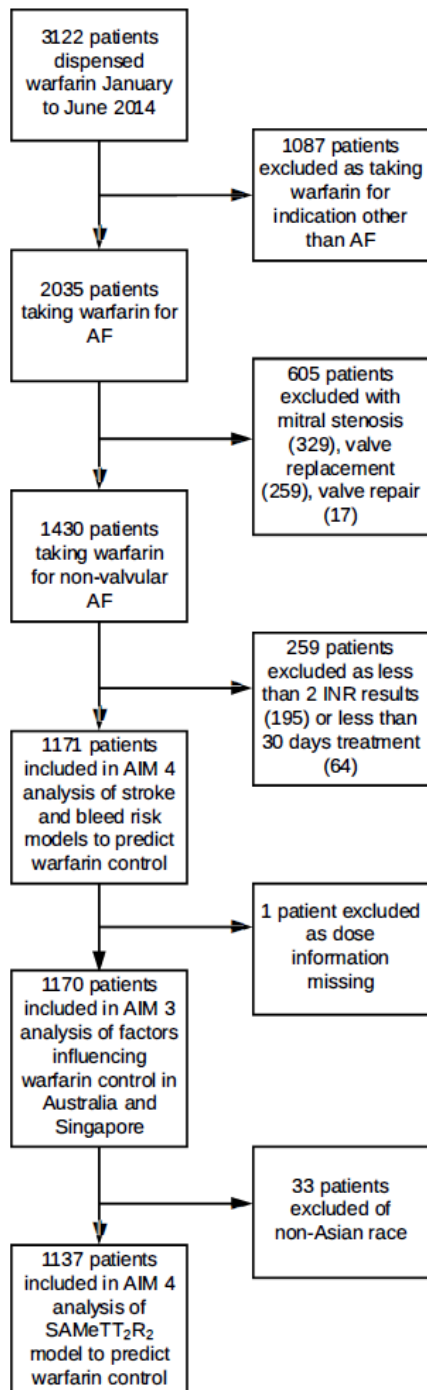


Figure 9 - Inclusion and exclusion criteria to address aim three and four at Singapore study site. AF = atrial fibrillation, SAME-TT₂R₂ = Sex, Age, Medical history, Treatment, Tobacco, Race predictor model

2.4. Study Endpoints

2.4.1 Warfarin control

Warfarin control was the basis of analysis for all aims and objectives of the study and included both TTR and INR control. Calculation of TTR for each individual patient was determined via the Rosendaal method [95] with software obtained from INR Pro[®]. Input of individual INR test dates and results together with INR target range for each patient calculated days within range, total days, and percentage of days within range via the Rosendaal method [95] together with total number of tests, number of tests in range, and percentage of tests in range (Figure 10). Results from this calculation were used to determine frequency of testing. Patients were excluded from analysis if TTR could not be calculated, i.e. less than two INR tests, or if less than thirty days of warfarin treatment was received to ensure adequate time for calculation of TTR. For some analyses, patients were categorised according to achieving good levels of control as defined by a TTR of 60% or 65%.

[illegible]

Figure 10 - Format of software obtained from INR Pro® to input INR test dates, results, and range for each individual patient and calculate time in therapeutic range and percentage of tests in range. First two columns (highlighted) indicate where input of data is required.

INR control was determined by the percentage of tests in range and percentage of tests that were sub-therapeutic or supra-therapeutic. Warfarin doses at each INR test was utilised to calculate weekly warfarin doses and number of dose changes for individual patients. For analysis of objective two, only patients with an INR target range of 2.0 to 3.0 were included and patients with any other target range excluded. This allowed for categorisation of INR results as in therapeutic range when INR was 2.0 to 3.0, sub-therapeutic for $\text{INR} < 2.0$, supra-therapeutic for $\text{INR} 3.1 \text{ to } 5.0$ and $\text{INR} > 5$, with extremes of INR considered to be results of $\text{INR} \leq 1.5$ and $\text{INR} \geq 4.0$. The time interval in days to next INR test was also calculated for each category of within therapeutic range, sub-therapeutic, supra-therapeutic and INR extremes for comparisons between time for repeat testing between GP management and Warfarin Care management. For analysis of objective one, time to therapeutic range was also investigated on return to warfarin therapy by determining the number of days to first INR test in range and number of days to two consecutive INR tests in range.

2.4.2 Warfarin adverse events

Adverse events from warfarin were another study endpoint and included bleed events, thromboembolic events, hospitalisation and death. Bleed events were classified into either minor or major bleeds using standardised definitions of bleeding in studies of anticoagulants in AF [416]. Minor bleeds included self-limiting bleeds, e.g. nose bleeds or rectal bleeding, that did not result in medical attention or intervention. Major bleeds included bleeding into critical organs and clinically relevant bleeds as defined by bleeds which required medical attention or intervention including vitamin K administration and hospitalisation. The number of adverse events was investigated in

addition to a comparison of the level of warfarin control between patients experiencing an event and not experiencing events.

2.5. Study Variables

2.5.1 Demographic data

Patient demographics were used to categorise patients according to specific factors, including gender and age category. For the purposes of some analyses, age was grouped as less than 50 years then in ten year increments, that is 51 - 60 years, 61 - 70 years, 71 - 80 years, 81 - 90 years, and 91 - 100 years. Australian Bureau of Statistics data was applied to residential postcodes to assign a decile of relative socio-economic advantage and disadvantage within Australia in which areas most disadvantaged are given a decile of 1 up to the highest 10% of areas which are given a decile of 10 [417]. The decile was used to group patients according to their residential location, namely decile 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10, and residential location was also grouped according to the state of residence, namely Queensland or New South Wales.

2.5.2 Clinical data

Patient clinical data was used to categorise patients according to INR test frequency and time of warfarin treatment. Grouping of frequency of testing was in 7 day increments, that is < 7 days, 7 - 13 days, 14 - 20 days, 21 - 27 days, and ≥ 28 days, and time of treatment in yearly intervals, i.e. ≤ 1 year (365 days), 1 - 2 years (366 – 730 days), 2 - 3 years (731 – 1095 days), 3 - 4 years (1096 – 1460 days), 4 - 5 years (1461 – 1825 days), 5 - 6 years (1826 – 2190 days), and 6 - 7 years (2191 – 2555 days). Clinical data was also used to categorise patients according to presence of specific concurrent

co-morbidities and medication groups, for example beta-blockers, calcium channel blockers and statins. For analysis of specific medication groups on warfarin control, e.g. aspirin and NSAIDs, patients were further sub-divided according to the individual agent prescribed, for example aspirin, ibuprofen and celecoxib. However, given aspirin and NSAIDs may influence bleed events, patients who also received other medication potentially influencing bleeds were excluded from analysis, utilising the Australian Medicines Handbook [68] to identify medications known to interact with warfarin (Table 2). Patients co-prescribed these medications were excluded and analysis performed on the categorised groups of NSAID users, no NSAID users, and individual NSAID prescribed. A similar process was followed for other medication, for example statins.

2.5.3 Risk assessment scores

Risk assessment scores were calculated for each patient utilising patient demographic data. NHCS data was utilised to calculate the SAME-TT₂R₂ score given the available data at this site included smoking status and race. These two parameters plus the other patient demographic factors of age, gender, medical conditions and medications were used to calculate the SAME-TT₂R₂ score (Table 4). The final SAME-TT₂R₂ score was used to categorise patients according to their individual score 0 - 7 and into group of 0 - 1, 2, and > 2. Patient ethnicity was also used to categorise patients as Chinese, Indian, or Malay and TTR analysed across SAME-TT₂R₂ scores and category.

Stroke and bleed risk scores were calculated at both sites, that is NHCS and SNP.

Individual CHADS₂ and CHA₂DS₂-VASc scores (Table 8) were used to classify patients as low- (0 - 1 point), moderate- (2 - 3 points), or high- (≥ 4 points) risk. Individual HAS-

bled (Table 7) scores were calculated but given labile INRs (defined by a TTR < 60%) is a factor in this model, two scores were calculated, namely one without this factor (start of study period) and one with this factor (end of the study period). Individual HAS-BLED scores were used to classify patients according to risk, namely low- (0 - 1 point), moderate- (2 points), or high- (≥ 3 points) risk.

2.5.4 Timeframes for analysis of individual aims

The length of warfarin treatment analysed differed according to the objective addressed. To address objective one (Figure 7), patterns of switching between anticoagulants were collected for the five year period from June 2012 to July 2017 with an annual breakdown per financial year. Total number and percentage of patients transitioning to each agent was represented together with indication for warfarin therapy and documented reason for therapy change. This included patients converting from warfarin to NOAC (n = 3036) and patients converting from NOAC to warfarin (n = 142). For analysis of objective one, warfarin control was calculated for 131 patients prior to conversion to a NOAC and on return to warfarin therapy.

For analysis of management systems as part of objective two (Figure 8), that is Warfarin Care compared to usual care by GP, warfarin control parameters were calculated for the eligible 200 patients for the entire time under both GP and Warfarin Care management and for only a six month period under both GP and Warfarin Care management. To complete objective two by investigating warfarin control and factors potentially influencing TTR only at SNP, data of 3692 patients with AF enrolled in Warfarin Care as of September 2014 was analysed utilising the entire time of treatment at Warfarin Care. Comparison of warfarin control in Queensland and

Singapore for objective three required an equivalent time of treatment at both NHCS and SNP. Ethics approval at NHCS was for January 2014 to June 2014 and thus warfarin control parameters were calculated for this six month period for the eligible patients at SNP (n = 3196) and at NHCS (n = 1170) (Figure 8 and 9). Data from SNP and NHCS was also utilised in application of bleed and stroke risk assessment scores to address objective four. The SAME-TT₂R₂ model was applied to data at NHCS to complete aim four (Figure 9).

2.6. Data and Statistical Analysis

Warfarin control parameters including TTR, percentage of tests in range, frequency of testing and warfarin doses were represented as mean \pm standard deviation.

Representing these continuous variables as mean \pm standard deviation provided a summary measure to characterise the population and evaluate data dispersion in a format allowing for further comparisons between groups and previous literature. Time to therapeutic range as a discrete variable was represented as median \pm interquartile range to ensure the measures was not distorted by outliers. INR tests in range were reported as number and percentage as was patients with at least one INR test in range by 30 days. Patient characteristics were reported as number and percentage for categorical data with continuous demographic and clinical parameters reported as mean \pm standard deviation. Risk scores of SAME-TT₂R₂, HAS-BLED, CHADS₂ and CHA₂DS₂-VASc were represented as median \pm interquartile range. Adverse events categorised as major bleeds, minor bleeds, stroke and death were calculated as incidence per patient for comparison across groups.

Warfarin control including TTR was used for analysis and comparison by age, gender, geographic location, duration of treatment and frequency of testing. Comparison and analysis was also done on patients categorised as good versus poor control according to gender, age, total days of treatment, test interval and dose changes. Analysis and comparisons in patients before and after NOAC treatment plus between GP and SNP management systems were performed using non-parametric Wilcoxon-matched pairs tests. Analysis and comparisons of warfarin control between groups were performed using ordinary analysis of variance via non-parametric methods using Kruskal-Wallis tests with a post-test of Dunn's multiple comparisons if applicable. Multiple regressions analysis was performed on factors influencing warfarin control in Australia and Singapore, with a R-squared value and confidence interval generated for each variable. Comparison between two groups, for example patients on NSAIDs and not on NSAIDs were made using ordinary analysis of variance (ANOVA) via nonparametric measures including with Mann-Whitney test. Bleed events amongst groups was compared via a chi-squared test using comparisons of proportions test on MedCalc® statistical software. Data was analysed using GraphPad InStat Version 3 and graphical representation produced using GraphPad Prism Version 6.0. Significance was defined at $p < 0.05$ (*), $p < 0.01$ (**), $p < 0.001$ (***) and $p < 0.0001$ (****).

Chapter Three - Prescribing of warfarin in patients with AF in Queensland since the introduction of the NOACs and potential impact on warfarin control for patients transitioning between anticoagulants

In Australia, the NOACs were listed for subsidy under the PBS for the prevention of stroke or systemic embolism in patients with NVAf in August 2013 (rivaroxaban) and September 2013 (apixaban, dabigatran). PBS data specific to Queensland shows a trend (Table 13) of NOAC use increasing and warfarin use decreasing, similar to that observed nationwide (Table 10 and 12).

Table 13 - Pharmaceutical Benefits Scheme statistics [411] for total items of anticoagulants processed per financial year in Queensland for all indications for warfarin and for codes with indications for AF for rivaroxaban (2268J, 2691P), dabigatran (2753X, 2769R), apixaban (2735Y, 2744K).

	2012/13	2013/14	2014/15	2015/16	2016/7	2017/8
Warfarin	481,518	450,991	384,596	342,700	290,308	250,470
Dabigatran	0	40,895	68,006	68,948	75,449	83,106
Rivaroxaban	3,097	108,629	244,103	335,289	393,267	446,813
Apixaban	0	12,088	57,610	117,666	179,212	237,645

Introduction of the NOACs has potentially increased prescribing of anticoagulants to patients with AF [330, 396, 407, 409]. Previous studies [89, 90, 328, 329, 412-414] have demonstrated underuse of warfarin in eligible patients and also sub-optimal warfarin use. However, warfarin remains the only available option for patients with valvular AF and an option for patients with non-valvular AF, particularly when well managed [319]. In Queensland, patients who are prescribed warfarin may be managed by their GP or through warfarin management programs including Warfarin Care offered by SNP. In July 2012, SNP had 10,806 patients receiving warfarin with

approximately 50% of patients having the primary indication of AF. Since the introduction of the NOACs, the number of patients receiving warfarin has decreased by almost 50% to 5524 in July 2017 (Figure 11).

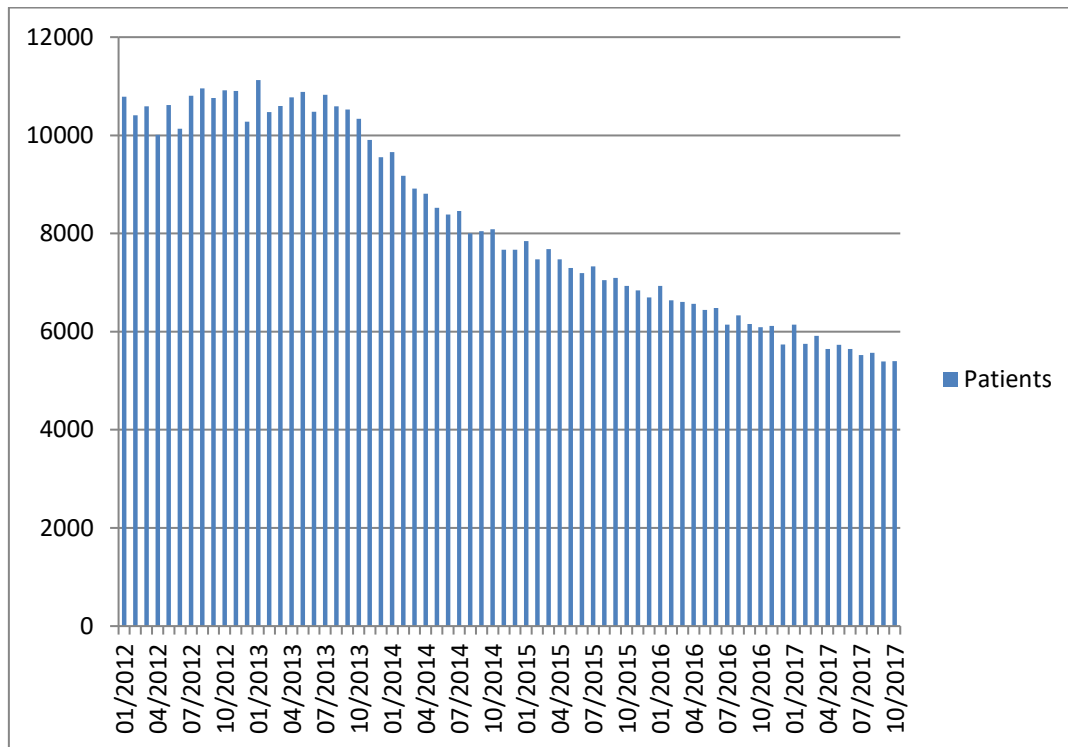


Figure 11 - Number of patients taking warfarin enrolled in the Warfarin Care program at Sullivan Nicolaides Pathology from January 2012 to October 2017. Where x axis is month and year and y axis number of patients.

Specific information on the patterns of switching anticoagulants is limited in Australian populations as is information of the impact on warfarin control in these patients.

Results published in the article “Warfarin control in patients transitioning to warfarin after non-vitamin K oral anticoagulant (NOAC) therapy” (Journal of Thrombosis and Thrombolysis 2018 Nov; 46(4): 461-465) outlines the prescribing of warfarin in patients with AF in Queensland since the introduction of the NOACs and the impact on warfarin control in terms of TTR, testing and dosing, and thus addresses specific objective one of the thesis regarding warfarin control for patients transitioning between anticoagulants.


STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

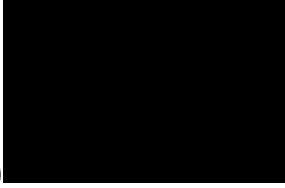
This chapter includes a co-authored paper. The paper “Warfarin control in patients transitioning to warfarin after non-vitamin K oral anticoagulant (NOAC) therapy” was published as a peer-reviewed paper in the Journal of Thrombosis and Thrombolysis 2018 Nov; 46(4): 461-465. The authors of the paper are: Nijole Bernaitis, Tony Badrick, Andrew K Davey, Julia Crilly, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: designing and conducting the study, collecting the data, providing direction on the scope and structure of the analysis, then categorising and analysing the data. I wrote the first draft, made revisions responding to supervisor comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

(Signed)  (Date) 4/12/18

Nijole Bernaitis

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Warfarin control in patients transitioning to warfarin after non-vitamin K oral anticoagulant (NOAC) therapy

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Key Points

- Although many warfarin patients are being switched to alternate anticoagulants, almost 5% of these patients revert back to warfarin with the majority (61%) reverting within six months.
- Patients switching from alternate anticoagulants to warfarin have a median time to first INR in range of 6 days with 96.2% of patients having at least one INR in range by 30 days.
- Significantly more frequent testing and significantly lower doses are required to achieve previous levels of warfarin control which may further complicate warfarin therapy.
- Further studies regarding transition strategies particularly from warfarin to NOAC are required to minimise potential risks to patients.

Abstract

Introduction

Warfarin has long been the most widely prescribed oral anticoagulant. Introduction of non-vitamin K oral anticoagulants (NOACs) has provided anticoagulant options but also presented the potential challenge of transitioning between agents. Changes from NOACs to warfarin are particularly problematic with delays to therapeutic effect and limited real-world data regarding the impact on warfarin control. The aim of this study was to investigate the frequency of switching anticoagulants and the effect on warfarin control.

Methods

Retrospective data was collected for patients at a warfarin program in Queensland Australia who had exited the program for NOACs plus those who had reverted to warfarin. Data included documented reasons for change and International Normalised Ratio (INR) results with time in therapeutic range (TTR) calculated as a measure of warfarin control.

Results

Over five years, a total of 3036 patients ceased warfarin to commence a NOAC but 142 (4.7%) reverted to warfarin. Majority of patients (60.6%) reverted to warfarin within six months of trialling NOACs with a median of 6 days to therapeutic INR. There was no significant difference in warfarin control before changing to NOACs and after reverting to warfarin (mean TTR 75%) but significantly more frequent testing and lower doses were required to achieve this control.

Conclusion

Transitions from warfarin to NOACs results in almost a week to therapeutic effect and warfarin therapy may be further complicated by a need for increased frequency of testing. Further studies are required to refine transition strategies particularly from warfarin to NOAC and minimise potential risks to patients.

Introduction

Warfarin has long been the oral anticoagulant used in the treatment and prevention of thromboembolic disease [94]. Warfarin's narrow therapeutic index and individualised response necessitates frequent monitoring of the International Normalised Ratio (INR), with time in therapeutic range (TTR) a commonly used measure of warfarin control

[94]. Concerns regarding warfarin including monitoring requirements, inadequate TTR, bleed risk and underuse in patients eligible for anticoagulation, has led to the development of non-vitamin K oral anticoagulants (NOACs) dabigatran, rivaroxaban, and apixaban [348]. Meta-analyses of the large comparative trials of the NOACs in non-valvular atrial fibrillation (AF) patients have demonstrated them to be slightly superior to warfarin in stroke and systemic embolism and associated with lower risk for intracranial haemorrhage [348].

The availability of the NOACs has given prescribers choice between oral anticoagulants and the potential challenge of transitioning between warfarin and individual NOACs [418]. In 2017, Hellfritsch et al [419] found 46.5% of anticoagulant users had experienced one or more treatment changes with transitions from warfarin to NOAC more common than NOAC to warfarin. Transitions from NOAC to warfarin are particularly troublesome due to fluctuating INRs during introduction and delays in reaching target INR [418]. However, there has been limited data on warfarin control in real-world patients changing between NOACs and warfarin. Therefore, the aim of this study was to investigate the frequency of changing oral anticoagulant therapies and the effect on warfarin control, particularly in patients changing to a NOAC then reverting back to warfarin.

Methods

Ethics approval was obtained - Griffith University PHM/09/14/HREC. A retrospective analysis was conducted for patients enrolled in a warfarin program at a private pathology practice in Queensland between June 2012 and July 2017. The warfarin

management program is available to any patient taking warfarin referred by their general practitioner with the service including blood collection, laboratory testing, result interpretation and dose instruction by specialist general practitioners, and information regarding subsequent follow-up provided by nurses or trained staff. Patients who had exited the program for a NOAC together with patients who had reverted to warfarin after a NOAC were identified. Documented reasons for changes were recorded together with INR results and warfarin doses for patients reverting to warfarin therapy. TTR was calculated using the Rosendaal method [95] with software downloaded from INRPro© with patients excluded from TTR analysis if there were insufficient tests to calculate TTR or less than thirty days of therapy before or after changes. Mean patient data was used for analysis and comparison of warfarin control before and after NOAC therapy via paired nonparametric tests using GraphPad InStat Version 3.

Results

From June 2012 to July 2017, a total of 3036 patients exited the warfarin program to commence a NOAC with the highest percentage (47.6%) in 2013 - 14 (Table 14). The majority of patients changed to rivaroxaban (61.6%), followed by apixaban (25.6%), and dabigatran (12.8%). Of the 3036 patients changing to a NOAC, a total of 142 (4.7%) patients reverted to warfarin therapy with the majority of patients (60.6%) reverting to warfarin less than six months after commencing a NOAC.

Table 14 - Information regarding patients switching between anticoagulants during the study period and warfarin control for patients reverting to warfarin.

	Warfarin to NOAC						NOAC to warfarin
	2012-13 N=106	2013-14 N=1446	2014-15 N=472	2015-16 N=502	2016-17 N=510	TOTAL N=3036	TOTAL 2012-2017 N=142
Agent							
Dabigatran	26 (24.5%)	220 (15.2%)	32 (6.8%)	37 (7.4%)	75 (14.7%)	390 (12.8%)	28 (19.7%)
Rivaroxaban	79 (74.6%)	1031 (71.3%)	291 (61.7%)	247 (49.2%)	221 (43.3%)	1869 (61.6%)	100 (70.4%)
Apixaban	1 (0.9%)	195 (13.5%)	149 (29.7%)	218 (43.4%)	214 (42.0%)	777 (25.6%)	14 (9.9%)
Indication							
AF	60 (56.6%)	1037 (71.7%)	315 (66.7%)	317 (63.1%)	329 (64.5%)	2058 (67.8%)	81 (57.1%)
DVT	10 (9.4%)	95 (6.6%)	37 (7.8%)	43 (8.6%)	38 (7.5%)	223 (7.3%)	14 (9.8%)
PE	16 (15.1%)	150 (10.4%)	52 (11.1%)	59 (11.8%)	64 (12.5%)	341 (11.2%)	22 (15.5%)
Other	20 (18.9%)	164 (11.3%)	68 (14.4%)	83 (16.5%)	79 (15.5%)	414 (13.6%)	25 (17.6%)
Reason							
GP	61 (57.5%)	917 (63.4%)	265 (56.1%)	268 (53.4%)	263 (51.6%)	1774 (58.4%)	73 (51.4%)
Specialist	22 (20.8%)	365 (25.2%)	139 (29.5%)	145 (28.9%)	130 (25.4%)	801 (26.4%)	8 (5.6%)
New GP/locum	0	4 (0.3%)	0	3 (0.6%)	3 (0.6%)	10(0.3%)	0
Thromboembolic	2 (1.9%)	3 (0.2%)	4 (0.8%)	3 (0.6%)	6 (1.2%)	18 (0.6%)	4 (2.8%)
Bleed	6 (5.7%)	5 (0.3%)	6 (1.3%)	0	0	17 (0.6%)	13 (9.3%)
Hospitalisation	5 (4.7%)	65 (4.5%)	37 (7.9%)	54 (10.7%)	68 (13.3%)	229 (7.5%)	8 (5.6%)
Planned procedure/operation	5 (4.7%)	42 (2.9%)	13 (2.8%)	13 (2.7%)	17 (3.4%)	90 (3.0%)	0
Travel	4 (3.8%)	11 (0.8%)	3 (0.6%)	3 (0.6%)	2 (0.4%)	23 (0.8%)	0
Compliance	0	7 (0.5%)	1 (0.2%)	3 (0.6%)	7 (1.3%)	18 (0.6%)	0
Testing	1 (0.9%)	13 (0.9%)	1 (0.2%)	3 (0.6%)	6 (1.2%)	24 (0.8%)	0
Subtherapeutic	0	11 (0.8%)	2 (0.4%)	6 (1.2%)	6 (1.2%)	25 (0.8%)	0
Intolerance	0	3 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.4%)	7 (0.2%)	33 (23.2%)
Renal function	0	0	0	0	0	0	3 (2.1%)
Demographics							
Female	47 (44.3%)	650 (45.0%)	217 (46.0%)	240 (47.8%)	276 (54.1%)	1430 (47.1%)	73 (51.4%)
Male	59 (55.7%)	796 (55.0%)	255 (54.0%)	262 (52.2%)	234 (45.9%)	1606(52.9%)	69 (48.6%)
Age	72.3 ± 11.9	73.3 ± 11.5	73.4 ± 11.9	74.9 ± 10.9	76.3 ± 11.7	74.1 ± 11.5	72.8 ± 12.5

Warfarin Control	Before NOAC	After NOAC
Time in Therapeutic Range (%)	74.6 ± 15.5	75.6 ± 13.4
Tests in Range (%)	69.5 ± 13.8	69.0 ± 12.9
Frequency of Testing (days) *	13.7 ± 5.4	12.7 ± 7.0
Average Daily Dose (mg) *	4.5 ± 2.0	4.1 ± 2.1
Patients with TTR<65% (number,%)	27 (20.6%)	24 (18.3%)
Time to first INR test in range (days)		6 (0-9)
Time to two consecutive INR tests in range (days)		14 (7-23)
At least one INR test in range by 30 days (number,%)		126 (96.2%)

Data shown is mean ± standard deviation for age and all measures of warfarin control except median (interquartile range) for day to first INR test in range, and number (percentage) for at least one INR test in range by 30 days and all other categories. Abbreviations used are AF=atrial fibrillation, DVT=deepvein thrombosis, PE=pulmonary embolism, GP=general practitioner, and *indicates statistical significance with $p < 0.05$.

Of the 142 patients that reverted to warfarin, a total of 131 patients were analysed for warfarin control following exclusions. After changing from NOAC to warfarin, the median time to first INR in range was 6 days and 96.2% of patients had at least one INR in range by thirty days. Before changing to a NOAC and after reverting to warfarin there was no significant difference in mean TTR ($74.6 \pm 15.5\%$ vs $75.6 \pm 13.4\%$ respectively) but the frequency of testing was significantly different (13.7 ± 5.4 days vs 12.7 ± 7.0 days, $p = 0.0075$ respectively) as was the average daily dose (4.5 ± 2.0 mg vs 4.1 ± 2.1 mg, $p < 0.0001$ respectively).

Discussion

There is now a choice between oral anticoagulants and potential for transitions between agents but there is limited real-world data on the frequency of switching and warfarin control in this transition period. The aim of this study was to determine the frequency of changing oral anticoagulant therapies and the impact on warfarin control. This study found that after changing to a NOAC, almost 5% of patients revert to warfarin with a median time to first INR in range of 6 days and 96.2% of patients

having at least one INR in range by 30 days. Warfarin control was not significantly different before changing to a NOAC and after reverting to warfarin (mean TTR 75%), however significantly more frequent testing and significantly lower doses were required to achieve this TTR.

In Australia, warfarin remains the most widely prescribed oral anticoagulant but use has declined since introduction of the NOACs [410]. An analysis of Australian prescribing estimated that in 2013 - 14 up to 53% of patients prescribed NOACs had previously used warfarin but this declined to 24% the following year [410]. Similar to this, our study found that almost 48% of patients were converted to NOACs in 2013 - 14 with rates declining to approximately 16% in subsequent years. Over the study period the percentage of patients changing to rivaroxaban decreased whilst changes to apixaban increased which is consistent with Hale et al [420] who reported increased percentages of patients on warfarin changing to apixaban.

Hellfritsch et al [419] estimated that 1 in 3 NOAC users had changed from a vitamin K antagonist but also found approximately 10% of NOAC initiators had reverted to warfarin within one year. Hale et al [420] reported about 13% of patients changing from warfarin to a NOAC reverted to warfarin. In contrast to these studies, we reported a lower rate of reverting to warfarin of 4.7%. Our study was conducted in a specialist warfarin management program and only included patients both recommencing warfarin and returning to the program thus potentially underestimated patients reverting to warfarin as patients may have recommenced warfarin but remained managed by their general practitioner. The majority of patients in our study returned to warfarin therapy less than six months after commencing a NOAC

with the reason in 23% of patients being intolerance. Similar to this, Hale et al [420] found roughly half of their patients reverted back to warfarin within six months of NOACs with the most common reasons being side effects (21.2%) or clotting events (17.3%). Interestingly, in our study a more common reason for returning to warfarin from a NOAC were bleeds (9.3%) rather than thromboembolic events (2.8%).

However, this is consistent with Hellfritzsche et al [421] who found bleeds more frequent than thromboembolic events in patients who discontinued NOACs.

The large comparative trials of NOACs and warfarin had structured transitions to warfarin [422, 423]. Mahaffey et al [422] reported a median time to first INR in range of 13 days in patients reverting to warfarin from rivaroxaban, whilst Ruff et al [423] found a lower median of 9 days to therapeutic INR in patients reverting to warfarin from edoxaban. Our study compares favourably to this with a median of 6 days to first INR in range. Similarly, we found 96% of patients with at least one INR ≥ 2 by 30 days which is superior to the 52% [422] and comparable to the 99% [423] reported from these studies. Australian guidelines [424] recommend transitioning from NOAC to warfarin with specialist consultation as INR results can be affected by both the NOAC and warfarin and thus the interpretation of INR and time to cease NOAC is dependent on the baseline INR of individual patients. This study did not investigate factors such as baseline INR before transitioning or other factors such as renal function or protein C & S levels which may have influenced the transition between NOAC and warfarin. Future research should investigate such factors to further investigate INR stability and the potential for any increased risk of bleeds or thrombosis at this time.

Hale et al [420] identified unstable INR was the most common reason for a change from warfarin to a NOAC with a mean TTR of 54% at the time of changing. In our study the mean TTR of patients changing to NOACs was almost 75% with only around 20% of these patients having TTR levels below 65%. In 2014, the Australasian Society of Thrombosis and Haemostasis suggested patients stably anticoagulated on warfarin (i.e. TTR > 65% over a three month period) are least suitable for NOACs [390]. Using the TTR < 65% criteria for changing from warfarin, it could be argued that 80% of these patients were not suitable candidates for a change from warfarin. However, a previous study of the same warfarin program found a mean TTR of 81% with less than 3% of patients with a TTR < 60% [425] suggesting slightly lower control in patients changed to NOAC. Interestingly Pokorney and Granger [426] found data does not support a substantially larger benefit of NOACs in patients with poor warfarin control but found a modest absolute benefit from NOACs in patients naïve to oral anticoagulants. Further studies are required to identify the subset of existing warfarin patients that would particularly benefit from changing to NOACs especially in the Australian context with relatively high levels of warfarin control reported.

In our study, patients reverting to warfarin obtained no significant difference in TTR but required significantly more frequent testing to achieve this. Arnsten et al [427] found non-compliant patients on warfarin considered frequent blood tests to be a major problem to warfarin use. The increased frequency of testing required when returning to warfarin could further contribute to perceived concerns regarding INR testing. In our study, significantly lower doses were also required when reverting to warfarin to achieve the 75% TTR. Leonhard et al [428] found 64% of patients on

warfarin were reinitiated on lower doses after temporary discontinuation but could not associate the dosing with specific patient factors. A number of genetic and clinical factors are known to influence dose requirements including age, race, and medications [94] so further investigation is needed to determine if the lower doses seen when recommencing warfarin can be explained by these patient factors.

In conclusion, this study found that whilst many patients on warfarin are changing to NOACs, approximately 5% of these are reverting to warfarin with a median of 6 days before obtaining therapeutic INR and more frequent testing required to achieve previous TTR levels. Further studies are required to refine transition strategies particularly from warfarin to NOAC to minimise potential risks to patients.

Compliance with Ethical Standards

Conflict of Interest: Nijole Bernaitis declares that she has no conflict of interest. Tony Badrick declares that he has no conflict of interest. Andrew K Davey declares that he has no conflict of interest. Julia Crilly declares that she has no conflict of interest. Shailendra Anoopkumar-Dukie declares that he has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: This study was a retrospective data analysis which met the conditions for a waiver of consent.

Chapter Four – Quality of warfarin control in patients with AF in South-East Queensland achieved by different management systems and factors contributing to levels of warfarin control

Australian approaches for management of warfarin therapy include usual care by the GP, patient self-monitoring or laboratory care program [384]. International studies have demonstrated that anticoagulation clinics result in improved warfarin control over standard care [115-123]. However, there is variation in the actual improvement in TTR demonstrated by anticoagulant clinics due to differences in routine medical care practices between countries impacting INR monitoring and subsequent warfarin control [133]. Currently, there is a lack of comparative data on Australian warfarin management practices, specifically routine GP care compared to anticoagulant clinics. The objective of this chapter was to investigate the quality of warfarin control in patients with AF in South-East Queensland by different management systems and determine factors contributing to the levels of warfarin control achieved. Data published in the article “Dedicated warfarin care programme results in superior warfarin control in Queensland, Australia” (International Journal of Clinical Practice 2018 Mar; 72(3): e13051) provides a comparison on the levels of warfarin control achieved in Queensland by two management options, i.e. GP and Warfarin Care, and investigates some factors potentially impacting TTR especially in relation to systems of care such as frequency of testing. The second published article “Quality of warfarin control in atrial fibrillation patients in South East Queensland, Australia” (Internal Medicine Journal 2016 Aug; 46(8): 925-31) further investigates factors potentially impacting TTR at SNP with a focus on the influence of various patient demographics.

Collectively, data from these published articles address specific objective two of the thesis regarding the quality of warfarin control achieved by differing management systems in South-East Queensland including factors contributing to these levels of warfarin control.

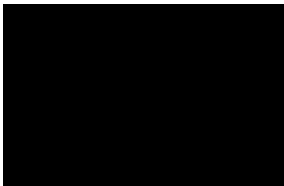
STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

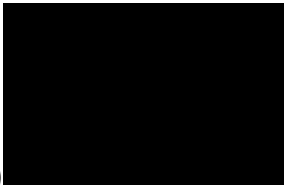
This chapter includes parts of a co-authored paper. The paper “Dedicated warfarin care programme results in superior warfarin control in Queensland, Australia” was published as a peer-reviewed paper in the International Journal of Clinical Practice 2018 Mar; 72(3): e13051. The authors of the paper are: Nijole Bernaitis, Tony Badrick, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: designing and conducting the study, collecting the data, categorising and analysing the data. I wrote the first draft, made revisions responding to supervisor comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

(Signed)  (Date) 4/12/18

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**Dedicated warfarin care program results in superior warfarin control in Queensland,
Australia**

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Abstract

Background

Warfarin is used to prevent stroke in patients with atrial fibrillation (AF). Ongoing monitoring of International Normalised Ratio (INR) is required and time in therapeutic range (TTR) commonly used to assess the quality of warfarin management.

Anticoagulant clinics have demonstrated improved TTRs, particularly in countries with poorer control in primary care settings. Reported TTR in Australia has been relatively high so it is unknown if benefit would be seen from dedicated warfarin clinics in Australia. The aim of this study was to compare the level of warfarin control in patients managed by their general practitioner (GP) and a warfarin care program (WCP) by Sullivan Nicolaides Pathology (SNP).

Method

Retrospective data was collected for AF patients enrolled in the warfarin care program at SNP and included patients with INR tests available whilst managed by their GP. INR tests were used to calculate TTR and frequency of testing for the time managed by GP and WCP, with mean data used for analysis and comparison.

Results

The eligible 200 warfarin patients had a TTR of 69% with GP management and 82% with WCP management (< 0.0001). Significant differences were also found between GP and WCP management in the percentage of tests in range, total number of tests, and frequency of testing. WCP had a reduced time to repeat test at extremes of INR results.

Conclusion

Australian warfarin control was good when managed by either GP or WCP, but WCP management increased TTR by 13%. Dedicated warfarin programs can improve warfarin control and optimise therapy for patients.

What's Known

Anticoagulant options for patients with atrial fibrillation have recently expanded but warfarin remains widely prescribed. Warfarin outcomes may be optimised by good control, as measured by time in therapeutic range (TTR), but this varies according to geographical areas and management practices. Dedicated anticoagulant clinics can improve TTR, but there is conflicting data on improvements in warfarin TTR in areas where the overall control is high.

What's new

This is the first study comparing warfarin management options in Australia. This study found a high level of warfarin control when managed by general practitioners (69% TTR) and a warfarin care program (82% TTR). Both management options achieved warfarin control above TTR targets of 65%, but the increased control by the dedicated warfarin program can further improve outcomes and optimise therapy for patients placed on warfarin.

Introduction

Warfarin is an oral anticoagulant used for both the prevention and treatment of thromboembolism, including stroke due to atrial fibrillation (AF) [62]. Patient variability in warfarin response and a narrow therapeutic index necessitates monitoring of the International Normalised Ratio (INR) to guide therapy [43]. Tight control of INR between 2.0 to 3.0 is the strategy used to ensure optimal benefit of warfarin whilst minimising risk [87]. Time in therapeutic range (TTR) is a routinely used measure of warfarin control in clinical settings, with patients obtaining lower TTR more likely to experience negative outcomes such as haemorrhage or stroke [429]. A minimum threshold TTR of 65% is recommended [298], but wide variations of TTR have been demonstrated by different countries and clinical settings [378].

Sub-analyses of the recent large comparative trials of warfarin and the newer oral anticoagulants (NOACs) have showed substantial variation in TTRs of 43 - 77% across countries [366, 368, 376]. Singer et al [376] found the highest TTRs in Canada, United States and Western European countries. Similarly, Wallentin et al [366] reported Sweden to be the country with the highest TTR of 77%, followed by Finland and Australia with 74%. Further to this, Wallentin et al [368] observed TTR variation not only between countries but also between sites within a country dependent on the processes of care at the site and country level. Van Walraven et al [130] showed time spent outside of therapeutic INR range was higher in patient groups from community based settings than anticoagulation clinics. The improvement in TTR achieved by anticoagulant clinics compared to general practitioner (GP) care has been reported to range from 8% [115] to 17% [118]. However, differences have again been reported

between countries. A meta-analysis of warfarin control in the United States by Baker et al [131] reported an 11% improvement in TTR for patients managed by an anticoagulation clinic. Wilson et al [119] and Young et al [120] reported a more modest improvement of warfarin control of 6 - 8% in Canada. However, in contrast, Lalonde et al [430] reported no difference in control for patients in Canada managed by anticoagulant services or physicians. Similarly, in Sweden, Wallvik et al [431] found no differences in complications between anticoagulation clinics and primary care, whilst Wieloch et al [222] found no differences in terms of TTR due to a high-level of warfarin control in primary care in Sweden.

In Australia, a high level of warfarin control has been demonstrated from sub-analyses of the large comparative trials of warfarin and the NOACs with TTR values of 73 - 76% [366, 368, 376]. However this was in controlled clinical trial conditions with limited data on warfarin TTR in real-world clinical practice. Bereznicki et al [383] reported an overall TTR of 64.0% in Australian veterans taking warfarin. Further Australian studies have reported regionally specific TTRs of 69.1% in southern Tasmanian patients [382], 55.4% in the top end of the Northern Territory [208], and 79 - 81% in Queensland [323, 425]. Australian approaches for managing patients taking warfarin include care by the GP or care by laboratory pathology programs [384]. However, to our knowledge, there is no Australian data comparing warfarin management by the GP and dedicated warfarin programs. Therefore, the aim of this study was to determine the level of warfarin control as measured by TTR in patients managed by their GP and when managed by a pathology laboratory offering a warfarin management program in Queensland, Australia.

Methods

Griffith University ethics was obtained PHM/09/14/HREC. A retrospective analysis was conducted for patients enrolled in the Warfarin Care program (WCP) at Sullivan Nicolaides Pathology. Warfarin Care is a service open to patients of the pathology practice's regular referring doctors and the program aims to manage the patient's warfarin in partnership with the patient, GP, and WCP staff. At enrolment, patient medical and medication history is recorded. At subsequent appointments for blood collections, patients are required to complete a questionnaire detailing any medication changes, compliance, adverse effects, and any planned surgery or holidays. Following INR testing, results are reviewed by specialists GPs employed at Warfarin Care and instructions on dosing and time to next appointment provided to the patients via telephone, text, or e-mail depending on patient preference.

Patients with AF enrolled in the WCP at Sullivan Nicolaides Pathology as of September 2014 were identified. Patients were ineligible for inclusion if they had been with the program since commencement of the current database in Nov 2007, or had enrolled at WCP less than six months after commencing warfarin. Remaining patients were screened to determine if they had INR results available prior to enrolment in the program, i.e. whilst managed by their GP. Further patient exclusions were less than six months of continuous pathology results during GP management, and INR target ranges not recorded or documented as mixed ranges.

Patients with greater than six months of continuous data for both GP and WCP management had their INR test dates and results recorded, together with date of commencing warfarin and date of commencing at WCP. Further data collected

included gender, age, medical conditions, and concurrent medications at the time of enrolment in the program. TTR was calculated using Rosendaal's linear interpolation method with software downloaded from INR Pro©. TTR for an individual patient was calculated for the entire time managed by both the GP and WCP, and for a six month period immediately prior and after enrolment with WCP. Percentage of tests in range, total number of tests, frequency of testing, and total days of testing were calculated. For the overall time of GP and WCP management, the mean time in days to next INR test was calculated for INR results in therapeutic range, i.e. 2.0 to 3.0, when INR was sub-therapeutic ($\text{INR} < 2.0$), supra-therapeutic ($\text{INR} 3.1 - 5.0$ and $\text{INR} > 5$), and at extremes of INR, i.e. ≤ 1.5 and ≥ 4.0 . Mean patient data was used for analysis and comparison between GP and WCP management, with comparisons made using ordinary analysis of variance via nonparametric methods including Kruskal-Wallis test. Statistical analysis was performed on GraphPad Instat Version 3.

Results

Of the 3954 patients with AF enrolled at WCP as of September 2014, 2804 were ineligible for inclusion in the study. Of the 1150 patients screened for further pathology results, 354 had data for the time managed by their GP. There were 200 patients included in the study following exclusions for continuous data being unavailable (83 patients), less than six months of continuous INR results with their GP (52 patients), and INR target ranges either not recorded or recorded as mixed ranges (19 patients).

Table 15 - Demographics of 200 patients at time of enrolment at Sullivan Nicolaides Pathology.

	Number (%)
Gender	
Male	104 (52%)
Female	96 (48%)
Age mean 78.9 ± 7.5 years	
Age <60 years	2 (1%)
Age 60-69 years	20 (10%)
Age 70-79 years	71 (35.5%)
Age 80-89 years	96 (48%)
Age ≥90 years	11 (5.5%)
Past Medical History	
Hypertension	83 (41.5%)
Diabetes	38 (19%)
Heart Failure	27 (13.5%)
Vascular Disease (CAD or IHD)	22 (11%)
Chronic Kidney Disease	16 (8%)
History of stroke or TIA	39 (19.5%)
History of cancer	25 (12.5%)
Anaemia	7 (3.5%)
Cardiomyopathy	4 (2%)
Dyslipidaemia	25 (12.5%)
Risk Model Scores	
CHA ₂ DS ₂ -VASc median (IQR)	3 (2-4)
CHA ₂ DS ₂ -VASc score 0	2 (1%)
CHA ₂ DS ₂ -VASc score 1	21 (10.5%)
CHA ₂ DS ₂ -VASc score 2	41 (20.5%)
CHA ₂ DS ₂ -VASc score 3	50 (25%)
CHA ₂ DS ₂ -VASc score 4	42 (21%)
CHA ₂ DS ₂ -VASc score 5	24 (12%)
CHA ₂ DS ₂ -VASc score 6	16 (8%)
CHA ₂ DS ₂ -VASc score 7	3 (1.5%)
CHA ₂ DS ₂ -VASc score 8	1 (0.5%)
HAS-BLED median (IQR)	2 (1-2)
HAS-BLED score 0	4 (2%)
HAS-BLED score 1	84 (42%)
HAS-BLED score 2	77 (38.5%)
HAS-BLED score ≥3	35 (17.5%)
Concurrent treatment	
Amiodarone	10 (5%)
Beta-blocker	118 (59%)
Digoxin	65 (32.5%)
Angiotensin Converting Enzyme Inhibitor	71 (35.5%)
Angiotensin Receptor Blocker	48 (24%)
Calcium channel blocker	43 (21.5%)
Statin	103 (51.5%)
Platelet Inhibitor	18 (9%)
Diuretic	99 (49.5%)
Proton Pump Inhibitor	73 (36.5%)

Data shown is number (percentage), mean (SD) for age, and median (IQR) for HAS-BLED and CHA₂DS₂-VASc scores.

Of the 200 patients included in the study, there were 104 (52%) males and 96 (48%) females (Table 15). The mean age of the patients at the time of enrolment at WCP was 78.9 ± 7.5 years. The overall mean TTR was $68.5 \pm 16.2\%$ when managed by the GP and $81.5 \pm 9.1\%$ when managed at WCP, which was significantly different ($p < 0.0001$) (Table 16). The percentage of tests in range was significantly different between management by GP and WCP ($62.8 \pm 15.4\%$ vs $75.5 \pm 9.4\%$, $p < 0.0001$), as was the total days of testing (741.5 ± 462.6 days vs 1287 ± 41.6 days, $p < 0.0001$ respectively), and frequency of testing (22.5 ± 9.1 days vs 15.9 ± 7.0 days, $p < 0.0001$ respectively). For the six month period immediately prior to enrolment in the program, the mean TTR for GP management was $67.6 \pm 25.1\%$. This was significantly different ($p < 0.0001$) to the mean TTR for WCP management of $79.8 \pm 13.3\%$ for the six month period immediately after enrolment in the warfarin management program. Significant differences were also found at this time period between GP and WCP management for percentage of tests in therapeutic range, total number of tests, and frequency of testing.

The percentage of INR tests < 2 was 22.9% for GP and 15.3% for WCP (Figure 12). At supra-therapeutic INRs of 3.1 - 5.0 and > 5.0 the percentage of INR tests for GPs was 15.9% and 0.9% respectively, compared to 10.3% and 0.2% respectively for WCP. The mean time interval to next INR test following a therapeutic test (i.e. INR 2.0 - 3.0) was 21.5 ± 19.8 days for GP and 15.4 ± 18.5 days for WCP management, which was significantly different ($p < 0.001$) (Table 17). Significant differences were also found in time interval to next INR test when the result was sub-therapeutic, supra-therapeutic in the range 3.1 - 5.0, and for extremes of INR, i.e. ≤ 1.5 and ≥ 4.0 .

Table 16 - Data on warfarin control for the 200 patients when managed by general practitioner (GP) and warfarin care program (WCP).

	GP	WCP	p Value
ENTIRE TIME			
Time in Therapeutic range (%)	68.5 (16.2)	81.5 (9.1)	<0.0001
Percentage tests in therapeutic range	62.8 (15.4)	75.5 (9.4)	<0.0001
Total number of tests	36.7 (26.6)	89.5 (66.1)	<0.0001
Frequency of testing (days)	22.5 (9.1)	15.9 (7.0)	<0.0001
Total days of testing	741.5 (462.6)	1287.1 (41.6)	<0.0001
SIX MONTHS			
Time in Therapeutic range (%)	67.6 (25.1)	79.8 (13.3)	<0.0001
Percentage tests in therapeutic range	63.3 (23.8)	75.2 (13.8)	<0.0001
Total number of tests	11.1 (6.8)	15.9 (4.8)	<0.0001
Frequency of testing (days)	21.5 (10.1)	12.9 (5.7)	<0.0001
Total days of testing	185.1 (1..0)	184.6 (9.5)	0.3899

Data is shown for the entire time of testing and for the six month period of management prior to enrolment in program for GP and after enrolment for WCP. Data represented is mean (standard deviation).

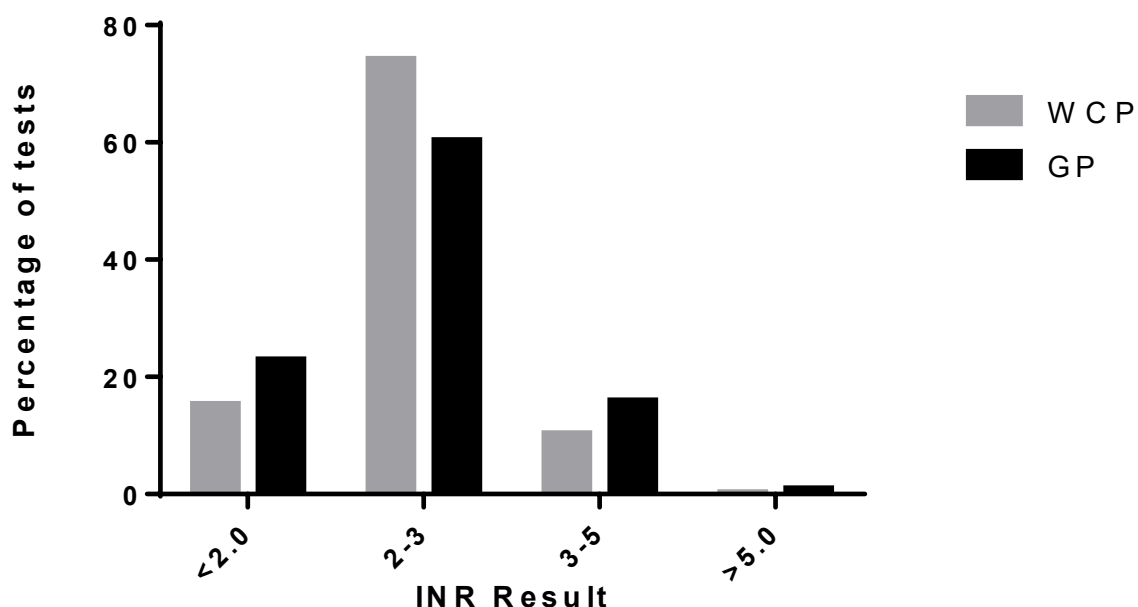


Figure 12 - Distribution of INR tests for 200 patients when managed by general practitioner (GP) and warfarin care program (WCP).

Table 17 - Time intervals in days to next International Normalised Ratio (INR) test for general practitioner (GP) and warfarin care program (WCP) when INR was sub-therapeutic (INR < 2.0), therapeutic (INR 2.0 - 3.0), and supra-therapeutic (INR 3.1 - 5.0 and INR > 5).

	FREQUENCY OF TESTING IN DAYS		
INR	GP	WCP	P Value
< 2.0	18.8 (20.0)	12.6 (12.9)	<0.0001
2.0 – 3.0	21.5 (19.8)	15.4 (18.5)	<0.0001
3.1 – 5.0	20.7 (22.5)	14.4 (11.4)	<0.0001
> 5.0	18.3 (21.9)	11.9 (14.2)	0.2231
INR EXTREMES			
≤ 1.5	16.8 (21.3)	12.3 (14.9)	0.0013
≥ 4.0	18.1 (16.2)	13.5 (13.1)	0.0146

Discussion

Warfarin is an effective therapy for the prevention of stroke in patients with AF, but differences in TTR can affect outcomes [378]. Anticoagulant clinics have been suggested to improve outcomes and optimise TTR [432], however reported TTR increases have varied. Further to this, studies from countries with a high quality of warfarin control in general practice have demonstrated no significant change in TTR with dedicated warfarin clinics. Warfarin control in Australia has been reported to be relatively high, with TTRs of 73 - 76% in clinical trial settings [366, 368, 376] and TTRs of 55% [208] to 81% [425] in real-world practice settings. However, to date, there is no Australian data comparing warfarin management by the GP and dedicated anticoagulant clinics. Therefore, the aim of this study was to determine the level of warfarin control in AF patients when managed by their GP and by a pathology practice offering a warfarin management program in Queensland, Australia. This study found significant differences in mean TTR between GP and WCP management for the overall time period (69% and 82% respectively), and for the six month period (68% and 80% respectively) either side of enrolment in the warfarin management program.

Significant differences were also found at these time periods between GP and WCP management in the percentage of tests in range, total number of tests, frequency of testing, and interval to next INR test.

The Australian TTR data from the comparative trials of warfarin and the NOACs was 73 - 76% [366, 368, 376]. In our study, the GP TTR of 69% was 4 - 7% below the mean Australian TTR, and the WCP TTR of 82% was 9 - 12% above these values. In comparison, van Walraven et al [130] reported 12% lower TTRs for studies from community practices compared to randomised trials, but found no difference between anticoagulation clinics and randomised trials. Further to this, Ansell et al [133] found a TTR of 57 - 61% in routine medical care across US, Canada and France in comparison to TTR of 64 - 69% in anticoagulation clinics in Italy and Spain. Genetic differences in warfarin metabolism may account for variable responses across ethnic groups [37]. However Van Spall et al [153] found clinical skill in warfarin dose decisions accounts for the majority of variation between countries and centres and is an important determinant of TTR. The GP TTR of 69% in our study is more comparable to the TTR reported for some overseas anticoagulation clinics, whilst the WCP TTR of 82% far exceeds these reported values and shows that WCP management with specialist GPs can improve TTR by 13%. This improvement in TTR by the dedicated clinic is comparable to data from the United States showing an improvement by anticoagulant clinics of 11% TTR [131], and exceeds the improvement of 6 - 8% TTR in Canadian studies [119, 120].

Mearns et al [90] in a meta-analysis of warfarin treated AF patients demonstrated 56% of INR tests to be within range. In our study, both the GP and WCP results were

superior to this with 63% and 76% of INR results in range respectively. This 13% increase of INRs in range between GP and WCP management is comparable to reports by Wilson et al [119] of a 6% increase of INRs in target range when changed to anticoagulant clinic management, and slightly lower than that found by Bungard et al [118] of a 17% increase. Chiquette et al [121] reported that patients managed by anticoagulation clinics have more INR values in range with less high risk INR values of greater than 5 compared to usual care. Consistent with this, our study found a significantly higher percentage of tests in range by WCP compared to GP management, and a lower percentage of INR > 5 by WCP compared to GP (0.2% versus 0.9%).

Wittkowsky et al [433] suggested the more consistent INR monitoring at anticoagulant clinics contributed to improved patient outcomes. In addition, Chamberlain et al [128] concluded that patients managed at anticoagulant clinics had 21% more INR tests performed per patient year of therapy. Likewise, our study showed WCP management to have more frequent INR tests and subsequently a higher number of tests per patient year. Interestingly in our study the testing frequency of 16 days by WCP and 22 days by GP achieved a TTR of 82% and 69% respectively. This is similar to findings by Singer et al [376] who correlated TTRs of around 66% to an average INR testing frequency of 19 - 21 days. In contrast, Carrier et al [429] associated poor control (TTR < 65%) with a median of 12 tests over a six month period or a testing interval of 15 days. In addition, Schaefer et al [211] identified poor control to be associated with long intervals between measurements but defined this as > 14 days. Therefore, given both GP and WCP management achieved above a TTR of 65% but the average testing interval was

16 and 22 days respectively, further investigation is required to determine the association with testing frequency and overall TTR.

The time interval to next INR test was significantly lower by WCP compared to GP management across a range of INR values, including extremes of ≤ 1.5 and ≥ 4.0 . This is in accordance with findings by Witt et al [115] of significantly lower time to follow-up testing by anticoagulant services when INR values were ≤ 1.5 or ≥ 4.0 . Similar to this, Nichol et al [116] reported significantly lower number of days between out-of-range INR tests for anticoagulation clinic patients compared to usual care. Rose et al [126] concluded that better anticoagulation control is achieved with shorter follow-up intervals after out-of-range INR values. Thus decreasing the time to next INR test, particularly for out-of-range INR, could assist in further improving the TTR by GP management.

The improved outcomes from anticoagulation clinics have been associated with more consistent INR testing [128], early recognition of patient risk factors [120], and improved patient education [433]. Due to the retrospective nature of our study and access only to INR results prior to enrolment at the clinic, we were unable to measure outcomes in terms of adverse events and influence of interacting medications.

However, TTR has been shown to be a good surrogate marker of outcomes with warfarin therapy [92, 96, 97], and enrolment in the dedicated warfarin clinic was shown to improve TTR even after only a six month period. This is likely to translate into improved outcomes from warfarin therapy but further investigation is required to confirm this improvement in terms of clinical efficacy and safety. Another limitation of this study is that the pre-post observational design does not control for other external

factors which may influence outcomes including concurrent illness and patient compliance. Further investigation should also include other Australian States and Territories to determine if warfarin management programs could improve warfarin control on a nation-wide level and ensure optimal outcomes for patients on warfarin.

In conclusion, this study found a high level of warfarin control in Australia with a TTR of 69% when managed by the GP and 82% when managed at WCP. The TTR for both management approaches is above recommended targets of 65%, suggesting good management by Australian GPs but superior control by the dedicated WCP. These findings suggest that dedicated warfarin management programs can improve warfarin control for Australian patients and are an important approach to optimise TTR and warfarin therapy for patients.

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Author Contributions

Nijole Bernaitis: Data collection; data analysis; drafting article; approval of article.

Tony Badrick: Data analysis/interpretation; statistics; critical revision of article; approval of article.

Shailendra Anoopkumar-Dukie: Concept/design; data interpretation; critical revision of article; approval of article.

STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

This chapter includes a co-authored paper. The paper “Quality of warfarin control in atrial fibrillation patients in South East Queensland, Australia” was published as a peer-reviewed paper in the Internal Medicine Journal 2016 Aug; 46(8): 925-931. The authors of the paper are: Nijole Bernaitis, Tony Badrick, Andrew K Davey, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: collecting the data, categorising and analysing the data, and graphical representation of the data. I wrote the first draft, made revisions responding to supervisor comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

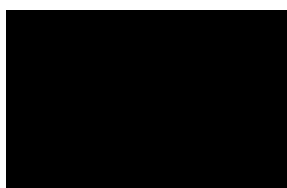
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(Date) 4/12/18

Nijole Bernaitis

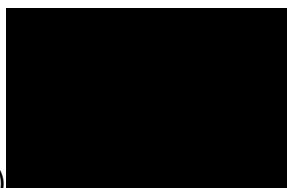
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(Countersigned)



(Date) 4/12/18

Supervisor: Shailendra Anoopkumar-Dukie

**Quality of warfarin control in atrial fibrillation patients in South East Queensland,
Australia**

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Abstract

Background: Warfarin is widely prescribed to decrease the risk of stroke in atrial fibrillation (AF) patients. Due to patient variability in response, regular monitoring is required, and time in therapeutic range (TTR) used to indicate quality of warfarin control with a TTR > 60% recommended. Recently, an Australian Government review of anticoagulants identified the need to establish current warfarin control and determine the potential place of the newer oral anticoagulants.

Aim: To determine warfarin control by a pathology practice in Queensland, Australia and identify factors influencing TTR.

Methods: Retrospective data were collected from Sullivan Nicolaides Pathology, a major pathology practice offering a warfarin care program in Australia. Patients enrolled in their program as of September 2014 were included in the study. TTR was calculated using INR test results, and test dates using the Rosendaal method with mean patient TTR were used for analysis and comparison. Exclusions were target therapeutic range outside 2.0 – 3.0, less than two INR tests and program treatment time of less than 30 days.

Results: The eligible 3692 AF patients had 73.6% of INR tests within the therapeutic range. The mean TTR was 81%, with 97% of patients above a TTR of 60%. TTR was not significantly influenced by age, gender or socioeconomic factors.

Conclusions: The observed mean TTR of over 80% is superior to the minimum recommended threshold of 60%. The TTR achieved by the Queensland pathology

practice demonstrates that dedicated warfarin programs can produce high-quality warfarin care, ensuring the full benefit of warfarin for Australian patients.

Introduction

Warfarin is the most widely prescribed oral anticoagulant in Australia with over 3 million prescriptions annually [411]. Anticoagulation with warfarin is a well-documented therapy for thromboembolic events including deep vein thrombosis and pulmonary embolism, and for treatment and prevention of cardio-embolic events such as ischaemic stroke due to atrial fibrillation (AF) [434]. Although warfarin therapy has been established to reduce the risk of stroke by 64% in AF patients [30], it is prescribed for only about half of eligible AF patients due to concerns regarding individual variability [29]. Patient variability in response necessitates ongoing monitoring of international normalised ratio (INR). Maintaining INR values within the range of 2.0 to 3.0 optimises the benefit to risk ratio of warfarin treatment [87] with time in therapeutic range (TTR) a recommended measure for quality of warfarin management [92]. A TTR minimum target threshold of 60% is recommended to ensure benefit from warfarin [330] with poor control (TTR < 60%) associated with higher mortality, major bleeding and systemic embolism events in patients treated with warfarin [100].

The introduction of newer oral anticoagulants (NOACs) which act as direct thrombin inhibitors or Factor Xa inhibitors has potentially simplified anticoagulation with these agents demonstrating fixed dosing and less monitoring [348]. Meta-analyses of large clinical trials have demonstrated the NOACs to be non-inferior [347] or slightly superior [348] to warfarin in stroke and systemic embolism rates, with a decreased risk

for intracranial bleeding compared to warfarin [347, 348]. Because of this, health care providers are increasingly faced with decisions regarding choice of anticoagulant and potentially switching patients from warfarin to the NOACs. However, comparative data between warfarin and individual NOACs is significantly impacted by variations in TTR of warfarin with quality of warfarin control demonstrated to be a major factor in determining the relative cost-effectiveness of the NOACs over warfarin [369]. Recently Shah and Gage [435] further demonstrated that the greatest benefit of the NOAC dabigatran was obtained in individuals that were poorly controlled by warfarin (TTR < 57%). Given the strong association between TTR and outcomes of warfarin therapy, there continues to be debate regarding the transferability of the trials into clinical practice and the resultant prescribing of warfarin and NOACS worldwide [385].

The quality of warfarin control is a major factor in prescribing warfarin or potentially switching from warfarin to a NOAC. While there have been studies that have looked at warfarin control in the United States [213], Europe [222], and Asia [163], to date there is limited data assessing the level of warfarin control in Australia. The majority of data in Australia arises from sub-analyses of clinical trials which have reported high levels of warfarin control with TTR above 70% [376]. An observational study by Bereznecki et al [382] in the Australian state of Tasmania reported a mean TTR for warfarin of 69.1% for 1137 patients monitored by a major private pathology provider. Recently a Government funded Australian review of anticoagulant therapies in atrial fibrillation, the Sansom report [24], identified the need to determine the current quality of warfarin use in Australia and identify patients who are unable to obtain satisfactory INR control and may benefit from the NOACs. Therefore, the aim of this study was to

determine warfarin control in patients managed by a pathology practice offering a warfarin care program in Queensland Australia and determine potential factors influencing TTR.

Methods

Study Design and Data Collection

Griffith University Ethics approval was obtained PHM/09/14/HREC. Sullivan Nicolaides Pathology (SNP) is an Australian private pathology practice offering pathology testing and warfarin management to any patient initialised on warfarin in Queensland, northern New South Wales and Darwin. Warfarin Care patients receive a complete service including blood collection, laboratory testing, result interpretation, dose instructions, and follow-up information. Prior to each venous blood collection patients complete a questionnaire regarding compliance, events, medication changes, and planned surgery or holidays. This information together with INR result is utilised by pathologists and specialist general practitioners to communicate ongoing dose instructions and date of next test to patients via their preferred communication method (telephone, text message, e-mail, facsimile, or if non-urgent post).

Retrospective data was collected from SNP for patients enrolled in their warfarin program as of September 2014. Information on treatment indications was obtained and further data was extracted for patients receiving warfarin management for atrial fibrillation including INR result and test date, together with demographic data such as gender, age, and residential location. Events reported by patients were recorded including hospital admissions and bleeds. Patients with a target INR range outside of

2.0 to 3.0 were excluded from the study. Additional exclusions were insufficient tests to calculate TTR (i.e. less than 2 tests) and a time of treatment with the program of less than 30 days. Possible influential factors on TTR was analysed including age, gender, frequency of testing, time at program, and geographical location.

Patients enrolled in the warfarin program lived in both Queensland and Northern New South Wales. Australian Bureau of Statistics data was applied to residential locations to group patients according to their socio-economic indexes. Indexes group areas into deciles with the lowest group given a decile of 1 up to the highest 10% of areas which are given a decile of 10, meaning decile 1 is the most disadvantaged relative to all other areas.

Statistical Analysis

Statistical analysis was performed on GraphPad InStat Version 3 and graphing performed with GraphPad Prism 6. Means and standard deviations were used to describe patient characteristics. Time in therapeutic range was calculated using Rosendaal's linear interpolation algorithm [95] with software downloaded from INR Pro®. The mean patient TTR was used for analysis and comparison by age, gender, geographic location, frequency of testing, and duration of treatment. Comparisons were made using ordinary ANOVA via nonparametric methods including Kruskal-Wallis test and Dunn's multiple comparisons test.

Results

A total of 7956 patients were being treated by the warfarin program for the main indications of atrial fibrillation (49.7%), pulmonary embolism (10.1%) and deep vein thrombosis (7.7%). Of the 3954 patients being treated for atrial fibrillation, a total of 262 were excluded from the study due to different target ranges (221 patients), insufficient tests to calculate TTR (11 patients), or treatment time of less than 30 days (30 patients). The remaining 3692 patients consisted of 1892 males (51.3%) and 1800 females (48.8%). The entire 3692 patients had received a total of 370126 tests with 73.6% of these within the therapeutic range of 2.0 - 3.0 (Figure 13). There were 15.9% of tests less than INR 2.0 and 10.5% greater than INR 3.0 with 0.2% of these between 5.0 and 8.0 and 0.02% of these greater than 8.0.

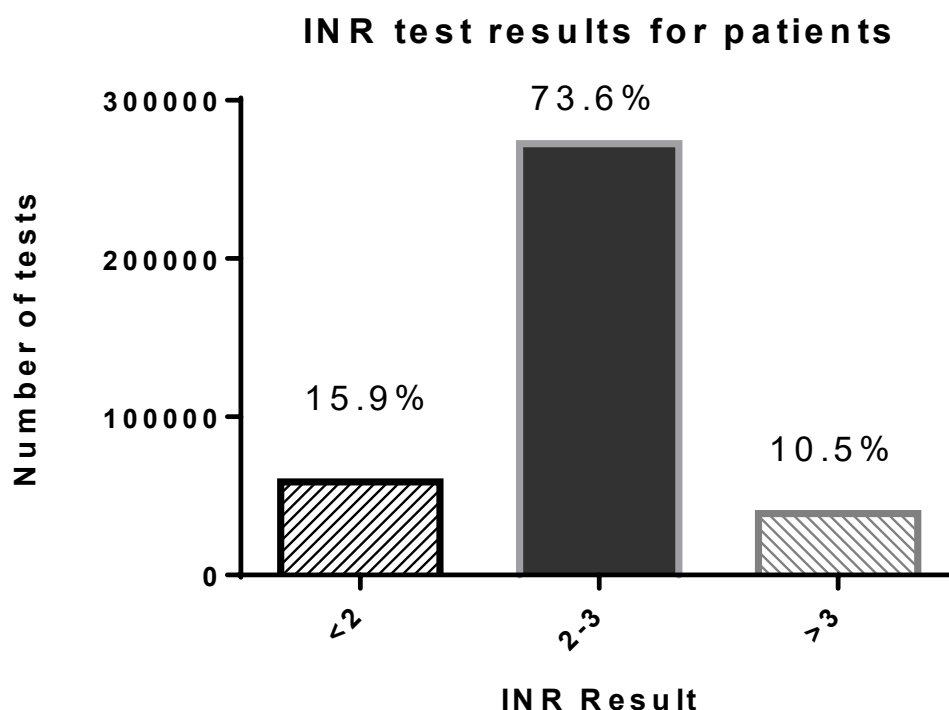


Figure 13 - Distribution of INR tests for 3692 AF patients having a total of 370 126 tests within the study period, with results of 2.0 – 3.0 for 289 480 (73.6%) of tests and < 2.0 for 61 819 (15.9%) of tests and > 3.0 for 47 253 (10.5%) of tests. AF, atrial fibrillation; INR, international normalised ratio.

The overall mean TTR for all the 3692 patients was $81.1 \pm 9.4\%$ (Table 18). The mean TTR for women was $81.4 \pm 9.1\%$ and for men $80.8 \pm 9.6\%$. The mean age of the atrial fibrillation patients was 78.8 ± 9.3 years with the mean age for women higher (80.8 ± 8.9 years) than in men (76.9 ± 9.3 years). The patients were treated for a mean of 1512.3 ± 778.6 days with a mean testing interval of 15.4 ± 5.0 days.

Table 18 - Atrial fibrillation patient data for TTR, age, tests, and time at program for all patients with data represented as mean (standard deviation) including breakdown of male and female patients

	All patients (n = 3692)	Male (n = 1892)	Female (n = 1800)
TTR	81.1 (9.4)	80.8 (9.6)	81.4 (9.1)
Age	78.8 (9.3)	76.9 (9.3)	80.8 (8.9)
Number of tests	100.2 (55.4)	99.2 (55.2)	101.3 (55.5)
Percent Tests in range	74.6 (9.8)	74.4 (9.9)	74.8 (9.6)
Days in treatment	1512.3 (778.6)	1537.2 (779.0)	1486.2 (777.6)
Test interval days	15.4 (5.0)	15.8 (5.3)	14.9 (4.6)

TTR, time in therapeutic range

Overall 3588 (97.2%) of patients had a TTR above 60% (Figure 14). A comparison of the patients with TTR greater or less than 60% (Table 19) showed a higher proportion of males in patients with a TTR below 60%. There were also significant differences between the patient groups in total days and test intervals with both these parameters being lower in the patients with TTR below 60%.

Table 19 - Comparative data for patients with TTR above & below 60% with data represented as mean (standard deviation) according to gender, age, total time, and test interval

	Patients with TTR >60% (n= 3588)	Patients with TTR <60% (n=104)
Male : Female Patients	1831:1757 (51.0%:49.0%)	61:43 (58.7%:41.3%)
Age	79.0 (9.1)	74.4 (13.3)
Total days	1533.5 (768.25)	783.9 (787.8)
Test interval	15.5 (4.9)	9.5 (4.5)

TTR, time in therapeutic range

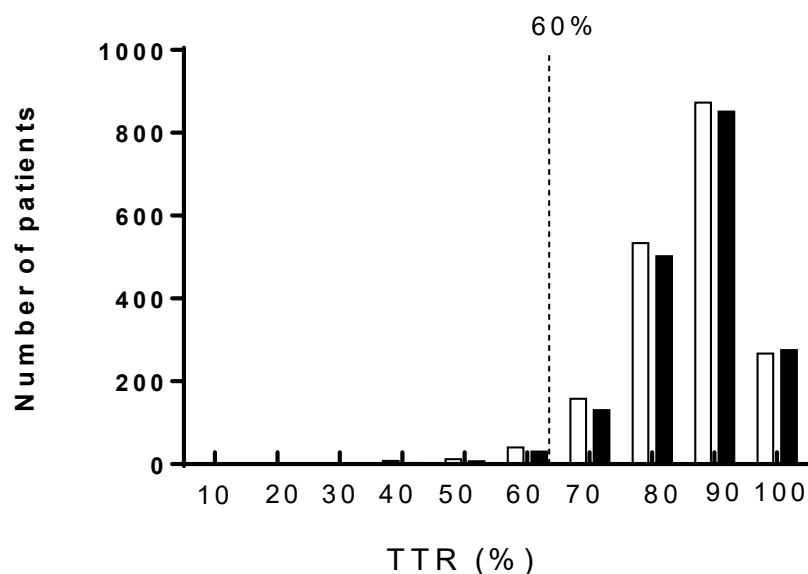


Figure 14 - Distribution of TTR according to number of female (■) and male (□) patients, with a line indicative of the minimum threshold recommended for warfarin treatment of 60% TTR. More than 97% of patients have a TTR > 60%. TTR, time in therapeutic range.

A total of 119 patients experienced an event during the treatment time. The 119 patients reported a total of 140 events consisting of major bleeds (20), vitamin K administration (85), stroke (27) and transient ischaemic attack (8). The mean TTR of the 119 patients experiencing an event was $77.3 \pm 9.1\%$ which was significantly lower ($p < 0.001$) than the TTR of $81.2 \pm 9.4\%$ of the patients which experienced no events. TTR was compared by age categories for both males and females (Figure 15). The mean TTR for the less than 50 age category was $69.9 \pm 20.4\%$ whilst all other age categories had a TTR above 79%, although this difference in TTR was not statistically different.

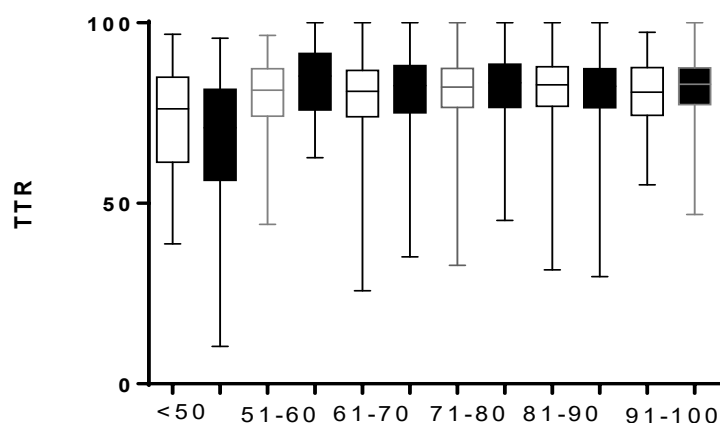


Figure 15 - Box plot of time in therapeutic range (TTR) divided into gender and age categories. The horizontal line indicates the mean, and the whiskers show minimum and maximum values. (□) Male; (•) female.

TTR was compared by test frequency with a breakdown of 7 days intervals (Figure 16).

Patients receiving testing with a frequency of less than 7 days had a mean TTR of

63.4% (± 16.8). The mean TTR increased to 76.6% (± 9.0) with a testing interval of 7 -

14 days and was more than 84% for frequencies of 14 days or greater. A significant

difference ($p < 0.001$) was found for testing of less than 7 days and 7 - 14 days

compared to all other testing intervals.

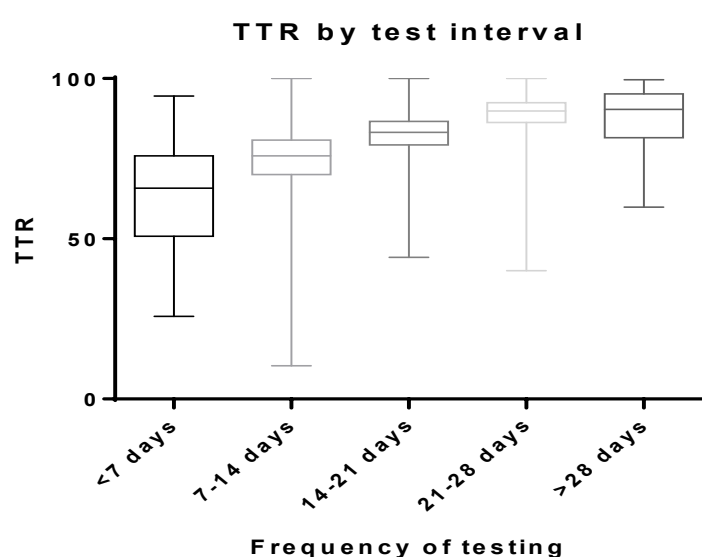


Figure 16 - Box plot of time in therapeutic range (TTR) divided into frequency of testing. The horizontal line indicates the mean, and the whiskers show minimum and maximum values.

TTR was compared to duration of treatment with the program divided into yearly intervals (Figure 17). Patients with treatment durations of less than 365 days had a mean TTR of 76.3% (± 16.8). A mean TTR above 79% was achieved with 1 - 2 years treatment with the program whilst a TTR above 80% was achieved with all durations greater than 2 years.

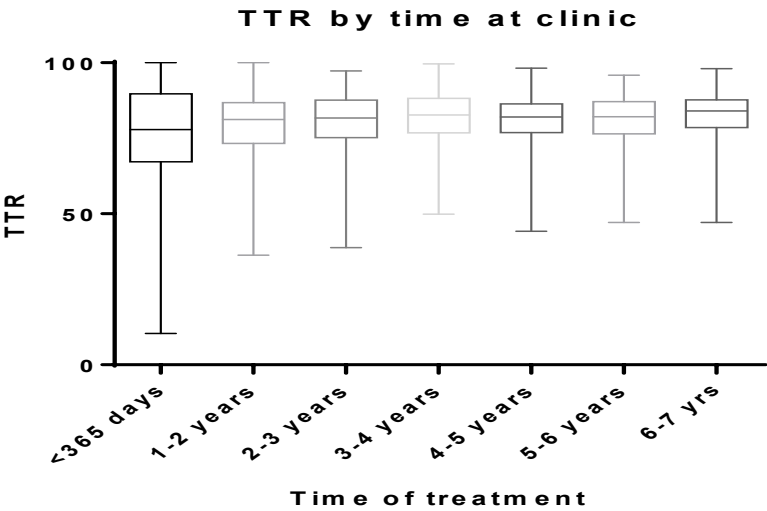


Figure 17 - Box plot of time in therapeutic range (TTR) divided into time of treatment. The horizontal line indicates the mean, and the whiskers show minimum and maximum values

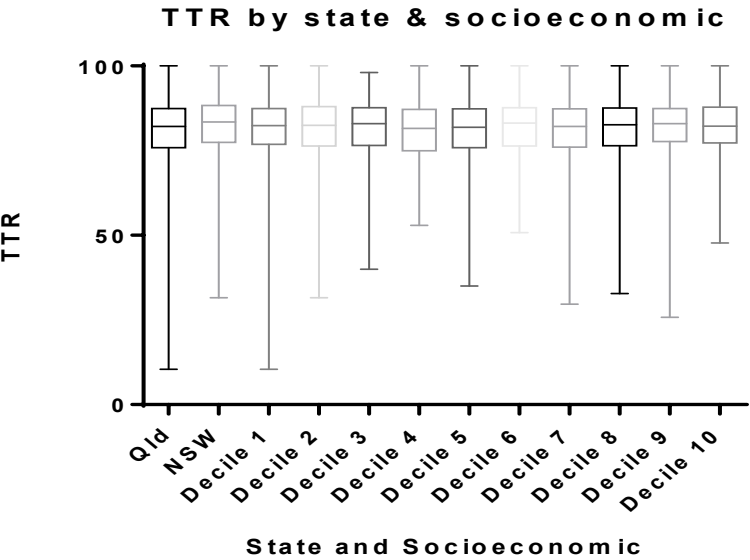


Figure 18 - Box plot of time in therapeutic range (TTR) divided by geographical area, namely the state of Queensland and New South Wales, and socioeconomic index, with decile 1 the most disadvantaged. The horizontal line indicates the mean, and the whiskers show minimum and maximum values.

Warfarin control according to geographic location, namely the two different Australian States, showed no statistical difference in TTR with both states above 80% TTR (Figure 18). Similarly no TTR difference was shown according to socioeconomic status with all deciles above 80% TTR.

Discussion

AF is a common cardiac arrhythmia affecting up to 400,000 Australians [24]. Mainstay therapy for AF patients includes stroke prevention with anticoagulants which now includes a choice between warfarin and NOACs. Recent evidence suggests the favourable net benefit of the NOACs over warfarin is dependent on the quality of warfarin control with no significant differences between the NOACs and warfarin seen with TTR > 65% [347]. Similarly Ruff et al [350] reported a greater relative reduction in major bleeding for NOACs over warfarin when the TTR was less than 66%. Therefore whilst a minimum target threshold of 60% TTR with warfarin is recommended to ensure benefit over antiplatelet therapy [378], a minimum TTR of 65% may be necessary to ensure benefit over NOAC therapy. To date, data on the quality of warfarin control in Australia has been limited with sub-analyses of randomised control trials reporting Australian TTR above 70% [376] and one study from the Australian state of Tasmania reporting a TTR of 69.1% [382]. Therefore the aim of our study was to determine warfarin control by a pathology practice offering a warfarin care program in Queensland Australia and determine potential factors influencing TTR. Our retrospective study of a pathology practice offering a warfarin care program in South-East Queensland demonstrated high quality warfarin control with a mean TTR of 81%.

Meta-analyses of warfarin treated AF patients demonstrated 56% of measured INRs to be within range and a TTR of 61% [90]. Our study demonstrated superior control with 73% of measured INRs in the range of 2.0 - 3.0 and a mean TTR of 81%. Furthermore, in our study, 97% of patients were above the minimum target threshold of 60% TTR required to obtain benefit from warfarin. Patients with poor TTR (< 60%) have higher mortality, major bleeding, plus stroke and systemic embolism rates [100]. Interestingly in our study patients experiencing an event had a significantly lower TTR (77.3%) than patients who had no event (TTR 81.2%) although this remained well above the recommended level of 60 - 65%. It has been reported that an improvement in TTR of 6.9% significantly reduces major haemorrhage rates by one event per 100 patient-years of treatment and an 11.9% increase in TTR reduces thromboembolic events by 1 event per 100 patient-years [109]. Therefore whilst the high mean TTR in our study should reflect good efficacy and safety, further investigations are required to determine precipitating factors, INR control, and TTR at the time of events. Furthermore given the suggested correlation between TTR and clinical outcomes [109], the minimum recommended level of TTR may need to be increased to ensure optimal patients outcomes.

Study setting has been reported to have a significant impact on warfarin control with patients managed by anticoagulant clinics achieving significantly greater anticoagulant control compared to those managed in community practices [130]. Superior control by anticoagulant clinics has been demonstrated across a number of geographically diverse health plans [436] and regions including the United States, Canada, and Europe [133]. Our study demonstrates that the Queensland based warfarin care program can also

achieve and maintain a TTR well above the minimum target threshold of 60% regardless of the influence of a number of demographic factors including age, gender, and socioeconomic status.

Influences associated with lower mean TTR at an individual patient level were identified by Singer et al [376] to be younger patients and female patients. Okumura et al [163] in a multicentre study from Japan reported no gender differences but concurred that age strongly affected TTR with patients aged over 70 years having better control. In addition Menzin et al [436] reported that patients aged < 70 years were less likely to achieve good control than older patients. We found no significant differences across age categories however the mean TTR for the less than 50 age category was 69.9% whilst all other age categories had a TTR above 79%. This finding is similar to Wieloch et al [222] who demonstrated a TTR > 70% consistent across all age groups in a Swedish national registry of warfarin patients with AF. Furthermore, Rouaud et al [152] demonstrated that growing older yields greater INR control and found no association between gender and warfarin control. Consistent with Rouaud et al [152] and Okumura et al [163] we also found no difference in TTR between genders suggesting that both male and female patients can be equally controlled.

Poor control of TTR < 65% was suggested by Carrier et al [429] to be associated with a median of 12 tests over a six month period (equating to a testing interval of 15 days). In contrast we report lower mean TTR with increased frequency of testing, in particular a frequency of less than seven days was associated with a TTR of 63.7%. The mean TTR increased to 76.6% with a testing interval of 7 - 14 days and was greater than 84% for all frequencies above this. It has been suggested by Dlott et al [213] that the inverse

association with TTR among those with more frequent testing may reflect increased testing among individuals with poor INR control. However, further investigations are needed to establish the precipitating factors behind the increased testing in our population and hence determine the optimal frequency of testing.

The mean TTR in our study was not influenced by geographic area (state of Queensland versus New South Wales) or by socioeconomic status. This is in direct contrast to Dlott et al [213] who found lower income to be independently associated with poorer anticoagulation control in a national assessment of warfarin management in the United States. Differences in socioeconomic status may directly impact treatment adherence and health status [213] together with patient knowledge and subsequent outcomes of therapy [437]. However Fang et al [437] reported that limited health literacy was not associated with warfarin INR control in patients managed at an anticoagulation clinic in the United States. These authors suggested that anticoagulation clinics can standardise warfarin treatment to reduce potential differences in patients' understanding [437]. Similarly Wittkowsly et al [433] linked improved patient outcomes at anticoagulation clinics to more consistent monitoring, improved patient education, and early recognition of influencing risks. Our study supports these views as demonstrated by the high TTR at the Queensland Warfarin Care program irrespective of a number of demographic factors.

In conclusion our findings demonstrate that a pathology practice offering a warfarin care program in South East Queensland achieved a high mean TTR of 81%. This is well above the minimum target threshold for warfarin management of 60 - 65% and the targets achieved in comparative trials with the NOACs. Patients achieving such high

TTR would be receiving the full benefit of warfarin. Our findings confirm that high TTR can be transferred into practice through use of dedicated warfarin management programs.

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Chapter Five – Factors influencing warfarin time in therapeutic range in patients with AF in South-East Queensland and Singapore

Warfarin management practices may influence the level of warfarin control [114, 130, 136] with medical care practices within specific regions or countries also known to influence warfarin TTR [153, 368, 376, 377]. Further to this, patient specific factors such as genetics, ethnicity, age, gender, co-morbid conditions and concurrent medication can influence response to warfarin [438]. In terms of concurrent medication, specific drugs within classes of medication can also differ in their impact on warfarin control due to differences in metabolic pathways [68, 152]. Whilst it is known that numerous factors can influence warfarin control, there are limited real-world studies comparing the influence of clinical characteristics on warfarin control across different medical practices. Further to this, there is sparse comparative information on factors influencing warfarin control in different ethnic populations, specifically Asian and Caucasian populations. Therefore, the objective of this chapter was to investigate factors influencing time in therapeutic range in patients with AF in South-East Queensland and Singapore, a comparator site within the Asia-Pacific region. Data presented in the published article “Factors influencing warfarin control in Australia and Singapore” (Thrombosis Research 2017 Sep; 157: 120-125) provides a comparison on the levels of warfarin control achieved in Queensland and Singapore and identifies factors influencing warfarin TTR at these sites including management systems (frequency of testing and dosing) and patient specific factors (gender, age, co-morbidities and concurrent medication).

Results from this initial analysis [439] demonstrated that some medication groups, e.g. statins, did not impact warfarin TTR despite the potential of individual agents to influence warfarin control. Specific to statins, atorvastatin and pravastatin do not appear to interact with warfarin whereas fluvastatin, rosuvastatin, and simvastatin may increase INR [68]. Therefore, further investigation was performed on the impact of statins on warfarin TTR at both sites which is presented in a published article “Long-term statin administration does not affect warfarin time in therapeutic range in Australia or Singapore” (Journal of Clinical Medicine 2018; 7(5): 97).

Similar to this, results from the initial comparative analysis [439] identified anti-platelets as influencing TTR compared to mean site TTR in Singapore but not in Australia. Anti-platelet agents such as aspirin have previously been reported to influence warfarin in terms of bleed events [60, 68, 98] with some evidence suggesting an influence of aspirin on TTR [160-162]. Therefore, aspirin was further investigated regarding the potential influence on warfarin control and adverse events. The Australian SNP site was used for this purpose as the population size allowed for statistical analysis after eliminating patients with other potentially interacting medication. The results of this data are presented in the published article “Impact of aspirin on warfarin control as measured by time in therapeutic range” (Basic & Clinical Pharmacology & Toxicology 2018 Oct; 123(4): 504-508). These three articles contribute to addressing specific objective three of the thesis regarding and comparison of warfarin control and influencing factors between South-East Queensland and Singapore.

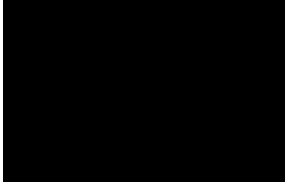
STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER


This chapter includes parts of a co-authored paper. The paper “Factors influencing warfarin control in Australia and Singapore” was published as a peer-reviewed paper in Thrombosis Research 2017 Sep; 157: 120-125. The authors of the paper are: Nijole Bernaitis, Chi Keong Ching, Siew Chong Teo, Liping Chen, Tony Badrick, Andrew K Davey, Julia Crilly, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: designing and conducting the study, collecting the data at both sites, providing direction on the scope and structure of the analysis, categorising and analysing the data. I wrote the first draft, made revisions responding to supervisor & co-authors comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

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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.

Introduction

Warfarin is widely used to prevent embolic stroke in patients with atrial fibrillation (AF) [53]. 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 [45]. This variability in response necessitates close monitoring of warfarin using the International normalised Ratio (INR) [440]. 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 [92]. Increasing the TTR can improve the safety and efficacy of warfarin, with target goals of 70% suggested to enhance patient outcomes [325]. However, Mearns et al [90] reported AF patients worldwide spend only 61% TTR but found differences reported between practice settings and according to geographical region. Similarly, Baker et al [131] 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) [330]. Comparative trials of warfarin to the NOACs in patients with non-valvular AF (NVAF) have demonstrated the NOACs to be non-inferior [347] or slightly superior [348] to warfarin in terms of stroke and systemic embolism, and associated with lower intracranial haemorrhage rates [347, 348]. However, Gomez-Outes et al [347]

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 [368, 376] and lowest in India [368] and East Asia [376]. Similar to this, Chiang et al [386] 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 [441] found significant regional differences in treatment strategies and clinical cardiovascular outcomes in AF patients across Asia-Pacific countries. Chen et al [25] 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 [366, 376]. Outside of these trials, the limited data on warfarin control in these countries have reported similar results with TTRs between 55% [208] and 81% [425] in Australia, and between 58% [442] and 65% [443] in Singapore. Wang et al [387] 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 [95] with software downloaded from INR Pro®. Patient exclusions were insufficient tests to calculate TTR (i.e. 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 \pm 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 20).

Table 20 - Patient demographics at the study sites in Australia and Singapore.

	Australia (n=3196)	Singapore (n=1170)	P-value
Gender			
Male	1671 (52.3%)	706 (60.3%)	P<0.0001
Female	1525 (47.7%)	464 (39.7%)	P<0.0001
Age - mean (SD)	77.2 (9.1)	69.7 (10.0)	
Age < 60 years	138 (4.3%)	176 (15.0%)	P<0.0001
Age 60 - 69 years	458 (14.3%)	370 (31.6%)	P<0.0001
Age 70 - 79 years	1185 (37.1%)	437 (37.4%)	P=0.8559
Age ≥ 80 years	1415 (44.3%)	187 (16.0%)	P<0.0001
Past Medical History			
Hypertension	1184 (37.0%)	697 (59.6%)	P<0.0001
Diabetes	562 (17.6%)	351 (30.0%)	P<0.0001
Heart Failure	278 (8.7%)	88 (7.5%)	P=0.2050
Vascular Disease	357 (11.2%)	279 (23.8%)	P<0.0001
Chronic Kidney Disease	149 (4.7%)	163 (13.9%)	P<0.0001
Abnormal liver function	11 (0.3%)	6 (0.5%)	P=0.3242
History of stroke or TIA	487 (15.2%)	46 (3.9%)	P<0.0001
History of bleeds	18 (0.6%)	0 (0%)	P=0.0079
History of cancer	277 (8.7%)	42 (3.6%)	P<0.0001
Anaemia	50 (1.6%)	64 (5.5%)	P<0.0001
Cardiomyopathy	136 (4.3%)	107 (9.1%)	P<0.0001
Dyslipidaemia	470 (14.7%)	607 (51.9%)	P<0.0001
Risk Model Scores			
CHA ₂ DS ₂ -VASc score 0	101 (3.2%)	93 (7.9%)	P<0.0001
CHA ₂ DS ₂ -VASc score 1	374 (11.7%)	170 (14.5%)	P=0.0131
CHA ₂ DS ₂ -VASc score 2	717 (22.4%)	266 (22.7%)	P=0.8334
CHA ₂ DS ₂ -VASc score 3	869 (27.2%)	294 (25.2%)	P=0.1857
CHA ₂ DS ₂ -VASc score 4	581 (18.2%)	197 (16.8%)	P=0.2844
CHA ₂ DS ₂ -VASc score 5	346 (10.8%)	106 (9.1%)	P=0.1024
CHA ₂ DS ₂ -VASc score 6	165 (5.1%)	35 (3.0%)	P=0.0032
CHA ₂ DS ₂ -VASc score 7	35 (1.1%)	9 (0.8%)	P=0.3822
CHA ₂ DS ₂ -VASc score 8	8 (0.3%)		P=0.0607
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%)	P=0.8142
Beta-blockers	1995 (62.4%)	912 (77.9%)	P<0.0001
Amiodarone & Betablocker	117 (3.7%)	54 (4.6%)	P=0.1759
Digoxin	1082 (33.9%)	331 (28.3%)	P=0.0005
Angiotensin Converting Enzyme Inhibitor	1116 (34.9%)	338 (28.9%)	P=0.0002
Angiotensin Receptor Blocker	887 (27.7%)	320 (27.4%)	P=0.8443
Calcium channel blocker	823 (25.8%)	386 (33.0%)	P<0.0001
Statin	1765 (55.2%)	852 (72.8%)	P<0.0001
Platelet Inhibitor	287 (9.0%)	300 (25.6%)	P<0.0001
Diuretic	1291 (40.4%)	420 (35.9%)	P=0.0070
Proton Pump Inhibitor	1163 (36.4%)	520 (44.4%)	P<0.0001

Data shown is number and percentage. Mean and standard deviation is also shown for age, and median and interquartile range for risk scores.

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 HAS-BLED 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).

During the study period there were a total of 35,898 INR tests in Australia and 6588 in Singapore (Table 21). The mean TTR was $82.3 \pm 15.6\%$ in Australia and $57.6 \pm 34.2\%$ in Singapore which was statistically different ($p < 0.0001$). The mean percentage of tests in range was statistically different between Australia and Singapore ($78.9 \pm 19.1\%$ versus $54.2 \pm 30.5\%$, $p < 0.0001$) 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.

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 22). There was a significantly reduced frequency of testing and number of dose changes in the patients with TTR > 65% in both Australia and Singapore.

Table 21 - Warfarin control at the study sites in Australia and Singapore

	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

Data shown is mean (standard deviation) for warfarin control with median (interquartile range) shown for warfarin dose information. Chi-square distribution P value was <0.0001 and Kruskal-statistic KW=12788 (corrected for ties).

Table 22 - Warfarin control at the study sites in Australia and Singapore according to time in therapeutic range (TTR) both above and below 65%.

	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)	

Data shown is mean (standard deviation) for warfarin control with median (interquartile range) also shown for warfarin dose information.

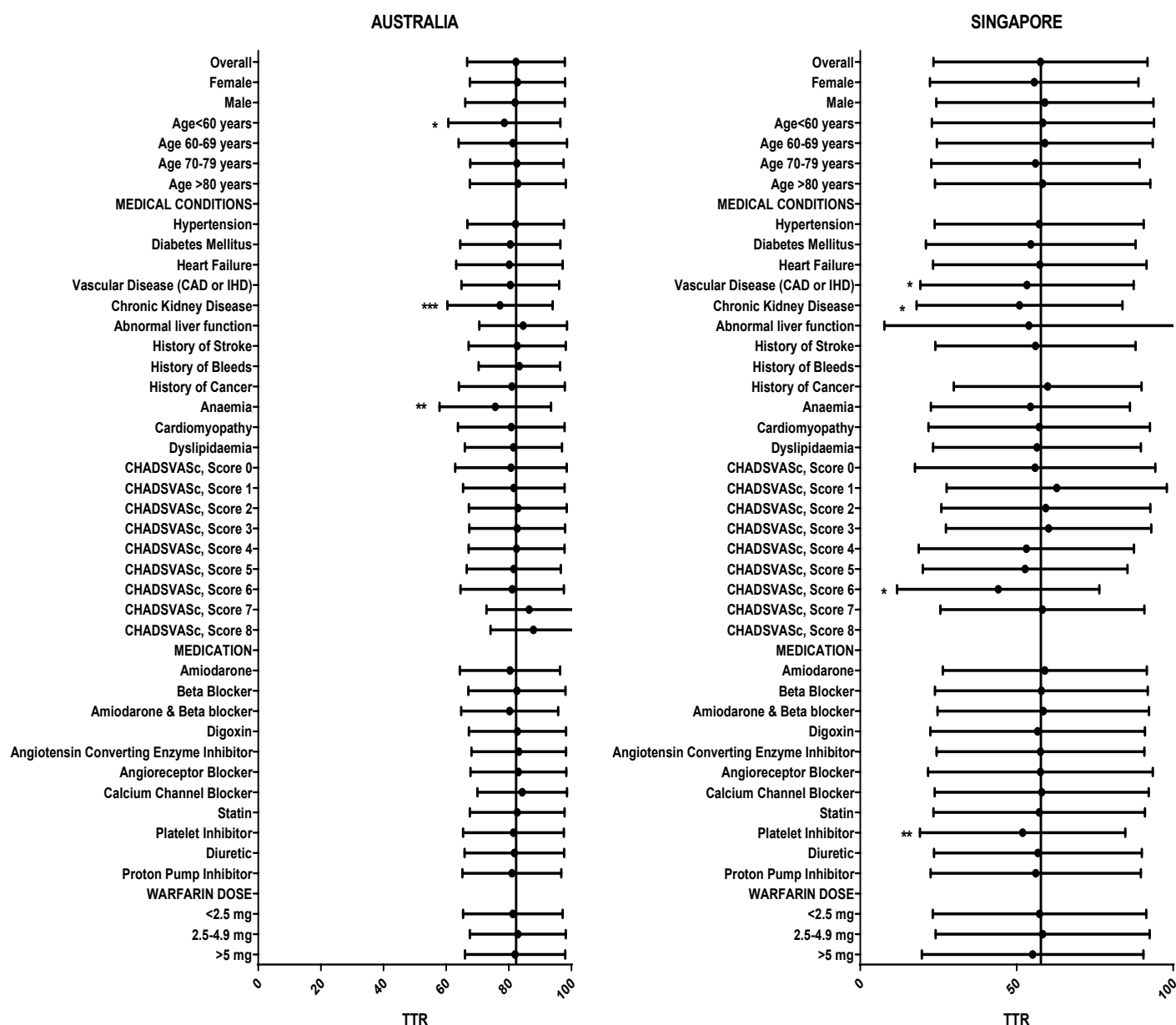


Figure 19 - Comparison of mean TTR in Australia and Singapore to demographic and clinical characteristics.

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 *** $p < 0.001$.

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 19). Chronic kidney disease was associated with a statistically lower

TTR in Australia ($77.2 \pm 16.8\%$, $p = 0.002$) 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.

Discussion

Warfarin has been used for decades in patients with AF but suboptimal use can lead to poor patient outcomes [444]. 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 [347]. Regional differences in warfarin control have been reported with higher TTRs in Western countries and lower TTRs in Asian countries [376]. Suboptimal control in Asians has been suggested to be due to genetic polymorphisms and demographic differences [387], 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 [370], 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 [20]. Chiang et al [27] 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 [27]. 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 [441] 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 [445], the mean age of patients with AF in our Asian population was younger. Similarly, as described by Frank et al [446], 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 [25] reported higher proportions of Asian patients on antiplatelet therapy and, further to this, revealed overuse of anticoagulant therapy in low risk (CHA₂DS₂-VASc = 0) patients in many countries. Similar to this, our warfarin study included patients with CHA₂DS₂-VASc scores of 0 however further investigation is required to determine the rationale for warfarin therapy in these patients.

Suarez et al [447] 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% [366, 376]. Real-world data of warfarin control in patients with AF reported similar results with a TTR of 81% in Australia [425] and 58% in Singapore [442]. 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 [448] who reported a median interval of testing of 14 days in other world regions compared to 28 days in Asia. Carrier et al [429] 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 [211] 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 [133] 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

[449] suggested the poorer TTRs in Asians may be attributed to the lack of structured anticoagulation services. Chua et al [443] 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 [163] and, in contrast, with lower doses by Palaretti et al [200]. There were significant differences in the weekly warfarin doses in Australia and Singapore (26 mg and 18 mg respectively). Jonas et al [32] 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 [37] 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 [37] 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 [161, 162, 177] 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 [450] with a proposed mechanism being altered warfarin disposition due to reduced hepatic cytochrome metabolism from cytokines and uremic toxins [451]. Pokorney et al [178] 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 [452] found no correlation with warfarin control and CHADS₂ score, whilst Gallagher et al [105] 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 [453], TTR increasing with age [222], and poorer anticoagulation control associated with younger age as defined by < 45 years [213] or < 60 years [159]. In addition to age, Dlott et al [213] and Apostolakis et al [159] 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 [105] and Okumura et al [163] 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 [193] 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 patients overall clinical status. Further to this, Apostolakis et al [159] 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 [163] who found no differences in TTR with co-administration of anti-platelet agents and Mueller et al [453] 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 [66]. Guo et al [454] 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 [455]. In global studies of warfarin, Singer et al [376] concluded that patient clinical factors were modest determinants of TTR but the strongest determinants was 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 [25, 169]. There are now alternate anticoagulant options to warfarin and the benefit of these NOACs over warfarin has been demonstrated in centres with TTR < 65% [347]. 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 [337] 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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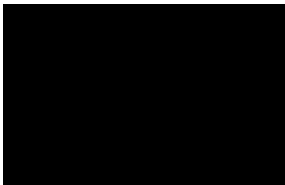
STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

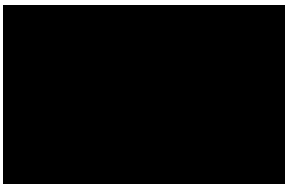
This chapter includes a co-authored paper. The paper “Long-term statin administration does not affect warfarin time in therapeutic range in Australia or Singapore” was published as a peer-reviewed paper in the Journal of Clinical Medicine 2018 May; 7(5): 97. The authors of the paper are: Nijole Bernaitis, Chi Keong Ching, Siew Chong Teo, Tony Badrick, Andrew K Davey, Julia Crilly, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: collecting the data, providing direction on the scope and structure of the analysis, together with categorising and analysing the data. I wrote the first draft, made revisions responding to supervisor and co-authors comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

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Long-term Statin Administration Does Not Affect Warfarin Time in Therapeutic Range in Australia or Singapore

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Abstract:

1) Background: Warfarin requires ongoing monitoring of International Normalised Ratio (INR) as numerous factors influence response including drug interactions with commonly prescribed medications including statins. Administration of statins with warfarin may change INR, however there is limited information regarding effects on warfarin control as measured by time in therapeutic range (TTR). Statins may also alter bleeds with warfarin, but there are conflicting reports demonstrating both increased and decreased bleeds, and limited data in diverse ethnic populations. Therefore, the aim of this study was to determine the effect of statin administration on warfarin control and bleeds for patients in Australia and Singapore.

2) Methods: Retrospective data was collected for patients on warfarin between January and June 2014 in Australia and Singapore. Patient data was used to calculate TTR and bleed events. Concurrent statin therapy was assessed and comparisons of TTR and bleed incidence made across patient subgroups.

3) Results: Warfarin control in Australia and Singapore was not significantly affected by statins as measured by TTR (83% and 58% respectively), frequency of testing, and warfarin doses. In Australia, statin use did not significantly affect bleeds, whilst in Singapore bleed incidence was significantly lower for patients on statins.

4) Conclusions: Chronic concurrent administration of statins with warfarin does not adversely affect warfarin TTR in Australia or Singapore. In Singapore, patients on statins compared to no statins had a lower bleed incidence and this requires further investigation, especially given the potential genetic influences of ethnicity on both statin and warfarin metabolism.

Introduction

Warfarin is a widely prescribed anticoagulant used for the prevention of stroke in patients with atrial fibrillation (AF) [53]. Close monitoring of warfarin treatment is necessary due to variation in individual response to dosing, with the efficacy and safety of warfarin dependent on maintaining levels within therapeutic range [440]. Achieving target International Normalised Ratio (INR) range is a measure of successful management of warfarin, with standards suggesting greater than 70% time in therapeutic range (TTR) is best [71]. Maintaining warfarin within the narrow therapeutic index is clinically challenging due to a number of influencing patient factors including drug-drug interactions [94]. Drug interactions with warfarin may be pharmacokinetic involving cytochrome p450 isoenzymes, or pharmacodynamic resulting in increased bleeding, the most common adverse reaction of warfarin [456].

Drug interactions with warfarin represent a common cause of bleeding and over-anticoagulation, particularly in the elderly with multiple co-morbidities and medications [64]. Wittkowsky et al [65] found almost 82% of patients receiving long-term warfarin were co-prescribed at least one potentially interacting drug. Further to this, Rikala et al [66] found over 90% of warfarin users are co-prescribed cardiovascular drugs and over a third prescribed a statin, i.e. simvastatin. The concurrent use of statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) and warfarin is therefore common, but the safety of the drug interactions requires further exploration [457]. Metabolism of the statins involves cytochrome p450 (CYP) 3A4 for simvastatin, atorvastatin, and lovastatin, CYP2C9 for fluvastatin and rosuvastatin, whilst pravastatin is not markedly metabolised by CYP [458]. Both CYP3A4 and 2C9 are involved in

warfarin metabolism, so co-administration of statins which utilise these CYP pathways can increase INR and increase risk of bleeding [62]. However, there have been conflicting reports regarding the outcomes of the interaction with warfarin and statins, particularly regarding bleed risk. Schelleman et al [459] found an increased risk of gastrointestinal bleeding with statins inhibiting CYP3A4, i.e. simvastatin and atorvastatin, but no change with fluvastatin metabolised via CYP2C9. Similar to this, Shin et al [460] found the incidence of gastrointestinal bleed risk highest with rosuvastatin, followed by atorvastatin and simvastatin, while pravastatin tended to reduce the risk. Interestingly, despite the different bleed rates for the individual statins, these authors found no difference in TTR between the statin groups during the study period [460]. Further to this, Douketis et al [461] associated long-term statin use with a decreased risk of warfarin bleeding, however they did not include anticoagulation control in the analysis or assess the risk of individual statins. The conflicting reports regarding the effects of statins on warfarin suggests further investigation is required into risks associated with this drug combination. In addition, the influence of ethnicity on the outcomes of warfarin and statins requires further investigation, as prescribing of statins may be influenced by potency, pharmacokinetics and toxicity of statins, particularly in Asian compared to Caucasian populations [462]. Therefore, the aim of this study was to determine the effect of statin administration on warfarin control and bleed risk in large cohorts of patients with AF in both Australia and Singapore.

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). A retrospective data analysis was conducted for patients receiving warfarin for non-valvular AF for the period of January 2014 to June 2014. Two sites were investigated, namely patients enrolled in a warfarin care program at Sullivan Nicolaides Pathology, Queensland, Australia, and patients managed at the outpatient warfarin clinic at The National Heart Centre Singapore. Data collected included age, gender, co-morbidities, concurrent medications, warfarin doses, INR test dates and results. HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile International Normalised Ratio or INR, Elderly > 65years, Drugs/alcohol concomitantly) score was calculated to assess bleed risk. Adverse events were recorded including self-reported bleeds (e.g nose bleeds, rectal bleeding), and major bleeds or stroke requiring hospital admissions. Patient data was screened to identify those who were concurrently prescribed a statin during the study period and divided into groups of statin users and no statin users. Patients taking statins were further divided according to the individual statin co-administered with warfarin.

TTR was calculated using Rosendaal's linear interpolation algorithm [95] with software downloaded from INR Pro©. Exclusions for analysis included patients for whom TTR was unable to be calculated (i.e. less than 2 test), and a time of treatment of less than 30 days. Mean data was used for analysis and comparison between groups. Events were categorised into minor or major bleeds, stroke, and death, and calculated as an incidence per patient for each group for comparison purposes.

Patient characteristics were reported as number and percentage for categorical data, and mean \pm standard deviation for continuous data. Statistical analysis was performed using GraphPad InStat Version 3 with comparisons made using ordinary analysis of variance through non-parametric methods, including Dunn's multiple comparisons test and Kruskal-Wallis test. Event incidence was compared using two-sided Fisher's exact test. Significance was defined as * or # $p < 0.05$, ** or ## $p < 0.01$, *** or ### $p < 0.001$, and **** or #### $p < 0.0001$.

Results

A total of 4366 patients with non-valvular AF were included in the study, with 3196 patients in Australia and 1170 in Singapore. This was following exclusions for insufficient data to calculate TTR for 48 patients in Australia and 260 patients in Singapore. The mean age of patients was 77.2 ± 9.1 years in Australia and 69.7 ± 10.0 years in Singapore which was statistically different ($p < 0.0001$) (Table 23). The majority of patients were male (52.2% in Australia and 60.3% in Singapore) and the median (IQR) HAS-BLED score was 1 (1 - 2) in both Australia and Singapore despite differences in the occurrence of co-morbidities. At both sites, the majority of patients were taking statins (57.3% in Australia and 73.4% in Singapore) and the majority of patients were prescribed either atorvastatin (53.4% in Australia, 21.9% in Singapore) or simvastatin (19.3% in Australia, 68.5% in Singapore). There was no significant difference in the mean age of patients taking statins and not taking statins (76.7 ± 8.6 vs 77.8 ± 9.7 years in Australia and 70.1 ± 9.6 vs 68.6 ± 11.0 years in Singapore).

Table 23 - Patient demographics at the study sites in Australia and Singapore.

	AUSTRALIA (n=3196)		SINGAPORE (n=1170)	
	STATIN (n=1831)	NO STATIN (n=1365)	STATIN (n=859)	NO STATIN (n=311)
Male	1016 (55.5%)	655 (48.0%)	527 (61.4%)	179 (57.6%)
Female	815 (44.5%)	710 (52.0%)	332 (38.6%)	132 (42.4%)
Age - mean (SD) ****	76.7 (8.6)	77.8 (9.7)	70.1 (9.6)	68.6 (11.0)
Past Medical History				
Hypertension ****	724 (39.5%)	460 (33.7%)	540 (62.9%)	157 (50.5%)
Diabetes ****	411 (22.4%)	151 (11.1%)	274 (31.9%)	77 (24.8%)
Heart Failure ****	157 (8.6%)	121 (8.9%)	70 (8.1%)	18 (5.8%)
Vascular Disease	274 (15.0%)	83 (6.1%)	239 (27.8%)	39 (12.5%)
Chronic Kidney Disease ****	94 (5.2%)	55 (4.0%)	120 (14.0%)	43 (13.8%)
Abnormal liver function	6 (0.3%)	5 (0.4%)	4 (0.5%)	3 (0.9%)
History of stroke or TIA ****	318 (17.4%)	169 (12.4%)	36 (4.2%)	10 (3.2%)
History of bleeds	7 (0.4%)	11 (0.8%)	0 (0%)	0 (0%)
HAS-BLED score ***	1.7 (0.8)	1.5 (0.8)	1.4 (0.8)	1.1 (0.8)
Concurrent Medication				
Amiodarone***	149 (8.1%)	66 (4.8%)	59 (6.9%)	17 (1.5%)
Beta Blocker****	1203 (65.7%)	792 (58.0%)	695 (46.0%)	217 (18.5%)
Digoxin***	565 (30.9%)	516 (37.8%)	238 (27.7%)	93 (7.9%)
Angiotensin Converting Enzyme Inhibitor****	695 (38.0%)	421 (30.8%)	272 (31.7%)	67 (5.7%)
Angiotensin Receptor Blocker***	538 (29.4%)	349 (25.6%)	249 (29.0%)	71 (6.1%)
Calcium Channel Blocker***	521 (28.5%)	302 (22.1%)	309 (36.0%)	77 (6.6%)
Platelet Inhibitor****	220 (12.2%)	67 (4.9%)	269 (31.3%)	32 (2.7%)

Data shown is number and percentage for patients concurrently prescribed statins or no statins. Mean and standard deviation is also shown for age, and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile International Normalised Ratio or INR, Elderly>65years, Drugs/alcohol concomitantly) score. Statistics shown are for patients on statin therapy in Australia compared to Singapore, and for patients on no statin therapy in Australia compared to Singapore with *** p<0.001 and **** p<0.0001

The mean TTR was 82.4 ± 15.6% in Australia and 57.6 ± 34.2% in Singapore which was statistically different (p < 0.0001) (Table 24). At the individual sites, no significant difference was found in the mean TTR, INR testing frequency, warfarin doses or frequency of dose changes for patients with or without statin therapy. The mean TTR and frequency of testing did not significantly differ regardless of the statin prescribed in either Australia or Singapore.

Table 24 - Time in Therapeutic Range (TTR) of patients at the two study sites, according to statin therapy.

	Patients	TTR	Testing frequency	Weekly warfarin dose	Warfarin dose changes
AUSTRALIA					
Entire Cohort	3196 (100%)	82.4 (15.6)	16.9 (8.1)	26.5 (18.7)	2.5 (2.7)
NO statin	1365 (42.7%)	82.1 (16.1)	17.1 (8.4)	26.8 (25.1)	2.5 (2.8)
Any Statin	1831 (57.3%)	82.5 (15.2)	16.7 (7.9)	26.2 (12.0)	2.5 (2.7)
Atorvastatin	977 (53.4%)	82.0 (15.4)	16.2 (7.5)	26.6 (12.3)	2.7 (2.9)
Simvastatin	354 (19.3%)	83.9 (14.9)	17.4 (8.4)	24.7 (11.0)	2.3 (2.5)
Pravastatin	106 (5.8%)	83.1 (14.7)	17.2 (8.9)	25.6 (12.1)	2.3 (2.7)
Rosuvastatin	392 (21.4%)	82.8 (15.0)	17.3 (8.0)	26.7 (12.1)	2.3 (2.6)
Lovastatin	2 (0.1%)	95.0 (7.1)	22.1 (17.5)	13.7 (4.5)	1 (1.4)
SINGAPORE					
Entire Cohort ****	1170 (100%)	57.6 (34.2)	29.3 (15.2)	18.4 (8.3)	1.0 (1.5)
NO statin ****	311 (26.6%)	59.2 (35.2)	29.7 (15.8)	18.4 (7.9)	1.0 (1.4)
Any Statin ****	859 (73.4%)	57.1 (33.8)	29.1 (15.0)	18.4 (8.4)	1.5 (1.5)
Atorvastatin ****	188 (21.9%)	52.0 (34.0)	27.1 (14.6)	20.6 (10.2)	1.4 (1.4)
Simvastatin****	588 (68.5%)	59.1 (33.6)	29.6 (14.7)	17.8 (7.6)	1.0 (1.5)
Pravastatin ****	5 (0.5%)	78.7 (36.2)	28.5 (14.9)	20.5 (18.3)	0.6 (0.9)
Rosuvastatin ****	31 (3.6%)	53.1 (32.2)	33.9 (19.1)	19.3 (8.7)	1.2 (1.4)
Lovastatin ****	47 (5.5%)	52.8 (34.4)	27.9 (16.1)	16.3 (7.0)	1.1 (1.5)

Number and percentage of patients is shown for with and without statin therapy, and for each individual statin. Mean (standard deviation) is shown for TTR, testing frequency, and warfarin dose information. Statistics shown are for patients in Australia compared to Singapore in each subgroup with **** p<0.0001.

No statistical differences were found in bleed incidences between Australia and Singapore (Table 25). In Australia, major bleed incidence per patient was not statistically different for patients with or without statins, but pravastatin was associated with a significantly higher incidence of major bleeds. In Singapore, incidence of bleeds was significantly lower for patients on any statin compared with no statin therapy for overall bleeds (0.030 versus 0.071, p = 0.0018) and major bleeds (0.008 versus 0.023, p = 0.0374). No significant effects on stroke risk or mortality were found (data not shown) but the overall incidence was low.

Table 25 - Number of events at the two study sites.

	Patients	All bleed events	Incidence per patient	Major bleed events	Incidence per patient
AUSTRALIA					
Entire Cohort	3196 (100%)	138	0.043	25	0.008
NO statin	1365 (42.7%)	54	0.040	10	0.007
Any Statin	1831 (57.3%)	84	0.046	15	0.008
Atorvastatin	977 (53.4%)	47	0.048	7	0.007
Simvastatin	354 (19.3%)	20	0.056	2	0.006
Pravastatin	106 (5.8%)	5	0.047	4	0.038 ##
Rosuvastatin	392 (21.4%)	12	0.031	2	0.005
Lovastatin	2 (0.1%)	0	0	0	0
SINGAPORE					
Entire Cohort	1170 (100%)	48	0.041	14	0.012
NO statin	311 (26.6%)	22	0.071 *	7	0.023 #
Any Statin	859 (73.4%)	26	0.030 **	7	0.008
Atorvastatin	188 (21.9%)	5	0.027	2	0.011
Simvastatin	588 (68.5%)	20	0.034	5	0.009
Pravastatin	5 (0.5%)	0	0	0	0
Rosuvastatin	31 (3.6%)	0	0	0	0
Lovastatin	47 (5.5%)	1	0.021	0	0

Data shown is number of events and incidence per patient for bleeds with and without statin therapy, and for each individual statin. Statistics shown are * overall bleed incidence for entire cohort compared to patients on statins in Singapore with $p < 0.05$, ** overall bleed incidence for patients on no statin compared to statin therapy in Singapore with $p < 0.01$, # major bleed incidence for patients on no statin compared to statin therapy in Singapore with $p < 0.05$, and ## major bleed incidence for patients on pravastatin compared to each subgroup in Australia with $p < 0.01$

Discussion

Despite the introduction of the new oral anticoagulants (direct thrombin inhibitors and factor Xa inhibitors), warfarin remains widely prescribed. Australia and Singapore have high rates of prescribing oral anticoagulants for stroke prevention [25] and in the Asia-Pacific region, Australia has the highest adjusted rate of warfarin use [447]. Warfarin is economical and well characterised but requires ongoing monitoring as many factors can influence response, including drug interactions [39]. Warfarin can potentially interact with around 250 different drugs through pharmacokinetic and/or pharmacodynamic interactions [1]. A full list of interactions can be found in resources such as the Australian Medicines Handbook [68] but cardiovascular drugs known to

interact with warfarin include amiodarone, fibrates, and statins. Statins and warfarin are amongst the most commonly prescribed prescription medications, and may be involved in both pharmacokinetic interactions and increased risk of adverse effects [463]. However, there have been conflicting reports on the risks associated with this combination, particularly regarding warfarin control and bleed risk. Therefore, the aim of this study was to determine the effect of long-term statin administration on warfarin TTR and bleed events in patients with AF in both Australia and Singapore. This study found that warfarin control, as measured by TTR, was not affected by concurrent long-term statin use. Statin use had no effect on bleeds in Australia whilst, in contrast, patients on statins had decreased incidence of bleeds in Singapore compared to patients not using statins.

The majority of patients at both sites were prescribed statins (57% in Australia, 73% in Singapore), with atorvastatin most frequently used in Australia and simvastatin in Singapore. The Australia results are similar to those reported by Gadzhanova and Roughead [464] who found 54% of elderly Australians treated with warfarin for AF were also prescribed a statin, with atorvastatin most frequent followed by simvastatin and rosuvastatin. Similarly, the higher statin use found in Singapore is consistent with Enas et al [465] who found South Asians to have higher rates of coronary artery disease due to dyslipidaemia. Pravastatin was the least commonly prescribed statin in Australia and Singapore, which is again consistent with Gadzhanova and Roughead [464] who found prescribing of pravastatin to be decreasing despite the lower potential for a drug interaction with warfarin. Furthermore, pravastatin use has

declined since the introduction of more potent statins with longer half-lives such as rosuvastatin and atorvastatin.

At both sites, the TTR of warfarin did not vary according to statin therapy or according to the individual statin prescribed. Similar to this, Shin et al [460] reported no significant difference in warfarin TTR among patients on four different statins. This is in contrast to Verhovsek et al [145] who found patients receiving interacting medicines such as simvastatin spent less time in therapeutic range. Other studies generally report effect on INR rather than TTR and they are conflicting. Jindal et al [466] reported no significant alteration of warfarin effect by rosuvastatin, whilst Yu et al [467] reported that INR increased significantly with rosuvastatin 40mg. Interestingly, van Rein et al [468] found immediate INR increases on statin initiation were insignificant and stratification of both INR and dose changes were similar between the different statins, although this was not with warfarin but other coumarin derivatives. Coumarin derivatives such as acenocoumarol or fenprocoumon are prescribed in some countries however in both Australia and Singapore warfarin is the only coumarin derivative used. Further to this, patients in this study in both Australia and Singapore had INR tests by the respective clinics and dose adjustments by physicians and did not utilise self-control methods including point-of-care testing which has the potential to influence frequency of dose changes. Our findings in this study were that the average weekly warfarin dose and number of warfarin dose changes were not significantly different in patients with or without statins. Previously, both Andrus [469] and Herman et al [470] found the limitation of described interactions with warfarin and statins was that the majority of data were only case reports. Further to this, Andrus

[469] suggested the interpatient variability in CYP enzyme activity may explain discrepancies in reports of warfarin and statins and clinicians should monitor INR closely after starting statin therapy. Our study investigated long-term control and found no effect on warfarin control by statin therapy, however further investigations may be required regarding the effects on warfarin when statin therapy is either commenced or ceased.

In Australia, bleed events showed no differences according to statin therapy. Similar to this, Leonard et al [471] found no association with increased serious bleeds when warfarin and statins were used concomitantly in a predominantly Caucasian population. Further to this in a Canadian population, Douketis et al [461] associated long-term (≥ 1 year) statin use with a decreased risk of bleeding on warfarin, but found no association between bleeding and recent statin use (≤ 6 months). Comparable to this, our study duration was six months and there was no increased bleeds with statins in Australia. Also similar to our study, Suh et al [472] found no significant change to bleed risk with warfarin and lipid lowering agents including statins taken on a long-term basis.

Hori et al [445] reported rates of total bleeding to be significantly higher in Asian patients compared to non-Asians. Barta et al [98] found TTR to be a predictor of clinically relevant bleed events, and further to this Rouaud et al [152] associated haemorrhagic events with low quality warfarin control. In our study, although not reaching significance, the incidence of major bleeds was higher in Singapore than in Australia and the lower TTR in Singapore compared to Australia may explain this higher incidence of major bleeds. Consistent with Chen et al [25], there was suboptimal

control in the Asian compared to Caucasian populations and genetic polymorphisms and differences in concomitant diseases may have been a contributing factor. However, in our study, despite differences in the frequency of co-morbidities, the median HAS-BLED scores were the same at both sites. However, at both sites the HAS-BLED scores were lower in the patients taking no statins but interestingly, only patients in Singapore that were on statins had a statistically lower bleed incidence than patients not on statins. This is similar to the previously mentioned findings by Douketis et al [461] associating warfarin and long-term statins with decreased bleeding. In an Asian population, Nadatani et al [473] demonstrated use of statins concurrently with aspirin had a tendency to decrease gastrointestinal bleeding. Although not specific to Asian populations, several authors [275, 474, 475] have previously found that patients receiving statins were less likely to have bleed events when used in combination with antiplatelet agents. Numerous co-prescribed medicines may affect bleed risk with warfarin including antiplatelets, non-steroidal inflammatory drugs, selective serotonin receptor inhibitors, and proton pump inhibitors [58]. In this study, bleed incidence and TTR may have been influenced by other potentially interacting medication so future studies assessing outcomes with warfarin and statins should adjust for all other potentially interacting medications.

Atar et al [476] found statins may exert a protective effect against gastrointestinal bleeding in patients with acute coronary syndrome with the proposed mechanism being that statins increase cyclooxygenase expression and prostaglandin release, with subsequent protective effects on gastrointestinal mucosa. Our study investigated overall bleed incidences and not specifically gastrointestinal bleeds, so additional

investigation is required into the specific locations of bleeding both with and without statins. It also remains unclear why the lowered bleed risk with statins was only in the Asian population. The genetic variants of CYP2C9 can directly increase the risk of warfarin bleeding [33] and variants are more common in Caucasian than Asians [44]. Further investigation into the particular influence of pharmacogenetics on the outcomes of warfarin and statins with regard to bleed risk may be beneficial in explaining the differences seen in the Asian population. Shin et al [460] assessed gastrointestinal bleeding among different statins in an Asian population but associated bleed risk with individual agents, finding rosuvastatin increased risk followed by atorvastatin, simvastatin, and pravastatin. In Singapore, overall bleed incidence was not statistically different across the individual statins. Both Andrus [469] and Guidoni et al [477] have found simvastatin to cause an increased risk of bleeding. Further to this, Schelleman et al [459] found simvastatin, atorvastatin, and fluvastatin was associated with an increased bleed risk while pravastatin was not. In contrast to this study, in Australia pravastatin had a statistically higher incidence of major bleeds compared to the other statins although patient numbers in this sub-group were relatively low. The retrospective nature of the study may have influenced the reported number of bleeds and limited access to more specific details surrounding bleed events, specifically data of influencing factors and INR at the time of the bleed. In addition, this study included self-reported bleed events and differences in the frequency of testing at the two sites may have influenced patient recall.

Conclusions

This study regarding the influence of long-term statins on warfarin control found no effect on warfarin control in either Australia or Singapore, as measured by TTR, testing frequency, warfarin dose and warfarin dose changes. Statin use did not affect bleed risk in Australia, whilst bleed incidence was lower in Singapore for patients on statins compared to no statins. Chronic concurrent administration of warfarin and statins is unlikely to affect warfarin control, however further investigation is still required especially regarding the lowered bleed incidence in the Asian population and the potential genetic influences on both statin and warfarin metabolism and outcomes.

Author Contributions: C.C. and S.A. conceived and designed the study; N.B. collected the data; N.B., T.B. and S.A. analyzed the data; N.B. wrote the paper; S.A., A.D., S.T. and J.C reviewed the paper; All authors approved the submitted version of the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

This chapter includes parts of a co-authored paper. The paper “Impact of aspirin on warfarin control as measured by time in therapeutic range” was published as a peer-reviewed paper in Basic & Clinical Pharmacology & Toxicology 2018 Oct; 123(4): 504-508. The authors of the paper are: Michelle Boyce, Alexa Zayac, Arie Davis, Tony Badrick, Shailendra Anoopkumar-Dukie, Nijole Bernaitis. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: collecting the data, providing direction on the scope and structure of the categorization of the data, and assisted with analysing the data. I wrote the first draft of introduction and discussion, made revisions responding to supervisor and co-authors comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

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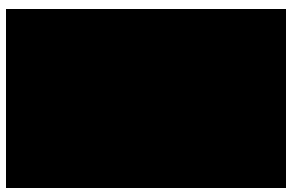
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(Date) 4/12/18

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Impact of aspirin on warfarin control as measured by time in therapeutic range

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Introduction

Warfarin is an oral anticoagulant widely prescribed for a variety of thromboembolic indications including venous thromboembolism (VTE), deep vein thrombosis (DVT), and the prevention of stroke associated for atrial fibrillation (AF) [14]. Warfarin requires ongoing monitoring of Internationalised Normalised Ratio (INR) due to a narrow therapeutic index and interactions with numerous drugs [478]. The time in therapeutic range (TTR) is often used to indicate the quality of warfarin therapy due to the established correlation between higher mean TTR and reduced complications such as bleeding and thromboembolism [110]. TTR is strongly associated with bleed risk but increased bleeding with warfarin has also been associated with patient comorbidities and concurrent administration of other medication linked to bleeding including anti-platelet agents and non-steroidal anti-inflammatories (NSAIDs) [94].

There is a high prevalence of patients on warfarin prescribed concurrent therapy with clinically relevant warfarin drug interactions [477]. Snaith et al [479] reported 68% of patients prescribed warfarin are issued a prescription for a potentially interacting drug, with long-term NSAIDs and low-dose aspirin prescribed to 21% and 17% of warfarinised patients respectively. Higher rates of concurrent warfarin and aspirin use of 30 - 40% were reported in the large comparative trials of warfarin and the non-vitamin K oral antagonists in patients with non-valvular AF [343-345]. Combination therapy with warfarin and antiplatelet agents may be indicated for specific subsets of patients with mechanical heart valve replacement and low bleed risk [480, 481]. However, Turan et al [482] reported the warfarin-aspirin combination being used inappropriately in around 21% of their AF patients on chronic warfarin therapy.

Similarly, Schaefer et al [483] found over one third of their patients are treated with warfarin together with aspirin for AF and/or VTE without a clear indication and associated this combination with a significant increase in major and non-major bleeding. Shireman et al [484] found that after adjusting for other risk factors, the combination of warfarin and antiplatelet therapy resulted in a 50% increased risk of a major bleed event.

An increased risk of bleeding from drug interactions with warfarin may occur due to additive effects, such as with aspirin or anti-platelet agents, or due to changes in warfarin absorption or metabolism [485]. The NSAIDs can have an antiplatelet action but selected NSAIDs including the cyclo-oxygenase-2 (COX-2) inhibitors can also alter warfarin levels through direct interaction with warfarin metabolism [486]. Hauta-Aho et al [273] demonstrated no change to INR values when the interacting drugs only affected platelet function but found significantly higher INR values in patients receiving inhibitors of cytochrome (CYP) 2C9. Similar to this, Choi et al [487] showed that almost 40% of patients on warfarin had an INR increase after initiation of a NSAID with the highest risk from meloxicam and lower risk from naproxen, celecoxib, and ibuprofen. In contrast, Turck et al [488] showed no significant change in INR with warfarin and meloxicam and similarly Dentali et al [489] found co-administration of celecoxib did not significantly affect warfarin control as measured by INR. Thus there is conflicting evidence on the effect of NSAIDs on warfarin control and the majority of literature available focusses on INR levels as opposed to overall control as measured by TTR. Therefore, the aim of this study was to determine the impact on warfarin control as

measured by TTR and bleeds by the co-administration of NSAIDs including aspirin and COX-2 inhibitors.

Methods

Griffith University Ethics approval was obtained PHM/09/14/HREC. A retrospective data analysis was conducted for patients enrolled at a private pathology practice in Queensland and receiving warfarin therapy for AF or DVT. Data collected included age, gender, current medications, co-morbidities, INR test results, reported thromboembolic events and bleeds. This information was used to group patients into those taking NSAIDs or not taking NSAIDs. The Australian Medicines Handbook [68] was utilised to identify concurrent medications that interact with warfarin and patients on these medications were excluded so patients on no other interacting drugs and taking NSAIDs or not taking NSAIDs were further analysed. Patients taking NSAIDs were further sub-categorised into groups taking aspirin, NSAIDs (excluding aspirin), COX-2 selective inhibitors (celecoxib and meloxicam), and NSAIDs (excluding COX-2 selective inhibitors and aspirin).

INR results were used to calculate TTR using the Rosendaal method [95] from the INR Pro© Patient Anticoagulation Software. In order to be eligible for the study, a minimum of two INR tests and 30 days of INR testing was required. HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile International Normalised Ratio or INR, Elderly > 65years, Drugs/alcohol concomitantly) score was calculated to assess bleed risk. Bleeds were categorized and calculated based on a per person basis and compared between the groups. Bleeding were

categorised in accordance with standardised definitions [416], namely : 1) major bleeding included bleeding into critical areas or major organs such as: gastrointestinal bleeding and included clinically relevant bleeds requiring diagnostic testing, any form of hospitalization, or intervention by a health care professional; 2) minor bleeding included bleeds such as nose bleeds that were not clinically relevant and required no intervention, no hospitalization or no medical attention. Mean and standard deviation were utilised to report age with number and percentages used for gender, co-morbidities, NSAID medications and bleed risk scores. Graph Pad InStat Version 3 (Graph Pad Software, Inc., La Jolla, CA, USA) was used to analyze the data with a p-value < 0.05 considered to be statistically significant. Patients on NSAIDs versus patients not on NSAIDs were compared using the Mann-Whitney Test. Patients that were not on NSAIDs versus individual NSAIDs were analyzed using the Kruskal-Wallis Test (Nonparametric ANOVA). Statistical significance was calculated for individual NSAIDs through Dunn's Multiple Comparisons Test. The Medcalc comparison of proportions calculator was used to compare minor bleeding and major bleeding of patients on NSAIDs to those not on NSAIDs.

Results

A total of 4494 patients were included in the study with the majority (70.6%) not taking NSAIDs (Figure 20). There was no statistical difference between the mean age of patients on NSAIDs (75.7 ± 10.5 years) and not on NSAIDs (76.2 ± 11.6 years) and approximately 70% of patients were between the ages of 70 - 89 years old (Table 26). There were approximately the same number of males and females in the study, with

the dominating comorbidity being atrial fibrillation followed by hypertension. The most commonly prescribed NSAID was aspirin (56.7%) followed by celecoxib (7.5%) and ibuprofen (7.3%).

Table 26 - Patient demographics for patient groups. Data shown is number and percentage.

	ALL PATIENTS (n=4494)		PATIENTS WITH ALL INTERACTING DRUGS EXCLUDED (n=1378)	
	Patients on NSAIDs (n=1322)	Patients not on NSAIDs (n=3172)	Patients on NSAIDs (n=313)	Patients not on NSAIDs (n=1065)
Gender				
Male	725 (54.8)	1572 (49.6)	188 (60.1)	572 (53.7)
Female	597 (45.2)	1600 (50.4)	125 (39.9)	493 (46.3)
Age				
<60 years	96 (7.3)	266 (8.4)	28 (8.9)	138 (13.0)
60-69 years	221 (16.7)	439 (13.8)	54 (17.3)	139 (13.1)
70-79 years	470 (35.6)	1027 (32.4)	108 (34.5)	317 (29.7)
80-89 years	460 (34.8)	1215 (38.3)	101 (32.3)	379 (35.6)
>=90 years	75 (5.7)	225 (7.1)	22 (7.0)	92 (8.6)
NSAIDs				
ASA	749 (56.7)		198 (63.3)	
ASA + NSAID	124 (9.4)		19 (6.1)	
Ibuprofen	96 (7.3)		25 (8.0)	
Celecoxib	99 (7.5)		20 (6.4)	
Meloxicam	69 (5.2)		15 (4.8)	
Diclofenac	79 (6.0)		14 (4.5)	
Naproxen	16 (1.2)		4 (1.3)	
Indomethacin	23 (1.7)		8 (2.6)	
Combo of NSAIDS	67 (5.1)		10 (3.2)	
Co-morbidities				
AF	1186 (89.7)	2769 (87.3)	264 (84.3)	873 (82.0)
DVT	194 (14.7)	494 (15.6)	67 (21.4)	214 (20.1)
HTN	484 (36.6)	1138 (35.9)	122 (39.0)	364 (34.2)
Diabetes	253 (19.1)	480 (15.1)	47 (15.0)	122 (11.5)
Hypercholesterolemia	78 (5.9)	198 (6.2)	13 (4.2)	59 (5.5)
Angina	36 (2.7)	61 (1.9)	7 (2.2)	17 (1.6)
HF	32 (2.4)	65 (2.0)	0 (0.0)	25 (2.3)
IHD	203 (15.4)	286 (9.0)	5 (1.6)	63 (5.9)
COPD	36 (2.7)	76 (2.4)	11 (3.5)	24 (2.3)
Asthma	85 (6.4)	173 (5.5)	14 (4.5)	43 (4.0)
Dyslipidemia	25 (1.9)	68 (2.1)	11 (3.5)	22 (2.1)
Cancer	36 (2.7)	66 (2.1)	9 (2.9)	21 (2.0)
Gout	76 (5.7)	126 (4.0)	16 (5.1)	39 (3.7)
GORD	157 (11.9)	261 (8.2)	29 (9.3)	72 (6.8)
Arthritis	158 (12.0)	320 (10.1)	84 (26.8)	275 (25.8)
Sleep Apnea	30 (2.3)	68 (2.1)	6 (1.9)	17 (1.6)
Renal Impairment	80 (6.1)	173 (5.5)	23 (7.3)	42 (3.9)
Hepatic Impairment	16 (1.2)	25 (0.8)	5 (1.6)	9 (0.8)
Anemia	20 (1.5)	35 (1.1)	4 (1.3)	7 (0.7)

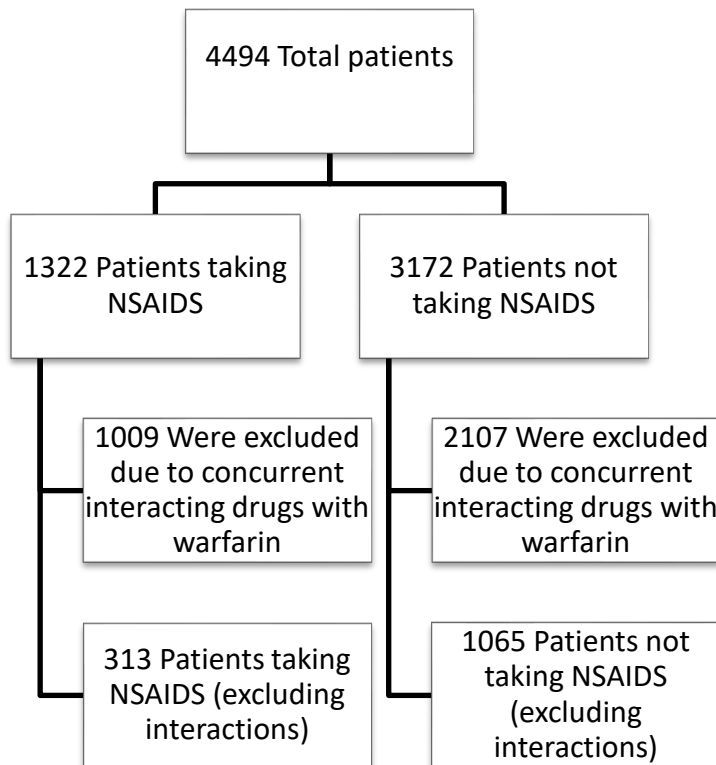


Figure 20 - Flow chart of patient groups

Before excluding interacting drugs with warfarin, there was a statistically significant difference in TTR for patients on NSAIDs compared to no NSAIDs ($78.9 \pm 9.7\%$ versus $80.9 \pm 10.2\%$ respectively, $p < 0.0001$). After excluding all interacting drugs with warfarin there was a significantly lower TTR ($p = 0.0080$) in patients taking NSAIDs ($80.2 \pm 10.3\%$) compared to those not taking NSAIDs ($82.0 \pm 11.2\%$) (Table 27). Patients taking aspirin alone had a significantly reduced ($p = 0.0488$) TTR of $80.4 \pm 10.3\%$ when compared to patients not taking NSAIDs ($82.0 \pm 11.2\%$). No significant difference was found in TTR when other groups of NSAIDs, including the COX-2 selective NSAIDs, were compared to TTR of patients not taking NSAIDs. No significant differences were found in the frequency of testing for patients on NSAIDs compared to no NSAIDs before or after excluding for interacting drugs (14.5 ± 4.5 vs 15.5 ± 5.1 days and 15.6 ± 4.7 vs 16.4 ± 5.4 days respectively).

Patients taking NSAIDs (excluding aspirin) had significantly more major and minor bleeding events than those not taking NSAIDs ($p = 0.0391$ and $p = 0.0359$ respectively). Compared to patients not taking NSAIDs, the use of aspirin alone significantly increased minor bleeding but had no significant difference in major bleed events. There was no significant difference in bleed events with the COX-2 selective NSAIDs.

Table 27 - Warfarin control and bleed events for patients not taking NSAIDs and taking NSAIDs with all drugs interacting with warfarin excluded.

	TTR %	P-value	Major Bleeding	P-value	Minor Bleeding	P-value	HAS-BLED
No NSAIDs (n=1065)	82.0 (11.2)		72 (6.8)		283 (26.6)		1 (1, 2)
NSAIDs (n=313)	80.2 (10.3)	0.0007	26 (8.3)	NS	102 (32.6)	0.0377	3 (2, 3)
Aspirin * (n=198)	80.4 (10.3)	0.0084	10 (5.1)	NS	70 (35.4)	0.0113	3 (2, 3)
NSAIDS * (excluding aspirin) (n=86)	80.6 (10.3)	NS	11 (12.8)	0.0391	14 (16.3)	0.0359	3 (2, 3)
COX-2 selective NSAIDS *† (n=35)	82.5 (8.5)	NS	4 (11.4)	NS	5 (14.3)	NS	3 (2, 3)
NSAIDs *†† (excluding COX-2 selective NSAIDS and aspirin) (n=51)	79.4 (11.2)	NS	7 (13.7)	NS	9 (17.6)	NS	2 (2, 3)

Data shown is number and percentage for major and minor bleeding, mean and standard deviation for TTR, median and interquartile range for HAS-BLED. $P < 0.05$ is considered statistically significant with NS not significant with comparisons made between patients on no NSAIDs and other categories. * Patients on any combination of NSAIDs were excluded from analysis.

†COX-2 selective inhibitors include celecoxib and meloxicam.

††COX-1/COX-2 non-selective inhibitors include diclofenac, ibuprofen, naproxen, and indomethacin.

Discussion

Several variables can affect warfarin control including patient specific factors such as concurrent medications. Concurrent medications may affect warfarin by increasing the risk of bleeding or interfering with warfarin metabolism, with some medication reported to do both such as selected NSAIDs. An increased risk of bleeding with NSAIDs has been reported but there is limited data on the effect on warfarin control, particularly as measured by TTR. The aim of this study was to determine the impact on warfarin control as measured by TTR by the concurrent administration of NSAIDs, particularly aspirin and COX-2 inhibitors. This study found aspirin significantly reduced TTR and was associated with an increase in minor bleeds, whilst the COX-2 inhibitors did not significantly affect TTR or events with warfarin.

Patients on any NSAIDs had significantly different TTRs than patients not on NSAIDs, however when categorised according to agent prescribed it was only patients on aspirin with significantly decreased TTR of around 2%. Similar to this, Williams et al [160] recently found aspirin to be a strong predictor of TTR and proposed predicting a decrease of around 5% TTR for newly initiated warfarin patients on aspirin.

Interestingly, Bernaitis et al [439] found antiplatelet agents reduced TTR in a Singapore population with poorer control (mean TTR 58%) but did not affect TTR in an Australian population with high control (mean TTR 82%). Further to this, Okumura et al [163] found TTR was not affected by co-administration of antiplatelet drugs in a Japanese population. The reduced TTR with aspirin is particularly noteworthy given the high level of warfarin control in this study, namely a mean above 80%. This study was conducted in a dedicated warfarin program which has been shown to have particularly

good warfarin control and levels above other management models, such as by general practitioners, which are more around the standard 70% TTR [490]. A limitation of this study is that subanalyses could not be performed in patients with good and poor control as only 13% of patients with no other interacting drugs had a TTR<70% (data not shown). However, a strength of this study compared to the previously mentioned two studies [163, 439] analysing TTR in patients on antiplatelet agents is that our study removed all other potentially interacting drugs and this could explain the difference in findings. Similarly, whilst studies have reported conflicting evidence regarding potentially no change [488, 489] or an increase in INR [487] with COX-2 inhibitors, in this study there was no change in TTR for patients taking COX-2 inhibitors. This study investigated long term control as measured by TTR and thus while changes in INR may have occurred the overall TTR may not have been affected with COX-2 inhibitors but was with aspirin alone. The groups of patients taking NSAIDs (excluding aspirin) and NSAIDs (excluding COX-2 selective NSAIDs and aspirin) did have reduced mean TTR of 80.6% and 79.4% respectively. Although this reduction in mean TTR was not statistically significant, possibly due to the small sample sizes of these groups, the difference may still be clinically meaningful and thus further study in larger populations is warranted. Further investigation of doses involved for both warfarin and the individual NSAIDs is warranted to determine the potential impact on doses and potential adjustments to warfarin which may have also impacted TTR in these patients.

There was a higher percentage of minor bleeding in patients who were on NSAIDs compared to those not on NSAIDs and when categorised according to NSAID involved,

aspirin alone significantly increased minor bleeding events. Similarly, Proietti and Lip [274] found that poor anticoagulation control (TTR < 65%) was associated with higher bleeding risk, which was even greater with concomitant aspirin use. In this study despite a high TTR of over 80%, aspirin users had a higher rate of minor bleeding and thus bleeds were less likely to be due to poor anticoagulant control but more likely to be due to additive effects with aspirin. Numerous studies have reported increased risk of major bleeding with warfarin and aspirin [483, 484]. Further to this, Battistella et al [491] demonstrated an increased risk of upper gastrointestinal bleeding with both selective COX-2 inhibitors and non-selective NSAIDs. In contrast to these findings, our study found no significant difference in major bleeds with aspirin alone or with the COX-2 inhibitors. Prostaglandin inhibition may be the main mechanism of damage to the upper gastrointestinal mucosa but other risk factors include older age, history of ulcer, or *Helicobacter pylori* infection [492] and lower doses of aspirin may have greater effects on thromboxane than prostaglandin inhibition [493]. Therefore it is likely that while NSAIDs decrease production of prostaglandins, including the GI protective ones, aspirin is debatably less likely to do this which may explain the non-significant difference in major bleed events seen with aspirin users and the significantly higher major bleeding seen with NSAIDs excluding aspirin. It was also unexpected that there was no increase in major bleeds with aspirin and NSAIDs given the HAS-BLED score of these patients was a median two points higher than those not on NSAIDs. The concurrent use of NSAIDs automatically adds one point to HAS-BLED but the median of 3 in patients taking NSAIDs and aspirin also suggests the presence of another co-morbidity that would place a patient at increased risk of bleeding which may contribute to explaining the increase in minor bleeds. However, the greatest

impact on these findings is the limitation that as with all retrospective studies bleeding was self-reported and detailed information was not provided for all events which may have impacted on the event number and categorisation. Future prospective investigations should include specific data on bleed location, INR at the time of bleed, and subsequent impact on TTR according to bleed events.

Conclusion

In conclusion, this study found that patients on aspirin had significantly reduced TTRs than patients not on aspirin with an associated increase in minor bleeds. Whilst previous studies have identified the concern regarding increased bleeds due to additive effects with warfarin, there may also be a decreased level of warfarin control as measured by TTR associated with concurrent aspirin use warranting further caution and monitoring of the combination.

Chapter Six – Efficacy of risk models recommended in AF guidelines to predict warfarin control in patients with AF in South-East Queensland and Singapore

Numerous guidelines for patients with AF recommend the use of risk models prior to commencement of oral anticoagulation including CHADS₂ and/or CHA₂DS₂-VASc to assess stroke risk [262-264, 296-300, 317-319] and HAS-BLED to assess bleed risk [263, 264, 296-300]. Further to this, some AF guidelines [262-264] suggest use of the SAME-TT₂R₂ score to assess likely warfarin control and assist in determining if warfarin is the most suitable oral anticoagulant. Early validations of the SAME-TT₂R₂ score were in Caucasian populations [241, 242, 250] thereby eliminating a key risk factor (R₂ = race and 2 points) identified in the model as a potential predictor of poor warfarin control. Therefore, the objective was to validate the model in a non-Caucasian population by applying the SAME-TT₂R₂ model to the Singaporean population. Results from this analysis is presented in the article “The Sex, Age, Medical History, Treatment, Tobacco Use, Race risk (SAME-TT₂R₂) score predicts warfarin control in a Singaporean population” (Journal of Stroke and Cerebrovascular Disease 2017 Jan; 26(1): 64-69) which was the second published study applying the SAME-TT₂R₂ score in an Asian population.

The SAME-TT₂R₂ has been suggested to be a predictor of warfarin control [159] but use of this model to predict warfarin control requires calculation of a score additional to stroke and bleed risk scores already calculated to assess suitability of oral anticoagulant therapy for patients AF. Studies had investigated the use of the CHADS₂ [185], CHA₂DS₂-VASc [178, 321] and HAS-BLED [323] scores to predict warfarin control

and therefore the objective was to determine the efficacy of these stroke and bleed risk models to predict warfarin control in South-East Queensland and Singapore. Data regarding the bleed risk model HAS-BLED is presented in the published article “A high HAS-BLED score identifies poor warfarin control in patients treated for non-valvular atrial fibrillation in Australia and Singapore” (Basic & Clinical Pharmacology & Toxicology 2017 Dec; 121(6): 499-504) which investigated HAS-BLED as a predictor of both warfarin control and incidence of bleeds. Investigation of the potential for the stroke risk scores CHADS₂ and CHA₂DS₂-VASc to predict warfarin control as compared to the bleed risk score HAS-BLED is then presented in the article “Identifying warfarin control with stroke and bleed risk scores” (Heart, Lung, Circulation 2018 June; 27(6): 756-759). Collectively these three articles address specific objective four of the thesis to determine the efficacy of commonly recommended risk models to predict warfarin control in patients with AF in South-East Queensland and Singapore.

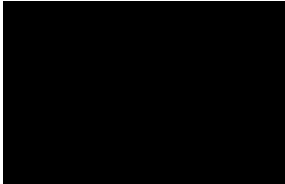
STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

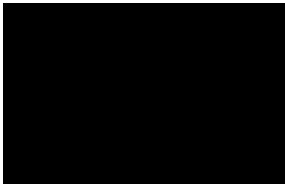
This chapter includes a co-authored paper. The paper “The SAME-TT₂R₂ risk score predicts warfarin control in a Singaporean population” was published as a peer-reviewed paper in the Journal of Stroke and Cerebrovascular Diseases 2017 Jan; 26(1): 64-69. The authors of the paper are: Nijole Bernaitis, Chi Keong Ching, Liping Chen, Jin Shing Hon, Siew Chong Teo, Andrew K Davey, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: designing and conducting the study, collecting the data at both sites, providing direction on the scope and structure of the analysis, categorising and analysing the data. I wrote the first draft, made revisions responding to supervisor & co-authors comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

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The SAME-TT₂R₂ risk score predicts warfarin control in a Singaporean population

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Abstract

Background

Warfarin reduces stroke risk in atrial fibrillation patients but requires ongoing monitoring. Time in therapeutic range (TTR) is used as a measure warfarin control with a TTR < 60% associated with adverse patient outcomes. The SAME-TT₂R₂ (Sex, Age, Medical history, Treatment, Tobacco use, Race) score has been identified as a model able to predict warfarin control but this has been tested in mainly Caucasian populations. Therefore, the aim of this study was to determine the ability of the SAME-TT₂R₂ score to predict warfarin control in a Singaporean population consisting of Chinese, Malay, and Indian race.

Method

Retrospective data was collected from the National Heart Centre Singapore for atrial fibrillation (AF) patients receiving warfarin between January and June 2014. The TTR and SAME-TT₂R₂ score was calculated for each patient.

Results

The 1137 non-valvular AF patients had a mean TTR of $58.0 \pm 34.3\%$ and a median SAME-TT₂R₂ score of 3. The categorised SAME-TT₂R₂ scores (2 vs > 2) showed a significant reduction in mean TTR for the entire population (63.2% vs 55.8%, $p = 0.0004$) and also when categorised according to race for Chinese (62.7% vs 56.9%, $p = 0.0075$) and Malay (68.4% vs 50.6%, $p = 0.0131$) populations.

Conclusion

The SAME-TT₂R₂ tool is effective in predicting warfarin control in a Singaporean population as patients with a score > 2 had poor control. The minimum score for non-

Caucasian patients is 2 thus in these patients the presence of any additional risk factors identified in the SAME-TT₂R₂ tool categorises them as unlikely to achieve adequate warfarin control and possible candidates for alternative anticoagulants.

Introduction

Oral anticoagulants decrease the risk of stroke in atrial fibrillation patients [452]. Vitamin K antagonists (VKA) such as warfarin have been the only anticoagulant option for decades but recently alternative agents targeting thrombin (dabigatran) or Factor Xa (rivaroxaban, apixaban) have provided practitioners with a greater choice of anticoagulants [391]. Studies comparing the newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) to warfarin found them at least as effective in preventing stroke but associated with less intracranial bleeding [494]. However the net benefit of these agents is dependent on the quality of anticoagulation with warfarin and is greater in situations when warfarin control is poor [347]. Recently Shah and Gage [435] demonstrated that warfarin was cost-effective compared to dabigatran unless the quality of international normalised ratio control was low, as measured by a time in therapeutic range (TTR) of < 57%. TTR is an important tool in evaluating the quality of warfarin treatment [81] with poor warfarin control (TTR < 60%) associated with increased mortality and adverse patient outcomes [100]. Recent international guidelines acknowledge the need to improve the quality of warfarin control and recommend efforts to achieve high TTR of > 70% [495]. Thus patient suitability for warfarin should be assessed based on the ability to achieve good control [104] and is an important factor in considering use of warfarin over other

anticoagulants [368]. Because of this, a scheme to predict the potential warfarin TTR for an individual would be beneficial in the decision making process.

In 2013, Apostolakis et al [159] proposed the SAME-TT₂R₂ (Sex female, Age < 60 years, Medical history [more than two co-morbidities], treatment [interacting drugs eg amiodarone], tobacco use [doubled], race [doubled]) (Table 4) scheme to predict control on VKA and identify those patients likely to do well on VKA (SAME-TT₂R₂ = 0 - 1) or those requiring additional intervention to achieve acceptable control (SAME-TT₂R₂ ≥ 2). Validations of the SAME-TT₂R₂ score have largely been studied in Caucasian populations demonstrating it to be a good predictor of TTR [241, 242, 250]. By comparison there is a scarcity of information looking at the ability of the SAME-TT₂R₂ to predict control in non-Caucasian populations, a key SAME-TT₂R₂ risk factor identified by the model. To our knowledge only a single application of the SAME-TT₂R₂ score in Chinese patients has demonstrated poorer TTRs at high SAME-TT₂R₂ scores [244]. However the overall population TTR in this was a low 38% [244], well below the minimum recommended 60% [81] or international guidelines of 70% [100] and may therefore not be the ideal application for a risk predictor model. Therefore, the aim of this study was to determine the ability of the SAME-TT₂R₂ score to predict different levels of anticoagulation control in a non-Caucasian population with an overall TTR close to the minimum recommendation of 60%. To achieve this we applied the SAME-TT₂R₂ model to a Singaporean population consisting of Chinese, Indian and Malay race to identify if the model could sufficiently predict poor control.

Methods

Patients receiving warfarin from the National Heart Centre Singapore between January 2014 and June 2014 were retrospectively identified. Patient records were assessed and those with non-valvular atrial fibrillation (AF) identified by excluding patients with valve replacement, mitral stenosis, or mitral valve repair. Further exclusions were insufficient Internationalised Normalised Ratio (INR) results to calculate TTR (i.e. less than two results) in the time period, less than thirty days treatment with warfarin, or non-Asian race.

Medical history and base clinical characteristics were recorded for each patient together with concurrent medications and social history (i.e. tobacco and alcohol use). The race identified in the medical notes was recorded for each patient. The available INR measurements were collected and used to calculate the TTR via the Rosendaal method [95]. Data on complications including thromboembolic and bleeding events was gathered from the medical records. Ethical approval was granted by the SingHealth Centralised Institutional Review Board (CIRB 2015/2435) and Griffith University Human Research Ethics Committee (PHM/08/15/HREC).

The SAME-TT₂R₂ score [159] was applied to the eligible patients with the score calculated as the sum of the points previously described. Stroke and bleeding risk was calculated using the CHA₂DS₂-VASc and HAS-BLED score respectively.

Statistical Analysis

Statistical analysis was performed on GraphPad InStat Version 3 (GraphPad Software, Inc, La Jolla, CA, USA) and graphing performed with GraphPad Prism 6. Time in therapeutic range was calculated using Rosendaal's linear interpolation algorithm [95]

with software downloaded from INR Pro®. Comparisons were made using ordinary ANOVA via nonparametric methods including Kruskal-Wallis test and Dunn's multiple comparisons test. Continuous variables are presented as means and standard deviations or median (interquartile range) and categorical variables as a number and percentages.

Results

Of the 3122 patients dispensed warfarin, there were 2035 AF patients but a total of 865 of these were excluded from the study due to valve replacement (n = 259), mitral stenosis (n = 329), mitral valve repair (n = 17), being of non-Asian race (n = 33), insufficient INR tests (n = 195) or less than thirty days of warfarin treatment (n = 65). Of the 1137 non-valvular AF patients eligible for the study, there were 689 (60.6%) males, 977 (85.9%) Chinese patients, and median age was 71 years with other baseline characteristics outlined in Table 28. The median CHA₂DS₂-VASc score was 3 (IQR 2-4) and the median HAS-BLED was 1 (IQR 1-4). The median SAME-TT₂R₂ score was 3 with 339 (29.8%) patients with a score of 2 and the remaining 798 (70.2%) patients with a score > 2 (Table 29). The mean TTR was 58.0 ± 34.3% with no significant difference between male (mean 59.2 ± 34.7%) and female (56.1 ± 33.4%) patients. Chinese patients had a mean TTR of 58.7 ± 34.3%, Malay patients a mean TTR of 55.2 ± 33.7%, and Indian patients 49.7 ± 32.8%.

Table 28 - Clinical Characteristics of Patients (n=1137).

Gender	
Male (%)	689 (60.6%)
Female (%)	448 (39.4%)
Age	
Median (IQR)	71 (63-77)
Age < 60years	172 (15.1%)
Ethnicity	
Chinese	977 (85.9%)
Indian	44 (3.9%)
Malay	116 (10.2%)
Past Medical History	
Hypertension	677 (59.5%)
Diabetes Mellitus	343 (30.2%)
Heart Failure	88 (7.7%)
Previous Stroke/TIA	45 (4.0%)
Hepatic Impairment	7 (0.6%)
Renal Impairment	156 (13.7%)
Coronary Artery Disease	271 (23.8%)
Social History	
Current Smoking habit	84 (7.4%)
Concomitant Treatment	
Amiodarone	78 (6.9%)
Beta-blockers	739 (65.0%)
Antiplatelet therapy	287 (25.2%)
Predictor Models	
CHA ₂ DS ₂ -VASc Score, median (IQR)	3 (2-4)
HAS-BLED Score, median (IQR)	1 (1-4)
SAME-TT ₂ R ₂ Score, median (IQR)	3 (2-3)
Warfarin Treatment in study period	
Duration in days, mean (SD)	112.5 (35.5)
INR tests, mean (SD)	5.62 (6.2)

The mean TTR in relation to the SAME-TT₂R₂ score is shown in Table 28 for all patients and according to race. The categorised SAME-TT₂R₂ scores (2 vs > 2) had a significant decline in mean TTR for the entire population (63.2% vs 55.8%, p = 0.0004) and for both Chinese (62.7% vs 56.9%, p = 0.0075) and Malay (68.4% vs 50.6%, p = 0.0131) populations as seen in Table 28.

Table 29 - Time in therapeutic range (TTR) in relation to the SAME-TT₂R₂ score.

	ALL PATIENTS		CHINESE		MALAY		INDIAN	
SAME-TT ₂ R ₂	Patients	TTR mean (SD)	Patients	TTR mean (SD)	Patients	TTR mean (SD)	Patients	TTR mean (SD)
0-1	0		0		0			
2	339	63.2 (34.1)	297	62.7 (34.5)	30	68.4 (30.7)	12	60.8 (31.9)
3	517	57.3 (34.0)	451	57.7 (33.9)	48	56.1 (35.1)	18	49.9 (34.1)
4	210	54.3 (34.7)	178	56.5 (35.3)	24	41.1 (30.3)	9	38.6 (27.3)
5	56	51.0 (32.1)	40	52.8 (32.2)	11	57.2 (29.0)	4	28.4 (28.8)
6-7	15	43.4 (33.4)	11	46.1 (30.6)	3	14.8 (16.5)	1	100 (0)
Categorised SAME-TT ₂ R ₂								
0-1	0		0		0		0	
2	339	63.2 (34.1)	297	62.7 (34.5)	30	68.4 (30.7)	12	60.8 (31.9)
> 2	798	55.8 (34.1)	680	56.9 (34.1)	86	50.62 (33.6)	32	45.6 (32.7)
P value score 2 vs >2		0.0004		0.0075		0.0131		0.1581

Discussion

Warfarin remains a widely prescribed anticoagulant but the efficacy and safety is largely dependent on the TTR. Evidence suggests greater stroke prevention with good quality warfarin control and recent international guidelines have endorsed efforts to achieve high individual TTRs of > 70% [495]. Therefore a tool able to predict patients likely to achieve a high TTR with warfarin would be extremely beneficial. The SAME-TT₂R₂ score was proposed by Apostolakis et al [159] to assess patient related parameters and predict the likelihood of poor warfarin control among patients with AF. Several recent applications have demonstrated good discriminatory capacity in prediction of TTR in Caucasian populations [240] however, to date there is very limited data of the SAME-TT₂R₂ score in non-Caucasian patients with only one study in a

Chinese population with a low overall TTR of 38% [244]. Therefore, the aim of our study was to apply the SAME-TT₂R₂ score to a Singaporean population and determine the predictive ability of the tool in patients of Chinese, Indian, and Malay race. This retrospective application of the SAME-TT₂R₂ score demonstrated it to be a good predictor of anticoagulation control as reflected by TTR with the categorised score of 2 equating to borderline control (TTR > 60%) and patients with a score > 2 showing poor control.

Previous studies have shown that warfarin metabolism is influenced by age, certain diseases and medications, plus ethnic background [37]. Interethnic differences in warfarin requirements have been reported between African Americans, European Americans and between different Asian ethnic groups [38]. Many Asian countries record suboptimal TTR values leading to high stroke rates and increased risk of bleeding [449, 496]. The comparative studies of warfarin to the newer oral anticoagulants demonstrated an overall higher TTR in non-Asians (55.2 - 68.9% TTR) compared to Asians (52.4 - 60% TTR) [386]. The overall mean TTR in our Asian population was 58.0% which was comparable to the TTR achieved by Asian populations in these large studies [386]. A minimum TTR target threshold of at least 60% is recommended to ensure benefit from warfarin [330] although current European guidelines recommend efforts to achieve good control of > 70% [495]. The mean TTR of 58.0% for our population was below the minimum target of 60%. Interestingly, when categorised according to SAME-TT₂R₂ score the mean TTR for patients with a score of 2 was 63.2% whilst patients with a score > 2 had a significantly reduced TTR of

55.8%. Thus the SAME-TT₂R₂ score was able to predict those likely to achieve the minimum target TTR of 60% and those likely to achieve poor control.

Suboptimal control in Asian populations may reflect genetic polymorphisms influencing warfarin metabolism [25]. Analyses of the comparative trial of warfarin and dabigatran demonstrated variations in mean TTR according to country with Singapore at 68%, Malaysia 57%, China 55%, and India 49% [366]. Our mean TTR according to race was similar to these figures with a TTR for Chinese patients 58.7%, Malay patients 55.2%, and Indian patients 49.7%. Furthermore over each of these races the SAME-TT₂R₂ score was able to predict a TTR > 60% for patients with a score of 2. The TTR appeared to decline with an increase in SAME-TT₂R₂ score however larger populations with SAME-TT₂R₂ scores of > 6 are needed to confirm this. Larger numbers are also required in the Indian subgroup.

Various independent applications the SAME-TT₂R₂ tool has demonstrated capacity to predict patients with good control [240]. However the mean TTR of previous cohorts has ranged from 64% [250] to 78% [242] whereas our population had a lower mean of 58%. Poli et al [241] recommended investigating the discriminatory value of the SAME-TT₂R₂ score in patient cohorts with an overall lower centre TTR. Chan et al [244] applied the SAME-TT₂R₂ score to a Chinese population demonstrating TTR decreased with an increase in SAME-TT₂R₂ score. However the mean TTR in this population was well below the recommended minimum and hence may not be a good indicator of the discriminatory ability to predict patients able to achieve good control. Our study has demonstrated predictive value of the SAME-TT₂R₂ score in a Singaporean cohort with a higher overall mean TTR of 58% and further demonstrated that this was maintained

when analysed according to Chinese, Indian, and Malay race. The SAME-TT₂R₂ score assigns two points to non-Caucasian race and thus our population had a minimum score of 2 with a high percentage (70.2%) of patients categorised into the subgroup > 2. Whilst Chan et al [244] had 82% of Chinese patients in the subgroup > 2, in contrast, the majority of previous validations have had relatively low proportion of patients achieving a SAME-TT₂R₂ score > 2 with percentages of 22% [242] and 16% [241] reported in similar sized cohorts. There is concern some factors, particularly tobacco use and non-White race, may be misrepresented in particular settings [257]. In a non-Caucasian population the minimum SAME-TT₂R₂ score is 2 and any other contributing factors raises this to > 2 and thus predicts suboptimal control and suggests warfarin would not be a good choice of anticoagulant for non-Caucasian patients with other risk factors.

Despite the variability of TTR for patients treated in Asian countries it has been suggested that medical care practices and not race determines anticoagulant control [376]. Suboptimal warfarin control may be due to a lack of a structured anticoagulation monitoring service [449]. In addition the low TTR may reflect low treatment adherence and/or compliance to warfarin regimes. Adherence and compliance would alter the effectiveness of any anticoagulant and hence it is unknown whether the SAME-TT₂R₂ score could predict that an alternate anticoagulant would indeed perform better [257]. One limitation of this study is the retrospective design and inability to determine if these patients would perform better on an alternate anticoagulant. Further investigation would be beneficial to address this and other potential impacting factors such as compliance on anticoagulation.

In conclusion our findings demonstrate that the SAME-TT₂R₂ tool is effective in predicting warfarin control in a Singaporean population. When categorised into SAME-TT₂R₂ scores, non-Caucasian patients with a score of 2 achieved adequate control (TTR > 60%) whilst those with a score > 2 had poor control. Thus non-Caucasian patients with any additional risk factors identified in the SAME-TT₂R₂ tool are unlikely to achieve adequate warfarin control and may be candidates for alternative oral anticoagulants.

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STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

This chapter includes parts of a co-authored paper. The paper “A high HASBLED score identifies poor warfarin control in patients treated for non-valvular atrial fibrillation in Australia and Singapore” was published as a peer-reviewed paper in Basic & Clinical Pharmacology & Toxicology 2017 Dec; 121(6): 499-504. The authors of the paper are: Nijole Bernaitis, Chi Keong Ching, Liping Chen, Jin Shing Hon, Siew Chong Teo, Tony Badrick, Andrew K Davey, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: collecting the data, providing direction on the scope and structure of the analysis, categorising and analysing the data, graphical representation of the data. I wrote the first draft, made revisions responding to supervisor and co-authors comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

(Signed)  (Date) 4/12/18

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A high HASBLED score identifies poor warfarin control in patients treated for non-valvular atrial fibrillation in Australia and Singapore

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Abstract

Warfarin reduces stroke risk in atrial fibrillation (AF) patients. The quality of warfarin control, measured by time in therapeutic range (TTR), impacts outcomes and adverse events. One tool evaluating risk of adverse events and potential warfarin control would simplify risk-benefit assessment of warfarin. Recently HAS-BLED was demonstrated effective for this purpose, but this was in well-controlled patients with deep vein thrombosis. HAS-BLED as a predictor of warfarin control has not been validated in other populations including differing indications, warfarin control levels, and ethnicities. The aim of this study was to determine if HAS-BLED can predict warfarin control in patients with AF in Australia and Singapore.

Retrospective data was collected for patients receiving warfarin between January and June 2014 in Australia and Singapore. Patient data was used to calculate HAS-BLED at the start and end of the study period. TTR was calculated for each patient, and mean TTR used for analysis to stratified HAS-BLED scores.

Of the 4370 patients, there were 3199 in Australia and 1171 in Singapore with mean TTRs of 82% and 58% respectively. At the start of the study, a HAS-BLED score ≥ 3 predicted significantly lower TTR in Singapore, whilst at the end of the study, this score identified patients with poor control in both Australia and Singapore.

A HAS-BLED score ≥ 3 in patients treated with warfarin can differentiate significantly lower TTRs in Australian and Singapore patients with AF. HAS-BLED may assess bleed risk and warfarin control, identifying patients at high risk of poor warfarin outcomes requiring additional INR monitoring or alternative anticoagulation.

Introduction

Anticoagulant therapy such as warfarin can effectively reduce the risk of ischaemic stroke in patients with atrial fibrillation (AF) [278]. Poor warfarin control is associated with complications including bleeds and thrombotic events [79]. The risk of these events is influenced by a number of patient factors including age, co-morbidities, and concurrent medications [64]. Some of these factors associated with an increased risk of adverse effects have been incorporated into risk predictor models. HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile International Normalised Ratio or INR, Elderly > 65years, Drugs/alcohol concomitantly) was proposed from the Euro Heart Survey population of patients with AF to assess the individual one year risk of major bleeding and assigns one point to each of the listed factors with the exception of abnormal renal/liver function and drugs/alcohol which may receive up to two points [286]. The calculated score ranges from 0 to 9 but patients are generally categorised as low-, intermediate-, or high-risk of bleeding based on scores of 0 - 1, 2, or ≥ 3 respectively [497]. HAS-BLED has been validated to provide accurate stratification of patients based on bleed risk and has the benefit of simplicity of application [292, 293]. Several international guidelines for patients with AF recommend HAS-BLED to conduct a formal assessment of bleed risk prior to the commencement of anticoagulant therapy [495, 498, 499].

The HAS-BLED model assigns one point to labile INRs, a measure indicative of poor anticoagulant control in patients taking a vitamin K antagonist such as warfarin [294]. Percentage of INRs in range can predict adverse events such as bleeding but a more accurate measure of control and outcomes is time in therapeutic range (TTR) [109]. A

strong relationship exists between TTR and both bleeding and thromboembolic events [97]. Increased warfarin control or TTR improves the safety and efficacy of warfarin and patients may not benefit from warfarin unless a certain level of control is achieved [325]. In 2013, Apostolakis et al [159] proposed a model to predict control with vitamin K antagonists, namely SAME-TT₂R₂ (Sex female, Age < 60 years, Medical history [more than two co-morbidities], treatment [interacting drugs e.g. amiodarone], tobacco use, race). In this model one point is assigned to each of the factors with the exception of race and tobacco which receive two points, and an overall score of ≥ 2 identifies patients as requiring additional intervention to achieve acceptable warfarin control [159]. The SAME-TT₂R₂ model specifically incorporates race as a factor known to influence warfarin control and it has been demonstrated to be a good predictor of control in both Caucasian [241, 242] and Asian [244, 425] patients with AF. The disadvantage to this model is the need to calculate an additional score to the already calculated bleed and stroke risk scores in patients with AF. Use of existing bleed risk scores such as HAS-BLED to predict warfarin control would simplify assessment of patients prior to commencement of anticoagulant therapy and potentially assist in selection of agents.

In 2017, Mueller et al [323] proposed that the existing HAS-BLED tool may be used to predict warfarin control and, specifically, patients with a HAS-BLED score ≥ 3 may be classified as high risk of poor warfarin control. However this study was in well controlled warfarin patients receiving warfarin for deep vein thrombosis in a predominantly Caucasian population [323]. It is unknown how effectively HAS-BLED can predict control outside this group, including in patients achieving poorer warfarin

control, of differing ethnicity, and with different indications such as AF. Therefore, the aim of this study was to determine if HAS-BLED could be used to predict warfarin control in patients with non-valvular AF (NVAf) in both Caucasian and Asian populations, namely Australia and Singapore.

Methods

Study Design

A retrospective analysis was conducted for patients treated with warfarin for NVAf for the period of January to June 2014 at two sites, one in Australia and one in Singapore. During the study period, data was collected in Australia for patients enrolled in the Warfarin Care program at Sullivan Nicolaides Pathology, Queensland, and in Singapore for patients dispensed warfarin at The National Heart Centre Singapore. Data collected included INR test date and results, INR target ranges, age, gender, co-morbidities, and concurrent medications. Adverse bleeding events were recorded which had been reported to the clinics either via self-reporting from patients, e.g. nose bleeds, excessive bleeding from cuts, or from other health professionals, e.g. hospital admission due to bleed. Bleed events were defined as either major events i.e. requiring medical intervention, hospitalisation, or discontinuation of warfarin, and all other events such as self-limiting nose bleeds defined as minor. Patients with mitral stenosis, valve replacement and/or valve repair were excluded from the study. Patients were also excluded if they had received less than 30 days of warfarin treatment or had insufficient tests to calculate INR, i.e. less than two tests. 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).

Data and Statistical Analysis

TTR was calculated for each patient using Rosendaal's linear interpolation algorithm with software downloaded from www.inrpro.com. The HAS-BLED risk score was calculated from patient characteristics as of the start of the study period, e.g. age as of 1 January 2014. Labile INRs were not included in this score but an additional HAS-BLED score was calculated at the end of the study period with a point assigned to labile INRs. Patients were categorised as low (0 - 1 points), moderate (2 points), or high risk (≥ 3 points) according to the total HAS-BLED score. Bleeding events were calculated as events per patient and applied to risk categories. Patient characteristics were reported as number and percentage for categorical data and mean \pm standard deviation for continuous data. Mean TTR was used for comparison across risk categories. Comparisons were made using ordinary analysis of variance through non-parametric methods, including Kruskal-Wallis test and Dunn's multiple comparisons test. Data were analysed using GraphPad InStat version 3 and figures drawn using GraphPad Prism version 6.0. Significance was defined as * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

Results

A total of 4370 patients with NVAf were included in the study with 3199 patients in Australia and 1171 in Singapore following exclusions for valvular AF (276 Australia, 605 Singapore) or insufficient INR tests in study period (44 Australia, 259 Singapore). In

total, there were 2380 (54.5%) male and 1990 (45.5%) female patients (Table 30).

There were 3730 (85.4%) patients over 65 years with the mean age of patients 77.2 ± 9.1 years in Australia and 69.7 ± 10.0 years in Singapore.

Table 30 - Patient demographics, warfarin control, bleed events, and HAS-BLED scores at the Australian and Singapore sites.

	Australia	Singapore
Number of Patients	3199	1171
Gender		
Male	1673 (52.3%)	707 (60.4%)
Female	1526 (47.7%)	464 (39.6%)
Age mean (SD) years	77.2 (9.1)	69.7 (10.0)
Age > 65 years	2912 (91.0%)	818 (69.9%)
Medical History		
Hypertension	1185 (37.0%)	698 (59.6%)
Abnormal renal function	149 (4.7%)	164 (14.0%)
Abnormal liver function	11 (0.3%)	7 (0.6%)
Stroke/TIA history	487 (15.2%)	46 (3.9%)
Warfarin control, mean (SD)		
TTR	82.3 (15.6)	57.7 (34.2)
Number of test per patient	11.2 (5.6)	5.6 (6.2)
Bleed events		
Minor	113 (0.035)	34 (0.029)
Major	26 (0.008)	14 (0.012)
Total bleeds per patient	139 (0.043)	48 (0.041)
HAS-BLED score Start of Study Period		
Median (IQR)	1 (0-5)	1 (0-4)
0 - 1	1624 (50.8%)	699 (59.7%)
2	1159 (36.2%)	401 (34.2%)
≥ 3	416 (13.0%)	71 (6.1%)
HAS-BLED score End of Study Period		
Median (IQR)		
0 - 1	1442 (45.1%)	431 (36.8%)
2	1160 (36.3%)	455 (38.9%)
≥ 3	597 (18.6%)	285 (24.3%)

Data shown is number and percentage for number of patients, gender, medical history, and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history, Labile International Normalised Ratio or INR, Elderly>65years, Drugs/alcohol concomitantly) score. Mean and standard deviation is also shown for age and warfarin control with median (IQR) shown for HASBLED scores.

The mean TTR was $82.3 \pm 15.6\%$ in Australia and $57.7 \pm 34.2\%$ in Singapore, which was significantly different ($P < 0.001$). The mean number of tests per patient was significantly different between the two sites with 11.2 ± 5.6 Australia vs 5.6 ± 6.2 Singapore, $p < 0.0001$. There were a total of 187 bleeding events reported across the two study sites with 147 (78.6%) classified as minor. The overall incidence of bleed

events per patient was 0.043 in Australia and 0.041 in Singapore. According to HAS-BLED category the incidence of bleeds in the low-, moderate- and high-risk groups were 0.033, 0.051, and 0.054 respectively in Australia and 0.030, 0.053, and 0.039 respectively in Singapore (Figure 21). The incidence of major bleeds was 0.008 in Australia and 0.012 in Singapore with the incidence of major bleeds in the low-, moderate- and high-risk groups 0.003, 0.011, and 0.015 respectively in Australia, and 0.000, 0.018, and 0.021 respectively in Singapore.

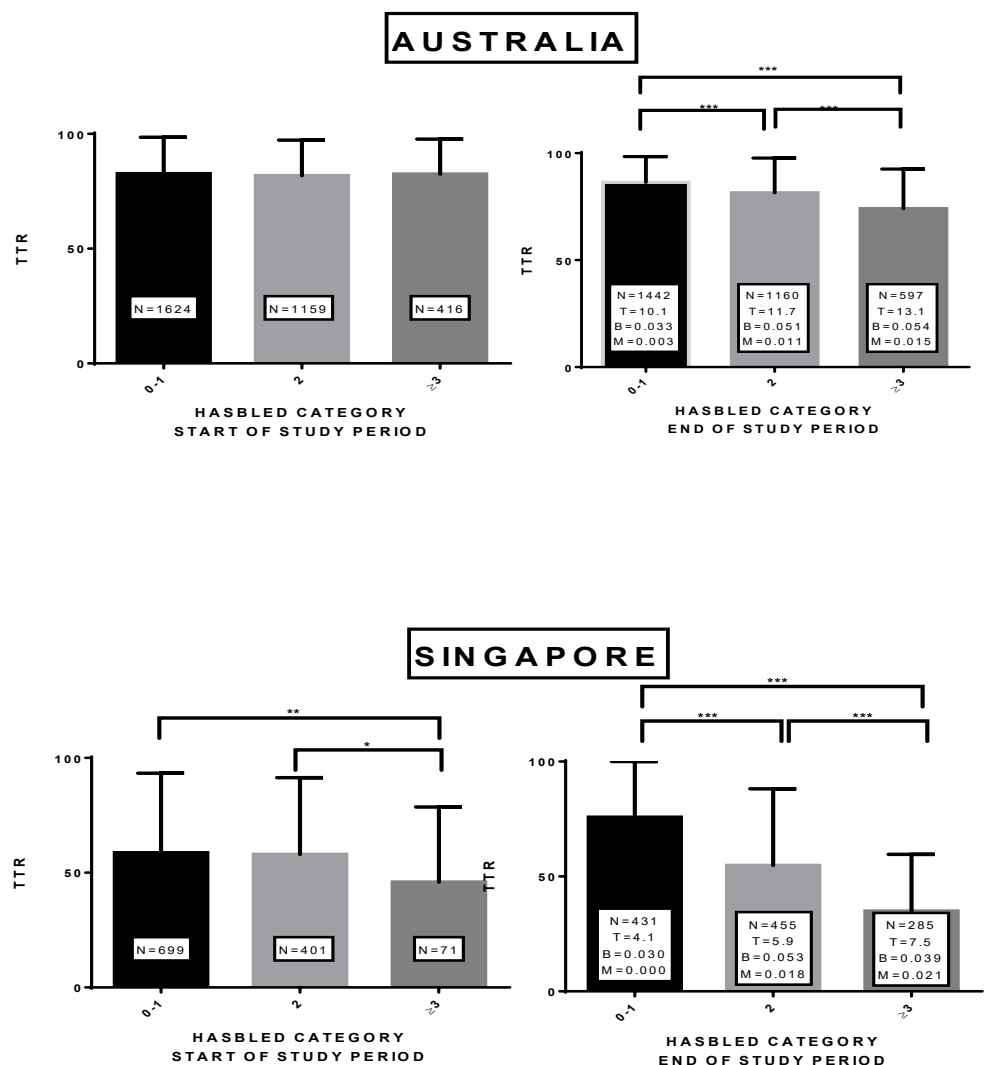


Figure 21 - TTR according to HAS-BLED Category at start and end of the six month study period for both sites, i.e. Australia and Singapore. TTR for each category is mean and standard deviation with statistical differences represented as * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$. N=number of patients, T=mean number of tests per patient, B=number of bleed events per patient, and M=major bleed events per patient.

The median HAS-BLED score at both sites was 1 at the start of the study. At this time, according to HAS-BLED score, 2323 (1624 Australia, 699 Singapore) patients were classified as low risk, 1560 (1159 Australia, 401 Singapore) moderate risk, and 487 (416 Australia, 71 Singapore) high risk. The mean TTR according to HAS-BLED category resulted in no significant differences at the Australian site between the low-, moderate-, or high-risk categories with all around 82% (Figure 21). At the Singapore site the mean TTR according to low-, moderate-, and high-risk categories was $58.7 \pm 34.6\%$, $58.0 \pm 33.4\%$, and $45.9 \pm 32.7\%$ respectively, with significant differences in TTR found between the low- and high-risk categories ($p < 0.01$) and between the moderate- and high-risk categories ($p < 0.05$).

At the end of the study, the median HAS-BLED at both sites was 2 with 1873 (1442 Australia, 431 Singapore) patients classified as low risk, 1615 (1160 Australia, 455 Singapore) moderate risk, and 882 (597 Australia, 285 Singapore) high risk. Application of this HAS-BLED score to mean TTR resulted in significant differences ($p < 0.001$) at both sites between all risk categories. At the Australian site the mean TTR for the low-, moderate- and high-risk categories was $86.4 \pm 12.0\%$, $81.5 \pm 16.2\%$, and $74.1 \pm 18.5\%$ respectively, whilst at the Singapore site the mean TTR for these categories was $75.8 \pm 30.4\%$, $54.8 \pm 33.3\%$, and $34.9 \pm 24.8\%$ respectively. The mean number of tests per patient according to low-, moderate- and high-risk HAS-BLED category differed significantly ($p < 0.001$) between each category at both sites with 10.1 ± 4.5 , 11.7 ± 6.1 , and 13.1 ± 6.3 tests respectively in Australia and 4.1 ± 4.1 , 5.9 ± 5.6 , and 7.5 ± 8.9 tests respectively in Singapore.

Discussion

The efficacy and safety of warfarin is highly dependent on the quality of warfarin control, commonly measured by TTR. Patients achieving high TTR are most suited to warfarin therapy and thus the ability to predict potential TTR would assist clinicians in determining a patient's suitability to warfarin therapy. The use of existing risk models for this purpose would ease the burden of calculating additional scores when prescribing anticoagulant therapy for patients with AF. Recently, Mueller et al [323] proposed the use of the existing HAS-BLED tool as a predictor of warfarin control, with a score ≥ 3 predicting poor control as defined by a TTR $< 70\%$. However, this was in a largely Caucasian population of patients with deep vein thrombosis who had good warfarin control. Despite the fact HAS-BLED has been well validated to predict bleed risk in patients with AF, the potential for this model to predict warfarin control in this population is yet to be tested. Furthermore, the ability of HAS-BLED to predict control in more diverse populations with differing levels of warfarin control has not been tested. Therefore the aim of this study was to determine if HAS-BLED could predict warfarin control in patients with NVAf in a largely Caucasian population in Australia and an Asian population in Singapore. This retrospective study found HAS-BLED calculated at the start of the study (i.e. without the inclusion of labile INRs) could not predict control in the Australian population but could predict poorer control in the Singapore population as patients with a HAS-BLED score ≥ 3 had significantly lower TTR than those in other categories. Recalculation of HAS-BLED at the end of the six month study period by including the measured parameter of labile INRs, was able to differentiate poorer warfarin control with a HAS-BLED score ≥ 3 for both the Australian and Singapore populations.

HAS-BLED is recommended by several international guidelines to assess bleed risk prior to anticoagulant therapy [495, 498, 499] and these guidelines also emphasise the need to optimise warfarin therapy by achieving a TTR over 65% [499] to 70% [495]. The Australian site achieved above these targets with a mean overall TTR of 82%, whilst the Singapore site with a mean TTR of 58% did not. The overall mean TTRs for each site was similar to those found in an analysis by geographical region by Singer et al [376] where Australia had a TTR of 73% and Singapore a TTR of 64%. Similarly, Chiang et al [386] demonstrated that in the large comparative trials of warfarin and the newer oral anticoagulants, Asians consistently had a lower TTR of < 60% compared to non-Asians. Suboptimal warfarin control in Asian populations compared to Caucasian populations has been associated with genetic polymorphisms but also differences in predominance of concomitant disease and medication [25]. Similar to this, our study found differences in patient demographics and concomitant disease with a higher incidence of hypertension and renal disease at the Singapore site, which may have influenced TTR. Further to this, Singer et al [376] concluded that patient clinical factors were only modest contributors of TTR, whilst regional variations in medical practices heavily influenced warfarin control and TTRs. The Australian site with a TTR around 80% conducted significantly more tests per patient compared to the Singaporean site suggesting differences in warfarin management practices. Further investigation is necessary to determine if the most significant factors influencing the differing TTRs in our populations were ethnicity, patient characteristics, or medical practices.

Rouaud et al [152] associated a high burden of patient co-morbidities with a low quality of warfarin control and similar to this Menzin et al [436] suggested a lack of co-morbidities was a predictor of good control as defined by 75% TTR. Given a number of concurrent conditions such as hypertension, abnormal liver/kidney disease, and a history of stroke are assessed in the HAS-BLED model, it is reasonable to assume this could be a predictor of warfarin control. In our study the HAS-BLED score calculated at the beginning of the study did not predict poor control in Australia but patients in all risk categories achieved TTRs over 80% and thus it could be argued that none of these patients fell into a poorly controlled TTR. In contrast, in Singapore a HAS-BLED score ≥ 3 was associated with significantly lower TTR (45%) than other categories (58%). Interestingly the mean TTR for patients in the low- and moderate-risk HAS-BLED categories was consistent with the overall mean for that site so the high HAS-BLED score could differentiate patients achieving TTR significantly below the mean for that site. Thus in Asian populations that have difficulty in maintaining high TTRs, a high HAS-BLED score may be more beneficial in identifying patients at particular risk of low quality warfarin control.

At the end of the study period, re-calculation of HAS-BLED with inclusion of labile INRs found a score of ≥ 3 was associated with significantly poorer control at both sites, with a TTR of 74% in Australia and below 35% in Singapore. This highlights the importance of continued assessment of patients as within this six month period significant differences were found according to TTR and the recalculated HAS-BLED score. International guidelines [495, 499] suggest patients at high risk according to HAS-BLED score warrant caution and regular review including efforts to correct potentially

reversible risk factors for bleeding such as labile INRs. A trend of increasing number of tests per patient was found according to increased HAS-BLED score, suggesting more regular follow-up of these patients. Despite this the TTR significantly decreased according to HAS-BLED category so further investigation is necessary as to whether these patients could achieve higher TTRs with additional interventions, and the level of intervention required to achieve acceptable control.

The level of warfarin control is directly related to the efficacy and safety of warfarin [500]. Connolly et al [378] have recommended a minimum TTR of 58 - 65% to ensure benefit of warfarin over antiplatelet therapy. In Australia the TTR was above this both overall and according to HAS-BLED category at the two time periods. In Singapore the overall mean TTR was at the minimum level of 58%, whilst the low- and moderate- risk categories had a mean TTR of 58% each at the start of the study but 75% and 54% respectively at the end of the study. Based on these results it would appear that application of the HAS-BLED score was not able to differentiate between good and poor control as defined by a minimum TTR threshold. At the end of the study, HAS-BLED was able to differentiate poor control at individual sites but this was compared to mean TTRs at each site and thus significantly different at our two study sites.

Therefore, whilst HAS-BLED appears to differentiate poor warfarin control at individual sites, each country or health system would need to define their acceptable minimum level of warfarin control before applying HAS-BLED as a predictor of control.

In our study, the overall incidence of bleeds was similar in Australia and Singapore however the incidence of major bleeds was 1.5 times higher in Singapore compared to Australia. This is consistent with the overall difference in TTR between the countries,

and similar to findings by Wan et al [109] who reported a TTR improvement of 6.9% reduced one major haemorrhagic event per 100 patient years. In both countries, HAS-BLED did not appear to be a good predictor of overall bleeds but the incidence of major bleed events increased according to HAS-BLED category. The retrospective nature of this study may explain this result as bleeds, particularly minor, were self-reported and patient recall of bleed events may have been higher in Australia due to the increased number of testing and hence reduced time between visits. The likelihood of adverse events increases with time outside therapeutic range, however bleeding complications can still occur in patients with INR within normal range [76]. Further investigation of the INR at the time of bleed events would assist in determining the most appropriate marker and possible predictor for clinical events.

The European guidelines [495] suggest a high HAS-BLED score should not exclude patients from oral anticoagulation but where warfarin is used, efforts to improve the quality of control is needed. Our study suggests that regular use of HAS-BLED could be used to assist in identifying patients at risk of poor warfarin control and hence be more suited to alternate oral anticoagulant therapy. For example, the Australian site achieved a good mean TTR of 80% across all categories but after six months a HAS-BLED score ≥ 3 was associated with a TTR $< 75\%$. As mentioned previously, this is considered a good level of control and above recommended guidelines of 70% [495] thus all patients would be potential candidates for warfarin. In contrast, in the Singapore population a HAS-BLED score ≥ 3 was able to identify patients achieving TTR significantly below the mean 58% for that site both at the beginning of the study (TTR 45%) and after the six month period (35%). Given the low level of warfarin control

achieved in these groups, it may be that these patients are not suitable candidates for warfarin and may be better suited to alternative anticoagulants. Further investigation would be required to test this hypothesis and consideration given to other patient factors, e.g. age and renal function, in deciding on the anticoagulant of choice.

In conclusion, HAS-BLED is commonly applied to patients with AF to assess bleed risk prior to the commencement of warfarin therapy. Consistent with Mueller et al [323], this study found a HAS-BLED score of ≥ 3 may also be a useful predictor of warfarin control and identify patients at high risk of poor warfarin control as measured by TTR, particularly in populations achieving poor overall control. HAS-BLED may serve a dual purpose of assessing bleed risk and warfarin control thus simplifying assessment of patients and enabling clinicians to identify patients at high risk of poor warfarin control who may require additional INR monitoring to achieve acceptable control, or who may benefit from alternate anticoagulants.

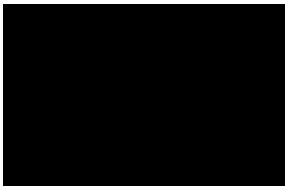
STATEMENT OF CONTRIBUTION TO CO-AUTHORED PUBLISHED PAPER

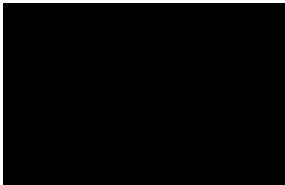
This chapter includes a co-authored paper. The paper “Identifying warfarin control with stroke and bleed risk scores” was published as a peer-reviewed paper in Heart, Lung and Circulation 2018 June; 27(6): 756-759. The authors of the paper are: Nijole Bernaitis, Chi Keong Ching, Tony Badrick, Shailendra Anoopkumar-Dukie. The final published version of this paper is in Appendix 2.

My contribution to the paper involved: collecting the data, providing direction on the scope and structure of the analysis, categorising and analysing the data, graphical representation of the data. I wrote the first draft, made revisions responding to supervisor and co-authors comments and feedback, prepared the final document, and submitted the article. I responded to and addressed the reviewer comments when they were received including incorporating appropriate revisions, and re-submitted the revised manuscript including modifications.

(Signed)  (Date) 4/12/18

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(Countersigned)  (Date) 4/12/18
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Identifying warfarin control with stroke and bleed risk scores

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Abstract

Warfarin decreases stroke risk in atrial fibrillation patients, with efficacy and safety impacted by the quality of warfarin control, as measured by time in therapeutic range (TTR). Stroke and bleed risk scores are calculated prior to commencing warfarin, so it would be beneficial if these scores also identified likely warfarin control. Some studies have investigated CHADS₂, CHA₂DS₂VASc, and HAS-BLED individually for this purpose, but application of all scores to diverse ethnic populations and at sites with differing overall control has not been investigated. The aim of this study was to determine if these commonly used risk scores could identify poor warfarin control.

Retrospective data was collected for non-valvular AF patients receiving warfarin between January and June 2014 in Australia and Singapore. Patient data was used to calculate TTR and risk scores. Mean TTR was used for analysis and comparison to categorised scores.

There were 3199 patients in Australia and 1171 in Singapore. At both sites, mean TTR decreased according to HAS-BLED category, and there was a statistically higher percentage of patients achieving a TTR > 65% in the low HAS-BLED category. The association between HAS-BLED scores and TTR was independent of lower dosing in higher risk patients, particularly in Australia. No significant differences were found in mean TTR according to CHADS₂ at either site. TTR significantly decreased according to high CHA₂DS₂VASc category in Singapore, but no differences were found in Australia.

Of the bleed and stroke risk models, HAS-BLED is most suitable to identify a patient's potential TTR and ability to achieve TTR > 65%. A high HAS-BLED score may assist

prescribers in determining potential suitability to warfarin, and assist prescribers in deciding on the most suitable anticoagulant for patients.

Introduction

Anticoagulant therapy has proven benefits in decreasing stroke risk in patients with atrial fibrillation (AF) [455]. Warfarin has long been used for this indication but there are now other non-vitamin K anticoagulant (NOAC) options, with clinicians needing to decide on the most suitable anticoagulant for individuals. Warfarin requires ongoing monitoring of International Normalised Ratio (INR) with time in therapeutic range (TTR) a recommended measure for quality of warfarin management [92]. Variations in warfarin TTR influences the efficacy and safety of warfarin, and has also been demonstrated to influence the comparative outcomes of warfarin to the NOACS [369]. Numerous patient factors including likelihood of achieving good warfarin control needs consideration in choosing suitable therapy.

Risk scores are widely used to assess stroke and bleed risk in patients with AF, namely CHADS₂ and/or CHA₂DS₂VASc scores for stroke, and HAS-BLED score for bleeds [501]. Recently, studies have investigated the ability of these scores to perform a dual purpose of identifying warfarin control. Poor warfarin control and high risk scores have been demonstrated for CHADS₂ [185] and HAS-BLED [323] scores, but these studies involved only individual scores and did not assess TTR with other risk models. Hellyer et al [321] demonstrated decreasing TTR across increasing CHA₂DS₂VASc and HAS-BLED scores, however this was in an American population with relatively low mean TTR i.e < 60%. Therefore, the aim of this study was to determine if commonly

used risk scores, i.e CHADS₂, CHA₂DS₂VASc, or HAS-BLED, could identify poor warfarin control in diverse ethnic populations and at sites with differing overall control.

Methods

Ethics approval was obtained from SingHealth Centralised Institutional Review Board (CIRB 2015/2435) and Griffith University Human Research Ethics Committee (PHM/08/15/HREC). A retrospective analysis of non-valvular AF patients receiving warfarin was conducted between January and June 2014 at Sullivan Nicolaides Pathology Queensland, Australia and the National Heart Centre in Singapore. Data collected included INR test dates/results, patient demographics, medical history, concurrent medications, and warfarin doses. Risk scores were calculated as of June 2014, and each patient categorised into low-, moderate-, and high-risk groups. TTR was calculated using the Rosendaal method with mean TTR and weekly warfarin dose used for analysis and comparison across risk categories. Comparisons were made using ordinary analysis of variance through non-parametric methods, including Kruskal-Wallis test, Dunn's multiple comparisons test, and chi-squared test. Data were analysed using GraphPad InStat version 3 and figures drawn using GraphPad Prism version 6.0.

Results

The study included 3199 patients in Australia and 1171 in Singapore, with a higher proportion of males at both sites (52.3% in Australia, 60.4% in Singapore). The mean age of patients was 77.2 ± 9.1 years in Australia and 69.7 ± 10.0 years in Singapore, and

the mean TTR was $82.3 \pm 15.6\%$ and $57.7 \pm 34.2\%$ respectively. In Australia, no significant differences were found in mean TTR according to CHADS₂ or CHA₂DS₂VASc category, but mean TTR significantly decreased according to HAS-BLED category with no significant difference in doses according to HAS-BLED category (Table 31).

Table 31 - Risk score categories and warfarin time in therapeutic range for the two study sites, namely Australia and Singapore.

Risk Score	Australia					Singapore				
	Number of Patients	TTR (%)	P value	Weekly Dose (mg)	P value	Number of Patients	TTR (%)	P value	Weekly Dose (mg)	P value
CHADS₂	Median (IQR) 1(1-2)					Median (IQR) 1 (1-2)				
Low 0 - 1	1743 (54.5%)	82.6 (15.6)		26.3 (11.8)		654 (55.8%)	59.4 (34.6)		19.1 (8.3)	
Med 2 - 3	1206 (37.7%)	81.9 (15.8)		26.2 (12.3)	ns	479 (40.9%)	55.7 (33.8)		17.5 (8.1)	<0.001
High ≥ 4	250 (7.8%)	82.9 (15.3)		25.7 (12.1)	ns	38 (3.3%)	53.2 (30.2)		16.1 (9.1)	<0.01
CHA₂DS₂VASc	Median (IQR) 3(2-4)					Median (IQR) 3(2-4)				
Low 0 - 1	475 (14.8%)	81.4 (16.5)		27.9 (12.4)		263 (22.5%)	60.3 (36.5)		20.9 (8.5)	
Med 2 - 3	1589 (49.7%)	82.7 (15.6)		26.2 (11.8)	<0.05	561 (47.9%)	59.8 (33.1)		18.4 (8.2)	<0.001
High ≥ 4	1135 (35.5%)	82.2 (15.3)		25.5 (12.2)	<0.001	347 (29.6%)	52.2 (33.6)	<0.01	16.5 (7.9)	<0.001
HAS-BLED	Median (IQR) 2(1-2)					Median (IQR) 2(1-2)				
Low 0 - 1	1442 (45.1%)	86.4 (12.0)		26.5 (11.8)		431 (36.8%)	75.8 (24.2)		20.2 (8.7)	
Med 2	1160 (36.3%)	81.5 (16.2)	<0.001	26.2 (12.4)	ns	455 (38.9%)	54.8 (33.3)	<0.001	17.5 (7.7)	<0.001
High ≥ 3	597 (18.6%)	74.1 (18.5)	<0.001	25.5 (11.9)	ns	285 (24.3%)	34.9 (24.7)	<0.001	17.0 (8.2)	<0.001

Data shown is number (percentage) of patients in each category, and mean (SD) for TTR in percentage and warfarin dose in mg. Statistics shown are in comparison with low risk category.

In Singapore, significant differences were found in mean TTR across all HAS-BLED categories and with high CHA₂DS₂VASc, with a non-significant trend to decreasing mean TTR according to CHADS₂. At this site all risk scores were associated with a significant decrease in warfarin dose between the low-risk and both the medium- and high-risk categories. At both sites, the percentage of patients achieving a TTR > 65% was statistically higher for low HAS-BLED scores (Figure 22).

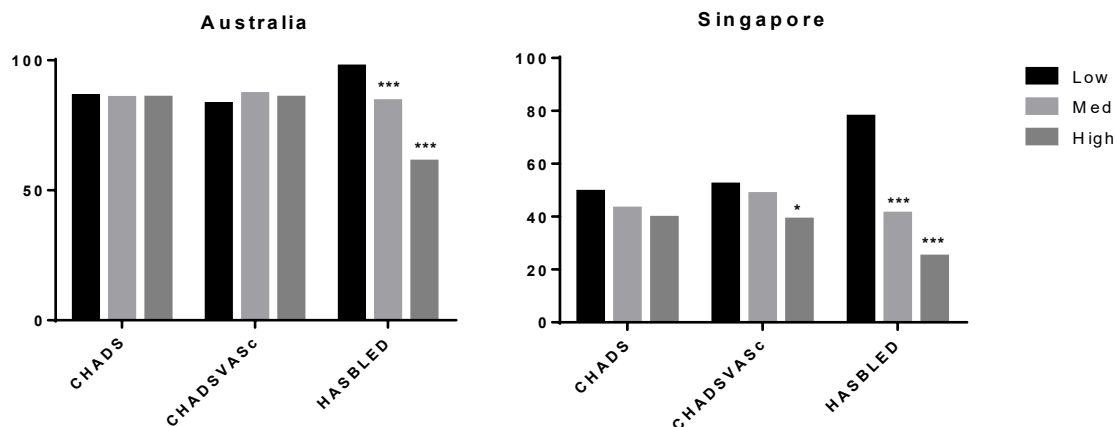


Figure 22 - Percentage of patients achieving a TTR > 65% in Australia and Singapore for each risk score category. Significance defined as * $p < 0.05$, ** $p < 0.01$, and * $p < 0.001$**

Discussion

The quality of warfarin control impacts therapy, with superior outcomes from higher TTRs. Identifying patients likely to achieve high warfarin TTR would be beneficial prior to commencing therapy. Stroke and bleed risk scores are already calculated for patients with AF, therefore it would be beneficial if these scores could also identify likely control. The aim of this study was to determine if commonly used stroke and bleed risk scores were suitable indicators of warfarin control. This retrospective study found HAS-BLED was the best indicator of warfarin control, whilst a high CHA₂DS₂VASC score was also indicative of poor warfarin control at the Singapore site.

Currently no single and/or combined score exists to assess all possible complications in patients with AF [502]. CHADS₂ and CHA₂DS₂VASC commonly assess stroke risk and HAS-BLED for bleed risk [455]. Hellyer et al [321] associated increasing HAS-BLED scores with decreasing TTR and lower odds of achieving TTR > 65%. Similarly, Mueller et al [323] found decreasing warfarin control with increasing HAS-BLED category. In

our study, TTR significantly decreased according to increased HAS-BLED category at both sites, and a low HAS-BLED score was associated with the highest percentage of patients with a TTR > 65%. This was the only risk score to identify control at both sites, i.e. diverse ethnic backgrounds and differing levels of warfarin control. The association between HAS-BLED scores and TTR appears to be independent of lower dosing in higher risk patients as there was no significant change in dose in Australia between HAS-BLED categories, whilst in Singapore there was no significant change in dose between the medium- and high- risk categories despite a significant decrease in TTR. In Singapore, the lower dosing in higher risk patients remains a potential contributing factor to the lower TTR achieved at this site and may reflect a more cautious approach to dosing due to known genetic influences on warfarin metabolism in the Asian population.

Recently, Odashiro et al [185] demonstrated CHADS₂ was a powerful predictor of warfarin treatment in Japanese patients. In contrast to this study, we found no significant difference in TTR according to CHADS₂ score category, however there was a trend towards decreasing warfarin control and increasing CHADS₂ score at the Singapore site, a predominantly Asian population. Pokorney et al [178] associated the CHA₂DS₂VASc score with patient TTR, specifically higher scores with significantly lower TTR. Furthermore, Hellyer et al [321] demonstrated increasing CHA₂DS₂VASc score with decreasing warfarin TTR, in particular the proportion of patients with TTR > 65% decreased substantially with increasing CHA₂DS₂VASc. Similar to this, we found TTR significantly decreased according to high CHA₂DS₂VASc category at the Singapore site and less patients in this category achieved a TTR > 65%. No TTR difference was found

at the Australian site for either CHADS₂ or CHA₂DS₂VASc score, however this site had a high TTR of 82% with a majority of patients having a TTR > 65%. This may indicate that high levels of control, as achieved by such dedicated warfarin clinics, may remove potential influencing factors on warfarin control. Further studies are required in dedicated warfarin clinics and other warfarin management strategies to test this hypothesis. Further investigation is also required to determine the most influential factor on warfarin control from components of risk scores.

In conclusion, increased HAS-BLED score was associated with decreased TTR at both sites and decreased ability to achieve TTR > 65%. In contrast to previous studies, a high CHA₂DS₂VASc score was not as predictive of warfarin control as HAS-BLED, as this only was associated with decreased TTR at the Singapore site. Currently used risk scores, particularly HAS-BLED, may also provide information regarding potential suitability to warfarin, thus assisting clinicians in choice of anticoagulant therapy.

Chapter Seven – Discussion, Future Directions and Conclusion

7.1 Discussion

An Australian government commissioned review into the use of anticoagulant therapies in AF [24] determined there was a lack of information regarding warfarin control in Australia and factors influencing this which resulted in significant barriers to optimising anticoagulant use in Australia. Therefore, the overall aim of this study was to determine predictors of warfarin control in patients with AF in both South-East Queensland and Singapore and thus inform prescribing and management of warfarin to patients with AF. To achieve this, a retrospective data analysis was conducted utilising records of patients receiving warfarin for AF in Queensland and Singapore. The two most commonly used warfarin management systems in Queensland, that is community GPs and Warfarin Care program, achieved warfarin TTRs of 69% and 82% respectively whilst in contrast, Singapore had significantly poorer warfarin control with a TTR of 58%. Warfarin management differed significantly with reduced frequency of testing in Singapore (29 days). In Queensland, management by GP and dedicated warfarin management program also had differences in frequency of testing (23 days GP and 16 days SNP), especially when INR values were sub-therapeutic and supra-therapeutic (19 vs 13 days and 21 vs 14 days respectively), contributing to the improved TTR achieved by the dedicated warfarin management program. Further to this, the Queensland warfarin management program obtained high levels of control for the majority of patients (97% with TTR > 60%) with no influence by gender, demographic or socioeconomic factors. Patient factors significantly contributing to reduced levels of warfarin control in Queensland and Singapore were CKD and

concurrent therapy with aspirin or NSAIDs, whilst age less than 60 years was also associated with reduced TTR in Queensland. In both Queensland and Singapore warfarin TTR decreased according to HAS-BLED category with a score greater than 3 associated with the lowest control. Similarly, in Singapore a high CHA₂DS₂VASc score and a SAME-TT₂R₂ score > 2 was also associated with poor warfarin control.

Australian PBS prescribing statistics nationwide and specific to Queensland indicates that whilst warfarin use is decreasing it still remains widely prescribed plus it is currently the only oral anticoagulant indicated for patients with valvular AF [411]. Recently released Australian guidelines for the diagnosis and management of AF recommend warfarin for patients with valvular disease and use of CHA₂DS₂VA to determine suitability of oral anticoagulation for patients with NVAf [319]. Due to the available choice of oral anticoagulants, international AF guidelines now recognise the need to optimise warfarin control for patients receiving warfarin [263, 300, 317, 389] with TTR levels above 65% commonly recommended [264, 297, 298]. Australian guidelines recommend warfarin control to be above a TTR of 60% [319] to 65% [390] with guidelines specific to Queensland recommending a minimum TTR of 60% [503]. This study has demonstrated that patients with AF in Queensland achieved warfarin control above the recommended minimum TTR of 60% [319, 503] to 65% [264, 297, 298, 390] with the two commonly used warfarin management systems in Queensland, GP and Warfarin Care program, achieving TTR levels of 69% and 82% respectively. Several studies have reported improved outcomes when warfarin control is above a TTR of 70% [104-106] whilst Lehto et al [107] demonstrated that increasing TTR continues to decrease risk of adverse events and improve mortality with TTR ≥ 80%.

Queensland GP management nears the higher suggested TTR of 70%, but the TTR of 82% achieved by the dedicated warfarin management program far exceeds this 70% threshold and even the superior 80% recommendation. In Australia, previously reported levels of warfarin control have been above 70% from controlled trials [366, 368, 376, 378] but below this level from most real-world Australian studies [208, 219, 381-383], that is non-controlled conditions. These studies [208, 219, 381-383] were from different Australian states with the only previous study from Queensland at the same dedicated warfarin management program reporting a TTR of 78% in patients with DVT [323]. The most recent Australian studies of warfarin control reported TTR of 64% [383] and 69% [382] from metropolitan areas, which is comparable to the reported 69% TTR by GPs in our study. The higher TTR of 82% by the dedicated warfarin management program has not been previously reported in Australian studies but this could be explained by the fact that such a program is currently only offered by some Australian states including Queensland, Victoria, and Western Australia.

The high TTR obtained by patients enrolled in the Queensland warfarin management program over GP management is in accordance with studies demonstrating improved control by anticoagulant clinics compared to usual care [115-123] and the 13% improvement in TTR observed in our study compares favourably to the 6 - 11% improvement reported in meta-analyses of overseas studies [130-132]. Wan et al [109] reported an improvement in TTR to be associated with a reduction of events, equating a 6.9% TTR increase to reducing one major haemorrhagic event per 100 patient years and an 11.9% TTR increase to reducing one thromboembolic event per 100 patient years. Thus it is likely that the 13% increase in TTR achieved by the

warfarin management program as opposed to GP care would result in improved outcomes for patients. Whilst this was not directly investigated in this study, supporting this theory was our finding that patients who experienced adverse events had significantly lower TTR than patients who experienced no events at the warfarin management program. In terms of ischaemic events, Sjölander et al [367] demonstrated no difference between high quality warfarin treatment as defined by a TTR > 70% and treatment with NOACs. In addition, Burn and Pirmohamed [363] suggested that in centres with warfarin TTR > 70% the NOACs are likely to be inferior to warfarin. This study has demonstrated good quality warfarin control in Queensland with potential to optimise warfarin therapy through a dedicated warfarin management program and thus warfarin remains a potentially suitable anticoagulant option for patients with NVAf.

This study demonstrated that Queensland had a significantly higher level of warfarin control compared to Singapore. At the Singapore site, the mean warfarin TTR of 58% was slightly lower than previously reported TTR levels from Singapore of 64% [376] and 68% [366, 376] in clinical trials and 65% TTR in real-world studies [443]. The Singapore site in our study manages warfarin through outpatient appointments with physicians, whilst in contrast the Singapore hospital site reporting the higher TTR of 65% has a pharmacist-managed anticoagulation clinic [443]. Wong et al [504] reported an inpatient pharmacist-managed anticoagulation service in Singapore reduced mean time to therapeutic INR and mean length of hospital stay after warfarin initiation. These studies [443, 504] suggest that a more dedicated warfarin management service could improve outcomes with warfarin in Singapore, and supports concerns from Lip et

al [449] that the lack of structured anticoagulation services may contribute to poorer TTRs observed in Asian patients. Singer et al [376] reported that Asian patients have an 8% lower TTR than Caucasian patients but this study demonstrated a higher difference of up to 24% TTR when compared to the dedicated warfarin management program. A subsequent sub-analysis by Singer et al [377] found poorer regional TTR was associated with longer intervals between INR tests and observed the longest intervals in East Asia with 23.7 days. In accordance with this, the interval between INR tests was found to be significantly different between Queensland and Singapore with a frequency of testing of 16.9 days compared to 29.3 days respectively. Even between management systems in Queensland, frequency of testing was also found to be a factor with significant differences between GP and warfarin management systems (23 vs 16 days respectively) particularly when INR was sub- and supra-therapeutic (19 vs 13 days and 21 vs 14 days respectively). Several authors have correlated improved warfarin control with more regular INR testing particularly following results outside of recommended INR ranges [115, 116, 126-128]. Chamberlain et al [128] suggested that more consistent INR testing potentially avoids large variation in values, whilst Matchar et al [127] correlated the improved warfarin control with the prompt correction of INR values. Holbrook et al [505] reinforced that high-quality anticoagulation management is required to guide warfarin therapy including a systematic method of testing INR with altered test frequency in response to the numerous factors associated with unstable control such as change of drug therapy, acute illness and exacerbations of medical conditions. Successful warfarin management services continuously adjust the interval between INR tests based on the combination of INR stability, possible influencing factors and patient convenience [506]. This active management approach is critical in

order to optimise warfarin TTR and subsequent outcomes with warfarin therapy. Specialised management with anticoagulants clinics provide such services through integration of coagulation knowledge, therapeutic intervention and patient education [507]. Nichol et al [116] suggested the increased intervention with anticoagulant clinics led to more effective dosing but also potentially promoted patient adherence. Due to the retrospective nature of this study, the relationship between adherence to warfarin therapy and warfarin control was not specifically analysed. However, if longer intervals between INR testing are associated with poorer adherence and thus lower TTR, then the reduced frequency of testing at the Singapore site may have also contributed to lower adherence and subsequently lower TTR observed at this site.

Frequency of testing and thus systems of management may have contributed to the lower TTR observed in Singapore compared to Queensland. However, Alsheikh-Ali et al [143] identified both practice and patient specific factors to be important contributors to TTR variability. Further to this, numerous studies [149, 150, 153, 178, 181, 193, 206, 207, 209] have identified non-Caucasian race to be associated with poorer warfarin control. Apostolakis et al [159] incorporated non-Caucasian race as a variable in the SAME-TT₂R₂ model which predicts the likelihood of poor warfarin control. In Singapore this study was amongst the first to demonstrate a SAME-TT₂R₂ score > 2 was indicative of poor warfarin control in an Asian population, and the first to demonstrate the predictive ability of SAME-TT₂R₂ when categorised according to Chinese and Malay race. Our published validation of the SAME-TT₂R₂ score in the Singapore population [442] is cited in the 2017 consensus of the Asia Pacific Heart Rhythm Society in stroke prevention in AF [263] as contributing to the rationale for

recommending the use of SAME-TT₂R₂ in the Asian population. However, a limitation of this study was the inability to validate this score in Queensland due to the lack of information regarding race at the main Queensland study site. Ethnicity is well documented to impact pharmacokinetics and pharmacodynamics of warfarin [13, 34-36, 38, 42-45] and subsequently impact overall warfarin control [149, 150, 153, 178, 181, 189, 193, 200-202, 206-209] but, despite this, race is not routinely recorded in Australia. The Australian Bureau of Statistics 2016 Census data [508] shows more than 1 in 5 Queenslanders were born overseas with India, China, and South Africa respectively being the third, fourth and fifth most common birthplace country. This would suggest that people of varying race were included in our study at the Queensland site and it is possible that the good control achieved by management systems in Queensland was maintained regardless of race, given 97% of these patients achieved a TTR > 60% and thus above the mean TTR of Singapore. However, in the absence of the ability to specifically correlate race with TTR and analyse this relationship, it remains inconclusive as to whether race is an influencing factor on warfarin control in Queensland and this requires further investigation. Equally, in Singapore, the lower TTR cannot be completely explained by ethnicity. Singer et al [376] determined that warfarin control was determined not by race but by medical practices. As previously discussed, the lack of structured warfarin monitoring may lead to suboptimal control [449]. Therefore, the potential impact of more structured monitoring of warfarin in the Singapore population warrants investigation to determine if this would increase TTR. In support of this, Chua et al [443] modelled an anticoagulation service in Singapore and demonstrated it would be cost-effective for the local health system. Thus implementation of a dedicated warfarin management

services, such as the Warfarin Care model used in Australia, could be investigated for Singapore.

Consistent with numerous other studies [147, 152, 161, 162, 174, 175, 177-182, 185], this study found CKD contributed to a reduction in warfarin TTR. Limdi et al [509] found lower glomerular filtration rate was associated with poorer anticoagulation control and identified patients with CKD and end stage renal disease as particularly challenging due to the change in warfarin metabolism and multitude of factors influencing coagulation in this population. Specifically, Lutz et al [510] described CKD to influence haemostasis via mechanisms including insufficient platelet function, activation of the fibrinolytic system, and disorders of coagulation factors. Limdi et al [511] describe a down regulation of CYP450 enzymes in patients with CKD altering warfarin requirements. Further to this, Dreisbach et al [512] demonstrated the decreased CYP2C9 activity in renal failure resulted in a 50% increase in the plasma warfarin S/R enantiomer ratio due to the differing metabolic pathways of the two enantiomers. Several studies [450, 511, 513, 514] have described the need for reduced warfarin dose requirements in patients with impaired kidney function. However, Hughes et al [515] suggested that despite the lower warfarin dose requirements and higher potential of labile INRs in patients with CKD, warfarin is still recommended and may be the preferred anticoagulant as the NOACs may be contraindicated depending on the level of kidney function. Patients with a CrCl < 30 mL/minute are also highlighted in Australian AF guidelines [319] due to the lack of prospective data showing benefit from anticoagulation in this population but also because NOACs are contraindicated in this population and thus warfarin should be

used if anticoagulant therapy is required. Inoue et al [183] particularly correlated CrCl levels less than 30 mL/minute to be associated with a warfarin TTR < 65%. Similarly, this study found warfarin control may be suboptimal in patients with CKD in both Queensland and Singapore. Kleinow et al [450] demonstrated patients with CKD required increased management including more frequent dose changes and decreased time between scheduled visits to enhance warfarin stability. Subsequent to this, Yang et al [177] also suggested patients with moderate to severe CKD may require more intensive warfarin monitoring to maximise control. Likewise, our suggestion is that patients with CKD may be at risk of poor warfarin control but a dedicated warfarin management service with reduced time between tests and increased potential for dose changes may optimise TTR, particularly in the subset of patients with CrCl levels which contraindicate NOACs.

An additional patient factor influencing TTR in Queensland was age less than 60 years. Previously, there has been conflicting data on the influence of age on TTR with reports ranging from no influence [148, 152, 184, 189, 192, 214, 216, 217] to older age being associated with both higher TTR [163, 176, 180, 181, 212, 221, 222] and lower TTR [153, 162, 182, 191, 223]. Younger age has also been associated with lower TTR [150, 173, 178, 213, 218-220] with Sawicka-Powierza et al [215] specifically correlating age less than 60 years with lower TTR which is supported by the findings from this study. Some challenges to anticoagulation outlined by Tay et al [516] included poor understanding of the importance of regular monitoring and poor medication compliance. Arnsten et al [427] correlated younger age with inadequate warfarin monitoring and found patients aged < 60 years more likely to be non-compliant.

Similar to this, Simons et al [408] found 79% of patients aged 50 - 64 years discontinued warfarin within 12 months of prescription but persistence with warfarin improved with age. Pamboukian et al [517] also demonstrated that non-adherence to warfarin therapy was associated with age. Therefore, one explanation as to why patients aged < 60 years were associated with reduced warfarin TTR would be non-compliance with dosing and increased inconvenience of monitoring in this population, particularly as they may still be employed and have less flexible commitments than older patients. Previously, Vanderpoel et al [518] found non-adherence to anticoagulant therapy higher among those who are employed, and Kneeland and Fang [227] also linked poor adherence to employment and younger age. Both Luger et al [519] and Alamneh et al [406] found younger age was a strong factor for prescribing NOAC instead of warfarin. However, Hellfritsch et al [419] demonstrated young age (defined as < 55 years) was the strongest predictor of NOAC discontinuation. It has also been well documented that patients non-adherent to medication may actually benefit from the slower offset of action of warfarin compared to a NOAC [39, 337, 385, 391, 455, 520-522]. Therefore, even though warfarin TTR may be reduced in patients aged < 60 years, NOACs may not automatically be the best option in these patients. Kimmel et al [235] found the association with poor adherence and poor warfarin control was independent of demographic factors. Therefore, regardless of age, consideration must be given to an individual's convenience of monitoring and dosing and possible medication adherence in determining the potential suitability of warfarin and likelihood of achieving good levels of control.

Another factor found to influence TTR in this study at the Singapore site was use of a platelet inhibitor and, more specifically, concurrent aspirin and NSAIDs were found to reduce warfarin TTR in Queensland, even after accounting for other potentially interacting drugs. This finding is consistent with several authors [160-162] who demonstrated reduced TTR with concurrent aspirin use but is in contrast with Okumura et al [163] who found no effect on TTR with concurrent anti-platelet drugs. Numerous drugs may affect warfarin via pharmacokinetic interactions particularly involving CYP metabolism [58, 59] or via pharmacodynamic effects resulting in potentiation of bleed risk [62, 63]. Interestingly, other than aspirin and NSAIDs, our study found the presence of medications previously reported to interact with warfarin did not significantly alter TTR from the mean in either Queensland or Singapore. Holbrook et al [63] recognised that INR monitoring may be of little help with drugs that potentiate bleeding but still suggest managing drug interactions with warfarin through more frequent INR testing during the 2 weeks of onset or discontinuation of medication treatment. Further to this, Bungard et al [523] developed a practical tool for common drug interactions accounting for the likely onset and extent of interaction in determining appropriate follow-up of INR and likely required change to warfarin dose. Drug interactions are prevalent with warfarin and clinicians should be aware of potential interactions [524] with a change in medication prompting more frequent INR monitoring to enhance potential stability of warfarin control [486]. This study found the majority of concurrent medication prescribed with warfarin resulted in no change to TTR. However INR values were not specifically investigated, particularly at times of medication changes, and it is possible that concurrent medications impacted INR but subsequent warfarin dose adjustments returned INR to therapeutic levels. In such

cases, TTR would be minimally impacted given TTR is a measure of long-term control and not always a good reflection of INR stability. Therefore, given the well documented influence of drug interactions on warfarin response, it is likely that good recognition and management of possible drug interactions reduced the likelihood of effect of concurrent medication on warfarin control as measured by TTR.

7.1.1 Proposed new prescribing guidelines for warfarin

Based on the patient factors found in this study to influence warfarin TTR, we propose new prescribing guidelines for warfarin (Figure 23) to potentially assist clinicians in decision making and managing warfarin. The first section of the proposed prescribing guidelines reflect the recently released Australian AF guidelines [319] recommending warfarin in valvular AF and use of CHA₂DS₂VA to determine suitability of anticoagulation in patients with NVAf. However the Australian AF guidelines [319] recommend NOACs in preference to warfarin in patients with NVAf, whereas these proposed prescribing guidelines still offers a choice of warfarin or NOACs for patients with NVAf requiring oral anticoagulation. This is based on the high level of warfarin control demonstrated in this study in Queensland, particularly 82% TTR by the dedicated warfarin management system, as the high level of warfarin control is likely to negate some comparative benefits demonstrated from NOACs although the data suggesting reduced bleeding with NOACs especially intracranial haemorrhage could not be ignored.

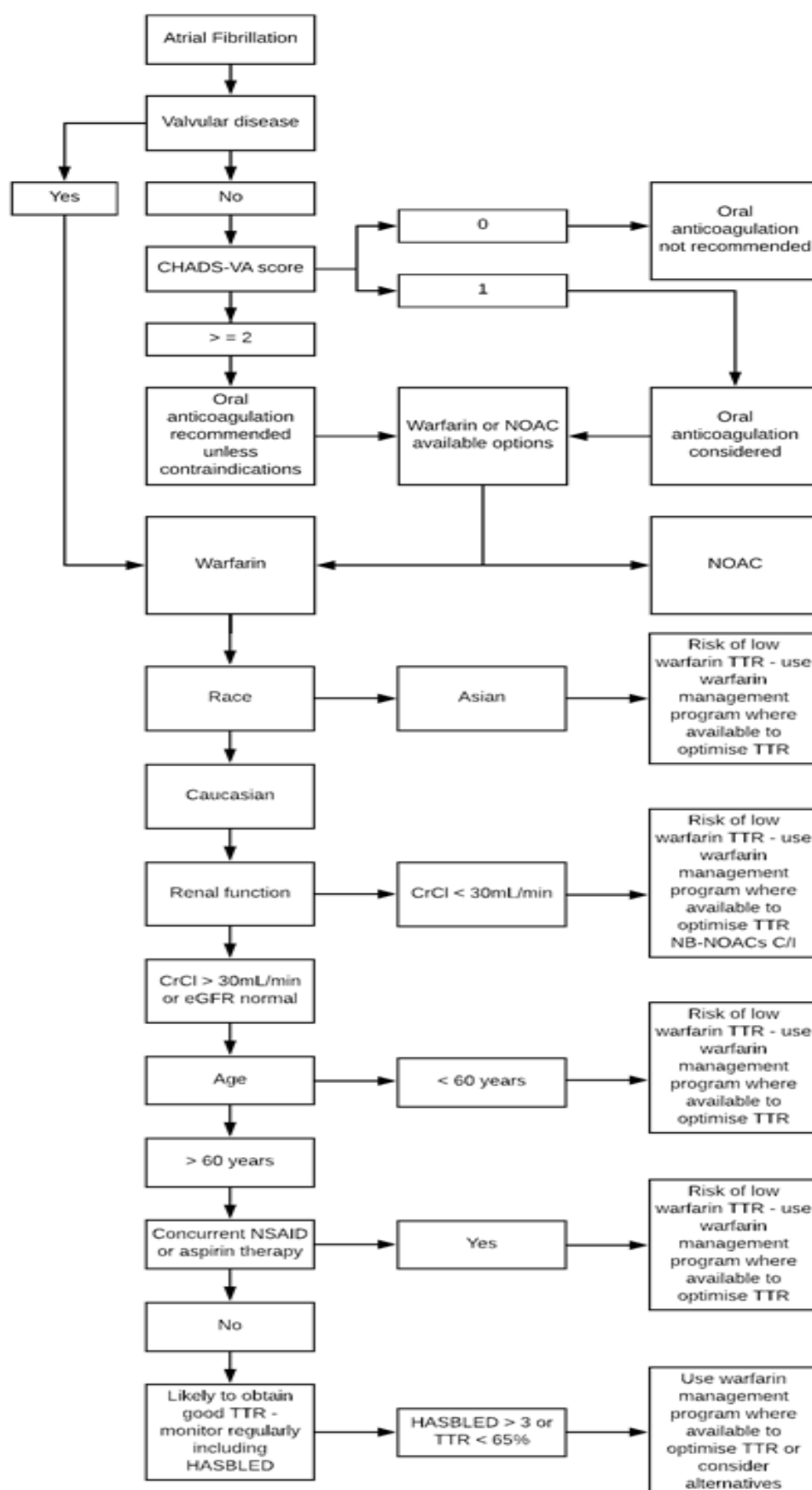


Figure 23 – Proposed prescribing guidelines to identify patients with atrial fibrillation requiring oral anticoagulation therapy and, if warfarin is chosen, identify subsets of patients who may require intervention to achieve adequate control.

Warfarin remains an option for patients with NVAf requiring anticoagulant therapy although patient preferences and factors which may impact control require consideration. Factors found in this study to reduced warfarin control have been specifically incorporated in our proposed guidelines (Figure 23). Based on the Singapore data, Asian ethnicity was identified as a factor potentially leading to poor warfarin control and a population that may benefit from the services of a dedicated warfarin management system. In addition, patients with CKD, aged less than 60 years, and taking concurrent NSAIDs or aspirin have been highlighted as a population at risk of poor warfarin control that could benefit from dedicated warfarin management systems. Some of the individual factors found to influence warfarin control in this study, that is renal disease and medication pre-disposed to bleeding like aspirin and NSAIDs, are components of the HAS-BLED score (Table 7). A HAS-BLED score > 3 was also associated with poor warfarin control in this study after six months of warfarin therapy at both the Queensland and Singapore site. Similar to this, other studies [151, 170, 180, 320] have associated lower TTR with high HAS-BLED scores and Hellyer et al [321] correlated an increasing HAS-BLED strata with a reduction in patients achieving a TTR > 65%. Labile INR (TTR < 60%) is a variable in HAS-BLED and thus warfarin control is a component of the score [324] yet some studies [193, 201, 214] have found no correlation with warfarin TTR and HAS-BLED. It has been previously demonstrated that HAS-BLED predicted warfarin control when calculated at the commencement of warfarin therapy for Australian patients with DVT [323]. In comparison, this study found a HAS-BLED score > 3 was a predictor of poor warfarin control at the start of therapy, that is without labile INR included in the HAS-BLED score, in Singapore but not in Queensland. For this reason, HAS-BLED has not been recommended as a predictor

of model at the start of warfarin therapy but instead has been incorporated into our proposed prescribing guidelines (Figure 23) as an ongoing measure to assess warfarin control and potential bleed risk.

This study found poor warfarin control in Singapore was associated with a high CHA₂DS₂VASc score but not with CHADS₂, whilst in Queensland no correlation was found with warfarin control and either CHADS₂ or CHA₂DS₂VASc score. Similarly, conflicting results with warfarin TTR and CHADS₂ or CHA₂DS₂-VASc scores have been previously reported with a number of studies [155, 172, 178, 185, 216, 320, 322] showing lower TTR with higher scores. In contrast, Kiliç et al [180] associated a high CHA₂DS₂-VASc score with increased TTR whilst other studies [163, 193, 201, 214] have found CHADS₂ or CHA₂DS₂VASc scores are not predictive of TTR. The conflicting results of the CHADS₂ or CHA₂DS₂VASc score on warfarin TTR may be influenced by the numerous components comprised in the score (Table 8). For example, female gender contributes to the CHA₂DS₂VASc score and we found no relationship between gender and warfarin TTR. Consistent with this, other studies [148, 163, 184, 185, 189, 192, 208, 214-217] have demonstrated no influence by gender on TTR whereas numerous other studies [111, 149-151, 153, 162, 172, 173, 175, 180, 190, 191, 193, 195, 210-213] have identified poorer warfarin control in females. Sullivan et al [525] suggested possible reasons for gender differences in TTR may be hormonal, social class, attention to self-care and access to medical care. Whitley and Lindsey [526] proposed altered response to medication may be due to gender differences in gastrointestinal motility, body composition, and slower glomerular filtration rates but also suggested the lower warfarin doses required by women may be explained by differences in cytochrome

metabolism. However, gender differences in warfarin metabolism due to genetic polymorphisms is not supported by Kabalak et al [527] who found no gender difference in VKORC1 genotypes distribution or Tabrizi et al [528] who found no gender differences in CYP2C9 polymorphism. Liew et al [529] compared men and women with the same VKORC1 genotype and found women required lower doses to achieve the same INR level as men. Previously, Okumura et al [163] found warfarin dose was a predictor of TTR and suggested that this was due to clinician caution when increasing the warfarin dose especially above 5 mg per day. We found no influence of warfarin dose on TTR for patients in either Queensland or Singapore across warfarin doses of < 2.5 mg, 2.5 - 4.9 mg, and > 5.0 mg per day. However, at both sites, patients with a TTR < 65% had significantly more dose changes and more frequent INR tests as compared to patients with a TTR > 65%. Warfarin dose changes and increased tests could reflect attempts to maintain INR control in the presence of other influencing factors. These frequent tests and dose changes, particularly at the warfarin management service in Queensland, could remove the influence on TTR of certain factors and possibly explain why some factors like dose and gender were not shown to affect TTR in this study.

Apostolakis et al [159] incorporated female gender into the SAME-TT₂R₂ score (Table 4) with a score ≥ 2 suggestive of requiring additional intervention to achieve acceptable warfarin control. However, Fauchier et al [257] proposed that some individual variables may be over-represented in the SAME-TT₂R₂ model depending on the setting, particularly non-Caucasian race and tobacco use. Subsequent to this, Lee et al [258] proposed a modified score with removal of the race and tobacco variables and still

found this a good predictor of TTR. As mentioned previously, whilst the SAME-TT₂R₂ model could be applied in Singapore and a score > 2 was associated with poor warfarin control, a limitation of this study was that the SAME-TT₂R₂ model could not be investigated in Queensland due to lack of information including tobacco use and race. Regardless of this, it is possible that the SAME-TT₂R₂ score may not be predictive of TTR in Queensland given the predominantly Caucasian population and the fact that in our study we did not find a relationship with TTR and gender or interacting medication such as amiodarone, both variables of this model. Björck et al [188] found the SAME-TT₂R₂ score was not predictive of warfarin control in a Swedish population due to the high overall mean TTR (68%) and the fact that predictors of control in their population (that is alcohol excess) was not included in the model. Further to this, Skov et al [259] demonstrated the SAME-TT₂R₂ score was not predictive of warfarin control in a specialised anticoagulant clinic with high mean TTR of 76%. The similarly high mean TTR of 82% in Queensland for patients managed by the dedicated warfarin program may result in the SAME-TT₂R₂ score not predictive of TTR in this population. The TTR calculator proposed by Rose et al [150] (Table 3) is of potential benefit at the Queensland warfarin management system as this model allows for input of mean site TTR and thus the high benchmark of 82% TTR can be used as a target for potential warfarin control of individuals managed at this site. However, this model by Rose et al [150] requires input of 18 variables including number of hospitalisations in the past 12 months which may not be readily available to clinicians when initiating warfarin therapy. The other existing predictor model PROSPER [166] has the benefit of including access to enhanced anticoagulation care and renal dysfunction as variables in the model (Table 5). These factors were specifically found to influence warfarin TTR in

our study and therefore the PROSPER [166] model may be a more suitable predictor of warfarin control in the Queensland population. However, PROSPER [166] combines seven variables including hospitalisation ≥ 7 days, pain medications, and prescriptions for antibiotics which may not be readily accessible to treating clinicians, similar to concerns regarding the Rose et al [150] model. Given the potential limitations of the existing proposed predictor models of warfarin control and the findings from this study that existing stroke and bleed risk models do not predict warfarin control at commencement of therapy, an alternate predictor model for warfarin control may be beneficial.

7.1.2 Proposed new predictor model for good warfarin control

All the factors found in this study to influence warfarin control have been combined into a proposed predictor model to identify patients most suited to warfarin therapy and likely to achieve good warfarin control which utilises the mnemonic WARFARIN (Table 32). Currently, one point has been allocated to each of the seven variables and the total score for a patient would be indicative of likely warfarin control with patients scoring ≥ 2 most likely to achieve benefit from warfarin through good control. Similar to other models, this proposed model would require validation not only in our patient population but also in other populations to determine if this model is indeed a reliably good predictor of warfarin control. This should include diverse populations with varying levels of warfarin control under different warfarin management systems to truly identify the predictive ability of this model. Application of this model in a wider population and further investigation could also determine the most suitable point

allocation for each variable and correlation between total score and warfarin control to potentially enhance the discriminatory performance of the model.

Table 32 - The predictor model with the mnemonic WARFARIN to identify patients most suited to warfarin therapy and likely to achieve good warfarin control.

Acronym	Clinical characteristic	Points
W	Warfarin management program available	1
A	Atrial Fibrillation Valvular i.e. presence of moderate to severe mitral stenosis or mechanical heart valve	1
RF	Renal Function normal	1
A	Age greater than 60 years	1
R	Race = Caucasian	1
I	Intolerance to Non-vitamin K oral anticoagulant (NOAC) therapy	1
N	Non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin NOT concurrently used	1
	Warfarin may not be most suitable oral anticoagulant – consider alternatives	Total = 0 - 1
	Warfarin suitable – likely to obtain good control	Total ≥ 2

7.2 Future Directions

The proposed prescribing guidelines (Figure 23) and predictor model (Table 31) require additional investigation to validate them and ensure clinical application. A recent study by Eek et al [530] found physicians chose anticoagulants based on patient factors such as renal function, bleed risk, and drug interactions. A study investigating prescriber usability and satisfaction with these guidelines would determine their suitability in practice. The proposed guidelines and predictor model for warfarin were developed based on this retrospective study. Retrospective studies utilise data recorded for reasons other than research but are commonly utilised in health care with data sourced from the medical record [531]. Retrospective studies can review clinical data on a large scale and over a long period of time to generate knowledge and form the basis of standards and guidelines [532]. These studies can investigate the

relationship between exposures and outcomes and provide valid results [533]

However, whilst a retrospective study can find associations between factors and health effects they cannot provide certainty of a causal relationship [534, 535]. For this reason, application to both retrospective and prospective data would assist in determining ability to further optimise prescribing of warfarin across a variety of populations.

Warfarin control in Queensland may also be further investigated, including control achieved by other management systems. This would include a comparison of dedicated warfarin management providers given a number of programs are available to patients receiving warfarin in Queensland. This comparative information could provide insight into individual elements of the dedicated clinics which provide the greatest contribution to optimising warfarin treatment. The other available monitoring of warfarin in Australia is via point-of-care testing which also warrants investigation, including the potential benefits of this testing in rural and remote areas. In addition, warfarin control in non-Caucasian patients within Queensland specifically requires investigation. Ethnicity is an important influence on warfarin control and the lack of available information regarding race is currently a limitation to fully investigating the potential impact of ethnicity on warfarin control in Australia. Routine collection of race in Australian medical records could be considered for the purpose of enhancing patient care across the multi-culturally diverse population. However, in the absence of this information being available within Australia, discussions for further research on the influence of ethnicity on warfarin control are underway with sites in India, Malaysia and South Africa.

Warfarin control in other Australian states also requires investigation including the potential to improve anticoagulation control with the introduction of dedicated management programs to states not currently offering this service. In recent years, the Warfarin Care program was introduced into Western Australia by the same providers as the Queensland clinic. The possibility of investigating the impact of this new service on warfarin control in Western Australia has been discussed and the details of this study currently being finalised. It would be pertinent to determine if the warfarin control achieved by the Warfarin care program can be replicated between different states of Australia before implementing such a model overseas, as suggested for Singapore. Ethics approval for a survey of patients enrolled in Queensland Warfarin Care is also awaiting final approval. This patient survey aims to investigate factors influencing patient satisfaction with treatment including burden of treatment/testing and subsequent impact on quality of life. This qualitative data can further assist prescribing by identifying potential factors influencing patient preferences regarding oral anticoagulant therapy.

Future studies are also required regarding NOAC therapy in patients with NVAf. The aim of future studies would be to determine subsets of patients most suited to NOACs and individual agents including dabigatran, rivaroxaban and apixaban. Further to this, investigation into the patients identified as likely to have poor warfarin control should be assessed as to their suitability to NOACs as this would assist in determining which oral anticoagulant would be most suitable for specific subsets of patients. For example, currently NOACs are contraindicated when renal function is below 15 to 30 mL/min depending on the individual agent, and thus warfarin remains the most

suitable oral anticoagulant in this group despite the fact that warfarin control may be poorer. However, recent studies investigating NOACs in kidney disease are documenting their potential safety in advanced CKD, particularly apixaban [536-538] and rivaroxaban [539, 540], so safety and efficacy of NOACs in this subset requires further investigation. Similarly, studies have reported potential benefit of NOACs as compared to warfarin in the Asian population [541, 542] so the most suitable anticoagulant in this population requires further investigation. In addition, Kim et al [543] demonstrated NOACs to have comparable safety profile in elderly patients aged ≥ 75 years. Our study specifically highlighted age < 60 years and concurrent NSAIDs and aspirin use as being predictive of poor warfarin control so these specific subsets of patients require further investigation as to their suitability to NOACs. Additional patient factors potentially influencing comparative outcomes with warfarin and NOACs also require investigation as recent studies have reported differences in the presence of co-morbidities including diabetes [544], prior stroke [545], cancer [546], and other patients factors including body weight [547, 548], frailty [549, 550] and stroke risk [551]. These investigations would allow for more complete prescribing guidelines which further incorporate patient factors guiding selection between warfarin and NOACs plus individual NOACs and thus provide greater assistance to clinicians in determining the most suitable oral anticoagulant for individual patients.

Further investigation of the NOACs would require measures of adverse events including bleeds and thromboembolisms and thus clinical data including hospitalisations would be required, especially as routine laboratory monitoring is not performed for the NOACs and thus cannot be used as a measure of control. A

limitation of this study was the retrospective nature and hence lack of detailed information regarding occurrence and management of adverse events. Retrospective studies utilise existing data which may be incomplete, inaccurate or inconsistent between records [552]. Greater information on adverse events in patients with AF taking warfarin could be obtained by linking hospital data with patient data from SNP. In addition, data from hospital sites can provide information on efficacy and safety relating to all oral anticoagulant therapies and thus provide greater comparative data on warfarin and NOACs. Discussions are in progress with the NHCS to conduct a comparative study on prescribing and outcomes with oral anticoagulants in Singapore by investigating admissions to NHCS by patients with NVAf on anticoagulant therapy. A study of this nature has commenced at two public hospital sites in Queensland, namely the Gold Coast University Hospital and Logan Hospital. Ethics approval has been obtained (HREC/14/QPAH/445 & GU 2015/863) to investigate anticoagulant therapy for patients with AF admitted to these Queensland hospitals to determine factors influencing the prescribing, efficacy and safety of warfarin and NOACs. Data collection has commenced at the Gold Coast University Hospital and thus far a total of 10,637 episodes of care for patients with AF have been screened and 2639 admissions involved patients taking oral anticoagulants. Of these, 1664 were warfarin, 750 rivaroxaban, 157 dabigatran and 68 apixaban. Clinical information on these patients is being collected and is thus far completed for 525 patients (about 20%).

7.3 Conclusion

There is a need to optimise warfarin therapy as it remains widely prescribed and is currently the only oral anticoagulant indicated for patients with valvular AF. An Australian government review of anticoagulant therapy in AF [24] determined a need to investigate warfarin control and factors influencing TTR variability to enable optimisation of warfarin therapy. A total of fifteen recommendations were made in this report [24], with findings from this study addressing five of these, specifically recommendation 3, 8, 9, 12 and 15.

Current recommended minimum targets for warfarin control range from 65 - 70% and this study demonstrated that patients with AF in Queensland have good quality warfarin control when managed by GPs (TTR 69%) or dedicated warfarin management programs (TTR 82%). This is in contrast to Singapore where patients with AF have levels of warfarin control below recommended targets (TTR 58%). This study identified management systems to be a major influence on warfarin control with the increased frequency of testing in Queensland, particularly by dedicated warfarin programs, in comparison to Singapore contributing to higher TTR levels. Patient factors found to influence warfarin control include chronic kidney disease, age less than 60 years, and concurrent therapy with aspirin or NSAIDs. These subsets of patients are at risk of poor warfarin control and have been identified in proposed prescribing guidelines and a proposed predictor model for warfarin control as patients who may require additional intervention to enhance TTR levels and ensure benefit from warfarin is optimised for patients with AF.

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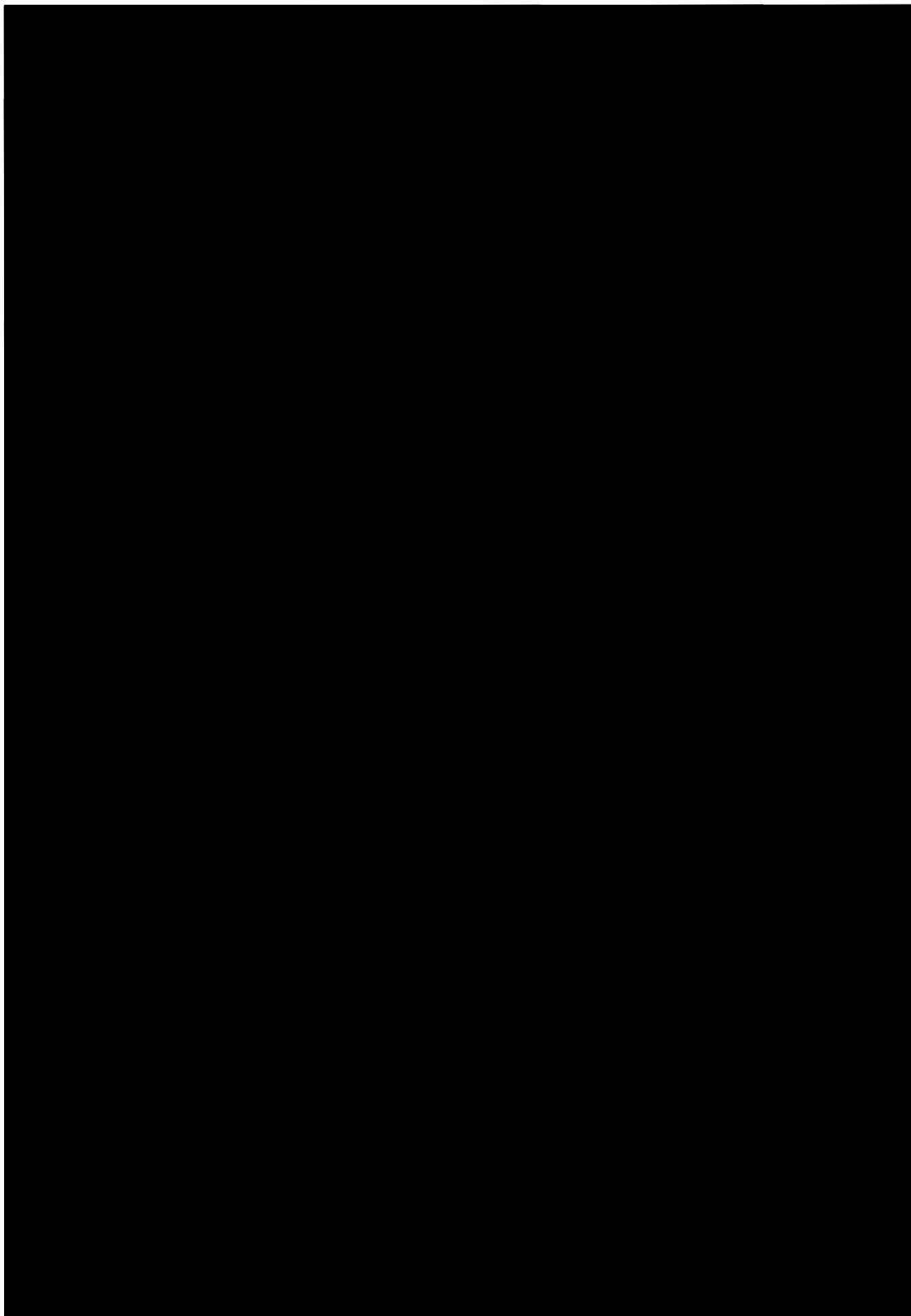
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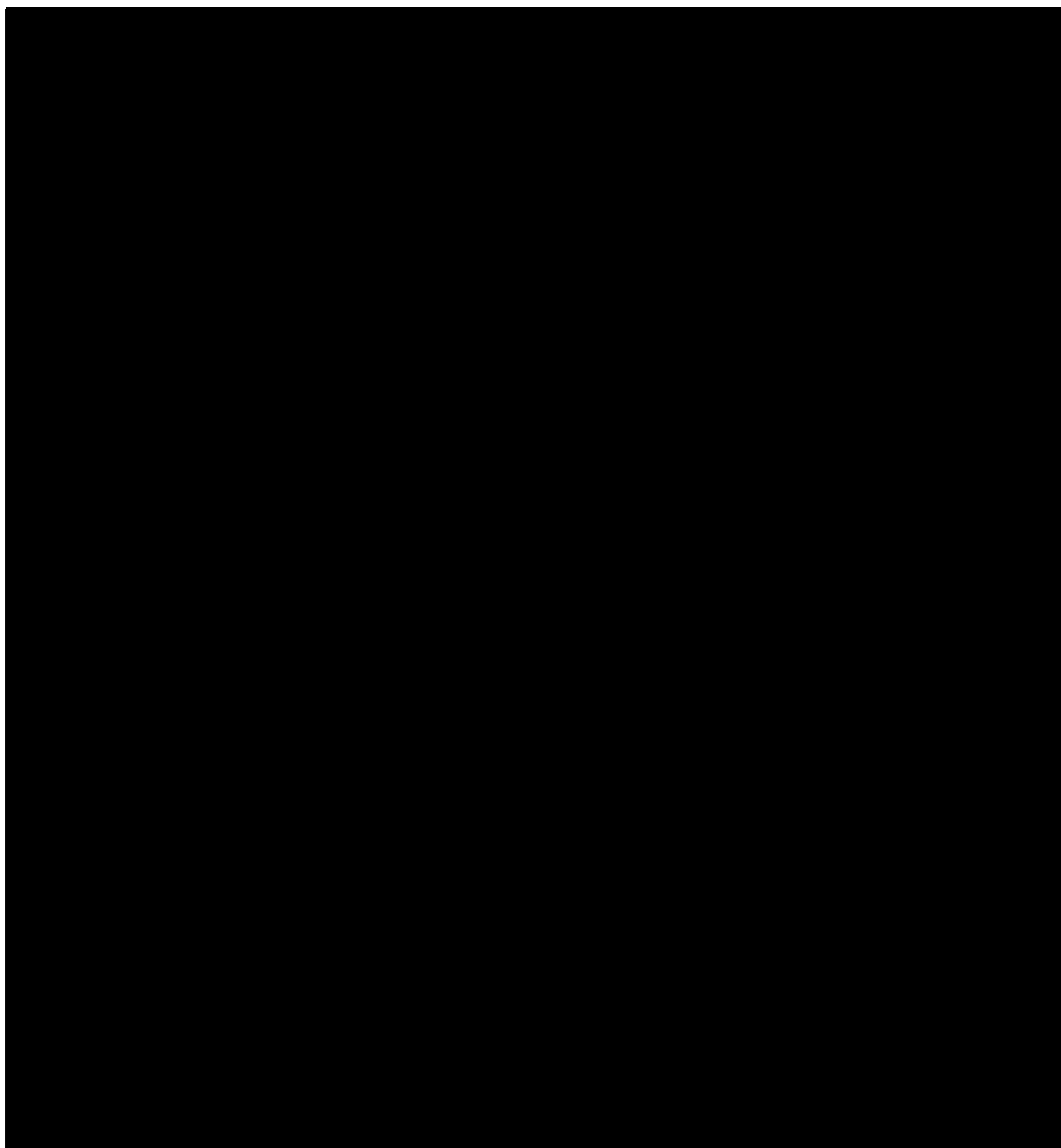
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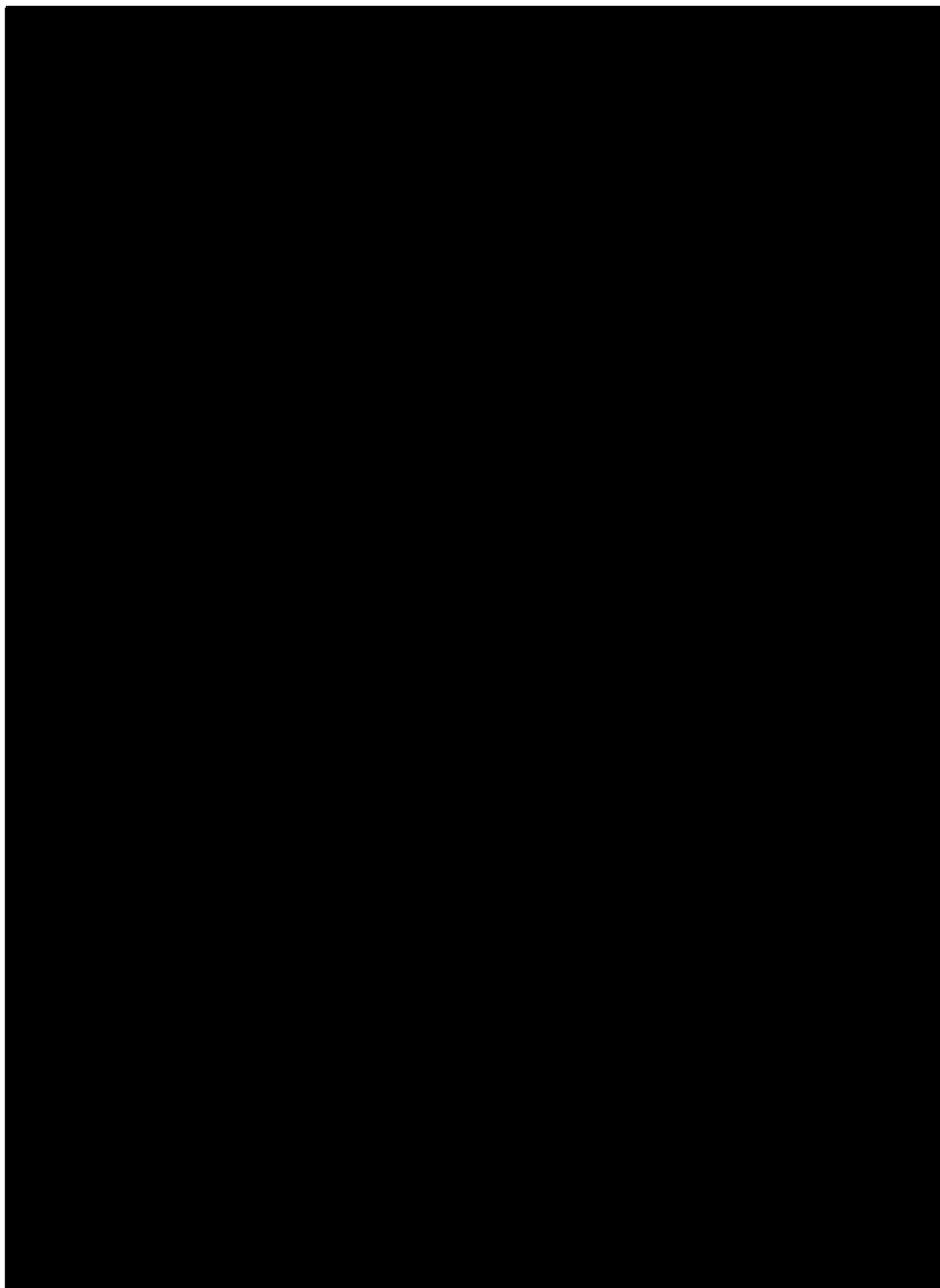
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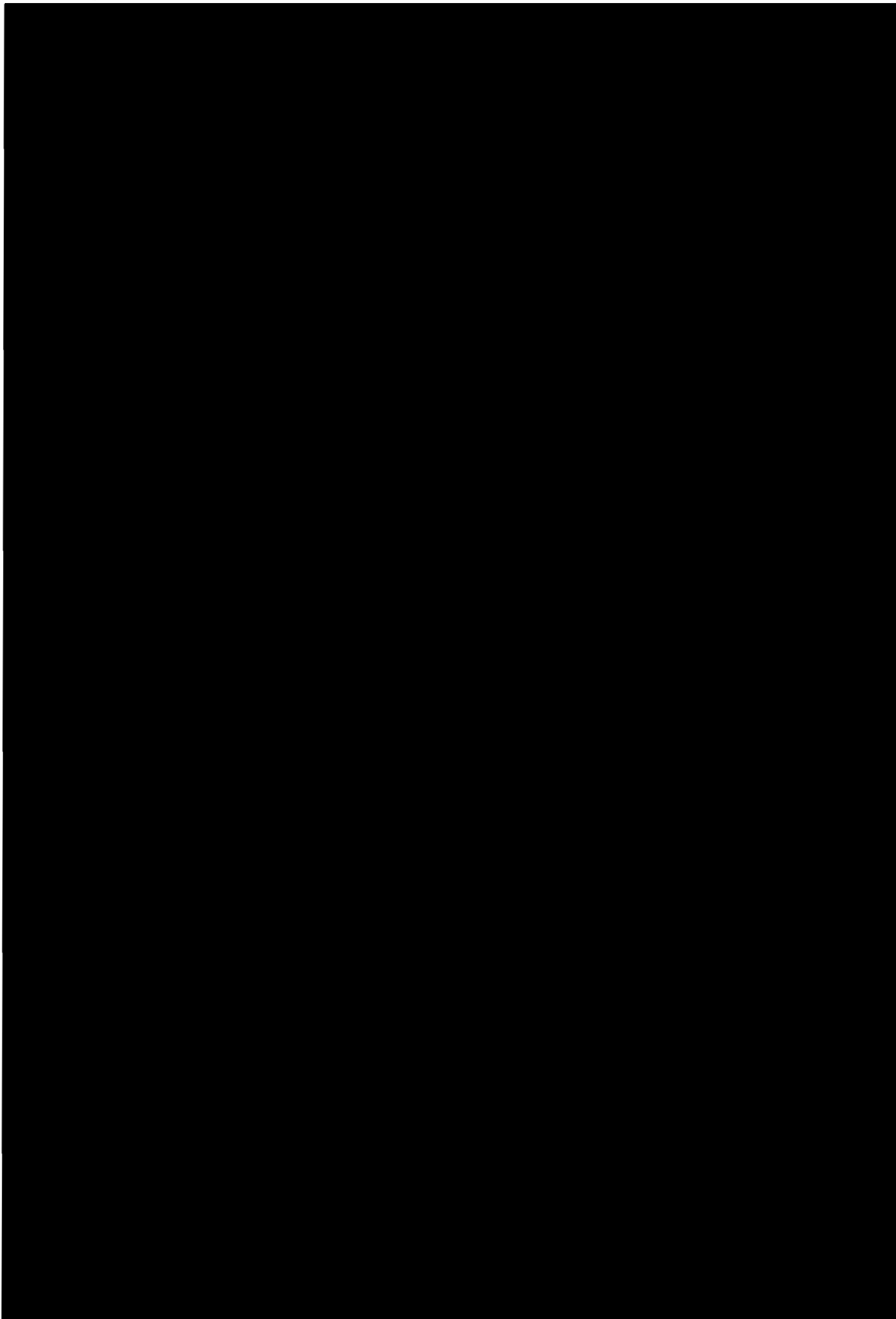
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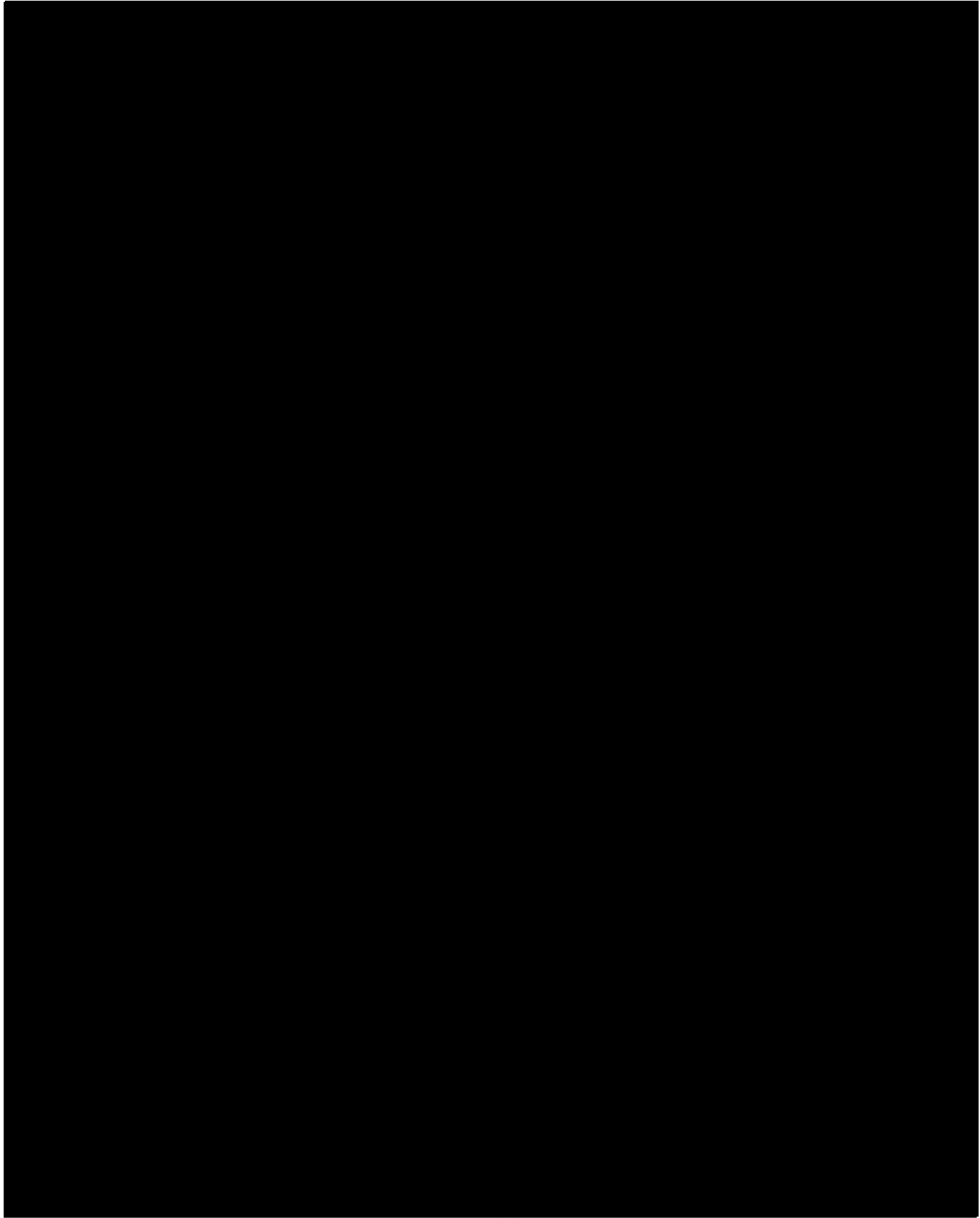
Appendix One – Ethics Approvals

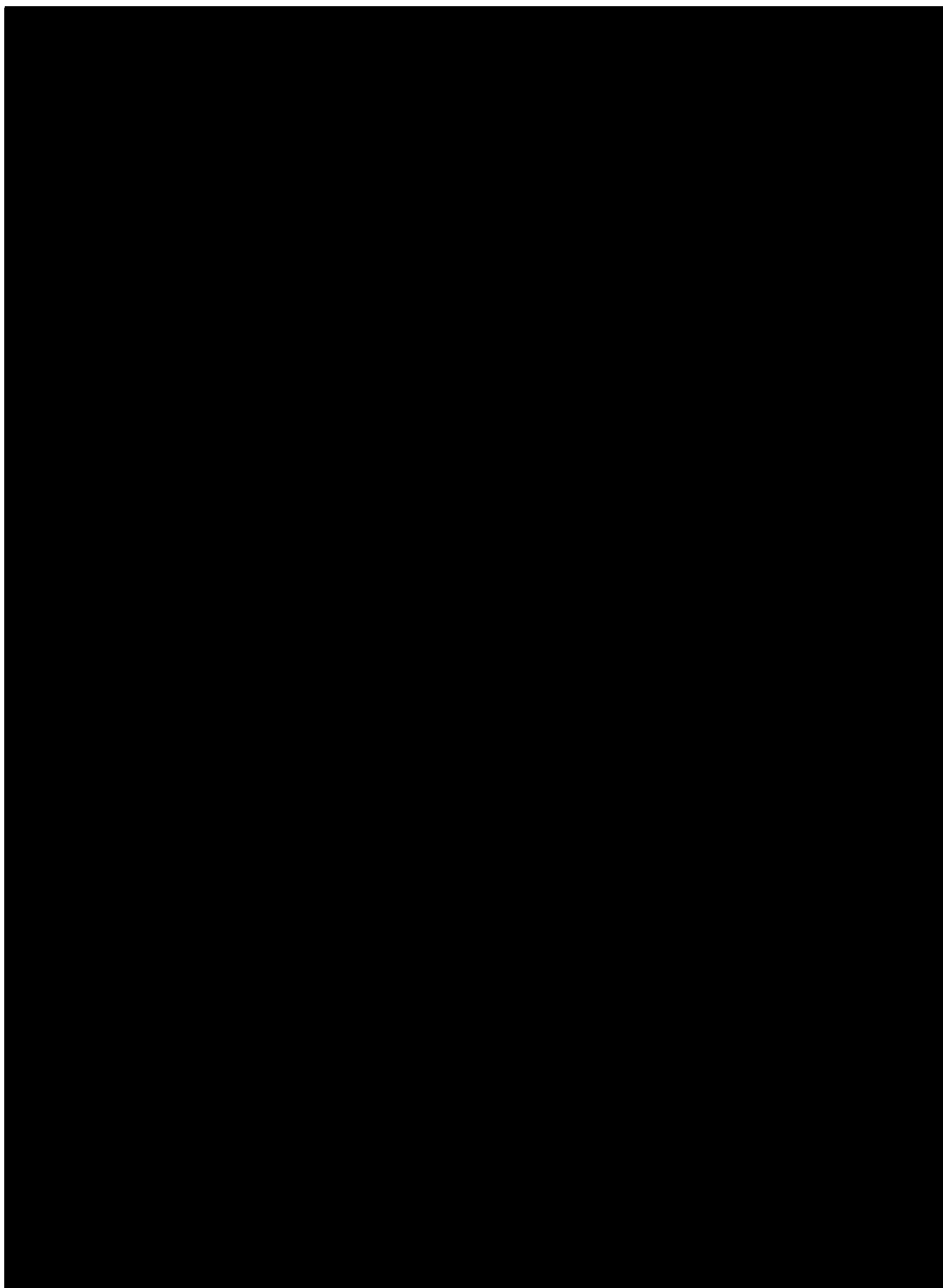


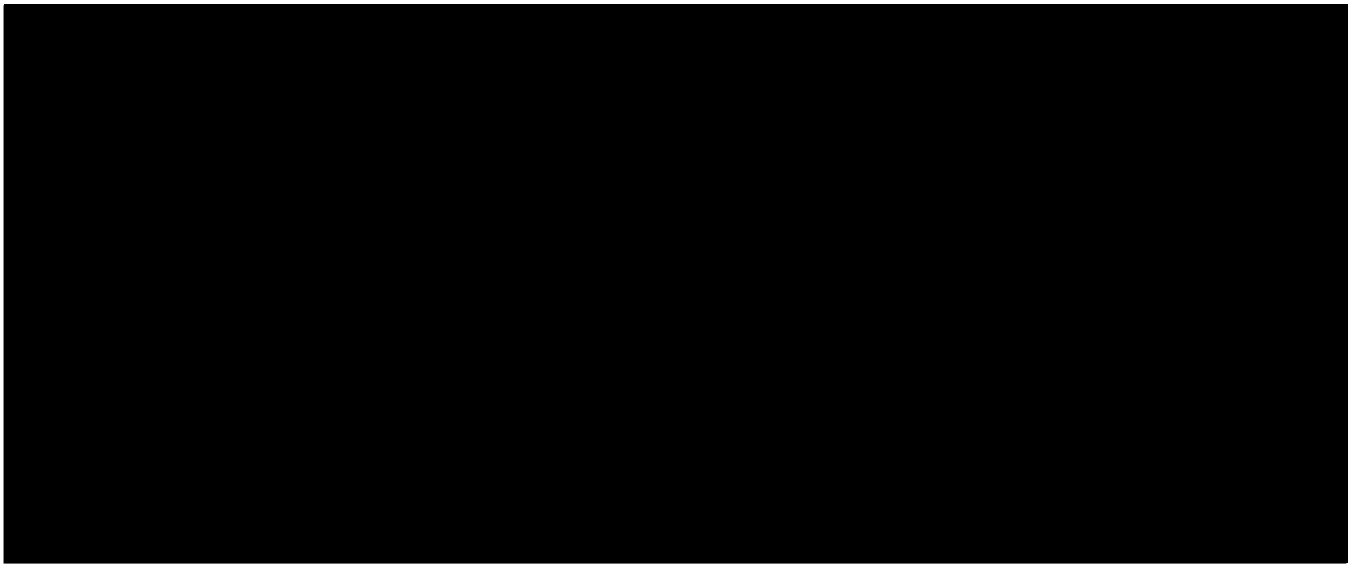


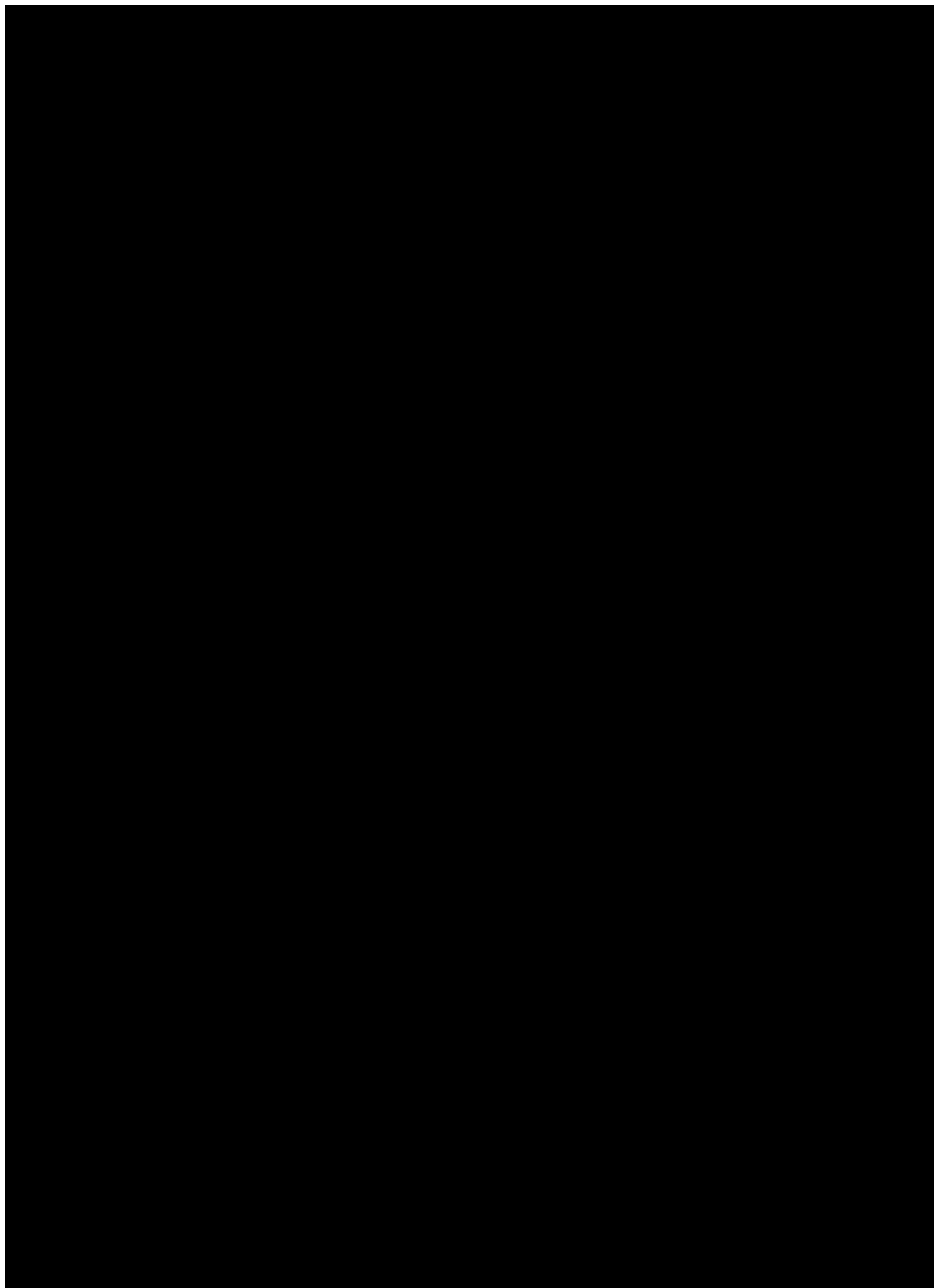












Appendix Two – Publications During Candidature

the 1990s, the number of people in the UK who are employed in the public sector has increased by 1.5 million, from 2.5 million in 1980 to 4 million in 1998. The public sector has also become an important employer of people with disabilities, with 1.5 million people with disabilities employed in the public sector in 1998, compared with 1.2 million in 1980.

There are a number of reasons why the public sector has become an important employer of people with disabilities. One reason is that the public sector has a long history of employing people with disabilities. In the 19th century, the public sector employed people with disabilities in a number of different roles, including as clerks, typists, and stenographers.

Another reason why the public sector has become an important employer of people with disabilities is that the public sector has a number of different departments and agencies, each of which has its own specific needs. This means that the public sector can employ people with disabilities in a wide range of roles, from clerical to professional.

Finally, the public sector has a number of different policies and procedures in place to support people with disabilities. This means that people with disabilities can find it easier to get a job in the public sector, and to stay in their jobs for a long time.

There are a number of challenges that the public sector faces when it comes to employing people with disabilities. One challenge is that the public sector has a number of different departments and agencies, each of which has its own specific needs. This means that the public sector can find it difficult to find people with disabilities who have the right skills and experience for the job.

Another challenge is that the public sector has a number of different policies and procedures in place to support people with disabilities. This means that the public sector can find it difficult to find people with disabilities who are familiar with these policies and procedures.

Finally, the public sector has a number of different challenges when it comes to supporting people with disabilities in the workplace. One challenge is that the public sector has a number of different departments and agencies, each of which has its own specific needs. This means that the public sector can find it difficult to find people with disabilities who have the right skills and experience for the job.

Another challenge is that the public sector has a number of different policies and procedures in place to support people with disabilities. This means that the public sector can find it difficult to find people with disabilities who are familiar with these policies and procedures.

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the 1990s, the number of people in the world who are under 15 years of age has increased by 1.2 billion, from 1.1 billion in 1980 to 2.3 billion in 1999. The number of people aged 15 years and over has increased by 1.1 billion, from 1.1 billion in 1980 to 2.2 billion in 1999.

There are a number of reasons why the world population is increasing so rapidly. One of the main reasons is that the number of children born to each woman has increased. In 1980, the average woman in the world had 2.5 children. In 1999, the average woman in the world had 2.7 children.

Another reason why the world population is increasing so rapidly is that the number of people who are living longer is increasing. In 1980, the average person in the world lived for 60 years. In 1999, the average person in the world lived for 65 years.

There are a number of reasons why the number of people who are living longer is increasing. One of the main reasons is that the number of people who are getting older is increasing. In 1980, there were 1.1 billion people aged 65 years and over. In 1999, there were 1.2 billion people aged 65 years and over.

Another reason why the number of people who are living longer is increasing is that the number of people who are getting younger is increasing. In 1980, there were 1.1 billion people aged 15 years and under. In 1999, there were 2.3 billion people aged 15 years and under.

There are a number of reasons why the number of people who are getting younger is increasing. One of the main reasons is that the number of people who are getting married is increasing. In 1980, there were 1.1 billion people aged 15 years and over who were married. In 1999, there were 1.2 billion people aged 15 years and over who were married.

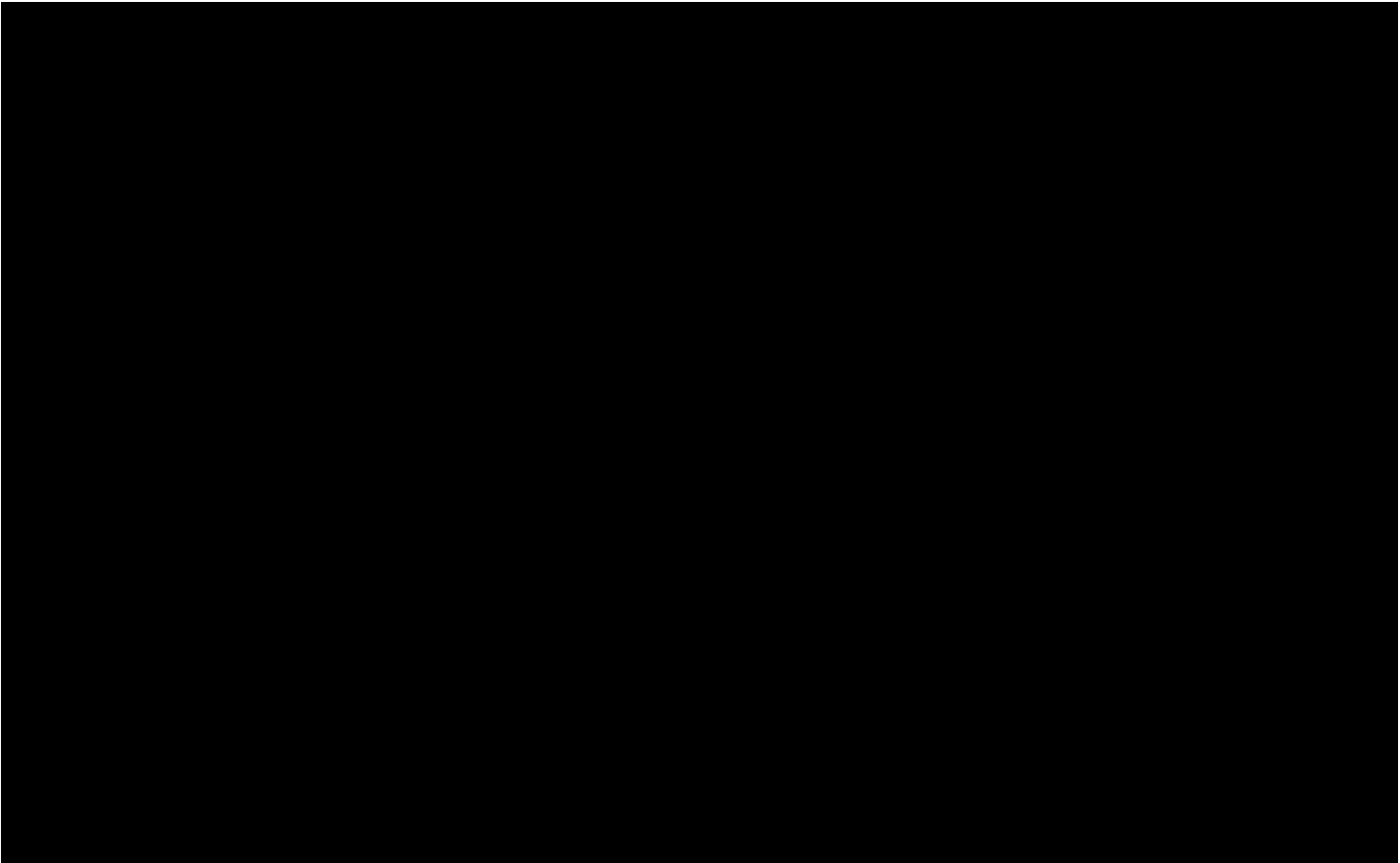
Another reason why the number of people who are getting younger is increasing is that the number of people who are getting divorced is increasing. In 1980, there were 1.1 billion people aged 15 years and over who were divorced. In 1999, there were 1.2 billion people aged 15 years and over who were divorced.

There are a number of reasons why the number of people who are getting divorced is increasing. One of the main reasons is that the number of people who are getting married is increasing. In 1980, there were 1.1 billion people aged 15 years and over who were married. In 1999, there were 1.2 billion people aged 15 years and over who were married.

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the 1990s, the incidence of *S. flexneri* infections has increased in the United Kingdom [10]. In the United States, *S. flexneri* has been reported as the most common serotype of *Shigella* isolated from patients with shigellosis [11].

There is a paucity of data on the epidemiology of *S. flexneri* in the United Kingdom. In the 1980s, *S. flexneri* was the most commonly isolated *Shigella* serotype from patients with shigellosis in the United Kingdom [12]. In the 1990s, *S. flexneri* was the most commonly isolated *Shigella* serotype from patients with shigellosis in the United Kingdom [13].

The aim of this study was to determine the prevalence of *S. flexneri* in the United Kingdom. The study was designed to determine the prevalence of *S. flexneri* in the United Kingdom. The study was designed to determine the prevalence of *S. flexneri* in the United Kingdom. The study was designed to determine the prevalence of *S. flexneri* in the United Kingdom.

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the 1990s, the number of people in the UK who are employed in the public sector has increased by 1.5 million (1990–1999) and the number of people in the public sector has increased by 2.5 million (1990–1999) (Department of Health 2000).

There is a growing emphasis on the need to improve the efficiency of the public sector and to ensure that the public sector is able to deliver the best possible value for money. This has led to a number of initiatives, including the introduction of the Public Finance Management (PFM) system, the introduction of the Public Sector Comparator (PSC), and the introduction of the Public Sector Audit Commission (PSAC).

The PFM system is a system of financial management that is designed to ensure that the public sector is able to deliver the best possible value for money. The PSC is a system of financial management that is designed to ensure that the public sector is able to deliver the best possible value for money. The PSAC is a system of financial management that is designed to ensure that the public sector is able to deliver the best possible value for money.

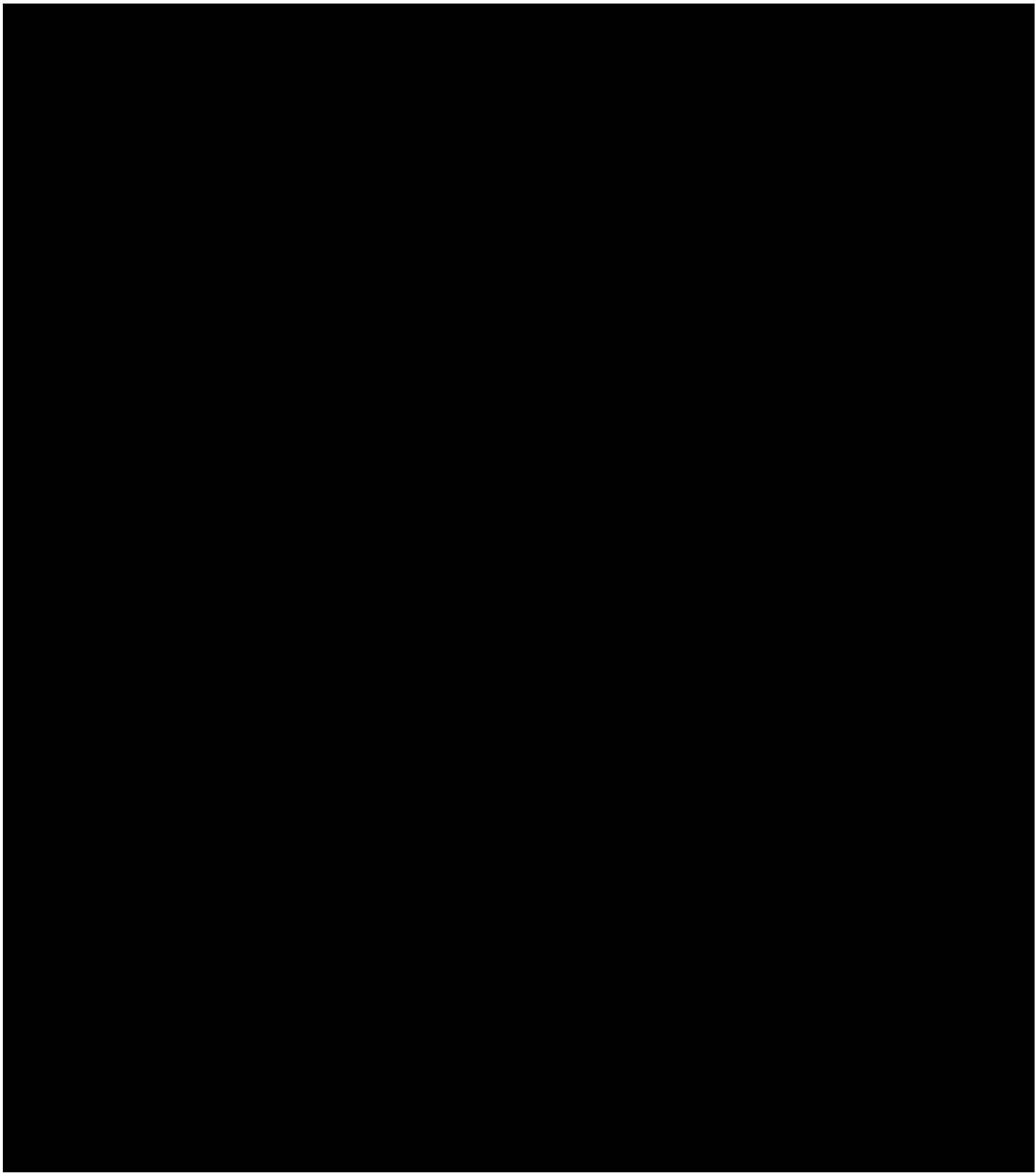
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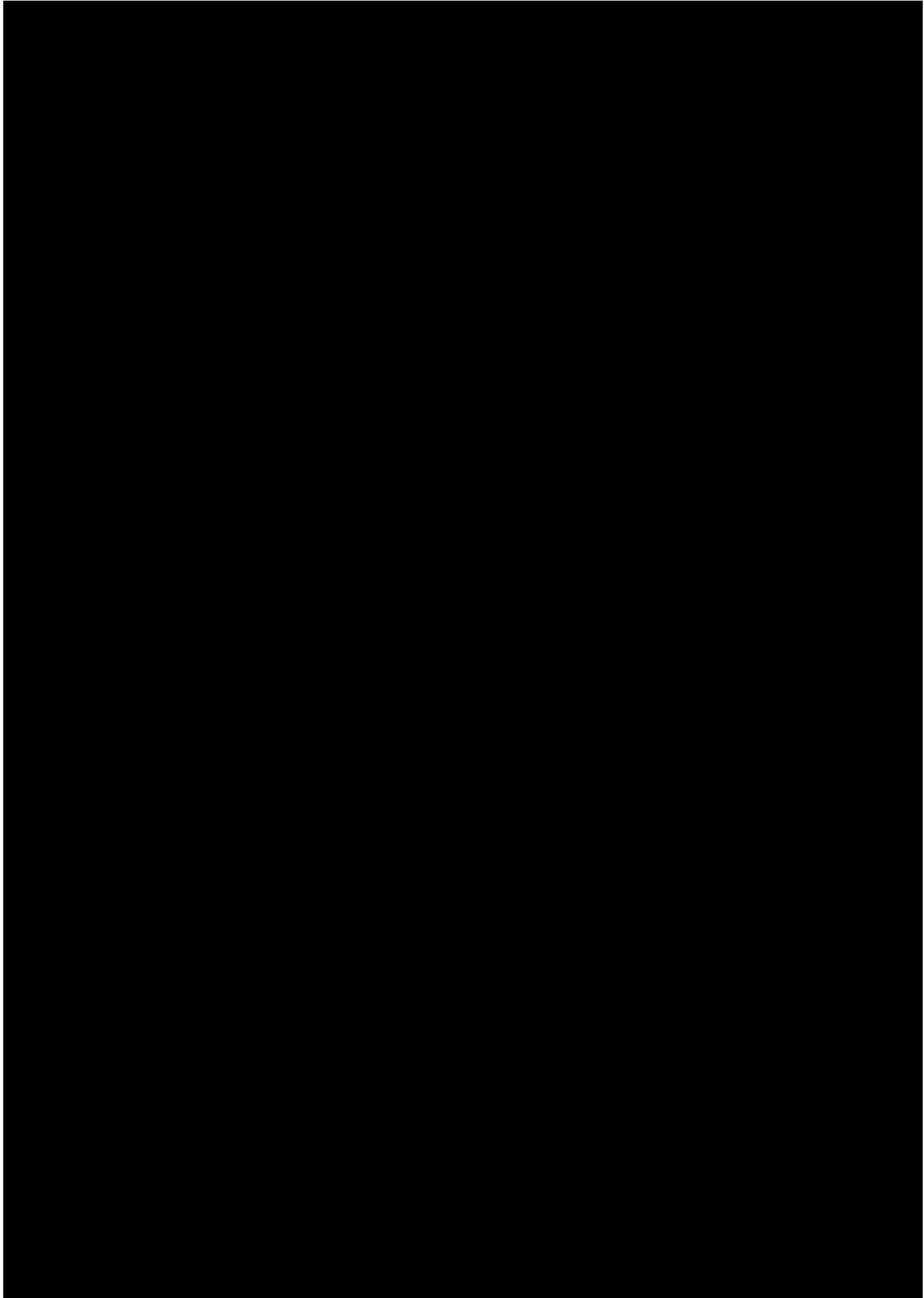
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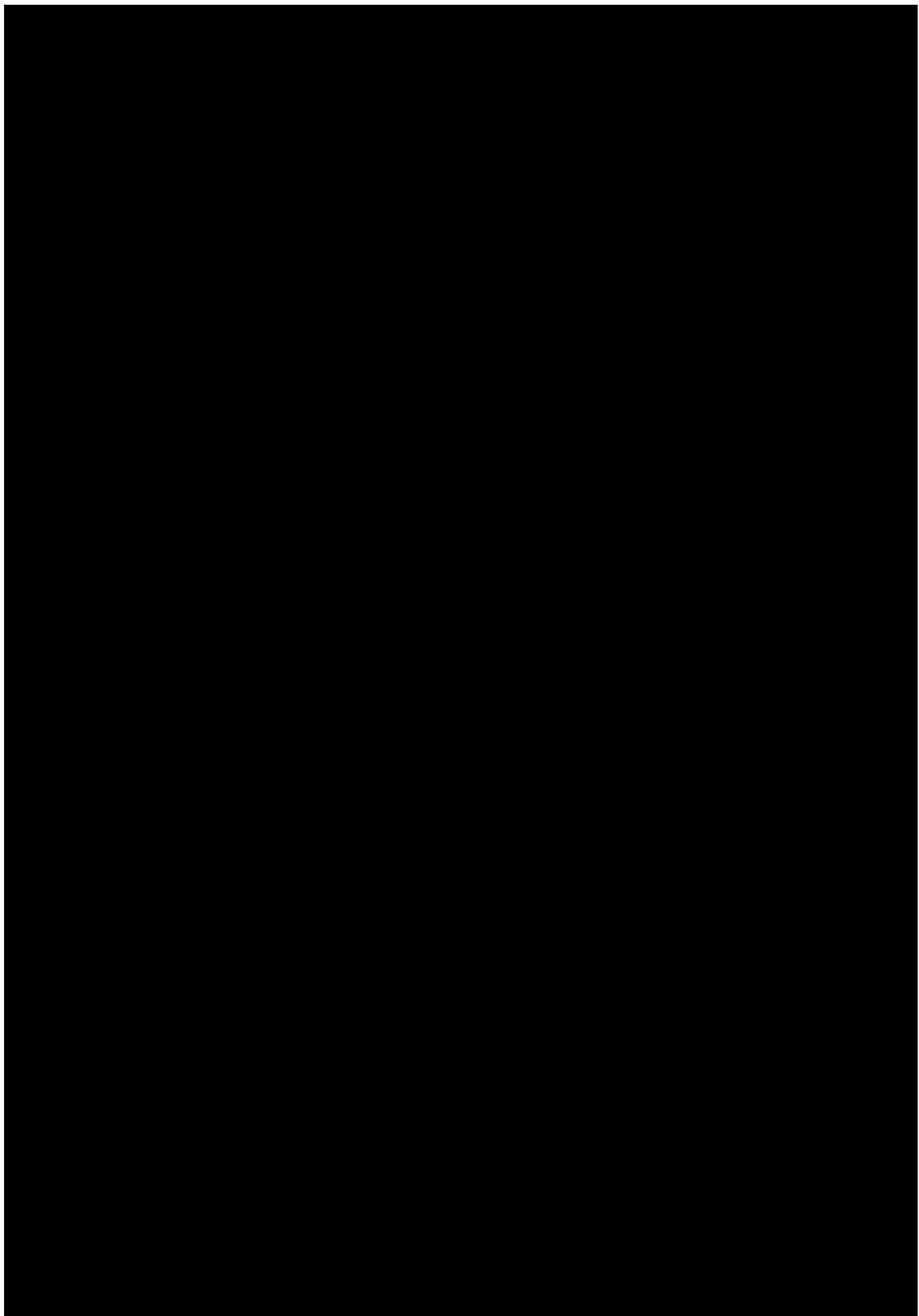
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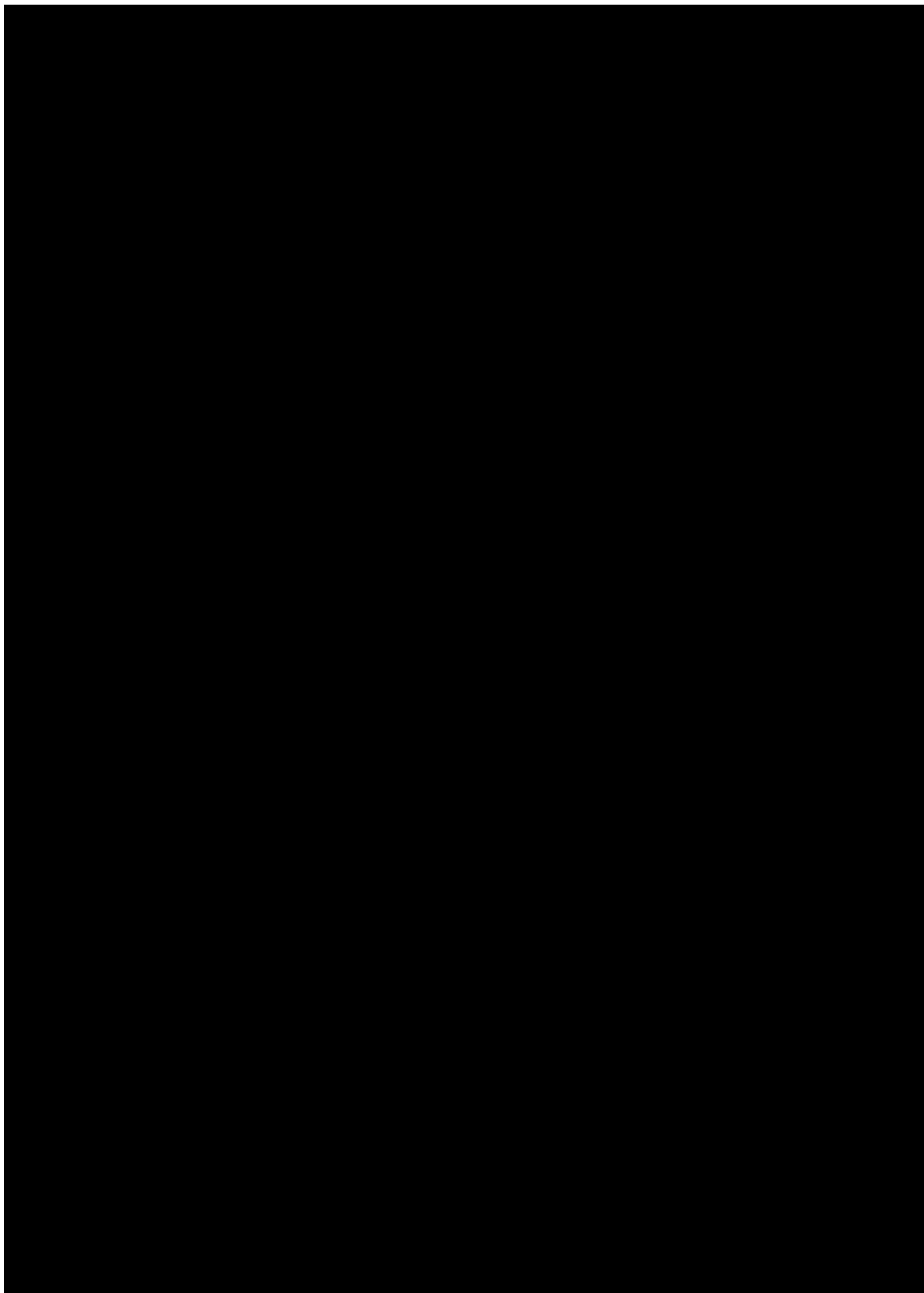
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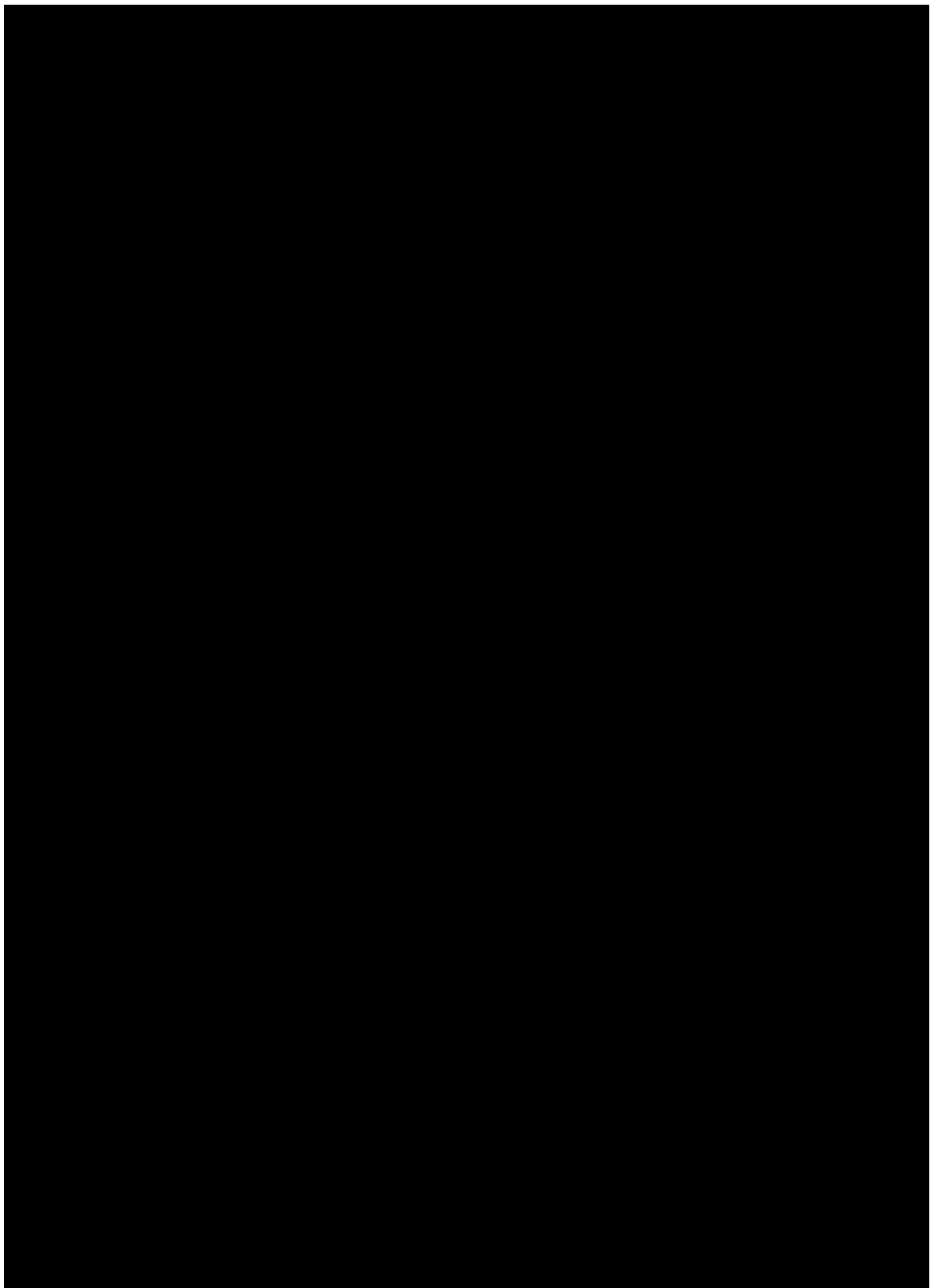




The first of these is the *Journal of the American Medical Association* (JAMA), which has been a leading voice in the medical profession for over a century. It is a weekly publication that covers a wide range of topics, from clinical medicine to public health. The second is the *New England Journal of Medicine* (NEJM), which is a leading journal in the field of internal medicine. The third is the *Lancet*, which is a leading journal in the field of general practice. The fourth is the *British Medical Journal* (BMJ), which is a leading journal in the field of general practice. The fifth is the *Medical Record*, which is a leading journal in the field of general practice. The sixth is the *Medical News*, which is a leading journal in the field of general practice. The seventh is the *Medical Record*, which is a leading journal in the field of general practice. The eighth is the *Medical News*, which is a leading journal in the field of general practice. The ninth is the *Medical Record*, which is a leading journal in the field of general practice. The tenth is the *Medical News*, which is a leading journal in the field of general practice.

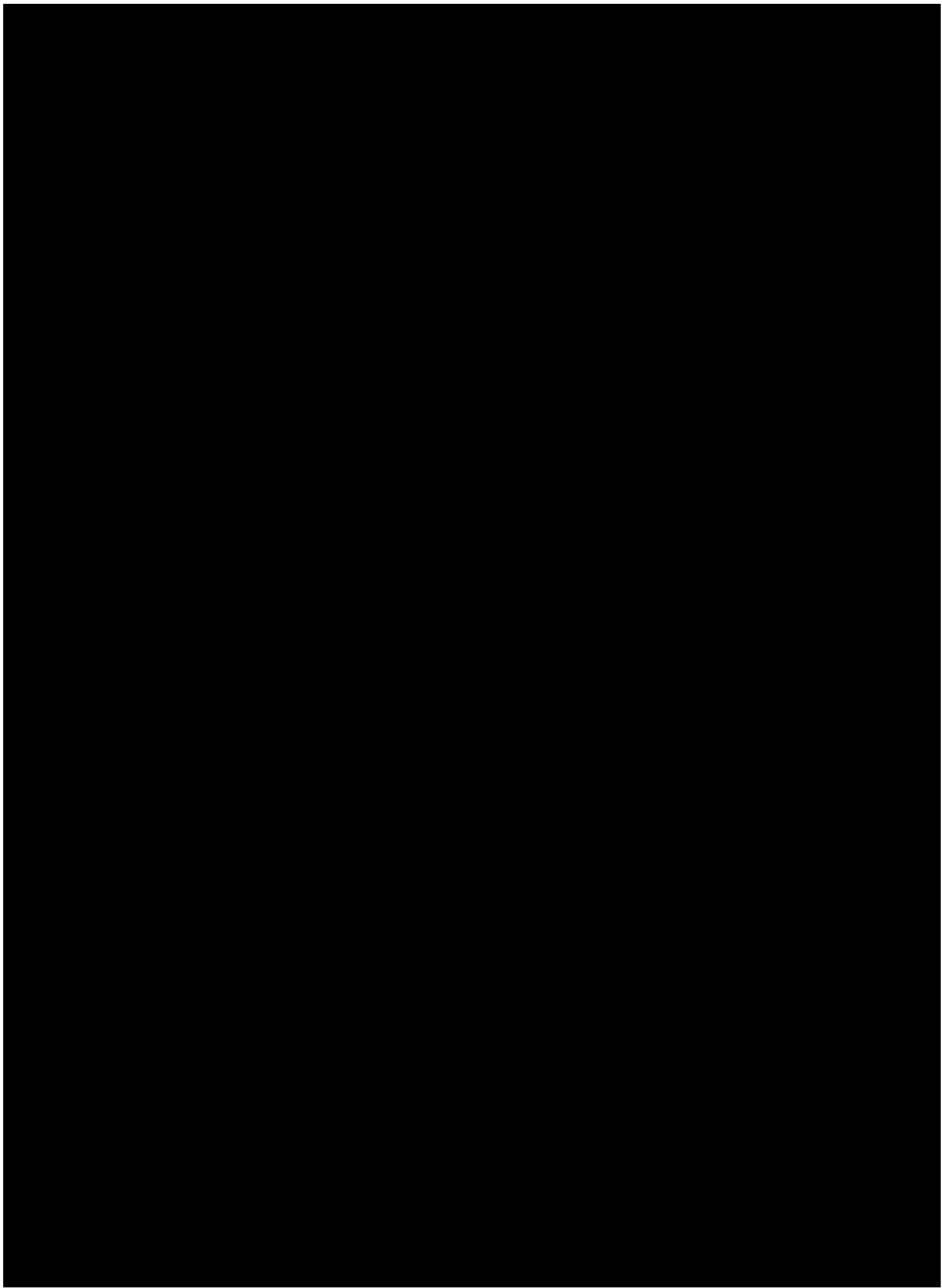


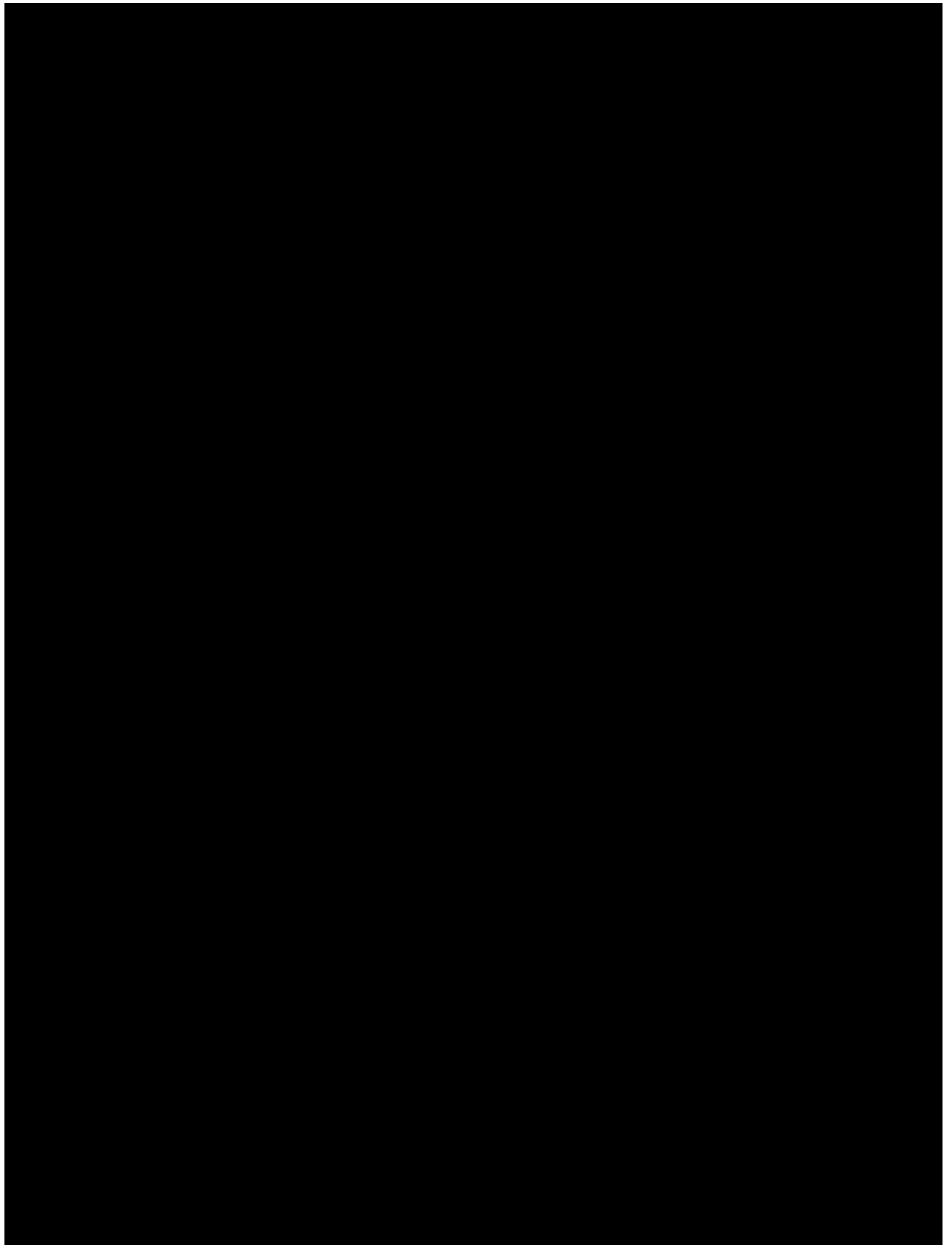




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the 1990s, the number of people in the world who are under 15 years of age has increased by 1.2 billion, from 1.1 billion in 1980 to 2.3 billion in 1999. The number of people aged 15 years and over has increased by 1.1 billion, from 1.1 billion in 1980 to 2.2 billion in 1999.

There are a number of reasons why the world population is growing so rapidly. One of the main reasons is that the number of children born to each woman has increased. In 1980, the average woman in the world had 2.5 children. In 1999, the average woman in the world had 2.7 children.

Another reason why the world population is growing so rapidly is that the number of people who are surviving to old age has increased. In 1980, the average person in the world lived for 55 years. In 1999, the average person in the world lived for 65 years.

There are a number of reasons why the number of people who are surviving to old age has increased. One of the main reasons is that the number of people who are dying from disease and violence has decreased. In 1980, there were 1.5 million deaths from disease and violence in the world. In 1999, there were 1.1 million deaths from disease and violence in the world.

Another reason why the number of people who are surviving to old age has increased is that the number of people who are living in poverty has decreased. In 1980, there were 1.5 billion people in the world who were living in poverty. In 1999, there were 1.1 billion people in the world who were living in poverty.

There are a number of reasons why the number of people who are living in poverty has decreased. One of the main reasons is that the number of people who are working has increased. In 1980, there were 1.5 billion people in the world who were working. In 1999, there were 1.9 billion people in the world who were working.

Another reason why the number of people who are living in poverty has decreased is that the number of people who are educated has increased. In 1980, there were 1.5 billion people in the world who were not educated. In 1999, there were 1.1 billion people in the world who were not educated.

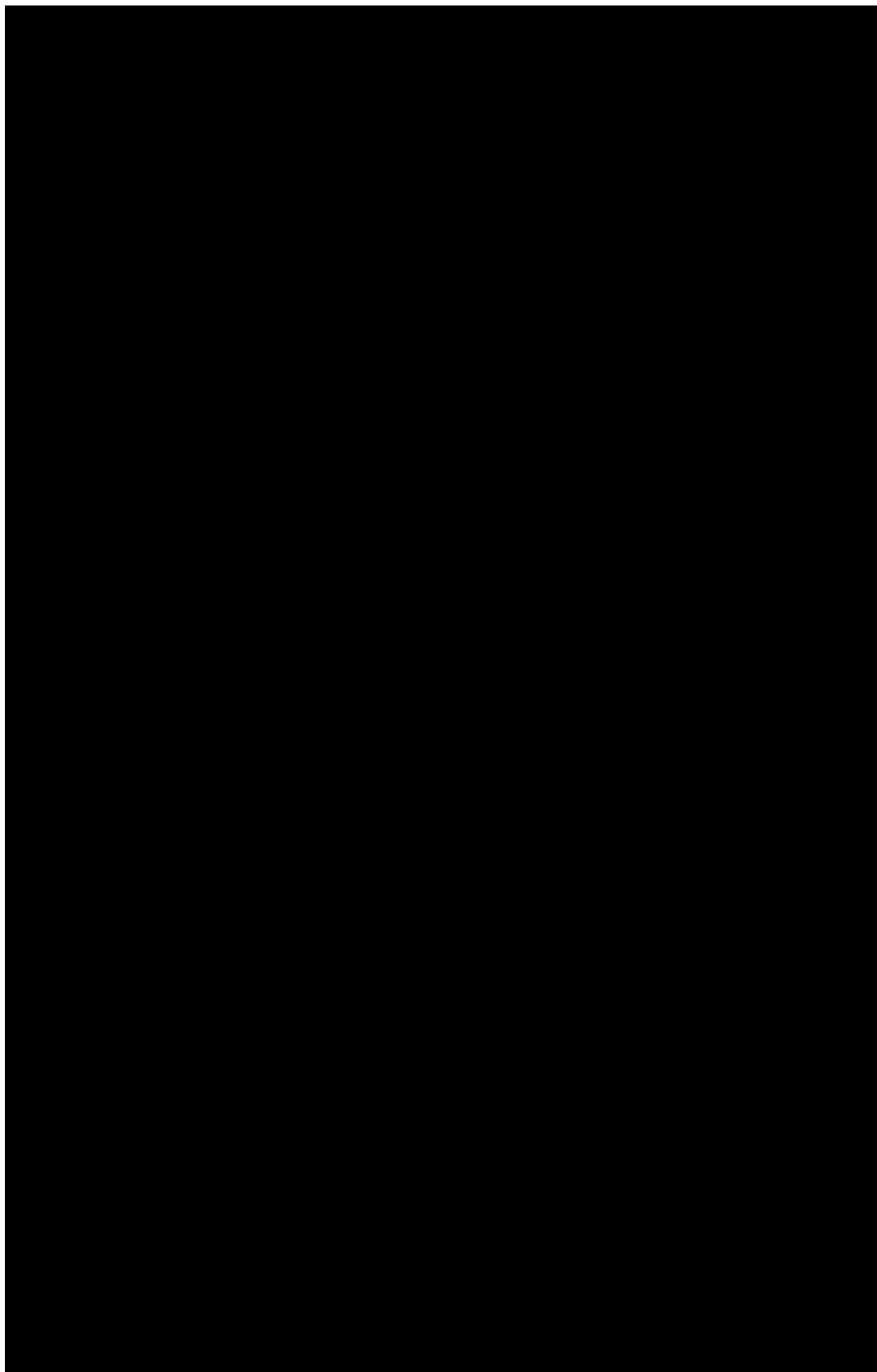
There are a number of reasons why the number of people who are not educated has decreased. One of the main reasons is that the number of people who are attending school has increased. In 1980, there were 1.5 billion people in the world who were not attending school. In 1999, there were 1.1 billion people in the world who were not attending school.

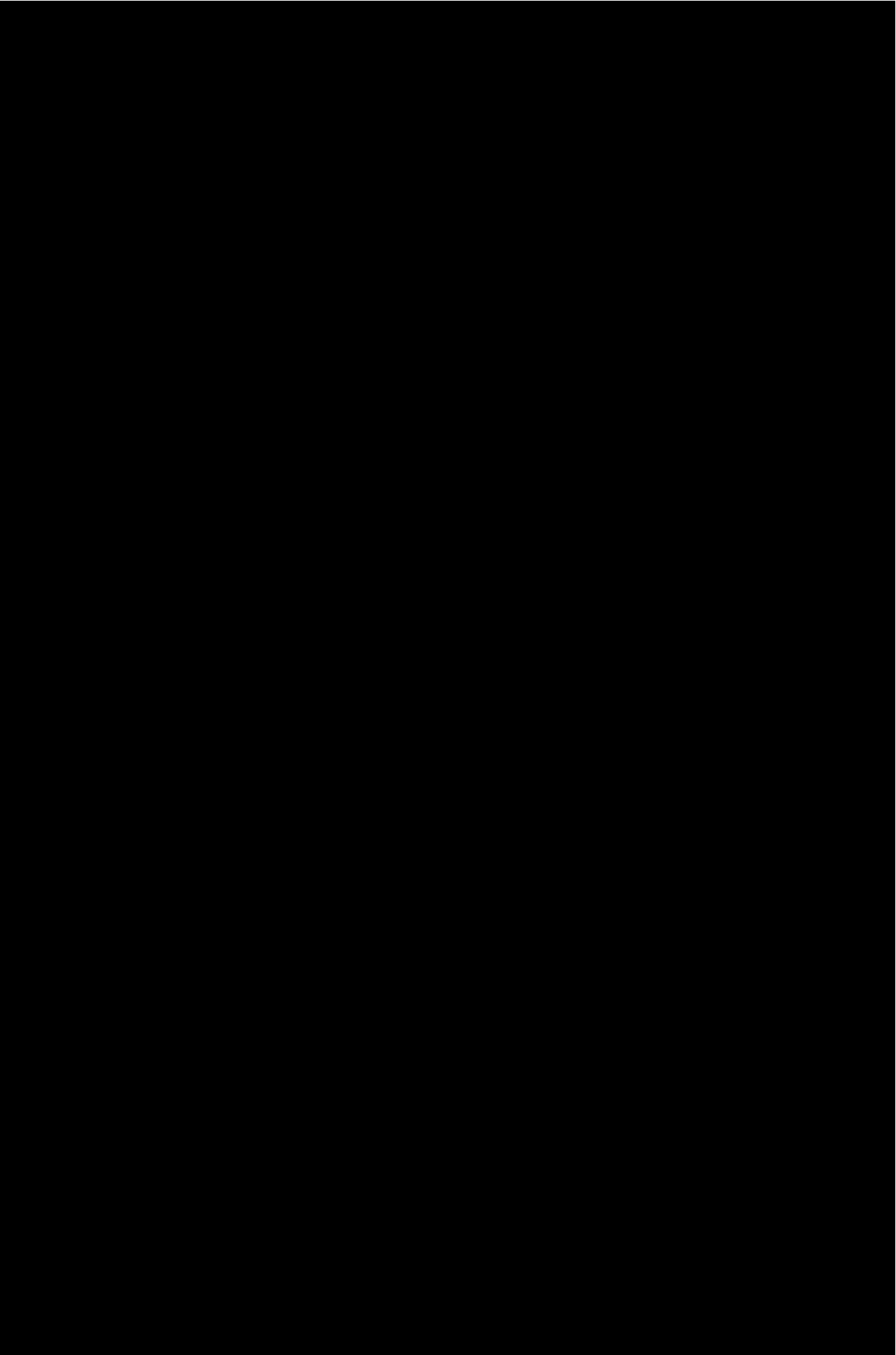
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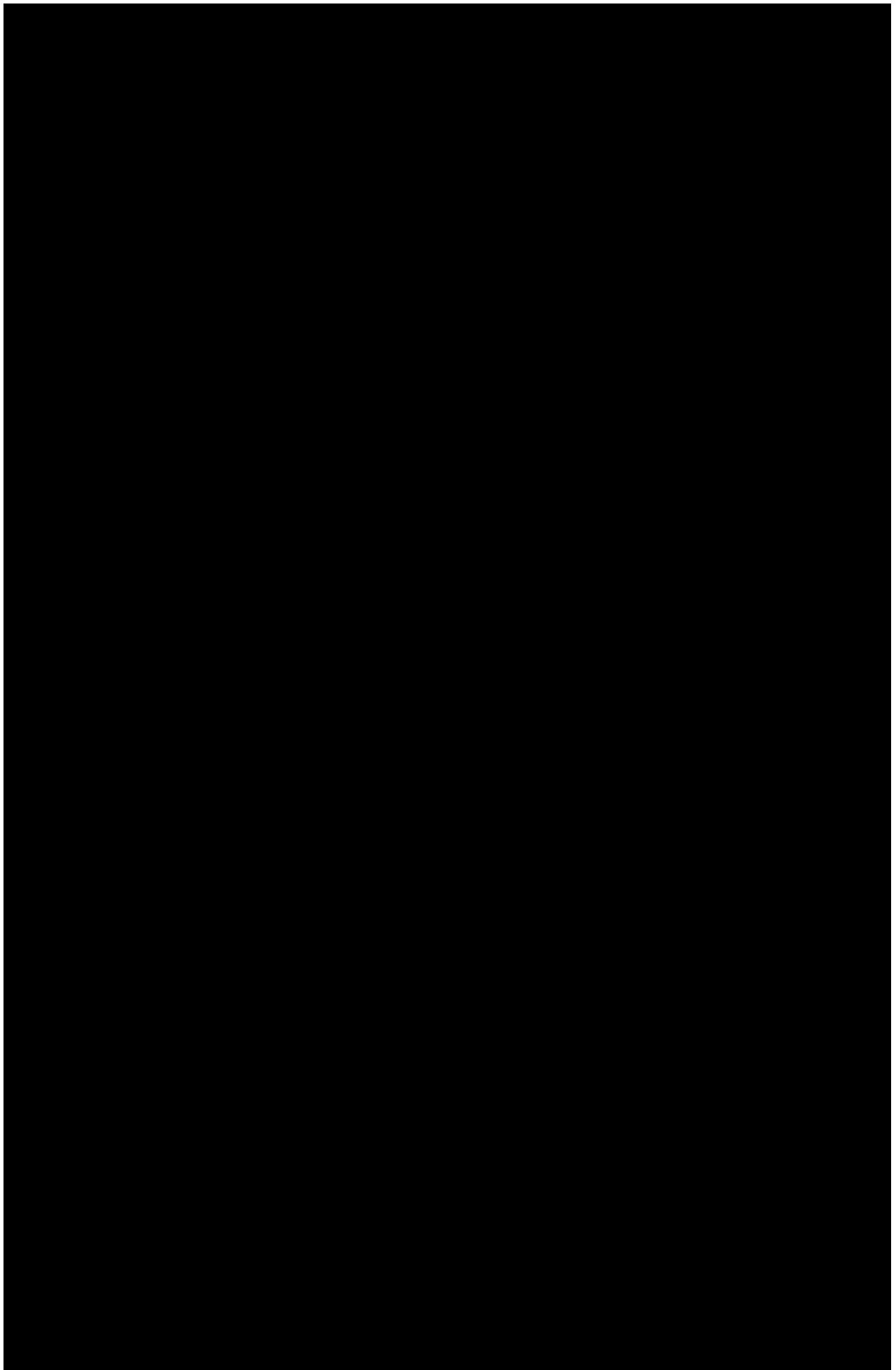
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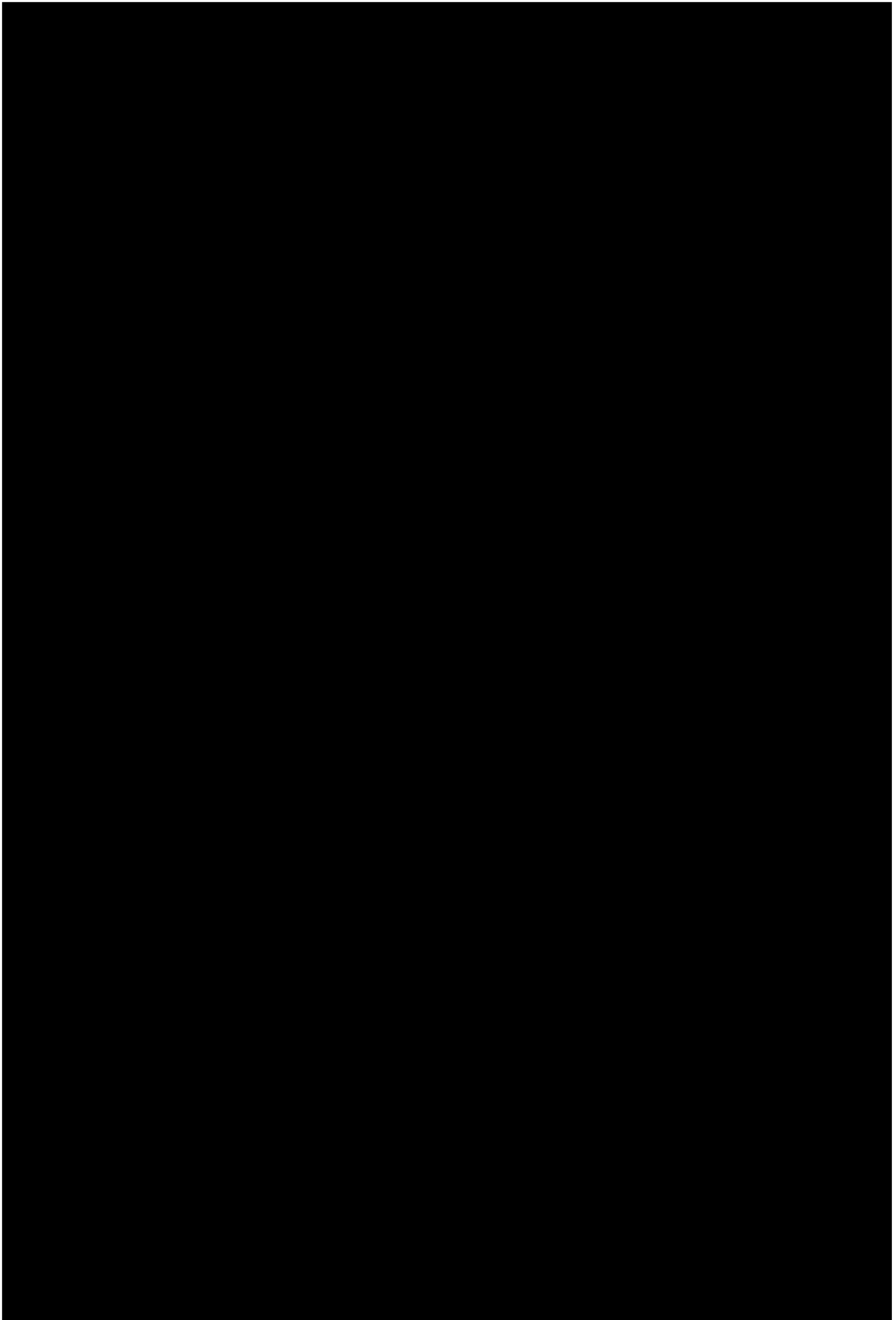
[The following text is a dense, handwritten manuscript, likely a letter or a page from a book. It is written in a cursive script and is mostly illegible due to the quality of the scan. The text appears to be a continuous paragraph or a series of connected sentences. The handwriting is somewhat slanted and the ink is dark. There are some visible ink blots and the paper has a slightly aged appearance. The text is written in a single column, filling most of the page area.]



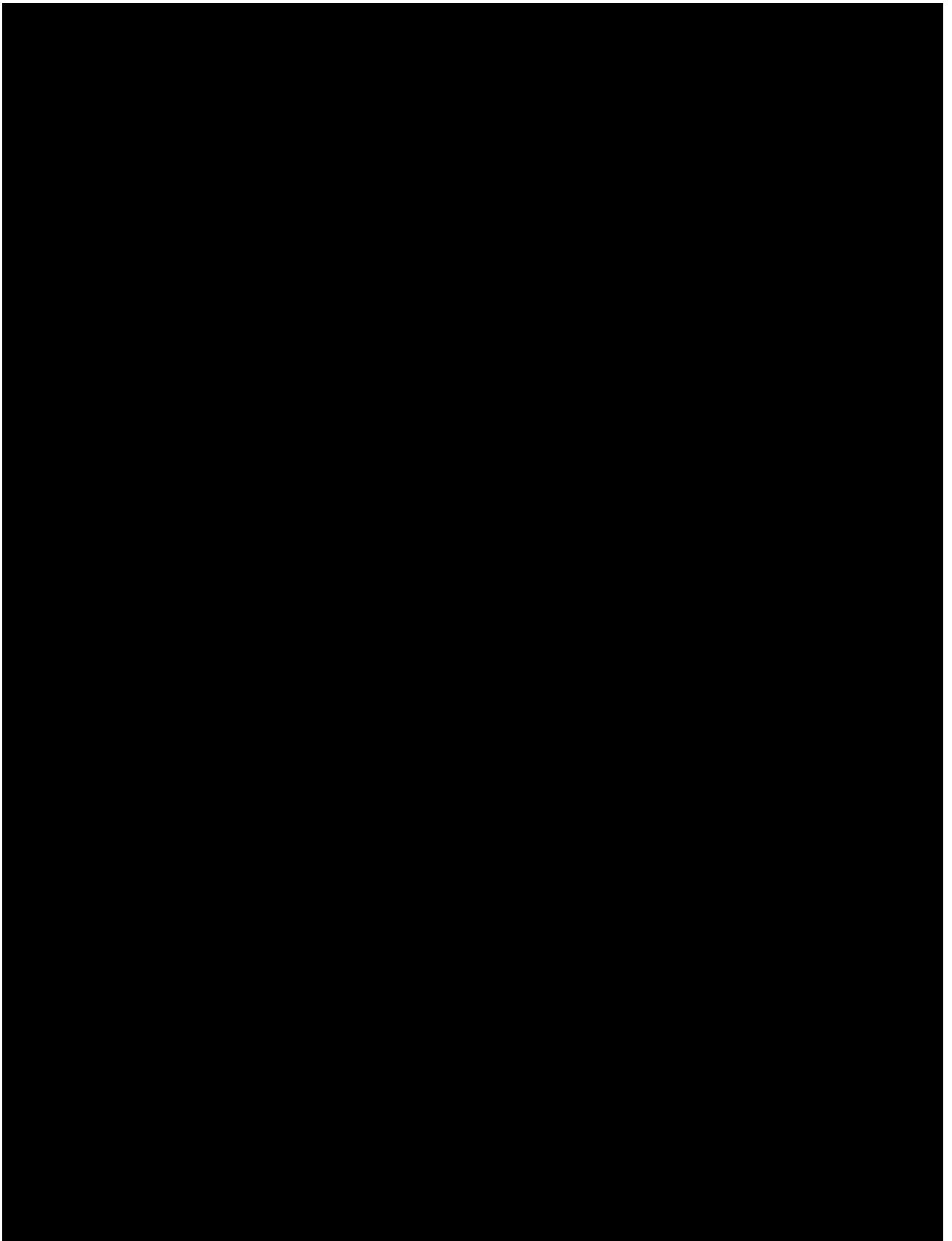


The first part of the paper discusses the importance of understanding the cultural context of the research. It highlights the need for researchers to be sensitive to the values and beliefs of the communities they are studying. This is particularly important in the field of education, where cultural differences can significantly impact learning outcomes. The paper then moves on to discuss the challenges of conducting research in culturally diverse settings. It notes that researchers often face difficulties in finding appropriate research methods and in interpreting the data they collect. To address these challenges, the paper suggests that researchers should adopt a more flexible and open-minded approach to their research. This involves being willing to learn from the community and to adapt their research methods as needed. The paper also emphasizes the importance of building trust and rapport with the community. This is essential for ensuring that the research is conducted in a respectful and ethical manner. Finally, the paper concludes by noting that while there are many challenges to conducting research in culturally diverse settings, it is also an opportunity to gain valuable insights into the lives of people from different cultures. By taking the time to understand and appreciate these differences, researchers can make a significant contribution to the field of education and to the well-being of the communities they study.









the 1990s, the incidence of *S. flexneri* has increased in the United Kingdom [10]. In the United States, *S. flexneri* has been reported to be the most common serotype of *Shigella* isolated from children with shigellosis [11].

There is a paucity of data on the epidemiology of *S. flexneri* in the United Kingdom. In the 1970s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [12]. In the 1980s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [13].

In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [14]. In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [15].

In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [16]. In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [17].

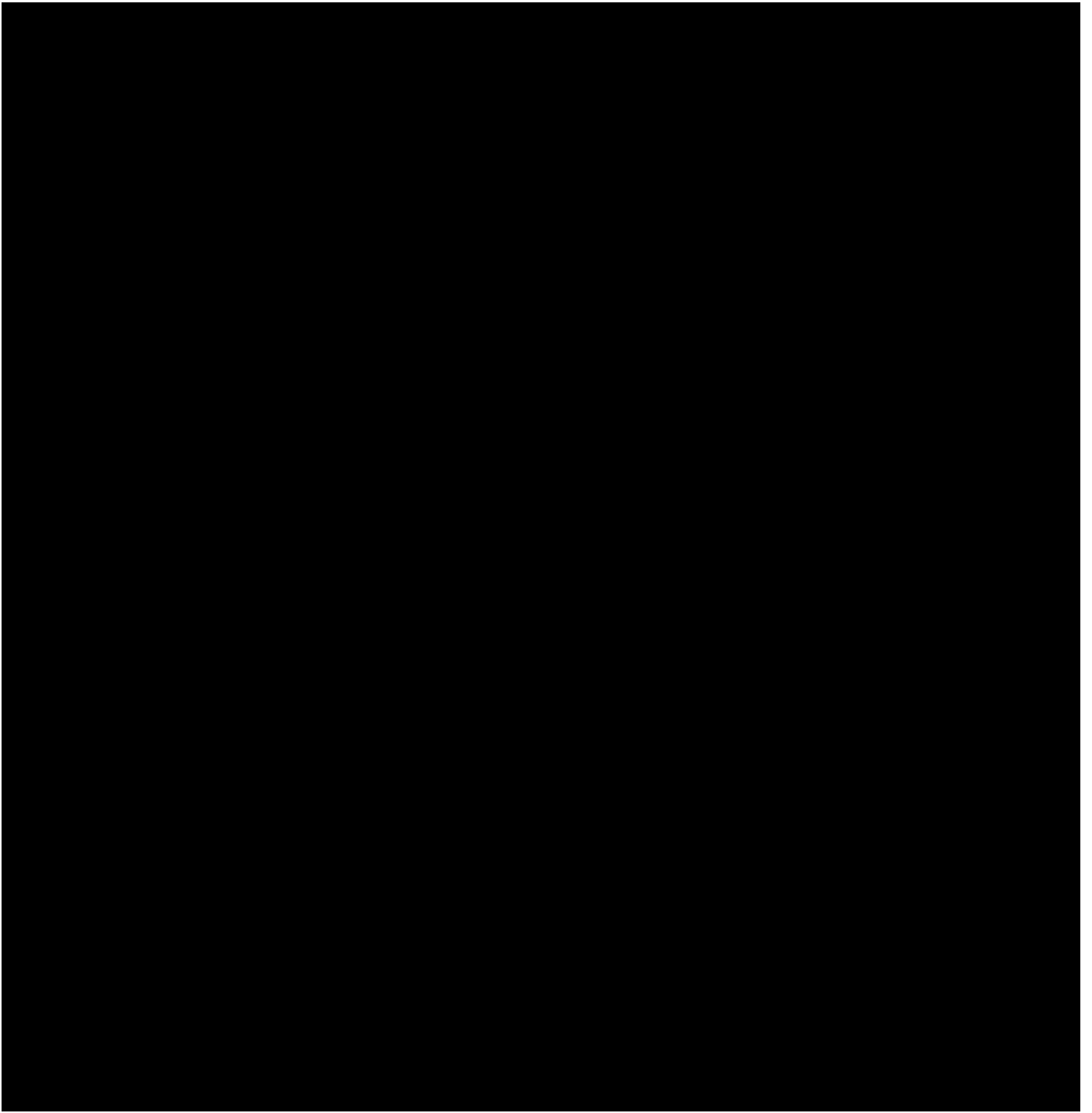
In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [18]. In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [19].

In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [20]. In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [21].

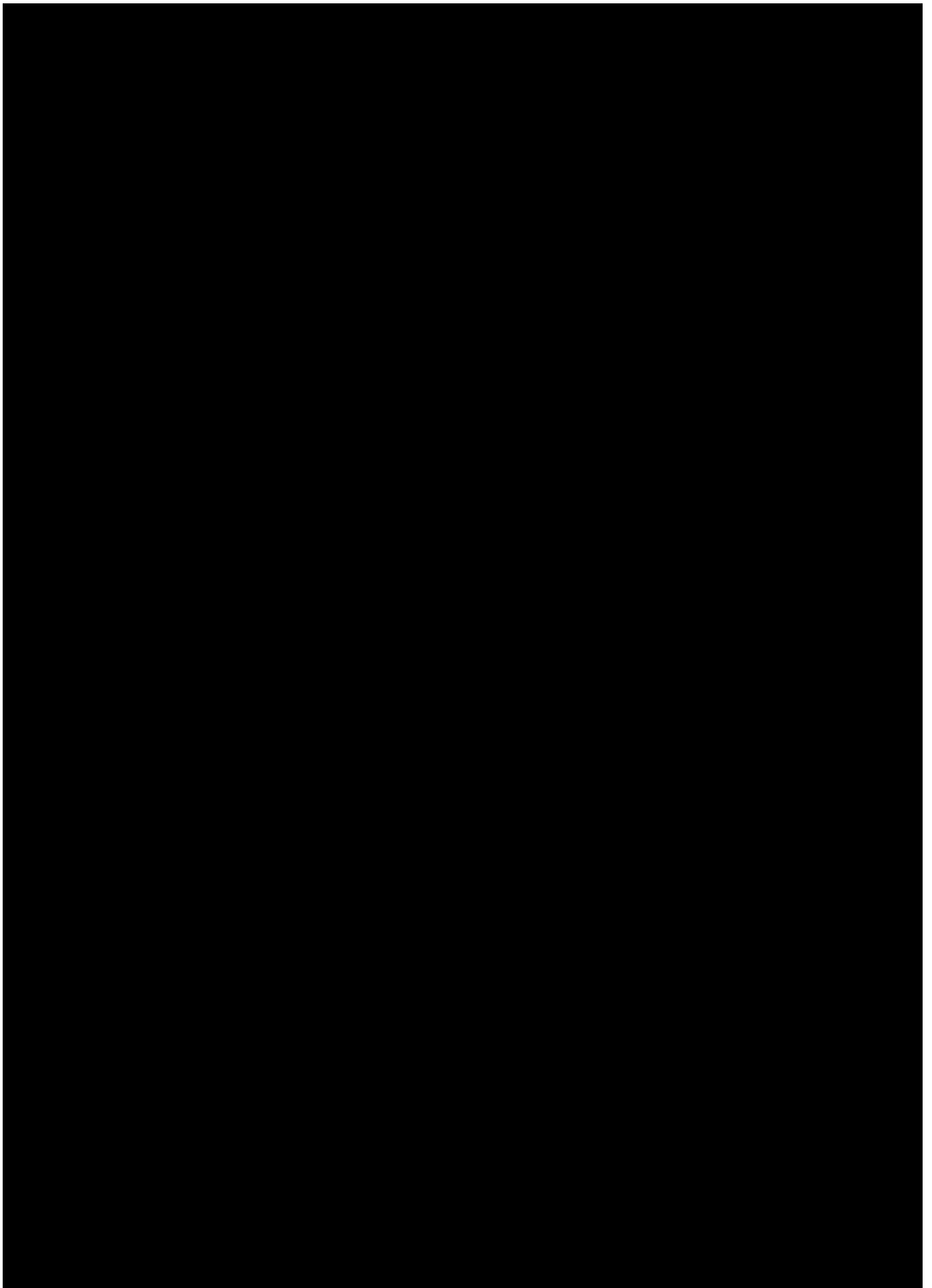
In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [22]. In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [23].

In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [24]. In the 1990s, *S. flexneri* was the most common serotype of *Shigella* isolated from children with shigellosis in the United Kingdom [25].

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The first of these is the fact that the system is not
 self-sufficient. It is dependent on the external
 environment for its survival. This is a major
 weakness of the system, and it is one that
 must be addressed if the system is to be
 successful. The second is the fact that the
 system is not flexible. It is rigid and
 inflexible, and it is unable to adapt to
 changing circumstances. This is another
 major weakness of the system, and it is
 one that must be addressed if the system
 is to be successful. The third is the fact
 that the system is not transparent. It is
 opaque and secretive, and it is unable to
 communicate its intentions to the
 outside world. This is a third major
 weakness of the system, and it is one
 that must be addressed if the system is
 to be successful.





the 1990s, the number of people in the UK who are aged 65 and over has increased by 1.5 million, and the number of people aged 75 and over has increased by 1.1 million (Office of National Statistics 1999). The number of people aged 65 and over is projected to increase to 6.5 million by 2010, and the number of people aged 75 and over to 3.5 million (Office of National Statistics 1999).

There is a growing awareness of the need to develop services to meet the needs of older people, and a number of initiatives have been launched in the UK to address this need. The Department of Health has launched the 'Ageing Well' initiative, which aims to improve the health and well-being of older people. The initiative includes a number of measures, such as increasing the number of health visitors, and providing more support for older people living in the community. The Department of Health has also launched the 'Ageing Well' campaign, which aims to raise awareness of the needs of older people, and encourage people to take steps to improve their health and well-being.

The 'Ageing Well' initiative is a multi-agency effort, involving the Department of Health, the Department of Social Security, and a number of other government departments. The initiative is also supported by a number of voluntary organizations, such as Age UK, which provides a range of services for older people, including advice, support, and information. The 'Ageing Well' initiative is a key part of the government's strategy for addressing the needs of older people, and is expected to have a significant impact on the health and well-being of older people in the UK.

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There is a growing awareness of the need to develop strategies to meet the needs of the ageing population. The Department of Health (2000) has identified the need to develop a 'new paradigm' for health care, which is based on the principles of prevention, promotion, and participation. This paradigm is based on the idea that health care should be based on the needs of the individual, rather than on the needs of the system. This paradigm is based on the idea that health care should be based on the needs of the individual, rather than on the needs of the system.

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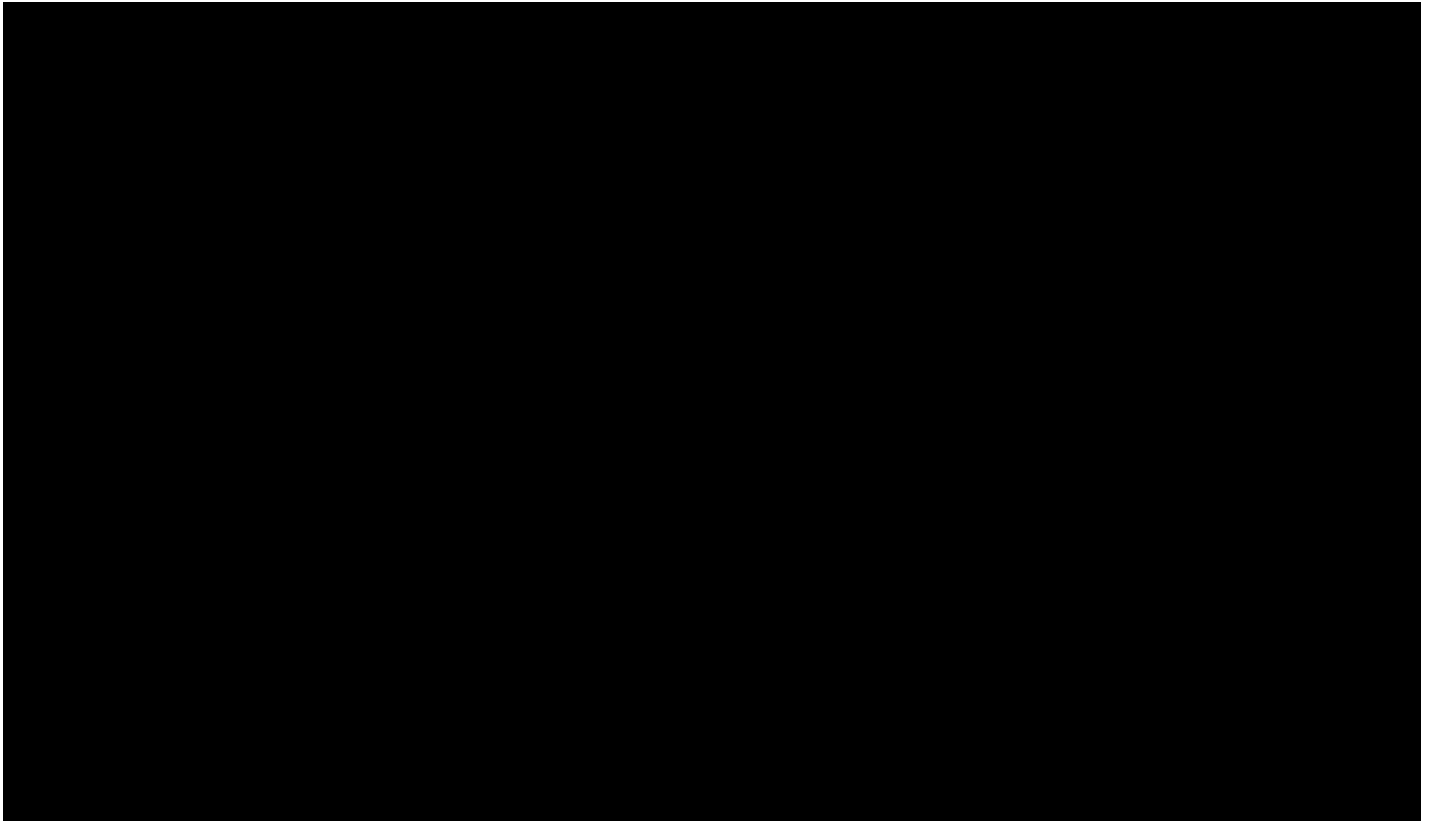
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There is a growing awareness of the need to develop strategies to meet the needs of the ageing population. The Department of Health (1999) has identified the need to develop a 'new paradigm' for the care of the elderly. This paradigm is based on the principle of 'active ageing', which is the process of maintaining and enhancing the functional ability of older people to live independently and to participate in society. The Department of Health (1999) has identified a number of key areas for action in order to achieve this paradigm, including: (1) the development of a 'new paradigm' for the care of the elderly; (2) the development of a 'new paradigm' for the care of the elderly; (3) the development of a 'new paradigm' for the care of the elderly.

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