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MEDICATION-RELATED PROBLEMS IN OLDER ADULTS: A FOCUS ON
UNDERUSE OF WARFARIN AND WARFARIN-ANTIBIOTIC INTERACTIONS

A dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy at Virginia Commonwealth University

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Table of Contents

List of Tables.....	vii
List of Figures.....	viii
List of Abbreviations.....	ix
Abstract.....	xi
CHAPTER 1. Introduction	
I. Medication-Related Problems in Older Adults.....	1
II. Use of High-Risk Medications in Older Adults.....	3
A. Warfarin Pharmacotherapy.....	4
B. Warfarin-Related Adverse Anticoagulation Outcomes.....	7
C. Warfarin-Drug Interactions.....	9
D. Summary.....	11
III. References.....	12
CHAPTER 2. Literature Review	
I. Warfarin-Use in Nursing Home Residents.....	19
A. Review of the Literature.....	19
B. Significance.....	21
II. Warfarin-Antibiotic Interactions.....	22
A. Warfarin-Fluoroquinolones Interaction.....	23
B. Warfarin-Macrolides Interaction.....	30
C. Warfarin-Penicillins Interaction.....	32
D. Discussion.....	32
E. Conclusion.....	35
F. Significance.....	36

III.	Potential Effect of Age on Warfarin-Fluoroquinolone Interactions.....	38
	A. Case Presentations.....	39
	B. Introduction.....	40
	C. Method.....	41
	D. General Pharmacokinetic and Pharmacodynamic Changes with Aging.....	42
	E. Effect of Age on Pharmacodynamic Response to Warfarin.....	43
	F. Safety of Warfarin Therapy in Older Adults.....	45
	G. Effect of Age on Pharmacokinetics of Fluoroquinolones.....	46
	H. Potential Mechanisms of Warfarin-Fluoroquinolone Interactions.....	48
	I. Discussion.....	50
IV.	References.....	51

CHAPTER 3. Warfarin Use in Nursing Home Residents: Results from the 2004 National Nursing Home Survey

I.	Abstract.....	61
II.	Introduction.....	63
III.	Methods.....	66
	A. Data Source and Study Sample.....	66
	B. Drug Exposure.....	68
	C. Statistical Analysis.....	69
IV.	Results.....	70
	A. Demographics and Anticoagulant Use.....	70
	B. Factors Associated with Warfarin Use.....	75
V.	Discussion.....	77
	A. Underuse of Warfarin in NH residents.....	77
	B. Factors Associated with Warfarin Use.....	80
VI.	Conclusion.....	85
VII.	References.....	85

CHAPTER 4. Warfarin-Antibiotic Interactions in Older Adults of an Outpatient

Anticoagulation Clinic

I.	Abstract.....	97
II.	Introduction.....	100
III.	Methods.....	102
	A. Study Setting.....	102
	B. Study Design and Patients.....	102
	C. Data Collection.....	104
	D. Outcome Measures.....	104
	E. Statistical Analysis.....	106
IV.	Results.....	107
V.	Discussion.....	116
VI.	Conclusion.....	120
VII.	Reference List.....	121

CHAPTER 5. Discussion and Conclusion

I.	Underuse of Warfarin in Nursing Home Residents.....	124
	A. Possible Explanations and Barriers to Prescribing Warfarin.....	124
	B. Barriers to Successful Implementation of Evidence-based Medicine in LTC Setting.....	126
	C. Evaluating Benefits and Risks to Warfarin Therapy in Older Adults.....	127
II.	Warfarin-Antibiotic Interactions.....	129
	A. Possible Explanations of Study Results.....	130
	B. Difficulties with Managing Drug Interactions in Older Adults.....	131
III.	Relationship Between Under-prescribing and Polypharmacy.....	132
IV.	Role of Newly Approved Oral Anticoagulants: Dabigatran and Rivaroxaban.....	133
V.	Conclusions and Future Research.....	135
VI.	References.....	136

Appendix A: List of validated ICD-9 codes used to identify disease and conditions of interest (Chapter 3).....	143
Appendix B: NAMCS reason for visit (RFV) codes to identify contraindications to warfarin (Chapter 3).....	144
Appendix C: List of long-term care drug database system (LTCDDS) codes used to determine drug exposure for nursing home residents with atrial fibrillation.....	145
Appendix D: Description of the variables collected from electronic medical records...	146
Appendix E: SAS codes for repeated measures ANOVA.....	148
Vita.....	151

List of Tables

CHAPTER 1

Table 1: Categories of medication-related problems in older adults.....	2
---	---

CHAPTER 2

Table 1: Summary of studies documenting underuse of warfarin in nursing home residents with atrial fibrillation.....	21
Table 2: Warfarin-ciprofloxacin case reports.....	27
Table 3: Warfarin-levofloxacin case reports.....	28
Table 4: Warfarin-moxifloxacin case reports.....	28
Table 5: Summary of warfarin-levofloxacin interaction studies.....	29
Table 6: Warfarin-azithromycin case reports.....	31
Table 7: Summary of warfarin-azithromycin interaction studies.....	31

CHAPTER 3

Table 1: Characteristics of nursing home residents with atrial fibrillation, with indications for and no contraindications to warfarin, stratified by warfarin use.....	72
Table 2: Factors associated with warfarin use in nursing home residents with atrial fibrillation, with indications for and no contraindications to warfarin.....	77

CHAPTER 4

Table 1: Baseline demographic and clinical characteristics of study patients.....	110
Table 2: International normalized ratio changes and secondary outcomes of over-anticoagulation.....	111
Table 3: International normalized ratio changes by type of indication for antibiotic use.....	113
Table 4: Mean INR values and change in INR values for subjects in the upper and lower age quartiles.....	113
Table 5: Details of patients with an absolute INR ≥ 4 after antibiotic use.....	114

List of Figures

CHAPTER 1

- Figure 1: Mechanism by which warfarin inhibits the vitamin-K dependent synthesis of biologically active forms of essential clotting factors, II, VII, IX, and X.....6
- Figure 2: Adjusted odds ratio for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation as measured by the international normalized ratio.....9

CHAPTER 3

- Figure 1: Summary of use of warfarin and other anti-platelet medications in eligible nursing home residents with atrial fibrillation.....74
- Figure 2: Use of warfarin and other anti-platelet medications by nursing home residents with atrial fibrillation.....75

CHAPTER 4

- Figure 1: Least squares means plot of change in INR values over time for different antibiotic.....112

List of Abbreviations

ADR	adverse drug reaction
AF	atrial fibrillation
ANOVA	analysis of variance
ASCP	American Society of Consultant Pharmacists
CDC	Centers for Disease Control and Prevention
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CPRS	Computerized Patient Recording System
CYP450	cytochrome P450
DDI	drug-drug interactions
DVT	deep venous thrombosis
FDA	Food and Drug Administration
GI	gastrointestinal
ICD	International Classification of Diseases
INR	international normalized ratio
IRB	institutional review board
LRI	lower respiratory infection
LTCDDS	Long-Term Care Drug Database System
MI	myocardial infarction
MVR	mitral valve replacement
NH	nursing home
NNHS	National Nursing Home Survey
NSAIDs	non-steroidal anti-inflammatory drugs
OBRI	Outpatient Bleeding Risk Index
OR	odds ratio
PD	pharmacodynamics

PE	pulmonary embolism
PK	pharmacokinetics
PT	prothrombin time
RCT	randomized controlled trial
SAS	statistical analysis software
SSTI	skin and soft tissue infection
TEE	thromboembolic event
TIA	transient ischemic attack
URI	upper respiratory infection
UTI	urinary tract infection
VAMC	Veterans Affairs Medical Center
VHD	valvular heart disease
VTE	venous thromboembolism

Abstract

MEDICATION-RELATED PROBLEMS IN OLDER ADULTS: A FOCUS ON UNDERUSE OF WARFARIN AND WARFARIN-ANTIBIOTIC INTERACTIONS

By Parinaz K. Ghaswalla, PhD

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

Virginia Commonwealth University, 2011

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Associate Professor, Department of Pharmacotherapy and Outcomes Science

The work presented in this dissertation focuses on two important medication-related problems in older adults, that is, untreated indication and drug-drug interactions, specifically with respect to a high-risk medication such as warfarin. Warfarin is a challenge to use in clinical practice due to its narrow therapeutic index, variability in dose-response and its interactions with numerous foods and drugs. This dissertation presents the research from two projects. In the first project the prevalence and predictors of warfarin use in nursing home (NH) residents with atrial fibrillation (AF), and use of secondary stroke prevention strategies was determined, in order to understand the patterns of anticoagulant use in frail NH residents and to identify patient characteristics associated with warfarin use. In the second project the effect of oral antibiotics on anticoagulation outcomes, when prescribed concomitantly with warfarin, was

determined, in order to provide evidence on the clinical significance of warfarin-antibiotic interactions in older adults.

In the first project a cross-sectional analysis of the prescription and resident files from the 2004 National Nursing Home Survey was done to determine the prevalence of AF and rates of use of warfarin and other anti-platelet agents, such as aspirin and clopidogrel. A multiple logistic regression model was used to determine factors associated with warfarin use. In this sample of older NH residents, 13% of residents had a diagnosis of AF, with indications for warfarin use and no contraindications to warfarin. From these patients, 30% received anticoagulant therapy with warfarin and 23% of the remaining patients received either aspirin or clopidogrel, suggesting that more than 50% of residents with AF did not receive any form of anticoagulant therapy. Non-white race, history of bleeding, and use of anti-platelet medications were associated with reduced odds of receiving warfarin.

The second project was a retrospective medical record review of older patients from an outpatient anticoagulation clinic at a Veterans Affairs medical center. Results of the repeated measures ANOVA suggested a significant increase in post-antibiotic INR values with fluoroquinolones, azithromycin and amoxicillin. In addition, the percentage of patients with warfarin dose adjustments was significantly greater with fluoroquinolones and azithromycin as compared to cephalexin. No bleeding events were reported for any of these patients.

In conclusion, the results of the projects suggest that there is underuse of warfarin in NH settings. Furthermore, antibiotics may be safely prescribed with warfarin in older adults as long as the INR is monitored closely.

CHAPTER 1

Introduction

I. Medication-Related Problems in Older Adults

Older adults are the largest consumers of medications, such that more than half the community-dwelling older adults in the US are prescribed 5 or more medications, over-the-counter medications or dietary supplements.(1) Nursing home residents are prescribed an average of 7-8 medications.(2) Due to this high use of medications, older adults have the greatest risk of a medication-related problem (MRP).(1) A medication-related problem may be defined as “an event or situation involving drug therapy that negatively interferes with a patient’s health”.(3) The average number of MRPs in older adults ranges from 2 to 3,(4) and these are generally more severe in older adults.(5) Aging increases the risk for MRPs since older adults become more sensitive to medications and may experience adverse drug reactions or increased side effects for several reasons. These reasons include- increased risk of chronic illnesses during which the body may metabolize or respond to drugs differently, multiple medications, complex dosing schedules, age-related physiological changes and higher likelihood of receiving un-coordinated care.(6) The high healthcare cost associated with MRPs may represent a serious economic problem. It has been estimated that for every dollar spent on drugs in nursing facilities, \$1.33 in healthcare resources are consumed in the treatment of medication-related morbidity and mortality.(7) The total cost of MRPs is approximately \$85 billion annually.(5) MRPs are commonly classified into eight general categories as shown in table 1.(3)

The research presented in this dissertation mainly focuses on two MRPs in older adults, i.e. untreated indication and drug-drug interactions, and specifically related to the high-risk drug warfarin. Rates of untreated indication or underuse of beneficial medications in older adults have been reported to be present in around 62-64% of older adults.(8, 9) Similarly, drug-drug interactions are highly prevalent in older adults, such that approximately 2.2 million older adults were found to be at a risk of a major potential drug-drug interaction in a national cross-sectional study.(1) Nearly, half of these involved the use of warfarin or the anti-platelet agent, aspirin.

Interestingly, many MRPs are believed to be predictable and therefore preventable. In a study that assessed the incidence and preventability of adverse drug events in ambulatory patients aged 65 years and above, of the 1523 adverse drug events that were reported, 27.6% (421) were judged preventable.(10) On December 9, 2008, the American Society of Consultant Pharmacists (ASCP) submitted a written report to the transition team of then President-Elect Barack Obama, to highlight the issues surrounding MRPs in older adults along with some suggestions for reducing the prevalence of these problems.(11) Thus this health care issue has received national importance. Furthermore, by 2030 the population of Americans aged 65 years or older is expected to double, given the longer life expectancy and aging baby boomers.(12) Thus MRPs in the aging population may have an even greater impact on health care costs as the population is expected to reach 71 million by 2030, which would roughly represent 20% of the US population.

Table 1: Categories of medication-related problems in older adults (3)

Type of MRP	Definition
1. Untreated Indication	Patient requires drug therapy but is not receiving medication for that indication
2. Improper Drug Selection	Patient requires drug therapy but is taking the wrong medication
3. Subtherapeutic Dosage	Patient is being treated with an inadequate dose of the correct medication
4. Failure to Receive Drugs	Patient has a medical problem that is the result of not receiving a drug
5. Overdosage	Patient is being treated with too much of the correct drug
6. Inverse Drug Reaction	Patient has medical problem that is the result of an unintended and detrimental adverse drug effect
7. Drug Interaction	Patient has medical problem that is the result of a drug-drug, drug-food, or drug-laboratory interaction
8. Drug Use Without Indication	Patient is taking a drug without a valid medical reason

II. Use of High-Risk Medications in Older Adults

Although warfarin is a frequently prescribed medication in the older population, it is also considered to be a high-risk medication.(13) Warfarin has been included in the list of high-alert medications developed by the Institute for Safe Medication Practices (ISMP).(14) This list was developed based on error reports submitted to ISMP's national reporting program, harmful error reports from the literature and inputs from practitioners and safety experts. An increased risk of adverse events due to warfarin has also been supported by previous research. National estimates of emergency department (ED) visits among US patients aged 65 years and older found that of 177,504 ED visits for adverse drug events in 2004-2005, only 3.6% of them visits were for medications considered to be potentially inappropriate according to the Beers criteria.(15) Instead 33% of visits

were due to adverse events from 3 other medications, i.e. warfarin (17.3%), insulin (13.0%) and digoxin (3.2%). However, warfarin, insulin and digoxin are critical medications that should not be labeled as ‘inappropriate’ due to the high rates of ED visits. Instead, greater efforts may be required for improving the quality of prescribing and monitoring for patients on these high-risk medications. According to Budnitz et al, “because of the high risk for adverse events and the common outpatient use of warfarin, insulin and digoxin, even small improvements in the use of these medications may have greater potential for reducing the burden of serious adverse drug events among older Americans, as measured by ED visits, than do large reductions in the prescription of lower-risk medications, such as those considered to be potentially inappropriate by the Beers criteria.”(15) Furthermore, warfarin is prescribed frequently for older adults. In a cross-sectional, nationally representative probability sample of community-residing individuals aged 57-85 years, it was found that cardiovascular agents were the most commonly used class of prescription medications and this included anticoagulants such as warfarin.(1)

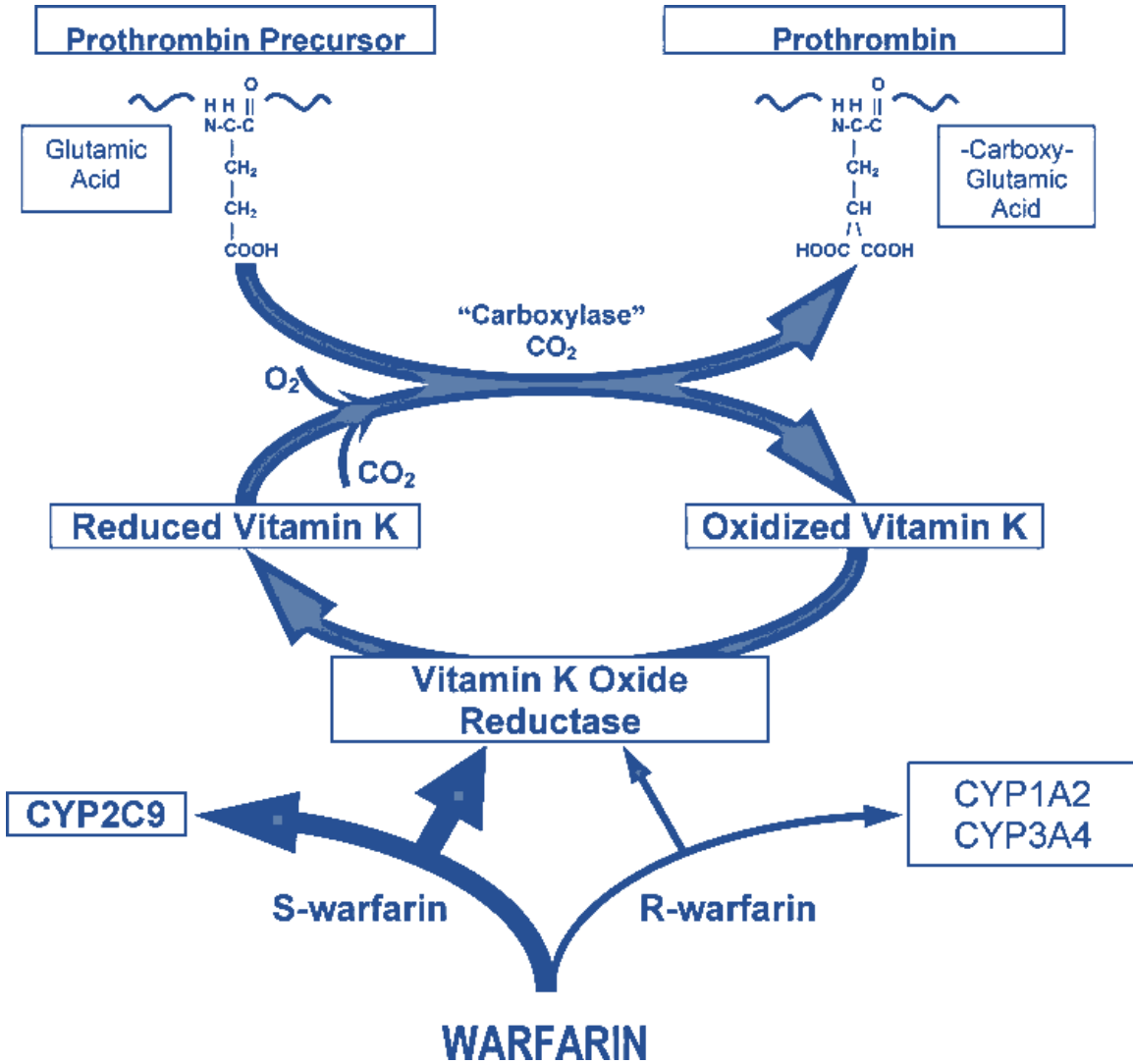
A. Warfarin Pharmacotherapy

Anticoagulation therapy with coumarins or vitamin K antagonists, such as warfarin, is recommended for the prevention and treatment of thromboembolic complications in patients with atrial fibrillation (AF), venous thromboembolism (VTE), and acute coronary syndromes and after invasive cardiac procedures.(16-18) It exhibits its anticoagulant effect by interfering with the γ -carboxylation of vitamin-K dependent coagulation factors II, VII, IX, and X, by preventing the cyclic interconversion of vitamin

K and its 2,3 epoxide (vitamin K epoxide), as shown in figure 1.(19) Warfarin is a racemic mixture of two optically active isomers, the R and S enantiomers, from which S-warfarin is 2.7-3.8 times more potent than R-warfarin and is metabolized by the CYP2C9 enzyme, whereas R-warfarin is metabolized by CYP1A2 and 3A4.(19) Warfarin is highly-water soluble and reaches maximal blood concentrations about 90 minutes after oral administration due to its high bioavailability.(19)

Although warfarin has been the mainstay of oral anticoagulant therapy for over 60 years, it remains a challenge to use in clinical practice since several factors may complicate warfarin therapy. It is a drug with a narrow therapeutic index and exhibits considerable variability in dose response; thus, maintaining therapeutic levels of warfarin is challenging.(19) It is due to these reasons that patients taking warfarin are required to have their international normalized ratio (INR) monitored frequently. INR is a standard used for assessing the clotting tendency of blood in patients receiving anticoagulant therapy. The recommended INR monitoring period is every 4 weeks; however, this may change depending on patient-related factors, number of medications or when changes are made to the patient's diet or drug regimen.(19) According to the American Geriatrics Society (AGS) guidelines for use of warfarin in older adults, the recommended INR range is 2.0-3.0 for prevention and treatment of venous thrombosis and thromboembolism, prevention of stroke in patients with non-valvular atrial fibrillation and/or acute myocardial infarction, and in patients with valvular heart disease.(20) The target INR range may be higher in patients who suffer recurrent systemic embolism despite adequate oral anticoagulant therapy (2.5-3.5; target INR=3.0).

Figure 1: Mechanism by which warfarin inhibits the vitamin-K dependent synthesis of biologically active forms of essential clotting factors, II, VII, IX and X.(19)



(Figure excerpted from Ansell J, et al. *Chest* 2008; 133 (6 Suppl):160S-98S)

B. Warfarin-Related Adverse Anticoagulation Outcomes

The most common adverse outcome caused by warfarin is a bleeding event. The rates of fatal or major bleeding have been determined to be about 1.35 per 100 patient years, and

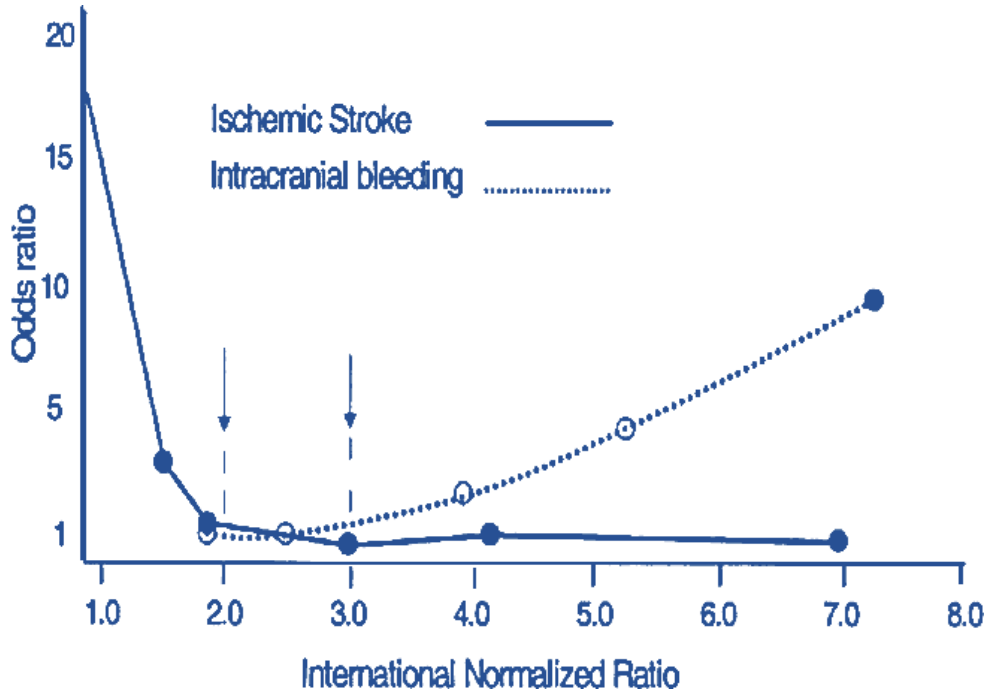
the rates of intracranial hemorrhage (ICH) was 0.4 per 100 patient-years.(21) Rates of major hemorrhage in patients treated with warfarin in routine clinical practice have been reported to range from 1.7-3.4%.(21) Some factors that directly govern the risk of a bleeding event during warfarin therapy include, the intensity of anticoagulation, patient characteristics such as age, concomitant use of drugs that may interfere with hemostasis and the length of therapy.(21) As shown in figure 2, the 'ideal' balance between prevention of ischemic stroke and avoidance of hemorrhagic complication is achieved at an INR from 2.0-3.0. According to the results of a meta-analysis, the risk for hemorrhage and thromboemboli was minimized when the patients' INR remained within 2.0-3.0, whereas, the risk of bleeding increased significantly for INR values within 5.0-9.0.(22) It is well established that the risk of hemorrhage is the highest during the first 3 months of warfarin therapy.(23)

The definition of a bleeding outcome may vary across studies. Some studies define bleeding as being minor, major or life threatening. Minor bleeds are those that are generally reported to the physician, but do not require additional testing, referrals or visits. Bleeding may be defined as major if it is intracranial or retroperitoneal, if it directly leads to death or if it results in hospitalization or transfusion.(21) Major bleeding may also be defined as life threatening bleeding in some cases. Although very rare, intracranial hemorrhage is the most feared complication during warfarin therapy, since most patients do not completely recover. Several different strategies are available for the management of supratherapeutic INR, i.e. $INR > 4.0$, or a bleeding event. Depending upon the INR or severity of the bleed, warfarin dose may either be lowered or omitted.

The patient may be administered vitamin K or more than one warfarin dose may be withheld. In the case of significant bleeding, the patient may be given a vitamin K infusion, supplemented with fresh frozen plasma, prothrombin complex concentrate or recombinant factor VIIa.(19, 24)

An association of increasing age with increased risk of serious bleeding has been demonstrated in a recent meta-analysis (adjusted hazard ratio per decade increase, 1.16; 95% CI, 1.47-1.77).(25) Since hemorrhagic events are the major complications of warfarin therapy, such events may limit warfarin use in older adults, especially frail older adults.(21, 23) Under-treatment of high-risk atrial fibrillation patients with warfarin therapy in clinical practice has been reported consistently in the past across all patient populations.(26) It is possible that the rates of under-treatment with warfarin may be even higher for older adults, especially for frail nursing home residents with atrial fibrillation, for whom the fear of bleeding events may be higher. Fear of bleeding complications is often cited as the reason for not adequately prescribing warfarin and the perception of stroke and bleeding risk has shown considerable variation among physicians.(27) Physicians are often more likely to overestimate the reported risks of major bleeds with warfarin, which may further result in under-treatment with anticoagulant therapy for patients with atrial fibrillation.(28) Due to this possible association between fear of bleeding complications in older adults and under-treatment with warfarin, it is important to determine the rates of warfarin use in older adults, especially frail nursing home residents in whom anticoagulation rates may not have been adequately studied previously.

Figure 2: Adjusted odds ratio for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation as measured by the international normalized ratio (16)



(Figure excerpted from Fuster V, et al. *Europace*. 2006; 8(9):651-745)

C. Warfarin-Drug Interactions

ASCP includes drug-drug interactions as one of the top 5 medication-related problems commonly seen in older adults. (29) Many medications undergo pharmacokinetic or pharmacodynamic interactions with warfarin,(30) and warfarin-drug interactions have been ranked at number 3 in the list of top 30 adverse events reported for warfarin in the FDA's Adverse Events Reporting system for the period from June 2003 to July 2006.(31) These top 30 adverse events were either indicative of, or associated with bleeding events. In addition, out of the top 10 dangerous drug interactions in nursing home residents, 5 of

the interactions involve warfarin, and 3 of these involve warfarin-antibiotic combinations. The second, third and fourth most dangerous drug interactions on this list involve warfarin with sulfa drugs, macrolides and fluoroquinolones respectively. This list was developed as one of the initiatives of the Multidisciplinary Medication Management Program.(32) Furthermore, the most recent systematic review on warfarin-drug interactions, recommends exercising caution while prescribing antibiotics to warfarin patients, since they may cause a change in the patient's hematological response to warfarin.(30) Among the various antibiotic classes, fluoroquinolones, macrolides, tetracyclines and penicillins have been listed in the review article.

Studies have shown that warfarin and antibiotics are commonly co-prescribed in older adults. For example, in a study of 256 patients discharged on warfarin, 54% received a potentially interacting medication, from which 67% of the prescriptions were for potentially interacting antibiotics.(33) In another study done in the Netherlands, almost 39% of all users of coumarin anticoagulants were co-prescribed an anti-bacterial drug that was considered to be potentially interacting with warfarin.(34) Potential warfarin interacting antibacterial agents, such as sulphonamides, quinolones and macrolides, were also found to be the most widely co-prescribed class of drugs with warfarin, in a study done in Scotland.(35) An interesting finding of this study was that the rate of prescribing of macrolides in warfarin patients was lower than the rate for non-warfarin patients. This may suggest an increased awareness among physicians regarding the risk of this potential interaction. However, no study done in the United States has shown this difference in prescribing patterns between users and non-users of warfarin. Adverse outcomes

associated with warfarin use have also been demonstrated previously. Of all the patients that were admitted to an emergency department, 11% were admitted due to a warfarin drug interaction.(36, 37) Antibiotics also led to over-anticoagulation in hospitalized patients receiving oral anticoagulants, such that 8 of the 13 patients that experienced an increase in $INR > 5.0$ had recently started therapy with antibiotics, antifungals or amiodarone.(38) Fluoroquinolones are a widely used class of antibiotics. A study that assessed the trends of antibacterial use in the United States from 2002 to 2006 concluded that out of all classes of antibiotics, fluoroquinolones were the most commonly used.(39) However, the clinical significance of warfarin-fluoroquinolone interactions is not clear,(40) suggesting that there is a need for further research on warfarin-antibiotic interactions.

D. Summary

This chapter gave an overview of medication-related problems in older adults with a focus on two types of MRPs, that is, untreated indication and drug-drug interactions. Certain issues with the use of warfarin therapy in older adults were also highlighted. The next chapter provides a detailed literature review of underuse of warfarin in nursing home settings and the available clinical evidence for warfarin-antibiotic interactions. It also provides a literature review of the effect of age on warfarin-fluoroquinolone interactions. The next section will provide some gaps in the literature as they relate to underuse of warfarin and warfarin-antibiotic interactions in older adults and the significance of conducting this research.

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CHAPTER 2

Literature Review

I. Warfarin Use in Nursing Home Residents

The purpose of this section is to review the available literature to determine the prevalence of warfarin use in nursing home (NH) residents. This would help to develop a better understanding of the use of this 'high-risk' medication in NH residents who generally tend to be frailer than community-dwelling older adults and are using multiple medications for multiple co-morbid conditions. The literature was also searched to identify the factors associated with use of warfarin in NH residents.

A. Review of the Literature:

Overall three studies have determined the prevalence of warfarin use specifically in NH residents. In the study by McCormick et al., the medical records of all residents from a convenience sample of 21 community-based long-term care facilities were reviewed to determine whether they had a diagnosis for atrial fibrillation (AF).(1) From a total of 2587 records, 429 (17%) residents had a diagnosis for AF. Of these 429 patients with AF, 180 (42%) were prescribed warfarin and from the 83 'ideal' candidates with AF and no contraindications to warfarin use, only 44 (53%) received warfarin. Similarly, in another study the medical records of patients residing in 30 long-term care facilities were reviewed to determine the prevalence of AF and the proportion of patients receiving

anticoagulation therapy.(2) A total of 5500 residents were studied from which 413 (7.5%) were residents with a diagnosis for AF. Of these 413 subjects with AF, 130 (32%) received a treatment with warfarin. One of the earliest studies to have documented an underuse of warfarin in nursing home residents showed that only 17 (20%) of 85 patients with AF received anticoagulation therapy with warfarin.(3) A summary of these studies has been presented in table 1. Furthermore, a recent study evaluated the treatments received by patients for stroke prevention using data from the Minimum Data Set (MDS).(4) From a total of 14,469 patients identified with a previous stroke event, 48% received warfarin or any kind of antiplatelet medication such as clopidogrel, aspirin, ticlopidine or dipyridamole. The biggest limitation of this study is that MDS does not differentiate between ischemic and hemorrhagic stroke. Since anticoagulant or antiplatelet therapy is not recommended for patients who have had a hemorrhagic stroke, the rates of underuse may have been over-estimated. Thus while determining the prevalence of warfarin use in patients with AF, it is beneficial to identify a group of patients with AF who do not have any contraindications to anticoagulant or antiplatelet therapy.

Table 1: Summary of studies documenting underuse of warfarin in nursing home residents with atrial fibrillation

Reference	Study Setting	Total no. of Residents (N)	N (%) of Residents with AF	N (%) Treated with Warfarin	Factors Associated with Warfarin Use
McCormick (2001)(1)	21 LTC facilities	2587	429 (17%)	180 (42%)	Number of bleeding risk factors
Gurwitz (1997)(2)	30 LTC facilities	5500	413 (7.5%)	130 (32%)	Age \geq 85 years, history of stroke, diagnosis of dementia
Lackner (1995)(3)	5 Nursing Homes	902	85 (9.4%)	17 (20%)	-

LTC = Long-term care

B. Significance

Based on a review of the literature, studies have consistently reported an underuse of warfarin in long-term care facilities with the rates of underuse ranging from 50-70%. However, most of these studies were done more than 10 years ago. Newer anti-platelet medications, such as clopidogrel have become available for secondary stroke prevention and are increasingly being used for patients in whom warfarin is contraindicated. Other antiplatelet medications such as ticlopidine are not recommended for use in older adults anymore. While previous studies have included a sample of residents from many long-term care facilities, none of them included a nationally representative sample of long-term care residents. An estimation of national rates of NH residents with AF and those

receiving anticoagulant or antiplatelet therapy would help to understand the current practices that are adopted for stroke prevention in NH settings and lack thereof. Furthermore, identifying factors that are associated with warfarin use may help to target these factors to develop future interventions to improve anticoagulant therapy in older adults.

II. Warfarin-Antibiotic Interactions

The purpose of this section is to review the published literature on warfarin-antibiotic interactions, separately for fluoroquinolones, macrolides and penicillins, in order to understand and evaluate the current state of knowledge of the clinical significance of warfarin-antibiotic interactions. MEDLINE, TOXLINE, International Pharmaceutical Abstracts (IPA), the FDA website and www.guideline.gov, were searched for relevant literature. The aim of the literature search was to identify studies that have assessed or reported any interaction between warfarin and quinolones. The search strategy used was (*warfarin AND (quinolones OR ciprofloxacin OR levofloxacin OR moxifloxacin)*).

Gatifloxacin was not included because it has been removed from the US market.

Similarly norfloxacin was not included due to its limited use. Articles were included if they were in English and were original research studies with data from human subjects.

Relevant articles that showed up in the related search and in bibliographies of the retrieved articles were also included. The search yielded a total of 107 articles from which 35 were reviews. From the remaining 72 articles, 35 were found to be relevant.

A. Warfarin-Fluoroquinolones Interaction

Most of the evidence for warfarin-fluoroquinolone interactions comes from case reports or case series and these reports have been summarized in **Tables 2, 3, and 4** for warfarin-ciprofloxacin, levofloxacin and moxifloxacin interactions respectively. As shown in **Table 2**, seven case reports or case series, reporting warfarin-ciprofloxacin interactions have been published.(5-11) These included a total of 9 patients, from which 5 patients were 70 years or above. There was a marked prolongation of prothrombin time in these patients, with 2 patients experiencing hematuria or hematemesis.

Four case series or case reports of a warfarin-levofloxacin interaction, involving a total of 11 patients, have been published and have been summarized in **Table 3**.(12-15) From these 11 patients, 8 patients were 65 years and above. All 11 patients experienced a substantial increase in INR values above the therapeutic range. This elevation in INR resulted in hemopericardium in 2 patients, retroperitoneal bleeding with psoas muscle bleeding in 1 patient and a case of minor bleeding in another patient. Some strategies that were used to manage this interaction were warfarin dose reduction, withholding warfarin therapy and administration of vitamin K and fresh frozen plasma (FFP). There have been 12 reported cases of a warfarin-moxifloxacin interaction as shown in **Table 4**, and bleeding events were reported for 2 of these cases.(16, 17)

Since most of the evidence for clinical significance of warfarin-fluoroquinolone interactions come from case reports they may represent a publication bias and there is minimal control on confounding factors such as diet, nutritional status, and concomitant

medications in case reports. For example, the pre-antibiotic INR was not reported in some of the case reports.(11, 15) If the patient's INR was not stable before the antibiotic was started, the INR may continue to fluctuate as compared to a patient with stable INR. The increase in INR may then be incorrectly attributed to the antibiotic for such cases. In one of the case series, a patient had a fluctuating INR even before moxifloxacin was started. This fluctuation may have been due to initiation of heparin therapy. Warfarin therapy had already been discontinued for this patient who was not on concomitant warfarin-moxifloxacin therapy during INR elevation.(16)

There have been 3 prospective studies to determine the interaction potential between warfarin and ciprofloxacin.(18-20) The first 2 studies showed that ciprofloxacin did not alter the pharmacokinetics (PK) or pharmacodynamics (PD) of warfarin and the third study showed that there was no increase in the patient's INR. However, since these were PK/ PD studies they were done in healthy male volunteers and only a single dose of warfarin and/ or ciprofloxacin was administered to the patients. In addition, healthy volunteers without any infection are not representative of patients who are normally prescribed an antibiotic for an active infection. In the presence of certain infections such as pneumonia, there may be greater inhibition of hepatic enzyme activity,(21) in addition to suppression of vitamin K producing bacterial flora by the antibiotic in question. These factors may further interfere with warfarin metabolism and increase the anticoagulant activity of warfarin. Such effects may not be evident in PK/ PD studies.

Table 5 is a summary of retrospective and prospective studies that assessed warfarin-levofloxacin interactions. From the 4 retrospective cohort studies that determined the mean change in INR after administration of levofloxacin to patients on stable warfarin therapy, 2 studies found a significant increase in mean INR change,(22, 23) whereas the other 2 did not find a significant change.(24, 25) One prospective study found no significant increase in INR with the addition of levofloxacin to warfarin therapy in 18 patients with an active infection.(26) However, 9 of the 18 patients had a warfarin dose adjustment based on the first INR values obtained after start of levofloxacin. For these patients only the first INR value was used in the analysis, and this may have limited the ability to identify the effect of levofloxacin on INR values if the interaction occurred after this INR value had been recorded.

The effect of warfarin-levofloxacin combination on the risk of bleeding has also been examined in 2 nested case-control studies.(21, 27) The outcome of interest was hospital admission due to hemorrhage, caused by a warfarin-levofloxacin interaction.(27) Cefuroxime was chosen as the comparator drug. Patients who were started on levofloxacin were not more likely to undergo hemorrhage (OR=1.21, 95% CI=0.84, 2.01), unlike those on cefuroxime (OR=1.62, 95% CI= 1.28-2.26). In another similar nested-case control study assessing the risk of GI bleeding due to warfarin-antibiotic interactions, levofloxacin was not shown to be associated with an increased risk of bleeding.(21) Thus both these studies did not show an increase in the risk of clinically significant hemorrhagic outcomes. Finally, as of January 15, 2004, Health Canada received 57 reports of suspected coagulation disorders possibly caused by warfarin-

fluoroquinolone interactions.(28) Health Canada is the department of the government of Canada that is responsible for national public health. From these, 10 cases involved an interaction with warfarin and ciprofloxacin, 13 involved gatifloxacin, 16 involved levofloxacin and 12 were with moxifloxacin.

Thus based on the literature review of warfarin-fluoroquinolone interactions, most of the evidence for an interaction comes from case series or case reports and prospective and retrospective studies suggest that this interaction may not be clinically significant.

Table 2: Warfarin-ciprofloxacin case reports

Reference	N	Mean age (years)	Mean INR Change	Mean PT Change (sec)	Bleeding Complications
Ellis (2000)(5)	2	53	28	15.7	Bilateral subdural hematomas, intractable epistaxis
Byrd (1999)(6)	1	77	3.17	9.1	Intracerebral bleed leading to death
Kramer (1991)(7)	1	70	-	15.5	None
Renzi (1991)(8)	1	48	-	50.4	None
Jolson (1991)(9)	2	85	-	69	Hematuria
Kamada (1990)(10)	1	72	-	6.5	None
Mott (1989)(11)	1	72	-	-	Hematemesis

Table 3: Warfarin- levofloxacin case reports

Reference	N	Mean age (years)	Mean INR Change	Mean PT Change (sec)	Bleeding Complications
Vadlamudi (2007)(12)	3	61	5.5	-	Hemopericardium, cardiac tamponade, retroperitoneal hematoma, death
Jones (2002)(13)	4	62	2.74	-	Epistaxis (1 case)
Ravnan (2001)(14)	2	73	3.6	-	None
Gheno (2001)(15)	2	77	-	-	None

Table 4: Warfarin-moxifloxacin case reports

Reference	N	Mean age (years)	Mean INR Change	Mean PT Change (sec)	Bleeding Complications
Yildiz (2008)(16)	1	74	10	-	Hematuria and diffuse ecchymosis
Elbe (2005)(17)	5	77	6.7	-	Upper GI bleed (1 case)
Arnold (2005)(29)	3	67	3.5	-	none
O'Connor (2003)(30)	3	80	-	-	none

Table 5: Summary of warfarin-levofloxacin interaction studies

Reference	N	Mean age (yrs)	Design	Outcome Measure	Comparator Drug	Result
Orfila (2009)(31)	21	75	Retrospective cohort	Mean change in INR	None	Significant increase in INR (p=0.001)*
Mathews (2006)(24)	54	78	Retrospective cohort	Anticoagulation-related outcomes ^a	Gatifloxacin	No difference in median INR changes between levofloxacin and gatifloxacin
Stroud (2005)(27)	-	79 ^b	Nested case-control	Hospital admission for hemorrhage (ICD-9 codes)	Cefuroxime	No significant increase in hospital admission for hemorrhage (OR = 1.21; 95% CI = 0.84 – 2.01)
McCall (2005)(25)	22	59.5	Retrospective cohort	Mean change in INR	Felodipine	No difference in mean change in INR between levofloxacin and felodipine (p=0.65)
Glasheen (2005)(32)	27	69	Retrospective cohort	Mean change in INR	Terazosin	Significant difference in mean INR change between levofloxacin and terazosin (p<0.01)*
Yamreudeewong (2003)(26)	18	68	Prospective open-label	Mean change in INR	None	No difference in mean INR change (p=0.419)

^a Anticoagulation-related outcomes = postfluoroquinolone INR > 4, > goal, ≥ 1 point above goal; INR change 0.5-0.99, 1-1.49, ≥ 1.5 points; vitamin K administration; warfarin dose withheld, warfarin dose reduced, major and minor bleed, ER visits, hospital admissions, any intervention.

^b Mean age at the start of cohort = 79 years

A. Warfarin-Macrolides Interaction

As compared to erythromycin, azithromycin and clarithromycin are considered to be safer antibiotics to prescribe with warfarin.(33) However, most of the evidence comes from single case reports and case series and should thus be interpreted with caution, since they are likely to represent a publication bias. Several case series have reported an elevation in INR or prothrombin time (PT) when clarithromycin was administered concomitantly with warfarin.(34-38) Similarly, warfarin-azithromycin interactions have mainly been reported via case series, as shown in **Table 6**.(39-43) There have been only 3 retrospective studies that have looked at the potential interaction between azithromycin and warfarin and these have been summarized in **Table 7**.(23, 33, 44) Two of these studies did not find any evidence for a significant interaction between warfarin and azithromycin.(32, 44) The sample size in these studies was very limited with the largest study having a sample size of only 52 patients and thus the power to detect a difference in the INR may have been low for most of them.

Table 6: Warfarin-azithromycin case reports

Reference	N	Mean age (yrs)	Mean INR Change	Mean PT change (sec)	Bleeding Complications
Shrader (2004)(43)	1	57	5.5	-	None
Williams (2003)(45)	1	72	10.4	95.5	Large hematoma
Foster (1999)(40)	1	71	12.16	-	Right upper quadrant hematoma
Woldtvedt (1998)(39)	1	53	Too high to quantify	- (Maximum PT = 106)	Coughing blood and blood streaked mucus

Table 7: Summary of warfarin-azithromycin interaction studies

Reference	N	Mean age (years)	Design	Outcome Measure	Comparator Drug	Result
Glasheen (2005)(23)	32	72	Retrospective cohort	Mean change in INR	Terazosin	Significant difference in mean INR change between groups (p<0.05)*
McCall (2004)(44)	17	59	Retrospective chart review	Mean change in INR	Felodipine	No difference in mean change between groups (p=0.74)
Beckey (2000)(33)	26	68.9	Retrospective chart review	Mean change in INR	Terazosin	No difference in mean change in INR between groups (p=0.60)

C. Warfarin-Penicillins Interaction

There have been very few case reports for warfarin-amoxicillin or warfarin-amoxicillin/clavulanic acid interaction.(46, 47) One article reported an interaction between amoxicillin and acenocoumarol, a coumarin anticoagulant that is not used in the United States.(48) So far 3 studies have reported either hospitalization due to bleeding or $\text{INR} \geq 6$ for amoxicillin/clavulanate for patients on other coumarin anticoagulants, such as acenocoumarol or phenprocoumon.(49-51) The only study to have assessed the risk of bleeding with amoxicillin for patients on warfarin was published recently.(52) This study did not find an association between risk of hemorrhage and use of warfarin-amoxicillin or warfarin-ampicillin combination. However, Micromedex lists warfarin-amoxicillin/clavulanate interactions as being of ‘moderate’ severity and the review by Holbrook et al. list this as a ‘probable’ (class II) interaction.(53)

D. Discussion

The clinical evidence for an interaction between warfarin and fluoroquinolones, macrolides and penicillins in older adults is very limited and most of the evidence comes from case reports and case series or from poorly designed retrospective studies. There were several limitations of the studies that were reviewed in this section. The effect of increasing age on warfarin-antibiotic interactions was not considered in these studies. Due to the high prevalence of thromboembolic conditions with increasing age, older adults represent the highest users of warfarin therapy.(54) In addition, indications such as urinary tract infections and pneumonia, for which antibiotics are prescribed, are more prevalent in older adults.(55, 56) Thus adequate representation of older adults in

warfarin-antibiotic studies may be important. If older age plays an important role in the potentiation of the drug interactions, it is possible that under-representation of older adults in some of these studies may have resulted in findings that were not significant. Since studies conducted so far have included patients with variable age ranges, the potential for increased anticoagulation due to warfarin-antibiotic interactions in older patients remains inadequately studied.

The active infection for which the antibiotic is prescribed may also be playing some role in intensifying the anticoagulant activity of warfarin. The activity of some CYP450 enzymes may be reduced during an infection or inflammation, which may further reduce warfarin metabolism.(21) Due to the potential role of infection, it may be important to study warfarin-antibiotic interactions in patients who have an acute infection. However, across the 4 prospective trials, only 26% of the patients had an acute infection.(57) The advantage of the retrospective studies was that the subjects had an active infection. The study by Schellman et al. found evidence for the role of infection in causing an increase in the bleeding risk for patients on warfarin therapy. This study suggested that infection or its sequelae, such as fever or reduced vitamin K intake may be responsible for an increased risk of bleeding since the odds ratio (OR) for the 'baseline' risk of bleeding was already significantly elevated for the subjects before the start date of the antibiotic.(21) In addition to the indication for which the antibiotic is prescribed, several other confounding factors are also important to consider while studying warfarin interactions. Older adults often have multiple comorbidities and use multiple medications. The decline in renal function with age may also necessitate dose reduction

of renally eliminated antibiotics such as quinolones. Prospective studies or pharmacokinetic and pharmacodynamic studies are limited in studying the effect of these confounders. Thus in addition to studying this interaction in older adults, and in patients with an infection, there is some value in studying this interaction in clinical settings, which include patients with multiple disease conditions.

The lack of a control drug or choice of a poor control drug was a common limitation seen in several studies. Retrospective studies of warfarin-levofloxacin interactions have used cefuroxime, felodipine and terazosin as the comparator drugs,(23, 25, 27) and studies of warfarin-azithromycin interaction have used felodipine and terazosin.(33, 44) While felodipine and terazosin have indications for use that are very different from antibiotics, the antibiotic cefuroxime was found to significantly increase hospital admissions due to hemorrhage in patients on stable warfarin therapy. Suitable choice of a control drug is a challenge, since many antibiotics are implicated to potentially interact with warfarin. Yet it may be important to assess the interaction effect using a control drug that is an antibiotic. This is because by comparing a warfarin user who is prescribed an antibiotic to a warfarin user who is prescribed a different antibiotic, it is possible to study subjects whose baseline bleeding risks are more comparable. This would help to reduce some bias due to confounding by indication and also help to distinguish between the effect of a drug interaction and the effect of infection or its sequelae, such as fever and reduced vitamin K levels. Although it is a challenge to find a suitable control drug to study warfarin-interactions, the importance of using a comparator drug cannot be underestimated.

Some studies did not use clinically meaningful outcomes such as bleeding events, hospital admissions, warfarin dose adjustments, or administration of vitamin K. Only mean change in INR before and after starting the antibiotic was assessed. Although, increase in INR is an important outcome since a supratherapeutic INR would increase the risk of a bleeding event, the use of secondary outcomes of over-anticoagulation or bleeding events may increase our understanding of the clinical significance of these drug interactions.

E. Conclusion

The most recent review that evaluated the possibility of increased anticoagulation due to warfarin-fluoroquinolone interactions concluded, “There are no consistent data to support the claim of an increased anticoagulation response in patients receiving warfarin and any of the three commonly prescribed fluoroquinolones”.(57) However, most of the studies included in this review had varied age ranges and may not adequately represent the older adult population. The prospective trials of concomitant administration of levofloxacin and ciprofloxacin in patients on warfarin did not demonstrate an increased anticoagulation response.(19, 20, 26) Meanwhile, the retrospective studies showed either significant increased elevation in INR,(23-25, 31) or significantly increased risk of hemorrhage.(27) However, these studies were not specifically done in older adults. Only 3 studies of warfarin-levofloxacin were done in older adults from which 2 showed evidence of an interaction,(24, 27) and 1 failed to show significant bleeding outcomes due to this interaction.(21) An outcome of a bleeding event always has to be considered in light of the patient care environment. If the dose is lowered due to an elevated INR,

then a bleeding event was avoided. Thus even though a warfarin-quinolone interaction may not result in adverse bleeding outcomes for all patients, over-anticoagulation caused by elevations in INR may still be an important outcome to consider for older patients due to the risks of hemorrhagic events associated with elevated INR.(58)

F. Significance

Changes in tissue distribution, declining renal function and presence of chronic disease states that require long-term drug therapy may put older adults at a higher risk for drug-drug interactions that may result in significant ADEs. Although warfarin clearance is not affected by a decline in renal function, serum levels of potentially interacting drugs, such as ciprofloxacin and levofloxacin may increase, thus enhancing the likelihood of a clinically significant interaction. Yet studies on warfarin-antibiotic interactions have not examined the effect of increasing age on the risk of over-anticoagulation or bleeding outcomes. Awareness of the differences in PK and PD profiles of warfarin and quinolones and the potential risk of this interaction in older adults may guide clinicians in making appropriate treatment choices while co-prescribing antibiotics with warfarin. Older adults are taking multiple medications for multiple co-morbid conditions. They are physically frailer, have poor nutritional status and due to their high risk of falls, the risk of bleeding events may be higher.

The levels of warfarin monitoring required for vulnerable older adults may be higher due to increased sensitivity to warfarin effects. Potential warfarin antibiotic interactions may further complicate the clinical management of warfarin therapy in older adults.

Physicians managing an older patient's warfarin therapy may sometimes be unaware of the co-prescription of antibiotics with warfarin due to the short course of therapy with antibiotics. Furthermore, it is possible that the risk of a warfarin-antibiotic interaction may be higher in older adults with multiple co-morbid conditions or for those taking multiple medications. In spite of the risks associated with warfarin use and the frequency with which it is prescribed in older adults, there are few precise estimates of the outcomes associated with co-prescribing potentially interacting medications such as antibiotics with warfarin. Thus the evidence base underlying the risk of warfarin-antibiotic interactions in older adults is weak and there is room for further research to better understand this risk.

The next section is a literature review to determine the effect of increasing age on warfarin-antibiotic interactions in older adults. The literature has been reviewed to describe general pharmacokinetic and pharmacodynamic changes that occur in older adults and the effect of increasing age on the pharmacodynamics of warfarin and on the pharmacokinetics of fluoroquinolones. Fluoroquinolones were chosen as the class of antibiotics to review in detail because age-related changes in pharmacokinetics of fluoroquinolones have been documented more often than the other antibiotics. This section also provides an understanding of how these factors may play a combined role in potentiating the risk of warfarin-antibiotic interactions in older adults. Two cases have been presented as examples in order to provide a real clinical scenario.

III. Potential Effect of Age on Warfarin-Fluoroquinolones

Interactions

Several medications may undergo a pharmacokinetic (PK) or pharmacodynamic (PD) interaction with warfarin, thus increasing the risk of a bleeding event. Fluoroquinolones are a widely used class of antibiotics in older adults and reports of an interaction between warfarin and fluoroquinolones have been conflicting and inconsistent. The risk of an interaction may be higher in older adults due to age-related physiologic changes that may result in altered PD response for warfarin and altered PK of fluoroquinolone antibiotics. A search for relevant articles using PubMed (1975-2011) and International Pharmaceutical abstracts (1975-2011) was conducted in order to review articles on age-related PK and PD changes in fluoroquinolones and warfarin and the possible mechanisms of the interaction. Case reports and evidence from other coumarin anticoagulants were excluded. The literature suggests an age-related increase in sensitivity to warfarin response and an age-related reduction in clearance of fluoroquinolones, due to declining renal function in older adults. The mechanism of warfarin-fluoroquinolone interactions has not been fully elucidated but higher drug exposure of warfarin and fluoroquinolones due to PK-PD changes may potentiate this interaction in older adults. Reports of warfarin-fluoroquinolone drug interaction studies in older adults are limited thus highlighting the need for studies that examine the effect of increasing age on the risk of over-anticoagulation or bleeding outcomes due to warfarin-fluoroquinolone interactions. This would lead to a better understanding of the

contribution of age-related PK-PD changes to this interaction. Finally, this may aid clinicians in making suitable treatment decisions while co-prescribing antibiotics with warfarin and may assist healthcare providers in anticoagulation clinics to better manage this potential drug interaction in older patients.

A. Case Presentations

A 72-year-old white male with atrial fibrillation was diagnosed with bronchitis. He was on stable warfarin therapy with a target INR range from 2.0 – 3.0. His weekly warfarin dose was 82.5mg and he was prescribed moxifloxacin 400 mg daily for 10 days to treat his bronchitis. In the one month prior to initiation of moxifloxacin his INR ranged between 2.0 and 2.4. However, following commencement of moxifloxacin his INR peaked to 6.5. His warfarin dose was withheld for 3 days and a large bruise was observed on patient's arm. A review of other concomitant medications revealed that moxifloxacin was the only potentially interacting medication that the patient was prescribed, suggesting that it may have caused the elevation in INR in this older patient.

An 83-year-old white male with a history of deep vein thrombosis and pulmonary embolism was on stable warfarin therapy with a target INR range from 2.0 – 3.0. His weekly warfarin dose was 10 mg. He was prescribed levofloxacin 500mg daily for 7 days for pneumonia. Prior to initiation of the antibiotic his INR of 2.6 was within his target range. However, on day 5 of levofloxacin therapy his INR rose to 8.0. Following this elevation his warfarin dose was withheld for 3 days and his INR was rechecked before initiating warfarin therapy. An elevation in INR in this older patient may be caused as a

result of a drug interaction between warfarin and levofloxacin, since the patient was not prescribed any other potentially interacting medications with warfarin.

B. Introduction

Warfarin is the most widely used oral anticoagulant and its use is higher in older adults due to increased prevalence of atrial fibrillation and other thrombotic disorders with advancing age.(54) In an analysis of national estimates of emergency department (ED) visits for adverse drug events in patients aged 65 years or older, 17% of all visits were from adverse drug events (ADEs) caused by warfarin, such that warfarin accounted for the highest rates of ED visits in this older adult population.(59) Ciprofloxacin, levofloxacin and moxifloxacin are the most widely used fluoroquinolone antibiotics in older adults.(60) Due to their potential to increase the anticoagulant activity of warfarin, co-prescription of quinolones with warfarin may cause a drug-drug interaction.(61) However, the clinical significance of warfarin-quinolone drug interactions has been questioned and the reports have been conflicting.(57) Yet warfarin-quinolones interactions were ranked as the fourth most dangerous drug interactions in a list of the top 10 dangerous drug interactions in nursing home residents. This list was developed as an initiative of the Multidisciplinary Medication Management Project.(62)

Since warfarin and antibiotics such as quinolones are commonly implicated for resulting in ADEs and due to the high rate of concurrent use of these medications in older adults,(63) it is important to understand if there exists a potential for a clinically significant drug-drug interaction in older adults. Increasing age is associated with several

pharmacokinetic (PK) and pharmacodynamic (PD) changes that may affect drug exposure in the older patient. A majority of the drug-drug interactions that affect older adults involve both PK and PD mechanisms. Thus the associated PK and PD changes in older adults may increase the potential of occurrence of an adverse event resulting from a drug-drug interaction. In addition, the adverse consequences of the drug-drug interaction may be more severe in older adults, especially frail older patients, since their physiologic reserve is already diminished. This review describes general pharmacokinetic and pharmacodynamic changes that occur in older adults, the effect of increasing age on the pharmacodynamics of warfarin, pharmacokinetic changes for fluoroquinolones with increasing age and how these factors may play a combined role in the mechanism of warfarin-quinolone interactions and potentially increase the risk of this interaction in older adults.

C. Method

The databases searched included PubMed and International Pharmaceutical Abstracts from the period, January 1975 to June 2011, using key words *aged, frail elderly, pharmacokinetics, pharmacodynamics, warfarin, fluoroquinolones, quinolones, drug interactions and hemorrhage*. Only English-language articles were included. Clinical trials and prospective and retrospective observational studies were included. Case reports and case series were excluded. Studies with a focus on other oral anticoagulants, such as phenprocoumon and acenocoumarol, were excluded from the review. Bibliographies of included articles were manually searched for additional studies that may be relevant.

D. General Pharmacokinetic and Pharmacodynamic Changes with Aging

For most drugs absorption is not significantly altered with aging.(64) Aging is associated with a decrease in the total body water as a proportion of body weight, which results in a reduction of the volume of distribution of water-soluble medications; thus increasing their serum concentrations in the older patient. With an increase in total body fat with aging, lipid soluble drugs have a larger volume of distribution and tend to remain in the body for longer periods. However, protein binding of drugs is not significantly affected by aging.(65) Liver oxidative metabolism of drugs is often reduced in older patients, mainly due to reduced blood flow to the liver (~20-50%) and reduced liver size (~20-30%).(64) The CYP450 enzyme system is responsible for the metabolism of warfarin and some fluoroquinolones, and intrinsic activity (oxidative metabolism) for this enzyme system is believed to be lower in older adults, compared to young adults.(66) Furthermore, renal function declines with age, thus necessitating dose reduction of certain renally eliminated medications in older patients. The Cockcroft-Gault equation is used to dose medications in older patients based on their creatinine clearance. However, this equation may overestimate renal function for frail patients, since their muscle mass is markedly decreased.(64)

There is a lack of general understanding of pharmacodynamic changes in aging since these changes have not been well studied. The older patients' response to drug therapy is generally affected by aging and disease-associated physiological changes. PD changes may occur due to changes in receptor affinity for medication, or post-receptor events such as altered signaling. In the case of warfarin, PD changes in older adults are mainly due to

altered homeostatic control mechanisms.(67) In some situations, PD changes may cause adverse drug events (ADEs) in older patients.

E. Effect of Age on Pharmacodynamic Response to Warfarin

Direct pharmacodynamic studies to determine the response to warfarin therapy are challenging as a result of a delayed therapeutic effect, which is mainly due to its mechanism of action. In addition, the effect of warfarin is sensitive to diet-associated changes in levels of vitamin K.(67) There is sufficient evidence from epidemiologic studies to suggest the association between older age and increased anticoagulant response, as a result of an increased sensitivity to warfarin with increasing age. Such an age-associated increase in sensitivity to warfarin has been demonstrated in an early pharmacodynamic study.(68) This was a prospective study of 4 older adults (age range 62-89 years) and 4 young (age range 27-37 years) patients who were administered a single loading dose of warfarin. The anticoagulant response, as measured by vitamin K-dependent prothrombin complex activity (PCA) using the Thrombotest procedure, was found to be greater in older patients as compared to younger patients. This was in spite of administering lower, weight-adjusted doses to the elderly. In addition, synthesis of vitamin-K dependent clotting factors was inhibited to a greater extent in older patients, at the same warfarin plasma concentrations as the younger patients. No age-related differences in warfarin pharmacokinetics were evident in this study. Thus, in addition to demonstrating the increased sensitivity to warfarin with age, this study demonstrated the mechanism of this altered sensitivity in older patients. The potential effect that coexisting clinical or medication factors may have on warfarin sensitivity could not be determined

in this study. In addition with increasing age these factors may further exaggerate warfarin response in older patients.

An age-related increase in sensitivity to warfarin has also been demonstrated in a prospective cohort study of 530 patients from a university outpatient anticoagulation clinic, over a 10-year period.(69) Results from the multivariate linear regression model suggested that anticoagulant response to warfarin therapy, as determined by the dose-adjusted mean PT ratio, was found to be exaggerated for older patients in the 60-69 and ≥ 70 years age group as compared to those < 50 years ($p < 0.001$). Furthermore, the mean daily warfarin dose declined substantially with increasing age (6.4 mg/day for patients < 50 years vs. 3.6 mg/day for patients ≥ 70 years; $p < 0.001$). However, this study did not demonstrate the mechanism for increase warfarin sensitivity in older adults.

Several other studies have also demonstrated similar age-related changes in warfarin dose requirements.(70-73) Husted et al. concluded that the difference between the mean daily warfarin maintenance dose between patients aged 50-60 years and 61-70 years was significantly different ($p < 0.05$) in their study of 114 patients on long-term anticoagulant therapy.(70) In a longitudinal study of 104 patients on stable warfarin therapy, a significant fall in warfarin requirements over time was observed, such that differences in warfarin dose requirements were significantly correlated with age differences ($r = 0.25$, $p < 0.01$).(71) The superiority of such a longitudinal study is its ability to identify true age-related changes in dose requirements using the same subjects over time. However, the low 'r value' indicates that age alone does not explain the fall in dosage requirement.

Similarly, the studies by Garcia et al. and Kamali et al. have also shown a significant correlation between decreasing dose and increasing age ($p < 0.001$ and $r = -0.42$, $p < 0.0001$ respectively).(72, 73)

The evidence for significant age-related changes in warfarin dose requirements may partly be explained by the increased sensitivity in warfarin response observed with increasing age. The exact mechanism of the age-related changes in warfarin activity is not known. However, two of the studies have attributed it to lower levels of vitamin K dependent coagulation factors in older adults.(68, 70) Furthermore, the higher prevalence of acute and chronic illnesses such as hypertension, peptic disease, liver disease, malignancy, cerebrovascular disease and serious heart disease in older adults may further increase the anticoagulant intensity of warfarin and thus increase the risk for serious bleeding.(74) For example, an age-related hepatic dysfunction may potentially increase the response to warfarin through impaired synthesis of clotting factors and through decreased metabolism of warfarin.(75) Thus age may have a potentially confounding effect on the risk of bleeding in older adults with several co-morbid conditions.

F. Safety of Warfarin Therapy in Older Adults

The trend towards increased bleeding in older patients, especially intracranial hemorrhage, has been suggested in several studies.(76-79) The safety of treatment with warfarin in older patients has been well documented in a systematic review.(80) Out of the 8 studies that compared the incidence rate of bleeding in older adults to younger individuals in this review, 7 found the incidence rate of bleeding to be almost 2 fold

higher in older adults as compared to younger patients, suggesting that there is a need to exercise caution with the use of warfarin in older patients. Similarly, increasing age has been implicated as a risk factor for increased bleeding experienced by older patients.(74) In addition, the authors reported that concomitant use of several medications in older adults was also believed to further increase the risk of bleeding.

G. Effect of Age on the Pharmacokinetics of Fluoroquinolones

Age-related physiologic changes have the potential to affect the pharmacokinetics of fluoroquinolones. The most important physiologic change in older adults that affects the pharmacokinetics of fluoroquinolones is the decline in renal function. Reduced renal function, as a result of reduced glomerular filtration rate, is associated with the aging process.(81) Co-morbid medical conditions may exacerbate this decline further.

Glomerular filtration rate is estimated by the patient's creatinine clearance and the reduction in creatinine clearance in almost 40% when old (>80 years) patients are compared to middle-aged patients.(60) This leads to a reduced clearance of drugs such as fluoroquinolones that are renally excreted. Levofloxacin is an example of a fluoroquinolone that is predominantly renally excreted and compared to other fluoroquinolones levofloxacin is the most dependent on renal excretion for elimination. High plasma concentrations of levofloxacin are normally achieved for elderly patients at recommended doses for younger individuals.(82) Early PK studies of levofloxacin have mainly attributed significant differences in PK parameters between younger individuals and older adults, to differences in renal functions among the subjects.(82) However, results from PK studies done in healthy older adults may not be entirely applicable to

older adults with several co-morbid conditions or to frail older adults. In a study of 183 hospitalized patients with community-acquired pneumonia (CAP), elderly patients receiving levofloxacin demonstrated significantly lower clearance (7.2 ± 1.8 vs. 10.4 ± 3.6 , $p < 0.05$), greater elimination half-life (9.8 ± 2.5 vs. 7.4 ± 2.5 , $p < 0.05$) and higher area under plasma concentration-time curve (AUC)/ minimum inhibitory concentration ratios (49.9 ± 9.7 vs. 34.8 ± 9.4 , $p < 0.05$) compared to younger patients.(83)

Ciprofloxacin on the other hand, is excreted unchanged renally (60-70% of total serum clearance) as well as extra-renally by hepatic routes.(60) In a study that included elderly patients and patients with renal impairment, the half-life of ciprofloxacin was almost two times the half-life in younger patients (3-4 hours).(84) Ciprofloxacin undergoes metabolism via the CYP1A2 and CYP3A4 enzymes. The less potent isomer of warfarin (R-warfarin) is also metabolized by CYP1A2 and CYP3A4.(58) It is generally believed, that aging decreases hepatic metabolism of medications through CYP1A2 and CYP2C19 pathways, and hepatic metabolism either decreases or remains normal for medications undergoing metabolism via CYP3A4 and CYP2C9. Substantial changes in ciprofloxacin metabolism have not been clearly demonstrated in older adults. However, if ciprofloxacin and warfarin are inhibiting and competing for the same metabolic pathway, there exist a potential for a clinically significant drug interaction. In addition, following a single oral 250mg dose, the absolute bioavailability of ciprofloxacin was found to be significantly higher in older adults compared to younger patients (72% vs. 58%).(60)

Finally, age does not have a significant effect on the PK of moxifloxacin since moxifloxacin is predominantly metabolized by phase II (conjugation) reactions and increasing age does not appear to have an effect on phase II metabolism of drugs.(65) Only 15-22% of moxifloxacin is excreted in the urine and no significant decrease in its clearance was observed in older subjects with renal function decline.(85) In conclusion, a decline in renal function with increasing age leads to reduced clearance of certain fluoroquinolones and dosage adjustments may be recommended for such patients. In addition, patients above >80 years and those with reduced lean body mass, such as frail older patients, should almost always have their quinolone doses adjusted. This is mainly due to age-related changes in PK for quinolones that may potentially lead to higher drug exposure.

H. Potential Mechanism of Warfarin-Fluoroquinolone Interactions

Several mechanisms have been proposed for a drug interaction between warfarin and antibiotics. Putting these proposed mechanisms into perspective for an older adult would help to understand how the risk for a drug interaction might be modified with increasing age. CYP1A2 and CYP3A4 enzymes metabolize the less potent isomer of warfarin, i.e. R-warfarin.(86) Firstly, fluoroquinolones are inhibitors of CYP1A2 activity and may thus inhibit metabolism of warfarin in this manner.(53) Since aging may decrease hepatic metabolism of medications through CYP2C9,(65) this may further inhibit metabolism of warfarin in older adults. Either or both of these mechanisms may result in increased drug exposures for warfarin in older adults. Secondly, antibiotics may impair the production of vitamin K by the gastrointestinal flora,(86) Vitamin K is required for coagulopathy and

their levels in the body are primarily determined by dietary intake.(86) During an infection or in a frail older patient with poor nutritional status, dietary vitamin K levels are generally low and may thus lead to increased warfarin sensitivity and over-anticoagulation. Vulnerable older adults may require closer monitoring with concomitant antibiotic use, especially if they are prone to more serious sequelae such as falls resulting in serious bleeding events.

Finally, the effect of the infection on warfarin metabolism cannot be underestimated. During an infection or inflammation the activity of some CYP450 enzymes may be reduced. This may occur due to the secretion of cytokines such as tumor necrosis factor (TNF) and interleukins (ILs) which could down-regulate CYP450 enzyme activity, thus reducing the metabolism of warfarin.(21) Thus the underlying infection for which the antibiotic is prescribed may affect the clearance of warfarin. This is especially true in the case of pulmonary infections such as pneumonia, since hepatic metabolism of drugs is reduced in the presence of pneumonia.(21) The incidence of community-acquired pneumonia has been shown to increase significantly with age, such that almost 80% of all cases are in those above 60 years.(55) Similarly, the frequency of urinary tract infections is the highest in older adults.(56) Furthermore, due to appetite suppression during an infection, vitamin K levels may also be low. Thus increased exposure to warfarin and quinolones associated with increasing age, increased sensitivity to warfarin in older adults, and effect of age on vitamin K and coagulation may result in an increased risk of warfarin-quinolone interactions in older adults.

I. Discussion

There is an age-related increase in sensitivity to warfarin response and the mechanism for this has not been entirely established. A possible reason is that older adults may have lower levels of vitamin K dependent coagulation factors. Reduced renal function associated with increasing age may reduce the clearance of the quinolone antibiotics. These factors combined may potentially lead to higher drug exposure for both warfarin and quinolones in older adults. Thus an interaction between warfarin and quinolone antibiotics in older adults may potentially result in significant elevations of INR and put them at greater risk for hemorrhagic complications. Given that hemorrhagic complications of warfarin are higher in older adults, understanding the clinical significance of the interaction between these two widely used medications may potentially help to improve the management of warfarin-antibiotic interactions in older adults. Thus there is a need for research in the area of warfarin-quinolones drug-interactions in older adults, rather than extrapolating what we already know from younger populations regarding the clinical significance of this drug interaction. The research proposed in this application is significant because it will help us to understand the clinical relevance and the risk of co-prescribing warfarin and antibiotics specifically in older adult, since they may be the population with a greater risk.

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CHAPTER 3

Warfarin Use in Nursing Home Residents: Results from the 2004 National Nursing Home Survey

I. Abstract

Background: Practice guidelines recommend anticoagulation therapy with warfarin for stroke prevention in patients with atrial fibrillation (AF). Despite this, warfarin is underused in older adults.

Objective: To determine the prevalence of AF in nursing home (NH) residents and use of warfarin or other anti-platelet medications in NH residents with AF, with indications for and without contraindications to warfarin use. The secondary objective is to determine the factors associated with warfarin use in NH residents with AF.

Methods: Cross-sectional analysis of prescription and resident data files from the 2004 National Nursing Home Survey was performed. Residents with a diagnosis of AF were identified using ICD-9-CM codes and prescriptions of warfarin and anti-platelet medications were identified using Long-term Care Drug Database System (LTCDDS) codes. Resident characteristics, stroke risk factors and potential bleeding risk factors significant at $p < 0.10$ in chi-square analyses were entered in the final multiple logistic regression model to determine the factors associated with warfarin use. All analyses were done using SAS 9.2.

Results: From 13,507 NH residents, 1904 (14%) had a diagnosis for AF and 1767 (13%) had a diagnosis for AF, with indications for and without contraindications to warfarin use. Of these 1767 residents, 30% were prescribed warfarin and of the remaining 1230

resident, 23% received either aspirin or clopidogrel, such that 54% of residents with AF did not receive any antithrombotic therapy in the form of warfarin, aspirin, clopidogrel or combination of these medications. Factors that were significantly associated with increased odds of receiving warfarin were congestive heart failure, previous stroke/transient ischemic attack, deep vein thrombosis/ peripheral embolus, valvular heart disease and total number of medications (≥ 6). Factors that were significantly associated with reduced odds of receiving warfarin were non-white race, history of gastrointestinal bleeding and use of anti-platelets (i.e. clopidogrel).

Conclusions: AF is common in NH residents and more than half the residents with AF, with indications for and no contraindications to warfarin use, were not prescribed either warfarin or anti-platelets such as aspirin or clopidogrel, suggesting that anticoagulation therapy may be underused in NH residents with AF.

Keywords: Warfarin, atrial fibrillation, underuse, nursing homes

II. Introduction

The Anticoagulation and Risk Factors in Atrial Fibrillation Study (ATRIA) study, estimated that approximately 2.3 million Americans were diagnosed with atrial fibrillation (AF) between 1996-1997, and this number is likely to increase 2.5 fold in the next 50 years.(1) The age-specific prevalence of AF is the highest in those above 80 years (11-12%) as compared to those 55 years and younger (0.1-0.2%).(2) Patients with AF have a five-fold increased risk of ischemic stroke; thus prevention of ischemic stroke is the primary goal in management of patients with AF. (2) Practice guidelines recommend anticoagulation therapy with a vitamin K antagonist, such as warfarin, for the prevention of ischemic stroke in these patients.(3-5) For patients who are at increased risk of bleeding events or have a contraindication to warfarin, anti-platelet therapy with aspirin may be an alternative, although aspirin is not as effective as warfarin in reducing the risk of stroke in AF patients.(6, 7) The combination of aspirin and clopidogrel was found to be more effective than aspirin alone and may be used in patients for whom warfarin is contraindicated.(8) In addition, long-term use of clopidogrel was considered more effective than aspirin alone in reducing the risk of thromboembolic events.(9) Ticlopidine is no longer used for anti-platelet therapy and according to the Beers criteria its use is discouraged in older adults.(10) Therefore, adjusted-dose warfarin still remains the most effective therapy for stroke prevention.

Currently, more than 1.6 million older Americans are residing in nursing homes. The prevalence of AF is also higher in NH residents (7.5-17%) as compared to community-

dwelling older adults.(14, 16) This may be a reflection of the higher age and increased prevalence of cardiovascular diseases among NH residents. In addition, NH residents are generally frailer as compared to community-dwelling older adults. Frail patients are less likely to receive warfarin, and this may partly be due to fear of hemorrhagic complications.(17) The relationship between increasing age and hemorrhagic complications is such that the tendency towards increased bleeding with oral anticoagulants is higher in older adults as compared to younger patients.(18) In addition to the increased incidence of bleeding, the severity of bleeding events has been shown to be greater in older adults.(19) Several studies have shown that the response to warfarin therapy increases with age, both in the early induction phase and during the long-term maintenance phase.(20) Age-related changes in warfarin dose requirements have been demonstrated in cross-sectional studies, (21-25) as well as in longitudinal studies.(22, 26) The risk of falls is higher in NH residents, such that the mean fall rate of 1.5 falls/ bed per year is three times the rate for community-dwelling older adults.(27) Higher prevalence of co-morbid conditions such as, congestive heart failure, hypertension, malignancy, ischemic stroke, peptic ulcer disease, liver disease, in older adults may also lead to an increased risk of bleeding.(19, 20) Thus, changes in homeostasis of coagulation associated with increasing age, increased fall risk and high prevalence of multiple co-morbid conditions may put NH residents at an increased risk of bleeding events. Due to perceived increased risk of bleeding, nursing home residents may be less likely to receive a prescription for warfarin, in spite of the presence of more than one stroke risk factor. Gurwitz et al have shown adverse warfarin-related events to be common among NH residents, of which 29% were judged to be preventable.(28) However, the benefits of

warfarin therapy in reducing the incidence of thromboembolic stroke have been demonstrated for patients with AF who do not have contraindications to warfarin, including patients that are 70 years and older.(29-31)

Despite the benefits of anticoagulation therapy with warfarin in AF patients, studies have reported an under-use of this drug in older adults.(11-13) Few studies have specifically documented the prevalence of AF and under-use of warfarin in NH residents and none of these used a nationally representative sample of NH residents.(14-16, 32) Some of these studies were done more than 10 years ago, and since then new anti-platelet agents such as clopidogrel have become available for secondary stroke prevention. Thus there is limited national level data on the prevalence of AF and use of warfarin in NH residents. The NH population is of interest due to their higher mean age and thus higher prevalence of AF. In addition, the increased prevalence of cardiovascular diseases in this population is a concern since some of these conditions may be potential stroke risk factors. Determining patterns of warfarin and anti-platelet medication use in NH residents would increase our understanding of treatment choices made for stroke prevention in this older population. Identifying resident characteristics or risk factors for stroke and bleeding that are related to warfarin use may further help to address the issue of underuse of anticoagulation therapy, if any. Therefore, the primary aim of this study was to determine the prevalence of AF in nursing home residents and use of warfarin or other anti-platelet medications in NH residents with AF, with indications for and without contraindications warfarin use. The secondary aim is to determine the factors associated with warfarin use in NH residents with AF.

III. Methods

A. Data source and study sample: This is a cross-sectional analysis of the prescription and the resident data file from the 2004 National Nursing Home Survey (NNHS). This survey uses two-stage sampling to obtain a representative sample of nursing home residents in the United States and is conducted periodically by the Centers for Disease Control and Prevention. The 2004 data is the more recent wave of the NNHS and contains information on 13,504 nursing home residents. The NNHS dataset is available for public use and was accessed after receiving approval from the Virginia Commonwealth University Institutional Review Board. More details of the NNHS may be found at <http://www.cdc.gov/nchs/nnhs.htm>.

The study sample included a nationally representative sample of NH residents with AF. Residents with a diagnosis for AF were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code 427.31. AF coding has been shown to have high sensitivity (81-91%) and specificity (83-100%) in a previous study that determined the accuracy of coding of stroke risk factors such as AF, by using ECG and physician history notes as the gold standard.(33) This study was not specific to the NNHS, but previous studies have also used the ICD-9-CM diagnostic code 427.31 to identify eligible patients with AF from large claims databases,(13, 34) or from hospital notes and discharge records.(12, 35)

From the full AF sample, residents for whom warfarin was not indicated according to the 2001 American College of Cardiology/ American Heart Association (ACC/AHA) guidelines for management of patients with AF were excluded.(36) The 2001 guidelines were applicable at the time of the 2004 NNHS sample. According to the ACC/ AHA guidelines, warfarin was not recommended for men and women < 60 years of age with or without stroke/ thromboembolism risk factors and men 60-74 years of age without thromboembolism/ stroke risk factors. This sample was further reduced to those residents for whom warfarin is indicated, i.e. women 60-74 years of age with or without stroke/ thromboembolism risk factors, men 60-74 with stroke/ thromboembolism risk factors and both men and women 75+ with and without stroke/ thromboembolism risk factors. Stroke/ thromboembolism risk factors included congestive heart failure, hypertension, diabetes mellitus, previous stroke or transient ischemic attack (TIA), coronary heart disease, deep vein thrombosis or peripheral embolus and valvular heart disease. The stroke risk for each resident with AF was also calculated using the CHADS₂ (congestive heart failure, hypertension, age \geq 75 years, diabetes mellitus and prior stroke or transient ischemic attack) index. This score is usually calculated to quantify the stroke risk for patients with AF and may help to guide suitable antithrombotic therapy.(37)

In addition, residents for whom warfarin is contraindicated according to the Coumadin[®] package insert were excluded.(38) These contraindications included hemorrhagic tendencies or blood dyscrasias such as thrombocytopenia, active GI ulceration and recent surgery. Furthermore, variables for potential bleeding risk factors were created. These included age \geq 65, renal failure/ chronic kidney disease, falls history, dementia, hepatic

disease, history of gastrointestinal bleeding, myocardial infarction, malignancy, use of warfarin interacting medications such as anti-platelets (i.e. clopidogrel) and NSAIDs. These potential bleeding risk factors were identified from the Coumadin[®] package insert, the Outpatient Bleeding Risk Index and the HAS-BLED score.(38-40) Variables for thromboembolism risk factors, contraindications for warfarin use and potential bleeding risk factors were created using information from primary and secondary diagnoses for NH admission and recent ER visits/ hospitalization from NNHS resident questionnaire and LTC medication data. The ICD-9-CM diagnosis codes used to identify residents with the above variables have been provided in Appendix A. These codes have been validated in previous studies and were identified using the ICD-9 coding manual and previous literature.(33, 41-48) These ICD-9 codes have been used previously in other studies.(49, 50) In addition to ICD-9 codes, NAMCS reason for visit codes were used to identify residents with contraindications to warfarin use. (Appendix B) A resident was said to have a positive fall history if they had a documented fall in the past 31-180 days, as per the definition used by the 2004 NNHS. Use of anti-platelets and NSAIDs were determined using the LTCDDS codes listed in Appendix C.

B. Drug exposure: The NNHS collected medication data using the medication administration records (MARs) in the resident's medical record. For each sampled resident the designated NH respondent answered medication questions such as 'what medications were taken by the resident during the 24 hours the day before the facility interview?' and 'what medications were taken regularly by the resident but not during the 24 hours before the facility interview?' The interviewer was allowed to enter up to 25

medications for each question using the computer-assisted personal interviewing (CAPI) instrument. The primary outcome of this analysis is the use of warfarin in NH residents with AF, with indications for and without contraindications to warfarin use. The Long-term Care Drug Database System (LTCDDS) codes were used to determine whether residents with AF received a prescription for warfarin or other anti-platelet agents, such as aspirin (at daily dose from 81mg to 325 mg to distinguish from its use as an analgesic and anti-inflammatory), clopidogrel, ticlopidine and dipyridamole. The LTCDDS codes for the above medications are provided in Appendix C and were used to scan all 25 medications for each sampled resident. Prevalence of warfarin use and use of other anti-platelet drugs in these residents with AF was determined.

C. Statistical analysis: The prescription and resident data files were merged for the purpose of the analysis based on the resident ID (RESNUM). Sampling weights were provided in the NNHS, and these were used to determine national estimates of medication use and prevalence. Descriptive statistics were used to summarize the characteristics of residents with AF. Since the data were normally distributed, mean and SD were used to describe continuous outcomes. Thus the dependent variable in this analysis was prescription of warfarin. Chi-square analysis was used to determine the association between warfarin use and resident characteristics such as age (60-79, 80-90, ≥ 90), sex, race (white and non-white), ethnicity (Hispanic and non-Hispanic), length of stay (≥ 90 days, < 90 days), total number of medications (0-5, 6-15, 16-30), stroke risk factors (congestive heart failure (CHF), hypertension, diabetes mellitus, previous stroke or TIA, DVT or peripheral embolus, valvular heart disease, CHADS2 score (0-1, 2, 3, 4-

5) and potential bleeding risk factors (renal failure/ CKD, dementia, history of falls, bleeding history, myocardial infarction, malignancy, use of anti-platelets or NSAIDs). Total number of medications was classified as either 0-5, 6-15 or 16-30, since surveys on patients living in nursing homes showed that these residents took on average 6-8 different drugs simultaneously. (51) Thus we would expect a majority of NH residents to be within the 6-15 category of total number of medication. The significance level for variables in the bivariate chi-square analysis was set to $\alpha = 0.10$. Factors that were found to be significantly associated with warfarin use in the bivariate chi-square analysis were included in the final multiple logistic regression model. Model building was done using the stepwise selection option under PROC LOGISTIC with SLENTY (significance level for entering) set at 0.10 and SLSTAY (significance level for stay) set at 0.15. All analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, NC, USA). P-values < 0.05 were considered significant. Survey procedures such as SURVEYMEANS, SURVEYFREQ and SURVEYLOGISTIC were used, since these procedures take into account the sampling weights.

IV. Results

A. Demographics and Anticoagulant Use

From the 13,507 NH residents sampled in the 2004 NNHS, a total of 1904 (14%) residents had a diagnosis for AF. Of these 1904 residents with AF, 64 (3.4%) residents did not have any risk factors for stroke and were excluded from the analytic sample.

Further from the remaining 1840 residents with an indication for warfarin use, 1767

residents had no contraindications to warfarin use. Thus from the total 13,507 NH residents, 1767 (13%) had a diagnosis for AF with indications for and no contraindications to warfarin use. The mean age (SD) of 1767 residents with AF was 85.6 (7.4) years and the range was 61-100 years. From this, 1259 (71%) residents were females. The mean (SD) number of medications prescribed for residents with AF was 10 (4) and the range was 0-24 medications.

Warfarin was prescribed in 537 (30%) residents with AF and of the remaining 1230 (70%) who did not receive warfarin, 278 (23%) received anti-platelet therapy either in the form of aspirin or clopidogrel. Figure 1 outlines the use of warfarin and anti-platelet medications in the 1767 residents with AF. As shown in Figure 2, 954 (54%) residents with AF did not receive any form of antithrombotic therapy in the form of warfarin, aspirin, clopidogrel or combination of these medications. Ticlopidine and dipyridamole were not prescribed in any resident. Table 1 summarizes the demographics, risk factors for stroke, residents CHADS₂ score and potential risk factors for bleeding, stratified by warfarin-users and non-users. Since the percentage of residents with hepatic failure was <1% this variable was not included in the analysis. The percentages included in this table are based on weighted frequencies calculated using the sampling weights provided and are thus national estimates.

Table 1: Characteristics of nursing home residents with atrial fibrillation, with indications for and no contraindications to warfarin, stratified by warfarin use

Resident Characteristic	Warfarin users N=58,779 (31%) %	Warfarin non-users N=133,284 (69%) %	p-value^a
Age groups (years)			
60-79	22	20	0.0007*
80-89	53	45	
≥ 90	25	35	
Sex			
Male	28	30	0.5024
Female	72	70	
Race			
White	96	90	0.0021*
Non-white	4	10	
Ethnicity			
Hispanic	3	2	0.1785
Non-hispanic	97	98	
Length of stay (days)			
< 90	24	22	0.3415
≥ 90	76	78	
Total no. medications			
0-5	7	16	<0.0001*
6-15	81	78	
16-30	12	6	
Stroke Risk Factors†			
Congestive heart failure	40	35	0.0948*
Hypertension	63	61	0.5477
Diabetes mellitus	24	23	0.7505
Previous stroke/ TIA	34	24	0.0002*
Coronary heart disease	31	30	0.7289
DVT ^c / peripheral embolus	8	3	<0.0001*
Valvular heart disease	4	2	0.0281*
CHADS2 score for stroke risk†			
0-1	40	50	
2	27	26	0.0026*
	26	19	

3	7	5	
4-5			
Bleeding risk factors†	4	7	
History of GI bleeding	6	5	0.0150*
Dementia	29	28	0.2750
Falls (past 31-180 days)	2	3	0.9570
Myocardial infarction	27	26	0.3043
CKD/ renal failure	4	6	0.7479
Malignancy			0.2056
Use of warfarin-			
interacting	4	24	
drugs:	13	10	<0.0001*
(i) Anti-platelets			0.0414*
(ii) NSAIDs			

† not mutually exclusive

^a p-value from chi-square analysis between warfarin users and non-users and resident characteristics

*p-value significant at <0.10

TIA = transient ischemic attack; **CKD** = chronic kidney disease; **NSAIDs** = Non-steroidal anti-inflammatory drugs; **CHADS₂** = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus and prior stroke or transient ischemic attack

Figure 1: Summary of use of warfarin and other anti-platelet medications in eligible nursing home residents with atrial fibrillation

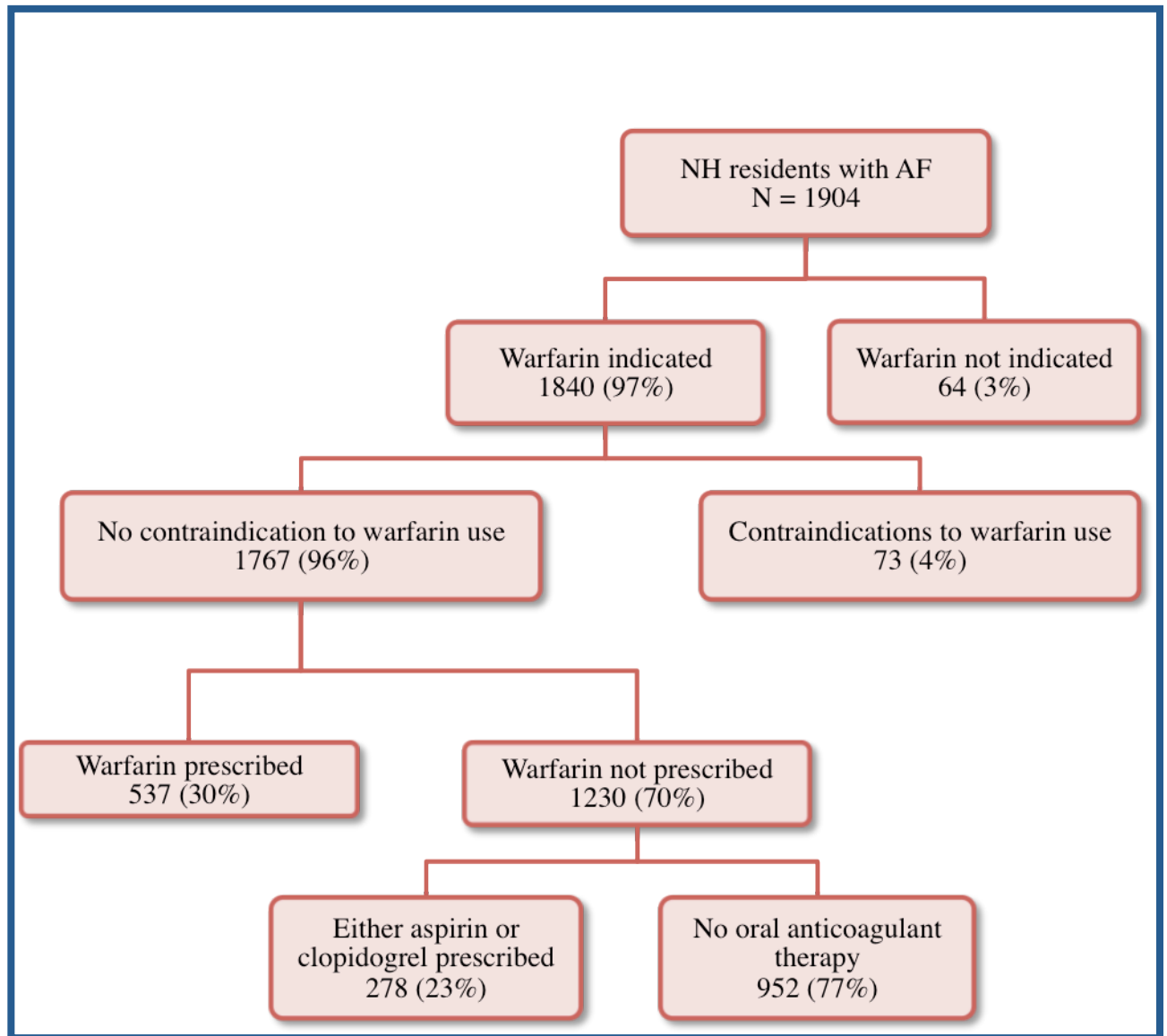
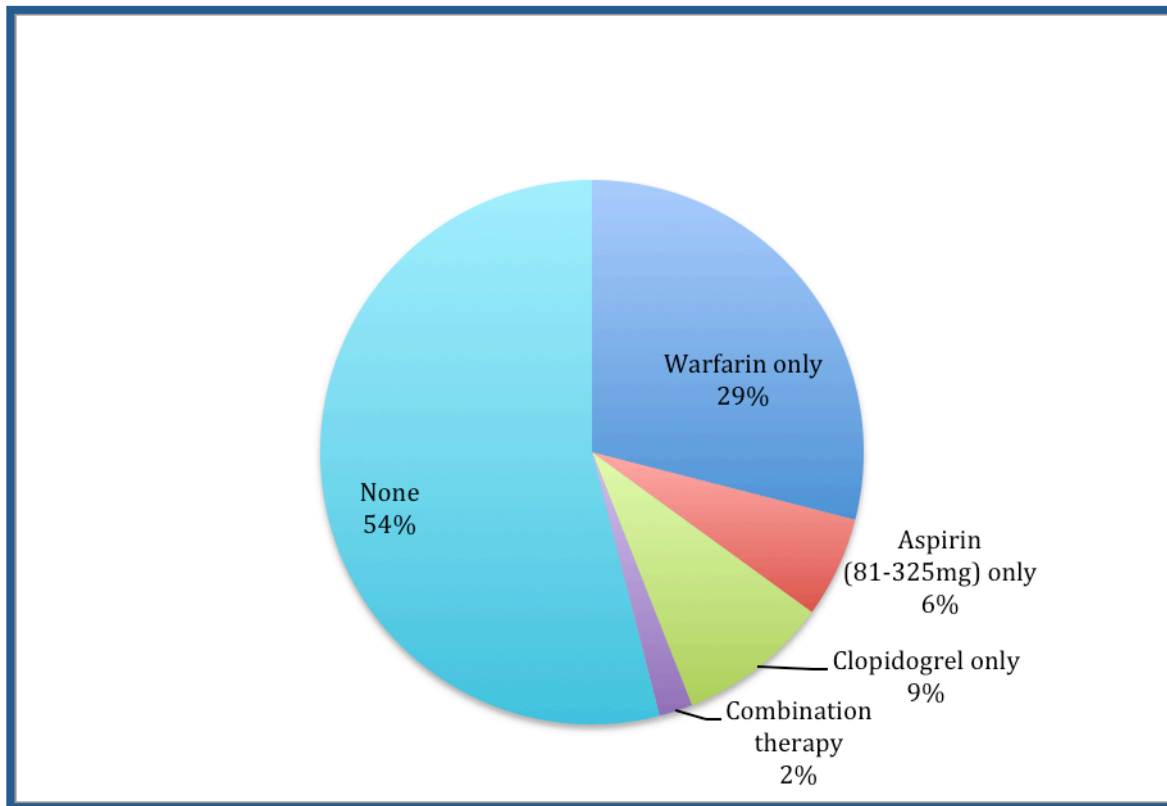


Figure 2: Use of warfarin and other anti-platelet medications by nursing home residents with atrial fibrillation (n = 1767)



Combination therapy includes (i) warfarin and aspirin (n=17) (ii) aspirin and clopidogrel (n=20) (iii) warfarin and clopidogrel (n=4)

B. Factors associated with warfarin use

Table 2 presents the results of the multivariable analysis with the adjusted odds ratio (OR), 95% CI and p-value for factors that were found to be significantly associated with warfarin use. These factors include age, race, total number of medications, stroke risk factors (CHF, previous stroke/ TIA, DVT/ peripheral embolism, and valvular heart disease) and potential bleeding risk factors (history of GI bleeding and use of anti-platelets or NSAIDs).

The association of age with warfarin use was such that residents in the ≥ 90 years age group were less likely to be receiving warfarin as compared to the 60-79 years age group. (OR=0.61, 95%CI = 0.44-0.85). Non-white residents had significantly lower odds for receiving warfarin as compared to white residents (OR= 0.37; 95% CI = 0.22-0.63)). With an increasing number of prescribed medications, residents were more likely to be receiving warfarin, such that residents taking 6-15 and 16-30 medications were more likely to be receiving warfarin as compared to those taking 0-5 medications (OR= 3.03, 95% CI = 2.03-4.50 and OR= 7.41 , 95% CI = 4.27-12.87 respectively). Among the stroke risk factors, residents with CHF (OR=1.29, 95% CI=1.03-1.62), previous stroke event/ TIA (OR=2.26, 95% CI=1.77-2.90), DVT (OR=5.83, 95% CI=3.18-10.70) and valvular heart disease (OR=1.77, 95% CI=0.93-3.39) were more likely to be receiving warfarin. The only potential bleeding risk factors for warfarin that was significantly associated with warfarin use was history of GI bleeding and use of anti-platelets (i.e. clopidogrel), such that residents with a prior GI bleeding event (OR = 0.51, 95% CI=0.31-0.84) and those using anti-platelets (OR=0.10, 95% CI=0.06-0.17) were less likely to be prescribed warfarin.

Table 2: Factors associated with warfarin use in nursing home residents with atrial fibrillation, with indications for and no contraindications to warfarin

Variable	Adjusted Odds Ratio (95% CI)	p-value
Age		
60-79	1.00	0.0001
80-89	1.05 (0.79 – 1.41)	
≥ 90	0.61 (0.44 – 0.85)	
Race		
White	1.00	0.0003
Non-White	0.37 (0.22– 0.63)	
Total no. medications		
0-5	1.00	<0.0001
6-15	3.03 (2.04 – 4.52)	
16-30	7.44 (4.28 – 12.93)	
Stroke risk factors		
Congestive heart failure	1.29 (1.03 – 1.63)	0.0275
Previous stroke/ TIA	2.26 (1.76 – 2.89)	<0.0001
DVT/ peripheral embolus	5.83 (3.17 – 10.70)	<0.0001
Valvular heart disease	1.76 (0.92 – 3.37)	0.082
Bleeding risk factors		
History of GI bleeding	0.48 (0.30 – 0.78)	0.0031
Use of anti-platelets	0.10 (0.06 – 0.17)	<0.0001

V. Discussion

A. Underuse of warfarin in NH residents:

The results of this cross-sectional analysis showed that 14% of all NH residents had a diagnosis of AF and 13% of all NH residents had a diagnosis of AF with indications for and without contraindications to warfarin use, of which about 30% received anticoagulation therapy with warfarin. Furthermore, about 23% of residents who did not receive warfarin, received secondary stroke prophylaxis with either aspirin or clopidogrel. Thus 54% of NH residents did not receive either warfarin or antiplatelet therapy with aspirin or clopidogrel. It was not surprising that none of the residents

received ticlopidine, since the use of this agent is discouraged in older adults.(10) Previous studies have found the prevalence of AF in NH residents to be around 7.5-17%; however, these studies were done more than 10 years ago.(14-16) The 30% rate of warfarin use in NH residents reported in this study was similar to what has been reported previously for NH residents. Gurwitz et al. reported that 32% of patients with AF were being treated with warfarin across 30 long-term care (LTC) facilities,(15) McCormick et al. reported 42% warfarin use in NH patients with AF(16) and Lackner et al. reported that only 20% of NH patients with nonvalvular AF were being treated with warfarin as per the ACCP guidelines.(14) Similar to these studies the results of this cross-sectional analysis suggest that anticoagulation therapy with warfarin or anti-platelet therapy with aspirin or clopidogrel may be underused in this nationally representative sample of NH residents.

Major practice guidelines, such as those by the American College of Chest Physicians (ACCP), the American Heart Association/ American Stroke Association and American College of Cardiology/ American Heart Association recommend warfarin as a class I recommendation for stroke prevention in patients with AF. (3-5) Furthermore, the ACCP guidelines have been adapted for use in older adults by the American Geriatrics Society and their recommendations also include the use of warfarin for prevention of stroke in patients with nonvalvular AF and without a contraindication to warfarin.(52) Thus in spite of these practice guidelines, underuse of warfarin is consistently being reported for older adults, not only in NH residents but also in community dwelling and hospitalized older adults.(34, 53-55) Safety of warfarin therapy in NH residents may be a cause of concern, leading to its underuse. A study done in 25 NHs by Gurwitz et al. found that

87% of all the 720 warfarin-related adverse events were minor, 11% were deemed serious and 2% were considered life-threatening or fatal.(28) Furthermore, 29% of adverse warfarin-related events were deemed preventable in NH settings.(28)

There may be several barriers to prescribing warfarin and these may be classified as patient, physician and health care system-related barriers.(56) Important patient-related barriers included increasing age, perceived embolic risk and perceived risk for hemorrhage and the most important and consistent physician-related barrier was the physician's perception of the benefit vs. risk of therapy.(56) A survey that assessed the attitude of LTC physicians towards warfarin use showed that 34% of the physicians believed the benefits of warfarin only slightly outweighed the risks, and 19% believed that the risks outweigh the benefits.(57) Future research may help to determine whether these barriers relate to possible warfarin underuse in NH residents.

The patterns of anti-coagulation use in NH settings for patients with AF may change with the newly approved oral anticoagulant, dabigatran. Since this medication was recently approved, little is known about the patterns of use and safety profile associated with dabigatran in the NH setting. Some features that may seem attractive for use of dabigatran are fixed doses, renal excretion and no monitoring of INR required.(58) In addition, dabigatran may be more expensive but would have lower costs associated with monitoring the patient.(59) However, lack of monitoring of older adults on anticoagulation therapy, especially frail nursing home residents, may be a cause of concern given the risks associated with anticoagulation therapy in general. Two cases of dabigatran-related adverse events were recently reported in 2 older frail women, from

which one had a fatal outcome.(60) Both women had low body weight and reduced renal function. Thus LTC physicians may need to be cautious while prescribing dabigatran to frail patients with moderate or severe renal insufficiency until there is more data available regarding its use in older adults. It would be interesting to know from future studies whether LTC physicians have started prescribing dabigatran to NH residents with AF, and how these prescribing patterns affect the possible underuse of anticoagulation in NH settings. Given the long track record of warfarin usage and knowledge about its potential adverse effects, it may be possible that LTC physicians would want to continue warfarin therapy for patients that are already stable on it.

B. Factors associated with warfarin use:

Residents aged 90 years and above were less likely to receive a prescription for warfarin as compared to those in the 60-79 year age group. Previous studies have also reported older age, usually ≥ 85 years, to be a predictor of warfarin underuse.(61-63) There is evidence to support an increased bleeding risk in patients >80 years.(64) Fear of increased bleeding risk, frailty and increased risk for falling may have led to a decreased use of warfarin in the oldest resident age group. This may raise a particular concern for warfarin therapy in those aged ≥ 90 years and above since older patients appear to be at the highest risk of ischemic stroke if not treated and have the highest absolute reduction in risk of ischemic stroke when treated.(65) Thus the oldest patients who are more likely to need and benefit from warfarin therapy are also at higher risk of warfarin-related bleeding events. Residents of the non-white race were less likely to receive warfarin as compared to whites. This kind of a racial difference in warfarin use has been shown in

previous studies as well.(11, 49) Residents using 6-15 or 16-30 total number of medications were more likely to be prescribed warfarin than those receiving 0-5 medications. This association may have important implications since warfarin is known to undergo interactions with several medications.(66) A study that assessed the use of warfarin-interacting medications in long-term care found that 79% of NH residents were prescribed at least one warfarin-interacting medication and these residents were found to spend significantly less time in the therapeutic range.(67) Future studies could provide more information on what percentage of these medications may be potentially interacting with warfarin. As expected, residents with stroke risk factors such as CHF, previous stroke/ TIA, DVT/ PE and VHD were more likely to receive warfarin as a measure for stroke prophylaxis. While history of stroke or TIA has consistently been reported as a predictor of warfarin use, the results for the other stroke risk factors have varied across studies.(35, 62, 63) The finding that CHADS₂ score was not part of the final logistic model in spite of it being an important predictor of stroke risk may seem unusual. A possible reason for this may be that most of the variables comprising this index were already inputted as independent predictors in to the logistic model. Two of these CHADS₂ variables, CHF and prior stroke/ TIA were found to be significant predictors of warfarin use. Thus due to reasons of collinearity of the CHADS₂ score with other variables, it may not have been significant in the final model. Of all the potential bleeding risk factors that were included in this study, only history of GI bleeding and use of anti-platelets was associated with a decrease in warfarin use. History of GI bleeding has been found to be a significant predictor in previous studies.(35, 61, 62) It seems logical that residents receiving warfarin were less likely to be prescribed anti-platelets (i.e.

clopidogrel) since these residents with AF are already receiving anticoagulation therapy. A secondary reason may be the fear of warfarin-clopidogrel drug interaction. On the other hand, there were no significant differences in NSAIDs prescriptions among warfarin users and non-users.

Based on the results of this study, the use of warfarin could be potentially increased in some ways. If fear of bleeding events is a concern for those above the age of 90 years, use of some of the bleeding risk scores such as HEMOR₂RHAGES, HAS-BLED or the Outpatient bleeding risk Index, in conjunction with the stroke risk index, such as CHADS₂ may help to assess the risk versus benefits of warfarin therapy.(37, 40, 68, 69) Interventions to increase the use of warfarin in the minority NH population could be implemented. Suboptimal effectiveness and less frequent monitoring of warfarin among black and Hispanic Medicare beneficiaries as compared to whites have been shown in a previous study.(11) In addition, genetic polymorphisms may affect the sensitivity of warfarin and are known to vary in prevalence according to race.(11) Thus possible reasons for underuse of anticoagulation therapy in non-whites could be an area of future research. If suboptimal effectiveness, lower monitoring and genetic polymorphisms are found to be potential reasons for decreased warfarin use in non-whites, alternate strategies for anticoagulation, such as dabigatran, could be employed for these patients. Some limitations of this study may be identified. Due to the nature of the data we could not confirm the diagnosis of AF clinically by means of an electrocardiogram and whether residents had paroxysmal, persistent or permanent AF. It was also not possible to know if patient was actively in AF or had been successfully cardioverted. Since patients go in

and out of AF, it is difficult to know if they are currently in AF at the time of assessment from the survey. Data on the type of medication order (i.e. standing, routine, or PRN), dosage, strength, route, or frequency information was not collected. The accuracy of stroke/ TIA codes (434-436) reported by some studies was poor.(42, 45) Determining 'suitable' ICD-9-CM codes to identify subjects of interest in epidemiological studies such as this will always be a shortcoming. One way of accounting for this limitation is to restrict the analysis to ICD-9 codes that have been used frequently in prior studies,(41, 49, 50) and codes with acceptable levels of sensitivity, specificity and positive predictive values (PPVs). Stroke and stroke risk factors such as atrial fibrillation, coronary artery disease, diabetes mellitus and hypertension have been coded with sensitivity from 81% to 91% and specificity ranging from 83% to 100%.(33)The potential bleeding risk factors and stroke risk factors included only those variables for which data were collected in the NNHS. Information on additional bleeding risk factors, such as vascular malformation, uncontrolled hypertension, seizure disorders, fluctuating INR values and pharmacokinetic drug interactions, or stroke risk factors such as left atrial size > 45mm and left ventricular ejection fraction <40% or contraindications to warfarin use such as planned surgery within a month, chronic alcohol abuse, poor compliance, patient refusal of warfarin and warfarin allergy was not available. In addition, there was a lack of knowledge regarding previous warfarin use. A resident may have been on warfarin in the past but may have been discontinued from it for reasons that were not captured in the survey. However, the analysis included all available stroke and bleeding risk factors to determine residents with AF who should potentially be receiving warfarin. Additionally, the validity of coding of warfarin and antiplatelets medications in the LTCDDS is not routinely checked. The

information on medications used by the resident is collected based on review of the medication administration record. Since this is supposed to be the record of actual medication administration, we would expect it to be valid; however, there may be some error and this is a known limitation of this type of data. According to the NNHS, history of falls was defined as those who ‘fell in past 31-180 days’. Thus this definition does not include residents who had a fall prior to 180 days or within 31 days from the time of the survey, suggesting that the percentage of those with falls may have been higher than what was actually reported in this analysis. Since this was a cross-sectional analysis it was not possible to determine whether residents who did not receive anticoagulation were more likely to have adverse stroke or thromboembolic outcomes as compared to those who received stroke prophylaxis. Finally, due to the cross-sectional nature of the study it is not possible to make any causal inferences for the factors associated with warfarin use. Thus the term ‘predictors’ was avoided for any of the factors that were found to be significantly associated with warfarin use. The study provided the prevalence of AF and warfarin use in NH residents at one point in time; the results may differ if another time frame had been chosen given the new oral anticoagulant, dabigatran that was recently approved in 2010. However, the 2004 NNHS survey was the mostly recent wave of the survey and no other study has recently determined these national prevalence estimates of AF for NH residents. These rates were not comparable to previous estimates of the NNHS since this was the first time in the survey’s history that medication data was collected.

VI. Conclusion

The overall prevalence of AF in NH residents was 14%, such that 13% of the total number of residents had a diagnosis for AF with indications for and no contraindications to warfarin use. The total rate of warfarin use in these residents with AF was about 30%, confirming the results of previous studies that suggest an underuse of warfarin in NH residents with AF. Age ≥ 90 years, non-white race, total number of medications, CHF, previous stroke/ TIA, DVT/ PE, VHD, GI bleeding history and use of anti-platelets were factors that were significant predictors of warfarin use. Suggestions for future research include development of effective strategies to impact anticoagulation prescribing patterns in order to ensure that NH residents most likely to benefit from anticoagulation therapy are actually receiving it. Furthermore, it would be interesting to know whether a change in anticoagulation prescribing patterns in NH residents would lead to improved patient outcomes in terms of reduced stroke rates and reduced adverse bleeding outcomes.

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CHAPTER 4

Warfarin-Antibiotic Interactions in Older Adults of an Outpatient Anticoagulation Clinic

I. Abstract

Background: Several drugs may interact with warfarin to cause an increase in its anticoagulant activity. There are conflicting reports on the nature of warfarin-antibiotic interactions and data on outcomes of over-anticoagulation associated with warfarin-antibiotic interactions is limited in older patients

Objective: To determine the effect of oral antibiotics, such as amoxicillin, azithromycin, cephalexin, ciprofloxacin, levofloxacin and moxifloxacin, on the international normalized ratio (INR) in patients on stable warfarin therapy, aged 65 years or above, and to determine and compare the effect of warfarin-antibiotic interactions on secondary outcomes of over-anticoagulation.

Methods: This is a retrospective cohort study utilizing data from a medical record review of patients from an outpatient anticoagulation clinic at a Veterans Affairs medical center. Patients aged 65 years or above, who were on stable warfarin therapy and received a prescription of the antibiotics of interest, during the period from January 1st, 2003 to March 1st, 2011, were included. Depending on the availability of INR values in the anticoagulation clinic notes, two INR values were recorded before antibiotic start date, i.e. pre-antibiotic INR 1 and 2, and two INR values were recorded after start of antibiotic, i.e. post-antibiotic INR 1 and 2. Mixed-effects repeated measures ANOVA model was used to determine the effect of antibiotics on the mean change in patient's INR over these

four periods of time. The secondary outcomes of interest were percentage of patients whose warfarin dose was adjusted/ withheld, INR > therapeutic, INR increase >1, INR increase >2, absolute INR ≥ 4 or ≥ 5 , vitamin K administration or major/ minor bleeding events. The Fisher's exact test was used to test whether there was an association between the type of antibiotic and the above secondary outcomes of over-anticoagulation, using cephalexin as the control. Statistical significance was defined as a p-value of < 0.05. All analyses were done using SAS 9.2 (SAS Institute Inc, Cary, NC, USA).

Results: There were 364 prescriptions of warfarin-antibiotics in a total of 205 patients during the study period. The ANOVA model indicated that there was a significant interaction between antibiotic and time ($F(15, 358) = 1.9$); $p\text{-value}=0.0221$). There was a significant increase in INR values from time point 2 to 3 for amoxicillin ($p=0.0019$), azithromycin ($p<0.0001$), ciprofloxacin ($p=0.002$), levofloxacin ($p<0.0001$) and moxifloxacin ($p<0.0001$). There was no significant increase in INR for cephalexin between time point 2 and 3 ($p=0.2807$). The Fisher's exact test indicated that there was a significant association between the type of antibiotic and secondary outcomes. Overall, the percentage of patients with warfarin dose withheld, INR > therapeutic, INR increase > 1, were significantly greater in the azithromycin, ciprofloxacin, levofloxacin and moxifloxacin group as compared to cephalexin ($p<0.05$ for all antibiotics). No bleeding events were reported in any of the patients.

Conclusion: Amoxicillin, azithromycin and fluoroquinolone antibiotics such as ciprofloxacin, levofloxacin and moxifloxacin, lead to a significant increase in INR values post-antibiotic use in older patients, when taken concomitantly with warfarin. However,

this increase in post-antibiotic INR did not lead to clinically significant outcomes of bleeding or hospitalization. Thus antibiotics may be prescribed to older adults on warfarin therapy; however, increased INR monitoring may be required to ensure the INR remains within therapeutic range during the course of antibiotic therapy.

Keywords: Warfarin, antibiotics, drug interactions, older adults

II. Introduction

Warfarin is the most widely used oral anticoagulant and its use is the highest in older adults due to the increased prevalence of conditions such as atrial fibrillation and other thromboembolic disorders with advancing age.(1) Warfarin therapy may be complicated by several factors and maintaining therapeutic levels of warfarin is challenging since it is a drug with a narrow therapeutic index and it exhibits considerable variability in dose response.(2) Several medications may undergo a pharmacokinetic or pharmacodynamic interaction with warfarin, thus increasing the risk of adverse outcome of over-anticoagulation. Drug interactions with warfarin were ranked at number 3 in a list of the top 30 adverse events reported for warfarin in the FDA's Adverse Events Reporting system, for the period from June 2003 to July 2006.(3) The most recent systematic review on warfarin-drug interactions recommends exercising caution while prescribing antibiotics to patients on warfarin, since antibiotics may cause a change in the patient's hematological response to warfarin.(4) The antibiotic classes that were listed include fluoroquinolones, macrolides, tetracyclines and penicillins. From the list of top 10 dangerous drug interactions in nursing home residents, developed by the American Society of Consultant Pharmacists as one of the initiatives of their Multidisciplinary Medication Management Program, 5 of these interactions involved warfarin and 3 of these were due to warfarin-antibiotic combinations such as sulfa drugs, macrolides and quinolones.(5)

The risk of an interaction may be higher in older adults due to age-related physiologic changes that may result in altered pharmacodynamic response for warfarin,(6) and altered pharmacokinetics of antibiotics, such as fluoroquinolones.(7) However, the literature fails to support the increased risk of bleeding events or over-anticoagulation with warfarin-antibiotic combinations.(8) Some of these studies were done in settings with close anticoagulation monitoring. However, if there was no dose reduction or holding of doses the risk of complications may be higher. The most recent review that evaluated the possibility of increased anticoagulation due to warfarin-quinolone interactions concluded that “there are no consistent data to support the claim of an increased anticoagulation response in patients receiving warfarin and any of the three commonly prescribed fluoroquinolones”.(9) The clinical evidence for warfarin-antibiotic interactions in older adults is very limited and most of the evidence comes from case reports and case series,(10-13) or from studies with very few subjects.(14-17)

Due to the conflicting nature of the reports on warfarin-antibiotic interactions and lack of studies done specifically in older patients, there is a need to understand the clinical relevance of warfarin-antibiotic interactions in older adults. The primary objective of the study was to determine the effect of antibiotics on INR values over time in patients on stable warfarin therapy from an outpatient warfarin clinic. The secondary objective was to determine and compare the effect on secondary outcomes of over-anticoagulation caused by the combination of warfarin-antibiotics since this may further help us to understand the potential clinical impact of supratherapeutic INR values due to warfarin-antibiotic interactions.

III. Methods

A. Study Setting

This study was conducted at the Hunter Holmes McGuire Veterans Affairs (VA) medical center, Richmond, VA, using data from the outpatient anticoagulation clinic. The study protocol was approved by the Richmond Veterans Affairs institutional review board (IRB) and the Virginia Commonwealth University IRB in January 2011. Due to the retrospective nature of the study, informed consent was waived.

B. Study Design and Patients

This was a single-center, retrospective review of medical and pharmacy records of patients aged 65 years and above, who received a prescription of warfarin and either amoxicillin, azithromycin, cephalexin, ciprofloxacin, levofloxacin or moxifloxacin, concomitantly from January 1, 2003 to March 1, 2011. Patients that were included were aged 65 years and above and were on stable warfarin therapy, defined as pre-antibiotic INR values within ± 0.2 of recommended therapeutic INR range during the 4-week period before the antibiotic start date. This would eliminate patients with fluctuating INR values. In the presence of 2 or more pre-antibiotic INR values, all INR values were recorded. Patients must also have had at least one INR value recorded during their antibiotic therapy or during the 14-day period after discontinuation of the antibiotic (i.e. post-antibiotic INR) in order to be included. In addition, patients must have had a prescription of the antibiotic for 3 days or more in order to be included.

Patients were excluded if there was a change in their warfarin dose from the date their pre-antibiotic INR was recorded to the date of starting their antibiotic prescription or if there was a change in the patient's warfarin dose after the antibiotic start date and before the post-antibiotic INR value was recorded. Patients were excluded if they did not have an anticoagulation clinic note before and after the period of starting the antibiotic.

Without a clinic note it would not be possible to ascertain whether patients were on stable warfarin therapy, were compliant to therapy or to gather information on other concomitant interacting medications that the patient may have been prescribed. Patients that were not compliant to warfarin therapy were excluded since non-compliance may lead to fluctuating INR values. Patients undergoing a dental procedure were not included because antibiotics are usually given prophylactically for these patients and may be prescribed as a one-time course of one day. These patients may also not be the same as the other study patients with an active infection. Patients receiving enoxaparin (LMWH) concomitantly with warfarin were excluded since this may further complicate anticoagulant activity. Finally, patients were excluded if they received a prescription for other potentially interacting medications during the period from the last pre-antibiotic INR measurement and the first post-antibiotic INR measurement. The potentially interacting medications that patients were screened for in this study included, amiodarone, metronidazole, trimethoprim-sulfamethoxazole, carbamazepine, phenytoin, fluconazole, ketoconazole, rifampin, isoniazid, prednisone and phenobarbital, since they are known to have a well-documented interaction with warfarin.(4) Patients newly initiated on amiodarone were not included since a warfarin dose reduction of 20-50% is generally done for these patients.

C. Data Collection

A list of patients meeting the inclusion criteria was electronically generated. The electronic medical recording system of the VA, known as the Computerized Patient Record System (CPRS), was used to collect patients' demographic data, such as age, sex and race; prescription data such as warfarin and antibiotics dose, duration of use, and indications for use, warfarin dose adjustments, vitamin K administration; laboratory data such as target INR range, pre- and post-antibiotic INR values and other medical data such as number of concomitant medications and disease conditions, interacting medications (as listed above), bleeding events, hospitalizations, or emergency department visits. Data were entered and stored in a secure, password-protected computer.

D. Outcome Measures

The outcomes of interest for the primary analysis were the post-antibiotic INR values. Pre-antibiotic INR values were collected during the 4-week period before start of the antibiotics. All INR values during this period were recorded as long as they were within ± 0.2 of the therapeutic INR range. Thus pre-antibiotic INR values were defined as the most recent INR values collected in the 4-week period before start of the antibiotic therapy. Post-antibiotic INR values were collected during the duration of use of the antibiotic or during the 14-day period following the discontinuation of antibiotic therapy. All available INR values during this period were recorded. Thus post-antibiotic INR values were defined as all INR values available after start of the antibiotic up to 14-days after discontinuation of the antibiotic therapy.

The secondary outcomes of interest were percentage of patients whose warfarin dose was adjusted (reduced or withheld); INR > therapeutic; INR increase >1, or INR increase > 2; absolute INR \geq 4, or absolute INR \geq 5; vitamin K administration; minor or major bleeding events; hospitalizations or emergency department visits. Cephalexin was chosen as a comparator drug to compare the percentages of patients with the above secondary outcomes of over-anticoagulation to the percentages of patients with the above outcomes for the amoxicillin, azithromycin, ciprofloxacin, levofloxacin and moxifloxacin groups. There were several reasons for choice of cephalexin as a comparator drug. More than 90% of cephalexin is excreted unchanged renally and does not undergo metabolism via hepatic CYP2C9 pathways.(18) Thus pharmacologically cephalexin would not have the potential to interact with warfarin since it would not inhibit warfarin metabolism. According to the consensus of clinical opinion, cephalexin is not known to interact with warfarin.(19) Standard drug-drug interaction compendia and systematic reviews of warfarin drug interactions do not classify cephalexin as a warfarin-interacting medication.(4) One way of reducing confounding by indication is to use a control drug that has similar prescription indications as the other antibiotics. Cephalexin has similar indications as the other antibiotics in this study.(20) Cephalexin is used to treat respiratory tract infections, otitis media, skin and skin structure infections, bone infection and genitourinary tract infections. Thus use of a control drug with similar indications will help to ensure that all patients being compared have an active infection.

E. Statistical Analysis

Continuous data are presented using means, SD and ranges. Categorical baseline data are presented as frequencies and percentages. Mixed-effects repeated measures ANOVA model was used to determine the effect of antibiotics on the mean change in patient's INR over time. Statistical significance was defined at an alpha level of 0.05. The changes in INR values between time point 2 (i.e. pre-antibiotic INR 2) and time point 3 (i.e. post-antibiotic INR 1) for each antibiotic were of interest (i.e. 6 comparisons). In addition, the change in INR values at time points 3 (i.e. post-antibiotic INR 1) between each antibiotic was also of interest (i.e.15 comparisons). Thus there were a total of 21 comparisons of interest. A Bonferroni adjustment of the alpha level was done to account for these multiple comparisons (adjusted alpha = $0.05/21 = 0.0023$).

A chi-square test or Fisher's exact test, where appropriate, was done to test whether there was an association between the type of antibiotic and the secondary outcomes of over-anticoagulation. The percentage of patients with the secondary outcomes of over-anticoagulation i.e., INR increase \geq therapeutic, INR increase ≥ 1 , INR increase ≥ 2 , absolute INR ≥ 4 , absolute INR ≥ 5 and warfarin dose adjustment, with azithromycin, amoxicillin, ciprofloxacin, levofloxacin and moxifloxacin were compared with those on cephalexin. All analyses were done using SAS 9.2.

IV. Results

A total of 205 patients received 364 prescriptions for the antibiotics of interest concomitantly while on warfarin therapy, such that there were 96 prescriptions for amoxicillin, 73 prescriptions for azithromycin, 49 prescriptions for cephalexin, 64 prescriptions for ciprofloxacin, 28 prescriptions for levofloxacin and 54 prescriptions for moxifloxacin during the time frame of the study. The mean age of the patients was 75.7 (SD = 6.7) years and the median age was 75.5 (interquartile range = 70-81) years. The mean pre-antibiotic INR values for patients ranged from 2.3 to 2.5 (SD = 0.4- 0.5) across the six antibiotics. The baseline demographic characteristics of the patients are shown in **Table 1**. The population primarily consisted of white males and the two most common indications for warfarin use were atrial fibrillation and deep vein thrombosis.

The ANOVA model indicated that there was a significant interaction between antibiotic and time ($F(15, 358) = 1.9$; p -value = 0.0221). These results indicate that the pattern of INR changes for the 6 antibiotics are significantly different across time. The mean change in INR from pre-antibiotic INR value 2 to post-antibiotic INR value 1, for each of the six antibiotics is shown in **Table 2**. This mean INR increase was significant for amoxicillin (0.31 ± 0.10 , $p=0.0019$), azithromycin (0.60 ± 0.11 , $p < 0.0001$), ciprofloxacin (0.38 ± 0.12 , $p=0.002$), levofloxacin (0.75 ± 0.18 , $p < 0.0001$) and moxifloxacin (0.70 ± 0.13 , $p < 0.0001$). There was no significant increase in INR for cephalexin between time point 2 and 3 ($p=0.2807$). This trend of change in INR values over time for each antibiotic is shown in **Figure 1**. Additionally, at time point 3 there were no significant differences in post-antibiotic INR values between the six different antibiotics.

The frequency and percentages of patients experiencing the secondary outcomes of over-anticoagulation for each antibiotic group are shown in **Table 2**. The percentage of patients who had a warfarin dose adjustment (either withheld or reduced) was the highest for levofloxacin (25%), followed by moxifloxacin (24%), ciprofloxacin (17%) and azithromycin (12%). The Fisher's exact test indicated that these percentages were significantly higher ($p < 0.05$) for the fluoroquinolone antibiotics and azithromycin as compared to cephalexin (2%). The percentages and p-values were computed from the Fisher's exact test using a separate 2x2 table for the comparison of each antibiotic group with the cephalexin group. For increase in INR above therapeutic range, the percentage of patients was significantly higher ($p < 0.05$) for azithromycin (41%), levofloxacin (46%) and moxifloxacin (40%) as compared to cephalexin (16%). For an increase in INR by more than one point, the percentages of patients were significantly higher ($p < 0.05$) for azithromycin (23%), ciprofloxacin (20%), levofloxacin (36%) and moxifloxacin (31%) as compared to cephalexin (4%). Finally, the percentage of patients with absolute INR ≥ 4 was significantly higher ($p < 0.05$) for the moxifloxacin group (15%) as compared to cephalexin (2%). There were no reports of major or minor bleeding events; hospitalizations or emergency department visits during concomitant warfarin antibiotic therapy.

Additional post-hoc analyses were done to explain the effect of infection and the effect of increasing age on INR changes. To test for the effect of infection, mean change in INR from pre- to post-antibiotic use was determined separately by type of infection for all fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) and azithromycin.

(There were not sufficient patients for this analysis in the other antibiotic groups). The results of the repeated-measures ANOVA model indicated that for the fluoroquinolone group the mean increase from pre- to post-antibiotic INR was significant for all patients with a lower respiratory tract infection (0.8 ± 0.2 ; $p = 0.0007$) or a urinary tract infection (0.4 ± 0.1 ; $p=0.0132$) but was not significant for patients with a skin or soft tissue infection (0.5 ± 0.3 ; $p=0.3870$). For the azithromycin group the mean increase in INR was significant for patients with lower respiratory infections (0.7 ± 0.1 ; $p < 0.0001$) and for those with upper respiratory infection (0.5 ± 0.1 ; $p=0.0103$). These results are shown in **Table 3**.

Furthermore, to test for the effect of increasing age, the mean change in post-antibiotic INR were compared for the lower age quartile (i.e. patients aged 65-70 years) and upper age quartile (i.e. patients aged ≥ 81 years). For the first recorded mean post-antibiotic INR value there was no difference between the lower and upper quartiles of age (mean difference in INR= 0.10 ± 0.13 ; $p=0.3783$). However, for the second recorded post-antibiotic INR values, the mean INR value was significantly greater in the upper age quartile, i.e. patients aged ≥ 81 years, as compared to the lower age quartile, i.e. patients aged 65-70 years (mean difference in INR= 0.70 ± 0.25 ; $p=0.0036$). These results are shown in **Table 4**. Additionally, **Table 5** provides details of patients with an INR ≥ 4 , such as dosage and duration of antibiotic, type of infection, pre- and post-antibiotic INR and warfarin dose adjustments, after start of the antibiotic.

Table 1: Baseline demographic and clinical characteristics of study patients

Characteristic	Amoxicillin (N = 96)	Azithromycin (N = 73)	Cephalexin (N = 49)	Ciprofloxacin (N = 64)	Levofloxacin (N = 28)	Moxifloxacin (N = 54)
Mean (SD)						
Mean Age, years	75.3 (6.6)	74.1 (6.7)	75.4 (6.1)	76.6 (6.5)	79 (7.2)	75.7 (6.6)
Median (IQR), years	74 (71-80)	74 (68-80)	75 (70-79)	77.5 (71-81)	82 (73-85)	76 (71-81)
Pre-antibiotic INR 1	2.4 ± 0.4	2.4 ± 0.5	2.4 ± 0.4	2.3 ± 0.4	2.4 ± 0.4	2.4 ± 0.5
Pre-antibiotic INR 2	2.4 ± 0.4	2.4 ± 0.4	2.5 ± 0.4	2.5 ± 0.4	2.4 ± 0.4	2.3 ± 0.4
Duration of antibiotic use, days	10 (2)	6 (3)	11 (6)	14 (10)	9 (6)	9 (5)
Total number of medications	11 (4)	11 (4)	11 (4)	11 (5)	12 (5)	12 (5)
Total number of disease conditions	12 (5)	12 (5)	12 (6)	12 (5)	13 (5)	13 (6)
No (%) of Patients						
Males	95 (99)	73 (100)	48 (98)	63 (98)	28 (100)	53 (98)
Race (white)	78 (81)	53 (73)	38 (78)	42 (66)	16 (57)	40 (74)
Indication for warfarin use						
Atrial fibrillation/ Atrial flutter	75 (78)	63 (86)	39 (80)	47 (74)	19 (68)	46 (85)
DVT/ PE	13 (14)	10 (14)	6 (12)	5 (8)	8 (29)	5 (9)
Mechanical valve replacement	2 (2)	-	2 (4)	2 (3)	1 (4)	1 (2)
Other	6 (6)	-	2 (4)	10 (16)	-	2 (4)
Indication for antibiotic use						
Lower respiratory infections (LRI)	16 (17)	35 (48)	-	1 (2)	4 (14)	34 (63)
Upper respiratory infections (URI)	19 (20)	35 (48)	1 (2)	1 (2)	1 (4)	12 (22)
Urinary tract infections (UTI)	17 (18)	-	3 (6)	43 (67)	18 (64)	2 (4)
Skin & soft tissue infection (SSTI)	33 (34)	1 (1)	40 (82)	2 (3)	3 (11)	6 (11)
Other	11 (12)	2 (3)	5 (10)	17 (27)	2 (7)	-

Table 2: International normalized ratio changes and secondary outcomes of over-anticoagulation

Variable	Amoxicillin (N = 96)	Azithromycin (N = 73)	Cephalexin (N = 49)	Ciprofloxacin (N = 64)	Levofloxacin (N = 28)	Moxifloxacin (N = 54)
INR change (from pre-antibiotic INR 2 to post-antibiotic INR 1)						
Mean (SE)	0.31 ± 0.10*	0.60 ± 0.11*	0.15 ± 0.14	0.38 ± 0.12*	0.75 ± 0.18*	0.70 ± 0.13*
	No. (%) of patients					
Intervention						
Warfarin dose withheld	9 (9)	9 (12)**	1 (2)	11 (17)†	7 (25)†	13 (24)†
Secondary outcomes of over-anticoagulation						
INR > therapeutic	25 (26)	30 (41)†	8 (16)	20 (31)	13 (46)†	22 (40)†
INR increase > 1	15 (16)	17 (23)†	2 (4)	13 (20)**	10 (36)‡	17 (31)‡
INR increase > 2	3 (3)	5 (7)	1 (2)	4 (6)	2 (7)	6 (11)
Absolute INR ≥ 4	6 (6)	7 (10)	1 (2)	5 (8)	3 (11)	8 (15)**
Absolute INR ≥ 5	1 (1)	-	-	1 (2)	1 (4)	-

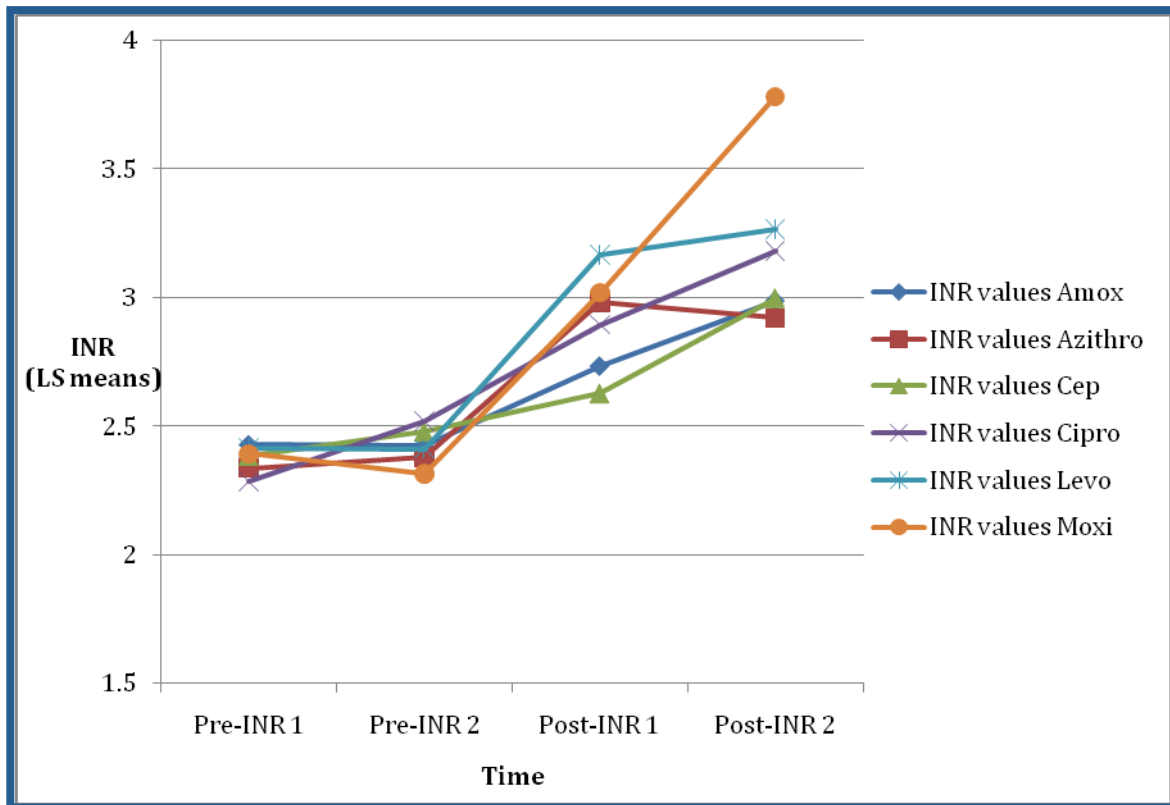
* p-value < 0.023 Bonferroni adjusted alpha-level

** p-value < 0.05 versus cephalixin

† p-value < 0.01 versus cephalixin

‡ p-value < 0.0001 versus cephalixin

Figure 1: Least squares means plot of change in INR values over time for different antibiotics



(INR = International Normalized Ratio)

Table 3: International normalized ratio changes by type of indication for antibiotic use

Type of Infection	INR change, from pre-antibiotic INR 2 to post-antibiotic INR 1	
	Fluoroquinolones (N = 146)	Azithromycin (N = 73)
1. Lower respiratory tract infection (LRI)	0.8 ± 0.2*	0.7 ± 0.1*
2. Upper respiratory tract infection (URI)	-	0.5 ± 0.1*
3. Urinary tract infection (UTI)	0.4 ± 0.1*	-
4. Skin and soft tissue infection (SSTI)	0.5 ± 0.3	-

*Denotes significant increase in INR from pre-antibiotic INR 2 to post-antibiotic INR from the ANOVA model

Table 4: Mean INR values and change in INR values for subjects in the upper and lower age quartiles

	N	Mean INR (65-70 yrs)	N	Mean INR (≥ 81 yrs)	Difference in INR	p-value
Pre-antibiotic INR 1	37	2.3 ± 0.4	37	2.5 ± 0.4	0.20 ± 0.10	0.1198
Pre-antibiotic INR 2	95	2.4 ± 0.4	98	2.4 ± 0.4	0.02 ± 0.06	0.7385
Post-antibiotic INR 1	95	2.9 ± 0.9	98	3.0 ± 1.0	0.10 ± 0.13	0.3783
Post-antibiotic INR 2	10	2.7 ± 0.6	18	3.5 ± 0.8	0.70 ± 0.25	0.0036*

* Denotes that the upper age quartile (i.e. ≥ 81 years) has significantly greater mean INR values at time point 4 as compared to lower age quartile (i.e. 65-70 years) at a Bonferroni adjusted significance level of 0.0125.

Table 5: Details of patients with an absolute INR ≥ 4 after antibiotic use

Age (yrs), sex	Warfarin Indication	Antibiotic	Antibiotic Dosage and Duration	Antibiotic Indication	Pre-antibiotic INR	Post-antibiotic INR	Days after starting antibiotic	Warfarin held/reduced
83, M	Afib	Moxifloxacin	400mg qd x 14 days	Pneumonia	2.4	4.6, 5.5	16	Yes
84, M	Afib	Moxifloxacin	400mg qd x 8 days	Pneumonia	2.7, 2.6	4.6	14	Yes
67, M	DVT/ PE	Cephalexin	500mg four times x 7 days	Cellulitis	2.4, 2.9	5.4	16	Yes
69, M	DVT/ PE	Levofloxacin	250mg qd x 7 days	UTI	2.8	4.3	24	Yes
82, M	Afib	Moxifloxacin	400mg x 14 days	Skin infection	1.9, 2	5.5	11	Yes
66, M	Afib	Moxifloxacin	400mg qd x 5 days	Pneumonia	3.2, 2.9	6.4	3	Yes
65, M	Afib	Moxifloxacin	400mg qd x 7 days	Pneumonia	1.7, 1.8	5.4	7	Yes
76, M	Afib	Azithromycin	500mg x 1 day,	Bronchitis	1.7	4.3	11	Yes
69, M	Afib	Ciprofloxacin	250mg x 4 days	Prostatitis	2.8	5.4	9	Yes
85, M	Afib	Levofloxacin	750mg qd x 10 days	UTI	1.7	4.1	6	Yes
85, M	Aflutter	Moxifloxacin	250mg qd x 7 days	Pneumonia	1.7	4.0	13	Yes
69, M	Afib	Moxifloxacin	400mg qd x 10 days	Pneumonia	1.7	4.0	13	Yes
69, M	Afib	Azithromycin	500mg x 1 day,	Cough	2.6	5.7	17	Yes
83, M	MVR	Ciprofloxacin	250mg x 4 days	Prostrate	2.6	5.7	17	Yes
83, M	MVR	Ciprofloxacin	500mg bd x 30 days	cancer	3.3	4.9	16	Yes
77, M	Afib	Azithromycin	500mg x 1 day,	Bronchitis	2.8, 3.2	4.1	4	Yes
77, M	Afib	Azithromycin	250mg x 4 days	Bronchitis	2.7, 3.0	4.1	4	Yes
74, M	Afib	Azithromycin	500mg x 1 day,	Congestion	1.8	4.1	3	Yes
73, M	Afib	Moxifloxacin	250mg x 4 days	Congestion	1.8	4.1	3	Yes
73, M	Afib	Moxifloxacin	400mg qd x 19 days	SOB, cough	2.5, 3.2	4.2	18	Yes
80, M	Afib	Amoxicillin	500mg tid x 7 days	Wound care	3.1	4.3	4	No

Age (yrs), sex	Warfarin Indication	Antibiotic	Antibiotic Dosage and Duration	Antibiotic Indication	Pre-antibiotic INR	Post-antibiotic INR	Days after starting antibiotic	Warfarin held/reduced
83, M	Afib	Moxifloxacin	400mg qd x 9 days	Pneumonia	2.7, 2.3	4.2	3	Yes
75, M	Afib	Moxifloxacin	400mg qd x 10 days	Pneumonia, cough, SOB	1.7, 2	4.9	3	Yes
82, M	Afib	Amoxicillin	875mg bd x 10 days	Cellulitis	2.8	4.4	12	Yes
83, M	DVT/ PE	Levofloxacin	500mg qd x 7 days	Pneumonia	2.6	8.0	5	No
71, M	Afib	Ciprofloxacin	500mg bd x 18 days	Prostatitis	2.7	4.8	20	Yes
68, M	Afib	Azithromycin	250mg x 4 days	URI	3.0	4.8	8	Yes
83, M	DVT/ PE	Azithromycin	500mg x 1 day, 250mg x 4 days	Mild COPD, cough, sore throat	2.1	4.3	14	Yes
71, M	pathy	Ciprofloxacin	250mg bd x 14 days	Prostrate biopsy	2.4	4.2	5	Yes
77, M	Afib	Amoxicillin	250 mg tid x 10 days	Pneumonia	2.2, 3.1	10.8, 6.6	3	Yes
85, M	Afib	Levofloxacin	250 mg qd x 7 days	UTI	2.7, 1.7	4.1, 4.5	3	Yes
73, M	Afib	Levofloxacin	500 mg qd x 10 days	Epididymitis	3.0, 3.1	4.3	14	Yes
77, M	Afib	Azithromycin	250mg bd x 1 day; qd x 4days	COPD exacerbation	2.1	4.3	12	No
69, M	AFib	Amoxicillin	1 tab bd x 20 days	Cold/ sinus infection	2.2, 3.0	5.0	15	Yes
80, M	Afib	Amoxicillin	1 tb bd x 7 days	Leg wound infection	3.1	4.3	4	Yes
83, M	Afib	Moxifloxacin	400 mg qd x 14 days	Pneumonia	2.4	4.2	5	Yes

V. Discussion

The results of this study showed that amoxicillin, azithromycin and fluoroquinolone antibiotics such as ciprofloxacin, levofloxacin and moxifloxacin, lead to a significant increase in INR values post-antibiotic use in older patients, when taken concomitantly with warfarin. This increase in post-antibiotic INR did not lead to clinically significant outcomes of bleeding or hospitalization. However, warfarin dose adjustments due to an increase in post-antibiotic INR was required for approximately 20% of patients across the 3 groups of fluoroquinolone antibiotics. In addition, patients experienced other outcomes of over-anticoagulation such as increase in INR above therapeutic range and increase in INR by more than 1 point while taking fluoroquinolones and azithromycin concomitantly with warfarin. Details of patients with an INR ≥ 4 after start of the antibiotic have been included and almost all these patients had their warfarin dose withheld or reduced, which may have further prevented any bleeding outcomes. However, these were patients at a high risk of a hemorrhage, since the risk of serious hemorrhage increases at INR ≥ 4 .(21) Furthermore, patients taking fluoroquinolones with an indication for skin and soft tissue infections did not experience an increase in post-antibiotic INR, whereas patients with lower respiratory infections and urinary tract infections did experience an increase in INR with fluoroquinolones. These results suggest that type of infection may play a role in the increase in patient's INR. A similar conclusion was made in a previous study, wherein the infection, or its sequelae (i.e. fever and reduced vitamin K intake and uptake) was suggested to increase the bleeding risk in patients receiving an anti-infective agent, since the 'baseline' bleeding risk for the patients was already elevated even before starting the anti-infective agent.(22)

Previously, four retrospective cohort studies have assessed the mean change in INR after administration of levofloxacin to patients on stable warfarin therapy, from which two studies found a significant increase in mean INR change,(23, 24) whereas the other two studies did not.(14, 16) There have been only three retrospective studies that have looked at the potential interaction between azithromycin and warfarin,(15, 17, 24)and two of these did not find any evidence for a significant interaction between warfarin and azithromycin.(17, 25) The sample size of these studies was limited with the largest study having a sample size of only 52 patients. Thus the power to detect a difference in the INR may have been low for most of the studies. The only study to have assessed the risk of bleeding with amoxicillin for patients on warfarin did not find an association between risk of hemorrhage and use of warfarin-amoxicillin or warfarin-ampicillin combination. (26)

Some strengths of this study may be noted. The mean age of patients that were included in this study was about 76 years. Thus the effect of warfarin-antibiotic interactions could be studied in older patients. This is important because the older population may be at higher risk of a drug interaction due to increased sensitivity in pharmacodynamic response to warfarin and reduced clearance of certain antibiotics such as fluoroquinolones.(6, 27) This was the only known study to have evaluated the effect on INR values separately for the lower and upper age quartiles. An age effect was seen such that patients aged ≥ 81 years had a significantly higher mean post-antibiotic INR value as compared to patients in the lower age quartile. However, this comparison was based on fewer observations at the second post-antibiotic INR values. The internal validity of the study was enhanced by only including those patients who were on stable warfarin therapy before starting the antibiotic. Thus any increase in INR value after starting the antibiotic may

become apparent in such patients. Anticoagulation clinic notes made by the Veterans Affairs clinical pharmacists increases the validity of the findings since the possible reasons for a supratherapeutic INR are often recorded in the clinical notes. If the clinical pharmacist suspected that the supratherapeutic INR might be due to the antibiotic this would be noted and would thus corroborate the findings of this study. However, there may be a systematic reporting bias in this situation depending on the clinical pharmacist's beliefs regarding the significance of the potential drug interaction. Due to this reason clinic notes were only regarded as providing additional but not definitive evidence. In addition, most patients receive almost all their health care at the VA and information on concomitant medications, dosage changes, coexisting disease conditions and health-care procedures is well documented in the patient's electronic medical record. This provides additional information on potential confounding factors, unlike large population-level, health care databases.

There were some limitations of this study given the retrospective nature of data collection. Changes in use of over-the-counter medications, herbal remedies and other vitamin supplements with a potential to interact with warfarin may not have been recorded in the patient's medical records. Although dietary changes, medication changes and compliance with warfarin therapy are assessed during each patient visit, patient recall bias may be a potential limitation. For example, cranberry juice, which is recommended for the treatment of UTIs, may also interact with warfarin and its use may not be recorded for all patients. However, attempts to control for potential confounding factors such as use of warfarin interacting medications, fluctuating INR values, and patient noncompliance were made in the study design by excluding patients with these factors. Since the data for the study were obtained from an anticoagulation clinic at a

Veteran's Affairs Medical Center, only antibiotics on the VA formulary were included. The results of this study are only generalizable to patients receiving routine monitoring in an anticoagulation clinic as compared to other models of anticoagulant care. Since warfarin dosage adjustments were done for patients with supratherapeutic INR values, it was not possible to ascertain whether supratherapeutic INR would have resulted in clinically significant outcomes of bleeding or hospitalization through this study. In a setting where patients are not as closely monitored, the outcomes of bleeding events may vary.

Another possible limitation of the study is that several patients had only one pre- and post-antibiotic INR value recorded. The presence of two or more pre- and post-antibiotic INR values for all patients would have further enhanced the internal validity of the study. However, the method of analysis chosen for this study was a repeated-effects mixed model ANOVA that does allow for missing data. In addition, the missing INR values were only for the pre-antibiotic INR 1 values and for the last post-antibiotic INR 2 values, whereas the comparisons were only made from pre-antibiotic INR 2 to post-antibiotic INR 1. The time points at which pre- and post-antibiotic INR values were recorded were not the same for all patients. For example, some patients may have a pre-antibiotic INR value recorded 10 days before starting the antibiotic and another patient may have a value recorded 2 days before starting the antibiotic. This may not be a major limitation since the sole purpose of recording pre-antibiotic INR values was to determine whether the patient was on stable warfarin therapy. However, post-antibiotic INR values were recorded within the pre-defined time frame of total duration of antibiotic use plus 14 days after completing the course of antibiotics. This time frame may have resulted in missing the drug interaction for some patients. As an attempt to increase the internal validity of the study, only

those patients on stable warfarin therapy before start of the antibiotic were included. Thus the results are not generalizable to those patients who may have fluctuating INR values or warfarin dosage adjustments being made before start of an antibiotic, as may be routinely seen in clinical practice. Finally, the aim of the study was to characterize warfarin-antibiotic interactions in older patients and a majority of the patients were white males, thus the results may not be entirely applicable to other patient populations. This may not be a big issue given that there have been no reports of gender differences in warfarin PK or PD. However, the prevalence of genetic polymorphisms for the enzymes that metabolize warfarin is higher in the non-white race and this may potentially have an effect on warfarin sensitivity in the non-white race. Due to the under-representation of the non-white race we were unable to study this effect.

VI. Conclusion

The results of this study provide evidence for an increase in patient's INR post-antibiotic use that may lead to a warfarin dose adjustment in several patients, however there was no evidence for clinical outcomes of bleeding or hospitalization as a result of this increase in INR. These clinically significant outcomes of bleeding and hospitalization may have been prevented due to warfarin doses being held or reduced. Based on the results of this study a change in clinical practice such as empirical reduction of warfarin dose when antibiotics are prescribed concomitantly with warfarin may not be required. However, the results of bleeding outcomes may be different in a setting where patients are not monitored as closely as those in an outpatient anticoagulation clinic. Thus antibiotics may be prescribed to older adults on warfarin therapy as long as their INR is closely monitored, especially with fluoroquinolones, both during and after the course of antibiotic therapy.

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CHAPTER 5

DISCUSSION AND CONCLUSION

I. Underuse of Warfarin in Nursing Home Residents

The results of this cross-sectional analysis of a large nationally representative survey dataset showed that 54% of nursing home residents with atrial fibrillation, who had indications for warfarin use and no contraindications to warfarin use, did not receive anticoagulation therapy with either warfarin or antiplatelet agents such as aspirin or clopidogrel. The next few sections will outline possible reasons for the observed underuse of warfarin therapy with a focus on common barriers to warfarin use, barriers to successful implementation of evidence-based medicine in long-term care settings and tools that may be employed to evaluate risks and benefits of warfarin therapy in order to assist healthcare providers to identify ‘ideal’ candidates for anticoagulant therapy.

A. Possible Explanations and Barriers to Prescribing Warfarin

The rate of warfarin use observed in this study was found to be similar to the rates reported previously.(1-3) It was surprising to find that more than half the NH residents were not receiving suitable anticoagulation therapy even after excluding those with contraindications to warfarin use and those without indications to warfarin use. Even though some patients may have characteristics that would require them to be on an anticoagulant, other reasons such as patient refusal, patient noncompliance, an upcoming planned surgery and reduced life expectancy may result in the patient not receiving a prescription for an anticoagulant. In addition, there exist

several barriers to prescribing warfarin therapy, especially in older adults. The most commonly cited reason among physicians for not prescribing warfarin is the higher perceived risk of bleeding associated with warfarin.(4, 5) Increasing age has also been consistently identified as a barrier to anticoagulant therapy.(6) This was supported by one of the findings of this study, wherein residents aged 90 years or above were less likely to be prescribed warfarin. However, the older population is believed to have the greatest absolute reduction in stroke rates with warfarin therapy.(7) In addition, the prevalence of atrial fibrillation increases with advancing age such that atrial fibrillation was present in 6% of those aged 65-74 years, 12% in people aged 75-84 and 16% in people aged 85 and over.(8) Other factors cited by physicians as challenges to managing warfarin therapy include, dealing with medications that interact with warfarin, maintaining patients within therapeutic range and making warfarin dose adjustments.(9) Risk of falls and dementia are also concerns physicians may have before initiating warfarin therapy.(10). Lack of reimbursement, time, facilities and/or expertise may be other possible reasons for which individual practitioners may not be willing to undertake anticoagulation monitoring.(11) Understanding barriers pertaining to warfarin use in NH residents is important since this would help to develop targeted interventions to address the issues of underuse of warfarin and other anti-platelet agents.

Pharmacists-managed anticoagulation services have been shown to improve anticoagulation control, reduce bleeding and thromboembolic events and reduce rates of anticoagulation-related emergency department visits.(12, 13) Thus if lack of monitoring or poor monitoring of anticoagulant therapy in NH residents is a concern, the implementation of pharmacist-managed anticoagulation services in NHs may be a potential solution towards improving low rates of

warfarin use in this population. A study that evaluated physician attitudes towards use of anticoagulation services in NHs found that only about half the physicians surveyed were open to the idea of an anticoagulation service for their LTC residents.(9) One of the biggest concerns with use of such services was the potential increase in the cost of care for NH residents on warfarin. Thus future research may be done to evaluate the usefulness of anticoagulation services in LTC settings in reducing bleeding and thromboembolic events and cost-effectiveness of implementing such services.

B. Barriers to Successful Implementation of Evidence-based Medicine in LTC setting

Robust evidence exists for the use of anticoagulant or antiplatelet therapy as stroke prevention strategies in patients with atrial fibrillation.(14-16) Use of warfarin and other medications such as aspirin for secondary stroke prevention, have been shown to cause significant reductions in thromboembolic complications and significant reductions in morbidity and death.(17, 18) Due to the higher mean age and presence of several cardiovascular conditions that are considered to be risk factors for a stroke event, the NH population would seem to benefit the most from anticoagulant therapy for stroke prevention. However, the results of the study outlined in chapter 3, show that a majority of NH residents with atrial fibrillation, with indications for warfarin use and without contraindications to warfarin, are not receiving anticoagulant therapy with either warfarin or with anti-platelet agents such as aspirin, clopidogrel or a combination of these medications. Thus the issue of importance here is the lack of use of evidence-based medicine for stroke prevention in NH residents. Several barriers to the successful implementation of evidence-based medicine in long-term care residents have been identified previously.(19) For example, developing evidence-based guidelines for NH residents is a challenge due to the few trials that

include adults over 80 years of age. The evidence base for clinical management of frail nursing home residents with AF is limited in terms of risk-benefits with warfarin vs. aspirin and clopidogrel, since the mean age of patients in the ACTIVE-W trial was 70 years.(20) In addition, the decision to initiate a medication in a NH resident is not just dependent on the physician, but also on the patient, the residential care staff and the patient's next of kin. While it is believed that NH residents may represent a 'captive' audience in a setting where close monitoring by trained clinical staff is possible on a daily basis and low-cost treatment options exists,(21) it is also important to note that the rates of staff attrition are very high in NHs.(22) This may further be complicated by multiple attending physicians, communication difficulties between physicians, the nursing staff and caregivers and physician visits that are only around once a month.(19) Since the day-to-day monitoring of residents is often dependent on caregivers and nurses, interventions to improve prescribing practices targeted solely towards physicians may not always suffice.(19)

C. Evaluating Benefits and Risks to Warfarin Therapy in Older Adults

According to Quilliam and Lapane 'non-treatment is not synonymous with under-treatment'.(23) This is because contraindications to warfarin may influence the decision to treat the patient. However, in our study patients with contraindications to warfarin use were not included. Furthermore, contraindications to warfarin therapy may not solely explain the high rates of underuse observed. Uncertainty regarding treatment risks and benefits may also contribute to the decision not to treat.(24) This sort of an uncertainty may be due to several factors. For example, the number and complexity of comorbid conditions, risks of drug interactions and adverse drug events with concomitant medications, frailty and higher risk of falls and dementia in NH residents may all be contributing to the uncertainty regarding the decision to treat with warfarin.

According to the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA),(25) and a meta-analysis,(26) the risk of bleeding with warfarin in older patients is no greater than that with aspirin. With advancing age, aspirin became progressively less effective and instead the risk of bleeding was found to increase.(26) Thus for patients older than 75 years, formal anticoagulation with warfarin may remain a preferred treatment option over aspirin.

One way to determine whether an older patient is an appropriate candidate for anticoagulant therapy would be to evaluate the benefits and risks to warfarin therapy. This may be done through the combined use of clinical prediction rules for stroke and bleeding risk schemes in order to identify patients with atrial fibrillation who are likely to benefit from anticoagulant therapy and less likely to experience an adverse bleeding outcome. A patient's stroke risk may be quantified by using one of the many available stroke risk stratification schemes such as CHADS₂,(27) Framingham,(28) NICE guidelines,(29) ACC/AHA/ESC guidelines,(16) ACCP guidelines,(30) CHA₂DS₂-VASc(31) and the Rietbrock modified CHADS₂ scheme.(32) A recent study that conducted a comprehensive assessment of these seven stroke risk stratification schemes in older people with atrial fibrillation, has demonstrated limited ability of these risk schemes to accurately predict stroke in older people.(33) The CHADS₂ and CHA₂DS₂-VASc scores performed the best, yet only had a C statistic of 0.60 for their predictive ability. Based on these results the authors made a pragmatic recommendation for clinicians to classify all patients over 75 years as being at a high stroke risk and provide them with anticoagulant therapy until better tools are available for older adults. Meanwhile these risk scores may be used in those under 75 years.

Several bleeding prediction models are available to estimate the risk for major bleeding during anticoagulation therapy. Three bleeding risk schemes that have been developed and validated to quantify the bleeding risk in patients with atrial fibrillation are known as the Outpatient Bleeding Risk Index (OBRI),(34) HEMORR₂HAGES score,(35) and the more recently developed HAS-BLED score.(36) Since perceived risk of bleeding may be contributing to underuse of anticoagulant therapy, use of these bleeding prediction models to quantify the patient's bleeding risk may aid in patient selection for anticoagulant therapy. Furthermore, benefits and risks should be evaluated taking patient preferences into consideration. Even if the decision to initiate warfarin therapy has been made after careful evaluation of risks and benefits in an individual patient, the importance of routinely monitoring warfarin therapy can never be replaced.

II. Warfarin-Antibiotic Interactions

The results of the warfarin-antibiotic research study in this dissertation suggested that there is an increase in the patient's INR value as a result of concomitant use of warfarin with antibiotics such as amoxicillin, azithromycin and fluoroquinolones, such as ciprofloxacin, levofloxacin and moxifloxacin. This increase in INR did not lead to clinically significant outcomes such as bleeding and hospitalization, but patients did experience an increase in outcomes of over-anticoagulation, such as INR values outside the therapeutic range. The implications of the study results are that empirical reduction of warfarin dose may not be required when these antibiotics are prescribed concomitantly with warfarin; however, it would be advisable to closely monitor patients during concomitant use of warfarin and antibiotics, and to adjust the warfarin dose as required. Healthcare providers may also need to be aware of this potential interaction between warfarin and antibiotics, especially in older patients, and the effect that infection or the

accompanying inflammatory process may have on warfarin metabolism. In the following section we shall discuss possible explanations for the results of this study and the difficulties with managing warfarin-drug interactions in older adults.

A. Possible Explanations of Study Results

The primary outcome of change in patient's INR as a result of warfarin-antibiotic interactions is an important outcome to consider since the increased risk of hemorrhagic complications as a result of increasing or fluctuating INR values has been well established previously.(37) Even though this increase in INR values did not result in bleeding events, the knowledge that concomitant use of warfarin-antibiotics led to fluctuating INR values is still important since it may interfere with the routine care and monitoring of patients on warfarin therapy. Maintaining the patient's INR between 2.0-3.0 is crucial to attain warfarin efficacy while minimizing the risk of bleeding. A target INR greater than 3.0 as compared to that between 2.0-3.0, doubles the frequency of major bleeding events.(38) In addition, anti-coagulated patients, regardless of INR, are still at bleeding risk. Furthermore, warfarin dose adjustments made by the clinical pharmacists at the VA anticoagulation clinic, as a result of supratherapeutic INR values, may have resulted in prevention of bleeding events.

The effect that the underlying infection may have on warfarin-antibiotic interactions is also an important factor to consider. Cephalexin was the only antibiotic that did not lead to a significant increase in the patient's INR post-antibiotic use in this study. One possible reason for this may be that majority of the patient's that were prescribed cephalexin had an indication for a skin or soft tissue infection. During a respiratory infection such pneumonia, there tends to be

accompanying sequelae such as fever and reduced vitamin K intake, which may increase the severity of the respiratory infection. However, during a skin infection this is rarely the case. While a formal analysis for the effect of infection was not done in this study, a post-hoc analysis revealed a trend for the role of infection. There was no significant increase in the patient's INR values when fluoroquinolones were prescribed for skin and soft tissue infections, but the increase in post-antibiotic INR values was significant when fluoroquinolones were prescribed for lower respiratory infections and urinary tract infections. Another method to evaluate the effect of infection on patient's INR while on warfarin therapy would be via a prospective study wherein infected patients would have to be denied treatment with an antibiotic. Since this is not feasible or ethical, healthcare providers should be aware of the potential role of infection in warfarin-drug interactions.

B. Difficulties with Managing Drug Interactions in Older Adults

Since antibiotics are usually prescribed for a short course of therapy, it may be possible that a patient is on antibiotics without the knowledge of all of their healthcare providers. Although this may not be a problem at the VA since patients get most of their prescriptions filled at the VA pharmacy and patients enrolled in the anticoagulation clinic are routinely evaluated for any additions or changes in drug therapy, patients across all healthcare settings should be encouraged to inform their provider about all courses of antibiotic therapy.

Another important issue with warfarin management, especially in NH residents, is the problem of poor information flow. There have been reported cases wherein a telephone call may have been made to a physician about a resident with a urinary tract infection without noting the use of

warfarin in the resident.(39) This would normally result in an order for an antibiotic that may interact with warfarin and thus result in an elevated risk of bleeding for the resident. While this may not be a problem in a healthcare setting such as the VA, where most of the patient's healthcare records are available electronically, it may pose a problem for older patients seeing multiple providers or in a NH setting with a lack of provider-to-provider communication. Provider-to-provider communication may be improved via alerts in the electronic-health record (EHR) systems. The success of an EHR-based Warfarin/Antibiotic Rule in reducing over-anticoagulation and adverse outcomes has been tested previously in a case study.(40) Currently there is no decision-support tool in the VA's electronic recording system to 'alert' providers against the prescription of these antibiotics for patients on warfarin, and based on the results of this study, there may not be a need to implement such a system for patients who are closely followed by an anticoagulation clinic.

III. Relationship Between Under-prescribing and Polypharmacy

There may be a possible relationship between under-treatment with medications and polypharmacy in older adults. In a study of 154 geriatric out-patients, polypharmacy, defined as the use of 5 or more medications, was present in 61% from which 43% of these patients were undertreated for a disease for which drug therapy was indicated.(30) In contrast to 43% of patients with polypharmacy that were under-treated, only 13.5% of patients using 4 or less drugs were under-treated (adjusted OR = 4.8, 95% CI = 2.0 – 11.2), suggesting that there is a relationship between polypharmacy and under-treatment. Possible reasons for this relationship may be that physicians are cautious while prescribing multiple medications to patients on complex drug regimens due to fear of adverse drug reactions, interactions and poor compliance.

In this dissertation the issues of underuse of warfarin and warfarin-drug interactions in older adults were highlighted. Both of these are important issues in older adults and they may also be related in some way. Warfarin is known to interact with many medications and due to this reason physicians may be cautious while prescribing warfarin to a patient who already has a complex medication regimen.

III. Role of Newly Approved Oral Anticoagulants: Dabigatran and Rivaroxaban

Since warfarin has a narrow therapeutic index, inter-individual variability in dose response, numerous drug and food interactions, routine monitoring and dose adjustments are required for a patient on warfarin. Due to these reasons the risk of under-treatment with warfarin is also very high. As a result of challenges associated with warfarin management several attempts have been made to develop newer and safer oral anticoagulants. The direct thrombin inhibitor, dabigatran gained FDA approval for prevention of stroke in patients with AF in September 2010 and the direct factor Xa inhibitor, rivaroxaban recently gained approval for use in patients with AF in November 2011, based on their demonstrated efficacy in phase 3 clinical trials towards prevention of stroke and systemic embolism in patients with AF.(41, 42) In addition to their recommended use in patients with AF, dabigatran and rivaroxaban have demonstrated efficacy and safety for use in venous thromboembolism prophylaxis in orthopedic surgery patients.(43) A lot of emphasis has been placed on the advantages of dabigatran and rivaroxaban in terms of reduced patient monitoring required, administration at fixed doses and renal excretion of these medications.(44) However, a point of caution is that the efficacy and safety of these medications have not been evaluated in patients with renal failure.(44) This may have important implications

for use in patients with moderate to severe renal insufficiency and especially for the older patient population that is known to have a decline in renal function. In addition, there is lack of a widely available antidote to these medications in case of a severe bleeding event or an emergency situation.(45) Further information is required from post-approval studies regarding the effectiveness of the newer oral anticoagulants and appropriate monitoring methods in the older adult population, especially frail nursing home residents. As long as caution is exercised while prescribing these medications during daily practice, they may still serve as alternate treatment options for patients with a high-risk profile for stroke but with contraindications to anticoagulation with warfarin. On the other hand switching a NH resident from stable warfarin therapy to the newer anticoagulants may not be necessary given the established benefits of warfarin for stroke prevention and lack of information on use of these newer agents for patients with mechanical heart valves or other indications. Furthermore, in certain situations a monitored anticoagulant such as warfarin may be preferred. For example, as long as warfarin is not contraindicated, due to the available methods of monitoring patients on warfarin, it may be a preferred anticoagulant for NH residents, for older patients with multiple co-morbid conditions and for patients using multiple medications that have a potential to interact with the anticoagulant. The ability to monitor the patient in such situations may be a more attractive option for the healthcare provider.

In terms of drug interactions with the newer anticoagulants, there is limited information about potentially interacting medications and strategies to manage these interactions. Since dabigatran is not metabolized by the CYP450 enzyme system, it appears to have the lowest drug interaction potential, whereas rivaroxaban is partly metabolized by CYP3A4. (46) A recent review article

has summarized some of the recognized food and drug interactions with the newer oral anticoagulants,(43) However, the data for most of these drug interactions were obtained from animal models or healthy subjects, suggesting that there is a lack of clinical experience with new oral anticoagulants and hence lack of information on clinical significance of drug interactions with these agents. Furthermore, patients with severe liver and renal diseases were excluded from the clinical trials of dabigatran and rivaroxaban.(43) Thus due to altered metabolic capacity in case of hepatic or renal diseases, or for older patients with hepatic or renal function decline, the pharmacokinetics and pharmacodynamics of new oral anticoagulants may be affected, and as a result the potential for a drug interaction may be augmented.(43) Due to a lack of reliable monitoring parameters, management of drug interactions with dabigatran and rivaroxaban may be further complicated.

V. Conclusions and Future Research

The research underlying this dissertation highlights two important medication-related problems in older adults, that is, under-treatment and drug-drug interactions, using a high-risk drug such as warfarin as the example. The first project highlighted the high rates of underuse of warfarin in nursing home residents with atrial fibrillation along with the factors associated with warfarin use, such as increasing age, race, stroke and bleeding risk factors. The second project provided evidence for an increase in anticoagulant activity for warfarin, as measured by the patient's international normalized ratio (INR), when antibiotics such as fluoroquinolones, azithromycin and amoxicillin were used concomitantly. While the currently available research on warfarin underuse and warfarin-antibiotic interactions has been conducted across the entire adult population, the research work undertaken in this dissertation represents the evidence for

underuse and drug interactions specifically for the older adult population, which is the population that tends to have the highest prevalence of conditions for which warfarin is indicated.

Drug interactions have been designated as a drug safety measure by the Center for Medicare and Medicaid Services (CMS) and several quality improvement organizations throughout the nation have invested time and efforts in reducing warfarin-drug interactions, including warfarin-antibiotic interactions as part of CMS's drug safety initiative. Thus warfarin-drug interactions is a medication-related issue that is given national importance and the results of this study shed light on the clinical significance of warfarin-antibiotic interactions in the older adult population from an anticoagulation clinic.

There remains room for future research to determine barriers to anticoagulation prescribing for NH residents and developing targeted interventions to increase rates of anticoagulation. The role of newly approved anticoagulants, dabigatran and rivaroxaban, in influencing the patterns of anticoagulation in NH settings remains to be determined. While warfarin-antibiotics may be safely prescribed to older adults as long as their INR is being frequently monitored, the safety of warfarin-antibiotic interactions in other models of anticoagulation care, such as home based care or the usual care model remains to be ascertained.

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APPENDIX A

List of validated ICD-9 codes used to identify diseases and conditions of interest

Disease/ conditions of interest	ICD-9 codes
Atrial fibrillation	427.31
Congestive heart failure	428, 398, 402, 404
Hypertension	401-405, 437
Diabetes	250
Previous stroke/ TIA	434-436
Coronary heart disease	410-414, 429, V45
Valvular heart disease or valve replcement	394- 398, 424, V42, V43
DVT/ arterial peripheral embolus	415, 444, 445, 451, 453
Hemorrhagic tendencies	286- 287
Recent surgery	Sepsis (038, 020, 790, 117, 112), cardiac catheterization (37), cardiac surgery [coronary artery bypass graft surgery (36), valve repair (35)]
History of GI bleeding	531-534, 578
Dementia	290
Myocardial infarction	410
Chronic kidney disease (CKD) or renal failure (RF)	CKD= 403, 404, 250, 581-583, V42; RF= 584-586, 638, 639, 403, 404
Cancer (malignancy)	Colon (153), breast (174), lung (162), prostate (185), melanoma(172), myeloma (203), kidney (189), bladder (188), HIV infection (042)
Hepatic (liver disease/ abnormal liver function)	Acute hepatic failure or necrosis (570), hepatic encephalopathy (573)

TIA= Transient ischemic attack; **DVT** = Deep vein thrombosis

APPENDIX B

NAMCS reason for visit (RFV) codes to identify contraindications to warfarin (according to Coumadin package insert)

Warfarin contraindications	RFV code	Description
1. Hemorrhagic tendencies or blood dyscrasias	1640	Abnormalities of urine: blood in urine (hematuria)
	2525	cerebrovascular disease: CVA, cerebral hemorrhage, stroke
2. Active GI ulceration	1580	GI bleeding; blood in stool (melena), vomiting blood
3. Recent surgery	4521	Major surgery

APPENDIX C

List of Long-term Care Drug Database System (LTCDDS) codes used to determine drug exposure for NH residents with AF

Drug	LTCDDS codes
Warfarin	07930, 34775
Aspirin	97174 (baby aspirin; 81mg), 10975 (ecotrin; 81mg), 00078 (aggrenox; aspirin-dipyridamole, 20mg/250mg), 00100 (ASA; 325mg), 93245 (halfprin; 81mg or 162mg)
Clopidogrel	99033, 98086
Ticlopidine	93192, 93362
Dipyridamole	23535, 09920
NSAIDs:	
Aspirin	51380, 00100, 02725, 25520, 23390, 12550, 04194, 21290, 02805, 41880, 01755, 27300, 97174, 10975, 00078, 00100, 93245
Celecoxib	99002
Diclofenac	02148, 34725, 92116, 98006
Diflunisal	
Etodolac	10126
Fenoprofen	92051, 92124
Ibuprofen	20210
Indomethacin	89050, 19675, 15395, 00597, 98043
Ketoprofen	15590, 15600
Meclofenamate	93432, 93312, 61100
Meloxicam	18558
Nabumetone	00048
Naproxen	93132, 94179
Oxaprozin	04382, 20285, 20290, 01838, 94125
Piroxicam	94127, 93399
Rofecoxib	12193, 92145
Salsalate	01048, 99067
Sodium salicylate	27405, 09925, 27407
Sulindac	29998, 06935
Valdecoxib	02014

APPENDIX D

Description of the Variables Collected from Electronic Medical Records

Variable	Variable Name	Type	Description
Patient number	PT_NO	Discrete	Unique number assigned by the researcher to each patient
Observation number	OBS	Discrete	Number assigned to observations from each patients
Age	AGE	Continuous	Exact value in years obtained from the medical records
Sex	SEX	Categorical	Male or Female
Race	RACE	Categorical	White, African-American or Hispanic
Indication for warfarin use	IND	Categorical	Indication for which patient was prescribed warfarin- atrial fibrillation; atrial fibrillation or atrial flutter; atrial flutter; deep vein thrombosis or pulmonary embolism; mechanical valve replacement; other conditions
INR goal	INR_GOAL	Continuous	Recommended INR therapeutic range
Warfarin Regimen	WAR_REGIMEN	Continuous	Daily and weekly warfarin dose recorded from anticoagulation clinic notes
Antibiotic prescribed	ANT	Categorical	Antibiotic generic name recorded from outpatient pharmacy prescription record
Antibiotic start date	ANT_START	Date	Date antibiotic was started; verified from patient medical record
Dose and duration of antibiotic use	ANT_DOSE_DUR	Continuous	Antibiotic dose and duration recorded from outpatient pharmacy prescription record; verified from patient medical record
Indication for antibiotic use	IND_ANT	Categorical	Indication for which antibiotic was prescribed to patient- upper respiratory infections (URIs); pulmonary infections; urinary tract infections (UTIs); skin; other infections
Pre-antibiotic INR 1	PRE_INR_1	Continuous	INR value collected during the 4-week period before start of antibiotic; exact INR values as recorded in the clinical notes (if available)
Date of pre-antibiotic INR 1	DATE_1	Date	Date pre-antibiotic INR value was recorded in clinical notes
Pre-antibiotic INR 2	PRE_INR_2	Continuous	INR value collected during the 4-week period before start of antibiotic; exact INR

Variable	Variable Name	Type	Description
			values as recorded in the clinical notes
Date of pre-antibiotic INR 2	DATE_2	Date	Date pre-antibiotic INR value was recorded in clinical notes
Post-antibiotic INR 1	POST_INR_1	Continuous	1 st INR value collected during the duration of use of antibiotic or during the 14-day period following discontinuation of antibiotic
Date of post-antibiotic INR 1	DATE_3	Date	Date post-antibiotic INR value was recorded in clinical notes
Post-antibiotic INR 2	POST_INR_2	Continuous	2 nd INR value collected during the duration of use of antibiotic or during the 14-day period following discontinuation of antibiotic (if available)
Date of post-antibiotic INR 2	DATE_4	Date	Date post-antibiotic INR value was recorded in clinical notes
Number of concurrent medications	TOTAL_MEDS	Continuous	Counted number of medications taken by each patient (from medical records)
Number of co-morbidities	TOTAL_COMOR	Continuous	Number of all co-existing conditions (from medical records)
Warfarin dose withheld	WAR_HELD	Categorical	'Yes' for warfarin dose withheld or 'No' for dose not withheld
Warfarin dose reduced	WAR_REDUCED	Categorical	'Yes' for warfarin dose reduced or 'No' for dose not reduced
New warfarin dose regimen	WAR_NEW_REG	Continuous	Change in warfarin dose regimen
Minor bleeding event	MINOR_BLEED	Categorical	'Yes' for minor bleed or 'No' for no minor bleed
Major bleeding event	MAJOR_BLEED	Categorical	'Yes' for major bleed or 'No' for no minor bleed
Vitamin K administered	VITK_AD	Categorical	'Yes' for vitamin K administered or 'No' for vitamin K not administered
Emergency department visit	ED_VISIT	Categorical	'Yes' for patient with emergency department visit, 'No' for no emergency department visit

APPENDIX E

SAS codes for Repeated Measures ANOVA

The SAS code

```
*****  
*****REPEATED MEASURES ANOVA*****
```

```
***** stacking the INR values *****
```

```
data Mylib.warfarin_long;  
set Mylib.warfarin_1;  
inr = pre_inr_1; time = 1; output;  
inr = pre_inr_2; time = 2; output;  
inr = post_inr_1; time = 3; output;  
inr = post_inr_2; time = 4; output;  
drop pre_inr_1 pre_inr_2 post_inr_1 post_inr_2;  
run;
```

```
proc sort data = Mylib.warfarin_long;  
by ant;  
run;
```

```
/*To test for effect of antibiotics on INR values over time, is there an interaction between  
antibiotic and time*/
```

```
/****** Method 1: Compound Symmetry ******/
```

```
proc mixed data = Mylib.warfarin_long;  
class ant time obs;  
model inr = ant time ant*time;  
repeated time / subject = obs type = cs;  
lsmeans time*ant/ diff adjust = tukey cl slice=ant;  
title 'antibiotic interaction: CS';  
run;
```

```
/******Method 2: Auto-regressive******/
```

```
proc mixed data = mylib.warfarin_long;  
class ant time obs;  
model inr = ant time ant*time;  
repeated time / subject = obs type = ar(1);  
lsmeans time*ant/ diff adjust = tukey cl slice=ant;  
title 'antibiotic interaction: AR(1)';  
run;
```

```
/******Method 3: Unstructured******/
```

```
ods trace on;
ods graphics on;
ods output Tests3= Mylib.type3test;
ods output LSmeans=Mylib.means;
ods output Slices=Mylib.slices;
ods output Diff=Mylib.difference;

proc mixed data = mylib.warfarin_long;
class ant time obs;
model inr = ant time ant*time;
repeated time / subject = obs type = un;
lsmeans time*ant/ diff adjust = tukey cl slice=ant;
title 'antibiotic interaction: UN';
run;

ods graphics off;
ods trace off;
```

Definition of the variable names in the Proc Mixed code

ant = the type of antibiotic received i.e. amoxicillin, azithromycin, cephalexin, ciprofloxacin, levofloxacin, moxifloxacin

time = 4 time periods during which INR values were recorded; first 2 INR values were recorded pre-antibiotic use, last 2 INR values were recorded post-antibiotic use

obs = patient

Description of the Proc Mixed code

Data = the name of the dataset to be analyzed

Class = the classification variables to be used in the analysis, i.e. the categorical variables are obs, ant and time.

Model = the statement that specifies the model for the analysis. The first variable, i.e. INR, is the response variable. Following the '=' are the explanatory variables, i.e. the variables which may be affecting the INR values. In this study we are looking to see if change in INR values over time is different for different antibiotics, so an interaction term *ant*time* is added in the model statement. Since this interaction term was found to be significant, the results are interpreted accordingly.

Repeated = is used to specify the correlation structure of the data. Here there are repeated measures on each patient. The *obs* variable uniquely identifies the patients. The repeated statement is followed by the repeated effect, here time. The *subject = obs* is used to specify the subject effect and the *type = UN* option is used to specify the correlation structure for the variance-covariance matrix.

All 3 covariance structures (CS, AR(1) and UN) are used and the model with the minimum AIC values is chosen (UN).

Random = specifies the variable which is causing the random variability within the study, i.e. *obs* (patient) in this case. In most analyses, the subject is conceived to be a random representative of all possible subjects. Year or time is the fixed-effect, that is, its values represent specific levels of the factor and these values are “fixed” in the sense that our hypotheses refer to comparisons between these specific levels. Since the final model includes both fixed and random effects, the model is termed a “mixed model”.

LSmeans = the statistical method used to test the differences in INR values across the time points and between antibiotics, i.e. comparing the estimated adjusted mean value of the INR values between the different antibiotics and across the different time points (2 and 3 time points are of interest for this study).

Ods output = outputs the results of the individual lsmeans to the ‘means’ dataset in the Mylib folder, and the difference of the lsmeans computed using test slices is outputted to the ‘differences’ dataset in the Mylib folder.

Information obtained from the SAS log

If the model is correct there will be a note in the log ‘Convergence criteria met’. If not, then the model need to be changed or the assumption of normality of the data is incorrect. In this case the convergence criteria was met using all 3 covariance structures and the model that gave the minimum AIC values (i.e. UN) was chosen.

VITA

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EDUCATION

August 2007-
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August 2003-
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Bachelor of Pharmaceutical Science

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PROFESSIONAL EXPERIENCE

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Research Assistant

Veterans Affairs Medical Center, McGuire Hospital, Richmond, VA

- Designed a research study, prepared and submitted protocol for the same to the VA IRB office
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Project Specialist

Virginia Health Quality Center (VHQC), Richmond, VA

- Specialist on a CMS-funded national drug safety project to reduce rates of potentially inappropriate medications (PIMs) and drug-drug interactions (DDIs) in older adults, across 25 physician practices in Virginia. Target reduction rate of 5% in PIMs and DDIs was met at the end of the project.
- Assisted with proposal development for submission to CMS
- Authored an introductory white paper for participating physician practices titled 'Strategy map for reducing drug-drug interactions and potentially inappropriate medication events'

- Developed interventions and educational materials specifically targeting physician practices
- Developed patient safety flyers for VHQC website and physician practices, through extensive literature review, on the following:
 - Polypharmacy and Drug Interactions'
 - 'Warfarin-Drug Interactions in Older Adults'
 - 'Drug Interactions and Safety of New Oral Anticoagulants: Focus on Dabigatran & Rivaroxaban'
 - 'Serotonin Syndrome in Older Adults: Causes, Diagnosis and Treatment Options'

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Graduate Teaching Assistant

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 - Taught and reviewed biostatistical methods for graduate-level students
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Summer Intern

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PUBLICATIONS AND PRESENTATIONS

Manuscripts

- **Ghaswalla PK, Harpe SE, Slattum PW, "Warfarin Use in US Nursing Homes: Results from the 2004 National Nursing Home Survey".**
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- **Ghaswalla PK, Slattum PW, Harpe SE, Tassone DE, "Warfarin-Antibiotic Interactions in Older Adults of an Outpatient Anticoagulation Clinic".**
Original research paper to be submitted in January 2012.
- **Ghaswalla PK, Slattum PW, "Effect of Age on Warfarin-Antibiotic Interactions in Older Adults"**
Review paper – to be submitted to The American Journal of Geriatric Pharmacotherapy, December 2011.

Posters

- **Ghaswalla PK, Slattum PW, Harpe SE, Tassone DM, 'Warfarin-Antibiotic Interactions in Older Adults of an Outpatients Anticoagulation Clinic'.**
 - Accepted for poster presentation at the 2012 American Society of Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting (Mach 2012)
- **Ghaswalla PK, Slattum PW, Harpe SE, Tassone DM, 'Retrospective Assessment of Potential Drug Interactions between Warfarin and Antibiotics in Older Adults'.**

- Presented at the Research & Career Day, VCU School of Pharmacy (October 2011) and the 14th Annual VCU Graduate Student Research Symposium & Exhibit (April 2011)
- **Ghaswalla PK, Slattum PW, Harpe SE, Tassone DM, 'Warfarin Use in US Nursing Homes: Results from the 2004 National Nursing Home Survey'.**
 - Presented at the 31st Annual Southern Gerontological Society Meeting (April 2010), the 13th Annual VCU Graduate Student Research Symposium & Exhibit (April 2010)
- Dotiwala ZJ, **Ghaswalla PK, 'Use of warfarin and potentially interacting medications in US nursing home residents'.**
 - Presented at the Midwest Social & Administrative Pharmacy Conference, Iowa (July 2010)

Other relevant work:

- Conducted data analysis for a study titled 'Influence of Continuous Venovenous Hemofiltration and Continuous Venovenous Hemodiafiltration on the Disposition of Doripenem' published in *Antimicrobial Agents and Chemotherapy*, 55:3, Mar 2011.

INVITED JOURNAL REVIEWER EXPERIENCE

- Reviewer for *The Annals of Pharmacotherapy*

SOFTWARE PROFICIENCY

- Data analysis software programs: SAS 9.2, SPSS 17.0, JMP 8.0, nQUERY 7.0
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- Microsoft Office Suite 2007

HONORS AND AWARDS

- VCU Graduate School **Thesis/ Dissertation Assistantship Award** (2010-2011)
- Invited to membership to **Honor Society of Phi Kappa Phi** for academic excellence (Oct '08 Present)
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