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Morbidity and Mortality With Warfarin Therapy Use in Elderly Patients With Atrial Fibrillation: A Systematic Review

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Morbidity and Mortality With Warfarin Therapy Use in Elderly Patients With Atrial Fibrillation: A Systematic Review

Abstract
Background: Atrial fibrillation (AF) is the most common dysrhythmia among elderly patients. A co-morbidity associated with this disease process is embolic stroke. In an effort to reduce the potential morbidity and mortality associated with stroke, patients are often placed on the anticoagulant warfarin. While warfarin has been statistically proven to reduce the rate of embolic stroke in patients with AF, it potentiates increased risk of bleeding. The elderly population has an elevated level of AF and increased risk for fall and bleeding abnormalities. This systematic review aims to evaluate the risk versus benefit of prescribing warfarin in elderly patients with AF.

Methods: A comprehensive database search was completed, using Medline, CINAHL and EBMR Multifile. Inclusion criteria of English text, human trials, at least one study group with age > 70, atrial fibrillation, warfarin use vs. no anticoagulation therapy, morbidity, mortality and hemorrhage were determined prior to the search. In addition, exclusion criteria consisted of use of anticoagulation therapy following ablation therapy or other surgical forms of AF management, studies which included patients with mechanical heart valves or target INR >3 or study populations that were too narrowly drawn. Four articles were identified and evaluated in this study. Validity was noted based on eight factors.

Results: All four articles reviewed were observational studies, with no randomized controlled trials. In total, 14,342 patients were analyzed between 1996 and 2007, with study duration from six to 28 months. All studies took into account age and/or frailty in elderly patients with AF. Study groups varied from warfarin users to non-users, all warfarin users of varying age and frail vs. non-frail warfarin users, and non-users. With regard to general warfarin practices, two studies showed providers did not prescribe warfarin in the oldest and frailest patients, and two studies found no variation in INR measures with age. When considering advancing age, independent of warfarin therapy, two studies found a significant increase in stroke rate and one study found a significant increase in death rate with advancing age. Three studies evaluated hemorrhage risk in relation to increasing age independent of warfarin use, with one study finding a significant increase, one finding a non-significant increase and one finding no difference. When evaluating the use of warfarin, one study displayed no significant variation and one found a non-significant increase in hemorrhage rates for warfarin users with advancing age. One study found a non-significant increase in hemorrhage with supratherapeutic warfarin use.

Conclusion: Throughout this systematic review, warfarin therapy does not prove to be more harmful than no therapy, in elderly or frail patients with atrial fibrillation. Elderly and frail individuals are at a greater risk for stroke, death and potentially hemorrhage independent of anticoagulant use. Additional research is necessary in order to develop prescribing guidelines for warfarin therapy with consideration of age and frailty. It is imperative that warfarin be prescribed and monitored carefully in all age ranges, in order to provide the most effective prevention of embolic stroke while minimizing the risk of hemorrhage.

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Morbidity and Mortality With Warfarin Therapy Use in Elderly Patients With Atrial Fibrillation
A Systematic Review

Kristi M. Crowell

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
Hillsboro, OR
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Clinical Graduate Project Coordinators: Annjanette Sommers MS, PAC & Rob Rosenow PharmD, OD
Biography

[Redacted for privacy]
Abstract

**Background:** Atrial fibrillation (AF) is the most common dysrhythmia among elderly patients. A co-morbidity associated with this disease process is embolic stroke. In an effort to reduce the potential morbidity and mortality associated with stroke, patients are often placed on the anticoagulant warfarin. While warfarin has been statistically proven to reduce the rate of embolic stroke in patients with AF, it potentiates increased risk of bleeding. The elderly population has an elevated level of AF and increased risk for fall and bleeding abnormalities. This systematic review aims to evaluate the risk versus benefit of prescribing warfarin in elderly patients with AF.

**Methods:** A comprehensive database search was completed, using Medline, CINAHL and EBMR Multifile. Inclusion criteria of English text, human trials, at least one study group with age > 70, atrial fibrillation, warfarin use vs. no anticoagulation therapy, morbidity, mortality and hemorrhage were determined prior to the search. In addition, exclusion criteria consisted of use of anticoagulation therapy following ablation therapy or other surgical forms of AF management, studies which included patients with mechanical heart valves or target INR >3 or study populations that were too narrowly drawn. Four articles were identified and evaluated in this study. Validity was noted based on eight factors.

**Results:** All four articles reviewed were observational studies, with no randomized controlled trials. In total, 14,342 patients were analyzed between 1996 and 2007, with study duration from six to 28 months. All studies took into account age and/or frailty in elderly patients with AF. Study groups varied from warfarin users to non-users, all warfarin users of varying age and frail vs. non-frail warfarin users, and non-users. With regard to general warfarin practices, two studies showed providers did not prescribe warfarin in the oldest and frailest patients, and two studies found no variation in INR measures with age. When considering advancing age, independent of warfarin therapy, two studies found a significant increase in stroke rate and one study found a significant increase in death rate with advancing age. Three studies evaluated hemorrhage risk in relation to increasing age independent of warfarin use, with one study finding a significant increase, one finding a non-significant increase and one finding no difference. When evaluating the use of warfarin, one study displayed no significant variation and one found a non-significant increase in hemorrhage rates for warfarin users with advancing age. One study found a non-significant increase in hemorrhage with supratherapeutic warfarin use.

**Conclusion:** Throughout this systematic review, warfarin therapy does not prove to be more harmful than no therapy, in elderly or frail patients with atrial fibrillation. Elderly and frail individuals are at a greater risk for stroke, death and potentially hemorrhage independent of anticoagulant use. Additional research is necessary in order to develop prescribing guidelines for warfarin therapy with consideration of age and frailty. It is imperative that warfarin be prescribed and monitored carefully in all age ranges, in order to provide the most effective prevention of embolic stroke while minimizing the risk of hemorrhage.

**Keywords:** Atrial Fibrillation, Elderly, Aged, Hemorrhage, Morbidity, Mortality
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To my family ~ Thank you for your patience, dedication, support and encouragement throughout my journey. I would not have made it through the long hours of studying or the countless trials and triumphs without you!
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List of Abbreviations

AF – Atrial Fibrillation
ATRIA – Anticoagulation and Risk Factors in Atrial Fibrillation Study
INR – International Normalized Ratio
GI – Gastrointestinal
Morbidity and Mortality With Warfarin Therapy Use in Elderly Patients With Atrial Fibrillation

BACKGROUND

The management of atrial fibrillation (AF) has been a topic of great debate throughout history. Management options include, but are not limited to, the use of medications to control heart rate and heart rhythm, radiofrequency catheter ablation, chemical or electrical cardioversion, pacemakers and surgical occlusion of the left atrial appendage.\(^1\)

In addition to managing the disease process itself, a significant amount of research and health care effort is placed on reducing the symptoms and co-morbidities associated with AF. Such consequences include thrombus formation with potential for embolization, fatigue, palpitations, hypotension, myocardial ischemia and tachycardia-induced myocardial dysfunction. One of the most significant consequences is cerebral artery embolization – which occurs at an approximate rate of “[five] events per 100 patient years.”\(^1\)

Atrial fibrillation is a disease that tends to present more in later life\(^1\) and is the most common arrhythmia in the elderly.\(^2\) Dr. Alan Go and colleagues\(^3\) in their “Anticoagulation and Risk Factors In Atrial Fibrillation” (ATRIA) study found that only 0.1% of individuals less than 55 years of age are affected by AF. The impacted population increases to 9.0% in those above the age of 80.\(^3\) As the occurrence of AF increases with age, so do the potential co-morbidities. The risk of stroke increases to “nearly 20 events per 100 patient years” in individuals affected by AF with multiple risk factors – including age greater than 75 years, significant obstructive valvular disease, chronic heart failure, left ventricle dysfunction, diabetes and/or hypertension.\(^1\)
In addition to the increased incidence of AF, the elderly population has a much higher likelihood of complications secondary to age-related decline in bodily function. For example, approximately 50% of patients hospitalized for gastrointestinal (GI) hemorrhage are over the age of 60.\textsuperscript{4} The incidence of intracerebral hemorrhage is also associated with advancing age.\textsuperscript{5} Likewise, the geriatric population has a higher fall risk, with roughly 1/3 of individuals greater than 65 falling each year.\textsuperscript{6} The CHADS\textsuperscript{2} score was developed as a measuring standard to determine an individual’s risk of stroke secondary to major concomitant conditions and determining when a patient might benefit from anticoagulation therapy (Table 1).\textsuperscript{7} While this score is used daily in clinical practice, it does not take into account the risk of potential morbidity and mortality to a patient while on anticoagulants.

One of the primary anticoagulants used in the management of AF is warfarin. Although warfarin has been shown to significantly reduce the risk of stroke in patients with AF,\textsuperscript{8} it also potentiates an increased risk of bleeding, especially following commencement of use or with higher doses.\textsuperscript{9}

Practitioners are faced with the determination of this benefit versus risk in their geriatric patients, yet, there are no standards delineating the guidelines for warfarin therapy in the elderly. The purpose of this study was to evaluate the risk of complications, primarily hemorrhage, in the elderly population with atrial fibrillation secondary to treatment with warfarin therapy; with the goal of decreasing the confusion associated with placing elderly patients affected by atrial fibrillation on warfarin.
METHODS

Search Strategy

A comprehensive literature search was completed in order to compose this systematic review. Multiple search engines and databases were used, including Medline, CINAHL and EBMR Multifile using the search words “Aged”, “Atrial Fibrillation”, “Mortality” and “Warfarin”. One hundred thirty-seven articles were found initially through the three major databases, with eight additional articles found in reference materials. Duplicates were removed and articles were screened for relevance. A total of 17 full text articles were assessed, with 13 articles excluded for lack of relevance to the specified population or management specifications (Figure1).

Validity Scoring

The validity of each article was assessed on a scale of eight self-determined validity criteria. Articles received one point for every criterion met. The criteria consisted of having a patient population greater than 100, a study duration greater than six months, more than one study group, the inclusion of statistical analysis, the inclusion of withdrawal or dropout patients, comparison of warfarinised versus non-warfarinised patients, comparison of two or more age groups and refraining from the use of financial support from drug-associated parties (Table 2).

Inclusion Criteria

English Language, human only, population >70 years of age, individuals with atrial fibrillation, use of warfarin therapy versus no anticoagulant therapy and discussion of morbidity, mortality or hemorrhage.
Some studies, of the available few, contained irrelevant information which was not considered substantively in this review. All relevant findings were analyzed fully.

*One study\(^{10}\) analyzed only warfarin users broken into two age categories.
*One study\(^{11}\) examined medical information from a population composed of only warfarin users. This study looked at the group collectively and did not differentiate comparison groups.
*One study\(^{12}\) evaluated patients in three groups, warfarin users, warfarin non-users and other anticoagulant users. This systematic review did not analyze data from the other anticoagulant group but did take into consideration the segments discussing the first two categories.

**Exclusion Criteria**

Studies referring to anticoagulation therapy following ablation therapy or other surgical forms of AF management, inclusion of patients with mechanical heart valves, inclusion of patients with target International Normalized Ratio (INR) $> 3$ or study populations that were too narrowly drawn.

*One study\(^{13}\) found maintained a focus of increasing age in their evaluation of the risk of oral anticoagulants, however, this study included patients with mechanical heart valves and patients with target INR $>3$, and thus, the paper in its entirety, was not include in this systematic review.

**RESULTS**

All four articles assessed were observational studies, with no randomized controlled trials. In total, 14 342 patients were analyzed between 1996 and 2007, with the largest cohort consisting of 13 559 patients and the smallest of 220 patients. Study
duration ranged from six months to 28 months. All studies took into account age or frailty in elderly patients with AF, with either a total patient population or at least one study group utilizing warfarin therapy. A condensed version of the details from each article, in addition to their findings and validity score can be found in Table 3 in the Article and Results Summary Matrix.

**Age and the Risk of Warfarin-Associated Hemorrhage: The ATRIA Study**

Dr. Margaret Fang and colleagues\textsuperscript{14} used the ATRIA cohort of 13 559 patients to determine the risk of warfarin-associated hemorrhage in AF patients stratified by age. Study information was gathered from hospitalization and billing databases. Patients were recruited between July 1, 1996 and December 31, 1997 and followed until August 31, 1999. Patients were separated into four categories: <60, 60-69, 70-79 and >80. Only those with a diagnosis of non-valvular, non-transient AF were evaluated. For those taking warfarin, INR intensity and variability were taken into account.\textsuperscript{14}

Hemorrhage was assessed as intracranial or extracranial. Major extracranial hemorrhages included those which were fatal, required two or more transfusions or involved bleeding into a critical anatomic site. Patients were followed for an average of 2.4 years. The mean age was 71, with 28% of the documented patient years obtained from those over the age of 80.\textsuperscript{14}

Fang et al\textsuperscript{14} found INR intensity and variability remained consistent between age groups. They also determined “[t]he rate of all major hemorrhage rose with older age” regardless of warfarin use; with a significant increase in both intracranial and extracranial hemorrhage in patients over the age of 80.\textsuperscript{14}
With regard to age categories, Fang et al\textsuperscript{14} noted an “average relative increase in the rate of hemorrhage from one age category to the next older age category was 1.3 (95% CI=1.1-1.6)” in warfarinised patients and 1.7 (95% CI = 1.5-2.1) in non-warfarinised patients. After adjusting for potential hemorrhage risk factors, the “relative increase in hemorrhage rate in warfarin users was 1.2 (95% CI=1.0-1.4)” and 1.5 (95% CI=1.3-1.8) for non-warfarin users. Lastly, Fang and colleagues\textsuperscript{14} resolved that “patients newly started on warfarin may be more likely to suffer hemorrhagic complications.”

Overall, there was no statistically significant difference in the occurrence of hemorrhage between patients taking warfarin and those not. They concluded that “well-managed warfarin therapy can be used safely in clinical practice to achieve substantial benefit in reducing the risk of atrial fibrillation-associated ischemic stroke.”\textsuperscript{14}

\textbf{Oral Anticoagulation and Hemorrhagic Complications in an Elderly Population With Atrial Fibrillation}

The 2001 study by Copland and colleagues\textsuperscript{10} assessed the quality of anticoagulation control and the incidence of hemorrhage between two age groups, both receiving warfarin therapy, with target INR of 2.5 via retrospective follow-up. Secondarily, they evaluated these same factors in patients newly started on warfarin therapy versus long-term warfarin users. In total, 328 patients were followed from January 1, 1998 to September 30, 1999, with 204 in the control group aged 60-69 (mean age 64.7), and 124 in the elderly study group age >75 (mean age 78.3). All individuals included at the commencement of the study were accounted for at its finale.\textsuperscript{10}

A major hemorrhage was defined as a fatal bleeding incidence, bleeding involving the central nervous system or bleeding requiring hospitalization, surgery or blood
transfusions. The incidence of major hemorrhage was 2.8% in the control group and 2.9% in the elderly group (P=0.96). Of those, the incidence of intracranial hemorrhage was 0.7% in the control group and 1.2% in the elderly group (P=0.61). INR levels were maintained within the therapeutic range for 66.1% of the control group and 71.5% of the elderly group (P=0.13).\(^{10}\)

As an additional note, INRs remained within target range in 62.1% of new warfarin users compared with 70.9% in long-term warfarin users (P<.005). The incidence of major hemorrhage was also significantly higher in the new-user group.\(^{10}\)

In conclusion, Copland et al\(^{10}\) determined there was no statistically significant variation in INR control or risk of major hemorrhage between patients in the 60-69 age group and those greater than 75 years of age with atrial fibrillation on warfarin therapy. Secondly, INR variability and incidence of major hemorrhage were statistically more likely in new warfarin users compared with long-term users.\(^{10}\)

**People Aged Over 75 in Atrial Fibrillation on Warfarin: The Rate of Major Hemorrhage and Stroke in More Than 500 Patient-Years of Follow-Up**

In their Australian retrospective observational cohort study, Johnson and colleagues\(^{11}\) set out “[t]o determine the incidence of major hemorrhage and stroke in people” over the age of 75 recently admitted to the hospital having the diagnosis of AF. A total of 235 patients were evaluated over an average period of 28 months. The study population was composed of patients with a discharge diagnosis of AF who had been started on warfarin via the inpatient pharmacy between July 1, 2001 and June 30, 2002 in four tertiary care hospitals. The mean age of the patient population was 81.1. All 235 patients were accounted for at the conclusion of this study, including 7 drop outs.
Findings were reported as percentages. No statistical analysis was completed. Additionally, participants were collectively evaluated, with no comparison groups delineated.11

Throughout this study, major bleeding episodes, strokes and warfarin use were measured by examining data from patients, relatives, physicians and medical records. Major hemorrhage was qualified in three categories, serious, which included hemorrhages resulting in hospital admission, a 2g/dL drop in hemoglobin or requiring no more than two units of blood; life-threatening, which included hemorrhages involving the central nervous system, causing a greater than 2 g/dL decrease in hemoglobin, requiring more than two units of blood, causing systolic hypotension, resulting in cardiopulmonary arrest or requiring an emergent procedure; and, lastly, fatal major hemorrhages.11

The study population was initially drawn from 933 patients with an age >75 and a diagnosis of AF. Only 25% of these individuals were prescribed warfarin during their hospital stay and thus were included in this study. As a result, Johnson and colleagues11 deduced that warfarin is under-prescribed for the elderly population diagnosed with AF.

Johnson et al11 reported an annual major hemorrhage rate of 10% in the study population. Of these, 45.3% were serious, 45.3% were life-threatening and 9.4% were fatal. The annual rate of fatal hemorrhage was 0.9%. The predominant major hemorrhages presented as GI bleeds (30.2%), with a small subset of reported intracranial hemorrhages (0.4%). Of note, 54.7% of all hemorrhages reported, were in patients with elevated INRs (>3).11
Throughout this study, a total of 17 strokes were documented. At the time of stroke, 29.4% of participants had a therapeutic INR (INR >2), while the remaining 70.6% were subtherapeutic (INR <2).

Johnson and colleagues discovered the risk of major hemorrhage was substantial in elderly patients with AF on warfarin therapy. They found, however, that the hemorrhages did not pose long-term sequelae when compared to the benefit of stroke reduction, concluding warfarin therapy was a safe and effective method of stroke prevention for elderly patients.

The Impact of Frailty on the Utilization of Antithrombotic Therapy in Older Patients With Atrial Fibrillation

In Perera and colleagues study, between April and July 2007, individuals greater than 70 years of age with an admission diagnosis of AF in a Sydney, Australia hospital were invited to participate. Medical records were evaluated at time of admission, and again at three months and six months. All participants were accounted for at the conclusion of the study, including drop out patients. Individuals were analyzed in two groups, frail and non-frail. They were also broken into subgroups including patients on warfarin therapy, non-warfarin anticoagulant therapy and no anticoagulant therapy. A total of 220 patients were evaluated and 207 followed for the full six month duration. Ninety-eight participants were designated as other anticoagulant users and were not included in this systematic review.

Stroke incidents were classified as cardioembolic or other. Hemorrhages were recorded in three categories: minor (not requiring hospitalization), major (requiring hospitalization) or severe (intracranial or fatal). Frailty was determined via a modified
Edmonton Frail Scale with consideration of age, nutritional deficits, decreased mobility, disease, social withdrawal, poor income, number of hospitalizations and cognitive impairment.\textsuperscript{12}

Using the Kaplan-Meier survival function, Perera and colleagues\textsuperscript{12} determined that frail patients seemed to have an elevated risk of major/severe hemorrhage compared to non-frail, but the difference was not statistically significant (HR=1.35, P=0.34). “The incidence of major/severe hemorrhage over 6 months was 30.0\% in the frail and 18.9\% in the non-frail participants prescribed warfarin” compared to “8.3\% for frail and 0\% for non-frail participants receiving no antithrombotic therapy.” The sample size was too small to determine statistical significance of antithrombotic modalities.\textsuperscript{12}

In evaluation of prescribing practices, frail patients were “significantly less likely to receive warfarin than non-frail on admission or discharge” based on the prescribing practices of three different specialty groups in the hospital. They also deduced frail patients had a higher probability of cardioembolic stroke (HR=3.37, P=0.04) and death (HR 2.62, P=0.009) than non-frail.\textsuperscript{12}

Perera et al\textsuperscript{12} concluded frailty is a determining factor in whether or not individuals with AF are prescribed warfarin. Secondly, the risk of hemorrhage is high in frail patients regardless of warfarin use, and frail patients are significantly more likely to experience stroke or death compared with non-frail. Lastly, they noted further research is recommended to determine the statistical significance of the affect of warfarin therapy in frail patients.\textsuperscript{12}
DISCUSSION

Overview

The intent of this systematic review was to examine the morbidity and mortality associated with warfarin therapy in elderly patients with AF. The initial literature search was aimed to find studies which evaluated the use of warfarin therapy compared with no anticoagulant therapy in patients greater than 70 years of age diagnosed with non-valvular, non-transient AF. A significant number of articles found addressed these issues, however, only a handful were focused on the geriatric population. Due to this, the inclusion and exclusion criteria were broadened, in order to incorporate all relevant articles focused on the elderly. For the purpose of this review, relevant findings were fully analyzed, while irrelevant information was disregarded.

Validity

Validity criteria consisted of having a patient population greater than 100, a study duration greater than six months, more than one study group, the inclusion of statistical analysis, the inclusion of withdrawal or dropout patients, comparison of warfarinised versus non-warfarinised patients, comparison of two or more age groups and refraining from the use of financial support from drug-associated parties (Table 2).

The study by Fang et al,\textsuperscript{14} was the only study to comply with the inclusion and exclusion criteria initially comprised for this review. Participants were assigned to two study groups, warfarin-users or non-users, and subdivided into four age categories. This study was given a validity score of 7/8 secondary to the fact that a primary author received funding from the drug company which produces Coumadin, the brand name of warfarin.
The Copland et al\textsuperscript{10} study only evaluated patients taking warfarin, but differentiated the study population into two groups based on age. Furthermore, the study did not include a discussion regarding financial contributions, and thus potential for bias could not be determined. As a result, the study received a validity score of 6/8.

Johnson and colleagues\textsuperscript{11} scored a total of 4/8 on the validity scale. Their study did not contain multiple study groups, it failed to include statistical analysis, it did not compare between warfarin-users and non-users, and finally, it did not include two or more age groups. Not only did this study fail to provide statistical analysis, it did not supply enough raw data for the reader to calculate such results. Characteristics of the cohort were detailed in a table, yet, these factors were not associated with individual results. In observing all warfarinised all elderly patients, the reader can gain some insight into hemorrhage rates in this population; however, it is difficult, if not impossible, to analyze these findings without some form of comparison.\textsuperscript{11}

The Perera et al\textsuperscript{12} study evaluated patients as frail or non-frail. While this determination included the aspect of age, it did not evaluate age independently, resulting in a validity score of 7/8. Authors assessed patients in the subgroups of warfarin-users, non-warfarin anticoagulant users and non-anticoagulant users. The 98 patients belonging to the group utilizing non-warfarin anticoagulants were excluded from analysis in this systematic review. With the removal of these participants, the study population was deduced from 220 to 122, close to the validity cutoff for this review. A total of 83 patients remained in the warfain group, with only 26 patients in the non-anticoagulant therapy group.
Warfarin Prescribing Practices

Two studies commented on the prevalence of warfarin prescriptions in AF populations. While Johnson and colleagues\textsuperscript{11} concluded that warfarin prescription was decreased in light of increasing age or frailty, this observational study evaluated patients collectively, without separating study groups based on age, frailty or any other factor. Subsequently, it is difficult to determine how this conclusion was drawn. This result would be more beneficial if providers were screened for prescribing reasons, perhaps including age, frailty, hemorrhage risk, fall risk or other, while tracking patient demographics.

In their findings, Perera et al\textsuperscript{12} noted a significant decrease in warfarin prescriptions among frail patients compared to non-frail patients. While these findings were consistent across three prescribing specialties (geriatric medicine, general medicine and cardiology), explicit reasons for the decreased prescriptions were not available secondary to the retrospective nature of their study. Again, prescriber rationale would be extremely helpful for future research regarding the production of standardized prescribing guidelines for warfarin in the elderly patient with atrial fibrillation.

Variation in INR With Age

With regard to INR control, two studies\textsuperscript{10, 14} concluded there was no variation in INR levels between age groups. Patients in both studies\textsuperscript{10, 14} were monitored closely via anticoagulation clinics, which may have decreased the likelihood of variation in this population. While maintaining an INR within the therapeutic range is imperative, doing so at a specialized anticoagulation clinic is a luxury that may not be available for all elderly patients with AF.
Hemorrhage, Stroke and Death Risk With Increasing Age

Fang et al\textsuperscript{14} concluded that hemorrhage and stroke risk increase with age, independent of warfarin use. Similarly, Perera and colleagues\textsuperscript{12} found a significant increase in stroke and death rate and a non-significant increase in hemorrhage rates among frail versus non-frail patients regardless of the anticoagulant method. These findings are expected and correlate with the increased risk of GI\textsuperscript{4} and intracerebral\textsuperscript{5} hemorrhage with age; as well as the increased stroke risk in patients with AF associated with increasing age discussed in other sources.\textsuperscript{1}

Hemorrhage Risk With Warfarin and Increasing Age

Hemorrhage risk in relation to Warfarin use with increasing age was one of the main focuses of this systematic review. Two studies\textsuperscript{10, 14} determined there was no variation in hemorrhage risk with warfarin use in relation to increasing age. This finding is surprising and counterintuitive, considering the primary side effect of warfarin is hemorrhage\textsuperscript{9}, that over 50\% of patients hospitalized for GI bleeds are over the age of 60\textsuperscript{4} and the fact that advancing age is associated with intracerebral hemorrhage.\textsuperscript{5} Many factors, not accounted for in these studies, may have affected the results. One explanation may be the duration of warfarin use between age groups. New warfarin-users are more likely to experience adverse bleeding effects.\textsuperscript{9} Perhaps the older age group had been on warfarin for a longer duration than the younger group. Findings may also be explained by the close INR monitoring, or secondary to a smaller study population of only 328 patients in the Copland et al\textsuperscript{10} study.

The study by Johnson and colleagues\textsuperscript{11} noted the prevalence of hemorrhage was high but posed minimal long-term sequelae. No details were included regarding the
evaluation of long-term stroke or hemorrhage effects. This conclusion would be more applicable if the authors had included specific long-term complications or lack there of, such as paralysis following stroke or continued anemia following hemorrhage.

Perera and colleagues\textsuperscript{12} displayed evidence of an increased hemorrhage risk in both the non-frail and frail warfarin-users compared to non-users, however, their study population was too small to determine statistical significance. These findings are consistent with the increased hemorrhage risk with age discussed above. Additional research is necessary to confirm or refute results found in all four articles.

**New Warfarin Users**

Fang et al\textsuperscript{14} found a non-significant increased risk of hemorrhage in new warfarin users. Similarly, Copland and fellow authors\textsuperscript{10} noted that hemorrhage risk and INR instability were both increased in patients newly started on warfarin. This was expected and complies with the adverse drug reactions noted in warfarin drug information sources.\textsuperscript{9} These findings only reiterate the necessity of close INR monitoring, especially with initiation of the anticoagulant warfarin.

**Non-Therapeutic INR**

Authors of the Johnson et al\textsuperscript{11} study stated stroke rates increased with subtherapeutic INRs and hemorrhage rates increased with supratherapeutic INRs. This information follows the general thinking behind warfarin therapy, and the need for closely-monitored INR levels, however, these findings are only generalized conclusions without the inclusion of statistical findings, which were non-existent in this study.
Study Limitations

The primary limitation shared by all four articles\textsuperscript{10-12, 14} assessed was the fact that each study took an observational approach. As a result, prescribing practices were unobtainable. Prescribing physicians may have avoided warfarin therapy in the very frail or very old, limiting the absolute applicability of each study to the generalized elderly population.

A secondary shared limitation\textsuperscript{10-12, 14} is the potential for non dokumented concomitant use of over-the-counter anticoagulants, such as aspirin or NSAIDs. While one study\textsuperscript{14} evaluated a subset of the population for other anticoagulant use, and another\textsuperscript{12} had a study group who only used non-warfarin anticoagulants, authors were limited in that they could not monitor or record what over-the-counter medications patients had consumed. There may be some overlapping effect secondary to these non-prescribed anticoagulants on the overall hemorrhage rate in the study populations.

A few studies had shared limitations which were not universal to all articles assessed. Both the Johnson et al\textsuperscript{11} and Perera et al\textsuperscript{12} studies were based on a populace of Australian individuals, and thus may not be as applicable to American patients with respect to potential variation in genetic and environmental factors affecting coagulation. The Fang et al\textsuperscript{14} and Copland et al\textsuperscript{10} studies evaluated a population of patients monitored closely via anticoagulation clinics. Although this supervision is ideal, it may not reflect the general population with regard to INR stability and control.

On an individual note, the Fang et al\textsuperscript{14} study was partially funded by the makers of Coumadin, the brand name of warfarin. While this does not necessarily indemnify the findings associated with this study, it does pose a potential for bias.
Likewise, the Copland et al\textsuperscript{10} study did not note financial contributors and thus may also be subject to bias. Additionally, the study\textsuperscript{10} did not compare the incidence of hemorrhage between patients not taking warfarin and those who were. Although this is not a significant downfall, it does limit the applicability in the debate between initiating anticoagulation therapy in the older AF patient and not.

The majority of limitations associated with the Johnson and colleagues\textsuperscript{11} study have been alluded to under the validity section of this discussion. The lack of study groups, and subsequently, statistical analysis drawn through comparison makes this article nearly irrelevant. It was impossible to determine the effect of warfarin in AF patients of increasing age, a primary goal of this systematic review.

While their information was helpful in light of general prescribing practices in elderly patients with AF, Perera and colleagues\textsuperscript{12} study population was too small to determine a significant difference in hemorrhage or stroke risk between warfarin users and non-users. This systematic review did not evaluate the non-warfarin anticoagulant group, which further decreases the study population size.

CONCLUSION

Throughout this systematic review, four relevant articles were identified and evaluated. Each article addressed the aspect of prescribing warfarin in elderly patients with atrial fibrillation. This review demonstrated that elderly and frail individuals are at greater risk for stroke and hemorrhage regardless of anticoagulant use. The use of warfarin therapy did not prove to be more harmful than no therapy in elderly or frail patients with atrial fibrillation according to these studies. Similarly, the risk of hemorrhage associated with warfarin did not vary statistically between age groups.
Additional research is necessary in order to develop prescribing guidelines with regard to advancing age/frailty and warfarin therapy. These studies would be most effective as randomized controlled trials without funding from drug-associated companies, which would limit physician bias in warfarin non-prescriptions for the very frail or very old and reduce the potential for study bias.

Anticoagulation with warfarin has been proven to significantly reduce the risk of stroke. While placing an individual on anticoagulants poses potential risk for increased bleeding, the benefit of stroke prevention outweighs the risk. Regardless of prescribing guidelines, it is imperative that warfarin be prescribed and monitored carefully in all age ranges in order to provide the most effective prevention of embolic stroke while minimizing the risk of hemorrhage and other deleterious effects.
REFERENCES


TABLES

Table 1 – CHADS² Score and Interpretation

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Event Rate (Per 100 Person Years, 95% CI)

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CHADS² Score Data from Go et al⁷

Table 2 – Validity Score

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Table 3 – Article and Results Summary Matrix

| Author with Citation | Study Date | Number of Participants | Duration (Median) | Average Age | Warfarinised vs. Non-Warfarinised of Varying Age | All Warfarinised of Varying Age | All Warfarinised vs. All Elderly | Frail vs. Non-Frail with Subgroups of Warfarinised vs Non-Warfarinised Warfarin Prescriptions | Warfarin Use or INR Use | Hemorrhage Risk | Stroke Risk | Death Risk | Stroke Risk | Stroke Risk | Hemorrhage Risk | Hemorrhage Risk | INR Instability | Validity* Score |
|----------------------|------------|------------------------|-------------------|-------------|-----------------------------------------------|-------------------------------|---------------------------------|--------------------------------------------------------------------------------------|---------------------------------|----------------|-------------|------------|-------------|-------------|-------------|----------------|----------------|----------------|----------------|
| Fang et al14          | 1996-1999  | 13 559                 | 2.4 Years         | 71          |                                               |                               |                                 |                                                                                        |                                 |                |             |             |             |             |             |                |                |                | 7/8           |
| Copland et al10       | 1998-1999  | 328                    | 21 Months         | 64.7 vs 78.3|                                               |                               |                                 |                                                                                        |                                 |                |             |             |             |             |             |                |                |                | 6/8           |
| Johnson et al11       | 2001-2001  | 235                    | 28 Months         | 81.1        |                                               |                               |                                 |                                                                                        |                                 |                |             |             |             |             |             |                |                |                | 4/8           |
| Perera et al12        | 2007       | 220                    | 6 Months          | 82.7        |                                               |                               |                                 |                                                                                        |                                 |                |             |             |             |             |             |                |                |                | 7/8           |

*Validity Determination (One Point Each, Total/6): Patient Population >100, Study Duration > 6 Months, > 1 Study Group, Inclusion of Statistical Analysis, Inclusion of withdrawals/dropouts, No Drug Company Funding

Symbol Key:
- No, Not Significant
- Significant Decrease
- Non-Significant Decrease
- Significant Increase
- Non-Significant Decrease
Figure 1 – Article Selection for this Systematic Review

Records identified through database searching (n = 137)

Additional records identified through other sources (n = 8)

Records after duplicates removed (n = 122)

Records screened (n = 31)

Records excluded (n = 14)

Full-text articles assessed for eligibility (n = 17)

Full-text articles excluded (n = 13)

Reasons:
- Not focused on Elderly (7)
- Not focused on AF (3)
- First stroke patients only (1)
- Patients with mechanical valves (1)
- Patients following AF procedures or surgeries (1)

Studies included in Systematic Review (n = 4)