

Complications of Warfarin Therapy in Older Adults: A Review

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Citation

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Abstract

Atrial fibrillation prevalence increases with age and is the most common arrhythmia in clinical practice.² Approximately half of patients with atrial fibrillation in the United States are over the age of 75 years of age. Due to aging of the general population, the number of patients aged 80 years and older are increasing.³ Warfarin, a vitamin K antagonist, is the most effective antithrombotic available for stroke prevention associated with atrial fibrillation but has been associated with risk of hemorrhage. Warfarin is the second most common cause of adverse drug events in emergency departments, and the overall risk of major bleeding averages 7-8% per year.⁴ Recent randomized-control trials conducted to identify the risks of bleeding complications of warfarin therapy in the older, frail, vulnerable adult support the net benefit of warfarin anticoagulant therapy for older adults with atrial fibrillation.

BACKGROUND

Warfarin, a vitamin K antagonist, is the most effective antithrombotic available for stroke prevention associated with atrial fibrillation.² Warfarin use increased from 28% during 1992 to 41% in 2000. The greatest increase in incidence of atrial fibrillation occurred in patients age 80 years and older.⁵ Despite the evidence supporting the use of warfarin for stroke prevention in patients with atrial fibrillation, clinicians may be reluctant to prescribe this agent to older patients.¹ Many factors have been identified that have resulted in reduced initiation of warfarin therapy. The chief concern for elderly patients taking warfarin is risk of intracranial hemorrhage.⁶ Intracranial hemorrhage is the most feared site for hemorrhage associated with warfarin therapy, because patients rarely recover.⁵ Studies have shown a tendency toward a higher bleeding risk in the elderly population but disparity exists between the rates of hemorrhage reported in clinical trials and clinical practice.^{1,7,8} Several reviews regarding use and complications of warfarin for prevention of stroke atrial fibrillation in older adults have been published.⁹ However, limited studies have been done with the oldest old, 80 years and up. The information yielded from these studies is limited and reduces generalizability.

AIM

This review of the literature was conducted to identify the

risks of bleeding complications of warfarin therapy used for stroke prevention in adults greater than 80 years with atrial fibrillation. Evidence from this review can be used as a guide for clinical practice and future research for this frail, vulnerable population.

METHOD

Pub Med, Scopus and Cochrane Library databases were searched using the terms “warfarin and atrial fibrillation and risks”, “atrial fibrillation”, “warfarin”, “complications OR risks” and “aging OR elderly” limited to English language, published from 1966, when Pub Med started. Citation article titles and abstracts were reviewed. Full text articles were obtained if they met the criteria. Studies comparing warfarin to other antithrombotics were excluded as they pertained to efficacy of treatment rather than complications of warfarin. Case studies, commentaries and editorials were also excluded.

SELECTION OF STUDIES

The databases were searched using the relevant terms. In the Cochrane Library, 121 citations were identified with the keyword searches listed above. From these searches one systematic review was identified providing a comprehensive review of randomized controlled trials (RCTs) evaluating oral anticoagulants for preventing strokes in patients with atrial fibrillation. Aguilar reviewed five RCTs involving older adults.⁹

In Pub Med, using search terms “warfarin” AND “atrial fibrillation/drug therapy, limits of “Aged 65+ years”, “clinical trial, meta-analysis, practice guideline, randomized controlled trial, review, multicenter study, English text from 1966, 122 studies were found. Articles were rejected if titles indicated drug studies or comparisons, economics of treatment, opinions, or commentaries. Seventeen articles were retrieved.

In Scopus, using search terms “atrial fibrillation and warfarin and complications or risks” and “aging or elderly” limited to English language, 356 articles were found. Articles were rejected unless they were specifically related to complications of warfarin therapy. Editorials and opinions were excluded. The Cochrane systematic review was considered the starting point of the literature review.¹ All articles predating this review were eliminated. Ten publications met the study criteria.

FINDINGS

The final sample of articles included 11 reports reflecting 15 studies. These studies represented 45,487 patients in seven countries, mostly from the United States, Australia and Great Britain. Table 1 summarizes selected studies that provide separate data on the occurrence of bleeding complications. The systematic review contained RCTs. All other designs were cohort studies, 7 were prospective studies and the remaining were retrospective cohort studies. One cohort study was a secondary analysis from a large cohort study. Heterogeneity existed in sample size, population and outcome measures. The most common threat to internal validity was selection bias as the patients were selected for warfarin by the referring physician.

The five RCTs reviewed by Aguilar, focused on primary prevention of stroke in patients with atrial fibrillation. Patients with prior history of stroke or transient ischemic attack (TIA) were excluded.⁸ The mean age of the 2313 sample was 69 years with 20% of participants over 75 years. The participant characteristics were homogeneous. All trials excluded patients with perceived contraindications to warfarin therapy. Study-affiliated investigators managed all warfarin therapy. Four of the trials were terminated earlier than planned when analyses revealed greater than expected efficacy or oral anticoagulation. The risk of intracranial hemorrhages (seven) was insignificant. Risk of extracranial hemorrhage was also insignificant but confidence intervals were wide due to the small number of events. Close standardized outpatient monitoring may have contributed to

the low rate of bleeding complications. Also, a longer trial may have impacted on overall risk of complications. A “healthy user” effect may have confounded the results. Generalizability to older, frail adults is limited.

INPATIENT STUDIES

Two studies included an inpatient sample of older adults. Perera identified 207 patients diagnosed with atrial fibrillation with a mean age of 82.7.¹ The sample was divided into 3 arms, those treated with warfarin, other anticoagulant and no anticoagulant. Each arm consisted of a subgroup of frail and non-frail participants. Three and six months after enrollment, participants were contacted by phone to report any complications. During hospitalization, prescription of warfarin to frail patients decreased by 10.7% and prescription of warfarin to non-frail patients increased by 6.3%. Analysis of the sub-groups revealed that the incidence of major hemorrhage over 6 months was 20 % (23% in the frail group and 16.9% in the non-frail group) which is the highest reported for a study of elderly with atrial fibrillation. Risk of complications was highly associated with frailty in this study. The high rate of complications may be due to their acutely ill and post hospitalization status. Also, the reliability and validity of the outcome data may be affected by self-report and memory.

Gage et al., conducted a retrospective review using the National Registry of Atrial Fibrillation II dataset created from 23657 anonymous patient records gathered by Quality Improvement Organizations for the National Stroke Project.¹⁰ Medical records from all Medicare beneficiaries who were hospitalized and coded for atrial fibrillation were selected randomly and stratified by state. The samples consisted of 1245 patients (mean age 83) with high risk of falls documented by their physicians in the medical records, 18261 (mean age 79) who did not have a documented fall risk and a “trial-like” sample of 3236 (mean age 73) who were younger and healthier. Thirty-three percent of the fall risk patients received warfarin at discharge compared to 48.9% on non-fall risk patients and 54% of the trial-like patients. The primary endpoint was subsequent hospitalization for an intracranial hemorrhage, based on hospital coding. The rates of intracranial hemorrhage were 2.8% in patients at high risk for falls, 1.1% in non-fall risk patients and 0.53% in trial-like patients. The large, national sample size provides greater generalizability. A limitation of this study is the possibility of incomplete records. Incomplete or inaccurate physician documentation that determined patients’ fall risk may also affect reliability.

Despite the rate of complications, the study authors support the use of anticoagulants in patients at high risk for falls that are at moderate to high risk of stroke but not in patients at high risk of fall but with low risk of stroke.

Burton et al. also conducted a retrospective review of 601 patients previously identified as having atrial fibrillation by their primary physicians.¹¹ Patients were selected by “invitation” to have their data reviewed. These data included baseline characteristics, strokes, bleeding events and international normalized ratio (INR) results. The cohort was divided into 2 subgroups: <75 and >75 years of age. Average patient age was 77 years. Both patients groups were within target INR range 68% of the time while treated with warfarin. Annual rates of severe bleeding complications and all bleeding complications on warfarin were 2.6% and 9% respectively. The incidence of severe bleeding was higher in those > 75 (10.1%) than those < 75 years (8.2%). Lost or missing data and the fact that all patients in this study were previously on warfarin may affect reliability of the findings. Also, the study lacked reports of minor bleeding complications which could have skewed the results.

INITIATION PHASE OF WARFARIN

Two studies were conducted to determine the incidence of complications in older people in the initiation phase of warfarin. Johnson et al. conducted a retrospective cohort study (n=228, mean age=81) in which patients were identified by computer-generated list of all patients hospitalized, aged 76 and with a discharge diagnosis code of atrial fibrillation and those dispensed warfarin by the hospital pharmacy during the admission.¹² Questionnaires were sent to determine reasons for starting and stopping warfarin, and to determine any bleeding episodes or strokes. The primary author followed up with a phone call for completion. Additional information was obtained from family, hospital medical records and primary physicians. The mean length of warfarin treatment was 27.9 months. Fifty-six percent started warfarin during the hospital admission. Eighteen percent of the cohort experienced major hemorrhage during warfarin treatment. Thirty percent of the cohort died within the study period which is representative of the level of frailty of this cohort. The annual event rate of major hemorrhage was 10%. The annual rate of life-threatening and fatal hemorrhage was 4.5% and 0.9% respectively. The high hemorrhage rate could be multifactorial. All patients in the sample were hospitalized indicating a sicker cohort. Warfarin was initiated in 56% of the patients regardless of the presence of contraindications.

These patients would typically be excluded from other studies.

Hyek et al. conducted a prospective cohort study to define the rate of major hemorrhage in patients in the initiation phase of warfarin and define the risk of bleeding in the early phase of therapy.¹³ The sample of 472 (mean age 72) were outpatients referred to the anticoagulation clinic and divided into age groups of > 80 years and < 80 years of age. Patients were followed through the first year of warfarin therapy. Use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDS) was recorded. During the study, participants were within desired international normalized ratio (INR) range of 2- 3 58% of the total time on warfarin. The rate of major hemorrhage was 7.2% and rate of intracranial hemorrhage was 2.5%. Patients >80 years of age experienced higher rates of major bleeding compared with younger patients (13.08 versus 4.75 per 100 person years, which is significant at P=0.010. Risk of hemorrhage was increased when INR was greater than 4.0 and within the first 90 days of therapy. The higher incidence of hemorrhage could be explained by the advanced age of the sample and the restriction to patients in the initiation phase of warfarin. The zero attrition rate and accurate documentation of patient use of aspirin and NSAIDS reduces confounding of the study. Generalizability to the long term care setting is limited as patients in the long term care setting were excluded from the study.

ANTICOAGULATION CLINIC MONITORING

In six studies, anticoagulation levels were monitored in designated anticoagulation clinics which likely contributed to tighter anticoagulation control resulting in a lower number of bleeding events. Poli et al. conducted two prospective studies.^{14,15} A 2007 study involved 290 patients (mean age 82) who were referred to an anticoagulation clinic. The sample was divided into groups as follows: 75-79 years, 80-84 years and 85-96 years. Two hundred fifty-one patients were newly started on warfarin. A computerized program monitored the INR. Comorbidities were assessed with patient interview and hospital records. Follow-up appointments documented warfarin dose, INR, other illnesses, hospital admissions and bleeding thrombotic events. The INRs were maintained at the therapeutic range of 2-3. Time spent within the therapeutic range of INR was 69%. The rates of total major bleeding were 1.4, 2.6 and 3.6 in the 3 groups respectively. Rate for cerebral bleeding was 1.35 for 100 patient years. Although these differences were not statistically significant, risk of bleeding increased with older age. The median INR related to bleeding events was

2.5. A higher risk of bleeding events was found in patients with diabetes. Complications of diabetes or medication prescribed for diabetes could be a factor due to the potential interactions with warfarin that may potentiate bleeding risk.⁴ The low statistical power and the single clinic setting limit the study's generalizability.

Poli et al. conducted another prospective study consisting of 783 nonvalvular atrial fibrillation patients who were referred for oral anticoagulation management to the anticoagulation clinic.¹⁵ The study was conducted from June 1998 to December 2007. The median age was 75 years and 180 patients were 80 years and older. All patients were treated with warfarin with goal INR as 2 to 3. Warfarin dose was adjusted by using a computer-assisted prescription system. Patient interview, echocardiography results and hospital records provided patients' demographic and clinical data. Patients spent a median of 14%, 71% and 15% of time below, within, and above the desired therapeutic range with no statistical significance between patients age <80 years and > 80 years old. During the study, 83 patients died, 9 from hemorrhagic complications. Forty-five of these patients were > 80 years old. Ninety-four patients suffered from bleeding complications: 37 major and 57 minor. The INR related to bleeding events was <3 in 67.5% of patients, between 3 and 4 in 19% in patients and > 4 in 13.5% of patients. Notably, major bleeding occurred at a median time of 36 months. Patients who were >80 years old with a history of previous ischemic event were associated with bleeding risk. History of hypertension or previous hemorrhage was not found to be associated with increased risk of bleeding which was presumed to be due to good blood pressure control in this sample. The authors of these two studies concluded that bleeding risk associated with warfarin administration is acceptably low in a clinic-monitored setting when anticoagulation levels are closely monitored. A strength of this study is the lengthy duration since major bleeding time occurred at a median time of 36 months. Studies that involve a shorter follow-up period may not accurately reflect bleeding complications.

Tincani et al. conducted a prospective cohort study (N = 90, Mean age 91.7) to assess the bleeding rates of extremely elderly patients with atrial fibrillation and examine risk factors that might predict bleeding.¹⁶ All patients were enrolled during an ambulatory visit and followed for one year by the anticoagulation clinic. Patients enrolled had been on warfarin therapy for an extended period at time of enrollment. During clinic visits, parameters were obtained

including INR, warfarin dose, history of other illness, hospital admissions and self-reported hemorrhagic and thrombotic events. Additional information was obtained from family, primary physician, hospital records and the laboratory as needed. Time spent within the therapeutic INR range of 2.5 was 66%. Potentially interacting medications were mentioned in the study. Two patients had intracranial hemorrhage and one patient had a minor hemorrhagic stroke (INR was 4.8 on day of the event). Two patients had major extracranial hemorrhage. Sixty-five percent of patients reported at least one bleeding episode. The author concluded that despite the elderly frail sample, risk of life-threatening bleeding was low and warfarin can be used to safely treat extremely elderly patients. Notably, the fatal hemorrhage was associated with an extremely high INR. Limitations in this study are the small sample size. Also, these patients had already passed the high risk initiation phase of warfarin which may explain the low rates of bleeding.

Torn et al. had similarly low bleeding rates in this three year retrospective cohort study n=4202 and were subtyped as follows: <60 n=842, 60-7- n=1200, 71-80 n=2742 and >80 n=1114.⁷ The sample was selected from the Leiden Anticoagulation Clinic in the Netherlands. Follow up appointments involved gathering information regarding adverse events, hospital admissions, concurrent illness and blood sample for INR was collected. Data were also collected from hospital admissions, discharge summaries and autopsies. Outcomes were judged by a panel of experts who were blinded for the INRs. Time spent within therapeutic range (INR 3.0) declined slightly as patient age increased. Major bleeding incidence rose gradually with increasing age from 1.5% in those <60 to 4.2% in those > 80 years old. The incidence rate of fatal hemorrhage was consistent (0.3) for all age groups except those < 60 who had the lowest rate (0.1). The author mentions that the anticoagulation clinic as a study eliminates selection bias. However, inherent selection bias does occur as the patients were prescreened by the referring physician to initiate warfarin therapy. Knowledge of the percentage of individuals on long term warfarin therapy prior to the start of the study would also provide some explanation of the lower bleeding risks in this study.

SECONDARY ANALYSIS

Finally, Fang conducted a secondary analysis using data from the large Anticoagulation and Risk Factors In Atrial Fibrillation (ATRIA) study to assess whether older age is associated with risk of bleeding complications in patients

with atrial fibrillation.⁷ The patients in this cohort received care within Kaiser Permanente of Northern California, a large integrated healthcare delivery system which allowed the investigators to identify hemorrhagic events even if they occurred at non-Kaiser Permanente medical facilities. Hospital and billing databases were searched using data from the ATRIA (n=13559) for primary and secondary discharge diagnoses of intracranial or extracranial hemorrhage. Complications resulting in hemorrhage were excluded. A specialized committee reviewed the records using a formal study protocol. The sample was divided into 2 groups, on or off warfarin, which were then divided into 4 age-specific categories (mean age 71) and followed for median of 2.4 years. Twenty-nine percent of the cohort was in the initiation phase of warfarin. The rate of intracranial and extracranial hemorrhage during the first month on warfarin was 0.92% and 1.2% respectively compared with 0.46% and 0.61% after the first month. Further analysis revealed a relative increase in the rate of hemorrhage with aging. The rate of intracranial hemorrhage remained relatively flat from age 60 to 80 and then increased sharply at 80 whether or not on warfarin. Generalizability exists in this large sample that included the oldest old. Also, study outcomes could be confounded by missing warfarin exposure and INR data. However, the majority of warfarin users were past the initiation phase of warfarin which may have affected the reliability of bleeding rates. In addition, data were not available on use of aspirin or NSAIDS because these agents are non-prescription and not recorded in the pharmacy database.

Figure 1

TABLE 1 Risk of Complications in Elderly with Atrial Fibrillation Treated with Warfarin

| Author | Purpose of Study | Design | N Mean Age (X) | Bleeding Complications | Comments |
|--|---|--|---|---|--|
| Poli, D. et al (2009) | To evaluate the rate of bleeding in relation to age (<60 and >80 years, the quality of anticoagulation and factors associated with bleeding events | Prospective cohort | N=783 X=75 | Increased in patients > 80 | Large sample size No patient lost to follow-up Possibility of selection bias as more frail patients unlikely to be referred to outpatient service |
| Peters, V. et al (2009) | Investigate the impact of frailty on the utilization of antithrombotic therapy in older patients with atrial fibrillation | Prospective cohort | N=207 X= 82.7 | 20.8% over 6 months | Baseline data from interviews/reccalls/telephone report could pose bias Generalizable due to adequate sample size of frail elderly population |
| Tincani, E. et al. (2009) | To determine bleeding rates in patients older than 90 years of age on vitamin K antagonist therapy for nonvalvular atrial fibrillation | Prospective cohort | N=90 X= 91.7 | 1% per year | Small sample size Patients enrolled already on warfarin and past the highest risk of complications Anticoagulation clinic |
| Poli, D. et al. (2007) | The risk of bleeding in very old atrial fibrillation patients on warfarin | Prospective cohort | N=390 X= 82 | Increased in patients >85 and in patients rated at high risk for stroke | Elderly adult sample Standardized measurements Small sample with decreased power All patients referred= possible selection bias |
| Hyek, E. et al. (2007) | To define the rate of major hemorrhage in patients at warfarin initiation and to define the risk of bleeding in the early phase of warfarin | Prospective cohort | N=472 X= 77 | 7.2% per year >80 higher rate of bleeding | Advanced age sample Findings limited to single academic setting Long-term care patients excluded Anticoagulation clinic |
| Burton, C. et al. (2006) | Compare the complication rates and adequacy of warfarin fibrillation in primary care | Retrospective cohort | N=601 X= 77 | 6.57% per year | Large sample, community based increases generalizability Sample selection could be affected due to "invitation" method and lost data Lacked report of minor bleeding complications |
| Fang, M. et al. (2006) | Is older age independently associated with risk of intracranial hemorrhage in patients with nonvalvular atrial fibrillation? | Retrospective cohort Secondary analysis | N=13559 X= 71 | 0.47% per year on warfarin 0.29% per year off warfarin | Large sample of older adults Missing warfarin exposure and INR data may confound results No data available on use of anti-inflammatories or aspirin |
| Gage, B. et al. (2005) | Incidence of intracranial hemorrhage in patients with atrial fibrillation who are prone to fall | Retrospective cohort | High risk: N=1245 Other pts: N=1261 Trial-like: N= 3236 High risk - X= 83 Other pts - X= 79.3 Trial-like - X= 73 | 2.9% per year-high risk 1.1% per year-other patients 0.53% per year-Trial-like patients | Large random stratified sample Multiple sample strengthened hypothesis Central data center Questionable reliability of data based on physician documentation regarding "falls" |
| Tom, M. et al. (2005) | Risk of oral anticoagulant therapy with increasing age | Retrospective cohort | N=4202 total <80 n= 842 60-70 n= 1200 71-80 n= 2742 >80 n=1114 | <80 1.5% per year 60-70 2.1% 71-80 2.5% >80 4.2% | Large sample, generalizable Blinded INRs Selection bias (MD selected) Target INR higher than most Anticoagulation clinic |
| Johnson, C., Lim, W., Workman B (2005) | The rate of major hemorrhage and stroke is more than 100 patient-years of follow-up | Retrospective cohort | N=228 X= 81 | 10% per year | Small sample Patients not pre-screened Representative of frail sample Data obtained from primary author strengthens reliability Longer trial period may contribute to higher complication rate |
| Aguiar M., Hut, R. (2005) | Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks | Cochrane Collaboration Systematic review | N=2313 X= 69 | Not significant | Younger, healthier sample decreases generalizability to older, frailer cohort Early termination Low bleeding rates may reflect patient selection |

DISCUSSION

Overall, consistent evidence is found of increased risk of bleeding on warfarin with advanced age. Despite these findings, study conclusions continue to support use of warfarin for stroke prevention with atrial fibrillation in the elderly. Variations of bleeding complications among the studies could be attributed to variable INR target ranges and time spent in the therapeutic range. The incidence of intracranial hemorrhage is directly related to INR intensity which significantly increases above an INR of 3.5.¹⁷ Also, the first 3 months of warfarin treatment are associated with

higher risk of bleeding.¹⁸ The question is whether the risk increases with prolonged exposure to warfarin especially in the vulnerable frail elder. A vascular factor may partly explain the higher incidence of bleeding in this group. Elderly patients have a higher prevalence of leukoaraiosis and cerebral amyloid angiopathy as well as gastric lesions that predispose them to a higher risk for intracranial and extracranial hemorrhage.¹⁸ Clearly, warfarin's narrow therapeutic margin is a factor when treating elderly patients.

Several strengths were identified across the studies review. Cohort patient samples were homogeneous and included "control" groups off warfarin. All of the studies included detailed methodology and statistical analysis. Disclosure of financial support was provided as applicable. The studies were international and conducted in various settings. Those cohorts managed in anticoagulation clinics had lower rates of bleeding complications which likely is associated to good quality of control. Some studies encouraged use of a risk stratification tool to assess appropriateness of warfarin therapy.

Despite the strengths, variance in the bleeding complications outcome could be attributed to duration of the studies, length of time the patient exposed to warfarin and whether the patient is past the initiation phase of treatment. Also, concomitant use of medications may also have a confounding effect on bleeding risks. Questions remain regarding the safe use of warfarin in the elderly. Better understanding is needed to understand risk factors related to patient characteristics.

CONCLUSIONS

The evidence supports the net benefit of anticoagulant therapy for older adults with atrial fibrillation. Although RCTs are considered the gold standard in evidence-based research, the cohort studies described here provide more generalizability to actual practice settings. Rates of hemorrhage in clinical trials may not reflect those experienced in the community setting. Clearly, elderly patients present more of a challenge in managing warfarin therapy due to tendency of polypharmacy, alterations in pharmacokinetics associated with aging, co-morbidities and increased risk of hemorrhage. Both treatment-specific and patient-specific factors must be assessed when estimating the risk of hemorrhage in an individual patient. In the oldest old, indication for continued warfarin treatment should be frequently evaluated. The advanced practice nurse has an essential role on the interdisciplinary team, in part by

providing much needed education to patients on warfarin therapy. Evidence supports that patient education reduces risk of complications during treatment.

Researchers should conduct further studies to develop better scoring systems to assist clinicians to better estimate the risk of bleeding complications. Continued studies to develop newer antithrombotic are also needed. Research in pharmacogenomics of anticoagulation will assist providers in decision-making regarding appropriateness of warfarin therapy and aid in successful dosing. As the number of elderly patients with atrial fibrillation increases, establishment of safe anticoagulation is required.

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