Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

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Objective: To determine whether the risk of falling (with a possible increased chance of subdural hematoma) should influence the choice of antithrombotic therapy in elderly patients with atrial fibrillation.

Design: A Markov decision analytic model was used to determine the preferred treatment strategy (no antithrombotic therapy, long-term aspirin use, or long-term warfarin use) for patients with atrial fibrillation who are 65 years of age and older, are at risk for falling, and have no other contraindications to antithrombotic therapy. Input data were obtained by systematic review of MEDLINE. Outcomes were expressed as quality-adjusted life-years.

Results: For patients with average risks of stroke and falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient; aspirin therapy, 11.17 quality-adjusted life-years; and no antithrombotic therapy, 10.15 quality-adjusted life-years. Sensitivity analysis demonstrated that, regardless of the patients' age or baseline risk of stroke, the risk of falling was not an important factor in determining their optimal antithrombotic therapy.

Conclusions: For elderly patients with atrial fibrillation, the choice of optimal therapy to prevent stroke depends on many clinical factors, especially their baseline risk of stroke. However, patients' propensity to fall is not an important factor in this decision.

Arch Intern Med. 1999;159:677-685

Approximately 5% of persons 65 years of age and older have atrial fibrillation. Their average yearly risk of stroke is 5%, and this risk is increased in the presence of certain risk factors, including left ventricular dysfunction, hypertension, a history of stroke, and increasing age. Long-term antithrombotic therapy with warfarin or aspirin reduces these patients' chance of stroke by 68% and 21%, respectively. There is no convincing evidence that these relative risk reductions vary according to patients' baseline chance of stroke. Therefore, among all age groups, elderly persons receive the greatest absolute benefit from warfarin or aspirin prophylaxis. In fact, an expert panel recommended that all elderly persons with atrial fibrillation should be considered for long-term warfarin therapy unless a contraindication exists.

Balanced against this benefit is the risk of antithrombotic-associated, life-threatening bleeding complications, including subdural hematomas and intracerebral hemorrhages. These complications also increase with age. Trauma to the head (often due to falls) may also be an etiologic factor in the development of SDHs. For this reason, many studies evaluating the effectiveness and appropriateness of warfarin therapy in patients with atrial fibrillation have excluded subjects with a predisposition to falls. Also, other studies have implicated aspirin use as a risk factor for development of SDHs in patients with head trauma. Thus, many physicians are reluctant to prescribe antithrombotic therapy (especially warfarin) for elderly patients with atrial fibrillation whom they deem at risk for falls.

The objective of this decision analysis was to compare the benefits and risks of antithrombotic therapy (either warfarin or aspirin) in community-living, elderly persons with atrial fibrillation based on their risk of falls.

RESULTS

Of 190 relevant scientific studies reviewed, 49 met the inclusion criteria. Intracranial hemorrhages (both SDHs and intracerebral hemorrhages) were exceedingly uncommon events in prospective cohort studies.
METHODS

THE DECISION MODEL

A decision analytic model was constructed to describe the possible outcomes of 3 different treatment strategies for elderly persons with atrial fibrillation who may be at risk for falling: (1) warfarin therapy, then switch to aspirin in the event of a nonfatal, non–central nervous system (non-CNS) major bleeding episode; (2) aspirin therapy, then switch to warfarin in the event of a transient ischemic attack or reversible ischemic neurologic deficit; and (3) no treatment, then switch to aspirin in the event of a transient ischemic attack or reversible ischemic neurologic deficit. An age-specific standardized mortality table was used to model the chance of all-cause mortality. Outcomes were expressed in terms of quality-adjusted life years (QALYs) for patients 65 years of age at the starting point of the analysis. All life-years were discounted at the rate of 3% per annum.

Markov subtrees with identical structures were used to model the chance events associated with the 3 treatment strategies (Figure). Probability of each event was based on a systematic review of the published literature. The Markov cycle length was fixed at 3 months, with all relevant probabilities and utilities adjusted to reflect this cycle length. Results of the analysis were reported for a 1-year period.

OUTCOMES

The 5 states considered in the analysis were based on the work of Gage et al in describing disability states after stroke:

1. Well: the state for patients who had no adverse events such as stroke, intracranial hemorrhage (SDH and intracerebral hemorrhage), and major non-CNS bleeding. The well state was the starting point for all patients;
2. Minor disability (modified Rankin Scale score 1 or 2 stroke): mild residual neurologic deficit (eg, mild right-sided arm and leg weakness but remaining essentially functionally independent);
3. Moderate disability (modified Rankin Scale score 3 or 4 stroke): moderate neurologic deficit (eg, right arm and leg weakness sufficient to require assistance for some functional activities, including bathing and dressing, but having independent ambulation with a walker or cane);
4. Major disability (modified Rankin Scale score 5 or 6 stroke): severe neurologic deficit (eg, total paralysis of the right arm and leg requiring almost total care with functional activities, including help with ambulation and feeding); and
5. Dead.

INPUT DATA

Search Strategy

Relevant data for input variables were gathered by performing a systematic literature search using the MEDLINE (1966 to August 1996) computerized database. Relevant articles were identified by using the following key words: accidental falls, anticoagulants, cerebral hemorrhage, subdural hematoma, aspirin, warfarin, cerebral hematoma, atrial fibrillation, outcome assessment (health care), treatment outcome, prognosis, and risk factors. The bibliographies of each article were hand searched to identify additional articles. Content experts were also consulted to identify other relevant published work.

Development of Article Inclusion Criteria

After initial review of the methodologic quality of studies available to estimate input variables, general criteria were developed for inclusion of studies into the decision analysis (Table 1). The appropriate set of criteria was applied to each article by 2 individuals (M.M.-S.-H. and A. Lau), with any disagreements settled by collaborative review.

Data Extraction and Pooling of Results

For each input variable, we extracted relevant information from each study that met the inclusion criteria. We preferentially sought data pertaining to persons 65 years and older. Point estimates for input variables were determined by arithmetic pooling of the results from all studies that met the inclusion criteria. Data extraction was performed independently by 2 individuals (M.M.-S.-H. and A. Lau), with any disagreements settled by collaborative review.

STROKE

Probability of Events

The meta-analyses2,3 (pooling of individual patient data from 5 randomized controlled trials) of the Atrial Fibrillation Investigators (AFI) were used to estimate the probability of stroke in elderly patients with atrial fibrillation who received no therapy, aspirin, or warfarin. Because the AFI did not specifically publish data for subjects 65 years of age and older, we requested and received this information from the investigators. Based on approximately 2000 patient-years of follow-up, the annual stroke rate was 6% for patients receiving no therapy. From the AFI meta-analyses,2,3 aspirin and warfarin provided 21% and 68% relative risk reductions, respectively.

The annual risk of persons having a transient ischemic attack or reversible ischemic neurologic deficit was assumed to be one third the rate of stroke for all groups.2 For persons having a stroke (either minor or major), their subsequent relative risk of having a second stroke was estimated at 3.1 times their prestroke rate.2

Outcomes

For persons having a stroke, the proportions who had fatal, major, or minor strokes were also estimated...
from the AFI data. The AFI classified stroke as follows: (1) fatal stroke, if the patient died within 1 month of occurrence of the stroke; (2) major stroke (corresponding closely to Rankin score 3-5); and (3) minor stroke (corresponding closely to Rankin score 1-2). With no firm evidence that the chance of suffering a fatal stroke varies with the type of antithrombotic therapy used, patients suffering a stroke were assigned an average fatality rate as determined from all patients with stroke in the AFI studies. For major strokes, the proportion of patients with moderate disability (Rankin score 3) compared with major disability (Rankin score 4-5) was unavailable. For simplicity, patients having a major stroke were assigned a utility that was an average of the utilities of a moderate and major disability.

**SDH AND INTRACEREBRAL HEMORRHAGE**

**Probability of Events**

Too few SDHs and intracerebral hemorrhages occurred during the AFI studies to use these data to precisely estimate the probability of such events when receiving no therapy, aspirin, or warfarin. Therefore, for persons who do not fall, we estimated the probability of developing an SDH when receiving no treatment, aspirin, or warfarin were estimated from randomized controlled trials and anticoagulation clinic cohort studies, respectively. We again pooled results from population studies to estimate the probability of intracerebral hemorrhage when receiving no therapy, aspirin, and anticoagulation clinic cohort studies when receiving warfarin.

**Outcomes**

For persons with SDH and intracerebral hemorrhage, we were unable to determine the likelihood of different outcomes from the AFI data. Therefore, SDH and intracerebral hemorrhage fatality rates when receiving no therapy, aspirin, and warfarin were estimated by pooling...
studies that reported consecutive cases. For persons receiving aspirin at the time of their SDH or intracerebral hemorrhage, information about their outcomes was not available. Therefore, we assumed that their probability of fatality was identical to persons receiving no therapy.

For persons who survived SDHs and intracerebral hemorrhages, data pertaining to the severity of their residual functional disability were not available. Thus, we assumed that a moderate disability occurred in all persons who survived their SDH or intracerebral hemorrhage.

MAJOR NON-CNS BLEEDING

Probability of Events

The probability of major non-CNS bleeding in patients receiving no treatment, aspirin, and warfarin was estimated from the AFI data. The AFI analysis defined major bleeding as one requiring blood transfusion, an emergency procedure, surgical intervention, or hospitalization. For simplicity, minor bleeding episodes (eg, external bruising, nosebleeds) were not modeled.

Outcomes

In the AFI, too few deaths occurred from major non-CNS bleeding episodes to precisely estimate these fatality rates. For persons receiving no treatment or aspirin, data from the Antiplatelet Trialists’ Collaboration were used to estimate the proportion of those dying as a result of a major non-CNS bleeding episode. For persons receiving warfarin, we estimated the fatality rate from major non-CNS bleeding from anticoagulation clinic cohort studies. We assumed that all patients who survived a major non-CNS bleeding episode returned to their pre-event health state.

FALLS

Probability and Risk Factors

Seven cohort studies that met the eligibility criteria prospectively observed 2181 community-living, elderly (≥65 years of age) persons for their rate and consequences of falls. Thirty-three percent of these persons experienced at least 1 fall after 1 year of follow-up. Tinetti and colleagues identified 6 major independent risk factors for falls: sedative use, cognitive impairment, disability of the lower extremity, palmar reflex, gait and
balance abnormalities, and foot problems. For persons with 1 risk factor, their chance of falling in 1 year was 19%; 2 risk factors, 32%; 3 risk factors, 60%; and 4 or more risk factors, 78%.

Relative Risk of SDHs in Persons Who Fall Compared With Those Who Do Not

The relative risk of SDHs in persons who fall was derived from the following information: 70% of elderly persons who develop an SDH have a history of head trauma, and 50% of SDHs due to head trauma are related to falls. Therefore, (a) 0.35 of SDHs are related to falls (50% of the 70% of SDHs due to head trauma); (b) 0.35 of SDHs are related to head trauma without falls (the remaining 50% of the 70% of SDHs due to head trauma); and (c) 0.30 of SDHs are unrelated to head trauma as ascertained by history and observation.

Given that one third (33%) of community-living, elderly persons fall in 1 year, and the rate of SDHs in elderly persons is 0.0004 for every patient-year, we calculated that the two thirds (67%) of the elderly population who do not fall in a year experience 67% of the SDHs related to (b) and (c) above: [0.67 × (b+c)] = 0.00017; and the one third (33%) of the elderly population who do fall in a year experience 100% of the SDHs due to (a) and 33% of (b) and (c) above: a + [0.33 × (b+c)] = 0.00023.

Therefore, the derived relative risk of developing an SDH in persons who fall compared with those who do not is 1.4 (0.00023/0.00017).

Outcomes

For adverse outcomes other than SDH, there were no data available to determine a possible etiologic role of falls in their occurrence and outcomes. Therefore, we assumed that the occurrence of falls does not affect the probability and outcomes of stroke, transient ischemic attack or reversible ischemic neurologic deficit, intracerebral hemorrhage, and major non-CNS bleeding.

UTILITIES

By interviewing 69 patients with atrial fibrillation, Gage et al determined utilities for disabilities associated with minor, moderate, and major strokes (Table 2). These utilities were assigned to the corresponding Markov states of mild, moderate, and major disability. Gage et al also determined utilities for long-term aspirin and warfarin use. By definition, the well state and death were assigned utilities of 1 and 0, respectively.

BASE-CASE ANALYSIS

The base-case analysis considered elderly persons with atrial fibrillation with average risks of stroke (6% per year) and falling (33% per year). The results showed that the quality-adjusted life expectancy for these patients was 12.90 years with warfarin therapy, 11.17 years with aspirin therapy, and 10.15 years with no therapy.

SENSITIVITY ANALYSES

Sensitivity analyses (Table 3) were performed to test the robustness of the results to changes in values of the base-case variables. We examined the influence of each throughout its entire reasonable range.

Sensitivity analysis showed that the values for variables related to SDH had little influence on the base-case scenario. For example, to switch the optimal choice of therapy from warfarin to no therapy, the relative risk of SDH must be at least 65-fold greater for persons receiving warfarin compared with those receiving no therapy. The probability of falls also had no influence on choice of optimal therapy. When the chance of falling in 1 year was varied from no chance (0%) to certainty (100%), warfarin remained the treatment associated with the highest QALYs. For warfarin to not be the optimal therapy, persons with an average fall risk must have a 535-fold greater risk of SDH compared with those who do not fall.

The results of the analysis were most sensitive to the probabilities related to intracerebral hemorrhage and non-CNS bleeding. If the probability of intracerebral hemorrhage was 12-fold or greater than our base-case rate of 0.001 cases per patient-year, then warfarin was not the preferred treatment option. Similarly, for warfarin to not be the preferred treatment option, the relative risk of intracerebral hemorrhage when taking warfarin compared with no therapy must be 29-fold or greater. Also, the base-case probability of major non-CNS bleeding when receiving no therapy must be 14-fold greater for warfarin to not be the preferred treatment strategy.

Varying the efficacy of aspirin and warfarin to prevent stroke affected the choice of optimal treatment. With the values of all other variables remaining constant, aspirin therapy was the preferred treatment choice if the efficacy of warfarin was reduced from 68% to 26%. Conversely, if the efficacy of aspirin was increased from 21% to 54% (all other values for variables remaining constant), it was the preferred therapy.

We also varied the values for utilities throughout their ranges. With values for all other variables remaining constant, warfarin was the preferred option when the utility of long-term warfarin therapy was 0.816 or higher. In the study by Gage et al, only 1 of the 69 patients who underwent formal utility assessment reported a utility score for long-term warfarin use of less than 0.92. The preferred treatment choice was insensitive to all other utilities throughout their ranges.

For patients with baseline stroke rates of less than 1.2% per year, no therapy was the preferred treatment option. If their baseline stroke rate was between 1.2% and 2.0% per year, aspirin was the preferred therapy. If their baseline stroke rate was greater than 2.0% per year, warfarin therapy was the preferred option. These results are compatible with the recent American College of Chest Physicians recommendations, which recognize that, as baseline risk of stroke diminishes, the absolute benefit of stroke prophylaxis provided by antithrombotic therapy (especially warfarin) also decreases. Thus, the appropriate antithrombotic therapy for individual patients depends on their baseline risk of stroke, with low-risk in-
individuals being less appropriate candidates for warfarin therapy.

According to the AFI data and the American College of Chest Physicians risk stratification scheme, all persons with atrial fibrillation who are 65 years of age and older have at least a 2% yearly risk of stroke. To determine the influence of falls on the choice of antithrombotic therapy in low-risk individuals, we repeated our analysis for those with this baseline risk of stroke. The results showed that warfarin was the preferred therapy (14.21 QALYs with warfarin, 14.17 with aspirin, and 13.98 with no therapy). At this low baseline risk of stroke, as one would expect, the preferred choice of therapy was very sensitive to variables related to SDH, intracerebral hemorrhage, non-CNS bleeding, and utilities (Table 3). However, even under these conditions,
the probability of falling did not influence the choice of optimal therapy.

Alternative Methods of Estimating the Rate of SDH, Intracerebral Hemorrhage, and Major Non-CNS Bleeding

A possible limitation of this study is the questionable accuracy of our estimates of the probability of SDH (when receiving no treatment, aspirin, or warfarin) in persons who do not fall. Because these estimates were derived from studies that did not exclude patients who fall, we may have overestimated the risk of SDH in persons who do not fall. Since the studies of AFI meta-analysis tended to exclude patients deemed at risk for falls, these data may more accurately reflect the probability of SDH in persons who do not fall. However, relatively few patients were enrolled in these trials, making precise estimation of the probability of SDH and intracerebral hemorrhage difficult from this source. We used AFI data in an attempt to confirm our base-case estimates of the probability of SDH and intracerebral hemorrhage in persons who do not fall. From the AFI data, we calculated the probability of SDH and intracerebral hemorrhage in patients taking warfarin as 0.0012 and 0.0028 per patient-year, respectively. These results were similar to our base-case estimates of SDH (0.0013 per patient-year; 95% confidence interval, 0.0008-0.0018) and intracerebral hemorrhage (0.0030 per patient-year; 95% confidence interval, 0.0022-0.0038). Substitution of AFI-derived values into the model had no significant impact on the analysis.

Similarly, an alternate method of estimating the rate of major non-CNS bleeding in persons receiving warfarin was derived using data from cohort studies of patients who attended anticoagulation clinics. Pooling the results from these studies produced a rate of 0.0176 major non-CNS bleeding events per patient-year (AFI rate, 0.0172 events per patient-year). Again, substitution of this value into the model resulted in no change in the choice of optimal therapy.

We also believed that the values for variables related to SDH in persons who fall and/or are taking aspirin or warfarin may be unreliable. To obtain alternative estimates for these variables, we surveyed 10 Canadian geriatric medicine specialists. Their subjective mean estimate of the relative risk of SDH in elderly persons who fall was 2.91 (95% confidence interval, 2.53-3.29) and 5.64 (95% confidence interval, 2.93-8.35) when taking aspirin and warfarin, respectively. These values were again substituted into the model and the analysis was repeated. No substantial effect on the results occurred with these substitutions.

Patients 75 Years and Older

Most clinicians perceive that the risk of warfarin- and fall-related SDH increases as elderly persons age. Certainly, the chance of falling and warfarin-related non-CNS bleeding increases as elderly persons age. Therefore, we repeated our analysis with the start age increased from 65 to 75 years. To estimate the risk of stroke in this population when following different therapies, we used AFI data pertaining exclusively to subjects 75 years and older (stroke rate when receiving no antithrombotic therapy was 8% per patient-year). For this age group, no specific data were available to estimate pertinent probabilities related to SDH, intracerebral hemorrhage, and major non-CNS bleeding. Therefore, compared with the base-case analysis, we arbitrarily tripled the estimated risks of these events. The results showed that, even under such unlikely conditions, warfarin therapy remained the preferred therapy (quality-adjusted life expectancy was 7.06 years with warfarin therapy, 6.52 years with aspirin therapy, and 6.76 years with no therapy).

A decision to prescribe antithrombotic therapy (either aspirin or warfarin) for elderly patients with atrial fibrillation balances the benefits of stroke prevention against the risk of adverse effects and inconvenience of the therapy. Many physicians assume that a combination of warfarin therapy and head trauma due to falls leads to an excessively high risk of SDH and choose not to prescribe warfarin for elderly persons with atrial fibrillation whom they deem prone to falling. We performed this decision analysis to ascertain whether this is reasonable clinical practice.

The base-case analysis and sensitivity analyses suggest that a history of and/or the presence of risk factors for falls should not be considered important factors in the decision whether to offer antithrombotic (especially warfarin) therapy to elderly patients with atrial fibrillation. In persons taking warfarin, fall-related SDHs are extremely infrequent. For elderly patients with atrial fibrillation with an average risk of stroke (6% per year), the chance of this complication is completely overshadowed by the benefit of stroke protection provided by warfarin.

Our results are consistent with previous studies examining the effectiveness of stroke prophylaxis in elderly patients with atrial fibrillation. In another decision analysis, Naglie and Detsky calculated a small net gain in QALYs with the use of warfarin over aspirin and no therapy. However, they overestimated the effectiveness of aspirin, which was not known at the time of their study. Gage and colleagues recently reported that warfarin is also cost-effective in this population. In general, our results agree with findings of earlier studies, with differences, if they exist, due to previously imprecise estimates of the efficacy of aspirin.

It is possible to calculate the number of falls that persons must have for warfarin to not be the optimal choice of therapy. Elderly persons who fall have a mean of 1.81 falls per year. Given that the risk of SDH must be 535-fold or greater for the risks of warfarin therapy to outweigh the benefits, persons taking warfarin must fall about 295 (535/1.81) times in 1 year for warfarin to not be the optimal therapy. Since approximately 1 in 10 falls causes major injury, including fractures, persons who fall are much more likely to suffer other serious morbidity before developing an SDH.

A major threat to the validity of this study is the possible inaccuracy of the input variables derived from the
literature. The sensitivity analysis showed that the base-case analysis was robust to all values for variables related to SDHs, falls, and warfarin therapy. Interestingly, this analysis was most sensitive to values related to intracerebral hemorrhage and major non-CNS bleeding. Our data suggest that warfarin-related intracerebral hemorrhage and major non-CNS bleeding episodes are more common events than warfarin-related SDH (with or without falls). The infrequency of SDH in patients who are receiving warfarin (whether they fall or not) accounts for the robustness of the analysis. However, even after perusing the results of this study, one may still wonder if fall-related SDHs are truly as rare as this analysis suggests. Further evidence supporting the rarity of fall-related SDHs comes from prospective cohort studies that examined the rate of falls and their outcomes in community-living, elderly persons. Pooling these studies (n = 6) showed that, from a total of 2590 falls, only 1 fall-related intracranial hemorrhage (0 intracerebral hemorrhage and 1 SDH) occurred. Why then do clinicians appear to overestimate the risk of and occurrence of fall-related SDHs? A likely explanation is that the occurrence of a fall-related SDH in elderly patients is a rare but dramatic event that clinicians easily remember.

Another potential source of error in this decision analysis is the possibility that the combination of warfarin therapy and falls may lead to adverse outcomes (other than SDH) for which we did not account. For example, do falls have an etiologic role in the development of intracerebral hemorrhage? Also, do elderly persons taking warfarin who have hip fractures experience excess morbidity and mortality? We were unable to identify published literature pertaining to these issues.

Two other notes of caution are appropriate. Clinically important factors such as recent serious gastrointestinal tract bleeding, alcoholism, nonsteroidal anti-inflammatory drug use, medication noncompliance, and improper monitoring of patients’ anticoagulation status increase the chance of warfarin-related serious bleeding. These factors were not studied in this decision analysis and must be considered in the clinical decision about whether to offer antithrombotic therapy to individual elderly persons with atrial fibrillation. Also, the values for stroke rates and subsequent outcomes used in this model were derived from randomized controlled trials during which subjects were observed more intensively than in usual clinical practice. Thus, in these trials compared with usual clinical practice, it is possible that the benefits and complications of antithrombotic therapy were overestimated and underestimated, respectively. Therefore, while the sensitivity analysis appeared robust, in-depth discussion with individual patients about the benefits and risks of antithrombotic therapy is still very important, and some caution may be necessary when applying the results of this study to usual care settings.

In summary, this study demonstrates that the risk of falling is not an important factor in the decision about whether to offer antithrombotic therapy to elderly patients with atrial fibrillation. Of all age groups with atrial fibrillation, patients 65 years and older gain the greatest absolute benefit from warfarin prophylaxis. Numerous studies have shown that many eligible patients with atrial fibrillation (especially older persons) are not being prescribed warfarin. Clinicians must realize that the propensity to fall is not a contraindication to the use of antithrombotic agents (especially warfarin) in elderly persons with atrial fibrillation.

Accepted for publication August 4, 1998.

We thank the Atrial Fibrillation Investigators for providing and Ruth McBride for tabulating unpublished AFI data. We also thank Robert Hart, MD, Brian Gage, MD, Ron Sigal, MD, and George Wells, PhD, for their helpful comments.

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REFERENCES


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24. Wintzen AR, de Jonge H, Loeliger EA, Bots GTA. The risk of intracerebral hemorrhage 
    16:553-558.
25. Wilberger JE, Harris M, Diamond DL. Acute subdural hematoma: morbidity, mortal- 
26. Jones NR, Blumberg PC, North JB. Acute subdural haematomas: aetiology, pa-
27. Fogelham R, Eskola K, Kimimkinen T, Kunnamo I. Anticoagulant treatment as a 
    risk factor for primary intracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 
28. Schuetz H, Dommer T, Boedecker R-H, Damian M, Krack P. Dorndorf W. Chang- 
    ing pattern of brain hemorrhage during 12 years of computed axial tomography. 
29. Portnoy RK, Lipton RB, Berger AR, Lesser ML, Lantos G. Intracerebral haemor-
    1987;50:976-979.
30. Broderick J, Brot T, Tomsick T, Tew J, Duldner J, Hister G. Management of in-
    tracerebral hemorrhage in a large metropolitan hospital. Neurosurgery. 1994; 
    34:882-887.
31. Akdemir H, Selcuklu A, Pasaoglu A, Canbay S, Kavuncu I. Management of pri-
32. Staf M, Nornberg B, Nilsson B. Intracerebral haematomas during anticoagulant 
33. Mattle H, Kohler S, Huber P, Rohner M, Steinsiepe IK. Anticoagulation-related 
    intracranial extracerebral haemorrhage. J Neurol Neurosurg Psychiatry. 1989; 
    52:829-837.
34. Diamond T, Gray WJ. Chee CP, Fannin TF. Subdural hematoma associated with 
36. Bewermeyer H, Hojer Ch, Schumacher A, Heiss W-D. Neurologische Komplika-
37. Ernestus RI, Speder B, Pakos P, Hildebrandt G, Klug N. Intracerebral hemor-
    rhage during treatment with oral anticoagulants: risk factors, therapy and prog-
38. Frideriksson K, Nornberg B, Stromblad L-G, Klug N. Emergency reversal of anti-
39. Kase CS, Robinson RK, Stein RW, et al. Anticoagulant-related intracerebral hemor-
40. Forsting M, Mattle HP, Huber P. Anticoagulation-related intracerebral hemor-
42. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: 
    incidence and prediction by factors known at the start of outpatient therapy. Am 
    J Med. 1989;87:144-152.
43. Gitter MJ, Jaeger TM, Peterson TM, Gersh BJ, Silverstein MD. Bleeding and throm-
    boembolism during anticoagulant therapy: a population-based study in Roch-
44. Maki BE, Holiday PJ, Topper AK. A prospective study of postural balance and 
    risk of falling in an ambulatory and independent elderly population. J Gerontol 
45. Campbell AJ, Spears GF, Borrie MJ. Examination by logistic regression model-
    ling of the variables which increase the relative risk of elderly women falling com-
46. Timetti ME. Speechley M, Ginter SF. Risk factors for falling amongst elderly 
47. Hale WA, Delaney MJ, McGaghie WC. Characteristics and predictors of falls in 
    331:821-827.
49. Speechley M, Timetti ME. Falls and injuries in frail and vigorous community eld-
    1993;137:342-354.
51. Black DW. Subdural hematoma: a retrospective study of the “great neurological 
52. King MB, Timetti ME. Falls in community-dwelling older persons. J Am Geriatr 
53. Naglie IG, Detsky AS. Treatment of chronic nonvalvular atrial fibrillation in the 
54. Bage BF, Cardinalll AB, Albers GW, Owens DK. Cost-effectiveness of warfarin 
    and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrilla-
55. Eckman MH, Levine JH, Pauker SG. Decision analytic and cost-effectiveness is-
    (suppl 4):S385-S499.
56. Middlekauff HR, Stevenson WG, Gombein JA. Antithrombotic prophylaxis vs war-
    farin anticoagulation to prevent thromboembolic events among patients with atrial 
57. Timetti ME, Doucette J, Claus E, Marottoli R. Risk factors for serious injury dur-
    ing falls by older persons in the community. J Am Geriatr Soc. 1995;43:1214- 
    1221.
58. Campbell AJ, Borrie MJ, Spears GF, Jackson SL, Brown JS, Fitzgerald JL. Cir-
    cumstances and consequences of falls experienced by a community population 
59. Stafford RS, Singer DE. National patterns of warfarin use in atrial fibrillation. Arch 
60. Antani MR, Beyth RJ, Covinsky KE, et al. Failure to prescribe warfarin to patients 
61. Lawson F, McAlister F, Ackman M, Ikuta R, Montague T. The utilization of anti-
    thrombotic prophylaxis for atrial fibrillation in a geriatric rehabilitation hospital. 