Optimizing the Effectiveness of Oral Vitamin K Antagonists for Stroke Prevention Among Elderly Individuals with Atrial Fibrillation

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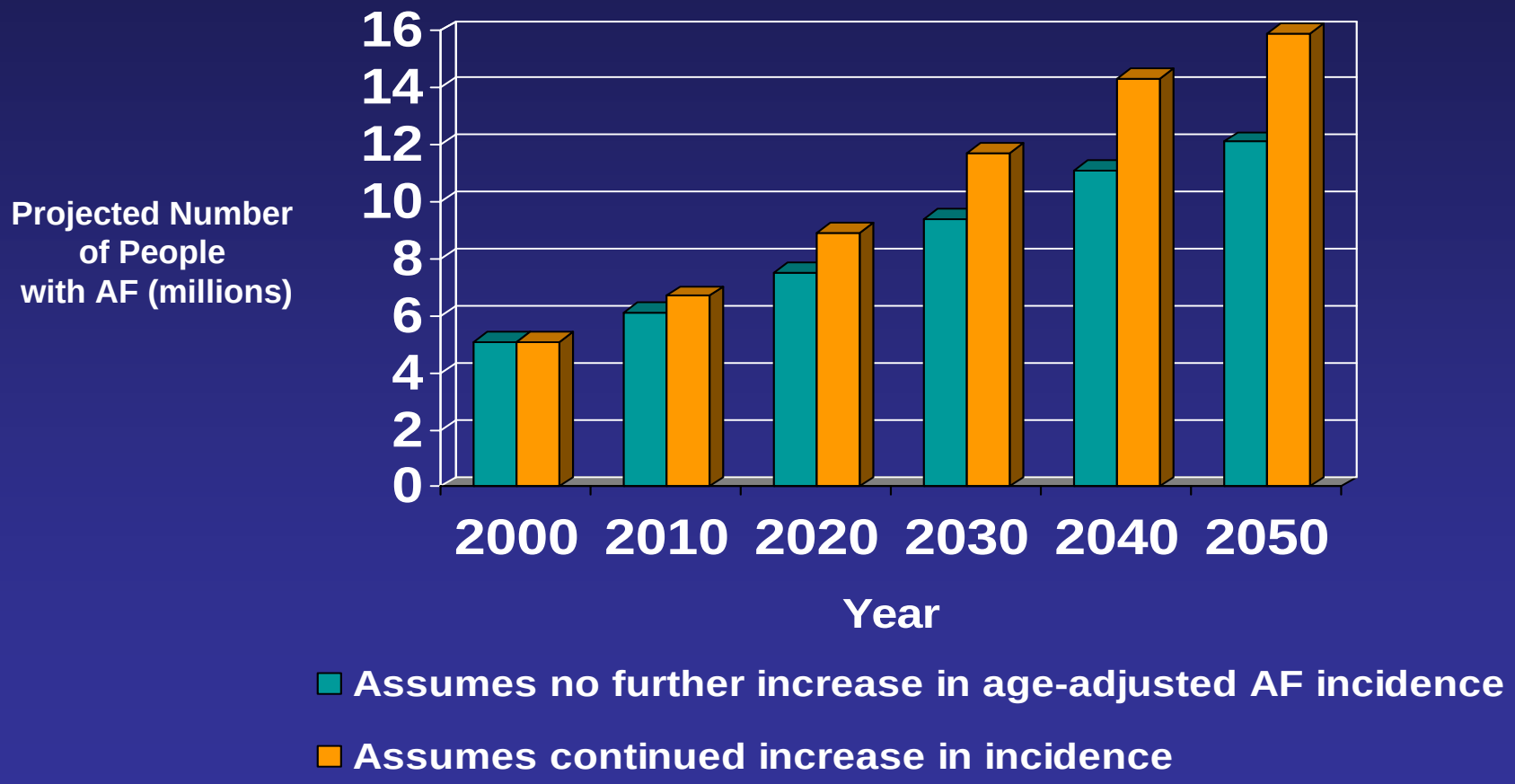
Projected number of persons with AF in the U.S. between 2000 and 2050



Adapted from: Miyasaka, Y et al. Circulation 2006;114:119-125

Miyasaka and colleagues examined trends in the incidence of AF in Olmsted County, Minnesota from 1980 to 2000 and project an estimated 7.5 million individuals will have AF by the year 2020 in the United States alone.

Reference: Miyasaka, Y. et al. Circulation 2006;114:119-125

The Epidemic of Atrial Fibrillation

Increasing prevalence of risk factors for AF:

- Older age
- Systemic hypertension
- Heart failure
- Valvular heart disease
- Diabetes mellitus
- Obesity

- **The reason for this increasing prevalence of AF is multifactorial and due in part to the increased prevalence of risk factors for AF.**
- **Reference: Miyasaka, Y. et al. Circulation 2006;114:119-125**

Prevalence of AF by Age

Age	Prevalence of AF*
<60	0-2%
60-70	2-5%
70-80	5-7%
>80	7-14%

*Data from 4 large, population-based studies: Framingham Heart Study, Cardiovascular Health Study, Mayo Clinic Study, and Western Australia

Chest 1995;108:352S

Multiple population-based studies have demonstrated increasing prevalence of AF with older age. The prevalence of AF among individuals less than 60 years of age is less than 2% and in stark contrast to that of individuals greater than 80 years of age in whom the prevalence approaches 14%.

Atrial Fibrillation: Morbidity and Mortality

- ~15% of all strokes occur in people with AF
- Risk of stroke in untreated AF patients averages ~ 5% per year
- Attributable risk of stroke in AF increases with age
  - 1.5% in 50 to 59 year age group
  - 23.5% in 80 to 89 year age group
- AF is associated with a 50 to 90% increase in risk of death after adjustment for coexisting CV conditions

- **The attributable risk of stroke in AF increases dramatically with age from 1.5% among individuals age 50-59 years to 23.5% among persons 80-89 years of age.**

- **Wolf PA, et al. *Stroke* 1991; 22: 983-988.**
  Benjamin EB, et al. *Circulation* 1998;98:946-952.
  American Heart Association. *Heart Disease and Stroke Statistics-2006 Update*. Dallas, TX: American Heart Association;2006. ©2006 American Heart Association

Global Impact of Stroke

- **3rd most common cause of death in developed countries**
  - 15 million strokes occur each year worldwide
  - 5.5 million deaths from stroke
- **Stroke is a leading cause of serious, long-term disability**
  - 5 million people permanently disabled each year
  - Disability-adjusted life years projected to reach 61 million years per 1000 population by the year 2020 (38 million in 1990

- **World Health Organization. The Atlas of Heart Disease and Stroke 2004.**
  American Heart Association. *Heart Disease and Stroke Statistics-2006 Update*. Dallas, TX: American Heart Association;2006. ©2006 American Heart Association

Economic Impact of Stroke

- >4% of the National Health Service expenditures in the United Kingdom in the year 2000

- Ranked second among most costly diseases for the elderly population in the Netherlands. By the year 2015, costs are estimated to rise by 40%.

- Total cost of stroke care approximated $57.9 billion in the United States in 2006.

- **World Health Organization. The Atlas of Heart Disease and Stroke 2004.**
  American Heart Association. *Heart Disease and Stroke Statistics-2006 Update*. Dallas, TX: American Heart Association;2006.

Efficacy of Warfarin in Atrial Fibrillation

Five Randomized Trials in Non-Valvular AF

Study	Warfarin (#)	Cont. (#)	INR	RR	p-Value
AFASAK	335	336	2.8-4.2	**60%**	0.027
SPAF	210	211	2.0-4.5	**67%**	0.01
BAATAF	212	208	1.5-2.7	**86%**	<0.05
CAFA*	187	191	2.0-3.0	**45%**	0.25
SPINAF	260	265	1.4-2.8	**79%**	0.001

*Stopped early due to published positive results

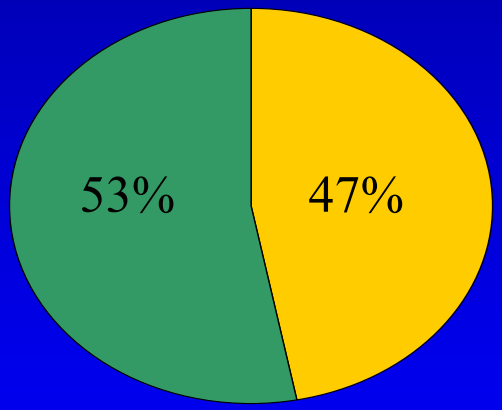
68% overall risk reduction for stroke

Oral vitamin K antagonists like warfarin are extremely effective in reducing the risk of stroke among patients with AF. The early AF trials consistently demonstrated benefit with an overall 68% risk reduction in stroke. This slide illustrates how few patients needed to be enrolled to show superiority of warfarin compared to placebo. It also illustrates the uncertainty during this period of the optimal INR range for stroke prevention in AF.

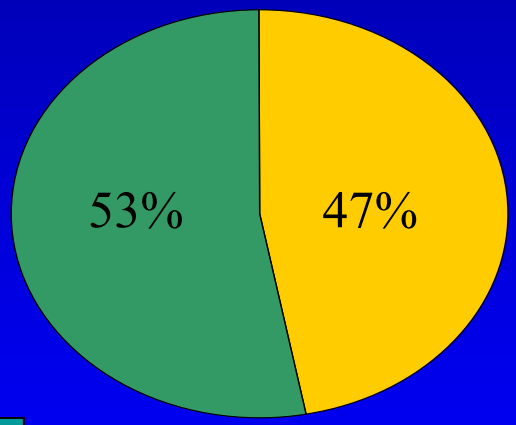
Underutilization of Anticoagulation Therapy in AF (Jan 2002 - Dec 2002)

Approximately half of high-risk patients with atrial fibrillation receive warfarin therapy

13 Community Hospitals



21 Academic Hospitals



Warfarin Therapy
No Warfarin Therapy

Age >80 and perceived bleeding risk were negative predictors of warfarin use.

Waldo et al. JACC 2005;46(9):1729-1736

Despite the dramatic benefit of oral VKA, multiple studies have convincingly shown that only about 50-60% of at-risk patients with AF are receiving anticoagulant therapy. In many parts of the world, the need for frequent INR monitoring represents a substantial barrier to its use. Old age is often cited as a reason for not prescribing oral VKA because of perceived bleeding risk. This is a true clinical dilemma because these are often the patients at highest risk of stroke.

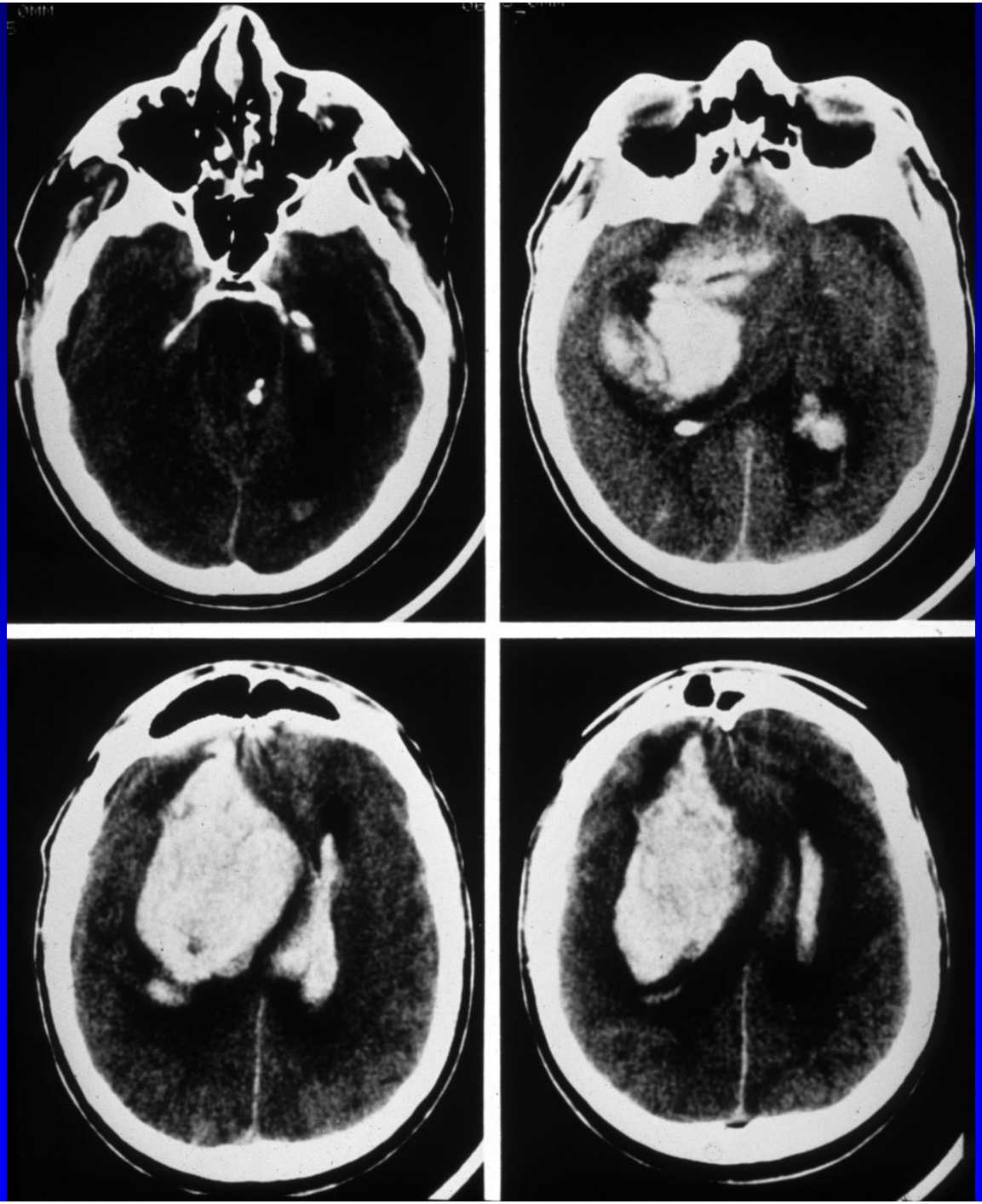
Factors Influencing Warfarin Under Use

1. Lack of consensus on absolute versus relative contraindications to anticoagulant therapy: e.g., fall risk, prior hemorrhage, need for concurrent antiplatelet therapy

2. Barriers to INR monitoring: e.g., dependence on caregivers for transportation, logistical constraints, cost

3. Suboptimal candidacy for anticoagulant therapy and inability to tolerate medication long-term

4. Fear of hemorrhage



Intracranial hemorrhage is the most feared complication of oral anticoagulant therapy. Mortality related to intracerebral hemorrhage approximates 50% and is related to hematoma volume and hematoma expansion.

Hylek EM, Singer DE. Ann Intern Med 1994;120:897-902. Flibotte JJ, et al. Neurology. 2004 Sep 28;63(6):1059-64.

Risk Factors for Intracranial Hemorrhage

- INR intensity
- Age
- Aspirin therapy
- Ischemic cerebrovascular disease
- Hypertension
- Vasculopathy-Leukoaraiosis, amyloid angiopathy

The paradox facing clinicians and patients is that many of the risk factors for intracranial hemorrhage are also risk factors for ischemic stroke. Age, hypertension, and prior stroke all increase the risk for both hemorrhagic and non-hemorrhagic stroke. Although leukoaraiosis and amyloid angiopathy are associated with increased risk of intracerebral hemorrhage, their utility for risk stratification remains unclear.

Major Hemorrhage Rates

Randomized Trials	**INR target**	**ICH**	**Major**	**Age**
AFI	1.5-4.5	0.3	1.0	69
SPAF II	2.0-4.5	0.9	1.4	70
AFFIRM	2.0-3.0	-----	2.0	70

Observational	**INR target**	**ICH**	**Major**	**Age**
van der Meer, et al (1993)	2.8-4.8	0.6	2.0	66
Palareti, et al (1996)	2.0-4.5	0.5	0.9	62
Go, et al (2003)	2.0-3.0	0.5	1.0	71

Published rates of ICH and other major hemorrhage from randomized trials and observational cohort studies have been reassuringly low. The most often reported rate of intracranial hemorrhage is 0.5% per year. Therefore, the risk versus benefit of anticoagulant therapy weighs in favor of anticoagulant use for the majority of patients at high risk of stroke.

Caveats Relating to Published Data on Hemorrhage

Randomized trials

- Enrolled few patients ≥ 80 years
- Highly selected, closely monitored
- Vitamin K antagonist at entry

Prospective cohort studies

- Predominantly non-inception cohort studies of prevalent warfarin use (survivor bias)
- Enrolled few patients ≥ 80 years
- Varying definitions of bleeding
- Most conducted within anticoagulation clinic setting

However, there are important caveats to the rates of major bleeding that have been published. Overall, few patients greater than 80 years of age have been enrolled in randomized trials and cohort studies. In addition, recent trials and most observational cohorts have largely reported the outcomes of prevalent users of warfarin. Because most major bleeding occurs early in the course of anticoagulation, enrollment of predominantly long-time users of warfarin will result in lower estimates of hemorrhage.

Balancing Risk and Benefit

- ? Lower target intensity
- Improve anticoagulation control
- Improve risk stratification
- Minimize use of concomitant antiplatelet therapy
- ? New antithrombotic therapies

There are several possible strategies to decrease the risk of major hemorrhage. Each of these will be discussed.

Balancing Risk and Benefit

- ? Lower target intensity

SPAF III Study

Randomized High Risk Cohort

1. Female >75 years
2. Systolic hypertension
3. Impaired LV function
4. Prior thromboembolism

Warfarin

INR, 2.0-3.0;
Monthly INR to adjust dose

Combination

1-3 mg warfarin +
325 mg aspirin;
fixed dose

Adapted from: SPAF Investigators. *Lancet.* 1996;348:633-638

The Stroke Prevention in Atrial Fibrillation III Study randomized high-risk patients to either standard intensity warfarin, INR 2.0 to 3.0, or low dose warfarin plus 325 mg of aspirin.

SPAF III Results: Event Rate Per Year in High-Risk Cohort (N=1,044)

Event	Aspirin + Fixed Dose Warfarin	Adjusted Dose Warfarin	
Ischemic Stroke or Systemic Embolism	7.9%	1.9%	*P* = .0001
Major Bleeding	2.4%	2.1%	
Intracranial Hemorrhage	0.9%	0.5%	

SPAF Investigators *Lancet.* 1996;348:633-638.

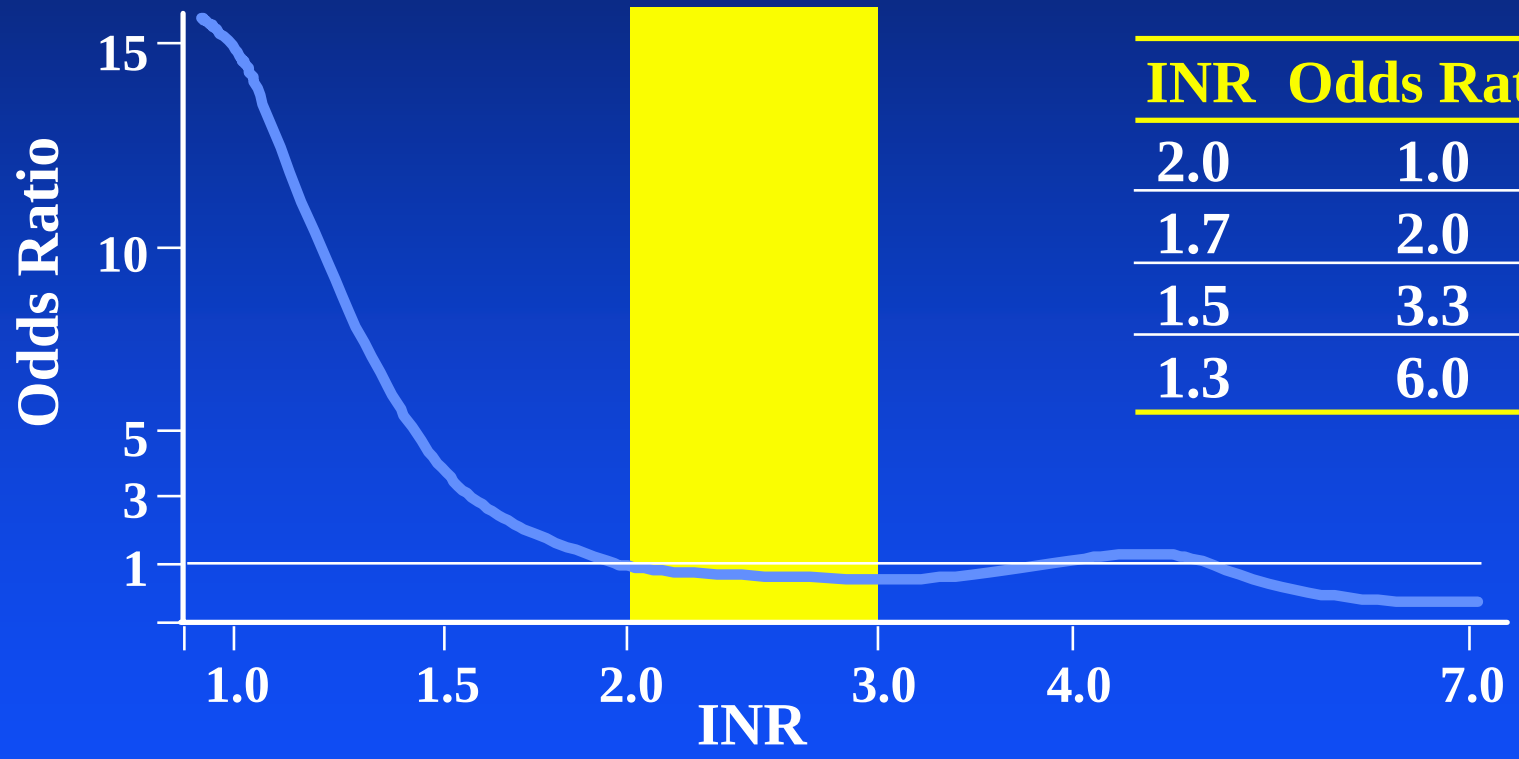
Key Point: Adjusted-dose warfarin therapy reduced the incidence of stroke in patients with AF, whereas aspirin and fixed-dose warfarin therapy did not.

The trial was stopped after a mean follow-up of 1.1 years when the rate of primary events (ischemic stroke or systemic embolism) in those receiving combination therapy reached 7.9% compared with 1.9% in those receiving adjusted-dose warfarin, an absolute reduction of 6% per year. The annual rates of disabling stroke and of primary event or vascular death were also significantly higher in the combination-therapy group. The rates of major bleeding, however, were similar in both treatment groups.

The study concluded that adjusted-dose warfarin therapy (target INR, 2.0 to 3.0) reduced stroke incidence, whereas low-intensity, fixed-dose warfarin therapy with aspirin was insufficient for stroke prevention in high-risk patients with AF.

SPAF Investigators. *Lancet.* 1996;348:633-638.

Lowest Effective Anticoagulation Intensity for Warfarin Therapy

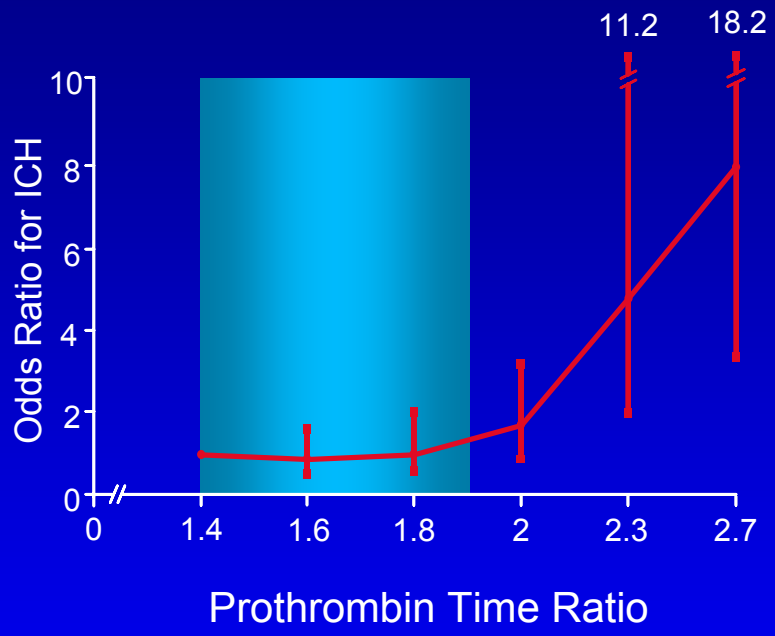


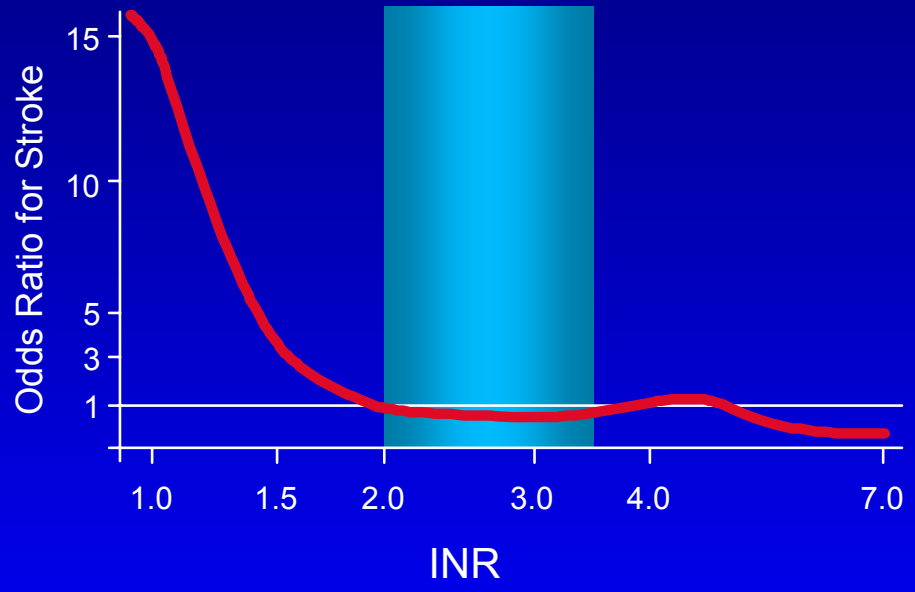
INR	Odds Ratio
2.0	1.0
1.7	2.0
1.5	3.3
1.3	6.0

Adapted from Hylek EM, et al.. N Engl J Med 1996;335:540-546.

Published the same year, this case-control study demonstrates the relationship between INR level and efficacy of anticoagulation for stroke prevention in AF. This slide plots the relative odds of ischemic stroke versus INR level among patients with AF who were taking warfarin. Efficacy was fairly constant at INR levels above 2.0, but the odds of stroke increased sharply at INR levels below 2.0.

Optimal Intensity for Warfarin Therapy In Atrial Fibrillation





- PTR above 2.0 (INR of 3.7 to 4.3) increases the risk of bleeding

- Odds Ratio of stroke by INR

INR	Odds Ratio
2.0	1.0
1.7	2.0
1.5	3.3
1.3	6.0

Adapted from Hylek EM, Singer DE. *Ann Int Med* 1994;120:897-902.
Adapted from Hylek EM, et al. *N Engl J Med* 1996;335:540-546.

Juxtaposed on this slide are the relationships between INR intensity and intracranial hemorrhage and ischemic stroke The odds of ICH begin to increase at approximately INR=3.7 and the odds of ischemic stroke increase with INR less than 2.0 emphasizing the narrow therapeutic range of oral vitamin K antagonists.

30-Day Mortality following AF-related Stroke by Antithrombotic-Medication Status on admission

Medication	30-Day Mortality Rate
Warfarin, INR ≥2.0	6%
Warfarin, INR <2.0	16%
Aspirin	15%
None	24%

p = 0.002

(P value refers to the overall difference among the groups.)

Hylek, et al. NEJM. 2003

In addition, subtherapeutic anticoagulation intensity is associated with more severe strokes. The 30-day mortality following an ischemic stroke was 16% for patients presenting with an INR less than 2.0 compared to 6% for patients with an INR of 2.0 or greater The mortality rate associated with an INR less than 2.0 was similar to that experienced among patients taking aspirin at the time of stroke. Among patients taking neither warfarin nor aspirin, the 30-day mortality was 24% similar to that reported in several other large population-based studies. The association between stroke severity and INR intensity at the time of stroke has subsequently been validated in two independent patient populations in Norway and Canada.

Balancing Risk and Benefit

- Lower target intensity
- Improved anticoagulation control

Use of lower INR targets is associated with increased frequency and increased severity of strokes. Lower INR target ranges have not been shown to decrease hemorrhage. A better understanding of the triggers for aberrant INR control is needed.

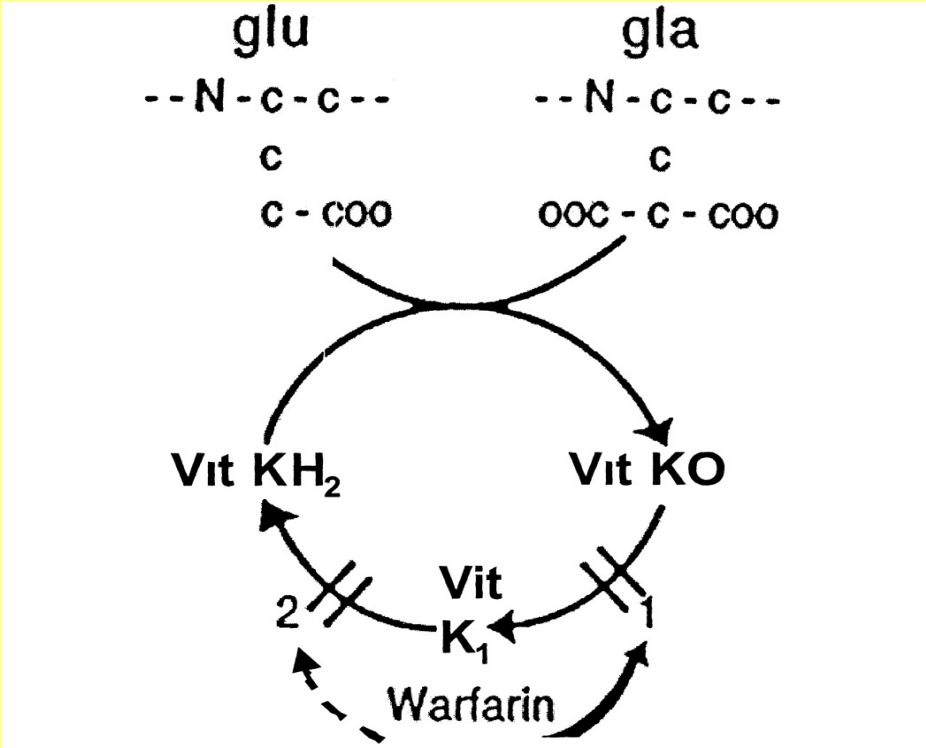
Warfarin Pharmacokinetics

- Rapidly absorbed from GI tract
- Peak plasma concentration within 90 minutes
- Average half-life 36 to 42 hours
- Metabolized by the liver P450 mixed oxidase enzymes
  - More potent S-isomer oxidized via CYP2C9

Mechanism of Action

- Racemic mixture of R- and S-isomers
  - (S-isomer is 3-5x more potent)
- Inhibits activation of vitamin K-dependent coagulant proteins (prothrombin, factor VII, factor IX, and factor X) and carboxylation of anticoagulant proteins (C and S)
- Vitamin K can overcome competitive inhibition

Vitamin K1 is reduced to vitamin KH2 by two warfarin-sensitive enzymes (KO-reductase to K-reductase), and the nicotinamide adenine dinucleotide-dependent reductase system that is insensitive to warfarin



1. KO - reductase - warfarin sensitive
2. K - reductase - relatively warfarin resistant

Adapted from Ansell, J. et al. Chest 2004;126:204S-233S

Challenges of Warfarin Use

- Variable dose response
- Individualized dosing
- Interactions with medications and diet
- Narrow therapeutic window
- Need for frequent monitoring
- Long half-life

Variable Dose Response

- **Drug interference**

Most potent:

- Amiodarone (inhibits R- and S-enantiomers)

Most under-appreciated:

- **Paracetamol (**touted interference with enzymes of the vitamin K cycle)

- **Dietary vitamin K**

- **Warfarin's narrow therapeutic index and variable dose response mandate frequent monitoring of the INR. Among the most powerful potentiators of warfarin's anticoagulant effect is the drug amiodarone. Amiodarone inhibits the metabolism of both the S- and R-enantiomers of warfarin. The dose of warfarin often needs to be reduced by approximately 30% with titraton of amiodarone over several weeks. New use of higher doses of paracetamol for up to 5 consecutive days has been associated with excessive levels of anticoagulation. It is now thought that this is due to interference with the enzymes of the vitamin K cycle and not a direct effect on warfarin's metabolism.**

Variable Dose Response

- **Genetic polymorphisms:**

  cytochrome P450 CYP2C9 and VKORC1 (vitamin K epoxide reductase complex 1)

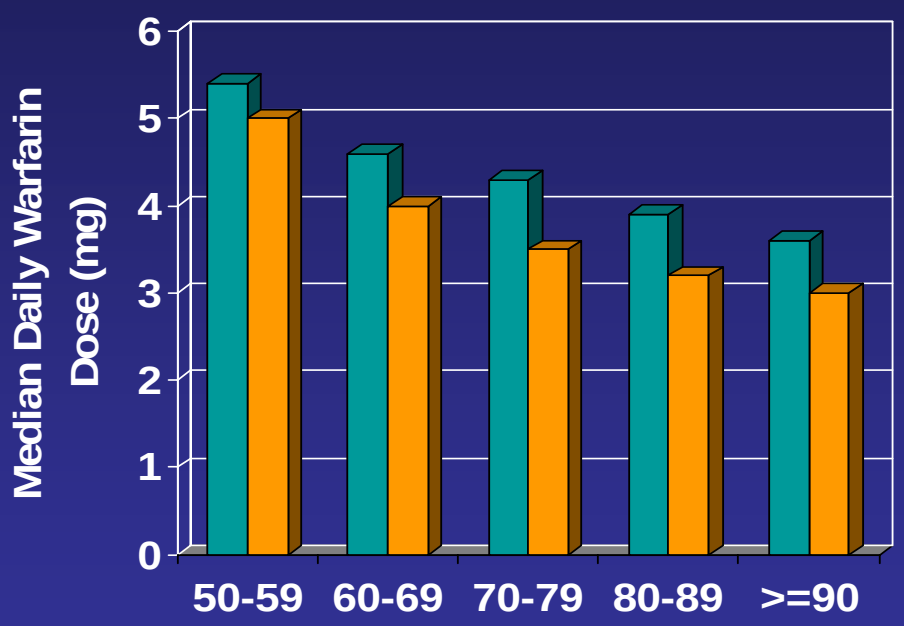
- **Disease States, e.g., CHF, malignancy**

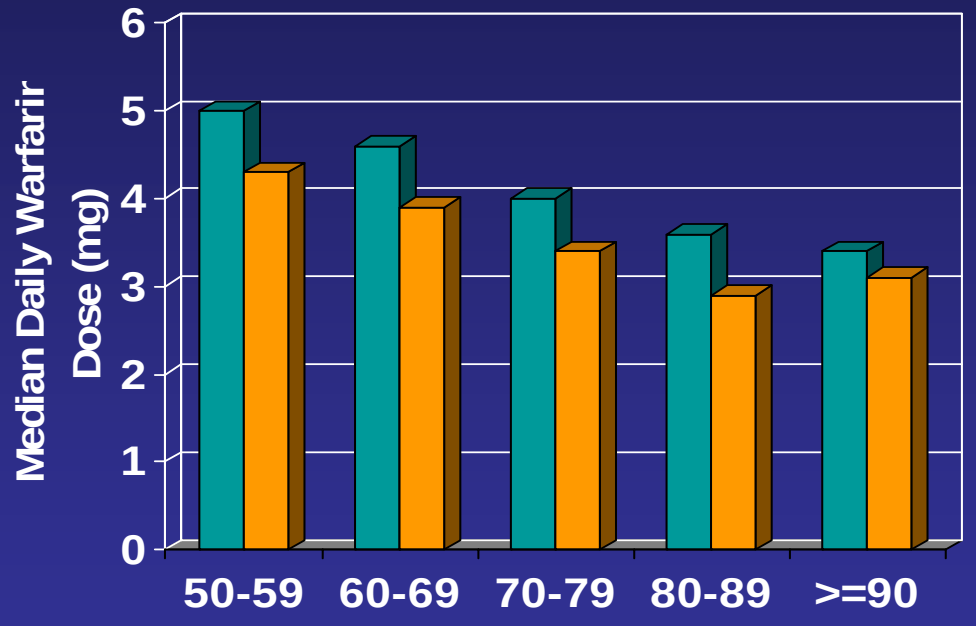
- **Pharmacodynamic changes with aging**

- **Several genetic polymorphisms relating to warfarin's metabolism have been discovered. Studies are ongoing to determine their use in clinical practice. Decompensated heart failure and treatment with chemotherapy have been identified as potent precipitants of INR variability. Anticipating these states will facilitate earlier dose modification, more frequent monitoring, and potentially fewer adverse events. It is interesting to note that the maintenance dose of warfarin declines significantly with age. This is poorly understood and does not appear to be related to changes in pharmacokinetics.**

Maintenance warfarin dose by age (AF)
INR target 2-3

Derived from two independent ambulatory populations





Male

Female

Adapted from: Garcia D, et al. Chest 2005;127:2049-2056

- **Warfarin dose requirements decline with advancing age. Women on average require less warfarin than men which is not entirely explained by differences in weight. Frequent INR monitoring during the first few weeks of warfarin therapy will help to prevent excessive warfarin anticoagulation particularly among elderly women. Consecutive daily doses of 5 mg of warfarin in the absence of frequent monitoring for dose adjustment would significantly overshoot the daily dose requirements of the majority of elderly patients with AF.**

Age-related differences in rate of INR normalization

- **Older age has been shown in multiple studies to be a predictor of major hemorrhage. Although multifactorial, age-related differences in the rate of INR normalization following an elevated INR may partly underlie this risk.**

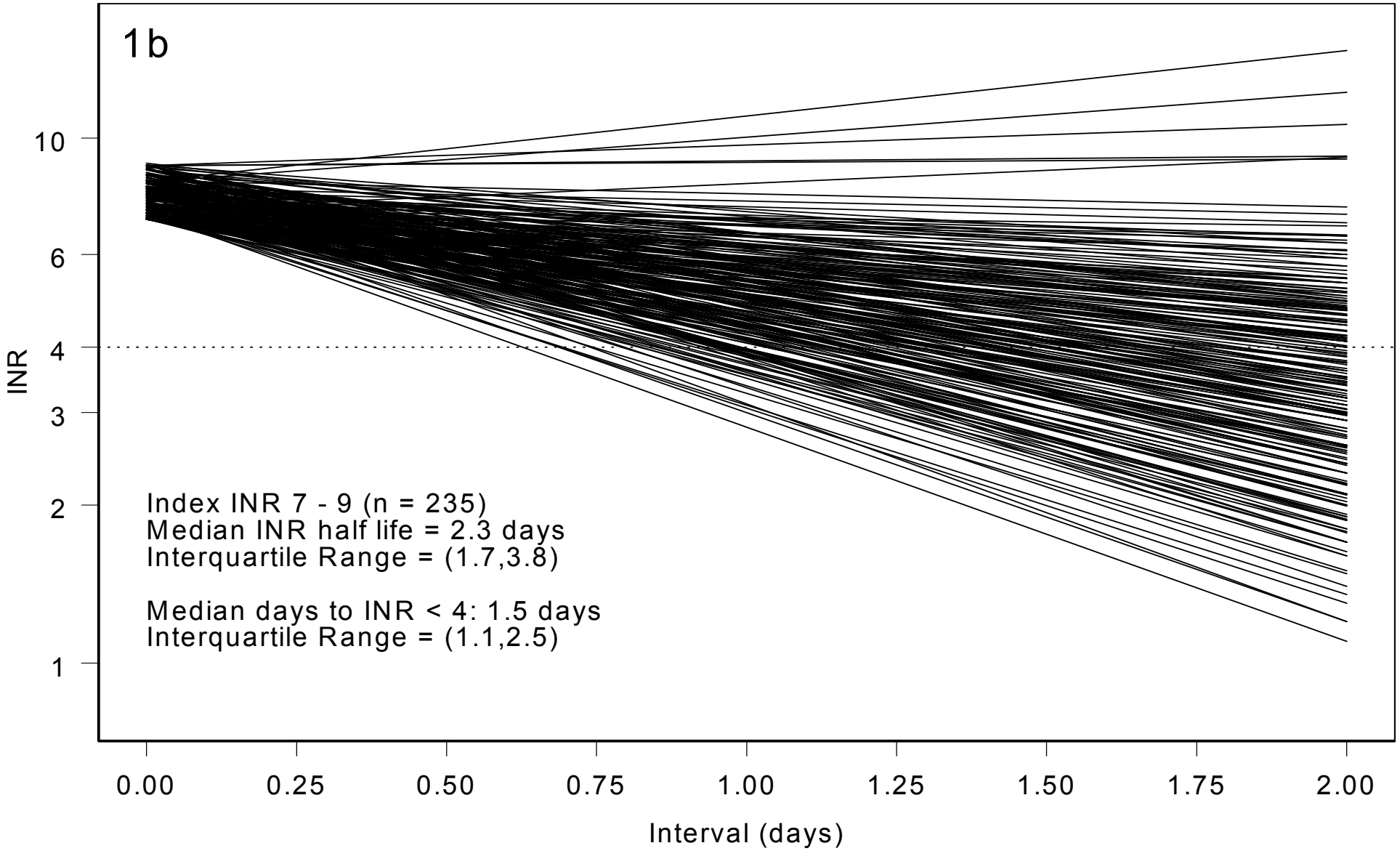
Patient scenario

Your patient presents for routine follow-up and is without complaint. You find that the INR is 7.2. What do you do?

Will all of these patients return to a therapeutic INR at the same rate?





Hylek et al, Ann Intern Med. 2001;135:393-400

- **In this study, outpatients were identified with an INR greater than 6.0. All patients were instructed to hold two doses of warfarin and return on Day 2 for a repeat INR measurement. The Figure displays the INR decay curves of these patients over the 48-hour period. Of the 633 patients identified, 63% of patients had an INR less that 4.0 and 37% of patients had an INR of 4.0 or higher on Day 2. Twelve percent of patients with an index INR between 6-9 had a subtherapeutic INR (less than 2.0) after holding two doses of warfarin.**

Risk factors for INR ≥ 4.0 after holding two doses of warfarin

	Adjusted Odds Ratio
• Warfarin dose, weekly per 10 mg	**0.87** (0.79-0.97)
• Age, per decade	**1.18** (1.01-1.38)
• Decompensated heart failure	**2.79** (1.30-5.98)
• Active malignancy	**2.48** (1.11-5.57)
• Index INR, per unit	**1.25** (1.14-1.37)

- **Risk factors associated with prolonged delay in return to the therapeutic range following an INR of 6.0 or greater included older age, lower warfarin dose requirements, decompensated heart failure, an actively treated malignancy, and degree of elevation of the index INR. For each decade of age, the risk of having an INR greater than 4.0 on Day 2 increased by 18%. The clinical implications of this study are that elderly patients, especially those who require lower doses of warfarin to attain an INR of 2.0-3.0, are at highest risk for prolonged exposure to risk-laden levels of anticoagulation. Studies are needed within this subgroup of patients to determine if more aggressive intervention for asymptomatic elevations in INR would result in fewer major hemorrhages.**

Balancing Risk and Benefit

- Lower target intensity
- Improved anticoagulation control
- Improved risk stratification

JAMA®

Validation of Clinical Classification Schemes for Predicting Stroke Results From the National Registry of Atrial Fibrillation

$CHADS_2$ Score	Points
Congestive heart failure	= 1
Hypertension	= 1
Age ≥75 years of age	= 1
Diabetes	= 1
Prior stroke/TIA/systemic embolus	= 2

82 y.o. male with HTN and prior stroke ($CHADS_2$ Score = 4)

Gage B, et. al. JAMA. 2001;285:2864-2870

- **The $CHADS_2$ risk stratification tool has a distinct advantage in that it was derived from a Medicare population (age >65 years) and is more representative of patients with AF seen in clinical practice than schemes derived from younger, highly selected, randomized clinical trial participants. Points are assigned for each risk factor and then added for a total risk-score. This risk-score can help guide physicians and patients in their individualized decision-making regarding use of anticoagulants for stroke prevention in AF.**

Estimated Stroke Risk by $CHADS_2$ Score

$CHADS_2$ Score	**Adjusted Stroke Rate (%/y)**
0	1.9 (1.2 to 3.0)
1	2.8 (2.0 to 3.8)
2	4.0 (3.1 to 5.1)
3	5.9 (4.6 to 7.3)
4	8.5 (6.3 to 11.1)
5	12.5 (8.2 to 17.5)
6	18.2 (10.5 to 27.4)

Gage B, et al. JAMA 2001; 285:2864-2870

- **Based on a CHADS score of 1, the estimated stroke rate per year is 2.8%. A CHADS score of 3 confers a rate of stroke per year of nearly 6%. A 78 year old woman with a prior history of stroke, hypertension and diabetes would have a CHADS score of 5 and an estimated stroke rate per year of 13%.**

August 15, 2006

ACC/AHA/ESC 2006 Guidelines for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): *Developed in Collaboration With the European Heart Rhythm Association and the Heart Rhythm Society*

Stroke Risk Factors

Less Validated or Weaker Risk Factors	Moderate Risk Factors	High Risk Factors
• Female gender • Age 65 to 74 y • CAD • Thyrotoxicosis	• Age ≥ 75 y • Diabetes • HTN • Heart failure • LV EF < 35%	• Prior CVA, TIA or embolism • Mitral stenosis • Prosthetic valve

Fuster, V. et al. Circulation 2006;114:700-752

Current Recommended Therapy by Risk Category

Risk Category	Recommended Therapy
No risk factors	Aspirin, 81 to 325 mg daily
One moderate-risk factor (CHADS=1)	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)
Any high-risk factor or >1 moderate-risk factor (CHADS >1)	Warfarin (INR 2.0-3.0, target 2.5)

Fuster, V. et al. Circulation 2006;114:700-752

Balancing Risk and Benefit

- Lower target intensity
- Improved anticoagulation control
- Improved risk stratification
- Minimize concomitant antiplatelet therapy

Combined ASA+OAC versus OAC alone among patients at risk for cardiovascular disease

METHODS: Meta-analysis of 10 clinical trials that compared oral anticoagulant (OAC) therapy alone to ASA+OAC.

RESULTS: 4,180 patients with either mechanical heart valve, AF, or CAD

Combined therapy was associated with a lower incidence of arterial thromboembolism (OR 0.66), but the benefits were limited to patients with mechanical valves (OR 0.27).

Combined therapy did not benefit patients with AF (OR 0.99) or CAD (OR 0.69) nor did it influence all cause mortality.

Combined therapy did increase the risk of major bleeding (OR 1.43).

- **This recently published meta-analysis suggests that the combination of aspirin with oral anticoagulant therapy is associated with significant bleeding risk and is of benefit only for patients with mechanical heart valves. There appears to be emerging consensus that combination therapy is associated with more harm than benefit. Combination therapy continues to be a pressing concern particularly for elderly patients following stent placement. Further research is needed to better clarify hemorrhagic risks.**

- **Dentali F, Douketis JD, Lim W, Crowther M.**
- **Arch Intern Med 2007; 167:117-124.**

Balancing Risk and Benefit

- Lower target intensity
- Improved anticoagulation control
- Improved risk stratification
- Minimize concomitant antiplatelet therapy
- New antithrombotic therapies

- **There are many novel antithrombotic drugs currently in Phase III testing or soon to start Phase III trials. It is hoped that these medications with wider therapeutic margins and limited need for monitoring will extend anticoagulant therapy to more patients with AF at high risk of stroke.**

Potential Challenges

- Size of trials necessary to establish non-inferiority
- Reversibility
- Safe dosing in the elderly patient
- Physician and patient acceptance of no monitoring
- Cost

SUMMARY POINTS

- Elderly patients with AF are at the highest risk of stroke and the highest risk of hemorrhage.
- 30-day mortality of AF-related stroke is approximately 24%.
- Rates of ischemic stroke significantly exceed rates of ICH on OAC.
- Intensive efforts to optimize OAC in this age group will help to minimize major bleeding.

- **In addition to the summary points noted on these final two slides, it is important to emphasize that more research is needed among elderly patients newly starting oral vitamin K antagonists. There also continues to be a scarcity of data regarding OAC outcomes among patients managed outside of organized anticoagulation clinic settings. From a public health perspective, it is imperative that the unique needs of at-risk patient populations be addressed who are unable to benefit from OAC therapy because of logistical barriers to adequate INR monitoring. Patients and health care providers eagerly await the arrival of equally efficacious and hopefully safer alternatives to oral vitamin K antagonists.**

CLINICAL CAVEATS

- Initiate warfarin with lower doses particularly in elderly women
- Older patients on average are slower to normalize an elevated INR.
- Combination therapy of ASA + OAC is associated with increased bleeding.
- Vigilant blood pressure control has been shown to decrease both ischemic and hemorrhagic stroke.
- Use of lower INR targets have not been convincingly shown to decrease major hemorrhage.

¡Thank you!