Anticoagulation Therapy: Clinical Recommendations for a New Paradigm

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Faculty Disclosure

- **The *faculty* reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests related to the content of this CME activity:**
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    - Consulting fees: Boehringer Ingelheim Pharmaceuticals, Inc.; Bristol-Myers Squibb; Ortho-McNeill/Johnson & Johnson; sanofi-aventis
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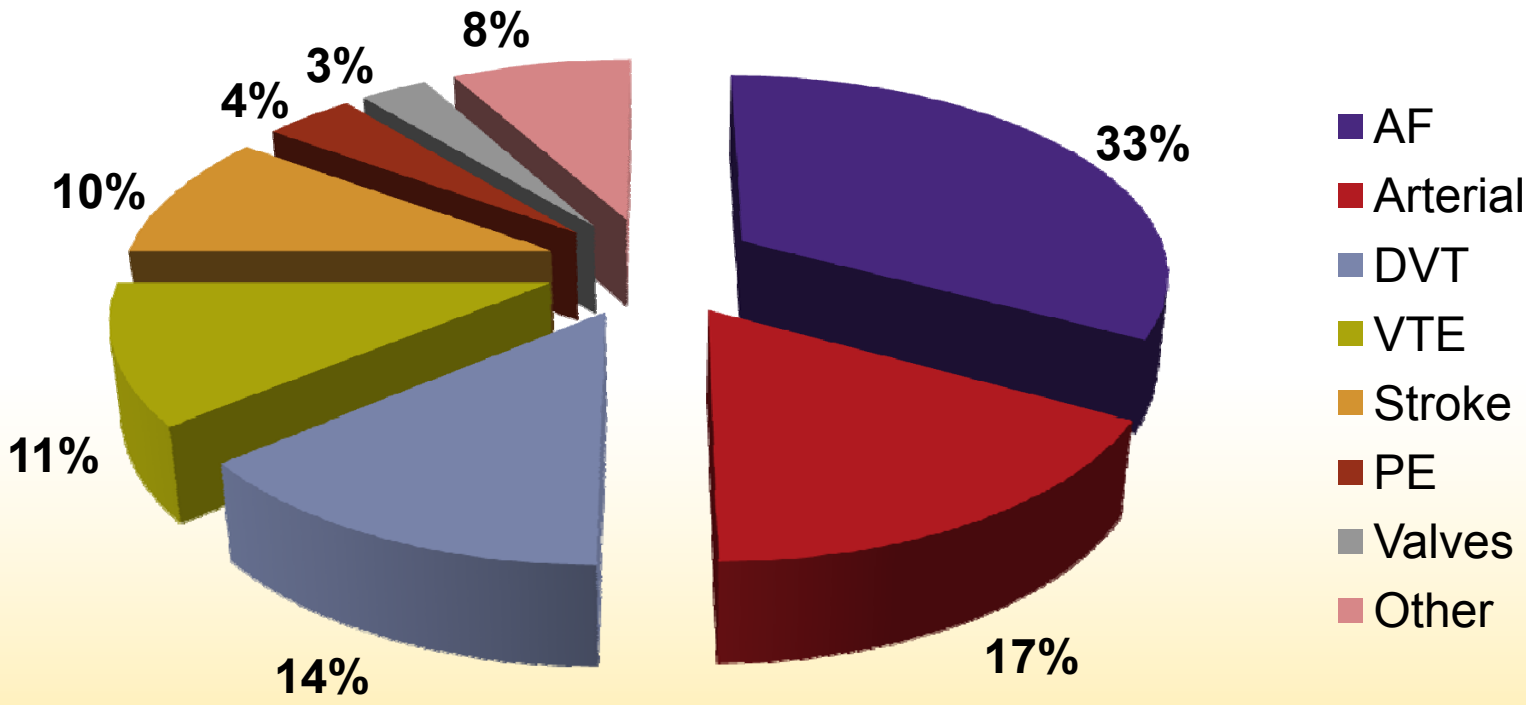
Uses of Oral Anticoagulation



AF=atrial fibrillation.
DVT=deep vein thrombosis.
VTE=venous thromboembolism.
PE=pulmonary embolism.

National Disease and Therapeutic Index. June 2002.

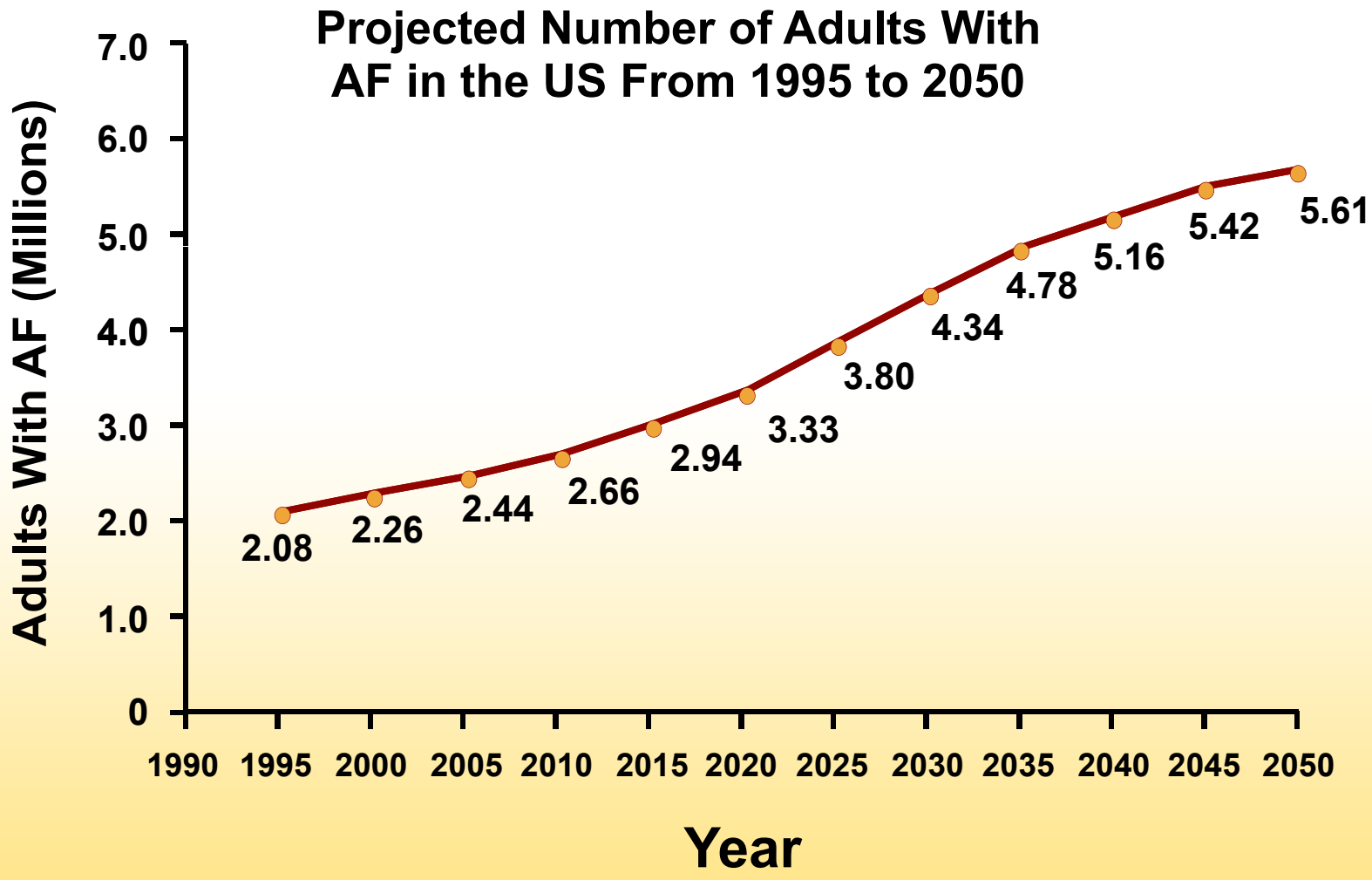
Epidemiology of Atrial Fibrillation

- Estimated to affect >2.6 million Americans
  - Prevalence increasing as population ages
- Presence of AF confers a 5-fold higher risk for ischemic stroke
- Most common arrhythmia requiring hospitalization
  - 461,000 hospital discharges/year
  - Associated with >90,000 deaths/year
  - Risk for recurrent severe stroke is increased 2.4-fold in patients not treated with anticoagulants

Lloyd-Jones D, et al. *Circulation*. 2010;121:e46-e215.

AF=atrial fibrillation.

Future of Atrial Fibrillation: *ATRIA Study*

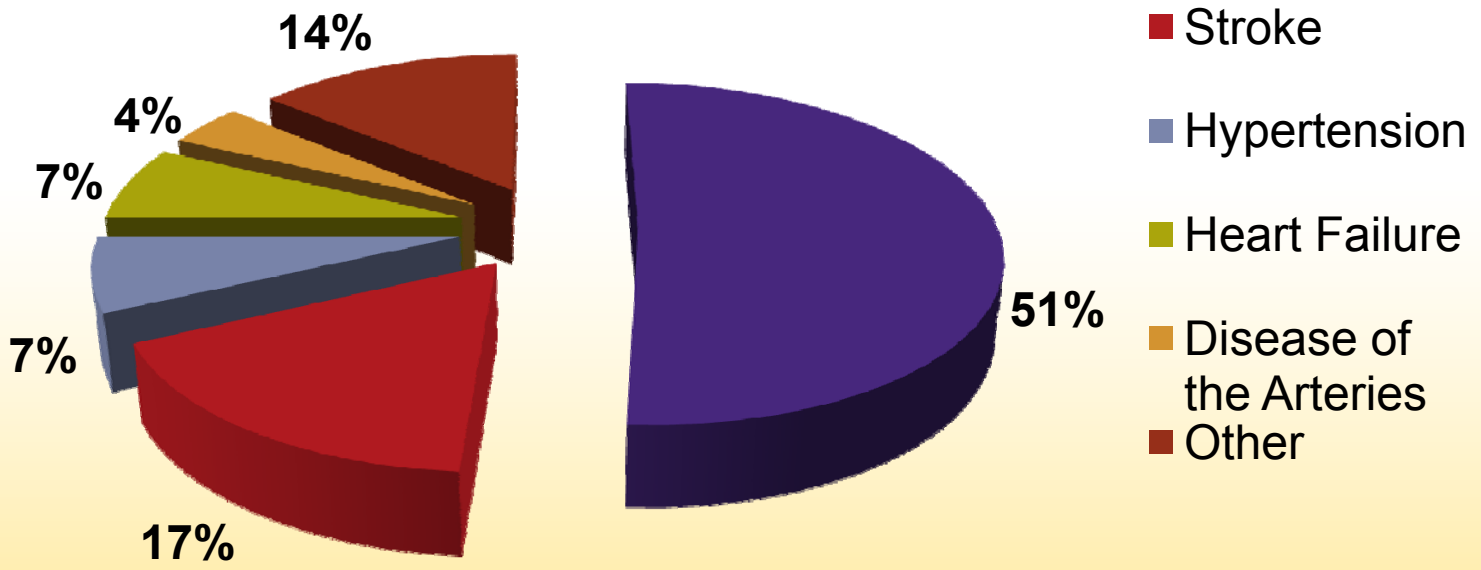


Go AS, et al. *JAMA*. 2001;285;2370-2375.

AF=atrial fibrillation.

Cardiovascular Deaths

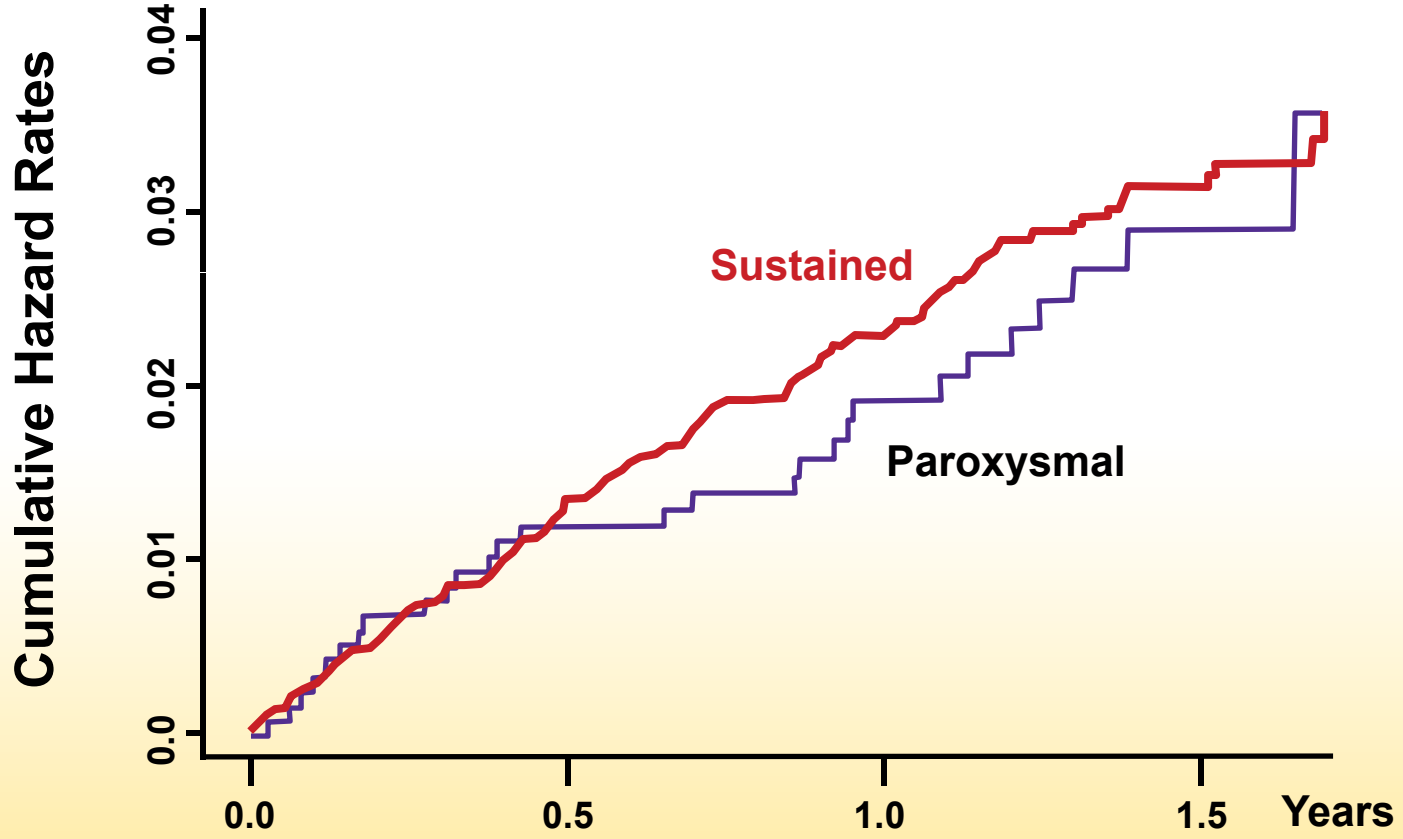
Percentage Breakdown of US Deaths From CVD, 2001



Source: National Center for Health Statistics.
American Heart Association. Heart Disease and Stroke Statistics—2010 Update.

CVD=cardiovascular disease.
CHD=coronary heart disease.

Incidence of Stroke According to Type of Atrial Fibrillation: *Paroxysmal vs Sustained*



Number at risk

P	1199	1121	862	304
S	5499	5264	4006	1560

Hohnloser SH, et al. *J Am Coll Cardiol*. 2007;50:2156-2161.

Outcome of Stroke

- Leading cause of serious disability in the US
- 50-70% of stroke survivors regain functional independence
- 15-30% are permanently disabled
- 20% require institutional care at 3 months after onset

Lloyd-Jones D, et al. *Circulation*. 2010;121:e46-e215.

Outcome of Stroke With AF

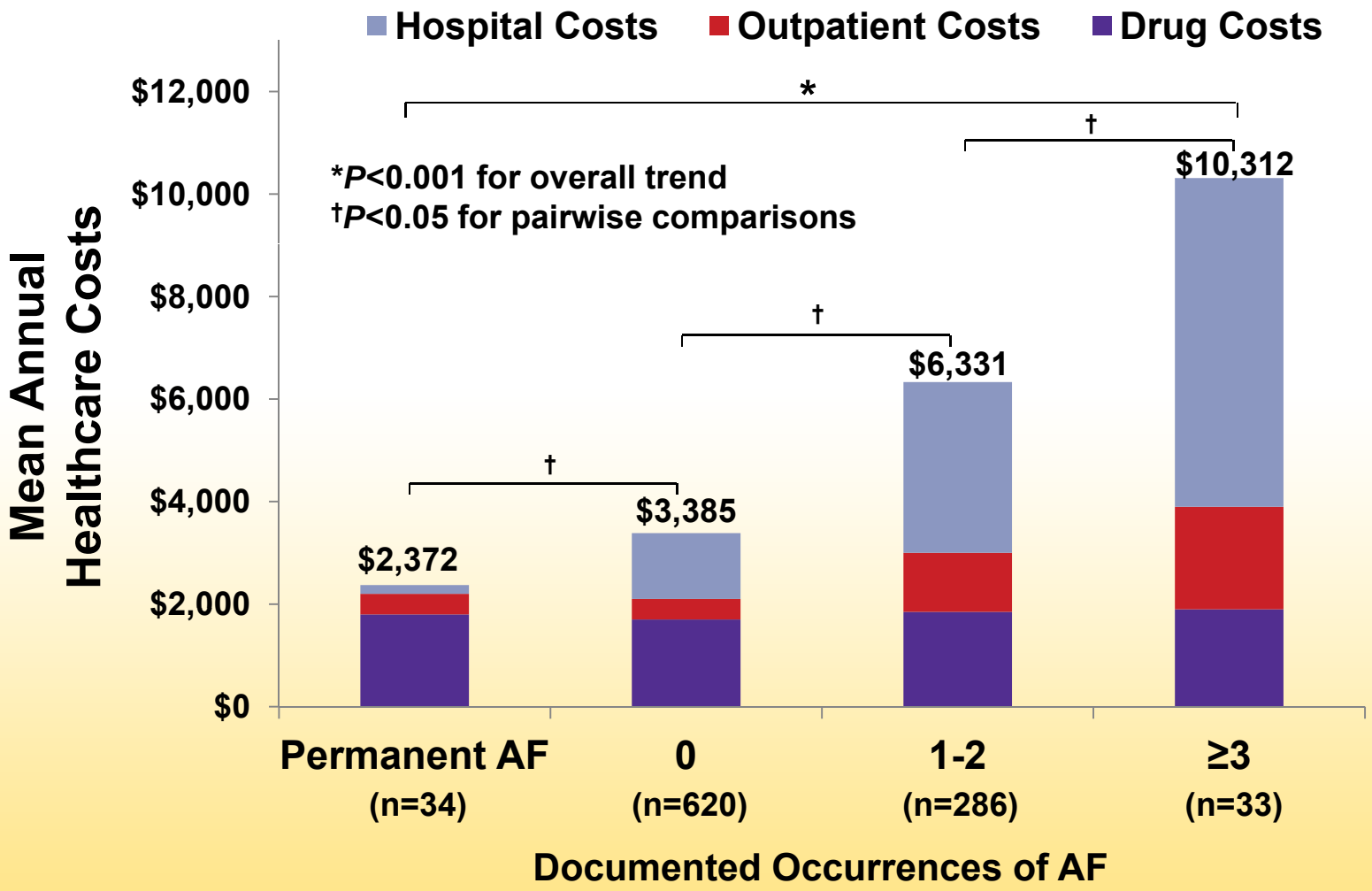
- 1061 patients admitted with acute ischemic stroke
  - 20.2% had AF
- Bedridden state
  - With AF 41.2%
  - Without AF 23.7%

  ***P*<0.0005**
- Odds ratio for bedridden state following stroke due to AF: 2.23 (95% CI, 1.87-2.59; *P*<0.0005)

Dulli DA, et al. *Neuroepidemiology*. 2003;22:118-123.

AF=atrial fibrillation.

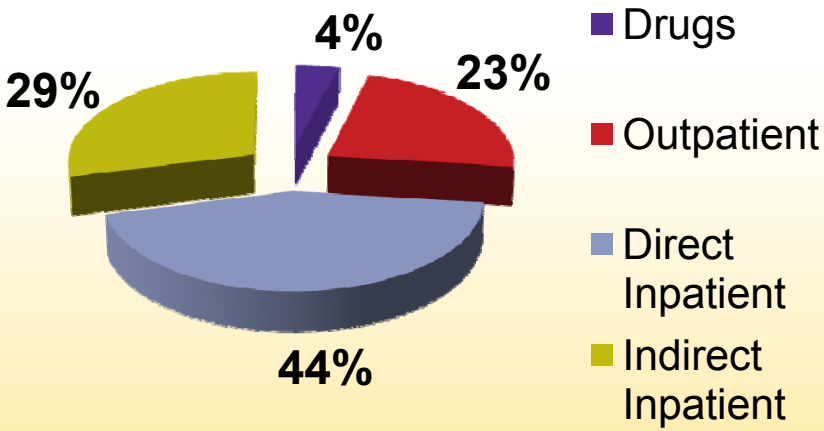
Costs of Care in Atrial Fibrillation
Healthcare Payer Perspective



Reynolds MR, et al. *J Cardiovasc Electrophysiol*. 2007;18:628–633.

Treatment of AF Represents a Significant Burden

Distribution of Inpatient and Selected Outpatient Costs for Treating AF



- $6.65 billion (2005 US dollars) for AF treatment in the inpatient, emergency department, and hospital outpatient settings
- $2.93 billion (44%) for hospitalizations with a principal discharge diagnosis of AF
- $1.95 billion (29%) for the incremental inpatient cost of AF as a comorbid diagnosis
- $1.53 billion (23%) for outpatient treatment of AF
- $235 million (4%) for prescription drugs

Coyne KS, et al. *Value Health.* 2006;9:348-356.

AF=atrial fibrillation.

Key Management Embolic Disease

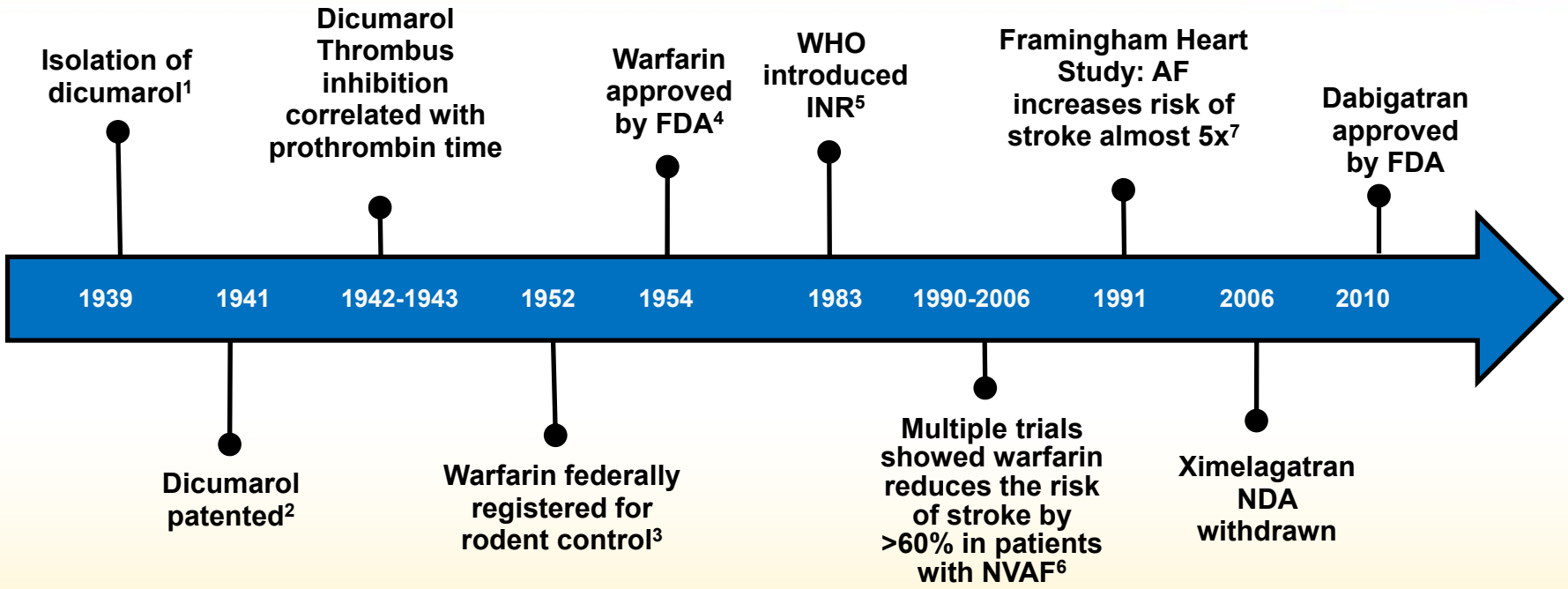
Stroke Prevention

VTE Prevention

VTE Treatment

VTE=venous thromboembolism.

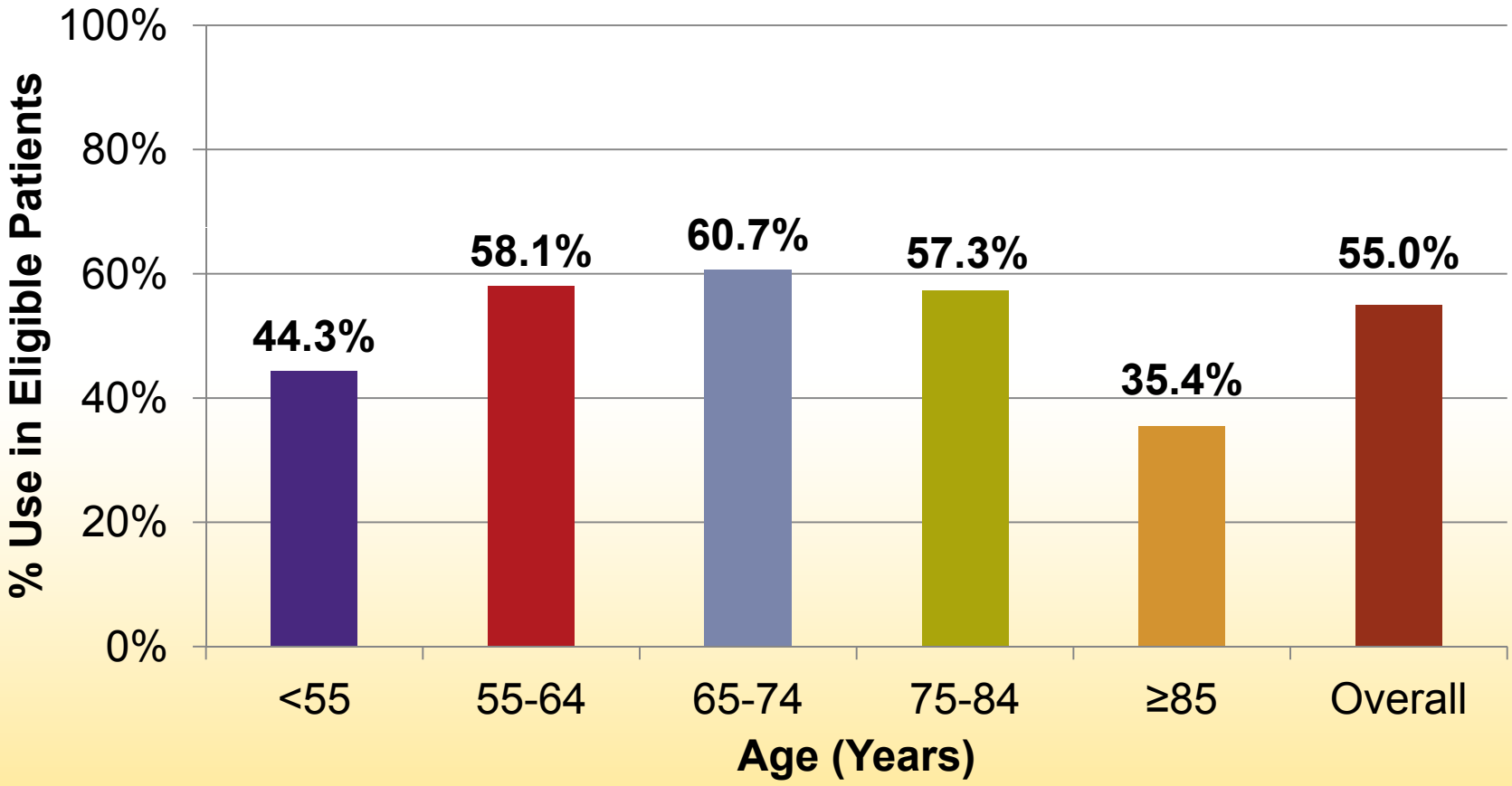
Chronology of Anticoagulation Care



AF=atrial fibrillation.
FDA=Food and Drug Administration.
INR=international normalized ratio.
NDA=new drug application.
NVAF=non-valvular atrial fibrillation.
WHO=world health organization.

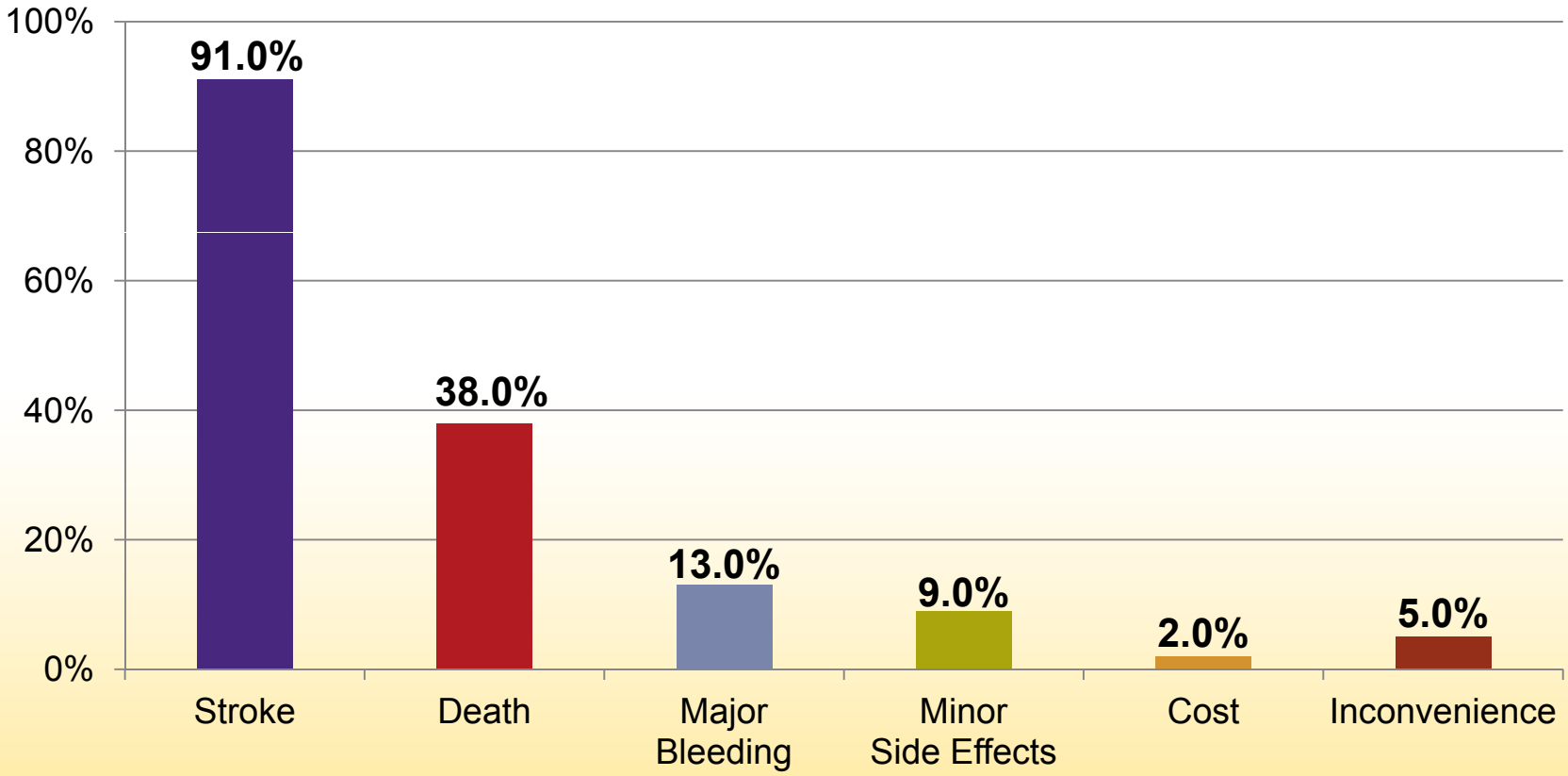
1. Link KP. *Circulation*. 1959:19:97-107.
2. Wisconsin Alumni Research Foundation. www.warf.org/about/index.jsp?cid=26&scid=34. Accessed August 2, 2010.
3. Environmental Protection Agency. June 1991.
4. Food and Drug Administration. www.accessdata.fda.gov/scripls/cder/drugsalfdalindex.cfm?fuseaclioN=Search.Label_ApprovalHislory#apphist. Accessed August 19, 2010.
5. WHO Expert Committee on Biological Standardization. Thirty-third Report.
6. Hart RG, et al. *Ann Intern Med*. 2007:146:857-867.
7. Wolf PA, Abbott RD, Kannel WB. *Stroke*. 1991:22:983-988.

Warfarin in Eligible Patients: *ATRIA Study*



Go AS, et al. *Ann Intern Med*. 1999;131:927-934.

Patient Concerns About AF



Man-Son-Hing M, et al. *Arch Intern Med*. 1996;156:1841-1848.

AF=atrial fibrillation.

Basis for Physician Choice of Warfarin in Stroke Prophylaxis: *Survey of Family Physicians*

- Physicians not prescribing warfarin (vs physicians prescribing warfarin)
  - 3-6 times more likely to believe inadequate evidence exists to support use of warfarin
  - 4-6 times more likely to be concerned with risk of hemorrhage
  - Beliefs did not change despite introduction of scenario describing high stroke risk patients
- Study conclusion: physician reluctance to use warfarin associated with false understanding of risk–benefit ratio

Pradhan AA, Levine MA. *Can J Clin Pharmacol*. 2002;9:199-202.

Physician Questionnaire Results on AF and Warfarin

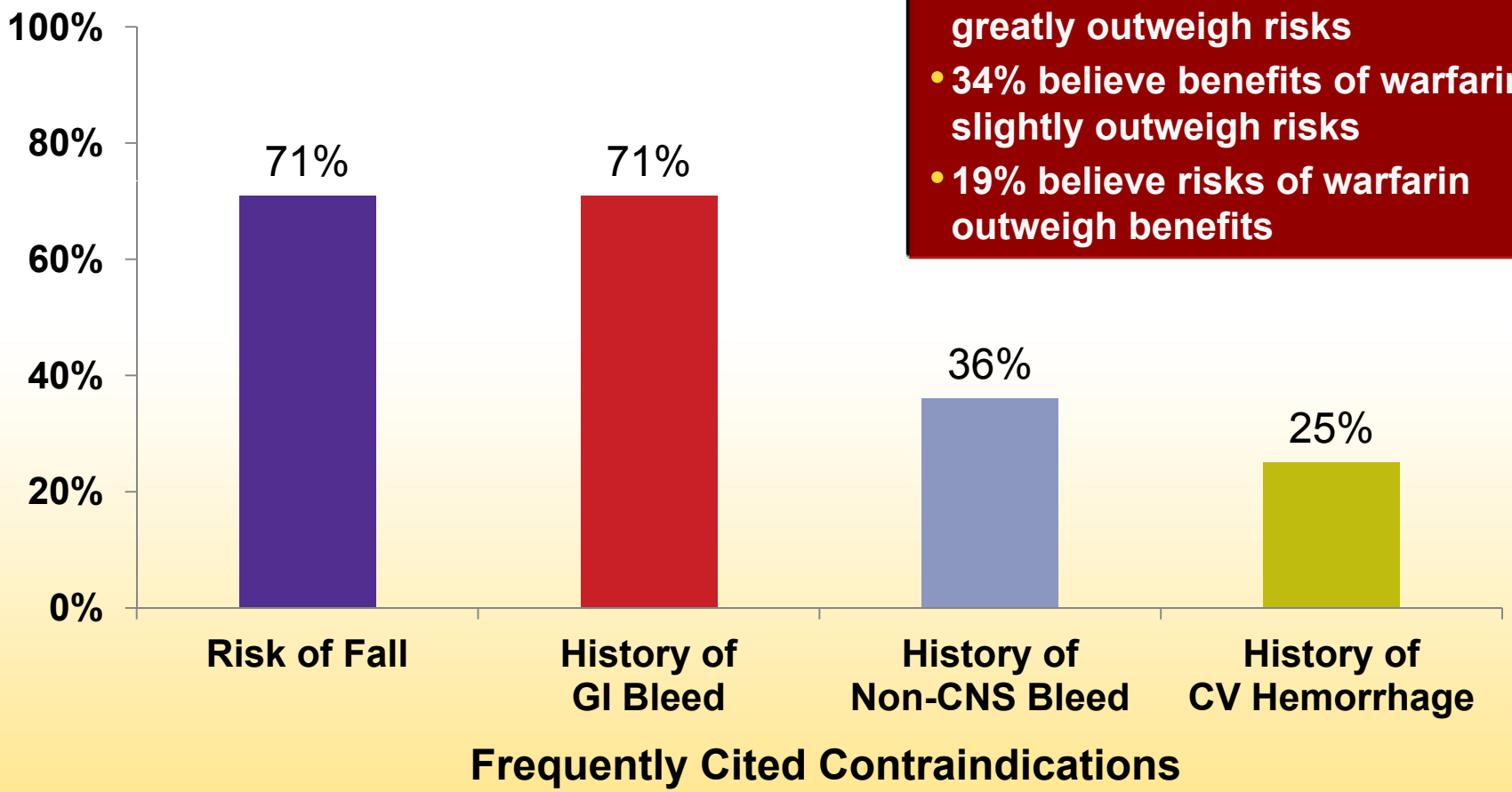
- No relationship between perceived benefits of warfarin and its use
- Perceived risk for hemorrhage strongly inversely associated with warfarin use ($P<0.001$)
- Estimated annual rates of warfarin-associated hemorrhage >10-fold higher than literature-based estimates
- Physician attitudes toward regret and risk aversion may impact treatment recommendations

Gross CP, et al. *Clin Ther*. 2003;25:1750-1764.

AF=atrial fibrillation.

Physician Concerns About Warfarin for Stroke Prevention in AF

- 47% believe benefits of warfarin greatly outweigh risks
- 34% believe benefits of warfarin slightly outweigh risks
- 19% believe risks of warfarin outweigh benefits



Monette J, et al. *J Am Geriatr Soc*. 1997;45:1060-1065.

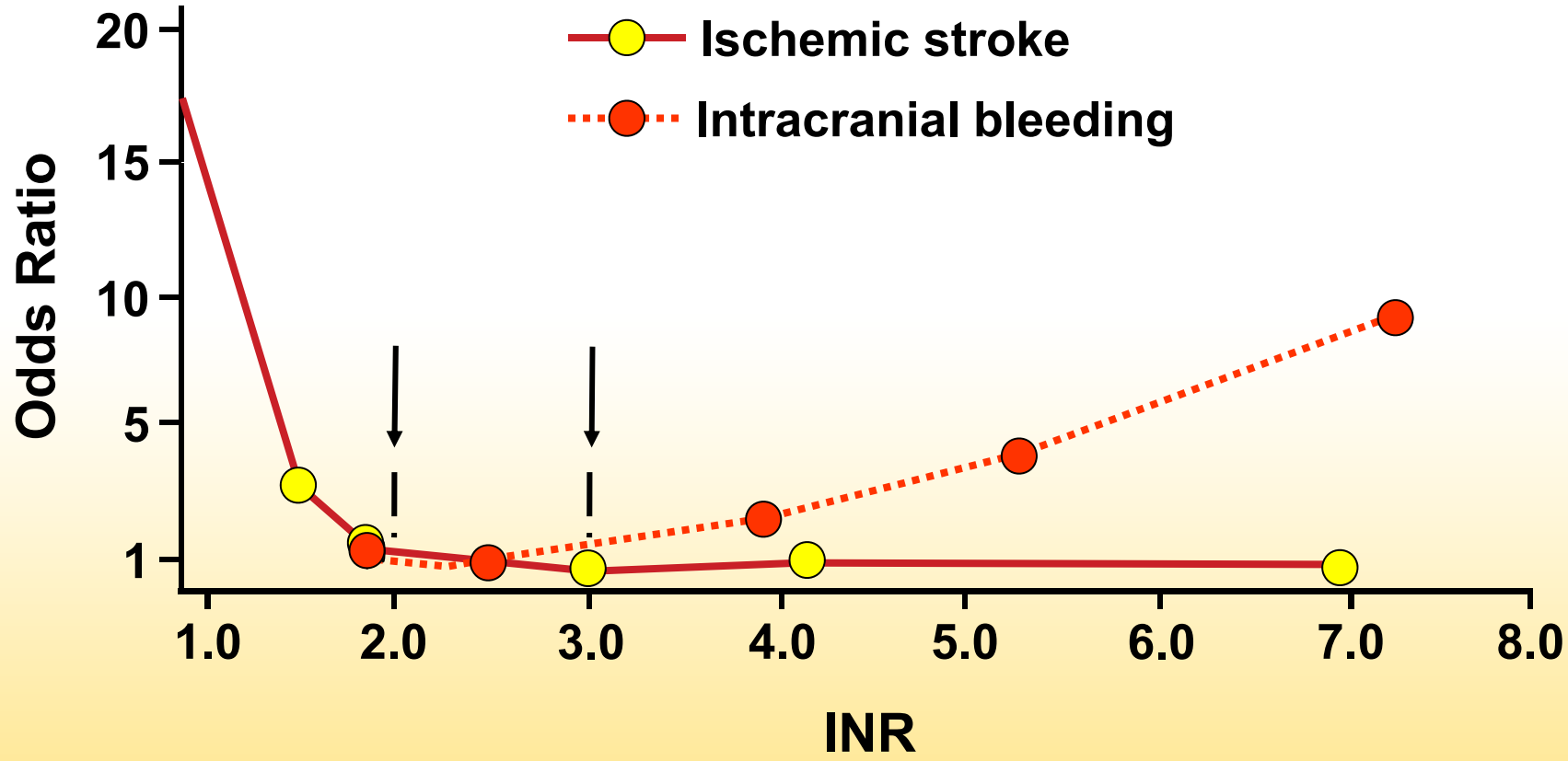
AF=atrial fibrillation.

Problems With Warfarin

- Delayed onset/offset
- Unpredictable dose response
- Narrow therapeutic range
- Drug–drug, drug–food interactions
- Problematic monitoring
- Slow reversibility

Ansell J, et al. *Chest.* 2001;119:22S-38S.
Hirsh J, et al. *Chest.* 2001;119:64S-94S.

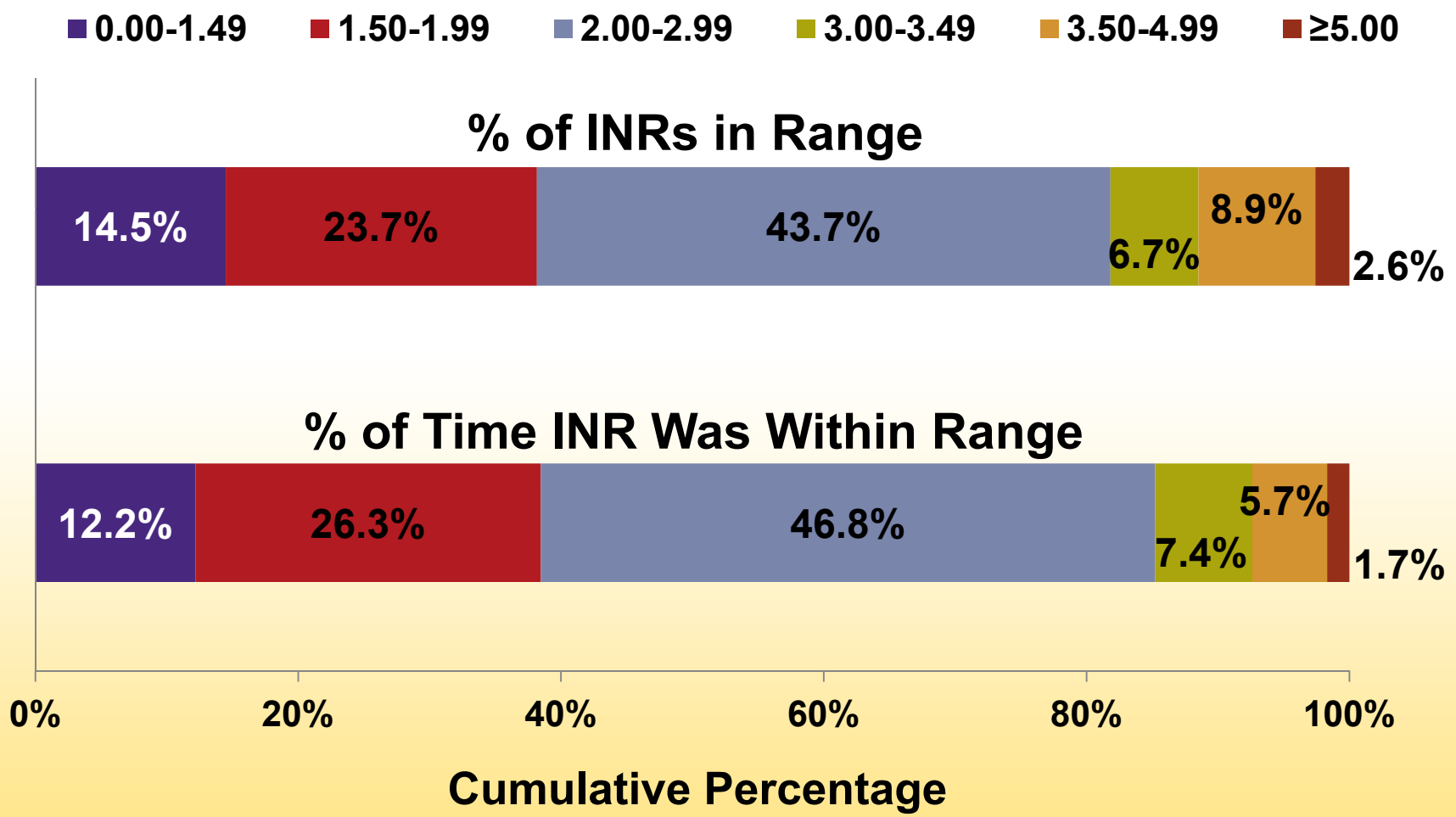
Ischemic Stroke and Intracranial Bleeding



Fuster V, et al. *J Am Coll Cardiol*. 2001;38:1231-1265.
Hylek EM, Singer DE. *Ann Intern Med*. 1994;120:897-902.

INR=international normalized ratio.

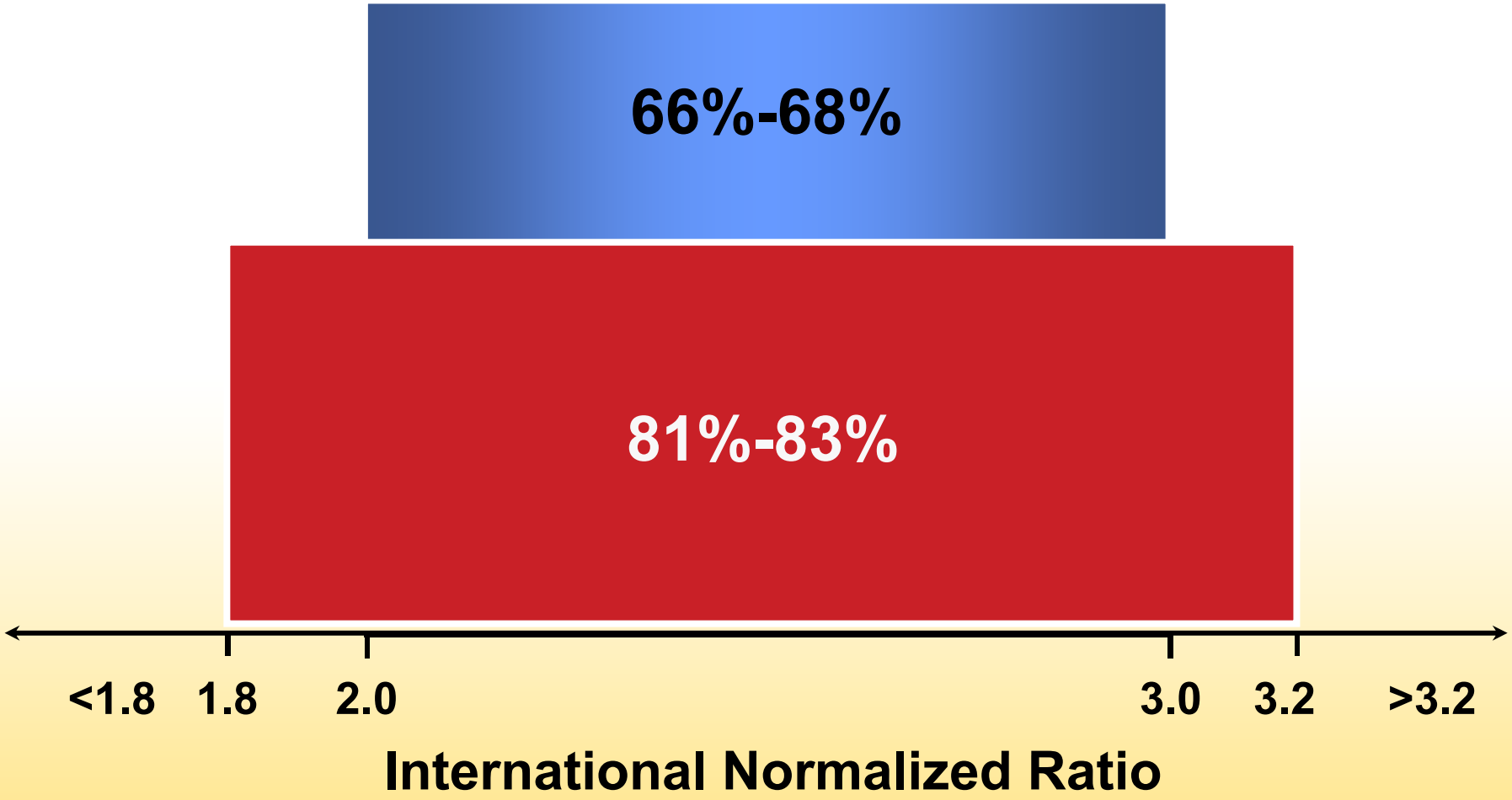
Quality of Anticoagulation



Samsa GP, et al. *Arch Intern Med*. 2000;160:967-973.

INR=international normalized ratio.

Quality of Warfarin Control
SPORTIF III and V



SPORTIF III Investigators. *Lancet*. 2003;362:1691-1698;
Halperin JL. Presented at the American Heart Association Annual Meeting. November 11, 2003; Orlando, FL.

Quality of Warfarin control RE-LY

- Warfarin administered at: 1, 3, or 5 mg
- Warfarin adjusted locally to an INR of 2.0-3.0
  - INR testing at least once every 4 weeks
  - TTR monitored closely throughout study
  - TTR reported back through the course of the trial with advice for optimizing INR control
- Mean TTR achieved: 64%
- Effects of dabigatran vs warfarin more apparent in patients with lower levels of INR control

INR=international normalized ratio.

RE-LY=randomized evaluation of long-term anticoagulant therapy.

TTR=time in therapeutic range.

Connolly SJ, et al. *N Engl J Med*. 2009;361:1139-1151.

Incorporation of Existing and Evolving Therapies Into Treatment Guidelines

ACCP Evidence-Based Clinical Practice Guidelines, 8th Edition

- In patients with AF, including those with paroxysmal AF, who have had prior ischemic stroke, TIA, or systemic embolism, we recommend long-term anticoagulation with oral vitamin K antagonist, such as warfarin, targeted at an INR of 2.5 (range, 2.0-3.0) (Grade 1A).

ACCP=American College of Chest Physicians.
AF=atrial fibrillation.
INR=international normalized ratio.
TIA=transient ischemic attack.

Singer DE, et al. *Chest*. 2008;133:546S-592S.

ACCP Evidence-Based Clinical Practice Guidelines, 8th Edition *(cont'd)*

- In patients with AF, including those with paroxysmal AF, who have ***two or more*** of the following risk factors for future ischemic stroke, we recommend long-term* anticoagulation with an oral VKA (Grade 1A):
  - Two or more of the following risk factors apply:
    1. Age >75 years
    2. History of hypertension
    3. Diabetes mellitus
    4. Moderately or severely impaired left ventricular systolic function and/or heart failure

***Lifelong unless a contraindication emerges.**

Singer DE, et al. *Chest*. 2008;133:546S-592S.

ACCP=American College of Chest Physicians.
AF=atrial fibrillation.
VKA=vitamin K antagonist.

ACCP Evidence-Based Clinical Practice Guidelines, 8th Edition *(cont'd)*

- In patients with AF, including those with paroxysmal AF, with only ***one*** of the risk factors listed below we recommend long-term* anticoagulation with an oral VKA (Grade 1A) or aspirin, at a dose of 75-325 mg/d (Grade 1B).
- For patients at intermediate risk, we suggest a VKA rather than aspirin (Grade 2A).
  - Risk factors:
    1. Age >75 years
    2. History of hypertension
    3. Diabetes mellitus
    4. Moderately or severely impaired left ventricular systolic function and/or heart failure

***Lifelong unless a contraindication emerges.**

Singer DE, et al. *Chest*. 2008;133:546S-592S.

ACCP=American College of Chest Physicians.
AF=atrial fibrillation.
VKA=vitamin K antagonist.

ACCP Evidence-Based Clinical Practice Guidelines, 8th Edition *(cont'd)*

- In patients with AF, including those with paroxysmal AF, aged ≤75 years and with none of the other risk factors listed, we recommend long-term* aspirin, at a dose of 75-325 mg/d because of their low risk for stroke (Grade 1B).
  - Risk factors:
    1. Age >75 years
    2. History of hypertension
    3. Diabetes mellitus
    4. Moderately or severely impaired left ventricular systolic function and/or heart failure

***Lifelong unless a contraindication emerges.**

Singer DE, et al. *Chest*. 2008;133:546S-592S.

ACCP=American College of Chest Physicians.
AF=atrial fibrillation.
VKA=vitamin K antagonist.

2011 ACCF/AHA/HRS Focused Update on the Management of Patients With AF (Update on Dabigatran)

- Dabigatran is useful as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal to permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance 15 mL/min), or advanced liver disease (impaired baseline clotting function) (Class I Recommendation; Level of Evidence: B).

ACCF=American College of Cardiology Foundation.
AHA=American Heart Association.
HRS=Heart Rhythm Society.
AF=atrial fibrillation.

Wann LS, et al. *Heart Rhythm*. 2011;8:e1-8.

Anticoagulation Clinics

- Pharmacist-managed anticoagulation services are the most widely utilized case management strategies for patients with AF
- Clinics provide coordinated clinical infrastructures for
  - Patient education
  - Therapeutic monitoring
  - Dose adjustment to keep warfarin within its narrow therapeutic window

Johnson SG. *J Manag Care Pharm*. 2009;15(Suppl):S19-S25.

AF=atrial fibrillation.

Future of Anticoagulation Clinics in the Era of New Oral Anticoagulants

- DTIs have many potential advantages over warfarin, including predictable therapeutic effect at fixed doses and limited drug–drug interactions[1]
  - These features may allow for routine therapy without monitoring and associated dosage adjustments
- DTIs present both an opportunity and a threat to anticoagulation service providers[2]
- Traditional anticoagulation monitoring services will have to retool if they are to remain relevant[2]

1. Ansell J. *Hematology*. 2010;221-228.
2. Nutescu EA, et al. *Pharmacotherapy*. 2004;24:199S-202S.

DTI=direct thrombin inhibitor.

Essential Elements of Optimal Anticoagulation Did Not Change for 60 Years…

- The successful use of (anticoagulation) depends on an "essential triad" which includes a
  - Vigilant clinician
  - Cooperative (well educated) patient
  - Readily available and reliable laboratory
- If these factors are present, continuous use of anticoagulation is practical...and effective; if not, the use of the drug is dangerous…

Foley WT, Wright IS. *Am J Med Sci*. 1949;217:136-144.
Aske JM, Cherry CB. *J Am Med Assoc*. 1950;144:97-100.

…However, the Arrival of New Oral Anticoagulants Will Impact Plan Policies and Processes

- Availability of new oral anticoagulants will impact the way plans think about care delivery and management for patients with atrial fibrillation
  - Clinical management including guidelines/algorithms, patient education, monitoring, etc.
  - Clinical infrastructure and staffing
  - Cost management including cost-sharing, benefit design, formulary structure, etc.

Kirsch B. *Manag Care*. 2011;20(2):33-36.

What Is the Role of Guidelines?

- Will guidelines be product-specific?
- Will guidelines allow flexibility in management?

Will Plans Restrict Access to New Oral Anticoagulants?

- Is there a reason to restrict the use of the new oral anticoagulants?
  - Step therapy through warfarin?
  - Prior authorization for an atrial fibrillation indication?

- Financial risk is high for use that has not been approved

What Is the Anticipated Impact of Future Indications and Additional New Therapies?

Anticoagulant Pipeline and Anticipated Indications (Projected)

	MOA	2010	2011	2012	2013	2014
Rivaroxaban	Xa		Hip & knee AF	Med ill ACS	VTE	
Dabigatran	DTI	AF	Hip & knee			
Apixaban	Xa			Med ill, VTE (2Q) AF (3Q) Hip & knee (4Q)	ACS	
Betrixaban	Xa				Hip & knee	AF
Edoxaban	Xa				AF, VTE	
Ticagrelor	ADP		ACS			
Tra-Sch	TRA			ACS	ACS/NSTEMI	
Clopidogrel*	ADP		AF			

ACS=acute coronary syndrome.
ADP=adenosine diphosphate.
AF=atrial fibrillation.
DTI=direct thrombin inhibitor.
MOA=mechanism of action.
NSTEMI=non-ST segment elevation myocardial infarction.
TRA=thrombin-receptor antagonists.
VTE=venous thromboembolism.
Xa=direct factor Xa inhibitors.

*Patent expiry: November 2011.

Adapted from Weitz JI. *Thromb Haemost*. 2007;5 Suppl 1:65-7.

New Oral Anticoagulants Have the Potential to Become a Replacement for Warfarin

- Given the challenges associated with warfarin, an oral anticoagulant is especially attractive
- Features of oral anticoagulants that may be associated with greater adherence include
  - Do not require monitoring
  - Fewer adverse effects, drug-drug, and drug-food interactions
- Improved adherence may reduce the risk of subtherapeutic INR and may lead to better treatment outcomes and possibly lower costs

Kirsch B. *Manag Care*. 2011;20(2):33-36.

INR=international normalized ratio.

Disadvantages of New Oral Anticoagulants

- Short half-life of oral anticoagulants makes adherence important
- Reduced monitoring may deny physician the opportunity for patient education and the earlier detection of problems
  - Denies practitioner the opportunity to tailor the intensity of anticoagulant therapy for patient-specific factors
- Acquisition costs associated with oral anticoagulants will be greater than for warfarin
  - Payers may erect barriers to access
  - Cost-sharing may decrease adherence

Ansell J. *Hematology*. 2010;221-228.

Formulary Management Considerations and Managed Care Issues

- Preferred agents
  - Collaborate with providers
  - Guidelines?
- Contracting opportunities?
- Limit to data and indications
  - Step edits
  - Prior authorizations
- PMPM and budgeting with employers
  - Direct current costs vs cost offsets

Ansell J. *Hematology*. 2010;221-228.

PMPM=per member, per month.

Impact of New Agents on Current and Future Guidelines and Protocols

- "These drugs will change the paradigm in stroke prevention for atrial fibrillation in the United States, and that is a very, very good thing"
- "…they are very relevant to managed care organizations"
- Their approval "should change the way health care organizations think about health care delivery for patients with atrial fibrillation"

Kirsch B. *Manag Care*. 2011;20(2):33-36.