CSRC Thinktank: Anticoag Bleeding and Reversal, April 22, 2014

[What is the unmet need?] How should the risks and benefits be balanced?

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Disclosures

- Daniel E. Singer, M.D.:
- Consultant/Advisory Board: Bayer Healthcare; Boehringer Ingelheim; CSL Behring, Bristol-Myers Squibb; Daiichi Sankyo; Johnson and Johnson; Pfizer; Medtronic; St. Jude Medical.
- Research Grants: Johnson and Johnson, Bristol-Myers Squibb; Medtronic.
- Executive Committee: ROCKET-AF trial of rivaroxaban in AF.

Framework: Balancing Risks and Benefits

Assuming an AF perspective: predominant indication; older, bleed-prone patients

"Rational," "Spockian," decision analytic approach:

- Inventory the events of interest
- Estimate probabilities of events on and off OAC (incidence); assign weights
- Add in impact of taking Rx
- Factor in life expectancy
- Determine net benefit as ΔQALYs

Framework: Balancing Risks and Benefits

Relevant event rates: Warfarin vs No OAC*

Thrombotic	**Δ Rate, per yr**	**Hemorrhagic**	**Δ Rate, per yr**
Ischemic stroke	(3%-1%)=2%	ICH: Intracerebral	(0.5%-0.2%)=0.3%
Systemic embolism	(too small)	ICH: Subdural	(0.2%-0.1%)=0.1%
(VTE)		ECH-m: GI	(2%-1.3%)=0.7%
(MI)		ECH-m: Other	(1%-0.6%)=0.4%
		ECH: NMCI	(12%-??)

*These are approximate estimates drawn from diverse sources and are meant to illustrate the general magnitude of risks and benefits considered.

Framework: Balancing Risks and Benefits

Relevant events: Impact: 30-day Mortality %

Thrombotic	Fatality: On OAC	Off OAC	Hemorrhagic	Fatality On OAC	Off OAC
Ischemic stroke	20%	28%	ICH: Intracerebral	60%	40%
Systemic embolism	(too small)		ICH: Subdural	31%	20%
(VTE)			ECH: GI	~7%	~7%
(MI)			ECH: Other	~3%	~3%
			NMCI	0%	

*Disability: Intracranial events >>> extracranial events

Fang et al. Neurology 2014;82:1–5; Stroke. 2012;43:1795-1799

Framework: Balancing Risks and Benefits

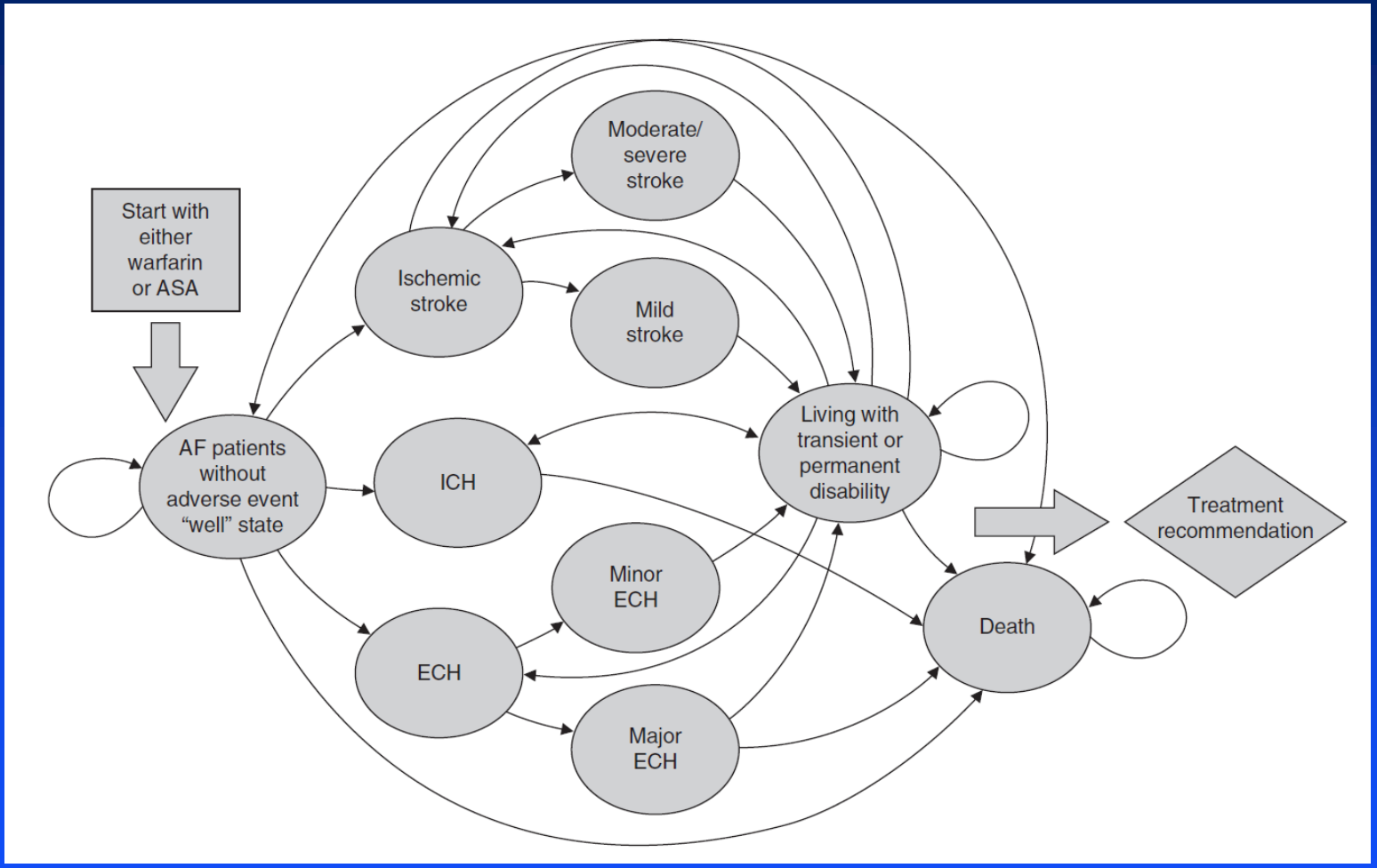
Impact of relevant outcomes: Formal utility weighting

Outcome	Utility
Well	100
Mild disability	0.76
Severe disability	0.11
Death	0

Extracranial hemorrhage gets 0.84 for hospitalization

Eckman et al. Circ Cardiovasc Qual Outcomes 2011;4;14-21

Framework: Balancing Risks and Benefits



Casciano et al. Am J Cardiovasc Drugs 2012;12:313-323

Formal AF RCT “Net Clinical Benefit”

Ischemic stroke, hemorrhagic stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding: Unweighted

N Engl J Med 2009; 361:1139-51.

ATRIA: Net Clinical Benefit of Warfarin in AF

Net Clinical Benefit is ~Net Intracranial Benefit as *TEs prevented minus ICHs induced:*

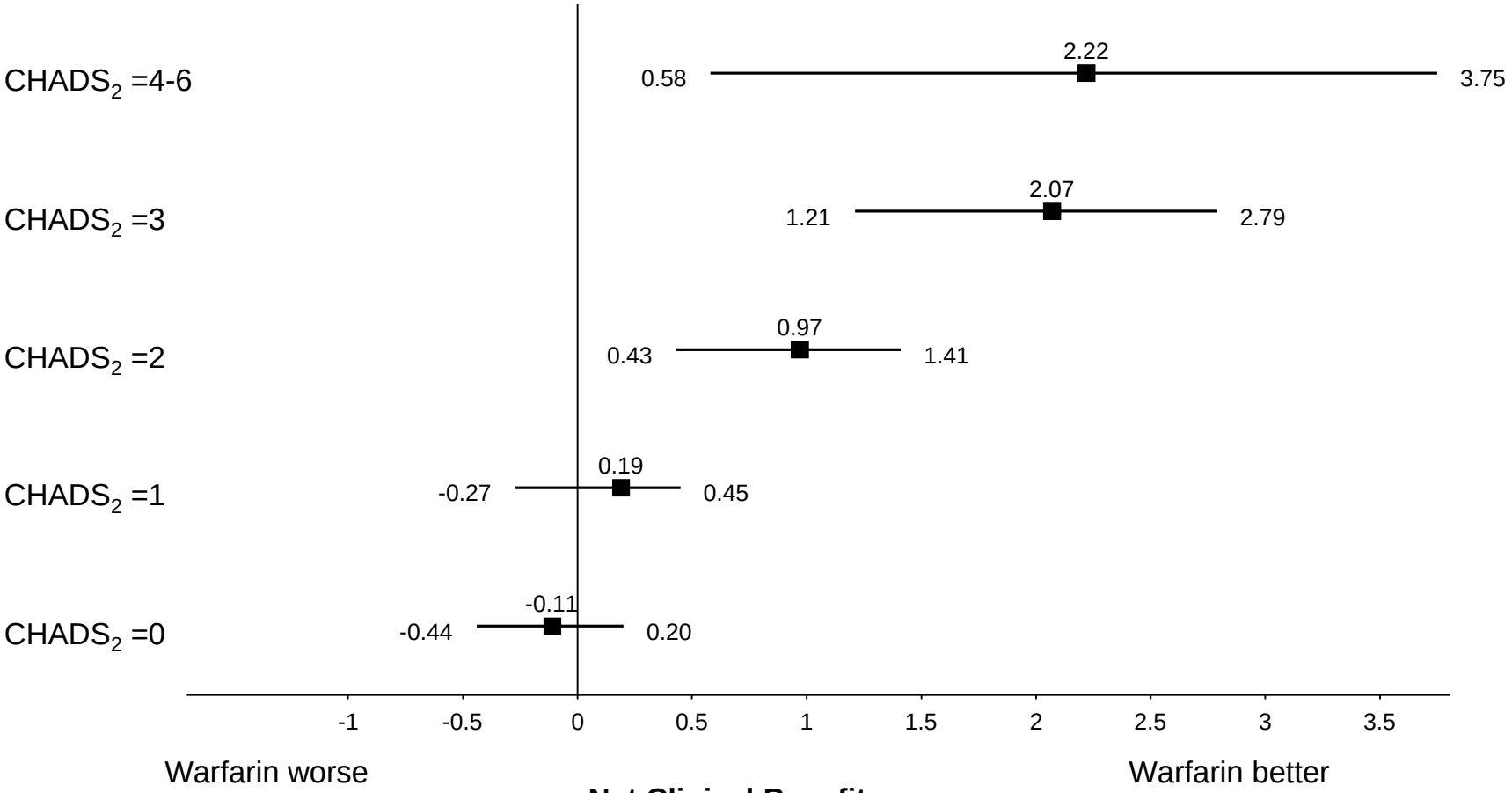
(TE rate off warfarin - TE rate on warfarin)

minus 1.5x

(ICH rate on warfarin - ICH rate off warfarin)

Ann Intern Med 2009;151:297-305

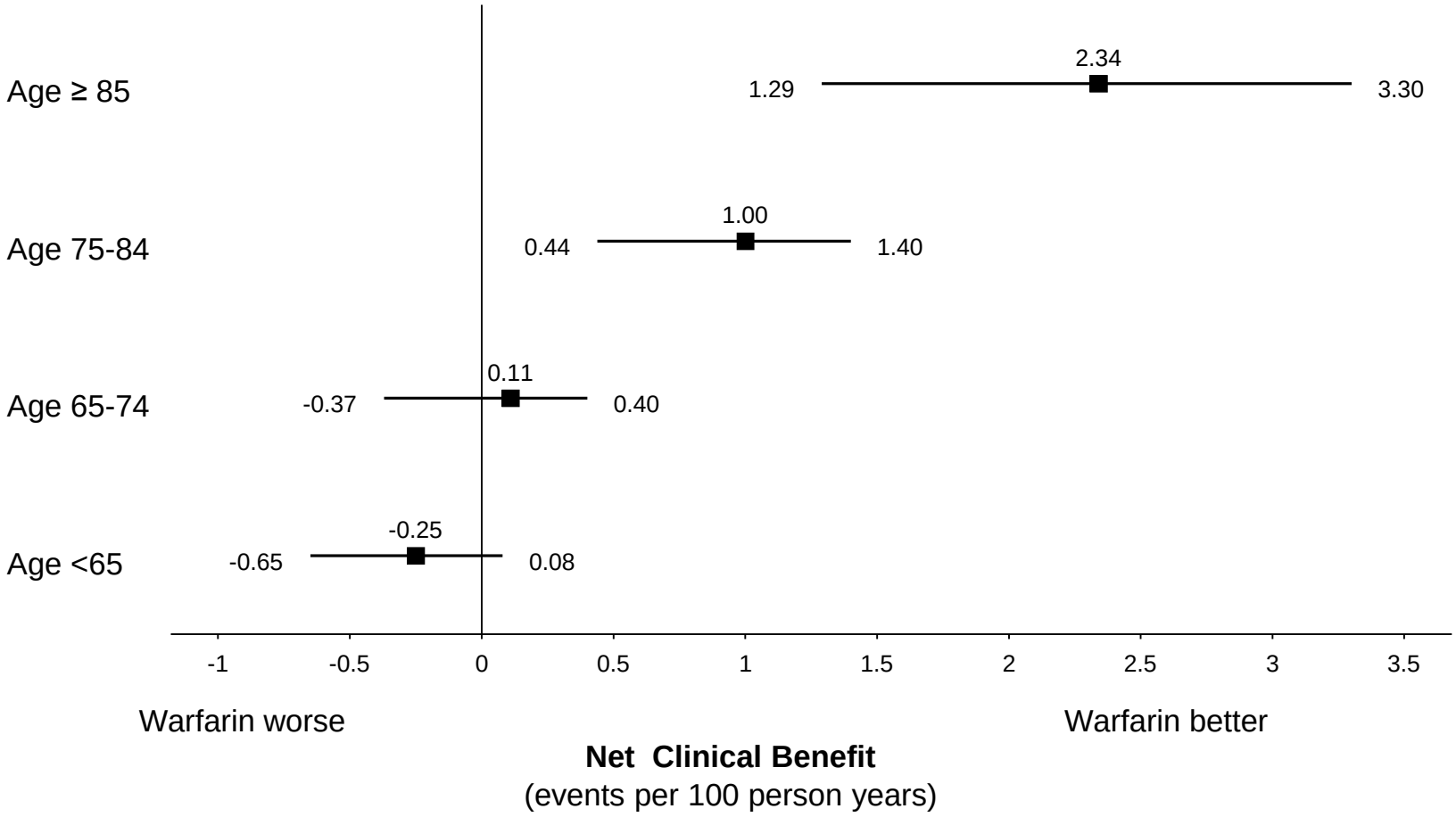
The net clinical benefit of warfarin by $CHADS_2$ score*



*$CHADS_2$ is a widely used stroke risk classification scheme for patients with AF.[6] C=congestive heart failure; H=hypertension; A=age≥75 years; D=diabetes; and S=prior ischemic stroke. The presence of each clinical feature confers one point except for S which confers 2 points.

Ann Intern Med 2009;151:297-305

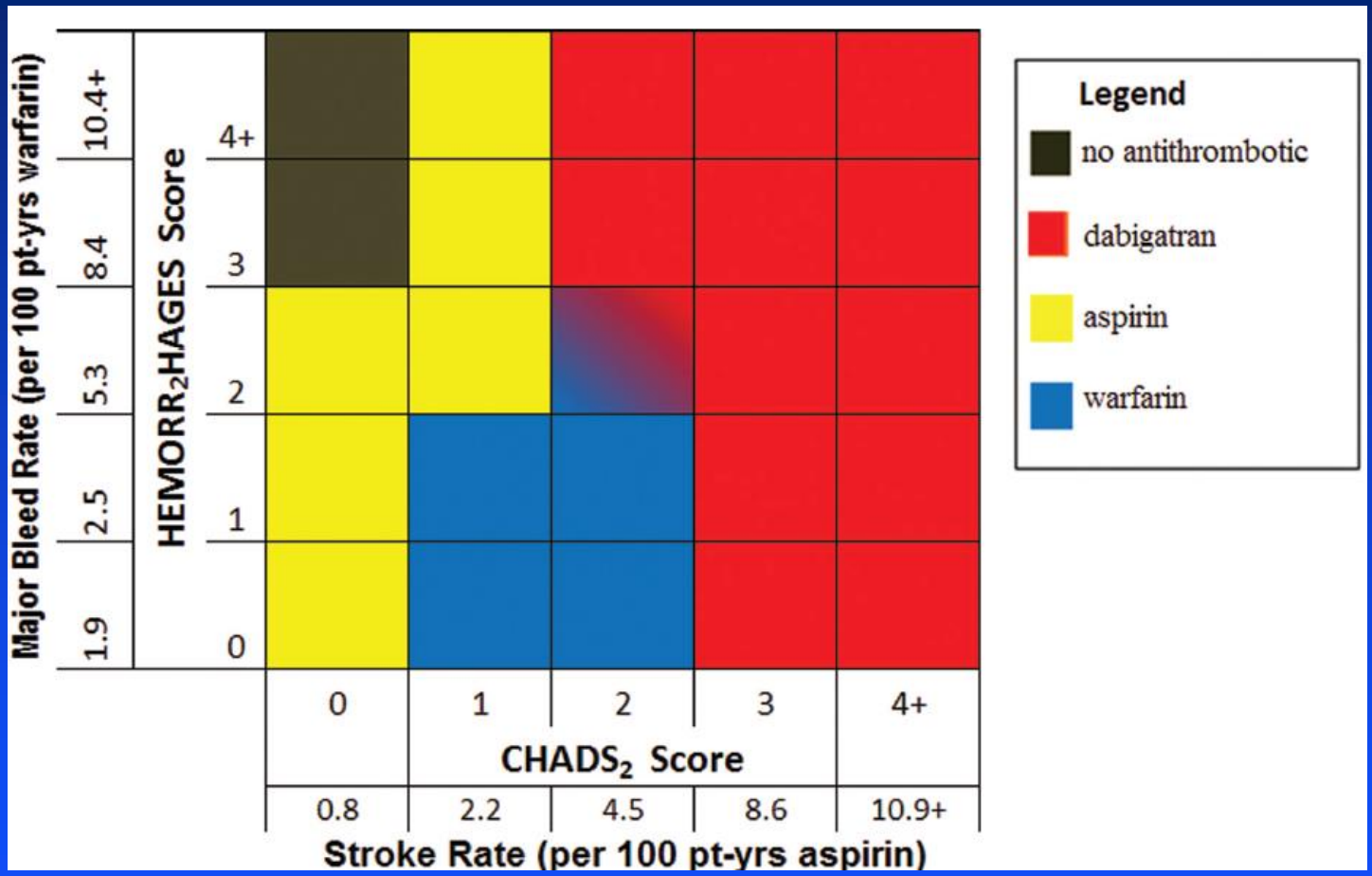
The net clinical benefit of warfarin by age group



Ann Intern Med 2009;151:297-305

The formal anticoagulation decision is highly sensitive to stroke risk but not bleed risk

The Anticoagulation Decision In AF: Relative Influence of Stroke vs Bleed Risk



Circulation 2011;123:2562-2570

The Anticoagulation Decision In AF: "Kahnemannian" irrationalities

Overweighting GI bleeds vs Strokes:

Relative importance: GI bleeds:Strokes	
Physicians	4:1
Patients	10:1

Adapted from Devereaux et al. BMJ 2001;323:1–7

Impact of reversal agents on the anticoag decision: Individual patient

Tip the decision towards OAC (i.e., NOAC):

- Respond to awkward patient questions re “reversal”
- Reduce physician overweighting of GI bleeds
- Reduce physician malpractice concern re OAC major bleeds without reversal agent

Impact of reversal agents on the anticoag decision: Population health

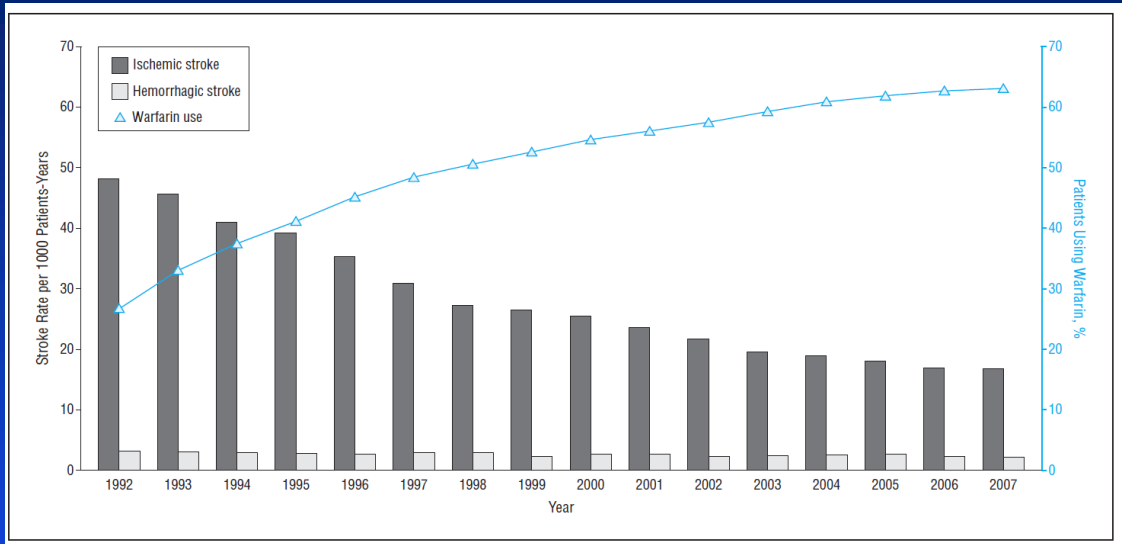


Figure. Trends in ischemic and hemorrhagic stroke rates and warfarin use among patients with prevalent atrial fibrillation.

The public health promise of NOACs: Expand the use of safe, effective anticoagulation beyond the “60%” barrier.

JAMA Intern Med. 2013 Jan 28;173(2):159-60.

END