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Thromboembolic risk factors after cardioversion  
of atrial fibrillation

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## The Burden of Hemorrhagic Complications in Patients Undergoing Cardioversion: Transesophageal Echocardiographically Guided Versus Conventional Anticoagulation Strategies.

Christoph Stellbrink,

Dept. Of Cardiology & Intensive Care Medicine  
Bielefeld Medical Center, Germany

# Increased Risk of Embolism After Cardioversion of AF

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- Pre-existing thrombi (left atrial appendage)
- Reduced atrial contractility („stunning“)
- Activation of procoagulant factors

# Embolic Risk After Cardioversion of AF

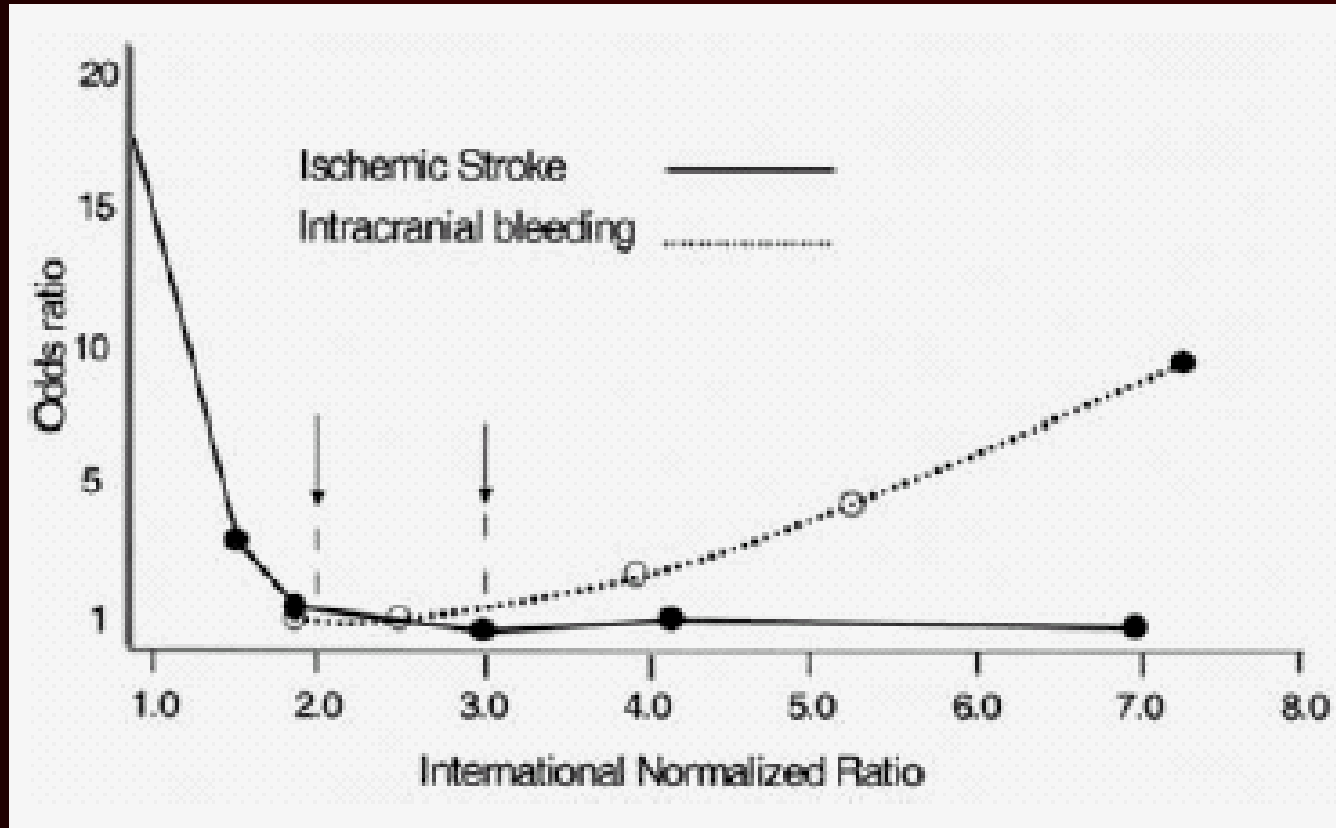


- 5-7% thromboembolic risk without anticoagulation<sup>1-3</sup>.
- thrombi mostly in the left atrial appendage; frequently develop after cardioversion<sup>4</sup>.
- Actualized guidelines of ACC/AHA<sup>5</sup> for AF > 48 h:
  - Anticoagulation (INR 2.0 – 3.0) for 3 wks. before and 4 wks. after CV
  - **OR**
  - Exclusion of LAA thrombi by TEE with UFH (or LMWH), followed by at least 4 weeks of oral anticoagulation

<sup>1</sup>Arnold et al., JACC 1992; <sup>2</sup>Bjerkelund Am J Cardiol 1969; <sup>3</sup>Weinberg et al. Am J Cardiol 1989;

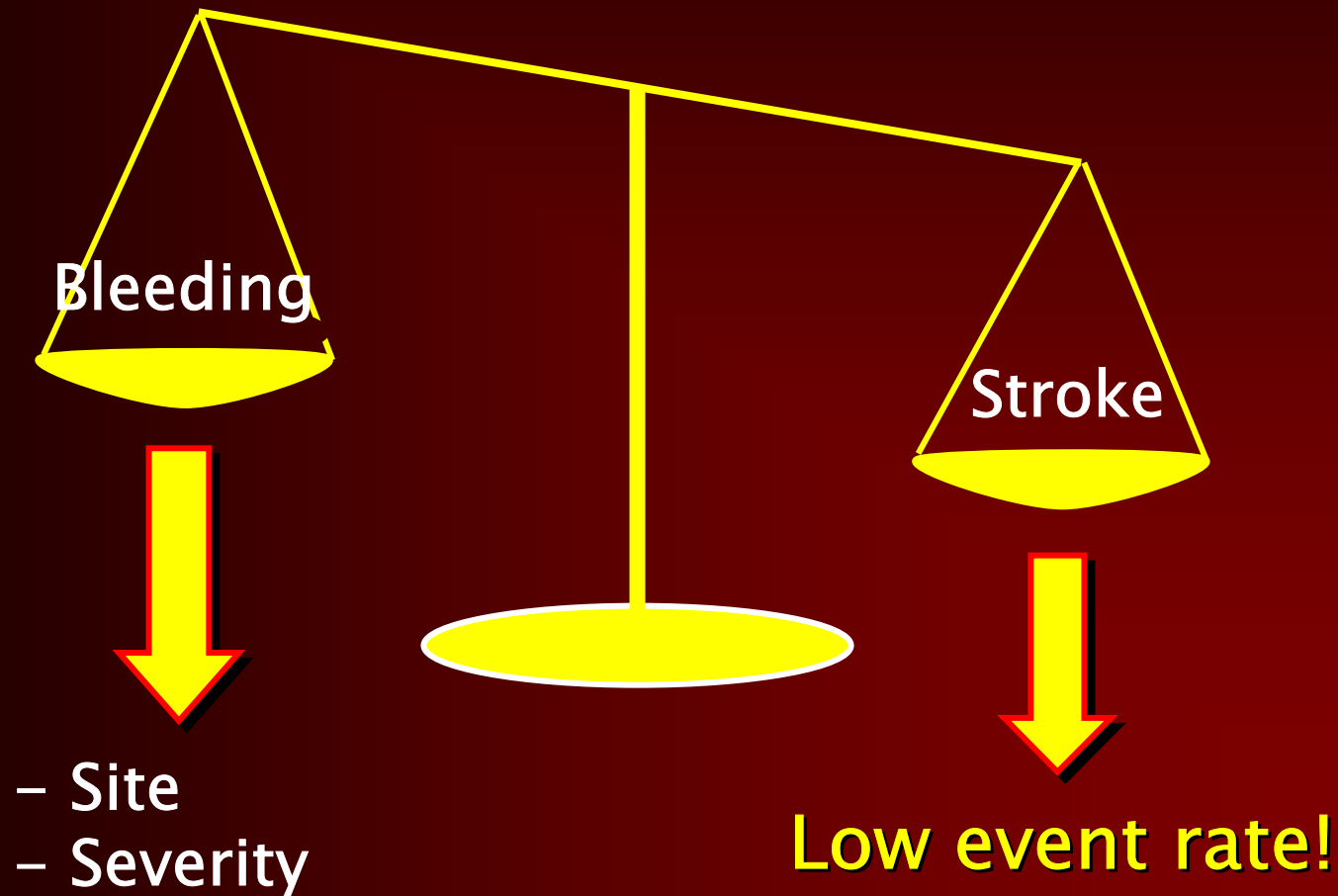
<sup>4</sup>Fatkin et al., JACC 1994; <sup>5</sup>ACC/AHA/ESC Guidelines, Eur Heart J 2006

# Optimal Dosing of Anticoagulants



*Hylek, Ann Intern Med 1994*

# Judging The Risk of Anticoagulation in AF




# Classification of Bleeding Severity

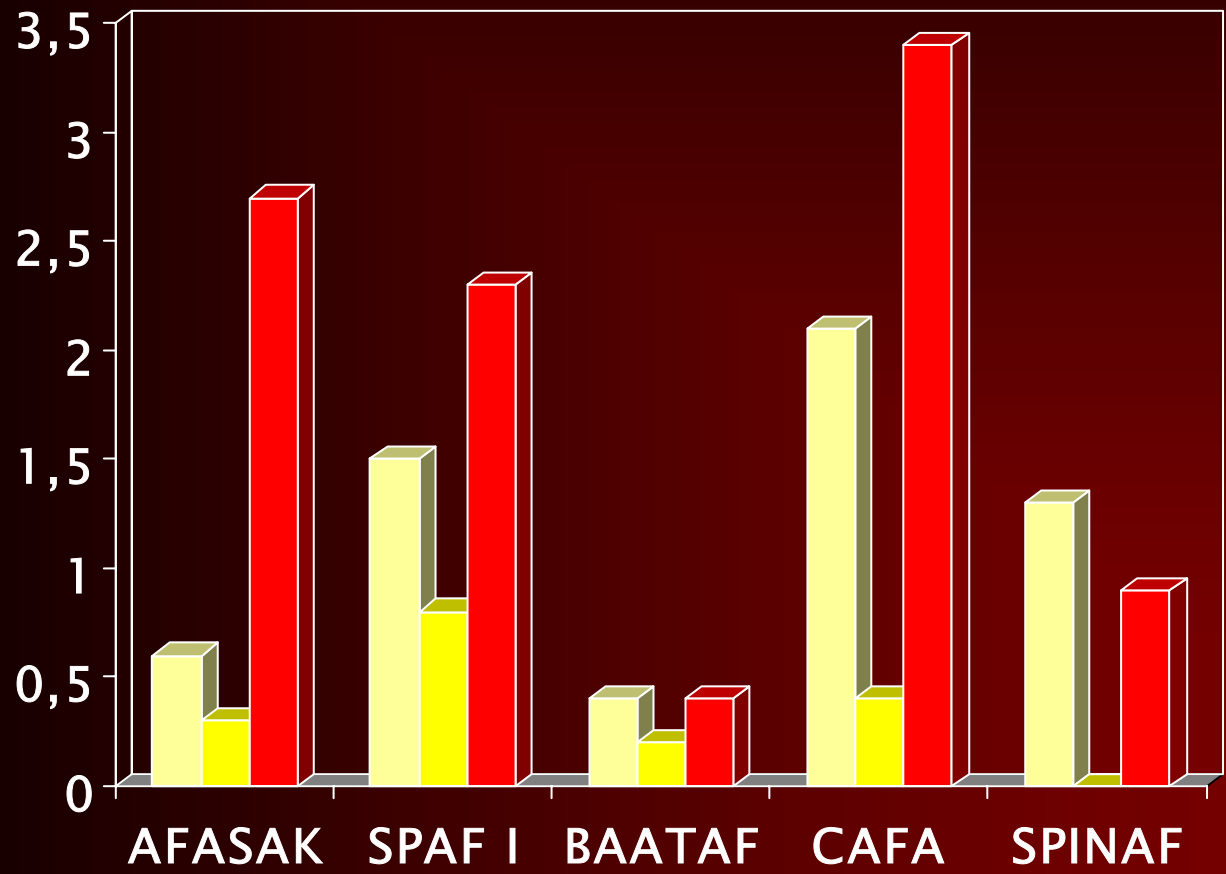
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- Major hemorrhage
  - Intracranial hemorrhage (ICH)
  - Causing death
  - Causing hospitalization, permanent disability
  - Requiring blood transfusion
- Minor hemorrhage
  - All other
  - Injection hematoma (e.g. with LMWH)

 ICH is the only hemorrhagic complication producing deficits as great or greater than ischemic stroke

# Major and Intracranial Bleeding Risk in Chronic Anticoagulation Trials



■ All major  
■ ICH  
■ I° endpoint\*

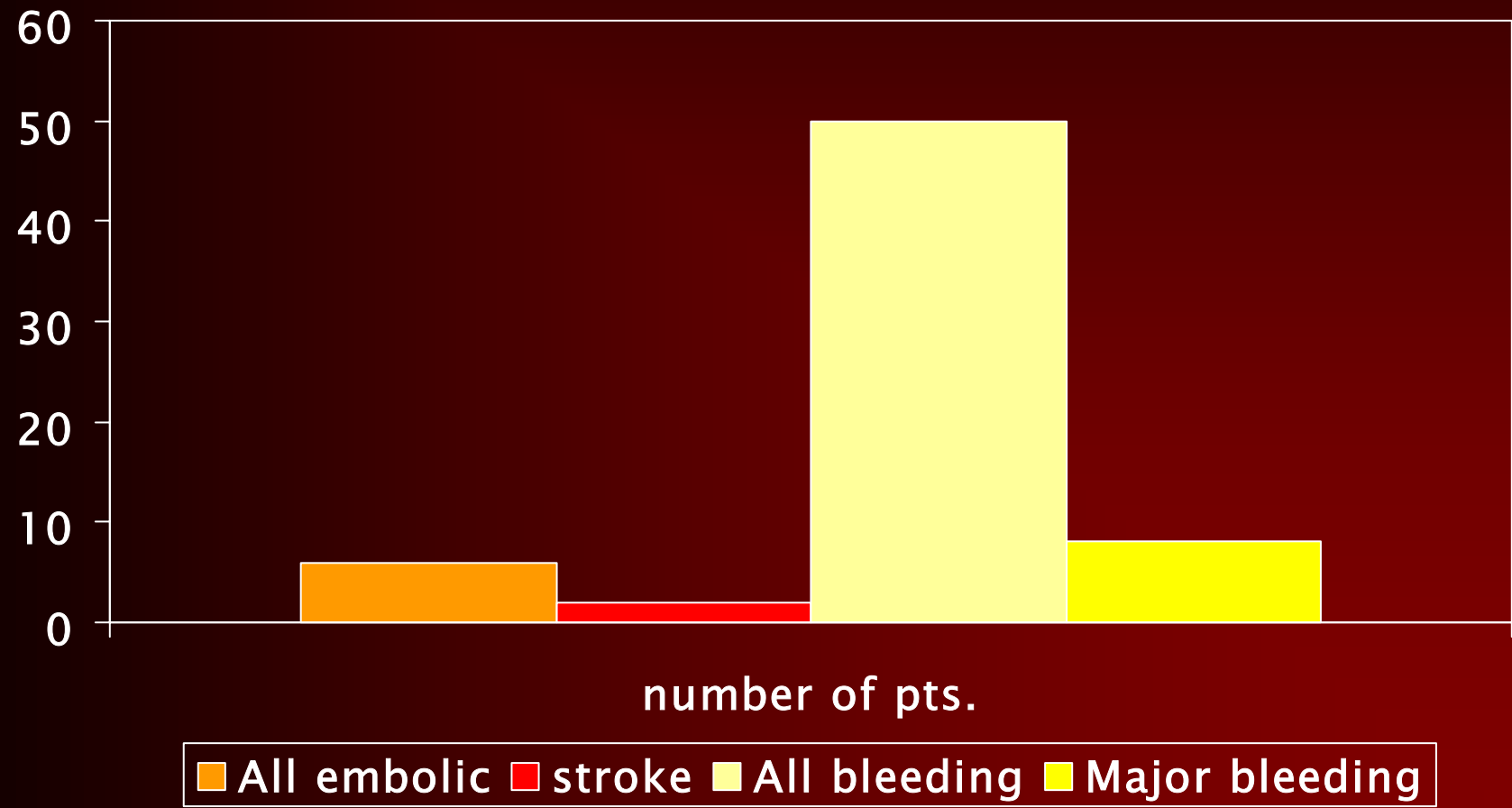
*ACCP conference,  
Chest 2004*

\*varies among studies;  
mostly composite of death, stroke and systemic embolism

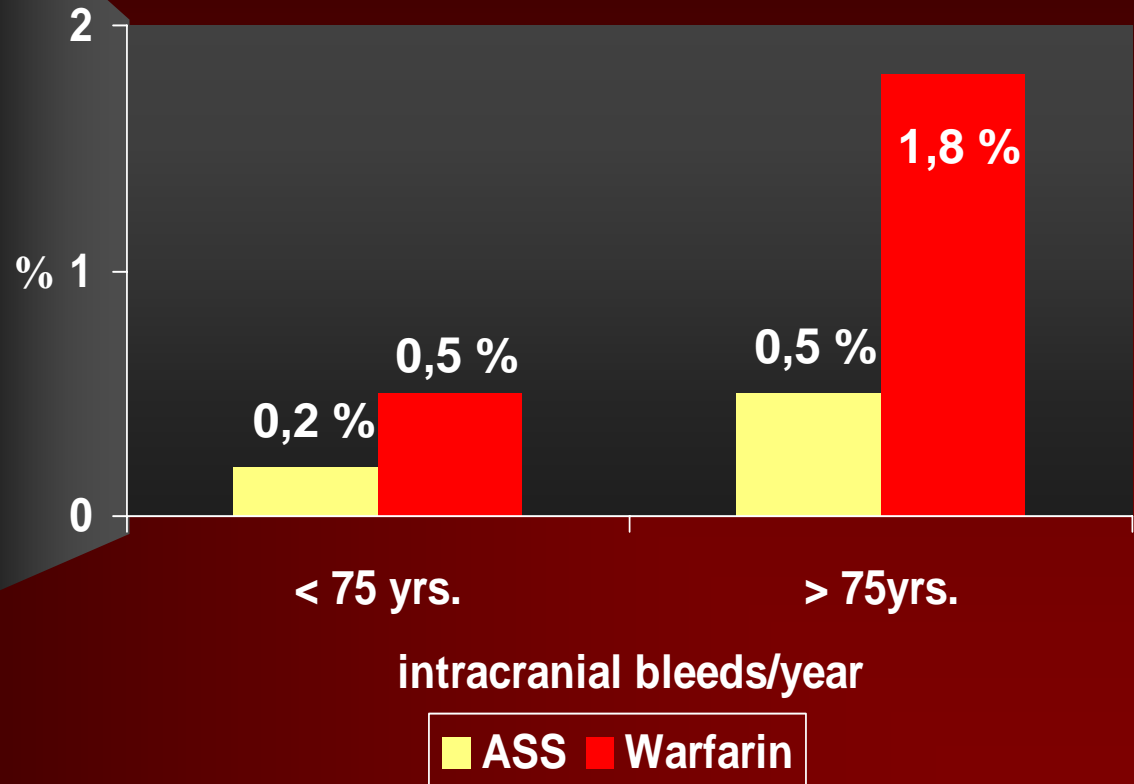
# Embolic and hemorrhagic events in the ACE trial



496 pts. with non-valvular AF randomized to LMWH or UFH/oral anticoag. before/after CV



# Bleeding risk with warfarin

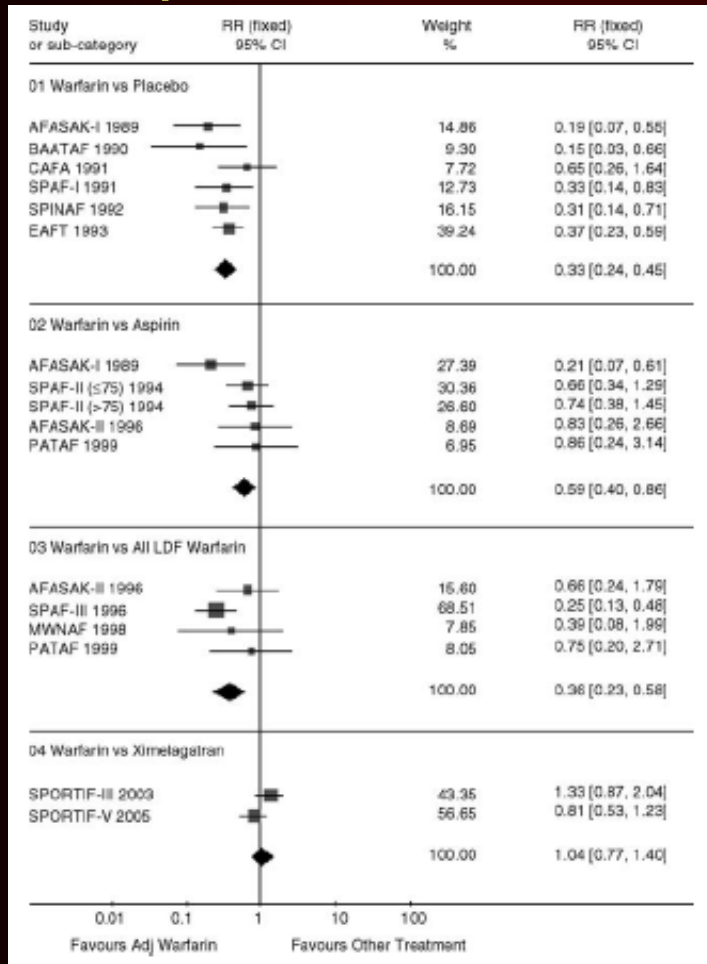


SPAF II Investigators, Lancet 1994

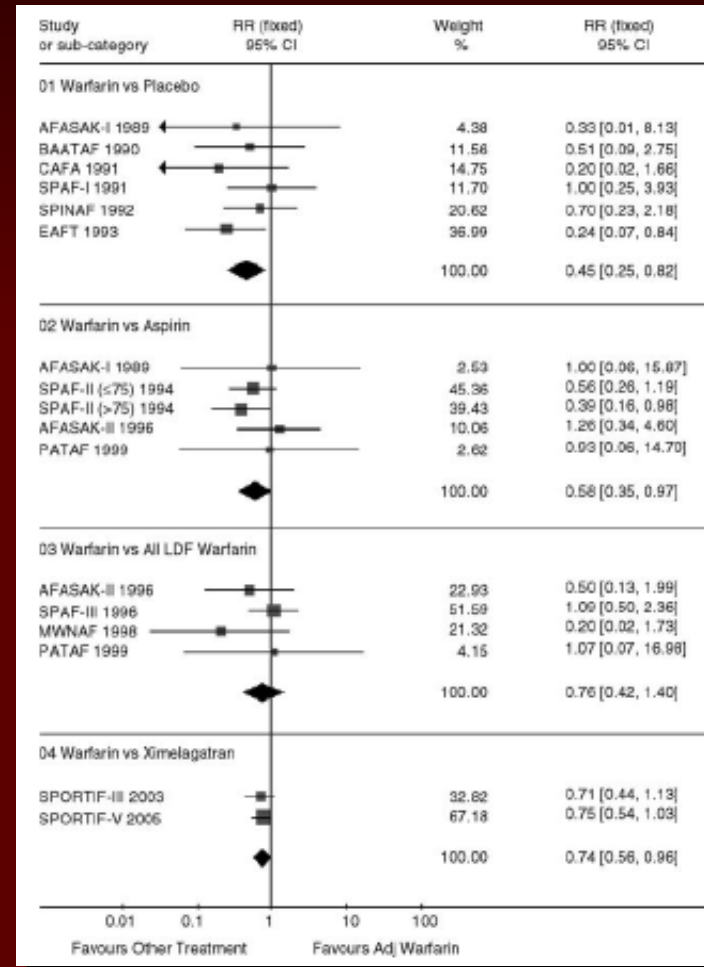
# Anticoagulation in AF – Effects on Stroke, Emboli and Bleeding



## Stroke or systemic embolism



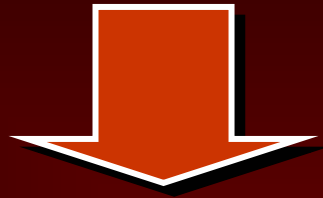
## Major bleeding



# Oral Anticoagulants are Often Underused in AF



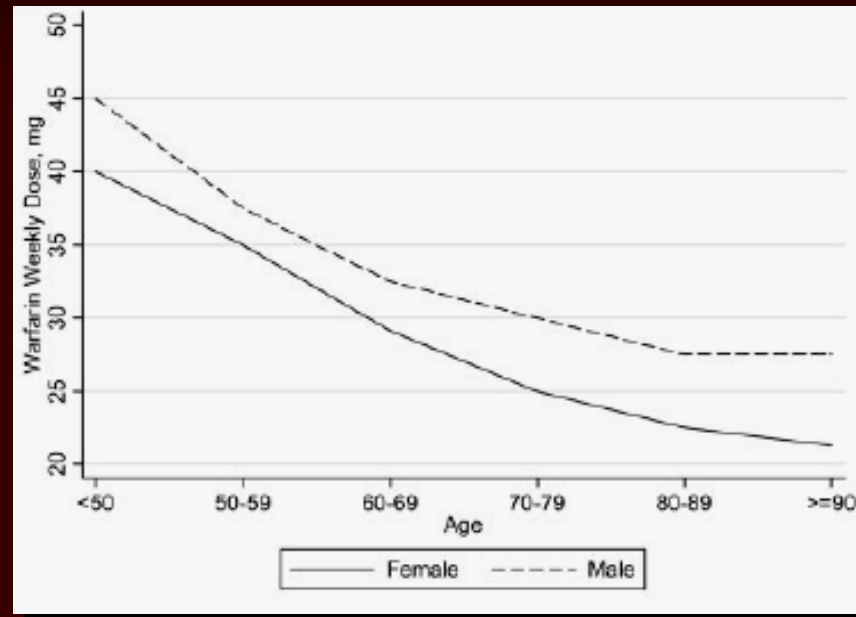
Retrospective Analysis von 78787 Emergency Room Visits in Cincinnati (OH) and Ann Arbor (MI), USA



- 866 pts. with non-valvular AF (1,1%), of these:
- 556 pts. with previously known AF:
  - 221 (40%) on warfarin alone
  - 155 (28%) on aspirin or ticlopidin/clopidogrel
  - 152 (27%) without antithrombotic therapy
- 61% of warfarin-treated pts. were outside the desired INR range of 2.0 – 3.0

*Scott et al., JACC 2002*

# Warfarin Dose Depends on Age and Gender



→ Suggested Initiation Dosage is Excessive in 82% of women and 65% of men >70 yrs.

Other factors:

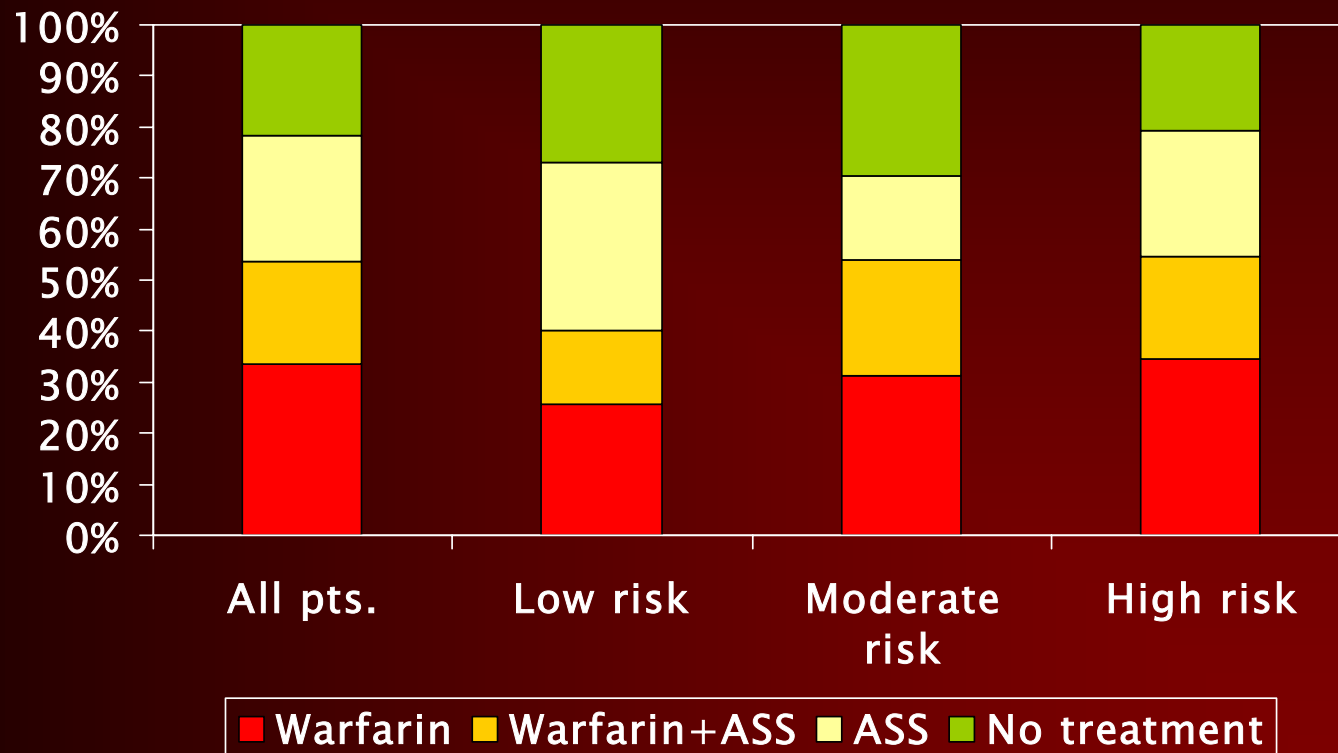
- CAD
- Heart failure
- Amiodarone
- Diabetes

*Garcia et al.,  
Chest 2005*

# Real-World Anticoagulation in AF



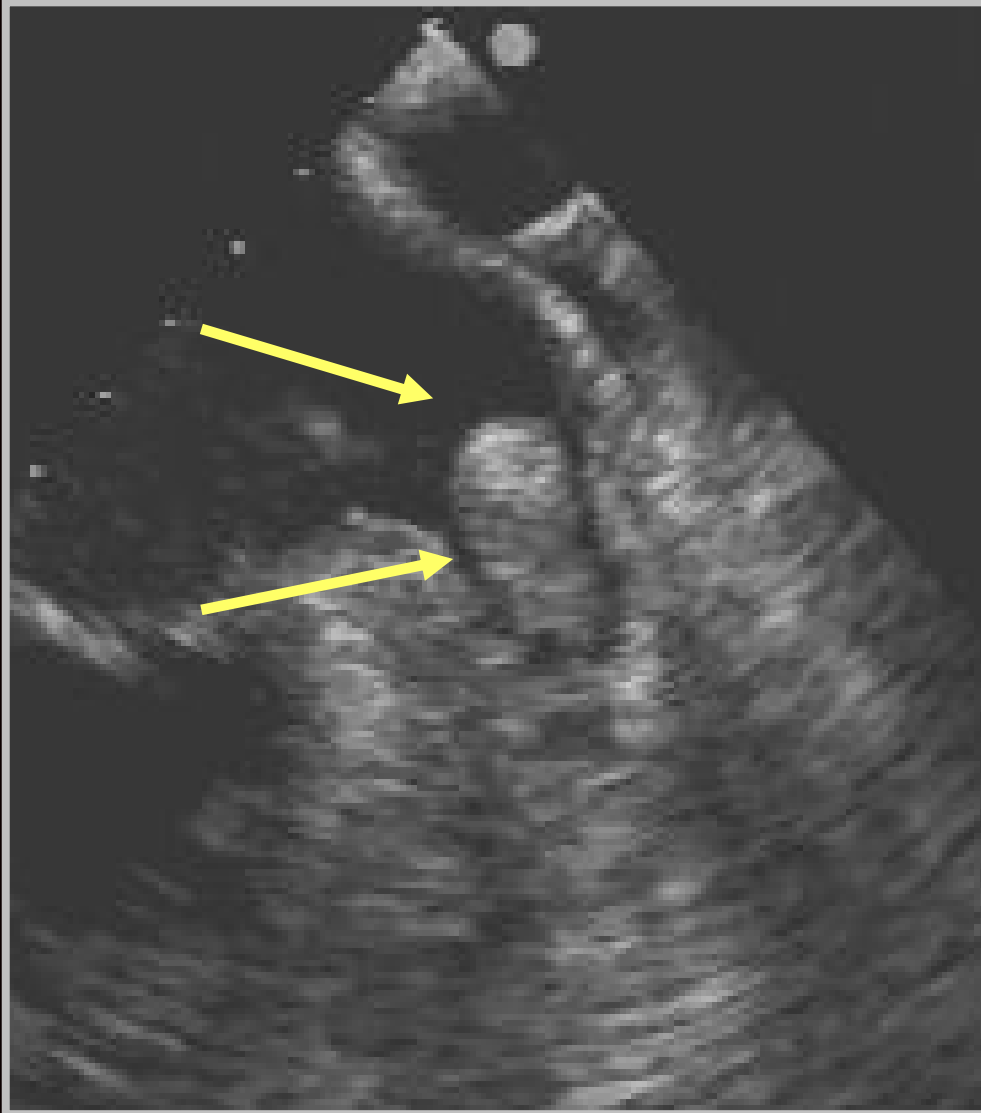
NABOR (National Anticoagulation Benchmark Outcomes Report) Database:  
945 pts., mean age 71.5 yrs.; 54.5% men, 67% hypertension



**Predictors of lack of anticoagulation:  
age > 80 yrs., perceived risk of bleeding**

*Waldo et al.,  
JACC 2005*

# Direct Visualization of LAA Thrombus by TEE

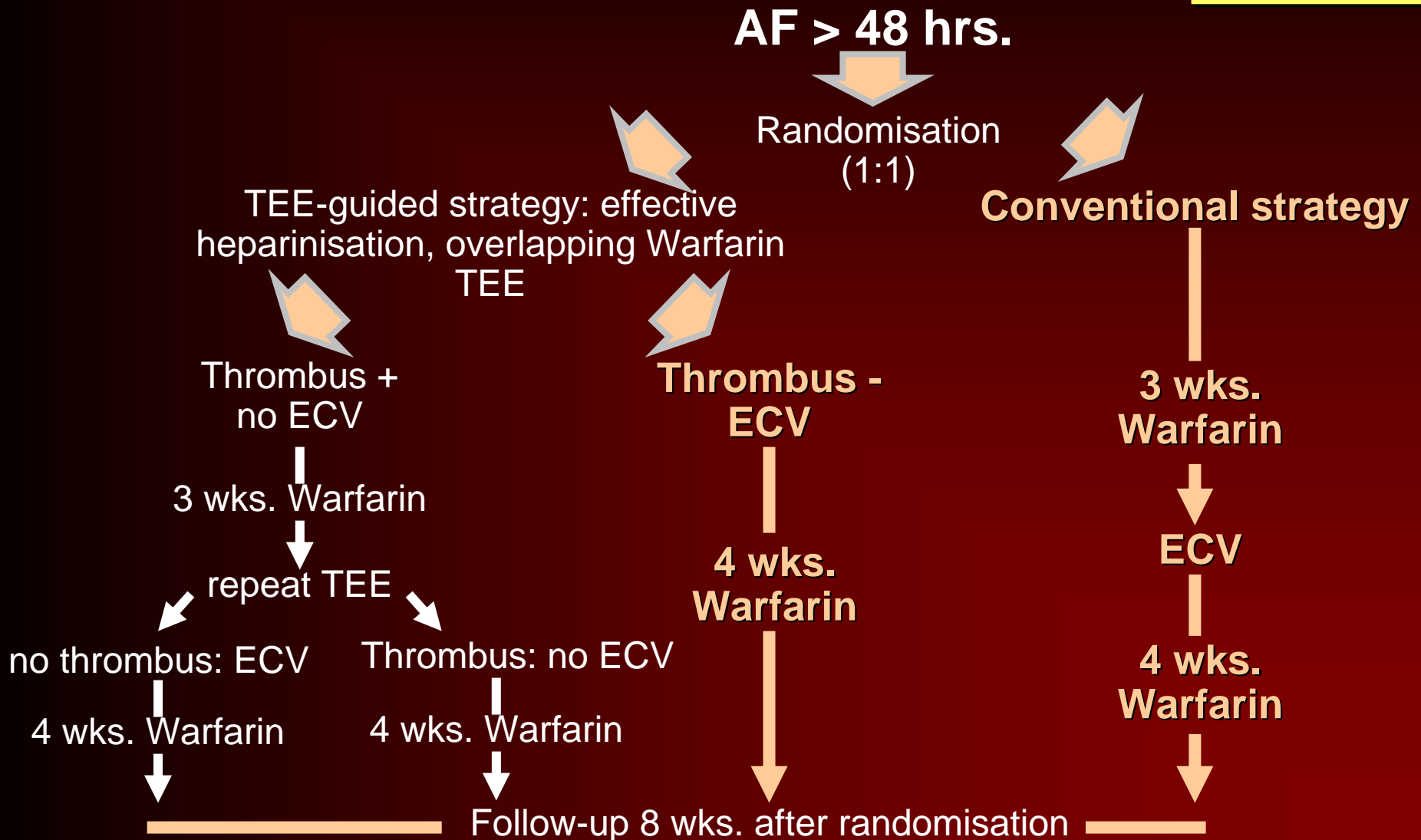


Main potential advantages of TEE-guided cardioversion:

Direct visualization of thrombi and earlier restoration of sinus rhythm:

- ↑ CV success?
- ↓ bleeding rate?
- ↓ embolic rate?

# ACUTE I Study



# ACUTE I: Embolic Events



	<b>TEE</b> <b>n = 619</b>	<b>no TEE</b> <b>n = 603</b>	<b>p</b>
<b>Stroke</b>	<b>4 (0.6%)</b>	<b>2 (0.3%)</b>	<b>0.43</b>
<b>TIA</b>	<b>1 (0.2%)</b>	<b>1 (0.2%)</b>	<b>0.99</b>
<b>Systemic Embolism</b>	<b>0</b>	<b>0</b>	<b>-</b>
<b>Composite: Stroke, TIA, &amp; systemic embolism</b>	<b>5 (0.8%)</b>	<b>3 (0.50%)</b>	<b>0.50</b>

*Klein et al., NEJM 2001*

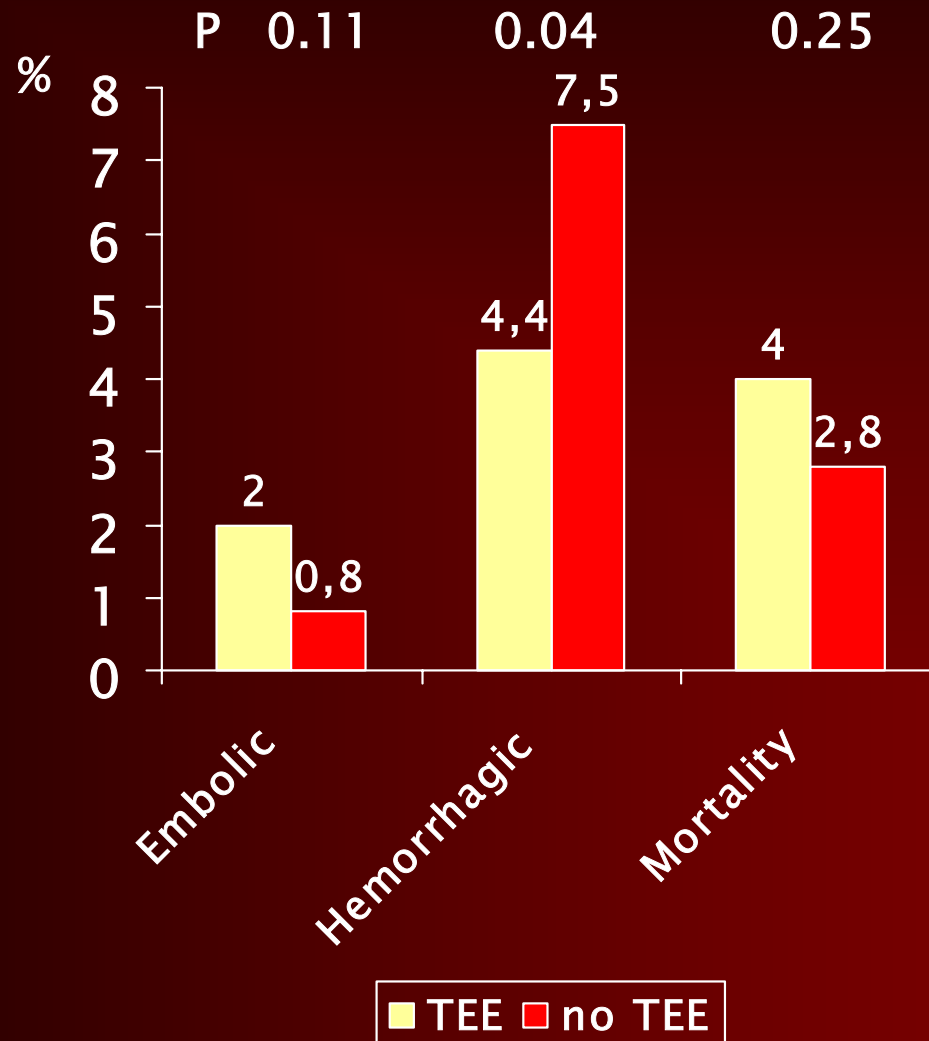
# ACUTE I: Bleeding complications



	<b>TEE n = 619</b>	<b>no TEE n = 603</b>	<b>p</b>
<b>Major bleeding</b>	<b>5 (0.8%)</b>	<b>9 (1.5%)</b>	<b>0.26</b>
<b>Minor bleeding</b>	<b>14 (2.3%)</b>	<b>24 (4.0%)</b>	<b>0.08</b>
<b>Composite: Major &amp; Minor bleeding</b>	<b>19 (3.1%)</b>	<b>33 (5.5%)</b>	<b>0.03</b>

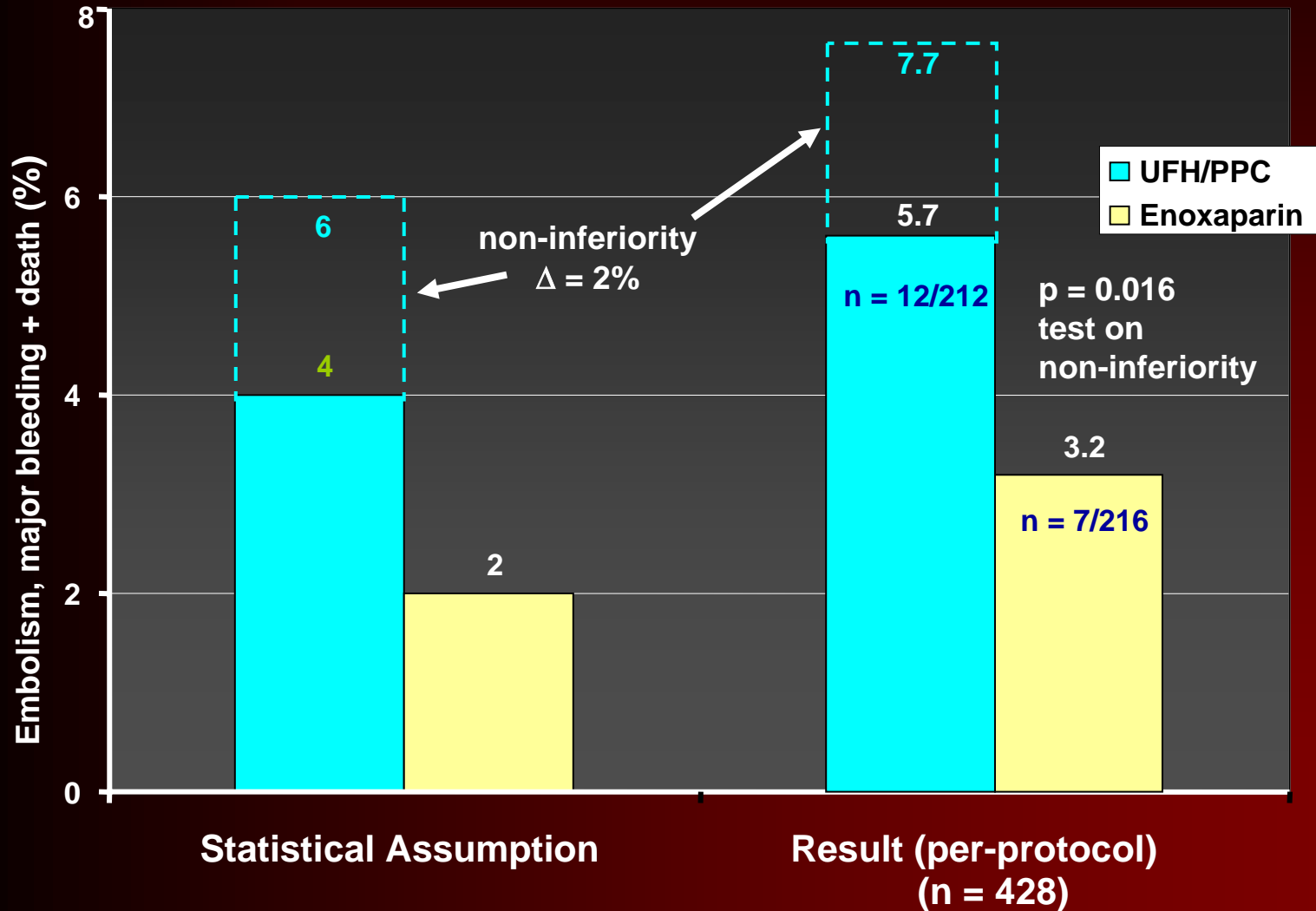
*Klein et al., NEJM 2001*

# 6- Month Follow-Up in the ACUTE trial



*Klein et al.,  
Am Heart J 2006*

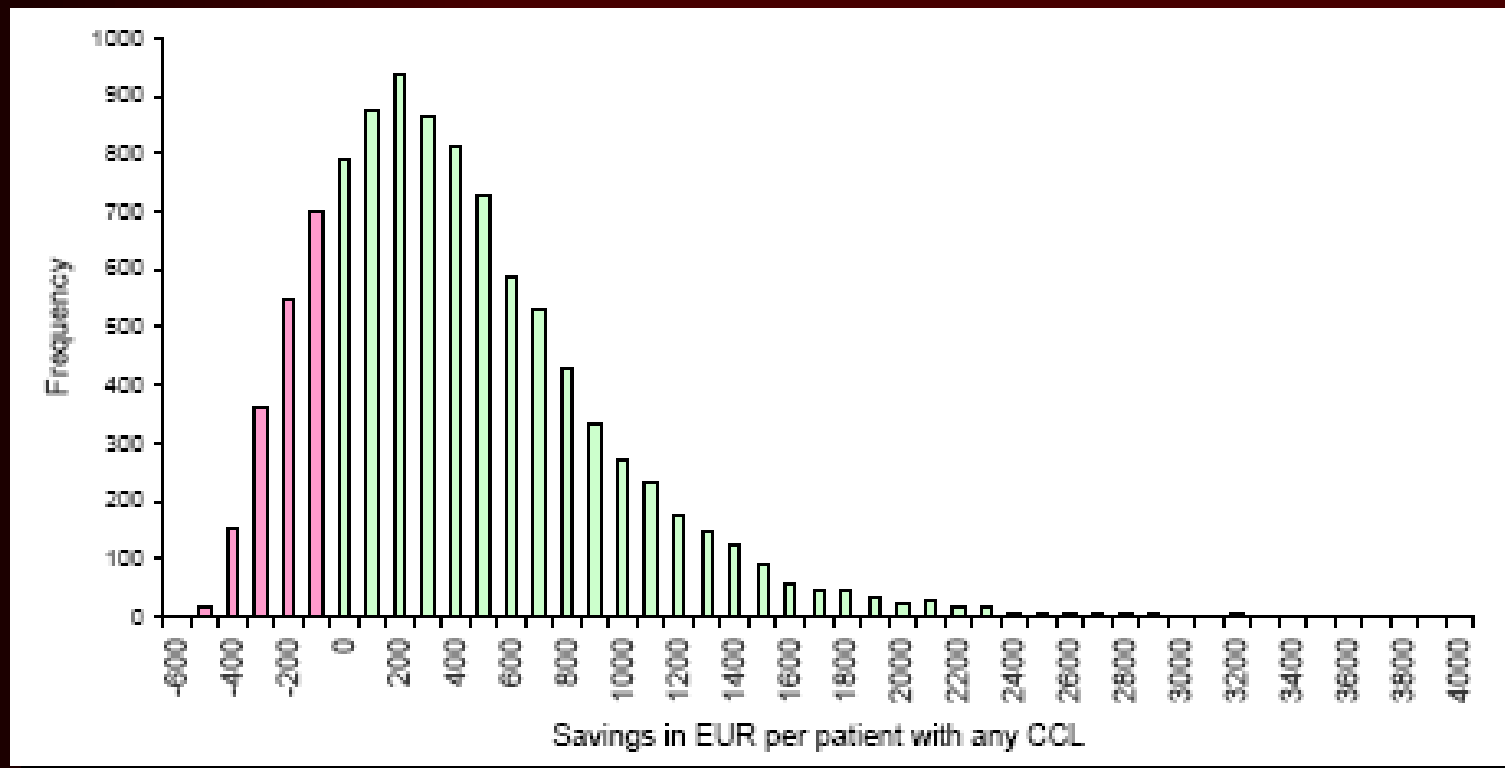
# ACE Trial: Results



# Economic analysis of LMWH vs. UFH/phenprocoumon – ACE trial



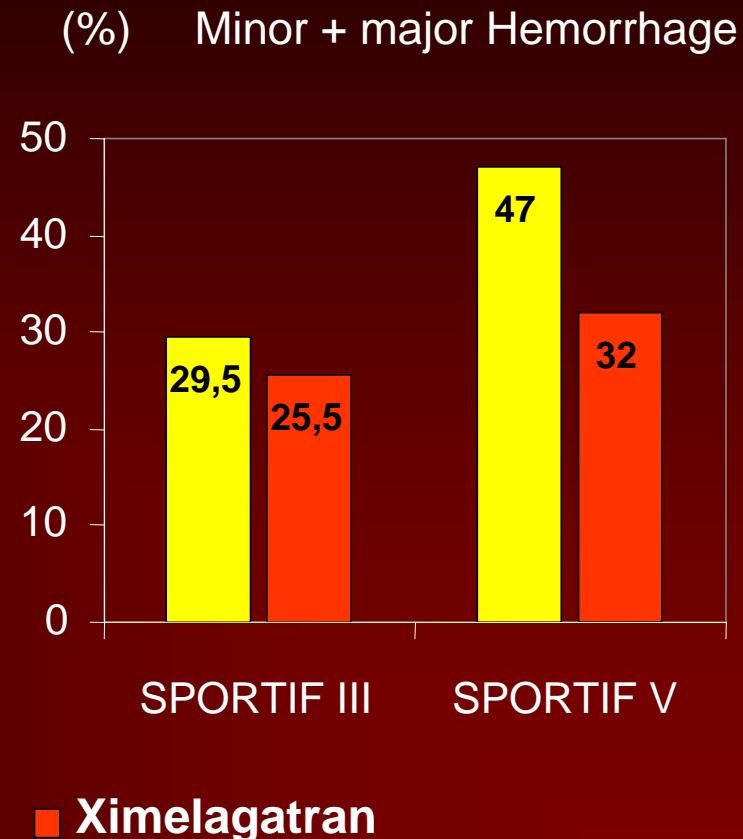
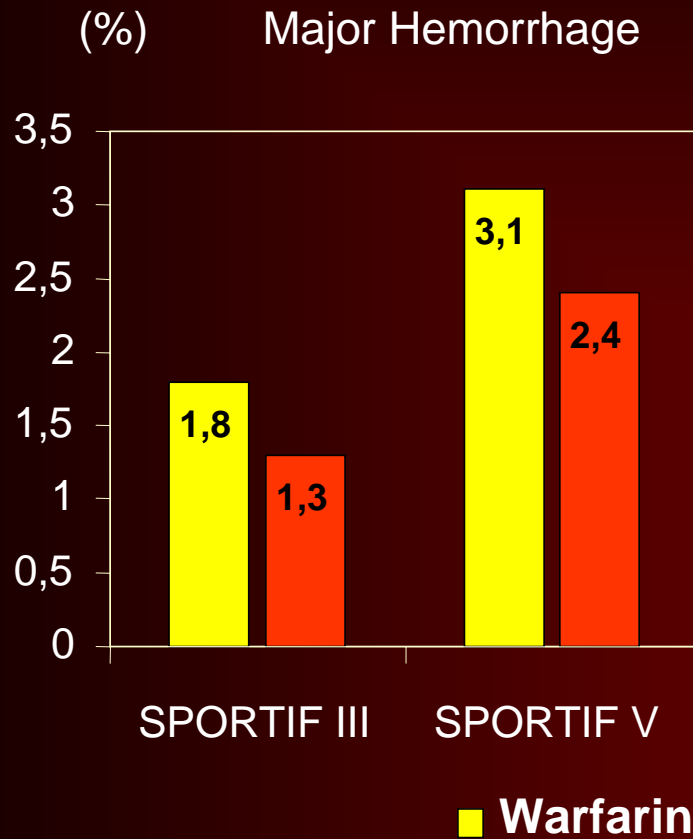
Variance of savings per patient  
(probabilistic sensitivity analysis, 10000 simulation steps)



*Schädlich et al., submitted*

# Ximelagatran: Oral Thrombin Inhibitor

## SPORTIF III+V trials – Bleeding rate



➔ Drug not market-released due to unclear hepatotoxic effects

# Conclusions (I)

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- Due to the low stroke event rate in AF trials, the number of bleeding events may actually outweigh the number of embolic strokes.
- However, bleeding events are mostly not as serious as strokes and ICH is rare if an INR of 2.0–3.0 is maintained. The incidence of ICH may, however, be substantially higher in elderly patients.

# Conclusions (II)

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- TEE–guided cardioversion may lead to a reduction in hemorrhagic but not embolic events. Mortality is low and unaffected by TEE guidance.
- New anticoagulation drugs (e.g. oral thrombin inhibitors) may be an interesting alternative to warfarin in the future but data are lacking in the setting of cardioversion and there is no market–released drug yet available.

# Predictors of Spontaneous Cardioversion to SR



Predictor	p Value	OR (95% Confidence Limits)
Shorter duration of atrial fibrillation	< 0.0001	2.63 (1.3–5.47)
New York Heart Association functional class 1 or 2	0.04	1.85 (1.02–3.34)
Smaller left atrial size	< 0.0001	2.2 (1.39–3.52)
Absence of spontaneous echo contrast	0.01	6.74 (2.79–16.25)

OR = odds ratio.

*Tejan–Sie et al., for the ACUTE Investigators, J Am Coll Cardiol 2003*