



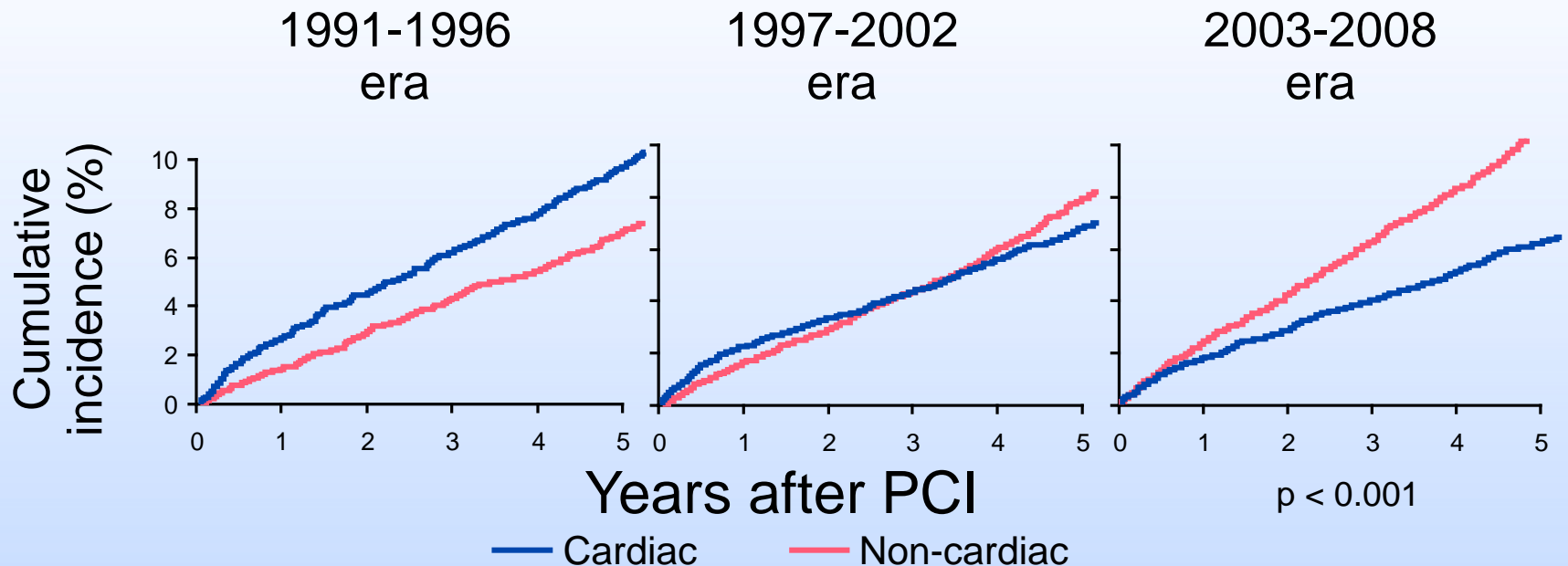
# Anticoagulants and antiplatelet therapy in the older patient: Choosing wisely

Rajiv Gulati, MD PhD

Advances in Cardiac Arrhythmias & Great Innovations in  
Cardiology  
Torino, October 2015

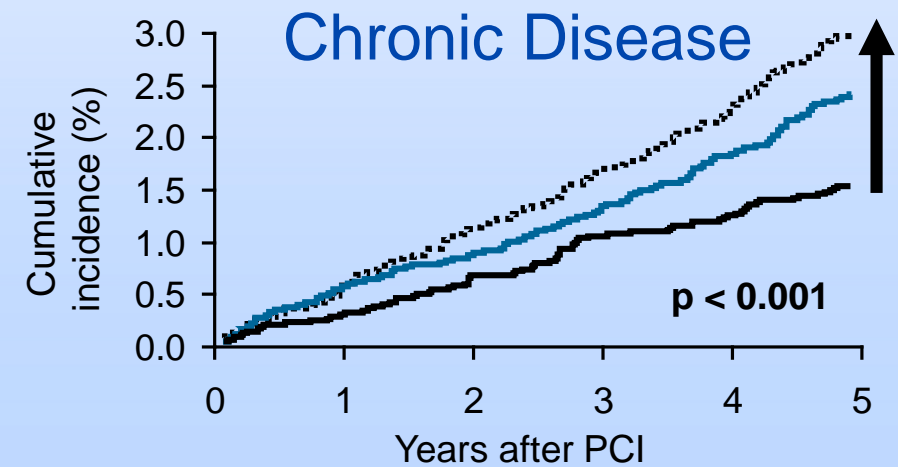
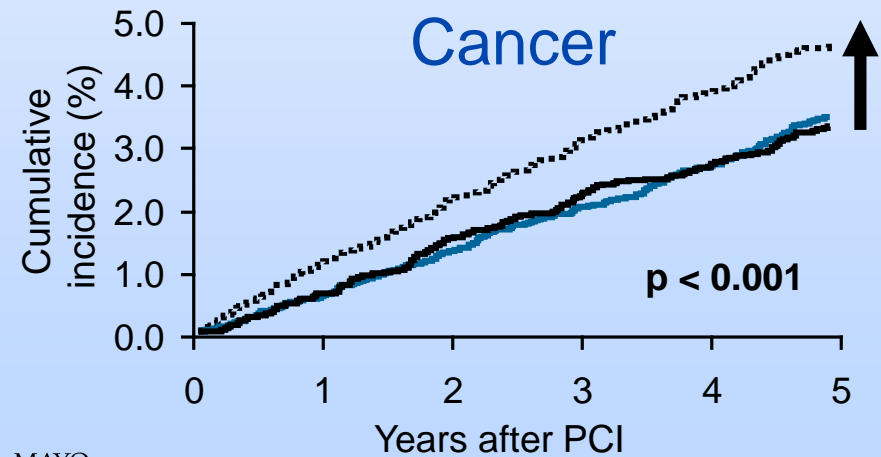
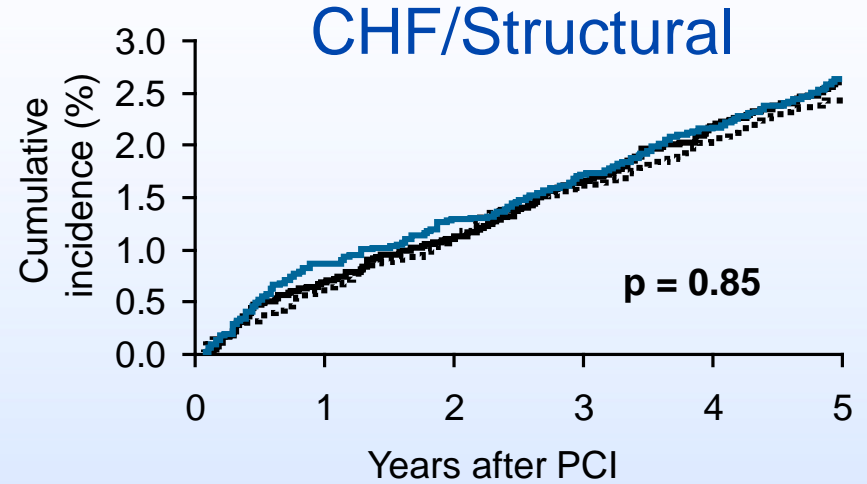
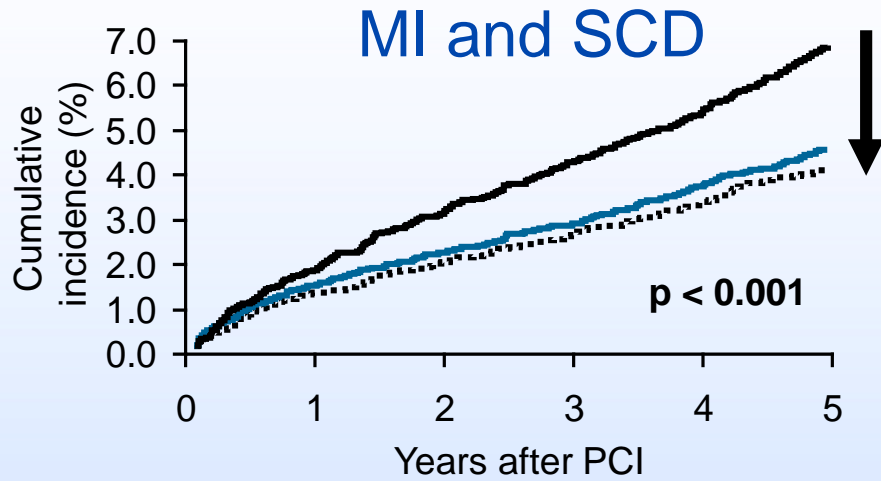
# How times have changed

## Trends in Cause of Death after PCI



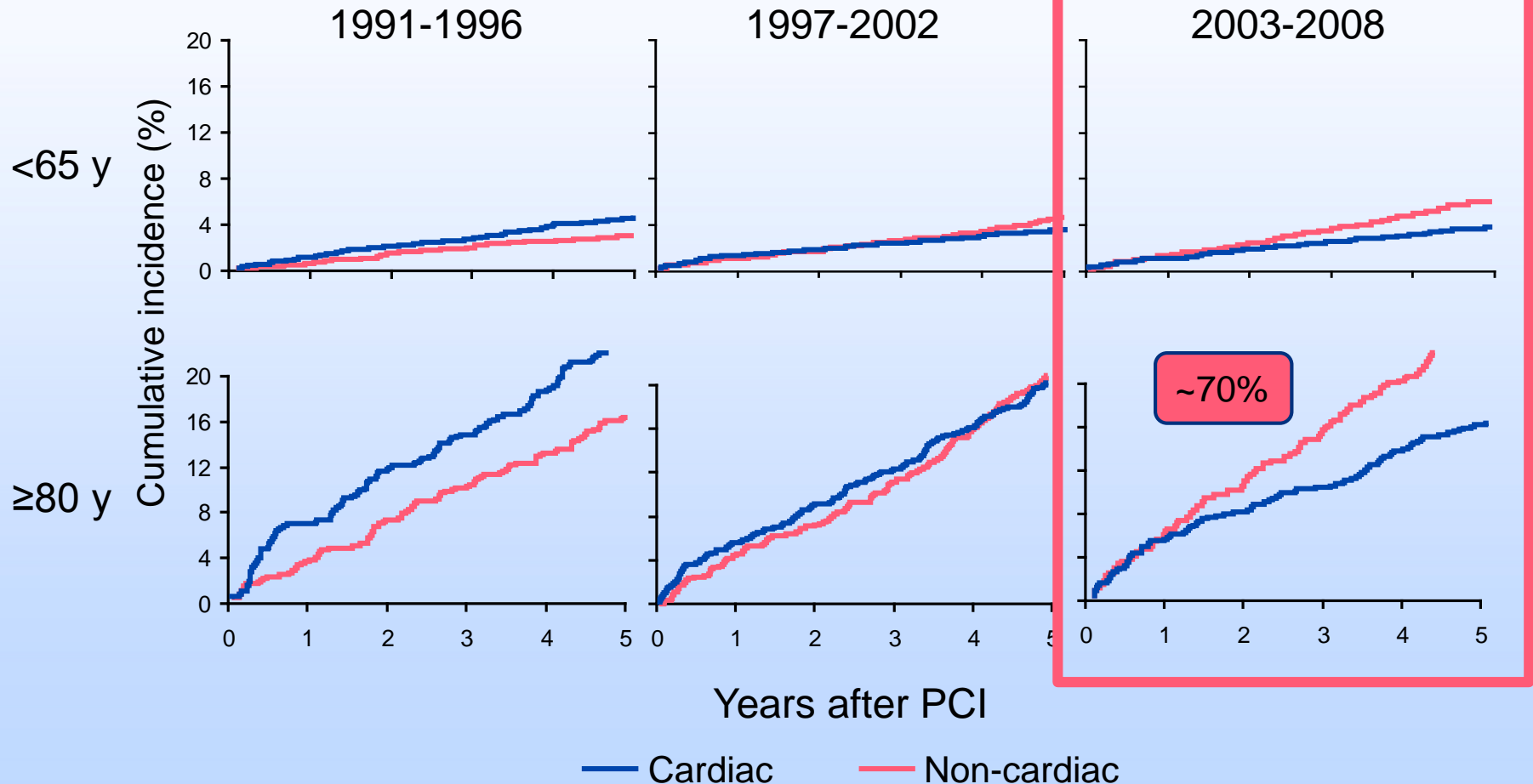
Better secondary prevention → fewer cardiac deaths  
Older/sicker patients → more non-cardiac deaths

# Trends in type of cardiac/non-cardiac death



# The older patient?

## Non-cardiac diseases cause majority of deaths after PCI



# Case

## 83 year old female

- Background
  - Breast cancer, Rx surgery and radiation
  - 3-agents for HTN, statin for HLP, aspirin 81mg
  - Chronic renal impairment
  - Parkinson's disease, prior history of falls
  - Hip replacement 6 mths earlier, postop GI bleed, stable on PPI
  - Main goal is to remain independent
- Presents with ant NSTEMI, HF and ongoing pain
- Given Plavix 600 mg and referred for angiography

# Case

## 83 year old female



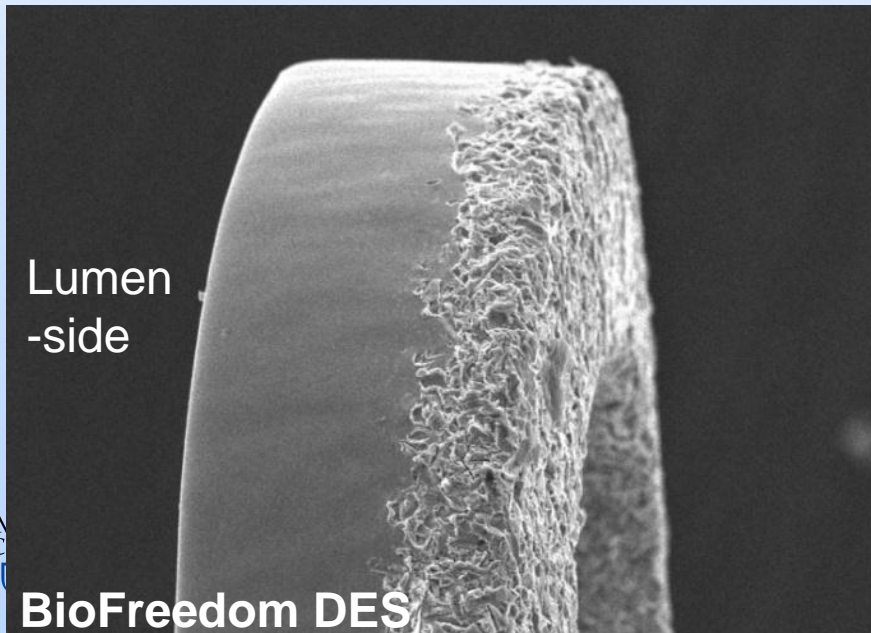
### Bare metal stents?

- Higher TVR, MI and LST vs current gen DES!
  - 3 mths DAPT is acceptable for DES
  - Is shorter DAPT duration possible?

# PCI in the older patient with higher bleeding risk:

## Reducing DAPT duration

- Guidelines suggest BMS with 1 mth DAPT or DES with “shortened” DAPT
- LEADERS-FREE RCT: BioFreedom DES vs Gazelle BMS and one month DAPT



- Lipophilic BA9 Limus
- Transfers to v wall in 1 mth
- No polymer

# BioFreedom DES vs Gazelle BMS and one month DAPT

## Baseline Patient Characteristics

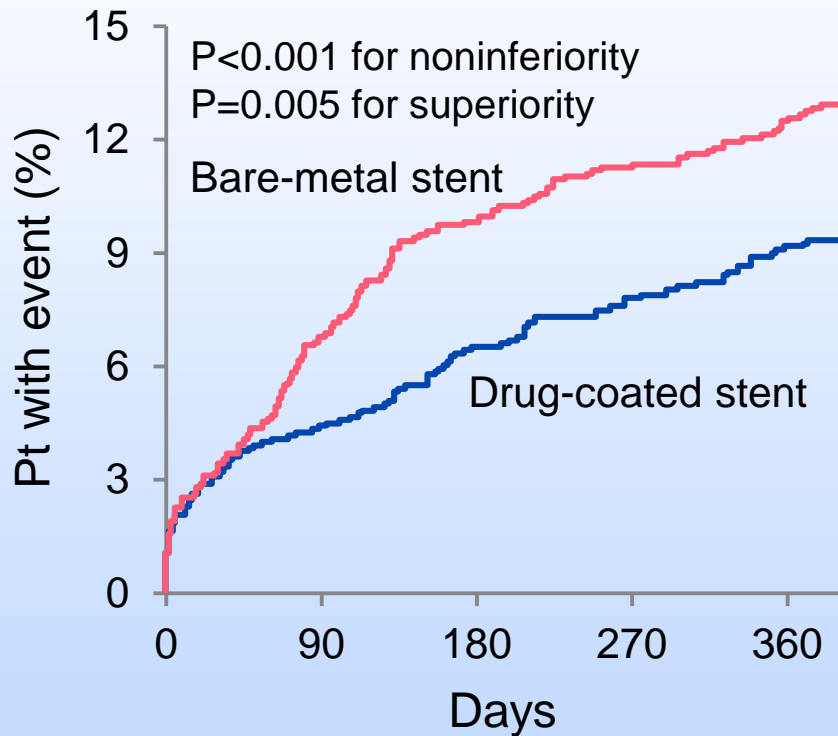
<b>Variable</b>	<b>Drug-coated stent (n=1221)</b>	<b>Bare-metal stent (n=1211)</b>
Age (yr)	75.7±9.4	75.7±9.3
Female sex, no. (%)	364 (29.8)	374 (30.9)
BMI	27.5±4.8	27.2±4.6
Diabetes, no./total no. (%)	414/1217 (34.0)	391/1210 (32.3)
HTN, no./total no. (%)	952/1219 (78.1)	961/1208 (79.6)
Hypercholesterolemia, no./total no. (%)	742/1197 (62.0)	746/1189 (62.7)
STEMI, no. (%)	57 (4.7)	48 (4.0)
NSTEMI, no. (%)	273 (22.4)	281 (23.2)
Unstable angina, no. (%)	177 (14.5)	193 (15.9)
Stable CAD, no. (%)	714 (58.5)	689 (56.9)

Urban et al: NEJM , 2015

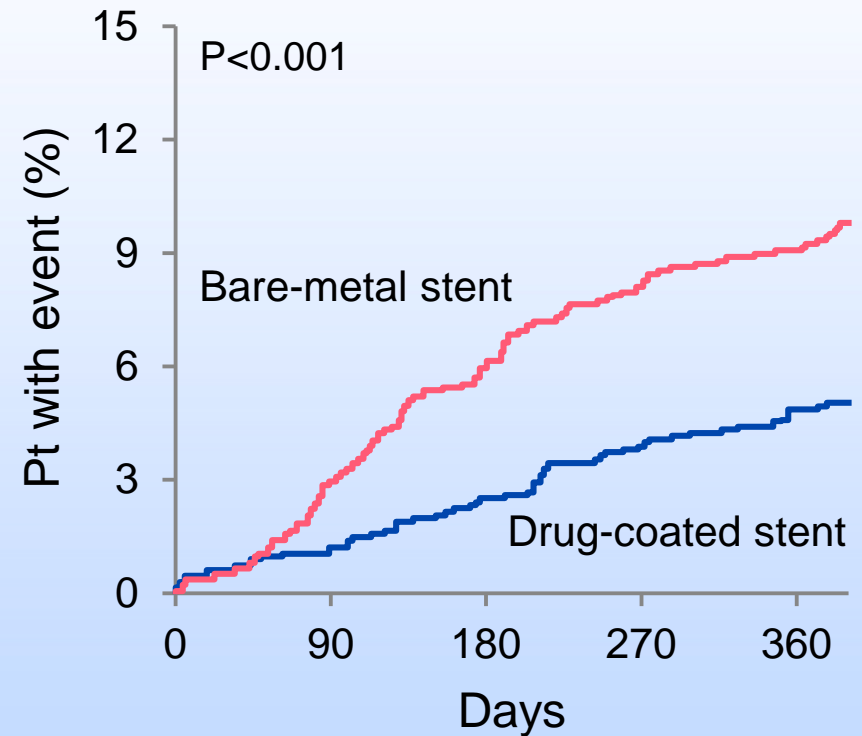


# Time-to-Event Curves for Primary Endpoints

## Primary Safety Endpoint

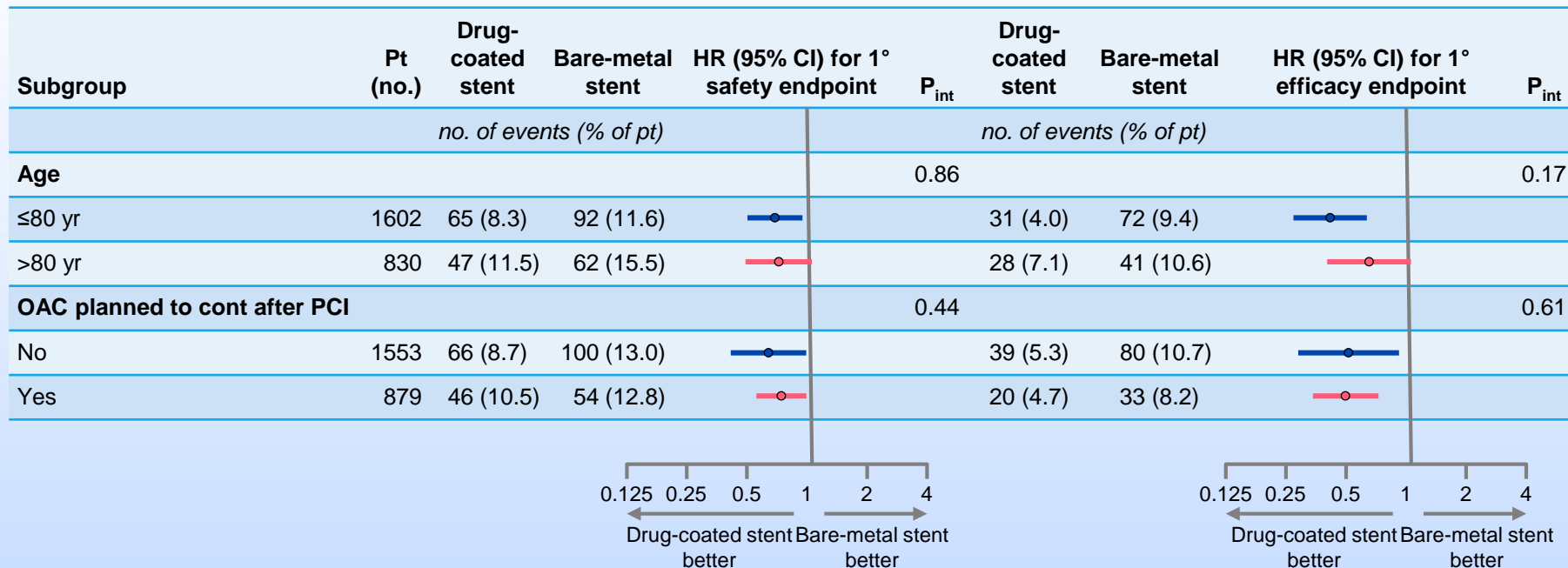


## Primary Efficacy Endpoint



Urban et al: NEJM , 2015

# Primary Safety and Efficacy Endpoints in the Older Patient, at 1 year



# The older patient undergoing PCI

- Is by definition a patient with high bleeding risk
- Frequent comorbidities are the norm
- In 2015, should only rarely be denied the advantages of a drug-eluting stent: Reduced MI, TVR, late stent thrombosis
- BioFreedom DES may allow only 1 mth DAPT
- Other DES? Shorter DAPT not studied

# Back to the case

## 83 yr female: What I didn't tell you

- Also history of paroxysmal A Fib
- CHADS-VASC 4
- Was on warfarin at presentation (INR 3.0) and aspirin
- And now Clopidogrel too

# A bewildering array of options to prevent stroke and cv events in older patients

- Warfarin
- NOACs

- Aspirin

- Clopidogrel
- Ticagrelor
- Prasugrel

Reduce  
Thrombosis

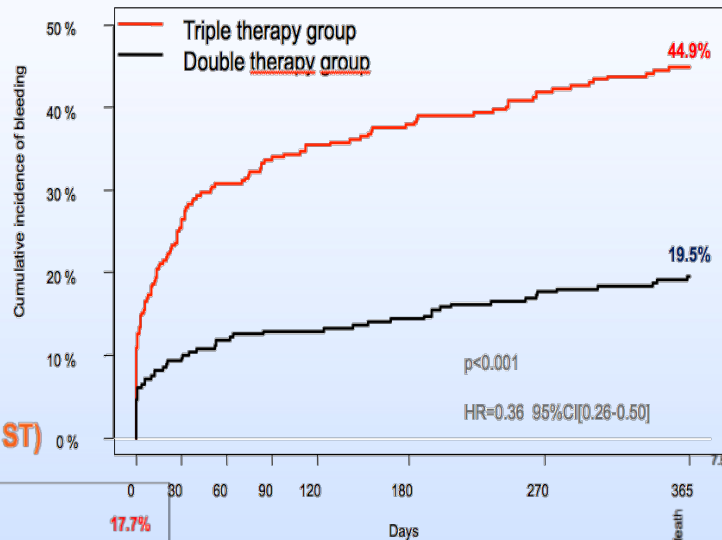
Increase  
Bleeding

# Most relevant to the 83 yr old female

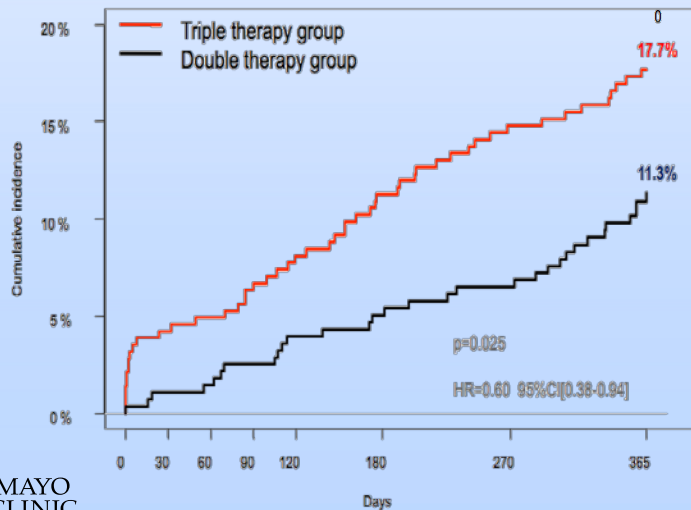
## The WOEST Trial:

### Triple Rx vs Warfarin/Clopidogrel

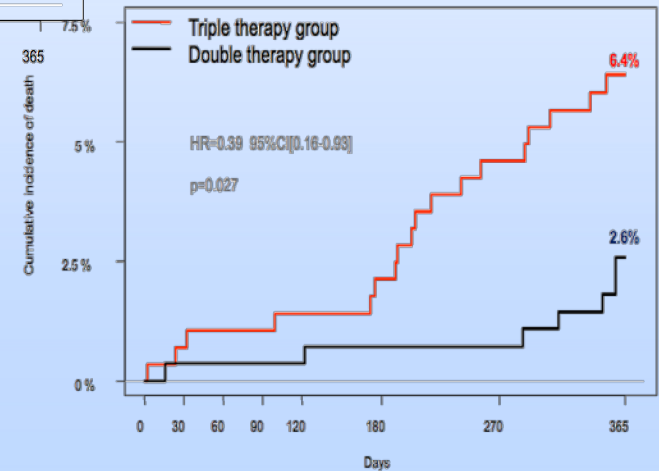
Primary Endpoint: Total number of TIMI bleeding events



Secondary Endpoint (Death, MI, TVR, Stroke, ST)



All-Cause Mortality



# Oral Anticoagulation and Antiplatelet Therapy in AF Patients With MI and Coronary Intervention

- 12,165 pts
- Danish Registry
- 1-year follow-up

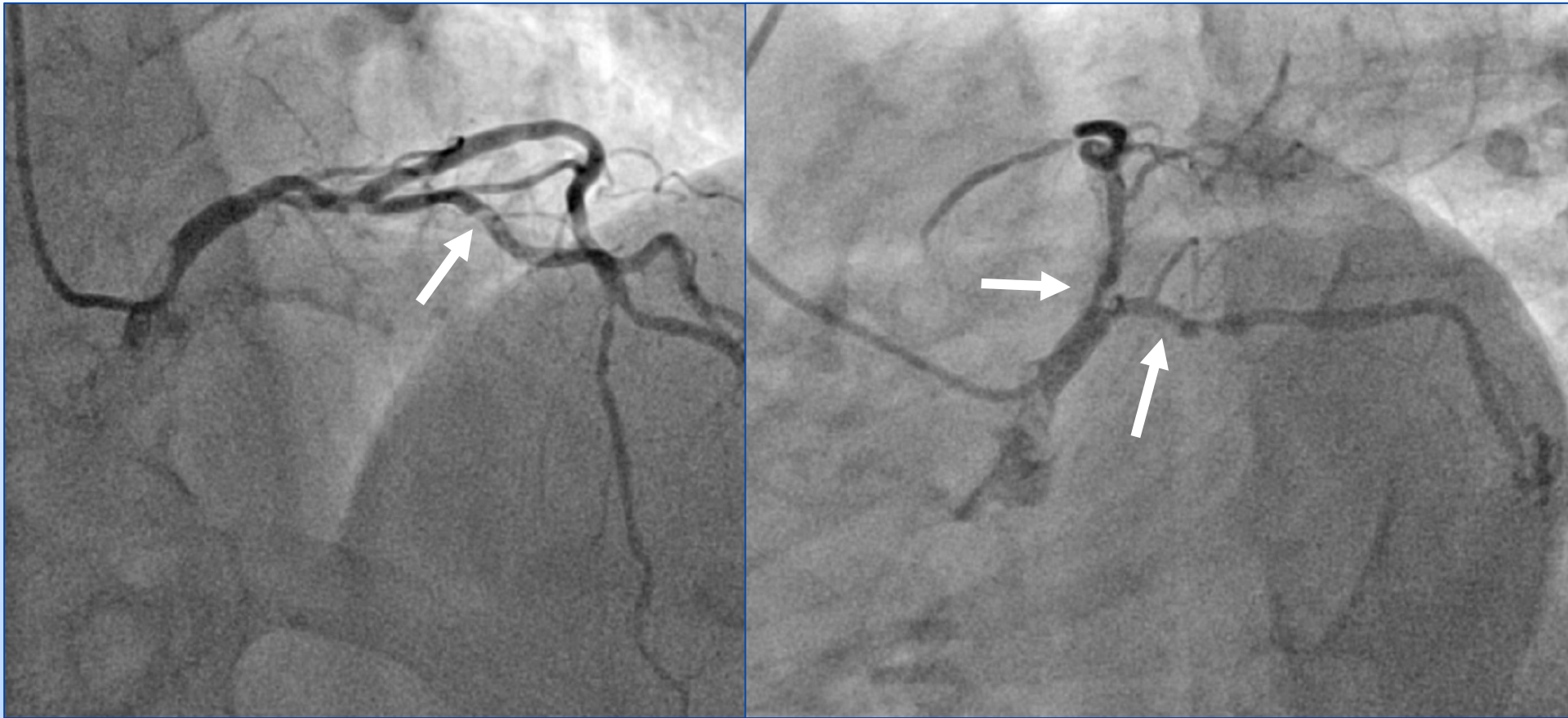
Compared to triple therapy

Endpoint	Warfarin plus aspirin	Warfarin plus clopidogrel	Aspirin plus clopidogrel
All cause mortality	1.52 (1.17-1.99)	0.87 (0.56-1.34)	1.60 (1.25-2.05)
MI/coronary disease	0.96 (0.77-1.19)	0.69 (0.48-1.00)	1.17 (0.96-1.42)
Bleeding complications	0.69 (0.53-0.90)	0.78 (0.55-1.12)	0.48 (0.38-0.61)

Conclusions: AF patients with indication for multiple antithrombotic drugs after MI/PCI, OAC and clopidogrel was equal or better on both benefit and safety outcomes compared to triple therapy

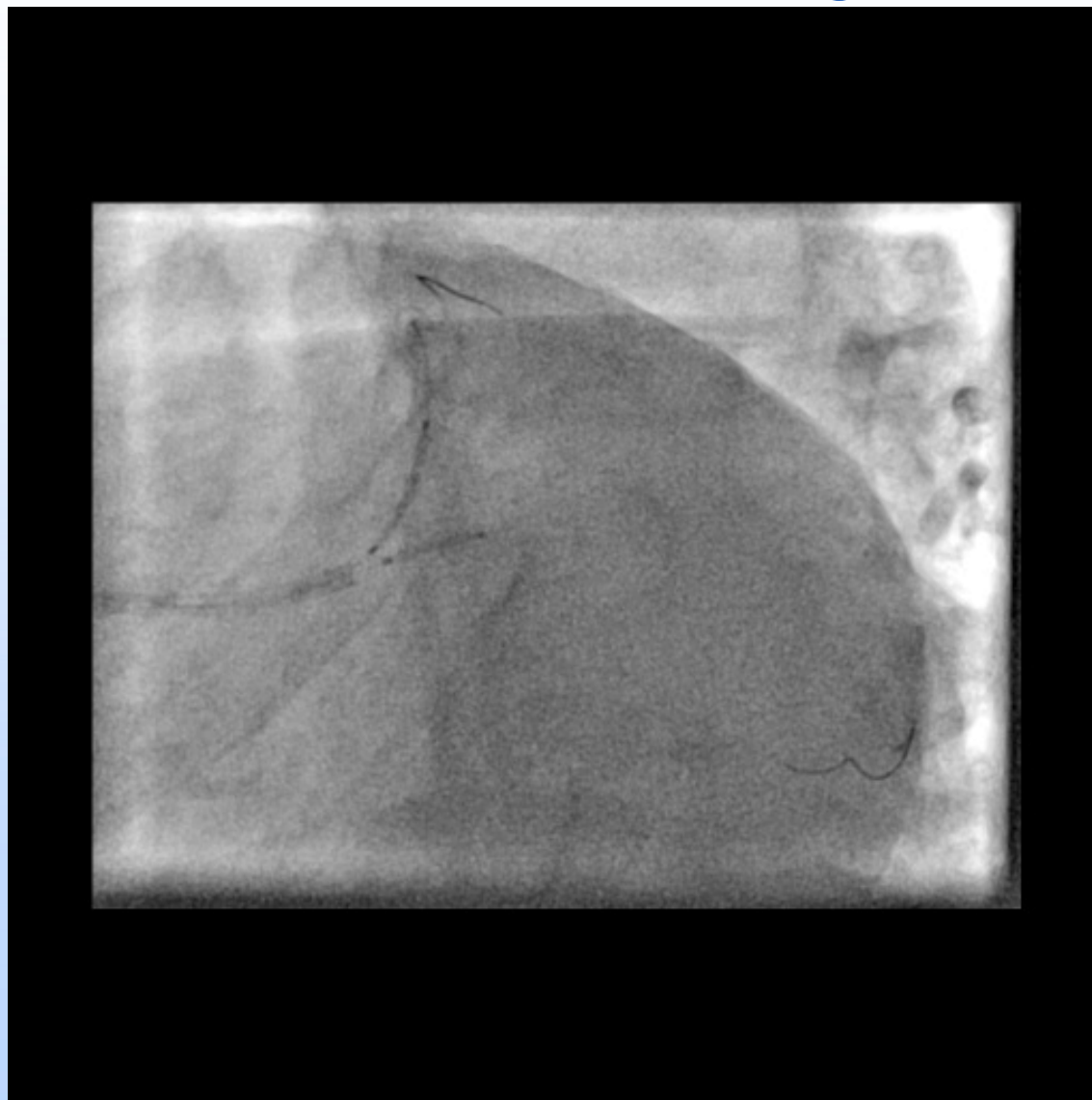
Lamberts: JACC, 2014

# Back to the case 83 year old female

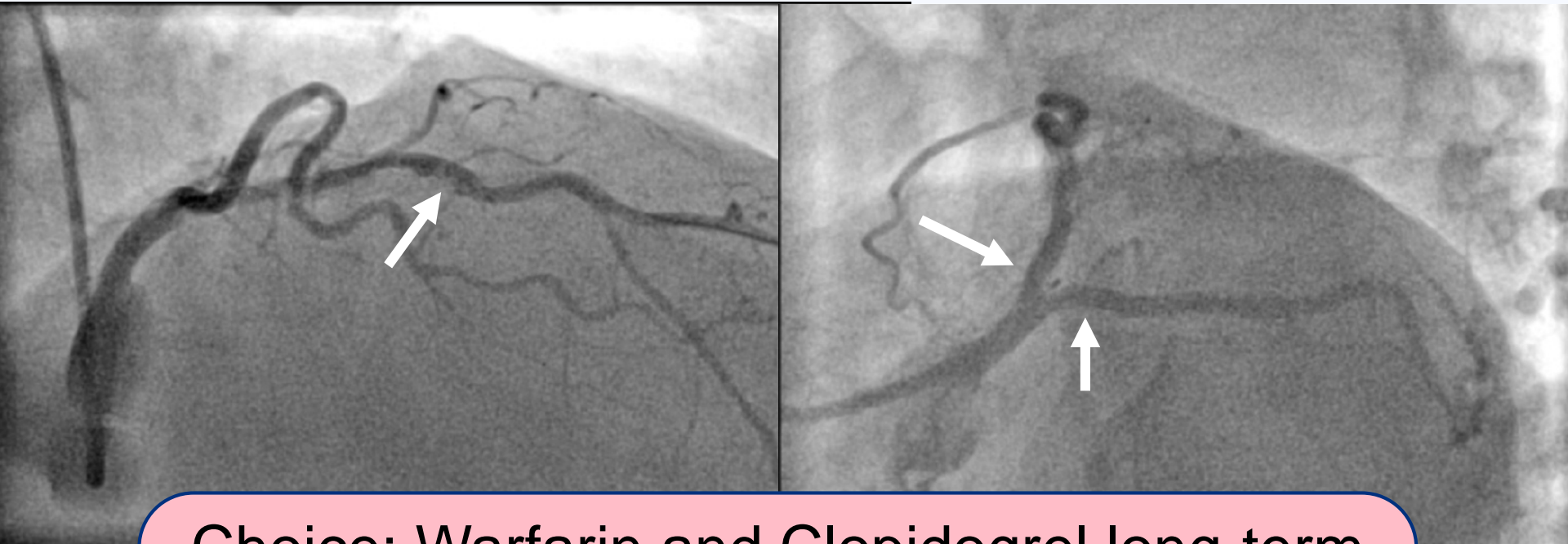




# 83 yr female with INR of 3.0 Transradial PCI, including 6F SKS



# 83 year old female 3 x Everolimus Eluting Stents

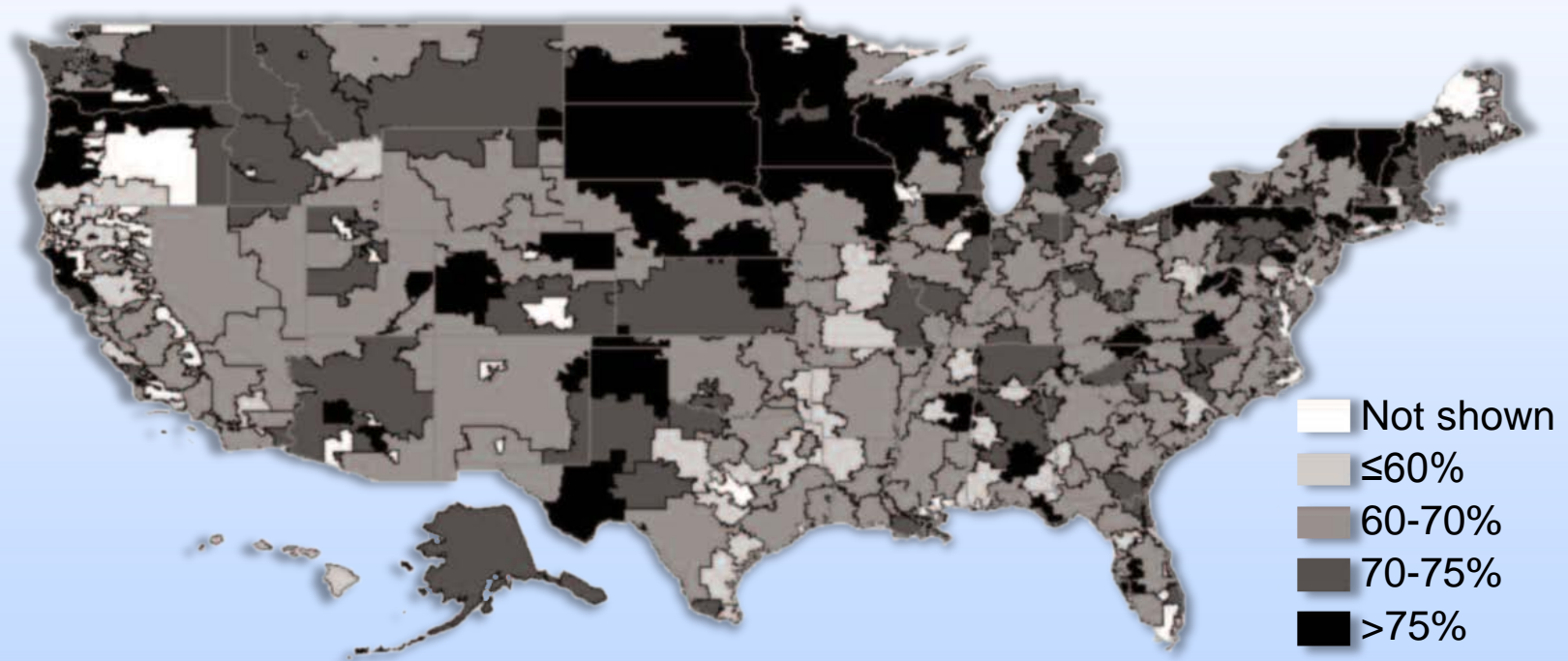


Choice: Warfarin and Clopidogrel long-term  
Consider switch to Aspirin at 12 mths  
“But, she has a risk of falls...does she really  
need warfarin?...”

# National Patterns of Warfarin Use in Eligible Older Patients With AF

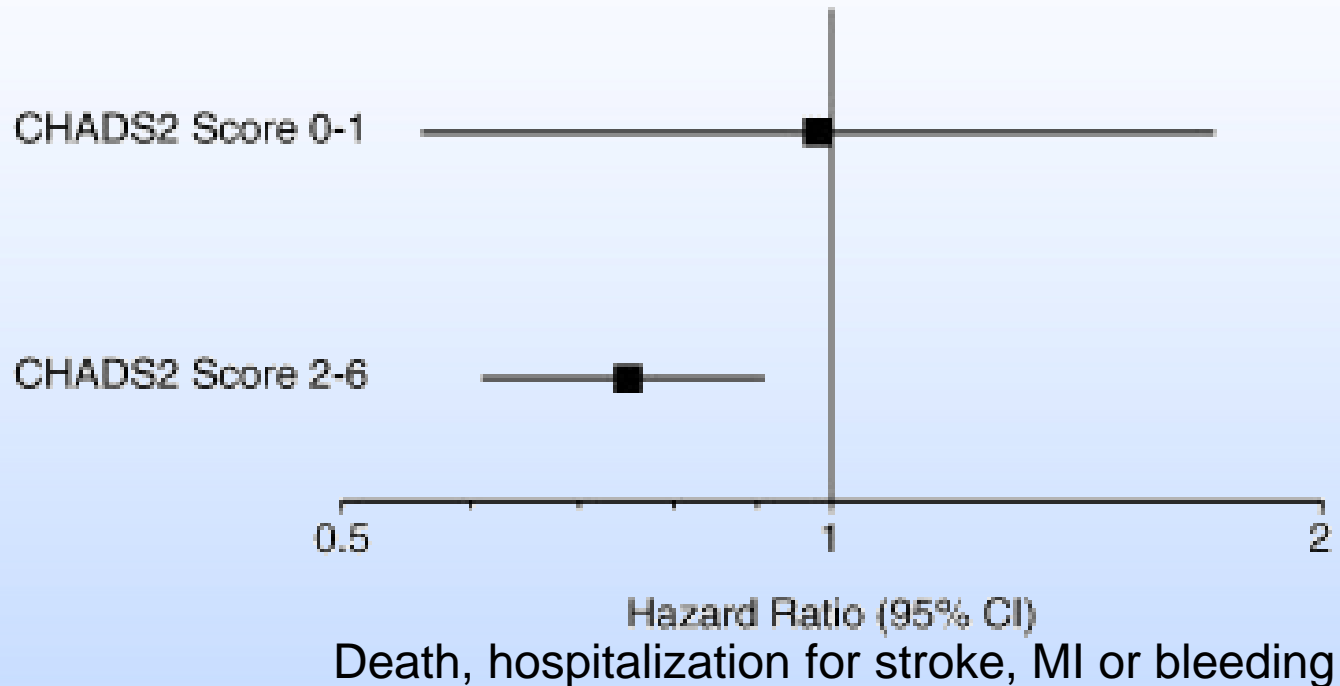
41,447 Medicare Beneficiaries With AF 2007-2008

Overall warfarin use rate – 66.8%



Raji: Ann Pharmacotherapy, 2013

# High fall-risk patients Warfarin vs no warfarin A Fib

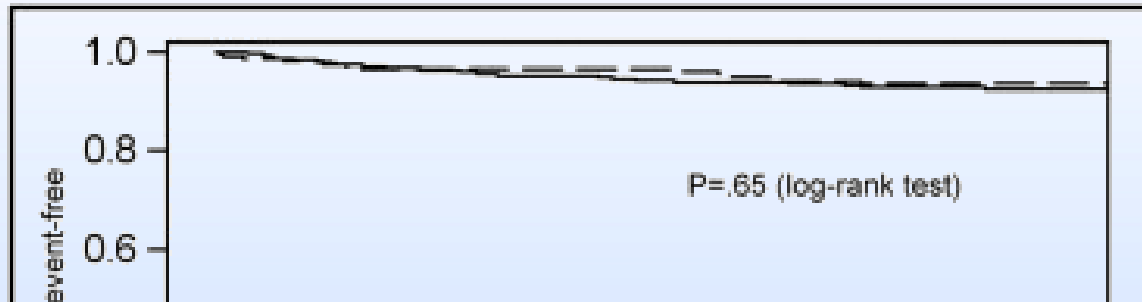


Matthew B. Sellers, L. Kristin Newby  
American Heart Journal 2011

# High fall-risk patients

## Warfarin vs no warfarin A Fib

### Time to first bleeding event



1. Physicians routinely over-estimate risk of falls, and underutilize strategies to reduce risk when present
2. “The risk of a subdural hematoma from falling is so small that patients with A Fib and an average risk of stroke (5%/yr) would have to fall ~300 times in a year for the risk of anticoagulation to outweigh its benefits

# Warfarin vs Aspirin for Stroke Prevention in the Elderly

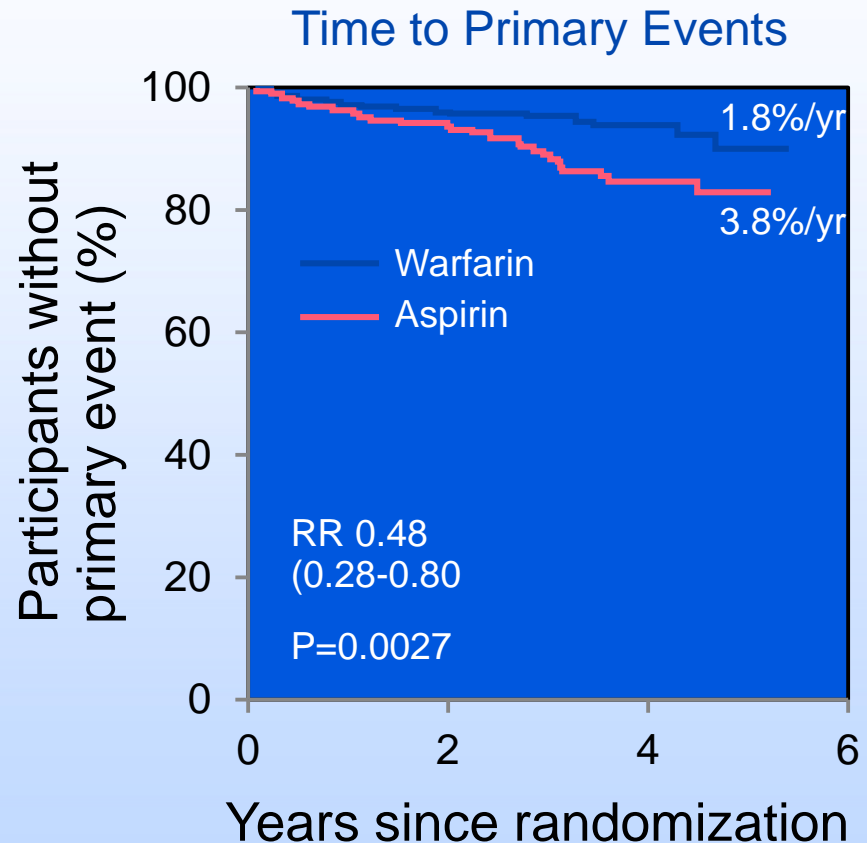
## BAFTA Trial, 973 Patients, Age $\geq 75$ Years

### Primary endpoint

- Fatal or disabling stroke
- Intracranial hemorrhage
- Systemic embolism (clinically significant)

### Risk of extracranial hemorrhage

	%/year	
Aspirin	1.6	} RR 0.87 (0.43-1.73)
Warfarin	1.4	



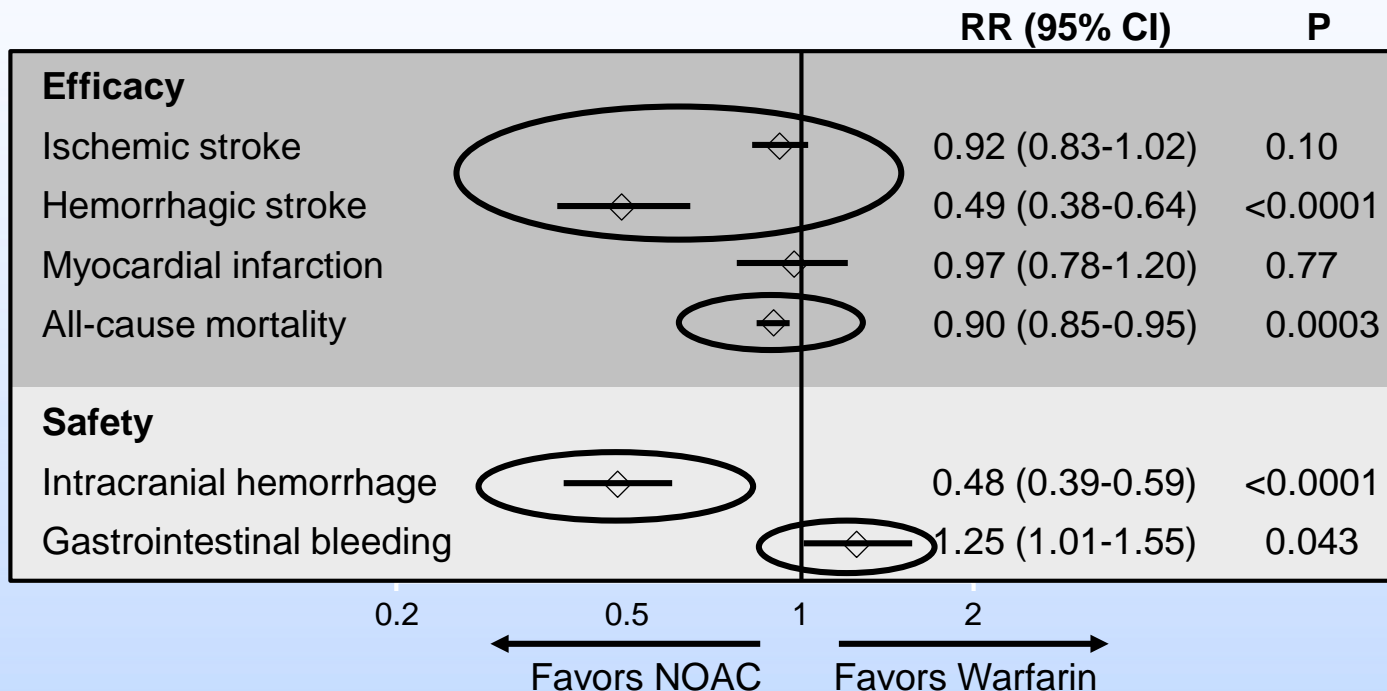
Mant: Lancet, 2007

# The problem we face

- A burgeoning population of older adults
- With manageable coronary disease
- But increased risk of non-cardiac death
- Increased burden of comorbidities including A Fib
- Increased risk med side effects, including bleeding
- For many older patients, the health priority is to avoid a disabling stroke. More important than to avoid death
- Choosing optimal combination of antithrombotic medications is a struggle

# What about Novel Oral Anticoagulants? A Meta-Analysis

4 Trials – 71,683 Participants



Ruff: Lancet, 2013



## If warfarin was discovered after NOACs, would it be approved by regulatory bodies?

- 10 to 50% increased risk of stroke
- 2-3 fold times rate of ICH
- As much as one third higher rate of major bleeding (versus apixaban)
- Requirement for monthly monitoring to adjust dose
- Falls out of target anticoagulation one third of the time in highly controlled trials and nearly one half the time in general practice
- Many food and drug interactions
- 10% significant increase in mortality
- \*\*But more data on warfarin + antiplatelet combinations, than NOAC + antiplatelet warfarin\*\*

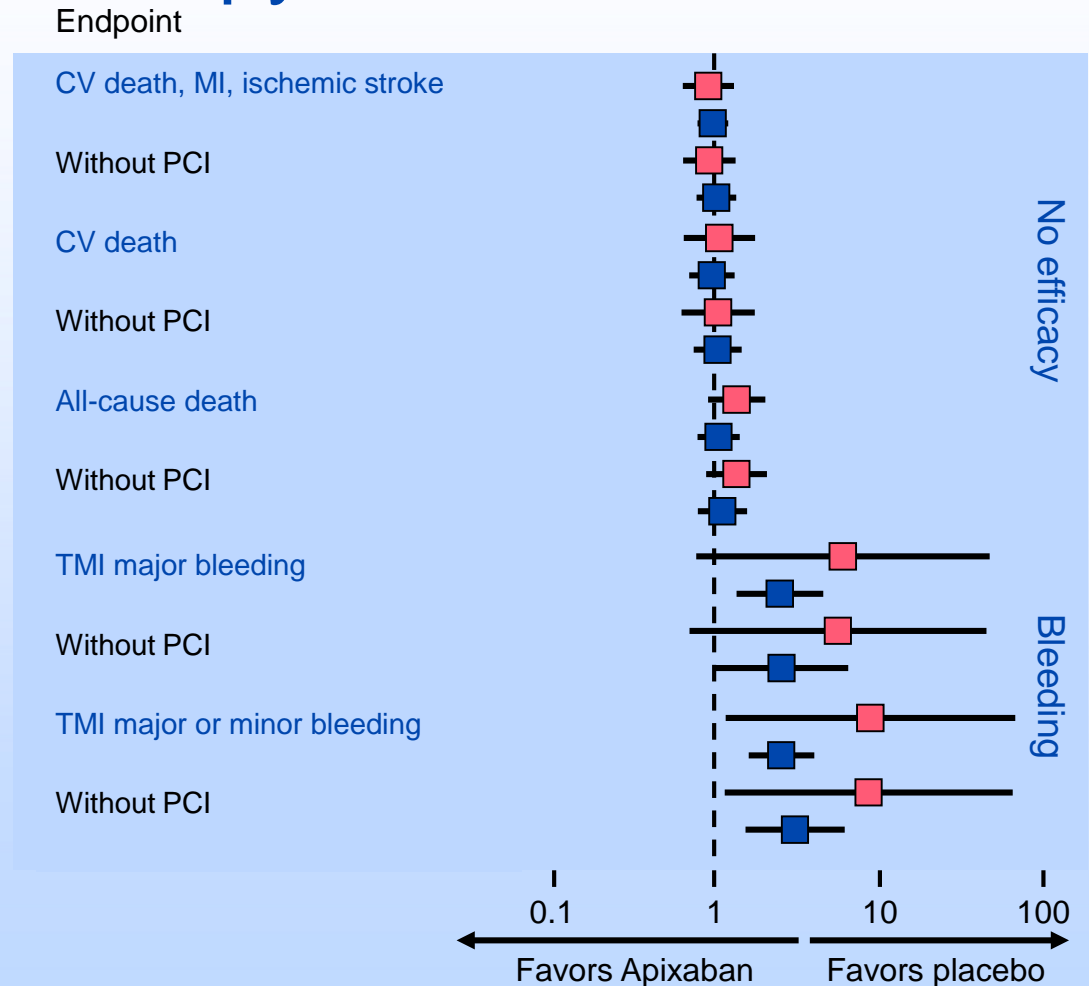
# Apixaban Plus Mono vs Dual Antiplatelet Therapy in ACS

- 7,364 pt
- APPRAISE-2 Trial
- Apixaban vs placebo

Aspirin alone 16.3%	Aspirin + Clopidogrel 79%
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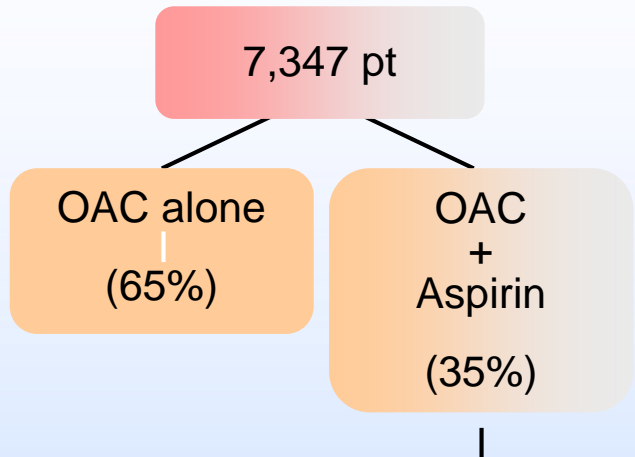
19% switched therapy  
During F-U

- Aspirin only
- Aspirin and clopidogrel



Hess: JACC 2015

# Effect of aspirin in addition to warfarin in the older patient



- 30% – no history of atherosclerotic vascular disease
- Higher ATRIA bleeding scores

6-Month Outcomes			
	OAC + ASA vs OAC Alone		
	HR	CI	P
Major bleeding	1.53	(1.2-1.96)	P=0.0006
Bleeding hospitalizations	1.52	(1.17-1.97)	P=0.002
Ischemic events			Low in both groups

• We use too much aspirin in pts with AF on OAC  
• Aspirin is the major cause of bleeding in pts on OAC

Steinberg: Circ, 2013

# Intracerebral Hemorrhage in the Older Patient

## The Worst Complication of Antithrombotic Therapy

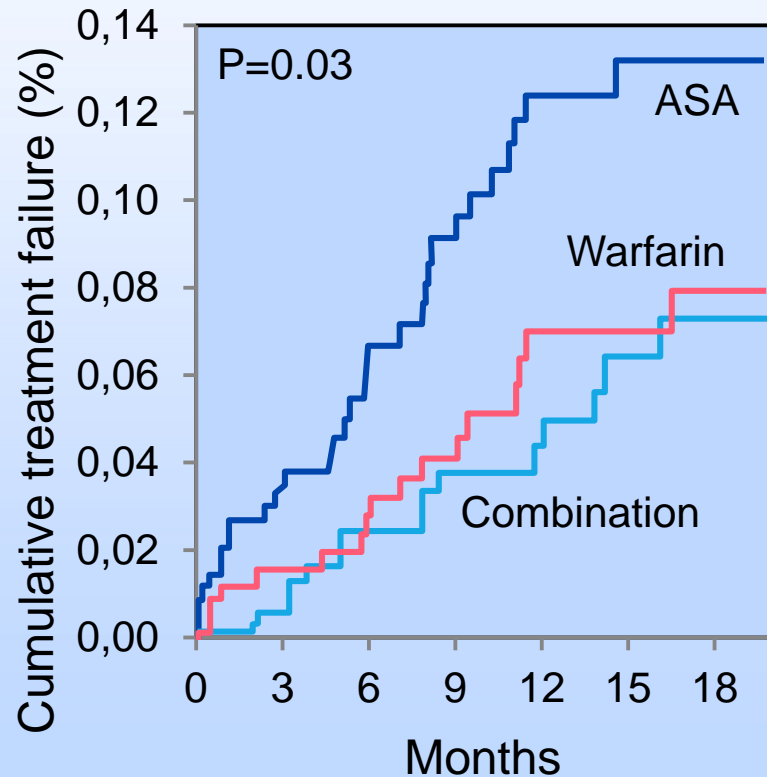
- >10% of intracerebral hemorrhages (ICH) occur in patients on antithrombotic therapy
- Aspirin increases the risk by ~40%
- Warfarin (INR 2-3) *doubles* the risk to 0.3-0.6%/year
- ICH during anticoagulation is catastrophic (~50% mortality in most studies)
- In anticoagulated patients with AF, concomitant antiplatelet therapy is the most important modifiable independent risk factor for ICH

Hart RG et al: Stroke 36:1588, 2005  
Hart RG et al: Stroke 43:1511, 2012

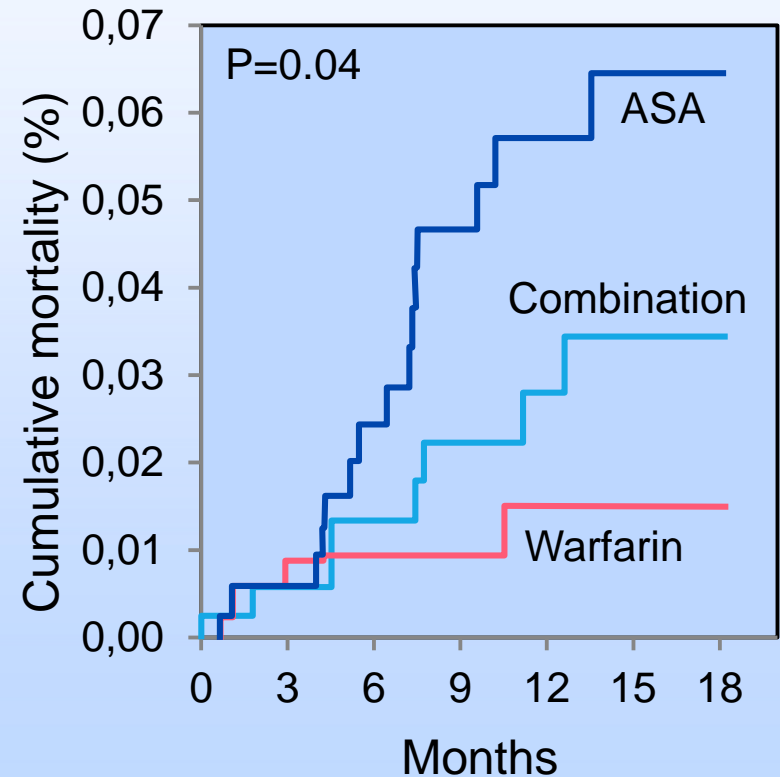
# But doesn't aspirin reduce coronary events in patients with CAD? ASPECT-2

## Prevention of Ischemic Events Following MI

Primary Endpoint  
(Death, MI, Stroke)



Mortality



van Es RF: Lancet 360:109, 2002

## Key Point

Warfarin works as well as aspirin to prevent MIs

# Conclusions

## Choosing wisely in the older patient

- Compared to warfarin, the NOACs are at least as good at preventing stroke in the older patient, with less ICH, lower mortality, and are easier to use
- Aspirin on top of warfarin/NOAC is over-utilized in the older patient with no CAD or with stable CAD
  - Questionable efficacy
  - Worse safety
- In patients with a DES, a warfarin-clopidogrel combination appears safe and efficacious
  - In those not on warfarin, DAPT can be reduced to 1 mth with the latest DES
- Don't overestimate risk of falls, or underestimate benefit of anticoagulation in reducing stroke risk in the older patient



Thank you for your time  
[gulati.rajiv@mayo.edu](mailto:gulati.rajiv@mayo.edu)



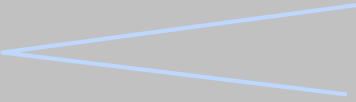
# In Which Patients is Warfarin Preferred ?

- Mechanical valves
- LV thrombi
- Rheumatic mitral valve disease

Pt with severe renal impairment (CrCl <30 mL/min)

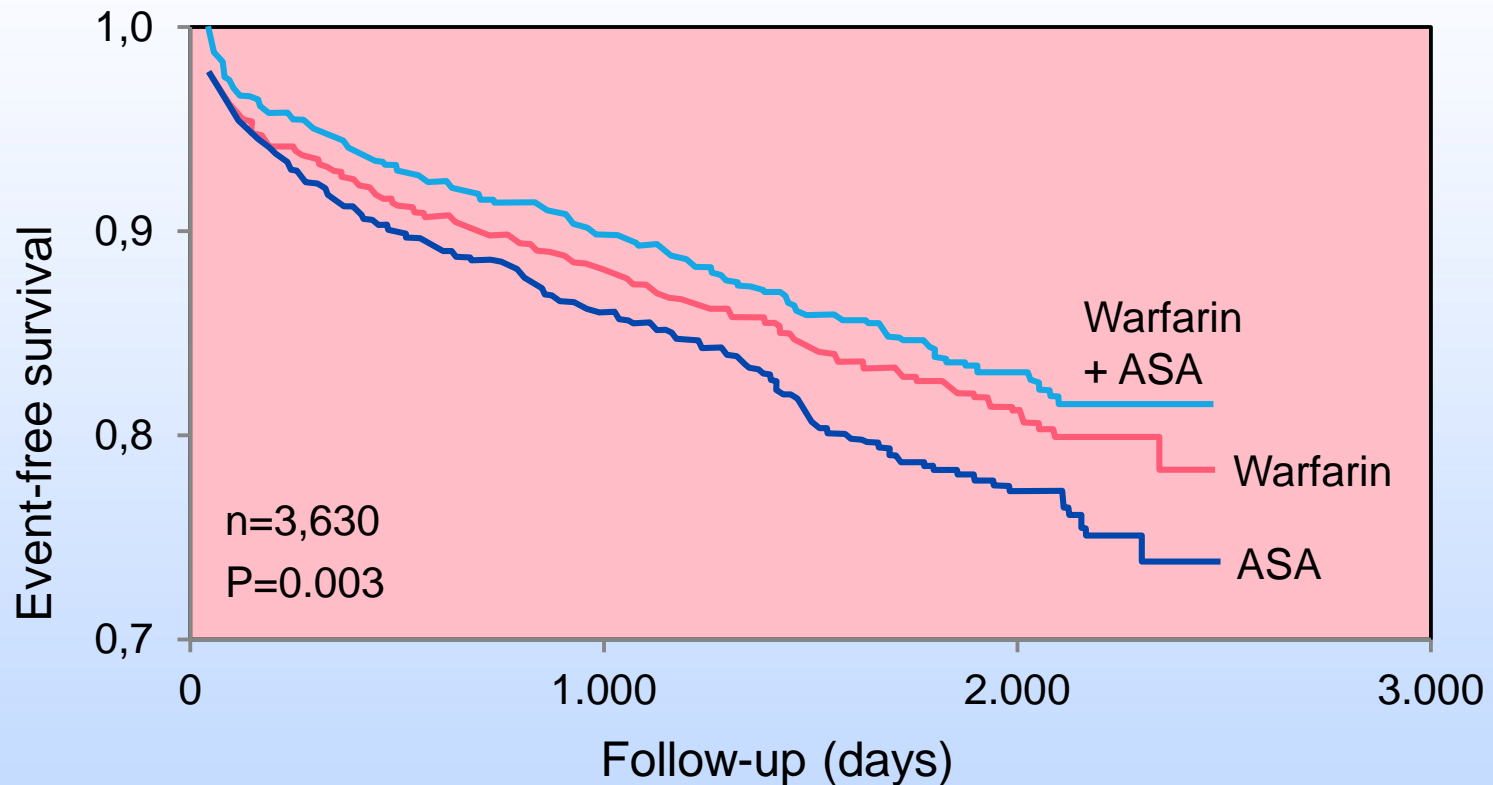
Stable INR and no bleeding  
Easy access to anticoagulation clinic  
and home INR monitoring

Noncompliant pt  INR as a monitoring tool  
Adherence to bid dosing?

Drug costs  Uncovered pt  
Need for societal economic analyses

# But doesn't aspirin reduce coronary events? WARIS-2 Study

## Secondary Prevention Following MI



Event-free survival curves for the composite endpoint of death, nonfatal reinfarction, and thromboembolic stroke. The P-value refers to the overall difference among the curves (Tarone-Ware method)

Hurlen et al: N Engl J Med;347:969, 2002