

# Triple therapy - which three drugs and for how long?

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# Who might need both antiplatelet therapy & anticoagulants?

Patients with an indication for oral anticoagulation who develop acute coronary syndrome or acute MI and undergo coronary stenting

Patients with CAD taking dual antiplatelet therapy who develop atrial fibrillation

Risks associated with antiplatelet therapy/oral anticoagulants

Bleeding

Risks associated with NOT giving antiplatelet therapy/oral anticoagulants

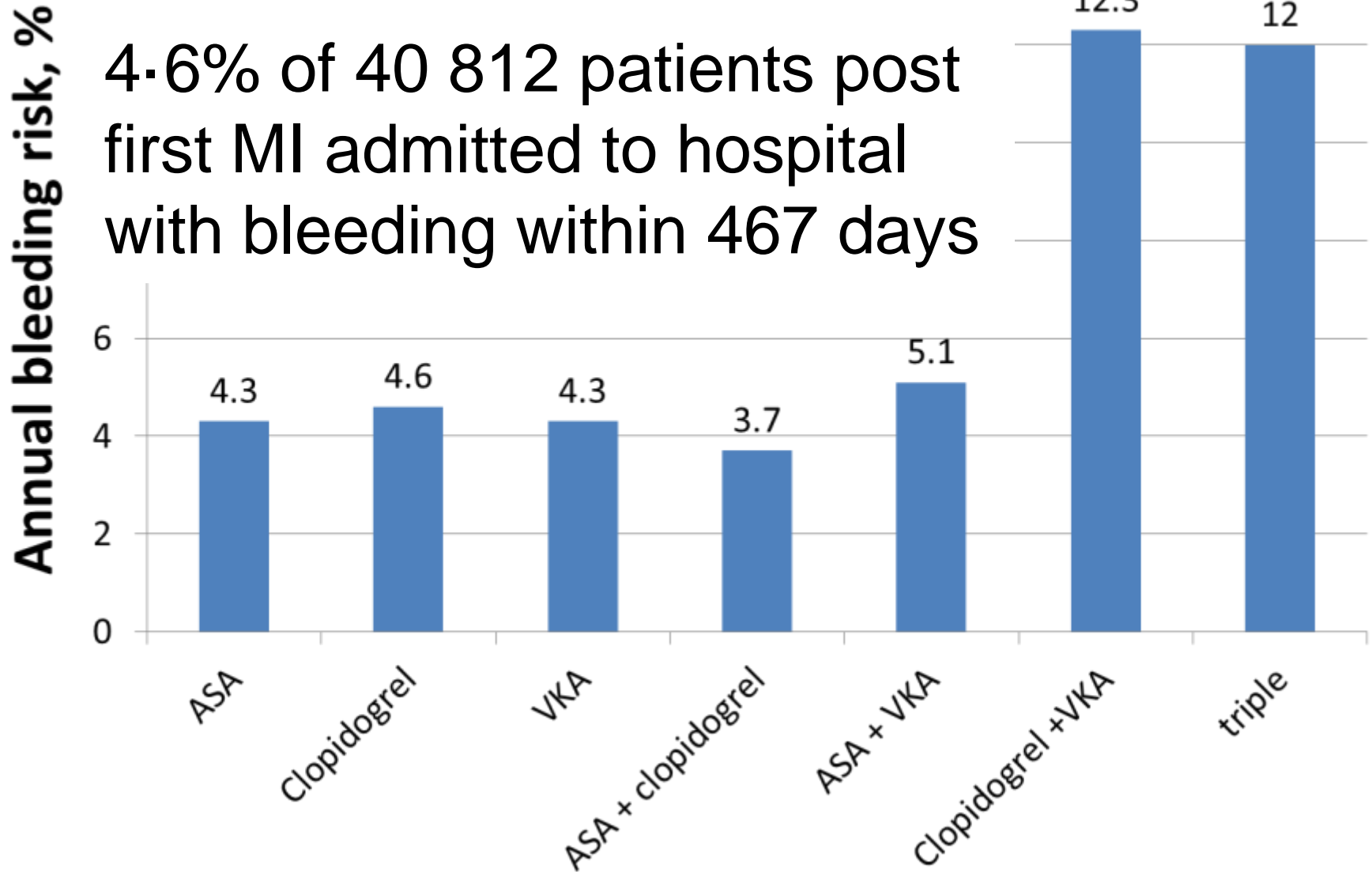
Thromboembolism

Stent thrombosis

Bleeding versus stent thrombosis

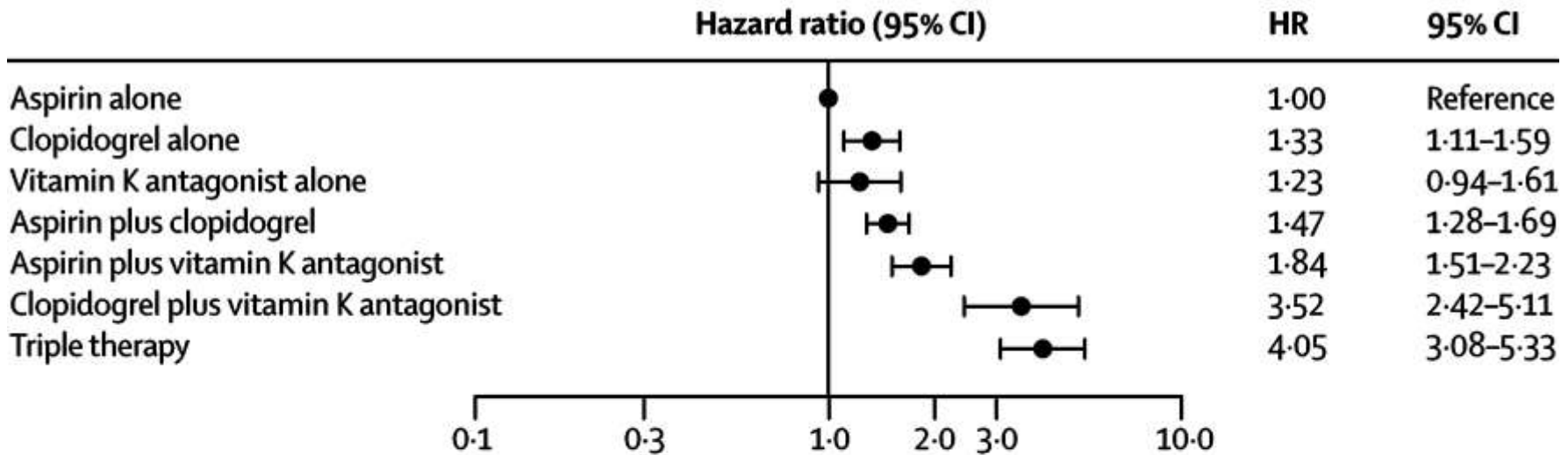
# Bleeding after MI

4.6% of 40 812 patients post first MI admitted to hospital with bleeding within 467 days

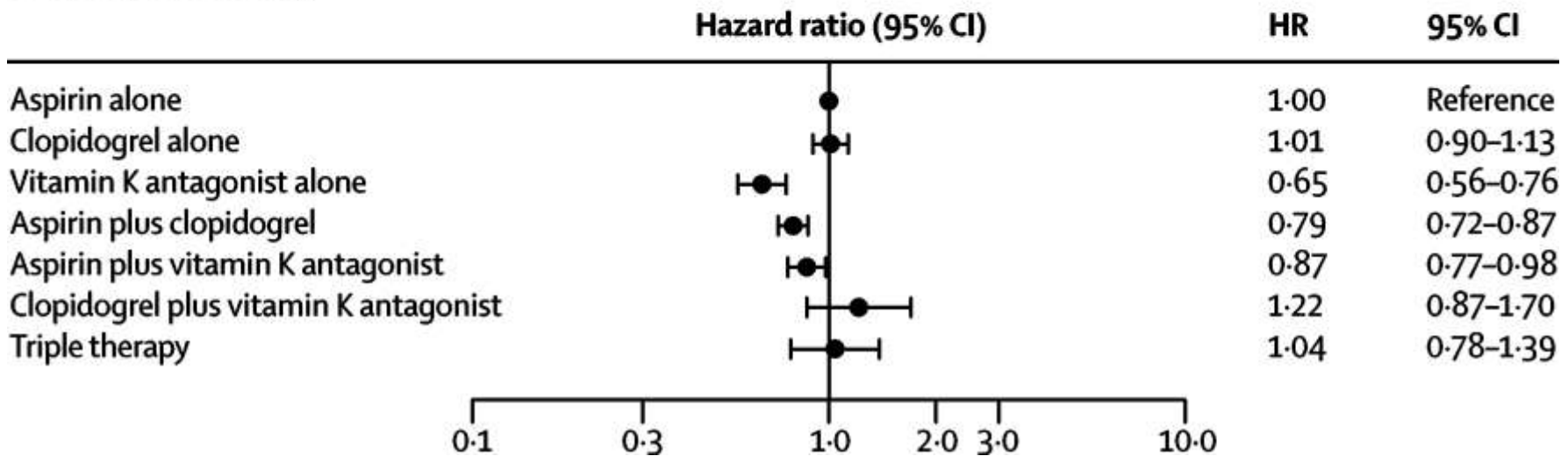


# Bleeding after MI

## A Non-fatal and fatal bleeding

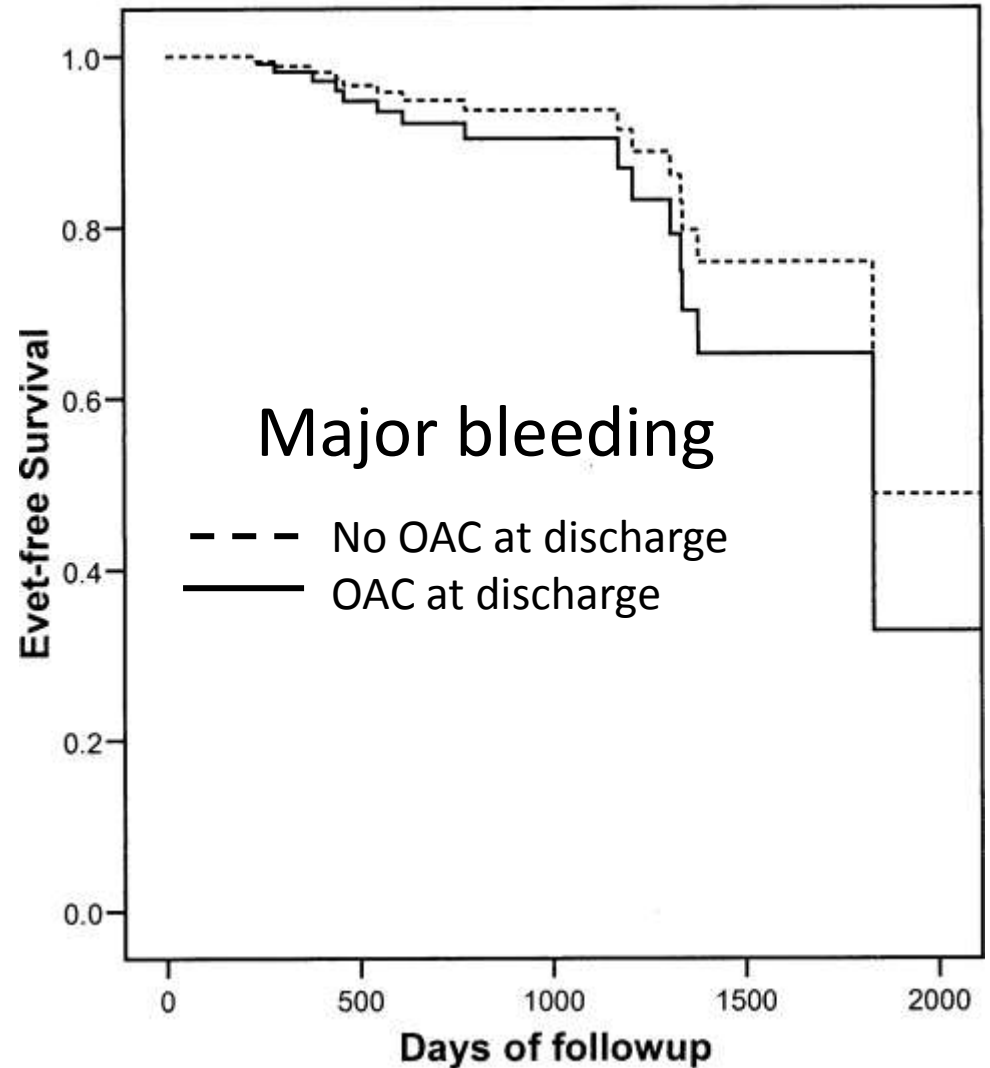
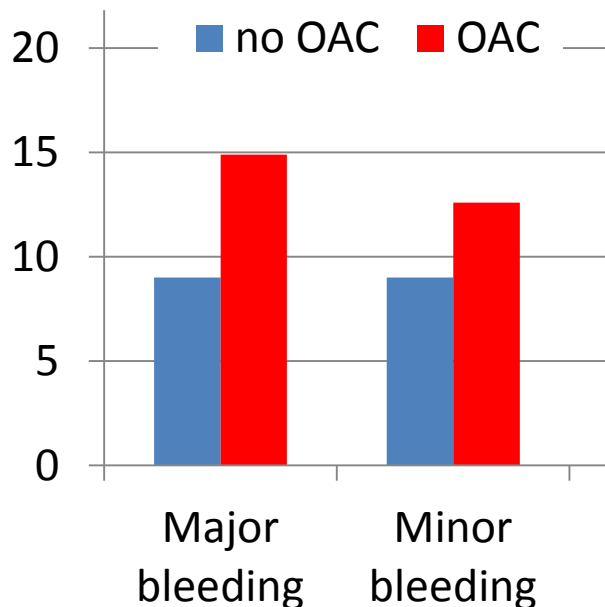


## B All-cause mortality



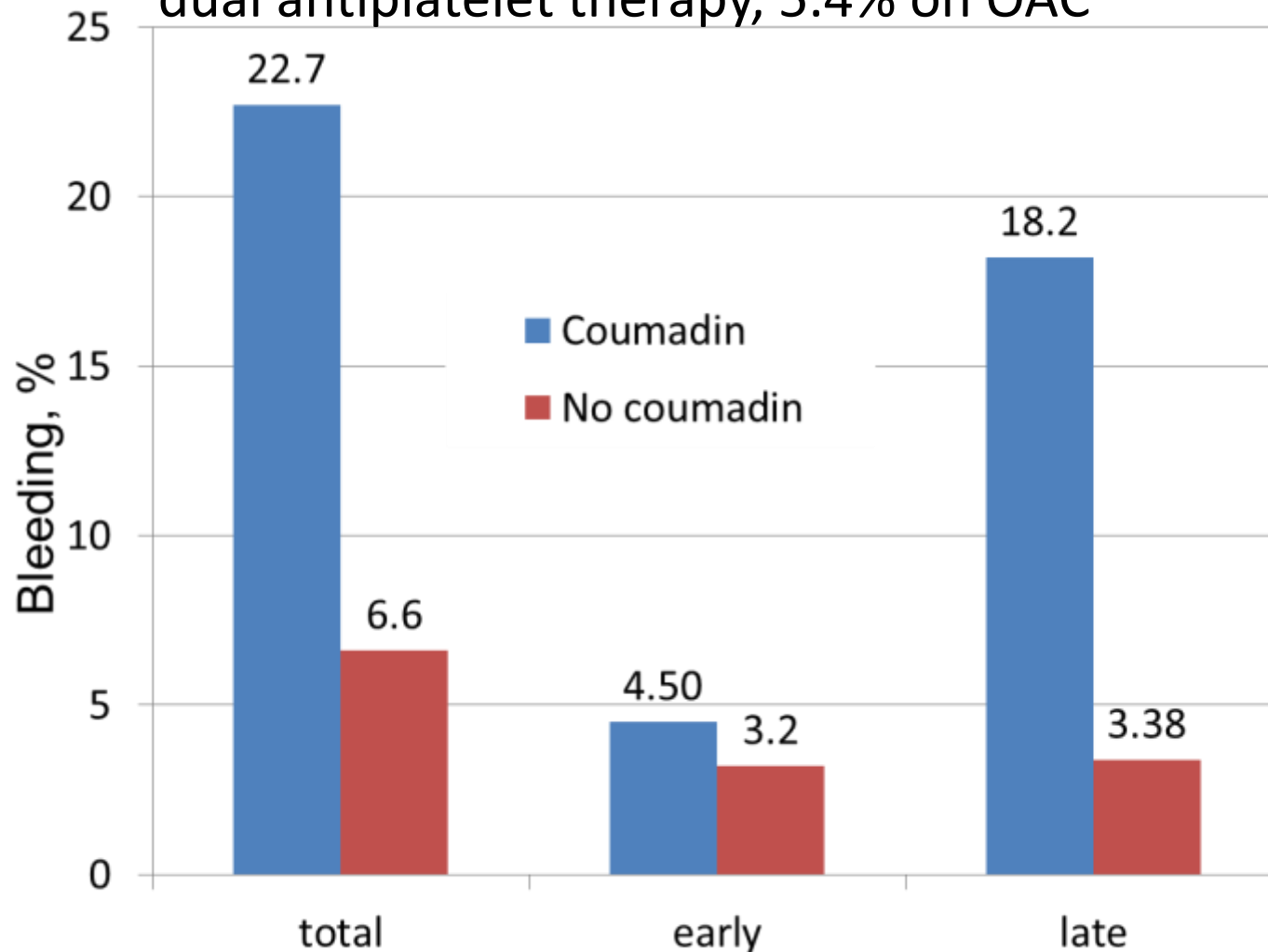
# Bleeding after stenting

Retrospective review of 426 patients with AF & stenting;  
71%♂, mean age 71.5y,  
80%  $\geq$  CHADS<sub>2</sub> 2



# Bleeding after stenting

Prospective review of 813 consecutive patients, all on dual antiplatelet therapy, 5.4% on OAC



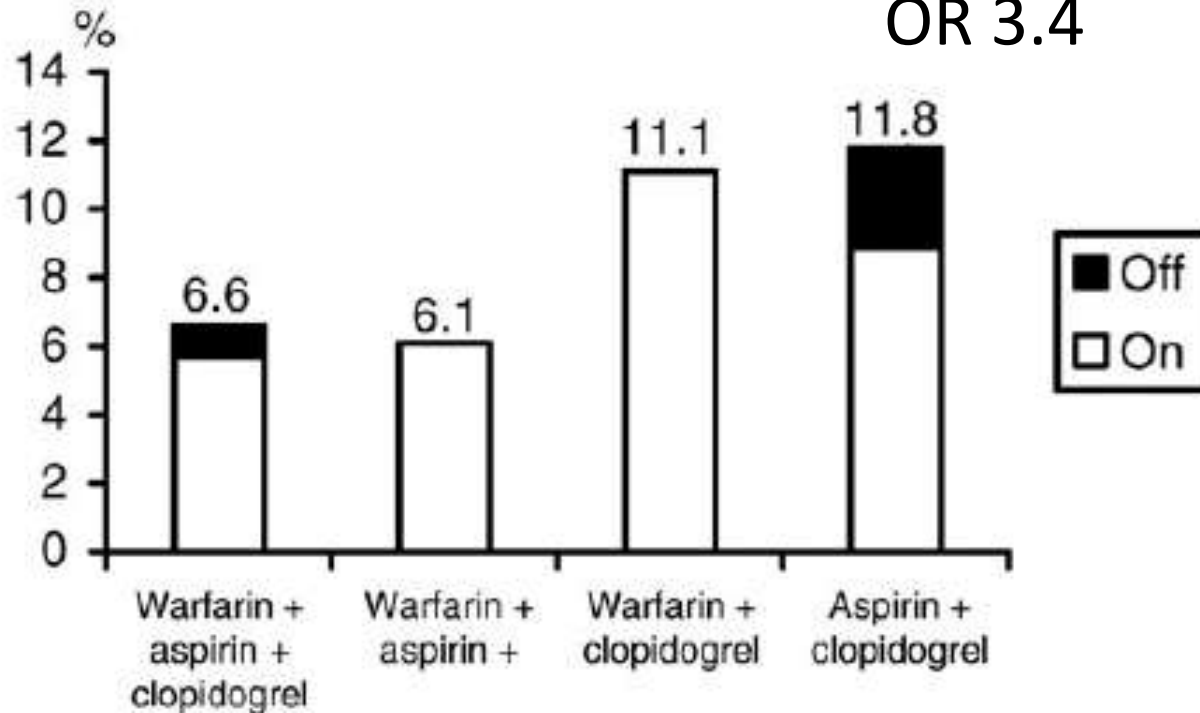
# Bleeding after stenting

Retrospective review of 239 consecutive patients, treated with warfarin, who underwent PCI

Warfarin predicted major bleeding

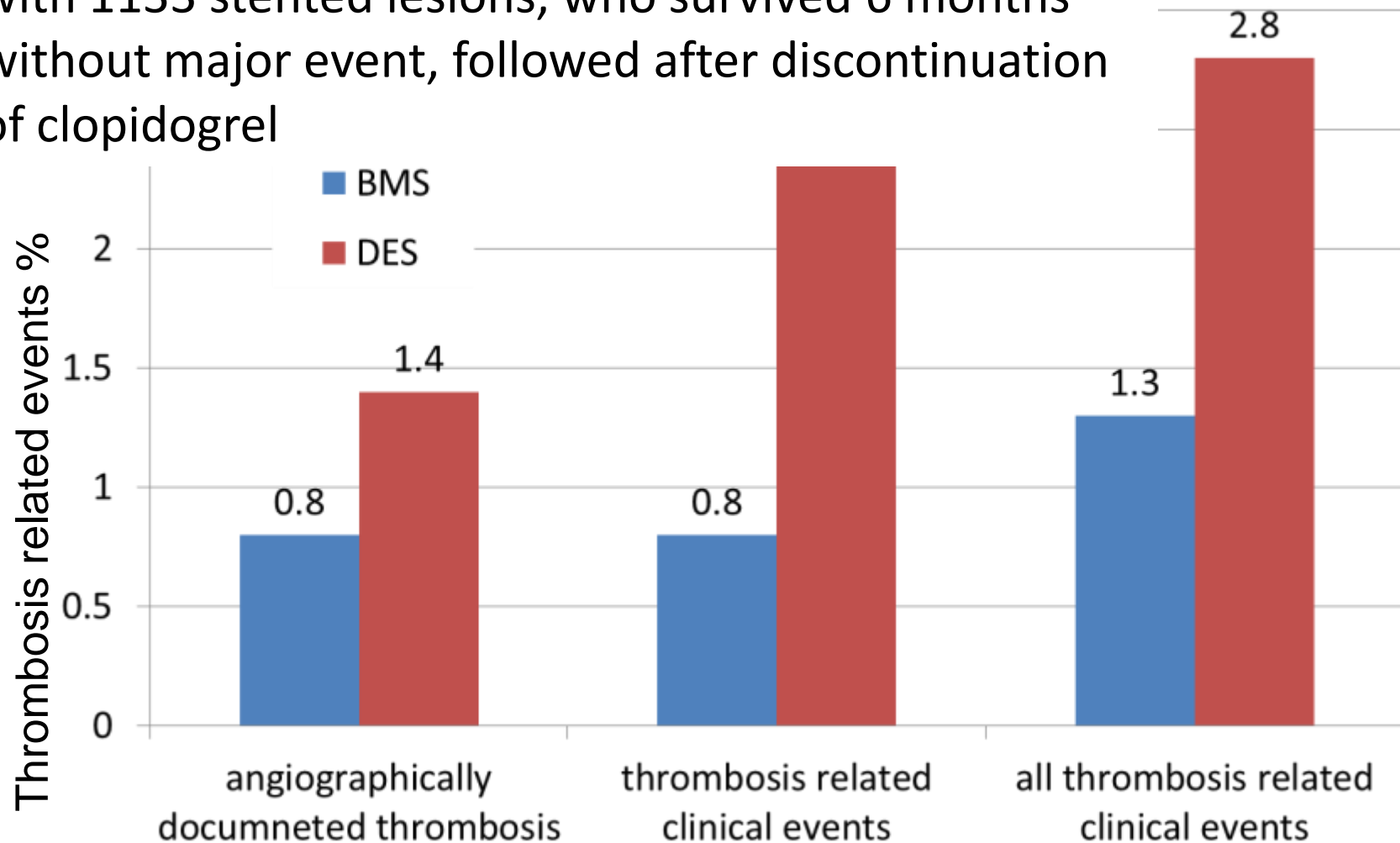
OR 3.4

Major bleeding



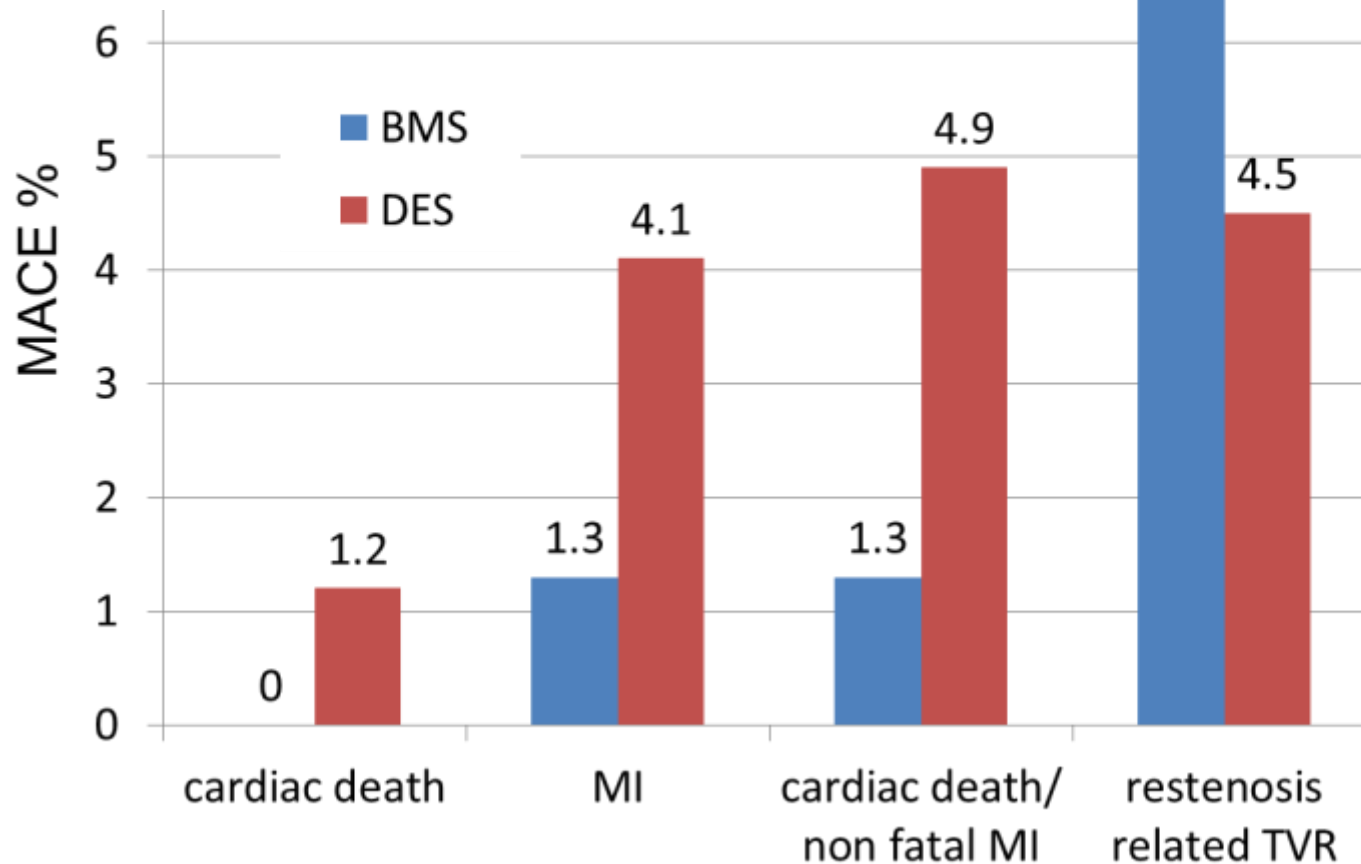
# Thrombosis after discontinuation of clopidogrel

Retrospective review of 746 consecutive patients with 1133 stented lesions, who survived 6 months without major event, followed after discontinuation of clopidogrel



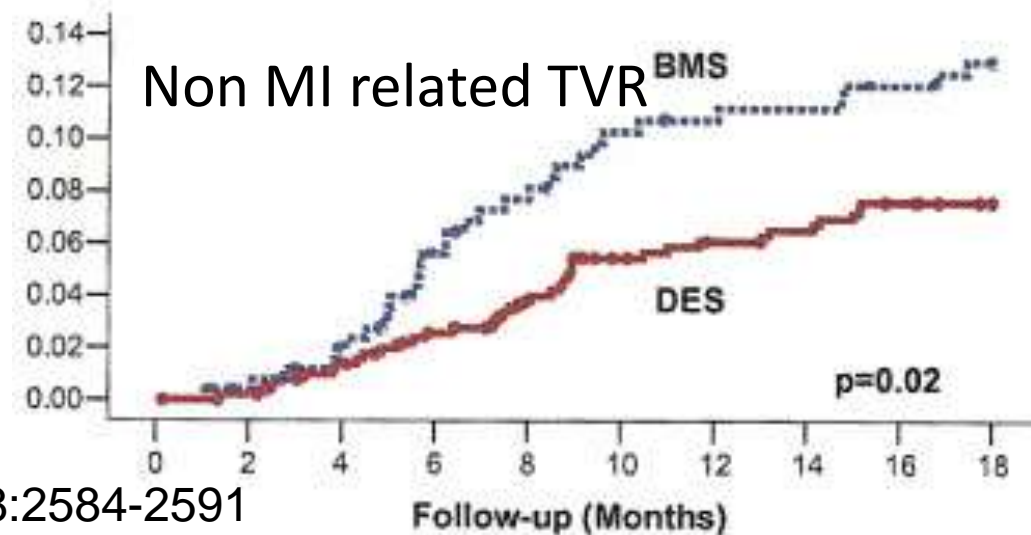
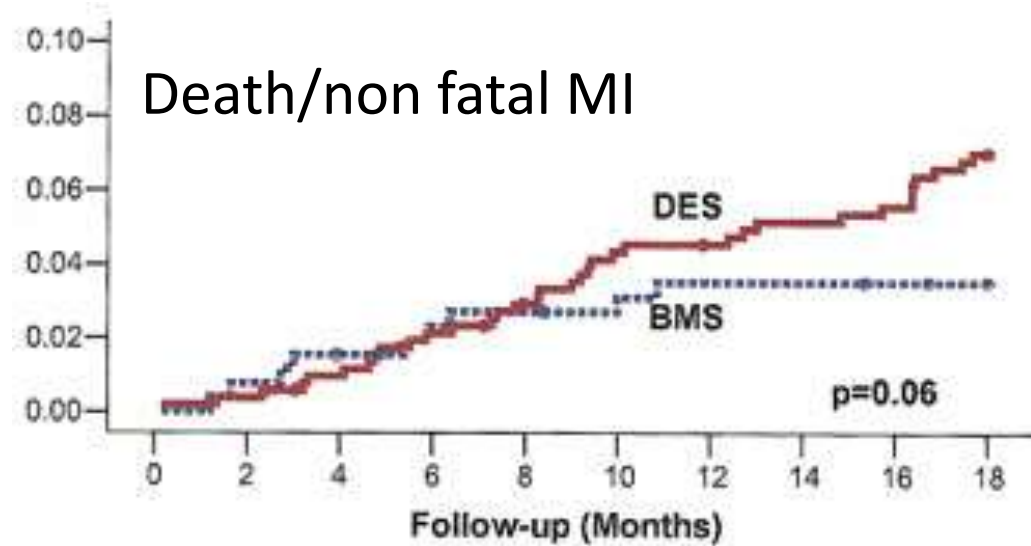
# Thrombosis after discontinuation of clopidogrel

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# Thrombosis after discontinuation of clopidogrel

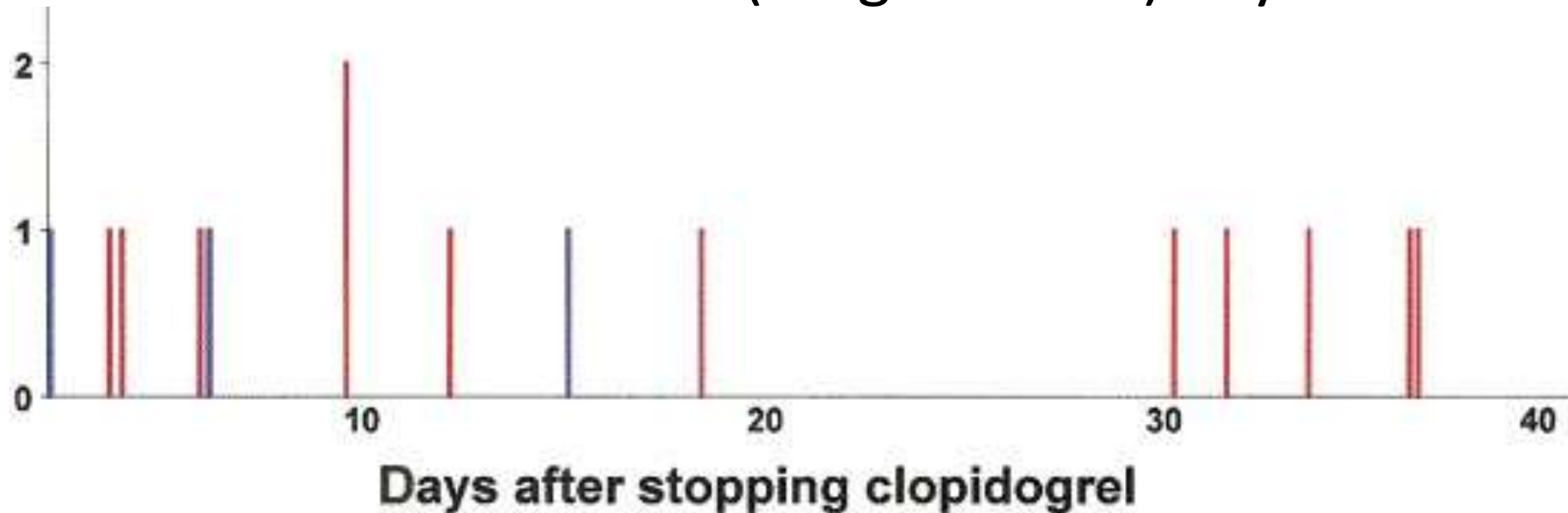
Retrospective review of 746 consecutive patients with 1133 stented lesions, who survived 6 months without major event, followed after planned discontinuation of clopidogrel @ 1 (BMS), 3 or 6 months



# Thrombosis after discontinuation of clopidogrel

Retrospective review of 746 consecutive patients with 1133 stented lesions, who survived 6 months without major event, followed after discontinuation of clopidogrel

median 116 (range 15-362) days



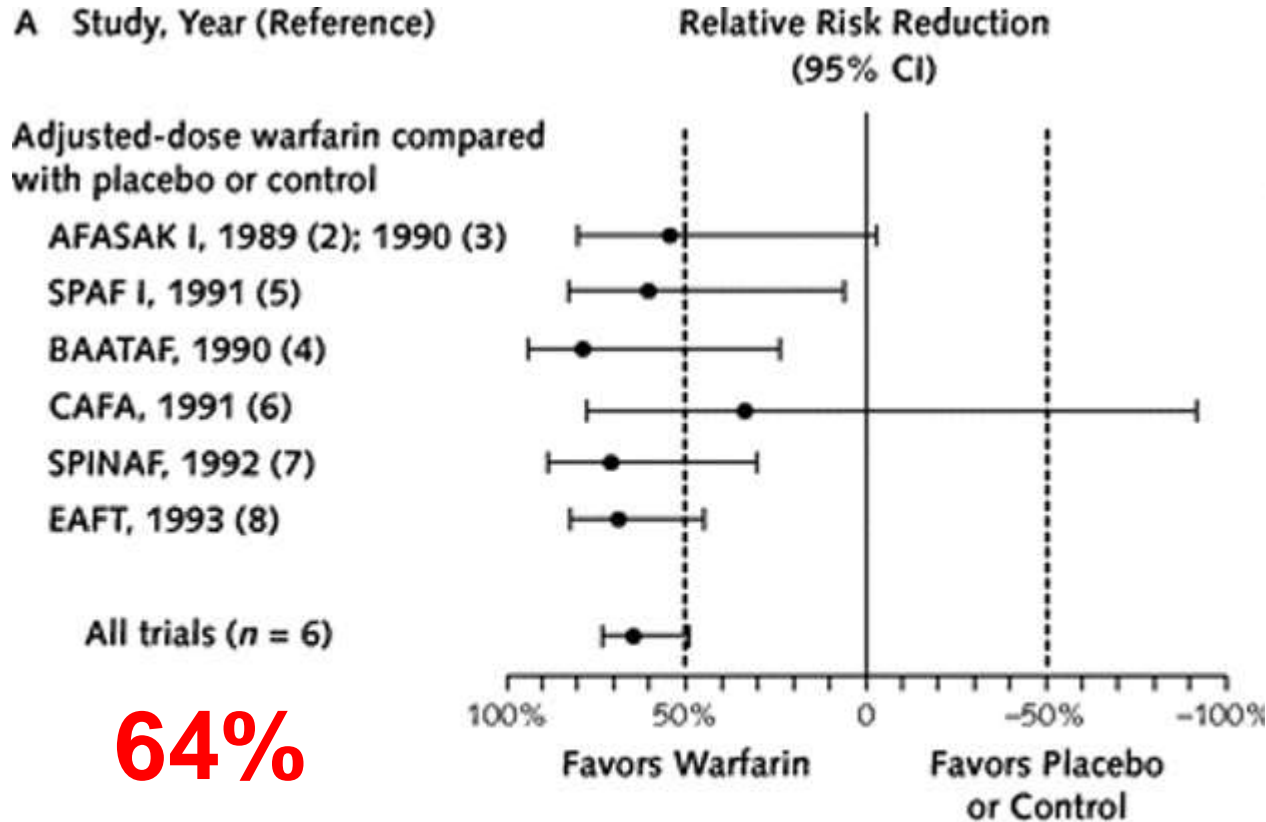
# Thrombosis after discontinuation of clopidogrel

Prospective cohort study in 2229 patients with 3797 lesions & 4495 DES; 1.3% stent thrombosis @ 9 months, mortality 45%

Risk factor	Hazard ratio	Confidence limits	Significance
Premature antiplatelet therapy discontinuation	89.78	29.9-269.9	P<0.001
Renal failure	6.49	2.6-16.15	P<0.001
Bifurcation lesion	6.42	2.93-14.07	P<0.001
Diabetes	3.71	1.74-7.89	P=0.001
Lower EF (each 10% decrease)	1.09	1.05-1.36	P<0.001

AF & prevention of stroke

# Relative effects of WARFARIN vs PLACEBO or CONTROL on all stroke from randomized trials in patients with atrial fibrillation



**64%**

# ANTIPLATELET AGENTS vs PLACEBO or CONTROL

B Study, Year (Reference)

Relative Risk Reduction (95% CI)

Antiplatelet agents compared with placebo or control

AFASAK I, 1989 (2); 1990 (3)

SPAF I, 1991 (5)

EAFT, 1993 (8)

ESPS II, 1997 (13)

LASAF, 1997 (17)

Daily

Alternate day

UK-TIA, 1999 (18)

300 mg daily

1200 mg daily

JAST, 2006 (26)

Aspirin trials (n = 7)

SAFT, 2003 (23)

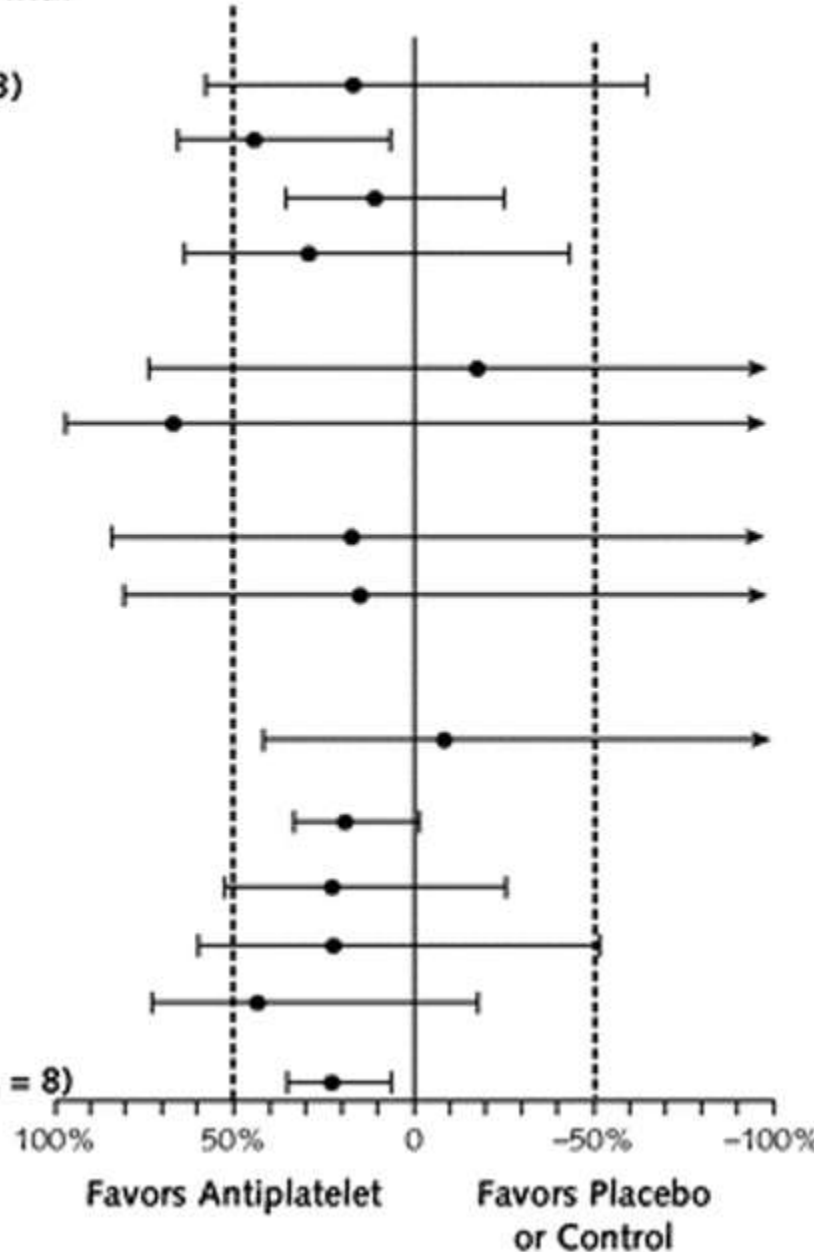
ESPS II, 1997 (13)

Dipyridamole

Combination

**22%**

All antiplatelet trials (n = 8)



# WARFARIN vs ANTIPLATELET AGENTS

C Study, Year (Reference)

Adjusted-dose warfarin compared with antiplatelet agents

AFASAK I, 1989 (2); 1990 (3)

AFASAK II, 1998 (14)

Chinese ATAFS, 2006 (30)

EAFT, 1993 (8)

PATAF, 1999 (16)

SPAF II, 1994 (10)

Age ≤75 y

Age >75 y

Aspirin trials (n = 8)\*

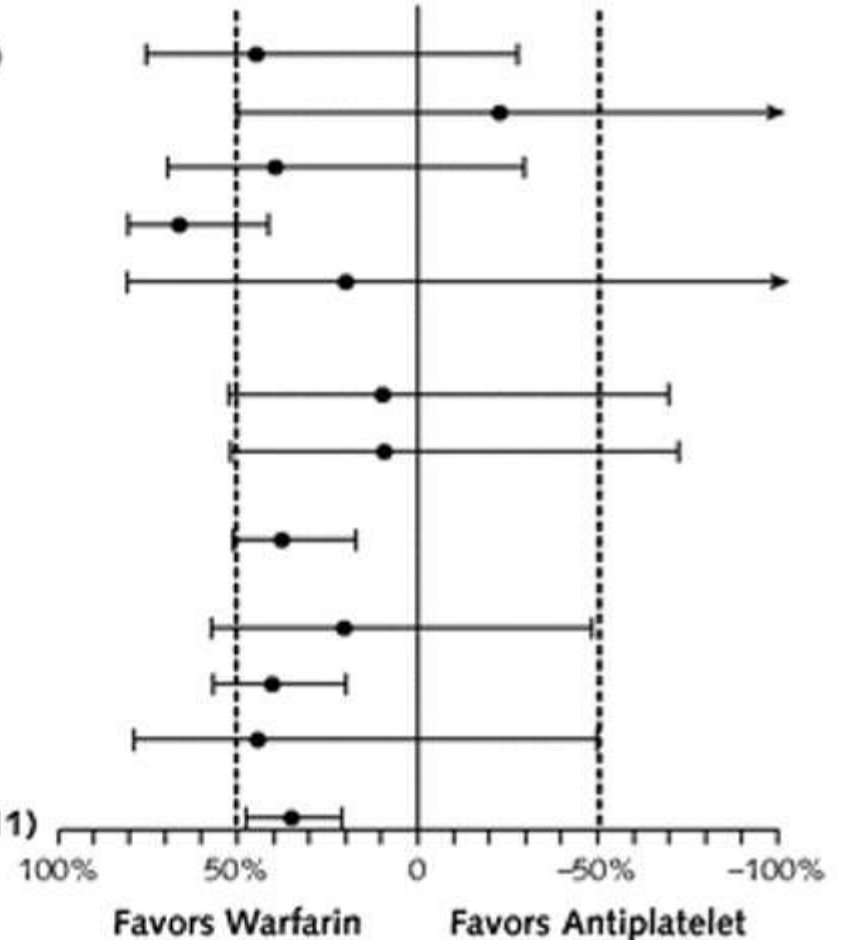
SIFA, 1997 (12)

ACTIVE-W, 2006 (28)

NASPEAF, 2004 (25)

All antiplatelet trials (n = 11)

Relative Risk Reduction (95% CI)



**39%**

# ASA & Clopidogrel versus warfarin

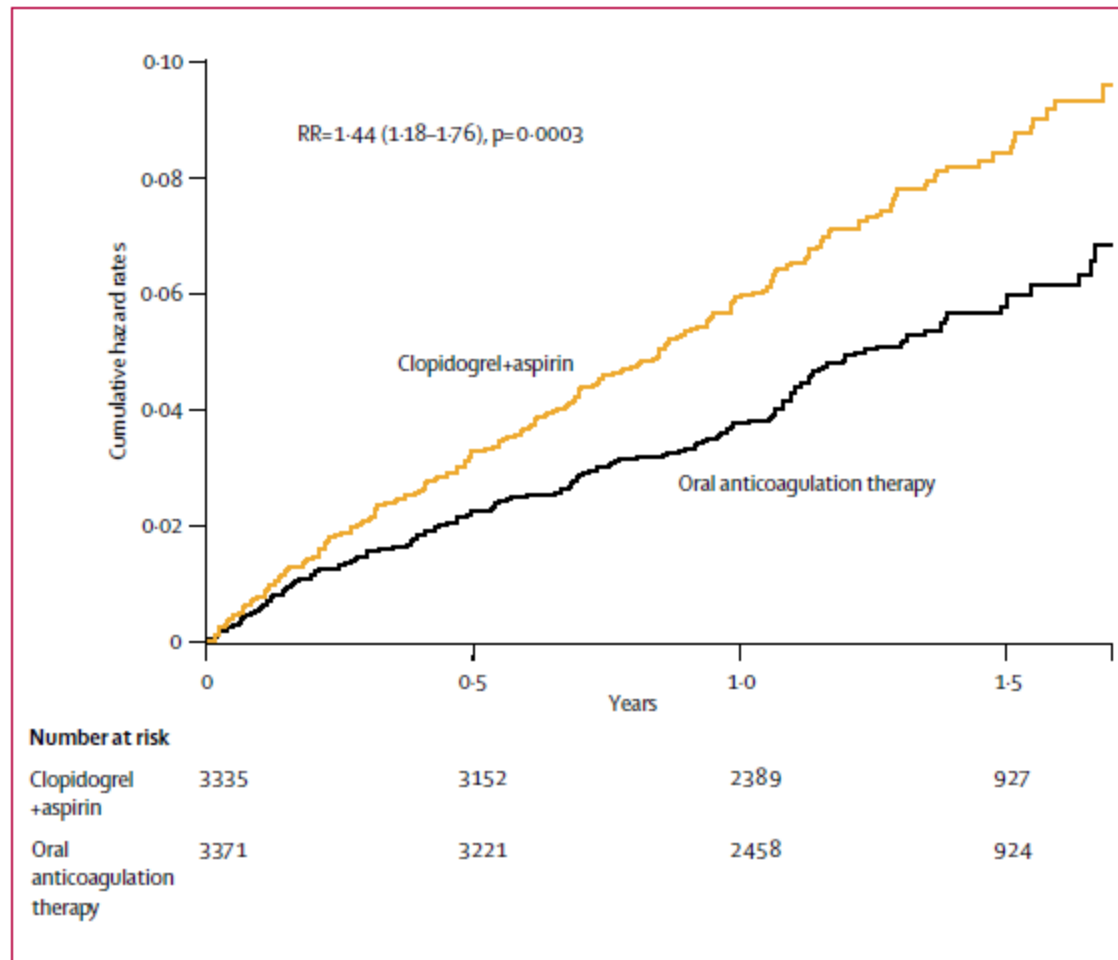
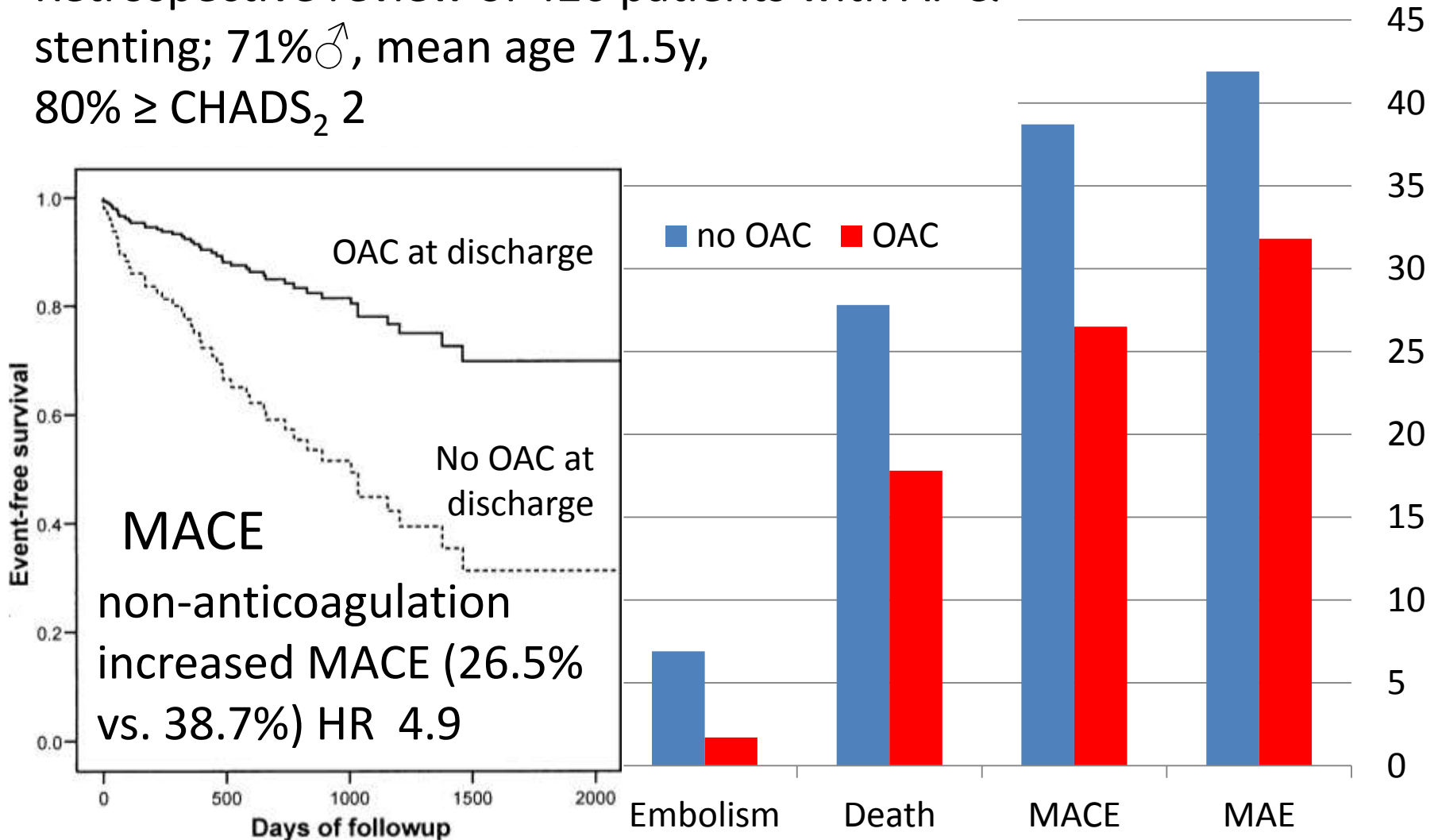


Figure 2: Cumulative risk of primary outcome

	<b>Anticoagulated</b>	<b>Not anticoagulated</b>
Major bleeding	14.9	9.0
Minor bleeding	12.6	9.0
Embolism	1.7	6.9
Death	17.8	27.8
Acute MI	6.5	10.4
TVR	7.1	8.4
TV failure	9.2	16.7
Other revascularisation	5.9	8.5
Subacute or late thrombosis	1.2	1.3
MACE	26.5	38.7
MAE	31.8	41.9

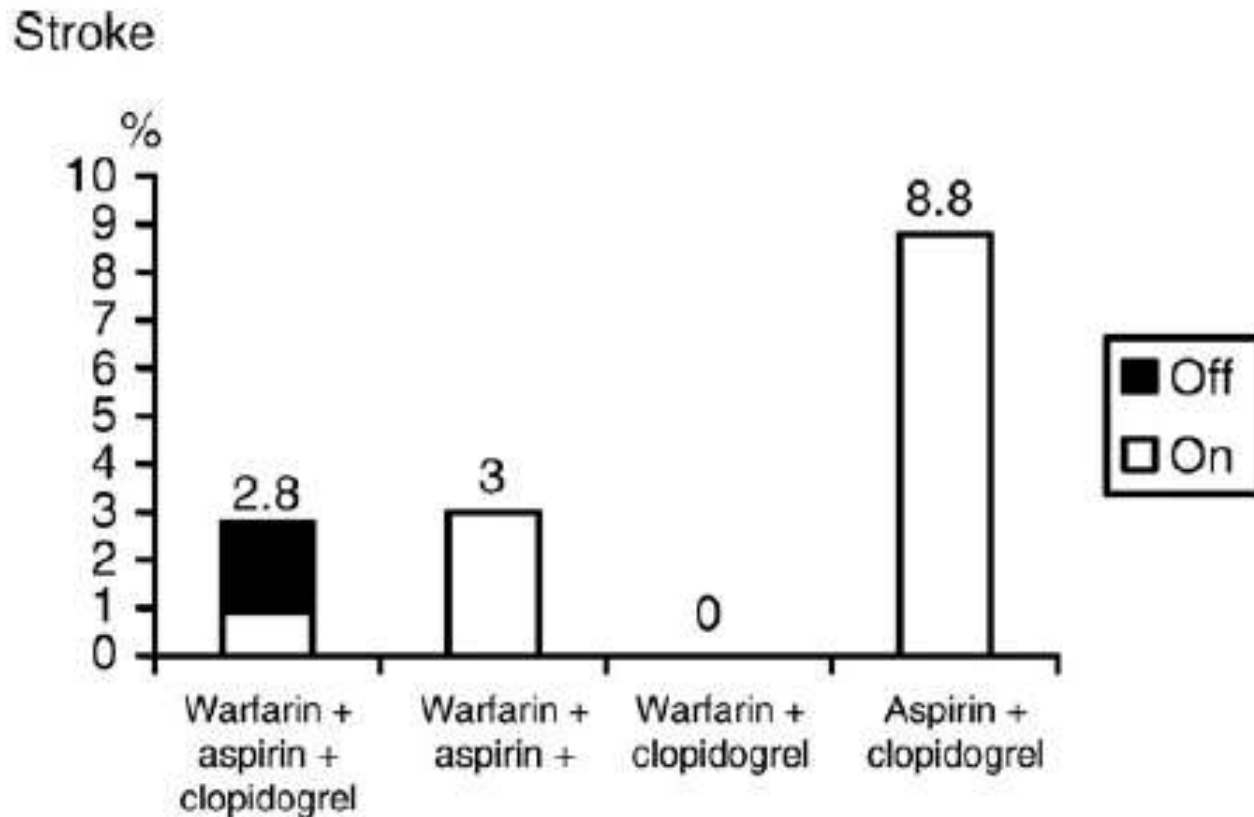
# Thrombosis/embolism

Retrospective review of 426 patients with AF & stenting; 71%♂, mean age 71.5y, 80%  $\geq$  CHADS<sub>2</sub> 2



# Stroke after stenting

Retrospective review of 239 consecutive patients, treated with warfarin, who underwent PCI



# Elective PCI & stenting <sup>\*Up to 12 months warfarin</sup> + clopidogrel /or aspirin

Haemorrhagic risk	Type of stent	Recommendation		
		Drug	Dose/day	duration
Low or intermediate	Bare metal	ASA	≤ 100 mg	1 month
		clopidogrel	75 mg	
		warfarin	INR 2.0–2.5	
	Drug eluting	ASA	≤ 100 mg	3 (-olimus group) to 6 (paclitaxel) months*
		clopidogrel	75mg	
		warfarin	INR 2.0–2.5	
High	Bare metal	ASA	≤ 100 mg	2–4 weeks
		clopidogrel	75mg	
		warfarin	INR 2.0-2.5	

Life long warfarin

# ACS PCI & stenting

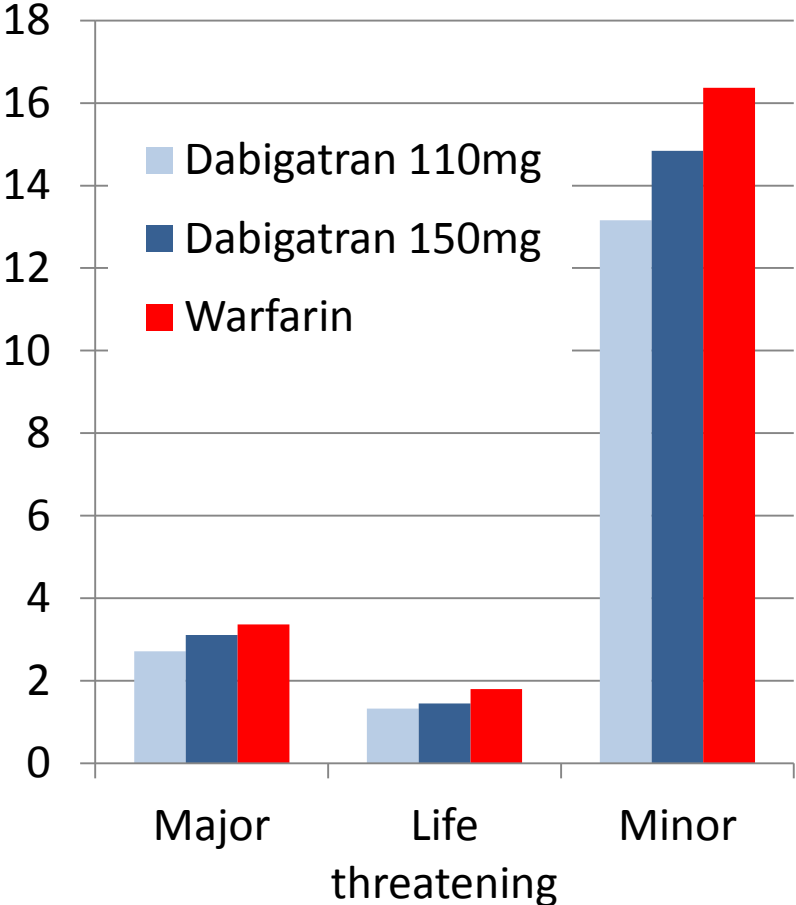
Haemorrhagic risk	Type of stent	Recommendation		
		Drug	Dose/day	duration
Low or intermediate	Bare metal or drug eluting	ASA	≤ 100 mg	6 months*
		clopidogrel	75 mg	
		warfarin	INR 2.0–2.5	
High	Bare metal	ASA	≤ 100 mg	4 weeks*
		clopidogrel	75mg	
		warfarin	INR 2.0-2.5	

\*Up to 12 months warfarin + clopidogrel/or aspirin  
 Life long warfarin

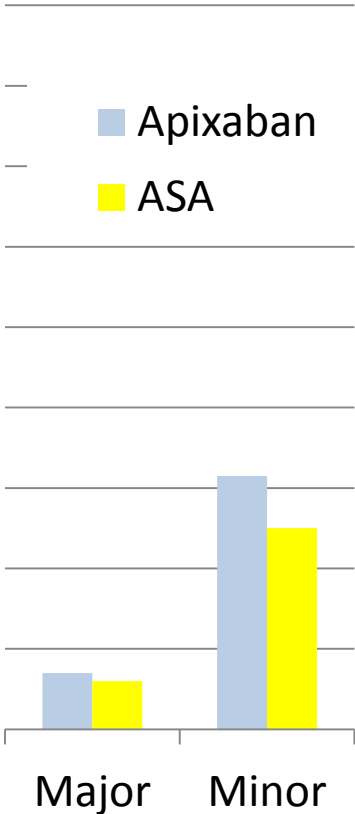
Newer anticoagulants:  
no excess bleeding risk

# Bleeding

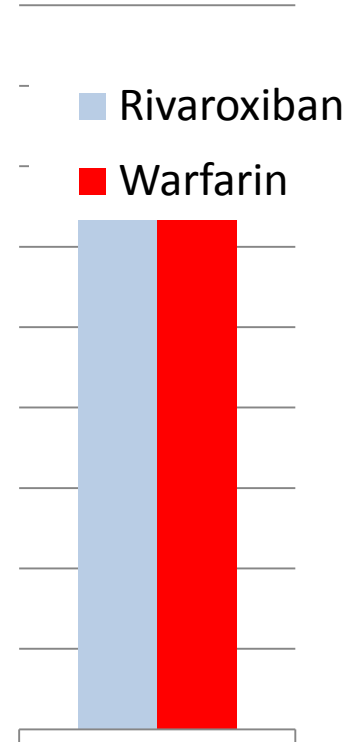
## Dabigatran



## Apixaban



## Rivaroxiban



Connolly et al N Engl J Med 2009;361:1139-51  
 Connolly et al N Engl J Med 2011;364:806-17  
 Patel et al N Engl J Med 2011; 365:883-891

Newer antiplatelet agents:

# Prasugrel:

## NICE recommendation TA 182

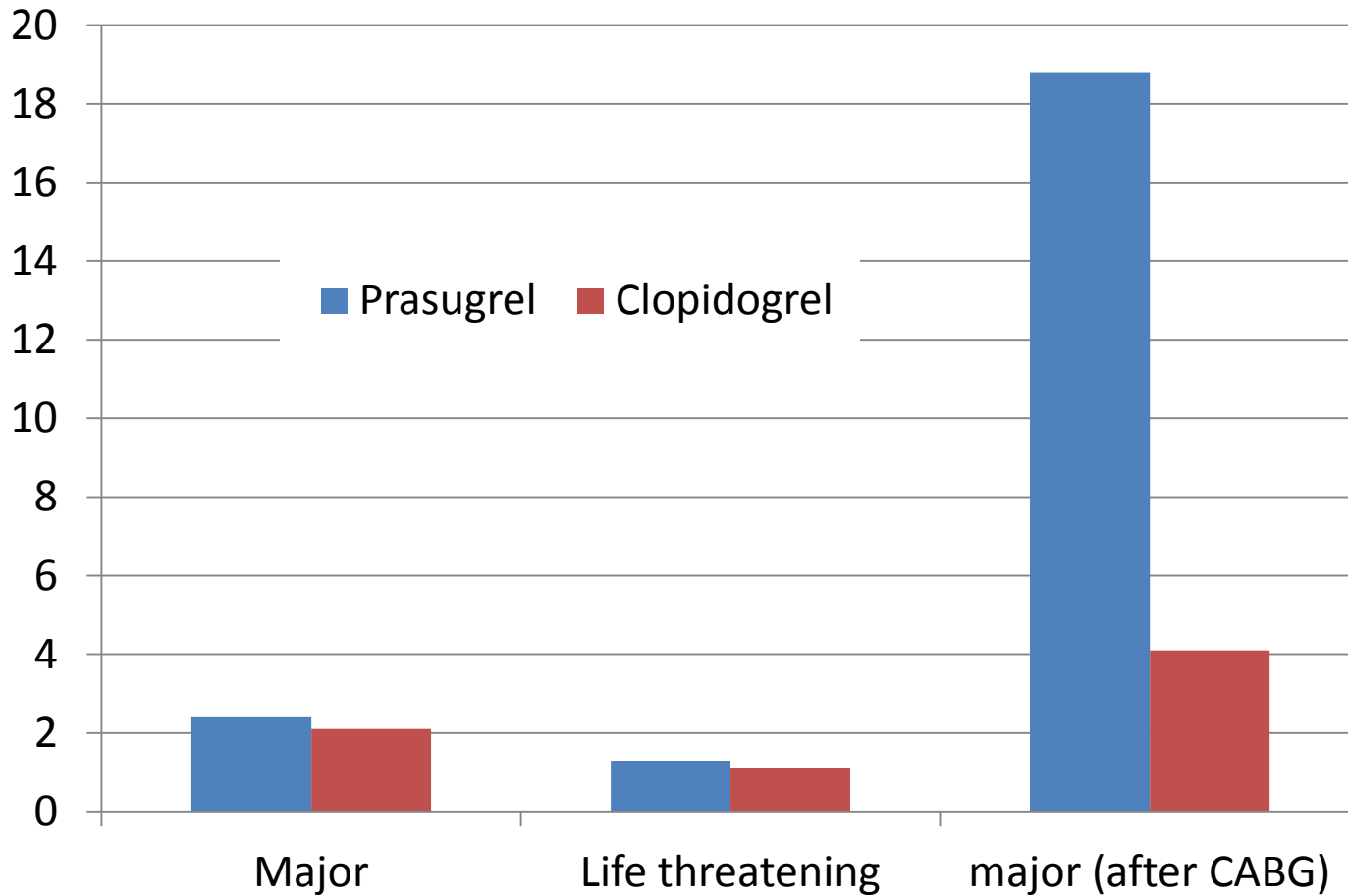
### 1 Guidance

1.1 Prasugrel in combination with aspirin is recommended as an option for preventing atherothrombotic events in people with acute coronary syndromes having percutaneous coronary intervention, only when:

- immediate primary percutaneous coronary intervention for ST-segment-elevation myocardial infarction is necessary **or**
- stent thrombosis has occurred during clopidogrel treatment **or**
- the patient has diabetes mellitus.

# Bleeding

Prasugrel compared with clopidogrel in 3534 patients with STEMI undergoing PCI  
TRITON TIMI 38



# Ticagrelor: proposed NICE recommendation

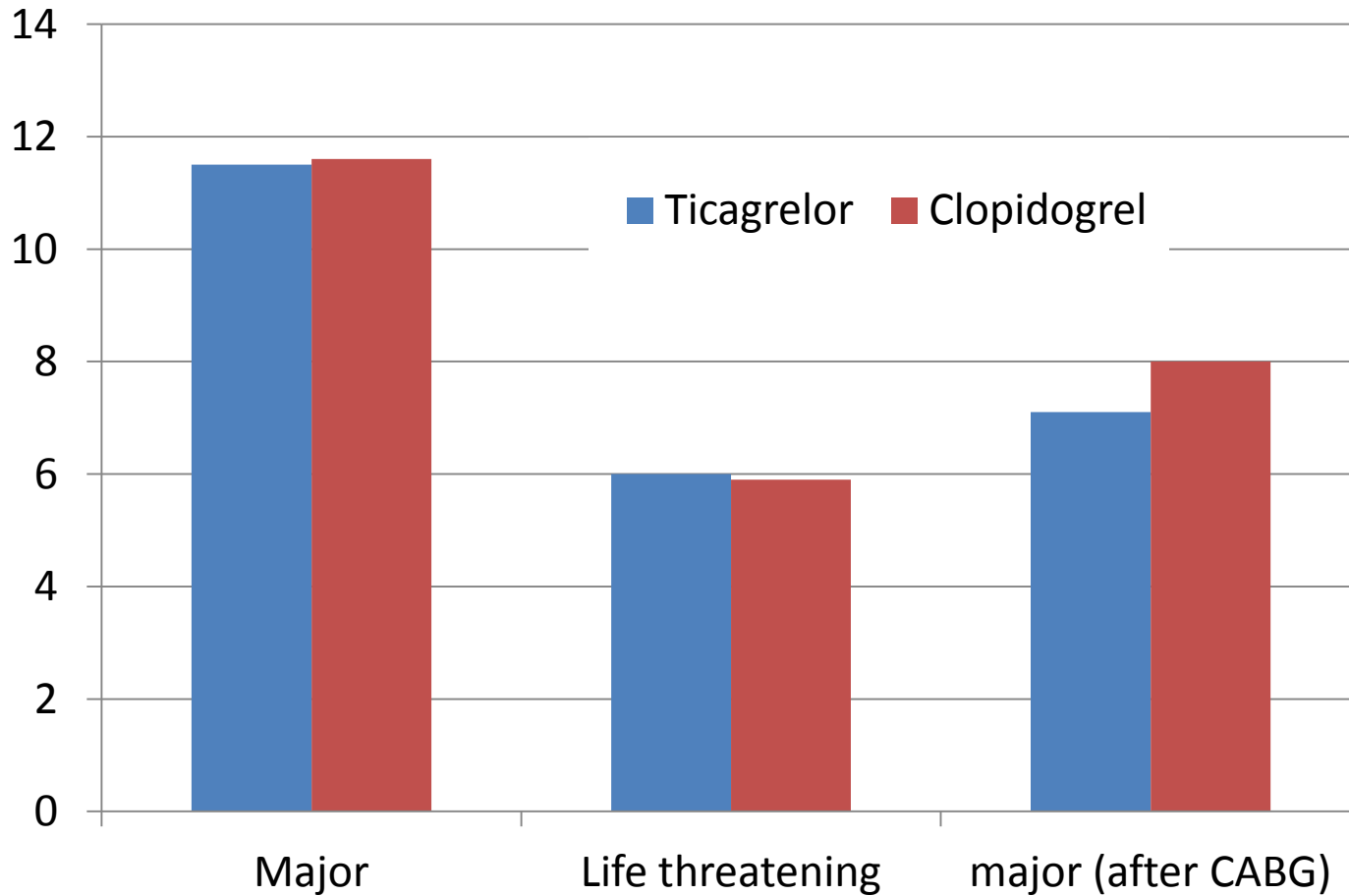
## 1 Guidance

1.1 Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in adults with acute coronary syndromes (STEMI, NSTEMI, unstable angina) at high risk:

- age 60 years or older
- previous MI or CABG
- coronary artery disease with stenosis of  $\geq 50\%$  or more in  $\geq 2$  vessels;
- previous ischaemic stroke; previous TIA or carotid stenosis of  $\geq 50\%$ , or cerebral revascularisation;
- diabetes mellitus;
- peripheral arterial disease;
- chronic renal dysfunction

# Bleeding

Ticagrelor compared with clopidogrel in 13 408 patients with ACS undergoing PCI PLATO



# Conclusions

Patients who might be suitable for triple therapy are already at high risk

Data on the combination of warfarin, ASA & clopidogrel are limited, observational and mostly retrospective

The addition of warfarin to dual antiplatelet therapy increases bleeding risk

This excess risk is outweighed by reduction in strokes

# Conclusions

The newer antiplatelet agents do not appear to increase bleeding risk (except after CABG)

The newer anticoagulants do not increase bleeding risk

There are no data on their combination