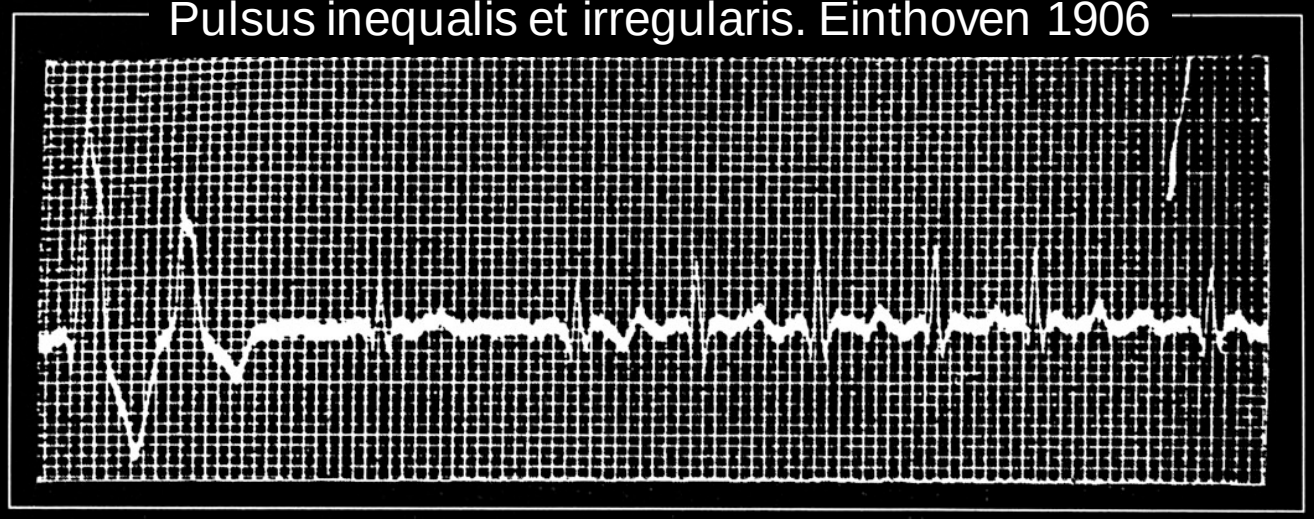
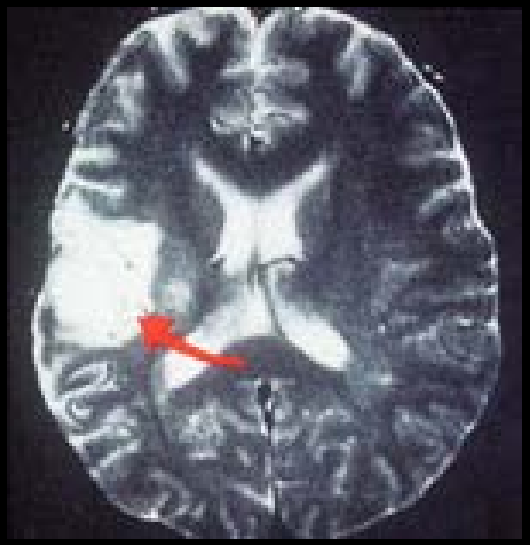




How does the presence of concomitant ischemic heart disease change atrial fibrillation management ?

Giuseppe Boriani, MD

Institute of Cardiology
University of Bologna, Italy

La FA è un FATTORE di RISCHIO INDIPENDENTE per STROKE

Tasso annuale di complicanze tromboemboliche (TE)
4.5 % in paz. con FA vs. 0.2-1.4 % nei controlli

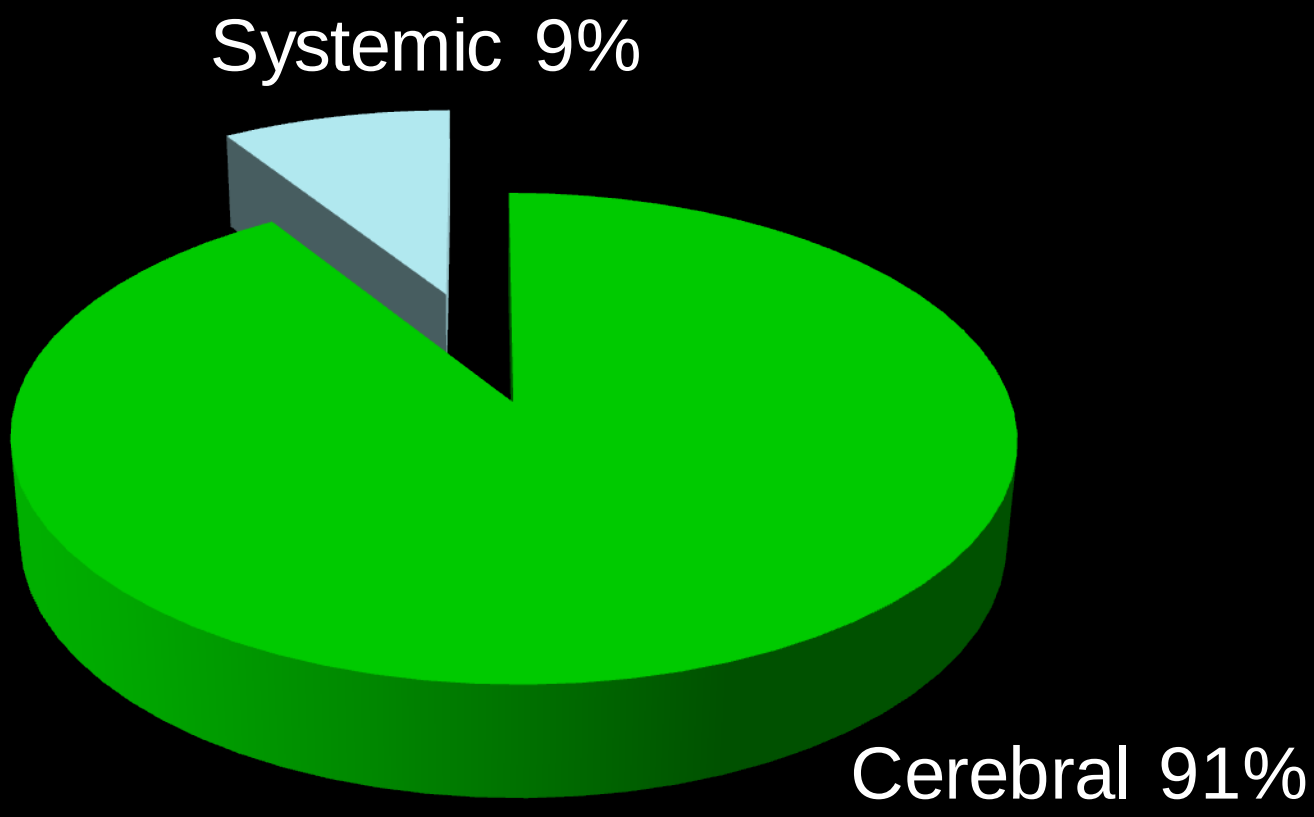
↓

5 x del rischio di TE

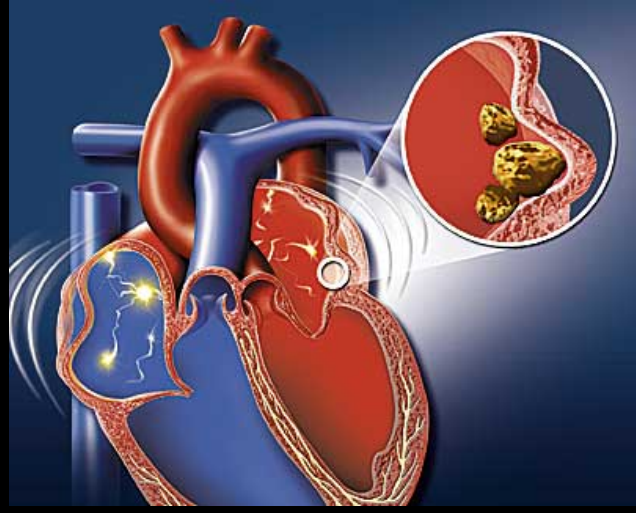
FA responsabile 15-18 % di tutti i casi di stroke

Thromboembolic events in AF

Control patients in AF Trials



THE BIBLE



Atrial Fibrillation*

The Ancient Conundrum Defies Simple Solution

Martin E. Goldman, MD, FACC,
Lori B. Croft, MD, FACC
New York, New York

"... Eli sat on his seat by the wayside watching;
for his heart trembled ..." Samuel I, 4:13

J. Am. Coll. Cardiol. 2005;45;1813-1814

European Heart Journal (2005) 26, 2422–2434
doi:10.1093/eurheartj/ehi505

Atrial fibrillation management: a prospective survey in ESC Member Countries

The Euro Heart Survey on Atrial Fibrillation

Robby Nieuwlaat[1*], Alessandro Capucci[2], A. John Camm[3], S. Bertil Olsson[4], Dietrich Andresen[5], D. Wyn Davies[6], Stuart Cobbe[7], Günter Breithardt[8], Jean-Yves Le Heuzey[9], Martin H. Prins[10], Samuel Lévy[11], and Harry J.G.M. Crijns[1] on behalf of the Euro Heart Survey Investigators

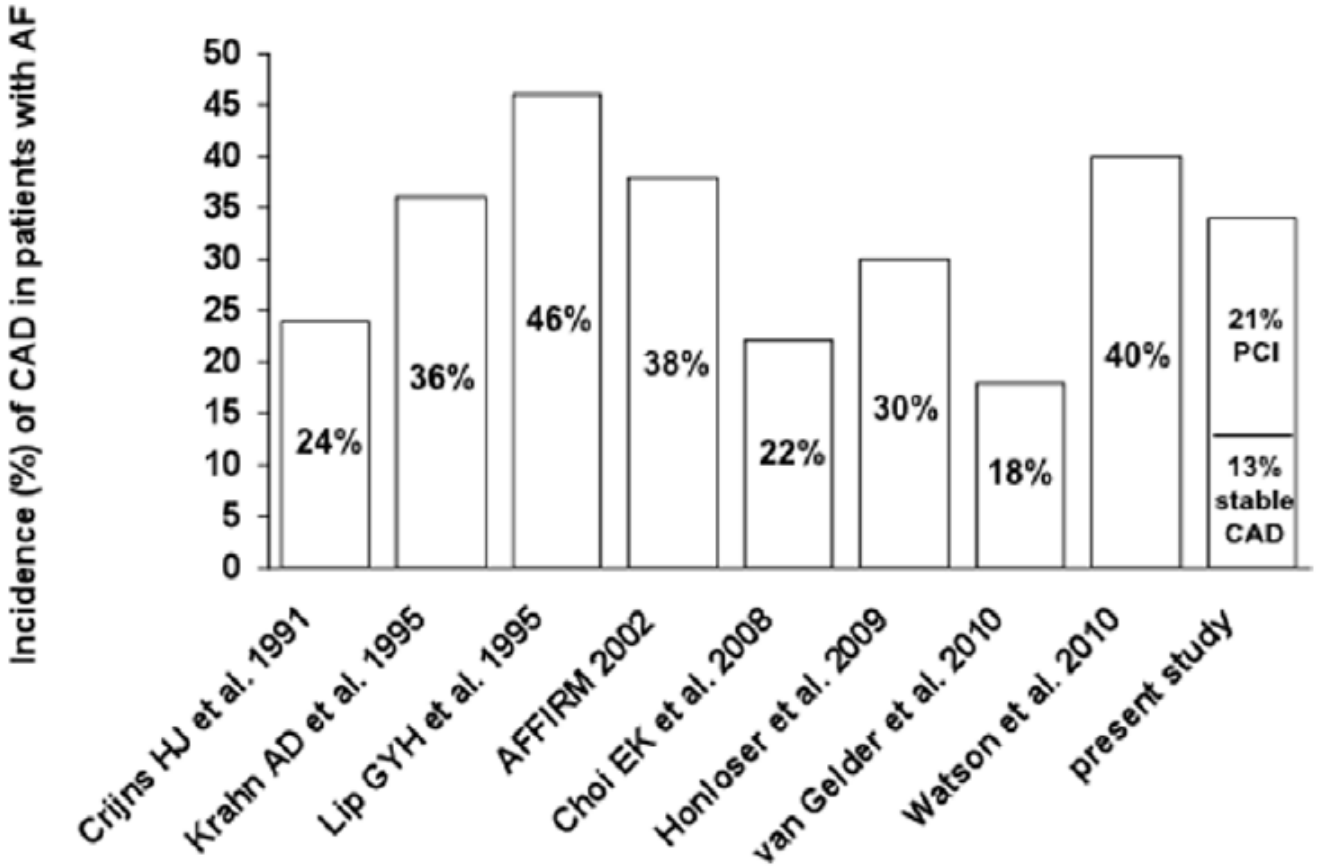
	First detected ($n = 978$)	Paroxysmal ($n = 1517$)	Persistent ($n = 1167$)	Permanent ($n = 1541$)	*P*-value
Demographics					
Age, years	65 (14)	64 (13)	66 (12)	71 (11)	*
Female gender	418 (43)	652 (43)	451 (39)	668 (43)	
Concomitant disease					
Hypertension	620 (63)	942 (62)	772 (66)	984 (64)	
Coronary artery disease	309 (32)	514 (34)	338 (29)	543 (36)	
Acute infarction	65 (7)	32 (2)	24 (2)	41 (3)	*
Old infarction	124 (13)	228 (15)	142 (12)	259 (17)	
Previous PCI / CABG	102 (11)	187 (12)	136 (12)	166 (11)	
Angina	179 (19)	350 (23)	172 (15)	304 (20)	*
Heart failure	255 (26)	341 (23)	401 (35)	754 (49)	*
Valvular heart disease	203 (21)	287 (19)	276 (24)	607 (40)	*
Cardiomyopathy	79 (8)	101 (7)	148 (13)	243 (16)	*
Tachycardiomyopathy	9 (1)	4 (0)	28 (2)	14 (1)	*
Hypertrophic	25 (3)	34 (2)	24 (2)	21 (1)	
Dilated	38 (4)	49 (3)	73 (6)	152 (10)	*
Other type	7 (1)	14 (1)	23 (2)	56 (4)	*
Sick sinus syndrome	9 (1)	93 (6)	55 (5)	82 (5)	*
Chronic obstructive pulmonary disease	103 (11)	185 (12)	133 (12)	272 (18)	*
Thyroid disease	61 (7)	148 (11)	132 (12)	149 (11)	
Idiopathic AF[a]	130 (14)	226 (15)	112 (10)	61 (4)	*

Risk for ischaemic stroke/TIA/TE in 182 678 patients with AF: the Swedish Atrial Fibrillation cohort study

Friberg, Rosenqvist, Lip. Eur Heart J 2012 ;33(12):1500-10

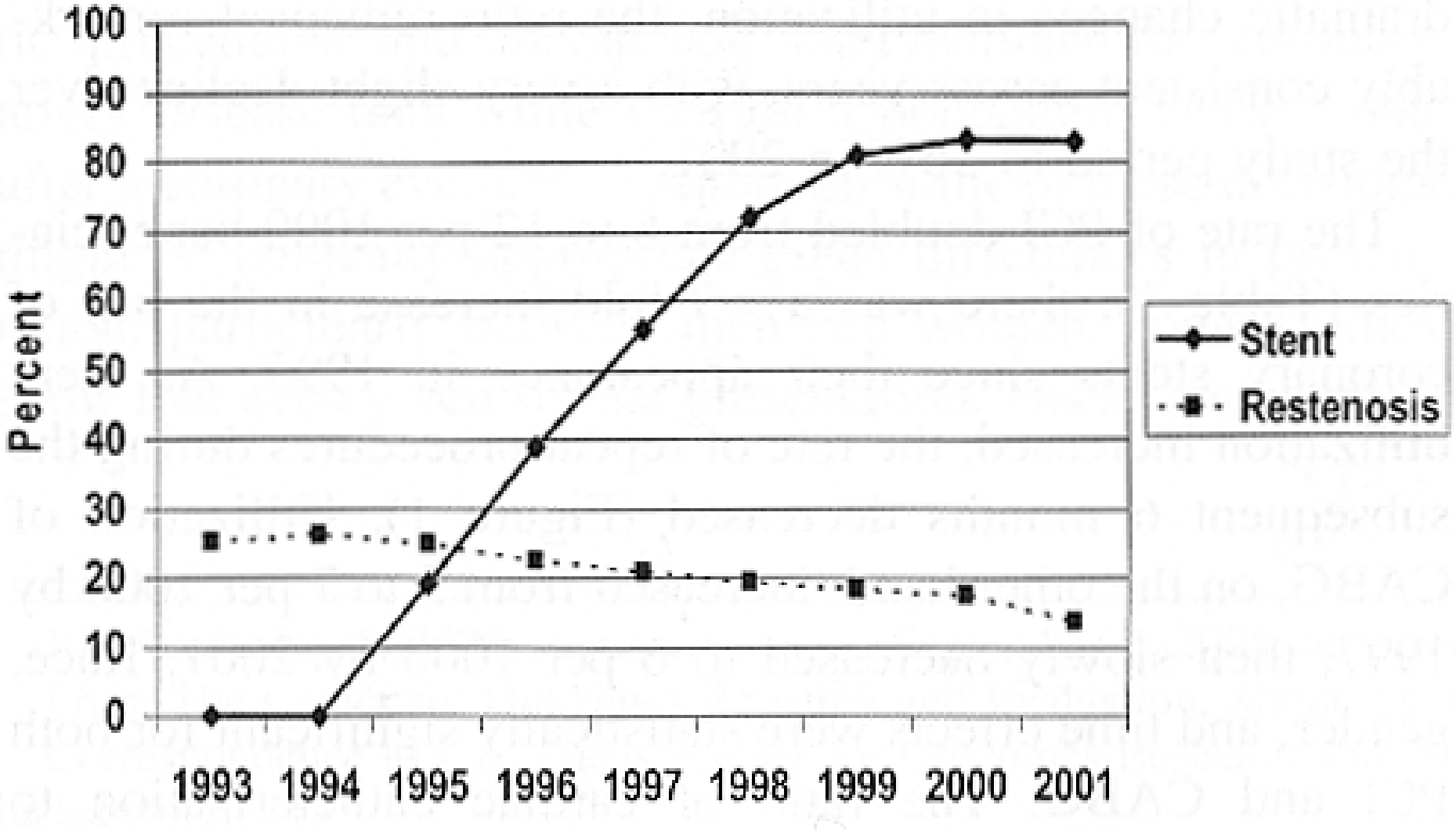
		Stroke/TIA/TE: Multivariable HR (95%CI)
Age	<65	Ref
	65-74	2.97(2.54-3.48)
	≥75	5.28(4.57-6.09)
Female		1.17 (1.11-1.22)
Previous ischaemic stroke		2.81 (2.68-2.95)
Intracranial bleeding		1.49 (1.33-1.67)
Vascular disease	MI	1.09(1.03-1.15)
	Previous CABG	1.19 (1.06-1.33)
	PAD	1.22 (1.12-1.32)
	Any vascular disease	1.14 (1.06-1.23)
Hypertension		1.17 (1.11-1.22)
Heart failure (history)		0.98 (0.93-1.03)
Diabetes		1.19 (1.13-1.26)
Thyroid disease		1.00 (0.92-1.09)
	Thyrotoxicosis	1.03 (0.83-1.28)

Incidence and Severity of Coronary Artery Disease in Patients with Atrial Fibrillation Undergoing First-Time Coronary Angiography



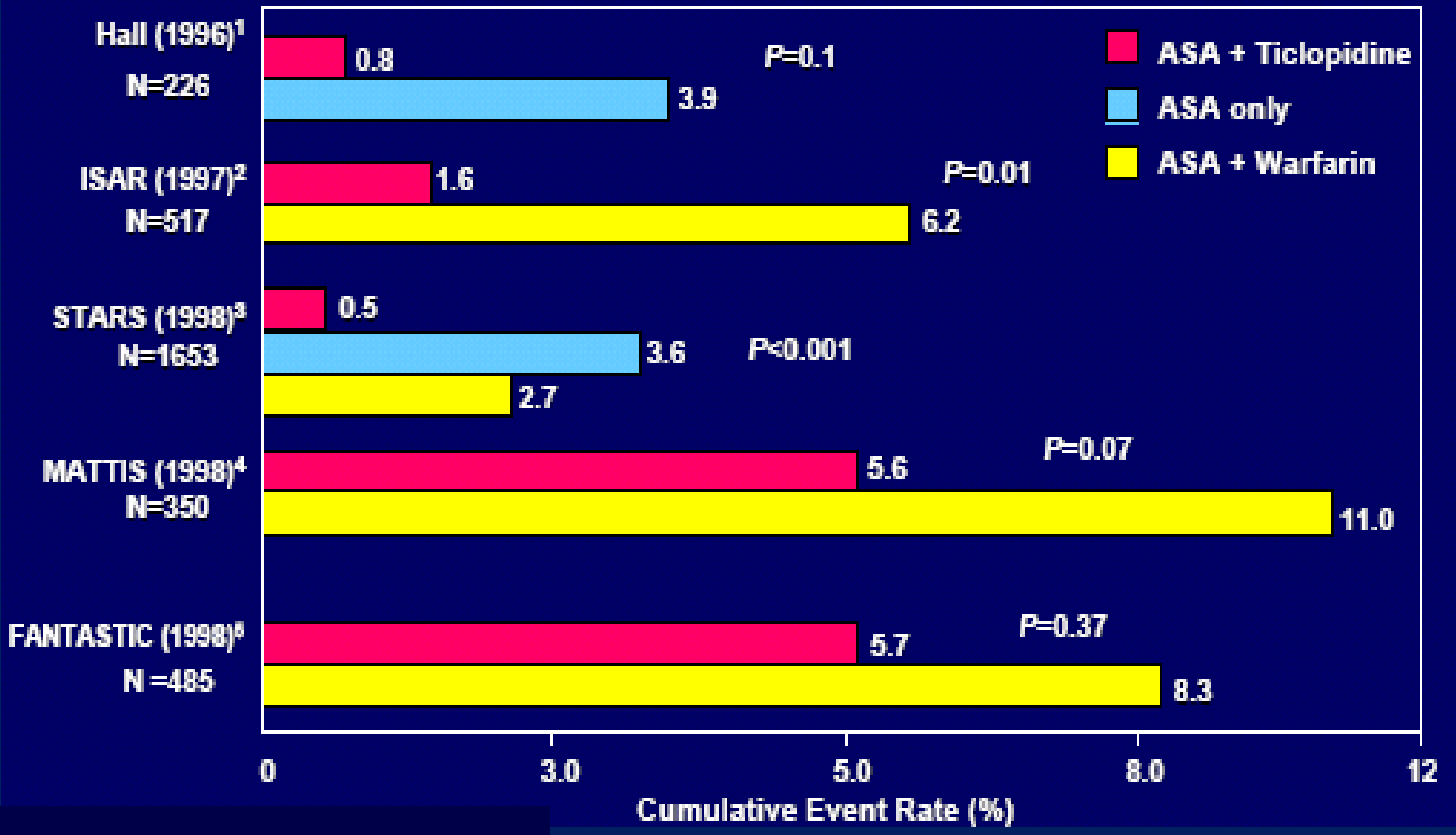
Kralev S et al. Plos ONE 2011;6:e24964

PCI procedures using STENTS in US 1993-2001
And proportion of PCIs with restenosis



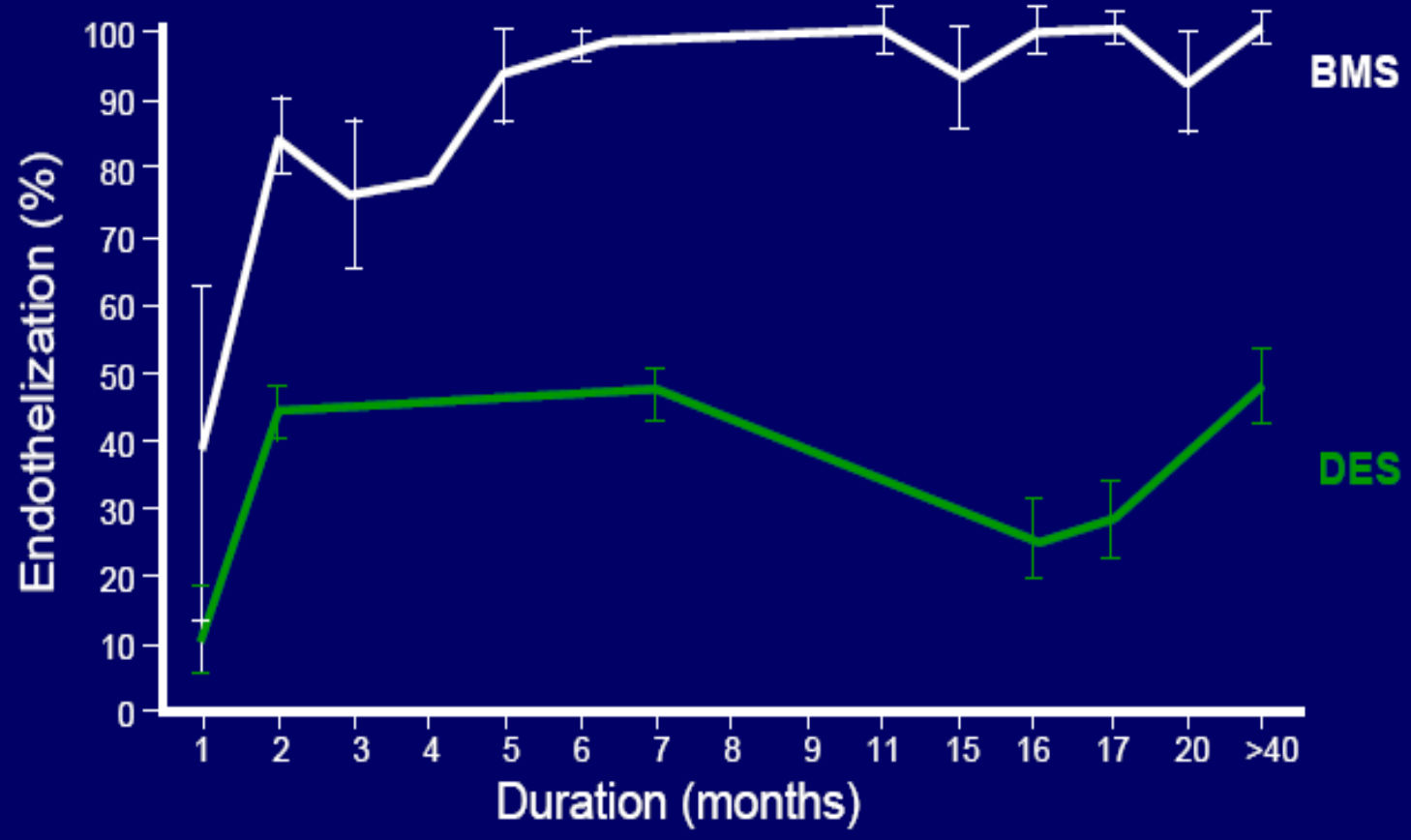
F.L. Lucas et al., Circulation 2006; 113: 374-379

Efficacy of Dual Antiplatelet Therapy in Reducing Coronary Events after Stenting → Need for dual antiplatelet tx



Endhotelialization in DES vs BMS

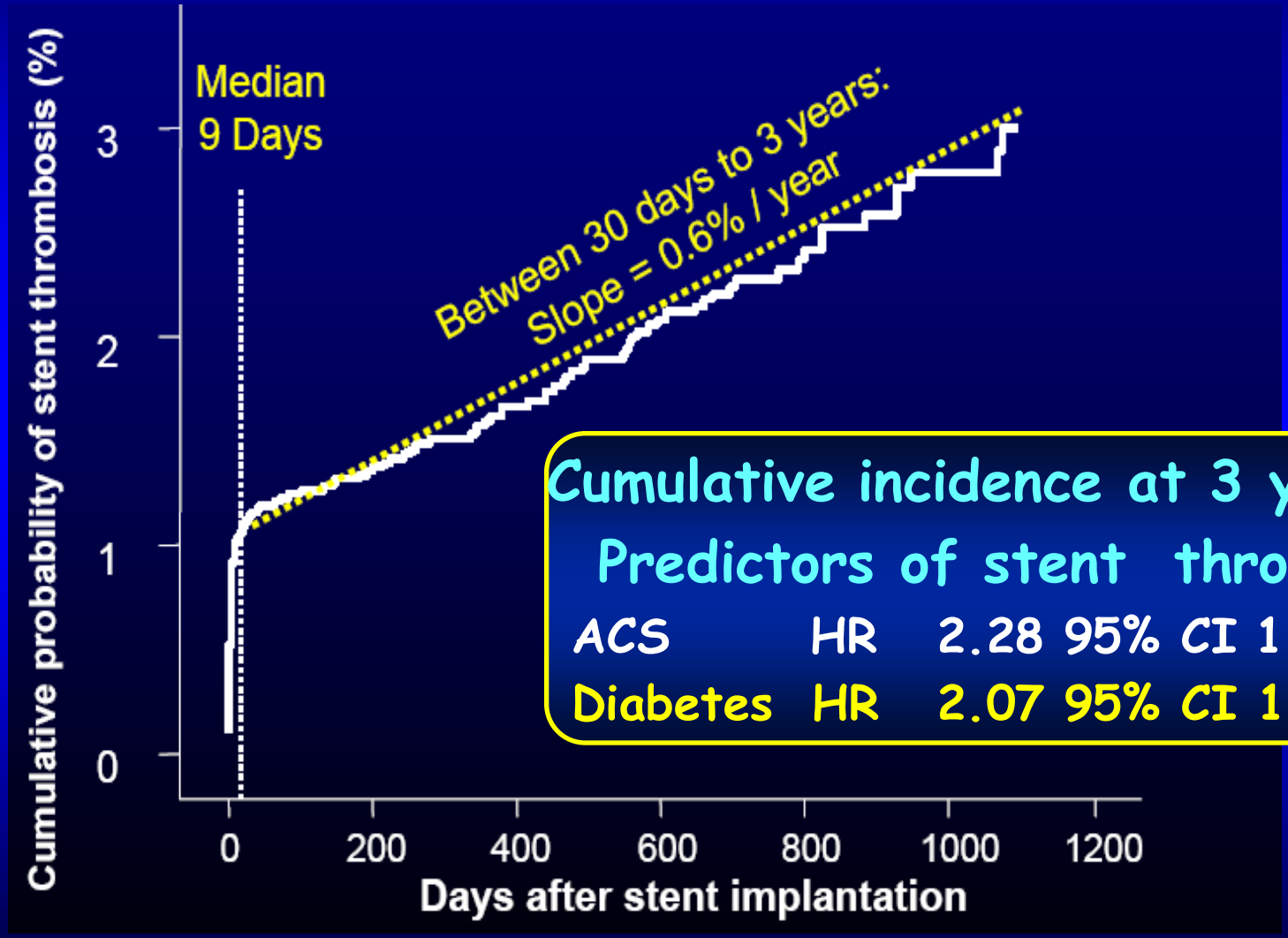
From autopsies of 23 patients treated with DES > 30 days and 25 matched BMS-treated autopsies.



Joner, Virmani, JACC 2006

Stent Thrombosis of DES

Data from a large two institutional cohort study



Cumulative incidence at 3 yrs 2.9%

Predictors of stent thrombosis

ACS	HR	2.28 95% CI 1.29-4.03
Diabetes	HR	2.07 95% CI 1.07-3.83

Daemen J et al. Lancet 2007;369:667-668

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

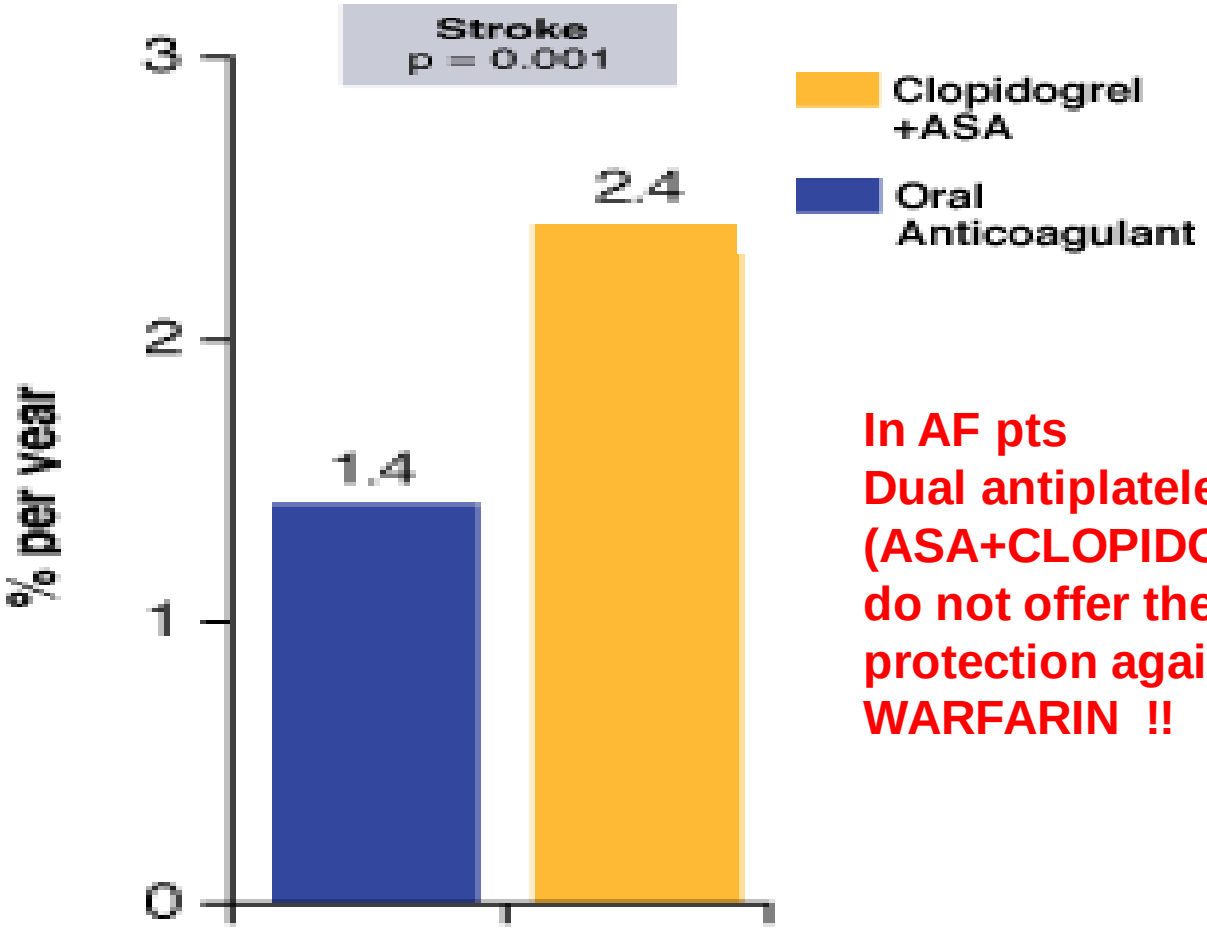
(b) Recommended duration of dual antiplatelet therapy

After percutaneous coronary intervention

- 1 month after BMS implantation in stable angina;[55,60,94]
- 6–12 months after DES implantation in all patients;[60,94]
- 1 year in all patients after ACS, irrespective of revascularization strategy.

Wijns W et al. Eur Heart J 2010;31:2501-55

Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial



In AF pts
Dual antiplatelet regimen (ASA+CLOPIDOGREL) do not offer the same protection against stroke of WARFARIN !!

$CHADS_2$ risk assessment tool

C	Congestive heart failure	1
H	History of hypertension	1
A	Age > 75years	1
D	Diabetes	1
S_2	Prior stroke or TIA	2

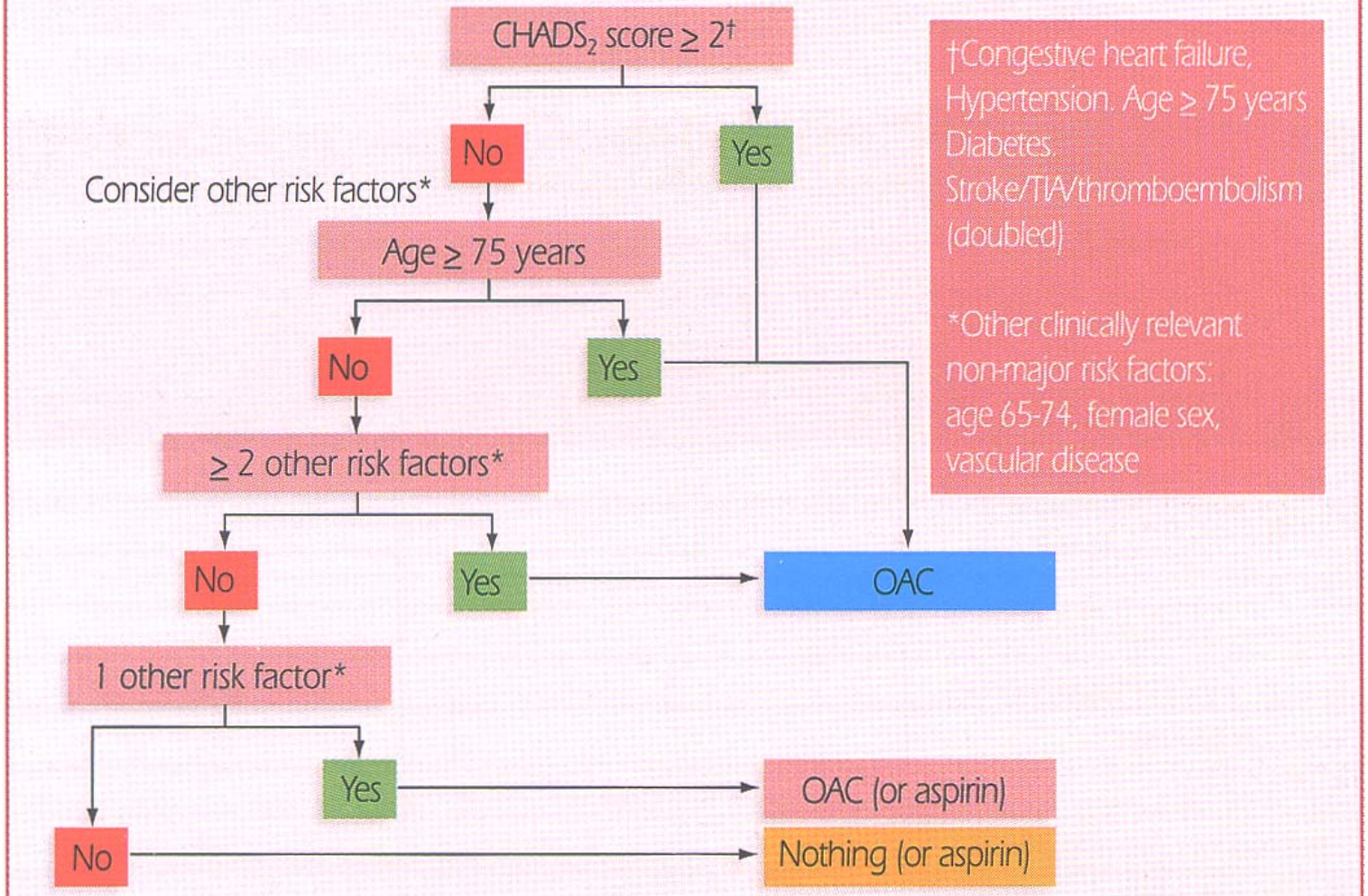
PLEASE NOTE

The benefit of Warfarin outweighs risk when

$CHADS_2$ Score ≥ 2

$CHADS_2$ Score	Adjusted Annual Stroke Rate (%)	NNT	Risk of major bleed (per 100 patient years)
0	1.9	80	
1	2.8	55	Aspirin 1.5
2	4.0	38	
3	5.9	26	
4	8.5	18	Warfarin 2.2
5	12.5	12	or NOVEL ANTICOAG
6	18.2	8	If available

Figure 4:
Clinical flowchart for the use of oral anticoagulation for stroke prevention in AF



AF = atrial fibrillation; OAC = oral anticoagulant; TIA = transient ischaemic attack. A full description of the $CHADS_2$ can be found on page 12.

Stenting in AF with mod-high TE risk … → triple therapy …

Table 11 Antithrombotic strategies following coronary artery stenting in patients with AF at moderate to high thrombo-embolic risk (in whom oral anticoagulation therapy is required)

Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0–2)	Elective	Bare-metal	1 month: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	Elective	Drug-eluting	3 (-olimus[a] group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal/ drug-eluting	6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
High (e.g. HAS-BLED score ≥3)	Elective	Bare-metal[c]	2–4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal[c]	4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day[b] (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone

ACS = acute coronary syndrome; AF = atrial fibrillation; INR = international normalized ratio; VKA = vitamin K antagonist.
Gastric protection with a proton pump inhibitor (PPI) should be considered where necessary.
[a]Sirolimus, everolimus, and tacrolimus.
[b]Combination of VKA (INR 2.0–3.0)+aspirin ≤100 mg/day (with PPI, if indicated) may be considered as an alternative.
[c]Drug-eluting stents should be avoided as far as possible, but, if used, consideration of more prolonged (3–6 months) triple antithrombotic therapy is necessary.
Adapted from Lip *et al.*[61]

Guidelines for the Management of Atrial Fibrillation. European Heart Journal 2010; 31: 2369 - 2429.

Triple therapy (3 antithrombotics) ? 3 dilemmas !

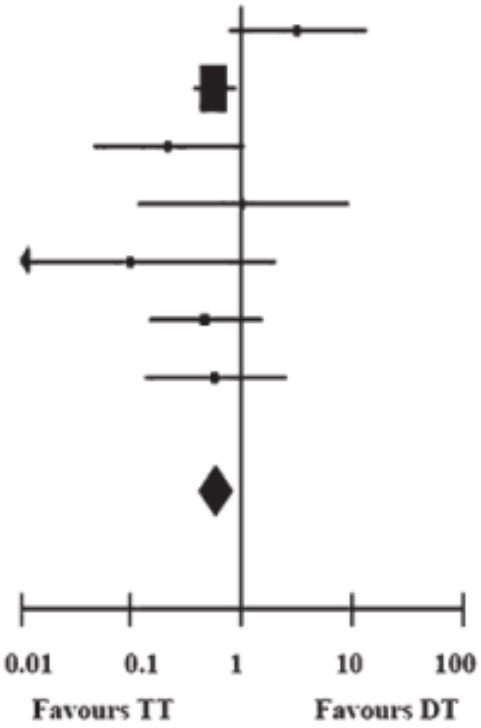
Risk of not prescribing/ discontinuing **clopidogrel** and increasing the possibility of **stent thrombosis**

Risk of prescribing/ continuing **warfarin + aspirin + clopidogrel** and increasing the possibility of **bleeding**

Risk of not prescribing/ discontinuing **warfarin** and increasing the possibility of stroke or **thromboembolic events**

Risk of major adverse cardiovascular events in patients receiving Triple Tx or Double Tx (ASA+Clop)

Study	Year	Triple Therapy Events	Triple Therapy Total	Dual Therapy Events	Dual Therapy Total	Odds Ratio M-H Fixed, 95% CI	Weight (%)	Odds Ratio M-H Fixed, 95% CI
Mattichak[29]	2005	8	40	3	42		2.9%	3.25 (0.80. 13.27)
Ruiz-Nodar[16]	2008	52	195	69	178		66.4%	0.57 (0.37. 0.89)
Karjalainen[10]	2007	3	106	4	34		7.4%	0.22 (0.05. 1.03)
Maegdefessel[32]	2008	1	14	7	103		2.0%	1.05 (0.12. 9.28)
M-Fernández[14]	2008	0	51	3	39		4.9%	0.10 (0.01. 2.02)
Sarafoff[31]	2008	5	306	7	209		10.3%	0.48 (0.15. 1.53)
Rossini[15]	2008	3	102	5	102		6.1%	0.59 (0.14. 2.53)
Total (95% CI)			**814**		**707**		**100.0%**	**0.60 (0.42, 0.86)**
Total events		**72**		**98**				



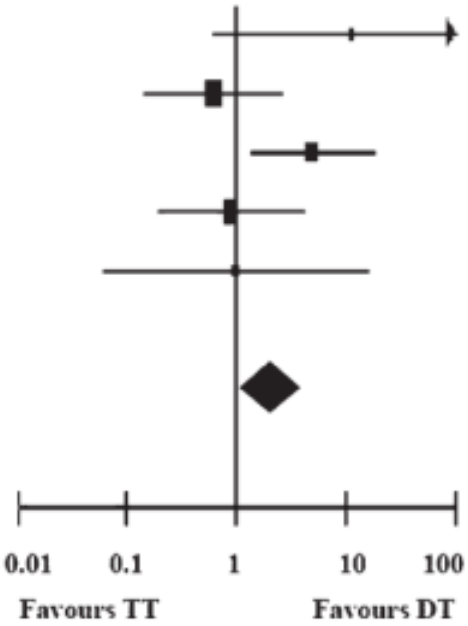
Heterogeneity: Chi² = 8.97, df = 6 (*P* = 0.18); I² = 33%

Test for overall effect: Z = 2.80 (*P* =0.005)

Zhao HJ et al. CHEST 2011; 139(2):260–270

Risk of major bleeding at 6-month follow-up in patients receiving Triple Tx or Double Tx (ASA+Clop)

Study	Year	Triple Therapy		Dual Therapy		Odds Ratio M-H Fixed, 95% CI	Weight (%)	Odds Ratio M-H Fixed, 95% CI
		Events	Total	Events	Total			
Khurram[11]	2006	5	107	0	107		4.0%	11.54(0.63, 211.28)
Karjalainen[10]	2007	6	106	3	34		36.4%	0.62 (0.15, 2.63)
DeEugenio[30]	2007	13	86	3	88		21.4%	5.05 (1.38, 18.40)
Sarafoff[31]	2008	4	306	3	209		29.9%	0.91(0.20, 4.11)
Rossini[15]	2008	1	102	1	102		8.4%	1.00 (0.06, 16.21)
Total (95% CI)			**707**		**540**		**100.0%**	**2.12 (1.05, 4.29)**
Total events		**29**		**10**				

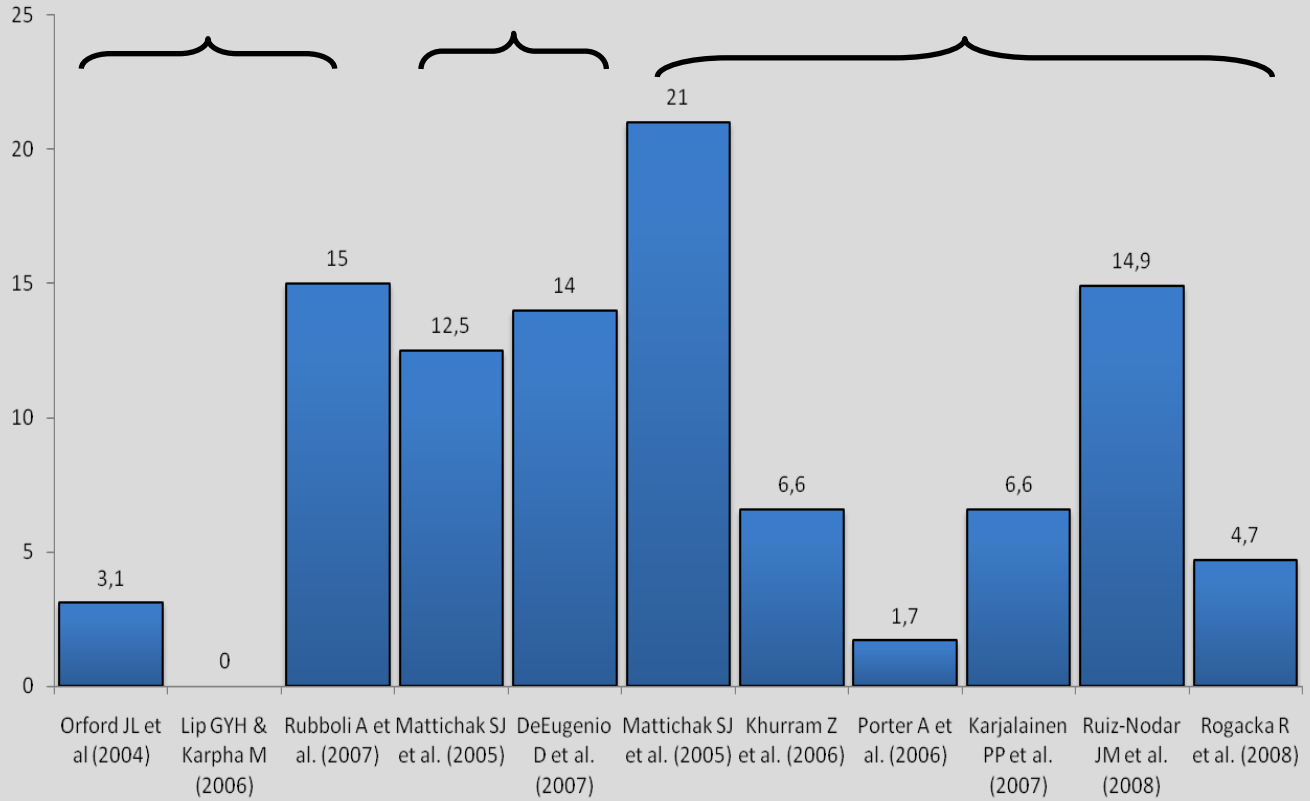


Heterogeneity: $Chi^2 = 7.31$, df = 4 ($P = 0.12$); $I^2 = 45\%$

Test for overall effect: Z = 2.09 ($P = 0.04$)

Zhao HJ et al. CHEST 2011; 139(2):260–270

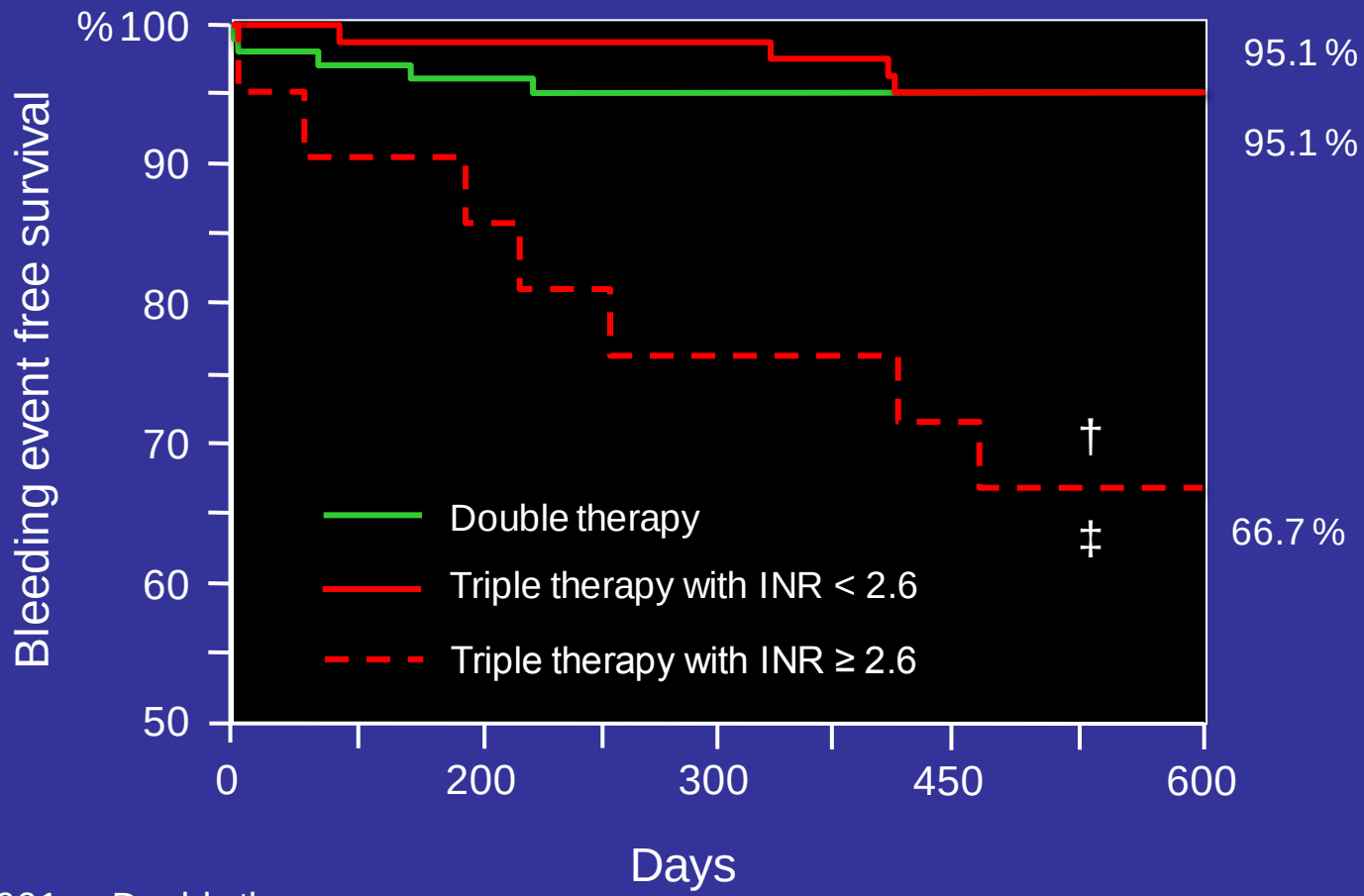
Triple therapy and major bleeding



Rubboli et al. Ann Med 2008;40:428-36

Bleeding Cumulative Distribution by INR

"Double" vs "Triple" TX



† P<0.0001 vs Double therapy

‡ P<0.0001 vs Triple with INR <2.6

Rossini, et al. Am J Cardiol 2008

Recommendations for antithrombotic therapy in AF and ACS/PCI

Recommendations	Class[a]	Level[b]	Ref.[c]
Following elective PCI in patients with AF with stable coronary artery disease, BMS should be considered, and drug-eluting stents avoided or strictly limited to those clinical and/or anatomical situations (e.g. long lesions, small vessels, diabetes, etc.), where a significant benefit is expected when compared with BMS.	IIa	C	
Following elective PCI, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term, followed by more long-term therapy (up to 1 year) with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with PPIs, H_2 antagonists, or antacids).	IIa	C	
Following elective PCI, clopidogrel should be considered in combination with VKA plus aspirin for a minimum of 1 month after implantation of a BMS, but longer with a drug-eluting stent (at least 3 months for a sirolimus-eluting stent and at least 6 months for a paclitaxel-eluting stent); following which VKA and clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with either PPIs, H_2 antagonists, or antacids) should be considered, if required.	IIa	C	
Following an ACS with or without PCI in patients with AF, triple therapy (VKA, aspirin, clopidogrel) should be considered in the short term (3–6 months), or longer in selected patients at low bleeding risk, followed by long-term therapy with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection with PPIs, H_2 antagonists, or antacids).	IIa	C	
In anticoagulated patients at very high risk of thrombo-embolism, uninterrupted therapy with VKA as the preferred strategy and radial access used as the first choice even during therapeutic anticoagulation (INR 2–3).	IIa	C	
When VKA is given in combination with clopidogrel or low-dose aspirin, careful regulation of the anticoagulation dose intensity may be considered, with an INR range of 2.0–2.5.	IIb	C	
Following revascularization surgery in patients with AF, VKA plus a single antiplatelet drug may be considered in the initial 12 months, but this strategy has not been evaluated thoroughly and is associated with an increased risk of bleeding.	IIb	C	
In patients with stable vascular disease (e.g. >1 year, with no acute events), VKA monotherapy may be considered, and concomitant antiplatelet therapy should not be prescribed in the absence of a subsequent cardiovascular event.	IIb	C	

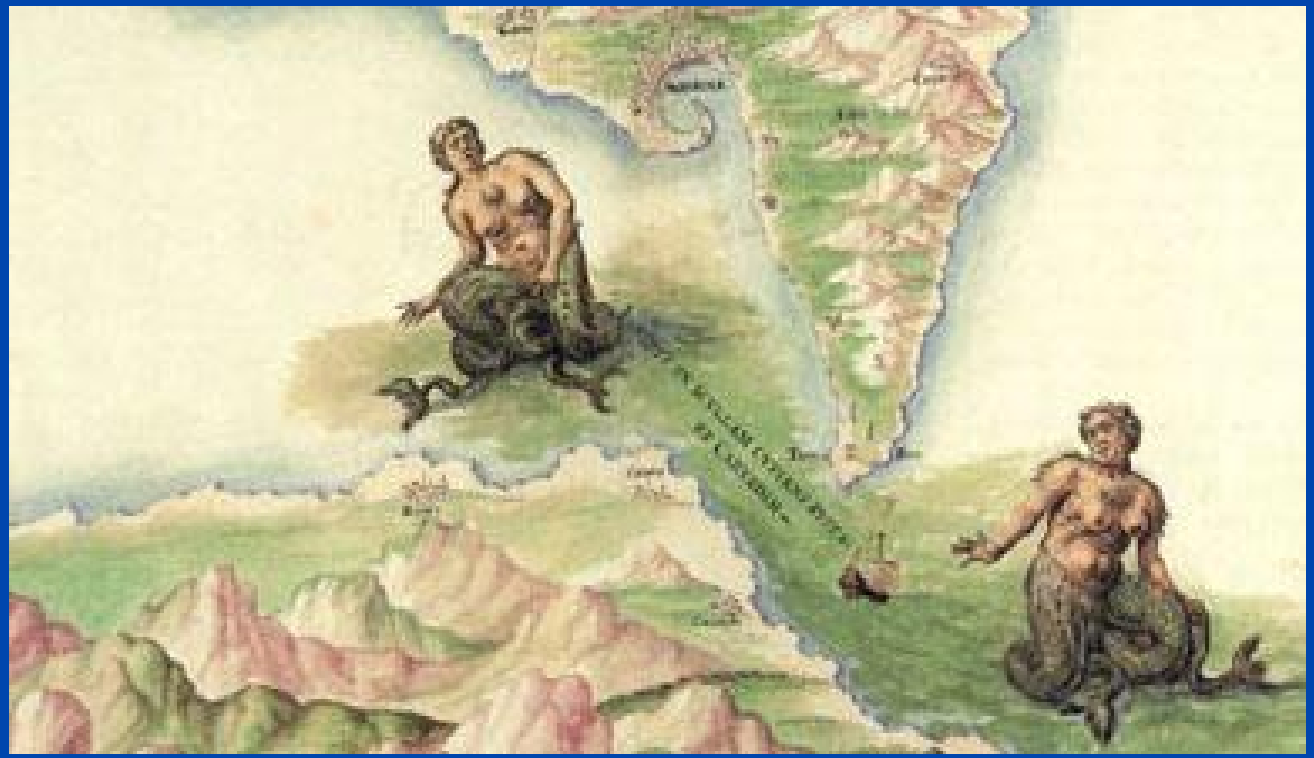
[a]Class of recommendation.
[b]Level of evidence.
[c]References.
ACS = acute coronary syndrome; AF = atrial fibrillation; BMS = bare-metal stent; INR = international normalized ratio; PCI = percutaneous intervention; PPIs = proton pump inhibitors; VKA = vitamin K antagonist.

Guidelines for the Management of Atrial Fibrillation. European Heart Journal 2010; 31: 2369 - 2429

Balancing the Risk of Hemorrhage vs Thromboembolism in Patients With Atrial Fibrillation : How To Navigate Between Scylla and Charybdis?

Giuseppe Boriani, Igor Diemberger, Mauro Biffi and Cristian Martignani

Chest 2010;138;1032-1033
DOI 10.1378/chest.10-0808



ACCP 9 (2012) Recommendations for Patients With AF and Concomitant ACS or CAD

Condition	Guideline recommendations
AF + stable CAD (no ACS or revascularization within the previous year)	• VKA alone (if patient chooses oral anticoagulation) rather than combination of VKA + ASA (Grade 2C)
$CHADS_2 \geq 2$ + BMS or DES	• Triple therapy rather than dual-antiplatelet therapy during the first month after BMS or first 3 – 6 months after DES (Grade 2C) • After initial period of triple therapy, VKA + single-antiplatelet therapy rather than VKA alone (Grade 2C) • At 12 months, antithrombotic therapy is suggested as for patients with AF + stable CAD
$CHADS_2 = 0 / 1$ + BMS or DES	• Dual-antiplatelet therapy rather than triple therapy during first 12 months after stent placement (Grade 2C) • At 12 months, antithrombotic therapy is suggested as for patients with AF + stable CAD

- For recommendations in favor of oral anticoagulation, guidelines suggest dabigatran 150 mg twice daily rather than adjusted-dose VKA.
- Triple therapy = VKA + ASA + clopidogrel; dual-antiplatelet therapy = ASA + clopidogrel

You JJ, et al. *Chest*. 2012.141;e531S–e575S.
http://chestjournal.chestpubs.org/content/141/2_suppl/e531S.full.html

WHAT TREATMENT HAS THE BEST RISK BENEFIT RATIO AFTER PCI-STENT ?

OAC

+

1 **antiplatelet agent**

(ASA *or* clopidogrel)

?

2 **antiplatelet agents**

(ASA *and* clopidogrel)

Comparison of Different Antithrombotic Regimens for Patients With Atrial Fibrillation Undergoing Drug-Eluting Stent Implantation

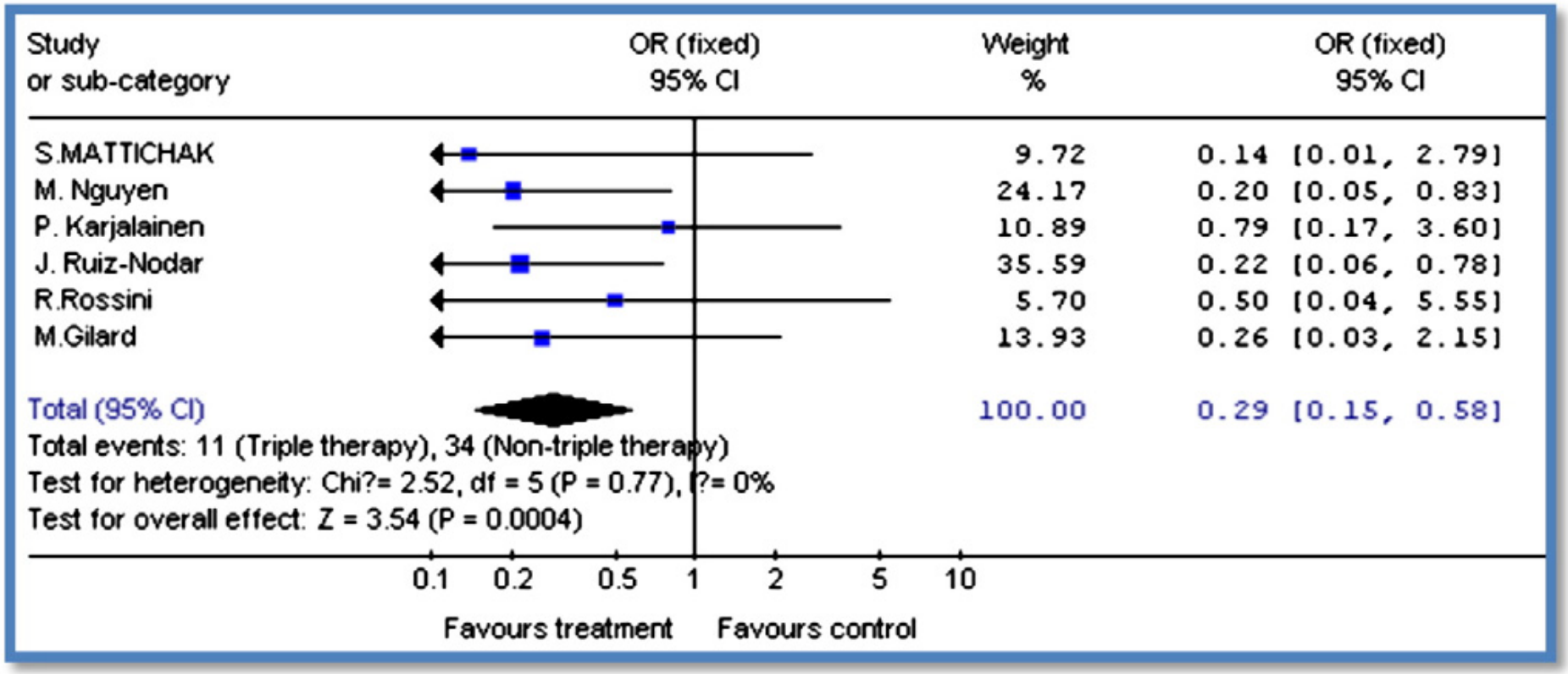
Gao F et al. Circ J 2010;74:701-8

	Triple antithrombotic therapy (n=136)	Warfarin+single antiplatelet (n=121)	Dual antiplatelet (n=334)	P value
MACCE				
Death (%)	4.4	5.8	9.0	0.174
MI (%)	2.9	5.8	5.4	0.474
TVR (%)	3.7	4.1	4.5	0.922
Stent thrombosis (%)	0.7	1.7	0.9	0.726
Stroke (%)	0.7	0.8	3.6	0.083
Overall MACCE (%)	8.8	14.9	20.1	0.010

MACCE = stroke and major adverse cardiac and cerebral events

EFFICACY of TRIPLE TX vs. NON TRIPLE TX on STROKE

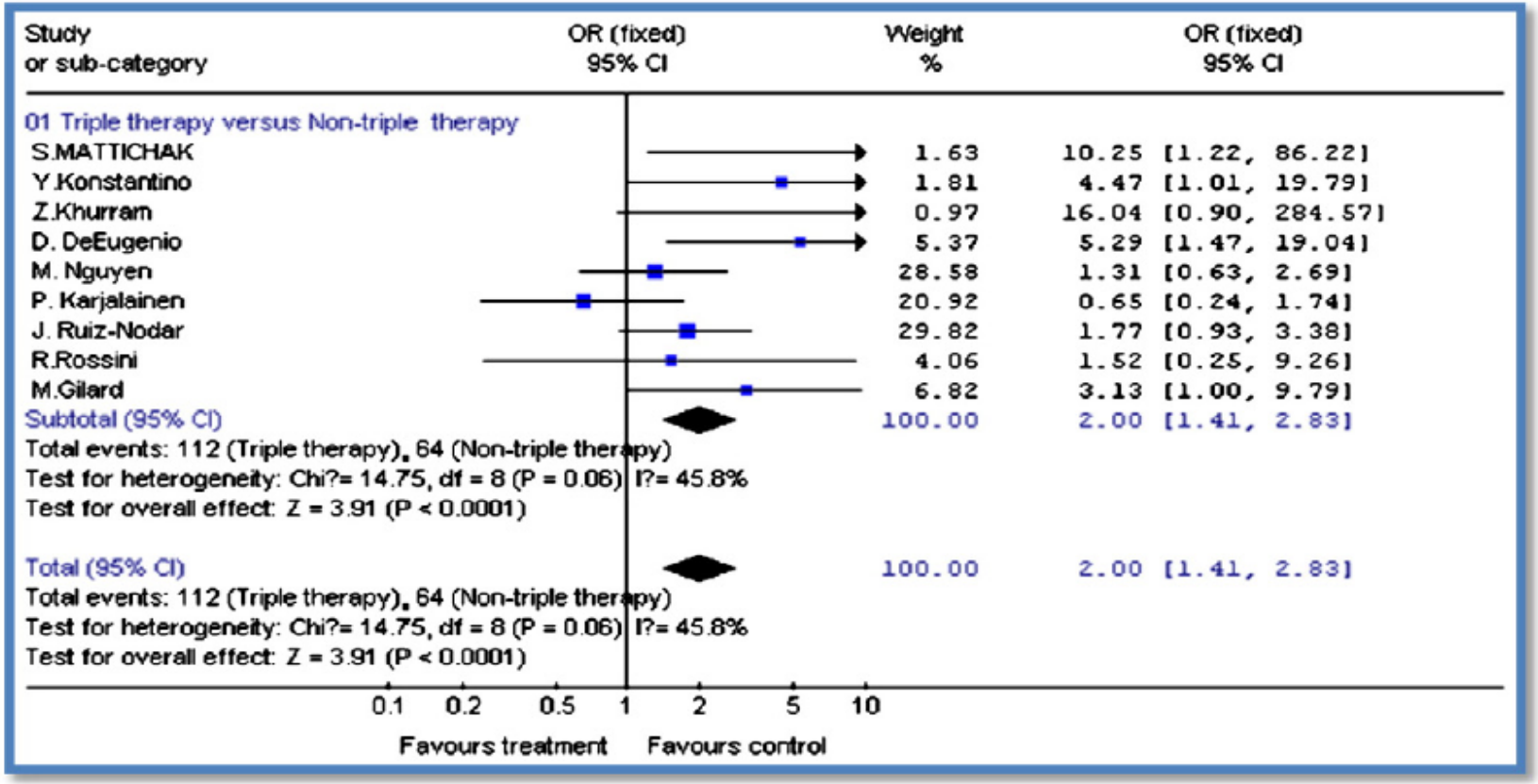
Risk of stroke OR = 0.29



Gao F et al. Int J Cardiol 2011;148:96-101

SAFETY : RISK of BLEEDING with TRIPLE TX vs. NON TRIPLE TX

Risk of major bleeding OR = 2.0

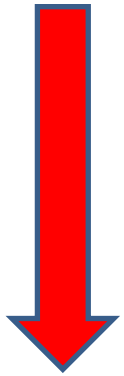


Gao F et al. Int J Cardiol 2011;148:96-101

The risk of bleeding of triple therapy with vitamin K-antagonists, aspirin and clopidogrel after coronary stent implantation increases along with time

	Major bleeding (%)	Minor bleeding (%)
In-hospital	3.3 ± 1.9	NR
≤ 1 mo	5.1 ± 6.7	5.2 ± 3.1
6 mo	8.0 ± 5.2	13.1 ± 2.6
12 mo	9.0 ± 8.0	3.6 ± 5.1
≥ 12 mo	6.2 ± 7.8	9.5 ± 7.5

NR: not reported.



Rubboli A. J Geriatr Cardiol 2011;8:207-14

SHORT DURATION of TRIPLE Tx can be applied if use of DES is limited to specific indications

	Class	*LOE*
❑ DES to be avoided, or strictly limited to those clinical and/or anatomical situations (long lesions, small vessels, diabetes, etc.) where significant benefit over BMS is expected	IIa	C

Lip GYH et al. Thromb & Haemost 2010;103:13-28

Circulation September 4, 2012

Editorial

Acute Coronary Syndrome in Patients With Atrial Fibrillation

What Is the Benefit/Risk Profile of Triple Antithrombotic Therapy?

Aldo Pietro Maggioni, MD, FESC

Bleeding After Initiation of Multiple Antithrombotic Drugs, Including Triple Therapy, in Atrial Fibrillation Patients Following Myocardial Infarction and Coronary Intervention

A Nationwide Cohort Study

Morten Lamberts, MD; Jonas Bjerring Olesen, MD; Martin Huth Ruwald, MD; Carolina Malta Hansen, MD; Deniz Karasoy, MD; Søren Lund Kristensen, MD; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc; Gunnar Hilmar Gislason, MD, PhD; Morten Lock Hansen, MD, PhD

Conclusions—High risk of bleeding is immediately evident with TT after myocardial infarction/percutaneous coronary intervention in patients with atrial fibrillation. A continually elevated risk associated with TT indicates no safe therapeutic window, and TT should only be prescribed after thorough bleeding risk assessment of patients. (*Circulation*. 2012;126:1185-1193.)

FATAL AND NON-FATAL BLEEDING IN THE DANISH REGISTRY

11 480 subjects, mean age 75.6 ±10.3 years

Table 2. Distribution and Type of Nonfatal and Fatal Bleedings

	Nonfatal Bleeding, n (%)	Fatal Bleeding, n (%)
Intracranial	38 (5.8)	36 (48.0)
Gastrointestinal	221 (33.8)	34 (45.3)
Respiratory	109 (16.7)	1 (1.3)
Urogenital	120 (18.4)	0 (0.0)
Anemia caused by bleeding	165 (25.3)	4 (5.3)
Total bleeding events	653	75

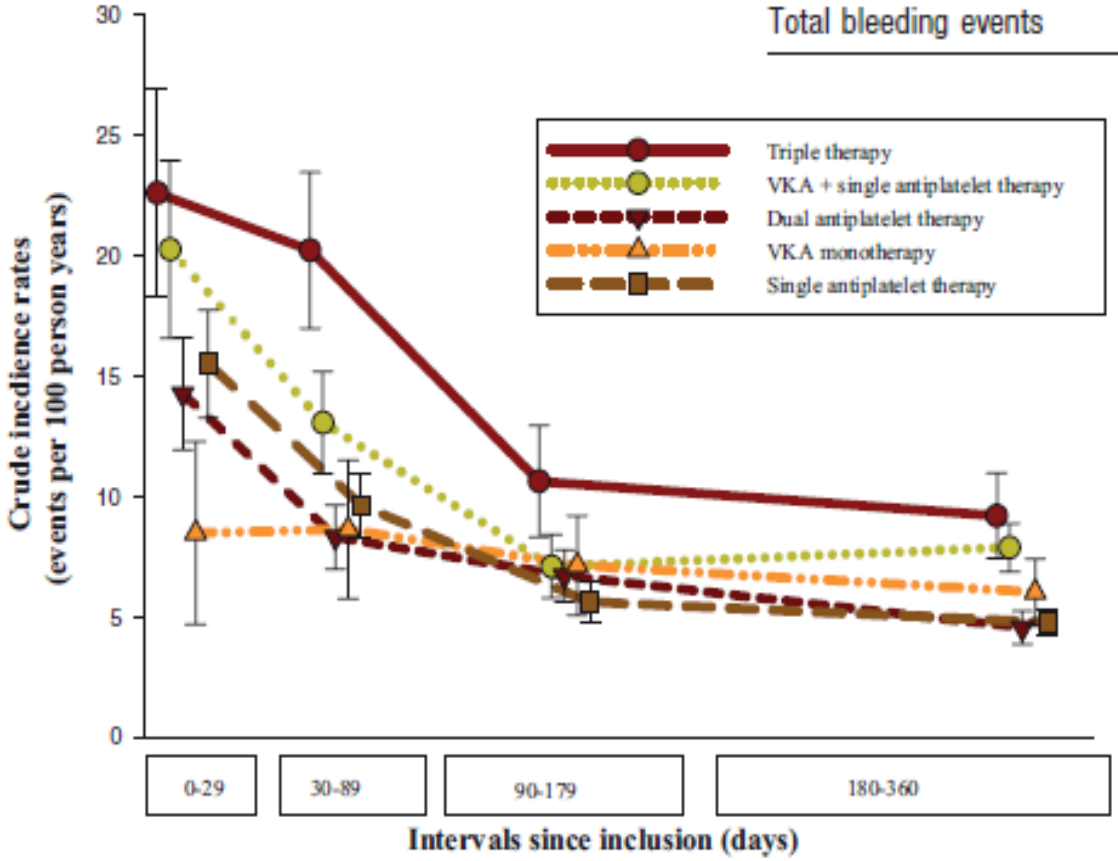
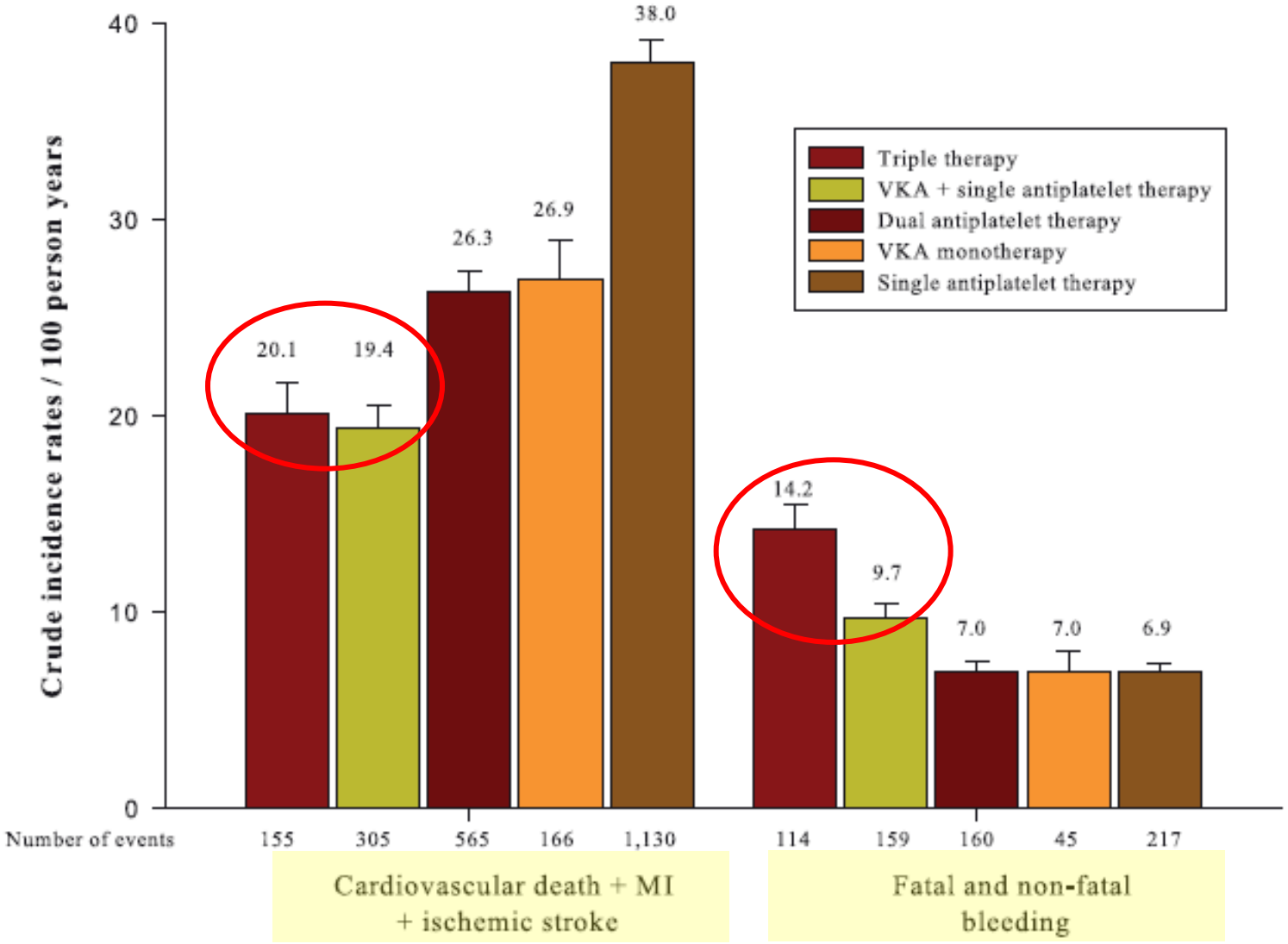


Figure 2. Crude incidence rates of fatal and nonfatal bleeding according to antithrombotic regimen in time periods following inclusion. Error bars show standard errors. Triple therapy includes aspirin, clopidogrel, and vitamin K antagonists (VKAs); VKA+single antiplatelet therapy includes VKA+aspirin or clopidogrel; dual antiplatelet therapy includes aspirin and clopidogrel; VKA monotherapy includes only VKA; single antiplatelet therapy includes aspirin or clopidogrel.

THROMBOEMBOLIC AND BLEEDING EVENTS IN THE REGISTRY



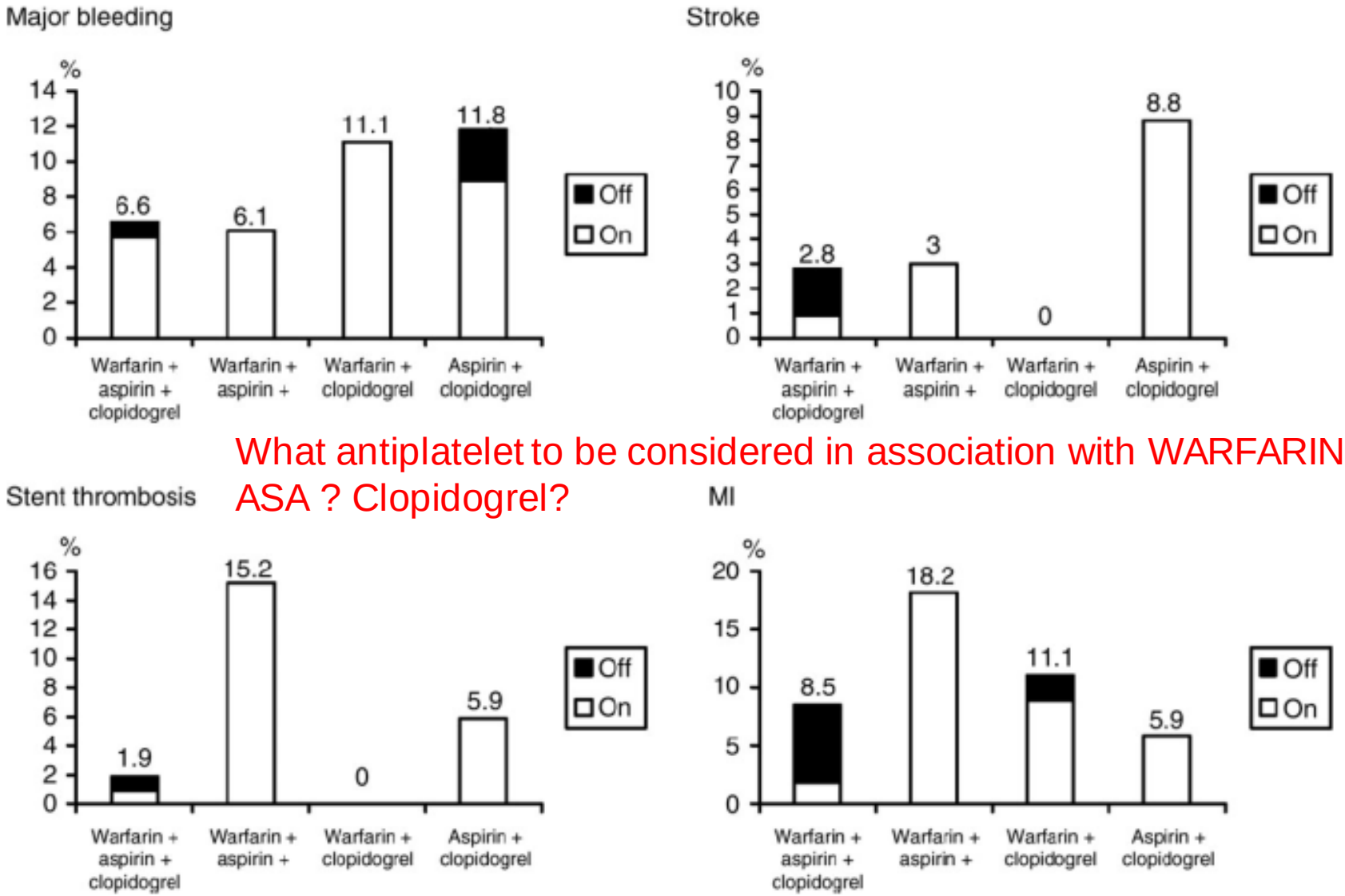


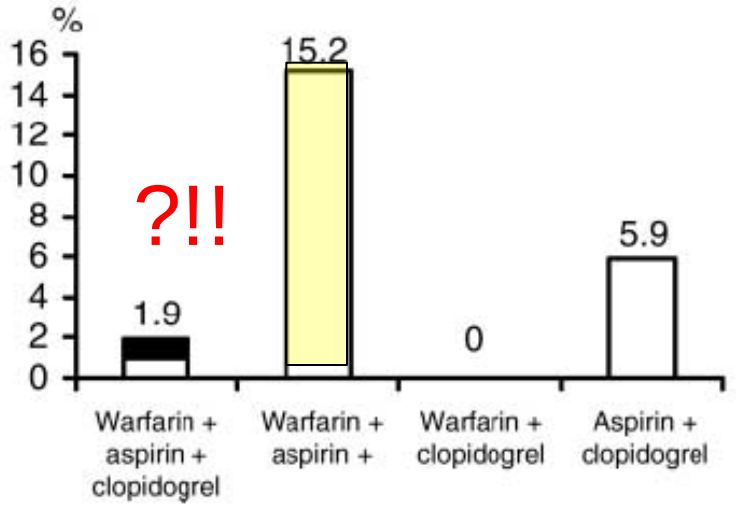
Figure 2 Complications during 12-month follow-up with various drug regimens adopted after stenting in warfarin group (prescribed drug combinations e
or Off at the time of the event).

Database on PCI in 6 Western Finnish hospitals

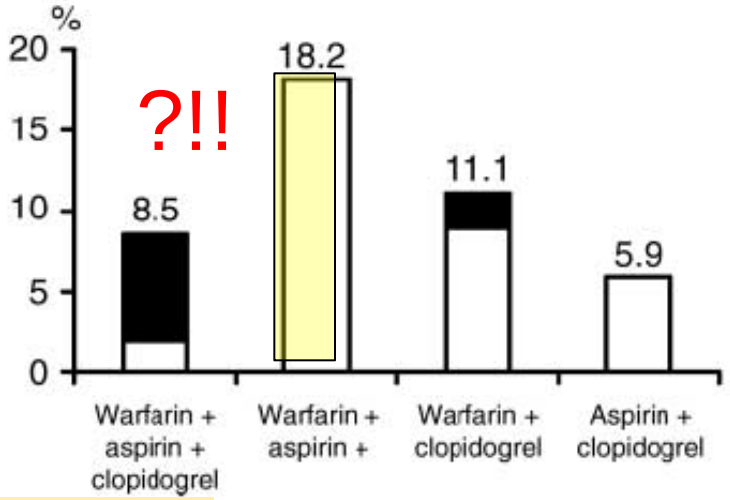
Karjalainen P, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. Eur Heart J 2007; 28:726–732

OAC (WARFARIN) + ASA : ?? Not a valid alternative to Triple Tx …

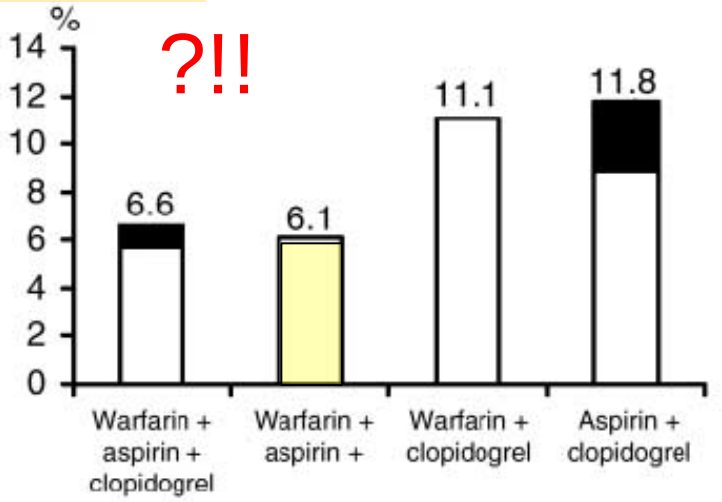
Stent thrombosis



MI



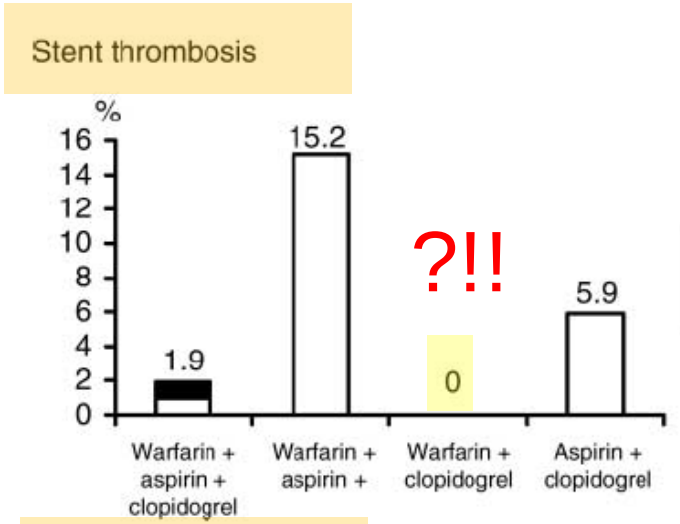
Major bleeding

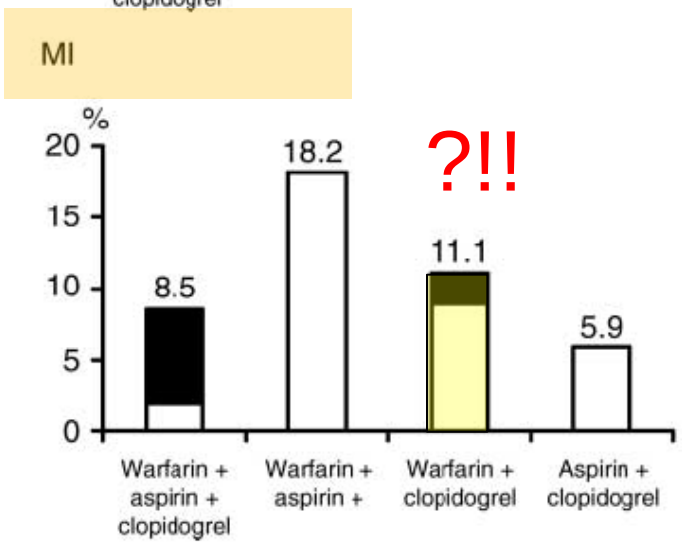


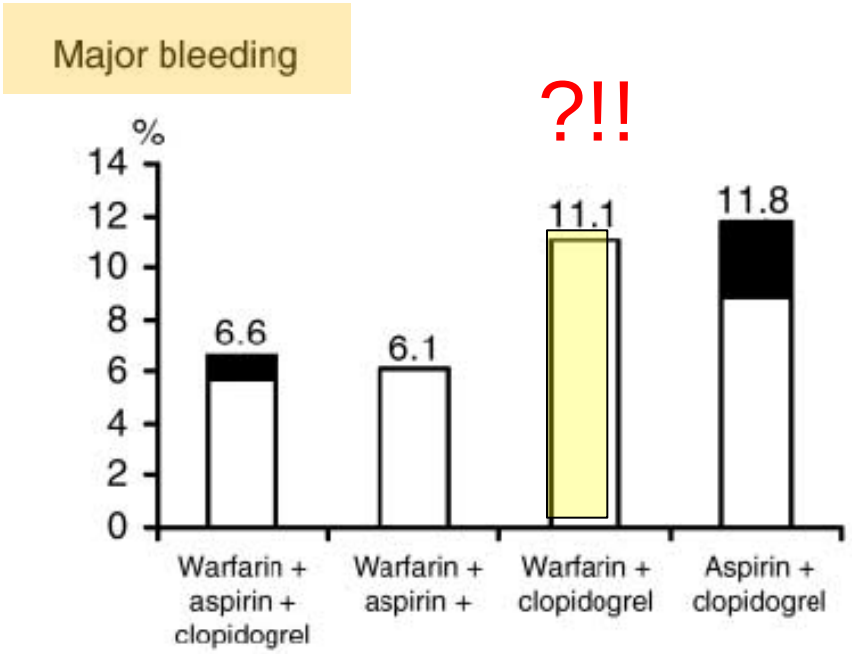
Aspirin + clopidogrel, *n* (%)	34 (15.5)
Warfarin + aspirin + clopidogrel, *n* (%)	106 (48.4)
Warfarin + aspirin, *n* (%)	33 (15.1)
Warfarin + clopidogrel, *n* (%)	45 (20.5)

Karjalainen PP et al. Eur Heart J 2007;28:726-32

OAC (WARFARIN) + CLOPIDOGREL : … maybe an alternative to Triple tx … but bleeding ??







Karjalainen PP et al. Eur Heart J 2007;28:726-32

RANDOMIZED TRIALS ON TRIPLE THERAPY

- ISAR-TRIPLE:
  600 patients after DES will be randomized to either a short course (6 weeks) or long course (6 months), followed by aspirin and warfarin.
  1°: Composite of death, MI, definite stent thrombosis, or major bleeding at 9 months
- WOEST:
  496 patients randomized oral anticoagulation and clopidogrel vs.triple therapy. 1°: Bleeding at 1 year
- MUSICA-2:
  304 patients (CHADS≤ 2) randomized to DAPT or triple Rx

The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet, Jurriën ten Berg

The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing (clinicaltrials.gov NCT00769938)

Study Design

1:1 Randomisation:

Dual therapy group:	Triple therapy group
OAC + 75mg Clopidogrel qd	OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS 1 year after DES	1 month minimum after BMS 1 year after DES

Follow up: 1 year

Primary Endpoint: The occurence of all bleeding events (TIMI criteria)

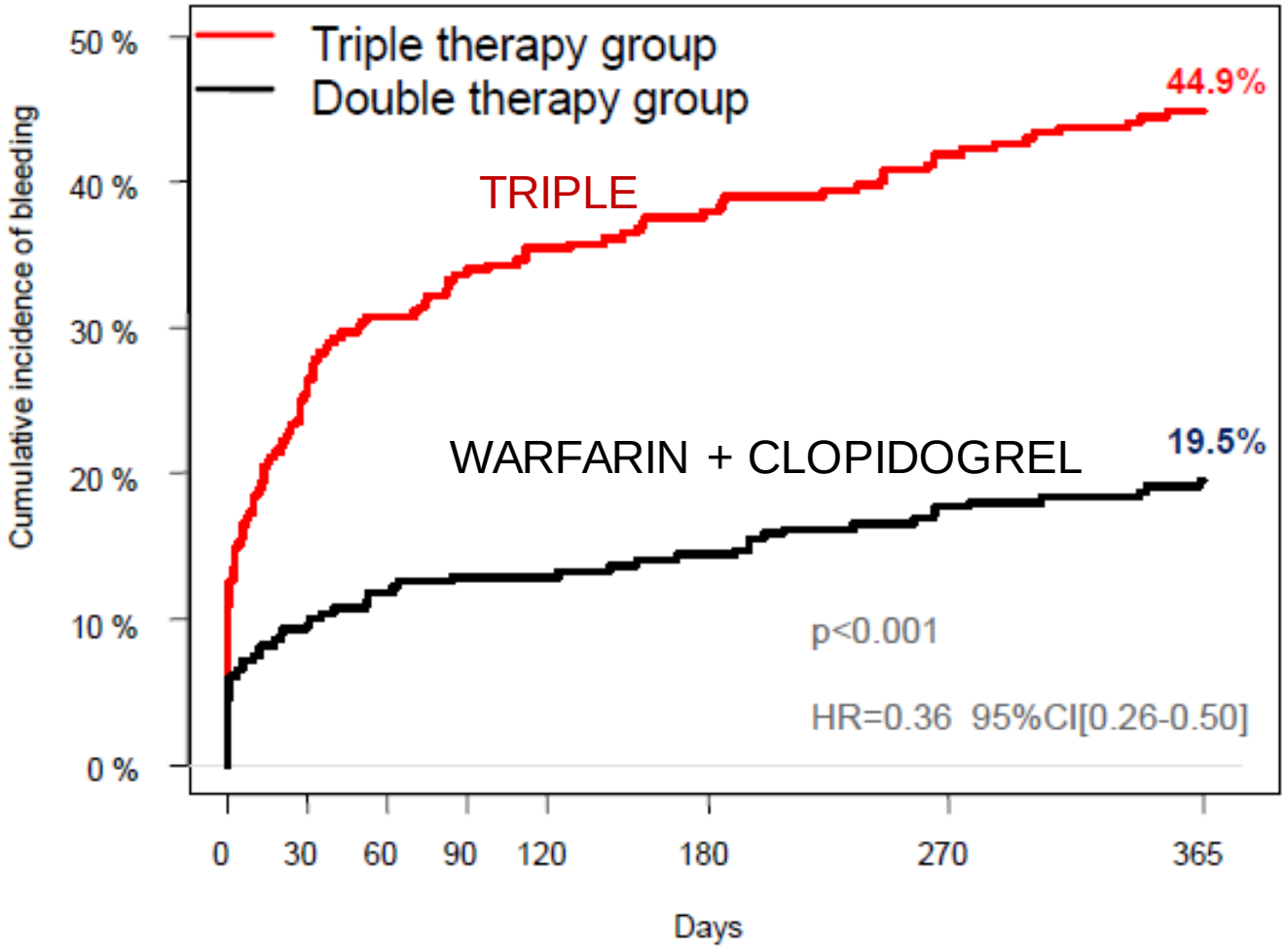
Secondary Endpoints:

- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints

WOEST trial - ESC 2012

In the WOEST trial, 573 patients were randomized to dual therapy with oral anticoagulation and clopidogrel (75 mg daily) or to triple therapy with oral anticoagulation, clopidogrel, and aspirin 80 mg daily. Treatment was continued for one month after bare-metal stenting (35% of patients) and one year after drug-eluting-stent placement (65% of patients). Follow-up was for one year.

Primary Endpoint: Total number of bleeding events



ZIEKENHUIS ST ANTONIUS

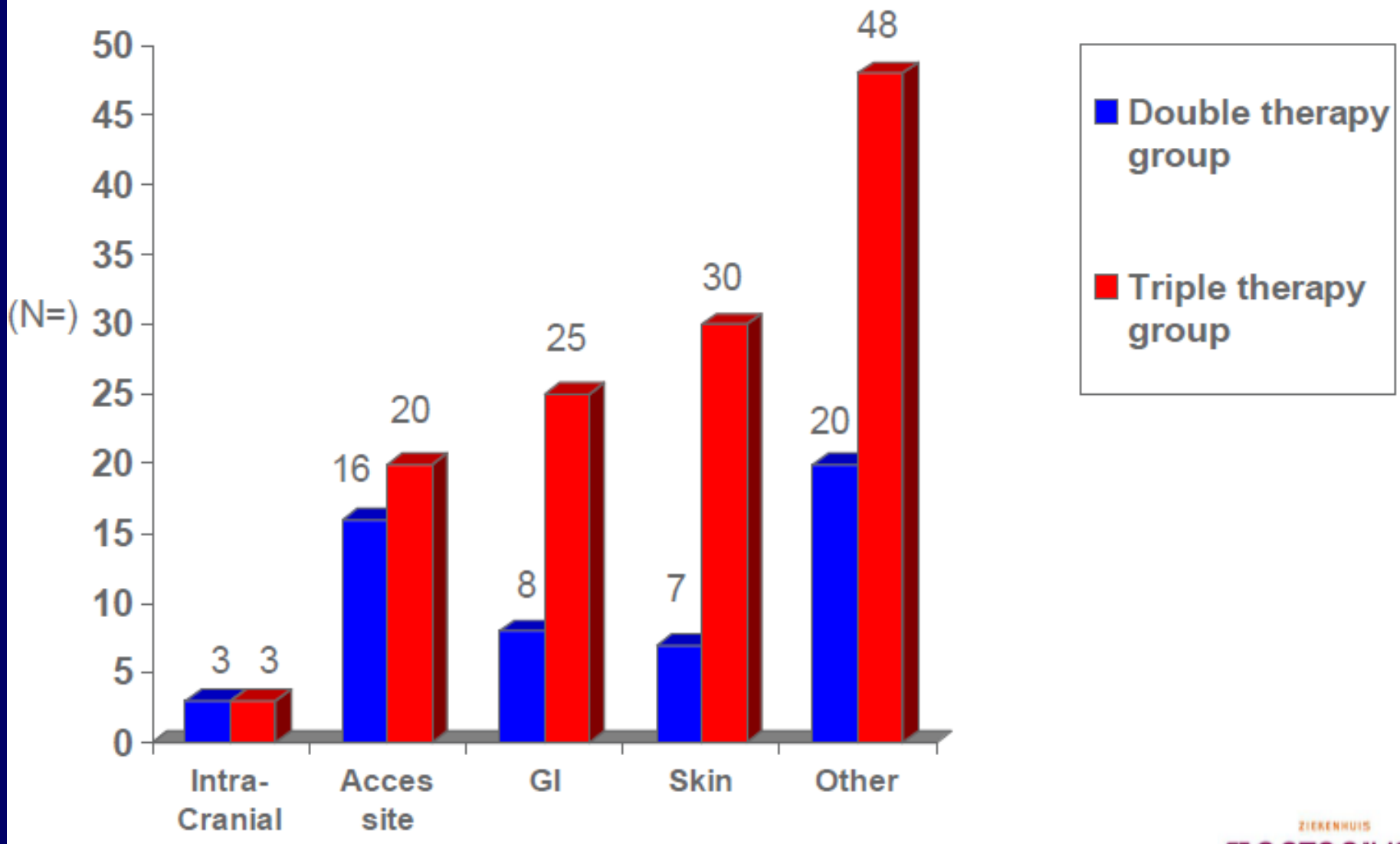
WOEST: Primary end point—all bleeding events (TIMI criteria)

	Dual therapy (%)	Triple therapy (%)	HR (95% CI)	p
All bleeding events	19.5	44.9	0.36 (0.26-0.50)	<0.001

Type of bleeding reduced

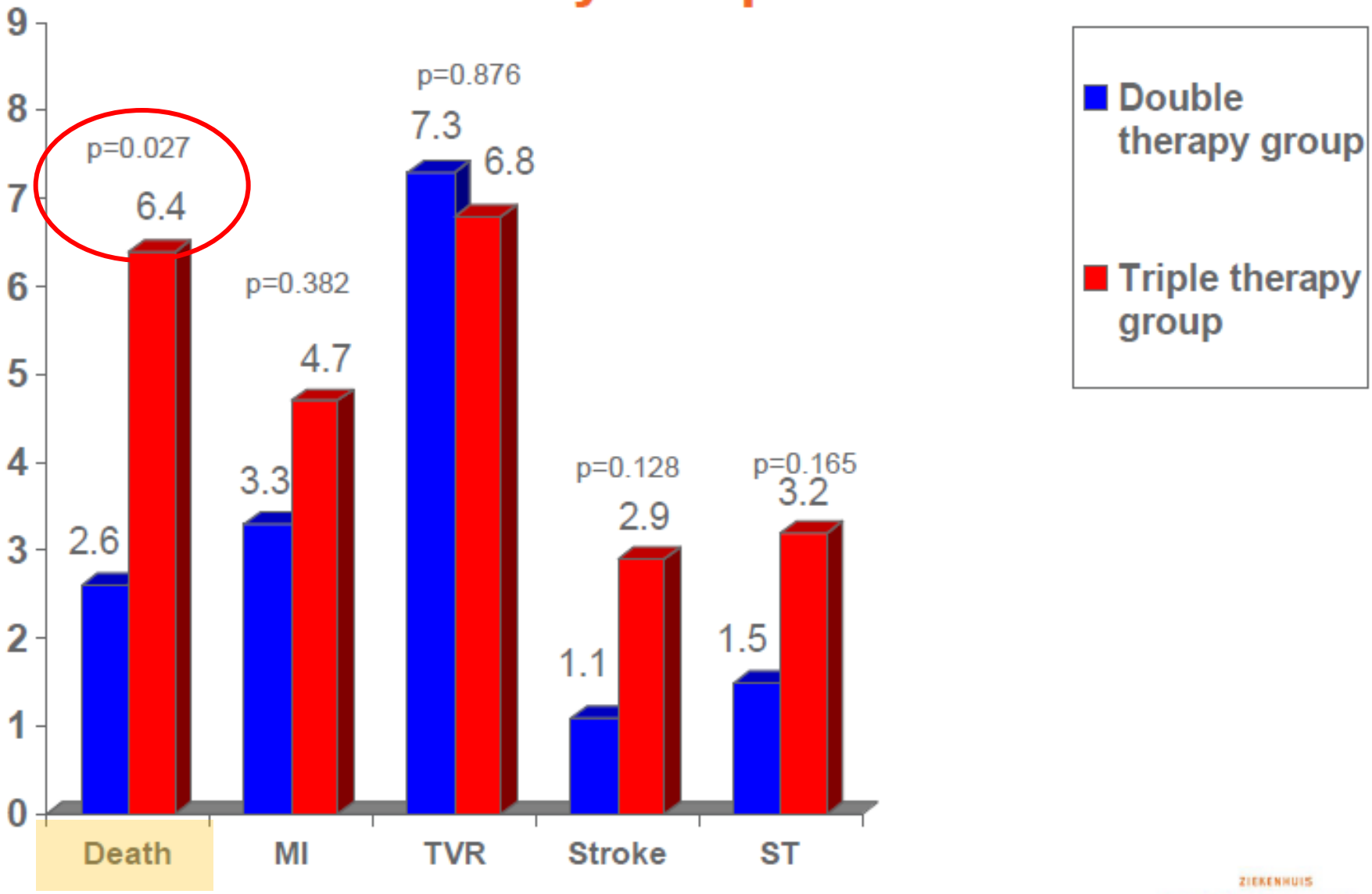
Type of bleeding	Dual therapy (%)	Triple therapy (%)
TIMI minimal	6.5	16.7
TIMI minor	11.2	27.2
TIMI major	3.3	5.8

Locations of TIMI bleeding: Worst bleeding per patient



GI=gastro intestinal; Other bleeding consists of eye, urogenital, respiratory tract, retroperitoneal, mouth, PMpocket bleeding

Secondary Endpoint



MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

ZIEKENHUIS ST ANTONIUS

Conclusions

1. First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting

2. Primary endpoint was met: as expected, OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way

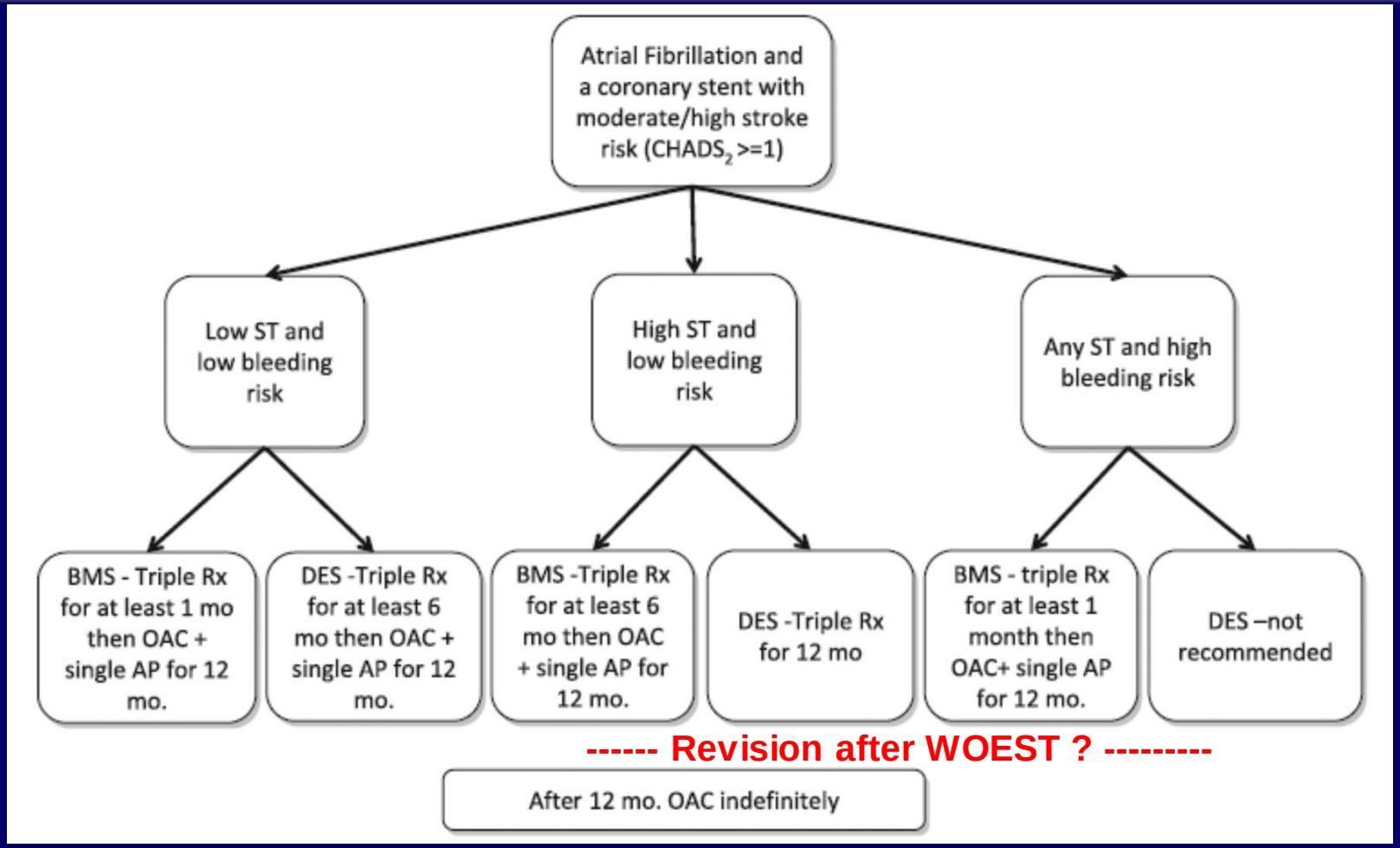
3. Secondary endpoint was met: with dual therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death

4. Less all-cause mortality with dual therapy

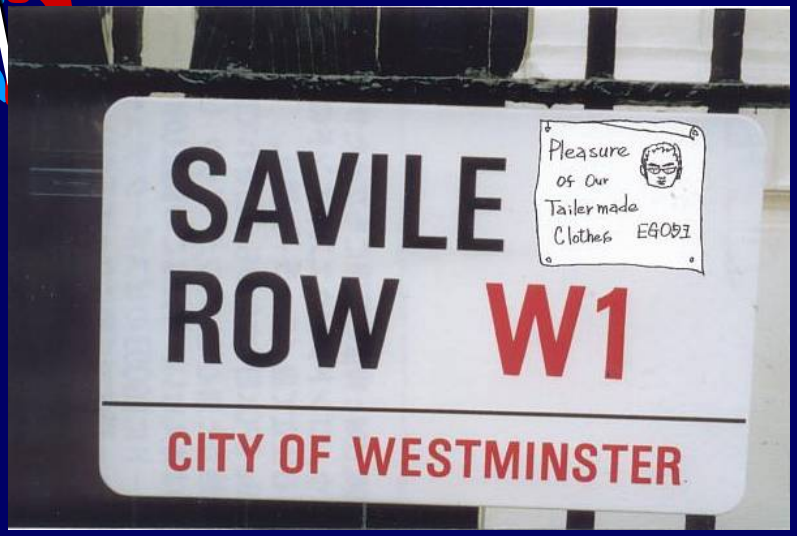
Implications

We propose that a strategy of oral anticoagulants plus clopidogrel, but without aspirin could be applied in this group of high-risk patients on OAC when undergoing PCI

Individualized Approach to Risk Management: Stent Thrombosis vs. Bleeding vs. Stroke



Faxon et al Hemostasis and Thrombosis 2011



...the value of individualized tailoring …

Schemes for bleeding risk assessment	
HEMORR$_2$HAGES score	**HAS-BLED score**
H Hepatic or renal disease 1 point	H Hypertension 1 point
E Ethanol abuse 1 point	A Abnormal renal and liver function (one point each) 1 or 2 points
M Malignancy 1 point	S Stroke 1 point
O Older age > 75 years, 1 point	B Bleeding 1 point
R Reduced platelet count or function 1 point	L Labile INRs 1 point
R Rebleeding risk 2 points	E Elderly (age > 65 years) 1 point
H Hypertension (uncontrolled) 1 point	D Drugs or alcohol (one point each) 1 or 2 points
A Anemia 1 point	
G Genetic factors (CYP 2C9 polymorphisms) 1 point	… BUT … some RISK FACTORS for BLEEDING are also RISK FACTORS for STROKE … !!!
E Excessive fall risk 1 point	
S Stroke 1 point	

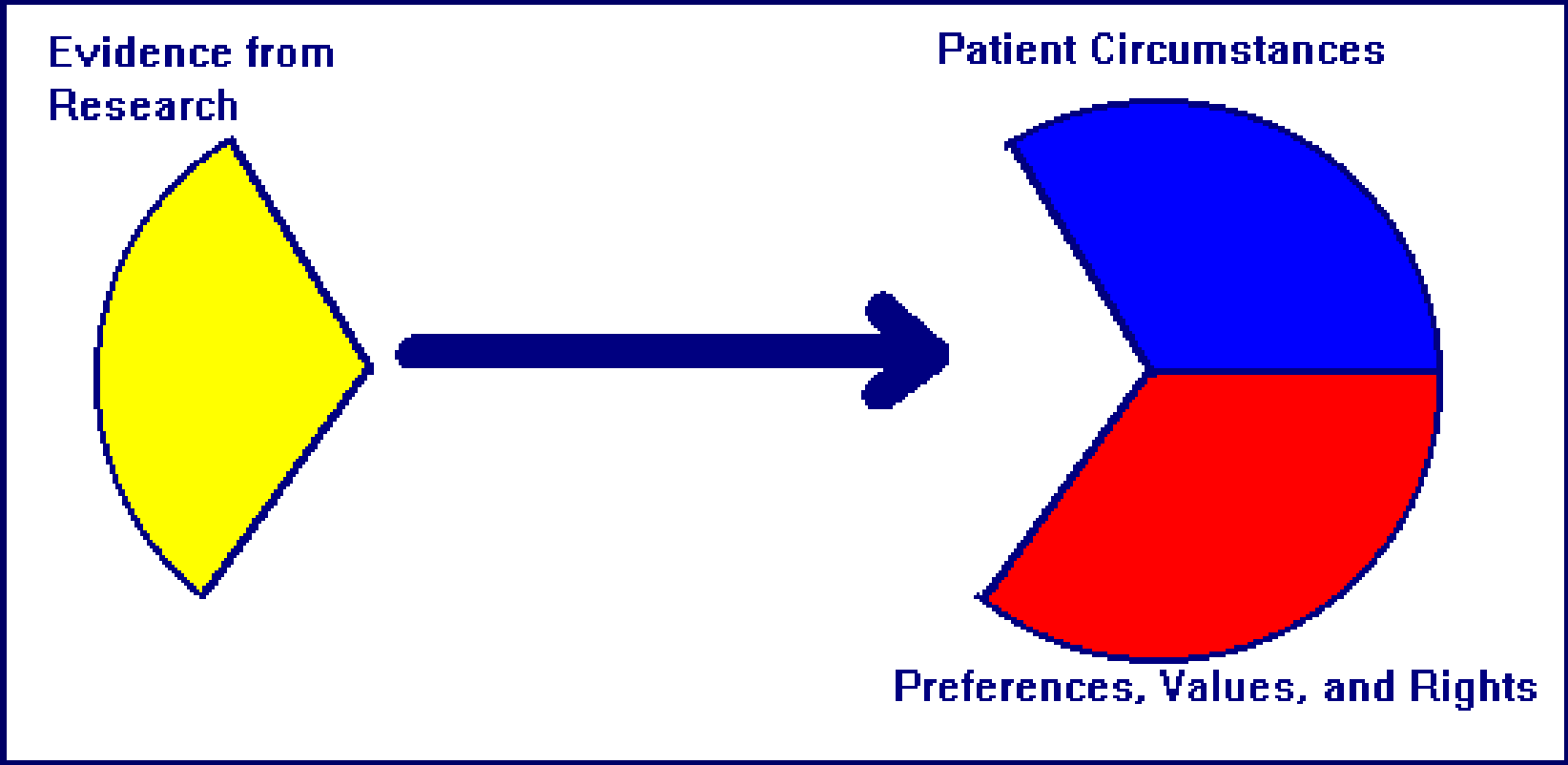
CRUSADE SCORE FOR BLEEDING

Predictor	Score
Baseline hematocrit, %	
<31	9
31–33.9	7
34–36.9	3
37–39.9	2
≥40	0
Creatinine clearance,* mL/min	
≤15	39
>15–30	35
>30–60	28
>60–90	17
>90–120	7
>120	0
Heart rate (bpm)	
≤70	0
71–80	1
81–90	3
91–100	6
101–110	8
111–120	10
≥121	11

Predictor	Score
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7
Prior vascular disease†	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mm Hg	
≤90	10
91–100	8
101–120	5
121–180	1
181–200	3
≥201	5

Subherwal et al, Circulation 2009

A patient-centered approach for Evidence Based Medicine



… approccio clinico … !!

… dialogo con il paziente … !!

Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study

P J Devereaux, David R Anderson, Martin J Gardner, Wayne Putnam, Gordon J Flowerdew, Brenda F Brownell, Seema Nagpal, Jafna L Cox

BMJ 2001;323:1–7

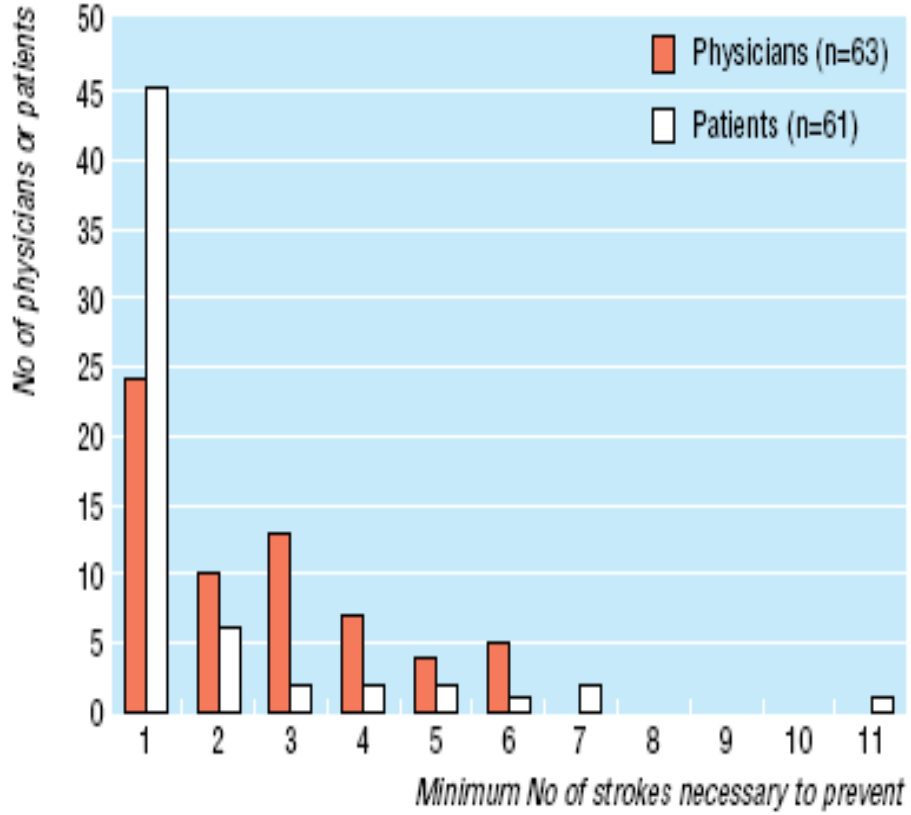


Fig 3 Stroke thresholds for warfarin

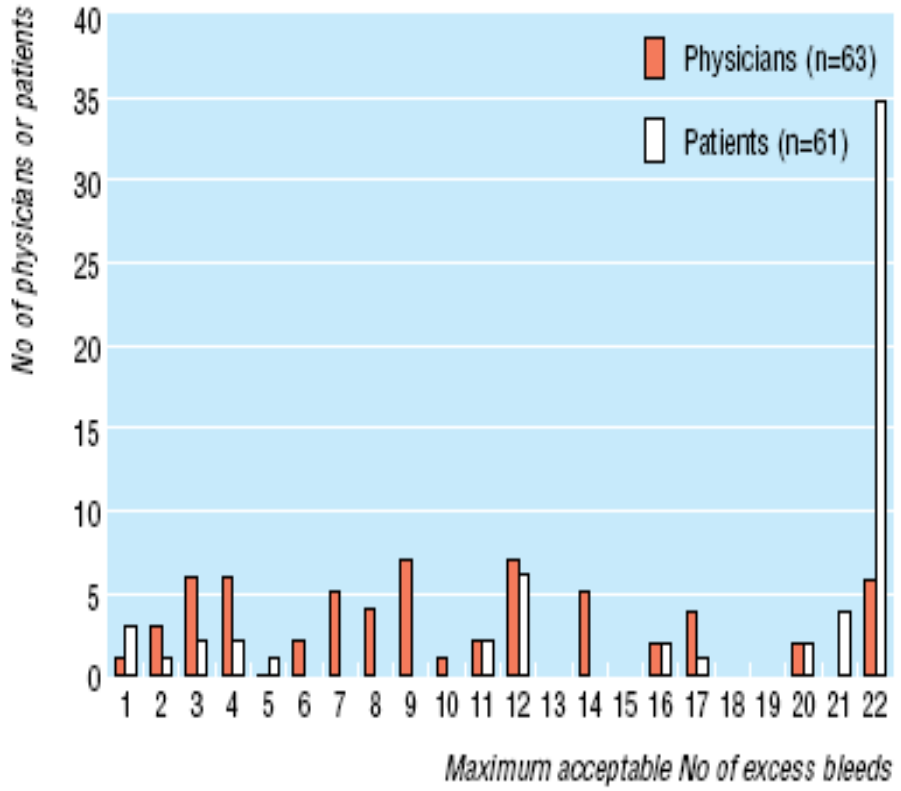


Fig 5 Bleeding thresholds for warfarin

Goal di una **medicina evoluta** con risorse multiple farmacologiche e non farmacologiche :

Necessità/opportunità di "individualizzare" la scelta del trattamento attuando una stima

del beneficio (a medio e lungo termine)

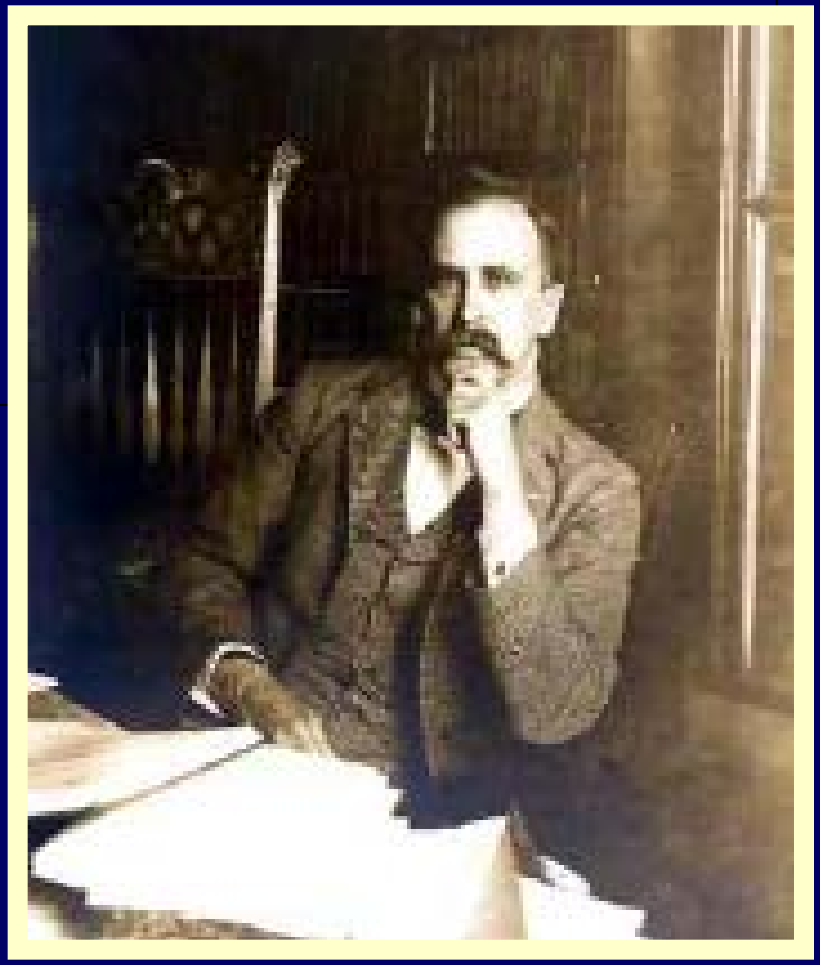
e

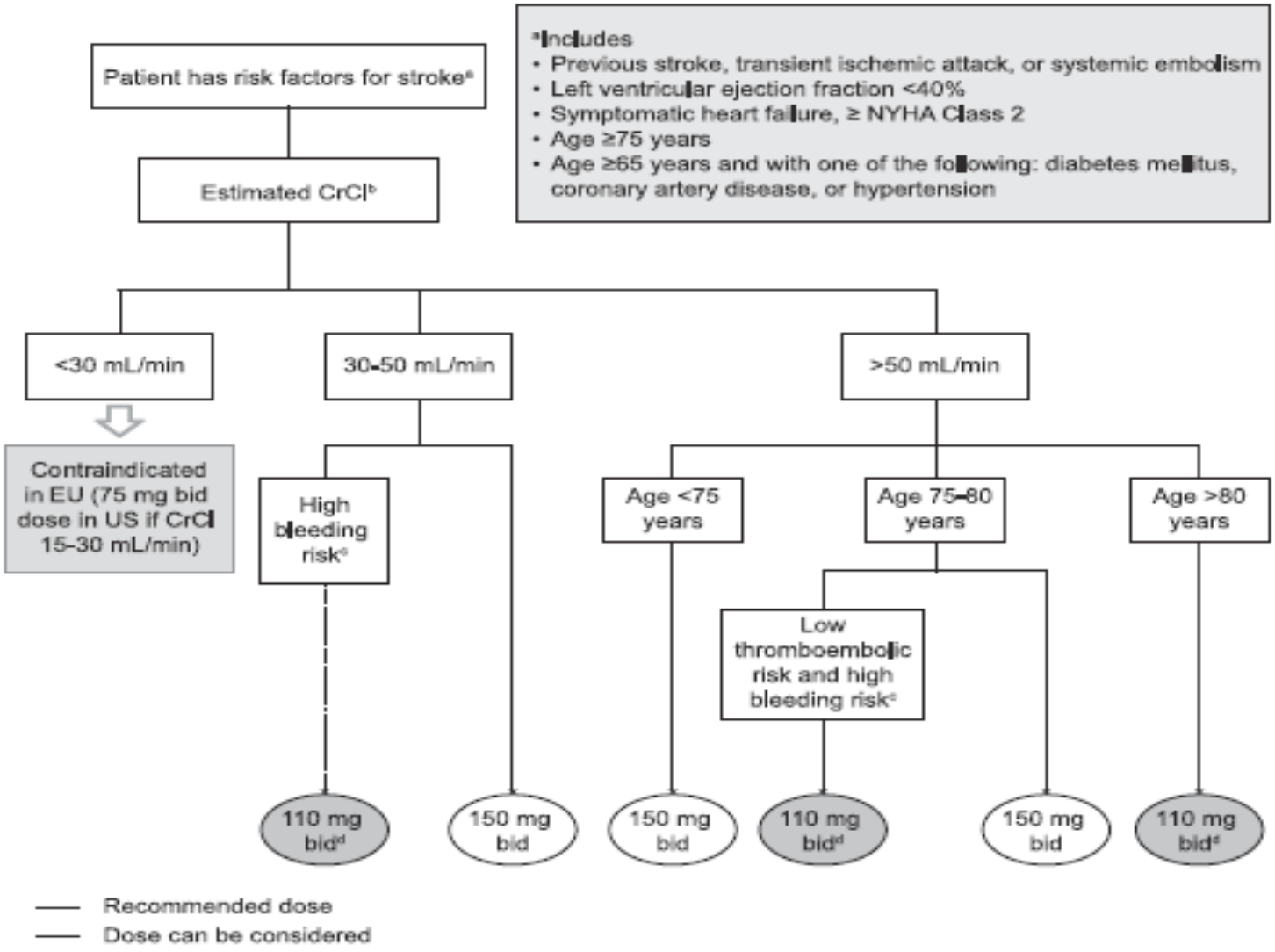
del rischio (a medio e lungo termine)

per ogni singolo paziente !

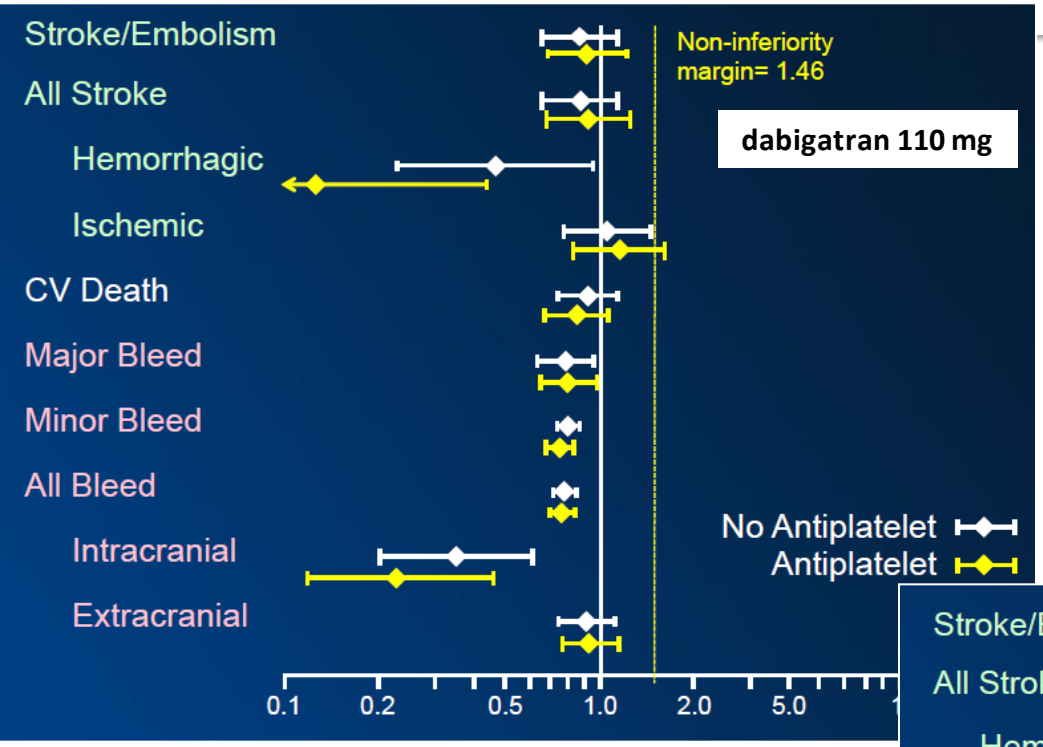
"If it were not for the great variability among individuals, Medicine might be a Science, not an Art"

Sir William Osler, 1882, The Principles and Practice of Medicine

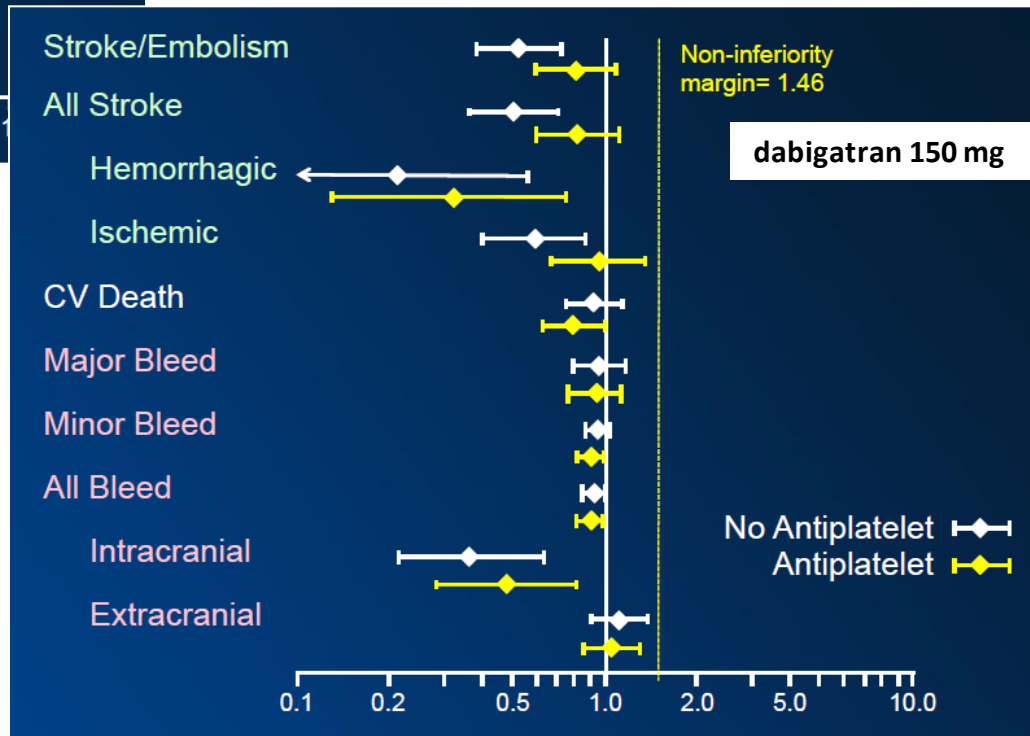



[a]Includes
• Previous stroke, transient ischemic attack, or systemic embolism
• Left ventricular ejection fraction <40%
• Symptomatic heart failure, ≥ NYHA Class 2
• Age ≥75 years
• Age ≥65 years and with one of the following: diabetes mellitus, coronary artery disease, or hypertension
Patient has risk factors for stroke[a]
Estimated CrCl[b]
<30 mL/min
30-50 mL/min
>50 mL/min
Contraindicated in EU (75 mg bid dose in US if CrCl 15–30 mL/min)
High bleeding risk[c]
Age <75 years
Age 75–80 years
Age >80 years
Low thromboembolic risk and high bleeding risk[c]
110 mg bid[d]
150 mg bid
150 mg bid
110 mg bid[d]
150 mg bid
110 mg bid[d]
Recommended dose
Dose can be considered

DABIGATRAN AND ANTIPLATELETS IN RE-LY



Dans AL et al. ESC Congress 2011



Relative/absolute risk of major bleeding

		DE 110	DE 150	Warfarin
Major Bleed	No Antiplatelet	2.2%	2.6%	2.8%
	With Antiplatelet	3.9%	4.4%	4.8%
	HR (95% CI)	1.5 (1.2, 1.9)	1.6(1.3, 2.0)	1.7(1.3, 2.0)

* Results were unaffected by duration of use or number of antiplatelets used.

Dans AL et al. ESC Congress 2011

Conclusions

1. **TT (VKA + ASA + clopidogrel) is *standard of care*, when TE risk is moderate-high**
2. ***bleeding risk stratification* recommended to determine "safest " duration of TT**
3. **throughout TT, INR to be targeted to *lower end of therapeutic range***
4. **short duration of TT (and therefore, *limited/selective use of DES*) safer and advisable**
5. **owing to undefined safety/efficacy, *no indication* for VKA + clopidogrel**
6. **owing to undefined safety/efficacy, *no indication* for newer antiplatelet agents and/or non-VKA oral anticoagulants (but promising data!)**