Stable CAD, Elective Stenting and AFib

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Declaration of Interest

Lecturing & Consulting Activities:

AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb,
Daiichi Sankyo, Pfizer, Sanofi Aventis

The Bleeding Problem in Antithrombotic Combination Therapy

Which patients have an increased bleeding risk during and after PCI ?

Pts. on more effective P2Y12-inhibitors

Pts. on prolonged dual antiplatelet therapy

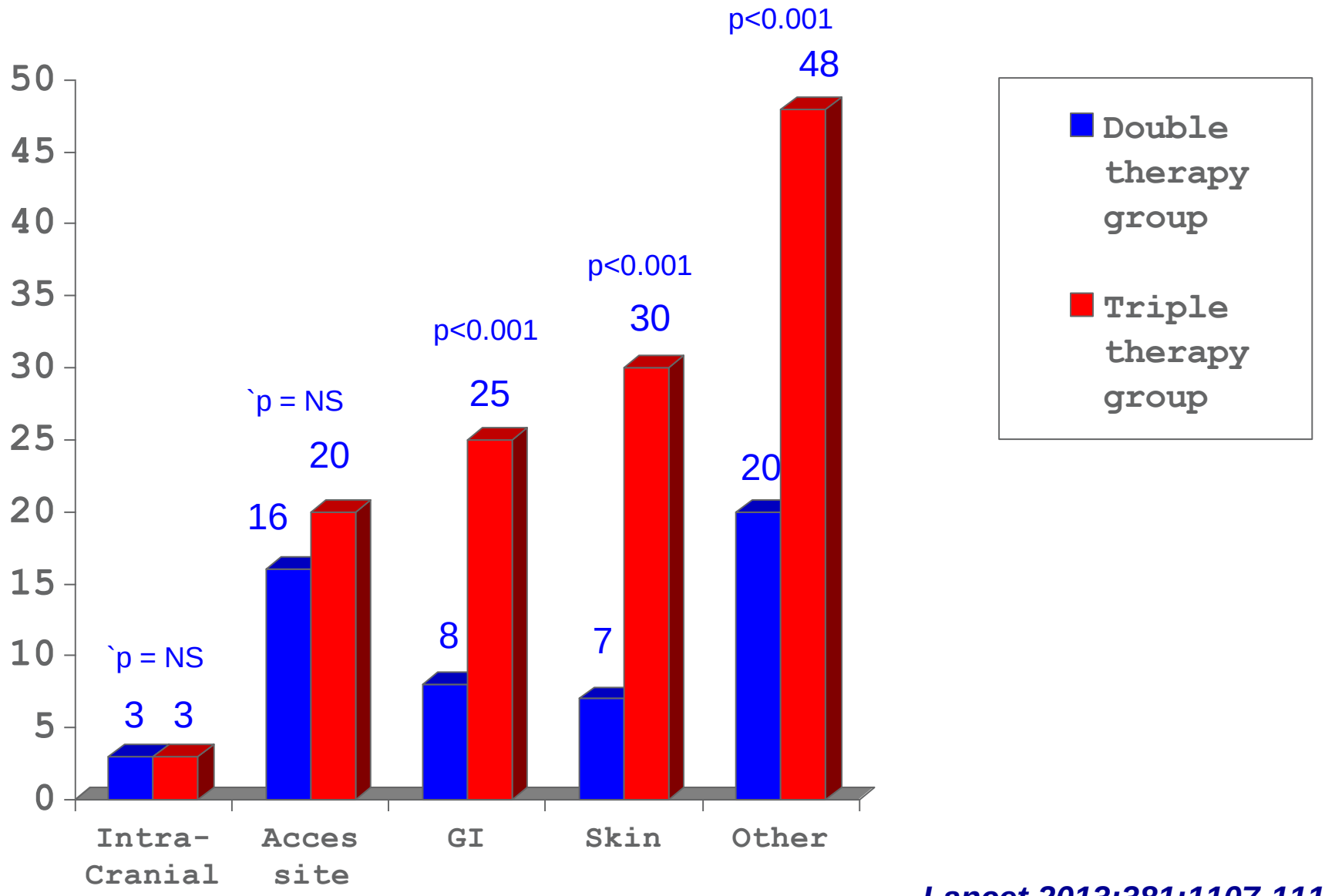
Pts. on antithrombotic combination therapy

Pts. with history of bleeding, high age (>80), women, chronic kidney dysfuntion

Huber et al. J Cardiol 2016, submitted

WOEST Trial:

Locations of TIMI bleeding: Worst bleeding per patient



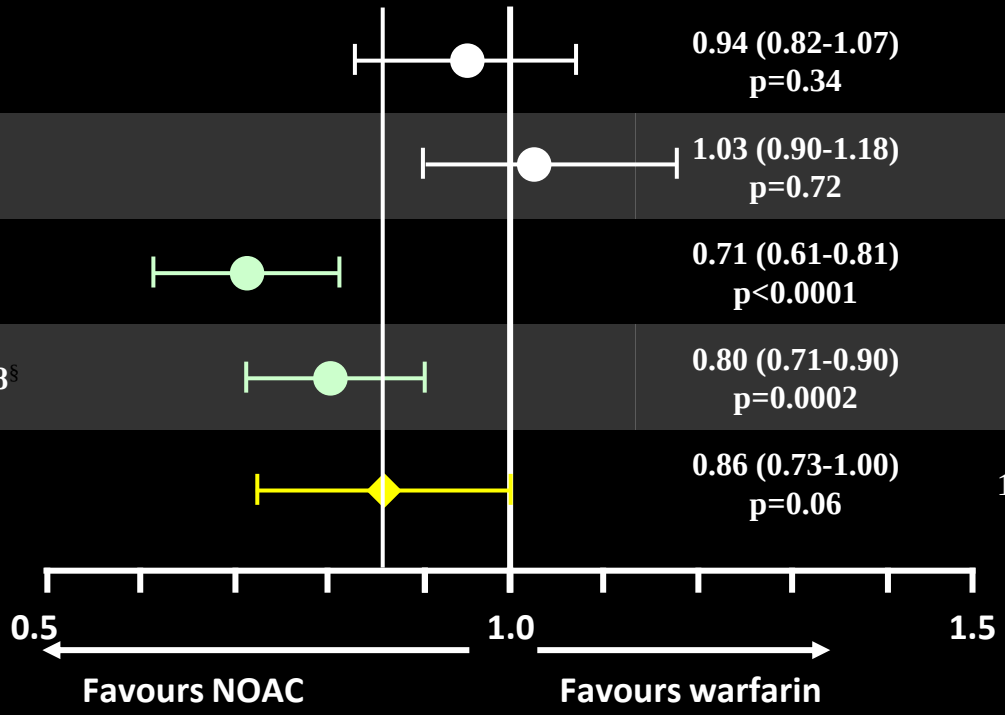
Lancet 2013:381:1107-1115

NOACS Are Safer than VKAs

Comparative safety of NOACs and warfarin

Major Bleeding

Study	Relative risk (95% CI)	NOAC events	Warfarin events
RE-LY*	0.94 (0.82-1.07) p=0.34	375/6076	397/6022
ROCKET AF†	1.03 (0.90-1.18) p=0.72	395/7111	386/7125
ARISTOTLE‡	0.71 (0.61-0.81) p<0.0001	327/9088	462/9052
ENGAGE AF-TIMI 48§	0.80 (0.71-0.90) p=0.0002	444/7012	557/7012
Combined	0.86 (0.73-1.00) p=0.06	1541/29,287	1802/29,211



*Dabigatran 150 mg BID; †rivaroxaban 20 mg QD;
‡apixaban 5 mg BID; §edoxaban 60 mg QD

Ruff CT et al. Lancet 2013; doi: 10.1016/S0140-6736(13)62343-0

Real-world Evidence – NOACs & Bleeding

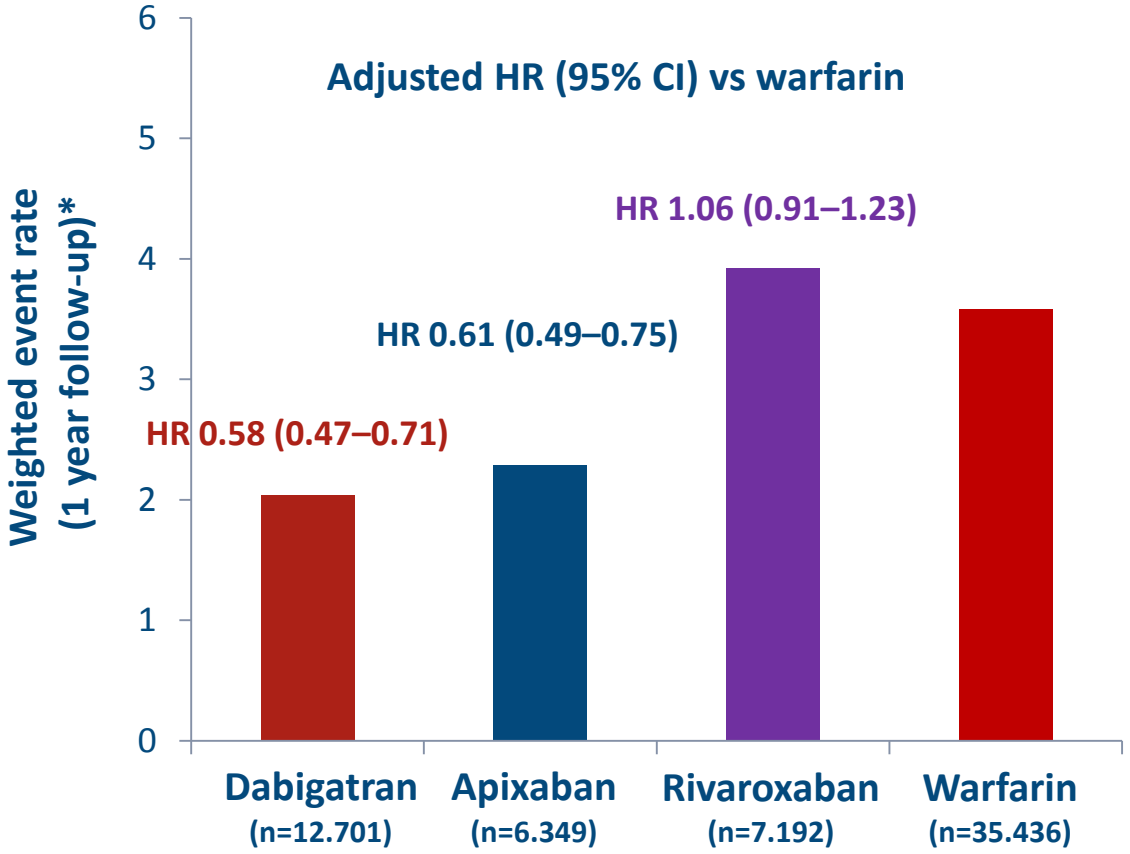
No difference in rates of major bleeding and sub-components between dabigatran and apixaban

	Apixaban (n = 8785)	Dabigatran (n = 20 963)	Rivaroxaban (n = 30 529)	Adjusted HR (Dabigatran vs Apixaban)	Adjusted HR (Rivaroxaban vs Apixaban)
	Unadjusted incidence (%/year)				
Major bleeding	14.5	13.2	20.2	0.99 (0.86-1.12)	**1.34** (1.20-1.51)
- Intracranial	1.7	1.6	2.4	1.08 (0.75-1.55)	**1.41** (1.01-1.97)
- Gastrointestinal	4.0	3.9	6.2	1.04 (0.83-1.32)	**1.54** (1.23-1.91)
- Other	9.7	8.5	13.7	0.96 (0.83-1.12)	**1.33** (1.15-1.53)

Real-world Comparison of Bleeding Risks among NVAF Patients on Apixaban, Dabigatran, Rivaroxaban: Cohorts Comprising New Initiators and/or Switchers from Warfarin

Tepper et al. Presented at ESC 2015

Real-world Evidence – NOACs & Bleeding



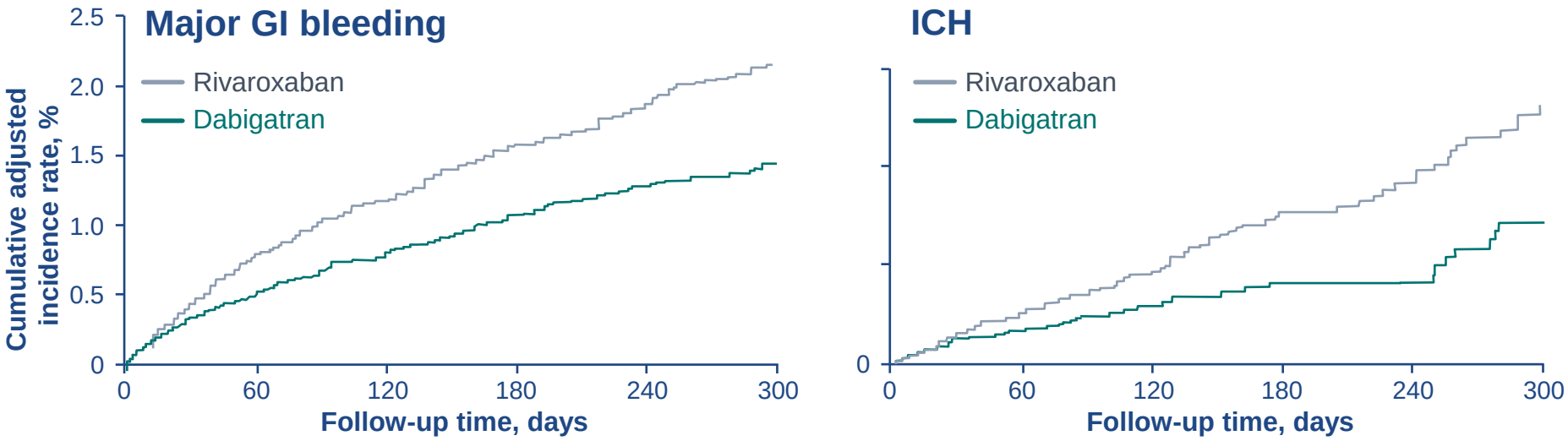
Larsen et al. BMJ 2016

An independent FDA study of >118 000 Medicare patients compared dabigatran 150 mg BID with rivaroxaban 20 mg OD[1]

FDA Medicare study

Kaplan–Meier analysis

Weighted failure curves



Patients initiating treatment with dabigatran experienced a statistically significantly lower risk of major GI bleeding than those initiating treatment with rivaroxaban

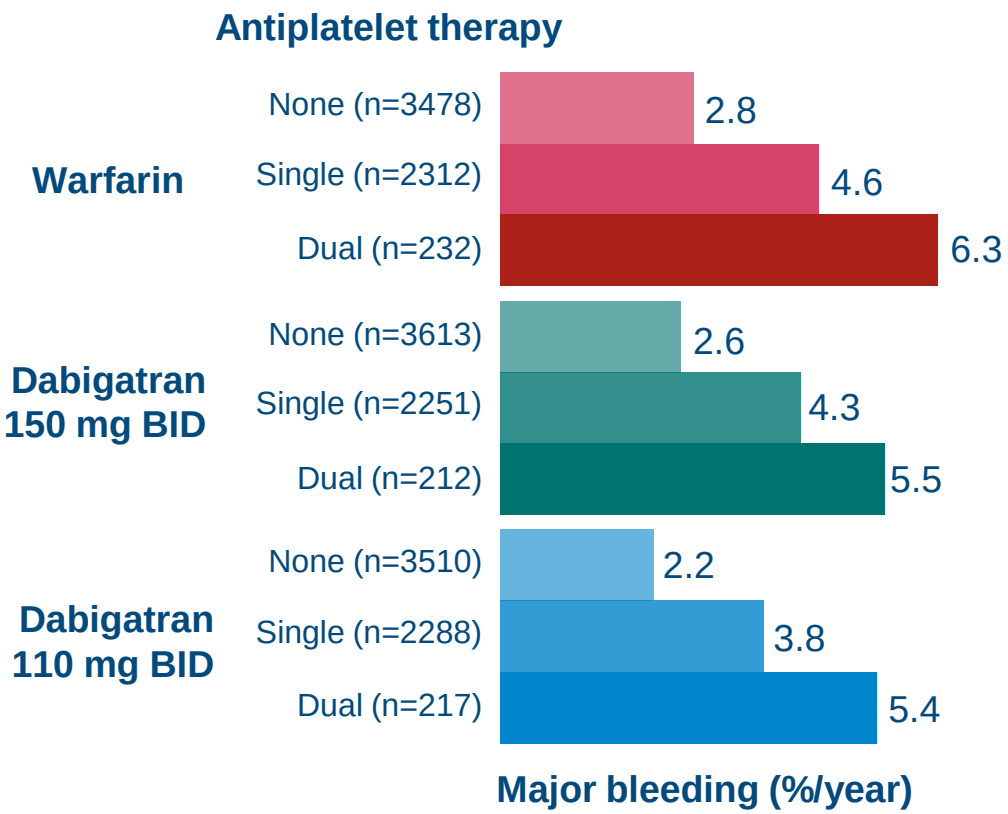
Note that the y-axis scales vary by outcome.

Average follow-up duration <4 months; Graham et al. JAMA Intern Med 2016

Graham et al. JAMA Intern Med 2016

NOACs and Antiplatelet Therapy

Triple therapy is associated with the greatest increase in bleeding risk regardless of OAC used



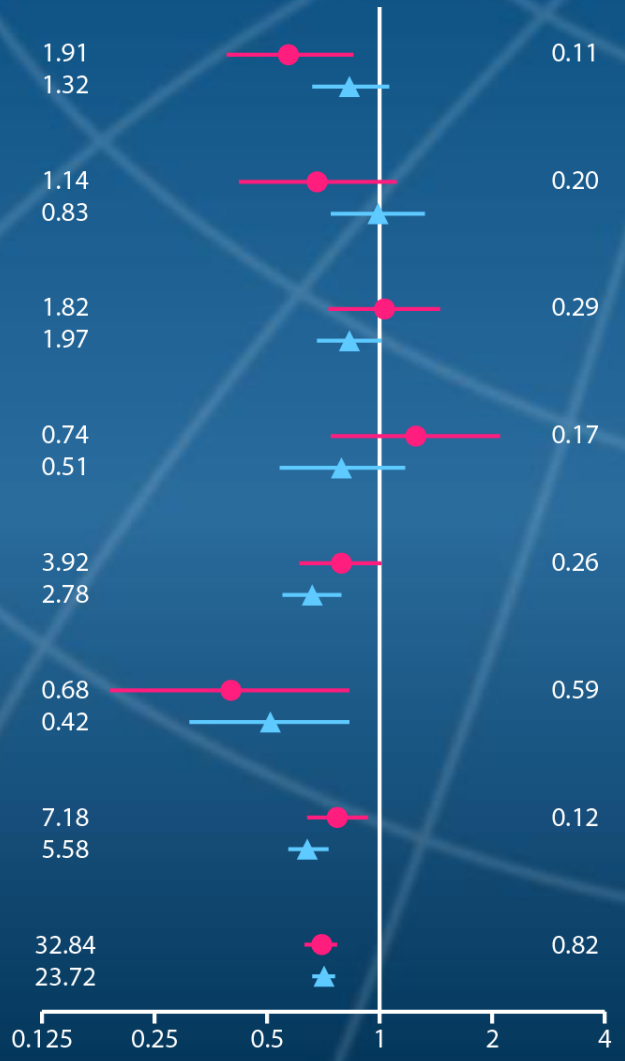
RE-LY® was the only Phase III trial of a NOAC vs VKA to allow concomitant treatment with both ASA and clopidogrel

Dans et al. Circulation 2013

ARISTOTLE

Effects of apixaban vs. warfarin with and without aspirin

Event	Apixaban (%/yr)	Warfarin (%/yr)	Interaction* P-Value
Stroke or Systemic Embolism			
Aspirin	1.12	1.91	0.11
No Aspirin	1.11	1.32	
Ischemic Stroke			
Aspirin	0.79	1.14	0.20
No Aspirin	0.83	0.83	
Death			
Aspirin	1.93	1.82	0.29
No Aspirin	1.64	1.97	
Myocardial Infarction			
Aspirin	0.90	0.74	0.17
No Aspirin	0.40	0.51	
ISTH Major Bleeding			
Aspirin	3.10	3.92	0.26
No Aspirin	1.82	2.78	
Hemorrhagic Stroke			
Aspirin	0.27	0.68	0.59
No Aspirin	0.22	0.42	
Major or CRNM Bleeding			
Aspirin	5.54	7.18	0.12
No Aspirin	3.59	5.58	
Any Bleeding			
Aspirin	22.64	32.84	0.82
No Aspirin	16.61	23.72	

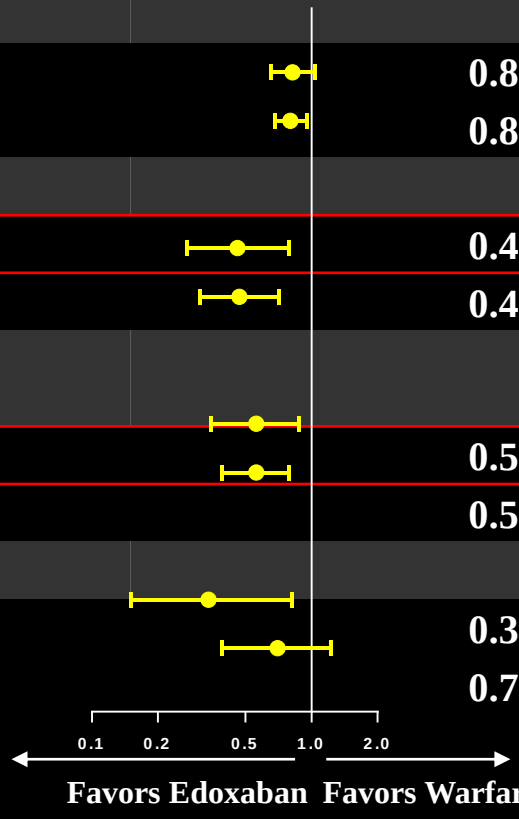


Alexander JH. Eur Heart J 2014

ENGAGE AF Trial

Safety Outcomes for Edoxaban by SAPT Use

	Warfarin (%/y)	Edoxaban 60/30 mg (%/y)	HR (95% CI)	P_{int}
Major Bleeding				0.91
SAPT	4.38	3.55	0.82 (0.65–1.04)	
No SAPT	2.54	2.04	0.80 (0.68–0.95)	
ICH				0.98
SAPT	1.18	0.54	0.46 (0.27–0.79)	
No SAPT	0.57	0.27	0.47 (0.31–0.71)	
Life-threatening Bleeding				1.00
SAPT	1.14	0.63	0.56 (0.35–0.88)	
No SAPT	0.64	0.36	0.56 (0.39–0.79)	
Fatal Bleeding				0.17
SAPT	0.56	0.19	0.34 (0.15–0.81)	
No SAPT	0.24	0.17	0.70 (0.39–1.23)	



CI = confidence interval; HR = hazard ratio; ICH = intracranial hemorrhage; SAPT = single antiplatelet therapy

Xu et al. *J Am Heart Assoc*. 2016; 5:e002587.

PIONEER AF-PCI

The NEW ENGLAND JOURNAL of MEDICINE

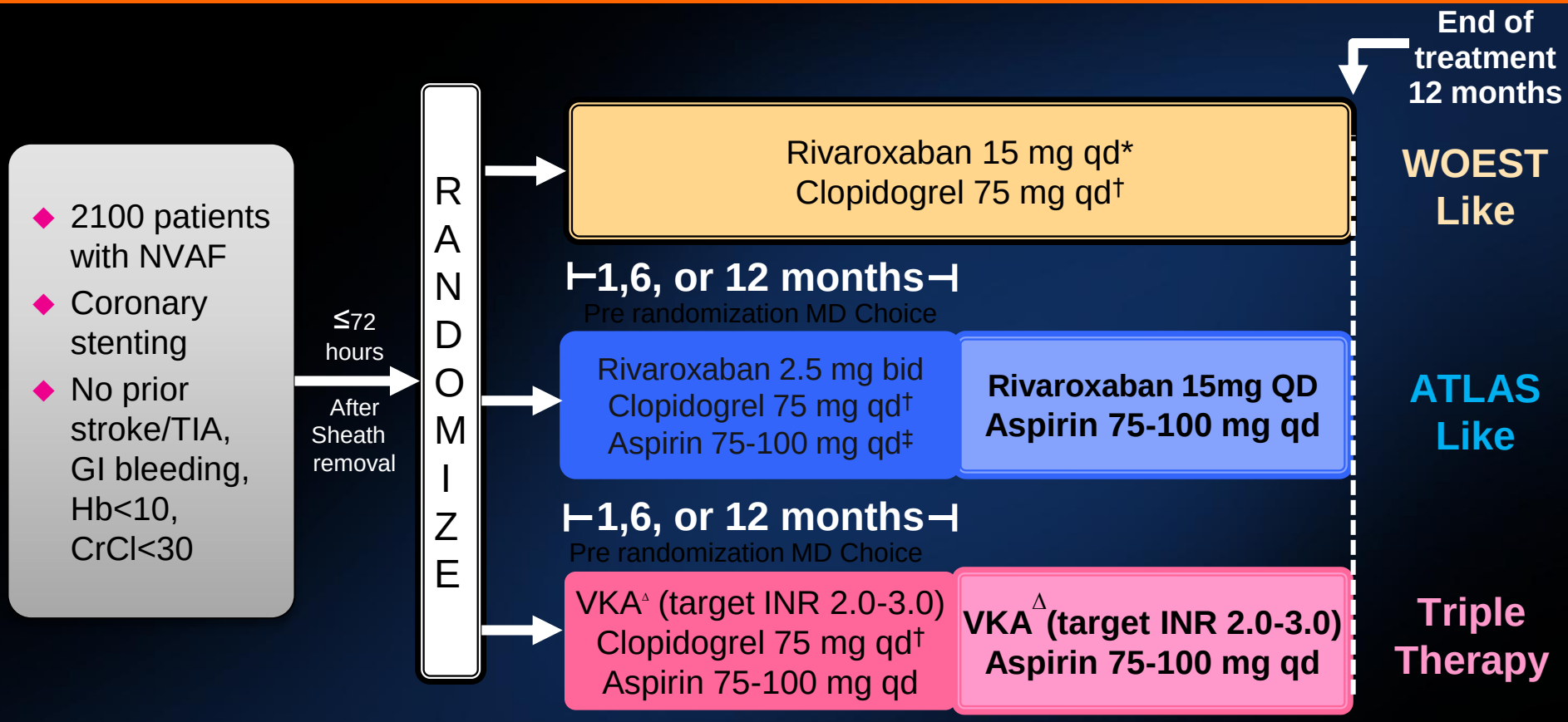
ORIGINAL ARTICLE

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

C. Michael Gibson, M.D., Roxana Mehran, M.D., Christoph Bode, M.D., Jonathan Halperin, M.D., Freek W. Verheugt, M.D., Peter Wildgoose, Ph.D., Mary Birmingham, Pharm.D., Juliana Ianus, Ph.D., Paul Burton, M.D., Ph.D., Martin van Eickels, M.D., Serge Korjian, M.D., Yazan Daaboul, M.D., Gregory Y.H. Lip, M.D., Marc Cohen, M.D., Steen Husted, M.D., Eric D. Peterson, M.D., M.P.H., and Keith A. Fox, M.B., Ch.B.

N Engl J Med 2016;3275:2432-2434

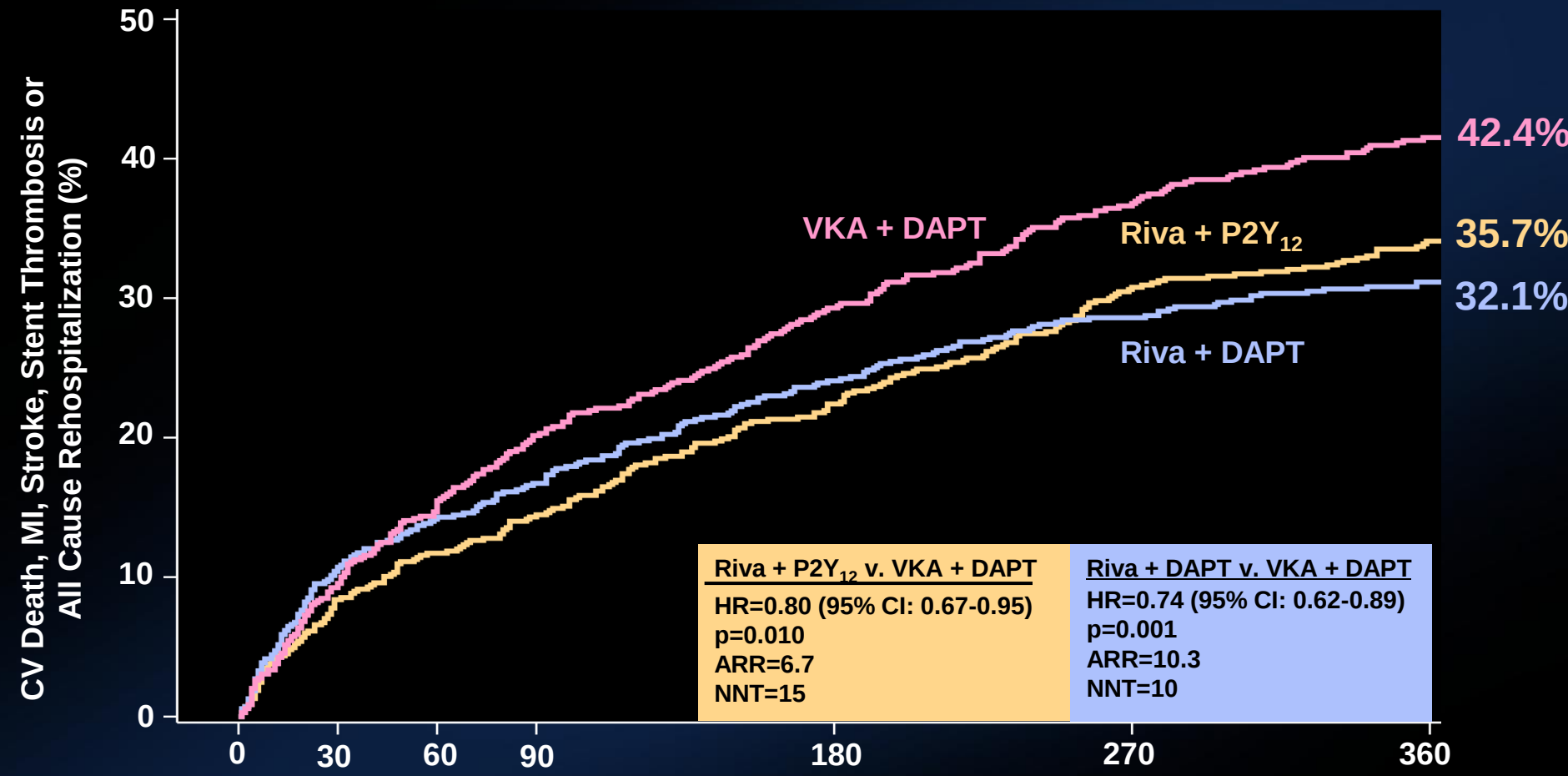
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



- **Primary endpoint: TIMI major + minor + bleeding requiring medical attention**
- **Secondary endpoint: CV death, MI, and stroke** (Ischemic, Hemorrhagic, or Uncertain Origin)

N Engl J Med 2016;3275:2432-2434

Time to First CV Death, MI, Stroke, Stent Thrombosis or All Cause Recurrent Hospitalization



No. at risk							
Riva + P2Y$_{12}$	696	609	582	559	496	437	322
Riva + DAPT	706	607	570	548	493	454	367
VKA + DAPT	697	592	540	490	422	369	272

N Engl J Med 2016;3275:2432-2434

Major Adverse Cardiac Events
All Strata

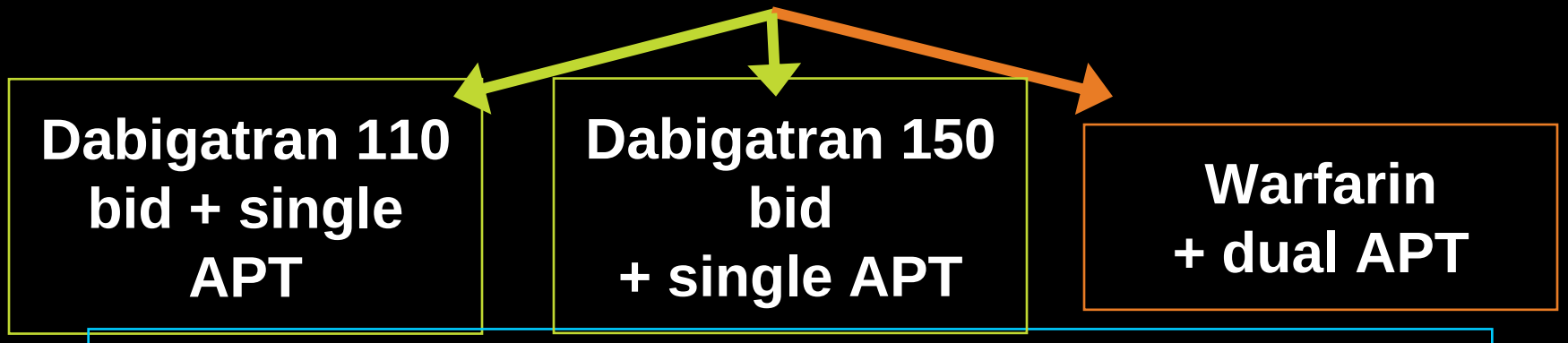
	Kaplan-Meier Estimates			Hazard Ratio (95% CI)	
Overall	**Riva + $P2Y_{12}$ (N=694)**	**Riva + DAPT (N=704)**	**VKA + DAPT (N=695)**	**Riva + $P2Y_{12}$ vs. VKA + DAPT**	**Riva + DAPT vs. VKA + DAPT**
Adverse CV Event	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) p=0.750	0.93 (0.59-1.48) p=0.765
CV Death	15 (2.4%)	14 (2.2%)	11 (1.9%)	1.29 (0.59-2.80) p=0.523	1.19 (0.54-2.62) p=0.664
MI	19 (3.0%)	17 (2.7%)	21 (3.5%)	0.86 (0.46-1.59) p=0.625	0.75 (0.40-1.42) p=0.374
Stroke	8 (1.3%)	10 (1.5%)	7 (1.2%)	1.07 (0.39-2.96) p=0.891	1.36 (0.52-3.58) p=0.530
Stent Thrombosis	5 (0.8%)	6 (0.9%)	4 (0.7%)	1.20 (0.32-4.45) p=0.790	1.44 (0.40-5.09) p=0.574
Adverse CV Events + Stent Thrombosis	41 (6.5%)	36 (5.6%)	36 (6.0%)	1.08 (0.69-1.68) P=0.750	0.93 (0.59-1.48) p=0.765

N Engl J Med 2016;3275:2432-2434

Antithrombotic Combination Therapy – New P2Y12-Inh., Skipping Aspirin

RE-DUAL PCI

All-comers
Randomized
Event driven



Outcomes:

Bleeding, death, MI, and stroke

Single or dual APT (antiplatelet therapy) includes CLOPIDOGREL (stable patients) or TICAGRELOR (ACS patients)

Cannon et al. Clin Cardiol 2016 Epub ahead of print

Apixaban in AF/ACS

(AUGUSTUS Trial design)

Patients (n~4500) w/ AF (CHADS ≥1) + PCI or ACS
Planned P2Y12 x ≥6 months

Randomise

2 x 2 Factorial

Apixaban 5.0 (2.5*) mg BD + P2Y12

VKA (INR 2–3) + P2Y12

Randomise

Aspirin 81 mg OD

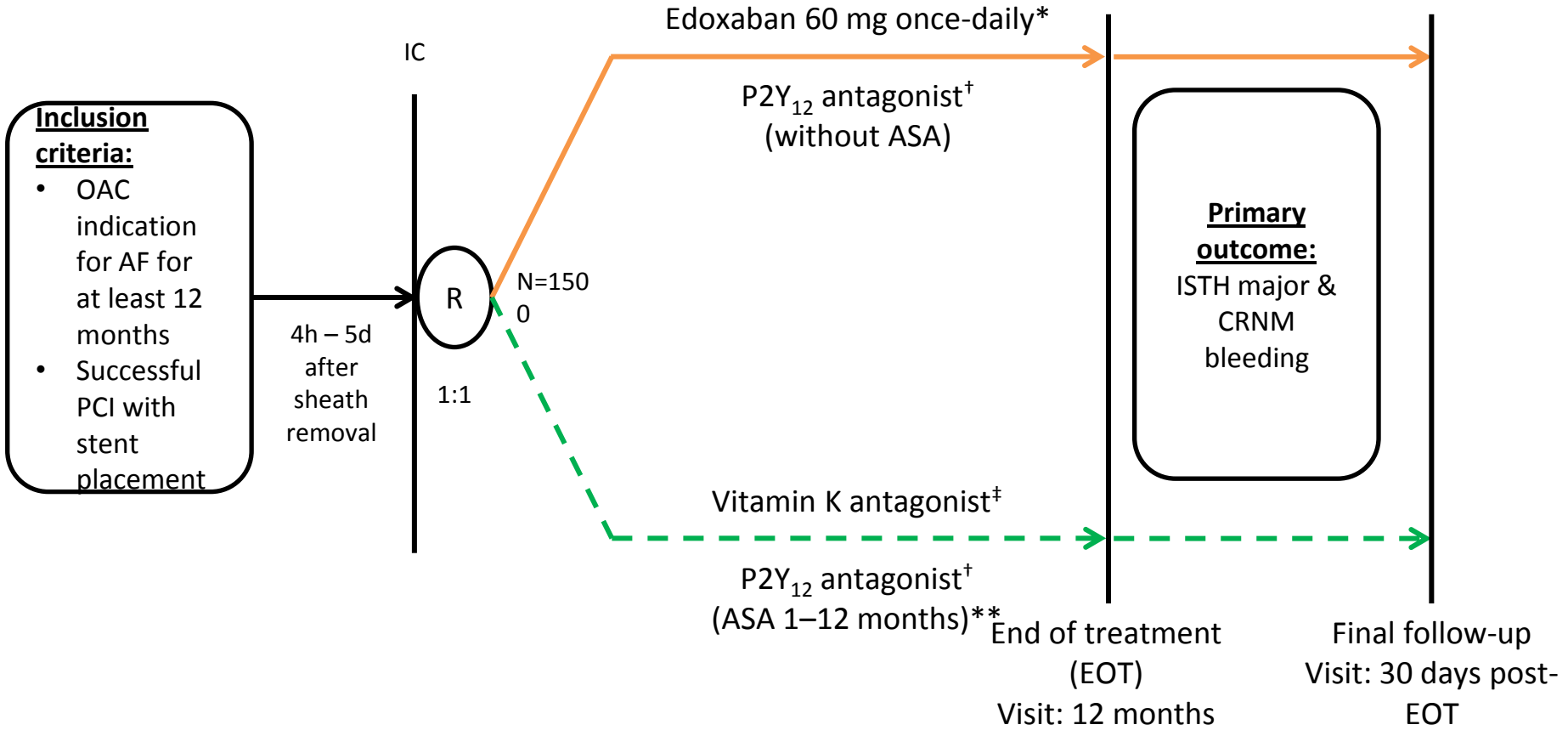
Aspirin Placebo

Primary: ISTH Major or CRNM Bleeding at 6 months
Secondary: Death, MI, stroke, stent thrombosis at 6 months

Cr, creatinine; CRNM, clinically relevant non-major.
***2.5 mg BD for patients with 2/3: age >80 years, weight <60 kg, Cr >1.5 mg/dL.**

ENTRUST-AF PCI Trial

EDOXABAN TREATMENT VERSUS VKA IN PATIENTS WITH AF UNDERGOING PCI – ENTRUST-AF PCI



Ongoing Trials in PCI for AFpatients with or without Aspirin

trial	n	experiment arm	control arm	clinicaltrials.gov	primary endpoint
RE-DUAL PCI	2,500	dabigatran* P2Y12	warfarin P2Y12 aspirin	02164864	bleeding
AUGUSTUS**	4,600	apixaban/warfarin P2Y12	warfarin P2Y12 aspirin	02415400	bleeding
ENTRUST AF-PCI	1,500	edoxaban P2Y12	warfarin P2Y12 aspirin	n.a.	bleeding
MANJUSRI[2]	296	warfarin ticagrelor	warfarin clopidogrel aspirin	02206815	bleeding

[1] *Contemp Clin Trials 2015;40:166-171*

* 150mg bid **vs** 110 mg bid

**ACS with or without PCI only

GLOBAL LEADERS

All-Comers PCI Population
ACS and Elective/Stable patients
(n=16,000)

Biolimus-eluting stent (BES)
BioMatrix Flex ™

1:1 Randomization, Open-Label Design

Study Treatment Strategy

1-month
ASA + Ticagrelor

23-months
monotherapy Ticagrelor

Reference Treatment Strategy

12-months DAPT
ACS pts (ASA + Ticagrelor)
Elective pts (ASA + Clopidogrel)

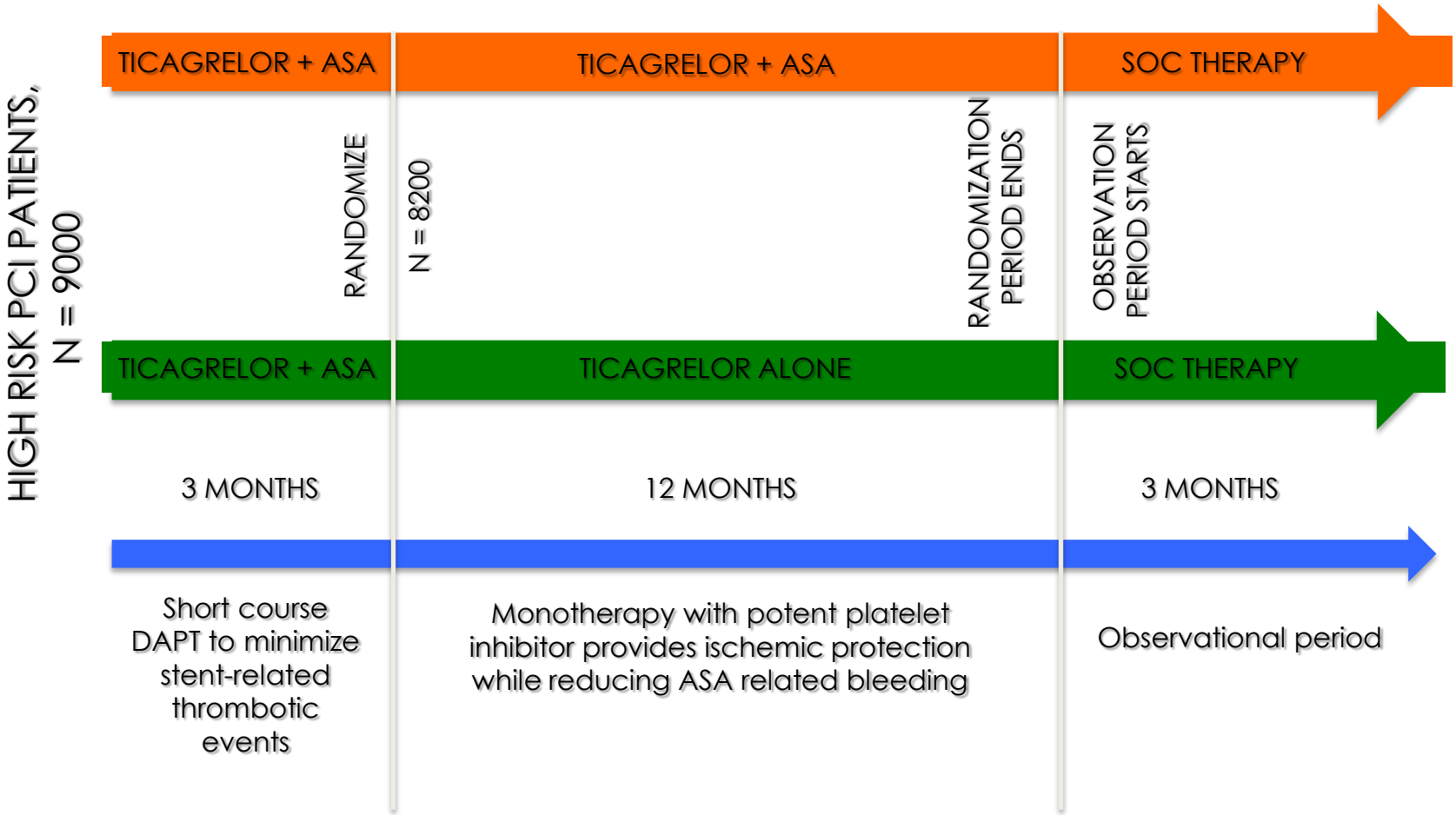
12-months
monotherapy ASA

Primary Endpoint

Study treatment strategy superior to reference treatment strategy on cumulative 2 year composite of all cause mortality and new Q-wave MI

TWILIGHT Study Design

Multicenter, prospective, blinded dual-arm study



What the Guidelines Say

Recommendations for antithrombotic treatment in SCAD patients undergoing PCI

Antiplatelet therapy after stenting			
DAPT is indicated for at least 1 month after BMS implantation.	I	A	791,799–801
DAPT is indicated for 6 months after DES implantation.	I	B	799,802,803
Shorter DAPT duration (<6 months) may be considered after DES implantation in patients at high bleeding risk.	IIb	A	804,805
Life-long single antiplatelet therapy, usually ASA, is recommended.	I	A	776,794
Instruction of patients about the importance of complying with antiplatelet therapy is recommended.	I	C	-
DAPT may be used for more than 6 months in patients at high ischaemic risk and low bleeding risk.	IIb	C	-

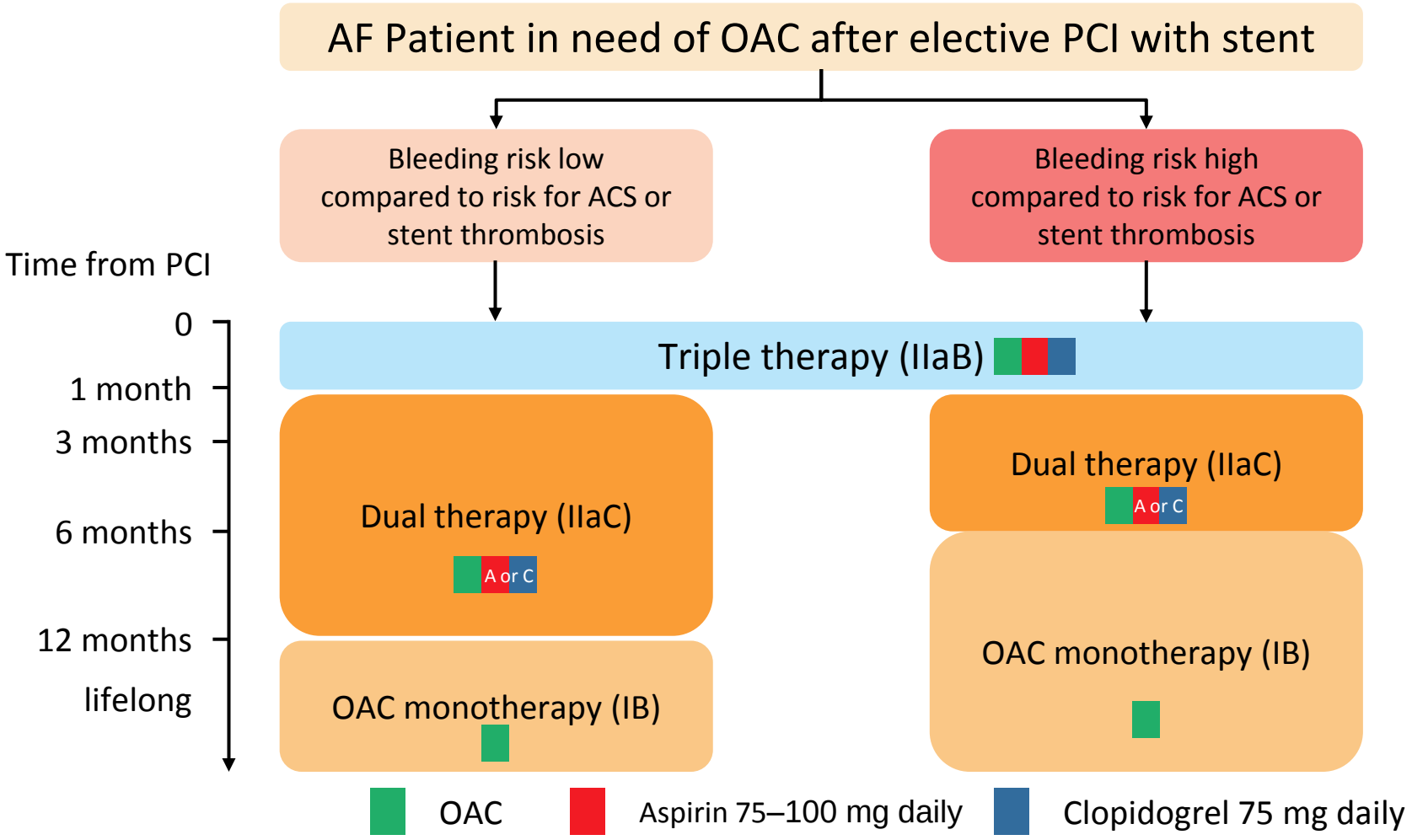
Wijns et al. Eur Heart J 2014

Recommendations for combination therapy with oral anticoagulants and antiplatelets

Recommendation	Class [a]	Level [b]
Oral antiplatelet therapy		
After elective coronary stenting for stable coronary artery disease in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1 month to prevent recurrent coronary and cerebral ischaemic events.	IIa	B
After an ACS with stent implantation in AF patients at risk of stroke, combination triple therapy with aspirin, clopidogrel and an oral anticoagulant should be considered for 1–6 months to prevent recurrent coronary and cerebral ischaemic events.	IIa	C
After an ACS without stent implantation in AF patients at risk of stroke, dual treatment with an oral anticoagulant and aspirin or clopidogrel should be considered for up to 12 months to prevent recurrent coronary and cerebral ischaemic events.	IIa	C
The duration of combination antithrombotic therapy, especially triple therapy, should be kept to a limited period, balancing the estimated risk of recurrent coronary events and bleeding.	IIa	B
Dual therapy with any oral anticoagulant plus clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients	IIb	C

Kirchoff et al. Eur Heart J 2016

Antithrombotic therapy after elective percutaneous intervention in atrial fibrillation patients requiring anticoagulation



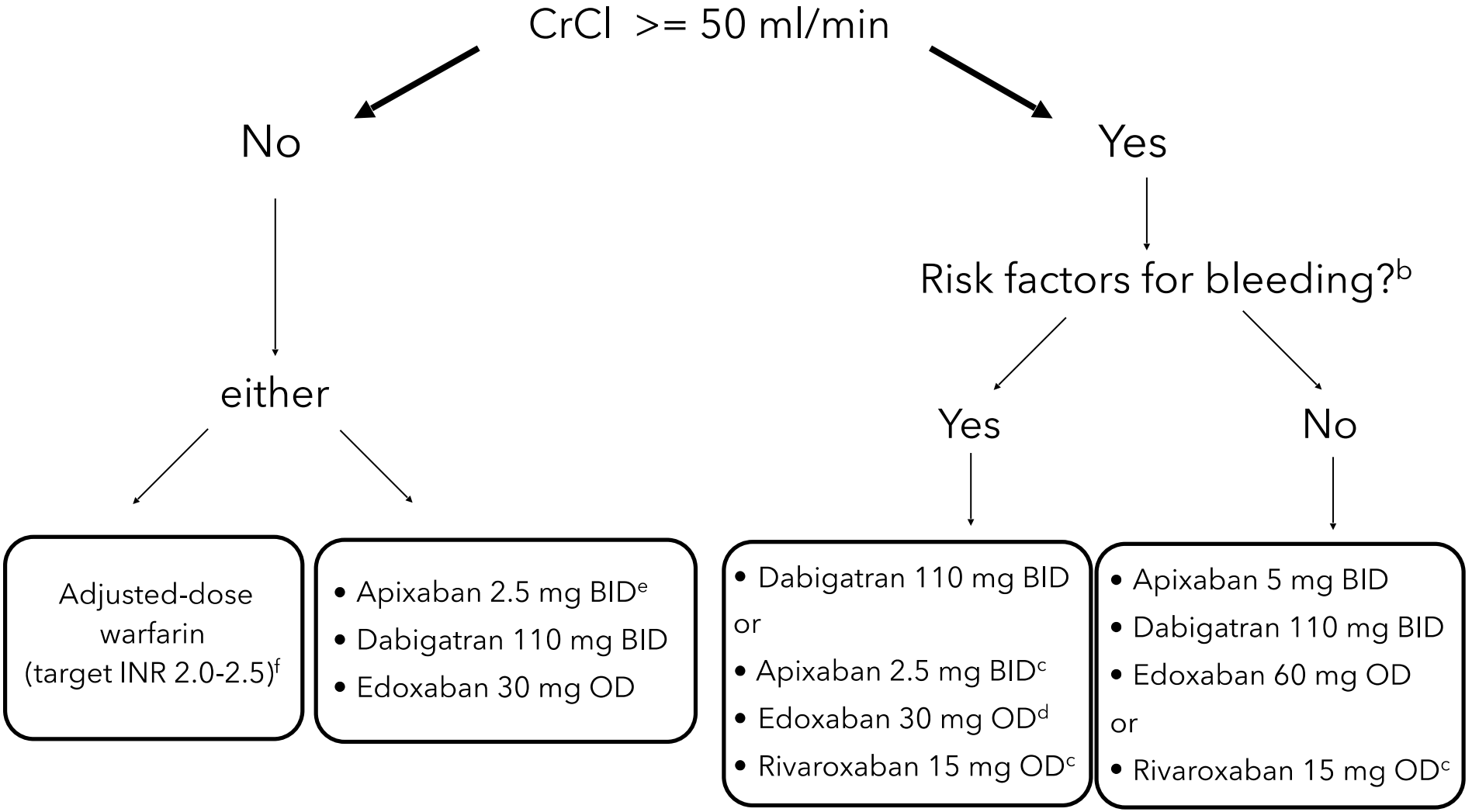
Kirchoff et al. Eur Heart J 2016

Recommendations for Combination Antithrombotic Therapy

- The use of all oral anticoagulants is possible (VKA, NOACs)
  - If VKA: INR 2,0-2,5
  - If NOAC: lower dose (2x110 mg dabigatran, 1x15 mg rivaroxaban, 2x2,5 mg apixaban, 1x30 mg edoxaban)
- Do NOT USE second generation $P2Y_{12}$-inhibitors in combination with OAC
  - However, current trials will assess the safety and efficacy of NOACs in combination with stronger $P2Y_{12}$ inhibitors
- Newer generation DES should be preferred over BMS in patients with AF undergoing coronary stenting (LEADERS Free and ZEUS trials)

Further Thoughts & Take Home Message

NOACs and Antiplatelet Agents



Rubboli, Agewall, Huber, Lip. submitted Int J Cardiol 2016

Triple Therapy in PCI: For Whom and for How Long?

Take Home Messages

Triple therapy (OAC, clopidogrel and aspirin) for PCI in AF leads to unacceptable bleeding. Possibly, aspirin may be skipped and a lower NOAC dose used (PIONEER)

The most recent guidelines recommend for most AF patients undergoing PCI triple therapy for the shortest period as clinically acceptable (1 mo). The balance bleeding/thrombotic risk must be taken into account. APT must be stopped at 12 mo

For AF patients undergoing PCI the NOACs seem preferable because of their safety profile. The first randomized trial data do support this, but more data are needed

THANK YOU
FOR YOUR INTEREST