31 GIORNATE CARDIOLOGICHE TORINESI

TURIN
October
24th-26th
2019

DOACs in particular settings: fragile patients undergoing PCI

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Conflict of Interest Statement

- Speaker honoraria: Astra Zeneca, Bayer, Biotronik, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer
- Grants (through institution): Bayer, Amgen, Chiesi, Astra Zeneca

P.L. Female, caucasian 79 yo

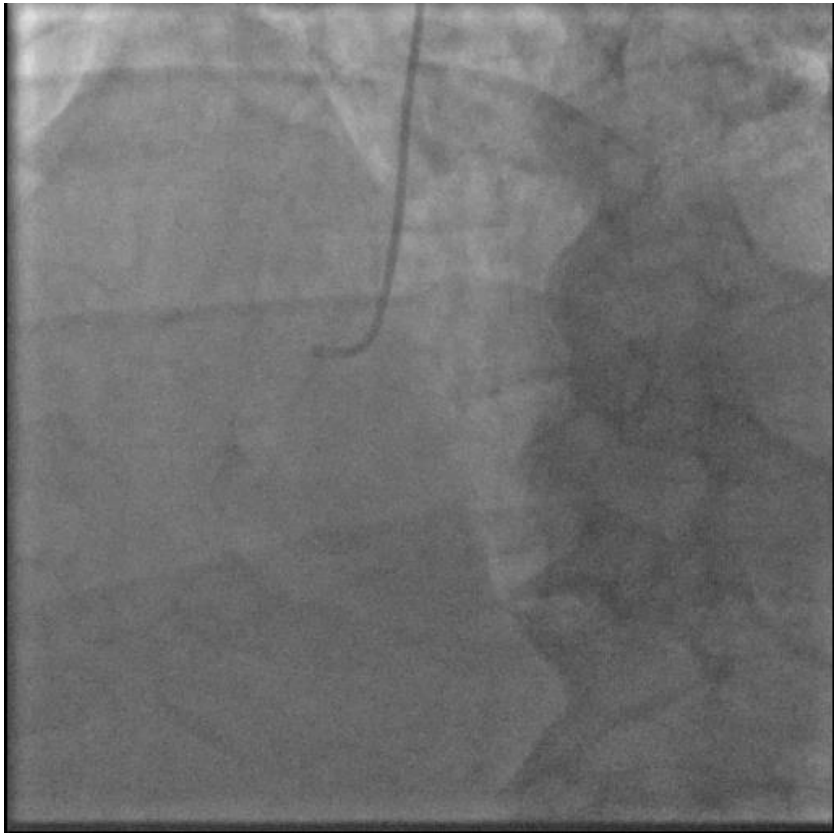
BMI: 24 kg/m2 **eGFR (MDRD):** 53 ml/min/1,73m2
CV risk factors: arterial hypertension, dyslipidemia

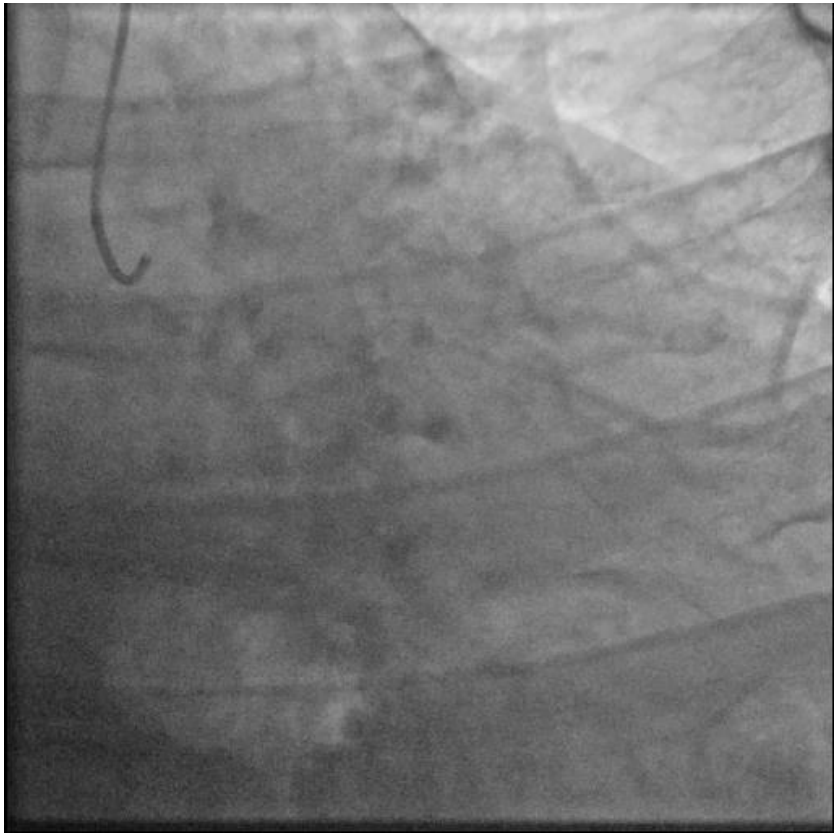
Comorbidities: COPD (moderate obstruction), mild IRC, previous surgery for colon cancer, TIA in the past (50% left carotid stenosis), severe osteoporosis

- **June 2017:** worsening dyspnea (NYHA III) -> **Echo:** EF = 28%, LV dilatation and mild-to-moderate MR
- **Coronary angiography:** Complex, severe 3VD

Syntax Score I 40

P.L. Female, caucasian 79 yo

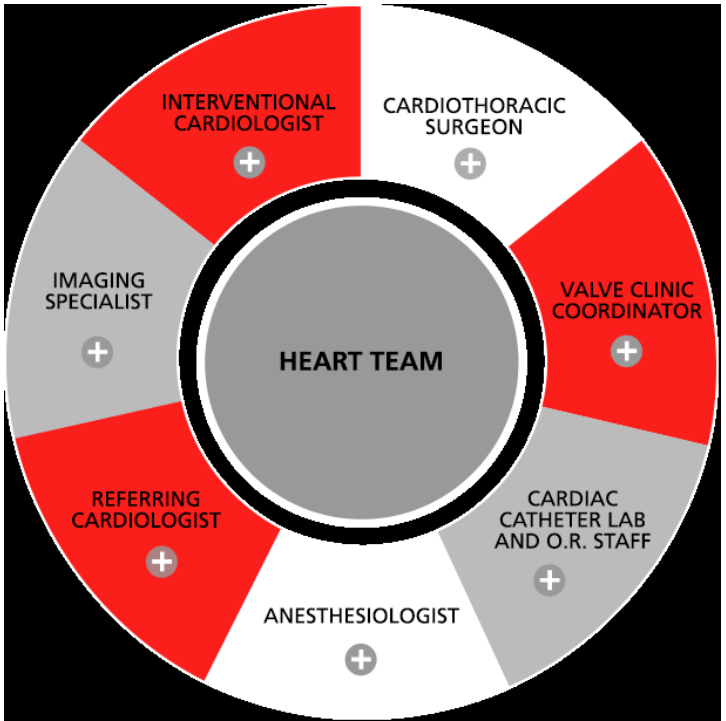




P.L. Female, caucasian 79 yo

October 2017: Heart Team discussion

not eligible neither for percutaneous nor surgical revascularization, CRT not indicated → medical therapy



P.L. Female, caucasian 79 yo

CARDIOLOGICAL HISTORY:

- **New hospitalization for NYHA III HFrEF (January 2018)**

- **Echo:** EDD 65 mm, EF 22%. E/E' 24. Moderate MR (Carpentier IIIB). PAPs 45 mmHg
  → **ICD Implantation (primary prevention), medical therapy optimized**

- After discharge @ ICD check **Atrial Fibrillation** → Apixaban 5 mg bid (added to aspirin).

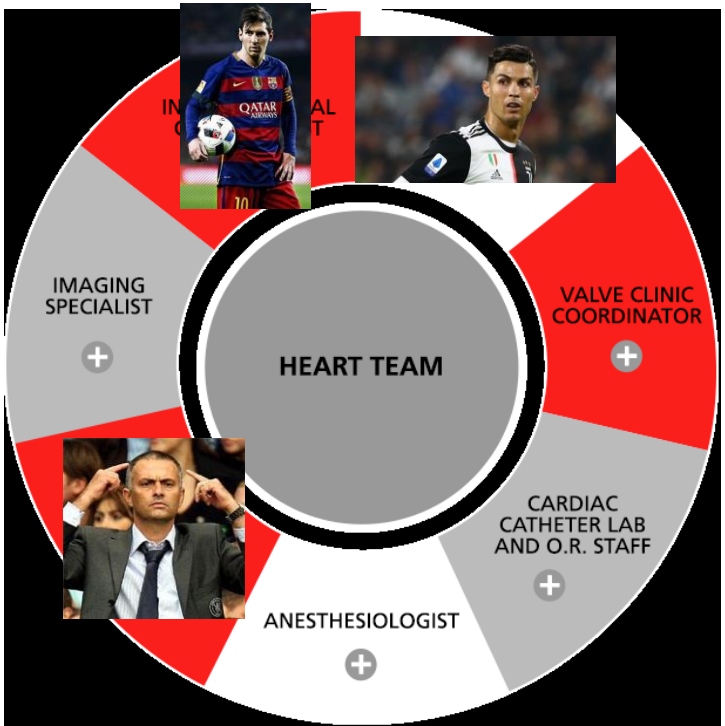
- **March 2018**: further hospitalization for worsening dyspnea → **Echo:** EF 22%. E/E' 32. Moderate MR (Carpentier IIIB). TAPSE 16 mm. RVFAC 35%. PAPs 40 mmHg.

P.L. Female, caucasian 79 yo

April 2018: Heart Team discussion

Coronary Revascularization with LV support

(Complex, High-Risk but Indicated PCI, CHiP)



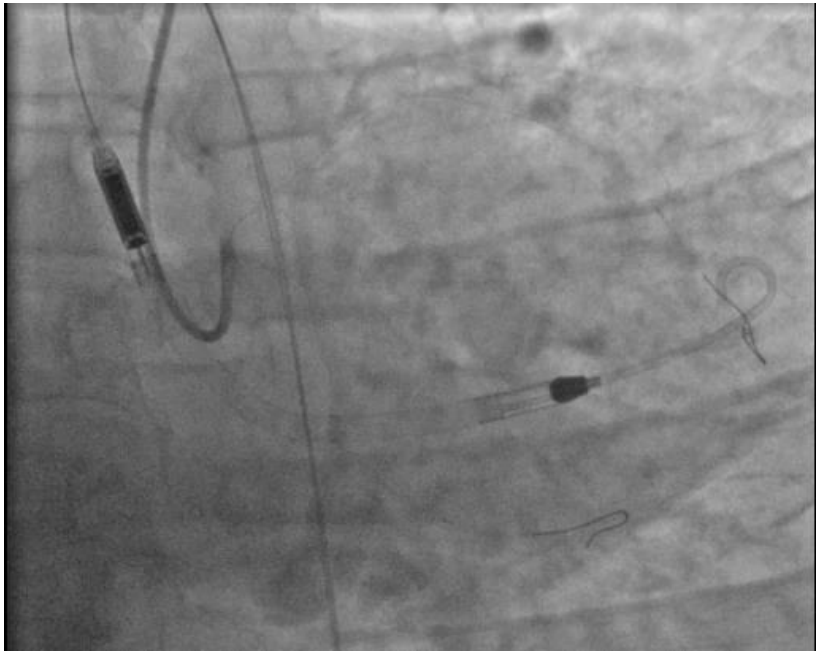
P.L. Female, caucasian 79 yo

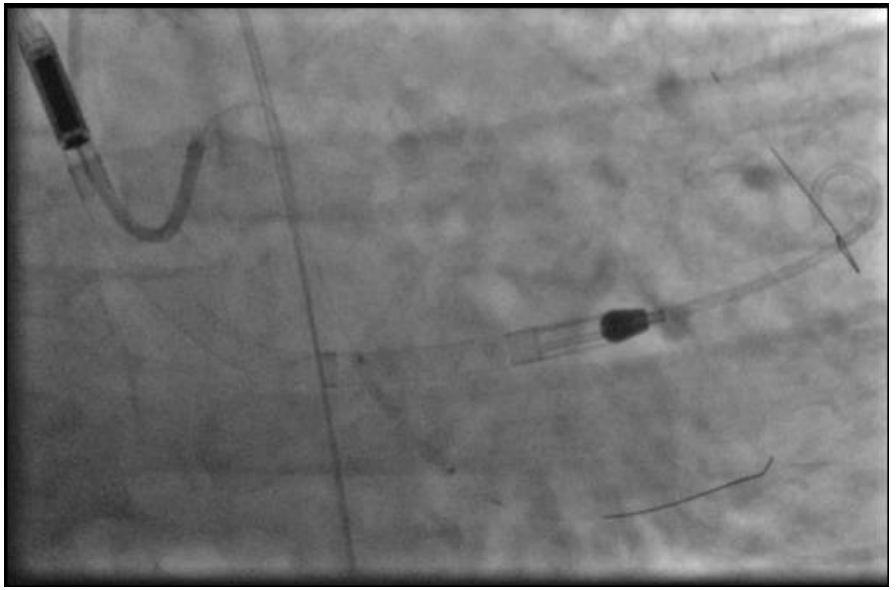
FRAILTY SCORES

Area					Punti	Compr.
Funzione Fisica (SPPB)	0-6 scarsa	7-9 intermedia	10-12 normale			☒
Stato cognitivo (SPMSQ)	8-10 severo	5-7 moderato	3-4 lieve	0-2 normale		☐
Stato Nutrizionale (MNA)	0-11 possibile malnutrizione		12-14 normale			☐
Fragilità (Criteri di Fried)	3-5 fragile	1-2 pre-fragile	0 normale			☒
Totale aree compromesse						
PAZIENTE FRAGILE (2 o più aree compromesse)					No ☐	Sì ☒

P.L. Female, caucasian 79 yo

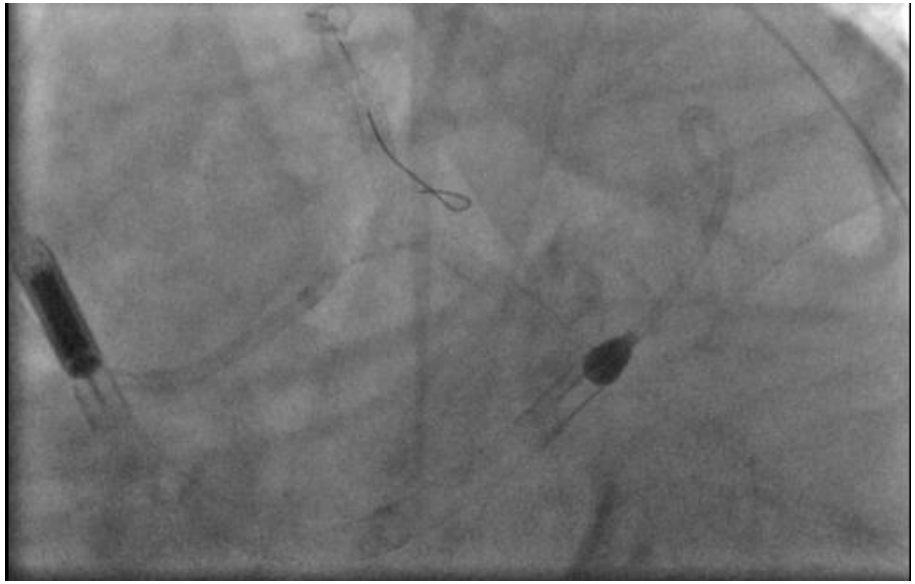
- Microaxial flow pump (Impella CP) up to 3.8 L/min support

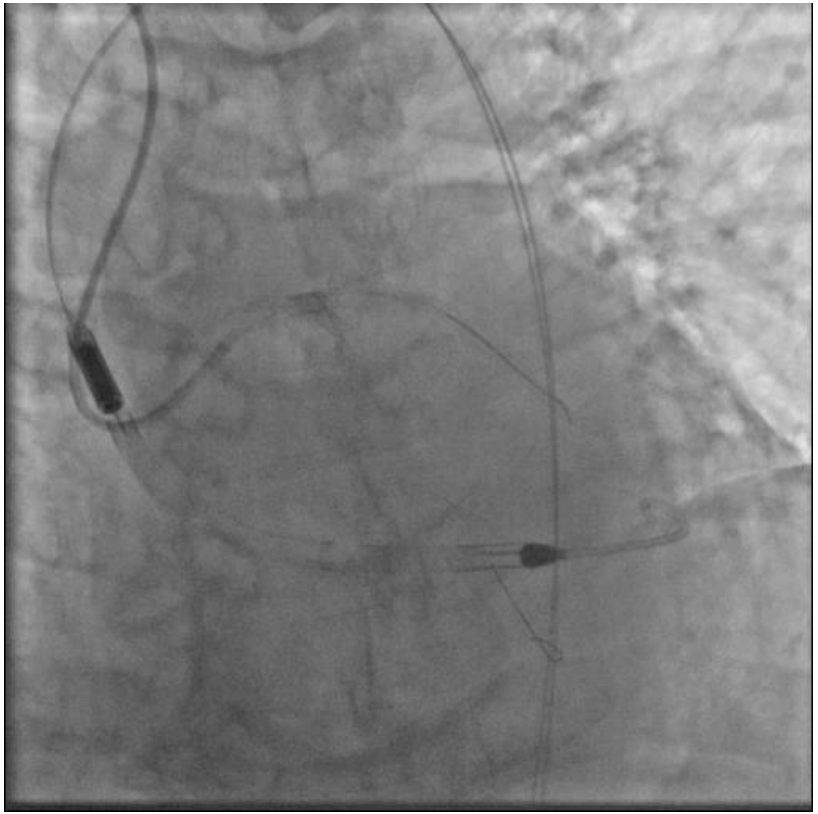




P.L. Female, caucasian 79 yo

- **End procedure, impella kept in for further CCU support**





P.L. Female, caucasian 79 yo

- In CCU→ **depression of cardiac function requiring inotropic support** (Norepinephrine 1,2 ml/h + Levosimendan 1,7 ml/h).

- **11/04: after 48 hours of LV support, UFH stopped and angio-assisted removal of IMPELLA with evidence of stent patency and TIMI flow 3.**

- **12/4:** On IMPELLA removal→ AF + 2 ICD shock on VT (→ Amiodarone) + severe cardio-circulatory depression requiring again inotropic support (Norepinephrine 2 ml / h + Dobutamine up to 4.2 ml/h). **On UFH&DAPT (clopidogrel-ASA)**

- **17/4**: **Speech disturbance → Head CT**: In the left temporo-fronto-parietal areas minimal subarachnoid blood level along the furrows. Hemoventricle in bilateral sites in the occipital horns.
  → **UFH withdrawn**; DAPT maintained after Neurosurgical consultation
  → **Rate control** to minimize cardio-embolic risk.
  After clinical stabilization→ logopedic and neuromotor rehabilitation

Discharged home after 20-day rehabilitation period

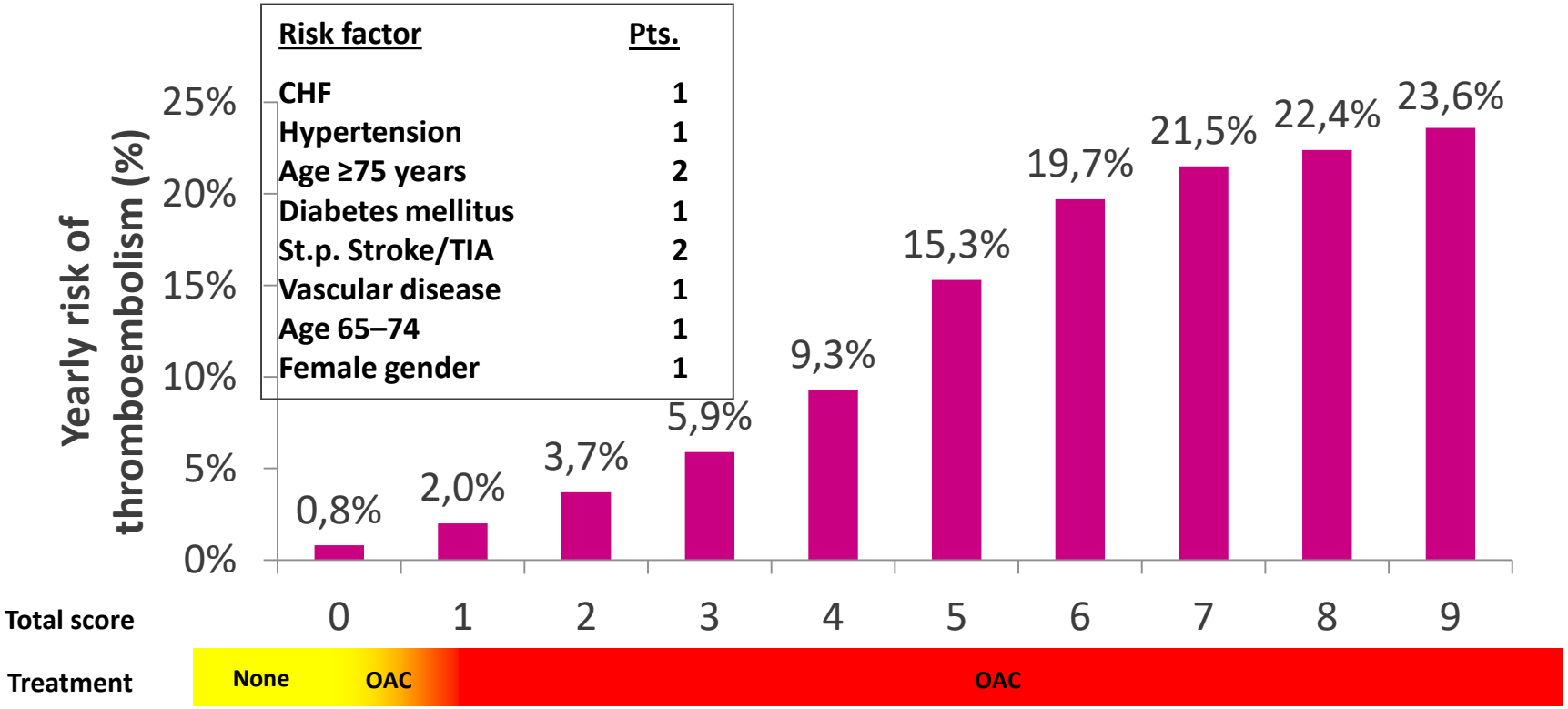
P.L. Female, caucasian 79 yo

CHA_2DS_2-VASc → 7
HAS BLED → 4
RECENT ICH

CORONARY ISCHEMIC RISK: VERY HIGH (8 stents, LM bifurcation stenting)

WHICH ANTITHROMBOTIC COMBINATION?

Frail patients have elevated CHA_2DS_2-VASc scores…



Kirchhof et al. Eur Heart J 2016;37:2893–962
Olesen et al BMJ 2011;342:d124

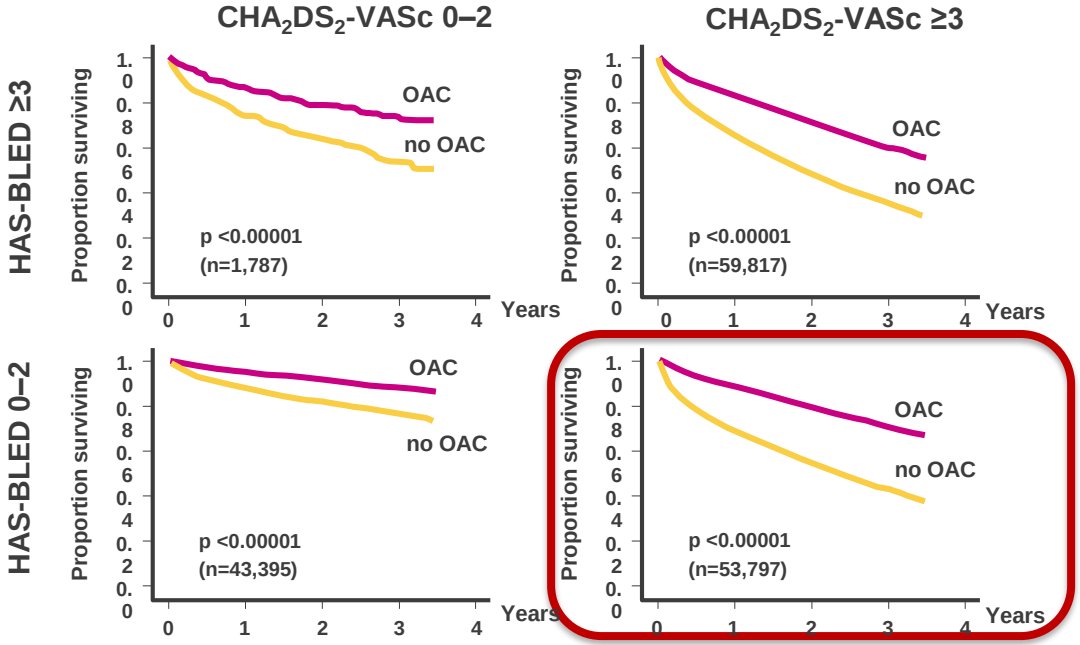
… and HAS-BLED scores

Hypertension BPsyst > 160 mmHg	**1**
Abnormal Liver or kidney levels - Creatinin > 200uml - Transaminases > 3x ULN + Bilirubin > 2x ULN etc.	**e. 1**
St.p. Stroke	**1**
St.p. Bleeding or predisposition (Diathesis, Anemia etc.)	**1**
Labile INR (< 60% TTR)	**1**
Elderly (Alter > 65 Jahre)	**1**
Drugs (NSAIDs, ASS etc.) **or alcohol or drug abuse**	**e. 1**
Max.:	**9 points**

Camm et al. Eur Heart J 2010;31:2369–429

Event-free survival with vs without oral anticoagulant by CHA_2DS_2-VASc and HAS-BLED

- Oral anticoagulation significantly improved event-free survival in patients at high risk of bleeding and of ischaemic events



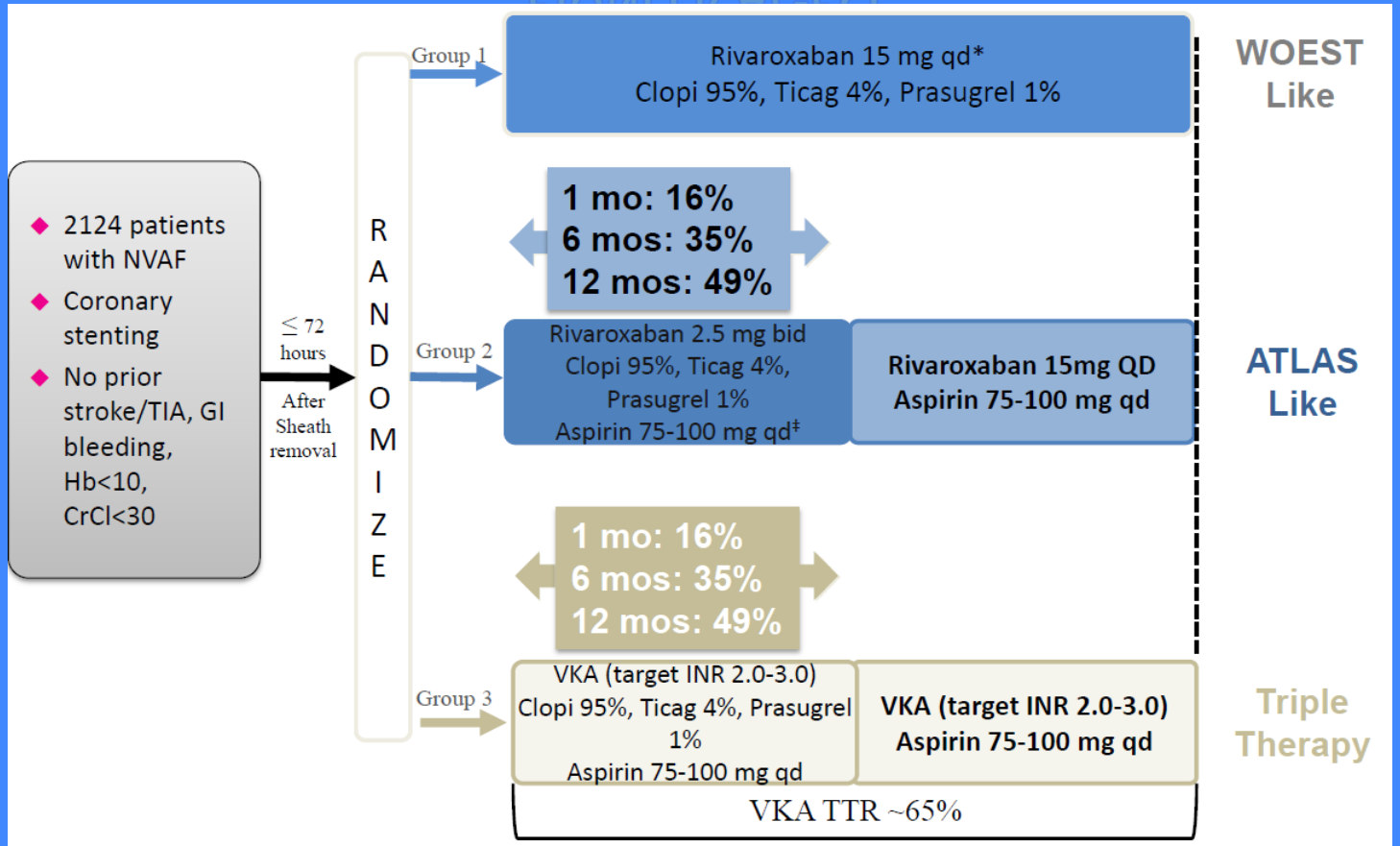
Friberg et al. Eur Heart J 2012;125:2298–307

… and high rates of complex CAD needing PCI

Increasing High Risk Population

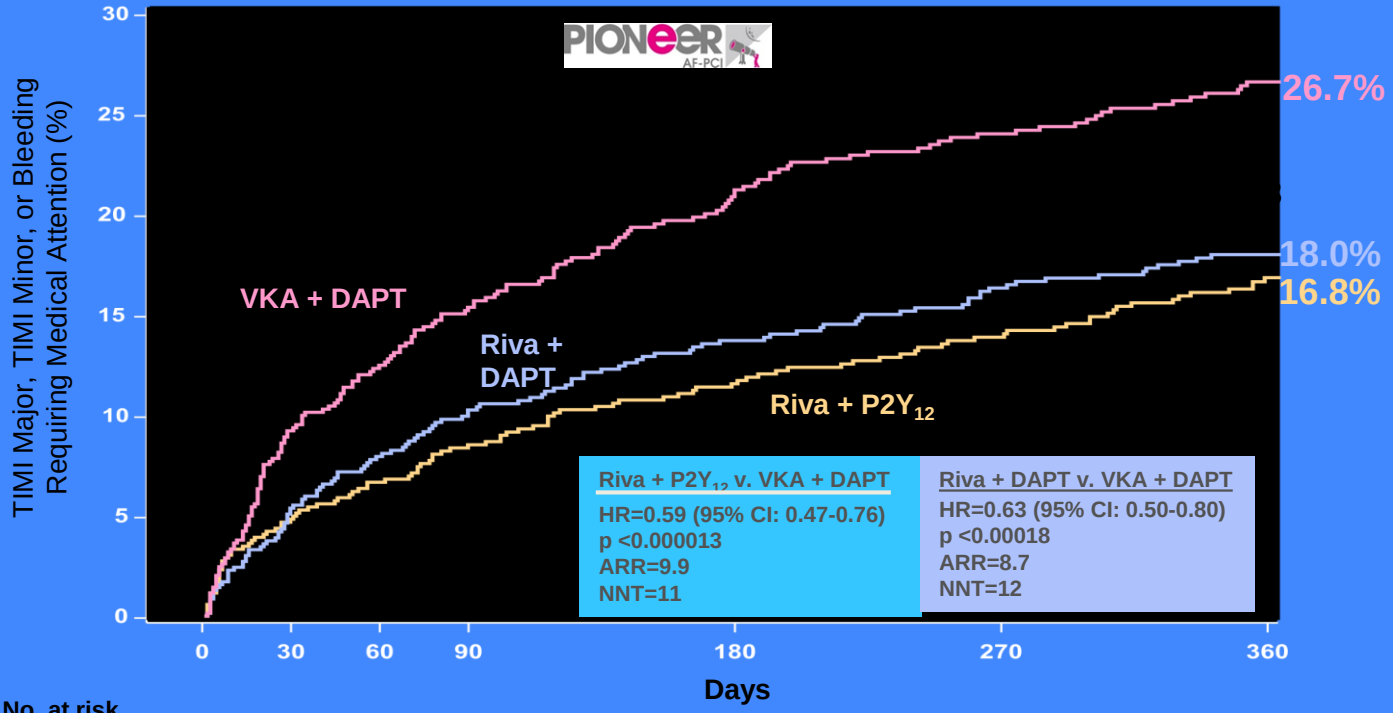
PRE-RANDOMIZATION CHOICE OF DURATION OF DAPT & THIENOPYRIDINE:

PIONEER AF-PCI



PRIMARY ENDPOINT: CLINICALLY SIGNIFICANT BLEEDING

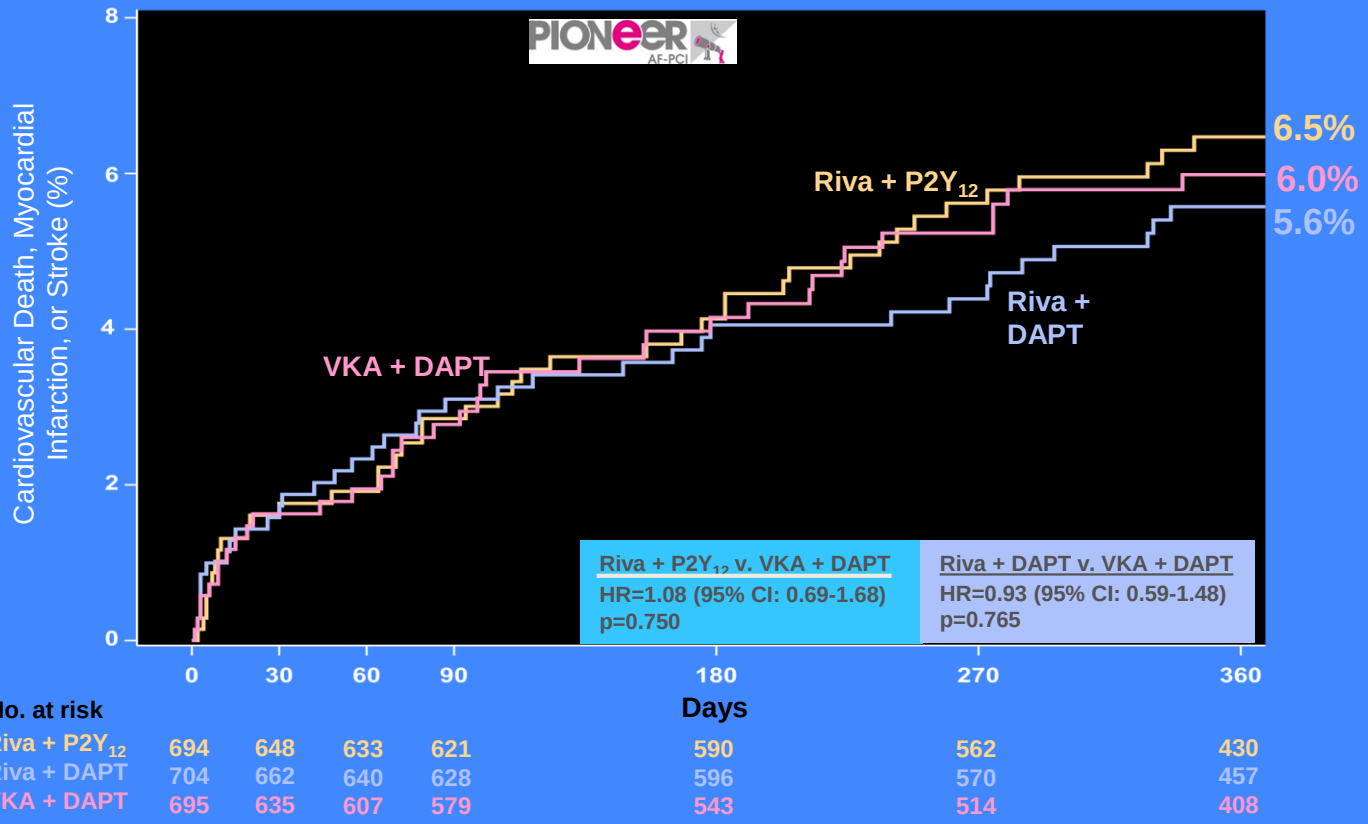
PIONEER AF-PCI



No. at risk

Riva + P2Y12	696	628	606	585	543	510	383
Riva + DAPT	697	598	555	529	461	426	329
VKA + DAPT	697	593	555	521	461	426	329

CV DEATH, MI OR STROKE:
PIONEER AF-PCI



PIONEER AF-PCI: SOME NOTES

Table S1

Sample size and power calculation of major adverse cardiovascular events required to detect a ≥ 15% risk reduction at a two-sided significance level of 0.05

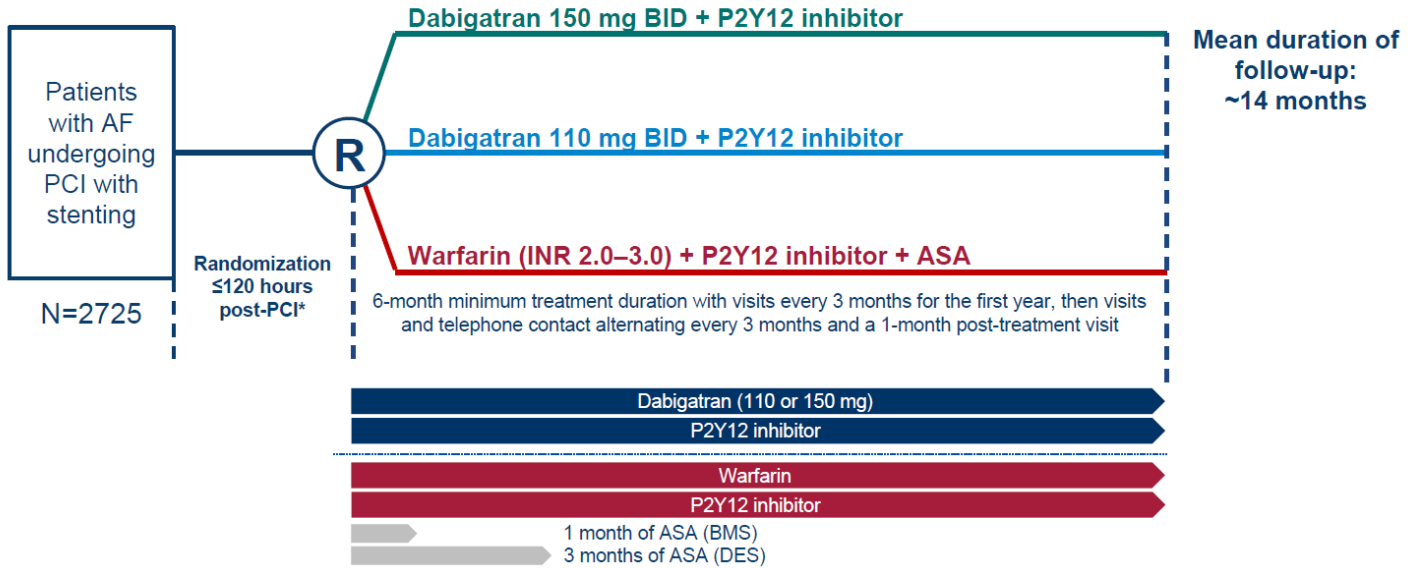
Endpoint	Event rate	No. per group to attain 90% power	Power with 700 subjects per group
Overall			
Adverse CV event	6.0%	13,598	11.4%
CV death	1.8%	47,196	6.8%
MI	3.5%	23,883	8.6%
Stroke	1.2%	71,195	6.2%
Stent thrombosis	0.7%	122,620	5.7%

RE-DUAL PCI

Study in NVAF patients undergoing PCI

Study Design: Multicenter, randomized, open-label trial following a PROBE design

Study in NVAF patients undergoing PCI



***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable).** PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

RE-DUAL PCI

Study in NVAF patients undergoing PCI

Baseline characteristics

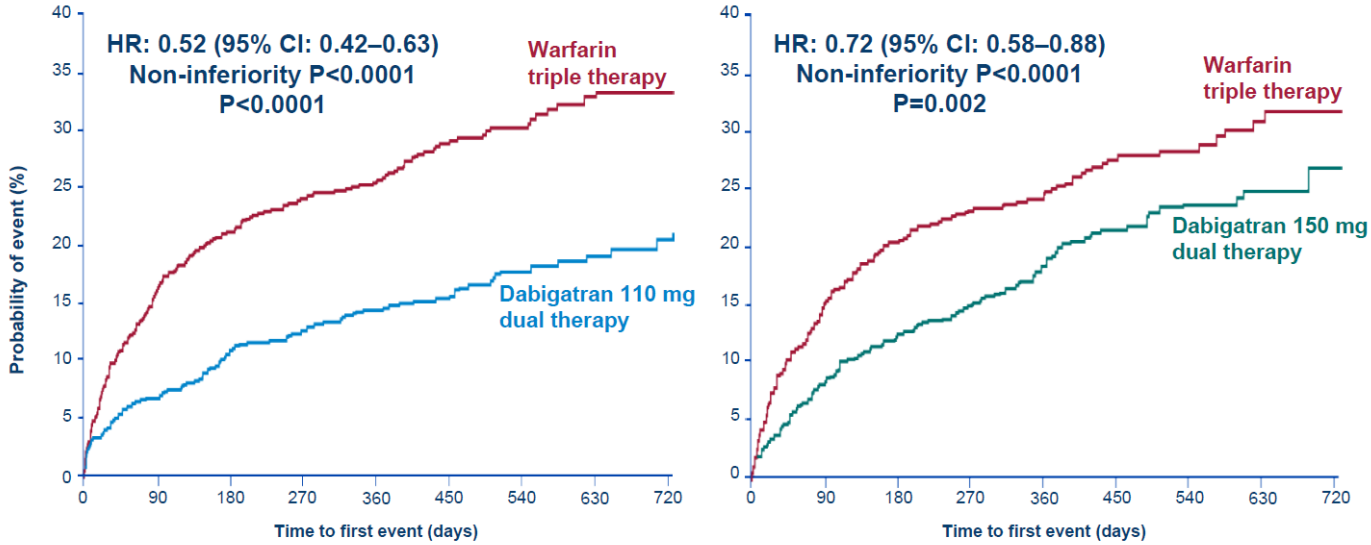
	Dabigatran 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabigatran 150 mg dual therapy (n=763)	Corresponding Warfarin triple therapy (n=764)
Age, years, mean	71.5	71.7	68.6	68.8
≥80 (US, ROW), ≥70 (Japan), %	22.9	22.9	1.0	1.0
<80 (US, ROW), <70 (Japan), %	77.1	77.1	99.0	99.0
Male, %	74.2	76.5	77.6	77.7
Baseline CrCl, mL/min, mean	76.3	75.4	83.7	81.3
Diabetes mellitus, %	36.9	37.8	34.1	39.7
CHA_2DS_2–VASc score (mean)	3.7	3.8	3.3	3.6
Modified HAS-BLED score at baseline (mean)	2.7	2.8	2.6	2.7
ACS indication for PCI, %	51.9	48.4	51.2	48.3
DES only, %	82.0	84.2	81.4	83.5

ROW, rest of world

RE-DUAL PCI

Study in NVAF patients undergoing PCI

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

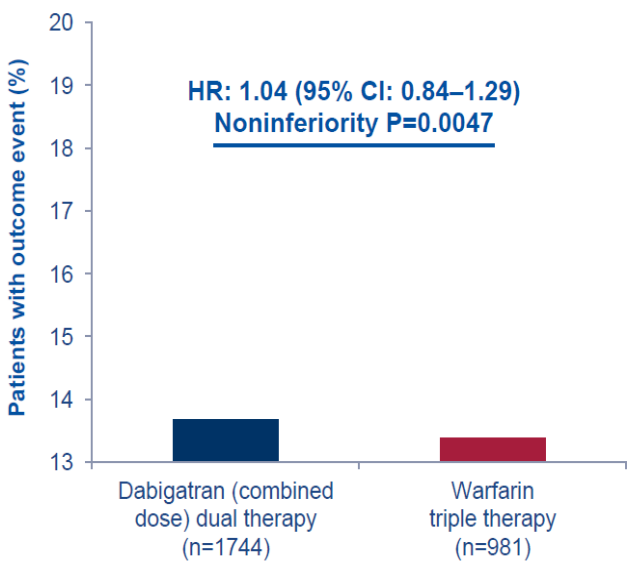


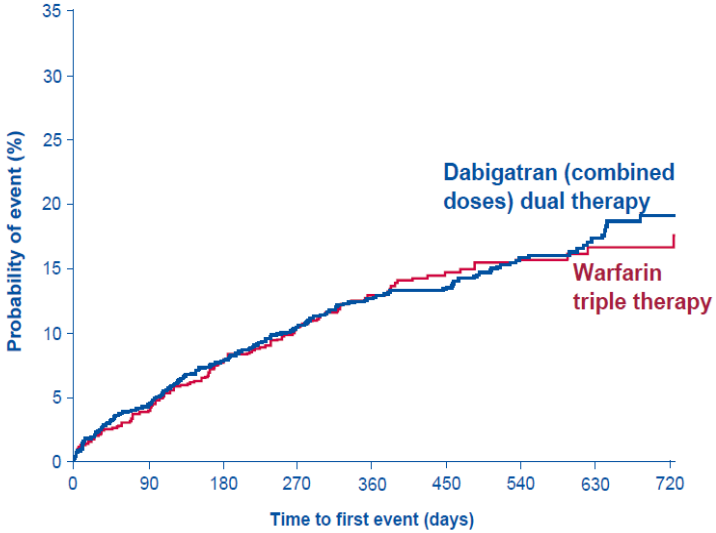
Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

RE-DUAL PCI

Study in NVAF patients undergoing PCI

Dabigatran dual-therapy was non-inferior to warfarin triple therapy in the composite efficacy endpoint





Noninferiority P-value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure testing noninferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularisation. Cannon et al. ESC 2017

RE-DUAL PCI

Study in NVAF patients undergoing PCI

March 2014

The dual primary endpoints for this trial are a composite endpoint of efficacy and a safety endpoint:

1. Time to death or first thrombotic event (DTE) (all death, MI, stroke/SE)
2. Time to first ISTH Major Bleeding Event (MBE)

The secondary endpoints of efficacy are (all time to event endpoints):

1. Individual outcome events:
   - All death
     - Cardiovascular death
     - Non-cardiovascular death
     - Undetermined
   - MI
   - Stroke
   - SE
   - Stent thrombosis
2. Composite endpoint of death + MI + stroke
3. Repeated revascularisation by PCI/CABG

2840 patients in each treatment group (i.e. 8520 randomised patients in total).

July 2016 (after 3 global amendments)

The primary endpoint for this trial is a safety endpoint. See section 5.2.1. There are no primary efficacy endpoints.

The secondary efficacy endpoints (all time to first event) are:

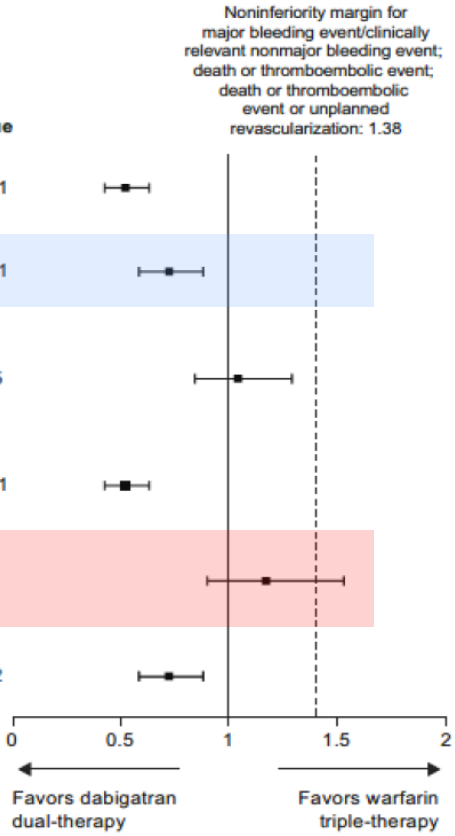
1. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI/CABG
2. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)
3. Individual outcome events:
   - All death
     - Cardiovascular death
     - Non-cardiovascular death
     - Undetermined
   - MI
   - Stroke
   - SE
   - Stent thrombosis
4. Composite endpoint of death + MI + stroke
5. Unplanned revascularisation by PCI/CABG

834 patients in each treatment group (i.e. 2502 randomised patients in total)

RE-DUAL PCI

Study in NVAF patients undergoing PCI

Step	Test	HR (95% CI)	P-value
1	Noninferiority of dabigatran 110 dual-therapy to warfarin triple-therapy in major bleeding event/ clinically relevant nonmajor bleeding event	0.52 (0.42 to 0.63)	<0.001
2	Noninferiority of dabigatran 150 dual-therapy to warfarin triple-therapy* in major bleeding event/ clinically relevant nonmajor bleeding event	0.72 (0.58 to 0.88)	<0.001
3	Noninferiority of dabigatran 150 dual-therapy and dabigatran 110 dual-therapy combined to warfarin triple-therapy in death or thromboembolic event or unplanned revascularization by PCI/CABG	1.04 (0.84 to 1.29)	0.005
4	Superiority of dabigatran 110 dual-therapy to warfarin triple-therapy in major bleeding event/ clinically relevant nonmajor bleeding event	0.52 (0.42 to 0.63)	<0.001
5	Noninferiority of dabigatran 150 dual-therapy and dabigatran 110 dual-therapy combined to warfarin triple-therapy in death or thromboembolic event	1.17 (0.90 to 1.53)	0.11
6	Superiority of dabigatran 150 dual-therapy to warfarin triple-therapy* for major bleeding event/ clinically relevant nonmajor bleeding event	0.72 (0.58 to 0.88)	0.002

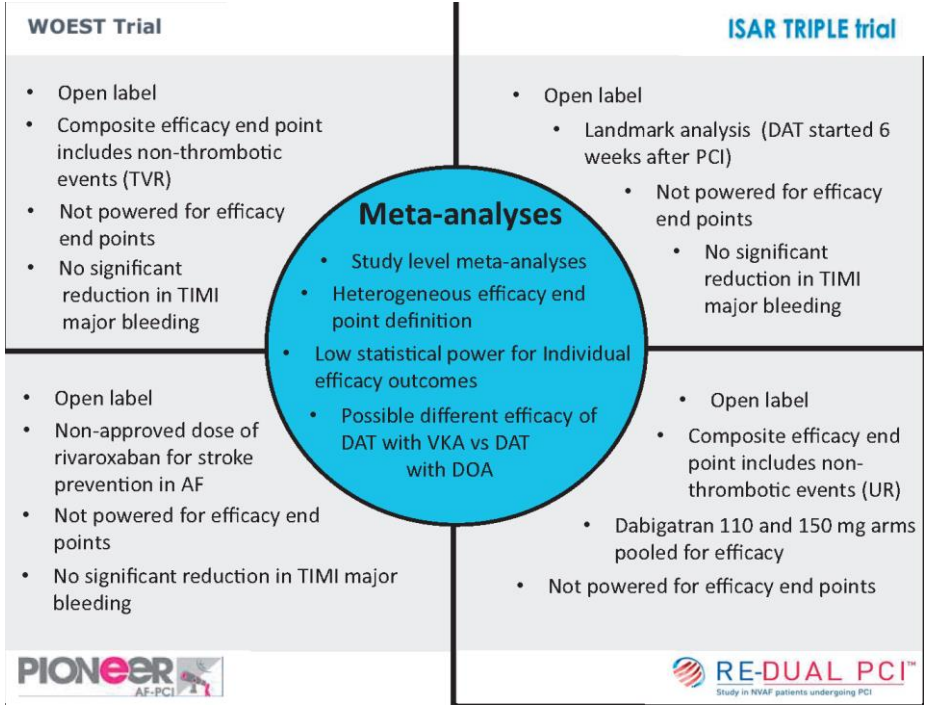


Dropping aspirin in patients with atrial fibrillation undergoing percutaneous coronary intervention: a jump with a weak parachute?

Mattia Galli, Felicita Andreotti, Gianluigi Savarese, Domenico D'Amario, Rocco Vergallo, Roberta Della Bona, Leonardo Calò, Italo Porto ✉, Filippo Crea

European Heart Journal - Cardiovascular Pharmacotherapy, Volume 5, Issue 1, January 2019, Pages 55–56, https://doi.org/10.1093/ehjcvp/pvy039

Published: 05 October 2018



Augustus

Prospective, multicenter, two-by-two factorial, randomized clinical trial

INCLUSION
- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned $P2Y_{12}$ inhibitor for ≥6 months

Randomize
n=4600 patients

EXCLUSION
- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, moderate / severe mitral stenosis)

Apixaban 5 mg BID
Apixaban 2.5 mg BID in selected patients

Open Label

VKA
(INR 2–3)

Aspirin for all on the day of ACS or PCI and before randomization

Aspirin — *Double Blind* — **Placebo**

Aspirin — *Double Blind* — **Placebo**

Primary outcome: ISTH major / CRNM bleeding
Secondary outcome(s): death / hospitalization, death / ischemic events

Lopes RD, et al. Am Heart J. 2018;200:17-23.

Baseline Characteristics

Augustus

	Total (N=4614)
Age, median (25^{th}, 75^{th}), years	70.7 (64.2, 77.2)
Female, %	29.0
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)
HAS-BLED score, mean (SD)	2.9 (0.9)
Prior OAC, %	49.0
$P2Y_{12}$ inhibitor, %	
Clopidogrel	92.6
Prasugrel	1.1
Ticagrelor	6.2
Number of days from ACS/PCI to randomization, mean (SD)	6.6 (4.2)
Qualifying index event, %	
ACS and PCI	37.3
ACS and no PCI	23.9
Elective PCI	38.8

The NEW ENGLAND JOURNAL of MEDICINE

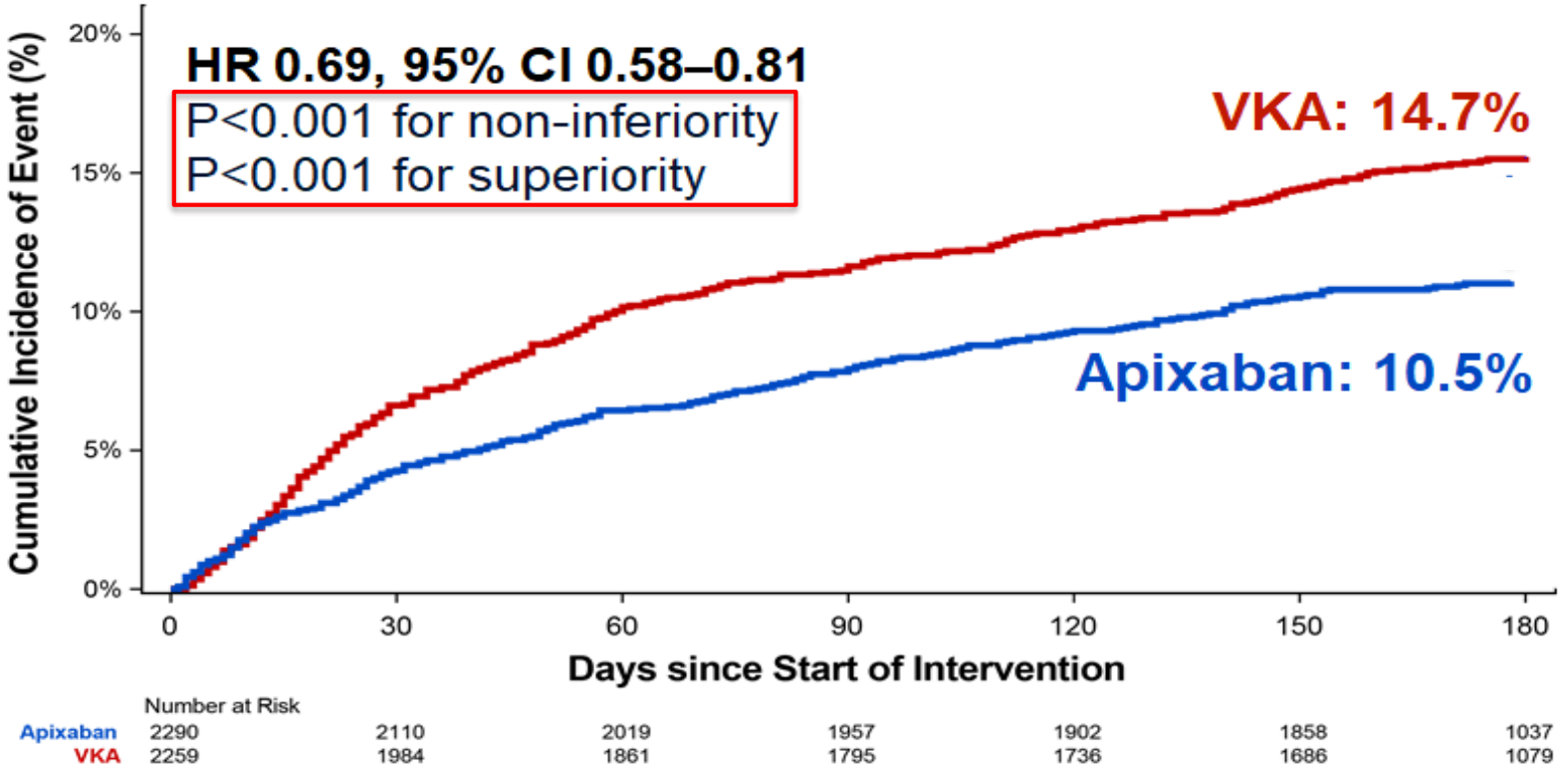
AUGUSTUS: due ipotesi indipendenti

NEI PAZIENTI CON FANV E SCA E/O SOTTOPOSTI A PCI
TRATTATI CON UN $P2Y_{12}$ INIBITORE (*)

1. Apixaban non è inferiore, ma possibilmente superiore, a VKA per emorragia maggiore o non maggiore clinicamente rilevante (CRNM) indipendentemente dall'associazione con ASA
2. L'Aspirina è inferiore al placebo per emorragia maggiore o non maggiore clinicamente rilevante (CRNM) nei pazienti in terapia anticoagulante orale (OAC)

APRIL 18, 2019 - N ENGL J MED 2019; 380:1509-1524

Major / CRNM Bleeding Apixaban verso VKA



The NEW ENGLAND JOURNAL of MEDICINE

AUGUSTUS: due ipotesi indipendenti

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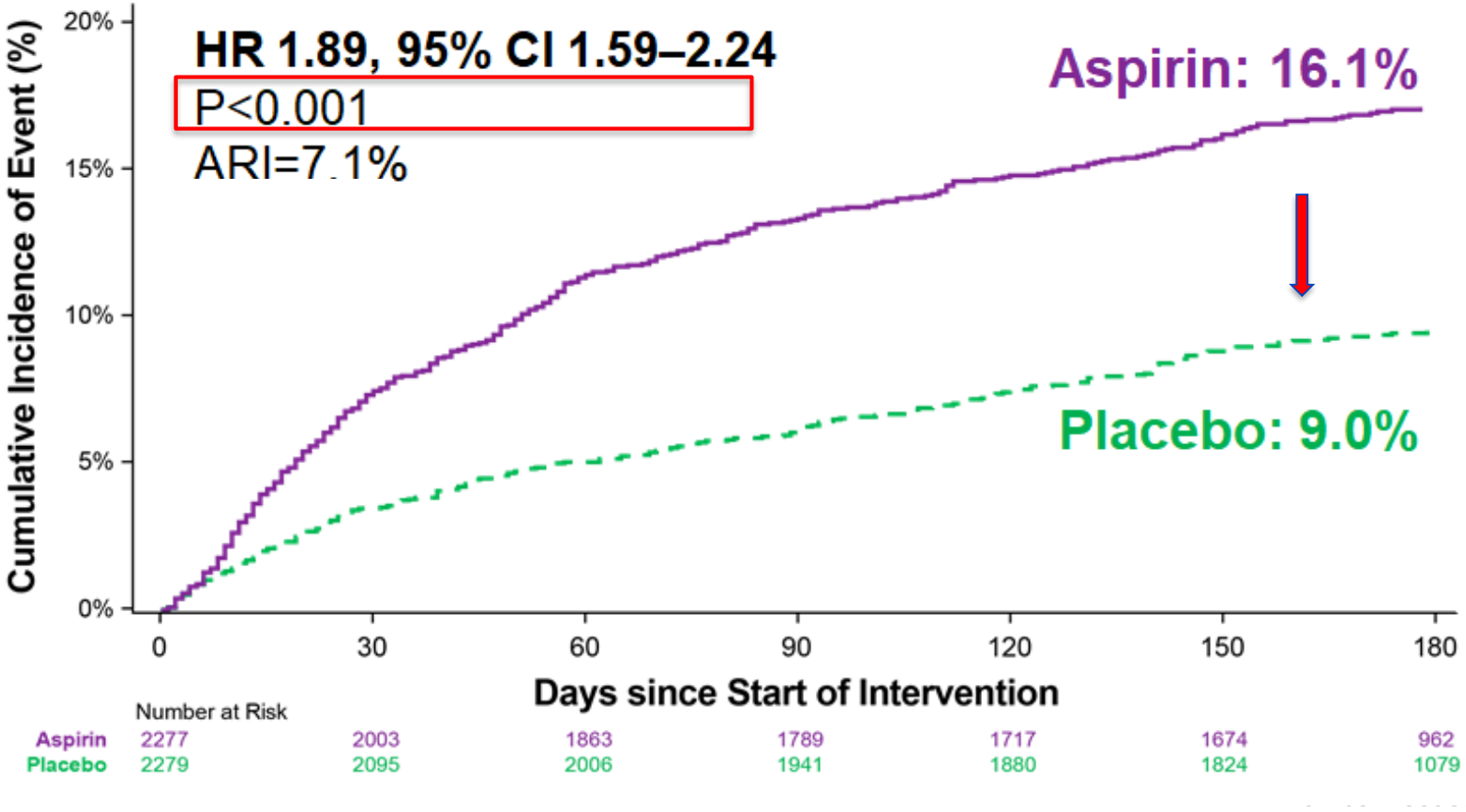
APRIL 18, 2019 - N ENGL J MED 2019; 380:1509-1524

Major / CRNM Bleeding

Aspirin verso Placebo

Augustus



ase

harm

Ischemic Outcomes

Aspirin verso Placebo

Augustus

Endpoint	Aspirin (N=2307)	Placebo (N=2307)	HR (95% CI)
Death / Ischemic Events (%)	6.5	7.3	0.89 (0.71–1.11)
Death (%)	3.1	3.4	0.91 (0.66–1.26)
CV Death (%)	2.3	2.5	0.92 (0.63–1.33)
Stroke (%)	0.9	0.8	1.06 (0.56–1.98)
Myocardial Infarction (%)	2.9	3.6	0.81 (0.59–1.12)
Definite or Probable Stent Thrombosis (%)	0.5	0.9	0.52 (0.25–1.08)
Urgent Revascularization (%)	1.6	2.0	0.79 (0.51–1.21)
Hospitalization (%)	25.4	23.4	1.10 (0.98–1.24)

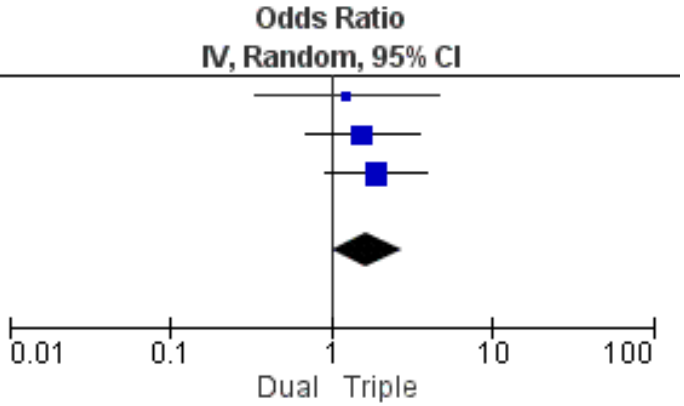
Dual therapy with direct oral anticoagulants significantly increases the risk of stent thrombosis compared to triple therapy

Mattia Galli, Felicita Andreotti, Domenico D'Amario, Rocco Vergallo, Rocco A Montone, Italo Porto ✉, Filippo Crea

European Heart Journal - Cardiovascular Pharmacotherapy, pvz030,
https://doi.org/10.1093/ehjcvp/pvz030
Published: 16 July 2019

Study or Subgroup	Dual Events	Dual Total	Triple Events	Triple Total	Weight	Odds Ratio IV, Random, 95% CI	Year
PIONEER AF PCI	5	694	4	695	14.5%	1.25 [0.34, 4.69]	2016
REDUAL PCI	22	1744	8	981	38.3%	1.55 [0.69, 3.50]	2017
AUGUSTUS	21	2279	11	2277	47.2%	1.92 [0.92, 3.98]	2019
Total (95% CI)		**4717**		**3953**	**100.0%**	**1.66 [1.01, 2.75]**	
Total events	48		23				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.35$, $df = 2$ ($P = 0.84$); $I^2 = 0\%$
Test for overall effect: $Z = 1.98$ ($P = 0.05$)



ENTRUST-AF-PCI Study Design

PROBE design: prospective, randomized, open label, blinded evaluation edoxaban based regimen vs VKA based regimen in N ≅ 1500 AF patients

12 months: end of treatment

Inclusion Criteria:
- OAC indication for AF for at least 12 months
- Successful PCI with stent placement (goal of at least 25% ACS)

4 hours – 5 days after sheath removal

RANDOMIZE

*Edoxaban 60 mg/day**

*$P2Y_{12}$ antagonist** (without ASA)*

*Vitamin K Antagonist****

*$P2Y_{12}$ antagonist (ASA 1 - 12 months)*****

Primary outcome: *ISTH major and clinically relevant non-major bleeding*

*Edoxaban dose reduction to 30 mg OD
- if CrCL≤50 ml/min
- BW≤60 kg
- certain P-gp inhibitors

**Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily . Predeclared at randomization

*** VKA, target INR 2-3

****ASA 100mg OD for 1-12 months guided by clinical presentation (ACS or stable CAD), CHA_2DS-$VASc_2$ and HAS_BLED

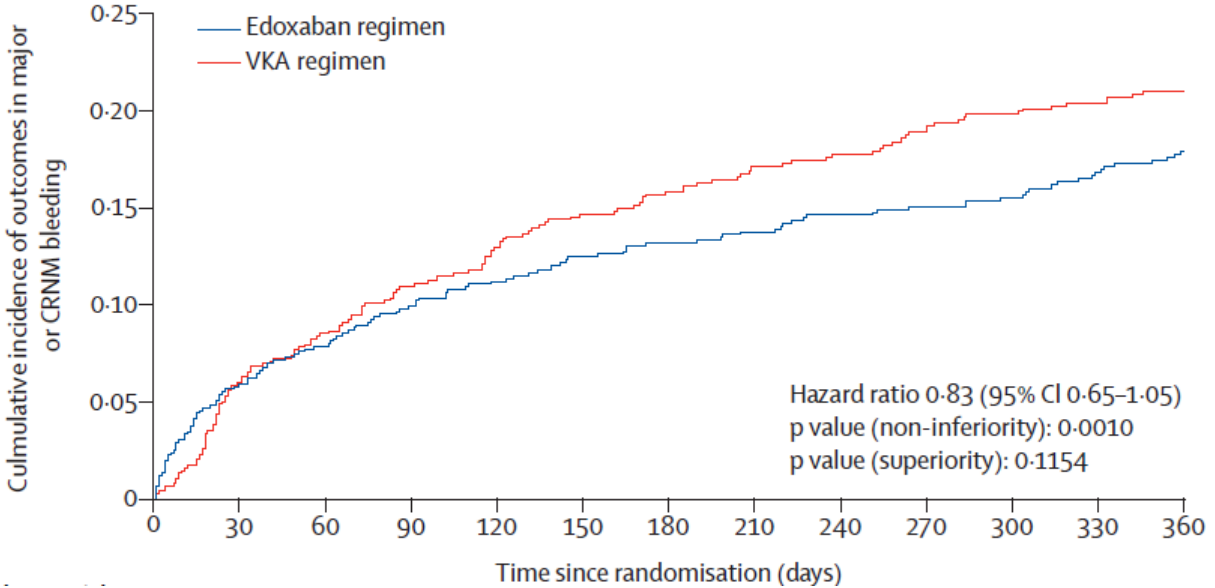
ClinicalTrials.gov Identifier: NCT02866175

Caratteristiche demografiche baseline

	Edoxaban regimen N = 751	VKA regimen N = 755
Age (years), median (Q1; Q3)	69 (63; 77)	70 (64; 77)
Sex. female	194 (26)	192 (25)
Weight (kg), median (Q1; Q3)	80 (71; 93)	83 (72; 94)
Type of AF, n (%)		
Paroxysmal	402 (54)	358 (47)
Persistent	140 (19)	146 (19)
Long-standing persistent or permanent	209 (28)	250 (33)
CHA_2DS_2-VASc score, median (Q1; Q3)	4.0 (3; 5)	4.0 (3; 5)
HAS-BLED score, median (Q1; Q3)	3.0 (2; 3)	3.0 (2; 3)
CrCl (mL/min)[a], median (Q1; Q3)	71.8 (53.7, 91.1)	71.7 (54.0, 90.9)
Clinical presentation, n (%)		
ACS	388 (52)	389 (52)
SCAD	363 (48)	366 (49)
OAC prio the index PCI, n (%)	408 (68.0)	413 (65.1)
Time (hours) between end of PCI and randomization, median (Q1; Q3)	45.1 (22.3; 75.6)	44.8 (22.1; 76.5)
Type of $P2Y_{12}$ antagonist, n (%)		
Clopidogrel	696 (92.8)	695 (92.1)
Prasugrel o Ticagrelor	54 (7.2)	60 (7.9)

[a]The minimum of the recalculated local lab CrCl and the recalculated central lab CrCl value has been used.
Data are presented as n (%) unless otherwise noted. Data are for the intention to treat analysis set (N = 1506).
Vranckx, P, et al. *Lancet.* 2019.

Outcome primario di sanguinamento (ITT analysis)

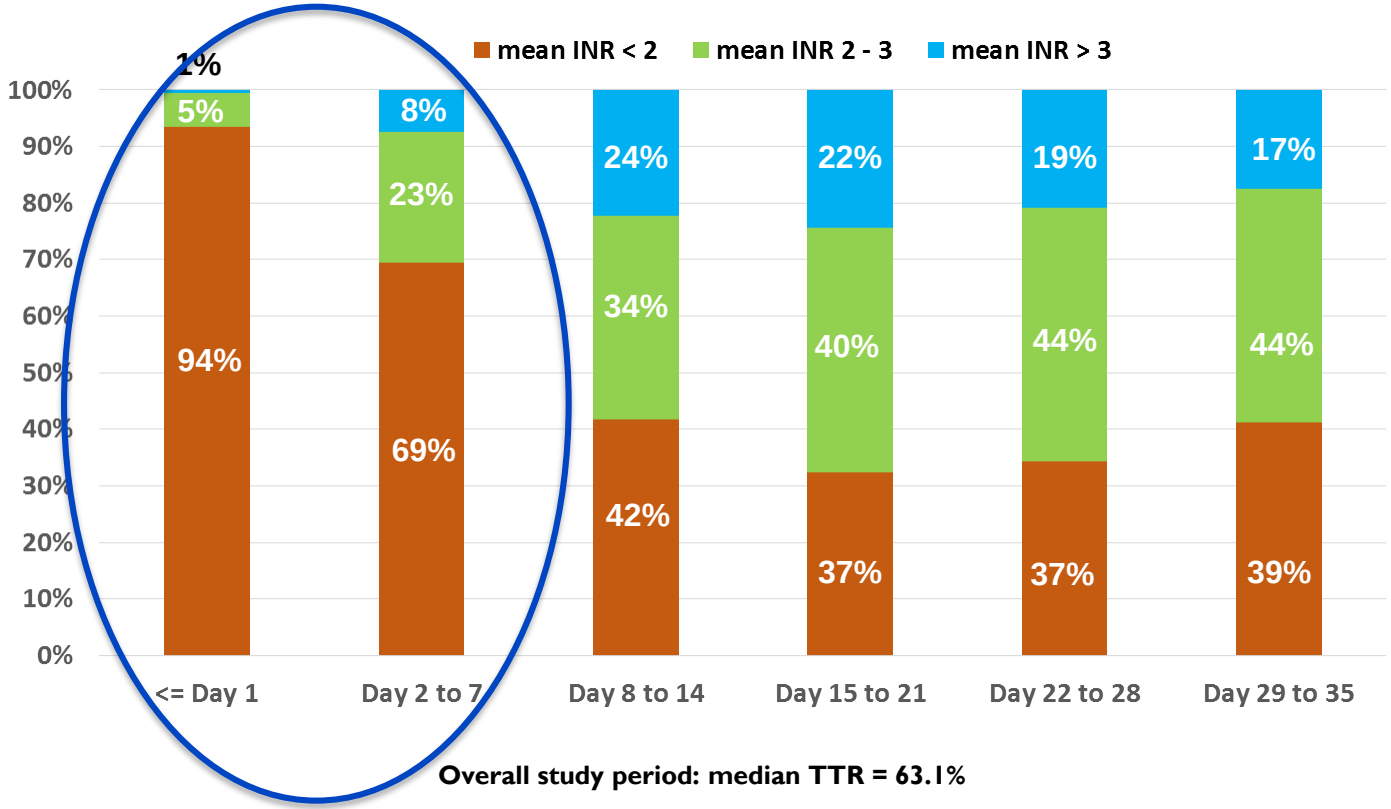


	Edoxaban regimen	VKA regimen
Intent-to-treat analysis		
Number of patients	751	755
Number of patients with event (%)	128 (17)	152 (20)
Annualized event rate (% per year)	20.7	25.6

ITT population (N = 1506); overall study period.
Vranckx, P, et al. *Lancet.* 2019.

INR nel braccio VKA nelle prime 5 settimane

Time from PCI to Randomisation:
- median – 45 h



Vranckx, P, et al. *Lancet.* 2019.

Overall RCTs testing dual versus triple antithrombotic therapy

Trial	Year	Study design	Sample size	Follow-up duration	Population	Time to randomisation	Treatment group (DAT)	Control group (TAT)	TIMI major bleeding	Myocardial infarction	Stent thrombosis
WOEST	2013	Randomised, open-label	573	1 year	PCI: 100% ACS: 27% AF: 69%	≤ 4 hours	VKA + clopidogrel	VKA + clopidogrel + aspirin	0.56 (0.25–1.27)	0.69 (0.29–1.60)	0.44 (0.14–1.44)
ISAR-TRIPLE	2015	Randomised, open-label (landmark-analysis)	614	9 months	PCI: 100% ACS: 32% AF: 84%	6 weeks	VKA + aspirin	VKA + clopidogrel + aspirin)	1.01 (0.35-2.88)	7.39 (0.15- 372.41)	No events
PIONEER AF-PCI	2016	Randomised, open-label	1389 (2124)	1 year	PCI: 100% ACS: 40% AF: 100%	≤ 3 days	Rivaroxaban 15 mg + clopidogrel (95%)	VKA + clopidogrel + aspirin	0.66 (0.33-1.31)	0.86 (0.46-1.59)	1.20 (0.32-4.45)
RE-DUAL PCI	2017	Randomised, open-label	2725	1 year	PCI: 100% ACS: 50% AF: 100%	≤ 5 days	Dabigatran 110/150 mg bid + clopidogrel (88%)	VKA + clopidogrel + aspirin	0.45 (0.27-0.73)	1.36 (0.88, 2.11)	1.51 (0.67, 3.41)
AUGUSTUS	2019	Randomised open-label (aspirin vs placebo double-blind)	4614 (2306)	6 month	PCI: 76% ACS: 62% AF: 100%	≤ 15 days	VKA/apixaban 5 mg bid + clopidogrel (93%)	VKA/apixaban 5 mg bid + clopidogrel + aspirin	0.52 (0.33-0.82)	1.24 (0.89-1.72)	1.91 (0.92-3.98)
ENTRUST-AF-PCI	2019	Randomised, open-label	1506	1 year	PCI: 100% ACS: 52% AF: 100%	≤ 5 days	Edoxaban 60 mg daily + clopidogrel (92%)	VKA + clopidogrel + aspirin	0.62 (0.32-1.18)	1.26 (0.72-2.16)	1.32 (0.46-3.79)

JAMA Cardiology | Original Investigation

Safety and Efficacy of Antithrombotic Strategies in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

A Network Meta-analysis of Randomized Controlled Trials

Renato D. Lopes, MD, PhD[1]; Hwanhee Hong, PhD[1]; Ralf E. Harskamp, MD, PhD[2]; et al

eTable 7. Network meta-analysis data: sample size and the number of participants who had each outcome in each study

Treatment	WOEST		PIONEER AF-PCI			RE-DUAL PCI			AUGUSTUS				ISAR-TRIPLE*	
	VKA + $P2Y_{12}$ inhibitor	VKA + DAPT	NOAC + $P2Y_{12}$ inhibitor	NOAC + DAPT	VKA + DAPT	NOAC (L) + $P2Y_{12}$ inhibitor	NOAC (H) + $P2Y_{12}$ inhibitor	VKA + DAPT	NOAC + DAPT	NOAC + $P2Y_{12}$ inhibitor	VKA + DAPT	VKA + $P2Y_{12}$ inhibitor	VKA + Aspirin	VKA + DAPT
Safety Outcome														
N (ITT)	279	284	696	706	697	981	763	981	1145	1143	1123	1126	307	307
TIMI (Major)	9	16	14	12	20	14	16	37	25	13	29	18	7	7
TIMI (Major and Minor)	39	89	21	19	33	29	27	69	64	32	80	51		
Trial-defined primary bleeding outcome	54	126	109											
Intracranial hemorrhage	3	3	3											
Efficacy outcome														
N (ITT)	279	284	694											
Trial-defined primary MACE outcome	31	50	41											
All cause death	7	18	16											
Cardiovascular death	3	7	15											
MI (Any)	9	13	17											
Stroke (Any)	3	8	8											
Stent thrombosis (Any)	4	9	5											
Hospitalization (Any)	60	86	221**											

VKA=Vitamin K Antagonist; DAPT=Dual AntiPlatelet Therap

Outcome	Anticoagulant-Regimen Comparison			Antiplatelet-Regimen Comparison		
	Apixaban	Vitamin K Antagonist	Hazard Ratio (95% CI)	Aspirin	Placebo	Hazard Ratio (95% CI)
Efficacy outcomes						
No. of patients in analysis	2306	2308		2307	2307	
Myocardial infarction						
No. of patients with event (%)	72 (3.1)	80 (3.5)	—	68 (2.9)	84 (3.6)	—
Event rate per 100 patient-yr	6.6	7.4	0.89 (0.65–1.23)	6.3	7.8	0.81 (0.59–1.12)
ARC definite or probable stent thrombosis						
No. of patients with event (%)	14 (0.6)	18 (0.8)	—	11 (0.5)	21 (0.9)	—
Event rate per 100 patient-yr	1.3	1.6	0.77 (0.38–1.56)	1.0	1.9	0.52 (0.25–1.08)
Urgent revascularization						
No. of patients with event (%)	40 (1.7)	44 (1.9)	—	37 (1.6)	47 (2.0)	—
Event rate per 100 patient-yr	3.7	4.1	0.90 (0.59–1.38)	3.4	4.3	0.79 (0.51–1.21)

tot 32

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. Lopes R, NEJM 2019

Intracranial Haemorrhages versus Stent Thromboses

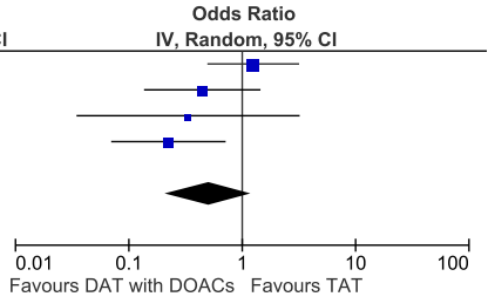
with Direct Oral Anticoagulant plus Single Antiplatelet Agent or Triple Antithrombotic Therapy

Intracranial haemorrhage

Study or Subgroup	DAT with DOACs Events	Total	TAT Events	Total	Weight	Odds Ratio IV, Random, 95% CI
AUGUSTUS	10	2279	8	2277	33.7%	1.25 [0.49, 3.17]
ENTRUST-AF-PCI	4	751	9	755	27.2%	0.44 [0.14, 1.45]
PIONEER AF-PCI	1	694	3	695	11.5%	0.33 [0.03, 3.21]
RE-DUAL PCI	4	1744	10	981	27.6%	0.22 [0.07, 0.71]
Total (95% CI)		**5468**		**4708**	**100.0%**	**0.50 [0.21, 1.19]**
Total events	19		30			

Heterogeneity: Tau² = 0.35; Chi² = 5.61, df = 3 (P = 0.13); I² = 47%

Test for overall effect: Z = 1.56 (P = 0.12)

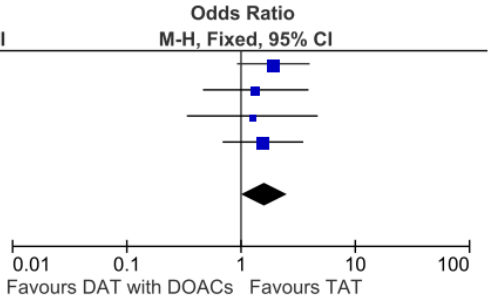


Stent thrombosis

Study or Subgroup	DAT with DOACs Events	Total	TAT Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AUGUSTUS	21	2307	11	2307	35.3%	1.92 [0.92, 3.99]
ENTRUST-AF-PCI	8	751	6	755	19.2%	1.34 [0.46, 3.89]
PIONEER AF-PCI	5	694	4	695	12.8%	1.25 [0.34, 4.69]
RE-DUAL PCI	22	1744	8	981	32.7%	1.55 [0.69, 3.50]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.60 [1.02, 2.52]**
Total events	56		29			

Heterogeneity: Chi² = 0.47, df = 3 (P = 0.92); I² = 0%

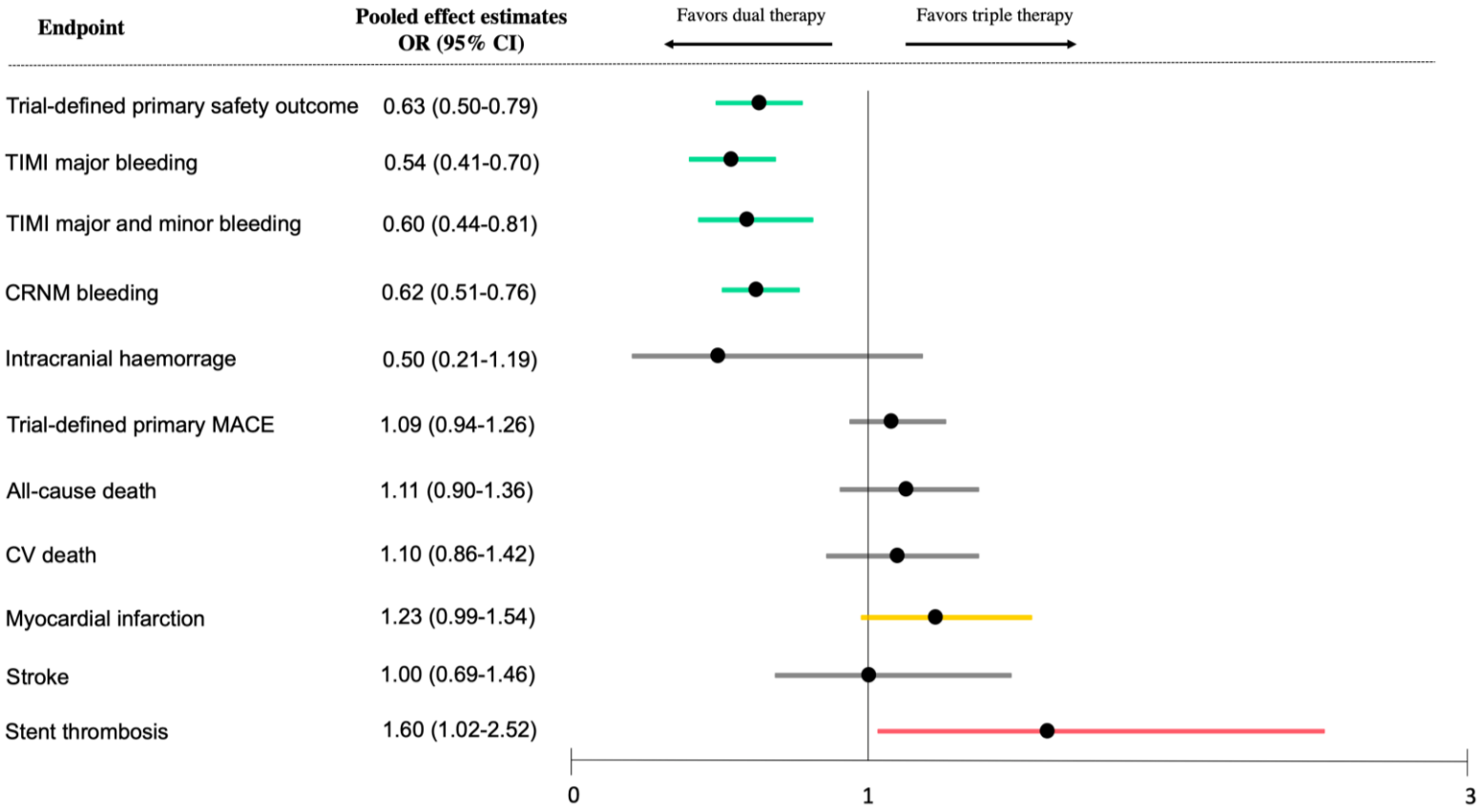
Test for overall effect: Z = 2.04 (P = 0.04)



Galli M, Andreotti F, Porto I, Crea F. Under revision

Intracranial Haemorrhages versus Stent Thromboses

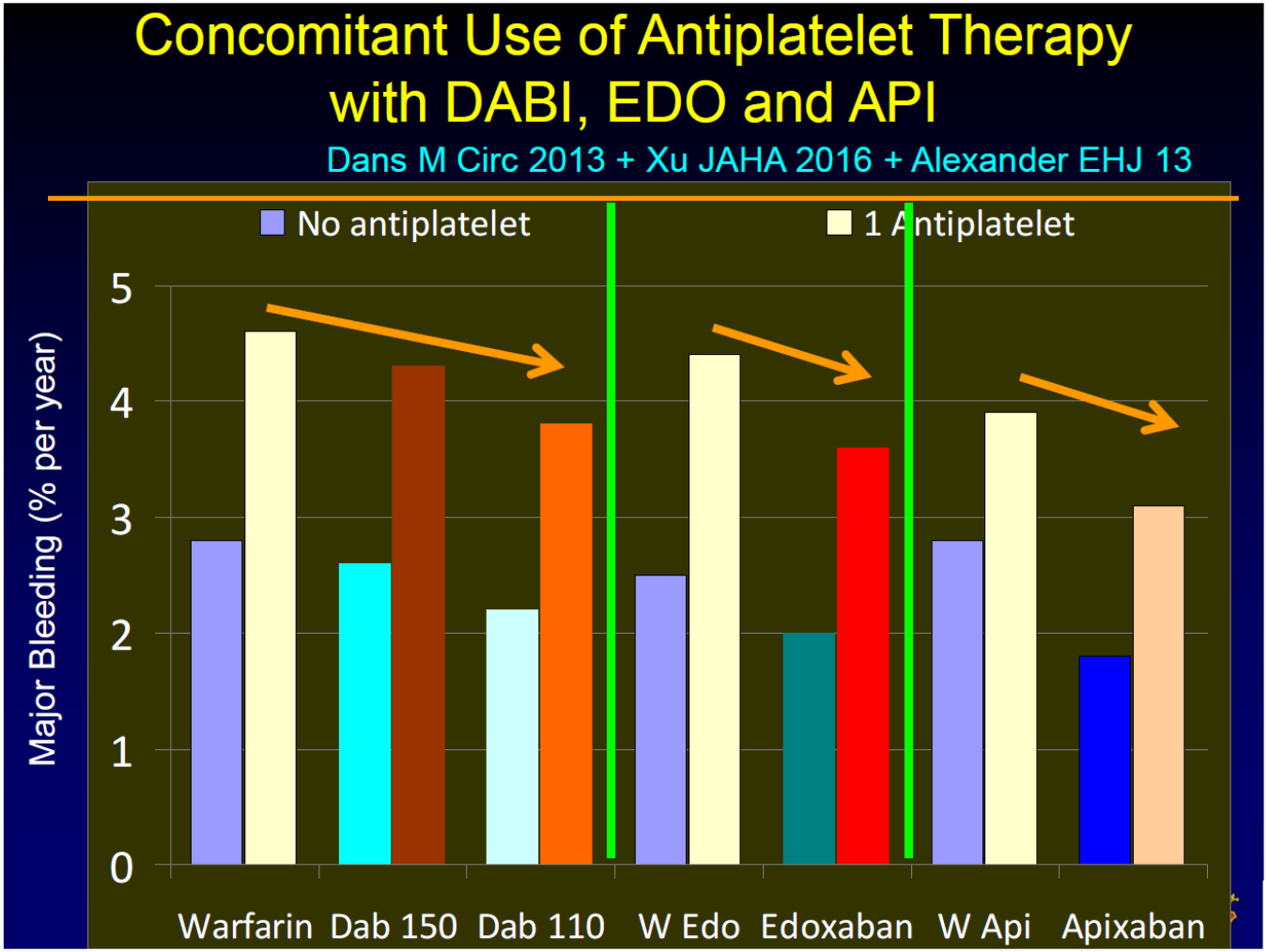
with Direct Oral Anticoagulant plus Single Antiplatelet Agent or Triple Antithrombotic Therapy



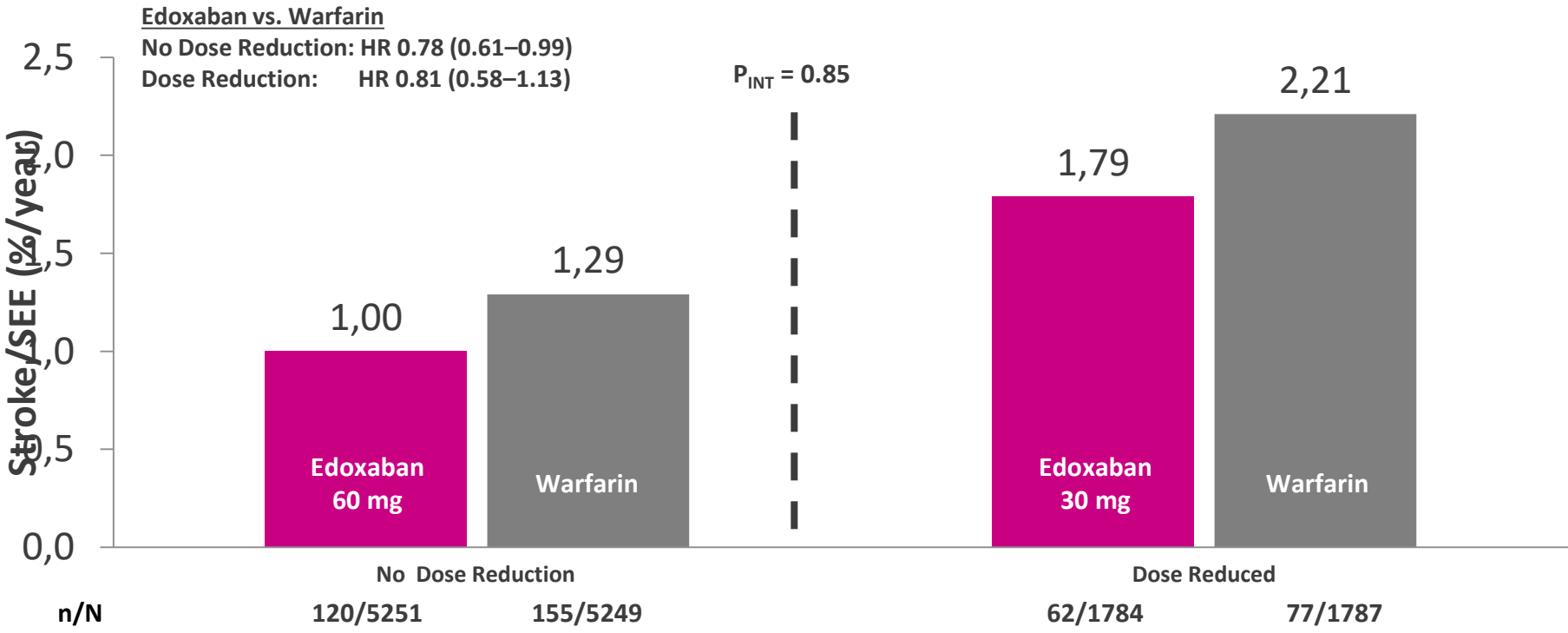
Galli M, Andreotti F, Porto I, Crea F. Under revision

Concomitant Use of Antiplatelet Therapy with DABI, EDO and API

Dans M Circ 2013 + Xu JAHA 2016 + Alexander EHJ 13

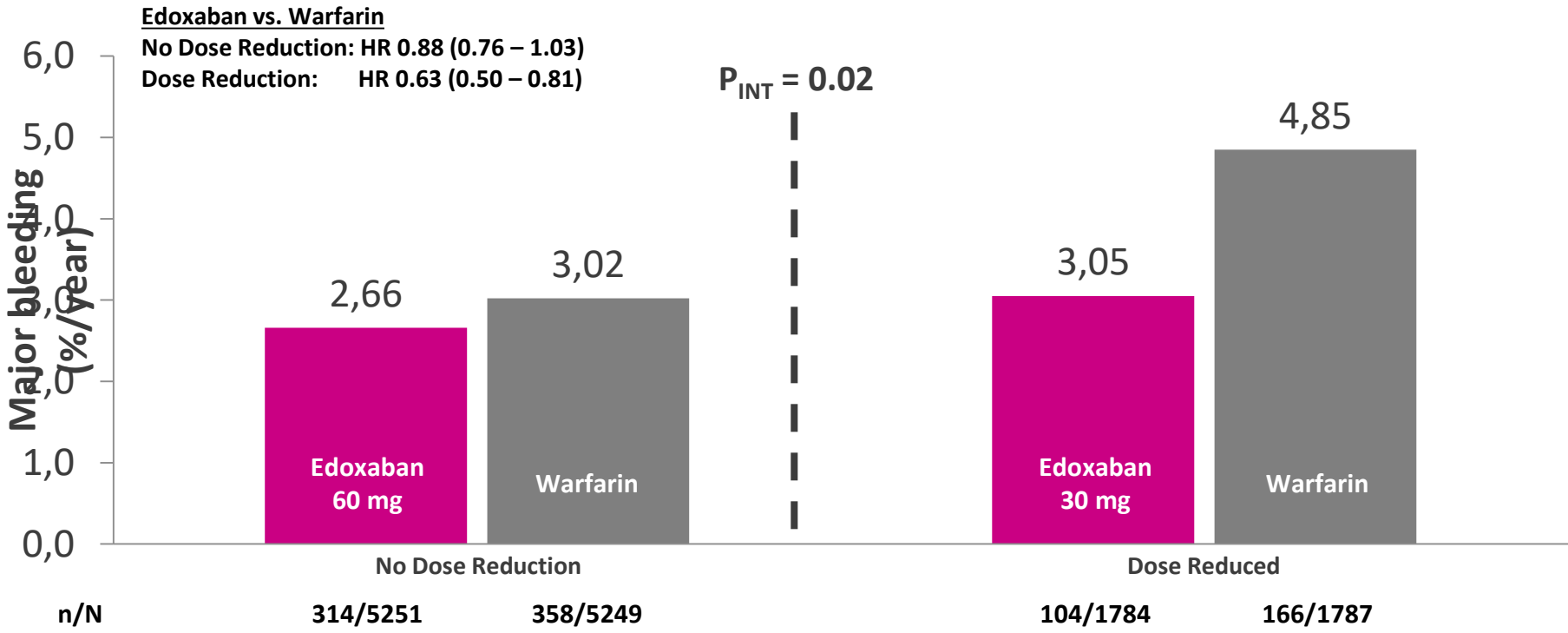


Efficacy is maintained with dose reduction



Ruff et al. Lancet. 2015;385:2288–95

Dose reduction enhances safety relative to warfarin



Ruff et al. Lancet. 2015;385:2288–95

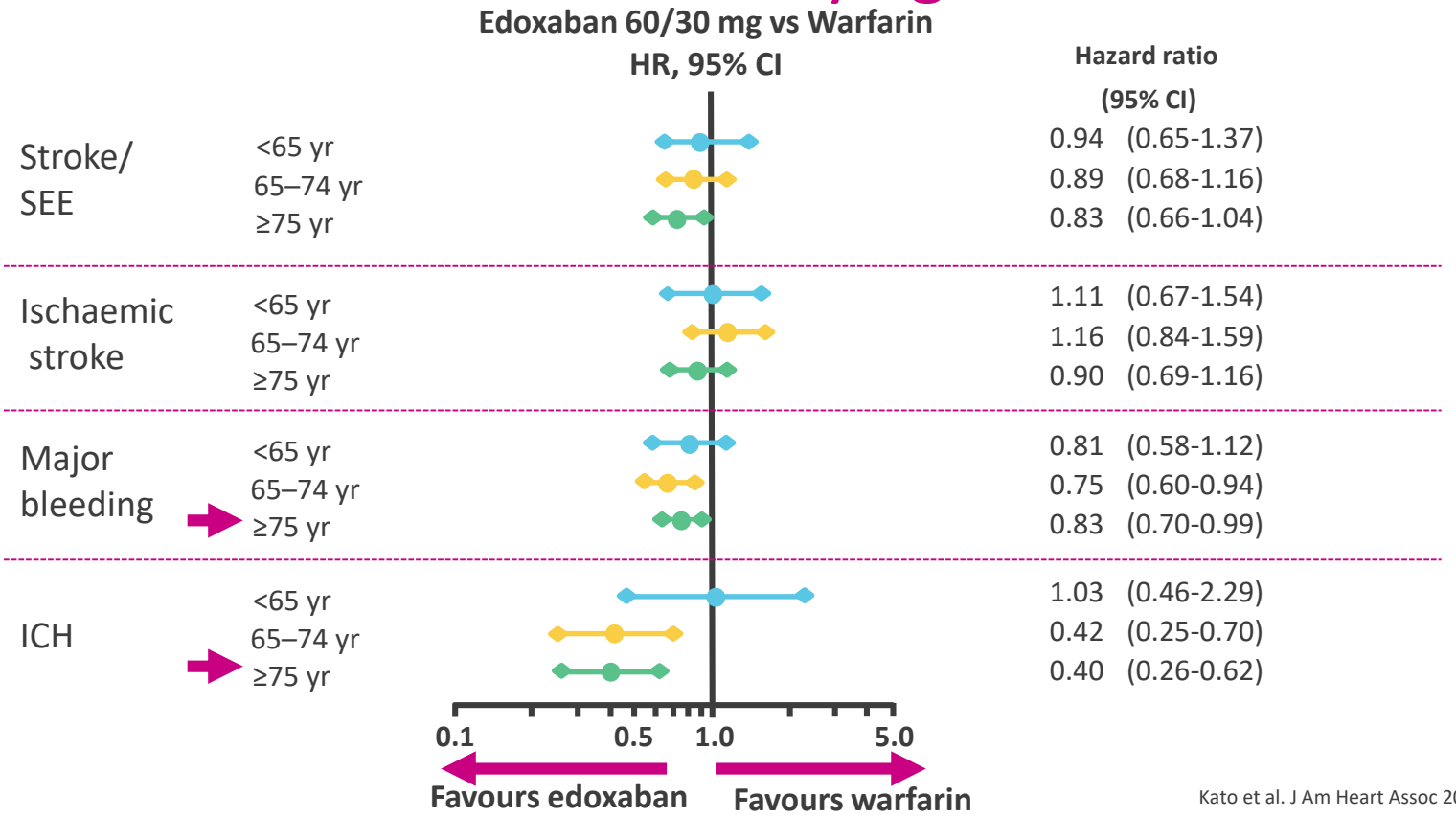
Elderly patients in ENGAGE AF-TIMI 48

- In a pre-specified analysis of elderly patients from ENGAGE AF-TIMI 48 patients were stratified into three age categories:
  - <65 years (26%, n=5,497)
  - 65–74 years (34%, n=7,134)
  - ≥75 years (40%, n=8,474)

	<65 years	65–74 years	≥75 years
Median age, years (interquartile)	59 (55–62)	70 (67–72)	79 (76–82)
Prior stroke or TIA , N (%)	1520 (28)	2334 (33)	2119 (25)
CHA_2DS_2-VASc score, mean (SD)	3.2 (1.1)	4.4 (1.1)	5.0 (1.3)
CHA_2DS_2-VASc score 4–9, N (%)	1815 (33)	5626 (79)	7478 (88)
HAS-BLED score ≥3, N (%)	894 (16)	4129 (58)	4779 (56)
Dose reduced at randomisation, N (%)	571 (10)	1297 (18)	3488 (41)

Kato et al. J Am Heart Assoc 2016;5:e003432

Efficacy and safety of edoxaban vs warfarin by age



Kato et al. J Am Heart Assoc 2016;5:e003432

P.L. Female, caucasian 76 yo

- Sinus Rhythm + Paroxysmal Atrial Fibrillation
- CHA_2DS_2-VASc → 7
- HAS BLED → 4

Edoxaban 30 mg + clopidogrel (after 1 month of aspirin)

Conclusions

DAT (with DOACs) as compared to TAT (with DOACs) confers a significant reduction of major bleeding rates. Overall ischaemic events do not differ significantly, except for the risk of stent thrombosis that is increased significantly (by 60% in our metanalysis) with DAT.

This should be taken into account in very complex PCIs in fragile patients, as the patients included in the DAT vs. TAT trials were “good” patients.

Choice among DOACS for fragile patients is difficult: edoxaban (OD, reduced dose can be often given, equally effective-less bleeding, good for frail patients at risk of falls) and apixaban (after AUGUSTUS, especially without aspirin in DAT) can be good choices.

Think about LAA closure!!!

Thanks to Mattia Galli & Myriana Ponzo

OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Thank you

UNIVERSITÀ DEGLI STUDI
DI GENOVA