Conoscere e Curare il Cuore 2018

VENERDI' 16 MARZO

IL TRAMONTO DELLA TRIPLICE TERAPIA NELLA FIBRILLAZIONE ATRIALE

Piera Capranzano

Unità di Cardiologia
Ospedale Ferrarotto, Catania
Università degli Studi di Catania

AF and Coronary Stents: Key Concepts

Atrial Fibrillation (ACTIVE-W)

"The combination of aspirin and clopidogrel is not as effective as **warfarin** in patients with atrial fibrillation"

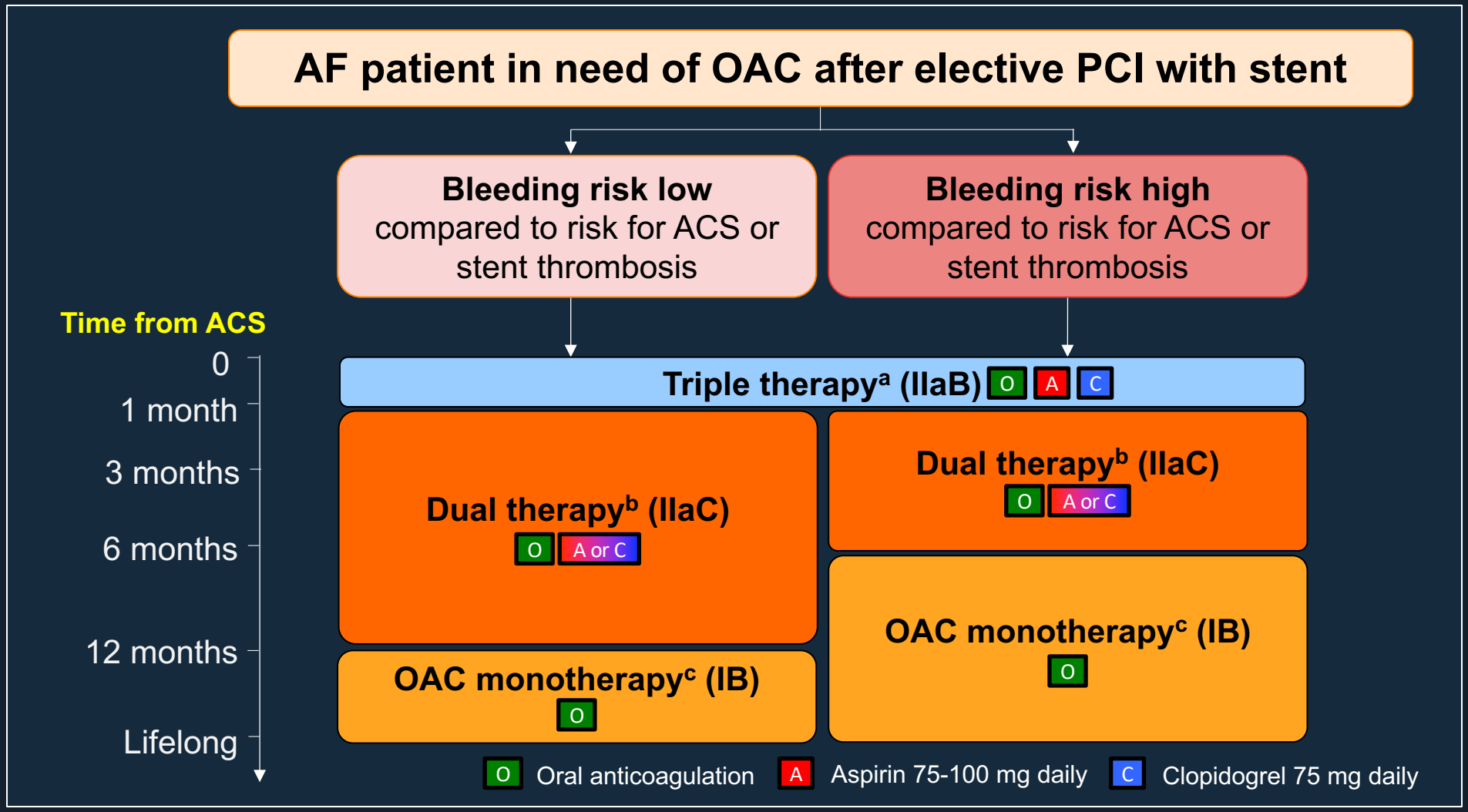
Coronary Stenting (STARS)

"The combination of **aspirin and a thienopyridine** is more effective than warfarin in patients with coronary stents"

UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Connolly S, et al. Lancet. 2006;367:1903-12
Leon MB, et al, N Engl J Med 1998;339:1665-71

Antithrombotic therapy in PCI patients on OAC

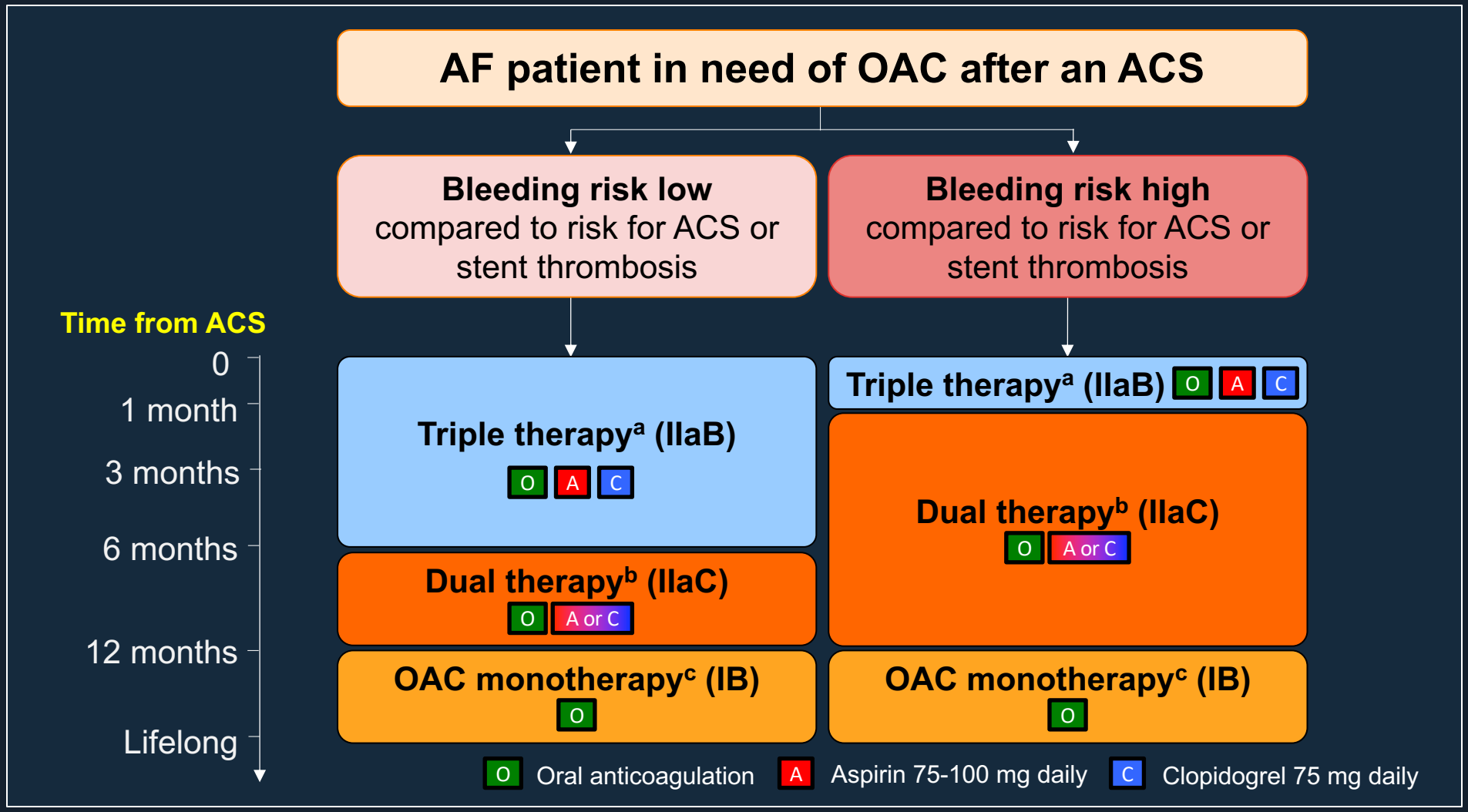


[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients, especially those not receiving a stent or patients at a longer time from the index event. [b]OAC plus single antiplatelet. [c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Kirchhof P et al. Eur Heart J 2016

Antithrombotic therapy in ACS patients on OAC



[a]Dual therapy with OAC and aspirin or clopidogrel may be considered in selected patients. [b]OAC plus single antiplatelet. [c]Dual therapy with OAC and an antiplatelet agent (aspirin or clopidogrel) may be considered in patients at high risk of coronary events.

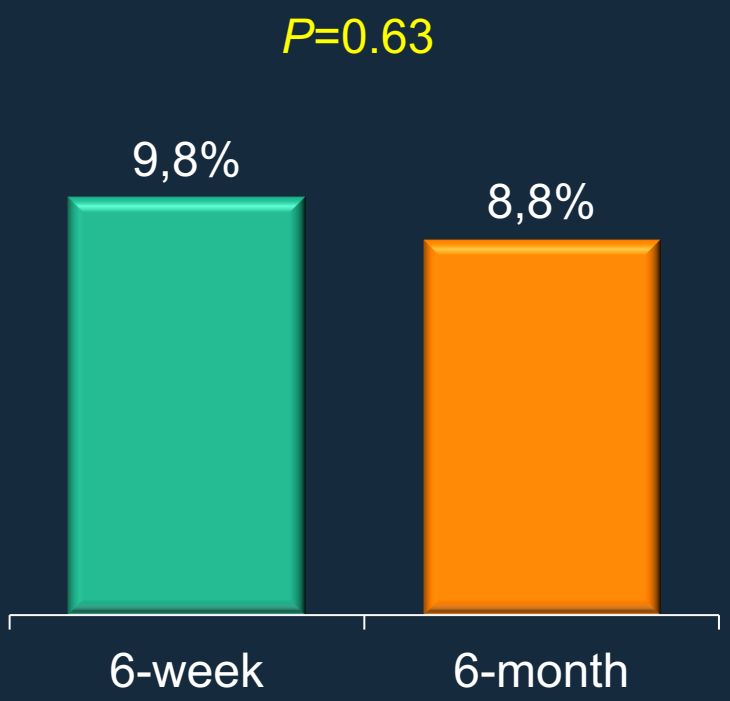
UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Kirchhof P et al. Eur Heart J 2016

ISAR-TRIPLE: Shorter vs Longer Triple Therapy

614 PCI patients with DES on OAT (only 32% ACS, STEMI 0.8%))

Death, MI, ST, stroke or TIMI major bleeding



	6-week	6-month	*P* value
CV death	1.7%	3.0%	0.29
MI	2.0%	0	0.03
Definite ST	0.7%	0	0.50
Ischemic stroke	1.0%	1.3%	0.99
TIMI major bleeding	5.3%	4.0%	0.44

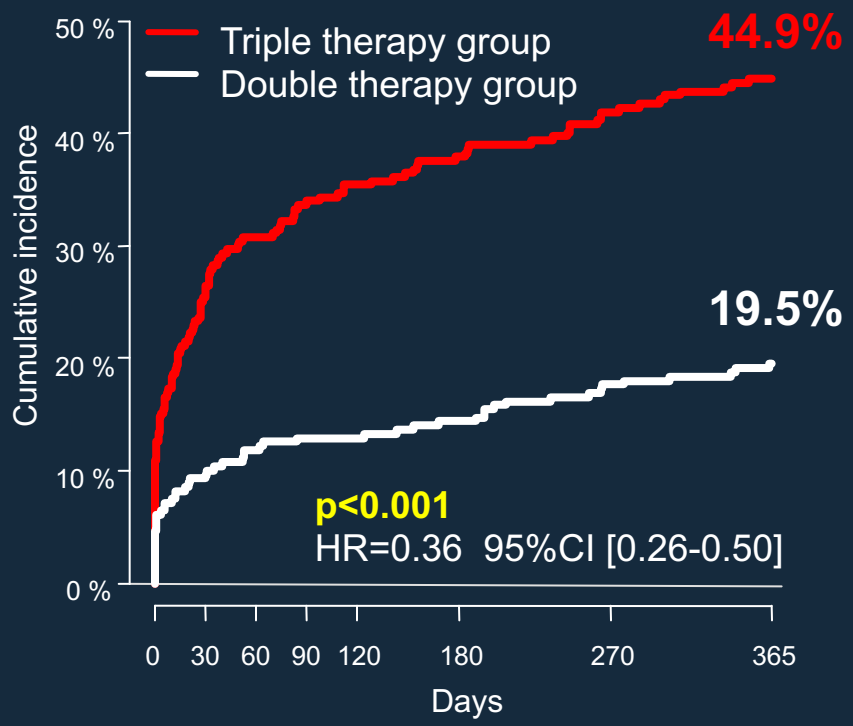
UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Fiedlrer KA, et al. J Am Coll Cardiol 2015;65:1619–29

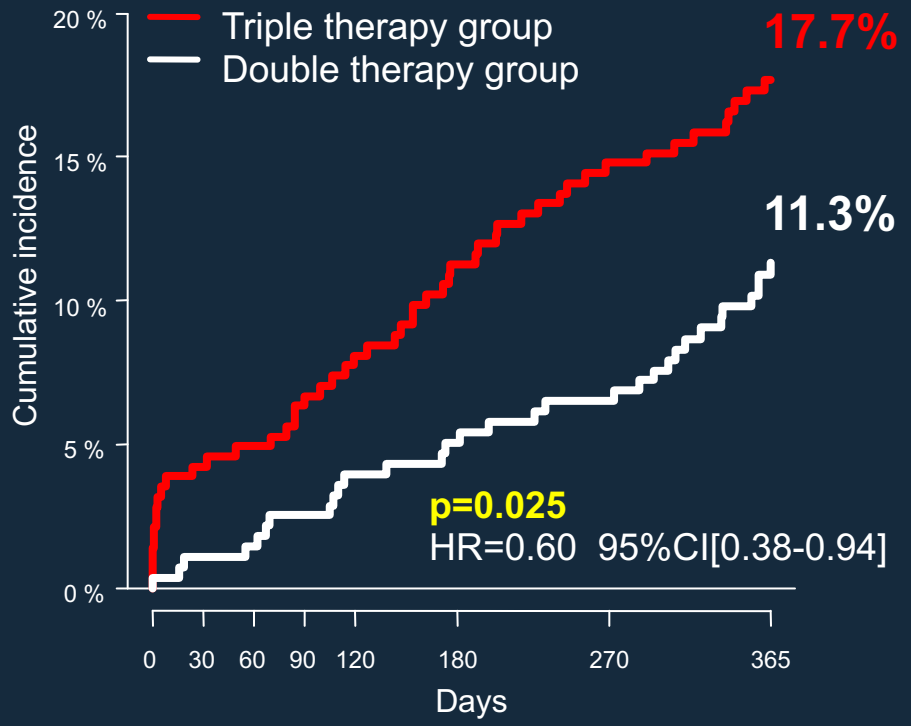
WOEST: Triple vs Dual Therapy

573 patients on oral anticoagulation undergoing PCI

Any TIMI Bleeding (Primary Endpoint)



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



UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Dewilde WJ et al. Lancet. 2013;381:1107-15

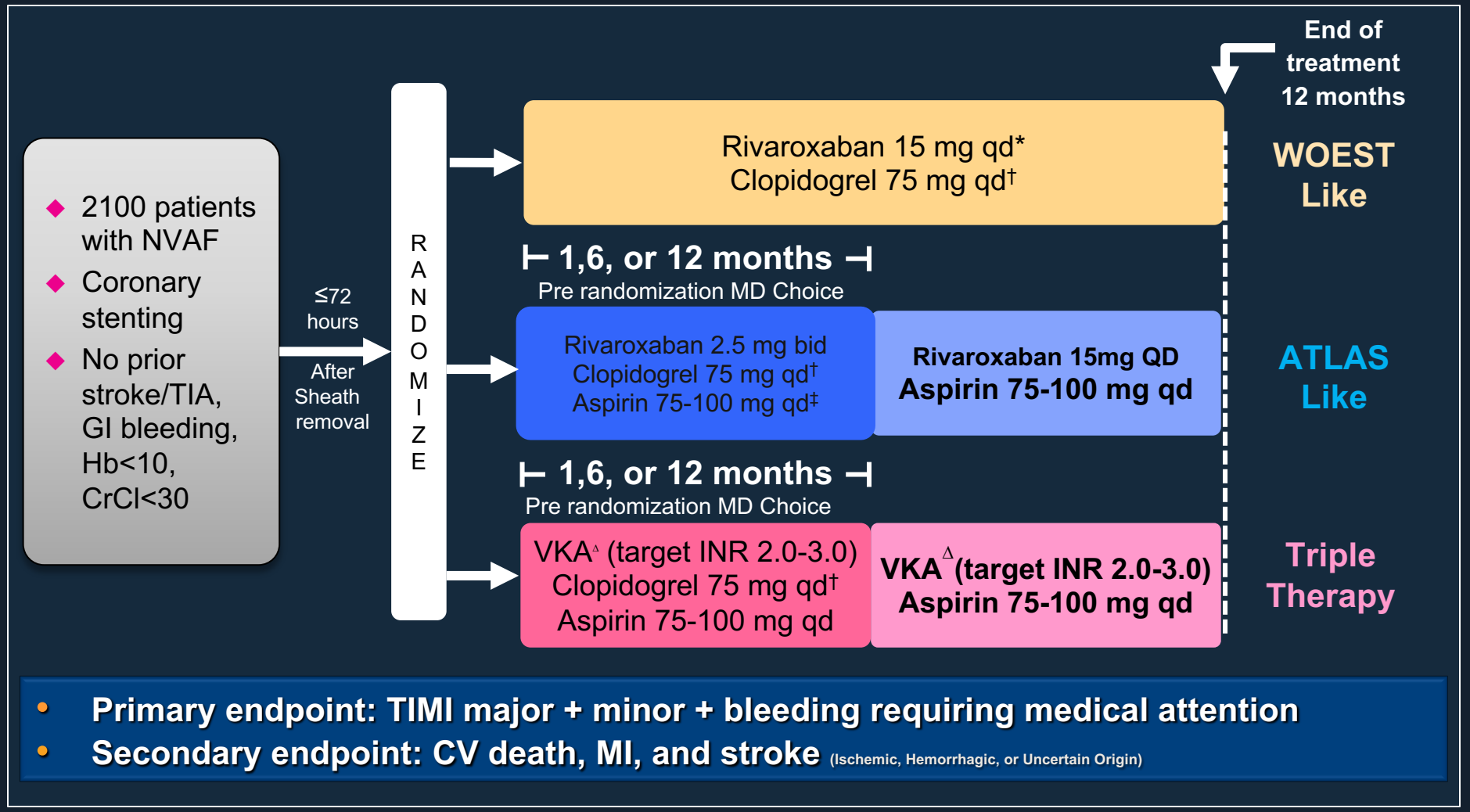
Trials of NOACs in AF pts undergoing PCI

Rivaroxaban **PIONEER-AF PCI**[2] (N=2,100)	Dabigatran **RE-DUAL**[1] (N=2,500)	Apixaban **AUGUSTUS**[3] (N=4,600)	Edoxaban **ENTRUST-AF PCI**[2] (N=1,500)
Rivaroxaban 15 mg od + $P2Y_{12}$ inhibitor or **Rivaroxaban 2.5 mg bid** + $P2Y_{12}$ inhibitor + ASA or **VKA (target INR 2–3)** + P2Y12 inhibitor + ASA	**Dabigatran 150 mg bid** + $P2Y_{12}$ inhibitor or **Dabigatran 110 mg bid** + $P2Y_{12}$ inhibitor or **VKA (target INR 2–3)** + P2Y12 inhibitor + ASA	**Apixaban 5 mg bid** + $P2Y_{12}$ inhibitor ± ASA or **VKA (target INR 2–3)** + $P2Y_{12}$ inhibitor ± ASA	**Edoxaban 30-60 mg od** + $P2Y_{12}$ inhibitor or **VKA (target INR 2–3)** + $P2Y_{12}$ inhibitor ± ASA
Completed! 1	**Completed!** 2	3	4

UNIVERSITÀ degli STUDI di CATANIA | Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Capodanno D, et al. EuroIntervention. 2015;10:1015-21

PIONEER AF PCI: Study Design



*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min. †Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor. ‡Low-dose aspirin (75-100 mg/d). △ Open label VKA

UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

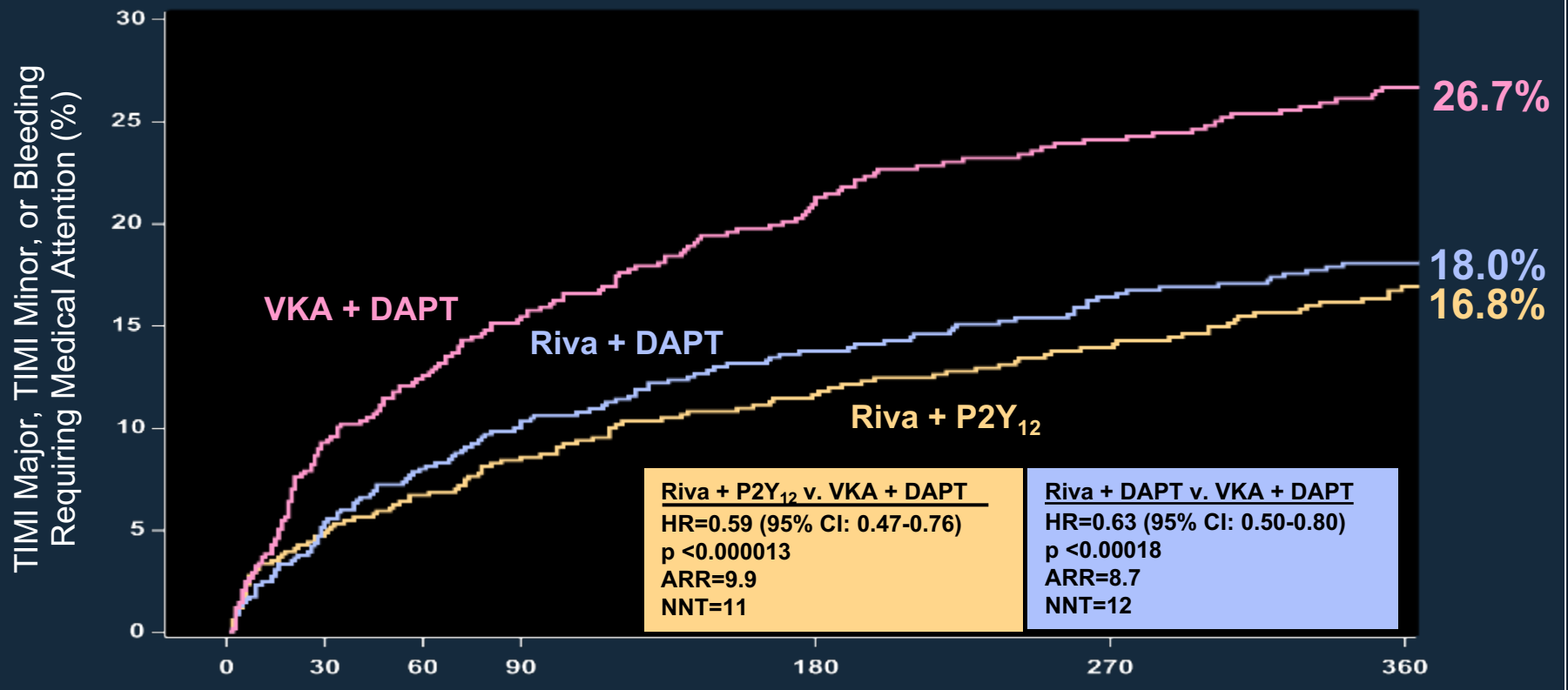
Gibson CM, et al. N Engl J Med 2016 [ePub Ahead of Print]

PIONEER AF PCI: Pts Characteristics

	Riva + $P2Y_{12}$ (N=709)	Riva + DAPT (N=709)	VKA + DAPT (N=706)
Age, mean ± SD	70.4 ± 9.1	70.0 ± 9.1	69.9 ± 8.7
Sex, female, n (%)	181 (25.5%)	174 (24.5%)	188 (26.6%)
Diabetes Mellitus, n (%)	204 (28.8%)	199 (28.1%)	221 (31.1%)
Type of Index Event, n (%)			
NSTEMI	130 (18.5%)	129 (18.4%)	123 (17.8%)
STEMI	86 (12.3%)	97 (13.8%)	74 (10.7%)
Unstable Angina	145 (20.7%)	148 (21.1%)	164 (23.7%)
Stable Angina	340 (48.5%)	329 (46.8%)	330 (47.8%)
Drug-eluting stent, n (%)	464 (65.4%)	471 (66.8%)	468 (66.5%)
Clopidogrel	660 (93.1%)	664 (93.7%)	680 (96.3%)
Type of Atrial Fibrillation, n (%)			
Persistent	146 (20.6%)	146 (20.6%)	149 (21.1%)
Permanent	262 (37.0%)	238 (33.6%)	243 (34.5%)
Paroxysmal	300 (42.4%)	325 (45.8%)	313 (44.4%)

Gibson CM, et al. N Engl J Med 2016 [ePub Ahead of Print]

PIONEER AF PCI: Study Results



No. at risk

Riva + P2Y$_{12}$	696	628	606	585	543	510	383
Riva + DAPT	706	636	600	579	543	509	409
VKA + DAPT	697	593	555	521	461	426	329

Treatment emergent period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

UNIVERSITÀ degli STUDI di CATANIA | Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Gibson CM, et al. N Engl J Med 2016 [ePub Ahead of Print]

PIONEER AF PCI: Which Bleeding?

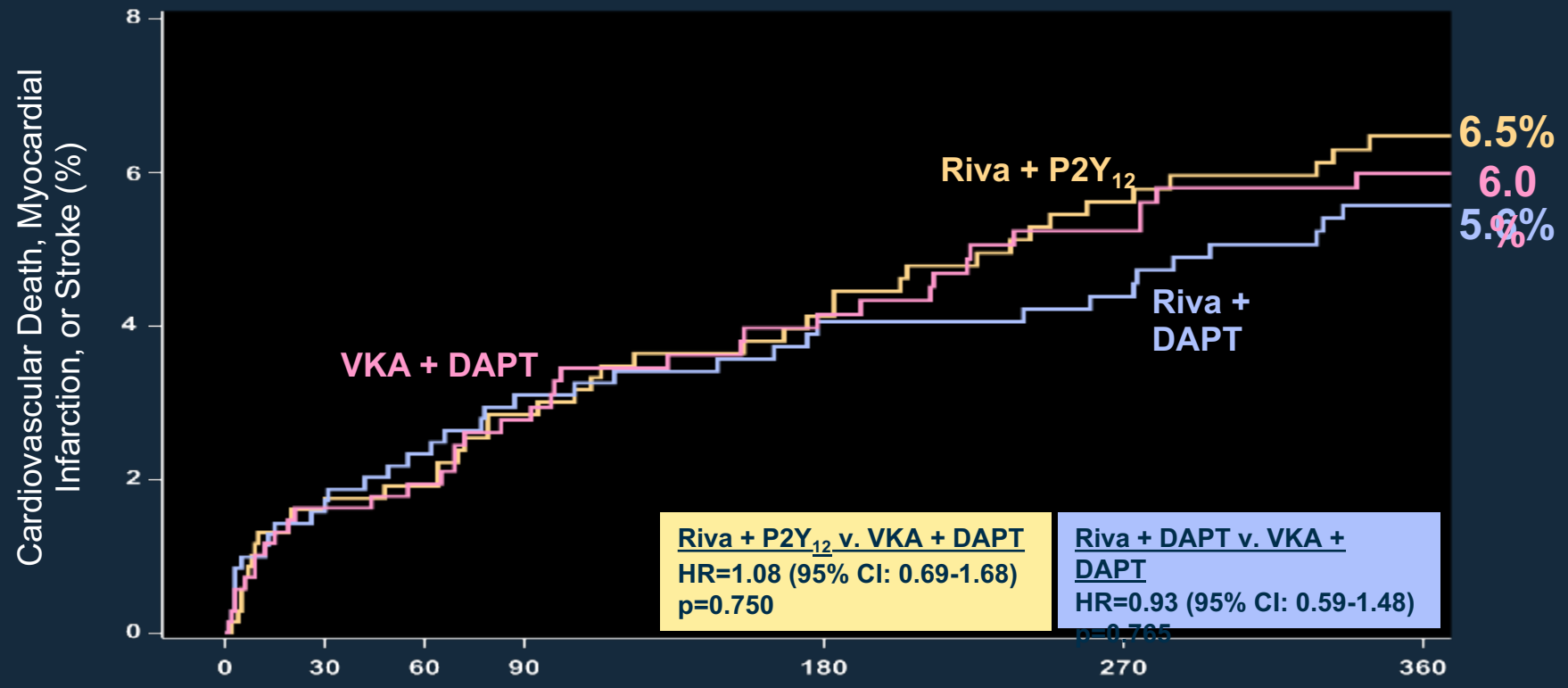
	Kaplan-Meier Estimates				Hazard Ratio (95% CI)		
	Riva + $P2Y_{12}$ (N=696)	Riva + DAPT (N=706)	Comb. Riva (N=1402)	VKA + DAPT (N=697)	Riva + $P2Y_{12}$ vs. VKA + DAPT	Riva + DAPT vs. VKA + DAPT	Combined vs. VKA + DAPT
Clinically significant bleeding	109 (16.8%)	117 (18.0%)	226 (17.4%)	167 (26.7%)	0.59 (0.47-0.76) **p<0.001**	0.63 (0.50-0.80) **p<0.001**	0.61 (0.50-0.75) **p<0.001**
TIMI Major	14 (2.1%)	12 (1.9%)	26 (2.0%)	20 (3.3%)	0.66 (0.33-1.31) p=0.234	0.57 (0.28-1.16) p=0.114	0.61 (0.34-1.09) p=0.093
TIMI minor	7 (1.1%)	7 (1.1%)	14 (1.1%)	13 (2.2%)	0.51 (0.20-1.28) p=0.144	0.50 (0.20-1.26) p=0.134	0.51 (0.24-1.08) p=0.071
BRMA	93 (14.6%)	102 (15.8%)	195 (15.2%)	139 (22.6%)	0.61 (0.47-0.80) **p<0.001**	0.67 (0.52-0.86) **p=0.002**	0.64 (0.51-0.80) **p<0.001**

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA events.

UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Gibson CM, et al. N Engl J Med 2016 [ePub Ahead of Print]

PIONEER AF PCI: Study Results



No. at risk							
Riva + P2Y12	694	648	633	621	590	562	430
Riva + DAPT	704	662	640	628	596	570	457
VKA + DAPT	695	635	607	579	543	514	408

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug. Composite of adverse CV events is composite of CV death, MI, and stroke. Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model. Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test. 6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines

UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Gibson CM, et al. N Engl J Med 2016 [ePub Ahead of Print]

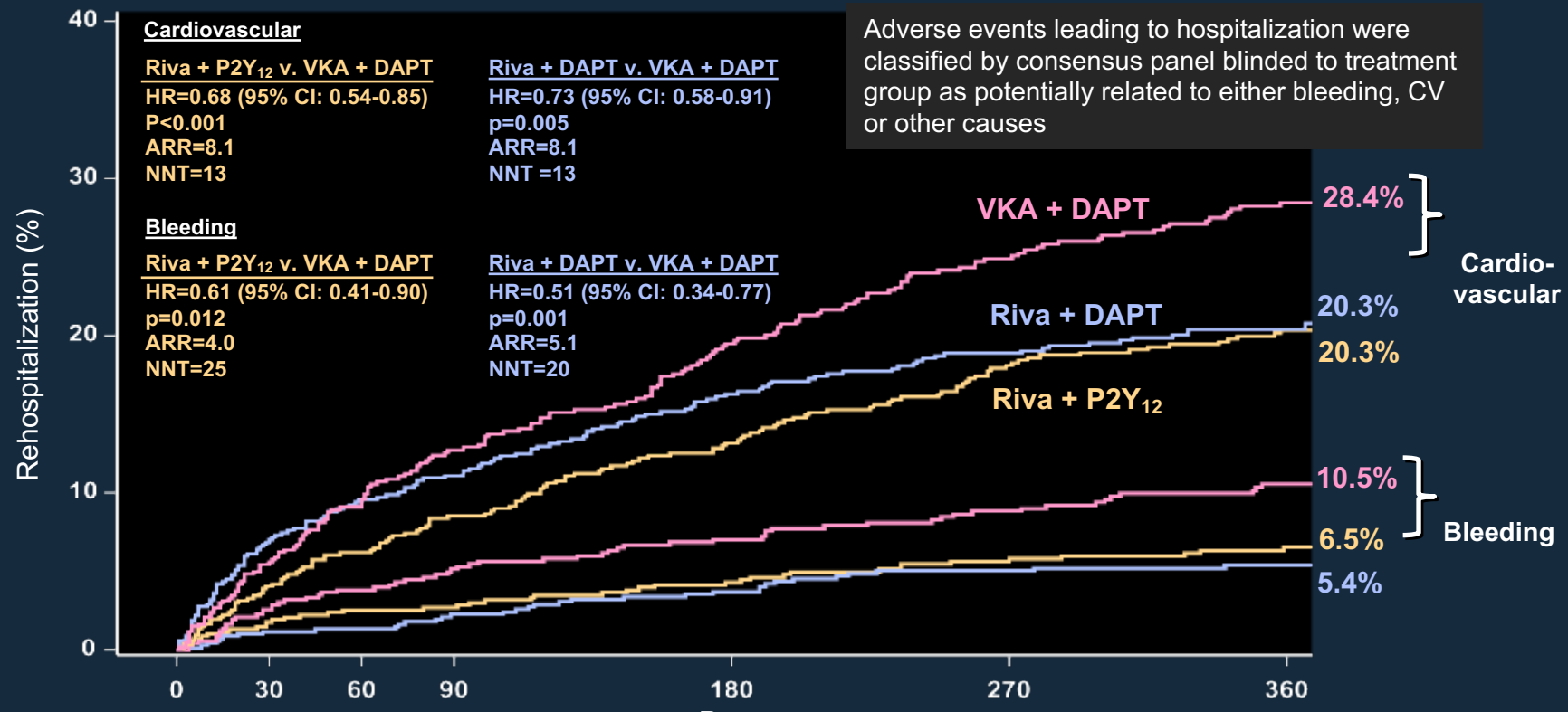
PIONEER AF PCI: Similar Efficacy

	Kaplan-Meier Estimates			Hazard Ratio (95% CI)	
	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

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
A subject could have more than component event. n = number of subjects with events, N = number of subjects at risk, % = KM estimate at the end of study.
Hazard ratios as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank p-values as compared to VKA group are based on the (stratified, only for Overall 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson CM, et al. N Engl J Med 2016 [ePub Ahead of Print]

PIONEER AF PCI: Hospitalization

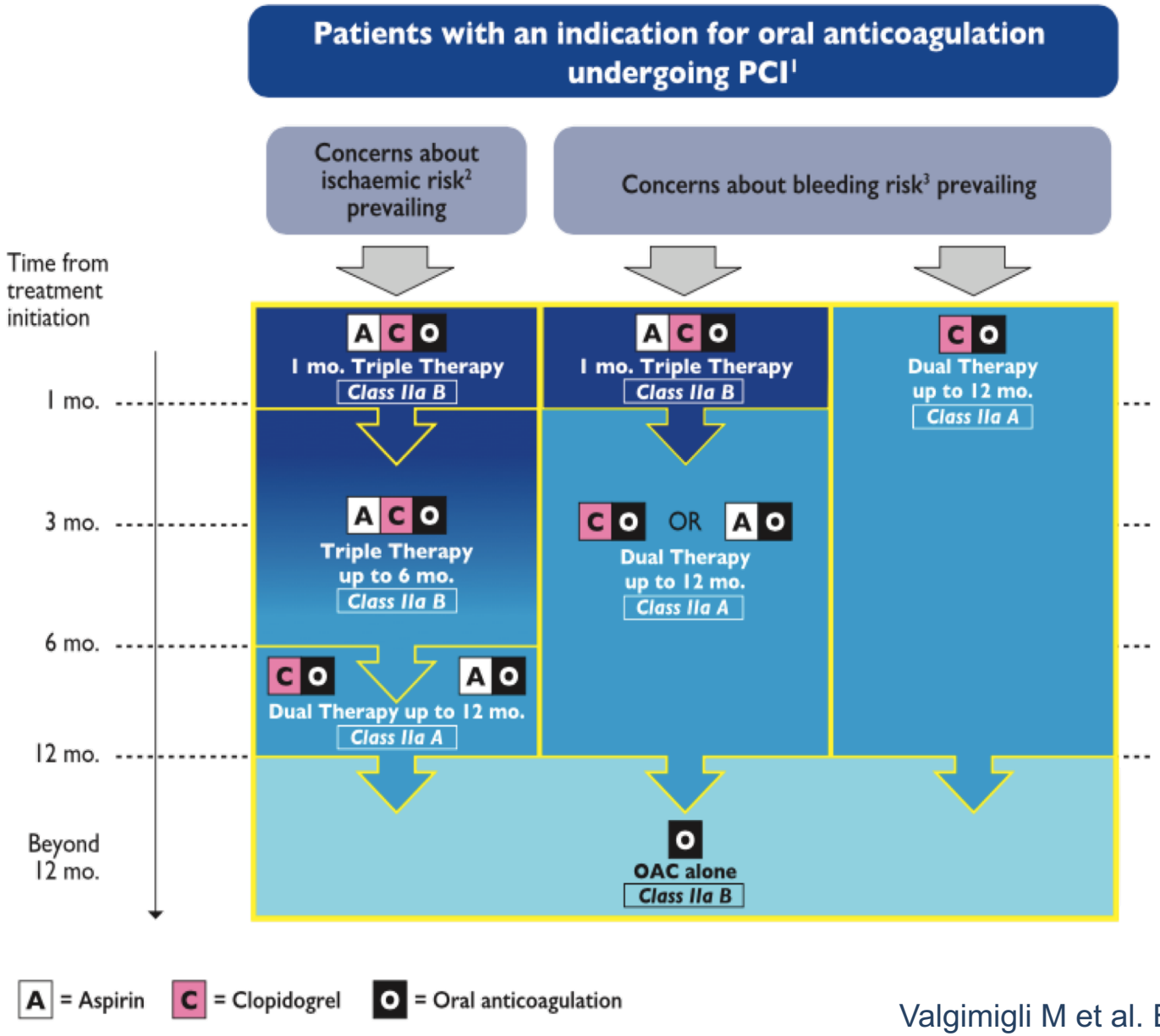


No. at risk cardiovascular							
Riva + P2Y12	696	632	607	586	537	491	367
Riva + DAPT	706	627	595	576	525	495	400
VKA + DAPT	697	609	560	517	457	410	314
No. at risk bleeding							
Riva + P2Y12	696	645	630	618	585	553	421
Riva + DAPT	706	659	636	621	590	560	453
VKA + DAPT	697	630	601	568	528	494	386

UNIVERSITÀ degli STUDI di CATANIA
Ferrarotto Hospital
A.O.U. Policlinico-Vittorio Emanuele
Catania, Italy

Gibson CM, et al. Circulation 2016 [ePub Ahead of Print]

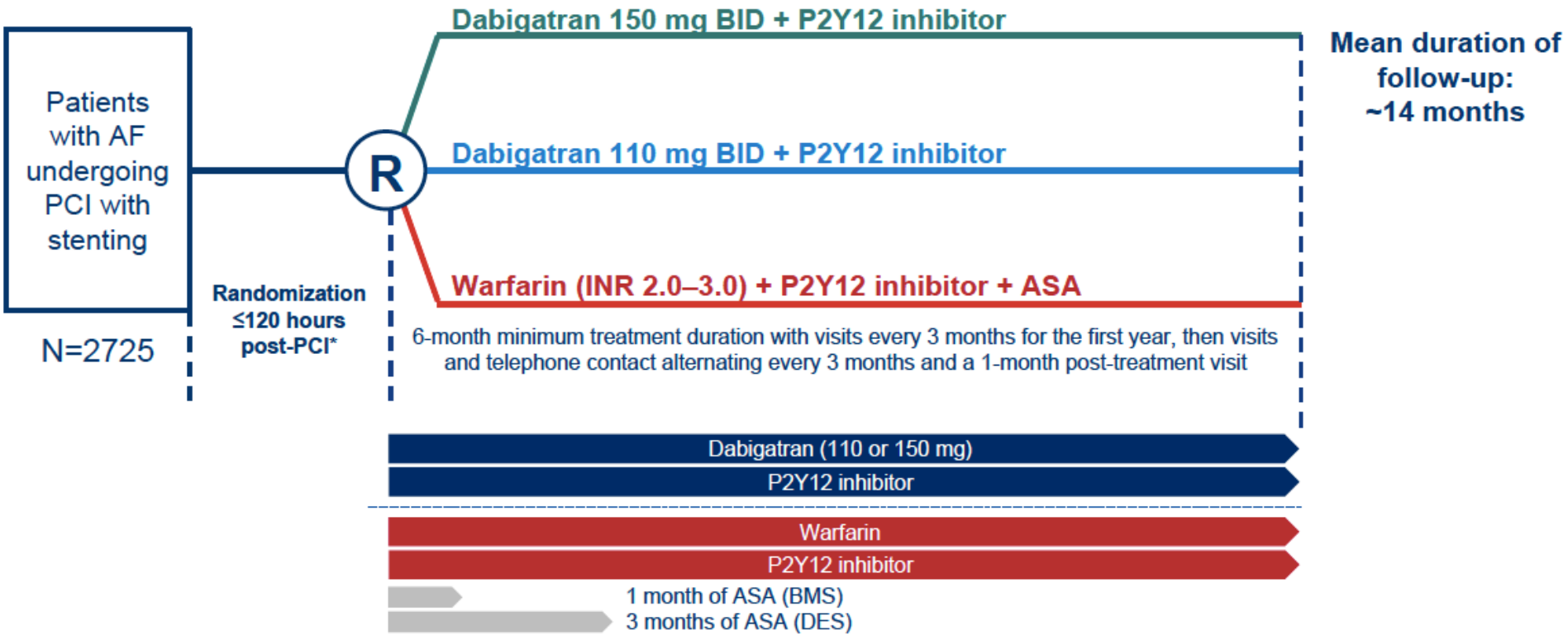
2017 DAPT ESC guidelines



Valgimigli M et al. Eur Heat J 2017.

RE-DUAL PCI: Study design

Multicenter, randomized, open-label trial following a PROBE design



***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

Presented at ESC 2017. Cannon CP et al. N Engl J Med 2017;377:1513-24.

RE-DUAL PCI: Baseline characteristics

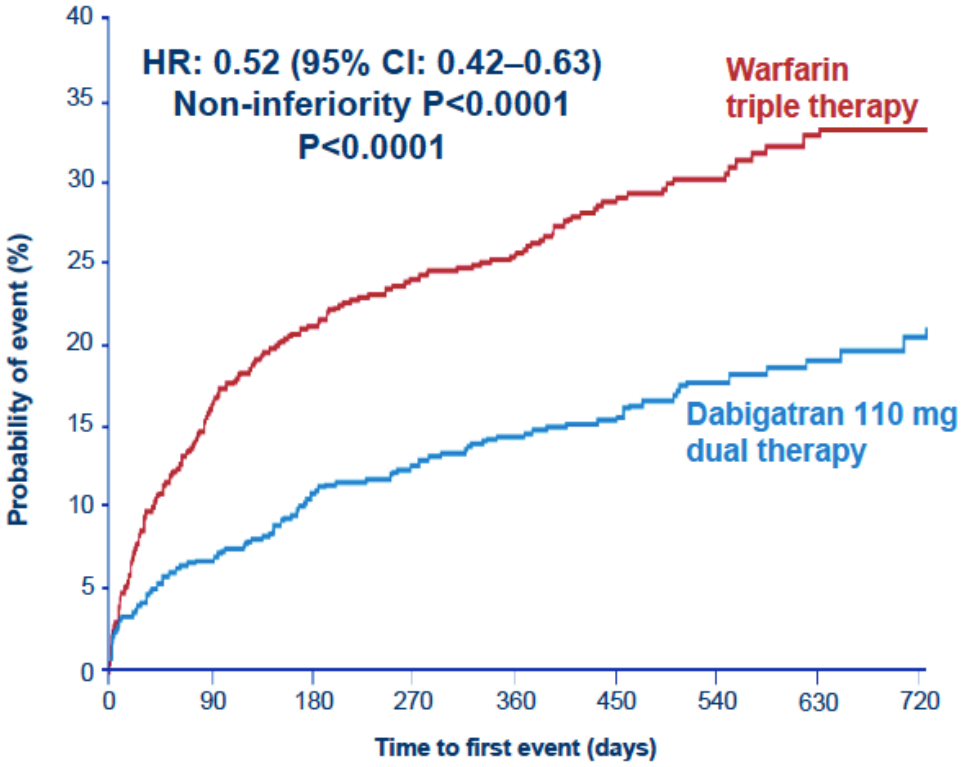
	Dabigatran 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabigatran 150 mg dual therapy (n=763)	Corresponding Warfarin triple therapy (n=764)
Age, years, mean	71.5	71.7	68.6	68.8
≥80 (US, ROW), ≥70 (Japan), %	22.9	22.9	1.0	1.0
<80 (US, ROW), <70 (Japan), %	77.1	77.1	99.0	99.0
Male, %	74.2	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

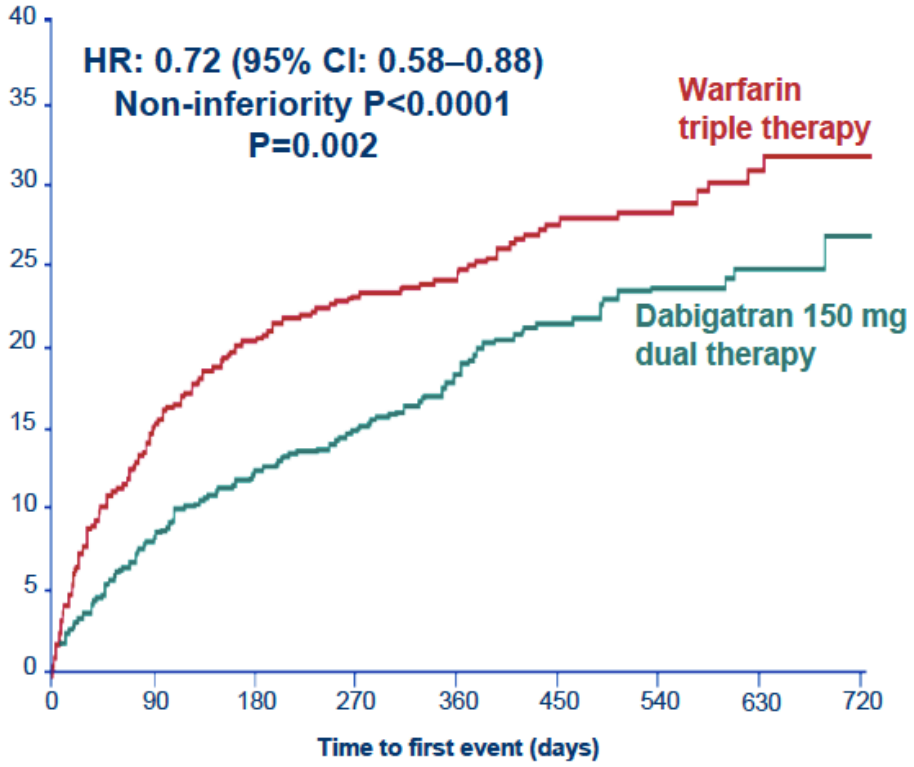
ROW, rest of world

Presented at ESC 2017. Cannon CP et al. N Engl J Med 2017;377:1513-24.

RE-DUAL PCI: Primary endpoint

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

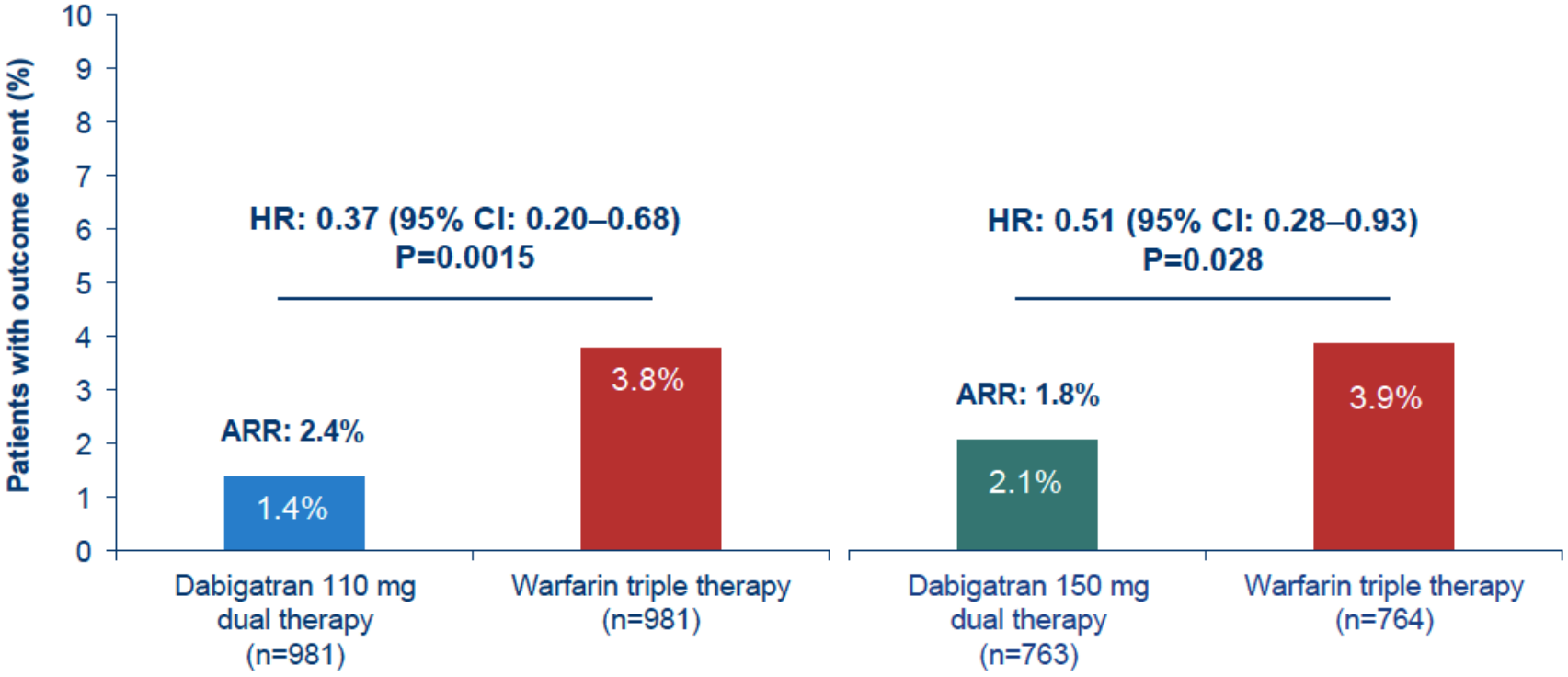




Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified 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)

Presented at ESC 2017. Cannon CP et al. N Engl J Med 2017;377:1513-24.

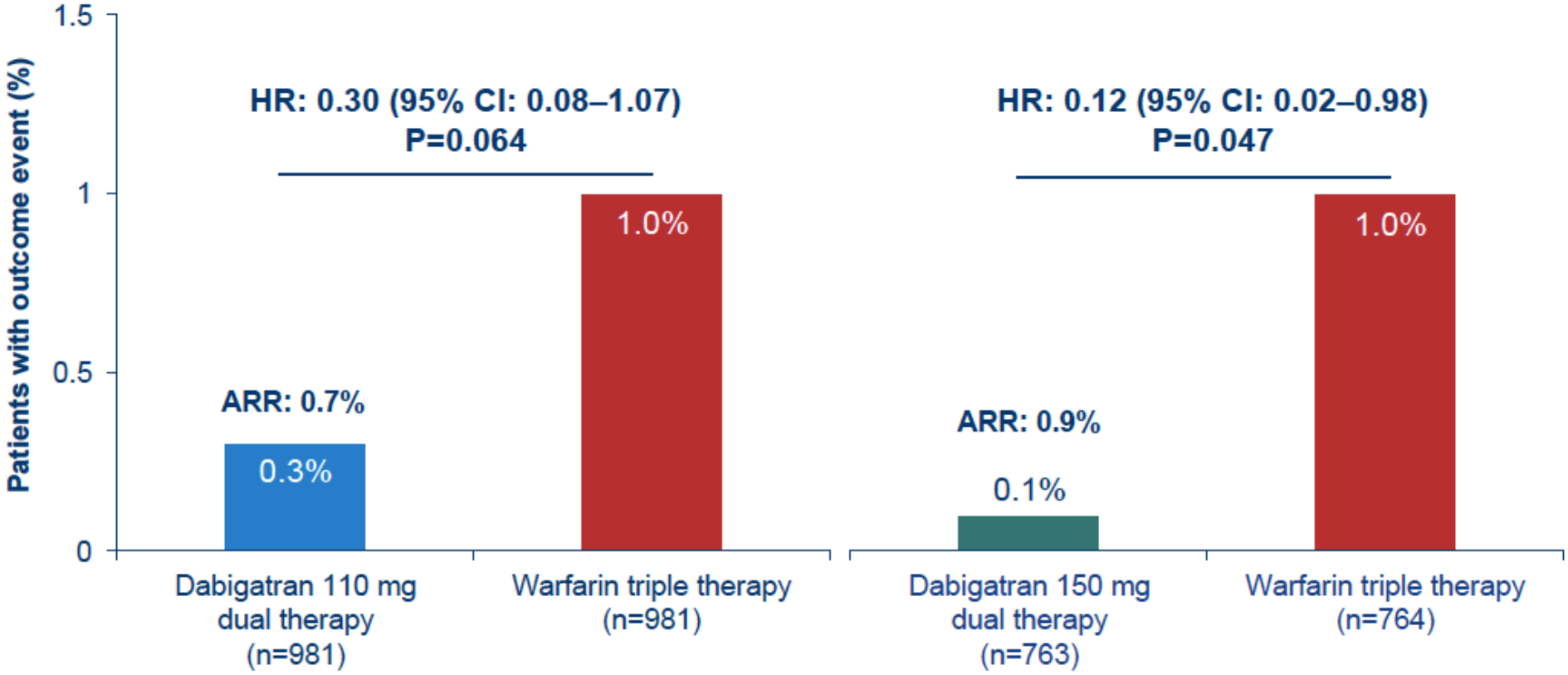
RE-DUAL PCI: TIMI major bleeding



Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05). TIMI major bleeding definition: fatal, intracranial haemorrhage, clinically overt bleeding with fall in Hb ≥5 g/dL.

Presented at ESC 2017. Cannon CP et al. N Engl J Med 2017;377:1513-24.

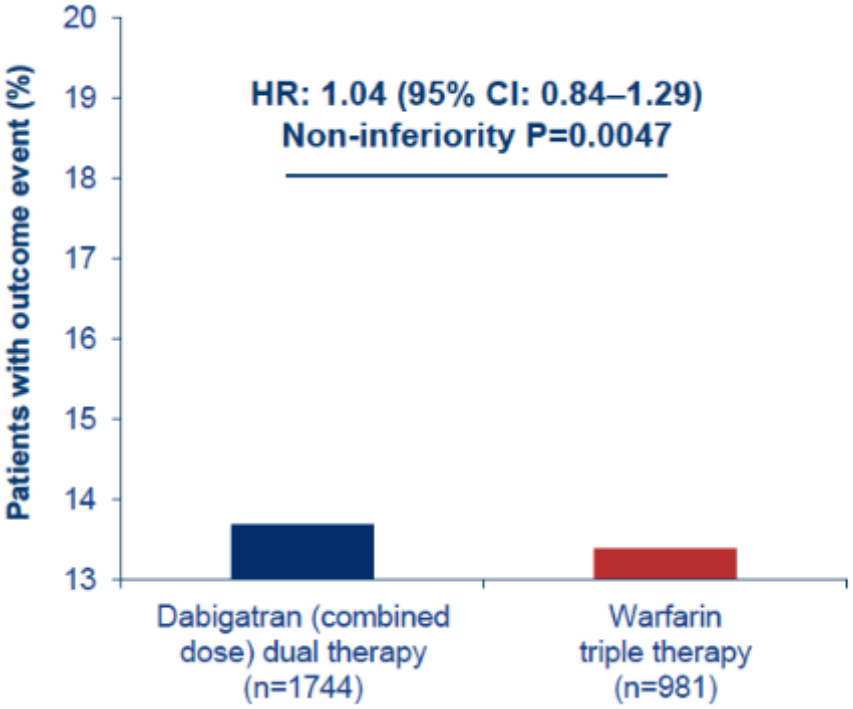
RE-DUAL PCI: intracranial haemorrhage

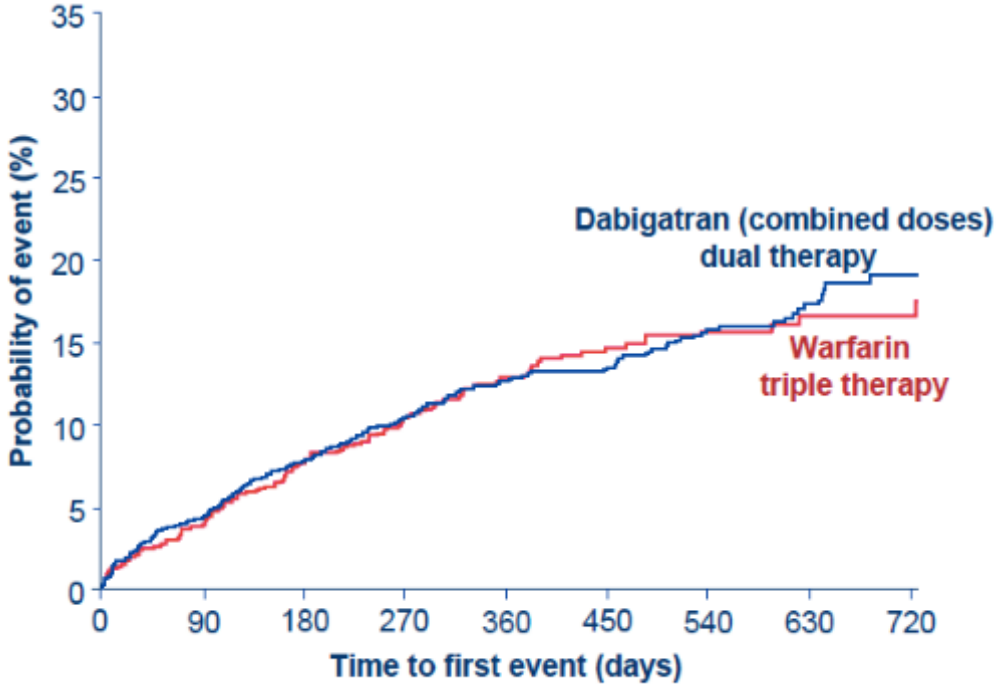


Presented at ESC 2017. Cannon CP et al. N Engl J Med 2017;377:1513-24.

RE-DUAL PCI: Efficacy results

Time to death or thromboembolic event, or unplanned revascularization





Presented at ESC 2017. Cannon CP et al. N Engl J Med 2017;377:1513-24.

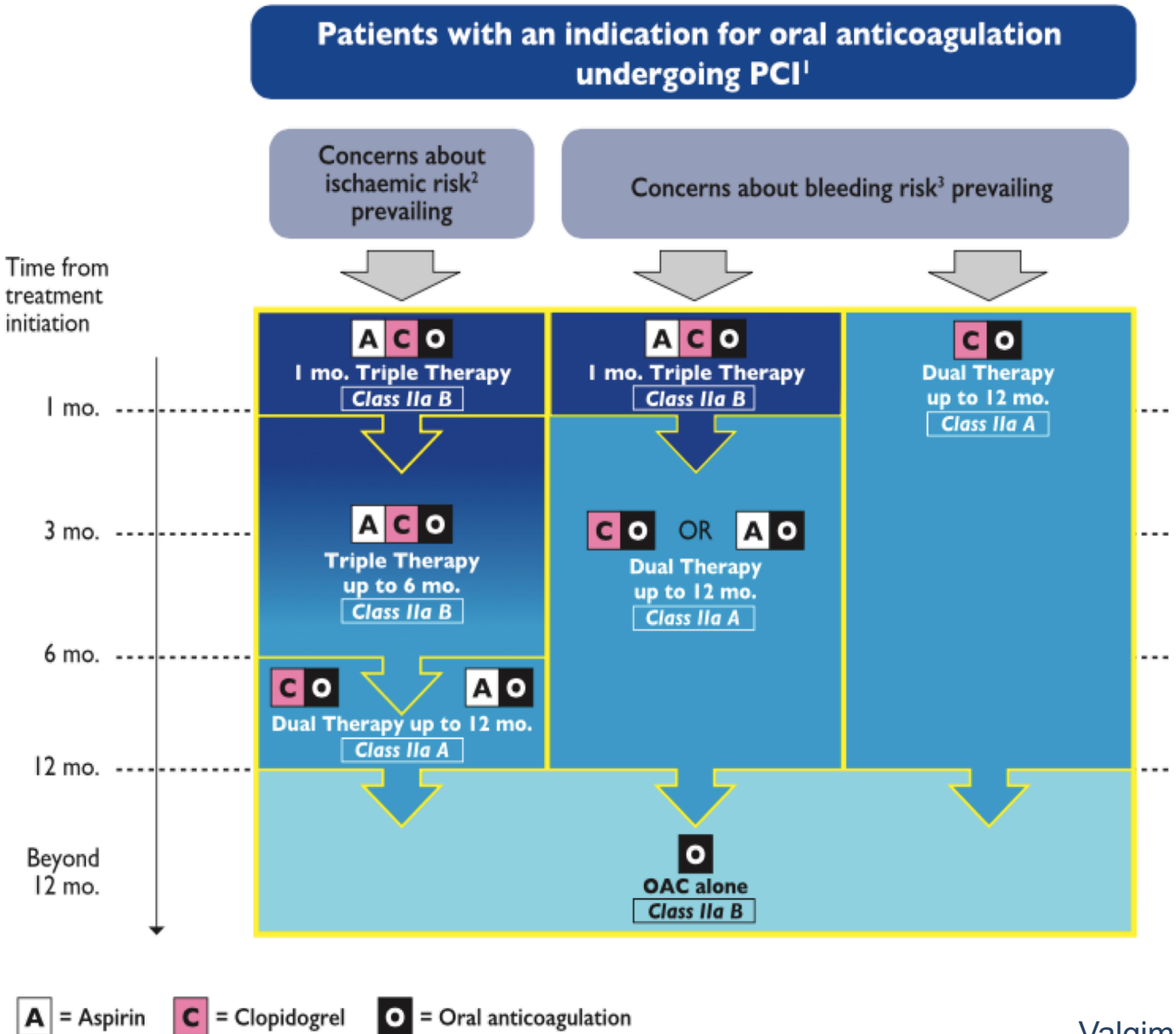
RE-DUAL PCI: Efficacy results

Individual thromboembolic endpoints

	Dabigatran 110 mg dual therapy (n=981) n (%)	Warfarin triple therapy (n=981) n (%)	D110 DT vs warfarin TT HR (95% CI)	D110 DT vs warfarin TT P value	Dabigatran 150 mg dual therapy (n=763) n (%)	Warfarin triple therapy (n=764) n (%)	D150 DT vs warfarin TT HR (95% CI)	D150 DT vs warfarin TT P value
All-cause death	55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Stroke	17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Unplanned revascularization	76 (7.7)	69 (7.0)	1.09 (0.79–1.51)	0.61	51 (6.7)	52 (6.8)	0.96 (0.65–1.41)	0.83
MI	44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stent thrombosis	15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

Presented at ESC 2017. Cannon CP et al. N Engl J Med 2017;377:1513-24.

2017 DAPT ESC guidelines



Still triple therapy after RE-DUAL PCI trial?

Valgimigli M et al. Eur Heat J 2017.

Closing Remarks

- Current ESC DAPT guidelines (post-PIONEER and pre-RE-DUAL PCI) recommend 1 to 6 months of triple therapy after PCI in AF patients. Double therapy may be considered in selected patients with HBR.
- The RE-DUAL PCI trial provides further consistent evidence on the net clinical benefit of dual therapy, that should give cardiologists confidence to drop aspirin in case of higher bleeding risk.
- While awaiting additional AF + PCI NOACs trials and updated guidelines my therapy would be:
  - Triple therapy for 1-3 months in NSTEMI/STEMI patients or complex PCI, if no high bleeding risk
  - Dual therapy immediately after not complex PCI in UA/elective patients
  - Dual therapy immediately after PCI in patients with HBR.