Antithrombotic Strategy in PCI and AF Patients: Updated Strategy

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott Vascular, Medtronic
• Scientific Advisory Board	• Medtronic, Abbott Vascular
• Executive Physician Council	• Boston Scientific Corp

The Optimal Management of Atrial Fibrillation and PCI/ACS Differ

Atrial Fibrillation (ACTIVE W)[1]:

*combination of aspirin and clopidogrel is not as effective as **warfarin** in patients with AF[1]*

AND

Stenting (STARS)[2]:

***aspirin and a thienopyridine** is more effective than warfarin in patients with coronary stents[2]*

1. Connolly S et al. Lancet 2006 Jun 10;367(9526):1903-12. 2. Leon MB et al. N Eng J Med 1998 Dec 3;339(23):1665-71.

Bewildering Number of Strategies in the Patient with PCI and Atrial Fibrillation

- ASA Dose: None Low High 2
- ASA Duration (mos): 1 3 6 12 4
- Thineopyridine: None Clop Ticlid Pras Ticag 4
- Thienopyridine duration (mos): 1 3 6 12 4
- AC: None Warf Dabi Riva Apix Edox 5
- AC INR/Dose: Low High 2

1+8 = 9 ASA

1+16 = 17 Thieno

1+10 = 11 ACs

Permutations of Single, Dual or Triple Therapy as *Early Initial Therapy* (0,1,3,6 mos) following ACS: 9 X 17 X 11 = 1,683

Permutations of Single or Dual Therapy *Late After Early Therapy (0,1,3,6 mos)* following ACS: 1,683

Total Permutations *throughout one year:* 2.8 Million

Slide by C. Michael Gibson, M.S., M.D.

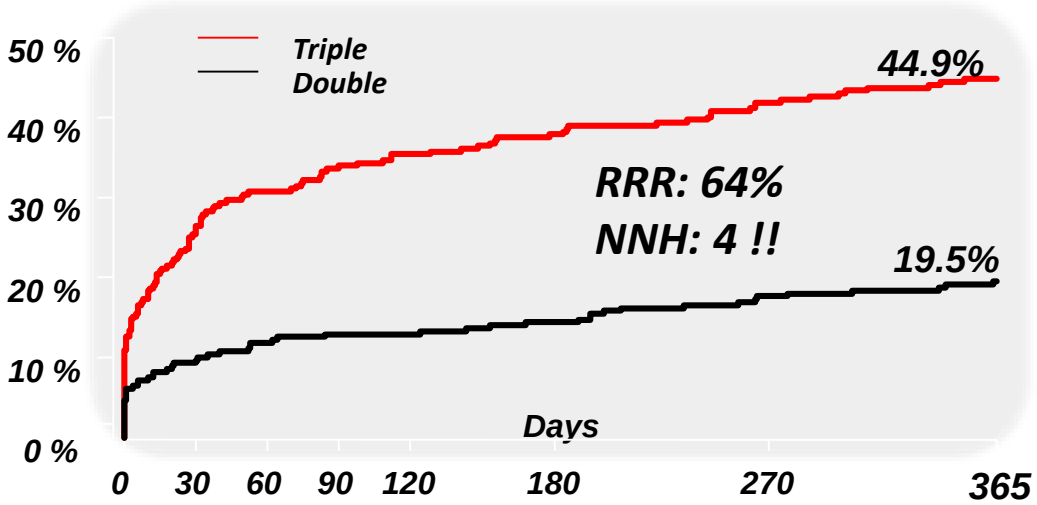
Gibson et al. AHA 2016

Gibson CM, J Am Coll Cardiol 2016

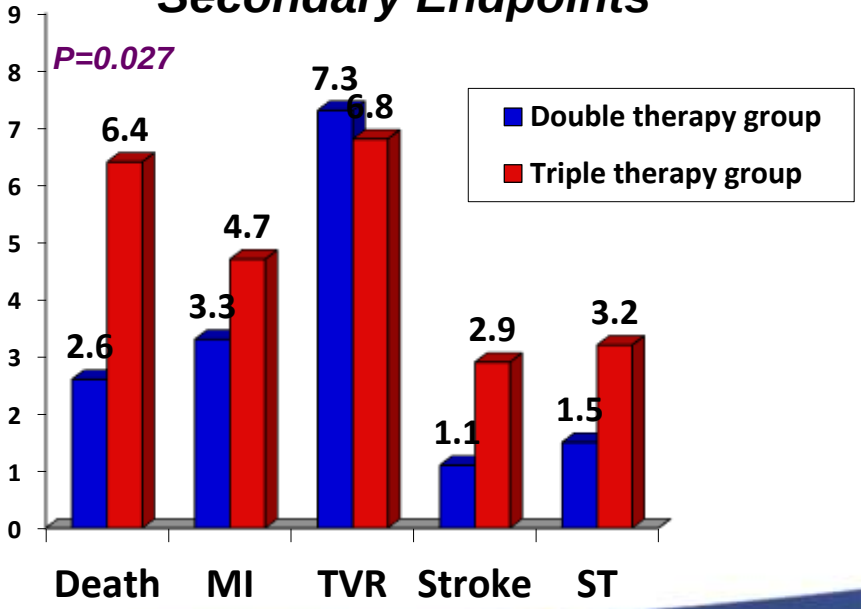
WOEST Trial

573 pts recruited at 15 sites in the Netherlands randomized to Triple vs Clopidogrel and OAC

Cumulative incidence of bleeding

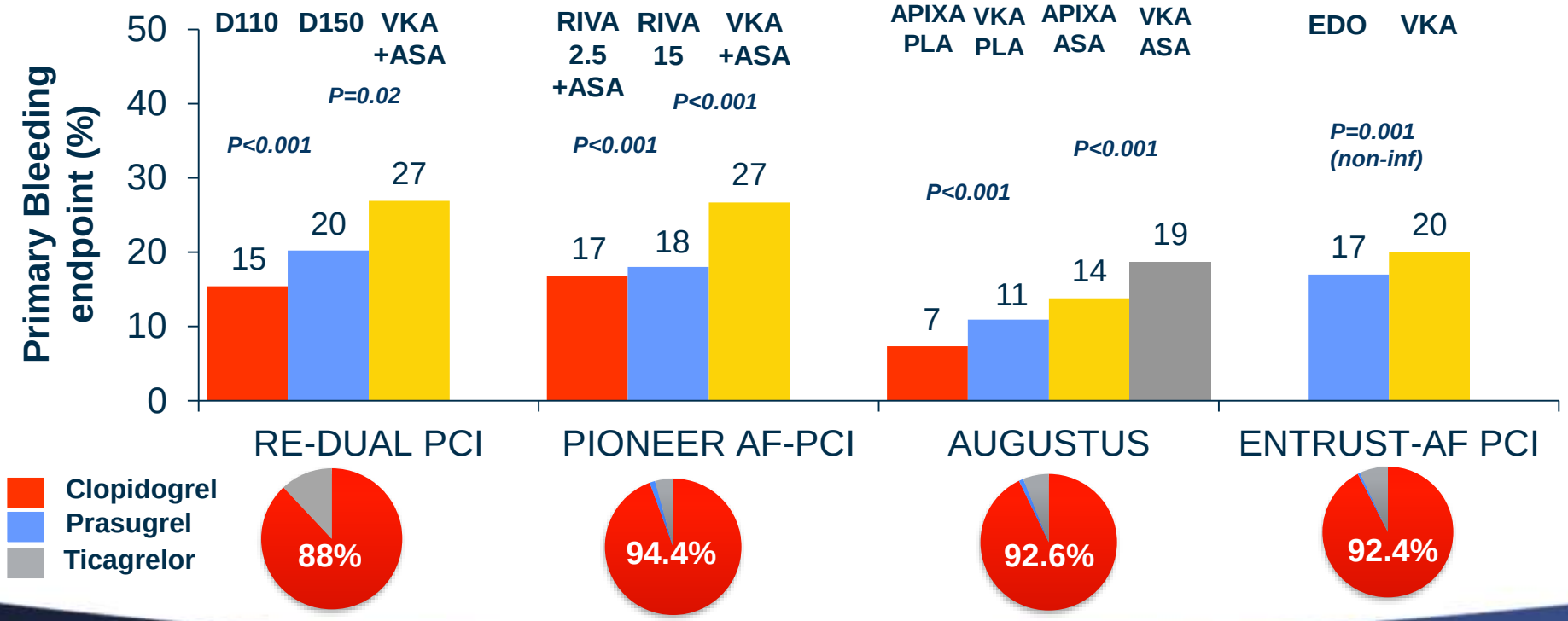


Secondary Endpoints



Dewilde WJ et al Lancet. 2013 Mar 30;381(9872):1107-15.

Rate of Primary Endpoint Events in RCTs investigating NOACs vs VKA in Patients With AF undergoing PCI



Cannon et al. N Engl J Med 2017; Gibson et al. N Engl J Med 2016; Lopes et al. N Eng J Med 2019; Vranckx et al. Lancet 2019

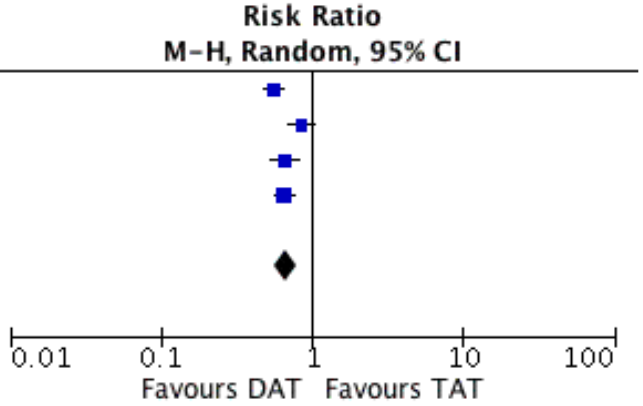
Pooled Analysis on ISTH Major or NMCR Bleeding

ISTH MAJOR OR CLINICALLY RELEVANT NONMAJOR BLEEDING

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	204	2279	367	2277	26.8%	0.56 [0.47, 0.65]
ENTRUST AF-PCI	128	751	152	755	22.3%	0.85 [0.68, 1.05]
PIONEER AF-PCI	117	696	178	697	22.7%	0.66 [0.53, 0.81]
RE-DUAL PCI	305	1744	264	981	28.2%	0.65 [0.56, 0.75]
Total (95% CI)		**5470**		**4710**	**100.0%**	**0.66 [0.56, 0.78]**
Total events	754		961			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.65$, df = 3 (P = 0.02); $I^2 = 69\%$

Test for overall effect: Z = 5.03 (P < 0.00001)



Gargiulo g et al, Eur H Journal, in press

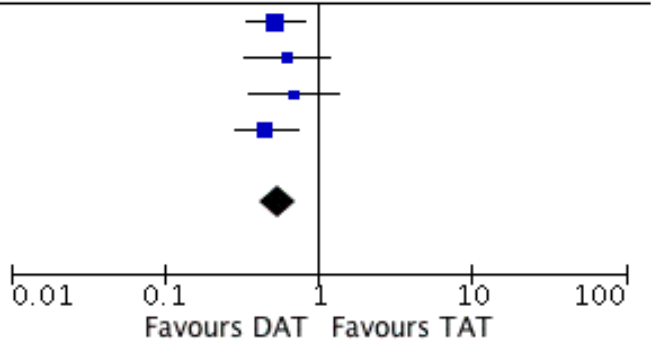
Pooled Analysis on TIMI Major Bleeding

TIMI MAJOR BLEEDING

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	29	2279	55	2277	35.6%	0.53 [0.34, 0.82]
ENTRUST AF-PCI	15	751	24	755	17.5%	0.63 [0.33, 1.19]
PIONEER AF-PCI	14	696	20	697	15.6%	0.70 [0.36, 1.38]
RE-DUAL PCI	30	1744	37	981	31.4%	0.46 [0.28, 0.73]
Total (95% CI)		**5470**		**4710**	**100.0%**	**0.54 [0.42, 0.71]**
Total events	88		136			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.29$, df = 3 (P = 0.73); $I^2 = 0\%$

Test for overall effect: Z = 4.50 (P < 0.00001)



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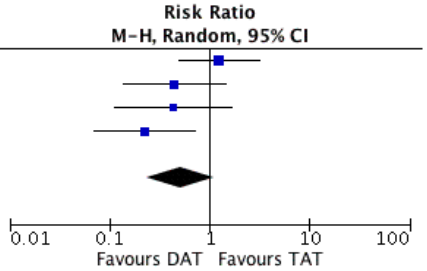
Pooled Analysis on ICH

INTRACRANIAL HAEMORRHAGE

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	10	2279	8	2277	30.6%	1.25 [0.49, 3.16]
ENTRUST AF-PCI	4	751	9	755	24.2%	0.45 [0.14, 1.44]
PIONEER AF-PCI	3	696	7	697	20.6%	0.43 [0.11, 1.65]
RE-DUAL PCI	4	1744	10	981	24.6%	0.23 [0.07, 0.72]
Total (95% CI)		**5470**		**4710**	**100.0%**	**0.51 [0.24, 1.11]**
Total events	21		34			

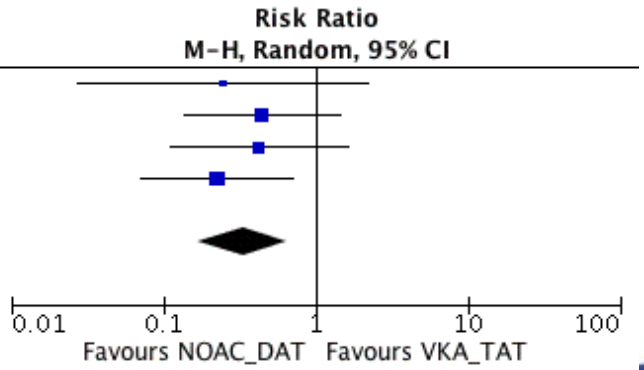
Heterogeneity: Tau² = 0.29; Chi² = 5.55, df = 3 (P = 0.14); I² = 46%
Test for overall effect: Z = 1.69 (P = 0.09)



INTRACRANIAL HAEMORRHAGE

Study or Subgroup	NOAC_DAT Events	NOAC_DAT Total	VKA_TAT Events	VKA_TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	1	1143	4	1123	9.3%	0.25 [0.03, 2.19]
ENTRUST AF-PCI	4	751	9	755	32.5%	0.45 [0.14, 1.44]
PIONEER AF-PCI	3	696	7	697	24.6%	0.43 [0.11, 1.65]
RE-DUAL PCI	4	1744	10	981	33.5%	0.23 [0.07, 0.72]
Total (95% CI)		**4334**		**3556**	**100.0%**	**0.33 [0.17, 0.65]**
Total events	12		30			

Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 3 (P = 0.83); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)



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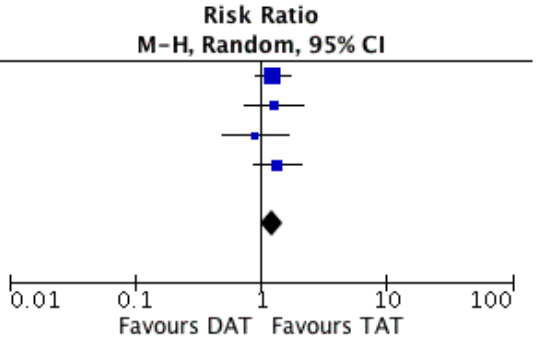
Pooled Analysis on Ischemic Coronary Events

MYOCARDIAL INFARCTION

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	84	2307	68	2307	46.5%	1.24 [0.90, 1.69]
ENTRUST AF-PCI	29	751	23	755	15.9%	1.27 [0.74, 2.17]
PIONEER AF-PCI	19	694	21	695	12.3%	0.91 [0.49, 1.67]
RE-DUAL PCI	70	1744	29	981	25.4%	1.36 [0.89, 2.08]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.22 [0.99, 1.52]**
Total events	202		141			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.18$, df = 3 (P = 0.76); $I^2 = 0\%$

Test for overall effect: Z = 1.84 (P = 0.07)

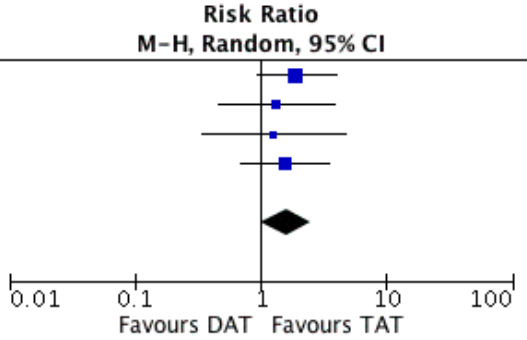


STENT THROMBOSIS

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	21	2307	11	2307	38.5%	1.91 [0.92, 3.95]
ENTRUST AF-PCI	8	751	6	755	18.3%	1.34 [0.47, 3.84]
PIONEER AF-PCI	5	694	4	695	11.8%	1.25 [0.34, 4.64]
RE-DUAL PCI	22	1744	8	981	31.4%	1.55 [0.69, 3.46]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.59 [1.01, 2.50]**
Total events	56		29			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.48$, df = 3 (P = 0.92); $I^2 = 0\%$

Test for overall effect: Z = 2.02 (P = 0.04)



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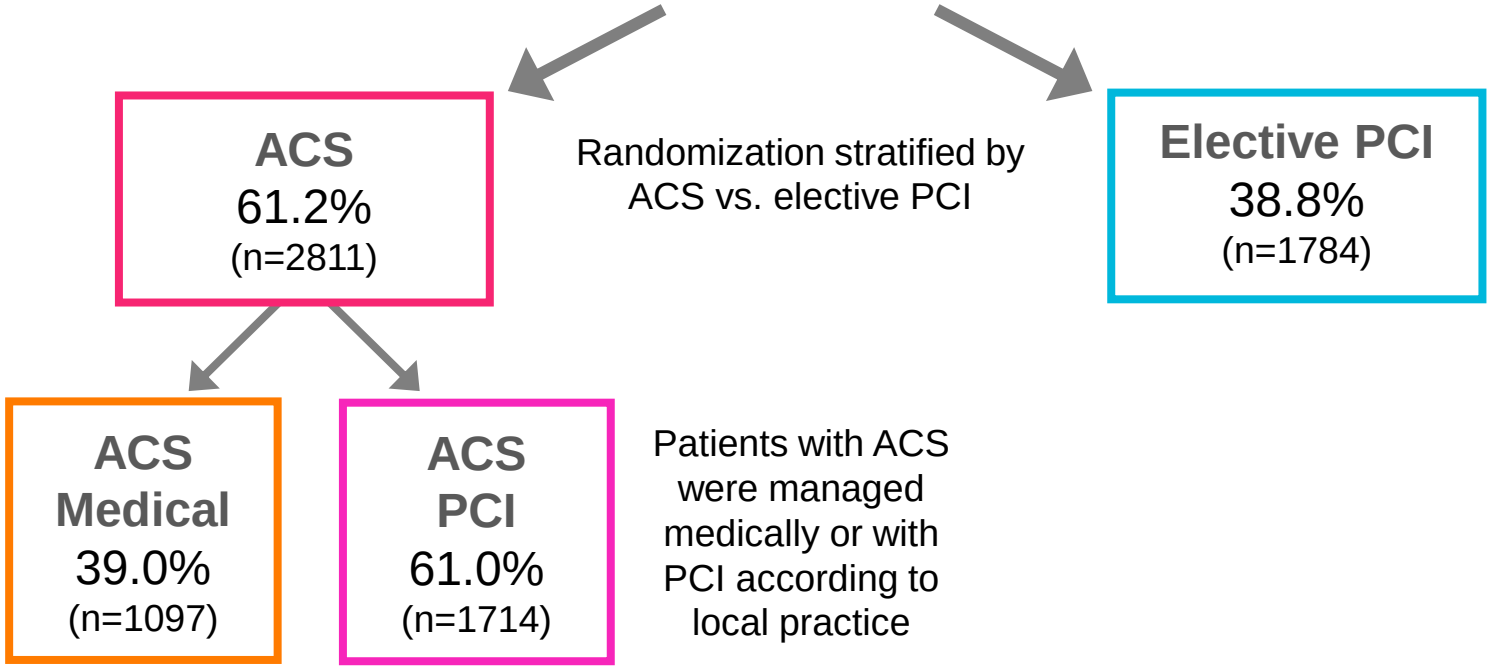
Patient Allocation

4614 patients (492 sites, 33 countries)

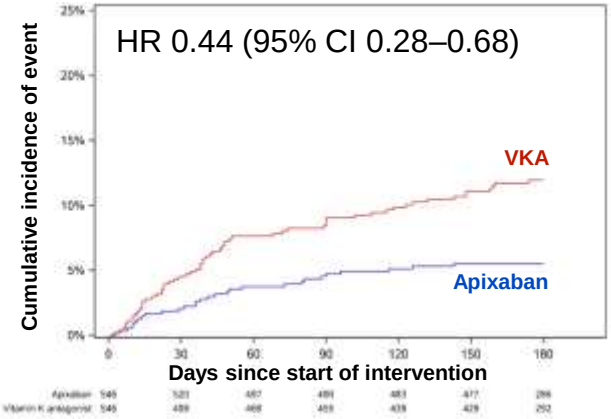


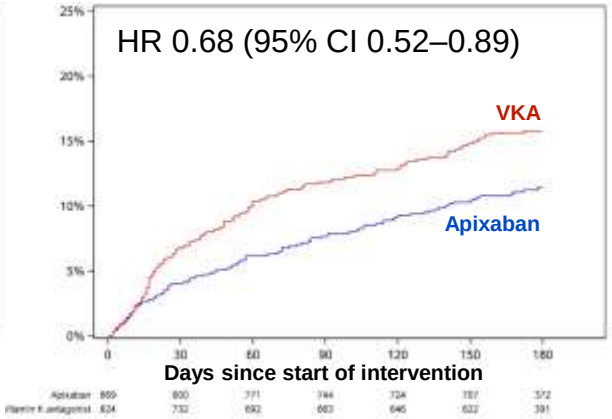
19 pts with missing information about ACS and PCI

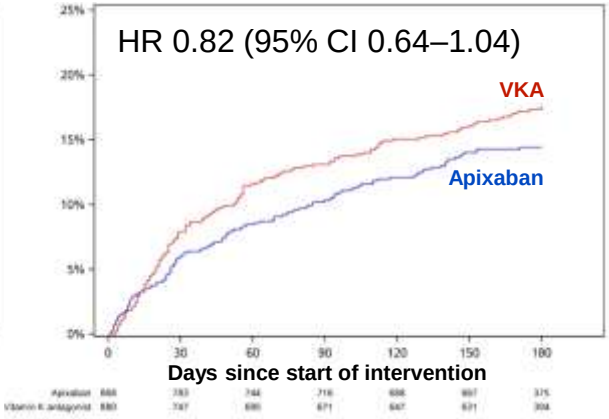
Primary Endpoint: ISTH and CRNM Bleeding Apixaban vs VKA

ACS Medical	ACS PCI	Elective PCI
N=1097	N=1714	N=1784

P for Interaction (ACS Medical, ACS PCI, Elective PCI) = **0.052**



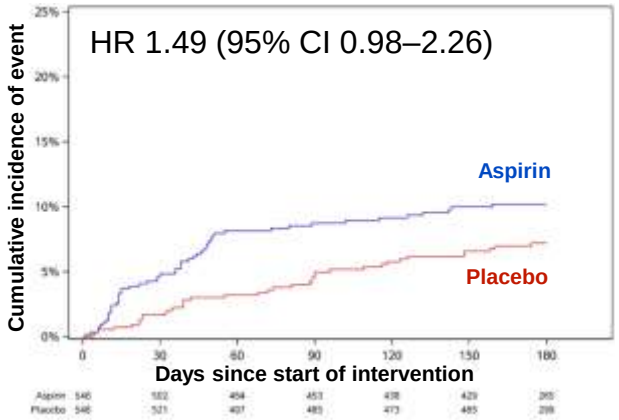


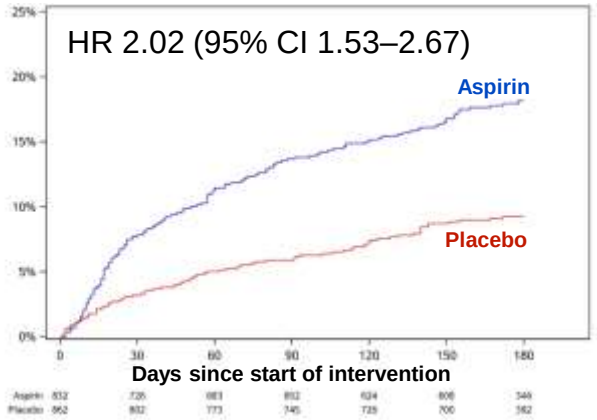


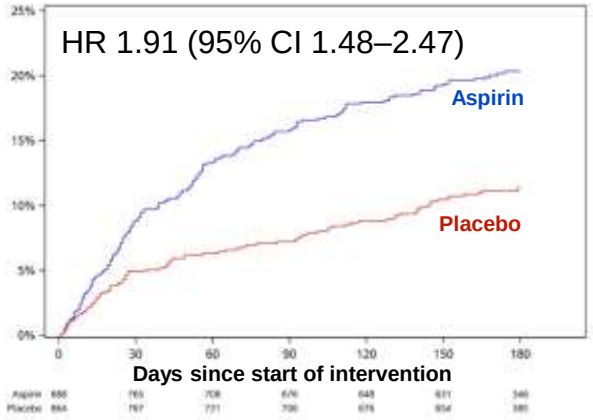
Primary Endpoint: ISTH and CRNM Bleeding Aspirin vs Placebo

ACS Medical	ACS PCI	Elective PCI
N=1097	N=1714	N=1784

P for Interaction (ACS Medical, ACS PCI, Elective PCI) = **0.479**

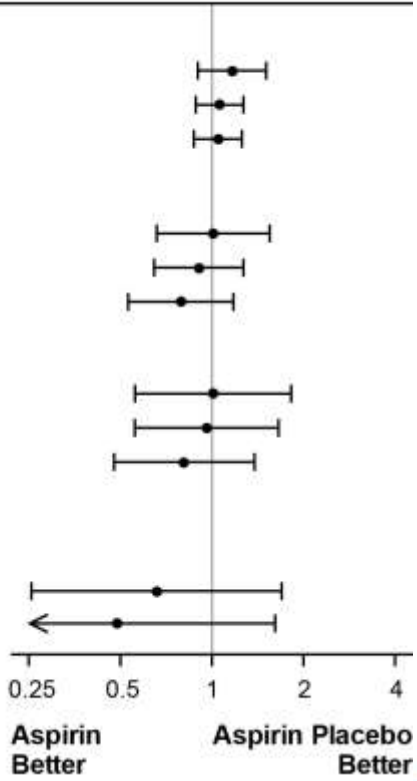






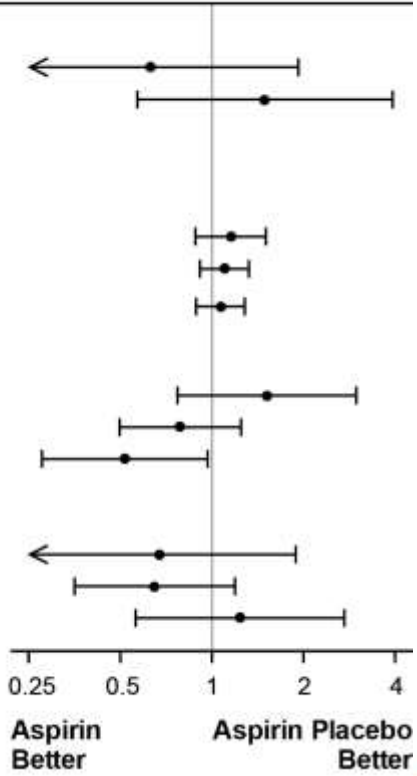
Ischemic Outcomes—Aspirin vs Placebo

Outcome	Aspirin n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	Interaction P-Value
Death or hospitalization					0.787
ACS and no PCI	123 / 547 (22.5%)	108 / 550 (19.6%)	1.16	0.90, 1.51	
ACS and PCI	237 / 844 (28.1%)	234 / 870 (26.9%)	1.06	0.88, 1.27	
Elective PCI	239 / 902 (26.5%)	226 / 882 (25.6%)	1.05	0.87, 1.25	
Death or ischemic event					0.710
ACS and no PCI	42 / 547 (7.7%)	42 / 550 (7.6%)	1.01	0.66, 1.55	
ACS and PCI	63 / 844 (7.5%)	72 / 870 (8.3%)	0.91	0.65, 1.27	
Elective PCI	44 / 902 (4.9%)	54 / 882 (6.1%)	0.79	0.53, 1.18	
Death					0.847
ACS and no PCI	22 / 547 (4.0%)	22 / 550 (4.0%)	1.01	0.56, 1.82	
ACS and PCI	25 / 844 (3.0%)	27 / 870 (3.1%)	0.96	0.56, 1.66	
Elective PCI	25 / 902 (2.8%)	30 / 882 (3.4%)	0.81	0.48, 1.38	
ARC definite or probable stent thrombosis					-
ACS and no PCI	0 / 547 (0.0%)	2 / 550 (0.4%)	-	-	
ACS and PCI	7 / 844 (0.8%)	11 / 870 (1.3%)	0.66	0.26, 1.70	
Elective PCI	4 / 902 (0.4%)	8 / 882 (0.9%)	0.49	0.15, 1.61	



Ischemic Outcomes—Aspirin vs Placebo (cont.)

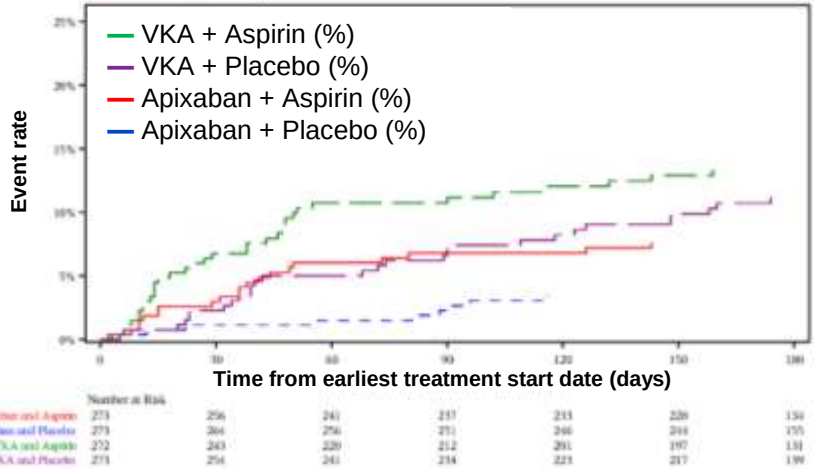
Outcome	Aspirin n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	Interaction P-Value
Stroke					-
ACS and no PCI	5 / 547 (0.9%)	8 / 550 (1.5%)	0.63	0.21, 1.92	
ACS and PCI	10 / 844 (1.2%)	7 / 870 (0.8%)	1.49	0.57, 3.93	
Elective PCI	5 / 902 (0.6%)	4 / 882 (0.5%)	-	-	
Hospitalization					0.893
ACS and no PCI	115 / 547 (21.0%)	102 / 550 (18.5%)	1.15	0.88, 1.51	
ACS and PCI	230 / 844 (27.3%)	219 / 870 (25.2%)	1.10	0.91, 1.32	
Elective PCI	235 / 902 (26.1%)	218 / 882 (24.7%)	1.07	0.89, 1.28	
Myocardial infarction					0.071
ACS and no PCI	21 / 547 (3.8%)	14 / 550 (2.5%)	1.52	0.77, 2.98	
ACS and PCI	32 / 844 (3.8%)	42 / 870 (4.8%)	0.79	0.50, 1.25	
Elective PCI	15 / 902 (1.7%)	28 / 882 (3.2%)	0.52	0.28, 0.97	
Urgent revascularization					0.421
ACS and no PCI	6 / 547 (1.1%)	9 / 550 (1.6%)	0.67	0.24, 1.89	
ACS and PCI	17 / 844 (2.0%)	27 / 870 (3.1%)	0.65	0.35, 1.19	
Elective PCI	14 / 902 (1.6%)	11 / 882 (1.2%)	1.24	0.56, 2.72	



ACS Medical

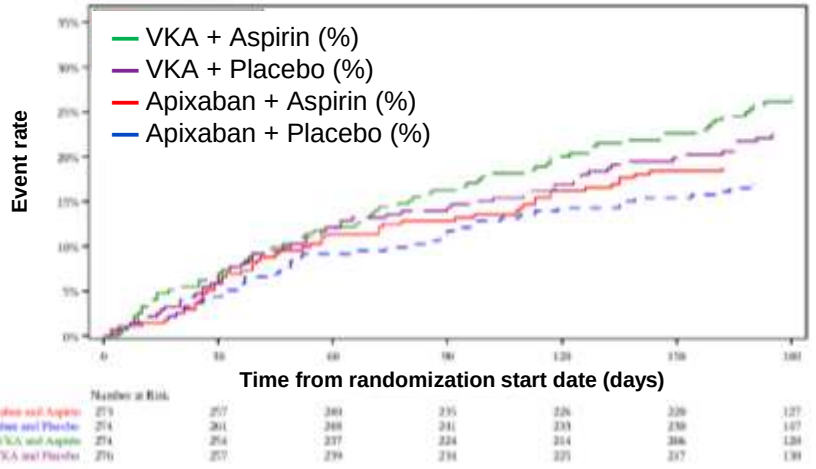
ISTH/CRNM Bleeding

Apixaban + Placebo vs. VKA + Aspirin:
10% absolute risk reduction (NNT=10)



Death/Hospitalization

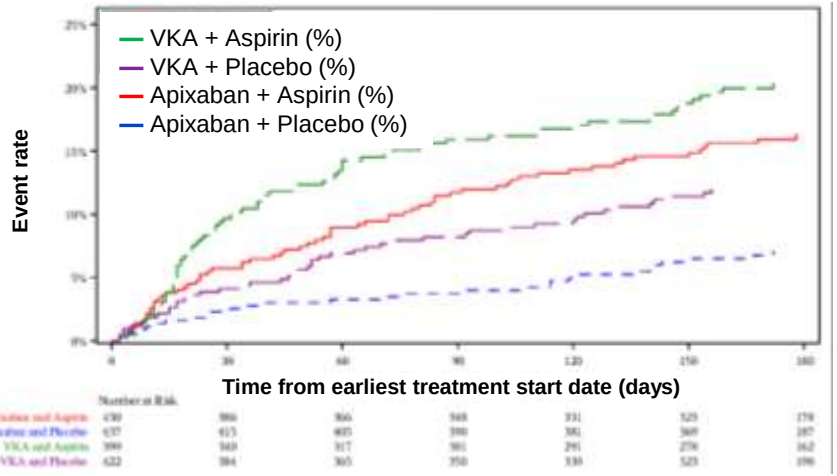
Apixaban + Placebo vs. VKA + Aspirin:
10% absolute risk reduction (NNT=10)



ACS PCI

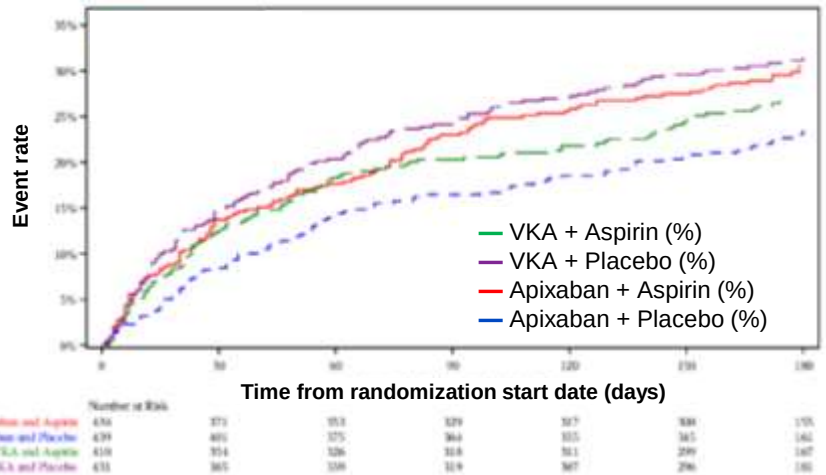
ISTH/CRNM Bleeding

Apixaban + Placebo vs. VKA + Aspirin:
12% absolute risk reduction (NNT=8)



Death/Hospitalization

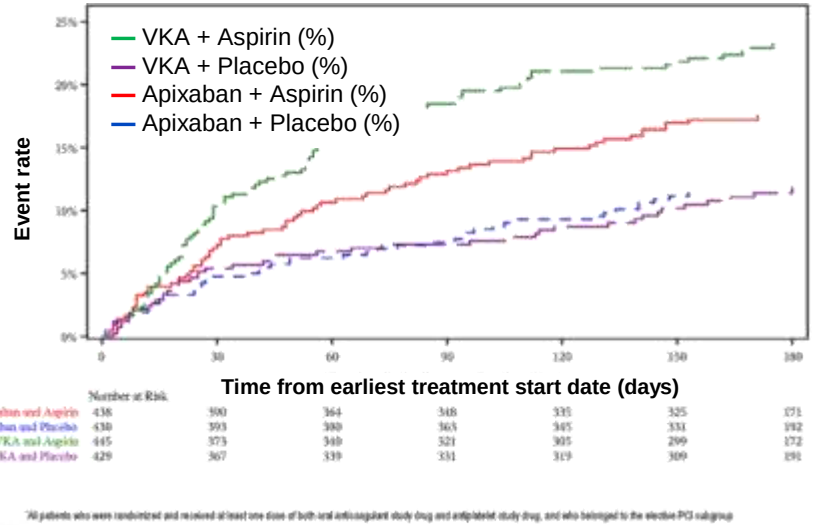
Apixaban + Placebo vs. VKA + Aspirin:
3.5% absolute risk reduction (NNT=29)



Elective PCI

ISTH/CRNM Bleeding

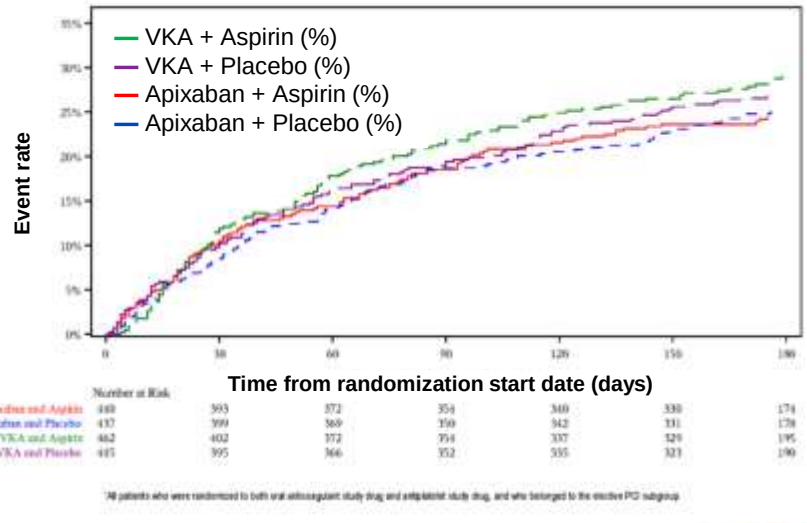
Apixaban + Placebo vs. VKA + Aspirin:
11% absolute risk reduction (NNT=9)



*All patients who were randomized and received at least one dose of both oral anticoagulant study drug and antiplatelet study drug, and who belonged to the elective PCI subgroup

Death/Hospitalization

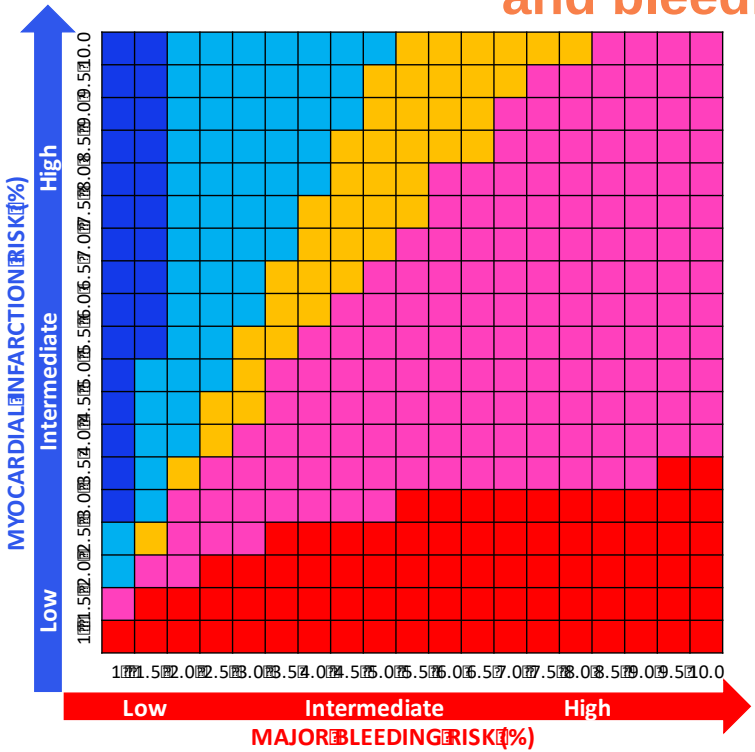
Apixaban + Placebo vs. VKA + Aspirin:
3.9% absolute risk reduction (NNT=26)



*All patients who were randomized to both oral anticoagulant study drug and antiplatelet study drug, and who belonged to the elective PCI subgroup

Understanding and Managing the Trade Off

NNT vs NNB across the entire spectrum of ischemic and bleeding risks



orange: equipoise with -10 +10
light red: slight benefit -10 to -100
light blue: slight harm 10 to 100
dark blue: relevant harm > 100
dark red: relevant benefit <-100

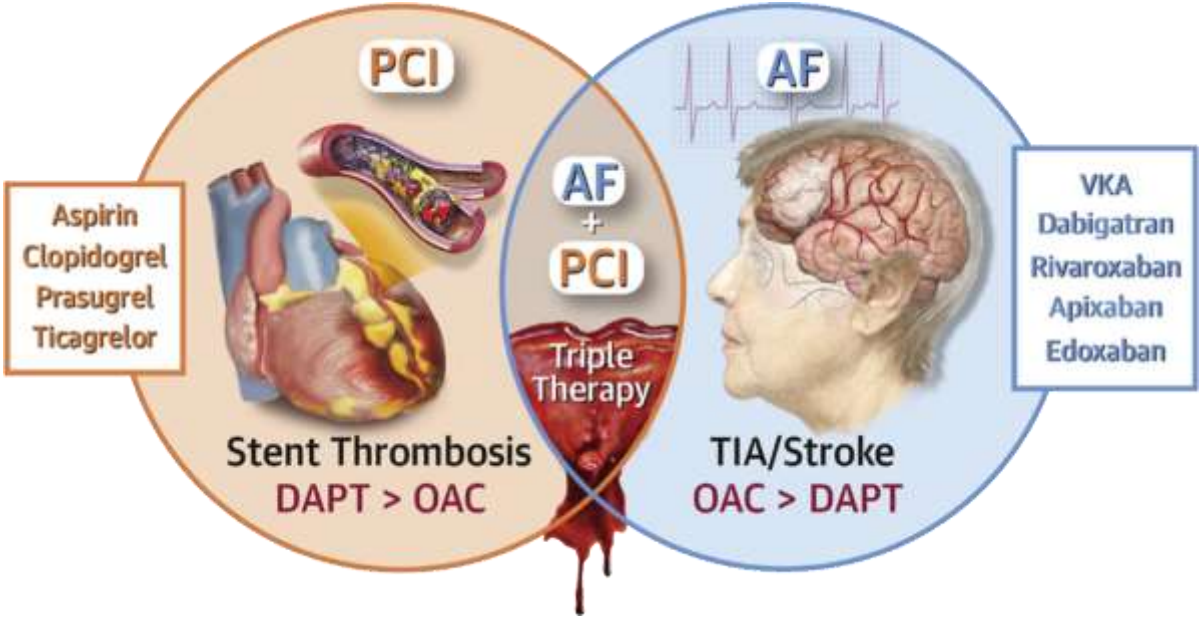
Conclusions

NOAC should be prioritized over VKA in all patients with AF undergoing PCI without contra-indications

The optimal timing for the transition from triple to dual AT (i.e. dropping ASA) should be probably individualized given the clear trade-off between bleeding benefit and ischemic risk.

VKA is dead…after the WOEST…PIONEER AF PCI, RE-DUAL….

ASA duration is short in ACS patients. Unknown is duration of P2Y12 vs switch back to ASA


PCI
Aspirin
Clopidogrel
Prasugrel
Ticagrelor
Stent Thrombosis
DAPT > OAC
AF
+
PCI
Triple Therapy
AF
VKA
Dabigatran
Rivaroxaban
Apixaban
Edoxaban
TIA/Stroke
OAC > DAPT