CUORE, RENE E DINTORNI
Domande e risposte su terapia, dieta, attività fisica e riabilitazione
Sabato 16 NOVEMBRE 2019
Fondazione Cassa di Risparmio di Gorizia – GORIZIA

Le basse dosi di NAO in tema di riperfusione coronarica: attualità

Dr. Andrea Perkan

S.C. Cardiologia

ASUI Trieste

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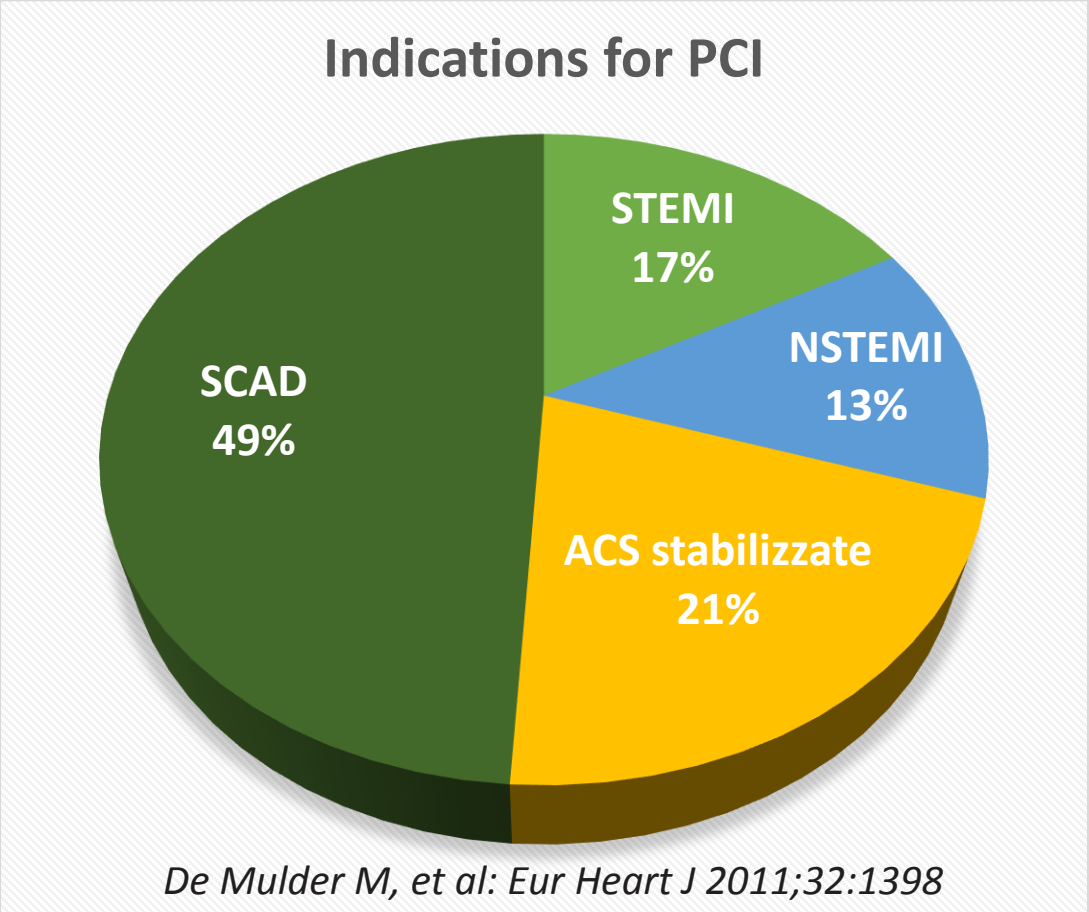
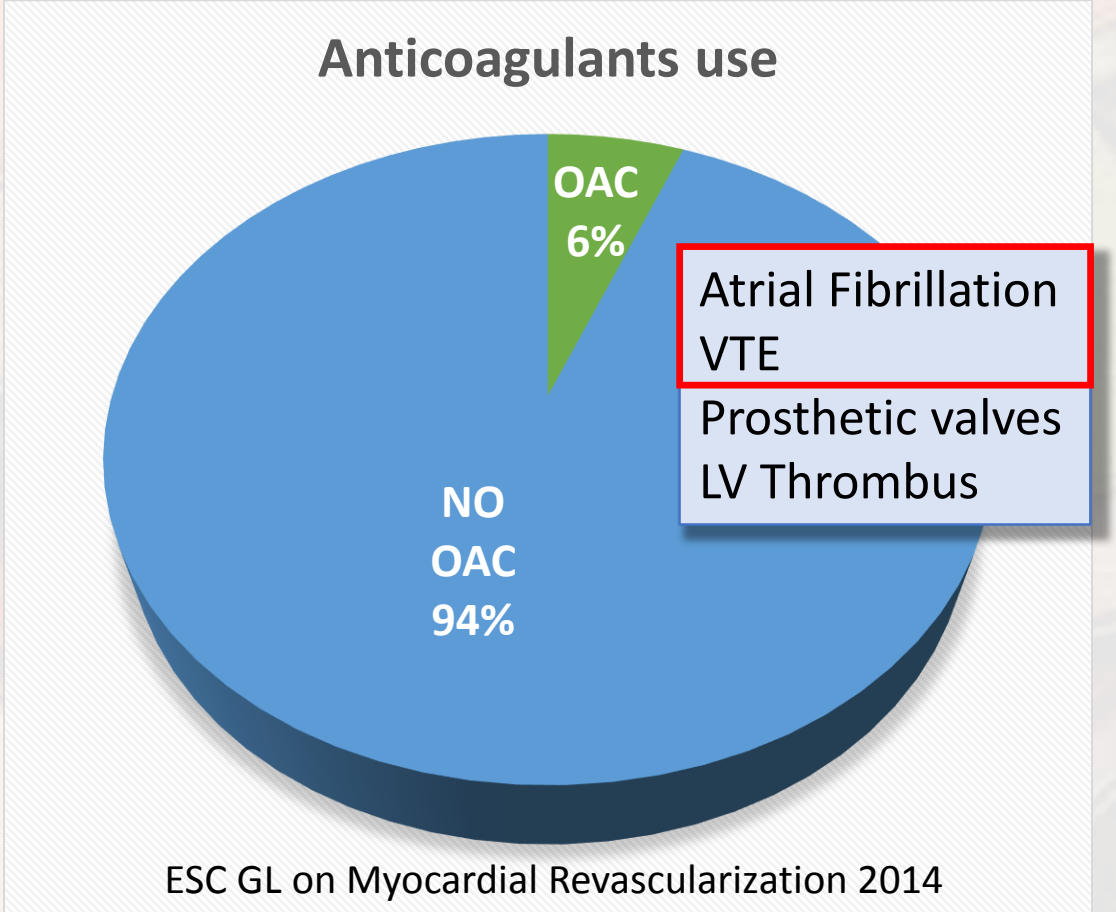
Coronary Procedures in Cath Lab

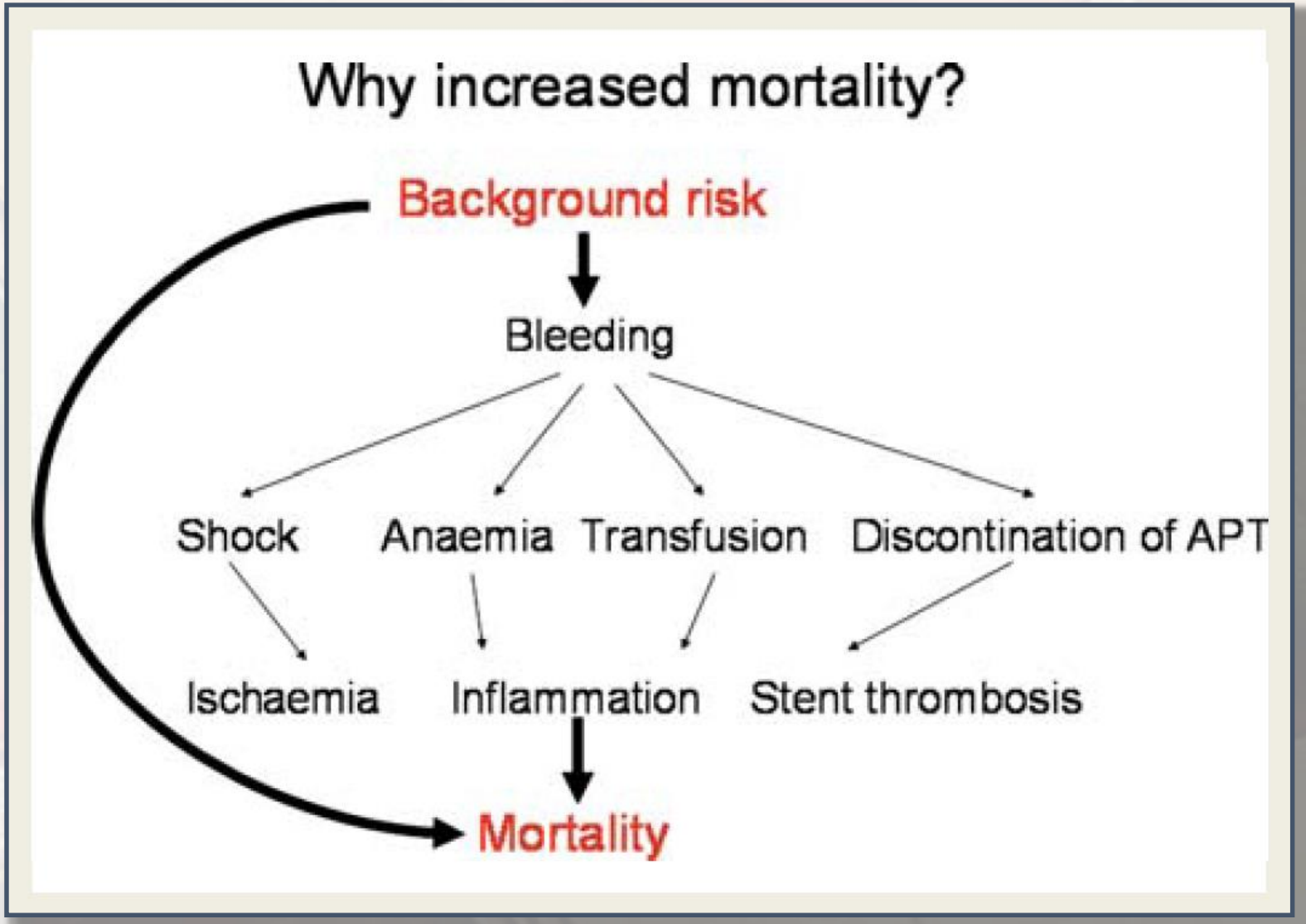


De Mulder M, et al: Eur Heart J 2011;32:1398



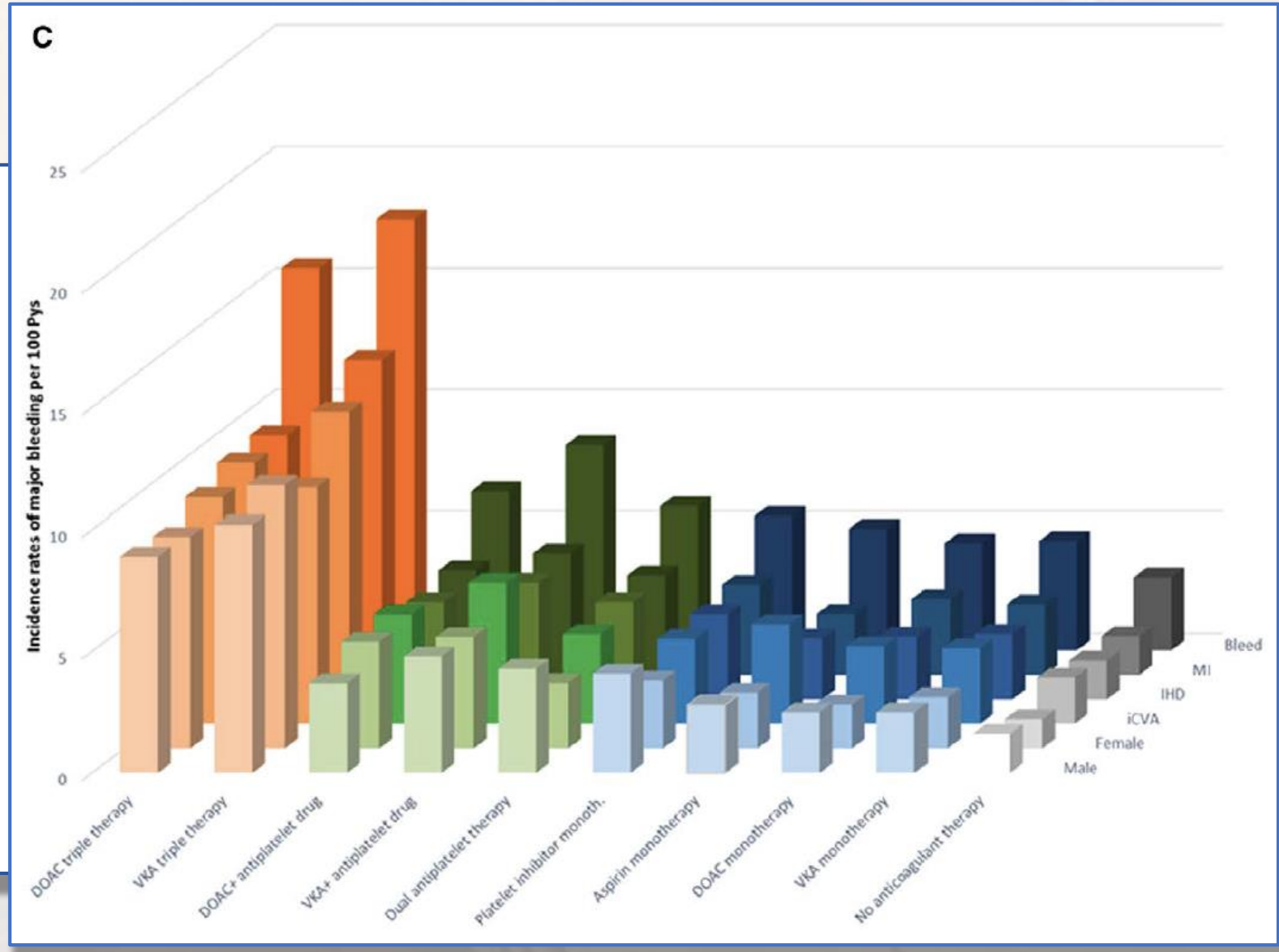
ESC GL on Myocardial Revascularization 2014

Hypothetical mechanisms linking bleeding and mortality



Steg PG, et al: Eur Heart J. 2011;32:1854

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, DOAC Aspirin, and Clopidogrel in Patients With Atrial Fibrillation



Van Rein N, et al: Circulation. 2019;139:775

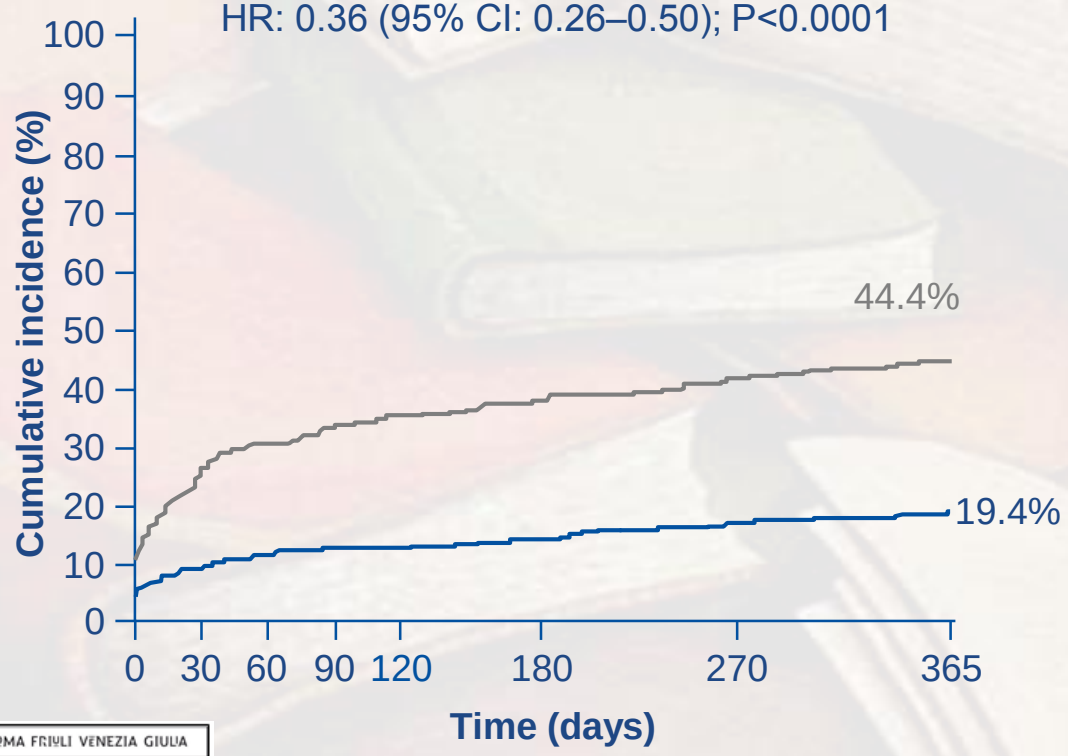
WOEST trial: the benefits of dual therapy over triple therapy with VKA in post-PCI patients

573 VKA-treated patients (any indication, 69% for AF/atrial flutter) undergoing PCI in the open-label, randomized WOEST trial

Triple therapy group (VKA + clopidogrel + ASA) — Double therapy group (VKA + clopidogrel)

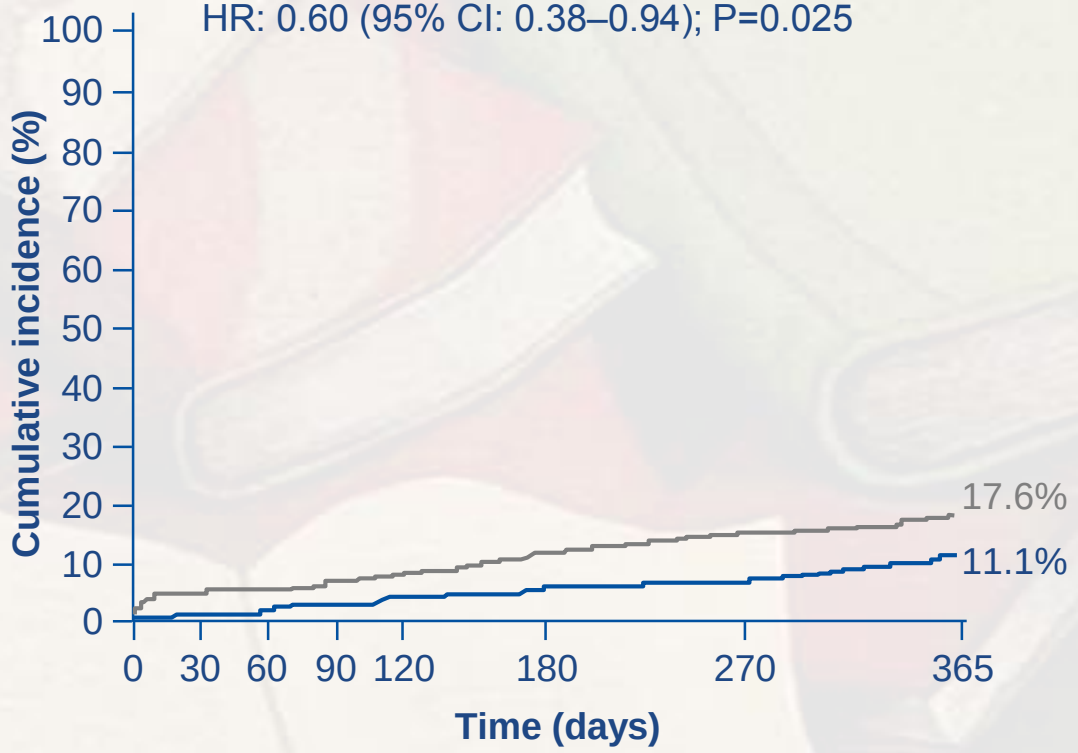
Total number of TIMI bleeding events

HR: 0.36 (95% CI: 0.26–0.50); P<0.0001



Death, MI, TVR, stroke, ST

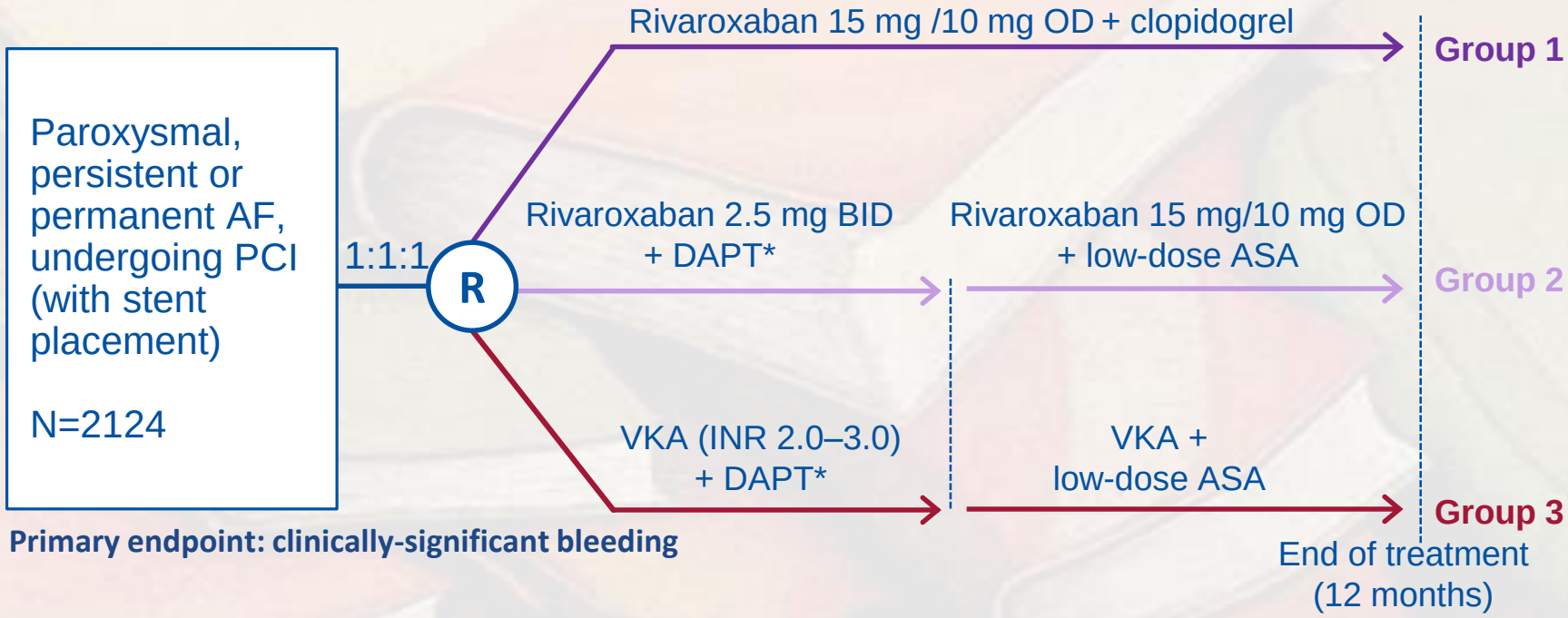
HR: 0.60 (95% CI: 0.38–0.94); P=0.025



Dewilde et al. Lancet 2013;381:1107

PIONEER AF-PCI compared regimens of rivaroxaban with single or dual antiplatelet therapy

Multicentre, randomized, open-label trial



- **Rivaroxaban 2.5 mg BID has not been tested or approved for stroke prevention in AF**
- **Rivaroxaban 15 mg OD regimen has been tested in 1474 in patients with moderate renal dysfunction (ROCKET-AF)**
- **Rivaroxaban 15/10 mg OD regimen has been tested in 639 Japanese patients for stroke prevention in AF (J-ROCKET)**

**DAPT duration 1, 6 or 12 months (physician choice)*

Gibson et al. N Engl J Med 2016; Fox et al. Eur Heart J 2011; Hori et al. Circ J 2012

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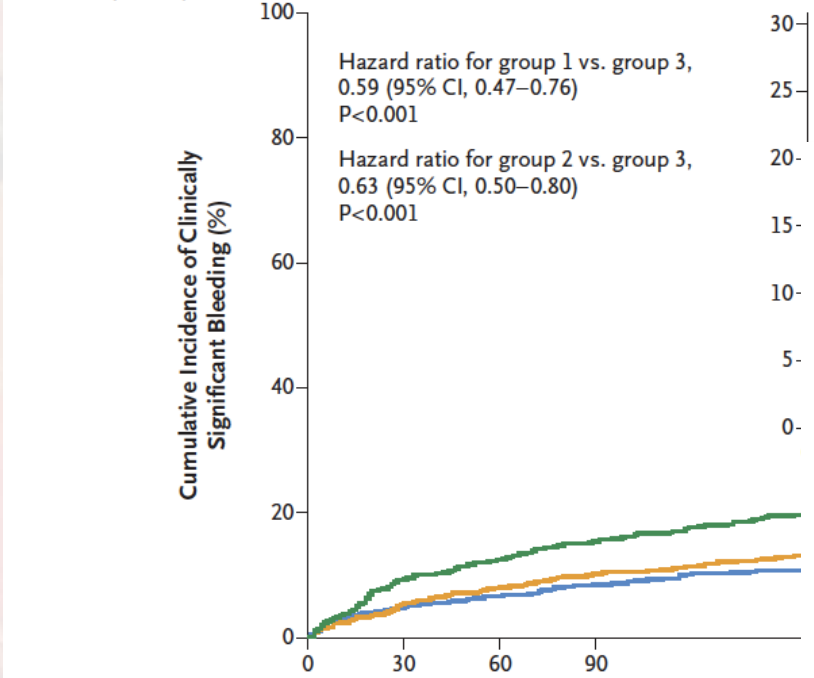
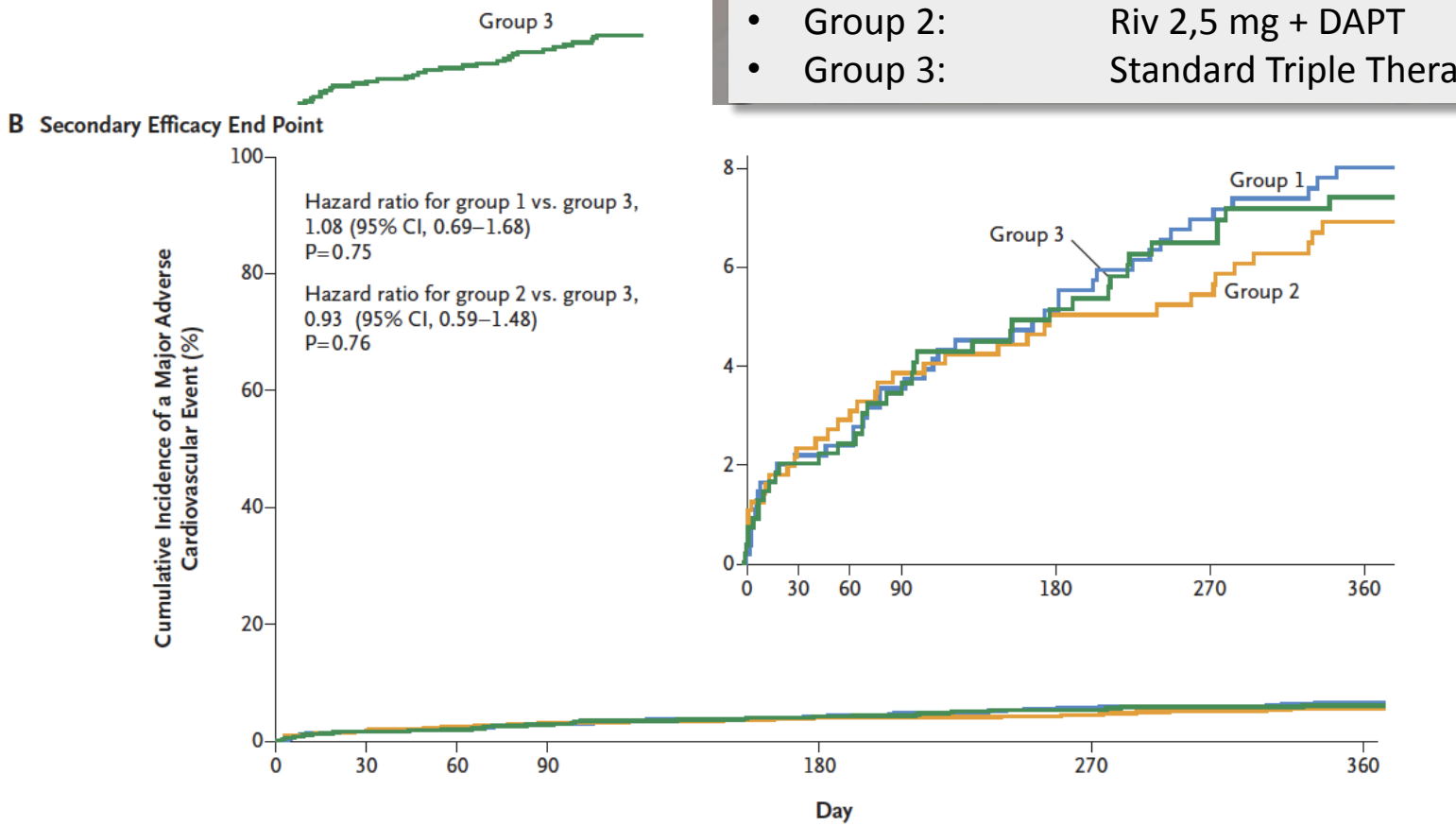
Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

- Group 1: Riv 15 mg + P2Y12 Inh
- Group 2: Riv 2,5 mg + DAPT
- Group 3: Standard Triple Therapy



No. at Risk				
Group 1	696	628	606	585
Group 2	706	636	600	579
Group 3	697	593	555	521



No. at Risk							
Group 1	694	648	633	621	590	562	430
Group 2	704	662	640	628	596	570	457
Group 3	695	635	607	579	543	514	408

Gibson CM, et al.: N Engl J Med. 2016

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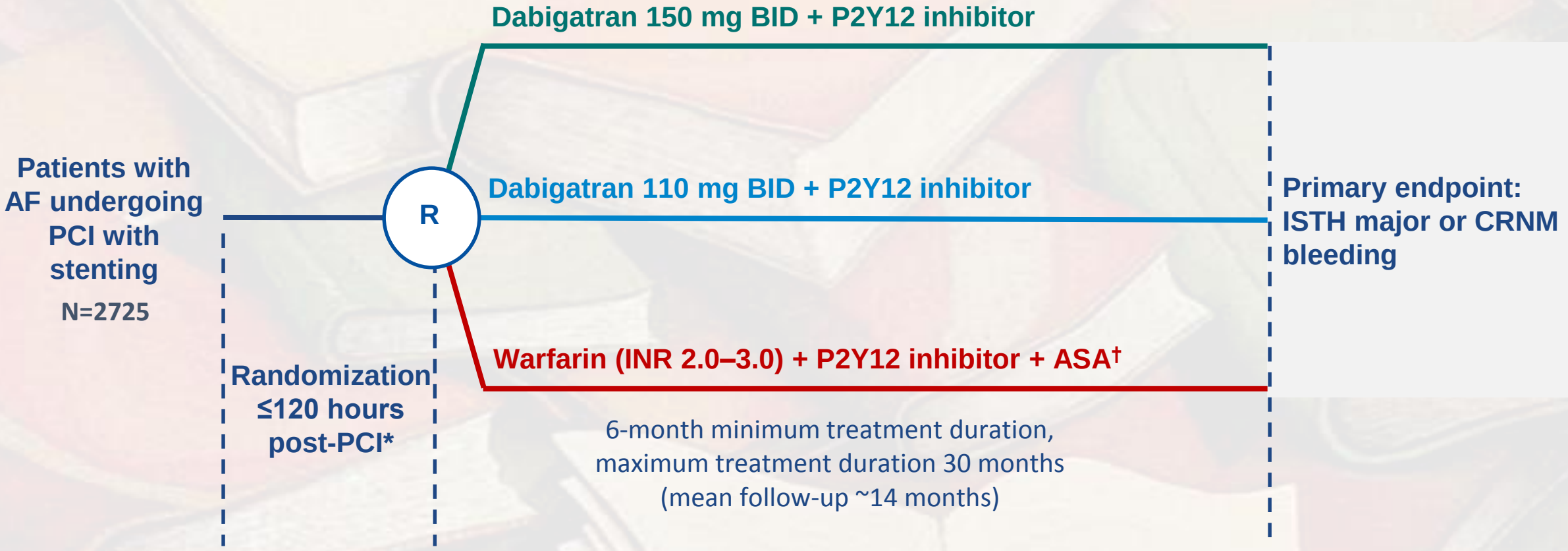
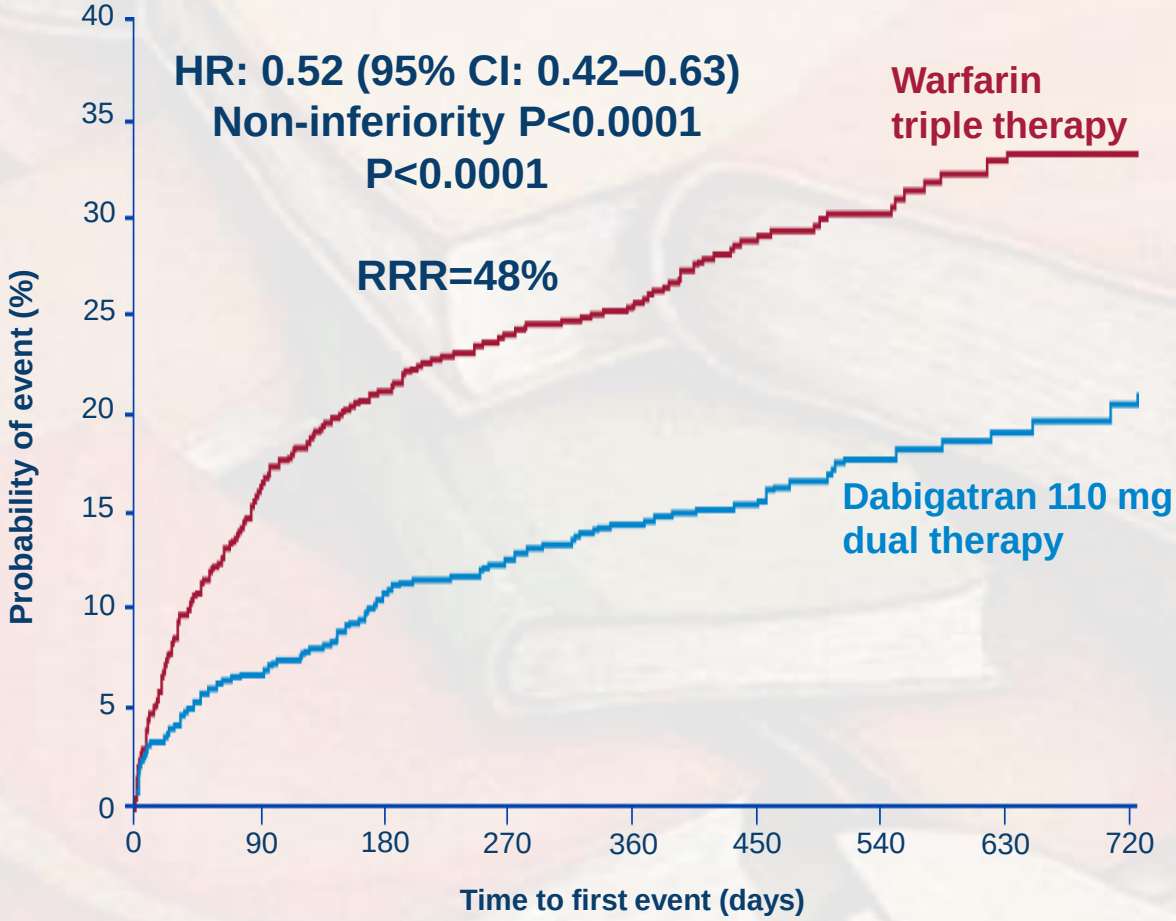
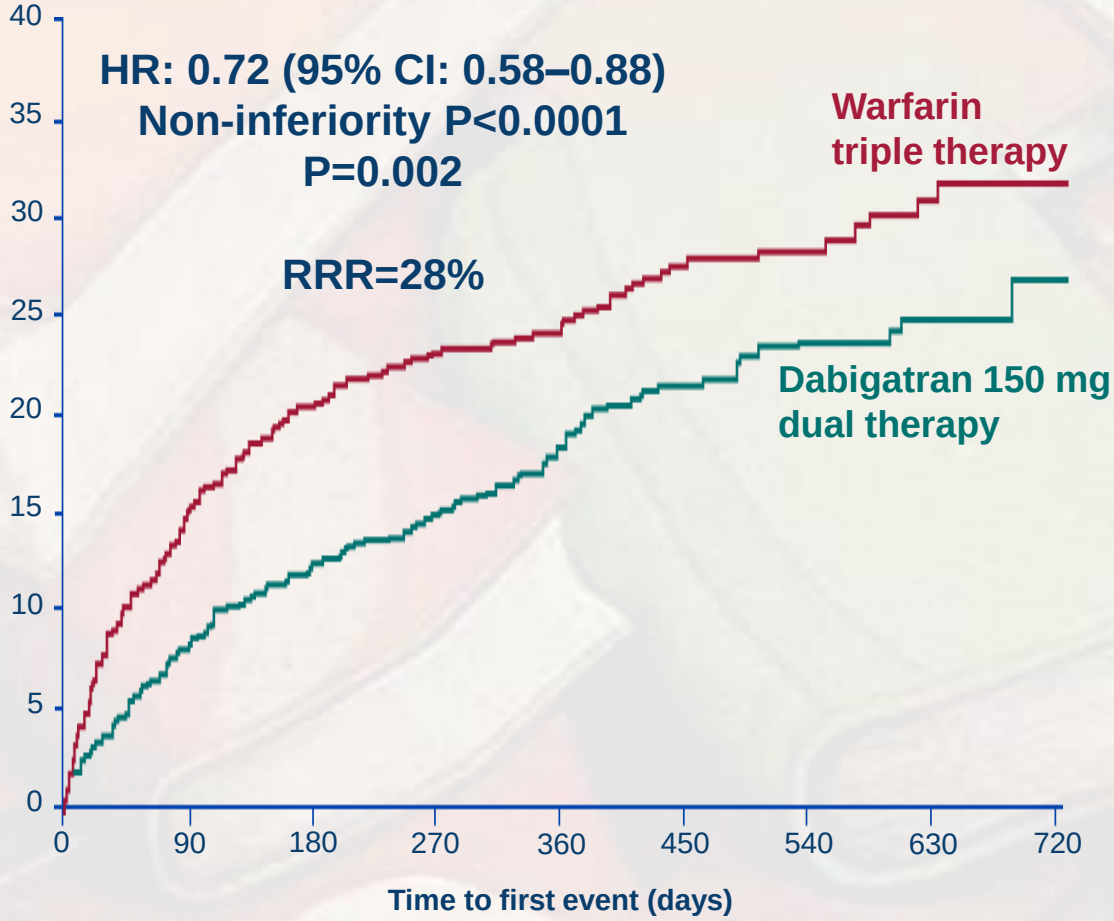
RE-DUAL PCI: safety and efficacy of two regimens of dual therapy with dabigatran without ASA vs triple therapy with warfarin



Cannon et al. Clin Cardiol 2016; Cannon et al. N Engl J Med 2017

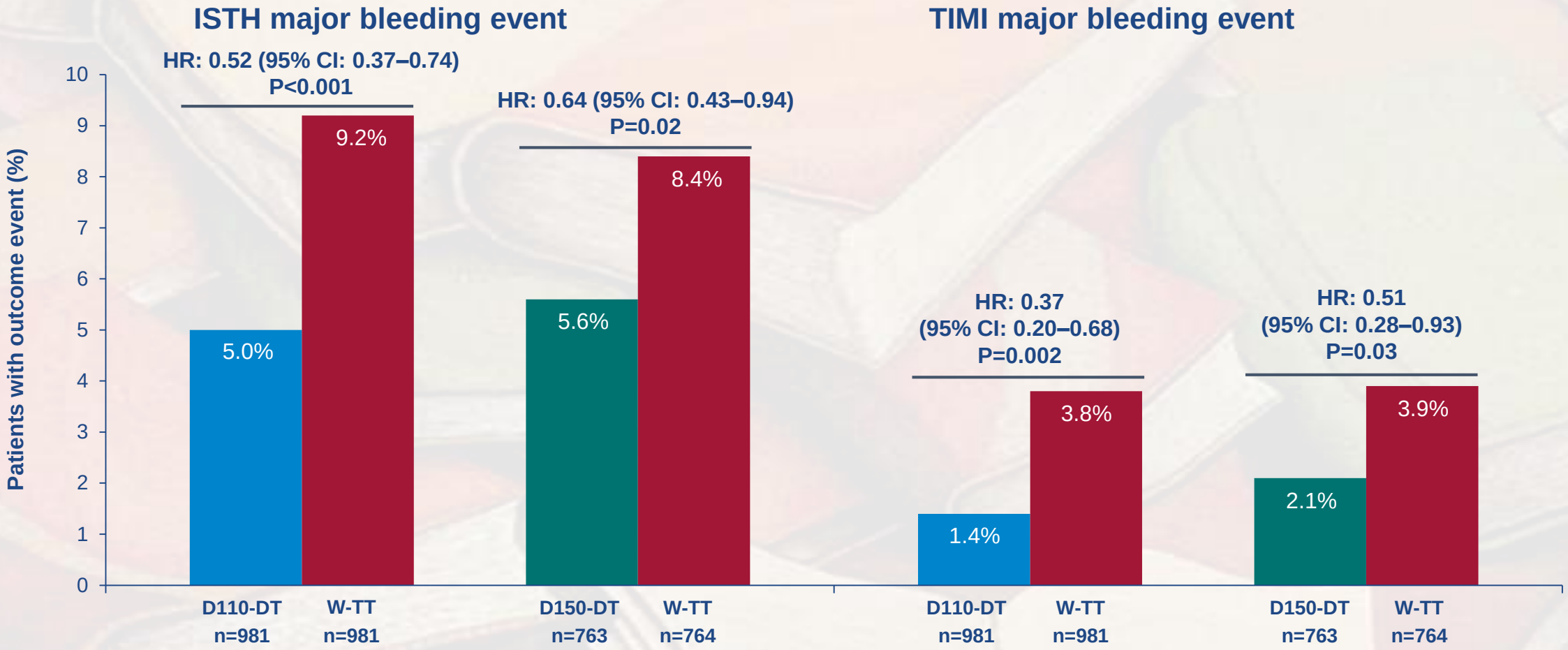
Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event





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)

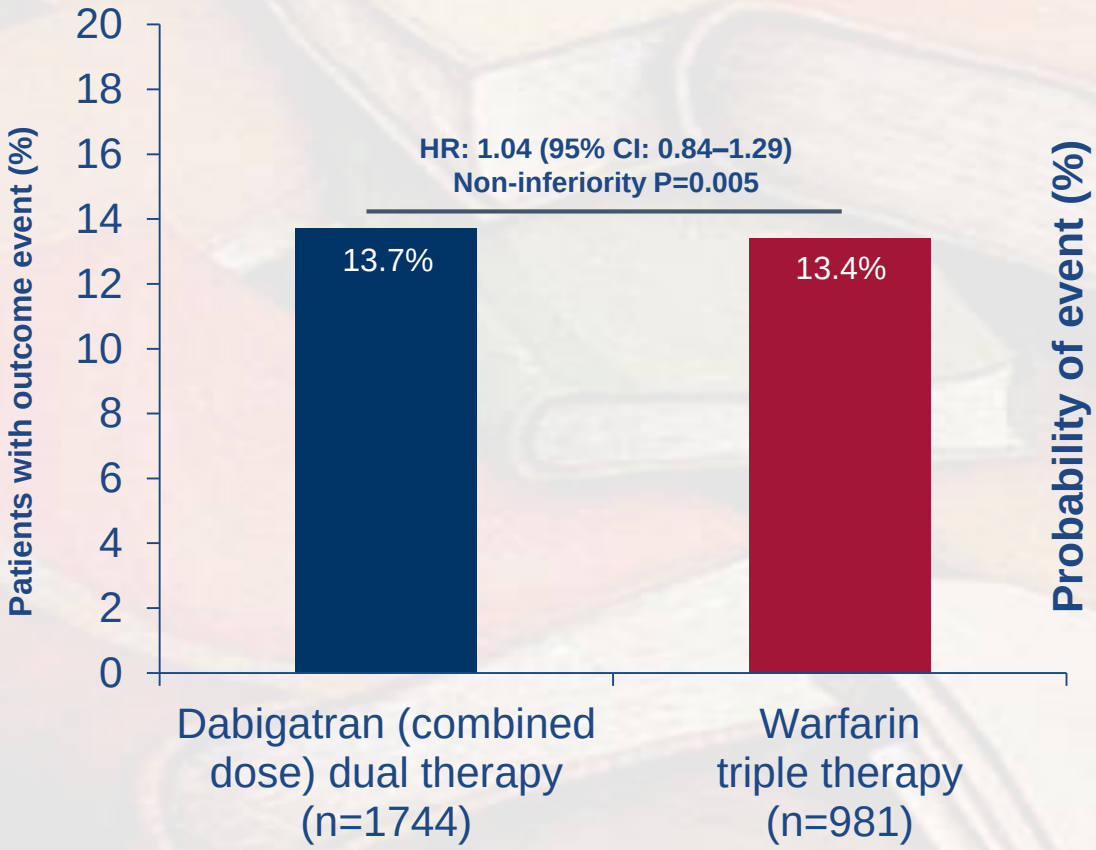
ISTH and TIMI major bleeding: significantly lower rates for dabigatran dual therapy

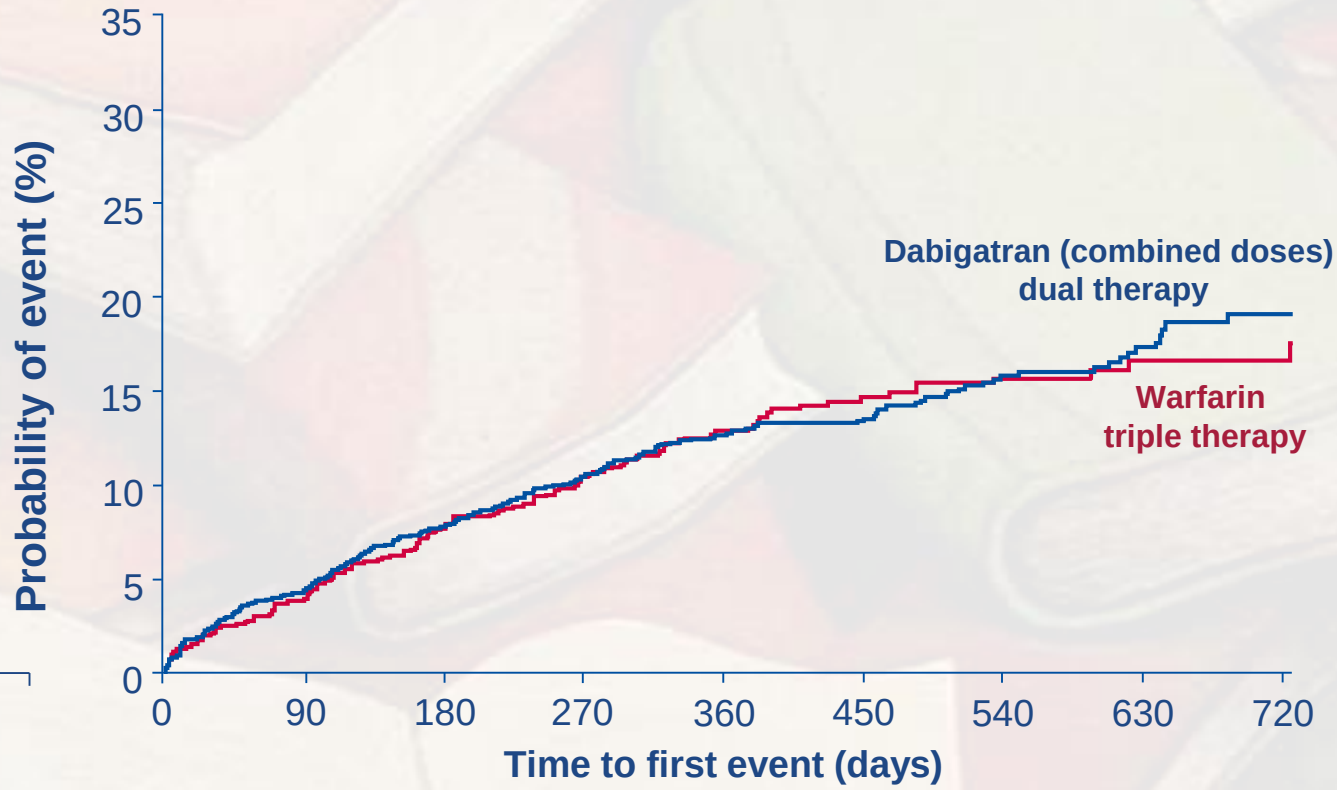


ISTH major bleeding definition: fatal, critical organ (including ICH), clinically overt bleeding with fall in Hb ≥2 g/dL; TIMI major bleeding definition: fatal, ICH, clinically overt bleeding with fall in Hb ≥5 g/dL. D110/150-DT, dabigatran 110 mg/150 mg dual therapy; ISTH, International Society on Thrombosis and Haemostasis; TIMI, Thrombolysis in Myocardial Infarction; W-TT, warfarin triple therapy; Cannon et al. N Engl J Med 2017

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

Composite endpoint of death or thromboembolic event (MI, stroke or systemic embolism) or unplanned revascularization (PCI/CABG)





Cannon et al. N Engl J Med 2017; Cannon et al ESC 2017

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ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

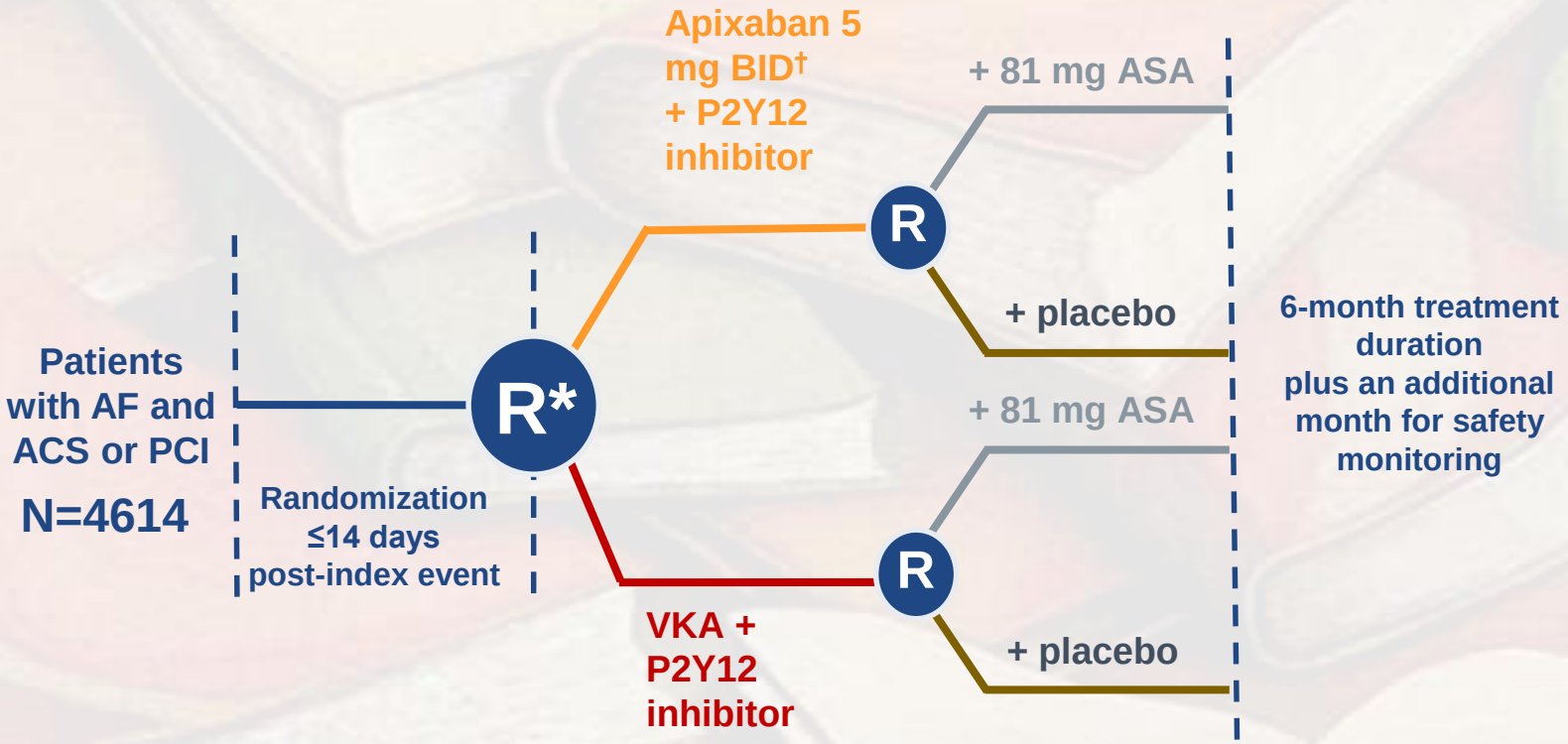
Table 3. Efficacy End Points.*

End Point	Dual Therapy with Dabigatran (Combined) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (110 mg) vs. Triple Therapy with Warfarin				Dual Therapy with Dabigatran (150 mg) vs. Triple Therapy with Warfarin			
	Combined Dual-Therapy Groups (N=1744)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	110-mg Dual-Therapy Group (N=981)	Triple-Therapy Group (N=981)	Hazard Ratio (95% CI)	P Value†	150-mg Dual-Therapy Group (N=763)	Corresponding Triple-Therapy Group (N=764)	Hazard Ratio (95% CI)	P Value†
	no. (%)				*no. (%)*				*no. (%)*			
Composite efficacy end point: thromboembolic events, death, or unplanned revascularization	239 (13.7)	131 (13.4)	1.04 (0.84–1.29)	0.74 (0.005 for noninferiority)	149 (15.2)	131 (13.4)	1.13 (0.90–1.43)	0.30	90 (11.8)	98 (12.8)	0.89 (0.67–1.19)	0.44
Thromboembolic events or death	168 (9.6)	83 (8.5)	1.17 (0.90–1.53)	0.25 (0.11 for noninferiority)	108 (11.0)	83 (8.5)	1.30 (0.98–1.73)	0.07	60 (7.9)	60 (7.9)	0.97 (0.68–1.39)	0.88
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
Myocardial infarction					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
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
Definite 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

Cannon CP et al: N Engl J Med 2017;377:1513

AUGUSTUS compared the safety of apixaban vs VKA and single vs dual antiplatelet therapy

Multicentre, prospective, open-label, 2x2 factorial, randomized trial



Primary endpoint: ISTH major or CRNM bleeding

**All patients received ASA on the day of ACS and/or PCI until randomization; †Apixaban 2.5 mg BID if ≥2 of the following criteria were met: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL (133 µmol/L)*

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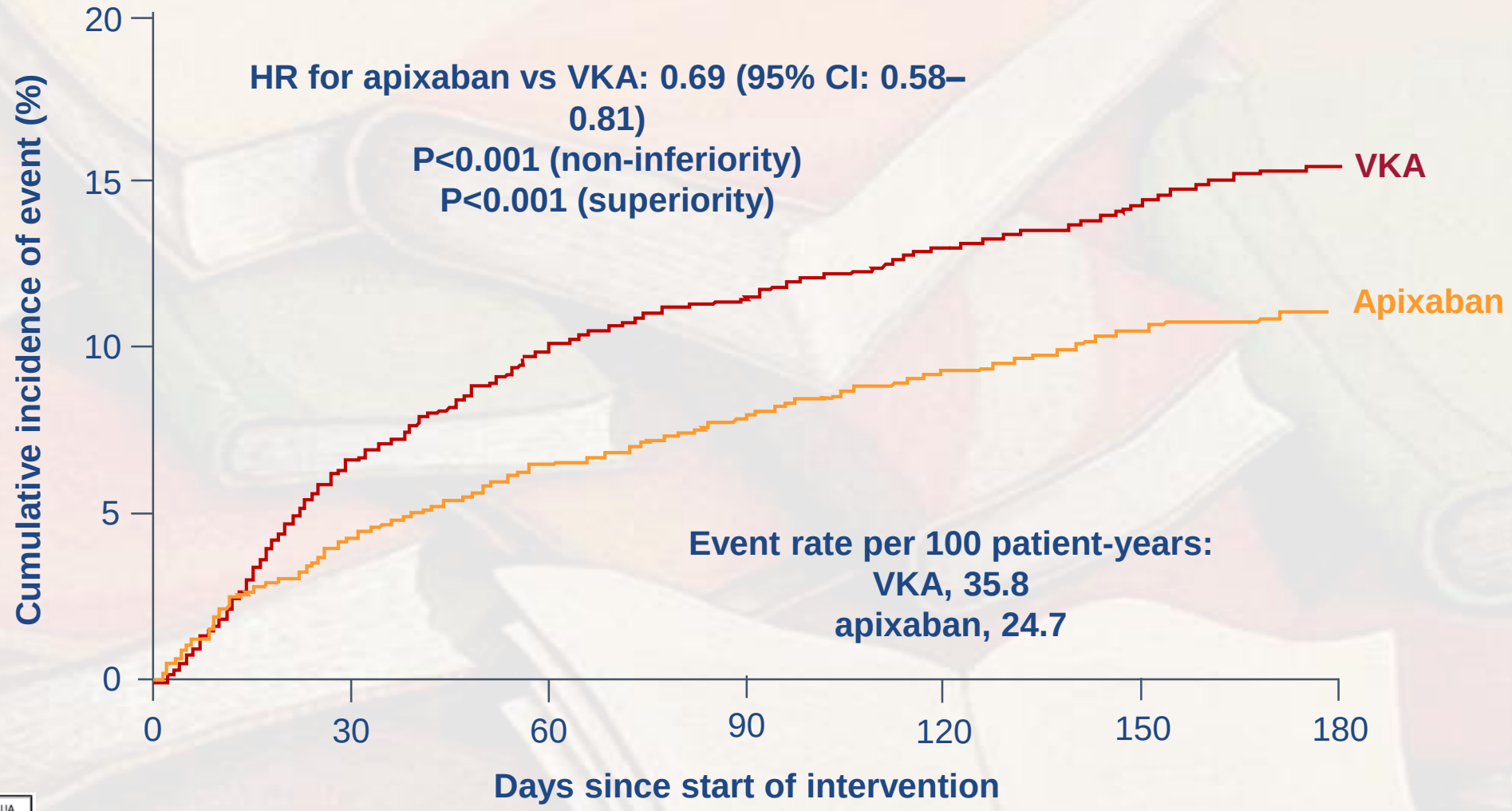
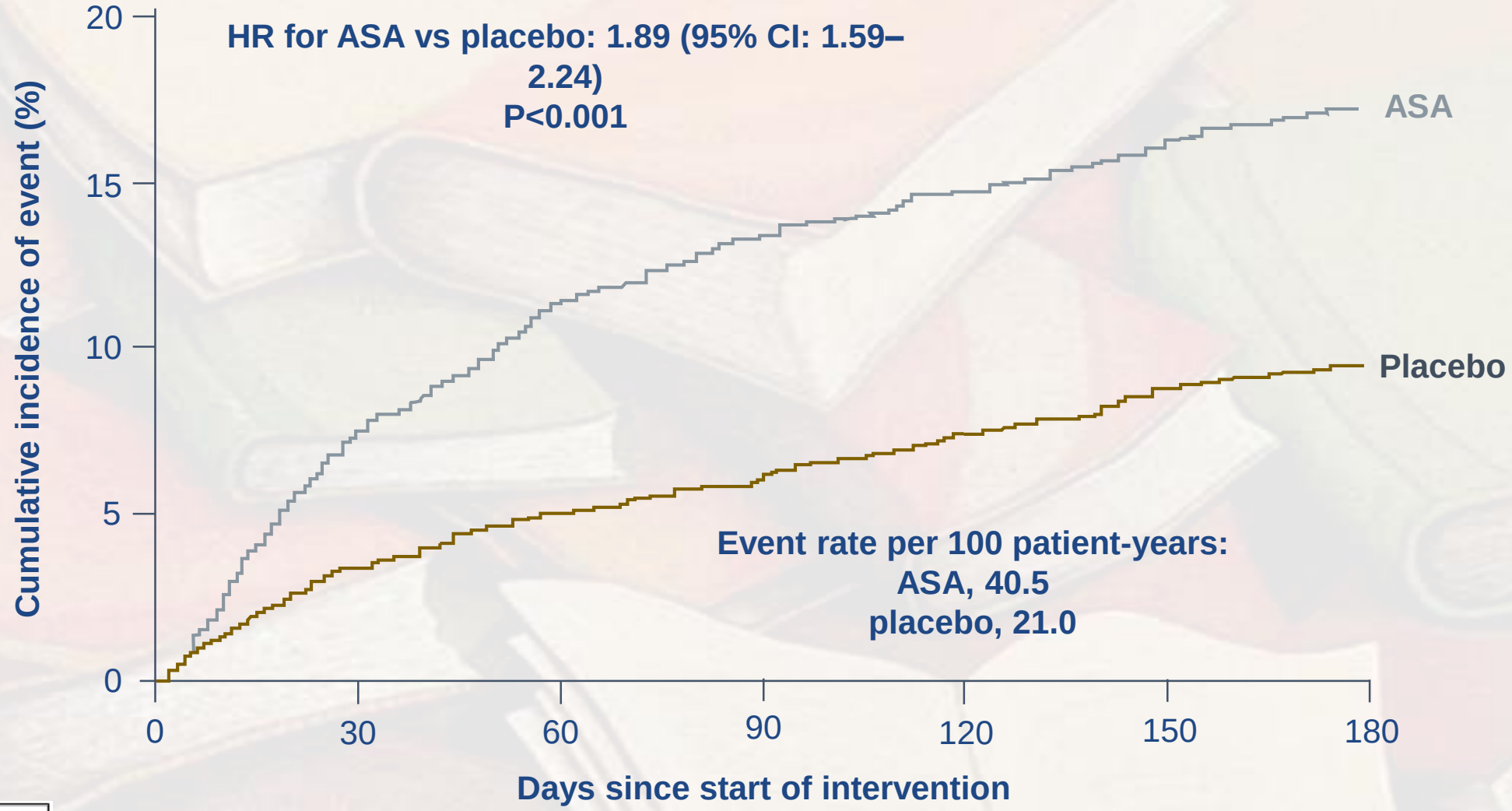
Lopes et al. Am Heart J 2018;200:17; Lopes et al. NEJM 2019; doi:10.1056/NEJMoa1817083

AUGUSTUS primary safety endpoint results: lower ISTH major or CRNM bleeding rates with apixaban vs VKA



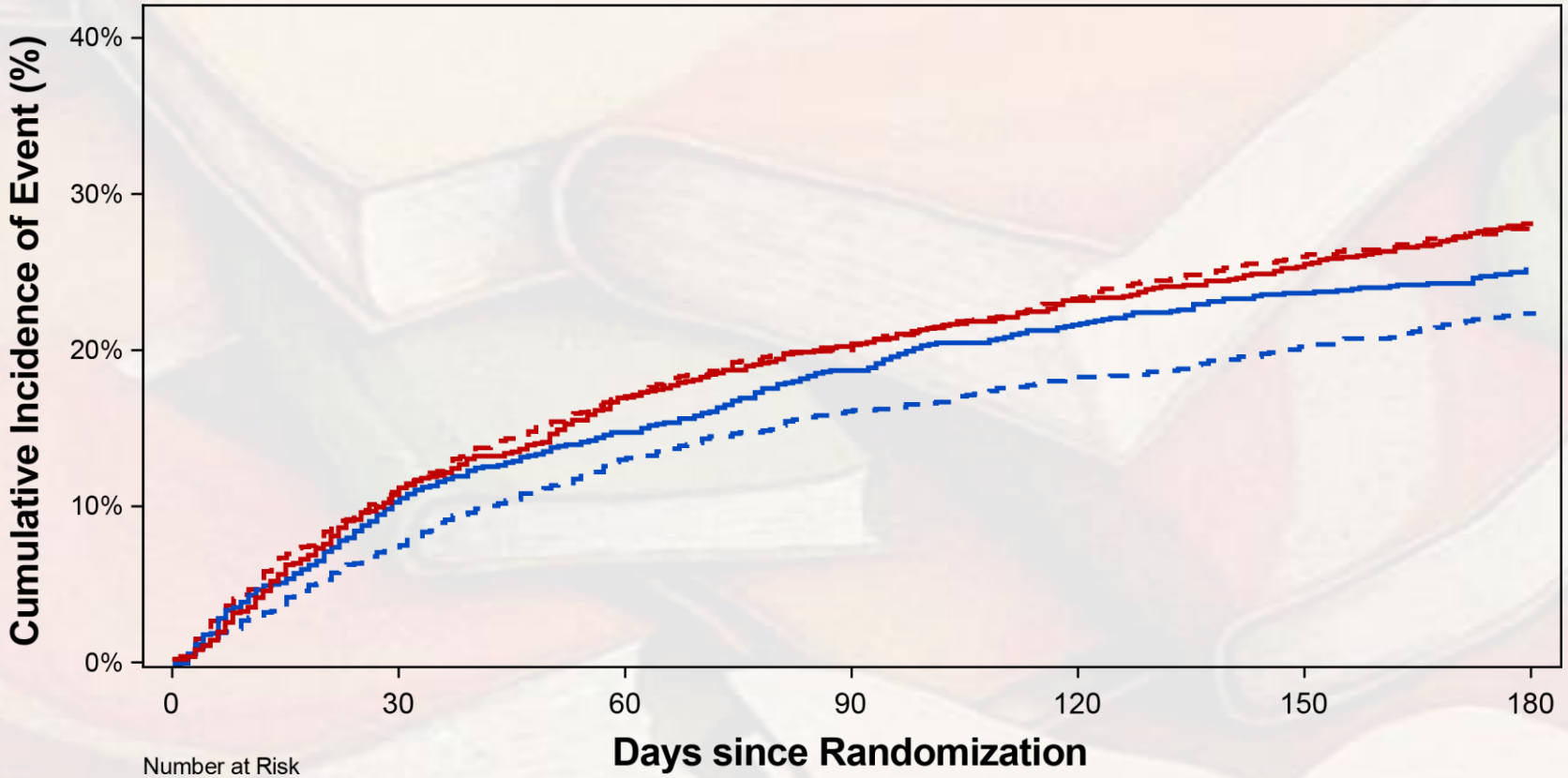
Lopes et al. NEJM 2019; doi:10.1056/NEJMoa1817083

AUGUSTUS primary safety endpoint results: lower ISTH major or CRNM bleeding rates with placebo vs ASA



Lopes et al. NEJM 2019; doi:10.1056/NEJMoa1817083

AUGUSTUS Trial: Death / Hospitalization



Number at Risk

Apixaban and Aspirin	1153	1026	970	923	888	863	459
Apixaban and Placebo	1153	1064	995	958	933	909	488
VKA and Aspirin	1154	1016	939	899	864	836	492
VKA and Placebo	1154	1019	946	906	868	837	509

VKA + Aspirin (27.5%)
VKA + Placebo (27.3%)
Apixaban + Aspirin (24.9%)
Apixaban + Placebo (22.0%)

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- *Lopes et al. NEJM 2019; doi:10.1056/NEJMoa1817083*

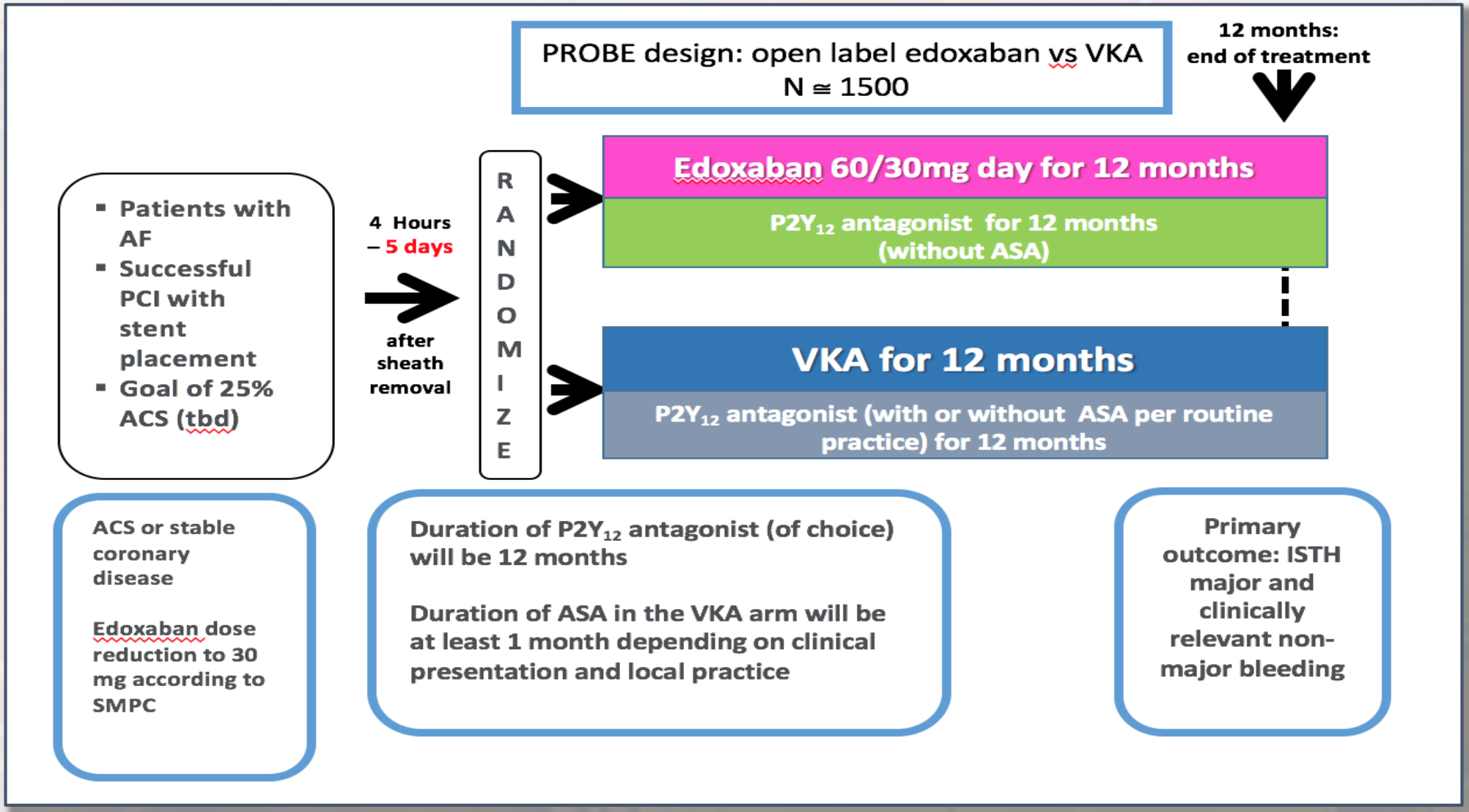
AUGUSTUS Trial: Safety Cardiovascular Events

Table 3. Additional Safety and Efficacy Outcomes of Interest.*

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	
Hospitalization						
No. of patients with event (%)	518 (22.5)	607 (26.3)	—	585 (25.4)	540 (23.4)	—
Event rate per 100 patient-yr	54.8	66.5	0.83 (0.74–0.93)	63.7	57.5	1.10 (0.98–1.24)
Death						
No. of patients with event (%)	77 (3.3)	74 (3.2)	—	72 (3.1)	79 (3.4)	—
Event rate per 100 patient-yr	7.0	6.7	1.03 (0.75–1.42)	6.6	7.2	0.91 (0.66–1.26)
Death from cardiovascular causes						
No. of patients with event (%)	57 (2.5)	54 (2.3)	—	53 (2.3)	58 (2.5)	—
Event rate per 100 patient-yr	5.2	4.9	1.05 (0.72–1.52)	4.8	5.3	0.92 (0.63–1.33)
Stroke						
No. of patients with event (%)	13 (0.6)	26 (1.1)	—	20 (0.9)	19 (0.8)	—
Event rate per 100 patient-yr	1.2	2.4	0.50 (0.26–0.97)	1.8	1.7	1.06 (0.56–1.98)
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)

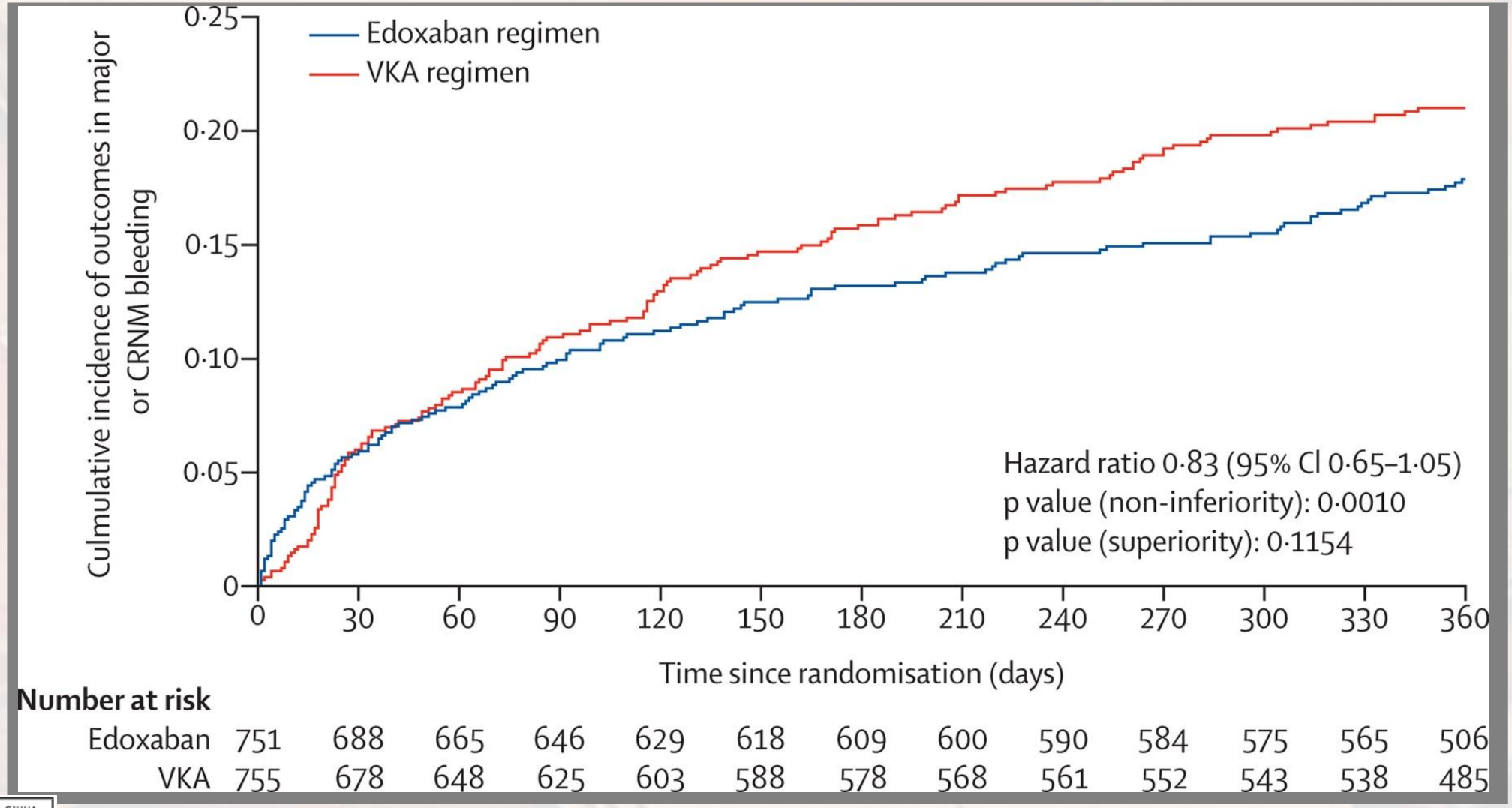
- *Lopes et al. NEJM 2019; doi:10.1056/NEJMoa1817083*

ENTRUST AF-PCI



Vranckx et al. Lancet 2019

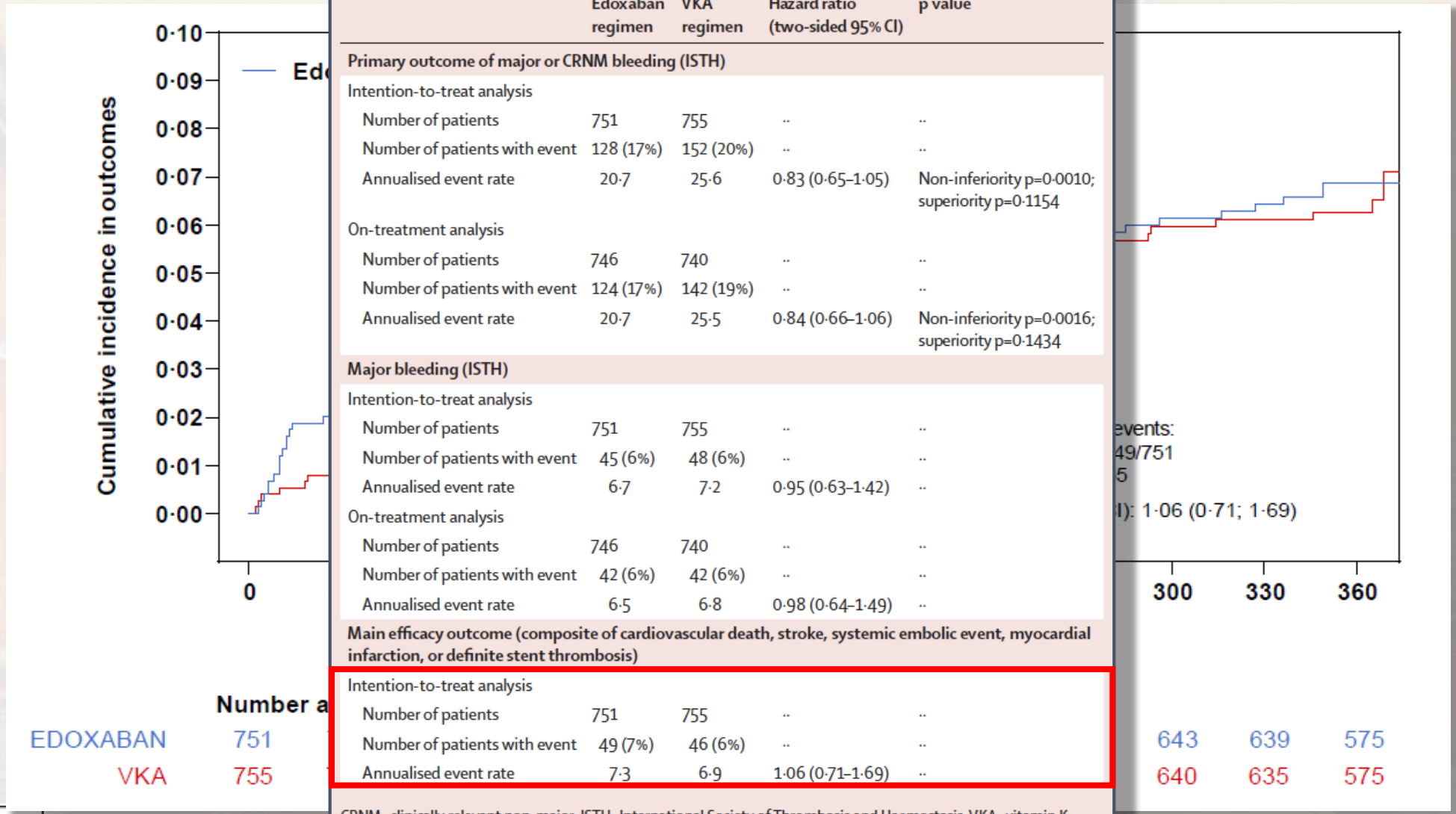
ENTRUST AF PCI primary safety endpoint results: edoxaban was non-inferior to warfarin ISTH major or CRNM bleeding



The Lancet DOI: (10.1016/S0140-6736(19)31872-0)

Vranckx et al. Lancet 2019

ENTRUST AF PCI efficacy endpoint results: edoxaban was non-inferior to warfarin



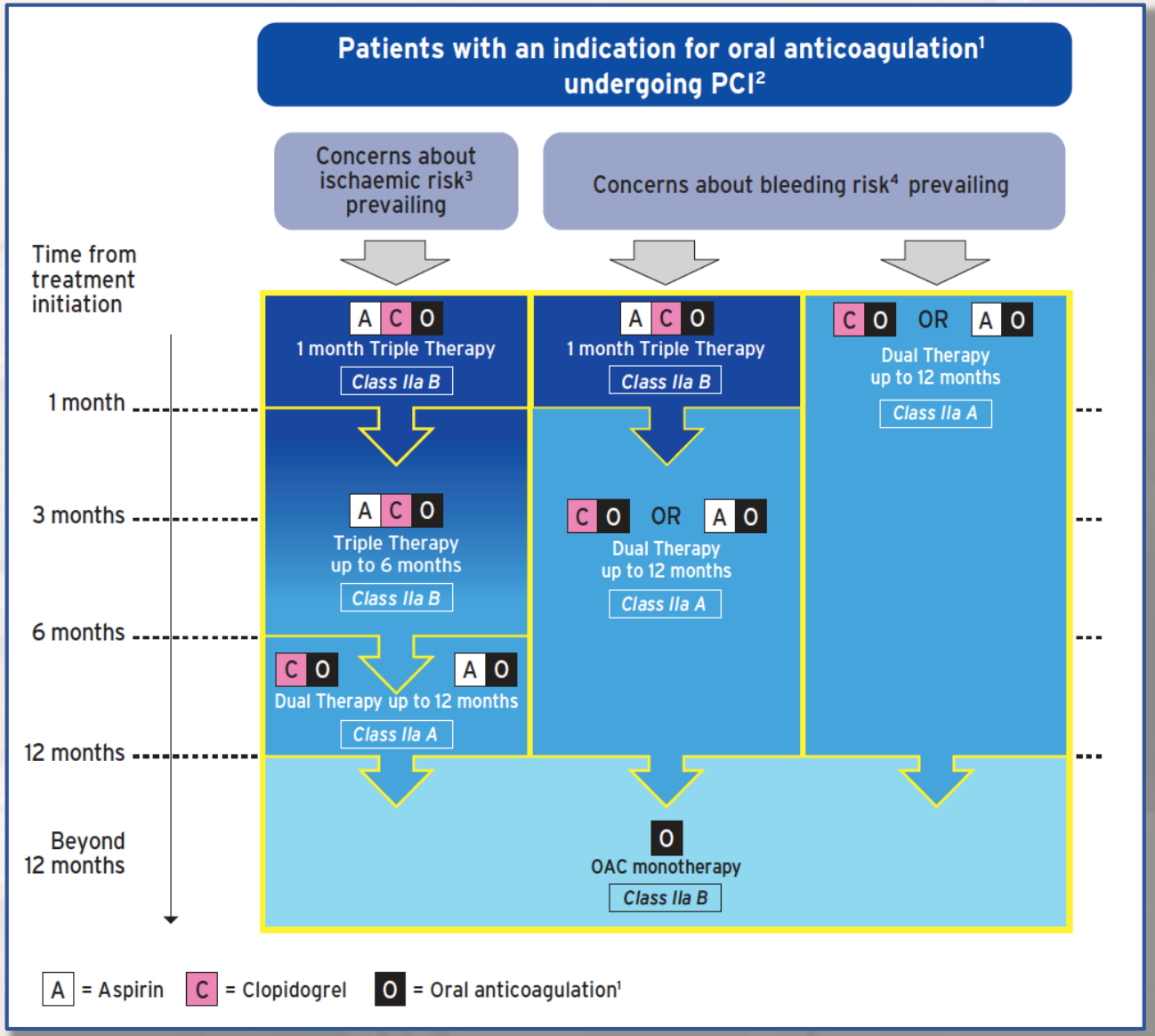
	Edoxaban regimen	VKA regimen	Hazard ratio (two-sided 95% CI)	p value
Primary outcome of major or CRNM bleeding (ISTH)				
Intention-to-treat analysis				
Number of patients	751	755	..	..
Number of patients with event	128 (17%)	152 (20%)	..	..
Annualised event rate	20·7	25·6	0·83 (0·65–1·05)	Non-inferiority p=0·0010; superiority p=0·1154
On-treatment analysis				
Number of patients	746	740	..	..
Number of patients with event	124 (17%)	142 (19%)	..	..
Annualised event rate	20·7	25·5	0·84 (0·66–1·06)	Non-inferiority p=0·0016; superiority p=0·1434
Major bleeding (ISTH)				
Intention-to-treat analysis				
Number of patients	751	755	..	..
Number of patients with event	45 (6%)	48 (6%)	..	..
Annualised event rate	6·7	7·2	0·95 (0·63–1·42)	..
On-treatment analysis				
Number of patients	746	740	..	..
Number of patients with event	42 (6%)	42 (6%)	..	..
Annualised event rate	6·5	6·8	0·98 (0·64–1·49)	..
Main efficacy outcome (composite of cardiovascular death, stroke, systemic embolic event, myocardial infarction, or definite stent thrombosis)				
Intention-to-treat analysis				
Number of patients	751	755	..	..
Number of patients with event	49 (7%)	46 (6%)	..	..
Annualised event rate	7·3	6·9	1·06 (0·71–1·69)	..

CRNM=clinically relevant non-major. ISTH=International Society of Thrombosis and Haemostasis. VKA=vitamin K antagonist.

The Lancet DOI: (10.1016/S0140-6736(19)31872-0)

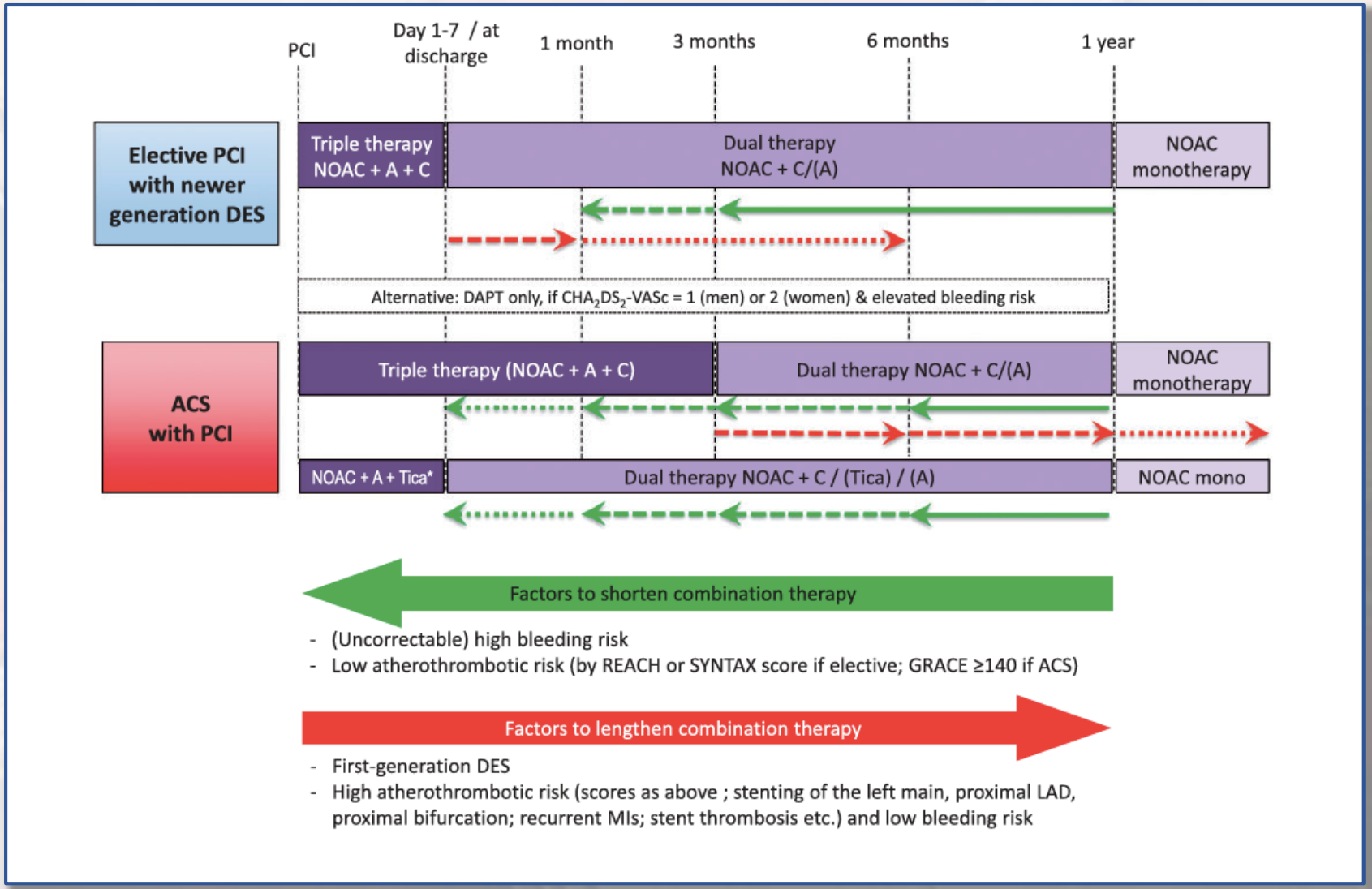
2018 ESC/EACTS Guidelines on myocardial revascularization

ESC European Society of Cardiology
European Heart Journal (2018) **00**, 1–96
doi:10.1093/eurheartj/ehy394



The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

ESC European Society of Cardiology
European Heart Journal (2018) **00**, 1–64
doi:10.1093/eurheartj/ehy136



High-risk features of stent-driven recurrent ischaemic events

ESC
European Society of Cardiology

- Prior stent thrombosis on adequate antiplatelet therapy.
- Stenting of the last remaining patent coronary artery.
- Diffuse multivessel disease especially in diabetic patients.
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min).
- At least three stents implanted.
- At least three lesions treated.
- Bifurcation with two stents implanted.
- Total stent length >60 mm.
- Treatment of a chronic total occlusion.

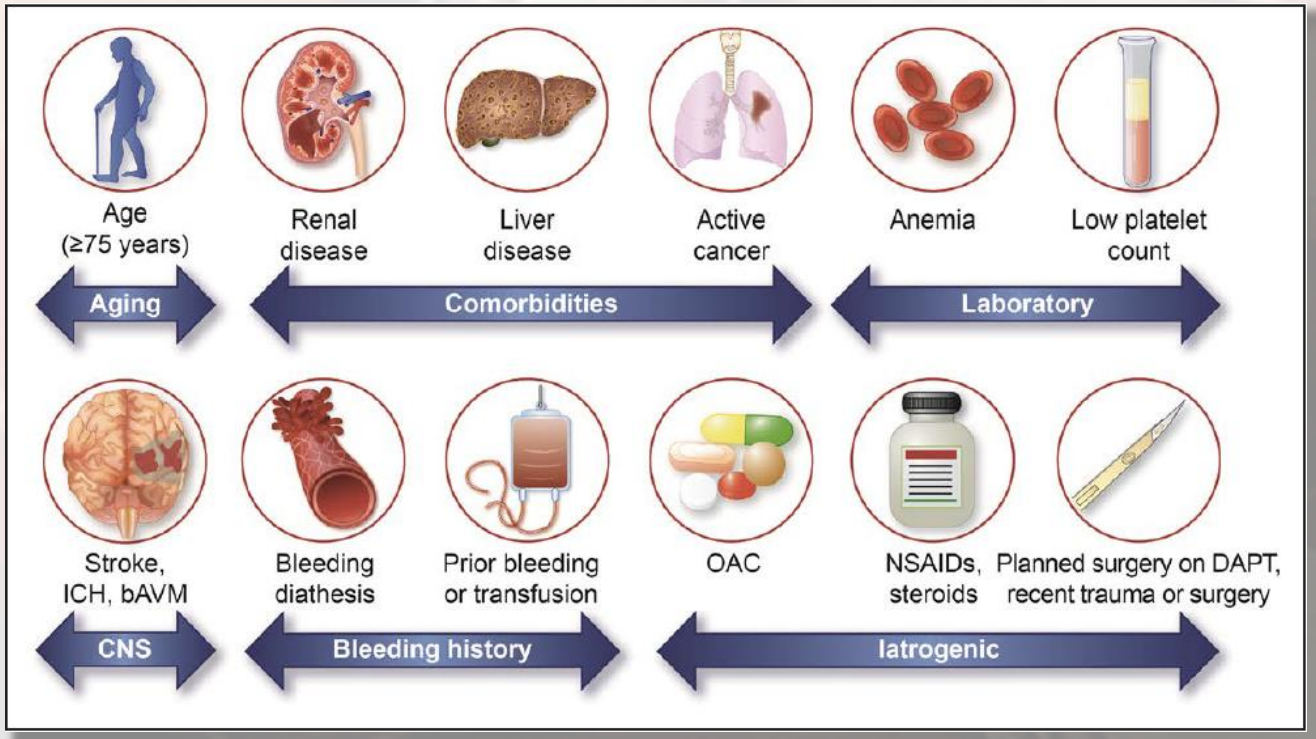
2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Defining High Bleeding Risk in Patients Undergoing PCI

A Consensus Document From the Academic Research Consortium for High Bleeding Risk

HBR: BARC 3 or 5 bleeding risk of ≥ 4% at 1 y
or intracranial hemorrhage (ICH) of ≥ 1% at 1 y

→ 1 criterio maggiore o 2 criteri minori



Major	Minor
	Age ≥75 y
Anticipated use of long-term oral anticoagulation*	
Severe or end-stage CKD (eGFR <30 mL/min)	Moderate CKD (eGFR 30–59 mL/min)
Hemoglobin <11 g/dL	Hemoglobin 11–12.9 g/dL for men and 11–11.9 g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 mo or at any time, if recurrent	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 mo not meeting the major criterion
Moderate or severe baseline thrombocytopenia† (platelet count <100×10⁹/L)	
Chronic bleeding diathesis	
Liver cirrhosis with portal hypertension	
	Long-term use of oral NSAIDs or steroids
Active malignancy‡ (excluding nonmelanoma skin cancer) within the past 12 mo	
Previous spontaneous ICH (at any time) Previous traumatic ICH within the past 12 mo Presence of a bAVM Moderate or severe ischemic stroke§ within the past 6 mo	Any ischemic stroke at any time not meeting the major criterion
Nondeferrable major surgery on DAPT	
Recent major surgery or major trauma within 30 d before PCI	

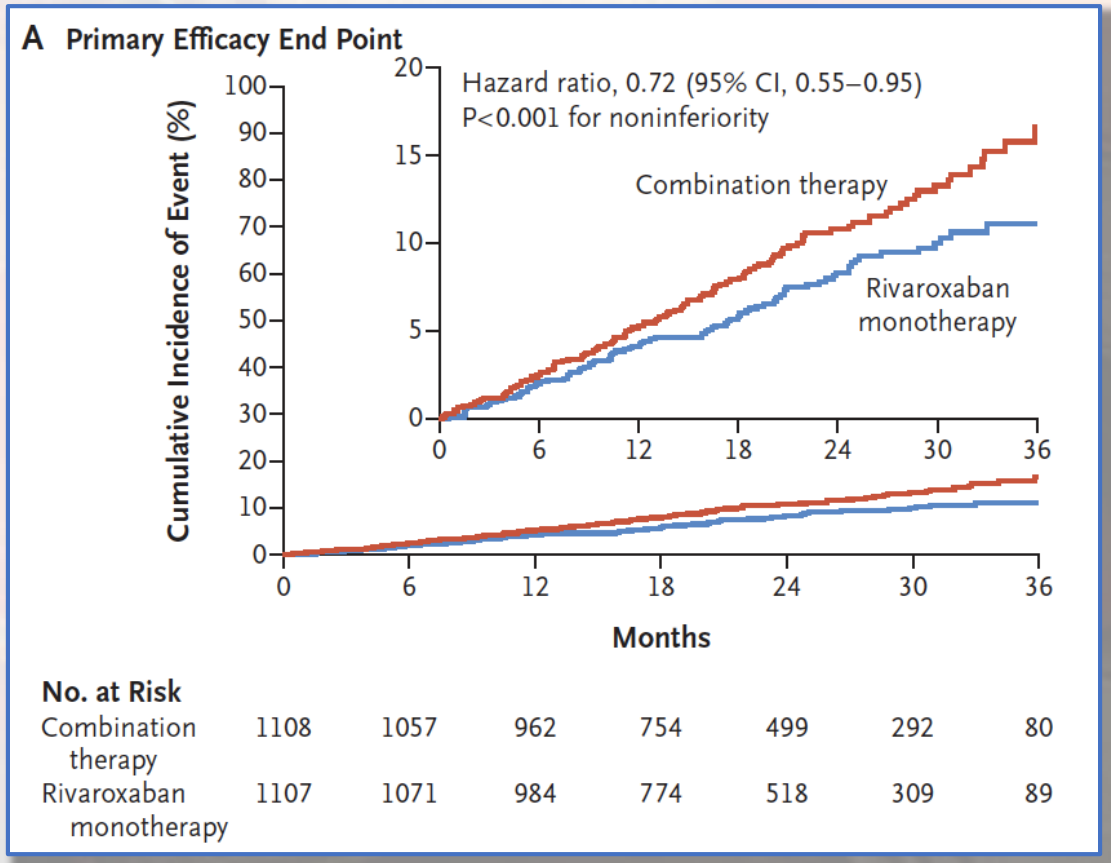
Urban P, et al: Circulation 2019;140:240

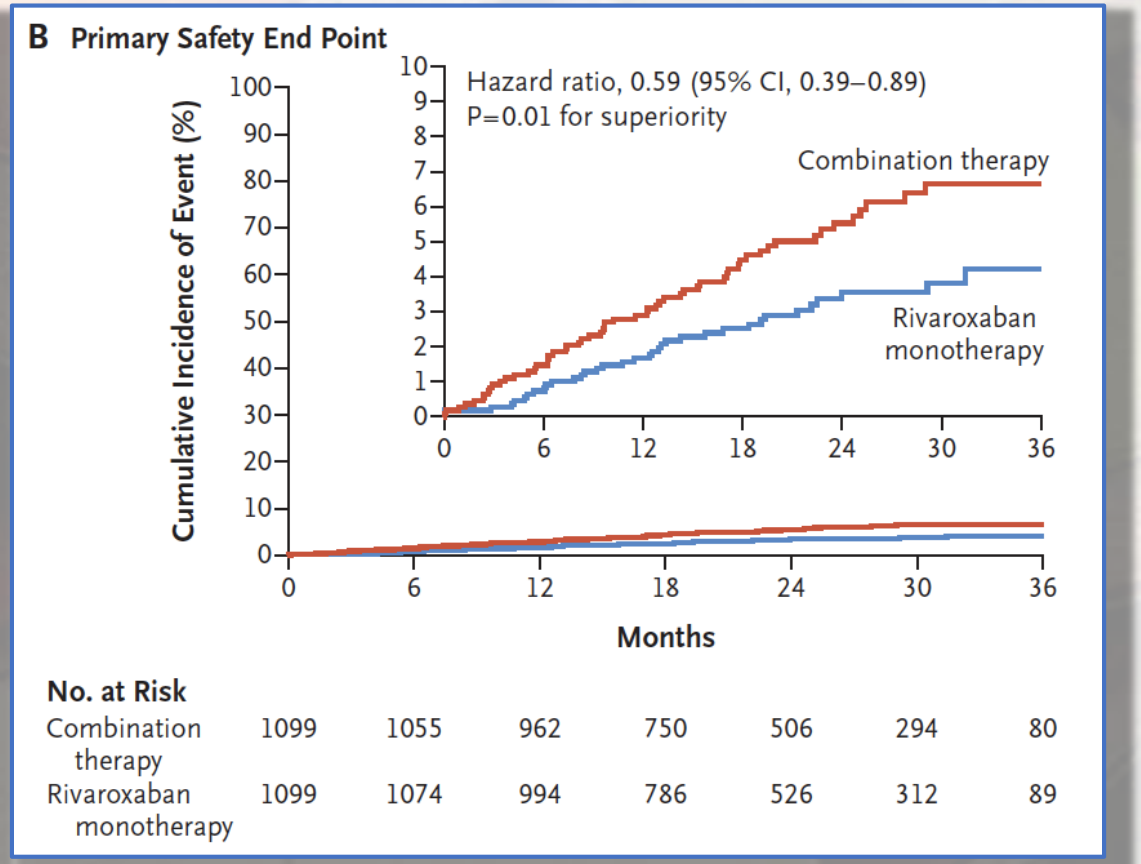
La terapia antitrombotica nei pazienti con FA e PCI: i problemi aperti

• Quale tipo di anticoagulante impiegare?	NOAC
• Per quanto tempo mantenere una triplice terapia?	Il più breve possibile: in-H → a 1-3 mesi
• Quale antiaggregante scegliere dopo la sospensione della triplice terapia?	Clopidogrel (Aspirina)
• Quale inibitore del recettore P2Y12 scegliere nella duplice terapia?	Clopidogrel (Ticagrelor)
• Quale dosaggio di NOAC scegliere in associazione all'antiaggregante?	Basso dosaggio nella triplice terapia Alto dosaggio nella duplice terapia
• Con quale terapia antitrombotica proseguire dopo 12 mesi dalla PCI (SCA)?	NOAC

ORIGINAL ARTICLE

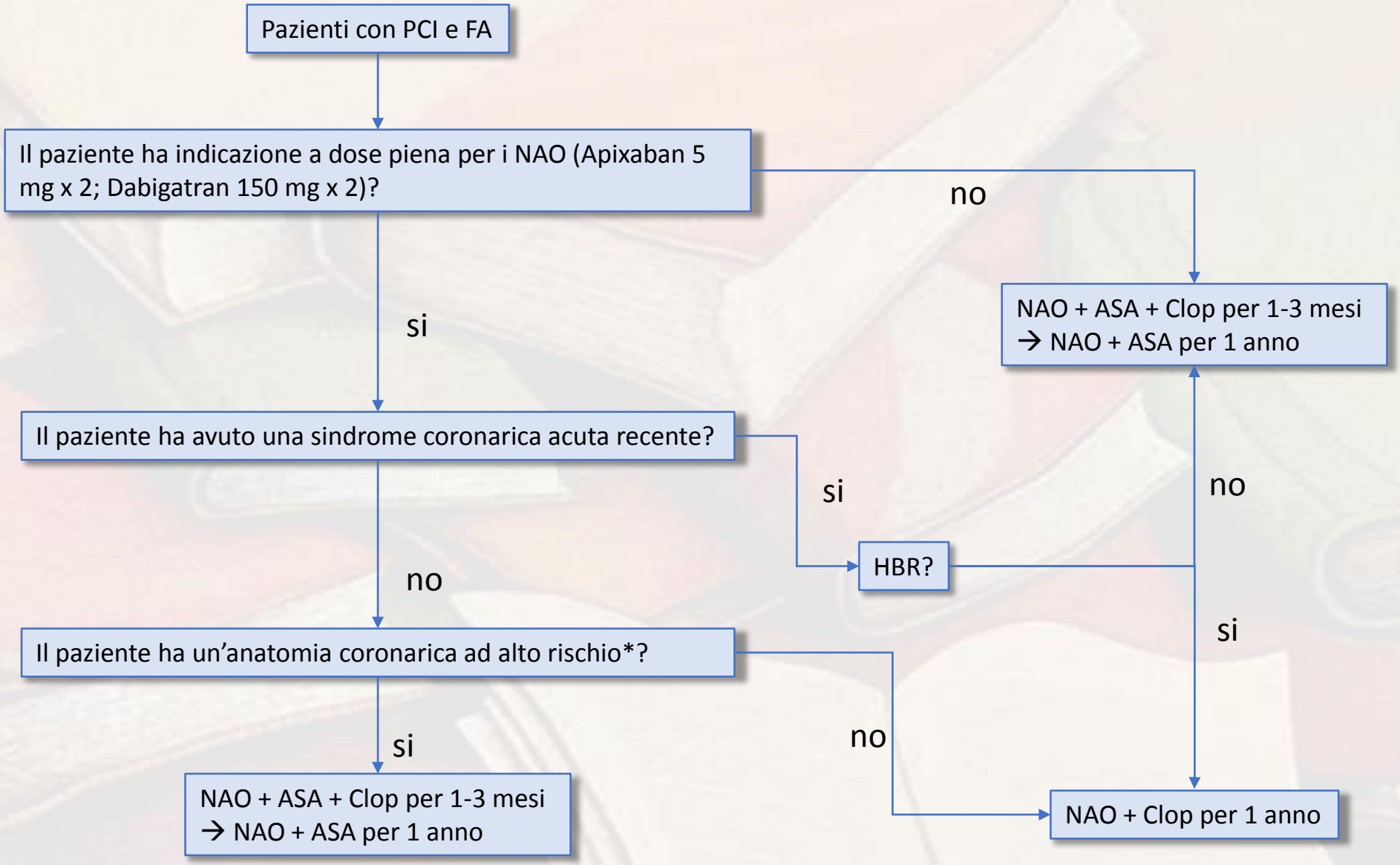
Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease





Yasuda S, et a: AFIRE Trial N Engl J Med 2019

Flow chart terapeutica per pazienti con indicazioni a triplice terapia antitrombotica



Criteri di scelta per la terapia antitrombotica

- Una SCA come indicazione alla PCI è considerata un fattore di rischio ischemico elevato
- Una rivascolarizzazione coronarica complessa è considerata un fattore di rischio ischemico elevato
- dosaggio ridotto del NAO è considerato un fattore rischio elevato di trombosi dello stent
- Il rischio emorragico viene definito sulla base della presenza di un fattore maggiore o 2 fattori minori del HBR Consortium
- Nella triplice terapia l'anticoagulante di scelta è il NAO (ove possibile)
- Nella triplice terapia l'inibitore $P2Y_{12}$ di scelta è il clopidogrel

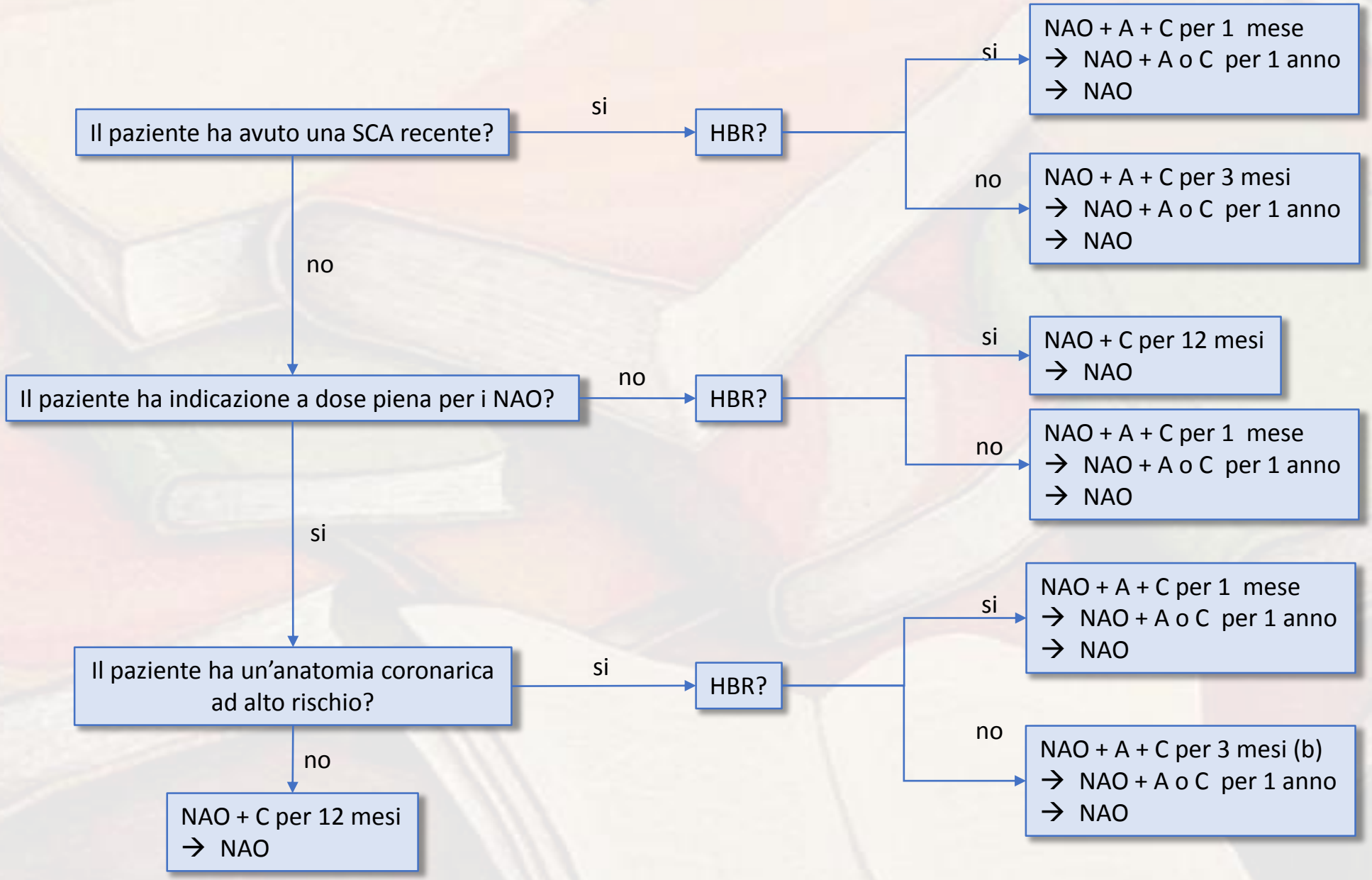
Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

ESC
European Society of Cardiology

• Short life expectancy.
• Ongoing malignancy.
• Poor expected adherence.
• Poor mental status.
• End stage renal failure.
• Advanced age.
• Prior major bleeding/prior haemorrhagic stroke.
• Chronic alcohol abuse.
• Anaemia.
• Clinically significant bleeding on dual antithrombotic therapy.

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Flow chart terapeutica per pazienti con FA trattati con PCI



REGIONE AUTONOMA FRIULI VENEZIA GIULIA
Azienda Sanitaria Universitaria Integrata di Trieste

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology

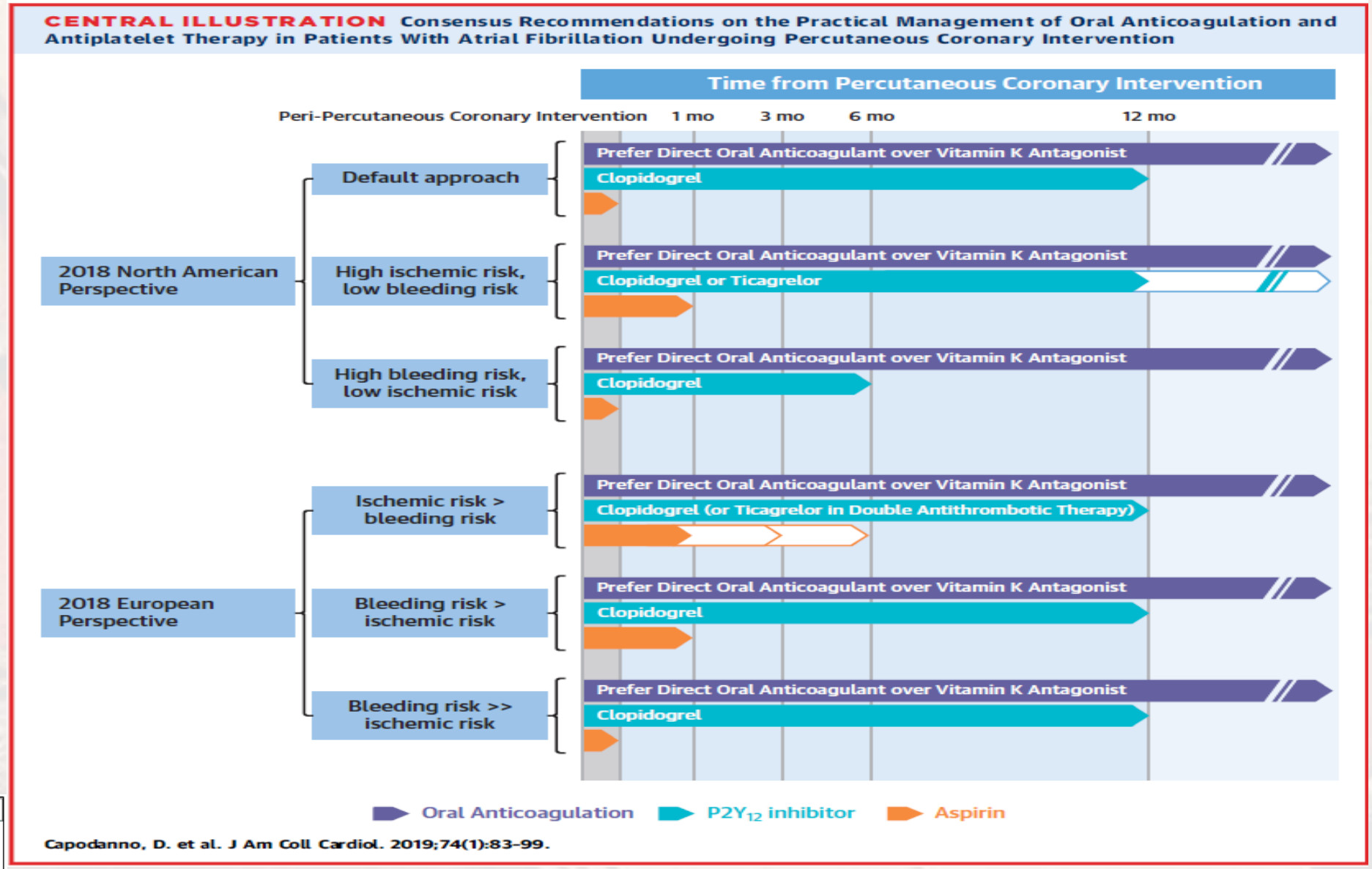
Antithrombotic therapy in patients with CCS and AF		
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC,[f] a NOAC is recommended in preference to a VKA.[299–301,308–311]	I	A
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) is recommended in patients with AF and a CHA_2DS_2-VASc score[g] ≥2 in males and ≥3 in females.[299]	I	A
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) should be considered in patients with AF and a CHA_2DS_2-VASc score[g] of 1 in males and 2 in females.[299]	IIa	B
Aspirin 75–100 mg daily (or clopidogrel 75 mg daily) may be considered in addition to long-term OAC therapy in patients with AF, history of MI, and at high risk of recurrent ischaemic events[c] who do not have a high bleeding risk.[d 295,297,299]	IIb	B

Knuuti, European Heart Journal (2019) 00, 1-71

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes The Task Force for the diagnosis and management of chronic coronary syndromes of the ES

Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.)[f] is used in preference to a VKA in combination with antiplatelet therapy.[300,301,308,310,311]	I	A
When rivaroxaban is used and concerns about high bleeding risk[d] prevail over concerns about stent thrombosis[h] or ischaemic stroke,[g] rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or dual antiplatelet therapy.[300,301,308,310]	IIa	B
When dabigatran is used and concerns about high bleeding risk[d] prevail over concerns about stent thrombosis[h] or ischaemic stroke,[g] dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or dual antiplatelet therapy.[300,301,308]	IIa	B
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and clopidogrel should be considered if the risk of stent thrombosis[h] is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis,[h] irrespective of the type of stent used.[301,308–310]	IIa	B
Triple therapy with aspirin, clopidogrel, and an OAC for ≥1 month should be considered when the risk of stent thrombosis[h] outweighs the bleeding risk, with the total duration (≤6 months) decided according to assessment of these risks and clearly specified at hospital discharge.	IIa	C
In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target international normalized ratio in the range of 2.0–2.5 and with time in therapeutic range >70%.[300,301,308–310]	IIa	B
Dual therapy with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis,[h] irrespective of the type of stent used.	IIb	C
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C

Management of Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing PCI



NOACs in AF and PCI: is it all comparable?

	RE-DUAL PCI (2725 pts)	PIONEER AF-PCI (2124 pts)	AUGUSTUS (4614 pts)	ENTRUST-AF PCI (1506 pts)
Trial design	Multicentre, randomized, open-label trial following a PROBE design Formal hypothesis testing	Multicentre, randomized, open-label trial No formal hypotheses were tested	Multicentre, randomized, 2x2 factorial, open-label trial Formal hypothesis testing	Randomised, multicentre, open-label, phase 3b study with masked outcome
Inclusion criteria	Patients with NVAF, with an ACS or stable CAD who had undergone PCI with stenting	Patients with NVAF, who had just undergone PCI with stenting	Patients with AF and ACS **and/or PCI** (Randomization: 1714 of 4595 (37.3%) had acute coronary syndrome and underwent PCI, **1097 (23.9%) had medically managed acute coronary syndrome**, and 1784 (38.8%) underwent elective PCI)	Patients had NVAF and had a successful PCI for stable coronary artery disease or acute coronary syndrome
ASA	Included only in the warfarin treatment arm for 1 or 3 months depending on stent type (≤100 mg)	Included only in the warfarin and rivaroxaban 2.5 mg BID treatment arms, for the full 12-month treatment duration	Either ASA or placebo given to patients in both treatment arms for the full 6-month treatment duration (ASA 81 mg)	VKA regimen: aspirin (100 mg once daily)for a minimum of 1 month and up to 12 months' duration at the discretion of the investigator. About 50% of patients stopped aspirin at 1 month
Randomization	≤120 hours post-PCI, ≤72 hrs preferable	≤72 hours after sheath removal	≤14 days after the ACS and/or PCI. The mean time from the index event to randomization was 6.6 days	Between 4 h after arterial sheath removal and 5 days after successful PCI (median 45h)
Efficacy assessment	Tested non-inferiority of D150 and D110 dual therapy combined to warfarin-triple antithrombotic therapy in death or thrombotic event and unplanned revascularization by PCI/CABG	Not powered for testing efficacy; descriptive statistics only (MI, stroke, CV death)	Tested superiority for death and hospitalization (apixaban vs VKA)	Composite of cardiovascular death, stroke, SEE, myocardial infarction and definite stent thrombosis
Primary endpoint and adiudication	ISTH major or CRNM bleeding event Primary safety endpoint fully adjudicated. Events were adjudicated by an independent committee whose members were unaware of the treatment assignments	Composite of TIMI major or minor bleeding, or bleeding requiring. Primary safety endpoint not fully adjudicated Bleeding requiring medical attention: 15% of events were adjudicated, remainder classified by algorithm	ISTH major or CRNM bleeding event. All bleeding and ischemic events (except for urgent revascularization) were independently adjudicated by the clinical-events classification committee at the DCRI, whose members were unaware of the trial-group assignments	ISTH major or CRNM bleeding event. Treatment allocation was open to participants, the clinicians caring for them in primary and secondary care, and local investigators. Outcome event adjudicators were masked to participant identity, treatment allocation, and drug use.
Planned follow-up	>12 months	12 months	6 months	12 months

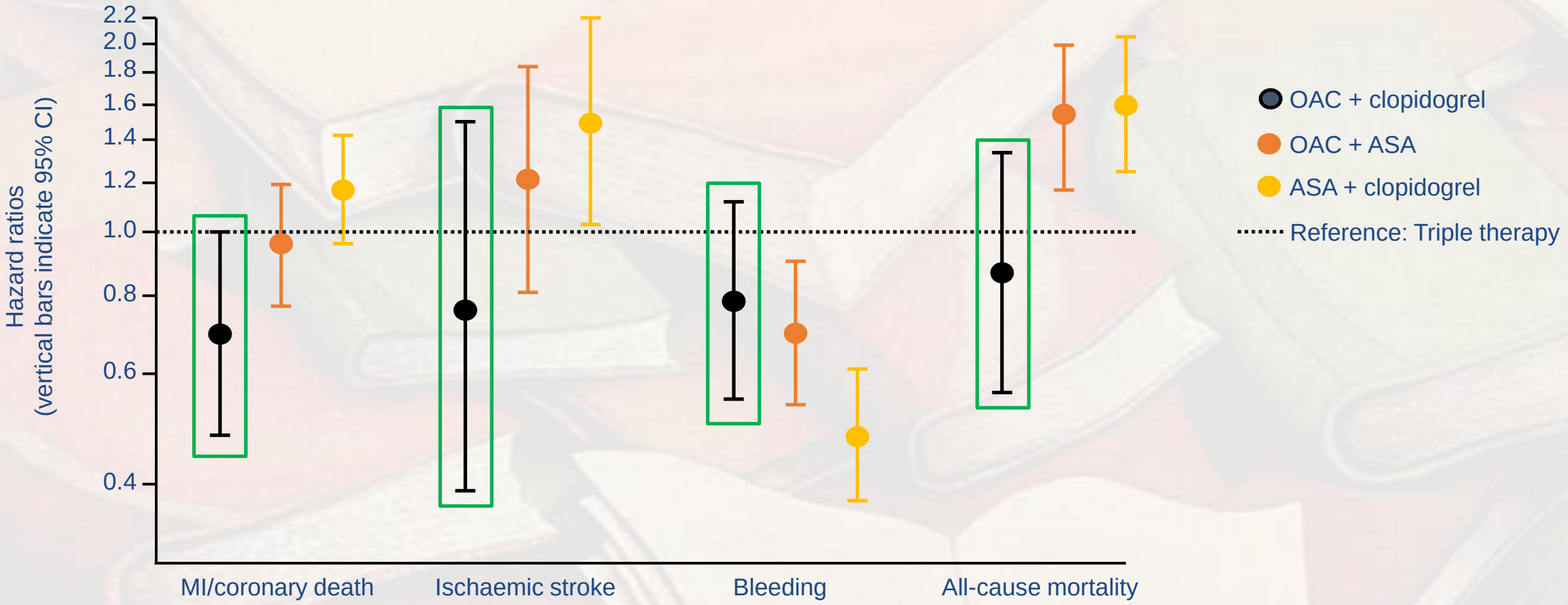
Gibson et al. NEJM 2016; Cannon et al. NEJM 2017; Lopes et al. NEJM 2019; Vranckx et al. Lancet 2019 and Supplementary Appendix

NOACs in AF and PCI: is it all comparable?

	RE-DUAL PCI (2725 pts)	PIONEER AF-PCI (2124 pts)	AUGUSTUS (4614 pts)	ENTRUST-AF PCI (1506 pts)
NOAC dose	Both doses of dabigatran approved for stroke prevention in AF (110 and 150 mg)	Rivaroxaban 2.5 mg BID has not been tested or approved for stroke prevention in AF. Rivaroxaban 15/10 mg OD regimen has been tested in 639 Japanese patients for stroke prevention in AF (J-ROCKET, exploratory study); non-inferiority for efficacy vs warfarin not shown	Doses of apixaban 5mg and 2,5mg (229 pts) approved for stroke prevention in AF	Doses of edoxaban 60mg and 30mg (147 pts/ 20%) approved for stroke prevention in AF
Bleeding risk	Excluded if major bleeding episode or ICH in past month, or GI bleeding within 1 month, unless cause has been eliminated	Excluded if any history of ICH or if GI bleeding in past year	Excluded if any history of ICH or know ongoing bleeding	Bleeding risk or systemic conditions: a. Known bleeding diathesis, including but not limited to i. Uncontrolled active bleeding, encompassing both ISTH major and clinically relevant non-major bleeding, preceding randomisation ii. Lesion or condition, if considered to be a significant risk for major bleeding
Stroke risk	Excluded if stroke in past month	Excluded if any prior stroke/TIA	Not excluded patients whith history of prior stroke	Ischaemic stroke within 2 weeks prior to randomisation
TTR	65% mean	65% (Excluding the First 14 days of Exposure)	59% median, 56% mean	median time was 63·1%
Ticagrelor	12% (223 pts)	5,2% (37 pts 15 mg arm)	5,4% (121 pts)	7% (49 pts)
Prasugrel	no data	1,70%	1,20%	<1%
DES	>80%	65,4 % (15 mg arm)	no data	no data
DAPT duration	DAPT duration predefined in protocol. Duration of triple therapy predefined (1 months after bare-metal stent, 3 months after drug-eluting stent)	DAPT duration defined by investigator; duration of triple therapy had to be prespecified by the investigator (1, 6 or 12 months)	DAPT duration 6 months	The choice of P2Y12 inhibitor and duration of aspirin treatment was predeclared by the investigator before random group assignment as guided by the clinical presentation (1-12 months)

Gibson et al. NEJM 2016; Cannon et al. NEJM 2017; Lopes et al. NEJM 2019; Vranckx et al. Lancet 2019 and Supplementary Appendix

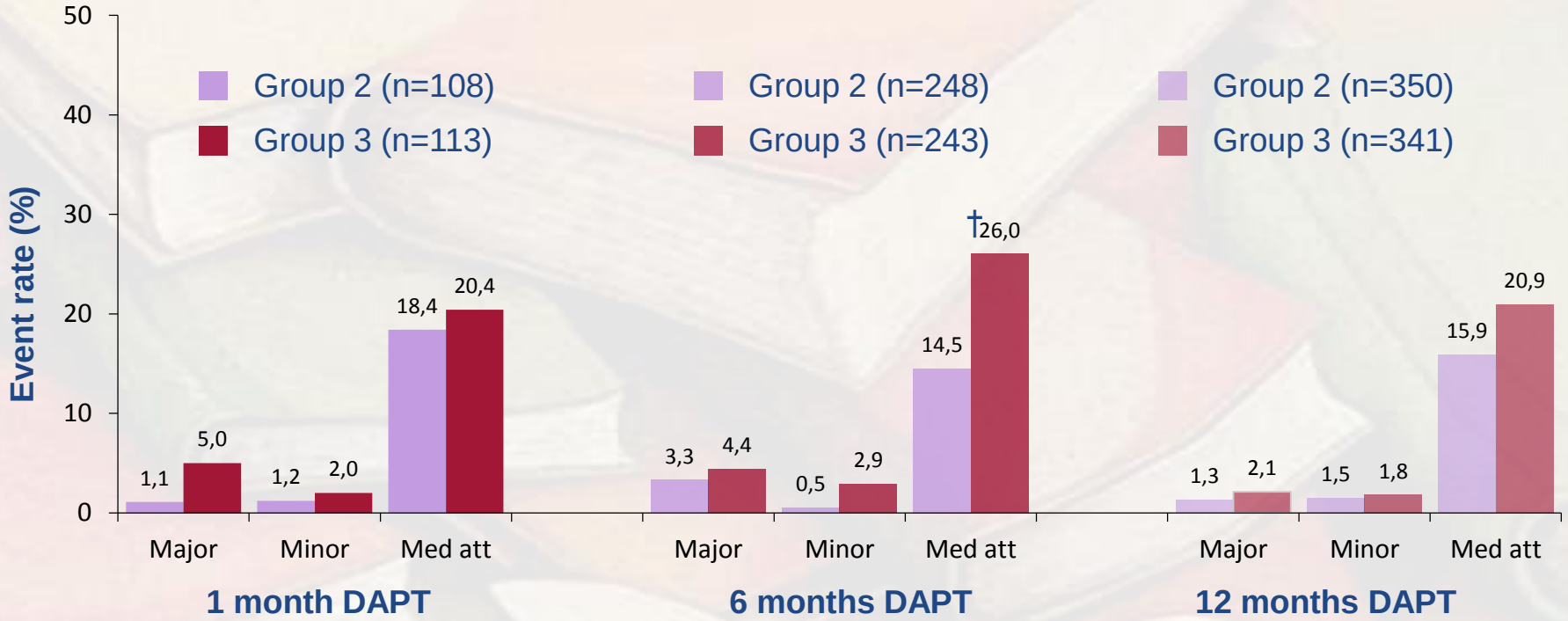
OAC plus single antiplatelet led to equal or better outcomes vs triple therapy in patients with AF and MI



12 165 patients with AF hospitalized with MI/undergoing PCI in Danish registries. ASA, acetylsalicylic acid.
Lamberts M et al. J Am Coll Cardiol 2013

PIONEER AF-PCI: event rates for primary endpoint components across DAPT durations[1]

Composite of bleeding events*



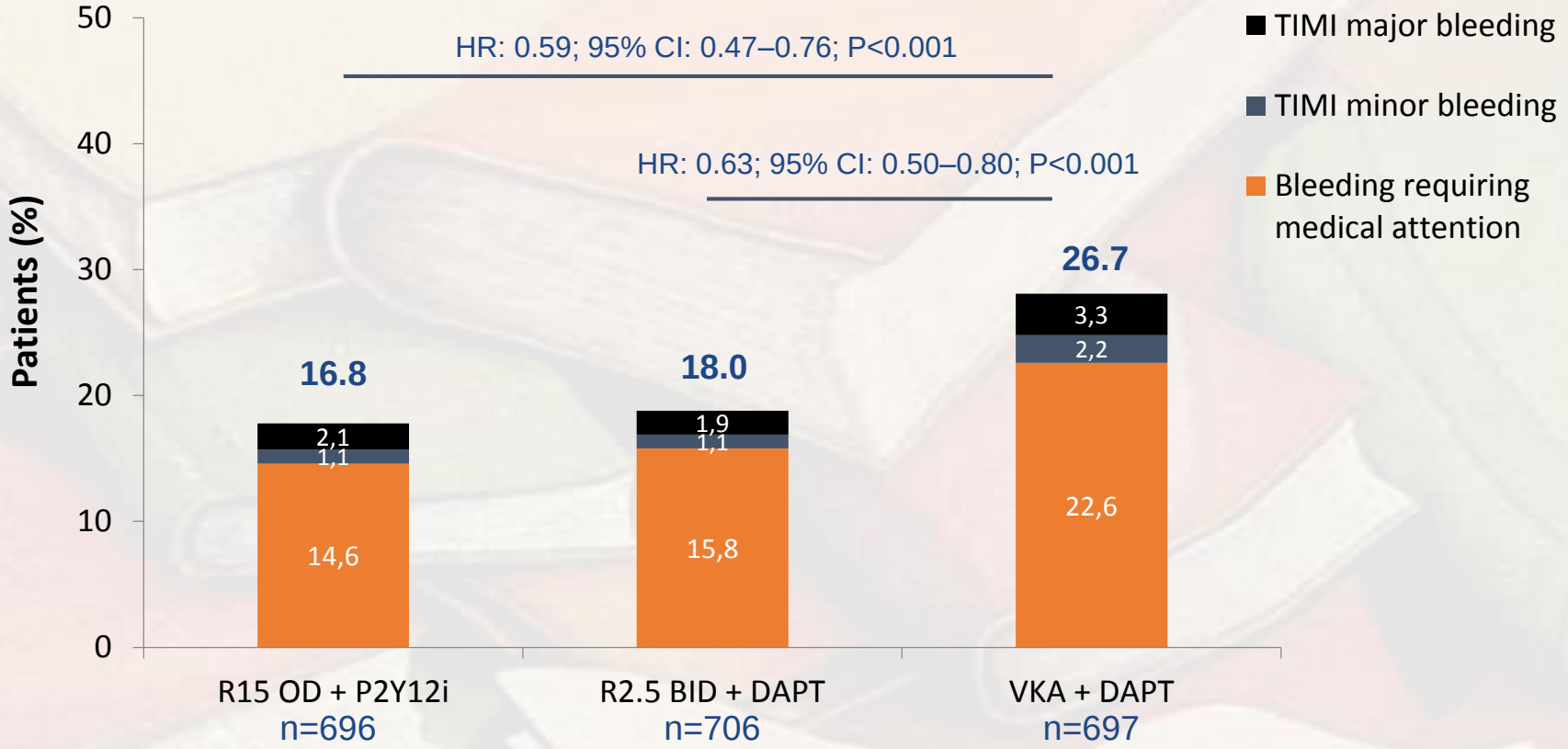
Guidelines recommend 1 month triple therapy in patients with AF undergoing elective PCI with stenting[2]

Most patients in PIONEER AF-PCI received triple therapy for 6 months (37%) or 12 months (53%)[1]

*Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention.

†P<0.05 Group 2 vs Group 3; DAPT, dual antiplatelet therapy; Med att, medical attention; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; 1. Gibson et al. NEJM 2016;375:2423; 2. Kirchhof et al. Eur Heart J 2016;37:2893

PIONEER AF-PCI: the lower rate of the primary endpoint in both rivaroxaban groups was driven by the incidence of bleeds requiring medical attention



There were no significant differences in the incidences of TIMI major or minor bleeding among the three groups

Only 15% of bleeding events requiring medical attention were adjudicated

Gibson et al. N Engl J Med 2016