31 GIORNATE CARDIOLOGICHE TORINESI

TURIN
October
24th-26th
2019

Non-valvular AF and ACS-related PCI: DOAC or VKA?

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Relazioni con soggetti portatori di interessi commerciali in campo sanitario

Ai sensi dell'art. 76 sul Conflitto di Interessi, pag. 34 dell'Accordo Stato-Regione del 2 febbraio 2017, dichiaro che negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

Chiesi

Bayer

AstraZeneca

Bristol Meyer Squibb

Pfizer

The Medicine Company

Background

- The optimal antithrombotic regimen for patients with atrial fibrillation (AF) who have an acute coronary syndrome (ACS) or require percutaneous coronary intervention (PCI) is unclear

- Prior studies were designed to identify strategies to reduce the bleeding associated with triple antithrombotic therapy that includes a vitamin K antagonis (VKA)
  - WOEST (n=**573**): less bleeding AND fewer ischemic events without aspirin compared with VKA + dual antiplatelet therapy (DAPT)
  - PIONEER AF-PCI (**3 arms**, n=**2124**): less bleeding with two *reduced-dose* rivaroxaban regimens compared with VKA + DAPT
  - RE-DUAL PCI (**3 arms**, n=**2725**): less bleeding with two standard-dose dabigatran regimens, without aspirin, compared with VKA + DAPT

- **The AUGUSTUS trial was designed to overcome some of the methodological limitations of prior RCTs in this setting by testing the independent effect of apixaban, as compared to VKA, and of aspirin, as compared with placebo.**

Dewilde WJ, et al. Lancet 2013;381:1107-15.
Gibson CM, et al. N Engl J Med 2016;375:2423-34.
Cannon CP, et al. N Engl J Med 2017;377:1513-24.

Two INDEPENDENT Hypotheses in a Factorial 2 x 2 Design

In patients with AF and ACS or PCI on a $P2Y_{12}$ inhibitor

1. Apixaban **is non-inferior to VKA** for International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding
2. Placebo **is superior** to aspirin for ISTH major or CRNM bleeding in patients on oral anticoagulation (OAC)

AUGUSTUS Design

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
- **Severe renal Insufficiency** (creatinine > 2.5 mg/dl or eGFR < 30 ml/min)
- **History of ICH**
- **Other reason for VKA** (prosthetic valve, moderate / severe mitral stenosis, pulmonary embolism)

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
Aspirin versus placebo after randomization

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

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

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

** 2 or more of the following dose-reduction criteria: > 80 years, weight < 60 kg, or creatinine > 1.5 mg/dl*

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

Statistical Analysis — Hierarchical Testing

Factor Apixaban vs. VKA:

1. Major / CRNM Bleeding[NI then Sup]
2. Death / Hospitalization[Sup]
3. Death / Ischemic Events[Sup]

Factor Placebo vs. Aspirin:

1. Major / CRNM Bleeding[Sup]
2. Death / Hospitalization[Sup]
3. Death / Ischemic Events[Sup]

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

NI = non-inferiority; Sup = superiority

Baseline Characteristics

	Total (N=4614)
Age, median (25th, 75th), years	70.7 (64.2, 77.2)
Female, %	29.0
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)
Creatinine > 1.5 mg/dL	8.4%
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

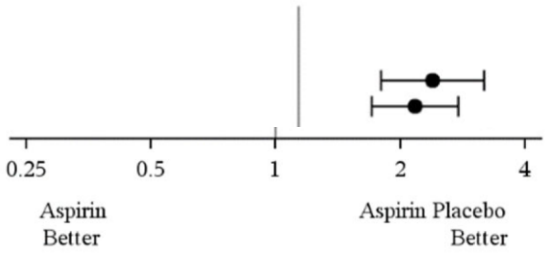
NO Significant Interactions Between Randomization Factors

Apixaban / VKA vs. Aspirin / Placebo

- Major / CRNM Bleeding: $P_{interaction} = 0.6$
- Death / Hospitalization: $P_{interaction} = 0.2$
- Death / Ischemic Events: $P_{interaction} = 0.3$

Figure S1B. Time to first ISTH major or clinically relevant nonmajor bleeding event in various subgroups: Aspirin vs. Aspirin Placebo

Subject Group	Interaction P-Value	n/N (%)	Hazard Ratio	95% CI
Anticoagulant therapy	0.608			
Apixaban		240 / 2,288 (10.5%)	1.99	1.53, 2.60
VKA		330 / 2,249 (14.7%)	1.82	1.45, 2.28

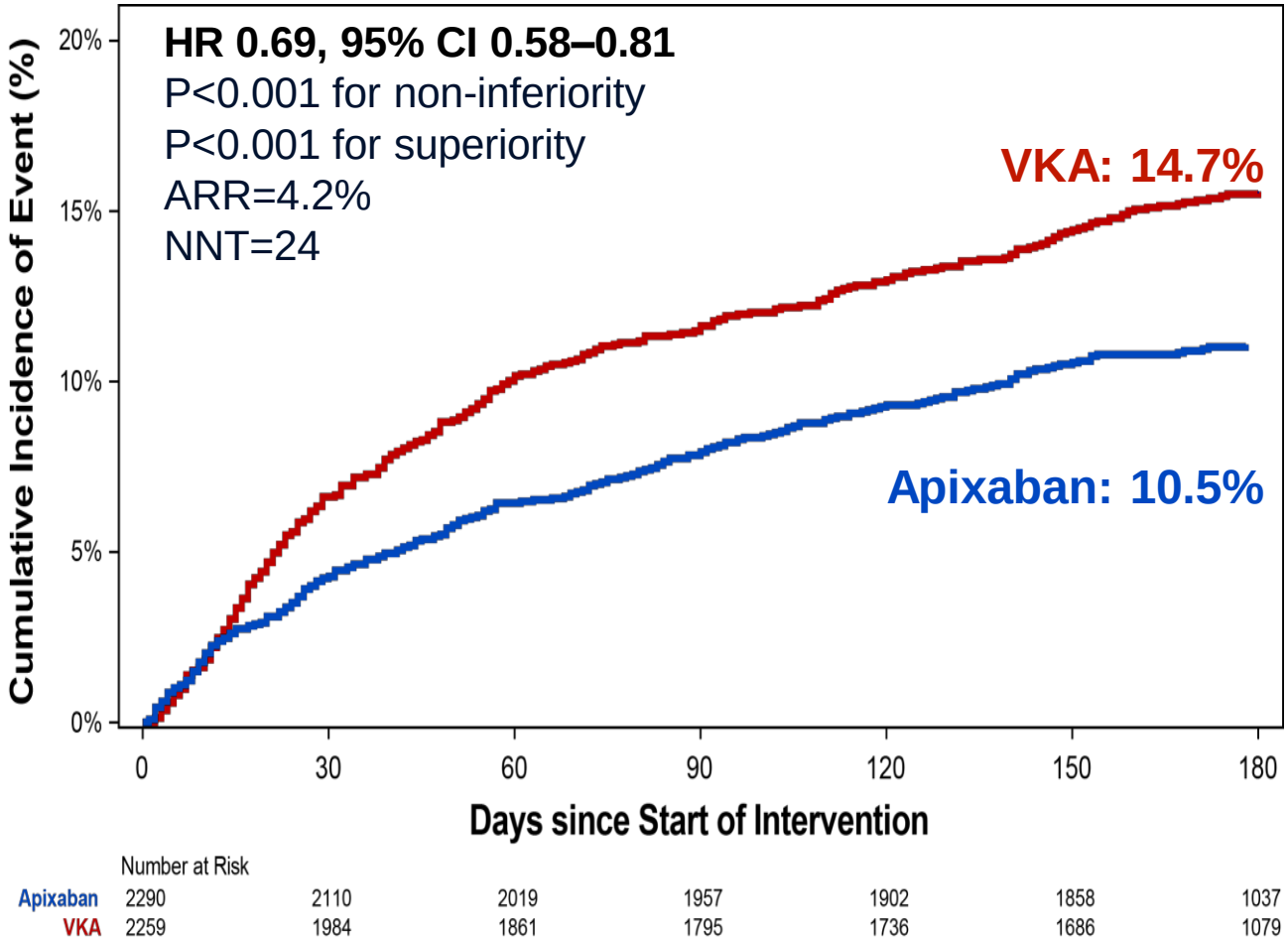


Factor 1: Apixaban or Vitamin K Antagonist

Primary Results

Primary endpoint Results: Major/CRNM Bleeding

Apixaban or VKA



ARR: absolute risk reduction
NNT: number needed to treat

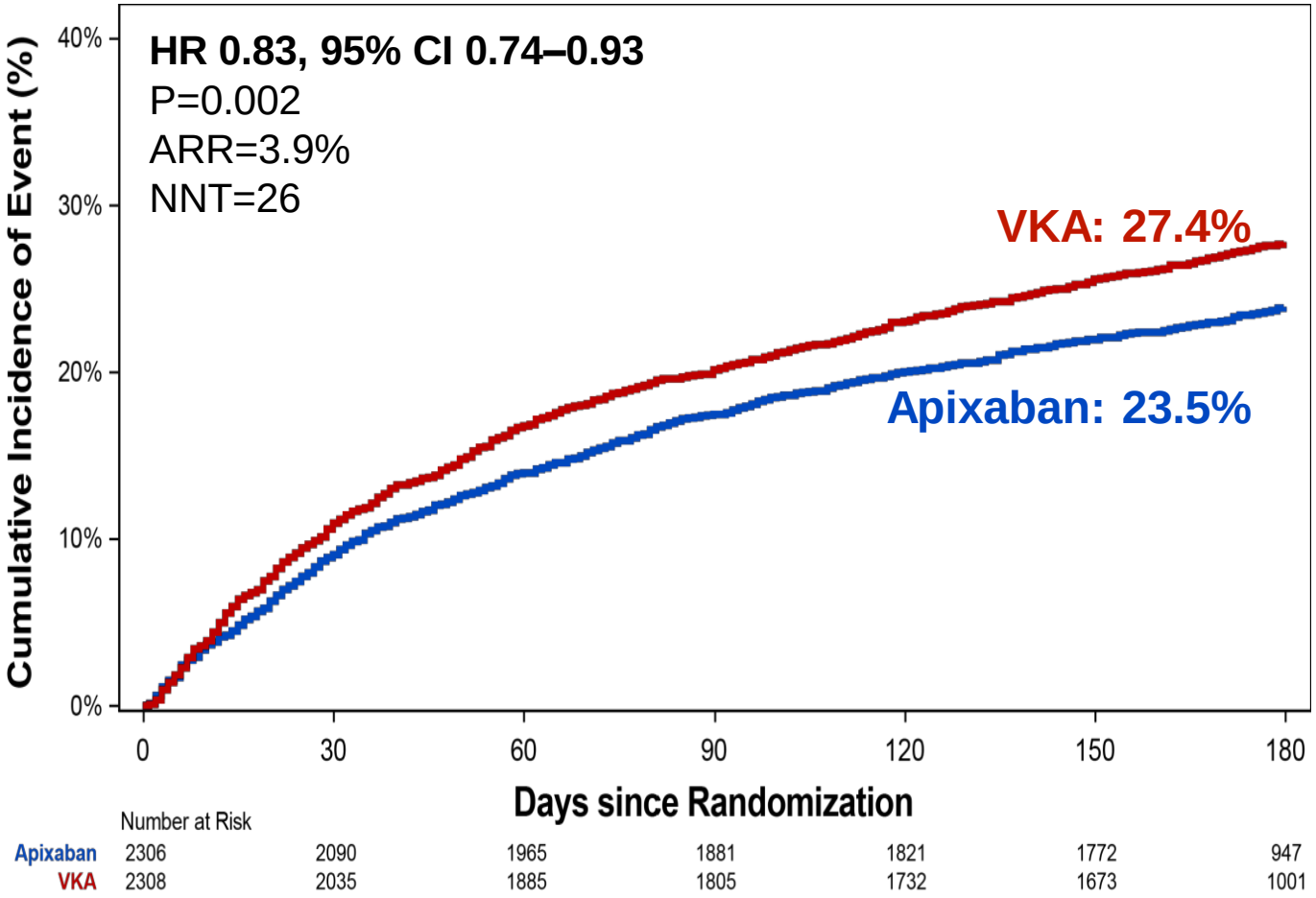
Bleeding Endpoint Components

Apixaban or VKA

Endpoint	Apixaban (N=2306)	VKA (N=2308)	HR (95% CI)
ISTH major bleeding n (%)	69 (3.0)	104 (4.6)	0.64 (0.47-0.86)
Clinically Relevant Non Major Bleed n (%)	180 (7.9)	246 (10.9)	0.69 (0.57-0.84)
Intracranial Hemorrhage	5 (0.2)	13 (0.6)	0.39 (0.14-1.12)

Key Secondary Endpoint Results:
Death/Hospitalization

Apixaban or VKA



ARR: absolute risk reduction
NNT: number needed to treat

Ischemic Outcomes

Apixaban vs. VKA

Endpoint	Apixaban (N=2306)	VKA (N=2308)	HR (95% CI)
(3). Death or Ischemic Events (%)	**6.7**	**7.1**	**0.93 (0.75–1.16)**
Endpoint Components			
Death (%)	**3.3**	**3.2**	**1.03 (0.75–1.42)**
CV Death (%)	2.5	2.3	1.05 (0.72–1.52)
Hospitalization (%)	**22.5**	**26.3**	**0.83 (0.74–0.93)**
Stroke (%)	**0.6**	**1.1**	**0.50 (0.26–0.97)**
Myocardial Infarction (%)	3.1	3.5	0.89 (0.65–1.23)
Definite or Probable Stent Thrombosis (%)	0.6	0.8	0.77 (0.38–1.56)
Urgent Revascularization (%)	1.7	1.9	0.90 (0.59–1.38)

AUGUSTUS Conclusions

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor:

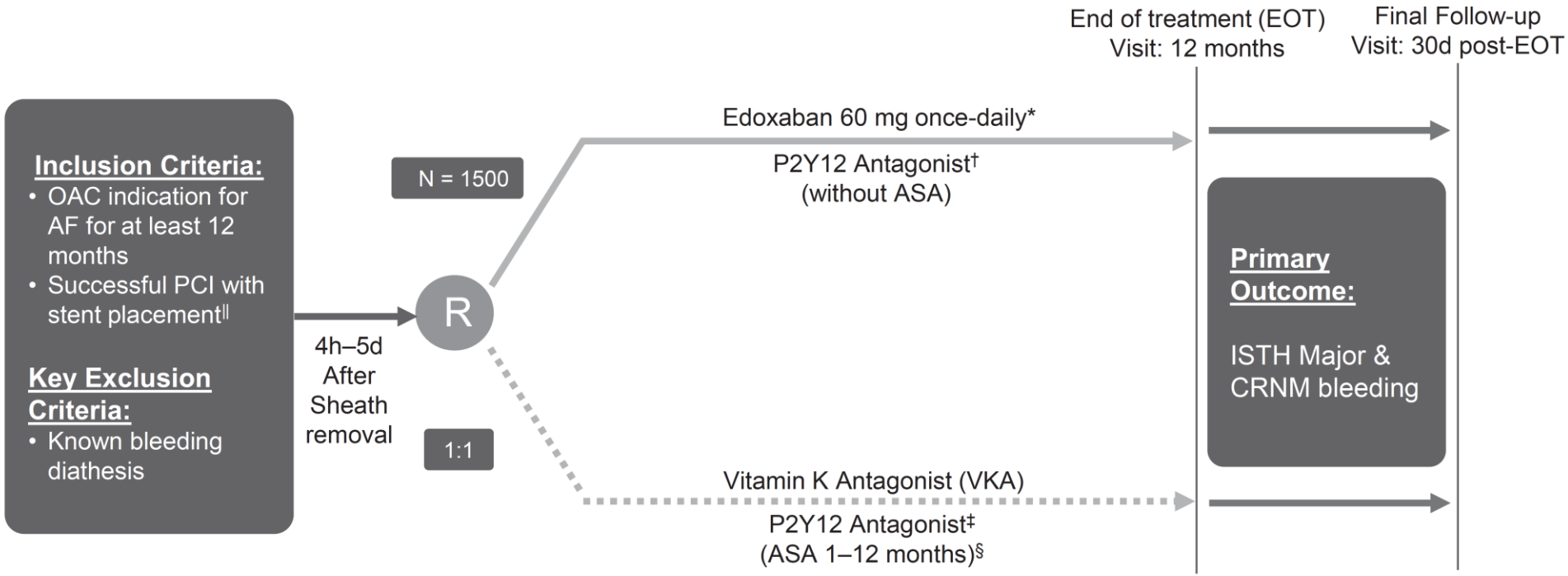
Apixaban, as compared with VKA, reduced the primary endpoint of major or clinically relevant bleeding, reduced the composite of death of hospitalization through a reduction of hospitalization and was associated with halved risk of stroke.

Implications

The AUGUSTUS results support a broad use of apixaban as compared with warfarin in patients with atrial fibrillation and a recent acute coronary syndrome or PCI.

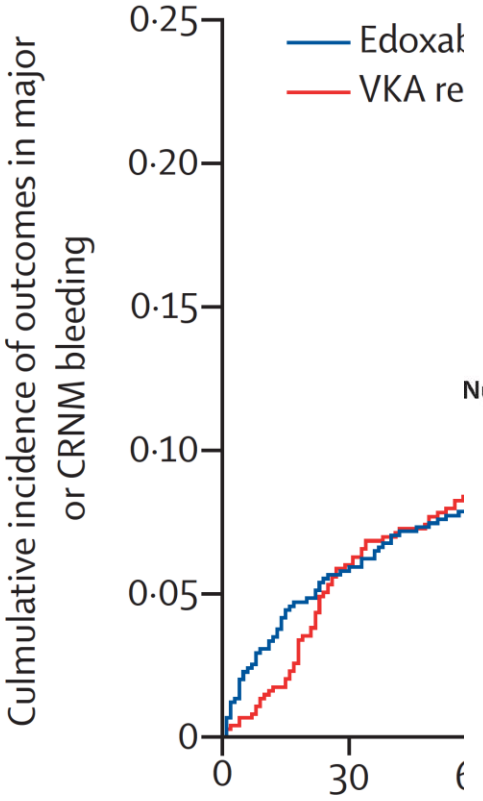
For the first time, a factorial design allows to compare directly treatments instead of strategies and better understanding the relative effect of oral anticoagulants and of aspirin in this setting.

ENTRUST AF PCI Design



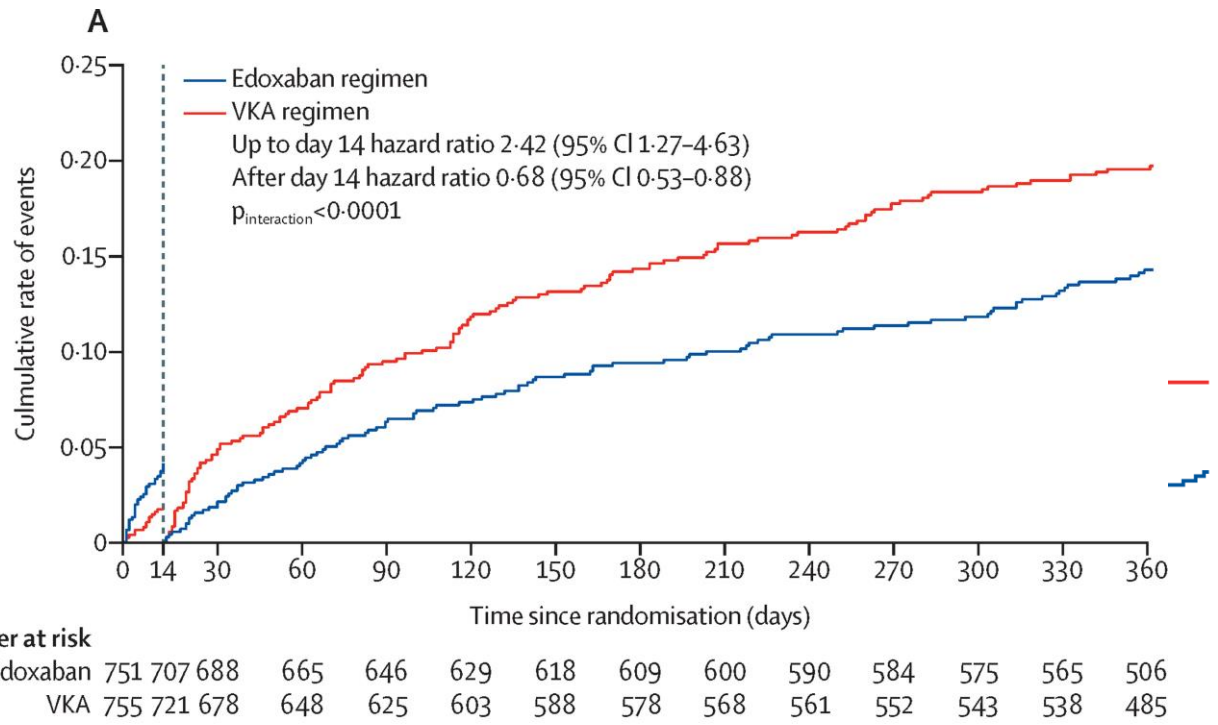
Vranckx P et al. *Am Heart J 2018;196:105-12.*

ENTRUST AF PCI



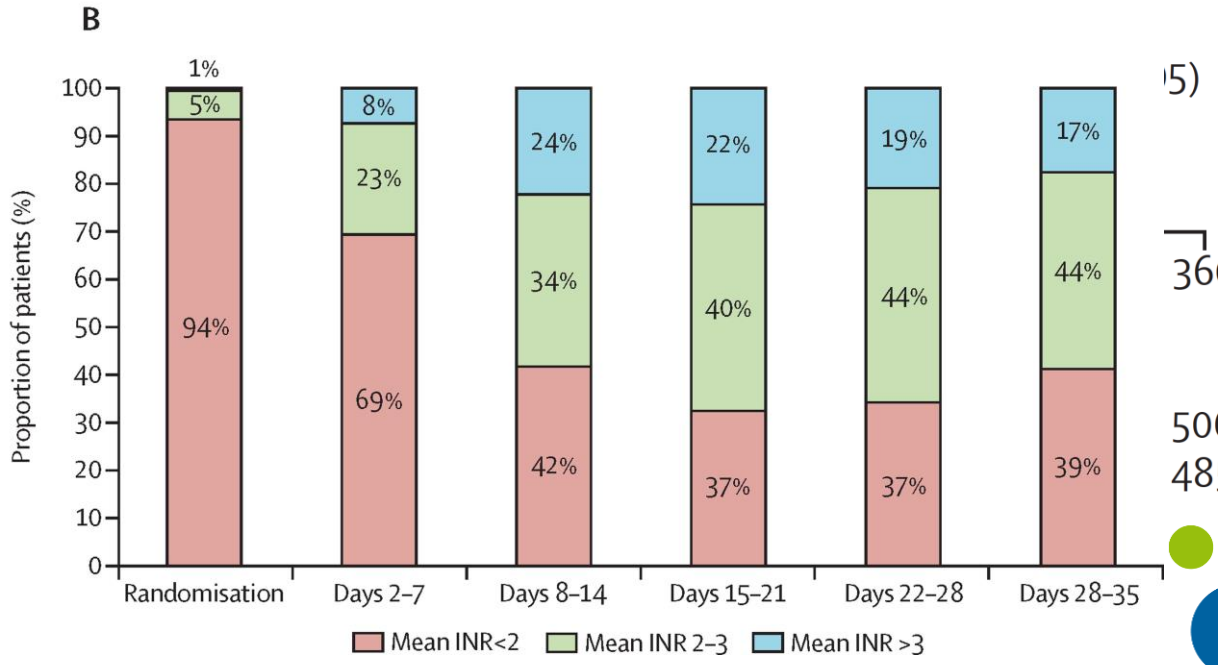
Number at risk

Edoxaban	751	688	6
VKA	755	678	6



Number at risk

Edoxaban	751	707	688	665	646	629	618	609	600	590	584	575	565	506
VKA	755	721	678	648	625	603	588	578	568	561	552	543	538	485



Vranckx P et al. *Lancet* 2019

Conclusions

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

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.) is used in preference to a VKA in combination with antiplatelet therapy.	I	A

DOACs (with direct evidence mostly on apixaban) **should be routinely considered in this population** over VKAs with few exceptions, such as patients with concomitant indications (LV thrombus, mechanical heart valve) or end-stage renal disease.