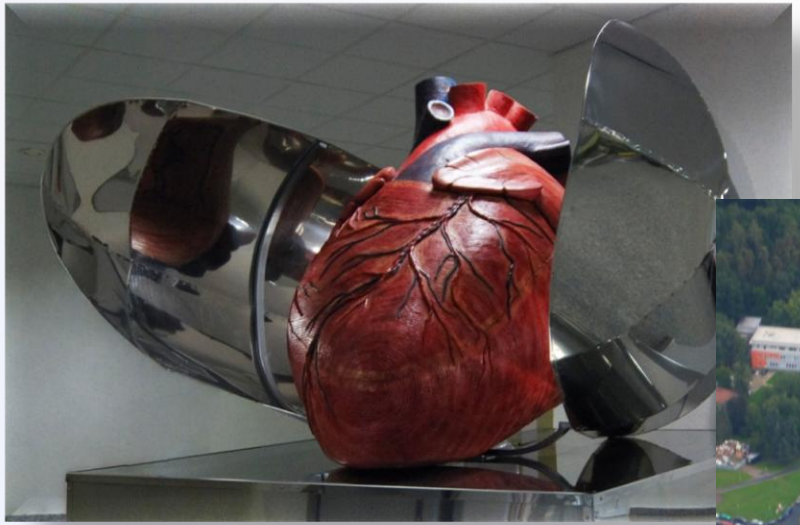
Studie ENTRUST AF PCI



Prof MUDr Josef Kautzner, CSc, FESC

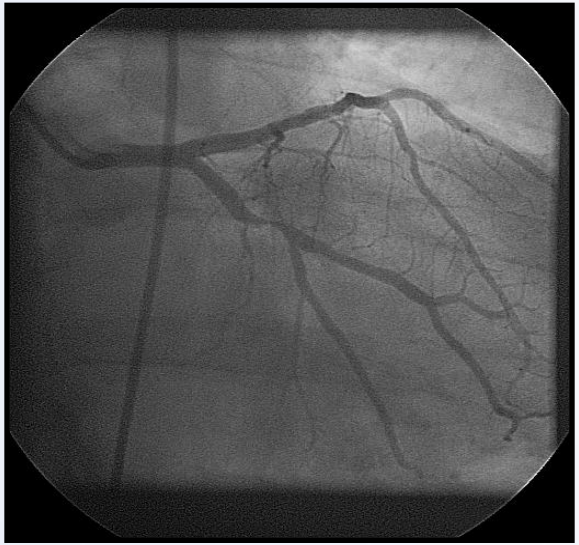
Institut Klinické a experimentální medicíny, Praha

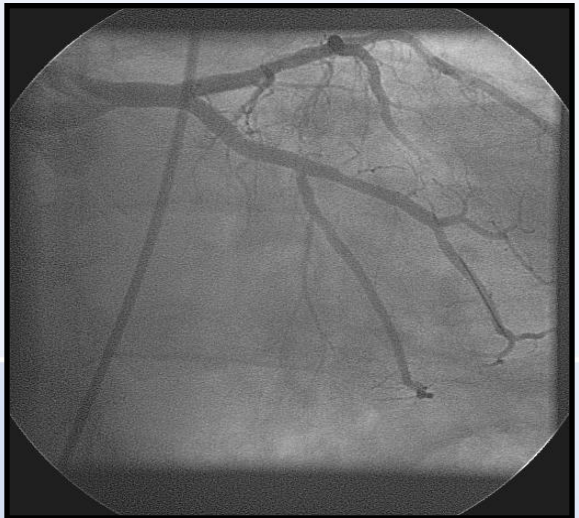
e-mail:joka@medicon.cz

www.ikem.cz

INSTITUT KLINICKÉ A EXPERIMENTÁLNÍ MEDICÍNY
KLINIKA KARDIOLOGIE

IK+E M



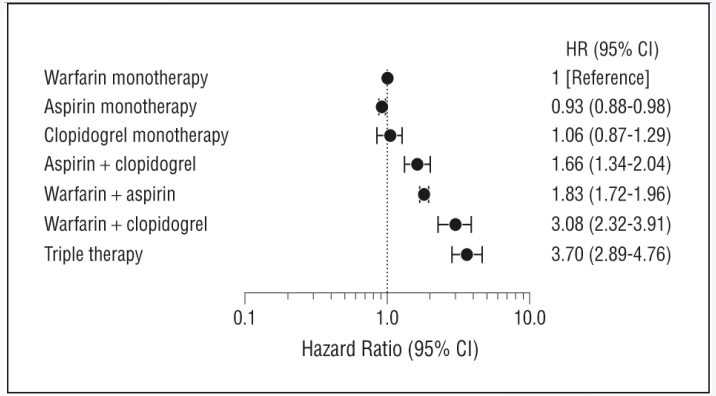


Kombinovaná antikoagulační a antiagregační léčba zvyšuje významně riziko krvácení

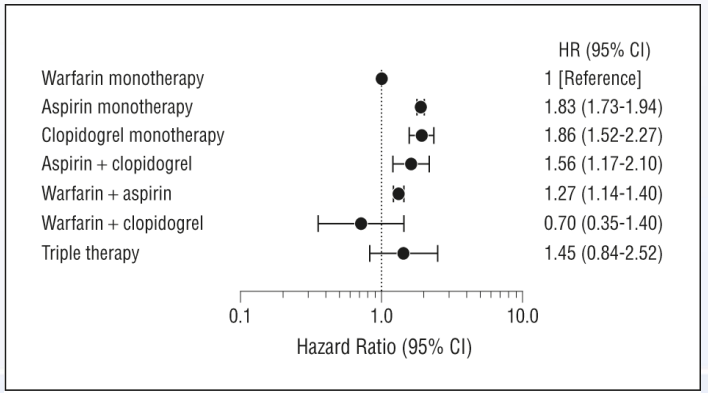
Danish registries
82 854 pts s FS a předpisem alespoň 1 antikoagulačního/antia gregačního léku

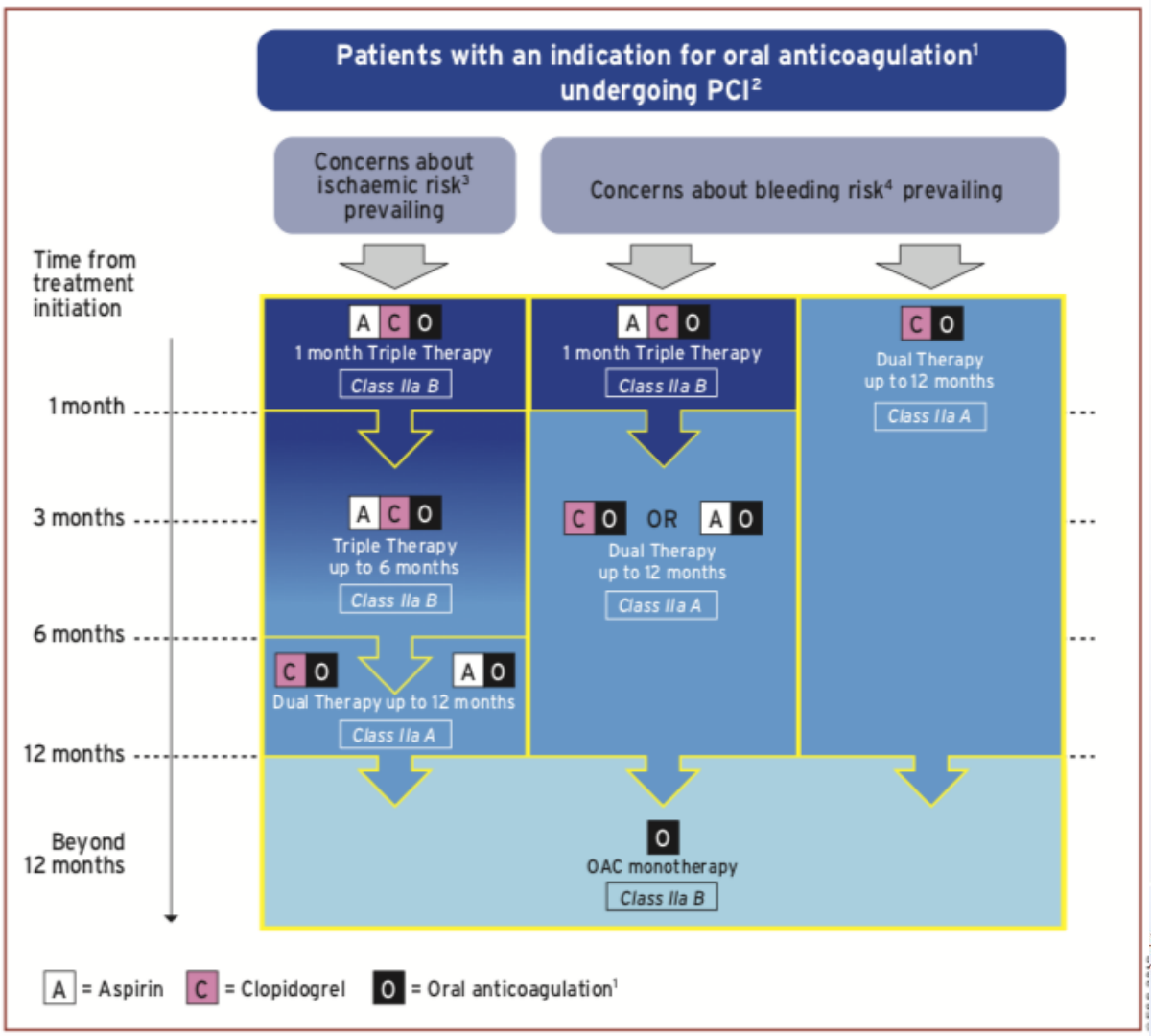
Hansen ML,et al.
Arch Intern Med
2010;170(16):1433-1441

Riziko nefatálního a fatálního krvácení



Riziko nefatální a fatální ischemické CMP





Algorithm for dual antiplatelet therapy in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention

Neumann, FJ et al.
Eur Heart J (2019) 40, 87–165

Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial

Pascal Vranckx, Marco Valgimigli, Lars Eckardt, Jan Tijssen, Thorsten Lewalter, Giuseppe Gargiulo, Valerii Batushkin, Gianluca Campo, Zoreslava Lysak, Igor Vakaliuk, Krzysztof Milewski, Petra Laeis, Paul-Egbert Reimitz, Rüdiger Smolnik, Wolfgang Zierhut, Andreas Goette

Summary

Background We aimed to assess the safety of edoxaban in combination with P2Y12 inhibition in patients with atrial fibrillation who had percutaneous coronary intervention (PCI).

http://dx.doi.org/10.1016/S0140-6736(19)31872-0

Methods ENTRUST-AF PCI was a randomised, multicentre, open-label, non-inferiority phase 3b trial with masked outcome evaluation, done at 186 sites in 18 countries. Patients had atrial fibrillation requiring oral anticoagulation, were aged at least 18 years, and had a successful PCI for stable coronary artery disease or acute coronary syndrome. Participants were randomly assigned (1:1) from 4 h to 5 days after PCI using concealed, stratified, and blocked web-based central randomisation to either edoxaban (60 mg once daily) plus a P2Y12 inhibitor for 12 months or a vitamin K antagonist (VKA) in combination with a P2Y12 inhibitor and aspirin (100 mg once daily, for 1–12 months). The edoxaban dose was reduced to 30 mg per day if one or more factors (creatinine clearance 15–50 mL/min, bodyweight ≤60 kg, or concomitant use of specified potent P-glycoprotein inhibitors) were present. The primary endpoint was a composite of major or clinically relevant non-major (CRNM) bleeding within 12 months. The primary analysis was done in the intention-to-treat population and safety was assessed in all patients who received at least one dose of their assigned study drug. This trial is registered with ClinicalTrials.gov, NCT02866175, is closed to new participants, and follow-up is completed.

Findings From Feb 24, 2017, through May 7, 2018, 1506 patients were enrolled and randomly assigned to the edoxaban regimen (n=751) or VKA regimen (n=755). Median time from PCI to randomisation was 45·1 h (IQR 22·2–76·2). Major or CRNM bleeding events occurred in 128 (17%) of 751 patients (annualised event rate 20·7%) with the edoxaban regimen and 152 (20%) of 755 patients (annualised event rate 25·6%) patients with the VKA regimen; hazard ratio 0·83 (95% CI 0·65–1·05; p=0·0010 for non-inferiority, margin hazard ratio 1·20; p=0·1154 for superiority).

ENTRUST-AFPCI

Study Design

PROBE design: Prospective, Randomized, Open label, Blinded endpoint Evaluation in 1500 AF patients with ACS or stable CAD

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*

$P2Y_{12}$ inhibitor** (without aspirin)

Vitamin K Antagonist***

$P2Y_{12}$ inhibitor aspirin 1 - 12 months****

12 m.

**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*

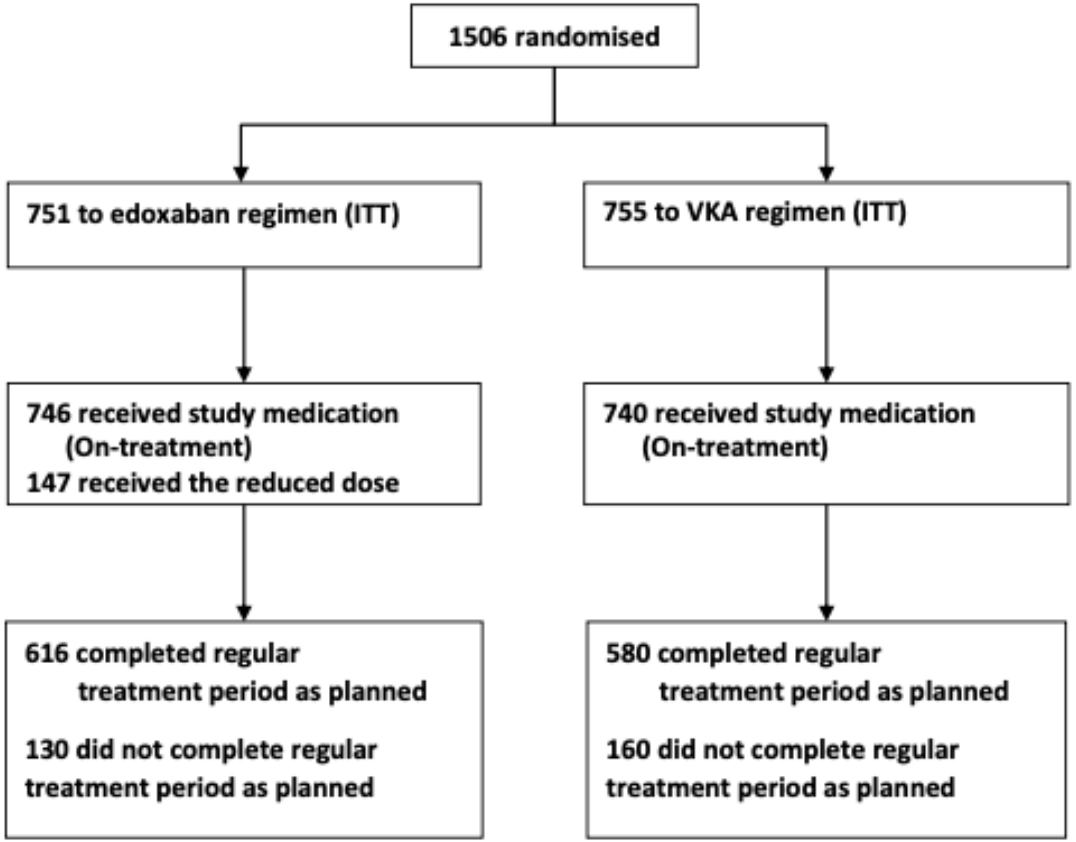
**** VKA, target INR 2-3*

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

Primary outcome:
ISTH major or clinically relevant non-major bleeding

ENTRUST-AF PCI

Consort Diagram



186 centres
18 countries

ENTRUST-AF PCI

Baseline Demographics

	Edoxaban regimen (N=751)	VKA regimen (N=755)
Age (years), median (Q1; Q3)	69 (63; 77)	70 (64; 77)
Sex, female	194 (25.8)	192 (25.4)
Weight (kg), median (Q1; Q3)	80 (71; 93)	83 (72; 94)
Type of AF, n (%)		
Paroxysmal	402 (53.5)	358 (47.5)
Persistent	140 (18.6)	146 (19.4)
Long-standing persistent or permanent	209 (27.8)	250 (33.2)
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), median (Q1; Q3)	71.8 (53.7, 91.1)	71.7 (54.0, 90.9)
Clinical presentation, n (%)		
ACS	388 (51.7)	389 (51.5)
Stable CAD	363 (48.3)	366 (48.5)
OAC prior to index PCI, n (%)	408 (68.0)	413 (65.1)
Time (hours) between end of PCI and randomisation, 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 or Ticagrelor	54 (7.2)	60 (7.9)

ENTRUST-AF PCI

Primary Study Endpoint

ITT Analysis (N=1506), overall study period

	Edoxaban regimen	VKA regimen	Hazard Ratio (2-sided 95% CI)	P-value
Primary outcome of major or CRNM bleeding (ISTH)				
Intent-to-treat analysis:				
Number of patients	751	755		
Number of patients with event (%)	128 (17)	152 (20)		
Annualised event rate (% per year)	20.7	25.6	0.83 (0.65; 1.05)	Non-inferiority: P=0.0010 Superiority: P=0.1154

Hierarchical test procedure (*confirmatory statistics*):

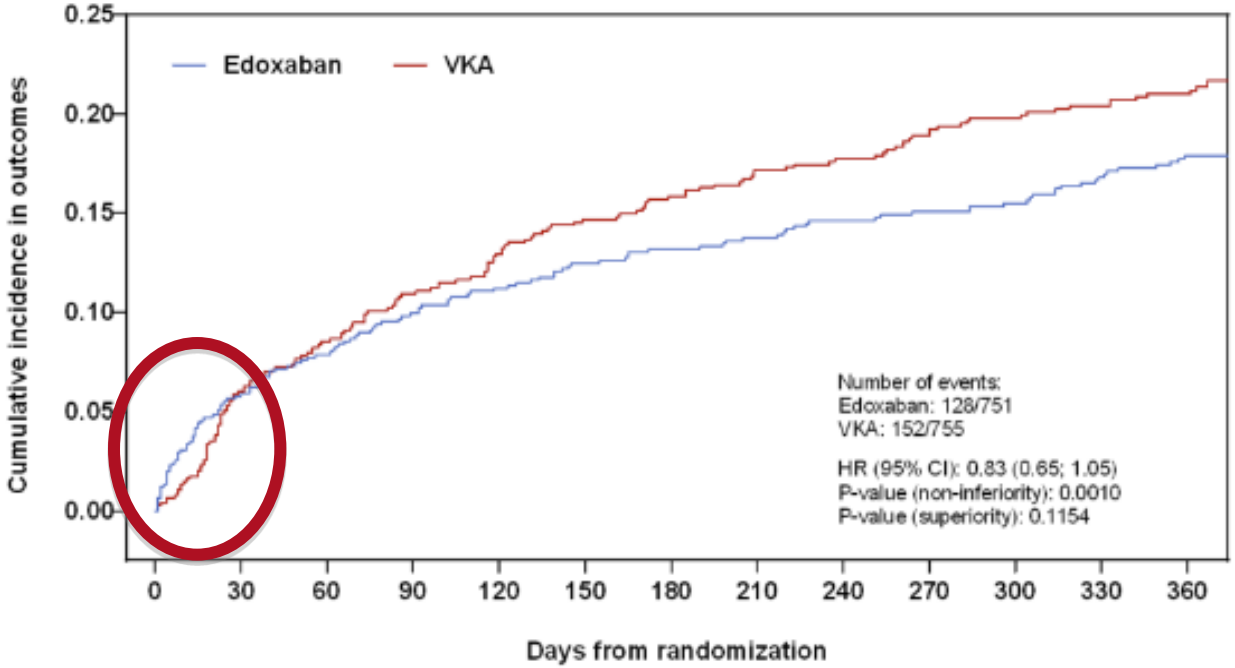
STEP 1: **1.047 < 1.20** → **The edoxaban regimen is non-inferior to the VKA regimen**

STEP 2: **1.047 > 1.00** → **superiority of edoxaban regimen could not be demonstrated**

ENTRUST-AF PCI

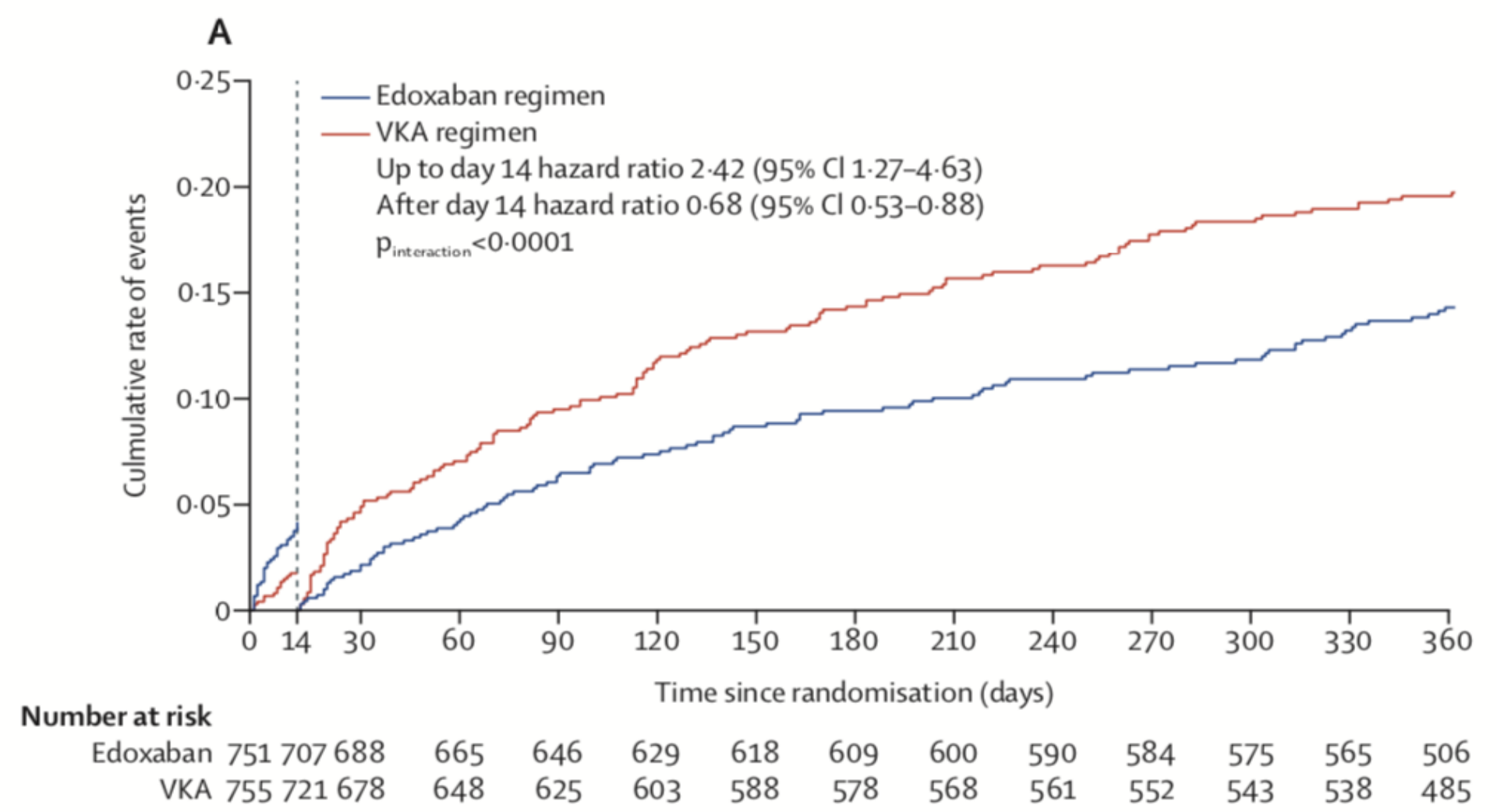
Primary Study Endpoint

ITT Analysis (N=1506), overall study period



Number at risk:

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


A
0·25
0·20
0·15
0·10
0·05
0
Culmulative rate of events
Edoxaban regimen
VKA regimen
Up to day 14 hazard ratio 2·42 (95% CI 1·27–4·63)
After day 14 hazard ratio 0·68 (95% CI 0·53–0·88)
$p_{interaction}$<0·0001
0 14 30 60 90 120 150 180 210 240 270 300 330 360
Time since randomisation (days)
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

ENTRUST-AF PCI

Main Efficacy Endpoint

ITT Analysis (N=1506), overall study period

	Edoxaban regimen	VKA regimen	Hazard Ratio (2-sided 95% CI)
Main efficacy outcome (composite of CV death, stroke, SEE, MI or definite stent thrombosis)			
Intent-to-treat analysis:			
Number of patients	751	755	
Number of patients with event (%)	49 (7)	46 (6)	
Annualised event rate (% per year)	7.3	6.9	1.06 (0.71; 1.69)

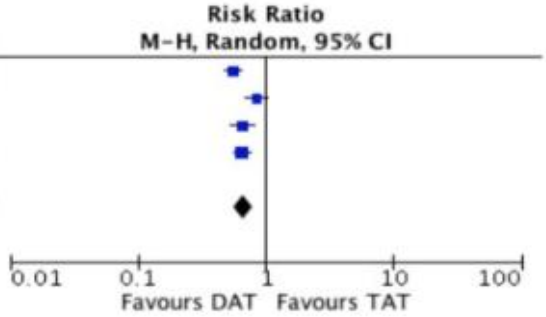
Meta-analýza studií s NOAC

Krvácení na DAT/TAT

A 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			

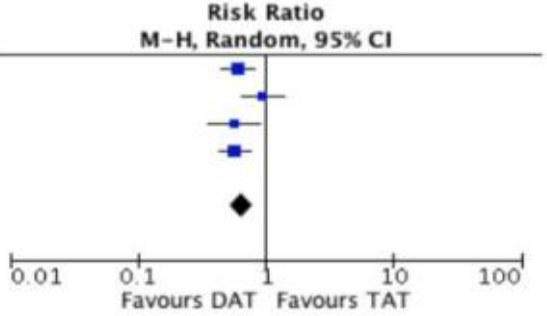
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 9.65$, df = 3 (P = 0.02); $I^2 = 69\%$
Test for overall effect: Z = 5.03 (P < 0.00001)



B ISTH MAJOR BLEEDING

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	65	2279	108	2277	29.6%	0.60 [0.44, 0.81]
ENTRUST AF-PCI	45	751	48	755	21.2%	0.94 [0.64, 1.40]
PIONEER AF-PCI	27	696	48	697	17.0%	0.56 [0.36, 0.89]
RE-DUAL PCI	92	1744	90	981	32.2%	0.57 [0.43, 0.76]
Total (95% CI)		**5470**		**4710**	**100.0%**	**0.64 [0.52, 0.80]**
Total events	229		294			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.73$, df = 3 (P = 0.19); $I^2 = 37\%$
Test for overall effect: Z = 3.94 (P < 0.0001)



Gargiulo G, et al. Eur Heart J 2019 (in press)

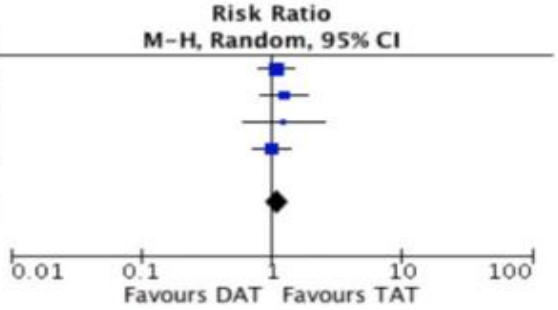
Úmrtnost na DAT/TAT

A

ALL-CAUSE DEATH

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	79	2307	72	2307	38.9%	1.10 [0.80, 1.50]
ENTRUST AF-PCI	46	751	37	755	21.6%	1.25 [0.82, 1.90]
PIONEER AF-PCI	16	694	13	695	7.3%	1.23 [0.60, 2.54]
RE-DUAL PCI	85	1744	48	981	32.2%	1.00 [0.71, 1.41]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.10 [0.91, 1.34]**
Total events	226		170			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.77$, df = 3 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 0.98 (P = 0.32)

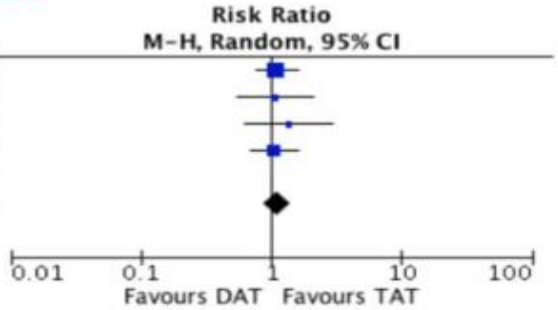


B

CARDIOVASCULAR DEATH

Study or Subgroup	DAT Events	DAT Total	TAT Events	TAT Total	Weight	Risk Ratio M-H, Random, 95% CI
AUGUSTUS	58	2307	53	2307	44.2%	1.09 [0.76, 1.58]
ENTRUST AF-PCI	17	751	16	755	13.1%	1.07 [0.54, 2.10]
PIONEER AF-PCI	15	694	11	695	10.1%	1.37 [0.63, 2.95]
RE-DUAL PCI	58	1744	31	981	32.5%	1.05 [0.69, 1.62]
Total (95% CI)		**5496**		**4738**	**100.0%**	**1.10 [0.86, 1.41]**
Total events	148		111			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.35$, df = 3 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 0.77 (P = 0.44)



Gargiulo G, et al. Eur Heart J 2019 (in press)

Ischemické údálosti na DAT/TAT

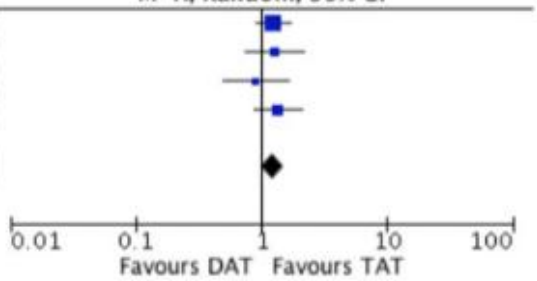
B

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)



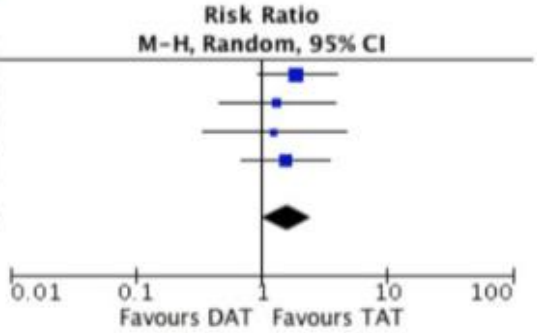
C

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)



Gargiulo G, et al. Eur Heart J 2019 (in press)

Závěry ENTRUST AF PCI

- U pacientů s FS, kteří prodělali úspěšnou PCI, není antikoagulační léčba s plnou dávkou edoxabanu s inhibitorem P2Y12 horší než trojkombinace VKA+ASA+P2Y12 z hlediska výskytu většího nebo klinicky relevantního menšího krvácení
- Tato dvojkombinace edoxaban-P2Y12 inhibitor nevedla k vyššímu výskytu složeného endpointu (úmrtí z KV příčin, CMP, IM, systémová embolizace nebo trombóza stentu)
- Pozn: všechny studie s NOAC a PCI ukazují numericky zvýšený počet IM a trombózy stentu při časném vyloučení ASA

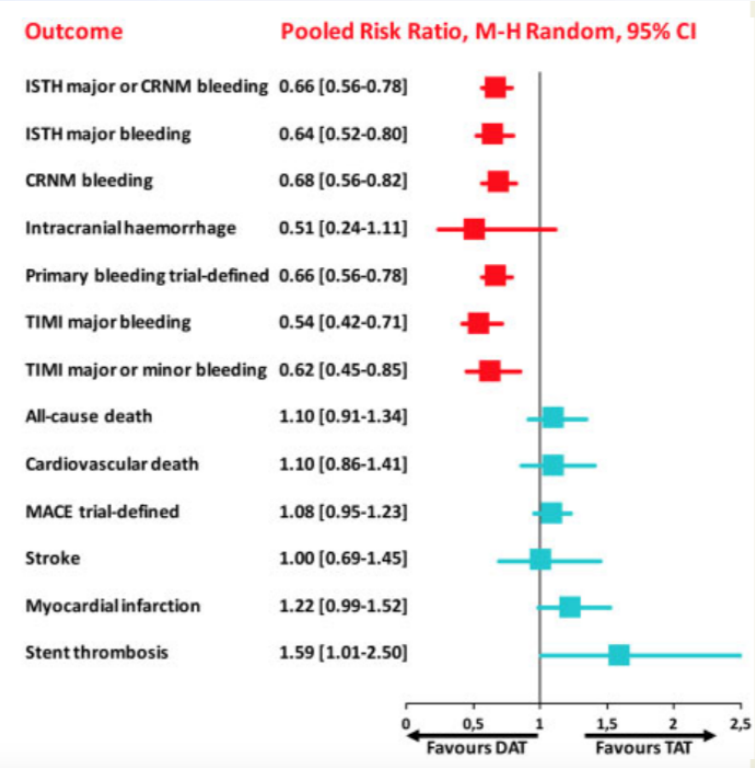
Děkuji za Vaši pozornost..

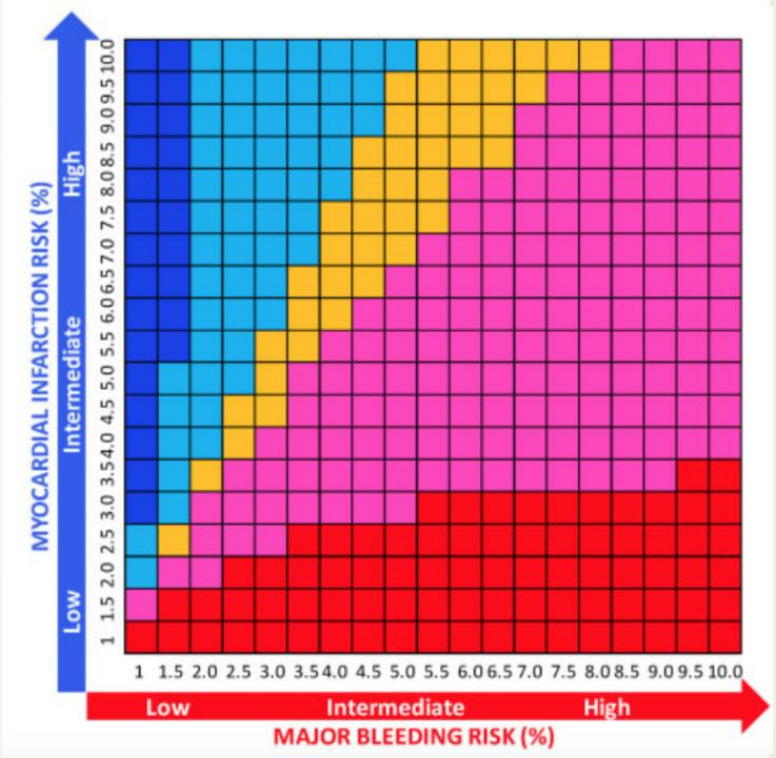
Strategie k omezení krvácivých komplikací

- Posouzení rizika ischemické a krvácivé příhody se zaměřením na modifikovatelné faktory
- Trojkombinace co nejkratší dobu, vždy zvážit duální léčbu (OAC a clopidogrel)
- Zvážit NOAC proti VKA
- U VKA zvážit nižší hranice INR a maximalizaci času v terapeutickém rozmezí (nad 65 %)
- Clopidogrel je P2Y12 inhibitor léčbou volby
- Aspirin v malé dávce (do 100 mg denně)
- Rutinní použití PPI

Neumann FJ, et al. Eur Heart J (2019) 40, 87–16

DAT vs TAT

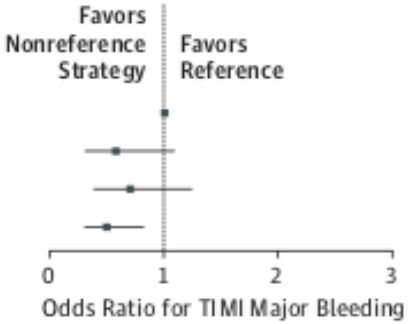




Gargiulo G, et al. Eur Heart J 2019 (in press)

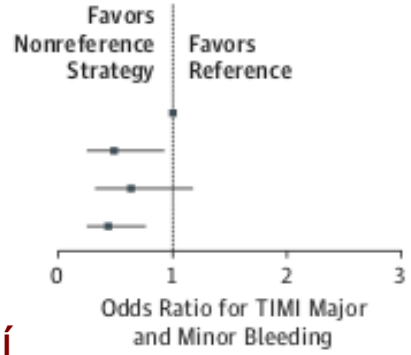
A TIMI major bleeding

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.58 (0.31-1.08)
NOAC + DAPT	0.70 (0.38-1.23)
NOAC + $P2Y_{12}$ inhibitor	0.49 (0.30-0.82)



B TIMI major and minor bleeding

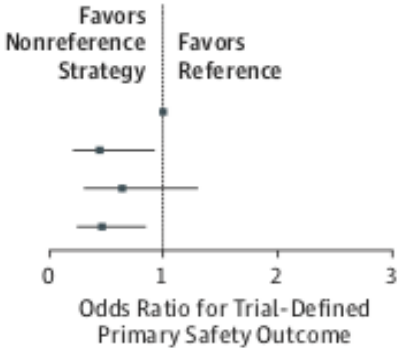
Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.49 (0.26-0.92)
NOAC + DAPT	0.63 (0.33-1.17)
NOAC + $P2Y_{12}$ inhibitor	0.43 (0.25-0.76)



Meta-analýza 4 studií

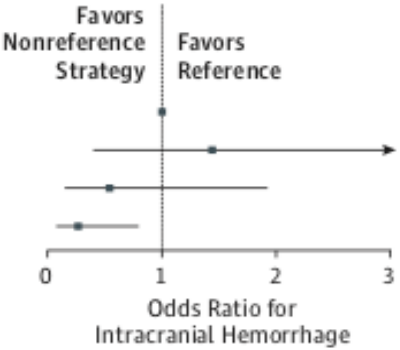
C Trial-defined primary safety outcome

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	0.45 (0.21-0.92)
NOAC + DAPT	0.64 (0.31-1.31)
NOAC + $P2Y_{12}$ inhibitor	0.47 (0.25-0.85)



D Intracranial hemorrhage

Odds ratio (95% CI)	
VKA + DAPT (reference)	
VKA + $P2Y_{12}$ inhibitor	1.44 (0.40-5.22)
NOAC + DAPT	0.54 (0.15-1.92)
NOAC + $P2Y_{12}$ inhibitor	0.26 (0.08-0.79)



Lopez RD, et al. JAMA Cardiol. doi:10.1001/jamacardio.2019.1880