Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease

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Disclosure

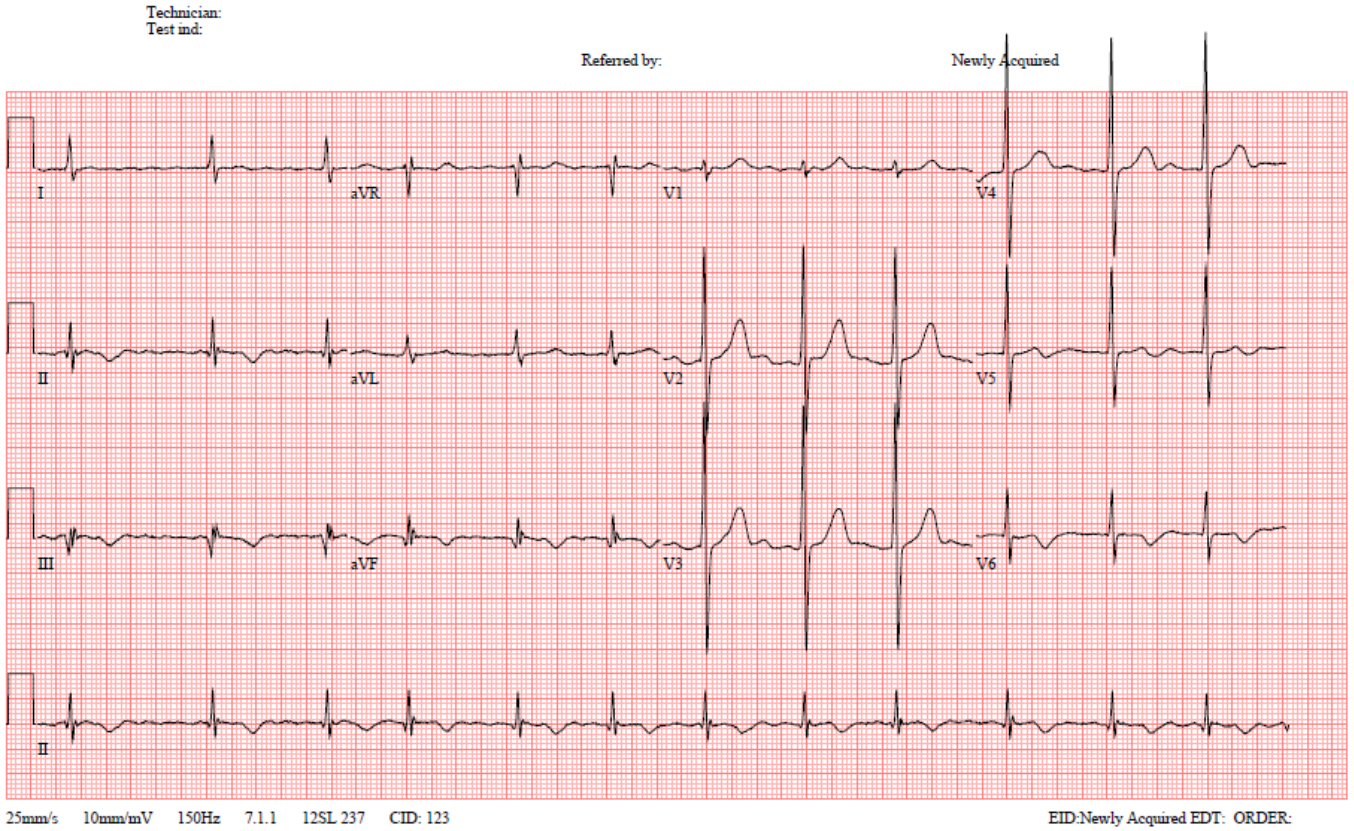
- I, Do-Yoon Kang, DO NOT have any relevant financial relationships to disclose.

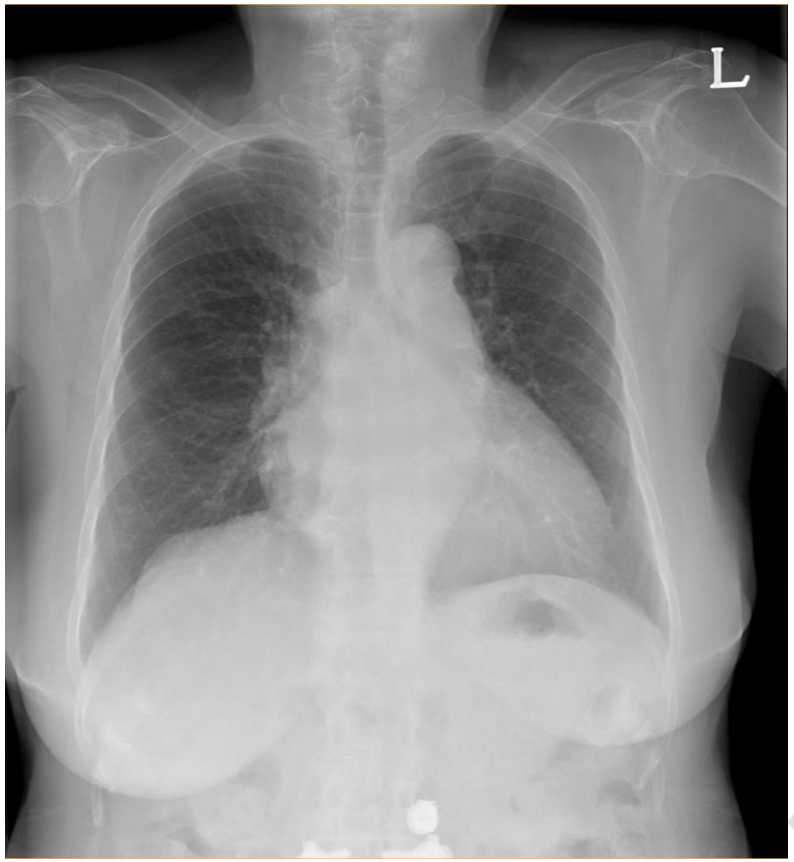
Anticoagulation Strategy in AF Patients after PCI

Case

F/82 with NSTEMI

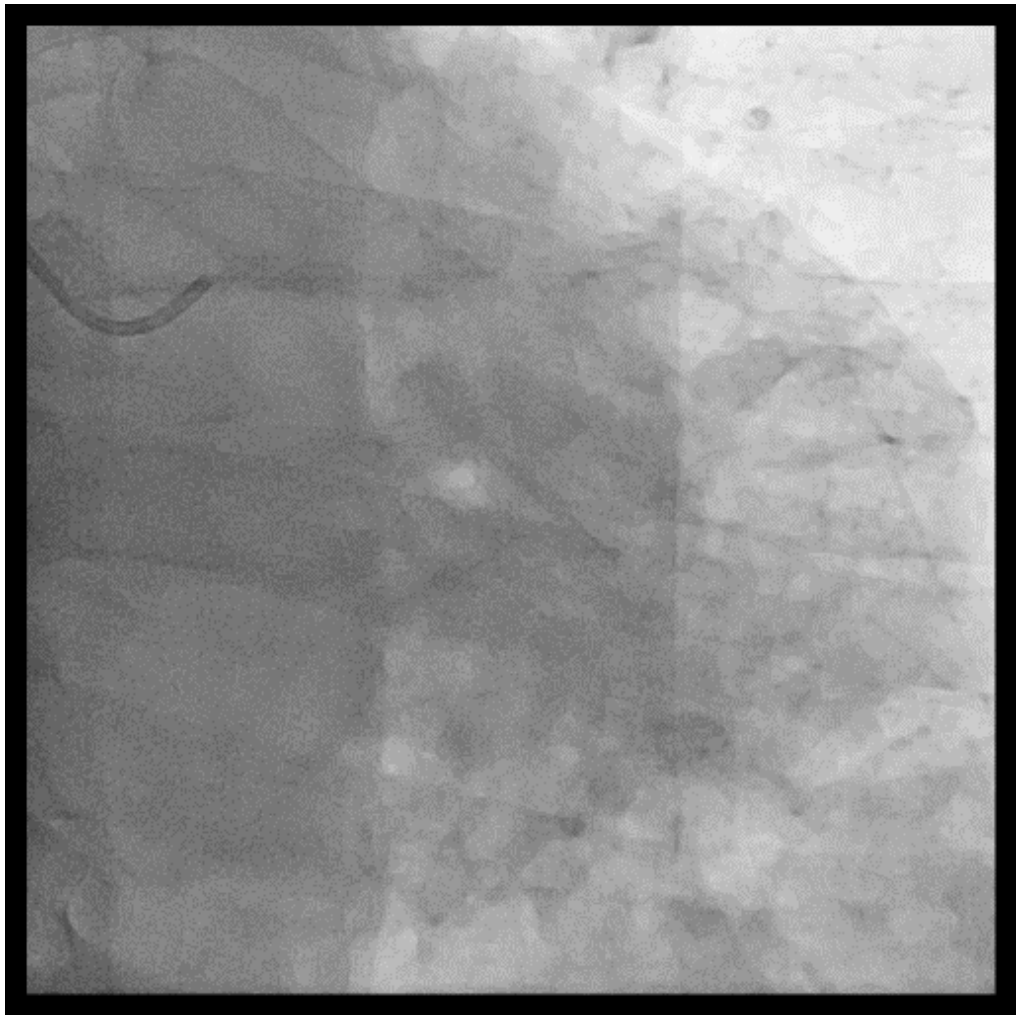
157cm, 52kg
Diabetes, Hypertension, Dyslipidemia, h/o gastric ulcer
Medication : Edoxaban, Metformin, Losartan, Amlodipine, Atorvastatin

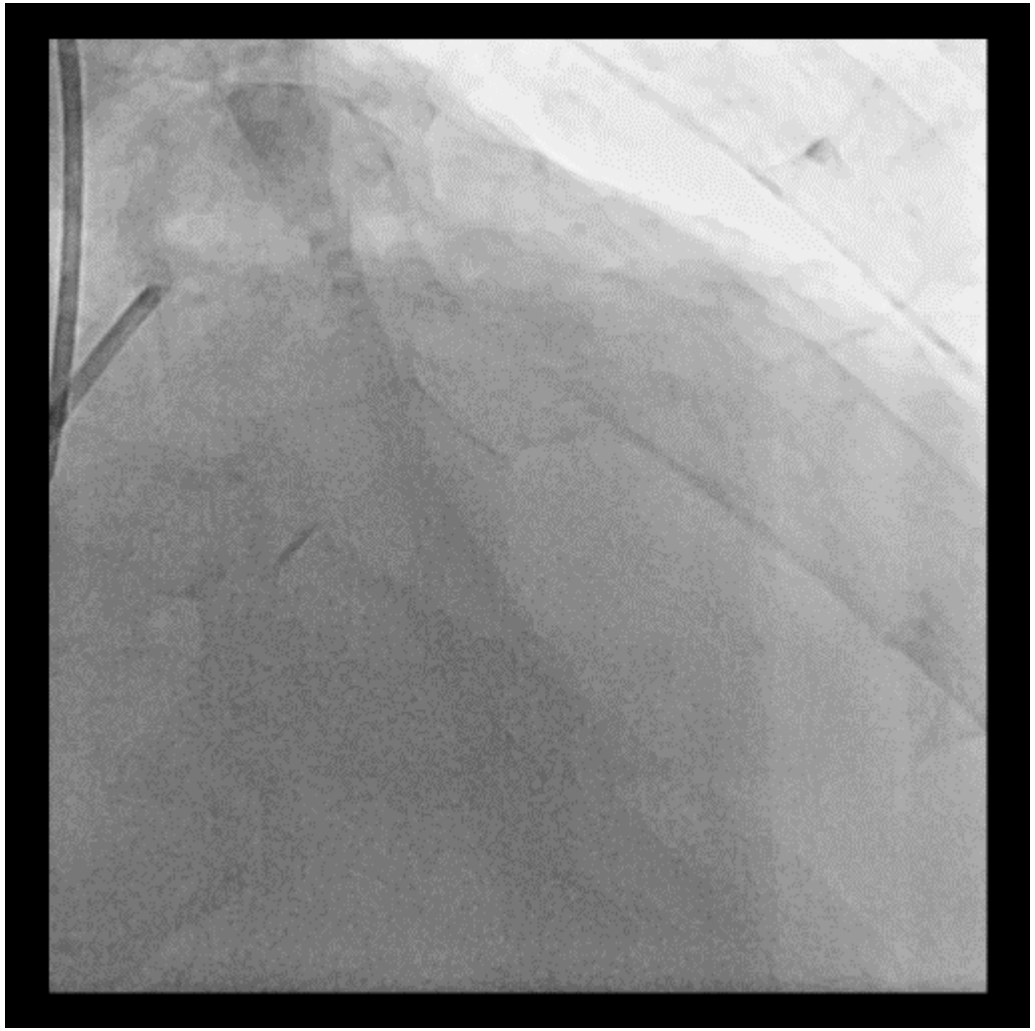




Case

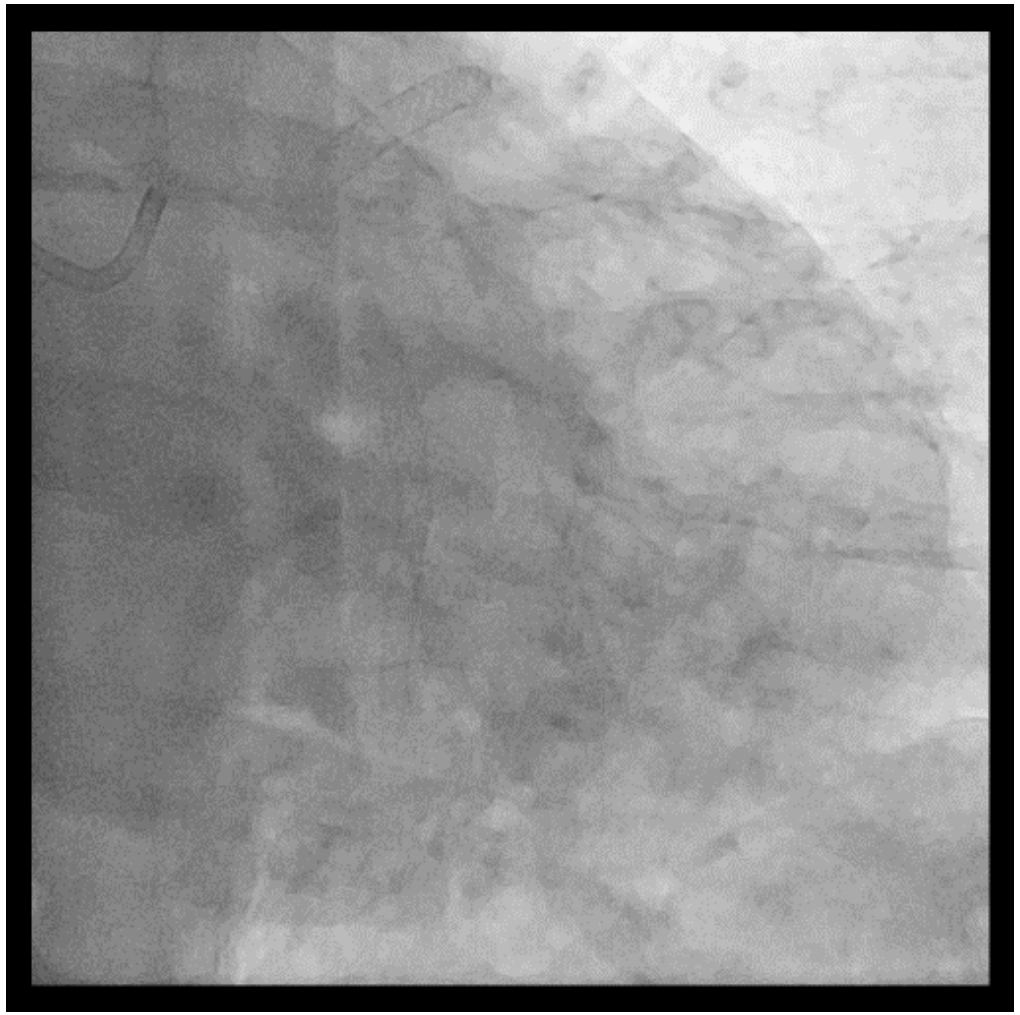
F/82, NSTEMI, 2VD on CAG

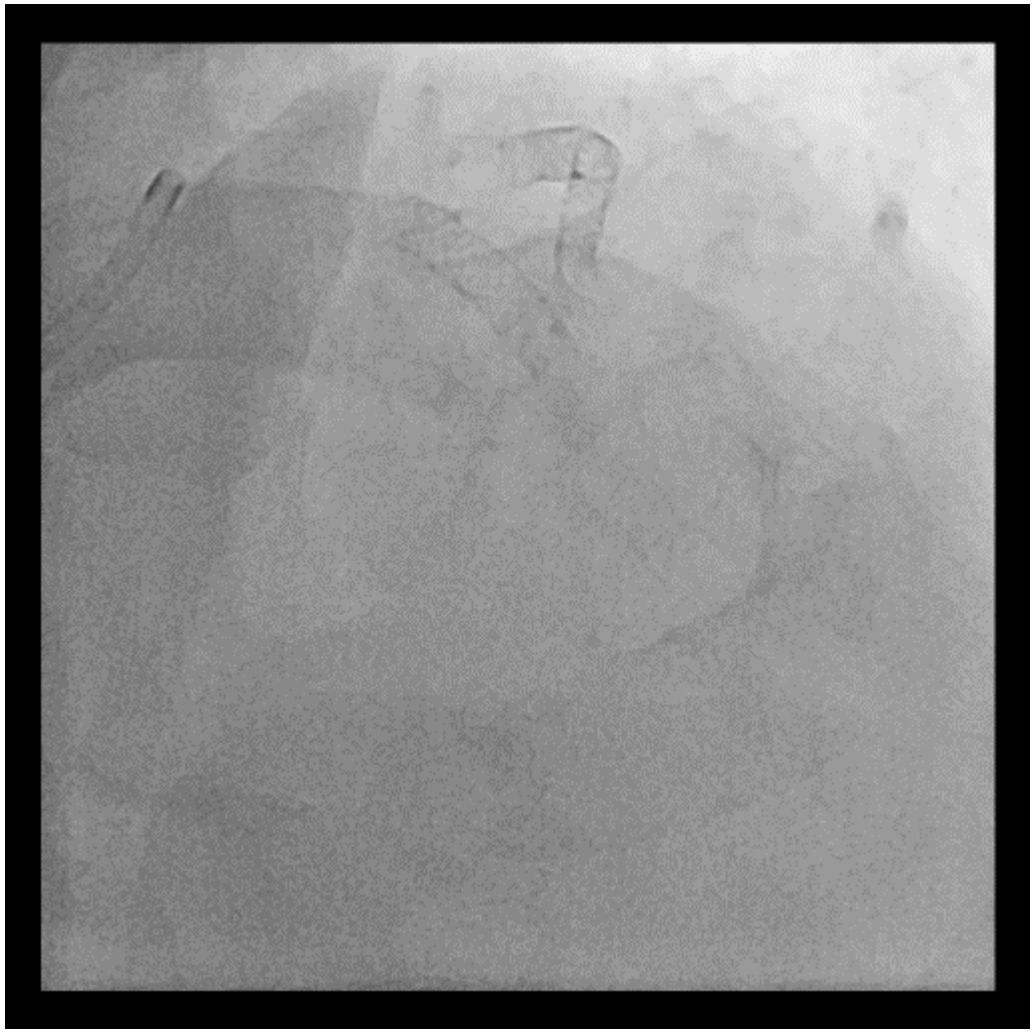




Case

F/82, NSTEMI s/p PCI, AF (C-V score 5)





Atrial Fibrillation & Coronary Artery Disease

AF & CAD Shares Clinical 8Risk Factors

AF Risk Factors

Old Age
Male Gender
Obesity
Alcohol Consumption
Smoking
Diabetes
Hypertension
Physical Inactivity

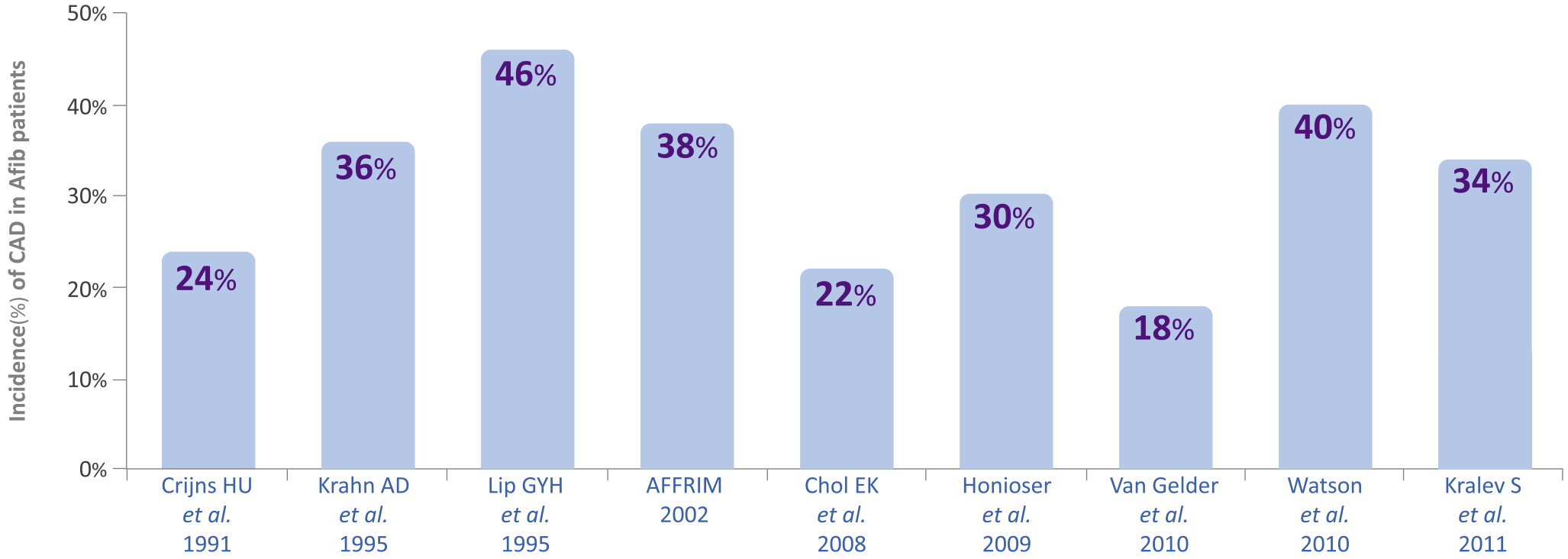
CAD Risk Factors

Old Age
Male Gender
Obesity
FHx of Premature CAD
Smoking
Diabetes
Hypertension
Dyslipidemia

Lau D et al. Circulation. 2017;136:583–596.
Goff DC Jr et al., Circulation. 2014;129»S49-S73.

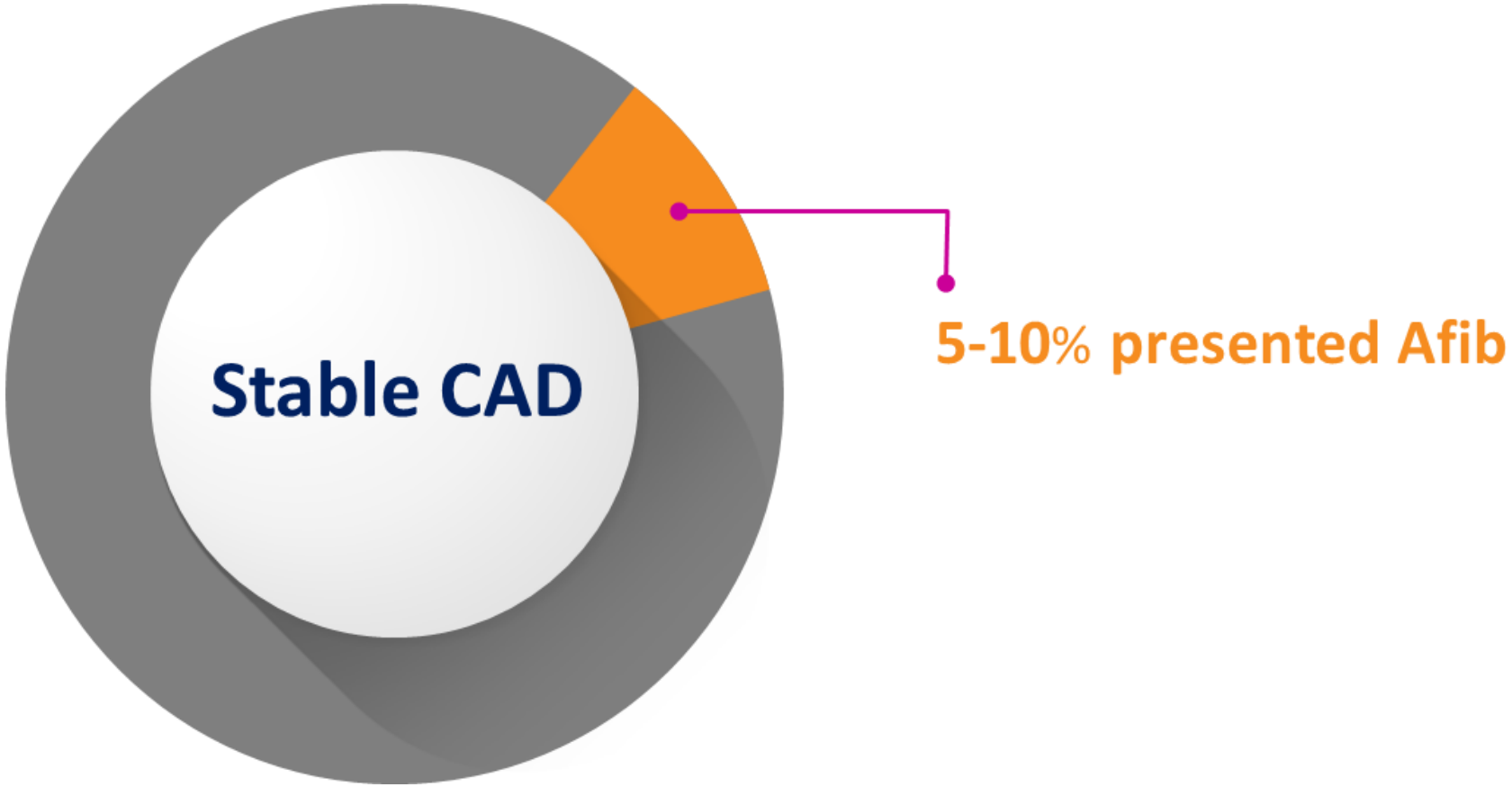
20~40% of AF Patients have Coronary Artery Disease

Reported incidences of CAD in Afib patients



Kralev S, et al. PLoS ONE 6(9): e24964.

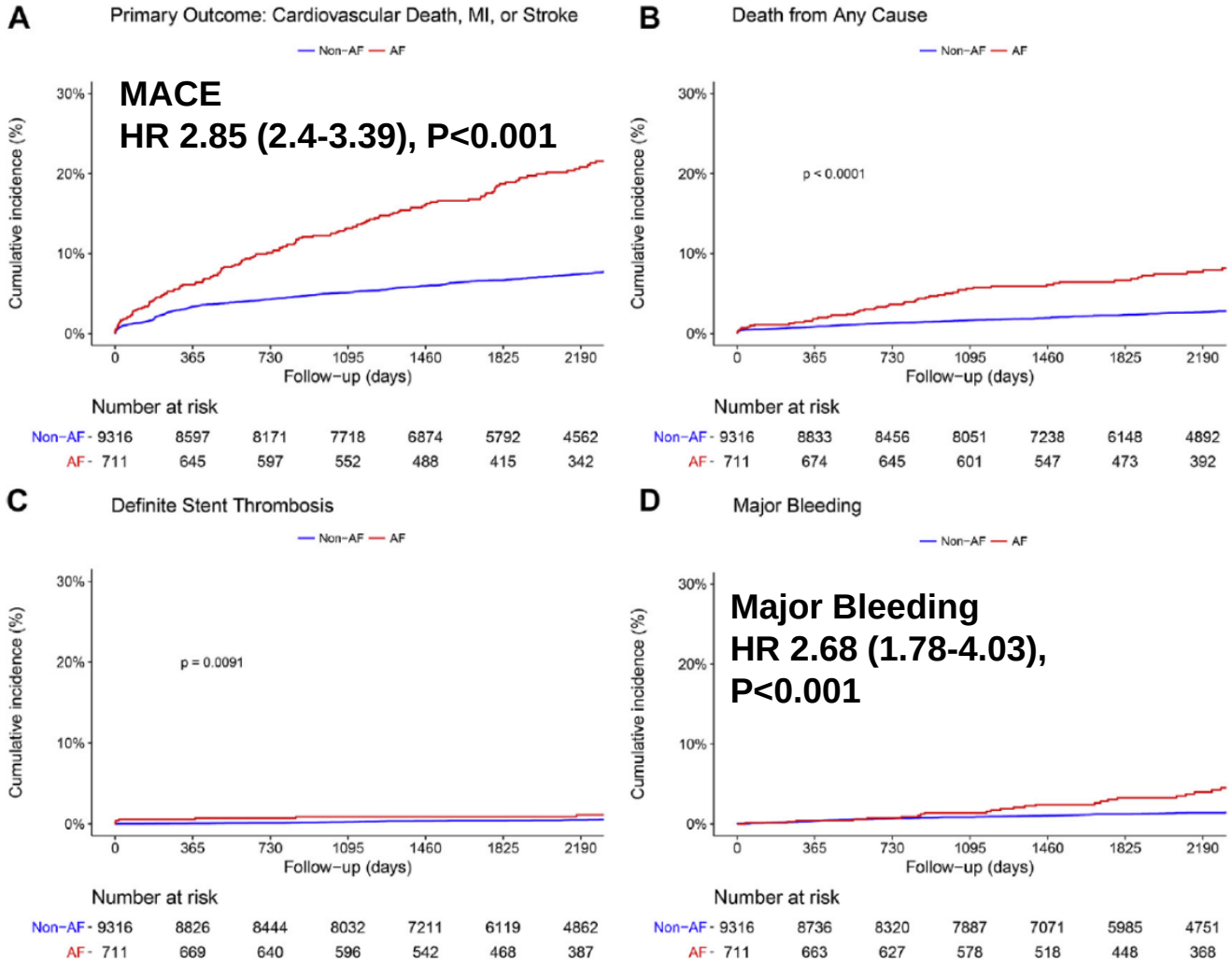
5~10% of CAD Patients have AF



Rohla M et al. Int J Cardiology 2015;184:108–114.
Pilgrim T, et al. 2013;8:1061-1071.

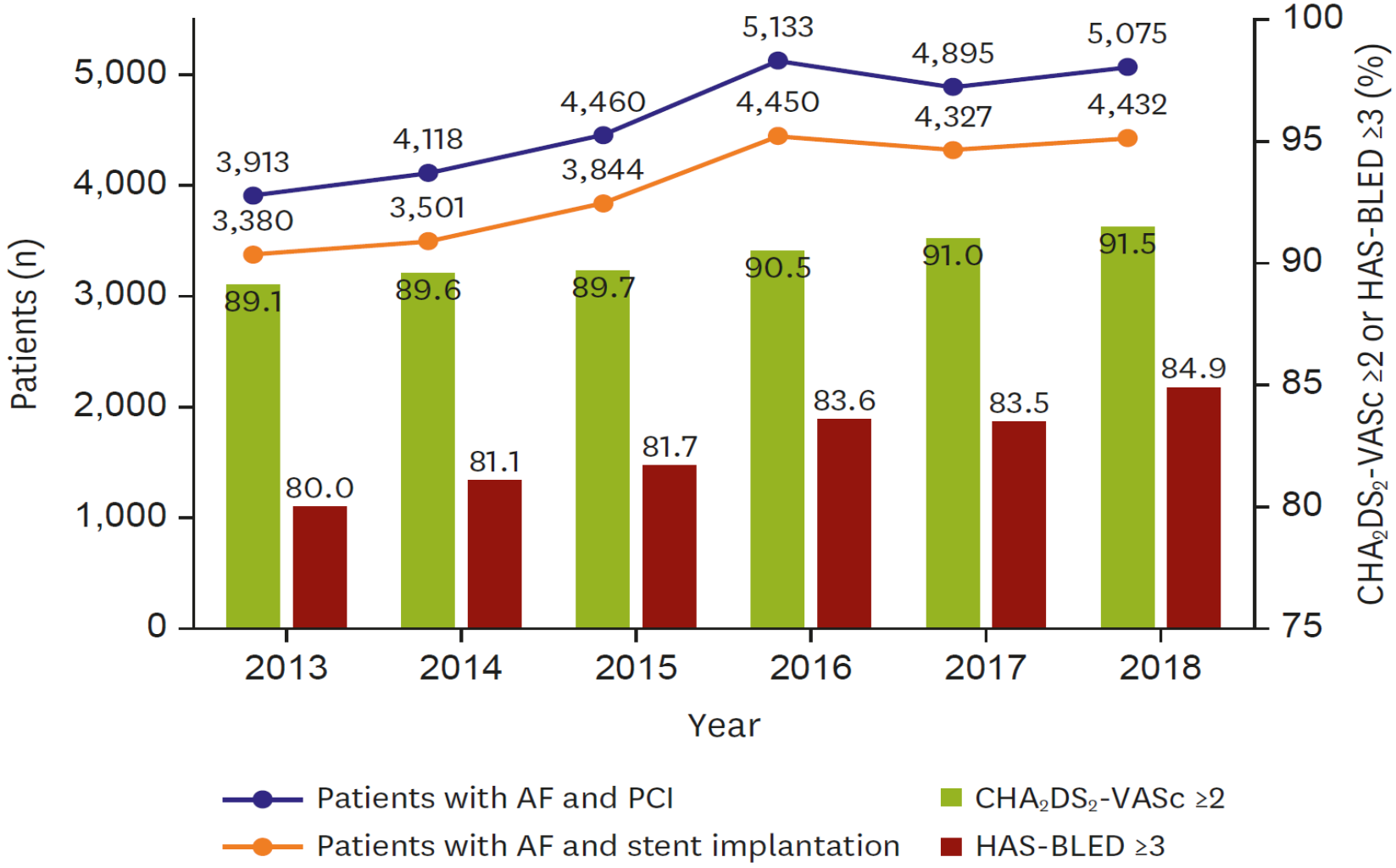
7.1% of PCI Patients had AF in AMC

- In ASAN-PCI registry, 711 of 10,027 PCI patients from 2003 to 2011 had AF.
- Patients with AF had more ischemic & bleeding events.



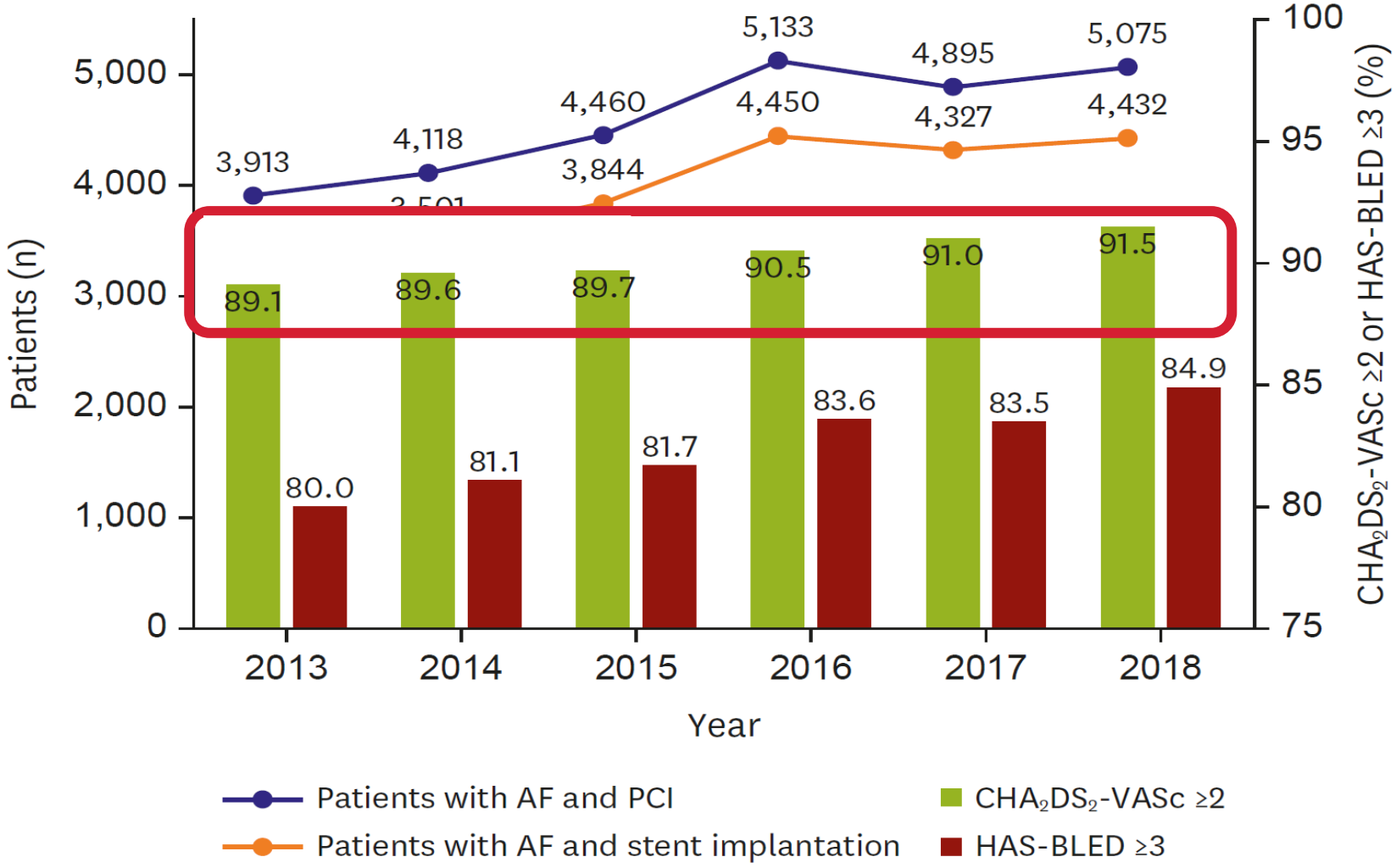
Choi HI et al., JACC CV Intervention. 2017;10(11):1075-85

7% of PCI Patients had AF in Korea



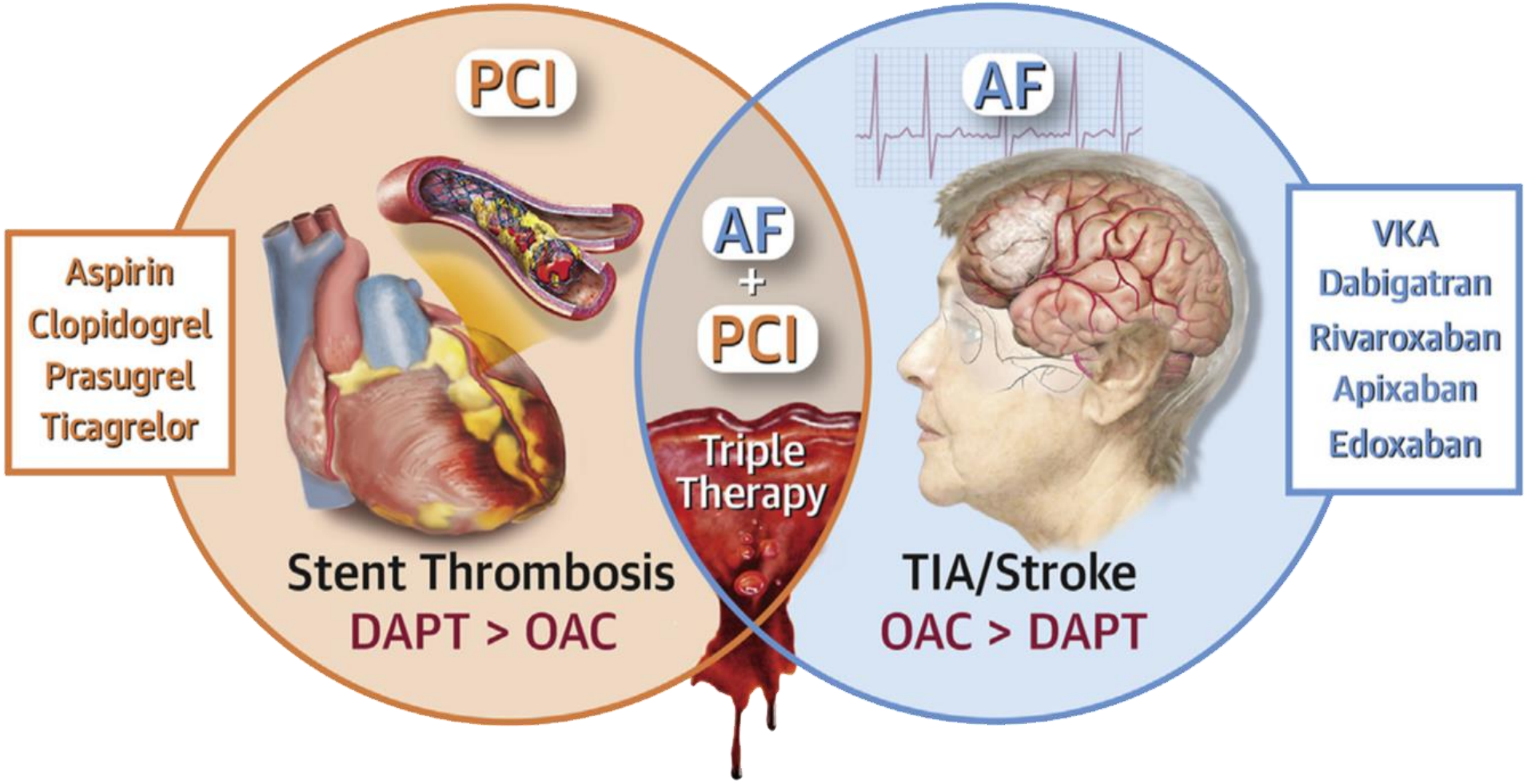
Kwon S et al. Korean Circ J. 2021 May;51(5):409-422.

90% of AF-PCI Patients are Indicated for Anticoagulation



Kwon S et al. Korean Circ J. 2021 May;51(5):409-422.

AF & CAD/PCI Patients, What is Different?

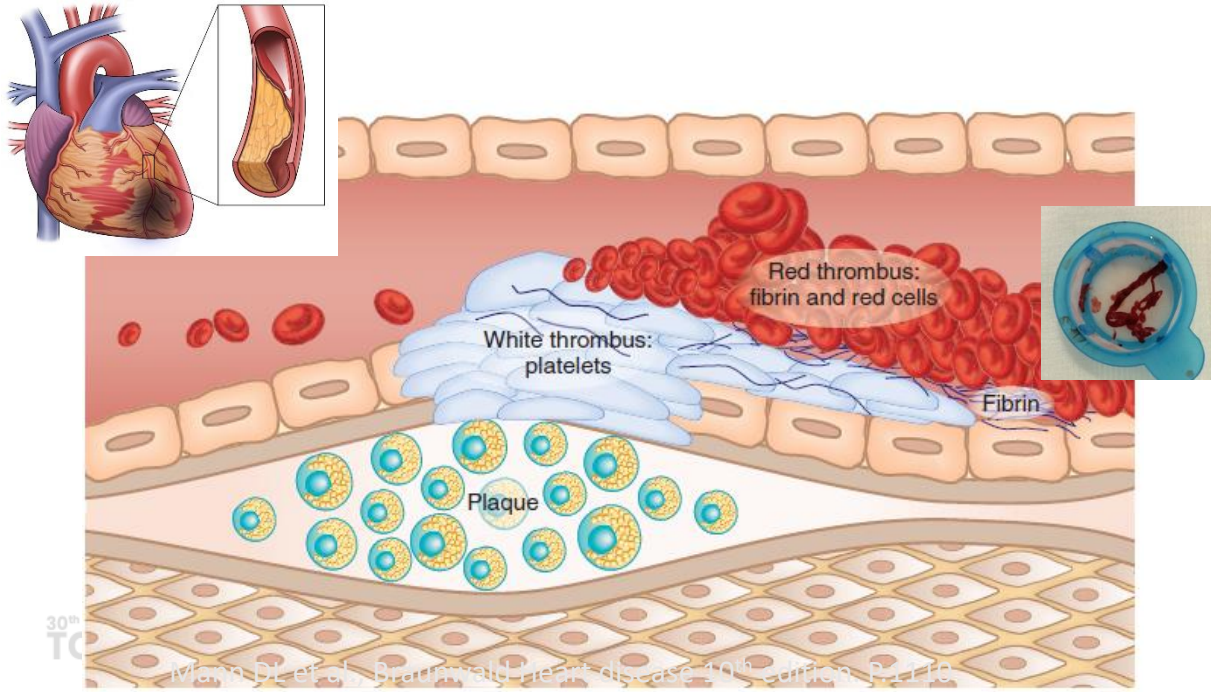


Capodanno D, Aniolillo DJ. JACC Cardiovasc Interv. 2017;10(11):1086-1088.

We Should Protect Coronary Artery & LA Together

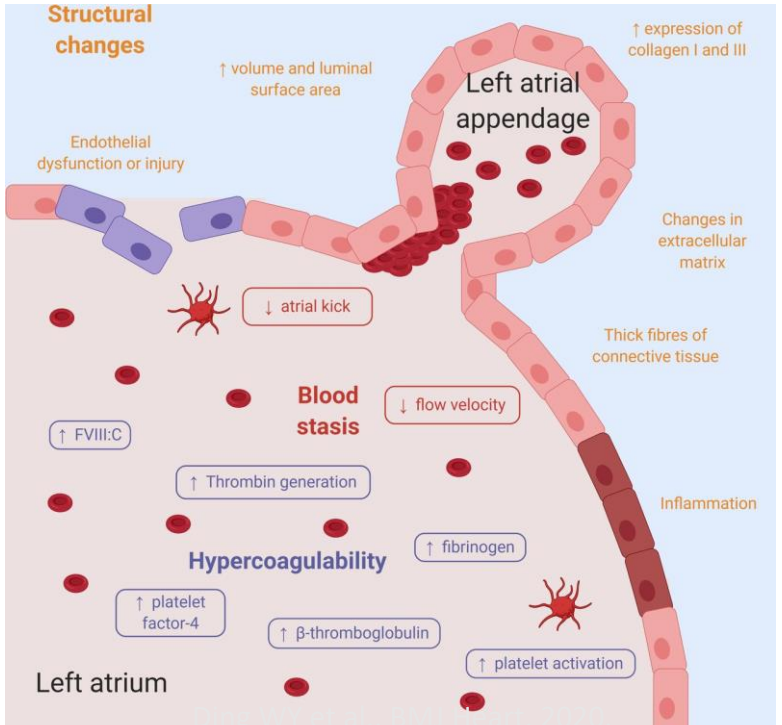
Coronary Artery Disease

High-velocity system
Atherosclerosis, Plaque rupture
Platelet is the main target



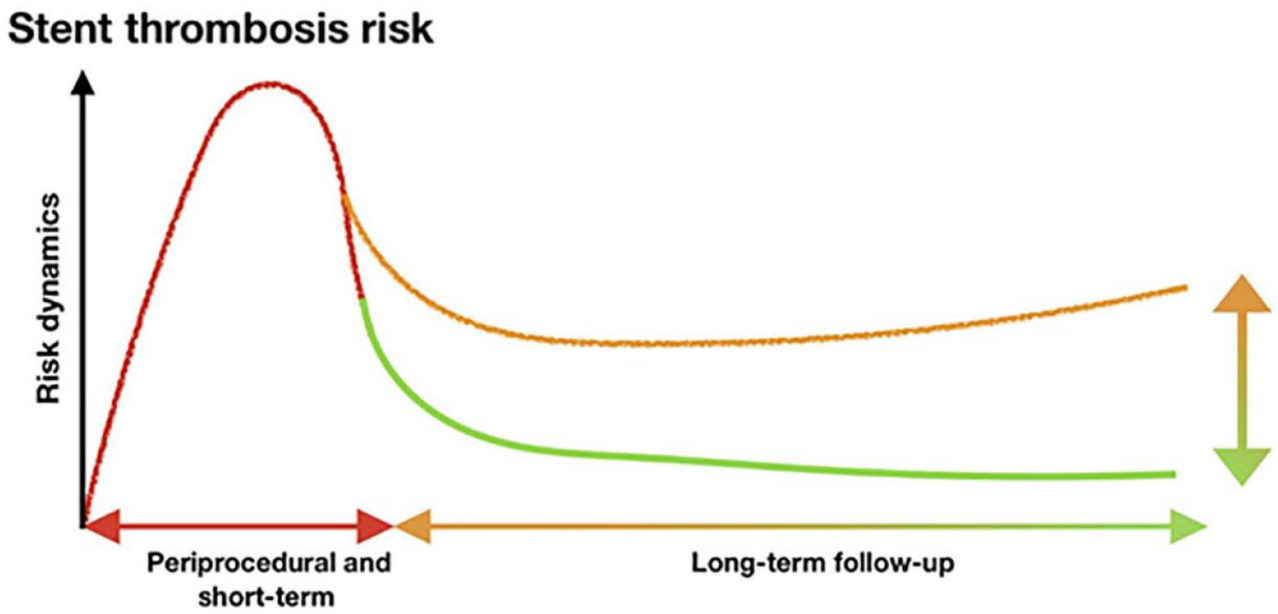
Left Atrium with AF

Low-velocity system
Hypercoagulability, Flow stasis
(Virchow's triad)



Optimal Antithrombotic Therapy in AF after PCI : Within 1 year

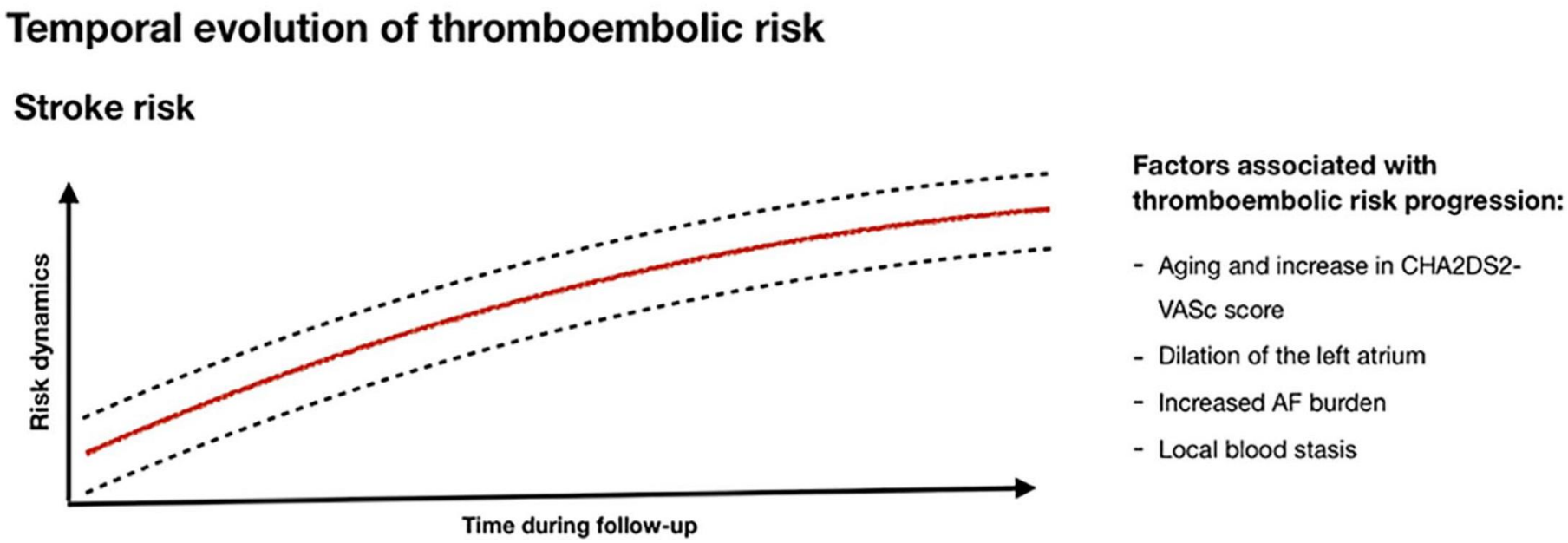
PCI



Factors associated with long-term increased risk of stent thrombosis:

- Prior stent thrombosis on adequate antiplatelet therapy
- 3 or more stents implanted
- 3 or more lesions treated
- Bifurcation with 2 stents implanted
- Total stent length >60 mm
- Treatment of chronic total occlusion

AF

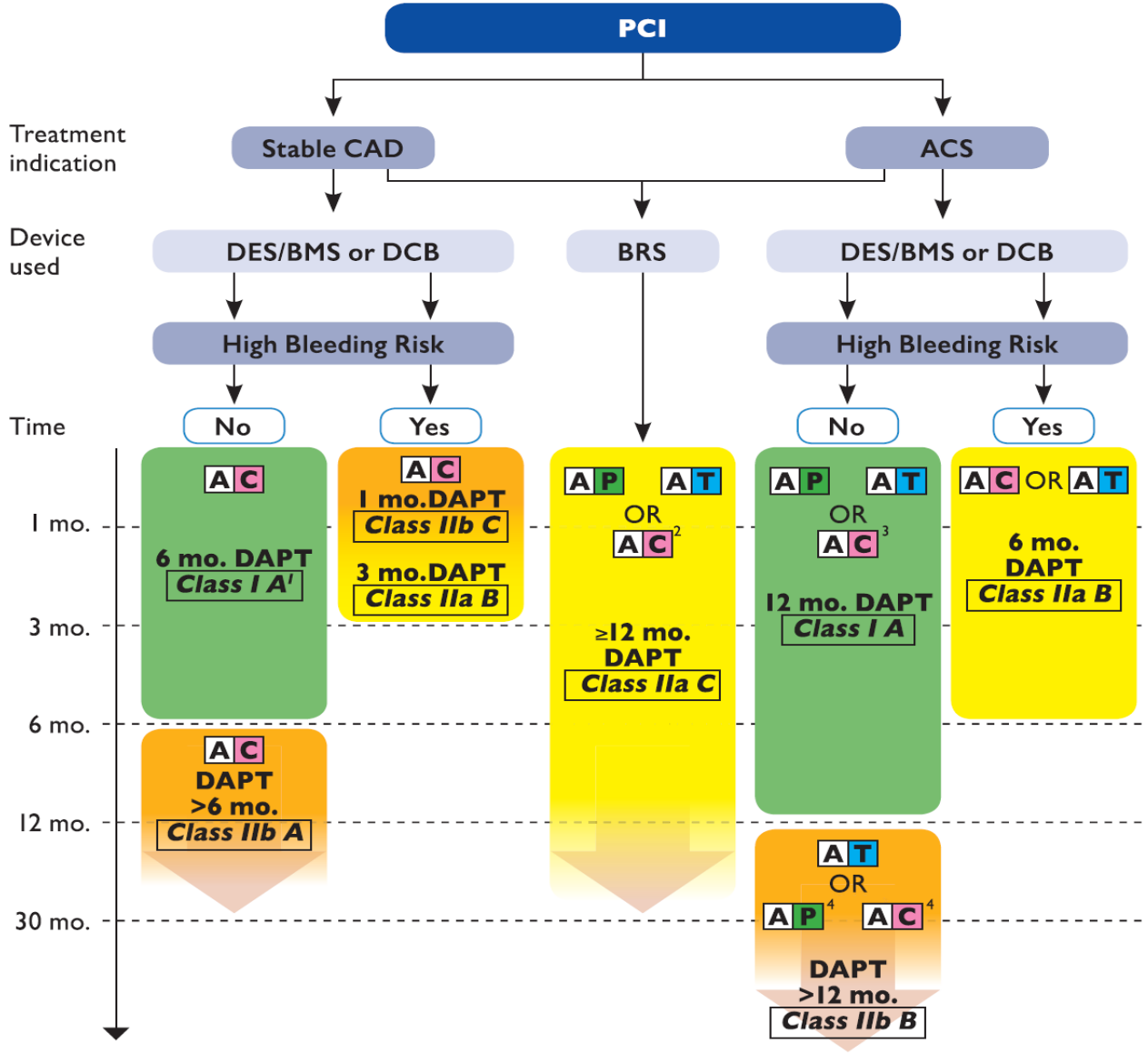


Factors associated with thromboembolic risk progression:

- Aging and increase in CHA2DS2-VASc score
- Dilation of the left atrium
- Increased AF burden
- Local blood stasis

Bucherri S et al. Ther Adv Cardiovasc Dis. 2019;13:1–17.

Recommendations of DAPT duration after PCI



Valgimigli M et al. Eur Heart J. 2018 Jan 14;39(3):213-260.

4 RCTs : NOAC vs Warfarin in AF – PCI Patients

	PIONEER AF-PCI Rivaroxaban	RE-DUAL PCI Dabigatran	AUGUSTUS Apixaban	ENTRUST-AF PCI Edoxaban
Trial size	N=2,124	N=2,725	N=4,614; 2x2 factorial	N=1,506
Eligibility	AF+PCI	AF+PCI	AF + ACS and/or PCI	AF+PCI
Enrolment window	~72 hours of sheath removal	6~120 hours of stent placement	~14 days of event (Median 6 d)	4h ~ 5days (median 45h)
Exclusion	History of ICH,stroke/TIA significant GI bleed <1y CrCl<30ml/min	MB <1 mo; GI bleed <1 mo, stroke <1 mo CrCl<30ml/min	History of ICH, ongoing bleeding, CrCl<30ml/min	Known bleeding diathesis; stroke <2 wks CrCl<15ml/min
Dose	Rivaroxaban 15/10mg QD, 2.5mg bid	Dabigatran 150mg, 110mg bid	Apixaban 5/2.5mg bid	Edoxaban 60/30mg QD
DAPT duration	1, 6 or 12 months	1 or 3 months	6 months	1 to 12 months

All 4 trials: powered for safety (bleeding); not for efficacy (ischemic endpoints)

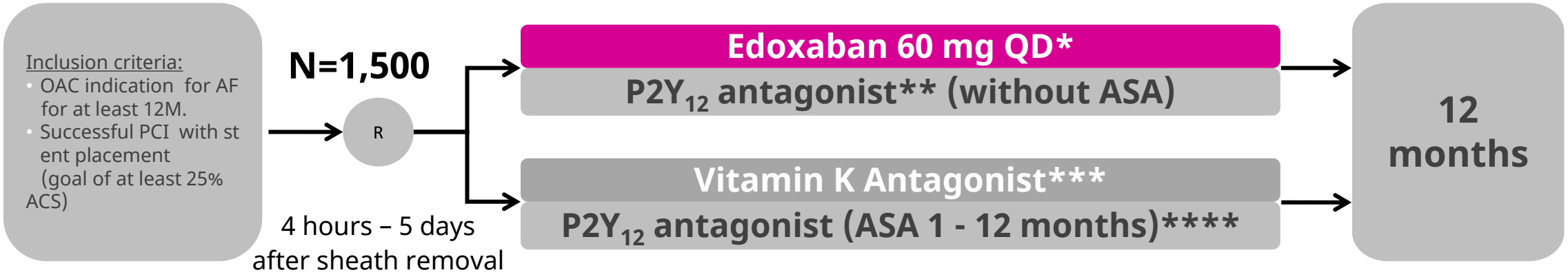
Gibson CM, et al. N Engl J Med 2016;375:2423–34. Cannon CP, et al. N Engl J Med 2017;377:1513–24.
Lopes RD, et al. N Engl J Med 2019;380:1509–24. Vrankx P et al. Lancet 2019;394:1335–43.

THE LANCET

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

ENTRUST AF – PCI : Study Design



*Edoxaban dose reduction to 30 mg QD if:
- CrCL ≤50 ml/min
- BW ≤60 kg
- Certain concomitant P-gp inhibitors

**Clopidogrel 75 mg OD or if documented need prasugrel 5 or 10 mg OD or ticagrelor 90 mg BID Declared at randomization

*** VKA pre-defined by country, target INR 2–3
****ASA 100 mg OD for 1–12 months guided by clinical presentation (ACS or stable CAD), CHA_2DS_2-VASc and HAS-BLED

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

Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Eligibility Criteria

Inclusion criteria	• OAC indication for AF for at least 12 months following • Successful PCI with stent placement (goal of ≥25% ACS)
Key exclusion criteria	• AF secondary to a reversible disorder (eg, MI, pulmonary embolism, recent surgery, pericarditis, or thyrotoxicosis) • Patients with mechanical heart valves, moderate to severe mitral stenosis, ESRD (CrCl <15 mL/min), or other major comorbidities, including known bleeding diasthesis

Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Study Outcomes

Primary Outcomes	• **Composite of ISTH-defined major or CRNM bleeding**
Secondary Outcomes	• C…f death from CV causes, stroke, SEE spontaneous MI, and definite stent …
Exploratory	

- ISTH Major:
  - **Fatal** bleeding,
  - and/or symptomatic bleeding in a **critical area or organ**, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
  - and/or bleeding causing a fall in **Hb levels of 2 g/dL** or greater or more, or leading to a transfusion of 2 U or more of whole blood or red cells.

- CRNM: Any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH major bleeding definition of major bleeding but does meet at least one of the following criteria:
  - Requiring medical intervention by a healthcare professional
  - Leading to hospitalisation or increased level of care
  - Prompting a face-to-face evaluation

Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Statistical Analysis

- Primary and Secondary endpoints were analyzed based on overall study period[a] using ITT analysis set[b]
- Two primary hypotheses comparing edoxaban-based vs. VKA based antithrombotic regimens were tested hiera rchically

Noninferiority test
for major and CRNM bleeding
(upper boundary of 95% CI <1.20)

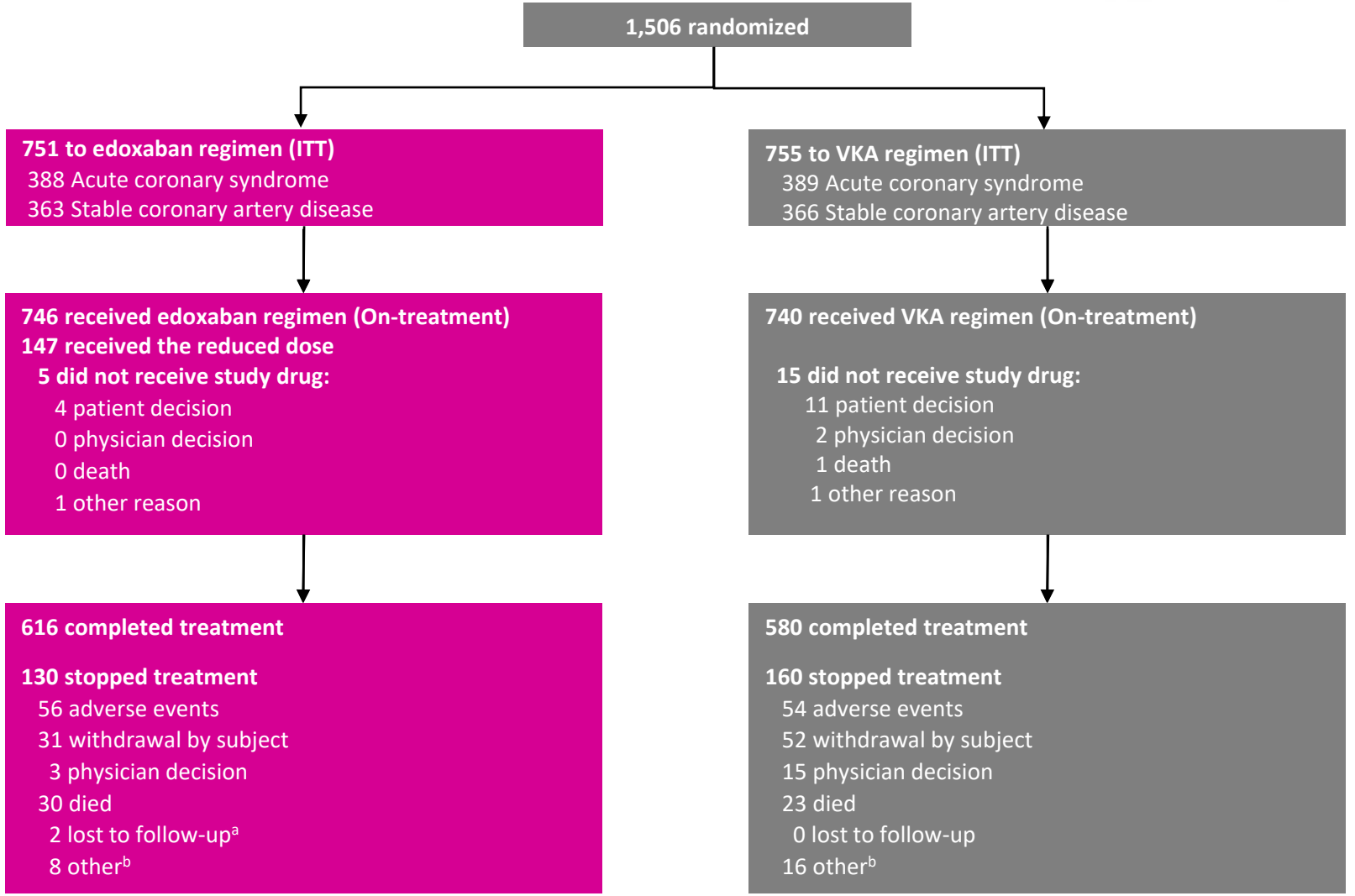
Superiority test
for major and CRNM bleeding
(upper boundary of 95% CI <1.00)

Continue if noninferiority is supported,
to control type-1 error rate

[a]Time from the reference date (date and time of randomization or first study drug intake) to date of end-of-treatment or month 12 visit.
[b]All randomized patients.

Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Patients Disposition



[a]One subject was lost to follow-up on day 14, the other one on day 57. : [b]Other: other including lack of efficacy, progressive disease.

Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Characteristics patients at Baseline

	Edoxaban regimen N = 751	VKA regimen N = 755
Age (years), median (Q1; Q3)	69 (63; 77)	70 (64; 77)
Sex, female	194 (26)	192 (25)
Weight (kg), median (Q1; Q3)	80 (71; 93)	83 (72; 94)
Type of AF		
Paroxysmal	402 (54)	358 (47)
Persistent	140 (19)	146 (19)
Long-standing persistent or permanent	209 (28)	250 (33)
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)[a], median (Q1; Q3)	71.8 (53.7, 91.1)	71.7 (54.0, 90.9)
Missing data	3 (<1)	5 (1)
Medical history		
Myocardial infarction	188 (25)	177 (23)
Previous PCI	199 (26)	195 (26)
Previous CABG	46 (6)	49 (7)
Congestive heart failure	418 (56)	408 (54)
Stroke	97 (13)	92 (12)
Peripheral artery disease	76 (10)	82 (11)
Non-CNS SEE	12 (2)	10 (1)
Diabetes mellitus	259 (34)	258 (34)
Hypertension	674 (90)	687 (91)
Hypercholesterolemia	497 (66)	484 (64)
Bleeding events	56 (7)	49 (6)
Valvular heart disease	210 (28)	221 (29)
Malignancy	43 (6)	46 (6)

[a]The minimum of the recalculated local lab CrCl and the recalculated central lab CrCl value has been used.
Data are presented as n (%) unless otherwise noted. Data are for the intention to treat analysis set (N = 1506).

Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Characteristics patients at Baseline

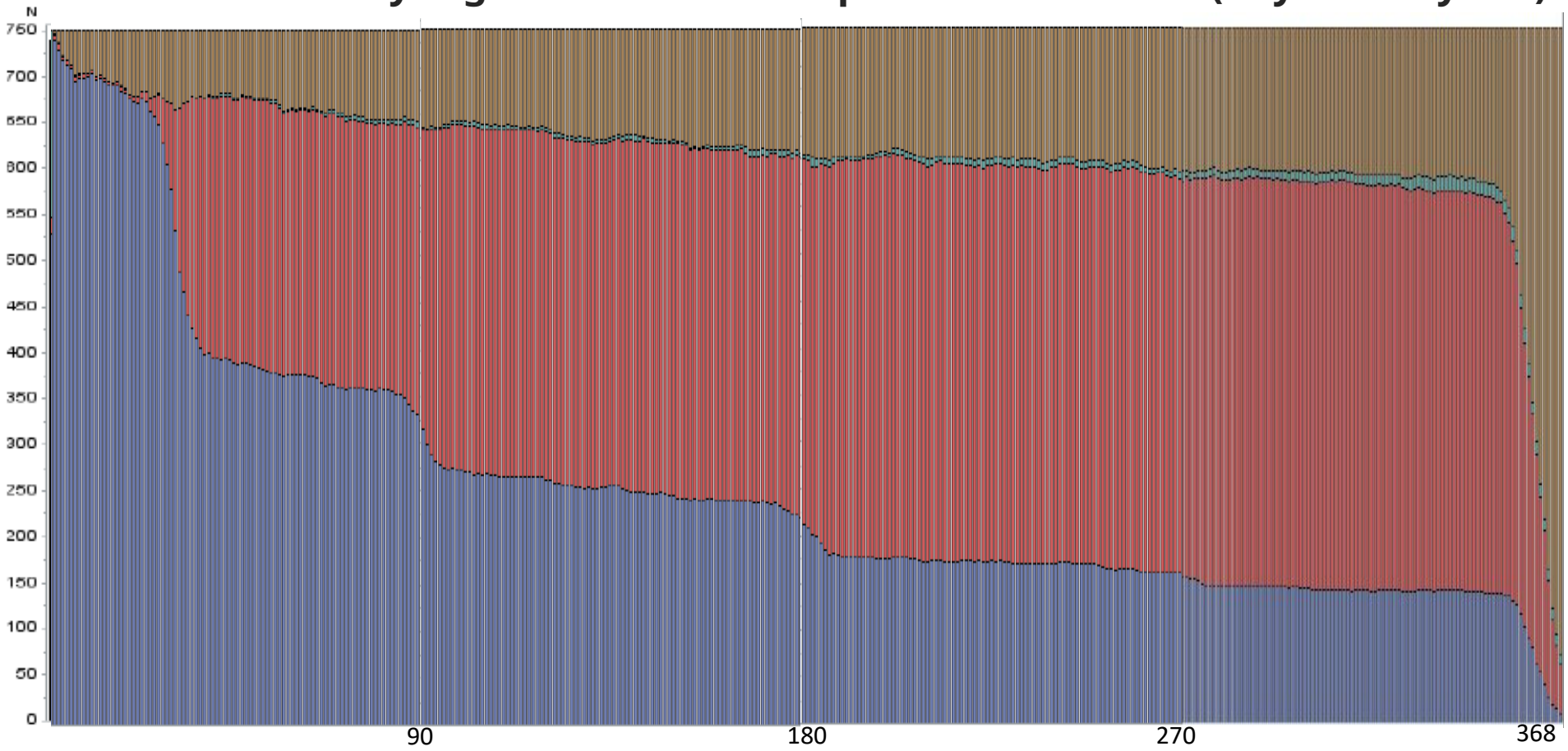
	Edoxaban regimen N = 751	VKA regimen N = 755
Geographic region		
Asia	82 (11)	87 (12)
Eastern Europe	350 (47)	349 (46)
Western Europe	319 (42)	319 (42)
Clinical presentation (documented in IXRS)		
ACS	388 (52)	389 (52)
SCAD	363 (48)	366 (49)
Type of therapy prior to index PCI		
VKA	232 (31)	224 (30)
NOAC	176 (23)	189 (25)
None	192 (26)	221 (29)
Data missing	151 (20)	121 (16)
Duration (hours) between end of PCI and randomization, median (Q1; Q3)	45.1 (22.3; 75.6)	44.8 (22.1; 76.5)
Type of $P2Y_{12}$ antagonist (documented in IXRS)		
Clopidogrel	696 (93)	695 (92)
Prasugrel 5 mg	2 (<1)	1 (<1)
Prasugrel 10 mg	3 (<1)	2 (<1)
Ticagrelor	49 (7)	57 (8)

[a]The minimum of the recalculated local lab CrCl and the recalculated central lab CrCl value has been used.
Data are presented as n (%) unless otherwise noted. Data are for the intention to treat analysis set (N = 1506).

Vranckx P et al. Lancet 2019;394:1335-1343.

ASA duration comparison in NOAC AF-PCI trials

Overview of study regimen used in VKA patients over time (day 1 to day 368)



Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Primary Outcomes

ENTRUST-AF PCI

<Primary Outcome: Major or CRNM Bleeding [ISTH]>

	Edoxaban regimen	VKA regimen	Hazard ratio (2-sided 95% CI)	P-value
Intent-to-treat analysis				
Number of patients	751	755		
Number of patients with event (%)	128 (17)	152 (20)		
Annualized event rate (% per year)	**20.7**	**25.6**	**0.83 (0.65; 1.05)**	**Noninferiority: P = 0.0010, margin hazard ratio 1.20; Superiority: P = 0.1154**
On-treatment analysis				
Number of patients	746	740		
Number of patients with event (%)	124 (17)	142 (19)		
Annualized event rate (%/year)	20.7	25.5	0.84 (0.66; 1.06)	**Noninferiority: P = 0.0016 Superiority: P = 0.1434**

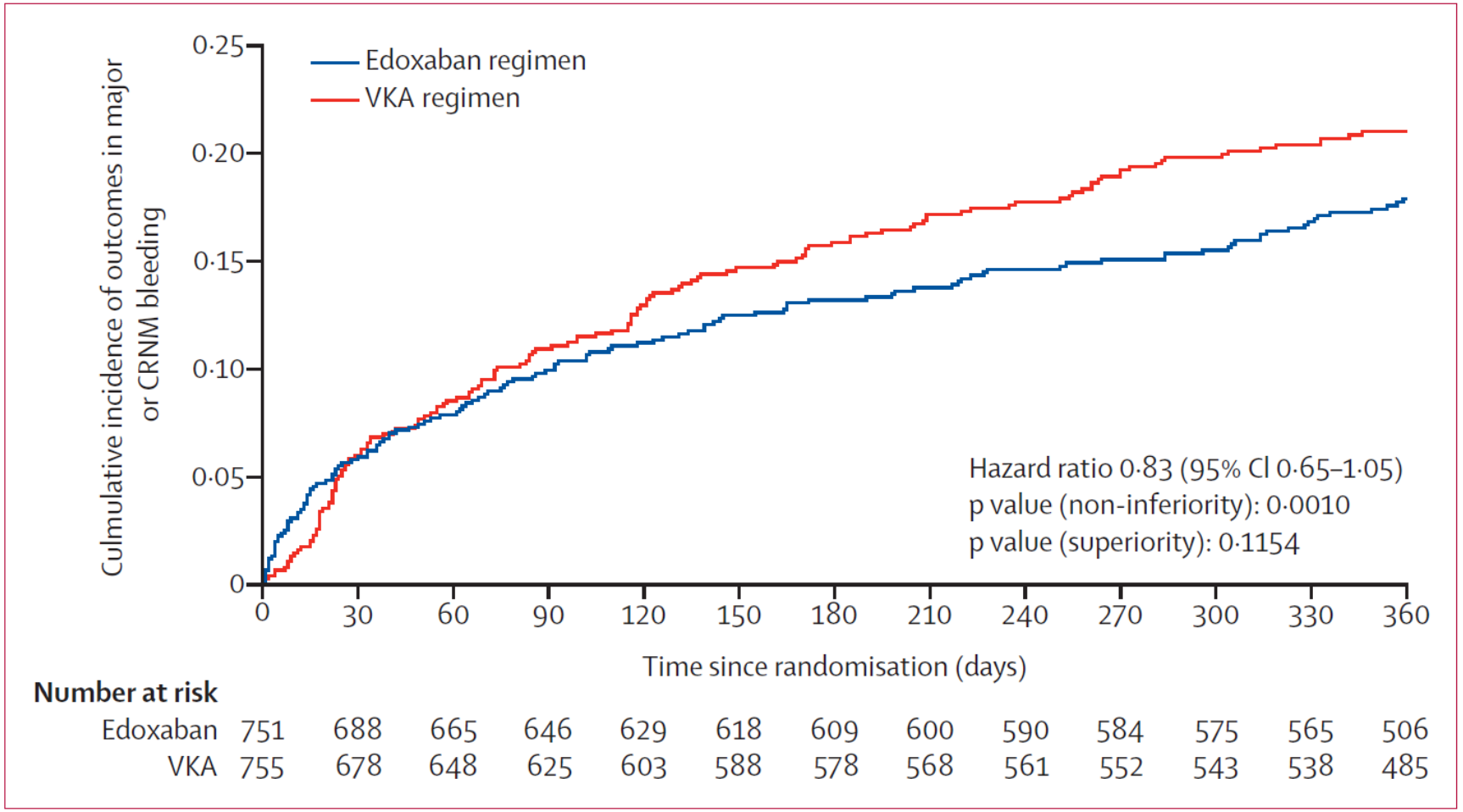
* Rates of bleeding according to ISTH, TIMI, and BARC definitions were consistent (appendix p39-40)

once-daily 릭시아나정 edoxaban

Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Primary Outcomes

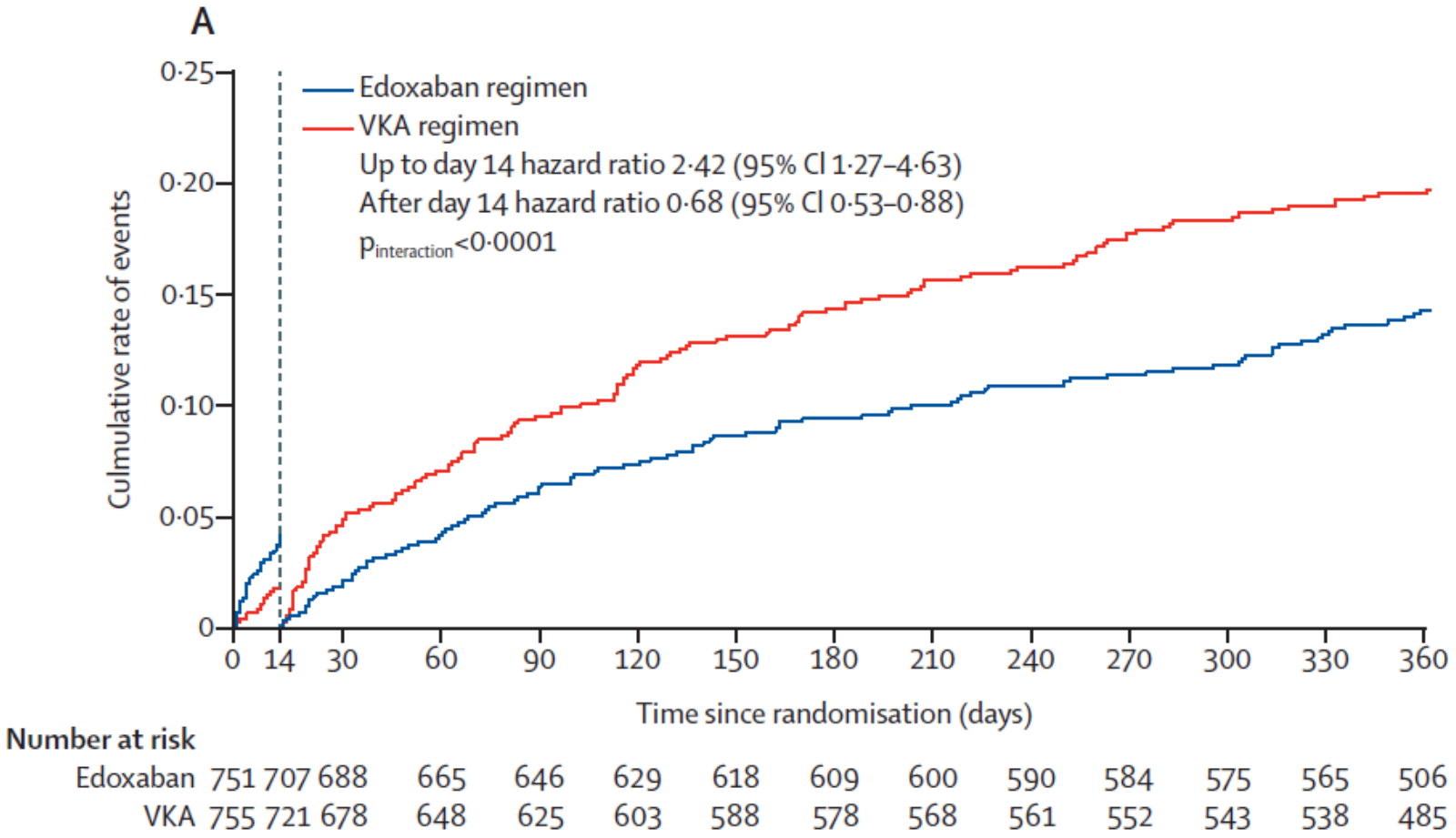
<Primary Outcome: Major or CRNM Bleeding [ISTH]>



Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Landmark Analysis of the Primary Outcomes

<Primary Outcome: Major or CRNM Bleeding [ISTH]>



Vranckx P et al. Lancet 2019;394:1335-1343.

ENTRUST AF – PCI : Main Secondary Efficacy Outcomes

<Main Secondary Outcomes: Composite of CV death, Stroke, SEE, MI or Definite Stent Thrombosis>

	Edoxaban regimen	VKA regimen	Hazard ratio (2-sided 95% CI)
Intent-to-treat analysis			
Number of patients	751	755	
Number of patients with event (%)	49 (7)	46 (6)	
Annualized event rate (% per year)	7.3	6.9	1.06 (0.71; 1.69)

Vranckx P et al. Lancet 2019;394:1335-1343.

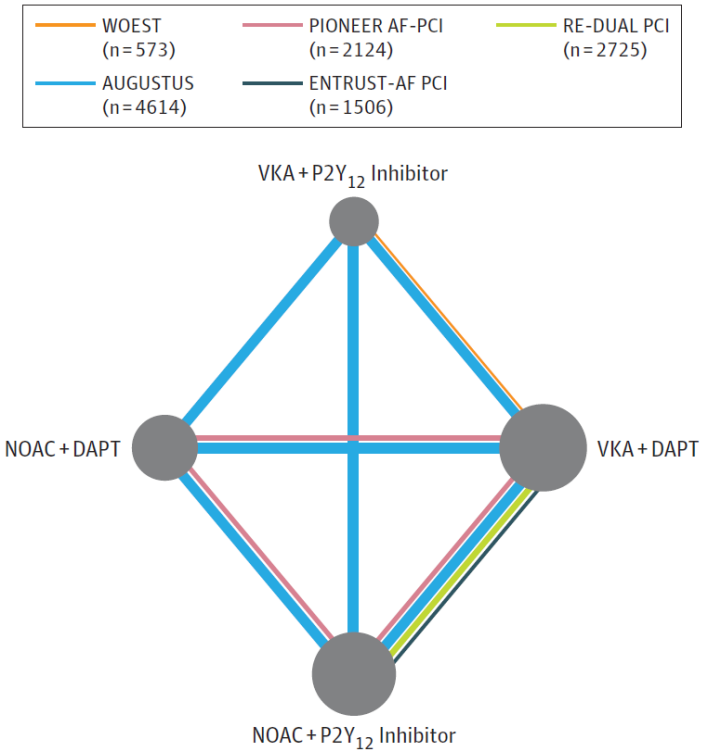
ENTRUST AF – PCI : Summary

- In patients with AF who underwent successful PCI, the full-dose edoxaban based DAT regimen was non-inferior for bleeding compared with the VKA based TAT regimen (aspirin given for 1-12 months) regarding risks of major or CRNM bleeding events at 12 months

- Rates for the main efficacy outcome were similar between the edoxaban based regimen and the VKA based regimen.

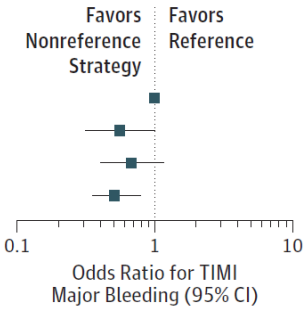
Vranckx P et al. Lancet 2019;394:1335-1343.

Network Meta-Analysis of 5 RCTs (N=11,542)



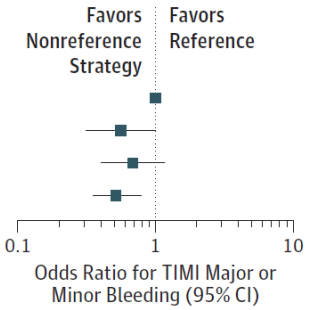
A Thrombolysis in myocardial infarction (TIMI) major bleeding

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	0.57 (0.31-1.00)
NOAC + DAPT	0.69 (0.40-1.16)
NOAC + $P2Y_{12}$ inhibitor	0.52 (0.35-0.79)



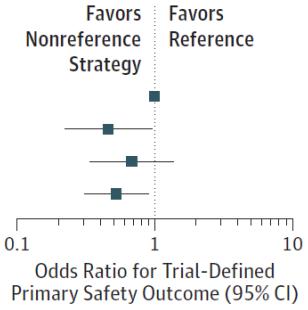
B TIMI major or minor bleeding

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	0.50 (0.24-1.04)
NOAC + DAPT	0.66 (0.32-1.34)
NOAC + $P2Y_{12}$ inhibitor	0.53 (0.30-0.89)



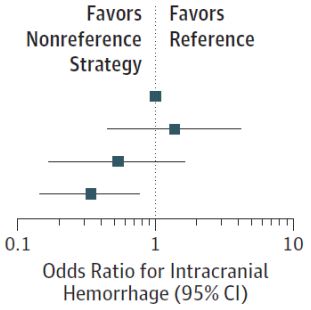
C Trial-defined primary safety outcome

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	0.46 (0.22-0.95)
NOAC + DAPT	0.68 (0.34-1.38)
NOAC + $P2Y_{12}$ inhibitor	0.53 (0.31-0.90)



D Intracranial hemorrhage

Treatment Regimen	Odds Ratio (95% CI)
VKA + DAPT	1 [Reference]
VKA + $P2Y_{12}$ inhibitor	1.38 (0.45-4.18)
NOAC + DAPT	0.54 (0.17-1.63)
NOAC + $P2Y_{12}$ inhibitor	0.34 (0.14-0.77)



- ✓ A regimen that includes a **NOAC plus a P2Y12 inhibitor** seems to be the most favorable treatment option.
- ✓ This study support the use of regimens in which aspirin therapy is discontinued a few days after PCI.

Lopes RD et al. JAMA Cardiol 2020.

2023 US Guideline for Atrial Fibrillation

- In patients with AF and an increased risk for stroke who undergo PCI, DOACs are preferred over VKAs in combination with APT to reduce the risk of clinically relevant bleeding.

I

A

- In most patients with AF who take OAC and undergo PCI, early discontinuation of aspirin (1-4 wk) and continuation of DAT with OAC and P2Y12 inhibitor is preferred over triple therapy.

I

A

JACC. 2024 Jan, 83 (1) 109–279.

2024 ESC Guideline for Atrial Fibrillation

- In AF patients eligible for DOACs, it is recommended to use DOAC in preference to VKA in combination with antiplatelet therapy

I A

- Uncomplicated PCI

  → Early cessation (≤1 week) of aspirin

  OAC + Clopidogrel for up to 6 mo

I A

If ischemic risk is low

Eur Heart J. 2024;45:3314-3414.

2024 ESC Guideline for Atrial Fibrillation

- **AF + ACS PCI**

→ Early cessation (≤1 week) of aspirin

OAC + P2Y12 inhibitor (clopidogrel) up to 12 mo

I A

If thrombosis risk is low or bleeding risk is high

- Aspirin + clopidogrel + OAC

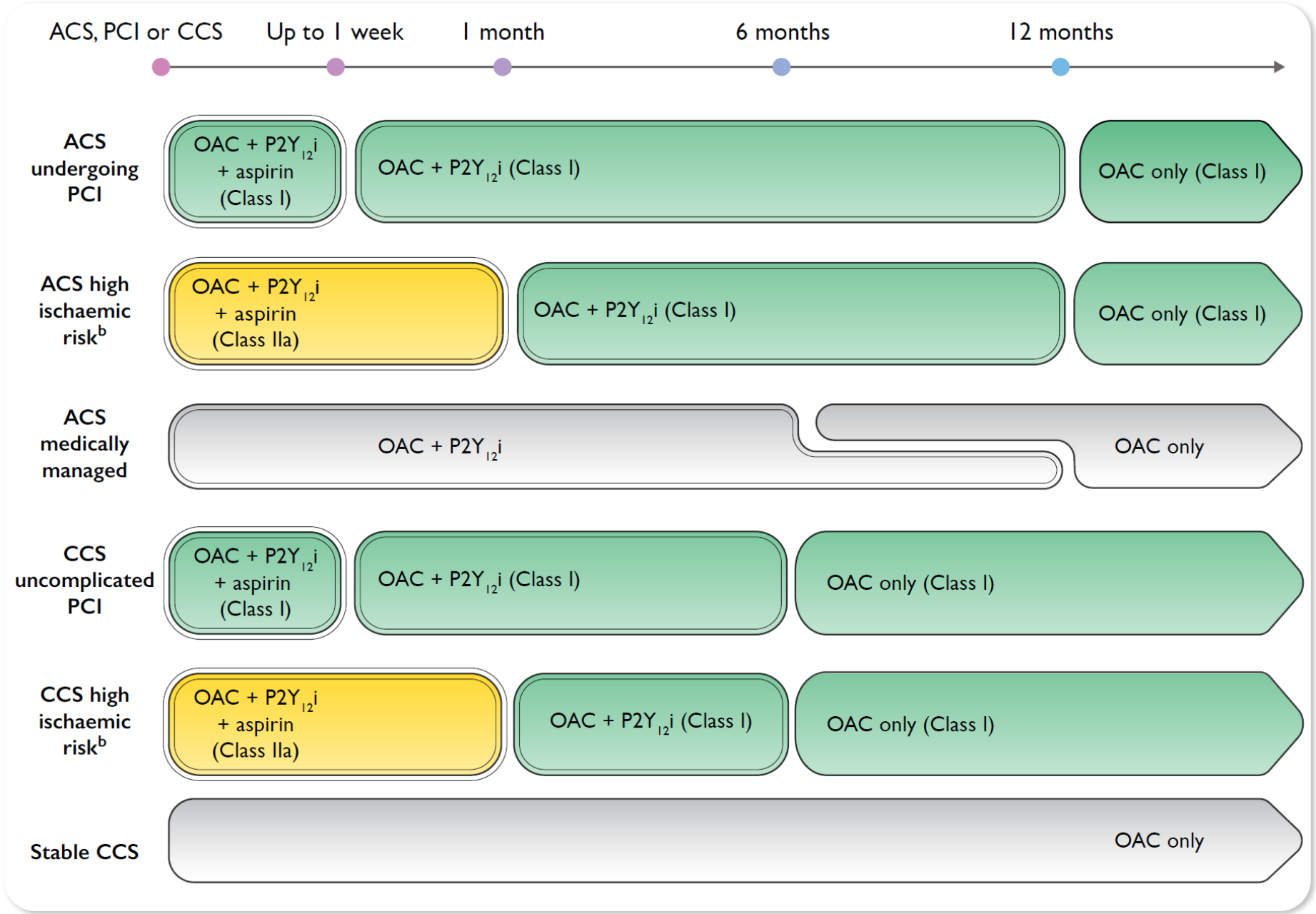
IIa C

1 wk ~ 1 mo after ACS

If ischemic risk outweighs the bleeding risk

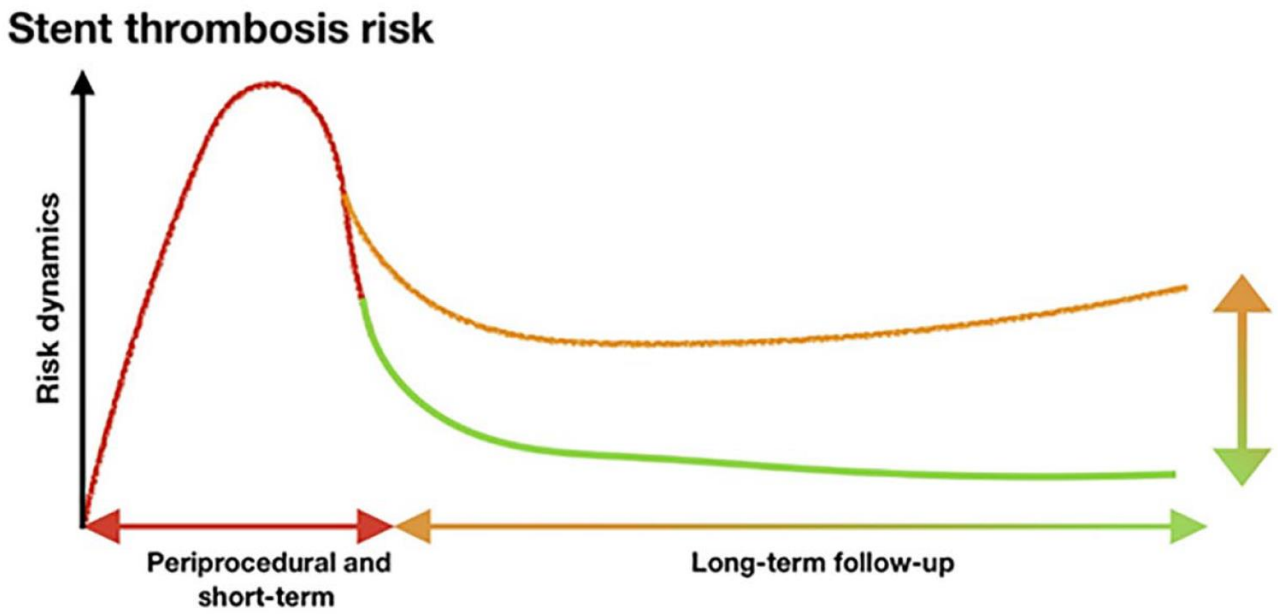
Eur Heart J. 2024;45:3314-3414.

2024 ESC Guideline for Atrial Fibrillation



Optimal Antithrombotic Therapy in AF after PCI – over 1 year, or in AF with Stable CAD

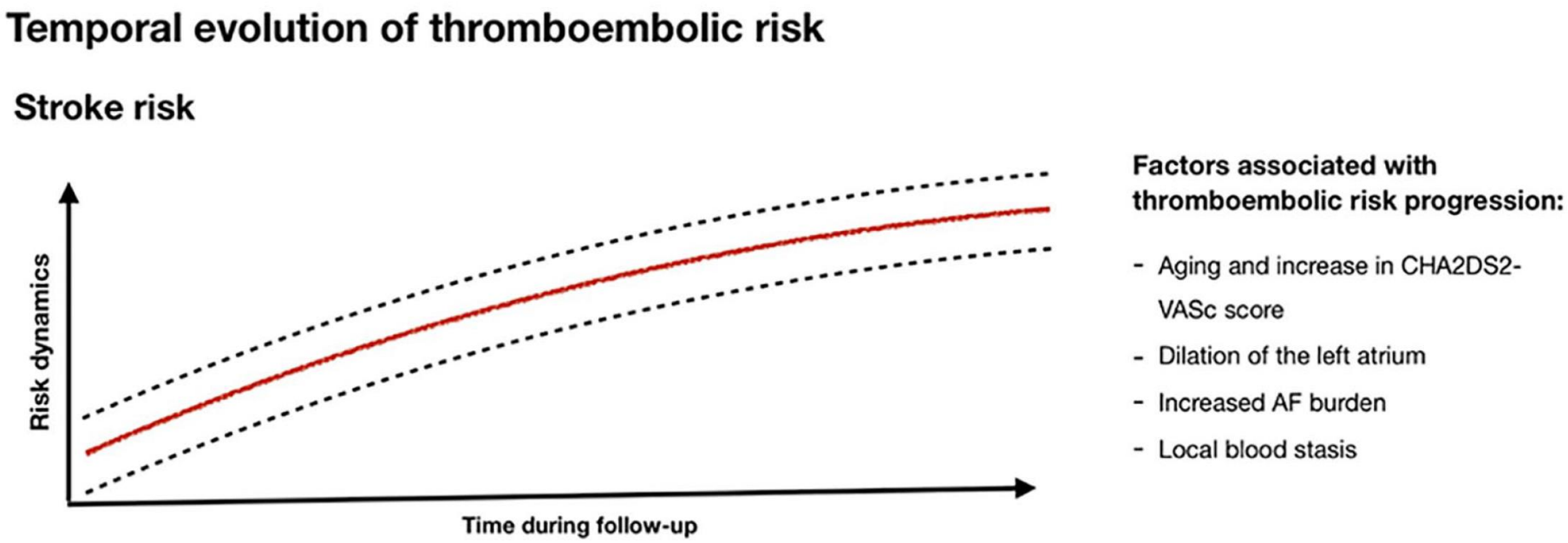
PCI



Factors associated with long-term increased risk of stent thrombosis:

- Prior stent thrombosis on adequate antiplatelet therapy
- 3 or more stents implanted
- 3 or more lesions treated
- Bifurcation with 2 stents implanted
- Total stent length >60 mm
- Treatment of chronic total occlusion

AF



Factors associated with thromboembolic risk progression:

- Aging and increase in CHA2DS2-VASc score
- Dilation of the left atrium
- Increased AF burden
- Local blood stasis

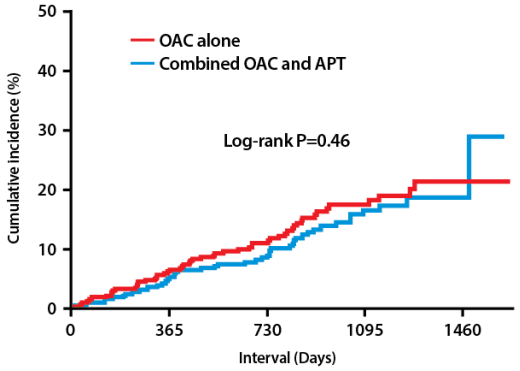
Bucherri S et al. Ther Adv Cardiovasc Dis. 2019;13:1–17.

Prior RCTs (OAC-ALONE and AFIRE)

OAC-ALONE trial

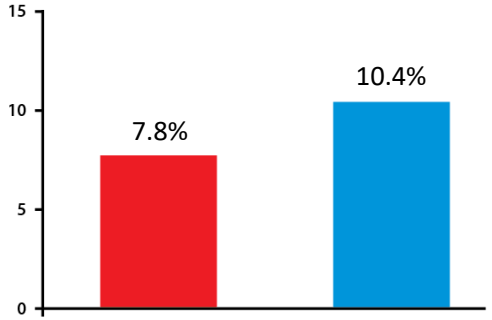
Efficacy endpoint*

HR 1.16 (0.79-1.72)



ISTH major bleeding

HR 0.73 (0.44-1.20)

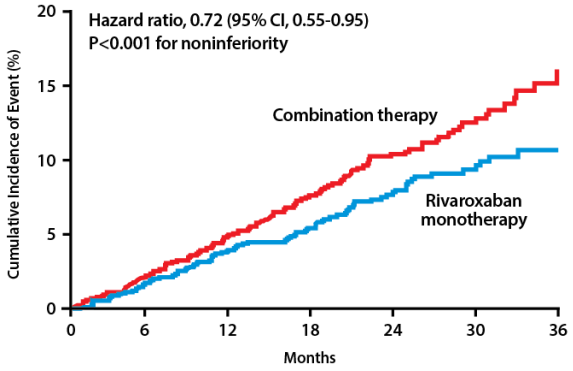


Circulation. 2019;139:604

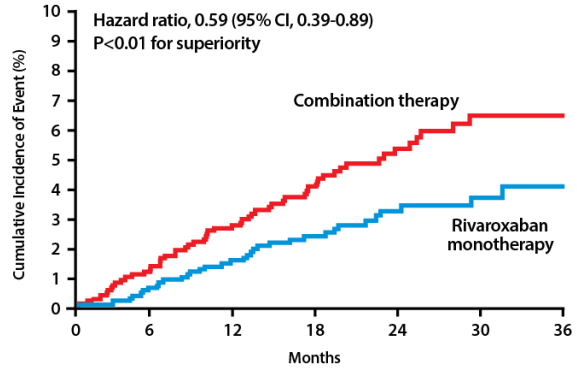
Early termination d/t futility
Failed to show noninferiority
Predominant warfarin use

AFIRE trial

Efficacy endpoint †



ISTH major bleeding



N Engl J Med 2019;381:1103

- Early termination d/t an increased mortality signal
- Use of locally approved dose rivaroxaban
  (15 or 10mg once daily in Japan)

* Composite of death, myocardial infarction, stroke, or systemic embolism
† Composite of death, myocardial infarction, stroke, systemic embolism, or unstable angina requiring revascularization

Edoxaban-Based Long-Term Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Disease
: The EPIC-CAD Randomized Clinical Trial

Gi-Byoung Nam, MD PhD and Duk-Woo Park, MD PhD
on behalf of the EPIC-CAD Investigators
Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

European Society of Cardiology Congress 2024 – Annual Scientific Session
Hot Line 6, September 1, 2024

Timeline

C

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban Antithrombotic Therapy for Atrial Fibrillation and Stable Coronary Artery Disease

M.S. Cho, D.-Y. Kang, J.-M. Ahn, S.-C. Yun, Y.-S. Oh, C.H. Lee, E.-K. Choi, J.H. Lee, C.H. Kwon, G.-M. Park, H.O. Choi, K.-H. Park, K.-M. Park, J. Hwang, K.-D. Yoo, Y.-R. Cho, J.H. Kim, K.W. Hwang, E.-S. Jin, O. Kwon, K.-H. Kim, S.-J. Park, D.-W. Park, and G.-B. Nam, for the EPIC-CAD Investigators*

2024.9
Presented in ESC 2024 with simultaneous publication

Objective

- To compare the efficacy and safety of standard-dose edoxaban monotherapy with the dual antithrombotic therapy (edoxaban + a single antiplatelet agent) in patients with high-risk AF and stable CAD.
- The primary hypothesis was that edoxaban monotherapy would be superior to dual antithrombotic therapy with respect to the primary net clinical outcome.

Cho MS, Kang DY et al. *Am Heart J* 2022;247:123-131

Trial Design

Edoxaban versus Edoxaban with antiPlatelet agent In patients with atrial fibrillation and Chronic stable Coronary Artery Disease

investigator-initiated, multicenter, open-label, superiority trial

EPIC-CAD Trial

1,038 patients with high-risk AF (CHA_2DS_2-VASc score ≥2) and stable CAD

A permuted block size of 4 or 6, stratified randomization by trial center

Edoxaban monotherapy (N=519)

Dual antithrombotic therapy (N=519)

Primary endpoint – net adverse clinical event (a composites of all-casuse death, stroke, systemic embolic event, myocardial infarction, unplanned urgent revascularization, major bleeding, and clinically relevant non-major bleeding) at 1 year after randomization

Cho MS, Kang DY et al. *Am Heart J* 2022;247:123-131

Enrollment Criteria

INCLUSION CRITERIA

1. Men or women at least age ≥ 18 years.

2. Patients with nonvalvular AF (prevalent or paroxysmal) with high embolic risk (CHA_2DS_2-VASc score ≥ 2)

3. Patients with stable CAD
   - Prior revascularization (PCI or CABG) ≥6M for chronic CAD and ≥12M for ACS
   - Anatomically confirmed CAD (≥50% stenosis in CAG or CCTA) on medical therapy alone

EXCLUSION CRITERIA

1. Patients with severe thrombocytopenia
2. High risk of bleeding or severe coexisting conditions prohibiting antithrombotic use
3. Prior history of intracranial hemorrhage
4. Mechanical prosthetic valve or moderate-to-severe mitral stenosis
5. Patients contraindicated for use of edoxaban or antiplatelets.
6. Planned PCI or CABG within 1 year after randomization.
7. Liver cirrhosis or severe hepatic dysfunction
8. Severe renal insufficiency (creatinine clearance <15 mL/min)
9. Life expectancy <12 months.

ACS, acute coronary syndrome; CAD, coronary artery disease; CAG, coronary angiography; CCTA, coronary computed tomographic angiography; PCI, percutaneous coronary intervention

Cho MS, Kang DY et al. *Am Heart J* 2022;247:123-131

Randomization and administration of study drug

- Eligible patients were randomly assigned in a 1:1 ratio to either standard-dose edoxaban monotherapy or dual-antithrombotic therapy (edoxaban + a single antiplatelet agent) by means of a central, IWRS with block sizes of 4 or 6, stratified according to the participating site.

- Standard-dose edoxaban was used in both group;
  - 60-mg once daily as a standard dose
  - 30-mg once daily with dose-reduction criteria
    - Body-weight ≤ 60 kg
    - Creatinine clearance of 15 – 50 mL/min
    - Concomitant use of P-glycoprotein inhibitors

- Type of a single antiplatelet agent (either aspirin or a clopidogrel) was selected according to the discretion of the treating physician

IWRS, interactive web-based randomization system

Primary trial endpoint

- Net adverse clinical event : defined as a composite of
  - Death from any causes
  - Myocardial infarction
  - Stroke
  - Systemic embolism
  - Unplanned urgent revascularization
  - Major or clinically relevant nonmajor bleeding event by ISTH definition

  at 1 year after randomization

CI, confidence interval; ISTH, International Society on Thrombosis and Haemostasis

Secondary trial endpoints

- Individual components of the primary outcome
- Stent thrombosis
- Major ischemic events
  - Composites of death, myocardial infarction ischemic stroke, and systemic embolism
- Any ischemic events (*post-hoc*)
  - Composites of death, myocardial infarction ischemic stroke, and systemic embolism, and urgent repeat revascularization
- Composite of major and clinically relevant nonmajor bleeding (by ISTH definition)
- Fatal bleeding
- Major bleeding
- Any bleeding event

Statistical Considerations

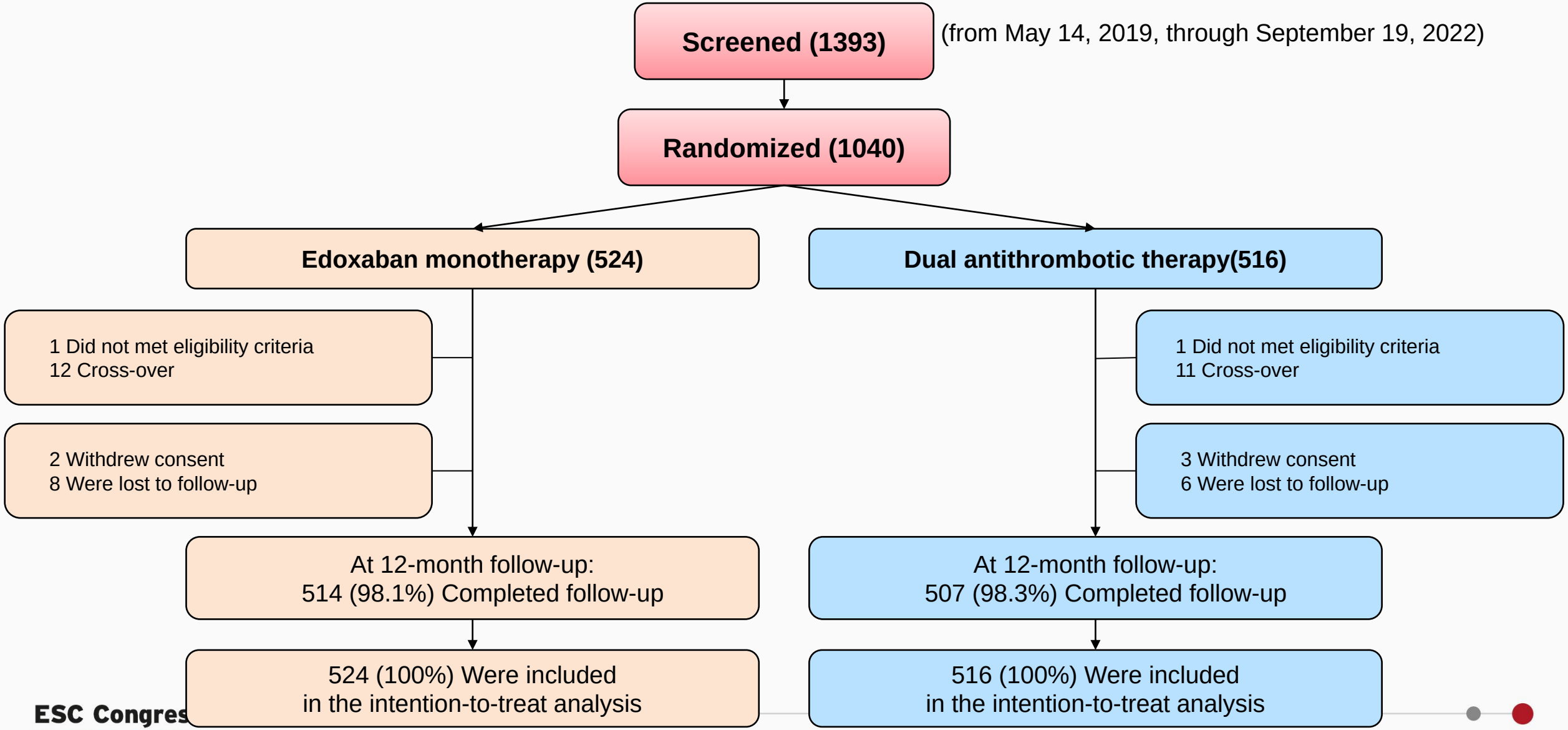
Power Calculation (N = 1,038)

- Assuming a 1-year event rate of 18% in the dual antithrombotic therapy group.
- Statistical power of 80% to detect a relative reduction of 30% in the primary outcome in the edoxaban monotherapy group compared with the dual antithrombotic therapy group at a significance level of 0.05 on the basis of a two-sided log-rank test of survival.

Statistical Analysis

- Primary intention-to-treat analysis
- Cumulative event rates calculated by Kaplan-Meier estimates and compared with log-rank test
- Cox proportional hazard models
  - Estimate the risk differences if proportional hazards assumption is not violated
- Sensitivity and subgroup analysis
  - Per-protocol analysis (randomized groups without major protocol violations)
  - Subgroup analysis for primary endpoint according to the prespecified clinical factors

Patient Flow and Follow-Up



Baseline Characteristics

	Edoxaban Monotherapy (N=524)	Dual Antithrombotic Therapy (N=516)
Age [yrs], mean (SD)	71.7±8.0	72.5±8.4
Male sex	396 (75.6)	406 (78.7)
Body-mass index	25.3±3.3	25.4±3.3
Diabetes mellitus — no. (%)	224 (42.7)	197 (38.2)
Hypertension — no. (%)	423 (80.7)	422 (81.8)
Previous cerebrovascular disease — no. (%)	77 (14.7)	77 (14.9)
Previous myocardial infarction — no. (%)	79 (15.1)	92 (17.8)
Creatinine clearance by Cockcroft–Gault formula — ml/min	67.0±23.6	66.0±21.4
CHA_2DS_2-VASc score	4.3±1.6	4.4±1.5
$CHADS_2$ score	2.1±1.2	2.2±1.2
HAS-BLED score	2.1±0.8	2.2±0.8
Type of atrial fibrillation — no. (%)		
Paroxysmal	292 (55.7)	283 (54.8)
Persistent or permanent	232 (44.3)	233 (45.2)
Indication for dose adjustment of edoxaban — no. (%)	178 (34.0)	168 (32.6)

Plus–minus values are means ± SD.

Baseline Characteristics

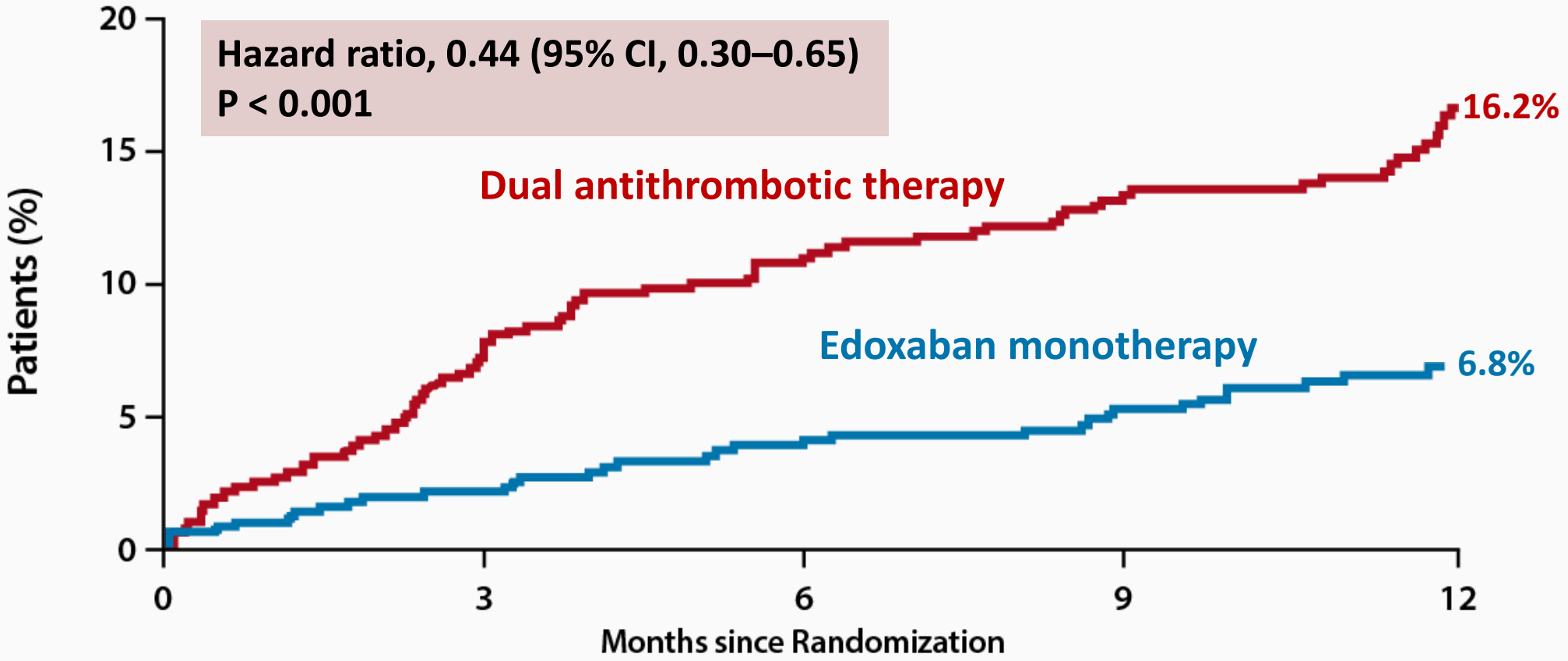
	Edoxaban Monotherapy (N=524)	Dual Antithrombotic Therapy (N=516)
Obstructive CAD managed by medical therapy alone — no. (%)	188 (35.9)	169 (32.8)
Previous coronary revascularization — no. (%)	336 (64.1)	347 (67.2)
Previous PCI — no. (%)	308 (58.8)	318 (61.6)
Drug-eluting stent	251 (81.5)	267 (84.0)
Bare-metal stent	13 (4.2)	7 (2.2)
Both stent types	8 (2.6)	4 (1.3)
Unknown stent type	36 (11.7)	40 (12.6)
Previous CABG — no. (%)	41 (7.8)	36 (7.0)
Disease extent — no. (%)		
1-vessel disease	268 (51.1)	260 (50.4)
2-vessel disease	127 (24.2)	135 (26.2)
3-vessel disease	81 (15.5)	77 (14.9)
Left main disease	48 (9.2)	42 (8.1)

CABG, coronary artery bypass grafting; CAD, coronary artery disease

Antithrombotic regiments before and after randomization

	Edoxaban Monotherapy (N=524)	Dual Antithrombotic Therapy (N=516)
Prior use of antithrombotic strategy before randomization – no. (%)		
None	7 (1.3)	6 (1.2)
Antiplatelet agent only	51 (9.7)	42 (8.1)
Oral anticoagulants only	253 (48.3)	217 (42.1)
Combination of antiplatelets and anticoagulants	213 (40.6)	251 (48.6)
Study drug regimens after randomization – no. (%)		
Actual dose of edoxaban used		
60mg	317 (60.5)	281 (54.5)
30mg	207 (39.5)	235 (45.5)
Type of a single antiplatelet agent		
Aspirin	1 (0.2)	319 (61.8)
Clopidogrel	2 (0.4)	195 (37.8)

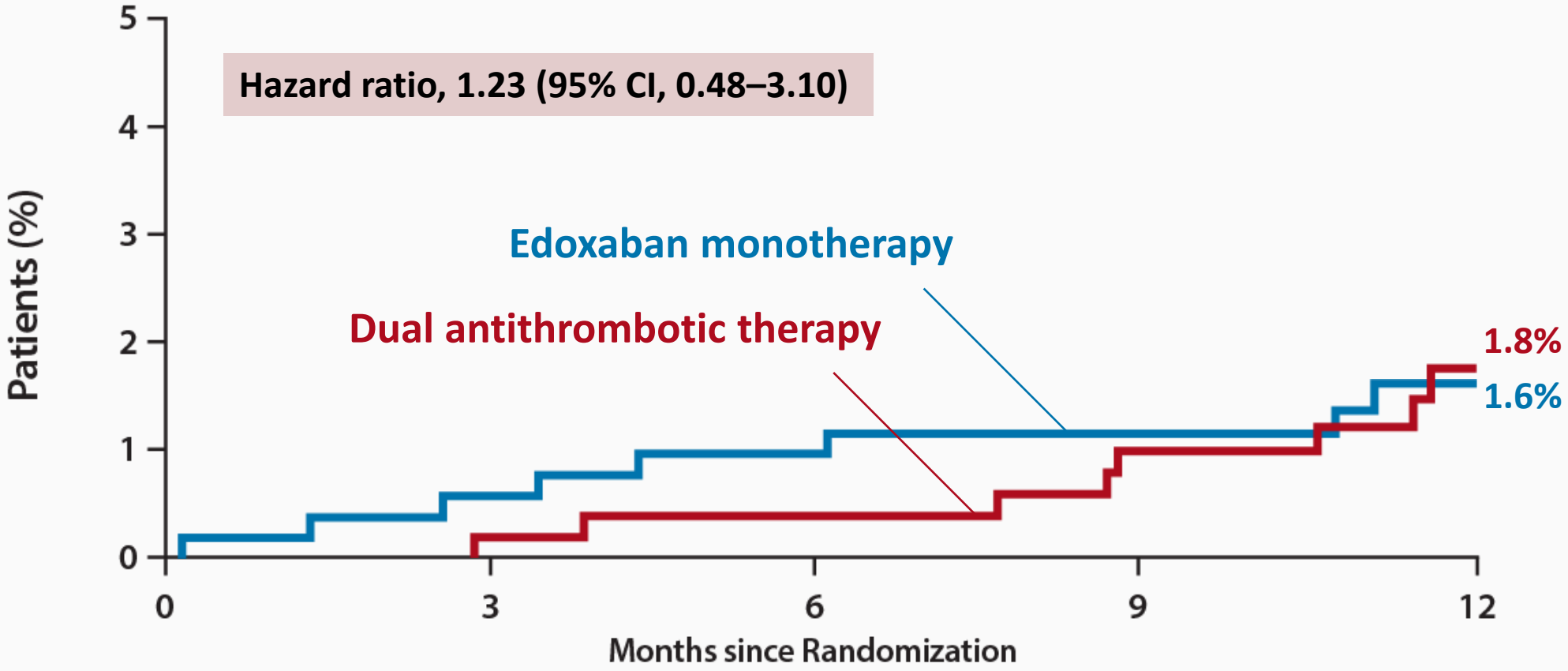
Primary Endpoint: Net adverse clinical event



No. at Risk					
Dual antithrombotic therapy	516	475	452	437	391
Edoxaban monotherapy	524	508	495	487	409

Primary net adverse clinical event was defined as a composite of death from any causes, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, and major or clinically relevant nonmajor bleeding event

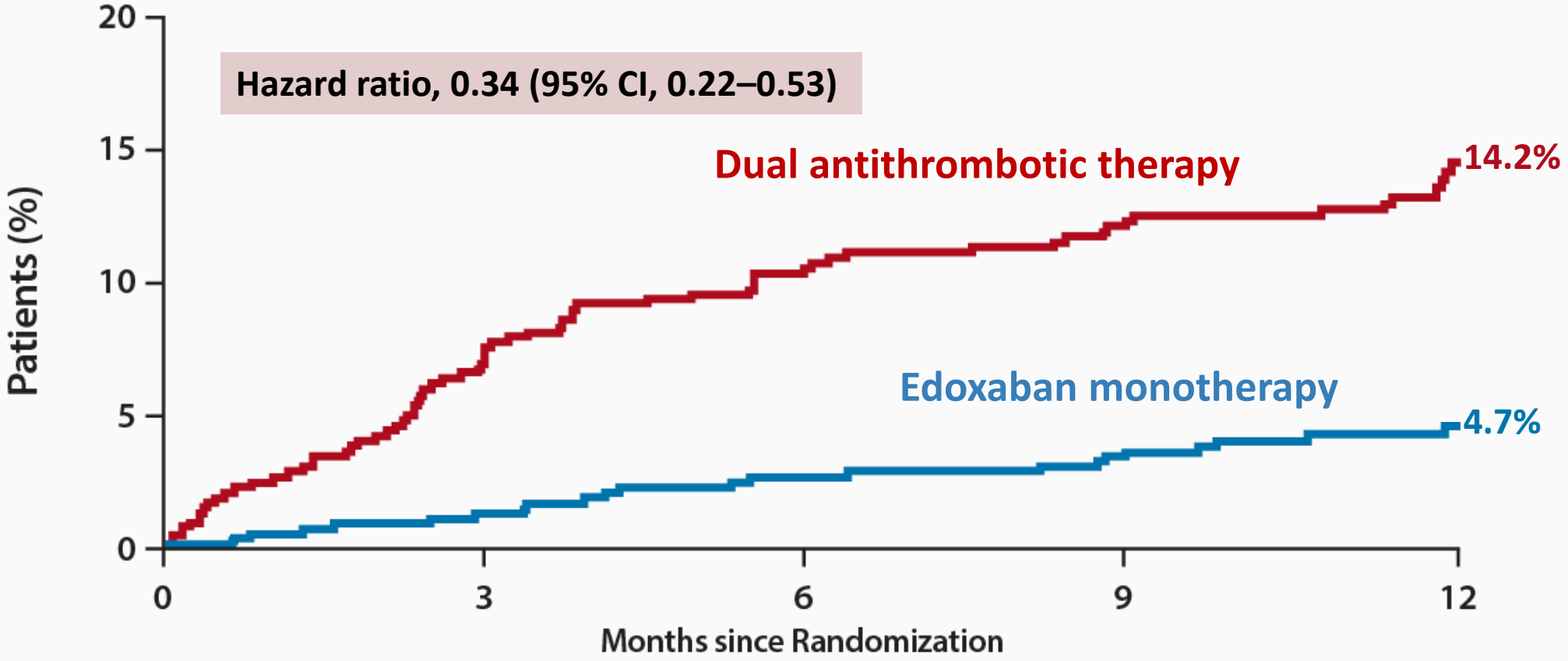
Key Secondary Endpoint: Major ischemic events



No. at Risk					
Dual antithrombotic therapy	516	510	505	499	446
Edoxaban monotherapy	524	516	510	506	428

Major ischemic events: composite of death from any causes, myocardial infarction, ischemic stroke, and systemic embolism

Key Secondary Endpoint: Major or clinically relevant non-major bleeding



No. at Risk					
Dual antithrombotic therapy	516	475	453	441	393
Edoxaban monotherapy	524	512	500	492	414

Type of CV outcomes

Outcome*	Edoxaban Monotherapy (N=524)	Dual Antithrombotic Therapy (N=516)	Risk Difference (95% CI)	HR (95% CI)†
Primary composite outcome‡	34 (6.8)	79 (16.2)	9.41 (5.40 to 13.42)	0.44 (0.30 to 0.65)
Secondary outcomes				
Efficacy outcomes				
Death	3 (0.6)	3 (0.7)	0.08 (-0.97 to 1.13)	1.29 (0.29 to 5.76)
Stroke	7 (1.4)	4 (0.8)	-0.60 (-1.89 to 0.69)	NR**
Myocardial infarction	0 (0)	2 (0.5)	0.46 (-0.18 to 1.11)	NR**
Unplanned urgent revascularization	7 (1.4)	6 (1.4)	0.0 (-1.50 to 1.50)	1.00 (0.35 to 2.85)
Stent thrombosis	0 / 308 (0)	0 / 318 (0)	NA	NA
Major ischemic events	8 (1.6)	8 (1.8)	0.13 (-1.52 to 1.78)	1.23 (0.48 to 3.10)
Any ischemic events	15 (3.0)	11 (2.4)	-0.55 (-2.63 to 1.53)	1.40 (0.67 to 2.93)

*The percentages were estimated by the Kaplan–Meier estimates. †Hazard ratios are for the edoxaban monotherapy compared to the dual antithrombotic therapy
‡The primary composite outcome was composite of death from any causes, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, and major or clinically relevant nonmajor bleeding event.
**Hazard ratios were not reported (NR) for outcomes that did not appear to satisfy the proportional-hazards assumption.
CI, confidence interval; HR, hazard ratio; NA, not available

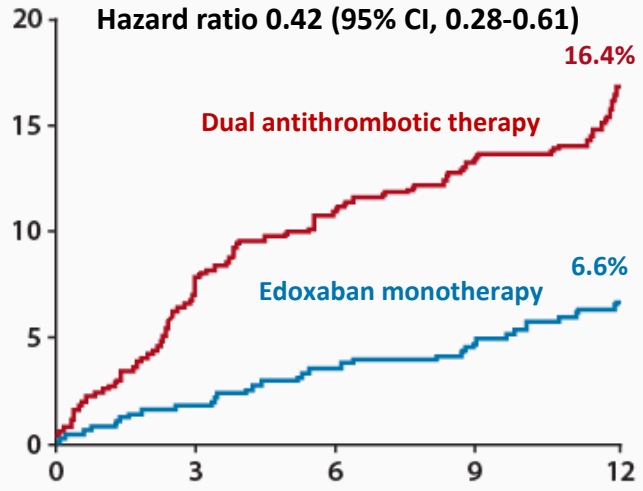
Type of CV outcomes

Outcome*	Edoxaban Monotherapy (N=524)	Dual Antithrombotic Therapy (N=516)	Risk Difference (95% CI)	HR (95% CI)†
Safety Outcomes				
Major or clinically relevant nonmajor bleeding	23 (4.7)	70 (14.2)	9.58 (5.92 to 13.24)	0.34 (0.22 to 0.53)
Major bleeding	6 (1.3)	22 (4.5)	3.12 (0.99 to 5.25)	0.32 (0.14 to 0.73)
Clinically relevant nonmajor bleeding	18 (3.5)	52 (10.6)	7.08 (3.89 to 10.27)	0.36 (0.21 to 0.59)
Fatal bleeding	0 (0)	0 (0)	NA	NA
Any bleeding	49 (9.9)	99 (20.1)	10.20 (5.73 to 14.67)	0.48 (0.35 to 0.67)
Intracranial hemorrhage	2 (0.4)	3 (0.6)	0.21 (-0.65 to 1.06)	0.70 (0.12 to 4.16)
Gastrointestinal hemorrhage	8 (1.6)	13 (2.6)	1.03 (-0.75 to 2.81)	NR**

*The percentages were estimated by the Kaplan–Meier estimates. †Hazard ratios are for the edoxaban monotherapy compared to the dual antithrombotic therapy.
**Hazard ratios were not reported (NR) for outcomes that did not appear to satisfy the proportional-hazards assumption.
CI, confidence interval; HR, hazard ratio; NA, not available.

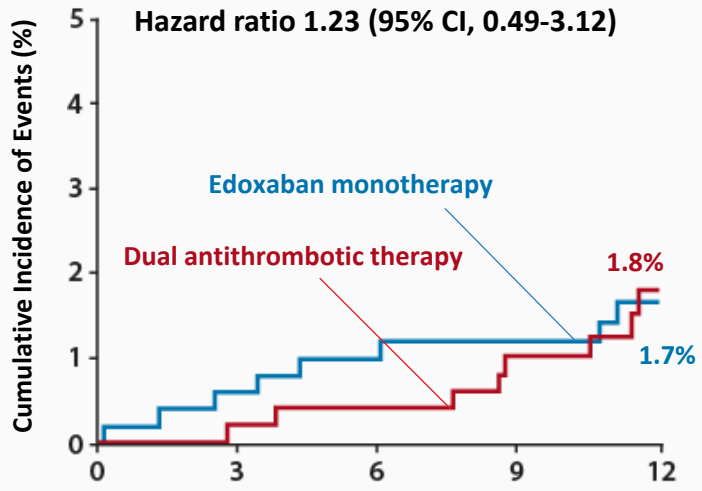
Sensitivity analysis: Per-protocol analysis

Primary net adverse clinical event



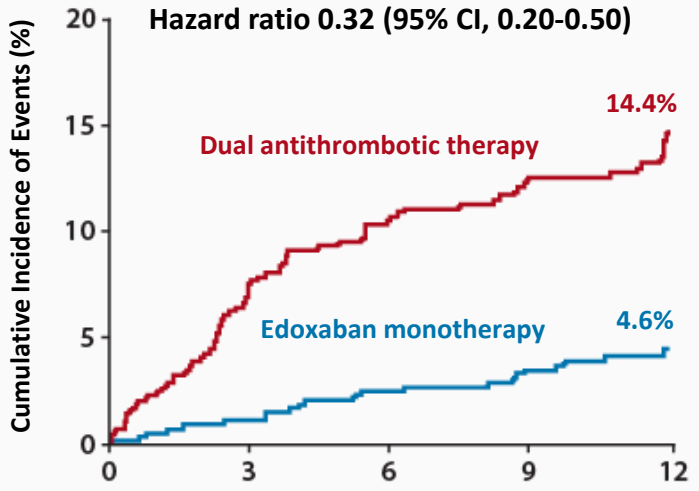
No. at Risk					
Dual antithrombotic therapy	504	464	441	427	382
Edoxaban monotherapy	511	497	484	476	399

Major ischemic event



No. at Risk					
Dual antithrombotic therapy	504	464	441	427	382
Edoxaban monotherapy	511	497	484	476	399

Major bleeding and clinically relevant non-major bleeding

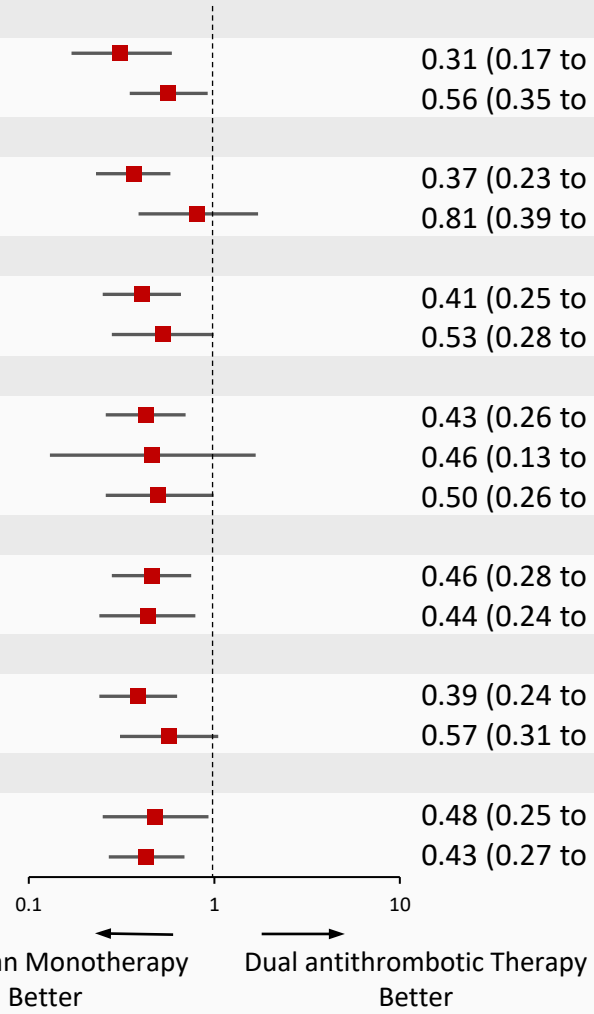


No. at Risk					
Dual antithrombotic therapy	504	464	441	427	382
Edoxaban monotherapy	511	497	484	476	399

Primary net adverse clinical event was composite of death from any causes, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, and major or clinically relevant nonmajor bleeding event.
Major ischemic event was as a composite of death from any cause, myocardial infarction, ischemic stroke, or systemic embolism.

Prespecified Subgroup Analysis

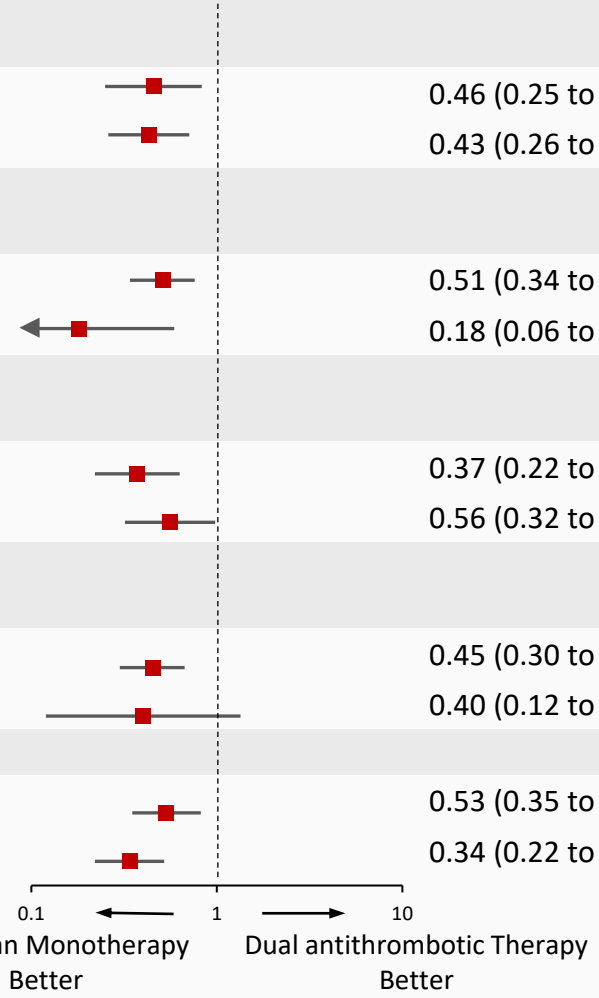
Subgroup	Percent of Patients	Estimated 1-Yr Event Rate (%)		Hazard Ratios (95% CI)
		Edoxaban monotherapy	Dual antithrombotic therapy	
Age				
≥75 years	42.2	5.3	18.7	0.31 (0.17 to 0.59)
<75 years	57.8	7.8	14.2	0.56 (0.35 to 0.92)
Sex				
Male	77.1	6.0	17.4	0.37 (0.23 to 0.58)
Female	22.9	9.4	12.1	0.81 (0.39 to 1.72)
Creatinine clearance				
≥50 mL/min	75.8	5.2	14.5	0.41 (0.25 to 0.66)
<50 mL/min	24.2	12.1	21.7	0.53 (0.28 to 0.99)
Last revascularization				
PCI	59.1	6.4	17.1	0.43 (0.26 to 0.70)
Bypass grafting	6.5	7.4	20.6	0.46 (0.13 to 1.67)
Medical treatment	34.3	7.1	13.7	0.50 (0.26 to 0.99)
Edoxaban dose				
60 mg	57.5	6.5	16.4	0.46 (0.28 to 0.75)
30 mg	42.5	7.5	16.1	0.44 (0.24 to 0.79)
Risk of stroke				
CHA_2DS_2-VASc ≥4	67.3	6.1	16.2	0.39 (0.24 to 0.63)
CHA_2DS_2-VASc <4	32.7	8.2	16.3	0.57 (0.31 to 1.05)
Risk of bleeding				
HAS-BLED ≥3	31.8	7.7	15.1	0.48 (0.25 to 0.93)
HAS-BLED <3	68.2	6.5	16.9	0.43 (0.27 to 0.69)



PCI, percutaneous coronary intervention

Post-Hoc Subgroup Analysis

Subgroup	Percent of Patients	Estimated 1-Yr Event Rate (%)		Hazard Ratios (95% CI)
		Edoxaban monotherapy	Dual antithrombotic therapy	
Prior dual antithrombotic therapy				
Yes	44.6	6.3	14.4	0.46 (0.25 to 0.83)
No	55.4	7.2	18.1	0.43 (0.26 to 0.71)
Prior anticoagulation Therapy				
Yes	89.8	7.0	14.9	0.51 (0.34 to 0.76)
No	10.2	5.2	30.1	0.18 (0.06 to 0.59)
Prior antiplatelet therapy				
Yes	53.6	6.2	17.3	0.37 (0.22 to 0.63)
No	46.4	7.4	15.2	0.56 (0.32 to 0.98)
Appropriateness of edoxaban dose				
Appropriate dose	86.0	7.1	16.5	0.45 (0.30 to 0.67)
Inappropriate dose	14.0	4.9	15.3	0.40 (0.12 to 1.34)
Type of antiplatelets				
Aspirin	62.1	6.8	12.8	0.53 (0.35 to 0.82)
Clopidogrel	37.9	6.8	22.3	0.34 (0.22 to 0.52)



PCI, percutaneous coronary intervention

Study Limitations

- Open-label design that entailed a risk of reporting or ascertainment bias
- Not designed to detect potential differences in less common but clinically relevant ischemic outcomes
- Net adverse clinical event as primary trial end point
  - Relatively higher incidence of bleeding events than ischemic events
  - Bias results in favor of the less potent antithrombotic strategy
- The generalizability and reproducibility of our trial findings may be potentially limited
  - East Asian population
  - Women were underrepresented

Summary for the EPIC-CAD Trial Findings

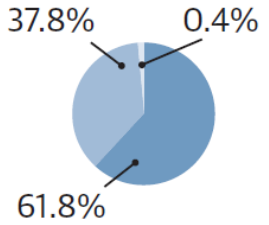
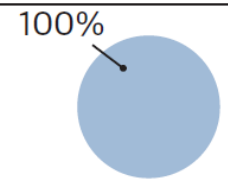
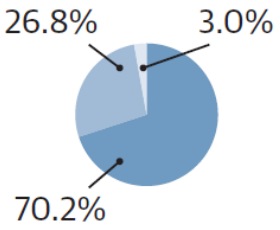
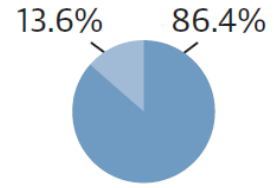
- In this multicenter RCT, use of standard-dose edoxaban monotherapy was associated with a lower risk of primary net adverse clinical events as compared with dual antithrombotic therapy (edoxaban and a single antiplatelet agent) in patients with AF and stable CAD.
- This result appeared to be driven mainly by a lower incidence of bleeding events.
- The incidence of ischemic events and mortality appeared to be similar in the trial groups.

Conclusion

In this EPIC-CAD involving patients with AF and stable CAD,

- edoxaban monotherapy was associated with a lower risk of a composite outcomes of death from any cause, myocardial infarction, stroke, systemic embolism, unplanned urgent revascularization, or major bleeding or clinically relevant nonmajor bleeding than dual antithrombotic therapy at 12 months.

Updated Meta-analysis

	Trial	Participants	Randomization	OACs*	Follow-Up (median)	Antiplatelet Agents: Aspirin / $P2Y_{12}$ Inhibitor† / Other
2024	**EPIC-CAD**	1,040	524 OAC alone 516 OAC + SAPT	Edoxaban 60 mg once daily	12 months	
2022	**PRAEDO-AF**	147	74 OAC alone 73 OAC + SAPT	Edoxaban 60 mg once daily	20.8 months	
2019	**AFIRE**	2,215	1107 OAC alone 1108 OAC + SAPT	Rivaroxaban 15 mg once daily	24.1 months	
2019	**OAC-ALONE**	690	344 OAC alone 346 OAC + SAPT	Warfarin (INR 2.0 to 3.0) Dabigatran 150 mg twice daily Rivaroxaban 15 mg once daily Apixaban 5 mg twice daily Edoxaban 60 mg once daily	30.0 months	

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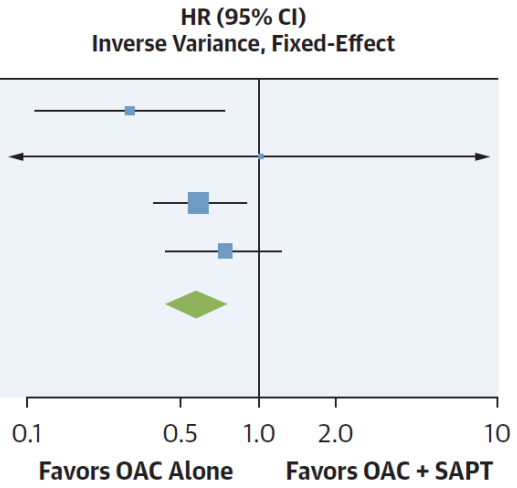
Updated Meta-analysis

A Major Bleeding

Trial	OAC Alone Event/Total	OAC + SAPT Event/Total	Weight (%)	HR (95% CI)
EPIC-CAD	6/524	22/516	12.8%	0.32 (0.14-0.73)
PRAEDO-AF	0/74	0/73	0.6%	1.00 (0.02-49.74)
AFIRE	35/1,107	58/1,108	51.5%	0.59 (0.39-0.89)
OAC-ALONE	27/344	36/346	35.2%	0.73 (0.44-1.20)
Total	**68/2,049**	**116/2,043**	**100.0%**	**0.59 (0.44-0.79)**

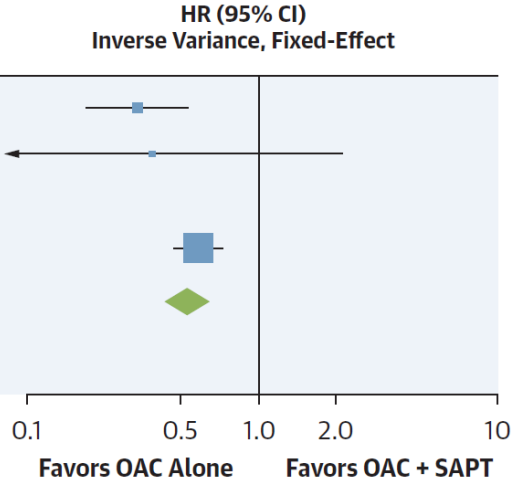
Heterogeneity: I^2 = 0%, P_Q = 0.41
Overall Effect: P = 0.0004



B Major or Clinically Relevant Nonmajor Bleeding

Trial	OAC Alone Event/Total	OAC + SAPT Event/Total	Weight (%)	HR (95% CI)
EPIC-CAD	23/524	70/516	17.0%	0.34 (0.22-0.53)
PRAEDO-AF	2/74	5/73	1.2%	0.39 (0.08-2.02)
AFIRE	146/1,107	238/1,108	81.8%	0.58 (0.47-0.71)
OAC-ALONE				Not available*
Total	**171/1,705**	**313/1,697**	**100.0%**	**0.53 (0.44-0.63)**

Heterogeneity: I^2 = 58%, P_Q = 0.09
Overall Effect: P < 0.00001



- OAC monotherapy was associated with a lower risk of major / major or CRNM bleeding than OAC plus SAPT.

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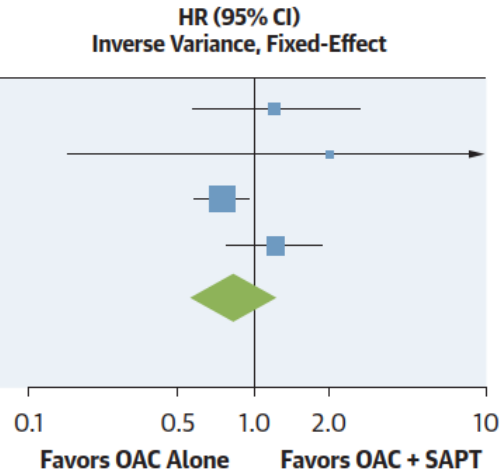
Updated Meta-analysis

Composite of Myocardial Infarction, Ischemic Stroke, Systemic Embolism, or Death

Trial	OAC Alone Event/Total	OAC + SAPT Event/Total	Weight (%)	HR (95% CI)
EPIC-CAD	8/524	8/516	5.9%	1.23 (0.49-3.10)
PRAEDO-AF	2/74	1/73	0.9%	1.99 (0.18-21.90)
AFIRE	86/1,107	115/1,108	62.2%	0.73 (0.55-0.97)
OAC-ALONE	53/344	43/346	31.0%	1.25 (0.84-1.87)
Total	**149/2,049**	**167/2,043**	**100.0%**	**0.90 (0.72-1.12)**

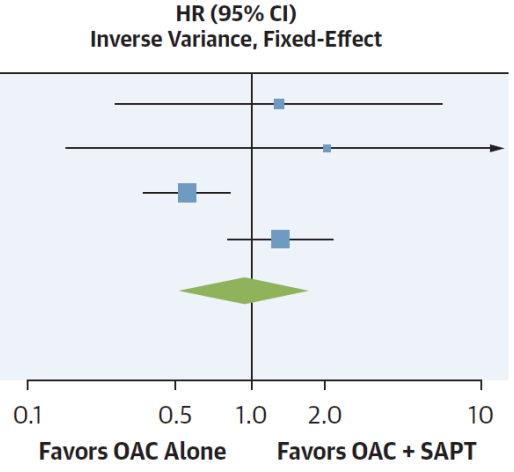
Heterogeneity: I^2 = 45%, P_Q = 0.14
Overall Effect: P = 0.34



D All-Cause Death*

Trial	OAC Alone Event/Total	OAC + SAPT Event/Total	Weight (%)	HR (95% CI)
EPIC-CAD	3/524	3/516	13.7%	1.29 (0.29-5.76)
PRAEDO-AF	2/74	1/73	6.5%	1.99 (0.18-21.90)
AFIRE	41/1,107	73/1,108	41.4%	0.55 (0.37-0.81)
OAC-ALONE	40/344	31/346	38.4%	1.30 (0.80-2.10)
Total	**86/2,049**	**108/2,043**	**100.0%**	**0.94 (0.49-1.80)**

Heterogeneity: I^2 = 65%, P_Q = 0.04
Overall Effect: P = 0.84



- There were no statistically significant differences between OAC monotherapy vs OAC plus SAPT in the primary effectiveness outcome.

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Current Guidelines for AF and CCD

US 2023 Guideline

- In patients with AF & CCD (beyond 1 yr after revasc or CAD not requiring coronary revasc) without history of ST, OAC monotherapy is recommended over the combination therapy of OAC and single APT to decrease the risk of major bleeding.

I

B-R

ESC 2024 Guideline

- Antiplatelet therapy beyond 12 mo is not recommended in stable patients with chronic coronary or vascular disease treated with OAC, due to lack of efficacy and to avoid major bleeding.

III

B

Summary – Antithrombotics for AF & PCI

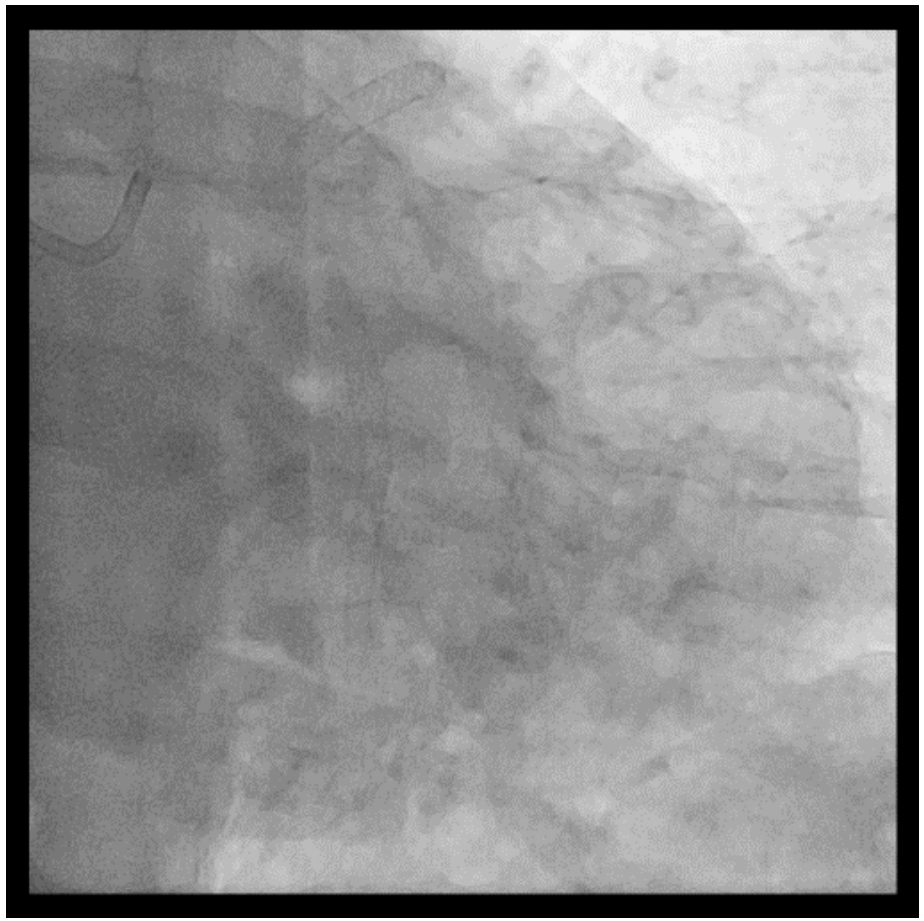
- About 7% of PCI patients have AF.
- Most of AF patients with PCI were indicated for stroke prevention.

- **Clopidogrel + NOAC is the best option for 1 year.**
  - In ENTRUST AF-PCI Trial, Edoxaban + PY212 inhibitor significantly improved safety. vs VKA plus DAPT. Comparable efficacy was observed.

- Guidelines recommend **OAC monotherapy post-12 months** after PCI.
  - In EPIC-CAD Trial, edoxaban monotherapy reduced a composite outcomes of efficacy and safety than dual antithrombotic therapy at 12 months.

Case

F/82, NSTEMI s/p PCI, AF (C-V score 5)



Aspirin + Plavix + Edoxaban 30 mg initially

Plavix + Edoxaban 30 mg from discharge to 1 year

Lifelong Edoxaban 30mg after 1 year

Thank you for your attention !