Edoxaban alone and Edoxaban with antiplatelet agent in patients with atrial fibrillation and chronic stable coronary artery disease : EPIC – CAD trial

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University of Ulsan College of Medicine,
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AF and CAD share major risk factors

AF Risk Factors

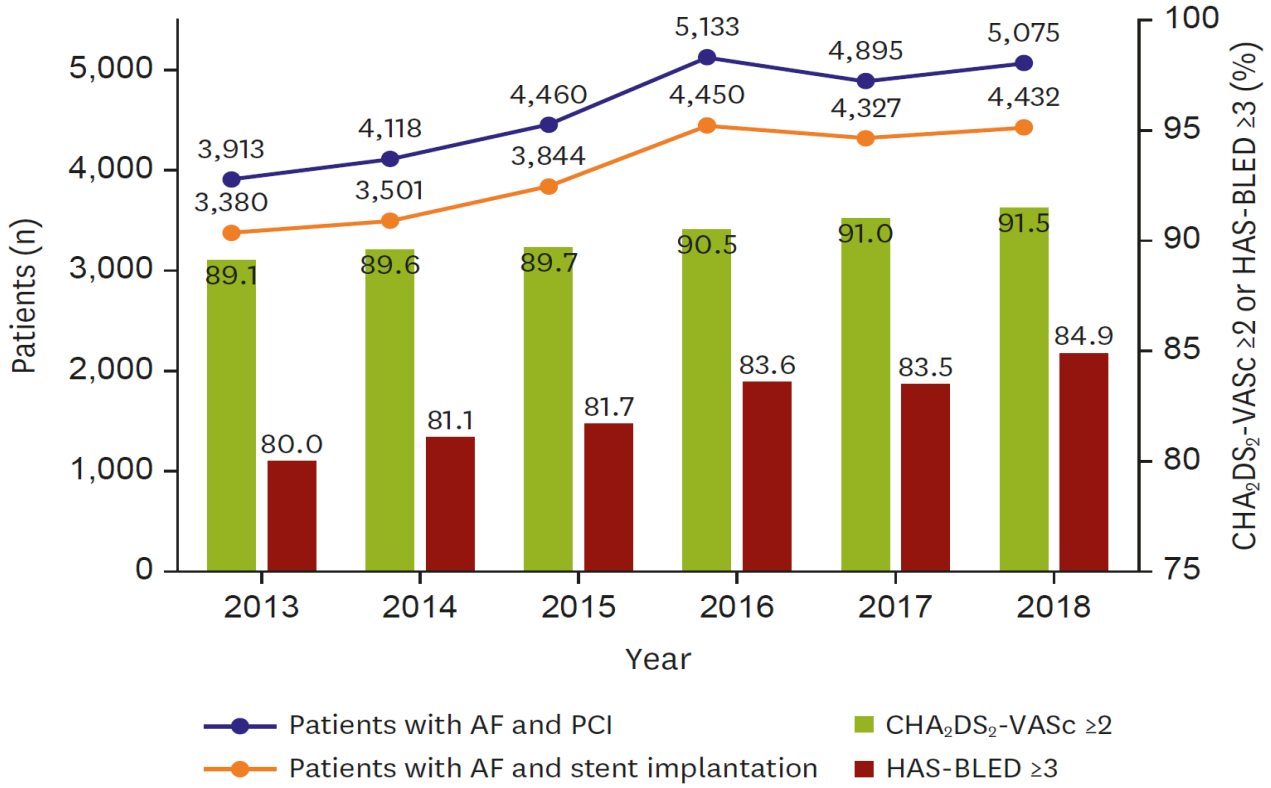
Old Age
Male Gender
Obesity
Alcohol Consumption
Smoking
Diabetes
Hypertension
Physical Inactivity

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.

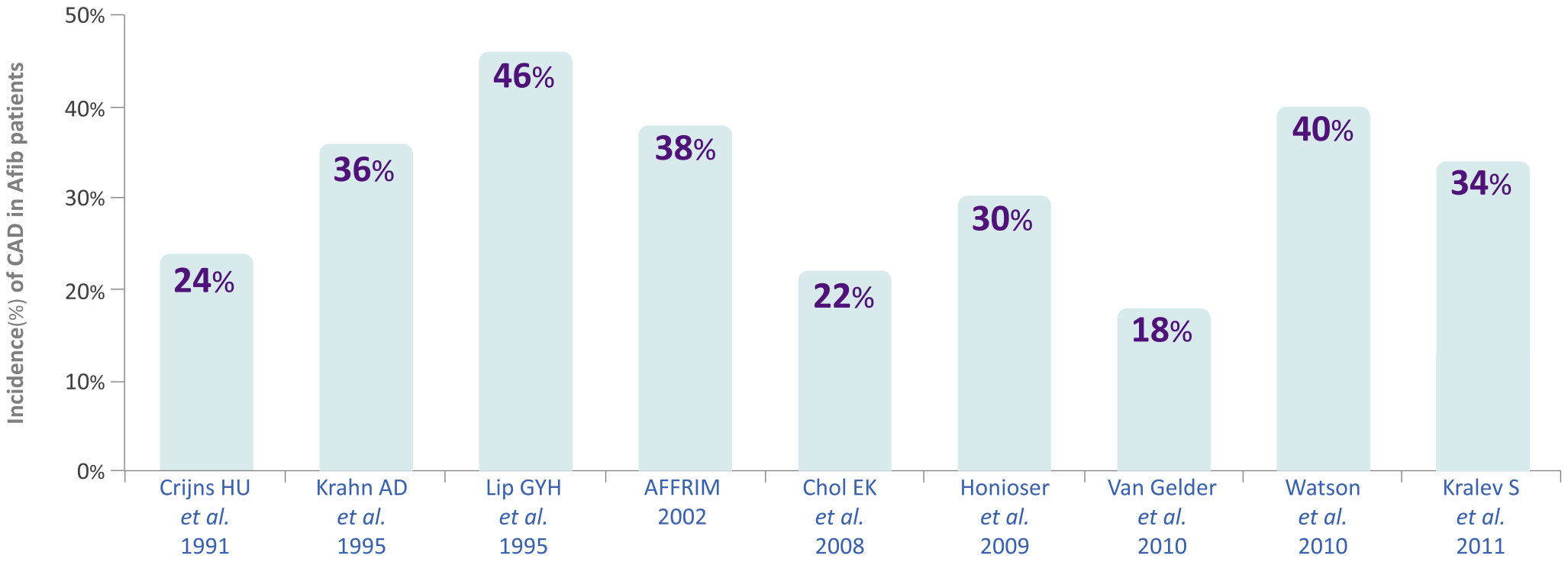
Trends in prevalence of AF patients with PCI in Korean population



- Approximately **7% of all patients undergoing PCI** had co-exist AF
- Among these patients >90% subjects were with CHA_2DS_2-VASc ≥ 2.

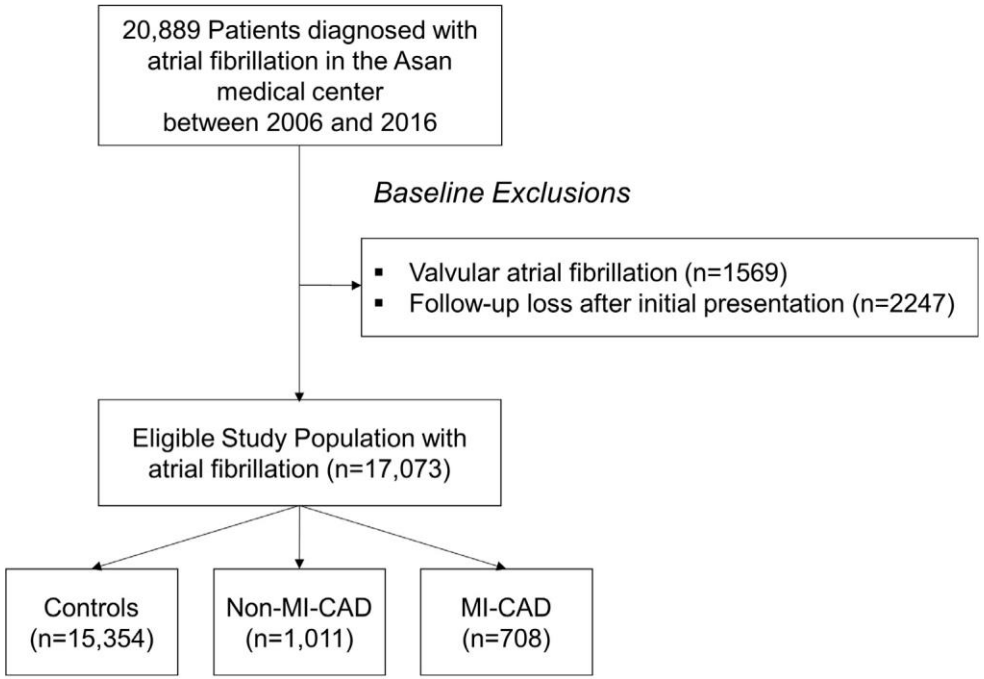
Kwon S et al. Korean Circ J. 2021 May;51(5):409-422.

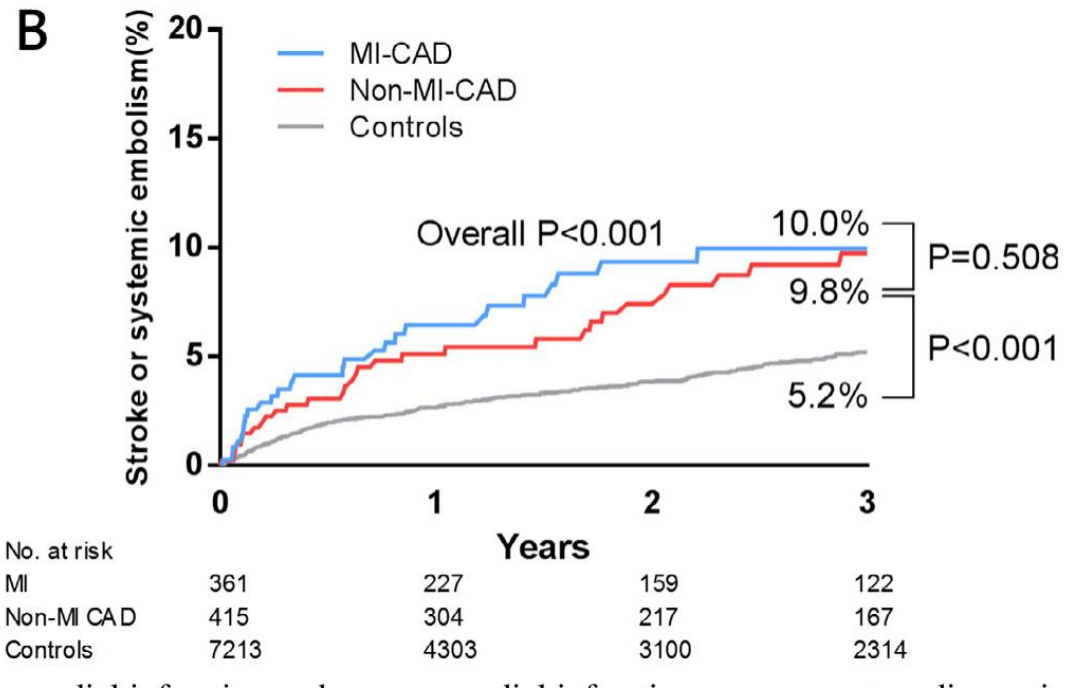
Reported incidences of CAD in Afib patients



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

AF + CAD are fundamentally at high-risk





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Cho MS, Choi KJ et al. AJC 2019

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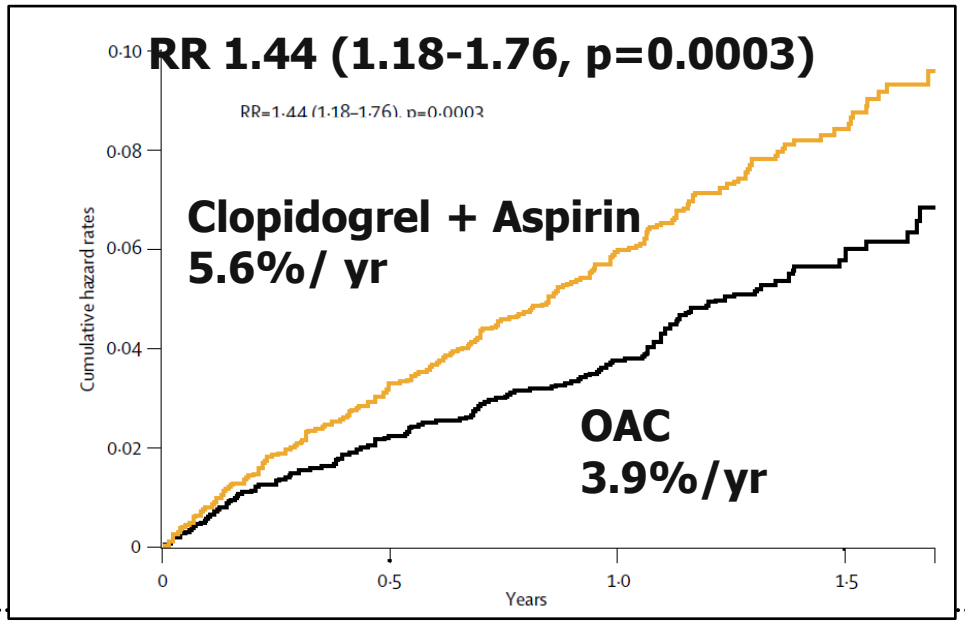
Omission of OAC in AF patients: ACTIVE W

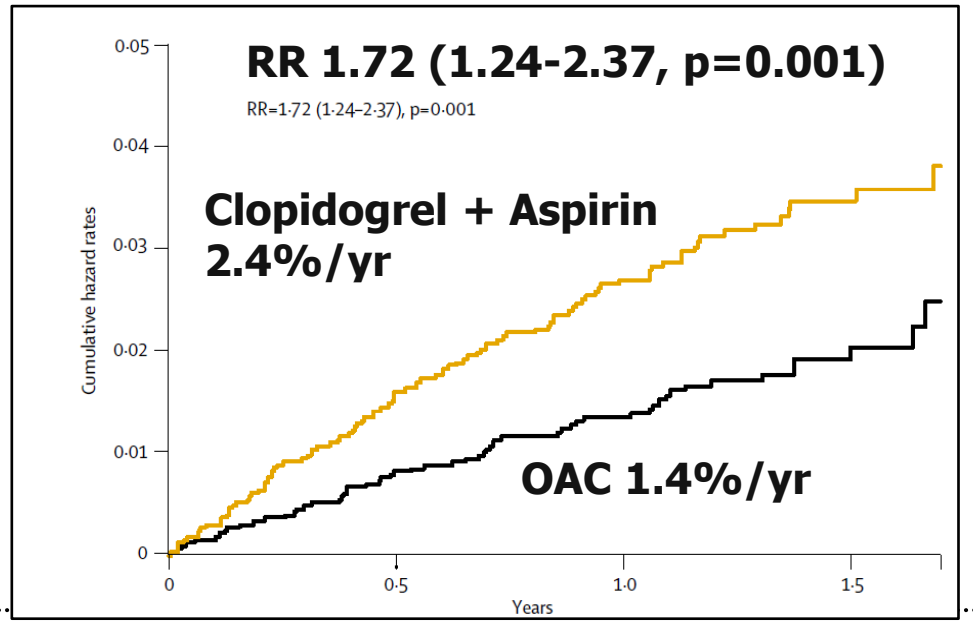
- AF + ≥ 1 risk factor for stroke
- OAC (target INR 2.0-3.0) (n=3371) vs. Clopidogrel + Aspirin (n=3335)
- Primary outcome: stroke, non-CNS systemic embolus, MI, or vascular death

OAC is superior to clopidogrel + aspirin for prevent of vascular events in patients with AF at high risk of stroke

Primary outcome



Stroke



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S Connolly et al., Lancet . 2006 Jun 10;367(9526):1903-12

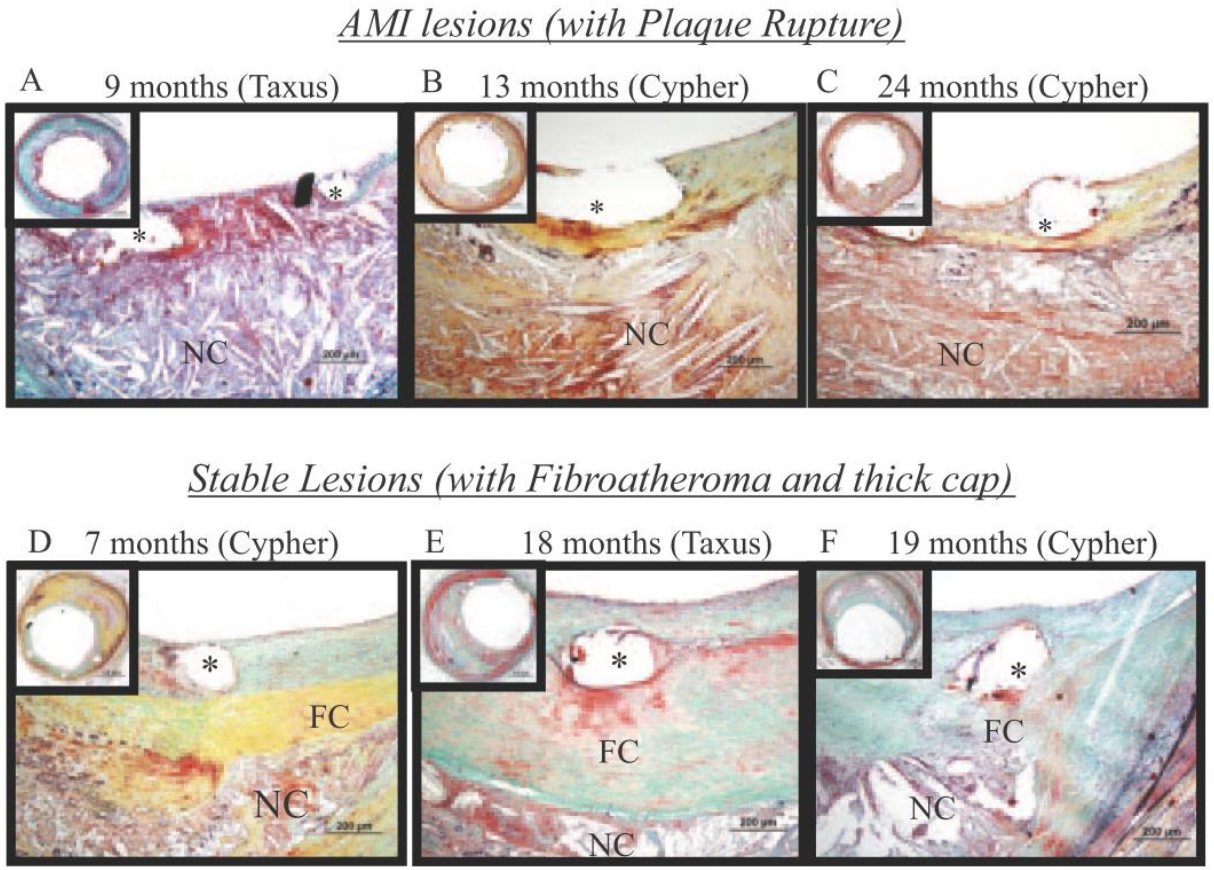
Antiplatelet therapy as an alternative to OAC

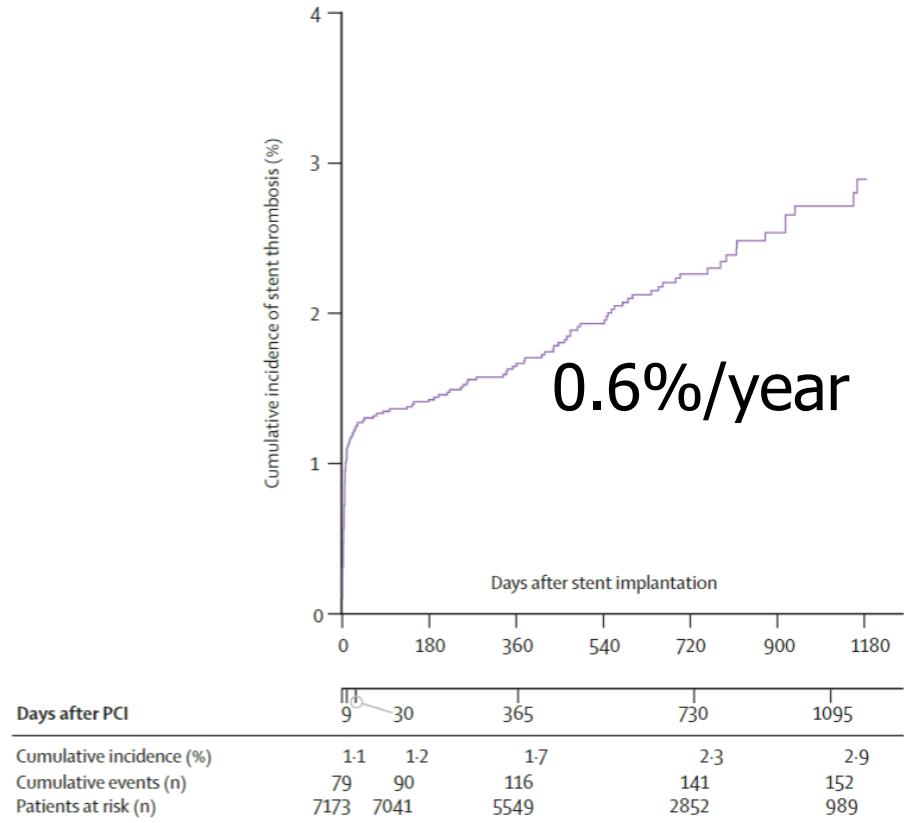
- VKA therapy prevents stroke, systemic embolism, myocardial infarction, and vascular death better than SAPT or DAPT (annual risk of 5.6% for aspirin + clopidogrel vs. 3.9% with VKA therapy)
- Antiplatelet therapy cannot be recommended for stroke prevention in AF patients, regardless of stroke risk.

Antiplatelet therapy alone (monotherapy or aspirin in combination with clopidogrel) is not recommended for stroke prevention in AF.[440,441,480,481]	III	A
Estimated bleeding risk, in the absence of absolute contraindications to OAC, should not in itself guide treatment decisions to use OAC for stroke prevention.	III	A
Clinical pattern of AF (i.e. first detected, paroxysmal, persistent, long-standing persistent, permanent) should not condition the indication to thromboprophylaxis.[160]	III	B

1. Connolly S et al. Lancet . 2006 Jun 10;367(9526):1903-12., 2. Kirchhof P et al. Eur Heart J . 2016 Oct 7;37(38):2893-2962

Early vs late stent thrombosis





- DAPT is a fundamental component of ST prevention
- Most BMSs are almost completely endotheialized by 1 month
- Delayed or incomplete endothelization of stent strut is common in 6-12 months

Circulation. 2008;118:1138, Lancet 2007; 369: 66

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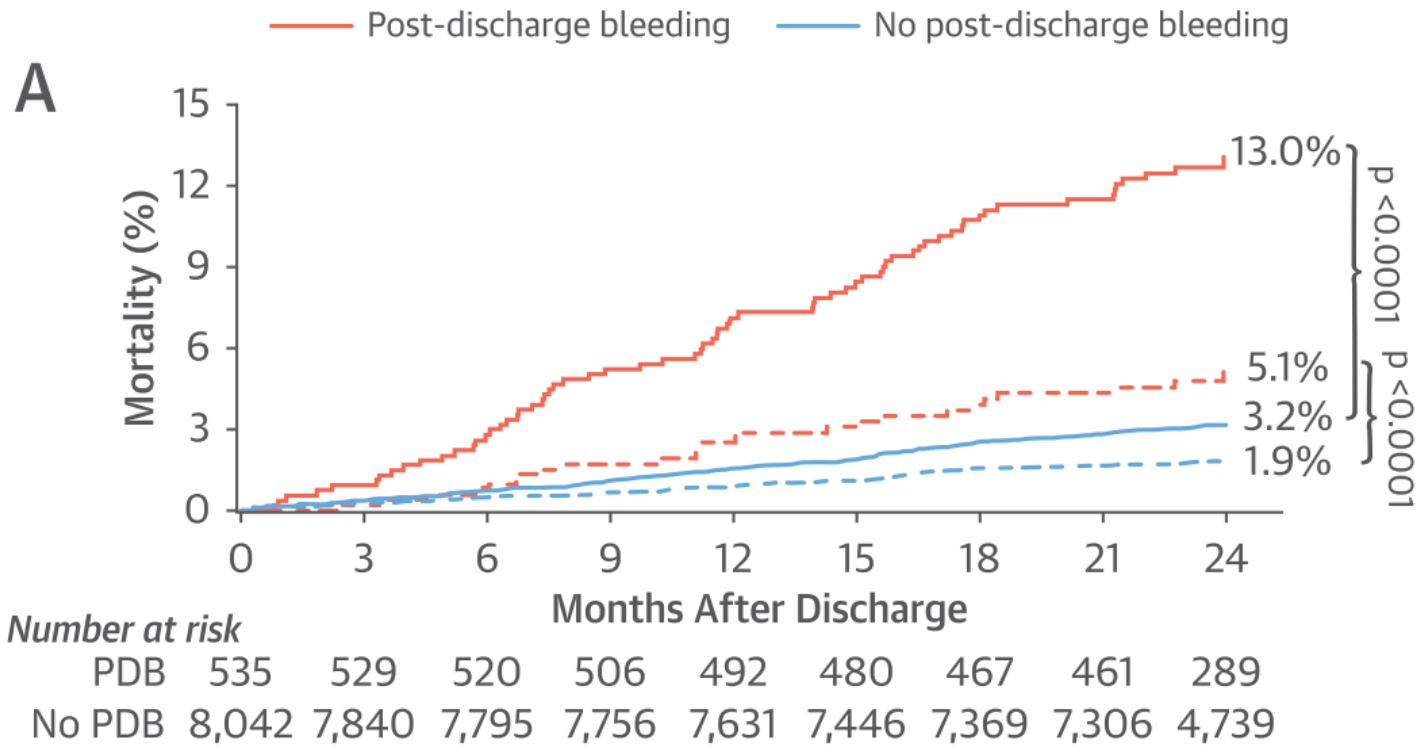
Clinical importance of bleeding

Post-HOC analysis of ADAPT-DES trial



Bleeding became a critical safety issue

Post discharge bleeding has a strong relationship with subsequent all-cause mortality

Généreux et al. JACC 2015

Antithrombotic therapy for AF and PCI : Is 1 plus 2 really 3?

Anticoagulation therapy

Low sheer stress thrombosis in left atrium

Antiplatelet therapy

High sheer stress thrombosis – platelet mediated in the arteries

Dual antiplatelet therapy superior to aspirin alone

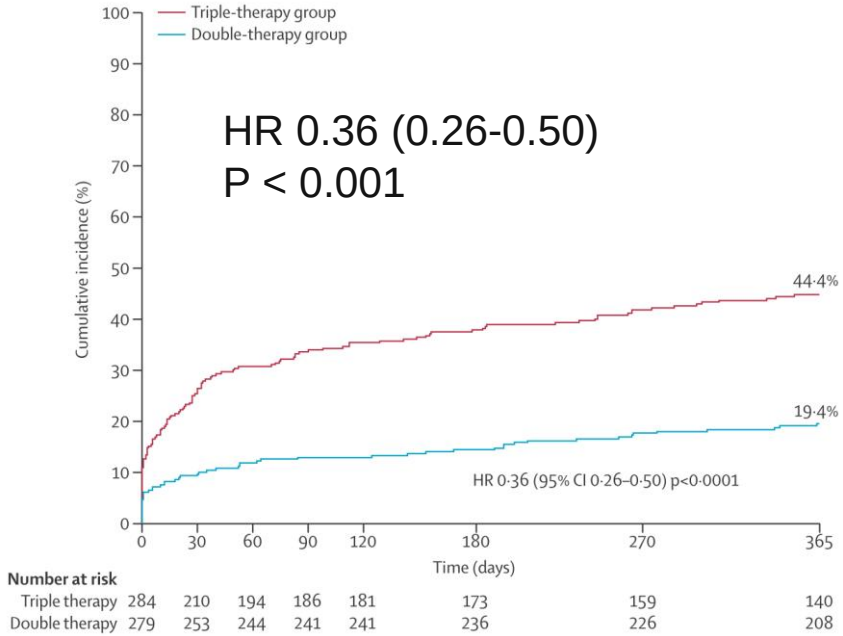
BOTH anticoagulation and dual antiplatelet therapy =

"Triple therapy" ?

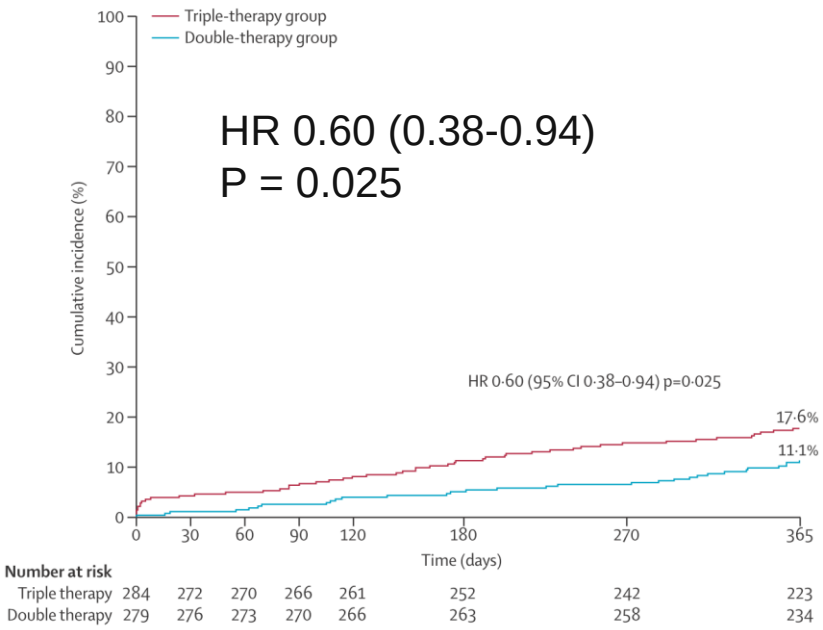
WOEST trial

- Double therapy preferred over triple therapy

TIMI major, minor or minimal bleeding



Death. MI, stroke, or stent thrombosis



Lancet 2013;381:1107

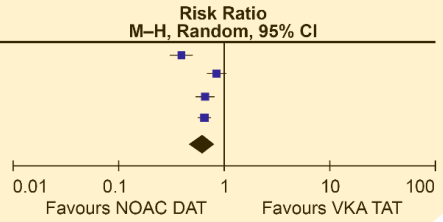
	PIONEER AF-PCI	RE-DUAL PCI	ENTRUST	AUGUSTUS
Objective	Rivaroxaban + P2Y12 inhibitor or DAPT vs VKA + DAPT in patients with NVAF undergoing PCI	Dabigatran + P2Y12 inhibitor vs VKA + DAPT in patients with NVAF undergoing PCI	Edoxaban + P2Y12 inhibitor vs VKA + DAPT in patients with NVAF undergoing PCI	Apixaban + ASA/placebo vs VKA + ASA/placebo in patients with NVAF and ACS or PCI
Population size	2124	2725	1500	4600
Treatments	• Rivaroxaban 15mg qd + P2Y12 inhibitor • Rivaroxaban 2.5mg bid + DAPT, then Rivaroxaban 15mg bid + ASA • VKA + DAPT, then VKA+ASA	• Dabigatran 150mg or 110mg bid + P2Y12 inhibitor • VKA + DAPT	• Edoxaban 60mg or 30mg qd + P2Y12 inhibitor • VKA + DAPT	• Apixaban 5mg or 2.5mg bid + ASA/placebo • VKA + ASA/placebo
Duration	12 months	6-30months	12 months	6 months
Primary outcomes	Clinically significant bleeding	Major or clinically relevant non-major bleeding	Major or clinically relevant non-major bleeding	Major or clinically relevant non-major bleeding
Analysis period	Treatment-emergent period	Time to first event	Day 1 to 12 months	Time to first event

Meta-Analysis of NOACs vs VKA in PCI

ISTH Major or Clinically Relevant Non-Major Bleeding

Study or Subgroup	NOAC DAT Events	NOAC DAT Total	VKA TAT Events	VKA TAT Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	84	1143	210	1123	23.7%	0.39 (0.31, 0.50)
ENTRUST AF-PCI	128	751	152	755	24.7%	0.85 (0.68, 1.05)
PIONEER AF-PCI	117	696	178	697	24.8%	0.66 (0.53, 0.81)
RE-DUAL PCI	305	1744	264	981	26.8%	0.65 (0.56, 0.75)
Total (95% CI)		**4334**		**3556**	**100.0%**	**0.62 (0.47, 0.81)**
Total events	634		804			

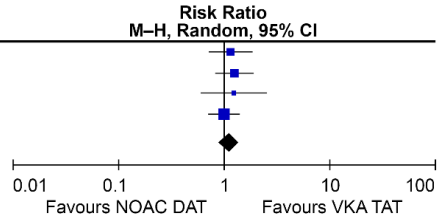
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 22.84$, df = 3 (P <0.0001); $I^2 = 87\%$
Test for overall effect: Z = 3.47 (P = 0.0005)



All-Cause Death

Study or Subgroup	NOAC DAT Events	NOAC DAT Total	VKA TAT Events	VKA TAT Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	39	1153	34	1154	23.4%	1.15 (0.73, 1.81)
ENTRUST AF-PCI	46	751	37	755	27.1%	1.25 (0.82, 1.90)
PIONEER AF-PCI	16	694	13	695	9.2%	1.23 (0.60, 2.54)
RE-DUAL PCI	85	1744	48	981	40.3%	1.00 (0.71, 1.41)
Total (95% CI)		**4342**		**3585**	**100.0%**	**1.12 (0.90, 1.39)**
Total events	186		132			

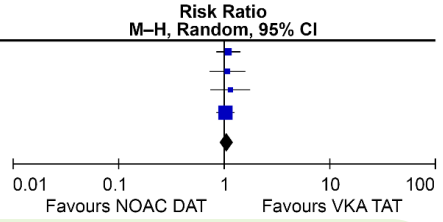
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.78$, df = 3 (P = 0.85); $I^2 = 0\%$
Test for overall effect: Z = 0.99 (P = 0.32)



Major Adverse Cardiovascular Events as Defined by Trials

Study or Subgroup	NOAC DAT Events	NOAC DAT Total	VKA TAT Events	VKA TAT Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	72	1153	66	1154	20.3%	1.09 (0.79, 1.51)
ENTRUST AF-PCI	49	751	46	755	14.1%	1.07 (0.73, 1.58)
PIONEER AF-PCI	41	694	36	695	11.3%	1.14 (0.74, 1.76)
RE-DUAL PCI	239	1744	131	981	54.3%	1.03 (0.84, 1.25)
Total (95% CI)		**4342**		**3585**	**100.0%**	**1.06 (0.91, 1.22)**
Total events	401		279			

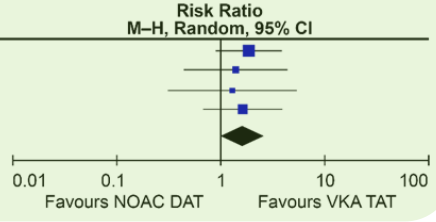
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 3 (P = 0.97); $I^2 = 0\%$
Test for overall effect: Z = 0.76 (P = 0.45)



Stent Thrombosis

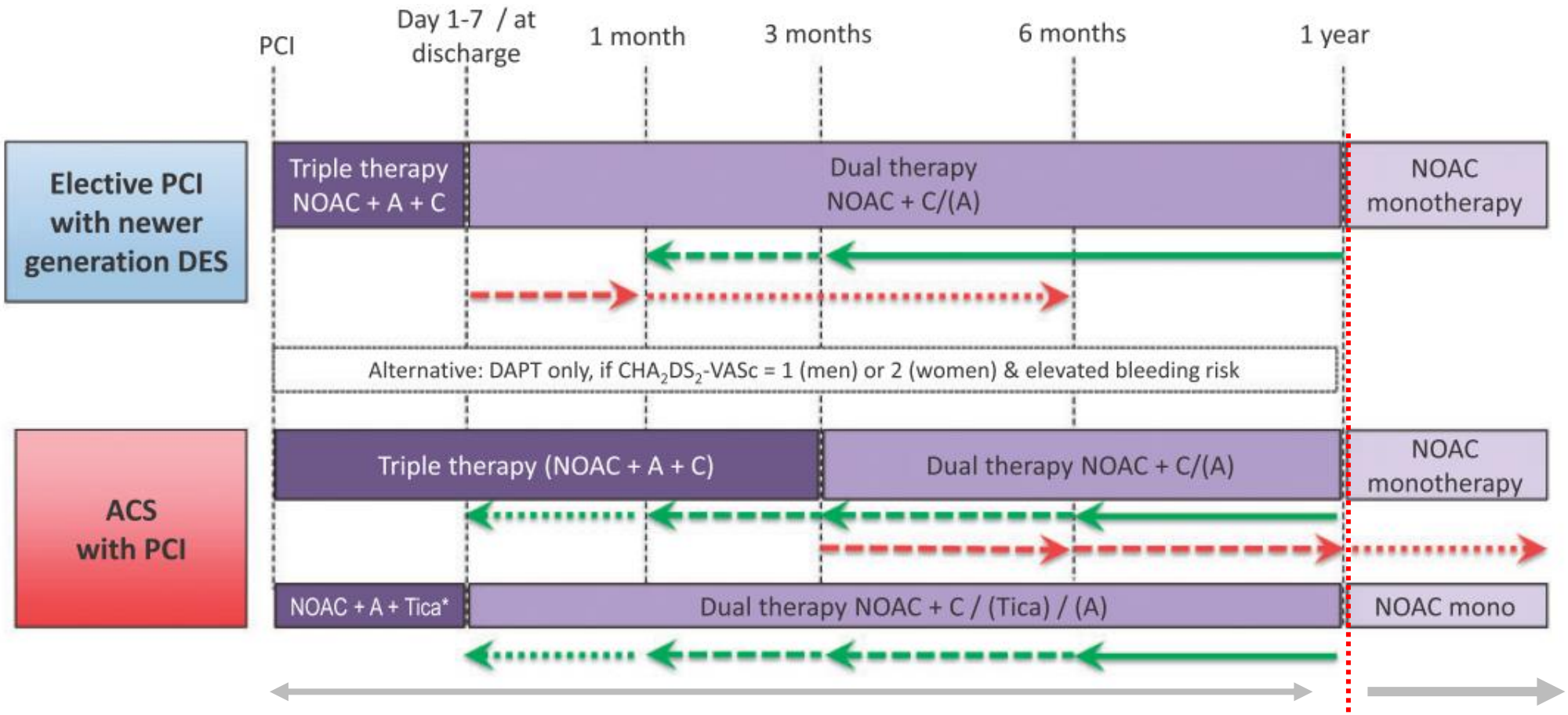
Study or Subgroup	NOAC DAT Events	NOAC DAT Total	VKA TAT Events	VKA TAT Total	Weight	Risk Ratio M–H, Random, 95% CI
AUGUSTUS	21	1153	12	1154	40.0%	1.75 (0.87, 3.54)
ENTRUST AF-PCI	8	751	6	755	17.9%	1.34 (0.47, 3.84)
PIONEER AF-PCI	5	694	4	695	11.6%	1.25 (0.34, 4.64)
RE-DUAL PCI	22	1744	8	981	30.6%	1.55 (0.69, 3.46)
Total (95% CI)		**4342**		**3585**	**100.0%**	**1.55 (0.99, 2.41)**
Total events	56		30			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, df = 3 (P = 0.96); $I^2 = 0\%$
Test for overall effect: Z = 1.92 (P = 0.06)



- NOAC > Warfarin
- Dual > Triple
- Concerns about stent thrombosis

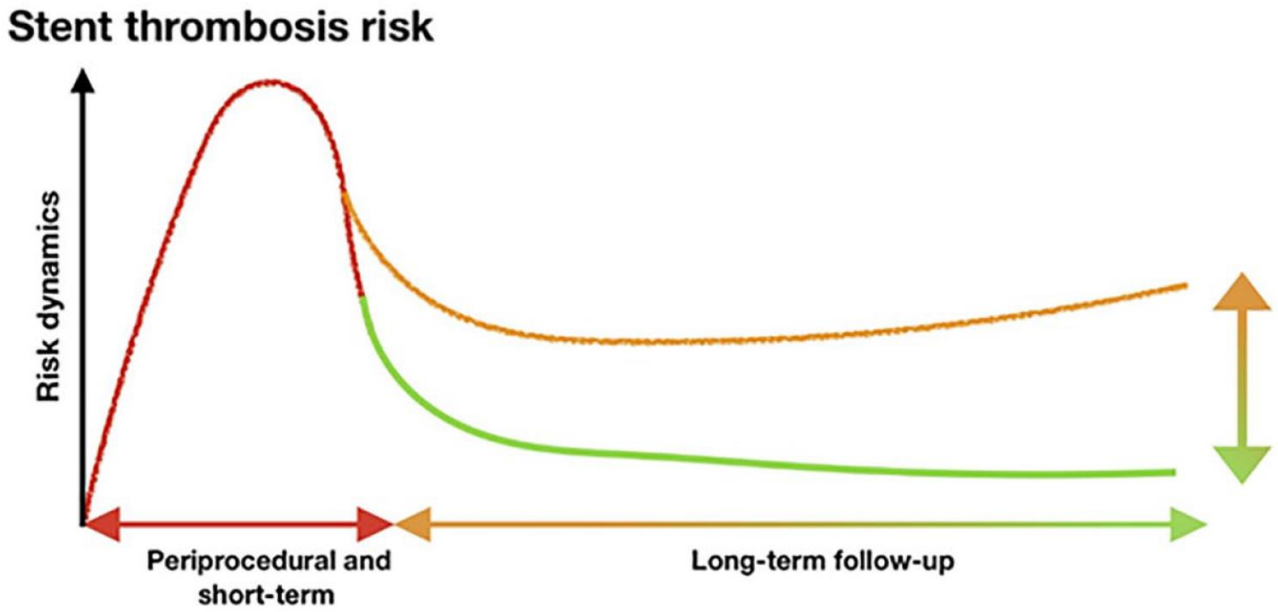
EHRA NOAC practice guideline



WOEST
REDUAL PCI
PIONEER AF
AUGUSTUS
ENTRUST-AF

?

PCI

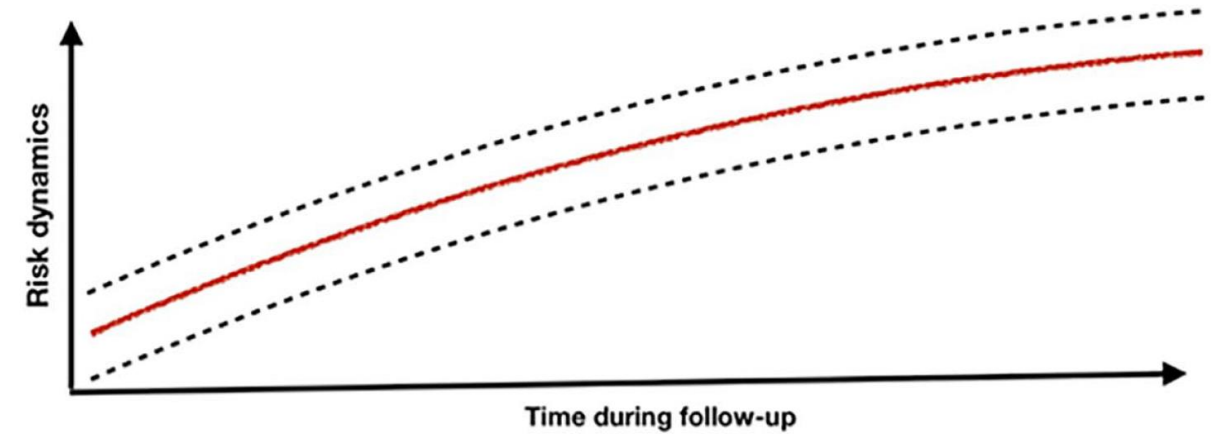


Factors associated with long-term increased risk of stent thrombosis:

- 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

Temporal evolution of thromboembolic risk

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.

Circulation

ORIGINAL RESEARCH ARTICLE

Open-Label Randomized Trial Comparing Oral Anticoagulation With and Without Single Antiplatelet Therapy in Patients With Atrial Fibrillation and Stable Coronary Artery Disease Beyond 1 Year After Coronary Stent Implantation

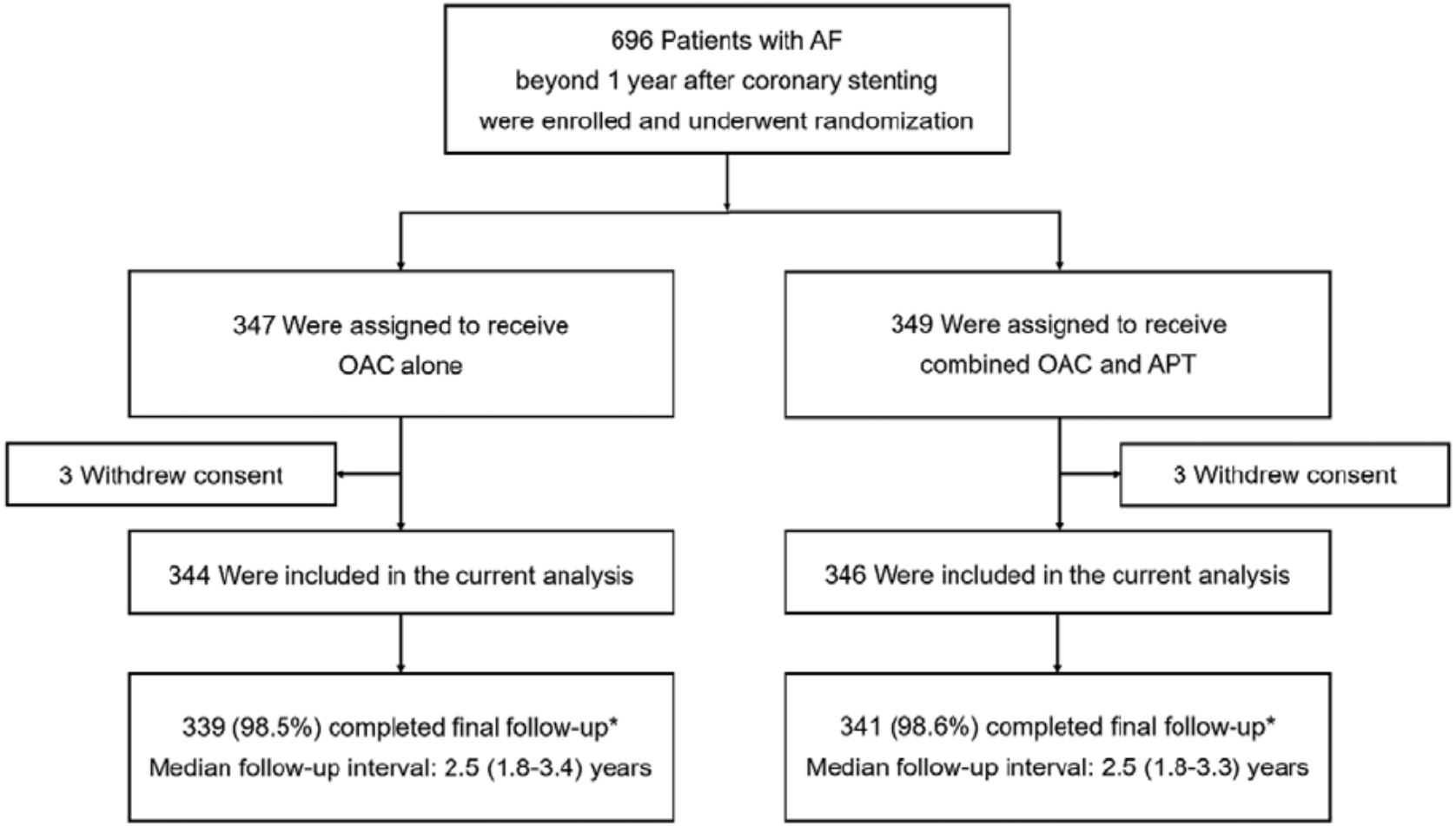
OAC-ALONE Study

서울아산병원 Asan Medical Center

울산대학교

Circulation. 2019;139:604–616. DOI: 10.1161/CIRCULATIONAHA.118.036768

Design



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Circulation. 2019;139:604–616. DOI: 10.1161/CIRCULATIONAHA.118.036768

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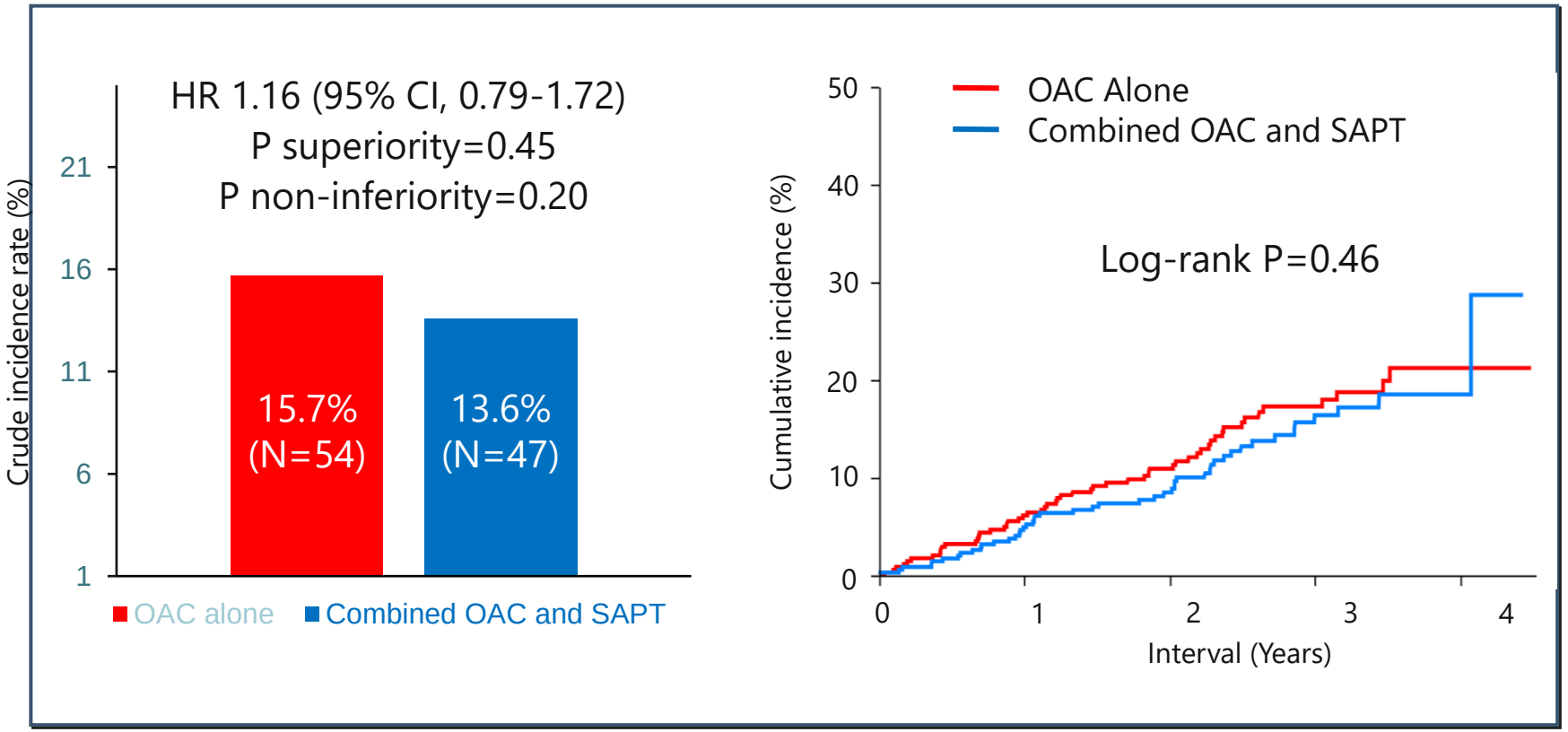
Primary End Points

- **Primary efficacy end point :** The composite of all-cause death, myocardial infarction, stroke, or systemic embolism



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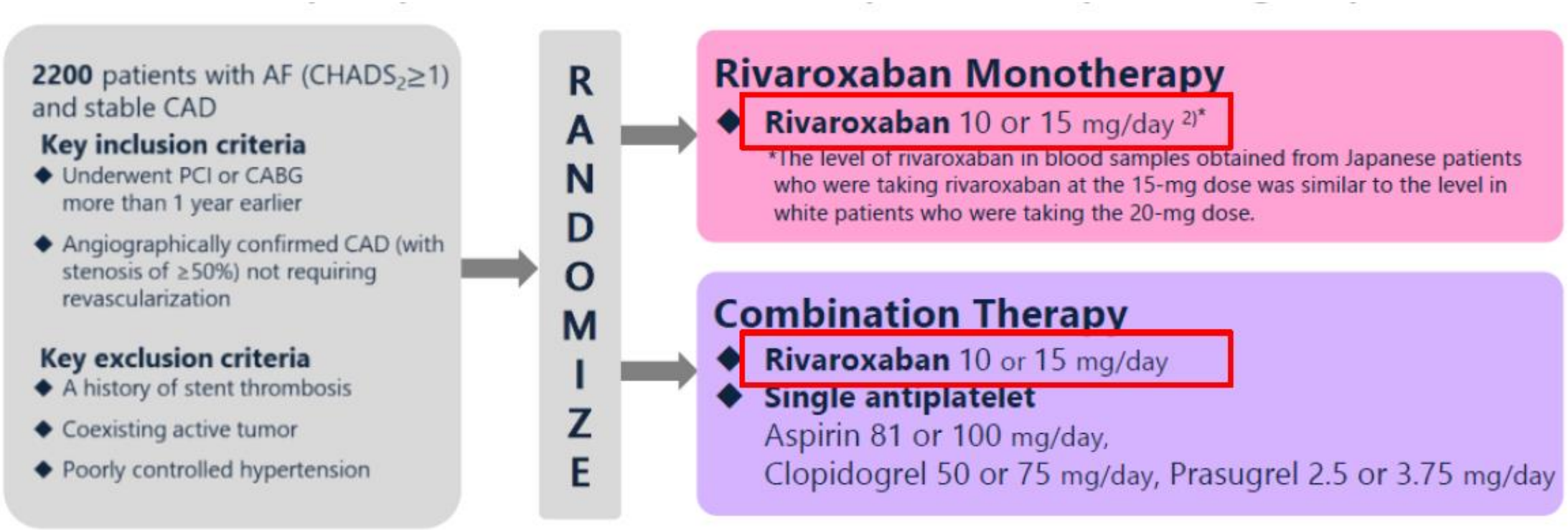
Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

Satoshi Yasuda, M.D., Ph.D., Koichi Kaikita, M.D., Ph.D., Masaharu Akao, M.D., Ph.D., Junya Ako, M.D., Ph.D., Tetsuya Matoba, M.D., Ph.D., Masato Nakamura, M.D., Ph.D., Katsumi Miyauchi, M.D., Ph.D., Nobuhisa Hagiwara, M.D., Ph.D., Kazuo Kimura, M.D., Ph.D., Atsushi Hirayama, M.D., Ph.D., Kunihiko Matsui, M.D., M.P.H., and Hisao Ogawa, M.D., Ph.D., for the AFIRE Investigators*

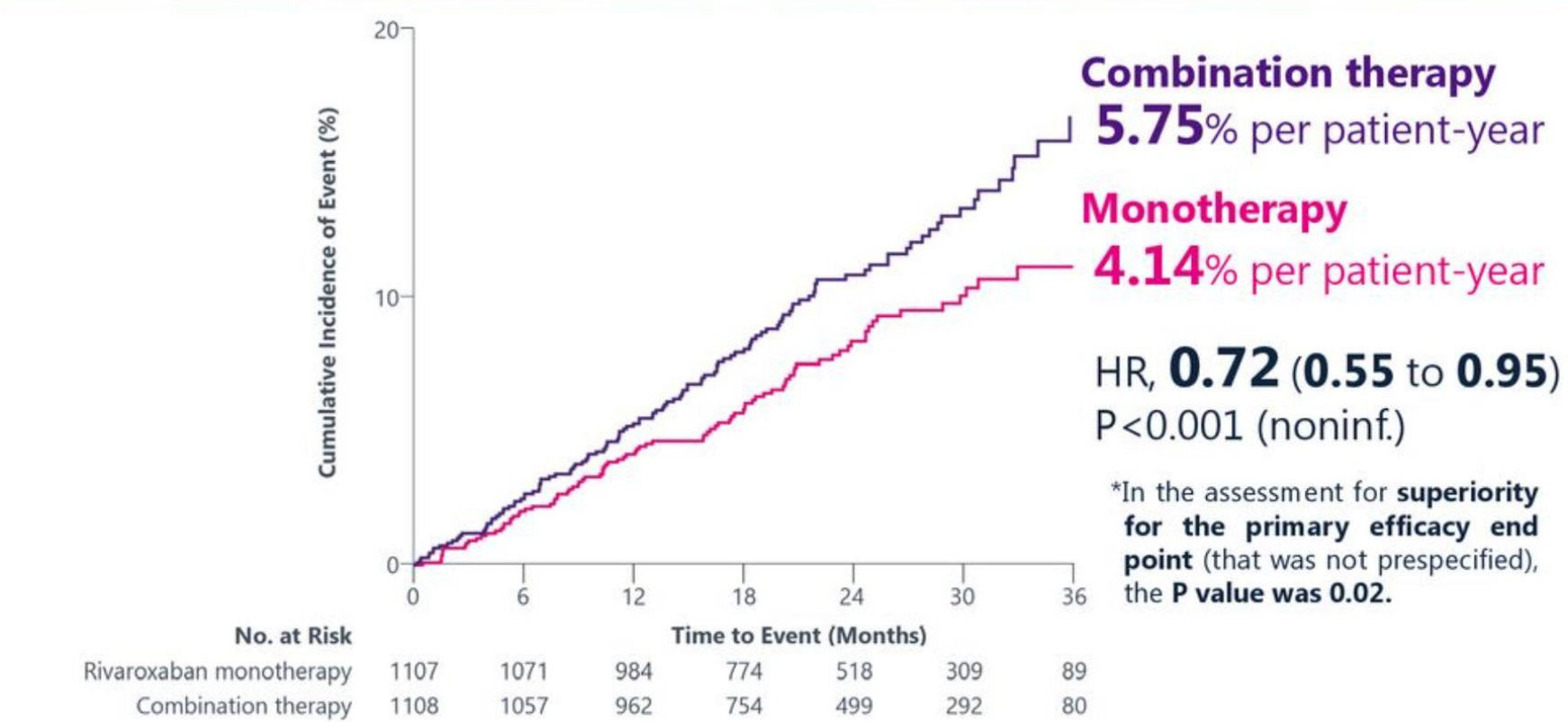
Design

- A multicenter, prospective, randomized, open-label, parallel-group trial



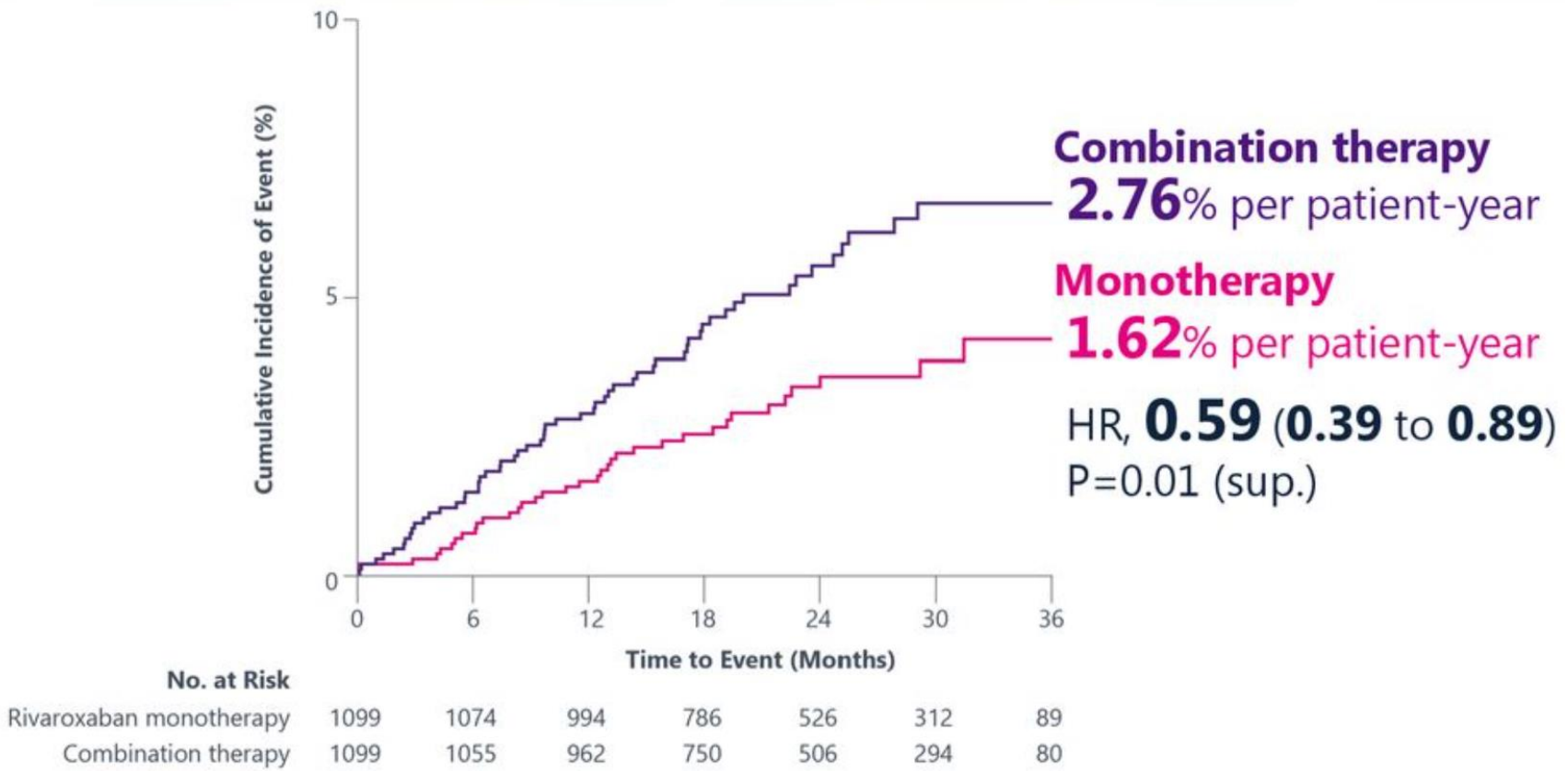
Primary efficacy end point

- The composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause

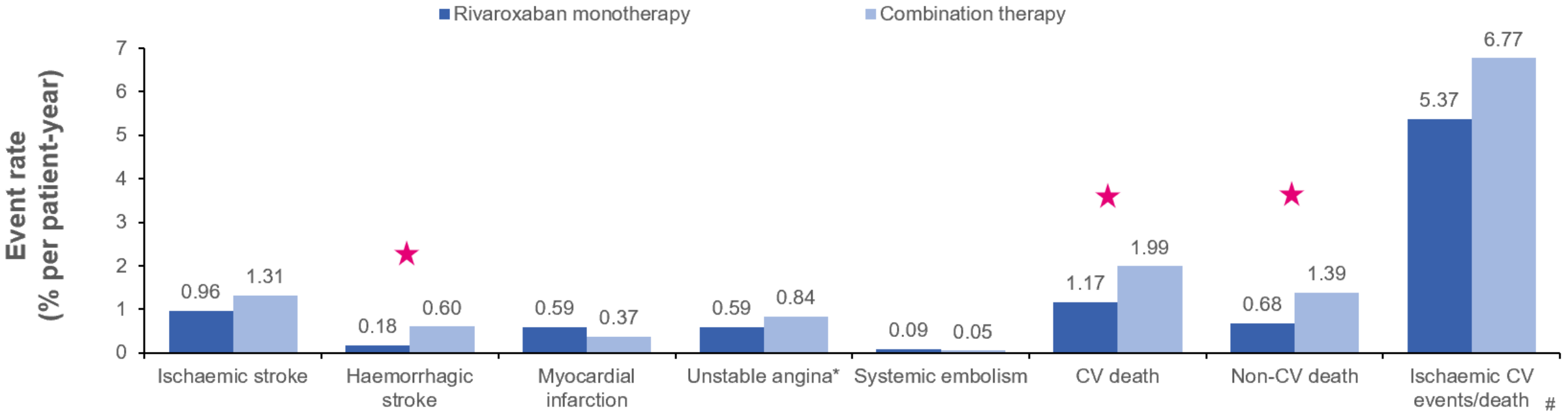


Primary Safety End Point

- Major bleeding, as defined according to the criteria of the ISTH



The respective Incidence Rates of Secondary End Points



- Lower rate of all-cause mortality for rivaroxaban monotherapy versus combination therapy (HR=0.55; 95% CI 0.38–0.81), due to lower incidences of CV and non-CV death
- Trial terminated early because of higher risk of death in the combination therapy group
- The most common causes of death were heart failure, stroke and cancer

Limitations of AFIRE

- The tested dose of rivaroxaban in this trial was off-label (15 mg and 10 mg), thus, more on-label NOAC dosing data are required
- Insufficient data on the extent and severity of CAD could influence the observed outcomes
- Early termination of the trial owing to an increased risk of death from any cause in the combination group may cause overestimation of the efficacy data.

EPIC-CAD trial

Edoxaban versus Edoxaban with anti**P**latelet agent **I**n patients with atrial fibrillation and **C**hronic stable **C**oronary **A**rtery **D**isease

Gi-Byoung Nam and Duk-Woo Park, MD, PhD
Heart Institute, University of Ulsan College of Medicine,
Asan Medical, Seoul, Korea

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Background Question

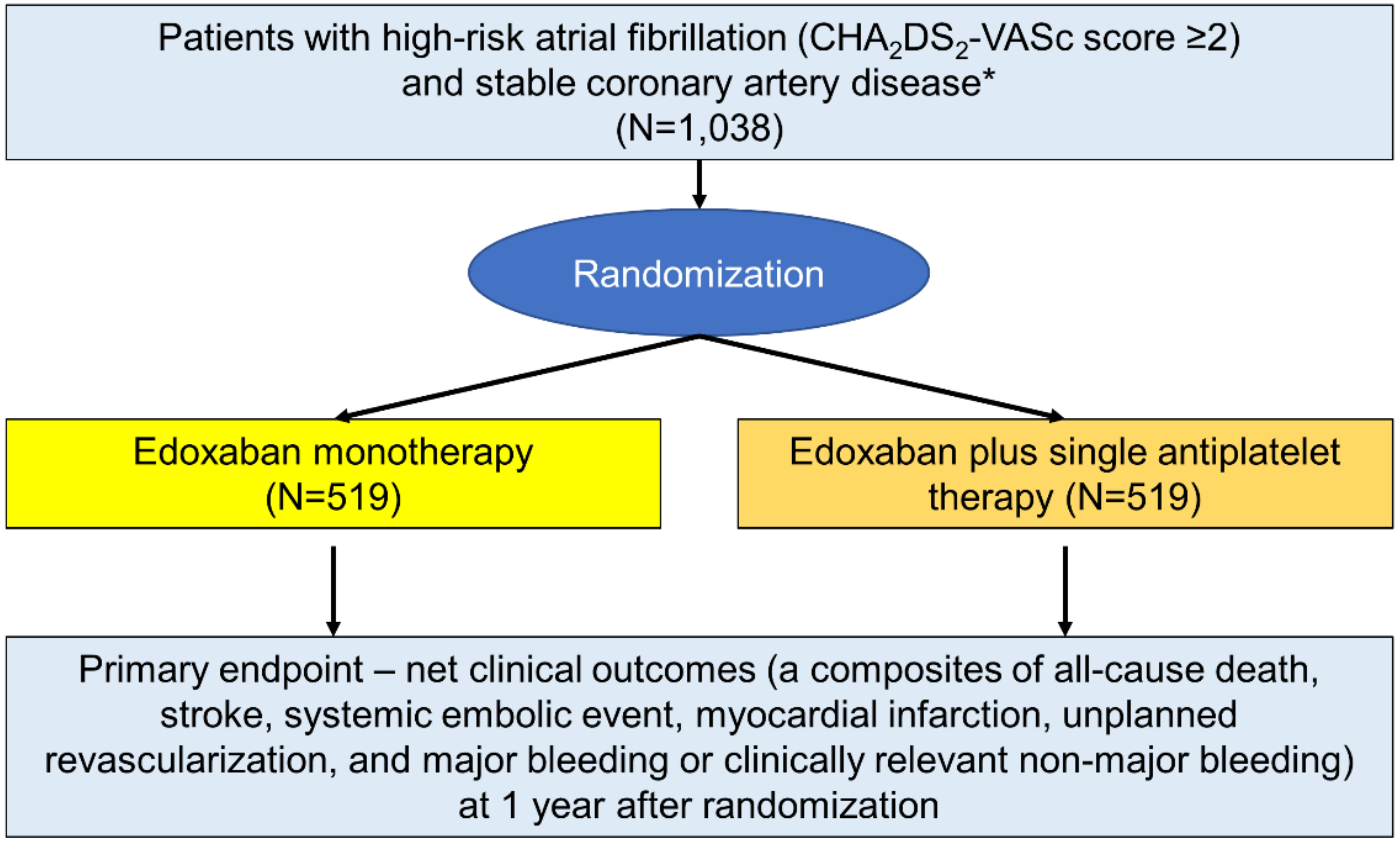
- What is the optimal anticoagulation treatment for patient with chronic stable coronary artery disease and atrial fibrillation?

Objective

- Multicenter, open-labeled, randomized controlled trial to compare the efficacy and safety of Edoxaban alone with the combination of Edoxaban and antiplatelet in patients with stable CAD and high-risk atrial fibrillation.

(**E**doxaban versus Edoxaban with anti**P**latelet agent **I**n patients with atrial fibrillation and **C**hronic stable **C**oronary **A**rtery **D**isease)

EPIC-CAD trial



*__Stable coronary artery disease__ was defined as (1) prior coronary revascularization (either PCI or CABG, ≥ 6 months for stable angina or ≥ 12 months for acute coronary syndrome, or (2) Anatomically confirmed obstructive CAD (≥50% stenosis on coronary angiography or CT angiography) on medical therapy not requiring revascularization.

Inclusion Criteria

- 1. Subject was ≥ 19 years of age
- 2. Patients with nonvalvular AF with high embolic risk (CHA2DS2-VASc score ≥2)
- 3. Patients with Stable CAD
  - CAG or CCTA confirmed CAD (≥50 % stenosis of major coronary artery) on medical treatment
  - Revascularized CAD (either PCI or CABG) whom the last revascularization should be performed ≥12 months before study enrollment for acute coronary syndrome and ≥6 months for stable angina pectoris.

Exclusion Criteria

- 1. Patients with thrombocytopenia
- 2. High risk of bleeding which prohibits the anticoagulant use
- 3. Prior history of intracranial hemorrhage
- 4. Mechanical prosthetic valve or moderate to severe mitral stenosis
- 5. Patients who contraindicated for edoxaban or antiplatelets.
- 6. Planned PCI or CABG was planned within 1 year after randomization.
- 7. Liver cirrhosis or liver dysfunction (AST or ALT > x3 of normal range)
- 8. Estimated glomerular filtration rate <30 mL/min per 1.73 m2
- 9. Life expectancy less than 12 months
- 10. Subject was unable to provide written informed consent
- 11. Pregnant and/or lactating women.
- 12. Patients who are actively participating in another drug or device investigational study

Study Endpoints

- Primary end-point:

  - Net Clinical Outcome – composites of death, stroke, systemic embolic event, myocardial infarction, unplanned revascularization of major coronary artery, major bleeding, and clinically relevant non-major bleeding event at 12 months

- Secondary end-point:

  - Efficacy
    - Death, stroke, systemic embolic event, myocardial infarction, unplanned revascularization
  - Safety
    - major bleeding and clinically relevant non-major bleeding

Methodologic features of EPIC-CAD

- On-label dosing of edoxaban
  - provide the clinical implication of untested NOAC under the standard dose in high-risk patients with AF and CAD
- Stable CAD of >6 months or ACS of >12 months after revascularization
  - which more closely relates to contemporary practice with a shorter DAPT duration
- Collect data on disease extent, functional studies, and revascularization status
  - providing valuable data for the tailored approach for individual patients with different risk–benefit ratios

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Trial design

Edoxaban-based long-term antithrombotic therapy in patients with atrial fibrillation and stable coronary disease: Rationale and design of the randomized EPIC-CAD trial

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Abstract

Background Anticoagulants are the standard therapy for patients with atrial fibrillation (AF) and antiplatelet therapy for those with coronary artery disease (CAD). However, compelling clinical evidence is still lacking regarding the long-term maintenance strategy with the combination of anticoagulant and antiplatelet drugs in patients with AF and stable CAD.

Design The EPIC-CAD trial is an investigator-initiated, multicenter, open-label randomized trial comparing the safety and efficacy of 2 antithrombotic strategies in patients with high-risk AF (CHA_2DS_2-VASc score $\geq$ 2 points) and stable CAD ($\geq$6 months after revascularization for stable angina or $\geq$12 months for acute coronary syndrome; or medical therapy alone). Patients (approximately $N = 1{,}038$) will be randomly assigned at a 1:1 ratio to (1) monotherapy with edoxaban (a non-vitamin K antagonist oral anticoagulant) or (2) combination therapy with edoxaban plus a single antiplatelet agent. The primary endpoint is the net composite outcome of death from any cause, stroke, systemic embolism, myocardial infarction, unplanned revascularization, and major or clinically relevant nonmajor bleeding at 1 year after randomization.

Results As of December 2021, approximately 901 patients had been randomly enrolled over 2 years at 18 major cardiac centers across South Korea. The completed enrollment is expected at the mid-term of 2022, and the primary results will be available by 2023.

Conclusions EPIC-CAD is a large-scale, multicenter, pragmatic design trial, which will provide valuable clinical insight into edoxaban-based long-term antithrombotic therapy in patients with high-risk AF and stable CAD. (Am Heart J 2022;247:123–131.)

- Enrollment was completed at September, 2022
- Protocol published in AHJ

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Summary

- Patients with both CAD and AF are fundamentally high-risk for clinical events.
- NOAC + single antiplatelet agent regimen resulted in better safety with similar efficacy compared to warfarin- based triple therapy in patients with AD and PCI < 1 year.
- NOAC monotherapy recommended in current practice guideline for patients with AF and PCI >1 year, but not based on the firm scientific evidence.
- We expect EPIC-CAD trial to yield definitive and unique data concerning edoxaban-based antithrombotic strategy in this complex, high-risk patient population.