TCTAP 2022 (8:00 PM ~ 9:36 PM. March 18, 2022)
Hot Topics III. Antithrombosis

Long-Term Antithrombotic Strategy in PCI and AF Patients: Insights From the AFIRE Trial

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Disclosure of Conflict of Interest

Name of the author: Satoshi Yasuda,MD,PhD

Matters requiring disclosure of COI
with regard to the presentation are as follows:

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②stock ownership/profit: none
③patent fees: none
④remuneration for lecture: Bristol-Meyers, Bayer, Daiichi-Sankyo
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⑨Other remuneration such as gifts: none

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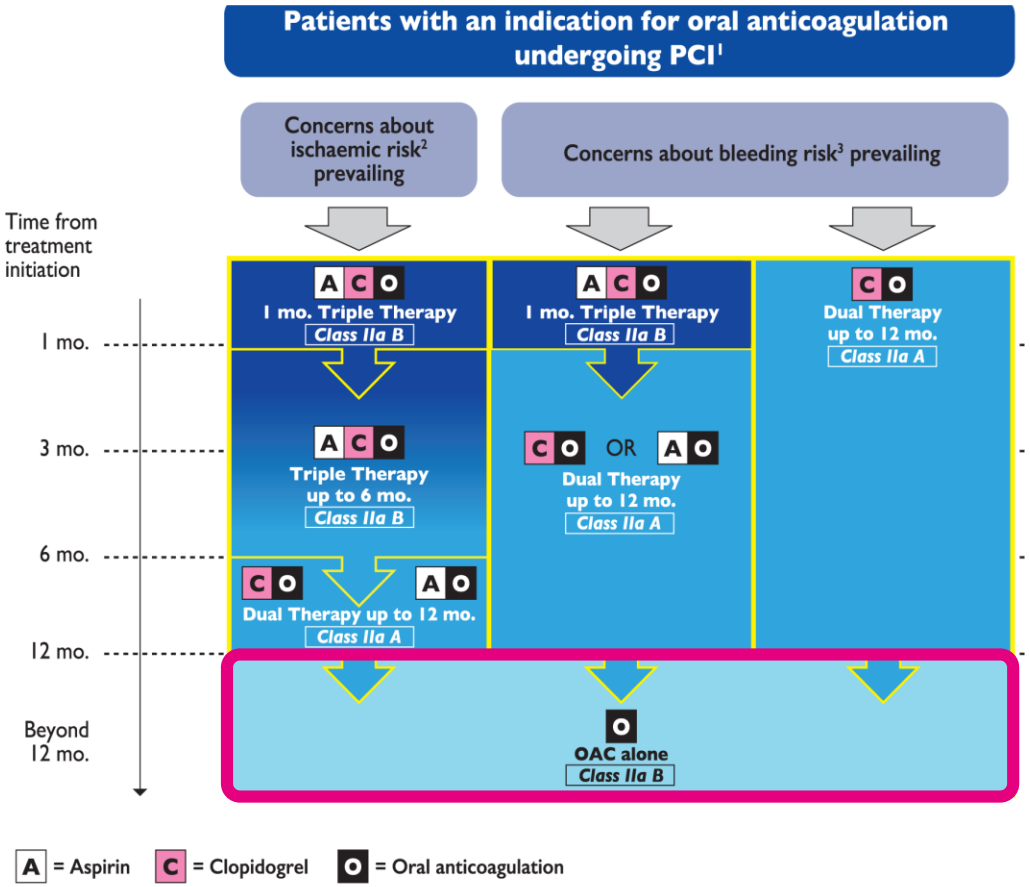
After 12 months following PCI, Guidelines Recommend Oral Anticoagulant Monotherapy

Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI). [1)]

ESC2018 GL



- After 12 months of combination therapy, or in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) not requiring intervention, **an oral anticoagulant (OAC) monotherapy is recommended.**
- However, this approach was not fully described with evidence from randomized, controlled trials.
- Furthermore, substantial numbers of patients in this situation continue to be treated with combination therapy, which indicates a gap between guidelines and clinical practice.[2)]

1) Valgimigli M, *et al.*, *Eur Heart J*, 2018

2) Ancedy Y, *et al.*, *Int J Cardiol* 2016

AFIRE

Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease: AFIRE Study

Purpose; To investigate whether **rivaroxaban monotherapy** is **noninferior** to **combination therapy (rivaroxaban plus an antiplatelet agent)** in patients with AF and stable CAD.

Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease: AFIRE Study

A multicenter, prospective, randomized, open-label, parallel-group trial [1)]

2200 patients with AF ($CHADS_2 \geq 1$) and stable CAD

Key inclusion criteria

- Underwent PCI or CABG more than 1 year earlier
- Angiographically confirmed CAD (with stenosis of ≥50%) not requiring revascularization

Key exclusion criteria

- A history of stent thrombosis
- Coexisting active tumor
- Poorly controlled hypertension

RANDOMIZE

Rivaroxaban Monotherapy

- **Rivaroxaban** 10 or 15 mg/day [2)*]

*The level of rivaroxaban in blood samples obtained from Japanese patients who were taking rivaroxaban at the 15-mg dose was similar to the level in white patients who were taking the 20-mg dose.

Combination Therapy

- **Rivaroxaban** 10 or 15 mg/day
- **Single antiplatelet**
  Aspirin 81 or 100 mg/day,
  Clopidogrel 50 or 75 mg/day, Prasugrel 2.5 or 3.75 mg/day

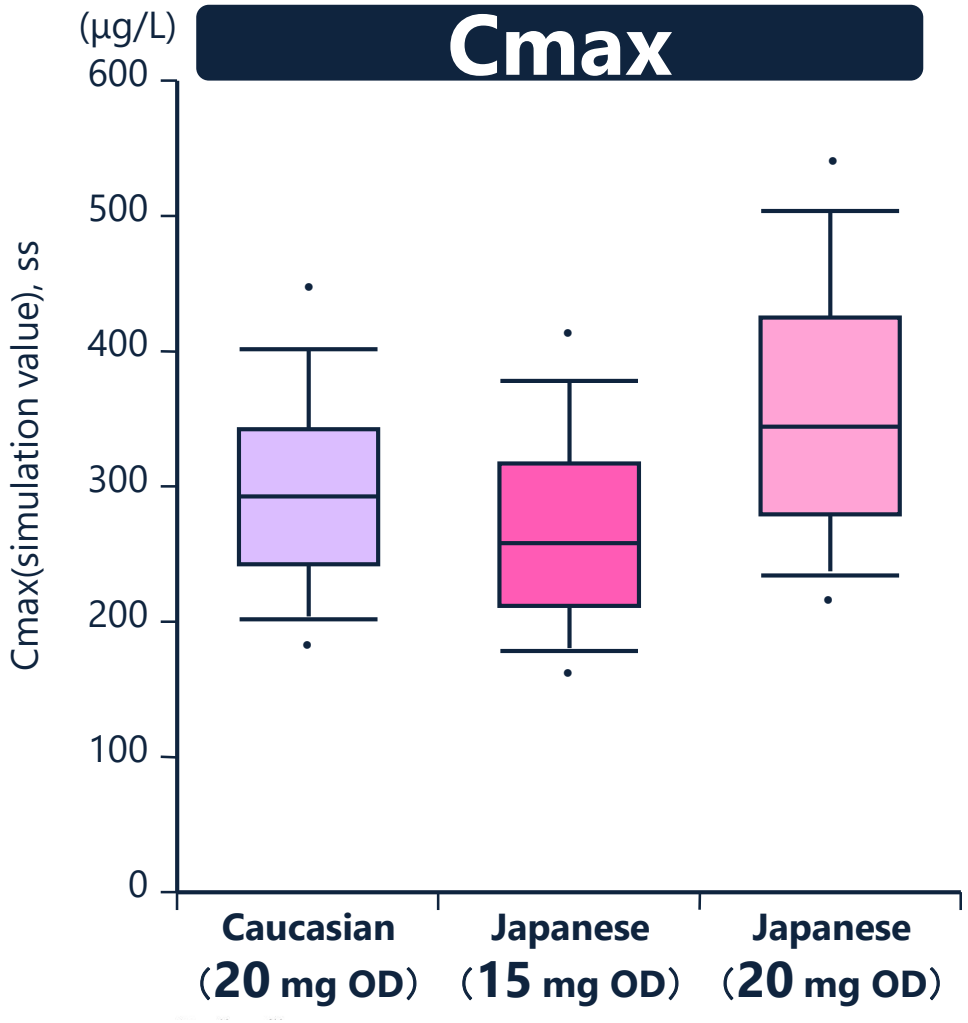
- **Primary Efficacy End Points**: stroke, SE, MI, UAP requiring revascularization, or death from any cause
- **Primary Safety End Points**: major bleeding (ISTH criteria)

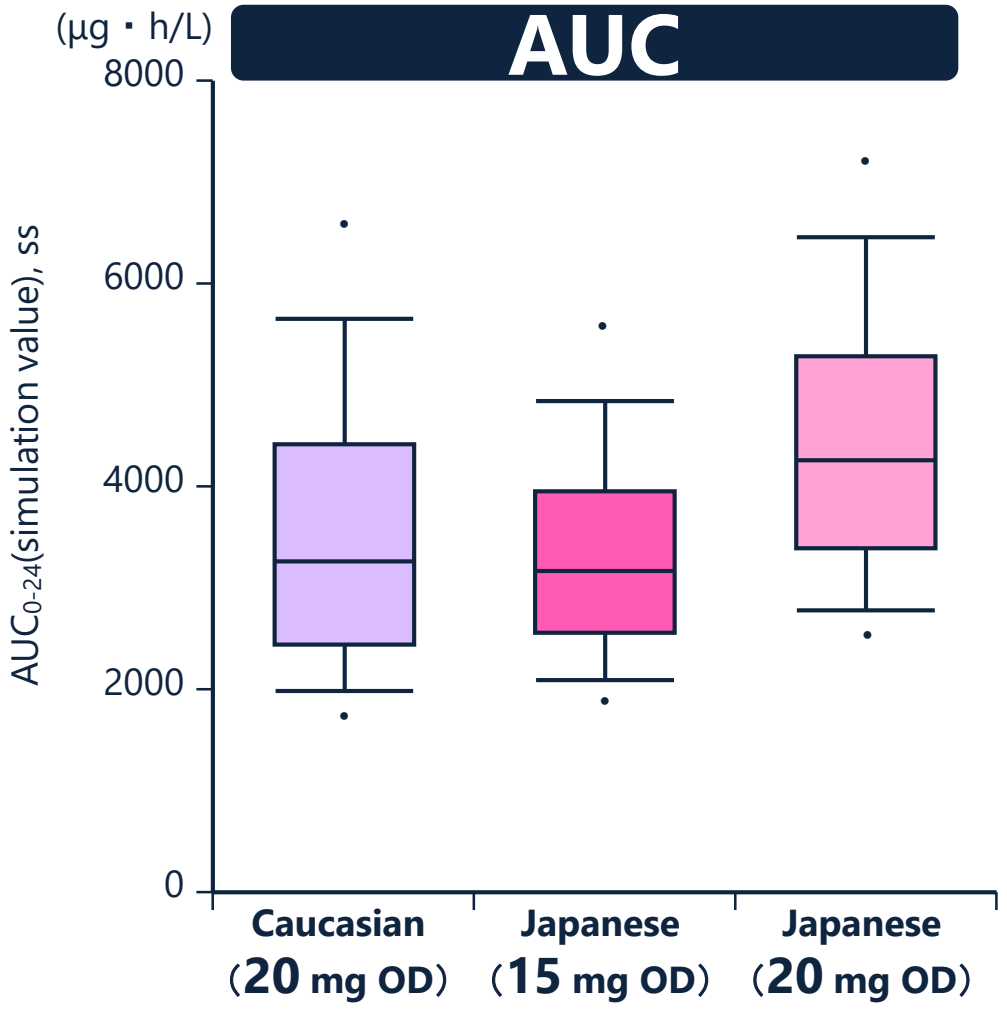
UMIN Clinical Trials Registry number, UMIN000016612. ClinicalTrials.gov number, NCT02642419.

1) Yasuda S, et al. *Int J Cardiol.* 2018. *2*) Tanigawa T, et al. *Drug Metab Pharmacokinet.* 2013.

20 mg/day in Caucasian = 15 mg/day in Japanese - pharmacokinetic / pharmacokinetic investigation -

AFIRE





Tanigawa T, et al. *Drug Metab Pharmacokinet* 2013;28:59-70.

Characteristics of Patients at Baseline

modified ITT population

	Rivaroxaban Monotherapy (N=1107)	Combination Therapy (N=1108)
Age – (yr) mean ± SD	74.3±8.3	74.4±8.2
Male sex – no. (%)	875 (79.0)	876 (79.1)
BMI – (kg/m^2) mean ± SD	24.5±3.7	24.5±3.7
CrCl – (ml/min) mean ± SD	62.8±25.7	61.7±24.0
Current smoker – no. (%)	146 (13.2)	146 (13.2)
Diabetes – no. (%)	461 (41.6)	466 (42.1)
Previous stroke – no. (%)	148 (13.4)	175 (15.8)
Previous MI – no. (%)	384 (34.7)	393 (35.5)
Previous PCI – no. (%)	781 (70.6)	783 (70.7)
Previous CABG – no. (%)	125 (11.3)	127 (11.5)

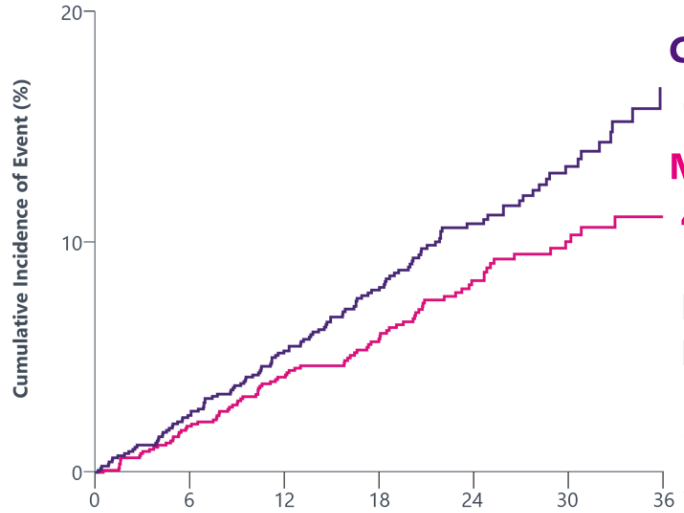
	Rivaroxaban Monotherapy (N=1107)	Combination Therapy (N=1108)
Type of stent – no. /total no. (%)		
DES	500/723 (69.2)	477/721 (66.2)
BMS	171/723 (23.7)	171/721 (23.7)
DES and BMS	19/723 (2.6)	36/721 (5.0)
Unknown	33/723 (4.6)	37/721 (5.1)
Type of AF – no. (%)		
Paroxysmal	596 (53.8)	580 (52.3)
Persistent	164 (14.8)	175 (15.8)
Permanent	347 (31.3)	353 (31.9)
$CHADS_2$ score - median	2	2
CHA_2DS_2 -VASc score - median	4	4
HAS-BLED score - median	2	2
Received Aspirin - no. (%)	8 (0.7)	778 (70.2)
Received $P2Y_{12}$ inhibitor- no. (%)	4 (0.4)	297 (26.8)

Yasuda S, et al. *N Engl J Med. 2019 Sep 19;381(12):1103-1113.*

Results

Kaplan-Meier Estimates of First Occurrence of Primary Efficacy and Safety Events

Primary Efficacy Events



Combination therapy
5.75% per patient-year

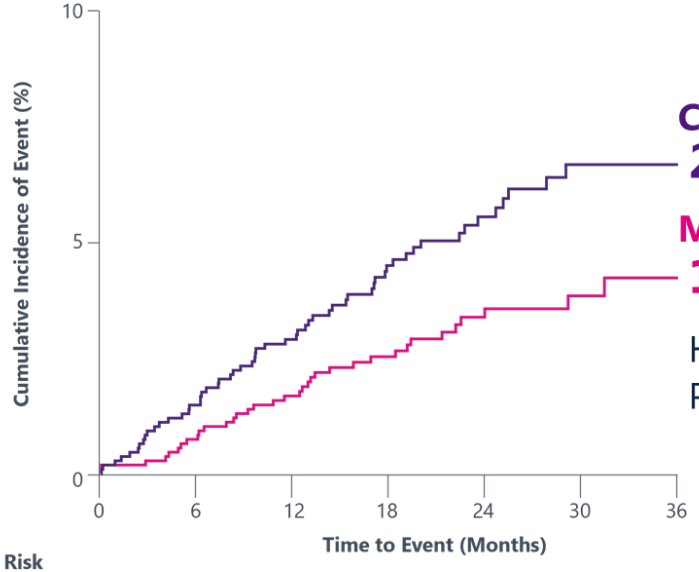
Monotherapy
4.14% per patient-year

HR, **0.72** (**0.55** to **0.95**)
P<0.001 (noninf.)

*In the assessment for **superiority for the primary efficacy end point** (that was not prespecified), the **P value was 0.02.**

No. at Risk							
Rivaroxaban monotherapy	1107	1071	984	774	518	309	89
Combination therapy	1108	1057	962	754	499	292	80

Primary Safety Events



Combination therapy
2.76% per patient-year

Monotherapy
1.62% per patient-year

HR, **0.59** (**0.39** to **0.89**)
P=0.01 (sup.)

No. at Risk							
Rivaroxaban monotherapy	1099	1074	994	786	526	312	89
Combination therapy	1099	1055	962	750	506	294	80

The primary efficacy end point — a composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause

The primary safety end point — major bleeding, as defined by the criteria of the International Society on Thrombosis and Hemostasis

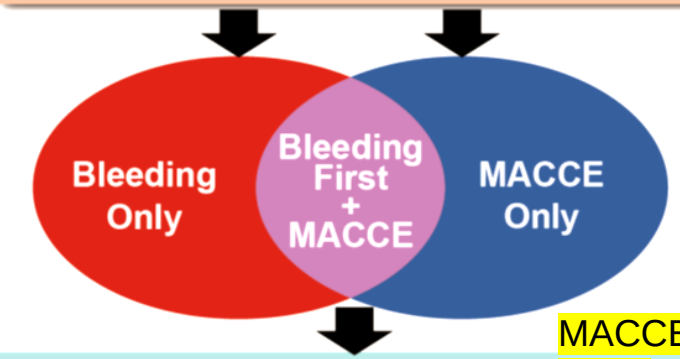
Key message of AFIRE; Our results support the general concept that rivaroxaban monotherapy without antiplatelet therapy is the better approach for patients with AF and stable CAD.

Yasuda S, et al. *N Engl J Med. 2019 Sep 19;381(12):1103-1113 .*

AFIRE
Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease Study

Bleeding and Subsequent Cardiovascular Events and Death in Atrial Fibrillation With Stable Coronary Artery Disease; Insights From the AFIRE Trial

AF Patients with Stable CAD from the AFIRE Study Population

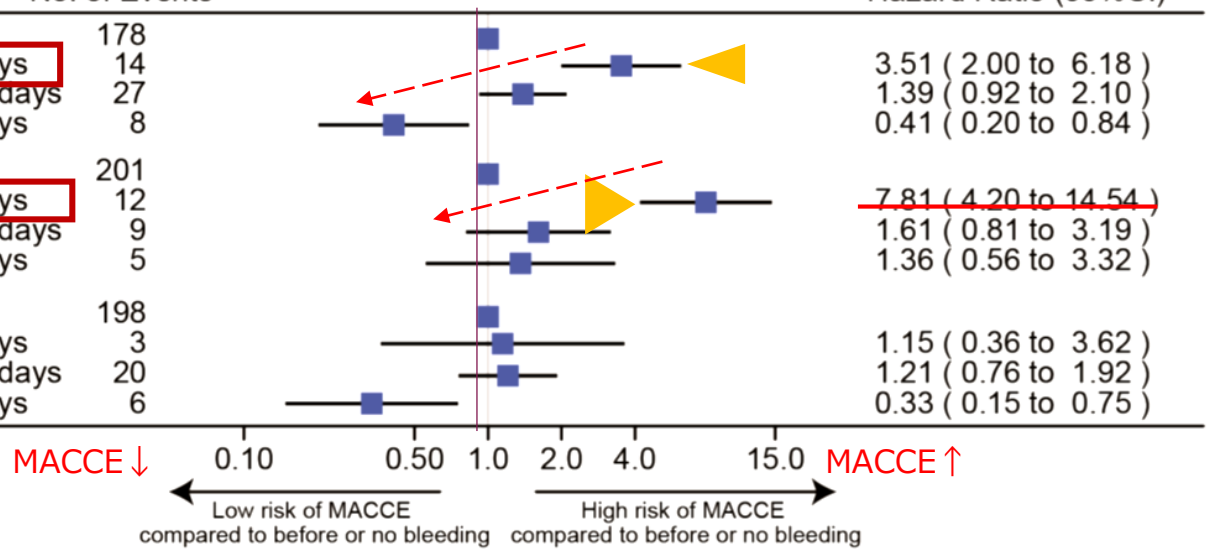


Bleeding Only
Bleeding First + MACCE
MACCE Only

MACCE incidence was higher in pts with bleeding than in pts without (8.38% vs 4.20% per pt-year.

Hazard Ratios for MACCE in Time-Adjusted Multivariate Analysis

Variable		No. of Events	Hazard Ratio (95%CI)
Before or no bleeding (ref.)		178	
After any bleeding	within 0–30 days	14	3.51 (2.00 to 6.18)
	31–365 days	27	1.39 (0.92 to 2.10)
	>365 days	8	0.41 (0.20 to 0.84)
Before or no bleeding (ref.)		201	
After major bleeding	within 0–30 days	12	7.81 (4.20 to 14.54)
	31–365 days	9	1.61 (0.81 to 3.19)
	>365 days	5	1.36 (0.56 to 3.32)
Before or no bleeding (ref.)		198	
After minor bleeding	within 0–30 days	3	1.15 (0.36 to 3.62)
	31–365 days	20	1.21 (0.76 to 1.92)
	>365 days	6	0.33 (0.15 to 0.75)



MACCE within 1 Month after Major Bleeding

High Risk AF Patients with Stable CAD

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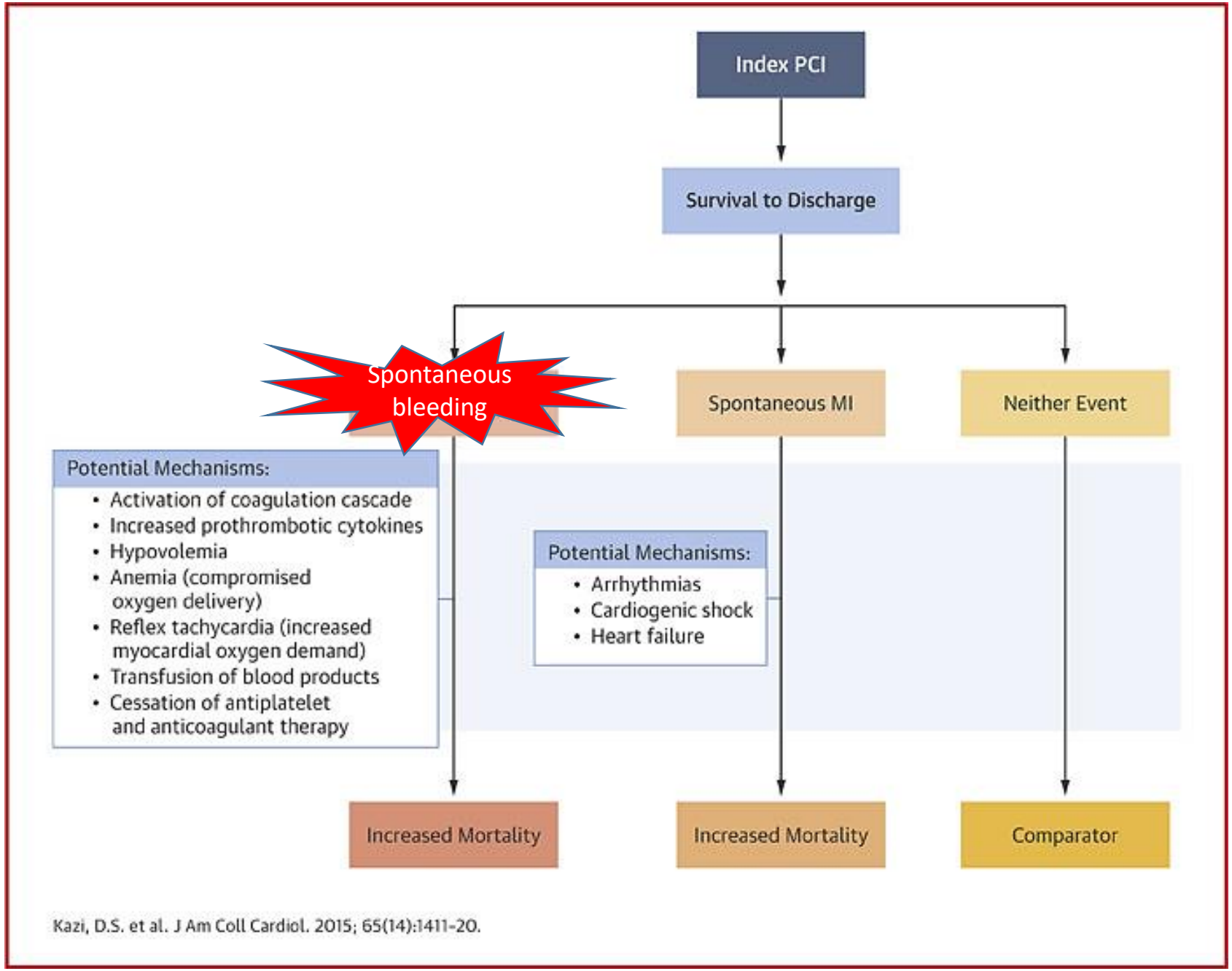
Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease Study

Potential pathogenetic mechanisms for the association between bleeding and CV events

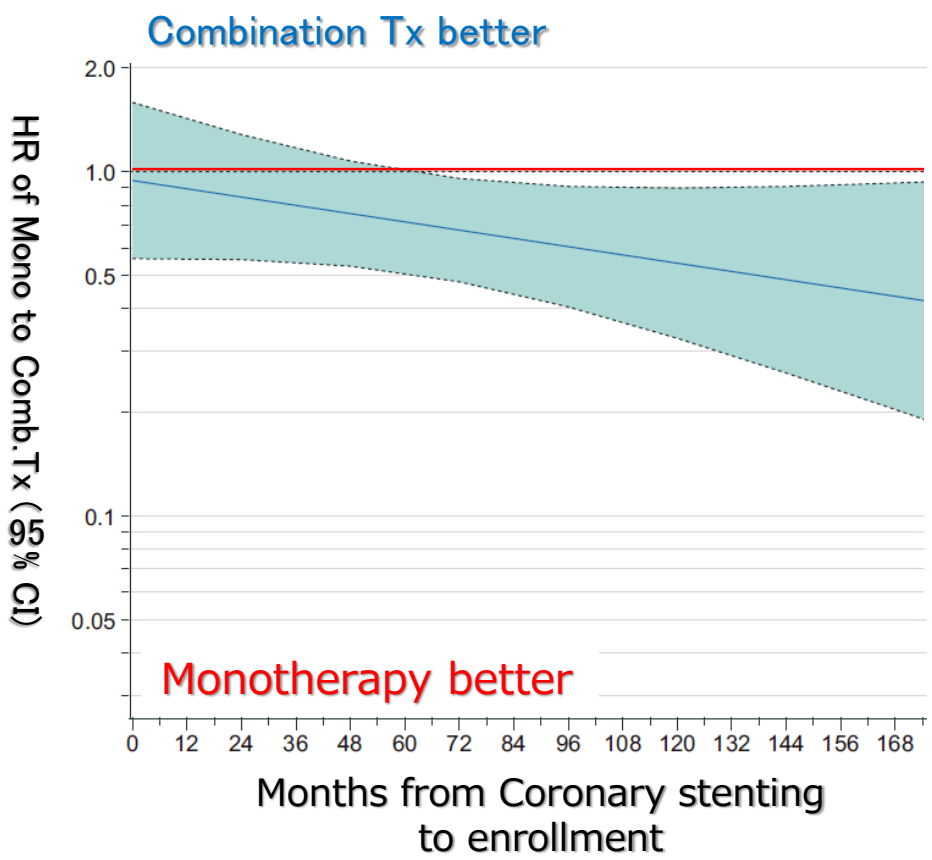


Kazi, D.S. et al. J Am Coll Cardiol. 2015; 65(14):1411-20.

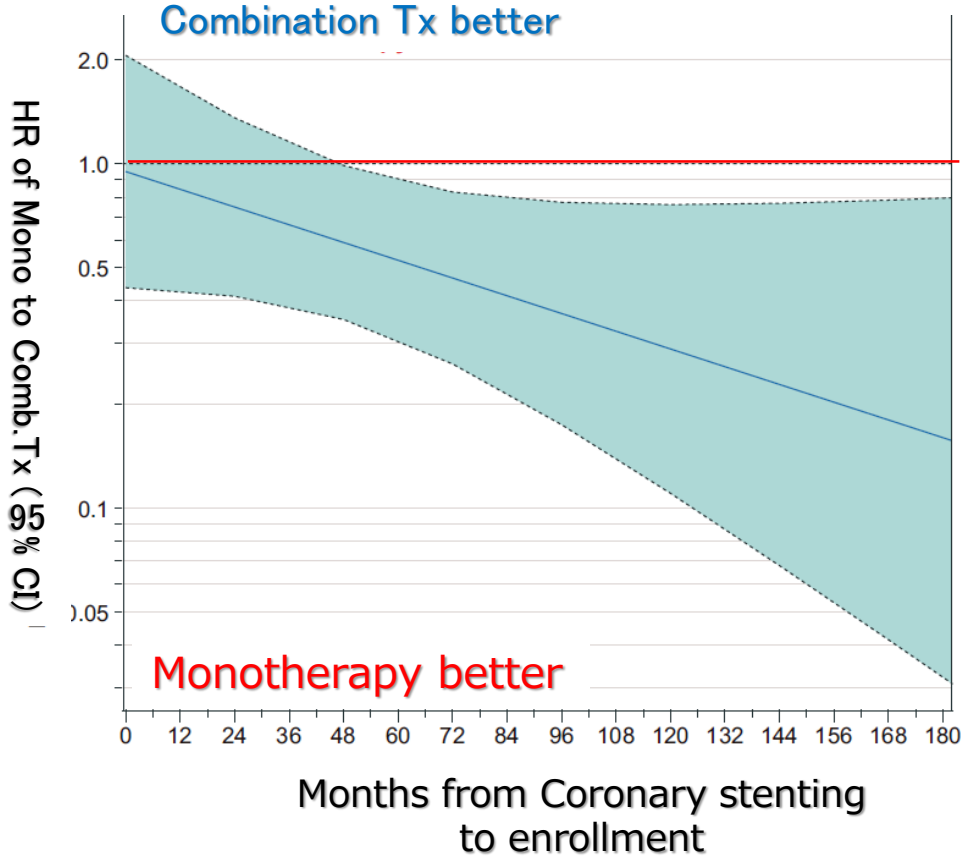
Rivaroxaban Monotherapy in Patients With Atrial Fibrillation After Coronary Stenting

We performed the subgroup analysis of the AFIRE trial examined the benefits of rivaroxaban monotherapy in patients with AF exclusively after coronary stenting in terms of efficacy and safety outcomes and the benefit correlation with time elapsed after coronary stenting. (N=1444 with coronary stenting >1 year before enrollment)

Primary Efficacy Endpoint



Primary Safety Endpoint

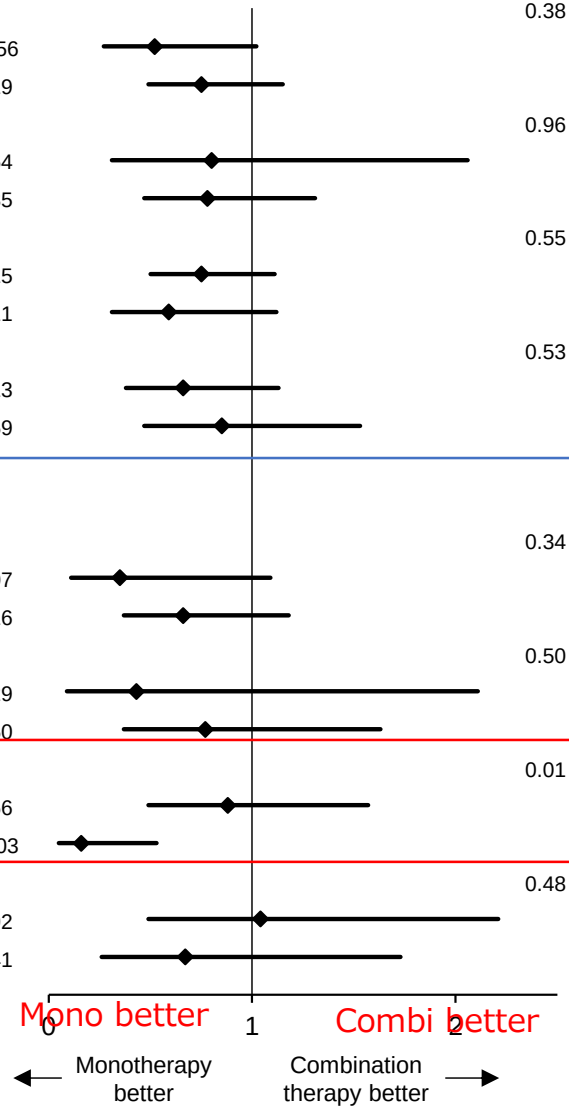


AFIRE
Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease Study

Matoba T, et al. JACC: Cardiovascular Interventions 2021;14:2330-40.

Rivaroxaban monotherapy versus combination therapy according to stent type and lesion site in patients with atrial fibrillation after coronary stent implantation

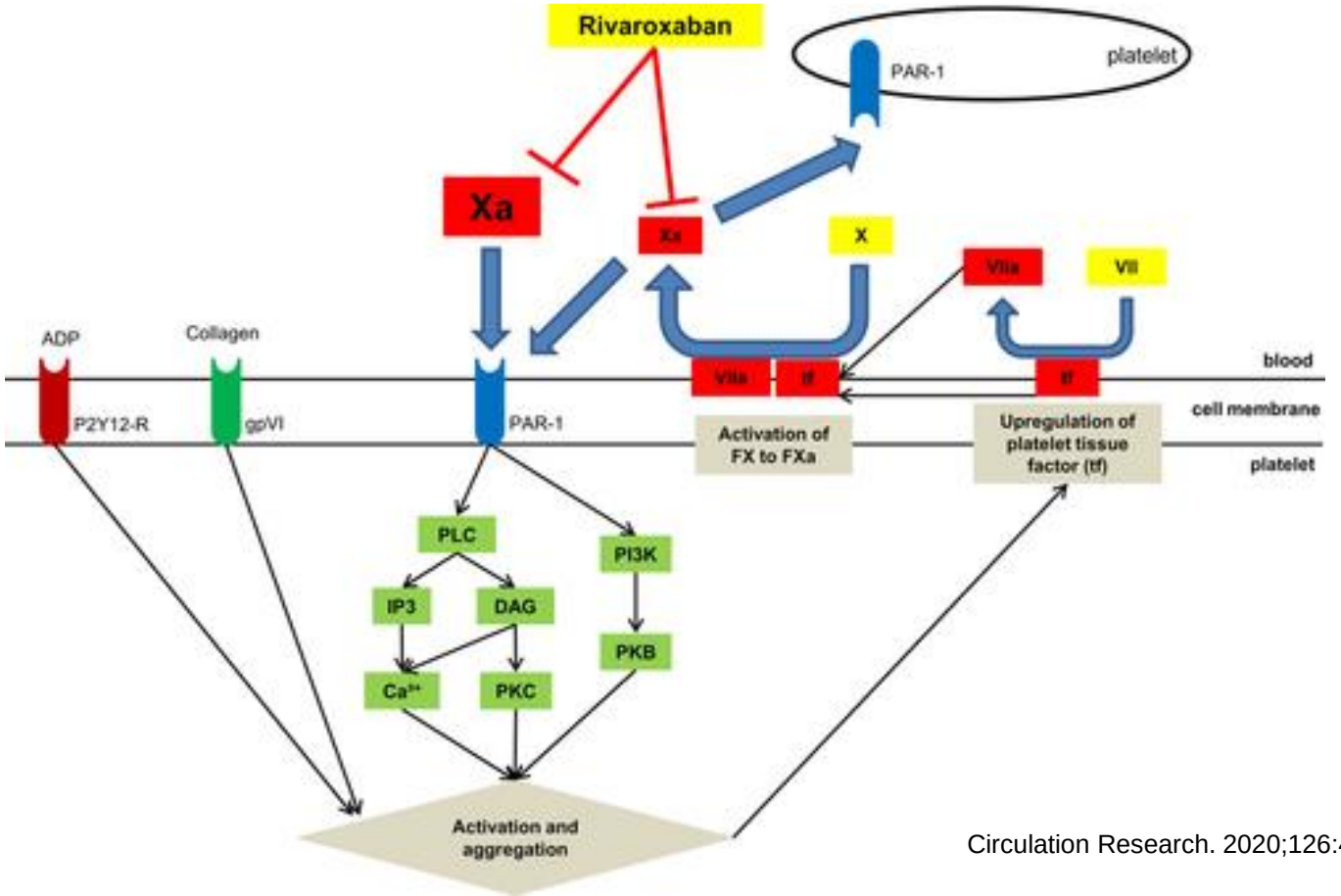
Subgroup	No of patients	Rivaroxaban Monotherapy	Combination Therapy	Hazard ratio	95% CI	P	P for interaction
		Incidence rate, % per patient-year (no.)					
Primary efficacy endpoint Promary Efficacy Endpoint							
Type of stent BMS vs DES							0.38
BMS	342	3.8 (13)	7.4 (25)	0.52	0.27-1.02	0.056	
DES	977	3.9 (38)	5.3 (48)	0.75	0.49-1.15	0.19	
Type of DES DES G1 vs G2							0.96
1st DES	174	4.6 (7)	5.7 (11)	0.80	0.31-2.06	0.64	
2nd DES	623	4.2 (27)	5.4 (31)	0.78	0.47-1.31	0.35	
Number of vessels N.of vessels							0.55
1VD	1020	4.3 (42)	5.7 (57)	0.75	0.50-1.11	0.15	
MVD / LMTD	382	4.0 (15)	6.8 (24)	0.59	0.31-1.12	0.11	
Lesion site Lesion site							0.53
LAD	551	4.0 (22)	6.1 (32)	0.66	0.38-1.13	0.13	
RCA / LCX	469	4.6 (20)	5.3 (25)	0.85	0.47-1.53	0.59	
Primary safety endpoint Primary Safety Endpoint							
Type of stent BMS vs DES							0.34
BMS	342	1.1 (4)	3.3 (11)	0.35	0.11-1.09	0.07	
DES	977	2.0 (19)	3.0 (27)	0.66	0.37-1.18	0.16	
Type of DES DES G1 vs G2							0.50
1st DES	174	1.3 (2)	3.1 (6)	0.43	0.09-2.11	0.29	
2nd DES	623	2.0 (13)	2.6 (15)	0.77	0.37-1.63	0.50	
Number of vessels N.Of vessels							0.01
1VD	1020	2.1 (21)	2.4 (24)	0.88	0.49-1.57	0.66	
MVD / LMTD	382	0.8 (3)	5.2 (18)	0.16	0.05-0.53	0.003	
Lesion site Lesion site							0.48
LAD	551	2.6 (14)	2.5 (13)	1.04	0.49-2.21	0.92	
RCA / LCX	469	1.6 (7)	2.4 (11)	0.67	0.26-1.73	0.41	



AFIRE
Atrial Fibrillation and Ischemic events with Rivaroxaban in patiEnts with stable coronary artery disease Study

Ishi M, Akao M, et al. In submission

Rivaroxaban Reduces Arterial Thrombosis by Inhibition of FXa-Driven Platelet Activation via Protease Activated Receptor-1

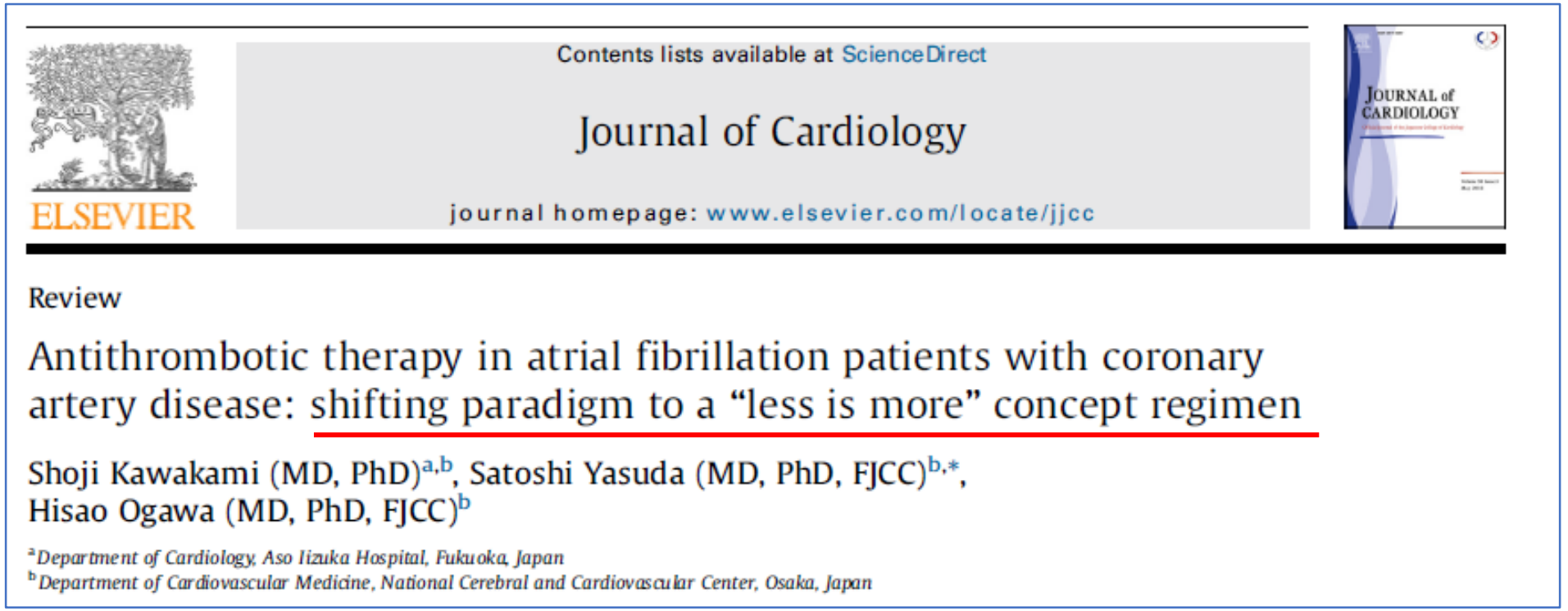


Circulation Research. 2020;126:486–500..

Tobias Petzold. Circulation Research. Rivaroxaban Reduces Arterial Thrombosis by Inhibition of FXa-Driven Platelet Activation via Protease Activated Receptor-1, Volume: 126, Issue: 4, Pages: 486-500, DOI: (10.1161/CIRCRESAHA.119.315099)

Conclusion;

- The clinical need for antithrombotic therapy with risk stratification for treatment duration and composition has been increasing, in particular for Asian population characterized as a higher risk of bleeding events and lower risk of ischemic events.
- Antithrombotic therapy for AF and CAD has been shifting to a **“less is more”** concept regimen.



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Review

Antithrombotic therapy in atrial fibrillation patients with coronary artery disease: shifting paradigm to a “less is more” concept regimen

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Kawakami S, Yasuda S, et al. *J Cardiol*. 2020 Jul;76(1):35-43.