SCA et FA: Nouveautés

Anticoagulation 2019: Cancer, Coronaires et Interactions

SSVQ 22 mars 2019

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Faculté de médecine
Université de Montréal et du monde.

Déclaration des conflits d'intérêt potentiels

Jean-François Tanguay, MD, FRCPC, FCCS, FACC, FAHA, FESC

- **Honoraires/consultant**: Abbott Vascular, Actelion, Astra-Zeneca, Bayer, Novartis.
- **Recherche clinique**: Abbott Vascular, Actelion, Astra-Zeneca, Bayer, Biosensors, Idorsia, Novartis.
- **Autres**: Research grants CIHR, HSFC, NIH, Co-Chair CCS Guidelines on Antiplatelet Therapy.
- **Conférencier**: Abbott Vascular, Actelion, Astra-Zeneca, Bayer, Novartis, Servier.

Objectifs

À la fin de cette activité, vous serez en mesure de :

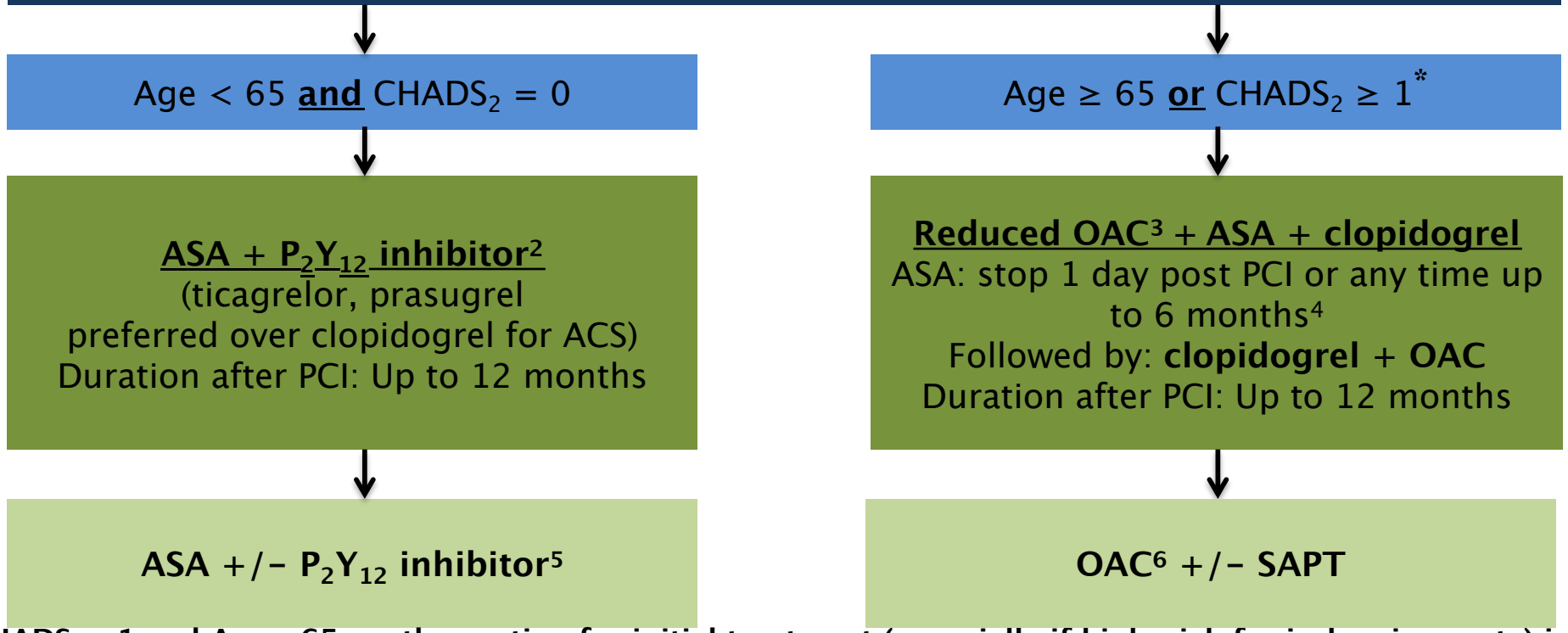
- **Discuter de l'importance de la thérapie antithrombotique en prévention secondaire post SCA.**
- **Évaluer l'interaction entre les thérapies antiplaquettaires et anticoagulantes chez les patients avec SCA et FA.**
- **Réfléchir comment appliquer les nouvelles données d'études randomisées utilisant un anticoagulant en association avec l'ASA ou la thérapie antiplaquettaire double.**

Cas #1

64 ANS
STEMI ANTÉRIEUR DILATÉ AVEC 1 DES
TICAGRELOR + ASA
AU CONGÉ ‘FA DE NOVO’ ET IVG
CHADS2 = 1 (CHF)

QUE FAIRE?

AF and PCI for ACS or high-risk[1] elective PCI



***If $CHADS_2$ =1 and Age< 65 another option for initial treatment (especially if high-risk for ischemic events) is DAPT alone using ASA+ticagrelor or ASA+prasugrel, similar to the recommendation for the $CHADS_2$=0 patient**

1. A PCI is considered high-risk based on clinical and angiographic features such as: diabetes, prior ACS, chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multi-vessel coronary artery disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold implantation.
2. Ticagrelor and prasugrel are recommended in ACS patients, whereas clopidogrel is recommended for elective PCI.
3. Regimens evaluated in the context of triple therapy include rivaroxaban 2.5 mg BID or warfarin. If warfarin is to be used, recommended INR target is 2.0-2.5. OAC options evaluated in the context of a dual pathway strategy include rivaroxaban 15 mg daily (plus clopidogrel) or dabigatran 110 mg/150 mg BID (plus clopidogrel).
4. DAPT will have been started as part of ACS management or prior to high risk elective PCI. ASA may be discontinued as early as the day following PCI or it can be continued longer term (eg. 1, 3 or maximum 6 months after PCI). The timing of when to discontinue ASA will vary, depending on the individual patient's ischemic and bleeding risk.
5. A P_2Y_{12} inhibitor can be added to ASA if high-risk clinical or angiographic features of ischemic events and low risk of bleeding.
6. The dose of OAC beyond 1 year after PCI should be standard stroke prevention doses as per the CCS Atrial Fibrillation Guidelines. Single antiplatelet therapy with either ASA or clopidogrel may be added to OAC if high-risk clinical or angiographic features of ischemic events and low risk of bleeding.

AF: atrial fibrillation; ACS: acute coronary syndrome; ASA: acetylsalicylic acid; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy

Dual Pathway and Triple Therapy Regimens Evaluated in Clinical Trials

Dual Pathway	Triple Therapy
1. Rivaroxaban 15 mg daily + clopidogrel 75 mg daily[1]	1. Rivaroxaban 2.5 mg BID + ASA 81 mg daily + clopidogrel 75 mg daily[1]
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3. Warfarin + clopidogrel 75 mg daily[3]	

*In the RE-DUAL PCI trial, the 110 mg BID dabigatran dose was associated with a trend to a higher risk of death or thrombotic events (11% versus 8.5%, hazard ratio 1.30, 95% CI 0.98-1.73, P=0.07). This risk was not observed with the 150 mg BID dose (7.9% versus 7.9%, hazard ratio 0.97, 95% CI 0.68-1.39, P=0.44). Therefore, in patients who are not at high risk of bleeding, the dabigatran 150 mg BID dose, when used in combination with clopidogrel 75 mg daily (ASA omitted), may be preferable.

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AF and PCI for ACS or high-risk[1] elective PCI

Age < 65 **and** $CHADS_2 = 0$	Age ≥ 65 **or** $CHADS_2 \geq 1$*
ASA + P_2Y_{12} inhibitor[2] (ticagrelor, prasugrel preferred over clopidogrel for ACS) Duration after PCI: Up to 12 months	**Reduced OAC[3] + ASA + clopidogrel** ASA: stop 1 day post PCI or any time up to 6 months[4] Followed by: **clopidogrel + OAC** Duration after PCI: Up to 12 months
ASA +/- P_2Y_{12} inhibitor[5]	**OAC[6] +/- SAPT**

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QUE FAIRE?

Risque ischémique vs thromboembolique vs saignement

ASA+ticagrelor 6-12 mois puis NACO + ASA

Cas #2

82 ANS

FA DE LONGUE DATE SOUS APIXABAN 2.5MG BID (POIDS= 55 Kg)

NSTEMI AVEC TROPONINE 850

DILATATION AVEC 4 STENTS DONT 1 KISSING IVA-D1

LE CARDIOLOGUE AIMERAIT TICAGRELOR X12 mois ET MEME 24-36 MOIS… (PEGASUS?)

QUE FAIRE?

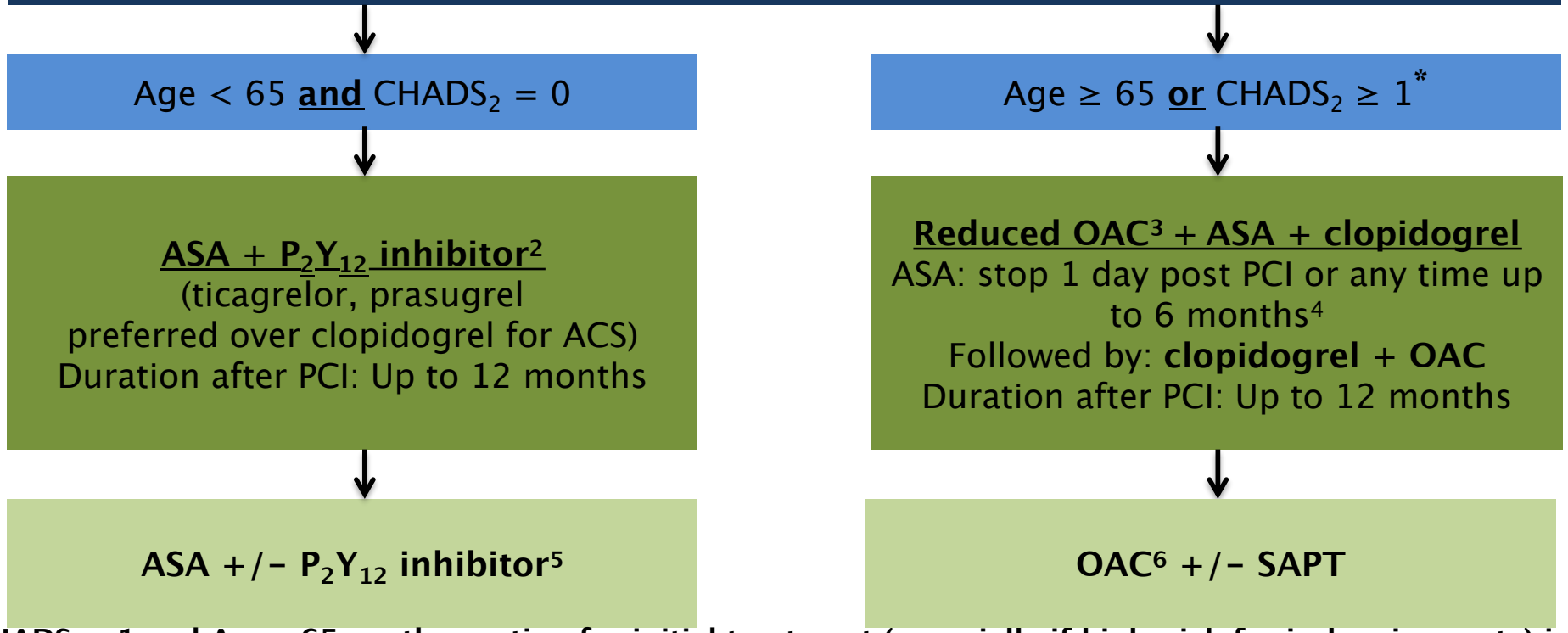
High-risk clinical and angiographic features for thrombotic events

Clinical	Angiographic
Prior myocardial infarction or troponin positive acute coronary syndrome	Multiple stents (≥ 3 stents implanted, ≥ 3 lesions stented)
Diabetes Mellitus treated with oral hypoglycemics or insulin+	Long lesion length (> 60 mm total stent length)
Chronic kidney disease (creatinine clearance ≤ 60 ml/min)	Complex lesions (bifurcation treated with 2 stents, stenting of chronic occlusion)
Prior stent thrombosis	Left main or proximal LAD stenting
	Multivessel PCI

Factors associated with increased bleeding risk

1.	Need for OAC in addition to DAPT
2.	Advanced age (> 75 years)
3.	Frailty
4.	Anemia with hemoglobin < 110 g/dL
5.	Chronic renal failure (creatinine clearance < 40 mL/min)
6.	Low Body Weight (< 60 kg)
7.	Hospitalization for bleeding within last year
8.	Prior stroke/intracranical bleed
9.	Regular need for NSAIDS or prednisone

AF and PCI for ACS or high-risk[1] elective PCI



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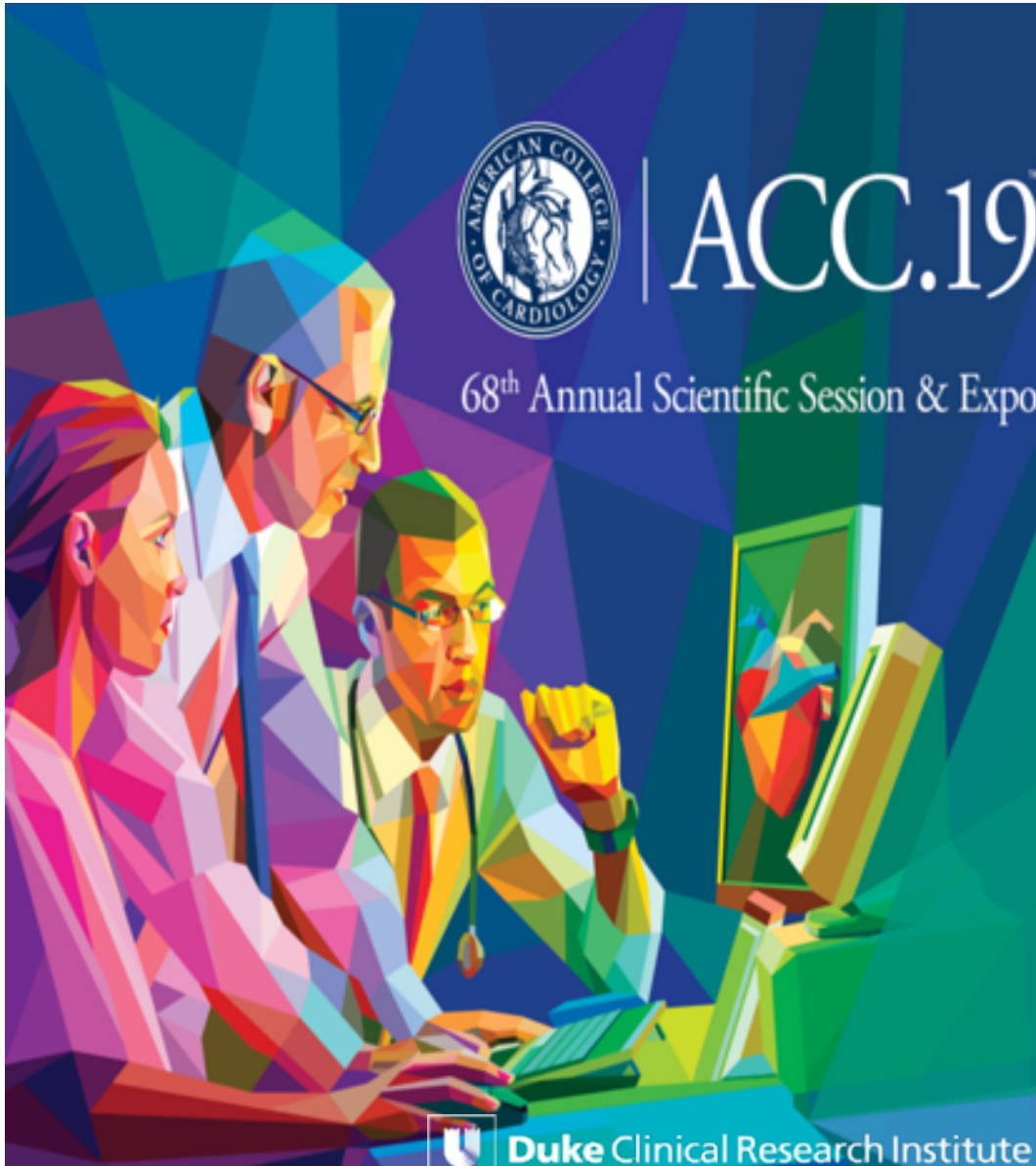


ACC.19

68th Annual Scientific Session & Expo

Apixaban vs VKA and Aspirin vs Placebo in Patients with Atrial Fibrillation and ACS/PCI: The AUGUSTUS Trial

Renato D. Lopes, MD, PhD
on behalf of the AUGUSTUS Investigators

Duke Clinical Research Institute

Bristol-Myers Squibb

Pfizer

NEW ORLEANS
MARCH 16 - 18
2019

Two Independent Hypotheses

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

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

Duke Clinical Research Institute

Trial Design

Augustus

INCLUSION
- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned $P2Y_{12}$ inhibitor for ≥6 months

Randomize
n=4600
patients

EXCLUSION
- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, moderate / severe mitral stenosis)

Apixaban 5 mg BID
Apixaban 2.5 mg BID in selected patients

Open Label

VKA
(INR 2–3)

Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

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

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

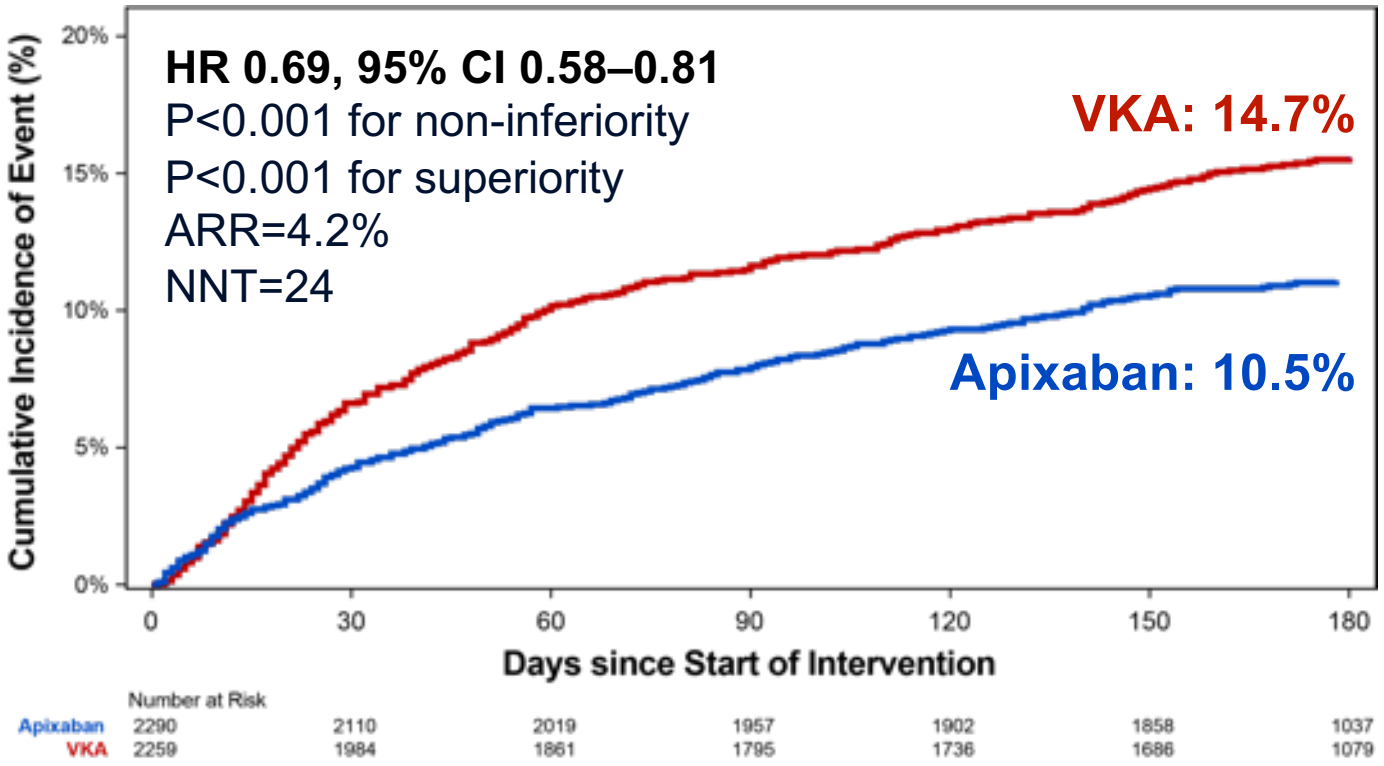
Primary outcome: ISTH major / CRNM bleeding
Secondary outcome(s): death / hospitalization, death / ischemic events

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

Baseline Characteristics

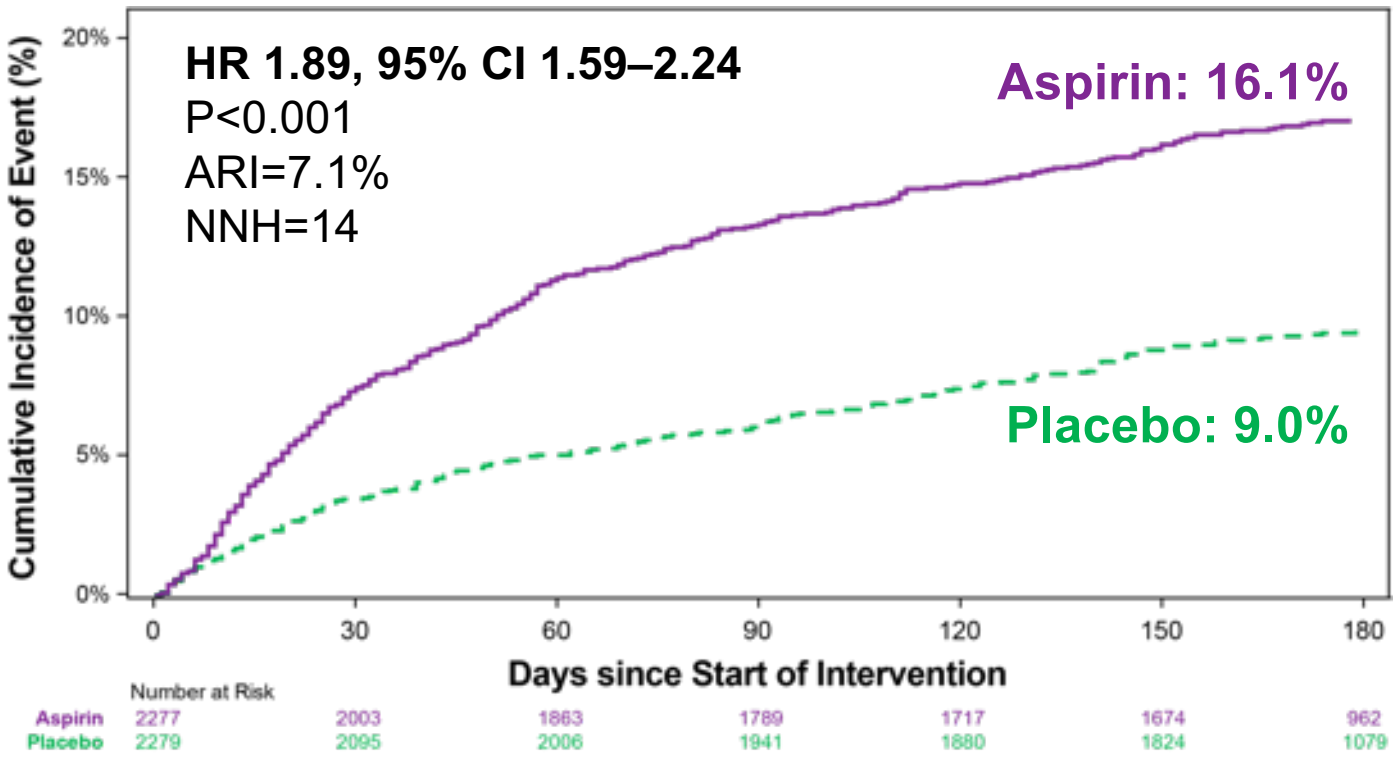
	Total (N=4614)
Age, median (25th, 75th), years	70.7 (64.2, 77.2)
Female, %	29.0
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)
HAS-BLED score, mean (SD)	2.9 (0.9)
Prior OAC, %	49.0
$P2Y_{12}$ inhibitor, %	
Clopidogrel	92.6
Qualifying index event, %	
ACS and PCI	37.3
ACS and no PCI	23.9
Elective PCI	38.8

Major / CRNM Bleeding
Apixaban vs. VKA



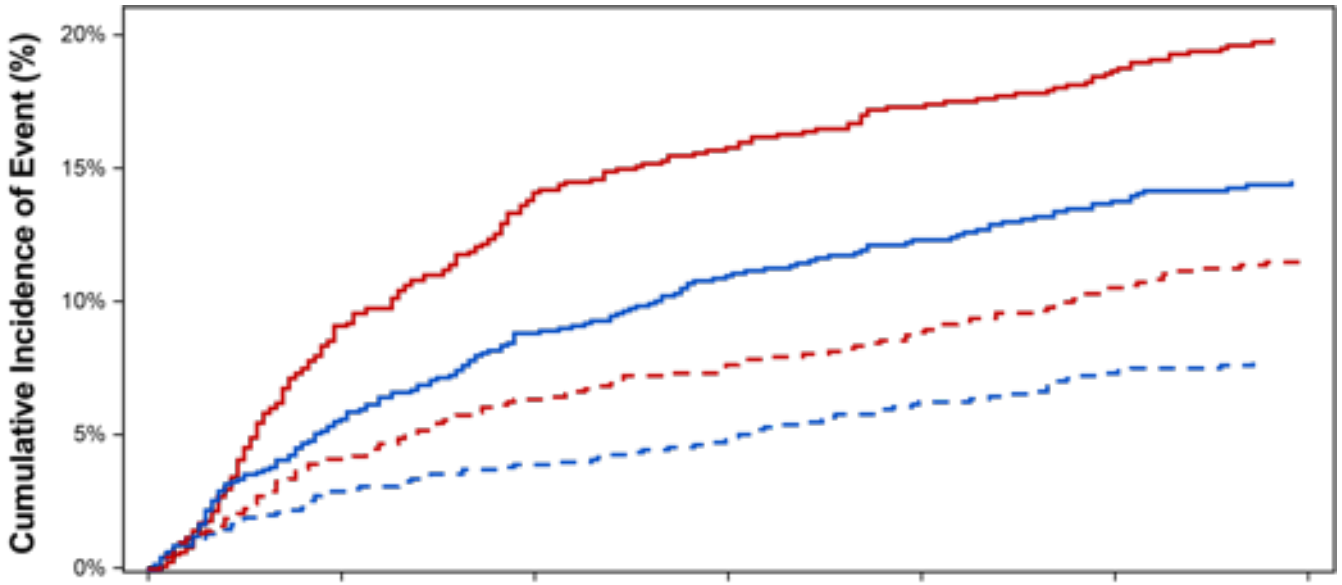
ARR: absolute risk reduction
NNT: number needed to treat

Major / CRNM Bleeding
Aspirin vs. Placebo



ARI: absolute risk increase
NNH: number needed to harm

Major / CRNM Bleeding



Number at Risk							
Apixaban and Aspirin	1145	1036	975	937	903	880	485
Apixaban and Placebo	1143	1075	1044	1007	975	947	536
VKA and Aspirin	1123	962	881	838	800	776	467
VKA and Placebo	1126	1007	947	917	883	851	528

VKA + Aspirin (18.7%)

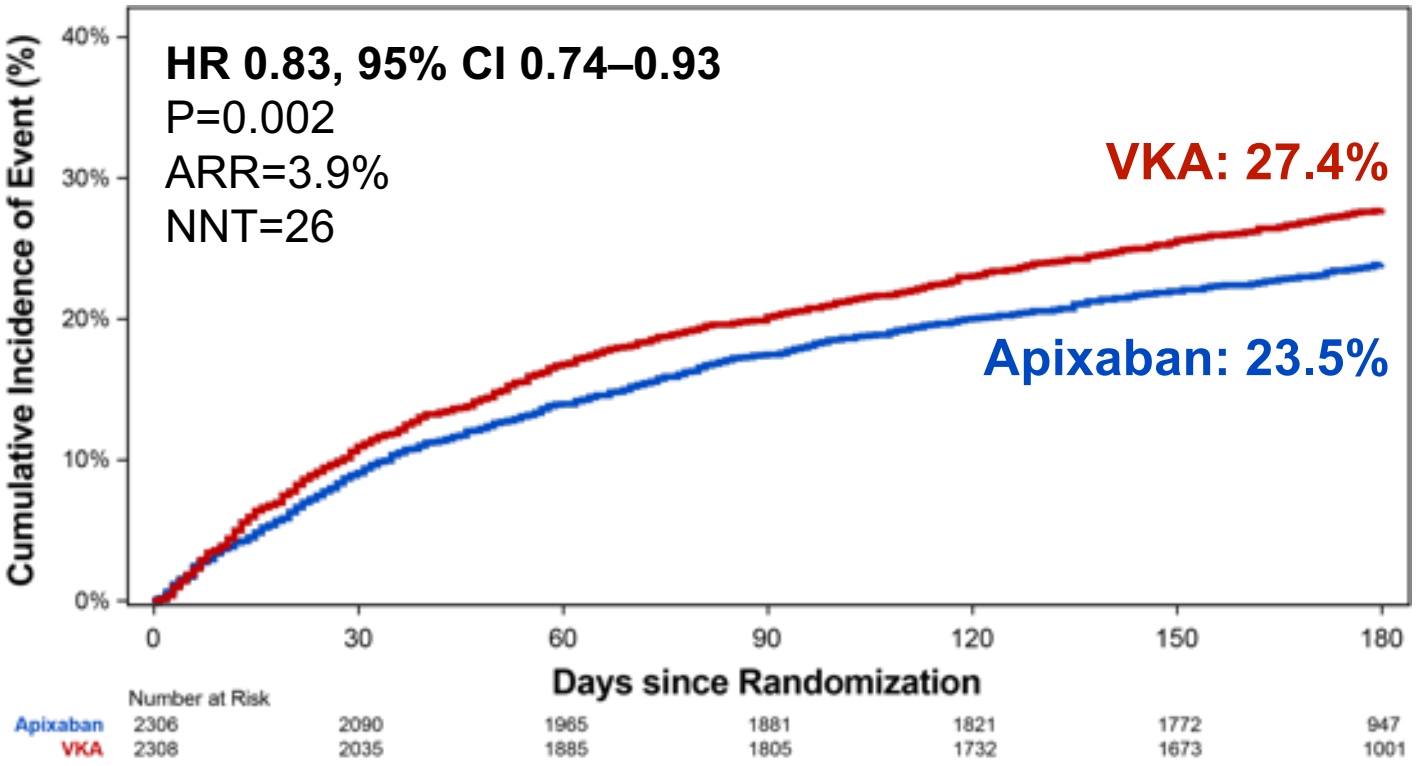
Apixaban + Aspirin (13.8%)

VKA + Placebo (10.9%)

Apixaban + Placebo (7.3%)

Apixaban + Placebo vs. VKA + Aspirin:
11.4% absolute risk reduction (NNT=9)

Death / Hospitalization
Apixaban vs. VKA



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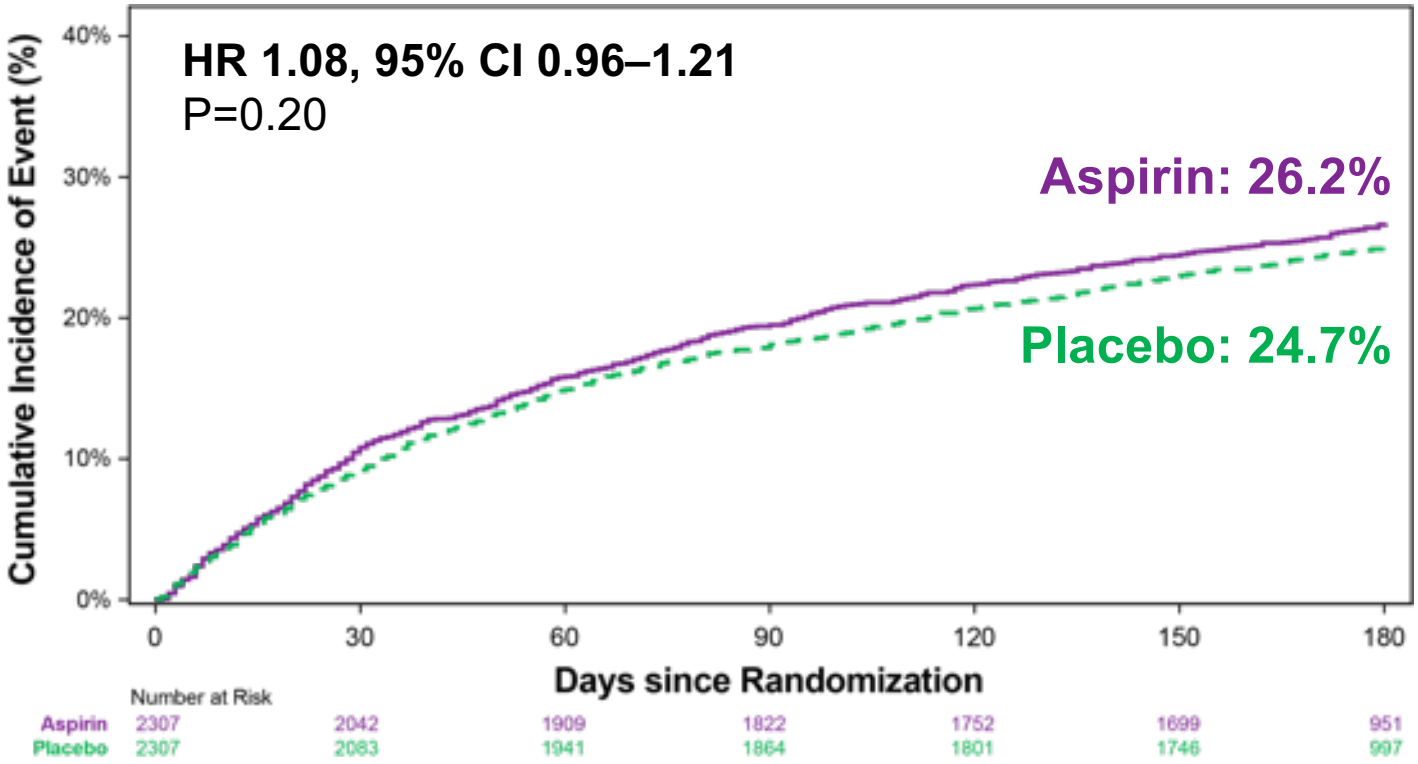
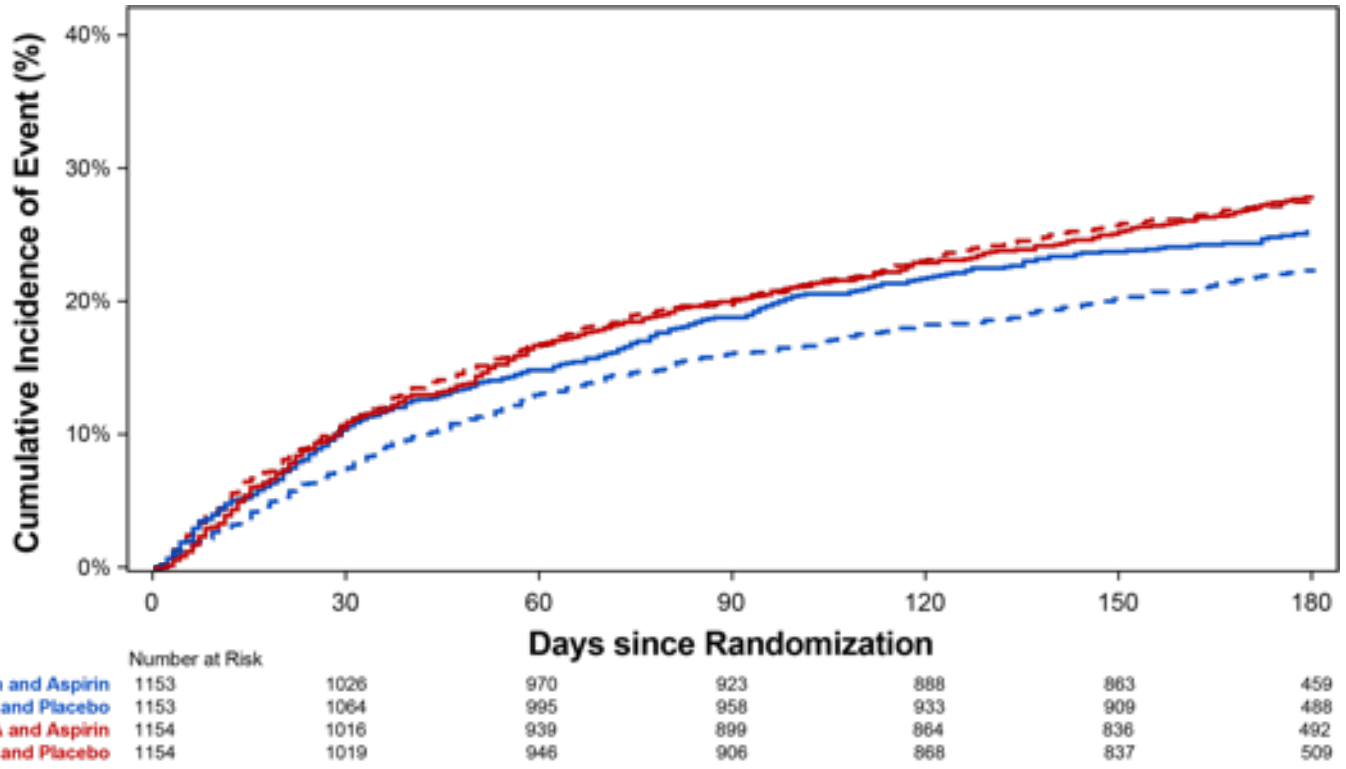
Death / Hospitalization
Aspirin vs. Placebo



Death / Hospitalization



Number at Risk							
Apixaban and Aspirin	1153	1026	970	923	888	863	459
Apixaban and Placebo	1153	1064	995	958	933	909	488
VKA and Aspirin	1154	1016	939	899	864	836	492
VKA and Placebo	1154	1019	946	906	868	837	509

VKA + Aspirin (27.5%)
VKA + Placebo (27.3%)
Apixaban + Aspirin (24.9%)
Apixaban + Placebo (22.0%)

Apixaban + Placebo vs. VKA + Aspirin:
5.5% absolute risk reduction (NNT=18)

Ischemic Outcomes
Apixaban vs. VKA

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

Ischemic Outcomes
Aspirin vs. Placebo

Endpoint	Aspirin (N=2307)	Placebo (N=2307)	HR (95% CI)
Death / Ischemic Events (%)	6.5	7.3	0.89 (0.71–1.11)
Death (%)	3.1	3.4	0.91 (0.66–1.26)
CV Death (%)	2.3	2.5	0.92 (0.63–1.33)
Stroke (%)	0.9	0.8	1.06 (0.56–1.98)
Myocardial Infarction (%)	2.9	3.6	0.81 (0.59–1.12)
Definite or Probable Stent Thrombosis (%)	0.5	0.9	0.52 (0.25–1.08)
Urgent Revascularization (%)	1.6	2.0	0.79 (0.51–1.21)
Hospitalization (%)	25.4	23.4	1.10 (0.98–1.24)

Conclusion

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a vitamin K antagonist, aspirin, or both

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

Renato D. Lopes, M.D., Ph.D., Gretchen Heizer, M.S., Ronald Aronson, M.D., Amit N. Vora, M.D., M.P.H., Tyler Massaro, Ph.D., Roxana Mehran, M.D., Shaun G. Goodman, M.D., Stephan Windecker, M.D., Harald Darius, M.D., Jia Li, Ph.D., Oleg Averkov, M.D., Ph.D., M. Cecilia Bahit, M.D., Otavio Berwanger, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Ziad Hijazi, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Peter Sinnaeve, M.D., Ph.D., Robert F. Storey, M.D., Holger Thiele, M.D., Dragos Vinereanu, M.D., Ph.D., Christopher B. Granger, M.D., and John H. Alexander, M.D., M.H.S., for the AUGUSTUS Investigators*

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Conclusions

À la fin de cette activité, vous êtes en mesure de :

- **Discuter de l'importance de la thérapie antithrombotique en prévention secondaire post SCA.**
- **Évaluer l'interaction entre les thérapies antiplaquettaires et anticoagulantes chez les patients avec SCA et FA.**
- **Réfléchir comment appliquer les nouvelles données d'études randomisées utilisant un anticoagulant en association avec l'ASA ou la thérapie antiplaquettaire double.**