The Role of Direct Oral Anticoagulants (DOACs) in Stable Coronary Disease

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Disclosure(s)

Dr. Pragnesh P. Parikh, faculty for this educational activity, has no relevant financial relationships with ineligible companies* to disclose, and have indicated that the presentations or discussions will not include off-label or unapproved product usage.

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Learning Objectives

Review the clinical data regarding the use of direct oral anticoagulants in different patient populations with coronary disease

Summarize the available data on the use of direct oral anticoagulants periprocedurally in patients undergoing percutaneous coronary intervention (PCI)

Discuss guideline recommendations and current place in therapy

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Case

A 66 year-old male with hypertension, diabetes, peripheral vascular disease, and diabetes presents to establish care. He has had two prior heart attacks, most recently 4 years ago. He has stopped smoking, and he has optimized his lifestyle, including diet and exercise. His blood pressure and cholesterol have both been optimized. He asks if there is anything more that can be done to lower his risk of future heart attack.

A. Increase aspirin to 325 mg daily
B. Add clopidogrel 75 mg daily
C. Add warfarin with goal INR 1.5-2
D. Add warfarin with goal INR 2-3
E. Add rivaroxaban 2.5 mg twice daily

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General Principles

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Chronic coronary disease (CCD)

Obstructive and nonobstructive CAD

With or without previous myocardial infarction (MI) or revascularization

Ischemic heart disease diagnosed only by noninvasive testing

Chronic angina syndromes with varying underlying causes

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Epidemiology in the US

20.1 million live with CCD

11.1 million have chronic stable angina pectoris

Despite an approximate 25% overall relative decline in death from coronary heart disease (CHD) over the past decade, it remains the leading cause of death in the United States and worldwide

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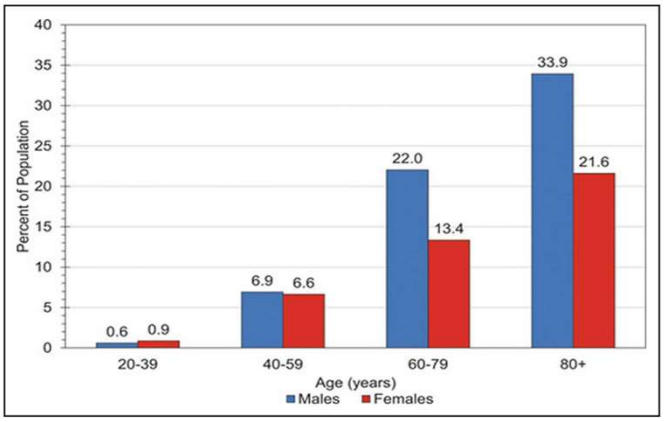
US Prevalence of CHD per 100,000, by Age and Sex (NHANES 2015 to 2018)



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Stable Atherosclerosis

One-quarter (200,000) of all MIs occur among the 8.8 million with CCD who have had a previous MI

Risk of recurrent ischemic events within 4 years

- Prior ischemic event: 18.3%
- Stable coronary, cerebrovascular, or peripheral artery disease: 12.2%

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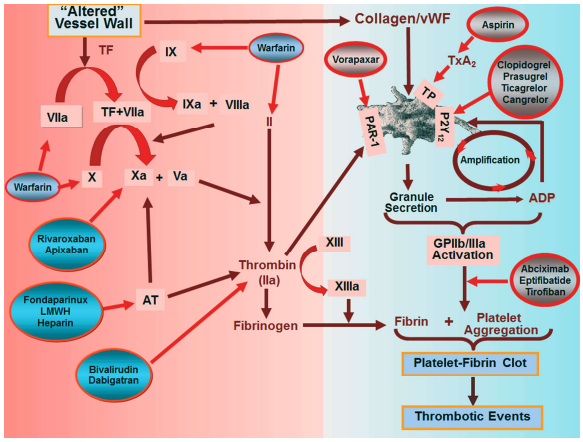
Pathophysiology

3 major clinically relevant pathways

- COX-1 (cyclooxygenase-1) → Aspirin
- ADP-P2Y$_{12}$ → Clopidogrel, ticagrelor, and prasugrel
- Xa-Thrombin → Direct oral anticoagulants (DOACs)



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Secondary Prevention

Aspirin 81 mg
- 19% relative risk reduction of major adverse cardiovascular events (MACE)

Aspirin 325 mg
- No significant difference in MACE or bleeding
- 41.6% assigned to take 325 mg daily switched to 81 mg daily

Clopidogrel plus aspirin
- No significant difference in MACE or bleeding

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Vitamin K antagonists (VKA)

Superior to aspirin alone (32% risk reduction)

Substantially elevated bleeding risk (2.71 relative risk)

Poor compliance (63.7%)

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Dabigatran

First DOAC to gain Food and Drug Administration approval

Competitive direct thrombin inhibitor

150 mg twice daily (110 mg twice daily with $P2Y_{12}$ inhibitor)

Renal Dosing
- CrCl 15-30 mL/minute: 75 mg twice daily
- CrCl ≤15 mL/minute: Not recommended
- Dialyzable

Hepatic Dosing: No dose adjustment

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Dabigatran

Time to peak 1-2 hours

Half-life
- Adults: 12-17 hours
- Mild-moderate renal impairment: 15-18 hours
- Severe renal impairment: 28 hours

Reversal: Idarucizumab

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Rivaroxaban

First direct factor Xa inhibitor

20 mg daily (15 mg daily with $P2Y_{12}$ inhibitor)

Renal Dosing
- CrCl 15-50 mL/min: 15 mg daily
- CrCl <15 mL/min: avoid use
- Not dialyzable

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Rivaroxaban

Time to peak 2-4 hours

Half life:
- Adults 5-12 hours
- Elderly 11-13 hours

Reversal agent: Andexanet alfa or 4-factor non-activated PCC

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Apixaban

Direct factor Xa inhibitor

5 mg twice daily

Dose adjustment to 2.5 mg twice daily if any 2 below:

- Age ≥80 years
- Weight ≤60 kg
- Creatinine ≥1.5 mg/dL

Not dialyzable

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Apixaban

Time to peak 3-4 hours

Half life: 12 hours

Reversal agent: Andexanet alfa or 4-factor non-activated PCC

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Edoxaban

Direct factor Xa inhibitor

Dosing
- Weight >60 kg: 60 mg daily
- Weight ≤60 kg: 30 mg daily

Renal Dosing
- CrCl 51-95 mL/minute 60 mg daily
- CrCl 15-50 mL/minute: 30 mg daily
- CrCl ≤15 mL/minute: Not recommended
- Not dializable

Hepatic Dosing: Not recommended for moderate-severe hepatic impairment

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Edoxaban

Time to peak 1-2 hours

Half life: 10-14 hours

Reversal agent: Andexanet alfa or 4-factor non-activated PCC

Black box warning: Reduced efficacy in nonvalvular atrial fibrillation patients with CrCl >95 mL/minute

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Pharmacokinetic and Clinical Properties of DOACs

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa	Factor Xa
Plasma peak concentration, h	≈1–2 h	≈2–4 h	≈2 h	≈1–2 h	≈3–4 h
Half-life	12-17 h	5- 12 h	~ 12 h	~10- 14 h	~19-27 h
Dosing	110 mg or 150 mg twice daily	2.5 mg twice daily or 15 mg daily	5 mg twice daily	60 mg daily	80 mg daily
Renal excretion, %	80 %	33 %	27 %	50 %	11 %
Renal dose adjustment	75 mg twice daily		2.5 mg twice daily	30 mg once daily	40 mg daily
Hepatic dose adjustment	No dosage adjustment	Avoid use in moderate to severe impairment	Not recommended in severe impairment	Not recommended in moderate to severe impairment	Avoid use in moderate to severe impairment

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Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS)

Double-blind, randomized control trial

27,395 patients

Assigned to:

- Rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg daily)
- Rivaroxaban (5 mg twice daily)
- Aspirin alone (100 mg daily)

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Inclusion Criteria

Presence of CAD or PAD

- CAD defined as any of:
  - Myocardial infarction within the last 20 years
  - Multivessel coronary disease with symptoms or with history of stable or unstable angina
  - Multivessel PCI
  - Multivessel CABG
- PAD defined as any of:
  - Previous aorto-femoral bypass surgery, limb bypass surgery, or PTCA of the iliac, infra-inguinal arteries
  - Previous limb or foot amputation for arterial vascular disease
  - History of claudication (peripheral extremity pain with either of ABI < 0.90 or ≥ 50% stenosis of peripheral artery by angiography or duplex ultrasound)
  - Previous carotid revascularization or asymptomatic carotid stenosis ≥ 50% by either angiography or duplex ultrasound

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Inclusion Criteria

If included for CAD, also requires either of:

Age ≥ 65 years

Age < 65 years with documented atherosclerosis or revascularization involving at least 1 additional vascular bed or presence of at least 2 of:

- Current smoker
- Diabetes
- Renal dysfunction with eGFR < 60mL/min
- Heart failure
- Non-lacunar stroke ≥ 1 month prior to randomization

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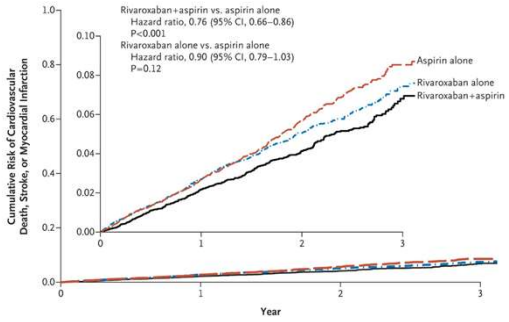
COMPASS Trial

Rivaroxaban plus aspirin

- 24% relative reduction in MACE
- 70% relative risk increase of bleeding
- Net Clinical benefit of composite outcome
  - Cardiovascular death, stroke, myocardial infarction (MI), fatal bleeding, or symptomatic bleeding into a critical organ favored the combination group (4.7% versus 5.9%, HR, 0.80 [95% CI, 0.70–0.91])



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AFIRE Trial

Atrial fibrillation prevalence 12.5% among patients with CAD

Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease

- Multicenter trial conducted in Japan
- 2236 patients with atrial fibrillation and known stable CAD
- 2 Groups
  - Rivaroxaban (10 mg daily or 15 mg daily depending on renal function)
  - Combination therapy with rivaroxaban and a single antiplatelet agent
    - Aspirin in 70%

The trial was stopped early because of increase in mortality in the combination group.

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Randomized Controlled Trials of DOACs and Patients With Stable CAD

Trial name	N	Study groups	Primary end point	Primary efficacy results	Major bleeding
COMPASS[21]	27 395; patients with stable CAD	Group 1: rivaroxaban 2.5 mg twice daily+Aspirin 100 mg daily	Composite of CV death, stroke, or MI	Group 1 (4.1%) vs group 3 (5.4%); HR, 0.76 (0.66–0.86)	Group 1 (3.1%) vs group 3 (1.9%); HR, 1.70 (1.40–2.05)
		Group 2: rivaroxaban 5 mg twice daily		Group 2 (4.9%) vs group 3 (5.4%); HR, 0.90 (0.79–1.03)	Group 2 (2.8%) vs group 3 (1.9%); HR, 1.51; (1.25–1.84)
		Group 3: Aspirin 100 mg daily			
AFIRE[22]	2236; patients with atrial fibrillation and stable CAD	Group 1: rivaroxaban	Composite of stroke, embolism, MI, unstable angina requiring revascularization, or death from any cause	Group 1 (4.14% per patient-year) vs group 2 (5.75% per patient-year); HR, 0.72 (0.55–0.95)	Group 1 (1.62% per patient-year) vs group 2 (2.76% per patient-year); HR, 0.59 (0.39–0.89)
		Group 2: rivaroxaban and single antiplatelet agent			

AFIRE indicates Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; CAD, coronary artery disease; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CV, cardiovascular; HR, hazard ratio; and MI, myocardial infarction.

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2023 ACC/AHA Guideline for the Management of Patients with Chronic Coronary Disease

2a	**B-R**	15. In patients with CCD without an indication for therapeutic DOAC or DAPT and who are at high risk of recurrent ischemic events but low-to-moderate bleeding risk, the addition of low-dose rivaroxaban 2.5 mg twice daily to aspirin 81 mg daily is reasonable for long-term reduction of risk for MACE.

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2023 ACC/AHA Guideline for the Management of Patients with Chronic Coronary Disease

2b	C-LD	14. In patients with CCD who require oral anticoagulation, DOAC monotherapy may be considered if there is no acute indication for concomitant antiplatelet therapy.

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Peripheral Artery Disease

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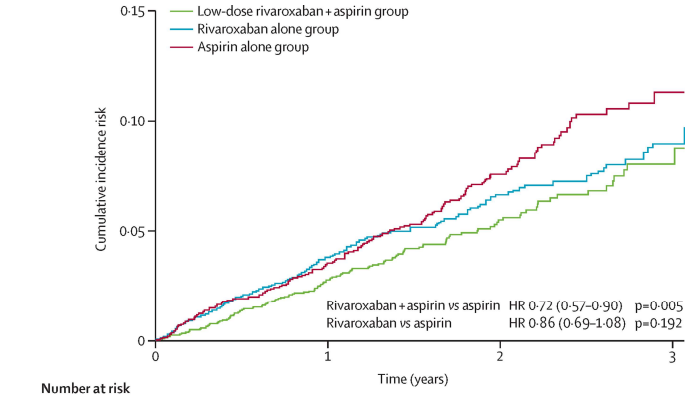
Rivaroxaban with or without Aspirin in Patients with Stable Peripheral or Carotid Artery Disease (COMPASS-PAD)



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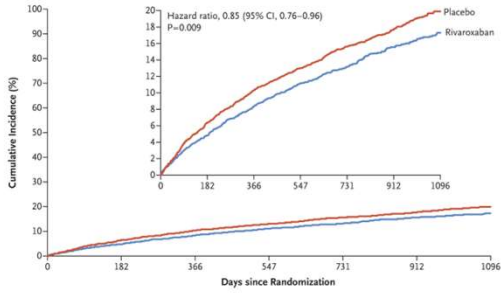
Rivaroxaban in Peripheral Artery Disease after Revascularization (Voyage PAD)

6554 patients with PAD who had undergone lower extremity revascularization

32% risk reduction in acute limb ischemia (4.7% with rivaroxaban versus 6.9% with placebo)

42% risk increase in major bleeding (1.90% with rivaroxaban group and 1.35% with placebo



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Periprocedural Management of DOACs

Last dose of the DOAC prior to elective procedure

	Low bleed risk procedure	High (moderate, unknown) bleed risk procedure
Apixaban, rivarxaban, edoxaban		
CrCl ≥30 mL/min	≥24 hours	≥48 hours
CrCl 15-30 mL/min	≥36 hours	Data lacking. Consider anti-Xa level or holding ≥72 hours
CrCl <15 mL/min	Data lacking. Consider anti-Xa level or holding ≥48 hours	
Dabigatran		
CrCl ≥80 mL/min	≥24 hours	≥48 hours
CrCl 15-80 mL/min	≥36 hours	≥72 hours
CrCl 30-49 mL/min	≥48 hours	≥96 hours
CrCl 15-29 mL/min	≥72 hours	≥120 hours
CrCl <15 mL/min	Not indicated. Consider measuring dilute thrombin time	

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DOACs in the Patients With Atrial Fibrillation After PCI or ACS

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WOEST Trial

Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention

- Open-label, multicenter, randomized controlled trial
- 573 patients
- 2 groups
  - Clopidogrel plus warfarin
  - Aspirin, clopidogrel, and warfarin

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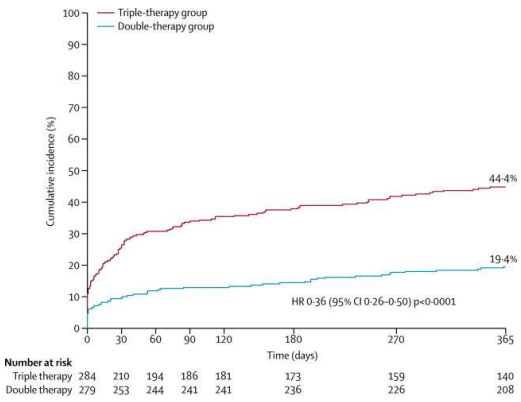
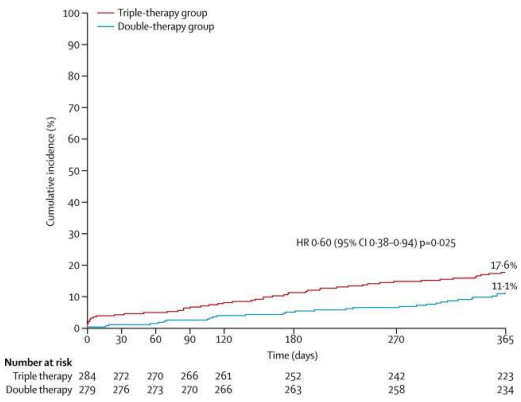
WOEST Trial Results

MAJOR BLEEDING



MACE



Use of clopidogrel without aspirin was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events.

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PIONEER AF-PCI

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

- Open-Label, randomized, controlled, multicenter study
- 2124 patients with nonvalvular atrial fibrillation who underwent PCI
- 3 Groups
  - Rivaroxaban 15 mg daily
  - Rivaroxaban 2.5 mg twice daily plus DAPT
  - Warfarin plus DAPT

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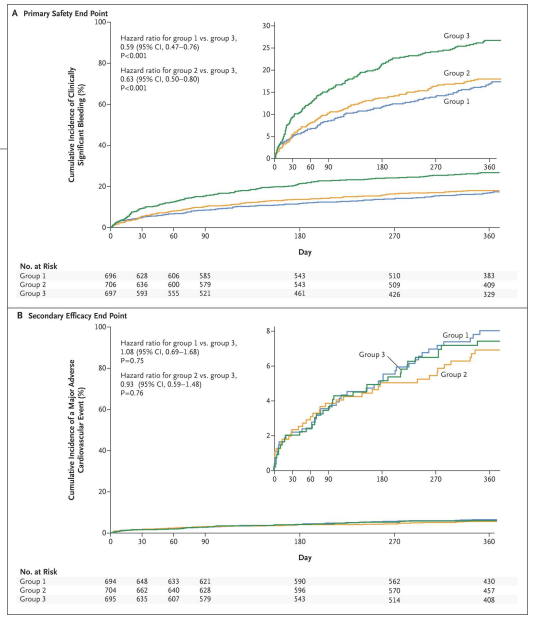
PIONEER AF-PCI

Significant decrease in major bleeding and no increase in MACE in the rivaroxaban group as compared to the VKA group



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RE-DUAL PCI

Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

- Randomized controlled trial
- 2725 patients with atrial fibrillation who underwent PCI
- 2 Groups
  - Dabigatran plus $P2Y_{12}$ inhibitor
  - Warfarin plus DAPT

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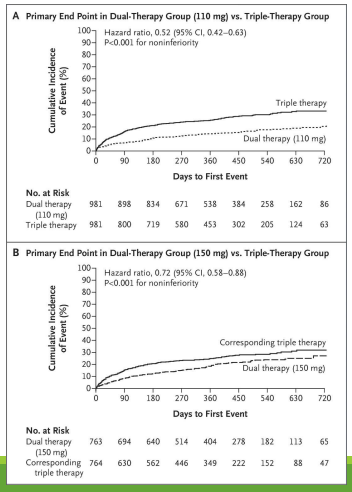
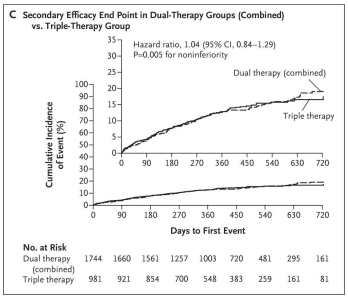
RE-DUAL PCI

MAJOR AND NON-MAJOR BLEEDING



MACE



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AUGUSTUS Trial

Antithrombotic Therapy in Patients With Atrial Fibrillation After Acute Coronary Syndromes or Percutaneous Intervention

- Randomized controlled trial
- 4614 patients with atrial fibrillation who had ACS or underwent PCI
- 2-by-2 factorial design to receive a $P2Y_{12}$ inhibitor and either apixaban or VKA and either aspirin or placebo for 6 months

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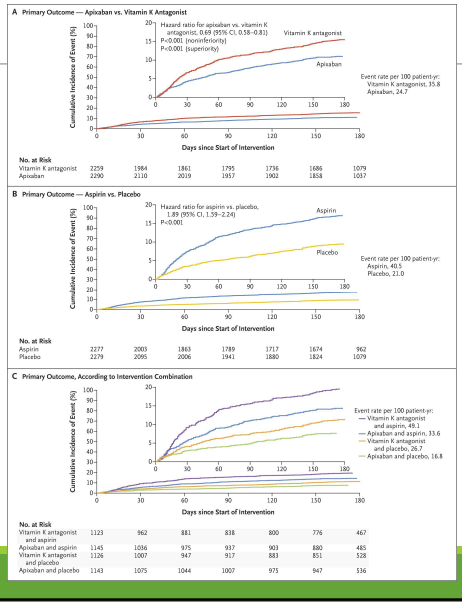
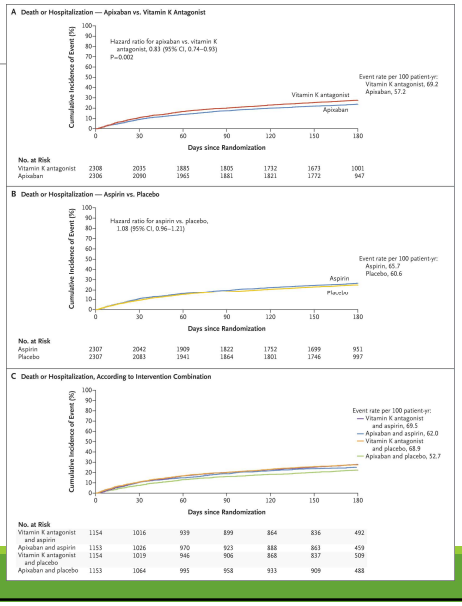
AUGUSTUS TRIAL

BLEEDING



MACE



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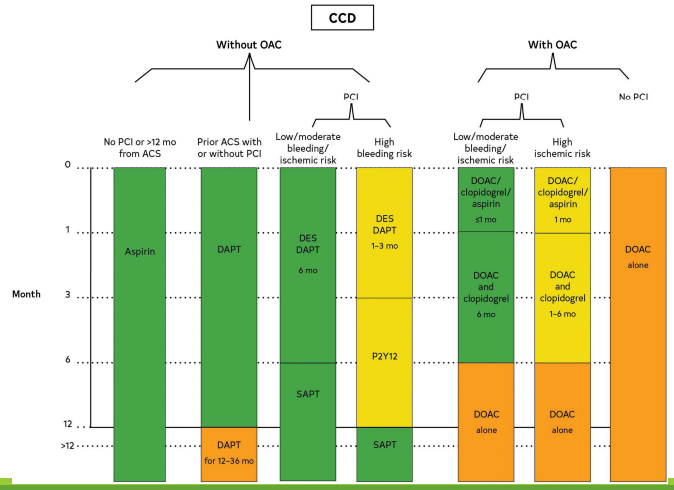
Duration of Antiplatelet Therapy



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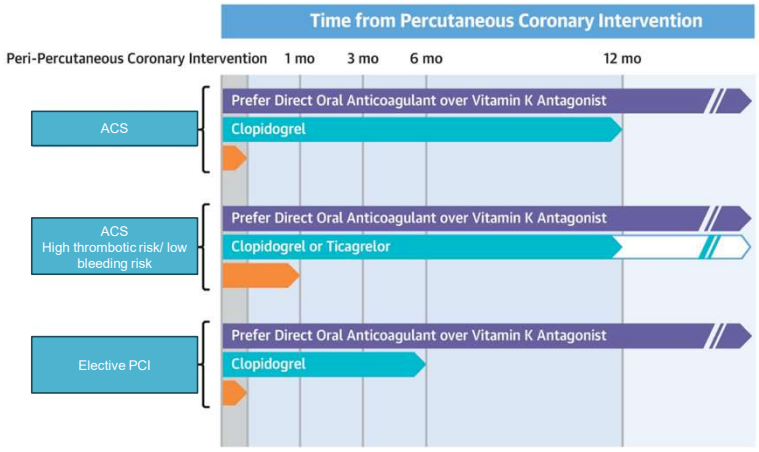
Management of Antithrombotic Therapy in Atrial Fibrillation Patients Undergoing PCI



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DOACs in Patients After CABG

30% of patients have at least 1 occluded graft 1 year after CABG

Rivaroxaban, Aspirin, or Both to Prevent Early Coronary Bypass Graft Occlusion: The COMPASS-CABG Study

- Randomized 1448 patients
- 3 Groups
  - Rivaroxaban (2.5 mg twice daily) plus aspirin
  - Rivaroxaban (5 mg twice daily) alone
  - Aspirin alone
- The combination of rivaroxaban plus aspirin or rivaroxaban alone as compared to aspirin alone did not significantly reduce graft failure in patients after CABG

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Bleeding Risk and DOACs

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ARISTOPHANES study

Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients

High risk bleeding factors

- HAS-BLED score of ≥3
- Age >75 years
- History of prior gastrointestinal bleeding conditions
- Chronic kidney disease between stage 3 to 5

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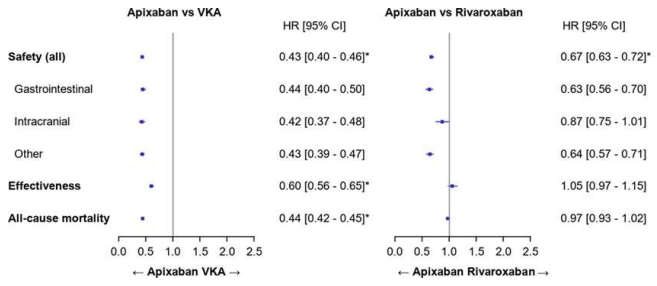
NAXOS study

Evaluation of Apixaban in Stroke and Systemic Embolism Prevention in Patients with Nonvalvular Atrial Fibrillation

- Observational study
- French National Health system claims data
- 321,501 patients



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Take Home Messages

Consider rivaroxaban 2.5 mg twice daily in addition to aspirin 81 mg daily for patients with stable coronary artery disease who are at increased risk

- Age ≥65
- Age <65 with 2 of the following:
  - Current smoker
  - Diabetes
  - Renal dysfunction with eGFR < 60mL/min
  - Heart failure
  - History of non-lacunar stroke

Consider rivaroxaban 2.5 mg twice daily in addition to aspirin 81 mg daily for patients with peripheral vascular (including carotid artery) disease.

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Take Home Messages

Hold DOACs for at least 48 hours prior to elective procedures with high bleeding risk

In patients with an indication for anticoagulation, prefer DOAC plus clopidogrel **without** aspirin within the first-year post PCI.

In patients with an indication for anticoagulation, prefer DOAC alone in stable patients without MI or PCI within the past year.

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Take Home Messages

Consider increased bleeding risk with DOACs:

- HAS-BLED score of ≥3
- Age >75 years
- History of prior gastrointestinal bleeding conditions
- Chronic kidney disease between stage 3 to 5

Apixaban has the lowest bleeding risk of the available DOACs.

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Thank you!

QUESTIONS AND DISCUSSION

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