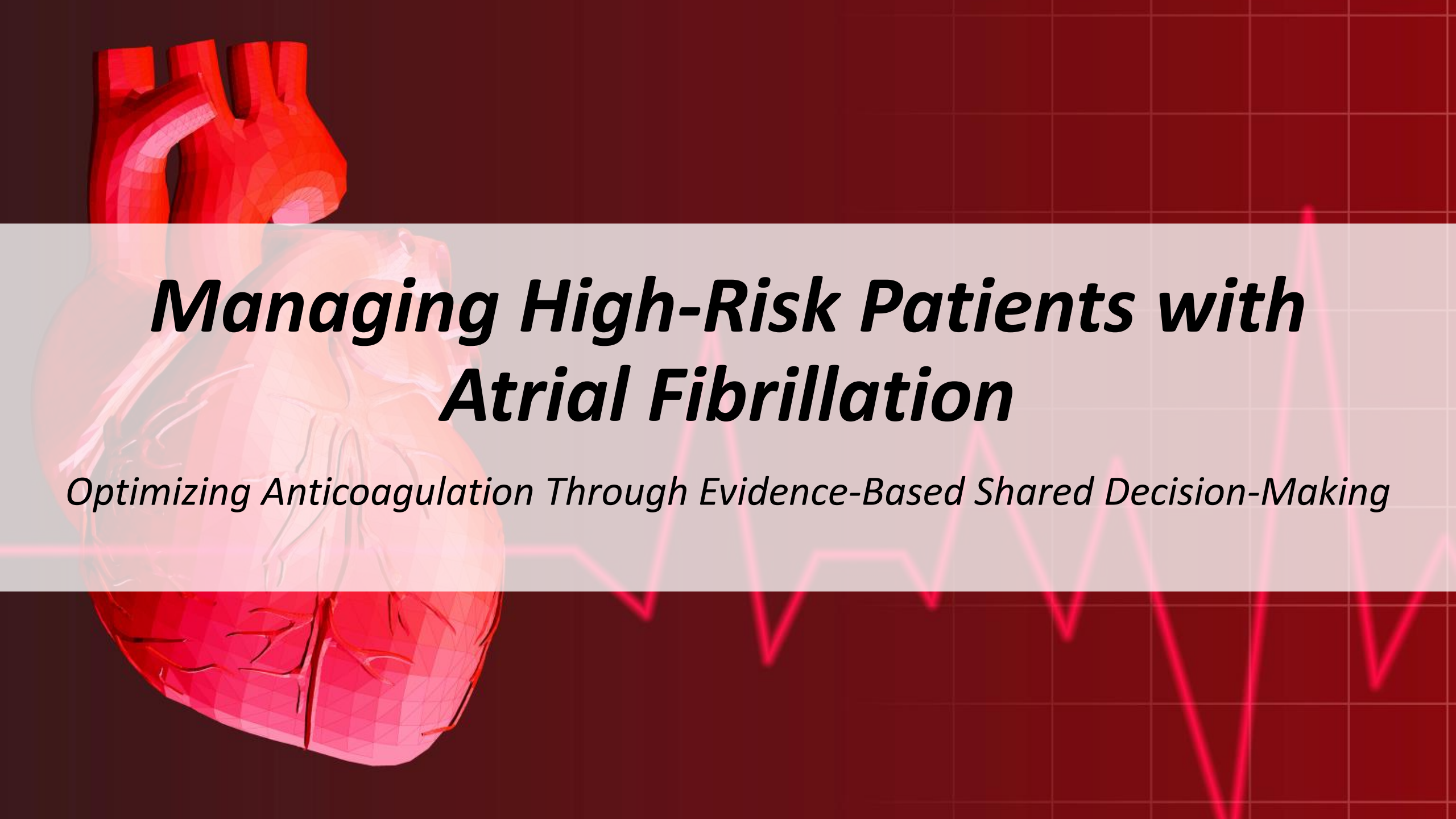
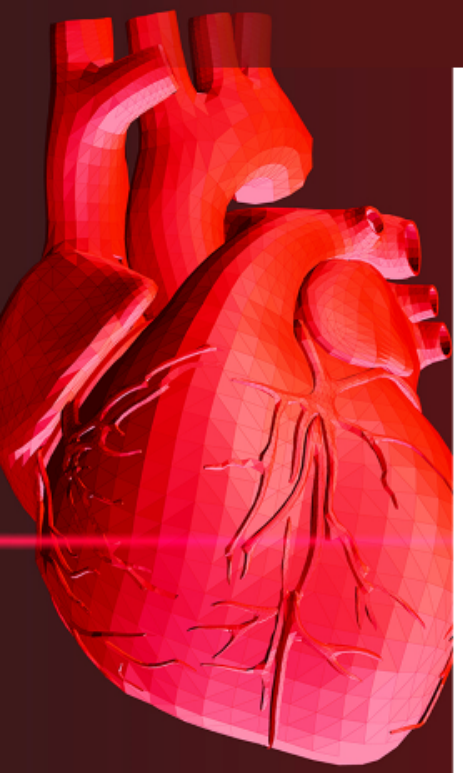


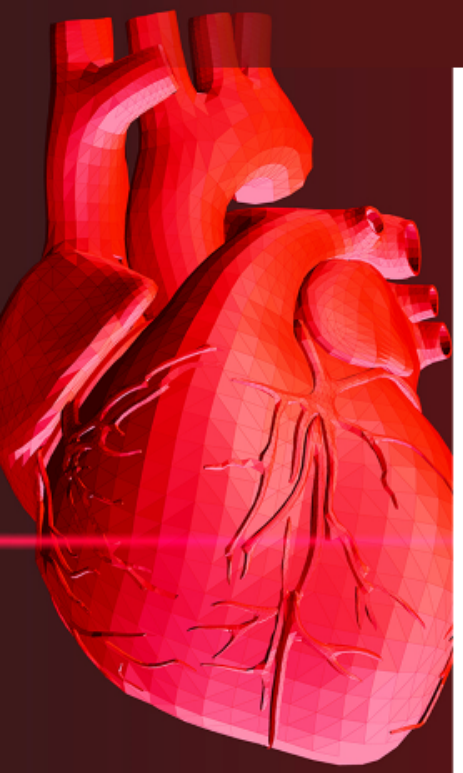
Managing High-Risk Patients with Atrial Fibrillation

Optimizing Anticoagulation Through Evidence-Based Shared Decision-Making



This educational activity is sponsored by Postgraduate Healthcare Education, LLC and supported by an educational grant from Bristol-Myers Squibb and the Pfizer Alliance

Faculty



Barbara S. Wiggins, PharmD, BCPS, CLS, FNLA, FAHA, FCCP, AACC

Affiliate Professor
University of South Carolina College of Pharmacy
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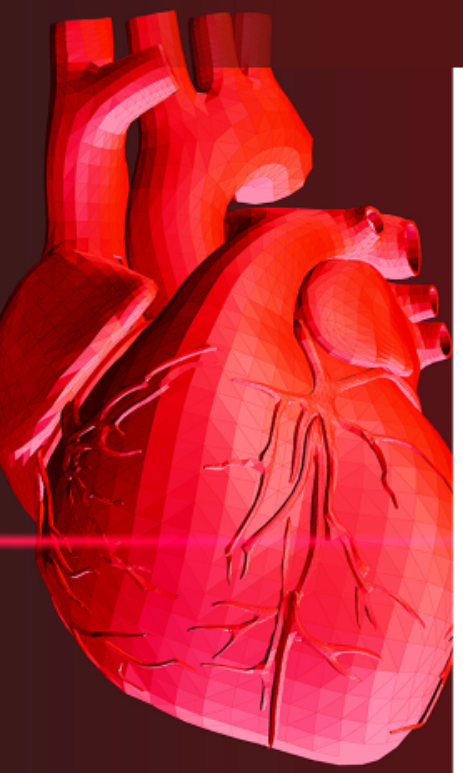
Disclosures



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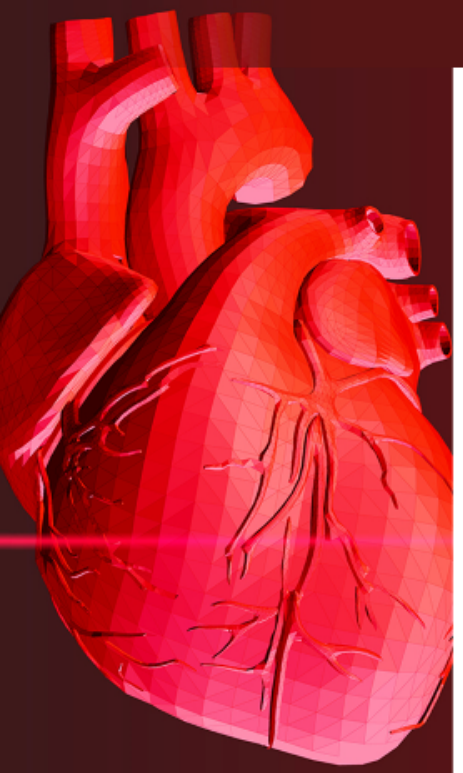

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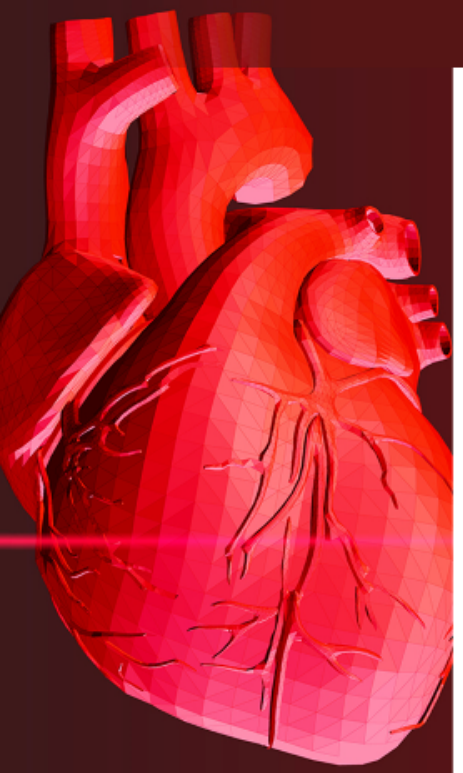
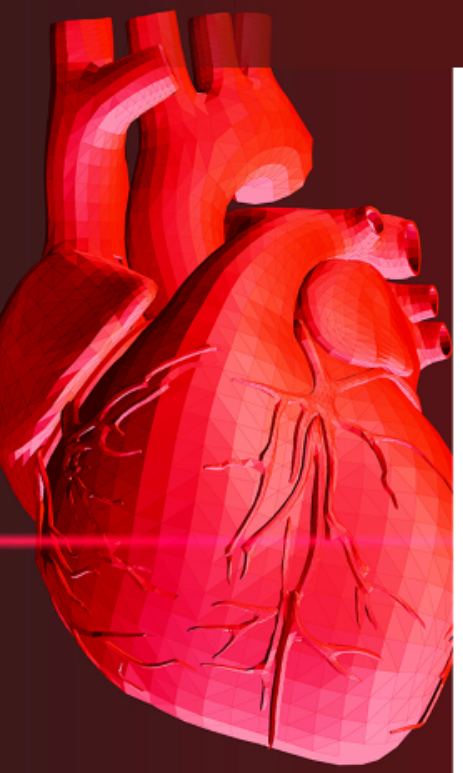
UAN: 0430-0000-20-023-H01-P
Credits: 1.25 hour (0.125 CEU)
Type of Activity: Application

Objectives



- **Describe** evidence for anticoagulant selection in high-risk atrial fibrillation (AF) subpopulations, including older patients, those with a history of stroke, those with renal dysfunction, and those undergoing percutaneous coronary intervention (PCI)
- **Recognize** the need to use the HAS-BLED score to identify and address modifiable risk factors for bleeding
- **Discuss** the benefits and drawbacks of various anticoagulant options in patients with AF, including monitoring requirements, drug interactions, and bleeding risk
- **Formulate** individualized, evidence-based anticoagulation plans for patients with AF using a shared decision-making process

Background: Atrial Fibrillation

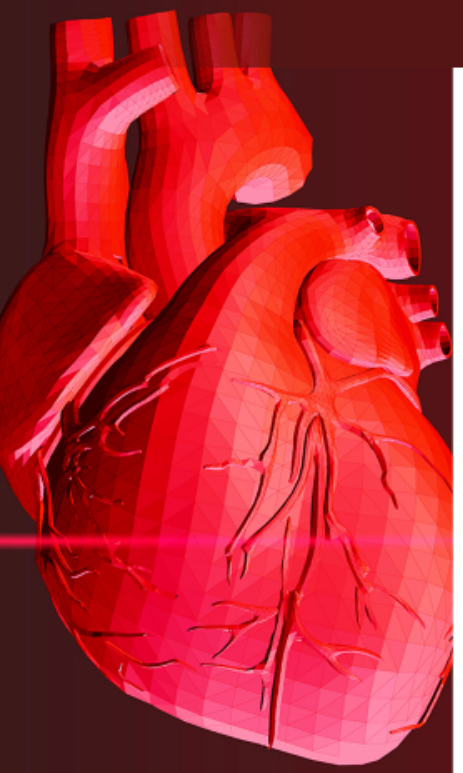


- Affects 2.7 to 6.7 million patients in the United States (U.S.)
  - Affects 33.5 million globally
- Risk increases with age
- Frequently seen with comorbidities
- Major cause of stroke (> 125,000/year)
  - Risk of stroke is 5 times higher in patients with AF
- Most common arrhythmia requiring hospitalization

Alkhouli M, et al. *J Am Coll Cardiol.* 2018;71(24):2790-801.; Du X, et al. *J Am Coll Cardiol.* 2017;69(15):1968-82.; January CT, et al. *J Am Coll Cardiol.* 2014;64(21):e1-76.; Lip GYH, et al. *Nat Rev Dis Primers.* 2016;2:16016.

Risk Factors for Stroke

Risk Factors for Stroke

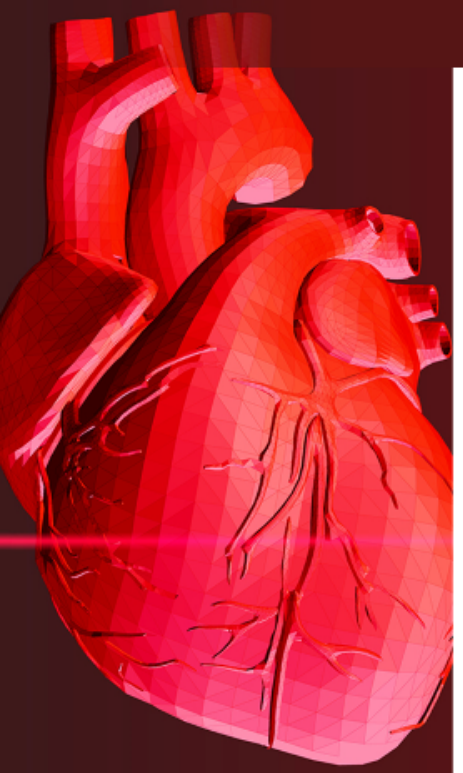


Non-modifiable	Modifiable
• Age • Gender • Race • Family history	• Hypertension • Diabetes • Smoking • Dyslipidemia • Atrial fibrillation • CHC use • Obesity • Heart failure • PAD

CHC, combined hormonal contraceptive;
PAD, peripheral artery disease.

Goldstein LB, et al. *Stroke.* 2011;42(2):517-84.

Risk Stratification – Stroke Risk Scoring



CHA_2DS_2-VASc

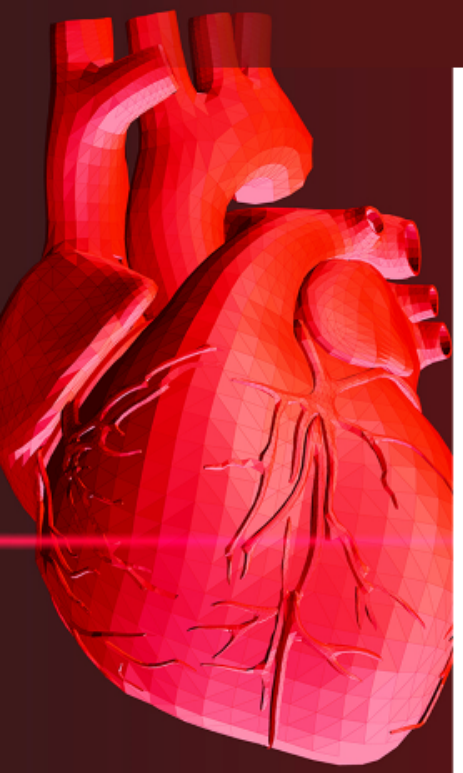
Risk factor	Score
CHF or LVEF ≤ 40%	1
Hypertension	1
A$_2$ge ≥ 75 years	2
Diabetes	1
S$_2$troke/TIA/thromboembolism	2
Vascular disease	1
Age 65-74 years	1
S$_c$ex category	1

Maximum of 9

CHF, congestive heart failure;
LVEF, left ventricular ejection fraction;
TIA, transient ischemic attack.

Pisters R, et al. *Chest*. 2010;138(5):1093-100.

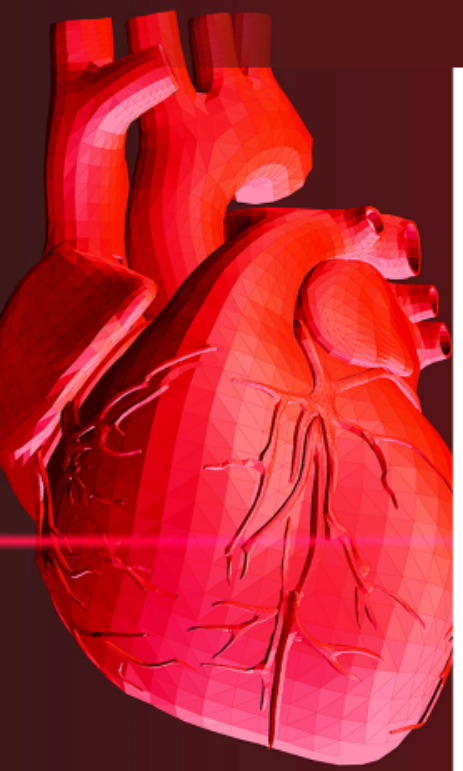
Age



- Framingham Study
  - Risk of stroke due to AF increased with each subsequent decade of life
    - 50-59 years old: 1.5%
    - 60-69 years old: 2.8%
    - 70-79 years old: 9.95%
    - 80-89 years old: 23.5%
- Atrial Fibrillation Investigators
  - Risk of stroke:
    - < 65 years old: 1% per year
    - 65-75 years old: 4.3%
    - ≥ 75 years old: 3.5%
- ATRIA Cohort
  - Risk of stroke:
    - 65-74 years old: 1.57 thromboembolic events/100 person-years
    - < 65 years old: 0.64 thromboembolic events/100 person-years

Lane DA, et al. *Thromb Haemost*. 2009;101(5):802-5.; Poli D, et al. *Thromb Haemost*. 2009;101(5):938-42.

Vascular Disease



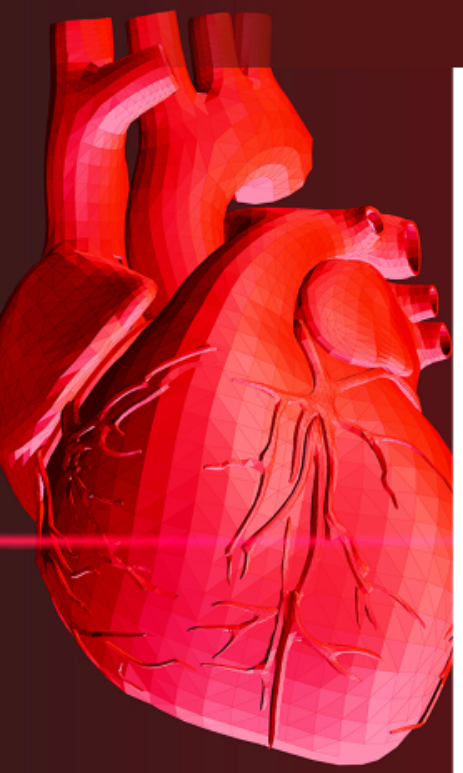
Risk of hospital admission and death due to thromboembolism in patients with AF

- 1 year: *non-significant,* HR 0.97 (95% CI 0.3-3.011, p=0.96)
- 5 years: *significant,* HR 2.04 (95% CI 1.29-3.22, p=0.002)
- 10 years: *significant,* HR 2.22 (95% CI 1.49-3.30, p<0.0001)

CI, confidence interval;
HR, hazard ratio.

Conway DSG, et al. *Am J Cardiol*. 2004;93(11):1422-5.;
Petersen P, et al. *Arch Intern Med.* 1990;150(4):819-21.;
Siu CW, et al. *Chest*. 2007;132(1):44-9.

Sex Category

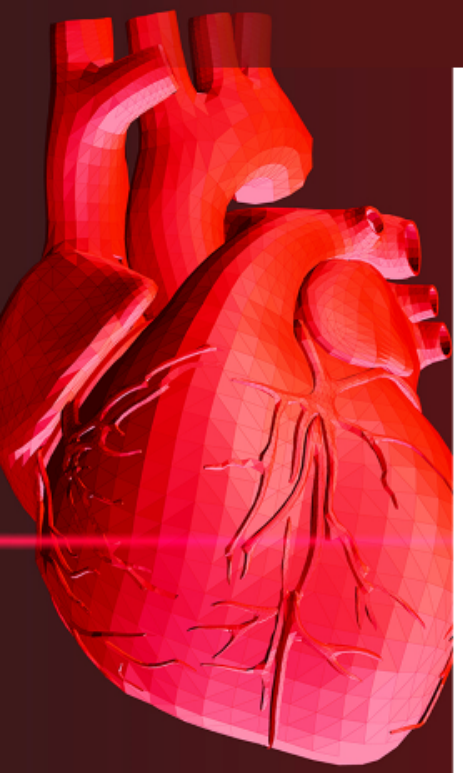


- Study by Poli D, et al evaluated 780 patients with AF on OAC
  - **Stroke rate:**
    - Males: 1.2 x 100 patient-years
    - Females: 2.43 x 100 patient-years
      - After correction for age: p=0.009
  - **Other findings:**
    - Females had greater disability
    - Females had more severe and more fatal strokes than males
      - RR 3.1 (95% CI 1.3-6.5; p=0.001)

OAC, oral anticoagulation; RR, relative risk.

Lane DA, et al. *Thromb Haemost*. 2009;101(5):802-5.;
Poli D, et al. *Thromb Haemost*. 2009;101(5):938-42.

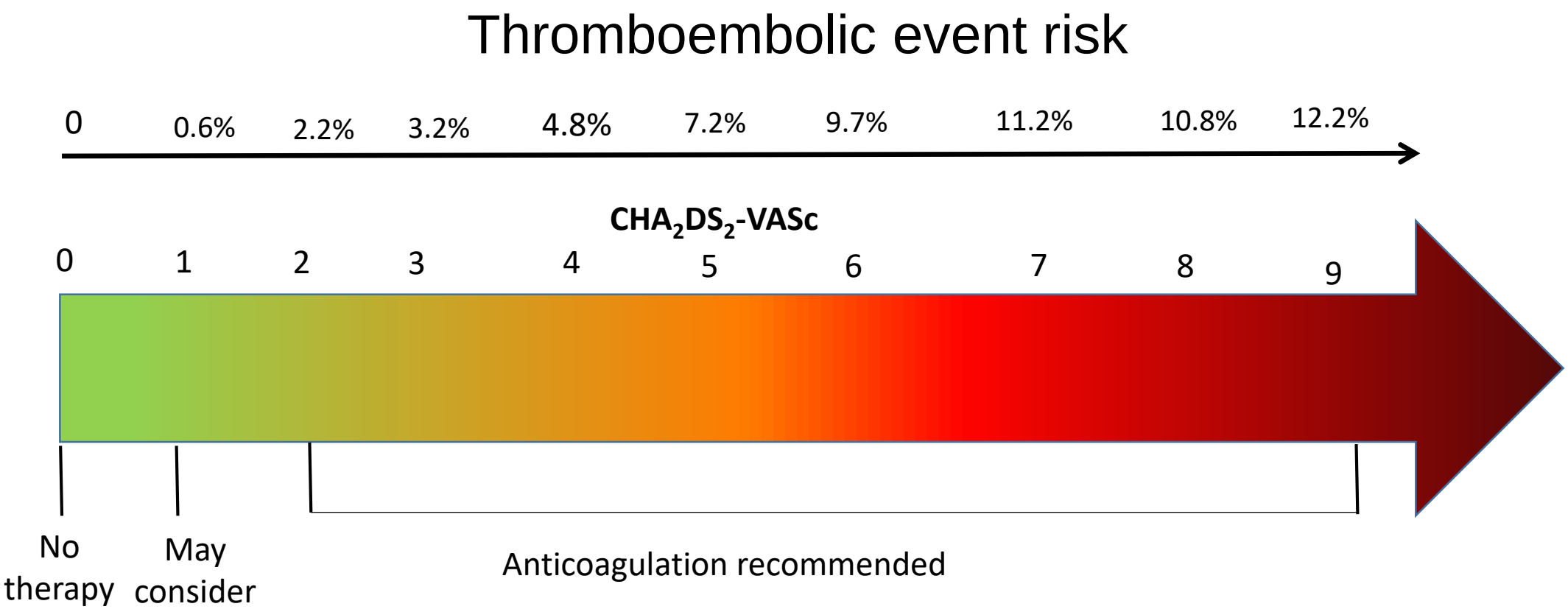
Anticoagulation



CHA_2DS_2-VASc Score = 0 in men or 1 in women	CHA_2DS_2-VASc Score = 1 in men or 2 in women	CHA_2DS_2-VASc Score ≥ 2 in men or 3 in women
For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), and a CHA_2DS_2-VASc score of 0 in men or 1 in women, it is reasonable to omit anticoagulant therapy	For patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), prescribing an oral anticoagulant to reduce thromboembolic stroke risk may be considered	For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women, oral anticoagulation is recommended

January CT, et al. *Circulation.* 2019;140(2):e125-51.

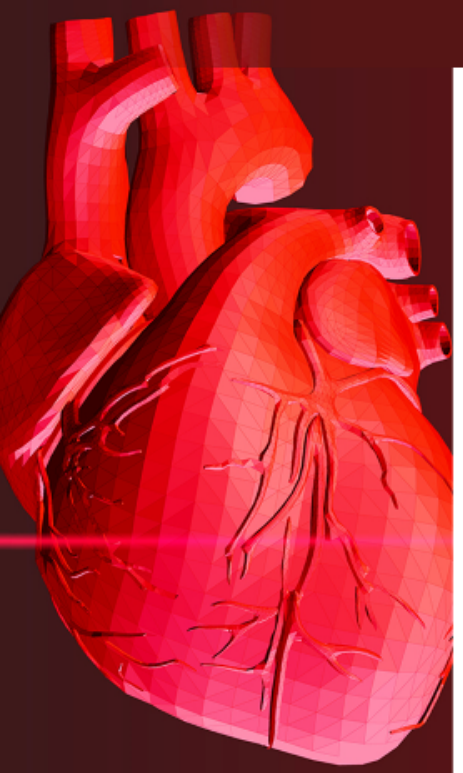
Choosing When to Anticoagulate



Friberg L, et al. *Eur Heart J.* 2012;33(12):1500-10.;
January CT, et al. *Circulation.* 2019;140(2):e125-51.

Bleed Risk

HAS-BLED Score



HAS-BLED	
Hypertension	1
Abnormal renal or hepatic function	1 1
Stroke	1
Bleeding	1
Labile INR*	1
Elderly (> 65 years old)	1
Drugs€ or alcohol use	1 1

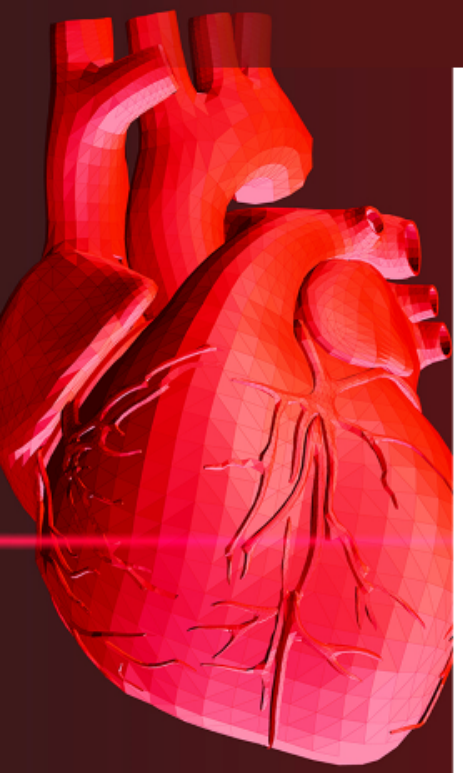
*unstable or poor time in range (< 60%)
€concomitant use of antiplatelet agents, aspirin, non-steroidal anti-inflammatory, etc.

Score	Bleeding risk (% bleeds per 100 patient-years)
0-1	Low risk (1.1%)
2	Intermediate risk (1.9%)
≥ 3	High risk (4.9%)

INR, international normalized ratio.

Pisters R, et al. *Chest*. 2010;138(5):1093-100.

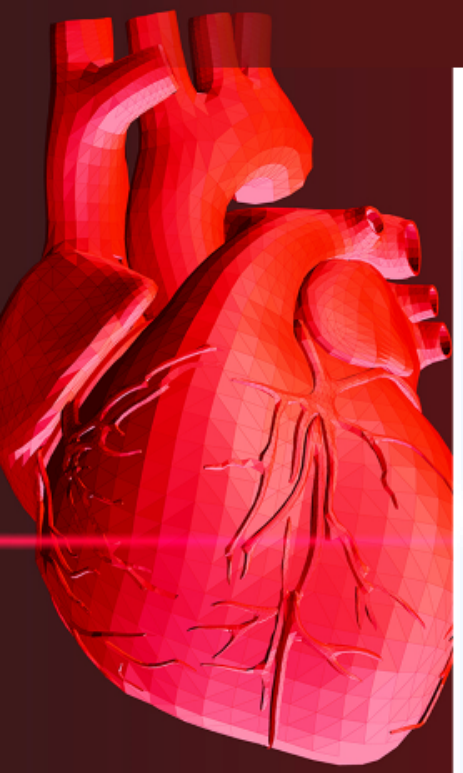
HAS-BLED Score



- A simple calculation that should be incorporated into clinical practice
- HAS-BLED is a better predictor of major bleeding than other bleeding risk scores
- HAS-BLED ≥ 3 is indicative of a high risk for bleeding
  - Should not be used on its own to determine anticoagulation
    - Helps to identify patients who need closer/more careful management
  - Control modifiable risk factors (hypertension, labile INRs)

Choosing an Anticoagulant

Types of Atrial Fibrillation

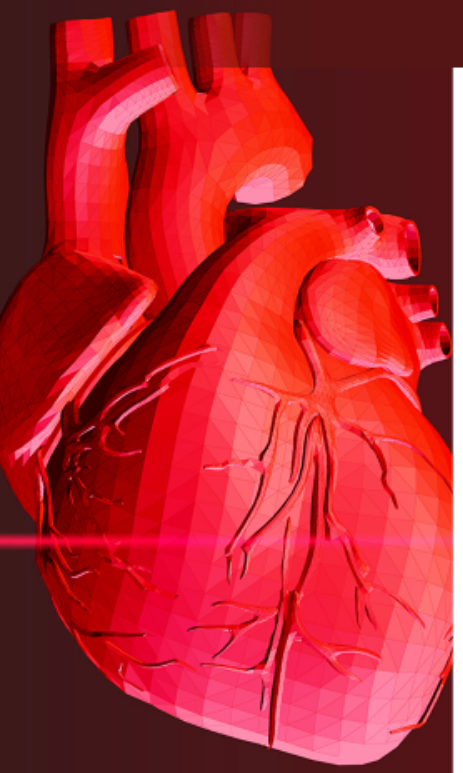


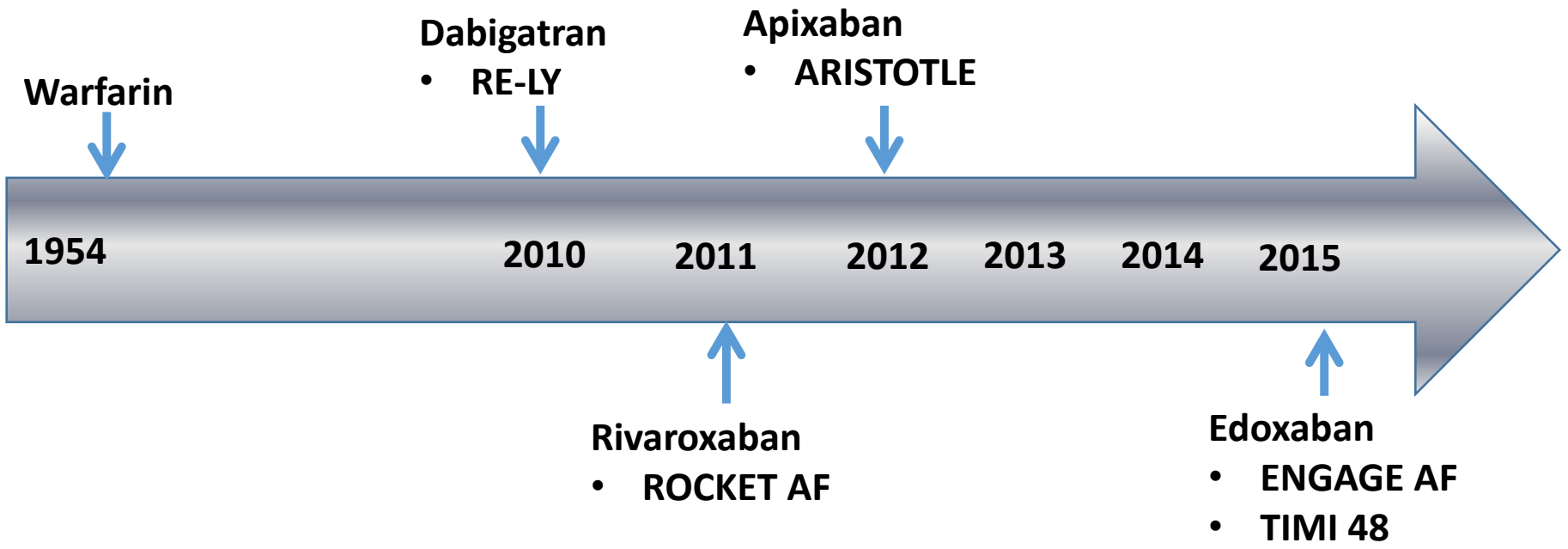
Classifications of Atrial Fibrillation

- **Paroxysmal** (≤ 7 days)
- **Persistent** (> 7 days)
- **Long-standing persistent** (> 12-month duration)
- **Permanent**
- **Non-valvular**

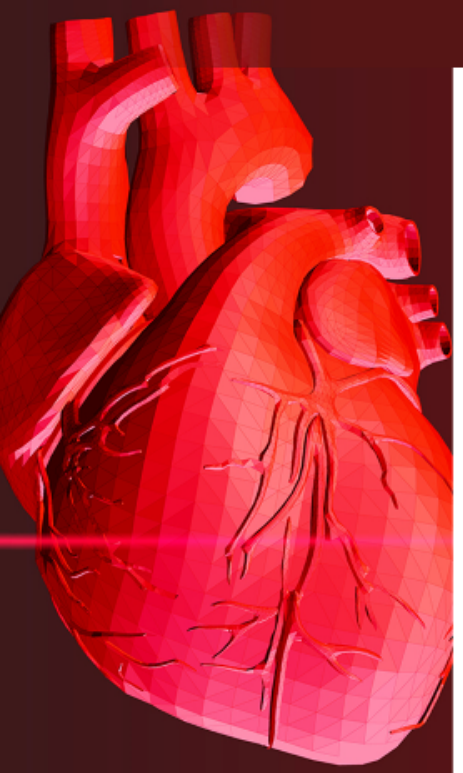
January CT, et al. *Circulation*. 2014;130(23):2071-104.

New Oral Anticoagulants for Stroke Prevention in Non-Valvular AF





Pharmacokinetic Properties of DOACs



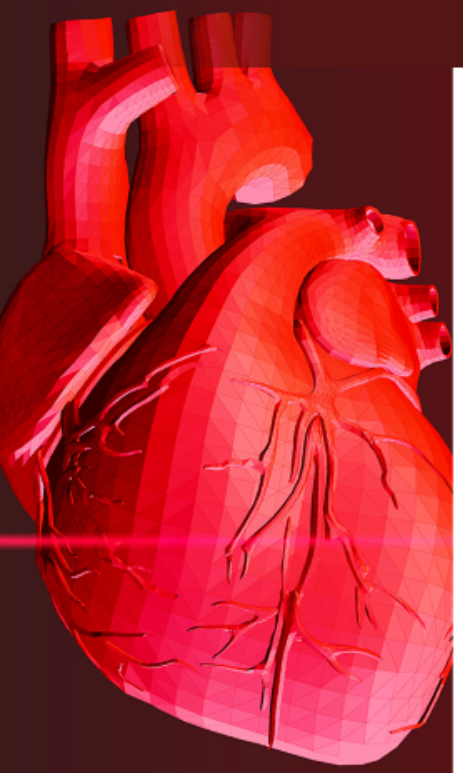
	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Anticoagulation target	Factor II	Factor Xa	Factor Xa	Factor Xa
Impact on coagulation assay	aPTT (2-3 x) INR 40%↑	aPTT 40% INR 40%↑	↑aPTT & INR	↑aPTT
Time to peak (hours)	1-3	2-4	1-3	1-2
Half-life (hours)	14-17	9-13	8-15	~ 10
% renal elimination	80%	66%	25%	50%
Dialyzable	Yes	No	No	No
CYP metabolism	No	30% CYP3A4	15% CYP3A4	< 4%
P-glycoprotein substrate?	Yes	Yes	Yes	Yes

aPTT, activated prothrombin time; CYP, cytochrome P450; DOAC, direct oral anticoagulant.

Garcia D, et al. *Blood*. 2010;115(1):15-20.;
Wittkowsky A. *Pharmacotherapy.* 2011;31(12):1175-91.

Choosing an Anticoagulant in Special Populations

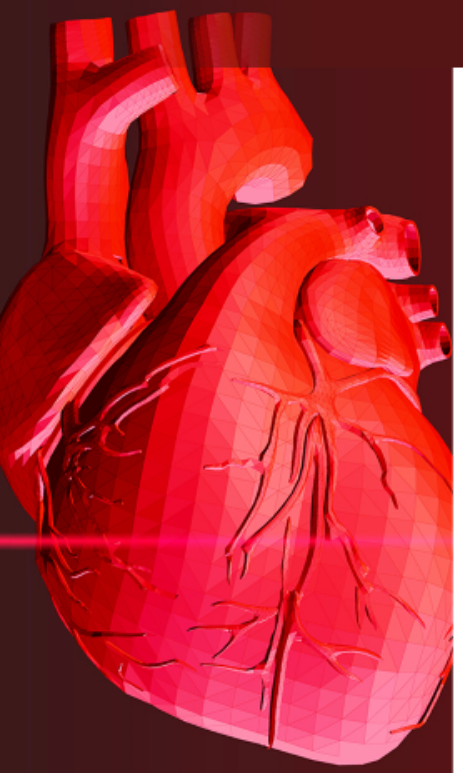
High-Risk Patient Groups



- Elderly
- Prior history of stroke
- Triple therapy
- Renal dysfunction

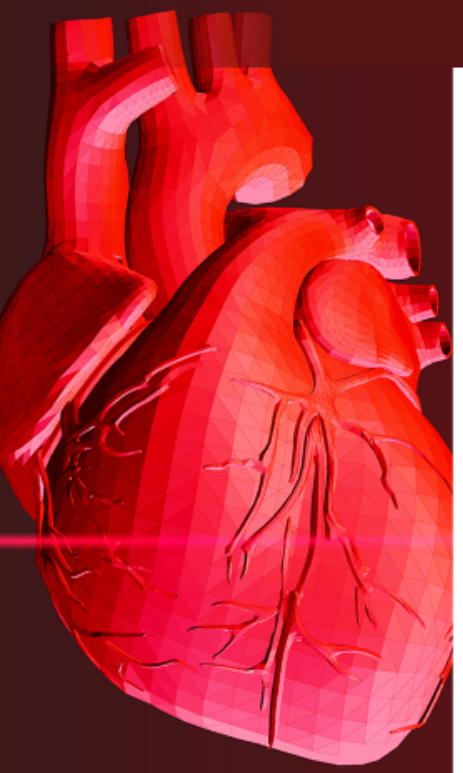
Elderly

High-Risk Patients: The Elderly



- Elderly
  - Increasing population
  - Number of people > 80 years old is expected to reach 25 million by 2050
  - Increased age brings an increase in chronic diseases
  - Many older adults live healthy, active lives
- Many are likely undertreated
  - Lack of adequate representation in clinical trials
  - Concern for overall risk (frailty, end organ dysfunction)

High-Risk Patients: The Elderly



Prevalence of AF:

- Most common arrhythmia in those > 65 years old
  - 10% of people over age 80 have AF
  - 70% of patients with AF are between 65 and 85 years old
- Primary reason for anticoagulation: stroke prevention
  - Strokes secondary to AF have high morbidity and mortality

Go AS, et al. *JAMA.* 2001;285(18):2370-5.;
Kistler PM, et al. *J Am Coll Cardiol*. 2004;44(1):109-16.

High-Risk Patients: The Elderly and Warfarin

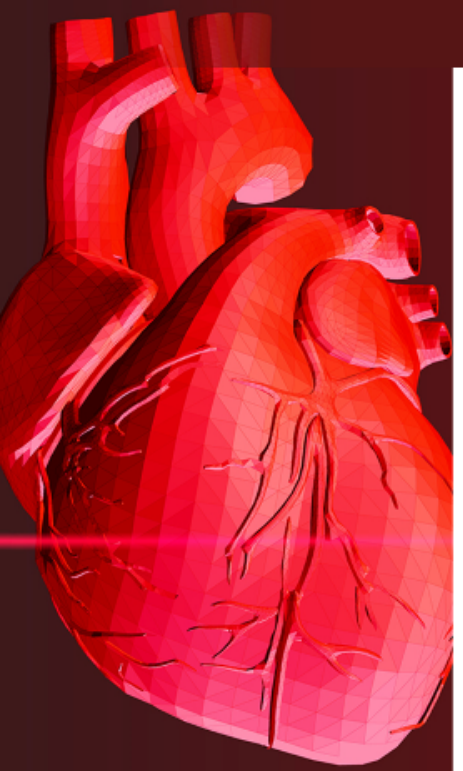
Study	Type (N)	Patient age	Comparison	Primary outcome	Results	Bleeding
BAFTA	RCT (973)	≥ 75 years	Warfarin vs. ASA 75 mg	Stroke/SEE/ICH	RR 0.48 (CI 0.28-0.80)	1.9 vs. 2% (p=0.90)
WASPO	RCT (75)	≥ 80 years	Warfarin vs. ASA 300 mg	Death, TE, bleeding	25% vs. 44% (p=0.11)	0 vs. 0.77%
Wolff et al	Retrospective (561)	≥ 85 years	Warfarin vs. antiplatelet vs. PLC	Stroke	OR with warfarin 0.53 (CI 0.22-1.28)	
SPAFII	Post-hoc (385)	≥ 75 years	Warfarin vs. ASA 325 mg	Stroke	3.6% vs. 4.8% (p=0.39)	
Patti et al	Retrospective (505)	≥ 85 years	Warfarin vs. antiplatelet vs. PLC	Stroke/TIA/SEE	OR 0.64 (CI 0.24-1.69; p=0.37	4.0 % vs. 4.2% (p=0.77)

ASA, acetylsalicyclic acid (aspirin); ICH, intracerebral hemorrhage; OR, odds ratio; PLC, placebo; RCT, randomized controlled trial; SEE, systemic embolic event; TE, thromboembolism.

High-Risk Patients: The Elderly and DOACs

Study	Type (N)	Patient age	Comparison	Primary outcome	Results	Bleeding
AVVEROES	Post hoc (≥ 75 years: 1898; ≥ 85 years: 366)	> 75 years > 85 years	Apixaban vs. antiplatelet	Stroke, SEE	≥ 75 years: HR 0.33 (CI 0.19-0.54) ≥ 85 years: HR 0.14 (CI 0.02-0.48)	≥ 75 years: 2.6% vs. 2.2% (p=0.50) ≥ 85 years: 4.7% vs. 4.9% (p=0.93)
RE-LY	Post hoc (7258)	≥ 75 years	Dabigatran 110 mg vs. dabigatran 150 mg vs. warfarin	Stroke, SEE	110 mg: HR 0.88 (CI 0.66-1.17) 150 mg: HR 0.67 (CI 0.49-0.9)	110 mg: 4.4% vs. 150 mg: 5.1% vs. warfarin: 4.4% (p=0.89; p=0.07)
ROCKET AF	Post hoc (75-84 years: 5566; ≥ 85 years: 663)	≥ 75 years	Rivaroxaban 20 mg vs. warfarin	Stroke, SEE	HR 0.80 (CI 0.63-1.02)	4.9% vs. 4.4% HR 1.11 (CI 0.92-1.34)
ARISTOTLE	Post hoc (2396)	≥ 75 years	Apixaban 5 mg vs. warfarin	Stroke, SEE	HR 0.71 (CI 0.53-0.95)	3.3% vs. 5.2% (p<0.05)
ENGAGE AF	Post hoc (8474)	≥ 75 years	Edoxaban 60 mg vs. warfarin	Stroke, SEE	HR 0.83 (CI 0.66-1.04)	4% vs. 4.8% (p<0.05)

Efficacy/Safety: Adults > 75 Years Old



Meta-analysis

- Subgroup analysis of ARISTOPHANES study
- Compare risk of stroke/SE and major bleeding in very old (DOACs vs. warfarin)

Stroke/SE

• Apixaban	HR 0.58 (CI 0.49-0.69)	p < 0.001
• Dabigatran	HR 0.77 (CI 0.65-0.85)	p = 0.045
• Rivaroxaban	HR 0.6 (CI 0.54-0.67)	p < 0.001

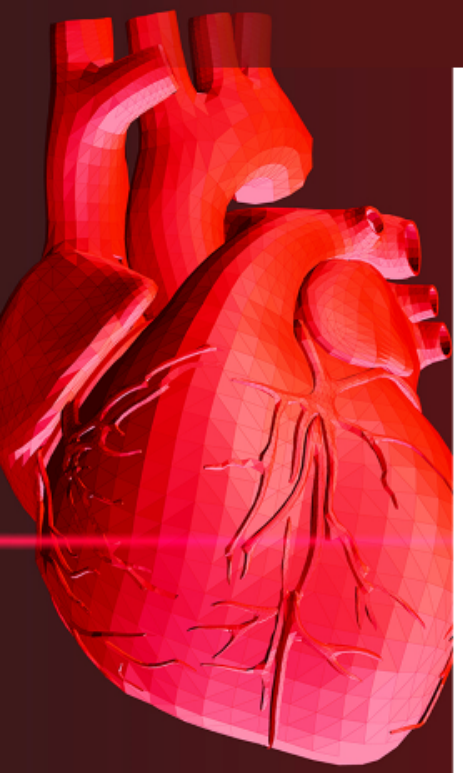
Major bleeding

• Apixaban	HR 0.60 (0.54-0.67)	p < 0.001
• Dabigatran	HR 0.92 (0.78-1.07)	p = 0.281
• Rivaroxaban	HR 1.16 (1.07-1.24)	p < 0.001

SE, systemic embolism.

Deitelzweig S, et al. *J Am Geriatr Soc*. 2019;67(8):1662-71.

High-Risk Patients: Very Elderly

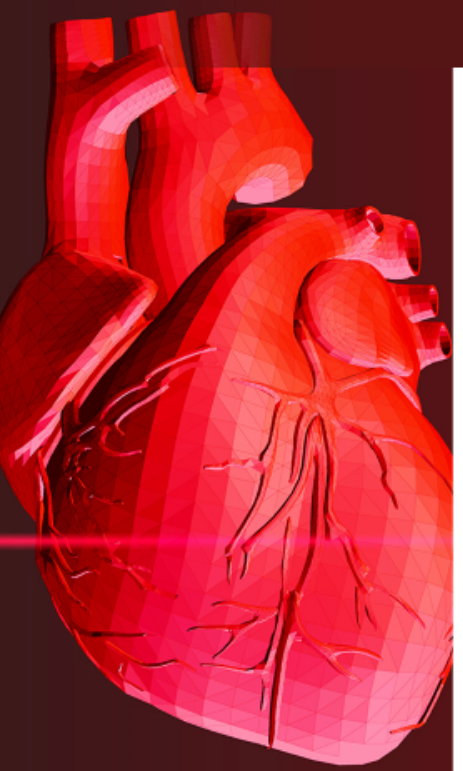


- National Health Insurance Research Database in Taiwan
- Risk of ischemic stroke and ICH in patients ≥ 90 years of age
- Warfarin versus DOACs
- DOACs = lower risk of ICH
  - 00.42%/year vs. 1.63%/year

Chao TF, et al. *Circulation*. 2018;138(1):37-47.

Patients with Prior Stroke

High-Risk Patients: Prior Stroke

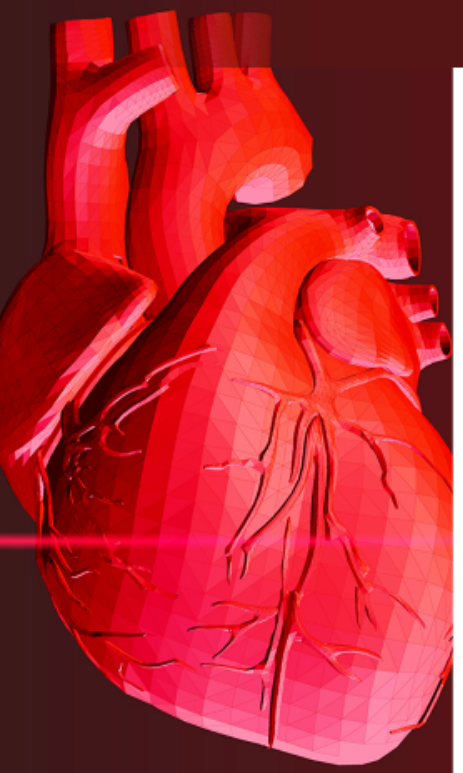


- Prosper Study
  - Evaluated the effectiveness of DOACs vs. warfarin after ischemic stroke in patients with AF
  - Cohort included patients > 65 years old and anticoagulation naïve
- Primary outcome
  - Home time and MACE

GWTG, Get With The Guidelines stroke registry;
MACE, major adverse cardiovascular events.

Xian Y, et al. *JAMA Neurol*. 2019;76(10):1192-202.

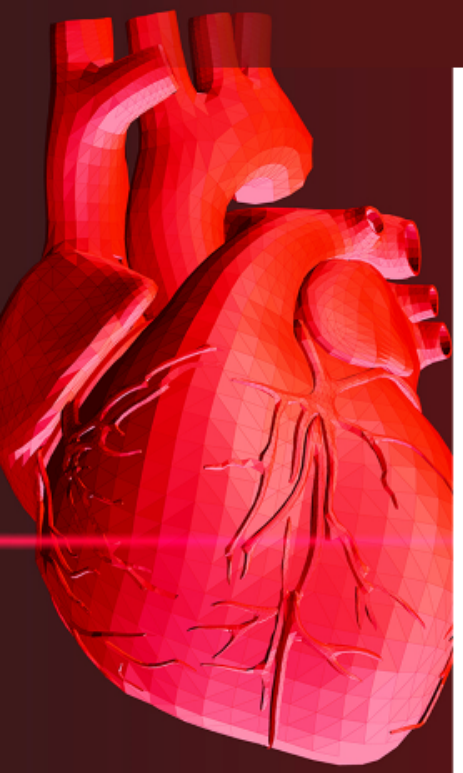
High-Risk Patients: Prior Stroke



- Results
  - 11,662 survivors of acute ischemic stroke
  - 34.7% discharged on DOACs (warfarin, 65.3%)
  - Patients discharged on DOAC had:
    - More days at home
      - 287.2 vs. 263 days
    - Fewer deaths
      - HR 0.88 (CI 0.82-0.9); p<0.001
    - Fewer all-cause readmissions
      - HR 0.93 (CI 0.88-0.97); p=0.003
    - Fewer cardiovascular admissions
      - HR 0.92 (CI 0.86-0.99); p=0.02
    - More gastrointestinal bleeding
      - HR 1.14 (CI 1.01-1.30); p=0.03

Xian Y, et al. *JAMA Neurol*. 2019;76(10):1192-202.

High-Risk Patients: Prior Stroke

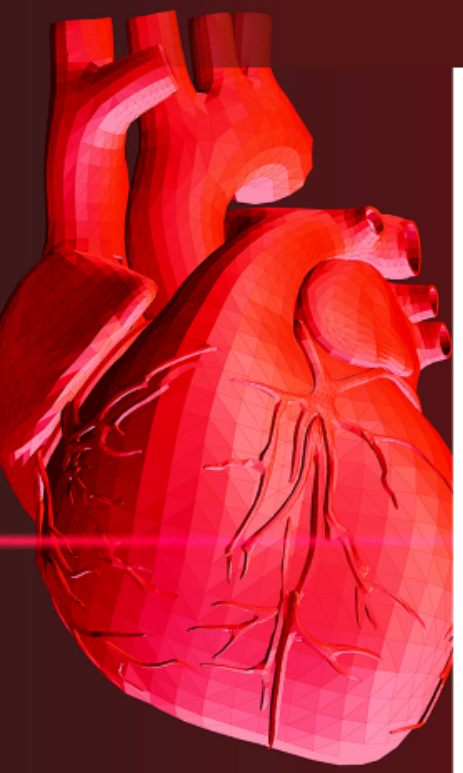


- Conclusions
  - The utilization of a DOAC was associated with better long-term outcomes than warfarin

Xian Y, et al. *JAMA Neurol*. 2019;76(10):1192-202.

Patients on Dual Antiplatelet Therapy (DAPT)

High-Risk Patients: The Triple Therapy Threat

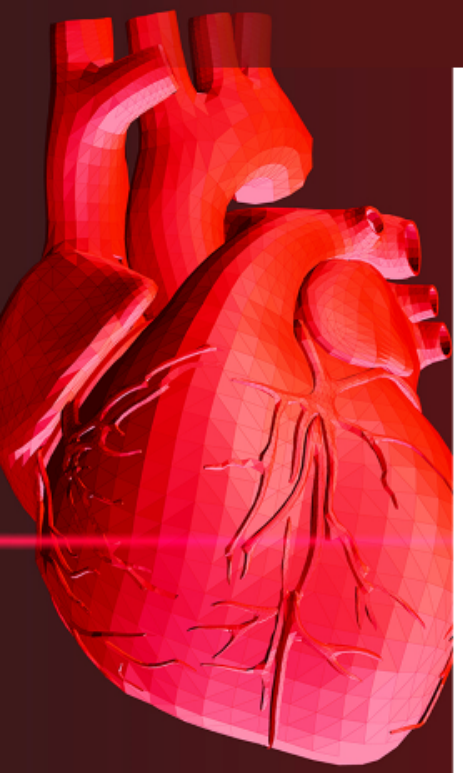


Triple Therapy Threat

- Patients require DAPT (aspirin + $P2Y_{12}$ inhibitor) and have an indication for systemic anticoagulation
- Approximately 5% to 10% of patients undergoing PCI have an indication for chronic anticoagulation
- Various strategies have been evaluated

Faxon DP, et al. *Thromb Haemost*. 2011;106(4):572-84.

WOEST Trial: What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting

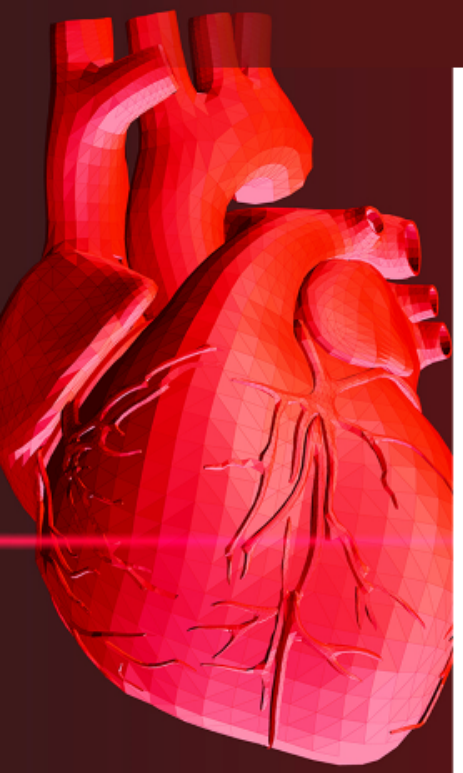


Objective	Evaluate the safety and efficacy of clopidogrel alone compared with clopidogrel plus aspirin in patients with an indication for OAC and s/p PCI
Trial design	Open-label, multicenter, randomized 1:1 ratio, controlled trial
Outcomes	**Primary:** occurrence of any bleeding within 1 year of PCI **Secondary:** composite of death, MI, stroke, stent thrombosis, and target-vessel revascularization

MI, myocardial infarction.

Dewilde WJM, et al. *Lancet*. 2013;381(9872):1107-15.

WOEST Trial: Inclusion and Exclusion Criteria

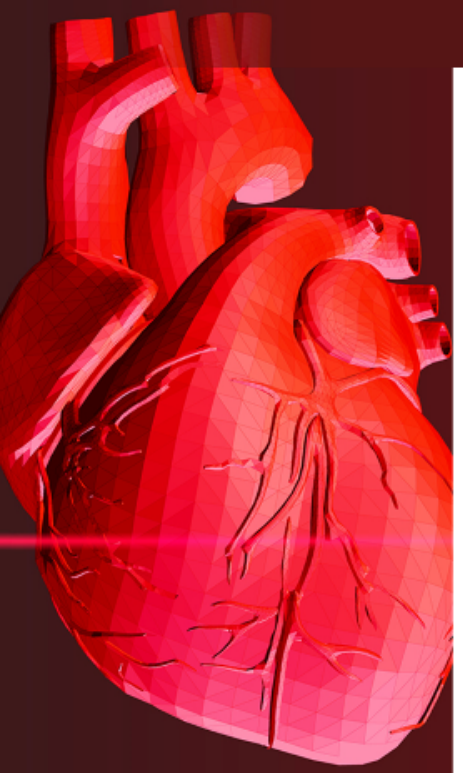


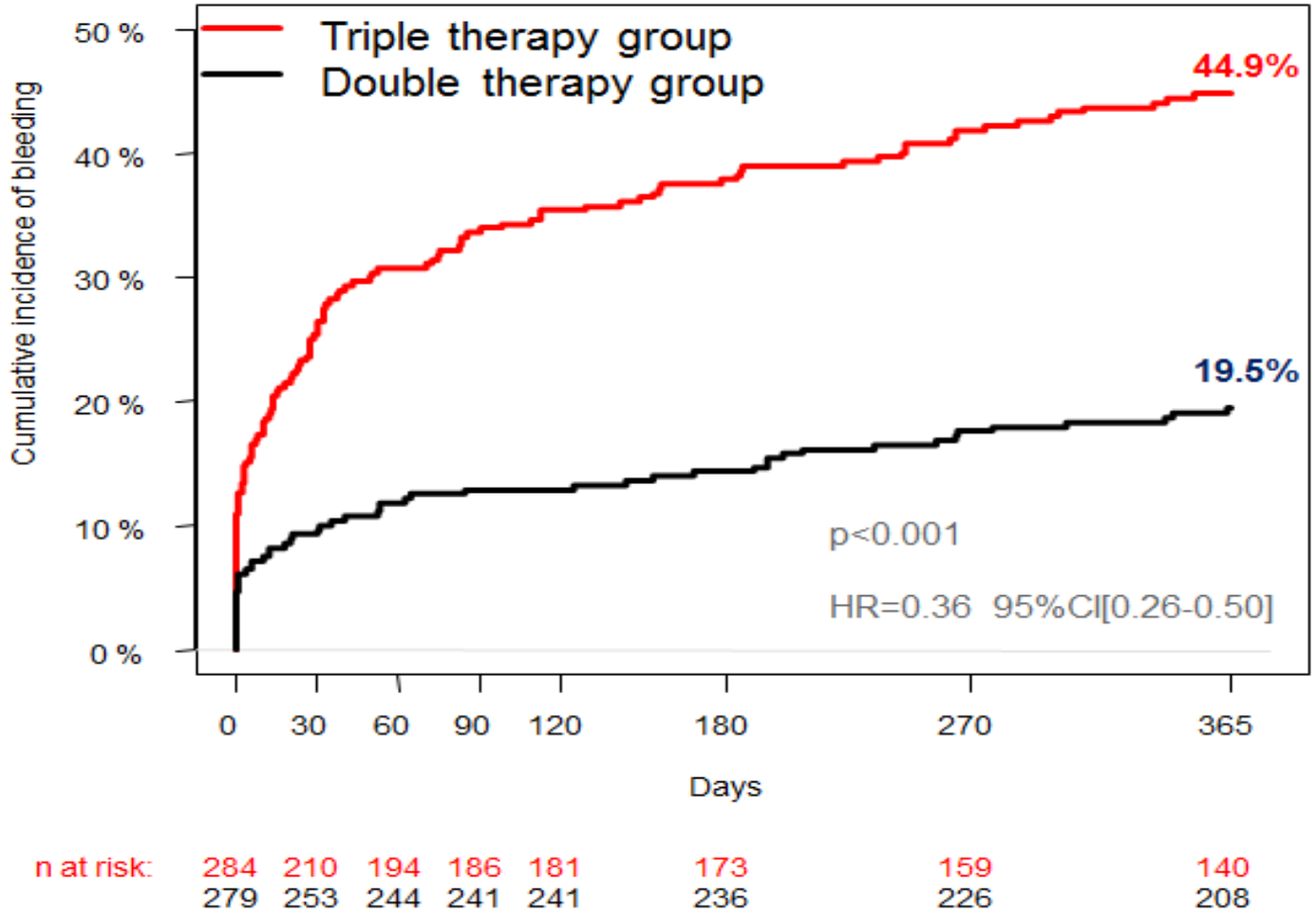
- Inclusion criteria:
  - Age > 18 years
  - Indication for OAC for at least 1 year
  - At least 1 coronary lesion with an indication for PCI

- Exclusion criteria:
  - History of intracranial bleeding
  - Cardiogenic shock
  - Peptic ulcer disease in the past 6 months
  - Thrombocytopenia (platelets < 50,000)
  - Major bleeding within the past year
  - Age > 80 years

Dewilde WJM, et al. *Lancet*. 2013;381(9872):1107-15.

WOEST Trial: Primary Endpoint - Bleeding





Dewilde WJM, et al. *Lancet*. 2013;381(9872):1107-15.

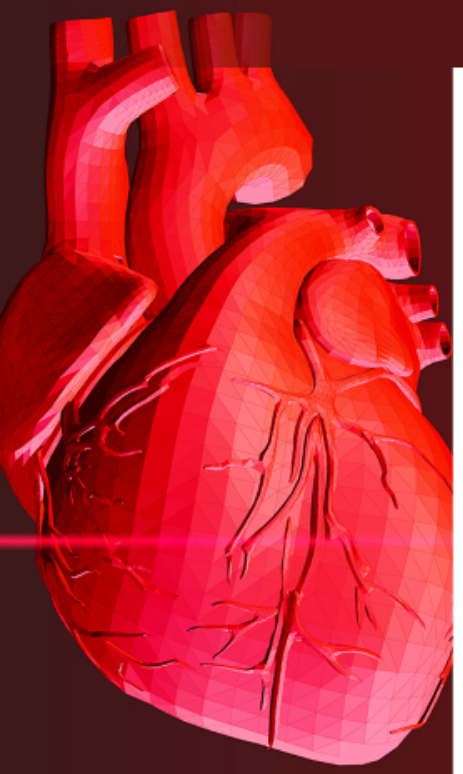
WOEST Trial: Primary Endpoint - Bleeding

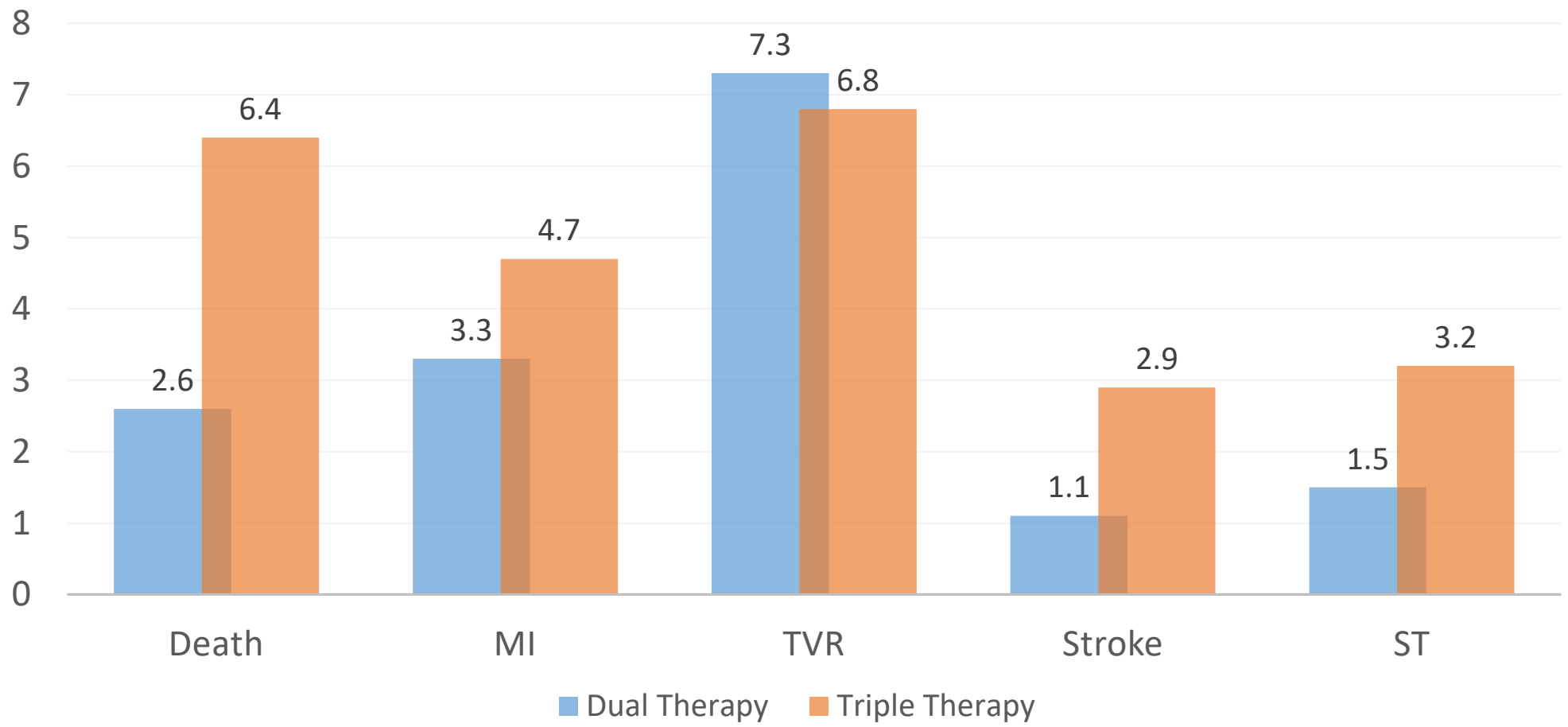
	DAPT (n=279)	TAT (n=284)	p-value
Any bleeding event	54 (19.4%)	126 (44.4%)	< 0.0001
TIMI			
Major	9 (3.2%)	16 (5.6%)	0.159
Major and minor	39 (14%)	89 (31.3%)	< 0.0001
GUSTO			
Severe	4 (1.4%)	10 (3.5%)	0.119
Severe and moderate	15 (5.4%)	35 (12.3%)	0.003
BARC			
3	18 (6.5%)	36 (12.7%)	0.011
2	23 (8.2%)	59 (20.8%)	< 0.0001
2 + 3	40 (14.3%)	90 (31.7%)	< 0.0001
1	18 (6.5%)	45 (15.8%)	0.0004
Any blood transfusion	11 (3.9%)	27 (9.5%)	0.011

BARC, Bleeding Academic Research Consortium; GUSTO, Global Strategies for Opening Occluded Coronary Arteries; TAT, triple anticoagulant therapy; TIMI, thrombolysis in myocardial infarction.

Dewilde WJM, et al. *Lancet*. 2013;381(9872):1107-15.

WOEST Trial: Secondary Endpoint

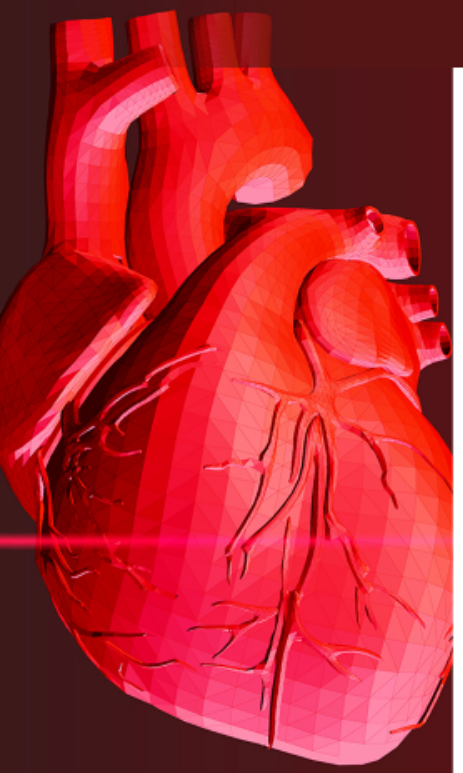




ST, stent thrombosis; TVR, target-vessel revascularization.

Dewilde WJM, et al. *Lancet*. 2013;381(9872):1107-15.

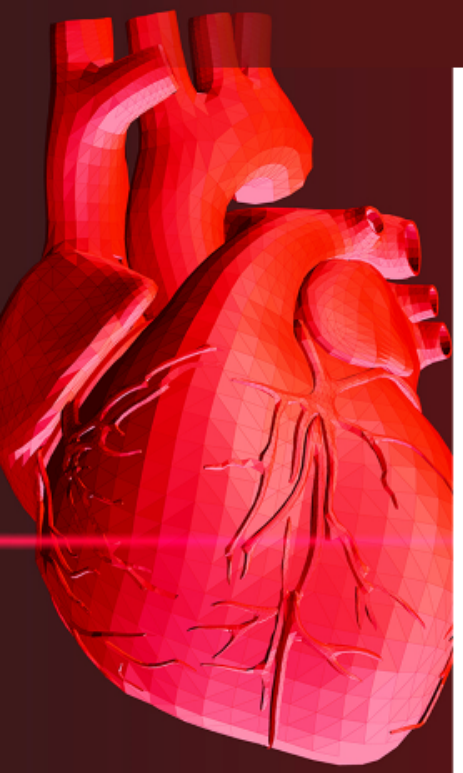
WOEST Trial: Conclusions



- First randomized trial to address optimal antiplatelet therapy in patients on OAC undergoing coronary stenting
- Specifically designed to evaluate bleeding events
- Primary endpoint: Dual therapy with OAC plus clopidogrel resulted in less bleeding than triple therapy
- Secondary endpoint: With dual therapy, there was no excess of thrombotic/thromboembolic events (stroke, stent thrombosis, target vessel revascularization, MI, or death)

Dewilde WJM, et al. *Lancet*. 2013;381(9872):1107-15.

PIONEER AF – PCI: An Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention



Design:

Patients (n=2124) with AF and PCI were randomized to:

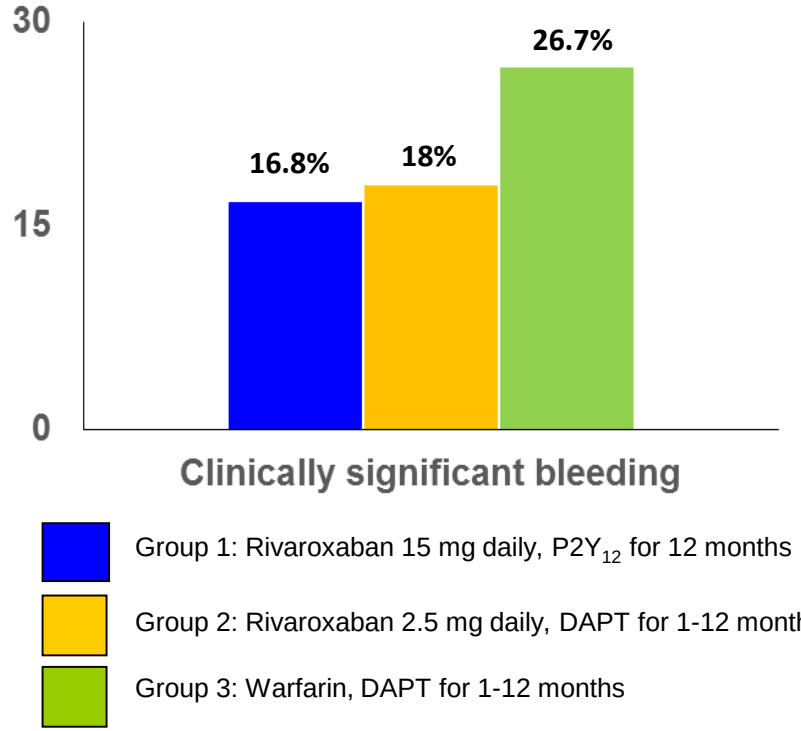
- Group 1: Rivaroxaban 15 mg daily plus $P2Y_{12}$ inhibitor for 12 months (n=709)
- Group 2: Rivaroxaban 2.5 mg twice daily plus DAPT for 1-12 months (n=709)
- Group 3: Warfarin plus DAPT for 1-12 months (n=706)

Results:

Clinically significant bleeding:

- 16.8% in Group 1
- 18% in Group 2
- 26.7% in Group 3

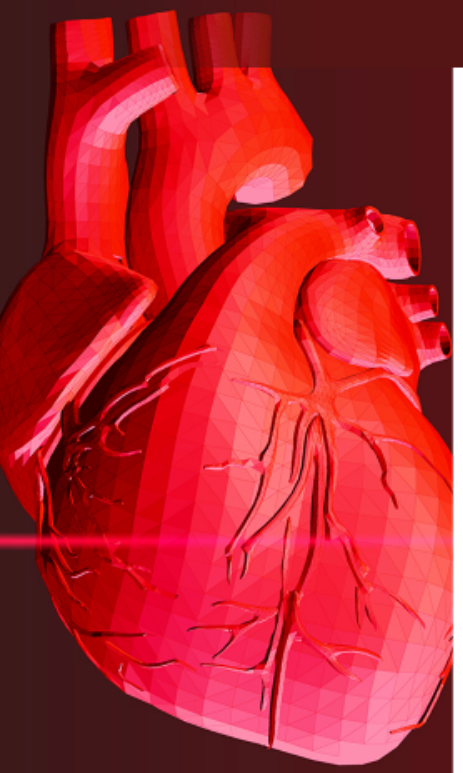
(HR 0.59, p<0.001 for group 1 vs. 3, ARR=9.9, NNT=11)
(HR 0.63, p<0.001 for group 2 vs. 3, ARR=8.7, NNT=12)



ARR, absolute risk reduction; NNT, number needed to treat.

Gibson CM, et al. *N Engl J Med*. 2016;375(25):2423-34.

PIONEER AF – PCI



Secondary Outcomes: MACE (composite and alone) and stent thrombosis

- Stent thrombosis: 0.8% in group 1 vs. 0.9% in group 2 vs. 0.7% in group 3

  (HR 1.20, p=0.79 for group 1 vs. 3; HR 1.44, p=0.57 for group 2 vs. 3)

- MACE: 6.5% in group 1 vs. 5.6% in group 2 vs. 6% in group 3

  (HR 1.08, p=0.75 for group 1 vs. 3; HR 0.93, p=0.76 for group 2 vs. 3)

Conclusion:

In patients with AF undergoing PCI w/ stents,

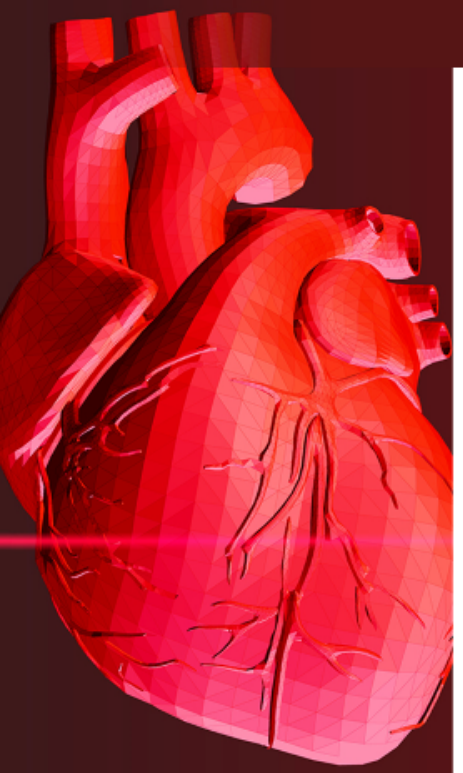
- Rivaroxaban 15 mg daily plus $P2Y_{12}$ monotherapy for 1 year *or*
- Rivaroxaban 2.5 mg BID plus 1, 6, or 12 months of DAPT

reduced the risk of clinically significant bleeding compared to VKA plus 1, 6, or 12 months of DAPT

BID, twice daily; VKA, vitamin K antagonist.

Gibson CM, et al. *N Engl J Med*. 2016;375(25):2423-34.

RE-DUAL PCI: Dual Antithrombotic Therapy with Dabigatran After Percutaneous Coronary Intervention in Patients with Atrial Fibrillation



Design:

Patients (n=2725) with AF undergoing coronary revascularization were randomized to:

- Dual therapy with dabigatran 110 mg (n=981)
- Dual therapy with dabigatran 150 mg (n = 763)
- Triple therapy with warfarin

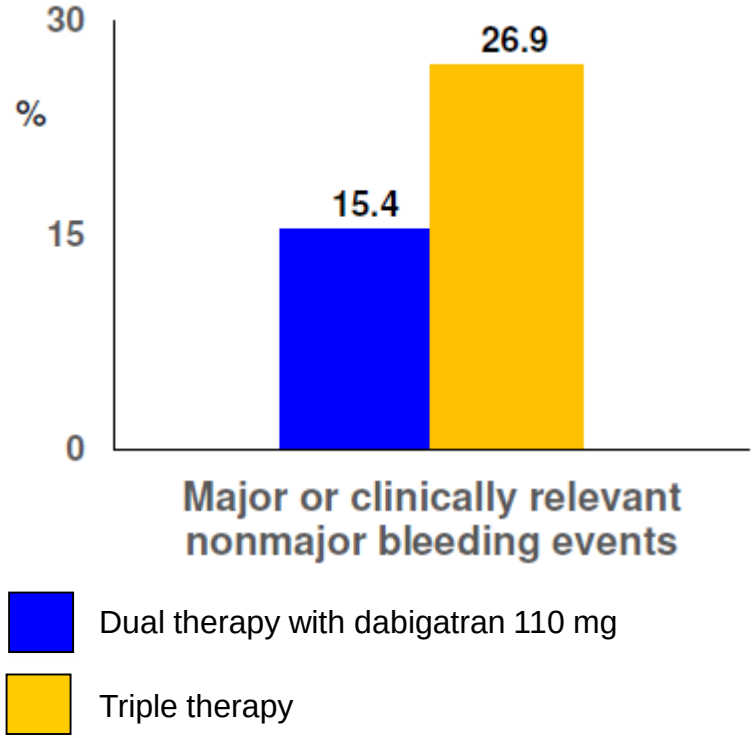
Results:

Major or CRNM bleeding events:

- 15.4% of the dual therapy with dabigatran 110 mg group
- 26.9% of the triple therapy group
  (p for non-inferiority <0.001, p for superiority <0.001)

Major or CRNM bleeding events:

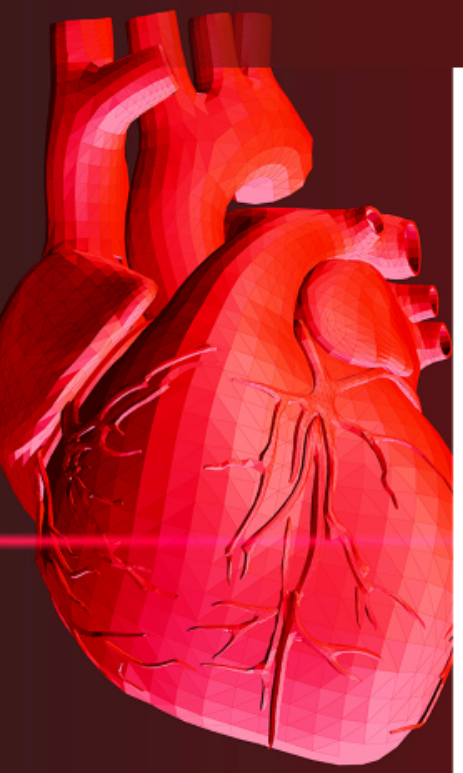
- 20.2% of the dual therapy with dabigatran 150 mg group
- 25.7% of the corresponding triple therapy group (excluding elderly participants outside the U.S.)
  (p for non-inferiority <0.001)



CRNM, clinically relevant non-major.

Cannon CP, et al. *N Engl J Med*. 2017;377(16):1513-24.

RE-DUAL PCI



Efficacy endpoint: composite of MI, stroke, systemic embolism

- 13.7% dual therapy vs. 13.4% triple therapy

HR 1.04 (CI 0.84-1.29), p=0.005 for non-inferiority

Conclusions:

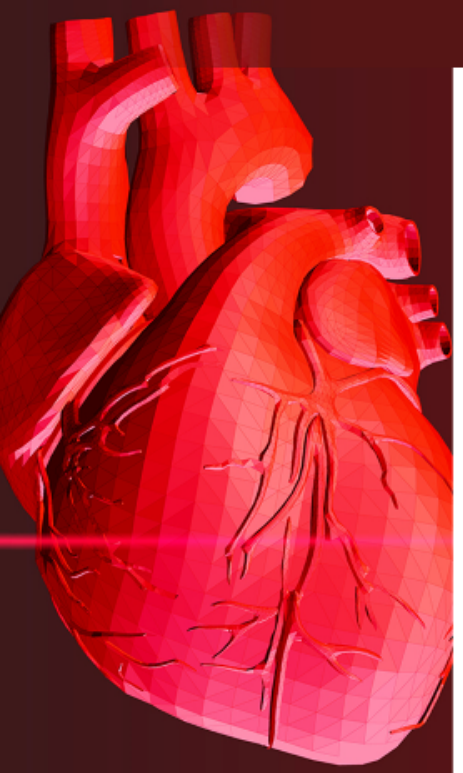
In patients with AF who have undergone PCI,

- Dual therapy with dabigatran + $P2Y_{12}$ antagonist **significantly reduced the risk of bleeding compared to warfarin triple therapy**, with non-inferiority for overall thromboembolic events
- Absolute risk reductions with dabigatran dual therapy were **11.5% and 5.5%** in ISTH major or CRNM bleeding at the 110 mg and 150 mg doses, respectively, compared with warfarin triple therapy

ISTH, International Society on Thrombosis and Haemostasis.

Cannon CP, et al. *N Engl J Med*. 2017;377(16):1513-24.

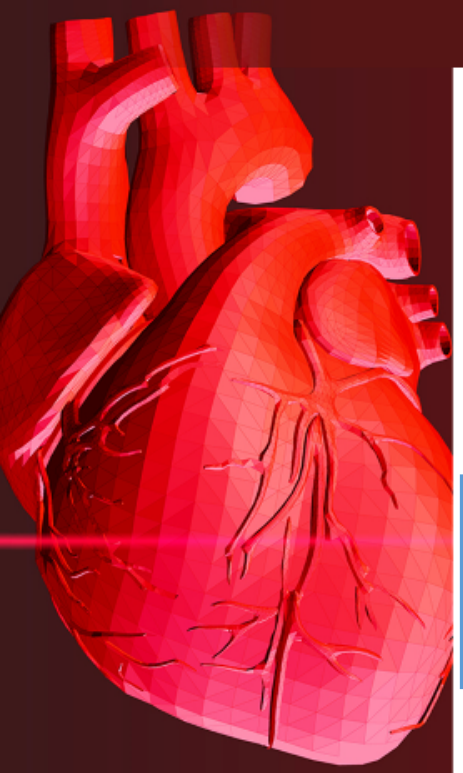
AUGUSTUS TRIAL: Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation



Objective	Assess the safety and efficacy of apixaban + aspirin compared to VKA + aspirin or PLC
Trial design	Prospective, multicenter, two-by-two factorial, RCT
Outcomes	**Primary:** ISTH major or CRNM bleeding **Secondary:** stroke, MI, stent thrombosis, urgent revascularization

Lopes RD, et al. *N Engl J Med*. 2019;380(16):1509-24.

AUGUSTUS TRIAL



Randomize
n=4614
patients

Apixaban 5 mg BID + $P2Y_{12}$ inhibitor
Apixaban 2.5 mg BID in selected patients

Open label

VKA + $P2Y_{12}$ inhibitor
(INR 2-3)

ASA for all on the day of ACS or PCI
ASA versus PLC after randomization

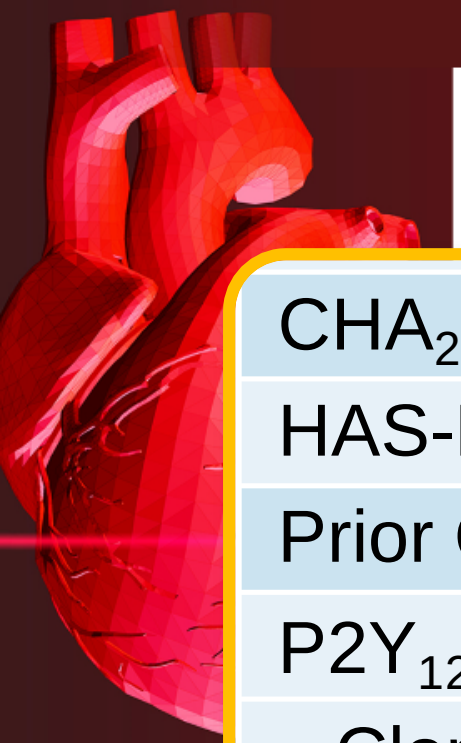
Aspirin — *Double blind* — **Placebo**

Aspirin — *Double blind* — **Placebo**

ACS, acute coronary syndrome.

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

AUGUSTUS TRIAL: Baseline Characteristics

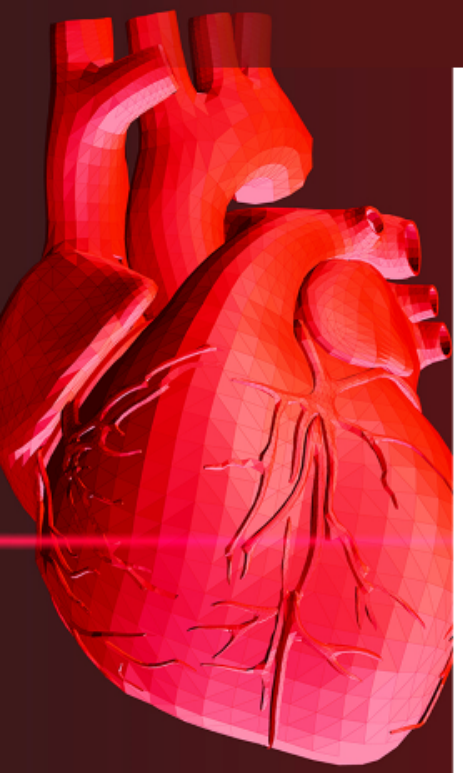


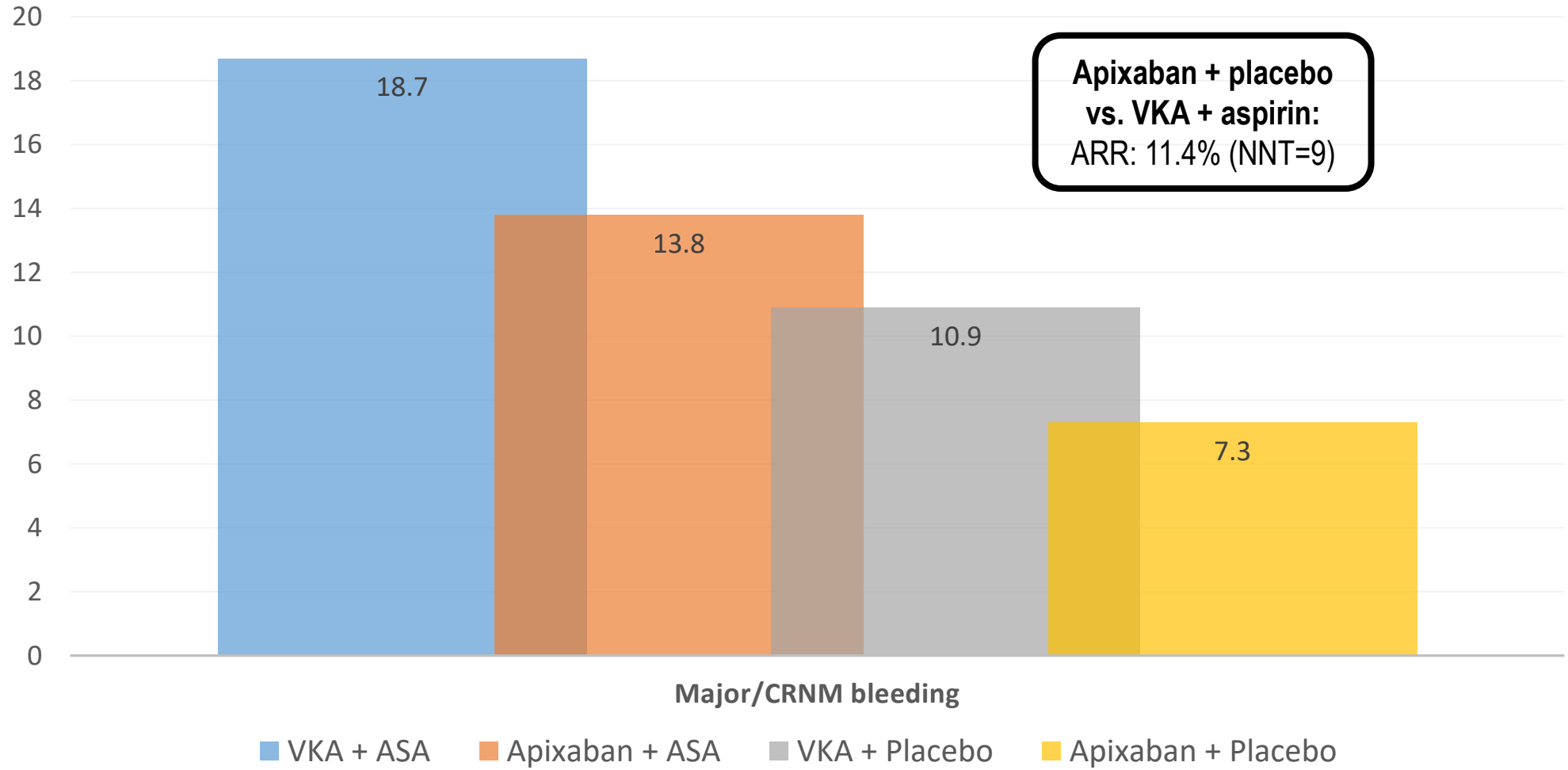
	Total (N=4614)
Age, median (25th, 75th), years	70.7 (64.2, 77.2)
Female, %	29.0
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)
HAS-BLED score, mean (SD)	2.9 (0.9)
Prior OAC, %	49.0
$P2Y_{12}$ inhibitor, %	
Clopidogrel	92.6
Qualifying index event, %	
ACS and PCI	37.3
ACS and no PCI	23.9
Elective PCI	38.8

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

Lopes RD, et al. *N Engl J Med*. 2019;380(16):1509-24.

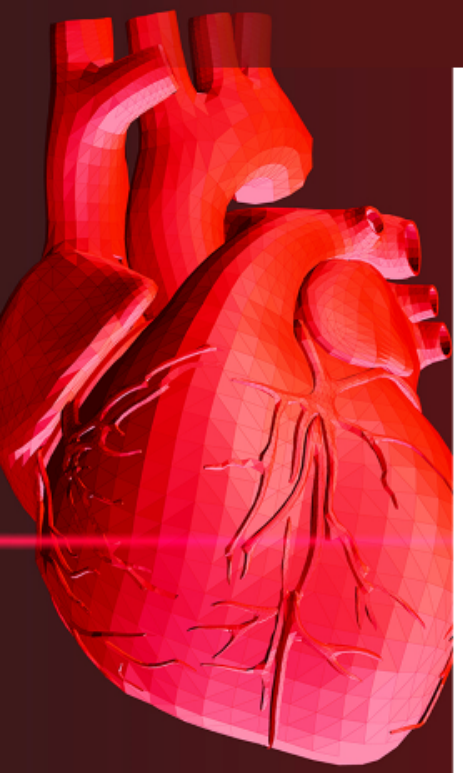
AUGUSTUS TRIAL: Major/CRNM Bleeding





Lopes RD, et al. *N Engl J Med*. 2019;380(16):1509-24.

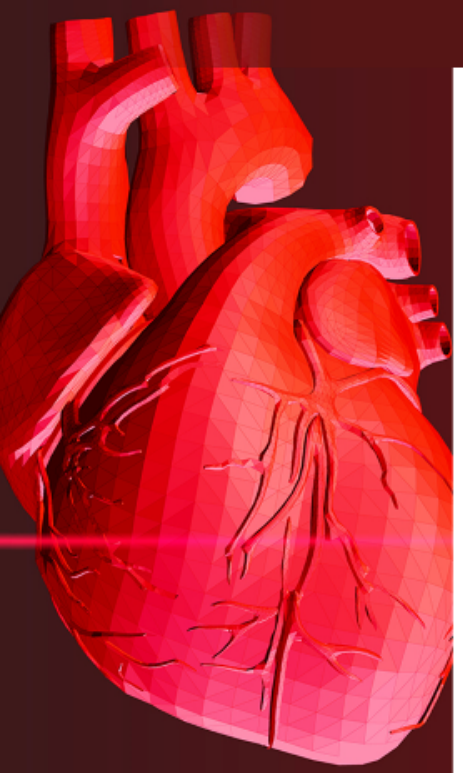
AUGUSTUS TRIAL: Ischemic Outcomes – Apixaban vs. VKA



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)
Cardiovascular 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)**

Lopes RD, et al. *N Engl J Med*. 2019;380(16):1509-24.

AUGUSTUS TRIAL: Endpoints



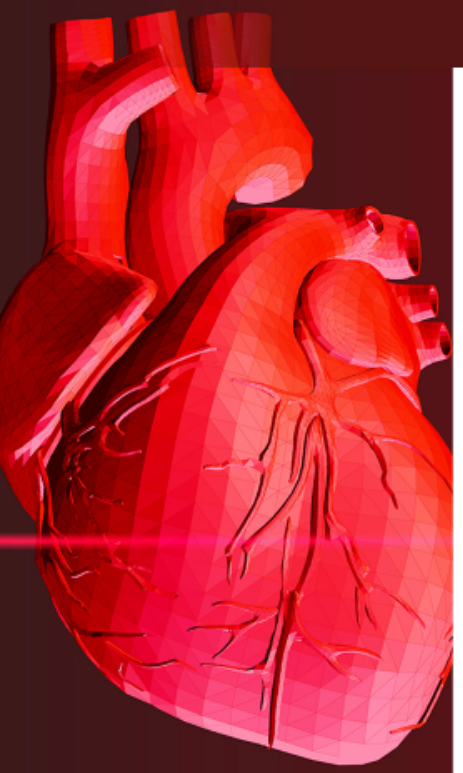
Endpoints	Apixaban	Warfarin	p-value
Major or CRNM bleeding	241/2290 (10.5%)	332/2259 (14.7%)	< 0.001
Death or hospitalization	541/2306 (23.5%)	632/2308 (27.4%)	0.002
Death or ischemic event	154/2306 (6.7%)	163/2308 (7.1%)	NS

Endpoints	Aspirin	Placebo	p-value
Major or CRNM bleeding	367/2277 (16.1%)	204/2279 (9.0%)	< 0.001
Death or hospitalization	604/2307 (26.2%)	569/2307 (24.7%)	NS
Death or ischemic event	149/2307 (6.5%)	168/2307 (7.1%)	NT

NS, not significant; NT, not tested.

Lopes RD, et al. *N Engl J Med*. 2019;380(16):1509-24.

AUGUSTUS TRIAL: Conclusions

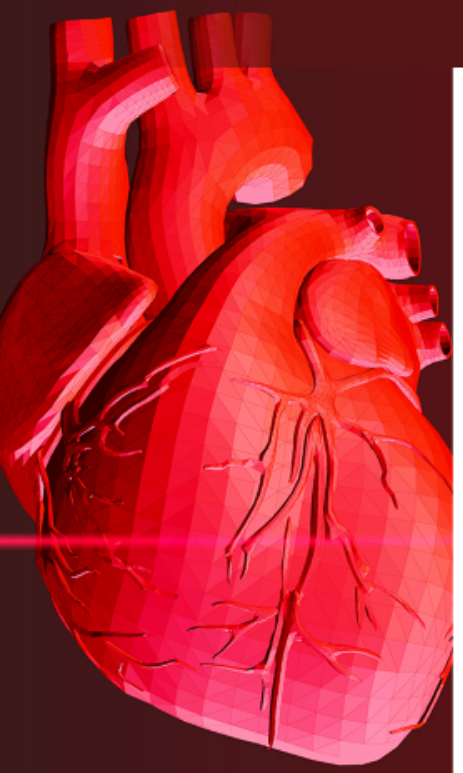


- In patients with AF and recent ACS or PCI treated with a $P2Y_{12}$ inhibitor, OAC regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a VKA, aspirin, or both

- *Largest trial available*
- *Stroke and bleeding risks were assessed*
- *Percentage of time in therapeutic INR was lower than other DOAC PCI trials*
- *Majority of patients were placed on clopidogrel*

Lopes RD, et al. *N Engl J Med*. 2019;380(16):1509-24.

DAPT vs. TAT: Guideline Recommendation

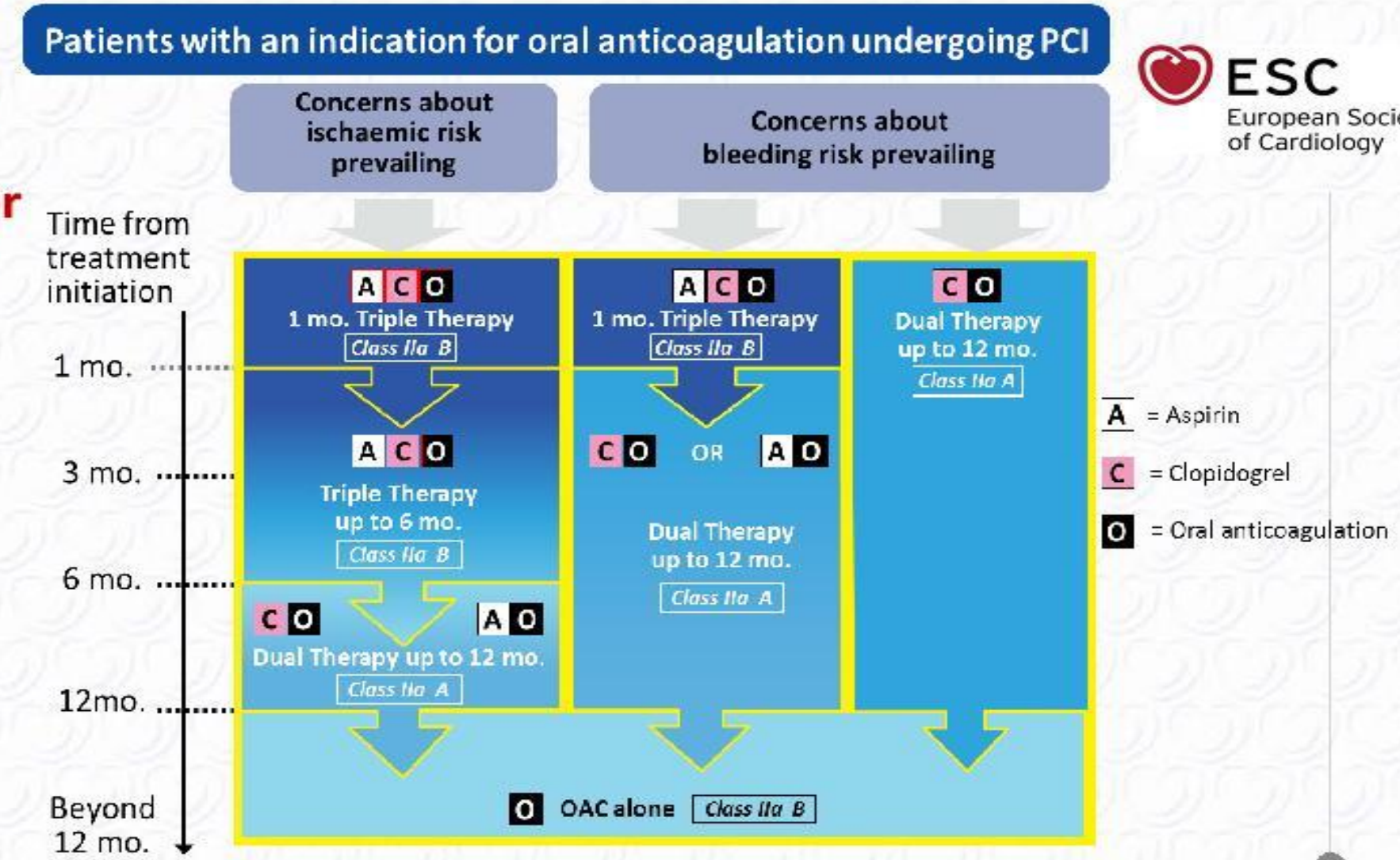


- ACC/AHA Guidelines
  - If TAT is used, it may be reasonable to choose clopidogrel over prasugrel
  - DAPT with a $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor) and dose-adjusted VKA, rivaroxaban 15 mg daily, or dabigatran 150 mg twice daily is reasonable
  - If TAT is used, then transition to DAPT may be considered at 4 to 6 weeks of TAT

ACC, American College of Cardiology;
AHA, American Heart Association.

January CT, et al. *Circulation.* 2019;140(2):e125-51.

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



ESC European Society of Cardiology

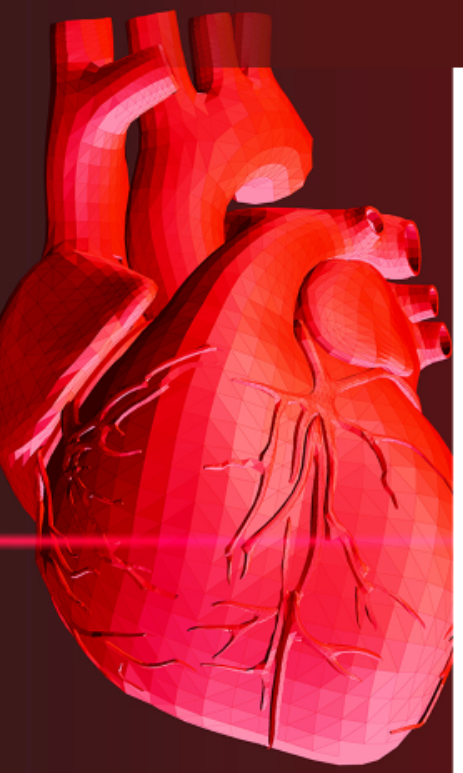
www.escardio.org/guidelines

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Valgimigli M, et al. *Eur Heart J*. 2018;39(3):213-60.

Patients with Renal Insufficiency

Renal Insufficiency

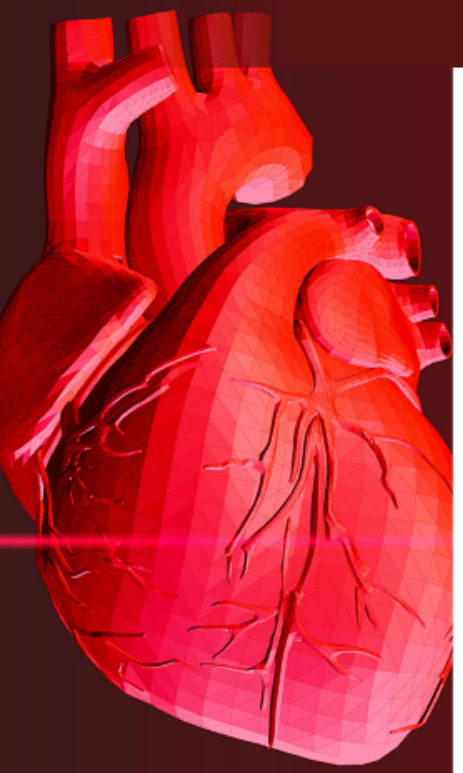


- AF is more common in patients with ESRD on hemodialysis than in the general population
  - Prevalence of 11%-13%
  - Increased risk of stroke and bleeding among patients with AF and ESRD
    - 1.5-fold increase in stroke
    - 2-fold increase in bleeding

ESRD, end-stage renal disease.

Wang TK, et al. *Heart Lung Circ.* 2016;25(3):243-9.

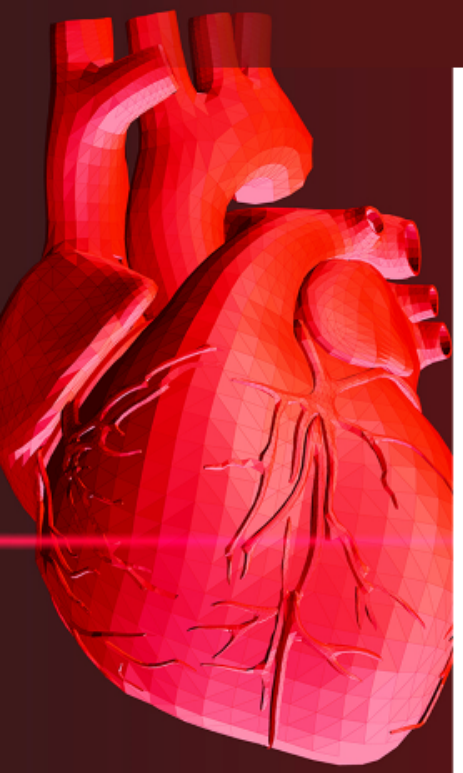
Pharmacokinetic Properties of DOACs



	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Anticoagulation target	Factor II	Factor Xa	Factor Xa	Factor Xa
Impact on coagulation assay	aPTT (2-3 x) INR 40%↑	aPTT 40% INR 40%↑	↑aPTT & INR	↑aPTT
Time to peak (hours)	1-3	2-4	1-3	1-2
Half-life (hours)	14-17	9-13	8-15	~ 10
% renal elimination	80%	66%	25%	50%
Dialyzable	Yes	No	No	
CYP metabolism	No	30% CYP3A4	15% CYP3A4	< 4%
P-glycoprotein substrate?	Yes	Yes	Yes	Yes

Garcia D, et al. *Blood*. 2010;115(1):15-20.;
Wittkowsky A. *Pharmacotherapy.* 2011;31(12):1175-91.

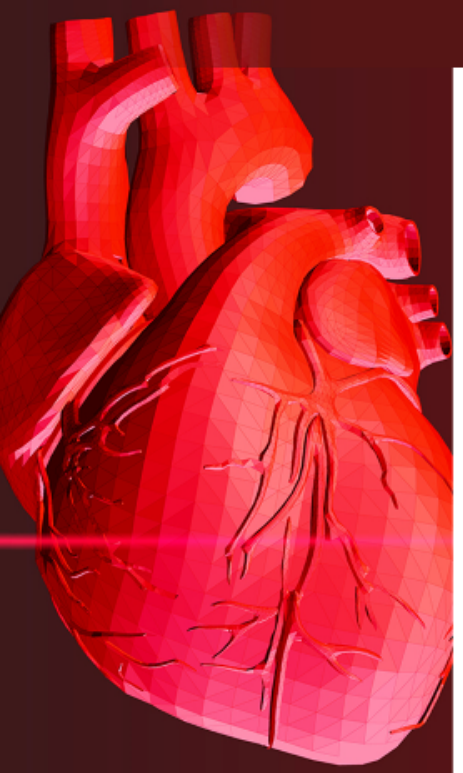
Renal Dosing of DOACs



Indication	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Non-valvular AF	Reduce dose to 2.5 mg BID (2 of 3 criteria: SCr ≥ 1.5 mg/dL, age ≥ 80 years, weight ≤ 60 kg)	Reduce dose to 75 mg BID if CrCl 15-30 mL/min; avoid use if CrCl < 15 mL/min	Avoid use if CrCl > 95 mL/min; reduce dose to 30 mg daily if CrCl 15-50 mL/min	Reduce dose to 15 mg daily if CrCL < 30-50 mL/min
VTE treatment	No dose reduction	Avoid if CrCl < 30 mL/min	Reduce dose to 30 mg daily if CrCl < 15-50 mL/min or weight ≤ 60 kg; avoid use if CrCl < 15 mL/min	Avoid use if CrCl < 30 mL/min

CrCl, creatinine clearance; SCr, serum creatinine; VTE, venous thromboembolism.

RENAL AF: Renal Hemodialysis Patients Allocated Apixaban versus Warfarin in Atrial Fibrillation



Objective	Assess the safety of apixaban versus warfarin with respect to major bleeding or CRNM bleeding in patients with AF and with ESRD on hemodialysis
Trial design	Open-label, randomized trial
Endpoints	**Primary:** ISTH major or CRNM bleeding **Secondary:** PK in patients randomized to apixaban: death, stroke, or systemic embolism

PK, pharmacokinetics.

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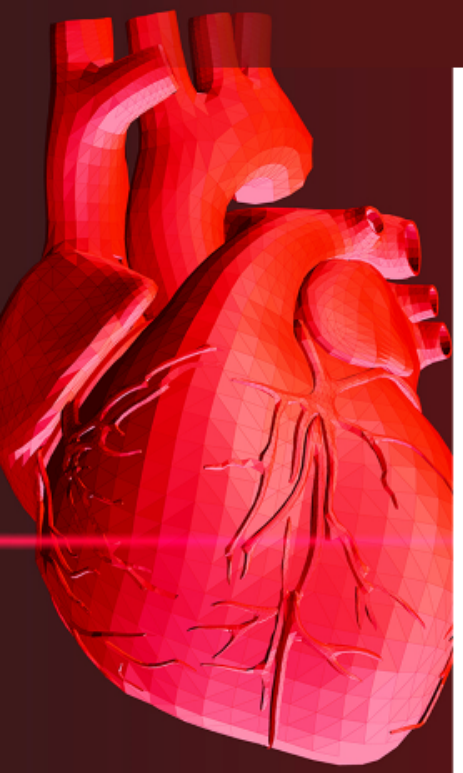
RENAL AF



- Inclusion criteria:
  - Atrial fibrillation
  - CHA_2DS_2-VASC ≥ 2
  - Hemodialysis
  - Candidate for OAC
- Exclusion criteria:
  - Moderate to severe mitral stenosis
  - Anticoagulation for other reasons than AF
  - Need for aspirin dose > 81 mg
  - DAPT

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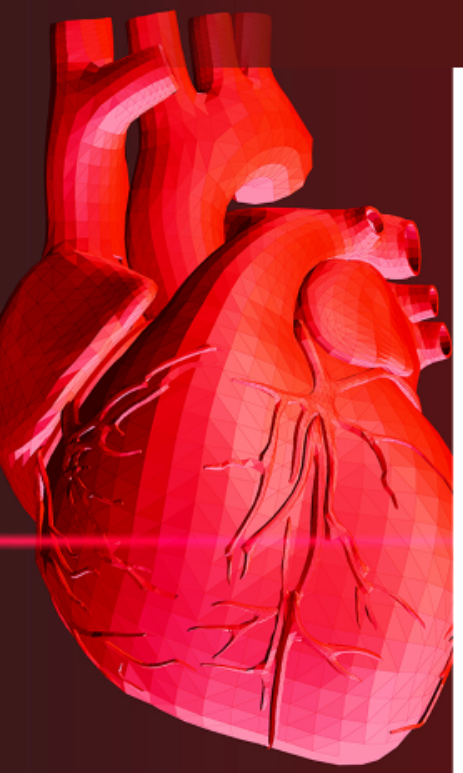
RENAL AF



Randomize

n=154

patients

Apixaban 5 mg BID

Apixaban 2.5 mg BID in selected patients

N=82

Warfarin

(INR 2-3)

N=72

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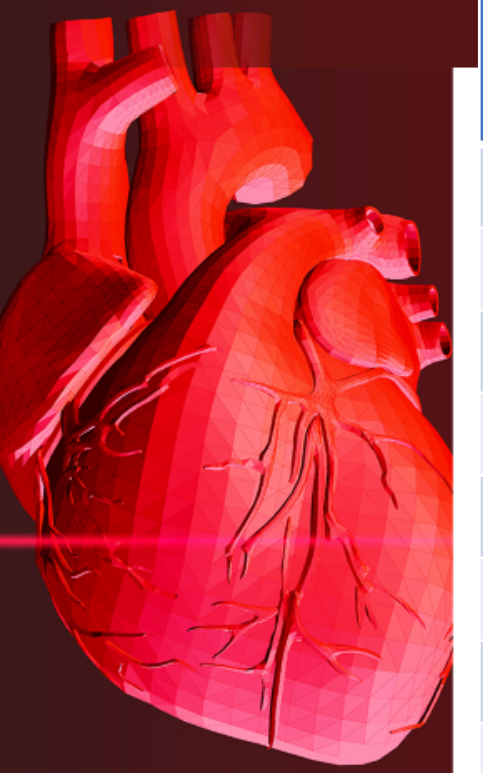
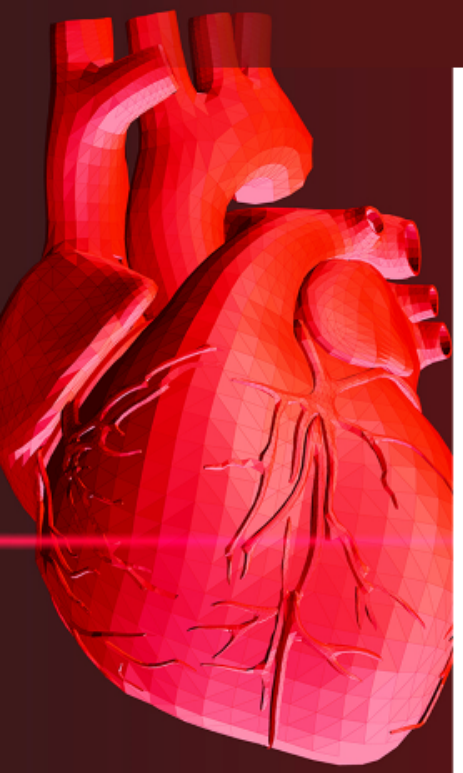
RENAL AF: Baseline Characteristics



	Apixaban (N=82)	Warfarin (N=72)
Age (median), years	69	68
• ≥ 75 years, n (%)	24 (29.3%)	15 (20.8%)
Female, n (%)	34 (41.5%)	22 (30.6%)
Black, n (%)	35 (42.7%)	34 (47.2%)
CHA_2DS_2-VASc, mean	**4**	**4**
Stroke, n (%)	17 (20.7%)	12 (16.7%)
Warfarin or DOAC naive, n (%)	10 (12.2%)	5 (5.6%)
Type of AF, n (%) • Paroxysmal • Persistent/permanent	 45 (54.9%) 37 (45.1%)	 40 (55.6%) 32 (44.4%)
Aspirin, n (%)	29 (36.7%)	32 (45.7%)
Prior clinically relevant bleeding, n (%)	**18 (22.0%)**	**14 (19.4%)**

RENAL AF: Characteristics



Randomized to apixaban	Apixaban (n=77)
First apixaban dose	
2.5 mg twice daily	22 (28.6%)
5 mg twice daily	55 (71.4%)
Apixaban dose reduced from 5 mg to 2.5 mg twice daily	15 (27.3%)

Patients randomized to warfarin	Warfarin (n=68)
Time in therapeutic range (INR 2-3)	44.3%

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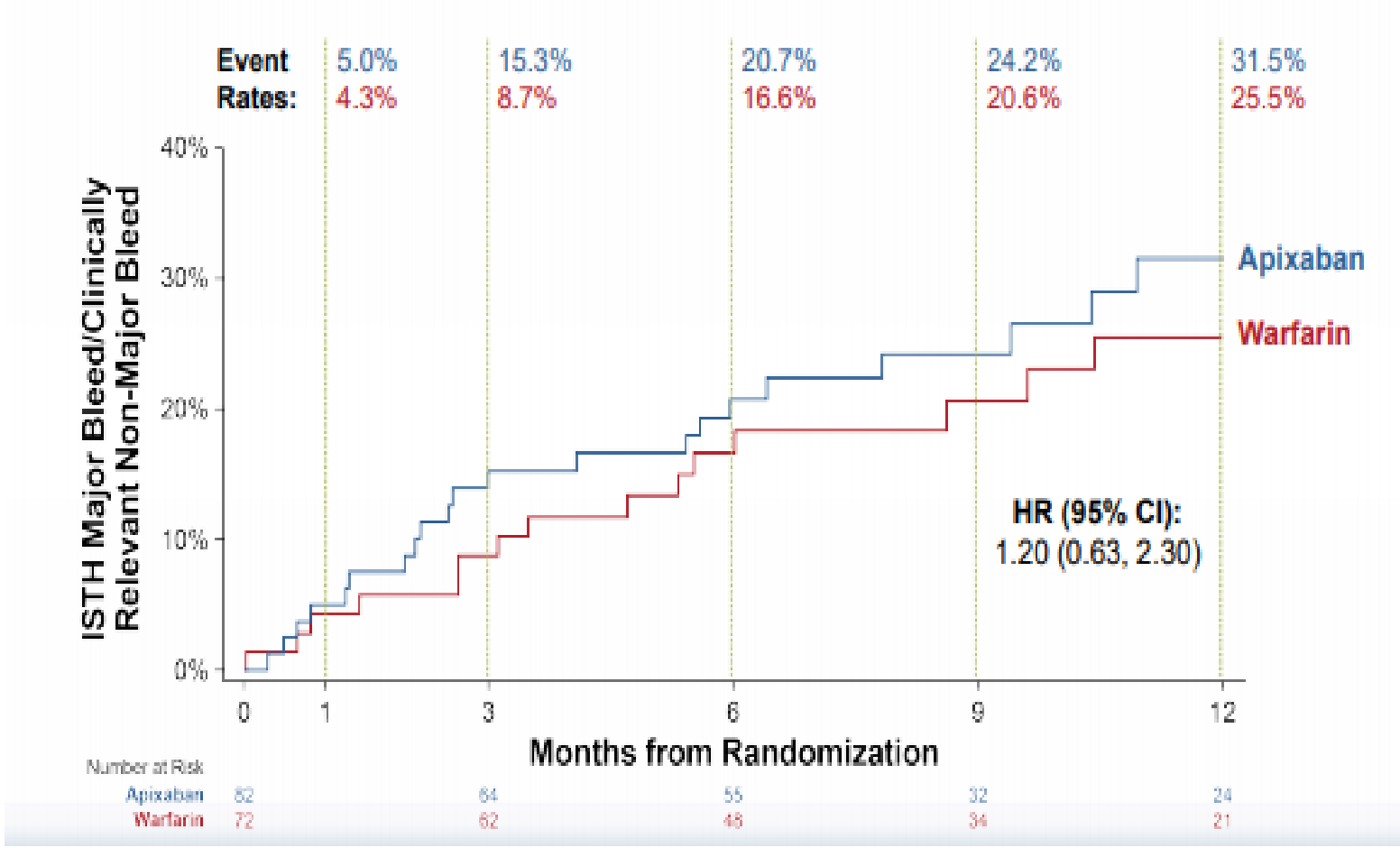
Time to Major or CRNM Bleeding



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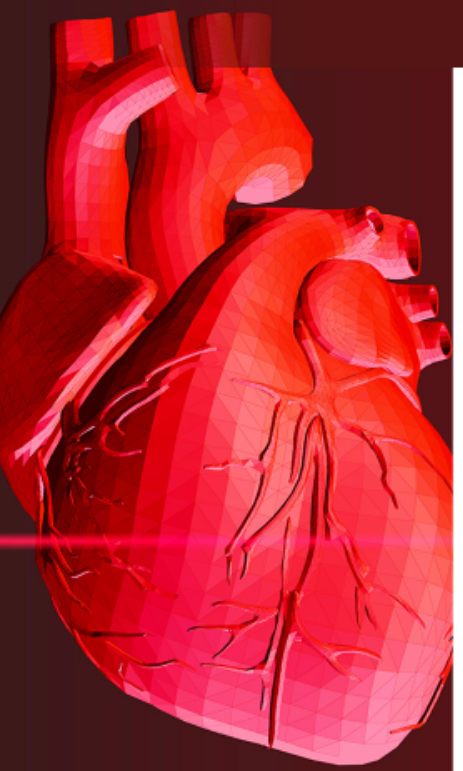
RENAL AF: Primary Safety Endpoint



	Apixaban (N=82)	Warfarin (N=72)
ISTH major bleed/CRNM bleed	21 (25.6%)	16 (22.2%)
• Intracranial	1 (1.2%)	1 (1.4%)
• Gastrointestinal	2 (2.4%)	6 (8.3%)
• Hemodialysis access site	11 (13.4%)	6 (8.3%)
ISTH major bleed	**7 (8.5%)**	**7 (9.7%)**
• Intracranial	1 (1.2%)	1(1.4%)
• Gastrointestinal	2 (2.4%)	5 (6.9%)
• Hemodialysis access site	1 (1.2%)	0 (0%)
ISTH CRNM bleed	14 (17.1%)	9 (12.5%)
• Gastrointestinal	**0 (0%)**	**1 (2.8%)**
• Hemodialysis access site	**10 (12.2%)**	**6 (8.3%)**

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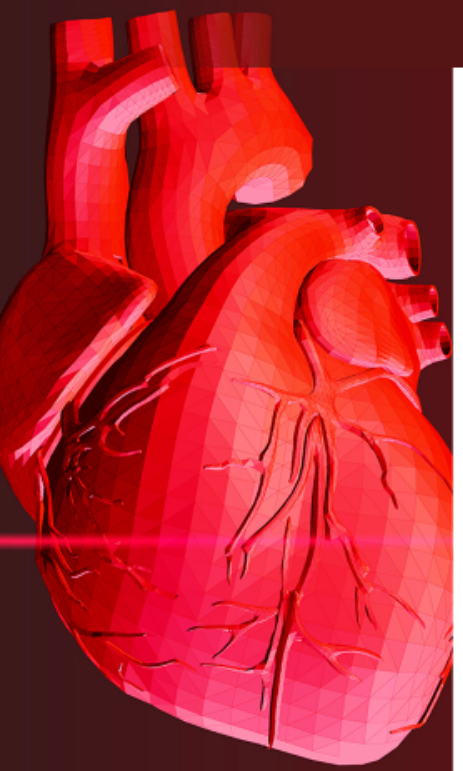
RENAL AF: Secondary Endpoint



	Apixaban (N=82)	Warfarin (N=72)
Stroke	2 (2.4%)	2 (2.8%)
• Ischemic	1 (1.2%)	2 (2.8%)
• Hemorrhagic	1 (1.2%)	6 (8.3%)
Systemic embolism	**0 (0%)**	**0 (0%)**
Death	21 (26.5%)	13 (18.1%)
• Cardiovascular	9 (11%)	4 (5.6%)
• Non-cardiovascular	5 (6.1%)	8 (11.1%)
Undetermined	7 (8.5%)	1 (1.4%)
Bleeding-related death	**1 (1.2%)**	**0 (0%)**

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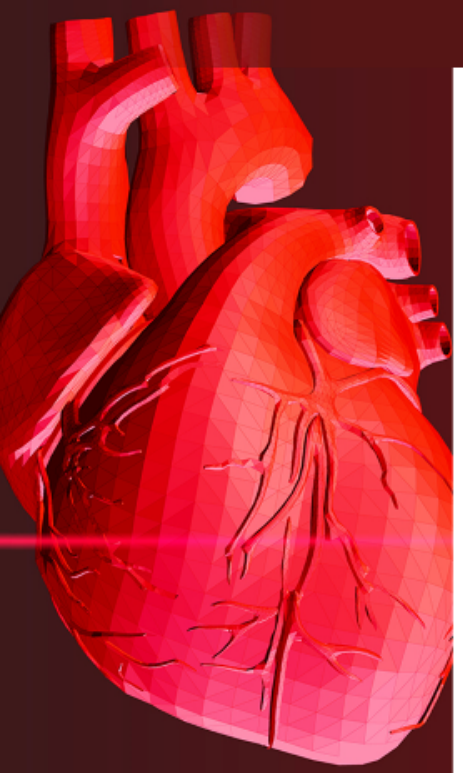
RENAL AF: Conclusions



- First randomized trial to assess the safety of a DOAC (apixaban) vs. warfarin for patients with AF and ESRD on hemodialysis
- Terminated prematurely and the power was limited by small sample size
- In this exploratory study, there were similar rates of major and CRNM bleeding with apixaban and warfarin
- Large proportion of warfarin patients in subtherapeutic range
- **Results:** apixaban may be a reasonable anticoagulant choice in patients on hemodialysis

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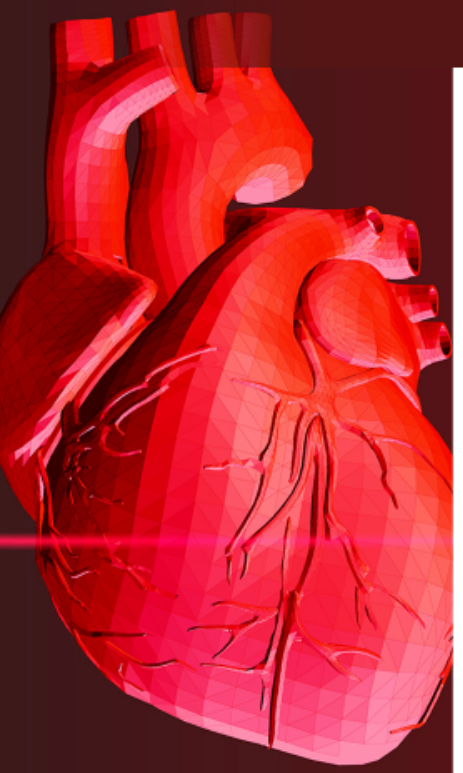
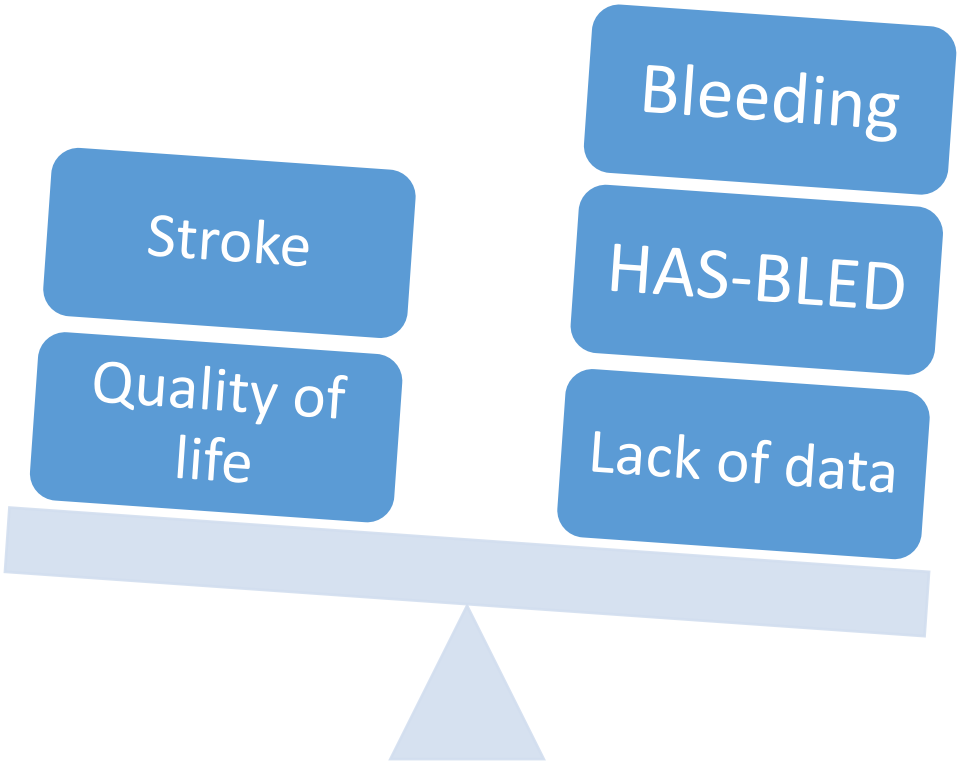
Anticoagulation: Striking a Balance

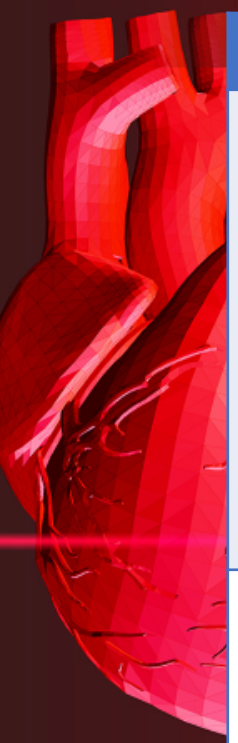


Benefit

Risk



Anticoagulants: Select Drug Interactions

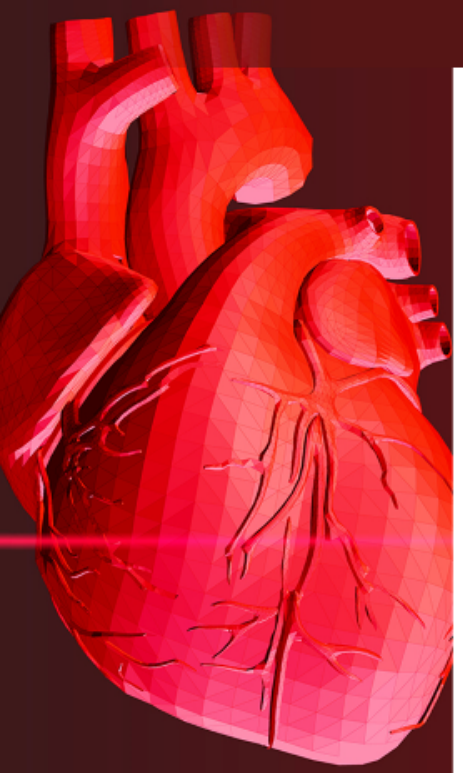


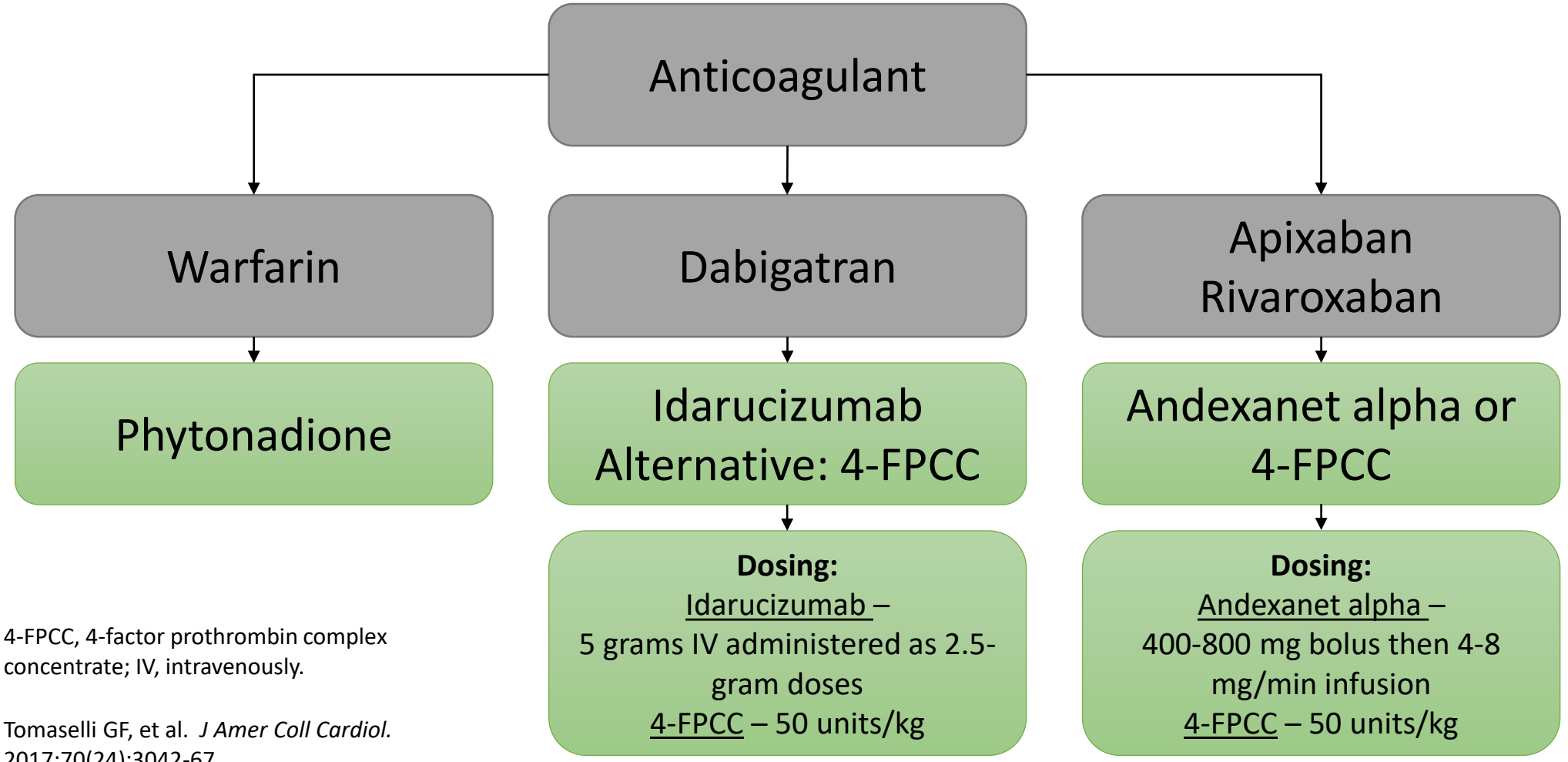
Rivaroxaban	Dabigatran	Apixaban	Edoxaban
Itraconazole, ketoconazole, nelfinavir, lopinavir/ritonavir, ritonavir, conivaptan **Avoid use*	Dronederone, ketoconazole **Consider reducing the dabigatran dose to 75 mg BID in the setting of mild renal impairment (CrCl 30-50 mL/min)* **Avoid use if CrCl < 30 mL/min*	Ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin **Decrease dose to 2.5 mg BID or avoid concomitant use* **If already on 2.5 mg dose and one of these agents is initiated, discontinue apixaban*	
Amiodarone, diltiazem, verapamil, quinidine, ranolazine, dronedarone, erythromycin, azithromycin **If CrCl 15-80 mL/min, avoid use*			
CYP3A4 or P-gP inducers **Avoid use*	CYP3A4 or P-gP inducers **Avoid use*	CYP3A4 or P-gP inducers **Avoid use*	CYP3A4 or P-gP inducers **Avoid use*

P-gP, P-glycoprotein.

Eliquis (apixaban) [prescribing information]. 2019.; Pradaxa (dabigatran) [prescribing information]. 2019.; Savaysa (edoxaban) [prescribing information]. 2019.; Xarelto (rivaroxaban) [prescribing information]. 2019.

Bleeding Reversal

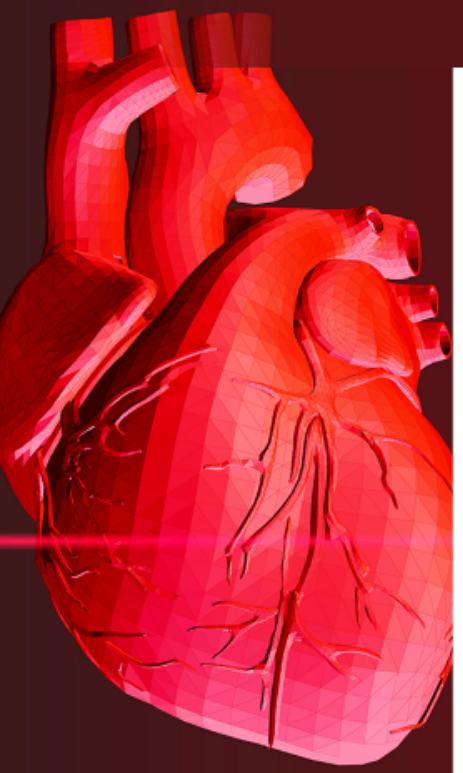




4-FPCC, 4-factor prothrombin complex concentrate; IV, intravenously.

Tomaselli GF, et al. *J Amer Coll Cardiol.* 2017;70(24):3042-67.

Team-Based Clinician-Patient Discussion



- Discuss stroke risk
- Assess presence of risk factors
- Discuss the importance of adherence and modifiable risk factors
- *What is the patient's perceived risk, as well as reduction in risk with therapy?*

- Establish patient's and family's goals and preferences
- *Is the patient willing to adhere to therapy?*

Patient education should be provided by all healthcare team members

Question & Answer

Thank You!