Triple Therapy: The Debate Goes On

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Disclosures

- Speaker has relevant financial relationships with the following commercial interests:

Speakers Bureau – Actelion Pharmaceuticals, Bristol-Myers Squibb, Pfizer

Clinical Research Support– Sanofi

Case Study

65 year old female with a history of DM, HTN and Atrial Fibrillation presents with acute onset chest pain consistent with an ACS/ STEMI. She was taken emergently to the catherization laboratory where she underwent PCI with a DES to the RCA.

- Home medications include: aspirin 81 mg daily, atorvastatin 40 mg po daily, lisinopril 20 mg po daily and rivaroxaban 20 mg daily with her largest meal. She was loaded with ticagrelor 180 mg and started on 90 mg po BID and transferred to the floor

- 48 hours after the event the patient is ready for discharge home. What is the most appropriate oral anticoagulant/ antiplatelet medication regimen at discharge?

Case Study

65 year old female with a history of DM, HTN and Atrial Fibrillation presents with acute onset chest pain consistent with an ACS/ STEMI. She was taken emergently to the catherization laboratory where she underwent PCI with a DES to the RCA.

- A. Rivaroxaban 20 mg, ticagrelor 90 mg BID and aspirin 81 mg daily
- B. Rivaroxaban 20 mg and aspirin 81 mg daily
- C. Rivaroxaban 20 mg and ticagrelor 90 mg BID
- D. Ticagrelor 90 mg BID and aspirin 81 mg daily
- E. None of the above

Case Study

65 year old female with a history of DM, HTN and Atrial Fibrillation presents with acute onset chest pain consistent with an ACS/ STEMI. She was taken emergently to the catherization laboratory where she underwent PCI with a DES to the RCA.

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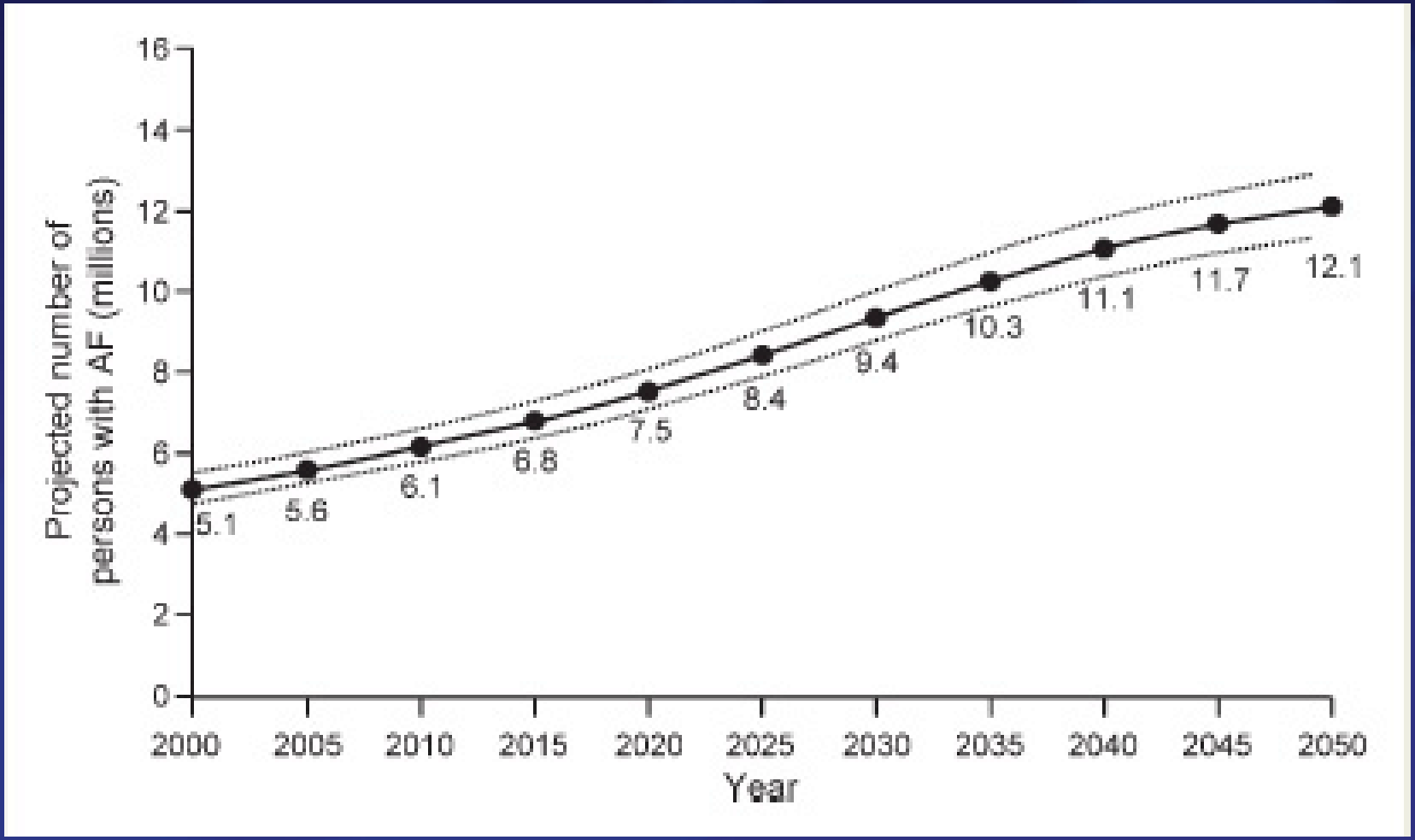
- E. None of the above

Background

- Atrial fibrillation is the most common sustained arrhythmia
- Affects 2 million Americans-- AF is 0.4% to 1% in the general population
- Expensive- 16 billion
- 6% over the age of 65 experience it
- Responsible for 15% strokes
- Unfortunately, warfarin is received by only 30-60% of appropriate patients
- In the FHS, the lifetime risk of atrial fibrillation (AFib) for adults is 26% for men and 23% for women.
- The 2014 ACC/AHA/HRS Atrial Fibrillation guideline defines Non Valvular Atrial Fibrillation as **AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic valve or mitral valve repair** (January CT et al. Journal of the American College of Cardiology 2014 doi 10/1016 JACC 2014 0.3.022)

Atrial Fibrillation: Prevalence Estimates



Turpie A. New oral anticoagulants in atrial fibrillation. EHJ 2007; 29:155-65

How do we determine stroke risk ?

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Developed in Collaboration With the Society of Thoracic Surgeons

Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits		
COR	**LOE**	**Recommendations**
I	**B**	**In patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve), the CHA_2DS_2-VASc score is recommended for assessment of stroke risk.** **MODIFIED**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. Patients with AF with bioprosthetic heart valves are addressed in the supportive text. (Section 4.1. in the 2014 AF guideline)

This slide set is adapted from the 2019 AHA/ACC/HRS FOCUSED UPDATE OF THE 2014 AHA/ACC/HRS GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH ATRIAL FIBRILLATION. Published on January 28, 2019, available at: *Journal of the American College of Cardiology* [(insert full link)] and *Circulation* [(insert full link)] The full-text guidelines are also available on the following Web sites: ACC (www.acc.org) and AHA (professional.heart.org)

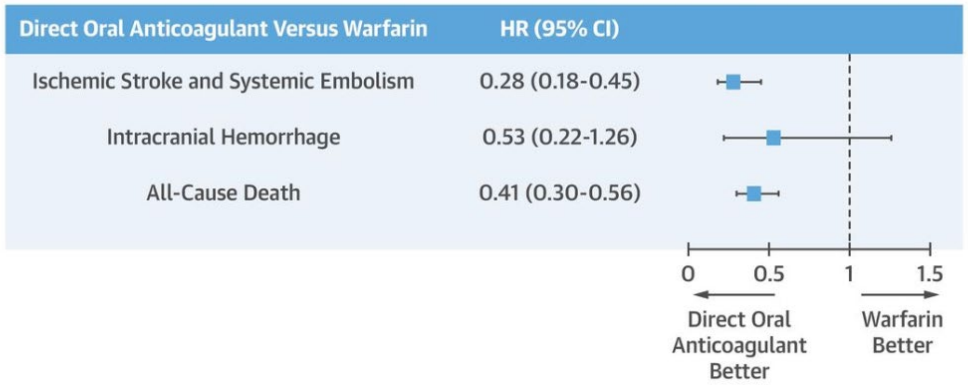
Journal of the American College of Cardiology

Outcomes of Direct Oral Anticoagulants in Patients With Mitral Stenosis

Ju Youn Kim, Sung-Hwan Kim, Jun-Pyo Myong, Yoo Ri Kim, Tae-Seok Kim, Ji-Hoon Kim, Sung-Won Jang, Yong-Seog Oh, Man Young Lee and Tai-Ho Rho

Conclusions In patients with AF accompanied with mitral stenosis, DOAC use is promising and hypothesis generating in preventing thromboembolism. Our results need to be replicated in a randomized trial.

CENTRAL ILLUSTRATION: Mitral Stenosis and Atrial Fibrillation for Direct Oral Anticoagulant Versus Warfarin: Hazard Ratios

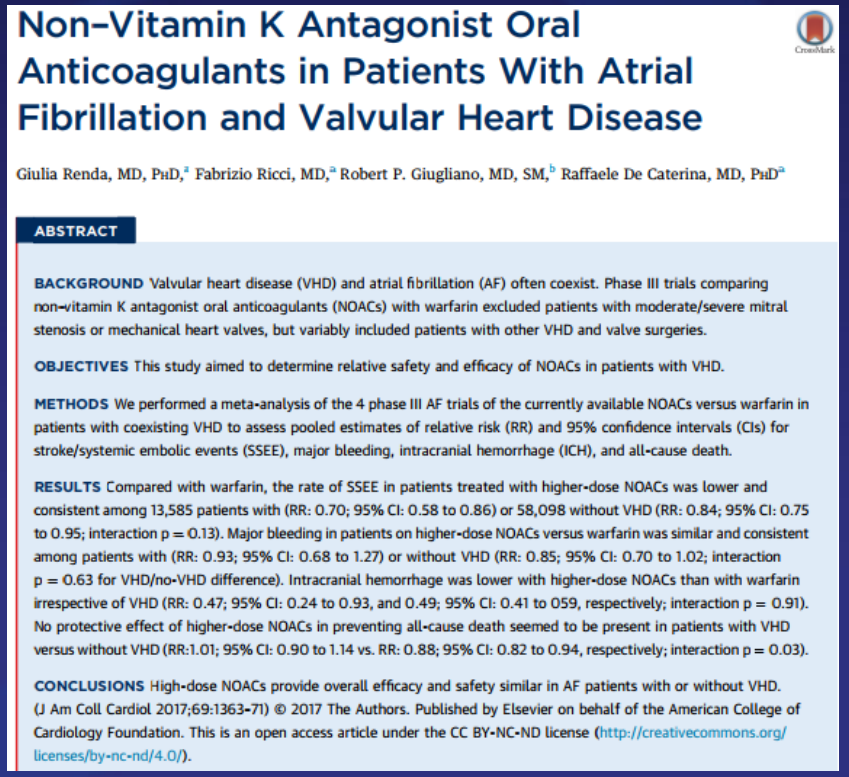


Kim, J.Y. et al. J Am Coll Cardiol. 2019;73(10):1123-31.

Volume 73, Issue 10, March 2019 DOI: 10.1016/j.jacc.2018.12.047

Guidelines for Management of AF

- In patients with AF and VHD (other than moderate/ severe mitral stenosis or mechanical heart valves) NOACs are attractive alternatives to VKAs because the coexistence of VHD does not affect the overall relative efficacy or safety of NOACs in terms of prevention of SSEE and major bleeding. Current definitions of “valvular” and “nonvalvular” AF are misleading, and the use of NOACs should be permitted in most patients with VHD.
- The recently proposed term “MARM-AF,” standing for “Mechanical And Rheumatic Mitral valvular AF” could be useful to identify the true high risk AF patients for whom VKAs are the anticoagulants of choice



Non–Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Disease

Giulia Renda, MD, PhD,[a] Fabrizio Ricci, MD,[a] Robert P. Giugliano, MD, SM,[b] Raffaele De Caterina, MD, PhD[a]

ABSTRACT

BACKGROUND Valvular heart disease (VHD) and atrial fibrillation (AF) often coexist. Phase III trials comparing non-vitamin K antagonist oral anticoagulants (NOACs) with warfarin excluded patients with moderate/severe mitral stenosis or mechanical heart valves, but variably included patients with other VHD and valve surgeries.

OBJECTIVES This study aimed to determine relative safety and efficacy of NOACs in patients with VHD.

METHODS We performed a meta-analysis of the 4 phase III AF trials of the currently available NOACs versus warfarin in patients with coexisting VHD to assess pooled estimates of relative risk (RR) and 95% confidence intervals (CIs) for stroke/systemic embolic events (SSEE), major bleeding, intracranial hemorrhage (ICH), and all-cause death.

RESULTS Compared with warfarin, the rate of SSEE in patients treated with higher-dose NOACs was lower and consistent among 13,585 patients with (RR: 0.70; 95% CI: 0.58 to 0.86) or 58,098 without VHD (RR: 0.84; 95% CI: 0.75 to 0.95; interaction p = 0.13). Major bleeding in patients on higher-dose NOACs versus warfarin was similar and consistent among patients with (RR: 0.93; 95% CI: 0.68 to 1.27) or without VHD (RR: 0.85; 95% CI: 0.70 to 1.02; interaction p = 0.63 for VHD/no-VHD difference). Intracranial hemorrhage was lower with higher-dose NOACs than with warfarin irrespective of VHD (RR: 0.47; 95% CI: 0.24 to 0.93, and 0.49; 95% CI: 0.41 to 059, respectively; interaction p = 0.91). No protective effect of higher-dose NOACs in preventing all-cause death seemed to be present in patients with VHD versus without VHD (RR:1.01; 95% CI: 0.90 to 1.14 vs. RR: 0.88; 95% CI: 0.82 to 0.94, respectively; interaction p = 0.03).

CONCLUSIONS High-dose NOACs provide overall efficacy and safety similar in AF patients with or without VHD.

Stroke Risk Stratification in AF

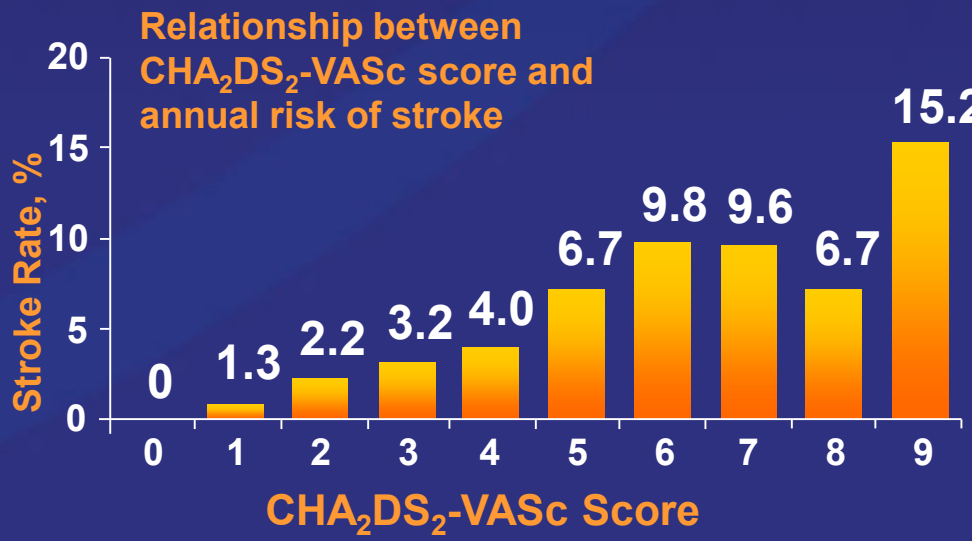
$CHADS_2$

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	1
Diabetes	1
Stroke	2

Total Score	Annual Risk of Stroke (%)
0	1.9
1	2.8
2	4.0
3	5.9
4	8.5
5	12.5
6	18.2

CHA_2DS_2-VASc

Risk Factor	Score
Cardiac failure	1
HTN	1
Age ≥75 y	2
Diabetes	1
Stroke	2
Vasc dz (MI, PAD, aortic ath)	1
Age 65-74 y	1
Sex **c**ategory (female)	1



Lip GY, Halperin JL. *Am J Med*. 2010;123(6):484-488.

Summary- Non Valvular AF

Risk Category	CHADs-2-VASC Score	Recommended Therapy American College of Cardiology (ACC) / European Society of Cardiology (ESC)
Two or more Risk Factors	2	ACC- Oral Anticoagulation ESC- Oral Anticoagulation
One Risk Factor	1	ACC- Aspirin 81 mg or Oral Anticoagulation (Exception Female Gender only) ESC- Oral Anticoagulation
No Risk Factors	0	ACC- Aspirin 81 mg daily ESC- No Therapy

Atrial Fibrillation

- Anticoagulation Strategies
  - Aspirin
  - Warfarin
  - Dabigatran (Direct Thrombin Inhibitor)
  - Rivaroxaban (Factor Xa Inhibitor)
  - Apixaban (Factor Xa Inhibitor)
  - Endoxiban (Factor Xa Inhibitor)

Atrial Fibrillation- Anticoagulation Strategies

- Non-vitamin K oral anticoagulants (NOACs), are now recommended as the preferred alternative to warfarin for reducing the risk of stroke associated with atrial fibrillation (AFib).

- The new recommendation comes from the 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation released Jan. 28 by the ACC, American Heart Association and Heart Rhythm Society and simultaneously published in the Journal of the American College of Cardiology.

Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits

COR	LOE	Recommendations
I	A	**NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe mitral stenosis or a mechanical heart valve).** **NEW**: Exclusion criteria are now defined as moderate-to-severe mitral stenosis or a mechanical heart valve. When the NOAC trials are considered as a group, the direct thrombin inhibitor and factor Xa inhibitors were at least noninferior and, in some trials, superior to warfarin for preventing stroke and systemic embolism and were associated with lower risks of serious bleeding.

This slide set is adapted from the 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation. Published on January 28, 2019, available at: *Journal of the American College of Cardiology* [(insert full link)] and *Circulation* [(insert full link)] The full-text guidelines are also available on the following Web sites: ACC (www.acc.org) and AHA (professional.heart.org)

Recommendations in patients with ACS (STEMI or NSTEMI) who receive PCI

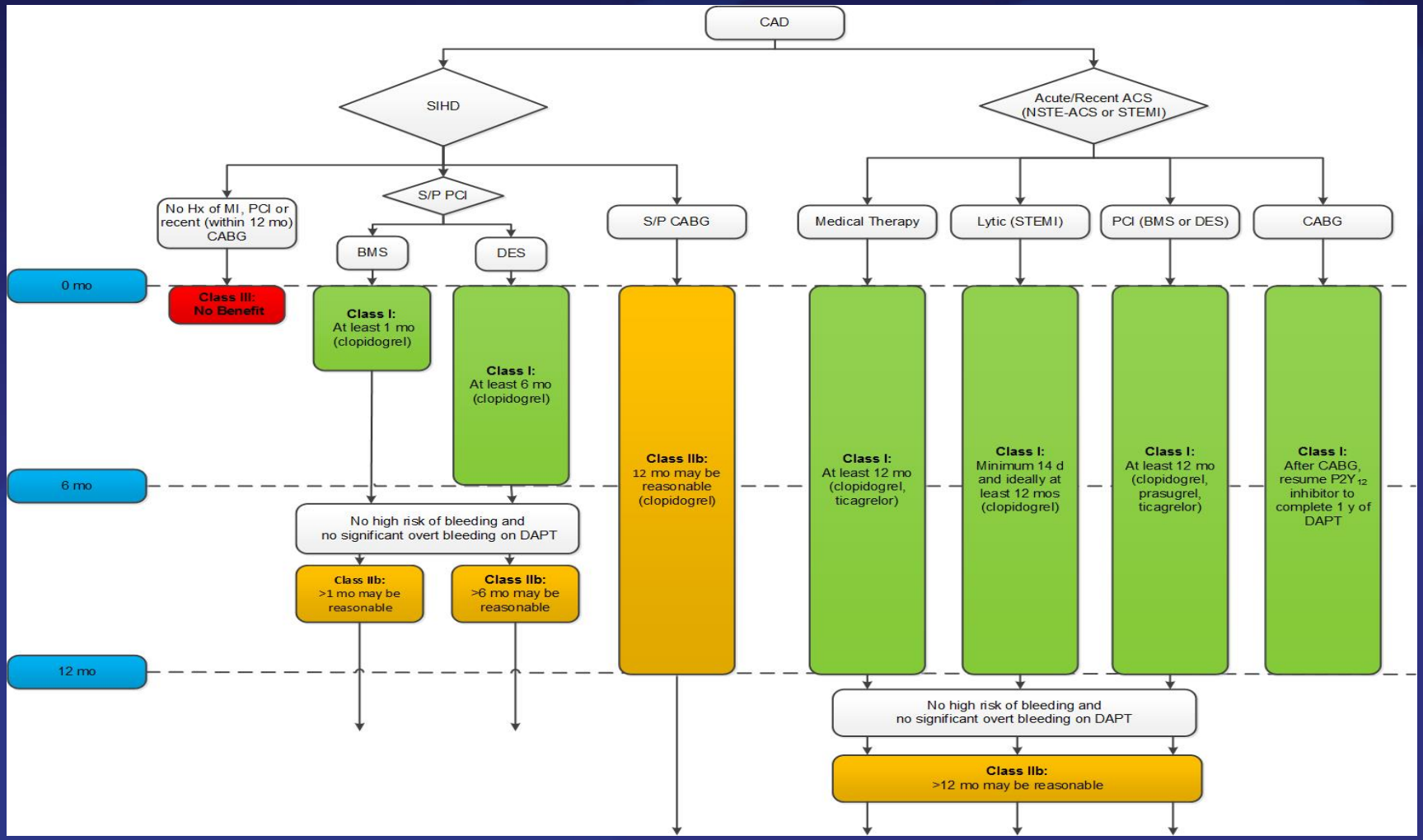
2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

Developed in Collaboration with American Association for Thoracic Surgery, American Society of Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

Endorsed by Preventive Cardiovascular Nurses Association and Society for Vascular Surgery

Duration of DAPT

Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT



Master Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients With CAD Treated With DAPT

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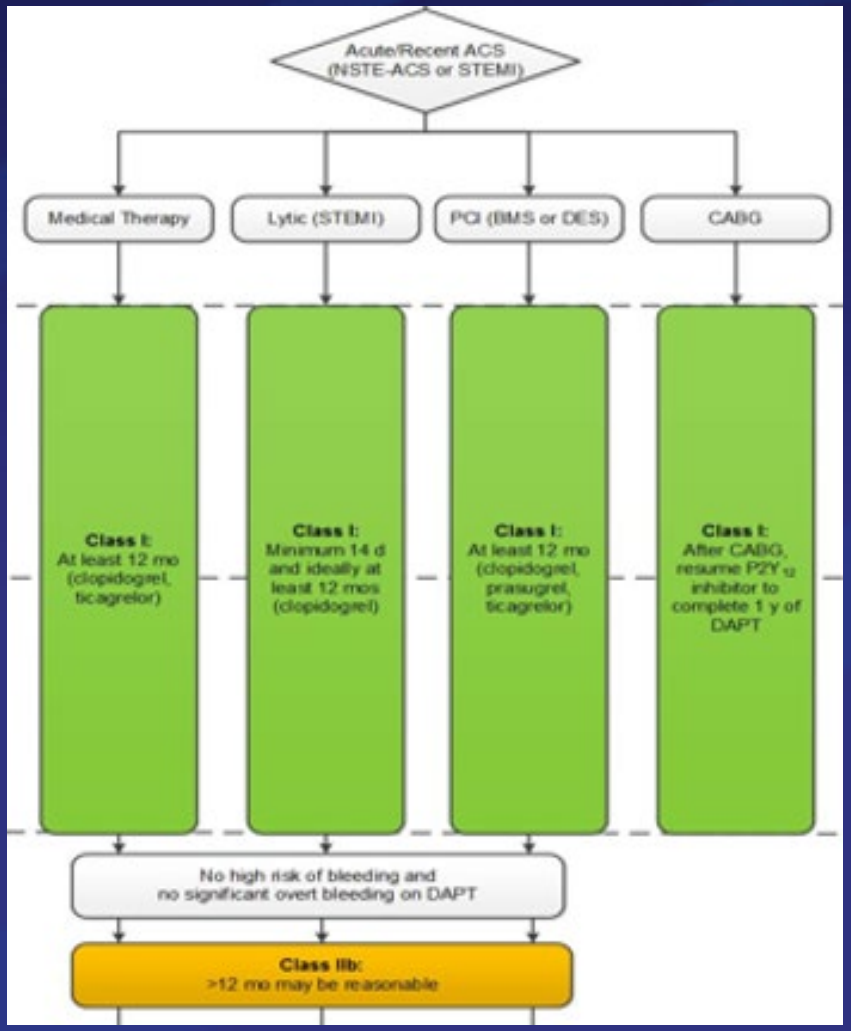
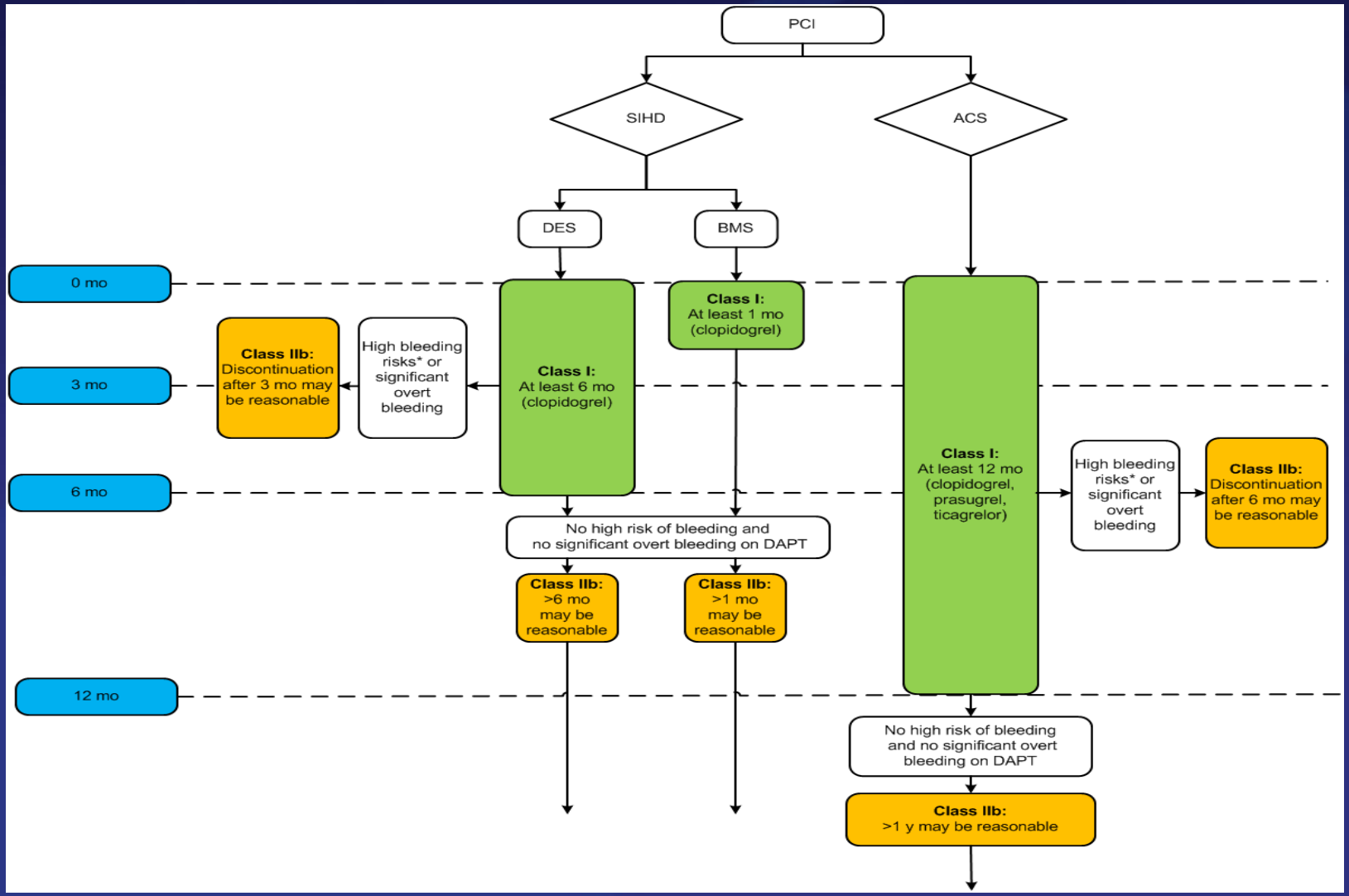
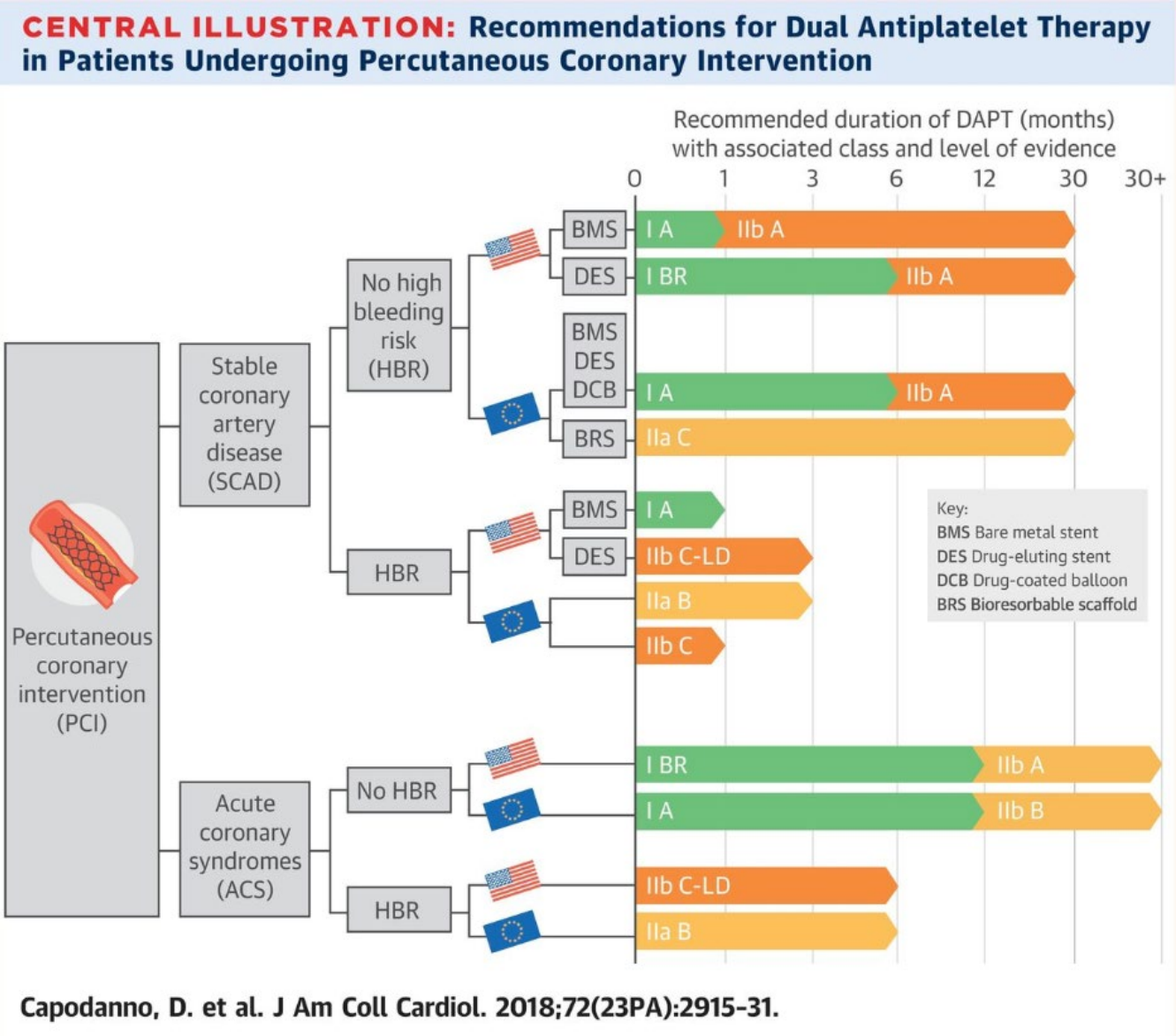


Figure 2. Treatment Algorithm for Duration of $P2Y_{12}$ Inhibitor Therapy in Patients Treated With PCI



Duration of DAPT



Capodanno, D. et al. J Am Coll Cardiol. 2018;72(23PA):2915-31.

Journal of the American College of Cardiology Volume 72, Issue 23 Part A, December 2018 DOI: 10.1016/j.jacc.2018.09.057 **ACC/AHA Versus ESC Guidelines on Dual Antiplatelet Therapy**
JACC Guideline Comparison Davide Capodanno, Fernando Alfonso, Glenn N. Levine, Marco Valgimigli and Dominick J. Angiolillo

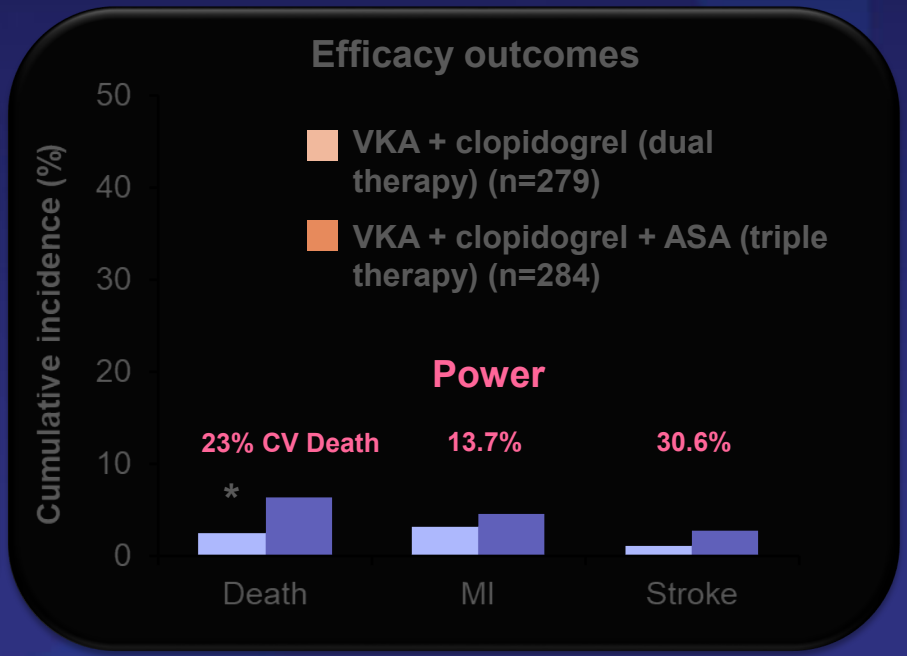
Recommendations in patients with ACS (STEMI or NSTEMI) who receive PCI with a History of Atrial Fibrillation

Current Randomized Trials of Oral Anticoagulation Following PCI (2008-2017)

Trials	Studied regimens	Primary endpoint	Comments
WOEST (n=573) Lancet 2008	Warfarin (target INR 2.0) + clopidogrel 75 mg daily Versus Warfarin (target INR 2.0) + clopidogrel 75 mg daily + ASA 80-100 mg daily	Any bleeding episode at 12 months Warfarin + clopidogrel: 19.4% Warfarin + clopidogrel + ASA: 44.4% (p<0·0001)	Prevalence of AF/flutter: 69% Use of PPI: <40% Stents used 65% DES, 35% BMS
ISAR-TRIPLE (n=614) JACC 2015	ASA 75-200 mg daily + clopidogrel 75 mg daily + warfarin (lowest recommended target INR) for 6 weeks versus 6 months	Composite of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months •6 weeks triple therapy: 9.8% •6 months triple therapy: 8.8% (p=0.63)	Prevalence of AF: 84% Use of PPI: 37.2% Stents used 99% DES INR therapeutic range 64%
PIONEER-AF (n=2124) NEJM 2016	Rivaroxaban 15 mg daily + P2Y12 inhibitor (group 1) vs Rivaroxaban 2.5 mg twice daily + DAPT (group 2) vs Warfarin (INR 2.0-3.0) + DAPT (group 3)	Clinically significant bleeding at 12 months Group 1: 16.8% Group 2: 18.0% Group 3: 26.7% (p<0.001 versus both groups 1 and 2)	Prevalence of AF: 100% Clopidogrel used in 93% of patients Use of PPI: <40% Stents used 65% DES, 32% BMS INR therapeutic range 65%
RE-DUAL PCI (n=2725) NEJM 2017	Dabigatran 110 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) vs Dabigatran 150 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) vs Warfarin (INR 2.0-3.0) + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) + aspirin ≤100 mg daily	Time to first major or clinically relevant non-major bleeding event 15.4% in 110mg dual therapy vs 26.9% comparable triple therapy group (P<0.001 for noninferiority; P<0.001 for superiority) 20.2% in 150mg dual therapy vs 25.7% comparable triple therapy group (P<0.001 for noninferiority)	Prevalence of AF: 100% Clopidogrel used in 88% of patients Stents used 83% DES, 35% BMS Use of PPI: unknown INR therapeutic range 64%

Is ASA Necessary In Triple Therapy? The WOEST trial

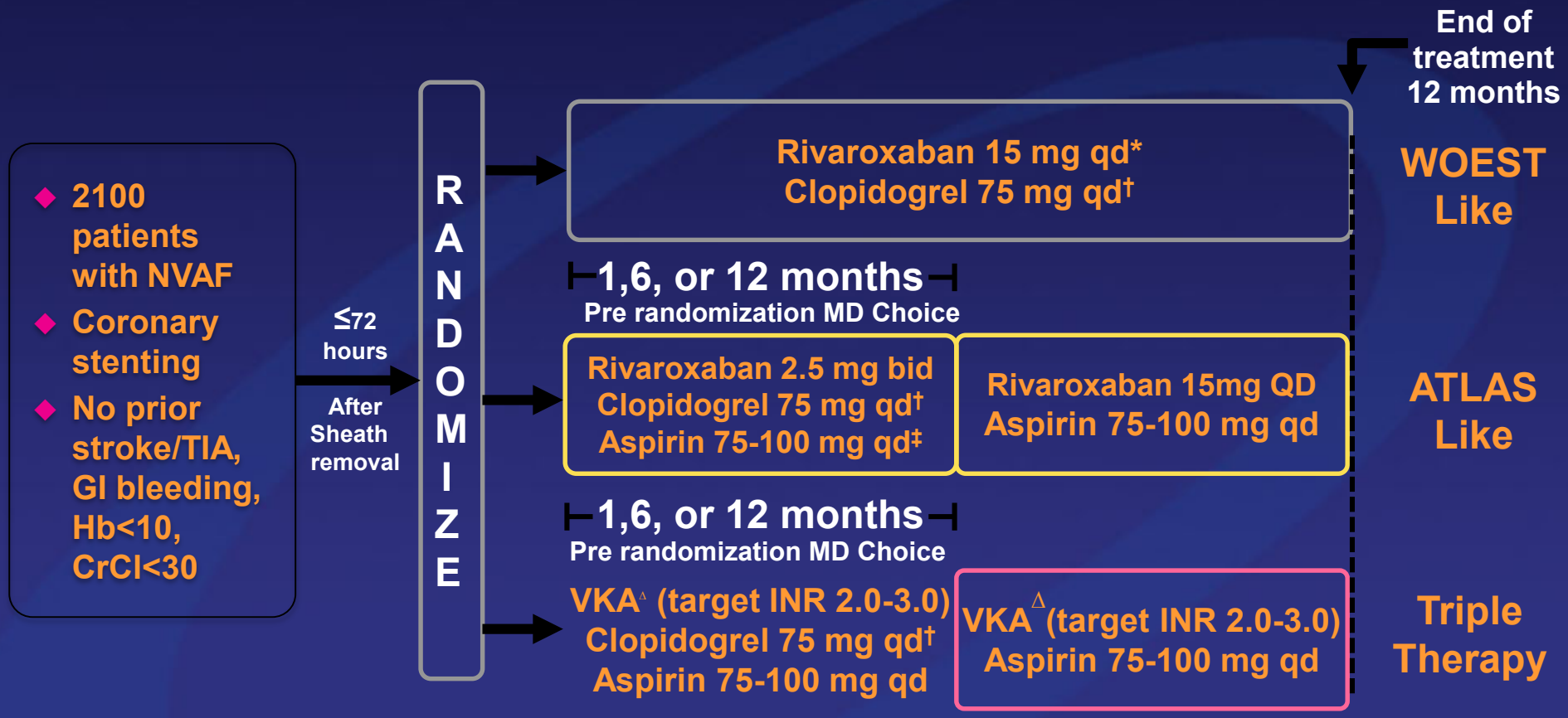
Modest-scale, open-label WOEST study (N=573) compared safety outcomes with triple therapy (VKA + clopidogrel + ASA) vs dual therapy (VKA + clopidogrel) 69% of WOEST patients had AF, included prosthetic heart valves



*$p<0.05$.
** All-cause death (CV & non-CV death p = 0.207 & 0.069)
Dewilde WJ *et al*, *Lancet* 2013;381:1107–1115

Gibson et al. AHA 2016,
http://clinicaltrialresults.org/Slides/AHA2016/Gibson_PIONEER.pptx

Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

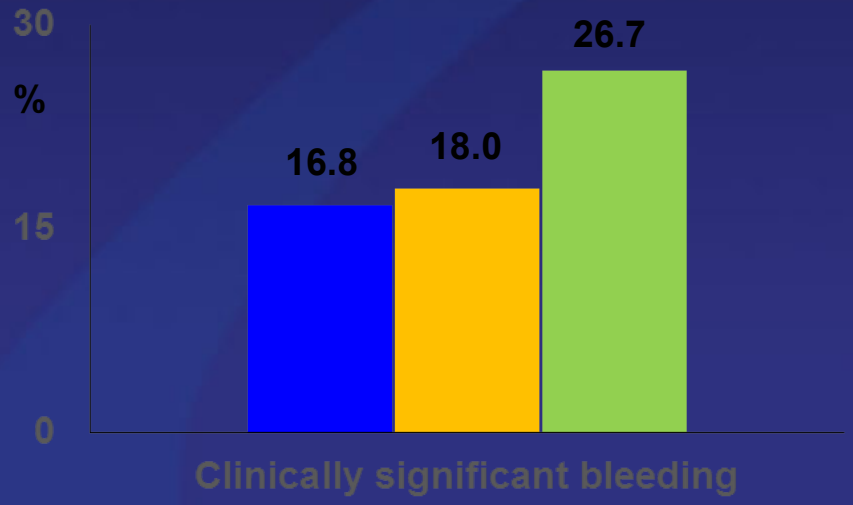
*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

Gibson et al. AHA 2016,
http://clinicaltrialresults.org/Slides/AHA2016/Gibson_PIONEER.pptx

PIONEER AF-PCI

Trial design: Patients with AF and PCI randomized to: Group 1: Rivaroxaban 15 mg daily plus P2Y12 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).

(p < 0.001 for group 1 or 2 vs. group 3)



Results

- Clinically significant bleeding: 16.8% in group 1 vs. 18.0% in group 2 vs. 26.7% in group 3 (HR 0.59, p < 0.001 for group 1 vs. 3); (HR 0.63, p < 0.001 for group 2 vs. 3)
- 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)

Conclusions

- **Among patients with nonvalvular AF who underwent PCI, a rivaroxaban-based strategy was associated with a lower frequency of clinically significant bleeding compared with a warfarin/DAPT strategy**
- **<u>Stent thrombosis appeared to be similar between the three groups</u>**

Gibson CM, et al. N Engl J Med 2016;375:2423-34, www.acc.org , https://www.acc.org/~/media/Clinical/Office-Files/PowerPoint/Approved%20PowerPoint/2016/12/29/10/19/PIONEER%20AF%20PCI%20Summary%20Slide.ppt

American College of Cardiology 2019

- March 16th - 18th, New Orleans, LA, USA.

Questions