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Anticoagulants in Interventional Cardiology:

Where Are We in 2018?

Moderator

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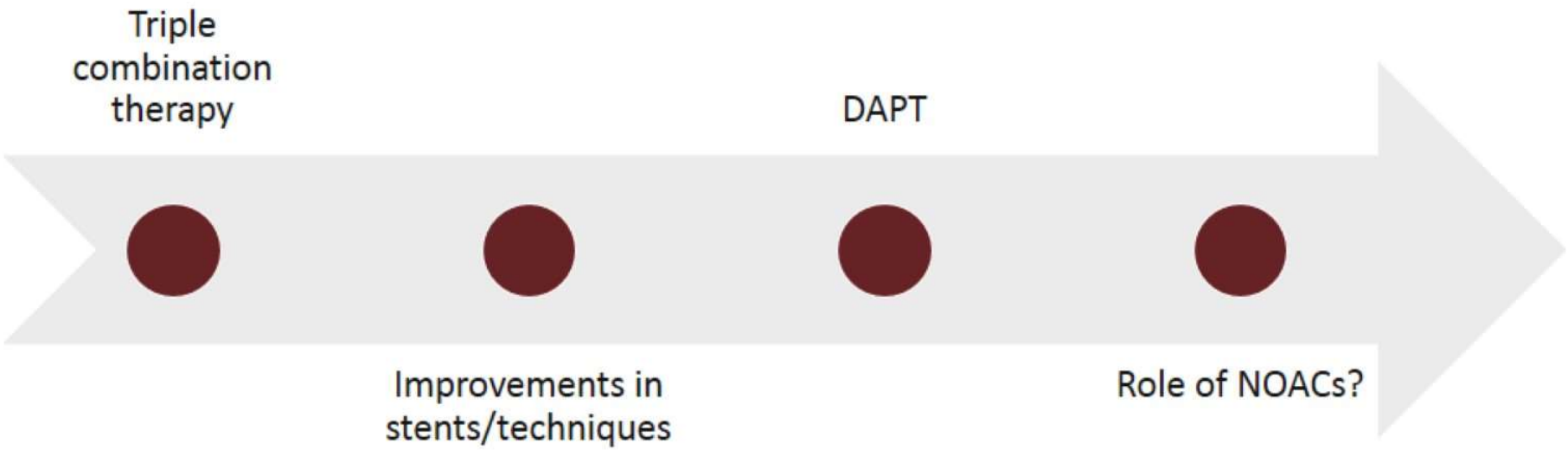
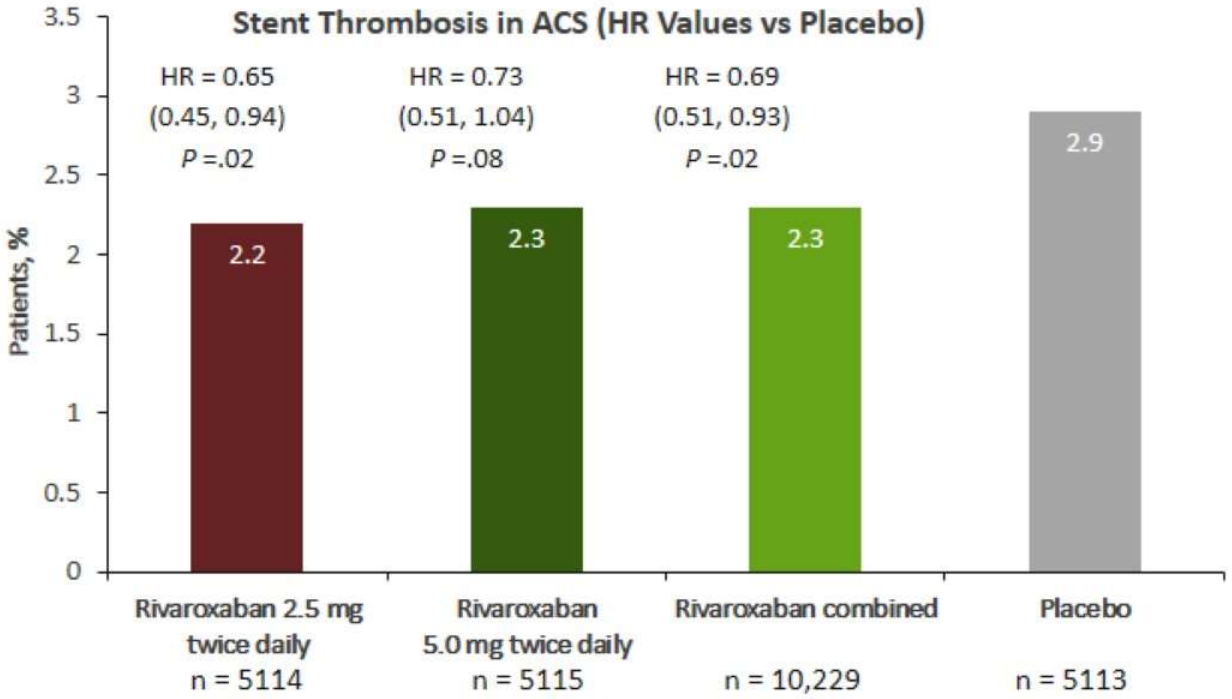
Overview of Anticoagulation in Interventional Cardiology

Treatment for ACS/post-PCI patients has evolved over time, resulting in lower morbidity, but the risk for secondary events and bleeding is still a concern



Rivaroxaban in Patients With Recent ACS: ATLAS ACS 2-TIMI 51

- Rivaroxaban 2.5 mg reduced risk of death from CV causes, MI, or stroke and increased risk of major bleeding and intracranial hemorrhage, but not fatal bleeding
- 2.5-mg dose approved in Europe but not United States



Mega JL, et al. *N Engl J Med.* 2012;366:9-19.

Apixaban After ACS: APPRAISE-2

Outcome	Apixaban* 5 mg Twice Daily Total Patients, n (%)	Placebo* Total Patients, n (%)	HR With Apixaban (95% CI)	*P* Value
Efficacy	3705	3687		
CV death, MI, or ischemic stroke	7.5	7.9	0.95 (0.80, 1.11)	.51
Safety: bleeding	3673	3642		
TIMI criteria: major bleeding	1.3	0.5	2.59 (1.50, 4.46)	.001
Fatal bleeding	0.1	0	NA	NA
Intracranial bleeding	0.3	0.1	4.06 (1.15, 14.38)	.03
Any bleeding	18.5	8.4	2.36 (2.06, 2.70)	<.001

Trial was terminated prematurely because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. Dose may have been too high to be given on top of antiplatelet therapy.

*Patients were also taking aspirin or DAPT.

Alexander JH, et al. *N Engl J Med.* 2011;365:699-708.

How Do You Treat Complex Patients?

Atrial fibrillation + OAC

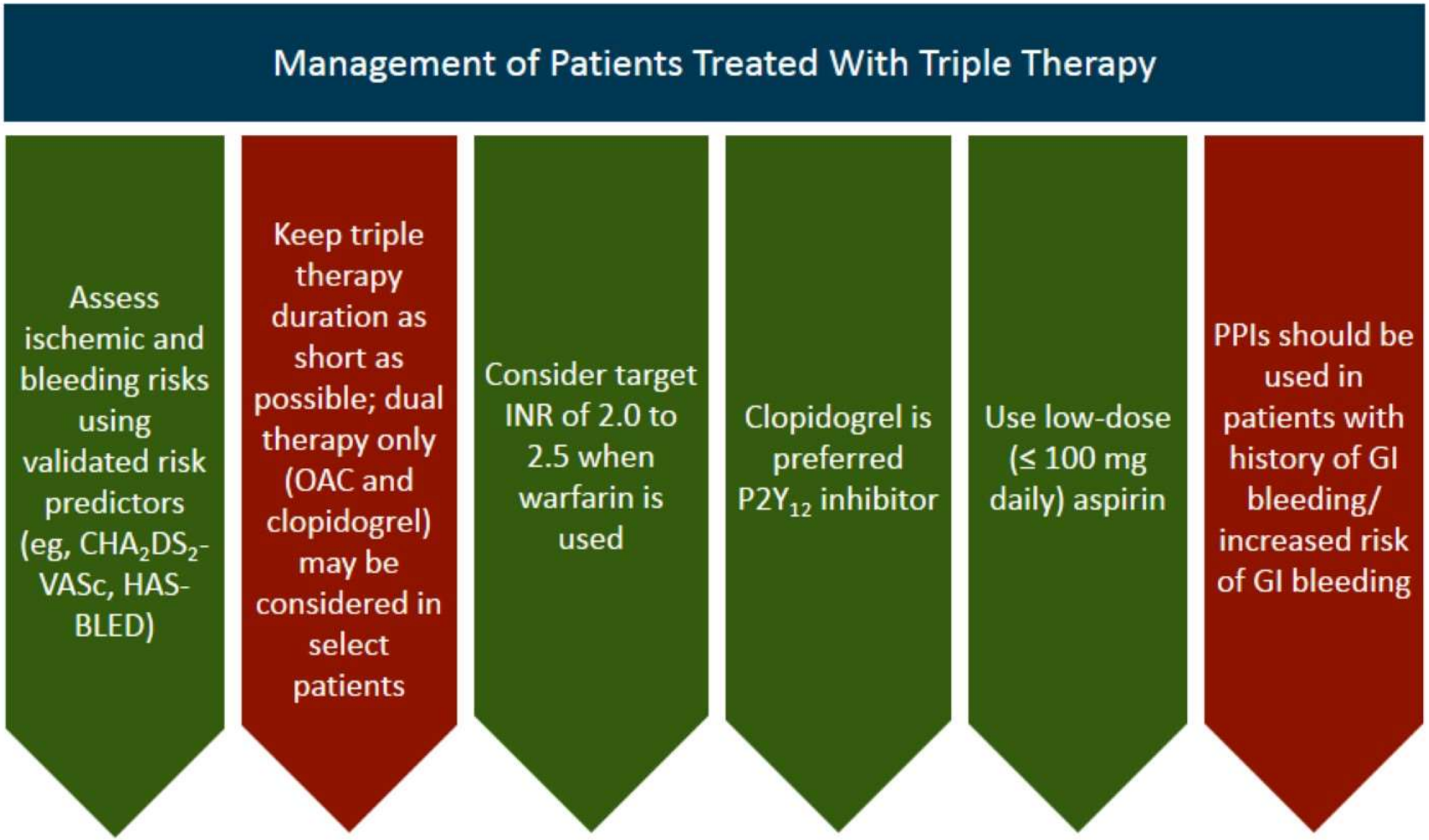
+

Stent + antiplatelet therapy

ACC/ESC guidelines both recommend that triple therapy be used for as short a time as possible[a,b]

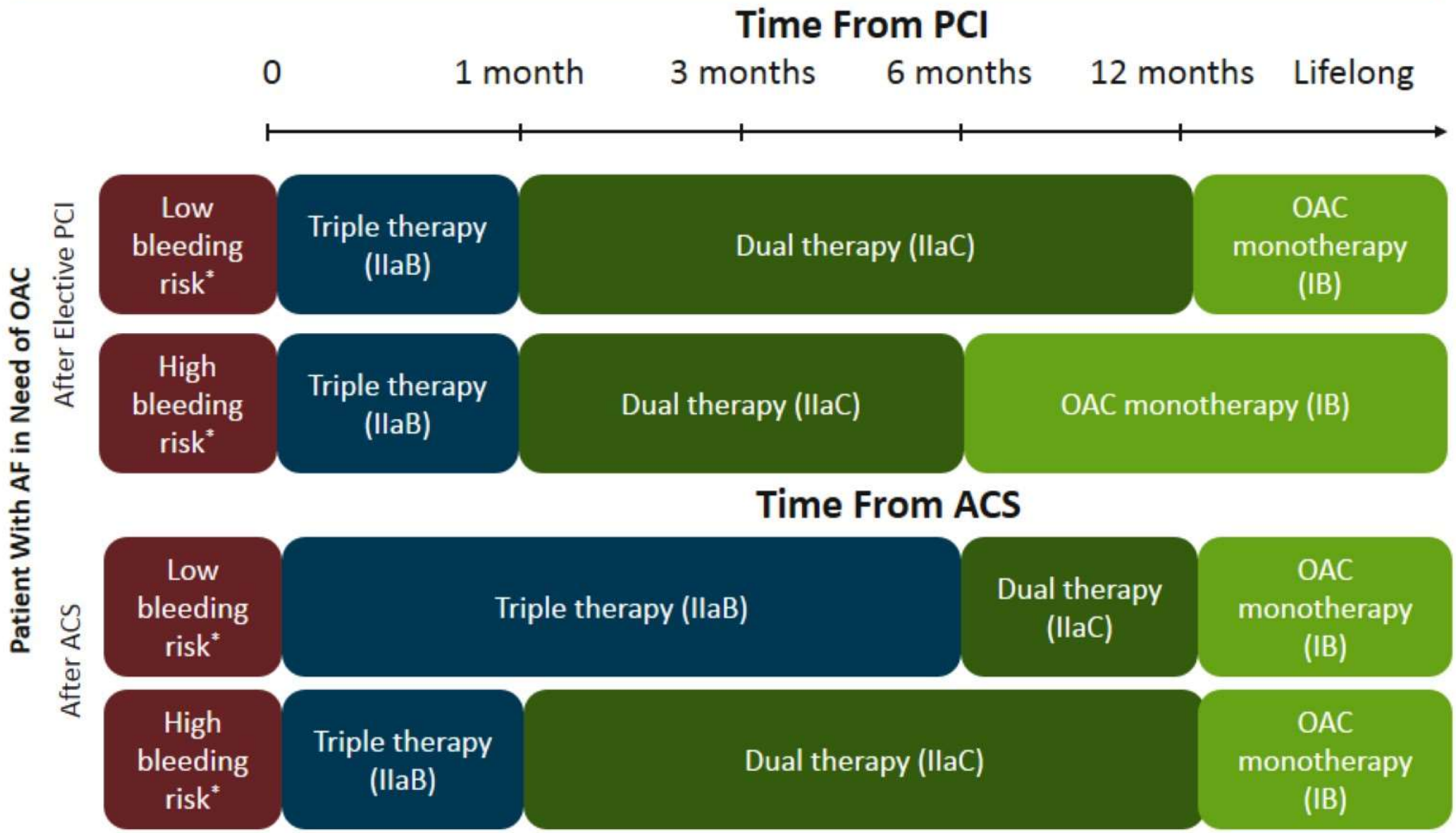
a. Levine GN, et al. *J Am Coll Cardiol.* 2016;68:1082-1115; b. Kirchhof P, et al. *Eur Heart J.* 2016;37:2893-2962.

ACC/AHA Guidelines



Levine GN, et al. *J Am Coll Cardiol*. 2016;68:1082-1115.

ESC Guidelines



*Compared with risk for ACS or stent thrombosis.

Kirchhof P, et al. *Eur Heart J*. 2016;37:2893-2962.

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The Use of NOACs in the Setting of AF and PCI

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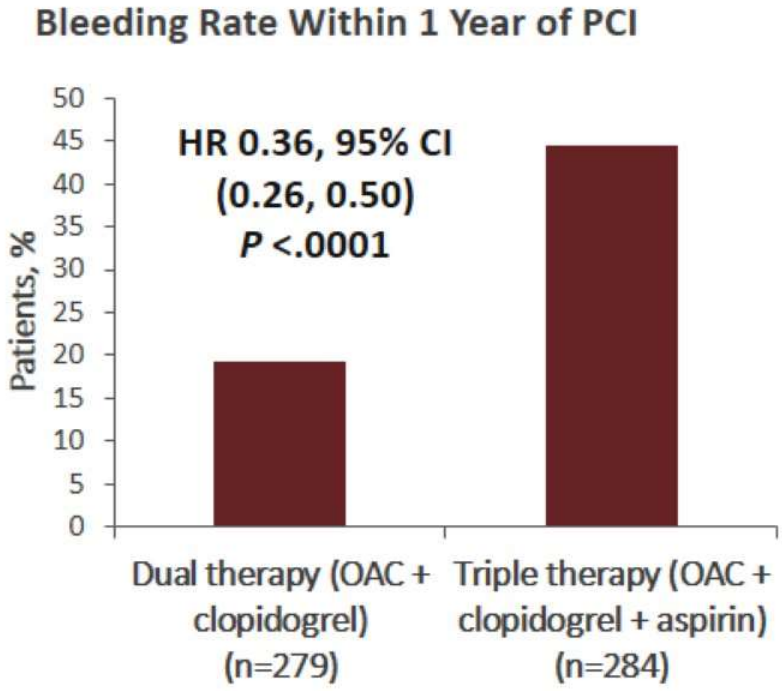
AF Patients Undergoing PCI

- No clear recommendations for this patient population
  - Clinical trials have not informed guidelines
- Many different combinations of antiplatelet agents/anticoagulants
  - Which combination?
  - Duration?
  - Bleeding vs thrombotic risk?
- Dilemma for physicians to choose the best possible therapy for these patients

Triple vs Dual Combination Therapy Post-PCI: WOEST Trial

573 patients receiving OAC* and undergoing PCI were assigned to clopidogrel alone (dual therapy) or clopidogrel + aspirin (triple therapy) for 1 year in open-label, multicenter, randomized trial



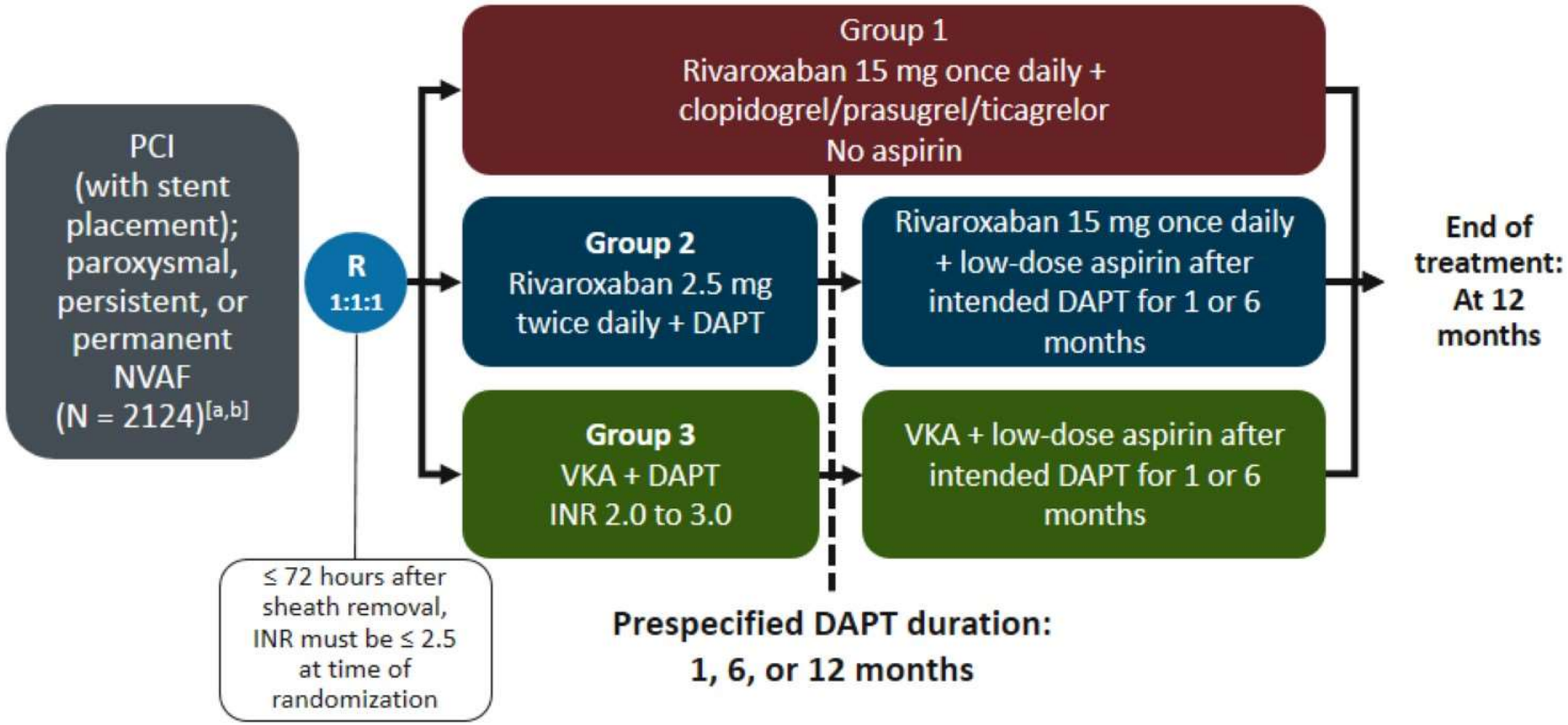
Results

- Most bleeding episodes occurred within 180 days of PCI
- Rate of thrombotic and thromboembolic events did not differ between treatment groups
- Study supported that OAC is as good as aspirin in preventing thrombotic events (eg, stent thrombosis) but was not powered to detect difference
- Prompted need for change in clinical decisions

*Vitamin K antagonist indicated for patients with AF/flutter, mechanical heart valve, apical aneurysm, pulmonary embolus, peripheral artery disease, or ejection fraction < 30%.

Dewilde WJM, et al. *Lancet.* 2013;381:1107-1115.

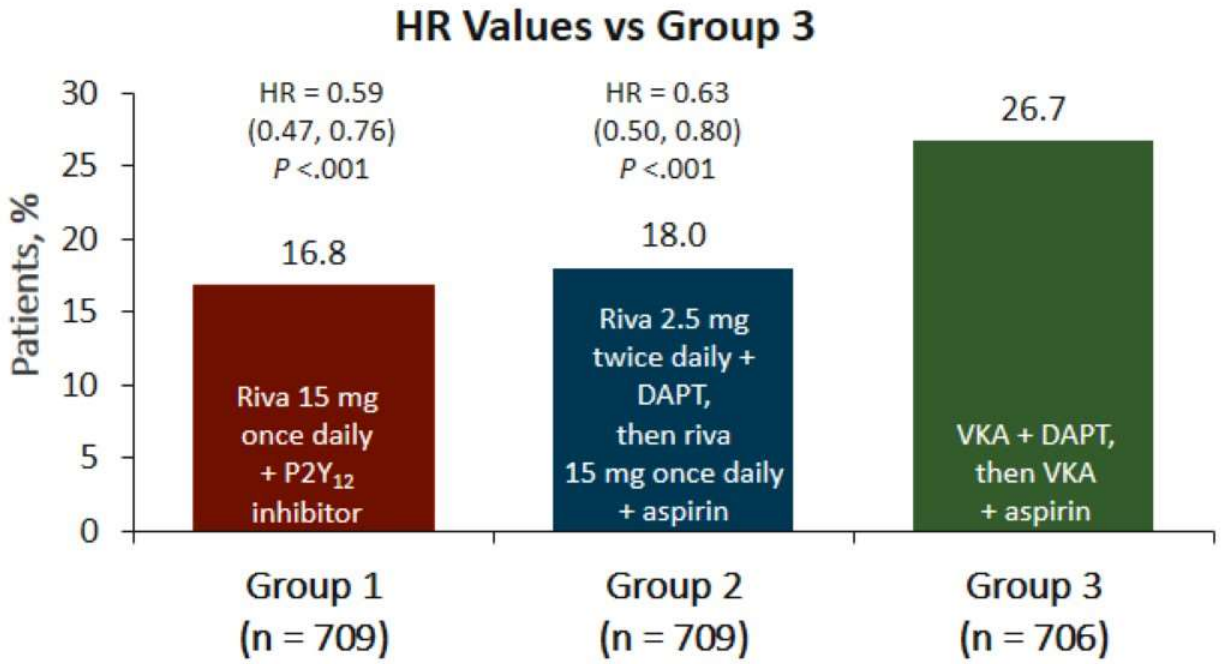
New Era With NOACs: PIONEER AF-PCI Study Design



- Primary outcome measure: clinically significant bleeding (composite of TIMI major or minor bleeding or bleeding requiring medical attention)
- Secondary outcome measure: MACE (composite of death from CV causes, MI, or stroke)

a. Gibson CM, et al. *Am Heart J.* 2015;169:472-478.e5; b. Gibson CM, et al. *N Engl J Med*. 2016;22;375:2423-2434.

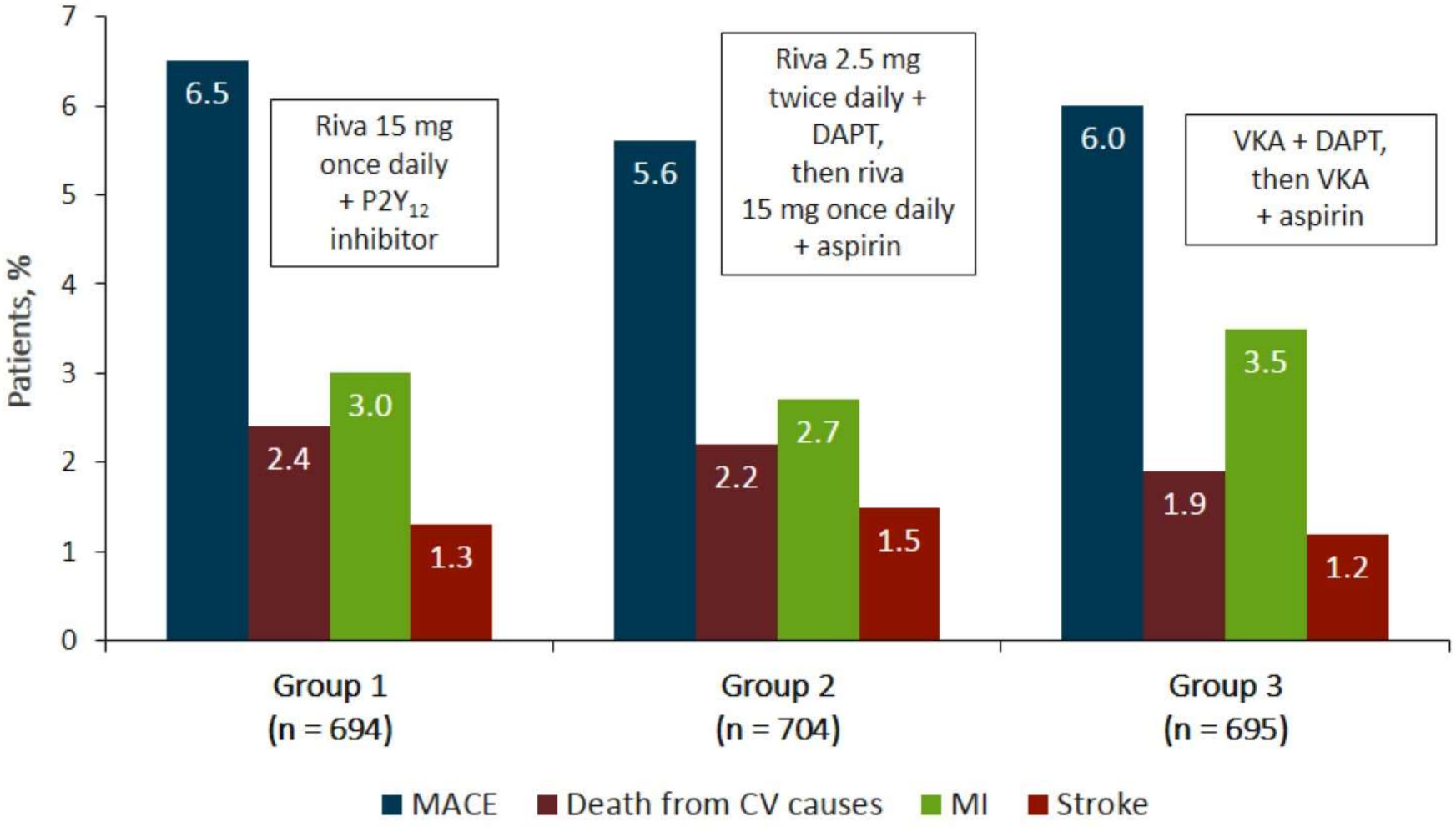
PIONEER AF-PCI: Clinically Significant Bleeding



- Both doses of rivaroxaban were lower than the dose traditionally used for stroke prevention and AF
  - Also reduced combined endpoint of rehospitalizations and all-cause mortality
  - Are we confident these doses maintain protection against stroke and systemic embolism?

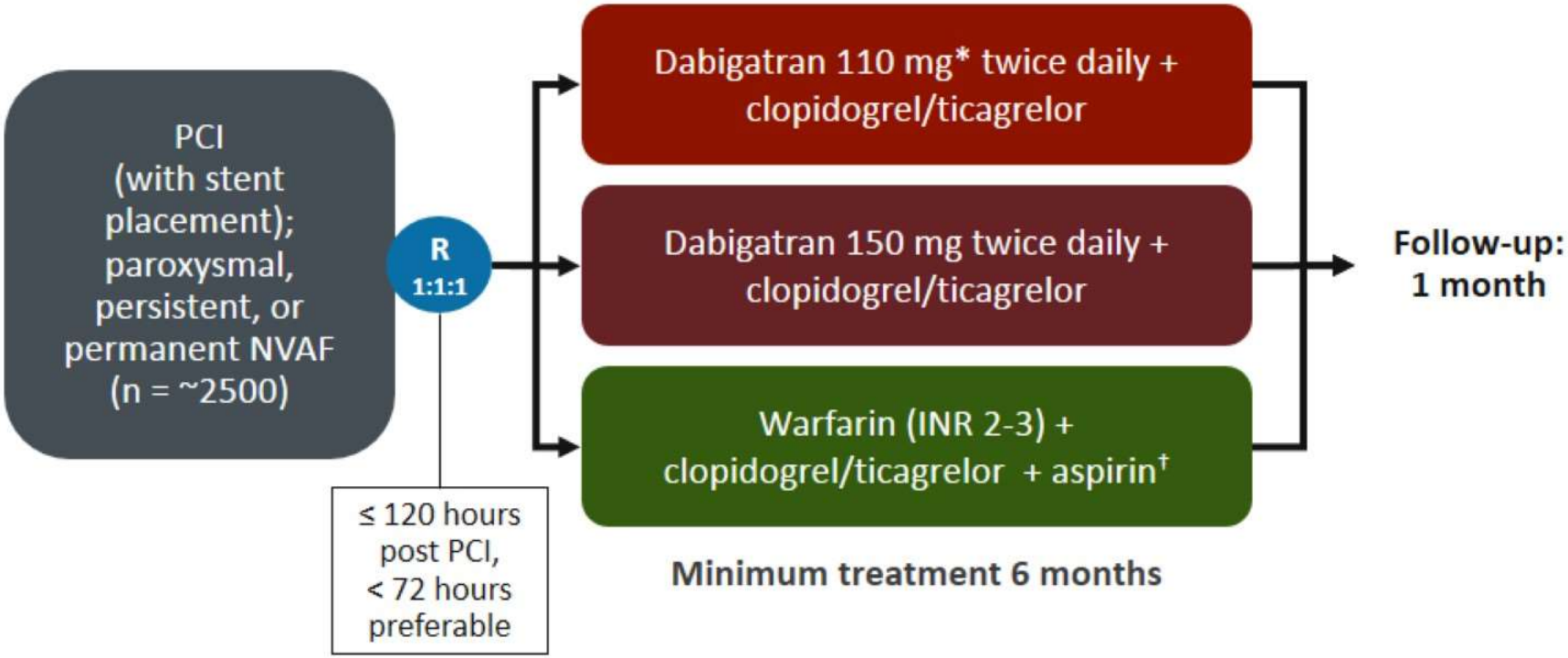
Gibson CM, et al. *N Engl J Med*. 2016;22;375:2423-2434.

PIONEER AF-PCI: MACE



Gibson CM, et al. *N Engl J Med.* 2016;22;375:2423-2434.

RE-DUAL PCI: Trial Design

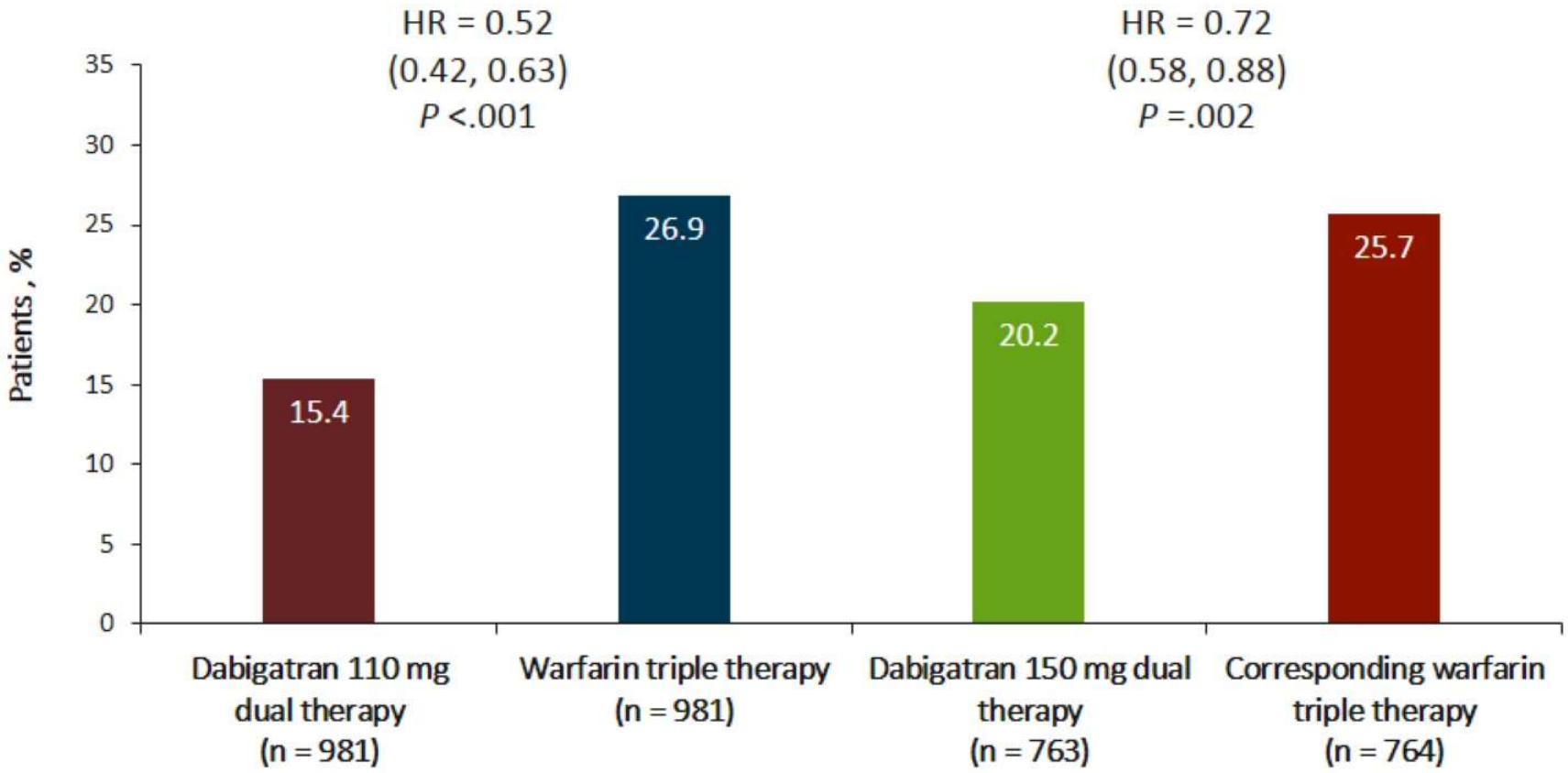


- Primary outcome measure: time to first ISTH major bleeding or CRNM bleeding event
- Secondary endpoints: composite of all-cause death or thrombotic events (MI or stroke/SE) and unplanned revascularization

*Loading doses of P2Y12 inhibitors and aspirin were given prior to PCI. †Currently only approved in United States for prophylaxis of DVT and PE following hip replacement surgery for patients with CrCl > 30 mL/min. ‡Aspirin discontinued at 1 month (BMS) or 3 months (DES).

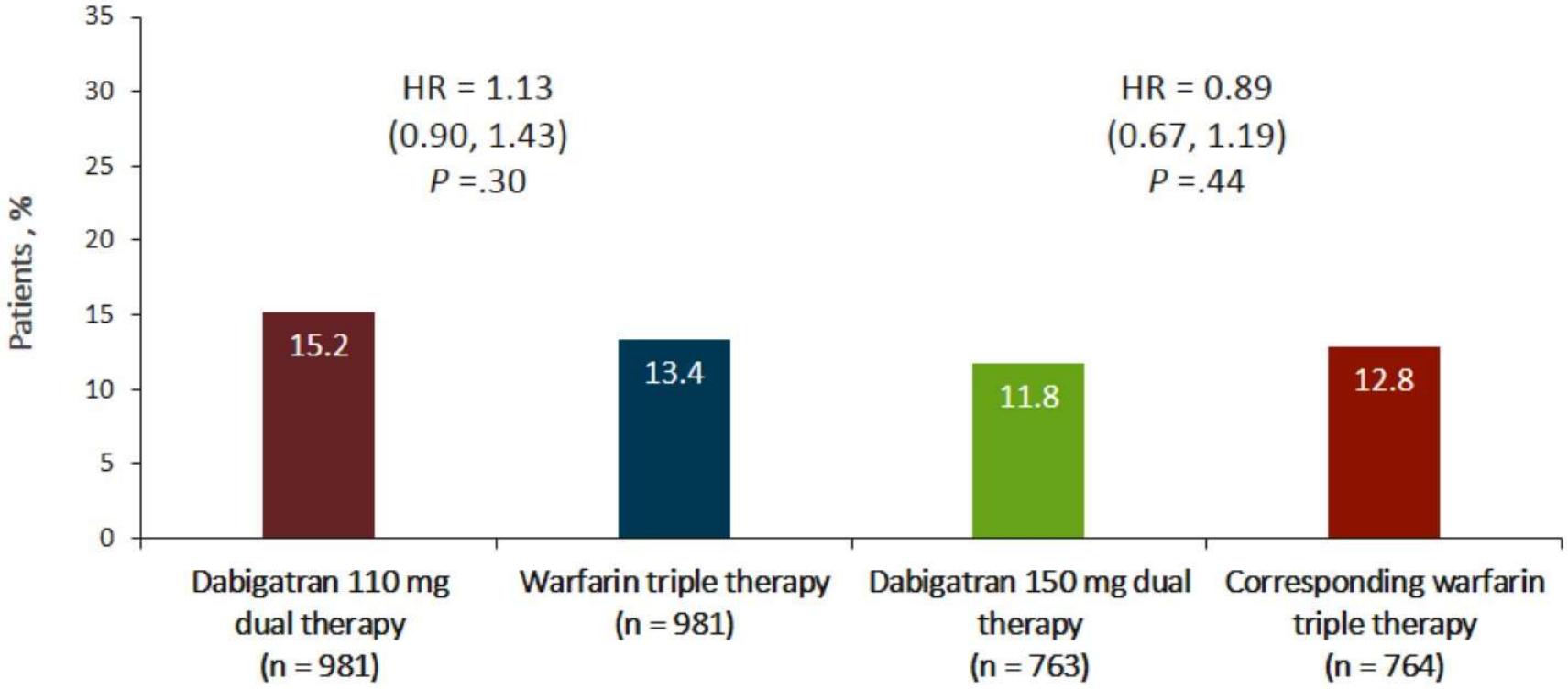
Cannon CP, et al. *Clin Cardiol*. 2016;39:555-564; Pradaxa® PI. March 2018.

RE-DUAL PCI: ISTH Major or CRNM Bleeding



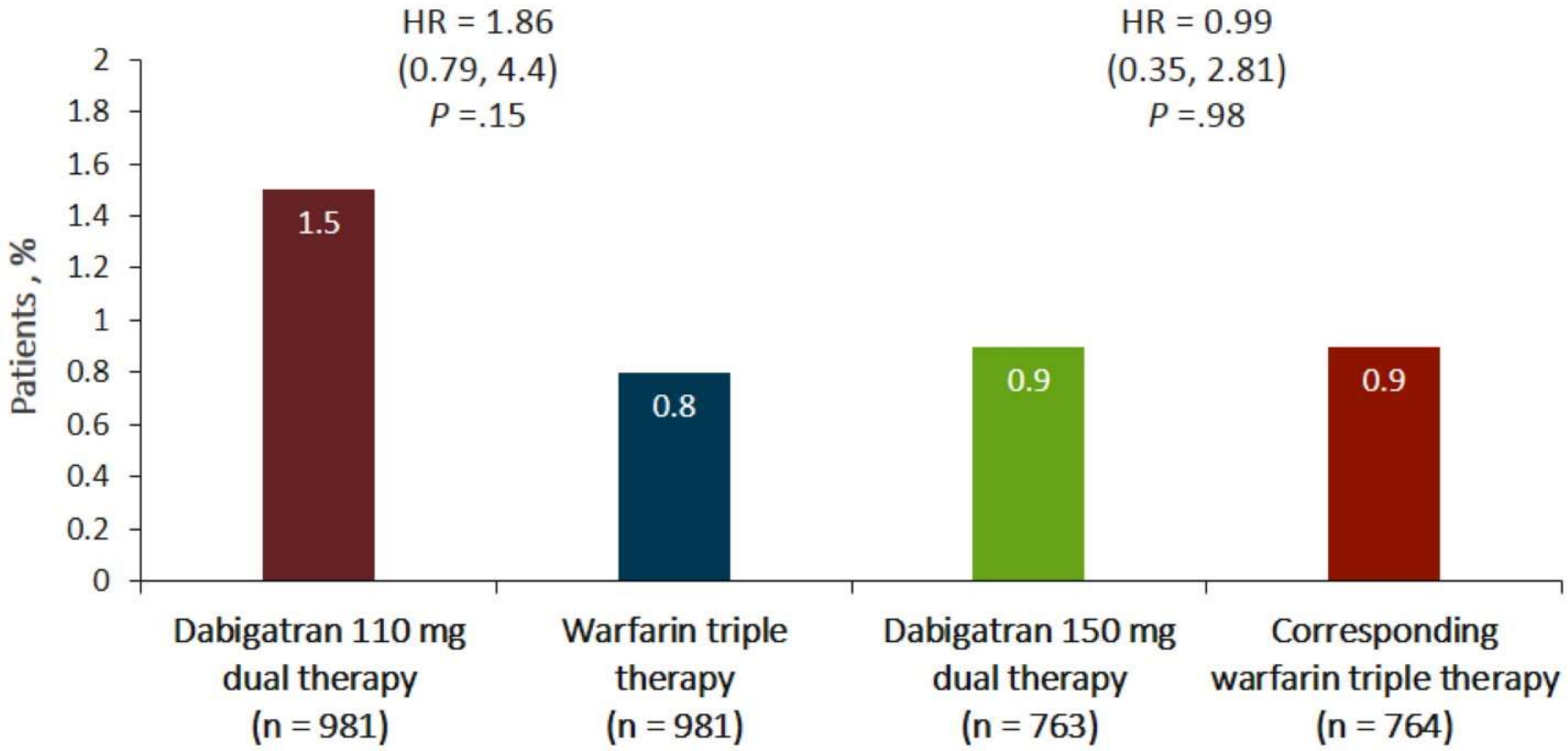
Cannon CP, et al. *N Engl J Med.* 2017;377:1513-1524.

RE-DUAL PCI: Thromboembolic Events, Death, or Unplanned Revascularization



Cannon CP, et al. *N Engl J Med.* 2017;377:1513-1524.

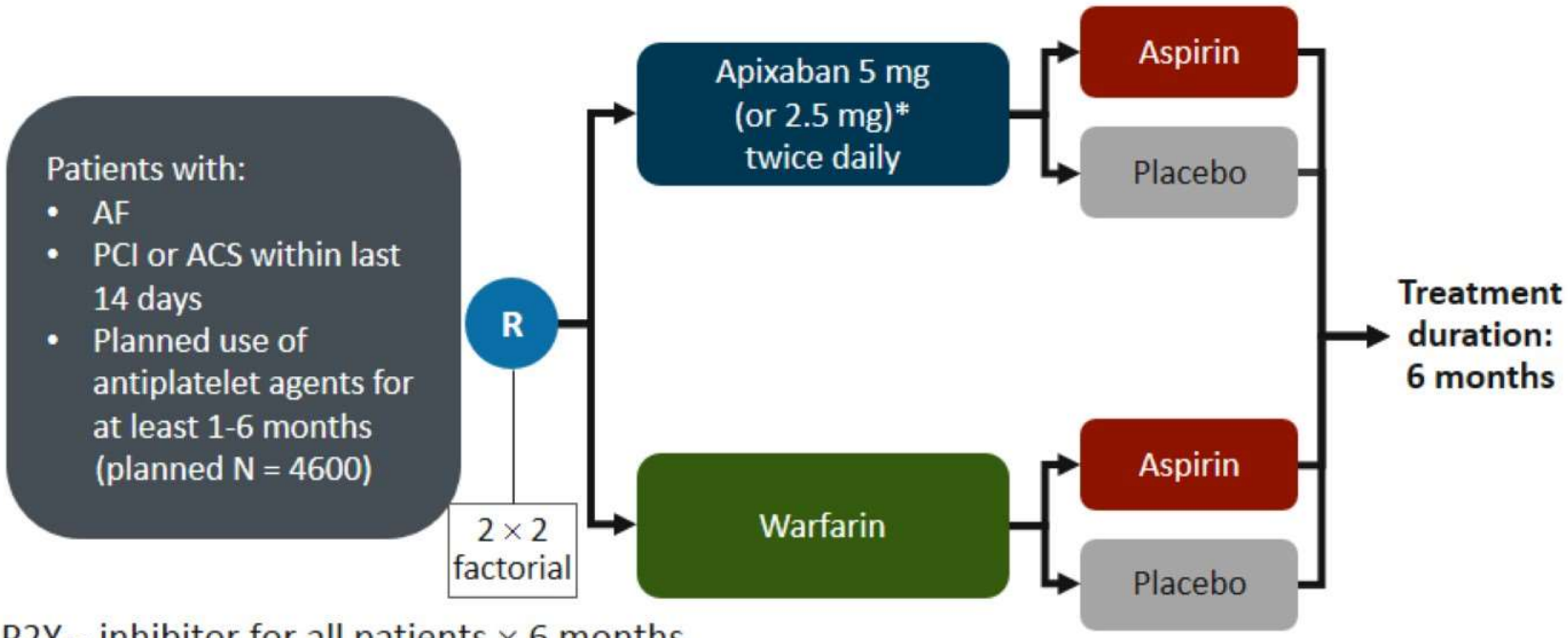
RE-DUAL PCI: Definite Stent Thrombosis



Dabigatran 110-mg dose potentially may have more thromboischemic events, whereas the 150-mg dose preserves efficacy with at least 30% reduction in bleeding

Cannon CP, et al. *N Engl J Med.* 2017;377:1513-1524.

AUGUSTUS: Study Design

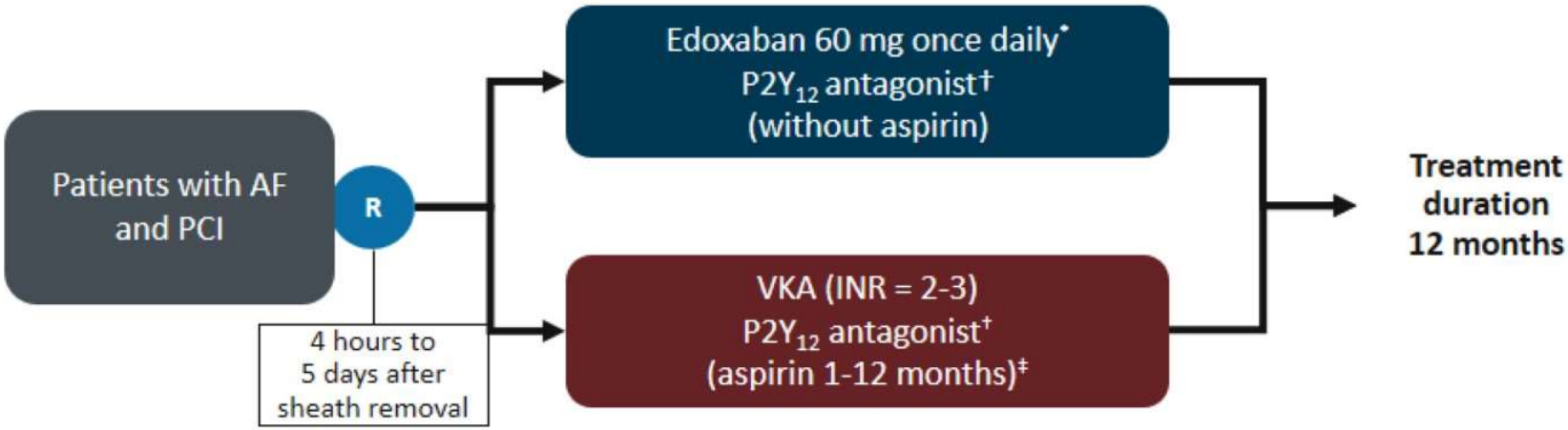


- $P2Y_{12}$ inhibitor for all patients × 6 months
- Blinded randomization for aspirin
- Estimated completion: December 2018

- Primary outcome measure: ISTH major or CRNM bleeding
- Secondary outcome measure: composite of death and ischemic events (stroke, MI, stent thrombosis, urgent revascularization)

*2.5 mg twice daily for patients with ≥ 2 criteria: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL.
ClinicalTrials.gov. NCT02415400.

ENTRUST-AF PCI: Study Design



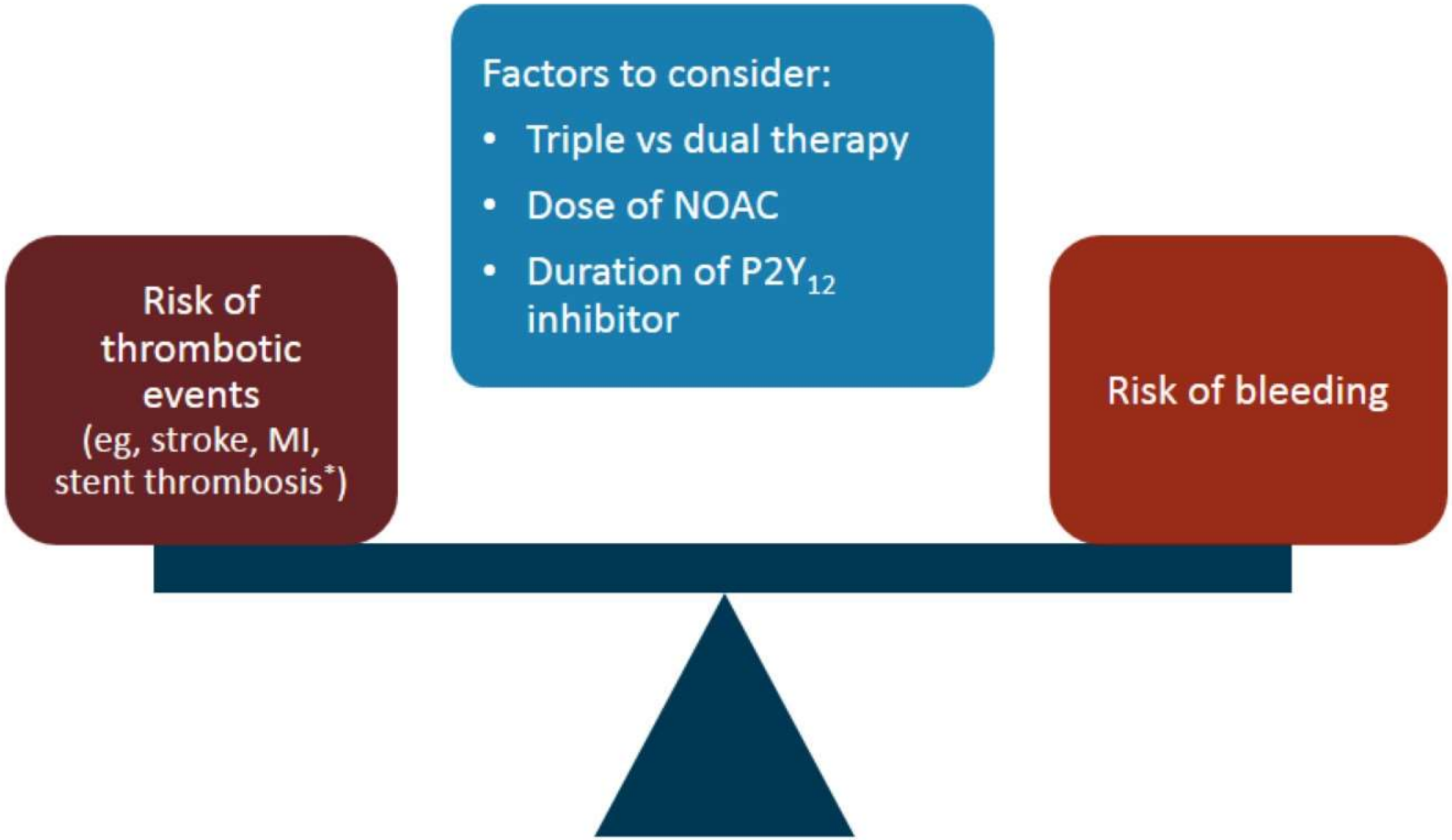
- Primary outcome measure: ISTH major or CRNM bleeding
- Secondary outcome measure: composite of CV death, stroke, SEE, MI, or definite stent thrombosis

- Estimated completion: March 2019

*Edoxaban dose reduction to 30 mg once daily if CrCl 15-50 mL/min, BW ≤ 60 kg, certain P-gp inhibitors.
†Clopidogrel 75 mg once daily or if documented need prasugrel 5 mg or 10 mg once daily or ticagrelor 90 mg twice daily. Predeclared at randomization.
‡Aspirin 100 mg once daily for 1-12 months guided by clinical presentation (ACS or stable CAD), CHA_2DS_2-VASc, and HAS-BLED.

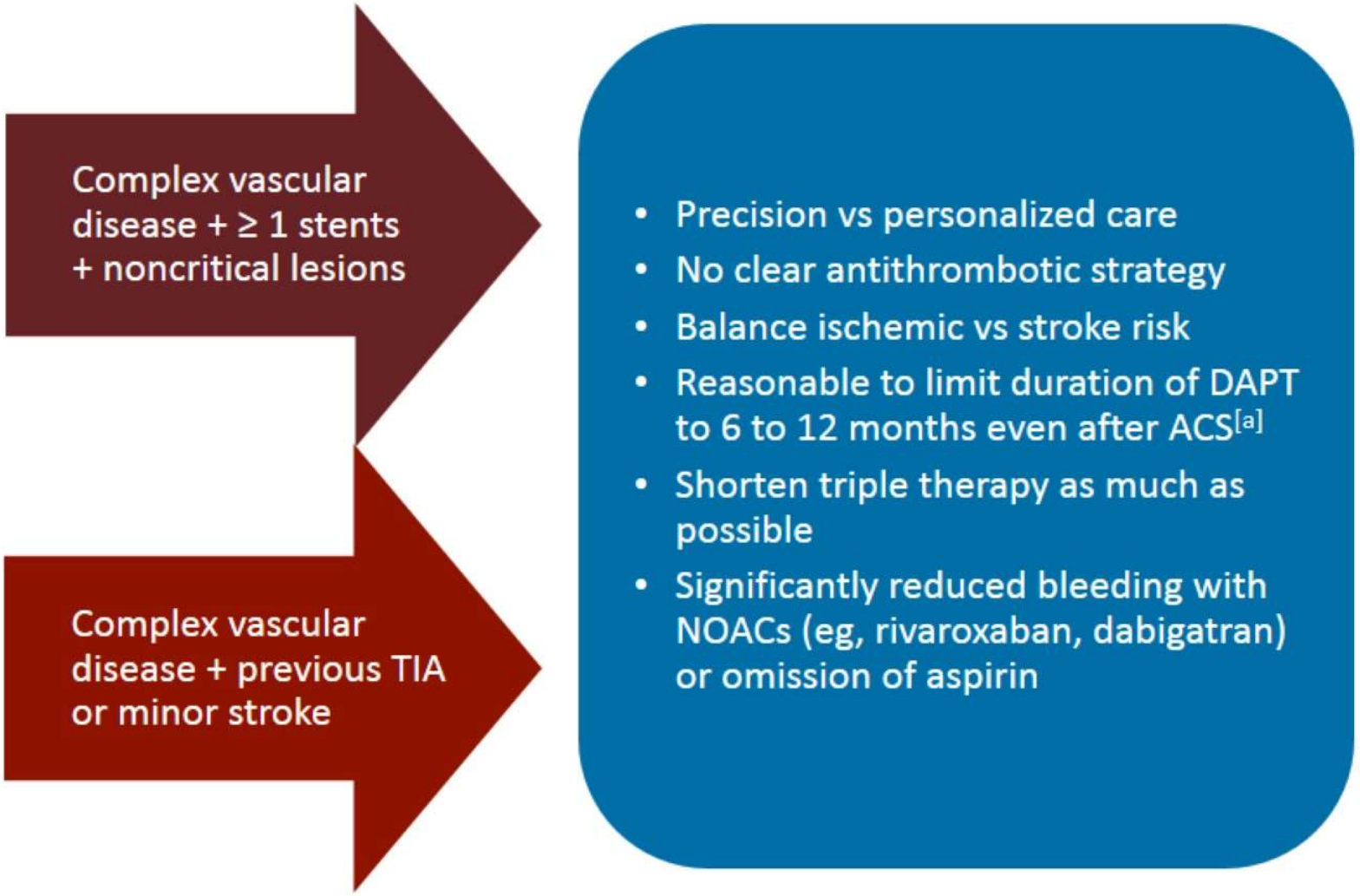
Vranckx P, et al. *Am Heart J*. 2018; 196:105-112.

Antithrombotic Strategy Considerations



*Newer-generation stents have lower risk of stent thrombosis.

Antithrombotic Strategies for Complex Patients With AF Following PCI



a. Levine GN, et al. *J Am Coll Cardiol*. 2016;68:1082-1115.

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Exploring the Use of NOACs in the Setting of TAVR

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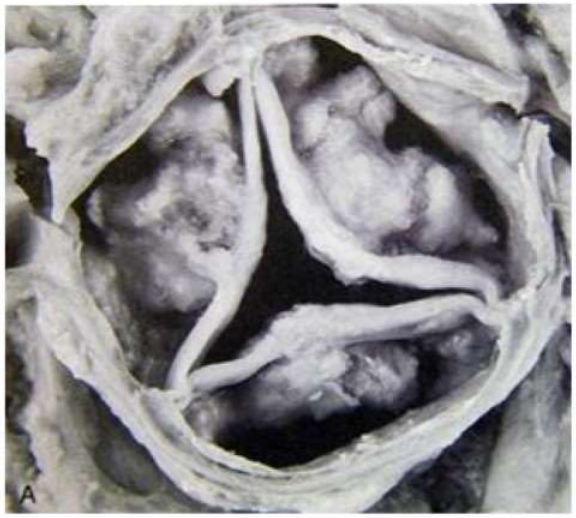
Transcatheter Aortic Valve Replacement/Implantation

- Similar to PCI, the TAVR procedure delivers a fully collapsible replacement valve to through a catheter for patients with severe aortic stenosis*[a,b]
  - Over 300,000 patients have now received TAVR (global worth $2 billion/year)[c]
- Patients are at high risk for bleeding and stroke complications, mechanical complications, and prothrombotic state[b]
  - Patients often have multiple comorbidities (ie, AF, high risk of stroke, recent PCI)[b]
- Recent clinical trials have demonstrated efficacy and safety in high-risk, inoperable, and intermediate-risk patients
  - Valve durability: up to ~5 years[d]



Degenerative calcified aortic valve
Image courtesy of Roxana Mehran, MD

*Alternative for patients who are at very high or prohibitive risk for standard SAVR.

a. AHA website; b. Rodés-Cabau J, et al. J *Am Coll Cardiol*. 2013;62:2349-2359; c. Cahill TJ, et al. *Eur Heart J*. 2018;0:1-13; d. Kapadia SR, et al. *Lancet*. 2015;385:2485-2491.

Post-TAVR DAPT

- Since there is a lack of evidence for DAPT regimens post-TAVR, recommendations are loosely based on coronary/peripheral vascular therapies
- DAPT (aspirin + clopidogrel 75 mg daily) for 3 to 6 months to reduce risk or thrombotic or thromboembolic events after TAVR
  - For patients with underlying AF post-TAVR, aspirin + warfarin or warfarin alone is considered the most effective and safest approach to anticoagulation
- Patients are at high risk for bleeding (ongoing risk cumulative over time)
- New onset of atrial arrhythmias are associated with a higher rate of CVE (within 24 hours to 30 days of TAVR)
- Greater 30-day and 1-year mortality post-TAVR

Rodés-Cabau J, et al. *J Am Coll Cardiol*. 2013;62:2349-2359.

Many Unknowns With TAVR

- There are many unknowns about the appropriate treatment and pathophysiology after valve surgery
  - Dual antiplatelet regimen?
  - Low dose NOAC or VKA for 3 months?
  - Treat what is seen in images or symptoms?
  - Subclinical thrombosis (ie, potential stroke or SE) and decreased mobility of valves related to late degeneration of TAVR or percutaneous valves?
- Main focus is on bleeding risk
- Surgical literature may have different recommendations to reduce the risk of stroke and SE early on

TAVR Trials

PARTNER-1 and -2A*[a,b]

- Data from > 2000 patients (per trial)
- Both trials confirmed TAVR noninferior to SAVR in terms of 2-year rates of death from any cause or disabling stroke
- PARTNER-1: Mean STS score: 12%
  - TAVR resulted in less AKI, severe bleeding, and NOAF
- PARTNER 2A: TAVR 31.0%, SAVR 35.2%
  - 4-10% predicted mortality rate
  - Mean STS 5.8%

Data From PARTNER and CoreValve Trials*[a-c]

- History of AF can be as high as 40%
- TAVR patients mostly age > 80 with multiple comorbidities
- Patients received DAPT for at least 6 months after TAVR procedure
- CoreValve (as treated): mean STS score 7.4%, TAVR 40.9%, SAVR 45.9%
- TAVR has higher rate of major vascular complications and residual moderate or severe paravalvular leak

*Trials were conducted in intermediate risk patients with severe symptomatic aortic stenosis.

a. Leon MB, et al. *N Engl J Med* 2016;374:1609-1620; b. Cahill TJ, et al. *Eur Heart J*. 2018;0:1-13; c. Adams DH, et al. *N Engl J Med.* 2014;370:1790-1798.

Current Guideline Recommendations for TAVR

ACCP[a]

Post-TAVR

- Clopidogrel 75 mg/day x 3 to 6 months + lifelong aspirin 75 mg to 100 mg/day

For patients indicated for anticoagulation:

- Follow AF guidelines for patients with prosthetic heart valves
- VKA may be considered for first 3 months in patients at risk for AF or valve thrombosis*

ACC/AHA[b]

Post-TAVR

- Aspirin 75-100 mg/day (Class I)
- Clopidogrel 75 mg daily reasonable for first 6 months after TAVR + lifelong aspirin 75 mg to 100 mg daily
- VKA (target INR: 2.5) for 3 to 6 months in patients with low bleeding risk (Class IIa/b, B-NR)†

For patients with AF and VHD:

- VKA or NOAC can be considered for prevention of thromboembolic events†

ESC[c]

Post-TAVR

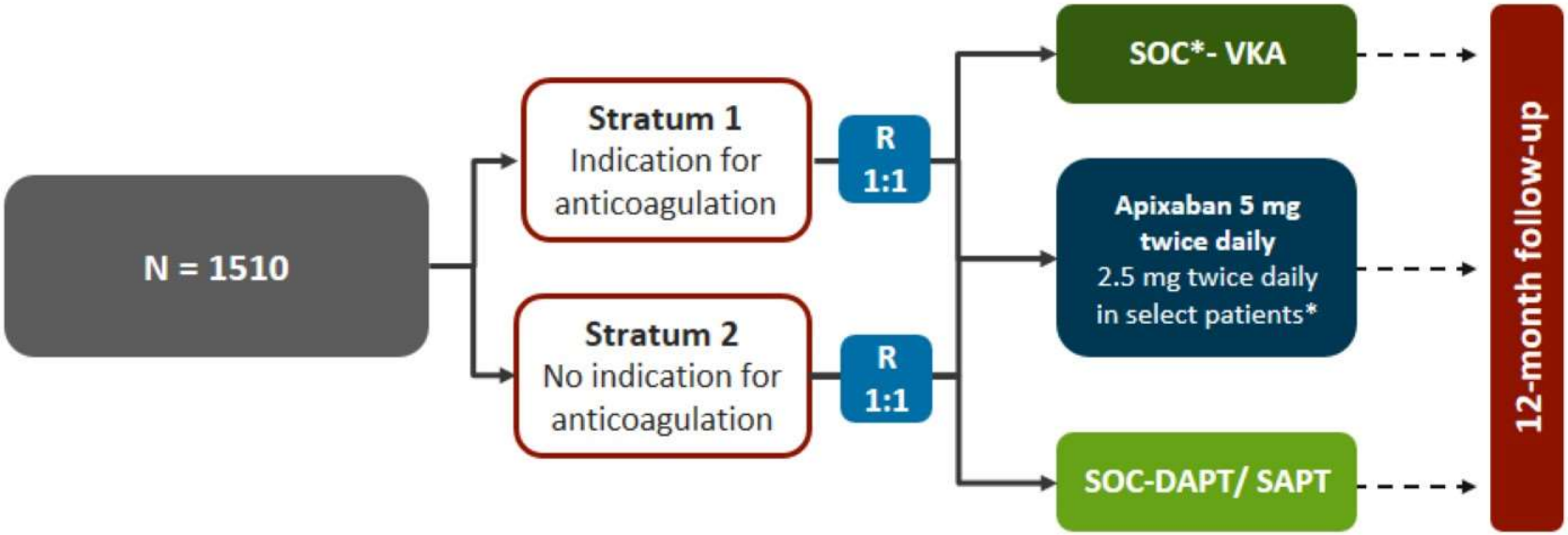
- Aspirin 75-100 mg/day for first 3 months after surgery (IIa/C)
- DAPT for first 3 to 6 months followed by lifelong SAPT in patients who are not indicated for OAC (IIa/C)
- SAPT if high bleeding risk (IIb/C)
- OAC for first 3 months after surgery (IIb/C)

*Depending on the specific risk-benefit ratio in that patient. When VKA therapy is used, continuation of aspirin is reasonable, but avoid other antiplatelet therapy due to increased risk of bleeding.
†New recommendation; see guidelines.

a. Otto CM, et al. *J Am Coll Cardiol*. 2017;69:1313-1346; b. Nishimura RA, et al. *J Am Coll Cardiol*. 2017;70:252-289; c. Baumgartner H, et al. *Eur Heart J*. 2017;38:2739-2791.

ATLANTIS Trial: Apixaban vs Standard of Care

Apixaban in Patients Who Underwent a Clinically Successful TAVI Procedure

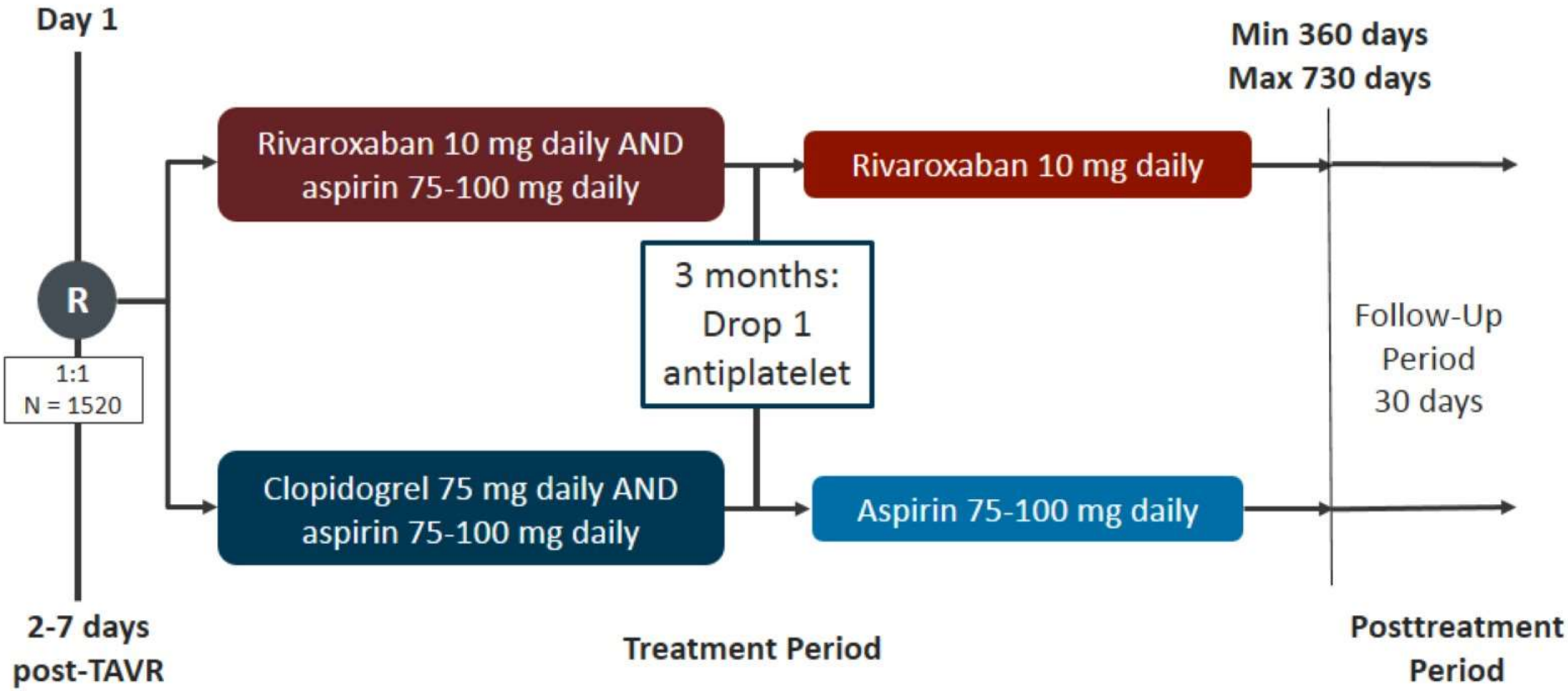


Primary endpoint: Composite of death, MI, stroke/TIA/systemic emboli, intracardiac or bioprosthesis thrombus, episode of DVT/PE, major bleeding, over 6 months of follow-up

*2.5 mg twice daily if CrCl 15 to 29mL/min or if 2 of the following criteria: age ≥ 80, weight ≤ 60 kg, or Cr ≥ 1.5 mg/dL (133 µmol).

ClinicalTrials.gov. NCT02664649.

GALILEO Trial Design: Rivaroxaban vs Clopidogrel



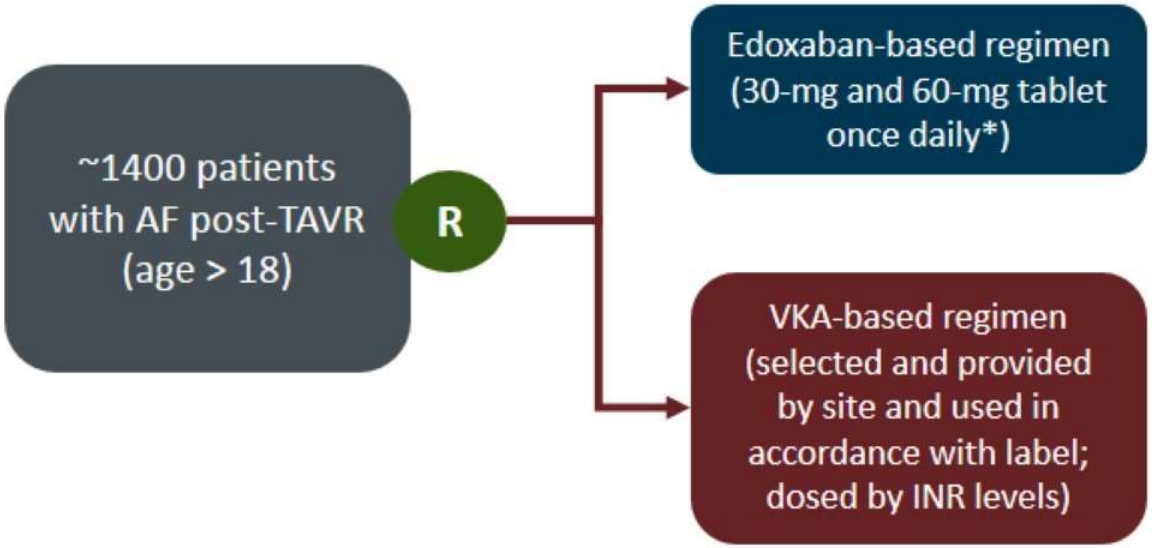
- **Primary efficacy endpoint:** Composite of death, stroke, MI, symptomatic valve thrombosis, systemic thromboembolism, or major VTE
- Estimated completion: December 2018

ClinicalTrials.gov. NCT02556203.

ENVISAGE-TAVI: Edoxaban- vs VKA-Based Regimen

Phase 3, randomized, open-label study assessing the safety and efficacy of edoxaban- vs VKA-based regimen in patients with AF and indication for OAC after TAVI

- 36-month follow-up
- Estimated completion: May 2020



Primary Outcomes at 36 months:
Adverse event composite: all-cause death, MI, ischemic stroke, SEE, thrombosis, major bleeding (ISTH definition)

*15-mg film-coated tablet for transitioning at end of treatment.
ClincialTrials.gov. NCT02943785.

Interim Treatment Suggestions Until More Data Become Available for TAVR Patients

Patient with recent stent placement

- Start aspirin + clopidogrel about 1 month after procedure (depending on bleeding and ischemic risk and if they are in sinus rhythm)
- If very high risk of bleeding, give aspirin alone
- VKA or OAC should be reserved for patients who require it

Patient with AF

- If they are already on a NOAC at admission, send them home on the same one
- Incorporation of aspirin depends on whether they have coronary disease

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Transitioning Care From Post-Procedure to Long-Term Management

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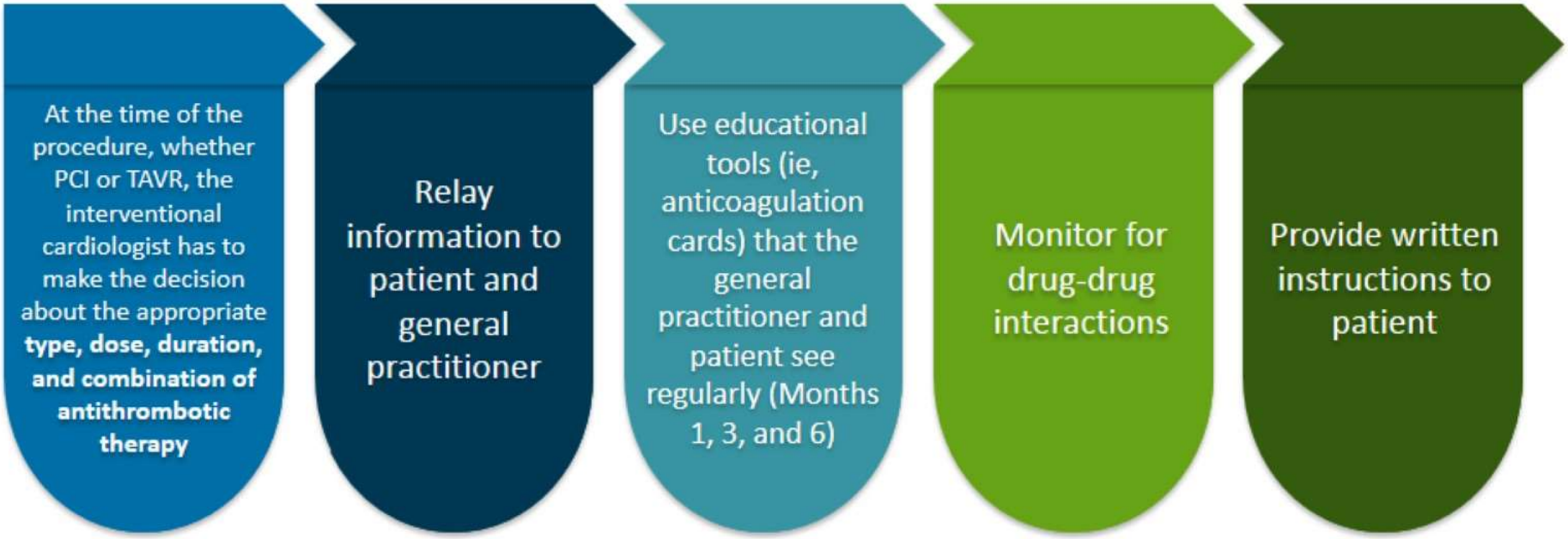
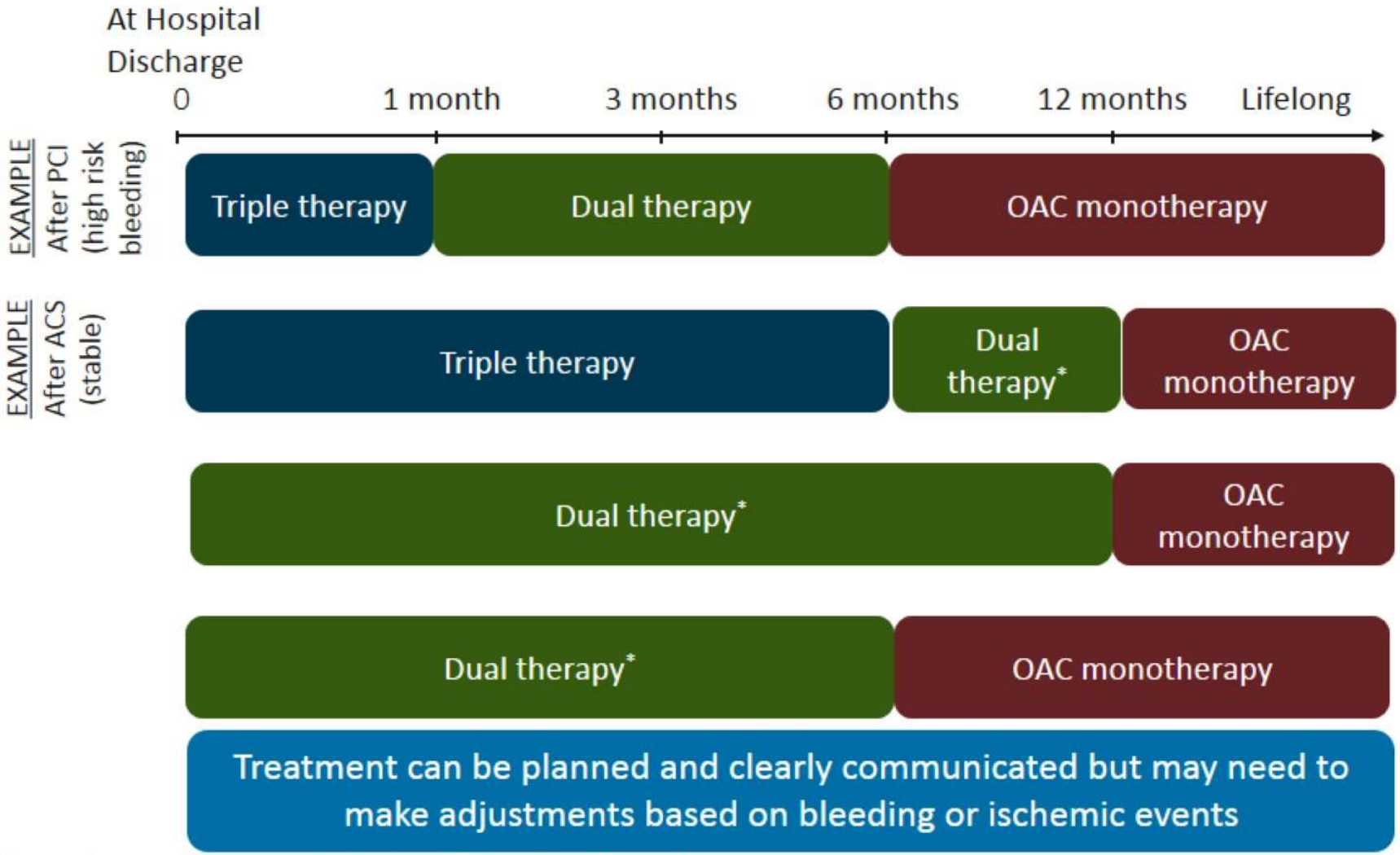
Follow-Up Considerations



Different Durations of Therapy
Patient Scenarios



*Assuming no other recurrent ischemic event while on therapy.

Patient Anticoagulation Education

Topics	Anticoagulation Educational Points
Anticoagulation Basics	Indicate the reason for initiating anticoagulation
	Review the name of the anticoagulant drug (generic and trade), how they work to reduce complications, onset, duration, and reversibility
	Duration of therapy
Risk:Benefit	Common signs and symptoms of bleeding and what to do when they occur
	Common signs and symptoms of a blood clot and what to do when they occur
	The need for birth control for women of child-bearing age
Self-Care	Precautionary measures to reduce the risk of trauma or bleeding (e.g. shaving, tooth brushing, acceptable physical activities)
Accessing Health Care	Which health care providers (eg, physicians, dentists) to notifying of the use of anticoagulant therapy
	When to notify an anticoagulation provider (dental, surgical, or invasive procedures or hospitalizations are scheduled)
	Carrying identification (eg, ID card, medical bracelet/necklace)
Adherence	Potential drug interactions
	When to take an anticoagulant medication and what to do if a dose is missed
Laboratory Monitoring	The meaning and significance of the INR*
	The need for frequent INR testing and the target INR values appropriate for treatment*
	The narrow therapeutic index and the emphasis on regular monitoring as a way to minimize bleeding and thrombosis risk*
Diet and Lifestyle	The need to limit or avoid alcohol; influence of dietary vitamin K use*

*If on VKA therapy.

NOAC Antidotes

Idarucizumab[a]

- Humanized monoclonal antibody fragment that binds dabigatran
- 300 × higher affinity for dabigatran than dabigatran has for thrombin
- 2.5 g IV x 2 bolus dose
- Approved for
  - Emergency surgery/urgent procedures
  - Life-threatening or uncontrolled bleeding

Andexanet alfa[b]

- "Decoy" recombinant FXa molecule with mutation in catalytic site, lacks GLA domain
- IV bolus followed by IV infusion*
- Accelerated approval based on change from baseline in anti-FXa activity in healthy volunteers for:
  - Apixaban
  - Rivaroxaban

*Low dose: 400-mg IV bolus x 30 mg/min; 4-mg/min IV infusion up to 120 mins. High dose: 800-mg IV bolus x 30 mg/min; 8-mg/min IV infusion up to 120 mins

a. Pollack CV, et al. *N Engl J Med*. 2017;377:431-441; b. Andexxa® PI.

Conclusion

- At the time of the procedure, whether PCI or TAVR, the interventional cardiologist has to decide on the appropriate type, dose, duration, and combination of antithrombotic therapy
  - Treatment may need to be adjusted based on comorbidities, concomitant medications, AF, bleeding, or thrombotic events
  - Clearly communicate treatment plan with the patient
- For PCI patients, it is reasonable to limit duration of DAPT to 6 to 12 months even after ACS or to shorten triple therapy as much as possible
- For patients undergoing valve surgery, there are many unknowns about the appropriate treatment and pathophysiology
  - Awaiting more clinical trial data
- Antidotes are available for serious life-threatening bleeds

Abbreviations

ACC = American College of Cardiology
ACCP = American College of Chest Physicians
ACS = acute coronary syndrome
AF = atrial fibrillation
AHA = American Heart Association
AKI = acute kidney injury
BMS = bare metal stent
B-NR = Level B, non-randomized
BW = body weight
CAD = coronary artery disease
CHA2DS2-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 – 74, and sex (female)
CI = confidence interval
CrCl = creatinine clearance
CRNM = clinically relevant nonmajor
CV = cardiovascular
CVE = cerebrovascular event
DAPT = dual antiplatelet therapy
DES = drug-eluting stent

Abbreviations (cont)

DVT = deep vein thrombosis
ESC = European Society of Cardiology
GI = gastrointestinal
GLA = gamma-carboxyglutamic acid
HAS-BLED = hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, labile INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each)
HR = hazard ratio
INR = international normalized rate
ISTH = International Society on Thrombosis and Haemostasis
IV = intravenous
MACE = major adverse cardiovascular event
MI = myocardial infarction
NA = not available
NOAC = non-vitamin K antagonist oral anticoagulants
NVAF = nonvalvular atrial fibrillation
OAC = oral anticoagulant
PCI = percutaneous coronary intervention
PE = pulmonary embolism

Abbreviations (cont)

P-gp = P-glycoprotein
PPI = proton pump inhibitor
R = randomization
riva = rivaroxaban
SAVR = surgical aortic valve replacement
SE = systemic embolism
SEE = systemic embolic event
SOC = standard of care
STS = Society of Thoracic Surgeons
TAVI = transcatheter aortic valve implantation
TAVR = transcatheter aortic valve replacement
TIA = transient ischemic attack
TIMI = thrombolysis in myocardial infarction
VHD = valvular heart disease
VKA = vitamin K antagonist
VTE = venous thromboembolism