Clinical Pearls and Updates in Cardiovascular Pharmacology

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Objectives

- Design a medication therapy regimen for patients with cardiovascular disease
- Distinguish the risks and benefits of cardiovascular medications
- Apply current guideline recommendations in patients with cardiovascular disease

Patient Case

- BA is a 63-year-old man who presents with worsening chest pain over the past week.
- Admitted for NSTEMI and probable PCI
- PMH and Medications:
  - Dyslipidemia: Atorvastatin 40 mg daily
  - Hypertension: Losartan 100 mg daily, Amlodipine 5 mg daily
  - Diabetes: Metformin 1000 mg BID, Aspirin 81 mg daily
  - Atrial Fibrillation: Warfarin, INR: 2.3

Patient Case

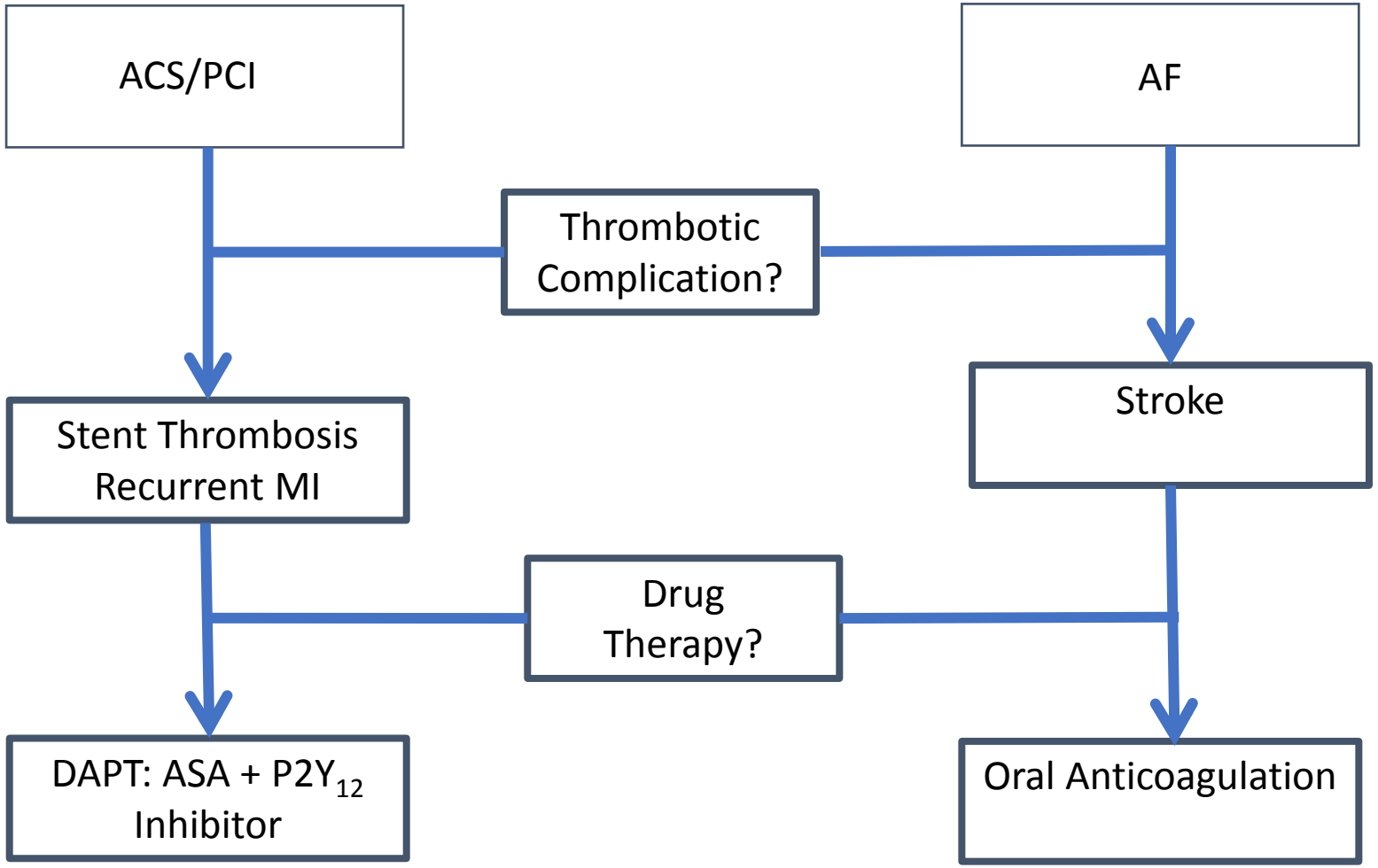
- Following morning, BA is taken for cardiac catheterization
  - Found to have 80% stenosis in his mid-LAD
    - Stented with Drug-eluting stent (DES)

- How do we manage his long-term antithrombotic therapy?
  - ACS + PCI with DES to mid-LAD
  - AF: previously taking warfarin

How would you manage his overall antithrombotic therapy?

a) Aspirin 81 mg daily + Clopidogrel 75 mg daily + Warfarin
b) Aspirin 81 mg daily + Prasugrel 10 mg daily + Warfarin
c) Aspirin 81 mg daily + Rivaroxaban 20 mg daily
d) Clopidogrel 75 mg daily + Dabigatran 150 mg BID

What's the Antithrombotic Challenge?



2019 ACC/AHA Focused Update on Atrial Fibrillation

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.

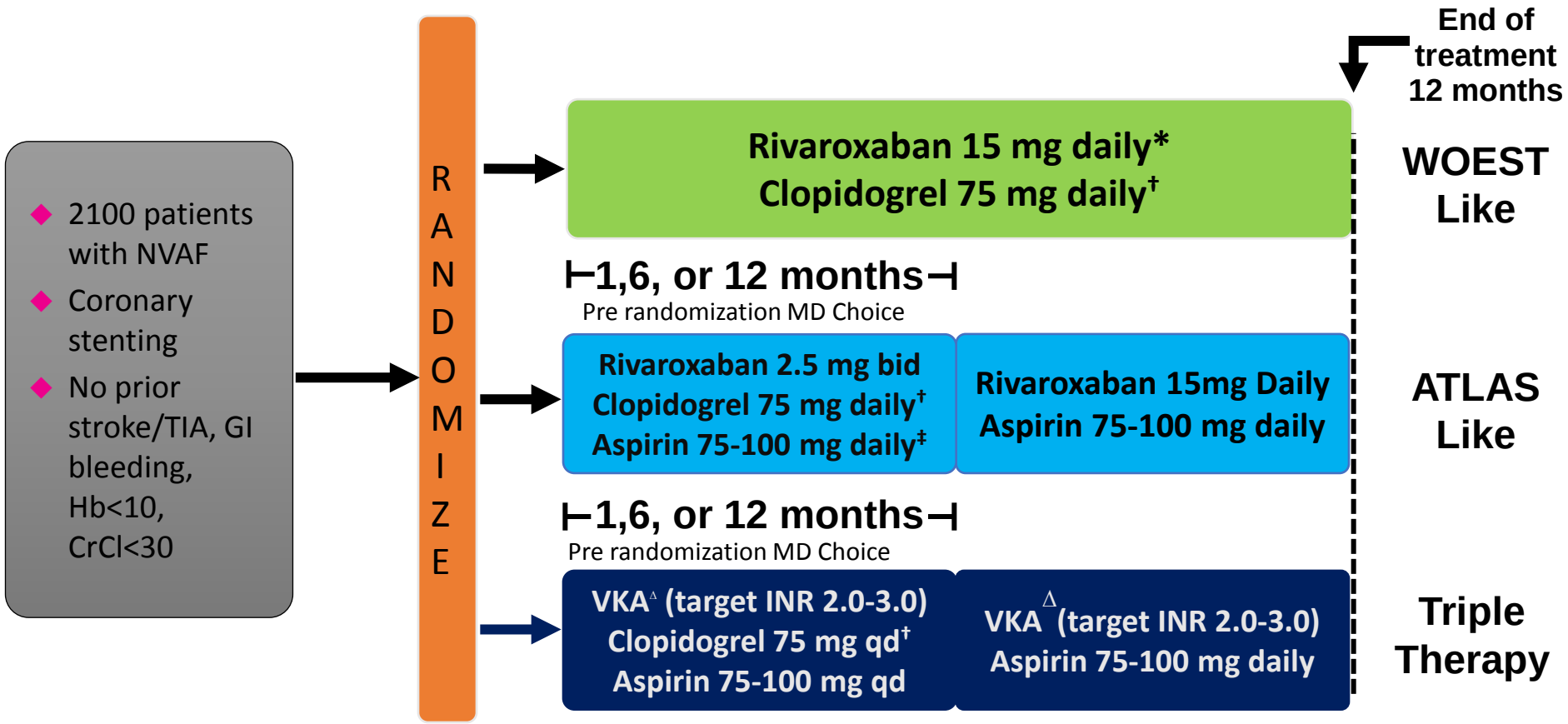
WOEST: Warfarin + P2Y12 vs. Triple Therapy

Age 18-80 years old with an indication for PCI and a clear need for ≥ one year oral anticoagulation

- Warfarin, Clopidogrel , ASA
- Warfarin and Clopidogrel

Dewilde, et al. Lancet, 2013; 381: 1107-15

PIONEER AF-PCI: Rivaroxaban + P2Y12 Inhibitor vs. Triple Therapy



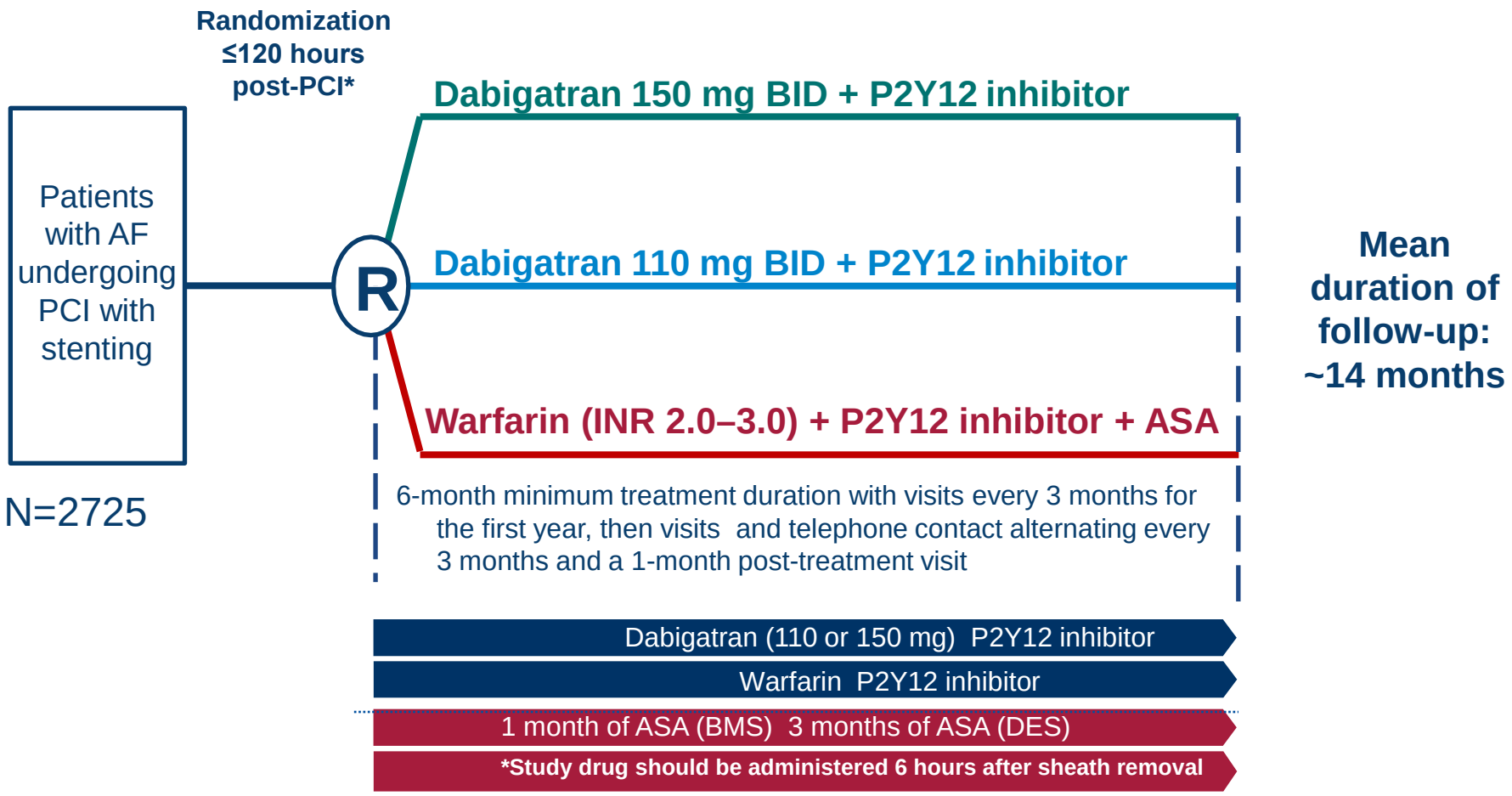
- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*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

RE-DUAL: Dabigatran + P2Y12 Inhibitor vs. Triple Therapy



Cannon CP et al. N Engl J Med 2017;377:1513-24.

AUGUSTUS: Apixaban + P2Y12 Inhibitor vs. Warfarin

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

Randomize
n=4600
patients

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

Apixaban 5 mg BID
Apixaban 2.5 mg BID in selected patients

Open Label

VKA
(INR 2–3)

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

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

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

Primary outcome: ISTH major / CRNM bleeding

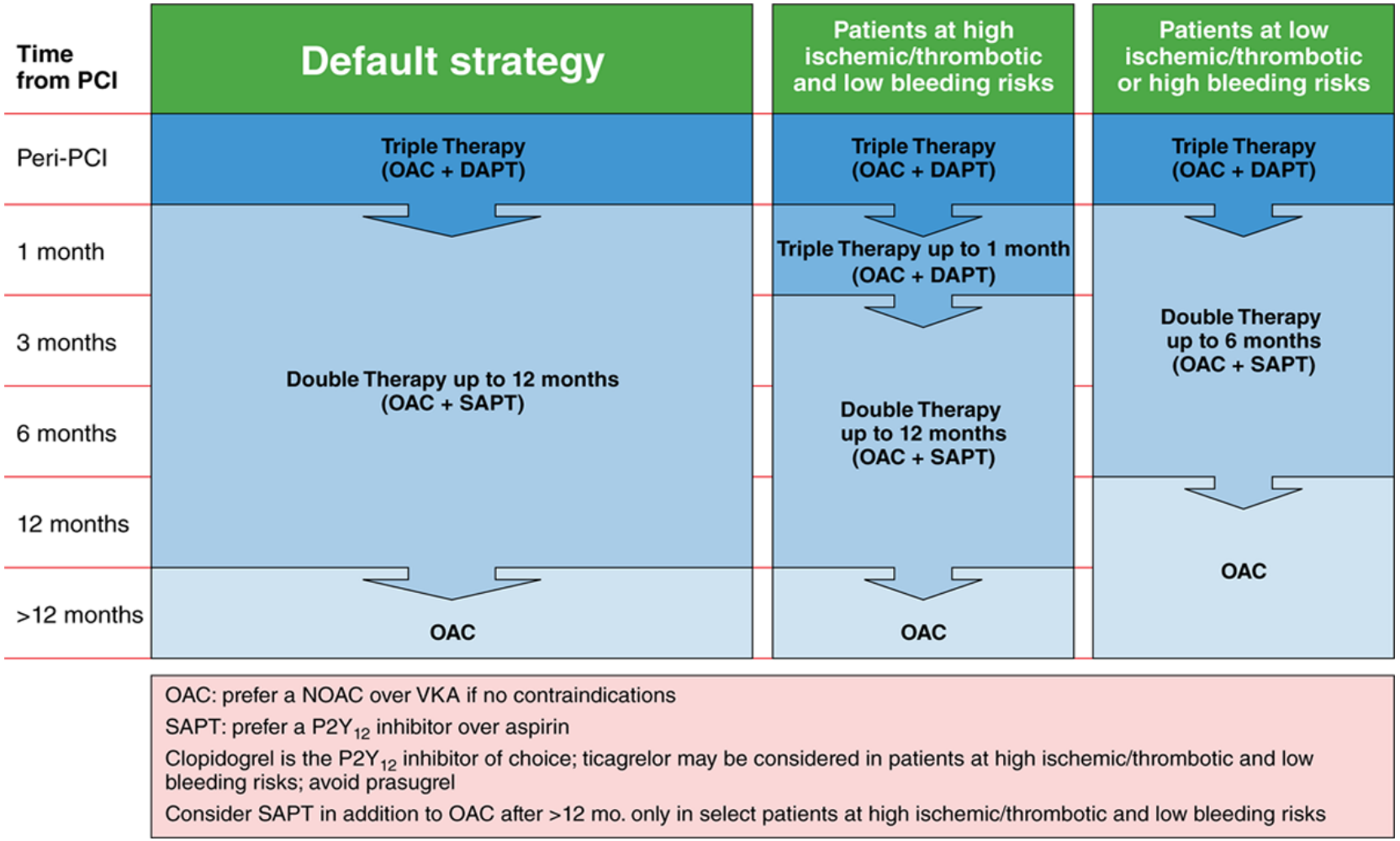
Secondary outcome(s): death / hospitalization, death / ischemic events

Lopes RD, et al. N Engl J Med 2019; 380:1509-1524.

Dual therapy = SAFER!

Study	Bleeding Dual Therapy (%)	Bleeding Triple Therapy (%)	Thrombotic Events Dual Therapy (%)	Thrombotic Events Triple Therapy (%)
WOEST	**19.5**	**44.9**	**11.1**	**17.6**
PIONEER	**16.8**	**26.7**	**6.5**	**6.0**
RE-DUAL	**20.2**	**25.7**	**11.8**	**12.8**
AUGUSTUS	**13.8**	**18.7**	**15.7**	**13.9**

North American Consensus White Paper



AMERICAN COLLEGE of CARDIOLOGY

Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention, Volume: 138, Issue: 5, Pages: 527-536, DOI: (10.1161/CIRCULATIONAHA.118.034722)

Rhode Island CHAPTER

Key take home points

- OAC + SAPT ($P2Y_{12}$ inhibitor) preferred over triple therapy in patients with AF + ACS
  - Clopidogrel is the preferred $P2Y_{12}$ inhibitor
    - Limited data with Ticagrelor; Prasugrel currently not recommended
  - DOACs are preferred over warfarin
    - Rivaroxaban 10 – 15 mg once daily (based on CLcr)
    - Dabigatran 150 mg BID
    - Apixaban 2.5 – 5 mg BID **PLEASE dose appropriately!!**

- Consider bleeding and thrombotic risk when considering choice of agents and duration of therapy
  - High bleeding risk = OAC + SAPT x 6 months, then OAC alone
  - High thrombotic risk = OAC + SAPT x 12 months, then OAC alone
    - Can consider triple therapy (OAC + DAPT) x 1 month

Which of the following would you recommend for stroke prevention for an AF Patient requiring Chronic Hemodialysis?

A. Warfarin
B. Apixaban
C. Aspirin
D. No therapy

Challenges in AF Patients with ESRD

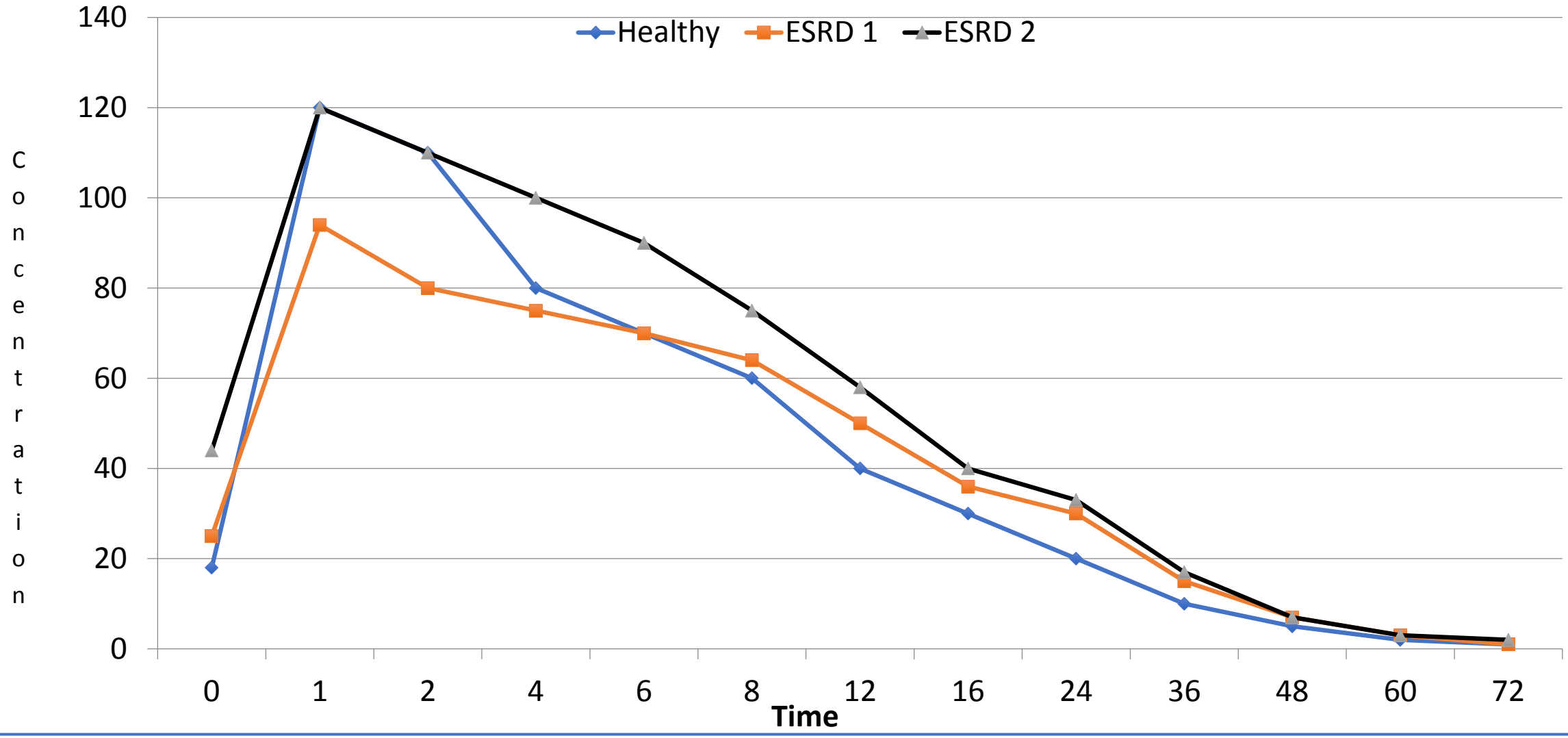
- What are there differences in stroke risk in ESRD/HD patients with AF compared with AF patients with normal/better renal function?
- CKD Stage 4-5 and chronic dialysis patients are not enrolled in clinical trials
  - Safe to extrapolate data from Stage 1 – 3 CKD?
- Challenges with Warfarin in ESRD/HD
- Challenges with DOACs in ESRD/HD

DOACs in ESRD/HD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Target	Factor II	Factor Xa	Factor Xa	Factor Xa
Renal Clearance	80%	27%	50%	36%
Dosing: AF	150 mg BID	5 mg BID	60 mg Daily	20 mg Daily
Renal dosing: AF	75 mg BID Calcar 15 - 30	2.5 mg BID*	30 mg Daily Calcar: 15 – 50	15 mg Daily Calcar < 50
AF dosing in HD?	NO	**YES**	NO	**YES**
HD Dosing in AF	N/A	5 mg BID**	N/A	15 mg Daily

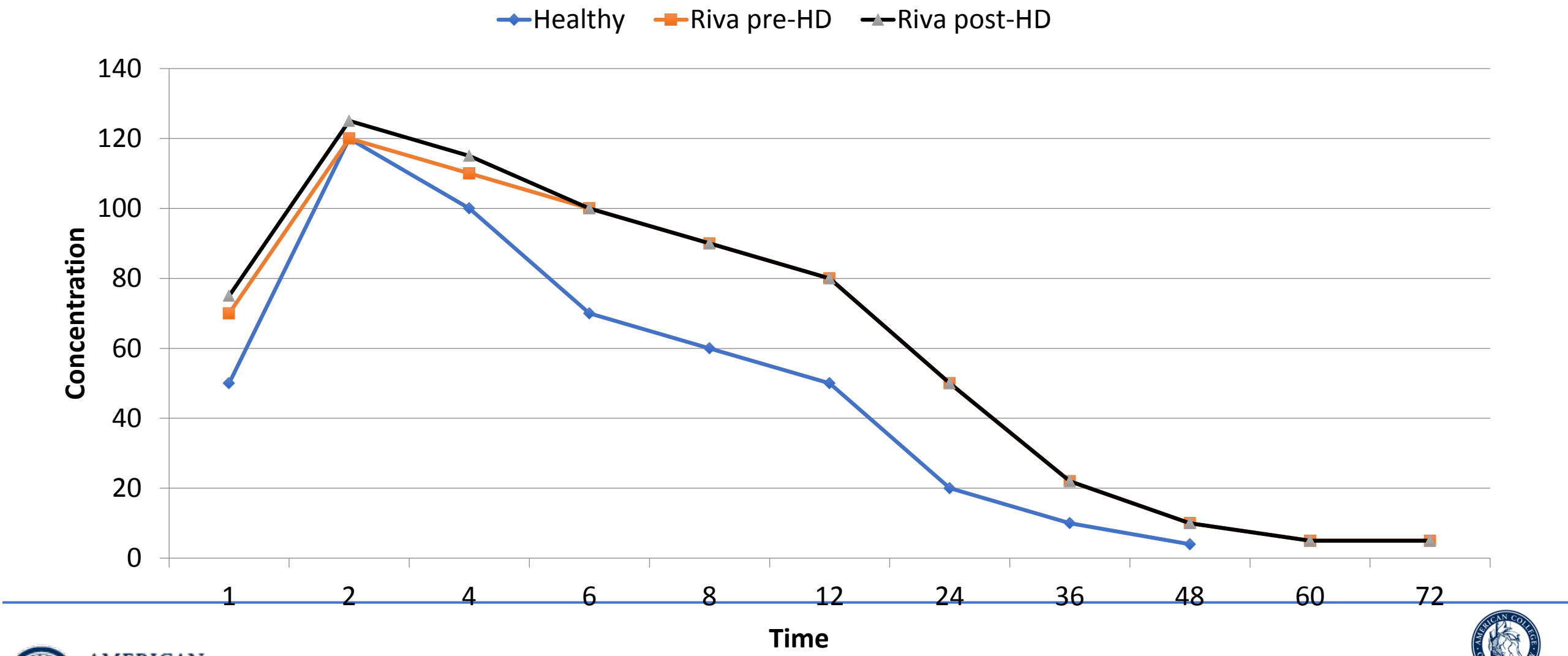
*Apixaban renal dosing is based on 2 of 3: Age ≥ 80 years-old, Weight ≤ 60 kg, Creatinine ≥ 1.5 mg/dL
** Apixaban HD dosing is 5 mg BID unless 1 additional factor listed above is present

Apixaban Pharmacokinetics (n=8)



Wang X et al. J Clin Pharmacol 2016; 56(5):628-36.

Rivaroxaban Pharmacokinetics (n=8)

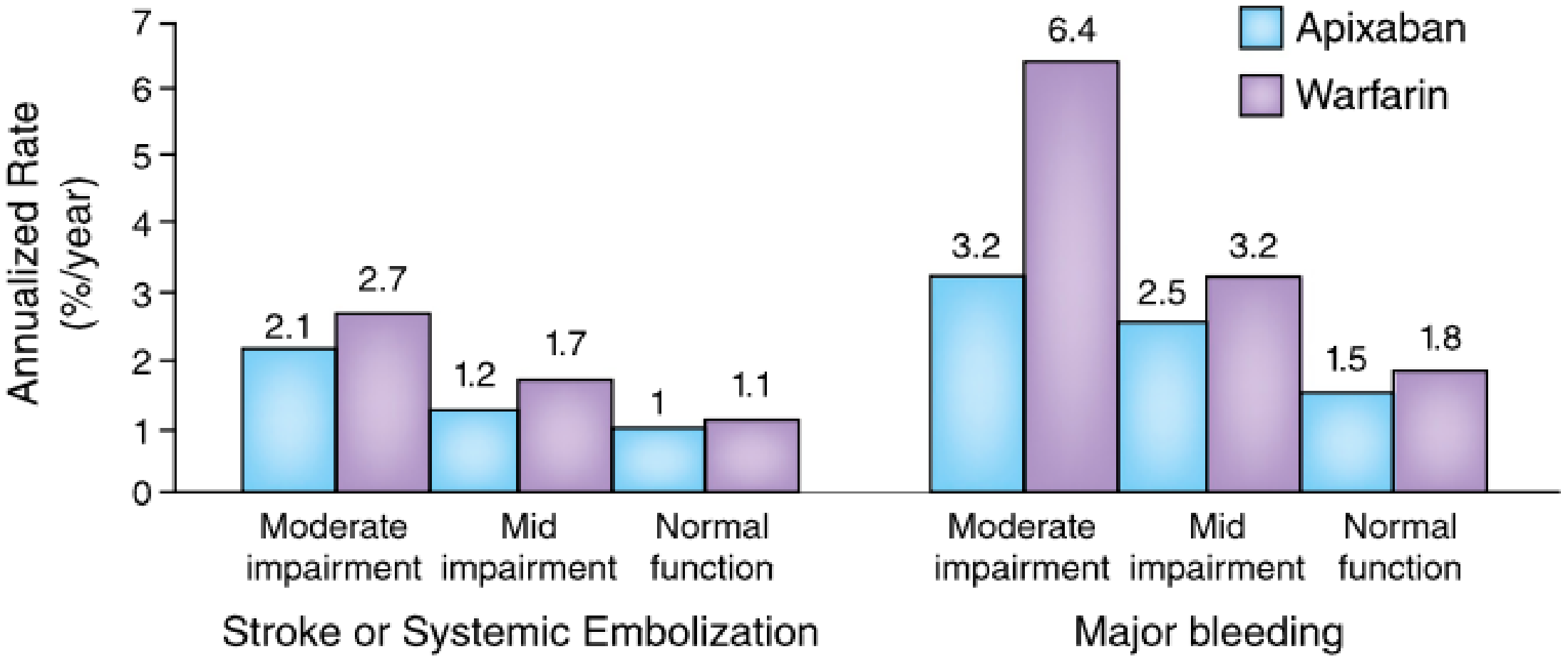


Dias C et al. Am J Nephrol 2016; 43:229-236.

AMERICAN COLLEGE of CARDIOLOGY

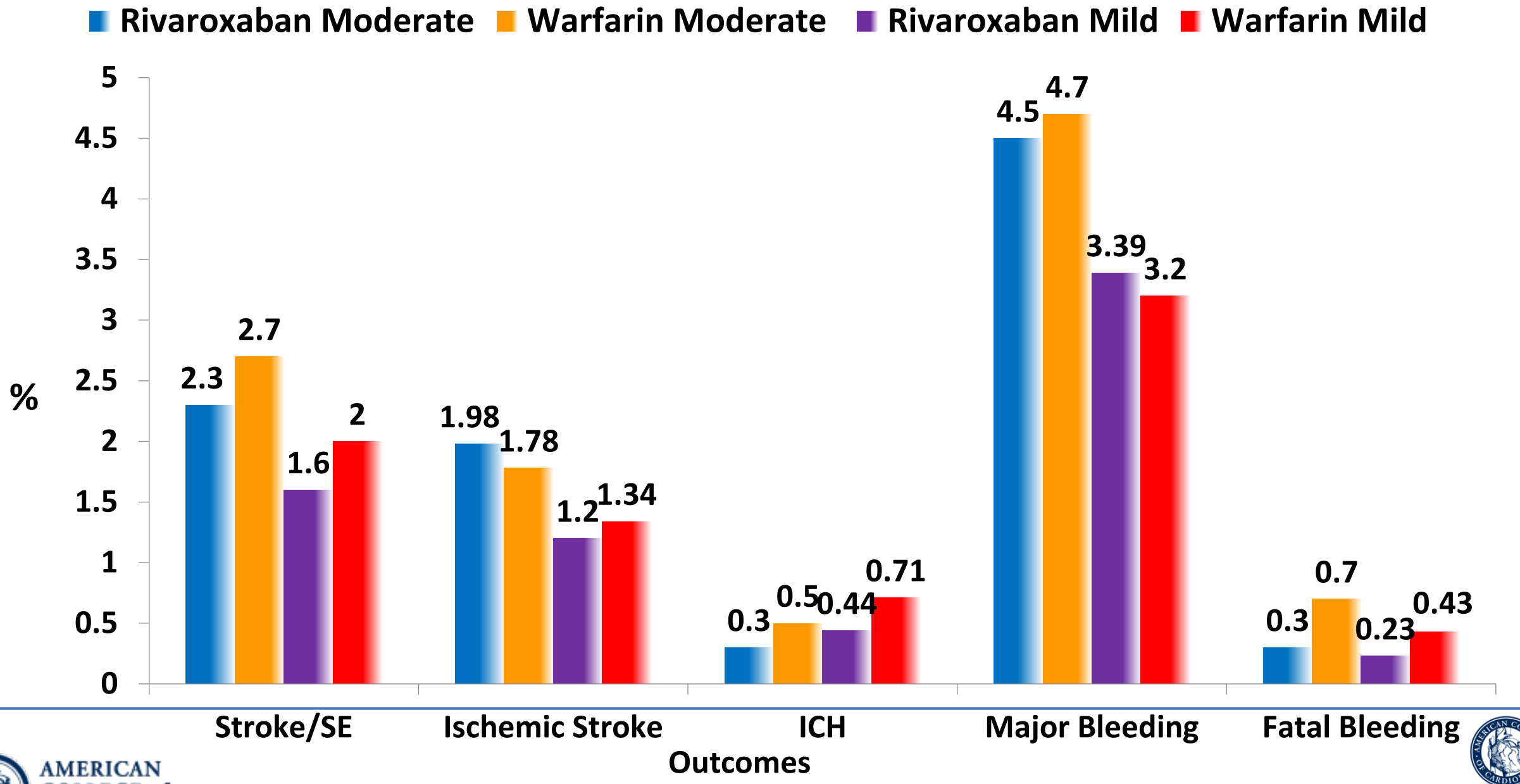
Rhode Island CHAPTER

Apixaban vs. Warfarin: Renal Impairment Outcomes (Aristotle)



Hohnloser SH et al. Eur Heart J 2012; 33:2821–2830.

Rivaroxaban vs. Warfarin: Renal Impairment Outcomes (ROCKET-AF)



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Fox KA et al. Eur Heart J 2011; 32(19):2387-94.

Rhode Island CHAPTER

Apixaban vs. Warfarin in ESRD

- Retrospective cohort study of 25,523 patients with AF
  - US Renal Data System 2010 - 2015
- 2351 patients on Apixaban matched to 23,172 warfarin patients
- Matched based on:
  - Age
  - Gender
  - Diabetes
  - CVA
  - Bleeding history
  - Obesity
  - Dialysis modality
  - Interacting Drugs
- Primary outcomes measures: Stroke/systemic embolism, major bleeding

Siontis KC et al. Circulation 2018; 138:1519-29.

Apixaban vs. Warfarin in ESRD

- No differences in stroke/systemic embolism between groups
  - Apixaban 12.4 vs. Warfarin 11.8 per 100 patient-years
  - HR: 0.88 (0.69 – 1.12; p=0.29)

- Major bleeding was reduced:
  - Apixaban 19.7 vs. Warfarin 22.9 per 100 patient-years
  - HR: 0.72 (0.59 – 0.87; p<0.001)
  - GI Bleeding reduced in Apixaban treated patients
  - No differences in intracranial hemorrhage 3.1 vs. 3.5 per 100 patient-years

- No differences in mortality:

Siontis KC et al. Circulation 2018; 138:1519-29.

Apixaban Dosing Influences Outcomes

- 44% patients received 5 mg BID vs. 56% received 2.5 mg BID

- Apixaban 5 mg BID group associated with better outcomes vs. Warfarin
  - Stroke: HR: 0.64 (0.42 – 0.97; *p*=0.04)
  - Major Bleeding: HR 0.71 (0.53 – 0.95; *p*=0.02)
  - Death: HR: 0.63 (0.46 – 0.85, *p*=0.003)

- Apixaban 2.5 mg group only had reduced bleeding:
  - Stroke: HR: 1.11 (0.82 – 1.50; *p*=0.49)
  - Major Bleeding: HR 0.71 (0.56 – 0.91; *p*=0.007)
  - Death: HR: 1.07 (0.87 – 1.33, *p*=0.52)

Siontis KC et al. Circulation 2018; 138:1519-29.

Future Studies in AF patients with ESRD/HD

Study Title	Methods	Inclusion Criteria	Primary Outcomes
ADAXIA	Apixaban 2.5 BID vs. Phenprocoumon	• ESRD with 3x week HD • AF, CHADSVASc ≥ 2	Major and clinically relevant non-major bleeding
RENAL-AF	Apixaban vs Warfarin	• ESRD with chronic HD • AF, CHADSVASc ≥ 2	Major and clinically relevant non-major bleeding
AVKDIAL	Warfarin vs. placebo	• ESRD with chronic HD • AF, CHADSVASc ≥ 2 • HASBLED ≥ 3	Cumulative incidence: severe bleeding and thrombosis
XARENO	Rivaroxaban vs. Warfarin vs. Placebo	• CKD: eGFR 15 – 49 • AF	• Decline in eGFR • Major Bleeding • Thromboembolic events (Stroke, VTE, MACE)

2019 ACC/AHA Focused Update for Atrial Fibrillation

Recommendations for Selecting an Anticoagulant Regimen—Balancing Risks and Benefits		
COR	**LOE**	**Recommendations**
IIb	**B-NR**	**For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation.** **MODIFIED**: New evidence has been added. LOE was updated from B to B-NR. (Section 4.1. in the 2014 AF Guideline)

Take Home Points

- ESRD/HD patients with AF may have different pathology for stroke risk than patients without renal disease:
  - OAC benefit in stroke reduction is less clear

- Warfarin use in ESRD/HD patients:
  - Lower doses required
  - INR control is challenging
  - Possible association with:
    - Worsening renal function (Risk: INR > 3.0)
    - Calcification

- DOACs have limited data in ESRD/HD patients
  - Unclear if renal dosing is safe/effective
  - 2 DOACs have FDA dosing based on limited data
  - Ongoing studies will clarify