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Clinical Meeting & Exhibition

Anticoagulation for Atrial Fibrillation: Difficult Clinical Conundrums

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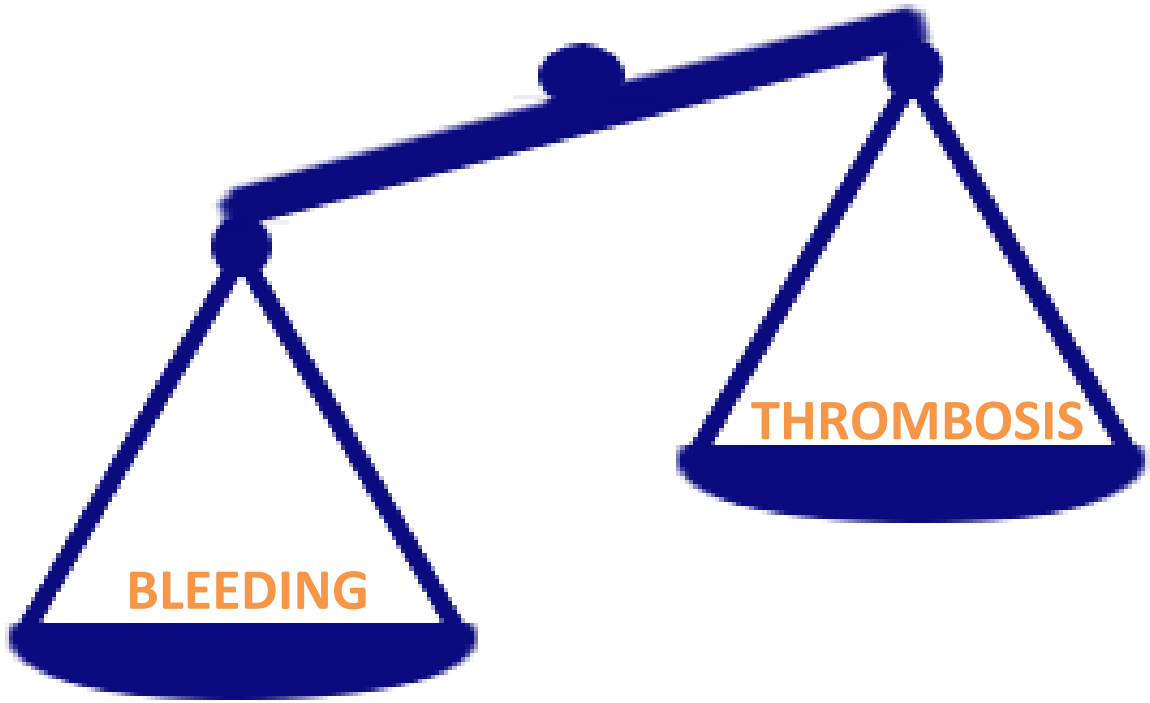
Disclosures

- **Snehal Bhatt:** Janssen Pharmaceuticals, Inc.: Advisory Board, Speaker's Bureau; Portola Pharmaceuticals: Advisory Board
- All other planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Objectives

- Assess individual patient risk of bleeding and thrombosis to formulate a perioperative plan for anticoagulation management.
- Formulate an approach to work with patients to help them decide their preferred antithrombotic choice with a CHAD2S2-VASc=1.
- Assess a patient's renal function and choose the best anticoagulation option for stroke prophylaxis.
- Assess if anticoagulation dosing is adequate and appropriate based on weight and body mass index (BMI).

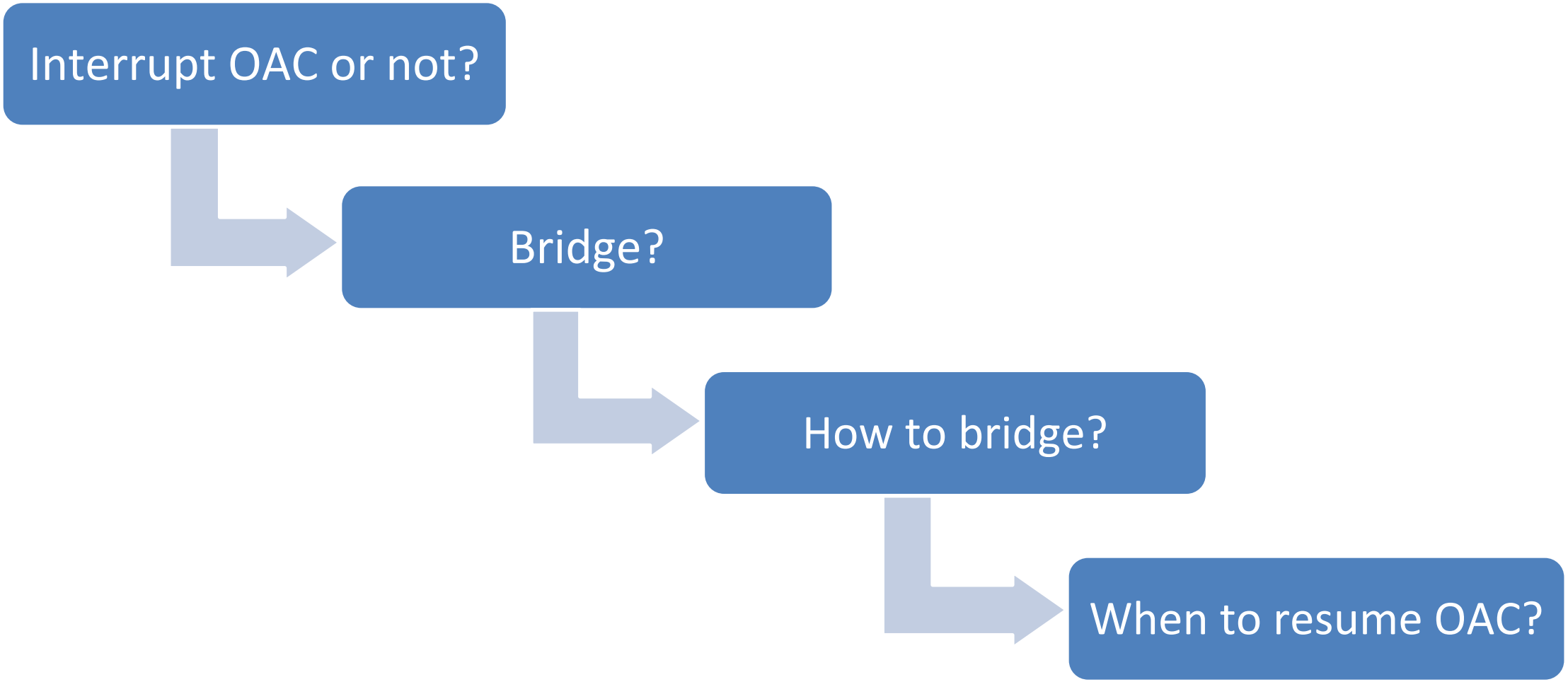
It’s time for surgery… what do I do with my blood thinner?



Patient Case: Perioperative Management

- GH is a 72 yo female with a PMH of hypertension, diabetes, hypothyroidism, and atrial fibrillation. Home medications include Lisinopril, Carvedilol, Levothyroxine, Aspirin, Atorvastatin, and Apixaban. She is being scheduled for routine colonoscopy in two weeks and the gastroenterologist has asked you what he needs to do with her Apixaban. You should:
  a. Hold Apixaban for 2 days prior to the colonoscopy and resume 72 hours after
  b. Continue Apixaban uninterrupted.
  c. Hold Apixaban 5 days prior to colonoscopy, start Enoxaparin 3 days before colonoscopy and continue until resuming Apixaban 2 days after procedure
  d. Hold Apixaban only on the morning of the colonoscopy
  e. Hold Apixaban 5 days prior to colonoscopy and resume 5 days after procedure

Steps of Evaluating Perioperative Anticoagulation



Does anticoagulation need to be interrupted?

- Assess the bleed risk of the procedure
  - Risk of bleeding due to the nature of the procedure
  - Consequences of having a bleeding event
  - Antithrombotic regimen of the patient

- Evaluate the patient's risk of a thromboembolic event periprocedurally
  - Past medical history
  - Risk score of developing a new thrombosis

J Am Coll Cardiol 2017; 69(7): 871 – 98
Chest, 2012; 141(2)(Suppl): e326S – e350S

Procedural Risk of Bleed

Low Risk	Moderate Risk	High Risk
Cataract or glaucoma surgery	Renal biopsy	Neurosurgery
Dental procedures/hygiene	Colon polyp resection	Spinal/epidural surgical procedure
Simple dental extractions	Prostate biopsy	Urologic surgery/procedures
Restorations	Pacemaker/Defibrillator Implantation	Vascular surgery
Endodontics	Major Intrathoracic surgery	Cardiac surgery
Prosthetics	Major intra-abdominal surgery	Major orthopedic surgery
Cutaneous surgeries (most)	More invasive dental procedures	Prostate surgery
Laparoscopic cholecystectomy or hernia repair	More invasive ophthalmic procedures	Reconstructive plastic surgery
Endoscopy +/- biopsy		Bowel polypectomy
Colonoscopy +/- biopsy		
Joint aspiration or injection		

J Am Coll Cardiol 2017; 69(7): 871 – 98 Chest, 2012; 141(2)(Suppl): e326S – e350S Clinical Medicine 2016; 16(6): 535 – 40

Bleeding Assessment Tools

HASBLED ≥3

- (H) Hypertension
- (A) Abnormal renal or liver function
- (S) Stroke history
- (B) Bleeding history or predisposition
- (L) Labile INR while on warfarin
- (E) Elderly
- (D) Drugs
  - Concomitant Antiplatelet or NSAID
  - Alcohol or other drug use

BleedMAP

- (Bleed) Prior Bleeding
- (M) Mechanical Mitral Valve
- (A) Active Cancer
- (P) Low Platelets

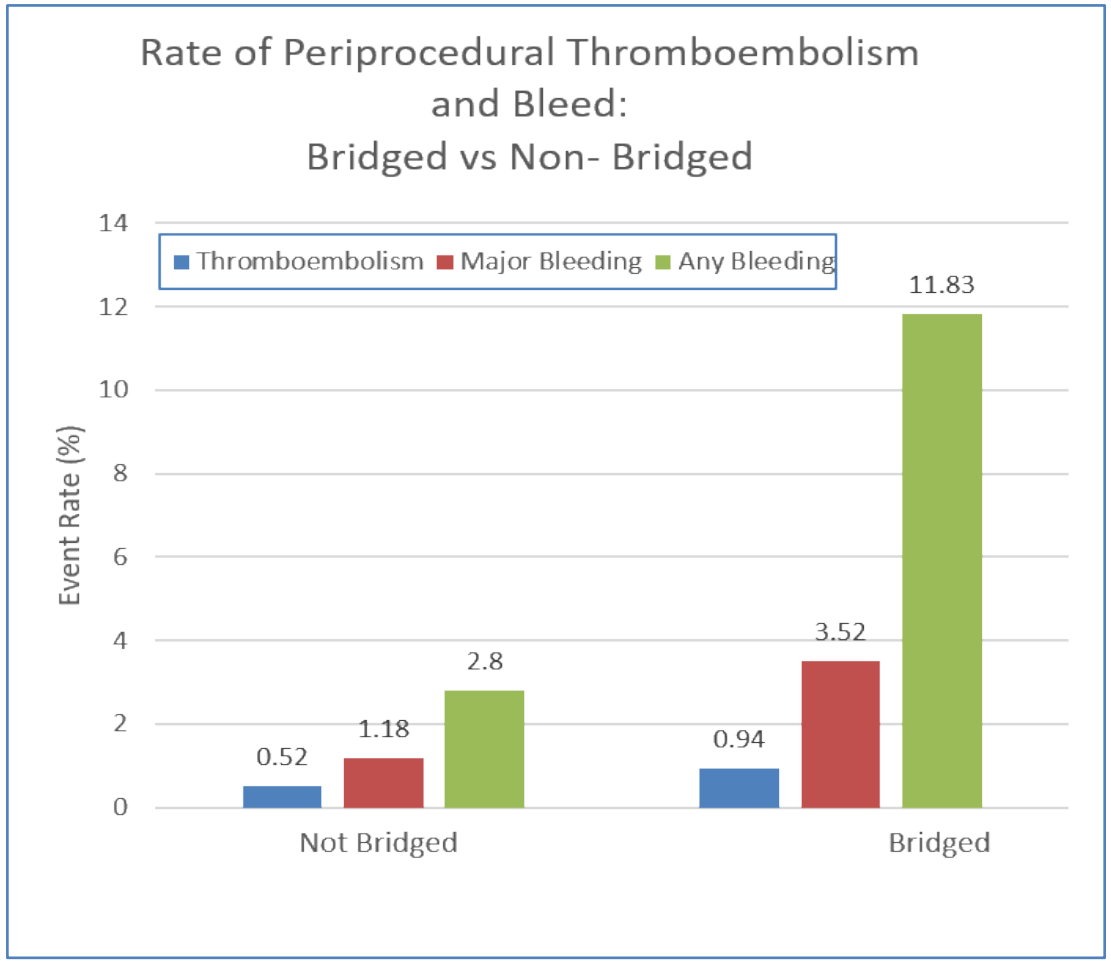
JACC 2015; 66(12): 1392-403

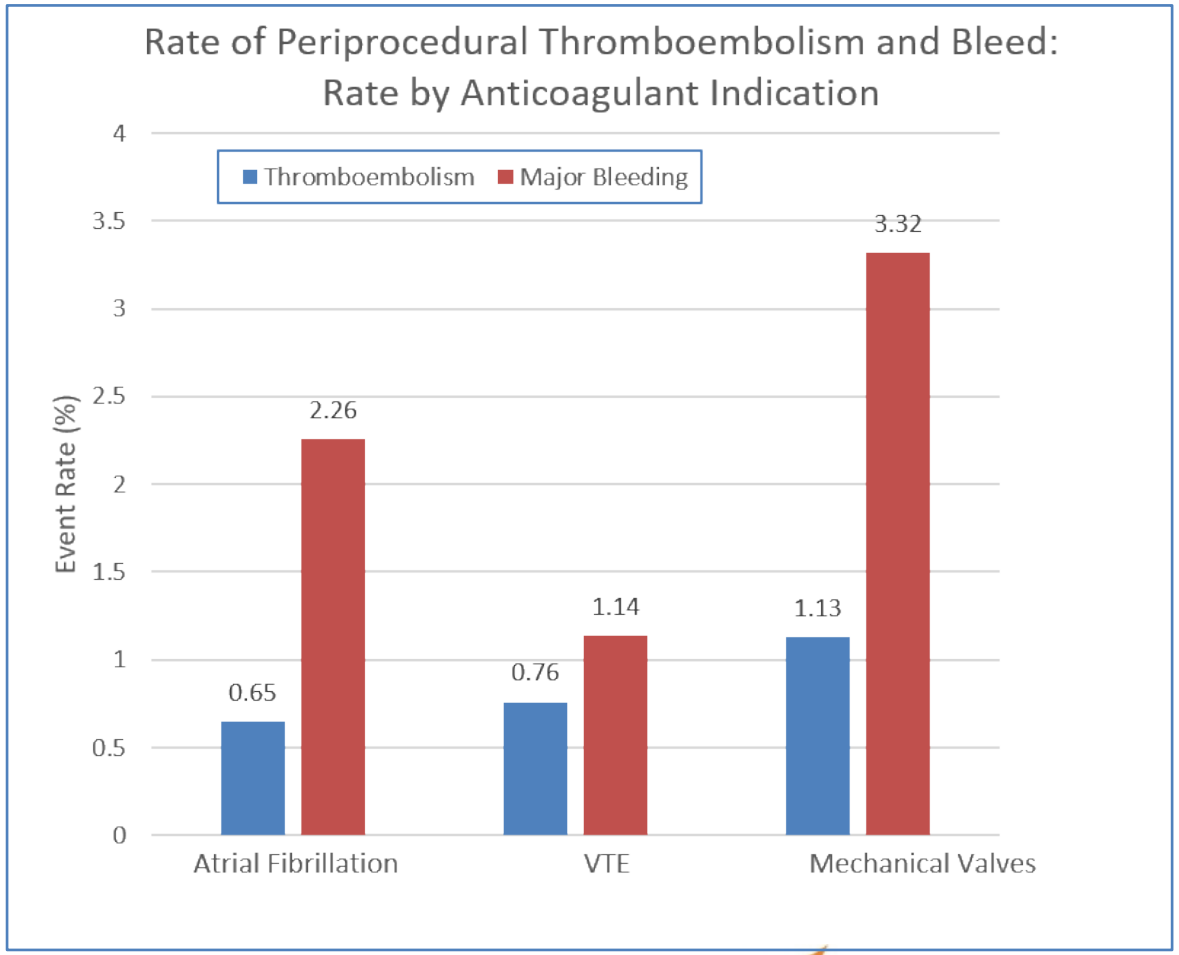
Patient-Specific Bleed Risks

- Some additional factors to evaluate in individual patients:
  - Recent history of significant bleeding
  - Concomitant medications (i.e. antiplatelet therapy)
  - Platelet or clotting factor dysfunction
  - Bleeding history with bridging
  - Bleeding history with similar procedure

Risk of Thrombosis

Risk of periprocedural thromboembolism while holding anticoagulation is relatively low





JACC, 2015; 66(12): 1395-403

Determining Thromboembolic Risk

High (>10% annual thromboembolic risk)	CHA_2DS_2-VASc of 7+
	Recent Stroke or Thromboembolic Disease (≤ 3 months)
	Rheumatic Valvular Disease or Mechanical Heart Valve
	Concomitant Hypercoagulable Disease
Intermediate (5 – 10% annual thromboembolic risk)	CHA_2DS_2-VASc of 5 – 6
	Remote Stroke (≥ 3 months)
Low (<5% annual thromboembolic risk)	CHA_2DS_2-VASc of 0 – 4

J Am Coll Cardiol 2017; 69(7): 871 – 98
Chest, 2012; 141(2)(Suppl): e326S – e350S

Therapeutic Interruption

- **Interrupting therapy**: allow for the systemic level of anticoagulant to drop to sufficiently low enough levels to minimize bleed risk during procedures

- Timing of interruption depends on several factors:
  - Procedural bleed risk
  - Pharmacokinetic properties of the anticoagulant
  - Renal function

DOAC Interruption

Agent	CrCl (ml/min)	Minimal Bleed Risk	Standard Bleed Risk	Elevated Bleed risk
Apixaban	>30	Plan to perform procedure at trough level	Give last dose 2 days before procedure	Give last dose 3 days before procedure
	15 – 30	Plan to perform procedure at trough level or 24 hours after last dose	Give last dose 2 days before procedure	Give last dose 3 days before procedure
Rivaroxaban or Edoxaban	>30	Plan to perform procedure at trough level	Give last dose 2 days before procedure	Give last dose 3 days before procedure
	15 – 30	Plan to perform procedure at trough level or 36 hours after last dose	Give last dose 2 days before procedure	Give last dose 3 days before procedure
Dabigatran	>50	Plan to perform procedure at trough level	Give last dose 2 days before procedure	Give last dose 3 days before procedure
	30 – 50	Plan to perform procedure at trough level or 24 hours after last dose	Give last dose 3 days before procedure	Give last dose 5 days before procedure

Data modified from the American College of Chest Physicians (ACCP) Guidelines.
Chest (2018), doi: 10.1016/j.chest.2018.07.040

Timing of Interruption: VKA

Measure INR 5 – 7 days prior to procedure

Subtherapeutic (INR < 2.0)	At Goal Level (INR 2.0 – 3.0)	Supratherapeutic (INR > 3.0)
Discontinue 3-4 days before procedure. Recheck INR 24 hours before procedure if normal INR desired.	Discontinue 5 days prior to procedure*. Recheck INR 24 hours before procedure	Discontinue ≥5 days prior to procedure*. Recheck INR 24 hours before procedure

*depends on current INR, time to procedure, and desired INR for procedure

J Am Coll Cardiol 2017; 69(7): 871 – 98

Warfarin Therapeutic Interruption

- **Low risk of thromboembolism:**
  - Consider interrupting oral anticoagulation.
  - No need to consider bridge therapy due to low risk.
- **Moderate risk of thromboembolism**
  - Will need to assess individual bleed risk to determine antithrombotic plan
    - Low bleed risk: interrupt oral anticoagulation, add bridge therapy if prior history of TIA/stroke
    - Elevated bleed risk: interrupt oral anticoagulation without bridge therapy
- **High risk of thromboembolism**
  - Generally recommend use of bridge therapy
    - Thrombotic event <3 months: delay elective procedures as able
    - Recent intracranial hemorrhage: No preoperative bridge therapy, consider risk/benefit of postoperative bridging

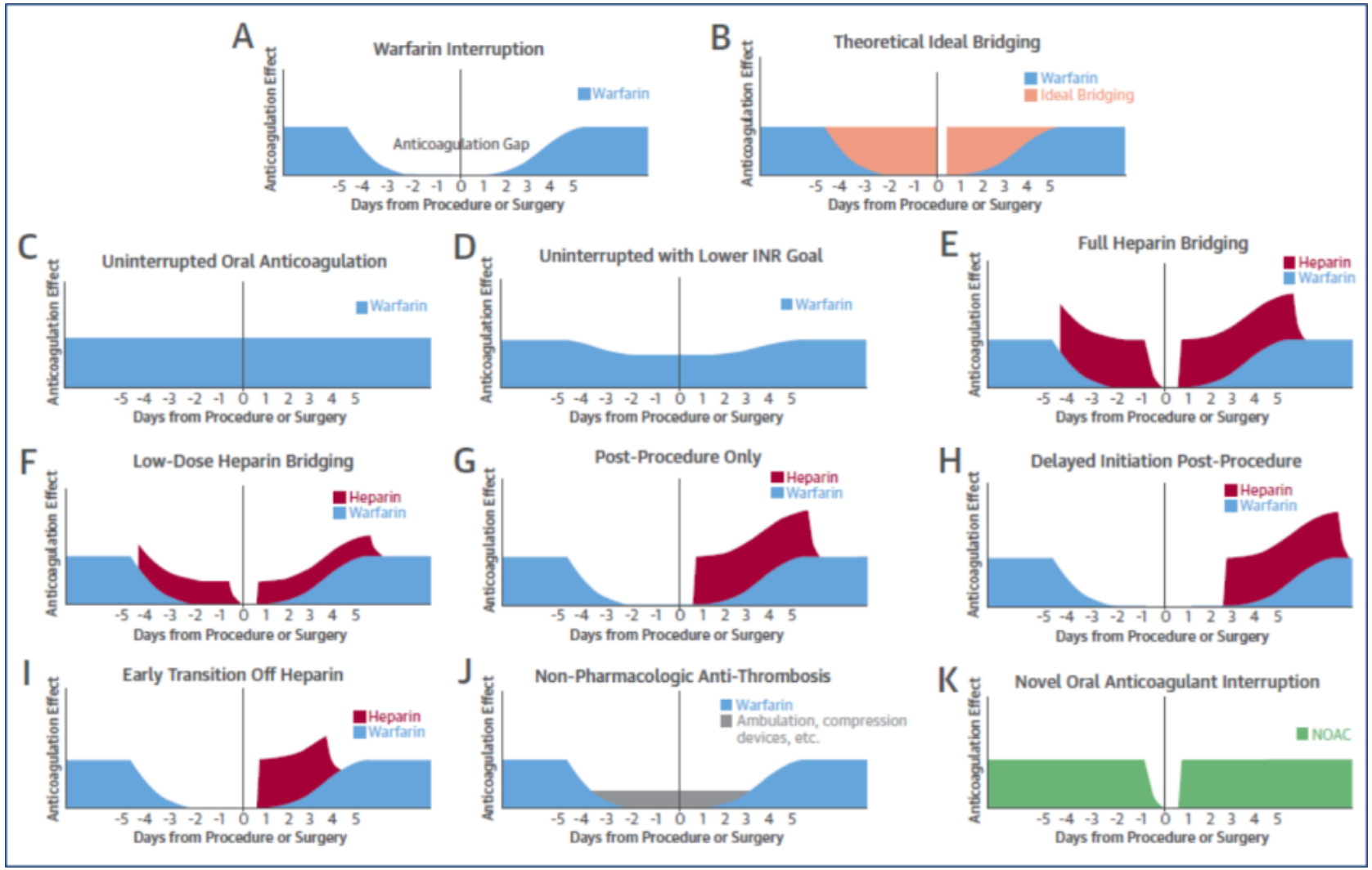
J Am Coll Cardiol 2017; 69(7): 871 – 98

Bridging Anticoagulation

- Strategy only implemented with VKA
  - DOACs do not require any bridge therapy unless they will not be resumed for a duration between surgical procedures
  - Recommended only for those patients with the highest risk of thromboembolism

- When the decision is made to bridge patients with oral anticoagulation, a thorough evaluation of both bleeding and thrombotic risk must be weighed before choosing a regimen

Periprocedural Antithrombotic Therapies



Many strategies have been implemented to attempt to decrease periprocedural time without anticoagulation

- Uninterrupted VKA
- VKA with lower INR goal
- Full dose heparin/LMWH
- Low-Dose heparin/LMWH
- Post-procedural only
- Non-drug therapy

JACC 2015; 66(12): 1392-403

BRIDGE Trial

- Only RCT comparing bridging with LMWH to no bridge therapy in patients with NVAF undergoing elective operations or invasive procedures
  - Warfarin discontinued 5 days prior to procedure
  - Dalteparin (100 IU/kg SubQ BID) or Placebo initiated 3 days prior to procedure
  - Warfarin resumed on day of procedure or day after

- Outcomes:
  - Primary:
    - Efficacy: All arterial thromboembolism (stroke, TIA, systemic embolism)
    - Safety: Major Bleeding
  - Secondary:
    - Efficacy: acute MI, DVT, PE, death
    - Safety: minor bleeding

NEJM, 2015; 373(9): 823-33

BRIDGE Trial

- Bridge therapy was associated with significantly more bleeding events with no resultant difference in thromboembolic complications
  - Lower than anticipated event rate
  - Used $CHADS_2$ rather than CHA_2DS_2-VASc
- Median time to events
  - Thromboembolism: 19 days [IQ 6 to 23 days]
  - Bleeding: 7 days [IQ 4 to 18 days]

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	4 (0.4)	0.88†
Myocardial infarction	7 (0.8)	14 (1.6)	0.10†
Deep-vein thrombosis	0	1 (0.1)	0.25†
Pulmonary embolism	0	1 (0.1)	0.25†
Minor bleeding	110 (12.0)	187 (20.9)	<0.001†

* P value for noninferiority.
† P value for superiority.

NEJM, 2015; 373(9): 823-33

RE-LY: Dabigatran vs. Warfarin for NVAF

Post-hoc analysis showed that 24.7% of study patients had therapy interrupted at least once during study period.

Renal function impairment (CrCl ml/min)	Estimated Half-Life, h (range)	Stopping Dabigatran before Surgery/Procedure	
		High Bleed Risk	Standard Bleed Risk
Mild: ≥50-80	15 (12-18)	2-3 days	24h (2 doses)
Moderate: ≥30-50	18 (18-24)	4 days	At least 2 days (48h)
Severe: <30	27 (>24)	>5 days	2-4 days

RE-LY Trial Perioperative Guidelines for managing Dabigatran for Patients Undergoing Surgery

- No significant difference in thromboembolic events between groups
  - Overall rate quite low at 0.6%
- No significant difference in major bleeding or any other secondary bleeding event
  - This was true for both the 110 mg and 150 mg Dabigatran doses

Circulation, 2012; 126(3): 343-348

ROCKET-AF: Rivaroxaban vs. Warfarin in NVAF

Post-Hoc analysis showed no significant difference in bleeding or TE for those with therapeutic interruption for surgical procedures

- Relatively low TE rate
- A small portion of patients received bridging (6% of all TI)

Events	Rivaroxaban (n=968, 1297 TIs)		Warfarin (n=1162, 1683 TIs)		HR (CI) for Riva vs Warfarin	P Value
	No. of Events	Rate per 30 d, %	No. of Events	Rate per 30 d, %		
Stroke/Systemic Embolism	4	0.27	8	0.42	0.65 (0.2-2.13)	0.48
Death	1	0.07	3	0.16	0.44 (0.05-4.25)	0.48
MI	4	0.27	3	0.16	1.70 (0.39-7.44)	0.48
Composite	8	0.55	14	0.73	0.75 (0.31-1.77)	0.51
Major/NMCR bleeding	34	3.03	42	2.69	1.13 (0.72-1.78)	0.59
Major bleeding	14	0.99	18	0.97	1.02 (0.50-2.06)	0.96

Circulation, 2014; 12189: 1850-1859

Aristotle: Apixaban vs. Warfarin for NVAF

- Landmark trial comparing Apixaban to Warfarin for stroke prophylaxis in atrial fibrillation

- Post-hoc analysis performed looking at the patients who had short-term interruptions during the study
  - Overall rate of TE was low
  - No difference in rate of major bleed or thromboembolic event

Thirty Day Rates of Major Events after Procedure

Event	Apixaban Events*/ Procedures (%) [n]	Warfarin Events*/ Procedures (%) [n]	OR (95% CI)
Stroke/ systemic embolism	16/4624 (0.35)	26/4530 (0.57)	0.601 (0.322-1.120)
Myocardial Infarction	12/4624 (0.26)	18/4530 (0.4)	0.652 (0.312-1.356)
All-Cause Death	54/4624 (1.17)	49/4530 (1.08)	1.082 (0.733-1.598)
Major Bleeding	74/4560 (1.62) [8]	86/4454 (1.93) [11]	0.846 (0.614-1.166)
Major/CRNM Bleeding	133/4560 (2.92) [8]	154/4454 (3.46) [12]	0.854 (0.670-1.089)

Blood, 2014; 124(25): 3692-3698

Bridging Recommendations

- Chest Recommendations (2018)
  - In AF patients on antithrombotic prophylaxis with warfarin with a high risk of thromboembolism or with a mechanical valve, we suggest pre-operative management with bridging (Weak recommendation, low quality evidence).
  - In AF patients on antithrombotic prophylaxis with a NOAC, we suggest pre-operative management without bridging (Weak recommendation, low quality evidence).

- 2017 ACC Expert Consensus on Periprocedural Management of Anticoagulation in NVAF
  - Use in those with moderate risk of thromboembolism but low bleed risk who have a history of TIA/stroke
  - High risk of thromboembolism except those with recent history of intracranial hemorrhage

Chest (2018), doi: 10.1016/j.chest.2018.07.040
J Am Coll Cardiol 2017; 69(7): 871 – 98

Neuraxial Procedures

Anticoagulant	Recommended interval between discontinuation of drug and interventional pain procedure (5 half-lives)	Recommended interval between procedure and resumption of drug
Warfarin	5 days, normalization of INR	24 hours
IV Heparin	4 hours	2 hours*
SubQ Heparin (BID/TID)	8-10 hours	2 hours*
LMWH	24 hours	24 hours
Dabigatran	4-5 days (normal renal function)	24 hours
	6 days (renal disease)	
Rivaroxaban	3 days	24 hours
Apixaban	3 – 5 days	24 hours

*If procedure was bloody, wait 24 hours instead

Reg Anesth Pain Med, 2015; 40: 182-212

Resuming Anticoagulation

- Multidisciplinary approach required to evaluate each individual patient's readiness to resume anticoagulation
  - Hemostasis has been achieved with no active bleeding complications or clinically significant bleeding locations
    - Low bleed risk procedures: May resume fully therapeutic anticoagulation within 24 hours of procedure.
    - Moderate/HIGH bleed risk procedures: may resume fully therapeutic anticoagulation within 48 – 72 hours of procedure
  - Consider delayed restart in the following populations:
    - Any periprocedural bleed complication
    - Procedure is at high-risk for bleeds
    - Patient-specific factors that predispose patient to bleeding periprocedurally

J Am Coll Cardiol 2017; 69(7): 871 – 98

Resuming VKA (+/- Bridge Therapy)

Vitamin K Antagonist	
For most patients: resume VKA the day of the procedure at usual home dose	
Parenteral bridge therapy	
Low post-procedure bleed risk	Start within 24 hours of procedure
Mod/High post-procedure bleed risk	Delay at least 48 – 72 hours post-procedure

- Alternative options in those with elevated bleed risk or history of prior bleed:
  - Use prophylactic doses of parenteral agents
  - Initiate heparin without using bolus doses
  - Omit bridge therapy and initiate VKA alone
- Peak risk of bleeding is at the time when VKA approaches goal INR

J Am Coll Cardiol 2017; 69(7): 871 – 98
NEJM, 2015; 373(9): 823-33

Resuming DOACs

	Procedural Bleed Risk		
	Minimal Bleed Risk	Standard Bleed Risk	Elevated Bleed risk
Apixaban Dabigatran Edoxaban Rivaroxaban	Resume therapy with no interruption or missed doses	Resume 24 hours after procedure	Resume 48 – 72 hours after procedure

Chest (2018), doi: 10.1016/j.chest.2018.07.040

Patient Case: Perioperative Management

- GH is a 72 yo female with a PMH of hypertension, diabetes, hypothyroidism, and atrial fibrillation. Home medications include Lisinopril, Carvedilol, Levothyroxine, Aspirin, Atorvastatin, and Apixaban. She is being scheduled for routine colonoscopy in two weeks and the gastroenterologist has asked you what he needs to do with her Apixaban. You should:
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  d. Hold Apixaban only on the morning of the colonoscopy
  e. Hold Apixaban 5 days prior to colonoscopy and resume 5 days after procedure

Key Takeaways

- When a surgical procedure is scheduled for a patient on oral anticoagulation, careful consideration of both bleed and thromboembolic risk factors needs to be done.
- Reserve bridge therapy only for those patients receiving VKA therapy who have a high risk of thrombosis and low bleed risk.
- Resuming anticoagulation postoperatively should occur only when hemostasis has been achieved and when bleed risk has subsided.

CHA_2DS_2-VASc = 1. I don't really need to worry, right?

Question

- Which of the following AF patients would you recommend OAC to reduce risk of stroke?

A. 54 year-old Taiwanese male with no additional risk factors
B. 62 year-old Caucasian female with no additional risk factors
C. Both patients warrant OAC therapy
D. Neither patient warrants OAC therapy

CHA_2DS_2-VASc = 1: Are All Patients The Same?

- Are women at greater risk than men?
- Does ethnicity influence stroke risk?
- Regional variations
- Alternative risk scores may add additional context

2018 Chest Guidelines: Antithrombotic Therapy in AF

- CHA_2DS_2-VASc = 0 (1 in women)
  - No therapy
- CHA_2DS_2-VASc ≥ 1 (2 in women)
  - OAC preferred over aspirin, dual antiplatelet therapy
- DOACs preferred over warfarin
- When using warfarin:
  - Goal TTR ≥ 70%

Lip GY et al. CHEST 2018; doi 10.1016/j.chest.2018.07.040

Female Gender: Risk Factor vs. Risk Marker

- 3 nation wide Danish registries
- 239,671 patients with new AF diagnosed between 1997 – 2015
  - 48.8% women
  - Mean CHA_2DS_2-VASc score 2.7 for women vs. 2.3 for men
- Aim: To explore sex differences in stroke

Nielsen PB et al. Circulation 2018; 137:832-40.

Female Gender: Risk Factor vs. Risk Marker

CHA_2DS_2-VA Score	Men			Women		
	Events	100 Person-Years	Rate per 100 Person-Years (95% CI)	Events	100 Person-Years	Rate per 100 Person-Years (95% CI)
1-year follow-up						
0	101	137.93	0.73 (0.60–0.89)	56	86.48	0.65 (0.50–0.84)
1	180	94.67	1.90 (1.64–2.20)	150	76.77	1.95 (1.67–2.29)
2	579	127.37	4.55 (4.19–4.93)	757	156.89	4.83 (4.49–5.18)
3	691	96.38	7.17 (6.65–7.72)	875	133.58	6.55 (6.13–7.00)
4	848	65.42	12.96 (12.12–13.86)	1175	78.61	14.95 (14.12–15.83)
5	554	33.81	16.39 (15.08–17.81)	916	42.04	21.79 (20.42–23.25)
≥6	346	18.74	18.46 (16.62–20.51)	414	20.90	19.81 (17.99–21.82)
Overall	3299	574.32	5.74 (5.55–5.94)	4343	595.27	7.30 (7.08–7.52)

No differences between men and women at all levels of risk at 1 year

Nielsen PB et al. Circulation 2018; 137:832-40.

Female Gender: Risk Factor vs. Risk Marker

CHA_2DS_2-VA Score	Men			Women		
	Events	100 Person-Years	Rate per 100 Person-Years (95% CI)	Events	100 Person-Years	Rate per 100 Person-Years (95% CI)
5-year follow-up						
0	275	525.16	0.52 (0.47–0.59)	143	342.31	0.42 (0.35–0.49)
1	418	315.12	1.33 (1.21–1.46)	362	274.45	1.32 (1.19–1.46)
2	1051	386.25	2.72 (2.56–2.89)	1569	497.89	3.15 (3.00–3.31)
3	1076	273.03	3.94 (3.71–4.18)	1683	397.81	4.23 (4.03–4.44)
4	1151	173.49	6.63 (6.26–7.03)	1670	218.21	7.65 (7.29–8.03)
5	715	84.33	8.48 (7.88–9.12)	1196	109.52	10.92 (10.32–11.56)
≥6	438	44.22	9.90 (9.02–10.88)	531	51.38	10.33 (9.49–11.25)
Overall	5124	1801.60	2.84 (2.77–2.92)	7154	1891.57	3.78 (3.70–3.87)

No differences between men and women at all levels of risk at 5 years

Nielsen PB et al. Circulation 2018; 137:832-40.

Ethnicity in Low Risk Patients

- "Low risk" patients generally not considered candidates for OAC
- Danish nationwide cohort
  - CHA_2DS_2-VASc score 0 = 0.66% (men)
  - CHA_2DS_2-VASc score 1 = 0.82% (women)

- Sweden
  - CHA_2DS_2-VASc score 0 = 0.2% (men)

- United States
  - CHA_2DS_2-VASc score 0 = 0.04% (men)

Chao TF et al. J Am Coll Cardiol 2015; 66:1339-47.

Are Asian AF Patients at Higher Risk?

- Asian patients
- Taiwan:
  - CHA_2DS_2-VASc score 0 = 1.15% (men)
- Hong Kong
  - CHA_2DS_2-VASc score 0 = 2.47%

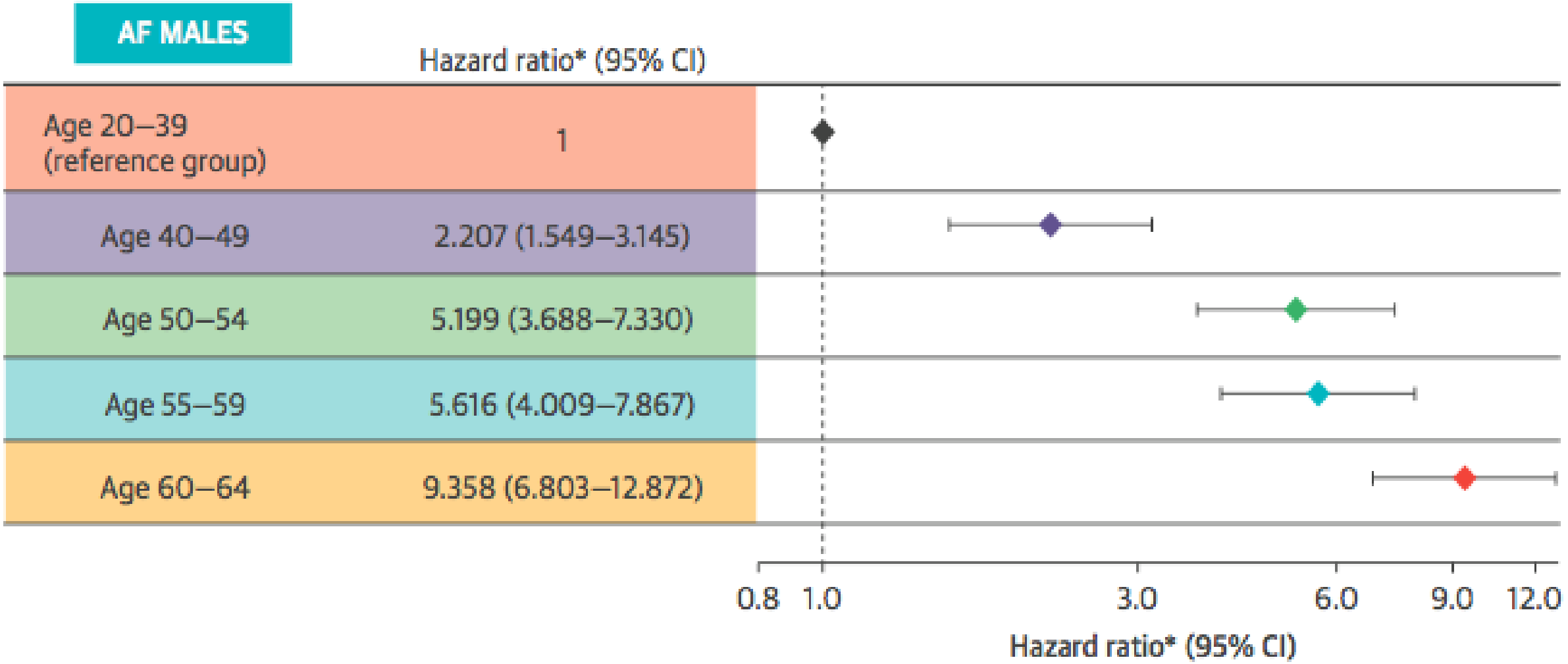
Are Asian AF Patients at Higher Risk?

- National Health Insurance Research Database in Taiwan
  - Age < 65 years-old
    - Mean age 48 years-old
  - 9416 men with CHA_2DS_2-VASc = 0
  - 6390 women with CHA_2DS_2-VASc =1

- Currently NOT receiving OAC

Chao TF et al. J Am Coll Cardiol 2015; 66:1339-47.

Are Asian AF Patients at Higher Risk?



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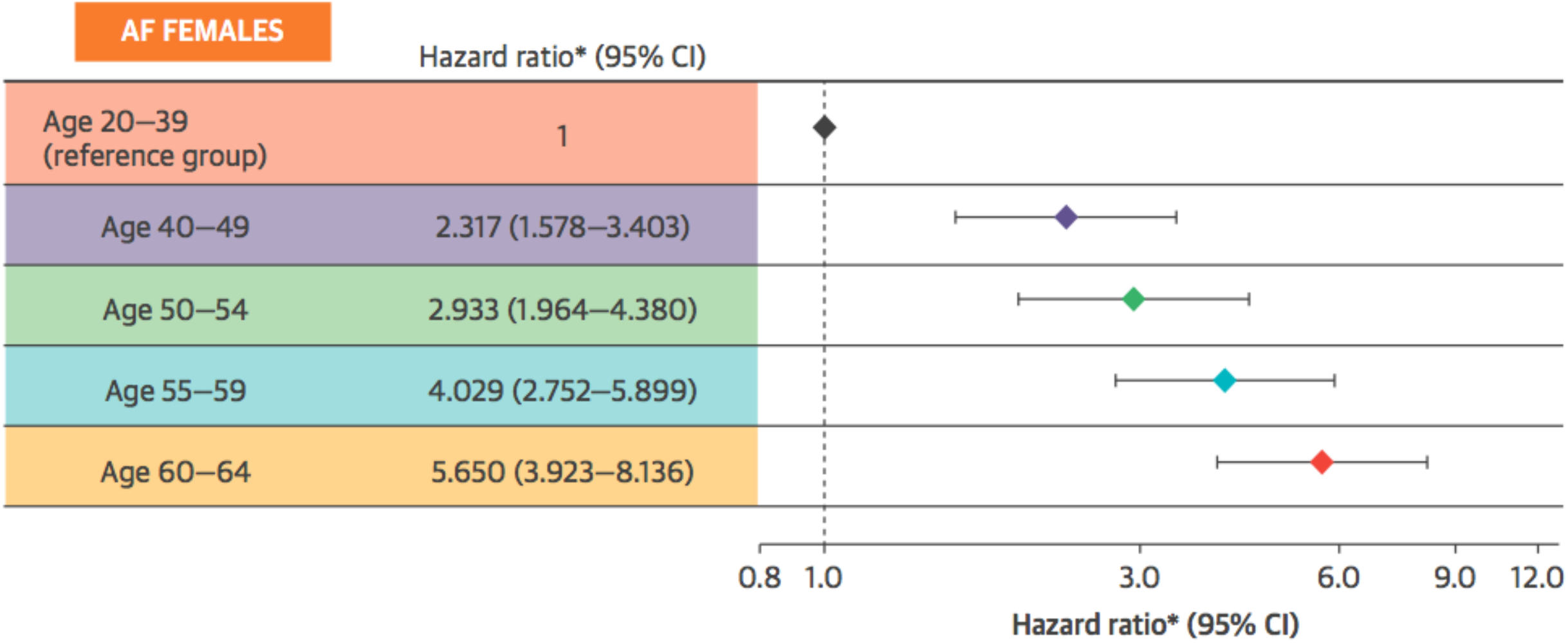
Are Asian AF Patients at Higher Risk?



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Are Asian AF Patients at Higher Risk?

- Overall rate of stroke:
  - Age < 50: 0.53% per year
  - Age > 50: 1.8% per year
- Men:
  - Age < 50: 0.46% per year
  - Age > 50: 1.95% per year
- Women:
  - Age < 50: 0.64% per year
  - Age > 50: 1.6% per year

Chao TF et al. J Am Coll Cardiol 2015; 66:1339-47.

Regional Variability

- Systematic review of cohort studies and randomized controlled trials in AF patients receiving OAC
- 3552 studies screened
  - 34 included
- Worldwide Cohorts:
  - Taiwan NHI Research Database
  - Swedish AF Cohort Study
  - Danish National Patient Registry
  - UK General Practice Research Database
  - Israel–Clalit Health Services
  - Stockholm Area Database
  - ATRIA
  - Women's Health Initiative
  - California Medicaid
  - Iwate Cohort (Japan)

Quinn GR et al. J Am Coll Cardiol 2015; 66:1339-47.

North American Cohort

Study Name	Midpoint Year	Subjects	Annual Stroke Rate (95% CI)
North American Cohorts			
Women's Health Initiative[17]	1997	5981	0.45 (0.41–0.51)
ATRIA CVRN[23]	2008	25 306	1.89 (1.73–2.06)
ATRIA[18]	2000	10 932	1.97 (1.82–2.12)
Framingham Heart Study[16]	1981	705	2.94 (2.37–3.65)
Nova Scotia[33]	2000	130	3.10 (1.67–5.75)
National Registry of AF[7]	1996	1733	3.35 (2.65–4.22)
California Medicaid[21]	2000	1787	3.50 (3.06–4.01)
Total		46 574	1.30 (1.24–1.26)

European Cohort

European Cohorts			
Loire Valley AF Project[19]	2005	2886	1.29 (1.13–1.47)
Spain–Atrial Fibrillation in the Barbanza Area[24]	2010	186	1.36 (0.71–2.62)
Euro Heart Survery on AF[8]	2004	1084	2.31 (1.56–3.41)
UK General Practice Research Database[28]	2005	60 594	2.99 (2.90–3.09)
Stockholm Area Database[20]	2008	24 195	3.29 (3.07–3.53)
Danish Diet, Cancer, and Health[31]	2002	1603	3.40 (2.56–4.53)
Swedish Atrial Fibrillation Cohort Study[22]	2007	90 490	4.50 (4.38–4.62)
Danish National Patient Registry[6]	2003	73 538	7.03 (6.82–7.24)
Total		254 576	4.14 (4.07–4.21)

Asian Cohorts

Asian Cohorts			
China–Yunnan Province[26]	2007	872	1.18 (0.90–1.54)
Taiwan–National Health Insurance Database[15]	2003	7920	1.27 (1.16–1.40)
Japan–Shinken, Fushimi, and J-RHYTHM (Pooled)[32]	2008	3588	1.33 (1.05–1.68)
Japan–Iwate Cohort[30]	2002	332	2.39 (1.71–3.33)
Japanese Multi-Arrhythmia Clinics[29]	1992	421	2.40 (1.72–3.34)
China–PLA General Hospital[25]	2009	885	3.70 (2.63–5.20)
Taiwan–National Health Insurance Research Database[14]	2004	186 570	3.74 (3.69–3.79)
China–Queen Mary Hospital Hong Kong[35]	2004	3881	9.28 (8.68–9.93)
Total		204 469	3.64 (3.60–3.69)

Stroke Risk Factors Beyond CHA_2DS_2-VASc

- Valvular heart disease
- Obesity
- Sleep Apnea
- Smoking
- Exercise
- Alcohol Use
- Hyperthyroidism
- LVH
- Genetic Variants
- Family History
- Left Atrial Enlargement
- Ethnicity

Framingham Heart Study Stroke Risk

Clinical Characteristic	Points Awarded	Clinical Characteristic	Points Awarded
Age (years)		Gender	
55 – 59	0	Male	0
60 – 62	1	Female	6
63 – 66	2	Systolic BP	
67 – 71	3	< 120	0
72 – 74	4	120 – 139	1
75 – 77	5	140 – 159	2
78 – 81	6	160 – 179	3
82 – 85	7	> 179	4
86 – 90	8	Diabetes	5
91 – 93	9	Prior Stroke/TIA	6
> 93	10	**Maximum Score**	**31**

Score predicts 5 year risk of stroke: 5 – 75%

Example of Differences in Risk Assessment

- 63 year-old female, with a BP: 125 mm/Hg
  - CHA_2DS_2-VASc = 1
  - Stroke risk: 1.3% (annual risk)

  - Framingham Score = 9
  - Stroke risk: 12%

- 4 years later, develops Diabetes, BP: 150 mmHg
  - CHA_2DS_2-VASc = 4 (4% annual risk of stroke)
  - Framingham Score = 16
  - 21% risk (5 year risk)

Take Home Points

- Not all CHA_2DS_2-VASc = 1 are low risk patients
  - CHA_2DS_2-VASc is a convenient risk estimator, but:
  - Doesn't include all risks for stroke
- Ethnicity, region and additional risk factors may warrant additional consideration beyond CHA_2DS_2-VASc
- Stroke risk in Asian patients might be underestimated with CHA_2DS_2-VASc
- Women may not be at higher risk for stroke
- Guidelines are evolving:
  - Greater emphasis with OAC in patients with CHA_2DS_2-VASc = 1

Obesity: Do all anticoagulants work the same?

Question

Which patient is most likely to experience treatment failure with a DOAC?

A. 67 yo male, weight 115 kg (BMI=35), receiving Rivaroxaban 20 mg daily
B. 48 yo female, weight 105 kg (BMI=42), receiving Apixaban 5 mg BID
C. 54 yo male, weight 135 kg (BMI=45), receiving Dabigatran 150 mg BID
D. 38 yo male, weight 120 kg (BMI=38), receiving Apixaban 5 mg BID

Question

- I would **NOT** recommend a DOAC for patients above this body weight:

A. 100 kg
B. 120 kg
C. 160 kg
D. 200 kg

Atrial Fibrillation and Obesity

- Obesity has long been a known, modifiable risk factor for developing new onset atrial fibrillation (AF).
  - Framingham data: Men showed a 5% increase and women a 4% increased risk of developing AF for each 1-unit increase in BMI
  - Meta-analysis (2007): obese individuals have a 49% increased risk of developing AF over non-obese individuals (RR 1.49, 95% CI 1.36 – 1.64)

- Obesity prevalence estimated to be 58% by 2030

JAMA, 2004; 29(20): 2471-2477
Am H J, 2008; 155(2): 310 – 315
Int J Obes, 2008; 32: 1431 – 7

Anticoagulation in Obesity

- Warfarin for years was one of the only options available for stroke prophylaxis in patients with atrial fibrillation.
  - INR monitoring allowed clinicians the ability to easily monitor and adjust individualized doses for each patient based on their particular response.

- DOACs provide an alternative that have a wider therapeutic window, have fewer drug interactions, and do not require regular lab monitoring.
  - Phase III trials noted that certain populations were at a higher risk of bleeding events, including those with low body weight.

- If low body weight increases risk for having bleeding events, will the other extreme of weight lead to an increase in thromboembolic events?

Pharmacokinetics of DOACs

Parameter	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Onset of Action	Slow	Fast	Fast	Fast
Absorption	Rapid	Rapid, acid-dependent	Rapid	Rapid
Bioavailability (%)	100	6.5	80*	50
V_d (L)	10	60-70	50-55	21
$t_{1/2\beta}$ (h)	40	12-17	9-13	8-15
Renal Excretion (%)	None	80	33	25
Fecal Excretion (%)	None	20	28	50-70
Food effect	None on absorption, Vit K on PD	Delayed absorption with food with no influence on bioavailability	Delayed absorption with food with increased bioavailability	None

Canadian J of Cardiol, 2013; 29: S24-S33

START Registry

- Observational, multicenter study in Italy following patients who have initiated Dabigatran, Rivaroxaban, or Apixaban.
  - Choice of DOAC prescribed at the discretion of the prescribing physician
  - Excluded if SrCr <30 ml/min

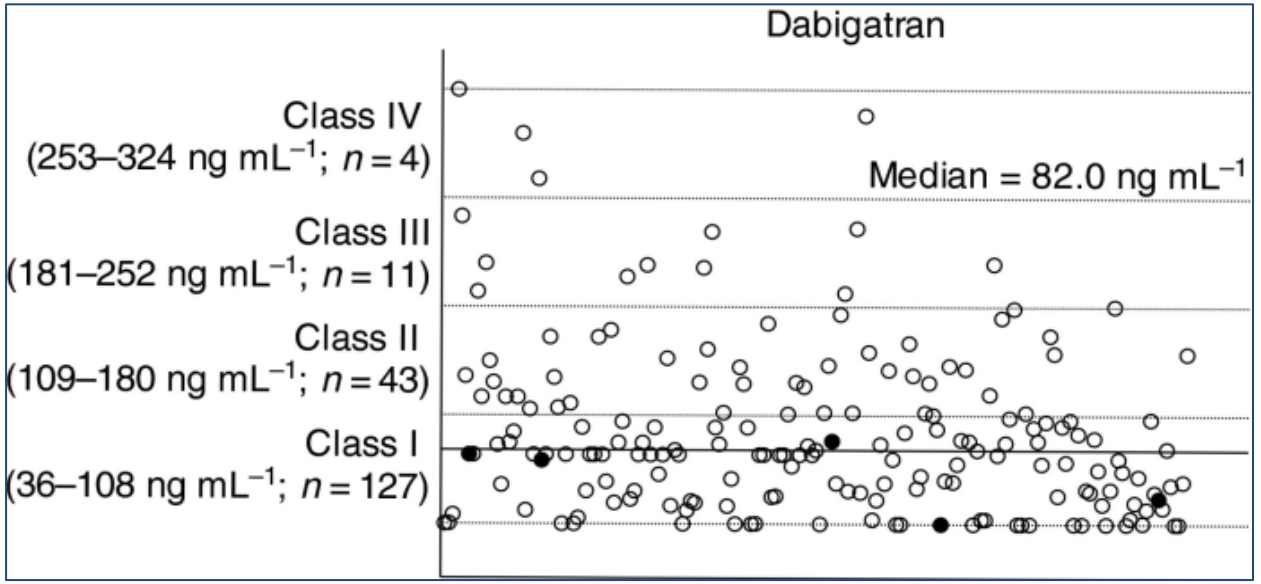
- Information gathered at visits:
  - **Baseline**: demographics, clinical characteristics, CHA_2DS_2-VASc score, HAS-BLED score, weight, BMI, kidney and liver function, other medications
  - **Follow-up**: adherence (pill counts), information about bleeding or thrombosis events
    - At 15-25 days post-drug initiation: drug C-trough levels

J Thromb Haemost, 2018; 16: 482-8

START Registry

Dabigatran

- Median C-trough level: 82 ng/ml (range 36 – 324 ng/ml)
- 4 of the 5 thrombotic events below the median



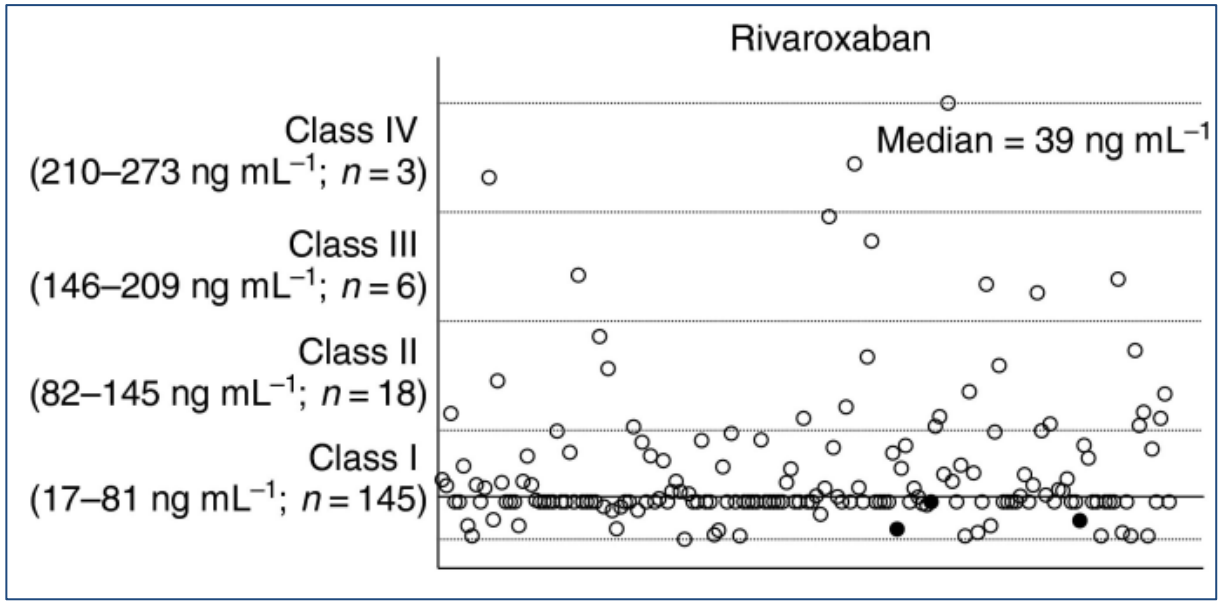
Drug	Dose	$CHAD_2DS_2$-VASc	C-trough	Type of TE
Dabigatran	150 mg BID	5	36	Stroke
Dabigatran	110 mg BID	7	67	Stroke
Dabigatran	110 mg BID	3	53	Stroke
Dabigatran	110 mg BID	4	78	Stroke
Dabigatran	150 mg BID	7	91	AMI

J Thromb Haemost, 2018; 16: 482-8

START Registry

Rivaroxaban

- Median C-trough level: 39 ng/ml (range17 – 273 ng/ml)
- All 3 of the thrombotic events at or below the median



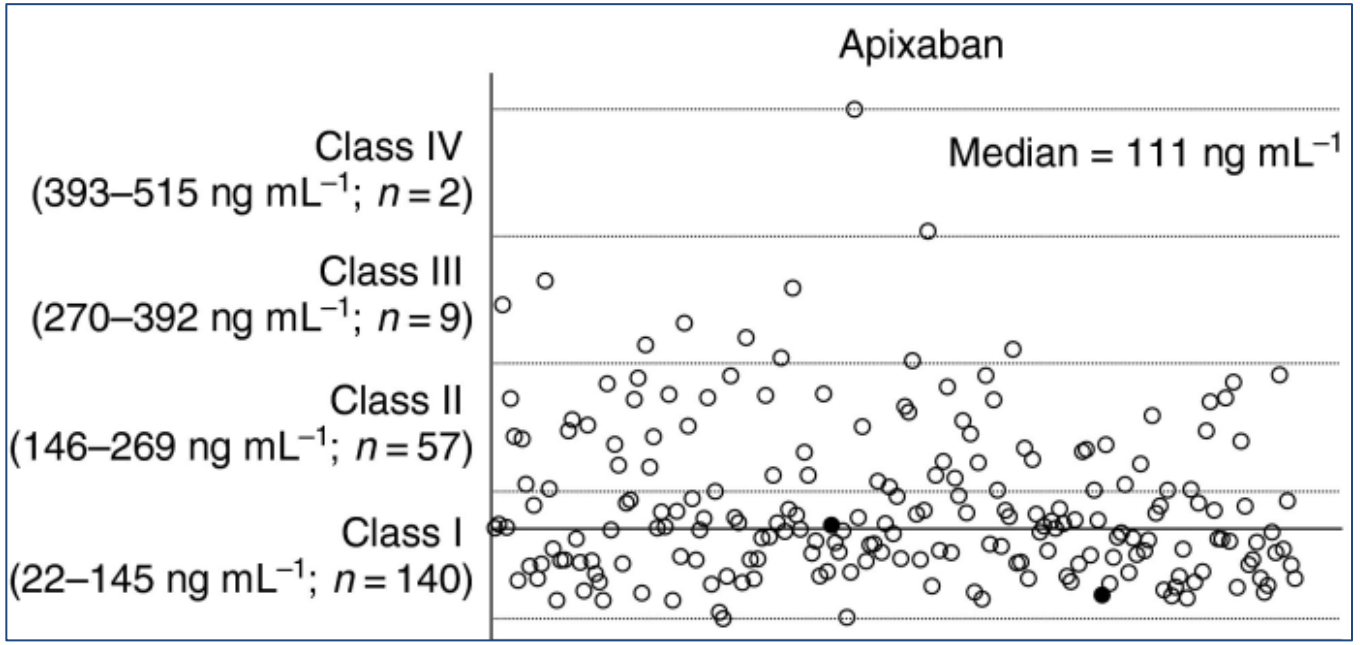
Drug	Dose	$CHAD_2DS_2$-VASc	C-trough	Type of TE
Rivaroxaban	20 mg	7	39	TIA
Rivaroxaban	15 mg	5	23	AMI
Rivaroxaban	15 mg	5	28	AMI

J Thromb Haemost, 2018; 16: 482-8

START Registry

Apixaban

- Median C-trough levels 111 ng/ml (range 22 – 515 ng/ml)
- One thrombotic event was below the median and the second just above



Drug	Dose	$CHAD_2DS_2$-VASc	C-trough	Type of TE
Apixaban	2.5 mg BID	6	113	Systemic Embolism
Apixaban	5 mg BID	4	45	DVT

J Thromb Haemost, 2018; 16: 482-8

Pharmacokinetic Changes in Obesity

Pharmacokinetic Parameter:	Effect of Obesity
Absorption	Not affected
Distribution	Increased for drugs with baseline high Vd; lipophilic medications
Elimination	
- Renal	Potentially increased in non-diabetics
- Hepatic	Increased liver mass and enzymatic function

- Drug specific factors to consider: molecular size, degree of ionization, lipid solubility, and ability to cross biological membranes

Clin Pharmacokinet, 2010; 49(2): 71-87

Pharmacokinetics of DOACs

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Absorption	Rapid	Rapid, acid-dependent	Rapid	Rapid
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V_d (L)	10	60-70	50-55	21
$t_{1/2\beta}$ (h)	40	12-17	9-13	8-15
Renal Excretion (%)	None	80	33	25
Fecal Excretion (%)	None	20	28	50-70
Food effect	None on absorption, Vit K on PD	Delayed absorption with food with no influence on bioavailability	Delayed absorption with food with increased bioavailability	None

Canadian J of Cardiol, 2013; 29: S24-S33

Apixaban in the Extremes of Body Weight

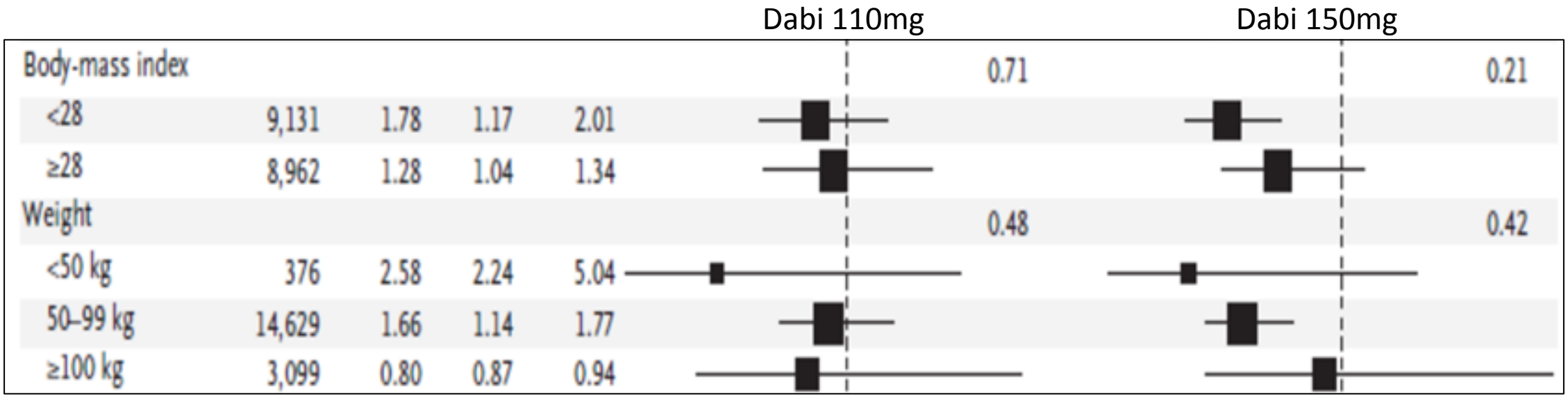
- Pharmacokinetic trial evaluating drug levels of Apixaban after a single dose of 10 mg in healthy volunteers:
  - Stratified into 3 groups: Low (≤50 kg), Reference(65–85 kg), and High (≥120 kg)

Parameter	Low (≤50 kg)	Reference(65–85 kg)	High (≥120 kg)	Low vs. Reference	High vs. Reference
Cmax (ng/ml)	264 (26)	207 (24)	144 (28)	1.272 (1.075 – 1.506)	0.692 (0.586 – 0.818)
AUC $_{(0-\infty)}$ (ng/ml)	2424 (26)	2024 (24)	1561 (31)	1.198(1.011 – 1.419)	0.771 (0.652 – 0.912)
Median t_{max} (h)(range)	3.00 (1.00 – 6.00)	3.03 (2.00 – 6.00)	3.98 (1.00 – 6.00)		
Mean $t_{1/2}$ (h)(SD)	15.8 (9.8)	12.0 (5.35)	8.8 (3.15)		
V_{ss}/F (l)	52.7 (45)	61.0 (22)	75.6 (28)		
CL_R (ml/min)	14.1 (25)	12.6 (45)	17.8 (42)		
CL_T/F (ml/min)	68.8 (40)	82.3 (19)	106.8 (35)		

Br J Clin Pharmacol, 2013; 76(6): 908-916

Dabigatran and Obesity

- RE-LY Trial
  - Subgroup analyses of patients enrolled suggest that Dabigatran is only superior at preventing stroke in patient of normal body weight and BMI receiving the 150 mg BID dose.



Use of Dabigatran According to BMI: The RE-LY Experience

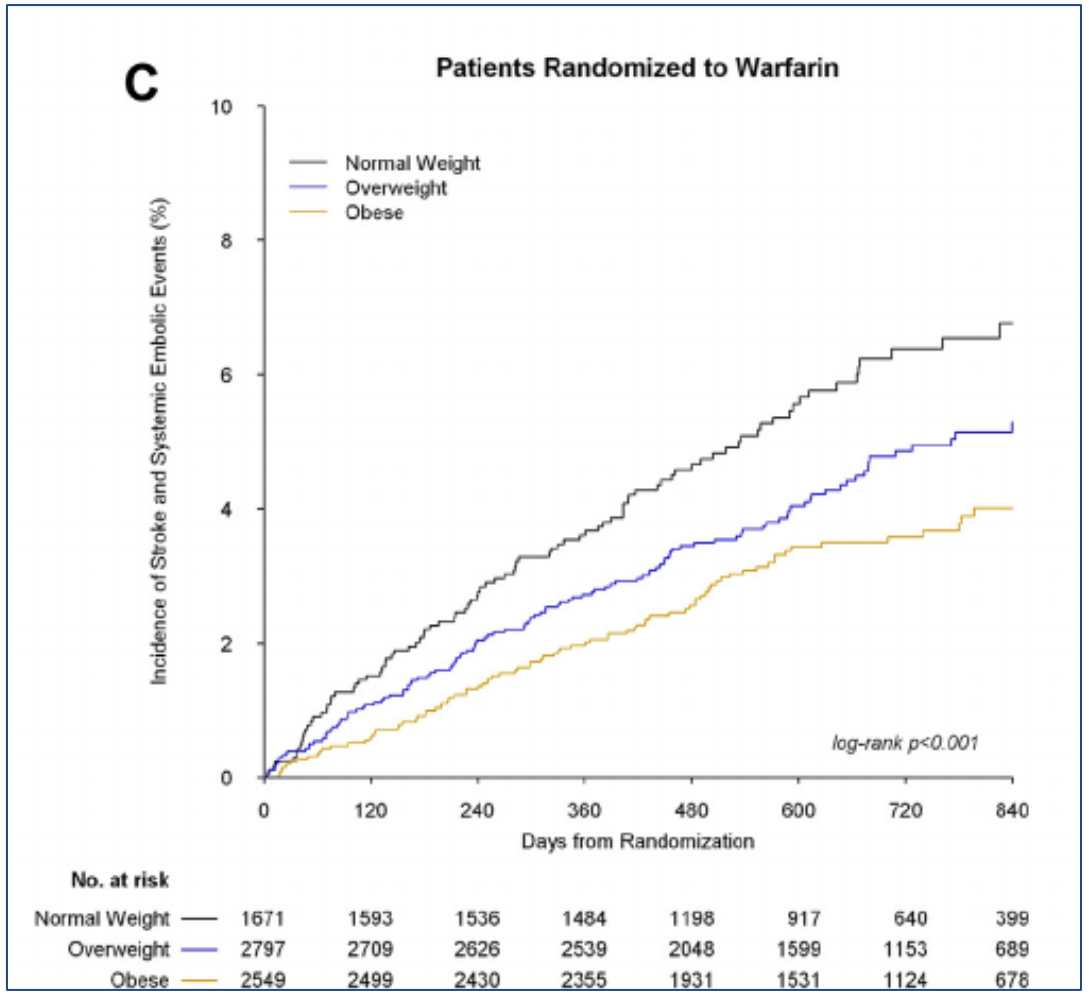
One Year Major Bleeding Rates (95% CI)					
	Overall	Dabi 110	Dabi 150	Warfarin	P-value
BMI Bottom 10% (n=1865)	4.6 (3.6, 5.6)	4.1 (2.5,5.6)	4.7 (3, 6.4)	5.1 (3.3, 6.7)	0.67
BMI Middle 80% (n=14435)	3.6 (3.3, 3.9)	3 (2.5, 3.5)	3 (3.4, 4.5)	3.8 (3.3, 4.4)	0.006
BMI Top 10% (n=1787)	3.7 (2.8, 4.6)	3 (1.6, 4.4)	4.4 (2.7, 6.1)	4.04 (2.2, 6.1)	0.55

One Year Stroke/Systemic Embolism Rates (95% CI)					
	Overall	Dabi 110	Dabi 150	Warfarin	P-value
BMI Bottom 10% (n=1865)	2 (1.3,2.6)	2 (0.9,3.1)	1 (0.2, 1.8)	2.9 (1.6, 4.2)	0.02
BMI Middle 80% (n=14435)	1.4 (1.2,1.6)	1.5 (1.2,1.9)	1.2 (0.9, 1.5)	1.6 (1.2, 1.9)	0.01
BMI Top 10% (n=1787)	1.1 (0.6,1.6)	1.2 (0.3, 2.0)	0.9 (0.1, 1.6)	1.3 (0.4, 2.3)	0.6

Eur Heart Journal, 2014; 35 (Abstract Supplement): 1111

ROCKET-AF Subgroup Analysis

- Subgroup analysis of patients in this trial performed, stratifying patients according to BMI (18.5 – 24.99, 25 – 29.99, ≥30)
  - Bleeding rates were not statistically significant across treatment groups.
  - $CHADS_2$ score slightly higher in overweight and obese groups
  - Primary endpoint of the composite of stroke and systemic embolism statistically **lower** in overweight and obese patient, with or without adjustment for age, sex, and paroxysmal AF



Am J Cardiol, 2017; 19(12): 1989 – 96

ARISTOTLE – Post-Hoc Analysis of Obesity Effect

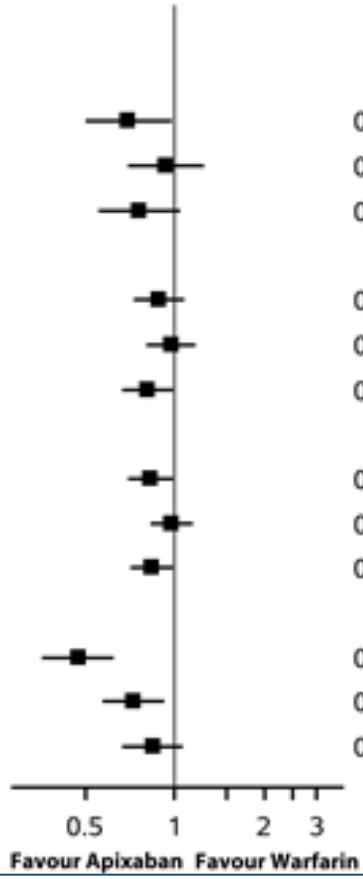
- Subgroup analysis of the original trial stratifying subjects by BMI category
- Overall, fewer strokes or systemic embolism in obese patients vs normal weight

Outcome BMI category (kg/m^2)	Number of patients in analysis	Events (%/year)	HR (95% CI) *BMI 18.5-<25 kg/m^2 as reference*	*P*-value *Effect of BMI category*
Stroke/SE				
18.5–<25	4038	142 (2.01)		
25–<30	6671	174 (1.43)	0.86 (0.68–1.08)	0.18
≥30	7131	150 (1.11)	0.79 (0.61–1.02)	
Death				
18.5–<25	4038	397 (5.45)		
25–<30	6671	429 (3.44)	0.67 (0.59–0.78)	<.0001
≥30	7131	398 (2.90)	0.63 (0.54–0.74)	
Stroke/SE/MI/Death				
18.5–<25	4038	510 (7.23)		
25–<30	6671	598 (4.92)	0.74 (0.65–0.84)	<.0001
≥30	7131	554 (4.13)	0.68 (0.60–0.78)	
Major bleeding				
18.5–<25	3984	217 (3.44)		
25–<30	6618	270 (2.44)	0.82 (0.68–0.99)	0.11
≥30	7074	281 (2.30)	0.91 (0.74–1.10)	

Eur Heart J, 2016; 37: 2869-78

ARISTOTLE – Post-Hoc Analysis of Obesity Effect

Outcome BMI category (kg/m^2)	No of patients	Apixaban Events (%/year)	Warfarin Events (%/year)	HR (95% CI)	*P*-value Interaction
Stroke/SE					
18.5–<25	4052	59 (1.65)	83 (2.36)	0.70 (0.50–0.97)	0.41
25–<30	6702	84 (1.37)	90 (1.47)	0.93 (0.69–1.26)	
≥30	7159	66 (0.97)	86 (1.28)	0.76 (0.55–1.05)	
Death					
18.5–<25	4052	188 (5.11)	210 (5.78)	0.89 (0.73–1.08)	0.45
25–<30	6702	212 (3.38)	218 (3.48)	0.97 (0.80–1.17)	
≥30	7159	181 (2.61)	220 (3.21)	0.81 (0.67–0.99)	
Stroke/SE/MI/Death					
18.5–<25	4052	234 (6.55)	277 (7.91)	0.83 (0.70–0.99)	0.31
25–<30	6702	296 (4.84)	303 (4.97)	0.97 (0.83–1.14)	
≥30	7159	256 (3.78)	302 (4.51)	0.84 (0.71–0.99)	
Major bleeding					
18.5–<25	4035	72 (2.22)	147 (4.70)	0.47 (0.36–0.63)	0.006
25–<30	6687	115 (2.04)	156 (2.82)	0.73 (0.57–0.92)	
≥30	7134	132 (2.12)	153 (2.51)	0.84 (0.67–1.07)	



- No significant difference in stroke/systemic embolism, death, or composite of all
- Significantly fewer bleeding events in patients receiving apixaban vs warfarin, although this effect diminished as BMI increased

Eur Heart J, 2016; 37: 2869-78

Dresden DOAC Registry – Obesity Effects

- Large prospective registry in Dresden, Germany that includes a network of >250 physicians in both private practices and hospitals
  - Patients enrolled voluntarily if planning to be on DOAC therapy for any indication for a minimum of 3 months duration.
    - No exclusion criteria
    - Collected data regarding efficacy, safety, and management of DOAC use

Int J Cardiol;262(2018): 85 - 91

Dresden DOAC Registry – Obesity Effects

- Analysis of all thromboembolic (TE) events while on DOAC therapy for any indications
  - Comparison based on BMI of ≥30 kg/m^2 vs < 30 kg/m^2
- Higher BMI patients were found to have fewer TE events

Stroke/TIA/Systemic Embolism/VTE During Treatment n (%)		
	BMI <30	BMI ≥30
Total (n=3432)	101/2358 (4.3)	40/1074 (3.7)
Male (n=1814)	48/1283 (3.7)	24/531 (4.5)
Female (n=1618)	53/1075 (4.9)	16/543 (2.9)
Age <65 yrs (n=825)	13/538 (2.4)	6/287 (2.1)
Age ≥65 yrs (n=2607)	88/1820 (4.8)	34/787 (4.3)
VTE (n=1055)	24/770 (3.1)	6/285 (2.1)
SPAF (n=2334)	74/1556 (4.8)	33/778 (4.2)
Off-label (n=43)	3/32 (9.4)	1/11 (9.1)
Standard Dose (n=2515)	62/1702 (3.6)	21/813 (2.6)
Reduced Dose (n=916)	39/656 (5.9)	19/260 (7.3)

Int J Cardiol;262(2018): 85 - 91

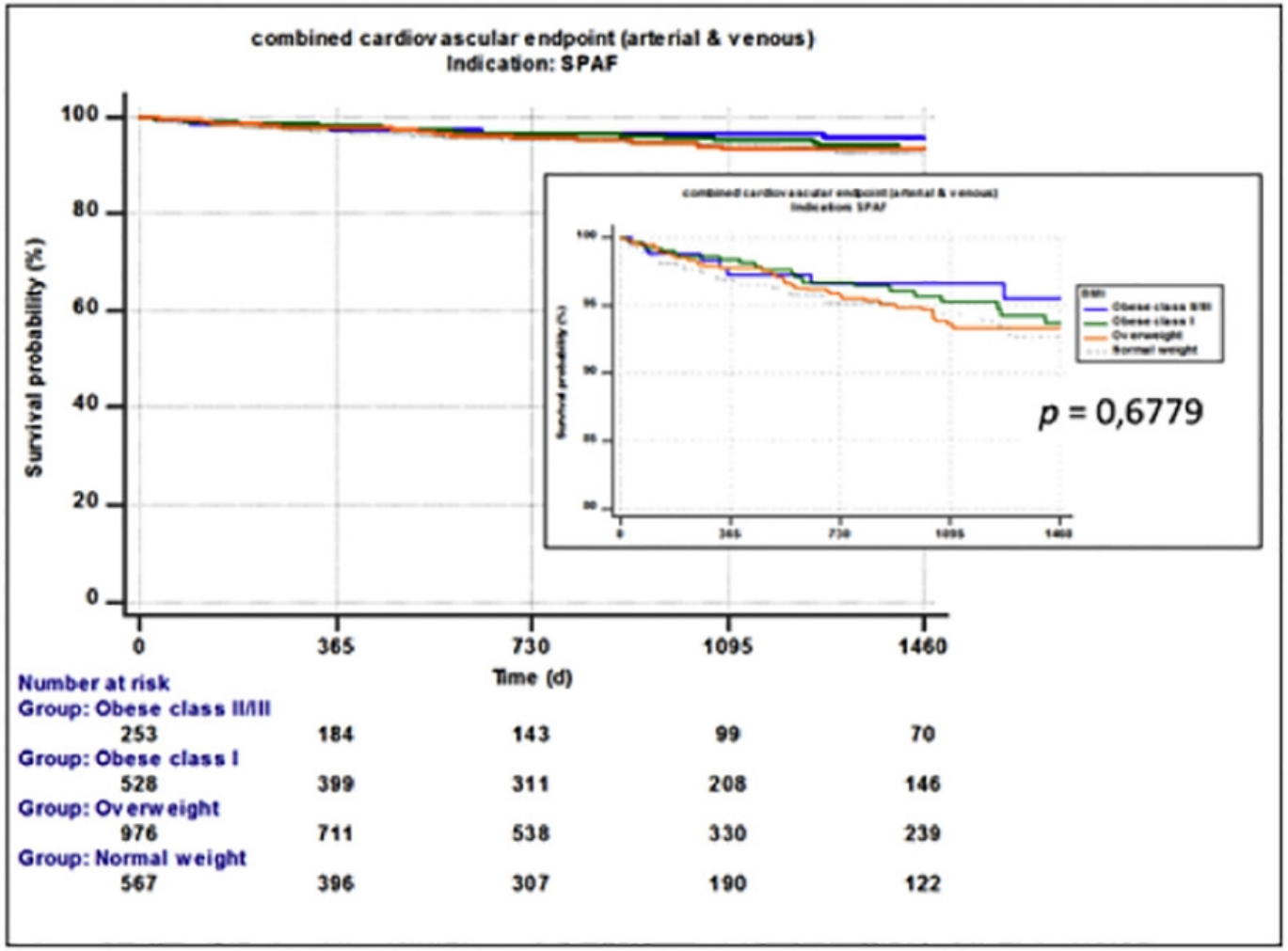
Dresden DOAC Registry – Obesity Effects

- The effectiveness outcome of major thromboembolic events occurred less often as degree of obesity increased.
  - Defined as the composite of stroke, TIA, and systemic embolism
- ISTH bleeding events were also more common as degree of obesity increased.

Clinical Effectiveness and Safety Outcomes in Patients with BMI ≥30 kg/m^2		
	Events (n)	Event/100 pt years (95% CI)
BMI 30 – 35 (n=731)		
Effectiveness	30	1.84 (1.24-2.63)
ISTH Bleeding	34	2.09 (1.44-2.91)
BMI 35 – 40 (n=248)		
Effectiveness	9	1.56 (0.71-2.96)
ISTH Bleeding	13	2.23 (1.19-3.81)
BMI >40 (n=98)		
Effectiveness	1	0.49 (0.01-2.71)
ISTH Bleeding	7	3.45 (1.39-7.12)

Int J Cardiol 2018; 262:85-91

Dresden DOAC Registry – Obesity Effects

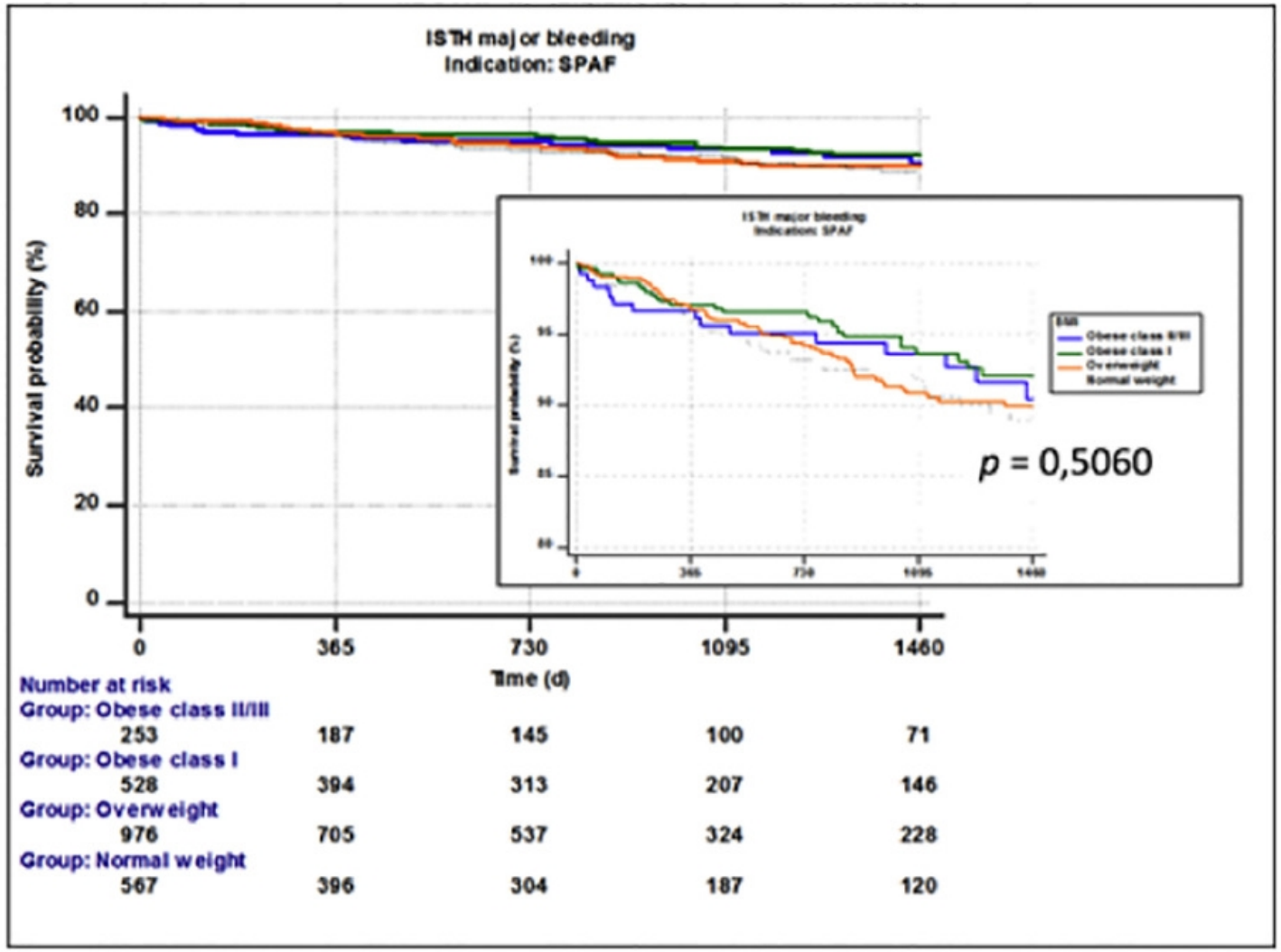


- Thromboembolic events did not differ between groups over the course of the 4 years of observation

Int J Cardiol;262(2018): 85 - 91

Dresden DOAC Registry – Obesity Effects

- Bleeding Events were numerically higher in patients who were in obese categories, but no statistical difference



Int J Cardiol;262(2018): 85 - 91

DOAC vs. Warfarin in a Morbidly Obese Population with Atrial Fibrillation

- Single-center, retrospective cohort comparing patients prescribed a DOAC for atrial fibrillation stroke prophylaxis vs patients prescribed warfarin
  - Included if: age over 18 yrs with BMI >40 kg/m^2 or weight >120 kg
  - Excluded if: mechanical heart valves, pregnant, or ESRD

- Outcomes:
  - Efficacy: incidence of ischemic stroke or TIA
  - Safety: major bleeding
    - Decrease in Hg of 2 gm/dL
    - Transfusion of 2 units PRBCs
    - Bleeding in a critical organ (per ISTH criteria)
    - Life threatening bleeding

Ann of Pharmacother, 2018; DOI: 10.1177/1060028018796604

DOAC vs Warfarin in a Morbidly Obese Population with Atrial Fibrillation

DOAC vs Warfarin Outcomes: Multivariate Logistic Analyses			
	Odds Ratio	**95% CI**	**P Value**
Stroke or TIA			
DOACs vs Warfarin	0.81	0.2 – 3.27	0.77
$CHAD_2DS_2$-VASc score	1.15	0.74 – 1.77	0.54
Serum Creatinine	0.72	0.19 – 2.78	0.63
NSAIDs	0.86	0.09 – 7.76	0.89
Major Bleeding			
DOACs vs Warfarin	0.37	0.12 – 1.15	0.09
HAS-BLED score	1.38	0.8 – 2.4	0.25
Serum Creatinine	0.53	0.17 – 1.66	0.28
NSAIDs	1.06	0.2 – 5.63	0.94

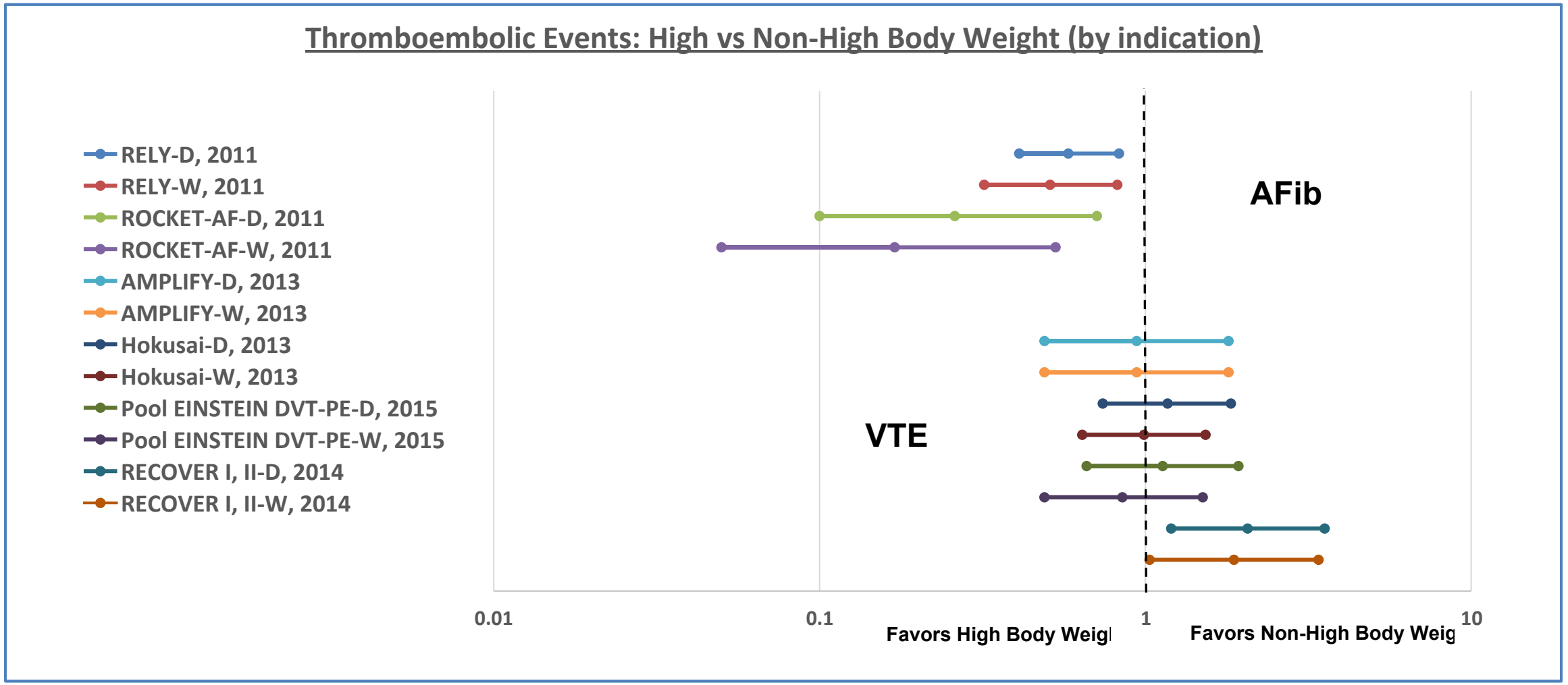
Ann of Pharmacother, 2018; DOI: 10.1177/1060028018796604

Meta-Analysis of DOAC Trials and Obesity Measures

- Meta-analysis of all RCTs investigating DOAC use for the indications of preventing systemic embolism in atrial fibrillation or venous thromboembolism treatment.
  - Must also report thromboembolic and bleeding outcome data by body weight (kg) or BMI (kg/m^2)
    - Patients stratified by body weight class
      - Low: ≤ 60 kg
      - Normal: 60 kg – 100 kg
      - High: ≥ 100 kg
    - Patients stratified by BMI:
      - Non-obese: ≤ 30 kg/m^2
      - Obese >30 kg/m^2

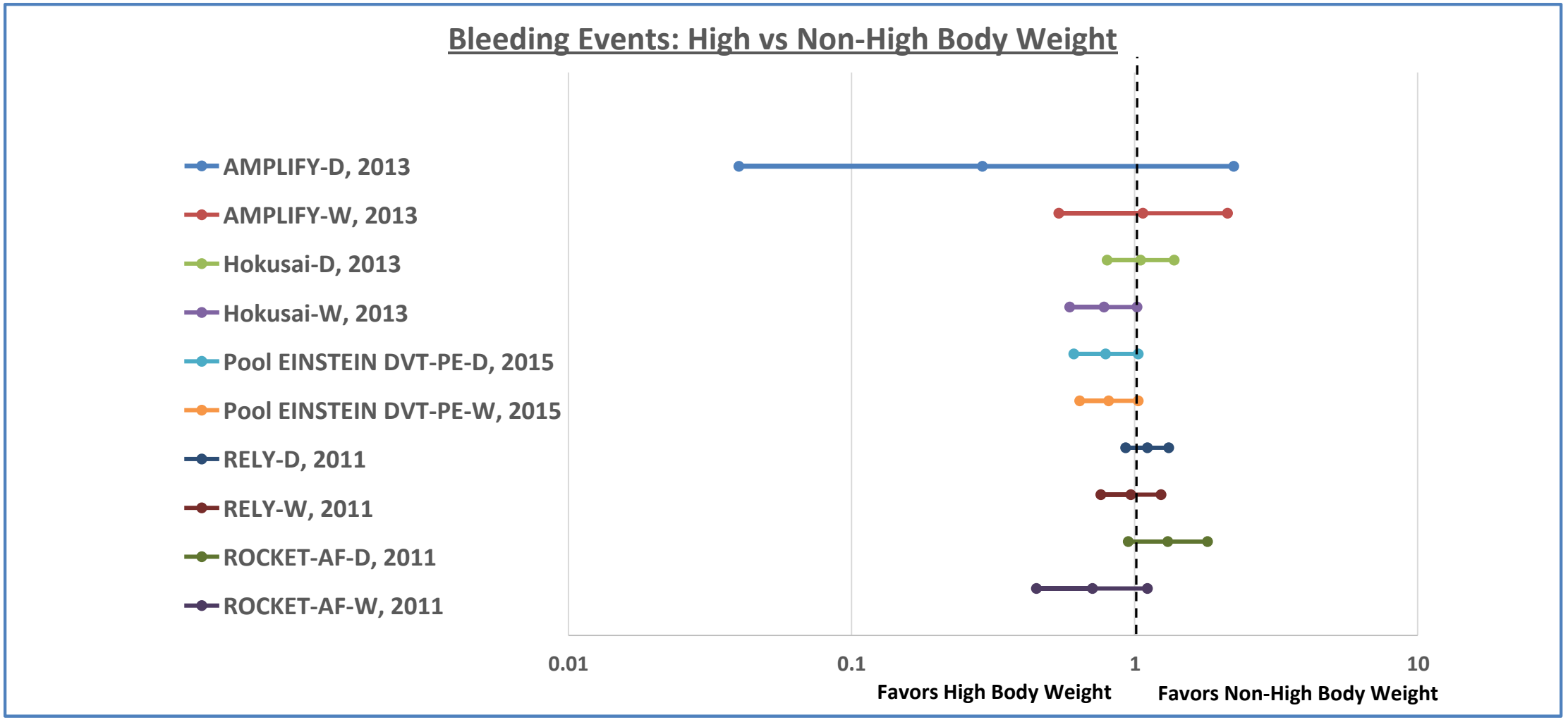
J Thromb Haemostat, 2017; 15: 1322 - 33

Meta-Analysis of DOAC Trials and Obesity



J Thromb Haemostat, 2017; 15: 1322 - 33

Meta-Analysis of DOAC Trials and Obesity



J Thromb Haemostat, 2017; 15: 1322 - 33

Meta-Analysis: DOACs in Atrial Fibrillation

- 2nd Meta-analysis: only included trials that were conducted in the atrial fibrillation population
  - ARISTOTLE
  - RE-LY
  - ROCKET-AF

- Compared outcome data on stroke/systemic embolism and bleeds in 3 groups
  - Overweight vs Normal Weight
  - Obese vs Normal Weight
  - Obese vs Overweight

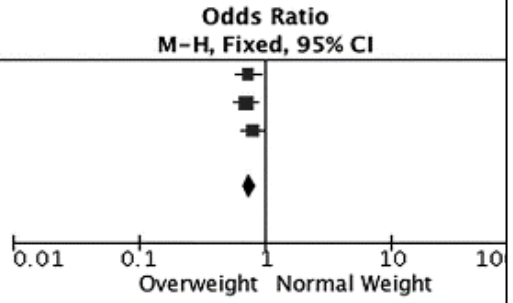
Stroke, 2017; 48: 1-10

Meta-Analysis: DOACs in Atrial Fibrillation

A Stroke/SEE

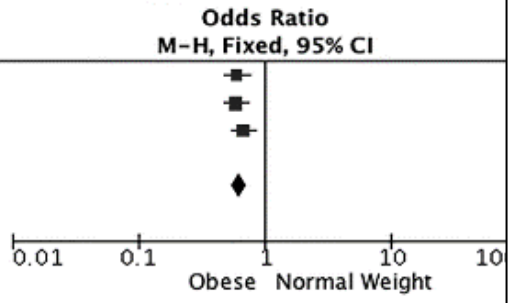
Study or Subgroup	Overweight Events	Overweight Total	Normal Weight Events	Normal Weight Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	174	6702	142	4052	29.4%	0.73 [0.59, 0.92]
RE-LY	196	7111	182	4697	36.4%	0.70 [0.57, 0.86]
ROCKET AF	225	5523	167	3314	34.2%	0.80 [0.65, 0.98]
Total (95% CI)		**19336**		**12063**	**100.0%**	**0.75 [0.66, 0.84]**
Total events	595		491			

Heterogeneity: $Chi^2 = 0.79$, $df = 2$ ($P = 0.67$); $I^2 = 0\%$
Test for overall effect: $Z = 4.73$ ($P < 0.00001$)



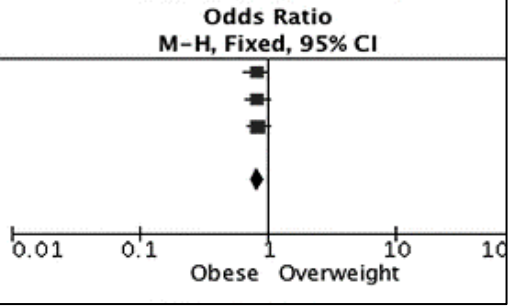
Study or Subgroup	Obese Events	Obese Total	Normal Weight Events	Normal Weight Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	152	7159	142	4052	30.7%	0.60 [0.47, 0.75]
RE-LY	145	6279	182	4697	35.2%	0.59 [0.47, 0.73]
ROCKET AF	179	5194	167	3314	34.1%	0.67 [0.54, 0.83]
Total (95% CI)		**18632**		**12063**	**100.0%**	**0.62 [0.54, 0.70]**
Total events	476		491			

Heterogeneity: $Chi^2 = 0.89$, $df = 2$ ($P = 0.64$); $I^2 = 0\%$
Test for overall effect: $Z = 7.31$ ($P < 0.00001$)



Study or Subgroup	Obese Events	Obese Total	Overweight Events	Overweight Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	152	7159	174	6702	31.1%	0.81 [0.65, 1.01]
RE-LY	145	6279	196	7111	31.7%	0.83 [0.67, 1.04]
ROCKET AF	179	5194	225	5523	37.2%	0.84 [0.69, 1.03]
Total (95% CI)		**18632**		**19336**	**100.0%**	**0.83 [0.73, 0.94]**
Total events	476		595			

Heterogeneity: $Chi^2 = 0.05$, $df = 2$ ($P = 0.98$); $I^2 = 0\%$
Test for overall effect: $Z = 2.98$ ($P = 0.003$)



Stroke, 2017; 48: 1-10

Meta-Analysis: DOACs in Atrial Fibrillation

B Major Bleeding

Study or Subgroup	Overweight Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	271	6687	219	4035	32.1%	0.74 [0.61, 0.88]
RE-LY	424	7111	344	4697	36.3%	0.80 [0.69, 0.93]
ROCKET AF	312	5555	183	3327	31.5%	1.02 [0.85, 1.23]
Total (95% CI)		**19353**		**12059**	**100.0%**	**0.84 [0.70, 1.01]**
Total events	1007		746			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 6.58$, df = 2 (P = 0.04); $I^2 = 70\%$
Test for overall effect: Z = 1.87 (P = 0.06)

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100
Overweight Normal Weight

Study or Subgroup	Obese Events	Total	Normal Weight Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
ARISTOTLE	285	7134	219	4035	32.2%	0.73 [0.61, 0.87]
RE-LY	394	6279	344	4697	37.3%	0.85 [0.73, 0.98]
ROCKET AF	279	5214	183	3327	30.5%	0.97 [0.80, 1.18]
Total (95% CI)		**18627**		**12059**	**100.0%**	**0.84 [0.72, 0.98]**
Total events	958		746			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.77$, df = 2 (P = 0.09); $I^2 = 58\%$
Test for overall effect: Z = 2.21 (P = 0.03)

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100
Obese Normal Weight

Study or Subgroup	Obese Events	Total	Overweight Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
ARISTOTLE	285	7134	271	6687	29.0%	0.99 [0.83, 1.17]
RE-LY	394	6279	424	7111	40.2%	1.06 [0.92, 1.22]
ROCKET AF	279	5214	312	5555	30.8%	0.95 [0.80, 1.12]
Total (95% CI)		**18627**		**19353**	**100.0%**	**1.00 [0.92, 1.10]**
Total events	958		1007			

Heterogeneity: $Chi^2 = 0.96$, df = 2 (P = 0.62); $I^2 = 0\%$
Test for overall effect: Z = 0.06 (P = 0.95)

Odds Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100
Favours Obese Favours Overweight

Stroke, 2017; 48: 1-10

The Atrial Fibrillation Obesity Paradox

- While increased body weight is a risk factor for developing atrial fibrillation, it is also associated with lower rates of stroke or systemic embolism relative to those with normal body weight.

- Analyses also suggest that there is a lower risk of bleeding complications due to oral anticoagulation.

ISTH Guidance on DOAC Use in the Morbidly Obese

- We recommend appropriate standard dosing of the DOACs in patients with BMI ≤ 40 kg/m2 or a weight of ≤ 120 kg.
- We suggest that DOACs should not be used in patients with BMI >40 kg/m2 or a weight of >120 kg.
- If DOACs are used in a patient with BMI >40 kg/m2 or a weight of >120 kg, we suggest checking a drug-specific peak and trough level
  - Anti-Xa (calibrated to drug)- Apixaban, Rivaroxaban, and Edoxaban
  - Ecarin time or dilute thrombin time, calibrated specifically to Dabigatran
  - Mass spectrometry drug levels for any available DOAC within the accepted range

J Thromb Haemos, 2016; 14: 1308-13

Question

Which patient is most likely to experience treatment failure with a DOAC?

A. 67 yo male, weight 115 kg (BMI=35), receiving Rivaroxaban 20 mg daily
B. 48 yo female, weight 105 kg (BMI=42), receiving Apixaban 5 mg BID
C. 54 yo male, weight 135 kg (BMI=45), receiving Dabigatran 150 mg BID
D. 38 yo male, weight 120 kg (BMI=38), receiving Apixaban 5 mg BID

Key Takeaways

- Patients who are obese (elevated body weight or elevated BMI) may not respond to oral anticoagulation in the same manner as those of normal body weight.
- Not all DOACs have the same pharmacokinetic and pharmacodynamic profiles, so each agent must be evaluated individually.
- Until more data is available, use of a DOAC for stroke prophylaxis in a patient of >120 kg or >40 kg/m^2 BMI is not recommended without some degree of close monitoring for both efficacy and bleeding.

My kidneys don't work now. Is Warfarin really my only option?

Patient Case

- JT is a 68-year-old male with newly diagnosed paroxysmal atrial fibrillation.

- Medical History notable for:
  - Hypertension
  - Type II Diabetes
  - Coronary Artery Disease
  - Stage 5 CKD (Baseline SrCr =), Current CrCl = 19 mL/min

Which of the following would you recommend for stroke prevention?

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

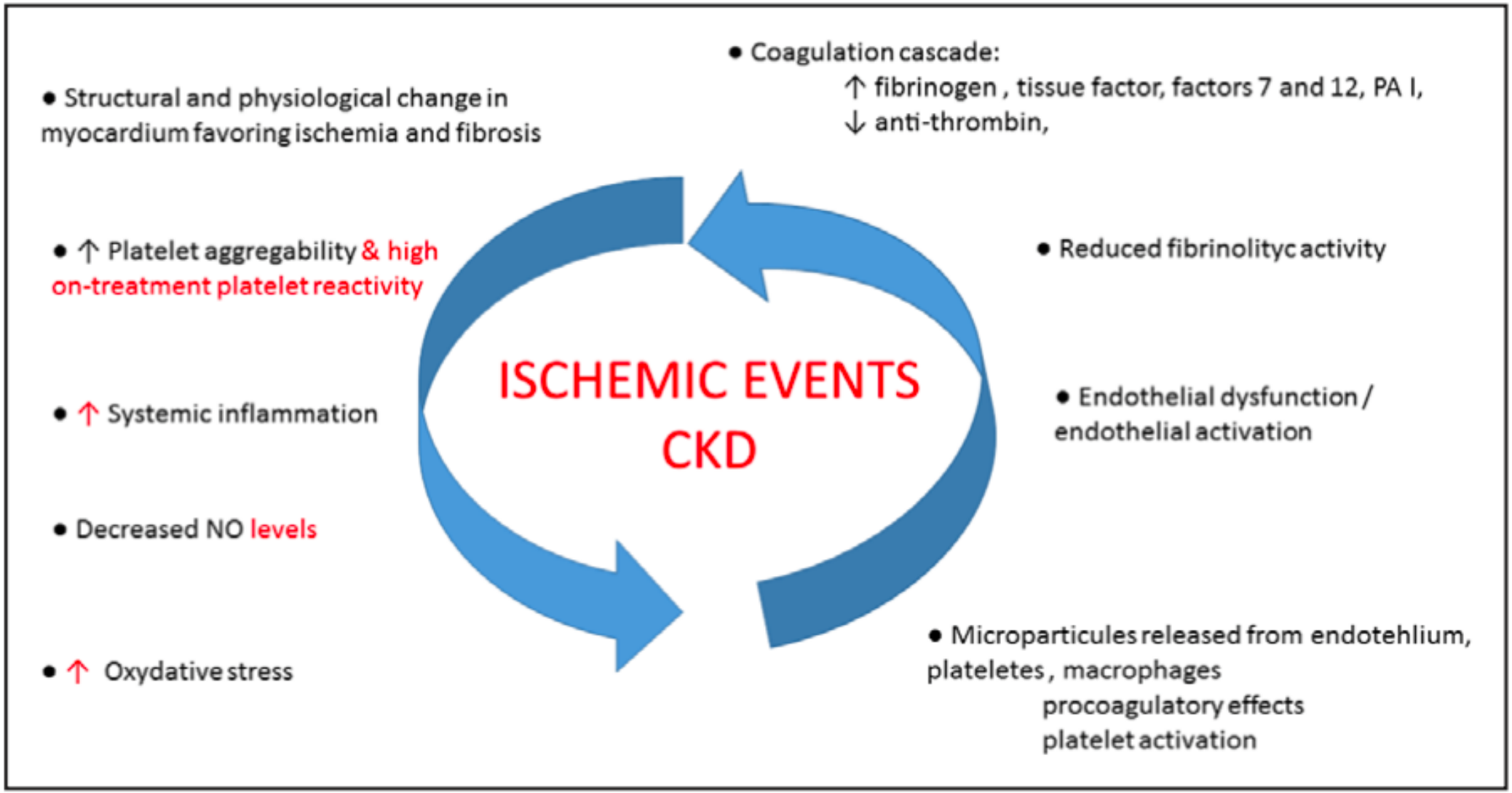
AF in End State Renal Disease

- Approximately 20 million US patients have ESRD
- AF is the most common arrhythmia in these patients
  - Prevalence of AF increases as renal function decreases
  - Approximately 10% of ESRD patients will develop AF (range: 3 – 27%)
- Most ESRD patients have additional risk factors for stroke
  - HTN
  - Diabetes
  - CAD/Vascular Disease
  - Age

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

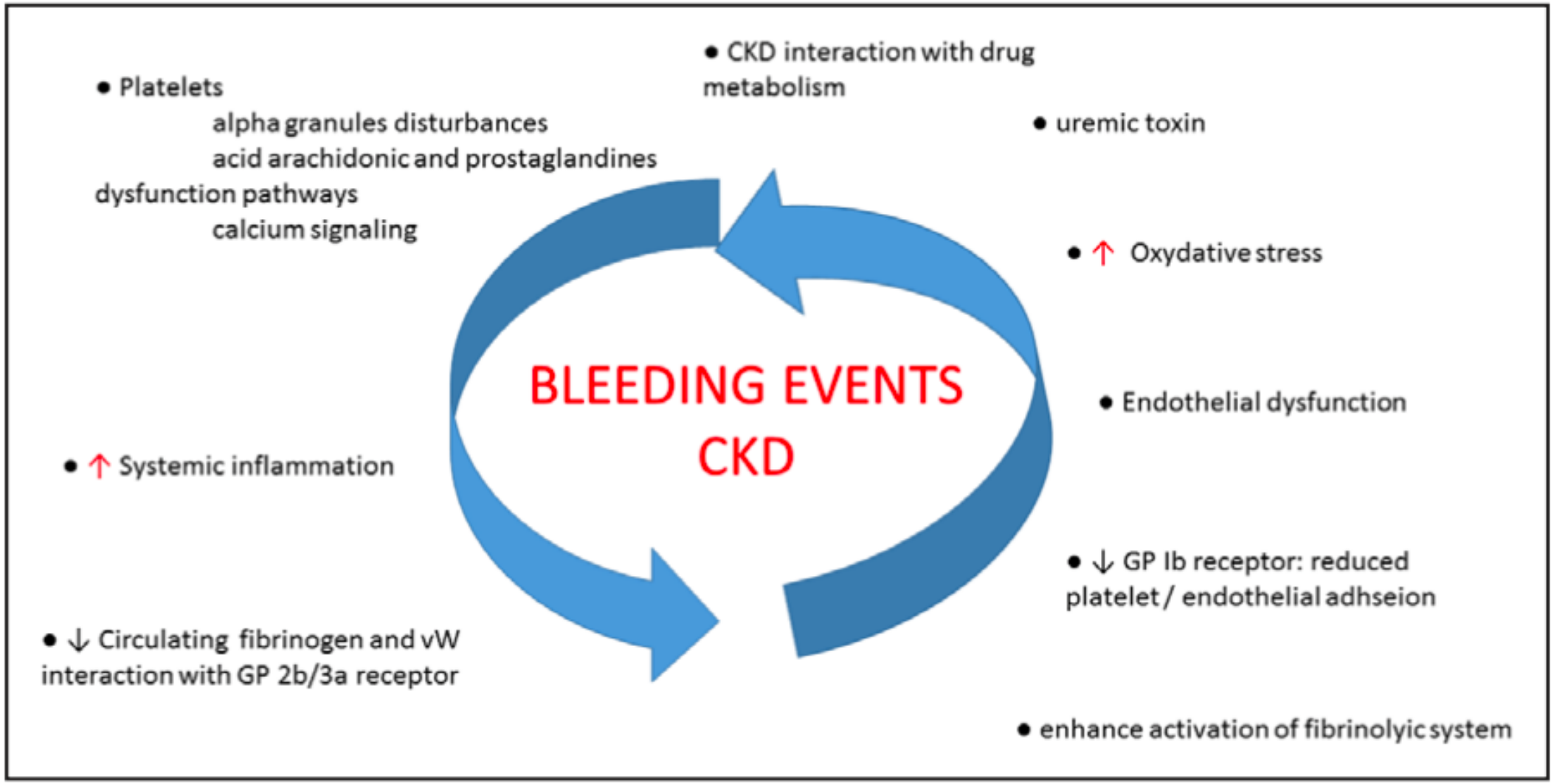
Stroke and Thrombotic Risk in ESRD/HD



Patients with CKD requiring dialysis have a 5-fold higher risk for new stroke!

Bonello L et al. Circulation 2018; 138:1582-96.

Bleeding Risk in ESRD



Additional risks for bleeding: Heparin exposure during dialysis

Bonello L et al. Circulation 2018; 138:1582-96.

Stroke Risk Factors in ESRD

- Do the CHA_2DS_2-VASc risks carry the same degree of risk?
  - HTN: how many ESRD/HD patients have hypotension?
  - Which measurement defines control or lack of control?
    - Pre-Dialysis measurements, Post-Dialysis measurements?
  - HF:
    - Volume overload from cardiac dysfunction? Or renal disease?
    - Volume overload is managed differently
  - Anemia in CKD is different than those without CKD
- How do these differences impact application of risks to ESRD patients?
  - Unknown as ESRD patients are not included
  - CHA_2DS_2-VASc = 3 in ESRD patients:
    - Equal risk, or lower risk?

Warfarin in non-end stage CKD

- Nationwide registry of 11,128 AF patients with non-end stage CKD
  - 1728 patients on Renal Replacement Therapy
  - CHA_2DS_2-VASc ≥ 2

- Warfarin therapy was associated with positive benefits on:
  - Fatal stroke/Fatal bleeding: HR 0.71 (0.57 – 0.88)
  - Cardiovascular Death: HR 0.80 (0.74 – 0.88)
  - All-cause Death: HR 0.64 (0.60 – 0.69)

Bonde AN et al. J Am Coll Cardiol 2014; 64:2471-82.

Warfarin in AF Patients With ESRD

Study (n)	Study Design	HR for Stroke	HR for Bleeding
Shen 2015 (1838 warfarin users)	Retrospective	0.73 (0.44 – 1.20) p=NS	GI: 1.36 (0.89 – 2.07) ICH: 1.92 (0.82 – 4.48)*
Shah 2014 (1626)	Retrospective	1.14 (0.78 – 1.67) p=NS	1.44 (1.13 – 1.85)*
Winkelmayer 2011 (2313)	Retrospective	0.92 (0.61 – 1.37) p=NS	GIB: 0.90 (0.60 – 1.35) Hemorrhagic stroke: 2.63 (1.01 – 6.88)*
Chan 2009 (1671, 507 warfarin users)	Retrospective	2.94 (1.60 – 5.40) p=0.001	Hemorrhagic stroke: 2.22 (1.01 – 4.91)*

NEUTRAL AT BEST, COULD BE ASSOCIATED WITH WORSENING OUTCOMES

Shen JI et al. Am J Kidney Dis 2015; 66: 677–688. Shah M et al. Circulation 2014; 129:1196 – 1203. Winkelmayer WC et al. Clin J Am Soc Nephrol 2011: 6:2662–2668
Chan KE et al. J Am Soc Nephrol 2009; 20: 2223–2233

INR Control in Declining Renal Function

- 565 patients receiving chronic warfarin therapy at a Pharmacogenomic Optimization Anticoagulation Therapy clinic

- Divided into 3 groups based on renal function:
  - GFR > 60 mL/min (n=336)
  - GFR 30 – 59 mL/min (n=176)
  - GFR < 30 mL/min (n=53)

- No differences between groups:
  - Age, gender, socioeconomic status
  - Genetic variation for warfarin dosing (CYP 2C19, VKORC1)
  - Indications for warfarin

Limdi NA et al. J Am Soc Nephrol 2009; 20:912-21.

INR Control in Declining Renal Function

	eGFR < 60	eGFR 30 – 59	eGFR < 30
% INR 2 – 3	50	48	40
% INR > 3.0	18	21	24
Incidence Rate INR > 4.0	84	104	189
Incidence Rate Minor Bleeding	31.4	32.4	105.7
Incidence Rate Major Bleeding	6.2	8.3	30.5

Hazard Ratio Major Bleeding eGFR < 30: 2.65 (1.19 – 5.62, p<0.001)

Limdi NA et al. J Am Soc Nephrol 2009; 20:912-21.

Warfarin INR Control in CKD: Nephropathy Risk

- Retrospective study of 12,528 patients on Warfarin between 2005 – 2009
- 6019 patients with at least 1 INR > 3.0
- 4848 patients with Creatinine measured within 1 week of INR > 3.0
- 4816 patients with Creatinine measured within the previous 3 months
- 821 patients with suspected nephropathy (SCr > 0.3 mg/dL) within 1 week of INR > 3.0 (20.5%)

Brodsky SV et al. Kidney International 2011; 80:181-9.

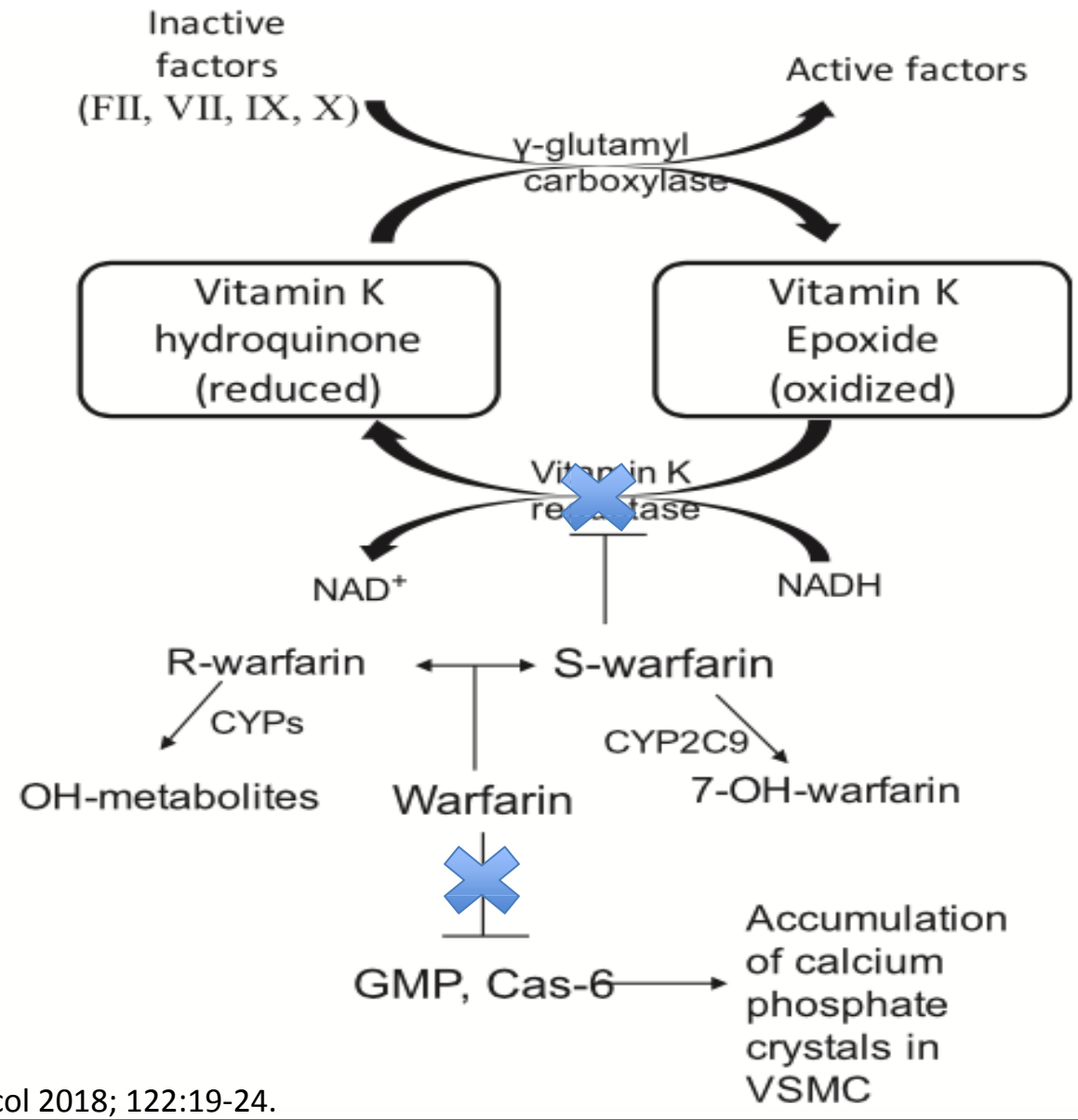
Warfarin INR Control in CKD: Nephropathy Risk

- Patients who developed Warfarin-induced Nephropathy:
  - Slightly older (mean age 63.6 years-old vs. 61.7 years-old)
  - Heart Failure (62% vs. 42%)
  - Hypertension (81% vs. 72%)
  - Known CKD history (37% vs. 19%)
  - Diabetes (47% vs. 37%)
  - Known Diabetic Nephropathy (10% vs. 4%)
  - More likely to take the following medications:
    - Aspirin
    - ACE/ARB, Hydralazine, Dihydropyridines

- Patients without CKD: 16% incidence of Warfarin-induced Nephropathy

Brodsky SV et al. Kidney International 2011; 80:181-9.

Warfarin Renal Calcification



Siltari A et al. Basic & Clin Pharmcol Toxicol 2018; 122:19-24.

Nephrologist Confidence in Prescribing Warfarin in ESRD and AF?

- Survey of Nephrologists within Canadian Society of Nephrology (n=56)
  - All active in clinical care of patients on HD
  - Average 11 years of practice experience
  - 68% Academic Medical Center Practice

- 6 patient case scenarios asking about OAC in CKD patients
  1. CHA_2DS_2-VASc = 3, No: HD, GI Bleed, Fall Risk
  2. CHA_2DS_2-VASc = 3, On HD, but No: GI Bleed, Fall Risk
  3. CHA_2DS_2-VASc =6, On HD, but No: GI Bleed, Fall Risk
  4. CHA_2DS_2-VASc = 8, On: HD, (+) Fall Risk, but No: GI Bleed
  5. CHA_2DS_2-VASc = 8, On: HD, (+) GI Bleed, but No: Fall Risk
  6. CHA_2DS_2-VASc = 8, On: HD, (+) Fall Risk, (+) GI Bleed

Juma S et al. BMC Nephrol 2013; 14:174-80.

Nephrologist Confidence in Prescribing Warfarin in ESRD and AF?

Case	CHA_2DS_2-VASc	HD	GI Bleed	Fall Risk	Likely Warfarin (%)	Unlikely Warfarin (%)	Uncertain (%)
1	3	No	No	No	80.4	3.6	16.1
2	3	Yes	No	No	50	14.3	35.7
3	6	Yes	No	No	76.7	3.6	19.6
4	8	Yes	No	Yes	23.2	28.6	48.2
5	8	Yes	Yes	No	48.2	8.9	42.9
6	8	Yes	Yes	Yes	3.6	67.9	28.6

Juma S et al. BMC Nephrol 2013; 14:174-80.

AURORA: Rosuvastatin in HD

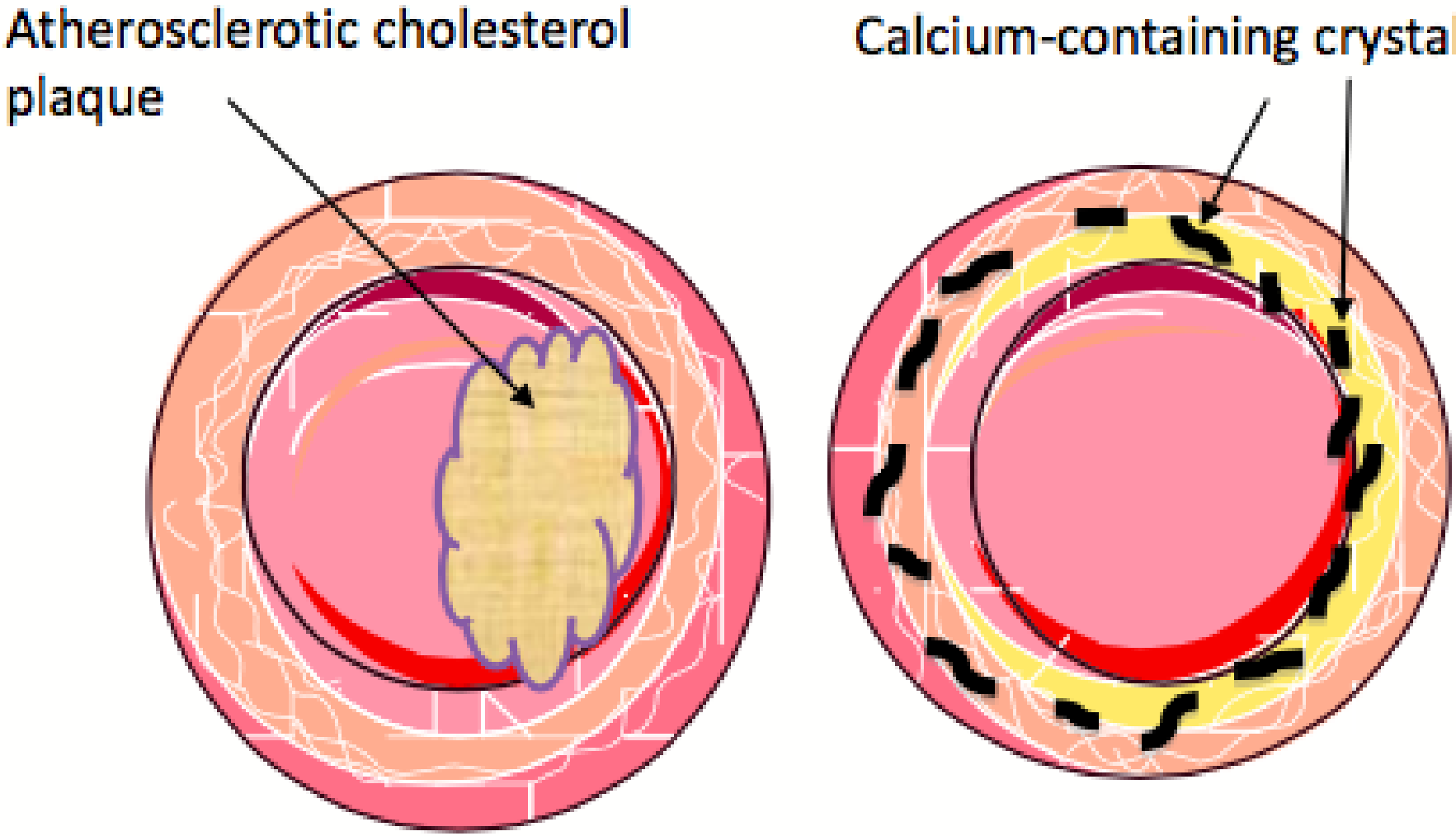
- 2776 patients undergoing chronic, maintenance HD
- Rosuvastatin 10 mg daily vs. Placebo
- Follow-up: Approximately 4 years

- Primary Endpoint: MACE – CV Death, MI, Stroke
  - No difference!
  - 9.2% vs. 9.5%, HR:0.96 (0.84 – 1.11; p=0.59)

- Did not assess vascular calcification, calcium/phosphate control, hyperparathyroidism

Fellstrom BC et al. N Engl J Med 2009; 360:1395-1407.

Vascular Calcification vs. Atherosclerosis



Siltari A et al. Basic & Clin Pharmcol Toxicol 2018; 122:19-24.

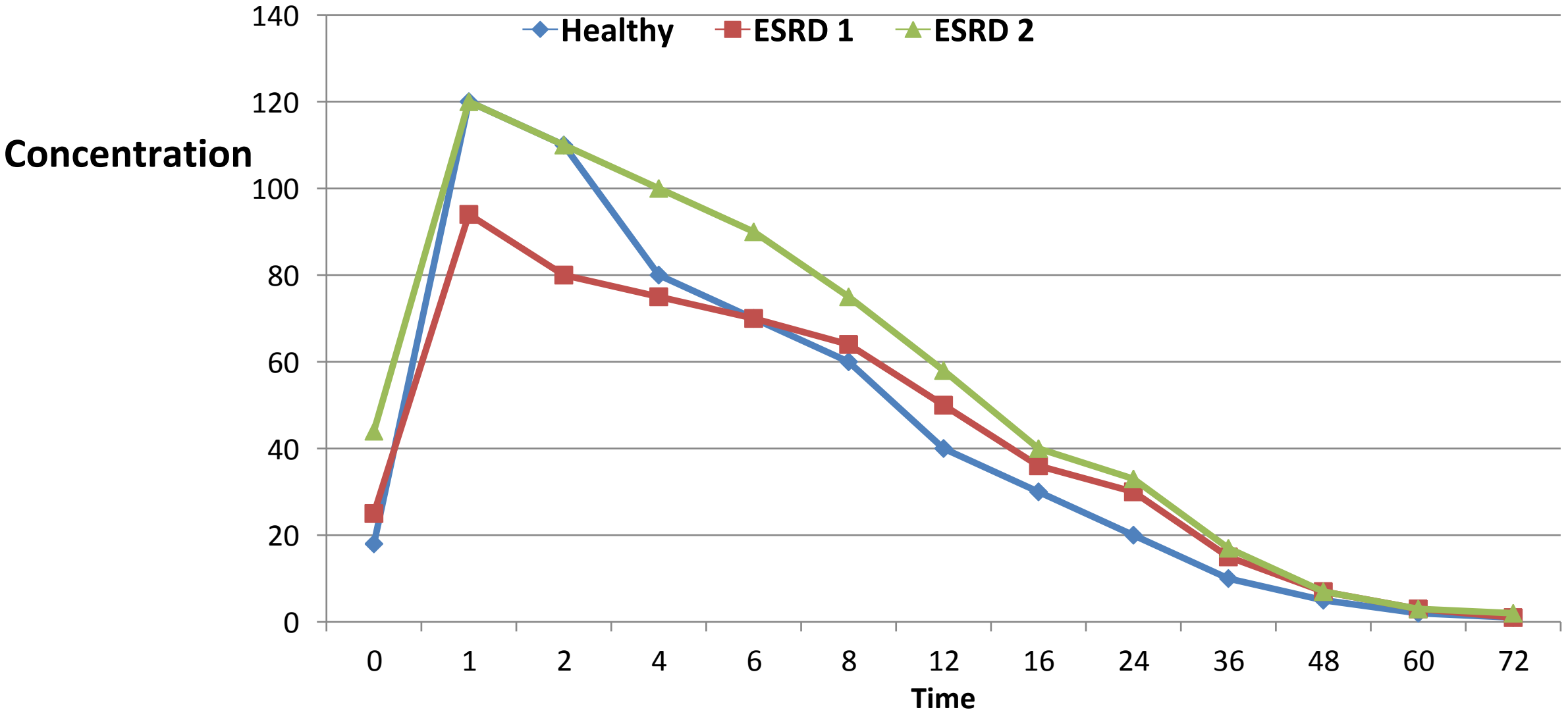
DOACs in ESRD/HD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Target	Factor II	Factor Xa	Factor Xa	Factor Xa
Renal Clearance	80%	27%	50%	33%
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

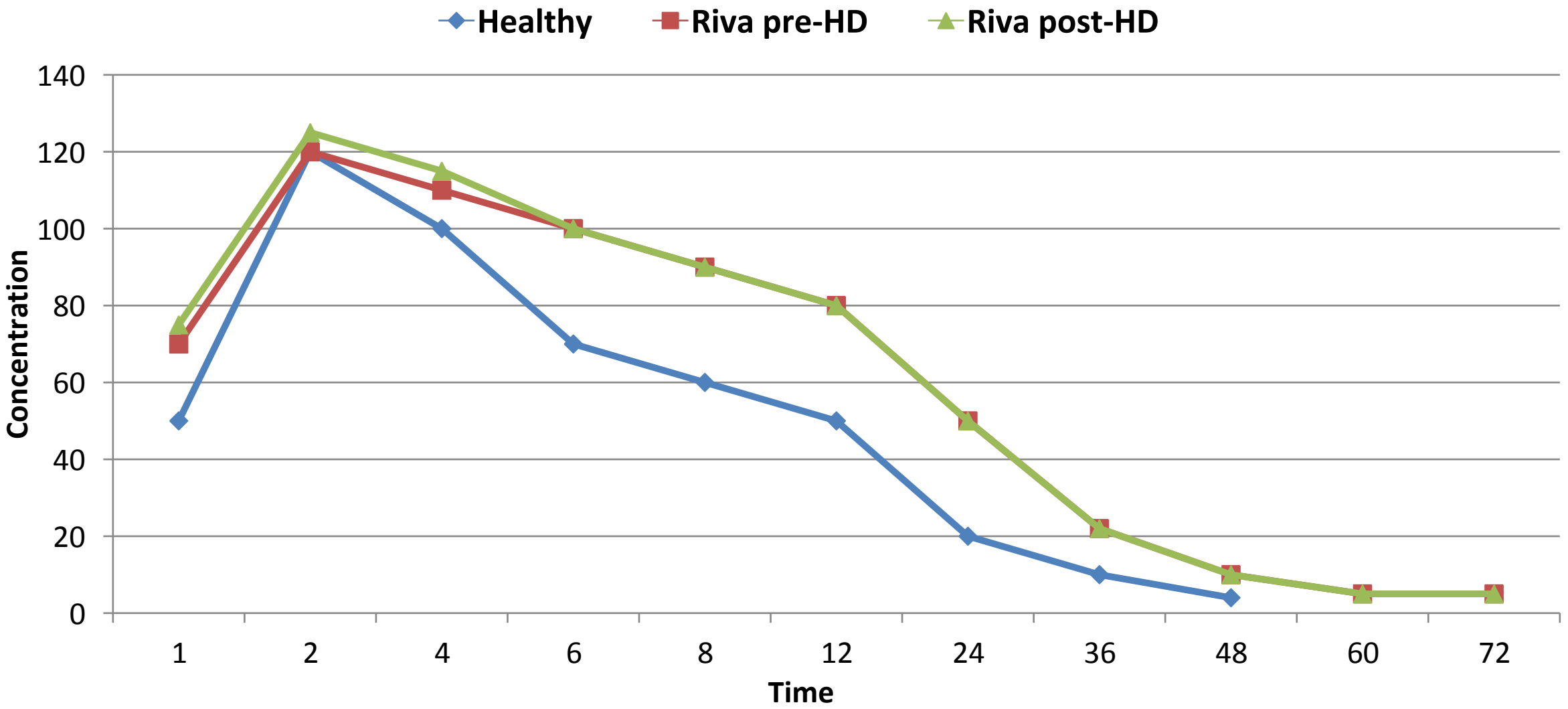
** Apixaban HD dosing is 5 mg BID unless 1 additional factor listed above is present

Apixaban Pharmacokinetics (n=8)



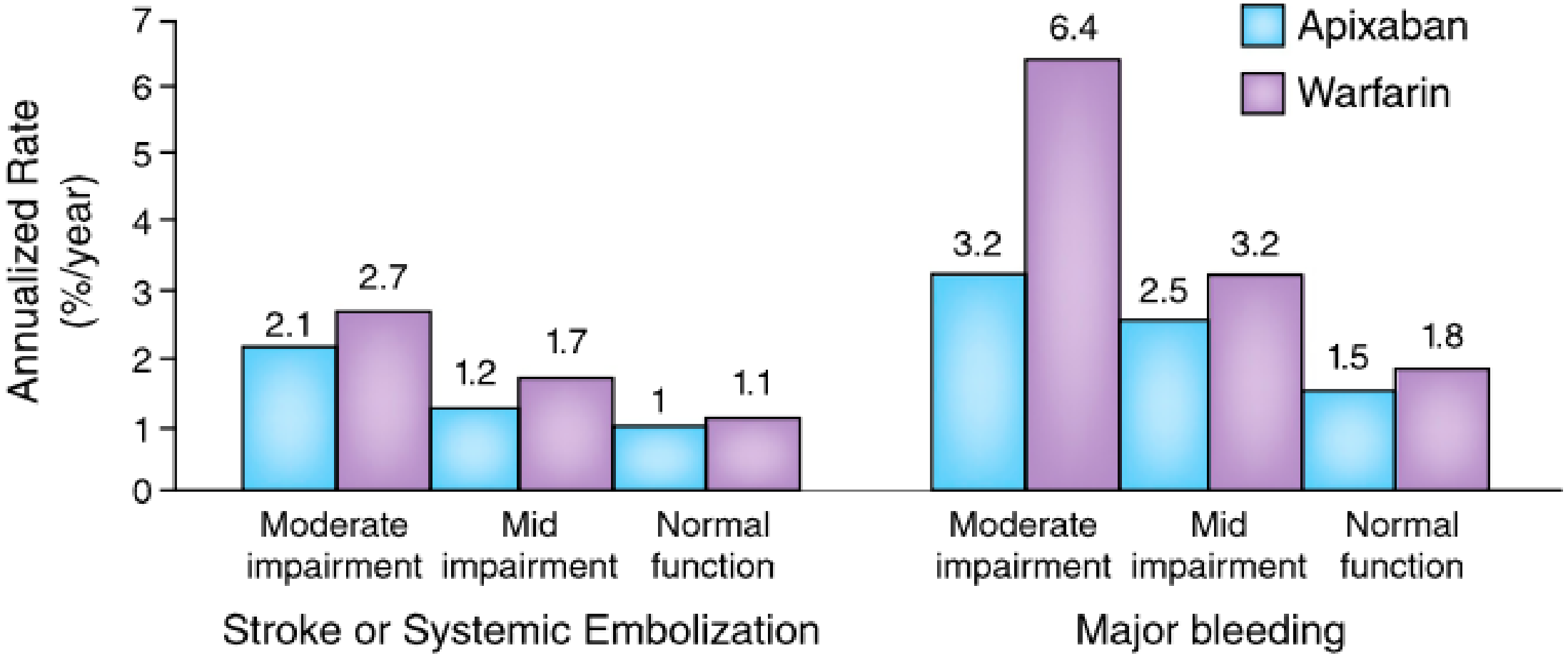
Wang X et al. J Clin Pharmacol 2016; 56(5):628-36.

Rivaroxaban Pharmacokinetics (n=8)



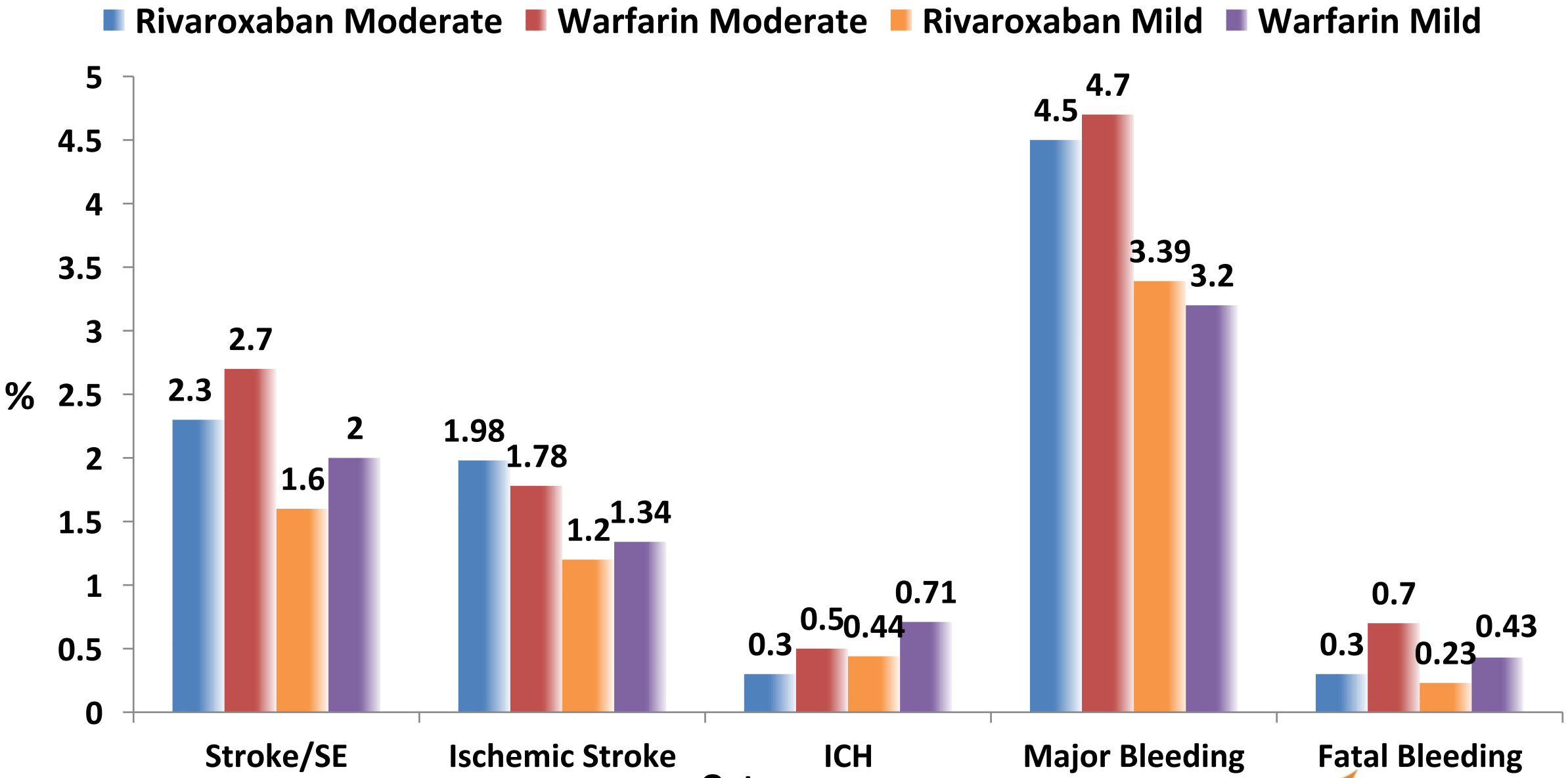
Dias C et al. Am J Nephrol 2016; 43:229-236.

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)



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

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, CHA_2DS_2-VASc ≥ 2	Major and clinically relevant non-major bleeding
RENAL-AF	Apixaban vs Warfarin	• ESRD with chronic HD • AF, CHA_2DS_2-VASc ≥ 2	Major and clinically relevant non-major bleeding
AVKDIAL	Warfarin vs. placebo	• ESRD with chronic HD • AF, CHA_2DS_2-VASc ≥ 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)

OACs Kinetics in HD: Which to Focus On?

	Warfarin	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
T ½ (hrs)	40	12 – 17	12	10 – 14	11 – 13
Renal Clearance	Minor	80%	27%	50%	36%
Dosing: AF	Dose to INR	150 mg BID	5 mg BID	60 mg Daily	20 mg Daily
Renal dosing: AF	Dose to INR	75 mg BID Calcar 15 - 30	2.5 mg BID*	30 mg Daily Calcar: 15 – 50	15 mg Daily Calcar < 50
FDA Dose for AF in HD?	Dose to INR	NO	**YES**	NO	**YES**
HD Dosing in AF	Dose to INR	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

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

Questions