PHARMACY VISION 2020

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Disneyland RESORT

Helping the Aging Heart: Use of Direct Oral Anticoagulants in the Geriatric population

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DISCLOSURE

I have no potential conflict of interest

Acknowledgment:
Laura Tsu Chen, PharmD, BCPS, BCGP contributed to this presentation.

Learning Objectives

At the end of this presentation, the attendee will be able to

1. Discuss characteristics that affect the use of direct oral anticoagulants (DOACs) in geriatric patients that differ from the general adult population.
2. Evaluate the evidence and recommendations for DOAC therapy in geriatric patients with atrial fibrillation, kidney disease, and those with peri-procedure and reversal needs.
3. Develop a patient care plan that considers the available evidence and patient specific variables, concomitant conditions and medications, for an older patient that requires DOAC therapy

TEST QUESTIONS

(will be discussed throughout the presentation)

1. What geriatric syndromes would contribute to a higher risk of bleeding while on oral anticoagulants?
2. What are potential mechanisms of drug interactions with DOACs?
3. An 80 yo patient, weighs 88 kg, SCr is 1.5 mg/dL, estimated CrCl is 49 mL/min, what is an appropriate DOAC dose for stroke prophylaxis?
4. What scenario would favor using reversal agent for DOACs?

CONTENT OUTLINE

I. Risks of thrombosis and bleeding in the geriatric population

II. Current use of oral anticoagulants for cardiac indications

III. Efficacy and safety of use of direct oral anticoagulants (DOACs) for stroke prophylaxis in older patients with atrial fibrillation

IV. Use of DOACs in patients with kidney disease

V. Peri-procedure interruption of DOAC therapy

VI. Reversal of DOAC therapy

BACKGROUND

- Atrial fibrillation (Afib) prevalence increases in advanced age[1,2]
  - < 49yo 0.1-0.16%
  - 65 and older 5%
  - >80yo 9-17%
- Stroke risk 5x higher than that of the general population[2,3]
  - 4.5% incidence for those not on AC treatment
  - 1.4% incidence for those with adjusted dose VKA
- 25-65% elderly in the real world is not prescribed oral anticoagulant (OAC)
- Under-utilization of oral anticoagulants in older adult patients with Afib for stroke prophylaxis despite introduction of DOACs[4]

[1]Cavallari 2018 [2]Robert-Ebadi 2009 [3]Diez-Villanueva 2019 [4]Alalwan 2017

I. Risk of Thrombosis and Bleeding in the Geriatric Population

GERIATRIC SYNDROMES[5] ASSOCIATED WITH INCREASE RISK OF

CLOTTING

Age

Disability → Sedentary / Immobility

Congestive Heart Failure

Hypertension

Dyslipidemia → Atherosclerosis

Valvular heart disease

Atrial fibrillation

Diabetes

BLEEDING

Falls

Impaired kidney function → anemia

Abnormal liver function → abnormal clotting

Polypharmacy → drug interactions

Dementia

Diminished sense of taste → malnutrition → Osteoporosis

[1]Cavallari 2018,

[5]Health in Aging Foundation 2019

THROMBOTIC VS. BLEEDING RISKS IN ATRIAL FIBRILLATION

CHA_2DS_2-VASc[6]

	Condition	Points (max 9)
C	Congestive Heart Failure	1
H	Hypertension: BP > 140/90	1
A_2	Age 75 or older	2
D	Diabetes Mellitus	1
S_2	Stroke or TIA or TE	2
V	Vascular disease	1
A	Age 65 – 74	1
Sc	Sex: female	1

Abn abnormal
LFTs liver function tests
TTR time in therapeutic range
SCr serum creatinine
INR international normalized ratio
nl normal limit

HASBLED[7]

	Condition	Points (max 9)
H	Hypertension, sBP > 160	1
A	• Abn renal function: SCr 2.26 mg/dL • Abn liver function: Cirrhosis, bilirubin > 2x nl, LFTs > 3x nl	1 1
S	Stroke history	1
B	History of major bleeding or high risk of bleeding	1
L	Labile INR: TTR < 60%	1
E	Elderly: age > 65 y	1
D	• 8 or more alcoholic drinks / week • Medications with bleeding risks	1 1

[6]Lip G 2010

[7]Pisters R 2010

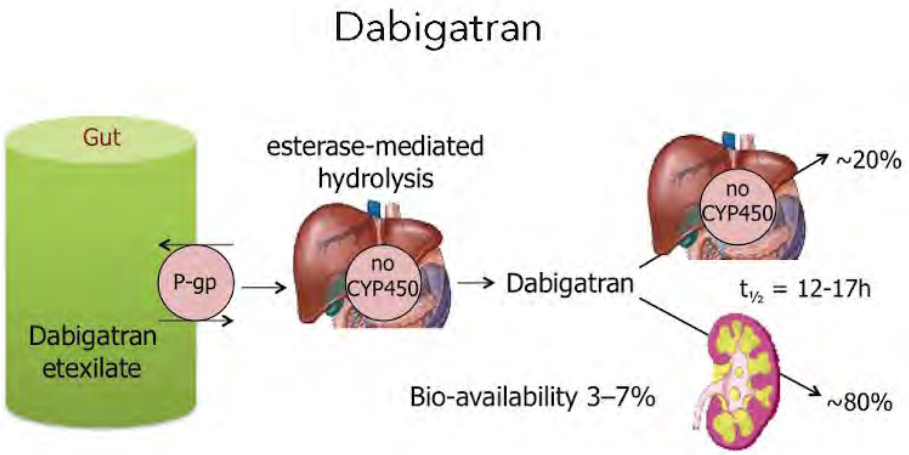
TEST QUESTION 1:

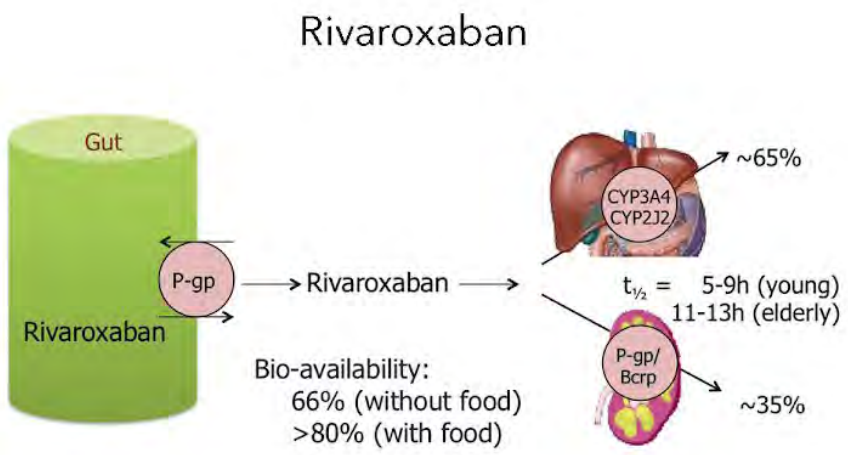
WHAT GERIATRIC SYNDROMES WOULD CONTRIBUTE TO A HIGHER RISK OF BLEEDING WHILE ON ORAL ANTICOAGULANTS?

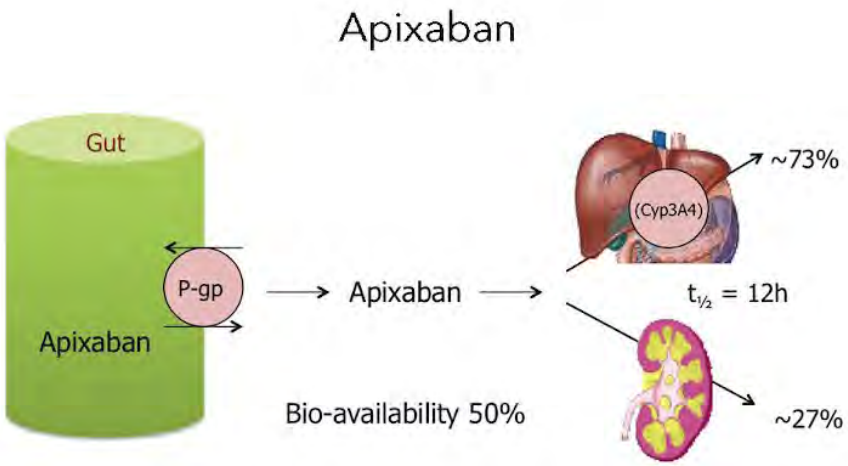
A. Impaired kidney function – Anemia
B. Polypharmacy – Drug Interactions
C. Fall Risk
D. Dementia
E. All of the above

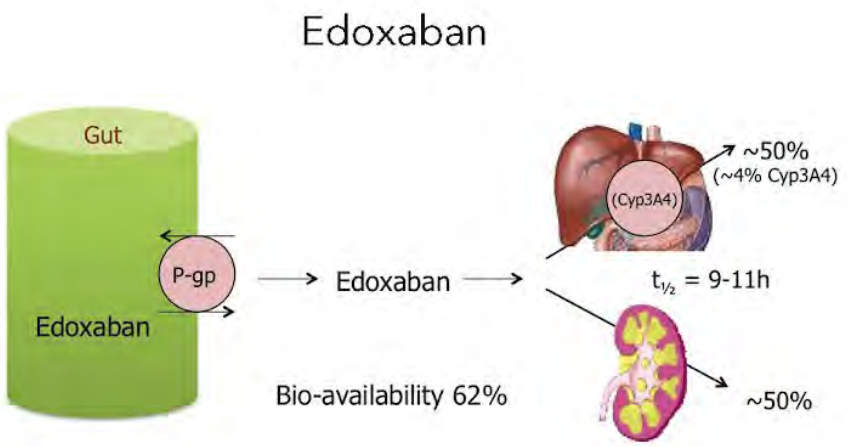
DRUG INTERACTIONS WITH DOACS

([8]Heidbuchel 2015)









Significant Drug Interactions with DOACs[9]

P-glycoprotein Inhibitors

- Amiodarone, dronedarone
- Clarithromycin*, erythromycin
- Conivaptan
- Diltiazem
- Grapefruit*
- Indivinavir, Kaletra®*, nelfinavir*, ritonavir, boosted saquinavir* or tipranavir*
- Itraconale*, ketoconazole*, pozaconazole*,
- Nefazodone*
- Verapamil

*strong inhibitors

[9]Clinical Resource, *Pharmacist's Letter* 2020

3A4 Inhibitors

- Amiodarone, dronedarone
- Aprepitant
- Atazanavir, fosamprenavir, indinavir*, Kaletra®*, nelfinavir*, ritonavir*, boosted saquinavir*or tipranavir*, Viekira Pak*
- Ciprofloxacin
- Clarithromyin*, erythromycin
- Cobicistat
- Conivaptan
- Diltiazem
- Fluconazole, itraconazole*, ketoconazole*, posaconazole*, voriconazole*
- Grapefruit*
- Nefazodone*

TEST QUESTION 2:

WHAT ARE POTENTIAL MECHANISMS OF DRUG INTERACTIONS WITH DOACS?

A. CYP 3A4 inhibition
B. P-glycoprotein inhibition
C. Anti-platelet agents
D. A and B
E. A, B, and C

Patient Case

HPI:

JK is a 80-year-old Hispanic female, recently discharged from admission due to heart failure exacerbation secondary to atrial fibrillation. She received a new prescription for rivaroxaban. Previous warfarin therapy was self-discontinued a year ago due to cumbersome monitoring and bruising from frequent falls.

Vitals:

BP 145/94 mmHg, HR 88 bpm, RR 20

Weight: 88 kg, Height: 5'4"

Echo from hospitalization: EF 25-30%

PMH:

- Hypertension
- Heart failure
- Stroke 2 years ago
- Atrial fibrillation

Medication list: (NKDA)

- Lisinopril 5 mg PO daily
- Metoprolol succinate 50 mg PO daily
- Furosemide 20 mg PO daily
- Amiodarone 200 mg PO BID
- Aspirin 81 mg PO daily
- Atorvastatin 40mg PO daily
- MVI, 1 tab PO daily
- NTG SL 0.4 mg prn chest pain
- Rivaroxaban 20 mg PO daily

Na 140	K 4.5	Cl 105	HCO_3 20	CrCl 49	BUN 20	SCr 1.5	Glu 138	Ca 8.2	Phos 4.3	Mg 2.1
AST 38	ALT 42	Alb 4	Alk Phos 128	Chol 204	Trig 265	HDL 38	LDL 110			
WBC 4.0 x 10^3 cells/mL			RBC 3.8 x 10^6 cells/µL	Hgb 10 g/dL		Hct 30.4%	Plt 200 x 10^9 cells/mL			

WHAT IS JK'S

Thrombotic risk?

CHA_2DS_2-VASc score: 6

Bleeding risk?

HASBLED score: 6

Potential drug interactions?

Amiodarone, aspirin

II. Current Use of Oral Anticoagulants for Cardiac Indications

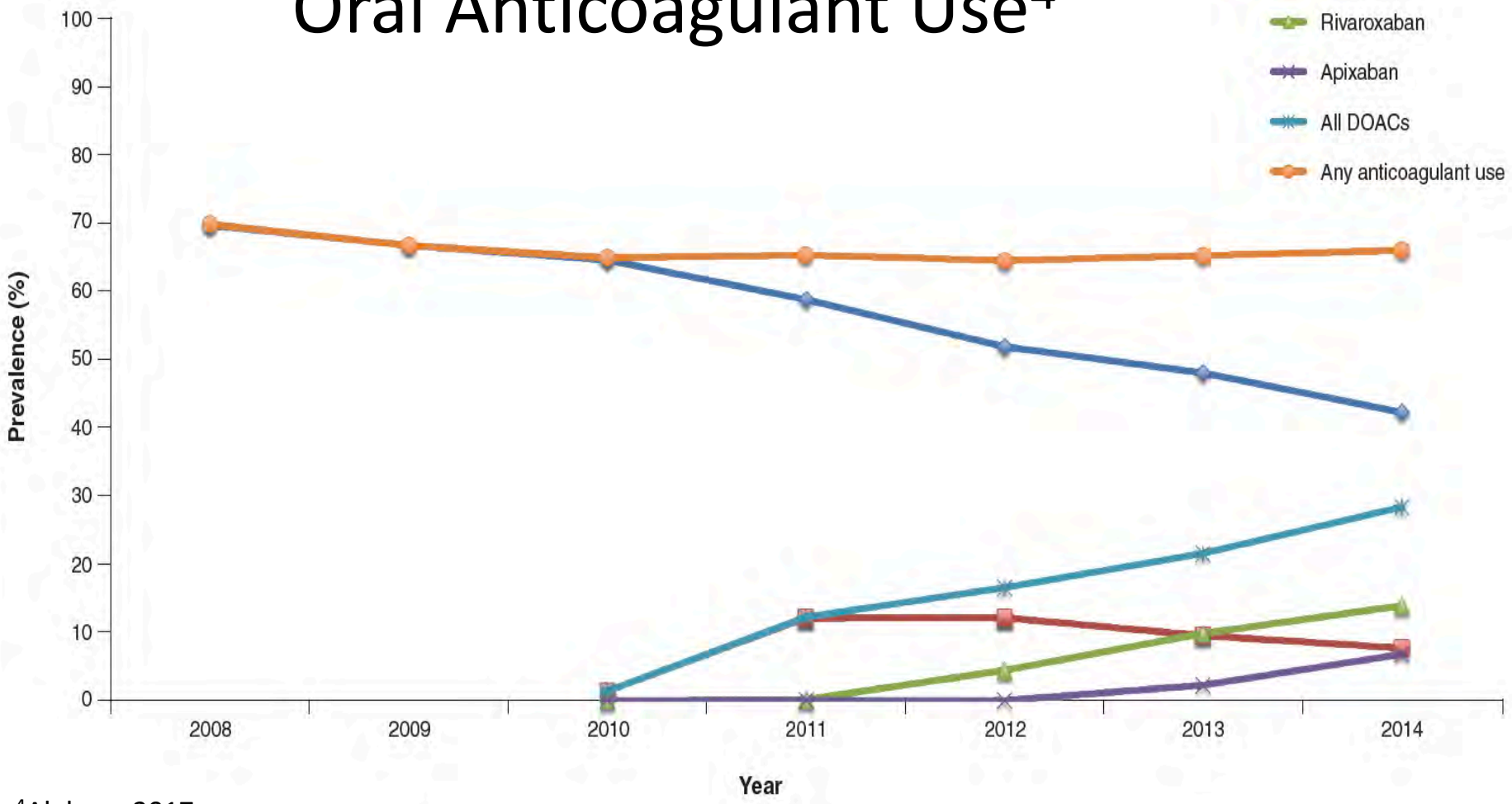
FDA Approved Cardiac Indications for DOACs

Agent	Indication	Dosage	Renal Dose Adjustment
Dabigatran (Pradaxa®)[10]	NVAF to reduce stroke and SE	150 mg BID	CrCl 15-30 mL/min: 75 mg BID
Apixaban (Eliquis®)[11]	NVAF to reduce stroke and SE	5 mg BID	2.5mg BID if 2 or more of: ≥ 80y, ≤ 60kg, SCr ≥ 1.5mg/dL
Edoxaban (Savaysa®)[12]	NVAF to reduce stroke and SE	60 mg daily for CrCl 51-95 mL/min	CrCl 15-50 mL/min: 30 mg daily, not recommended CrCl < 15 or > 95 mL/min
Rivaroxaban (Xarelto®)[13]	NVAF to reduce stroke and SE	20 mg daily with food	CrCl < 50 mL/min: 15mg daily
	CAD or PAD to reduce MACE risk	2.5 mg BID (with aspirin 81 mg daily)	na

NVAF non-valular atrial fibrillation SE systemic embolism CrCl creatinine clearance SCr serum creatinine
CAD coronary artery disease PAD peripheral arterial disease MACE major adverse cardiac events

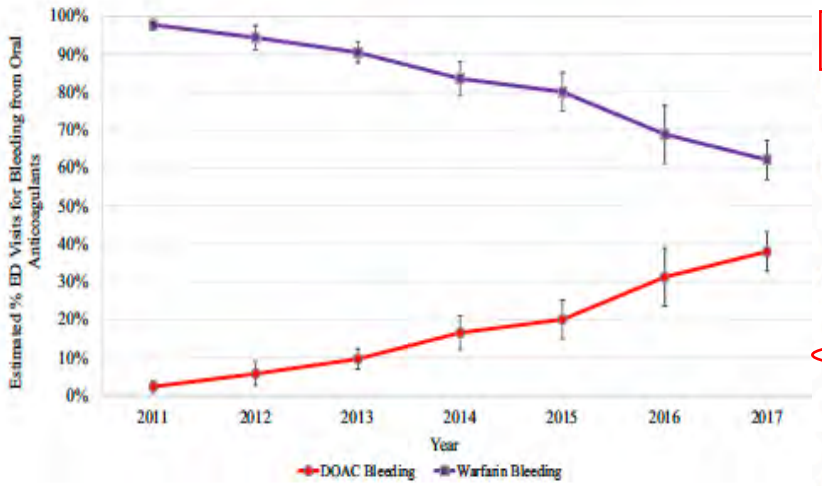
[10-13]Pradaxa, Eliquis, Savaysa, Xarelto (package inserts)

Overall Prevalence of Oral Anticoagulant Use[4]



[4]Alalwan 2017

Emergency Visits for Oral Anticoagulant Bleeding[14]



[14]Geller 2019

Table 1 US Emergency Department Visits for Oral Anticoagulant-Related Bleeding, by Case Characteristics, 2017

Case characteristic	ED visits for bleeding					
	DOAC			Warfarin		
	Cases (no.)	National estimate		Cases (no.)	National estimate	
		%	(95% CI)		%	(95% CI)
Patient age group (years)						
0–17	0	~	~	5	~	~
18–34	18	~	~	39	1.2	(0.6–1.8)
35–49	66	4.5	(3.0–5.9)	103	4.9	(3.9–5.9)
50–64	221	14.4	(12.4–16.5)	367	16.4	(13.7–19.2)
65–79	600	44.7	(40.9–48.5)	863	40.1	(37.3–42.9)
80+	522	35.4	(31.0–39.8)	846	37.2	(33.5–41.0)
Patient sex						
Female	712	48.8	(44.0–53.6)	1019	45.9	(42.9–48.9)
Male	715	51.2	(46.4–56.0)	1204	54.1	(51.1–57.1)
Drug*						
Rivaroxaban	696	49.3	(42.3–56.3)			
Apixaban	617	41.8	(36.5–47.0)			
Dabigatran	113	8.9	(3.7–14.2)			
Bleeding manifestation†						
Central nervous system bleeding‡	79	4.3	(2.3–6.3)	131	5.3	(4.0–6.7)
Pulmonary bleeding	41	2.6	(1.6–3.7)	65	3.1	(1.3–4.9)
Gastrointestinal bleeding	522	40.2	(30.5–50.0)	649	29.7	(23.9–35.6)
Genitourinary bleeding	123	9.1	(5.4–12.8)	189	9.0	(5.8–12.1)
Epistaxis	252	21.2	(13.1–29.3)	390	19.6	(14.6–24.6)
Skin/wound or other minor bleeding	303	17.6	(9.6–25.6)	610	25.8	(18.0–33.5)
Other types of hemorrhage	107	4.9	(2.1–7.7)	189	7.5	(5.5–9.5)
Discharge disposition						
Admitted/transferred to another facility	736	48.9	(39.6–58.1)	1,063	45.5	(37.8–53.1)
Observation admission	31	2.2§	(0.0–4.5)	47	1.9§	(0.4–3.3)
Not hospitalized‖	660	48.9	(40.7–57.0)	1113	52.7	(45.5–59.9)
Total	1427			2223		

GUIDANCE FOR DOAC USE

- Beers Criteria from American Geriatrics Society (AGS)

- National Patient Safety Goals (NPSGs)

2019 AGS Beers Criteria® Regarding DOACs[15]

- Potentially Inappropriate Medications
  - Dabigatran and Rivaroxaban for ≥ 75 yo
- Medications that Should be Avoided or Dosage Reduced with Reduced Kidney Function
  - Dose reduction follows manufacturers' recommendations
  - Dabigatran
    - Adjust dose when CrCl > 30 mL/min in the presence of drug interactions
  - Apixaban
    - Lack of evidence for efficacy and safety when CrCl < 25 mL/min*
  - Dabigatran, edoxaban, rivaroxaban
    - Lack of evidence for efficacy and safety when CrCl < 30 mL/min*

[15]American Geriatrics Society 2019

CrCl Creatinine Clearance

NPSG.03.05.01[16]

New or Amended to include DOACs (Effective July 1st, 2019)

- EP-1: Initiation and maintenance of anticoagulants
- EP-2: Reversal and bleeding events
- EP-3: Perioperative management
- EP-4: Laboratory monitoring to monitor and adjust
- EP-5: Identify, respond to, and report ADEs
- EP-6: Patient and family education

[16]National Patient Safety Goals 2019

TEST QUESTION 3:

JK IS 80 YO, WEIGHS 88 KG. SCR IS 1.5 MG/DL, ESTIMATED CRCL IS 49 ML/MIN. WHAT IS AN APPROPRIATE DOAC DOSE FOR STROKE PROPHYLAXIS?

A. Dabigatran 75 mg BID
B. Apixaban 2.5 mg BID
C. Edoxaban 60 mg daily
D. Rivaroxaban 20 mg daily

III. EFFICACY AND SAFETY OF USE OF DIRECT ORAL ANTICOAGULANTS (DOACS) FOR STROKE PROPHYLAXIS IN OLDER PATIENTS WITH ATRIAL FIBRILLATION

POST-HOC DATA FOR ≥ 75YO FROM MAJOR DOAC TRIALS[1]

Studies	Type	N. patients	Age	Treatment comparison	Follow-up (yrs)	Primary outcome	Results on primary outcome	Major bleeding
RE-LY (17)	Post-hoc from CRT	7.258	≥75 yrs	Dabigatran 110 mg/ 150 mg vs. warfarin	Median 2.0	Stroke/SEE	D110 vs. W: HR 0.88 (0.66-1.17) D150 vs. W: HR 0.67 (0.49-0.90)	D110 4.4% yr / D150 5.1% yr vs. W 4.4% yr D110 vs. W: *P*=0.89 D150 vs. W: *P*=0.07
ROCKET AF (18)	Post-hoc from CRT	6.229	≥75 yrs	Rivaroxaban 20 mg vs. warfarin	2	Stroke/SEE	HR 0.80 (0.63-1.02)	4.9% yr vs. 4.4 % yr HR 1.11 (0.92-1.34)
ARISTOTLE (19)	Post-hoc from CRT	5.678	≥75 yrs	Apixaban 5 mg vs. warfarin	1.8	Stroke/SEE	HR 0.71 (0.53-0.95)	3.3%yr vs. 5.2 %yr *P*<0.05
ENGAGE AF (20)	Post-hoc from CRT	8.474	≥75 yrs	Edoxaban 60 mg vs. warfarin	2.8	Stroke/SEE	HR 0.83 (0.66-1.04)	4.0% yr vs. 4.8% yr *P*<0.05

[1]Cavallari 2018

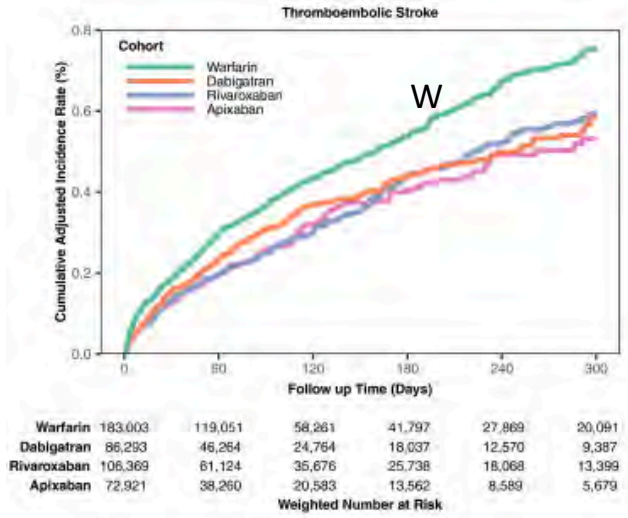
Comparative Stroke, Bleeding, and Mortality Risks in Older Medicare Patients Treated with Oral Anticoagulants for Nonvalvular Atrial Fibrillation[17]

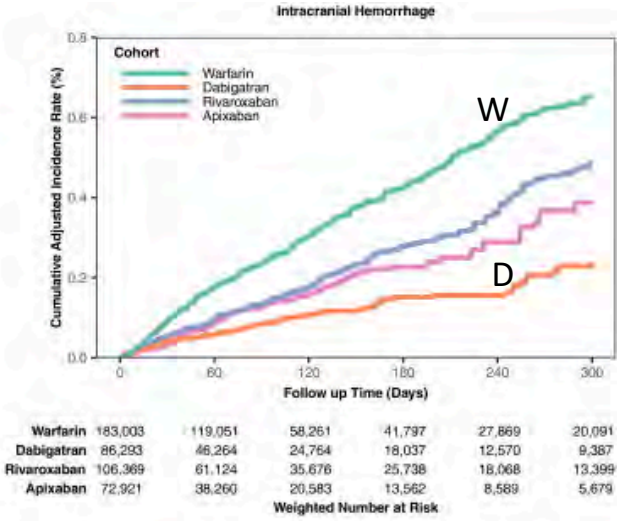
- Retrospective study on Medicare patients initiated on OACs
- October 2010 to September 2015, N=183,318 (dabigatran 86k, rivaroxaban 106k, apixaban 73k)
- Propensity score-adjusted Cox proportional hazards regression → HR and 95% CI for thromboembolic stroke, intracranial hemorrhage, major extracranial bleeding, all cause mortality
- Compare each DOAC with warfarin, and with each other DOAC

[17]Graham 2019

EFFICACY AND SAFETY OUTCOMES IN MEDICARE PATIENTS[17]

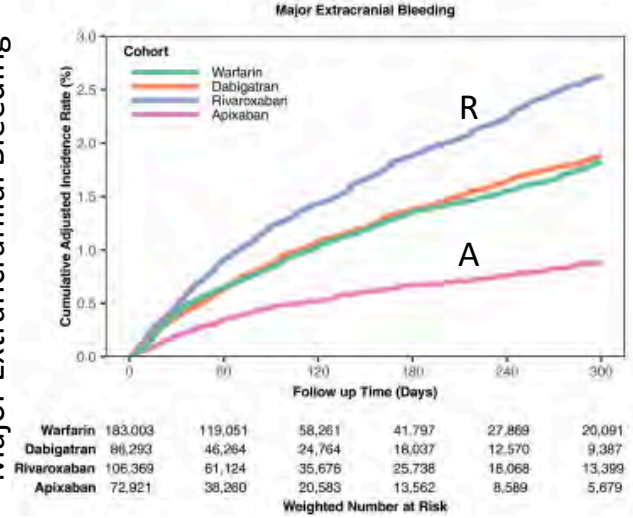
Thromboembolic Risk

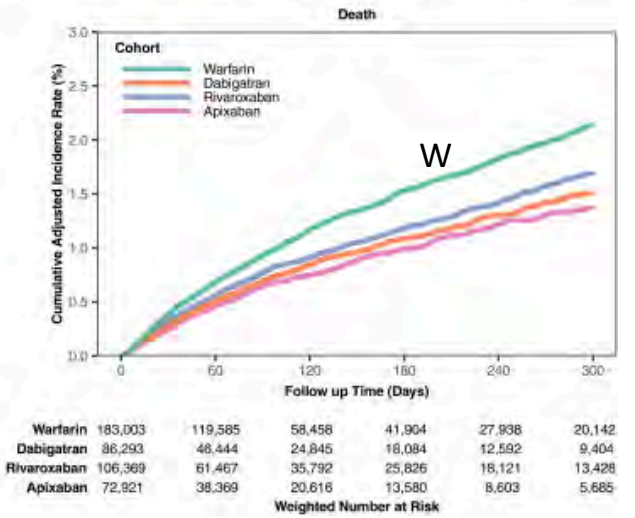




Intracranial Hemorrhage

Major Extrancraniial Bleeding

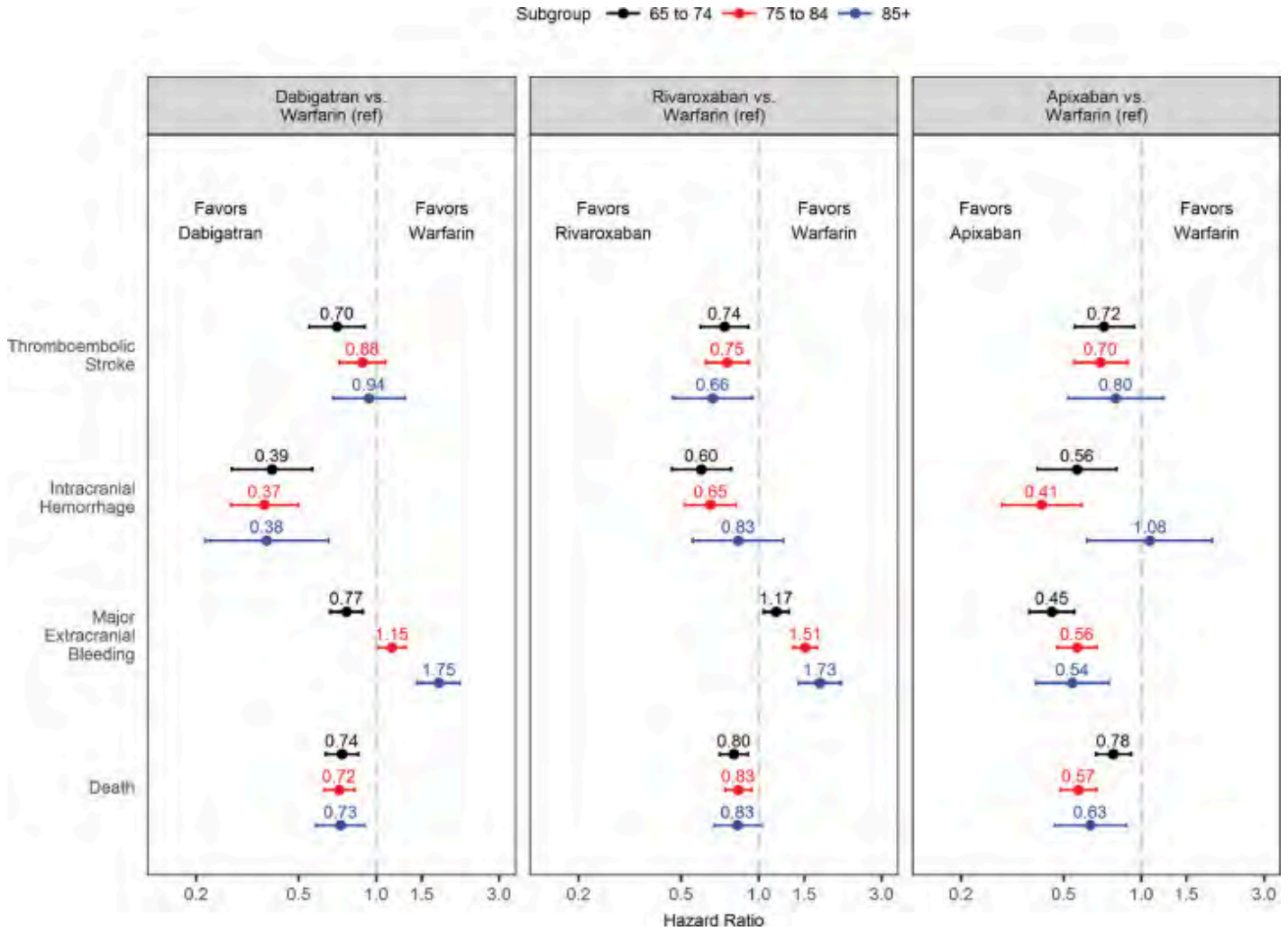




Death

[17]Graham 2019

SUB-ANALYSIS OF MEDICARE PATIENTS BASED ON AGE GROUP[17]



[17]Graham 2019

IV. Use of DOACs in Patients with Kidney Disease

CREATININE CLEARANCE OF DOACS IN CKD[8]

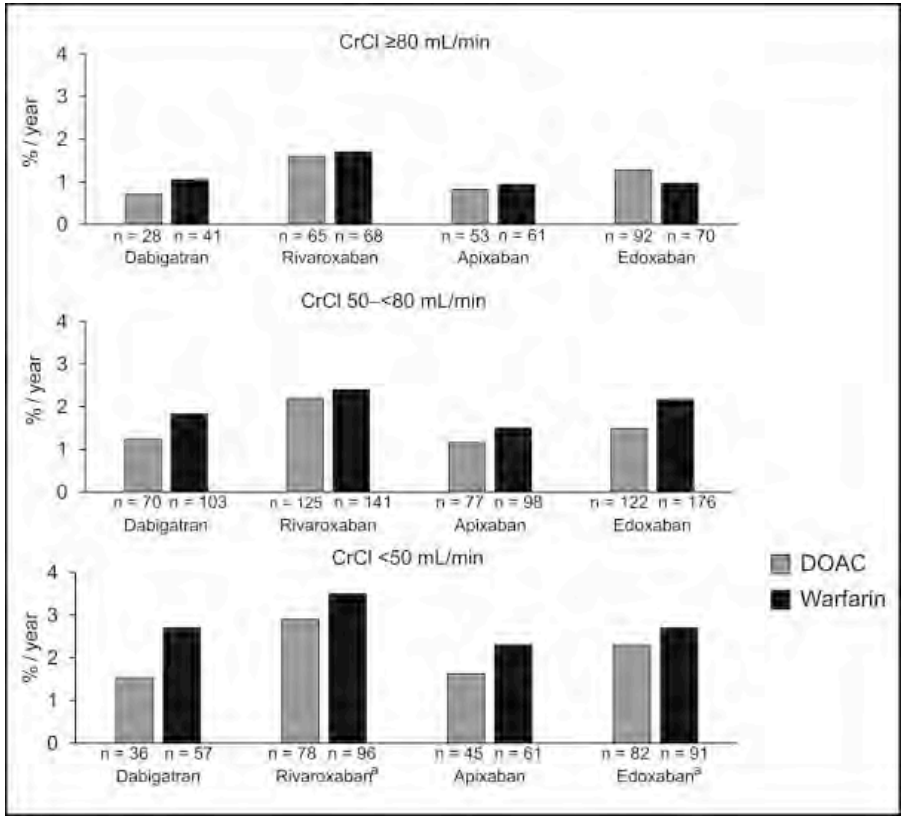
	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
CrCl >80 mL/min	12–17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)
CrCl 50–80 mL/min CKD Stages I and II	~17 h[122] (+50%)	~14.6 h[123] (+16%)	~8.6 h[124] (+32%)[SmPC]	~8.7 h[125] (+44%)[126]
CrCl 30–50 mL/min CKD Stage III	~19 h[122] (+320%)	~17.6 h (+29%)	~9.4 h[124] (+74%)[SmPC]	~9.0 h (+52%)[126]
CrCl 15–30 mL/min CKD Stage IV	~28 h[122] (+530%)	~17.3 h (+44%)	~16.9 h[124] (72%)[SmPC]	~9.5 h (+64%)[126]
CrCl ≤ 15 mL/min CKD Stage V; off-dialysis	No data	– (+36%)	– (+93%)[SmPC]	– (+70%)[127]

CKD, chronic kidney disease; CrCl, creatinine clearance.

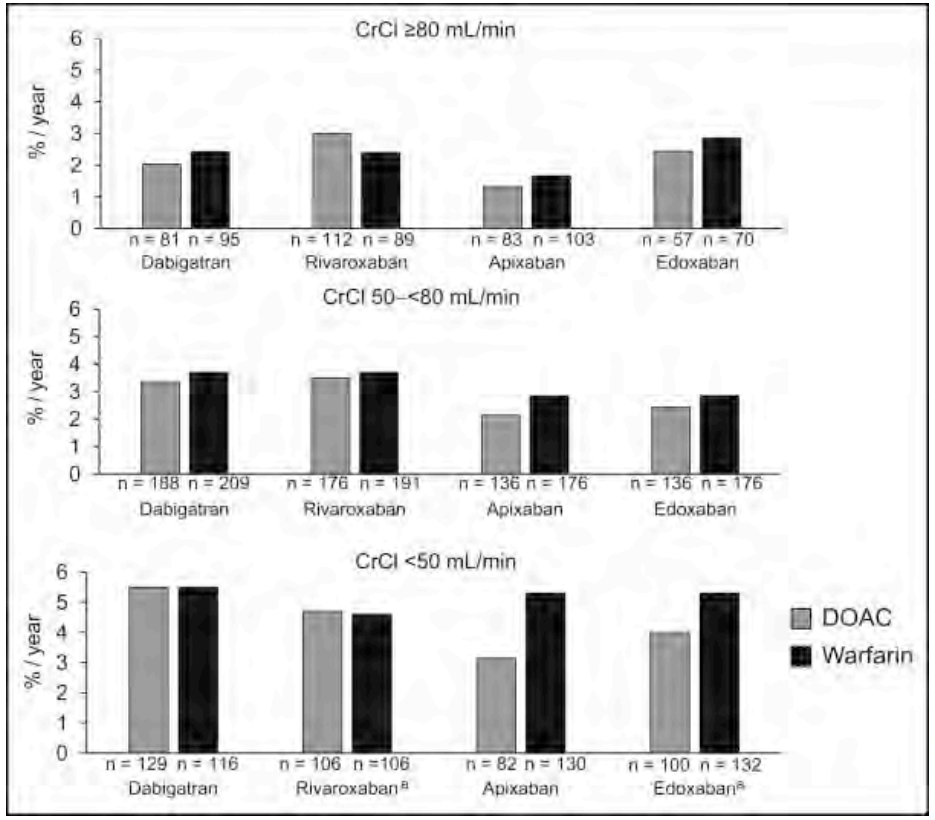
([8]Heidbuchel 2015)

Renal Function Considerations for Stroke Prevention in Atrial Fibrillation[18]

THROMBOTIC RISK

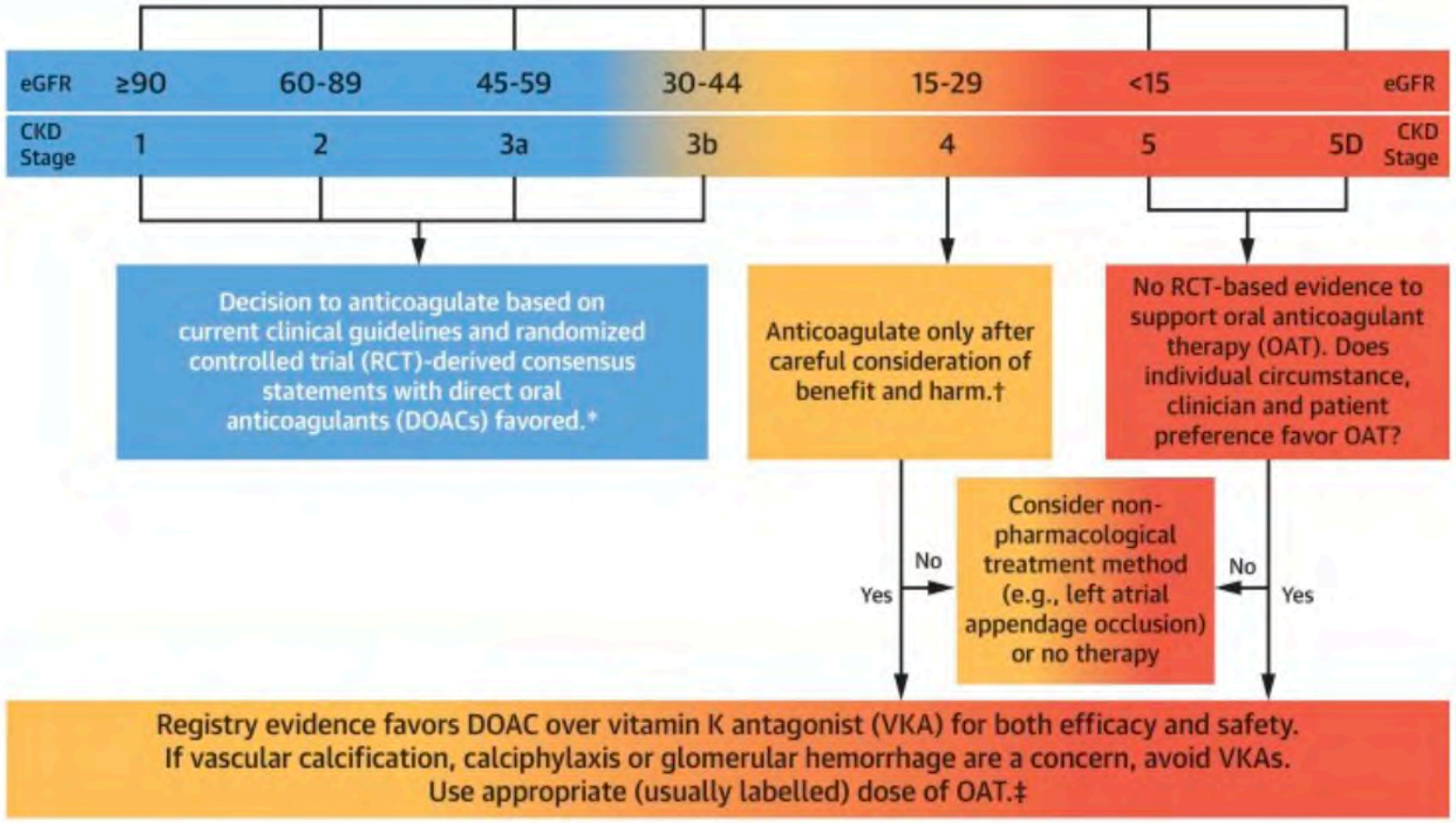


BLEEDING RISK



[18]Fanikos 2017

Proposed Approach of Anticoagulation in CKD and Atrial Fibrillation[19]



[19]Kumar 2019

V. Peri-procedure Interruption of DOAC therapy

A. CARDIOVERSION AND ABLATION

B. OTHER PROCEDURES

PREVENTION OF THROMBOEMBOLISM (TE) FOR CARDIOVERSION

- Current guidelines: therapeutic anticoagulation for at least 3 weeks before and at least 4 weeks after cardioversion[20] in patients with atrial fibrillation
- More TE with INR 1.5-2.4 (0.93%) vs INR $\geq$ 2.5 (0%), p=0.012[21]
- Rivaroxaban, edoxaban, and apixaban shown to have no difference from warfarin +/- UFH or LMWH in TE or major bleeding[22-24]
- Advantages of DOACs over warfarin
  - Faster therapeutic anticoagulation → reduced time to cardioversion
  - Avoidance of LMWH or UFH bridging
  - Improved patient satisfaction

UFH unfractionated heparin LMWH low molecular weight heparin

[20]2019 AHA/ACC/HRS Afib Guidelines [21]Gallagher (2002) [22]X-VeRT: Cappato 2014 [23]ENSURE-AF: Goette 2016. [24]EMANATE: Ezekowitz 2018

Prevention of thromboembolism (TE) and Bleeding for Ablation[25]

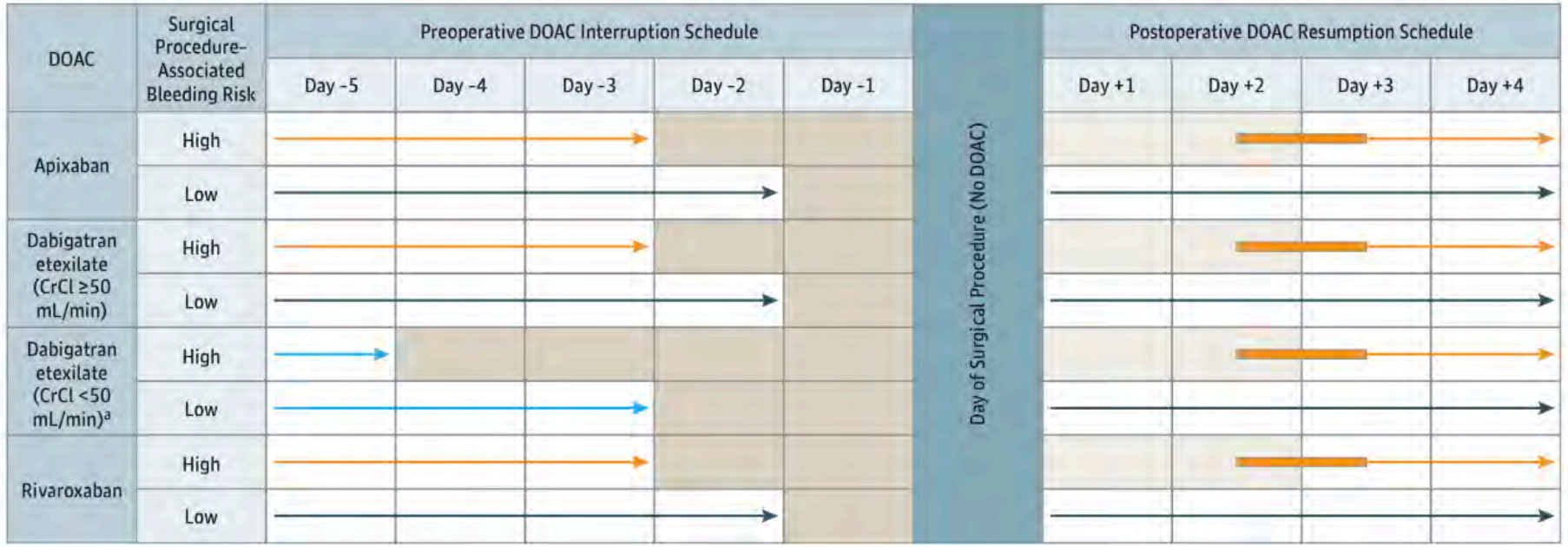
- Current guidelines recommend 3 weeks of therapeutic anticoagulation or TEE to exclude presence of left atrial thrombus
- Pre-ablation
  - Warfarin or dabigatran or rivaroxaban: no interruption recommended
  - Apixaban or edoxaban: no interruption reasonable
  - Dabigatran, rivaroxaban, apixaban showed similar TE rates compared to warfarin[26-28]
- Post-ablation
  - Oral anticoagulants recommended for at least 2 months after procedure

[25]2017 HRS/EHRA/ECAS [26]RE-CIRCUIT: Calkins 2017 [27] VENTURE-AF:Cappato 2015 [28]Kuwahara 2016

PAUSE: Perioperative Anticoagulation Use for Surgery Evaluation[29]

- 23 clinical centers in Canada, US, Europe; Aug 2014 – July 2018
- N=3007 patients with AFib, avg age 73 years, elective surgery, 3 cohorts
- Standardized perioperative interruption and resumption schedule based on DOAC pharmacokinetic properties, procedure-associated bleeding risk and creatinine clearance levels

Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol



[29]Douketis 2019

PAUSE
RESULTS AND CONCLUSIONS[29]

Standardized perioperative without heparin bridging or coagulation testing

- < 2% major bleeding
- < 1% arterial thromboembolism
- < 5% 30d post-op major bleeding

Table 3. Primary Study Outcomes

Outcome	DOAC Cohort		
	Apixaban (n = 1257)	Dabigatran Etexilate (n = 668)	Rivaroxaban (n = 1082)
Primary			
Major bleeding[a]			
No. (%)	17 (1.35)	6 (0.90)	20 (1.85)
1-Sided 95% CI	0-2.00	0-1.73	0-2.65
P value	.051	.02	.36
Arterial thromboembolism[b,c]			
No. (%)	2 (0.16)	4 (0.60)	4 (0.37)
1-Sided 95% CI	0-0.48	0-1.33	0-0.82
P value	<.001	.03	.001
Procedure-Associated Bleeding Risk	**Apixaban Cohort (n = 1257)**	**Dabigatran Etexilate Cohort (n = 668)**	**Rivaroxaban Cohort (n = 1082)**
Low bleeding risk			
No. (%)	851 (67.7)	440 (65.9)	709 (65.5)
30-d Postoperative rate of major bleeding, % (95% CI)	0.59 (0-1.20)	0.91 (0-2.01)	1.27 (0-2.17)
High bleeding risk			
No. (%)	406 (32.3)	228 (34.1)	373 (34.5)
30-d Postoperative rate of major bleeding, % (95% CI)	2.96 (0-4.68)	0.88 (0-2.62)	2.95 (0-4.76)

[29]Douketis 2019

VI. REVERSAL OF DOAC THERAPY

JK: BLEEDING COMPLAINTS

- Rivaroxaban 20mg daily, last dose taken 12 hours ago
- Patient started taking naproxen 500mg BID for her arthritis pain
- Recent complaints include stomach pain and tarry stool
- Patient admitted after feeling dizzy and fell, Hgb now at 8 and SCr 1.8

Do we give andexanet alfa to the patient?

- Factors favoring reversal
- Factors favoring supportive measure

Reversal of Direct Oral Anticoagulants: Guidance from the Anticoagulation Forum ([30]Cuker 2019)

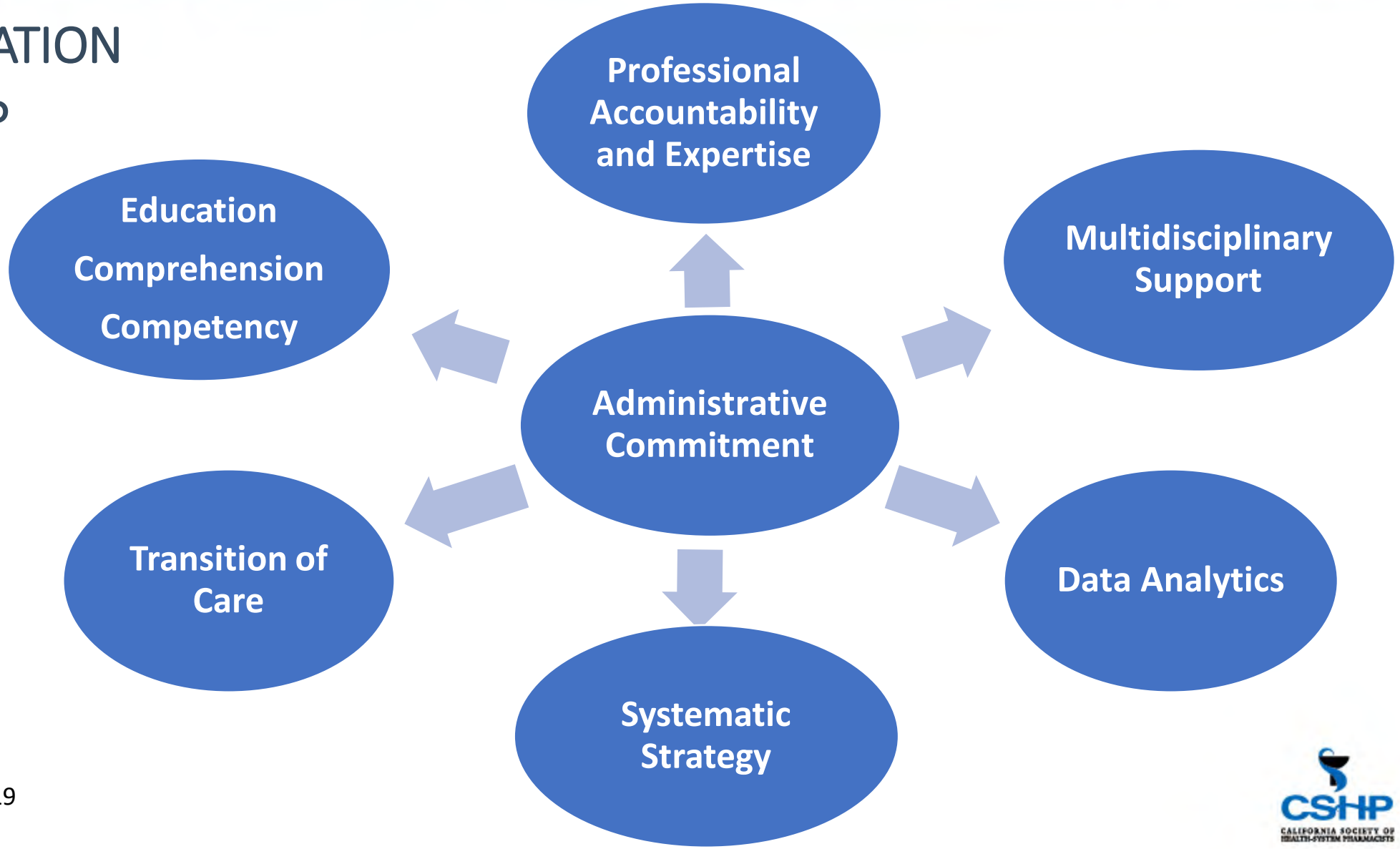
- Patient on DOAC, not bleeding, invasive procedure cannot be delayed and cannot be performed safely while still anticoagulated
- When bleeding is life-threatening, in critical organ, or major bleeding not responding to maximal supportive measures
- How should reversal agents be used? Major bleeding…

Dabigatran-associated: Idarucizumab	Anti-Xa agent-associated: Andexanet alfa	
5 gm IV	Rivaroxaban dose ≤ 10 mg Apixaban ≤ 5mg	400 mg IV blous at 30 mg/min, then CIV at 4 mg/min, up to 120 minutes
	Rivaroxaban dose > 10mg or unknown Apixiban > 5mg or unknown	800 mg IV bolus at 30 mg/min, then CIV at 8 mg/min, up to 120 minutes
If Idarucizumab not available, APCC 50 units/kg IV	If adnexanet not available, 4-factor PCC 2000 units	

TEST QUESTION 4:
WHICH SCENARIO(S) MOST FAVOR USING REVERSAL AGENT FOR DOACS?

A. 4 weeks before a colonoscopy
B. After a motor vehicle accident and there is internal bleeding
C. When catheter ablation is scheduled tomorrow morning and the last rivaroxaban dose is taken last night
D. B and C

ANTICOAGULATION STEWARDSHIP PROGRAM[31]



[31]Anticoagulation Forum 2019

HAVE WE ACHIEVED THE NPSGs[16] FOR JK?

- **EP-1: Initiation and maintenance of anticoagulants**
- **EP-2: Reversal and bleeding events**
- **EP-3: Perioperative management**
- **EP-4: Laboratory monitoring to monitor and adjust** — **CBC w/diff, SCr & LFTs at BL and +/- every 6 mos**
- **EP-5: Identify, respond to, and report ADEs**
- **EP-6: Patient and family education** — **Care Transitions, followup with patient, family and caretaker**

[16]National Patient Safety Goals 2019

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SESSION CODE: