Antithrombotic Update

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PRESENTER DISCLOSURE

- DR. ROBERT E. ARIANO
- RELATIONSHIPS WITH RELATED COMMERCIAL INTERESTS:
  - GRANTS/RESEARCH SUPPORT: NONE
  - SPEAKERS BUREAU/HONORARIA: NONE
  - CONSULTING FEES: NONE

The history of oral anticoagulants

The discovery of warfarin is 79 years old today!
In recent years drug manufacturers were challenged with producing a new oral anticoagulant that:

- ✓ Prevented clotting in a wide variety of clinical disorders
- ✓ Resulted in minimal bleeding compared to warfarin
- ✓ Wasn’t affected by food or drug interactions
- ✓ One dose fits all
- ✓ Didn’t have to be monitored

Dabigatran - June 2008

Rivaroxaban – Sept. 2008

Edoxaban – November 2016

Apixaban - Dec 2011

The Latest in Direct Oral Anticoagulants (DOAC's)

All indicated in Canada for DVT/PE treatment and NVAF

Overview:

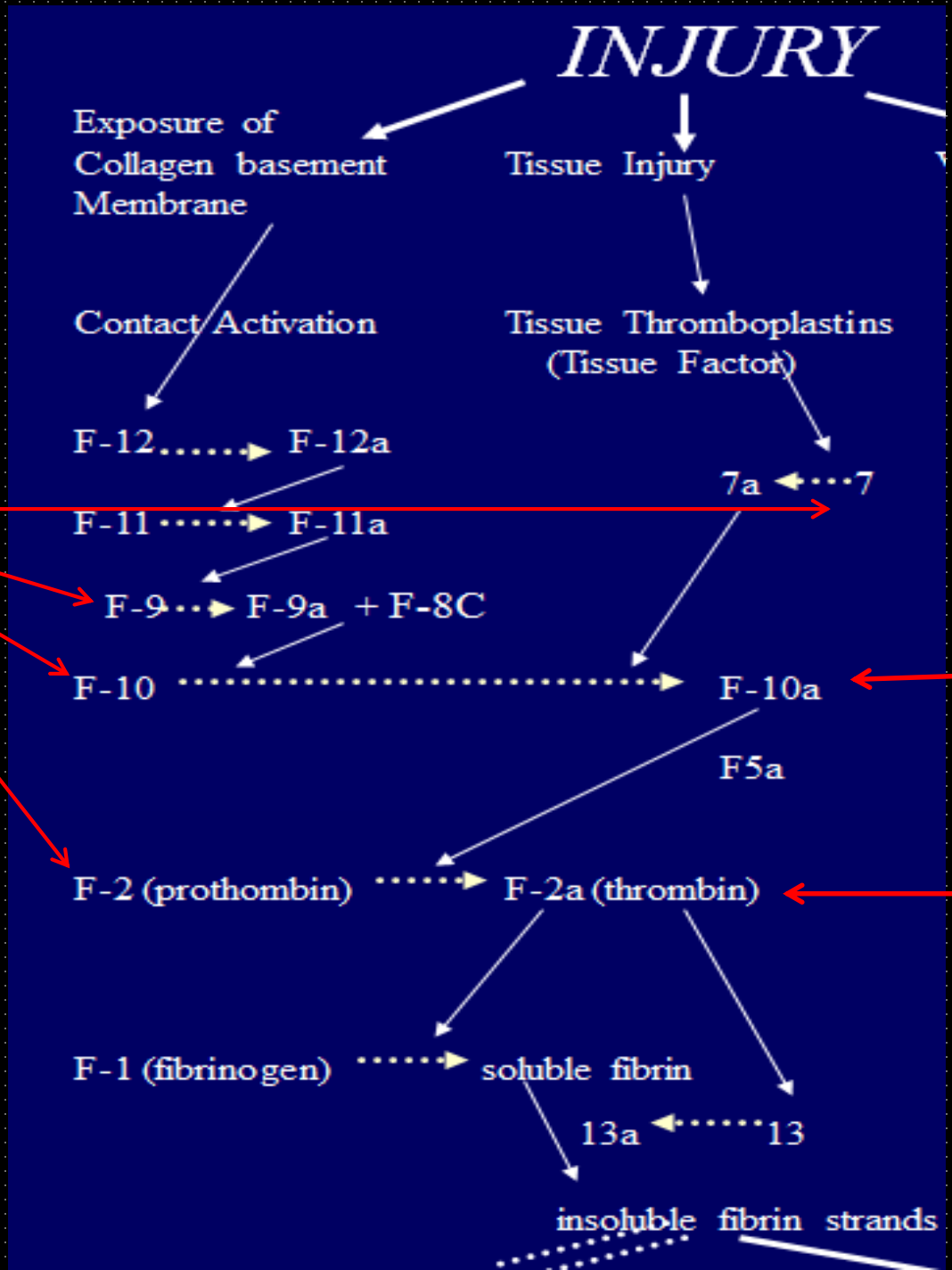
Topics reviewed…

1. The Pharmacology of DOAC's
2. Selection of antithrombotic therapy for your patient
3. Combinations of antiplatelets with anticoagulants
4. Patients going for surgery – what to do?
5. Transitioning between anticoagulant agents

The Pharmacology of DOAC's

Pharmacology of Oral Anticoagulants

Warfarin decreases Synthesis of



Rivaroxaban, Apixaban, Edoxaban direct inhibition

Dabigatran direct inhibition

Comparative pharmacology of the DOACs

Drug	Dabigatran (Pradaxa)
T ½	12 – 17 hours
Dosing	BID
Target	Factor IIa
Creatinine clearance mL/min/1.73m2	No if < 30 80% renal excretion
Drug interactions	Inhibitors/ inducers of P-gP

Comparative pharmacology of the DOACs

Drug	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)
T ½	12 – 17 hours	5 – 13 hours
Dosing	BID	Once daily * with food!
Target	Factor IIa	Factor Xa
Creatinine clearance mL/min/1.73m2	No if < 30 80% renal excretion	No if < 15 36% renal excretion unchanged
Drug interactions	Inhibitors/ inducers of P-gP	Inhibitors/ inducers of P-gP & CYP-3A4

Comparative pharmacology of the DOACs

Drug	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
T ½	12 – 17 hours	5 – 13 hours	9 – 14 hours
Dosing	BID	Once daily * with food!	BID
Target	Factor IIa	Factor Xa	Factor Xa
Creatinine clearance mL/min/1.73m2	No if < 30 80% renal excretion	No if < 15 36% renal excretion unchanged	No if <25 27% renal excretion
Drug interactions	Inhibitors/ inducers of P-gP	Inhibitors/ inducers of P-gP & CYP-3A4	Inhibitors/ inducers of P-gP & CYP-3A4

Comparative pharmacology of the DOACs

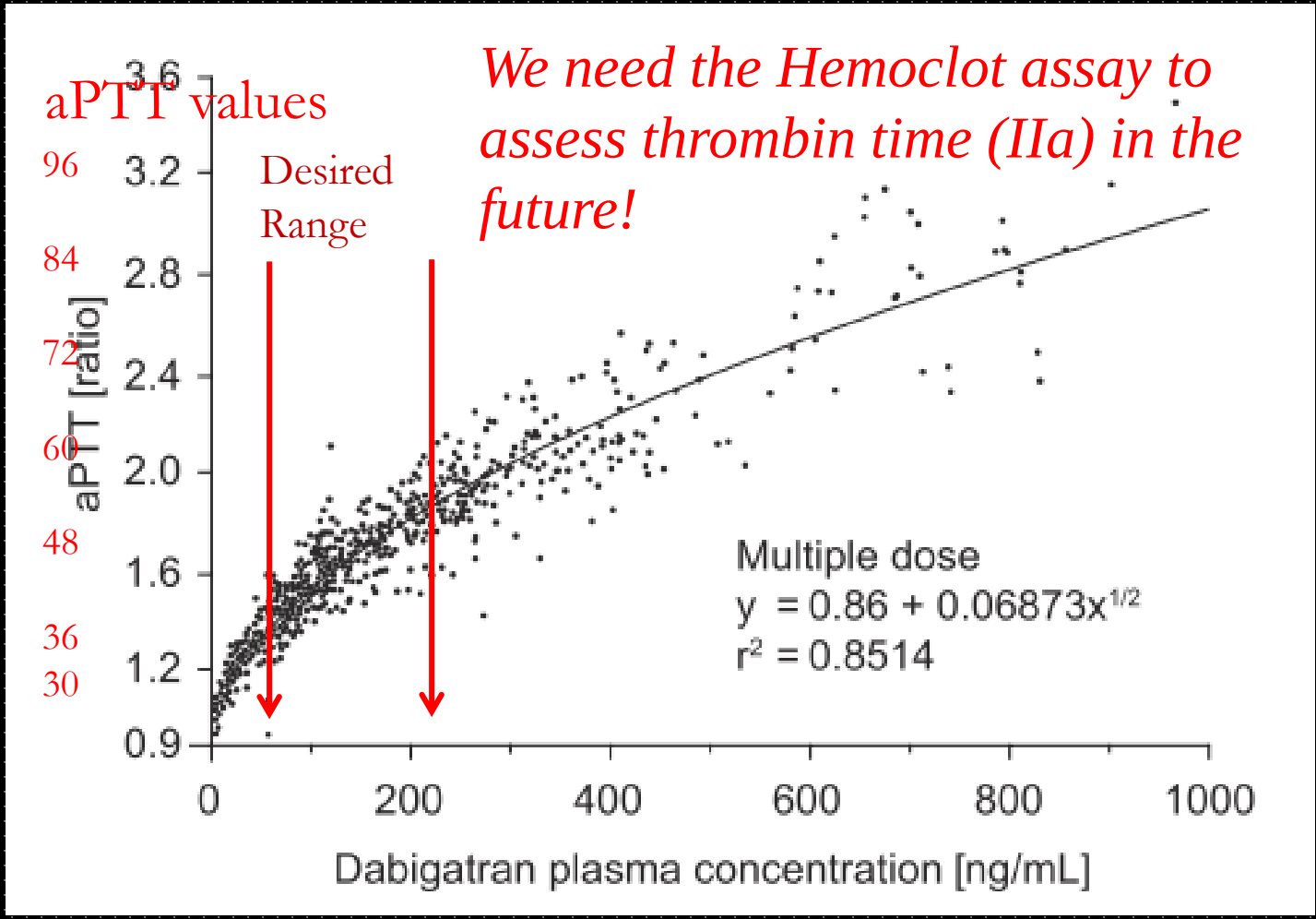
Drug	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)	Edoxaban (Lixiana)
T ½	12 – 17 hours	5 – 13 hours	9 – 14 hours	10 – 14 hours
Dosing	BID	Once daily * with food!	BID	Once daily
Target	Factor IIa	Factor Xa	Factor Xa	Factor Xa
Creatinine clearance mL/min/1.73m2	No if < 30 80% renal excretion	No if < 15 36% renal excretion unchanged	No if <25 27% renal excretion	No if < 15. 50% renal excretion
Drug interactions	Inhibitors/ inducers of P-gP	Inhibitors/ inducers of P-gP & CYP-3A4	Inhibitors/ inducers of P-gP & CYP-3A4	Inhibitors/ inducers of P-gP

Can we use standard coagulation monitoring tests for DOACs?

aPTT's ?

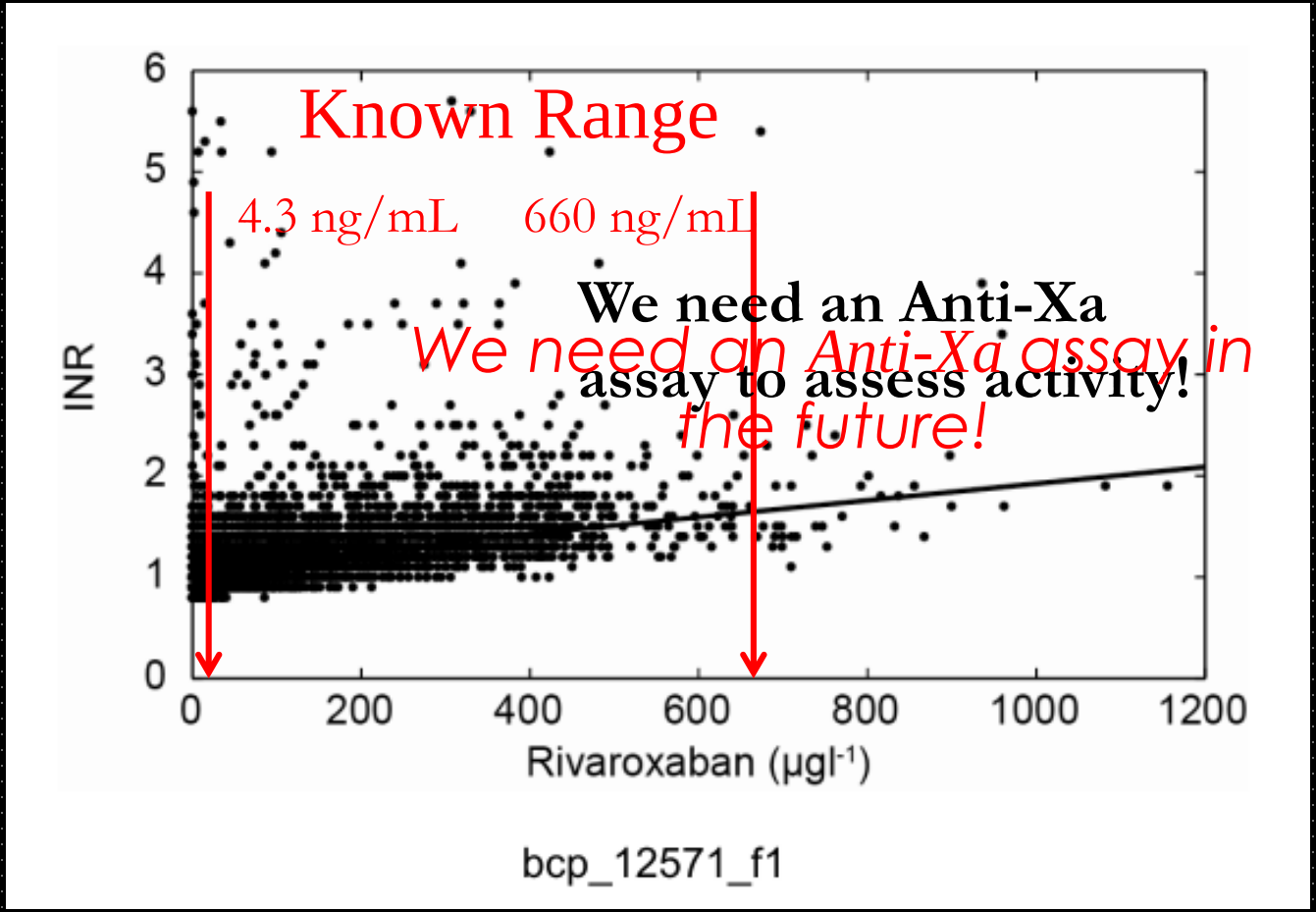
INR's ?

There is a non-linear relationship between aPTT and [Dabi]



Joanne van Ryn et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor. Thromb Haemost 2010; 103: 1116–1127

There is a very poor relationship between [Rivaroxaban] and INR's



S-Franckart et al. Performance of coagulation tests in patients on therapeutic doses of rivaroxaban. Thromb Haemost 2014; 111: 1133–1140

Case study in selection of Antithrombotics

A.R. is 74 year old male admitted with new onset of shortness of breath; but no chest pain.

He had taken a single 325 mg dose of ASA and the pain gradually resolved over the next few hours. The family decided to bring him in to emergency.

No ST changes on 12-Lead EKG, however atrial fibrillation (AF) was noted with rapid ventricular response (RVR); and biochemically he was troponin-negative. Mild mitral stenosis was detected on TTE.

PMHx: significant for hypothyroidism, dyslipidemia, and ex-smoker, remote diverticular disease.

Meds Reconciliation: Levothyroxine 75 mcg daily, Atorvastatin 10 mg daily

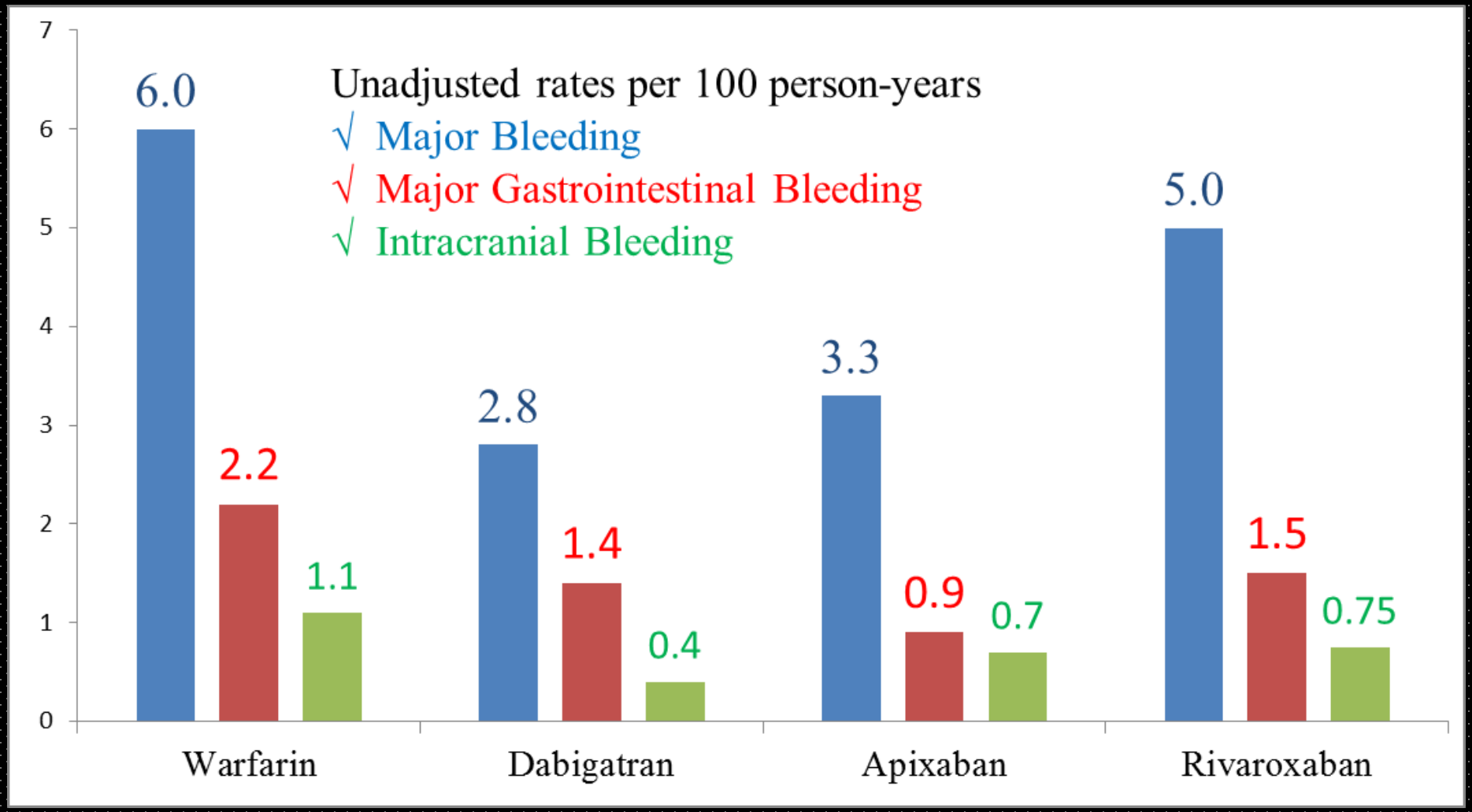
Atrial fibrillation (AF) is an independent risk factor for stroke & systemic embolism and death

Is he a candidate for warfarin or a DOAC?

Overall DOACs' have been shown to be:

- ✓ as effective as warfarin for stroke prevention in patients with AF and are associated with
- ✓ less intracranial hemorrhage
- ✓ reduced all-cause mortality

Comparative major bleeding rates from *Real-World* data



Xantus trial – RIVA Prospective Data:

Major bleeding

2.1 (1.8 – 2.5)

Major GI

0.9 (0.6 – 1.1)

Intracranial

0.4 (0.3 – 0.6)

Adeboyeje-G, Major bleeding risk during anticoagulation with {DOAC's vs Warfarin} in NVAF; J Manag Care Spec Pharm 2017; 23: 968-78

Tailoring Antithrombotic therapy

With all the DOAC's exhibiting similar clinical benefits over warfarin; selection of an agent can be tailored to your patient's unique characteristics!

** Patient characteristics & selection of the best agent for your patient

Characteristic:	Preferred DOAC:
Increased risk of GI bleeding	Apixaban
Increased bleeding risk (overall)	Apixaban, Dabigatran
Renal Impairment	Apixaban, Rivaroxaban
Adherence	Rivaroxaban once daily
Drug interactions	Dabigatran (fewest)

Additionally:

Dabigatran is associated with more dyspepsia & gastritis; and discontinuations than any other DOAC

It does however have a reversal agent; which may make it a better option for patients at high risk of bleeding

Going back to A.R., and their Mitral Stenosis!
Would he be considered a case of AF with 'Valvular Heart Disease'?

You've heard the Advertisement:

{*Insert DOAC name here*} is used to decrease the risk of stroke and systemic embolism in individuals with ***nonvalvular*** atrial fibrillation.

DOAC's in 'valvular heart disease'; there are some exceptions!

Various types of valvular heart disease	Dabigatran	Rivaroxaban	Apixaban
Aortic Regurgitation	Yes	Yes	Yes
Aortic Stenosis	Yes	Yes	Yes
Mitral Regurgitation	Yes	Yes	Yes
Mitral Stenosis * mod-sev	No	No	No
Mitral Valve Repair	No	No	No
Rheumatic Valve Disease	No	No	No
Bioprosthetic Heart Valve	No	No	No
Mechanical Heart Valve	No	No	No
Decompensated Valvular heart disease	No	No	No

If A.R. went on to receive a Mechanical Mitral Valve in the future, would he still be a candidate for a DOAC?

Avoid Any off-label use of a DOAC!

The heart.org release

September 26, 2012

Ottawa, ON - Primary-care practitioners may be putting the lives of patients with prosthetic heart valves at risk by switching their anticoagulation from warfarin to newer agents such as dabigatran (Pradaxa, Boehringer Ingelheim), say Canadian researchers.

Dr Joel Price (University of Ottawa Heart Institute, ON) and colleagues report the cases of two women who had undergone valve replacement some years before and had been faring well on warfarin; they were switched to dabigatran and subsequently suffered valve thromboses.

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2013; 369: 1206-14

ORIGINAL ARTICLE

Dabigatran versus Warfarin in Patients with Mechanical Heart Valves

John W. Eikelboom, M.D., Stuart J. Connolly, M.D., Martina Brueckmann, M.D.,

released Sept.26th, 2013

CONCLUSIONS

The use of dabigatran in patients with mechanical heart valves was associated with increased rates of thromboembolic and bleeding complications, as compared with warfarin, thus showing no benefit and an excess risk. (Funded by Boehringer Ingelheim; ClinicalTrials.gov numbers, NCT01452347 and NCT01505881.)

They postulated that release of the Tissue Factor from damaged tissue and contact pathway activation by exposure of blood to artificial surfaces of valve leaflets and sewing ring generated thrombin excessively!!

A quick review of warnings with DOAC's for AF

1. Platelet count < 50,000
2. Concurrent neuraxial anesthesia – treat as a high-bleed risk
3. Severe renal dysfunction - this may be rapidly changing
4. Cancer-related thrombosis - LMWH's are still treatments of choice
5. Inherited and acquired thrombophilia – some negative outcomes have been noted!
6. Valvular heart disease - exceptions as noted earlier
7. Going for major surgery in < 2 days
8. Extremes of body weight < 50kg & > 120kg

Who should continue to take warfarin:

- ❑ patients with severe renal dysfunction (CrCl < 15 mL/min/72kg)
- ❑ those with drug interactions to DOAC's!
- ❑ history of peptic ulcer bleeding or GI bleeding
- ❑ any thrombotic condition for which there is NO clinical supporting evidence with a DOAC

Combinations of antiplatelets with anticoagulants

N.S. a Case Study of Combinations

N.S. is an 82 year old female who presents with SOB, fatigue, ‘racing heart’ which started ~ 2 days earlier

EKG demonstrates AF with rapid ventricular response (RVR) of 120

PMHx: was significant for an NSTEMI 2 months earlier treated with 2xDES, but she also has HBP (140/85), Dyslipidemia, & OA

Med Rec: metoprolol 50 mg BID, ramipril 10mg daily, atorvastatin 40 mg daily, and Ticagrelor 90 mg BID x 12mo, and ASA 81mg for life

New onset AF mandates a CHA2DS2-VASc assessment

	Points
C: Congestive Heart Failure	1
H: Hypertension	1
A: Age ≥75 years	2
D: Diabetes	1
S: Previous stroke/transient ischemic attack/systemic embolus	2
V: Vascular disease (prior myocardial infarction, angina, coronary artery bypass grafting, aortic plaque)	1
A: Age 65–74 years	1
Sc: Sex category (female)	1

Total Points
= Stroke Rate (%/year)

5 = 6.7 %

January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guidelines for the management of patients with atrial fibrillation. J Am Coll Cardiol 2014;64:e1-76.

N.S.'s HAS-BLED BLEEDING SCORE

(A SIMPLIFIED METHOD FOR ASSESSING BLEEDING RISK)

Letter	Clinical Characteristic*	Points Awarded: Score
H	Hypertension (uncontrolled, SBP>160)	1
A	Abnormal renal (CrCl<30) or Abnormal liver function	1 each
S	Stroke history	1
B	Bleeding history (or anemia)	1
L	Labile INRs (< 60% of the time therapeutic)	1
E	Elderly (Age > 65 years of age)	1
D	Drugs (antiplatelet, NSAIDs) or Excessive Alcohol	1 each

Our patient's score is 2… or more!

>1.9 % risk of major bleed

Pisters R, et al. *Chest* 2010; 138(5):1093–1100

So she has a strong indication for oral anticoagulant therapy for her AF; but she's also at risk for major bleeding!

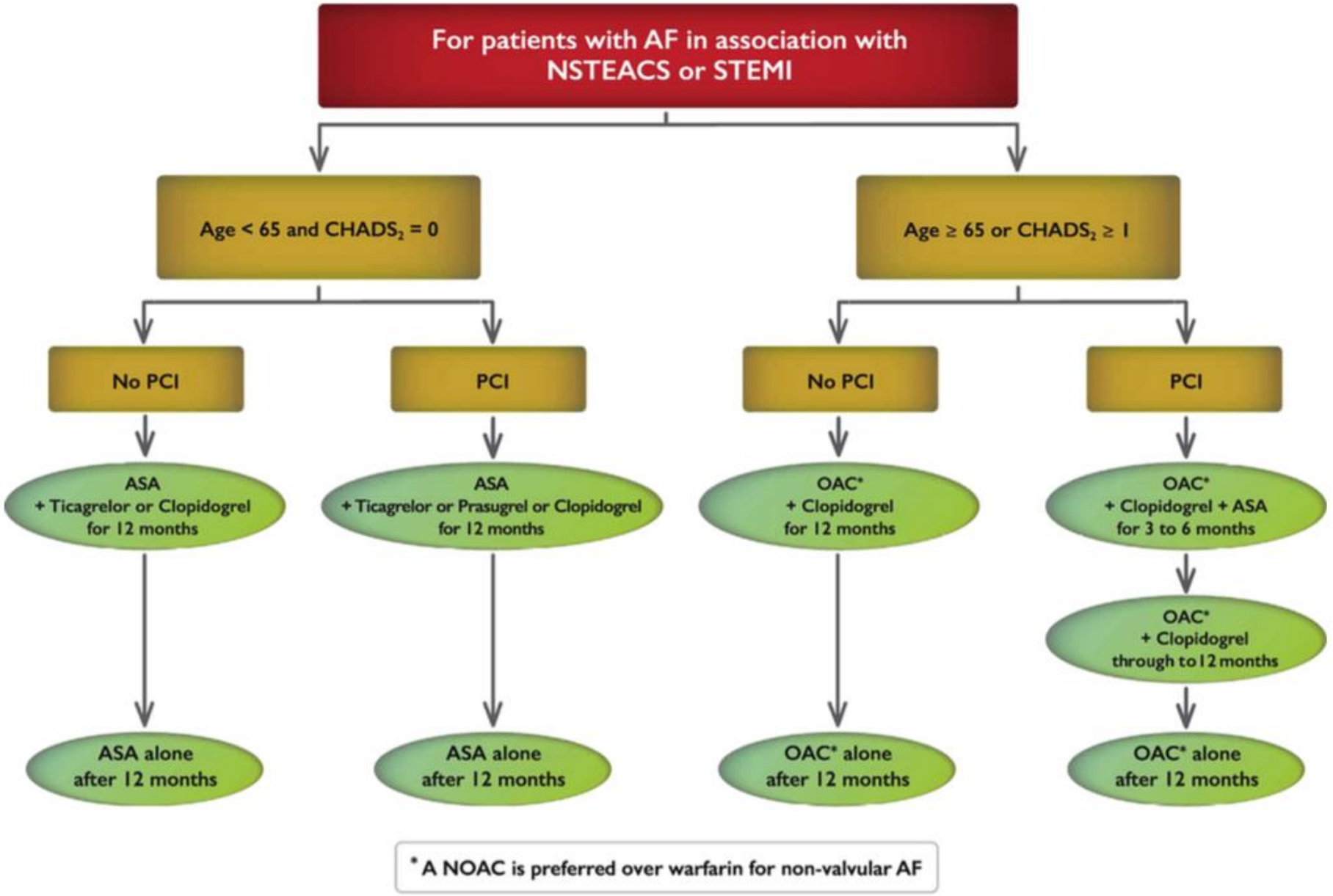
Which is the safest way to proceed in order to protect the coronary stent from thrombosis and yet simultaneously protect her from a thromboembolic AF-related stroke events?

✓ASA plus Clopidogrel or Ticagrelor or Prasugrel

AND

✓Warfarin or any of the specific DOAC's

Do we use Triple therapy??


For patients with AF in association with NSTEACS or STEMI
Age < 65 and CHADS2 = 0
Age ≥ 65 or CHADS2 ≥ 1
No PCI
PCI
No PCI
PCI
ASA + Ticagrelor or Clopidogrel for 12 months
ASA + Ticagrelor or Prasugrel or Clopidogrel for 12 months
OAC* + Clopidogrel for 12 months
OAC* + Clopidogrel + ASA for 3 to 6 months
OAC* + Clopidogrel through to 12 months
ASA alone after 12 months
ASA alone after 12 months
OAC* alone after 12 months
OAC* alone after 12 months
*A NOAC is preferred over warfarin for non-valvular AF

Our plan was to stop the ticagrelor…

Start clopidogrel 75 mg daily (12 hrs from last ticagrelor dose) and that should run for a total of 12 months

Continue low-dose ASA for 1 more month and then D/C (i.e. she will have received a total of 3 months of ASA post-PCI)

Our oral anticoagulant choices are:

- Warfarin and target INR to 2 to 2.5 and DAPT
- low dose Rivaroxaban 15 mg daily and DAPT

Patients going for surgery

How to manage patients on DOAC's

Is there a need for Bridging in DOAC-treated Patients?

In general, the rapid offset and onset of action (~30 mins; and peak ~2 hrs) of DOACs obviates the need for ‘heparin’ bridging’ as was done historically with warfarin-treated patients.

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How the decision is made on ‘when to operate’ on various surgeries & procedures

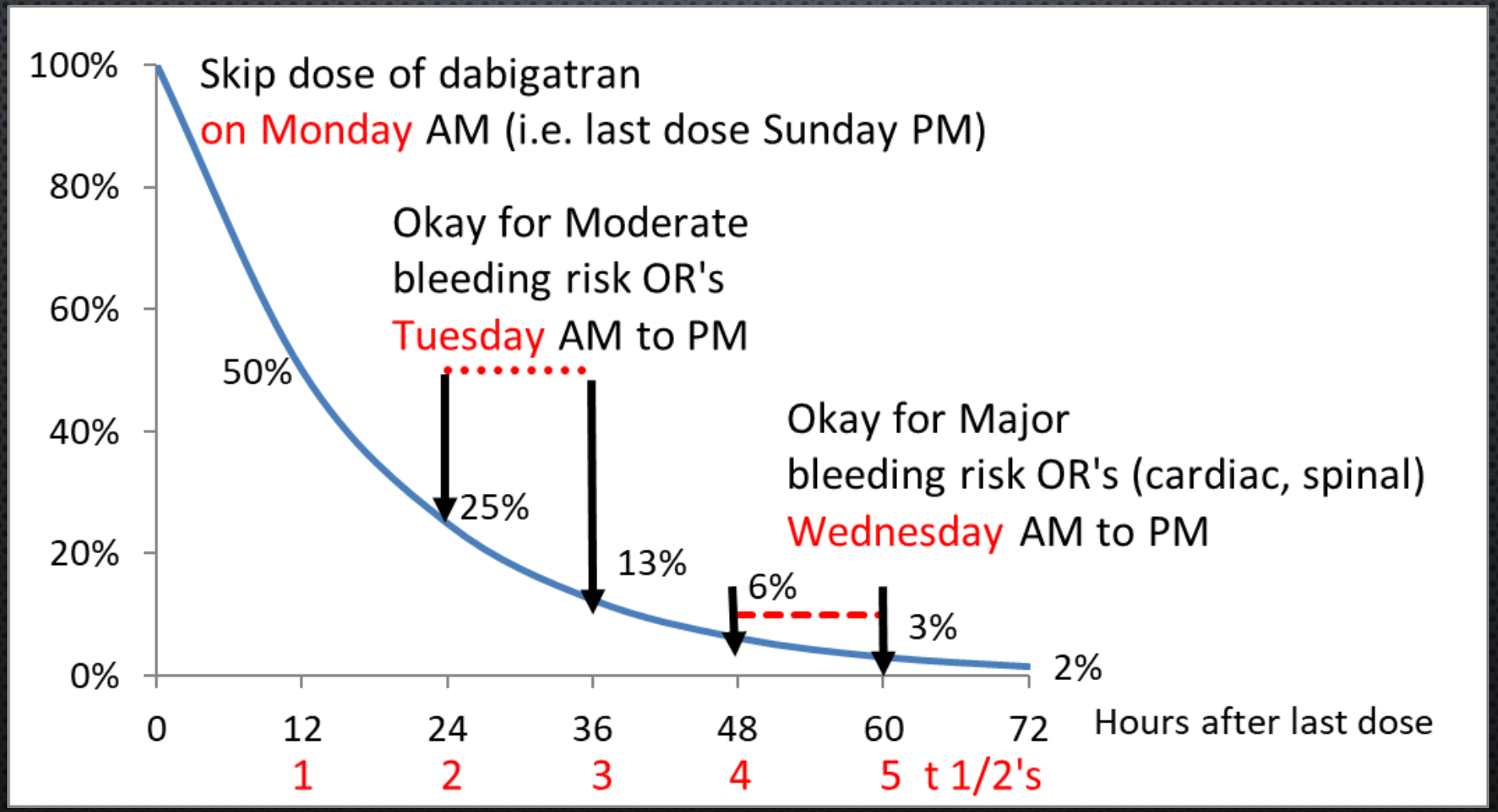

Table 2. Suggested Guide for Pre-Operative Management of Patients Receiving a DOAC

Drug (dose regimen)	Renal function	Moderate Bleed Risk Surgery/Procedure*	High Bleed Risk Surgery/Procedure* (including any use of neuraxial anesthesia†)
Dabigatran (twice daily)	Normal renal function or mild impairment (CrCl ≥50 mL/min) $t_{1/2}$ 7-17 hours	Give last dose 2 days before surgery/ procedure (i.e. skip 2 doses)	Give last dose 3 days before surgery/procedure (i.e. skip 4 doses)
	Moderate renal impairment (CrCl 30-49 mL/min) $t_{1/2}$ 17-20 hours	Give last dose 3 days before surgery/ procedure (i.e. skip 4 doses)	Give last dose 5 days before surgery/procedure (i.e. skip 8 doses)
Rivaroxaban (once daily)	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 7-11 hours	Give last dose 2 days before surgery/procedure (i.e. skip 1 dose)	Give last dose 3 days before surgery/procedure (i.e. skip 2 doses)
Apixaban (twice daily)	Normal renal function, mild or moderate impairment (CrCl ≥30 mL/min) $t_{1/2}$ 8-12 hours	Give last dose 2 days before surgery/procedure (i.e. skip 2 doses)	Give last dose 3 days before surgery/procedure (i.e. skip 4 doses)

Edoxaban is the same as this

A consideration for minor surgeries & procedures

- For minor procedures in which the DOAC is NOT stopped; try to ensure the procedure is at a time when the anticoagulant effect of the DOAC is at its lowest!
- Ideally anytime within 2 hours of the next scheduled dose; e.g. Rivaroxaban once daily at noon. Can then perform procedure between 10 AM and noon.
- And consider delaying that day's dose for 4 to 6 hours after the procedure; e.g. delay that day's dose until 4 PM.

Adapted from Thrombosis Canada - Date of Version: 2017 Sep11

Restarting DOAC's post-operatively

Resumption of the DOAC should be done cautiously after major surgery or in patients at increased bleeding risk.

Only restart once hemostasis is secure and bleeding risk is considered low!

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Table 3. Suggested Guide for *Post-Operative* Management of Patients Receiving a DOAC

Drug	MODERATE BLEED RISK SURGERY/PROCEDURE	HIGH BLEED RISK SURGERY/PROCEDURE
Dabigatran	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Rivaroxaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim
Apixaban	Resume on day after surgery (~24 hours post-operative)	Resume therapeutic doses 2-3 days after surgery (~48-72 hours post-operative); prophylactic dose anticoagulants can be considered in the interim

Edoxaban is the same as this

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LOW/VERY LOW RISK	MODERATE RISK	HIGH RISK
• Dental extractions (1 or 2 teeth), endodontic (root canal) procedure, • Subgingival scaling or other cleaning • Cataract surgery • Dermatologic procedures (e.g. biopsy) • Gastroscopy or colonoscopy without biopsies • Coronary angiography • Permanent pacemaker insertion or internal defibrillator placement (if bridging anticoagulation is not used) • Selected procedures (e.g. thoracentesis, paracentesis, arthrocentesis)	• Other intra-abdominal surgery (e.g. laparoscopic cholecystectomy, hernia repair, colon resection) • Other general surgery (e.g. breast) • Other intrathoracic surgery • Other orthopedic surgery • Other vascular surgery • Non-cataract ophthalmologic surgery • Gastroscopy or colonoscopy with biopsies • Selected procedures (e.g. bone marrow biopsy, lymph node biopsy) • Complex dental procedure (e.g. multiple tooth extractions)	• Any surgery or procedure with neuraxial (spinal or epidural) anesthesia • Neurosurgery (intracranial or spinal) • Cardiac surgery (e.g. CABG, heart valve replacement) • Major intra-abdominal surgery (e.g. intestinal anastomosis) • Major vascular surgery (e.g. aortic aneurysm repair, aortofemoral bypass) • Major orthopedic surgery (e.g. hip or knee replacement) • Lung resection surgery • Urological surgery (e.g. prostatectomy, bladder tumour resection) • Extensive cancer surgery (e.g. pancreas, liver) • Reconstructive plastic surgery • Selected procedures (e.g. kidney biopsy, prostate biopsy, cervical cone biopsy, pericardiocentesis, colonic polypectomy)
Maintain the OAC	Hold for 13 to 25% activity	Hold for 3 to 6% activity

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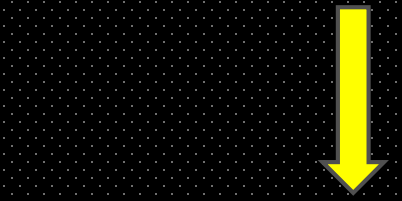
Transitioning between Antithrombotics

DOAC to Warfarin or back!

Transitioning off of Warfarin to a DOAC

Warfarin	Warfarin	Stop warfarin		
INR = 2.5 5 mg PM Sunday	INR = 2.5 5 mg PM Monday	INR = 2.5 **No warfarin!** Tuesday	INR = 2.1 Wednesday	INR = 1.8 Thursday



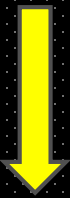
Start the DOAC here once INR < 2.0

Transitioning off Dabigatran to Warfarin

Note the overlap in anticoagulants!

DABI 150mg bid Sunday	DABI 150mg bid **Start 5mg warfarin** Monday INR = 1.1	DABI 150mg bid **5 mg warfarin** Tuesday INR = 1.4	DABI 150mg bid **5 mg warfarin** Wednesday INR = 1.8	DABI 150mg bid **5 mg warfarin** Thursday INR = 2.1

Start warfarin here



D/C Dabigatran once INR > 2.0

Transitioning off Rivaroxaban to Warfarin

Note the overlap in anticoagulants!

RIVA 20 mg daily Sunday	RIVA 20 mg daily Monday	d/c RIVA 5 mg warfarin Tuesday INR = 1.7	5 mg warfarin Wednesday INR = 1.5	5 mg warfarin Thursday INR = 1.8

D/C Riva

Start warfarin

Consider parenteral bridging in high-risk patients!

Summary:

1. With similar efficacy for AF, DOAC's may be tailored to your patient
2. Antithrombotic combinations may be necessary
3. Great care in the management of patients going for surgery
4. The future should on tailoring of antithrombotic therapy using laboratory feedback and identifying better markers of bleeding and thrombosis in our patients

Questions?

Management of Bleeding while on a DOAC

Non-Major (Minor) Bleeding with DOAC's

e.g. extremity bruising, hemorrhoidal bleeding, subconjunctival bleed, self-limited epistaxis

- ✓ *Continue the DOAC anticoagulant*
- ✓ Confirm the patient is receiving the appropriate drug and dose based on indication, age, weight, and creatinine clearance.
- ✓ Hgb, PLT, creatinine & urea; to see if they are stable?
- ✓ Review concomitant medications which may contribute to bleeding (e.g. ASA, NSAIDs) *… I'd also add check for potentially interacting drugs!*

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Non-Life Threatening Bleeding with DOAC's

e.g. hemodynamically stable gastrointestinal bleed, epistaxis, hematuria, or menstrual bleeding, requiring medical attention and/or intervention

- ✓ Hold the DOAC anticoagulant
- ✓ Assess the cause of bleeding
- ✓ Apply local hemostatic measures (e.g. compression, packing) if able
- ✓ Hgb, PLT's, INR, aPTT, creatinine & urea (measure [DOAC] if avail)
- ✓ Determine the likely presence of drug ?? Based on time since last dose!

Transfusion therapy should be given as per standard supportive measures

- ✓ PRBC's if symptomatic anemia
- ✓ Platelet transfusion if platelets less than 50,000
- ✓ Consultations

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Severe/Life-threatening bleeding with DOAC's

e.g. intracranial hemorrhage, or severe gastrointestinal bleed with actual or impending hemodynamic instability, retroperitoneal bleed, intramuscular bleed with compartment syndrome

- ✓ *Hold DOAC anticoagulant therapy*
- ✓ Initiate resuscitation in a monitored setting
- ✓ Apply local hemostatic measures (e.g. compression, packing, splinting)
- ✓ Hgb, PLT's, INR, aPTT, creatinine & urea (measure [DOAC] if avail)
- ✓ Consult an expert urgently (hematologist, internist, ER physician, pharmacist) for advice
- ✓ Refer for procedural/surgical intervention if appropriate

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Severe/Life-threatening bleeding with DOAC's *(continued)*

Determine the likely presence of drug?

Transfusion therapy should be given as per standard supportive measures:

- ✓ PRBC's if symptomatic anemia. Maintain hemoglobin > 70 g/L during active bleeding.
- ✓ Platelet transfusion if platelet count less than 50,000. Consider higher platelet count threshold of 100,000 in patients with bleeding into a critical site (e.g. intracranial hemorrhage).
- ✓ Plasma and/or cryoprecipitate transfusion only if concomitant coagulopathy (e.g. massive transfusion, disseminated intravascular coagulation, liver disease).

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Reversal for Severe/Life-threatening bleeding

Dabigatran

- ✓ If dabigatran is likely still active (as per time of last dose and creatinine clearance) give idarucizumab (Praxbind®). Complete reversal is expected within minutes.
- ✓ If idarucizumab (Praxbind®) is not available, consider alternative therapies such as prothrombin complex concentrate (PCC) Octaplex®
- ✓ Adjunctive therapy to consider:
  - ✓ hemodialysis (~65% removal after 4 hrs) if feasible
  - ✓ tranexamic acid.

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Reversal for severe/life-threatening bleeding *(continued)*

Rivaroxaban or Apixiban

✓ If drug is likely still active (as per time of last dose and creatinine clearance) give PCC or *Octaplex*. Reversal may or may not occur!

✓ Inform patients/families regarding small thrombotic risk of PCC (e.g. stroke, MI, DVT, PE), but consequences of uncontrolled bleeding likely exceed this risk

✓ Adjunctive therapy to consider: *Tranexamic acid*

✓ Specific antidote in development and NOT available yet!

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