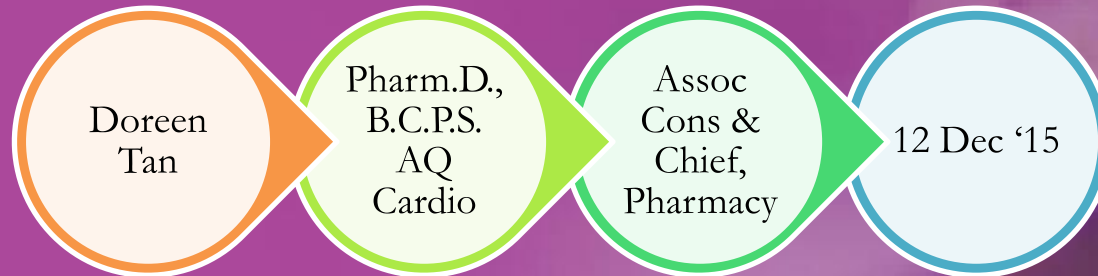
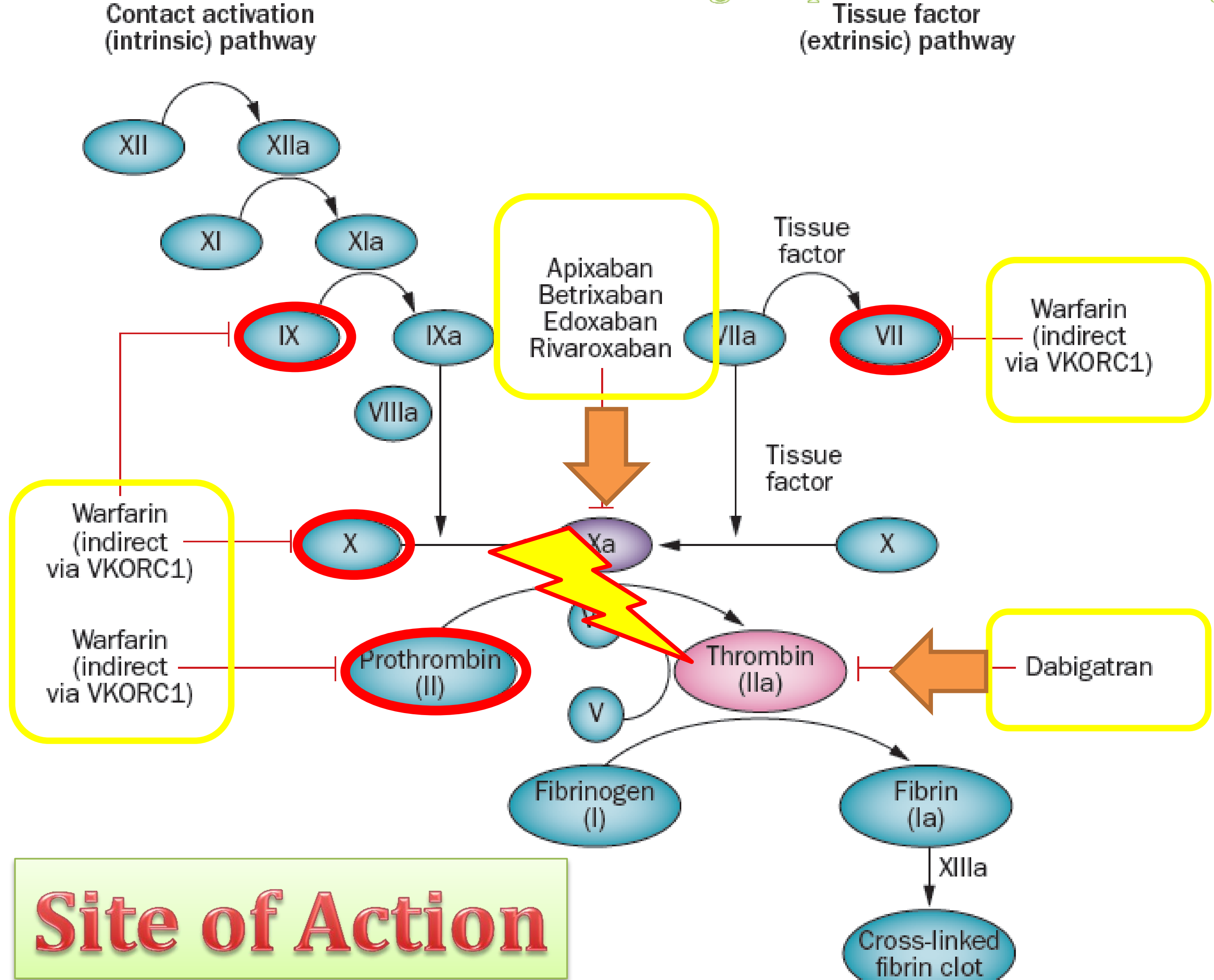
JCR 2015

Clinical Experience with DOACs in AF & DVT



Khoo Teck Puat Hospital
Alexandra Health

Non-Vit K Oral Anticoagulants
Direct-Acting Oral Anti-Coagulants
Target-Specific Oral Anti-Coagulants



Site of Action

Mr CTF 77yo Chinese Male

- Presents with new stroke, Left MCA infarction, NIHSS 25
- PMH:
  - AF CHADS 5 on Dabigatran since Jul'11, sp Ablation Nov'08 with recurrence and re-ablation Feb'10, cardioversion Aug'15
  - Chronic mild thrombocytopenia, platelets 100-140k
  - Stroke Mar'06 with complete resolution of symptoms echo EF 55%, no intracardiac clot/thrombus, LV NAD
  - h/o Hemoptysis due to high INR Jul'15
  - Hypertension, Ca protate s/p radiotx, previous Churg-Strauss syndrome treated with prednisolone

1. What would you like to know?
2. How would you manage this patient?

CTF 77yo male

Renal function ~ 35-40ml/min

EF 60%, LDL 1.8, HbA1c 5.8%

- AF with new stroke (current admission)
  - Warfarin > Dabigatran 110mg BD (2011) > Dabigatran 75mg BD (2012)
  - Planned for clopidogrel for current admission while discussing change to warfarin
  - CT D7 – haemorrhagic conversion. Hold off clopidogrel for a week more
  - CT D14 – worsened haemorrhage

Q: What would you do now?

Khoo Teck Puat Hospital
Alexandra Health

CTF 77yo male

- CT brain repeated ~ D35, haemorrhage resolved
- Platelets 184, CrCl ~ 43ml/min
- Which anticoagulant will you prescribe?

A.	• Warfarin, target INR 2-3
B.	• Aspirin or Clopidogrel only
C.	• Dabigatran 150mg BD
D.	• Apixaban 5mg BD
E.	• Rivaroxaban 20mg OM

CTF

Currently on Apixaban 2.5mg BD (3 Nov'15)

Is it appropriate?

Khoo Teck Puat Hospital
Alexandra Health

YHK 83yo chinese male

- Presents with fever and SOB x a few days
  - COPD exacerbation
- PMH:
  - Heroin addict, treated with methadone
  - DVT dx May'15, tx'd with rivarox x 3m; thrombus still seen on Aug'15 scan
  - DM last HbA1c 8.4%
  - COPD, self-titrates prednisolone 10mg OM x 1 year, obtained from Thailand
    - Osteoporosis secondary to chronic steroid use, T score -1 (spine), -2.3 (hip), -3.3 (NOF)
    - Possible steroid-induced adrenal insufficiency
  - Right pleural TB dx Feb'14, sp 9m TB meds in Nov'14
  - Depression with pseudo-dementia, dx April'14
  - Hearing impairment – on hearing aid
  - Scabies

This admission, US reveals persistent residual deep venous thrombosis - partial thrombosis of distal ext iliac vein, common femoral vein, sup fem vein, popliteal vein

Comparing NOACs vs Warfarin: Pharmacology & Dosing (VTE)

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
VTE Prophylaxis *No studies in hip fracture surgery for all new anticoagulants*	Haemostasis achieved, start within 1-4h post-surgery: 220mg/day x 10 days (TKR) or 28-35 days (THR) CrCl 30-50ml/min: Use with caution; 150mg OM for same duration as above	Haemostasis achieved, start 6-10h post-surgery: 10mg/day x 2 weeks (TKR) or 5 weeks (THR)	Haemostasis achieved, 12-24h post-surgery: 2.5mg BD x 10-14 days (TKR) or 32-35 days (THR)	30mg/day	None INR-directed request yet
VTE Treatment	Parenteral anticoagulant for 9 days followed by 150mg BD for 6m	15mg BD for 3 weeks followed by 20mg/day for up to 12 months [EMA: followed by 15mg per day] Avoid use if CrCl < 30ml/min	10mg BD x 7d followed by 5mg BD up to 6 months	Initial parenteral anticoagulatnt, 60mg/day	Individualised dosing, target INR 2-3

Khoo Teck Puat Hospital
Alexandra Health

83yo chinese male

- What would you do?

A.	LMWH + Warfarin, target INR 2-3
B.	Rivaroxaban 15mg OM, lifelong
C.	Rivaroaban 15mg BD x 3w followed by 20mg OM, up to 12m
D.	Apixaban 10mg BD x 1w followed by 5mg BD, up to 6m
E.	Nothing

Comparing NOACs vs Warfarin: Pharmacology & Dosing (AF)

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Stroke prevention in AFib	150mg BD (vs Warfarin INR target 2-3) vs 110mg BD	20mg per day (vs Warfarin INR target 2-3)	5mg BD 2.5mg BD for any 2 of the following: Age ≥80yo, weight ≤60kg, SCr ≥ 1.5mg/dL or 132.6 mmol/L	60mg per day 30mg per day 30mg per day if any of the following: CrCl 30-50ml/min, weight ≤60kg, concom verapamil, quinidine, dronedarone	Individualised dosing, target INR 2-3
Dosage adjustments	CrCl 30-50ml/min: No dose reduction required *unless DDI; CrCl < 30ml/min: CONTRA-INDICATED (EU,SG) CrCl 15-30ml/min (FDA): 75mg BD Elderly above 80yo: 110mg BD	CrCl 30-50ml/min: 15mg per day [EMA]: 15mg per day if 15-49ml/min CrCl 15-30ml/min [HSA]: Use with caution CrCl < 15 ml/min: CONTRA-INDICATED	CrCl 30-50ml/min: As above CrCl 15-29ml/min (solely)*: 2.5mg BD CrCl < 15 or dialysis: not recommended *Adjustment for poor renal function if additional risk factor (see above)	CrCl 30-50ml/min: 30mg CrCl < 30ml/min: No data Potentially, DDI with amio, erythro, ketoconazole, quinidine, verapamil & moderate renal impairment	-

Khoo Teck Puat Hospital
Alexandra Health

CTF 77yo male

- CT brain repeated ~ D35, haemorrhage resolved
- Started on Apixaban 2.5mg BD

1. Dosing appropriate?
2. Could adequate dosing of dabigatran prevented this stroke?
3. Would you use Warfarin instead?

Khoo Teck Puat Hospital
Alexandra Health

68yo European male

- Presents with severe abdominal pain, suspect pancreatitis, urgent ERCP required
- PMH: AF CHADS 2 on Rivaroxaban 20mg OM for Atrial Fibrillation for the last 3 years, DM and HTN
- The general surgery team calls you for a consult for reversal for urgent surgery. “Is PCC suitable?” They ask.

68yo European male

- What will you assess for?
- Will you give PCC or FFP?
- When will you restart rivaroxaban?

Khoo Teck Puat Hospital
Alexandra Health

76yo Malay male

- Presents with dehydration, fever and poor oral intake x 1 week – Sepsis
- PMH:
  - Paroxysmal AF on Rivaroxaban 20mg OM, Carvedilol 12.5mg BD
  - HFrEF (EF20%) on Spironolactone 25mg OM, Frusemide 40mg OM
  - DM on Gliclazide 80mg BD, Linagliptin 5mg OM
  - Hyperlipidaemia on Atorvastatin 40mg ON
- His current creatinine clearance is ~ 25ml/min (baseline between 30-35ml/min)

What would you do with the Rivaroxaban?

Thank You!

tan.doreen.sy@alexandrahealth.com.sg

Khoo Teck Puat Hospital
Alexandra Health

Comparing NOACs vs Warfarin

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
MOA	Direct factor IIa inhibitor	Direct factor Xa inhitor	Direct factor Xa inhitor	Direct factor Xa inhitor	VKOR inhibitor
Bioavailability (%)	6-7	>80	66	45	Almost 100%
Tmax (h)	2-3	2.5-4	3	4	4-5 days
T1/2 (h)	12-14	9-13	8-15	9-11	36-42, var.
Protein binding (%)	35	>90	>80	40-59	99%
Dialyzable?	Yes (80% renally cleared)	Not expected (33% renally cleared)	Unlikely (25% renally cleared)	Unlikely	Probably not
Metabolism	Plasma esterases	Hepatic, CYP3A, CYP 2J2 & others	Hepatic, CYP 3A	Hepatic, CYP 3A (~4%)	CYP 2C9 (S-warfarin), 3A (R-warfarin), 1A2
P-glycoprotein transport	Yes	Substrate & BCRP	Yes	Yes	No
Lab interferences	May derange aPTT and possibly PT	May derange PT/INR	May derange PT/INR	May derange PT/INR	-

Comparing NOACs vs Warfarin: Pharmacology & Dosing

	Dabigatran			Rivaroxaban			Apixaban			Edoxaban			Warfarin		
Stroke prevention in AFib	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR/ SG	JAP	USA/C	EUR	SG
	✓	✓	✓	✓	✓	✓	✓	✓	✓	P	P	✓	✓	✓	✓
VTE Prophylaxis *Hip fracture surgery data only available for Edoxaban*	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	JAP	USA/ EUR		USA/C	EUR	SG
	✓ THR / TKR	✓	✓	✓	✓	✓	✓	✓	✓	✓ +HFS	P		✓	✓	✓
VTE Treatment & prevent recurrence	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	JAP	USA/ EUR		USA/C	EUR	SG
	✓	✓	✗	✓	✓	✓	✓	✓	✓	✓	P		✓	✓	✓
ACS	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG
	✗	✗	✗	✗	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗

Khoo Teck Puat Hospital
Alexandra Health

Comparing NOACs vs Warfarin: Pharmacology & Dosing

	Dabigatran			Rivaroxaban			Apixaban			Edoxaban			Warfarin		
Stroke prevention	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG
	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-	-		✓	✓
Pro[...] *[...] surge[...]														EUR	SG
														✓	✓
Tr[...] & [...] rec[...]														EUR	SG
														✓	✓
[...]CS	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG	USA/C	EUR	SG
	×	×	×	×	✓	✓	×	×	×	×	×	×	×	×	×

Heart valves?
LV thrombus?
VTEP in medically ill?
ACS??

Khoo Teck Puat Hospital
Alexandra Health

Comparing NOACs vs Warfarin: Pharmacology & Dosing (AF)

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Stroke prevention in AFib	150mg BD (vs Warfarin INR target 2-3) vs 110mg BD	20mg per day (vs Warfarin INR target 2-3)	5mg BD ... for any	60mg per day 30mg per day 30mg per day if any of the following: CrCl 30- ...l/min, weight ≤60kg, ... verapamil, ... dronedarone	Individualised dosing, target INR 2-3
Dosage adjustments	CrCl 30-50ml/m... dose re... require... DDI; CrCl < 30ml/m... CONTRA-INDICATED... CrCl 15-30ml/min (FDA): 75mg BD Elderly above 80yo: 110mg BD	... CrCl < 15 ml/min: CONTRA-INDICATED	... ... renal function if additional risk factor (see above)	... o ...y, DDI ...io, ...ro, ...toconazole, quinidine, verapamil & moderate renal impairment	-

Khoo Teck Puat Hospital
Alexandra Health

Comparing NOACs vs Warfarin: Pharmacology & Dosing (ACS)

HSA approved for use in ACS as at Jan 2014

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
ACS	50 or 75mg BD, escalation up to 150mg BD (RE-DEEM, phase II)	2.5mg BD – 10mg BD (ATLAS ACS TIMI 46 & 51)	2.5mg BD - 20mg OM; 5mg BD (APPRAISE, phase II & APPRAISE-2, prematurely halted)	NA	Adjunct to aspirin (no stents), aspirin + warfarin vs DAPT, target INR 2-3.

Khoo Teck Puat Hospital
Alexandra Health

Comparing NOACs vs warfarin: Key Studies

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
ACS	REDEEM	ATLAS TIMI-51	APPRAISE 1&2	-	Studies in post-MI subjects but not recommended
Stroke prevention in AFib	RE-LY	ROCKET-AF	AVERROES ARISTOTLE	ENGAGE AF-TIMI 48	Numerous studies, including AFASAK, SPAF series of studies
VTE Prophylaxis (VTEP)	RE-NOVATE (THR) RE-NOVATE II (THR) RE-MOBILIZE (TKR) RE-MODEL (TKR)	RECORD I (THR) RECORD II (THR) RECORD III (TKR) RECORD IV (TKR) MAGELLAN (Medically Ill)	ADVANCE 3 (THR) ADVANCE 1 (TKR) ADVANCE 2 (TKR) ADOPT (Medically Ill)	STARS J5 (THR) & E3 (TKR)	Recommended for high-risk THR subjects as one of the modalities (grade 1A) and for TKR subjects (grade 1B) [USA]
VTE Treatment	RE-COVER RE-MEDY RE-SONATE (ongoing)	EINSTEIN DVT EINSTEIN EXT EINSTEIN PE	AMPLIFY AMPLIFY-EXT	HOKUSAI	Hirsh et al
Stroke prevention in Valve Replacment	RE-ALIGN	-	-	-	

Hospital
Alexandra Health