Practical Management of Patients receiving Rivaroxaban

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심장내과

최 기 준

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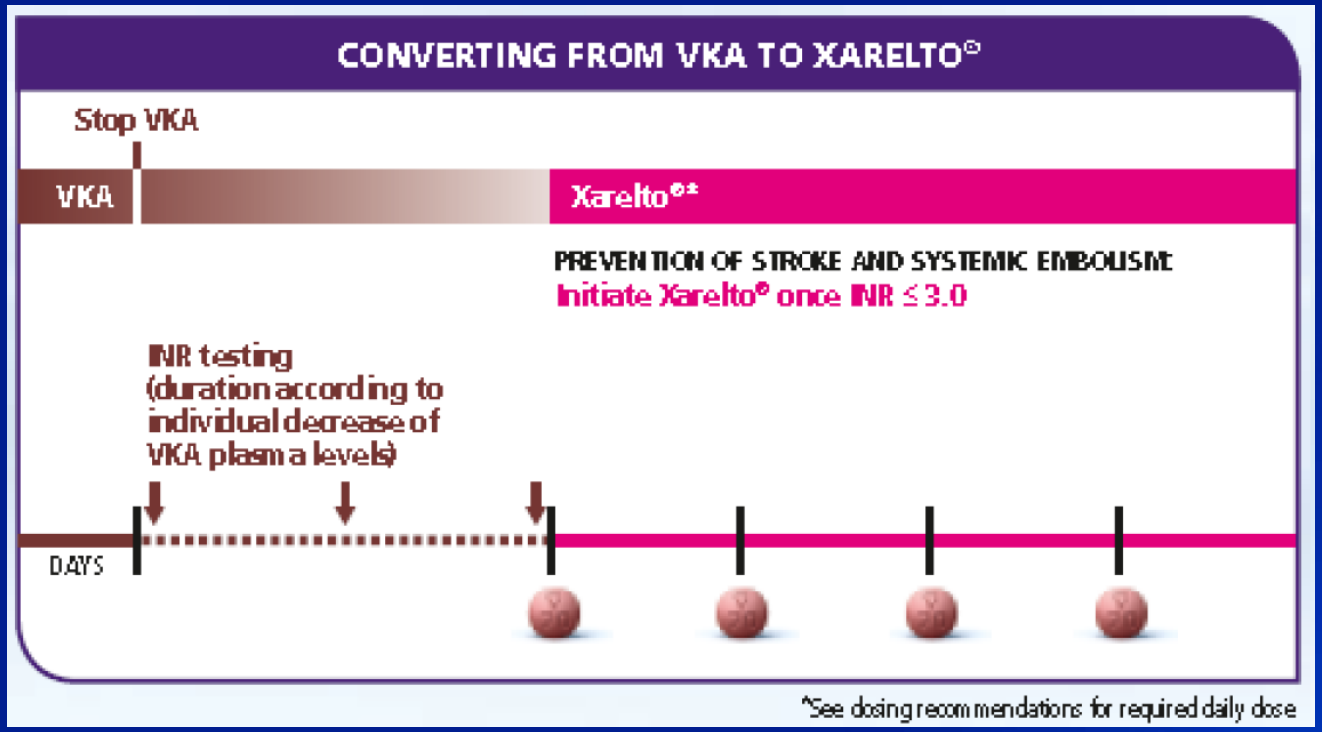
- Converting to/from rivaroxaban
  - Measuring levels of rivaroxaban
- Patients potentially at higher risk of bleeding
  - Renal impairment
  - Hepatic impairment
  - Concomitant drugs
  - Other haemorrhagic risk factors
- Perioperative management, Antidote

How to switch patients to rivaroxaban?

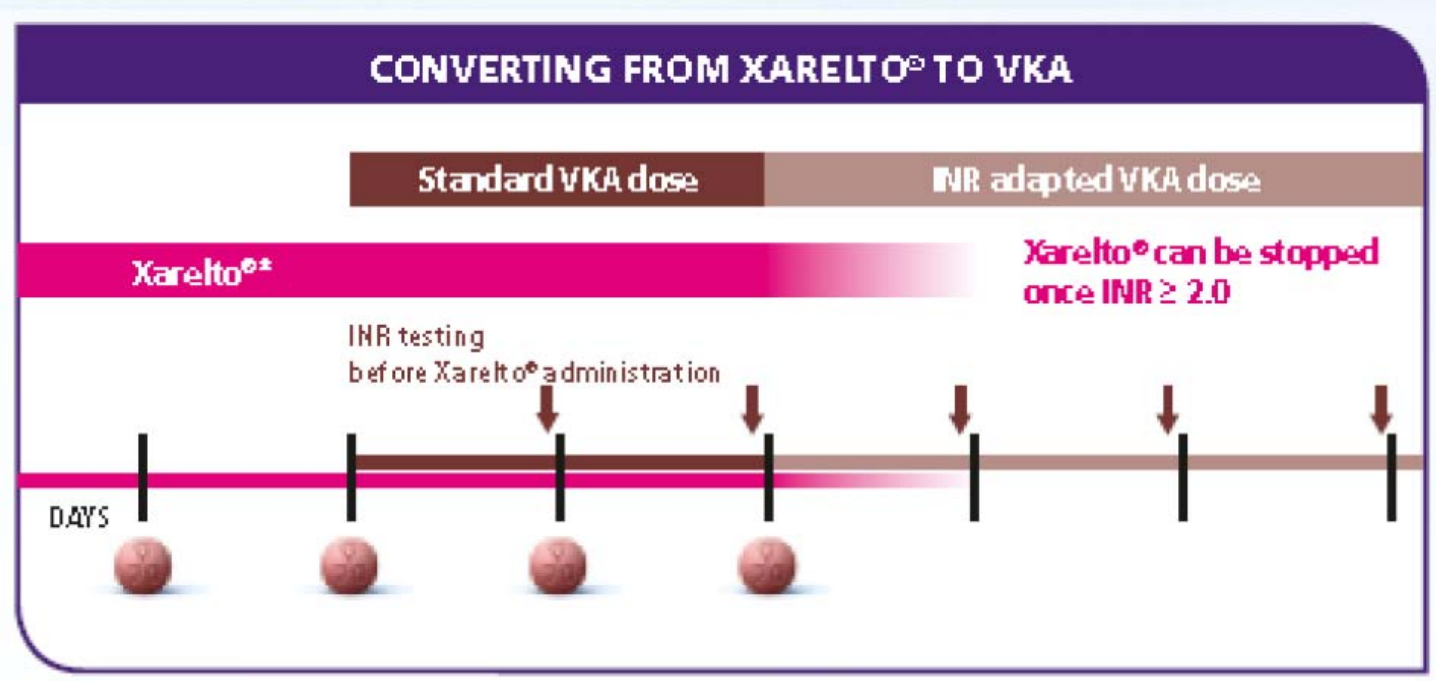
- Vitamin K Antagonists → Rivaroxaban



- VKA treatment should be stopped and rivaroxaban therapy should be initiated when the ***INR is ≤ 3.0***
  - When converting patients from VKAs to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban, and therefore should not be used

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

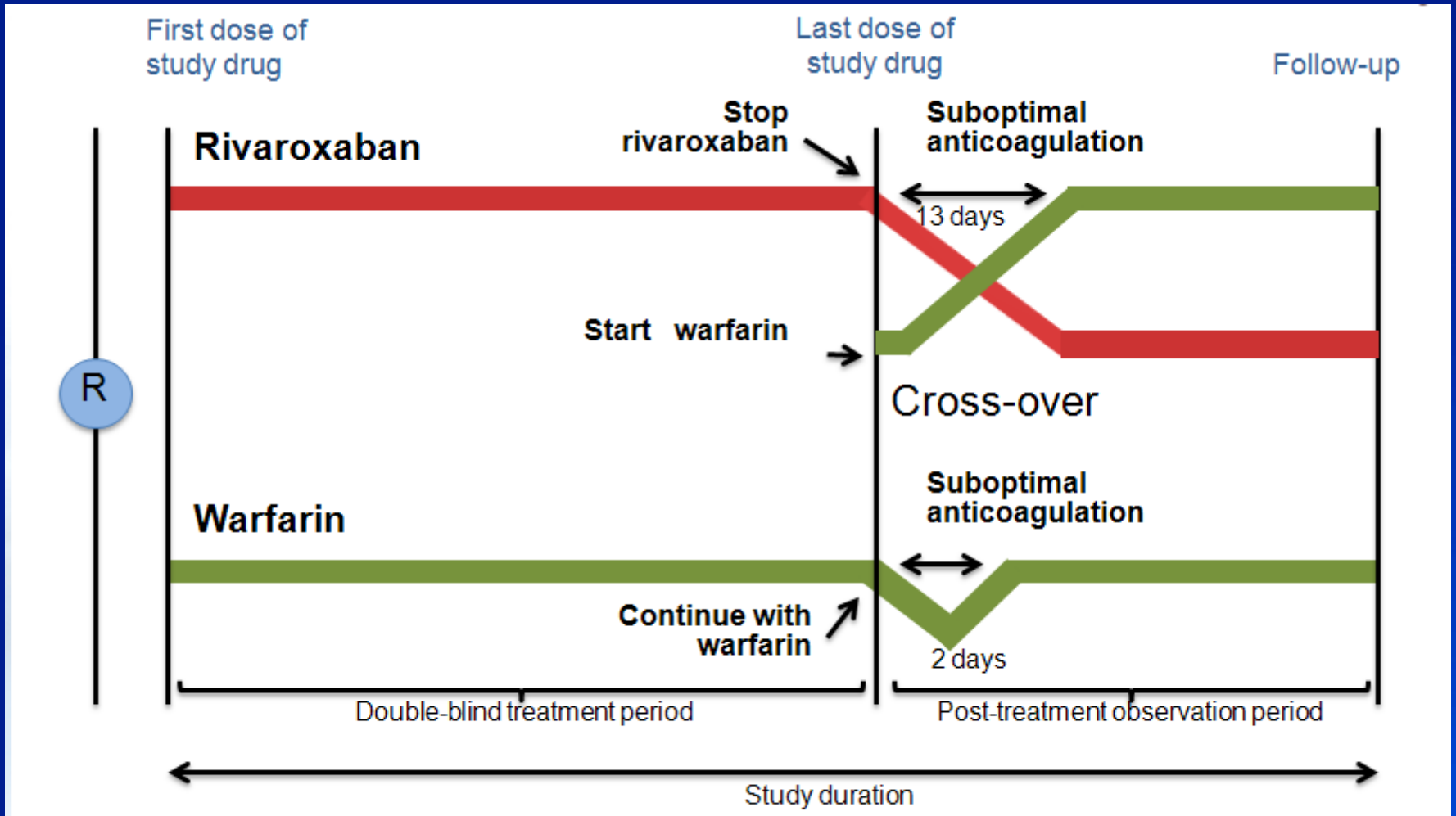
How to switch patients from rivaroxaban?
- Rivaroxaban → Vitamin K Antagonists



- VKA and rivaroxaban have to be given concomitantly, rivaroxaban can be stopped ***once INR is ≥ 2.0***
  - INR measurement should be done 24 hrs after the last administration of rivaroxaban and prior to the next one

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

ROCKET-AF : transition to open-label VKA

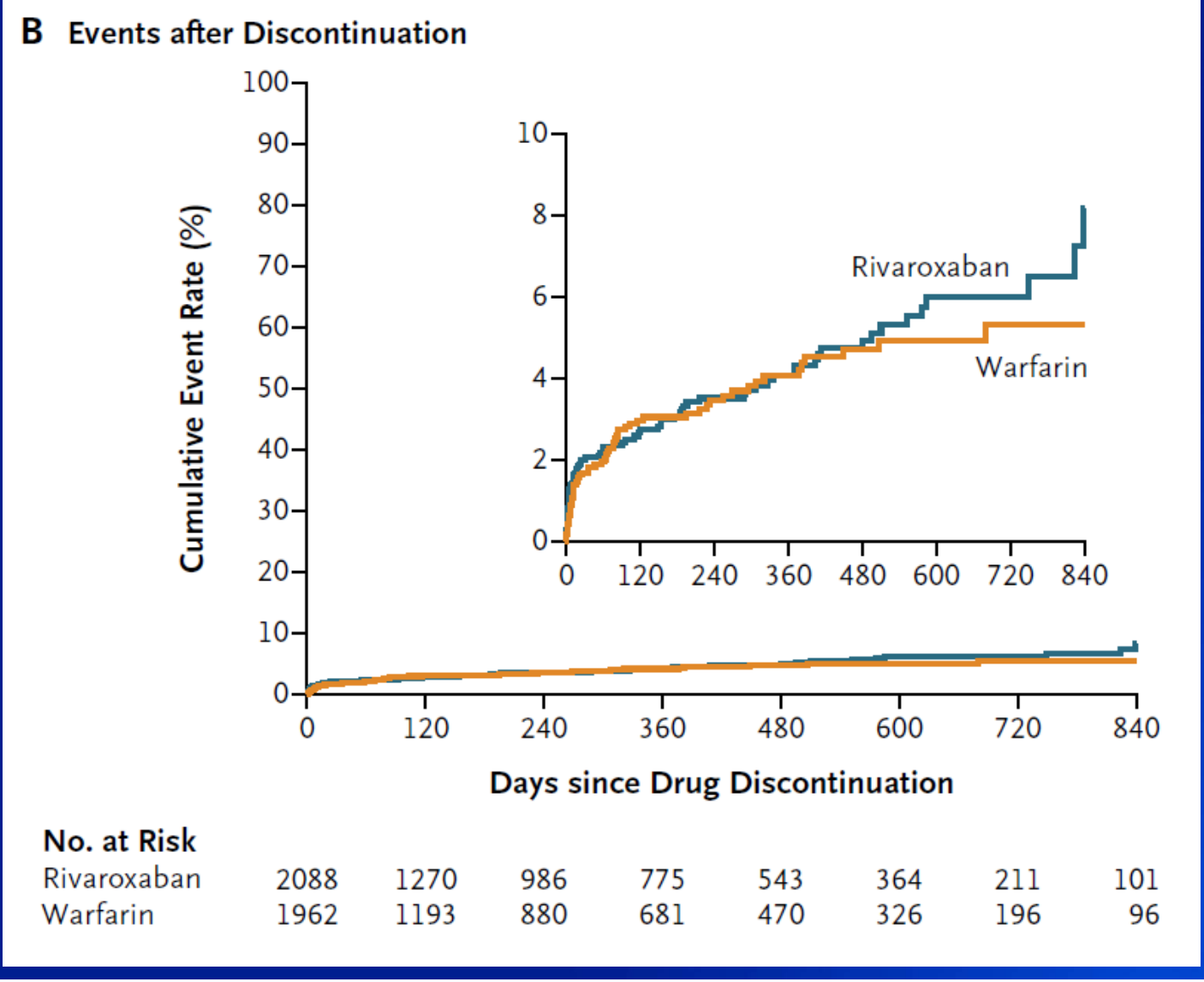


VKA = Vitamin K antagonist
R = randomization

Patel *N Engl J Med* 2011;365:883

Rocket-AF : Event after discontinuation of Rivaroxaban

Patel et al, N Eng J Med 2011;365:883



No. at Risk								
Rivaroxaban	2088	1270	986	775	543	364	211	101
Warfarin	1962	1193	880	681	470	326	196	96

Converting from Heparin/LMWH to Rivaroxaban and vice versa

- Patients with **continuous heparin** :
  Xarelto should be **started at the time of discontinuation**

- Patients with **a fixed dosing of LMWH** :
  Xarelto should be **started 0 to 2 hours before the time of the next** scheduled administration

- Patients who receive Xarelto and **converted to parenteral anticoagulation:**
  The first dose of the parenteral drug should be administered **instead of the next Xarelto dose** at the planned time

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

INR measurement / lab testing

- Xarelto does not require routine coagulation monitoring
- Coagulation tests (PT, aPPT, INR) are increased
- INR : not an appropriate tool for Xarelto
  If necessary, heamostatic status can also be assessed with **PT using Neoplastin** only
- **Anti-FXa chromogenic assays** have been developed and are now commercialized

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

Patients potentially at higher risk of bleeding

- Patients with higher bleeding risk
  - Patients with renal impairment
  - Patients with hepatic impairment
  - Patients concomitantly receiving certain other medications
  - Patients with other hemorrhagic risk factors
- Treatment decision in these patients should be done after assessment of treatment benefit against the risk for bleeding

Patients with renal impairment

Guidance

- General advice:
  - Use with caution in patients with severe renal impairment
  - **Use not recommended in patients with CrCl <15ml/min**
- DVT Tx：Moderate and severe renal impairment - 15 mg BID for the first 3 weeks, then 15 mg OD
- SPAF：Moderate and severe renal impairment - **15 mg OD (CrCl < 50ml/min)**

Evidence

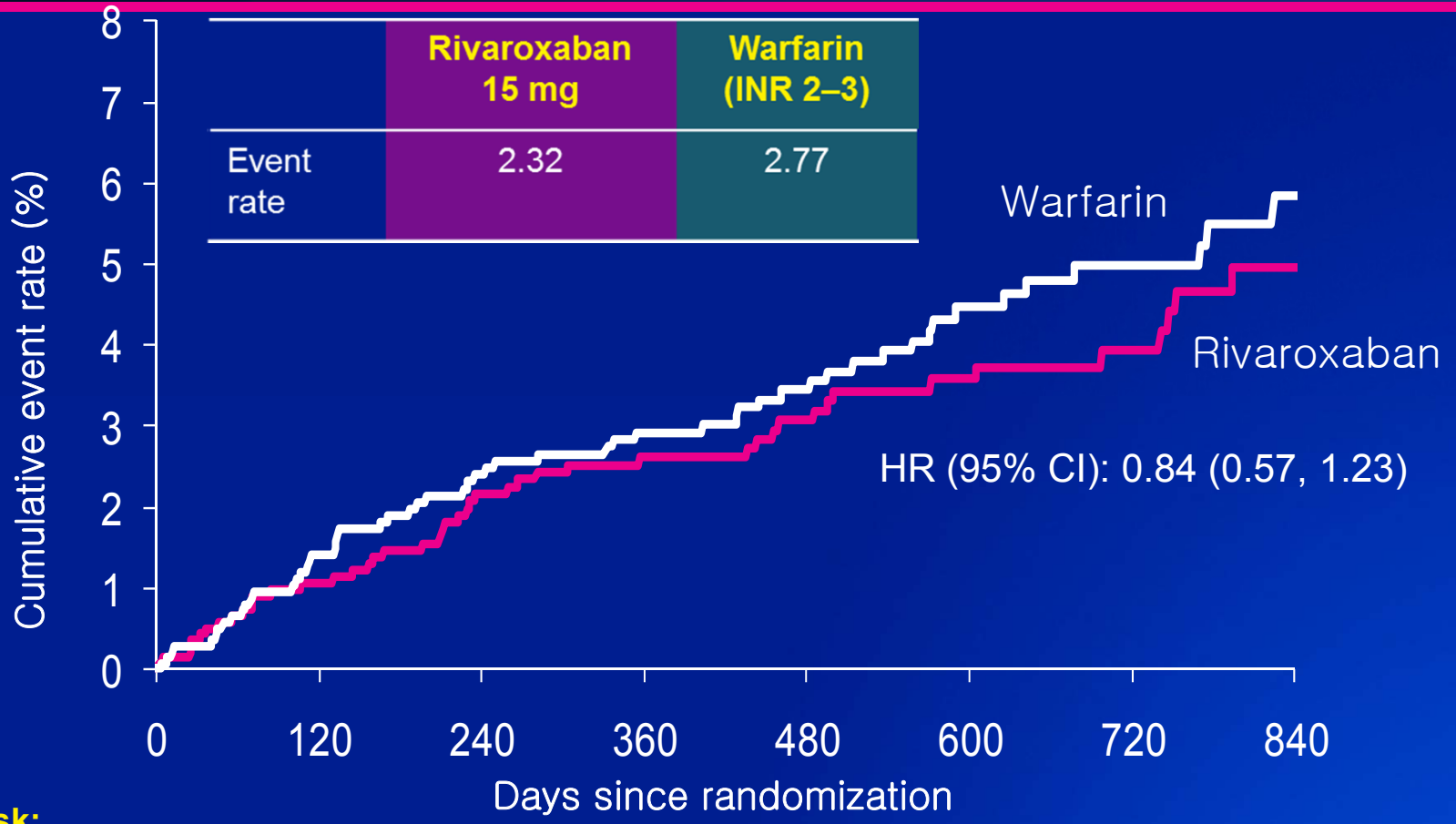
- In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average)
- Further information can be found in PK/PD studies

Patients potentially at higher risk of bleeding: Patients with renal impairment

Level of renal impairment	Indication	Dose
Moderate renal (CrCl 30–49 ml/min)	VTE prevention	10 mg once daily
	Prevention of stroke in patients with non-valvular AF	**15 mg once daily**
	DVT treatment and prevention of recurrent DVT and PE	15 mg twice daily for first 3 weeks 15 mg once daily for continuous treatment
Severe renal (CrCl 15–29 ml/min)	VTE prevention	10 mg once daily. Use with caution
	Prevention of stroke in patients with non-valvular AF	**15 mg once daily. Use with caution**
	DVT treatment and prevention of recurrent DVT and PE	15 mg twice daily for first 3 weeks 15 mg once daily for continuous treatment. Use with caution
Renal failure (CrCl <15 ml/min)	**not recommended for patients with CrCl rates < 15ml/min**	

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

ROCKET AF: stroke or non-CNS embolism among patients with CrCl 30–49 ml/min



No. at risk:

Rivaroxaban	1,434	1,226	1,103	1,027	806	621	442	275
Warfarin	1,439	1,261	1,140	1,052	832	656	455	272

Event rates are % per year

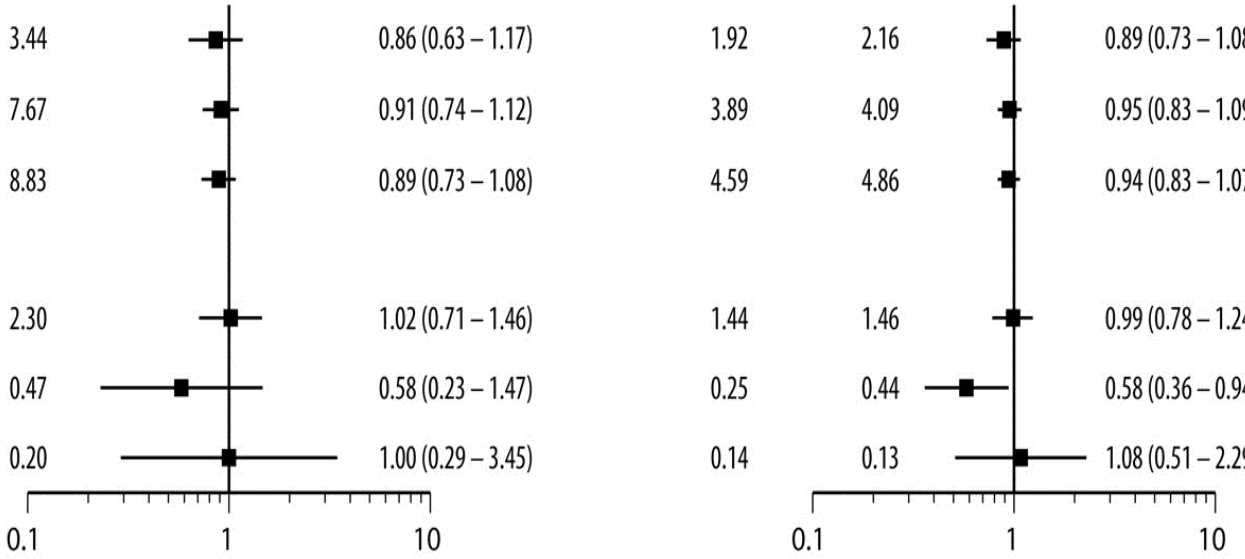
Based on Protocol Compliant on Treatment Population

Fox KA *et al.* Eur Heart J 2011; 32 (19): 2387–2394

ROCKET-AF sub-study : Efficacy According to Renal Function

➢ **Intention to Treat Analysis**

Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value
	Rivaroxaban 15 mg (N=1462)*	Warfarin N=1459	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban 20 mg (N=5619)*	Warfarin N=5622	HR (95% CI) Rivaroxaban vs Warfarin	Interaction
Principal Efficacy Endpoint (Stroke and Systemic Embolism)	2.95	3.44	0.86 (0.63 – 1.17)	1.92	2.16	0.89 (0.73 – 1.08)	0.85
PE + Vascular Death	7.00	7.67	0.91 (0.74 – 1.12)	3.89	4.09	0.95 (0.83 – 1.09)	0.74
PE + MI, Vascular Death	7.86	8.83	0.89 (0.73 – 1.08)	4.59	4.86	0.94 (0.83 – 1.07)	0.61
Stroke							
Ischemic	2.34	2.30	1.02 (0.71 – 1.46)	1.44	1.46	0.99 (0.78 – 1.24)	0.89
Hemorrhagic	0.27	0.47	0.58 (0.23 – 1.47)	0.25	0.44	0.58 (0.36 – 0.94)	0.99
Undetermined	0.20	0.20	1.00 (0.29 – 3.45)	0.14	0.13	1.08 (0.51 – 2.29)	0.92



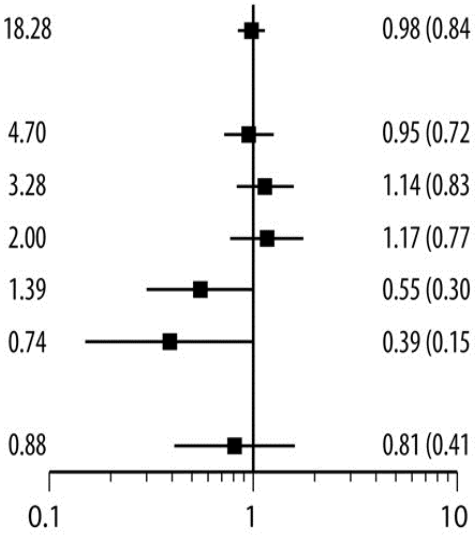
* Event rates per 100 pt/yrs of follow-up

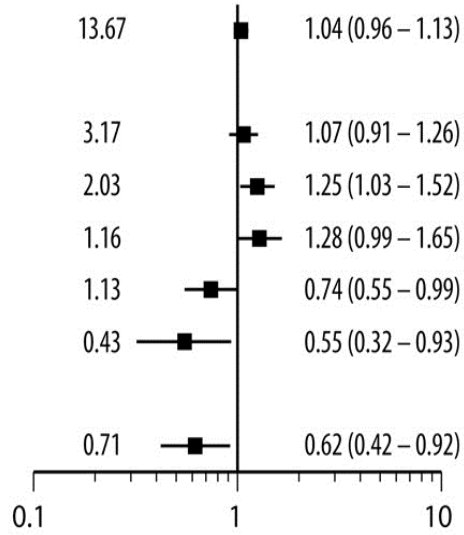
Fox KA et al. Eur Heart J 2011; 32 (19): 2387–2394

European Heart Journal

ROCKET-AF sub-study : Safety According to Renal Function

Clinical Endpoint	CrCl 30 – 49 ml/min			CrCl ≥50 ml/min			P Value
	Rivaroxaban 15 mg (N=1474)†	Warfarin N=1476	HR (95% CI) Rivaroxaban vs Warfarin	Rivaroxaban 20 mg (N=5637)†	Warfarin N=5640	HR (95% CI) Rivaroxaban vs Warfarin	Interaction
Primary Safety Endpoint	17.82	18.28	0.98 (0.84 – 1.14)	14.24	13.67	1.04 (0.96 – 1.13)	0.45
Major Bleeding	4.49	4.70	0.95 (0.72 – 1.26)	3.39	3.17	1.07 (0.91 – 1.26)	0.48
Hematocrit or Hemoglobin Drop	3.76	3.28	1.14 (0.83 – 1.58)	2.54	2.03	1.25 (1.03 – 1.52)	0.65
Transfusion	2.34	2.00	1.17 (0.77 – 1.76)	1.49	1.16	1.28 (0.99 – 1.65)	0.71
Clinical Organ	0.76	1.39	0.55 (0.30 – 1.00)	0.83	1.13	0.74 (0.55 – 0.99)	0.39
Fatal Bleeding	0.28	0.74	0.39 (0.15 – 0.99)	0.23	0.43	0.55 (0.32 – 0.93)	0.53
Intracranial Hemorrhage	0.71	0.88	0.81 (0.41 – 1.60)	0.44	0.71	0.62 (0.42 – 0.92)	0.51





* These data are from the safety population on treatment, which included patients who received at least 1 dose of study drug and were followed regardless of adherence to protocol for events while on study drug or within 2 days of last dose.

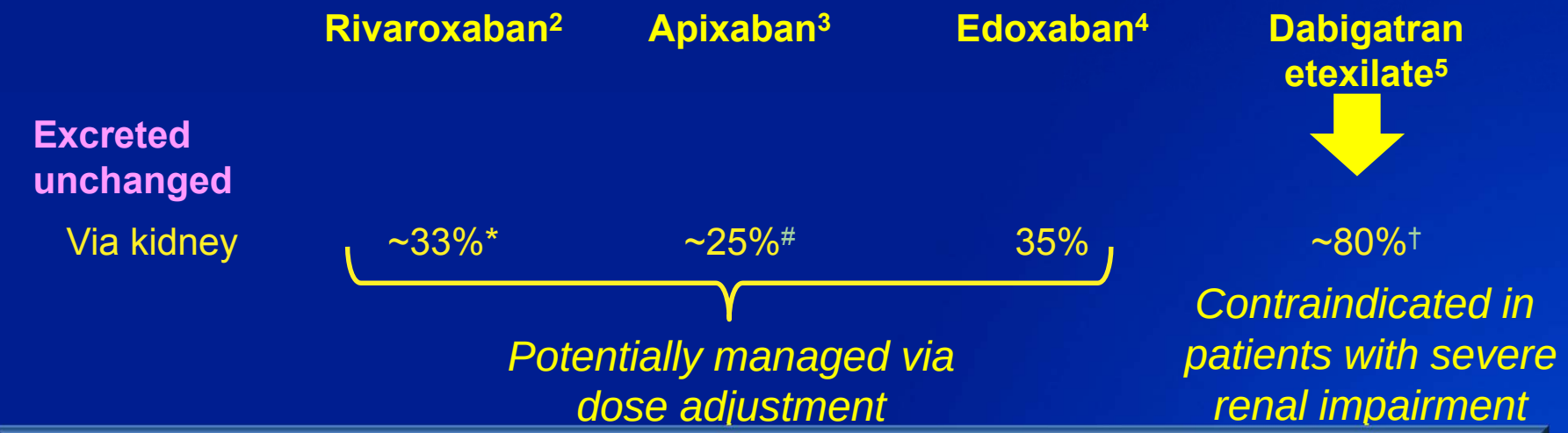
† Event rates per 100 pt/yrs of follow-up

Fox KA et al. Eur Heart J 2011; 32 (19): 2387–2394

European Heart Journal

OAC therapy in patients with renal impairment

- Newer anticoagulants are partially cleared via the renal route
- However, not all new anticoagulants rely on this route to the same extent[1]



- No dabigatran if CrCl < 30 ml/min (role of 75 mg BID dose?)
- No rivaroxaban if CrCl < 15 ml/min (15 mg OD for CrCl 15–50)

1. Eriksson BI *et al*, 2011; 2. Weinz C *et al*, 2009; 3. Raghavan N *et al*, 2008; 4. Ogata K *et al*, 2010;
5. Blech S *et al,* 2008; 6. Xarelto Summary of Product Characteristics 2011.

Japanese safety Issue for Dabigatra

- **6명의 사망사례는 모두, 사용되지 말아야 하거나 특별한 주의가 필요로 했던 환자 : 5명의 환자는 CrCL< 30ml/min이하의 중증 신장애로 사용상의 금기환자**

Case ID	Sex	Age	Weight	Derived Drugs combined	Derived Events combined	Disease (Concomitant Disease)	Disease (Past	Assessment of renal function (based on information from Japan
2011-B								Crea 2.21 mg/dl; CrCL 13 ml/ min
2011-B				CELECOX | LASIX | DEPAS | MAGLAX | KREMEZIN | LAC-B | MUCOSTA | ACTONEL | PATANOL	obstruction		PROLAPSE, SF COMPRESSIO FRACTURE	Crea 1.7 mg/dl, CrCL 11 ml/min
2011-BP-16407NB	Female	100	40	Suspecte drug: PRAZAXA (PRADAXA) Comed: EVISTA | STOMARCON | DOMPERIDONE | ACARDI | ZYLORIC | PIROLACTON	Gastrointestinal haemorrhage | Marasmus | Haemorrhage subcutaneous	Atrial fibrillation, Cardiac failure chronic		Crea 1.2 mg/dl; CrCL 27 ml/ min
2011-BP-18851NB	Male	85	43	Suspecte drug: PRAZAXA (PRADAXA) Comed: BAYASPIRIN | LOCHOL | MECOBALAMIN | MICARDIS | TENORMIN | WARFARIN	Gastrointestinal haemorrhage | Disseminated tuberculosis | Nausea | Dehydration | Decreased appetite | Heat illness | Headache	DIABETES MELLITUS, HYPERLIPIDAEMIA, HYPERTENSION, MYOCARDIAL INFARCTION	CEREBRAL INF	Crea 1.2 mg/dl; CrCL 53 ml/ min
2011-BP-18855NB	Male	76	67	Suspecte drug: PRAZAXA (PRADAXA) | BAYASPIRIN Comed: TAKEPRON | BIOFERMIN | LENDORMIN D | KETOBUN | NITREZIC Past Med: WARFARIN	Shock haemorrhagic | Haemorrhage | Retroperitoneal haemorrhage | Haemorrhagic diathesis | Haemoglobin decreased | Fall | Gingival bleeding	CHRONIC RENAL FAILURE, GOUT, HEPATOPATHY ALCOHOLIC, HYPERTENSION, NORMAL PRESSURE HYDROCEPHALUS	GASTRIC ULC	
2011-BP-19279NB	Female	83	39	Suspecte drug: PRAZAXA (PRADAXA) | BAYASPIRIN Comed: GASTER | ARTIST | DIART | VASOLAN | ASPARA POTASSIUM Past Med: WARFARIN | DIOVAN	Haemorrhagic diathesis | Melaena | Gastrointestinal haemorrhage | Shock haemorrhagic | Haematuria | Disseminated intravascular coagulation | Multi-organ failure	CARDIAC FAILURE CHRONIC, VENTRICULAR TACHYCARDIA	FRACTURE OF DISTAL RIGHT	Crea 1.15 mg/dl CrCL 23 ml/min

Patients with hepatic impairment

Guidance

- Xarelto is contraindicated in patients with hepatic disease associated **with coagulopathy and clinically relevant bleeding risk**, including cirrhotic patients with **Child class B and C**

Evidence

- Child-Pugh is a scoring system to assess the severity of hepatic impairment
- It takes into account a number of clinical and lab parameters including haemostasis parameters
- Patients with significant hepatic disease (eg, acute clinical hepatitis, chronic active hepatitis, liver cirrhosis) were excluded from clinical trials

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

Populations potentially at higher risk of bleeding: Concomitant drugs

Guidance

- Rivaroxaban has **a low propensity for drug-drug interactions** with frequently used medications*
- Due to the dual mode of metabolism of rivaroxaban (via the **CYP3A4 and P-GP pathway**), **drugs that are strong inhibitors of both pathways** cause a clinically relevant influence on rivaroxaban and are not recommended for concomitant use
  - **Systemic azole-antimycotics** or **HIV protease inhibitors**

Evidence

- Substances that are strong inhibitors of both CYP3A4 and P-gp may increase plasma concentrations of Xarelto
- Drugs that affect the hemostatic system may further increase the risk of bleeding
- More details can be found in the SmPC

*Use with care when there is concomitant renal impairment

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

Concomitant drugs

Co-medications	Recommendation
Macrolide antibiotics • Clarithromycin • Erythromycin	**No clinical relevant interactions** have been noted and rivaroxaban can be used in patients taking these medications
Non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors or other antithrombotic agents such as: • Naproxen • Acetylsalicylic acid • Clopidogrel • Enoxaparin • Warfarin • Acenocoumarol, etc	**Care is to be taken**, due to the increased bleeding risk.
Other commonly used medications: • Midazolam (substrate of CYP3A4) • Digoxin (substrate of P-gp) • Atorvastatin (substrate of CYP3A4 and P-gp).	**No clinically significant** pharmacokinetic or pharmacodynamic interactions were observed with rivaroxaban

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

Concomitant drugs

Co-medications	Recommendation
Strong CYP3A4 inducers • Rifampicin • Phenytoin • Carbamazepine • Phenobarbital • St. John's Wort	Medications in this class should be co-administered *with caution.*
Strong CYP3A4 and P-gp inhibitors: • Ketoconazole • Itraconazole • Voriconazole • Posaconazole **Or HIV protease inhibitors**: e.g. Ritonavir	It is ***not recommended*** to co-administer these drugs with rivaroxaban due to an increased bleeding risk. BUT • **Fluconazole** is expected to have less effect on rivaroxaban exposure and **can be co-administered with caution**
Dronedarone **Amiodarone**	Co-administration with rivaroxaban **should be avoided** due to limited clinical data Can be used **with caution**, esp. renal impairment case

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

Populations potentially at higher risk of bleeding: AF and ACS dual indication

Guidance

- There is currently **very limited experience** in patients with AF receiving rivaroxaban 20 mg once daily concomitantly **with dual antiplatelet therapy**
- Once dual antiplatelet therapy is stopped and **single antiplatelet therapy** is continued, **rivaroxaban 20 mg once daily** (15 mg once daily for patients with moderate or severe renal impairment) is the recommended dose to ensure adequate protection from AF related stroke

Evidence

- The addition of antiplatelet therapy to OAC therapy increases the risk of bleeding
- Patients on dual antiplatelet therapy were excluded from the ROCKET-AF study
- Based on results from **ATLAS clinical trial**, doses of rivaroxaban higher than 5 mg twice-daily should not be given concomitantly with dual antiplatelet therapy

The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology *Eur Heart J* 2010;31:2369–2429

Patients with other hemorrhagic risk factors

Guidance

- Xarelto is to be used **with caution** in patients with other hemorrhagic risk factors such as:
  - uncontrolled severe arterial hypertension
  - active ulcerative gastrointestinal disease
  - recent gastrointestinal ulcerations
  - vascular retinopathy
  - recent intracranial or intracerebral haemorrhage
  - intraspinal or intracerebral vascular abnormalities
  - recent brain, spinal or ophthalmological surgery
  - bronchiectasis or history of pulmonary bleeding
- Xarelto **is contraindicated during pregnancy.** Women of child-bearing potential should avoid becoming pregnant during treatment with Xarelto

Evidence

- Patients with medical conditions that are predisposing for bleeding are at higher risk when receiving anticoagulation therapy
- Further described in the SmPC and medical literature

Ref: Summary of Product Characteristics. http://www.xarelto.com/html/downloads/Xarelto_Summary_of_Product_Characteristics_Dec2011.pdf

Perioperative Management

- **Alteration of oral anticoagulant regimen *may not be necessary for most patients undergoing low risk procedures:***
  - Dental procedures (including extractions of up to 4 teeth), joint and soft tissue injections, arthrocentesis, cataract surgery, upper endoscopy or colonoscopy with/without biopsy
- **For other invasive and surgical procedures, oral anticoagulation needs to be withheld:**
  - Decision should be individualized based on an estimation of the patient's risks of thromboembolism and bleeding

Perioperative management – Summary of CCS Guidelines

- **Patients with Very Low to Moderate Stroke Risk ($CHADS_2$ ≤2):**
  - In patients with **low bleeding risk**:
    - Continue antithrombotic therapy
  - In patients with **high bleeding risk:**
    - Stop antithrombotic therapy pre-procedure and reinstitute when risk of bleeding is reduced
- **Patients with High Stroke Risk ($CHADS_2$ ≥3):**
  - In patients with **low bleeding risk**:
    - Continue antithrombotic therapy or provide bridging therapy perioperatively
  - In patients with **high bleeding risk:**
    - Stop antithrombotic therapy and provide bridging therapy perioperatively

Cairns *et al*. *Can J Card* 2011 27:74-90

Antidote

- rFactor VII
- PCC (Prothrombin complex concentrates) : Beriplex®, FEIBAS® --
- PRT064445: FXa Inhibitor Antidote

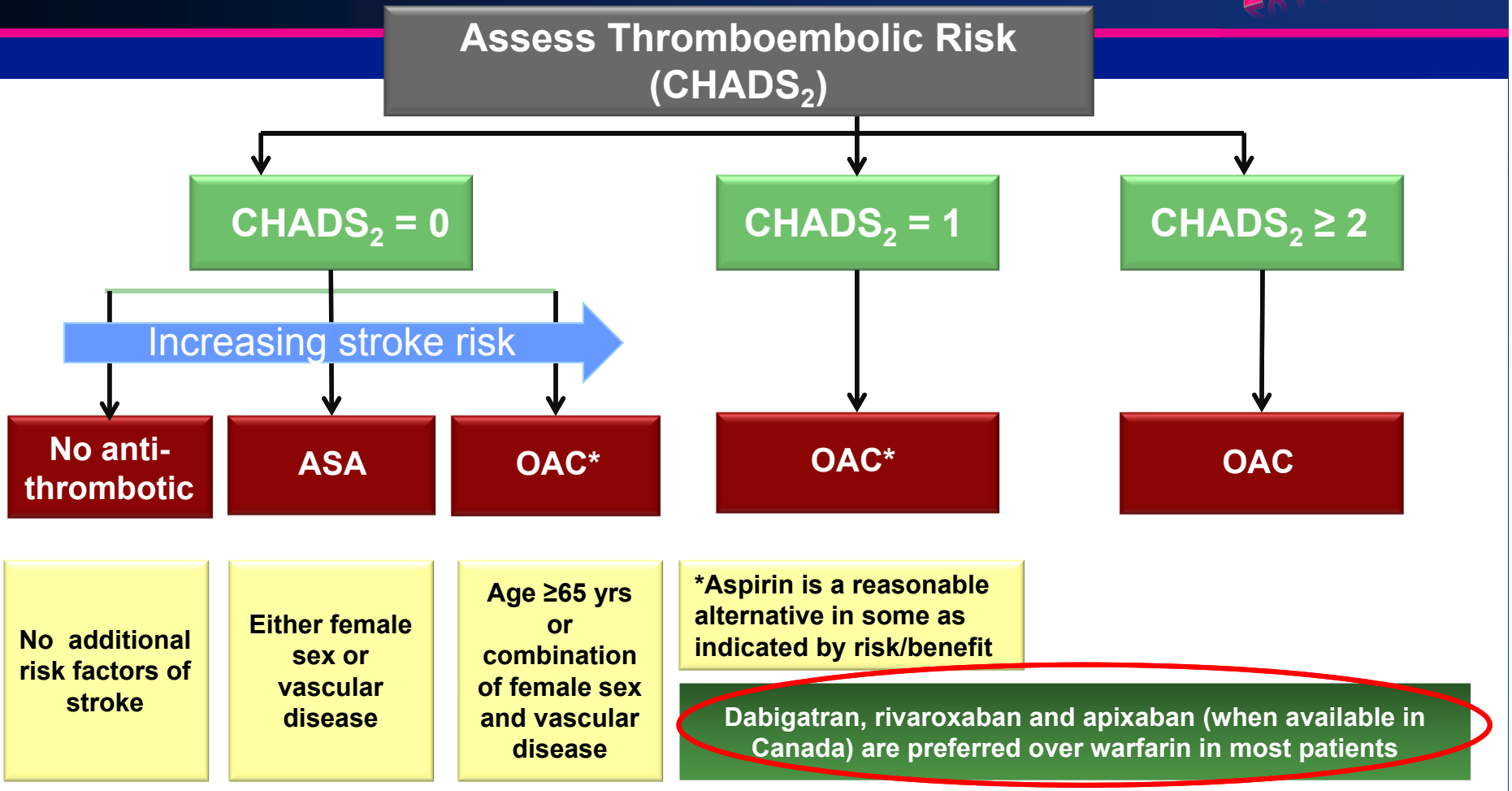
ESC2011-Abstract 3715

Reversal of Rivaroxaban-Mediated Anticoagulation in Animal Models by a Recombinant Antidote Protein (r-Antidote, PRT064445)

- Short half-life of new agents →anti-dote의 필요성↓

Overview of Thromboembolic Management

2012 UPDATE!




감사합니다!