Characteristics of NOAC

Wonkwang University Hospital

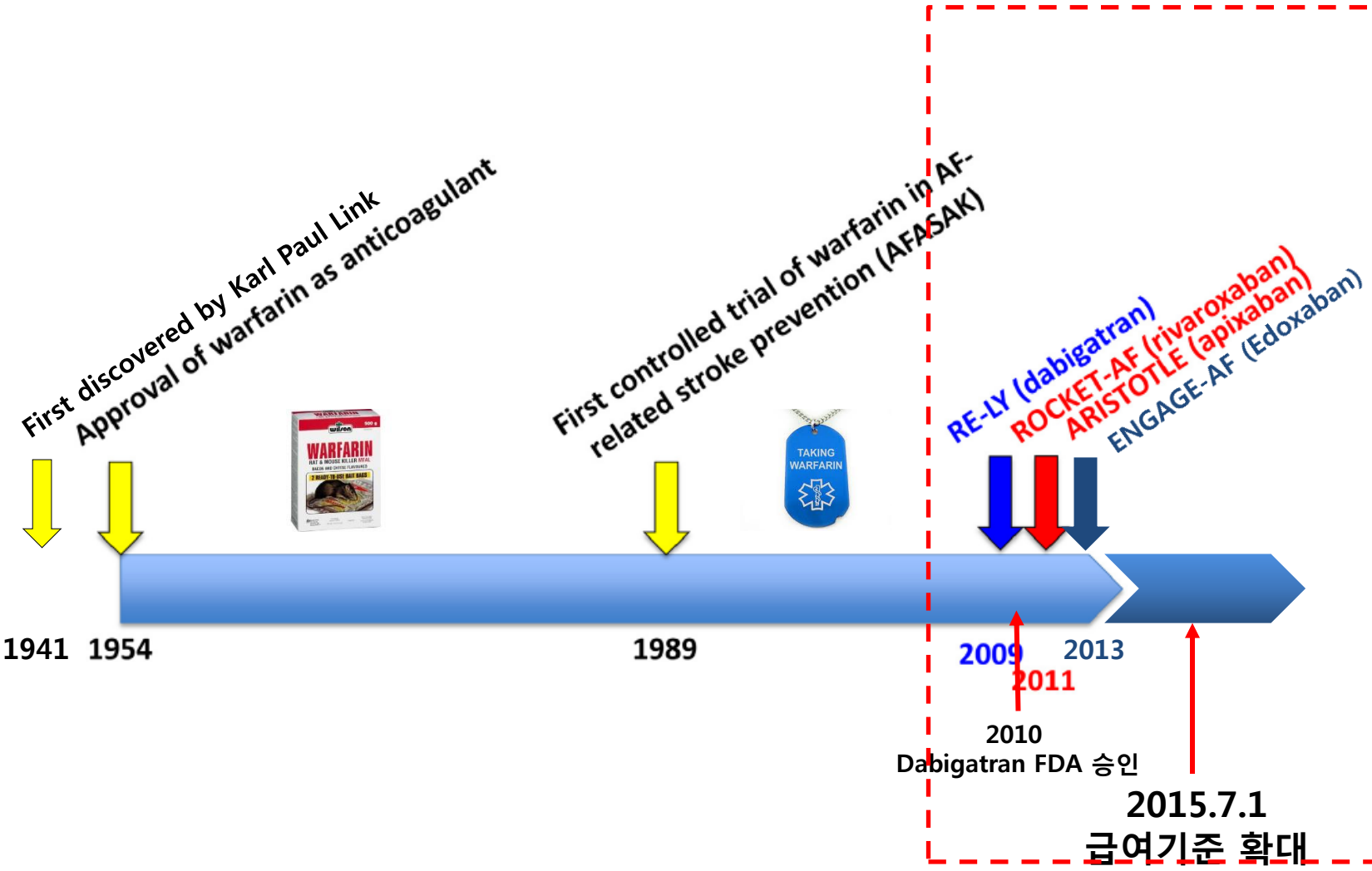
Kim, Nam-Ho

Difference

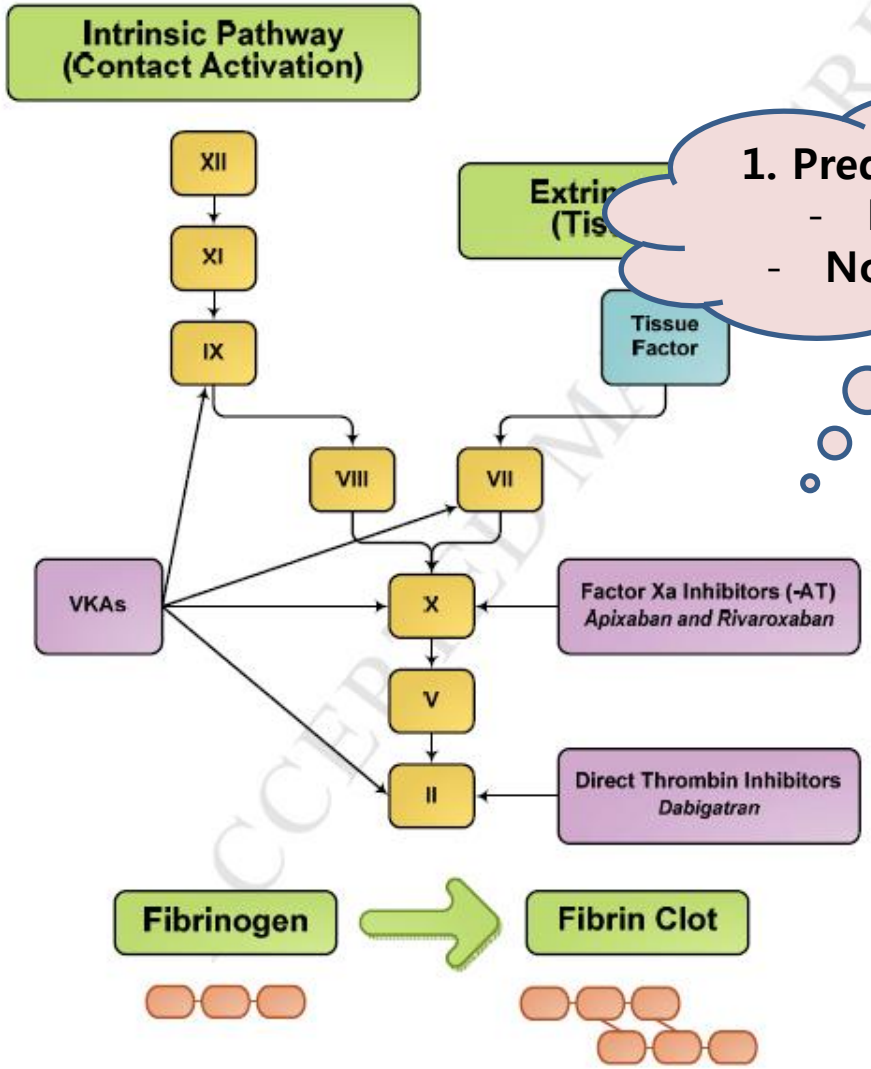
NOAC

- Target specificity
- Absorption and metabolism
- Race difference

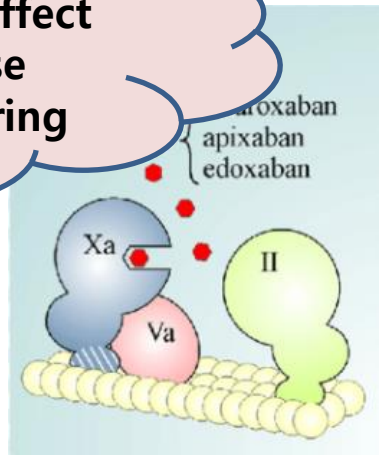
Oral Anticoagulants

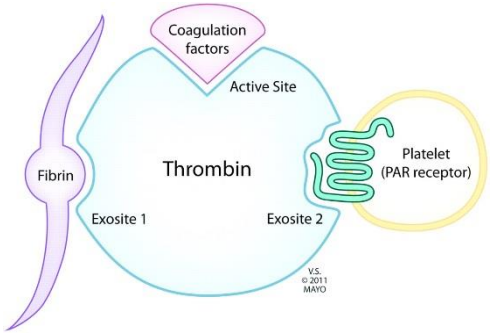


1. Target Specificity



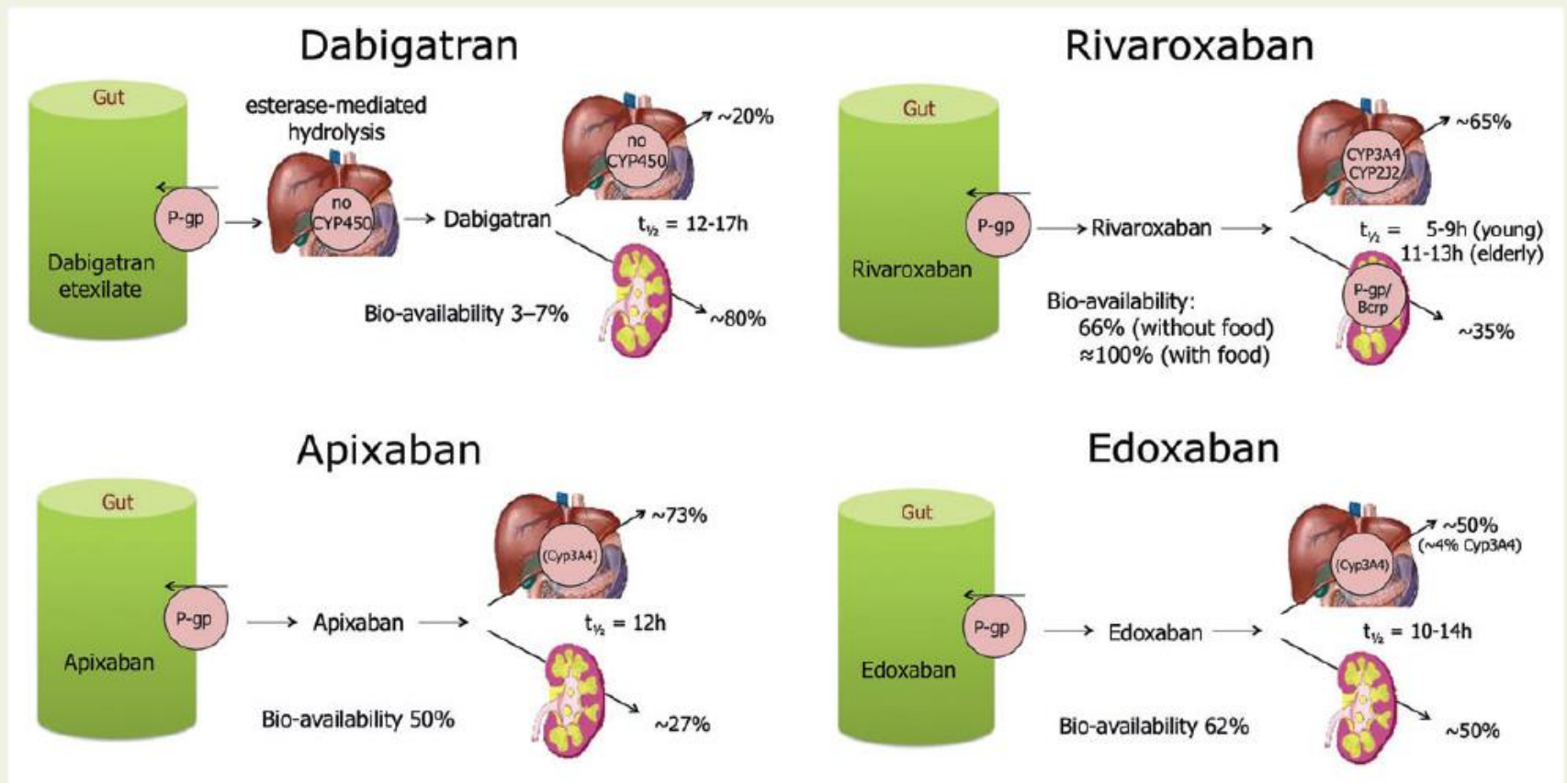
1. Predictable effect
   - Fixed dose
   - No monitoring





Nutescu EA, et al. Cleve Clin J Med 2005

2. Uptake, Metabolism, and Elimination



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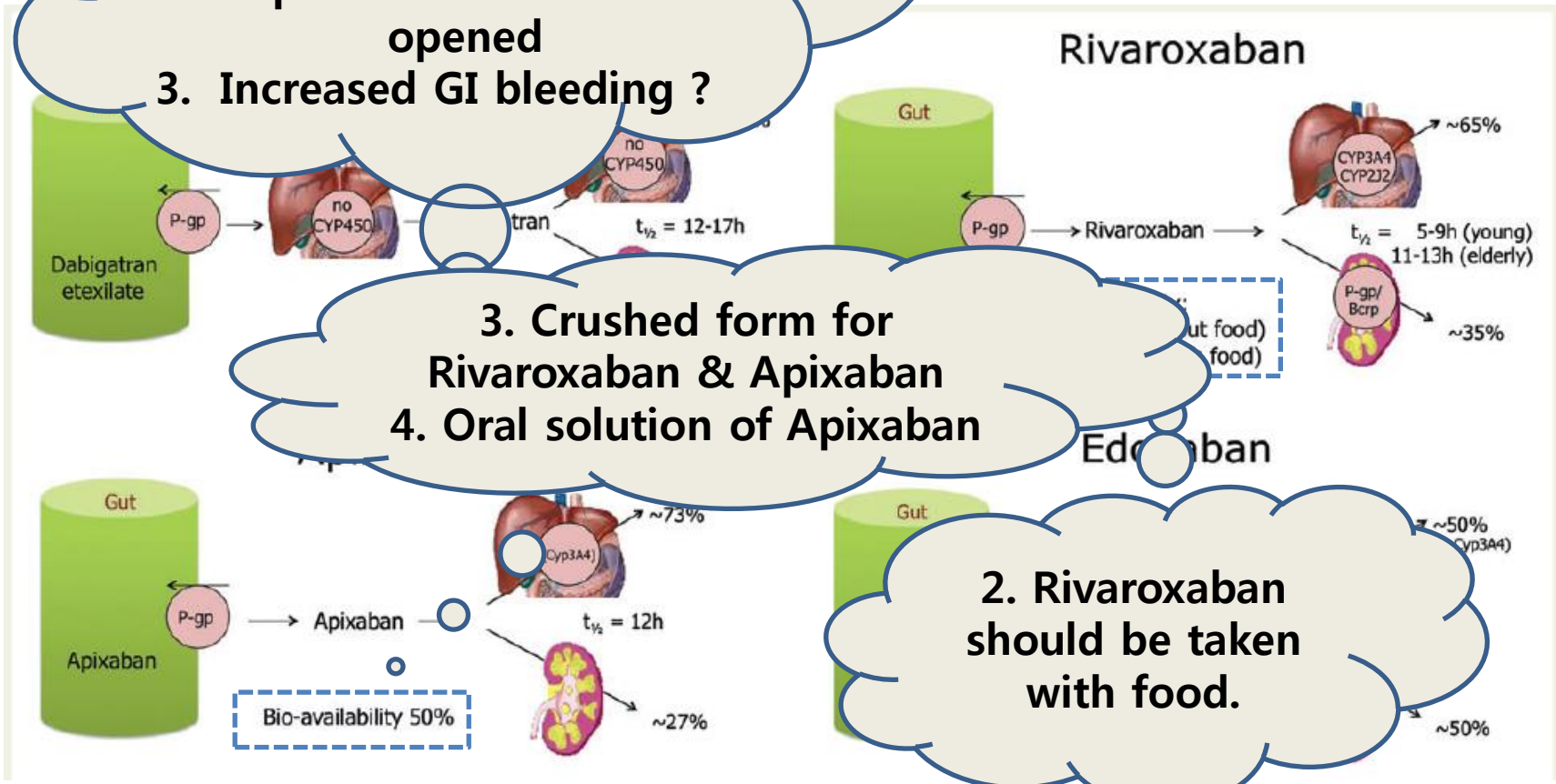
2 Concentration

1. Slight fluctuation in absorption >>> greater impact on plasma levels : PPI & H2B
2. Capsules should not be opened
3. Increased GI bleeding ?



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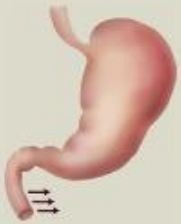
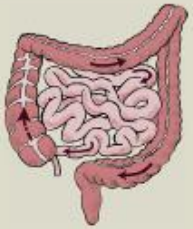
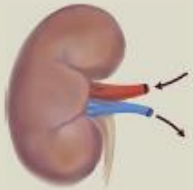
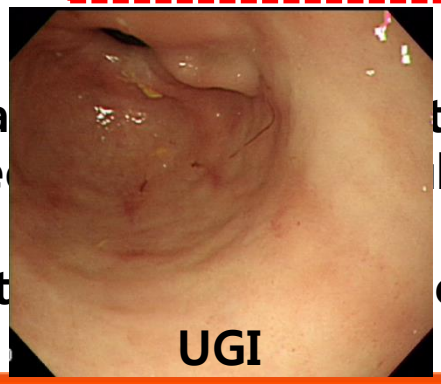
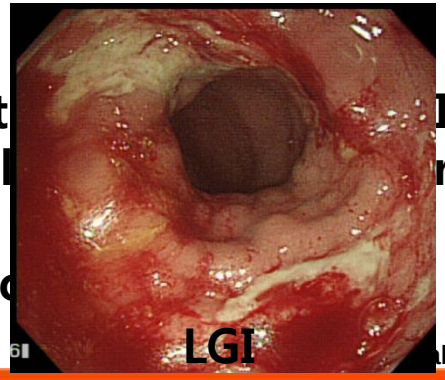
2.1.1. GI Bleeding

	Bioavailability	Active anticoagulant present in GI tract	Renal excretion	Hepatic metabolism
				
Warfarin	100%	None	None	High
Dabigatran	7%	High	High	Low
Rivaroxaban	66%	Moderate	Moderate	Moderate
Apixaban	50%	Moderate	Moderate	Moderate

Dabigatran

1. non-absorbed, a t I tract lumen promotes GI ble l rosions or angiectasia)
2. The drugs direct c

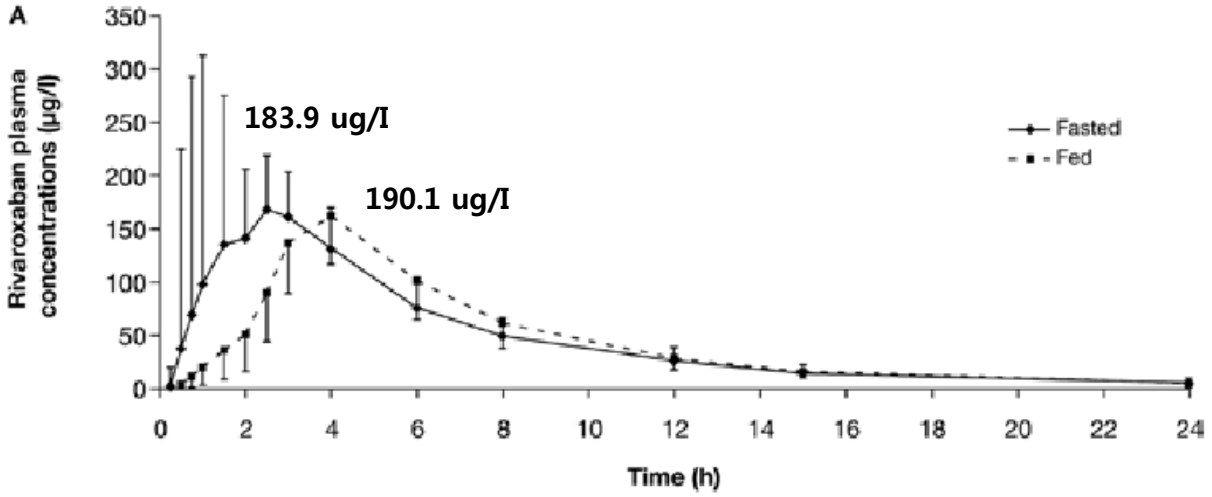




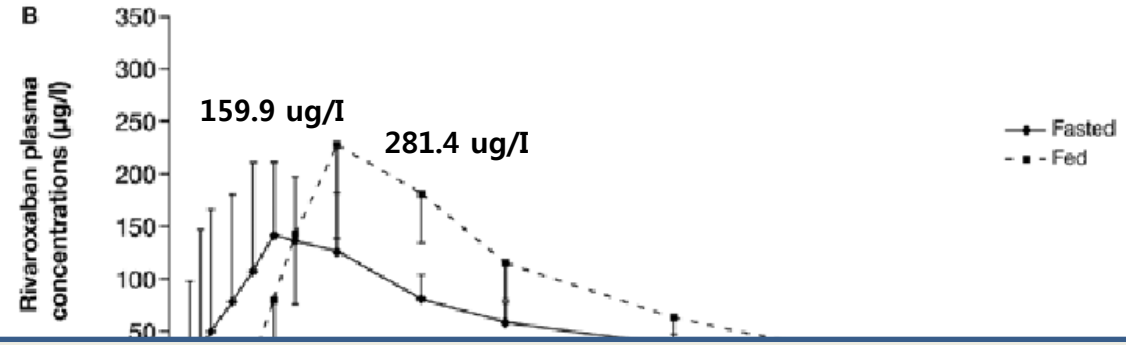
l. Gastroint Endoscopy 2013;78:227-239

2.1.2. Effect of Food on Rivaroxavan

10 mg



20 mg

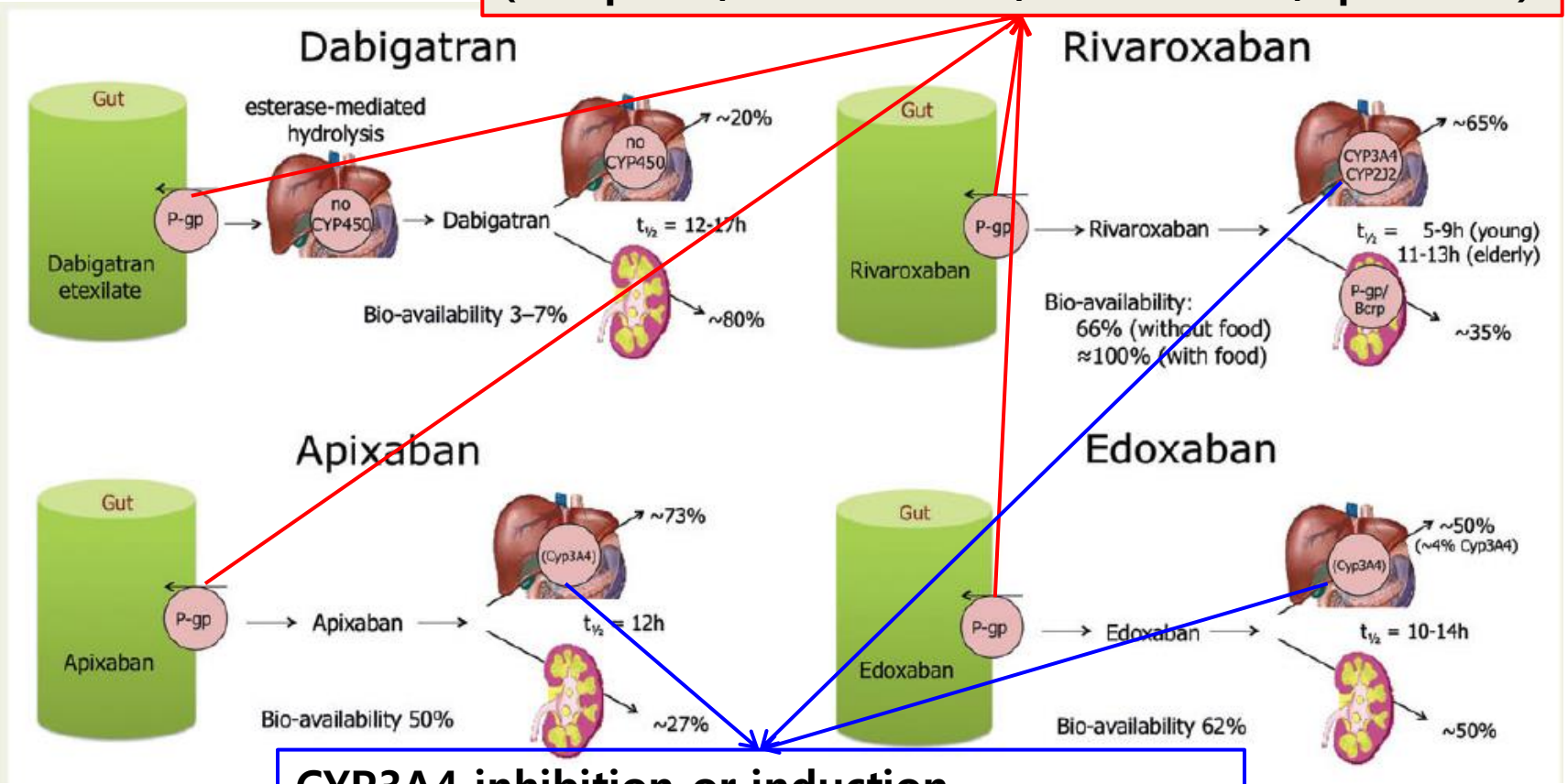


High bioavailability (≥ 80%) of 15 mg and 20 mg rivaroxaban was achieved when taken with food; therefore, these doses need to be taken with food.

49-561.

2.2. Metabolism - Drug Interaction

P-glycoprotein inhibitors
(verapamil, dronedarone, amiodarone, quinidine)



CYP3A4 inhibition or induction
- Induction : rifampicin, carbamazepine etc

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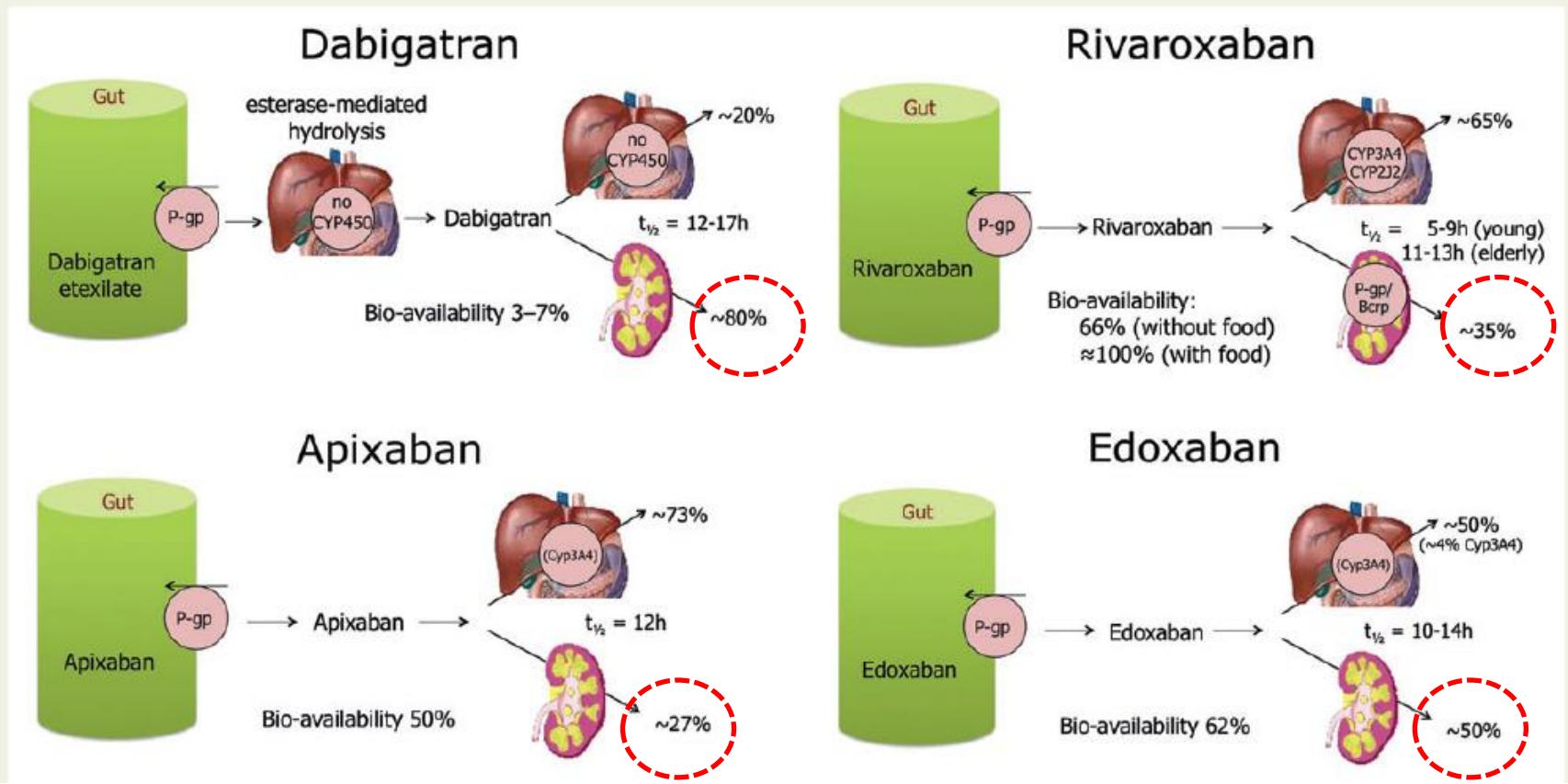
2.2.1. Drug-Drug Interaction

			via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic dru	**Other cardiovascular drugs**	**Fungostatics**					
Amiodarone	Atorvastatin	Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[247]
Digoxin	**Antibiotics**	Itraconazole; Ketoconazole; Posaconazole; Voriconazole;	potent P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg if CrCl 30-50 ml/min)	+100%[60]	+87-95%[64] (reduce NOAC dose by 50%)	Up to +160%[247]
Diltiazem	Clarithromycin; Erythromycin	**Immunosuppressive**					
Dronedarone	Rifampicin***	Cyclosporin; Tacrolimus	P-gp competition	Not recommended	No data yet	+73%	Extent of increase unknown
Quinidine		**Antiphlogistics**					
Verapamil	**Antiviral drugs**	Naproxen	P-gp competition	No data yet	+55%[254]	No effect (but pharmacodynamically increased bleeding time)	No data yet
	HIV protease inhibitor (e.g. ritonavir)	**Antacids**					
		H2B; PPI; Al-Mg-hydroxide	GI absorption	Minus 12-30%[45, 53, 58]	No effect[55]	No effect	No effect[241, 242]
		Others					
		Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	**minus 66%[253]**	**minus 54%[SmPC]**	minus 35%	**Up to minus 50%**

2.3. Elimination - CKD



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2.3.1 Estimated Drug Half-lives & Plasma Concentration in Different Stages of CKD

	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.

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2.3.2. Approved European Labels for NOACs and Their Dosing in CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Red: contra-indicated/not recommended. **Orange**: reduce dose as per label. **Yellow**: consider dose reduction if two or more 'yellow' factors are present (see also *Table 6*).
CKD, chronic kidney disease; CrCl, creatinine clearance; BID, twice a day; OD, once daily; SmPC, summary of product characteristics.

[a]The SmPC specifies dose reduction from 5 to 2.5 mg BID if two of three criteria are fulfilled: age ≥80 years, weight ≤60 kg, serum creatinine >1.5 mg/dL.

[b]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high CrCl after a careful evaluation of the individual thrombo-embolic and bleeding risk' because of a trend towards reduced benefit compared to VKA.

[c]No EMA indication. FDA recommendation based on PKs. Carefully weigh risks and benefits of this approach. Note that 75 mg capsules are not available on the European market for AF indication.

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3. Race Difference

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Bioavailability	3 to 7%	50%	62%[51]	66% without food. Almost 100% with food
Prodrug	Yes	No	No	No
Clearance non-renal/renal of absorbed dose (if normal renal function; see also 'Patients with chronic kidney disease' section)[a]	20%/80%	73%/27%[52–55]	50%/50%[36,51,56]	65%/35%
Liver metabolism: CYP3A4 involved	No	Yes (elimination, moderate contribution)[57]	Minimal (<4% of elimination)	Yes (elimination, moderate contribution)
Absorption with food	No effect	No effect	6–22% more; minimal effect on exposure[58]	+39% more[59]
Intake with food recommended?	No	No	No	Mandatory
Absorption with H2B/PPI	−12 to 30% (not clinically relevant)[60–62]	No effect[63]	No effect	No effect[59,64]
Asian ethnicity	+25%[62]	No effect	No effect[58]	No effect
GI tolerability	Dyspepsia 5 to 10%	No problem	No problem	No problem
Elimination half-life	12 to 17 h[61]	12 h	10–14 h[51,65]	5–9 h (young) 11–13 h (elderly)

H2B, H2-blocker; PPI, proton pump inhibitor; GI, Gastrointestinal.
[a]For clarity, data are presented as single values, which are the mid-point of ranges as determined in different studies.

3.1. Effect of Race on Dabigatran - RE-LY trial -

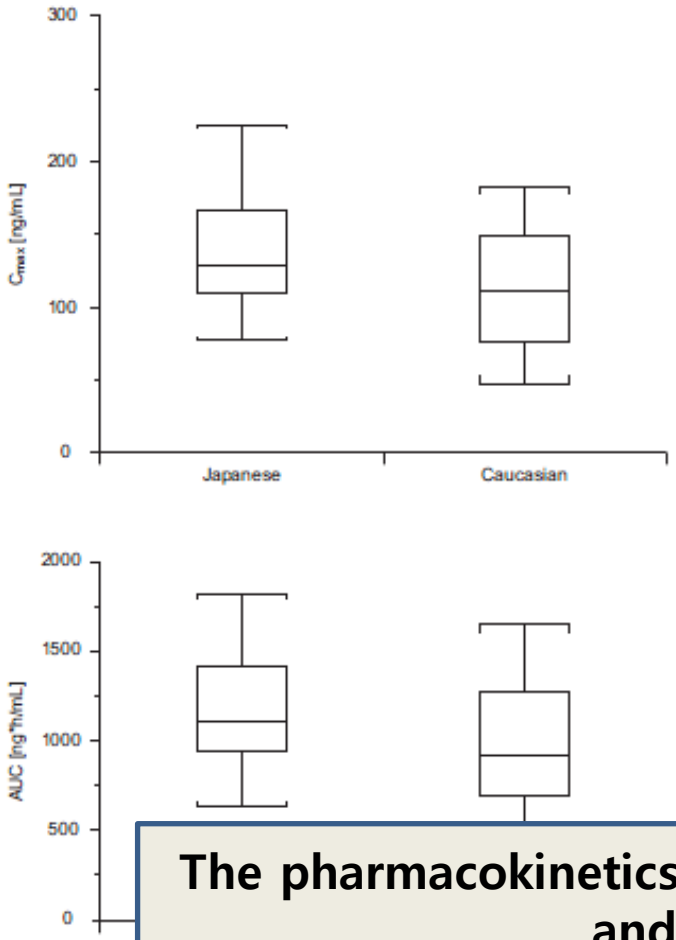
Covariate	Effect on model parameters	Effect on AUC_{ss}
CRCL	Increase in CL/F according to an E_{max} function with E_{max} = 124 L h^{-1}, EC_{50} = 56.7 mL min^{-1} and power = 1.29. CL/F increases with increasing CRCL	Patients with CRCL of 30 and 50 mL min^{-1} have a 1.8-fold and 1.2-fold increased AUC_{ss}, respectively, as compared with the median CRCL of 69 mL min^{-1}
Age	Decrease of 0.41% in CL/F per year older than the median of 72 years (and vice versa)	A 97-year-old patient has an approximately 11.5% increased AUC_{ss} as compared with a 72-year-old patient
Sex	Decrease of 8.3% in CL/F in female patients	Females have a 9.1% increased AUC_{ss} as compared with male patients
South Asian	Decrease of 20.3% in CL/F in the ethnic group of South Asian patients	AUC_{ss} is increased by 25.5% in South Asians as compared with other ethnicities
HF	Decrease of 6.7% in CL/F in patients with HF of class II, III, or IV	AUC_{ss} is increased by 7.2% in patients with HF of class II–IV as compared with patients without HF or with class I HF
Weight	Increase of 0.77% in V_2/F per 1-kg increase above the median weight of 80 kg (and vice versa)	Weight has no effect on AUC_{ss}
Hemoglobin	Decrease of 4.0% in V_2/F per 1 g dL^{-1} increase above the median hemoglobin concentration of 14.3 g dL^{-1} (and vice versa)	Hemoglobin has no impact on AUC_{ss}
Verapamil	Increase of 23% in bioavailability with coadministration of verapamil	Patients with coadministration of verapamil have 23% increased AUC_{ss}
Amiodarone	Increase of 12% in bioavailability with coadministration of amiodarone	Patients with coadministration of amiodarone have 12% increased AUC_{ss}
PPIs	Decrease of 12.5% in bioavailability with coadministration of PPI	Patients with coadministration of PPI have 12.5% decreased AUC_{ss}

CRCL, creatinine clearance; HF, heart failure; PPI, proton-pump inhibitor. For the calculation of the effect of a particular covariate, all other covariates are assumed to have no effect (i.e. either at the median value or not present, e.g. in case of comedications).

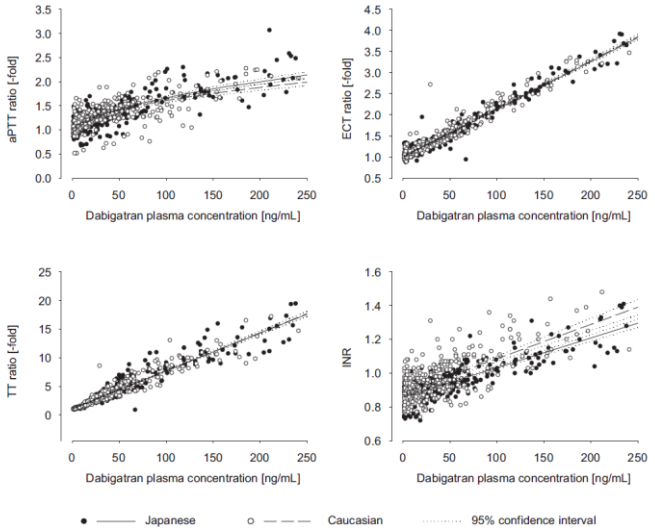
Liesenfeld KH, et al. J Thromb Haemost 2011;9:2168-2175.

3.2. Pharmacokinetic Effect of Dabigatran in Japanese and Caucasian

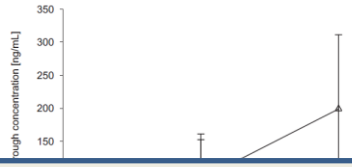
A. Cmax and total AUC after oral administration of dabigatran etexilate 150 mg



B. Anti-coagulation parameters vs plasma concentration of dabigatran



C. Correlation between trough plasma concentration and dabigatran dose

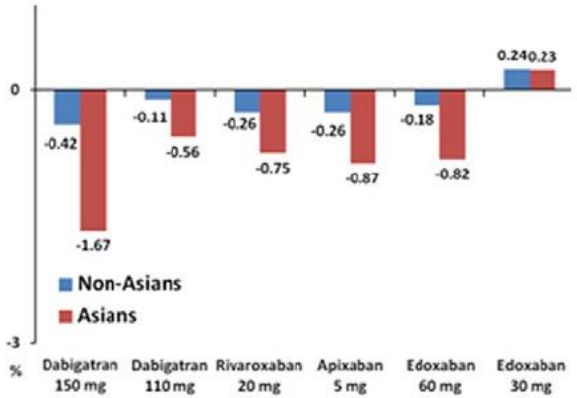


The pharmacokinetics of dabigatran are similar in Japanese and Caucasian subjects.

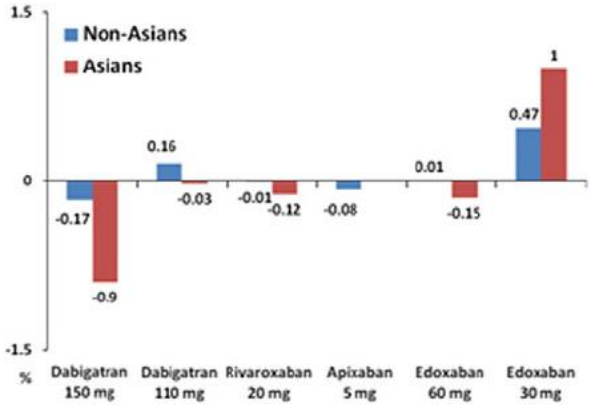
J Thromb Haemost 2012;107:260-269.

3.3. Absolute Risk Reduction in Efficacy with NOACs vs Warfarin

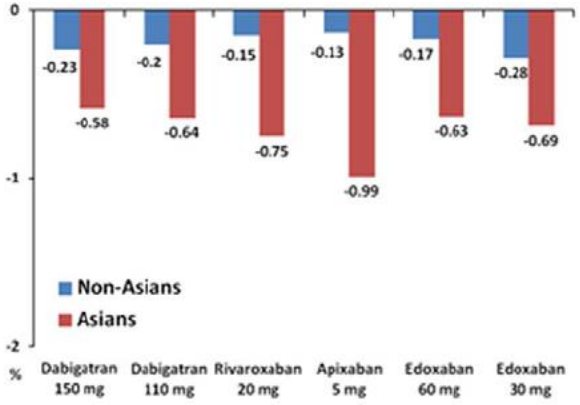
Stroke and Systemic Embolism



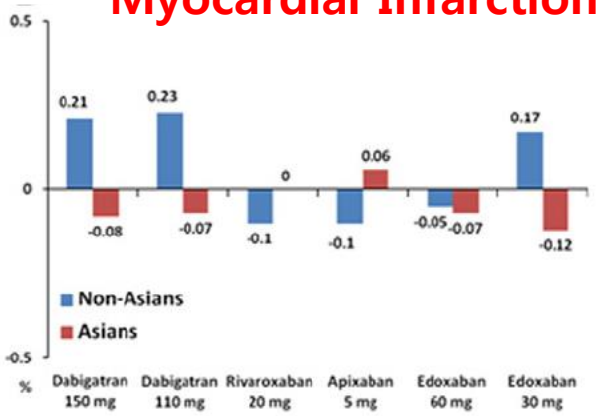
Ischemic Stroke



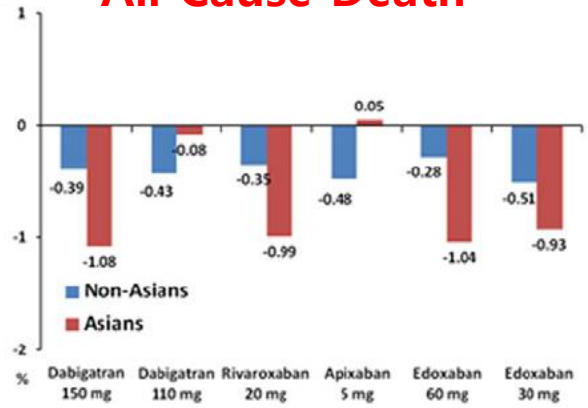
Hemorrhagic Stroke



Myocardial Infarction



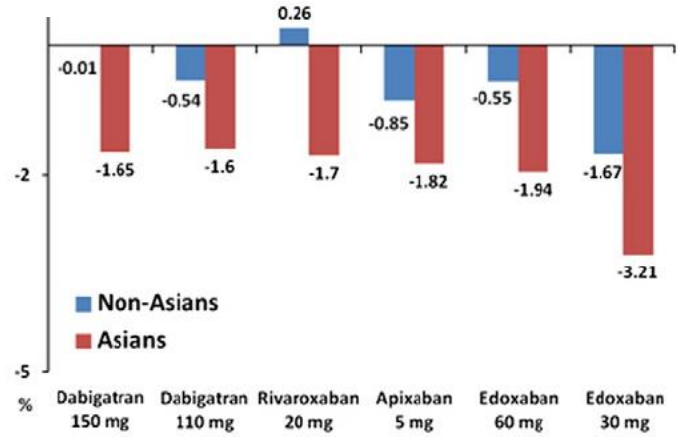
All Cause Death



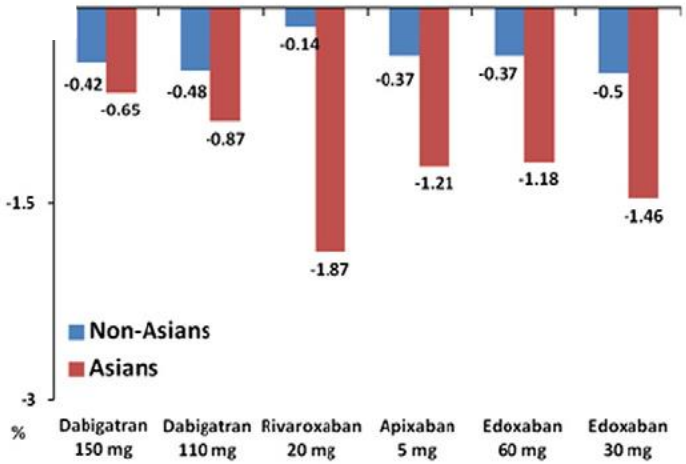
Lip GY, et al. Int J Cardiol 2015;180:246-254

3.3. Absolute Risk Reduction in Safety with NOACs with Warfarin

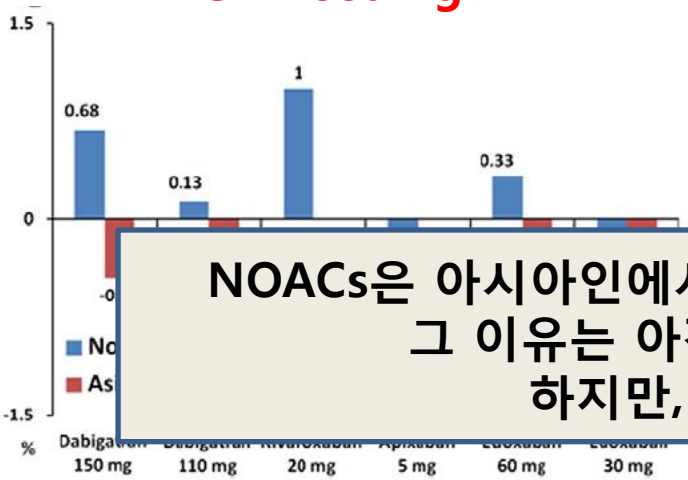
Major Bleeding



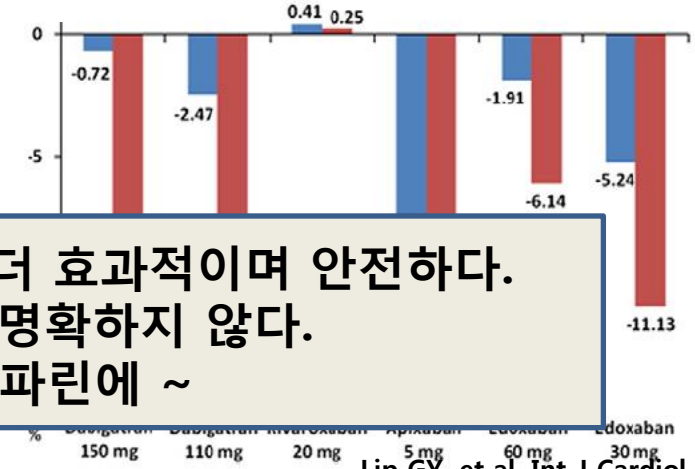
Intracranial Hemorrhage



GI Bleeding



All Bleeding



NOACs은 아시아인에서 더 효과적이며 안전하다.
그 이유는 아직 명확하지 않다.
하지만, 와파린에 ~

Lip GY, et al. Int J Cardiol 2015;180:246-254

Summary

- NOACs은 specific target을 갖는 항응고제이다.
- NOACs은 비슷하면서도 각자 조금씩 다른 약리학적 성질을 갖고 있다. 그러므로 이를 잘 이해하여 약물을 선택하여야겠다.

감사합니다.