

“Experience with NOAC in high risk bleeding patients at Severance Hospital”

Boyoung Joung, MD, PhD

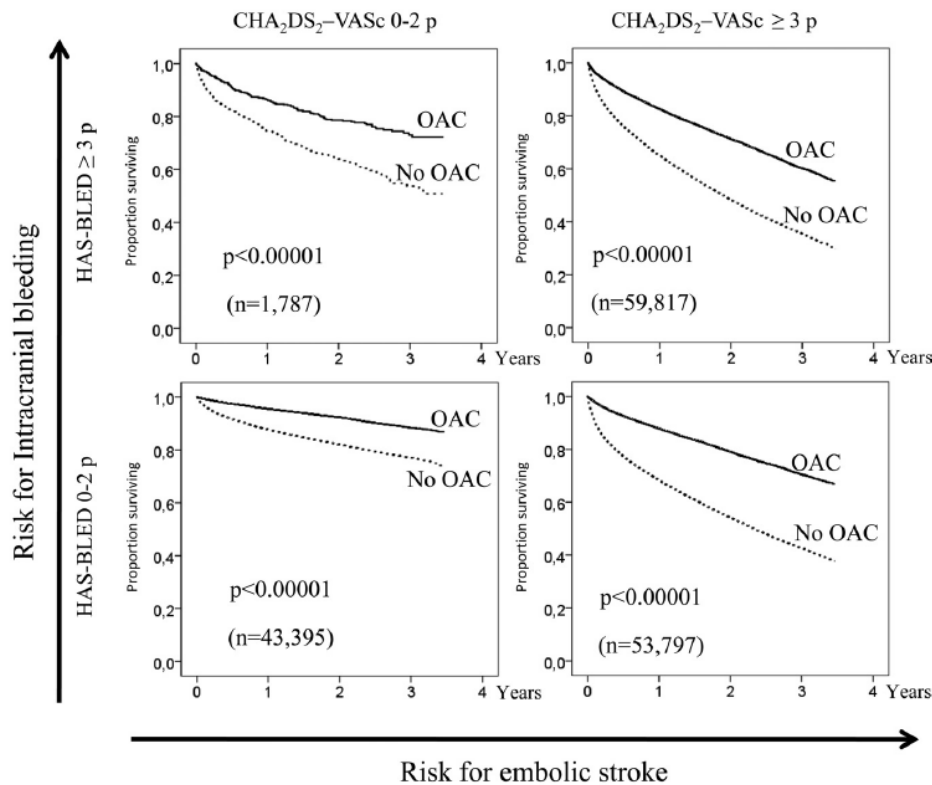
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Division of Cardiology, Department of Internal Medicine
Severance Cardiovascular Hospital
Yonsei University College of Medicine**

Experience with NOAC in patients with high risk bleeding

Background: Unknown anticoagulation effect in high risk subgroups

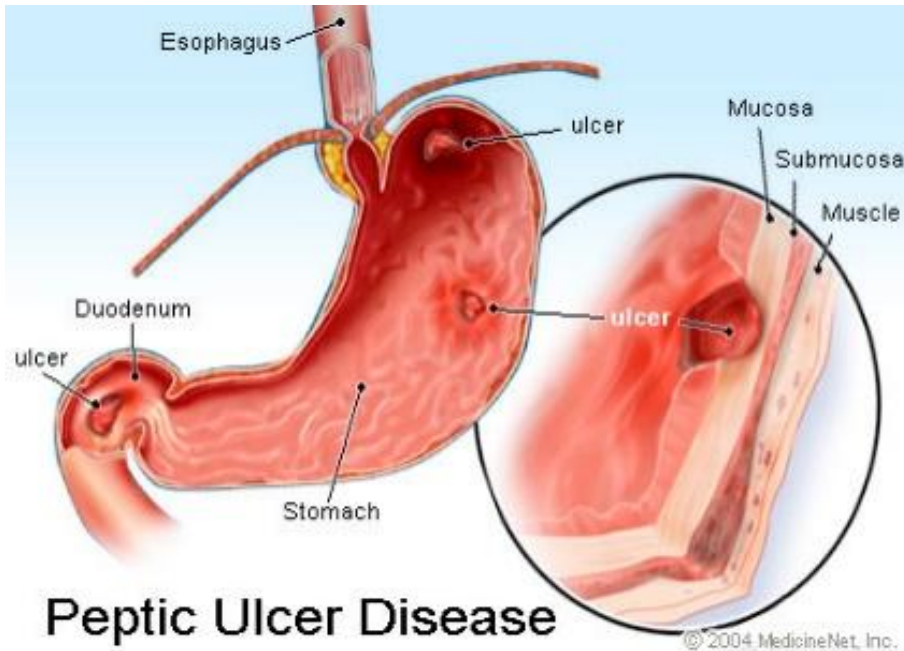
Net clinical benefit of warfarin in patients with AF:
a report from the Swedish AF cohort study.

NOAC 제외군 (출혈 고위험군)



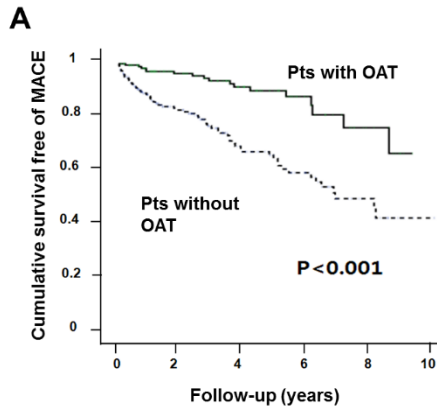
- 최근 주요 수술
- 수술 예정
- 뇌출혈, 안구출혈, 관절 출혈
- 소화기 출혈
- 위십이지장궤양
- 출혈 질환, 출혈 성향
- 종양, 방사선 치료

Friberg L, et al. Circulation 2012;125:2298-307



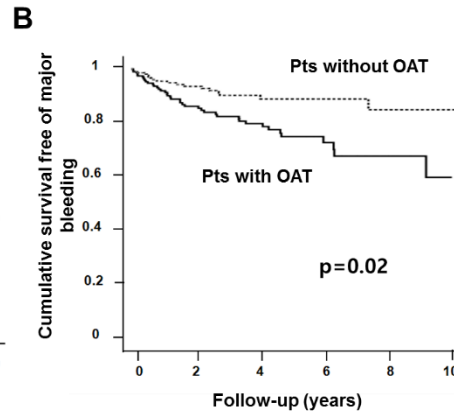
Peptic Ulcer Disease

Peptic Ulcer Disease



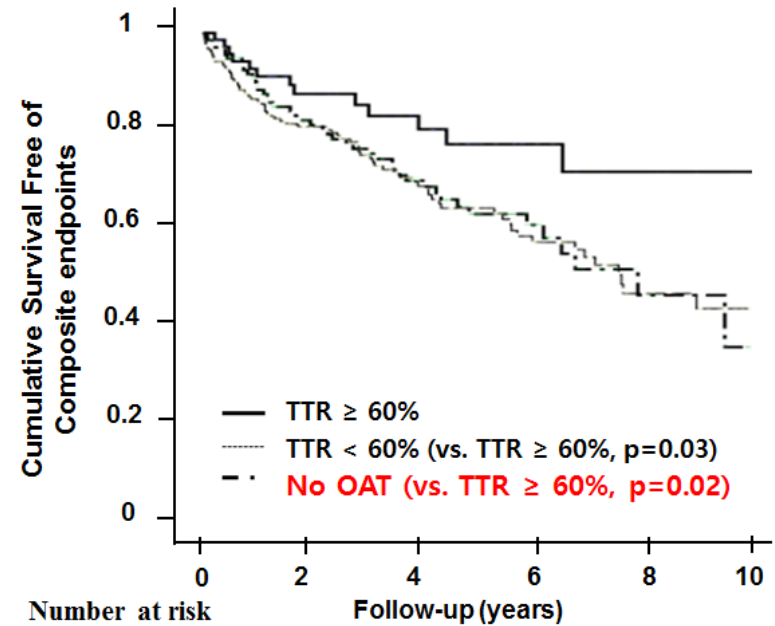
Number at risk

OAC +	200	122	80	35	14	1
OAC -	230	130	72	41	17	2



Number at risk

OAC +	200	135	83	40	19	2
OAC -	230	127	79	35	17	1

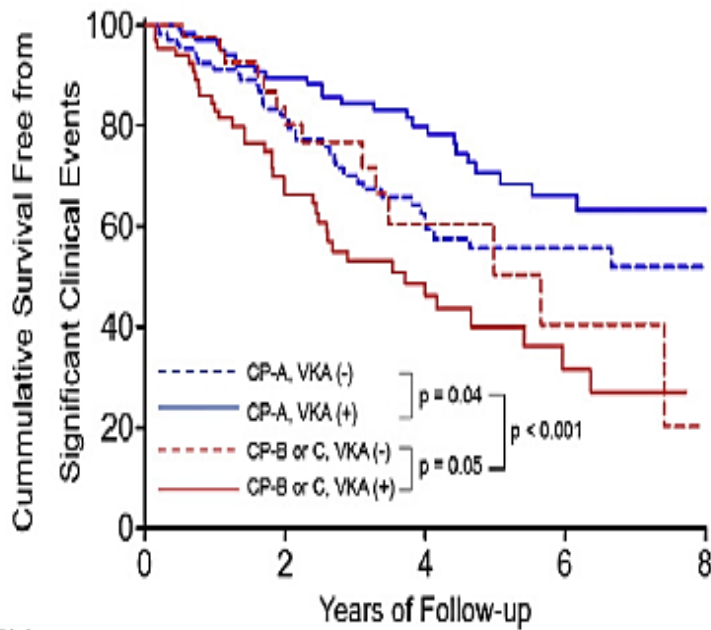
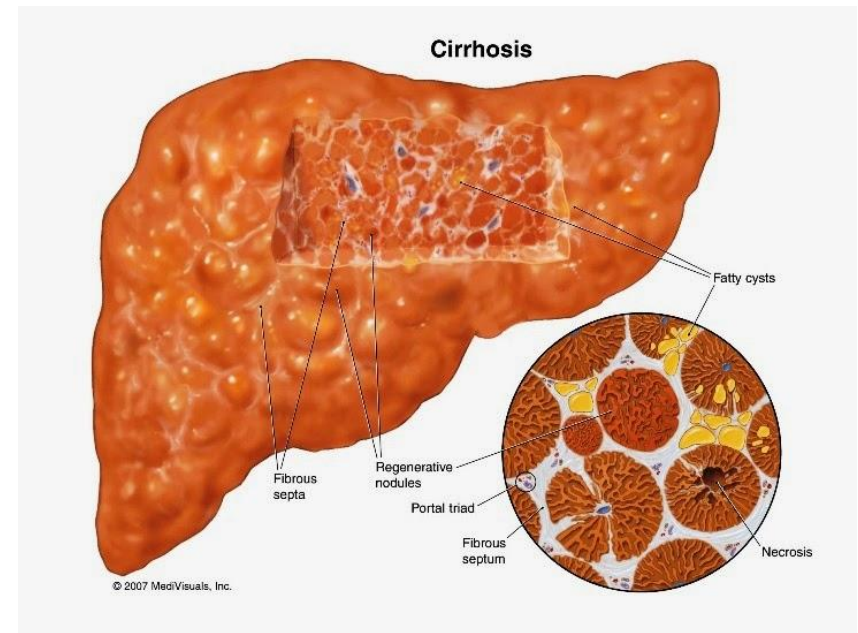


Number at risk

		Follow-up (years)					
		0	2	4	6	8	10
TTR ≥ 60%	71	43	25	15	8	0	0
TTR < 60%	129	80	52	21	6	0	0
No OAC	230	129	71	41	17	1	1

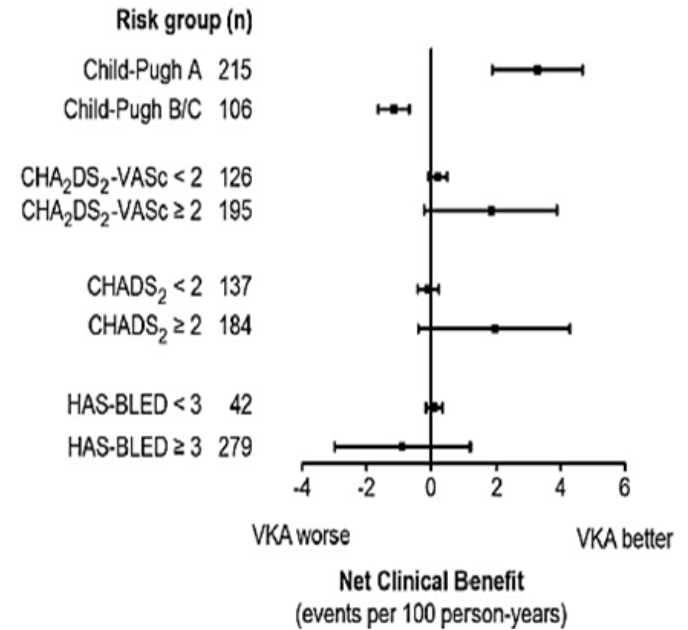
이승준 등. Am J Cardiol 2012;110:373-377

Liver Cirrhosis

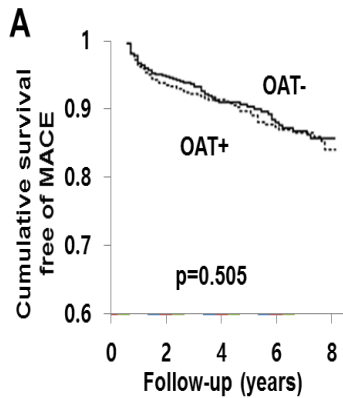
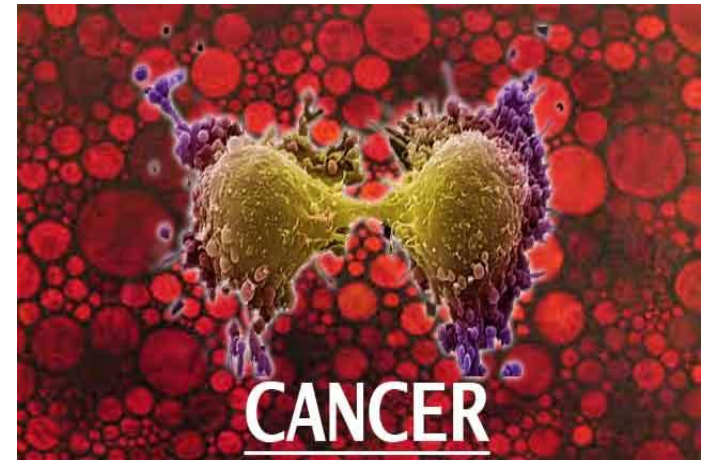


No. at Risk					
	0	2	4	6	8
CP-A, VKA (-)	107	67	37	20	9
CP-A, VKA (+)	108	76	49	25	5
CP-B or C, VKA (-)	41	26	10	4	0
CP-B or C, VKA (+)	65	41	20	8	0

이승준 등. Int J Cardiol 2015;180:185-191

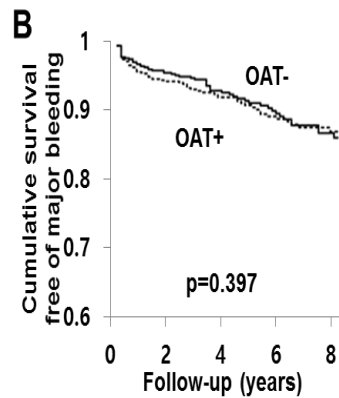


Cancer



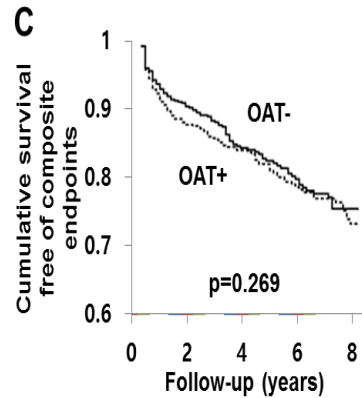
Number at risk

OAT+	690	482	319	200	58
OAT-	690	488	296	193	50



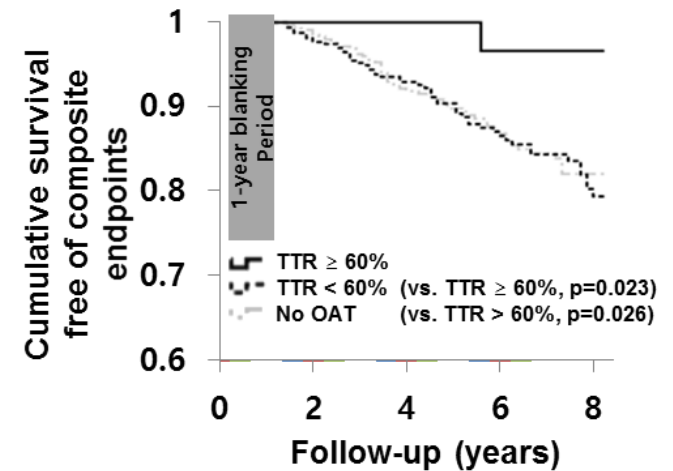
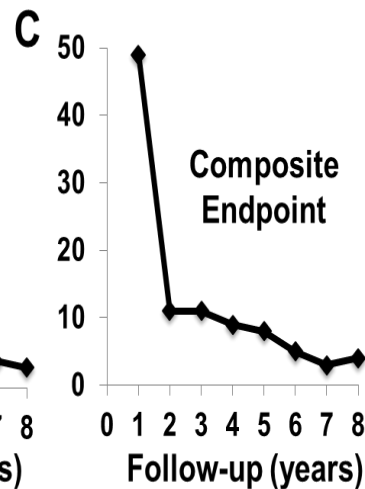
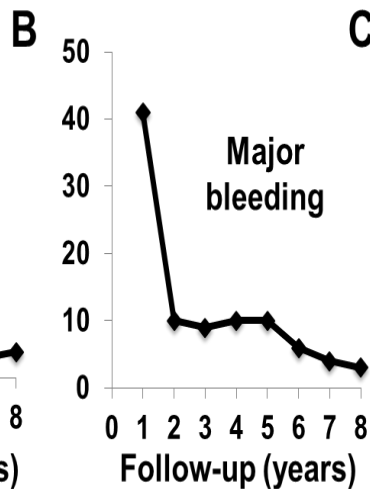
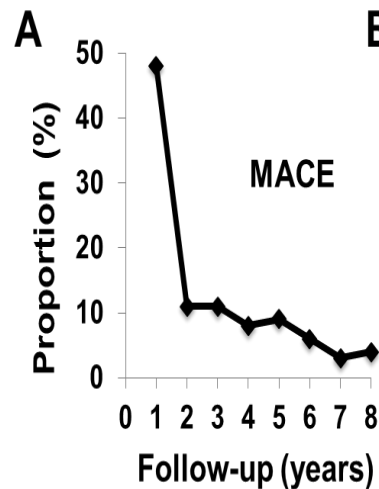
Number at risk

OAT+	690	489	327	207	67
OAT-	690	495	305	198	53



Number at risk

OAT+	690	456	296	182	54
OAT-	690	469	278	178	45

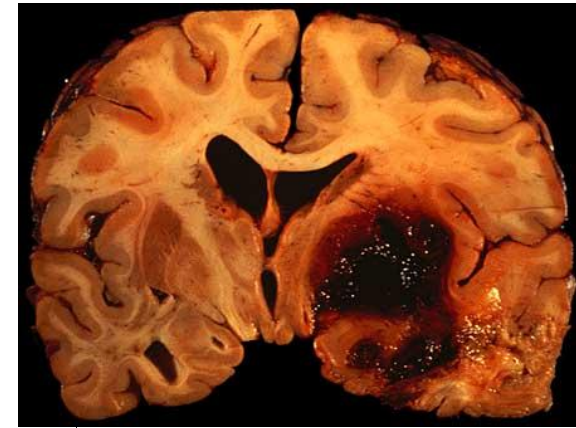


Number at risk

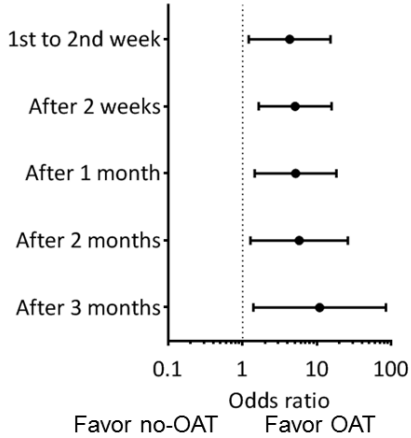
TTR \geq 60%	65	53	34	26	11
TTR < 60%	498	403	261	156	44
OAT-	576	469	278	178	45

이용준, 정보영. Int J Cardiol 2015;203:372-8

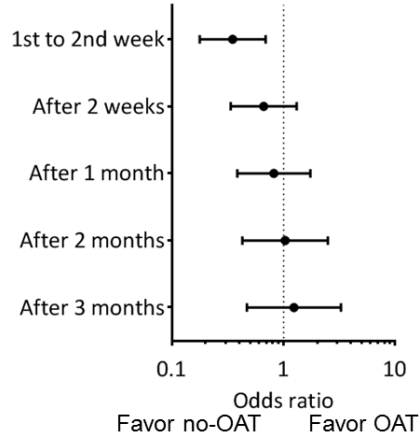
Brain Hemorrhage



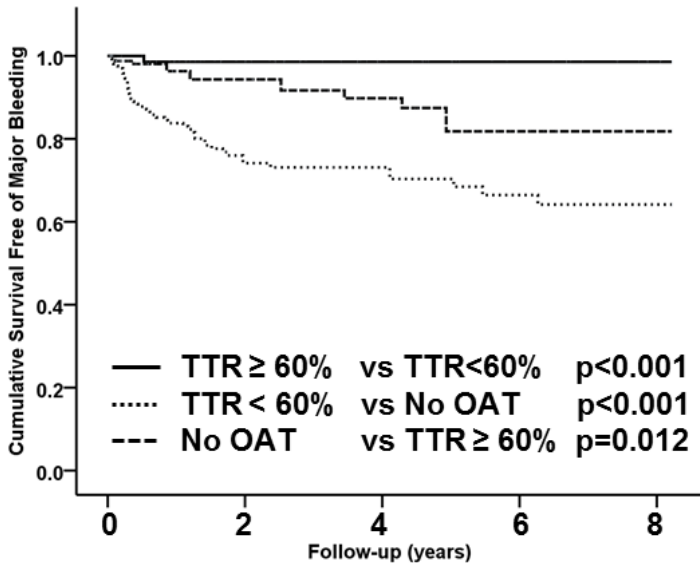
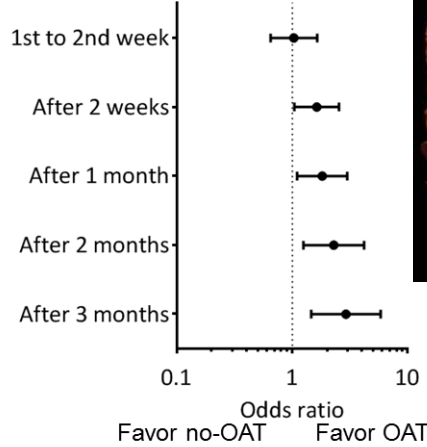
B. Ischemic Stroke



C. Major Bleeding



D. Composite Endpoint



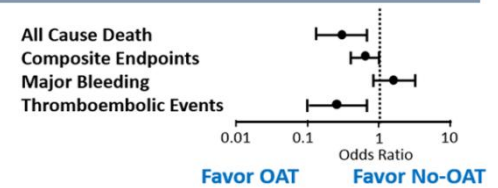
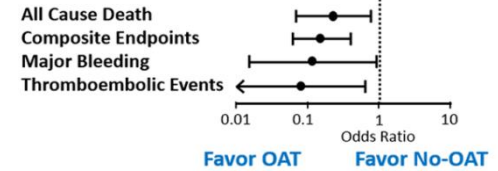
INR control

TTR > 60%

Clinical Events

Timing of WFR initiation

After > 2 weeks



박영아, 정보영. Heart Rhythm 2016 (accepted)

Methods

- **Single center, retrospective**
- **From 2012.11.26 to 2016.01.30**
- **Patients: AF with high risk (n=1,671)**
 - **PUD: 413, LC: 47, Cancer: 573, ICH: 276, CKD: 344**
- **NOAC: Dabigatran, Rivaroxaban, Apixaban**
- **Outcome: Major bleeding, Stroke**

Baseline clinical characteristics (1)

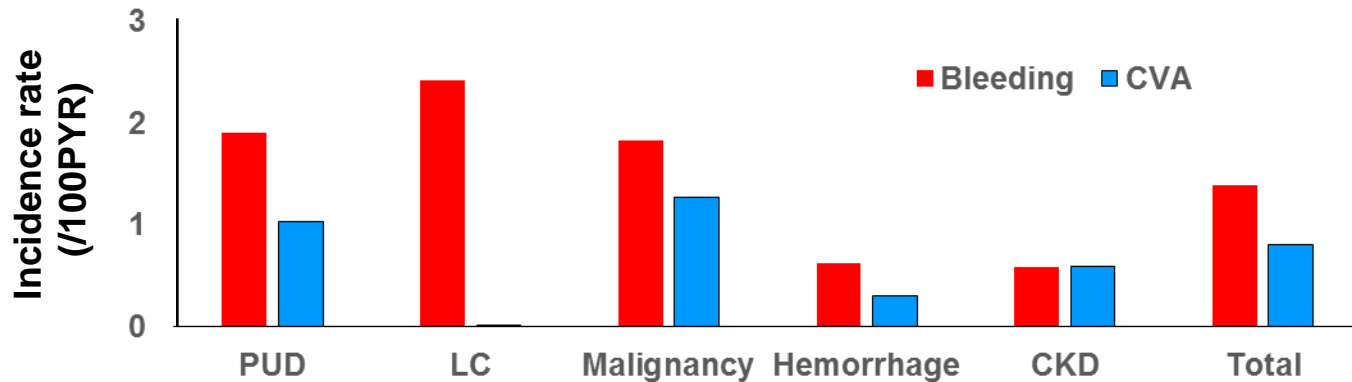
	PUD (n=413)	LC (n=47)	Cancer (n=573)	ICH (n=276)	CKD (n=344)
Age, yr	73.3±9.4	72.3±8.0	74.2±8.3	75.0±8.3	74.8±9.0
Female, n	157(38.0)	15(31.9)	180(31.4)	102(37.0)	100(29.1)
Hypertension, n	353(85.5)	34(72.3)	486(84.8)	246(89.1)	321(93.3)
Diabetes, n	163(39.5)	20(42.6)	234(40.8)	124(44.9)	193(56.1)
CHF, n	107(25.9)	16(34.0)	107(18.7)	68(24.6)	127(35.2)
Vascular disease, n	46(11.1)	3(6.4)	33(5.8)	40(14.5)	67(19.5)
Previous stroke, n	124(30.0)	10(21.3)	176(30.7)	122(44.2)	109(31.7)
CHADS2-VASC	3.9±1.8	3.5±1.6	3.8±1.7	4.4±1.6	4.4±1.6
0~1	41(9.9)	5(10.6)	36(6.3)	8(2.9)	8(2.3)
>1	372(90.1)	42(89.4)	537(93.7)	266(97.1)	336(97.7)
HAS-BLED	2.9±1.1	3.5±1.0	2.6±1.1	2.9±0.9	2.9±1.0
0~2	165(40.0)	6(12.8)	258(45.0)	88(31.9)	119(34.6)
>2	248(60.0)	41(87.2)	315(55.0)	188(68.1)	225(65.4)

Baseline clinical characteristics (2)

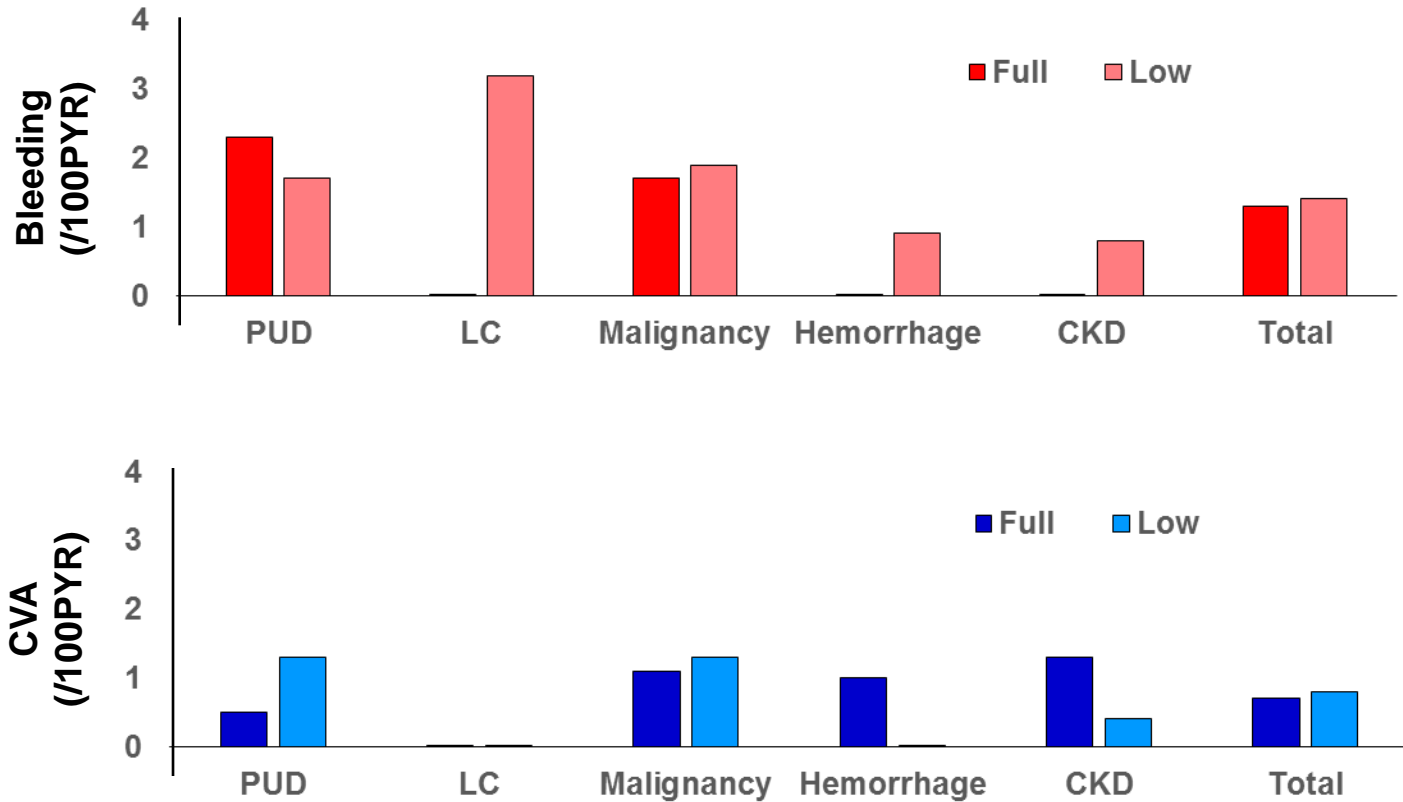
	PUD (n=413)	LC (n=47)	Malignancy (n=573)	Hemorrhage (n=276)	CKD (n=344)
NOAC					
Dabigatran	154(37.3)	19(40.4)	191(33.3)	97(35.1)	100(29.1)
Apixaban	144(34.9)	15(31.9)	214(37.3)	91(33.0)	147(42.7)
Ribaroxaban	115(27.8)	13(27.7)	168(29.3)	88(31.9)	97(28.2)
Dose					
Full	135(32.7)	7(14.9)	156(27.2)	78(28.3)	64(18.6)
Low	278(67.3)	40(85.1)	417(72.8)	198(71.7)	280(81.4)
Antiplatelet, %	314(76.0)	33(70.2%)	386(67.4)	190(68.8)	249(72.4)
Follow up (days)	413±365	322±330	343±337	421±400	355±358

Outcome

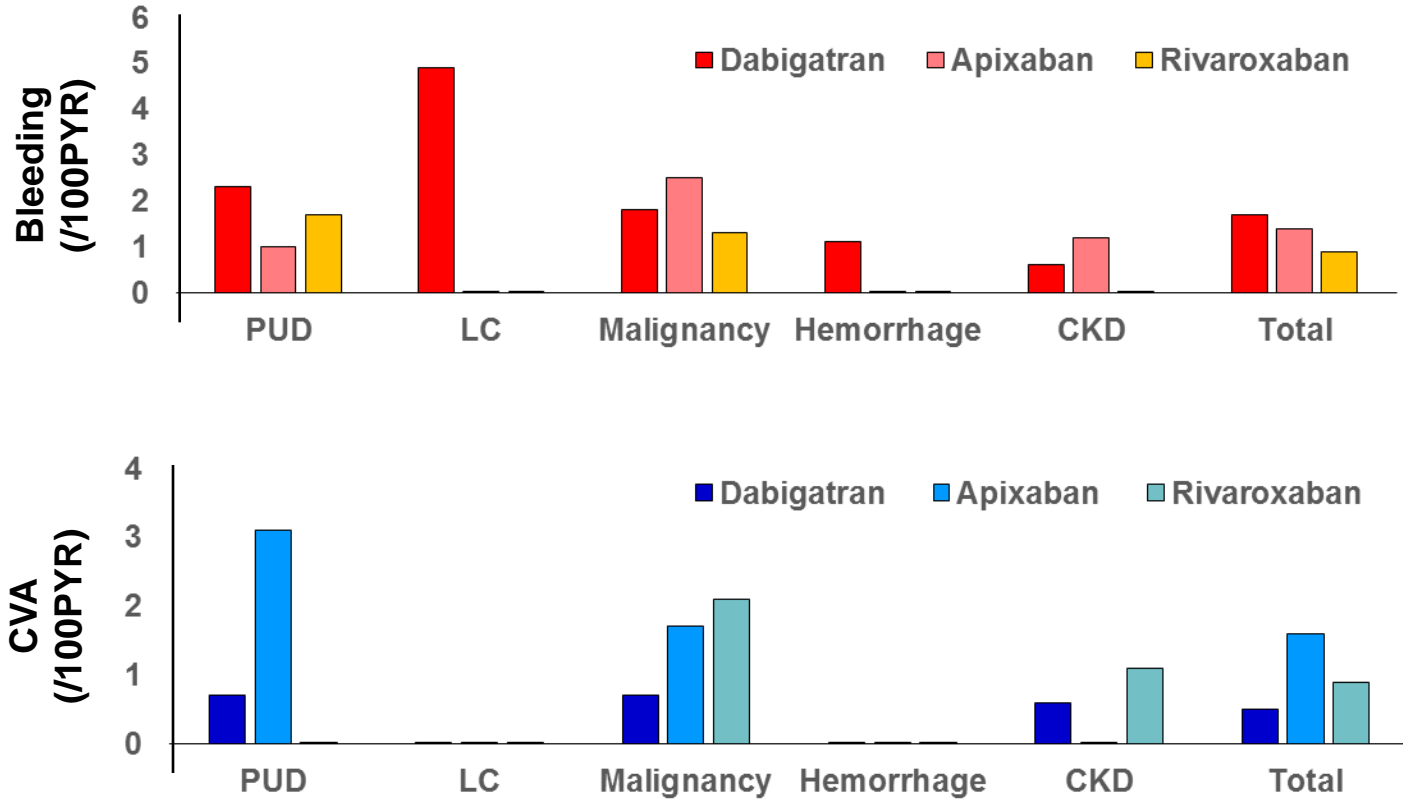
	PUD (n=413)		LC (n=47)		Malignancy (n=573)		Hemorrhage (n=276)		CKD (n=344)	
	Bleeding	CVA	Bleeding	CVA	Bleeding	CVA	Bleeding	CVA	Bleeding	CVA
Total, n	9 (2.2)	5 (1.2)	1 (2.1)	0	10 (1.7)	7 (1.2)	2 (0.7)	1 (0.4)	2 (0.6)	2 (0.6)
Incidence rate (/100 PYR)	1.9	1.03	2.41	0	1.83	1.27	0.63	0.31	0.59	0.59



Outcome: Full vs. Low dose



Outcome: NOACs



Dabigatran Experience in Severance Hospital

Methods

- From 2012.11.26 to 2016.01.30
- Total n = 1,540
- Patients diagnosed AF, AFL
 - AF (n=1,485, 96.4%), AFL (n=55, 3.6%)
- Male:Female = 1,005:535 (65%:35%)
- Mean age = 69.5 ± 10.9 (rage 22~95)
- Dosage of Dabigatran
 - 110 mg bid:150 mg bid = 588:952 (38%:62%)
- Outcome
 - Stroke, bleeding

Baseline Clinical Characteristics

	Total (n=1,540)	Dabigatran 110 mg bid (n=588)	Dabigatran 150 mg bid (n=952)	P-value
Female	535 (34.7)	135 (23)	400 (42)	<0.001
Age(Mean, SD)	69.5 ± 10.9	62.3 ± 11.1	71.3 ± 9.2	<0.001
≥ 75	462 (30.0)	75 (12.8)	387 (40.7)	<0.001
≥ 65	554 (36.0)	181 (30.8)	373 (39.2)	
< 65	524 (34.0)	332 (56.5)	192 (20.2)	
Hypertension	1,130 (73.4)	386 (65.6)	744 (78.2)	<0.001
Diabetes mellitus	503 (32.7)	152 (25.9)	351 (36.9)	<0.001
Vascular disease	70 (4.5)	13 (2.2)	57 (6.0)	<0.001
CHF	241 (15.6)	57 (9.7)	184 (19.3)	<0.001
CVA	355 (23.1)	137 (23.3)	218 (22.9)	0.85
Previous bleeding	133 (8.6)	35 (26.3)	98 (73.7)	0.004
CHA ₂ DS ₂ _VASc	3.0 ± 1.8	2.3 ± 1.8	3.5 ± 1.7	<0.001

Stroke & Bleeding

	Total (n=1,540)	Dabigatran 110 mg bid (n=588)	Dabigatran 150 mg bid (n=952)	P-value
Follow-up, days	152±270	162±277	146±266	0.24
Stroke, %/year	0.6	0.8	0.5	
Patients, n	4 (0.3)	2 (0.3)	2 (0.2)	0.64
Duration, days	35 ± 11	38 ± 11	33 ± 14	0.75
Bleeding, %/year	2.8	0.8	4.2	
Patients, n	18 (1.2)	2 (0.3)	16 (1.7)	0.017
Duration, days	33 ± 14	94 ± 93	71 ± 160	0.85

* Type of bleeding and outcome.

GI bleeding 14 (Cancer 2, expire 1)

Intracranial hemorrhage 3 (SAH 1, Subdural 1)

Post AF ablation 1

Dabigatran was highly effective in the prevention of stroke with low risk of bleeding.

한국인의 NOAC 적정 용량??

4개 대표 NOAC의 용량 조절

RE-LY¹

- None

ROCKET-AF²

- 20→15 mg QD for:
 - Creatinine clearance <30–49 mL/min

ARISTOTLE³

- 5→2.5 mg BID for ANY TWO of:
 - Age ≥80 years
 - body weight ≤60 kg
 - Serum creatinine ≥15 mg/dL

ENGAGE-AF⁴

- 60→30 mg QD or 30→15 mg QD for:
 - Creatinine clearance 30–50 mL/min
 - body weight ≤60 kg
 - Use of quinidine, verapamil or dronedarone

신기능에 따른 용량 조절

○ 금기증

- CrCl < 30 ml/min: dabigatran
- CrCl < 15 ml/min: apixaban, edoxaban, rivaroxaban

○ 감량

- CrCl 30–49 ml/min: dabigatran*
- CrCl 15–29 ml/min: apixaban
- CrCl 15–49 mL/min: edoxaban, rivaroxaban

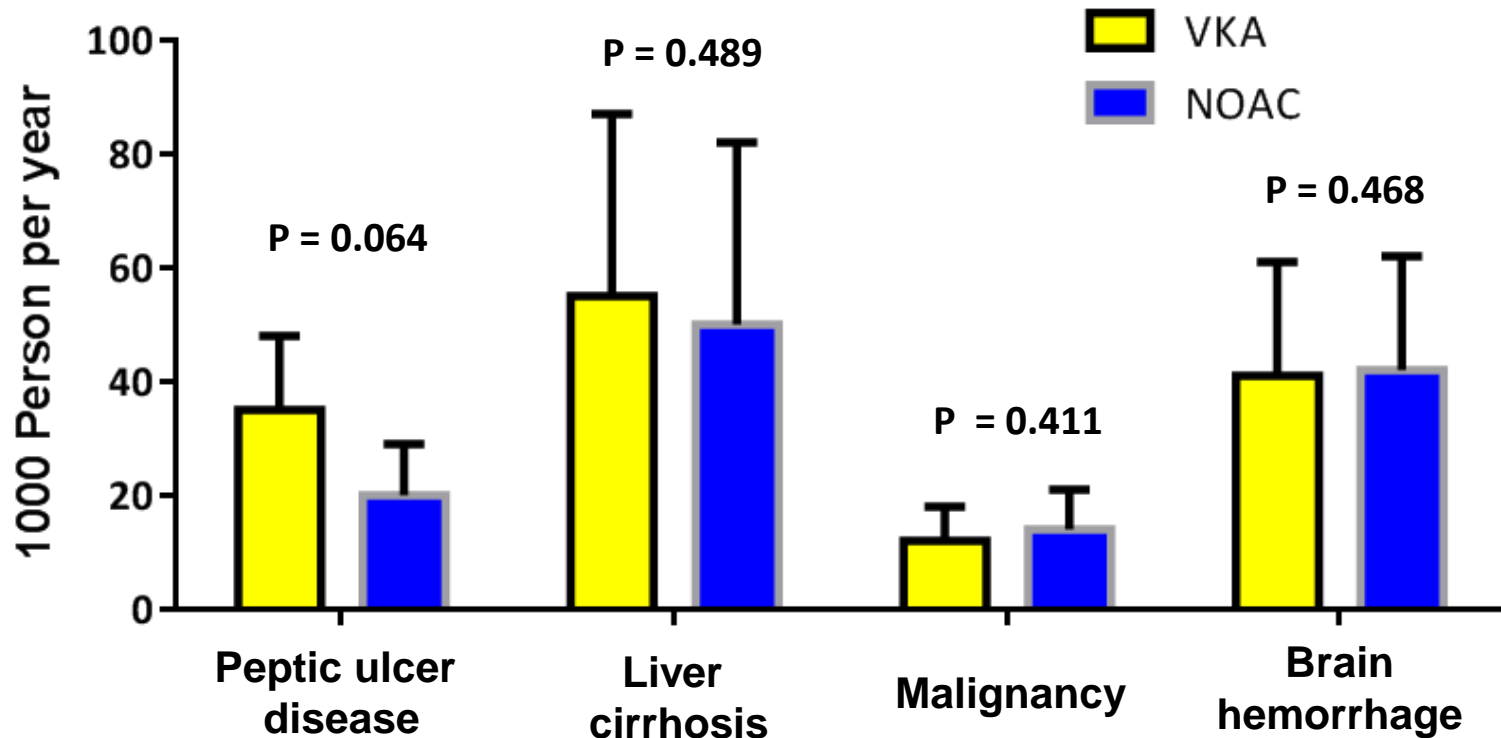
1. Connolly et al. N Engl J Med 2009;361:1139–1151; 2. Patel et al. N Engl J Med 2011;365:883–891
3. Granger et al. N Engl J Med 2011;365:981–992; 4. Giugliano et al. N Engl J Med 2013; DOI: 10.1056/NEJMoa1310907

Summary & Conclusion

- In patients with high risk bleeding, NOAC showed a trend of reducing major bleeding and stroke.
- Pradaxa was highly effective in the prevention of stroke with low risk of bleeding.
- Study limitation: The follow up duration and number of patients with NOAC is short and small.

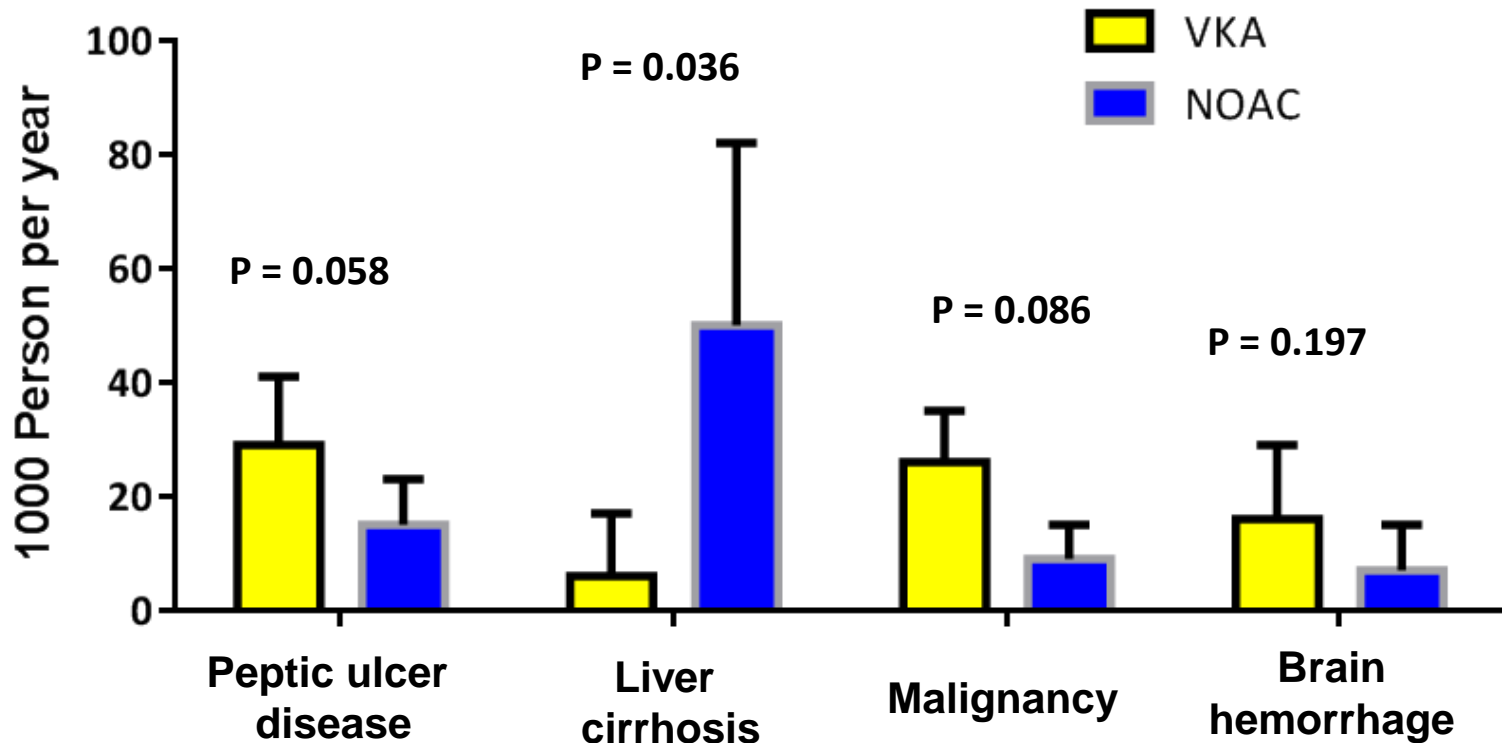
Thanks for your attention

Outcome – Major bleeding



In patients with high risk bleeding, NOAC showed a trend of reducing major bleeding.

Outcome – Stroke



In patients with high risk bleeding, NOAC showed a trend of reducing stroke.