

# Current challenges in stroke prevention in atrial fibrillation

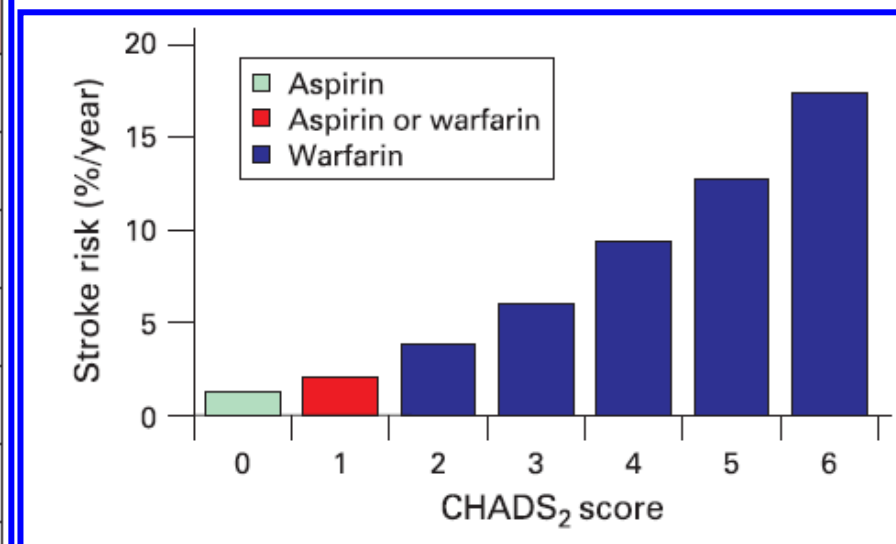
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# 심방세동 (Atrial Fibrillation)

- 심장부정맥 중에서 가장 흔한 부정맥
- 뇌졸중의 위험이 약 5배 증가
- 매년 뇌졸중의 발생률 약 5%
- 혈색전증에 의한 뇌졸중 중에서 심방세동에 의한 뇌졸중이 약 20%
- 심방세동의 치료에 있어 뇌졸중의 예방이 매우 중요

## CHADS2 score and stroke rate

CHADS <sub>2</sub> score	Patients (n=1733)	Adjusted stroke rate (%/year) <sup>a</sup> (95% confidence interval)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)



CHADS2 risk: cardiac failure, hypertension, age, diabetes, stroke (doubled)  
 CHADS2 score : 0 as low risk, 1~2 as moderate risk, and >2 as high risk

*Gage BF, et al. JAMA 2001;285:2864–2870.*

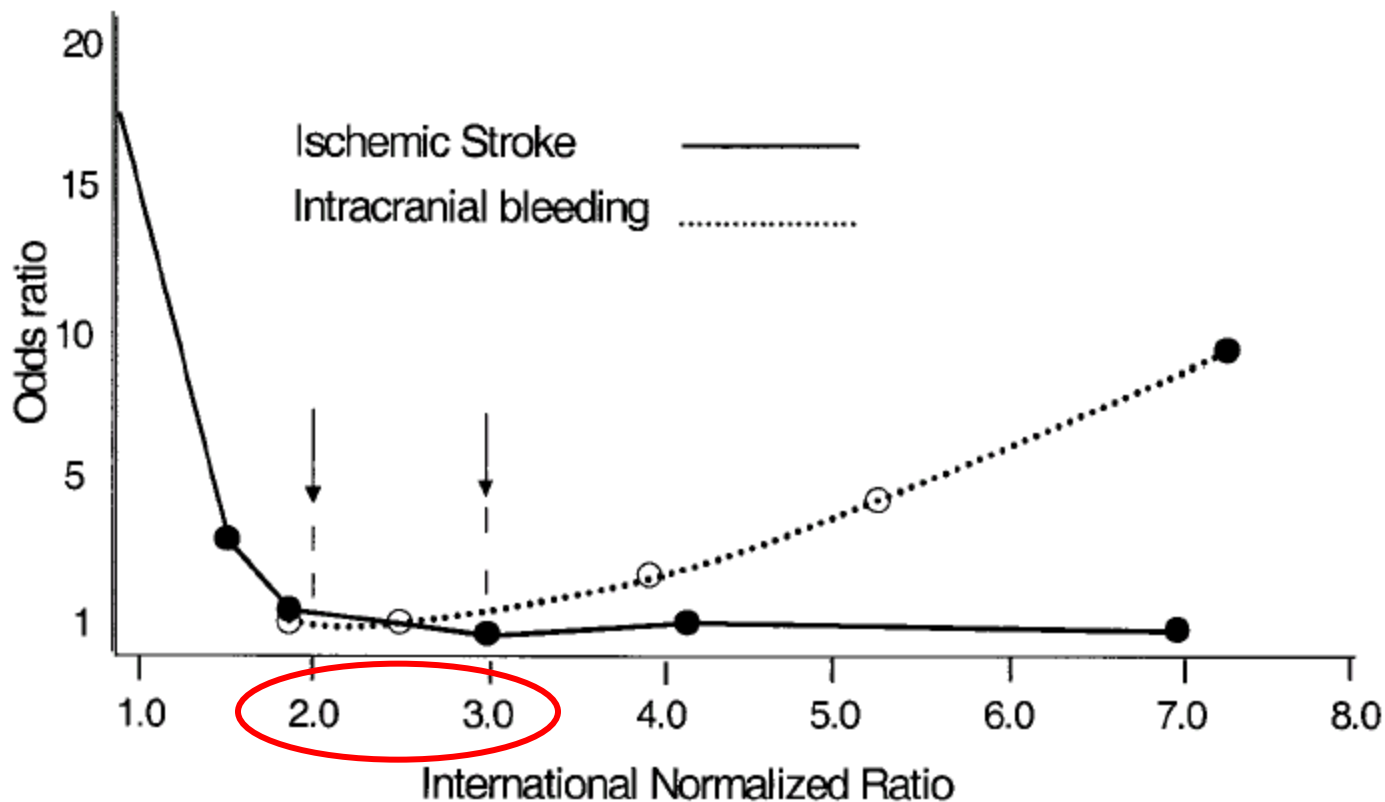
# CHA<sub>2</sub>DS<sub>2</sub>VASc score and stroke rate

## 뇌졸중 위험인자

- 75세이상 고령 (2점)
- 뇌졸중 (2점)
- 심부전 (1점)
- 고혈압 (1점)
- 당뇨 (1점)
- 혈관질환 (1점)
- 65~75세 (1점)
- 여성 (1점)

(c) Adjusted stroke rate according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score

CHA <sub>2</sub> DS <sub>2</sub> -VASc score	Patients (n=7329)	Adjusted stroke rate (%/year) <sup>b</sup>
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%



Adjusted odds ratios for ischemic stroke and intracranial bleeding in relation to intensity of anticoagulation in antithrombotic therapy for patients with AF.

*Hylek EM et al, N Engl J Med 1996;335:540*

- **Doubling** of the rate of intracranial hemorrhage  
when the **INR exceeds 3.0**
- **70% increase** in the rate of stroke  
when the INR is **less than 2.0**

# 심방세동 환자의 출혈 위험도 평가

## 뇌출혈 위험인자

- 65세이상 고령 (1점)
- 뇌졸중 (1점)
- 고혈압 (1점)
- 간기능 이상 (1점)
- 신장기능 이상 (1점)
- 출혈 (1점)
- 심한 INR 변화 (1점)
- 약물 (1점)
- 음주 (1점)

Letter	Clinical characteristic <sup>a</sup>	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

뇌출혈의 빈도는 과거에 비해 최근 많이 감소하여 0.1~0.6% 로 보고 되고 있다.

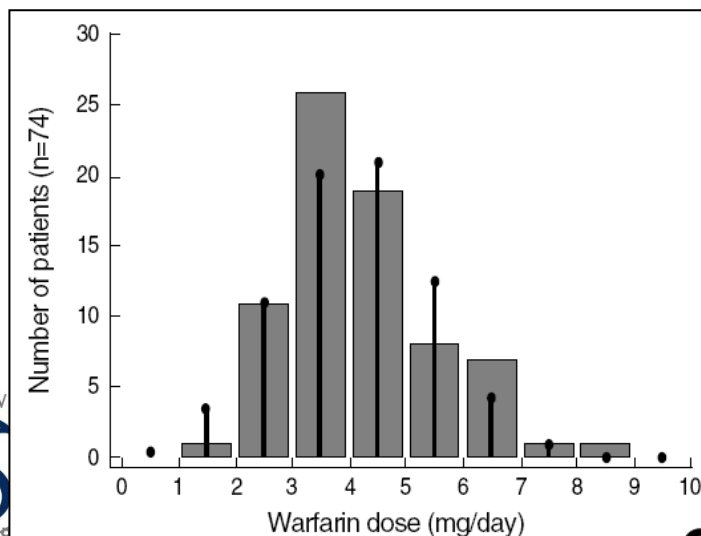
*Pisters R, et al, Chest 2010*

## 심방세동에서의 혈전색전증 예방

- **와파린** 약물 복용 (61% 혈전색전증 예방효과)
- 문제점: 와파린의 개인차가 너무 크다. (target INR range 50~60%)  
정기적인 혈액 검사 (narrow therapeutic index, monitoring)  
여러가지 음식물 및 약제의 제한  
출혈위험성 증가 (life-threatening bleeding 12%)
- **아스피린** 약물 복용 (19% 혈전색전증 예방효과)
- 문제점: 와파린에 비해 예방효과 적다.  
위장 장애

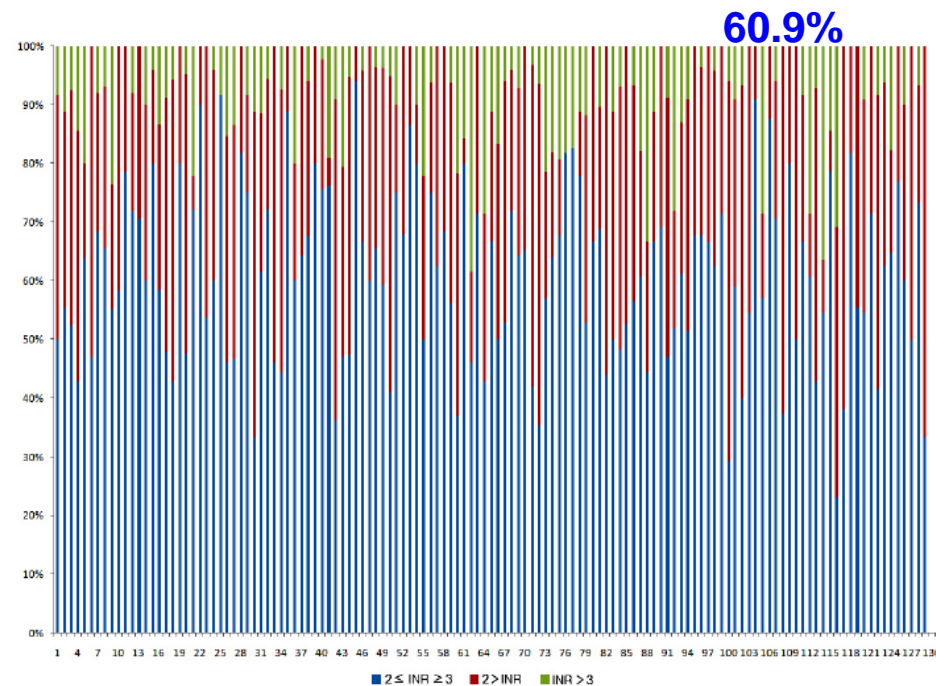
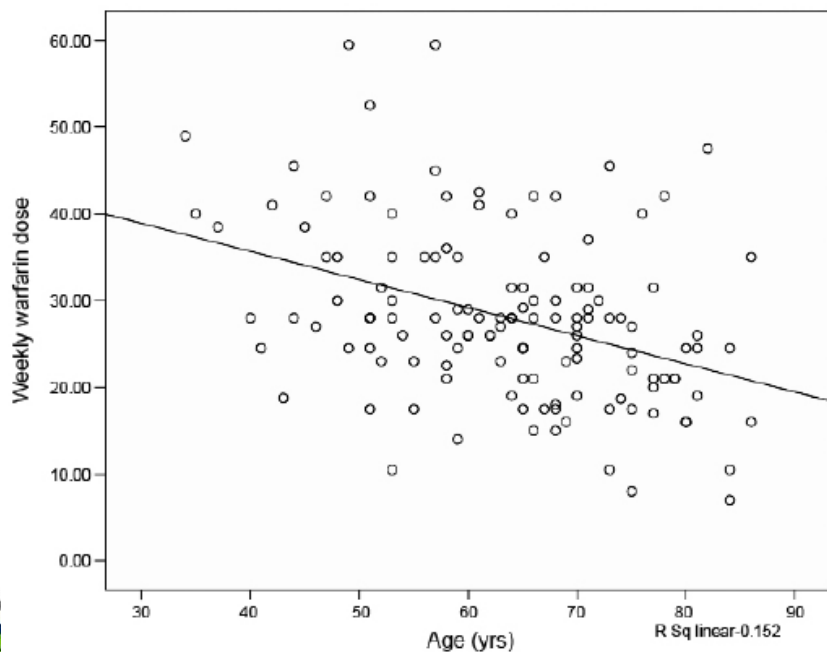


- Mean maintenance dose of warfarin in 105 patients :  $4.1 \pm 1.3$  mg/day (range, 1.7-8.0 mg/day)
- Mean plasma warfarin concentration :  $1.3 \pm 0.5$  mg/L.
- 74 patients (70%) showing INR within target range despite of constant INRs within the target range (2.0~3.0) over at least 3 consecutive monthly clinic visits just before the index visit.
- 49.5% (52/105) of patients experienced a variety of bleeding complications, including epistaxis, gum bleeding, melena, and hematuria.
- 5.7% (6/105) of patients experienced thrombotic complications during warfarin treatment, including cerebral infarction and mesenteric infarction.



# INR level in warfarin-treated patients with non-valvular AF

- 129 patients, men (71.3%), with nonvalvular AF,
- Average age : 63.6 years (range 34~86 years)
- 36.4% were less than 60 years old.
- The median duration of follow up was 2.03 years.
- Correlation between weekly warfarin dose and age.  $p < 0.001$



- **Warfarin** is widely used as an oral anticoagulant for AF
- Warfarin has a **narrow therapeutic index** and may be associated with adverse events.  
: thromboembolic complications or bleeding.
- **Life-threatening bleeding** episodes after initiation of warfarin therapy have been reported in approximately **12%**.  
*(Levine MN, et al. Chest 2001;119:S108-21)*
- During maintenance therapy, only **50-60%** of patients can be expected to achieve their **target INR range**.
- Marked within- and between-individual variability in warfarin dose requirements
- Monitoring the safety and efficacy of warfarin treatment.

## Weakness of Current Anticoagulants

- Indirect : **Unpredictable**
- **Ideal Anticoagulants :**

High Efficacy & Safety

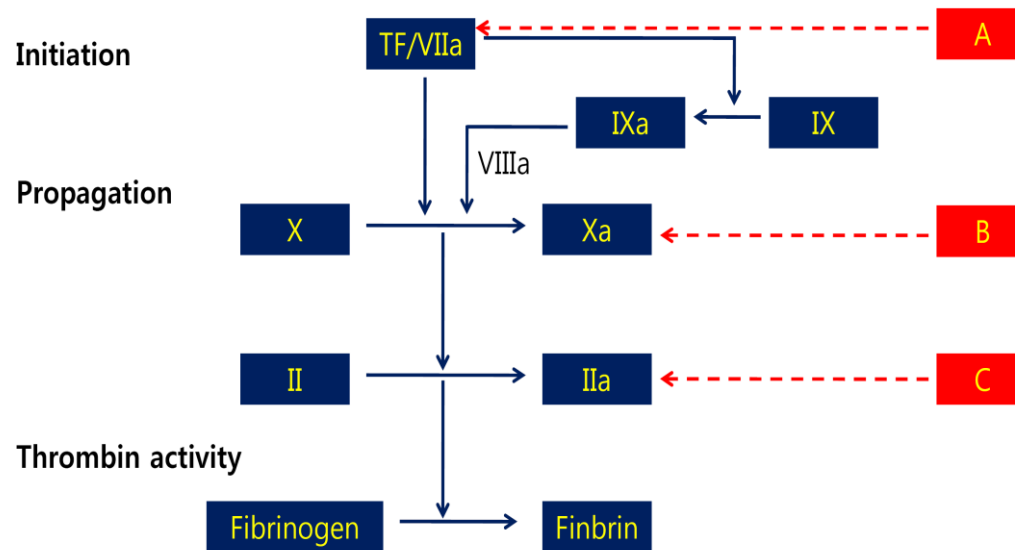
Low level of Bleeding

Rapid Onset of Action

Action on Clot-bound coagulation factors

Fixed Dosing & No Requirement for Monitoring

# Mode of Action of New Anticoagulants

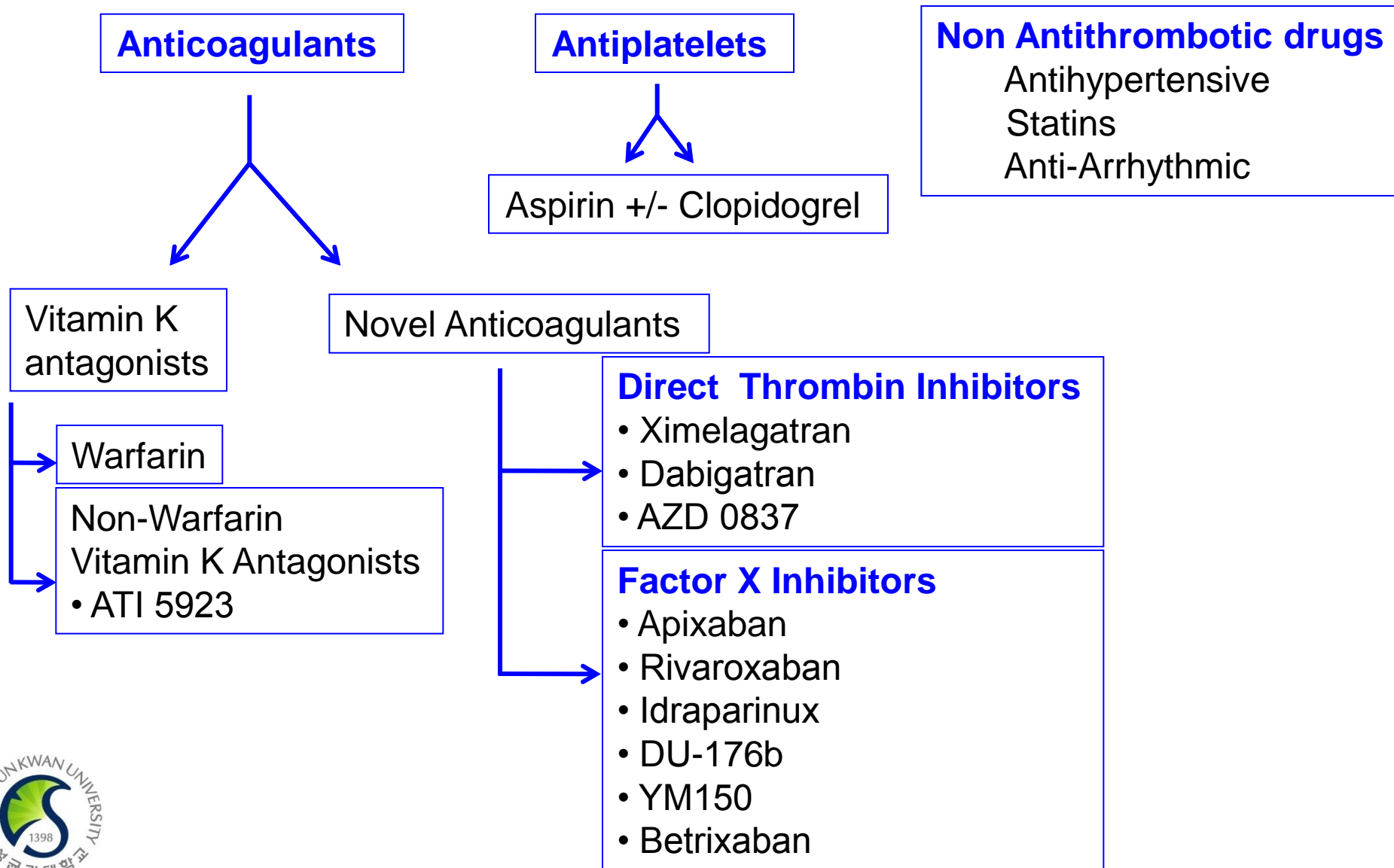


A: Tissue factor/ factor VIIa inhibitors

B: Factor Xa inhibitors

C: Direct thrombin inhibitors

# Prevention of Thromboembolism of AF



# Anticoagulants in development

Agent	Company	Status, phase
<b>Direct thrombin inhibitors</b>		
Dabigatran etexilate	Boehringer Ingelheim	3
AZD0837	Astra Zeneca	2
MCC 977	Mitsubishi Pharma	2
<b>Direct factor Xa inhibitors</b>		
Rivaroxaban	Bayer, Ortho-McNeill	3
Apixaban	Bristol-Myers Squibb, Pfizer	3
Betrixaban	Portola	2
YM150	Astellas	2
Edoxaban (DU-176b)	Daichi Sankyo	3
TAK-442	Takeda	2
Otamixaban*	Sanofi-Aventis	2
<b>Indirect factor Xa inhibitor</b>		
Idraparinux*	Sanofi-Aventis	3
Idrabiotaparinux*	Sanofi-Aventis	3
<b>Novel VKA</b>		
ATI-5923	Aryx Therapeutics	2b

\*Parenteral agent.

# Conclusions

- Prevention of thromboembolism of AF
- 와파린 사용 중 INR 2~3 : 50~60%
- 와파린 사용 중 출혈 경험 약 50%

Life-threatening bleeding episodes 12%

- 새로운 항혈전제  
direct thrombin inhibitor: Dabigatran  
factor Xa inhibitors : Apixaban and Rivaroxaban