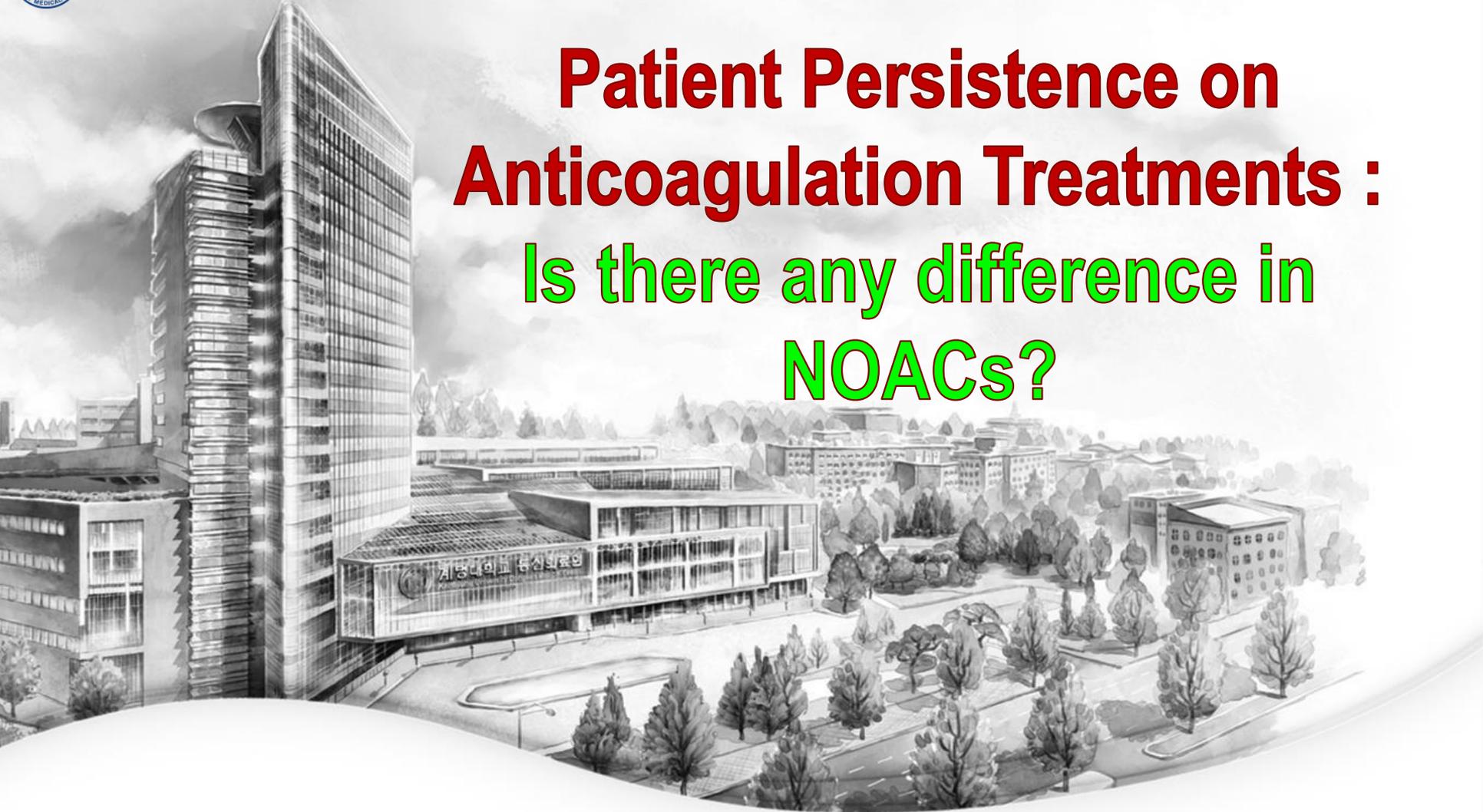




# Patient Persistence on Anticoagulation Treatments : Is there any difference in NOACs?



**Seongwook Han**, MD.PhD.

Professor of Medicine, Keimyung University School of Medicine  
Arrhythmia Service, Cardiology, Dongsan Medical Center

# Disclosure

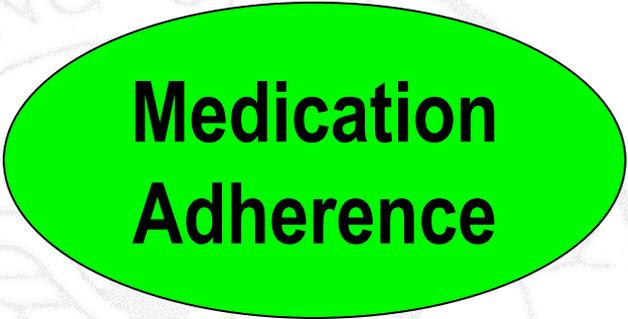
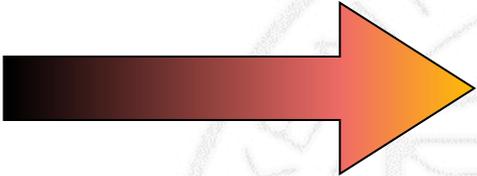
- **Speaker Bureau/Honoraria:** Bayer, Biosense Webster, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Medtronic Inc., Pfizer
- **Grants/Research support:** Boston Scientific, Boehringer Ingelheim, Chong Kun Dang, Medtronic Inc., Servier, Yuhan
- **Advisory board:** Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic Inc.



# *Drugs don't work* in patients who *don't take them*

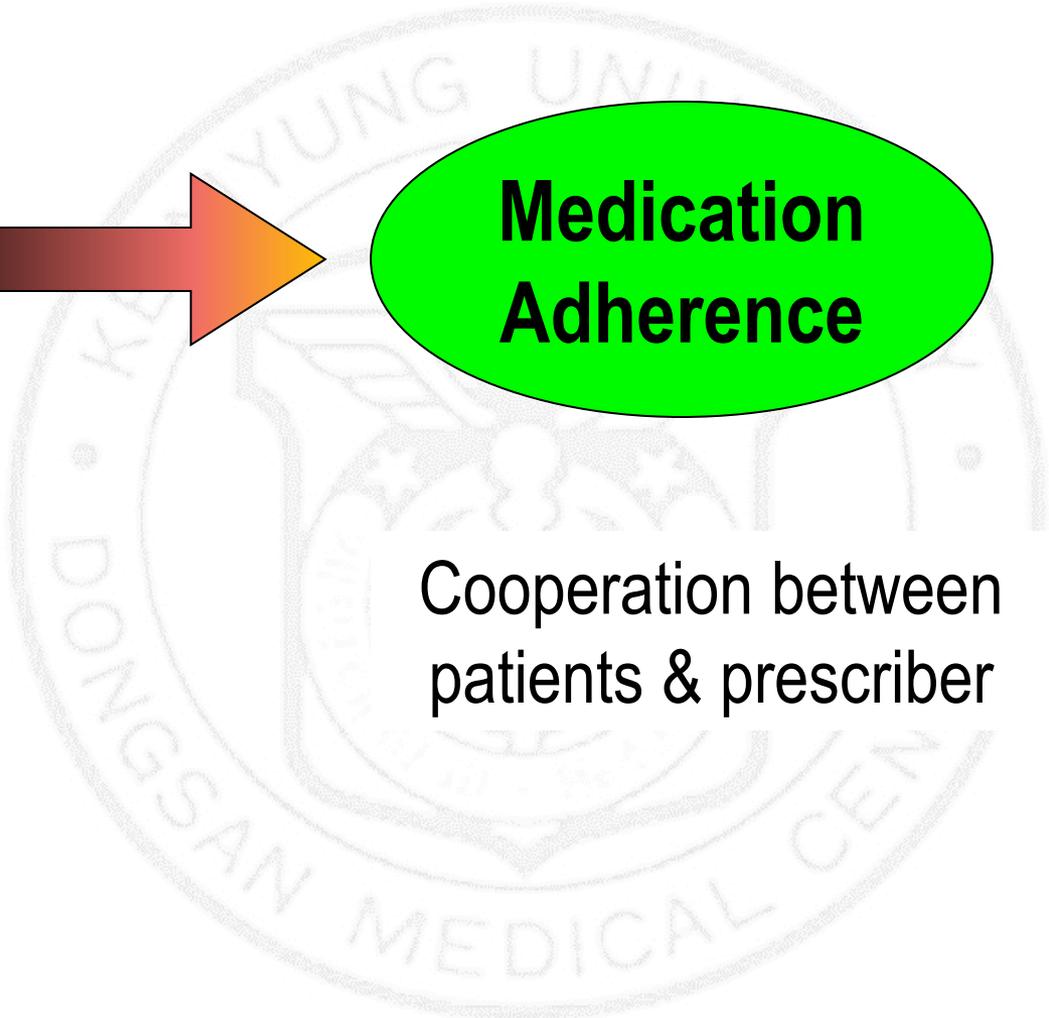
C. Everett Koop, MD

# Paradigm shift



Patient's passive  
obedience to the  
physician's instruction

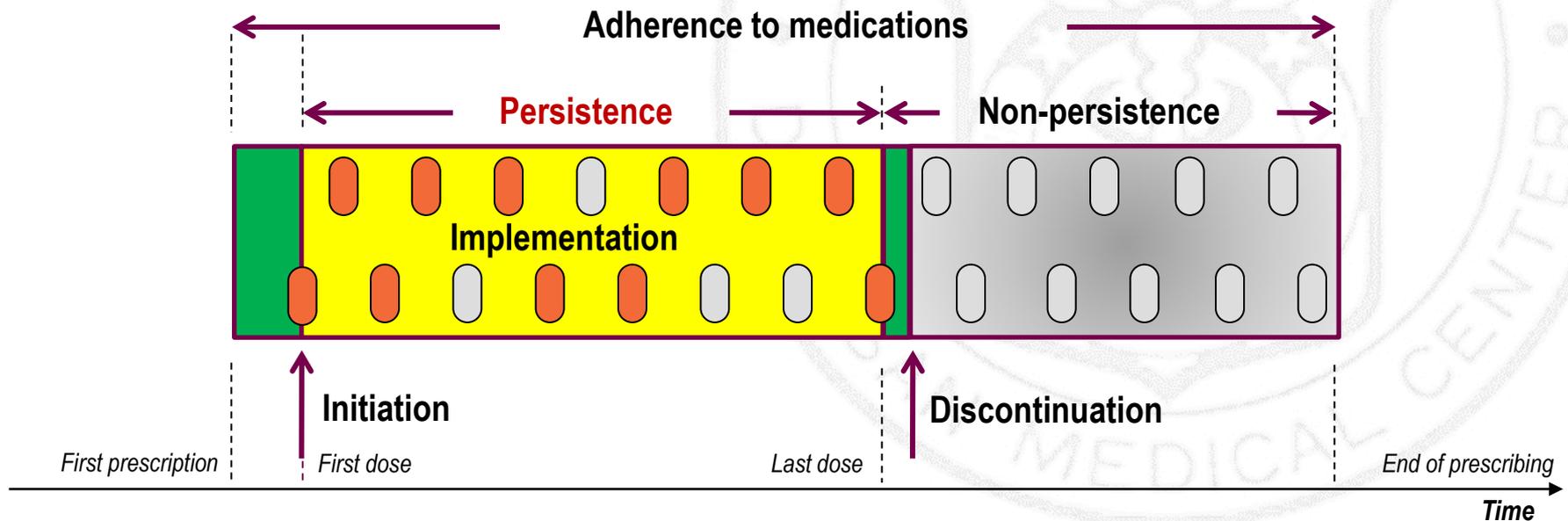
Cooperation between  
patients & prescriber



# Medication Adherence

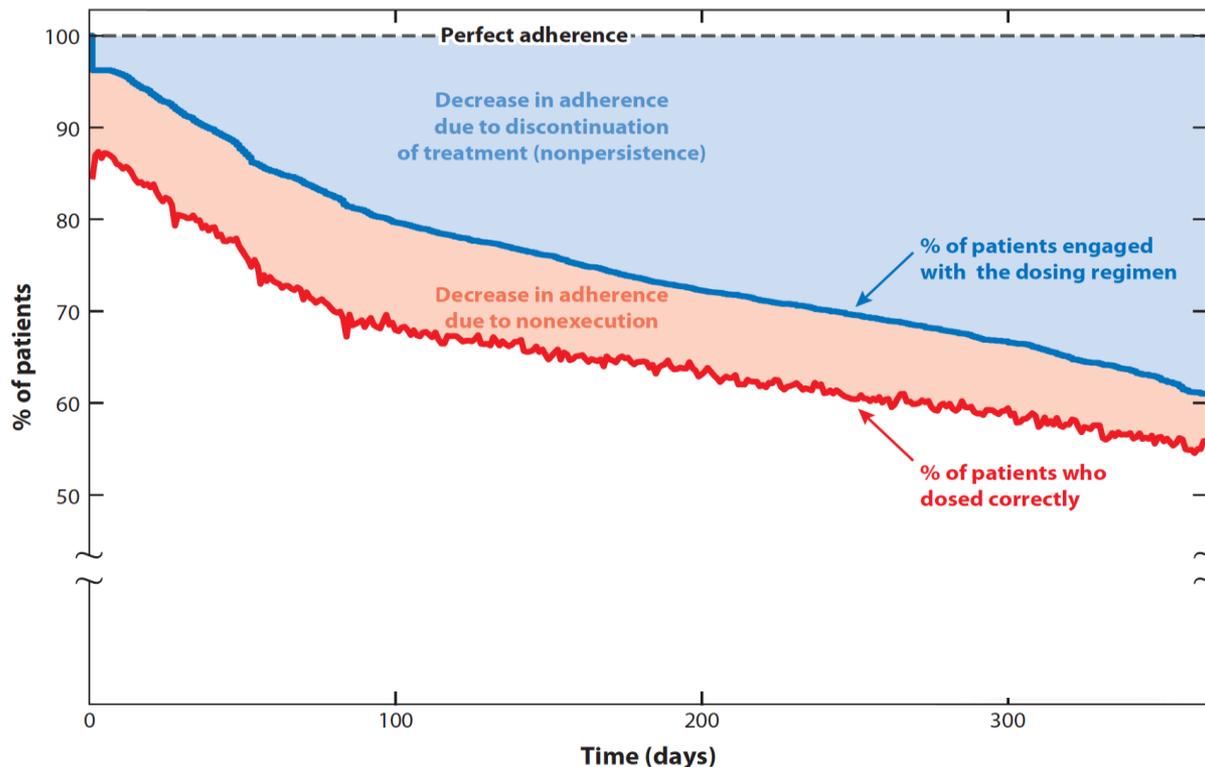
Process by which patients take their medications as prescribed

- **Initiation**: occurs when the patient takes the first dose
- **Implementation**: patient's actual dosing history corresponds to the prescribed dosing regimen
- **Discontinuation**: when the patient stops taking the prescribed medication



# Extent of non-adherence in clinical trials

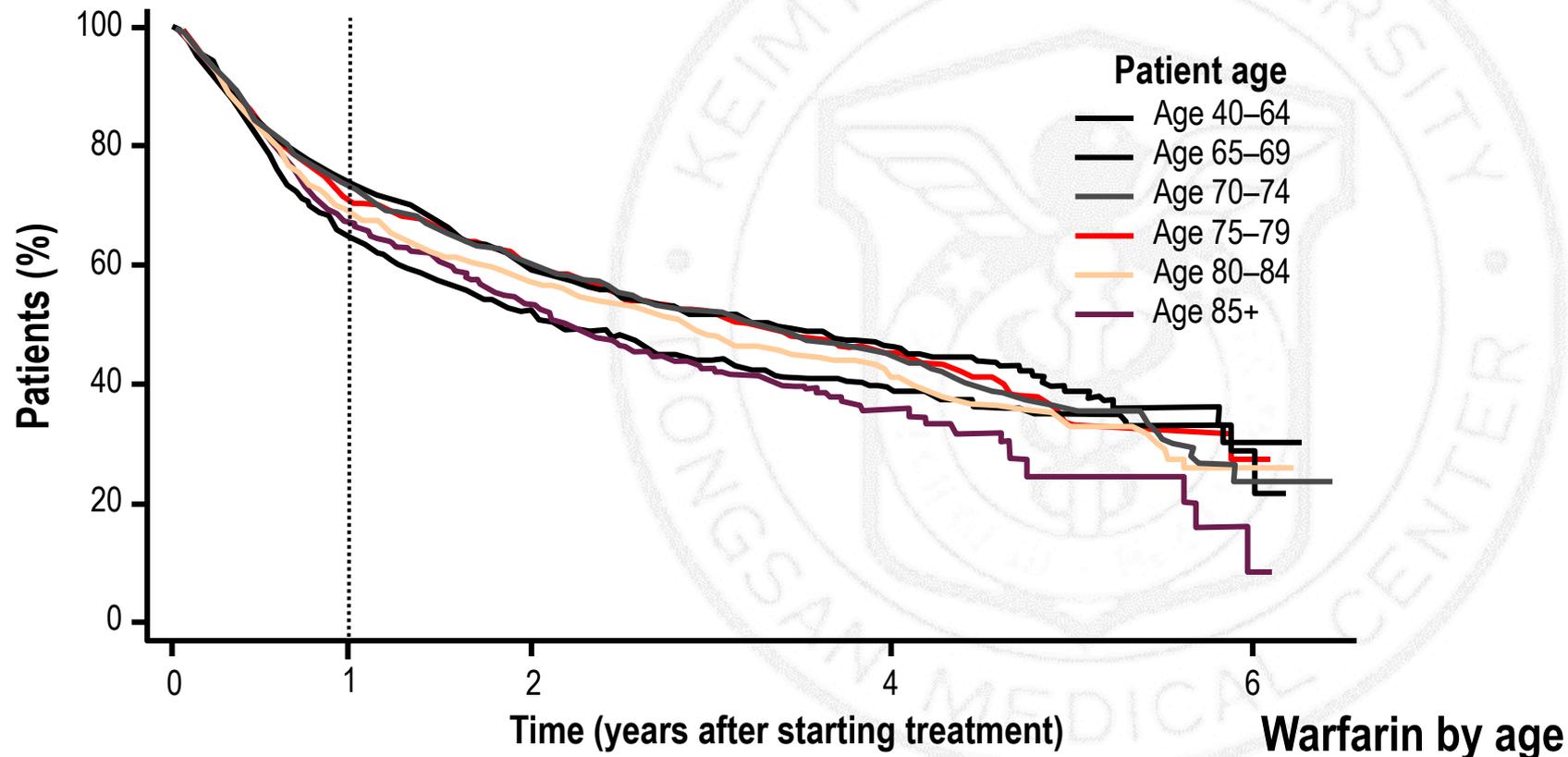
- ❖ 16,907 participants from 95 clinical studies
- ❖ Almost **40% of participants stopped** taking medication by the end of 1 year



# Adherence of warfarin: Persistence

1-year persistence of warfarin: 70%

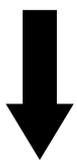
41,910 Patients with chronic AF from general practice research database (UK)



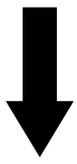
# The Influence of Patient Adherence on Anticoagulation Control With Warfarin

- 136 patients with mean 32 weeks follow up
- Medication Event Monitoring System medication bottle caps

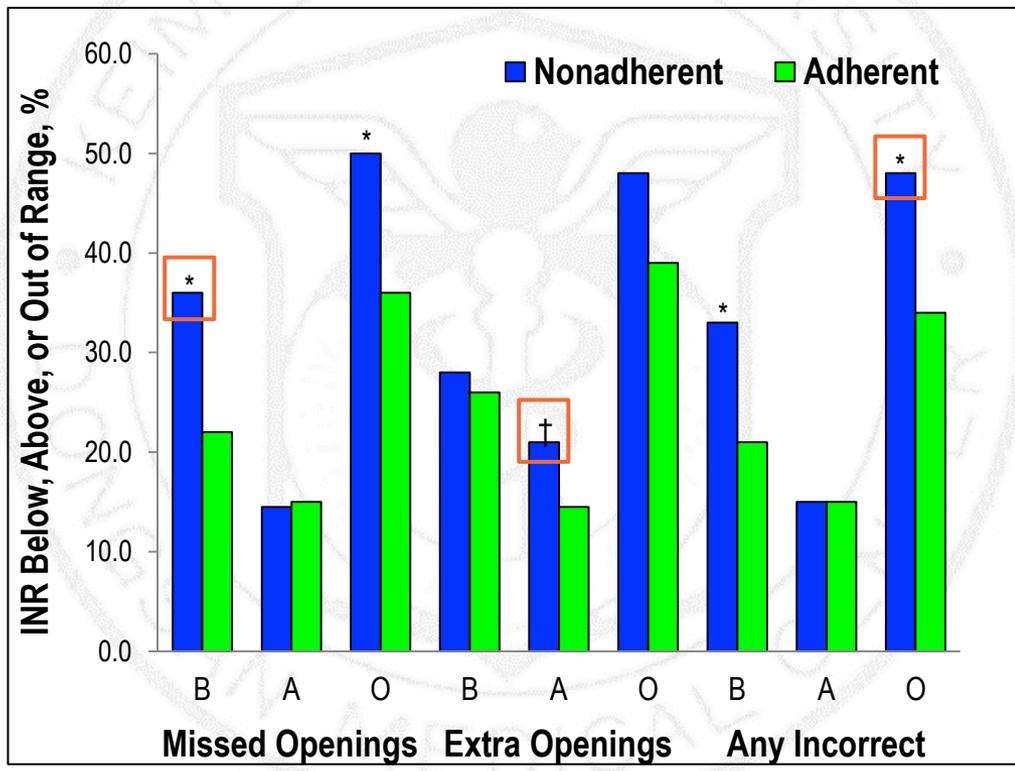
92%: at least one extra/ missed dose  
 36%: missed ≥ 20% of doses  
 4%: had ≥ 10% of extra doses



Increased odds of subtherapeutic INR  
 Increased risk of too high INR



**Poor implementation had significant effect on INR control**



# Once- vs. Twice daily dosing



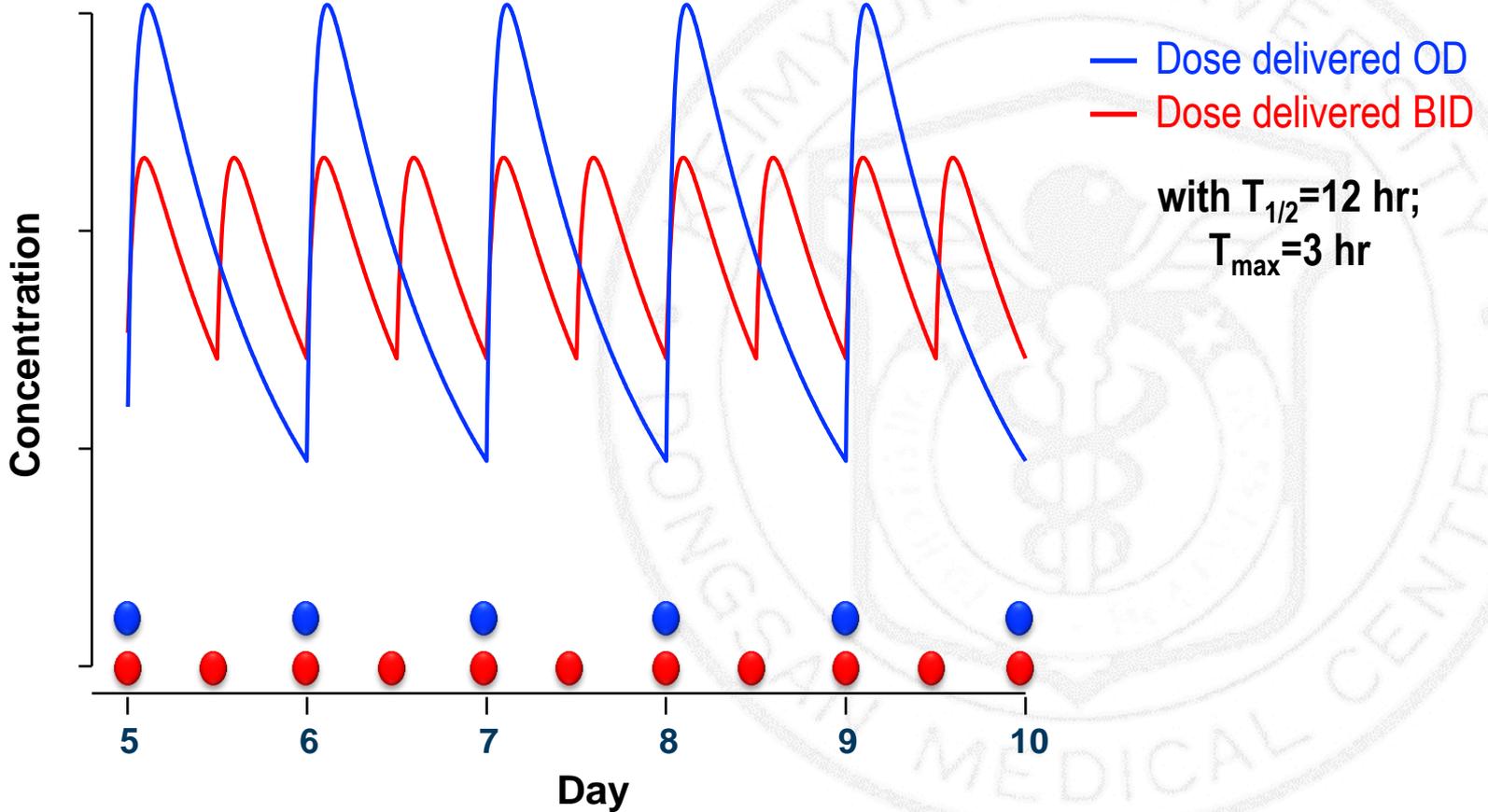
# OD vs. BID dosing

- **Reducing the dosing frequency** can **improve medication adherence**
- Percentage of dose taken is generally higher with less dosing regimen
  - It is not sufficient to represent medication adherence because it is aggregated summary
- **A twice-daily dosing regimen maintains a better continuity** of drug plasma levels for drugs with a half-life of 12 h

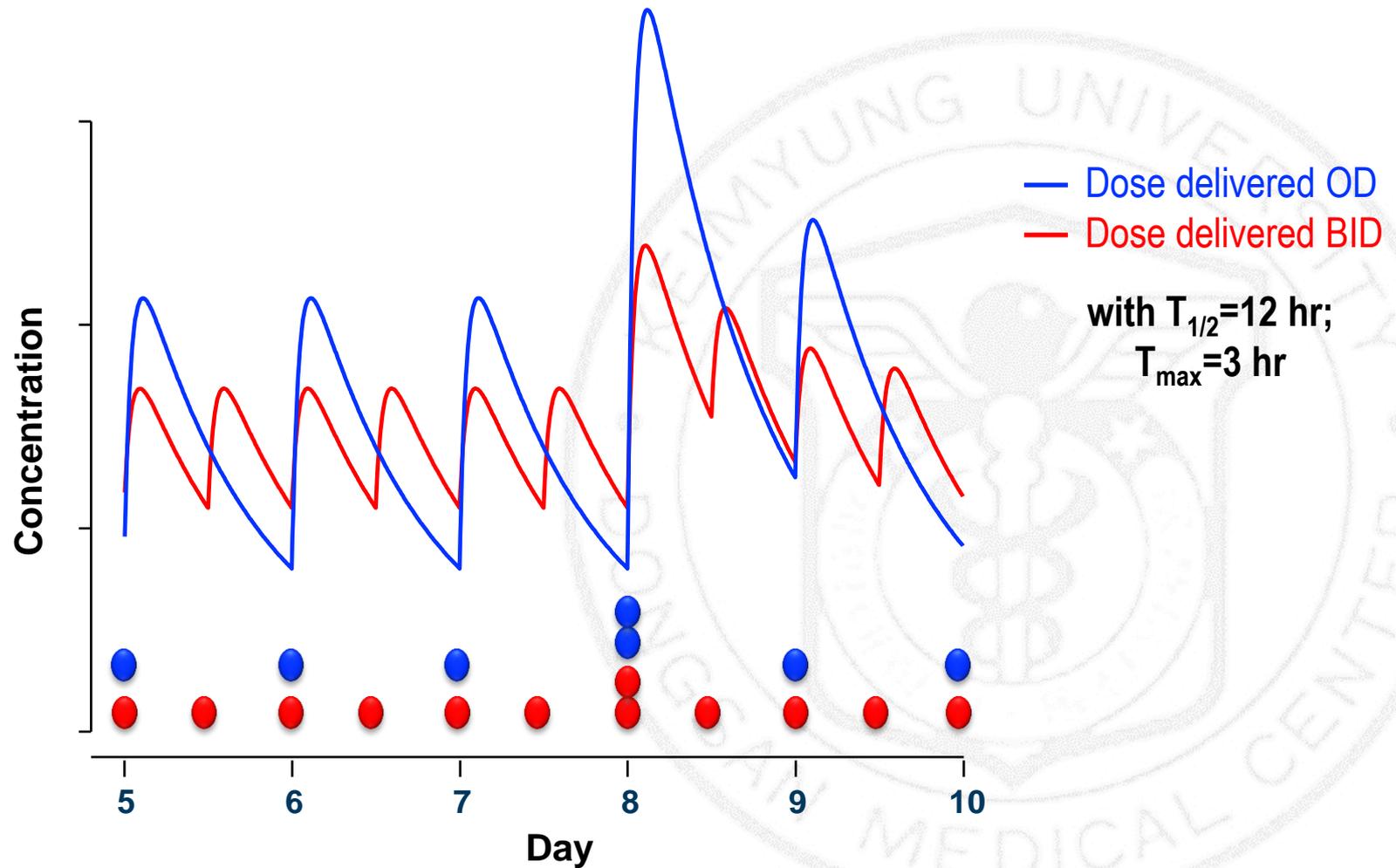


# Lower peak-trough ratio at steady state for BID vs OD

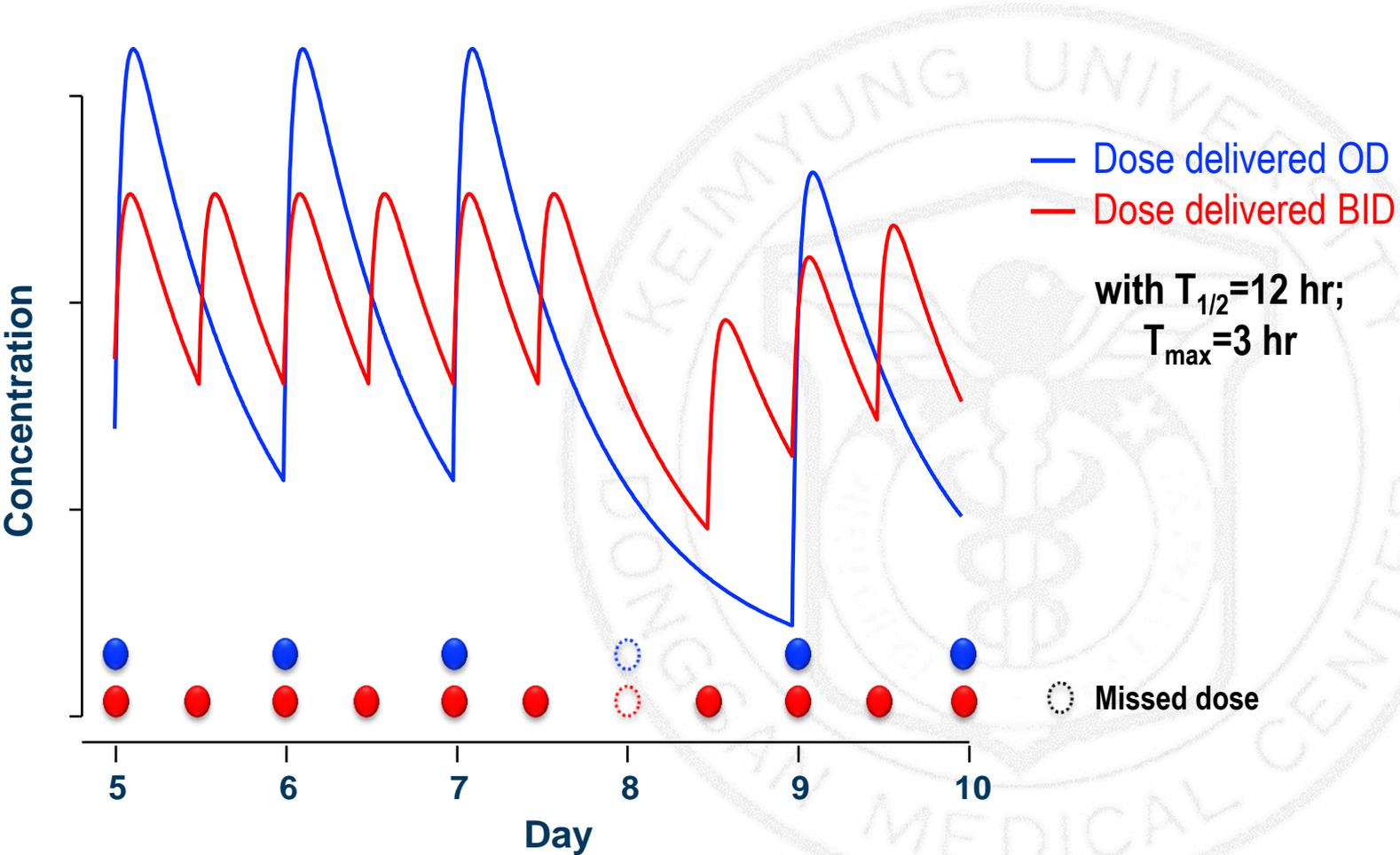
Repeated dosing assuming perfect adherence



# Simulating one extra dose for BID vs OD

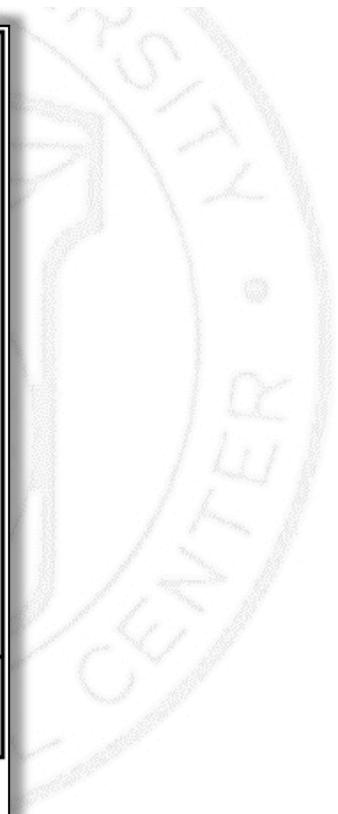
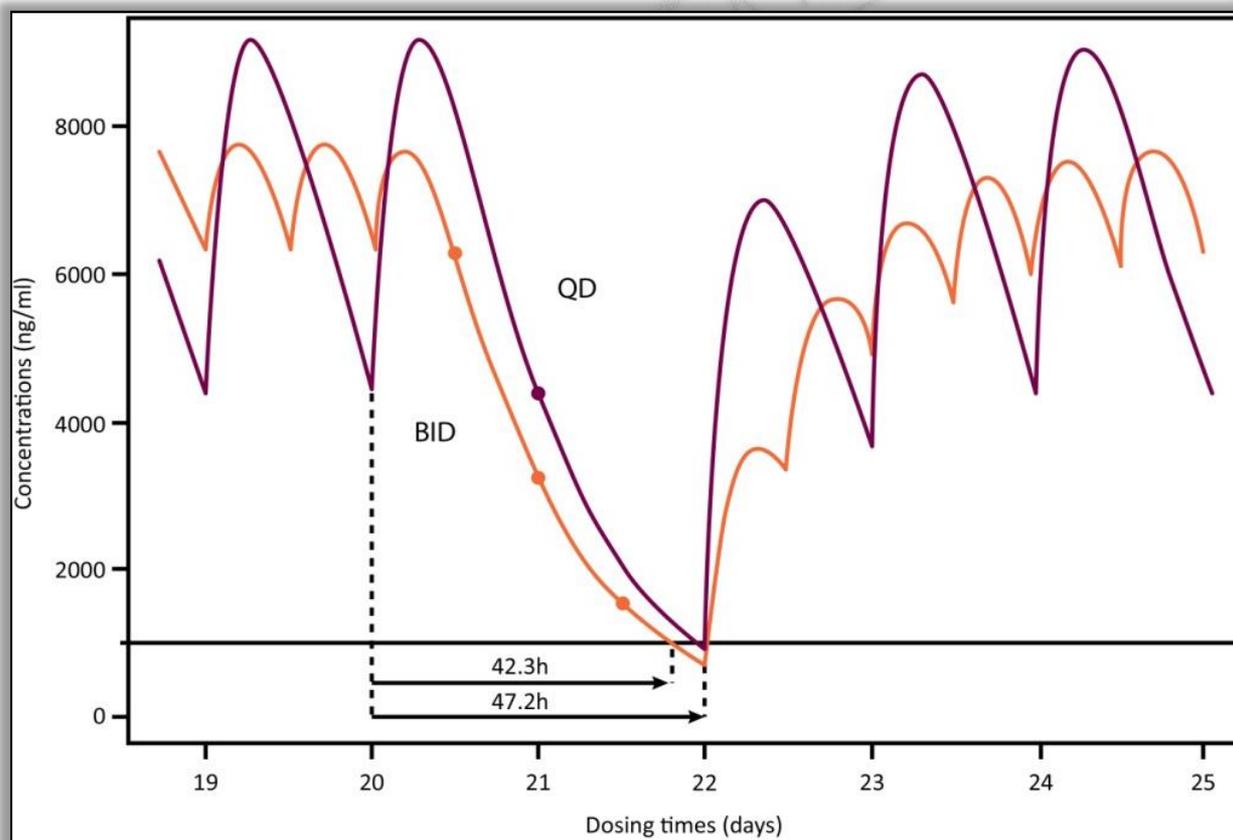


# Simulating one single missed dose for BID vs OD



# Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics

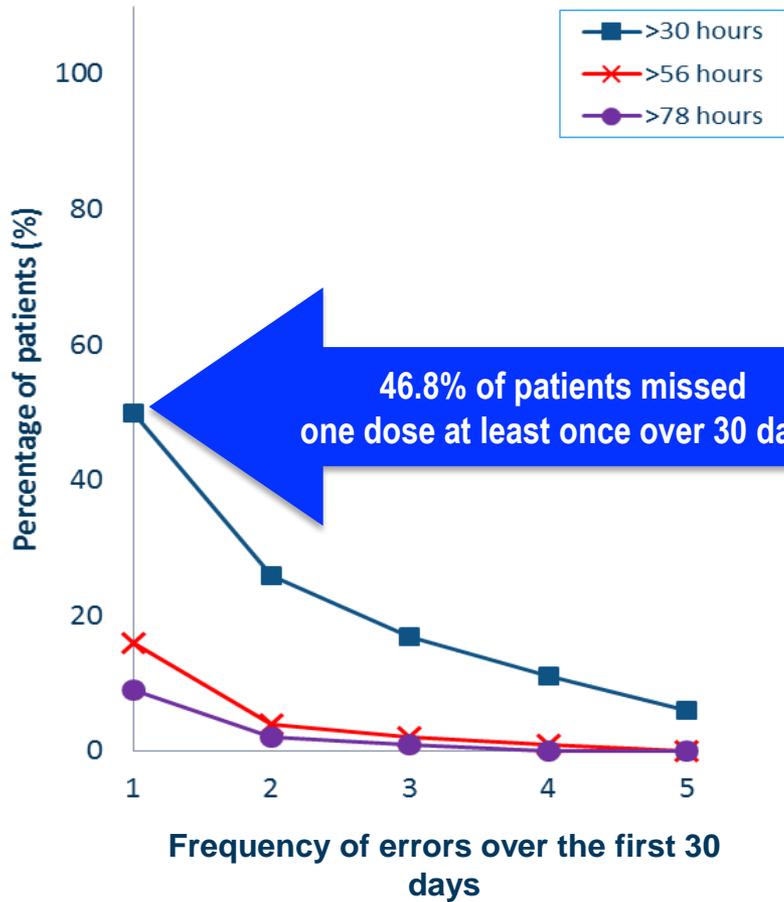
pharmacokinetic equivalent of a **single missed once-daily dose** is **2–3 sequentially omitted twice-daily doses**



# How frequently do patients miss consecutive doses?

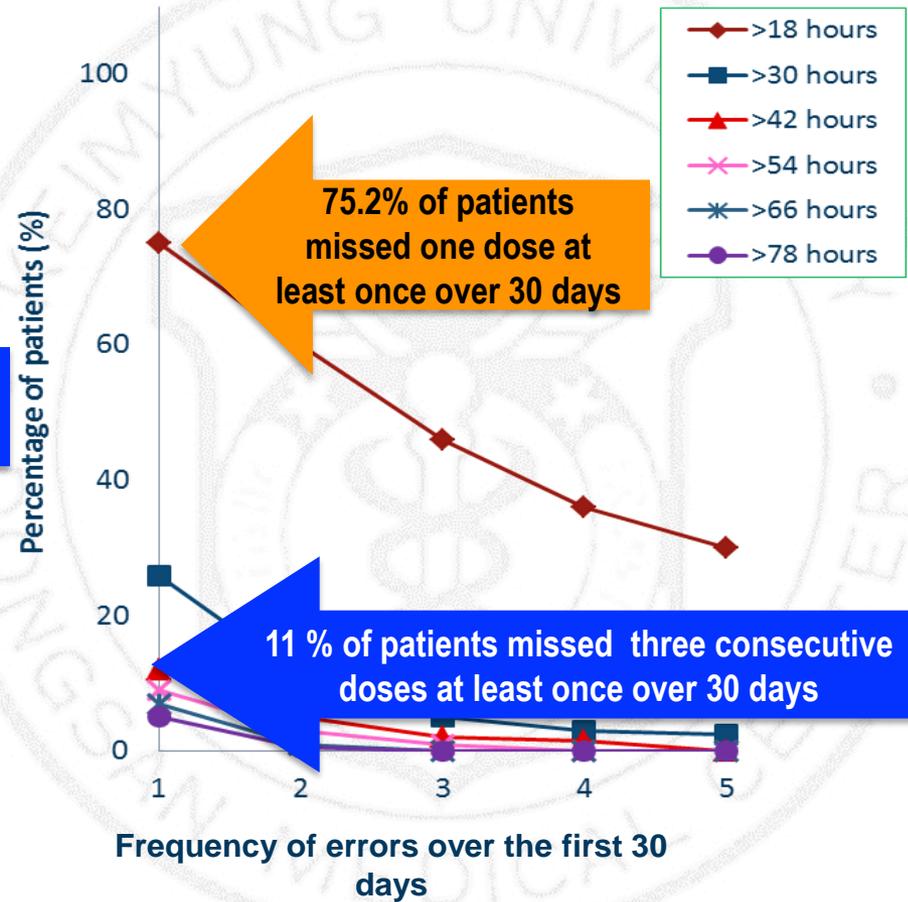
## Once daily

N=677



## Twice daily

N=677

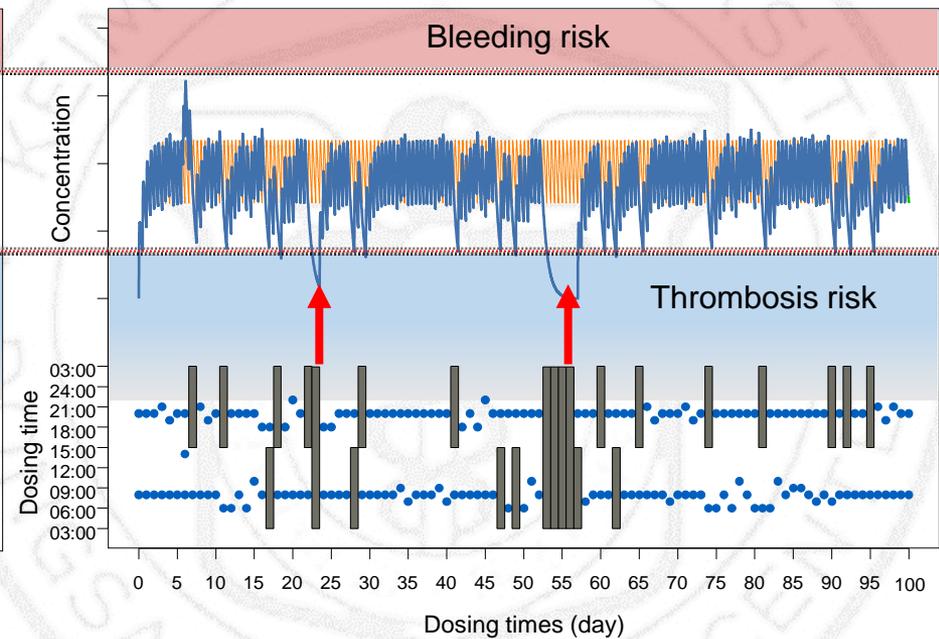
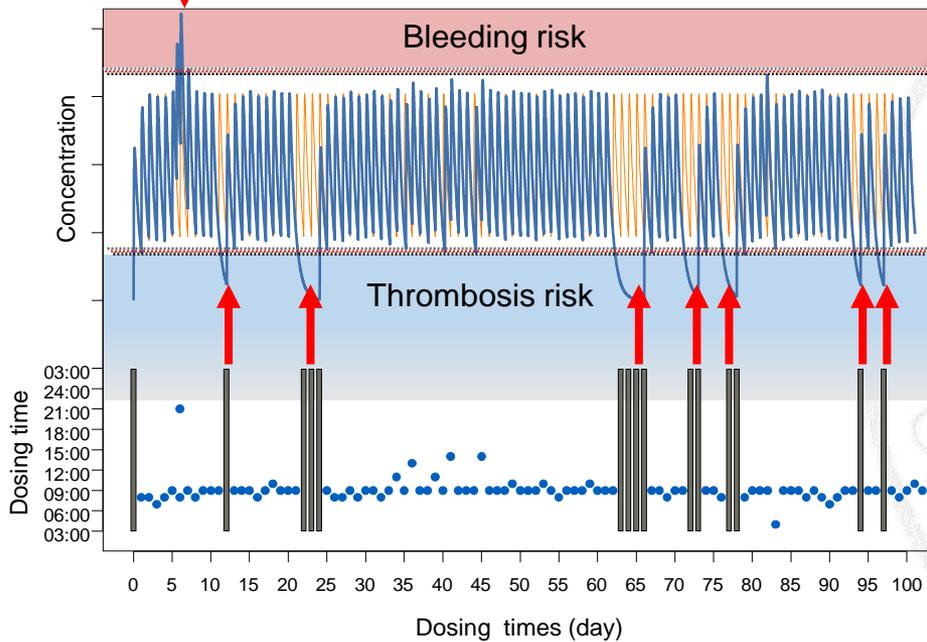


# BID regimen increases forgiveness for similar deviations in adherence

model-projected continuous time-course of the concentrations resulting from a dosing history

**Once daily\***

**Twice daily\***



- 15% missed doses
- 15 OD missed doses vs 30 BID missed doses over 100 days

Assuming  $T_{1/2}=12$  hr;  $T_{max}=3$  hr

# Measurement of Adherence

	Initiation	Implementation	Discontinuation
<b>Self-report</b>	Desirability bias	Recall bias	Desirability bias
<b>Pill count</b>	Easily censored by patient	Only aggregate summary	Easily censored by patient
<b>Direct Methods (PK/PD)</b>	Requires sampling after prescription	Sampling is too sparse	Subject to white coat adherence
<b>Prescription and refill databases</b>	Gold standard if both databases are combined	Only aggregate summary	Gold standard but retrospective
<b>Electronic Monitoring</b>	Gold standard in clinical trials needs activation	Gold Standard	Gold standard in clinical trials needs patient engagement

# What may be the surrogate marker of adherence?

**Vitamin K antagonist**

—————→ **INR**

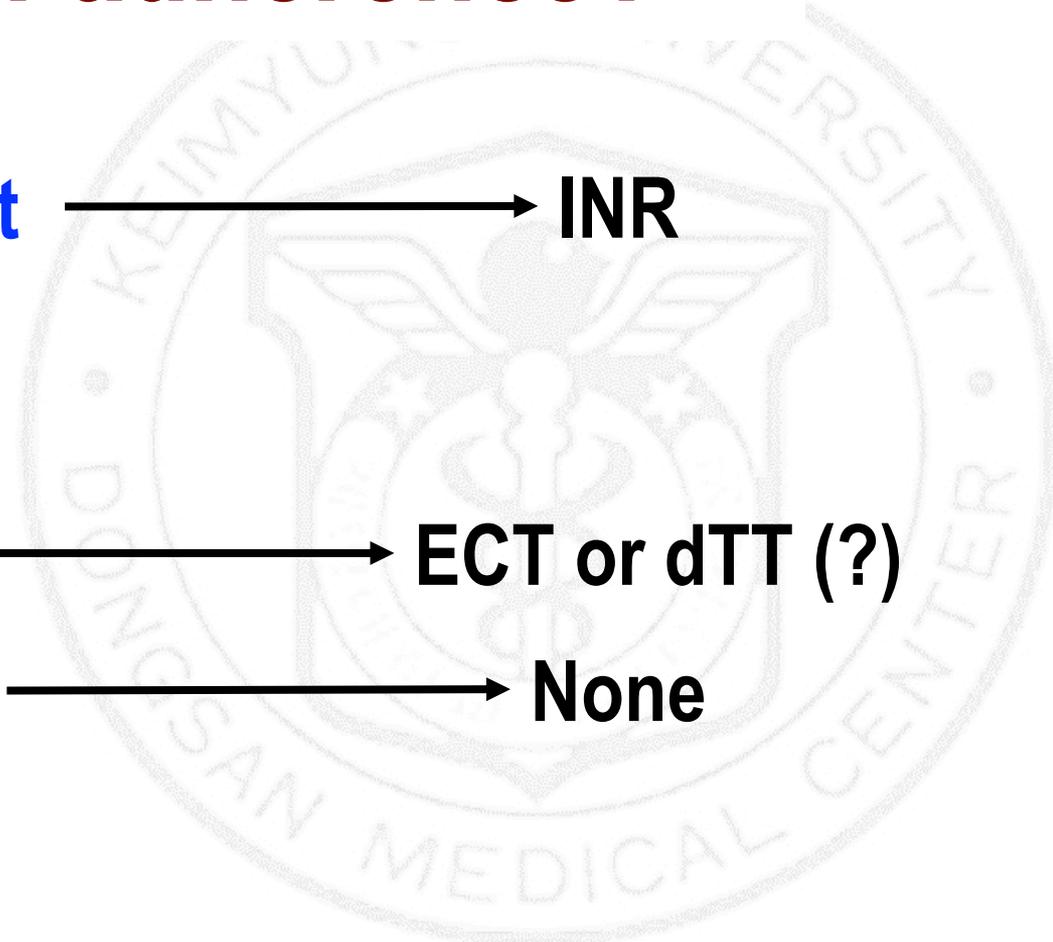
**NOAC**

**Dabigatran**

—————→ **ECT or dTT (?)**

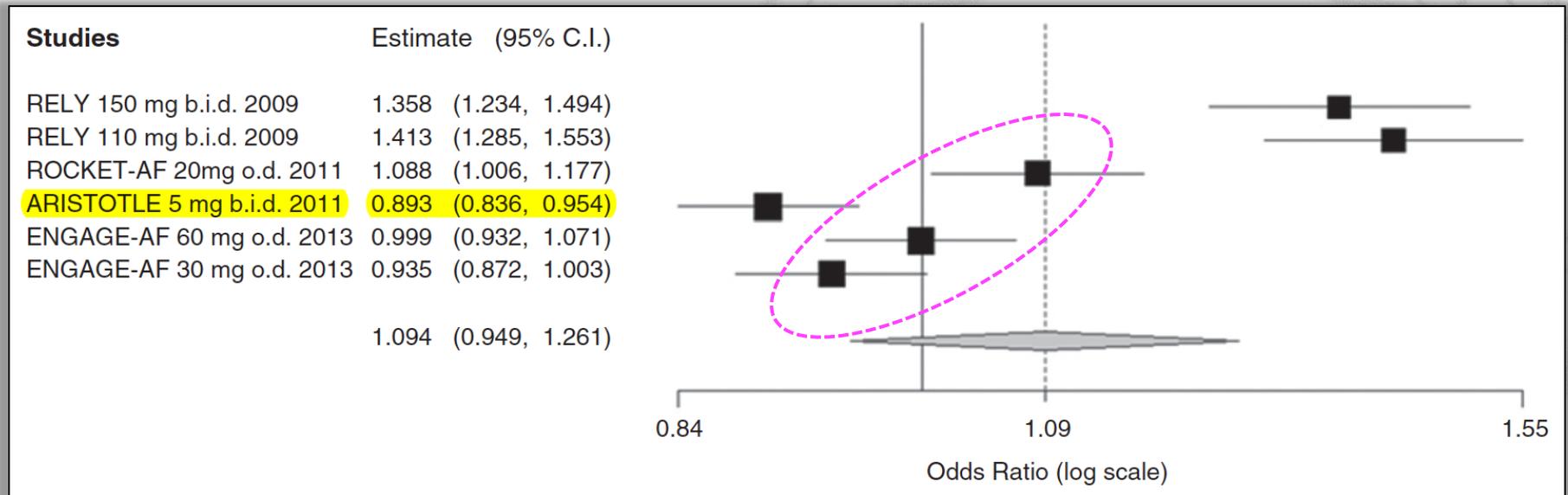
**Factor Xa Inhibitors**

—————→ **None**

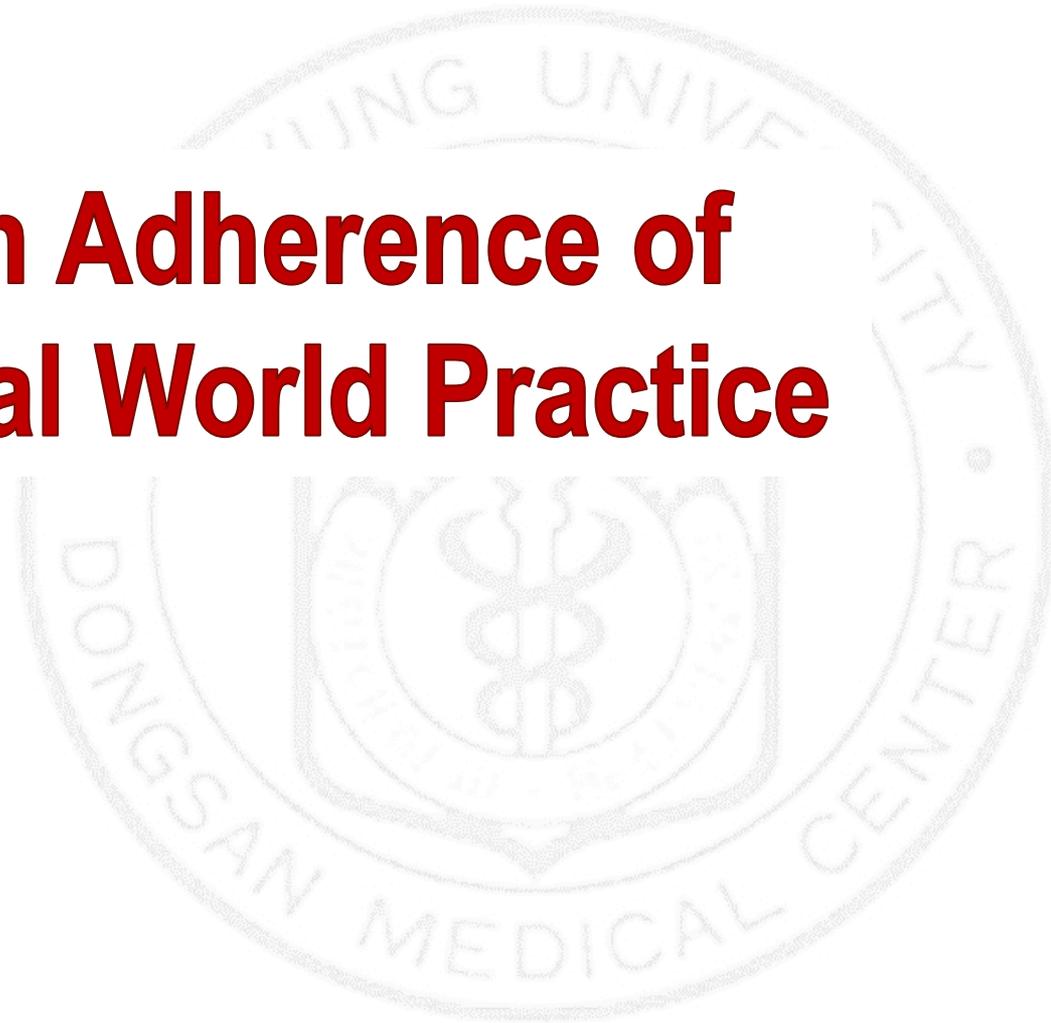


# Discontinuation of anticoagulant treatment: from clinical trials to medication persistence

## **Frequency treatment discontinuation** in phase 3 trials of anticoagulant treatment in NVAF



# Medication Adherence of NOAC in Real World Practice



# Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation

- ❖ Retrospective cohort analysis: US commercial insurance database: 11/01/2010~12/31/2014
- ❖ 64,661 patients who initiated warfarin, dabigatran, rivaroxaban, or apixban
- ❖ **Definition of adherence**
  - ✓ Proportion of days covered over a patient's entire follow-up
  - ✓ **Days covered by OAC: based on fill date and the days of supply on the pharmacy claims**

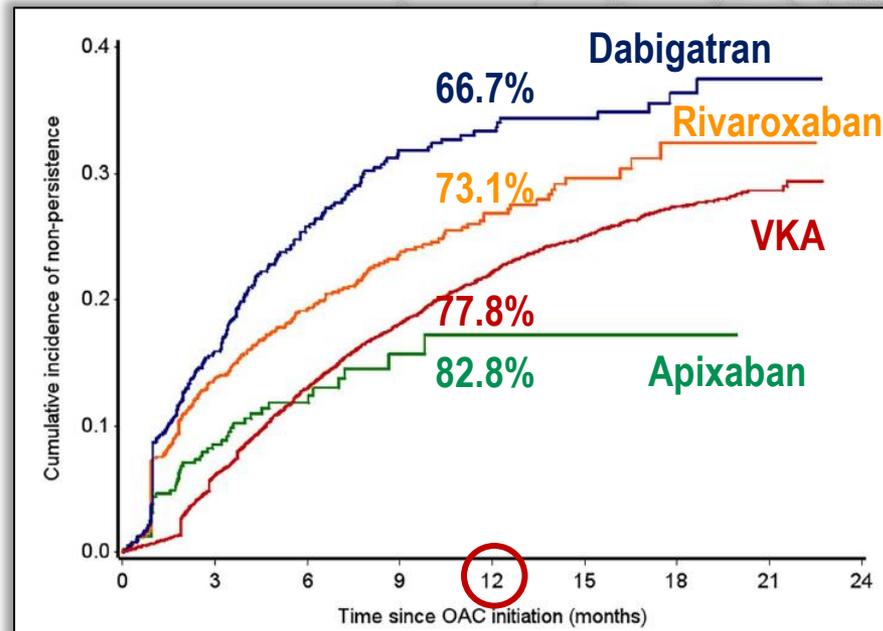
# Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation

## Adherence to OACs (PDC ≥ 80%)

	Apixaban (n=3900)	Dabigatran (n=10 235)	Rivaroxaban (n=12 336)	All NOACs (n=26 471)	Warfarin (n=38 190)	P Value (All NOACs Pooled vs Warfarin)
Unadjusted adherence*						
All	61.9%	38.5%	50.5%	47.5%	40.2%	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score 0 or 1	50.1%	24.6%	36.5%	32.6%	27.1%	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score 2 or 3	62.0%	40.3%	52.8%	49.1%	38.1%	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥4	64.0%	42.4%	53.2%	51.1%	42.3%	<0.001
Adjusted adherence, 95% CI†						
All	52.1% (50.3–53.9)	45.9% (44.8–47.1)	47.6% (46.6–48.7)	47.5% (46.7–48.2)	38.7% (38.1–39.3)	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score 0 or 1	40.6% (35.8–45.4)	28.6% (26.3–30.9)	30.8% (28.7–32.9)	30.8% (29.3–32.3)	25.2% (23.4–27.0)	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score 2 or 3	51.9% (48.9–55.0)	46.9% (45.1–48.6)	48.8% (47.2–50.5)	48.3% (47.2–49.5)	37.3% (36.3–38.4)	<0.001
CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥4	54.1% (51.8–56.5)	48.7% (47.1–50.3)	50.1% (48.7–51.5)	50.1% (49.0–51.1)	42.0% (41.3–42.7)	<0.001

# Early real-world evidence of *persistence* on oral anticoagulants for stroke prevention in NVAF: a cohort study in *UK primary care*

- ❖ 15,242 patients: NVAF, newly prescribed OAC: 12/01/2012 ~ 10/31/2014
- ❖ **Discontinuation period**: *twice the median duration of a single prescription* (56~60 days)
- ❖ **Gap**: *more than the length of the discontinuation period*
- ❖ **Non-persistence**: regimen change or Gap

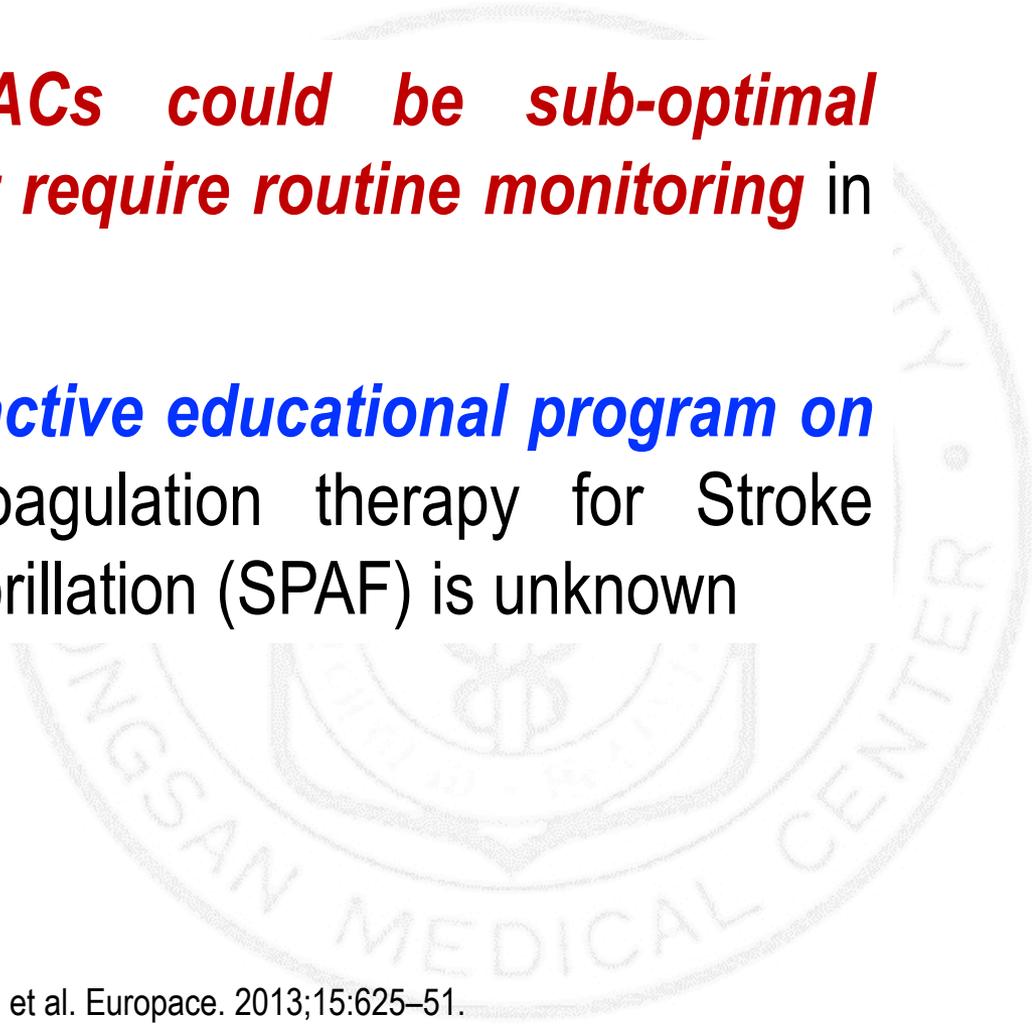


**Assessment of an Education and Guidance program for Eliquis Adherence in Non-valvular atrial fibrillation: the randomized AEGEAN study**



# AEGEAN Rationale

- ❖ **Adherence to NOACs could be sub-optimal because they do not require routine monitoring** in anticoagulation clinics
- ❖ The **impact of a proactive educational program on adherence** to anticoagulation therapy for Stroke Prevention in Atrial Fibrillation (SPAF) is unknown



# AEGEAN Objectives

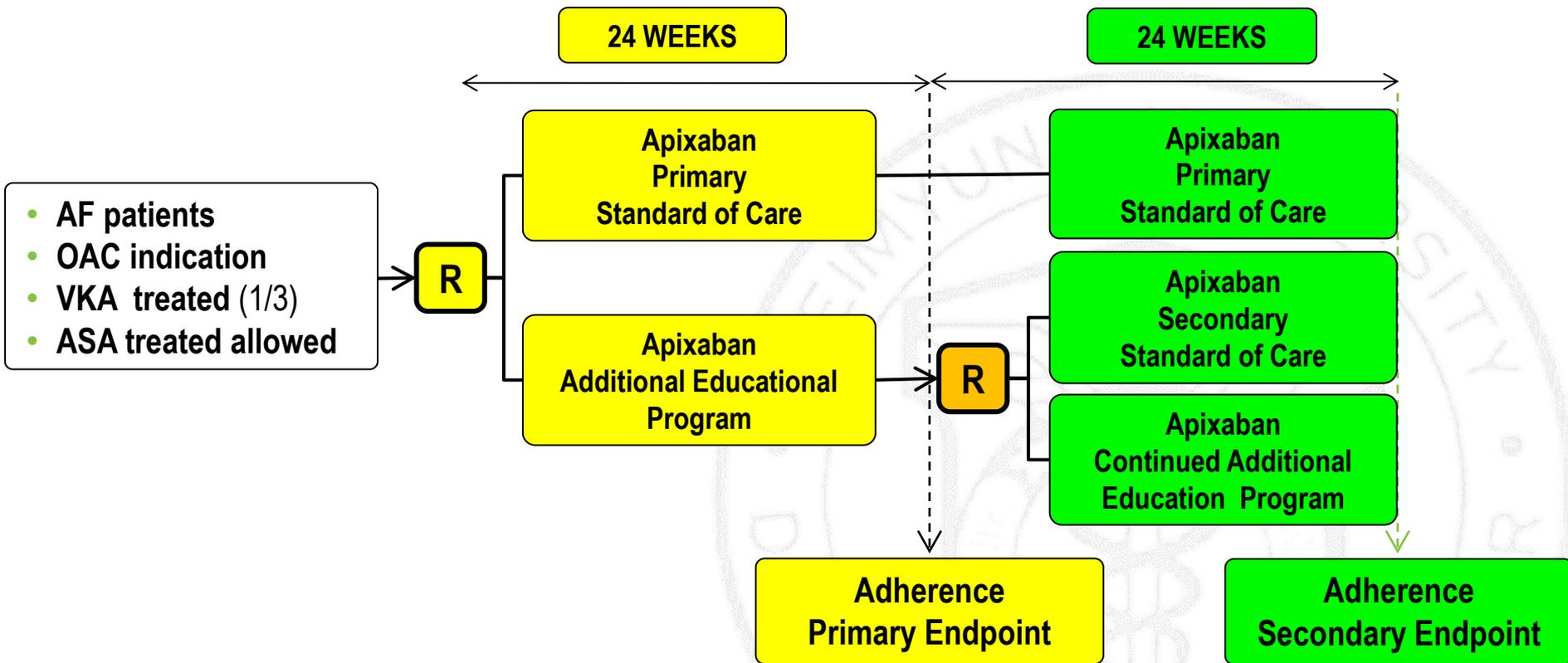
## **Primary Objective:**

- To assess the **impact of an education** program on **implementation phase**
- Adherence in patients taking apixaban for SPAF
- **Assessed @ 24 weeks after initiation using an EMD, Helping Hand®**

## **Secondary Objectives:**

- To assess the impact of an educational program on persistence at 24 weeks in patients taking apixaban
- To identify predictive risk factors linked to non-adherence in patients treated with apixaban
- To evaluate impact of an educational program on efficacy/safety profile of apixaban

# AEGEAN Design



**Standard of care:** usual information about apixaban treatment

**Additional educational program:**

- an additional patient education booklet explaining AF and anticoagulant treatment for stroke prevention
- reminder tools: key ring, short message service (SMS) alert on mobile phone, or Smart Phone application
- access to a virtual clinic organized at country level utilising the staff from existing anticoagulant clinics

# AEGEAN study Definitions

## **Day of adherence:**

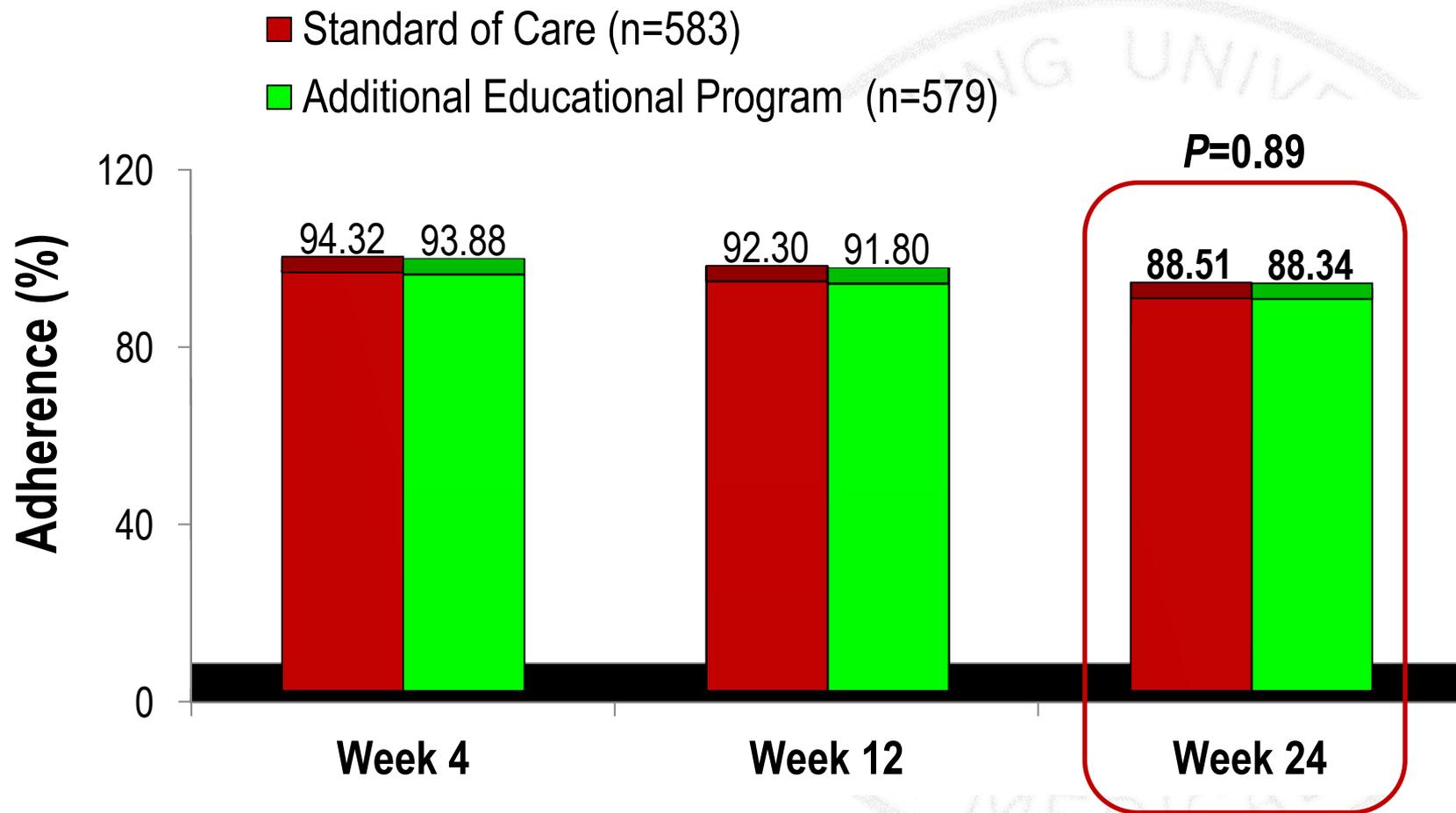
- ***If only one tablet was missed in 24 hours in isolation***

## **Day of non-adherence:**

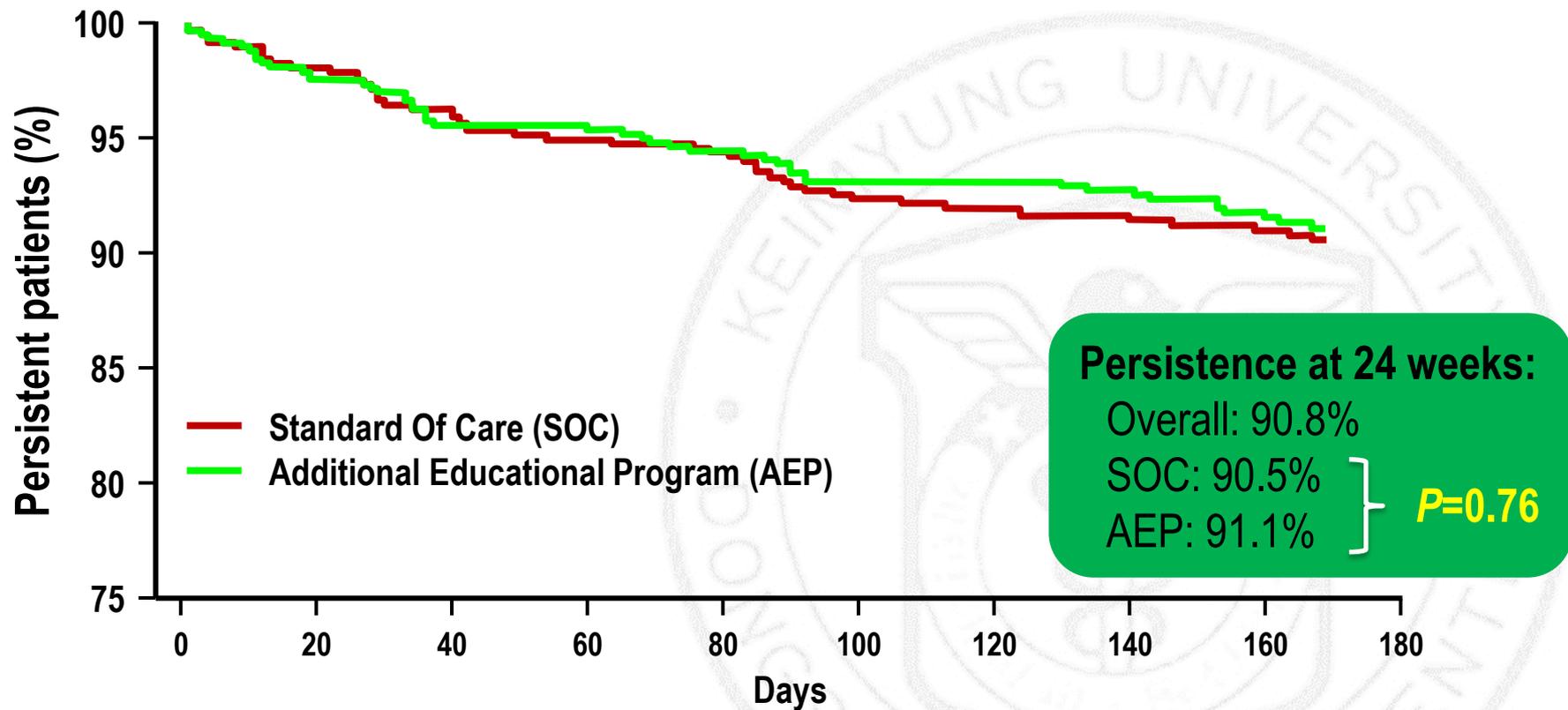
- ***Two consecutive tablets*** within 24 hours were missed
- ***One tablet was missed for several consecutive days***
- ***One tablet was missed on alternate days***

**Persistence** was defined as the absence of permanent discontinuation, which was defined as **no doses taken for at least 30 consecutive days**

# Primary Endpoint: Adherence

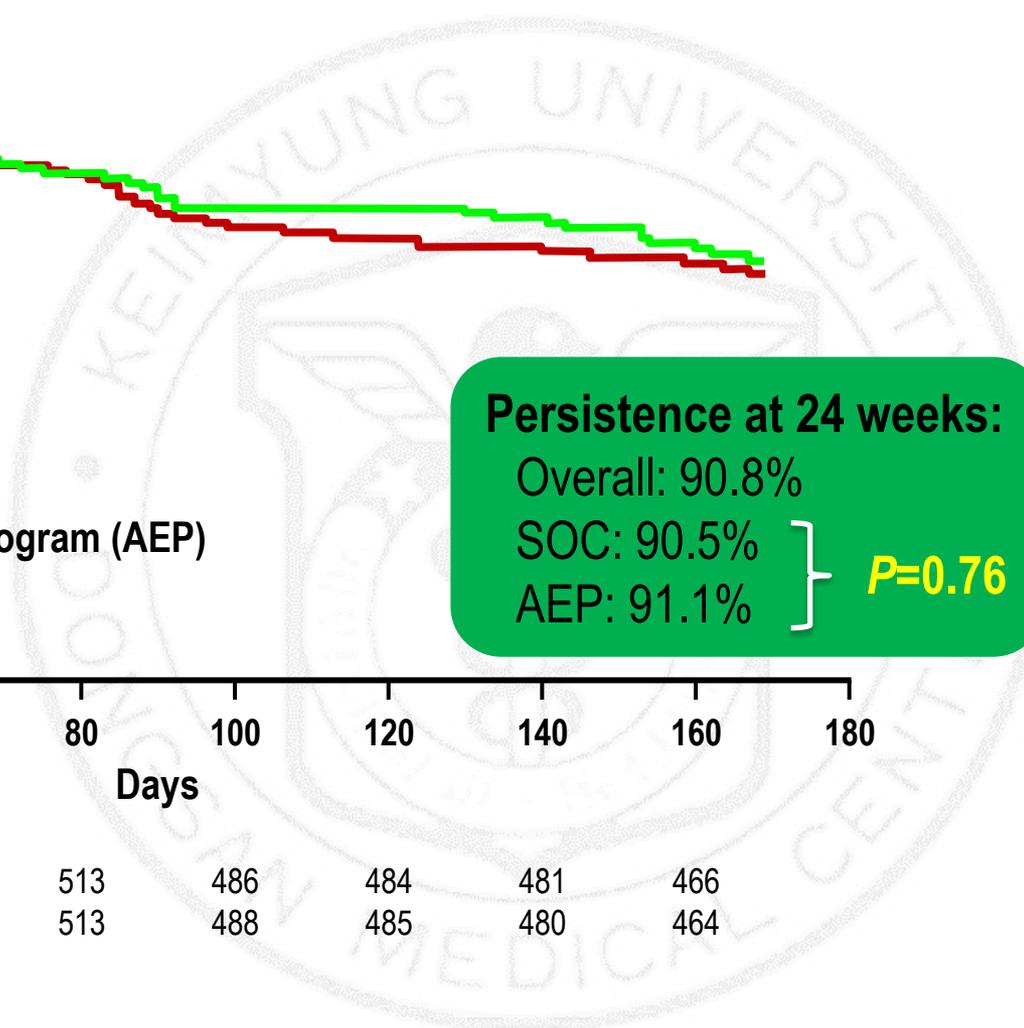


# Secondary Endpoint: Persistence



Number of patients still persistent

AEP	556	541	523	523	513	486	484	481	466
SOC	554	541	526	519	513	488	485	480	464



# AEGEAN limitations

- ❖ As there was patient selection, this may not fully represent real life patients
- ❖ ***Measuring adherence increases per-se adherence because the patient is aware of it***
- ❖ All measures of adherence tend to overestimate the real adherence of the patient to a medication
- ❖ However, AEGEAN as a prospective, randomized trial used a low bias, rich sampling method (EMD Helping Hand®) that precisely records day and time of medication access
- ❖ Adherence may decrease over time beyond 6 months



# AEGEAN Conclusions

- ❖ The first part of this study shows
  - ✓ a **high adherence rate (88%)** in the first 6 months of apixaban twice daily treatment for SPAF
  - ✓ a **high persistence rate (90.8%)** in the first 6 months of apixaban twice daily treatment for SPAF
- ❖ There was ***no additional value of a proactive educational program*** on adherence in the first 6 months of treatment
- ❖ Long-term adherence as well as the value of an educational program beyond 6 months will be further evaluated in the second part of AEGEAN

# NOAC Adherence Of The Patients With NVAF In Real Practice

- ❖ We enrolled consecutive 722 patients who have been prescribed NOACs for NVAF in the cardiology department from May 2016 to Sep 2016
- ❖ The term of study could include all patients with NOAC in this institution because the maximal duration of prescription from the OPD is 4 months
- ❖ Patients who are currently taking NOACs were ***contacted by phone or text on the day before the appointment to bring the remnant pills of prescribed medication without any information***
- ❖ The patients who can not take NOACs voluntarily were excluded

# NOAC Adherence Of The Patients With NVAF In Real Practice

- **Medication adherence**: measured by pill count (MPR)
- **Morisky Medication Adherence Scale** (MMAS-8) was checked
  - Adherence index (%)
    - ✓ taken pills were counted

$$\frac{\text{No. of taken doses}}{\text{No. of doses dispensed from the last prescription}} \times 100$$

# NOAC Adherence Of The Patients With NVAf In Real Practice

## Patients Characteristics

N=722	Value	N=722	Value
Male, n(%)	395 (54.8)	Medical history	
<b>Age, years</b>	<b>69.5±9.6</b>	CHF, n(%)	192 (26.6)
Weight, Kg	65.0±11.7	Hypertension, n(%)	469 (65.0)
Cr, mg/dl	0.8±0.3	Diabetes mellitus, n(%)	150 (20.8)
CCR, mL/min	78.6±28.1	History of Stroke, n(%)	102 (14.1)
Classification of AF		History of MI, n(%)	32 (4.4)
Paroxysmal	75 (10.4)	Peripheral Artery Disease, n(%)	6 (0.8)
Persistent	253 (35.0)	Medication	
Long standing Persistent	320 (44.3)	History of warfarin, n(%)	220 (30.5)
Permanent	67 (9.3)	<b>Duration of NOAC, weeks</b>	<b>7.2±5.7</b>
others	6 (1.0)	<b>Duration of AF, months</b>	<b>43.2±50.5</b>
<b>CHA2DS2VAsc score</b>	<b>2.9±1.4</b>	MMAS	2.6±0.8

# NOAC Adherence Of The Patients With NVAf In Real Practice

## 모리스키 복용 순응 척도 (Morisky Medication Adherence Scales: MMAS-8)

1. 약 먹는 것을 잊어 버린 적이 있습니까? (예 / 아니요 )
2. 환자들은 잊어 버린 경우 말고 다른 이유로 약을 먹지 않는 경우가 있습니다. 지난 2주 동안 약을 먹지 않은 경우가 있습니까? (예 / 아니요 ), 있었다면 이유는 ? (      )
3. 약을 먹고 더 **않** 좋아져서, 의사한테 이야기 하지 않고 약을 먹지 않거나 줄여서 먹은 적이 있습니까? (예 / 아니요 )
4. 여행을 가거나, 일하러 나갈 때 약을 가져가는 것을 잊어 버린 적이 있습니까? (예/아니요)
5. 어제 환자분이 처방받은 약을 모두 먹었습니까? (예 / 아니요 )
6. 약을 먹고 좋아졌을 때 가끔 약 먹는 것을 빼먹은 적이 있습니까? (예 / 아니요 )
7. 약을 매일 계속 먹는 일은 실제로 힘든 일입니다. 환자분은 약을 처방대로 먹는데 힘든 적이 있습니까? (예 / 아니요 )
8. 얼마나 자주 약먹는 것을 잊어버립니까?
  - 1) 절대로/거의 잊어버리지 않는다
  - 2) 아주 가끔
  - 3) 가끔
  - 4) 자주
  - 5) 항상

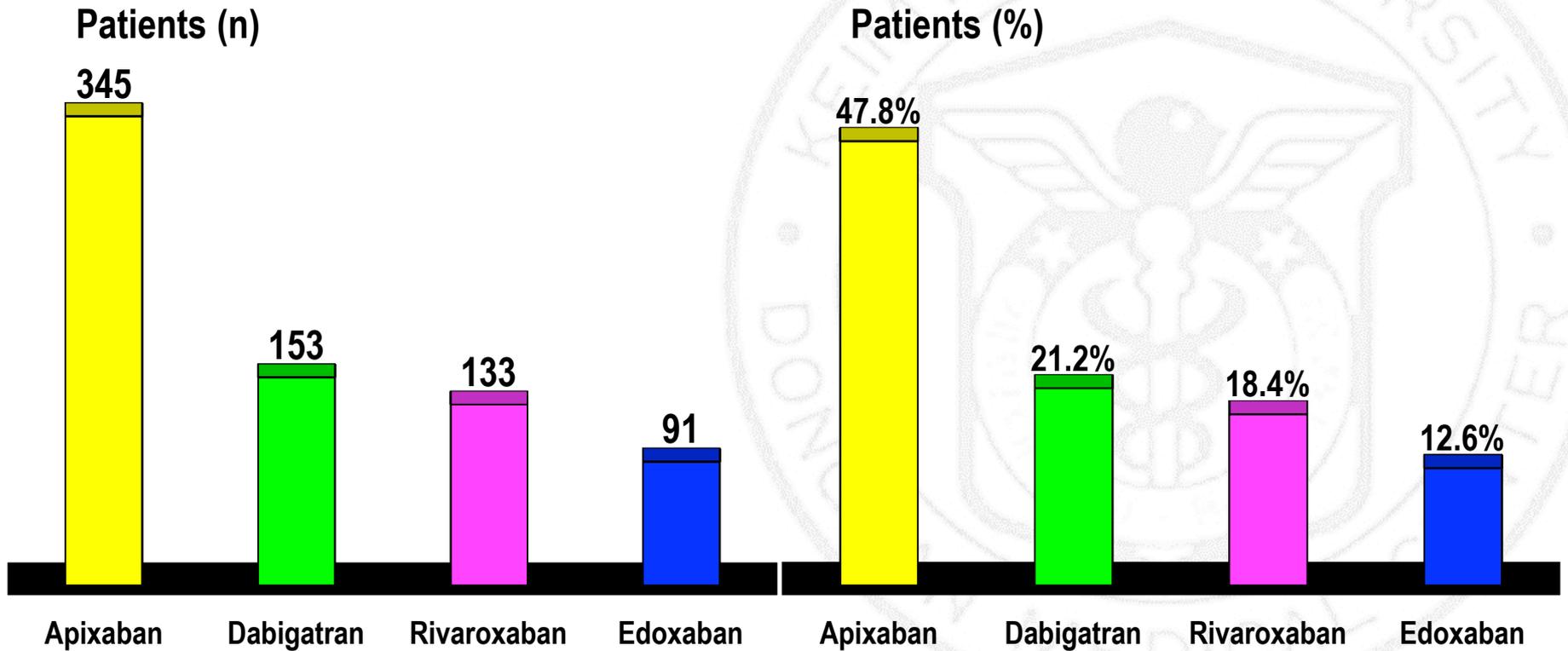
# NOAC Adherence Of The Patients With NVAF In Real Practice

## 모리스키 복용 순응 척도 (Morisky Medication Adherence Scales: MMAS-8)

순응도	MMAS-8 점수
좋음	0
중간	1~2
낮음	3~8

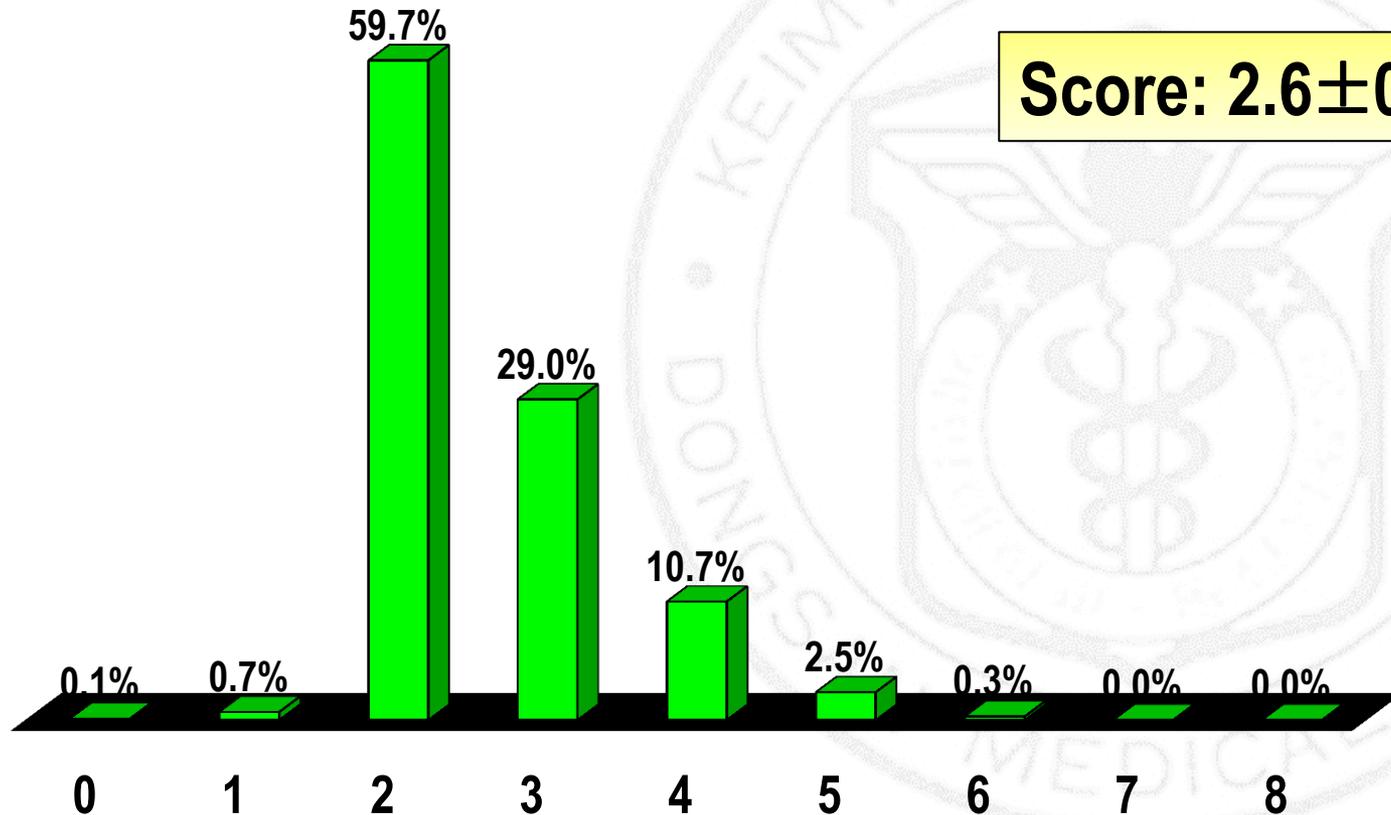
# NOAC Adherence Of The Patients With NVAf In Real Practice

## Distribution of the NOAC



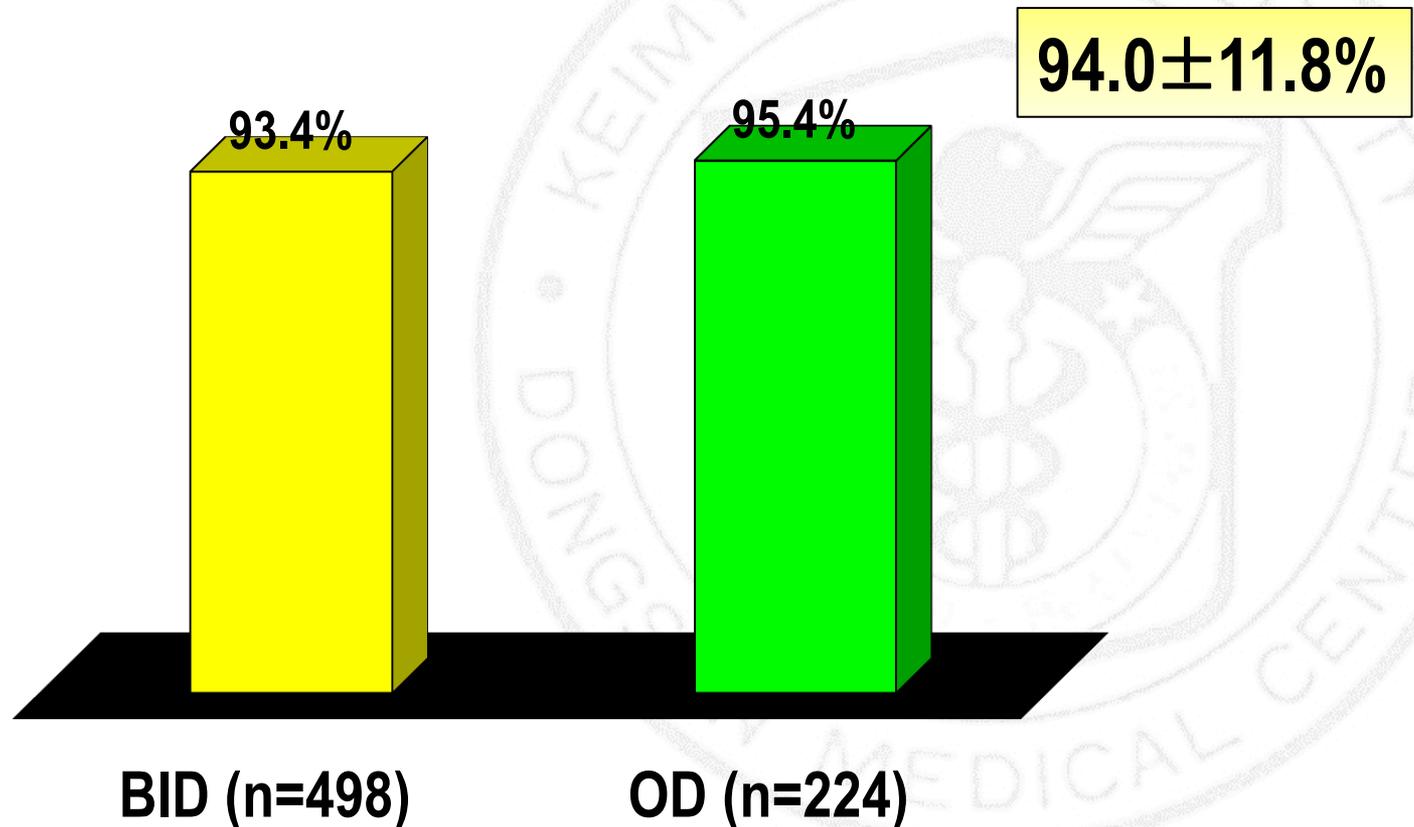
# NOAC Adherence Of The Patients With NVAf In Real Practice

## Distribution of the MMAS



# NOAC Adherence Of The Patients With NVAF In Real Practice

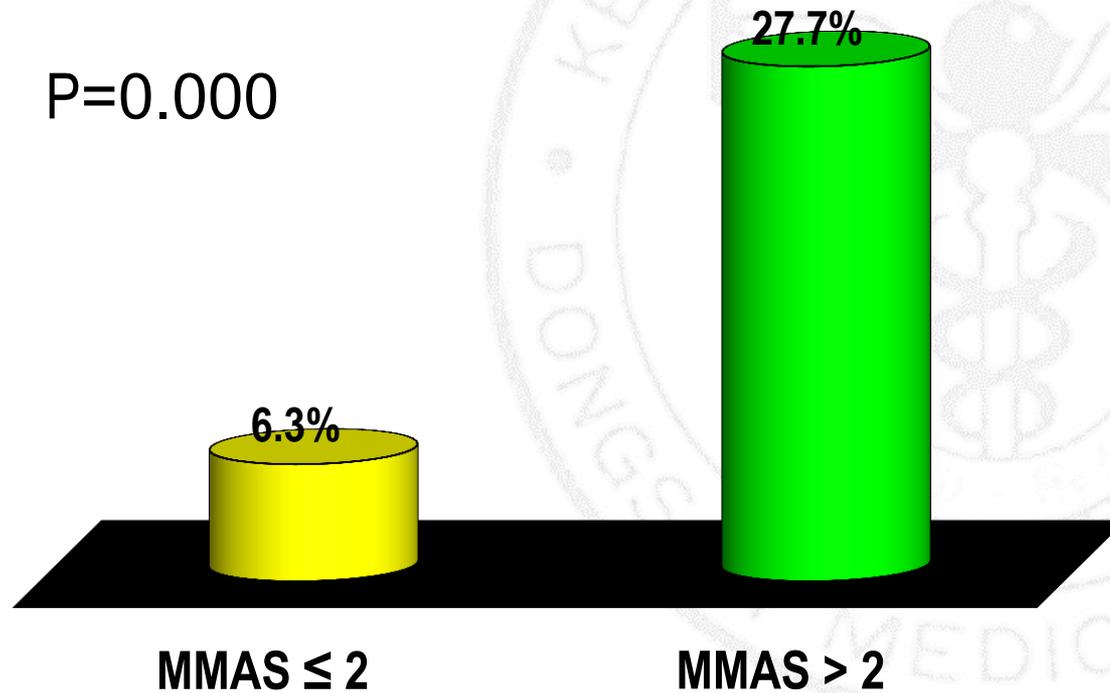
## Medication Adherence: *BID* vs. *OD*



# NOAC Adherence Of The Patients With NVAF In Real Practice

**Proportion of adherence < 82%**

(1 SD of the mean)

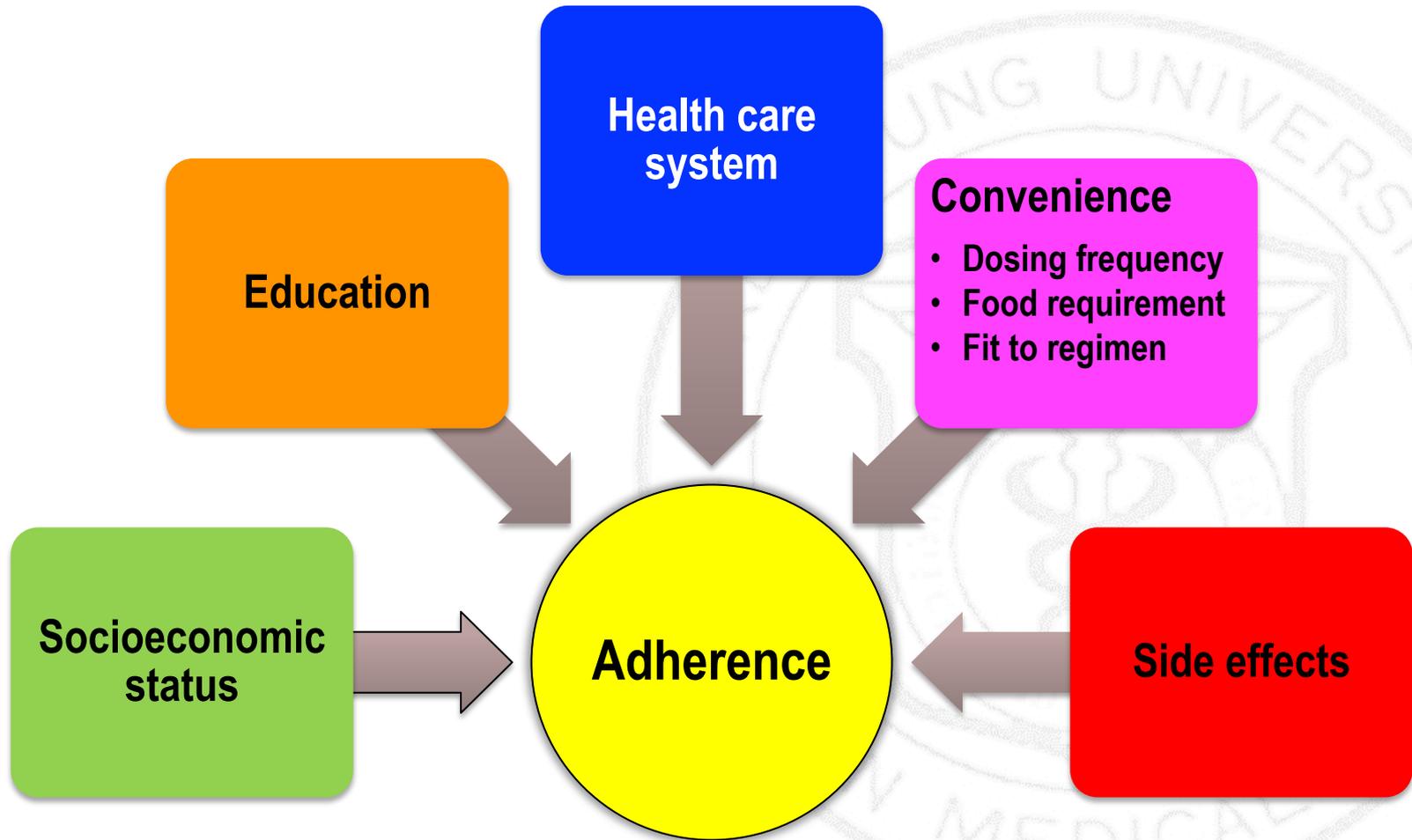


# NOAC Adherence Of The Patients With NVAF In Real Practice

## Conclusion:

- Most patients who had been taking NOAC showed **excellent adherence** in real world practice in Korea
- The patients who showed low adherence (<80%) is **only 7.5%**
- **MMAS  $\geq$  3** can be used as a surrogate marker for relatively poor adherence with NOAC

# Factors affecting adherence



# Profile of NOACs



	Pradaxa dabigatran etexilate	Eliquis (apixaban) tablets	Xarelto rivaroxaban tablets	Lixiana edoxaban tablets
<b>administration</b>	bid	bid	<b>QD (with food)</b>	QD
<b>formulation</b>	capsule	tablet	tablet	tablet
<b>CYP metabolism</b>	None	extensive	extensive	<4%
<b>Renal elimination</b>	80%	25%	35%	50%
<b>Protein binding</b>	35%	87%	92~95%	40~59%
<b>Half life</b>	14~17 hrs	8~15 hrs	9~13 hrs	9~10 hrs
<b>Tmax</b>	2~3 hrs	3~4 hrs	2.5~4 hrs	1~2 hrs
<b>bioavailability</b>	6~7 %	50~60 %	<b>66~100 %</b>	62%
<b>transporter</b>	P-gp	P-gp/BCRP	P-gp/BCRP	P-gp
<b>Dialysis</b>	Yes	Not expected	Not expected	Data NA

# Use of Chronic Medications Among Patients with Non-Valvular Atrial Fibrillation

- ❖ Large, national database of health insurance claims, patients with a diagnosis of **NVAF** between 07/01/2008 ~ 09/30/2011
- ❖ 324,172 patients: CHA<sub>2</sub>DS<sub>2</sub>VASc scores of 3.08
- ❖ **92.5 % took chronic medications: 6.9 medications/patient**
- ❖ Percentage of patients prescribed > bid dosing: **66.5%**

Medication Group	Number of Patients	% of Patients	Patients Prescribed Chronic Medications	% Patients Prescribed Chronic Medications	Patients Prescribed Chronic Medications >1 per Day	% of All Patients	% of Chronic Medication Patients
All patients	324,172		299,716	92.5	215,527	66.5	71.9
No anticoagulant	151,761	46.8	130,302	85.9	91,580	60.3	70.3
Any anticoagulant	172,411	53.2	169,414	98.3	123,947	71.9	73.2
Warfarin	162,871	50.2	159,997	98.2	116,732	71.7	73.0
Dabigatran	9358	2.9	9237	98.7	7082	75.7	76.7
Rivaroxaban	182	0.1	180	98.9	133	73.1	73.9

# Summary

- ❖ Once-daily dosing may increase absolute adherence, but twice daily dosing regimens may be ***more forgiving in patients with suboptimal adherence***
- ❖ Twice-daily dosing of NOACs could be ***beneficial for maintaining continuity*** of drug effect without extreme fluctuation of drug level

# Summary

- ❖ Increase the patients' level of ***awareness of the complications of AF and impact of non-adherence of NOAC*** is important
- ❖ The ***adherence of twice daily regimen*** of the NOAC is ***comparable to the once daily*** regimen in the Korean real world



# Thank You for Your Attention !



**Seongwook Han**, MD.PhD.

Professor of Medicine, Keimyung University School of Medicine  
Arrhythmia Service, Cardiology, Dongsan Medical Center