

# Debate of New Oral Anticoagulant Drugs for Stroke Prevention in Atrial Fibrillation

새 항응고제를 1차 선택약으로  
먼저 사용하여야 한다.

최 기 준

서울아산병원 심장내과

# LIMITATIONS OF Warfarin THERAPY

Unpredictable  
response

Narrow therapeutic  
window (INR 2.0–3.0)

Slow onset/  
offset of action

VKA therapy has  
several limitations  
that make it  
difficult to use in  
practice

Numerous food–drug  
interactions

Numerous drug–drug  
interactions

Warfarin resistance

Routine coagulation  
monitoring



Frequent dose  
adjustments

INR = International normalized ratio; VKA = vitamin K antagonist.

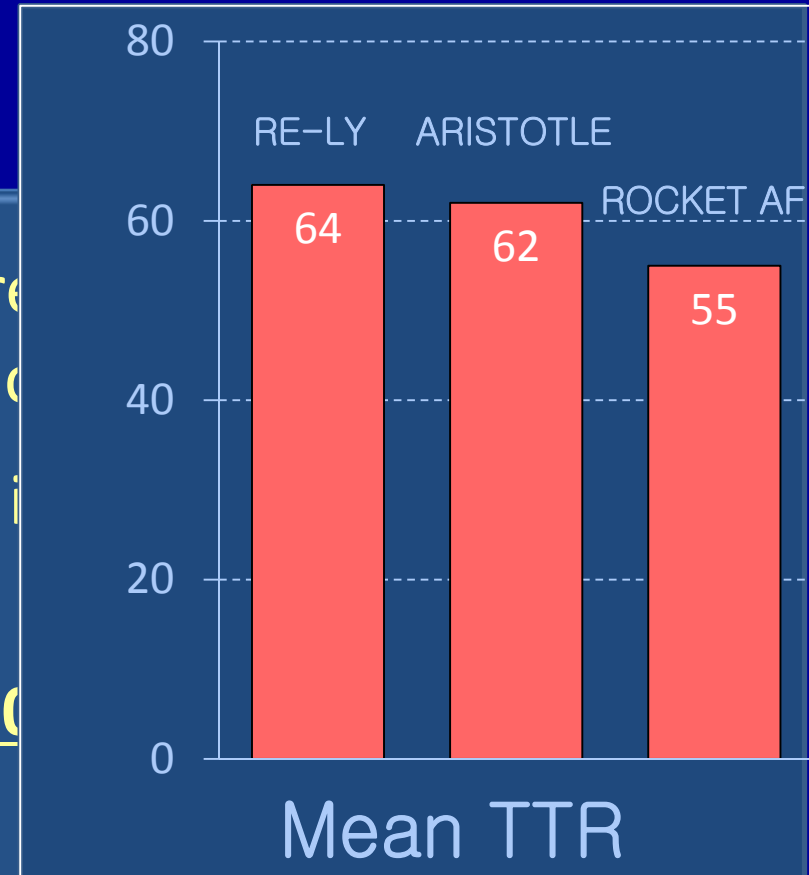
Ansell J, et al. *Chest* 2008;133:160S-198S.

Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008;22:129-137.

Nutescu EA, et al. *Cardiol Clin* 2008;26:169-187.

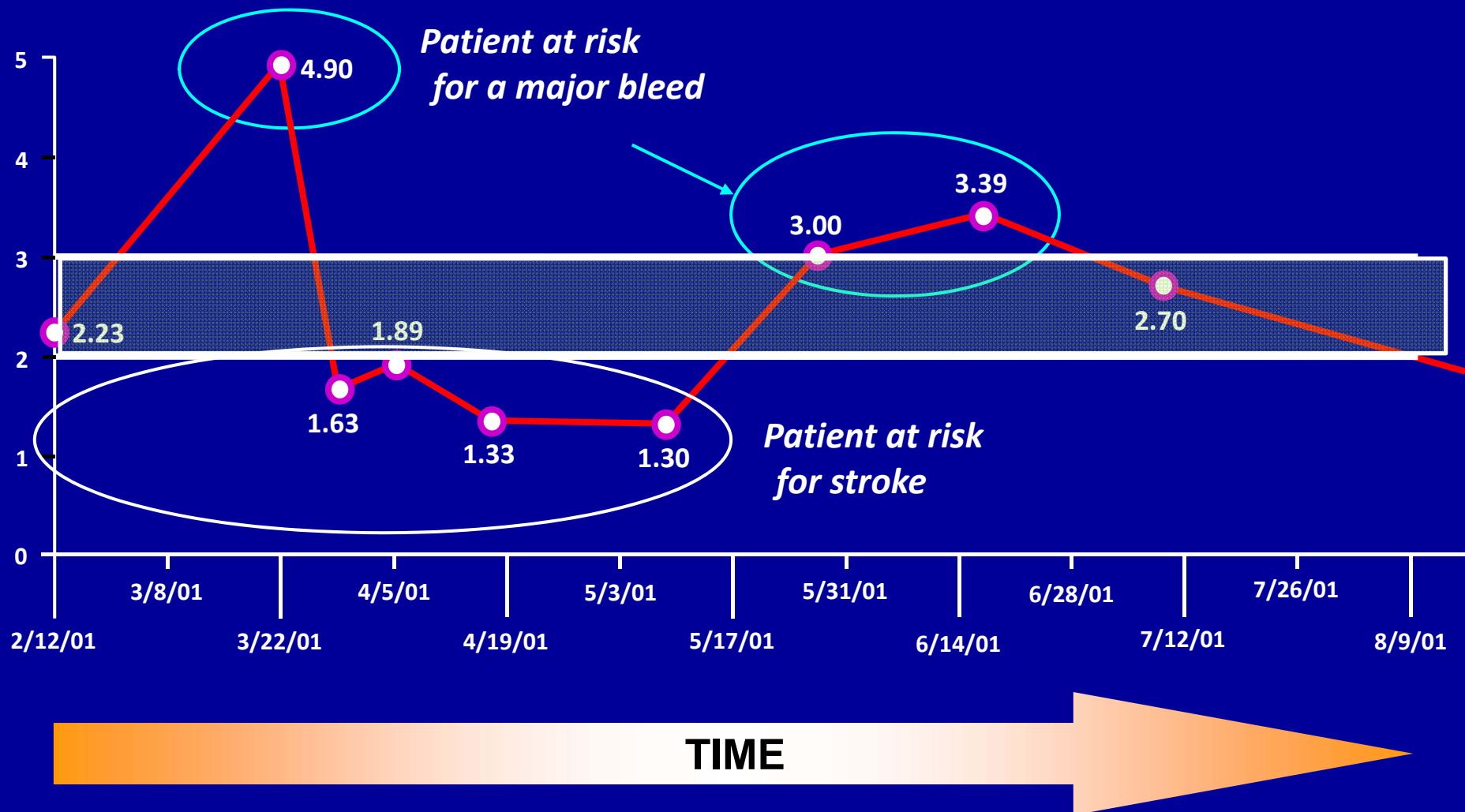
# Warfarin is Underused and Suboptimally Used in Atrial Fibrillation

- Warfarin is highly effective – reduces stroke risk by 64% – its use is problematic
    - Associated with significant bleeding and other hemorrhage
    - Registries show that only 50% of patients receive warfarin
    - In clinical trials, time in therapeutic range (TTR) is 60-68%; in general practice, TTR is typically <50%
- Only about 1 in 4 patients are optimally treated

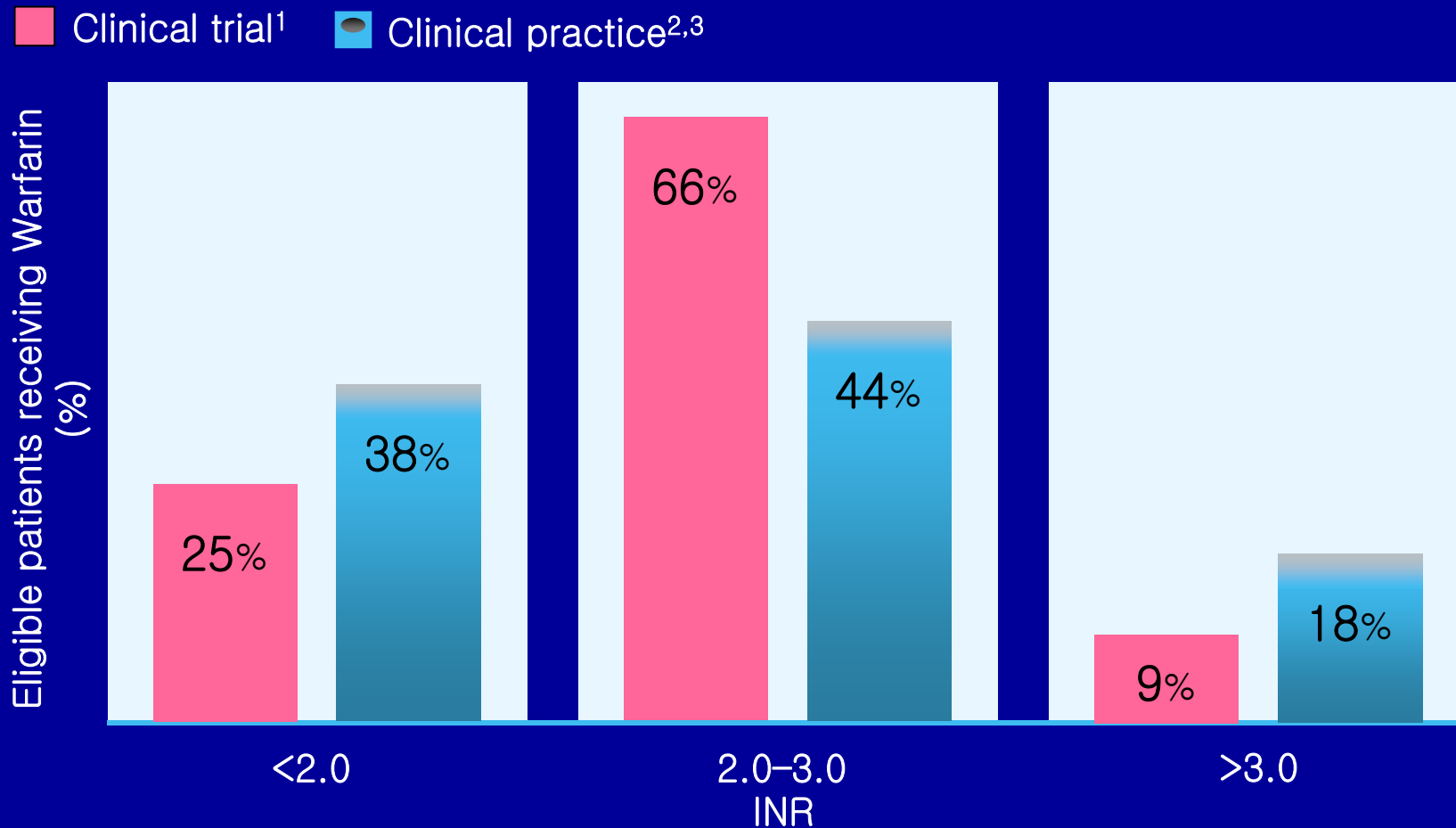


# Warfarin: INR Variability

INR Values of a Patient on Warfarin Over 6 Months



# INR CONTROL(TTR) : Clinical Trials vs. Clinical Practice

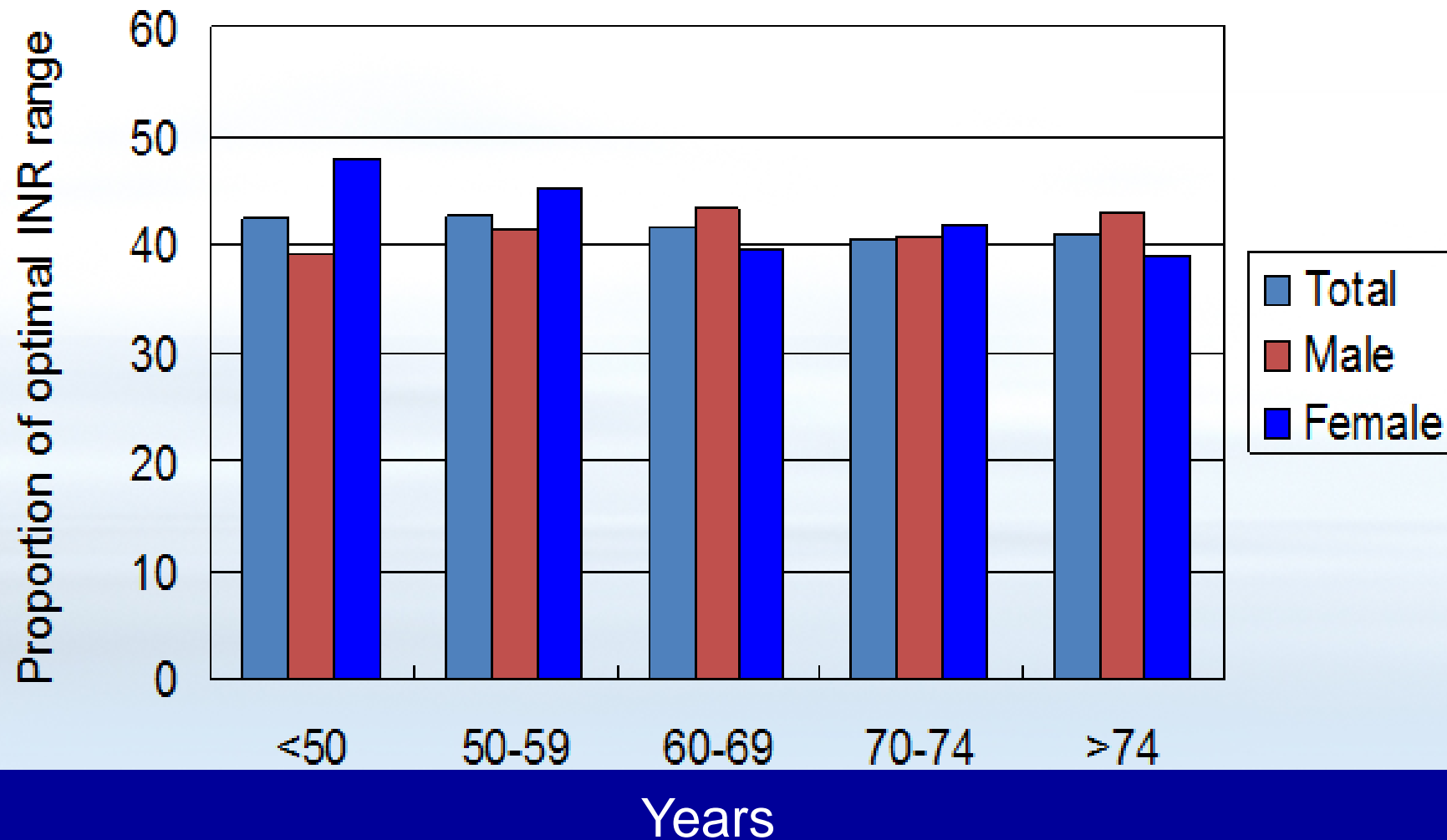


INR = international normalized ratio ; TTR = time-in-therapeutic-range (INR 2.0–3.0).

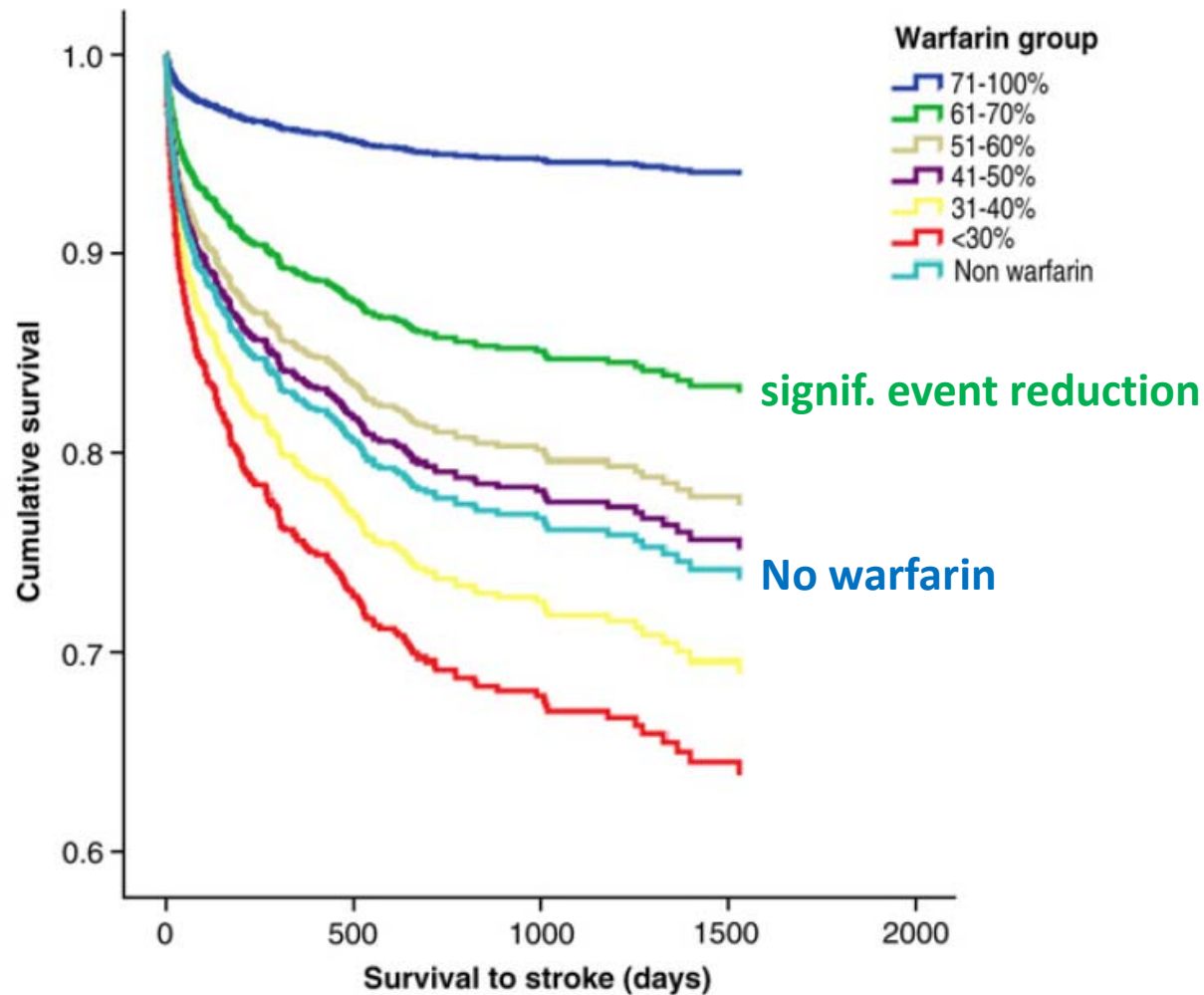
1. Kalra L, et al. *BMJ* 2000;320:1236–1239; \*Pooled data: up to 83–71% in individualized trials.

2. Samsa GP, et al. *Arch Intern Med* 2000;160:967–973. 3. Matchar DB, et al. *Am J Med* 2002;113:42–51.

## Proportion of INR range of 2 ~ 3 (in KORA연구)

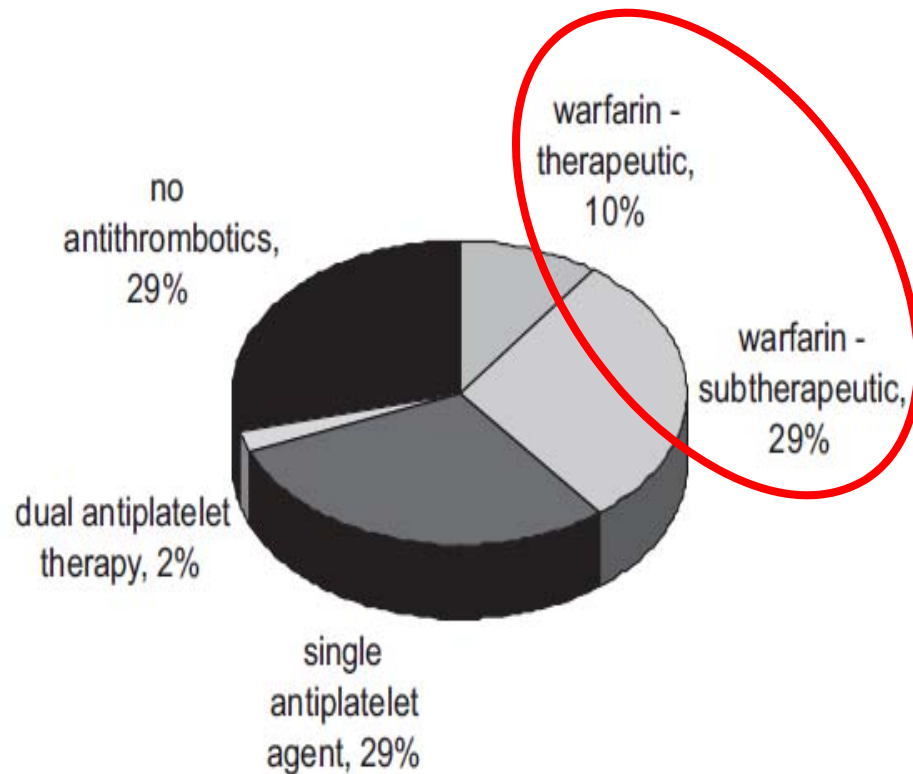


# Time in Therapeutic Range (TTR)

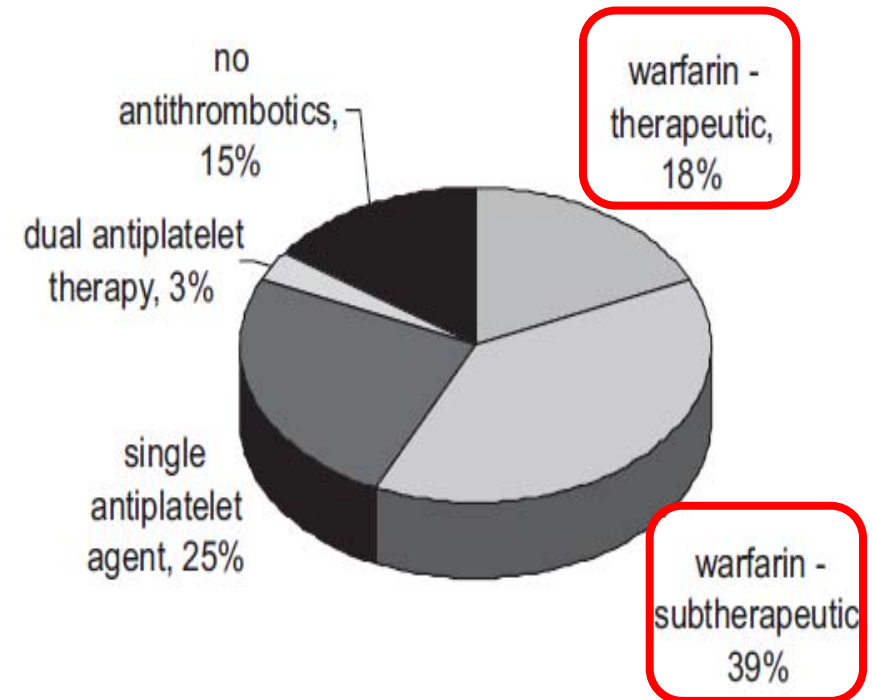


**Fig. 1.** Cox proportional hazards model for survival to post atrial-fibrillation stroke for patients at moderate or high risk of stroke  $\text{CHADS}_2 \geq 2$  by level of warfarin control.

# Subtherapeutic use of warfarin



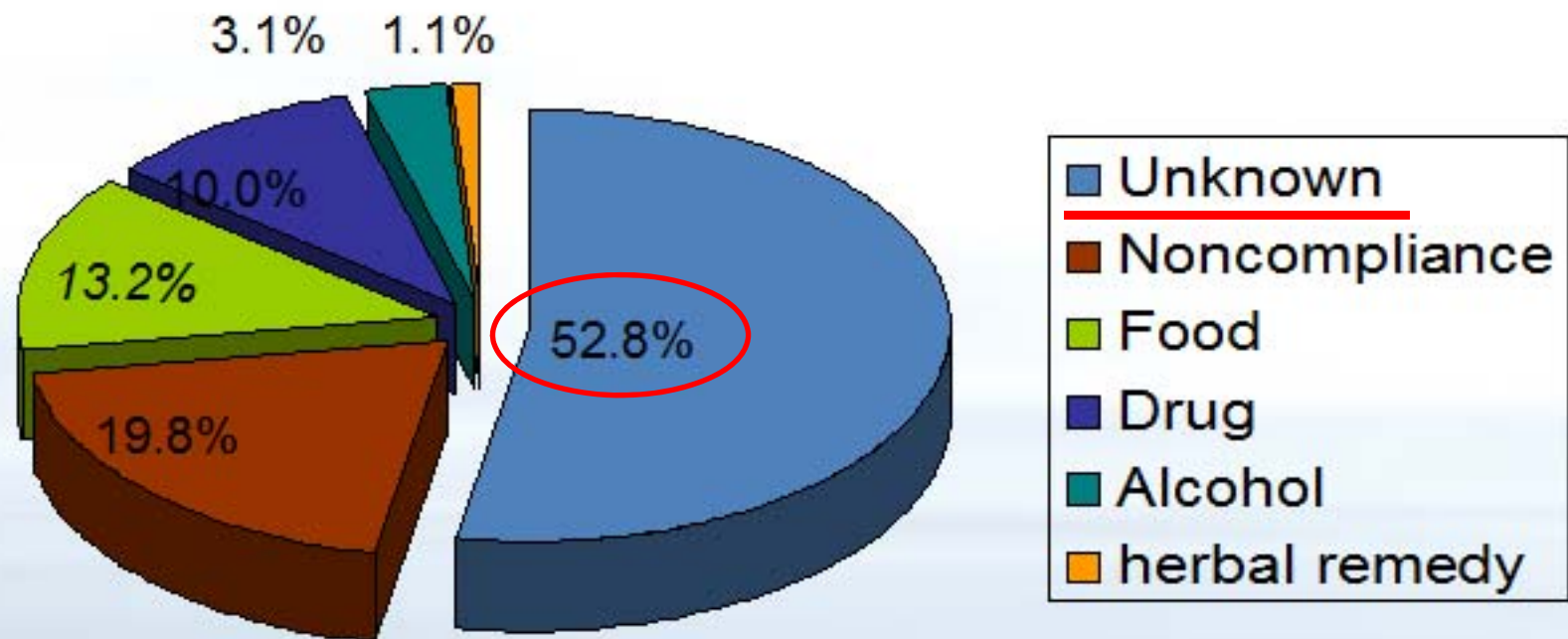
**Figure 1.** Preadmission medications in patients with known atrial fibrillation who were admitted with acute ischemic stroke (high-risk cohort, n=597).



**Figure 2.** Preadmission medications in patients with known atrial fibrillation and a previous ischemic stroke/TIA who were admitted with acute ischemic stroke (very high-risk cohort, n=323).



# Factors affecting INR stability



(Kim et al., Yonsei Med J 2009;50:83-8)

## 정확한 INR control method (in RE-LY연구)

- Calculation of 'weekly warfarin dose'
- Dose change needed → 10% up or down

Ex) warfarin daily 3mg (weekly 21mg)

1) INR 1.7 → dose up to weekly 23mg

➤ 3-3-3-3-3-4-4mg or 3.5-3-3.5-3-3.5-3-3.5mg

2) 1주 후 INR 1.8 → dose up to weekly 25.5mg

➤ 3.5mg at weekday and 4mg at weekend

- INR check at least every 4week

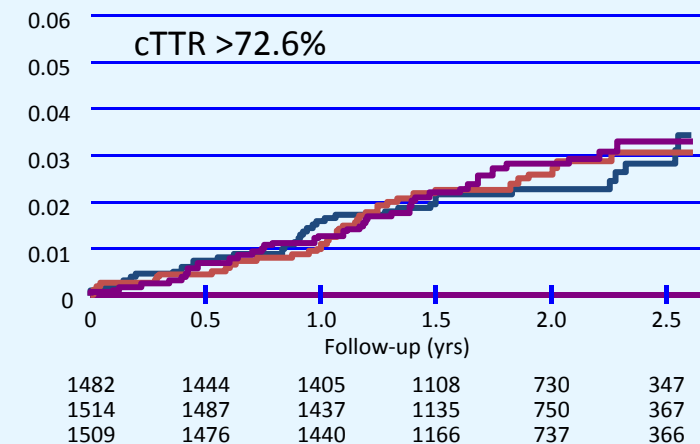
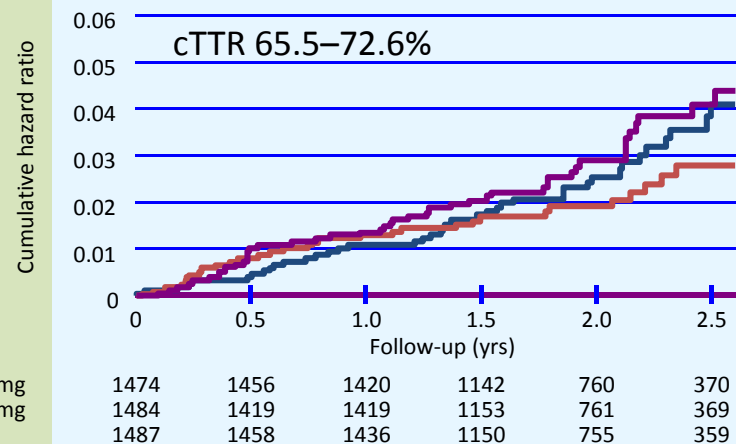
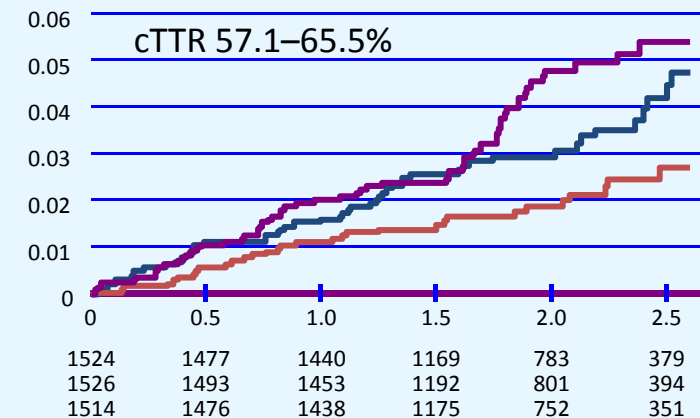
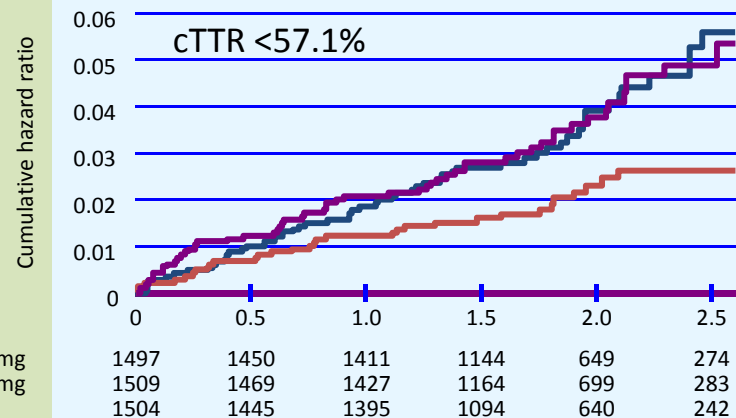
# TTR Subgroup Analysis in RE-LY:

## TIME TO PRIMARY OUTCOME (stroke or SE)

● Dabigatran 150 mg

● Dabigatran 110 mg

● Warfarin

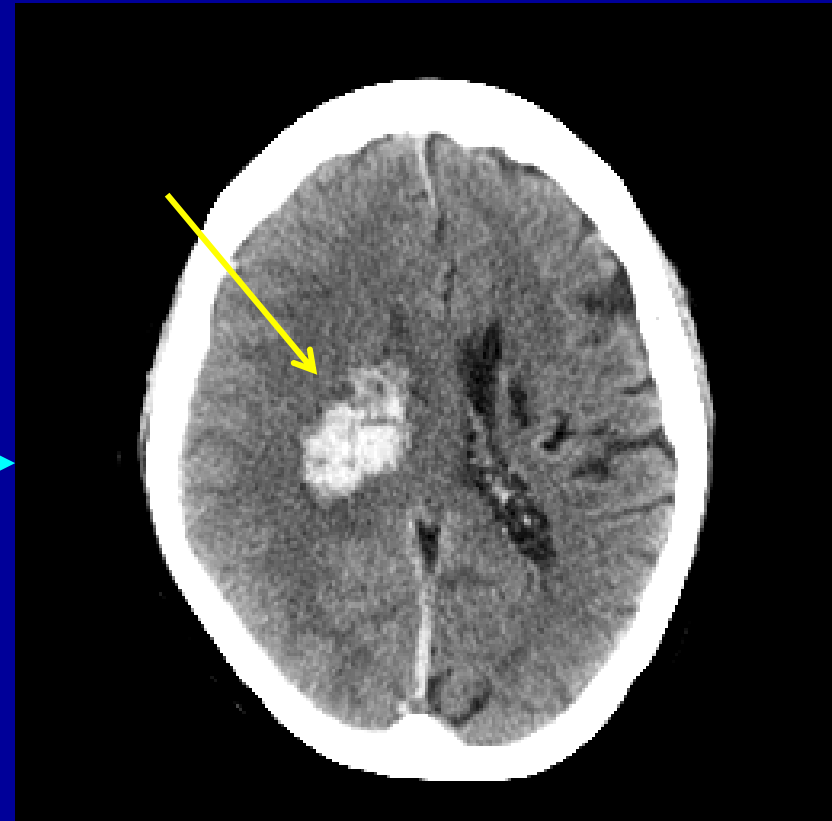


TTR = time in therapeutic range; cTTR = centre mean TTR.  
Wallentin L, et al. *Lancet* 2010;376:975-983.

## Doctor's concern during warfarin Tx



For prevention of stroke

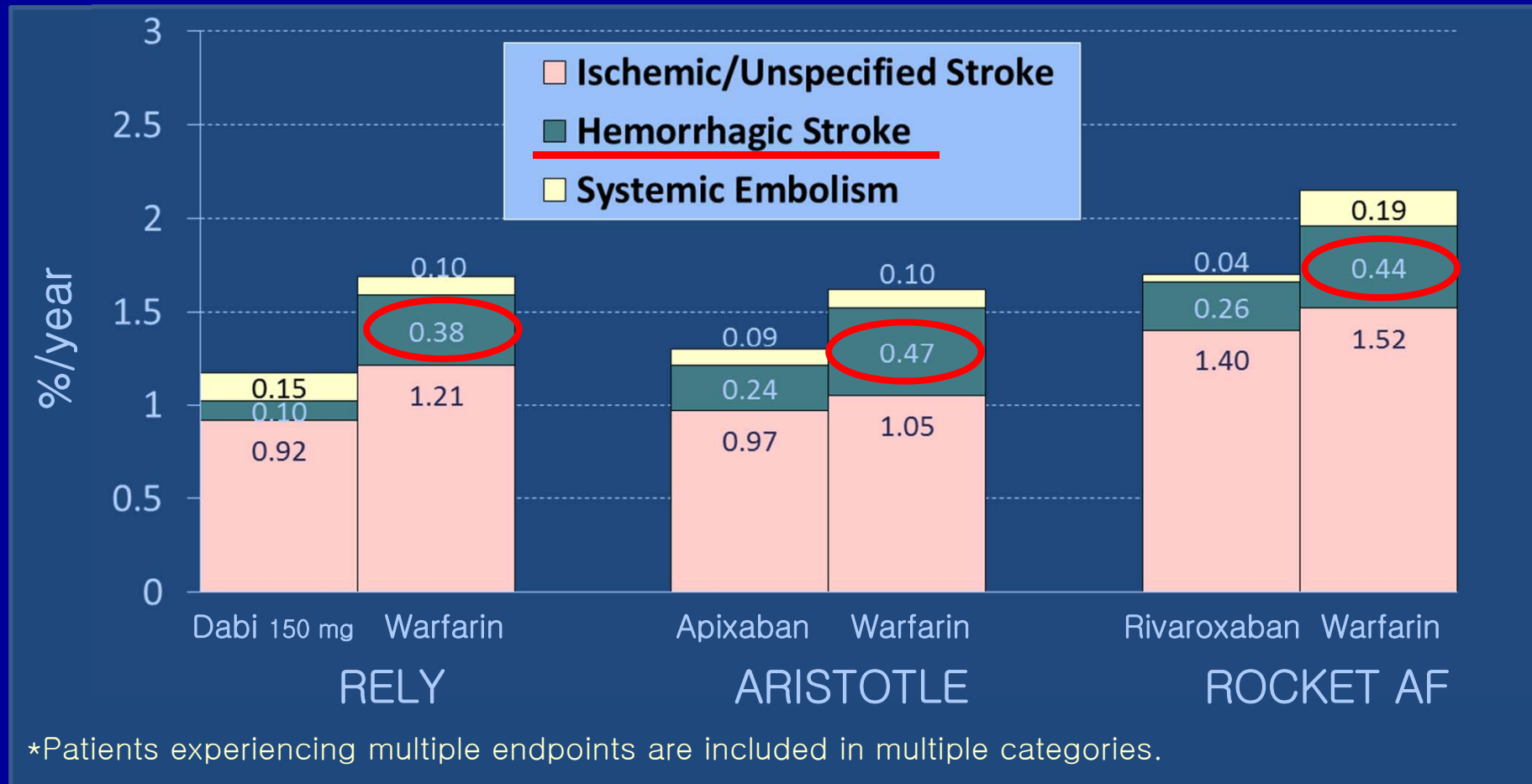


Complication of cerebral  
Hemorrhage

**“Worst problem with warfarin”**

# Elements of Primary Endpoint:\*

## Annual Event Rates



- All 3 agents reduced hemorrhagic stroke vs. warfar

“Most intracranial hemorrhages (62%)  
occur at INRs < 3.0”

Characteristic	Case-Patients (n = 170)	Controls (n = 1020)
Median age (interquartile range), y	78 (72–84)	75 (69–81)
Median international normalized ratio (interquartile range)†	2.7 (2.1–3.6)	2.3 (1.9–2.8)
Men, %	57	59
White, %‡	93	96
Comorbid conditions, %§		
Hypertension	69	61
Cerebrovascular disease	37	20
Diabetes mellitus	19	21
Congestive heart failure	27	36
Coronary artery disease	41	40
Cancer	20	21
Aspirin use, %	20	19

# DRUG INTERACTIONS associated with an INCREASED POTENCY of WARFARIN

- **Analgesics** – acetaminophen, propoxyphene, salicylates
- **Antiarrhythmics** – amiodarone, propafenone, quinidine
- **Antibiotics** – ciprofloxacin, erythromycin, isonazid, metronidazole, norfloxacin, ofloxacin, tetracycline, trimethoprim/sulphamethoxazole
- **Antifungals** – fluconazole, itraconazole, miconazole
- **Beta-blockers** – propranolol
- **H2-receptor antagonists/proton pump inhibitors** – cimetidine, omeprazole
- **Lipid-lowering agents** – lovastatin
- **Miscellaneous** – alcohol (if concomitant liver disease), anabolic steroids, disulphiram, influenza vaccine, phenytoin, tamoxifen, thyroxine
- **Herbals** – danshen, devil's claw, dong quai, garlic, ginkgo, papain, vitamin E

# **DRUG INTERACTIONS associated with a REDUCED POTENCY OF WARFARIN**

- **Antibiotics** – dicloxacillin, nafcillin, rifampicin
- **Antifungals** – griseofulvin
- **Barbiturates**
- **Immunosuppressants** – azathioprine, cyclosporin
- **Lipid-lowering agents** – cholestyramine
- **Miscellaneous** – carbamazepine, sucralfate, trazodone
- **Herbal products/dietary supplements** – coenzyme Q10, Ginseng, St John's Wort



# Interaction with Foods

- **비타민K가 많이 함유된 음식(100g당 함유량 기준)**
  - 청국장, 콩기름, 두부, 콩가루, 올리브유, 유채씨기름, 마아가린 등
  - 김, 미역, 다시마, 고사리(말린것) 등
  - 파슬리, 갓, 시금치, 유채, 케일, 브로콜리, 오이깍질, 양배추 등 (특히 녹즙!!!)
  - 근대, 냉이, 순무잎, 쑥, 쑥갓, 부추, 미나리, 상추, 파, 호박잎
  - 녹차, 홍차, 마요네즈, 샐러드 드레싱, 카레, 호박씨(말린것) 등
- **쿠마딘 흡수/활성 감소** : 비타민 C, 아연, 마그네슘, 인삼, 술 등
- **쿠마딘 효과 증대** : 생강, 마늘, 은행, 크렌베리, 비타민 E

# AN UNMET NEED

Requirement for alternative stroke prevention drug :

- **Equivalent or improved efficacy** vs. the current standard of care (adjusted-dose VKAs)<sup>1</sup>
  - : Effective stroke prevention
- **Improved bleeding rates** vs. the current standard of care<sup>1</sup>
  - : Low incidence and severity of adverse events<sup>2</sup>
- **No requirement for routine monitoring<sup>1</sup> and a predictable response<sup>2</sup>**
- **Low rates of drug–drug interactions and no food-drug interactions<sup>1</sup>**
- **Oral fixed dose<sup>2</sup>**
- **Fast onset/offset of action<sup>2</sup>**

1. Weitz JI, Hirsh J, Samama MM. *Chest* 2008; 133(6 Suppl):234S–256S. 2. Lip G *et al.* *EHJ suppl* 2005; 7:E21–E25.

# New Anticoagulants for Stroke Prevention in AF

- Direct Thrombin Inhibitors

- Dabigatran

- Factor Xa Inhibitors

- Rivaroxaban

- Phase III results published Aug. 2011

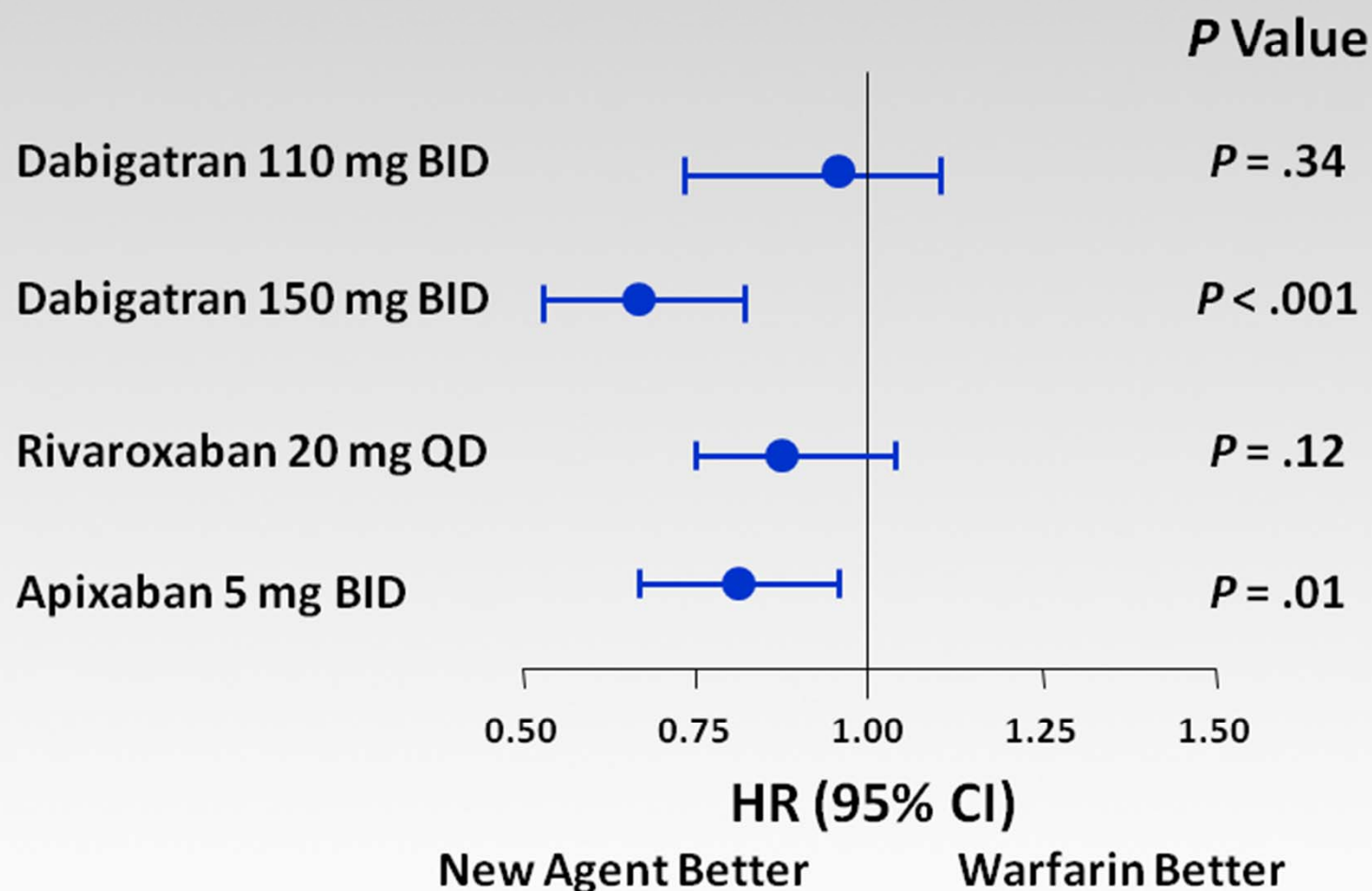
- Apixaban

- Phase III results published Aug. 2011

- Edoxaban

- Phase III trial results expected at 2012-2013

## Recent Oral Anticoagulation Trials: Stroke or Systemic Embolism

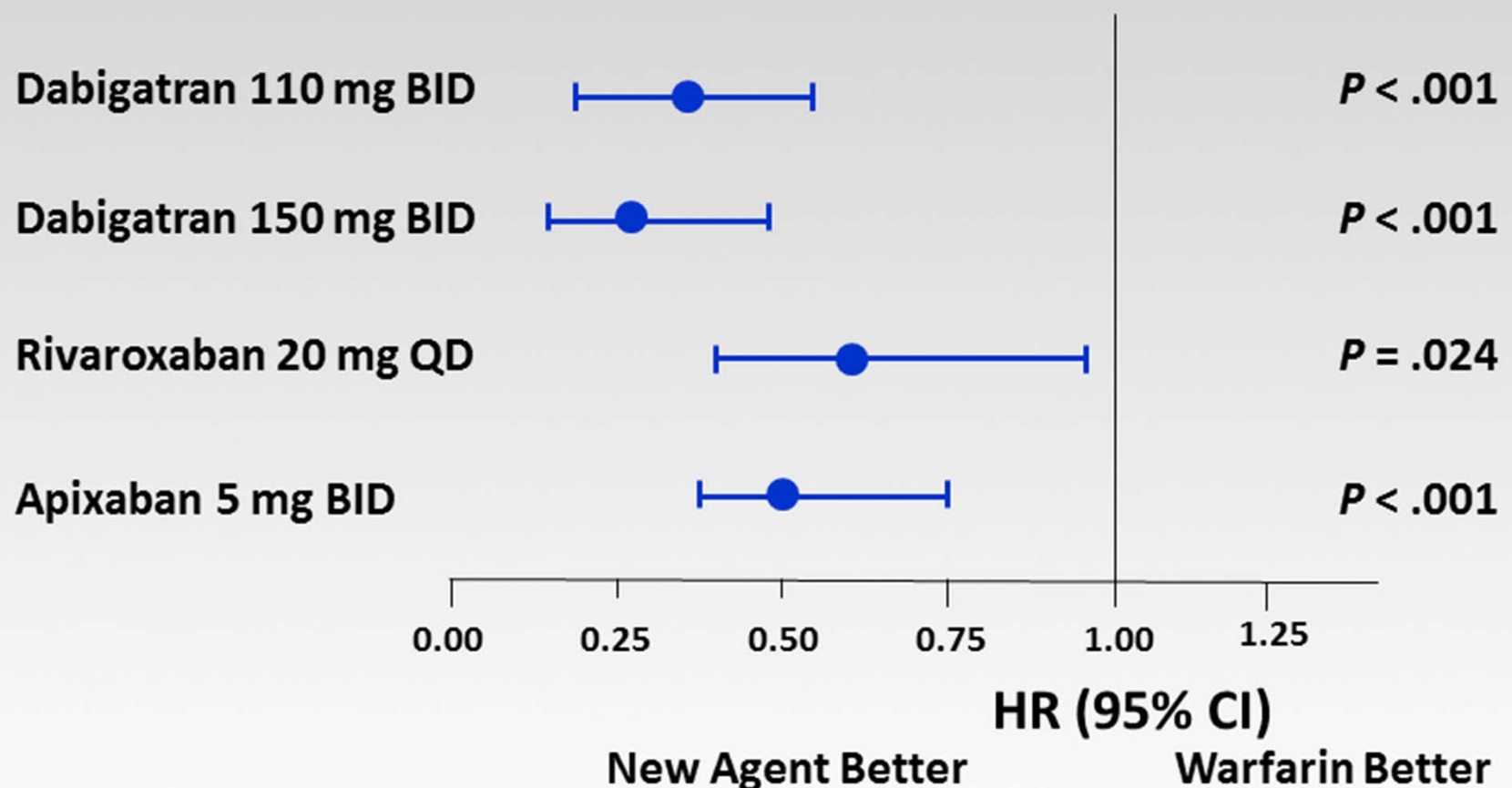


Connolly SJ, et al. *N Engl J Med.* 2009;361:1139–1151.

Patel MR, et al. *N Engl J Med.* 2011;365:883–891.

Granger C, et al. *N Engl J Med.* 2011;365:981–992.

## Recent Oral Anticoagulation Trials: Hemorrhagic Stroke

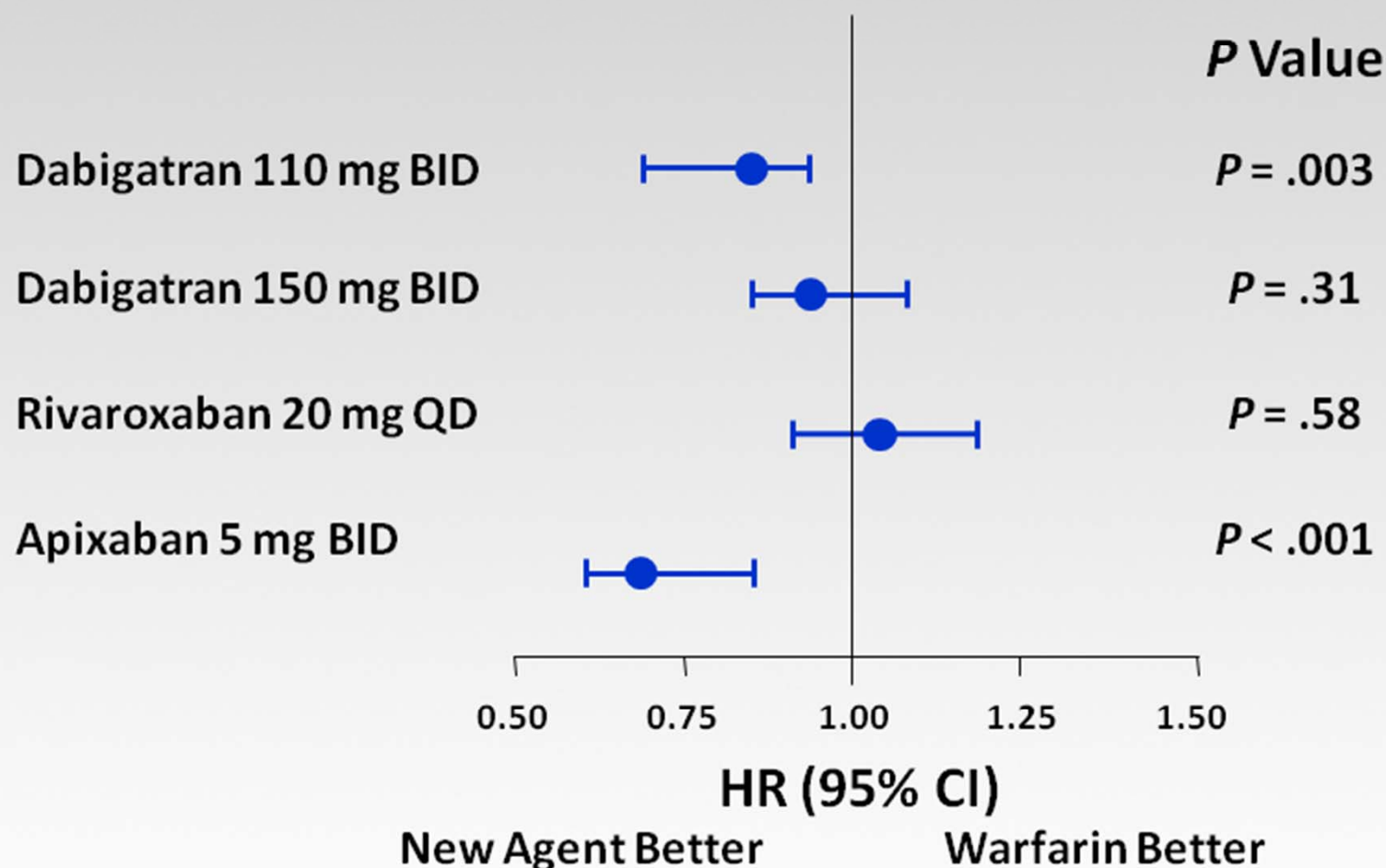


Connolly SJ, et al. *N Engl J Med*. 2009;361:1139–1151.

Patel MR, et al. *N Engl J Med*. 2011;365:883–891.

Granger C, et al. *N Engl J Med*. 2011;365:981–992.

## Recent Oral Anticoagulation Trials: Major Bleeding



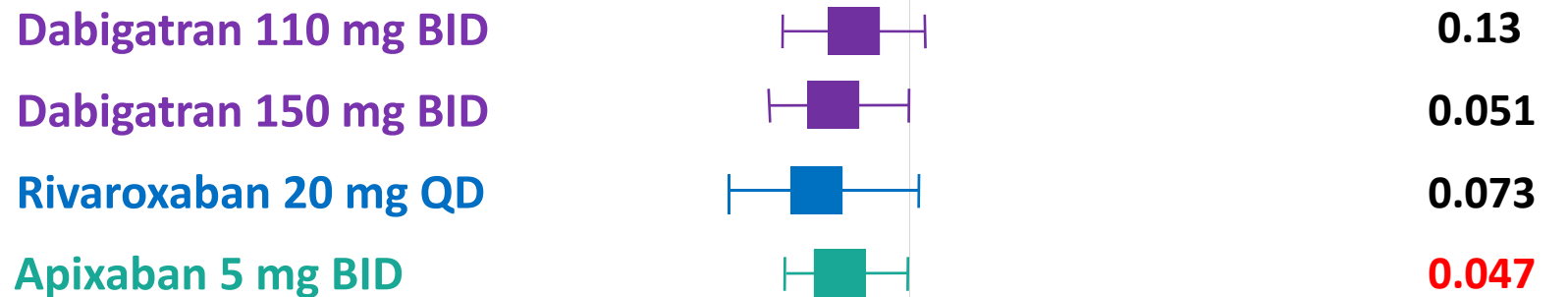
Connolly SJ, et al. *N Engl J Med*. 2009;361:1139–1151.

Patel MR, et al. *N Engl J Med*. 2011;365:883–891.

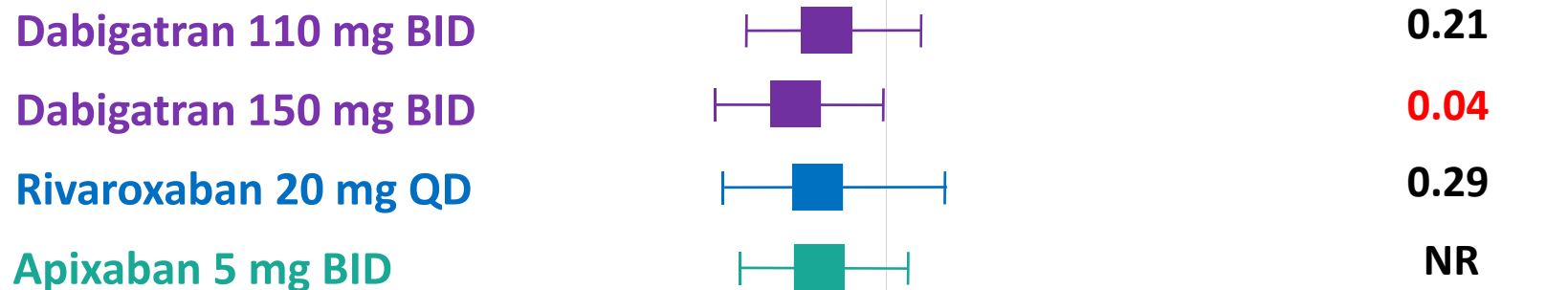
Granger C, et al. *N Engl J Med*. 2011;365:981–992.

# Mortality

## All-Cause Mortality



## Cardiovascular Mortality



0.50 0.75 1.00 1.25 1.50  
HR (95% CI)

Comparator better

Warfarin better

NR: Not Reported

## Similarities Across the 3 Novel Oral Anticoagulants: Dabigatran, Rivaroxaban, and Apixaban Vs. Warfarin

- All 3 agents were non-inferior to warfarin in reducing the risk of stroke / systemic embolism
- All 3 agents reduced intracranial hemorrhage
- The 3 agents seem to demonstrate a consistent trend towards mortality reduction
  - RRR approximates 10%/year



# Net clinical benefit of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus no treatment in a 'real world' atrial fibrillation population: A modelling analysis based on a nationwide cohort study

(Thromb Haemost 2012;107:584-9)

Amitava Banerjee<sup>1</sup>; Deirdre A. Lane<sup>1</sup>; Christian Torp-Pedersen<sup>2</sup>; Gregory Y. H. Lip<sup>1</sup>

<sup>1</sup>University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; <sup>2</sup>Department of Cardiology, Copenhagen University Hospital Gentofte, Denmark

The concept of net clinical benefit has been used to quantify the balance between risk of ischaemic stroke (IS) and risk of intracranial haemorrhage (ICH) with the use oral anticoagulant therapy (OAC) in the set-

...ance between risk of ischaemic stroke (IS) and risk of intracranial haemorrhage (ICH) with the use oral anticoagulant therapy (OAC) in the setting of non-valvular atrial fibrillation (AF), and has shown that at highest risk of stroke and thromboembolism gain the greatest benefit from OAC with warfarin. There are no data for the new OACs (dabigatran, rivaroxaban and apixaban), as yet. We calculate net clinical benefit balancing IS against ICH using data from the National Patient Registry on patients with non-valvular AF from 1997–2008, for dabigatran, rivaroxaban and apixaban on the

...benefit. In patients with CHADS<sub>2</sub> score  $\geq 1$  or  $\geq 2$ , the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding.

net clinical benefit. In patients with CHADS<sub>2</sub> score  $\geq 1$  or CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 2$ , the three new OACs (dabigatran, rivaroxaban and apixaban) appear superior to warfarin for net clinical benefit, regardless of risk of bleeding. When risk of bleeding and stroke are both high, all three new drugs appear to have a greater net clinical benefit than warfarin. In the absence of head-to-head trials for these new OACs, our

**"New OACs are significantly better than warfarin at all levels of CHA<sub>2</sub>DS<sub>2</sub>-VASc, but they are particularly better at the higher scores"**

## Society Guidelines

# Focused 2012 Update of the Canadian Cardiovascular Society Atrial Fibrillation Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control

### RECOMMENDATION (Fig. 1)

We recommend that all patients with AF or AFL (paroxysmal, persistent, or permanent), should be stratified using a predictive index for stroke risk (eg, CHADS<sub>2</sub>) and for the risk of bleeding (eg, HAS-BLED), and that most patients should receive either an OAC or ASA (Strong Recommendation, High-Quality Evidence).

We suggest, that when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban (once approved by Health Canada), in preference to warfarin (Conditional Recommendation, High-Quality Evidence).

**Values and preferences.** This recommendation places a relatively high value on comparisons with warfarin showing that dabigatran and apixaban have greater efficacy and rivaroxaban has similar efficacy for stroke prevention; dabigatran and rivaroxaban have no more major bleeding and apixaban has less; all 3 new OACs have less intracranial hemorrhage and are much simpler to use. The recommendation places less value on the following features of warfarin: long experience with clinical use, availability of a specific antidote, and a simple and standardized test for intensity of anticoagulant effect. The preference for 1 of the new OACs over warfarin is less marked among patients already receiving warfarin with stable INRs and no bleeding complications.

We suggest, that when OAC therapy is indicated, most patients should receive dabigatran, rivaroxaban, or apixaban (once approved by Health Canada), in preference to warfarin (Conditional Recommendation, High-Quality Evidence).

coagulant effect. The preference for 1 of the new OACs over warfarin is less marked among patients already receiving warfarin with stable INRs and no bleeding complications.

## In 2012 Canadian AF guideline--

- “New OAC drugs can be considered as **alternatives** to warfarin.” (2010)



- “New OAC drugs are **preferable** to warfarin for most patients” (2012)

# Practical Issues

- No monitoring tool
- Usage in patients with renal dysfunction
- Antidote?
- Cost



# 사용상 주의사항 (Pradaxa®)

## ◎ 용법용량

### 1. 신장장애 환자

경도의 신장장애 환자 (크레아티닌 청소율 CrCl : 50mL/min 이상)에서는 용량 조절이 필요하지 않다. 중등도의 신장장애 환자 (30 mL/min  $\leq$  CrCl < 50 mL/min)에서는 출혈의 위험이 증가할 수 있으므로 1회 110mg, 1일2회 투여를 고려할 수 있다. **중증 신장장애 환자 (CrCl < 30mL/min) 에게 이 약을 투여하는 것이 권장되지 않는다.**

### 2. 75세 이상의 고령자 환자

출혈의 위험이 증가할 수 있으므로 1회 110mg, 1일2회 투여를 고려할 수 있다.

➤ 이 약의 투여 전에 크레아티닌 청소율(CrCl) 계산을 통해 신기능을 검사하여야 한다. 또한, 이 약의 투여 중에는 1년에 1회 이상 신기능을 검사하며, 신기능이 감소하거나 악화될 것으로 의심되는 특정 임상 상황 (예: 혈량 저하, 탈수, 특정 약물과의 병용투여 등)에서 필요시 보다 자주 신기능을 검사하여야 한다 (2012년 1월 추가).

## **New oral anticoagulant이 필요한 경우**

- **New patients with OAC 1x**
- **Poor INR control**
  - Unknown reasons despite good compliance
  - Need frequent interruption
  - Unable to control food or drug interaction
- **Patients with history of / increased risk of intracranial hemorrhage**
- **Patient preference**



# 와파린 = 쥐약(anticoagulant rodenticide) 성분



## Advantages of warfarin

- Long experience with clinical use
- Adequate and well-established efficacy
- Reversal of anticoagulant effect by Vitamin K
- Very low cost (국내보험가격: 30 ~ 70원/T)
- Less side effects, except intracranial hemorrhage



## Which patients remain on warfarin?

- Patients with long lasting experience with warfarin and stable INRs
- Patients with renal dysfunction (GFR < 15-30ml/min)
- Patients with prosthetic heart valves
- Patients who cannot afford high-payment
- Patients with inconsistent compliance?

## Consider...

A new anticoagulant for stroke prevention is tested against standard therapy

- Ischemic stroke: ↑ by 240%
- Major bleeding: ↑ by 15%

**Not approvable**

**Dabigatran 150mg vs. Warfarin!**

New OAC should be standard care  
in AF patients?

**YES!**





Thank You !