# New Guideline for Anticoagulation and Pitfalls in the Medical Practice

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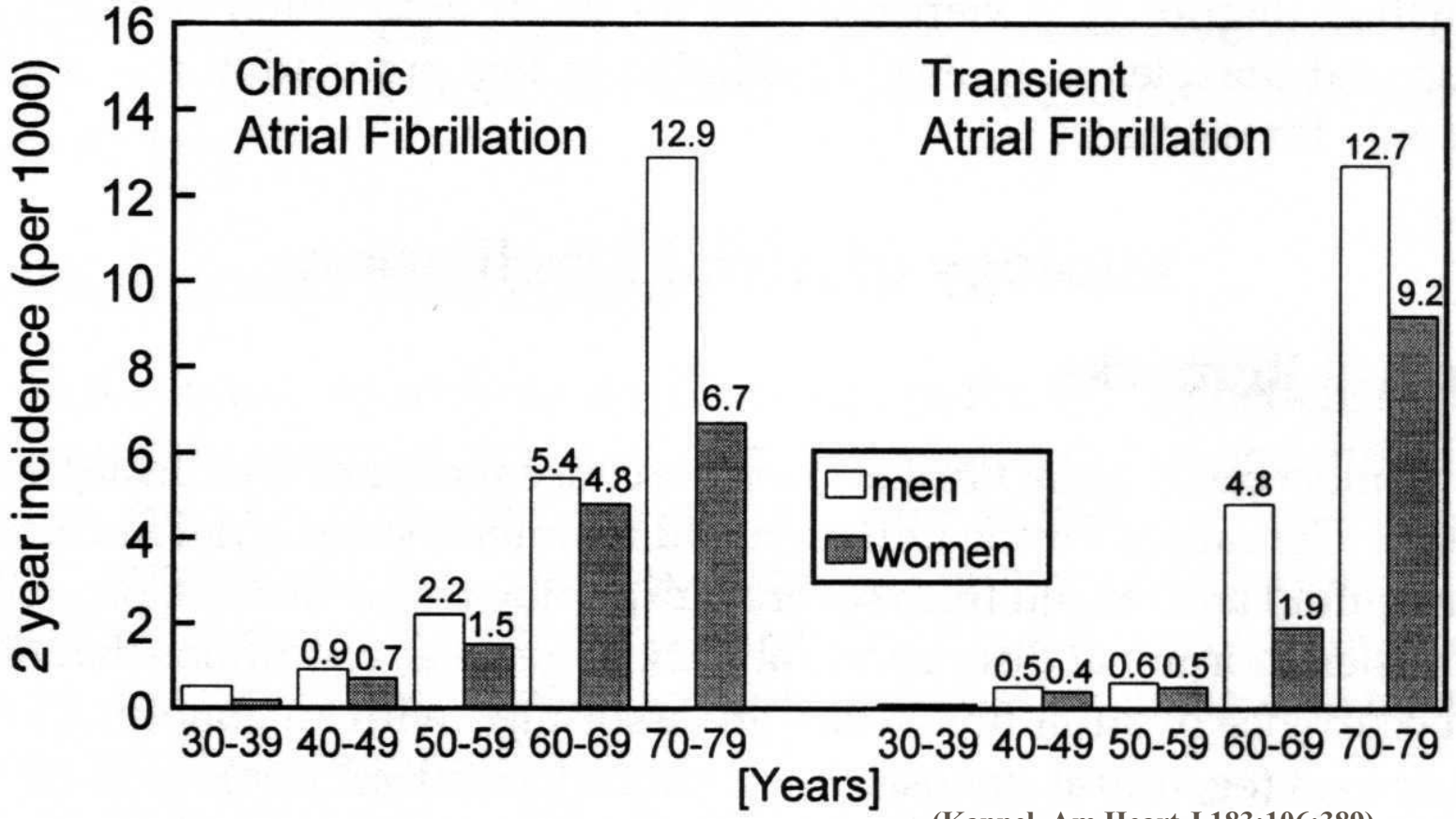
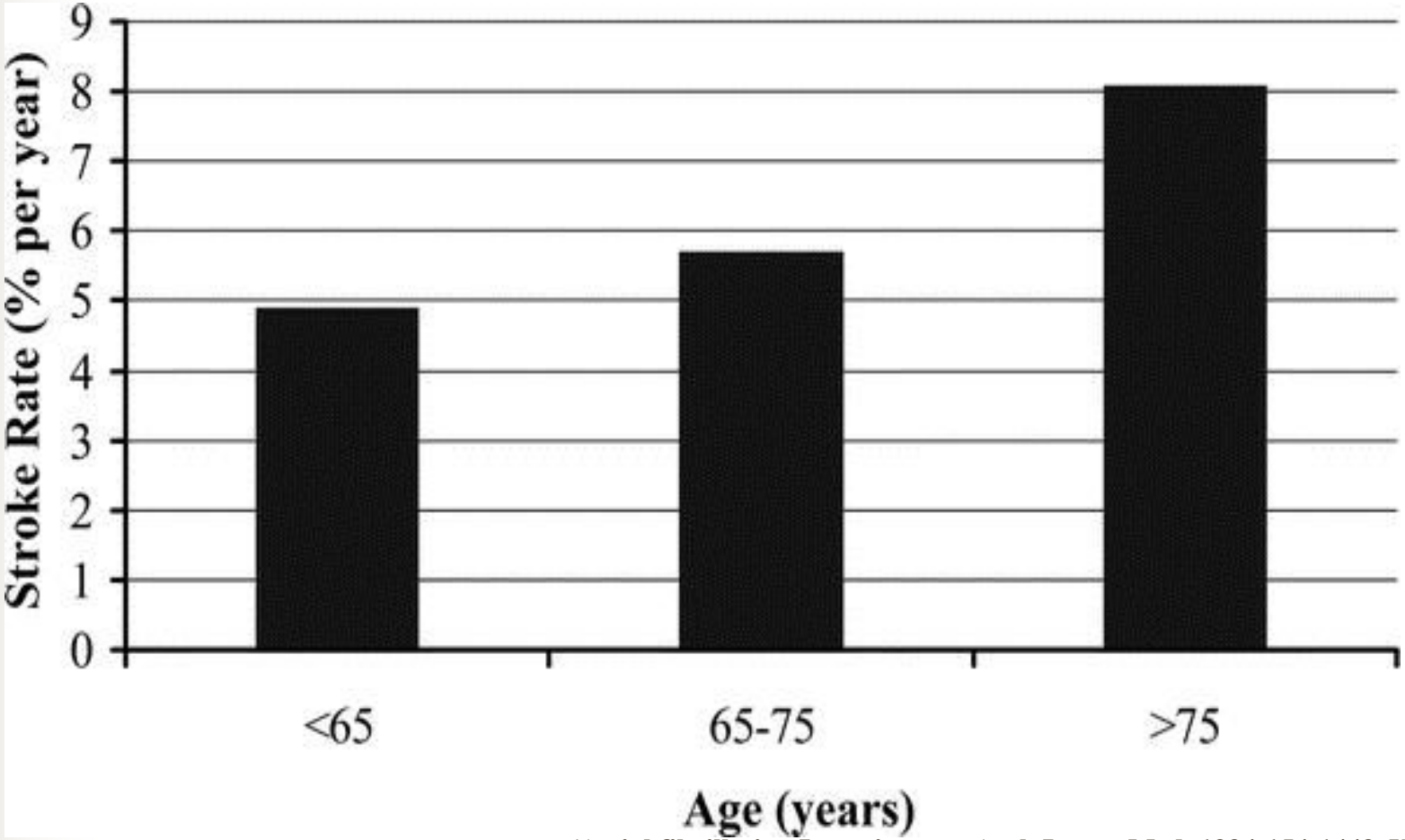
# Incidence of AF



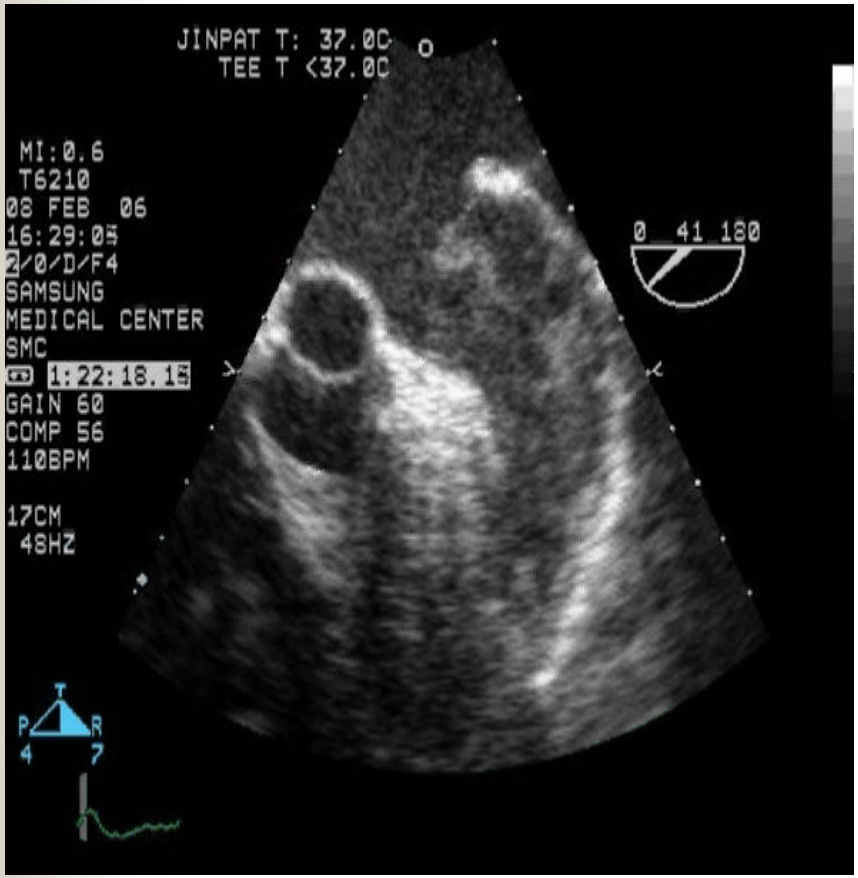

(Kannel, Am Heart J 183;106:389)

# Stroke Rates in Relation to Age

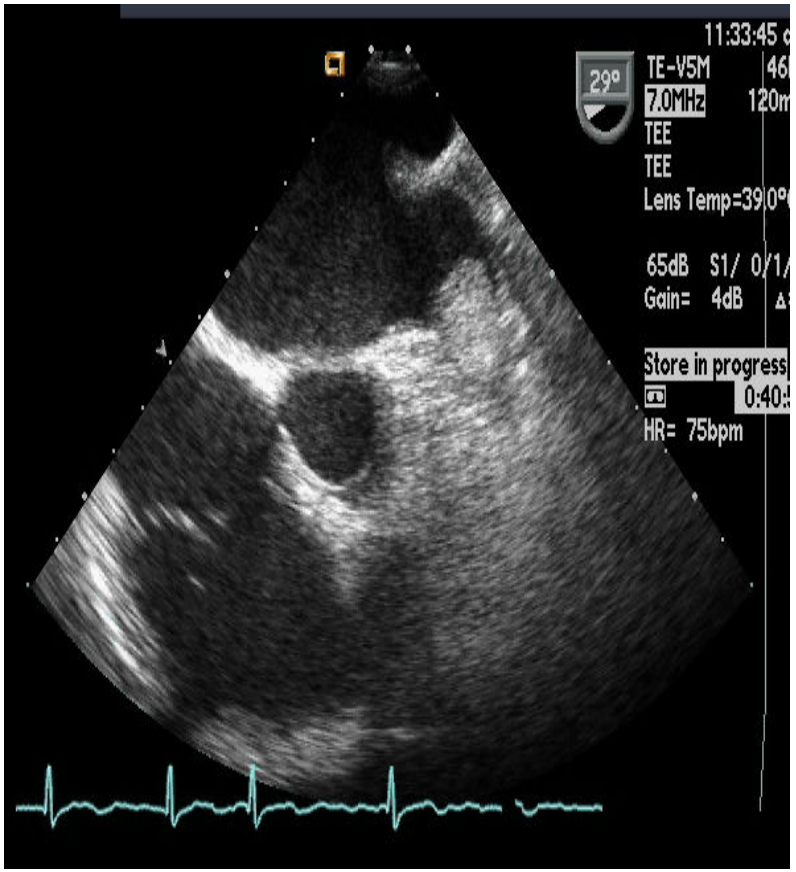



(Atrial fibrillation Investigators. Arch Intern Med. 1994;154:1449-57)

## Spontaneous Echo Contrast in Left Atrial Appendage



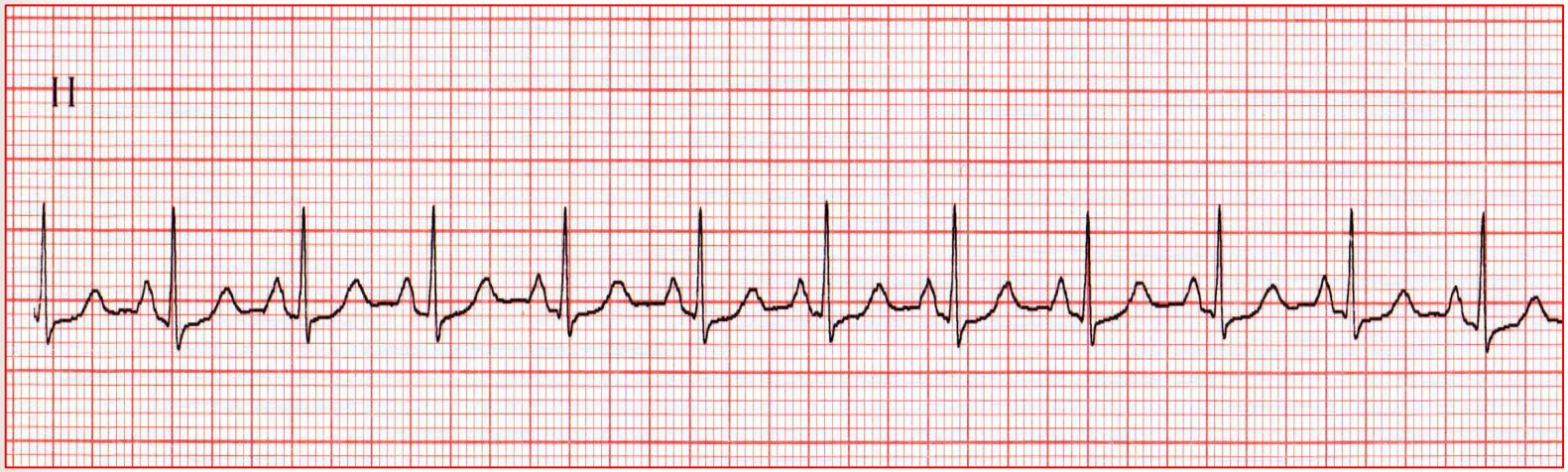

## Thrombus in Left Atrial Appendage



# Case Presentation

- A 75-year-old male
  relatively healthy
- Symptoms:
  mild chest discomfort & palpitations
- Past medical history:
  no significant disease except hypertension
- Current medication:
  medication for hypertension

## ECG recording without symptoms




## ECG recording during symptoms

# What is an optimal treatment for atrial fibrillation?

# Treatment Options for Atrial Fibrillation

- **Heart rate control**
  - **Drugs**
    - **Verapamil, diltiazem**
    - **Beta-blockers**
    - **Digoxin**
  - **AV nodal ablation plus pacemaker**

- **Rhythm control**
  - **Antiarrhythmic drugs (class Ia, Ic, III)**
  - **RF catheter ablation (PV isolation)**
  - **Maze operation**

# A COMPARISON OF RATE CONTROL AND RHYTHM CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

THE ATRIAL FIBRILLATION FOLLOW-UP INVESTIGATION
OF RHYTHM MANAGEMENT (AFFIRM) INVESTIGATORS*

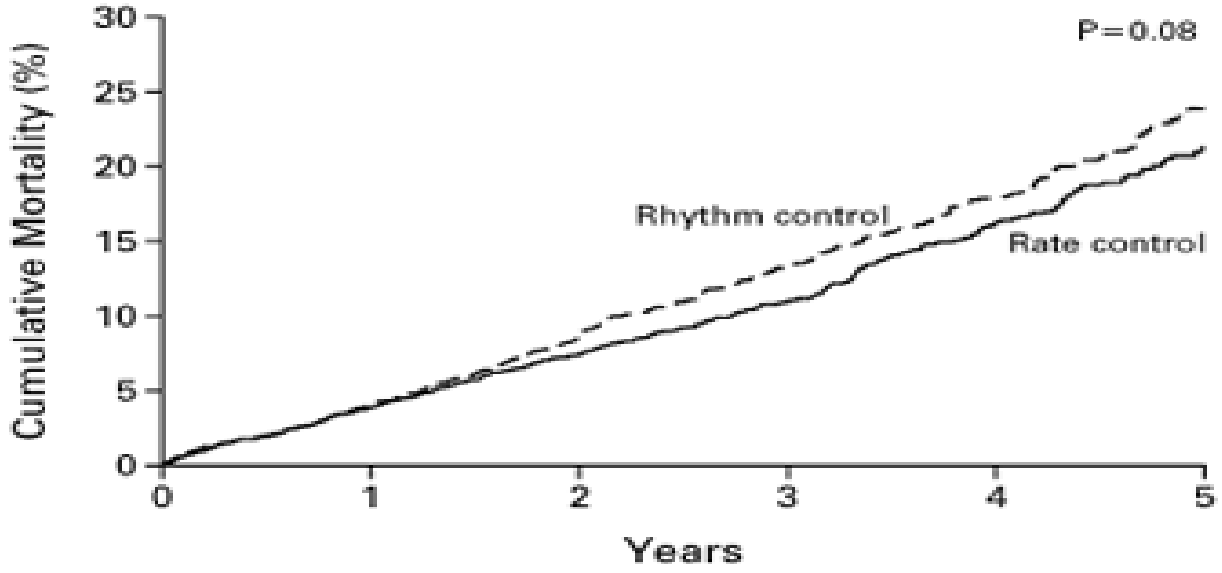
**Conclusions:**

Management of atrial fibrillation with the rhythm-control strategy offers no survival advantage over the rate-control strategy, and there are potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy.

Anticoagulation should be continued in this group of high-risk patients.

**(N Engl J Med 2002;347:1825-33)**

# Cumulative Mortality in the Rhythm-Control Group and the Rate-Control Group




| No. of Deaths | | number (percent) | | | | |
|---|---|---|---|---|---|---|
| Rhythm control | 0 | 80 (4) | 175 (9) | 257 (13) | 314 (18) | 352 (24) |
| Rate control | 0 | 78 (4) | 148 (7) | 210 (11) | 275 (16) | 306 (21) |

(Wyse et al. N Engl J Med 2002:347:1825-33)

# What is an optimal treatment for atrial fibrillation?

**Heart rate control plus anticoagulation**

# What is an optimal treatment for prevention of thromboembolism?

# Antithrombotic Treatment Options

- Aspirin 81~325mg daily
- Aspirin 325mg daily plus low-intensity, fixed-dose warfarin (target INR 1.2 ~ 1.5)
- Aspirin 75~100mg daily plus clopidogrel 75mg daily
- Adjusted-dose warfarin (target INR 2~3)
- Surgical obliteration of LAA
- Percutaneous LAA transcatheter occlusion

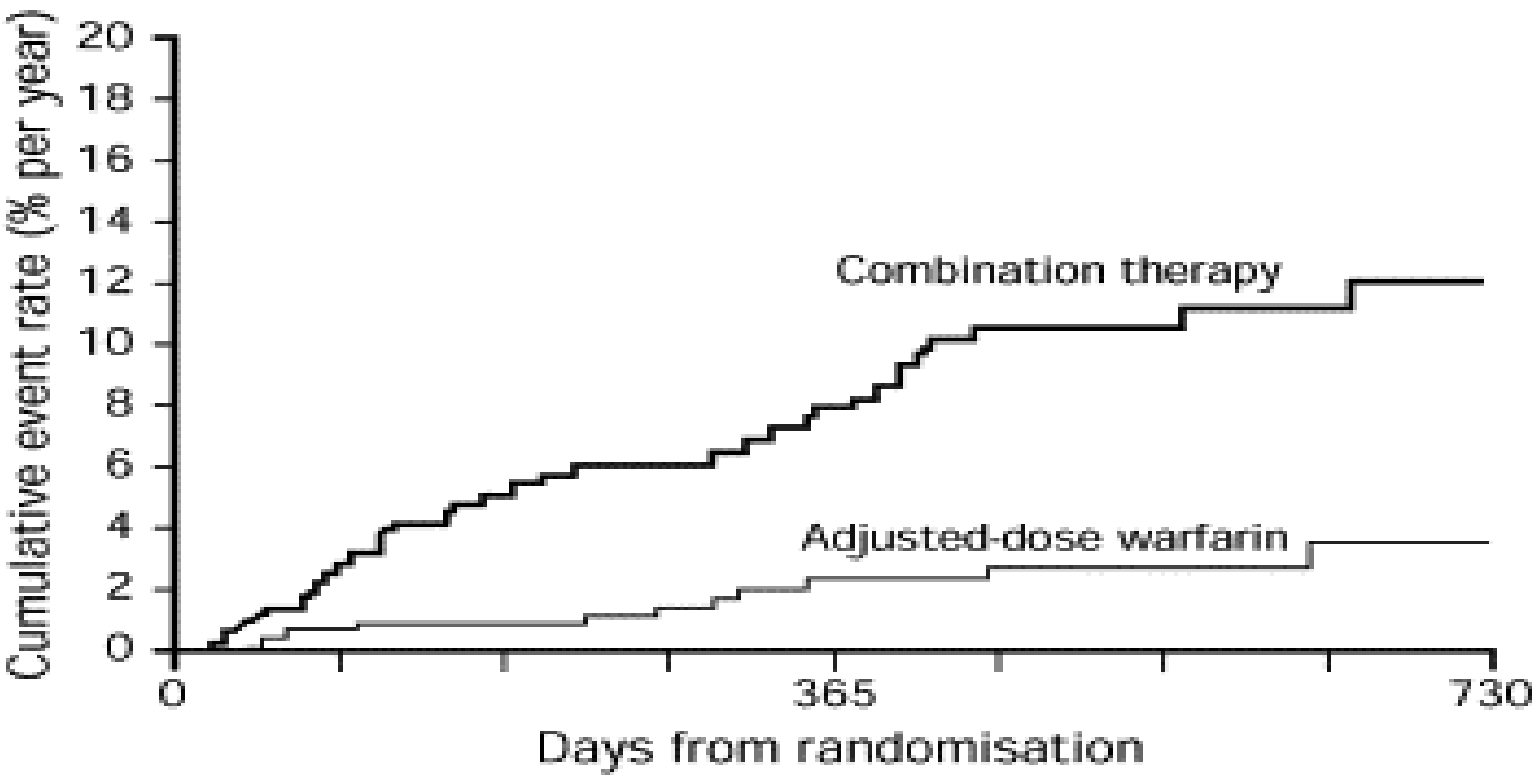
**Adjusted-dose warfarin versus low-intensity, fixed-dose warfarin plus aspirin for high-risk patients with atrial fibrillation: Stroke Prevention in Atrial Fibrillation III randomised clinical trial**

Stroke Prevention in Atrial Fibrillation Investigators*

**Interpretation:**

Low-intensity, fixed-dose warfarin plus aspirin in this regimen is insufficient for stroke prevention in patients with non-valvular AF at high-risk for thromboembolism; adjusted-dose warfarin (target INR 2·0–3·0) importantly reduces stroke for high-risk patients.

**(Lancet 1996; 348: 633–38)**




**Number at risk**

| | | | | |
|---|---|---|---|---|
| Combination therapy | | | | |
| 521 | 378 | 265 | 166 | 61 |
| Warfarin therapy | | | | |
| 523 | 397 | 273 | 173 | 65 |

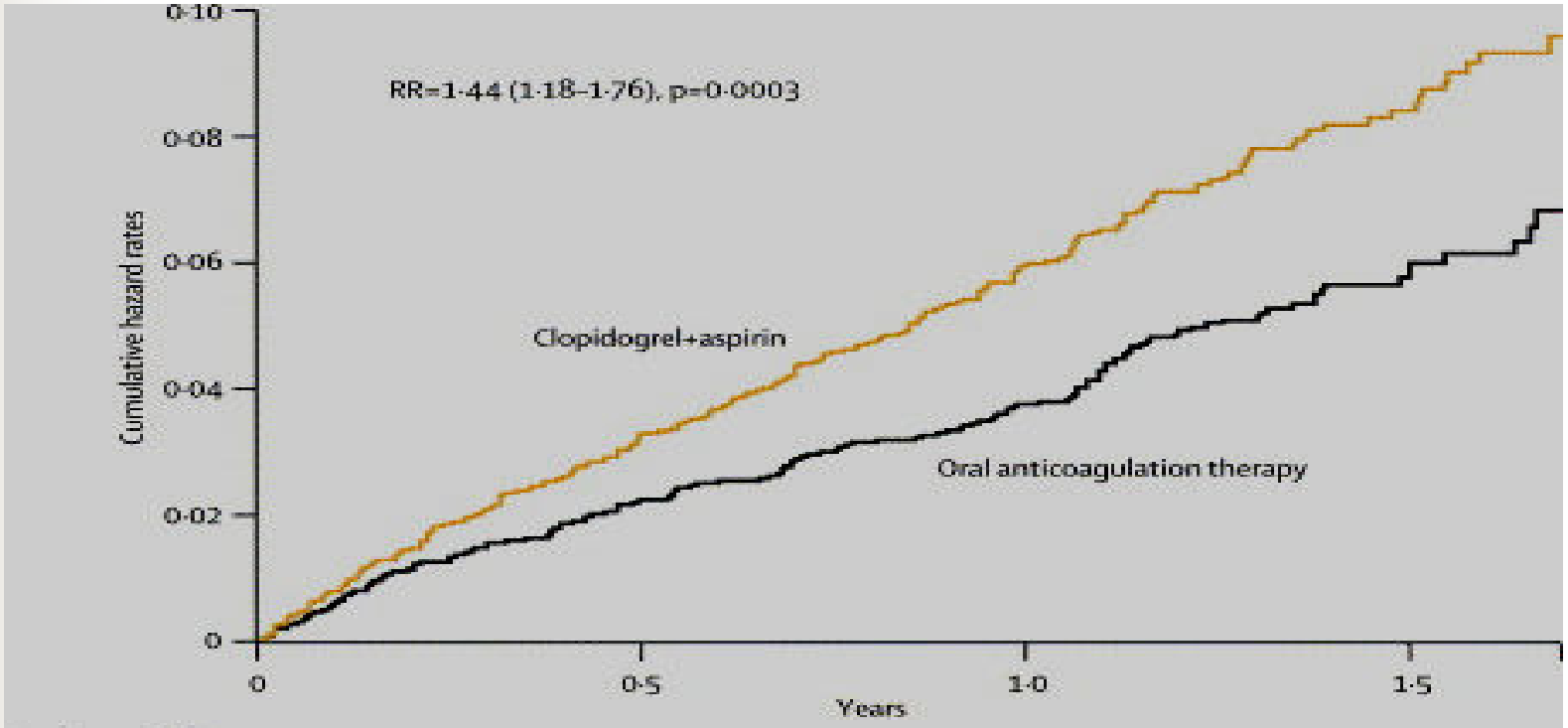
**Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial**

The ACTIVE Writing Group on behalf of the ACTIVE Investigators*

**Conclusion:**

Oral anticoagulation therapy is superior to clopidogrel plus aspirin for prevention of vascular events in patients with atrial fibrillation at high risk of stroke, especially in those already taking oral anticoagulation therapy.

**(Lancet 2006; 367: 1903–12)**




| Number at risk | | | | |
|---|---|---|---|---|
| Clopidogrel +aspirin | 3335 | 3152 | 2389 | 927 |
| Oral anticoagulation therapy | 3371 | 3221 | 2458 | 924 |

# New Guideline for Anticoagulation

**(Fuster et al. ACC/AHA/ESC Practice Guidelines Circulation 2006;114:700-52)**

# Risk Factors of Thromboembolism

- **High-Risk Factors**
  - Previous stroke, Transient ischemic attack, Embolism
  - Mitral stenosis
  - Prosthetic heart valve
- **Moderate-Risk Factors**
  - Age $\geq$ 75 years
  - Hypertension
  - Heart failure
  - LV EF $\leq$35%
  - Diabetes Mellitus
- **Less Validated or Weaker Risk Factors**
  - Female gender
  - Age 65 to 74 years
  - Coronary artery disease
  - Thyrotoxicosis

**(Fuster et al. ACC/AHA/ESC Practice Guidelines Circulation 2006;114:700-52)**

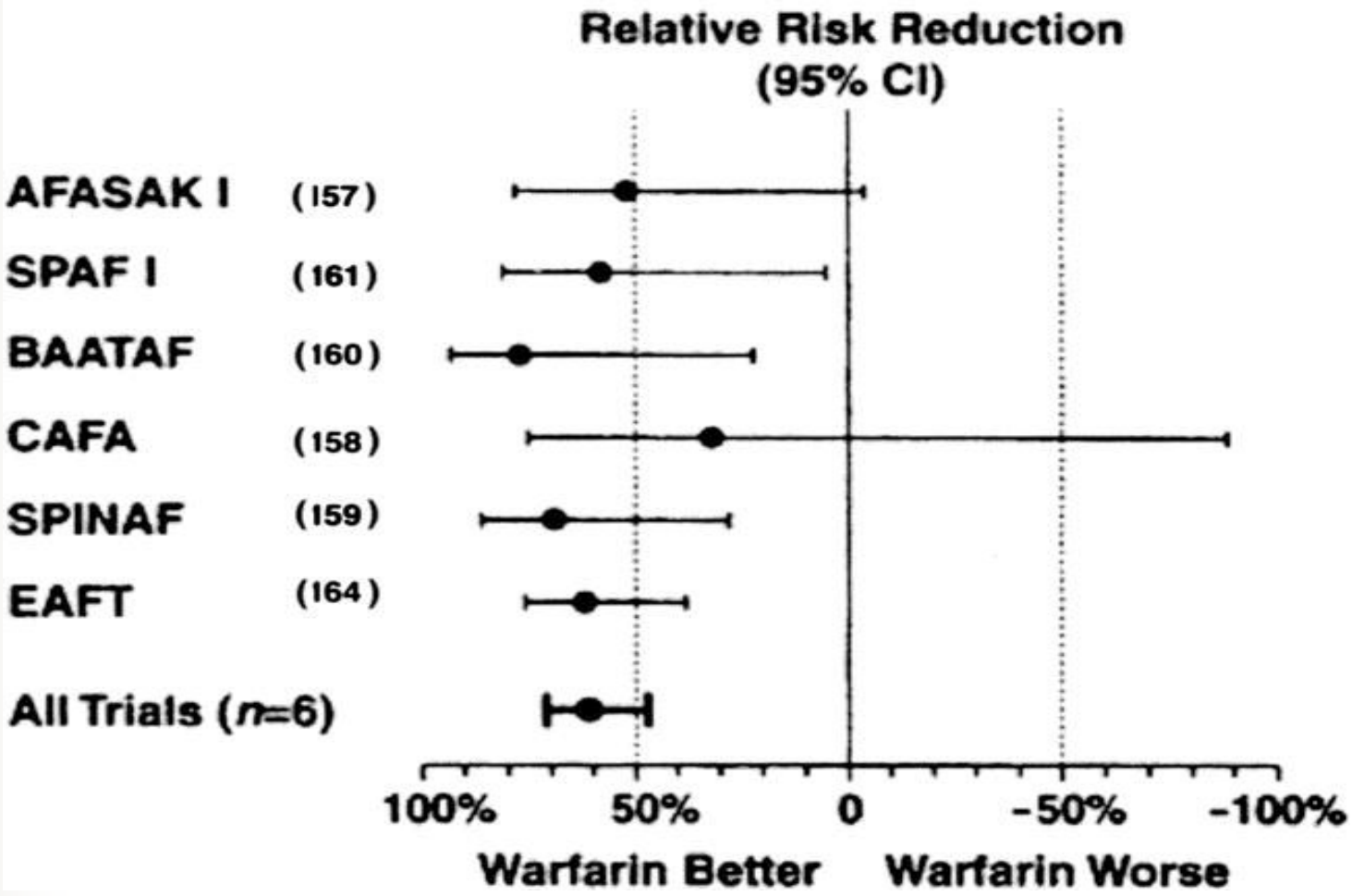
# Antithrombotic Therapy

| Risk Category | Recommended Therapy |
|---|---|
| **No risk factors** | Aspirin, 81 to 325mg daily |
| **One moderate-risk factor** | Aspirin, 81 to 325mg daily or<br>Warfarin (INR 2.0 to 3.0, target 2.5) |
| **Any high-risk factor or**<br>**More than 1 moderate-risk factor** | Warfarin (INR 2.0 to 3.0, target 2.5)* |

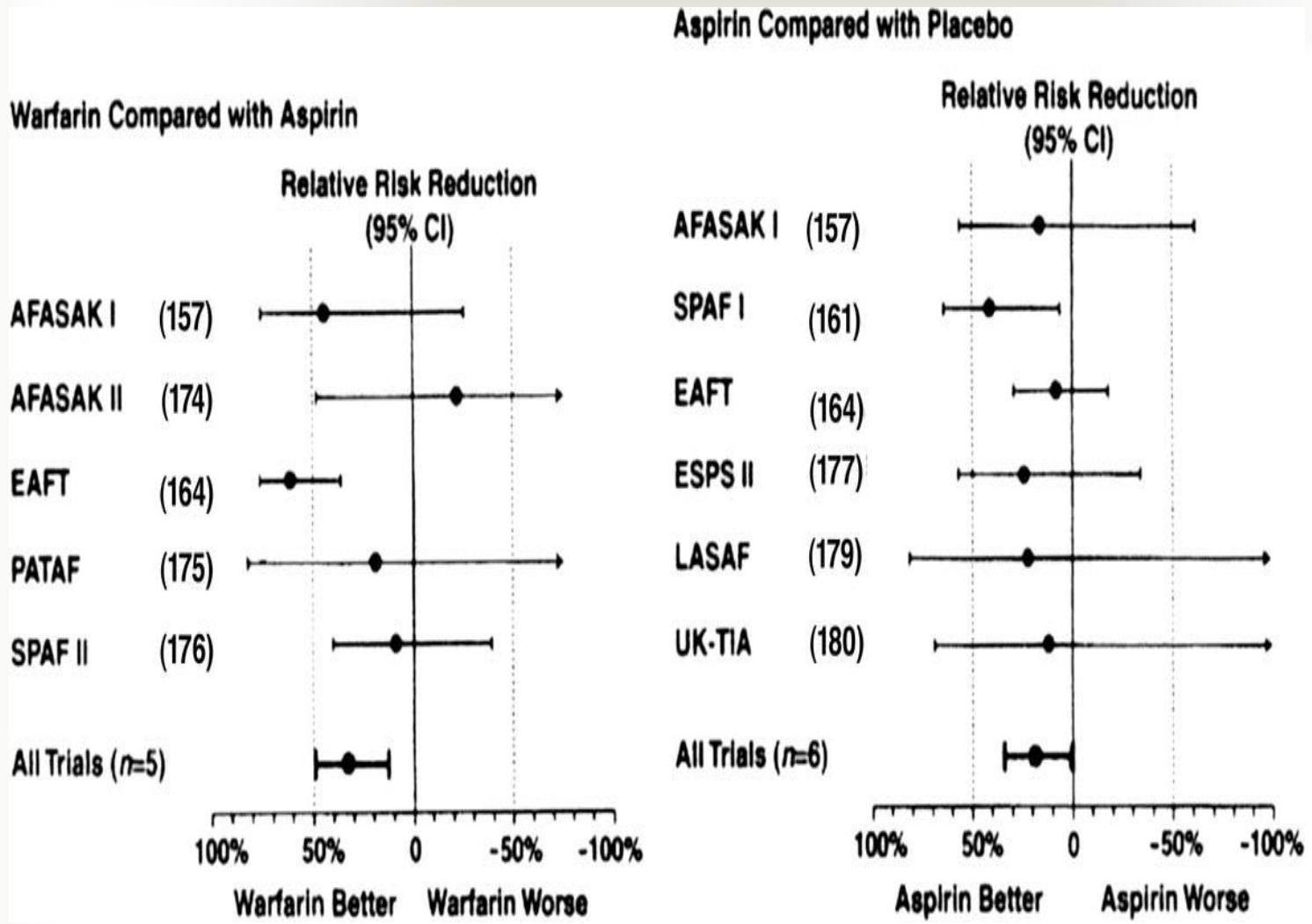
If mechanical valve, target INR greater than 2.5

( **Fuster et al. ACC/AHA/ESC Practice Guidelines. Circulation 2006;114:700-52)**

## Adjusted-Dose Warfarin Compared with Placebo




(Hart et al. Ann Intern Med 1999;131:492-501)




(Hart et al. Ann Intern Med 1999;131:492-501)

**Stroke With Intermittent Atrial Fibrillation:**

**Incidence and Predictors During Aspirin Therapy**

Robert G. Hart, MD,* Lesly A. Pearce, MS,† Robert M. Rothbart, MD, FACC,‡

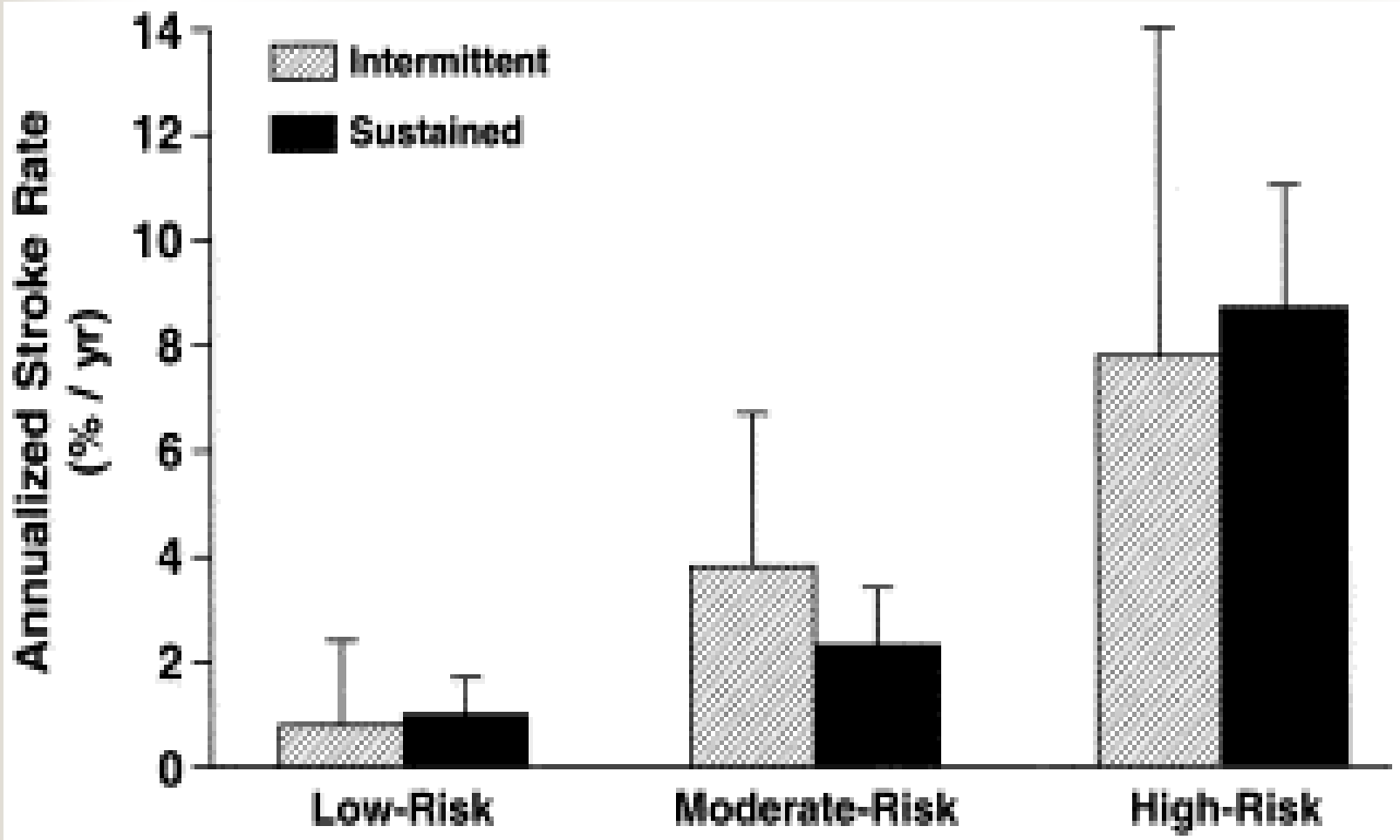
John H. McAnulty, MD, FACC,§ Richard W. Asinger, MD, FACC,\

Jonathan L. Halperin, MD, FACC,¶ for the Stroke Prevention in Atrial Fibrillation Investigators

**CONCLUSIONS:**

In this large cohort of AF patients given aspirin, those with intermittent AF had stroke rates similar to patients with sustained AF and similar stroke risk factors. Many elderly patients with recurrent intermittent AF have substantial rates of stroke and likely benefit from anticoagulation. High-risk patients with intermittent AF can be identified using the same clinical criteria that apply to patients with sustained AF.

**(J Am Coll Cardiol 2000;35:183–7)**




(Hart et al. J Am Coll Cardiol. 2000;35:183-7)

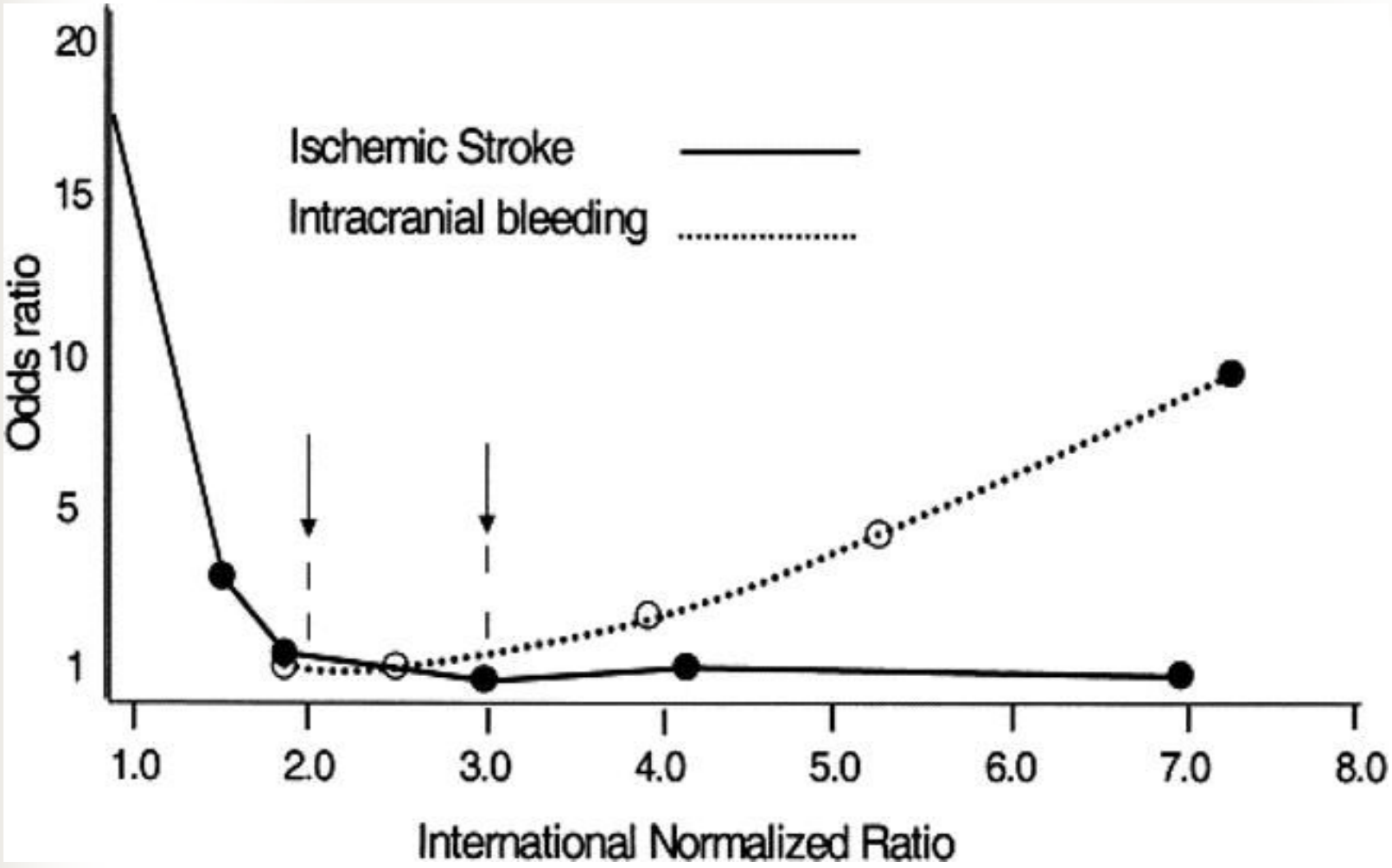
# What is an optimal treatment for prevention of thromboembolism?

Two moderate-risk factors: 75-year-old, hypertension

Adjusted-dose warfarin (target INR 2~3)

# Antithrombotic Therapy in Clinical Practice

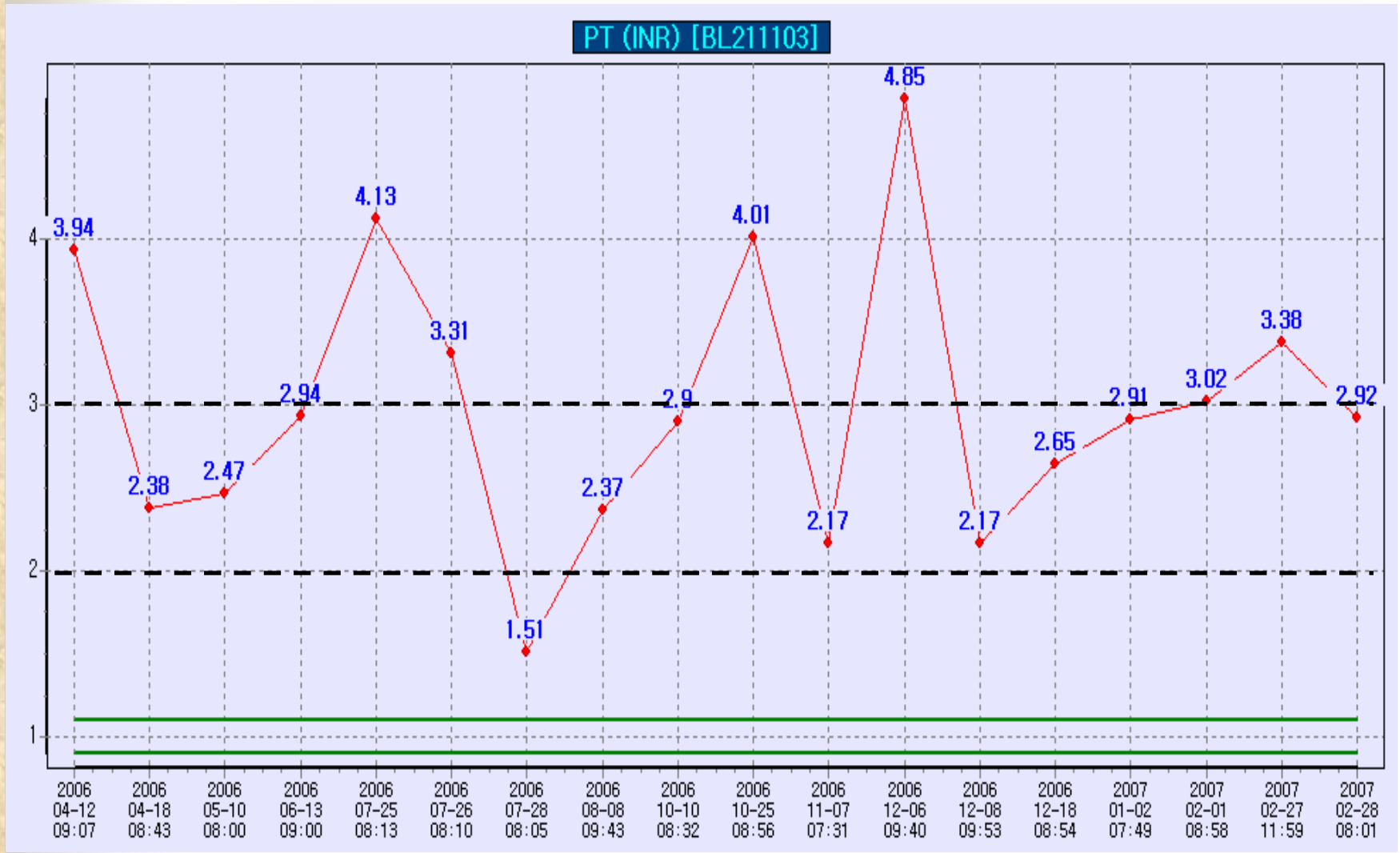
- Difficulty in maintaining target INR level
- Bleeding complications




(Hylek et al. Ann Intern Med 1994;120:897-902)

(Oden et al. Thromb Res 2006;117:493-9)

# Difficulty in Maintaining Target INR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4
3
2
1
3.94
2.38
2.47
2.94
4.13
3.31
1.51
2.37
2.9
4.01
2.17
4.85
2.17
2.65
2.91
3.02
3.38
2.92
2006 04-12 09:07
2006 04-18 08:43
2006 05-10 08:00
2006 06-13 09:00
2006 07-25 08:13
2006 07-26 08:10
2006 07-28 08:05
2006 08-08 09:43
2006 10-10 08:32
2006 10-25 08:56
2006 11-07 07:31
2006 12-06 09:40
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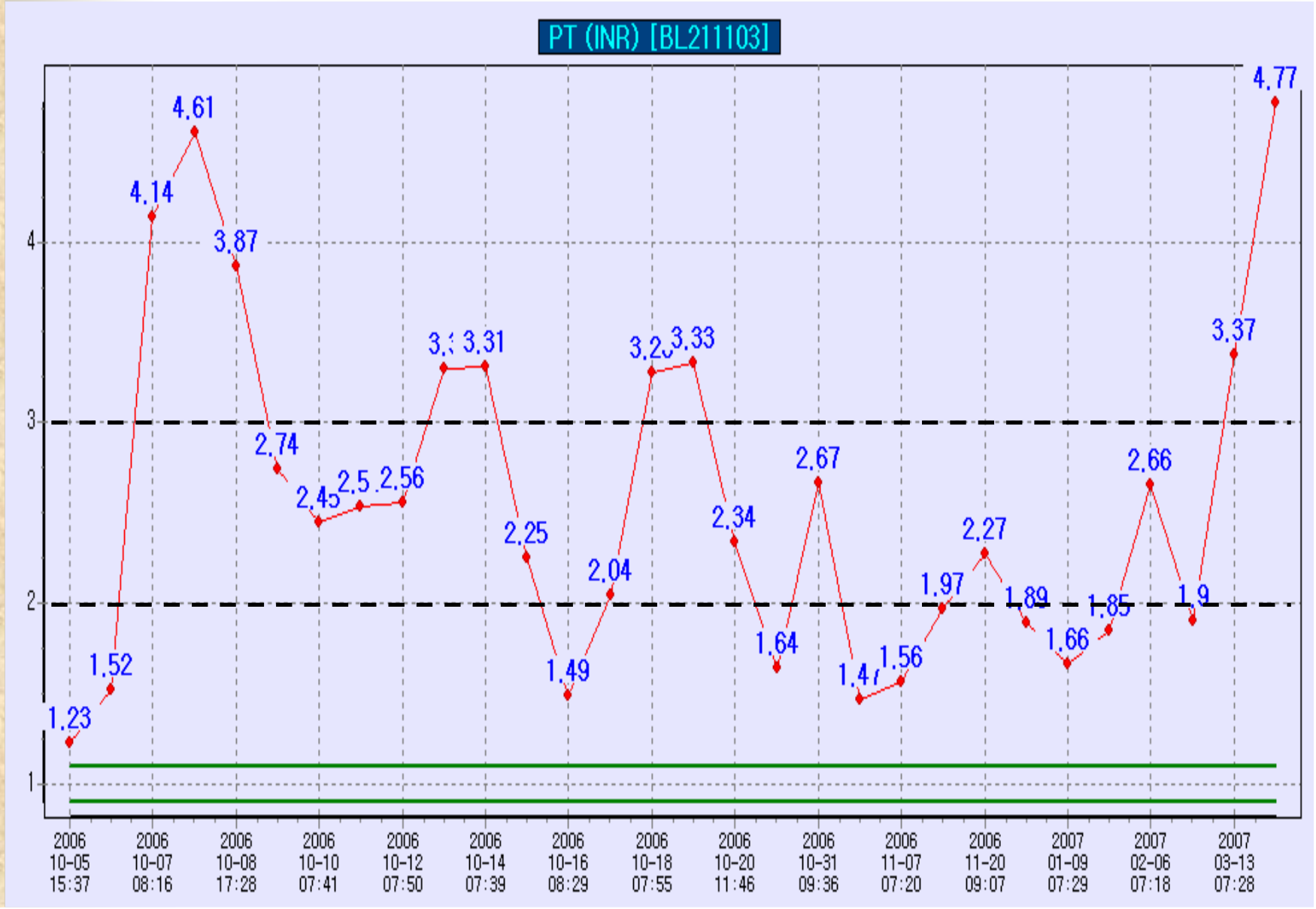
2006 12-18 08:54
2007 01-02 07:49
2007 02-01 08:58
2007 02-27 11:59
2007 02-28 08:01


PT (INR) [BL211103]
4
3
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1.23
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2.74
2.45
2.5
2.56
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2.25
1.49
2.04
3.33
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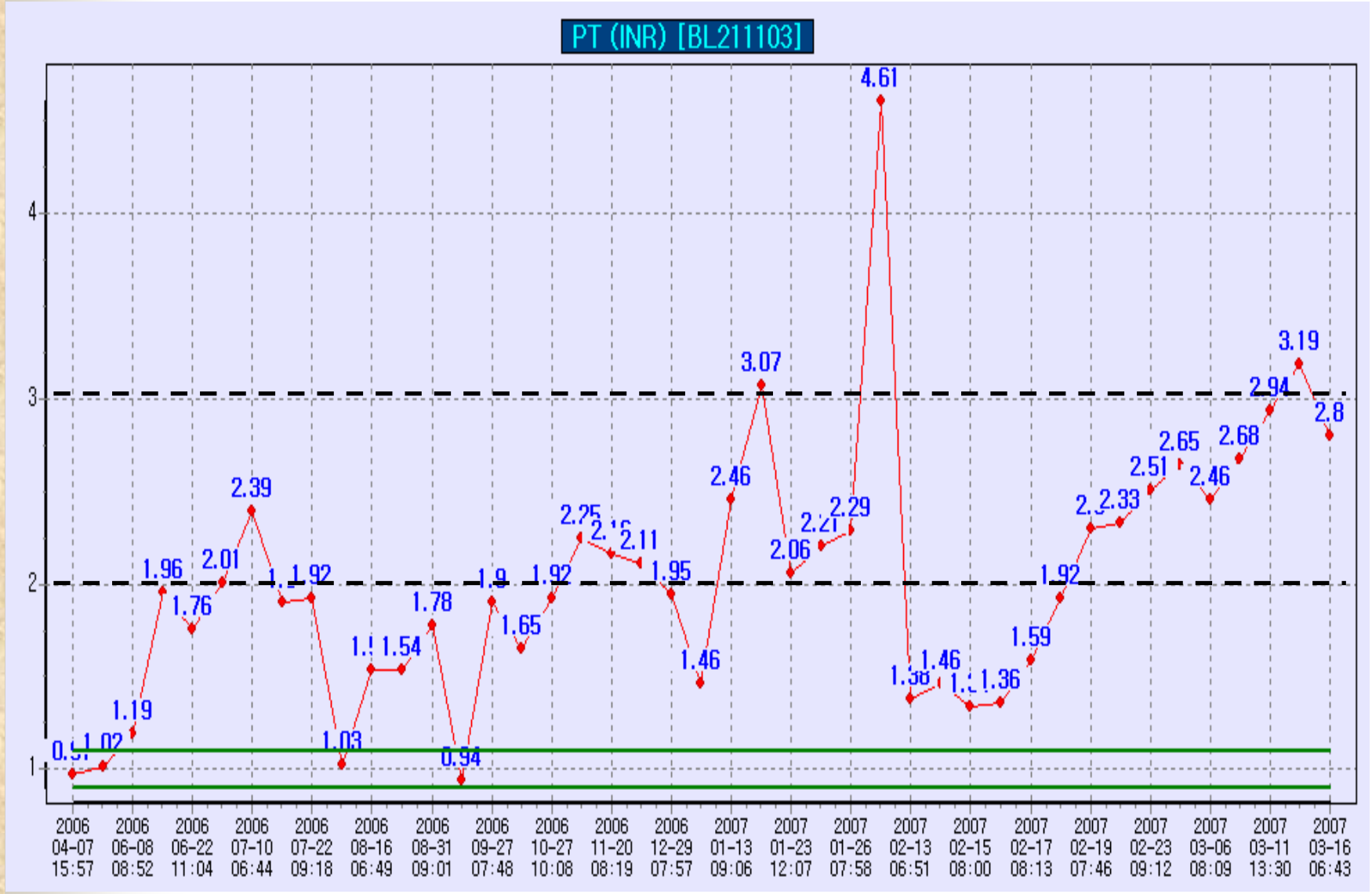
2007 02-06 07:18
2007 03-13 07:28


PT (INR) [BL211103]
4
3
2
1
4.61
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3.19
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2.8
2.68
2.65
2.51
2.46
2.46
2.39
2.33
2.29
2.25
2.11
2.06
2.01
1.96
1.95
1.92
1.92
1.92
1.78
1.76
1.65
1.59
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1.46
1.36
1.19
1.03
1.02
0.94
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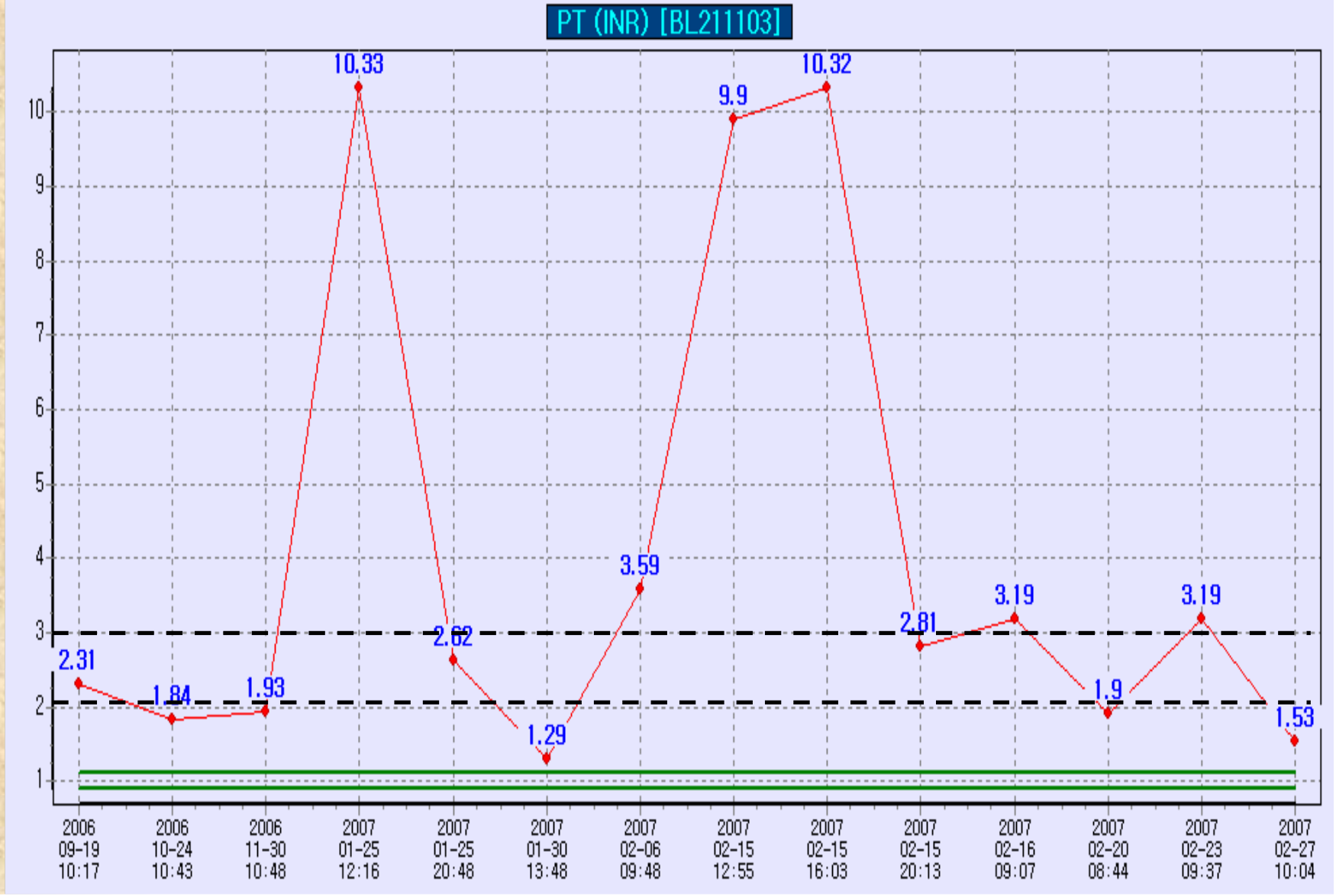
PT (INR) [BL211103]
10.33
10.32
9.9
3.59
2.81
3.19
3.19
2.62
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1
2006 09-19 10:17
2006 10-24 10:43
2006 11-30 10:48
2007 01-25 12:16
2007 01-25 20:48
2007 01-30 13:48
2007 02-06 09:48
2007 02-15 12:55
2007 02-15 16:03
2007 02-15 20:13
2007 02-16 09:07
2007 02-20 08:44
2007 02-23 09:37
2007 02-27 10:04

# Major Bleeding Complications in AF Studies

| Studies | Annual rate of major bleedings(%) Warfarin | Control | Annual rate of major bleedings(%) Aspirin | Control | Annual rate of major bleedings(%) Warfarin | Aspirin |
|---|---|---|---|---|---|---|
| AFASAK- I | 0.6 | 0.0 | 0.3 | 0.0 | 0.6 | 0.3 |
| AFASAK-II | | | | | 1.7 | 1.6 |
| BAATAF | 0.4 | 0.2 | | | | |
| CAFA | 2.1 | 0.4 | | | | |
| SPAF-I | 1.5 | 1.6 | 1.4 | 1.9 | | |
| SPAF-II<br>≤ 75<br>> 75 | | | | | <br>1.7<br>4.2 | <br>0.9<br>1.6 |
| SPINAF | 1.3 | 0.9 | | | | |
| EAFT | 2.6 | 0.7 | 0.7 | 0.6 | | |

# New Antithrombotic Drugs

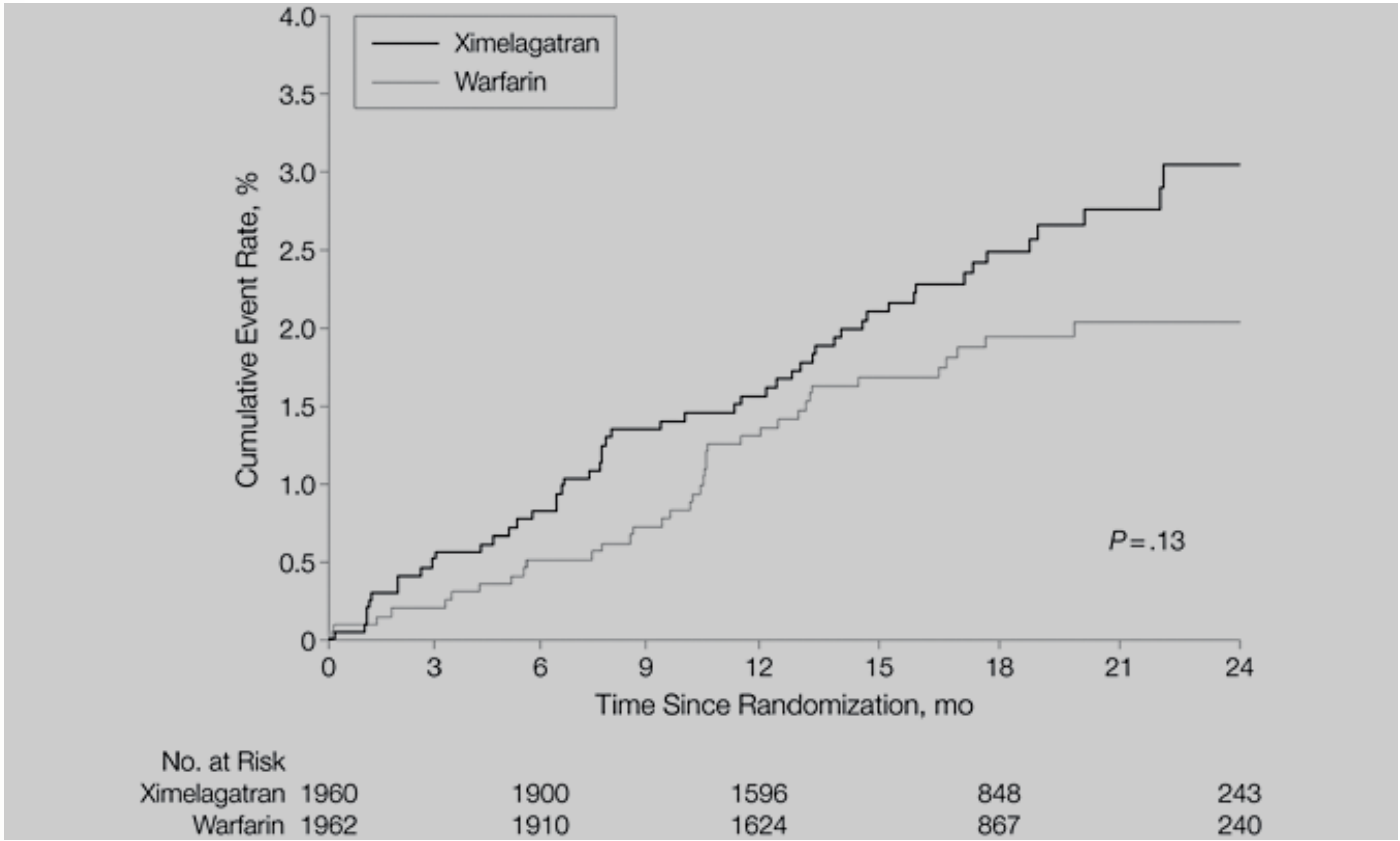
**Ximelagatran vs Warfarin for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation A Randomized Trial**

SPORTIF Executive Steering Committee for the SPORTIF V Investigators*

**Conclusions :**

The results establish the efficacy of fixed-dose oral ximelagatran without coagulation monitoring compared with well-controlled warfarin for prevention of thromboembolism in patients with atrial fibrillation requiring chronic anticoagulant therapy, but the potential for hepatotoxicity requires further investigation.

***(JAMA. 2005;293:690-698)***


Ximelagatran
Warfarin
Cumulative Event Rate, %
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
P=.13
0
3
6
9
12
15
18
21
24
Time Since Randomization, mo
No. at Risk
Ximelagatran 1960 1900 1596 848 243
Warfarin 1962 1910 1624 867 240

# In Summary

- Atrial fibrillation, the most significant tachyarrhythmias, is associated with thrmboembolic complications in elderly patients.
- New guideline recommends oral anticoagulation with adjusted-dose warfarin in high risk patients.
- Despite clear guidelines on oral anticoagulation in atrial fibrillation, it is not easy to maintain appropriate therapeutic range of INR in clinical practice. Bleeding complication is also concerned in elderly patients.
- A promising alternative drug for anticoagulation in atrial fibrillation is direct thrombin antagonists. The drug does not need frequent dose titration and PT test. One of drugs, Ximelagatran, showed similar stroke-prevention efficacy and bleeding complication compared with warfarin in large clinical trials. However, US FDA has not approved the drug because of severe hepatotoxic effects.
- Other direct thrombin antagonists are now undergoing clinical trials.