

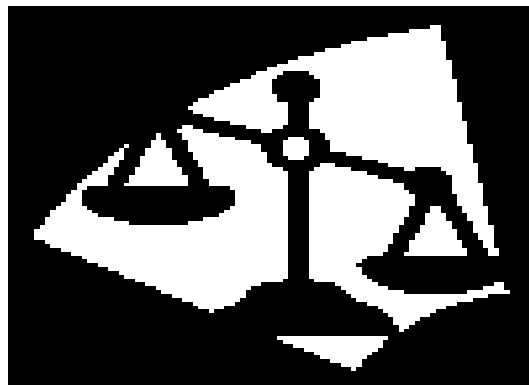
# Evaluation of Benefit and Risk

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# Benefit-Risk Assessment

**Benefit**



**Risk**

- Qualitative\*
- Quantitative

## Benefit-risk Evaluation Takes the Following into Consideration:

- Condition to be treated, prevented, or diagnosed, i.e., use
- Availability of alternative therapies
- Nature of the benefit
- Strength and weaknesses of evidence of efficacy
- Nature of the risks
- Extent to which risks can be mitigated

## Use (1)

- What is the condition to be treated, prevented, or diagnosed?
- Its manifestations, i.e., symptoms, disability?
- What is known about the natural history/progression of the condition?
- Range of severity? Seriousness?
- What about the population to be treated?
  - Healthy? Little risk acceptable, i.e., vaccine
  - Sick? More risk acceptable, i.e., cancer

## Use (2)

- What is the basis for your assessments, e.g., literature, clinical experience/perspective?
- What are the uncertainties in the available information? What are their implications?

## Alternative Therapies (1)

- What other therapies are approved for this condition (pharmacological and/or non-pharmacological)?
- How effective are they? How well tolerated?
- Does their effectiveness vary by sub-population?
- Does tolerability vary by sub-population?
- Are any off-label therapies thought to be effective? How effective? What is the level of evidence? Are they well tolerated?
- What are the major uncertainties in the evidence? What are the implications?

## Alternative Therapies (2)

- How well is the medical need being met by currently available therapies?
- If medical need is generally met, are there subpopulations whose needs are unmet, e.g., patients with more severe symptoms, other subgroups?

## Conclusions on Alternative Therapies

1. No effective therapies – approved or off-label.
2. No approved therapies; standard of care is off-label treatment, +/- effective.
3. Approved therapies exist, but this drug represents an advance: greater efficacy; efficacy for greater numbers of patients; improved tolerability and/or convenience (includes route of administration)
4. Similar to approved drugs, but different drug class and/or mode of action.
5. Not an advance or new drug class: current therapeutics are reasonably well tolerated and have demonstrated efficacy – just a new option



## Nature of Clinical Benefit

- Nature of the benefit, e.g., diagnostic, preventive, symptomatic, or disease-modifying treatment?
- Important endpoints that support the benefit, e.g., longer life, reduced symptoms, improved patient reported outcome?
- If surrogate endpoint, what is its validity?
- Is duration of effect known?
- Any evidence of efficacy in patients who are non-responders to existing treatments?

## Strengths & Weaknesses of Findings

- Number of trials: one? two? more?
- Consistency of findings across trials?
- Comparator(s): Active treatment? Placebo?
- Superiority or non-inferiority shown?
- Size of treatment effect?
- Clinical relevance of treatment effect?
- Statistical persuasiveness of results?
- Methodological strengths and weaknesses?
- Demonstration of dose-response?
- Are results robust to exploration?

# Generalizability

- What population was studied?
- Generalizability of treatment effect across sub-populations of interest, e.g., demographic, genetic, disease-specific?
- Are the findings generalizable to the US patient population, i.e., the practice of medicine in the USA?

## Uncertainty in Efficacy

- Which endpoints were not assessed in the trials but would have been relevant, and what is their significance?
- What are the major uncertainties and their significance?
- Is information missing on important subgroups?
- Are additional trials recommended to characterize further the clinical benefit of the product?

## Risk/Safety (1)

- What are the adverse events?
- What is their seriousness?
- What is their importance? Do patients stop taking the drug because of them?
- What is their frequency?
- To what extent can risk be mitigated:
  - Is toxicity predictable? Or not?
  - Is toxicity preventable? Or not?
  - Is toxicity reversible? Or not?

## Risk/Safety (2)

- How well is the risk characterized?
- Is there important missing information?

# Use of Drug Influences Benefit-Risk

## Chronicity of treatment:

- Single use, e.g., thrombolytic agent for acute stroke; vaccine for Herpes Zoster
- Short-term use, e.g., antibiotics for acute infection; analgesics for short-term use
- Chronic use, e.g., alpha1-blockers for benign prostatic hypertrophy
- Near-lifetime use, e.g., statins for hypercholesterolemia; antihypertensives

## Can an individual patient recognize whether they are gaining benefit from the drug? (1)

If so, use can be shunted away from those who don't benefit, increasing overall benefit for the treated population.

Examples where you probably can direct use to enhance overall benefit for the population:

- Hypnotics for sleep; alpha1-blockers for BPH – patients know if they are deriving benefit, can stop drug if not doing better.
- Drugs for HTN and hypercholesterolemia – one never knows if a given patient will benefit, but measurable biomarkers provide a clue; can guide use (BP; LDL cholesterol).



## Can an individual patient recognize whether they are gaining benefit from the drug? (2)

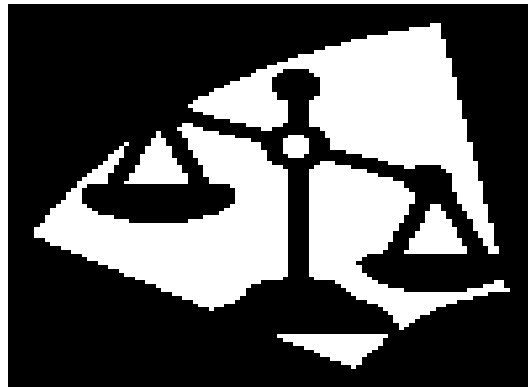
Examples where it is difficult to direct use to enhance overall population benefit:

- Acetylcholinesterase inhibitors for dementia – difficult to know if patient has improved; difficult to stop drug; caregiver thinks the patient *might* be better, worried about stopping drug
- Antiplatelet agents after acute MI – one never knows if the drug will prevent a second MI, and there are no biomarkers to guide use. Drug is continued “on faith.”

# Benefit-Risk Assessment

## Efficacy:

- What is the disease?
- What does the drug do?  
(endpoints/indication)
- What is the effect size?



## Safety:

- Nature of AEs?
- Their seriousness?
- Their frequency?
- Ability to predict/  
prevent AEs?
- Their reversibility?
- Impact of the AEs on  
the particular patient



# Two Examples of “Quantitative” Benefit-Risk Evaluation

- Prasugrel benefit and risk  
(antiplatelet agent; approved 7/2009)
- Dabigatran benefit and risk  
(anticoagulant; approved 10/2010)

Both drugs are *preventive therapies*

Both drugs are well-suited for B-R analyses:

- At a basic level, both are “blood thinners”
- Benefits are well-characterized
- Risks are well-characterized
- All important known benefits and risks are related to the drugs’ pharmacological effects
- One drawback – both drugs were compared to active treatments; difficult to characterize B-R relative to placebo.

## B-R Analyses – Both Drugs:

- Benefits:
  - prevention of stroke, heart attack, and cardiovascular death (prasugrel);
  - prevention of stroke and systemic embolism (dabigatran)
- Risk: bleeding

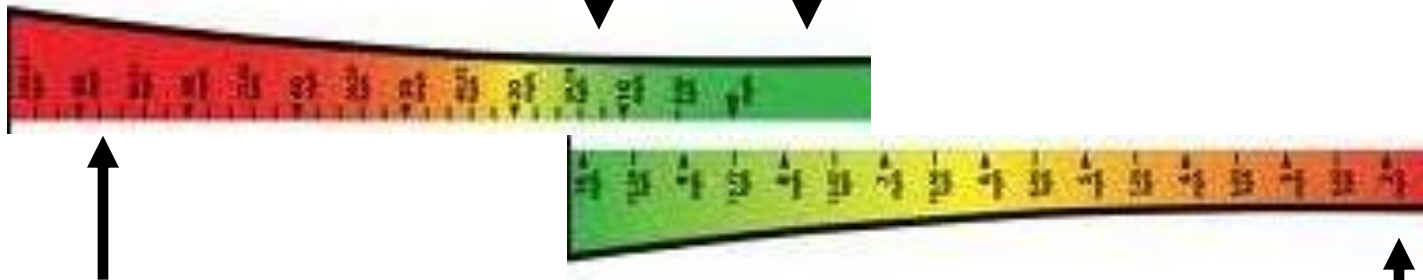
# “Spectrum” of Benefits and Risks:

Sought-for balance:  
prevention of strokes,  
heart attacks, and death;

without bleeding

Too little drug activity

Too much drug activity



strokes, heart  
attacks, and deaths  
are not prevented

**bleeding**

- Prasugrel benefit and risk  
(antiplatelet agent; approved 7/2009)

*A preventive therapy* – indicated for the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome who are to be managed with PCI...



- Prasugrel's efficacy and safety established on the basis of a comparison to clopidogrel (approved drug), an active control.
- Both prasugrel and clopidogrel are anti-platelet agents - inhibit platelet activation and aggregation

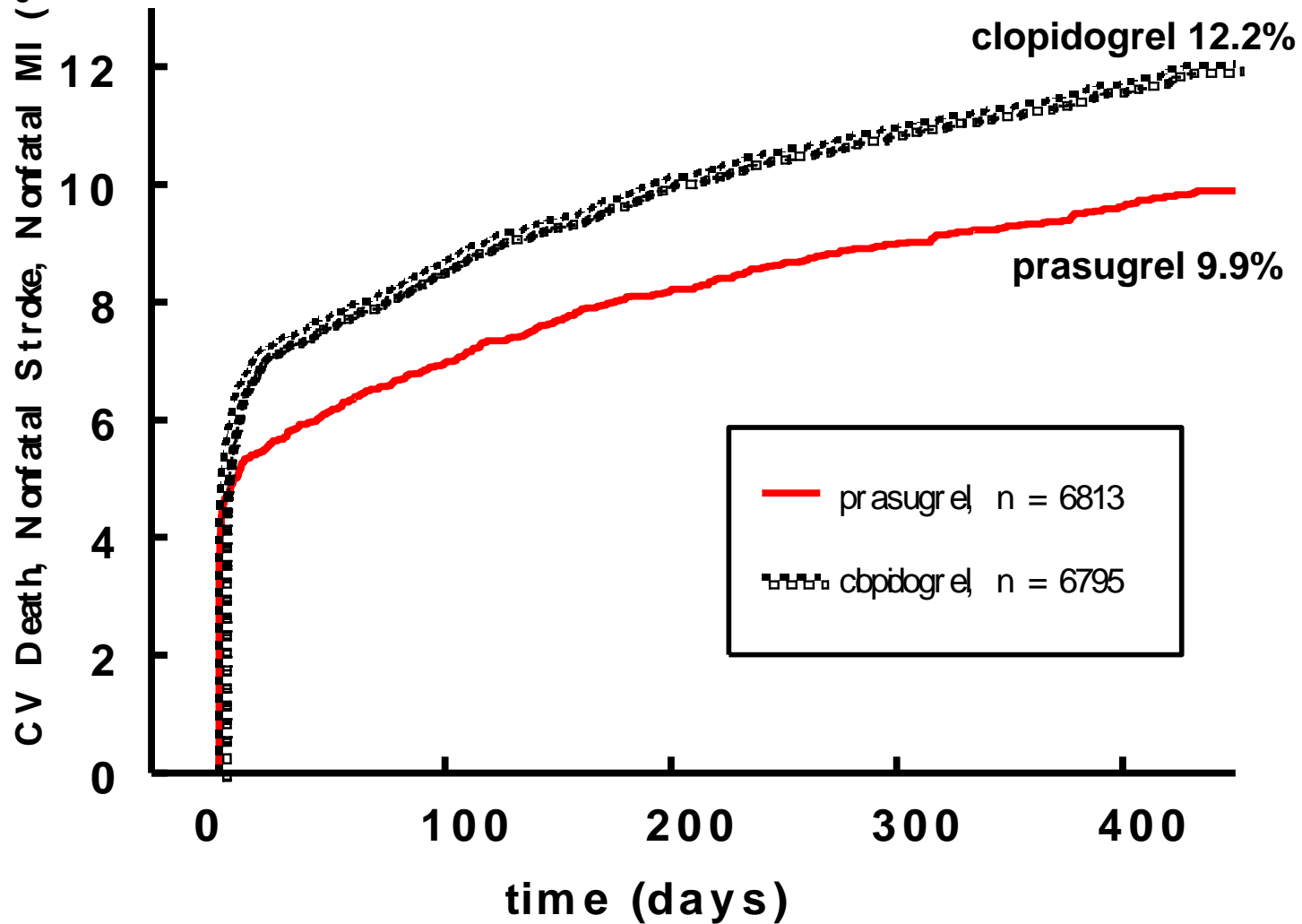
# Prasugrel: Evidence of Efficacy & Safety

## TRITON-TIMI 38

- Phase 3, randomized, double-blind, active-controlled study
- Patients with acute coronary syndrome (ACS); angioplasty planned ( $\pm$  stent)
- Patients received aspirin; randomized 1:1 to:
  - prasugrel
  - clopidogrel (active control - standard of care)
- Hypothesis: prasugrel plus aspirin is superior to clopidogrel plus aspirin

- Randomization stratified by clinical presentation:
  - Unstable angina or non-ST-segment elevation myocardial infarction (UA/NSTEMI)
  - ST-segment elevation myocardial infarction (STEMI)
  
- Composite endpoint:
  - cardiovascular death
  - non-fatal myocardial infarction
  - non-fatal stroke
  
- 13,608 subjects enrolled
- Median follow-up = 15 months (mean = 12 months)

# 1° Efficacy Endpoint: both UA/STEMI and non-STEMI





## Prasugrel Benefit

1000 patients treated with prasugrel instead  
of clopidogrel for ~ 1 year:

24 endpoint events prevented:

21 non-fatal myocardial infarctions

3 cardiovascular deaths

0 strokes

## Prasugrel Risk – Risk = Bleeding

- TIMI Major Bleed  $\equiv$  any intracranial hemorrhage, or overt bleeding requiring intervention associated with a decrease in hemoglobin  $\geq 5$  g/dL
- TIMI Minor bleeding  $\equiv$  overt bleeding with a decrease in hemoglobin  $\geq 3$  g/dL but  $< 5$  g/dL
- Bleeding was categorized as related to, or not related to, coronary artery bypass graft (CABG) surgery.

# Adjudicated Bleeding by Category

	Prasugrel (N=6741)	Clopidogrel (N=6716)
TIMI Major or Minor bleeding	4.5	3.4
TIMI Major bleeding	2.2	1.7
Life-threatening	1.3	0.8
Fatal	0.3	0.1
Intracranial hemorrhage	0.3	0.3
Requiring inotropes	0.3	0.1
Requiring surgery	0.3	0.3
Requiring transfusion (≥4 units)	0.7	0.5
TIMI Minor bleeding	2.4	1.9

\*\* Patients may be counted in more than one row.

For all major/minor bleeding,  $\Delta$  is ~1%, or 10/1000<sub>32</sub>



## Prasugrel: Overall Benefit-Risk Profile

**1000 patients treated with prasugrel instead of clopidogrel for 15 months:**

**24 endpoint events prevented:**

**21 non-fatal myocardial infarctions**

**3 cardiovascular deaths**

**0 strokes**

**10 excess TIMI Major or Minor bleeding events:**

**2 bleeding deaths**

**3 non-fatal TIMI Major bleeds (ICH, or hemoglobin decrease  $\geq 5$  g/dL)**

**5 TIMI Minor bleeds (hemoglobin  $\downarrow\downarrow \geq 3$  to  $< 5$  g/dL)**

**and 19 TIMI Minimal bleeds.**

- Dabigatran benefit and risk  
(anticoagulant; approved 10/2010)

*A preventive therapy* – indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation

## **Dabigatran – Efficacy and Safety:**

- Efficacy and safety established on the basis of a comparison to warfarin (an approved drug). Both are anticoagulants:
- Warfarin inhibits vitamin K-dependent coagulation factors.
- Dabigatran is a competitive, direct thrombin inhibitor (thrombin converts fibrinogen to fibrin).

# Dabigatran – RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51. [Erratum, *N Engl J Med* 2010;363:1877.]

# Dabigatran: RE-LY Study Design

Phase 3, randomized, active-controlled study:

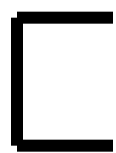
Patients with atrial fibrillation and at least 1 additional risk factor for stroke

Patients randomized 1:1:1 to:

warfarin (titrated to INR 2-3)

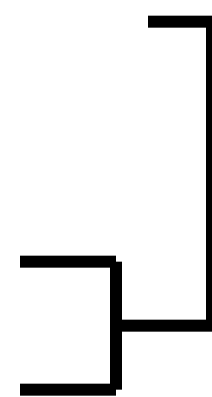
dabigatran (1 of 2 doses):

Double  
blind



lower dose (110 mg bid)

higher dose (150 mg bid)



Open-label

## RE-LY: 1° Endpoint/Hypothesis

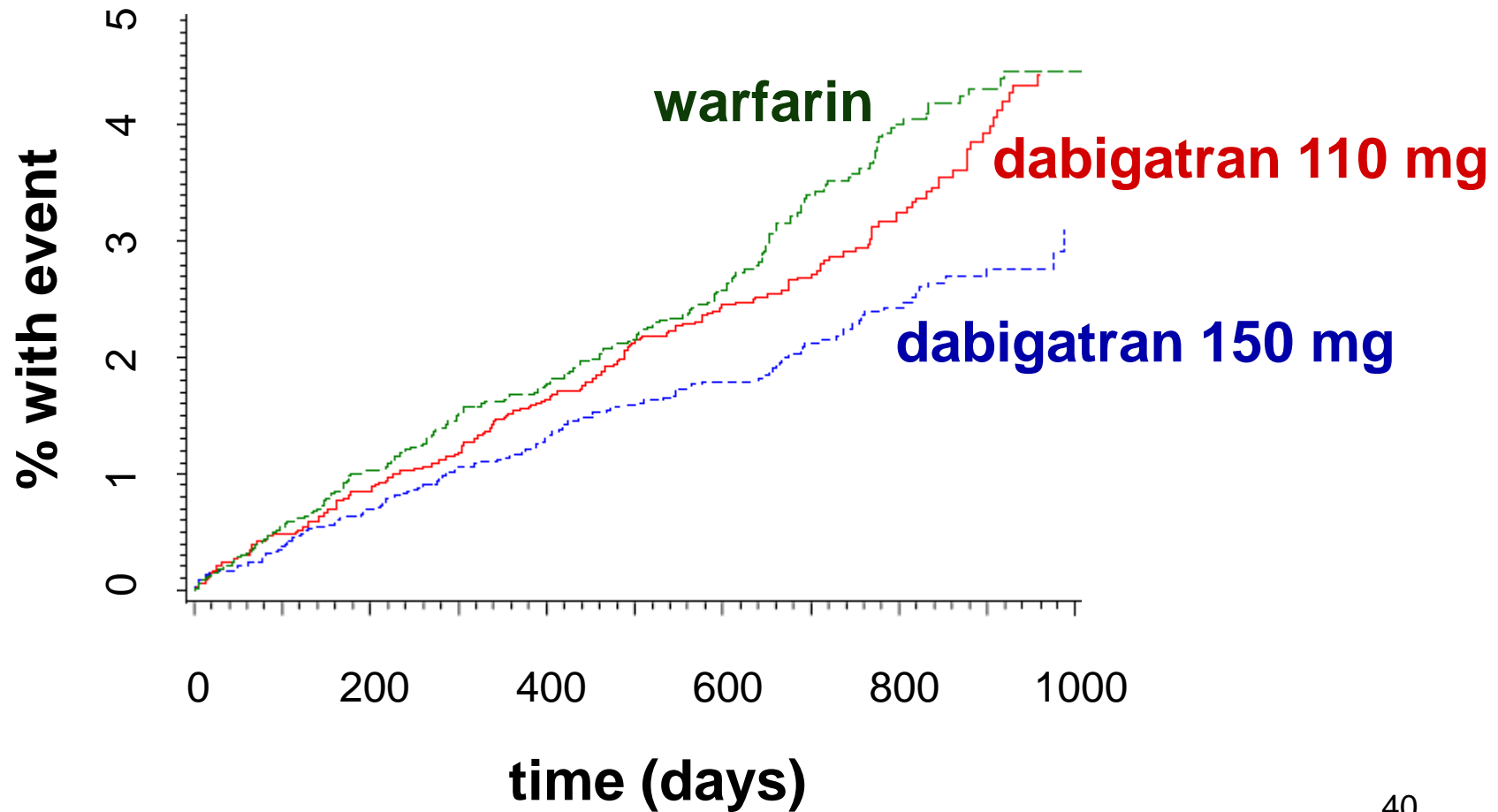
- Primary composite endpoint: time to first occurrence of:
  - stroke (either ischemic or hemorrhagic) or
  - systemic embolism
- Primary hypothesis: dabigatran at either dose was non-inferior to warfarin in preventing stroke and systemic embolism.
- Non-inferiority margin = 1.38

## Re-LY: Results

18,113 subjects enrolled, ~ 6,000 per group

Median follow-up = 2 years

## Primary Endpoint: Time to First Stroke or Systemic Embolism





# RE-LY: 1st Occurrence of Stroke or Systemic Embolism

	<b>dabigatran 150 bid</b> n=6076	<b>dabigatran 110 bid</b> n=6015	<b>warfarin</b> n=6022
Patients with 1° endpoint event (%)	2.2	3.0	3.4
1° endpoint; HR vs. warfarin (95% CI)	0.65 (0.52, 0.81)	0.90 (0.74, 1.10)	-
p-value for superiority	<0.05	0.3	-
stroke (%)	2.0	2.8	3.1
ischemic (%)	1.7	2.5	2.2
hemorrhagic (%)	0.2	0.2	0.7
systemic embolism (%)	0.2	0.2	0.3
	↓	↓	
	superior to warfarin superior to dabigatran 110		NI to warfarin

## Major Bleeding Events in RE-LY (%)

	<b>dabigatran 150 bid</b> n=6076	<b>dabigatran 110 bid</b> n=6015	<b>warfarin</b> n=6022
Major bleeding events (%)	399 (6.6)	342 (5.7)	421 (7.0)
Life-threatening bleeding events (%)	193 (3.2)	159 (2.6)	233 (3.9)
Intracranial hemorrhage (%)	38 (0.6)	27 (0.4)	90 (1.5)

\*\* Patients may be counted in more than one row.

Dabigatran 110 mg bid was superior to warfarin.

Dabigatran 150 bid was non-inferior to warfarin.

Major bleeding = bleeding with decrease in Hgb of  $\geq 2$  g/dL or necessitating a transfusion of  $\geq 2$  units of blood/RBCs or symptomatic bleeding in a critical area or organ

# Dabigatran: Overall Benefit-Risk

**1000 patients treated with dabigatran 150 mg bid instead of warfarin for 12 months:**

**Prevented (difference statistically significant):**

- **6 strokes (~3 ischemic; ~3 hemorrhagic)**
- **<1 systemic embolism**

**A trend towards less bleeding:**

- **3 fewer non-fatal major bleeding events**
- **4 fewer life-threatening bleeds**
- **4 fewer intracranial hemorrhages**

## Dabigatran: Overall Benefit-Risk

**1000 patients treated with dabigatran 110 mg bid instead of warfarin for 12 months:**

**Prevented (non-statistically significant trend):**

- **2 strokes (4 fewer hemorrhagic; 2 excess ischemic)**
- **<1 systemic embolism**

**Statistically significantly less bleeding:**

- **7 fewer non-fatal major bleeding events**
- **6 fewer life-threatening bleeds**
- **5 fewer intracranial hemorrhages**

## Dabigatran – Decision Conundrum:

- Approve 110 mg bid? Non-inferior on stroke prevention, superior on bleeding
- Approve 150 mg bid? Superior on stroke prevention; non-inferior on bleeding
- Both met evidentiary standards for safety and effectiveness; if the company had studied either dose alone, we would have approved it.
- Approve both? Let practitioners choose?<sup>45</sup>

## Advantage for Lower Dose?

- To approve dabigatran 110 mg bid, there should be a patient population for whom the B-R assessment of 110 mg bid is more favorable than that of 150 mg bid.
- Review team examined patient sub-populations that would be exposed to higher dabigatran concentrations and/or greater risk of bleeding:
  - Elderly patients
  - Patients with impaired renal function
  - Patients with bleeding episodes during the study (higher risk of subsequent bleeding)

## Patients 75 and older

n = 7238; higher risks of stroke and bleeding

### Stroke and Significant Bleeding – Rates per 1000 Patient-years

	stroke	bleeding
Dabigatran 110	19	44
Dabigatran 150	14	51

Trade-off: with lower dose, 5 extra strokes, 7 fewer bleeding events. Trade not accepted!

Renal Disease; Creatinine Clearance 30 - 50

n = 3343; ~2- to 3-fold increase in exposure

## Stroke and Significant Bleeding – Rates per 100 Patient-years

	stroke	bleeding
Dabigatran 110	24	57
Dabigatran 150	13	53

Trade-off: with lower dose, 11 extra strokes, 4 extra bleeding events. Trade not accepted!



## Previous Bleeding on Treatment

### Significant Bleeding Subsequent to an Initial Bleeding Event (%)

Dabigatran 110	16%
Dabigatran 150	14%
Warfarin	12%

- No evidence that switching patients with bleeding events from the higher to the lower dose would decrease risk of subsequent bleeding event

## Approval of Higher Dabigatran Dose

- In none of these populations was the R-B more favorable for the lower dose:
  - Elderly patients
  - Patients with impaired renal function
  - Patients with bleeding episodes during the study
- FDA approved only the higher dose of dabigatran, 150 mg bid.

## **Challenge Question 1**

In considering the benefit-risk evaluation of a drug, the following are important:

1. the condition to be treated, prevented, or diagnosed
2. the availability of other therapies for this condition
3. the nature of the benefit
4. the risk of the drug

Which of the above are true?

- A. 1, 2, and 3
- B. 3 and 4
- C. 1, 3, and 4
- D. All of the above are true

## **Challenge Question 2**

In considering the strength of the efficacy findings, the following are important:

1. the number of efficacy trials
2. the comparator(s) used in the trials
3. methodological strengths and weaknesses of the trials
4. the extent to which adverse events can be prevented

Which of the above are true?

- A. 1, 2, and 3
- B. 1 and 2
- C. Only 3 is true
- D. All of the above



# Questions?

