COST-EFFECTIVENESS OF DABIGATRAN EXILATE IN TREATMENT OF ATRIAL FIBRILLATION

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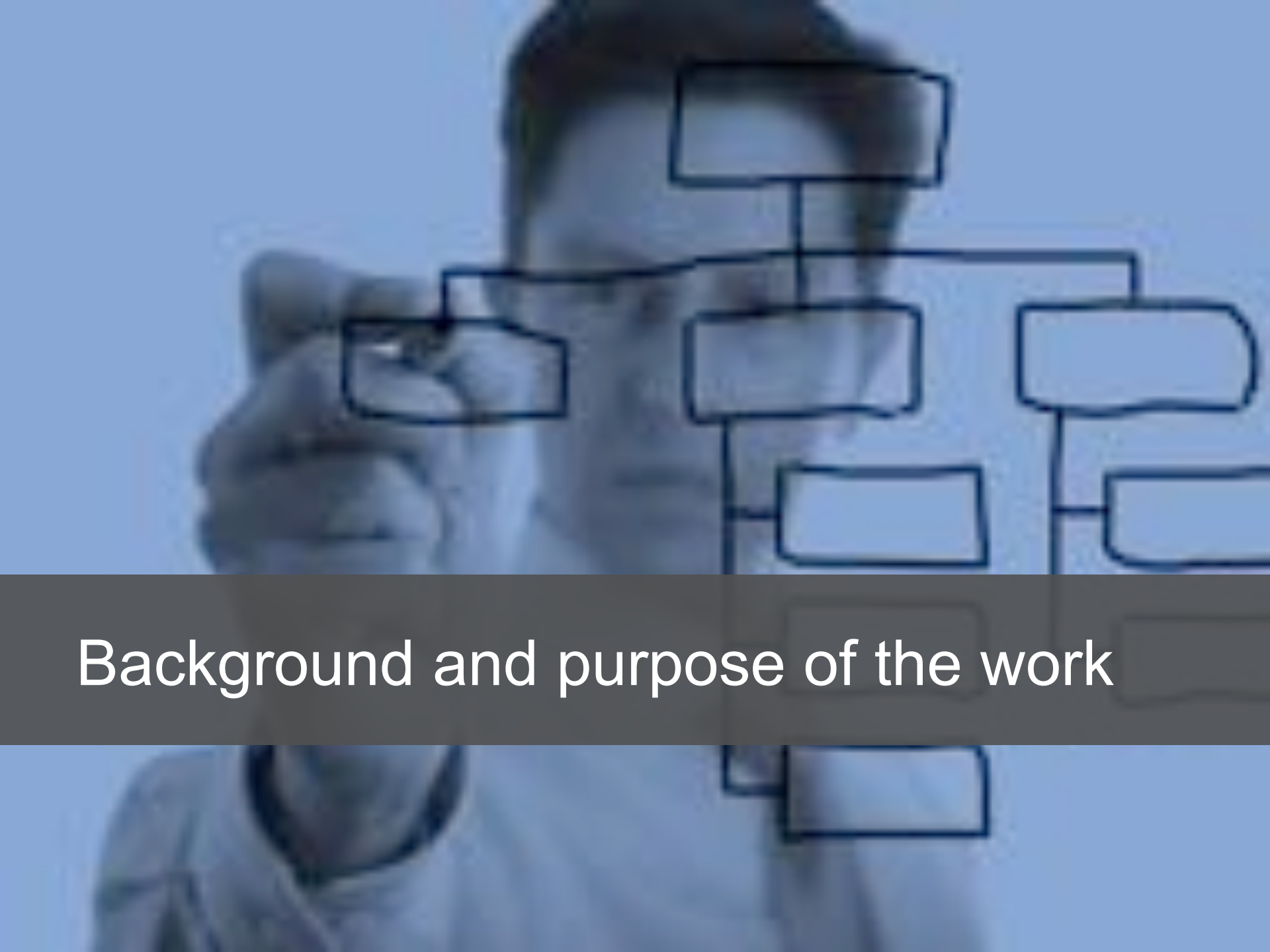
Agenda

- Background and purpose of the work
- Anticoagulant therapies
- Cost analysis
- The “RE-LY” study
- Our model
- Results and optimal use of Dabigatran



Background and purpose of the work

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STUDY BACKGROUND

- Increase in incidence and prevalence of AF imposes a big burden on public finances (€13.5bn in European Union in 2013)
- Safe and effective antithrombotic therapy is a primary objective to be pursued without delay

PURPOSE OF THE WORK

- **Determination of relative convenience**, in terms of cost and overall utility, **of oral anticoagulants therapies for each category of AF patients** (i.e. at high risk of embolic stroke and at high risk of ischemic stroke)

Anticoagulant therapies

Anticoagulant therapies

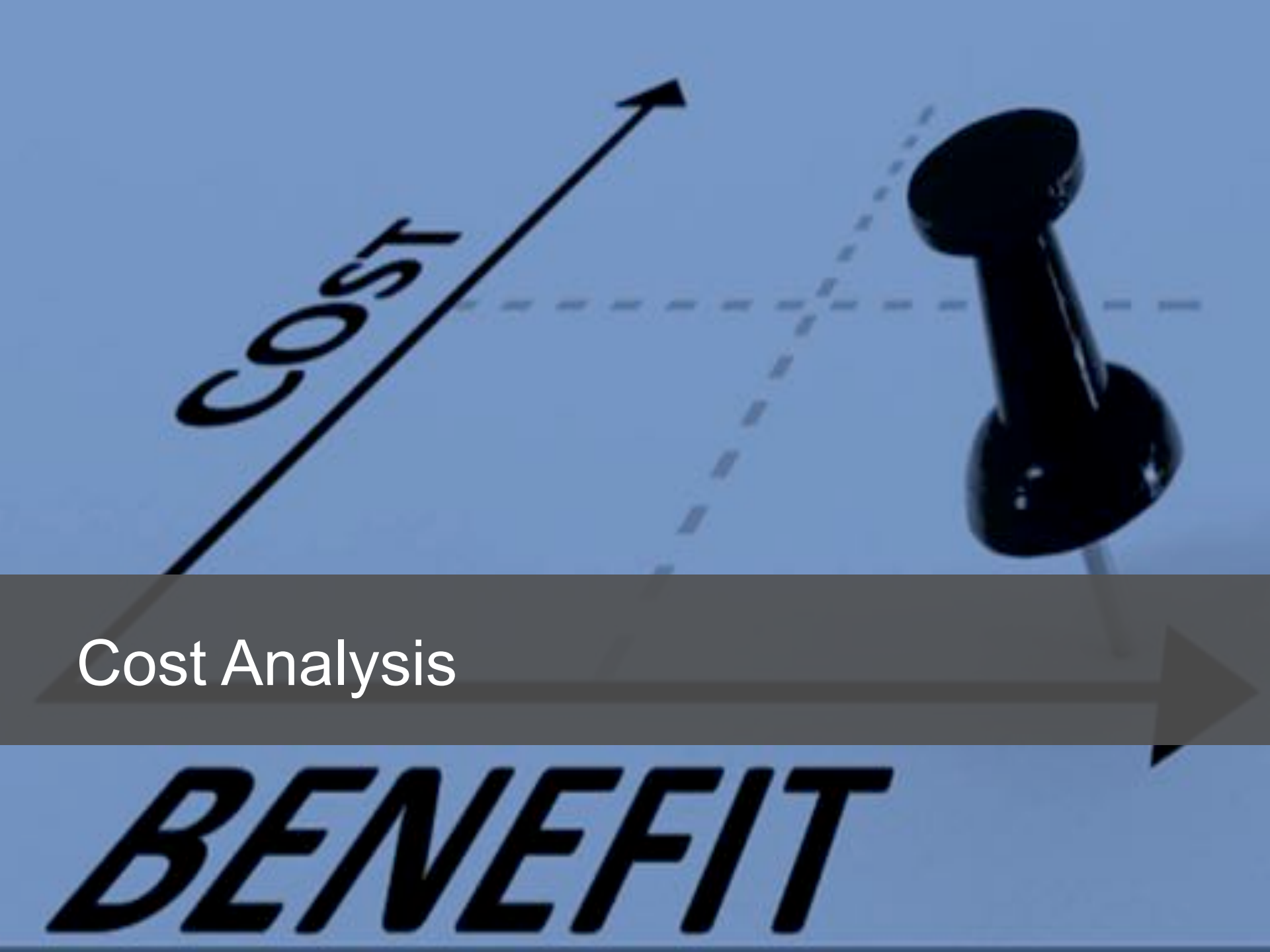
ORAL TREATMENTS CONSIDERED IN OUR WORK:

ASPIRIN

DABIGATRAN 2*110mg/die

WARFARIN

DABIGATRAN 2*150mg/die



Cost Analysis

Cost-Analysis: the QALY and the ICER

KEY CONCEPTS

- The **QALY** (Quality-Adjusted Life Years). Represents the equivalent of years lived in perfect health:

$$QALY\ value = U[given\ state\ of\ health] * years\ lived\ in\ that\ state$$

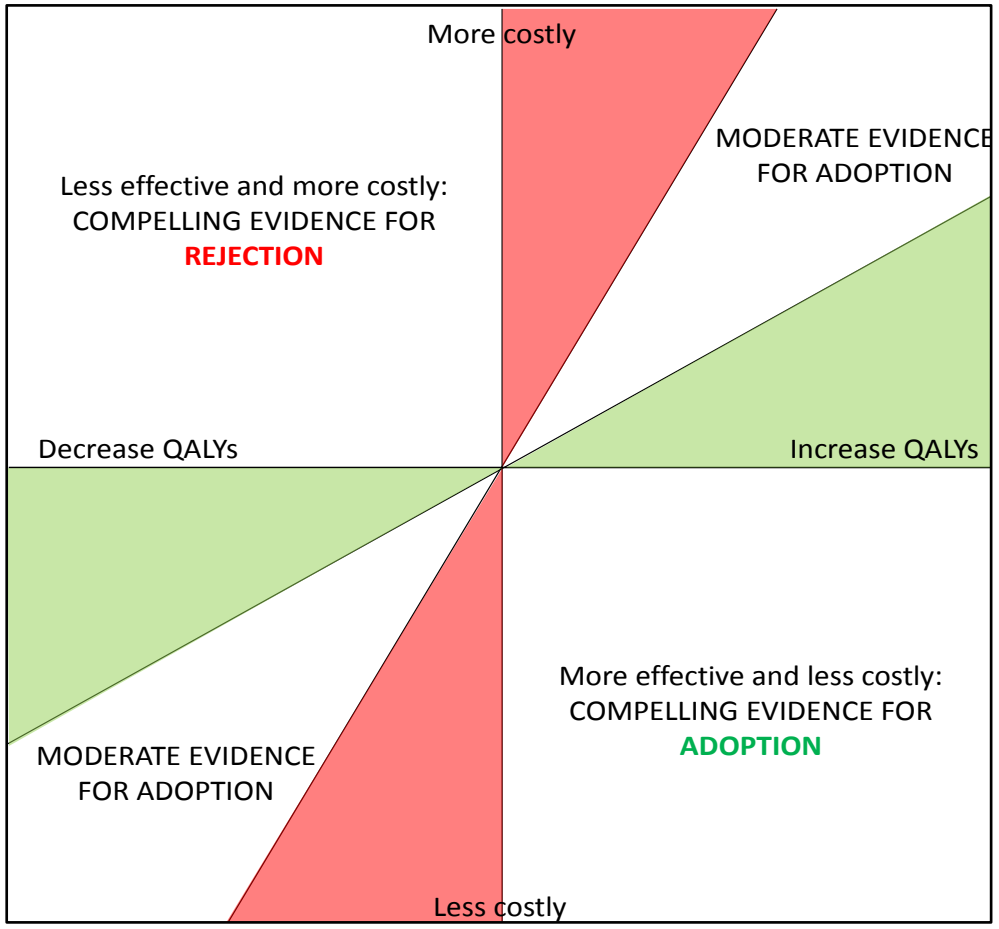
- The **ICER** (Incremental Cost-Effectiveness Ratio). Defines the marginal increase in cost for a determined increase in efficacy:

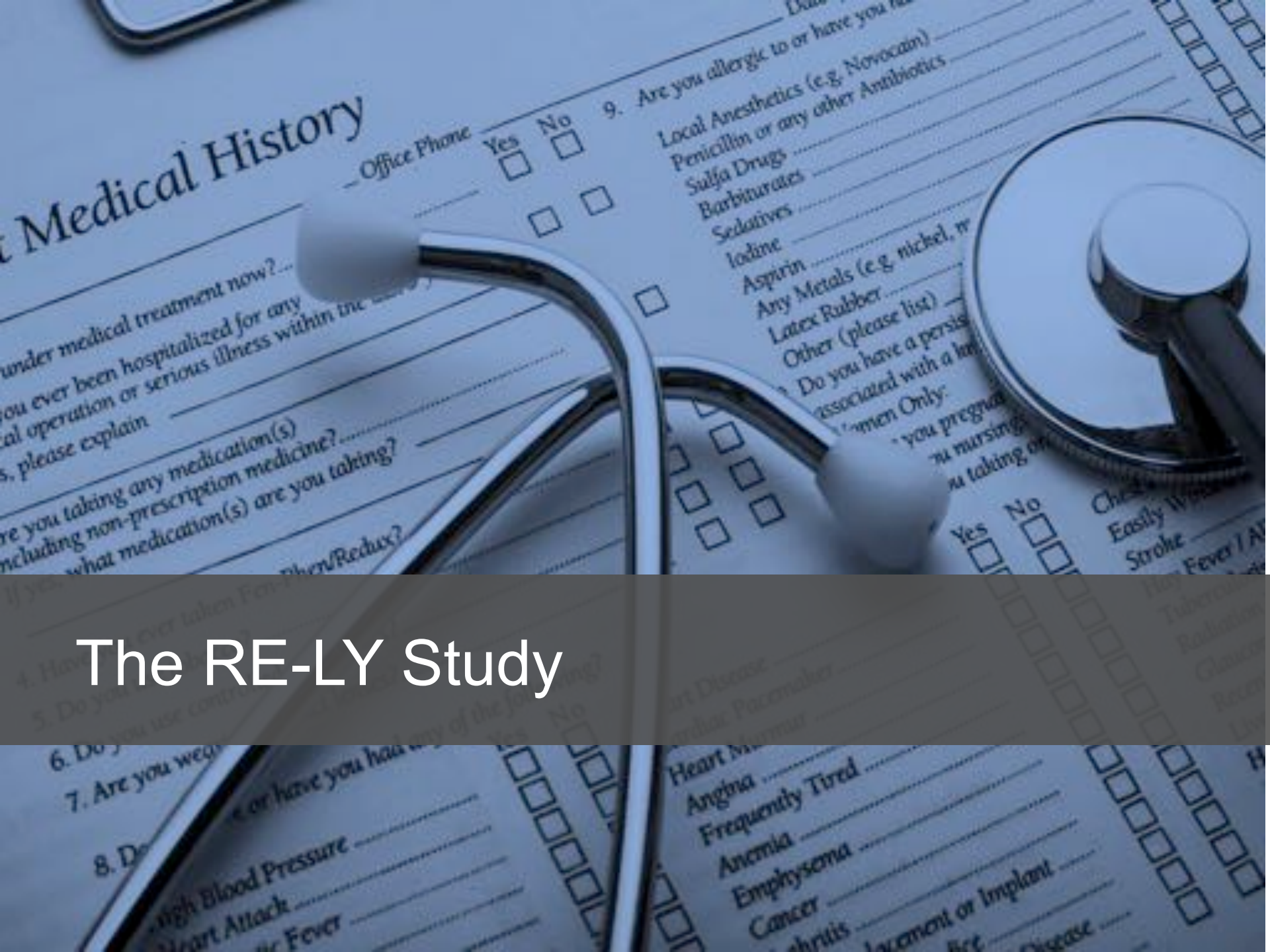
$$ICER = E[\Delta\ cost] / \Delta\ efficacy$$

Cost-Analysis: A practical example

EXAMPLE

- Incremental cost: €100,000
- Survival 5 Years
- Quality of life factor: 0.8x
- ICER: €100,000 / 5 X 0.8 = €25,000 / QALY





The RE-LY Study

The “RE-LY” study: Overview

DESCRIPTION

- Massive authoritative trial conducted between 2006 and 2008 to test the non-inferiority of Dabigatran vs. Warfarin
- Over 18,000 patients from 44 countries were treated with either Dabigatran or Warfarin (with target INR of 2.0-3.0)

CRITERIA FOR INCLUSION OF PATIENTS

- AF within 6 months from screening plus at least one of:
  - Previous stroke/transient ischemic attack
  - Left ventricular ejection fraction of less than 40%,
  - NYHA class II or higher heart-failure symptoms within 6 months before screening
  - Age >75 or between 65 and 74 with diabetes mellitus/hypertension/coronary artery disease.

The “RE-LY” study: Results

DABIGATRAN ≥ WARFARIN

- Non-inferior for **stroke or systemic embolism** in both low and high dose subministration
- Superior to Warfarin for patients at **high risk of stroke** in high dose
- Superior to Warfarin for patients at **high risk of hemorrhagic stroke** in high dose

DABIGATRAN < WARFARIN

- Both doses of Dabigatran were associated with a higher rate of myocardial infarction

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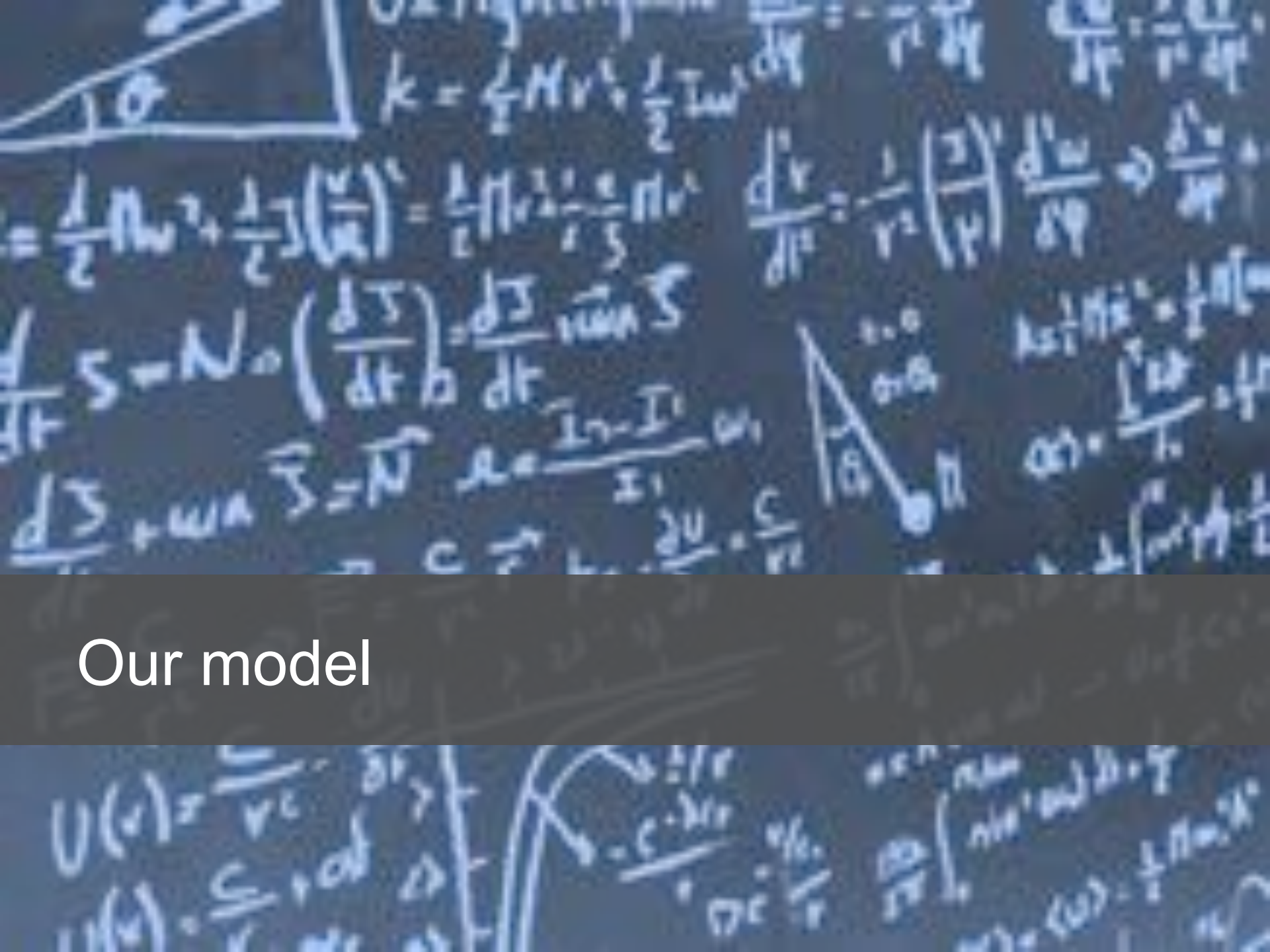


Our model

Our model: Overview

OBJECTIVE

- Determination of most cost-effective oral anticoagulant drug for each category of patients (at high risk of embolic stroke, at high risk of ischemic stroke, etc.)

FEATURES

- 1,000 virtual patients with average age of 75 years, grouped into subsets according to $HEMORR_2AGES$ and $CHADS_2$ scores
- Use of Markovian model to determine progression of patients' health state
- Ischemic and hemorrhagic risks periodically adjusted to factor in morbidity and mortality related to age and gender

ASSUMPTIONS

- Cost-effectiveness threshold set at €50,000/QALY
- Dabigatran treatment cost set at €2,190/yr (€6.00/day)
- Warfarin treatment cost set at €630/yr (including INR monitoring)

Our model: Building the model

Creation of a virtual sample of 1,000 patients affected by AF

Grouping of the patients based on risk of stroke and hemorrhage

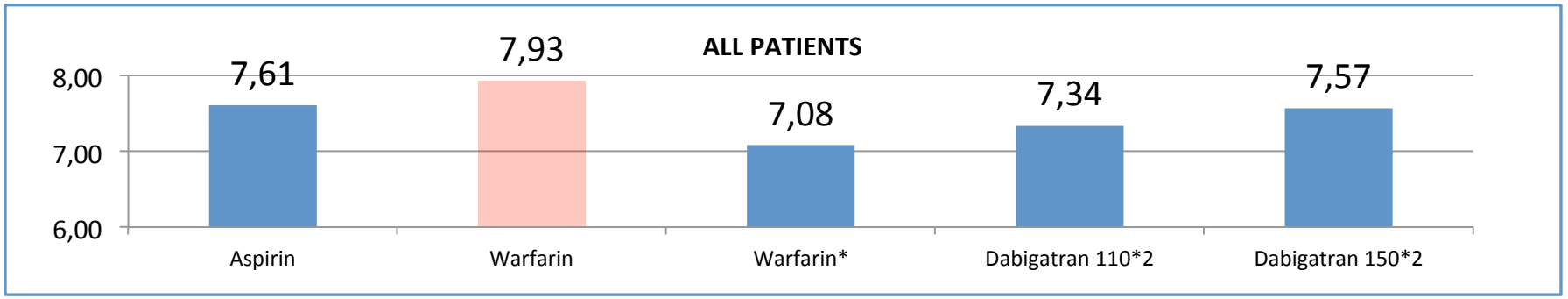
30-year follow-up period for each patient through a Markovian model

Computation of average utility associated to each of the drugs considered

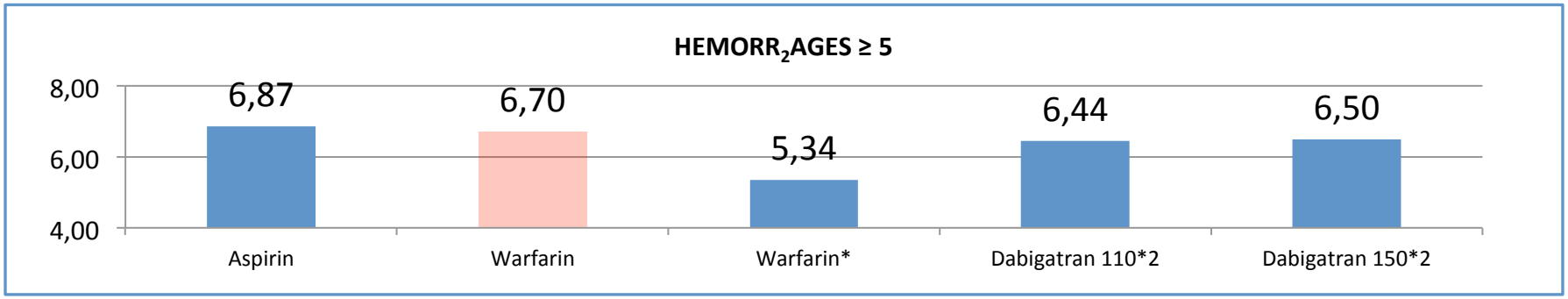
Identification of the most cost-efficient solution for each patient's category

Results

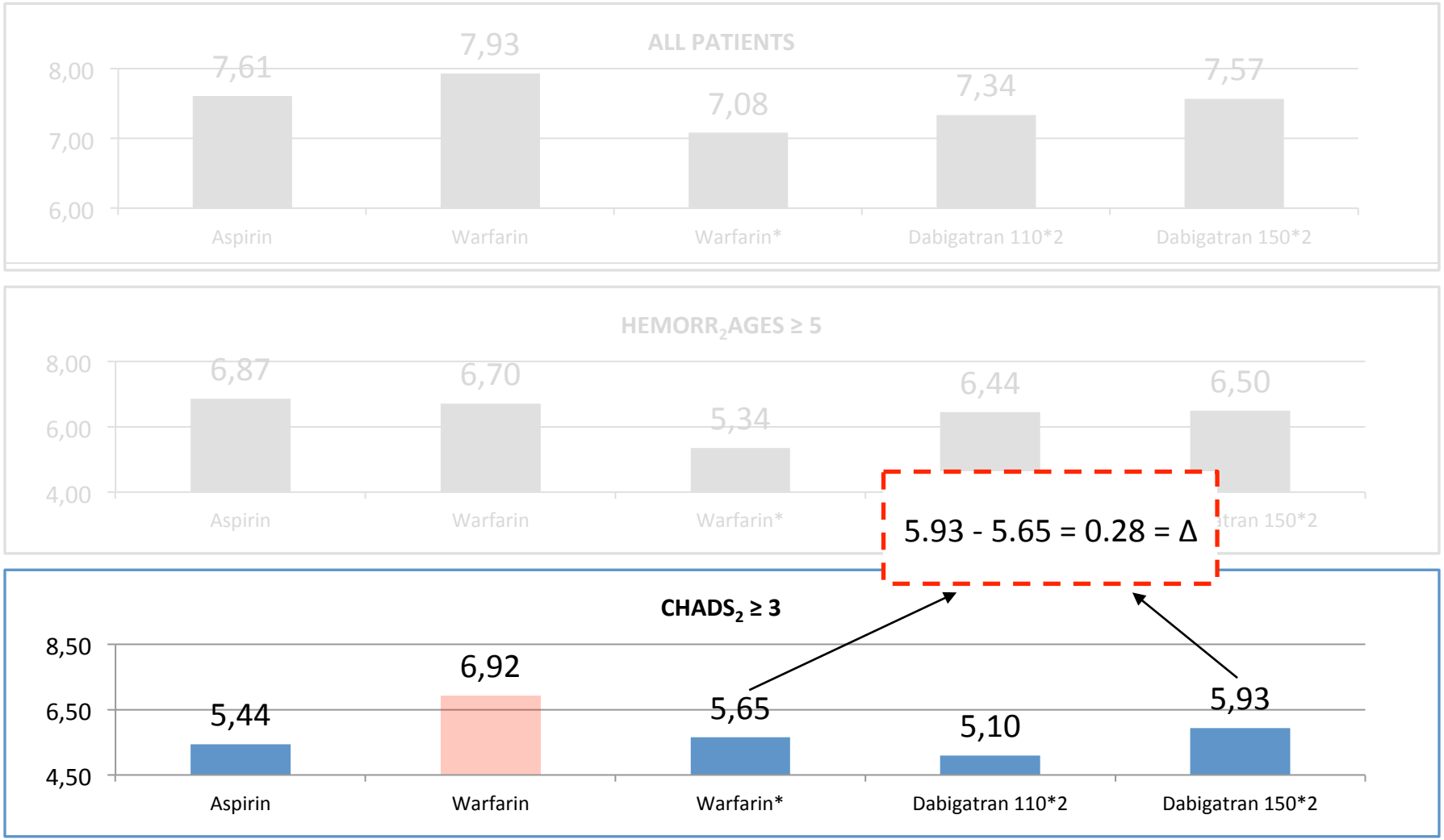
Results: All patients



Results: High risk of Bleeding



Results: High risk of Stroke



Results: Cost effectiveness in detail

HIGH DOSE DABIGATRAN VS. WARFARIN

- €2,190 per year for Dabigatran 150mg (2/die)
- €690 per year for Warfarin (incl. INR monitoring)

+

- Differential of 0.28 QALYs between Dabigatran 2*150mg/ die and Warfarin

=

Incremental Cost-Effectiveness Ratio (ICER) of €7,759.48 / QALY

Every QALY earned with Dabigatran costs ~€8,000 more than the treatment with Warfarin

Results: To sum up…

- Unless INR management is excellent (top quartile), high dose Dabigatran is the most clinically safe solution for patients at high risk of stroke,
- Provided an excellent TTR, Warfarin is the best choice overall and especially for patients with high risk of stroke

WARFARIN

Best choice:

- Overall (if TTR in the top quartile)
- High risk of stroke (if TTR in the top quartile)

DABIGATRAN

Best choice:

- High risk of stroke (TTR less than top quartile)

ASPIRIN

Best choice:

- High risk of bleeding (TTR less than top quartile)


Q&A

Appendix 1: HEMORR$_2$AGES score

- HEMORR$_2$AGES is the acronym of a 11-item scoring system[1] for estimating the risk of major bleeding in patients
- It is based on
  - Hepatic or renal disease
  - Ethanol abuse
  - Malignancy
  - Older age (≥75)
  - Reduced platelet count or function
  - Rebleeding risk (ie: prior bleed)
  - Anemia
  - Genetic factors (CYP2C9 variant)
  - Excessive fall risk
  - Stroke

Every risk factor contributes 1 point to the final score (except prior bleeding which is assigned a weight of 2) which will be between 0 and 12.

Risk Score	Incidence of Major Bleeding (per 100 patient-yrs)	95% CI
0	1.9	(0.6-4.4)
1	2.5	(1.3-4.3)
2	5.3	(3.4-8.1)
3	8.4	(4.9-13.6)
4	10.4	(5.1-18.9)
≥5	12.3	(5.8-23.1)

[1] developed by Gage BF, Yan Y Milligan PE, et al.

Appendix 2: $CHADS_2$ score

- $CHADS_2$ is a clinical prediction rule[1] for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF).
- It is based on the following conditions It is based on
  - Congestive heart failure
  - Hypertension: blood pressure consistently above 140/90 mmHg
  - Age ≥75 years
  - Diabetes mellitus
  - Prior stroke or Transient Ischemic Attack (TIA)

Every condition contributes 1 point (with the exception of prior stroke or TIA which is assigned a weight of 2) to the final score.

Risk Score	Incidence of Stroke (%)	95% CI
0	1.9	(0.6-4.4)
1	2.8	(1.3-4.3)
2	4.0	(3.4-8.1)
3	5.9	(4.9-13.6)
4	8.5	(5.1-18.9)
≥5	12.5	(5.8-23.1)
6	18.2	(10.5-27.4)

[1] developed by Gage BF, Waterman AD et al.

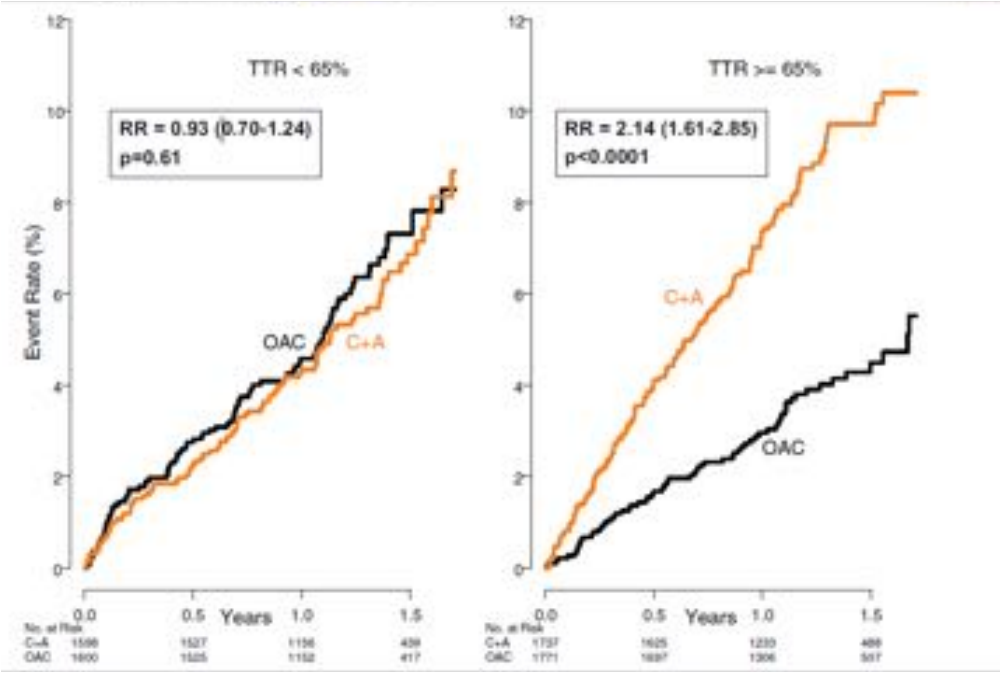
Appendix 3: Adjusting for TTR

- TTR is the percentage of time the patients treated with vitamin K antagonists manage to stay inside their prescribed INR
- Patients treated with Warfarin had their overall utility also affected by the TTR
- Little benefit over antiplatelet therapy if the TTR falls below a 58%-65% range

$$[U]\ W\ adjusted = [U]\ W\ in\ range * p(in\ range) + [U]\ W\ not\ in\ range * p(not\ in\ range)$$

- Where

$$[U]\ W\ not\ in\ range = [U]\ no\ AF - ([U]\ no\ AF - [U]\ W\ in\ range) * RR.$$



Cumulative risk of stroke, myocardial infarction, systemic embolism, or vascular death for patients treated at centers with a TTR below or above the study median (65%). RR indicates relative risk (C+A, clopidogrel plus Aspirin).