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**
- **WARFARIN**
- **DABIGATRAN** 2*110mg/die
- **DABIGATRAN** 2*150mg/die
KEY CONCEPTS

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

\[QALY\ \text{value} = U[\text{given state of health}] \times \text{years lived in that state}\]

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

\[\text{ICER} = \frac{E[\Delta \text{ cost}]}{\Delta \text{ efficacy}}\]
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

\[
\text{ICER} = \frac{\text{Incremental cost}}{\text{Quality of life factor}} = \frac{€100,000}{5 \times 0.8} = €25,000 / \text{QALY}
\]
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
The “RE-LY” study: Results

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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\textsubscript{2}AGES and CHADS\textsubscript{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

**ALL PATIENTS**

<table>
<thead>
<tr>
<th>Therapy</th>
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**HEMORR\(_2\) AGES ≥ 5**

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**CHADS\(_2\) ≥ 3**

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Results: High risk of Bleeding

**Results: High risk of Bleeding**

**HEMORR² AGES ≥ 5**

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Results: High risk of Stroke

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- Warfarin*: 7.08
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- Dabigatran 150*2: 7.57

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- Aspirin: 6.87
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- Aspirin: 5.44
- Warfarin: 6.92
- Warfarin*: 5.65
- Dabigatran 110*2: 5.10
- Dabigatran 150*2: 5.93

\[5.93 - 5.65 = 0.28 = \Delta\]
**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
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.

**Results:** To sum up...

- **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)
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 ($\geq 75$)
- Reduced platelet count or function
- Rebleeding risk (i.e., 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.

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Incidence of Major Bleeding (per 100 patient-yrs)</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>0</td>
<td>1.9</td>
<td>(0.6-4.4)</td>
</tr>
<tr>
<td>1</td>
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<td>(1.3-4.3)</td>
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<tr>
<td>2</td>
<td>5.3</td>
<td>(3.4-8.1)</td>
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<td>8.4</td>
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$^1$ developed by Gage BF, Yan Y Milligan PE, et al.
CHADS$^2$ is a clinical prediction rule\textsuperscript{1} for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF).

It is based on the following conditions:

- Congestive heart failure
- Hypertension: blood pressure consistently above 140/90 mmHg
- Age $\geq$ 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.

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\textsuperscript{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.

\[
[U] W_{\text{adjusted}} = [U] W \text{ in range} \times p(\text{in range}) + [U] W \text{ not in range} \times p(\text{not in range})
\]

- Where

\[
[U] W \text{ not in range} = [U] \text{ no AF} - ([U] \text{ no AF} - [U] W \text{ in range}) \times RR.
\]

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).