# Cost-effectiveness analysis of dabigatran etexilate in stroke prevention in patients with non-valvular atrial fibrillation in Spain

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## Introduction

- Atrial fibrillation (AF) is the leading cause of ischemic stroke and its importance as etiologic factor, increases with patient age[1].
- Evidence-based clinical guidelines recommend anticoagulation treatment in patients with AF and associated embolism risk[2].
- Vitamin K antagonists (warfarin) have showed high efficacy [3,4], but they require a narrow INR monitoring and frequent doses adjustments to avoid stroke or bleeding associated risks.
- The RE-LY study was designed to demonstrate the safety and efficacy of dabigatran (150 and 110 mg bid) for stroke prevention in non-valvular AF patients[5,6].

## Objective

Assessment of the cost-effectiveness of dabigatran for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation in Spain, under the National Health System perspective.

## Methods

**• MODEL DESIGN:**

- A sequential Markov model (Figure 1) which simulates the natural history of the disease in patients with non-valvular AF was adapted to the Spanish setting[7].
- Sequential model where all patients enter into the model with dabigatran 150mg (BID) and once aged 80 years they change to dabigatran 110 mg (BID), according to the summary of product characteristics.
- Markov cycle duration was 3 months with half-cycle correction.
- Cost and outcomes were discounted at a 3% rate[8].

**• CLINICAL EVENTS:**

- Patients could suffer any of the events described in Figure 1 or die.
- Patients who suffered an IS, HS or ICH could experience a change on the disability level.

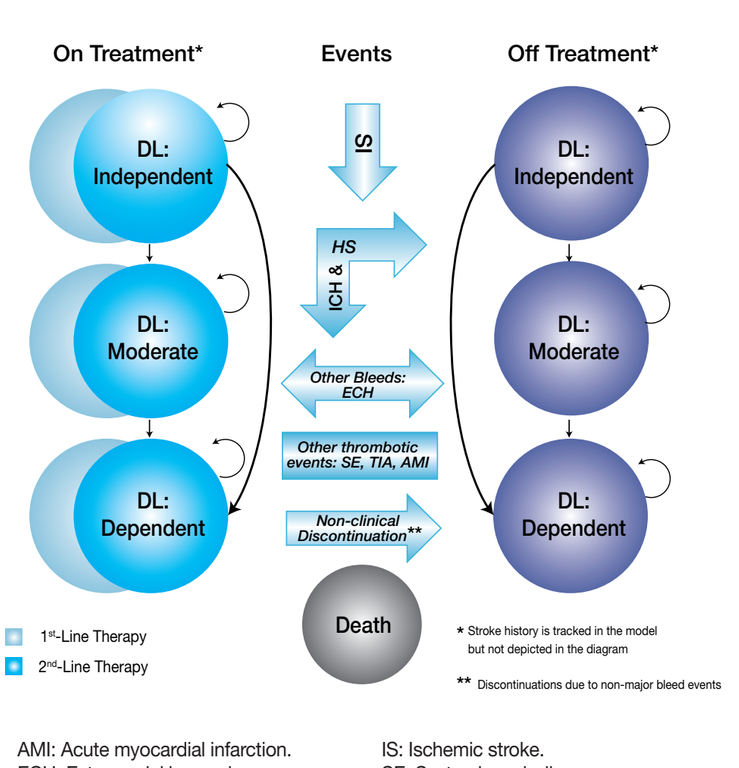
**• COMPARATORS:**

- First scenario: Warfarin.
- Second scenario: Real-world prescription pattern, 60% of patients treated with vitamin K antagonist, 30% with acetylsalicylic acid and 10% received no treatment.

**• INPUTS**

- A 10,000 patients cohort, totally independent and aged 69.1 years, following the RE-LY[5,6] patient profile (CHADS2 stroke risk and INR time in therapeutic range) was followed during a lifetime period.
- Clinical efficacy, disability and discontinuation rates and utility estimates were kept as in the original model[7].
- Age-adjusted, all cause mortality was obtained from Spanish national statistics[9].
- Costs (€, 2010) are detailed in Table 1.

**Figure 1. Sequential Markov model diagram**




AMI: Acute myocardial infarction.
ECH: Extracranial hemorrhage.
HS: Hemorrhagic stroke.
ICH: Intracranial hemorrhage.
IS: Ischemic stroke.
SE: Systemic embolism.
TIA: Transient ischemic attack.

- Deterministic and probabilistic sensitivity analyses (SA) were performed.
  - One-way deterministic SA was carried out with several parameters. Additionally the model was run, considering the societal perspective. Thus direct non-health care costs[10,11] were included. (Table 2)
  - A MonteCarlo SA (10,000 simulations) was also performed.

**Table 1. Unit cost (€, 2010)**

| DRUG | DAILY COST, Public cost + VAT (including RD 8/2010, 7,5% deduction) | DRUG | DAILY COST, Public cost + VAT (with RD 8/2010, 7,5% deduction) |
|---|---|---|---|
| Dabigatran 150mg (twice daily) | 3.03 [12] | Warfarin 2.1 mg | 0.05 [12] |
| Dabigatran 110mg (twice daily) | 3.03 [12] | Acetilsalicilic acid [average with 100 mg (70%) and 300 mg (30%)] | 0.10 [12] |
| **EVENT** | **COST** | **EVENT** | **COST** |
| Fatal IS | 4,237.76 [13] | Fatal ICH | 5,830.96 [13] |
| IS, Independent | 4,407.58 [13,14] | ICH, independent | 6,000.78 [13,14] |
| IS moderate disability | 4,827.18 [13,14] | ICH, moderate disability | 6,250.56 [13,14] |
| IS totally dependent | 5,483.06 [13,14] | ICH, totally dependent | 6,486.84 [13,14] |
| Fatal SE | 1,834.94 [13] | Fatal ECH | 3,724.68 [13] |
| Non-fatal SE | 1,834.94 [13] | Non-fatal ECH, no gastrointestinal | 2,581.82 [13] |
| TIA | 2,453.36 [13] | Non-fatal ECH, gastrointestinal | 2,581.82 [13] |
| Fatal, HS | 5,830.96 [13] | Minor bleeding | 188.96 [15] |
| HS, Independent | 6,000.78 [13,14] | Fatal AMI | 4,072.94 [13] |
| HS, moderate disability | 6,250.56 [13,14] | Non-fatal AMI | 4,072.94 [13] |
| HS, totally dependent | 6,486.84 [13,14] | | |
| **ASSOCIATED DISABILITY LEVEL** | **COST PER 3 FOLLOW-UP MONTHS** | **INR MONITORING** | **YEARLY COST** |
| Post-stroke, independent | 169.82 [14] | Well controlled patients | 382.83 [16,17] |
| Post-stroke, moderate disability | 419.60 [14] | Poor controlled patients | 472.70 [16,17] |
| Post-stroke, totally dependent | 655.88 [14] | | |

* assuming silent form for 11%

**Table 2: Incremental costs by disability level used for SA with societal perspective (€, 2010)**

| | Independent | Moderate disability | Totally dependent |
|---|---|---|---|
| **Drug costs** | | VAT taxes not included [12] | |
| For each IS, HS and ICH | | | |
| Investment (house renovation) [11] | 0.0 | 31.1 | 31.1 |
| Public institutionzalization [11] | 0.0 | 125.8 | 125.8 |
| For each 3 follow-up months period in post-stroke patients | | | |
| Private institutionalization [11] | 0.0 | 76.9 | 76.9 |
| Day-care centers [11] | 0.0 | 426.6 | 426.6 |
| Informal care (cost per hour = € 10.6) [10] | 5,970.1 | 9,596.6 | 11,958.9 |

## Results

- Dabigatran reduced the occurrence of clinical events in both scenarios, providing gains in quantity and quality of life. (Table 3)
- The incremental cost-effectiveness ratio (ICER) for dabigatran compared to warfarin was €17,581/QALY gained and €14,118/QALY gained when compared to the real world prescription pattern. (Table 3).

**Table 3. Cost-effectiveness analysis results**

| Perpatient (lifetime) | Drug cost (€, 2010) | Event cost (€, 2010) | Follow-up costs (€, 2010) | Total cost (€, 2010) | LYG | QALYs | Incremental costs | Incremental QALYs | ICER (€/QALY) |
|---|---|---|---|---|---|---|---|---|---|
| **SCENARIO 1 (dabigatran vs warfarina RE-LY)** | | | | | | | | | |
| Warfarin | 3,475 | 3,678 | 3,190 | 10,343 | 11.13 | 8.45 | 4,851 | 0.28 | 17,581 |
| Dabigatran | 8,857 | 3,409 | 2,927 | 15,193 | 11.39 | 8.73 | | | |
| **SCENARIO 2 (dabigatran vs real world prescription pattern)** | | | | | | | | | |
| Prescription pattern | 2,178 | 3,889 | 3,358 | 9,426 | 11.02 | 8.32 | 5,769 | 0.34 | 14,118 |
| Dabigatran | 8,857 | 3,409 | 2,927 | 15,193 | 11.39 | 8.73 | | | |

LYG: Life year gained. QALY: Quality Adjusted Life Year. ICER: Incremental cost-effectiveness ratio

- The model proved to be robust according to the SA performed. (Table 4)
- Probabilistic SA results show that for a €30,000/QALY threshold[18], probability of being cost-effective is 96.4% and 99.9% in first and second scenario.
- When the social costs were included in the analysis, dabigatran resulted in a dominant strategy (i.e. more effective and less costly).

**Table 4. Deterministic SA results**

| Parameter | BC Value | SA value | Dabigatran vs Warfarin RE-LY ICER (€/QALY) | Dabigatran vs Warfarin RE-LY Variation (%) vs BC | Dabigatran vs Prescription pattern ICER (€/QALY) | Dabigatran vs Prescription pattern Variation (%) vs BC |
|---|---|---|---|---|---|---|
| **BASE CASE (BC) RESULTS** | | | **17,581** | | **14,118** | |
| Discount rate | 3% | 0% | 15,127 | -14% | 11,971 | -15% |
| | | 5% | 19,348 | 10% | 15,684 | +11% |
| Time Horizon | Lifetime | 5 years | 57,719 | 228% | 52,160 | +269% |
| | | 10 years | 32,001 | 82% | 27,829 | +97% |
| Ischemic stroke Relative risk | <80 years: 0,77; >80 years: 0,82 | <80 a: 0.58; >80 a: 0.51 | 13,217 | -25% | 11,519 | -18% |
| dabigatran vs. Warfarin | | <80 a: 1.03; >80 a: 1.33 | 32,175 | +83% | 20,520 | +45% |
| Patients (%) post- ischemic stroke totally dependent | 150mg: 4,1%; 110mg: 0,1% | 150mg: 13.3%, 110mg: 14.6% | 21,475 | +22% | 16,137 | +14% |
| Time in INR therapeutic range (%)* | 64.5% | 72.6% | 21,095 | 20% | 15,072 | +7% |
| | | 57.1% | 13,952 | -21% | 12,776 | -10% |
| Patient average age | 69.1 years | +80 (82.9 years) | 24,034 | 37% | 17,501 | +24% |
| INR monitoring cost | 382.8 € | +20% | 15,202 | -13% | 13,954 | -7% |
| | 472.7 € | -20% | 19,563 | +11% | 14,921 | +6% |
| Total health cost | | +20% | 21,097 | 20% | 16,666 | +18% |
| | | -20% | 14,651 | -17% | 11,765 | -17% |
| Perspective | National Health System perspective | Societal perspective with non-health direct cost (table 3) | Dominant | | Dominant | |

## Conclusions

- From the Spanish National Health System perspective, dabigatran is an efficient strategy for the prevention of stroke in patients with non-valvular atrial fibrillation compared to warfarin and to the real-world prescription pattern. ICERs were below the €30,000/QALY threshold in both scenarios.
- From the societal perspective, dabigatran shows to be a dominant strategy, providing higher effectiveness and lower costs compared to both alternatives.

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