

Economic evaluation of dabigatran etexilate in stroke prevention in patients with non valvular atrial fibrillation

José R. González-Juanatey¹, José Álvarez-Sabin², José M Lobos³, Antoni Martínez-Rubio⁴, Joan C. Reverter⁵, Itziar Oyagüez⁶, Nuria González-Rojas⁷, Virginia Becerra⁷
¹ Servicio de Cardiología, Hospital Clínico Universitario de Santiago, Santiago de Compostela, A Coruña, Spain; ² Unidad Neurovascular, Servicio de Neurología, Hospital Universitario Vall d'Hebron, Universidad Autónoma de Barcelona, Barcelona, Spain; ³ Centro de Salud Jazmín, Area Este, Atención Primaria, Madrid, Spain; ⁴ Servicio de Cardiología, Hospital Universitari Parc Taulí, Sabadell, Barcelona, Spain; ⁵ Servicio de Hemoterapia Hemostasia, Hospital Clínic, Barcelona, Spain; ⁶ Pharmacoeconomics and Outcomes Research Iberia, Madrid, Spain; ⁷ Departamento de Economía y Resultados en Salud, Boehringer Ingelheim, Barcelona, Spain.

Introduction

- Atrial fibrillation (AF) is the leading cause of ischemic stroke and its importance as etiologic factor, increases with patient age¹.
- Evidence-based clinical guidelines recommend anticoagulation treatment in patients with AF and associated embolism risk².
- Vitamin K antagonists (warfarin) have shown high efficacy^{3,4}, but they require a narrow INR monitoring and frequent dosing 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

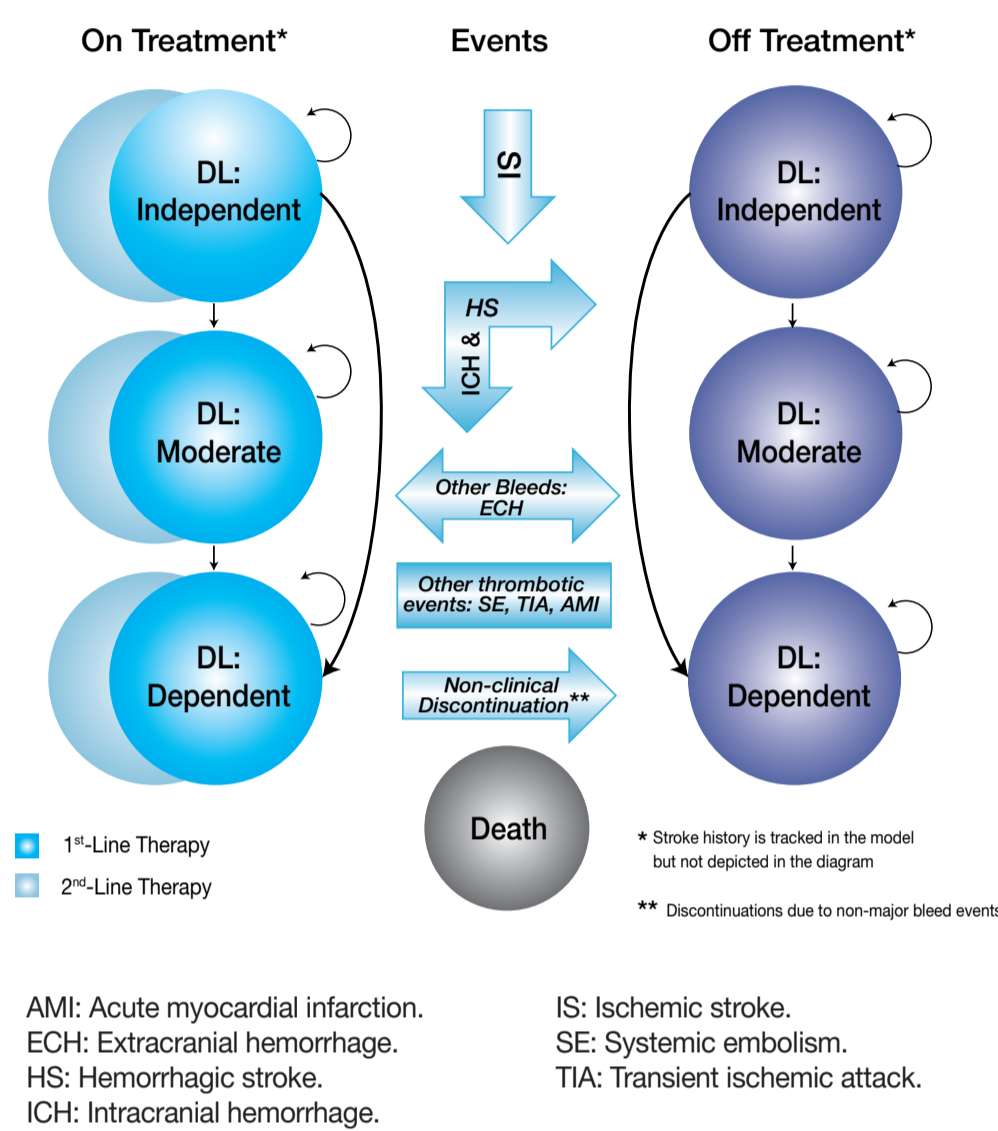
Assessment of the cost-effectiveness of dabigatran for stroke and systemic embolism prevention in patients with non-valvular atrial fibrillation in Spain, under the National Health System perspective.

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 setting⁷.
- Sequential model where all patients enter into it with dabigatran 150 mg (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% rate⁸.

Figure 1. Sequential Markov model diagram



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 worsening in the disability level.

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 model⁷.
- Age-adjusted, all cause mortality was obtained from Spanish national statistics⁹.
- Costs (€, 2010) are detailed in Table 1.

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	Acetylsalicylic 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 institutionalization 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

- 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.

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 threshold¹⁸, probability of being cost-effective is 96.4% and 99.9% in first and second scenario.

Table 4. Deterministic SA results

Parameter	BC Value	SA value	Dabigatran vs Warfarin RE-LY		Dabigatran vs Prescription pattern	
			ICER (€/QALY)	Variation (%) vs BC	ICER (€/QALY)	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 a: 0.58;	13,217	-25%	11,519	-18%
	>80 years: 0.82	>80 a: 0.51				
dabigatran vs. Warfarin		<80 a: 1.03;	32,175	+83%	20,520	+45%
		>80 a: 1.33				
Patients (%) post- ischemic stroke totally dependent	150mg: 4.1%;	150mg: 13.3%;	21,475	+22%	16,137	+14%
	110mg: 0.1%	110mg: 14.6%				
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	

- When the social costs were included in the analysis, dabigatran resulted in a dominant strategy (i.e. more effective and less costly) saving €698 per patient in the comparison versus warfarin and 4,128€ per patient versus real word prescription pattern.

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.

References

- García-Castelo A et al. Int J Cardiol. 2011;153:68-73.
- Cam AJ et al. Eur Heart J. 2010;31:2369-429.
- Singer DE et al. Ann Intern Med. 2009;151:297-305.
- Hobbs FD. QJM. 2011;104:739-46.
- Connolly SJ et al. NEJM. 2009;361:1139-51.
- Connolly SJ et al. NEJM. 2010;363:1875-6.
- Sorensen SV et al. Thromb and Haem. 2011;105:908-19.
- Lopez Bastida et al. Eur J Health Econ 2010;11:513-20.
- Statistics National Institute. Mortality tables. Available at URL: www.ine.es (accessed 2010, april 21st).
- Hidalgo A et al. Gac Sanit. 2011; 25(Espec Congr 1):1-2.
- Hervas-Angulo A et al. Rev Neurol.2006;43:518-25.
- Health Ministry. Nomenclator DIGITALIS-INTEGRA. Available at URL: http://www.msc.es/profesionales/farmacologia/nomenclatorDI.htm (accessed 2011, March).
- Health Ministry. Available at URL: http://www.msc.es/estadEstudios/estadisticas/inforRecopilaciones/anaDesarrolloGDR.htm
- López-Bastida J et al. The Social Economic Costs and Health-Related Quality of Life of Stroke Survivors in the Canary Islands Spain. Working paper.
- eSalud database. Available at URL: www.oblikue.com (accessed 2011, october 10th).
- de Solà-Morales Serra O CatSalut. Generalitat de Catalunya;2003.
- Navarro JL et al. Rev Esp Cardiol. 2007;60:1226-32.
- Sacristán JA et al. Gac Sanit. 2002;16:334-43.