



ORIGINAL  
RESEARCH

# Budget impact analysis of dabigatran compared with rivaroxaban in the prevention of the thromboembolic risk in patients with non-valvular atrial fibrillation

Maria Grazia Celeste<sup>1</sup>, Francesca De Marco<sup>2</sup>, Claudio Fresco<sup>3</sup>, Giuseppe Musumeci<sup>4</sup>, Roberto Ravasio<sup>5</sup>

<sup>1</sup>UOC Farmacia Clinica, Fondazione PTV Policlinico Tor Vergata, Rome, Italy

<sup>2</sup>UOC Pronto Soccorso e Breve Osservazione. Azienda Ospedaliera San Giovanni Addolorata, Rome, Italy

<sup>3</sup>Dipartimento Cardiotoracico Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy

<sup>4</sup>S.C. Cardiologia, Ospedale Santa Croce e Carle, Cuneo, Italy

<sup>5</sup>Health Publishing & Services Srl, Milan, Italy

## ABSTRACT

**BACKGROUND:** Dabigatran 150 mg BID (D150) and rivaroxaban 20 mg (R20) are indicated for the prevention of thromboembolic events in patients with Non-Valvular Atrial Fibrillation (NVAf). Outcomes from observational study demonstrated that D150 and R20 reduced the rate of thromboembolic events.

**OBJECTIVE:** This analysis estimated the budget impact of the use of D150 and R20 for the treatment of NVAf patients in Italy.

**METHODS:** A budget-impact model (BIM) was developed to estimate the direct costs up to 12 months from an Italian NHS perspective. The resource utilization (drugs and intracranial hemorrhage or major extracranial bleeding event) was derived from an observational study. Only direct medical costs were considered. Ex-factory prices and National Tariffs were considered to estimate the costs of drugs and medical resource used, respectively. The BIM showed the difference of expenditure and clinical events (intracranial hemorrhage or major extracranial bleeding) generated by the base case calculated for current prescription volumes (D150 30%, R20 100%), and for different prescription volume scenarios (D150 at 70% and 100%). Key variables were tested in the sensitivity analysis.

**RESULTS:** D150 was associated with a medical cost offset driven by fewer intracranial hemorrhage and major extracranial bleeding event, these offset the incremental drug cost and results in an annual saving per patient treated (D150: € 1,052.78; R20: € 1,161.23). The present scenario determines an annual cost of € 262,543,583. The impact of total annual costs for the Italian NHS would be lower if D150 prescription volumes would be higher. The total cost is predicted to decrease by 3.8% if the D150 prescription increase to 70% and it is predicted to decrease by 6.7% if the D150 prescription increase to 100%.

**CONCLUSION:** The use of D150, as an alternative to R20 to prevent events in patients with NVAf, could represent a cost-saving option for the Italian NHS.

## Keywords

*Dabigatran, Rivaroxaban; Non-Valvular Atrial Fibrillation; Budget impact analysis*

## INTRODUCTION

Oral anticoagulant treatment with either vitamin K antagonist or non-vitamin K antagonist is essential for the prevention of stroke or systemic embolism and all cause of mortality in patients with non-valvular atrial fibrillation. Direct thrombin inhibitor dabigatran etexilate (hereinafter referred to as “dabigatran”)

[1] and direct factor Xa inhibitor rivaroxaban [2] are two non-vitamin k oral anticoagulants (NOACs). They showed a better efficacy profile compared to warfarin, as well as a greater simplicity of dosage, since they don't require a periodic monitoring of the prothrombin time (expressed through the INR – International Normalized Ratio – index) [3,4].

**Corresponding author**  
Roberto Ravasio  
rravasio@aboutpharma.com

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In the RE-LY study, 18,113 patients with Non-Valvular Atrial Fibrillation (NVAF) were followed for two years, with the aim of comparing dabigatran 150 mg BID (*bis in die*) and 110 mg BID vs warfarin [3]. The incidence of the events stroke or systemic embolism formed the primary efficacy endpoint investigated by the study, while the presence of major bleeding was the primary safety endpoint. In the comparison with warfarin, dabigatran 150 mg significantly reduced the primary efficacy endpoint (Relative Risk – RR: 0.66; 95% CI: 0.53-0.82;  $p < 0.001$ ), while the improvement associated with dabigatran 110 mg (RR: 0.91; 95% CI: 0.74-1.11;  $p = 0.34$ ) was not significant [3]. Dabigatran 150 mg resulted in a borderline significant reduction in mortality (RR: 0.88; 95% CI: 0.77-1.00;  $p = 0.051$ ) [3]. Again compared to warfarin, the reduction in the incidence of major bleeding with dabigatran 110 mg was significant (RR dabigatran: 0.80; 95% CI: 0.69-0.93;  $p = 0.003$ ), while it was not for dabigatran 150 mg (RR: 0.93; 95% CI: 0.81-1.07;  $p = 0.31$ ) [3].

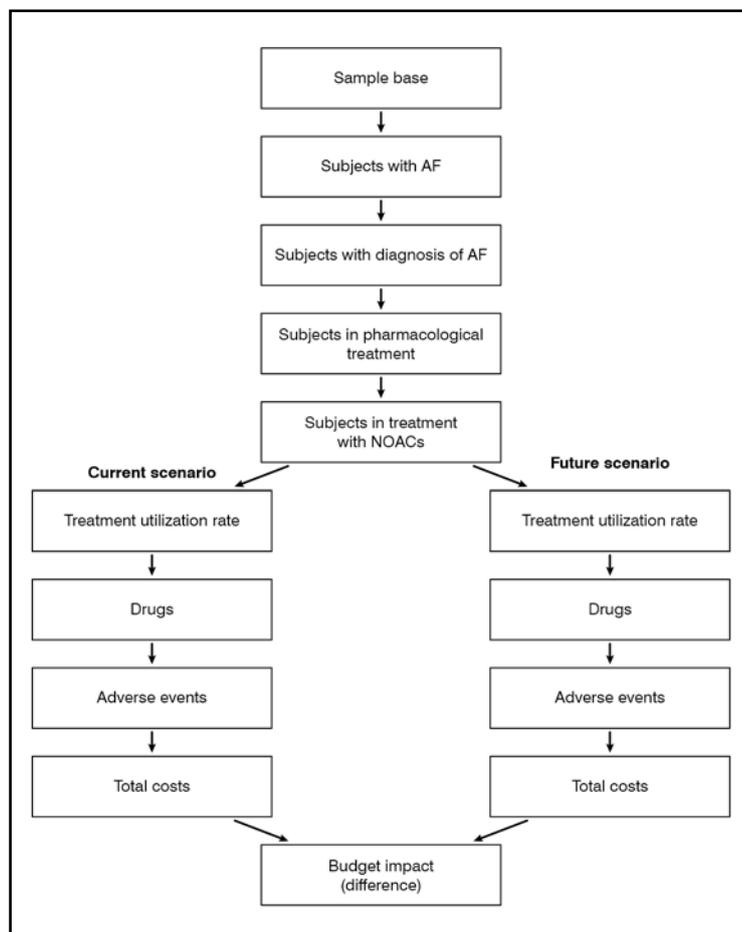
The ROCKET-AF study observed – during a 19-month (mean) follow-up – 14,264

NVAF patients treated with rivaroxaban 20 mg daily or warfarin [4]. Also in this case, the primary efficacy endpoint was the incidence of the events stroke or systemic embolism, while the primary safety endpoint was constituted by major or clinically relevant minor bleeding. In the *Per-Protocol* analysis, stroke or systemic embolism occurred in 188 patients receiving rivaroxaban (1.7% per year) and in 241 patients receiving warfarin (2.2% per year) (Hazard Ratio – HR: 0.79; 95% CI: 0.66-0.96;  $p < 0.001$  non-inferiority) [4]. In the analysis referred to the *Intention-To-Treat* population (which included all events, from randomization to the completion of the study, regardless of how correctly patients had assumed the comparator drugs), a substantial equality between rivaroxaban and warfarin in the prevention of the primary efficacy endpoint was achieved (HR: 0.88; 95% CI: 0.74-1.03;  $p = 0.12$ ) [4]. However, mortality from all causes (4.5% and 4.9% per year, respectively; HR: 0.92; 95% CI: 0.82-1.03;  $p = 0.15$ ) and the primary safety endpoint (14.9% and 14.5% per year, respectively; HR: 1.03; 95% CI: 0.96-1.11;  $p = 0.44$ ) did not show statistically significant differences between the two treatment groups [4].

Since the results of a recent economic evaluation conducted at national level suggest the cost-effectiveness of dabigatran and rivaroxaban compared with warfarin in the prevention treatment of NVAF patients [5], it seemed appropriate to assess the financial impact on the National Health Service (NHS), through a Budget Impact Analysis (BIA) aimed at estimating the sustainability. As a secondary objective, the BIA estimated the economic impact due to the use of idarucizumab in patients treated with dabigatran. Idarucizumab, in fact, is a monoclonal antibody used in the cases of emergency/urgency in which a rapid and specific inactivation of the anticoagulant effect of dabigatran is required [6].

## METHODS

The BIA was conducted from the Italian NHS perspective. Direct healthcare consumption considered in the Budget Impact Model (BIM) describe, for NVAF patients, the cost of treatment with the two NOACs and the management of potential associated events, such as thromboembolic stroke, intracranial hemorrhage or major extracranial bleeding. The analysis did not consider other direct medical costs, nor indirect costs. The time horizon covered by the model is 1 year. The BIM structure is illustrated schematically in Figure 1. This BIA was carried out



**Figure 1.** Budget Impact model structure

AF = atrial fibrillation

by following the Guidelines of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [7,8].

## Assumptions and input data

### Clinical Data

The clinical data used for the comparison between dabigatran and rivaroxaban derive from the results of the retrospective observational analysis conducted by Graham and colleagues [9]. This analysis was performed with the aim to compare the rates of risk for thromboembolic stroke, intracranial hemorrhage, major extracranial bleeding (including gastrointestinal bleeding) and mortality for NVAf patients in prevention treatment with dabigatran 150 mg (BID) or with rivaroxaban 20 mg. Between November 2011 and June 2014, the analysis collected the data from 118,891 NVAf patients (Medicare) aged  $\geq 65$ , of which 52,240 being treated with dabigatran and 66,651 with rivaroxaban. Compared to dabigatran, the use of rivaroxaban resulted in a non-significant reduction in thromboembolic stroke (HR 95% CI: 0.80;  $p = 0.7$ ) and a significant increase in the risk for intracranial hemorrhage (HR 95% CI: 1.58;  $p = 0.002$ ) and major extracranial bleeding (HR 95% CI: 1.47;  $p < 0.001$ ), including gastrointestinal bleeding (HR 95% CI: 1.39;  $p < 0.001$ ).

From the study by Graham and colleagues, this analysis considered the efficacy data related to i) intracranial hemorrhages and ii) major extracranial bleeding; that is, the only events for which a statistically significant difference between the two pharmacological options considered here were identified [9].

### Population

The number of patients was estimated starting from the population resident in Italy on 1<sup>st</sup> January 2016 [10]. By applying a 2% prevalence rate [11], the population with AF was then calculated. From this, through market surveys and IMS data [12,13], it was possible to stratify the population to determine the number of NAVF patients treated with dabigatran 150 mg and rivaroxaban 20 mg. Such selection was made so that the population subject of the BIM was homogenous to that considered in the study of Graham and colleagues [9], on which this analysis is based. This choice, however, has in actual fact excluded from the analysis the low doses of dabigatran (110 mg), rivaroxaban (15 mg) and two other NOACs (apixaban and edoxaban) with indication for the prevention treatment of NVAf patients. Table I shows in detail the flow of patients.

	n.	Source
Population resident in Italy on 1 January 2016 (n.)	60,795,612	[10]
Patients with AF (2%)	1,215,912	[11]
Patients with diagnosis of AF (84%)	1,021,366	[12]
Patients with diagnosis of AF in pharmacological treatment (92%)	939,657	[12]
Patients with diagnosis of AF in pharmacological treatment with NOACs (65%)	610,702	[12]
Patients in treatment with dabigatran (28.2%)	172,292	[13]
• of whom in treatment with dabigatran 150 mg (40.8%)	70,295	[13]
Patients in treatment with rivaroxaban (42%)	256,495	[13]
• of whom in treatment with rivaroxaban 20 mg (63.3%)	162,361	[13]

**Tabella I.** Population subject of the budget impact analysis

### Drugs

In accordance with the time frame of one year, to which the risk rates estimated by the study of Graham and colleagues [9] are related, an administration period of 12 months was assumed for dabigatran and rivaroxaban, at an average daily dose of 150 mg BID (two 150 mg capsules) and 20 mg (one 20 mg tablet), respectively [9].

In the base case, an average cost per treatment day of € 2.23 for dabigatran and € 2.20 for rivaroxaban was considered. These costs reflect the relevant ex-factory prices, net of the discounts required by law (-5%).

In the sensitivity analysis, two other scenarios that, instead, reflect alternative price hypotheses for the two NOACs are presented. In addition to the discounts required by law (base case), further discounts – negotiated between the Regulatory Body (AIFA, the Italian Drug Agency) and the Pharmaceutical Companies – were considered. Unlike what happens for rivaroxaban, whose net price is generated by the application of a confidential discount, the additional discount applied to dabigatran is composed of a fixed part (confidential discount for public facilities) and a variable portion, linked to a price-volume agreement. According to the price-volume agreement, additional incremental discounts are applied to the sale price to public structures, provided by the company in the form of payback, based on specific brackets of annual expenditure. In the first scenario, a parity price condition for the two treatments was simulated [14,15]. In the second, based on the most recent market data, we tried to present a situation that would reflect the actual sales prices to public structures of the two NOACs, a scenario in which dabigatran would have a lower average cost per treatment day compared to rivaroxaban [14,15].

	Without idarucizumab				With idarucizumab			
	GI	IC	OB	ES	GI	IC	OB	ES
Idarucizumab	0.00	0.00	0.00	0.00	2,369.06	2,369.06	2,369.06	2,369.06
Diagnostic procedures	93.13	125.50	42.00	31.27	93.13	125.50	42.00	31.27
Treatments	3,112.30	3,769.07	3,140.74	1,098.29	606.47	773.16	624.90	66.36
Hospitalizations	8,800.17	8,800.17	8,800.17	1,855.25	6,766.39	8,800.17	6,766.39	10,859.48
Complications	247.69	274.81	247.69	732.96	12.90	12.90	12.90	281.99
ES	0.00	0.00	0.00	6,047.47	0.00	0.00	0.00	6,047.47
<b>Total</b>	<b>12,253.29</b>	<b>12,969.55</b>	<b>12,230.60</b>	<b>19,765.23</b>	<b>9,847.95</b>	<b>12,080.79</b>	<b>9,815.25</b>	<b>19,655.63</b>

**Table II.** Mean cost per patient without and with idarucizumab

GI = gastrointestinal bleeding; IC = intracranial bleeding; OB = other type of bleeding; ES = emergency surgery

### Number and cost of the events

The BIM also provided an estimate of the average annual number of events associated with the two therapeutic strategies: intracranial hemorrhage and major extracranial bleeding. These events were subsequently quantified using the costs reported in a recent Italian analysis, which assessed the cost-effectiveness of the non-vitamin k oral anticoagulants in the prevention therapy in NVAF patients [16]. An average cost of € 14,500 for the intracranial hemorrhage event (this amount takes into account the management of a moderate stroke – *Barthel Index*  $\leq 14$  and  $\geq 10$  – and a possible disability) and € 6,940.80 for the major extracranial bleeding event were considered. By means of the sensitivity analysis, in addition to the base case, two other scenarios in which the event management cost was reduced first by 30% and then by 50% were evaluated.

### Market Share

The market shares considered in the base case, equal to 30% and 70%, respectively, represent the percentage of current use of dabigatran 150 mg and rivaroxaban 20 mg in the prevention treatment of NVAF patients [12,13]. These percentages were calculated by relating the number of patients treated with dabigatran 150 mg (70,295) or rivaroxaban 20 mg (162,361) to the total of patients considered in the BIM (232,656) (Table I).

In addition to the base case – which had the purpose of providing a dimension of the current annual expenditure generated by the use of the two NOACs (high doses) in the prevention treatment of NVAF patients – two alternative scenarios are presented, in which the market share of dabigatran 150 mg covers 70% or 100% of the patients treated. These alternative scenarios have the function to highlight the financial impact associated with a possible switch from rivaroxaban 20 mg to dabigatran 150 mg.

### Impact of idarucizumab

The economic impact borne by the NHS and generated by idarucizumab was evaluated only for the additional number of patients who, with regard to the base case, would be treated in the alternative scenarios (dabigatran 70% and 100%), following the switch from rivaroxaban 20 mg to dabigatran 150 mg. The use of idarucizumab only for patients treated with dabigatran is in line with the current therapeutic indications of the product [6]. Idarucizumab is in fact a specific inactivator of dabigatran, in the cases where the rapid inactivation of its anticoagulant effects is necessary (emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding). Most of the data used here to estimate the financial impact of idarucizumab refer to what was found by Belisari and colleagues [17]. Thanks to the results of the REVERSE AD study [18] and the data collected through the CORE-CINECA database [19], it is estimated that 0.48% of patients receiving dabigatran may cope with an emergency surgery (ES), while 1.05% can manifest uncontrolled or life-threatening bleeding events. The latter were divided into gastrointestinal bleeding (GI – 39.2%), intracranial bleeding (IC – 35.3%) and other type of bleeding (OB – 25.5%) [18]. The estimate of the healthcare resources needed for the management of uncontrolled or life-threatening bleeding

Healthcare costs item	Cost per patient (€)		
	Dabigatran 150 mg	Rivaroxaban 20 mg	$\Delta$
Drugs	813.95	803.00	10.95
Intracranial hemorrhage	54.17	84.71	-30.54
Major extracranial bleeding	184.65	273.52	-88.87
<b>Total</b>	<b>1,052.78</b>	<b>1,161.23</b>	<b>-108.45</b>

**Table III.** Mean annual treatment cost

and emergency surgery reproduces what was calculated by the study of Belisari and colleagues [17], to which it is hereby referred to for details. Table II shows the overall cost per patient treated for each of the events considered in the hypothesis of use or non-use of idarucizumab.

## Output data of the model

### Budget Impact

In relation to the estimated number of treatable patients and the average annual cost associated therewith (pharmacological treatment and management of events), the results of the BIM describe – during 12 months of analysis – the difference in the spending generated by the base case scenario with respect to two alternative scenarios, in which an increase in the market shares of dabigatran 150 mg (70% and 100%) is assumed. In addition to the expenditure data, the BIM provides for the same comparison also the variation in the number of events avoided (intracranial hemorrhage and major extracranial bleeding). Finally, as a secondary objective, the BIM presents the budget impact resulting from the use of idarucizumab in patients who were being treated with rivaroxaban 20 mg and who were then switched to dabigatran 150 mg.

## RESULTS

### Dabigatran vs rivaroxaban (base case)

#### Cost per patient treated

The patient treated with dabigatran 150 mg shows a reduction of 9.3% (€ -108,45) in the mean annual cost with regard to that associated with the patient being treated with rivaroxaban 20 mg (Table III). The higher cost associated with the drug therapy (+1.4%; € 10.95) is completely offset by the lower cost for the management of intracranial hemorrhage (-36.1%; € -30.54) and major extracranial bleeding (-32.5%; € -88.87).

#### Expenditure borne by the NHS

The annual expenditure borne by the NHS, calculated on the current number of patients in treatment with the two therapeutic strategies (dabigatran 150 mg: n. = 70,295; rivaroxaban 20 mg: n. = 162,361) is equal to € 262,543,628, of which € 74,004,954 generated by dabigatran 150 mg and € 188,538,628 by rivaroxaban 20 mg (Figure 2). The number of events that would occur during the year would amount to 9,480, of which 1,211 due to intracranial bleeding and 8,268 to major extracranial bleeding (Figure 3).

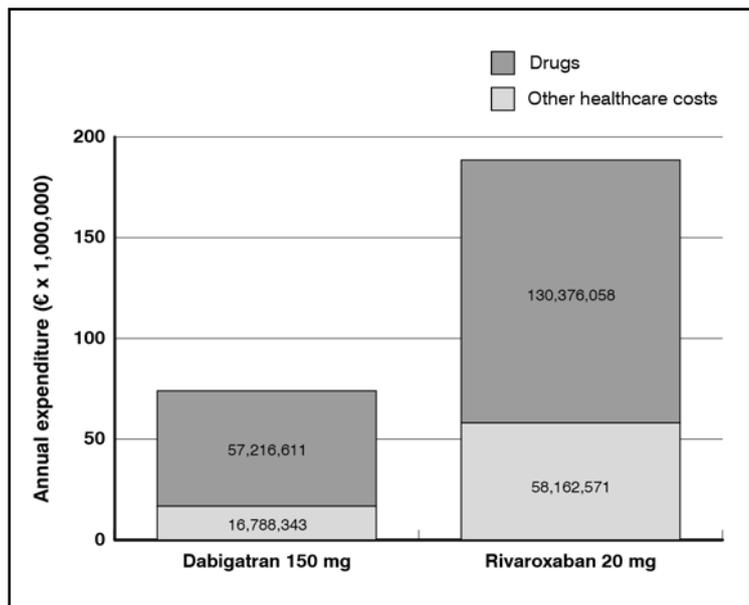


Figure 2. Annual expenditure borne by the NHS: base case scenario

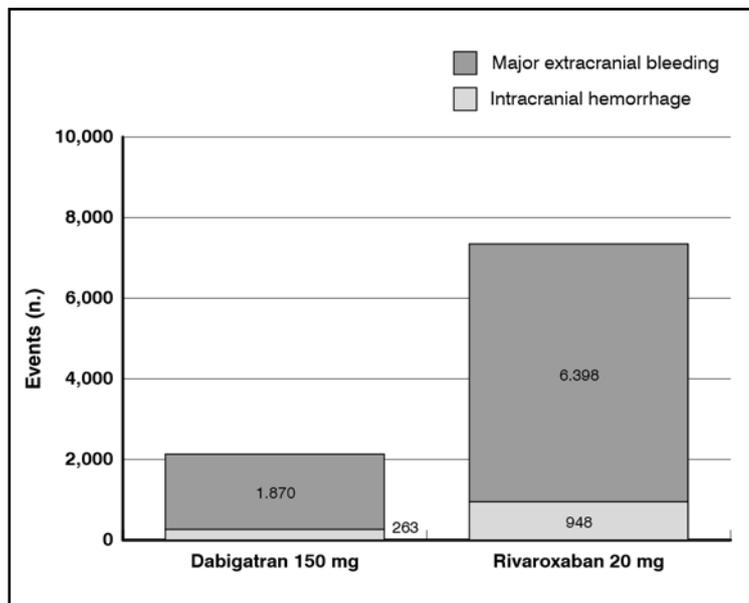


Figure 3. Number of events: base case scenario

In correspondence of an increase in the market share of dabigatran 150 mg that, compared to the base case scenario, would lead to treat 70% or 100% of NVAF patients, there would be at the same time a significant reduction in the expenditure borne by the NHS (dabigatran 150 mg 70% : -3.8% [€ -10,038,831]; dabigatran 150 mg 100%: -6.7% [€ -17,608,472]) and a slight increase in the number of the events avoided (dabigatran 150 mg 70%: +1,380 events avoided; dabigatran 150 mg 100%: +2,241 events avoided) (Figure 4).

#### Sensitivity analysis

Table IV shows the main results of the sensitivity analysis. The two scenarios that in-

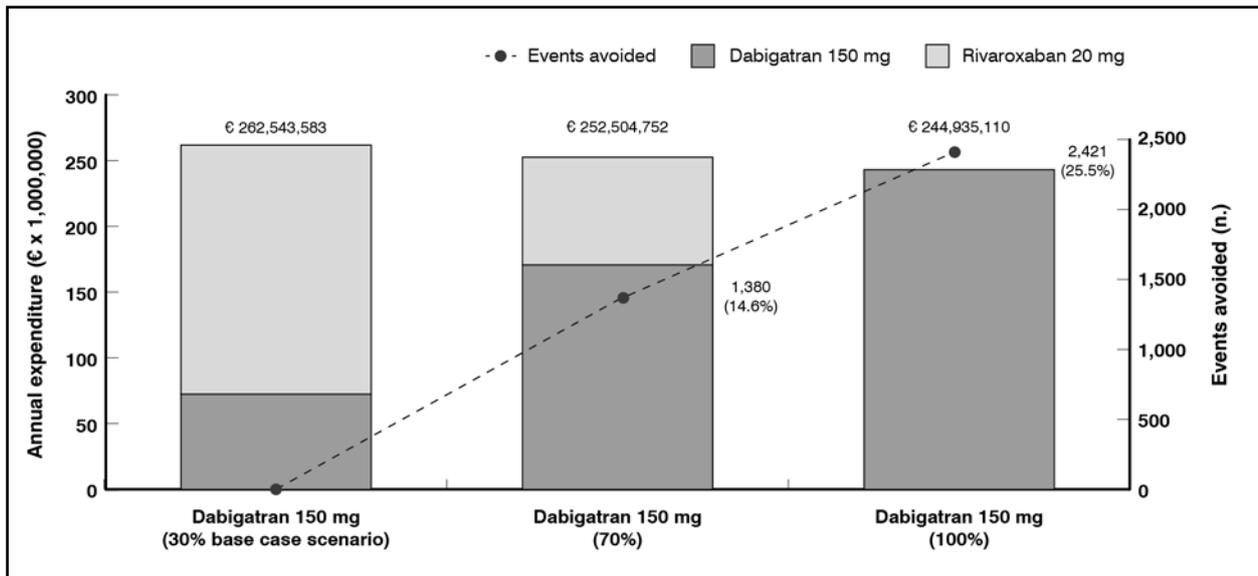


Figure 4. Annual expenditure borne by the NHS: base case scenario vs increase in the market share of dabigatran 150 mg

Scenario	Vs base case <sup>1</sup>	Vs dabigatran 150 mg 70% <sup>2</sup>	Vs dabigatran 150 mg 100% <sup>2</sup>
Base case (€)	262,543,583	252,504,752	244,935,111
• Variation (€)		-10,038,831	-17,608,472
• Variation (%)		-4.0	-7.2
Parity price (€) [14,15]	217,615,704	206,563,293	198,229,376
• Variation (€)	-44,927,879	-11,052,411	-19,386,328
• Variation (%)	-17.1%	-5.4%	-9.8%
Lower cost/die dabigatran (€) [14,15]	216,845,973	204,779,983	195,681,790
• Variation (€)	-45,697,610	-12,065,991	-21,164,183
• Variation (%)	-17.4	-5.9	-10.8
-30% event costs (€) <sup>3</sup>	240,058,309	233,335,201	228,265,735
• Variation (€)	-22,485,274	-6,723,108	-11,792,574
• Variation (%)	-8.6	-2.9	-5.2
-50% event costs (€) <sup>3</sup>	225,068,126	220,555,500	217,152,817
• Variation (€)	-37,475,457	-4,512,626	-7,915,309
• Variation (%)	-14.3	-2.0	-3.6

Table IV. Sensitivity analysis

<sup>1</sup>Variations are calculated compared to the base case scenario

<sup>2</sup>Variations are calculated compared to the alternative scenarios

<sup>3</sup> Major extracranial bleeding and intracranial hemorrhage

volve the inclusion of additional discounts for dabigatran 150 mg (discount to public facilities and price-volume agreement) and rivaroxaban 20 mg (discount to public facilities) result in a reduction in the expenditure of around 17%, compared to the base case. Compared to the base case, the 30% or 50% reduction in the costs considered to quantify intracranial hemorrhage and major extracranial bleeding causes a variation in the 8.6-14.3% range.

Considering instead the alternative scenarios, in which an increase in the number of patients treated with dabigatran 150 mg (70%

and 100%) is assumed, no parameter determines any significant variations of the results vs the base case (never higher than 11%). Finally, the situation in which all patients are treated with rivaroxaban 20 mg was also evaluated. The expenditure for the NHS would increase by 2.9% compared to the base case (€ 270,167,248 vs € 262,543,628), with an increase of 11.1% in the number of events (10,528 vs 9,480).

### Idarucizumab

In view of the increases in the number of patients treated with dabigatran 150 mg assumed

in the alternative scenarios (scenario 70%: +92,564 patients; scenario 100%: +162,361 patients) compared to the base case, 1,416 (scenario 70%) and 2,484 (scenario 100%) events would occur in which idarucizumab could be administered to quickly inactivate the anticoagulant effects of dabigatran (emergency surgery/urgent procedures and life-threatening or uncontrolled bleeding) (Table V). The use of idarucizumab would result in additional reductions in the treatment costs of € 1,868,758 and € 3,277,870, respectively (Table V).

## DISCUSSION AND CONCLUSIONS

With the aim of providing a realistic scenario of the expenditure incurred by the NHS for the management of NAVF patients treated with dabigatran 150 mg or rivaroxaban 20 mg, the BIM did not only provide a financial estimate of the pharmacological costs alone, but – in a more extended perspective – also considered the costs associated with the management of intracranial hemorrhage and major extracranial bleeding, events for which a significant difference between the two NOACs was recorded [9]. With regard to the base case scenario, a greater use of dabigatran 150 mg would lead to a reduction in both the healthcare expenditure borne by the NHS (dabigatran 150 mg 70%: -3.8%; dabigatran 150 mg 100%: -6.7%) and the number of intracranial hemorrhage (dabigatran 150 mg 70%: -16.1%; dabigatran 150 mg 100%: -28.2%) and major extracranial bleeding (dabigatran 150 mg 70%: -14.3%; dabigatran 150 mg 100%: -25.1%).

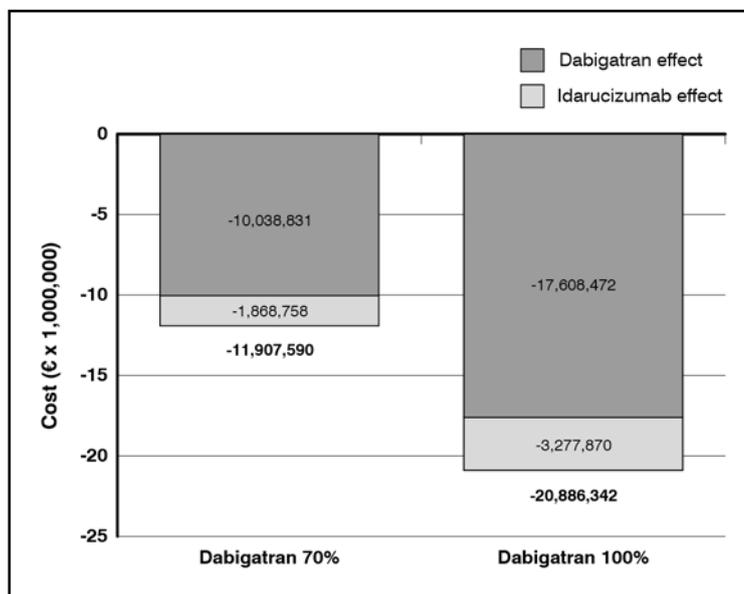
The subsequent adoption of idarucizumab in the cases of additional patients treated with dabigatran, for whom the rapid inactivation of the anticoagulant effects becomes necessary, would result in a further reduction in the overall cost of the management of the clinical events (gastrointestinal, intracranial, extracranial bleeding and other type of bleeding) equal to about € 1.8 million for the scenario dabigatran 150 mg: 70% and € 3.3 million for the scenario dabigatran 150 mg: 100%.

The dual effect determined by the increase in market shares of dabigatran 150 mg and the use of idarucizumab would result in an overall reduction in the expenditure borne by the NHS of around € 12 million (dabigatran 70%) or € 21 million (dabigatran 100%) (Figure 5).

As is the case whenever it is necessary to use a simulation model, the results should be read in light of some remarks/limitations. Perhaps the most critical aspect is the choice of the clinical data used to populate the BIM. Since

	Dabigatran 150 mg scenario	
	70%	100%
Increases in the number of patients treated with dabigatran 150 mg compared to rivaroxaban (n.)	92,564	162,361
Total events/year (n.)	1,416	2,484
• GI bleeding	381	669
• Intracranial hemorrhage	343	602
• Other type of bleeding	248	435
• Emergency surgery	444	779
<b>Costs (€) – Scenario without idarucizumab (A)</b>		
• GI bleeding	4,670,309	8,191,891
• Intracranial hemorrhage	4,448,979	7,803,670
• Other type of bleeding	3,030,078	5,314,867
• Emergency surgery	8,781,869	15,403,716
Total	20,931,236	36,714,144
<b>Costs (€) – Scenario with idarucizumab (B)</b>		
• GI bleeding	3,753,518	6,583,806
• Intracranial hemorrhage	4,144,104	7,268,907
• Other type of bleeding	2,431,686	4,265,265
• Emergency surgery	8,733,170	15,318,296
Total	19,062,478	33,436,274
<b>Difference Scenario B - A</b>	<b>-1,868,758</b>	<b>-3,277,870</b>

**Table V.** Economic impact of idarucizumab  
GI = gastrointestinal



**Figure 5.** The dual effect determined by the increase in market shares of dabigatran and the use of idarucizumab

the objective of the analysis was the direct (head-to-head) comparison between the two molecules, the analysis focused on what was available in the literature. The two pivotal clinical trials were excluded because they had been conducted to estimate the efficacy and safety of dabigatran [3] or rivaroxaban

[4] vs. warfarin alone. Also the results of subsequent indirect comparison studies were not considered suitable, since they had been conducted on non-homogeneous populations and therefore, in actual fact, were not comparable [20,21]. From the clinical studies, research was then directed towards real life observational analyses. Four large retrospective observational analyses were therefore identified, three conducted in Europe [22-24] and one in the United States [9]. The three European analyses, all carried out on Danish registers, concern approximately 140,000 patients diagnosed with NVAF in treatment with dabigatran (150 mg/110 mg), rivaroxaban (15 mg/20 mg), apixaban (2.5 mg/5 mg) or warfarin. Despite the fact that they present an overall better efficacy profile (mortality rate, bleeding, or major bleeding) for dabigatran compared with rivaroxaban, in our view these analyses are characterized by a basic limitation of the study design, which in fact precluded their choice: clinical outcomes are always calculated with respect to warfarin, and not between NOACs [22-24]. Unlike the observational analysis of Graham and colleagues, conducted on approximately 120,000 patients enrolled in the Medicare program, it is the only one to have been conducted with the objective to compare directly dabigatran 150 mg with rivaroxaban 20 mg, highlighting, when present, any significant differences between the two treatment groups [9]. For this reason, our choice fell on the latter observational analysis [9]. The adoption of the results of the observational analysis by Graham and colleagues [9], as a clinical basis of this budget impact model, is not in turn exempt from some criticism, such as the exclusion of the low doses of dabigatran (110 mg) and rivaroxaban (15 mg), the American patient case histories and the fact that it includes only patients aged over 65. As a partial justification of these limits, it is emphasized that the observational analysis of Graham and colleagues [9] reflects results similar to

those found by Larsen and colleagues [22] in the comparison between high doses of dabigatran and rivaroxaban.

The sensitivity analysis tried to overcome, as far as possible, the limitations associated with other assumptions adopted, such as the price of the drugs or the cost associated with the management of intracranial hemorrhage and major extracranial bleeding. All comparisons substantially confirmed the results of the base case.

A recent study [25] assessed the cost-effectiveness of dabigatran 150 mg BID versus rivaroxaban 20 mg QD for the treatment of patients with NVAF; the assessment was conducted using clinical events based on a US real-world evidence study by Graham et al. [9]. The same real-world data set was considered in our analysis. Patients on dabigatran were found to experience fewer bleeding events than patients on rivaroxaban. This lower incidence in bleeding events led to lower costs among dabigatran which in turn was the key driver in the US study conclusion that dabigatran was dominant over rivaroxaban in the US Medicare setting.

In conclusion, we believe that this analysis presents a reliable scenario – deriving from the use of dabigatran 150 mg and rivaroxaban 20 mg in the treatment of NAVF patients in Italy – of how a larger prescription of dabigatran 150 mg may result in a lower cost for the NHS. Since this analysis is one of the first attempts, it would be desirable, in the near future, to be able to confirm this result against what will be evidenced by the clinical practice. Data obtained from Italian registers will in fact be able to definitively validate the analyses deriving from the impact budget models.

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#### Conflict of interest

The authors have no conflict of interest to declare.

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