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Cost Effectiveness and Resource Allocation

RESEARCH

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Cost-effectiveness of dabigatran for thromboembolic events prevention in atrial fibrillation patients in Chile

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Abstract

Background Atrial fibrillation (AF) is the most common sustained arrhythmia in adults, associated with significant morbidity, mortality, and economic burden due to thromboembolic events. In Chile, acenocoumarol is the most widely used anticoagulant, while access to direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, and apixaban remains limited for AF patients. Among DOACs, dabigatran is the only one with an approved specific reversal agent (idarucizumab) available in the Chilean public system. Evaluating the cost-effectiveness of these alternatives is critical for informing resource allocation.

Aims To evaluate the cost-effectiveness of dabigatran compared to acenocoumarol, rivaroxaban and apixaban, for thromboembolic events prevention in atrial fibrillation (AF) patients, from the Chilean public health payer perspective.

Methods A Markov cohort model was used to represent the natural history of AF in terms of ischemic and hemorrhagic complications. Direct costs were obtained from local official sources and converted to US dollars (1 USD = 710.9 CLP at 2022). Data about major events and utilities were obtained from the literature. We applied an undifferentiated discount rate of 3% for costs and outcomes over a lifetime time horizon. Uncertainty was characterized through deterministic and probabilistic sensitivity analysis. We also examined the use of idarucizumab and prothrombin-complexes-concentrate (PCC) as reversal agents in an emergency setting as an additional scenario-analysis.

Results Dabigatran was the most (cost-)effective among all alternatives (8.53 QALYs). Considering the Chilean cost-effectiveness threshold of USD 17,200 (1 GDP per capita), dabigatran was cost-effective (USD 11,042 per QALY gained), while both rivaroxaban and apixaban were dominated by dabigatran. Regarding the second-order uncertainty, at the suggested threshold, dabigatran exhibit the highest probability of being cost-effective (approximately 60%). In the reversal agent scenario, dabigatran plus idarucizumab was also found to be cost-effective in the Chilean context.

Conclusion Dabigatran is cost-effective and dominates both rivaroxaban and apixaban at current publicly available prices in Chile. In addition, we expect dabigatran-idarucizumab is also expected to be cost-effective for Chilean health system when is compared against acenocoumarol-PCC as reversal agents.

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Keywords Cost-effectiveness, Atrial fibrillation, Dabigatran, Thromboembolic events

Introduction

Atrial fibrillation (AF) is the most frequent sustained arrhythmia in adults, affecting between 1 and 2% of the general population [1]. AF is highly correlated with age, reaching 9% for the population between 80 and 90 years [2] and also associated with significant morbidity and mortality, which translates into an impactful burden for patients and health systems [3, 4]. Worldwide estimates indicate that around 6 million disability-adjusted life years are attributable to AF; and 6.65 billion are annually spent in AF hospitalization alone in the US [5, 6]. There is a lack of local epidemiological data on atrial fibrillation in Chile. However, regional estimates from Latin America suggest that the prevalence of AF is comparable to that reported in high-income countries, ranging from 1 to 2% in the general population and increasing with age [7].

One of the main objectives of the therapy of AF is the prevention of thromboembolic events, which are the principal component of the economic and health burden related to AF [5]. Thromboembolic prevention is achieved with the administration of anticoagulants, such as vitamin K antagonist (VKA), acenocoumarol and Warfarin, and direct oral anticoagulants (DOAC's) — dabigatran, rivaroxaban, apixaban, and edoxaban.

VKA usage represents a great challenge since these drugs have a narrow therapeutic margin, that requires frequent monitoring of the international normalized ratio (INR), which in case of imbalance, may propitiate serious hemorrhagic or ischemic events [8]. On the contrary, DOAC's do not require monitoring — fewer drugs interaction and a more predictable pharmacokinetic profile [9]. In this context, DOAC's can be seen as an attractive alternative, not only for patients but also from health decision-makers' perspective. Among DOAC's, dabigatran stands out not only because clinical trial reported the same efficacy to VKAs, but also due to its more favorable safety profile– particularly a lower risk of intracranial hemorrhage-, and because it is the only anticoagulant currently available in Chile with a specific reversal agent (idarucizumab), which may be especially beneficial in emergency settings [3, 10–12].

In Chile, the most used anticoagulant is acenocoumarol, and even though the health system has advanced towards the coverage of DOAC's for specific diagnoses, i.e. patients who have patients who have suffered a stroke, its access is not guaranteed for atrial fibrillation patients [13, 14]. One important constraint to make this decision is whether the resources needed to finance this change from VKA to DOAC´s can be considered a good use of the limited public budget. This study aims to evaluate the cost-effectiveness of dabigatran compared to other relevant comparators for preventing thromboembolic events in patients with AF from the Chilean health system perspective. In addition, we explored whether idarucizumab compared to prothrombin-complexes-concentrate (PCC) as reversal agents in an emergency setting can also be considered cost-effective in Chile.

Methods

We run a model-based cost-effectiveness study comparing dabigatran with apixaban, rivaroxaban and acenocumarol (edoxaban has been excluded because it is not on the Chilean public market). The modelled population matched that described in the RE-LY trial, i.e. AF patients in moderate or higher risk to stroke as defined by the $CHADS_2$ score [10]. The baseline characteristics and $CHADS_2$ score stratification, which defined the baseline risk of stroke, are presented in Supplementary Material Table 1. These characteristics were relatively similar to those reported in the Chilean AF cohort GARFIELD [15]; therefore, the modeled risk profile was consistent with what would be expected for the Chilean population.

Model structure

The population was modelled using the Markov cohort model presented in Fig. 1. This model describes the natural history of a patient with AF in terms of the consequences derived from the occurrence of ischemic events — primary and recurrent ischemic stroke (IS), systemic embolism (SE), transient ischemic attack (TIA), myocardial infarction (MI) and/or hemorrhagic events, such as primary and recurrent Intracranial hemorrhage (ICH), extracranial hemorrhage (ECH) and minor bleeds. Each of these events was defined based on the clinical criteria used in the RE-LY trial [2, 3, 10]. The proposed model and its conceptual framework have been described in detail elsewhere [16, 17].

Regarding the short-term consequences considered in the model, we considered the economic cost associated with the treatment of the events, the immediate detriment in terms of quality of life attributable to those events, and the potential change in treatment status, or death — either fatal events related to the occurrence of IS/SE/ICH/ECH/MI or death by any cause. Patients who suffer an ICH are assumed to discontinue treatment (off treatment). Transition to second-line treatment is determined by safety issues non-related to major events occurrence (adverse events).

For long term-consequences, the model records the functional disability outcomes related to the occurrence of IS and ICH, measured by Rankin Score and Glasgow Outcomes Scale respectively, establishing three possible

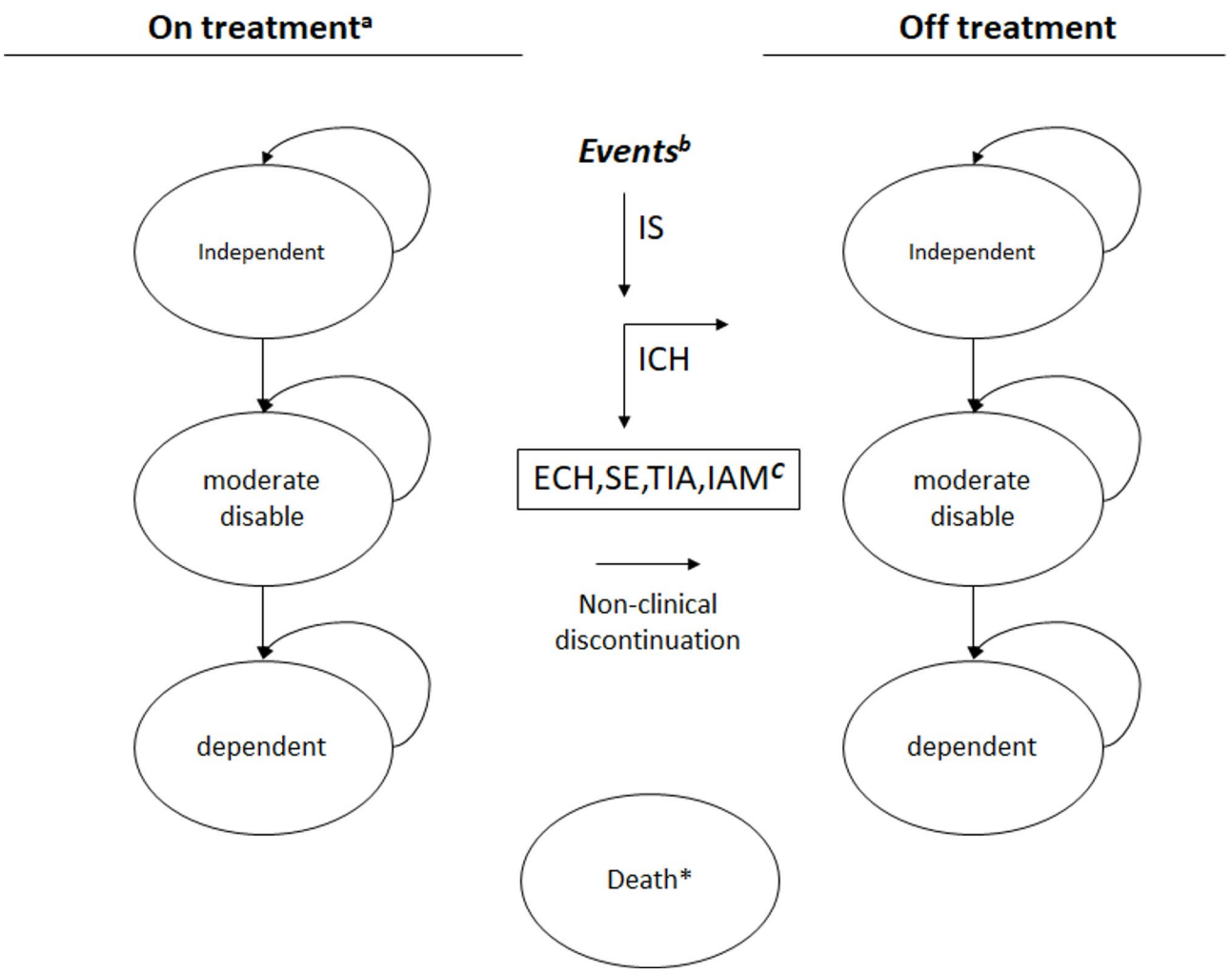

Fig. 1 Markov model structure. IS: Ischemic Stroke. ICH: Intracranial hemorrhage. ECH: Extracranial hemorrhage. SE: Systemic embolism. TIA: Transient ischemic attack. MI: Myocardial Infarction. **a**: Individuals in treatment may be under first and second line treatment. Transition to second-line treatment is determined by safety issues non-related to major events occurrence (adverse events). **b**: Main events recorded by the model, which could generate a degree of disability or treatment interruption. The direction of the arrow informs the potential impact on patient disability and treatment status — Patients who suffer an ICH are assumed to discontinue treatment. **c**: Major events that do not result in disability or treatment interruption

outcomes: independent, moderate disability, and dependent patient.

The modeling considered a lifetime horizon, assuming that the efficacy of the antithrombotic therapy remained constant throughout the patient´s life. We also assumed that individuals who discontinued treatment did not gain additional clinical benefits. The cycle length was three months, because according to clinical experts' advice, it reflects appropriately the time over which major event can occur [18]. Both, QALYs and costs were discounted at a 3% yearly rate [19].

Model inputs

Two main sources were consulted to populate the decision model: the RE-LY trial and the network meta-analysis (NMA) published by Lopez-Lopez et al. [10, 20]. The rates of occurrence for major events for acenocoumarol were obtained from the RE-LY trial (we assumed acenocoumarol and warfarin to be equally efficacious), while the comparative efficacy of DOAC's was obtained from Lopez-Lopez. For those major events not reported in the NMA — SE, TIA and minor bleedings — the efficacy reported for dabigatran versus warfarin in the RE-LY trial was assumed for all the DOAC's.

It is worth noting that Lopez-Lopez reports the efficacy in terms of odds ratios, which were converted into risk ratios following established methods [21]. The rate for major events occurrence and outcomes, comparative efficacy, risk modifiers, and distribution of possible outcomes attributable to major events are presented in Table 1. It is important to highlight that, because there are two dosages for dabigatran, each with different efficacy, a combined treatment effect was used in the model, which was calculated as the weighted sum of the efficacy

Table 1 Parameters related to the occurrence and consequences of major events

Annual rate of major complication for VKA's		
Inputs	**Estimator**	**Primary Source**
Stroke rate for VKA by $CHADS_2$ score:		
CHADS2 0 (100 patient/year)	0.62	[9]
CHADS2 1 (100 patient/year)	0.8	[9]
CHADS2 2 (100 patient/year)	1.01	[9]
CHADS2 3 (100 patient/year)	1.75	[9]
CHADS2 4 (100 patient/year)	1.75	[9]
CHADS2 5 (100 patient/year)	3.34	[9]
CHADS2 6 (100 patient/year)	3.34	[9]
Rates of major events:		
Systemic embolism (100 patients/year)	0.18	[9]
Transient ischemic attack (100 patients/year)	0.84	[9]
Intracranial hemorrhage (100 patient/year)	0.81	[9]
Extracranial hemorrhage (100 patient/year)	2.88	[9]
Minor bleeds (100 patients/year)	16.37	[9]
Acute myocardial infarction (100 patient/year)	0.64	[9]
Comparative efficacy estimators for DOAC's and other therapies against VKA's		
Inputs	**Risk ratio (95% CI)**	**Primary Source**
Ischemic Stroke		
Dabigatran combined	0.85 (0.66 to 1.18)	[9]
Dabigatran 150 mg	0.76 (0.58 to 0.98)	[5]
Dabigatran 110 mg	1.14 (0.90 to 1.43)	[5]
Rivaroxaban	0.93 (0.74 to 1.16)	[5]
Apixaban	0.92 (0.74 to 1.14)	[5]
Antiplatelet	2.47 (1.61 to 3.85)	[5]
Off treatment	3.35 (2.23 to 5.03)	[3]
Systemic embolism		
Dabigatran combined	0.55 (0.25 to 1.24)	[9]
Dabigatran 150 mg	0.61(0.28 to 1.33)	[9]
Dabigatran 110 mg	0.49 (0.21 to 1.13)	[9]
Rivaroxaban	0.26 (0.10 to 0.71)	
Apixaban	0.76 (0.62 to 0.86)	
Antiplatelet	1.77 (0.66 to 4.77)	[3]
Off treatment	4.44 (1.78 to 11.08)	[3]
Transient ischemic attack		
Dabigatran combined	0.79 (0.59 to 1.07)	[9]
Dabigatran 150 mg	0.86 (0.65 to 1.15)	[9]
Dabigatran 110 mg	0.74 (0.55 to 1.00)	[9]
Rivaroxaban	0.79 (0.59 to 1.07)	Assumption
Apixaban	0.79 (0.59 to 1.07)	Assumption
Antiplatelet	1.56 (0.86 to 2.83)	[3]
Off treatment	1.23 (0.59 to 2.5)	[3]
Intracranial hemorrhage		
Dabigatran	0.38 (0.19 to 0.47)	[5]
Dabigatran 150 mg	0.40 (0.27 to 0.59)	[5]
Dabigatran 110 mg	0.31 (0.13 to 0.39)	[5]
Rivaroxaban	0.65 (0.46 to 0.91)	[5]
Apixaban	0.41 (0.30 to 0.58)	[5]
Antiplatelet	0.50 (0.21 to 1.23)	[5]
Off treatment	0.33	[3]
Extracranial hemorrhage		
Dabigatran combined	1.41 (1.12 to 1.75)	[5]
Dabigatran 150 mg	1.50 (1.19 to 1.86)	[5]

Table 1 (continued)

Comparative efficacy estimators for DOAC's and other therapies against VKA's		
Inputs	**Risk ratio (95% CI)**	**Primary Source**
Dabigatran 110 mg	1.11 (0.87 to 1.40)	[5]
Rivaroxaban	1.45 (1.19 to 1.77)	[5]
Apixaban	0.89 (0.69 to 1.15)	[5]
Antiplatelet	1.03 (0.47 to 2.35)	[5]
Off treatment	0.61 (0.10 to 3.78)	[3]
Minor bleeds		
Dabigatran combined	0.87 (0.82 to 0.93)	[9]
Dabigatran 150 mg	0.91 (0.86 to 0.97)	[9]
Dabigatran 110 mg	0.79 (0.74 to 0.84)	[9]
Rivaroxaban	0.87 (0.82 to 0.93)	Assumption
Apixaban	0.87 (0.82 to 0.93)	Assumption
Antiplatelet	0.63 (0.32 to 1.22)	[3]
Off treatment	0.55 (0.38 to 0.80)	[3]
Acute myocardial infarction		
Dabigatran combined	1.30 (0.96 to 1.75)	[5]
Dabigatran 150 mg	1.29 (0.96 to 1.75)	[5]
Dabigatran 110 mg	1.32 (0.97 to 1.75)	[5]
Rivaroxaban	0.80 (0.62 to 1.04)	[5]
Apixaban	0.87 (0.67 to 1.15)	[5]
Antiplatelet	1.02 (0.65 to 1.61)	[5]
Off treatment	1.55 (0.67 to 3.45)	[3]

ischemic and hemorrhagic events specific risk adjustment		
Inputs	**Risk ratio (95% CI)**	**Primary Source**
Intracranial hemorrhage: >= 80 years adjust	1.80 (1.1 to 3.10)	[13]
Extracranial hemorrhage: < 70 years adjust	0.50 (0.12 to 0.90)	[13]
Acute myocardial infarction: history of previous Myocardial infarction	3.11 (2.33to 3.88)	[14]

Proportion of disability and mortality following ischemic and Hemorrhagic event					
Outcome	**Stroke**	**Systemic embolism[b]**	**Intracranial hemorrhage[c]**	**Extracranial hemorrhage[d]**	**Myocardial infarction[a]**
Independent (non-disability)	52%	na	7.8%	na	na
moderate disability	18%	na	8.8%	na	na
dependent patient (greater disability)	4%	na	31.8%	na	na
Fatal	25%	13%	51.6%	1.13%	1.11%

Note: The efficacy of Dabigatran combined was estimated as the weighted sum between the efficacy estimators of the 150 and 110 mg presentations, and the proportion of the Chilean AF patients using them according to the 2018 Chilean national health survey, 76% and 24% for the 150 mg and 110 mg presentation a respectively [21]

a: [9]

b: [15]

c: [3]

d: [13]

estimators for each dosage, and the proportion of AF patients using them according to the Chilean national health survey, 76% and 24% for the 150 mg and 110 mg presentation a respectively [22].

Resource use related to major/minor ischemic and hemorrhagic events was validated by a cardiologist, neurologist, and internal medicine specialist. As for the healthcare resources provided for the management of the different disability levels, these were estimated through the insight collected from several clinical experts, physicians, kinesiologists, rehabilitation experts and occupational therapists.

The model incorporates health-related quality-of-life from three edges, health state utilities, disutilities attributable to the occurrence of major events, and disutilities associated with previous MI history. Due to lack of local data on preferences, a literature review was conducted to incorporate the utilities and disutilities in the model — although these were revealed on a different population [23–25]. It was assumed that the duration of the utility detriment given a major event affected only one cycle

(three months), which is consistent with prior HTA publications [26]. Importantly, all the sources we considered for utilities/disutilities used time-trade-off as method to reveal estimates.

Drug costs were obtained from the database of the public health institution for centralized procurement [27]. Costs related to health states, major events, and monitoring were obtained from verification health cost study, which is a national health cost study, endorsed by the Ministry of Health, that focus on some of the most burdensome diseases for the local population [28]. For those cases where information was not available, costs were estimated by the construction of health services baskets that contemplate current management protocols established by Chilean public health facilities. Unitary prices of health services were obtained from the Chilean public tariff [29]. Information about costs was collected in Chilean pesos 2022 and converted into US dollars (USD) using a conversion rate of 710.9 CP = 1USD. Utilities and cost parameters are presented in Table 2.

We characterized second-order uncertainty, through deterministic and probabilistic sensitivity analysis following established methods [30]. For efficacy and utility inputs, lower and upper bounds of 95% confidence intervals were used to inform prior distributions. For cost parameters, a ± 50% variation around the mean value was assumed to reflect uncertainty. In the probabilistic sensitivity analysis, 5,000 Monte Carlo simulations were undertaken to analyze the overall effect of parameters' uncertainty over the model.

To investigate the clinical and economic consequences associated with the use of idarucizumab as a reversal agent in an emergency setting, we conducted an exploratory analysis. Because there is no evidence on the effect of idarucizumab over clinical outcomes (avoided death, length of stay, etc.) and only limited to hemostatic effects; it was assumed that the reversing agent can prevent, at least to some extent, the disability patients can suffer. This scenario is consistent with the statement that early control of hemostasis favors prompt surgical management which would limit the extension of the vascular injury and the disability sequel [31].

The reversing agent scenario is presented in Fig. 2. It should be noted that the efficacy of the reversal agent is restricted to those ICH that would have generated the highest disability outcome. This assumption highlights the judgments that only the most serious episodes of ICH may benefit from the use of the reversing agent and its narrow therapeutic window. As it is impossible to identify ex-ante the disability outcomes for each ICH, we assumed the reversal agent will be administered to all patients that develop ICHBoth, Food and Drugs Administration (FDA) and European Medicines Agency, have approved the use of prothrombin complexes concentrate (PCC) for VKA's urgent reversal; hence, the use of PCC was also considered in this analysis. Reversal agents were evaluated at multiple efficacy scenarios ($p = 1$, 0.75, 0.5, 0.25, 0.1). Since there is none reversing agent for factor Xa inhibitors available in Chile, rivaroxaban and apixaban were excluded from this analysis.

Results

Over the lifetime horizon, DOAC'S were associated with fewer major ischemic/hemorrhagic events compared to acenocoumarol, which accounted for 10.83 events per 100 patient-years. Specifically, dabigatran amounted for 9.98 events per 100 patient-years, rivaroxaban 9.99 events per 100 patinet-years and apixaban 8.47 events per 100 patient-years. Although apixaban was associated with the lowest number of major events, dabigatran reported the lowest number of events causing disability, i.e., stroke/ICC − 2.92 events vs. 3.07 events per 100 patient-years for dabigatran and apixaban respectively.

Dabigatran compared with acenocumarol showed an ICER of USD 11.042 per QALY gained. The incremental QALYs, costs and the expected incremental cost effectiveness ratio (ICER) are presented in Table 3. In comparison with acenocoumarol and taking into account the established Chilean threshold of 17,200 USD (1 GDP per capita), both dabigatran (11,042 per QALY gained) and apixaban (14,119 per QALY gained) are cost-effective, while rivaroxaban is not. When comparing against dabigatran, it is observed that both rivaroxaban and apixaban become dominated — dabigatran generates more health benefits at a lower cost.

Our results also show that dabigatran and apixaban are practically equivalent (0.42 versus 0.41 incremental QALYs). In this context, the main driver of the comparative value between both alternatives is the expected cost, and particularly, the price of the technology, which is its main driver. As long as dabigatran stays cheaper, apixaban will be dominated. To address this issue, a price discount sensitivity analysis over Factor Xa inhibitors (with the same price for dabigatran) was carried out (SM Table 2). This analysis shows that dabigatran is still the most cost-effective alternative up to a discount of 15%, although rivaroxaban and apixaban are no longer dominated. It should be noted that with a 20% discount, apixaban becomes the most cost-effective alternative.

Regarding the probabilistic sensitivity analysis, the 5,000 paired estimates of incremental costs and QALYs are represented in the incremental cost-effectiveness plane in Fig. 1 of supplementary material (SM Fig. 1). A significant proportion of the clouds overlaps for the 3 DOACs alternatives, with rivaroxaban having the highest fraction of points above the linear threshold, followed by apixaban and then dabigatran. Figure 3 shows the cost-effectiveness acceptability curve. It is observed that

Table 2 Utilities and cost parameters

	Estimates (SE)	Primary source
Health states utilities:		
Independent (non-disability)	0.81 (0.005)	[23]
Independent (with previous stroke history)	0.76 (0.005)	[22]
Moderate disability	0.39 (0.002)	[22]
Dependent patient (greater disability)	0.11 (0.001)	[23]
Previous Myocardial infarction disutilities:		
History of previous myocardial infarction (permanent disability)	0.037 (0.026)	[24]
Acute events occurrence disutilities:		
Stroke	0.14 (0.011)	[23]
Systemic embolism	0.12 (0.009)	[23]
Transient ischemic attack	0.10 (0.008)	[23]
Intracranial hemorrhage	0.18 (0.014)	[23]
Extracranial hemorrhage	0.18 (0.014)	[23]
Myocardial infarction	0.12 (0.009)	[23]
Minor bleeds	0.004 (0.001)	[23]
Cost parameter	**Estimates (ES)**	**Primary source**
Treatment cost (per cycle):		
Dabigatran	$143 ($143)	[28]
Dabigatran 150 mg	$143 ($143)	[28]
Dabigatran 110 mg	$146 ($146)	[28]
Rivaroxaban 20 mg	$150 ($150)	[28]
Apixaban 5 mg	$186 ($186)	[28]
Acenocoumarol 4 mg	$10 ($10)	[28]
Warfarin 5 mg	$117 ($117)	[28]
Antiplatelet 100 mg	$2 ($2)	[28]
Off treatment	-	
INR monitoring cost (per cycle)		
Vitamin K antagonist	$10	Own estimate
Acute events cost		
Stroke	$2,659 ($2,659)	[28]
Systemic embolism	$1,740 ($1,740)	Own estimate
Transient ischemic attack	$1,629 ($1,629)	Own estimate
Intracranial hemorrhage	$16,855 ($16,855)	[28]
Extracranial hemorrhage (GI)	$934 ($934)	Own estimate
Extracranial hemorrhage (Non-GI))	$1,492 ($1,492)	Own estimate
Myocardial infarction	$1,319 ($1,319)	[28]
Minor bleeds	$81 (81)	Own estimate
Health state costs and follow up cost (per cycle)		
Independent (non-disability)	$54 ($54)	Own estimate
Independent (with previous stroke history)	$191 ($191)	Own estimate
Moderate disability	$347 ($191)	Own estimate
Dependent patient (greater disability)	$556 ($556)	Own estimate
Previous myocardial infarction	$49 ($49)	[28]
Other cost		
Treatment discontinuation nonrelated to hemorrhagic events	$17 ($17)	[28]

for the established threshold (17,200 USD) dabigatran presents the highest probability of being cost-effective (approximately 60%). For higher thresholds, dabigatran competes with apixaban to be the most cost-effective alternative, converging to a probability of 60% and 40%, respectively. The proposed univariate analysis shows that daily costs of dabigatran and the RR for IS and ICH were the main drivers of the ICERs estimate. However, all variations were under the Chilean threshold.

Reversal agent scenario results are shown in Table 4. For the two most effective scenarios, $p = 1$ and $p = 0.75$, expected costs are lower than those reported in the base case. In other words, the additional cost associated with the use of reversal agents is offset by the savings from

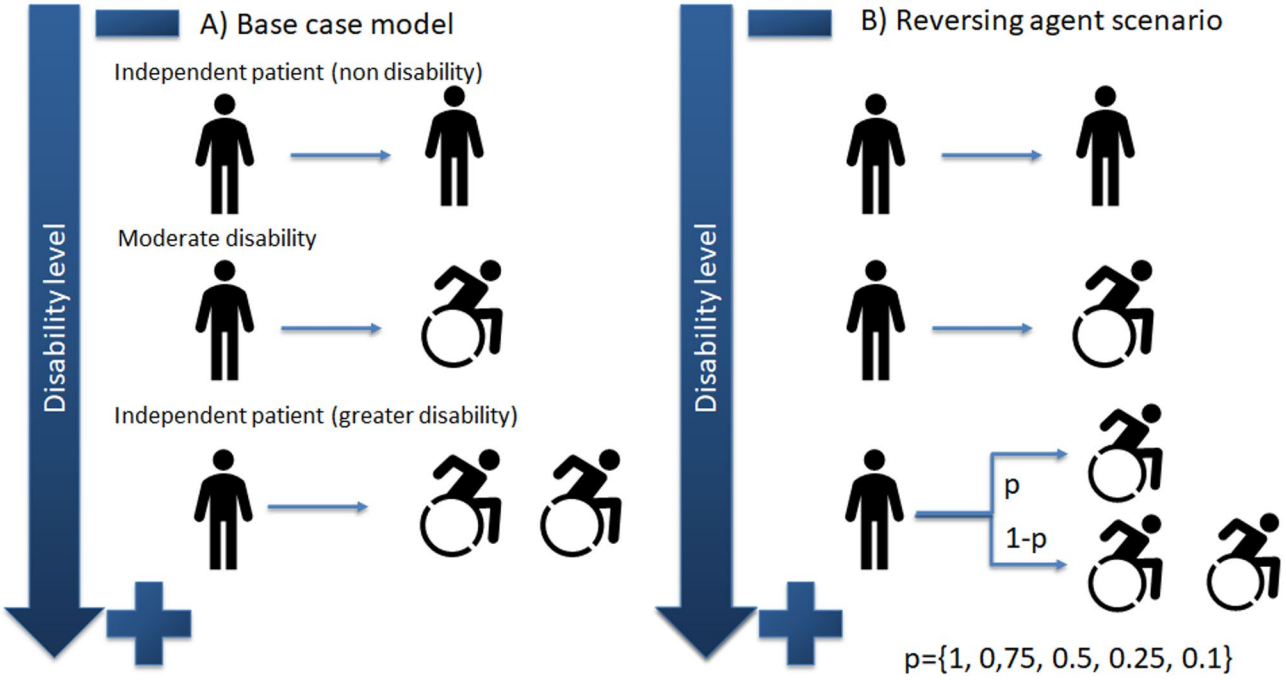

Fig. 2 Reversal agent scenario. p: Represents the capability of the reversal agent to prevent the disabilities associated with the onset of ICH. For this scenario analysis, multiple efficacy values for p ($p = 1$, 0.75, 0.5, 0.25, and 0.1) will be evaluated, ranging from the most optimistic possible scenario — the reversal agent prevents the outcome of total disability in 100% of patients— to a very conservative scenario, the reversal agent prevents the outcome of total disability in only 10% of patients

Table 3 Cost effectiveness of DOAC'S against acenocoumarol

Costs and benefits for each technology		**Expected Costs**	**Expected QALYs**
Acenocoumarol		$8,775	7.99
Dabigatran		$13,444	8.41
Rivaroxaban		$13,890	8.29
Apixaban		$14,615	8.40
Cost-effectivenes analysis versus acenocoumarol	**Incremental costs (discounted)**	**Incremental QALYs (discounted)**	**ICER**
Dabigatran	$4,669	0.42	$11,042.22
Rivaroxaban	$5,115	0.29	$17,386.33
Apixaban	$5,840	0.41	$14,119.78
Cost-effectivenes analysis versus Dabigatran	**Incremental costs (discounted)**	**Incremental QALYs (discounted)**	**ICER**
Rivaroxaban	$446	-0.13	Dominated
Apixaban	$1,171	-0.01	Dominated

Note: The establish Chilean threshold amount is $ 17,200 USD

reduced disability. For the medium effective scenario ($p = 0.5$), additional costs related to reversal agents are still compensated for dabigatran but not for acenocoumarol, i.e. the cost of PCC is greater than the cost of idarucizumab. For the last two scenarios, the additional costs associated with the use of the reversal agent are no longer compensated for both alternatives.

Regarding health outcomes, for each of the scenarios about effectiveness, using the reversing agent generates more health benefits. Finally, in terms of the ICER estimated, it is observed that for scenarios where reversal agent efficacy ranges between 1 and 0.5 — "high efficacy scenarios"— the ICER is higher than the one reported in the base case. This accounts for the fact that, because patients under acenocoumarol have a higher risk of ICH, the use of reversal agent favours VKA to a greater extent. On the contrary, for the "low efficacy scenarios", the estimated ICER is lower, which is explained because the additional costs associated with the use of the reversing agent do not translate into tangible benefits in terms of costs avoided and QALYs, which is particularly true for acenocoumarol (due to the higher number of ICHs).

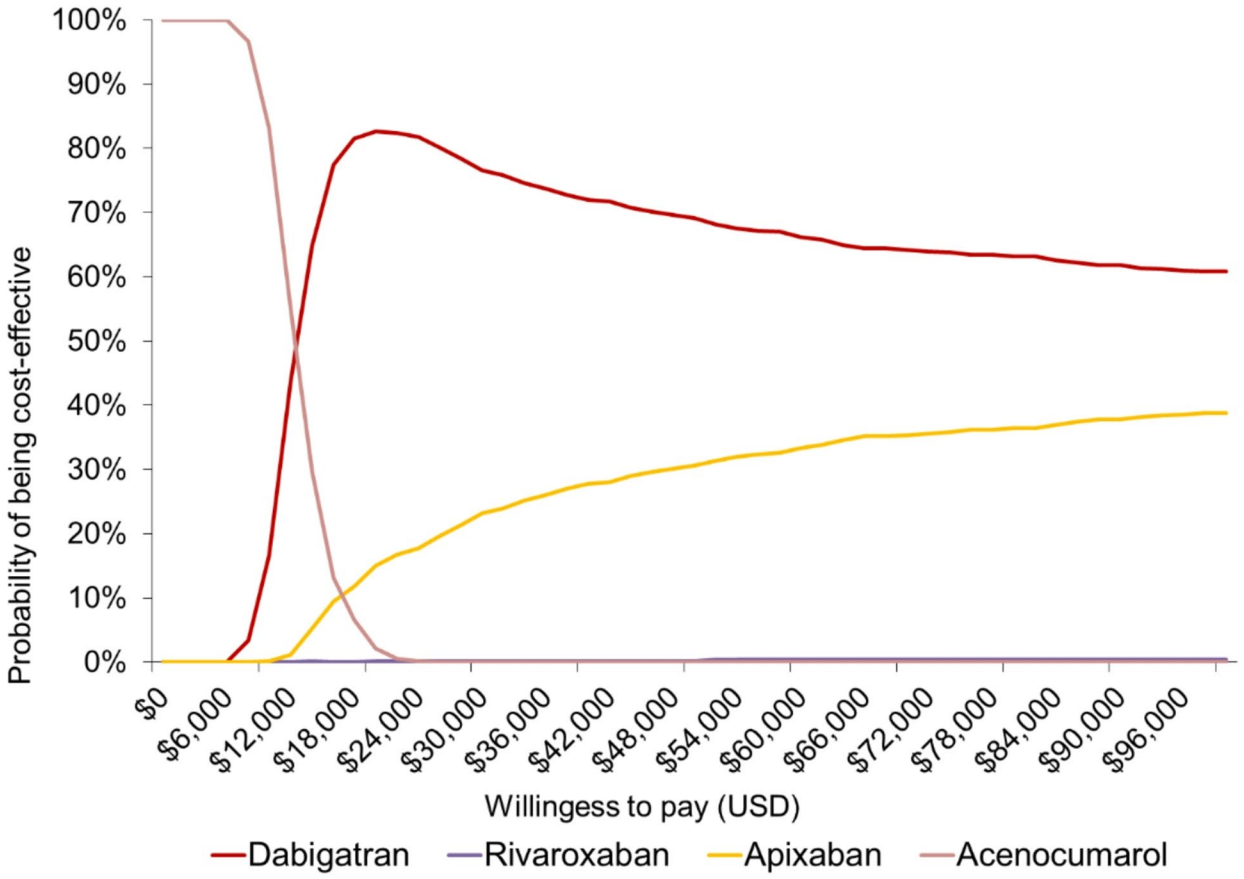

Fig. 3 Cost-effectiveness analysis acceptability curve

Table 4 Reversal agents scenario results

	Expected costs	Expected QALYs	Incremental QALYs (discounted)	Incremental costs (discounted)	ICER
Reversal agents efficacy scenario; *p* = 1					
Acenocoumarol	$8,725	8.04	-	-	-
Dabigatran	$13,367	8.45	0.41	$4,642	$11,322.16
Reversal agents efficacy scenario; *p* = 0.75					
Acenocoumarol	$8,763	8.03			
Dabigatran	$13,393	8.44	0.41	$4,630	$11,292.58
Reversal agents efficacy scenario; *p* = 0.50					
Acenocoumarol	$8,802	8.02			
Dabigatran	$13,420	8.43	0.41	$4,618	$11,263.01
Reversal agents efficacy scenario; *p* = 0.25					
Acenocoumarol	$8,841	8.00			
Dabigatran	$13,447	8.42	0.42	$4,606	$10,965.97
Reversal agents efficacy scenario; *p* = 0.10					
Acenocoumarol	$8,864	8.00			
Dabigatran	$13,463	8.42	0.42	$4,598	$10,948.64

Note: The establish Chilean threshold amount is $ 17,200 USD

Discussion

The aim of this study was to evaluate the cost-effectiveness of dabigatran compared to acenocoumarol, rivaroxaban, and apixaban, for thromboembolic events prevention in AF patients. Our results suggest that both dabigatran and apixaban can be considered a cost-effective when compared with acenocoumarol. Furthermore, the comparison among DOACs, both factor Xa inhibitors — rivaroxaban and apixaban — are dominated by dabigatran at the reference threshold for Chile.

Regarding the comparison against VKA, this result is in line with other international experiences [32–35]. In contrast, the literature on comparisons among DOACs is less conclusive. A study conducted in China found that dabigatran was cost-effective compared to rivaroxaban for the prevention of stroke and systemic embolism in patients with AF [36]. However, there are some studies that identify apixaban as the most cost-effective DOAC. Although differences in economic models may partly explain these discrepancies, a key factor is the variation in sources of clinical efficacy data, including different network meta-analyses (NMAs) or real-world evidence [37–39]. Importantly, a common finding across these studies, including our own, is the high degree of uncertainty in PSA regarding the cost-effectiveness comparison between apixaban and dabigatran.

When comparing our results with those reported by López-López et al. it is evident that despite using the same treatment effect, we obtain different results. It is important to highlight that the assumptions or other parameters used in our base case analysis are different from the ones proposed in Lopez-Lopez [20]. For instance, López-López et al. assumed that patients on dabigatran who experience a myocardial infarction (MI) switch to VKA therapy, which alters long-term outcomes by increasing the likelihood of major events. According to our clinical experts that assumption is no based on clinical data and is not likely to happen in Chile. Additionally, their study uses a larger acute event disutilities (for Stroke and ICH) whereas our study uses a lower utility to inform the chronic impact of major events on quality of life.

Despite the aforementioned considerations, the results obtained from PSA remain robust. At the established threshold, dabigatran exhibits approximately a 77% chance of being the more cost-effective alternative compared to acenocoumarol. However, it's worth noting that as the willingness to pay increases, the uncertainty between apixaban and dabigatran becomes more apparent. In our view, this is primarily driven by the higher price of apixaban rather than a difference in clinical effectiveness. As depicted in supplementary Fig. 1, the incremental cost-effectiveness clouds of both alternatives are nearly identical in terms of health effects, but apixaban is associated with higher costs.

In analyzing the overall shape of the incremental point clouds, we find that the uncertainty concerning health benefits aligns with the treatment effects applied to each alternative. As shown in Table 1, aside from the ICH outcome, the reported relative risks (RRs) exhibit imprecision (crossing the null value). This leads to optimistic scenarios where the reduction in DOACs shields against the occurrence of all major events, or pessimistic scenarios where they solely protect against the incidence of ICH.

The univariate analysis indicated that the price of dabigatran, and the treatment effect for the outcomes IS, ICH and ECH, are the most influential parameters among the clinical parameters. These findings are reinforce the notion that variations in treatment effects directly influence the disutilities applied, thereby potentially impacting the ICER through fluctuations in QALYs associated with dabigatran. In the analysis of reversal agents, dabigatran-idarucizumab was found to be cost-effective in all efficacy scenarios. This result can be explained by the low incidence of hemorrhagic events and reduced use of hospital resources [40, 41]. To our knowledge, this is the first study to evaluate the costs and benefits of idarucizumab compared to PCC. Other studies have evaluated Andexanet (another reversal agent indicated for factor Xa anticoagulation) with PCC, concluding that Andexanet is not cost-effective, mainly because this reversal agent has a high incidence of thromboembolic events. Therefore, idarucizumab could be positioned as an alternative for the treatment of severe bleeding with an adequate safety profile [11].

One of the limitations of this study is the assumption that acenocoumarol and warfarin have equivalent clinical efficacy. Thus, the comparative effectiveness of Warfarin was used as a proxy to populate the model. Evidence supports similar efficacy across VKAs for the prevention of thromboembolic events [42–44]. Therefore, this assumption does not pose a major limitation in comparing acenocoumarol with DOACs [45]. The key differences between VKAs are pharmacokinetic—for example, warfarin has a longer half-life than acenocoumaro [46]. Some studies also suggest that warfarin achieves a higher time in therapeutic range (TTR), which may translate into better anticoagulation quality [46]. This could theoretically affect costs by requiring more acenocoumarol to achieve target anticoagulation. However, given its low unit cost, the impact on the ICER is likely to be marginal.

Another limitation of the study corresponds to the prices of the technologies analysed. These were obtained according to data from CENABAST, the public entity in Chile for centralized procurement, which reflects the average of public purchases over the last 5 years The

introduction of bioequivalent generics could reduce drug prices in the future, potentially affecting the ICER. To account for this, we performed scenario analyses in which the prices of factor Xa inhibitors were varied, while the price of dabigatran remained fixed. These results showed that dabigatran remained the most cost-effective option up to a 15% price discount. At a 20% discount, however, apixaban became the most cost-effective alternative.

Although there is a study that asses the cost-effectiveness of dabigatran versus warfarin [47], to our knowledge, this is the first study that compares multiple DOACs cost-effectiveness against VKA in an in a Latin American Country. Given that many Latin American countries share common characteristics—such as constrained healthcare budgets—these findings may be relevant for decision-makers across the region. Furthermore, this is the first study that explores the economic value of idarucizumab usage in an emergency setting. Despite the fact this scenario relied on several strong assumptions (I.e the usage of the reversal agent may prevent, at least partially, the disability outcome related to ICH), it is in line with the evidence that shows the reversal anticoagulation properties of idarucizumab and the clinical intuition. Therefore, it provides a reasonable exploratory framework to reveal the economic value of the reversal agent.

In conclusion, dabigatran is a cost-effective intervention for preventing thromboembolic events in patients with AF from the Chilean health system's perspective. Apixaban and rivaroxaban are dominated by dabigatran in the base case scenario which is highly determined by its final price Regarding reversal agents, the combination of dabigatran and idarucizumab is also expected to be cost-effective compared with acenocoumarol and PCC. These findings support the value of dabigatran and idarucizumab as therapeutic options within the Chilean context for the prevention and emergency management of thromboembolic events in patients with AF.

Abbreviations

AF	Atrial fibrillation
VKA	Vitamin K antagonist
DOAC's	Direct oral anticoagulant
INR	International normalized ratio
PCC	Prothrombin-complexes-concentrate
IS	Ischemic stroke
SE	Systemic embolism
TIA	Transient ischemic attack
MI	Myocardial infarction
ICH	Intracranial hemorrhage
ECH	Extracranial hemorrhage
NMA	Network meta-analysis
HTA	Health technology assessment
FDA	Food and drugs administration
ICER	Incremental cost-effectiveness ratio

Supplementary Information

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Supplementary Material 1

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Author contributions
TA: Conceptualization, Methodology, Data analysis, Validation, Writing, Review and Editing. NA: Validation, Writing, Review and Editing. LO: Clinical Insights; Review and Editing. AG: Clinical Insights; Review and Editing. CB: Validation, Supervision, Writing, Review and Editing. ME: Conceptualization, Supervision, Methodology, Validation, Writing, Review and Editing.

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The authors declare no competing interests.

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