Scientific letters

Population-based analysis of the cost of direct oral anticoagulants versus vitamin K antagonists in nonvalvular atrial fibrillation

Análisis poblacional del coste de los anticoagulantes orales de acción directa frente a los antagonistas de la vitamina K en fibrilación auricular no valvular

To the Editor,

Both vitamin K antagonists (VKA) and direct oral anticoagulants (DOAC) have demonstrated efficacy and effectiveness in the prevention of cardioembolic events in patients with nonvalvular atrial fibrillation (NVAF). Various reports indicate that DOAC might be more cost-effective than VKA.[1] However, there is scarce real-world evidence on the impact of these treatments on health care expenditures, which should encompass costs related to hospitalization and monitoring as well as pharmacy costs.

We report data from a population-based study using an intention-to-treat analysis comparing the direct health care costs of VKA and DOAC as oral anticoagulant treatment for patients with NVAF in Catalonia over a 1-year time horizon. The study included all patients presenting to a primary care center of the Catalan Public Health Service (*Servei Català de la Salut*) with a history of NVAF for more than 1 year who had been treated with VKA (warfarin or acenocoumarol) or DOAC (dabigatran, rivaroxaban, apixaban, or edoxaban) for at least 2 months before the beginning of the study period.

The population database was drawn from the Information System for the Development of Primary Care Research. Drug costs were obtained from actual invoices recorded in the database of medicines dispensed at the pharmacy offices within the Catalan Public Health Service. Hospital data originated from the minimum data set of hospital discharges, while the cost of medical visits, nursing care, and diagnostic tests were obtained from the *Diari Oficial de la Generalitat de Catalunya.* Hospitalization costs were estimated by applying the payment formula used by the Catalan Public Health Service for contracting health care services.[2]

Using 1:1 propensity score matching without replacement, 1500 patients treated with DOAC were randomly selected and matched with a patient with similar characteristics treated with VKA. A sensitivity analysis was conducted by updating costs to 2022 levels and capitalizing them to 2024 using appropriate discount rates.

In 2017, there were 82 034 patients with NVAF receiving anticoagulant treatment through primary care in Catalonia. Of these, 64 732 (79%) were treated with VKA and 17 302 (21%) with DOAC.

Results for the overall population and the matched sample for 2017 are presented in table 1. The annual health care cost of anticoagulant treatment for patients with NVAF, including hospitalization, drug therapy, and monitoring, was €207 067 314.34. The largest cost component was hospitalization (€98 112 374.77), followed by patient monitoring (€93 069 877.87) and pharmacy (€15 885 061.70). More patients switched from the VKA to the DOAC group than vice versa (3 899 vs 157, respectively). Anticoagulant switching doubled the per-patient cost, particularly among those switching from VKA to DOAC, resulting in a difference of €74.02 per patient.

In the matched sample, we observed higher costs for VKA vs DOAC for hospitalizations (€1688.32 vs €1240.64; $P < .001$) and monitoring (€1066.81 vs €742.69; $P < .001$) but lower costs for pharmacy (€12.52 vs €843.80; $P < .001$). The overall annual cost per patient was €2767.65 for VKA and €2827.12 for DOAC (a difference of €59.47 per patient; $P < .001$).

Estimated data for 2024 are shown in table 2. The direct health care cost is expected to range from €257 743 969 to €257 246 394 (€3041.09-€3046.98 for VKA and €3490.37-€3497.12 for DOAC).

Our results reveal similar direct health care costs for VKA and DOAC for cardioembolic event prophylaxis in NVAF. Although DOAC are used in patients with a higher baseline cardiovascular risk, monitoring and hospitalization costs for these patients were lower despite higher drug costs. The highest costs were found in patients who switched anticoagulant therapy, particularly from VKA to DOAC, due to the increased cost of inpatient care. One of the limitations of comparing cost analyses conducted in different countries is the range of costs assigned to the different elements under analysis, such as drugs and hospitalization.[3,4] Our study may inform recommendations on anticoagulant therapy in Spain, as it draws on real-life data rather than cost simulations. Additionally, the introduction of generic drugs will coincide with a reduction in the price of these drugs, potentially creating a significant cost advantage for DOAC, with implications for health care policy.

Our data have some limitations. First, they do not allow us to determine the reason for hospitalization, so hospital costs were calculated based on admissions for any cause. Second, we did not analyze the impact of improper DOAC dosing or poor VKA control. Third, we were unable to assess indirect health care costs, such as productivity loss or nonmedical expenses related to the care of patients with poststroke sequelae, which could potentially result in lower overall costs for DOAC.

In conclusion, the difference in direct health care costs between VKA and DOAC is minimal. VKA are associated with higher monitoring and hospitalization costs, while DOAC have higher pharmaceutical costs. Since DOAC have lower hospitalization and monitoring expenses, they may offer a cost advantage in clinical practice.

FUNDING

The database was obtained with support from a grant from the Information System for the Development of Primary Care Research (SIDIAP, 2017 Call for Proposals, SIDIAP file 17/02; resolution date, April 27, 2018). The project was carried out within the framework of the 2018 Industrial Doctorates program through the *Agència de Gestió d'Ajuts Universitaris i de Recerca de la Generalitat de Catalunya*, under file number 2018-DI-044, and received financial support from the *Fundació Dr. Ferran* (2018 edition), awarded on May 17, 2018. The institutions mentioned above did not participate in any phase of the study.

ETHICAL CONSIDERATIONS

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the *Fundació Institut*

Table 1

Results of follow-up, hospitalizations, and costs in the overall population and matched sample of individuals treated with VKA and DOAC and those who switched anticoagulants

	Population					Matched sample				
Characteristics	VKA	DOAC	Total	Switch (VKA-DOAC)	Switch (DOAC-VKA)	VKA	DOAC			Total
NVAF with anticoagulation	64 732	17 302	82 034	3899	157	1500	1500			3000
Follow-up	**Total (per patient)**	**Total (per patient)**	**TOTAL**	**Total (per patient)**	**Total (per patient)**	**Total (per patient)**	**Total (per patient)**	**Rate ratio (95% CI)**	**P[a]**	
Medical visits to primary care	728 325 (11.25)	156 327 (9.03)	884 652	53 941 (13.83)	1975 (12.58)	15 563 (10.38)	13 403 (8.94)	1.16 (1.13-1.18)	<.001	28 966
Primary care nursing visits	1 198 096 (18.50)	115 557 (6.67)	1 313 653	66 817 (17.13)	2352 (14.98)	22 441 (14.96)	9624 (6.42)	2.33 (2.27-2.38)	<.001	32 065
Medical visits to the hospital	18 553 (0.28)	5637 (0.32)	24.19	1949 (0.5)	85 (0.54)	373 (0.25)	516 (0.34)	0.72 (0.63-0.83)	<.001	889
INR test strips	879 913 (13.59)	0 (0)	879 913	34 057 (8.73)	1735 (11.05)	14 200 (9.47)	(0.00)	0	0	14.2
Hospitalization	32 435 (0.50)	8463 (0.48)	40 898	3528 (0.90)	148 (0.94)	1087 (0.72)	757 (0.50)	1.44 (1.31-1.58)	<.001	1844
COST (€, 2017)	**Total (per patient)**	**Total (per patient)**	**TOTAL**	**Total (per patient)**	**Total (per patient)**	**Total (per patient)**	**Total (per patient)**	**Rate ratio (95% CI)**	**P[b]**	**Total**
Inpatient costs	77 223 296.7 (1 192.96)	20 889 078.07 (1 207.32)	98 112 375	8 863 303.88 (2 273.22)	388 399.20 (2 473.88)	2 532 475.44 (1 688.32)	1 860 952.56 (1 240.64)	0.33 (0.32-0.33)	<.001	4 393 428
Total hospitalization costs	77 223 296.7 (1 192.96)	20 889 078.07 (1 207.32)	98 112 375	8 863 303.88 (2 273.22)	388 399.20 (2 473.88)	2 532 475.44 (1 688.32)	1 860 952.56 (1 240.64)	0.33 (0.32-0.33)	<.001	4 393 428
Oral anticoagulant laboratory sale price	1 190 254.84 (18.38)	14 694 806.86 (849.31)	15 885 062	1 927 435.21 (44 340.91)	48 600.63 (309.56)	18 786.73 (12.52)	1 265 694.33 (843.80)	0.01 (0.01-0.02)	<.001	1 284 481.06
Total pharmacotherapy cost	1 190 254.84 (18.38)	14 694 806.86 (849.31)	15 885 062	1 927 435.21 (494,340.91)	48 600.63 (309.56)	18 786.73 (12.52)	1 265 694.33 (843.80)	0.01 (0.01-0.02)	<.001	1 284 481.06
Medical visits to primary care	33 772 430.25 (521.72)	7 248 882.99 (418.96)	41 021 313	2 501 244.17 (641.50)	91 580.75 (583.31)	721 656.31 (481.10)	621 497.11 (414.33)	1.16 (1.15-1.16)	<.001	1 343 153.42
Primary care nursing visits	38 890 196.16 (600.78)	3 750 980.22 (216.79)	42 641 176	2 168 879.82 (556.26)	76 345.92 (486.28)	728 434.86 (485.62)	312 395.04 (208.26)	2.33 (2.32-2.34)	<.001	1 040 829.9
Medical visits to the hospital	2 595 379.17 (40.09)	788 559.93 (45.57)	3 383 939	272 645.61 (69.92)	11 890.65 (75.73)	52,178.97 (34.79)	72 183.24 (48.12)	0.72 (0.71-0.73)	<.001	124 362.21
INR test strips	369 563.46 (5.70)		369 563	14 303.94 (3.66)	728.7 (4.64)	5964 (3.98)	0 (0)	0 (0)	0	5964
Laboratory tests	3 220 836.1 (49.75)	909 689.27 (52.57)	4 130 525	274 043.67 (70.28)	16 431.1 (104.65)	70 093.72 (46.73)	81 646.81 (54.43)	0.86 (0.85-0.87)	<.001	151 740.53
Additional tests	1 194 909.49 (18.45)	328 450.83 (18.98)	1 523 360	102 818.5 (26.37)	3661.47 (23,32)	21 882.82 (14.59)	26 317.85 (17.55)	0.83 (0.82-0.85)	<.001	48 200.67
Total follow-up	80 043 314.63 (1236.53)	13 026 563.24 (752.89)	93 069 878	5 333 935.71 (1368.02)	200 638.59 (1277.95)	1600 210.68 (1066.81)	1 114 040.05 (742.69)	1.43 (1.43-1.44)	<.001	2 714 250.73
Total (€)	**158 456 866.17 (2447.89)**	**48 610 448.17 (2809.52)**	**207 067 314**	**16 124 674.8 (4135.59)**	**637 638.42 (4061.39)**	**4 151 472.85 (2767.65)**	**4 240 686.94 (2827.12)**	**0.97 (0.97-0.98)**	**<.001**	**8 392 159.79**

DOAC, direct oral anticoagulant; INR, international normalized ratio; VKA, vitamin K antagonist.

[a] Mann-Whitney U test.

[b] Difference of proportions (Z score).

Table 2
Sensitivity analysis

Characteristics	2024 (3.6% June 2024)			2024 (3.4% December 2024)		
Cost (€)	VKA Total (per patient)	DOAC Total (per patient)	TOTAL	VKA Total (per patient)	DOAC Total (per patient)	TOTAL
NVAF with anticoagulation	64 732	17 302	82 034	64 732	17 302	82 034
Hospitalizations	96 122 553.59 (1,484.93)	26 001 370.21 (1502.8)	122 123 924	95 936 988.81 (1482.06)	25 951 174.51 (1499.89)	121 888 163
Drug therapy						
Laboratory sale price - VKA	1 272 563.34 (19.66)	0 (0)	1 272 563.34	1 270 106.66 (19.62)	0 (0)	1 270 106.66
Laboratory sale price - DOAC	0 (0)	15 710 982.14 (908.04)	15 710 982.10	0 (0)	15 680 652.06 (906.29)	15 680 652.10
Total pharmacy cost	1 272 563.34 (19.66)	15 710 982.14 (908.04)	16 983 545.50	1 270 106.66 (19.62)	15 680 652.06 (906.29)	16 950 758.70
Follow-up						
Medical visits to primary care	42 037 731.81 (649.41)	9 022 939.62 (521.5)	51 060 671.40	41 956 577.89 (648.16)	9 005 520.82 (520.49)	50 962 098.70
Primary care nursing visits	48 407 995.05 (747.82)	4 668 977.01 (269.85)	53 076 972.10	48 314 543.32 (746.38)	4 659 963.54 (269.33)	52 974 506.90
Medical visits to the hospital	3 230 559.74 (49.91)	981 548.28 (56.73)	4 212 108.02	3 224 323.14 (49.81)	979 653.40 (56.62)	4 203 976.54
INR test strips	460 008.64 (7.11)	0 (0)	460 008.64	459 120.59 (7.09)	0 (0)	459 120.59
Laboratory tests	4 009 087.98 (61.93)	1 132 322.23 (65.44)	5 141 410.21	4 001 348.43 (61.81)	1 130 136.28 (65.32)	5 131 484.71
Additional tests	1 487 345.87 (22.98)	408 834.30 (23.63)	1 896 180.17	1 484 474.55 (22.93)	408 045.05 (23.58)	1 892 519.59
Total follow-up cost	99 632 729.09 (1539.16)	16 214 621.45 (937.15)	115 847 351	99 440 387.92 (1536.19)	16 183 319.09 (935.34)	115 623 707
Total (€)	**197 236 834.75 (3046.98)**	**60 507 134.62 (3497.12)**	**257 743 969**	**196 856 068.65 (3041.09)**	**60 390 325.48 (3490.37)**	**257 246 394**

DOAC, direct oral anticoagulant; INR, international normalized ratio; NVAF, nonvalvular atrial fibrillation; VKA, vitamin K antagonist.

Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina on May 30, 2018 (code P18/080). Data contained in databases of the Information System for the Development of Research in Primary Care (SIDIAP) are anonymized and comply with Spanish legislation on confidentiality and data protection (Organic Law 15/1999 of December 13 on the protection of personal data). Therefore, it was unnecessary to request patient informed consent.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

The authors did not use any artificial intelligence tools to conduct this research.

AUTHORS' CONTRIBUTIONS

Concept and study design: Z. Hernández Rojas, M.R. Dalmau Llorca, C. Aguilar Martín, E. Castro Blanco, M. García-Goñi M, J.M. Alegret. Acquisition of funding: Z. Hernández Rojas, M.R. Dalmau Llorca, C. Aguilar Martín. Methodology: Z. Hernández Rojas, M.R. Dalmau Llorca, C. Aguilar Martín, J.M. Alegret. Data collection and analysis: Z. Hernández Rojas, M.R. Dalmau Llorca, E. Castro Blanco. Data interpretation: Z. Hernández Rojas, M.R. Dalmau Llorca, E. Castro Blanco, J.M. Alegret. Statistical analysis: Z. Hernández Rojas, M.R. Dalmau Llorca, E. Castro Blanco. Analysis of economic data: Z. Hernández Rojas, M.R. Dalmau Llorca, M. García-Goñi, J.M. Alegret. Drafting of the manuscript: Z. Hernández Rojas, M.R. Dalmau Llorca, J.M. Alegret. Review and editing: Z. Hernández Rojas, M.R. Dalmau Llorca, C. Aguilar Martín, E. Castro Blanco, M. García-Goñi, J.M. Alegret. Review and editing of the final version: Z. Hernández Rojas, M.R. Dalmau Llorca, C. Aguilar Martín, E. Castro Blanco, M. García-Goñi, J.M. Alegret. Senior authors: M.R. Dalmau Llorca, C. Aguilar Martín.

CONFLICTS OF INTEREST

Z. Hernández Rojas, M.R. Dalmau Llorca, and C. Aguilar Martín participated in a study partially sponsored by Bayer. Z. Hernández Rojas has received training support from Boehringer and Salvat. M. R. Dalmau Llorca has received support for conference attendance from Bayer. E. Castro Blanco, M. García-Goñi, and J.M. Alegret have no conflicts of interest.

ACKNOWLEDGEMENTS

The authors are grateful for the contributions of: Regional Management and Primary Care Management of the Terres de l'Ebre, Catalan Institute of Health, Information Systems of the Primary Care Services, *Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina*, *Fundació Dr. Ferran*, and *Doctorats Industrials*.

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Available online 15 March 2025

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https://doi.org/10.1016/j.rec.2022.08.013

Recurrent chronic thromboembolic pulmonary hypertension following balloon pulmonary angioplasty

Hipertensión pulmonar tromboembólica crónica recurrente tras angioplastia pulmonar con balón

To the Editor,

Approximately 2% to 3% of patients who experience acute pulmonary thromboembolism develop chronic thromboembolic pulmonary hypertension (CTEPH) within the following 2 years.[1] The prevalence of CTEPH is estimated at 26 to 38 cases per million population. The prognosis of this condition depends on clinical, analytic, hemodynamic, and imaging parameters, with a 1-year mortality rate of > 20% in high-risk patients.[1] Pulmonary balloon angioplasty (PBA) is a key treatment in patients who are not candidates for surgery.[2] This intervention provides a demonstrated hemodynamic and functional improvement, which, according to some studies, is maintained over medium- and long-term follow-up.[3] However, certain clinical situations may predispose to recurrence of the disease despite initially successful PBA. This report describes 2 patients with CTEPH and severe pulmonary hypertension (PH) who underwent successful PBA but experienced disease recurrence with severe resting PH several years after completing treatment.

The first case involves a patient with congenital hydrocephalus secondary to stenosis of the aqueduct of Silvius, initially managed with a ventriculoperitoneal shunt, and later with 2 ventriculoatrial shunts (VAS). At the age of 19 years the patient was diagnosed with inoperable CTEPH and underwent 9 PBA procedures, which resulted in a pronounced clinical and hemodynamic improvement (table 1). Three years later, following suboptimal adherence to acenocoumarol anticoagulation therapy, the patient experienced clinical deterioration. Cardiopulmonary exercise testing revealed findings indicative of a poor prognosis: reduced peak VO_2 (14.2 mL/kg/min, 28% of predicted) and elevated VE/VCO_2 ratio (62.7). Pulmonary angiography confirmed rethrombosis of the pulmonary arteries and severe PH (table 1). The case was discussed in a multidisciplinary session. The group decided to repeat PBA and switch from acenocoumarol to edoxaban to ensure proper anticoagulation. The neurosurgery team ruled out the possibility of removing the VAS, the potential embolic source; hence, aspirin was added to the patient's therapy. The improvements achieved after 4 additional PBA procedures are shown in table 1 and figure 1.

The second patient had a posterior fossa brain tumor, which led to the development of hydrocephalus. Surgery and VAS implantation were carried out in infancy. At the age of 27 years, the patient experienced bilateral pulmonary thromboembolism and later developed inoperable CTEPH. Six PBA procedures were performed, resulting in a marked improvement (table 1), and he was discharged with acenocoumarol therapy. Six years later, the

Table 1
Changes in clinical and hemodynamic parameters

Parameters		Before 1st PBA program	After 1st PBA program	Before 2nd PBA program	After 2nd PBA program
Patient 1	Pulmonary artery pressure mean, mmHg	64	38	57	34
	Pulmonary vascular resistance, uW	17	5.1	9	3.6
	Cardiac index, L/min/m^2	1.85	3.52	3.24	4.20
	6-min walk test	50	613	537	538
	World Health Organization classification	IV	I	III	I
	TAPSE	14	26	19	20
	TAPSE/sPAP ratio	0.09	0.51	0.19	0.22
	Number of pulmonary vasodilator drugs	1 (epoprostenol)	2 (macitentan, tadalafil)	3 (treprostinil, macitentan, tadalafil)	3 (selexipag, macitentan, tadalafil)
Patient 2	Pulmonary artery pressure mean, mmHg	51	27	46	26
	Pulmonary vascular resistance, uW	15.3	3.4	9.5	2.72
	Cardiac index, L/min/m^2	1.8	2.25	1.86	2.3
	6-min walk test	373	572	420	474
	World Health Organization classification	III	I	III	I
	TAPSE	17	19	13	22
	TAPSE/sPAP ratio	0.16	0.30	0.14	0.58
	Number of pulmonary vasodilator drugs	2 (epoprostenol, sildenafil)	0	3 (treprostinil, macitentan, sildenafil)	1 (riociguat)

PBA, pulmonary balloon angioplasty; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion