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Budget Impact Analysis of Anticoagulation Clinics in Patients with Atrial Fibrillation under Chronic Therapy with Oral Anticoagulants

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Abstract

Objectives: To assess budget impact of the implementation of an anticoagulation clinic (AC) compared to usual care (UC), in patients with non-valvular atrial fibrillation (NVAF). **Method:** A decision tree was designed to analyze the cost and events rates over a 1-year horizon. The patients were distributed according to treatment, 30% Direct Oral Anticoagulant (DOAC) regimens and the rest to warfarin. The thromboembolism and bleeding were derived from observational studies which demonstrated that ACs had important impact in reducing the frequency of these events compared with UC, due to higher adherence with DOACs and proportion of time in therapeutic range (TTR) with warfarin. Costs were derived from the transactional platform of Colombian government, healthcare authority reimbursement and published studies. The values were expressed in American dollars (USD). The exchanged rate used was COP $3.693 per dollar. **Results:** During 1 year of follow-up, in a cohort of 228 patients there were estimated 48 bleedings, 6 thromboembolisms in AC group versus 84 bleedings, and 12 thromboembolisms events in patients receiving UC. Total costs related to AC were $126 522 compared with $141 514 in UC. The AC had an important reduction in the cost of clinical events versus UC ($52 085 vs $110 749) despite a higher cost of care facilities ($74 436 vs $30 765). A sensibility analysis suggested that in the 83% of estimations, the AC produced savings varied between $27 078 and $135 391. **Conclusions:** This study demonstrated that AC compared with UC, produced an important savings in the oral anticoagulation therapy for patients with NVAF.

Keywords

budget impact analysis, Colombia, economic, anticoagulation, anticoagulation clinic, chronic therapy with oral anticoagulants, atrial fibrillation

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Introduction

Oral anticoagulants have shown their efficacy and safety in thrombosis prevention for various indications, such as valvular and non-valvular atrial fibrillation (NVAF) and deep vein thrombosis (DVT),[1] thus contributing to an improvement in patients' quality of life.[2] In patients with NVAF, it is increasingly more frequent to use Direct Oral Anticoagulants (DOACs). For this reason, in 2014, at least 1310 patients were under treatment with DOACs, according to a database that included 6.5 million members of the Colombian general social security/health system (*Sistema General de Seguridad Social en Salud de Colombia*).[3] The reported usage rate of warfarin in anticoagulation clinics (AC) accounts for 50% to 70%.[4-6]

Due to the relevance of these therapies, the anticoagulation management services used to monitor anticoagulation is a fundamental element when it comes to obtain clinical results. Prior studies demonstrated that anticoagulation management with warfarin in ACs allowed patients to have an increased likelihood of reaching the desired results in the international normalized ratio (INR) control, values between $\leq$4.0 and $\geq$1.5,[7] and, therefore, to reduce the

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costs per person-year of follow-up, compared to usual medical care.[8]

In patients that receive chronic oral anticoagulant therapy (OAT), ACs can also have an impact on factors, such as the education of the patient, family or caregiver, patient adherence, renal function control, reduction in unnecessary specialist visits, reduction in emergency department visits, reduction in hospitalizations, barriers to drugs procurement, bleeding that leads to discontinuation, and prescriptions that deviate from approved dosing regimens.[9–12] Patients that are monitored through ACs have been shown greater adherence,[13] which is associated with a reduction in thromboembolic events risk[14] and to bleeding risks minimization.[15]

The ACs offer other potential benefits—that have not been measured yet–to patients that receive chronic OAT, such as a reduction in emergency service visits due to values outside the therapeutic ranges and the impact of supporting to anticipate and address clinical needs. Likewise, the impact of educational activities and hospitalization times of patients at high bleeding risk due to elevated INR values but who do not experience the event has not been evaluated yet.

Currently, there are several ACs in the country, some of which were implemented in large urban hospitals.[4–6] Two of them have shown that the development of these care models leads to an optimization of the Time in Therapeutic Range (TTR) in patients under warfarin therapy.[5,6] In Colombia, the economic impact of chronic OAT management via ACs is still unknown. Therefore, the purpose of this study is to evaluate the economic impact of ACs in patients diagnosed with NVAF who are receiving chronic OAT with any oral anticoagulant (apixaban, dabigatran, rivaroxaban, or warfarin), compared to usual care (UC).

Methods

A budget impact analysis study was designed using a decision tree. This model allows to project the impact of ACs on clinical complication rates and expected costs, as well as to compare same simulations with UC in patients that are receiving chronic OAT with warfarin or any DOACs, by using available evidence. The model parameters were established according to oral anticoagulant type and monitoring services. The model quantified the impact of clinical outcomes, use of resources, and related costs. The payer perspective was used, and only direct costs within a one-year time frame were considered. The model established a hypothetical cohort of 228 patients with NVAF that initiated or received chronic OAT, based on prior studies with NVAF published in the ACs in Colombia. Patients that received chronic OAT were distributed as follows: 70% (170 patients) treated with warfarin and 30% (68 patients) under any DOAC, according to the distributions reported in prior research studies in the country.[4,5] Regardless of the anticoagulant type, in order to reflect the behavior of the population in an AC, patients were distributed between new and follow-up patients (Figure 1).

Alternatives

The model compares 2 follow-up types: UC vs. AC. Under the anticoagulation management services defined as UC, physicians are responsible for managing anticoagulation within routine times, which include a monthly visit and the cost of INR, either requested during the visit, or previously performed by the patient in clinical laboratories where a venous blood sample of the patient is collected. For new patients treated with warfarin, receive 4 INR measurement in the first month, and in the maintained period this control is conducted according to routine visits. They have monthly visits by general practitioner and every 3 months by specialized physicians. In the case the patients with DOACs, they are only visit by specialized physicians.

Conversely, the AC, which follows the comprehensive care approach, includes a multidisciplinary team, uses explicit and standardized protocols, and complies with monitoring and dose adjustment processes that are carried out during the visit, depending on the oral anticoagulant type. In patients under warfarin, 4 INR measurements are initially performed, and they are accompanied by a medical evaluation. Then, monthly follow-up is performed by a general practitioner. In turn, patients that receive DOAC only attend monthly follow-up visits with a general practitioner. In both groups, a quarterly visit with a specialist was considered. In addition, the AC program is accompanied by other patient communication channels and continued education processes. These definitions were based on the data were the inputs were extracted.

Parameters

A literature search was conducted to identify evidence on ACs pertaining to patients that start or continue OAT and its effect on clinical results. While studies addressing the direct effect of ACs on clinical outcomes in patients that receive DOAC were not identified, evidence on adherence was found (Table 1).

The differential impact of an anticoagulation monitoring service in the AC and UC on the clinical outcomes associated with warfarin use was obtained from the quasi-experimental study by Chiquette et al[12]; while those associated with DOAC use were obtained from the observational study by Volkan et al[16] and Shore et al[13]

The study by Chiquette et al[12] compared the UC and AC anticoagulation management services in new anticoagulated patients and showed that with a greater TTR, a reduction in the thromboembolic events risk is achieved, along with better safety outcomes. Bearing in mind the results of

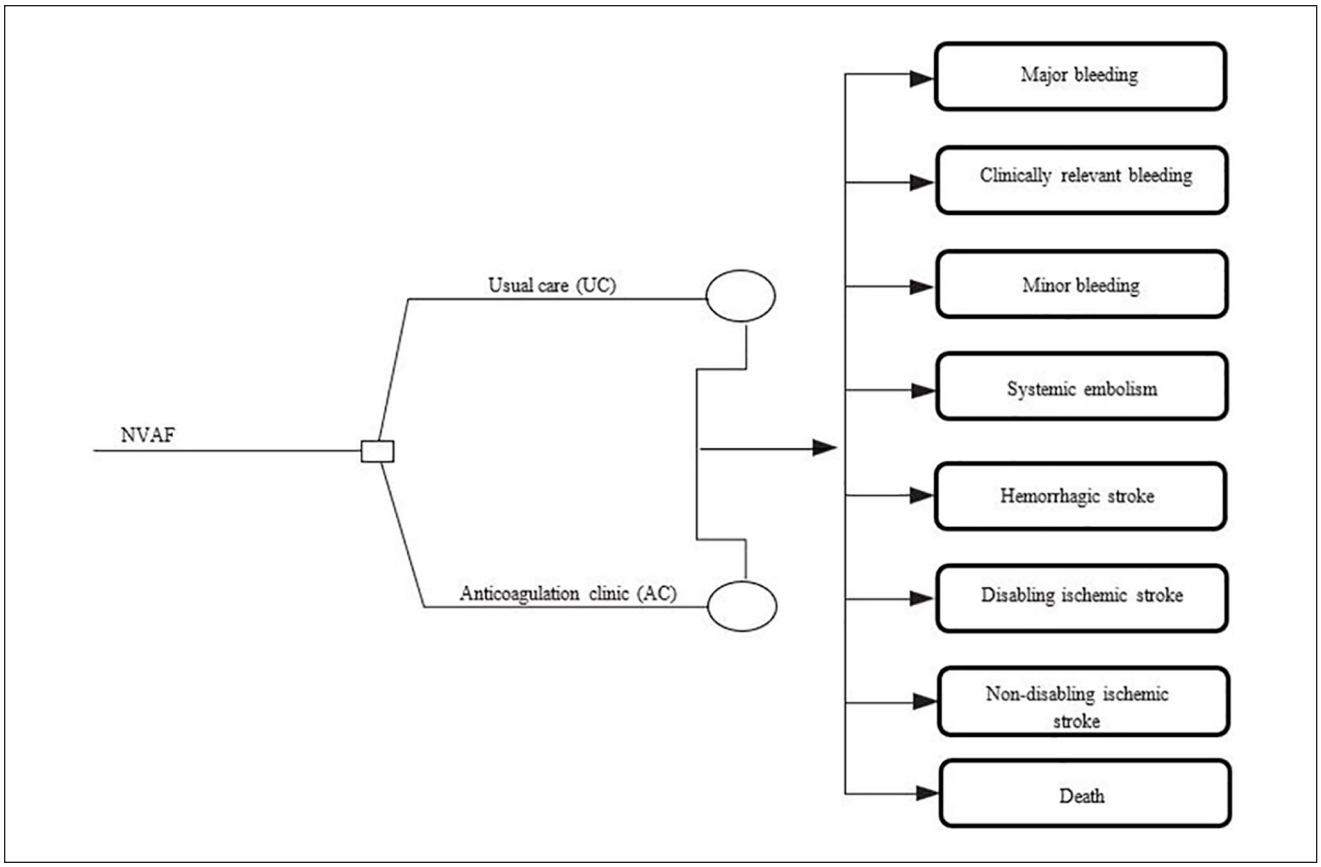

Figure 1. Model structure.
Representation of the model used. Patients that receive chronic OAT may be treated under any of the two types of follow-up, UC or AC; and the likelihood of them developing hemorrhagic and thromboembolic events is different.
Abbreviations: AC, anticoagulation clinic; NVFA, non-valvular fibrillation auricular; OAT, oral anticoagulant treatment ; UC, usual care.

Table 1. Parameters Used*

	Warfarin		DOAC	
Parameters	AC%	UC%	AC%	UC%
Major bleeding	0.13	0.00	0.32	0.61
Clinically relevant bleeding	0.67	2.90	0.00	0.00
Minor bleeding	1.49	2.27	1.00	0.82
Systemic embolism	0.00	0.00	0.02	0.02
Hemorrhagic stroke	0.00	0.00	0.01	0.03
Disabling ischemic stroke	0.00	0.08	0.04	0.09
Non-disabling ischemic stroke	0.27	0.65	0.14	0.11
Mortality	1.24	1.24	1.24	1.24

*Monthly probability of clinical events for warfarin and DOAC within each alternative.
Abbreviations: AC, anticoagulation clinic; DOAC, direct oral anticoagulant; UC, usual care.

this study, the following health states were included in the analysis for the warfarin patients' group:

- Major bleeding, which is a bleeding that requires blood transfusions of at least 2 units of blood.
- Clinically relevant bleeding, which is a bleeding that requires evaluation or referral or is associated to a greater than 3% decrease in hematocrit levels or a greater than 1.2 mg/dL decrease in hemoglobin levels.

- Minor bleeding, which is a bleeding that had little or no clinical significance and did not require a referral or additional visits.
- Disabling ischemic stroke, which is a stroke that caused irreversible damage, required an emergency procedure, or required admission into an intensive care unit.
- Non-disabling ischemic stroke, which is a stroke that did not have a significant impact on medical care.[12]

Unlike the warfarin group, in the case of DOACs, treatment adherence was related to clinical outcomes and to how monitoring at ACs positively impacts adherence. The study by Shore et al[13] found that being a member of an AC was associated to a greater likelihood of adherence than the UC was in one of the DOACs, while the study by Volkan Emren et al[16] identified the effects of clinical events associated with adherence in therapy. In this case, the considered events were major bleeding, minor bleeding, systemic embolism, hemorrhagic stroke, disabling ischemic stroke, and non-disabling ischemic stroke.

In relation to mortality, no differences were found between anticoagulation management services evaluated. However, it was considered as part of events within the model. To do this, and adjustment was made from the mortality tables published by the National Administrative Department of Statistics (DANE, *Departamento Administrativo Nacional de Estadística* in Spanish) (9), adjusted by the relative risk (RR) of dying in patients with a 3.02 NVAF (95% CI 1.73-5.27).[17]

Use of Resources and Costs

Direct medical costs were differentiated as anticoagulation monitoring- or management-associated costs and thromboembolic and hemorrhagic events costs. Costs are expressed in American dollars (USD). The exchanged rate used was COP $3693 per dollar. In relation to the costs associated with anticoagulation management, the activities were identified under each alternative, UC or AC, from the review of clinical practice guidelines for the treatment of NVAF patients as well as AC guidelines, depending on the type of patient therapy and by distinguishing if the patient was new or a the routine follow-up.[15] Afterwards, the cost of human capital was determined as part of required supplies.

When care is provided under the UC, either in a medical visit or a laboratory exam, a fee that includes the professional service and, implicitly, the use of facilities is charged. Once the information on amount and frequency for each type of patient was collected, the cost was estimated by using the fees in the Manual of the 2020 Compulsory Traffic Accident Insurance (SOAT, *Seguro Obligatorio de Accidentes de Tránsito* in Spanish).

In the case of AC, the costs of service provision, materials, and equipment that can be used for multiple activities, such as education and laboratory exams, were included. Likewise, the working time of each professional involved in each activity and the corresponding unitary cost for working time were calculated, as well as other general expenses. Education and technology infrastructure are considered as 1-time costs, as they are incurred once. Total costs were calculated by adding the variable costs incurred by each patient and the fixed costs of the cohort assisted in the clinic, which was divided by the number of patients.

Costs were assessed from the public tender processes found in the transactional platform of procurement of the Colombian government; that is, the Electronic System of Public Procurement (SECOP, *Sistema Electrónico de Contratación Pública* in Spanish).

The costs associated to thromboembolic and hemorrhagic events were collected from published Colombian studies in patients with NVAF, and the cost of clinically relevant bleeding was obtained from a cross-sectional study conducted in a hospital in the country.[18] The costs of other complications were taken from a study conducted by the Institute of Technology Assessment in Health (IETS, *Instituto de Evaluación Tecnológica en Salud* in Spanish),[19] its estimation are derived from a review of the clinical practice guidelines and protocols. Relevance was validated with clinical experts, and the assessment was obtained on the basis of the Costs Manual ISS 2001, and it was adjusted by 30% in the case of the medicines in the Drug Price Information System (SISMED, *Sistema de información de precios de medicamentos* in Spanish). These costs do not correspond to the analysis period; therefore, they were adjusted according to the price index of 2020.

Sensitivity Analysis

A univariate sensitivity analysis was carried out to examine the impact in the key model variables, such as the operational capacity of ACs, keeping in mind that the costs of this alternative depend to a great extent on the allocation of fixed costs. In relation to the impact of other variables used in the study, each one of the variables was individually evaluated within a range of plausible values, while the rest of the variables remained constant. A Monte Carlo simulation was run 1000 times for the probabilistic sensitivity analysis, in which gamma distributions were assigned for costs, and beta distributions for clinical parameters.

Results

Baseline Scenario

Total annual number of clinical events in 228 patients for follow-ups in AC and UC. In a year, 35 hemorrhagic events

and 6 strokes can be avoided in patients treated in ACs, compared to patients treated in UC, without differentiating between the type of anticoagulant they received (Table 2).

The costs associated with thromboembolic and hemorrhagic events accounted for 80% of total costs in the UC group patients, while, in the AC group, the costs related to the clinical follow-up of chronic OAT were 59% of total costs. This was due to the more stringent monitoring of patients by the AC, both in the case of patients that received warfarin and in the case of those that received DOAC. The total average costs for the group of patients treated in ACs was $126 522, compared to $141 514 for the UC group, which implies a difference of $14 992 in 1 year of follow-up (Table 3).

Sensitivity Analysis

By increasing the number of patients that enter ACs or the UC, our analysis suggests that when the follow-up patient cohort reaches 170 patients, the costs between the types of management services is similar. Once this number is exceeded, ACs would generate an important cost reduction, compared to UC (see Figure S1).

The univariate sensitivity analyzes show that the variable of the death RR of a patient with NVAF, as well as that of the non-disabling ischemic stroke, it had an important impact on the variability of total costs of ACs and the UC. Specifically, in ACs, when the office lease equals $4314 and the death RR is 5.27 times higher, a cost varies between 64 and 1.5 thousand, respectively, would be generated, compared to the UC. For the rest of the variables, it was found that ACs generate savings that range from 1.5 to 24 thousand (see Figure S2).

The probabilistic sensitivity analysis allowed the evaluation of the potential results of the total costs of ACs and UC by means of 1000 simulations. Consequently, it was possible to identify that in the 83% of the simulated cases, ACs generated savings, compared to UC. Likewise, it was observed that 95% of the savings were between $27 and $135, which implies savings between $119 and $594 per patient/year.

Table 2. Total Clinical Events in the Patient Cohort within One Year.

	AC	UC	Difference
Major bleeding	5	3	−2
Clinically relevant bleeding	11	41	29
Minor bleeding	32	40	8
Systemic embolism	0	0	0
Hemorrhagic stroke	0	0	0
Disabling ischemic stroke	0	2	1
Non-disabling ischemic stroke	6	10	5
Mortality	1	1	0

Number of events in the cohorts in the follow-up year per type of chronic.
Abbreviations: AC, anticoagulation clinic; OAT, oral anticoagulant therapy and type of follow-up; UC, usual care.

Discussion

The management services of chronic OAT through the ACs resulted more expensive than in the UC, as ACs include expenses associated with verifying medication adherence, the patient education program, adverse event monitoring, assessing any change in medicines, and performing and reviewing laboratory tests during the visit, which is not carried out in the UC group patients. However, an impact on the reduction of thromboembolic events by 49% and in hemorrhagic events (ie, major bleeding, clinically relevant non major bleeding, and major bleeding) by 42% were observed.

Similar findings were reported in patients under warfarin, in the study by Parry et al[20], where ACs were more

Table 3. Total Cost for Patient Cohort per Year.

	AC	UC
Clinical follow-up costs	**$ 274,892,859**	**$ 113,615,037**
Events costs	**$ 192,351,435**	**$ 408,994,775**
Major bleeding	$ 14,203,147	$ 8,128,493
Clinically relevant bleeding	$ 12,472,874	$ 45,204,238
Systemic embolism	$ 1,321,190	$ 1,077,081
Hemorrhagic stroke	$ 1,418,393	$ 1,878,601
Disabling ischemic stroke	$ 9,907,278	$ 48,729,984
Non-disabling ischemic stroke	$ 153,028,555	$ 303,976,378
Total cost	**$ 467,244,294**	**$ 522,609,811**

The costs of the patient cohort of 228 patients are reflected per type of follow-up, and the differentiation is made between the costs associated with anticoagulation follow-up and those associated with hemorrhagic and thromboembolic events. Bold values in the Table signifies that the total cost is the sum of events and clinical follow up cost.
Abbreviations: AC, anticoagulation clinic; UC, usual care.

effective, thus generating an increase in quality-adjusted life years, compared to the UC, with a greater cost of follow-up. The study by Lafata et al[21] showed savings in the costs of ACs due to the reduction in thromboembolic and hemorrhagic events. In relation to the impact of clinical outcomes, most of the studies did not compare ACs to the UC. Instead, they used other follow-up methods, such as immediate diagnostic devices,[22] with results suggesting, in different medical care systems of different countries, that ACs may provide better results with regards to the target INR range from 2.0 to 3.0 and the increase of TTR.[23]

In relation to the patients treated with DOAC, no information related to the economic impact of ACs or to the impact of ACs on clinical complications was found. Despite their ease of use, the response of DOAC may be affected by treatment adherence, interruption due to bleeding, or inadequate dosing. Therefore, it has been recommended that follow-up for patients under DOAC be performed in the ACs, highlighting patient and/or caregiver education.[9]

ACs generate better care in patients under chronic OAT, which implies an increase in follow-up costs. Nevertheless, this increase is compensated by the reduction in costs associated with hemorrhagic and thromboembolic events. In the baseline case, the AC showed savings when compared to the UC, as it generated total savings for $66 per patient-year, while in the sensitivity analyzes, ACs showed an 83% likelihood of generating savings, compared to the UC. These results were affected by changes in mortality parameters and by the cost of leasing the offices where the ACs would operate, which implies an additional cost between $1.3 and $54 thousand, respectively.

An important systematically reported difference with regards to the follow-up of AC patients compared to UC patients is the patient education. The technology assessment carried out by INAHTA (International Network of Agencies for Health Technology Assessment) shows that as the level of education of the patient increases, treatment adherence improves, and so does their empowerment toward the disease.[24]

Savings are greater with the ACs compared to the UC in patients under warfarin due to the greater risk of experiencing complications and the greater follow-up that these patients require. Some studies suggest that patients with a high TTR have a smaller number of complications. According to the systematic review conducted by Wan et al[25], an 8.3% increase in TTR reduces major bleeding by 1 event per 100 patient-years, and a 10.2% increase reduces thromboembolic events by 1 event per 100 patient-years.

One of the main limitations of this study is the definition of ACs as an intervention, due to the wide heterogeneity in the structure, function, and services, including in-person or telephonic care models.[1] Therefore, several factors make up the AC, which leads to a variation in the costs attributed to this anticoagulation management service. However, the different sensitivity analyzes aimed to reflect the possible differences in costs of ACs. The study was limited to patients with NVAF, and patients with any other diagnosis were not included. Another relevant limitation is that, since there are no data from randomized clinical trials for the population receiving chronic OAT (warfarin or DOAC) under the studied follow-up anticoagulation management services, it was necessary to use safety and efficacy data from observational studies. For that reason, further studies should explore different approaches for anticoagulation care in a wide range of ACs, involving different types of anticoagulants. Additionally, it must be considered that the budget for the chronic oral treatment of NVAF patients depends on each country's healthcare system.

Conclusions

Results of this study showed that Anticoagulation Clinics compared to Usual Care generate important savings in the treatment of patients under chronic oral anticoagulant therapy, both with warfarin and DOAC, for non-valvular atrial fibrillation. Further clinical studies that evaluate the impact of both interventions on relevant outcomes for the healthcare systems are necessary.

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Supplemental Material

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