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Cost-effectiveness analysis of propafenone and amiodarone for atrial fibrillation initial treatment

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ABSTRACT

Introduction: Atrial fibrillation is the most common sustained arrhythmia due to progressive prevalence given population aging. Its treatment must be constantly improved, also considering cost-effective therapies. **Objectives:** To determine cost-effectiveness and budget impact analysis of propafenone versus amiodarone in atrial fibrillation patients without structural heart disease in Brazilian Public and Private Healthcare System. **Methods:** Decision analytic model was designed to compare two treatment strategies. Study endpoint was "atrial fibrillation reversion with hospital admission". Costs were valued in Brazilian Real (BRL) for 2009. Effectiveness data were taken from randomized controlled clinical trials through literature critical analysis. For budget impact analysis, total direct cost per patient was multiplied by population eligible for treatment. **Results:** Total 1-year cost per patient with amiodarone treatment was BRL 484.45, whereas with propafenone was BRL253.70 in the public healthcare system. These costs were BRL1,059.08 and BRL 832.69 in the private healthcare system, respectively. The budget impact analysis shows that a reduction of approximately BRL 29 million and BRL9 million a year in public and private healthcare system was estimated with the incorporation of propafenone into treatment of target population studied. **Conclusion:** The incorporation of propafenone into atrial fibrillation baseline treatment in patients without structural heart disease is able to restore the sinus rhythm in a shorter period of time and prevent increasing the number of hospital admissions. This model suggests that the use of propafenone could generate fewer costs in the short-term within public and private healthcare system.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and accounts for approximately one-third of all hospitalizations for cardiac rhythm disturbances (Sociedade Brasileira de Cardiologia, 2003). A prevalence of 0.4% in general population and, for those aged over 50 years, a two-fold increase in prevalence for every decade were observed in an international data analysis (Sociedade Brasileira de Cardiologia, 2003). In approximately 30% of cases, AF can occur in the absence of any heart disease (lone AF) or any other disease (idiopathic AF) (Levy *et al*., 1999).

AF can be classified as paroxysmal, persistent or permanent. Paroxysmal AF terminates spontaneously with no need of pharmacological treatment or electrical cardioversion (CV) for less than 7 days (often less than 24 hours), with or without recurrence. Persistent AF is sustained without interruptions with or without recurrence (unless electrical CV or pharmacological treatment is performed for more than 7 days, usually). This category also includes longstanding AF, which lasts over one year. In permanent AF, reversion attempts failed or arrhythmia reversion was not performed. However, although these three AF forms differ from each other, patients can migrate from one to another (Fuster *et al*., 2006).

Propafenone was found to be efficacious in the CV of recent-onset AF in patients without structural heart disease with lower median conversion time compared to amiodarone (2.4 hours versus 6.9 hours) in clinical trials by Blanc *et al*. (Blanc *et al*., 1999). In a systematic review by Khan *et al*. to evaluate efficacy of 600 mg single oral propafenone dose for recent-onset AF, this treatment was found to be the chosen therapy for patients without structural heart diseases (Khan, 2001). Capucci *et al*. demonstrated that this treatment was reproducible with efficacy of 93% (p<0.001) (Capucci *et*

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al., 2003) and in 2004 Alboni *et al*. conducted a clinical trial testing this treatment protocol in a setting without daily prophylaxis (Alboni *et al*., 2004). Results demonstrated that propafenone was effective in 94% of cases with mean period for symptom resolution of 113±84 minutes preventing great number of hospitalizations.

The objective of this study was to determine cost-effectiveness and budget impact analysis for the use of propafenone versus amiodarone in acute AF baseline treatment patients without structural heart diseases treated in Brazilian Public Health System.

Methods

Clinical decision models are designed in chronological sequence for problem identification, problem structuring (treatment flow chart and Markov model), parametering decision model (probabilities for endpoint occurrences, according to literature critical analysis), and model analysis (cost, endpoint and risk estimation) (Hunink & Glasziou, 2001).

Cost-effectiveness analysis measures costs in monetary units divided by a non monetary unit called natural unit (e.g. "life years saved"), allowing cost estimation incurred per effectiveness unit. A health intervention is considered to be cost-effective as long as it produces a clinical benefit that justifies its cost.

Flowcharts schedule demonstrating all patients' treatment program sequence with propafenone and amiodarone (Figure 1) were designed.

For cost and endpoint estimation of treatments, a Markov decision analytic model simulated the disease treatment and hospitalization occurrence for AF patients in the both perspectives, Brazilian Public Healthcare System (SUS) and Private Healthcare System. In such analysis, two treatment strategies were compared: the use of propafenone or amiodarone. Patients were entered into the model when the first acute AF episode occurred and were treated for disease control with propafenone or amiodarone. Quarterly cycles were considered and, at the end of each cycle, heath status of all patients was reassessed. Patients under treatment could suffer a new AF or remain with no recurrence. After a new episode, some patients achieve success only with pharmacological CV interference, while others need undertake electrical CV. Amiodarone patients started daily prophylaxis upon the second episode. Not all propafenone patients followed daily prophylaxis upon the second episode. The majority of these patients (78%) did not take daily preemptive therapy with propafenone; at a new episode medication was only administered at the moment of occurrence. The remainder 22% started daily prophylaxis right after the second episode. Only 12% patients remained without daily prophylaxis, either with or without successful pharmacological CV, and 88% needed to start daily prophylaxis (Alboni *et al*., 2004).

In order to validate some conducts for the current practice in acute AF treatment of patients without structural heart disease in Brazil and guarantee that the designed flow charts correspond to the reality for AF treatment, a discussion panel was organized with two cardiologists with a minimum 10-year experience, representing public and private institutions.

Probability data for occurrence of events

"AF reversion with hospital admission" was considered as health endpoint.

Table 1 presents probability data used by the model for patients treated with propafenone or amiodarone.

Mortality rate reduction was not verified for any of the treatments. Therefore, mortality was not considered in the model.

The following protocols were considered for patients requiring pharmacological CV:

Propafenone: 600 mg for each episode (oral adminis tration)

Amiodarone: 300 mg intravenous (IV) for 1 hour followed by 20 mg/Kg for the consecutive 24 hours. We consider as mean weight 70Kg per patient.

For patients without daily prophylaxis, the same used propafenone dosage during pharmacological CV must be administered during AF episodes.

The following protocols were considered for patients under daily prophylactic treatment:

Propafenone: 450 mg daily (oral administration)

Amiodarone: 200 mg daily (oral administration)

Patients under daily propafenone prophylactic treatment do not require any routine follow-up. Controversially, those under amiodarone daily prophylaxis require liver and thyroid function tests every six months, besides chest radiography, electrocardiogram (ECG), dermatologic, neurologic and ophthalmologic visits once a year (Vassallo & Trohman, 2007).

Cost data used in the model for the Public Institution perspective

Direct costs concerning hospitalizations of AF treatment patients without structural heart disease were considered economic endpoints. Those costs are directly incurred for the treatment of a patient, such as costs related to medications, hospital admission, and medical procedures. These data were collected from the Brazilian Unified Healthcare System.

Drug prices and the unitary values of other items associated with treatment and used in the model are listed in Table 2. Costs related to medical examinations and visits were collected from the Management Procedures Table System (SIGTAP) by DATASUS. Every monetary value refers to 2009. (Revista Kairos, 2009) (Ministério da Saúde, 2009).

The mean-cost of one hospitalization for AF was charged from all patients requiring pharmacological CV during amiodarone treatment. That is all patients who underwent phar-

Table 1. Probability data used in the model for both perspectives

Patients under amiodarone treatment			
	%	**Source**	
Acute AF - 1st episode	100%	Requirement for entering into the model	
Reversion – Pharmacological CV	89.13%	Kochiadakis *et al.*, 2007	
Reversion – Pharmacological. CV + Electrical CV	10.87%	Kochiadakis *et al.*, 2007	
Discharge without regular medication after 1st episode	100%	Panel of experts	
Discharge with daily prophylaxis after 2nd episode	100%	Panel of experts	
	%	**Source**	**Study mean-period**
Paroxysmal AF - 2nd episode	80%	Alboni *et al.*, 2004	15 months
Discontinue treatment	16.67%	Kochiadakis *et al.*, 2004	19 months
Recurrence after 2nd episode	34.72%	Kochiadakis *et al.*, 2004	19 months
Patients under propafenone treatment			
	%	**Source**	
Acute AF - 1st episode	100%	Requirement for entering into the model	
Reversion - Pharmacological CV	80.21%	Kochiadakis *et al.*, 2007	
Reversion - Pharmacological CV + Electrical CV	19.79%	Kochiadakis *et al.*, 2007	
Discharge without regular medication after 1st episode	100%	Panel of experts	
Discharge without daily prophylaxis after 2nd episode	78%	Alboni *et al.*, 2004	
Discharge with daily prophylaxis after 2nd episode	22%	Alboni *et al.*, 2004	
Patients without daily prophylaxis requiring change to daily prophylaxis	88%	Alboni *et al.*, 2004	
	%	**Source**	**Study mean-period**
Paroxysmal AF - 2nd episode	80%	Alboni *et al.*, 2004	15 months
Without daily prophylaxis			
Recurrence after 2nd episode	100%	Panel of experts	
With daily prophylaxis			
Discontinue treatment	2.70%	Kochiadakis *et al.*, 2004	21 months
Recurrence after 2nd episode	44.59%	Kochiadakis *et al.*, 2004	21 months

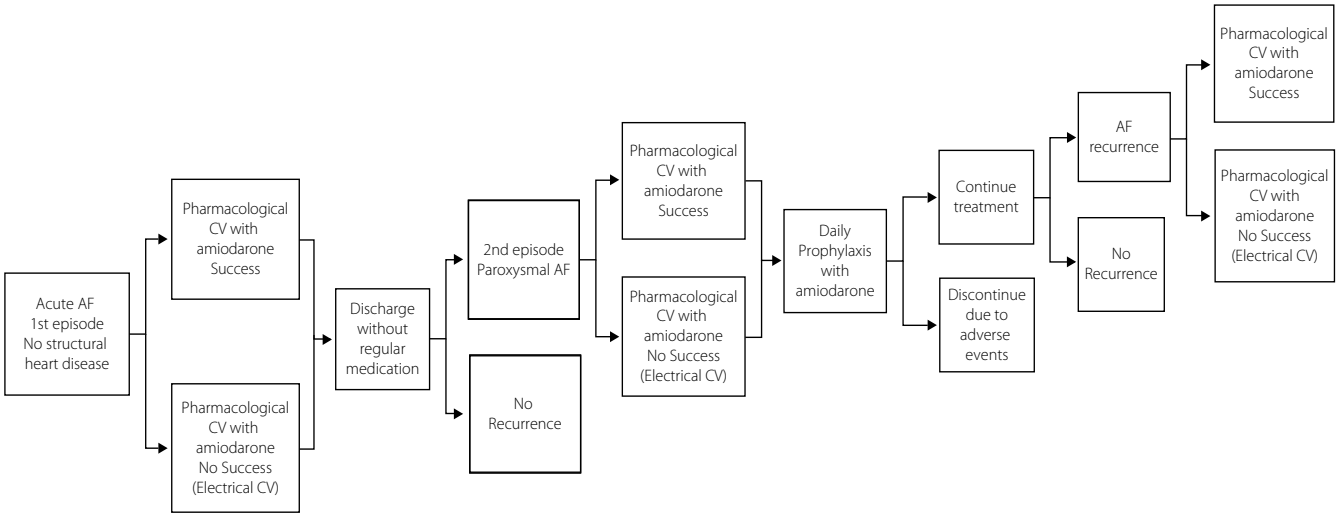

Figure 1. Chart flow for patients under amiodarone or propafenone treatment

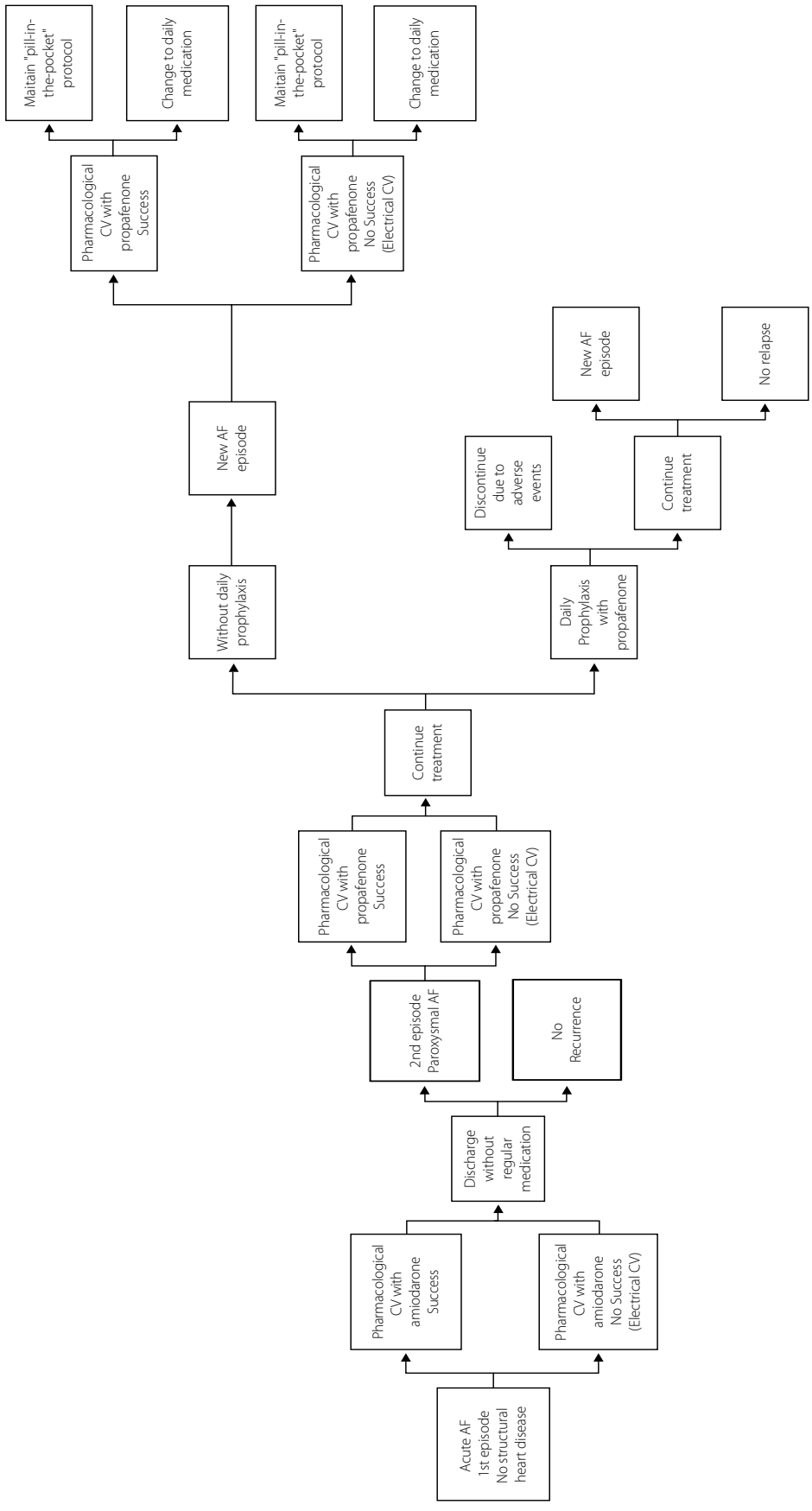

Figure 1 (cont.). Chart flow for patients under amiodarone or propafenone treatment

Table 2. Unit Costs

	Public	Private
Medications	**Price (R$)**	**Price (R$)**
Propafenone (tablet)	1.72	2.52
Amiodarone (tablet)	0.80	1.16
Amiodarone (vial)	2.08	3.05
Complementary Tests	**Unit Cots (R$)**	**Unit Cots (R$)**
Chest x-ray	9.50	36.25
ECG	5.16	24.63
Electrolytes (Na, K, Mg, Ca)	7.56	18.12
Thyroid Function	12.00	70.49
Liver Function	4.02	16.64
Medical visit	10.00	42.00
Pulmonary function test	0.00	48.00
Emergency room treatment	10.00	214.70
Hospital admission for AF*	342.21	461.50

* Mean hospital stay of 4.6 days (Instituto Brasileiro de Geografia e Estatística, 2009).

macological CV with amiodarone generate an authorization for hospitalization (AIH - 03.03.06.002-6). This value represents the mean-cost associated with patients admitted to a public hospital for AF, including medicines, tests, and procedures. Therefore, no additional cost was charged to amiodarone-treated patients, only the hospitalization cost (BRL 219.65).

AIH has a length of stay (LOS) of 4 days, thus the minimum LOS needed to charge the AIH is 2 days (mean time divided by 2). However, patients who perform amiodarone pharmacological CV restore the sinus rhythm in a mean time of 6.9 hours (Blanc *et al.*, 1999). We have assumed that those patients needed at least one day hospitalizated; the hospital billing area charges one AIH, justifying the LOS less than the minimum when required.

Propafenone-treated patients requiring pharmacological CV did not need to be admitted in hospital generating an AIH. For these patients the cost for medication (propafenone), for an emergency care with observation and cost related to medical tests (1chest radiography, 3 electrocardiographs and 1 electrolytes dosage) were considered.

Nonetheless, all patients requiring electrical CV after failure pharmacological CV with propafenone or amiodarone had to be hospitalized and the cost related to hospital admission (AIH - 03.03.06.002-6) was included.

Cost data used in the model for Private perspective

Hospitalizations direct costs for AF treatment patients without structural heart disease for were considered economic endpoints. Those are directly incurred for treatment, such as costs related to medications, hospital admission, and medical procedures. These data were collected from Brazilian Supplementary Healthcare System.

Drug prices and the unitary values of other items associated with treatment and used in the model are listed in Table 2. Costs related to medical examinations and visits were collected from the Brazilian Hierarchical Classification of Medical Procedures (Associação Médica Brasileira, 2008). Every monetary value refers to 2009. (Revista Kairos, 2009). The mean cost of daily hospitalization was collected from PROAHSA (Fundação Getúlio Vargas, 2001).

Propafenone-treated patients requiring pharmacological CV did not need to be maintained in hospitals. For these, the costs for an emergency care with observation were considered, while for amiodarone-treated patients, costs for a daily hospitalization were included. For both patients' medication costs (propafenone or amiodarone) and costs concerning medical tests (1chest radiograph, three electrocardiographs and 1 electrolytes dosage) were considered.

Results were calculated for 1-year time horizon (short-term period), with no discount applied for this timeframe.

Results

Treatment Alternative strategies comparative results were measured by incremental cost-effectiveness ratio (ICER), defined as the additional treatment cost divided by the extra gain in attained health for two specific alternatives of treatment. This benefit was expressed as AF reversion with hospital admission.

Results for costs consolidated by treatment, costs per patient for 1 year, and both perspectives are presented in Table 3 and Table 4, as well as effectiveness data (Table 5).

Treatment costs with propafenone are observed to be lower than with amiodarone, in 1-year time horizon, mainly because of the reduction in hospital admissions. Consequently, the result is less costly and more effective, in other words, a lower number of hospitalizations with less expensive treatment. A cost-saving health intervention produces clinical benefit that is justified by lower cost. Therefore, propafenone acute AF treatment patients without structural heart disease is cost-saving compared with amiodarone treatment, in both perspectives.

A budget impact analysis was conducted allowing the financing source to estimate the necessary resources to implement propafenone incorporation as a new therapeutic alternative to eligible AF treatment patients.

Brazilian population is estimated to reach 133,956,985 male and female inhabitants aged over 18 years by 2010 (Instituto Brasileiro de Geografia e Estatística, 2009). According to Brazilian guideline for AF, 0.40% of the general population

Table 3. Cost results for 1-year horizons for Public Institution perspective

Consolidated cost per treatment (R$)		
	Amiodarone	**Propafenone**
Pharmacological CV cost	219.65	48.63
Pharmacological CV + Electrical CV cost	219.65	219.65
Daily prophylaxis cost (for 3 months)	75.78	246.04
Follow-up cost (for 3 months)	30.67	0.00

Cost per patient during 1-year time horizon (R$)			
	Amiodarone	**Propafenone**	**Incremental**
Total cost	484.45	253.70	- 230.74
Pharmacological CV cost	310.67	98.86	- 211.81
Electrical CV cost	37.89	86.79	48.90
Prophylaxis cost	96.73	68.06	- 28.67
Follow-up cost	39.15	0.00	- 39.15

Table 4. Cost results for 1-year horizons for Private Institution perspective

Consolidated cost per treatment (R$)		
	Amiodarone	**Propafenone**
Pharmacological CV cost	429.55	183.29
Pharmacological CV + Electrical CV cost	1172.48	926.22
Daily prophylaxis cost (for 3 months)	104.76	340.13
Follow-up cost (for 3 months)	90.53	0.00

Cost per patient during 1-year time horizon (R$)			
	Amiodarone	**Propafenone**	**Incremental**
Total cost	1,059.08	832.69	-226.39
Pharmacological CV cost	607.55	372.64	-234.92
Electrical CV cost	202.25	365.96	163.72
Prophylaxis cost	133.73	94.09	-39.64
Follow-up cost	115.56	0.00	-115.56

is affected by AF, of which 30% without structural heart disease (Sociedade Brasileira de Cardiologia, 2003). With these data, it was possible to estimate the Brazilian population, aged over 18 years, eligible for acute AF treatment.

The National Health Agency (ANS) claims that 23.8% of the population residing in Brazil (generally composed of 158,837 individuals in 2009) is treated by health-operating companies; therefore, 76.2% is left for SUS users. Accordingly, public and private healthcare system users from population eligible for treatment, aged over 18 years, are estimated to be 120,975 and 37,862, respectively. This study considered annual cost per patient, upon treatment start, calculated based on Markov model, which was used to reach the total expenditure by the health financing source with acute AF treatment in Brazil over one year. The budget impact for incorporating propafenone is demonstrated in Tables 6 and 7.

Table 5. Effectiveness results for 1- year horizons for both perspectives (Private and Public Intitutions)

	Amiodarone	**Propafenone**	**Incremental**
Effectiveness during 1-year time horizon			
AF reversion with hospital admission	0.63	0.00	- 0.63

Conclusion

Economic studies have been increasingly applied on health due to the advent of new technologies and the scarcity of resources from paying sources. Economic studies for AF patients are only found for the prophylactic use of antiarrhythmic agents (Lumer *et al*., 2002) (Nattel *et al*., 2003). No economic analyses were published on the comparison of outpatient versus hospital treatment for AF in Brazil. Some economic analyses in cardiology were already published with national data, however evaluating other interventions such as inhospital versus prehospital thrombolysis (Araújo *et al*., 2008) and the use of pharmacological versus standard stents (Polanczyk *et al*., 2007).

Propafenone is currently a therapeutic option for acute AF treatment and prevention in patients without structural heart disease because it is effective and faster in CV than amiodarone, reducing the period of hospital stay (Blanc *et al*., 1999), (Kochiadakis *et al*., 2007), (Kochiadakis *et al*., 1998).

Propafenone can also be used by patients after the second FA only when th e episode occurs. Whenever first symptoms are detected by patients, they can take propafenone orally in an emergency room visit. The treatment without daily prophylaxis is associated to a 94%-sinus rhythm conversion rate and prevents many hospitalizations (Capucci *et al*., 2003), (Alboni *et al*., 2004).

Considering the great number of patients who evolve to AF chronic forms, long-term use of amiodarone is associated with a great number of severe adverse events.

Table 6. Budget impact for incorporating propafenone in AF acute treatment in patients without structural heart disease in Public Institution perspective

	Amiodarone cost	Propafenone cost	Budget impact
Within 1 year	R$ 61.536,48	R$ 32.226,55	-R$ 29.309,93

Table 7. Budget impact for incorporating propafenone in AF acute treatment in patients without structural heart disease in Public Institution perspective

	Amiodarone cost	Propafenone cost	Budget impact
Within 1 year	R$ 42.103,309	R$ 33.103,155	-R$ 9.000,154

This fact requires strict follow-up of patients with medical visits and regular complementary tests, besides the need for treatment discontinuation in approximately 17% of patients (Kochiadakis *et al*., 2004), (Vassallo & Trohman, 2007). The propafenone long-term use, whenever necessary, is not related to severe adverse events and provides safety.

Current clinical practice guidelines recommend using amiodarone for pharmacological CV only when patients' structural heart diseases associated, in which cases propafenone usage would be contraindicated.

The incorporating propafenone as a therapeutic alternative for patients eligible for AF treatment impact was thoroughly analyzed in an economic evaluation comparing propafenone versus amiodarone, and both perspectives related, for 1-year time horizon.

The propafenone resources decrease is mostly due to the reduction of hospitalization, and also to a higher associated cost in comparison with the amiodarone patients' follow-up (regular medical visits and complementary tests).

Besides economic advantage, the fact of preventing increasing hospital admissions is relevant for SUS, taking into consideration the lack of available beds for patients. Accordingly, only patients with real need for hospital care are admitted.

One limitation of this study is the probability data use for endpoints occurred in population and scenario different from those for public and private healthcare system. However, although reported in national guidelines (Sociedade Brasileira de Cardiologia, 2003), the purpose of a panel of experts was the adaptation of conducts to the national reality to minimize this bias. AF prevalence data used in the budget impact analysis were also collected from international studies because of the absence Brazilian data.

The incorporation of propafenone in the initial treatment for AF patients without structural heart disease is able to promote CV in shorter period of time and prevent a large number of hospitalizations. Its regular use by prophylactic treatment patients with indication represents lesser use of resources than amiodarone use incurs. In Public and Private Healthcare System, these facts are able to generate fewer costs in the short-term. By considering every AF patients without structural heart disease in Brazil as eligible for treatment, in the first year was estimated, with the incorporation of propafenone for target population treatment studied, a reduction of approximately BRL 29 million and BRL 9 million in Public and Private healthcare system, respectively.

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