ORIGINAL ARTICLE

Rev Bras Cir Cardiovasc 2010; 25(4): 457-465

Oral anticoagulation in carriers of mechanical heart valve prostheses. Experience of ten years

Anticoagulação oral em portadores de próteses valvares cardíacas mecânicas. Experiência de dez anos

Nelson Leonardo Kerdahi Leite de CAMPOS[1], Rubens Ramos de ANDRADE[2], Marcos Augusto de Moraes SILVA[3]

RBCCV 44205-1215

Abstract

Background: **Published data suggest that rates of thromboembolism and bleeding in patients with mechanical heart valve prostheses can be greatly reduced if anticoagulant therapy is optimized.**

Objectives: **To evaluate the occurrence of complications in patients with mechanical prosthetic heart valves undergoing anticoagulant therapy optimized by means of specialized clinics.**

Methods: **We studied the occurrence of complications during 10 years in 261 patients with mechanical heart valve prostheses with anticoagulation and followed up in specialized clinics. These patients were divided into two groups according to percentage of consultations with prothrombin time (INR) within the desired range: G1-0% to 50.00% and G2-50, 01% to 100% of the consultations. We evaluated the occurrence of thromboembolic complications and bleeding in their entirety or subdivided into major and minor, according to severity. The results are presented in an actuarial study and linearized frequency of occurrence of events.**

Results: **The actuarial study showed that, over time, in G2 (with 50.01% to 100% of the consultations with INR in desired range) more patients were free of the occurrence of any event type, minor bleeding events or the accentuated increase of INR. The linearized frequency of occurrence in all event types was also lower in group G2.**

Conclusions: **The length of stay within the desired range of anticoagulation is directly related to the occurrence of complications. However, even with optimized monitoring by specialized outpatient clinic, only about a third of patients had adequate anticoagulation level in more than half of the consultations.**

Keywords: **Anticoagulants. Embolism and thrombosis. Hemorrhage. Heart valve prosthesis.**

1. Assistant Professor in the Department of Cardiovascular Surgery, Department of Surgery and Orthopedics, Faculty of Medicine of Botucatu - UNESP.
2. Assistant Professor in the Department of Cardiovascular Surgery, Department of Surgery and Orthopedics, Faculty of Medicine of Botucatu, UNESP.
3. Associate Professor (Lecturer Professor) Head of the Cardiovascular Surgery - Department of Surgery and Orthopedics, Faculty of Medicine of Botucatu, UNESP.

Work performed at Faculdade de Medicina de Botucatu - Universidade Estadual Paulista - UNESP, Botucatu, SP, Brazil.

Ciorrespondence address:
Nelson Leonardo Kerdahi Leite de Campos. Rua Francisco Lyra Brandão, 608 – Vila Sônia – Botucatu, SP, Brasil – CEP: 18607-000.
E-mail: ncampos@fmb.unesp.br

The study is part of the PhD thesis in the Postgraduate Course in General Surgery, Faculty of Medicine of Botucatu - UNESP.

Article received on June 22nd, 2010
Article accepted on September 15th, 2010

Resumo

Introdução: **Dados da literatura sugerem que as taxas de tromboembolismo e sangramento em pacientes com próteses valvares cardíacas mecânicas podem ser muito reduzidas se a terapia anticoagulante for otimizada.**

Objetivos: **Avaliar a ocorrência de complicações em portadores de próteses valvares cardíacas mecânicas submetidos à terapêutica anticoagulante, otimizada por meio de ambulatório especializado.**

Métodos: **Estudou-se a ocorrência de complicações ao longo de 10 anos em 261 pacientes com próteses valvares cardíacas mecânicas, anticoagulados e acompanhados em ambulatório especializado. Esses pacientes foram divididos em dois grupos conforme porcentual de consultas com tempo de protrombina (RNI) dentro do intervalo desejado: G1-0% a 50,00% e G2-50,01% a 100% das consultas. Foram avaliadas as ocorrências de complicações tromboembólicas e hemorrágicas na sua totalidade, ou subdivididas em maiores e menores, de acordo com a gravidade. Os resultados estão apresentados sob forma de estudo atuarial e de frequência linearizada de ocorrência de eventos.**

Resultados: **O estudo atuarial mostrou que, ao longo do tempo, no grupo G2 (com 50,01% a 100% das consultas com a RNI no intervalo desejado) maior número de pacientes esteve livre da ocorrência de qualquer tipo de evento, de eventos hemorrágicos menores ou da elevação exacerbada da RNI. As frequências linearizadas de ocorrência, em todos os tipos eventos, também foram menores nos pacientes do grupo G2.**

Conclusões: **O tempo de permanência dentro do intervalo de anticoagulação desejado está diretamente relacionado com a ocorrência de complicações. Entretanto, mesmo com acompanhamento otimizado por meio de ambulatório especializado, apenas cerca de um terço dos pacientes apresentaram nível de anticoagulação adequado em mais da metade das consultas.**

Descritores: **Anticoagulantes. Embolia e trombose. Hemorragia. Próteses valvulares cardíacas.**

INTRODUCTION

It has been shown in many publications that patients with mechanical heart valve prostheses must be kept continuously anticoagulated, aiming to reduce the risk of thromboembolic complications [1-6].

In Brazil, studies were conducted to evaluate complications in patients with mechanical heart valve prostheses [7-9].

The anti-vitamin K drugs are among the most used worldwide. Warfarin is the most commonly and frequently used anticoagulant in North America, Scandinavia and the UK. Phenprocoumon is used mainly in continental European countries, among them, Germany [10].

The survey of prothrombin time (PT) is sensitive to reductions in coagulation factors II, VII and X. The model calibration INR (international normalization ratio), adopted in 1982 has since been used in a standardized way to report the results of PT, measured with thromboplastin used in each laboratory [11].

According to Bussey [12], the available literature advises that the rates of thromboembolism and major bleeding in patients with prosthetic heart valves could be lowered from 50% to 90% if the current anticoagulant therapy was optimized.

The Seventh Conference of the *American College of Chest Physicians* 2004 makes recommendations for anticoagulation with oral anti-vitamin K drugs in patients with mechanical heart valve prosthesis, indicating the following conduct in the maintenance of INR, target of 2.5 ranging from 2.0 to 3, 0 in the prostheses St. Jude Medical (bi-leaflet) in the aortic position, target 3.0, range from 2.5 to 3.5 in the mitral position (single disc and bi-leaflet) and aortic single disk, and target 3, 0, ranging between 2.5 and 3.5, administering 75 to 100 mg of aspirin per day for cage-ball prosthesis [13].

Cannegieter et al. [14] published a study conducted at four regional clinics of anticoagulation control in Holland, aiming to determine the optimal intensity of prophylactic anticoagulation in patients with mechanical heart valve prostheses, based on thromboembolic and hemorrhagic complications. These authors showed a lower incidence of thromboembolism in patients with aortic prostheses compared to patients with mitral prostheses and those with two prostheses, being that the occurrence of this complication was higher in the latter.

Lourenço et al. [9] presented a study on 100 patients using oral anticoagulation for various indications, with only six of them being patients with mechanical heart valve prosthesis. In this study we investigated 952 consultations, where 53% were within the range of desired INR, 35% below and 12% over this range.

The aim of this study was to evaluate the level of anticoagulation and hemorrhagic or thromboembolic complications in a cohort of patients with prosthetic mechanical heart valves, followed up for ten years optimally through special outpatient clinics.

METHODS

The study was based on outpatient clinic data and hospital records of patients with mechanical heart valve

prostheses, followed in the Outpatient Anticoagulation Control in the Department of Cardiovascular Surgery, Hospital das Clinicas, Faculdade de Medicina de Botucatu, UNESP, for ten years between January 1st, 1993 and December 31st, 2002. All data were collected and organized by the same researcher, who also participated in the period in the outpatient care.

This study was submitted to the Ethics Committee of the Faculdade de Medicina de Botucatu and approved (OF.68/2005-CEP).

The sample includes 261 patients with mechanical prosthesis, being 113 in aortic position, 125 in mitral position and 23 in mitral and aortic position. We excluded from the study patients whom we were unable to obtain sufficient or reliable data for the study.

Participants were 135 women and 128 men. Mean age of 40.60 years for women and 41.04 years for men.

In G1, we found 172 patients (65.9% of patients) and G2, 89 patients (34.1% of patients).

The models of mechanical prosthetic valves are listed in Table 1. In some patients, it was not possible to identify the model introduced; nonetheless, they were included in the study only after checking with the hospital records that these were mechanical prostheses. The cases that eventually presented uncertainty were excluded.

Square 1. Models of mechanical heart valve prostheses and their distribution according to the position.

Model	Total	Aortic	Mitral	Mitral-aortic
Bicarbon-Sorin	116	40	60	16
St Jude Medical	63	25	23	15
Omnicarbon	32	11	17	4
Omniscience	28	12	15	1
Starr-Edwards	12	12	0	0
Carbomedics	2	2	0	0
Lilliehi-Kaster	2	1	1	0
Edwards	1	0	1	0
Hall-Kaster	1	0	1	0
Mira	1	1	0	0
Not recognized	26	9	7	10
TOTAL	284	113	125	46

Desired range of INR

We consider the intervals of the desired INR at each visit, according to the positions of the prostheses studied: aortic prosthesis: INR 2.00 to 3.50; mitral: INR 2.50 to 3.50 and mitral-aortic: INR 2.50 to 3.50.

Follow-up time of patients

The study covered the period from January 1st, 1993 to December 31st, 2002, varying the duration of monitoring for each patient. The sum of the periods considered was 1139.78 years.

Groups

Patients were divided into two groups according to the percentage of total consultations in which the INR was within the desired range for the comparison of complication reports:

Group 1 (G1) included patients from 0% to 50.00% of consultations were within the INR target range.

GROUP 2 (G2) included patients from 50.01% to 100.00% of consultations were within the INR target range.

Complications

The complications were divided into thromboembolic complications (major and minor) and hemorrhagic (major and minor).

Thromboembolic complications

Every type of complication in which the patient records evidenced the occurrence of thromboembolic episodes.

Major thromboembolic complications

Severe episodes that required hospital treatment, which may or may not have left patients seriously affected. Event types: ischemic stroke, acute arterial occlusion in limbs, heart valve prosthesis thrombosis.

Minor thromboembolic complications

Episodes of low gravity, allowing outpatient treatment and monitoring. Event type: cerebral transient ischemic stroke.

Hemorrhagic complication

Every type of complication in the patient records which evidenced the occurrence of bleeding episodes.

Major hemorrhagic complication

Severe episodes that required hospital treatment, which may or may not have left patients seriously affected. Event types: severe hematuria, bleeding in MMII (hematoma), vaginal bleeding (uterine), hemoperitoneum bleeding, hemopericardium bleeding, gastrointestinal bleeding, hemorrhagic stroke, intestinal bleeding, retroperitoneal hematoma and severe tongue bleeding.

Minor hemorrhagic complication

Episodes of low gravity, which usually allowed outpatient treatment and clinical care. Event types: ecchymosis, epistaxis, hematuria, vaginal bleeding, mild bleeding in feces, mild optical bleeding, mild hemoptysis, bleeding gums, hematoma during surgical incision to implant a pacemaker, mild gastric bleeding.

Accentuated increase of INR

Outpatient consultations have been observed in INR equal to or higher than 7.0, with no effective bleeding but with potential risk of severe bleeding.

Complications were analyzed in two ways: 1) calculations and actuarial curves, which showed the percentage of patients free of events during the years of study, 2) linear rates of occurrence of events - event number calculations patient-years (number of events. Some patients may have contributed to more than one event).

Statistical study

In actuarial calculations, we used the program Statistical Calculations for Windows V. 1.8, developed by Dr. Domingo Marcolino Braile and Dr. Moacir Fernandes de Godoy and implemented in Power Builder 6.5 by M. Sc. Djalma Domingos da Silva. For construction of the actuarial curves it was used the Microsoft Excel program.

RESULTS

Figure 1 shows the distribution in intervals, of the number of consultations in accordance with the INR (International Normalization Ratio) of PT (Prothrombin Time), obtained in the Outpatient Control Anticoagulation Clinic of the Faculty of Medicine of Botucatu, UNESP, in the period between January 1st, 1993 and December 31st, 2002, a total of 9714 consultations evaluated. It can be observed in the figure that most of the INR consultations were in the range 2.0 to 3.5, suitable for anticoagulation of patients with aortic valve prostheses. For patients with mitral prostheses and mitral-aortic prostheses, even excluding the consultations corresponding to the range of INR between 2.0 and 2.49, which is inadequate for these patients, we still observed a large number of consultations within the range from 2.50 to 3, 50 represented by the higher column of the chart and suitable for all patients being monitored.

The behavior of patients free of any event of G1 and G2 is shown in Figure 2.

Figure 3 shows the behavior of patients free of bleeding and thromboembolic events, including increased exacerbation of INR.

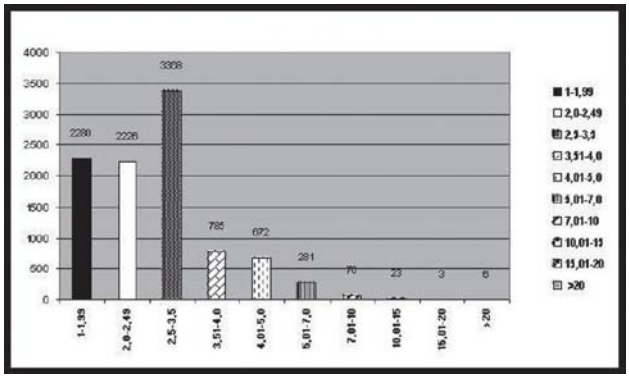

Fig. 1 - Number of consultations in accordance with the range of INR, y-axis: time intervals in prothrombin INR; abscissa axis: number of consultations

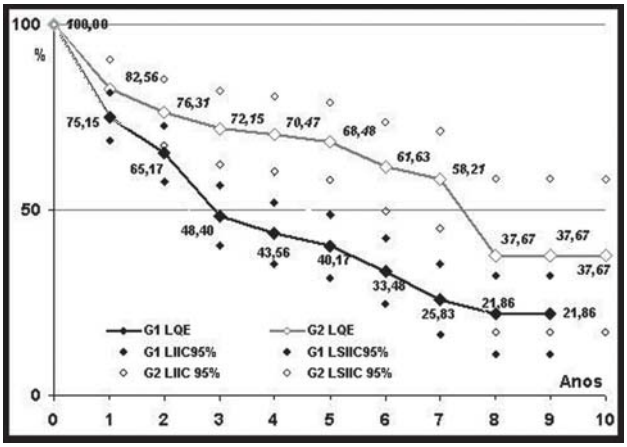

Fig. 2 - Actuarial curves and points of upper and lower limits of the range of 95%, according to the sets of groups (G1 and G2) Free of any event - FAE. Acronyms: Lower limit of the confidence interval 95% - 95% LLCI; upper limit of the confidence interval 95% - 95% UPIC. The numbers next to the points of inflection of the curves are related to the percentage of patients free of events at that time

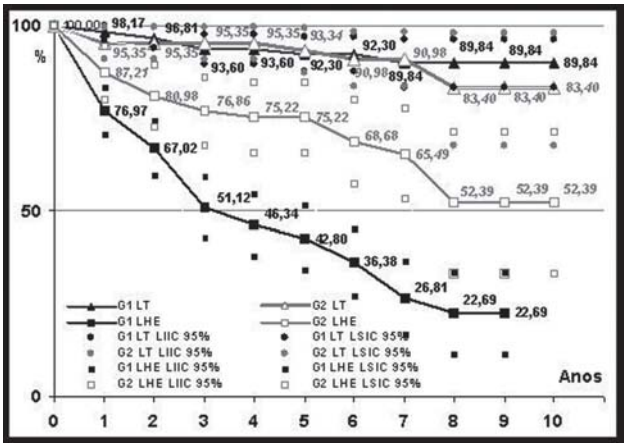

Fig. 3 - Actuarial curves and points of upper and lower limits of the confidence interval of 95%, according to the sets of groups (G1 and G2), free of thromboembolic events - FT and free of hemorrhagic events or exacerbated increase of INR - FHE. Lower limit of the confidence interval 95% - LLCI 95%; Upper limit of the confidence interval 95% - ULCI95%. The numbers next to points of inflection of the curves are related to the percentage of patients free of events at that time

Figures 4 and 5 show the behavior of patients in groups 1 and 2 regarding the major and minor thromboembolic events.

Figure 6 shows the behavior of patients in group 1 and 2 regarding the occurrence of major bleeding events. The minor bleeding events, including or not the exacerbated increases in the INR are shown in Figure 7.

The percentages of patients in groups 1 and 2, with their respective standard errors and lower and upper confidence interval of 95%, corresponding to different types of complications studied are presented in Tables 1, 2 and 3.

The linearized rates per 100 patients/year of the occurrence of different studied complications are presented in Table 4.

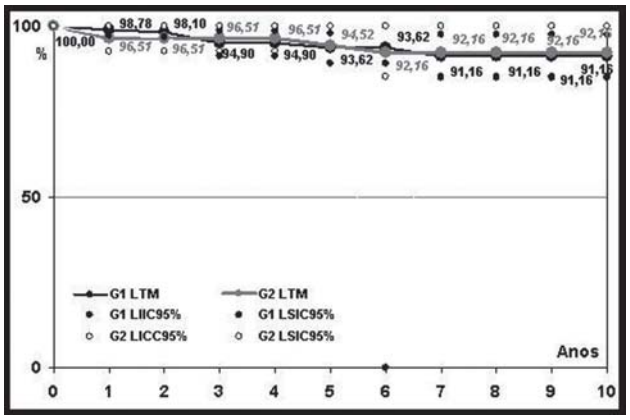

Fig. 4 - Actuarial curves and points of upper and lower limits of the confidence interval of 95%, according to the sets of groups (G1 and G2): Free of major thromboembolic events - FMT. Lower limit of the confidence interval 95% - LLCI 95%; upper limit of the confidence interval 95% - ULCI 95%. The numbers next to points of inflection of the curves are related to the percentage of patients free of events at that time

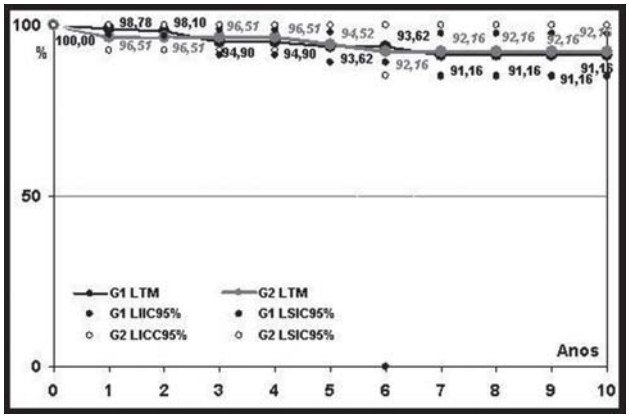

Fig. 5 - Actuarial curves and points of upper and lower limits of the range of 95%, according to the sets of groups (G1 and G2) Free of minor thromboembolic events - FmT; lower limit of confidence interval 95% - LLCI 95%; upper limit confidence interval 95% - ULCI 95%. The numbers next to points of inflection of the curves are related to the percentage of patients free of events at that time

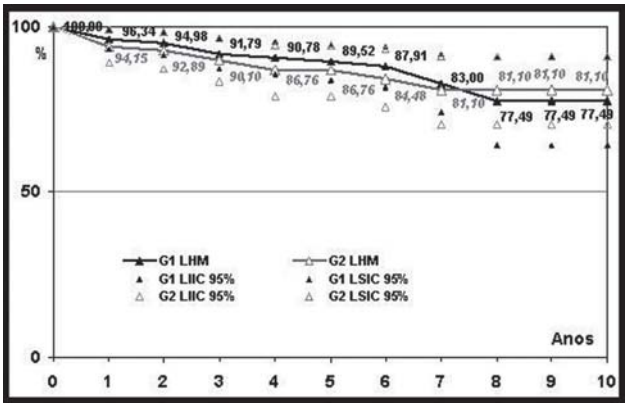

Fig. 6 - Actuarial curves and points of upper and lower limits of the confidence interval of 95%, according to the sets of groups (G1 and G2) Free of major hemorrhagic events (FMH). Lower limit of the confidence interval 95% - LLCI95%; upper limit of the confidence interval 95% - ULCI 95%. The numbers next to points of inflection of the curves are related to the percentage of patients free of events at that time

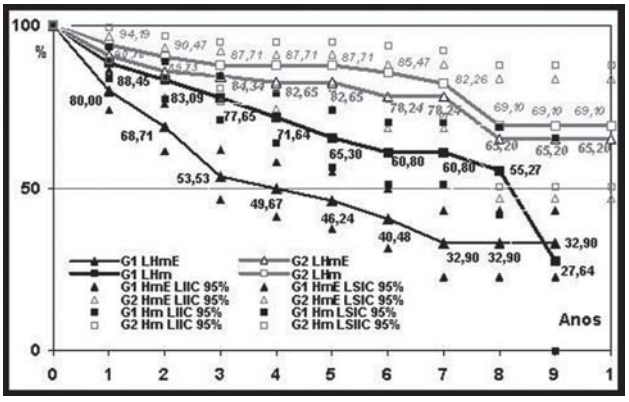

Fig. 7 - Actuarial curves and points of upper and lower limits of the confidence interval of 95%, according to the sets of groups (G1 and G2); Free of minor hemorrhagic events or exacerbated increase of INR (FmHE) and Free of minor hemorrhagic events (FmH). Lower limit of the confidence interval 95% - LLCI 95%; upper limit of the confidence interval 95% - ULCI 95%. The numbers next to points of inflection of the curves are related to the percentage of patients free of events at that time

Table 1. Actuarial data according to sets of groups (G1 and G2); Free of any event - FAE, Free of thromboembolic events - FT and Free of hemorrhagic events or exacerbated increase of INR - FHE.

G1												
Years	PFE%			SE%			LLCI95%			ULCI95%		
	FAE	FT	FHE	FAE	FT	FHE	FAE	FT	FHE	FAE	FT	FHE
1	75.15	98.17	76.97	3.36	1.05	3.28	68.58	96.12	70.55	81.74	100.00	83.39
2	65.17	96.81	67.02	3.78	1.41	3.73	57.77	94.06	59.71	72.57	99.56	74.33
3	48.40	93.60	51.12	4.17	2.08	4.16	40.23	89.52	42.97	56.57	97.68	59.27
4	43.56	93.60	46.34	4.28	2.08	4.28	35.18	89.52	37.95	51.94	97.68	54.73
5	40.17	92.30	42.99	4.37	2.43	4.39	31.61	87.54	34.39	48.73	97.06	51.59
6	33.48	92.30	36.38	4.55	2.43	4.60	24.56	87.54	27.36	42.20	97.06	45.40
7	25.83	89.84	26.81	4.86	3.39	5.00	16.30	83.20	17.01	35.36	96.48	36.61
8	21.86	89.84	22.69	5.50	3.39	5.69	11.07	83.20	11.55	32.36	96.48	33.83
9	21.86	89.84	22.69	5.50	3.39	5.69	11.07	83.20	11.55	32.36	96.48	33.83
10	-	89.84	-	-	3.39	-	-	83.20	-	-	96.48	-
G2												
Years	PFE%			SE%			LLCI95%			ULCI95%		
	FAE	FT	FHE	FAE	FT	FHE	FAE	FT	FHE	FAE	FT	FHE
1	82.56	95.35	87.21	4.09	2.27	3.60	74.59	90.90	80.15	90.58	99.80	94.27
2	76.31	95.35	80.98	4.64	2.27	4.29	67.21	90.90	72.57	85.41	99.80	89.39
3	72.15	95.35	76.86	4.97	2.27	4.68	62.41	90.90	67.68	81.89	99.80	86.04
4	70.47	95.35	75.22	5.13	2.27	4.86	60.41	90.90	65.69	80.53	99.80	84.75
5	68.48	93.34	75.22	5.36	2.98	4.86	57.98	87.50	65.69	78.98	99.18	84.75
6	61.63	90.98	68.68	6.11	3.73	5.72	49.66	83.68	57.47	73.60	98.28	79.89
7	58.21	90.98	65.49	6.66	3.73	6.28	45.16	83.68	53.18	71.26	98.28	77.80
8	37.67	83.40	52.39	10.47	8.02	9.69	17.15	67.68	33.40	58.19	99.12	71.38
9	37.67	83.40	52.39	10.47	8.02	9.69	17.15	67.68	33.40	58.19	99.12	71.38
10	37.67	83.40	52.39	10.47	8.02	9.69	17.15	67.68	33.40	58.19	99.12	71.38

Percentage of patients free of events - PFE% Standard error – SE% ; lower limit confidence interval 95% - LLCI 95% ; upper limit of the confidence interval 95% - ULCI 95%

Table 2. Actuarial data according to sets of groups (G1 and G2): Free of major thromboembolic events - FMT and Free of minor thromboembolic events - FmT.

G1								
Years	PFE%		SE%		LLCI95%		ULCI95%	
	FMT	FmT	FMT	FmT	FMT	FmT	FMT	FmT
1	98.78	98.78	0.86	0.86	97.10	97.10	100.00	100.00
2	98.10	98.10	1.09	1.09	95.97	95.97	100.00	100.00
3	94.90	98.10	1.89	1.09	91.19	95.97	98.61	100.00
4	94.90	98.10	1.89	1.09	91.19	95.97	98.61	100.00
5	93.62	98.10	2.26	1.09	89.19	95.97	98.05	100.00
6	93.62	98.10	2.26	1.09	89.19	95.97	98.05	100.00
7	91.16	95.62	3.28	2.67	84.73	90.38	97.59	100.00
8	91.16	95.62	3.28	2.67	84.73	90.38	97.59	100.00
9	91.16	95.62	3.28	2.67	84.73	90.38	97.59	100.00
10	91.16	95.62	3.28	2.67	84.73	90.38	97.59	100.00
G2								
Years	PFE%		SE%		LLCI95%		ULCI95%	
	FMT	FmT	FMT	FmT	FMT	FmT	FMT	FmT
1	96.51	98.84	1.98	1.16	92.63	96.57	100.00	100.00
2	96.51	98.84	1.98	1.16	92.63	96.57	100.00	100.00
3	96.51	98.84	1.98	1.16	92.63	96.57	100.00	100.00
4	96.51	98.84	1.98	1.16	92.63	96.57	100.00	100.00
5	94.52	98.84	2.76	1.16	89.10	96.57	99.94	100.00
6	92.16	98.84	3.56	1.16	85.17	96.57	99.15	100.00
7	92.16	98.84	3.56	1.16	85.17	96.57	99.15	100.00
8	92.16	91.78	3.56	6.89	85.17	78.28	99.15	100.00
9	92.16	91.78	3.56	6.89	85.17	78.28	99.15	100.00
10	92.16	91.78	3.56	6.89	85.17	78.28	99.15	100.00

Percentage of patients free of events - PFE% Standard error - SE% ; lower limit confidence interval 95% - LLCI 95%; upper limit of the confidence interval 95% - ULCI 95%

Table 3. Actuarial data according to sets of groups (G1 and G2): Free of major hemorrhagic events (FMH), Free of minor hemorrhagic events or exacerbated increase of INR (FmHE) and Free of minor hemorrhagic events (FmH).

						G1						
Years	PFE%			SE%			LLCI95%			ULCI95%		
	FMH	FmHE	FmH	FMH	FmHE	FmH	FMH	FmHE	LHm	FMH	FmHE	FmH
1	96.34	80.00	88.45	1.47	3.11	2.49	93.47	73.90	83.57	99.21	86.10	93.33
2	94.98	68.71	83.09	1.73	3.69	2.98	91.59	61.48	77.26	98.37	75.94	88.92
3	91.79	53.53	77.65	2.29	4.15	3.42	87.29	45.39	70.95	96.29	61.67	84.35
4	90.78	49.67	71.64	2.48	4.28	3.94	85.92	41.29	63.92	95.64	58.05	79.36
5	89.52	46.24	65.30	2.75	4.41	4.49	84.13	37.59	56.49	94.91	54.89	74.11
6	87.91	40.48	60.80	3.14	4.65	4.88	81.76	31.77	51.24	94.06	49.99	70.36
7	83.00	32.90	60.80	4.48	5.18	4.88	74.26	22.76	51.24	91.90	43.04	70.36
8	77.49	32.90	55.27	6.79	5.18	6.89	64.19	22.76	41.77	90.79	43.04	68.77
9	77.49	32.90	27.64	6.79	5.18	19.85	64.19	22.76	0.00	90.79	43.04	65.54
10	77.49	-	-	6.79	-	-	64.19	-	-	90.79	-	-
						G1						
Years	PFE%			SE%			LLCI95%			ULCI95%		
	FMH	FmHE	FmH	FMH	FmHE	FmH	FMH	FmHE	FmH	FMH	FmHE	FmH
1	94.15	90.70	94.19	2.54	3.13	2.52	89.18	84.56	89.24	99.12	96.84	99.14
2	92.89	85.73	90.47	2.80	3.82	3.21	87.40	78.24	84.18	98.38	93.22	96.76
3	90.10	84.34	87.71	3.34	4.01	3.66	83.55	76.49	80.54	96.65	92.19	94.88
4	86.76	82.65	87.71	3.96	4.27	3.66	78.99	74.29	80.54	94.53	91.01	94.88
5	86.76	82.65	87.71	3.96	4.27	3.66	78.99	74.29	80.54	94.53	91.01	94.88
6	84.48	78.24	85.49	4.47	5.05	4.19	75.72	68.34	77.29	93.24	88.14	93.69
7	81.10	78.24	82.26	5.42	5.05	5.12	70.48	68.34	72.22	91.12	88.14	92.30
8	81.10	65.20	69.10	5.42	9.41	9.55	70.48	46.76	50.38	91.12	83.64	87.82
9	81.10	65.20	69.10	5.42	9.41	9.55	70.48	46.76	50.38	91.12	83.64	87.82
10	81.10	65.20	69.10	5.42	9.41	9.55	70.48	46.76	50.38	91.12	83.64	87.82

Percentage of patients free of events - PFE% Standard error - SE%; lower limit of confidence interval 95% - LLCI 95%; upper limit of the confidence interval 95% - ULCI 95%.

Table 4. Distribution of the number of events per 100 patient/year, according to the groups - G studied.

Number of events per 100 patients/year - Groups				
			G1 708.68 years	G2 431.10 years
T	NTE	Total	25.26	11.37
		Major	2.40	1.86
		Minor	1.55	1.39
		Total	0.85	0.47
			22.86	9.51
H		Major	3.25	2.78
		Minor or ER	19.61	6.73
		Minor	8.18	4.87
		ER	11.43	1.86

Total events - TE, Thromboembolic events - T, hemorrhagic events - H, with exacerbated increase of INR (INR higher than or equal to 7.0) - ER

DISCUSSION

In the opinion of Rosendaal [15] the control of oral anticoagulation must be performed by specialist clinics in order to minimize risks and improve this practice. This opinion was endorsed by *The American College of Chest Physicians Consensus Conference on Antithrombotic Therapy* [16].

Chiquette et al. [17] compared conventional care (ACV) for control of anticoagulation, i.e., regular attendance at clinics and follow-up in specialized clinics for anticoagulation control (AEC). At the AECs were found linear rates of occurrence of minor events for both thromboembolic events (major, minor and fatal) and for bleeding episodes (major, minor and fatal).

Witt et al. [18] compared 3323 patients followed for AEC (362 by mechanical heart valve prosthesis) and 3322 followed

for ACV (370 by mechanical heart valve prosthesis) for a period of 6 months. This AEC has the characteristic that most follow-ups are done by telephone. The results showed that the AEC group remained in the range of desired anticoagulation in 63.5% of the observation time, while in the ACV group; the corresponding percentage was 55.2%. The percentage of consultations in which the INR was less than or equal to 1.5 and higher than or equal to 4.0 was significantly lower in the AEC group than in the ACV group (15.1% and 20.4% respectively). The linear rates of occurrence for the total of complications: 3.26 events per 100 patient-year in AEC and 5.19 events per 100 patient-year in ACV. Thromboembolic events were 62% lower in the patients followed for AEC than those for ACV, while in larger hemorrhagic events; the differences were not significant between the two types of monitoring. The authors concluded that centralized specialist clinics improve the quality of oral anticoagulation control, reducing the risk of complications.

We believe that the objectives of an outpatient clinic specialized in oral anticoagulation monitoring will be achieved when patients remain most of the time with PT (INR) within desired ranges, or the percentage of tests in which INR is in this range will be increasingly higher. This should be reflected in fewer complications.

The results show (Figures 2-7) than the group with better control of anticoagulation (G2) showed a higher percentage of patients free of any event (FAE) and hemorrhagic events or exacerbated increase of INR (FHE) than the group where the quality control was less efficient (G1). For the patients free of thromboembolic events (FT), however, the difference was mild and was limited to the last two years of monitoring. By analyzing the curves of patients free of major thromboembolic events (FMT) and minor thromboembolic events (FmT) separately (Figures 4 and 5), we noted that the differences between G1 and G2 were minimal or nonexistent.

The relatively small number of thromboembolic events may have been a factor that complicated the comparison between groups. For the patients free of major hemorrhagic events (FMH), G1 and G2 in the early years of follow-up showed similar behavior, but in the final years, the percentage of patients free of these events was lower in G1 (Figure 6). In contrast, the curves of the patients free of minor hemorrhagic events or with exacerbated increase of INR (FmHE) and patients free of minor hemorrhage (FmH) show that this difference (lower percentage of events in G2), occurred strikingly in almost the entire period of follow-up (Figure 7).

The linear rate of occurrence for the total events in G1 was more than double that of G2. Also for thromboembolic events with their subdivision (total of thromboembolic events: TMm; major thromboembolic events: TM and minor: Tm) and hemorrhagic with their subdivisions (hemorrhagic or with exacerbated increase of INR: HP; Major hemorrhagic HM; minors or with exacerbated increase of INR: HmE; minors: Hm and exacerbated increase of INR: ER), the occurrence rates were higher in G1 (Table 1).

CONCLUSION

We concluded that although more than 50% of all outpatient consultations in the INR was within the desired range, when considering the patients, only over a third of them remained on anticoagulation considered stable, i.e., with INR within the desired range in more than 50% of their consultations, whereas the more stable patients had fewer complications. We further noted that, even through a specialized clinic, with fair commitment to the treatment, prompt care and delivery of anticoagulant when necessary it is difficult to obtain the ideal control of anticoagulation.

This study shows that the control of anticoagulated patients is complex and suggests that it would be interesting to create, in Brazil, control centers of anticoagulated patients distributed regionally, as those existing in other countries.

ACKNOWLEDGEMENTS

The authors thank the professionals of the Laboratory and Outpatient Anticoagulation Control, and Research Support Group (GAP), Faculty of Medicine of Botucatu, UNESP.

REFERENCES

1. Björk VO, Henze A. Management of thrombo-embolism after aortic valve replacement with the Björk-Shiley tilting disc valve. Medicamental prevention with dicumarol in comparison with dipyridamole - acetylsalicylic acid. Surgical treatment of prosthetic thrombosis. Scand J Thorac Cardiovasc Surg. 1975;9(3):183-91.

2. Fuster V, Pumphrey CW, McGoon MD, Chesebro JH, Pluth JR, McGoon DC. Systemic thromboembolism in mitral and aortic Starr-Edwards prostheses: a 10-19 year follow-up. Circulation. 1982;66(2 Pt 2):I157-61.

3. Larsen G, Alexander JA, Stanford W. Thromboembolic phenomena in patients with prosthetic aortic valves who did not receive anticoagulants. Ann Thorac Surg. 1977;23(4):323-6.

4. Limet R, Lepage G, Grondin CM. Thromboebolic complications with the cloth-covered Starr-Edwards aortic prothesis in patients not receiving anticoagulants. Ann Thorac Surg. 1977;23(6):529-33.

5. Myers ML, Lawrie GM, Crawford ES, Howell JF, Morris GC Jr, Glaeser DH, et al. The St. Jude valve prosthesis: analysis of the clinical results in 815 implants and the need for systemic anticoagulation. J Am Coll Cardiol. 1989;13(1):57-62.

6. Starr A, Bonchek LI, Anderson RP, Wood JA, Chapman RD. Late complications of aortic valve replacement with cloth-covered, composite-seat prostheses. A six-year appraisal. Ann Thorac Surg. 1975;19(3):289-300.

7. Braile DM, Ardito RV, Zaiantchick M, Santos JLV, Campos NLKL, Lorga AM, et al. Estudo comparativo entre válvulas biológicas e válvulas mecânicas nas posições mitral ou aórtica até 14 anos. Rev Bras Cir Cardiovasc. 1988;3(3):141-58.

8. Brandão CMA, Pomerantzeff PMA, Cunha CRC, Morales JIE, Puig LB, Stolf NAG, et al. Substituição valvar com próteses mecânicas de duplo folheto. Rev Bras Cir Cardiovasc. 2000;15(3):227-33.

9. Lourenço DM, Lopes LHC, Vignal CV, Morelli VM. Avaliação clínica e laboratorial de pacientes em uso de anticoagulantes orais. Arq Bras Cardiol. 1997;68(5):353-6.

10. Ufer M. Comparative pharmacokinetics of vitamin K antagonists: warfarin, phenprocoumon and acenocoumarol. Clin Pharmacokinet. 2005;44(12):1227-46.

11. Hirsh J, Fuster V, Ansell J, Halperin J; American Heart Association; American College of Cardiology Foundation. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation. 2003;107(12):1692-711.

12. Bussey H. Better delivery of standard antithrombotic care. Am Heart J. 2001;141(6):1038-42.

13. Salem DN, Stein PD, Al-Ahmad A, Bussey HI, Horstkotte D, Miller N, et al. Antithrombotic therapy in valvular heart disease - native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest. 2004;126(3 Suppl)):457S-82S.

14. Cannegieter SC, Rosendaal FR, Wintzen AR, van der Meer FJ, Vandenbroucke JP, Briët E. Optimal oral anticoagulant therapy in patients with mechanical heart valves. N Engl J Med. 1995;333(1):11-7.

15. Rosendaal FR. The Scylla and Charybdis of oral anticoagulant treatment. N Engl J Med. 1996;335(8):587-9.

16. Hirsh J, Dalen JE, Deykin D, Poller L, Bussey H. Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 1995;108(4 Suppl):231S-46S.

17. Chiquette E, Amato MG, Bussey HI. Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. Arch Intern Med. 1998;158(15):1641-7.

18. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ. Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. Chest. 2005;127(5):1515-22.