Antithrombotic Strategy in the Three First Months following Bioprosthetic Heart Valve Implantation

Andre R. Durães, Milena A. O. Durães, Luis C. L. Correia, Roque Aras
Hospital Ana Nery, Salvador, BA - Brazil

Abstract

Heart valve prosthesis unquestionably improve quality of life and survival of patients with severe valvular heart disease, but the need for antithrombotic therapy to prevent thromboembolic complications is a major challenge to clinicians and their patients. Of the articles analyzed, most were retrospective series of cases or historical cohorts obtained from the database. The few published randomized trials showed no statistical power to assess the primary outcome of death or thromboembolic event. In this article, we decided to perform a systematic literature review, in an attempt to answer the following question: what is the best antithrombotic strategy in the first three months after bioprosthetic heart valve implantation (mitral and aortic)?

After two reviewers applying the extraction criteria, we found 1968 references, selecting 31 references (excluding papers truncated, which combined bioprosthesis with mechanical prosthesis, or without follow-up).

Based on this literature review, there was a low level of evidence for any antithrombotic therapeutic strategy evaluated. It´s therefore interesting to use aspirin 75 to 100 mg / day as antithrombotic strategy after bioprosthesis replacement in the aortic position, regardless of etiology, for patients without other risk factors such as atrial fibrillation or previous thromboembolic event. In the mitral position, the risk of embolism, although low, is more relevant than in the aortic position, according to published series and retrospective cohorts comprised mostly of elderly non-rheumatic patients.

The current evidence is limited to have a consistent and safe level of evidence regarding the best therapeutic strategy. Based on these studies, 75 to 100 mg/day of aspirin is interesting as antithrombotic strategy after implantation of aortic bioprosthesis, regardless of etiology, for patients with no other risk factors such as atrial fibrillation or previous thromboembolic event. As for mitral bioprosthesis, the risk of embolism, although low, is more relevant than in the aortic position, according to published series and retrospective cohorts - usually elderly non rheumatic patients.

Keywords

Heart Valve Prosthesis Implantation; Fibrinolytic Agents; Platelet Aggregation Inhibitors; Thromboembolism.

Mailing Address: Andre Rodrigues Duraes •
Rua Alberto Silva, 439, Itaigara. Postal Code 41815-000, Salvador, BA - Brazil
E-mail: andreduraes@gmail.com , andredecord@ig.com.br
Manuscript received February 27, 2013, revised manuscript June 10, 2013, accepted on 07/02/13.

DOI: 10.5935/abc.20130202

Introduction

The chronic rheumatic heart disease (CRHD) is responsible for at least 200 to 250 thousand premature deaths each year and is the leading cause of cardiovascular death among children and young adults in developing countries[1]. Heart valve prosthesis (HVP) unquestionably improve quality of life and survival of patients with severe valvular heart disease, but the need for antithrombotic therapy to prevent possible thromboembolic complications remain a major challenge to clinicians and their patients[2].

Since the beginning of its use in the 60s, the bioprosthesis emerged with the expectation of replacing existing metal prosthesis, due to not theoretically requiring permanent oral anticoagulation, a fact justified by their predominant tissue composition, thereby reducing the high thrombogenicity of the prosthesis used until then. However, these prosthesis had a significant negative point: relatively short durability (mean 10-15 years), caused by early structural deterioration that resulted in the need for reoperations, which, in turn, would increase morbidity and mortality[3].

The recommendations of the main international consensuses[2,4,5] on antithrombotic therapy after bioprosthesis implantation demonstrate a low level of evidence (Grade C), which may be explained by the lack of randomized trials and scarcity of prospective cohorts representing current diverse therapies, generating considerable variation in behavior between the different services. In Brazil, the main cause of valve disease in children, adolescents and young adults is the CRHD, leading to a high social and economic cost[6]. In spite of that, the authors of this review do not know any study in the literature that have specifically addressed patients with CRHD in relation to any antithrombotic strategy in the postoperative period of HVP implantation.

Moreover, CRHD has a direct association with poverty and poor health[6], creating a vicious circle of recurrent pharyngotonsillitis, crossed immune reaction, heart valve involvement, debilitating sequelae, cardiac surgery at an economically active age, costs to the health system and society. In this article, we decided to perform a systematic review of the literature in an attempt to answer the following question: what is the best antithrombotic therapy strategy in the first three months after implantation of bioprosthetic heart valve?

Review Methodology

The Medline, Embase, Cochrane and SciELO databases were reviewed regarding the period between 1970 and 2012. The terms or keywords used were: heart valve

prosthesis, bioprosthesis, aspirin or anticoagulants or thromboembolism and bioprosthesis. The search was limited to articles written in English or Portuguese and that referred to humans. The articles identified were assessed by two reviewers. Inclusion criteria were: original articles in English or Portuguese, prospective or retrospective, observational or intervention design, preferably having a control group and sample size > 19 patients.

Articles that included patients with metal prosthesis (alone or in conjunction), articles without abstracts, or articles with incomplete or confusing methodology, not allowing identification of a therapy group, and a control group were excluded.

Results

Using the aforementioned methodology, 1,968 references were found. Of these, after applying the extraction criteria, 31 articles were selected. Found there were only three randomized studies with a total population of 472 patients, in whom different levels of anticoagulation or warfarin (WAR) versus antiplatelet agents were tested. Moreover, two prospective observational studies were found, resulting in a sample of 433 patients. The remaining studies were retrospective and several addressed the combined implantation of bioprosthesis in the aortic position (BAP) and bioprosthesis in the mitral position (BMP). No study had found a sample that was specific or predominant for patients with CRHD.

Most of the selected articles consisted of retrospective series or historical cohorts extracted from databases. The few published randomized trials showed no statistical power to assess the primary outcome of death or thromboembolic event. The use of several antithrombotic therapies, such as aspirin (ASA), triflusal, ticlopidine or WAR, isolated or combined, hindered data systematization to perform a more homogeneous joint analysis. We chose to divide the studies according to the main therapeutic strategy to facilitate result analysis.

Table 1 shows the list of studies that had no report on the use of any antithrombotic drug strategy after ABP and/or MBP implantation. Tables 2 and 3 show the selected studies that compare WAR with ASA, while Table 4 lists the articles that used ASA or WAR alone, often comparing them with the follow-up without any specific antithrombotic drug therapy.

Therefore, the incidence of thromboembolic events without any specific therapy ranged from 0.011 to 0.900 and 0.01 to 2.3% / person-year when evaluating ABP and MBP, respectively, for a follow up ranging from 6-120 months involving publications of the year 1979 to 1995, according to Table 1.

Table 1 – Main comparative studies after bioprosthetic valve implantation with outcome focused on thromboembolic events with no specific antithrombotic therapy

Author-Year	N	Study design and follow-up (months)	Location and incidence of embolic events (%/person-year)	Stipulated therapy	Conclusion (embolic events)
Cohen et al[12] 1979	323	Retrospective; 84	ABP: 0.55* MBP: 3.9*	NAT: sinus Rhythm WAR: AF	Low incidence;
Fuster et at[13] 1982	302	Retrospective; 120	ABP: 0.26# MBP: 0.30#	Not informed	P < 0.01; BPM high risk of events;
Ionescu et al[14] 1982	366	Retrospective; 120	MBP: 0.6	Not used	Very low risk
Cohn et al [15] 1984	663	Retrospective; 108	ABP: 0.07	Not informed	-
Joyce et al[16] 1984	469	Retrospective; 36.2	ABP: 0.011-0.024 MBP: 0.01-0.028	Not informed	-
Gallo et al[17] 1985	189	-	ABP: 0.5 MBP: 2.3	Not informed	
Hartz et al[18] 1986	589	Retrospective; 38	ABP: 208 pcts MBP: 209 pts Total: 0.3 a 0.8	Not informed	Low incidence
Gonzalez-Lavin et al[19] 1988	240	Retrospective; 100	ABP: 0.9	Not used	Peak of events between 60-70 months.
Braile et al[20] 1991	663	Retrospective, 132	MBP: 0.3	-	CVA – 0.3%
Babin-Ebell et al[21] 1995	57	Retrospective. 6	ABP: 0.035–1.75	Not used	
Orszulak et al[22] 1995	561	Retrospective; 42	ABP: 1.57	NAT overall;	p = 0.01 Higher risk for the elderly (> 73 years), AF, decreased EF.

*N: sample size; AF: atrial fibrillation; ABP: aortic bioprosthesis; MBP: mitral bioprosthesis; NAT: No antithrombotic therapy; EF: ejection fraction; pts: Patients; CVA: cerebrovascular accident; WAR: Warfarin; p: statistical significance; * Embolic events only occurred in patients with AF.*

Table 2 – Main comparative studies after bioprosthetic valve implantation with outcome focused on thromboembolic events, comparing warfarin with aspirin

Author-Year	N	Study design and follow-up (months)	Location and incidence of embolic events (%/person-year)	Stipulated therapy	Conclusion (embolic events)
Louagie et al[8] 1993	100	Retrospective; 70	MBP 2.01 overall 0.5 x 1.3	WAR x ASA	Previous MS and AF are predictors of permanent OA, mechanical prosthesis recommended.
Blair et al[23] 1994	748	Retrospective; 3	ABP: 378 pts WAR 2.9 ASA: 0.8 NAT: 1.5 MBP: 370 pts	WAR x ASA X NAT	BPM: WAR reduced events but increased bleeding; ABP: ASA was similar to WAR;
Heras et al[9] 1995	816	Retrospective; 99.6	0-10/10-90/> 90 d ABP: 41/3.6/1.9 MBP: 55/10/2.4	Warfarin, dipyridamole and aspirin were used;	High risk of thromboembolism on the first 10 days; OA ≥ Reduced risk of embolism from 3.9% to 2.5%;
Aramendi et al[24] 1998	168	Retrospective; 38.4	ABP and MBP Ticlopidine 0.5 Warfarin 3	Ti: 137 x WAR 40 x ASA 14 x NAT 18 pts	The first three months are high risk; Ti was superior to WAR.
Guerli et al[25] 2004	249	Prospective; Observational; 3	ABP	WAR 141 x ASA 108 pts	Similar incidence in both groups;
Ramos et al[26] 2004	184	Prospective; Observational; 3	APB MBP 18.25	ASA 159 and WAR 25 pts	Embolism incidence of 18.25%/ patient-year

N: sample size; AF: atrial fibrillation; ABP: aortic bioprosthesis; MBP: mitral bioprosthesis; NAT: No antithrombotic therapy; EF: ejection fraction; OA: oral anticoagulation; CVA: cerebrovascular accident; pts: Patients; Ti: Ticlopidine; WAR: Warfarin; ASA: Aspirin; MS: mitral stenosis.

Table 3 – Main comparative studies after bioprosthetic valve implantation with outcome focused on thromboembolic events, comparing warfarin with aspirin

Author-Year	N	Study design and follow-up (months)	Location and incidence of embolic events (%/person-year)	Stipulated therapy	Conclusion (embolic events)
Aramendi et al[27] 2005	193	Prospective, open, randomized, multicenter; 3	ABP 181 pts MBP 10 pts	Triflusal 600 mg Acenocoumarol INR 2 to 3	Similar reduction in embolism, and less bleeding with triflusal;
Sundt et al[28] 2005	1151	Retrospective; 3	ABP: 2.4 x 1.9	WAR 624 x ASA 410 pts	WAR did not protect against events;
Colli et al[29] 2007	69	Randomized; Prospective	ABP	ASA x WAR	No statistical difference
Jamieson et al[30] 2007	1372	Retrospective;	ABP	ASA x WAR	No statistical difference
Colli et al[31] 2010	99	Retrospective;	MBP	ASA 51 x WAR 36 x NAT 12 pts	No statistical difference
ElBardissi et al[32] 2011	861	Retrospective; 3	ABP	ASA 728 x WAR 133 pts	p = 0.67
Brennan et al[7] 2012	25.656	Retrospective; 3	ABP	ASA 12,457 x WAR 2,999 x ASA + WAR 5,972 pts	Events: ASA – 1% WAR – 1% Both – 0.6%

N: sample size; AF: atrial fibrillation; ABP: aortic bioprosthesis; MBP: mitral bioprosthesis; NAT: No antithrombotic therapy; EF: ejection fraction; OA: oral anticoagulation; CVA: cerebrovascular accident; pts: Patients; p: statistical significance; WAR: Warfarin; ASA: aspirin.

Regarding the comparison between WAR and ASA, alone or in combination, for patients who had ABP implantation, there was an incidence of thromboembolic events of 0.8 to 4.8% / person-year and 0.6 to 3.9% / person-year, respectively. More recently, Brennan et al[7] demonstrated, through a retrospective cohort study with large sample size (25,656 patients), that this is the incidence of 1%/person-year for any of the aforementioned therapies.

Table 4 – Main comparative studies after bioprosthetic valve implantation with outcome focused on thromboembolic events, comparing warfarin with aspirin alone

Author-Year	N	Study design and follow-up (months)	Location and incidence of embolic events (%/person-year)	Stipulated therapy	Conclusion (embolic events)
Gonzalez-Lavin et al[33] 1984	528	Retrospective; 30.5	MBP Group 1 = 4.6 Group 2 = 0.36	Group 1: WAR < 6 weeks 206 pts; Group 2: > 8 weeks 322 pts	Bovine pericardial bioprosthesis; low risk.
Turpie et al[34] 1988	210	Randomized; 3	ABP MBP	Group 1: INR 2.5-4.0 108 pts; Group 2: INR 2.0-2.25 102 pts	Less intensive regimen was similar for embolic events and had fewer bleeding episodes.
Orszulak et al[10] 1995	285	Retrospective;	MBP 2.5	Not informed	High risk of CVA (40%/ person-year) in the first month;
Goldsmith et al[35] 1998	145	Retrospective;	ABP 0.3	ASA	In the first three months there was no increased risk of thromboembolism;
Moinuddeen et al[36] 1998	185	Retrospective; 3	ABP 2.8 x 2.6	WAR 109 x NAT 76 pts	Early OA was not effective in reducing embolic events
Brueck et al[37] 2007	288	Retrospective; Observational; 12	ABP	ASA 132 x NAT 156 pts	No benefit of ASA versus nothing;
Duraes et al[11]	184	Prospective. Observational	MBP and ABP	ASA 59 x NAT 125 pts	Low incidence. No benefit of ASA versus nothing.

N: sample size; AF: atrial fibrillation; ABP: aortic bioprosthesis; MBP: mitral bioprosthesis; NAT: No antithrombotic therapy; EF: ejection fraction; OA: oral anticoagulation; CVA: cerebrovascular accident; pts: Patients; ASA: aspirin.

For those submitted to MBP implantation, Louagie et al[8] found a low incidence of thromboembolic events (0.5 and 1.3%/person-year) when compared WAR and ASA, respectively. However, there are Retrospective with an incidence much higher, reaching levels of 55% / person-year in the first 10 days, as Heras et al[9] found in 1995.

In the same year, Orszulak et al[10] showed an incidence of 40% in the first 30 days postoperatively. Finally, more recently, in 2013, in an article still in press, Duraes et al[11] prospectively analyzed a cohort of rheumatic patients in the first three postoperative months after mitral and/or aortic bioprosthetic implantation, showing a rare incidence of embolic events, regardless of being the aortic or mitral bioprosthesis, being even more sporadic in the latter, even when aspirin is compared with no antiplatelet agent, as shown in Tables 2, 3 and 4.

Discussion

Current recommendations for antithrombotic therapy in the first three months following bioprosthetic valve implantation have a low level of evidence, as observed in the studies selected for this article. The American Heart Association/American College of Cardiology (AHA/ ACC)[4] recommend the use of ASA as class I and level of evidence C, alone or in combination with WAR (IIa / C), in accordance with the presence or not of some factor risk (atrial fibrillation, previous thromboembolic event, left ventricular dysfunction, and hypercoagulability state). The European Society of Cardiology (ESC)[2] and the American College of Chest Physicians (ACCP)[5] innovated by recommending the use of ASA (instead of WAR) when the replacement is performed in the aortic position only, keeping the use of the latter (WAR) for isolated or combined mitral position (IIa/C and II/C, respectively) based on recent studies focused on ABP implantation.

The Brazilian guideline of valve disease - SBC 2011[38] recommends as Class I and level C, bioprosthesis replacement in patients who have contraindications to the use of vitamin K antagonists (VKA), and use these drugs in patients with atrial fibrillation (Class I and level of evidence B), or within three months after initial implantation of a bioprosthesis (Class IIb and level of evidence B), not specifying whether in the aortic and / or mitral position.

Regarding patients with aortic replacement, Brennan et al7, as already mentioned, published an impressive retrospective cohort consisting mainly of elderly patients. In this study, the authors evaluated three antithrombotic strategies (WAR, ASA or both) and found an incidence of embolism similar between the WAR and the ASA alone group (1% / person-year), occurring significant reduction in embolic events only when using simultaneous ASA and WAR: 0.6% / person-year, with the number of patients needed to treat (NNT) of 212, benefit was offset by an increase in bleeding rate of almost 3-fold, with the number needed to harm (NNH) of 55, being for the most part, according to the authors, gastrointestinal bleeding with no increase in bleeding into the central nervous system.

Regarding patients with isolated or combined BMP, the most cited reference in the literature is still byHeras et al[9] published in 1995, becoming an important negative paper. It was a retrospective and observational study, with database from the Mayo Clinic. The authors showed a high incidence of embolic events in the first 90 days, with 55%/person-year

in the first 10 days, and 10%/person-year between 10 and 90 days, postoperatively. In univariate analysis, they observed a reduction of 3.9% to 2.5% in the incidence of embolism with WAR use. When analyzing the linear rate of embolism in this same work, it was observed that the benefit of reducing events with anticoagulation was significant in the first 10 days, with no statistical difference (even numerically) within 10 to 90 days postoperatively. In the same year, Orszulak et al[10] found in another retrospective observational cohort, a high incidence of thromboembolic events - which reached 40% in the first 30 days in the same scenario. These disappointing results may have discouraged new studies since it seemed clear the need for the use of WAR in the first months after surgery, especially after implantation of BMP. Currently, there are doubts about the real incidence of embolism events after implantation of modern biological prosthesis, especially in patients with CRHD, and about the best antithrombotic strategy postoperatively. Thus, there is a large gap regarding the actual incidence of embolic events with current biological prosthesis, and there are no cohorts that specifically address individuals with CRHD following MBP and ABP implantation.

With this lack of impact studies justifies the low level of evidence the main internationals and Brazilian guidelines. Most studies reported represents individual experiences of referral services in cardiac surgery, performed in the last century, during a natural stage of technological development of prosthesis, different in many aspects of current valve prosthetic devices - theoretically less thrombogenic.

As already said, bioprosthesis have a great advantage over mechanical prosthesis, which is the exemption from continuous use of anticoagulants, in general, the AVK. However, several clinical circumstances do increase the probability of an embolic event postoperatively, even in patients with bioprosthesis, which is a challenge to the clinician and the patient involved in choosing the best antithrombotic strategy (VKA or ASA, alone or combined). This decision always takes into account the pros and cons of such conduct, also due to the difficulty in handling these drugs caused by the need for regular monitoring of the international normalized ratio (INR), which directly influences the risk of bleeding added by this type of drug. Patients with CRHD are generally from low socioeconomic level areas, difficult the management of VKA.

It is also noteworthy the fact that patients affected by this disease are different from the group affected by degenerative or senile valvular heart disease, more prevalent in developed countries. The first (patients with CRHD) are generally younger and thus less likely to have other comorbidities, which are known to increase cardioembolic risk, such as severe left ventricular dysfunction, atrial fibrillation and previous embolic event. Regarding the latter, they are generally elderly patients that commonly have other diseases or risk factors compatible with aging, such as arterial hypertension, diabetes and atrial fibrillation, which causes inevitable increase in surgical risk of death and complications, as well as greater probability of embolic events during follow-up after surgery and greater risk of bleeding during the instituted anticoagulant therapy.

In short, the best antithrombotic strategy to be adopted in the first three months after aortic and mitral replacement is based mainly on the experience of each service, and expert opinion - justify the level of evidence C - due to scarcity of prospective and randomized controlled trials. In BAP the use of ASA is similar to the use of WAR in the elderly patients, and in BMP remains a worldwide trend to WAR use. Patients with CRHD have not been adequately representative in previous studies to date.

Author contributions

Conception and design of the research: Durães AR; Acquisition of data: Durães AR, Durães MAO; Analysis and interpretation of the data: Durães AR, Durães MAO, Correia LC, Aras Junior R; Writing of the manuscript: Durães AR, Durães MAO, Aras Junior R; Critical revision of the manuscript for intellectual content: Correia LC, Aras Junior R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by André Rodrigues Durães, from Universidade Federal da Bahia.

References

1. Marijon E, Mirabel M, Celermajer DS, Jouven X. Rheumatic heart disease. *Lancet*. 2012; 379(9819):953-64.
2. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Barón-Esquivias G, Baumgartner H, et al. tGuidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42(4):S1-44.
3. Nowell J, Wilton E, Markus H, Jahanngiri M. Antithrombotic therapy following bioprosthetic aortic valve replacement. Eur J Cardiothorac Surg. 2007;31(4):578-85.
4. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr., Faxon DP, Freed MD. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force

on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation.* 2008; 118(15):e523-e661.

5. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH,American College of Chest Physicians. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.2012;141(2 Suppl):e576S-e600S.*

6. Barbosa PJB, Müller RE, Latado AL, Sociedade Brasileira de Cardiologia. Sociedade Brasileira de Pediatria. Sociedade Brasileira de Reumatologia. Diretrizes brasileiras para diagnóstico, tratamento e prevenção da febre reumática. Arq Bras Cardiol.2009;93(3 supl.4):1-18.

7. Brennan JM, Edwards FH, Zhao Y , O Brien`S, Booth ME, Dokholyan RS, et al. Early anticoagulation of bioprosthetic aortic valves in older patients: results from the Society of Thoracic Surgeons Adult Cardiac Surgery National Database. J Am Coll Cardiol. 2012; 60(11):971-7.

8. Louagie YA, Jamart J, http://www.ncbi.nlm.nih.gov/pubmed?term=Eucher%20P%5BAuthor%5D&cauthor=true&cauthor_uid=8215671Buche M, Schoevaerdts JC. Mitral valve Carpentier-Edwards bioprosthetic replacement, thromboembolism, and anticoagulants. Ann Thorac Surg. 1993;56(4):931-6.

9. Heras M, Chesebro JH, Fuster V, Penny WJ, Grill DE, Bailey KR, et al. High risk of thromboemboli early after bioprosthetic cardiac valve replacement. J Am Coll Cardiol. 1995;25(5):1111-9.

10. Orszulak TA, Schaff HV, Pluth JR , Danielson GK, Riga FJ, Jestrup DM, et al.The risk of stroke in the early postoperative period following mitral valve replacement. Eur J Cardiothorac Surg. 1995;9(11):615-9.

11. Duraes AR, Duraes MAO, Correia LC , Fernandes MAS, Aras Jr R. Impact of aspirin use on the incidence of thromboembolic events after bioprosthesis replacement in patients with rheumatic disease. Rev Bras Cir Cardiovasc. 2013; (ahead of print)).

12. Cohen LH, Koster JK, Mee RB, Collins JJ Jr. Long-term follow-up of the Hancock bioprosthetic heart valve: a 6-year review. Circulation. 1979; 60(2 Pt 2):87-92.

13. Fuster V, Pumphrey CW, McGoon MD, Chesebra JH, Pluth JR, McGoon DC, et al. Systemic thromboembolism in mitral and aortic Starr-Edwards prosthesis: a 10-19 year follow-up. Circulation. 1982;66(Pt 2):1157-61.

14. Ionescu MI, Smith DR, Hasan SS, Chidambaram M, Tandon AP. Clinical durability of the pericardial xenograft valve: ten years experience with mitral replacement. Ann Thorac Surg. 1982;34(3):265-77.

15. Cohn LH. The long-term results of aortic valve replacement. Chest. 1984;85(3):387-96.

16. Joyce LD, Nelson RM. Comparison of porcine valve xenografts with mechanical prosthesis. A 7 1/2 year experience. J Thorac Cardiovasc Surg. 1984; 88(1):102-13.

17. Gallo I, Artinano E, Nistal F. Four- to seven-year follow-up of patients undergoing Carpentier-Edwards porcine heart valve replacement. Thorac Cardiovasc Surg. 1985; 3(6)3:347-51.

18. Hartz RS, Fisher EB, Finkelmeier B, De Boer A, Sanders JH Jr, Moran JM, et al. An eight-year experience with porcine bioprosthetic cardiac valves. J Thorac Cardiovasc Surg. 1986;91(6):910-7.

19. Gonzalez-Lavin L, Amini S, Gonzalez-Lavin J, McGrath LB, Fernandez J, Graf D. Instantaneous risk of events following aortic valve replacement with pericardial valves: a ten-year experience. Tex Heart Inst J. 1988;15(1):31-4.

20. Braile DM, Ardito RV, Greco OT, Lorga AM. IMC bovine pericardial valve: 11 years. J Card Surg. 1991;6(4 Suppl):580-8.

21. Babin-Ebell J, Schmidt W, Eigel P, Elert O. Aortic bioprosthesis without early anticoagulation--risk of thromboembolism. Thorac Cardiovasc Surg. 1995;43(4):212-4.

22. Orszulak TA, Schaff HV, Mullany CJ , Anderson BJ, Ilstrup DM, Puga FJ, et al.Risk of thromboembolism with the aortic Carpentier-Edwards bioprosthesis. Ann Thorac Surg. 1995;59(2):462-8.

23. Blair KL, Hatton AC, White WD, Smith LR, Lowe JE, Wolfe WG, et al. Comparison of anticoagulation regimens after Carpentier-Edwards aortic or mitral valve replacement. Circulation. 1994;90(5Pt 2):214-9.

24. Aramendi JL, Agredo J, Llorente A, Lavirarte C, Pijoan J. Prevention of thromboembolism with ticlopidine shortly after valve repair or replacement with a bioprosthesis. J Heart Valve Dis. 1988;7(6):610-4.

25 Gherli T, Colli A, Fragnito C, Nicolini F, Borrello B, Saccani S, et al. Comparing warfarin with aspirin after biological aortic valve replacement: a prospective study. Circulation. 2004;110(5):496-500.

26. Ramos AI, Magalhaes HM, Maldonado M, Togna DJ, Meneghelo ZM, Arnoni AS, et al. Incidence of intracardiac thrombus and thromboembolism in the first three months after bioprosthetic valve implantation. Arq Bras Cardiol. 2004;83 (Spec N.):46-52.

27. Aramendi JI, Mestres CA, Martinez-Leon J, Campos V, Munoz G, Navas C. Triflusal versus oral anticoagulation for primary prevention of thromboembolism after bioprosthetic valve replacement (trac): prospective, randomized, co-operative trial. Eur J Cardiothorac Surg. 2005;27(5):854-60.

28. Sundt TM, Zehr KJ, Dearani JA, Daly RC, Mullany CJ, McGregor CG, et al.Is early anticoagulation with warfarin necessary after bioprosthetic aortic valve replacement? J Thorac Cardiovasc Surg. 2005;129(5):1024-31.

29. Colli A, Mestres CA, Castella M , Gherli T. Comparing warfarin to aspirin (WoA) after aortic valve replacement with the St. Jude Medical Epic heart valve bioprosthesis: results of the WoA Epic pilot trial. J Heart Valve Dis. 2007;16(6):667-71.

30. Jamieson WR, Moffatt-Bruce SD, Skarsgard P, Hadi MA, Ye J, Fradet GJ, et al. Early antithrombotic therapy for aortic valve bioprosthesis: is there an indication for routine use? Ann Thorac Surg. 2007;83:549-56.

31. Colli A, D'Amico R, Mestres CA, Pomar JL, Camara ML, Ruyra X, et al. Is early antithrombotic therapy necessary after tissue mitral valve replacement? J Heart Valve Dis. 2010;19(4):405-11.

32. ElBardissi AW, DiBardino DJ, Chen FY , Yamashita MH, Cohn LH. Is early antithrombotic therapy necessary in patients with bioprosthetic aortic valves in normal sinus rhythm? J Thorac Cardiovasc Surg.139(5):1137-45.

33. Gonzalez-Lavin L, Tandon AP, Chi S , Blair TC, McFaddon PM, Lewis B, et al. The risk of thromboembolism and hemorrhage following mitral valve replacement. A comparative analysis between the porcine xenograft valve and Ionescu-Shiley bovine pericardial valve. J Thorac Cardiovasc Surg. 1984;87(3):340-51.

34. Turpie AG, Gunstensen J, Hirsh J , Nelson H, Gent M. Randomised comparison of two intensities of oral anticoagulant therapy after tissue heart valve replacement. Lancet. 1988;1(8597):1242-5.

35. Goldsmith I, Lip GY, Mukundan S, Rosin MD. Experience with low-dose aspirin as thromboprophylaxis for the Tissuemed porcine aortic bioprosthesis: a survey of five years' experience. J Heart Valve Dis. 1998;7(5):574-9.

36. Moinuddeen K, Quin J, Shaw R , Dewar M, Tellides G, Kopf G, et al. Anticoagulation is unnecessary after biological aortic valve replacement. Circulation. 1998;98(Suppl.19);II95-8.

37. Brueck M, Kramer W, Vogt P, Steinert N, Roth P, Gorlach G, et al. Antiplatelet therapy early after bioprosthetic aortic valve replacement is unnecessary in patients without thromboembolic risk factors. Eur J Cardiothorac Surg. 2007;32(1):108-12.

38. Tarasoutchi F, Montera MW, Grinberg M, Barbosa MR, Piñeiro DJ, Sánchez CRM; et al. Sociedade Brasileira de Cardiologia. Diretriz brasileira de valvopatias - SBC 2011 / I Diretriz Interamericana de Valvopatias - SIAC 2011. Arq Bras Cardiol. 2011; 97(5 supl. 1): 1-67.