Longest Event-Free Survival without Anticoagulation in a Mechanical Aortic Valve Replacement

Chadi Salmane[1], Bhavi Pandya[1], Kristen Lafferty[2], Nileshkumar J Patel[1] and Donald McCord[3]

[1]Department of Internal Medicine, Staten Island University Hospital, New York, NY, USA. [2]NOVA Southeastern University College of Osteopathic Medicine, Fort Lauderdale, FL, USA. [3]Department of Cardiology, Staten Island University Hospital, New York, NY, USA.

ABSTRACT: Sixty percent of the patients going for valve replacement opt for mechanical valves and the remaining 40% choose bioprosthetics. Mechanical valves are known to have a higher risk of thrombosis; this risk further varies depending on the type of valve, its position, and certain individual factors. According to current guidelines, long-term anticoagulation is indicated in patients with metallic prosthetic valve disease. We report two unique cases of patients who survived 27 and 37 years event free, respectively, after mechanical aortic valve replacement (AVR) without being on any form of anticoagulation. The latter case described the longest survival in a human with a prosthetic aortic valve without anticoagulation. A review of literature demonstrated few cases of prosthetic valves with no anticoagulation in the long term without significant embolic events reported as case reports. These cases have been summarized in this article. Some cases of long-term survival (in the absence of anticoagulation) were attributed to *good luck*, and others as the result of genetic variations. New mechanical prosthetic valves can be promising, such as microporus-surfaced valves that may be used without full anticoagulation. The use of dual antiplatelet agents alone can be currently recommended only when a patient cannot take oral anticoagulation after AVR, and it should be followed with measuring and monitoring of platelet reactivity.

KEYWORDS: mechanical aortic valve, anticoagulation

CITATION: Salmane et al. Longest Event-Free Survival without Anticoagulation in a Mechanical Aortic Valve Replacement. *Clinical Medicine Insights: Cardiology* 2016:10 47–50 doi: 10.4137/CMC.S31670.

TYPE: Case Report

RECEIVED: July 13, 2015. **RESUBMITTED:** January 26, 2016. **ACCEPTED FOR PUBLICATION:** January 27, 2016.

ACADEMIC EDITOR: Thomas E. Vanhecke, Editor in Chief

PEER REVIEW: Six peer reviewers contributed to the peer review report. Reviewers' reports totaled 1688 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: dr.bhavipandya@gmail.com

Case 1

A male patient in his early 90s with a past medical history of hypertension and dyslipidemia and a surgical history of prosthetic (mechanical) aortic valve replacement (AVR) performed 27 years ago (1988) for aortic stenosis presented to our hospital with a chief medical complaint of fatigue, weakness, and chills for a duration of one day. His medications at home included clopidogrel, chlorthalidone, valsartan, and metoprolol. He had discontinued taking warfarin a few weeks after being discharged from his valve replacement surgery because of excessive bruising. His primary care doctor later started him on clopidogrel in 2001.

His initial vitals in the emergency department were stable, except for a low-grade temperature of 100.4 °F. The physical examination revealed dry mucous membranes and a grade 3/6 systolic murmur, and metallic aortic valve opening and closing clicks at the aortic area along with a grade 2/6 systolic murmur at the apex. His electrocardiography revealed a normal sinus rhythm with signs of chamber enlargements. Chest X-ray revealed enlarged cardiac silhouette and the presence of heart valve prosthesis. Initial blood tests included total biochemistry, complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, and thyroid function tests. All were unremarkable, except for creatinine of 2.30 and BUN of 51. A functional aortic prosthetic (metallic) valve with a maximum/mean gradient of 72/39 mmHg was verified with transthoracic echocardiography. In addition, a mildly elevated pulmonary artery pressure of 40 mmHg and a left ventricular ejection fraction of 55–65% were estimated; there was no evidence of thrombus or pannus formation.

The patient was admitted with a diagnosis of acute kidney injury secondary to dehydration, and he was successfully treated with intravenous (IV) hydration. After educating the patient about the consequences of thrombosis and thromboembolism (TE) in patients with metallic heart valves, he was immediately bridged with IV heparin onto oral warfarin, with which he was discharged on. His international normalized ratio (INR) at discharge was in the therapeutic range at 2.6.

Case 2

The second case is a male patient in his 60s with a past medical history of chronic hepatitis C and rheumatic aortic valve disease and a surgical history of prosthetic AVR performed 37 years ago for aortic valve incompetence. He underwent AVR with Braunwald-Cutter prosthesis at 22 years of age. The aortic valve was replaced again five years later with a Björk–Shiley (B-S) valve due to fractures of the valve's outlet

struts and escape of the disk, resulting in embolization, massive regurgitation, and often death, which began to be reported shortly after the valve's introduction, leading to its withdrawal from the market. He was notified of the potential dangers of the Braunwald-Cutter prosthesis at that time, and he was maintained on anticoagulation for eight years until he had right retinal hemorrhage, leading to right eye blindness. Since that incident, he preferred not to be anticoagulated and was instead started on aspirin 325 mg QD (once a day) and dipyridamole 50 mg QD. The patient's liver function tests, including INR and complete blood counts, were normal. Information on the timing of acquiring hepatitis C was not available. Later on, this patient was found to have a new-onset atrial fibrillation but continued to refuse treatment with anticoagulation therapy. The patient was managed on the above antiplatelet regimen for 35 years and was being monitored by platelet survival study for dose monitoring. Though this was recognized as suboptimal therapy, the patient was later lost to follow up.

Background

Sixty percent of the patients going for valve replacement select mechanical valves, and the remaining 40% choose bioprosthetics.[1,2] This is likely because mechanical valves have the reputation of being durable and long-lasting as compared to bioprosthetics. However, the one drawback of mechanical valves is the need for long-term anticoagulation, which is associated with an increased risk of bleeding.

Mechanical valves carry a high risk of thrombosis; this risk further varies depending on the type of valve, its position, and various individual factors. The incidence rate of thrombosis due to mechanical valve replacement was five times higher when it involved the mitral valve as compared to the aortic valve, and the incidence rate of embolism is ~1.5 times higher for mitral valve involvement as compared to the aortic valve.[2] This increased risk associated with mitral valve replacements may be secondary to the lower velocity of blood flow and more eddy current formation in the mitral area, which can promote thrombus formation.

The types of mechanical aortic valve prostheses, which are used in the United States, include ball-and-cage valves, single tilting disk prostheses, and bileaflet prostheses. The risk of thrombosis is highest for ball-in-cage valves, followed by single tilting disk prostheses and finally bileaflet tilting disk prostheses.

Discussion

The cases we reported here are unique because our patients survived event free for 27 and 37 years after AVR without being on any form of anticoagulation. The term "event free" describes the time period without experiencing any thromboembolic events. To date, there have been very few event-free cases reported on patients with mechanical valves without being on anticoagulation therapy for many years.[3–5]

Most of the recommendations for antithrombotic prophylaxis are from nonrandomized case series without controls.[6] The American College of Cardiology and American Heart Association practice guidelines propose early anticoagulation with warfarin and a target INR of 2.5–3.5 during the first three months from the date of the implant (regardless of the type and position of the valve) as a class I recommendation in patients with prosthetic heart valves. For mechanical valves in the aortic area, the guidelines recommend the INR to be maintained between 2.0 and 3.0 on warfarin plus the addition of aspirin (75–325 mg per day).[1] Anticoagulation with a vitamin K antagonist (VKA) to achieve an INR of 2.5 is recommended in patients with a mechanical AVR (bileaflet or current-generation single tilting disk) and no risk factors for TE.

In patients who are at higher risk of thromboembolic complications, the INR should be maintained at 2.5–3.5 and the addition of aspirin should be considered. Recently, a large study involving 4075 patients (data retrieved from the Danish National Patient Register) who had bioprosthetic AVR surgery performed between January 1, 1997, and December 31, 2009, showed that discontinuation of warfarin treatment within six months of bioprosthetic AVR surgery (bioprosthetic valves are considered to have less thrombotic events than metallic valves) was associated with increased cardiovascular death.[7] This further supports the need for antithrombotic therapy in AVR.

Anticoagulation plays a very important role in the management of patients with valve replacements. Anticoagulation mismanagement is reported to cause major valve-related events (VREs), such as TE, anticoagulation-related hemorrhage, and valve thrombosis, which account for more than 75% of all VREs.[8] These VREs occur more frequently in the first six months following surgery.[8,9] Even with anticoagulation (warfarin), the frequency of systemic embolization in patients with mechanical valves is ~0.7–1.0% per patient per year.[6,10,11] However, the risk goes up to 2.2% per patient per year only on aspirin and 4.0% with no anticoagulation. This might be due to the fact that the patients treated with warfarin spend less than 65% of the time within the target INR range.[12] The INR in the first three months following valve replacement surgery has been reported to be subtherapeutic in 48.5% of cases.[13]

Some reports in the literature demonstrated cases that were not managed on anticoagulant regimens for long term and were free of significant embolic events.[5] The protection of these valves has thus far been reported as unknown, and the potential factors underlying the normal valvular mechanics in these patients are still unknown. Perez-Zaldivar et al attributed the long-term survival seen in these patients without anticoagulation to be purely good luck.[14]

A review of literature as demonstrated in Table 1 shows few cases where no anticoagulation was used in the long term and with no significant embolic events reported. There are eight cases of aortic valves, three of mitral valves, one of pulmonary valve, and one of tricuspid valve; there are also

Table 1. A summary of cases with long event-free survival in patients with mechanical valve replacement.

CASES	AGE	POSITION	TYPE	YEARS
Kucukaksu et al.[19]	56	Aortic	B-S	30
Uzun et al.[23]	45	Aortic	S-E	2
Yildiz et al.[20]	42	Aortic	B-S	22
Ozkokeli et al.[21]	58	Aortic	S-E	37
Ikizler et al.[22]	58	Aortic	S-E	34
Sharma et al.[23]	68	Aortic	St Jude	23
Bjo¨rk et al.[16]	–	Mitral	–	–
Perez-Zaldivar et al.[14]	26	Mitral	St Jude	10
Cicekcioglu et al.[24]	21	Tricuspid	B-S	15
Iscan hz et al.[25]	25	Pulmonary	St Jude	15
Enes et al.[5]	46	Mitral	St Jude	27
Present case 1	92	Aortic	–	23
Present case 2	66	Aortic	B-S	35

three cases of B-S valves, three of S-E valves, and four of St. Jude valves without embolic episodes, who were not under anticoagulation treatment in the literature.

Gul et al.[5] describe the longest survival in humans with a prosthetic mitral valve without anticoagulation to be 27 years; however, in that case, the patient presented with a thrombus in the left atrial appendage and they reported that it is simply *the end of good luck*. In contrast to other cases, Gul et al succeed to demonstrate a genetic mutation in the coagulation cascade, which may contribute to and explain the long-term survival of patients who are not anticoagulated. They found a homozygous mutation in the vitamin K epoxide reductase complex 1 that resulted in the inhibition of coagulation. The patient with this mutation survived for 27 years without anticoagulation, having none of the thromboembolic complications.

Andersen et al.[15] examined the prognosis of 43 patients, 37 men and 6 women (mean age 52 years), who were treated with anticoagulation for approximately one year (mean 13 months; after isolated AVR with a mechanical valve). The mean follow-up period was seven years and three months. After five years, 70% were free of thromboembolic events, 65% were free of VREs, and 87% had survived. After 10 years, 59% were free of thromboembolic events, 55% were free of VREs, and 83% had survived. These figures correspond to the linearized rates of thromboembolic events of 5.2% per patient per year, VREs of 6.2% per patient per year, and death of 2.9% per patient per year. They conclude that the best postoperative treatment in isolated AVR with a mechanical valve replacement is lifelong anticoagulation.

Bjork et al.[16,17] postulated that all thromboembolic complications in mechanical heart valves start from a thrombus lining that covers the suture ring. The thrombus organizes to a fibrous white sheet over the suture ring, which then can protrude out over the polished surface of the valve ring flange. Pieces of the thrombus can be knocked off by the disk and cause emboli. To diminish thromboembolic complications, one must either prevent this thrombus from protruding into the groove between the suture ring and the valve flange or allow the thrombus to be organized as a thin covering with endothelium-like cells as a continuation from the suture ring over the valve flange. This type of covering was obtained during a short period of anticoagulation by applying a microporous surface to the B-S Monostrut mitral valve. In 11 patients with sinus rhythm (including 5 children and 6 young women), mitral valve replacement was performed with a microporous-surfaced valve similar to the B-S Monostrut valve. After the first three months, permitting endothelialization of the suture ring to continue over the groove and adjacent metal valve ring, no long-term anticoagulant treatment was given. After 11–13 years of follow-up of the 12 patients with the B-S Monostrut mechanical mitral valve with a microporous surface and without anticoagulation, 9 children have been born and no thromboembolic complications have been encountered.

A valuable theory suggests that aortic mechanical prosthesis generates shear stress and causes erythrocyte fragmentation with Adenoside Diphosphate (ADP) release that leads to platelet activation as the cause of TE.[6] Therefore, thromboprophylaxis with the antiplatelet agents, such as clopidogrel and aspirin (Clop-ASA), should reduce thromboembolic events in those patients.

In order to test the theory, Garcia-Rinaldi[18] conducted a study over an eight-year period at the authors' institutions with a total of 135 patients who underwent metallic AVR, with or without concomitant thoracic aortic procedures, and received Clop-ASA as thromboprophylaxis. Platelet reactivity was measured using the VerifyNow system. What they found was that Clop-ASA in combination seems to be effective. Patients had a low incidence of bleeding, transient ischemic attack, and ischemic stroke and no valve thrombosis. The use of assays to determine platelet reactivity helped to identify those patients who were resistant to clopidogrel, hypo-responders, and poorly compliant patients. Notably, the incidence of strokes after implementing assays to monitor platelet reactivity was reduced. The recommendation was that patients receiving Clop-ASA should undergo routine testing of platelet reactivity.

Conclusion

In conclusion, anticoagulation post mechanical valve prosthesis is still indicated. Few cases of event-free life without anticoagulation were reported in the literature. Some explained these event-free scenarios as good luck, and others as favorable genetic variations. New mechanical prosthetic valves may be promising, such as microporous-surfaced valves, because they may be used without the necessity of full anticoagulation. In addition, the use of dual antiplatelet agents alone is currently indicated only when the patient cannot take oral anticoagulation after AVR, and it should be followed with measuring and monitoring of platelet reactivity.

Acknowledgements

Extensive attempts by the authors to contact the patients regarding publication of this report were not successful. As a result, the cases have been anonymized for publication.

Author Contributions

Wrote the first draft of the manuscript: CS, BP. Contributed to the writing of the manuscript: CS, BP, KL. Agree with manuscript results and conclusions: NP, BP. Jointly developed the structure and arguments for the paper: NP, DM. Made critical revisions and approved final version: DM. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Bonow RO, Carabello BA, Chatterjee K, et al; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 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:e523–661.
2. Bonow RO, Carabello BA, Chatterjee K, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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. *J Am Coll Cardiol*. 2008;52:e1–42.
3. Verrier ED, Tranbaugh RF, Soifer SJ, Yee ES, Turley K, Ebert PA. Aspirin anticoagulation in children with mechanical aortic valves. *J Thorac Cardiovasc Surg*. 1986;92:1013–20.
4. Bradley SM, Sade RM, Crawford FA Jr, Stroud MR. Anticoagulation in children with mechanical valve prostheses. *Ann Thorac Surg*. 1997;64:30–4. discussion 35–6.
5. Gul EE, Altunbas G, Kayrak M, Ozdemir K. "The end of good luck" – long-term survival without anticoagulation: a case report and review of the literature. *Clin Appl Thromb Hemost*. 2012;18:222–4.
6. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89:635–41.
7. Merie C, Kober L, Skov Olsen P, et al. Association of warfarin therapy duration after bioprosthetic aortic valve replacement with risk of mortality, thromboembolic complications, and bleeding. *JAMA*. 2012;308:2118–25.
8. Emery RW, Emery AM, Raikar GV, Shake JG. Anticoagulation for mechanical heart valves: a role for patient based therapy. *J Thromb Thrombolysis*. 2008;25:18–25.
9. Emery RW, Krogh CC, Arom KV, et al. The St. Jude Medical cardiac valve prosthesis: a 25-year experience with single valve replacement. *Ann Thorac Surg*. 2005;79:776–82. discussion 82–3.
10. 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;333:11–7.
11. Kontozis L, Skudicky D, Hopley MJ, Sareli P. Long-term follow-up of St. Jude Medical prosthesis in a young rheumatic population using low-level warfarin anticoagulation: an analysis of the temporal distribution of causes of death. *Am J Cardiol*. 1998;81:736–9.
12. Eitz T, Schenk S, Fritzsche D, et al. International normalized ratio self-management lowers the risk of thromboembolic events after prosthetic heart valve replacement. *Ann Thorac Surg*. 2008;85:949–54. discussion 55.
13. Meijer K, Kim YK, Schulman S. Decreasing warfarin sensitivity during the first three months after heart valve surgery: implications for dosing. *Thromb Res*. 2010;125:224–9.
14. Perez-Zaldivar JI, Orjiako O, Tutunovic S. Long term survival with a metallic mitral valve prosthesis on no anticoagulation or antiplatelet therapy. A case presentation. *Internet J Cardiol*. 2010;9:1–4.
15. Andersen PV, Alstrup P. Long-term survival and complications in patients with mechanical aortic valves without anticoagulation. A follow-up study from 1 to 15 years. *Eur J Cardiothorac Surg*. 1992;6:62–5.
16. Bjork VO, Ribeiro A, Canetti M. Mechanical mitral valves without long-term anticoagulation up to thirteen years. *J Thorac Cardiovasc Surg*. 1999;118:767–9.
17. Bjork VO, Wilson GJ, Sternlieb JJ, Kaminsky DB. The porous metal-surfaced heart valve. Long-term study without long-term anticoagulation in mitral position in goats. *J Thorac Cardiovasc Surg*. 1988;95:1067–82.
18. Garcia-Rinaldi R. Clopidogrel-aspirin inhibit the thrombogenicity of St. Jude mechanical aortic prostheses. *Ann Thorac Surg*. 2006;81:787. author reply 88.