Trends in Anticoagulation Practices Post Tissue Aortic Valve Replacement (AVR)

Sunil Stephenson[1], Sanjeet Avtaar Singh[1], Ahmed Al-Adhami[1], Rajdev Singh Toor[2]

[1]Department of Cardiothoracic Surgery, Golden Jubilee National Hospital, Glasgow, UK

[2]Department of Anaesthesiology, Fiona Stanley Hospital, Murdoch, Australia

Email address:

Sanjeet_86@hotmail.com (S. A. Singh)

Abstract: Biological aortic valve replacements are commonplace in cardiac surgery and is highly recommended for patients older than 65 years old as there is no need for anticoagulation. However, there is a significant incidence of post-operative atrial fibrillation in this cohort of patients which results in some surgeons preferring to anticoagulated patients for short term. The practice at a tertiary referral centre was reviewed.

Keywords: Anticoagulation, Warfarin, Tissue Aortic Valve Replacement

1. Introduction

Biological aortic valve replacement is recommended in patients older than 65 years old. This is an effort to avoid lifelong anticoagulation that is necessary with mechanical valves. Anticoagulation in this age group is associated with a definite increase in bleeding complications per year while biological valves undergo structural degeneration at a much slower rate. With newer generation biological prostheses, there is excellent long-term freedom from reintervention with most patients over age 65 needing no redo replacement or just one over their remaining lifetime as valve integrity can be maintained for over 15 years. However, early after biological valve replacement, there are reports of an increased risk of thromboembolism for the first three months while the sewing ring is undergoing endothelialization. To reduce this risk, there are studies showing that anticoagulation during this time will reduce thromboembolic complications. This is widely debated as most reports favouring warfarin are based on observational data from largely historic studies. Also, there reports of comparable protection from using aspirin or even no anticoagulation at all. Based on this conflicting data, there is a wide variation in anticoagulation practice amongst practicing cardiac surgeons post biological AVR. In fact, the current ESC and ACC/AHA guidelines recommend a 3 month course of warfarin followed by aspirin in patients with no other indication for anticoagulation. This recommendation is however still based on the currently available disputed data therefore the deviation from the guidelines by some surgeons.

2. Aim

To ascertain the trend in anticoagulation prescribing practice amongst adult cardiac surgeons at the Golden Jubilee Hospital post biological/tissue aortic valve replacement [tAVR].

3. Methods

An audit was conducted to review the data of a representative sample. Data on all patients post tAVR over a one-year period from April 2013 to March 2014 was retrospectively reviewed. A sample of 5-9 patients from each consultant was analyzed to detect a trend in anticoagulation practice. In total, 65 patients were included. If there was no other indication for anticoagulation, biological AVR was determined to be the primary reason for warfarin prescription. Patients with a contraindication for anticoagulation were excluded. The duration of warfarin and follow up anticoagulation was also analyzed.

4. Results

In total, results from 9 consultants were analyzed.

Prescribed anticoagulation included aspirin, warfarin and clopidogrel. Only 2 consultants [22%] routinely prescribe warfarin post tAVR while 7 [78%] prescribe aspirin only beginning on day 1. Duration of warfarin ranged from 6-8 weeks. There was no prescription of warfarin for 12 weeks duration. In three consultants who trended to use aspirin, there was a slight variation when warfarin was prescribed with no other indication for anticoagulation but most of their patients were prescribed aspirin more frequently. One consultant used clopidogrel only indefinitely in a patient who had a history of a cerebrovascular accident. Clopidogrel was used for 6 weeks followed by aspirin by one consultant and another used warfarin for 6 weeks followed by clopidogrel. Even though a variety of biological valve was used from different manufacturers, anticoagulation prescription is independent of the brand of valve used.

Table 1. Anticoagulation trend distribution among consultants.

Consultant	Total number of patients	Warfarin [n]	Aspirin [n]	Clopidogrel [n]	Patients with other indications for warfarin [n]	Predominant
Consultant 1	8	2	6		2	Aspirin
Consultant 2	6	2	4		1	Aspirin
Consultant 3	8	1	6	1	1	Aspirin
Consultant 4	9	3	6		2	Aspirin
Consultant 5	8	2	5	1	1	Aspirin
Consultant 6	5	1	4		1	Aspirin
Consultant 7	8	8	0		3	Warfarin
Consultant 8	5	5	0		1	Warfarin
Consultant 9	8	3	5		3	Aspirin

5. Discussion

Surgical aortic valve replacement remains the standard of care for patients with significant aortic valve disease. Bioprosthetic valves were developed with the hope of total avoidance of anticoagulation which would be a great advantage over their mechanical counterpart that require indefinite antithrombotic therapy. However, immediately post-surgery and prior to endothelialization of the sewing ring, there is an increased risk of thromboembolism even with the bioprosthesis. [1] There is a wide variation in practice as to what anticoagulation agent is best and this is due to the limitation of available studies on which decisions are based. The debate as to whether to administer aspirin or warfarin is ongoing and there is currently a need for large randomized studies to show which agent is better at preventing thromboembolic compilations. Most of the available evidence consists of retrospective studies pulled from databases, or small prospective studies which were underpowered. In general, there are more studies showing that aspirin on its own is sufficient, with only a few mainly historical ones advocating for warfarin. There is also limited data that no anticoagulation whatsoever is necessary. Administration of warfarin has the inherent effect of causing more bleeding complications.

Heras and his team of investigators studied the rate of thromboembolism at three time intervals after operation [1 to 10, 11 to 90 and >90 days] in 816 patients who had undergone bioprosthetic replacement of the aortic or mitral valve, or both, at the Mayo Clinic between January 1975 and December 1982. The effect of antithrombotic therapy with warfarin, aspirin or dipyridamole, alone or in combination was evaluated. Within the AVR only group, 51 patients [12%] [2.2% per year] had one thromboembolic episode and 10 patients [2%] [4.6% per year] had two episodes. Of the 51 patients, 8% were on warfarin, 25% on aspirin, 25% on dipyridamole and 41% were not on any antithrombotic therapy. The rate of TE episodes during the first 10 days following isolated AVR was extremely high [41% per year] in patients without anticoagulation and was significantly higher than the rate at 11—90 days [3.6% per year] and > 90 days [1.9%/year] [p < 0.001] [1]. They concluded that anticoagulation was indicated in all patients as early as possible for 3 months and thereafter in patients with risk factors. This paper became influential among those in the surgical community in favour of anticoagulation and encouraged further research, but the conclusions should be treated with caution as they examined mainly first-generation bioprosthetic valves that are more thrombogenic than those currently utilized. Guidelines from major societies were also based on the results of this trial. Around the same time, Babin-Ebel and coworkers retrospectively reviewed 57 patients who had not received aniticoagulation between 1983 and 1993 after implantation of a bioprothesis in the aortic position. A risk for thromboembolic complications of 1.75% was calculated for the first six months following surgery, being 3.5 per 100 patients/year. [2] This calculated rate was much lower then that achieved by Heras and his team. To further examine the effects of anticoagulation, Moinuddeen and colleagues in another retrospective study compared two groups of patients. These patients had an aortic bioprosthesis implanted between 1987 and 1996. One group had heparin followed by warfarin for 3 months while the second group had no anticoagulation. Patients were followed for cerebral ischemic events, bleeding, repeat operation, hospital stay, and survival. There were 5 [4.6%], 3 [2.8%], and 12 [11%] postoperative cerebral ischemic events for the anticoagulated group at time points of < 24 hours, 24 hours to 3 months, and > 3 months, respectively; for the no anticoagulation group patients, 3 [3.9%], 2 [2.6%], and 9 [11.8%] events were seen during the same respective time periods. There were no statistically significant differences for ischemic events during any of these time periods for the 2 groups. Bleeding was similar in both groups. They concluded that early anticoagulation was

unnecessary. [3] Since then the practice of differing antithrombotic strategies became commonplace with some surgeons offering anticoagulation while others would offer aspirin [ASA] or no anticoagulation at all.

Orszulac et al after reviewing the records of 561 patients having the Carpentier-Edwards bioprosthesis in the aortic position as an isolated valve procedure made a recommendation only for a subset of patients. They described a vulnerable period for neurologic events whereby the incidence of stroke was high; these were increased in the patient variables of compromised ejection fraction [0.54; $p \le 0.003$], older age [≤ 73 years; $p \le 0.02$], and preoperative atrial fibrillation or paced rhythm [$p \le 0.01$]. This pattern was similar for both transient ischemic events and strokes and rapidly decreased over the first few months of the first year and the first few years of the 12-year follow-up. These patients were not routinely anticoagulated but they recommended anticoagulation only for the first three months in this identified patient subset and not routinely. [4]

ASA vs Warfarin

Proponents of early anticoagulation with warfarin argue that there is a high risk of thromboembolism prior to the prosthetic valve ring becoming endothelialized and protection from this is better achieved by warfarin. Al-Atassi and co workers however, showed that warfarin was no more protective than simple aspirin in reducing cerebral microembolism. They prospectively enrolled 56 patients who had no other indication for oral anticoagulation, who underwent bioprosthetic AVR and received, in an open-label fashion, either daily warfarin [for INR 2.0–3.0] plus 81 mg of aspirin [n=28] or 325 mg of aspirin only [n=28]. Cerebral microembolization was quantified at 4 hours [baseline] and at 1 month postoperatively, by recording 1-hour bilateral middle cerebral artery [MCA] microembolic signals. There was no mortality, stroke, or transient ischemic attack at 1 year in either group and no significant differences were found in microembolic signals among those receiving warfarin plus aspirin versus aspirin only, at baseline [68% versus 82%, respectively; P=0.4] and at 1 month [46% versus 43%; P=1.0]. [5]

To study the efficacy of aspirin prophylaxis in patients receiving a porcine bioprosthetic implant in the aortic position Goldsmith et al reviewed their database of 145 patients who underwent AVR between 1991 and 1996. Following AVR, low-dose aspirin prophylaxis [75 mg/day] was commenced in all patients in sinus rhythm. There were three minor thromboembolic episodes, all occurring at least one year after surgery; there were no major thromboembolic complications and bleeding events. Thromboembolic complication was seen at a rate of 0.7%/patient year and haemorrhage at 0.4%. They concluded that following AVR, bleeding complications were minimal with no increase in thromboembolic events in the first three months when low-dose aspirin prophylaxis was started in patients in sinus rhythm. [6] In essence, this study revealed that ASA on its own could be quite effective in reducing embolic complications.

Gherli et al investigated the efficacy of warfarin compared with ASA in a group of post AVR patients between 2001-2002. One hundred forty one [141] patients received warfarin for the first 3 months, and 108 patients received only aspirin. The major end points evaluated were the rate of cerebral ischemic events, bleeding, and survival. There were 3 and 5 postoperative cerebral ischemic events between 24 hours and 3 months for patients treated with aspirin and warfarin, respectively. After 3 months, the incidence of cerebral ischemic events did not differ between the 2 groups. The rate of major bleeding events, the stroke-free survival, and the overall survival rates were not statistically significant between the warfarin and aspirin groups. [7] Sundt and colleagues had a similar finding in their retrospective review when they investigated a cohort of patients who underwent bioprosthetic aortic valve replacement with [641] or without [510] associated coronary artery bypass between 1993 and 2000. By surgeon preference, 624 had early postoperative anticoagulation and 527 did not. In the group without anticoagulation, 410 patients [78%] received antiplatelet therapy with ASA. They discovered that postoperative cerebrovascular accident occurred in 2.4% of anticoagulated patients and 1.9% of patients without and that postoperative cerebrovascular accident was unrelated to warfarin use [P =.32]. [8] In another retrospective study, Blair et al. identified patients who had undergone valve replacement, aortic [n = 378] or mitral [n = 370], with the Carpentier-Edwards bioprosthesis and recorded the antithrombotic therapy they received [warfarin, aspirin or no treatment]. Whilst the incidence of thromboembolism tended to be greatest in the first 90 days, the rate did not differ between warfarin, aspirin or no therapy [p=0.07]. They concluded that treatment with aspirin alone following AVR was sufficient, if no other risk factors are present. [9] El Bardissi and colleagues found that only patients with certain high risk factors might benefit from adding anticoagulation. They found this benefit in females, those who are highly symptomatic and in NYHA III/IV, and those with a small aortic prosthesis [19mm]. [10]

More recently in a prospective randomized study, Colli and associates in a pilot study investigated the efficacy of postoperative warfarin compared to ASA in patients after isolated AVR with the St. Jude Epic porcine bioprosthesis. They were randomly assigned to receive warfarin for three months with target INR 2-3 followed by aspirin 100mg daily thereafter, or to receive aspirin 100mg only. A total of 75 patients were included. However, six patients were excluded later due to post op atrial fibrillation that did not revert to sinus rhythm. One postoperative cerebral ischemic event occurred in each group between 24h and three months [2.8% versus 2.9%, p = NS]. The rates of major bleeding, stroke-free survival and overall survival were similar in both groups. [11] In a much larger study even more recently, Colli et al in a multicenter prospective non-randomized trial collected data at 47 medical centers in Europe, Canada and India between 2006-2009. The investigators were free to prescribe the postoperative antithrombotic regimen of their choice and 1118 patients underwent AVR alone or combined with

coronary artery bypass graft [CABG], of whom 500 received warfarin and 618 received ASA. At 180 days, 14 anticoagulated patients [2.8%] suffered a thromboembolism versus 9 patients [1.5%] treated with ASA [P=0.12] and 18 anticoagulated patients [3.6%] suffered major bleeding versus 8 patients [1.3%] in the ASA group [P=0.01]. Major bleeding or thromboembolism occurred in 31 patients [6%] treated with warfarin versus 17 patients [2.8%] treated with ASA [P=0.003]. Propensity score matching was performed for the group that had isolated AVR: 290 [92.4%] of the 314 patients in the warfarin group were matched to 290 [71.8%] patients of the 404 in the ASA group. The proportions of patients who died or suffered from major bleeding or thromboembolism were similar in both groups. In the CABG + AVR group, the proportions of patients who a] died within 30 days after the index operation [2.7% versus 0%; P = 0.0211], b] suffered major bleeding [5.4% versus 0.5%; P = 0.0036], and c] suffered a cerebral thromboembolism [4.3% versus 0.9%; P = 0.0499], were significantly higher in the warfarin than in the ASA treatment group. Furthermore, the rates of any thromboembolism and major bleeding were 9.1% with warfarin versus 1.4% in the ASA group [P<0.0001]. They came to the conclusion that compared with ASA, treatment with warfarin was associated with higher morbidity within 6 months after bioprosthetic AVR, suggesting that, particularly after concomitant CABG surgery, recipients of bioprosthetic AVR should receive prophylactic ASA instead of warfarin. [12]

Interestingly recently, to assess if ASA alone is sufficient post AVR, Duraes and colleagues showed a low incidence of thromboembolism in a cohort of rheumatic heart disease patients who had undergone bioprosthetic AVR or mitral valve replacement using a bovine pericardial valve. Between January 2010 to July 2012, all consecutive rheumatic patients, with baseline sinus rhythm, who had bioprosthetic mitral and aortic valve replacement were included in the study. 184 patients were enrolled. They assessed for embolic events and also if there was any difference created by administering ASA. In the first 30 days, there were three cerebral ischemic events among the patients treated with ASA [5.2%] compared with two events in patients without [1.7%], HR = 3.18; 95% CI 0.5 to 19.6; P=0.33. Between 31 and 90 days postoperatively, no patient had a primary outcome. The embolism-free survival, bleeding events and the overall survival were not statistically significant between the aspirin and no-antiplatelet groups. [13] Likewise Brueck had previously shown an even lower risk of cerebral ischemia within 3 months after AVR in his group [ASA 0.8% vs no ASA 1.3%: p=0.884]. [14] This is in keeping with other studies showing that newer generation bioprosthetic valves are not as thrombogenic as during the time that Heras [1] published his results.

Based on the pharmokinetics of warfarin, there is a delay of approximately 3 days before any effects can be seen. Achieving a therapeutic international normalized ratio [INR] can also be an issue with anticoagulated patients having either a supratherapeutic or subtherapeuric result. Higher

results will no doubt place patients at a greater risk for bleeding during a time period when they are quite vulnerable. Brennan et al in their report showed similar rates of embolic events [2.8% versus 3.1%, p = 0.884], but a substantially higher incidence of bleeding in those treated with warfarin [12% versus 3%, p = 0.0012]. [15] In a review of 25, 656 post bioprosthetic AVR patients in the Society of Thoracic Surgeons Adult Cardiac Surgery database Brennan and associates found those receiving aspirin-only, 3-month adverse events were low [death, 3.0%; embolic events, 1.0%; bleeding events, 1.0%]. Relative to aspirin-only, those treated with warfarin plus aspirin had a lower adjusted risk of death [relative risk [RR]: 0.80, 95% confidence interval [CI]: 0.66 to 0.96] and embolic event [RR: 0.52, 95% CI: 0.35 to 0.76] but a higher risk of bleeding [RR: 2.80, 95% CI: 2.18 to 3.60]. Relative to aspirin-only, warfarin-only patients had a similar risk of death [RR: 1.01, 95% CI: 0.80 to 1.27], embolic events [RR: 0.95, 95% CI: 0.61 to 1.47], and bleeding [RR: 1.23, 95% CI: 0.85 to 1.79]. [16] In that report the lower adjusted incidence of early embolic events in the warfarin plus ASA group was balanced by an increased risk of repeat hospital stay for bleeding. However, as can be seen, there was some advantage to be gained from a warfarin plus aspirin strategy in this large cohort of patients albeit at an increased bleeding risk and there was no benefit of warfarin only over ASA only.

In most studies to date which show an added protection of warfarin, this benefit has only been limited to the first three months post op. However, recently one report has shown that warfarin maybe protective for up to six months and that discontinuation of warfarin treatment within 6 months after bioprosthetic AVR surgery was associated with increased cardiovascular death. This study was a retrospective review of 4075 patients in the Danish National Patient Registry. [17]

6. Conclusion

Based on the available evidence, there is a wide variation in anticoagulation practice amongst cardiac surgeons post tissue AVR. Most decisions are based on retrospective, observational cohorts with a lack of high quality randomized trials. Recent large database reviews have shown some benefit of an ASA plus warfarin strategy with one paper suggesting an advantage for up to 6 months. However, most of the available evidence point towards prescribing ASA only as this not only offers comparable protection to warfarin only, but also reduces the bleeding risk in this group of elderly patients who are usually offered bioprosthetic aortic valves. Studies of cerebral microembolization have also shown no benefits of warfarin. This conflicting evidence underscores the variation in practice as surveys of practicing cardiac surgeons in other centres have shown. [18, 19] In fact, the 2012 ESC guidelines on antithrombotic therapy post AVR recommend ASA as class IIa based on level C evidence and for a three month period of oral anticoagulation as class IIb [level C]. [20] The ACC/AHA 2006 guidelines give a class I indication for ASA and IIa for warfarin in post bioprosthetic AVR patients for 3 months if

low risk but a class I for warfarin if risk factors such as atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and a hypercoagulable condition is present. [21] As mentioned before and also reflected on our results, these guidelines are not strictly followed based on the weak level of evidence supporting warfarin. It will remain a matter of surgeon choice and this variation in practice will continue until we have the results of high quality prospective controlled randomized trials.

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