An Overview of Anticoagulants, Antiplatelet Agents, and the Combination in Patients with Mechanical Heart Valves

Henry I. Bussey

College of Pharmacy, The University of Texas at Austin, Austin, Texas, USA

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Currently, and for the near future, well-managed warfarin appears to be the most effective method to prevent thromboembolism and bleeding in patients with mechanical heart valves. These patients, when in an anticoagulation management service, have 50-90% fewer complications than patients not managed in this way. Further, the complication rate in such settings approximates that in patients with bioprosthetic, tissue valves not receiving anticoagulation. Oral direct thrombin inhibitors are safe and effective in patients with atrial fibrillation, but this is not proven in those with prosthetic heart valves. The idea of using a combination of different antiplatelet agents is attractive on a theoretical basis, but the available data are limited and do not support this approach. Combined aspirin (or another antiplatelet agent) and warfarin has been recommended, but close scrutiny of this combination suggests that it causes more bleeding and may offer no more protection than well-managed warfarin therapy. Recently, interest has been shown in the significance of high-intensity transient signals (HITS), which may represent gaseous or microemboli, and whether therapy to reduce HITS might influence the development of neurological symptoms. However, present data related to HITS are too limited and conflicting to make any firm conclusions.

The Journal of Heart Valve Disease 2004;13:319-324

In 1999, the Duke University Clinical Research Institute held a conference to discuss the future options of improving antithrombotic outcomes in patients with a mechanical heart valve prosthesis. The consensus reached at that conference was that the greatest improvement in this area would not come from changes in valve design, changes in valve materials, or even from the development of new antithrombotic agents. The participants predicted that the greatest benefit would come from improved use of antithrombotic agents available at that time. Although there have been new developments over the past four years, it is difficult to be persuaded that the basis for that group's consensus has changed substantially. This report will provide a brief overview of key issues regarding: (i) the use of anticoagulants alone; (ii) the use of antiplatelet agents only; and (iii) the use of combined anticoagulation and antiplatelet therapy in patients with mechanical heart valve prosthesis.

Presented at the Second Biennial Meeting of the Society for Heart Valve Disease, 28th June-1st July 2003, Palais des Congrès, Paris, France

Address for correspondence:
Henry I. Bussey PharmD, FCCP, FAHA, Clinical Pharmacy Programs, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, MSC: 6220, San Antonio, Texas 78229, USA
e-mail: Bussey@uthscsa.edu

Anticoagulants alone

Coumarin derivatives

At the present time, conventional dose warfarin with tight control of the International Normalized Ratio (INR) provides the best thromboembolic prophylaxis for mechanical heart valve patients. If such therapy is managed well, the annualized thromboembolic event rate is less than what has been described in some reports of bioprosthetic valve patients. Similarly, the incidence of major bleeding is also quite low as long as the INR is kept within the target range. Cannegieter et al. reviewed their complication rates in a population of over 1,600 mechanical heart valve recipients (1). After analyzing over 6,000 patient-years of data in this population, which had a high percentage of older and more thrombogenic valves than are used today, these authors found a very low rate of thromboembolism and major bleedings when the INR was kept between 2.5 and 4.9. Careful extrapolation of their data would

J Heart Valve Dis
Vol. 13. No. 3
May 2004

Table I: Combined ischemic and major hemorrhage rates (%/year) versus INR values.[*]

INR range	Combined event rates: ischemia and major hemorrhage
1-1.4	27.0
2-2.4	7.5
2.5-4.9	2.0 (±)
5-5.5	4.8
≥6.5	75

[*]Adapted from reference (1).

indicate that the annual combined rate of ischemic events and major hemorrhage is approximately 2% if the INR is kept in this range (Table I). As the INR deviated from the target range, however, the complication rates increased exponentially. How best to maintain the INR within the target range has been the focus of several publications. In the United States, the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy recommended that specialized anticoagulation management services (e.g. anticoagulation clinics) are the preferred way to manage these patients (2). In support of this recommendation, that group cited four studies which reported a 50% to 90% reduction in complication rates when patients were managed by an anticoagulation management service versus 'usual medical care' (Table II).

Oral direct thrombin inhibitors

Thrombin, a key component in the final stages of the clotting cascade, has a number of functions. In addition to promoting the formation of fibrin, thrombin also modulates fibrinolysis, promotes platelet activation, activates protein C (in conjunction with thrombomodulin and protein S), and promotes wound healing. Because of its effect on both the clotting cascade and platelet activation, it is a logical target for efforts to prevent prosthetic valve-induced thrombosis. Although several oral thrombin inhibitors are in development, ximelagatran is the one that appears to be closest to being approved for marketing. Ximelagatran is a pro-drug which exists as a small molecule that allows it to be given orally. After absorption, it is converted to megalatran, which is a specific and potent direct (antithrombin-independent) inhibitor of thrombin. Ximelagatran has a rapid onset of action and an elimination half-life of approximately 3 h; hence, twice-daily dosing is required. Because of its effects on thrombin, melagatran inhibits the activation of clotting factors V, VIII, and XIII, the activation of platelets by thrombin, and the conversion of fibrinogen to fibrin. Furthermore, the available evidence suggest that the pharmacodynamics of the drug are predictable enough that a fixed dose can be used for almost all patients, without the need of dosage titration against a blood test for anticoagulation effect.

Although clinical trial data suggest that ximelagatran may replace warfarin for a number of indications, the drug has not yet been studied in patients with prosthetic heart valves. At the 2003 American College of Cardiology Annual Scientific Meeting, however, data were presented from the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF III) study (3). SPORTIF III enrolled 3,407 non-valvular atrial fibrillation patients into an open-label, randomized trial that compared ximelagatran 36 mg twice daily with warfarin (target INR of 2 to 3).

Table II: Anticoagulation management services versus usual care.[*]

Model	Patient-years	Major bleed	TE	Combined	Savings ($)[+]
UC	64	12.4	6.2	18.6	860
AMS	42	2.4	0	2.4	-
UC	677	4.7	6.6	11.3	-
AMS	669	1.0	0.6	1.6	NA
UC	44	17.8	42.8	60.6	-
AMS	68	0.0	0.0	0.0	4,072
AMS	199	2.0	3.5	5.5	-
UC	102	3.9	11.8	11.8	-
AMS	123	1.6	3.3	4.9	1,621

[*]Adapted from reference (2).
[+]Savings is per patient per year in the AMS.
AMS: Anticoagulation management service; NA: Data not available; TE: Thromboembolic event; UC: Usual care.

After 21 months of follow up, the cumulative event rate for stroke and systemic embolism was lower in the ximelagatran group than in the warfarin group (1.6 versus 2.3% per year by intention to treat analysis (p = NS) and 1.3% versus 2.2% per year by on-treatment analysis (p = 0.018)). The INRs were between 1.8 and 3.2 for approximately 80% of the time, and major bleeding rates were not significantly different (1.8% with warfarin versus 1.3% with ximelagatran). Similar results were presented from the SPORTIF V trial by Hampering JL, et al at the American Heart Association Scientific Session, Orlando, Florida, November, 2003 (4). The one troublesome finding was that 6.5% of patients taking ximelagatran experienced an increase in liver enzyme activities to greater than three times normal. It is anticipated that approval of this drug for marketing will carry a requirement for periodic liver enzyme monitoring. While these data from patients with atrial fibrillation suggest that this agent may also be useful in prosthetic heart valve patients, its use in these patients must await results from clinical trials which have not yet been started.

Antiplatelet agents only

For mechanical heart valve patients, aspirin alone does not provide adequate protection from thromboembolism (5). However, there is reason to suspect that combination antiplatelet therapy might offer additional benefit as platelets may be activated by a number of different mechanisms, and individual antiplatelet agents tend to block only one of these mechanisms. Consequently, platelet inhibition with a single agent provides only partial suppression. Combining two agents which inhibit different mechanisms of platelet activation logically would be expected to provide superior protection to that achieved with either agent alone. One such combination that has proven very beneficial following the placement of coronary artery stents is aspirin plus clopidogrel. This combination is being studied in patients with atrial fibrillation. In a small study that compared this combination with warfarin (INR 2 to 3) in a total of 70 patients, warfarin significantly reduced biochemical indicators of thrombogenesis, but the combination of aspirin and clopidogrel did not. However, ex-vivo ADP- and epinephrine-induced platelet aggregation were reduced (6).

One study evaluating the aspirin/clopidogrel combination with warfarin in patients with mechanical aortic valves was terminated early. After enrolling only 11 patients into each of the two groups, the steering committee stopped the study early when a 67-year-old woman in the antiplatelet group developed valve thrombosis of her MIRA aortic valve at day 66 after starting the antiplatelet regimen (7). Unfortunately, as discussed with ximelagatran above, data from patients with atrial fibrillation may be encouraging, but this regimen clearly cannot be recommended in the absence of more data from patients with mechanical heart valves.

Anticoagulant and antiplatelet combination therapy

Does aspirin improve thromboembolic protection, increase bleeding risk, or both?

For mechanical heart valve patients, the combination of aspirin and warfarin is, by far, the most thoroughly studied and promising combination. At least one set of published recommendations favors this regimen over warfarin alone in high-risk patients (5). Even so, close scrutiny of the data provide some justification to question both the benefits and risks of adding aspirin to warfarin therapy. If one compares the benefits reported in different studies (with the acknowledged limita-

Table III: Landmark studies of combining aspirin with warfarin.

Outcome	W+Pl* (n = 184)	W+ASA* (n = 186)	W+ASA+ (n = 258)	W alone+ (n = 245)	W alone‡ (n = 1,608)
High INR	>4.5, 11%		>3.5, 25%	>4.5, 25%	>4.8, 8%
Low INR	<3.0, 49%		<2.5, 28%	<3.5, 40%	<3.6, 31%
In range	3-4.5, 40%		2.5-3.5, 47%	3.5-4.5, 36%	3.6-4.8, 61%
TE events	4.6	1.7	1.32	1.48	0.71
Major bleed	6.6	8.5	1.13	2.33	2.68
Total	11.2	10.2	2.45	3.81	3.39
Fatal, ICH	1.4	2.0	0.0	0.64	0.57

*From reference (8).
+From reference (9).
‡From reference (1).

tions of comparing results across studies), one might conclude that well-managed warfarin is both more effective and safer than combined aspirin and warfarin. For example, two landmark studies (8,9) are compared with the previously cited paper by Cannegieter et al. (1) in Table III. Although the frequently cited paper by Turpie et al. (8) appeared to show that the addition of 100 mg of aspirin to warfarin therapy (target INR 3 to 4.5) reduced the annual thromboembolic event rates (1.7 versus 4.6), the benefit was largely offset by a higher major bleeding rate (8.5 versus 6.6). However, the fact that 49% of patients' INRs were below the target range raises the question that the warfarin group might have had a lower embolic rate if INRs had been better controlled. The study by Meschengieser et al. (9) suggested that the addition of aspirin to a lower intensity warfarin regimen (INR 2.5 to 3.5) might be slightly more effective and cause slightly less bleeding than a warfarin regimen with a target INR of 3.5 to 4.5. This study, however, had two significant limitations. First, the bleeding rates were low in both groups, even though 25% of INRs were above the target range. The low bleeding rates may have been due to the fact that the open-labeled study excluded patients with known bleeding risk. Second, although the absolute thromboembolic event rate was higher in the group assigned to the higher INR, the control of INR was not as good in this group. Specifically, the group assigned to the lower INR plus aspirin had only 28% of their INRs below target, while those assigned to the higher INR (without aspirin) had 40% of their INRs below target. Consequently, the thromboembolic events in the group not receiving aspirin may have been due to suboptimal control of the INR. Finally, even though Cannegieter's group included patients with older and more thrombogenic valves and did not use aspirin, they actually had the lowest thromboembolic event rate of the three studies included in Table III. The degree of INR control in their report (61% of INRs were in range) was considerably better than that reported by either Turpie et al. (40% in range) or Meschengieser et al. (36% and 47% in range). Major bleeding rates in the Cannegieter report were lower than those reported by Turpie et al., and comparable to those reported by Meschengieser et al. Whether the addition of aspirin to warfarin adds increased protection or bleeding risk cannot be clearly determined from these studies. It is possible that an appropriate and well-controlled INR intensity may provide equivalent protection without the increased bleeding risk that aspirin affords.

This controversy of risk versus benefit of adding aspirin to warfarin has been explored further in two additional studies (Table IV). In the study by Laffort et al., the addition of 200 mg aspirin to warfarin (target INR of 2.5 to 3.5) appeared to cause more harm than good (10). Further, the findings that 76% of major bleeds occurred when the INR was above the target, and 72% of thromboembolic events occurred when the INR was below the target, would suggest that better INR control would reduce these complications further. In the study by Turpie et al., the addition of 100 mg aspirin to warfarin (target INR of 2 to 2.5) was not superior to warfarin alone (INR 3 to 3.5) (11). The degree to which the INRs were kept within the target range was not reported. Because aspirin at any effective dose increases bleeding risk, it is difficult to recommend the routine combination of aspirin and warfarin in patients without embolic events whose INRs are adequate and well controlled. However,

Table IV: More recent studies of combining aspirin with warfarin.

Outcome	W+Pl* (n = 120)	W+ASA* (n = 109)	W+ASA+ (n = 226)	W alone+ (n = 230)	W alone‡ (n = 1,608)
High INR	13% (76% of major bleed)		?	?	8%
Low INR	7% (72% of TE)		?	?	31%
In range	2.5 to 3.5 (79%)		2.0-2.5	3.0-3.5	61%
Major TE	4.1	0.9	4.2	3.0	0.71
Major bleed	8.3	19.2	8.5	9.1 (ICH 1.7)	2.68 (ICH 0.9)
Combined	12.4	20.1	12.7	12.1	3.39
Mortality	4	9	8.5	8.3	-
Complications	16	29	21.2	20.4	-

*From reference (18).
+From reference (11).
‡From reference (1).
TE: Thromboembolism.

when the INR cannot be maintained within the target range, the addition of aspirin may provide some measure of added protection during periods when the INR is below the target range.

Can combination therapy reduce HITS, and is that important?

The occurrence of high-intensity transient signals (HITS) as detected by transcranial Doppler has been a source of interest for some time, especially in the European literature. These HITS are thought to represent nitrogen bubbles and platelet microemboli that are generated by turbulence of blood flow through prosthetic heart valves. Several studies have demonstrated that the frequency of HITS is significantly higher in patients with bileaflet valves (St. Jude Medical and CarboMedics) than with the Medtronic Hall tilting disc valve (12-15). The clinical significance of this increased frequency of HITS, however, is in question since the data are conflicting as to whether an increased frequency of HITS represents an increased thromboembolic risk (15-18). In one study of patients with mechanical heart valves, 14 of 26 had significant HITS, and four of these experienced central nervous system complications (16). Similarly, in another study eight of 26 prosthetic heart valve patients who experienced a cerebrovascular event had a higher number of HITS per 30 min (median of 75) than did those who did not experience such events (median of 23) ($p < 0.05$) (17). In contrast, one large study of 580 prosthetic heart valve patients (13) and another study that included 42 patients (18) found no correlation between HITS and neurological symptoms.

Similarly, there is considerable controversy as to whether aspirin can reduce the frequency of HITS. In one trial of 30 patients on adequate anticoagulation (INR >2.5), the addition of aspirin reduced the frequency of HITS by between 16% and 41% (12). However, in an evaluation of five prosthetic heart valve patients who were suffering recurrent ischemia in spite of adequate anticoagulation (INRs of 3.0 to 4.3), the addition of aspirin failed to reduce the frequency of HITS (19).

In addition to the interest in HITS and cerebrovascular events, one study which comprised 12 patients with mechanical heart valve prostheses found that an increased frequency of HITS was associated with a greater loss of memory (20). Unpublished observations have suggested that aspirin in these patients may have a beneficial effect on memory (personal communication, Irv Krukenkamp, M.D., Stoneybrook Medical Center, Stoneybrook, New York).

Summary

For patients with mechanical prosthetic heart valves, adequately managed anticoagulation with warfarin is a remarkably safe and effective therapy. Although single antiplatelet therapy is considered inadequate in these patients, combined antiplatelet therapy with two agents of different platelet-inhibiting mechanisms might, in theory, offer an alternative approach. Such dual antiplatelet therapy has not been studied in patients with mechanical heart valve prosthesis, but ongoing studies in atrial fibrillation may yield valuable results. Whether it is advisable to combine aspirin and warfarin routinely in mechanical heart valve patients is an unsettled issue. Proponents will point to some studies which suggested that aspirin provided some additional protection with limited to moderately increased bleeding risk. Opponents will point out that those studies in which aspirin was found to be beneficial often had poor INR control, while studies with good INR control and no aspirin showed good results. One position that is something of a compromise of these divergent opinions is that warfarin alone should be used if the INR can be well controlled, but the addition of aspirin may be considered if the INR cannot be well maintained. Finally, the relationship of HITS to clinically important events and memory changes is another interesting focus of conflicting data. Further, whether aspirin can reduce the frequency of HITS, and whether such a reduction has clinically important benefits, requires further study.

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