World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/1949-8462office
wjc@wjgnet.com
doi:10.4330/wjc.v4.i3.54

World J Cardiol 2012 March 26; 4(3): 54-59
ISSN 1949-8462 (online)
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EDITORIAL

Management dilemmas in patients with mechanical heart valves and warfarin-induced major bleeding

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Received: December 19, 2011 Revised: March 20, 2012
Accepted: March 23, 2012
Published online: March 26, 2012

Abstract

Management of warfarin-induced major bleeding in patients with mechanical heart valves is challenging. There is vast controversy and confusion in the type of treatment required to reverse anticoagulation and stop bleeding as well as the ideal time to restart warfarin therapy safely without recurrence of bleeding and/or thromboembolism. Presently, the treatments available to reverse warfarin-induced bleeding are vitamin K, fresh frozen plasma, prothrombin complex concentrates and recombinant activated factor Ⅶa. Currently, vitamin K and fresh frozen plasma are the recommended treatments in patients with mechanical heart valves and warfarin-induced major bleeding. The safe use of prothrombin complex concentrates and recombinant activated factor Ⅶa in patients with mechanical heart valves is controversial and needs well-designed clinical studies. With regard to restarting anticoagulation in patients with warfarin-induced major bleeding and mechanical heart valves, the safe period varies from 7-14 d after the onset of bleeding for patients with intracranial bleed and 48-72 h for patients with extra-cranial bleed. In this review article, we present relevant literature about these controversies and suggest recommendations for management of patients with warfarin-induced bleeding and a mechanical heart valve. Furthermore, there is an urgent need for separate specific guidelines from major associations/professional societies with regard to mechanical heart valves and warfarin-induced bleeding.

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Key words: Warfarin; Major bleeding; Mechanical heart valve; Thromboembolism; Vitamin K; Fresh frozen plasma; Prothrombin complex concentrate; Recombinant activated factor Ⅶa

Peer reviewer: Ulrich Nellessen, Professor, Medical Director, Chief Department of Cardiology, Johanniter-Krankenhaus Genthin-Stendal GmbH, Wendstraße 31, 39576 Stendal, Germany

Panduranga P, Al-Mukhaini M, Al-Muslahi M, Haque MA, Shehab A. Management dilemmas in patients with mechanical heart valves and warfarin-induced major bleeding. *World J Cardiol* 2012; 4(3): 54-59 Available from: URL: http://www.wjgnet.com/1949-8462/full/v4/i3/54.htm DOI: http://dx.doi.org/10.4330/wjc.v4.i3.54

INTRODUCTION

Warfarin acts by inhibiting the enzymes involved in the formation of a reduced form of vitamin K, which is essential for γ-carboxylation of glutamate residues at the amino terminus of coagulation factors Ⅱ, Ⅶ, Ⅸ and Ⅹ and anticoagulant factors protein C and S. This results in production of partially carboxylated, biologically inactive clotting factors. Unlike older mechanical heart valves (MHV), the newer valve design with very low thrombogenicity has reduced markedly the rate of valve thrombosis and thromboembolism events (TEs), along with the required level of anticoagulation [< 3.5 international

normalized ratio (INR)], which has led to use of a lower dosage of warfarin as well as bleeding complications[1]. Despite this trend, patients with MHV on warfarin therapy develop major bleeding complications due to a narrow therapeutic index of warfarin, an unpredictable biological response (including genetic polymorphisms in warfarin metabolism) and multiple interactions with concomitant drugs/food and other patient-related factors. Furthermore, management of warfarin-induced major bleeding in patients with MHV is challenging and controversial.

INCIDENCE OF MAJOR BLEEDING AND THROMBOEMBOLISM IN PATIENTS WITH MECHANICAL HEART VALVE AND WARFARIN

In recent studies, the incidence of major bleeding complications in patients with MHV and taking oral anticoagants has varied from 0.34% to 1.32% per patient-year[2-4]. The International Society on Thrombosis and Hemostasis in 2005[5], defined major bleeding in non-surgical patients as: (1) fatal bleeding; and/or (2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular (iliopsoas) with compartment syndrome; and/or (3)bleeding causing a fall in hemoglobin level of 2 gm% or more, or leading to transfusion of two or more units of whole blood or red cells.

Among the factors increasing warfarin-induced major bleeding, an INR level over the therapeutic range is the most important risk factor, independent of the indication for therapy, with the risk increasing dramatically with INR > 4-5[6,7]. Other risk factors which can increase major bleeding in patients on oral anticoagulation include age > 75 years, hypertension, previous stroke, concomitant antiplatelet agents, and a previous history of bleeding[6,7]. Overall, in clinical studies associated with careful monitoring of INR, treatment with oral anticoagulants increases the risk of major bleeding by 0.3%-0.5% per year and the risk of intracerebral hemorrhage (ICH) by approximately 0.2% per year compared to controls[6].

In an earlier study, the incidence of prosthetic valve thrombosis in patients not anticoagulated or taking antiplatelet drugs was 1.8% per patient-year (95% CI: 0.9-3.0)[8]. The incidence of TE resulting in death, stroke, or peripheral ischemia requiring surgery was 4% per patient-year (95% CI: 2.9-5.2). This was reduced to 2.2% by antiplatelet drugs and 1.0% per patient-year with warfarin[8]. In the German Experience With Low-Intensity Anticoagulation study involving > 2000 patients with MHV, the annual incidence of major and minor TE on various levels of therapeutic anticoagulation was 0.75% with 0.32% per patient-year minor, 0.15% per patient-year moderate and 0.28% per patient-year severe events[2]. TEs following aortic valve replacement were significantly lower than mitral valve replacement (0.53% per patient-year *vs* 1.64% per patient-year)[2].

MORTALITY AND MORBIDITY ASSOCIATED WITH WARFARIN-INDUCED BLEEDING

The common sites of major bleeding related to warfarin are the gastrointestinal tract (40%-60%) and urinary tract (15%) followed by ICH/subdural hematoma and retroperitoneal bleed/abdominal compartment syndrome[9-11]. Of all bleeding episodes, nearly 50% are major bleeds[10]. Warfarin-related bleeding results in significant morbidity related to transfusion and hospitalization. Approximately 1 in 10 major bleeds are fatal, and 1 in 12 patients will re-bleed after warfarin resumption[10]. Among those who develop warfarin-related major bleeds, the fatality rate may be as high as 9.5%-13.4%[10,11].

TREATMENT OF WARFARIN INDUCED MAJOR BLEED

Currently, the treatments available to reverse warfarin-induced bleeding in combination with cessation of oral anticoagulant therapy are vitamin K, fresh frozen plasma (FFP), prothrombin complex concentrate (PCC) and recombinant activated factor Ⅶa (rFⅦa)[12-14]. The American College of Chest Physicians (2008) guidelines recommends oral doses of vitamin K 1-2.5 mg for an INR between 5 and 9 and 2.5-5 mg for all patients with an INR ⩾ 9, but with no significant bleeding[12]. In patients with serious bleeding and elevated INR, regardless of the magnitude of the elevation, 10 mg vitamin K is recommended by slow IV infusion supplemented with FFP, PCC, or rFⅦa, depending on the urgency of the situation. Repeat vitamin K administration every 12 h is also recommended for persistent INR elevation[12].

Vitamin K

Historically, vitamin K and FFP are well-known standard therapies to reverse warfarin anticoagulation. However, neither of them is ideal during a major bleed, specifically when emergency surgical intervention or urgent invasive diagnostic intervention is needed, as they take a long time to act, when INR levels of < 1.5 (< 1.2 for neurosurgery) are desirable[9]. Administration of vitamin K (10 mg intravenously at an infusion rate of 1 mg/min, diluted in dextrose 5% in water or dextrose 5% in normal saline) alone will require 12-24 h (reversal begins within 6 h) to reverse warfarin-induced coagulopathy[14-17]. A dose of 5-10 mg may be repeated every 12 h, up to a total dose of 25 mg[14]. The advantage of vitamin K injection is the ease of administration, wide availability, promotion of the formation of factor Ⅱ, Ⅶ, Ⅸ and X in the liver and an effect that lasts beyond the relatively short half lives of FFP and PCC, hence producing a well sustained correction of the coagulopathy[17]. The disadvantages of vitamin K are risk of development of anaphylaxis which is thought to be due to the castor oil in the dilu-

ent and a state of "warfarin resistance"[13-15,17]. To avoid anaphylactic reactions (an estimated 3/100 000 risk of anaphylaxis), a few authors advise vitamin K to be mixed in a minimum of 50 mL of intravenous fluid and administered using an infusion pump, over a minimum of 30 min[15,16]. The oral route of vitamin K is used if reversal is warranted over 24 h in patients with high INR without bleeding, but this is of no benefit in patients with a major bleed. Subcutaneous administration is unreliable and may take up to 72 h to reverse the INR[14,15,17]. Intramuscular administration of vitamin K can cause hematoma and response is unpredictable[15].

American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend that high-dose (10 mg) vitamin K must not be used routinely in patients with MHV as this may create a hypercoagulable state with risk of valve thrombosis and TEs[18]. In addition, high dose vitamin K may lead to "warfarin resistance" (up to 3%; for 1 wk or more) due to accumulation of vitamin K in the liver, necessitating use of higher doses of warfarin later to achieve therapeutic INR levels and increasing the risk of TEs during this period. However, vitamin K does not affect subsequent use of heparin which is commonly used in MHV with warfarin overlap. Furthermore, ACC/AHA guidelines recommend that FFP is preferable to high-dose vitamin K in patients with MHV. Alternatively, low-dose vitamin K (e.g., 1-2 mg intravenous) with FFP may be appropriate.

Fresh frozen plasma

FFP contains vitamin K-dependent clotting factors and consists of the fluid portion of 1 unit of human blood, frozen within 8 h after collection and used within 12 mo[16,19]. The suggested dose is 15 mL/kg infusion (range 10-30 mL/kg), about 3-4 units of plasma in the average-sized adult (one unit = 250 mL), but optimal dose is unknown[14,15,17]. Time to effect of FFP is 10 min, but it takes a few hours for partial reversal and at least 9 hours for complete reversal of INR (INR < 1.5)[13,17]. Other limitations in using FFP include fluid overload and transfusion-related acute lung injury, and it carries a minimal risk of infection[13,16,17,19]. In addition, since the plasma is frozen, it has to be thawed and blood type-matched, which will cause delay in administration, but in emergency situations AB Rh D FFP can be used without previous blood typing[16,17].

Prothrombin complex concentrate

Although FFP is commonly used, as it is widely available and costs less, PCC has been noted to have significant benefits over FFP and according to a few authors it is the "gold standard" therapy[14,15,17,20]. This is because of the concentration of clotting factors in PCCs being approximately 25 times higher than in FFP and because FFP contains an inadequate concentration of factor Ⅸ[20-22]. Approximately 60 mL of PCC corresponds to 1500 mL of FFP leading to a minimal risk of volume overload[17]. PCC is pooled from donor plasma, reconstituted for clotting factor replacement; virus inactivated and is available from the pharmacy in powder form[17]. Four-factor PCC includes coagulation factors Ⅱ, Ⅶ, Ⅸ and Ⅹ, and anticoagulant proteins C and S. The typical recommended dose is 25 to 50 U/kg[20,21]. After initial infusion of 500-1000 IU at a rate of 100 IU/min, subsequent infusion should be at 25 IU/min or less[14,20,21]. Some have safely infused higher doses (3500 IU) over 10 min[21]. The advantages of PCC are rapid preparation (time taken getting PCC 15 min *vs* 1-2 h for FFP), and complete reversal of warfarin effect within 10-30 min of administration[9,14,17,20-22]. INR should be measured within 30 min of PCC administration. If it remains ⩾ 1.5, a further PCC dose should be administered[9]. The INR must be measured again after 6 to 8 h and then daily while the situation remains critical. The major issues that have limited the use of PCC in patients with a major bleed are the fear of thrombotic complications (around 0%-7%, mean of 2.3%), and limited availability of these products[15,16]. One suggested cause of PCC-associated thrombotic risk is a high level of factor Ⅱ in the PCC (relative to the other factors), which is known to increase thrombin generation[20]. If either FFP or PCCs are administered without vitamin K, initially there will be rapid normalization of the INR with a "rebound" increase 12-24 h later; this phenomenon is commonly seen when vitamin K is not given simultaneously with FFP or PCC or an inadequate dose of vitamin K is administered. This is because the half-life of warfarin far exceeds the half-life of the administered coagulation factor complexes (FFP T½: 1.5 h-2 d; PCC T½: 6-8 h; Warfarin T½: 20-60 h)[14,16].

Recombinant activated factor Ⅶa

Recombinant FⅦa (used in hemophilia patients), is also effective in reversing elevated INR at doses of 10-40 μg/kg bolus dose[14-16,23-25]. It should be reconstituted with sterile water for injection and used within 3 h of reconstitution. Recombinant FⅦa gives a rapid and complete biochemical reversal of INR within 10 min, but has a short half-life of < 1 h[17]. The disadvantage of rFⅦa is that it does not replace all clotting factors and even though INR is reduced immediately, clotting may not be restored in vivo. Hence, repeat infusions are necessary unless vitamin K and FFP are used concomitantly. In a recent large meta-analysis of rFⅦa use involving > 4000 patients, 11.1% developed TEs[24]. Hence, the most recent guidelines on management of these patients advise against use of rFⅦa in the treatment of warfarin-associated bleeding/ICH or limit its use only if PCC or FFP are not available[9,26]. In general, most of the guidelines recommended use of PCC over FFP, but they do not comment specifically whether PCC can be used in MHV patients[6,9,25-29].

DO CURRENT TREATMENT MODALITIES APPLY TO PATIENTS WITH MECHANICAL VALVES?

Currently, there is limited information, especially case

reports, about the use and safety of giving either PCC or rFVIIa in patients with mechanical valve replacement and warfarin-induced bleeding[22,30-33]. Hence they cannot be routinely recommended in this group of patients. In addition both PCC and rFVIIa potentially produce thrombotic complications which may restrict their use by physicians in MHV as there is a chance of valve thrombosis which can be catastrophic. Hence, in patients with MHV and major bleeding, ACC/AHA guidelines should be followed by using FFP and vitamin K intravenous injection. The predominant concern is the need for large quantities of FFP to bring down the INR within a few hours. In patients who cannot tolerate a large volume of FFP, adjunctive use of diuretics may be needed or cautious use of PCC may be considered. Even though high dose intravenous vitamin K is not routinely advised in patients with mechanical valves, in emergency situations with major bleed and hemorrhagic shock or need for emergency surgery, higher doses can be used to bring the INR down fast and prevent rebound anticoagulation. In these situations the risk of death from major bleeding far exceeds the risk of death from TEs[15]. In a case series, 7 patients with MHV and subdural hematoma were treated with 10 mg intravenous vitamin K and FFP to reverse INR completely and were off any anticoagulation for a mean of 20 d without any TEs[13]. Whether PCC/rFVIIa can be used safely in patients with MHV needs further study.

HOW LONG CAN YOU STOP WARFARIN? WHEN TO RESTART WARFARIN AFTER A MAJOR BLEED

In patients with MHV, stopping warfarin and reversing anticoagulation therapy with the ensuing risk of valve thrombosis/TEs must be weighed against the risk of continued bleeding. No large prospective trials have evaluated the issue of when to restart anticoagulation after warfarin-induced major bleed. The publications report withholding all anticoagulation for 1 to 2 wk[34,35], 4 to 6 wk[36] or advise the use of bridging therapy with intravenous unfractionated heparin (UFH)/subcutaneous low-molecular weight heparin (LMWH) immediately after the INR is corrected to normal[37,38]. In an earlier study, Phan *et al*[34] reported withholding of anticoagulation for mean of 10 d in patients with ICH, but the 30-d TE rate estimated was high at 3% for those with prosthetic valves. In another study, involving patients with MHV and ICH, anticoagulation therapy was discontinued from 2 d to 3 mo (median, 8 d) and there were no TEs. They concluded that for most patients, discontinuation for 1 to 2 wk should be sufficient to observe the evolution of a parenchymal hematoma to prevent its expansion, to clip or coil a ruptured aneurysm, or to evacuate an acute subdural hematoma[35]. Butler *et al*[38] reported withholding anticoagulation in MHV patients with ICH with the INR remaining < 2.0 for 0-19 d (median 7) with no short-term TEs.

It has been observed that the presumed risk of TEs with a MHV is generally overestimated. Crawley *et al*[36] reporting on MHV patients off anticoagulation observed that if the risk of embolism from MHV resulting in major stroke or death is 4% a year and the risk of valve thrombosis is 1.8% a year[8], the daily risk can be estimated to be 0.016%. Thus stopping anticoagulation for 6 wk is associated with a risk of major stroke or death of 0.67% and suggested that with such low risk of TEs, the use of heparin as a bridging therapy cannot be recommended in patients with major warfarin-induced bleeding[36]. In another study, among patients with prosthetic heart valves and major hemorrhage, the mean duration of anticoagulation withholding was 15 ± 4 d with no episodes of TE during hospitalization and at 6 mo, but on re-starting warfarin, the patients with gastrointestinal bleed were at high risk of re-bleed[39]. In one large prospective study, 1300 cases (in 1024 patients, 10% with MHV) of warfarin interruption (80% < 5 d) before an invasive procedure were examined[40]. Only 0.7% patients had a post procedure TE within 30 d of the procedure and none of these patients received bridging therapy. Nearly 60% of the patients had periprocedural bleeding and all of them were on bridging heparin therapy[40]. In a similar study from The Mayo Clinic[41], 556 MHV patients off warfarin therapy for 5 d, undergoing surgery underwent bridging therapy with UFH or LMWH with very low TEs of 0.9% over 3 mo with 3.6% major bleeding episodes. It was concluded that post-procedural heparin use must be reserved for patients with the highest thromboembolic risk (mitral MHV, multiple MHVs, and MHV with prior stroke or atrial fibrillation) waiting at least 48 h before initiating treatment. Even though these two studies involved MHV patients without a major bleed, they indicate that the incidence of TEs off warfarin therapy with or without bridging therapy is very low at 0.7% to 0.9%, respectively and even for very high risk patients among MHVs, a minimum 48 h with no bridging therapy should be given[41]. In addition, TE risk is high during the first 6 mo of MHV implantation[42].

In an analysis, Aguilar *et al*[14] reported that, overall, the data (8 studies involving 132 patients) suggest a low risk of TE complications between 7 and 14 d after anticoagulation reversal in patients with warfarin-associated ICH and prosthetic valves. In a recent systematic review of the literature on the management of oral anticoagulant therapy after an ICH in patients with a mechanical heart valve, stopping anticoagulant therapy for few days (7-14 d) after ICH was found to be safe[43]. The risk of TE in a patient with a MHV during 7 d without anticoagulation can be estimated between 1 in 1300 and 1 in 240, assuming an annual incidence of between 4% and 22%[38]. Romualdi *et al*[43] estimated that in the worst-clinical-case scenario, the incidence of TEs without anticoagulation in patients with MHV is 22 per 100 patient-years which is a high risk on a yearly basis, but this corresponds to a 0.06% daily risk (i.e., 6 in 10 000 patients).

Therefore, they concluded that short interruption of anticoagulation may not be as dangerous as is often presumed. The risk of damage to organs by bleeding when anticoagulation is not fully interrupted is probably much higher in these situations. The European Stroke Initiative recommends that patients with very high risk for TE should be restarted on warfarin after 10 to 14 d, and the AHA recommends 7 to 10 d after ICH[26,44,45]. The most recent French guidelines recommend holding any anticoagulation for 1-2 wk in MHV patients with intracranial bleed and for 48-72 h for extra cranial major bleed[9].

CONCLUSION

After reviewing the available literature, we suggest the following treatment strategies in patients with MHV and warfarin-induced major bleeding: (1) high dose vitamin K therapy (5-10 mg) should be administered immediately by slow intravenous infusion over 10-30 min, and a repeat dose should be considered at 12 h; (2) large volume of type-specific FFP (initially, emergency-released AB plasma = universal plasma donors, maximum 4 units) should be infused as tolerated according to desired INR levels as well as to stop bleeding. Caution is needed during large volume FFP infusion and diuretic therapy should be used when needed. Four hourly INR needs to be checked for the first 24 h, if INR is not to the desired level, repeat FFP infusion; (3) PCC should be reserved for patients who are allergic or intolerant to FFP and in those who cannot tolerate a large volume of FFP such as patients with heart failure in view of its potential thrombotic complications till further data prove that it is safe to be used routinely in MHV patients; (4) recombinant FⅦa should not be used in patients with MHV in view of its high incidence of thrombotic complications till further studies prove its safety in MHV patients; and (5) with regard to restarting any anticoagulation in patients with warfarin-induced major bleeding and MHV (especially in patients with high risk MHV = mitral MHV, multiple MHVs, MHV with prior stroke or atrial fibrillation, and MHV implanted within 6 mo), any anticoagulation should be withheld (or safe to re-start) for 7-14 d in patients with intracranial bleed and 48-72 h for patients with extra cranial bleed.

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