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Review Article: Venous thromboembolism after total joint replacement

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ABSTRACT

Venous thromboembolism can occur in up to 84% of cases following total joint replacement. It can result in pain, swelling, chronic post-thrombotic syndrome, and pulmonary embolism. Its prevention is vital to the success of the surgery. To achieve a safe and effective prophylaxis, a combination of mechanical and pharmacologic agents should be used. New generation of thromboprophylactic agents target different factors of the coagulation pathway.

Key words: *arthroplasty, replacement, hip; arthroplasty, replacement, knee; postthrombotic syndrome; pulmonary embolism; venous thromboembolism*

INTRODUCTION

Venous thromboembolism (VTE) includes conditions from asymptomatic deep vein thrombosis (DVT) to fatal pulmonary embolism (PE). DVT of popliteal and femoral veins (proximal DVT) is clinically more significant than that of calf veins (distal DVT). Proximal DVT is associated with a higher frequency of PE.[1] Distal DVT rarely causes PE, unless it extends to proximal veins.[2] Asymptomatic distal DVT can be associated with post-thrombotic syndrome and recurrent DVT. VTE can occur spontaneously or secondary to coagulation disorders or lower limb surgery. This study reviews the clinical presentation, pathogenesis, prophylaxis, and management of VTE after total hip replacement (THR) or total knee replacement (TKR).

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical features of DVT following total joint replacement are typically non-specific. Individual symptoms per se do not reliably predict DVT.[3] Thigh and calf swelling, especially calf swelling by >3 cm, is the most usual presentation. Symptoms of DVT include swelling (85%), pain (78%), positive Homen's sign (56%), erythema (24%), and fever (5%).[4,5] Venography is considered the gold standard

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for investigation, but it is invasive and involves exposure to contrast media and radiation.[6] Doppler ultrasonography is non-invasive and has near 100% sensitivity in the detection of proximal DVT.[7]

Symptoms of PE include shortness of breath (70%), tachycardia (43%), hypoxia (18%), and hypotension (10%).[8] Many patients also complain of chest pain. Pulmonary angiography is considered the gold standard for diagnosing pulmonary embolism, but it is invasive and may cause serious complications (cardiac arrhythmia or even cardiac perforation).[9] Contrast helical computed tomographic angiography of the thorax is non-invasive, more readily available, and has up to 90% sensitivity and 95% specificity in the detection of PE.[10]

The probability for detecting PE using ventilation-perfusion scanning depends on the degree of ventilation-perfusion mismatch. It is an imaging option for PE and is most helpful when the result is normal, which rules out the diagnosis. For more than half of the patients, the probability is either intermediate (in which 30% have PE) or low (in which 14% have PE). Thus ventilation-perfusion scanning is frequently non-diagnostic and inconclusive.[11] For patients in shock in whom PE is suspected, bedside echocardiography may be an appropriate investigative tool.[12]

INCIDENCE AND RISK FACTORS

The incidence of DVT is 39 to 74% following THR and 1 to 84% following TKR.[13,14] Such a wide range is due to different investigative tools used to identify thrombosis. Venography and Doppler ultrasonography typically record higher rates of VTE. Symptoms are present in only a small proportion of VTE patients. According to the Scottish Arthroplasty Registry, the incidence of clinically significant VTE within 3 months of THR and TKR is 2.27 and 1.79%, respectively, whereas that of fatal PE is 0.22 and 0.15%, respectively.[15]

VTE was thought to be less common in Asians than Caucasians, owing to the rarity of the Factor V Leiden trait in non-Caucasians.[16,17] The rate of VTE after major orthopaedic surgery is low in Asians.[18] However, in the SMART venography study including 326 patients undergoing THR or TKR in 3 Asian countries, the rate of asymptomatic VTE detected by venography was 36.5%.[19] Similarly, the VTE rate was 33.8% after THR and 65.3% after TKR in Japanese populations,[20] and was 41% after TKR in Korean populations.[21] These studies showed that the rates of VTE in Asian populations are actually comparable to those of Caucasians. Other unknown genetic or environmental factors (e.g. genetic loci for protein S, protein C, and antithrombin deficiencies) may be responsible for the occurrence of VTE in non-Caucasian populations.[22]

Haemostasis (normal coagulation cascade) is essential for human survival (Fig.). The aetiology of VTE depends on the pathological triad of venous stasis, hypercoagulability, and trauma.[23] Prolonged bedrest, presence of malignancy, use of contraceptive pills, hypercoagulable states, and a history of DVT are risk factors. THR and TKR can cause venous stasis and endothelial injury in the lower limb.[24] Other factors that increase the risk (in THR patients) include age >70 years, primary osteoarthritis as the indication for surgery, operation through the lateral approach, and undertransfusion of blood.[25] Regional anaesthesia and rheumatoid arthritis patients have lower relative risks for VTE.[25,26]

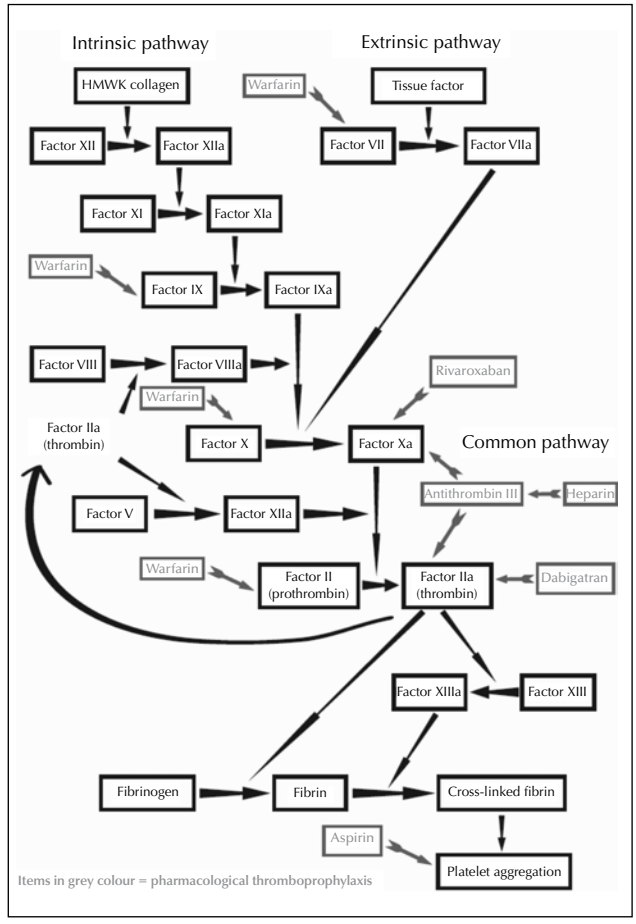

Figure Coagulation cascade and the sites of action of commonly used anticoagulants.

TREATMENT

The goals of treatment are to prevent propagation of thrombus, restore venous patency, prevent PE, and decrease the risk of post-thrombotic syndrome (persistent leg swelling, dermatitis, recurrent cellulitis, and ulceration). Low-molecular-weight heparin (LMWH) and compression stocking are commonly used to control lower-limb swelling.[27] Warfarin is started at the same time and titrated until the international normalised ratio (INR) is in the range of 2 to 3. The LMWH can then be stopped and warfarin can be continued for at least 3 months. The duration of anticoagulation is controversial; a period of 3 months is considered adequate in patients with THR or TKR as the only identifiable risk factor.[28,29] Anticoagulation therapy for PE should be started as soon as possible.[30,31] Selected patients with massive PE and haemodynamic instability may be candidates for intra-arterial thrombolysis or surgical embolectomy. In patients already receiving anticoagulation or those contraindicated to anticoagulation, insertion of an inferior vena cava filter should be considered when PE occurs.

PROPHYLAXIS

All patients undergoing THR or TKR should receive some form of mechanical and/or pharmacological prophylaxis. The effectiveness of various prophylactic agents is difficult to compare. Fatal PE is so rare that even large trials (e.g. the RECORD trial for rivaroxaban[32]) may not have adequate power to detect any difference. Joint registries can provide large numbers of patients for analysis, but cannot establish causal relationships.

In addition, many studies are funded by pharmaceutical companies and may involve conflicts of interest. For example, the Asia-Pacific Thrombosis Advisory Board meeting and consensus statements were sponsored by the Bayer Schering Pharma AG.[33]

Two of the most influential guidelines for thromboprophylaxis are those of the American College of Chest Physician (ACCP) and the American Academy of Orthopaedic Surgeons (AAOS). Both are based on systematic reviews of the literature and have been regularly renewed. The first edition of the AAOS guideline was published in 2008,[34] in response to the seventh edition of the ACCP guideline in 2004.[35] The ACCP published its ninth edition in 2011,[36] and the AAOS published its second edition in 2012.[37] Deviation from the guideline is sometimes needed for individual patients. It is more important to understand the rationale behind the guideline than to follow it blindly. Thus, the ACCP and AAOS guidelines can be regarded as complementing each other.

Mechanical prophylaxis

The AAOS recommended that mechanical prophylaxis be started early and continued until discharge. Patients should also be mobilised as soon as feasible.[37] The ACCP also supported the use of intermittent pneumatic compression devices.[36] Mechanical prophylaxis includes graduated compression stocking, intermittent calf compression, foot pump, and early mobilisation. These act by increasing the velocity of venous blood flow and preventing stasis,[38,39] as well as decreasing the coagulability of blood by stimulating fibrinolysis.[40]

Graduated compression stocking is easy to apply. It can reduce the probability of DVT to 39% from 50%.[41] It reduces the relative risk of developing DVT by 25%.[42] Nonetheless, it is much less effective than anticoagulants or other mechanical prophylaxis devices such as intermittent calf compression. Therefore, it is not recommended as the sole prophylactic measure.

Intermittent calf compression can reduce the probability of DVT to 22% and the relative risk by 60%.[41–43] Nonetheless, it is also inferior to anticoagulants (LMWH and warfarin) for preventing proximal DVT.[13]

The use of the foot pump can decrease the rate of DVT in THR and TKR patients.[44–47] Active mobilisation exercises of the foot and ankle can increase venous flow,[38,39] but their effectiveness as a prophylactic measure is unknown.

Mechanical prophylaxis has a low risk of bleeding complication and enhances the effectiveness of anticoagulants. Although it may result in rare complications such as peroneal nerve palsy and compartment syndrome,[48,49] it is in general very safe. The main factor limiting its efficacy is patient non-compliance, which is around 3 to 14%.[44,45,50,51] Poor patient compliance may be due to ankle discomfort, noise generation, and sleep disturbance.[51]

Pharmacological prophylaxis

Pharmacological prophylactic agents include aspirin, warfarin, LMWH, and newer agents such as dabigatran and rivaroxaban (Fig.). These agents are all recommended by the ACCP.[36] Nonetheless, controversies exist regarding which the most appropriate agents are, the optimal treatment

duration, and the need to use them especially in populations with low risk of VTE.

The need for pharmacological prophylaxis in Asian populations

VTE rates were thought to be low in Asian populations.[52,53] In 1970s, autopsy studies on Chinese indicated that the incidence of PE was 0.75%, and that of lower-limb DVT was 18%.[54] The incidence of DVT in Hong Kong Chinese receiving surgery for fractures of the proximal femur was 53% on the operated side and 14.3% on the normal side.[55] In the SMART study, the DVT rate was 36.5% in Asians having total joint replacement.[19] In Japanese patients, the DVT rate was 65.3% after TKR and 33.8% after THR.[20] In our hospital, the PE rate was 0.5%, of which one fifth (0.1%) were fatal.[56] Nonetheless, pharmacological prophylaxis is not routinely used in many Asian countries. The DVT rates in Japanese THR patients receiving placebo, LMWH, or synthetic pentasaccharide were not significantly different.[57] Mechanical prophylaxis alone is considered adequate in Japanese patients.[57,58] However, there are limitations in these conclusions. The mean time to develop DVT is about 22 days,[59] but in one study outcome was measured on day 11 using duplex ultrasonography and thus may not be representative.[57] The other study was a retrospective review of medical records and only symptomatic VTE was analysed (asymptomatic DVT was not detected).[58] Asymptomatic DVT is associated with post-thrombotic syndrome and recurrent DVT and should be prevented if feasible.[60]

According to the Asia-Pacific Thrombosis Advisory Board, the risk of VTE in Asian patients is clinically significant.[33] The advisory board recommends anticoagulation as the main preventive strategy for VTE following total joint replacement.

Aspirin

Aspirin is an inhibitor of the COX enzyme system.[61] There are 2 COX isoenzymes (COX1 and COX2) and aspirin inhibits COX1 more than COX2. COX1 is chiefly expressed on platelets and is responsible for the synthesis of prostaglandin H2, which later becomes thromboxane A2. Without thromboxane A2, platelets cannot aggregate and thrombus cannot form. Using aspirin is definitely contraindicated in patients with allergy to non-steroidal anti-inflammatory drugs. Its should also be used with caution in patients with renal impairment or gastrointestinal bleeding.[61]

Aspirin is mildly effective for the prevention of VTE. Meta analysis showed that aspirin was effective in reducing the rate of DVT to 30.6% from 48.5%.[13,41] Aspirin is inferior to warfarin or LMWH in terms of preventing symptomatic PE or proximal DVT.[13,43]

Earlier editions of the ACCP guideline recommended against the use of aspirin as the sole prophylactic agent after total joint replacement.[35] The first edition of AAOS guideline recommended aspirin as one of the prophylactic agents,[34] because the occurrence of symptomatic or fatal PE in the aspirin group was as low as that in the LMWH or warfarin groups.[13,62–64] In addition, aspirin has the lowest risk of bleeding complication among all the pharmacological agents.[13] This is important because bleeding and formation of haematoma are associated with postoperative infection, and an infected joint is considered the most disastrous complication. Aspirin can offer effective prophylaxis when combined with mechanical prophylaxis.[65–70] Aspirin is one of the pharmacological agents in the latest edition of the ACCP guideline[36] and in the second edition of the AAOS guideline.[71]

Aspirin is an effective antithrombotic agent at doses of 50 to 1500 mg daily.[72] The lowest effective daily dose for various vascular disorders such as ischaemic stroke (50 mg daily) or angina (75 mg daily) was well established, but this was not the case in VTE. The venous system has slower flow than the arterial system, and thus a higher dose of aspirin (around 325 mg daily) is needed to prevent VTE.[65–70]

If a more potent anticoagulant is used instead of aspirin, prevention of DVT is more effective but at higher risk of bleeding complications. If aspirin is used alone, symptomatic or fatal PE remains rare and bleeding complication is less likely, but asymptomatic DVT may progress to post-thrombotic syndrome. Thus, aspirin should be used as part of multi-modality treatment.

Warfarin

Warfarin is a vitamin K antagonist. Vitamin K is an essential substrate of liver enzymes responsible for the final synthesis of clotting factors II, VII, IX, and X. Warfarin inhibits the maturation of these factors in the coagulation cascade.[73] Excessive intake of dietary vitamin K, which is mainly contained as phylloquinone in green vegetables reduces the anticoagulant effect of warfarin.[73] Warfarin should be used cautiously in patients taking aspirin or other non-steroidal anti-inflammatory drugs, because of the increased risk of gastrointestinal bleeding. Warfarin also interacts with several commonly used medications, including antibiotics, proton pump inhibitors, and cholecystaramine.[73] The anticoagulant effect can either be counteracted or potentiated, because of alterations in intestinal absorption or metabolic clearance.

Warfarin has been used in total joint replacement patients for more than 40 years.[74,75] It is more effective than aspirin but less effective than LMWH in reducing rates of proximal DVT and symptomatic PE.[13,43] Warfarin is relatively safe in terms of bleeding complications. Both the ACCP and AAOS guidelines recommended warfarin for VTE prophylaxis.

Frequent monitoring of the INR is needed. It takes a few days to establish an adequate INR. Patients started on warfarin should be covered with a fast-acting anticoagulant (such as LMWH) for a few days after the operation until the therapeutic INR is attained. The optimal INR range should be 2 to 3 according to the ACCP,[35,36] and 1.5 to 2 according to the AAOS.[34] The discrepancy arises because the ACCP was based on studies using warfarin as a monotherapy,[76–78] whereas the AAOS recommended a multimodal regimen. When mechanical prophylaxis (such as pneumatic compression and early mobilisation) is used, an INR of 1.5 to 2 is effective.[79,80] Higher INR values are associated with higher rates of postoperative bleeding complications and infection.[81–83]

Low-molecular-weight heparin

LMWHs are fragments of heparin produced by chemical or enzymatic depolymerisation. They have a lower affinity than standard heparin for von Willebrand Factor and thus produce less bleeding.[84] LMWHs have longer plasma half life and more predictable anticoagulant response than standard heparin, enabling less frequent injection and monitoring. LMWHs work by binding to antithrombin III through a unique pentasaccharide sequence. This binding leads to a conformational change in antithrombin III and markedly accelerates its ability to inactivate thrombin and factor X.[84]

LMWH has the highest efficacy in terms of preventing VTE.[13,14,43] The ACCP recommends the use of LMWH in preference to other agents.[36] However, LMWH is also associated with complications related to wound drainage, haematomas, thrombocytopenia, and injection.[13,85–88] Compared with warfarin, LMWH further reduces the DVT rate to 29% (from 45%) in TKR patients and to 18% (from 23%) in THR patients; the rate of fatal PE is reduced to 0.04% (from 0.16%).[43] However, the rate of clinically significant bleeding increased from 1.67% to 2.22%.[13] This is a concern because wound haematomas are associated with postoperative infection.[82,83]

A high dose (30 mg every 12 hours) of LMWH (enoxaparin) results in frequent bleeding episodes.[85–87] The dose-response effect is well-recognised; the complication rate can be reduced if a lower dosage is used. Together with mechanical prophylaxis, the dosage of LMWH can be reduced while retaining the same efficacy.[89–91]

Dabigatran

Thrombin is an enzyme in the coagulation cascade responsible for converting fibrinogen to fibrin and stimulating platelet aggregation. Dabigatran is an oral thrombin inhibitor. A drug from the same family named ximelagatran was superior to warfarin, but was withdrawn from market because of hepatotoxicity.[92] Dabigatran 150 or 220 mg daily is as effective as LMWH (enoxaparin) 40 mg daily when given for at least 6 days to TKR patients and at least 28 days to THR patients.[93–95] Higher dosage is associated with more bleeding complications.[96] Thus the optimal regimen of dabigatran should be 150 to 220 mg daily. In Asian patients, it is 110 to 220 mg daily.[97]

Gastrointestinal absorption of dabigatran is fast, but can be reduced if co-administered with a proton pump inhibitor. Maximal plasma concentrations of dabigatran can be reached within 6 hours of administration.[98] Routine coagulation tests (prothrombin time, activated partial thromboplastin time, and INR) are altered in patients receiving dabigatran, but the results are highly variable and poorly reflect the circulating plasma concentration.[99] Regular monitoring of coagulation is therefore not recommended.

Dabigatran has a satisfactory safety profile and does not cause any organ toxicity. It is not metabolised by the cytochrome P450 enzyme system,[100] and has low potential for drug interaction. Over 80% of drug elimination was through the kidneys; elderly patients or those with impaired renal function should receive a smaller dose (≤150 mg daily).[101]

Owing to the fast onset of action of dabigatran and its long half life (12 to 13 hours in elderly patients), the timing of removal of epidural catheters on day 2 becomes challenging.

Rivaroxaban

Factor X is an important enzyme in the coagulation cascade. Activated Factor X (Xa) is responsible for converting factor II to thrombin. Rivaroxaban is an oral Factor Xa inhibitor. It has an inhibitory effect on thrombin and tissue factor.[102] Similar to dabigatran, it can be given postoperatively and routine monitoring is not necessary.[99] In the RECORD programme, rivaroxaban (10 mg daily) was compared to enoxaparin (40 mg daily).[32] When given for at least 11 days in TKR patients and 30 days in THR patients, rivaroxaban was more effective than enoxaparin in reducing the risk of symptomatic VTE and all cause

mortality. Nonetheless, the rate of major bleeding was not significantly different. Rivaroxaban is at least as effective as enoxaparin in VTE prophylaxis in THR and TKR patients without increasing the risk of bleeding.[103]

When compared with tinzaparin (another LMWH), rivaroxaban resulted in more wound problems including clinical signs of wound infection or haematoma (1.8 vs 3.9%), but infection rates were similar.[104] Further clinical trials are needed to evaluate the safety and efficacy of rivaroxaban. The timing to remove the epidural catheter in patients on rivaroxaban is also not yet settled.

Timing of prophylaxis

The mean time for VTE to occur was 21.5 days after THR and 9.7 days after TKR.[59] DVT and PE occurred at a median of 21 and 34 days respectively after THR, and at a median of 20 and 12 days respectively after TKR.[105] 10 days of thromboprophylaxis after TKR and up to 35 days for THR patients are recommended.[106] The ACCP recommends extending thromboprophylaxis for up to 35 days for all joint replacement patients.[36] The AAOS does not state the duration of prophylaxis and suggests surgeons discussing this with their patients.[37]

As the risk of VTE extends beyond the usual length of hospitalisation, oral prophylaxis should be provided after discharge. LMWH requires subcutaneous injection, whereas aspirin, warfarin, dabigatran, and rivaroxaban can be taken orally once daily, and for the latter 2 routine monitoring is not needed.

Multimodal prophylaxis

Combining mechanical and pharmacological prophylaxis enables reduction of the dosage of anticoagulants and thus the risk of bleeding, and achieving the same or even better thromboprophylaxis than monotherapy.[43,107,108] There are numerous multimodal prophylaxis regimens (differing in combination, dosage, and duration) involving pre-, intra-, and post-operative measures. Preoperative measures include discontinuation of procoagulant medication and autologous blood donation. Intra-operative measures include administration of hypotensive epidural anaesthesia, intravenous heparin, aspiration of intramedullary contents, elastic stocking, and pneumatic compression of the non-operated limb. Postoperative measures include early mobilisation and pharmacological prophylaxis (oral warfarin or aspirin for 4 to 6 weeks). In a study using multimodal prophylaxes, the incidence of DVT was only 2.8% and of non-fatal PE was 0.6%. There was no instance of fatal PE. The rate of bleeding complication was also low, and no patient underwent surgical drainage of any wound haematoma.[109]

In a study combining the use of epidural anaesthesia, intra- and post-operative exercises, elastic stocking or intermittent compression, and aspirin, the rate of clinical DVT was only 0.64% and that of non-fatal PE was 0.18%, whereas wound haematoma developed in 0.2% of patients.[110] In another study combining the use of low-dose warfarin (target INR, 1.5–2), pneumatic compression during the in-patient period, and elastic compression stocking after discharge, the rate of clinical DVT was only 0.2% and that of non-fatal PE was 0.1%, whereas wound haematoma developed in 0.4% of patients.[80]

Classifying patients into low or high risk of developing VTE is advocated.[90] Low-risk patients received aspirin and intermittent calf compression, whereas high-risk patients received LMWH or warfarin and intermittent calf compression. All patients were allowed mobilisation within 24 hours of surgery. There was no fatal PE. The overall rate of clinical DVT was only 0.4% and of PE was 0.25%. Wound haematoma occurred in only 0.4% of patients. The 2 groups were not significantly different. The use of less potent pharmacological prophylaxis agent for low-risk patients and the use of more potent agent for high-risk patients was effective.[90]

The addition of intermittent mechanical leg compression augments the efficacy of anticoagulants in preventing DVT.[111] The ACCP guideline recommends using dual prophylaxis with an antithrombotic agent and an intermittent pneumatic compression device during the hospital stay.[36] The AAOS guideline also adopts a multimodal approach which incorporates pre-, intra-, and post-operative measures.[37] Preoperatively, the risk of VTE (history of thromboembolism) and bleeding (known bleeding disorder or active liver disease) should be determined. Intra-operatively, in consultation with the anaesthesiologist, regional anaesthesia is preferred. Postoperatively, a combination of mechanical prophylaxis, early mobilisation, and pharmacological prophylaxis is recommended.

CONCLUSION

Appropriate prophylaxis of VTE aims to balance risks and benefits. Asian populations are not free from VTE, and prophylaxis should be given. In patients with no increased risk of bleeding, a multimodal

prophylaxis regimen combining both mechanical and pharmacological agents offers the best outcome while minimising complications. Aspirin (325 mg daily), warfarin (targeting INR of 1.5 to 2), LMWH (enoxaparin 20 to 40 mg daily), dabigatran (110 to 220 mg daily) and rivaroxaban (10 mg daily) are all appropriate pharmacological agents. The duration of prophylaxis should be 35 days. Oral anticoagulants are preferred after discharge.

DISCLOSURE

No conflicts of interest were declared by the authors.

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