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REVIEW

Mechanical Prosthetic Valves and Pregnancy

A therapeutic dilemma of anticoagulation

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صمامات القلب الصناعية والحمل

المعضلة العلاجية لمنع تخثر الدم

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ABSTRACT: Choosing the best anticoagulant therapy for a pregnant patient with a mechanical prosthetic valve is controversial and the published international guidelines contain no clear-cut consensus on the best approach. This is due to the fact that there is presently no anticoagulant which can reliably decrease thromboembolic events while avoiding damage to the fetus. Current treatments include either continuing oral warfarin or substituting warfarin for subcutaneous unfractionated heparin or low-molecular-weight heparin (LMWH) in the first trimester (6–12 weeks) or at any point throughout the pregnancy. However, LMWH, while widely-prescribed, requires close monitoring of the blood anti-factor Xa levels. Unfortunately, facilities for such monitoring are not universally available, such as within hospitals in developing countries. This review evaluates the leading international guidelines concerning anticoagulant therapy in pregnant patients with mechanical prosthetic valves as well as proposing a simplified guideline which may be more relevant to hospitals in this region.

Keywords: Heart Valve Prosthesis; Pregnancy; Warfarin; Low-Molecular-Weight Heparin; Thrombosis.

الملخص: لا يزال ەختيار العلاج الأمثل لمنع تخثر الدم على الصمامات الصناعية أثناء الحمل محل نقاش كما أن الإرشادات العلاجية لا تحوي توجيهات واضحة بالنسبة للعلاج الأمثل. والحقيقة أن السبب الرئيس لذلك هو عدم توفر العلاج الذي يمنع تخثر الدم وفي ذات الوقت لا يضر بالجنين. في الوقت الحالي هناك طريقان للعلاج: الأول يتمثل في استمرار تعاطي دواء الوارفارين والآخر استبدال الوارفارين بحيث يتعاطى المريضا لهيبارين غير المجزأ المعطى تحت الجلد أو الهيبارين ذا الوزن الجزيئي المنخفض من 6–12 أسبوع من الحمل أو خلال أي فترة أثناء الحمل.ورغم أن أنواع الهيبارين ذات الوزن الجزيئي المنخفض تستعمل وبكثرة في هذه الحالات إلا أن متابعة العلاج تحتاج إلى فحص مستويات مضاد العامل (Xa) في الدم، وللأسف فإن هذا الفحص غير متوفر في معظم مستشفيات البلاد النامية. إن الغرض من هذا البحث يتمثل في مراجعة الإرشادات والتوجيهات الطبية العالمية التي نشرت بخصوص علاج تخثر الدم في النساء الحوامل وكذلك محاولة تقديم طريقة مبسطة للعلاج الأمثل لمثل هذه الحالات في هذه المنطقة.

مفتاح الكلمات: صمامات القلب الصناعية؛ الحمل؛ الوارفارين؛ الهيبارين ذا الوزن الجزيئي المنخفض؛ تخثر الدم.

Currently, the optimal anticoagulant therapy to use during pregnancy in patients with mechanical prosthetic valves (MPVs) remains controversial, with the published international guidelines lacking a clear-cut consensus on the issue.[1–4] This is due to the fact that presently there is no anticoagulant available which results in both an excellent maternal outcome, defined by fewer thromboembolic events (TEs), and minimal fetal damage, which is defined by the prevention of fetal loss or embryopathy. The case study that follows focuses on a pregnant patient with prosthetic valve thrombosis who was administered a fixed dose of low-molecular-weight heparin (LMWH) throughout her first pregnancy. The leading international guidelines are then evaluated and a simplified approach to managing this type of patient is proposed.

Case Study

A 28-year-old Omani pregnant woman was admitted to a regional hospital in Oman in August 2009 for monitoring. She had received a St. Jude Medical™ standard bileaflet MPV (St. Jude Medical, Inc., Saint Paul, Minnesota, USA) for mitral regurgitation in the UK 15 years previously. The patient had been on regular warfarin (6 mg per day) since receiving the implant with good international normalised ratio (INR) control. When her pregnancy had become apparent in January 2009, the warfarin was stopped and she was begun on LMWH instead. She was prescribed dalteparin which was administered subcutaneously once daily at a dosage of 10,000 IU. She continued taking LMWH throughout her pregnancy without being monitored for her anti-factor Xa levels as such monitoring was not available at the regional hospital.

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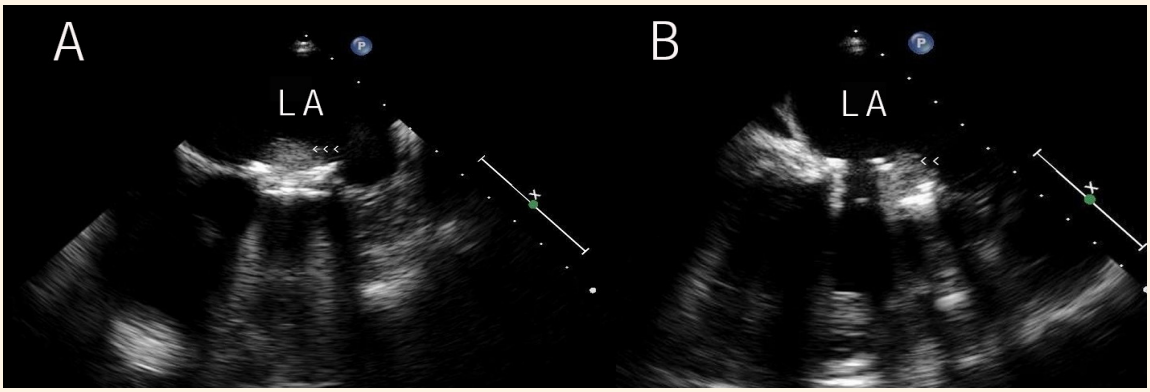

Figure 1 A & B: Transoesophageal echocardiograms showing **(A)** a large, soft clot over the mechanical prosthetic bileaflet mitral valve on the atrial side (arrowheads) and **(B)** a thrombus with the immobile leaflet of a mechanical prosthetic bileaflet mitral valve in a closed position (arrowheads). The other leaflet can be seen to be opening well.
LA = left atrium.

At 36 weeks, the patient underwent an emergency Caesarean section due to fetal distress, with a resultant live birth. Post-operatively, she developed acute pulmonary oedema which was managed with diuretics. The patient was then moved to the Royal Hospital, a tertiary hospital in Muscat, Oman, for further management. Her INR was 1.0 and her activated partial thromboplastin time (aPTT) was 30.1 seconds (range: 27.2–39.1 seconds).

A transthoracic echocardiogram of the MPV showed a peak pressure gradient of 43 mmHg, a mean gradient of 25 mmHg (which had risen from a previously reported gradient of 16 mmHg at her regional hospital) and a calculated mitral valve area of 0.9 cm^2. There was a loss of movement in one of the leaflets of the MPV. There was mild tricuspid regurgitation with a pulmonary artery systolic pressure of 85 mmHg and a left ventricular ejection fraction of 60%. Transoesophageal echocardiography confirmed the presence of one immobile leaflet and detected a large soft immobile thrombus (1 cm^2) towards the atrial side [Figures 1A & B]. In view of the patient's recent surgery, thrombolysis was contraindicated. After a week-long continuous infusion of unfractionated heparin (UFH) with aPTT monitoring, the mean gradient on a repeat transthoracic echocardiogram was 16 mmHg. There were no embolic complications or bleeding. However, fluoroscopy showed that one of the leaflets was stuck in the closed position [Figures 2A & B]. The patient underwent a successful redo mitral valve replacement surgery using a size 27 St. Jude Medical™ MPV (St. Jude Medical, Inc.). At a one-year follow-up, the patient was doing well and had a normally functioning MPV.

International Guidelines

Current management strategies for pregnant women

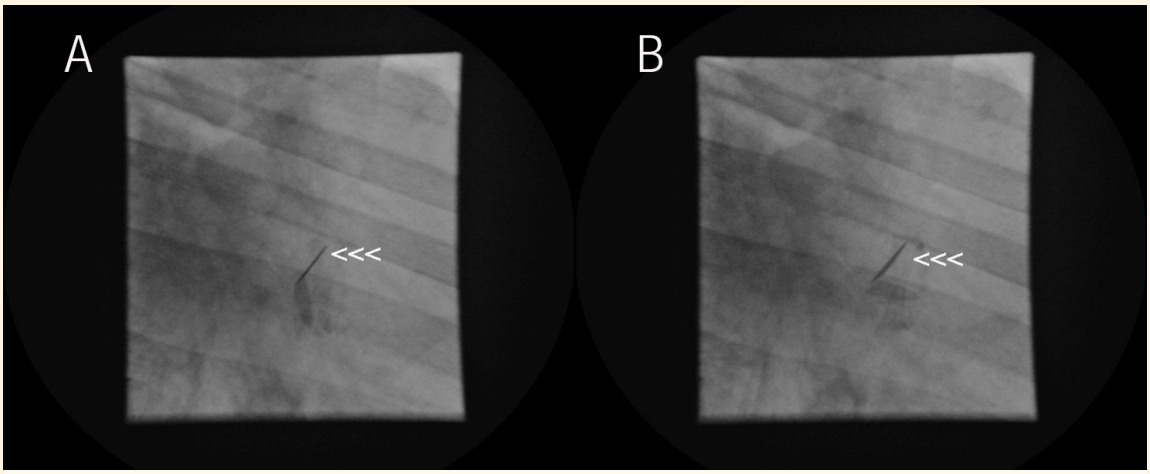

Figure 2 A & B: Fluoroscopy showing **(A)** the immobile leaflet of the mechanical prosthetic bileaflet mitral valve stuck in the closed position, while **(B)** the opposite leaflet opens well.

(up until 36–38 gestational weeks) with MPVs are varied. They include continuous oral warfarin; changing from warfarin to subcutaneous UFH or LMWH in the first trimester and then back to warfarin; continuous subcutaneous UFH, or continuous LMWH throughout the duration of the pregnancy.[1–4] In the absence of controlled clinical trials, most, if not all, of these recommendations are based on limited observational data.

AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION

In their 2008 and 2014 guidelines for the selection of an anticoagulation regimen in pregnant patients with MPVs, the American College of Cardiology (ACC) and American Heart Association (AHA) suggest a detailed discussion with the patient regarding all of their anticoagulation therapeutic options during pregnancy.[1,2] Specifically, warfarin is strongly recommended in pregnant patients with a MPV to achieve a therapeutic INR in the second and third trimesters. However, recommendations regarding the subcutaneous use of LMWH and UFH throughout pregnancy, as well as the subcutaneous use of UFH in the first trimester, have been removed completely from these guidelines.

According to the 2014 ACC/AHA guidelines, the main risk period for complications is within the first trimester.[1,2] The continuation of warfarin during the first trimester is permissible if the dose of warfarin does not exceed 5 mg per day. For those who require stronger doses of warfarin in the first trimester or among those whose preferred treatment option is LMWH, the LMWH should be administered twice daily and the dose should be adjusted to attain peak anti-factor Xa levels of 0.8–1.2 U/mL approximately 4–6 hours after the injection. Alternatively, to achieve a therapeutic anticoagulation, dose-adjusted continuous intravenous (IV) UFH (with an aPTT at least twice that of the control) during the first trimester is permissible if the dose of warfarin is greater than 5 mg per day. In addition, the guidelines recommend adding low-dose aspirin (75–100 mg per day) in the second and third trimesters. If warfarin is the preferred method of treatment throughout the pregnancy, the dose should be adjusted to attain a target INR of 3.0 (range: 2.5–3.5).[1] However, the use of IV UFH in the first trimester is difficult from a practical standpoint, as a three-month hospital admission is required.

EUROPEAN SOCIETY OF CARDIOLOGY

Despite being released three years earlier than the ACC/AHA guidelines, the 2011 European Society of Cardiology (ESC) guidelines for managing patients with valvular heart disease is very similar.[3] These guidelines recommend that patients requiring less than 5 mg of warfarin per day should continue warfarin until 36 weeks of gestation (with an embryopathy risk of <3%), while those requiring more than 5 mg should switch to dose-adjusted IV UFH or LMWH between 6–12 gestational weeks.[3] In addition, they specifically recommend that pregnant patients using LMWH should have their anti-factor Xa levels monitored on a weekly basis; peak anti-factor Xa levels should not exceed 0.8–1.2 U/mL approximately 4–6 hours after the dose was administered.[3]

AMERICAN COLLEGE OF CHEST PHYSICIANS

The American College of Chest Physicians (ACCP) 2012 guidelines recommend the continuation of warfarin throughout pregnancy in high-risk patients, including patients with an older generation prosthesis, a mitral prosthesis or a history of TE, atrial fibrillation or left ventricular dysfunction.[4] In low-risk patients, the dosage should include subcutaneous UFH adjusted to attain mid-interval aPTTs of at least twice that of the control or anti-factor Xa levels of 0.35–0.70 U/mL.[4] Alternatively, LMWH may be given after 6–12 gestational weeks or throughout the entire pregnancy. The starting dose should be 100 U/kg of dalterparin and 1 mg/kg of enoxaparin. The patient should receive 12 hourly doses subcutaneously to achieve the correct peak anti-factor Xa levels four hours post-injection and these levels should be checked every week. With LMWH, the guidelines suggest that physicians should consider additionally prescribing low-dose aspirin in high-risk women with MPVs.[4] In women with a bileaflet aortic valve prosthesis who have been prescribed warfarin, the INR target can be 2–3 instead of 2.5–3.5.[4]

All of the above guidelines agree that LMWH should be given twice daily and that it is harmful to administer LMWH without regularly monitoring the patient's anti-factor Xa levels.[1–4]

GUIDELINES FOR PATIENTS AFTER 36 GESTATIONAL WEEKS

With regard to patient management after 36 gestational weeks, there is a vast disparity among the ACC/AHA, ESC and ACP guidelines. The ACC/AHA guidelines suggest stopping warfarin at 36 weeks and starting continuous IV UFH with aPTT monitoring, which should be continued until approximately 2–3 weeks before the planned delivery.[2] Additionally, they recommend that UFH be discontinued 4–6 hours

before the planned delivery and restarted 4–6 hours after delivery. In the absence of significant bleeding, oral warfarin should then be initiated 24 hours after the birth.[2]

ESC guidelines suggest stopping warfarin at 36 weeks and starting dose-adjusted IV UFH or LMWH.[3] This treatment should continue until 36 hours before delivery, when LMWH should be replaced by IV UFH.[3]

ACCP guidelines suggest continuing warfarin until the patient is close to term (although the word *term* is not specified, it is generally accepted to signify 48 hours before delivery). At this point, warfarin should be replaced by IV UFH or LMWH.[4] If labour begins spontaneously while the patient is still undergoing oral anticoagulation therapy, a Caesarean section is indicated due to the baby's increased risk of intracranial bleeding in the case of a vaginal delivery or due to other obstetric-related causes.

Clinical Trials

In a retrospective systematic review, Chan *et al.* reported that the use of warfarin in women between 6–12 gestational weeks resulted in fewer maternal TE episodes (3.9%) at the cost of increased fetal loss and fetal anomalies (12% and 6.4%, respectively).[5] As warfarin crosses the placenta, it is associated with a high incidence of fetal loss and an increased risk of embryopathy which mainly presents as skeletal abnormalities (nasal hypoplasia and stippling of the vertebrae or bony epiphyses of the extremities).[4–7] The risk of warfarin-associated embryopathy is markedly reduced if warfarin is used after the first trimester, even though there are some reports of central nervous system structural anomalies such as microcephaly, hydrocephalus and eye abnormalities, including microphthalmia and optic atrophy.[4–7] The overall rate of major bleeding in pregnant patients with MPVs is reported to be 2.5%; this rate does not change according to the type of anticoagulation therapy used.[5] However, the risk of embryopathy is lower among patients whose warfarin doses do not exceed 5 mg per day.[6]

In a prospective cohort study of 250 pregnant patients with MPVs, 150 patients continued warfarin throughout their pregnancies; there were no incidences of valve thrombosis or coumarin-induced fetal malformations among this group in comparison to those receiving UFH.[7] In another study of 196 pregnancies in 110 women, 142 women continued warfarin during their pregnancy, with an increased incidence of fetal loss (46% *versus* 14% for those in the UFH group).[8] In contrast, the UFH group demonstrated a higher rate of valve thrombosis (13% *versus* 2.1%) when used during the first trimester.[8] A study by Chan *et al.* found that UFH (dose-adjusted so that the aPTT is twice that of the control six hours after the injection) appears to demonstrate good fetal outcomes, with the treatment not crossing the placenta.[5] However, this result came at the cost of an increased rate of TE complications, with TEs occurring in 33% of cases when UFH was used throughout the pregnancy and 9% of cases when it was used for the first trimester only.[5]

Therapeutic doses of LMWH, which does not cross the placenta, are increasingly being used as an alternative option either in the first trimester or throughout the entire pregnancy, both with and without anti-factor Xa monitoring, as seen in a single-centre study by Quinn *et al.*[9] However, in a study of 81 patients, Oran *et al.* found an overall incidence of prosthetic valve thrombosis in 8.6% and an overall TE rate of 12.3%.[10] Of the 10 patients who suffered a TE, nine had received a fixed dose of LMWH; in two of these, a low fixed dose was used without anti-factor Xa monitoring.[10] This was the same therapy option used for the 28-year-old woman in the aforementioned case study. In the same study, only one patient was reported to have had a TE among 51 pregnancies where anti-factor Xa levels were monitored.[10] Thus, a careful review of previously reported cases of prosthetic valve thrombosis while on LMWH indicates that most of these cases were associated with an inadequate dosage, a lack of monitoring or sub-therapeutic anti-factor Xa levels.

Another study observed TE complications in seven out of 47 pregnancies, of which five were associated with the use of enoxaparin therapy.[11] The predominant causative factors for these complications, which were identified in all cases, were poor compliance with the therapy requirements and sub-therapeutic peak anti-factor Xa levels.[11] There is evidence that, as LMWH undergoes renal clearance, there is an increase in the glomerular filtration rate and plasma volume expansion during pregnancy, which leads to a higher clearance of LMWH with lower plasma concentrations.[12,13] In addition, there is increased activity of the placental heparinase, which means that an increased dose of LMWH is required in order to achieve therapeutic anti-factor Xa levels.[12,13] Quinn *et al.* found that, in order to maintain adequate anti-factor Xa levels during pregnancy, the mean LMWH dose had to be increased over the initial dose by 54%.[9]

Fixed-dose regimens or the administration of LMWH by weight alone have therefore proven to be inadequate; as a result, guidelines advise peak anti-factor Xa level monitoring. However, even peak

anti-factor Xa levels may not reflect the adequacy of anticoagulation for periods between 12–24 hours.[14–17] Fan *et al.* studied the relationship between 177 paired peak and trough anti-factor Xa levels during pregnancy.[18] They found that that pregnant patients who received adjusted-dose enoxaparin (given every 12 hours with peak levels of 0.7–1.2 IU/mL) were associated with sub-therapeutic trough levels, with a pre-dose level of <0.6 IU/mL in >50% of the cases.[18] Thus, the previously mentioned guidelines ignore manufacturer recommendations to monitor both peak and trough levels.[16,19]

A Large Meta-Analysis

In a recent large meta-analysis of studies evaluating anticoagulation in pregnant patients with mechanical heart valves, Malik *et al.* identified eight out of 281 articles that gave the best evidence towards answering the research question, *Is there a suitable method of anticoagulation in pregnant patients with mechanical prosthetic heart valves?*[20] Malik *et al.* observed that while it is traditionally believed that oral anti-coagulation in pregnancy can lead to warfarin embryopathy, only one study reported a higher incidence of fetal anomalies with warfarin use (6.4%), while two others reported no instances of embryopathy at all.[20] Fetal mortality with oral anticoagulation therapies ranged from 1.52–76% and all of the studies demonstrated excellent maternal outcomes with warfarin use, with TE events ranging from 0–10% in comparison to 4–48% when heparin was used. Thus, it was concluded that warfarin is a more durable anticoagulant with improved maternal outcomes, despite the increased fetal risk.[20]

This finding was confirmed in a study of 32 pregnancies by Basude *et al.*[21] While the rate of fetal loss in the warfarin group was high, all women in the LMWH group, and half of those who received LMWH in the first trimester and then subsequently received warfarin, had serious adverse maternal events, including valve thrombosis, maternal death and postpartum haemorrhage.[21] In an Omani study, Al-Lawati *et al.* reported on 63 pregnancies in 21 women with mechanical heart valves.[22] The women received either warfarin throughout the entire duration of their pregnancy or subcutaneous heparin in their first trimester and oral warfarin for the rest of their pregnancy.[22] No cases of warfarin-associated embryopathy were observed and there were no instances of maternal death. Life-threatening valve thrombosis occurred in two patients, both of whom were in the heparin group and needed emergency prosthetic valve replacements. The warfarin group had a higher incidence of spontaneous abortion than the heparin group, although this was not statistically significant.[22] This study concluded that the role of warfarin in warfarin-associated embryopathy had been overstated.[22]

Is There a Role for Prevention?

Of late, the surgical community has advocated against giving mechanical prostheses to women of a childbearing age.[23] In addition, great progress has been made in valve-sparing surgeries.[24] If a prosthesis is really necessary, the ESC guidelines for valvular diseases outline the possibility of giving bioprostheses to younger patients who choose this option and have been informed of the risks (class I).[25] Bioprostheses should also be considered in young women contemplating pregnancy (class IIa), with the understanding that they may have to undergo another operation in the future or a transcatheter valve-in-valve implantation procedure.[25] Moreover, the Ross procedure for aortic valve replacement surgery could be used in carefully selected patients.[24]

A Simplified Guideline

Based on the above review of the three major guidelines and large meta-analysis, the authors of this review recommend a simple approach with regards to anticoagulation therapy during pregnancy in patients with an MPV. This recommendation is easy for both patients and physicians to follow and takes into account the fact that anti-factor Xa level monitoring may not be available in all centres.

It is recommended that pregnant women with an MPV continue warfarin until 37 gestational weeks or one week prior to delivery. This recommendation is appropriate for patients who require warfarin at doses of either above or below 5 mg per day. However, it is important that practitioners discuss the significant maternal benefit and the fetal risk of this therapy option with their patient and advise them that fetal loss is more common than embryopathy. The patients' INR should be measured on a monthly basis in order to maintain a target INR of 3.0 (range: 2.5–3.5).

After 37 weeks' gestation, or one week prior to a planned delivery, warfarin should be stopped and INR levels should be monitored on a daily outpatient basis. Once the patient's INR decreases to <2.5, a therapeutic dose of weight-based LMWH should be administered subcutaneously twice daily to attain peak anti-

factor Xa levels of 0.8–1.2 U/mL at 4–6 hours post-administration.

At 36 hours before delivery, the patient should be admitted to the hospital. LMWH should be continued, with the last dose given 12 hours prior to the delivery and restarted six hours after the delivery. Oral warfarin should be given after 24 hours, in the absence of any significant bleeding.

In centres where anti-factor Xa level monitoring is not available, the patient should be admitted to the hospital at 37 gestational weeks or one week prior to a planned delivery. At this point, warfarin should be stopped and the INR should be measured daily. Once INR levels fall to <2.5, IV UFH therapy should commence, with six-hourly aPTT monitoring in order to keep the aPTT twice that of the control. The UFH should be discontinued 4–6 hours before delivery and restarted 4–6 hours after delivery. Oral warfarin should be administered after 24 hours, in the absence of any significant bleeding.

For patients who were receiving a very high pre-pregnancy dose of warfarin (>10 mg), practitioners should consider LMWH treatment in the first trimester with anti-factor Xa level monitoring. If required, treating physicians should seek facilities to monitor anti-factor Xa levels in such special cases.

In all cases, the management and treatment of patients should follow a 'team' approach, with input from cardiologists, haematologists and obstetricians. Additionally, these recommendations have been suggested for the management of patients in developing countries and regional hospitals without regular access to anti-factor Xa level monitoring and in whom alternative treatments are difficult to apply.

Conclusion

In summary, the best anticoagulant treatment for pregnant women with an MPV is dependent on the availability of anti-factor Xa level monitoring facilities, the patient's pre-pregnancy dose of warfarin and the type of anticoagulant preferred by the patient in relation to the maternal and fetal risks. Regardless of the facilities available or previous treatment received, a pregnant woman who requires anticoagulants due to the presence of an MPV should be closely monitored by a team of healthcare practitioners, including cardiology, haematology and obstetric specialists. The simplified guidelines proposed in this review article are primarily for patients in hospitals that are not able to measure anti-factor Xa levels regularly or those who are unable to consider alternative treatments.

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