Valvular Heart Disease and Pregnancy
Part II: Prosthetic Valves
Uri Elkayam, MD, FACC, Fahed Bitar, MD
Los Angeles, California

A large number of prosthetic heart valves (PHV) are being implanted in patients with both congenital and acquired valvular disease. Many of the recipients of such valves are women of childbearing age who desire to have children. The main issues involved with pregnancy in a patient with PHV include the selection of PHV in women during their childbearing age, risks to both the mother and the fetus associated with pregnancy and the management of the patients with PHV during gestation. [J Am Coll Cardiol 2005;46:403–10] © 2005 by the American College of Cardiology Foundation

The first successful replacement of heart valve in human was reported in 1960 (1). Since then, prosthetic heart valves (PHV) have been developed into remarkably useful devices. A large number of PHVs are being implanted every year around the world, and many of them in women of childbearing age who desire to have children (2). There are three main issues related to PHV and pregnancy that will be discussed in this review: 1) selection of PHV in women of childbearing age who desire to become pregnant; 2) maternal and fetal risks associated with pregnancy in patients with PHV; and 3) the management of patients with PHV during pregnancy.

**SELECTION OF PHV IN WOMEN OF CHILDBEARING AGE**

A selection of PHV in women during their childbearing age is still problematic, because an ideal valve is not available. The two major groups of artificial heart valves (i.e., the mechanical prostheses and the bioprostheses) both provide advantages and limitations. Important areas of difference are durability, incidence of thromboembolism, valve hemodynamics, and effect on fetal outcome. **Tissue valves.** Tissue valves (bioprostheses) can be separated into three categories: heterografts, homografts, and autografts. Most of the information regarding pregnancy in women with bioprosthetic valves has been obtained in women with porcine heterografts. The use of tissue valves during childbearing age reduces the risk of thromboembolism and anticoagulation during pregnancy, but is associated with a high risk of structural valve deterioration (SVD) in young women. Patients between the age of 16 and 39 at the time of surgery, with either Hancock (Hancock Jaffe Laboratories, Irvine, California) or Carpentier-Edwards porcine bioprostheses (Edwards Lifesciences, Irvine, California), demonstrated a high incidence of SVD, which became significant as early as 2 to 3 years after surgery and was as high as 50% at 10 years and 90% at 15 years (3). Similarly, Jamieson et al. (4) reported an increased rate of Carpentier-Edwards porcine bioprosthetic SVD in younger patients (27% freedom from SVD at 10 years for patients <30 years of age compared with 77% and 85% for patients between 30 and 59 years and >60 years, respectively). More recently, North et al. (5) have reported valve loss at 10 years in 82% of 73 women with a mean age of 23 ± 6 years at the time of valve replacement with bioprosthetics of various types (Hancock, Carpentier-Edwards, Medtronic Intact [Medtronic, Minneapolis, Minnesota]). The risk of SVD was seven-fold greater in the mitral than the aortic or tricuspid position. These data indicate that at least one-half of porcine heterografts implanted in young women of childbearing age can be expected to fail within 10 years after surgery, with higher likelihood of failure in patients with mitral bioprosthesis. Because women of childbearing age who receive bioprosthetic valves are likely to need re-operation, the risk associated with a second surgery has to be considered when a PHV is being selected. Early mortality for re-operation in such patient populations has been reported to be 3.8% in one study (6) and 8.7% in another (7).

The hemodynamic profile of the stented porcine heterografts is, in general, inferior to that of low profile mechanical prostheses of comparable size (8). New bioprosthetic valves have been increasingly used in the aortic position and could possibly provide some advantages in young women. The stentless porcine xenografts might provide superior hemodynamic profile compared with stented porcine aortic heterografts, especially in patients with small aortic root (9). The Carpentier-Edwards Pericardial (xenograft) valve seems to have a better long-term durability than the porcine bioprosthesis (10). In spite of the potential advantages of these new bioprosthetic valves, very little information is available regarding their use in young women and in pregnant patients, and duration of follow-up in older populations is also limited.

Homograft (allograft) aortic valves offer some advantages...
that include superior hemodynamics compared with stented porcine valves and low thrombogenicity compared with mechanical valves (11). Because of low rate of infections, they are often used in patients with endocarditis (1). Although there is no proven benefit regarding patient re-operation rate for SVD at 15 years with homograft valves respectively (13–15). Sadler et al. (14) recently reported on 41 homograft from a 30-year-old donor was 82% and 39%, year freedom from SVD in a 30-year-old patient receiving a valve replacement, 81% and 35%. Estimated 10- and 20- freedom from SVD was 62% and 18% and redo valve replacement, 81% and 35%. Estimated 10- and 20- year freedom from SVD in a 30-year-old patient receiving a homograft from a 30-year-old donor was 82% and 39%, respectively. Only limited data, however, are available regarding outcome of pregnancy in women with aortic homografts (13–15). Sadler et al. (14) recently reported on 41 pregnancies in 21 women after homograft valve replacement. Of 32 pregnancies with known outcome, 94% had live births, and there was no preterm birth. Two women developed cardiac failure during pregnancy, without evidence of valve-related complications. Mortality after a second aortic valve homograft replacement was reported to be 3.4% in 144 patients with a mean age of 49 years, and freedom from re-operation was 97% and 82% at 5 and 10 years, respectively (16).

The Ross procedure involves the removal of the patient’s own pulmonary valve and adjacent main pulmonary artery, which are used to replace the diseased aortic valve, usually with the neighboring aorta, and reimplantation of the coronary arteries into the graft as well as the insertion of a human pulmonary or aortic homograft into the pulmonic valve (17). This procedure is not thrombogenic and provides excellent valve hemodynamics (18) and has, therefore, been recommended by some authors as an attractive procedure for aortic valve replacement in young women who wish to become pregnant (1). The operation, however, is technically difficult, and associated mortality was reported between 6.6% and 13% in earlier studies (19) and approximately 2.0% in later studies (20,21). Information about pregnancy in women after the Ross procedure is limited (22,23). The only follow-up longer than 10 years did not include pregnant women and showed, in 131 hospital survivors with a mean age of 32 years, survival of 85% and 60% and freedom from any operation of 76% and 62% at 10 and 20 years, respectively (24). The majority of re-operations were performed for severe valve regurgitation, and mortality associated with re-operation was 20% within one year of surgery. Dore and Somerville (22) reported on 14 pregnancies in eight women who had undergone pulmonary autograft valve replacement. All women were in New York Heart Association functional class I, had normal left ventricular function, and none required anticoagulation during pregnancy. Six had mild aortic regurgitation, three had mild pulmonary regurgitation, and two had mild pulmonary stenosis. There was no maternal death, thromboembolic event, hemorrhagic complications, or SVD during pregnancy.

Does pregnancy accelerate the rate of bioprosthetic SVD? A number of reports have provided a strong indication of pregnancy-related accelerated deterioration of tissue valves. Hanania et al. (25) reported SVD and need for re-operation in 7 of 74 bioprostheses exposed to pregnancy an average of 5.9 years after the initial operation. An even higher incidence was reported by Kadri et al. (26), who described SVD in 4 of 14 patients; by Sbarouni et al. (27), who found SVD in 17 of 49 women, leading to valve replacement during pregnancy in 2 and postpartum in 13; and by Born et al. (28), who reported re-operation during pregnancy or the puerperium in 14% of 20 patients. Lee et al. (29) reported SVD during pregnancy in only 4 out of 95 pregnancies in 57 women with bioprosthetic valves, although a lower 10-year graft survival rate was noted in women with a history of two subsequent pregnancies after their valve replacement (17%), compared with only one subsequent pregnancy (55%). In addition, Badduke et al. (7) studied long-term performance of biological prostheses in 87 women <35 years of age; 17 of these women experienced 37 pregnancies. Structural valve deterioration was reported in 47% of patients with a history of pregnancy, compared with only 14% in the non-pregnant group (p = 0.05). Re-operation, primarily due to SVD, which presented as calcification and obstruction, was performed in 59% of the pregnancy group and 19% of the non-pregnancy group (p = 0.05). More recently, Sadler et al. (14) reported SVD that occurred during pregnancy in 10% of patients with mitral bioprosthetic valves.

Although the previously mentioned reports make a strong case for pregnancy–related accelerated SVD of tissue valves, other reports have failed to support these findings. Avila et al. (30) conducted a 5-year prospective follow-up of 48 patients with bioprosthetic valves who became pregnant and 37 comparable women who did not and found a comparable rate of SVD (27% and 30%, respectively) and re-operation (8% in both groups). Jamieson et al. (6) compared 53 women who experienced pregnancy and 202 women under
the age of 35 years who did not. The rate of SVD and valve-related operation at a mean follow-up of approximately seven years was slightly, but not significantly, higher in the pregnancy group (51% vs. 41%, and 51% vs. 42%, respectively). Similarly, Salazar et al. (31) reported deterioration of bovine pericardial bioprostheses at a rate of 3.5% per patient-year in 48 women who had 58 pregnancies, which was comparable to 3.4% per patient-year found in a comparable control group of 107 patients. The actuarial freedom from dysfunction was 77% at 8 years for the pregnancy group and 73% for the control group. In a Cox proportional hazard regression analysis, pregnancy did not influence SVD.

In summary, deterioration of bioprosthetic heart valves during pregnancy has been reported in several studies, but could not be confirmed by others. Although most available data might support an accelerated SVD of bioprosthetic valves during pregnancy, this could simply reflect the well-established deterioration of tissue valves in young individuals.

**Mechanical prostheses.** Mechanical PHV are classified into three major groups: caged-ball, tilting-disc, and bileaflet valves (1). The most widely employed mechanical valves are currently the bileaflet valves (St. Jude valve). The old-generation Bjork Shiley valve, a tilting-disc prosthesis no longer used in the U.S., and the Starr-Edwards caged-ball valve, the oldest PHV in continuous use, have an historical importance and were extensively used in women of child-bearing age and during pregnancy (5,25,27–29).

Mechanical PHVs, including those in the smaller sizes (8), offer excellent long-term durability (32) and superior hemodynamic profile; however, their thrombogenicity and need for life-long anticoagulation are associated, during pregnancy, with a risk of thromboembolism and maternal bleeding. In addition, available information on fetal outcome suggests an increased risk of fetal loss as well as prematurity, low birth weight, birth defects, and neonatal mortality (14,25,27,28,33) in patients with mechanical PHVs, most probably due to the mandatory use of anticoagulation.

**Summary and recommendation.** The selection of PHV for women of childbearing age remains difficult and needs to be individualized. The bileaflet mechanical valves provide a superb record of durability, excellent hemodynamic profile, and relatively small risk of thromboembolic and bleeding complications with careful anticoagulation. Because durability is a major factor in young patients, these valves seem to be a reasonable choice for women who are compliant and committed to the rigor of continuous and careful anticoagulation. In women who are not interested in anticoagulation or for whom close follow-up is not possible, a tissue valve is preferred. In the aortic position, homografts, pericardial valves, and stentless porcine xenografts have not been extensively used in pregnancy, but seem to offer better hemodynamics and possibly better long-term durability (homograft) than stented porcine heterografts. The pulmonary autograft (Ross procedure) is associated with a very low incidence of thromboembolism and also seems to provide hemodynamic and possibly durability benefit compared with the standard porcine valve, but is associated with higher rate of SVD and need for re-operation compared with the new-generation mechanical prostheses. Because of the complexity of the operation, only experienced surgeons should perform it.

**Preconception evaluation and consultation.** The risk of complications during pregnancy in a patient with PHV depends on type, position, and function of the valve as well as cardiac function, patient symptoms, and functional capacity. Pregnancy evaluation should include a careful history and physical examination as well as an echo-Doppler study to evaluate cardiac and valvular function. Exercise testing, including the determination of maximum oxygen consumption, can provide an objective estimation of functional capacity. The patient and her family should be advised on potential complications that might occur during pregnancy, including: hemodynamic and symptomatic worsening; higher incidence of thromboembolism; deterioration of bioprosthetic valves; and potential harm to the fetus due to cardiac medications, including anticoagulation (increased rate of fetal loss, prematurity, and fetal growth retardation). Because clinical deterioration often occurs during pregnancy, patients with marked impairment of left ventricular and/or valvular function that are moderately or severely symptomatic (class III and IV) should be advised against pregnancy.

**MANAGEMENT OF COMPLICATIONS**

**Heart failure.** Physiological hemodynamic changes during pregnancy might result in cardiac decompensation in patients with PHV, especially those with left ventricular dysfunction and small valve sizes. In addition, increased incidence of arrhythmias during pregnancy (34) might also lead to hemodynamic and symptomatic deterioration. Although most patients who are asymptomatic or only mildly symptomatic before conception tolerate the hemodynamic burden of pregnancy, decreased functional capacity, the development of pulmonary edema, and even death have been reported (14,27,28,35–37). The treatment of heart failure in patients with PHV depends on its cause. Safe drugs include digoxin, diuretics, nitrates, hydralazine, and beta blockers. In contrast, angiotensin-converting enzyme inhibitors and angiotensin receptor antagonist are contraindicated, and amiodarone as well as sodium metropurusside should be avoided (38).

**Valve thrombosis.** Pregnancy is associated with an increased incidence of thromboembolism due to a hypercoagulable state. Available reports have described thromboembolic events in 7% to 23% (average 13%) of patients, one-half of them with valve thrombosis (14,25,27–29,31). Although this complication is more likely in patients with older-generation valves (Bjork-Shiley, Starr-Edwards) in
the mitral position, thrombosis of newer-generation mechanical PHV, including in the aortic position, have been reported (39–45). Recent guidelines for management of PHV thrombosis recommend thrombolysis as a first-line treatment if there are no contraindications (46). Heparin might be used initially for small non-obstructive thrombi, particularly if thrombolysis is contraindicated (47). This therapy has been shown to achieve hemodynamic success, which has been similar across valves, in 85% of the cases. Overall complications, including peripheral embolization and bleeding, were reported in 18% and death in 5.6% (48). Although pregnancy has been perceived as a contraindication to thrombolytic treatment (49), this therapy has been used in pregnant women for various indications (25,27,39,45,50–57). Thrombolysis was effective and safe in most patients; however, failure of therapy, leading to death (45,56), bleeding (45,50,57), and embolic complications (39) has been reported during pregnancy. Because of the high risk of fetal loss during pregnancy (58), surgery should be reserved for patients in whom thrombolysis is contraindicated (50), might be associated with high risk of complications, or has been ineffective.

**Anticoagulation.** The risk associated with pregnancy in women with mechanical PHV is related mainly to the increased incidence of thrombosis due to pregnancy-related hypercoagulability. Effective anticoagulation, therefore, is critical in patients with mechanical PHV, but remains problematic because both oral anticoagulation and heparins have been associated with important fetal and maternal side effects (33).

Decisions on the choice of anticoagulation should be made by both physicians and patients, who need to be fully informed of the potential risks and benefits associated with the various therapeutic options. The American Heart Association/American College of Cardiology Task Force report in 1998 (59) (Table 1) recommended the use of warfarin, especially in high-risk women, through week 35, when unfractionated heparin (UFH) should be substituted, in anticipation of labor. These recommendations also recognized that the risk of warfarin embryopathy was unacceptable to many women and suggested an alternative treatment with heparin, intravenously during the first trimester. More recent recommendations, published in 2004 as part of the seventh American College of Chest Physicians (ACCP) consensus on antithrombotic therapy (60) (Table 2), include one of three regimens: 1) aggressive adjusted-dose of low molecular weight heparin (LMWH) throughout pregnancy; 2) adjusted-dose of UFH, throughout pregnancy; or 3) use of either LMWH or UFH between 6 and 12 weeks and close-to-term only and the use of warfarin at other times; the use of warfarin during the first trimester was not recommended. Our recommended regimen (Table 3) combines the two aforementioned recommendations and, in addition, differentiates between patients at higher and lower risk and emphasizes the importance of monitoring trough level of heparin in addition to peak levels (61).

### Table 1. ACC/AHA Recommendation for Anticoagulation During Pregnancy in Patients With Mechanical Prosthetic Valves

1. The decision whether to use heparin during the first trimester or to continue oral anticoagulation throughout pregnancy should be made after full discussion with the patient and her partner; if she chooses to change to heparin for the first trimester, she should be made aware that heparin is less safe for her, with a higher risk of both thrombosis and bleeding, and that any risk to the mother also jeopardizes the baby.
2. High-risk women (a history of thromboembolism or an older-generation mechanical prosthesis in the mitral position) who choose not to take warfarin during the first trimester should receive continuous unfractionated heparin intravenously in a dose to prolong the mid-interval (6 h after dosing) activated partial thromboplastin time to 2 to 3 × control value. Transition to warfarin can occur thereafter.
3. In patients receiving warfarin, the international normalized ratio should be maintained between 2.0 and 3.0 with the lowest possible dose of warfarin, and low-dose aspirin should be added.
4. Women at low risk (no history of thromboembolism, newer low-profile prosthesis) might be managed with adjusted-dose subcutaneous heparin (17,500 to 20,000 U twice daily to prolong the mid-interval (6 h after dosing) activated partial thromboplastin time to 2 to 3 × control value.
5. Warfarin should be stopped no later than week 36 and heparin substituted in anticipation of labor.
6. If labor begins during treatment with warfarin, a cesarean section should be performed.
7. In the absence of significant bleeding, heparin can be resumed 4–6 h after delivery, and warfarin begun orally.

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ACC = American College of Cardiology; AHA = American Heart Association.

Thromboembolic prophylaxis in high-risk patients (older-generation PHV in the mitral position, atrial fibrillation, history of thromboembolism while receiving anticoagulation) seems to be best achieved with oral anticoagulation for the first 35 weeks (Tables 1 and 3). Because pregnancy is associated with increased risk, a target international normalized ratio of 3.0 (2.5 to 3.5) should be achieved (60). Exposure to warfarin during the first 8 to 12 weeks of gestation, however, is associated with high incidence of fetal loss, mostly due to spontaneous abortion, and of warfarin embryopathy (33). The reported incidence of warfarin embryopathy has varied and has been a subject of debate (62,63). Although recent authoritative text has estimated the incidence of warfarin embryopathy to be as low as 1.6% of live births (1), one recent review indicated an incidence of 6.4% (33), and another review indicated 7.4% (64). Furthermore, these reviews probably represent an underestimation, due to the retrospective nature and lack of pathological assessment of the aborted fetuses in most series (64). This assumption is supported by a prospective study reporting facial defects suggestive of warfarin embryopathy in 29% of viable offspring (65) and two recent retrospective studies reporting skeletal deformity and nasal hypoplasia in 10% of babies exposed to warfarin (14,66). A recent study has suggested that warfarin risk was dose related and occurred mostly in women taking a daily dose >5 mg (67). This finding, however, could not be confirmed by another
Two retrospective surveys conducted in Europe and a prospective study performed in Mexico reported a high incidence of valve thrombosis in patients with old-generation mechanical PHVs treated with subcutaneous UFH (25,27,36). Although the clinical implications of these findings are questionable (72), owing to lack of information related to the level of anticoagulation and its monitoring, these reports might suggest resistance to moderate doses of UFH in high-risk women with old-generation PHV. For this reason, a high heparin dose should be used (7,500 to 20,000 U every 12 h) (72) and adjusted to a mid-interval activated partial thromboplastin time (aPTT) ratio of ≥2.5 × control value. Continuous intravenous heparin might provide a consistent therapeutic level and is preferred over subcutaneous administration (Table 1). At the same time, infection of the central line and even endocarditis are potential complications (73). Because of the relative short duration of effect of subcutaneous UFH, pre-dose aPTT should be measured to determine a possible need for every-eight-h dosing to prevent subtherapeutic levels.

Low molecular weight heparin has been recommended as an alternative to UFH (60). Low molecular weight heparin does not cross the placental barrier (74) and it offers potential advantages (74,75), including fewer bleeding complications, a lower frequency of heparin-induced thrombocytopenia (although incidence of heparin-induced thrombocytopenia seems to be rare in pregnancy [76]), a lower incidence of osteoporosis, superior subcutaneous absorption and bioavailability, a longer half-life, more predictable dose response, and a lower rate of spontaneous abortion in patients with PHV compared with UFH (77). Recent review of 81 pregnancies in 75 women with mechanical PHVs treated with LMWH during pregnancy (77) reported an 8.6% rate of valve thrombosis. Although this seemingly high incidence of thrombotic events could reflect a biased reporting of cases with complications, it raised a concern regarding the safety of the drug and resulted in a warning by a LMWH manufacturer regarding their use in patients with mechanical PHV (78). A careful review of the reported cases, however, indicated that most, if not all of these cases

Table 3. Recommended Approach for Anticoagulation Prophylaxis in Women With PHV During Pregnancy

<table>
<thead>
<tr>
<th>First generation PHV (e.g., Starr-Edwards, Bjork Shiley) in the mitral position, atrial fibrillation, history of TE on anticoagulation</th>
<th>Second generation PHV (e.g., St. Jude Medical, Medtronic-Hall) and any mechanical PHV in the aortic position</th>
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<tr>
<td>Warfarin (INR 2.5–3.5) for 35 weeks, followed by UFH (mid-interval aPTT &gt;2.5) or LMWH (pre-dose anti-Xa ~0.7) + ASA 80–100 mg q.d.</td>
<td>SC UFH (mid-interval aPTT 2.0–3.0) or LMWH (pre-dose anti-Xa ~0.6) for 12 weeks, followed by warfarin (INR 2.5–3.0) for 35 weeks, then SC UFH (mid-interval aPTT 2.0–3.0) or LMWH (pre-dose anti-Xa level ~0.6)</td>
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<tr>
<td>UFH (aPTT 2.5–3.5) or LMWH (pre-dose anti-Xa ~0.7) for 12 weeks, followed by warfarin (INR 2.5–3.5) to 35th week, then UFH (aPTT &gt;2.5) or LMWH (pre-dose anti-Xa ~0.7) + ASA 80–100 mg q.d.</td>
<td>SC UFH (mid-interval aPTT 2.0–3.0) or LMWH (pre-dose anti-Xa ~0.6) throughout pregnancy</td>
</tr>
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Reprinted, with permission, from Elkayam et al. (61).

aPTT = activated partial thromboplastin time; ASA = acetylsalicylic acid; INR = international normalized ratio; PHV = prosthetic heart valve; SC = subcutaneous; TE = thromboembolism; other abbreviations as in Table 2.
were associated with an inadequate dose, lack of monitoring, or subtherapeutic anti-Xa levels (40–43, 61, 63, 77, 79, 80). Among 51 pregnancies whose anti-factor Xa levels were monitored, only one patient was reported to have thromboembolic complication (77). A recent review has concluded that all three anticoagulation options have been under-studied and that LMWH could be the best available option (79). More recently (80), the earlier warning by the LMWH manufacturer has been rephrased to “use of Lovenox for thromboprophylaxis in pregnant women with mechanical PHV has not been adequately studied.” How should anticoagulation with LMWH be monitored? Because of an increased and changing dose requirement in pregnancy, administration of LMWH on the basis of weight alone is inadequate, and measurement of anti-Xa activity is necessary to ensure effective anticoagulation (81). The most recent ACCP recommendations call for the use of LMWH at a dose aiming to achieve peak (4-h post-injection) anti-factor Xa levels of around 1.0 U/ml. Recent work by Barbour et al. (81), however, has clearly demonstrated that such peak levels were associated with subtherapeutic trough levels of <0.5 U/ml in the great majority of cases. These data, in addition to documented risk of valve thrombosis with subtherapeutic pre-dose anti-Xa levels, suggest the importance of routine measurement and maintenance of trough levels at therapeutic range (0.6 to 0.7 U/ml) in the highly thrombogenic population of pregnant women with mechanical PHV (Table 3). Peak levels should also be monitored to prevent excessive anticoagulation (i.e., >1.5 U/ml), in which case, an 8-hourly rather than a 12-hourly dosing should be used. To ensure patient compliance and adequate prophylaxis, anti-factor Xa activity or a partial thromboplastin time should be measured at least every two weeks. Catheter placement for epidural anesthesia is not advisable within 10 to 12 h of the last dose, because of longer half-life of LMWH (82). For this reason, and to prevent spinal or epidural hematoma, LMWH should be withdrawn 18 to 24 h before an elective delivery and substituted with intravenous UFH. Because of the potential added benefit (83), a small dose of aspirin (60 to 150 mg/day), which is safe during pregnancy (84), might be added in high-risk patients to further reduce the incidence of thromboembolism.

In summary, the choice of anticoagulation in pregnant patients with PHV needs to be made after detailed discussion with the patient and her family. Potential risks and benefits of available therapeutic options and the fact that available data are insufficient to reliably predict efficacy and safety need to be emphasized. Clinical experience, however, strongly suggests that the risk of anticoagulation is greatly related to inadequate dosing and monitoring and can be minimized by a strong commitment to a strict therapeutic regimen and a close follow-up by both the patient and her physician.

References

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