“Bridging” and Mechanical Heart Valves
Perils, Promises, and Predictions

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Mechanical heart valves require anticoagulation to prevent valve-associated thrombosis and thromboembolic stroke. Oral vitamin K antagonists such as warfarin are prescribed universally; however, oral agents do not act immediately and usually require at least 5 days to achieve a therapeutic effect.

Measurement of the prothrombin time, which is standardized by reporting the result as the international normalized ratio (INR), assesses the anticoagulant effect of warfarin. For most mechanical heart valves, the target INR ranges between 2.0 and 3.5. In the postoperative cardiac surgical setting, patients are usually started on low doses of warfarin because they tend to have impaired hepatic metabolism and suboptimal nutritional status. Even with low initial doses of warfarin, mechanical heart valve replacement patients are susceptible to excessively high INRs.1 This known exaggerated initial response to warfarin after heart valve replacement can lead to the habitual prescription of such low warfarin doses that warfarin as monotherapy may not achieve a stable and therapeutic INR for weeks after its initiation.

To minimize the delay in achieving therapeutic anticoagulation, a “bridging” anticoagulant is prescribed. The “bridge” is administered parenterally, thereby providing an immediate anticoagulant effect. Traditionally, the “bridging” agent has been unfractionated heparin (UFH). More recently, physicians tend to select low-molecular-weight heparin (LMWH), even though few studies exist to validate the efficacy and safety of either LMWH or UFH in this setting.

The rationale for shunning UFH has been to avoid the known perils and inconveniences of its use as a continuous peripheral intravenous infusion. UFH is rarely administered in an immediately therapeutic dose because of fear of precipitating bleeding complications. Especially in postoperative mechanical valve replacement patients, there is reluctance to follow the high dosing requirements for initial bolus and infusion regimens published in standardized nomograms. Instead, UFH is usually started in cautious small doses, sometimes without an initial bolus, or with a reduced bolus dose that is so low that one can predict several days will be needed before adequate anticoagulation is achieved. In addition, UFH is commonly implicated in medication errors.

At Brigham and Women’s Hospital, we found 1.67 medication errors for every 1000 patients treated with anticoagulants.2 UFH caused more anticoagulation medication errors than all other anticoagulants combined. Overall, 66% of the errors were associated with UFH, followed by 22% with LMWH and 9% with warfarin.

In theory, there are a multitude of advantages for LMWH compared with UFH, especially after a patient has stabilized and is otherwise ready for hospital discharge after mechanical heart valve replacement. First, in the setting of normal or even moderately reduced renal function, LMWH is administered as a fixed dose, according to weight, and does not require continuous dosing adjustments, as does UFH, which is titrated to the activated partial thromboplastin time. Second, in contrast to continuous-infusion intravenous UFH, LMWH is administered subcutaneously, which does not hinder patient mobility and facilitates early hospital discharge. (Although UFH can be given subcutaneously in high, therapeutic doses, it is ordinarily prescribed as a continuous peripheral intravenous infusion.) Third, the dreaded rare complication of heparin-induced thrombocytopenia with thrombosis occurs less often with LMWH than with UFH.

Theoretical advantages of a contemporary bridging approach with LMWH must be tempered by consideration of its potential disadvantages. First, if bleeding complications do occur, UFH is more rapidly reversible than LMWH. Second, with respect to costs, UFH is less expensive to purchase unit for unit than LMWH. However, this “silo approach” to cost does not account for other expenses related to UFH administration, such as coagulation monitoring and physician and nursing time required for dose adjustment and proper maintenance of the infusion pump and execution of frequently changing UFH dosing orders.

With respect to patients on established long-term anticoagulation therapy who require interruption of therapy for surgery, all costs must be considered, not just drug costs. For patients taking warfarin who require surgery, we estimated the theoretical cost of bridging therapy with LMWH self-administered at home versus continuous-infusion UFH in the hospital. The overall cost for a LMWH bridging strategy compared with a UFH bridging strategy was estimated at $672 versus $3816, respectively, even though the actual purchase of LMWH was assumed to be 7 times more expensive than UFH.3 Similar findings were observed in a retrospective analysis of a health maintenance organization serving New Mexico.4

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To maximize efficacy and safety of LMWH, the most important element to ensure success with bridging is to utilize a standardized periprocedural anticoagulation regimen. This requires stratifying patients before the procedure into high or nonhigh bleeding risk groups. In the Douketis protocol, the classification of bleeding risk is subjective. After surgery, hemostasis must be assessed, and bleeding risk is reevaluated. Mechanical heart valve replacement patients are at very high risk of bleeding with periprocedural anticoagulation, especially UFH and LMWH. That is why at some centers performing heart valve operations, anticoagulation is initiated with warfarin as monotherapy so that bridging does not even become necessary unless there is unusual delay in achieving a therapeutic INR.

The ideal target INR is still controversial for mechanical heart valve patients. Many surgeons believe that current guidelines mandate excessive anticoagulation and that patients could safely be managed with lower-intensity INRs. In the German Experience With Low Intensity Anticoagulation study, patients undergoing St Jude heart valve replacement were enrolled into 3 strata: very-high-intensity anticoagulation (target INR between 3.0 and 4.5), moderate-intensity anticoagulation (target INR between 2.5 and 4.0), and low-intensity anticoagulation (target INR between 2.0 and 3.5). Of the 2735 patients, 553 received mitral valve replacement and were enrolled into 3 strata: very-high-intensity anticoagulation (target INR between 2.5 and 4.0), and low-intensity anticoagulation (target INR between 2.0 and 3.5). Of the 2735 patients, 553 received mitral valve replacement and 158 received combined mitral and aortic valve replacement. Patients receiving aortic valve replacements had fewer thromboembolic events but a similar number of serious bleeding events as patients receiving mitral valve replacements; however, the overall incidence of moderate and severe thromboembolic and bleeding complications was similar in all 3 anticoagulation strata. If lower warfarin anticoagulation intensity proves safe and effective for mechanical heart valve patients, then the duration of bridging with LMWH or UFH will shorten.

In 2004, we reported a small case-control study of 29 patients who received LMWH and 34 control subjects who received UFH after mechanical heart valve replacement. Efficacy and safety were similar in both groups; however, there were marked advantages for LMWH with respect to a dramatically shorter postoperative length of stay compared with UFH: 6.6 versus 15.9 days. Although the average inpatient anticoagulation medication cost was higher with LMWH ($129 compared with $25 for UFH), the average total cost of care was less expensive with LMWH ($29 141) than with UFH ($50 542). Using the LMWH strategy, 112 inpatient days were eliminated, resulting in an average savings of $5984 per patient.

There remains a paucity of data on bridging newly implanted prosthetic heart valve replacement patients with LMWH. Therefore, Meurin and colleagues have performed a great service by enrolling 250 patients in a well-executed case series published in this issue of Circulation. Many of these patients were at high risk for stroke. Half had atrial fibrillation at baseline. One quarter had either mitral valve replacement or double-valve replacement. More than 10% had suffered a prior stroke.

In the study by Meurin et al, the LMWH bridging strategy was remarkably successful. Only 3 of the 250 patients experienced adverse events: hemorrhagic pericardial tamponade, abdominal muscle hematoma, and transient ischemic attack. No patient had valve thrombosis, and all patients survived.

These investigators deserve special commendation for performing their study in a cardiac rehabilitation center rather than an acute care hospital. Their selected venue for clinical research is often overlooked and underutilized, but it may reflect “real-life” results more accurately than the highly monitored and intensively staffed acute tertiary care hospital setting.

Some aspects of the study do warrant special comment. Perhaps the cost-savings advantages of LMWH bridging would have become more apparent if the investigators had initiated LMWH sooner. Their average patient began LMWH bridging on the 16th hospital day. This delayed LMWH strategy may have reduced potential cost-savings that might have been achieved with a shorter hospital length of stay. On the other hand, the late start of LMWH bridging on postoperative day 16 may have screened out the highest-risk patients, who, with early initiation of LMWH, might theoretically have experienced a higher rate of major bleeding or thromboembolism.

The investigators began bridging with enoxaparin 1 mg/kg twice daily. However, they measured anti-Xa activity 4 hours after the third injection. Although one cannot quibble with their excellent clinical outcomes, the dose adjustment of enoxaparin to achieve a target therapeutic range between 0.5 and 1.0 IU/mL may have unnecessarily complicated their LMWH dosing regimen. In our Anticoagulation Service at Brigham and Women’s Hospital, we have noted very little correlation between adverse events and anti-Xa activity in patients receiving LMWH. Paradoxically, Meurin’s group noted “therapeutic” anti-Xa levels in their 3 patients with adverse bleeding or clotting events. This raises the question of whether anti-Xa monitoring of LMWH really plays a useful role. In our hospital, we restrict the use of anti-Xa levels to very special circumstances, such as dosing patients who are massively obese or checking medication compliance in patients whom we suspect have omitted injections.

We are trained to monitor the effects of most of our therapies with blood tests. Whether anti-Xa activity monitoring is helpful remains controversial. A consensus group recently reviewed in detail approximately 80 publications on bridging anticoagulation in patients with mechanical prosthetic heart valves. The panel generated 2 algorithms. The algorithm for nonpregnant patients categorized anti-Xa activity monitoring as optional; however, the algorithm for pregnant patients mandated anti-Xa level monitoring on a weekly basis for the first month of use of LMWH. Overall, we concluded from our literature review that LMWH may be a safe and effective agent compared with UFH in patients with mechanical prosthetic heart valves. Although we recommended the undertaking of large-scale randomized trials, the lack of feasibility of such an undertaking makes it unlikely to occur.

At the time of our consensus panel meeting on anticoagulation of prosthetic heart valves, the Food and Drug Administration (FDA) had just changed the product labeling for
enoxaparin. The FDA had issued a new “black box warning” that enoxaparin is “not recommended for thromboprophylaxis in patients with prosthetic heart valves.” Subsequently, the FDA recognized that anticoagulation is hazardous for prosthetic heart valve patients regardless of the specific anticoagulant: LMWH, UFH, or warfarin. Accordingly, the black box warning for enoxaparin use in prosthetic mechanical heart valves was removed, and warning language was softened to reflect the pervasiveness of the problem irrespective of the specific anticoagulant agent. Currently, the package labeling states, “The use of Lovenox Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism.”

The data from Meurin et al.8 provide valuable additional information to reassure the clinician that bridging with LMWH appears effective, safe, and feasible. Previously, only 1 case series with >100 patients reported results with LMWH bridging after mechanical heart valve replacement. The investigators found that LMWH provided superior laboratory evidence of anticoagulation, but there was no difference in adverse end points compared with a previously studied cohort of patients bridged with UFH.10

Centralized hospital-based anticoagulation services can play a valuable role in caring longitudinally for patients undergoing mechanical heart valve replacement. Our Anticoagulation Service began in December 1996 with a modest 72 active patients. Our current enrollment exceeds 1800 active patients. The first 3 points of our 6-point mission statement are directly relevant to heart valve patients. Our goal is to maximize the effectiveness and safety of anticoagulation management by (1) providing careful monitoring and dosing of injectable and oral anticoagulants among hospitalized patients and outpatients, (2) facilitating and coordinating anticoagulation care among various providers, and (3) transitioning (bridging) anticoagulation management between the hospital and home settings.11

In a retrospective, observational cohort study, a centralized, telephonic, pharmacist-managed anticoagulation monitoring service reduced the risk of anticoagulation therapy-related complications compared with usual care.12 The complication rate was reduced by 39%. This good outcome correlated with improved maintenance of the targeted INR.

Optimal anticoagulation of patients with new mechanical heart valves will remain problematic. The stakes are high. These patients are especially susceptible to devastating clotting and bleeding complications. It is particularly unfortunate when a technically excellent operation is soon thereafter complicated by a thromboembolic stroke or by hemorrhagic pericardial tamponade.

Until now, the field has been overshadowed by rhetoric and by widely differing institution-based anticoagulation protocols. Meurin and colleagues8 have set the stage for an improved scientific basis to our practice. Their carefully performed case series should now be followed by the establishment of multicentered registries to track anticoagulation early after mechanical heart valve replacement.

Clearly, the bridging of mechanical heart valve patients is burdened with the dual perils of thromboembolism and major bleeding. The promise is that careful assessment of risk, coupled with standardized approaches using optimal anticoagulation regimens, can avert catastrophic complications. I predict that future studies will allow us to lower the intensity of anticoagulation in patients receiving mechanical heart valves. I suspect that overall clinical assessment will prove more useful in determining who is at highest risk of clotting or hemorrhagic complications than serial anti-Xa activity monitoring.

Disclosures

None.

References

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