BRIDGE: Bridging Warfarin With LMWH Increases Bleeding in Patients With AF

Written by Emma Hitt Nichols, PhD

Bridging warfarin interruption with low molecular weight heparin (LMWH) around the time of surgery or invasive procedures in patients with atrial fibrillation (AF) resulted in similar rates of arterial thromboembolism but significantly greater rates of minor and major bleeding. Thomas L. Ortel, MD, PhD, Duke University Medical Center, Durham, North Carolina, USA, presented data from the BRIDGE trial [Douketis JD et al. *N Engl J Med*. 2015].

It is uncertain whether bridging with LMWH is optimal practice to reduce the risk of thromboembolism during the perioperative interruption of warfarin. The purpose of the BRIDGE trial was to determine the safety and efficacy of bridging with LMWH in patients with AF who required interruption of warfarin for surgery or an invasive procedure. The investigators hypothesized that a strategy of foregoing bridging would be noninferior to bridging for the prevention of arterial thromboembolism and would be superior to bridging for major bleeding.

The double-blind, phase 3 BRIDGE trial randomly assigned 1884 patients with AF to receive bridging with LMWH or matched placebo 3 days prior to and for 5 to 10 days after surgery or a procedure. Warfarin was stopped 5 days prior to the surgery or procedure and was restarted within 24 hours afterward. The study drug was stopped when patients achieved a therapeutic INR. Patients were followed for 30 days after the initial surgery or procedure. The primary outcomes were arterial thromboembolism or major bleeding. The secondary outcomes were acute myocardial infarction, venous thromboembolism, or death, and minor bleeding.

All patients had nonvalvular or valvular AF or atrial flutter, were receiving warfarin for ≥ 3 months with a target INR of 2.0 to 3.0, and had a $CHADS_2$ score of ≥ 1. Exclusion criteria included presence of a mechanical heart valve, major bleeding within the past 6 weeks, venous thromboembolism within the past 12 weeks, creatinine clearance < 30 mL/min, and platelet count $< 100 \times 10^3/m^3$, as well as a stroke, systemic embolism, or transient ischemic attack (TIA) within the past 12 weeks or planned cardiac, intracranial, or intraspinal surgery.

The mean age was 71.7 years and the mean $CHADS_2$ score was 2.35, with about 23%, 39%, 24%, and 11% of patients having a score of 1, 2, 3, or 4, respectively. At baseline, the mean INR was 2.4, about 87% of patients had hypertension, about 31% had chronic heart failure or left ventricular dysfunction, 41% had diabetes mellitus, 8% had a history of TIA, and 16% had mitral valve disease.

Bridging with LMWH was noninferior, but not superior, to no bridging ($P_{Noninferiority} = .01$). However, there was significantly more major bleeding in the bridging arm (3.2%) compared with the no-bridging arm (1.3%; $P_{Superiority} = .005$). In addition, minor bleeding was also significantly greater with LMWH bridging (20.9%) compared with no bridging (12.0%; $P_{Superiority} < .001$). There was no significant difference among the other secondary outcomes.

Dr Ortel commented that the study was limited by the low mean $CHADS_2$ score and that most patients underwent low-risk procedures. In addition, he stated that these results are not applicable to patients who are receiving a nonwarfarin oral anticoagulant instead of warfarin.

Recombinant Human Coagulation Factor IX Fc Fusion Protein Effective in Kids B-LONG Study

Written by Muriel Cunningham

The Kids B-LONG study [NCT01440946] was conducted to evaluate the pharmacokinetics, safety, and efficacy of recombinant human coagulation factor IX Fc fusion protein (rFIXFc) in previously treated pediatric subjects with hemophilia B. Kathelijn Fischer, MD, PhD, University Medical Center Utrecht, Utrecht, The Netherlands, provided a summary of the Kids B-LONG study results.

Eligible subjects were boys aged < 12 years with ≤ 2 IU/dL endogenous factor IX (FIX) and with ≥ 50 previous exposure days (EDs) to FIX without a history of FIX inhibitor. The study schematic is illustrated in Figure 1. All subjects had pharmacokinetic assessment with FIX 50 IU/kg and then with rFIXc 50 IU/kg before this study. Then, all received weekly prophylaxis with rFIXFc and were followed for 50 EDs. Surgery was allowed after 3 EDs.

Thirty subjects were enrolled in the study; 15 patients were < 6 years old, and 15 were between 6 and 12 years. All subjects were treated with FIX prophylaxis before entering the study, and 77% were receiving FIX ≥ 2 times per week. Twenty-seven subjects (90%) completed the study, with a median study duration of 49.4 weeks. A total of 24 subjects (80%) had at least 50 EDs of rFIXFc.

Pharmacokinetic analyses indicated that rFIXFc had an increased half-life and reduced clearance in children compared with FIX products administered in the earlier phase of pharmacokinetic assessment. Also, incremental recovery with rFIXFc was similar to or slightly better than that with FIX.