EINSTEIN DVT: Rivaroxaban Noninferior to Enoxaparin and Warfarin in Patients with DVT

Treatment with rivaroxaban provided a simple, safe, and effective alternative to standard anticoagulation therapy for patients with deep vein thrombosis (DVT), according to findings from the phase III Oral Direct Factor Xa Inhibitor Rivaroxaban In Patients With Acute Symptomatic Deep-Vein Thrombosis Without Symptomatic Pulmonary Embolism (Einstein-DVT; NCT 00440193). Harry R. Buller, MD, PhD, Academic Medical Center, Amsterdam, The Netherlands, presented findings from EINSTEIN DVT.

Rivaroxaban is an investigational oral factor Xa inhibitor. For patients who require anticoagulation, single-agent rivaroxaban presents an attractive alternative to standard combination therapy with low-molecular-weight heparin and warfarin, which requires subcutaneous injections, dietary restrictions, and close monitoring to confirm clotting time. One potential limitation of rivaroxaban is the lack of antidote to rapidly reverse its anticoagulation activity. By comparison, the effects of warfarin can be reversed with the administration of vitamin K.

The open-label EINSTEIN DVT trial included 3449 patients with symptomatic DVT and without symptomatic pulmonary embolism (PE). Patients were randomly assigned to treatment with rivaroxaban 15 mg twice daily for 3 weeks, followed by a 20-mg maintenance dose (n=1731), or body weight-adjusted subcutaneous enoxaparin 1 mg/kg twice daily for at least 5 days, followed by warfarin (n=1718). Anticoagulation treatment continued for 3, 6, or 12 months at the discretion of the treating physician. The primary endpoint was symptomatic venous thromboembolism (VTE), which was defined as a composite of recurrent DVT, nonfatal PE, and fatal PE.

Rivaroxaban reduced the risk of recurrent VTE compared with standard therapy (2.1% vs 2.0%), meeting the criteria for noninferiority ($p<0.0001$) and approaching statistical significance for superiority ($p=0.076$). Among individual efficacy outcomes, rivaroxaban reduced the risk of recurrent DVT by half compared with enoxaparin and warfarin (0.8% vs 1.6%). Other outcomes were comparable in the rivaroxaban and standard therapy groups, including nonfatal PE (1.2% vs 1.0%) and fatal PE (0.2% vs 0.3%).

The net clinical benefit, which accounted for symptomatic VTE plus major bleeding, also favored rivaroxaban over enoxaparin and warfarin (HR, 0.67; 95% CI, 0.47 to 0.95). An analysis of safety outcomes showed similar rates of bleeding, including major and clinically relevant nonmajor bleeding, for rivaroxaban compared with standard therapy (8.1% vs 8.1%; $p=0.77$). Rivaroxaban was not associated with liver toxicity, a safety concern with other factor Xa inhibitors.

The EISTEIN DVT trial supports the use of rivaroxaban as a simplified approach for treating DVT and preventing recurrent VTE, Prof. Buller concluded. A companion trial, EINSTEIN PE, is currently underway to compare the efficacy and safety of rivaroxaban versus enoxaparin and warfarin in patients with symptomatic PE.

UFH and Fondaparinux in ACS Patients Undergoing PCI: Results from the FUTURA/OASIS-8 Trial

The addition of a standard-dose regimen of unfractionated heparin (UFH) to fondaparinux (FONDA) during percutaneous coronary intervention (PCI) preserves the bleeding reduction benefit of fondaparinux therapy while minimizing associated catheter thrombosis risk in patients with acute coronary syndromes (ACS). However, a low-dose UFH regimen did not reduce the rate of major peri-PCI bleeding or major vascular access site complications compared with standard-dose UFH when added to FONDA treatment in this cohort. Sanjit S. Jolly, MD, McMaster University, Hamilton, Ontario, Canada, presented findings from the Fondaparinux Trial with Unfractionated Heparin During Revascularization in Acute Coronary Syndromes (FUTURA)/Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS)-8 Study (NCT00790907).

FONDA was determined to reduce major bleeding and improve long-term morbidity and mortality rates compared with enoxaparin in OASIS-5. However, catheter thrombosis was more common among patients who were treated with FONDA compared with enoxaparin alone, and this risk appeared to be attenuated by adjunct UFH during PCI [OASIS-5 Investigators. *N Engl J Med* 2006; Mehta SR et al. *J Am Coll Cardiol* 2007]. FUTURA/OASIS-8 was designed to compare the safety of 2 UFH regimens in patients who were undergoing PCI (within 72 hours) who had non-ST-segment elevation ACS and had been treated with FONDA.

Patients were randomized to receive either intravenous low-dose (50 U/kg; n=1024) or standard-dose (85 U/kg or 60 U/kg if taking glycoprotein IIb/IIIa inhibitors;

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n=1002) UFH, adjusted by blinded activated clotting time. The primary outcome was the composite of major bleeding, minor bleeding, or major vascular access site complications within 48 hours of PCI (Table 1). Key secondary outcomes included the composite of major bleeding within 48 hours of PCI with death, myocardial infarction (MI), or target vessel revascularization (TVR) within 30 days.

Table 1. Study Outcome Definitions.

Major Bleeding (OASIS 5)	• Fatal • Symptomatic ICH • Retroperitoneal hemorrhage • Intraocular bleeding leading to significant vision loss • Requiring surgical intervention • Hb drop of ≥3 g/dL • Blood transfusion of ≥ two units RBCs
Minor Bleeding	• Any other significant bleeding leading to transfusion of one unit of blood or discontinuation of antithrombotic therapy
Major Vascular Access Site Complications	• Large hematoma (≥5cm or requiring intervention • Pseudoaneurysm requiring treatment • Arteric-venous fistula • Other vascular surger related to the access site

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The rates that were associated with the composite primary outcome were similar for both UFH groups. Analysis of individual primary outcome components revealed similar rates between the two groups, with the exception of minor bleeds, which was lower in the low-dose UFH group (0.7% vs 1.7% in the standard group; p=0.04). The secondary composite outcome of peri-PCI major bleeding with death, MI, or TVR at 30 days favored the standard UFH regimen over low-dose UFH (3.9% for standard vs 5.8% for low-dose; OR, 1.51; 95% CI, 1.00 to 2.28; p=0.05). The rate of death, MI, or TVR at 30 days was also lower in the standard-dose group (2.9%) than in the low-dose group (4.5%; p=0.06). Catheter thrombus rates were low in both treatment groups (0.5% vs 0.1% in the standard-dose group).

The FUTURA/OASIS-8 results confirm the strength of current guidelines that recommend the standard-dose regimen of UFH during PCI. There was no significant difference in major bleeding or vascular complication between the two doses of UFH. The use of UFH in patients with ACS who are treated with FONDA who are undergoing PCI appears to be safe, but current UFH dose recommendations should be followed. It is important to note that patients who required urgent (<120 minutes) coronary angiography were excluded from participation in this study, which may have resulted in a lower-risk study population. Additionally, the study was not powered to fully compare the doses with regard to ischemic events alone, which influences the bleeding-versus-thrombotic risk assessment. Therefore, caution should be used when interpreting these data.

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New Potassium Binder Prevents Hyperkalemia in Patients with HF

An investigational potassium binder, RLY5016, prevented hyperkalemia in patients with heart failure (HF), according to findings from the phase II PEARL-HF study (NCT00868439). The new agent may allow more HF patients to use renin-aldosterone-angiotensin system (RAAS) blockers, which have been shown to reduce mortality but cause hyperkalemia in up to 25% of HF patients.

The PEARL-HF study included 104 patients with HF and either stage 3 or 4 chronic kidney disease or a history of hyperkalemia that resulted in RAAS inhibitor discontinuation. Patients were randomly assigned to treatment with RLY5016 30 mg/day (n=55) or placebo (n=49). The primary endpoint was the change from baseline in serum potassium by Week 4. Bertram Pitt, MD, University of Michigan School of Medicine, Ann Arbor, Michigan, USA, presented findings from the PEARL-HF study.

At baseline, all patients were receiving standard heart failure therapy with a RAAS inhibitor or β-blocker. Patients also received spironolactone 25 mg/day for the first 2 weeks of the study, and those with serum potassium levels ≤5.1 mEq/L on Day 15 increased the spironolactone dose to 50 mg/day. More RLY5016-treated patients than patients in the placebo group were able to increase the spironolactone dose for the remaining 2 weeks of treatment (91% vs 74%; p=0.019).

After 4 weeks, treatment with RLY5016 reduced mean serum potassium levels from 4.69 mEq/L at baseline to 4.48 mEq/L (mean change, -0.22 mEq/L). By comparison, potassium levels increased in the placebo group from 4.65 mEq/L to 4.93 mEq/L (mean change, +0.23 mEq/L), resulting in a between-group difference of 0.45 mEq/L that favored RLY5016 (p<0.001).

The new potassium binder also provided protection against hyperkalemia, which was defined as serum potassium ≥5.5 mEq/L. Fewer patients in the RLY5016 group than in the placebo group developed hyperkalemia at any point