gastroscopy, a biphasic enhanced CT scan of the liver, a parenchymal pancreatogram, and a uniphasic enhanced CT scan of the distended bladder.

The primary end point was confirmed cancer detected within 1 year that was missed by screening. The secondary end points included total number of occult cancers diagnosed, total number of early cancer diagnoses, 1-year cancer-related mortality, 1-year overall mortality, time to cancer diagnosis, and recurrent VTE. The intention-to-treat analysis included 854 patients. At baseline, the mean age was 53.5 years, 67.5% were men, and the mean weight was 90.1 kg. In addition, 5.9% of patients had a prior cancer, 5.5% had a prior provoked VTE, 15.5% were current smokers, and 33.3% were former smokers. Deep vein thrombosis occurred in 67.5% of patients, pulmonary embolism in 32.5%, and both in 12.3%.

There was no significant difference in new cancer diagnoses among patients in either arm of the study, with 3.2% of patients in the limited-screening arm (95% CI, 1.9% to 5.4%) and 4.5% of patients in the limited screening with comprehensive CT arm (95% CI, 2.9% to 6.9%; $P=.28$). In addition, the time to cancer diagnosis was similar among both arms, with 4.2 months in the limited screening group and 4.0 months in the limited plus CT screening group ($P=0.88$). Furthermore, there was no significant difference in the detection rate of early cancers, overall mortality, cancer-related mortality, time to cancer diagnosis, and rate of recurrent VTE.

Dr Carrier stated that it is possible that an even more extensive screening strategy may have missed fewer occult cancers. He highlighted that there was an overall low rate of occult cancers in patients with unprovoked VTE, and the results of this study indicate that a comprehensive CT scan of the abdomen and pelvis does not provide a clinical benefit.

Risk Factors for Recurrent Venous Thromboembolism Revealed in PADIS-PE Trial

Written by Muriel Cunningham

Patients who have experienced an unprovoked pulmonary embolism (PE) may experience recurrence after stopping anticoagulant therapy, but the optimal duration of anticoagulation treatment is unclear. The primary objective of the double-blind multicenter PADIS-PE study [Couturaud F et al. *JAMA*. 2015] was to evaluate the efficacy and safety of an additional 18 months of oral anticoagulant treatment following an initial 6 months of therapy. The ability to classify patients according to risk of recurrence is also of benefit given the risks associated with anticoagulation therapy. Another objective of the study was to identify such risk factors. Findings from the study were presented by Francis Couturaud, MD, PhD, European Brittany University, Brest, France.

In the PADIS-PE study, 371 patients with their first unprovoked PE received 6 months of vitamin K antagonist treatment and were randomized to an additional 18 months of warfarin treatment (n=184) or placebo (n=187). At randomization, blood samples were taken, and patients underwent a ventilation/perfusion (V/Q) lung scan, echocardiography, and compression ultrasound of the legs. Patients were evaluated at the end of the 18-month treatment period and followed for an additional 2 years.

During 18 months of treatment, the primary outcome (composite of recurrent symptomatic venous thromboembolism [VTE] and major bleeding at 18 months) occurred in 3.3% of warfarin-treated patients vs 13.5% of placebo-treated patients (HR, 0.22; 95% CI, 0.09 to 0.55; $P=.001$). Recurrent symptomatic VTE occurred in 1.7% of warfarin-treated patients and 13.5% of those receiving placebo (HR, 0.11; 95% CI, 0.03 to 0.37; $P<.0001$). Major bleeds were not significantly different between the 2 groups (2.2% warfarin, 0.5% placebo; HR, 4.07; 95% CI, 0.45 to 36.38; $P=.18$). Over the entire study period, there were no statistically significant differences between the 2 treatment groups in composite events (20.8% warfarin vs 24.0% placebo; HR, 0.74; 95% CI, 0.47 to 1.17; $P=.19$), recurrent symptomatic VTE (17.9% warfarin vs 22.1% placebo; HR, 0.67; 95% CI, 0.41 to 1.08; $P=.10$), or major bleeds (3.5 warfarin vs 3.0 placebo; HR, 1.12; 95% CI, 0.38 to 4.10; $P=.71$).

One of the secondary objectives was to determine risk factors for recurrent symptomatic VTE during the 42-month follow-up period. Symptomatic recurrent VTEs were defined as follows: nonfatal recurrent PE (clinical suspicion of PE with positive V/Q lung scan, spiral computed tomography angiography, pulmonary angiography, or new noncompressibility of a proximal vein on ultrasound), fatal recurrent VTE (autopsy or unexplained sudden death), and symptomatic recurrent deep vein thrombosis (DVT; clinical suspicion of DVT and noncompressibility of a new segment of a proximal vein on ultrasound). Univariate analysis and a multivariate model were used to identify risk factors for recurrent VTE.

Age, residual perfusion defect at study inclusion, and residual DVT at study inclusion were identified as independent risk factors associated with recurrent VTE based on multivariate analysis (Table 1). On the basis of these findings, Dr Couturaud noted that it may be useful to perform a V/Q lung scan and lower limb ultrasound after 6 months of anticoagulation to help determine a patient's risk of recurrent VTE if treatment is discontinued.

Table 1. Multivariate Analysis (Adjusted for Treatment Effect)

Variable	OR (95% CI)	*P* Value
Age	2.38 (1.30 to 4.38)	.005
Residual perfusion defect at inclusion[a]	2.22 (1.23 to 4.01)	.009
Residual deep vein thrombosis at inclusion	2.02 (1.06 to 3.85)	.03

[a]Residual perfusion defect on ventilation/perfusion lung scan, >10%.

ANNEXA-A: Andexanet alfa Reduces Anti-fXa Activity in Apixaban-Treated Subjects

Written by Muriel Cunningham

Andexanet alfa is an agent developed to reverse the activity of factor Xa (fXa) inhibitors. Phase 2 proof-of-concept studies in patients taking rivaroxaban, apixaban, edoxaban, and enoxaparin have been completed and andexanet is now being studied in phase 3 confirmatory trials. In part 2 of the phase 3 ANNEXA-A trial [NCT02207725], subjects were treated with apixaban, dosed to steady state, and randomized 3:1 to receive an andexanet bolus plus an infusion or placebo. Mark Crowther, MD, McMaster University, Hamilton, Ontario, Canada, presented the study results.

Because of the difficulty in conducting trials in actively bleeding patients, the ANNEXA-A study was designed to enroll older subjects (50 to 75 years) who were otherwise healthy and to utilize biomarker end points. The primary end point was the percentage change in anti-fXa activity from baseline to the nadir after infusion. Baseline was defined as the measurement at peak anti-Xa before the start of bolus, and the nadir was the lowest anti-Xa value between 10 minutes prior to and 5 minutes after the end of infusion.

A total of 32 subjects were enrolled, 24 to the andexanet arm and 8 to placebo. Twenty-two patients (68.8%) were male and 29 patients (90.6%) were white with a mean age of approximately 59 years (range, 50 to 73). Subjects who were randomized to active treatment received an andexanet bolus of 400 mg followed by 480 mg for a 2-hour continuous intravenous infusion (4 mg/min).

The safety results were consistent with those observed in earlier studies of andexanet. One subject discontinued during the andexanet infusion after experiencing mild hives; there were no other allergic symptoms or cardiorespiratory effects. Six subjects had mild infusion-related reactions, 4 (16.7%) in the andexanet group and 2 (25.0%) receiving placebo. None experienced severe or serious adverse events. Transient elevation of prothrombin fragment 1+2 was seen in most subjects who received andexanet but it returned to ≤2 times the upper limit of normal by the fourth day after treatment. D-dimer did not increase for more than 1 day. Dr Crowther commented that no thrombotic events were noted in anyone infused with this product across all studies. No clinically important antibodies to factor X or fXa were reported.

Subjects in part 2 of the ANNEXA-A study met its primary study end point. The mean anti-fXa significantly decreased by 92% from baseline, which was also significantly lower than the placebo group ($P<.001$). In addition, andexanet significantly reduced free apixaban ($P=.0002$ vs placebo). Thrombin generation was restored to preapixaban levels in all andexanet-treated subjects ($P<.0001$). A large, multicenter, open-label phase 4 study of andexanet is now being conducted at centers in North America and Europe. This study will enroll subjects with acute bleeding who are taking fXa inhibitors to determine the change in anti-fXa activity as well as the number of patients who can achieve effective hemostasis.

AFFINITY: rVIII-SingleChain Efficacious and Well Tolerated in Pivotal Study

Written by Muriel Cunningham

rVIII-SingleChain is an investigational recombinant, single-chain factor VIII being studied in adolescents and adults with hemophilia A. Johnny Mahlangu, MD, University of the Witwatersrand, Johannesburg, South Africa, presented the pharmacokinetic, efficacy, and safety results from the phase 1 rVIII-SingleChain AFFINITY trial [NCT01486927].

This was a large, international, open-label study. Based on investigator judgment, patients were assigned to either prophylaxis or on-demand therapy. For prophylaxis, patients received 20 to 40 IU/kg rVIII-SingleChain every second day or 20 to 50 IU/kg rVIII-SingleChain 2 to 3 times per week. For prophylaxis prior to surgery the regimen was individualized based on the type of surgery. Dose and frequency of rVIII-SingleChain could be adjusted at the investigator's discretion. The World Federation of Hemophilia recommendation was used to guide the treatment of bleeds.

A total of 174 patients were enrolled, 146 (83.9%) for prophylaxis and 27 (15.5%) for on-demand therapy. These included 120 subjects (68.9%) with >50 exposure days (EDs) and 52 subjects (29.9%) with >100 EDs; as a result, there were a total of 14306 EDs. Among the