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EMBARGOED FOR RELEASE UNTIL: Saturday, December 8, 2007, at 10:00 a.m. EST

RESEARCH HIGHLIGHTS NEW APPROACHES TO MANAGEMENT OF BLOOD CLOTTING AND BLEEDING DISORDERS

(ATLANTA, December 8, 2007) – Data that shed new light on the treatment of residual vein thrombosis, thromboprophylaxis after total hip replacement, chronic immune thrombocytopenic purpura, and venous thrombosis in relation to postmenopausal hormone replacement therapy will be presented at the 49th Annual Meeting of the American Society of Hematology in Atlanta, GA. A press conference will reveal this new research on Saturday, December 8, from 10:00 to 11:00 a.m.

“Complications related to blood clotting and bleeding affect millions of Americans. In this session we will see exciting breakthroughs in the treatment and approach to mitigating the risk of thrombosis and bleeding disorders, which will directly impact the quality of treatment for many patients,” said Andrew Schafer, MD, President, American Society of Hematology, and Chairman, Department of Medicine, New York Presbyterian-Weill Cornell Medical Center, New York, NY, who will be moderating the press conference on blood clotting and bleeding disorders.

- **Investigational drug, AMG 531, demonstrates efficacy in sustaining platelet counts in splenectomized patients with chronic immune thrombocytopenic purpura in phase III study [Abstract #2]**

Terry Gernsheimer, MD, Puget Sound Blood Center, Seattle, WA

In this randomized, placebo-controlled phase III study, investigators evaluated the efficacy and safety of AMG 531 in previously splenectomized patients with chronic immune thrombocytopenic purpura (ITP) per ASH guidelines and baseline platelet counts <30,000/ μ L. Chronic ITP is an autoimmune disorder in which patients produce antiplatelet autoantibodies that destroy their blood platelets and, in some cases, damage their megakaryocytes (the cells that

produce platelets in the bone marrow) causing defective platelet production. These result in a low blood platelet count that may cause bruising or excessive bleeding. Splenectomy (removal of the spleen) is sometimes undertaken in patients with chronic ITP, as platelets targeted for destruction will often meet their fate in the spleen. Splenectomy is said to be successful in 60 percent of cases although it is less successful in older people. AMG 531 is a novel “peptibody” that acts by stimulating platelet production at the thrombopoietin receptor. Thrombopoietin is a hormone that promotes platelet production by the bone marrow. In this study, subcutaneous AMG 531 or placebo was administered weekly for 24 weeks at a starting dose of 1µg/kg, and adjusted to maintain a target platelet count of 50–200x10⁹/L in the 63 enrolled splenectomized patients with ITP. The results indicated that AMG 531 was well tolerated and effectively increased and sustained platelet counts in patients. AMG 531-treated patients required less frequent rescue medications (medications needed in an emergency to re-stabilize platelet counts and prevent or treat bleeding) in comparison with those receiving the placebo, and were able to reduce their use of concurrent ITP therapies.

- **RECORD1 is the first pivotal trial to demonstrate the efficacy and safety of a fixed, unmonitored dose of an oral, direct Factor Xa inhibitor – rivaroxaban – for extended prevention of blood clotting after a total hip replacement [Abstract #6]**

Bengt I. Eriksson, MD, PhD, Ortopedkliniken, Sahlgrenska University Hospital/Ostra, Goteborg, Sweden

This multinational, randomized, double-blind, double-dummy phase III trial studied the efficacy and safety of oral rivaroxaban in comparison to subcutaneous enoxaparin to prevent blood clotting (a process known as thromboprophylaxis) for five weeks in patients undergoing a total hip replacement (THA). Thromboprophylaxis is recommended for at least 10 days and for up to four to five weeks after total hip replacement in order to avoid the formation of a thrombembolism, or a clot in a blood vessel that breaks loose and is carried by the blood stream to plug another vessel. This type of clot may cause a number of fatal complications, including blocking a vessel in the lungs (pulmonary embolism) or brain (stroke). Rivaroxaban is an oral, direct Factor Xa inhibitor – the newest class of antithrombotic agents – in advanced clinical development for the prevention and treatment of thromboembolic disorders. Enoxaparin is a traditional blood thinner used to prevent deep vein thrombosis. The study included a total of 4,541 randomized patients who either received rivaroxaban 10 mg beginning six to eight hours after surgery and once daily thereafter, or enoxaparin 40 mg once daily beginning the evening

before surgery and restarting six to eight hours following surgery. Results showed that rivaroxaban was significantly more effective than enoxaparin for extended prophylaxis after THA. This is the first pivotal trial to demonstrate the efficacy and safety of a fixed, unmonitored dose of an oral, direct Factor Xa inhibitor for extended thromboprophylaxis patients after THA.

- **Women's Health Initiative evaluates coagulation factors, postmenopausal hormone replacement therapy, and the risk of venous thrombosis [Abstract #127]**

Mary Cushman, MD, MSc, University of Vermont, Burlington, VT

This session will present preliminary data from two trials of the Women's Health Initiative on two different estrogen regimens to evaluate coagulation markers as susceptibility factors for postmenopausal hormone-related venous thrombosis (VTE). Postmenopausal estrogen (E) therapy, especially in combination with progestin (P), doubles the relative risk of venous thrombosis (VTE). Risk with hormones is higher with increasing age, obesity, and the presence of factor V Leiden, the most common hereditary blood coagulation disorder in the United States. These two placebo-controlled double-blind randomized trials evaluated two E regimens – E (conjugated equine estrogens) or E+P (E + medroxyprogesterone acetate), in 16,608 postmenopausal women age 50–79. The investigators performed a nested case control study that measured baseline levels of coagulation markers in 215 women who developed VTE during follow-up and 867 age-matched controls. The joint effects of treatment assignment to either E regimen or placebo and prespecified abnormal levels of each coagulation factor on relative risk of VTE were estimated by logistic regression adjusting for age, race, body-mass index, and type of E regimen. The study reported new findings of elevated coagulation markers, F1-2 and PAP, as VTE risk factors in women in this prospective study nested in trials of E or E+P vs. placebo. Lower levels of other coagulation markers protein C and free protein S and higher D-dimer F1-2 and PAP, all identified women at increased risk of VTE with hormones. If these findings are confirmed in further studies, measurement of these factors might assist women with decision-making on safety of E or E+P.

- **Extended Dacus study indicates that short-term anticoagulation is safe for patients with idiopathic deep vein thrombosis [Abstract #301]**

Sergio Siragusa, MD, Istituto di Ematologia Policlinico Universitario di Palermo, Palermo, Italy

This study evaluated whether short-term oral anticoagulation therapy (OAT) is safe for patients with deep vein thrombosis (DVT) after an episode of idiopathic deep vein thrombosis

(DVT of an obscure or unknown cause). OAT is a standard treatment for patients who have experienced venous thrombosis. It is used to reduce the risk of recurrent blood clotting and is typically administered using drugs such as warfarin and acenocoumarol. While anticoagulation therapy mitigates some risks for patients, it also increases the risk of major bleeding and therefore raises the question of how long patients can safely receive OAT. Currently, a period of three months is indicated for VT due to transient risk factors (i.e. surgery) while at least three to six months are required for idiopathic DVT. It has already been determined that the optimal duration of OAT for DVT can be tailored according to the presence of residual vein thrombosis (RVT), long-lasting blood clots that remain inside the vein, as RVT serves as a marker to assess the individual risk for recurrent thrombosis. However, in patients with idiopathic DVT who have not demonstrated RVT, the safety of early interruption of OAT is still debated. This prospective controlled study evaluated the safety of withholding OAT in patients with idiopathic DVT and without RVT, three months after the index thrombotic episode. The study evaluated two groups: DVT patients without RVT who stopped OAT after three months and those with RVT who continued OAT for an additional three months. During the period from 1999-2006, 518 patients were included in the study. In 206 patients (39.7 percent), RVT was considered absent (RVT negative group) and OAT was stopped; the remaining 312 patients continued receiving anticoagulants for an additional three months (RVT positive group). The study found that in patients without RVT, three months of OAT was safe even after an episode of idiopathic DVT. This indicates that individual markers for VT, such RVT, may help in the management of VT and can allow OAT duration to be tailored. The RVT finding applies to at least 30 percent of the entire DVT population and has an important clinical impact, indicating that patients at low risk of recurrent thrombosis can now safely withdraw from OAT after three months. This approach also carries a negligible risk for bleeding.

The study authors and press program moderator will be available for interviews after the press program or by telephone. In addition to blood clotting and bleeding disorders, additional press briefings will take place focusing on leukemias, sickle cell disease and thalassemia, hematologic malignancies, and transplantation. For the complete annual meeting schedule and additional information, please visit www.hematology.org/meetings/2007.

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The American Society of Hematology (www.hematology.org) is the world's largest professional society concerned with the causes and treatment of blood disorders. Its mission is to further the understanding, diagnosis, treatment, and prevention of disorders affecting blood, bone marrow, and the immunologic, hemostatic, and vascular systems, by promoting research, clinical care, education, training, and advocacy in hematology.

[2] Evaluation of AMG 531 Efficacy in Splenectomized Patients with Chronic Immune Thrombocytopenic Purpura (ITP) in a Randomized Placebo-Controlled Phase 3 Study. Session Type: Plenary Session

Terry B. Gernsheimer, Vinod Pullarkat, Francis M. Senecal, Louis M. Aledort, Craig M. Kessler, Miguel A. Sanz, Howard A. Liebman, Frank T. Slovic, Reggie Kelly, Matthew Guo, Janet Nichol Univ of Washington, Seattle, WA, USA; City of Hope Natl Medical Ctr, Duarte, CA, USA; Northwest Medical Specialties, Tacoma, WA, USA; Hematology, Mt Sinai Hosp, New York, NY; Georgetown Univ Medical Ctr, Washington, DC; Hospital Universitario La Fe, Valencia, Spain; USC Keck Sch of Medicine, Los Angeles, CA, USA; Heartland Hem Onc Associates Inc., Kansas City, MO, USA; Amgen Inc., Thousand Oaks, CA, USA

AMG 531 is a novel thrombopoiesis-stimulating peptibody that acts by stimulating the thrombopoietin (TPO) receptor. We report efficacy data in splenectomized patients from a randomized, double blind, placebo-controlled Phase 3 study designed to evaluate the efficacy and safety of AMG 531 in patients with chronic ITP. Sixty-three splenectomized patients were enrolled (placebo, 21; AMG 531, 42), with a median age of 52 years (range 26 to 88) and a mean baseline platelet count $14.7 \times 10^9/L$. Subcutaneous AMG 531 or placebo was administered weekly for 24 weeks at a starting dose of $1 \mu g/kg$, and adjusted to maintain a target platelet count of $50-200 \times 10^9/L$. The primary study endpoint was the incidence of a durable platelet response, defined as a platelet count $\geq 50 \times 10^9/L$ for ≥ 6 weeks during the last 8 weeks of the 24 week treatment period in the absence of rescue medications. Sixteen of the 42 splenectomized patients (38.1%) receiving AMG 531 achieved a durable platelet response compared to 0/21 (0.0%) receiving placebo ($p=0.0013$). Overall response, defined as either durable or transient platelet response (≥ 4 weekly platelet responses), was observed in 33/42 (78.6%) patients receiving AMG 531, compared to 0/21 (0%) placebo patients. The mean number of weekly platelet responses (platelet count $\geq 50 \times 10^9/L$) was significantly greater in patients receiving AMG 531 (12.3/24 weeks, 51%) compared to placebo (0.2/24 weeks, 1%) ($p<0.0001$). AMG 531 reduced the proportion of patients requiring ITP rescue medications, defined as either increase from baseline in dose of concurrent medication or use of new medication to increase platelet counts. Twelve of 21 (57.1%) placebo-treated patients received rescue medications compared to just 11/42 (26.2%) AMG 531-treated patients ($p=0.0175$). In addition, 12/12 (100.0%) AMG 531-treated patients compared to 1/6 (16.7%) placebo-treated patients either discontinued or reduced by $>25\%$ their concurrent ITP medications. AMG 531 was well-tolerated. There were 2 treatment-related serious adverse events; 1 patient with elevated bone marrow reticulin that returned to baseline 3 months after withdrawal of AMG 531, and 1 patient experienced thrombosis that was successfully treated allowing study continuation. No patient developed neutralizing antibodies against either AMG 531 or endogenous TPO. In summary, AMG 531 was well-tolerated, and effectively increased and sustained platelet counts in splenectomized patients with ITP. AMG 531-treated patients required less frequent rescue medications in comparison to those receiving placebo, and were able to reduce their use of concurrent therapies.

Abstract #2 appears in Blood, Volume 110, issue 11, November 16, 2007

Keywords: Platelet|Immune Thrombocytopenia (ITP)|Clinical Trial

Sunday, December 9, 2007 1:30 PM

Session Info: Plenary Scientific Session (1:30 p.m.-4:00 p.m.)

[6] Oral Rivaroxaban Compared with Subcutaneous Enoxaparin for Extended Thromboprophylaxis after Total Hip Arthroplasty: The RECORD1 Trial. Session Type: Plenary Session

Bengt I. Eriksson, Lars C. Borris, Richard J. Friedman, Sylvia Haas, Menno V. Huisman, Ajay K. Kakkar, Tiemo J. Bandel, Eva Muehlhofer, Frank Misselwitz, William Geerts Sahlgrenska University Hospital/Östra, Gothenburg, Sweden; Aarhus University Hospital, Aarhus, Denmark; Medical University of South Carolina, Charleston, SC, USA; Institute for Experimental Oncology and Therapy Research, TU, Munich, Germany; Leiden University Medical Center, Leiden, Netherlands; Barts and the London School of Medicine, London, United Kingdom; Thrombosis Research Institute, London, United Kingdom; Bayer HealthCare, Wuppertal, Germany; University of Toronto, Toronto, Canada

Background Thromboprophylaxis for at least 10 days and for up to 4–5 weeks is recommended after total hip arthroplasty (THA). Rivaroxaban is an oral, direct Factor Xa inhibitor in advanced clinical development for the prevention and treatment of thromboembolic disorders. RECORD1 was a phase III, multinational, randomized, double-blind, double-dummy trial, conducted to determine the efficacy and safety of oral rivaroxaban, compared with subcutaneous enoxaparin, for 5 weeks of thromboprophylaxis in patients undergoing THA. Methods Patients received rivaroxaban 10 mg beginning 6–8 hours after surgery and once daily (od) thereafter, or enoxaparin 40 mg od, beginning the evening before surgery (restarting 6–8 hours after surgery). Therapy continued for 35±4 days and mandatory, bilateral venography was conducted the next day. The primary efficacy endpoint was the composite of any deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and all-cause mortality. The primary efficacy analysis was a test for non-inferiority in the per-protocol (PP) population, followed by a test for superiority in the modified intention-to-treat (mITT) population. The main secondary efficacy endpoint was major venous thromboembolism (VTE): the composite of proximal DVT, non-fatal PE and VTE-related death. Major and non-major bleeding during the active treatment period were the primary and secondary safety endpoints, respectively. Results A total of 4541 patients were randomized; 4433 were eligible for the safety population, 3153 for the mITT population, and 3029 for the PP population. The criteria for non-inferiority were met and testing for superiority was performed. Rivaroxaban significantly reduced the incidence of the primary efficacy endpoint ($p<0.001$) and major VTE ($p<0.001$), compared with enoxaparin, in the mITT population (Table). The incidence of major and non-major bleeding events was similar in both groups (Table). Conclusions Rivaroxaban was significantly more effective than enoxaparin for extended prophylaxis after THA, with a similar safety profile. This is the first pivotal trial to demonstrate the efficacy and safety of a fixed, unmonitored dose of an oral, direct Factor Xa inhibitor – rivaroxaban – for extended thromboprophylaxis after THA.

	Rivaroxaban 10mg od % (n/N)	Enoxaparin 40 mg od % (n/N)	Relative risk reduction % (95% CI)	P-value for difference
DVT, non-fatal PE, and all-cause mortality	1.1% (18/1595)	3.7% (58/1558)	70% (49–82%)	P<0.001
Major VTE	0.2% (4/1686)	2.0% (33/1678)	88% (66–96%)	P<0.001
Major bleeding	0.3% (6/2209)	0.1% (2/2224)	-	P=0.178
Non-major bleeding	5.8% (128/2209)	5.8% (129/2224)	-	P=1.000

Abstract #6 appears in Blood, Volume 110, issue 11, November 16, 2007

Keywords: Factor Xa Inhibitor|Venous Thromboembolism|Oral Anticoagulant

Sunday, December 9, 2007 1:30 PM

Session Info: Plenary Scientific Session (1:30 p.m.-4:00 p.m.)

[127] Coagulation Factors, Postmenopausal Hormone Replacement Therapy and the Risk of Venous Thrombosis: The WHI Clinical Trials of Postmenopausal Hormone Therapy. Session Type: Oral Session

Mary Cushman, Joseph Larson, Frits R. Rosendaal, Lawrence S. Phillips, Barbara V. Howard, J. David Curb, Jennifer Hays-Grudo, Alison Baird, Charles B. Eaton, Susan R. Heckbert, Randall S. Stafford *Medicine, University of Vermont, Burlington, VT, USA; Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; Epidemiology, Leiden University, Leiden, Netherlands; Medicine, Emory University, Atlanta, GA, USA; MedStar Research Institute, Hyattsville, MD, USA; Pacific Health Research Institute, University of Hawaii, Honolulu, HI, USA; Medicine, Texas A&M, Temple, TX, USA; National Institutes of Health, Bethesda, MD, USA; Warren Alpert Medical School of Brown University, Providence, RI, USA; Epidemiology, University of Washington, Seattle, WA, USA; Stanford Prevention Research Center, Stanford University, Stanford, CA, USA*

Background. Postmenopausal estrogen (E) therapy, especially in combination with progestin (P) doubles the relative risk of venous thrombosis (VTE). Risk with hormones is higher with increasing age, obesity and with factor V Leiden. We studied coagulation markers as susceptibility factors for postmenopausal hormone-related VTE. Methods. The Women's Health Initiative program included two placebo-controlled double-blind randomized trials of two E regimens, E (conjugated equine estrogens) or E+P (E + medroxyprogesterone acetate), in 16,608 postmenopausal women aged 50-79. We performed a nested case control study that measured baseline levels of coagulation markers in 215 women who developed VTE during follow up and 867 age-matched controls. The joint effects of treatment assignment to either E regimen vs placebo and prespecified abnormal levels of each coagulation factor on relative risk of VTE were estimated by logistic regression adjusting for age, race, body-mass index and type of E regimen. Results. Low levels of protein C and free protein S (<5th percentile), high D-dimer (top quartile), and high plasmin antiplasmin complex (PAP) and prothrombin fragment 1-2 (top decile) were all associated with risk of VTE with adjusted odds ratios (95% CI) of 2.0 (1.0-4.1), 2.9 (1.5-5.6), 2.8 (2.0-4.0), 2.5 (1.6-4.0) and 1.9 (1.2-3.1), respectively. Elevated factors II, VIII, IX and fibrinogen were not VTE risk factors. Compared to women with normal coagulation marker levels assigned to placebo, the joint odds of VTE with either E regimen plus an abnormal coagulation marker were more than additive compared to the separate effects of hormones and coagulation abnormalities for low protein C, low free protein S, and elevated D-dimer, PAP and F1-2. The odds ratios of VTE with the combination of an abnormal coagulation factor and assignment to hormones were (in order listed in prior sentence), 4.5 (95% CI 2.0-10.2), 6.7 (3.0-14.5), 6.1 (3.7-10), 5.8 (3.2-10.5) and 4.4 (2.4-7.7). Conclusions. We report new findings of elevated F1-2 and PAP as VTE risk factors in women in this prospective study nested in trials of E or E+P versus placebo.

Protein C or S values below the 5th percentile were also clinically relevant even though they do not represent inherited deficiency. Lower protein C and free protein S, and higher D-dimer, F1-2 and PAP all identified women at increased risk of VTE with hormones. If our findings are confirmed in management studies, measurement of these factors might assist women with decision-making on safety of E or E+P. Abstract #127 appears in *Blood*, Volume 110, issue 11, November 16, 2007

Keywords: Venous Thromboembolism|Protein C|D-dimer

Sunday, December 9, 2007 4:30 PM

Session Info: Simultaneous Session: Pathophysiology of Thrombosis: Risk Factors (4:30 p.m.-6:00 p.m.)

[301] Absence of Residual Vein Thrombosis after an Episode of Idiopathic Deep Vein Thrombosis: Short-Term Anticoagulation Is Safe. The “Extended Dacus Study”. Session Type: Oral Session

Sergio M. Siragusa, Alessandra Malato, Mario Bellisi, Maria Teresa Attanzio, Valeria Cigna, Domenica Caramazza, Lucio Lo Coco, Glauco Milio, Guido Bajardi U.O. di Ematologia con Trapianto, Dipartimento di Oncologia, Policlinico Universitario di Palermo, Palermo, Italy; U.O. di Chirurgia Vascolare, Policlinico Universitario di Palermo, Palermo, Italy

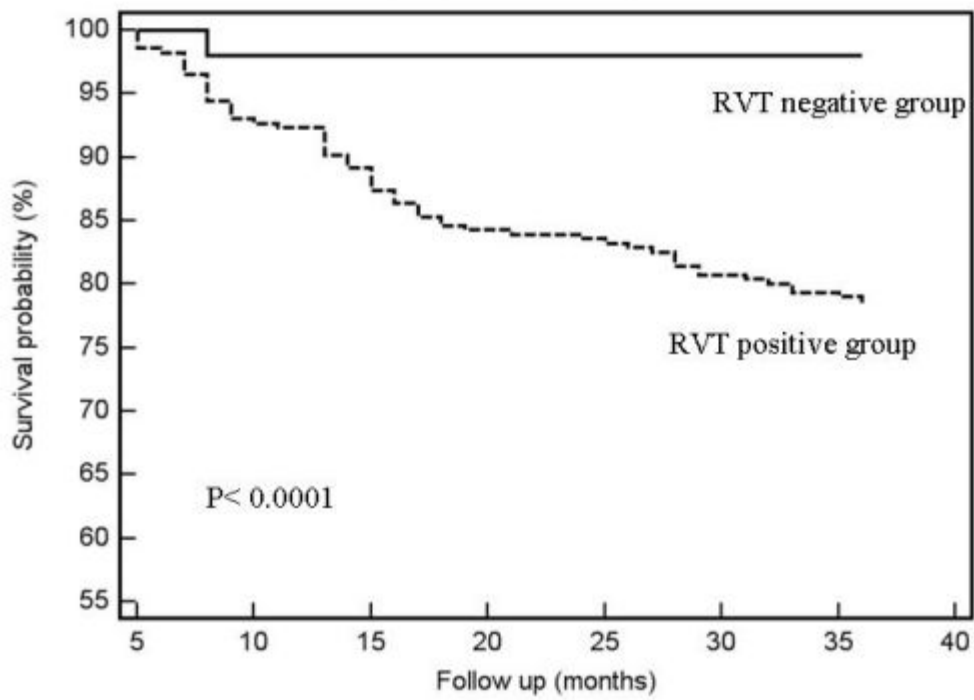
Background. The optimal duration of Oral Anticoagulant Therapy (OAT) for Deep Vein Thrombosis (DVT) can be tailored by Residual Vein Thrombosis (RVT) (Siragusa S et al. Blood 2003;102(11):OC183), a marker able to assess the individual risk for recurrent thrombosis. However, in patients with idiopathic DVT the safety of early interruption of OAT, because of absence of RVT, is still debated. Objective of the study. In the present study, we evaluated the safety of withholding OAT, in patients with idiopathic DVT and without RVT, three months after the index thrombotic episode. Study design. Prospective controlled study with two groups: patients without RVT stopped OAT after 3 months while those with RVT continued for additional 3 months. Materials and Methods. Consecutive patients with a first episode of idiopathic DVT of the lower limbs; patients with cancer or known thrombophilia were excluded. At the third months of OAT, RVT was assessed as previously described; briefly, RVT was considered absent when a clot occupying less than 40% of the vein lumen was detected by compression ultrasonography. Events, classified as recurrent DVT and/or Pulmonary Embolism (PE) and/or major and minor bleeding were evaluated; all patients were followed-up for at least 12 months after OAT discontinuation. Results. During the period 1999-2006, 518 patients were included in the study. In 206 (39.7%) RVT was considered absent (RVT negative group) and they stopped OAT; the remaining 312 patients continued anticoagulants for additional 3 months (RVT positive group). Total duration of follow-up (FU) was 184.7 years for RVT negative group (with a mean FU of 3.0 ± 0.83 years) and 191.3 years for RVT positive group (with a mean FU of 3.1 ± 0.89 years). The rate and type of events during FU is reported in table and figure. Conclusions. This investigation shows that in patients without RVT, three months of OAT are safe even after an episode of idiopathic DVT. This hold for at least 30% of the entire DVT population and has an important clinical impact; in fact, it is possible to select a group of patients with a very low risk for recurrences over a period of 3 years. This approach carries also a negligible risk for bleeding.

Events between RVT Negative and Positive Groups

Outcomes	RVT Neg. group (206)	RVT Pos. group (312)	"p" value
Recurrences, n/total (%)*	2/206 (0.9)	63/312 (20.2)	<0.0005
Recurrences, n/100 person-year (%)*	2/184.7 (1.1)	63/191.3 (32.9)	<0.0005
Type of recurrent VTE			
DVT	1	43	
DVT + PE	0	6	
Isolated PE	0	3	
Controlateral	1	11	
Major bleeding, n/total (%)**	0/206	3/312 (0.9)	
Major bleeding, n/100 person-Yr (%)**	0/184.7	3/191.3 (1.5)	

*After OAT discontinuation, **During OAT

Recurrent thrombotic events



Abstract #301 appears in Blood, Volume 110, issue 11, November 16, 2007

Keywords: Oral Anticoagulant|Thromboembolism|Recurrence

Monday, December 10, 2007 11:00 AM

Session Info: Simultaneous Session: Antithrombotic Therapy: Management of Anticoagulation (11:00 a.m.-12:30 p.m.)