Randomized, Placebo-Controlled Trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients

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Venous thromboembolism is a major cause of morbidity and mortality[1–6] in hospitalized patients, including those with acute medical illnesses.[7,8] Approximately 75% of venous thromboemboli occur among these acutely ill nonsurgical patients. Nevertheless, thromboprophylaxis use in medical patients is not universally accepted or adopted, even though medical patients are at risk for venous thromboembolism.[9–12] Additionally, even when prophylaxis is used, it may be inadequate to prevent venous thromboembolism.[13,14] Current guidelines for the prevention of venous thromboembolism in medical patients are based mostly on a reduction in asymptomatic isolated calf vein thrombosis detected by venography.[15] This has resulted in inconsistent recommendations and variable interpretation and application of guidelines.[16,17] Thus, there was a need for a further placebo-controlled study to examine the effect of thromboprophylaxis on clinically relevant end points using compression ultrasonography to screen all patients at a suitably early time point. The Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilized Patients Trial (PREVENT) was designed to examine the efficacy and safety of the low-molecular-weight heparin dalteparin in the prevention of clinically important venous thromboembolic events in medical patients.

Methods

PREVENT was a randomized, double-blind, placebo-controlled, multicenter, multinational trial. The study methodology has been described previously in detail.[18]

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In memory of Amiram Eldor, Tel-Aviv, Israel.

*A complete list of the PREVENT Study Investigators appears in the Appendix.

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TABLE 1. Patient Randomization and Evalulation

	Dalteparin, n (%)	Placebo, n (%)
Randomized	1856 (100)	1850 (100)
Patients receiving ≥1 dose of study drug	1848 (99.6)	1833 (99.1)
Patients included in primary analysis	1518 (81.7)	1473 (79.7)
Patients not included in primary analysis		
Compression ultrasonography not evaluable	155 (8.4)	172 (9.4)
Compression ultrasonography not performed (death, adverse events, protocol violation, protocol-specific withdrawal criteria, consent withdrawn, lost to follow-up)	175 (9.5)	188 (10.3)
Patients evaluable for venous thromboembolism at day 90	1615 (87.0)	1583 (85.6)

Study Population

Patients were considered for inclusion if they were ≥40 years of age with an acute medical condition requiring a projected hospitalization of ≥4 days and had ≤3 days of prior immobilization.

Inclusion criteria were acute congestive heart failure, acute respiratory failure that did not require ventilatory support, infection without septic shock, acute rheumatologic disorders, or inflammatory bowel disease. Except for congestive heart or acute respiratory failure, patients had to have ≥1 additional risk factors for venous thromboembolism: age ≥75 years, cancer, previous venous thromboembolism, obesity, varicose veins and/or chronic venous insufficiency, hormone replacement therapy, history of chronic heart failure, chronic respiratory failure, or myeloproliferative syndrome.

Patients were ineligible if they had acute coronary syndrome within the previous month, a major surgical or invasive procedure performed in the previous month or to be undertaken within the next 2 weeks, bacterial endocarditis, immobilized lower limb because of a cast or fracture, stroke within 3 months, high risk of bleeding, a platelet count $<100\times10^9$/L, heparin or low-molecular-weight heparin prophylaxis given for >48 hours before randomization, contraindication to heparin anticoagulation, creatinine >2.0 mg/dL, hepatic insufficiency or active hepatitis, pregnancy or breastfeeding, or life expectancy of <1 month.

Study Design

Eligible patients were randomized to receive once-daily subcutaneous injections of either 5000 IU dalteparin sodium (Fragmin, Pharmacia Corp) or placebo for 14 days. If the patient was discharged before day 14, study medication was continued out of hospital.

Patients were evaluated for signs and symptoms of venous thromboembolism daily during hospitalization, on the last day of treatment, on day 21, and on day 90. Prophylaxis was discontinued if venous thromboembolism requiring treatment was objectively confirmed, in the event of suspected or verified heparin-induced thrombocytopenia, at the discretion of the investigator, or at the patient's request. Patients' physicians managed documented venous thromboembolism in accordance with their established practices.

The study was conducted in accordance with the Declaration of Helsinki and local regulations. Written informed consent was obtained from all patients, and independent ethics committees approved the protocol.

End Points

The primary efficacy end point was the incidence of venous thromboembolism by day 21, a composite of objectively confirmed symptomatic deep vein thrombosis (proximal or distal), fatal or symptomatic nonfatal pulmonary embolism, sudden death (unexpected death within 24 hours of onset of symptoms), and asymptomatic proximal deep vein thrombosis detected by systematic compression ultrasound at day 21.

TABLE 2. Patient Characteristics at Baseline*

	Dalteparin (n=1848)	Placebo (n=1833)
Age, mean (SD), y	68.5 (11.1)	68.5 (11.7)
Sex, n (%)		
Male	884 (47.8)	888 (48.4)
Female	964 (52.2)	945 (51.6)
BMI, mean (SD), kg/m^2	27.4 (5.9)	27.5 (6.0)
Primary diagnosis, n (%)		
Acute congestive heart failure (NYHA class III or IV)	965 (52.2)	940 (51.3)
Acute respiratory failure	561 (30.4)	560 (30.6)
Other acute conditions	749 (40.5)	781 (42.6)
Infectious disease	673 (36.4)	687 (37.5)
Rheumatologic disorder	200 (10.8)	198 (10.8)
Inflammatory bowel disease	10 (0.5)	8 (0.4)
Risk factors, n (%)		
Age ≥75 y	611 (33.1)	615 (33.6)
Cancer	85 (4.6)	105 (5.7)
Previous deep vein thrombosis or pulmonary embolism	62 (3.4)	80 (4.4)
Obesity	558 (30.2)	560 (30.6)
Varicose veins	487 (26.4)	530 (28.9)
Hormone therapy	33 (1.8)	30 (1.6)
Chronic heart failure	925 (50.1)	946 (51.6)
Myeloproliferative syndrome	5 (0.3)	9 (0.5)
Chronic respiratory failure	176 (9.5)	183 (10.0)

BMI indicates body mass index.
*Patients could have >1 reason for inclusion.

Secondary end points were all-cause mortality by days 14, 21, and 90; objectively verified symptomatic deep vein thrombosis or asymptomatic proximal deep vein thrombosis at day 21; major and minor bleeding, drug-related allergic reactions, and thrombocytopenia by day 21; and symptomatic venous thromboembolism at day 90. Bleeding and thrombocytopenia were assessed at days 21 and 14 to capture events that might have been occult during the treatment period and whose recognition may have been delayed.

Symptomatic venous thromboembolism required confirmation by objective imaging[18] or autopsy. Patients who did not have a confirmed symptomatic venous thromboembolism underwent compression ultrasonography between days 21 and 24. All examinations were videotaped and sent to a central reading facility.

Safety outcomes included death, hemorrhage, thrombocytopenia, and all suspected drug-related adverse reactions.

Bleeding was classified as major if it was intraocular, spinal/epidural, intracranial, or retroperitoneal; if hemoglobin decreased by ≥2 g/dL; if transfusion of ≥2 U of blood or significant medical or surgical intervention was required; or if it resulted in death. All other bleeding was classified as minor.

All clinical end points were centrally adjudicated by a blinded Clinical Events Committee.

Statistical Analysis

Assuming an incidence of clinically relevant venous thromboembolism and sudden death at day 21 of 8% in the placebo group[19] and hypothesizing a 50% reduction in the dalteparin group, 1471 patients were needed in each treatment group for 90% power to detect a difference at $\alpha=0.001$. To compensate for nonevaluable patients, we planned to enroll 1650 patients per treatment group. The primary analysis was based on the adjudicated events.

TABLE 3. Venous Thromboembolic Events

	Dalteparin, n/N (%)	Placebo, n/N (%)	RR (95% CI)
Primary end point (day 21)			
Venous thromboembolism and sudden death	42/1518 (2.77)	73/1473 (4.96)	0.55 (0.38–0.80)
Sudden death	5/1829 (0.27)	3/1807 (0.17)	1.65 (···)
Pulmonary embolism, fatal	0/1829 (0.00)	2/1807 (0.11)	0.00 (···)
Pulmonary embolism, symptomatic	5/1759 (0.28)	4/1740 (0.23)	1.22 (···)
Deep vein thrombosis: distal, symptomatic	3/1759 (0.17)	4/1739 (0.23)	0.74 (···)
Deep vein thrombosis: proximal, symptomatic	2/1759 (0.11)	7/1739 (0.40)	0.28 (···)
Deep vein thrombosis: proximal, asymptomatic	27/1507 (1.79)	53/1453 (3.65)	0.48 (0.31–0.77)
Secondary end point at day 14			
All-cause mortality	8/1846 (0.43)	7/1831 (0.38)	1.13 (0.41–3.12)
Secondary end point at day 21			
Deep vein thrombosis: proximal and symptomatic distal	32/1508 (2.12)	64/1464 (4.37)	0.49 (0.32–0.74)
All-cause mortality	43/1829 (2.35)	42/1807 (2.32)	1.01 (0.66–1.54)
Secondary endpoint at day 90			
Symptomatic venous thromboembolism (all deep vein thrombosis and pulmonary embolism)	15/1615 (0.93)	21/1583 (1.33)	0.70 (0.36–1.35)
All symptomatic pulmonary embolism	5/1615 (0.31)	6/1583 (0.38)	0.82 (0.25–2.67)
All symptomatic deep vein thrombosis	10/1614 (0.62)	15/1579 (0.95)	0.65 (0.29–1.45)
All-cause mortality	107/1747 (6.12)	103/1715 (6.01)	1.02 (0.78–1.33)

RR indicates relative risk. Only 1 event per patient (most severe) was recorded.
95% CIs were not produced if <5 patients in either treatment group experienced an event.

The primary end point was analyzed on the intention-to-treat population with observed cases using a Cochran-Mantel-Haenszel test[20] stratified by geographic region. The Breslow-Day test was used to test for homogeneity of strata.[21] Randomized patients who had a documented clinical end point or an evaluable compression ultrasonography examination by day 21 were included in the primary end-point analysis. However, the entire enrolled cohort was eligible for evaluation of symptomatic secondary end points. Patients who received ≥1 dose of study drug were included in the safety analysis. An independent data-monitoring committee performed periodic safety reviews.

Results

Study Population

Between July 2001 and April 2002, 3706 patients were enrolled at 219 study centers in 26 countries. Eight patients randomized in the dalteparin group and 17 in the placebo group did not receive study medication. Patients were also excluded from the primary end-point analysis if the compression ultrasound examination at day 21 was either not evaluable (155 and 172 patients in the dalteparin and placebo groups, respectively) or not performed (175 and 188 patients in the dalteparin and placebo groups, respectively). Thus, 1518 and 1473 patients in the dalteparin and placebo groups, respectively, were assessed for the primary end point (Table 1). The mean number of injections was 12.6 in both patient groups, indicating a high degree of compliance with the intended regimen.

Patient Characteristics

Baseline characteristics were similar in both groups (Table 2). One third of patients were ≥75 years of age. Patients were discharged from hospital at a median of 13 days after randomization in both groups. The median duration of treatment of 14 days did not differ between groups.

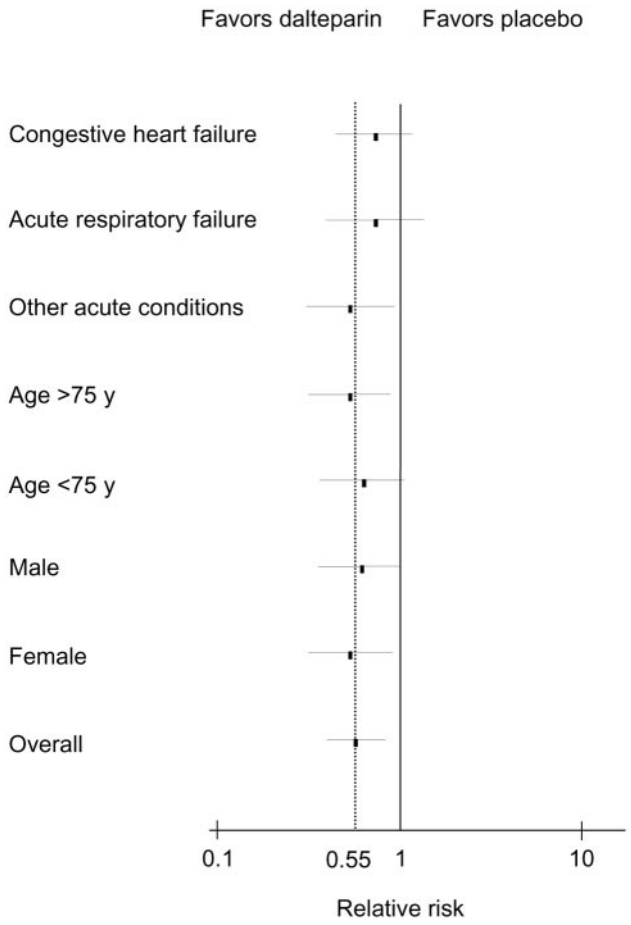
Thromboembolic Events

The incidence of the primary end point was 2.77% (42 of 1518 patients) in the dalteparin group and 4.96% (73 of 1473 patients) in the placebo group, a risk reduction of 45% (relative risk, 0.55; 95% CI, 0.38 to 0.80; $P=0.0015$; Table 3).

Two placebo and no dalteparin patients had fatal pulmonary embolism by day 21 (Table 3). The incidence of proximal deep vein thrombosis by day 21 was lower among patients receiving dalteparin than in those receiving placebo (29 versus 60 patients; Table 3). Sudden death by day 21 occurred in 5 patients randomized to dalteparin and in 3 randomized to placebo (Table 3).

By day 90, the incidence of symptomatic venous thromboembolism was 0.93% in the dalteparin group and 1.33% in the placebo group, a relative risk reduction of 30% (relative risk, 0.70; 95% CI, 0.36 to 1.35; Table 3).

Dalteparin reduced the rate of venous thromboembolism in all major subgroups (the Figure).



Effect of dalteparin on prevention of venous thromboembolism in major patient subgroups, presented as relative risk (logarithmic axis) and 95% CI.

Safety Outcomes

There was no significant difference in mortality at 14, 21, or 90 days (Table 4). By day 90, 210 patients had died, 107 (6.12%) in the dalteparin group and 103 (6.01%) in the placebo group. By day 21, major bleeding had occurred in 12 patients, 9 (0.49%) receiving dalteparin and 3 (0.16%) receiving placebo ($P=0.15$; Fisher's exact test; Table 4). Two patients in the dalteparin group and 1 in the placebo group died of hemorrhage. The proportion of patients reporting ≥1 adverse events was similar in both treatment groups (39.7% and 39.8% in the dalteparin and placebo groups, respectively).

TABLE 4. Adverse Events (Safety Population)

	Dalteparin, n (%)	Placebo, n (%)
Mortality		
Day 14	8 (0.43)	7 (0.38)
Day 21	43 (2.35)	42 (2.32)
Day 90	107 (6.12)	103 (6.01)
Hemorrhage		
Fatal, day 21	2 (0.11)	1 (0.05)
Major, day 14	8 (0.43)	0 (0.00)
Major, day 21	9 (0.49)	3 (0.16)
Minor, day 14	16 (0.87)	5 (0.27)
Minor, day 21	19 (1.03)	10 (0.55)
Thrombocytopenia		
Day 14	10 (0.54)	6 (0.33)
Day 21	10 (0.54)	8 (0.44)

Discussion

Thromboprophylaxis with dalteparin resulted in a 45% reduction ($P=0.0015$) in the primary end point, a composite of venous thromboembolism and sudden death at day 21. Overall, thromboprophylaxis with dalteparin for 14 days resulted in the prevention of 22 events per 1000 patients treated. This benefit was observed in a broad population of medical patients and was achieved with a low risk of major bleeding.

This study provides added evidence of the benefits of thromboprophylaxis with low-molecular-weight heparin in medical patients.[19,22] MEDENOX showed a reduction in asymptomatic venous thrombosis, driven largely by venographically detected distal vein thromboses.[19] However, the clinical relevance of distal deep vein thrombosis is uncertain. Thromboprophylactic studies performed in patients undergoing surgery have established that low-molecular-weight heparins reduce asymptomatic deep vein thrombosis and pulmonary embolism.[15] In contrast, available evidence for implementing routine prophylaxis of venous thromboembolism in acutely ill medical patients is sparse, and this strategy has not been universally accepted.[10,13] Both symptomatic proximal or calf deep vein thrombosis and asymptomatic proximal deep vein thrombosis are widely accepted as clinically relevant.[23,24] Symptomatic and asymptomatic proximal deep vein thromboses are closely linked to the risk of pulmonary embolism.[25,26]

The population enrolled in PREVENT was a lower-risk population than that reported in MEDENOX in terms of venous thromboembolism and mortality. In MEDENOX, the overall rate of venous thromboembolism was attributed mostly to asymptomatic distal deep vein thrombi, an end point not included in PREVENT because of its uncertain clinical relevance. If we limit the comparison to examining similar events, the overall risk in PREVENT was still somewhat lower than in MEDENOX. Proximal deep vein thrombosis occurred in 4.9% of MEDENOX placebo patients and 3.7% of PREVENT placebo patients. The overall mortality at 90 days was 13.9% in MEDENOX placebo patients and 6.01% in PREVENT placebo patients. Whereas MEDENOX established that a low-molecular-weight heparin may be beneficial in a higher-risk medical population, PREVENT has extended this observation to a lower-risk population and therefore should encourage more widespread application of thromboprophylaxis in an even broader medical population.

This study differs from previous studies of thromboprophylaxis in medical patients in that compression ultrasonography was used to assess efficacy. Compression ultrasonography was used as the diagnostic technique because this noninvasive approach has in many countries almost completely supplanted contrast venography in clinical practice.

Central adjudication of videotaped results limited the impact of interinvestigator differences.

We found no difference between treatment groups in total mortality, but the study was not designed or powered to show a mortality difference. This is in agreement with previous similar studies, which did not establish a significant effect of low-molecular-weight heparins on total mortality. Most deaths were due to underlying medical conditions, and the causes of death were similar in both groups.

In summary, this large, randomized controlled trial of thromboprophylaxis in medically ill patients showed that dalteparin 5000 IU daily reduced clinically important venous thromboembolism with a low risk of bleeding. This benefit was seen in medical patients with identifiable risk factors for venous thromboembolism. These findings should encourage routine thromboprophylaxis of medically ill patients who are hospitalized for ≥4 days and lower the incidence of venous thromboembolism in this large group of patients, resulting in improved clinical outcomes.

Appendix

PREVENT Study Investigators

Steering Committee: A. Leizorovicz (chairman), S.Z. Goldhaber (cochairman), A.T. Cohen, A. Eldor, C.-G. Olsson, A.G. Turpie. Clinical Endpoint Committee: J. Weitz (chairman), R. Becker, M. Gent, J. Ginsburg, J. Heit. Core Laboratory Site for Ultrasound: A. Leizorovicz (administrative director), Z. Akkal, M. Alves, F. Becker (scientific director), H. Boulet, B. Fevrier, A. Junod, C. Noize-Pin, N. Visele. Independent Data-Monitoring Committee: B. Davidson (chairman), T. Fleming, M.M. Samama. Principal Investigators: Argentina (177 patients, 10 centers): M. Amuchastegui, A. Caccavo, H. Colombo, A. Liprandi, J.G. Lopez, A. Marinesco, O. Moisés, S. Notta, D.H. Torres; Australia (29 patients, 3 centers): D. Colquhourn, J. Karrasch, B. Singh; Bulgaria (443 patients, 13 centers): A. Djurdjev, D. Guenova, K. Kostov, R. Marinov, P Milkov, D. Raev, N. Runev, P. Solakov, V. Stoyanovsky, G. Todorov, C. Tsekov, M. Tzekova, S. Yancheva; Canada (22 patients, 5 centers): R. Colwill, K. Gowda, J. Kassis, P. Ma, M. Weigel; Chile (138 patients, 6 centers): G. Arenas, L. Manríquez, R. Maturana, V. Muñoz, L. Núñez, A. Sierralta; Croatia (74 patients, 5 centers): I. Francetic, B. Jaksic, A. Knezevic, Z. Rumboldt, V. Vlahovic; Czech Republic (335 patients, 20 centers): L. Ballek, J. Bruthans, V. Cepelak, M. Choura, J. Drazka, T. Janaskova, V. Jirka, J. Kabrt, K. Klenha, J. Malik, O. Mayer, J. Musil, I. Oliva, P. Reiterer, J. Roubec, M. Soucek, P. Stverak, P. Svitil, M. Vitovec, J. Zajic; Denmark (31 patients, 6 centers): S. Husted, M.R. Lassen, J.E. Poulsen, S.L. Rasmussen, E. Sebelin, J.E. Sonne; Estonia (204 patients, 8 centers): A. Arro, J. Eha, T. Laks, M. Lember, S. Meriste, E. Mesimaa, T. Peets, M. Viigimaa; France (42 patients, 5 centers): J.-F. Bergmann, C. Conri, P. Jacqueme, B. Lorcerie, D. Mottier; Israel (111 patients, 12 centers): B. Brenner, D. Ezra, J. Jarchowsky, M. Lahav, M. Lishner, A. Livneh, G. Lugassy, M. Mittelman, E. Naparstek, M. Rapoport, Z. Sthoeger, J.R. Viskoper, A. Weinberger; Italy (74 patients, 8 centers): M. Berrettini, M. Carnovali, D. Imberti, A. Pagnan, G.B. Ponti, R. Quintavalla, M. Silingardi, D. Sommariva; Latvia (75 patients, 5 centers): D. Andersone, E. Gailiss, I. Smiltena, J. Verbovenko, I. Zakke; Lebanon (11 patients, 1 center): E. Salameh; Lithuania (131 patients, 7 centers): L. Grigoniene, G. Gumbrevicius, R. Jurgutis, A. Laucevicius, M. Palaikis, G. Varoneckas, R. Zaliunas; Mexico (105 patients, 6 centers): C. Garcia, M. Guadalupe Castro, H. Hernandez, A. Herrera, C. Rivera, F. Velasco; Peru (84 patients, 2 centers): R. Cotrina, V. Ulloa; Poland (263 patients, 16 centers): A. Bodzenta-Lukaszyk, H. Lewandowska, M. Madalinski, J. Malolepszy, R. Matusiewicz, P. Miekus, M. Olszewski, M. Pasowicz, M. Piepiorka, K. Pilarska, M. Regulski, R. Sciborski, I. Tyszkiewicz, W. Waldman, K. Wlodarczyk, K. Wrabec; Romania (257 patients, 16 centers): E. Apetrei, O. Bajenaru, D. Bartos, R. Capalneanu, E. Carasca, M. Cinteza, G.A. Dan, M.D. Datcu, S.I. Dragulescu, C. Georgescu, D. Iordachescu, C.E. Macarie, A.S. Nica, C. Olariu, N.C. Olinic, C.J. Sinescu; Russian Federation (367 patients, 14 centers): D. Andeev, G. Arutyunov, S. Fitilev, I. Fomina, M Glezer, V. Mareev, V. Moiseev, E. Pantchenko, E. Semernin, E. Shlyakhto, B. Sidorenko, A. Smirnov, L. Sokolova, A. Stroutynski, K. Tebloev; South Africa (96 patients, 16 centers): M.S. Abdool-Gaffar, T.I. Branken, D.J. Du Toit, J.H. Jansen van Rensburg, O.T. Jannasch, D. Kelbe, G.J. Klopper, A. Lubbe, F.J. Maritz, D.P. Myburgh, M. Prins, H. Prinsloo, R.S. Siebert, G.J.J. Smit, J.J. Viljoen, N.C. Wright; Sweden (42 patients, 8 centers): H. Eriksson, J. Grubbström, L. Johansson, C-G Olsson, C. Paul, B. Persson, S. Schulman, T. Strand; Tunisia (59 patients, 9 centers): H. Ammar, A. Belhani, A. Ben Khalfallah, E. Boughzela, M. Boujnah, H. Haouala, A. Jaafari, M. Kafsi, L. Slimane; Turkey (54 patients, 4 centers): N. Eskiyurt, A. Karan, O. Kayhan, A. Oktay; United Kingdom (445 patients, 5 centers): D. Bevan, A.T. Cohen, J.J. Gardner, A. Moriarty, M. Welfare; United States (37 patients, 8 centers): D. Amin, D. Bloomfield, D. Buffington, L.M.D. Gilbert, F. Lenz, M. Rumbak, J. Southard, L. Wesselius.

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Disclosure

Dr Leizorovicz was a consultant for Pharmacia Corporation, Aventis, Sanofi-Synthelabo, and AstraZeneca. Dr Cohen was a consultant for Pharmacia Corporation, Aventis, Sanofi-Synthelabo, AstraZeneca, and Organon and was a paid investigator for this study. Dr Turpie was a consultant for Pharmacia Corporation, Aventis, Sanofi-Synthelabo, AstraZeneca, and Organon. Dr Olsson was a consultant for Pharmacia Corporation, AstraZeneca, and Leo Pharma. Dr Vaitkus was an employee of Pharmacia Corporation. Dr Goldhaber was a consultant for Pharmacia Corporation and Aventis.

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Randomized, Placebo-Controlled Trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients

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