OPEN

Sulodexide for the Prevention of Recurrent Venous Thromboembolism

The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

Giuseppe M. Andreozzi, MD; Angelo A. Bignamini, PhD; Giovanni Davì, MD; Gualtiero Palareti, MD; Jiří Matuška, MD; Martin Holý, MD; Katarzyna Pawlaczyk-Gabriel, MD; Andrej Džupina, MD; German Y. Sokurenko, MD; Yury P. Didenko, MD; Laurentia D. Andrei, MD; Gianfranco Lessiani, MD; Adriana Visonà, MD; on behalf of the SURVET Study Investigators*

Background—Patients with a first episode of unprovoked venous thromboembolism have a high risk of recurrence after discontinuation of anticoagulant therapy. Extending anticoagulation reduces the risk of recurrence but is associated with increased bleeding. Sulodexide, a glycosaminoglycan, exerts antithrombotic and profibrinolytic actions with a low bleeding risk when administered orally, but its benefit for preventing recurrent venous thromboembolism is not well known.

Methods and Results—In this multicenter, double-blind study, 615 patients with first-ever unprovoked venous thromboembolism who had completed 3 to 12 months of oral anticoagulant treatment were randomly assigned to sulodexide 500 lipasemic units twice daily or placebo for 2 years, in addition to elastic stockings. The primary efficacy outcome was recurrence of venous thromboembolism. Major or clinically relevant bleeding was the primary safety outcome. Venous thromboembolism recurred in 15 of the 307 patients who received sulodexide and in 30 of the 308 patients who received placebo (hazard ratio, 0.49; 95% confidence interval [CI], 0.27–0.92; *P*=0.02). The analysis in which lost to follow-up was assigned to failure yielded a risk ratio among treated versus control subjects of 0.54 (95% confidence interval, 0.35–0.85; *P*=0.009). No major bleeding episodes occurred; 2 patients in each treatment group had a clinically relevant bleeding episode. Adverse events were similar in the 2 groups.

Conclusion—Sulodexide given after discontinuation of anticoagulant treatment reduced the risk of recurrence in patients with unprovoked venous thromboembolism, with no apparent increase of bleeding risk.

Clinical Trial Registration—URL: https://www.clinicaltrialsregister.eu/. Identifier: EudraCT number 2009-016923-77.

(*Circulation*. 2015;132:1891-1897. DOI: 10.1161/CIRCULATIONAHA.115.016930.)

Key Words: glycosaminoglycans ■ randomized controlled trial ■ recurrence ■ venous thromboembolism

The risk of recurrence of venous thromboembolism (VTE) persists for many years after anticoagulant treatment is withdrawn[1] and is particularly high among patients with unprovoked VTE.[2] About 20% of patients have a recurrence within 2 years after discontinuation of treatment with a vitamin K antagonist (VKA).[3–6] Extending the treatment with VKA reduces the risk of recurrence but increases the risk of

Editorial see p 1856
Clinical Perspective on p 1897

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received April 9, 2015; accepted August 28, 2015.

From Angiology Unit, University Hospital, Padua, Italy (G.M.A.); School of Specialization in Hospital Pharmacy, Department of Pharmaceutical Sciences, University of Milan, Italy (A.A.B.); Department of Medicine and Aging, "G. D'Annunzio" University, Chieti, Italy (G.D., G.L.); Cardiovascular Diseases, University of Bologna, Italy (G.P.); Angiologická Ambulance, Hodonín, Czech Republic (J.M.); Nemocnice České Budějovice–Interní Oddělení, České Budějovice, Czech Republic (M.H.); Department of Hypertensiology, Angiology and Internal Diseases, Medical University, Poznań, Poland (K.P.-G.); ALIAN s.r.o., Bardejov, Slovakia (A.D.); Federal State Institute, Nikiforov Russian Center of Emergency and Radiation Medicine, St. Petersburg, Russia (G.Y.S.); St. Petersburg State Medical Institution, City Multidisciplinary Hospital No. 2, Russia (Y.P.D.); Spitalul Clinic Judetean de Urgenta, Braşov, Romania (L.D.A.); and Angiology Unit, Hospital of Castelfranco Veneto, Italy (A.V.).

*A complete list of the SURVET Study Investigators can be found in the online-only Data Supplement.

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.115.016930/-/DC1.

Correspondence to Giuseppe M. Andreozzi, MD, University Hospital of Padua, Angiology Unit, Via Siracusa 7 - 35142 Padova, Italy. E-mail gm.andreozzi@gmail.com

bleeding, as well as the inconvenience and costs of laboratory monitoring and dose adjustments.[7,8] The effects of the newer non-VKA oral anticoagulants for therapy of acute VTE events[9–12] and for extended treatment to avoid recurrences[13,14] have recently been investigated by a number of clinical trials that, as a whole, showed an efficacy noninferior to VKA and rates of bleeding in general inferior to VKA, especially for extended treatment.

Sulodexide is a natural glycosaminoglycan with antithrombotic and profibrinolytic activities[15] that can be administered orally or parenterally and affects the normal hemostasis to a lower extent than heparin with a very low risk of bleeding. Several clinical studies proved that prolonged sulodexide administration was associated with no or negligible risk of bleeding,[16–18] as also highlighted in a recent review.[19] Sulodexide exerts its actions through complexation with antithrombin and heparin cofactor II and the attending inhibition of some factors of the coagulation cascade.[20–22] It also exerts favorable effects on endothelial dysfunction, release of cytokines and chemokines, and metalloprotease-9 secretion from white blood cells.[23,24]

The pharmacological and clinical profiles suggest that oral sulodexide may have a role in the prevention of recurrent VTE when classic anticoagulation is discontinued. Indeed, recent clinical studies proved a positive effect of oral sulodexide administration in reducing the risk of recurrence compared with either anticoagulation with acenocoumarol[25] or standard of care after withdrawal of VKA treatment.[18] The aim of this randomized, double-blind, controlled trial (Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis [SURVET]) was to verify the efficacy and safety of sulodexide in the prevention of recurrent VTE after the end of the VKA treatment in patients with a first-ever unprovoked VTE.

Methods

Patients

We recruited patients of ≥18 years of age with a documented first-ever unprovoked proximal deep vein thrombosis or pulmonary embolism treated with VKA for 3 to 12 months. VTE was considered unprovoked when it occurred in the absence of any known risk factor for this event. We excluded patients with persistent pulmonary hypertension after pulmonary embolism, those with solid neoplasm or blood disease, those with anti-phospholipid antibody syndrome or antithrombin congenital deficit, patients with New York Heart Association class III to IV cardiorespiratory failure, and patients with known hypersensitivity to glycosaminoglycans. Fertile women were enrolled if not lactating if their pregnancy test at screening was negative and they were willing to use contraception (except oral contraceptives) throughout the study period. Each subject was enrolled only after having issued the written informed consent to participate to the study.

Study Design and Intervention

SURVET was a multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled clinical trial. Eligible patients were allocated to treatment for 2 years with oral sulodexide (2×250–lipasemic unit capsules twice daily) or matching placebo in a 1:1 ratio based on a computer-generated randomization list in blocks of 4 produced by an independent operating unit. This same unit also packaged drug and matching placebo in identical-looking treatment units, 1 for each randomized patient, identified exclusively by the randomization number. Patients, recruiting physicians, physicians or pharmacists delivering the treatments units, physicians or technicians assessing the outcome, and Steering Committee members were blinded to the intervention and to the block size until the end of the statistical analysis. Each sequentially numbered treatment unit was accompanied by an opaque, sealed envelope that allowed unblinding of the individual patient treatment in case of need. Randomization occurred within 1 to 12 weeks after VKAs had been withdrawn, with the patient assigned to the treatment unit with the lowest number available at the relevant study center.

Outcome Measures

The central adjudication committee members who were unaware of the group assignments and who reviewed all the patients' raw data assessed all suspected study outcome events. The primary efficacy outcome was symptomatic, objectively confirmed recurrence of VTE, defined as the composite of deep vein thrombosis objectively confirmed by compression ultrasonography[26] and nonfatal or fatal pulmonary embolism objectively confirmed by computed tomography or lung scanning. Secondary efficacy outcomes included distal or superficial vein thrombosis and nonfatal or fatal myocardial infarction, stroke, or acute ischemia of the lower limbs.

The principal safety outcome was major or clinically relevant nonmajor bleeding. An overt bleeding event was defined as major if fatal, if it occurred in a critical location, or if it required a transfusion of ≥2 U whole blood or red cells. Clinically relevant nonmajor bleeding was defined as overt bleeding that did not meet the criteria for major bleeding but was associated with the need for medical intervention, contact with a physician, interruption of the study drug, or discomfort or impairment of activities of daily life.[27]

Surveillance and Follow-Up

The investigators, according to the study protocol, recommended to each participant the use of a class II elastic stocking after the diagnosis of proximal deep vein thrombosis. Their use was to be continued for 2 years. The investigators renewed this recommendation at each periodic visit. Patients were re-examined at the relevant clinical center every 3 months for 24 months after randomization. Patients were instructed to report to the study center if they had symptoms suggestive of VTE, other circulatory events, or bleeding complications for objective evaluation. Each patient was contacted by telephone every month between examinations. In case of symptoms suggesting that an end point occurred, the patient was invited to the center of reference for an unplanned interview. Symptoms and signs suggestive of adverse events (AEs) were also recorded. At month 24, we contacted by telephone all patients who prematurely interrupted or left the study without formally withdrawing consent so that we could monitor whether symptoms or signs suggestive of a vascular event had occurred.

Study Oversight

The members of the Steering Committee designed the study, registered in the EU Clinical Trials Register with the EudraCT number 2009-016923-77 (https://www.clinicaltrialsregister.eu/ctr-search/search?query=SURVET). Independent contract research organizations monitored the study and collected and maintained the data. The Department of Pharmaceutical Sciences of the University of Milan (Milan, Italy) analyzed the data. Each study center initiated the trial only after the local Ethics Committee or Institutional Review Board had approved the protocol. The study was performed in accordance with the protocol, with the Declaration of Helsinki, with Good Clinical Practice, and with local regulations.

The Steering Committee had final responsibility for verification and analyses of the data, wrote the manuscript, and vouches for the accuracy and completeness of the reported data. All authors contributed to the interpretation of the results, approved the final version of the manuscript, and made the decision to submit the manuscript for publication. The study was supported by Alfa Wassermann SpA (Via Ragazzi del 99, 5-Bologna, Italy), which supplied its commercially available capsules of sulodexide and manufactured the matching placebo. A separate, independent contract organization prepared the randomization list and the treatment units. Alfa Wassermann funded the

study but played no role in the design of the study, in data collection or analysis, or in manuscript preparation.

Statistical Analysis

Assuming an incidence of recurrent VTE with standard care of ≈17.5% in 2 years[3–7] and hypothesizing a 50% relative reduction by adding sulodexide,[18] we determined that a total of 620 patients (≈310 per group) had 90% power to show superiority of sulodexide over placebo at a 2-sided level of α=0.05.

The primary efficacy analysis, which considered all outcome events occurring from randomization to the end of treatment, was performed according to the intention-to-treat (ITT) principle and included all patients who had been randomized (except 2 blinded administrative exclusions). Hazard ratios, 95% confidence intervals (CIs), and *P* values were calculated with the Cox proportional hazards models and SPSS statistical software, version 17.0, with treatment as the only covariate. A Cox proportional hazards model analysis was also performed with adjustment for age (in decades), sex, type of index event (pulmonary embolism or deep vein thrombosis), country, dichotomized (<6/≥6 months) exposure to VKA, and dichotomized (<1/≥1 month) delay between the end of VKA treatment and randomization. An "all failures" efficacy analysis was performed in which all patients for whom no information on health status at 24 months was available were considered as having had an event (failure), the proportions of failures were compared by the Fisher exact probability test, and the incidence risk ratio and 95% CI were estimated with "epiR"[28] in R.[29] The outcome for patients lost to follow-up was also estimated by assigning the outcome of the nearest neighbor estimated by propensity score, computed from the same predictors as for the Cox regression except treatment. An additional sensitivity analysis was performed on the per-protocol population that included all patients of the ITT population who had the 24-month evaluation, had taken at least 75% of the planned study medication, and were exempt of major protocol violations as indicated by the study Steering Committee in a blind review. The safety analysis included all randomized patients.

Results

Patients and Study Treatment

Between September 2010 and May 2012, 629 patients were screened in 43 centers in 7 European countries. The follow-up was closed on May 2014. Twelve patients were screening failures; 617 were included in the safety population. Two patients were excluded from efficacy analysis because of administrative reasons: 1 was the sole individual recruited in 1 of the planned countries, and 1 entered twice in the trial at 2 different sites, and the first entry was excluded from efficacy analysis. A total of 308 patients received placebo and 307 received sulodexide for a median duration of 23.9 months. The blinded review by the study Steering Committee included 521 patients in the per-protocol analysis (Figure 1). The study drug was discontinued prematurely in 28 patients given sulodexide (9.1%) and in 29 patients given placebo (9.4%; Figure 1). There were no significant differences between groups in baseline characteristics of the patients (Table 1), except for exposure to VKA (slightly more sulodexide patients in the <6-month category; *P*=0.044).

Recurrent VTE

Recurrence of VTE occurred in 45 patients as a result of proximal deep vein thrombosis in 36 patients and pulmonary embolism in 9 patients (fatal in 1 patient).

The primary outcome, recurrence of VTE, occurred in 15 of the 307 patients who received sulodexide (4.9%; 95% CI, 2.9–8.1) compared with 30 of the 308 patients who received placebo (9.7%; 95% CI:, 6.8–13.7; hazard ratio, 0.49; 95% CI, 0.27–0.92; *P*=0.02; Figure 2A).

The analysis adjusted for age, sex, index event (pulmonary embolism or deep vein thrombosis), country, duration of exposure to VKA, and delay between the end of VKA treatment and randomization confirmed that sulodexide treatment reduced the risk of recurrence (adjusted hazard ratio, 0.45; 95% CI, 0.24–0.84; *P*=0.01; Figure 2B). Independent risk factors for recurrent VTE included age (hazard ratio, 1.33 per decade; 95% CI, 1.06–1.65; *P*=0.01) and male sex (hazard ratio, 2.45; 95% CI, 1.25–4.78; *P*=0.01). No association was found between recurrent VTE and length of exposure to VKA (hazard ratio, 0.79; 95% CI, 0.41–1.53; *P*=0.48), delay between the end of VKA treatment and randomization (hazard ratio, 0.71; 95% CI, 0.37–1.36; *P*=0.71), country (*P*=0.09), or index event (hazard ratio, 1.67; 95% CI, 0.63–4.44; *P*=0.30).

Under the "all failures" assumption, the proportion of failures among control subjects was 48 of 308 or 15.6% (95% CI, 11.7–20.1) and that among treated patients was 26 of 307 or 8.5% (95% CI, 5.6–12.2; *P*=0.009, Fisher test). The incidence risk ratio of failure among treated patients was 0.54 (95% CI, 0.35–0.85) versus control subjects. The results of the logistic analysis adjusted for the same confounders indicated for the Cox analysis are reported in the text and in Table I in the online-only Data Supplement.

Applying the nearest-neighbor outcome to the 29 patients lost to follow-up using the propensity score yielded a proportion of events of 30 of 308 (9.7%) among control subjects and 16 of 307 (5.2%) among treated subjects (*P*=0.045, Fisher test; incidence risk ratio, 0.54; 95% CI, 0.30–0.96).

In the per-protocol population, VTE recurred in 14 of the 263 patients who received sulodexide compared with 30 of the 258 patients who received placebo (hazard ratio, 0.45; 95% CI, 0.24–0.85; *P*=0.014). In addition, the results of the adjusted Cox analysis in the per-protocol population did not differ appreciably from those in the ITT population (data reported in the online-only Data Supplement). The different procedures used to estimate the outcome in the ITT population resulted in a number needed to treat ranging 15 to 24, with variable width of the CI. The number needed to treat estimated from the adjusted Cox regression was 24 (95% CI, 16–98; details given in the online-only Data Supplement).

We also performed an unplanned subgroup analysis of recurrence rates by major potentially prognostic subgroups that failed to indicate subgroups more or less likely to respond to treatment (details in the text and Figure I in the online-only Data Supplement).

Hemorrhagic Complications

There were no episodes of major bleeding. Clinically relevant, nonmajor bleeding occurred in 2 patients who received sulodexide (occasional nose bleeding in 1 patient, and 2 episodes of bleeding after evacuation in the other) and in 2 patients who received placebo (occasional events of rectal bleeding in 1 patient, and a dysfunctional uterine bleeding in the other). The hazard ratio for clinically relevant bleeding was 0.97 (95% CI, 0.14–6.88; *P*=0.98).

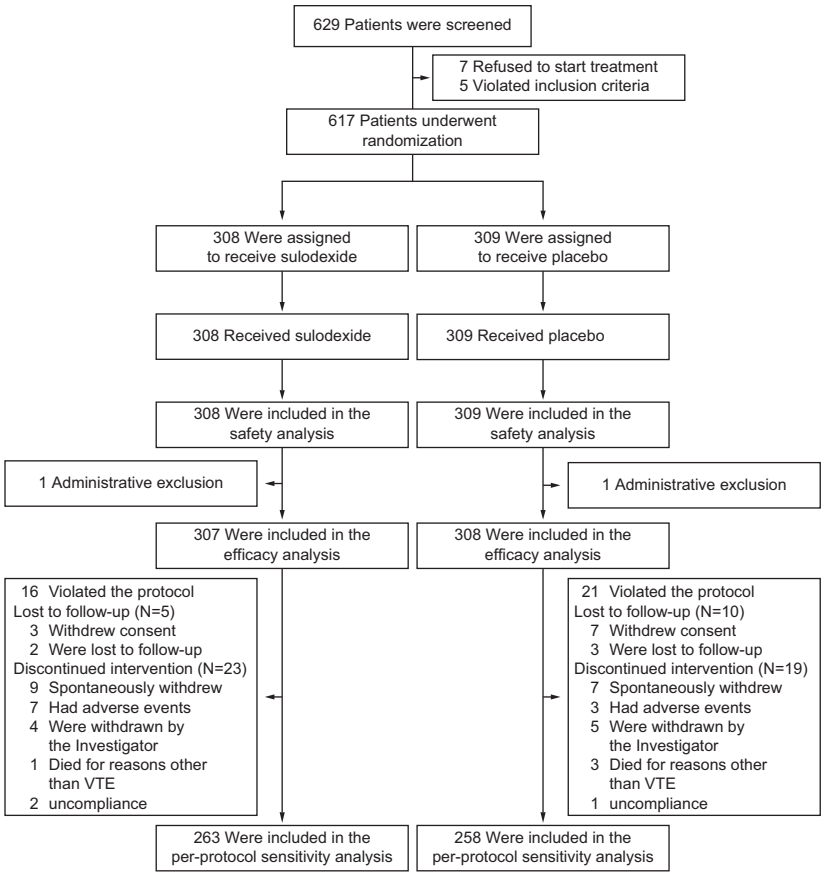


Figure 1. Enrollment and randomization. VTE indicates venous thromboembolism.

Secondary End Points

Individually, none of the protocol-defined secondary end points was frequent enough to warrant a separate analysis (details in the online-only Data Supplement). The total incidence of primary plus secondary vascular events was 43 of 308 (14.0%; 95% CI, 10.3–18.3) among control subjects and 22 of 307 (7.2%; 95% CI, 4.5–10.6) among treated subjects (P=0.008, Fisher test; Table 2). Death occurred in 1 patient in the sulodexide group (as a result of stroke) and 3 patients in the placebo group (1 as a result of lower-limb ischemia, and 2 resulting from acute coronary syndrome).

Safety End Points

We analyzed the AEs in the safety data set. The 309 control and 308 treated patients reported 397 and 368 treatment-emergent AEs, respectively. There was no significant difference in the number of patients with at least 1 AE (52.4% of control versus 48.7% of treated subjects), at least 1 serious AE (11.0% versus 8.1%), at least 1 AE causing discontinuation (13.6% versus 9.1%), at least 1 AE resulting in death (1.3% versus 0.3%), and at least 1 not definitely unrelated AE (12.9% versus 16.6%). The most frequent (>1% of patients) AEs, regardless of the potential correlation with treatment, are reported in Table II in the online-only Data Supplement.

Discussion

This study aimed at assessing whether a standard oral treatment with sulodexide after an anticoagulant regimen could, in addition to compression therapy, decrease the risk of recurrent deep vein thrombosis or pulmonary embolism over a period of 2 years.

The hazard ratio of qualifying events with sulodexide was 0.45 (95% CI, 0.24–0.84; *P*=0.01) after adjustment for age, sex, type of index event, country, exposure to VKA, and delay between the end of VKA treatment and randomization. Similar results were seen in the per-protocol population, in the "all failures" approach to the ITT population, and in the sensitivity analysis by propensity score in the ITT population.

The generalizability of these results appears sufficiently supported. The study included patients from different European countries with different healthcare systems without showing statistically significant heterogeneity.

The results of the SURVET study were similar to those of the trials performed with aspirin, the Warfarin and Aspirin (WARFASA) trial[30] and the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial,[31] which were published while the SURVET study was underway. The pooled ASPIRE-WARFASA hazard ratio for VTE was 0.68 (95% CI, 0.51–0.90)[31]; the unadjusted hazard ratio in SURVET was 0.49 (95% CI, 0.27–0.92). The pooled ASPIRE-WARFASA hazard ratio for major vascular events was 0.66 (95% CI, 0.51–0.86) and that in SURVET was 0.50 (95% CI, 0.30–0.83). Finally, the ASPIRE-WARFASA pooled hazard ratio for clinically relevant bleeding was 1.47 (95% CI, 0.70–3.08) and that in SURVET was 0.97 (95% CI: 0.14–6.88). The studies performed with the newer direct anticoagulants, similarly published while the SURVET study was in progress, reported high efficacy compared with placebo for preventing

Table 1. Demographic and Clinical Characteristics of the Patients According to Study Group

Characteristic	Sulodexide (n=307)	Placebo (n=308)
Age, mean±SD, y	55.7±14.1	55.9±14.4
Male sex, n (%)	175 (57)	155 (50)
White, n (%)	307 (100)	308 (100)
Country, n (%)		
Czech Republic	39 (13)	42 (14)
Italy	33 (11)	34 (11)
Poland	84 (27)	82 (27)
Romania	27 (9)	26 (8)
Russia	103 (33)	102 (33)
Slovakia	21 (7)	22 (7)
Index event		
Deep vein thrombosis, n (%)	284 (92)	284 (92)
Pulmonary embolism, n (%)	23 (8)	24 (8)
Time from index event, mean±SD, mo	9.9±12.5	9.9±7.7
Duration of VKA treatment before randomization <6 mo, n (%)*	134 (44)	110 (36)
Interval from end of VKA treatment to randomization ≥1 mo, n (%)	128 (42)	137 (45)

VKA indicates vitamin K antagonist.
*P=0.044, χ^2 test.

recurrence (1.7% versus 8.8% with apixaban, 0.4% versus 5.6% with dabigatran, and 1.3% versus 7.1% with rivaroxaban) at the expense of increased major or clinically relevant nonmajor bleeding (3.2% versus 2.3%, 5.3% versus 1.8%, and 6.0% versus 1.2%, respectively).[10,13,14]

Our study, however, has some limitations. The total incidence of qualifying events was less than expected but similar to that of other trials.[32,33] A better preventive approach during the period immediately after the index events and perhaps more frequent application of compressive therapy in the studied population could have contributed to decrease this incidence that, however, under the "all failures" assumption was close to the one anticipated in the sample size calculation. The smaller incidence of primary end point therefore appears unlikely to have biased the estimate of the effect size.

The proportion of patients entered in the study with major protocol violations was larger than expected. These violations included cases at lesser (longer anticoagulant treatment or short interval from anticoagulant withdrawal to randomization) and at higher (shorter or no anticoagulant treatment or long untreated interval before randomization) risk. None of these factors significantly affected the risk of recurrence in the multivariable analysis. Furthermore, the results in the per-protocol population were similar to those in the ITT population. There is therefore no evidence that the potential bias associated with protocol violations may have affected the estimate of the effect to an appreciable extent.

The proportion of patients prematurely interrupting the study without having reached the end point was also higher than expected yet limited for a 2-year study (5% total; 18 of 308 among control subjects and 11 of 307 among treated subjects). We performed a number of sensitivity analyses to monitor whether, and in which direction, this could have affected the assessment of the effect size. Applying constant risks ranging from 0 ("all successes" case) to 1 ("all failures" case) to the patients lost to follow-up yielded risk ratios from 0.50 (95% CI, 0.28–0.91; P=0.029) to 0.54 (95% CI, 0.35–0.85; P=0.009). Assigning instead the outcomes at random resulted in 228 possible combinations, with a median value of P=0.016. Not statistically significant results could occur only if the risk ratio of having the event among those randomized to treatment and lost to follow-up versus those randomized to control and lost to follow-up was ≥1.5. It was considered clinically improbable that patients extracted from a group who, when monitored, had a risk ratio of 0.49 (15 of 296 versus 30 of 290) could exhibit a risk ratio of ≥1.5 when not monitored. Finally, we performed a number of sensitivity analyses applying the nearest-neighbor outcome to the patients lost to follow-up using the propensity score, which was considered essentially independent from any assumption and more clinically reliable (more details are given in the online-only Data Supplement). These analyses yielded risk ratios between 0.44 (95% CI, 0.22–0.86; P=0.014) and 0.54 (95% CI, 0.30–0.96; P=0.045). The combination of the results of the survival analysis, those under the "all failures" assumption, those estimated by sensitivity analyses (in particular by propensity score), and those estimated per protocol, all comparable to each other, suggests that the subjects who left the study prematurely were a random subset of the total population and that the estimates

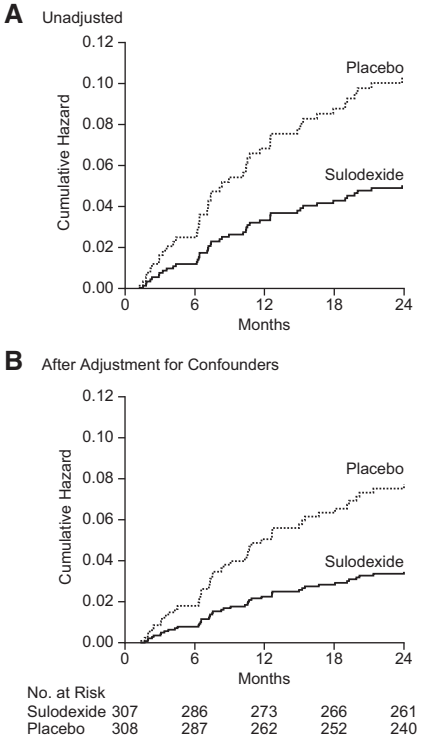


Figure 2. Risk of recurrence of venous thromboembolism in patients randomly assigned to sulodexide or placebo. **A**, Cumulative risk of recurrent venous thromboembolism. **B**, Results of an analysis of risk after adjustment for age, sex, index event (pulmonary embolism, or deep vein thrombosis), duration of anticoagulant therapy, and time from completion of anticoagulation therapy to randomization.

Table 2. Number of Outcome Events According to Study Group

Event	Sulodexide (n=307)	Placebo (n=308)	Hazard Ratio (95% CI)	*P* Value
Recurrent VTE				
Total episodes	15	30	0.49 (0.27–0.92)	0.025
Pulmonary embolism	3	6	0.49 (0.12–1.97)	0.32
Deep vein thrombosis	12	24	0.49 (0.25–0.99)	0.045
Bleeding				
Clinically relevant nonmajor bleeding	2	2	0.97 (0.14–6.88)	0.98
Secondary events				
Distal venous thrombosis	1	4	0.25 (0.03–2.20)	0.21
Superficial venous thrombosis	4	6	0.62 (0.18–2.21)	0.47
Lethal and nonlethal arterial event	2*	3†	0.63 (0.11–3.79)	0.62
Total of recurrent VTE and secondary events	22	43	0.50 (0.30–0.83)	0.008

CI indicates confidence interval; and VTE, venous thromboembolism.

*These events included 1 nonlethal acute myocardial infarction and 1 lethal ischemic stroke.

†These events included 1 episode of acute lower-limb ischemia and 2 episodes of acute coronary failure, all lethal.

of the effect size were sufficiently accurate for all practical purposes.

The proportion of patients with pulmonary embolism as the index event was low (7.6%). The results of this study should therefore be considered poorly applicable to this specific subpopulation.

Safety was favorable without unexpected AEs, likely in correlation with the treatment and clinically irrelevant risks of bleeding despite the 2-year continued treatment. It should be noted, however, that the absence of serious bleeding could be a chance finding because this study was underpowered to detect events occurring with very small frequency.

Conclusions

Treatment with oral sulodexide at 500 lipasemic units twice daily for 2 years along with compression therapy decreased the incidence of recurrences of thromboembolic events without detectable risks for the patient safety. Future investigations should examine whether a similar effect can be obtained after treatment of the index event with non-VKA oral anticoagulants; whether there is a summation of effects with aspirin; whether prevention of recurrence could equally be performed with sulodexide, antiplatelets, or extended anticoagulation; and whether specific subgroups are more or less likely to benefit from sulodexide or other treatments.

Acknowledgments

We are indebted to all the patients who agreed to participate in this study and to all clinical centers (listed in the online-only Data Supplement) that contributed to recruiting the patients. Study Committee: The SURVET study was monitored by a Steering Committee of 3 experts: Drs Andreozzi, Davì, and Palareti. The same committee, having full blinded access to all the data, acted also as Adjudication Committee to define the occurrence of events and the attribution of individual subjects to the analysis populations, after which the database was frozen. The same committee monitored the statistical analysis, which was performed blinded by the study statistician (Dr Bignamini) on the frozen database.

Sources of Funding

The study was financed by Alfa Wassermann, manufacturer of sulodexide.

Disclosures

Dr Andreozzi received consultancy fees or lecture grants from Mediolanum Farmaceutici, Alfa Wassermann, and Laboratorios Elmor. Drs Bignamini and Davì received consultancy fees from Bayer Healthcare and Alfa Wassermann. Dr Palareti received consultancy fees from Alfa Wassermann and Daiichi-Sankyo, as well as lecture fees from Werfen Group and Stago. Dr Sokurenko received lecture grants from Alfa Wassermann and Sanofi. The other authors report no conflicts.

References

1. Schafer AI. Venous thrombosis as a chronic disease. *N Engl J Med*. 1999;340:955–956. doi: 10.1056/NEJM199903253401209.
2. Prandoni P, Lensing AW, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. *Ann Intern Med*. 1996;125:1–7.
3. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Lärfars G, Nicol P, Loogna E, Svensson E, Ljungberg B, Walter H. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism: Duration of Anticoagulation Trial Study Group. *N Engl J Med*. 1995;332:1661–1665. doi: 10.1056/NEJM199506223322501.
4. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, Moia M, Guazzaloca G, Bertoldi A, Tomasi C, Scannapieco G, Ageno W; Warfarin Optimal Duration Italian Trial Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis: Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med*. 2001;345:165–169. doi: 10.1056/NEJM200107193450302.
5. Kearon C, Gent M, Hirsh J, Weitz J, Kovacs MJ, Anderson DR, Turpie AG, Green D, Ginsberg JS, Wells P, MacKinnon B, Julian JA. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med*. 1999;340:901–907. doi: 10.1056/NEJM199903253401201.
6. Agnelli G, Prandoni P, Becattini C, Silingardi M, Taliani MR, Miccio M, Imberti D, Poggio R, Ageno W, Pogliani E, Porro F, Zonzin P; Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med*. 2003;139:19–25.
7. Agnelli G, Becattini C. Treatment of DVT: how long is enough and how do you predict recurrence. *J Thromb Thrombolysis*. 2008;25:37–44. doi: 10.1007/s11239-007-0103-z.
8. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, Nelson ME, Wells PS, Gould MK, Dentali F, Crowther M, Kahn SR; American College of Chest Physicians. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines [published correction appears in *Chest*. 2012;142:1698-1704]. *Chest*. 2012;141(suppl):e419S–e494S.
9. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med*. 2009;361:2342–2352. doi: 10.1056/NEJMoa0906598.
10. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363:2499–2510. doi: 10.1056/NEJMoa1007903.
11. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med*. 2013;369:799–808. doi: 10.1056/NEJMoa1302507.

12. Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwocho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med*. 2013;369:1406–1415. doi: 10.1056/NEJMoa1306638.
13. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368:699–708. doi: 10.1056/NEJMoa1207541.
14. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med*. 2013;368:709–718. doi: 10.1056/NEJMoa1113697.
15. Coccheri S, Mannello F. Development and use of sulodexide in vascular diseases: implications for treatment. *Drug Des Devel Ther*. 2014;8:49–65. doi: 10.2147/DDDT.S6762.
16. Condorelli M, Chiariello M, Dagianti A, Penco M, Dalla Volta S, Pengo V, Schivazappa L, Mattioli G, Mattioli AV, Brusoni B, Trotta E, Bignamini A. IPO-V2: a prospective, multicenter, randomized, comparative clinical investigation of the effects of sulodexide in preventing cardiovascular accidents in the first year after acute myocardial infarction. *J Am Coll Cardiol*. 1994;23:27–34.
17. Coccheri S, Scondotto G, Agnelli G, Aloisi D, Palazzini E, Zamboni V; Venous arm of the SUAVIS (Sulodexide Arterial Venous Italian Study) Group. Randomised, double blind, multicentre, placebo controlled study of sulodexide in the treatment of venous leg ulcers. *Thromb Haemost*. 2002;87:947–952.
18. Errichi BM, Cesarone MR, Belcaro G, Marinucci R, Ricci A, Ippolito A, Brandolini R, Vinciguerra G, Dugall M, Felicita A, Pellegrini L, Gizzi G, Ruffini M, Acerbi G, Bavera P, Renzo AD, Corsi M, Scoccianti M, Hosoi M, Lania M. Prevention of recurrent deep venous thrombosis with sulodexide: the SanVal registry. *Angiology*. 2004;55:243–249.
19. Hoppensteadt DA, Fareed J. Pharmacological profile of sulodexide. *Int Angiol*. 2014;33:229–235.
20. Buchanan MR, Liao P, Smith LJ, Ofosu FA. Prevention of thrombus formation and growth by antithrombin III and heparin cofactor II-dependent thrombin inhibitors: importance of heparin cofactor II. *Thromb Res*. 1994;74:463–475.
21. Iacoviello L, D'Adamo MC, Pawlak K, Polishchuck R, Wollny T, Buczko W, Donati MB. Antithrombotic activity of dermatan sulphates, heparins and their combination in an animal model of arterial thrombosis. *Thromb Haemost*. 1996;76:1102–1107.
22. Borawski J, Dubowski M, Rydzewska-Rosolowska A, Mysliwiec M. Intravenous and oral sulodexide versus coagulation activation markers in humans. *Clin Appl Thromb Hemost*. 2009;15:596–598. doi: 10.1177/1076029609333674.
23. Andreozzi GM. Sulodexide in the treatment of chronic venous disease. *Am J CardiovascDrugs*.2012;12:73–81.doi:10.2165/11599360-000000000-00000.
24. Masola V, Zaza G, Onisto M, Lupo A, Gambaro G. Glycosaminoglycans, proteoglycans and sulodexide and the endothelium: biological roles and pharmacological effects. *Int Angiol*. 2014;33:243–254.
25. Cirujeda JL, Granado PC. A study on the safety, efficacy, and efficiency of sulodexide compared with acenocoumarol in secondary prophylaxis in patients with deep venous thrombosis. *Angiology*. 2006;57:53–64.
26. Prandoni P, Lensing AW, Bernardi E, Villalta S, Bagatella P, Girolami A; DERECUS Investigators Group. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. *Thromb Haemost*. 2002;88:402–406. doi: 10.1267/THRO88030402.
27. van Gogh Investigators, Buller HR, Cohen AT, Davidson B, Decousus H, Gallus AS, Gent M, Pillion G, Piovella F, Prins MH, Raskob GE. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med*. 2007;357:1094–1104. doi: 10.1056/NEJMoa064247.
28. Stevenson M, Nunes T, Sanchez J, Thornton T, Reiczigel J, Robison-Cox J, Sebastiani P, Solymos P. epiR: An R package for the analysis of epidemiological data. R package version 0.9-48. 2013. http://CRAN.R-project.org/package=epiR. Accessed January 2, 2015.
29. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013. URL http://www.R-project.org/. Accessed January 2, 2015.
30. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, Bianchi M, Moia M, Ageno W, Vandelli MR, Grandone E, Prandoni P; WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism. *N Engl J Med*. 2012;366:1959–1967. doi: 10.1056/NEJMoa1114238.
31. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R, Kirby A, Simes J; ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med*. 2012;367:1979–1987. doi: 10.1056/NEJMoa1210384.
32. Jiménez D, Díaz G, Marín E, Vidal R, Sueiro A, Yusen RD. The risk of recurrent venous thromboembolism in patients with unprovoked symptomatic deep vein thrombosis and asymptomatic pulmonary embolism. *Thromb Haemost*. 2006;95:562–566. doi: 10.1267/THRO06030562.
33. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. *Thromb Haemost*. 2014;112:255–263. doi: 10.1160/TH13-09-0793.

CLINICAL PERSPECTIVE

Patients with unprovoked venous thromboembolism are at high risk for recurrence after discontinuation of treatment with vitamin K antagonists (VKAs). Extending treatment with VKAs reduces the recurrence risk but increases the bleeding risk. In clinical practice, VKAs are generally discontinued when the perceived risk of bleeding outweighs the risk of recurrence. Drugs with low or no bleeding risk and less aggressive antithrombotic activity may represent adequate alternatives to continue anticoagulation with VKAs, or patients should be left to only physical management (elastic stockings) in cases of doubt. Rates of bleeding in general inferior to VKAs and efficacy not inferior to VKAs have been shown by the newer non-VKAs. However, compared with placebo, the extended anticoagulation with dabigatran, rivaroxaban, or apixaban, although reducing the risk of venous thromboembolism recurrence, carried a higher risk of major or clinically relevant nonmajor bleeding. The pooled data of the Warfarin and Aspirin (WARFASA) and Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trials showed a significant risk reduction of venous thromboembolism recurrence, although at a lower extent than with the new non-VKAs, but still a worse result than placebo in terms of the occurrence of clinically relevant bleeding. In the 2 years of treatment in the Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) study, venous thromboembolism recurred in 15 of 307 patients on sulodexide and 30 of 308 on placebo (hazard ratio, 0.49; 95% confidence interval, 0.27–0.92; P=0.02). There were no differences in major or clinically relevant nonmajor bleeding between the sulodexide and placebo groups. Sulodexide appears to be an important treatment option when extended anticoagulation is potentially useful but associated with unwanted bleeding risk.

Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The Sulodexide in Secondary Prevention of Recurrent Deep Vein Thrombosis (SURVET) Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

Giuseppe M. Andreozzi, Angelo A. Bignamini, Giovanni Davì, Gualtiero Palareti, Jirí Matuska, Martin Holý, Katarzyna Pawlaczyk-Gabriel, Andrej Dzupina, German Y. Sokurenko, Yury P. Didenko, Laurentia D. Andrei, Gianfranco Lessiani and Adriana Visonà
on behalf of the SURVET Study Investigators*

Circulation. 2015;132:1891-1897; originally published online September 25, 2015;
doi: 10.1161/CIRCULATIONAHA.115.016930
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

SUPPLEMENTAL MATERIAL

Sulodexide for the Prevention of Recurrent Venous Thromboembolism: The SURVET Study: A Multicenter, Randomized, Double-Blind, Placebo Controlled Trial

SUPPLEMENTAL RESULTS

Results of the logistic analysis assigning all lost to follow-up to failure

All patients without confirmed information as to the health status at 24 months after randomization were classified as failures, as if they had had reached the endpoint (recurrence of thromboembolism). All patients with confirmed recurrent thromboembolism were also classified as failure. Only patients with definite information that in the 24-month period after randomization had not had the event were classified as success.

The logistic regression analysis adjusted the results observed by treatment, for sex, age, length of exposure to VKA (<6 months/≥6months), delay from the end of VKA treatment and randomization (<1 month/≥1 month), country, and type of index event (deep vein thrombosis/pulmonary embolism).

The model resulted to fit well (Hosmer and Lemeshow test: P=0.620) and to improve by almost 10% the accuracy of prediction over the null model (Nagelkerke R square=0.098).

The results confirmed that also in terms of failure under the worst-case assumption, the significant predictors were the same as those indicated by the Cox analysis (Table S-1).

Proportion of events assigning the outcome to patients lost to follow-up by propensity score

A sensitivity analysis of the outcome was also performed by assigning the outcome to the patients lost to follow-up by propensity score.

If we assume that the risk of recurrence among those who abandoned the study is determined by the factors considered putative predictors of the event - with the exclusion of treatment – we can estimate the propensity score for recurrence from the monitored patients. From the relevant equation, we can estimate the score for those lost to follow-up; subsequently the patients lost to follow-up are assigned the status (event/no-event) of the nearest neighbor.

We estimated the propensity score for having the primary event using the data from the 586 patients who either had the event or reached the 24 months without event. As predictors, the same used for the Cox survival analysis were employed, once considering treatment and once not considering treatment.

The equations estimating the propensity score were then applied to the 29 patients lost to follow-up.

CASE: CONSIDERING TREATMENT IN THE EQUATION

The 29 patients lost to follow-up were assigned the outcome exhibited by the subject of the same treatment group, having the nearest propensity score. This assigned 1 case among placebo and none among treated to the category FAILURE. The resulting estimate of the proportion of events was 31/308 (10.1%) among controls, and 15/307 (4.9%) among treated (P=0.021, Fisher's test; incidence risk ratio: 0.49 [0.27-0.88]).

We repeated the same procedure, assigning to the 29 cases the outcome exhibited by the subject with the nearest propensity score, regardless of the treatment group. This assigned 2 cases among placebo and none among treated to the category FAILURE. The resulting

estimate of the proportion of events was 32/308 (10.4%) among controls, and 15/307 (4.9%) among treated (P=0.014, Fisher's test; incidence risk ratio: 0.44 [0.22-086]).

CASE: NOT CONSIDERING TREATMENT IN THE EQUATION

The 29 cases were assigned the outcome exhibited by the subject with the nearest propensity score, regardless of the treatment group. This assigned 0 cases among placebo and 1 among treated to the category FAILURE.

The resulting estimate of the proportion of events was 30/308 (9.7%) among controls, and 16/307 (5.2%) among treated (P=0.045, Fisher's test; incidence risk ratio: 0.54 [0.30-0.96]).

Regardless of the approach taken, the results consistently confirmed that the probability of having a recurrence of DVT/PE was significantly greater among controls than among treated patients.

The variations that could be seen with the different procedures to assign outcomes to the patients lost to follow-up affected the size, but not the direction, of the effect.

NNT estimates for the primary clinical endpoint (recurrence of DVT)

We estimated the NNT to avoid one event more of recurrent DVT/PE in two years with the indicated dosage scheme of sulodexide added to the standard of care, vs. the standard of care alone. Since the probability of recurrence was estimated under different assumptions and with different techniques, several different estimates of NNT were computed.

ESTIMATES FROM THE ABSOLUTE RISK REDUCTION

The most common estimate of NNT is from the absolute risk reduction that, however, in this study should be estimated under the different assumptions made about the cases lost to follow-up.

1. The estimate from the absolute risk reduction (considering all lost to follow-up as non-events) yielded NNT=21 [95% CI: 10-232].
2. The estimate from the absolute risk reduction (considering all lost to follow-up as events) yielded NNT=15 [95% CI: 7-60].
3. The estimate from the absolute risk reduction (excluding all lost to follow-up) yielded NNT=19 [95% CI: 10-159].

However, these estimates do not take into account neither the actual exposure to treatment, nor the effect of potential confounders that, even in a randomised study, is definitely evident (as shown by the significant effects of predictors at the Cox analysis). We therefore estimated the NNT from the Kaplan-Meyer procedure, the unadjusted NNT from the Cox regression analysis and the NNT from the adjusted Cox regression analysis (using the covariates indicated in the text). (Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. BMJ. 1999;319:1492-1495)

ESTIMATES FROM SURVIVAL ANALYSES

4. The estimate from the Kaplan-Meyer was NNT = 19 [95% CI: 10-102].

5. The estimate from the unadjusted Cox regression was NNT = 20 [95% CI: 13 - 121].

6. The estimate from the adjusted Cox regression was NNT = 24 [95% CI: 16-98].

Overall, while the NNT is approximately 20, the width of the confidence interval is largely determined by the application of adjustments for exposure to treatment (that, being longer for the treated group, reduces the point estimate of the NNT) and for the potential confounders (which results in substantially smaller width of the confidence interval). Under actual clinical conditions, the NNT estimated from the adjusted Cox regression of 24 [16-98] can be considered to reflect the true treatment effect.

Further studies, which will allow estimating the NNT from the summary measure of effect, would allow to better estimate the point NNT and to reduce the width of the confidence interval.

Results in the per-protocol population

The per-protocol population was composed of 521 patients, of whom 263 received sulodexide and 258 received placebo (Figure 1). Venous thromboembolism recurred in 44 patients (one patient with a primary event was excluded from this population because of a major protocol violation) and was due to deep-vein thrombosis in 36 patients and to pulmonary embolism in 8 patients (fatal in 1 patient).

The primary outcome, recurrence of venous thromboembolism, occurred in 14 of the 263 patients who received sulodexide, as compared with 30 of the 258 patients who received placebo (hazard ratio, 0.45; 95% CI, 0.24 to 0.85; P = 0.014).

The analysis adjusted for age, sex, index event (pulmonary embolism or deep-vein thrombosis), country, duration of exposure to VKA, and delay from end of VKA treatment and randomization, confirmed that sulodexide treatment reduced the risk of recurrence (adjusted hazard ratio, 0.43; 95% CI, 0.23 to 0.81; P = 0.01). Independent risk factors for recurrent venous thromboembolism included age (hazard ratio, 1.03; 95% CI, 1.01 to 1.05; P = 0.02), male sex (hazard ratio, 2.40; 95% CI, 1.23 to 4.70; P = 0.01), and marginally the country (P=0.042 without any country differing significantly from the overall trend). No association was found between recurrent venous thromboembolism and length of exposure to VKA (hazard ratio, 0.84; 95% CI, 0.43 to 1.68; P = 0.63), delay from end of VKA treatment and randomization (hazard ratio, 0.71; 95% CI, 0.37 to 1.38; P = 0.31), or index event (hazard ratio, 1.74; 95% CI, 0.65 to 4.64; P = 0.27).

Unplanned subgroup analysis of the incidence of primary events

We estimated the risk ratio of recurrence in different subgroups of potential prognostic relevance, after exclusion of the cases lost to follow-up. The analysis was performed with epiR in R. No formal comparison was performed across subgroups, since the 95% confidence intervals are already sufficient to estimate the extent of superposition across levels of subgroups, and the displacement of the individual estimate from the overall estimate of the effect.

This unplanned subgroup analysis was performed with the exclusive aim of detecting whether there was any major discrepancy across potentially important subgroups, that could suggest major modifications to protocol in future randomized controlled trials. Indeed, being the analysis unplanned, any possible difference seen by subgroups levels, could only be considered a hypothesis-generating finding.

The results are summarized in Figure S-1.

Secondary vascular events

Five patients had distal leg DVT (4 randomized to placebo *vs.* 1 randomized to sulodexide), 10 had superficial vein thrombosis (6 *vs.* 4), and 5 had arterial events considered secondary endpoints (3 *vs.* 2). The incidence of these events did not differ between groups, although each of these events occurred more frequently among controls. The number of patients who had any one of these secondary events was 13/308 among the patients randomized to placebo, and 7/307 among those randomized to sulodexide (4.2% vs. 2.3%), without evidence of a significant difference (P=0.26).

Some arterial events were considered secondary study endpoint (AMI, stroke, peripheral ischemia); others were not (identification of carotid stenosis or peripheral artery thrombosis). Overall, 9/308 patients among controls exhibited arterial events (2.9%; 95% CI: 1.3-5.5%) *vs.* 4/307 among treated patients (1.3%; 95% CI: 0.4-3.3%; P=0.262, Fisher test). The IRR with sulodexide was comparable with that observed for the occurrence of venous events: 0.45 [0.14-1.43].

SUPPLEMENTAL TABLES

Table S-1. Odds ratio (OR) for the putative predictors in the multivariable logistic analysis of failures under the worst-case scenario.

Predictor	OR [95% confidence interval]	P
Treatment: sulodexide	0.467 [0.277-0.787]	0.004
Male sex	1.837 [1.083-3.116]	0.024
Age	0.979 [0.961-0.997]	0.024
Exposure to VKA ≥6months	0.855 [0.495-1.478]	0.574
Randomization ≥1 month after the end of VKA treatment	0.830 [0.479-1.439]	0.507
Country*		0.127
Index_event: pulmonary embolism	1.251 [0.512-3.057]	0.624

* none of the countries deviated significantly from the overall trend

Table S-2. Number of Patients with Adverse Events and Number of Adverse Events by Study Groups.*

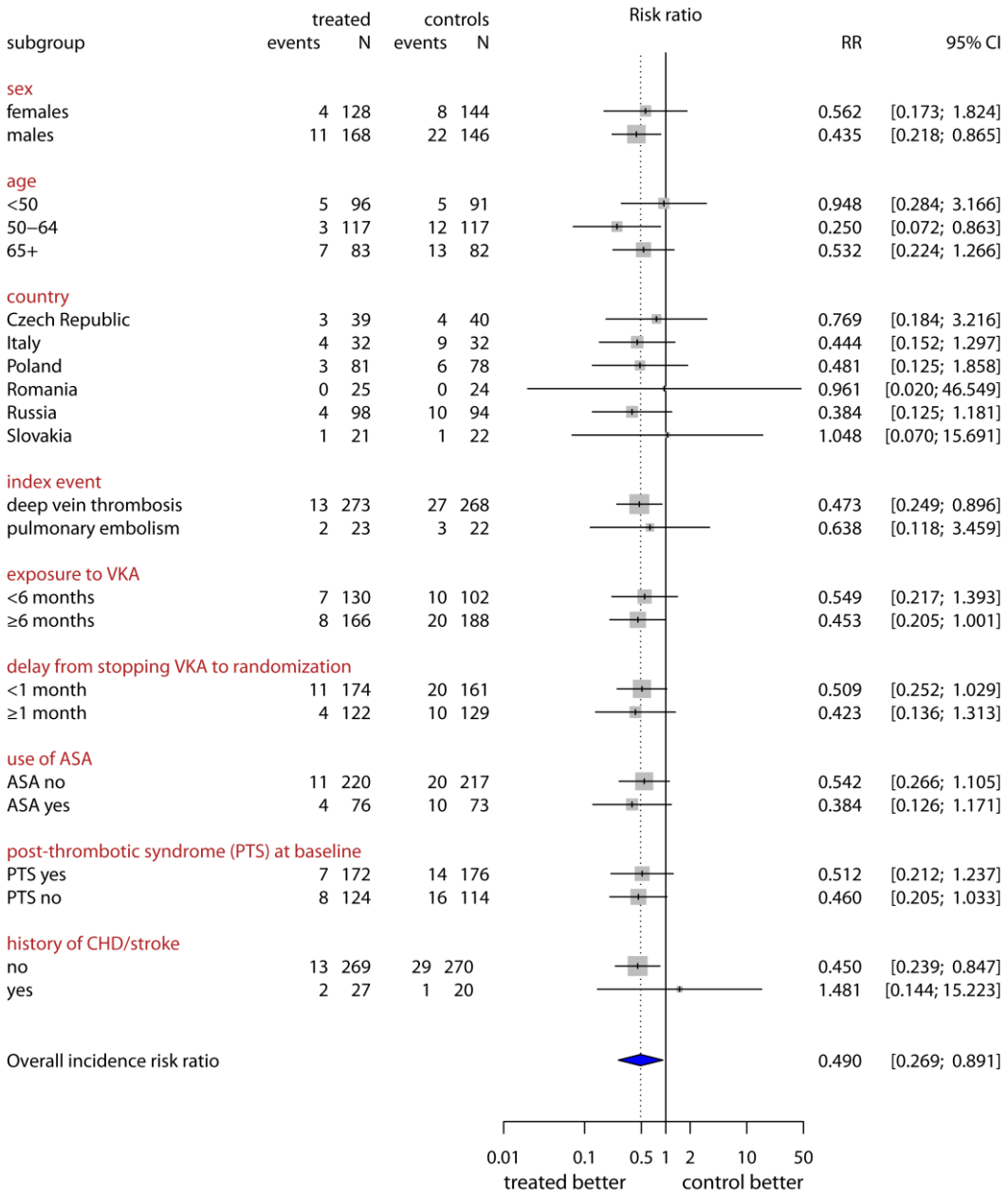
	Sulodexide (N=308)	Placebo (N=309)
regardless of correlation		
any	150 (48.7) [368]	162 (52.4) [397]
severe	22 (7.1) [35]	25 (8.1) [36]
causing treatment interruption	28 (9.1) [31]	42 (13.6) [48]
serious	25 (8.1) [30]	34 (11.0) [45]
causing death	1 (0.3) [1]	4 (1.3) [5]
potentially correlated		
any	51 (16.6) [94]	40 (12.9) [77]
severe	7 (2.3) [10]	6 (1.9) [9]
causing treatment interruption	13 (4.2) [14]	12 (3.9) [13]
serious	9 (2.9) [11]	5 (1.6) [7]
causing death	0 (0.0)	0 (0.0)
most frequent (>1%), regardless of correlation		
Pain in extremity	15 (4.9) [23]	16 (5.2) [19]

Deep vein thrombosis	12 (3.9) [13]	24 (7.8) [24]
Arthralgia	13 (4.2) [20]	8 (2.6) [10]
Hypertension	10 (3.2) [11]	13 (4.2) [13]
Oedema peripheral	13 (4.2) [13]	6 (1.9) [8]
Nasopharyngitis	11 (3.6) [11]	8 (2.6) [10]
Respiratory tract infection viral	9 (2.9) [9]	7 (2.3) [8]
Headache	2 (0.6) [2]	11 (3.6) [15]
Pulmonary embolism	5 (1.6) [5]	8 (2.6) [8]
Vertigo	5 (1.6) [6]	5 (1.6) [7]
Diarrhoea	5 (1.6) [5]	7 (2.3) [7]
Abdominal pain upper	6 (1.9) [6]	5 (1.6) [5]
Urinary tract infection	1 (0.3) [1]	9 (2.9) [9]
Hypercholesterolaemia	6 (1.9) [8]	2 (0.6) [2]
Blood pressure increased	1 (0.3) [2]	7 (2.3) [7]
Back pain	2 (0.6) [2]	5 (1.6) [7]
Blood glucose increased	5 (1.6) [5]	3 (1.0) [3]
Gout	4 (1.3) [5]	3 (1.0) [3]
Pain	4 (1.3) [4]	2 (0.6) [3]
Dyspnoea	4 (1.3) [4]	2 (0.6) [3]

Upper respiratory tract infection	3 (1.0) [3]	4 (1.3) [4]
Bronchitis	3 (1.0) [3]	4 (1.3) [4]
Sciatica	2 (0.6) [2]	4 (1.3) [4]
Pruritus	4 (1.3) [5]	1 (0.3) [1]
Nausea	0 (0.0) [0]	4 (1.3) [6]
Carotid arteriosclerosis	1 (0.3) [2]	4 (1.3) [4]
Vomiting	0 (0.0) [0]	5 (1.6) [6]
Condition aggravated	5 (1.6) [5]	0 (0.0) [0]

* number of patients with the events (%). Square brackets denote the number of nonconsecutive events.

SUPPLEMENTAL FIGURES



Supplemental Figure S-1. Unplanned analysis of the risk ratio for recurrent VTE (with 95% confidence interval) in the SURVET Study patients (after exclusion of the cases lost to follow-up), stratified by clinically relevant subgroups.

STUDY GROUP MEMBERS

Czech Republic: IKEM - Kardiologická klinika, Praha: *Karel Roztočil*; Fakultní nemocnice Plzeň - Interní oddělení, Plzeň – Bory: *Jana Hirmerova*; Angiologická ambulance - Horní Valy 13 - 69501 Hodonín: *Jiří Matuška*; Angiologická ambulance, Brno: *Václav Pecháček*; Nemocnice České Budějovice - Interní oddělení, České Budějovice: *Martin Holý*.

Poland: Gabinet Lekarski, Katowice: *Tomasz Urbanek*; Nzoz Perełka, Łódź: *Jacek Śmigielsk*i; Poradnia Chorób Naczyń Obwodowych MIKOMED, Łódź: *Jacek Mikosiński, Mirosla Wasiewicz, Tomasz Lesiak*; Specjalistyczny Gabinet Lekarski Chorób Tętnic i Żył, Lublin: *Piotr Niedziela*; Specjalistyczna Praktyka Lekarska, Giżycko: *Marek Sajkowski*; Life - Med. Lecznica, Grodzisk Mazowiecki: *Grzegorz Madycki*; ProfMedica, Poznań: *Katarzyna Pawlaczyk-Gabriel, Marcin Gabriel, Zbigniew Krasiński.*

Slovakia: ALIAN s.r.o., Bardejov: *Andrej Džupina*; Ústredná vojenská nemocnica - Interná klinika, Ružomberok: *Antonín Hruboň, Miroslav Urban*; VASA CARE, s.r.o. -Angiology Lab, Trnava: *Ivar Vacula*

Russian Federation: Moscow State Medical Institution «City Clinical Hospital № 1 n.a. Pirogov», Moscow: *Kirienko Alexander Ivanovich*; Clinical Hospital of Russian Academy of Sciences, St. Petersburg: *Balluzek Marina Feliksovna, Basos Sergey*; Municipal Medical Institution «City Emergency Care Hospital», Kursk: *Chernyatina Marina Aleksandrovna, Gladchenko Mikhail*; St. Petersburg State Medical Institution «City Multidisciplinary Hospital № 2», St. Petersburg: *Didenko Yury Pavlovich, Androsova Svetlana*; Municipal Medical Institution «City Hospital № 3», Chelyabinsk: *Fokin Alexey Anatolievich, Degtyarev Maxim*; Municipal Medical Institution «Clinical Hospital № 8, Yaroslavl», Yaroslavl: *Malygin Alexander Yurievich, Korzhova Valeria*; Municipal Medical Institution «Vsevolozhsk Central District Hospital», Vsevolozhsk: *Matevosyan Elena Nikolaevna, Vorontsova Tatiana*; St.

Petersburg State Medical Institution «City Hospital № 40 of Kurortny Administrative Region», St. Petersburg: Sarana Andrey Mikhailovich, Agafina Alina; St.Petersburg State Institution of Public Health «Consultive and Diagnostic Center # 85», St. Petersburg: S*okurenko German Yurievich, Popovich Vladimir*; Federal State Institution «National Medical Surgical Center n.a. Pirogov of Roszdrav», Moscow: *Stoyko Yuriy Mikhailovich, Linchak Ruslan*; Federal State Medical Institution «Clinical Hospital № 122 n.a. Sokolov of FMBA of Russia», St. Petersburg: *Svetlikov Alexei Vladimirovich, Gamzatov Temirlan*; State Medical Institution «Voronezh Regional Clinical Hospital № 1» Voronezh: *Esipenko Viktor Vasilievich*; State Medical Institution of Moscow «City Hospital № 13», Moscow: *Rodoman Grigory Vladimirovich, Zakhovskaya Elena*; Non-governmental Medical Institution «Road Clinical Hospital of public corporation «Russian Railways» St. Petersburg: *Sonkin Igor Nikolaevich, Melnik Valerii*.

Romania: CMI Dr Militaru, Craiova: *Constantin Militaru*; Quantum Medical Center, Bucharest: *Radu Dumitru Stoenescu*; C.M.Dr. Blaj Stefan, Bucharest: *Stefan Blaj*; Spitalul Clinic Judetean de Urgenta, Brasov: *Stefan Blaj*; Spitalul Clinic Judetean de Urgenta, Brasov: *Laurentia Doina Andrei*.

Portugal: Hospital Pulido Valente, Lisboa: *Albino Pereira*.

Italy: Dipartimento di Medicina e Scienze dell'Invecchiamento, Ce.S.I. Università "G.D'Annunzio" Chieti (Italy): *Giovanni Davì, Gianfranco Lessiani*; Angiology Care Unit, University Hospital, Padua: *Giuseppe Camporese, Romeo Martini, Chiara Tonello*; Presidio Ospedaliero di Castelfranco Veneto, Castelfranco Veneto: *Adriana Visonà, Laura Zotta*; U.O.S.D. di Angiologia - Medicina Interna - Ospedale SS. Giovanni e Paolo, Venezia: *Roberto Parisi*; Medicina Generale II - Azienda Ospedaliera di Vimercate, Vimercate: *Guido Giuseppe Arpaia, Gabriella Spezzigu*; Azienda Ospedaliera Complesso Osped. S. Giovanni

Addolorata, Roma: *Claudio Allegra*; U.O. Angiologia Azienda Ospedaliera Universitaria Policlinico P. Giaccone, Palermo: *Filippo Ferrara, Corrado Amato*; Azienda Ospedaliera Universitaria Ospedale Vittorio Emanuele e Ferrarotto, Catania: *Michelangelo Di Salvo, Giacomo Failla*.