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 Davi, 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.

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The risk of recurrence of venous thromboembolism (VTE) persists for many years after anticoagulant treatment is withdrawn1 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
bleeding, as well as the inconvenience and costs of laboratory monitoring and dose adjustments. The effects of the newer non-VKA oral anticoagulants for therapy of acute VTE events and for extended treatment to avoid recurrences 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 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, as also highlighted in a recent review. Sulodexide exerts its actions through complexation with antithrombin and heparin cofactor II and the attending inhibition of some factors of the coagulation cascade. It also exerts favorable effects on endothelial dysfunction, release of cytokines and chemokines, and metalloprotease-9 secretion from white blood cells. 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 or standard of care after withdrawal of VKA treatment. 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 (2x250-350-lipasecapsule 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 VKA as 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 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.

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 suggesting 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 \( \approx 17.5\% \) in 2 years\(^{11}\) and hypothesizing a 50\% relative reduction by adding sulodexide,\(^{18}\) we determined that a total of 620 patients (\( \approx 310 \) per group) had 90\% power to show superiority of sulodexide over placebo at a 2-sided level of \( \alpha=0.05 \).

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/\( \geq 6 \) months) exposure to VKA, and dichotomized (<6/\( \geq 6 \) 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 proportion of failures among control subjects was 48 of 308 (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.

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).

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; \( P=0.98 \)).
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 and the Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) trial, which were published while the SURVET study was underway. The pooled ASPIRE-W ARFASA hazard ratio for VTE was 0.68 (95% CI, 0.51–0.90); the unadjusted hazard ratio in SURVET was 0.49 (95% CI, 0.27–0.92). The pooled ASPIRE-W ARFASA 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-W ARFASA 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...
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 \( \geq 1.5 \). 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 \( \geq 1.5 \) 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

| 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.

* \( P = 0.044 \), \( \chi^2 \) test.

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                              |                     |                 | 0.50 (0.30–0.83)      | 0.008   |
| 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                           | 1                   | 4               | 0.25 (0.03–2.20)      | 0.21    |
| Distal venous thrombosis                   | 4                   | 6               | 0.62 (0.18–2.21)      | 0.47    |
| Superficial venous thrombosis              |                     |                 |                       |         |
| Lethal and nonlethal arterial event        | 2*                  | 3†              | 0.63 (0.11–3.79)      | 0.62    |
| Total of recurrent VTE and secondary events| 22                  | 43              |                       |         |

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.

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.

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Disclosures

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**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 occurred 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.

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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*

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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/≥6 months), 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]   |
| Condition                              | Incidence | N (prevalence) | Incidence | N (prevalence) |
|----------------------------------------|-----------|----------------|-----------|----------------|
| Deep vein thrombosis                   | 12 (3.9)  | 24 (7.8)       |
| Arthralgia                             | 13 (4.2)  | 8 (2.6)        |
| Hypertension                           | 10 (3.2)  | 13 (4.2)       |
| Oedema peripheral                      | 13 (4.2)  | 6 (1.9)        |
| Nasopharyngitis                        | 11 (3.6)  | 8 (2.6)        |
| Respiratory tract infection viral      | 9 (2.9)   | 7 (2.3)        |
| Headache                               | 2 (0.6)   | 11 (3.6)       |
| Pulmonary embolism                     | 5 (1.6)   | 8 (2.6)        |
| Vertigo                                | 5 (1.6)   | 5 (1.6)        |
| Diarrhoea                              | 5 (1.6)   | 7 (2.3)        |
| Abdominal pain upper                   | 6 (1.9)   | 5 (1.6)        |
| Urinary tract infection                | 1 (0.3)   | 9 (2.9)        |
| Hypercholesterolaemia                  | 6 (1.9)   | 2 (0.6)        |
| Blood pressure increased               | 1 (0.3)   | 7 (2.3)        |
| Back pain                              | 2 (0.6)   | 5 (1.6)        |
| Blood glucose increased                | 5 (1.6)   | 3 (1.0)        |
| Gout                                   | 4 (1.3)   | 3 (1.0)        |
| Pain                                   | 4 (1.3)   | 2 (0.6)        |
| Dyspnoea                               | 4 (1.3)   | 2 (0.6)        |
| Condition                                      | No. Patients | Percentage | No. Patients | Percentage |
|-----------------------------------------------|--------------|------------|--------------|------------|
| 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 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 Śmigielski; Poradnia Chorób Naczyń Obwodowych MIKOMED, Łódź: Jacek Mikosiński, Mirosław 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 Krasinski.

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 Anatoliyevich, 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: Sokurenko 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 Vasilevich; 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 Stoinescu; 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.
Sulodexide는 정맥 혈전색전증 환자의 재발을 줄일 수 있다:

SURVET 연구

나승운 교수 고려대학교 구로병원 순환기내과

초록

배경
정맥 혈전색전증이 처음 발생한 환자는 항혈전제의 투여가 중단되면 혈전의 재발 위험이 높다. 항혈전제 투여기간을 연장하면 재발의 위험은 감소될 수 있으나, 출혈의 위험을 높이는 문제가 발생한다. Sulodexide는 glycosaminoglycan으로 경구 투여하였을 경우, 출혈 위험이 적고, 항혈전(antithrombotic) 및 전구 혈전존재(profibrinolytic) 작용을 가지고 있다고 알려져 있으나, 정맥 혈전색전증 환자의 재발을 줄이는 데 유익한지에 대해서는 잘 알려져 있지 않다.

방법 및 결과
본 다기관, 이중맹검 연구는 첫 정맥 혈전색전증이 나타난 이후 3-12개월간의 경우 항혈전제 치료를 마친 615명의 환자를 대상으로 하였으며, 대상 환자들은 암박 스티킹을 착용하고 하루 2회 sulodexide 500 lipasemic unit 또는 위약을 2년간 투여 받았다. 일차 효과 관련 종료점은 정맥 혈전색전증의 재발이었고, 안전성 관련 종료점은 주요 또는 임상적으로 관련된 출혈의 발생 여부였다. 정맥 혈전색전증의 재발은 sulodexide를 처방 받은 307명 중 15명, 위약군 308명 중 30명에서 발생하였다(HR, 0.49; 95% CI, 0.27-0.92; P=0.02). 그리고 추적관찰에 실패한 사람들을 고려한 치료군과 위약군의 발생빈도 위험비는 0.54(95% CI, 0.35-0.85; P=0.009)였다. 주요 출혈은 발생하지 않았으나, 약제 관련 출혈은 2명의 환자에서 발생하였고, 두 군 간에 약제 관련 부작용의 발생빈도는 유사하였다.

결론
처음 발생한 정맥 혈전색전증에 대해 항혈전제 치료 중단 후 sulodexide를 투여하면, 출혈 병발은 증가하지 않으면서 혈전의 재발 위험이 줄어든다.