JACC Vol. 23, No. 1
January 1994:27–34

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

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Objectives. **This study was conducted to assess the efficacy of sulodexide, a glycosaminoglycan compound with antithrombotic properties, in preventing death and thromboembolic events after acute myocardial infarction.**

Background. **Antithrombotic therapy has been found to play an important role in the prevention of cardiovascular events and death after acute myocardial infarction. Glycosaminoglycan-containing compounds, including sulodexide, show profibrinolytic and antithrombotic properties that render them suitable for use in patients after infarction.**

Methods. **A total of 3,986 patients who had recovered from acute myocardial infarction were randomized to receive either the standard therapy routinely administered at each study center, excluding antiplatelet and anticoagulant drugs (control group, 1,970 patients), or the standard therapy plus sulodexide (treated group, 2,016 patients). Between 7 and 10 days after the episode of acute myocardial infarction, sulodexide was administered as a single daily 600-lipoprotein-lipase–releasing unit (LRU) intramuscular injection for the 1st month, followed by oral capsules of 500 LRU twice daily. Patients were evaluated for ≥12 months.**

Results. **At the end of the study, 140 deaths (7.1%) were recorded in the control group and 97 (4.8%) in the sulodexide group (32% risk reduction, p = 0.0022, chi-square test). A total of 90 patients (4.6%) in the control group had a further infarction, compared with 66 (3.3%) in the sulodexide group (28% risk reduction, p = 0.035). Furthermore, a reduction in left ventricular thrombus formation (evaluated by echocardiography) was observed in the sulodexide group (n = 12; 0.6%), compared with values in the control group (n = 25; 1.3%) (53% risk reduction, p = 0.027). Sulodexide was well tolerated and devoid of significant adverse events. All significant results were confirmed by "actual treatment" analyses.**

Conclusions. **The study provides evidence that long-term therapy with sulodexide started early after an episode of acute myocardial infarction is associated with reductions in total mortality, rate of reinfarction and mural thrombus formation.**

(J Am Coll Cardiol 1994;23:27–34)

It is now generally accepted that plaque rupture leading to thrombus formation and coronary occlusion is the most frequent pathophysiologic basis for acute coronary syndromes (1–3). Because survivors of acute myocardial infarction are at risk of recurrent infarction and cardiac death (4–6), several clinical trials (7–10) have been conducted using different antithrombotic drugs alone or in combination for secondary prevention of coronary heart disease. It has been shown (9) that platelet inhibitors are able to reduce the cardiovascular mortality rate by 13%, nonfatal reinfarction by 31% and all important vascular events by 25%. Similar results have been obtained with subcutaneous injections of low dose heparin (10) and warfarin (8).

Sulodexide is a highly purified preparation containing an endogenous-like, fast-moving heparin fraction (iduronyl-glycosaminoglycan sulfate) with a high affinity for antithrombin (80%) and a dermatan fraction with an affinity for heparin cofactor (20%) (11). In vivo antiatherosclerotic activity has been demonstrated by sulodexide (12,13) and may be related to a hypolipidemic activity linked to lipoprotein-lipase release (12,14), a more rapid catabolism of cholesterol-rich lipoproteins (very low density lipoproteins-low density lipo-

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Manuscript received April 22, 1993; revised manuscript received July 23, 1993, accepted July 28, 1993.

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0735-1097/94/$6.00

proteins [VLDL-LDL]) by the liver (15) and an antiproliferative effect on smooth muscle cell types (16). In various animal models, sulodexide also shows antithrombotic activity, probably by blocking platelet activation by thrombin, by an inhibitory effect on platelet adhesion (17) and through its anticoagulant and profibrinolytic activity (18).

At therapeutic doses in patients, sulodexide inhibits activated factor X without influencing the activated partial thromboplastin time and thrombin time (19,20). It also exerts a profibrinolytic activity, evidenced by tissue-plasminogen activator (t-PA) activation and plasminogen activator inhibitor (PAI-1) inhibition (21–24). Plasma and serum viscosity are also reduced by sulodexide (24–30). Sulodexide has been widely demonstrated in patients with peripheral atherosclerotic obstructive disease to be clinically efficacious (25,31–41).

The aim of this prospective, multicenter, randomized trial was to determine whether sulodexide was effective in preventing cumulative mortality and cardiovascular mortality and events in patients after an acute myocardial infarction.

Methods

Eligibility criteria. Patients, irrespective of gender or age, who had had an AMI were potential candidates for the study, provided that they did not have severe impairment of renal (plasma creatinine >2 mg/dl) or hepatic function, malignant disease with a life expectancy of <2 years or required the use of anticoagulant or antiaggregant treatment. Diagnosis of myocardial infarction was based on the criteria of the World Health Organization (42). Patients gave written informed consent to participate in the study before entry. A total of 71 hospitals throughout Italy participated in the study, and the trial was approved by their individual ethics committees.

Design of the trial. The study was a prospective multicenter trial. On discharge from the coronary care unit, eligible patients were allocated to one of two parallel groups (sulodexide or control), according to a randomization schedule arranged in blocks of 10 for each center. Patients in both groups were receiving cardiovascular therapy as prescribed by their specialist. Patients receiving nitrate derivatives, beta-adrenergic blocking agents, calcium channel blockers, digitalis, diuretic drugs and antiarrhythmic drugs were included in the study. Patients receiving heparin, oral anticoagulants, antiplatelet or fibrinolytic agents were excluded from the study, and any patient requiring these medications during the course of the study was excluded.

Adherence to the study protocol was recorded at each follow-up visit. Data were collected and analyzed by an independent contract research organization (Hyperphar srl, Milan). An independent Ethical Committee and a Safety Monitoring Board were responsible for decisions regarding the safe conduct and continuation of the study.

Treatment and patient evaluation. Patients who were assigned to the test group were treated with sulodexide between 7 and 10 days after acute myocardial infarction at a dose of 600 of lipoprotein-lipase–releasing units (LRU)/day intramuscularly for 30 days and subsequently at an oral dose of 1,000 LRU/day in two equally divided doses for 11 months. Follow-up appointments were scheduled at 3, 6, 9 and 12 months after entry. Each visit included a medical history, physical examination, 12-lead electrocardiogram (ECG) at rest and a two-dimensional echocardiographic study. Particular care was taken to obtain images of the cardiac apex from both long- and short-axis projections, minimizing near field artifacts. Left ventricular thrombus was diagnosed when an echogenic mass distinct from the ventricular wall was seen in association with a wall motion abnormality from the apical four chambers of the long-axis and short-axis views of the left ventricle and cardiac apex (43).

End points. Cumulative mortality, cardiovascular mortality and cardiovascular events were the primary end points of the study. Cardiovascular events were defined as reinfarction (confirmed by ECG and assay of cardiac enzymes), deep vein thrombosis (confirmed by phlebography), pulmonary embolism (confirmed by scintigraphy), systemic arterial embolism (confirmed by angiography), cerebral vascular accidents and development of ventricular thrombus at the first echocardiographic evaluation. After a clinical episode of transient ischemia or stroke, the diagnosis of cerebral thromboembolism was made when a computed tomographic scan performed within 14 days either showed normal findings or evidence of cerebral infarction.

Both fatal and nonfatal events were considered; recurrent events in the same subject were considered as separate events. All events were documented and verified by medical records, autopsy reports or death certificates. Supplementary evidence was provided by relatives.

Whenever the patient reported an undesirable event that the attending physician believed could have been related to treatment, the patient was recorded as having withdrawn from the study because of treatment intolerance and the associated treatment was stopped.

Statistical analysis. In calculating the number of patients required for the study, it was assumed that the 1-year rate of cardiovascular events would be 10% in the control group and that it would be reduced to 7% with sulodexide treatment (3,6). The type I error (alpha) was set at 5% (two-sided) and the type II error (beta) at 10%. The chi-square test (corrected according to Yates where appropriate) and the Student independent sample t test were used to analyze the difference between the groups at baseline. Survival was evaluated by means of log-rank chi-square statistics, regardless of stratification, and with the Mantel-Haenszel test when stratified according to the use of beta-blockers. Additional statistics used for preliminary analysis included logit-log multiple regression and the Lee and Desu survival analysis test (44).

Table 1. Characteristics of Patients at Baseline

Variable	Sulodexide Group (n = 2,016)	Control Group (n = 1,970)
Male/female	1,667/349	1,613/357
Age (yr)	59.3 ± 9.8	60.1 ± 9.9*
Weight (kg)	72.7 ± 10	72.9 ± 9.5
Hypertension (%)	29	28
Diabetes (%)	11	10
Previous myocardial infarction (%)	18	19
Site of myocardial infarction (%)		
Anterolateral	27.0	27.5
Extensive anterior	5.3	6.3
Inferior	31.4	30.8
Other (specified)	5.9	6.7
Undefined	30.4	28.7
CK peak (mU/ml)	1,264.6 ± 1,150.4	1,269.1 ± 1,133.3
CK-MB peak (mU/ml)	108.6 ± 163.3	109.9 ± 207.3
Therapy in ICU (%)		
Standard therapy (excluding fibrinolytic agents and heparin)	59.1	56.5
Heparin	22.1	25.3
Fibrinolytic agents and heparin	18.8	18.2
Days from onset of myocardial infarction to randomization	7.2 ± 5.5	7.6 ± 13.9

*$p < 0.05$. Unless otherwise indicated, values expressed are mean value ± SD. CK = creatine kinase, CK-MB = creatine kinase isoenzymes; ICU = intensive care unit.

Results

Overall, 69 centers took part in the study, contributing between 11 and 121 cases each. Four centers contributed <20 patients and 10 centers contributed >80. Patient entry at each center was well balanced between treatment groups because of the block design of the randomization table. Preliminary analysis of the effect of the allocation to a center in the overall model showed that this factor had no significant influence and thus no corrections for the center were made in subsequent analyses. A total of 2,016 patients were assigned to receive sulodexide and 1,970 were allocated to the control group. Apart from age, where a small, clinically unimportant yet statistically significant difference was detected (59.3 ± 9.8 years in the sulodexide group vs. 60.1 ± 9.9 years in the control group; $p = 0.05$), patient characteristics were well balanced between the two groups (Table 1). Consequently, the age effect and the age/treatment interaction were considered in all preliminary analyses and are reported here whenever they affect data interpretation.

Mortality. In the control group, 1,681 patients were still alive at the end of the study; 140 had died: 129 of cardiovascular causes and 11 of unrelated noncardiovascular causes. In addition, 17 patients were lost to follow-up and 132 withdrew from the treatment. Of those lost from the control group, three had reached the "survival to 1 year" end point, as had four of those who subsequently withdrew.

In the sulodexide group, 1,705 patients were still alive at the end of the study; 97 had died, 83 of cardiovascular causes and 14 of unrelated noncardiovascular causes. In addition, 20 patients were lost to follow-up and 194 withdrew from treatment (Table 2). Of those lost from the sulodexide group, three had reached the "survival to 1 year" end point, as had 11 of those who withdrew. The need for aortocoronary graft surgery was the same in both groups, as was the proportion

Table 2. Reasons for Withdrawal From the Study

Factor	Control Group (n = 1,970)			Sulodexide Group (n = 2,016)			p Value (log-rank chi-square test)
	No.	%	95% CI	No.	%	95% CI	
Total	132	6.7	5.6–7.8	194	9.6	8.3–10.9	0.0008
Adverse drug reactions				18	0.9	0.5–1.3	
Nonallowed treatments	23	1.2	0.7–1.6	54	2.7	2.0–3.4	0.0006
Antiplatelet agents	9	0.5	0.2–0.8	19	0.9	0.5–1.4	0.0988
NSAIDs with known antiplatelet activity	14	0.7	0.3–1.1	35	1.7	1.2–2.3	0.0052
Coronary bypass surgery	25	1.3	0.8–1.8	23	1.1	0.7–1.6	0.7114
Nonmedical causes	68	3.5	2.6–4.3	80	4.0	3.1–4.8	0.3898
Non-CV diseases	16	0.8	0.4–1.2	19	0.9	0.5–1.4	0.6660

CI = confidence interval; CV = cardiovascular; NSAIDs = nonsteroid anti-inflammatory drugs.

Table 3. Death From All Causes in the Entire Study Sample

Factor	Control Group (n = 1,970)			Sulodexide Group (n = 2,016)			Risk Reduction			
	No.	%	95% CI (%)	No.	%	95% CI (%)	%	95% CI (%)	p Value	Experimental Power
Death (all reasons)	140	7.1	6.0–8.2	97	4.8	3.9–5.7	32	12–53	0.0022	0.85
Reinfarction	15	0.8	0.4–1.1	18	0.9	0.5–1.3	−17	−91–57	0.6456	
Heart failure	30	1.5	1.0–2.1	13	0.6	0.3–1.0	58	15–100	0.0074	0.75
Sudden death	50	2.5	1.8–3.2	33	1.6	1.1–2.2	36	1–71	0.0464	0.47
All other CV accidents	34	1.7	1.2–2.3	19	0.9	0.5–1.4	45	4–87	0.0308	0.55
Non-CV causes	11	0.6	0.2–0.9	14	0.7	0.3–1.1	−24	−112–63	0.5865	

CI = confidence interval; CV = cardiovascular.

of nonmedical withdrawals and those due to the onset of other diseases. A total of 18 patients withdrew from treatment in the sulodexide group after the onset of adverse drug reactions, and significantly more (2.7%) patients given sulodexide withdrew because of disallowed treatments in comparison with the control group (1.2%, p = 0.0005, log-rank chi-square).

Data on mortality, including 95% confidence intervals, are shown in Table 3. Analysis of the total study group revealed that death occurred in 140 patients (7.1%) in the control group and 97 patients (4.8%) in the sulodexide group, indicating a statistically significant (32%) reduction in risk for the sulodexide group compared with the control group (p = 0.0022, log-rank chi-square test) (Fig. 1).

To avoid the risk of bias due to the relatively large proportion of patients withdrawn from the trial, the analysis of mortality was repeated for those patients who reached one of the study end points (Table 4) and confirmed the preceding results (p = 0.0011). The observed mortality risk reduction in the sulodexide group, regardless of considered sample, appears to be due to a decreased risk of death from heart failure (p = 0.0101), other cardiovascular events (including three fatal cerebrovascular events, p = 0.0417) and to some extent from sudden death (p = 0.0659) (p = 0.0464 for the total study group).

Multiple regression analysis of the percent of survivors versus time indicated a significant effect of gender; mortality rate 5.1% in men and 9.8% in women (p = 0.0001 by log-rank corrected chi-square test) and a significant age effect (the mortality rate increasing with age).

Preliminary analysis by logit-log multiple regression indicated that gender and age, although significant by themselves in predicting survival, did not influence the treatment effect to a significant extent. Thus, neither factor was considered in the overall evaluations.

The treatment effect was also confirmed after stratifying patients according to whether they were prescribed beta-blockers during the follow-up period (Mantel-Haenszel test

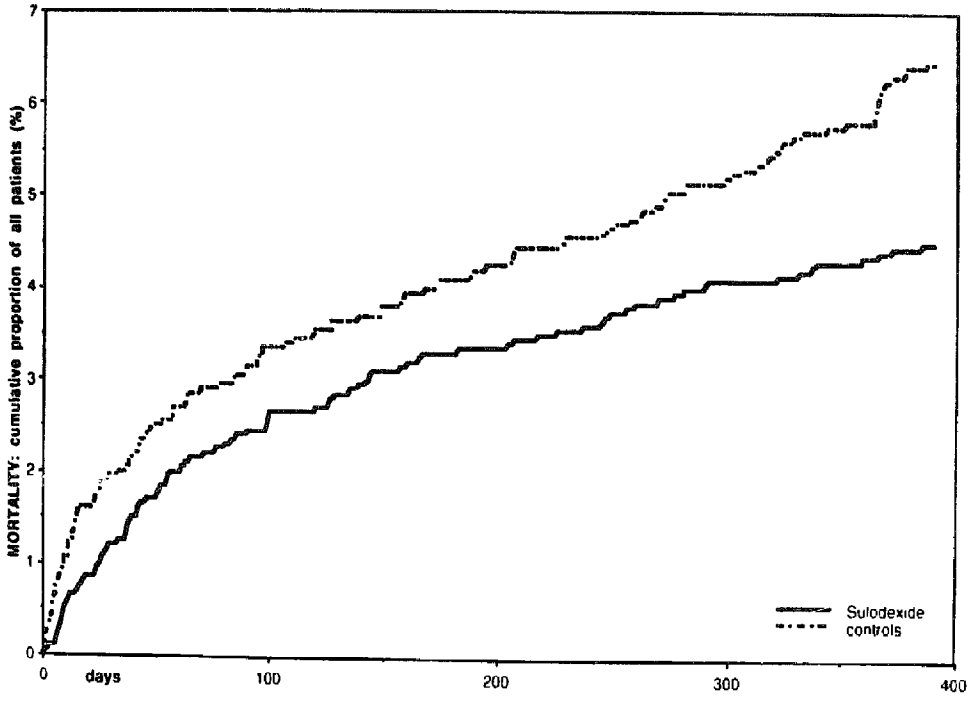

Figure 1. Cumulative proportion of death from all causes in the study group according to the assigned treatment.

Table 4. Death From All Causes in the Patients Reaching an End Point

Factor	Control Group (n = 1,788) No	%	95% CI (%)	Sulodexide Group (n = 1,769) No.	%	95% CI (%)	Risk Reduction %	95% CI (%)	p Value	Experimental Power
Death (all reasons)	134	7.5	6.3–8.7	86	4.9	3.9–5.9	35	14–56	0.0010	0.88
Reinfarction	15	0.8	0.4–1.3	18	1	0.5–1.5	−21	−96–54	0.5789	
Heart failure	30	1.7	1.1–2.3	13	0.7	0.3–1.1	56	14–99	0.0101	0.73
Sudden death	50	2.8	2.0–3.6	33	1.9	1.2–2.5	33	−2–69	0.0695	0.38
All other CV accidents	34	1.9	1.3–2.5	19	1.1	0.6–1.6	44	2–85	0.0417	0.45
Non-CV causes	5	0.3	0.0–0.5	3	0.2	0.0–0.4	39	−72–151	0.4883	

Abbreviations as in Table 3.

= 9.407; p = 0.002). The mortality rate for the entire study group, irrespective of cause, was 6.2% (227 of 3,649 patients) for those who had not received beta-blockers and 3% (10 of 337 patients) for those who had received beta-blockers. According to treatment group, the mortality rate for the control group was 7.4% (134 of 1,803 patients) and 3.6% (6 of 167 patients), respectively. In the sulodexide group, the mortality rate was 5% (93 of 1,846 patients) and 2.4% (4 of 170 patients), respectively. Even allowing for treatment effect, there was still a significant effect of beta-blockers on survival (Mantel-Haenszel test = 5.860; p = 0.015), suggesting that a combination of sulodexide and beta-blockers may be beneficial in enhancing long-term survival after the acute infarction phase.

Cardiovascular events. During the follow-up period, 158 fatal and nonfatal cardiovascular events occurred in 148 patients (7.5%) in the control group and 112 fatal and nonfatal cardiovascular events occurred in 104 patients (5.2%) in the sulodexide group (Table 5). Analysis of both the number of patients and events yielded a significant risk reduction in the sulodexide group (31%, 95% confidence interval 11% to 51, p = 0.0023 by log-rank chi-square test). Among the events observed, a significant protection appeared evident on left ventricular mural thrombosis (53%, 95% confidence interval 6% to 100%, p = 0.0266) and fatal and nonfatal reinfarction (28%; 95% confidence interval 2% to 55%, p = 0.0351). No risk reduction was associated with monitored treatment with respect to events such as deep vein thrombosis, cerebrovascular accidents, peripheral vascular accidents or lung embolism.

The time course of the occurrence of both mural thrombosis and reinfarction indicated that the risk reduction was detectable from approximately the end of the 3rd month of treatment. It therefore seems that the pharmacodynamic action of sulodexide requires a "prompting" period to cause detectable risk reduction of these cardiovascular events.

Discussion

Background. Antithrombotic therapy has been shown to reduce the occurrence of cardiovascular events and death after acute myocardial infarction. Oral anticoagulants and low dose heparin similarly reduce the risk of death (8), reinfarction (8,10), the incidence of postinfarction left ventricular mural thrombosis (45,46) and cerebrovascular accidents (47). However, aspirin is associated with a relatively high incidence of gastrointestinal events, especially in the elderly, and long-term anticoagulant therapy carries a significant risk of bleeding and requires repeated monitoring by coagulation tests.

An 11-month period of oral administration of sulodexide after 1 month of treatment by the intramuscular route is

Table 5. Cardiovascular Events (lethal and nonlethal) in the Entire Study Sample

Factor	Control Group (n = 1,970) No.	%	95% CI (%)	Sulodexide Group (n = 2,016) No.	%	95% CI (%)	Risk Reduction %	95% CI (%)	p Value	Experimental Power
Occurrence (total patients)	148	7.5	6.3–8.7	104	5.2	4.2–6.1	31	11–51	0.0022	0.83
Occurrence (total events)	158	8	6.8–9.2	112	5.6	4.6–6.6	31	11–50	0.0020	0.84
Reinfarction	90	4.6	3.6–5.5	66	3.3	2.5–4.1	28	2–55	0.0351	0.53
Deep vein thrombosis	8	0.4	0.1–0.7	3	0.1	0.0–0.3	63	−17–144	0.1217	
Cerebrovascular accidents	25	1.3	0.8–1.8	20	1.0	0.6–1.4	22	−30–74	0.4077	
Peripheral vascular accidents	5	0.3	0.0–0.5	3	0.1	0.0–0.3	41	−68–151	0.4592	
Left ventricular thrombosis	25	1.3	0.8–1.8	12	0.6	0.3–0.9	53	6–100	0.0266	0.56
Pulmonary embolism	5	0.3	0.0–0.5	8	0.4	0.1–0.7	−56	−195–83	0.4284	

CI = confidence interval.

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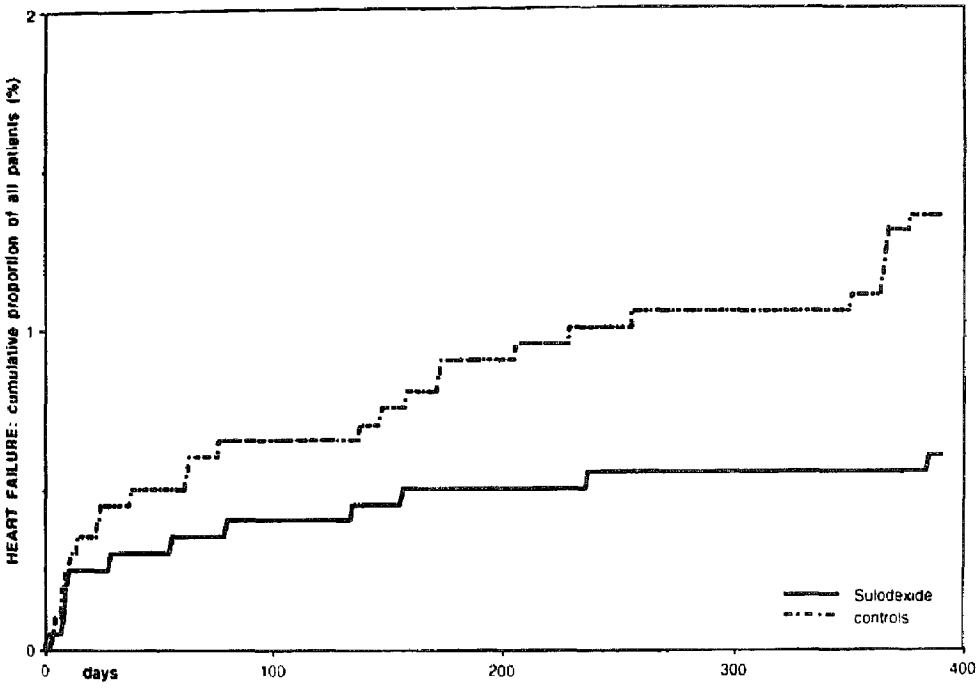

Figure 2. Cumulative proportion of death from heart failure in the study group according to the assigned treatment.

effective in maintaining the anti-Xa activity levels and the antithrombotic effects obtained after initial intramuscular injections (25). These previously documented features of sulodexide provide the rationale for its use in patients after myocardial infarction, particularly in those who, because of advanced age or risk of hemorrhagic complications, require a drug that is easy to use, is well tolerated and can be used for long-term treatment.

Evidence. The main result of the present study is the reduction in total mortality rate that was demonstrated for all patients allocated to receive sulodexide and for those who reached only one end point. This appears to be due to a reduction in death secondary to heart failure, death due to other cardiovascular events and sudden death. Although the mortality curves for the sulodexide and control groups diverge from the beginning of the study (Fig. 1), the risk reduction for reinfarction occurs to a detectable extent from approximately the beginning of the 4th month of treatment. Similarly the risk reduction for mural thrombosis is only evident after 50 days. The most likely explanation for the beneficial effects of sulodexide is the antithrombotic property of the drug, which leads to a reduction in the rate of ischemic episodes, reinfarction and sudden death. The chronologic dissociation between the prompt initial benefit on mortality and the delayed benefits on reinfarction and mural thrombosis could be related to a significantly earlier occurrence of heart failure ($p = 0.0143$) (44) (Fig. 2), sudden death ($p = 0.0544$) and other cardiovascular deaths ($p = 0.0540$) in the control group.

Study limits. The design of this trial did not allow any antithrombotic therapy, even in the control group. When this study was designed in 1985, no clear benefit from antithrombotic therapy in terms of survival had been shown in any trial.

No comparison between sulodexide and other antithrombotic drugs can be deduced from this study. However, our results (reductions in mortality, reinfarction rate and left ventricular thrombus formation) are consistent with the reported effects of antiplatelet drugs (9) and oral anticoagulant agents (8).

An acknowledged limitation of this study is the lack of double-blind design. It was considered unethical to administer a placebo by the intramuscular route for a relatively long period of time (1 month), causing the patient inconvenience and discomfort without any possible benefit. Furthermore, by not introducing a placebo-treated group, changes in therapeutic procedures were minimized at the study centers. However, the end points of the study (death, reinfarction and thromboembolic events) are unlikely to have been influenced by the absence of blinding.

Tolerability. Only a few minor side effects were observed with sulodexide treatment and no reported event was fatal, or life-threatening, required hospitalization or resulted in permanent disability. The adverse drug experiences were two cases of hematoma during intramuscular treatment, four skin reactions, five cases of epigastralgia and seven cases of nausea or vomiting (side effects were not considered to be a reason for withdrawal in the control group).

Conclusions. The present study provides evidence that sulodexide reduces the rate of cardiovascular death and late reinfarction in survivors of myocardial infarction. The drug also reduces the rate of left ventricular thrombus formation after infarction. The treatment appears to be safe and well

tolerated, even in the elderly, and does not require laboratory monitoring or hemostasis.

We appreciate the kind and useful collaboration of Dr. E. Palazzini and Dr. P. Ferrari, Alfa Wassermann S.p.A., Bologna, Italy.

Appendix

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