Anticoagulant properties, clinical efficacy and safety of efegatran, a direct thrombin inhibitor, in patients with unstable angina

P. Klootwijk*, T. Lenderink†, S. Meij*, H. Boersma*, R. Melkert†, V. A. W. Umans‡, J. Stibbe§, E. J. Müller‖, K. J. Poortermans¶, J. W. Deckers§ and M. L. Simoons*

*Department of Cardiology, Rotterdam Heart Centre, Division Thoraxcentre, §Division of Haemostasis, Department of Haematology, University Hospital Dijkzigt, Erasmus University Rotterdam, Rotterdam; †Cardialysis B.V., Rotterdam; ‡Medisch Centrum Alkmaar, Alkmaar; ‖Spaarne Ziekenhuis, Heemstede; ¶Medisch Spectrum Twente; Enschede, The Netherlands

Aims Thrombin plays a key role in the clinical syndrome of unstable angina. We investigated the safety and efficacy of five dose levels of efegatran sulphate, a direct thrombin inhibitor, compared to heparin in patients with unstable angina.

Methods Four hundred and thirty-two patients with unstable angina were enrolled. Five dose levels of efegatran were studied sequentially, ranging from 0.105 mg . kg^{-1} . h^{-1} to 1.2 mg . kg^{-1} . h^{-1} over 48 h. Safety was assessed clinically, with reference to bleeding and by measuring clinical laboratory parameters. Efficacy was assessed by the number of patients experiencing any episode of recurrent ischaemia as measured by computer-assisted continuous ECG ischaemia monitoring. Clinical end-points were: episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA or CABG), and death.

Results Efegatran demonstrated dose dependent ex-vivo anticoagulant activity with the highest dose level of 1.2 mg . kg^{-1} . h^{-1} resulting in steady state mean activated partial thromboplastin time values of approximately three times baseline. Thrombin time was also increased. Neither of the efegatran doses studied were able to suppress myocardial ischaemia during continuous ECG ischaemia monitoring to a greater extent than that seen with heparin. There were no statistically significant differences in clinical outcome or major bleeding between the efegatran and heparin groups. Minor bleeding and thrombophlebitis occurred more frequently in the efegatran treated patients.

Conclusion Administration of efegatran sulphate at levels of at least 0.63 mg . kg^{-1} . h^{-1} provided an antithrombotic effect which is at least comparable to an activated partial thromboplastin time adjusted heparin infusion. There was no excess of major bleeding. The level of thrombin inhibition by efegatran, as measured by activated partial thromboplastin time, appeared to be more stable than with heparin. Thus, like other thrombin inhibitors, efegatran sulphate is easier to administer than heparin. However, no clinical benefits of efegatran over heparin were apparent.

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Key Words: Anti-thrombin, efegatran, unstable angina, ECG ischaemia monitoring.

Introduction

Acute coronary ischaemic syndromes are usually the result of a ruptured atherosclerotic plaque, followed by platelet aggregation, often in combination with increased vasomotor tone, leading to a sudden increase in the pre-existing stenosis[1,2]. This process may culminate in one or more episodes of impaired flow without myocardial necrosis and the syndrome of unstable angina[3], or progress into total coronary occlusion and myocardial infarction. Thrombin plays a key role in this process. It causes fibrin formation through proteolytic cleavage of plasma fibrinogen, and induces platelet activation and aggregation[4,5]. Thus, drugs which directly inhibit thrombin, such as efegatran sulphate,

have been considered for the treatment of unstable angina, in order to prevent recurrent ischaemic episodes and progression into myocardial infarction.

Efegatran sulphate is a tripeptide, direct acting thrombin inhibitor. Unlike heparin it has the capacity to bind directly to thrombin, and to inactivate both circulating and clot-bound thrombin[6]. Efegatran sulphate also inhibits thrombin-induced platelet aggregation. The primary objective of the present study was to assess the safety and efficacy of different doses of efegatran sulphate compared to heparin in patients with unstable angina. Safety was assessed clinically with particular reference to bleeding occurrences and by measurement of laboratory parameters. Efficacy was assessed primarily by comparison of the number of patients experiencing any episode of recurrent ischaemia, as measured by computer-assisted 48 h continuous ECG ischaemia monitoring during different treatment regimens. The latter technique has proven to be useful for detection and quantification of recurrent ischaemia (related to clinical outcome) and for assessment of treatment efficacy in patients with refractory unstable angina who are treated with a platelet glycoprotein IIb-IIIa receptor blocker[7,8]. Clinical end-points were the incidences of recurrent angina, myocardial infarction or coronary intervention (PTCA or CABG) and death at 7 days and 30 days follow-up. The first stage of this study was a dose ranging programme to assess the ex-vivo anticoagulant and anti-thrombotic effect and the bleeding risk associated with administration of five dose regimens of efegatran sulphate in 132 patients with unstable angina, compared to heparin. These results were used for selection of two dose levels of efegatran sulphate which were compared to heparin in a subsequent study of 300 patients.

Patients and methods

Study patients

Patients between 21 years and 75 years old with a clinical diagnosis of unstable angina were eligible for the study. For inclusion, patients should exhibit at least one episode of angina at rest or minimal exertion and have concomitant transient ST- and/or T-wave changes on their ECG, either at admission, or during observation in hospital. Patients were excluded for any of the following reasons: ECG abnormalities making ST-T segment interpretation unreliable, such as left bundle branch block, left ventricular hypertrophy or artificial pacemaker rhythm; suspected acute myocardial infarction or recent myocardial infarction (within the hospitalization period), unless creatine kinase had returned to less than twice the normal upper limit; heparin treatment since the most recent episode of ischaemia prior to study enrolment; known aspirin allergy or other contraindication for aspirin; concurrent use of oral anticoagulants (coumarins) at the time of study entry, or anticipated

need for oral anticoagulants during the study period; recent administration of a thrombolytic agent, unless fibrinogen values had returned to more than 50% of the normal lower limit; activated partial thromboplastin time and prothrombin time values exceeding the normal upper limits, within the 24 h prior to study enrolment; active internal bleeding or peptic ulcer; bleeding risk factors such as recent surgery, major trauma, gastrointestinal or genito-urinary bleeding, puncture of non-compressible vessels or organ biopsy in the 3-month period prior to enrolment; a history of cerebrovascular accident, transient ischaemic attack, cranial or intraspinal surgery; underlying medical conditions such as persistent hypertension despite treatment, a history of haemorrhagic diathesis, or a platelet count of less than $100 \times 10^9 . 1^{-1}$ within the 24 h prior to the study; known, or suspected major hepatic or renal disease and known haemostatic defects, including those secondary to hepatic or renal insufficiency, or a bleeding time ≥ 8 min (Ivy method), or ≥ 20 min (Simplate method) while receiving aspirin; women with childbearing potential.

Study design

A single, blind randomized multicentre comparison of different dose levels of efegatran sulphate vs heparin was performed in patients with unstable angina. The study consisted of a dose ranging phase, where five doses of efegatran were assessed in a sequential manner. Based on the safety and efficacy findings of this dose ranging phase, two dose levels of efegatran were chosen by the Steering Committee for further evaluation in a parallel phase, in which two doses of efegatran were compared to heparin. In this second phase of the study, subjects were randomly assigned to receive either one dose level of efegatran or heparin and safety was assessed on an ongoing basis by the Steering Committee.

Efficacy criteria were the number of patients experiencing any episode of recurrent ischaemia as measured by computer-assisted 48 h continuous ECG ischaemia monitoring and the incidence of recurrent angina, myocardial infarction or coronary intervention (PTCA or CABG) and death at 7 days (dose ranging phase) and 30 days follow-up (parallel phase).

Study drug regimens

In the dose ranging phase, the patients of dosage groups 1–4 received efegatran sulphate as an initial loading i.v. bolus of 0.1 mg . kg^{-1} over 15 min, followed by continuous infusion of either 0.105, 0.32, 0.63 or 0.84 mg . kg^{-1} . h^{-1}. In the fifth dosage group, an i.v. loading bolus of 0.3 mg . kg^{-1} over 1 min was given, followed by continuous infusion of 1.2 mg . kg^{-1} . h^{-1}. The infusions were to be continued for 48 ± 10 h. The parallel design phase compared group 3 (loading dose

of $0 \cdot 1 \, mg \cdot kg^{-1}$ over 15 min followed by continuous infusion of $0 \cdot 63 \, mg \cdot kg^{-1} \cdot h^{-1}$), and group 5 (loading dose of $0 \cdot 3 \, mg \cdot kg^{-1}$ over 1 min followed by $1 \cdot 2 \, mg \cdot kg^{-1} \cdot h^{-1}$) with heparin.

Control patients were treated with a bolus injection of 5000 IU heparin, followed by a continuous infusion of $1000 \, IU \cdot h^{-1}$ heparin for 48 ± 10 h. After this period, treatment could be continued with heparin at the discretion of the treating physician. Throughout any heparin infusion, the heparin dosage was adjusted to an activated partial thromboplastin time ratio of 2·0 to 2·5 times normal, based on local laboratory activated partial thromboplastin time values. Heparin treatment was not allowed before the start of the study, or during the infusion of efegatran sulphate. After termination of the efegatran sulphate infusion, heparin could be initiated for treatment of recurrent or continuing ischaemia, at the discretion of the treating physician.

All patients were concomitantly treated with aspirin. If the patient was on aspirin treatment prior to the start of study, aspirin was continued at a dose of 80 mg once daily for the first 4 days. If a patient was not on aspirin, the initial dose was a minimum of 250 mg chewed, or intravenously, followed by an oral dose of 80 mg aspirin once daily during the first 4 days. After day 4, aspirin was continued at the discretion of the physician. Nitroglycerin, beta-blockers, calcium channel blockers and other cardiovascular drugs were allowed.

Laboratory tests

The effect of efegatran sulphate and heparin on markers of thrombosis and haemostasis was assessed by measuring bleeding time (Ivy, Simplate, Surgicut and Duke method, local laboratory, dose-ranging part only), the activated partial thromboplastin time (local, and central laboratory), prothrombin time (local, and central laboratory) and fibrinogen levels (central laboratory). Levels of fibrinogen were measured using both the ACL and Clauss methods. Levels of activation markers of platelets (beta-thromboglobulin, platelet factor 4), coagulation (prothrombin fragment 1·2, fibrinopeptide A, thrombin–antithrombin complexes) and fibrinolysis (fibrin degradation products) were measured in the dose finding phase only (central laboratory). General haematology (local laboratory), chemistry (central laboratory) and urinanalysis (local laboratory) were also performed.

Efficacy criteria

The efficacy of efegatran sulphate as compared with heparin was assessed by its effect on the percentage of patients experiencing any episodes of recurrent ischaemia, measured by computer-assisted continuous ECG ischaemia monitoring, as described below. Episodes of recurrent angina, myocardial infarction, coronary intervention (PTCA with balloon or other devices, CABG) and death were also evaluated at 7 days (dose ranging phase) and 30 days follow-up (parallel phase).

Definition of a myocardial infarction required either documentation of an increase in creatine kinase or creatine kinase-MB levels, or electrocardiographic changes. Creatine kinase or creatine kinase-MB levels should exceed twice the upper limit of normal (in two samples collected at different sampling times) and increase by at least 50% over the baseline value. If both creatine kinase and creatine kinase-MB values were available creatine kinase-MB took preference. Electrocardiographic changes were defined as new significant Q waves of $\geq 0 \cdot 04$ s duration or with an amplitude of at least one-fourth of the corresponding R-wave amplitude in two or more contiguous leads. The onset of a myocardial infarction was derived from the occurrence of chest pain of at least 30 min duration. In the absence of chest pain, the time of measurement of the trough creatine kinase (-MB) level immediately preceding creatine kinase (-MB) rise was taken as the moment of onset of myocardial infarction, unless the time interval between these two samples was greater than 6 h.

Recurrent angina was defined as a re-occurrence of chest pain after the moment of randomization, with concomitant transient ST or T wave changes, not leading to a creatine kinase (or creatine kinase-MB) rise or to the development of new significant Q waves.

Each patient was carefully observed for signs or symptoms of bleeding. Bleeding was classified as major, or minor. Major bleeding was defined as clinically overt, and accompanied by either transfusion of two or more units of blood, surgery for treatment of the bleeding, or intracranial location of the bleeding. Bleeding was defined as minor if it was clinically overt but did not meet the other criteria for major bleeding.

Computer-assisted continuous ECG ischaemia monitoring

Continuous ECG monitoring was performed using the ELI-100 continuously updated 12-lead ECG monitoring system (Mortara Instruments, Milwaukee, U.S.A). ECG monitoring was started preferably before the start of the study drug and continued for at least 6 h following termination of the study-drug infusion.

The system was programmed to store median ECG complexes from the 12 ECG leads every 20 s if $\geq 100 \, \mu V$ ST segment shift was present in one lead relative to the baseline ECG of that patient, or if $\geq 50 \, \mu V$ ST shift was present in any two leads of the 12-lead ECG. If less or no ST change was present, a baseline median ECG was stored every 20 min. Median ECG complexes and ST trend data were stored on a removable hard disk or floppy disk. After completion of the recording, this disk was sent to the central ECG core-laboratory of Cardialysis Rotterdam, The Netherlands, for subsequent editing and analysis. ST changes were evaluated in a blinded fashion and considered indicative of ischaemia if $\geq 100 \, \mu V$ for more than 1 min duration.

Table 1   Baseline data

	Efegatran 0·105 (n=10)	Efegatran 0·32 (n=25)	Efegatran 0·63 (n=122)	Efegatran 0·84 (n=24)	Efegatran 1·2 (n=128)	Heparin (n=123)	All (n=432)
Male	5 (50%)	17 (68%)	83 (68%)	19 (79%)	100 (78%)	77 (63%)	301 (70%)
Mean (SD) age in years	60 (9)	60 (10)	62 (10)	59 (10)	60 (10)	61 (10)	61 (10)
Anthropometry: mean (SD)							
Weight (kg, SD)	75 (9)	77 (12)	77 (12)	79 (10)	82 (13)	77 (12)	79 (12)
Height (cm, SD)	170 (11)	171 (10)	172 (9)	173 (7)	175 (9)	172 (9)	173 (9)
Number of patients with							
previous myocardial infarction	7 (70%)	10 (40%)	41 (34%)	11 (46%)	38 (30%)	43 (35%)	150 (35%)
PTCA	0 (0%)	0 (0%)	15 (13%)	0 (0%)	13 (10%)	14 (11%)	42 (10%)
CABG	0 (0%)	2 (8%)	15 (12%)	2 (8%)	13 (10%)	14 (11%)	46 (11%)
Risk factors							
Diabetes	0 (0%)	2 (8%)	12 (10%)	3 (13%)	14 (11%)	10 (8%)	41 (10%)
Hypercholestolaemia	5 (50%)	9 (36%)	45 (37%)	12 (50%)	56 (44%)	51 (42%)	178 (42%)
Hypertension	2 (20%)	1 (4%)	14 (12%)	0 (0%)	11 (9%)	12 (10%)	40 (9%)
Current smokers	4 (40%)	11 (44%)	42 (34%)	9 (38%)	58 (45%)	44 (36%)	168 (39%)

Percentages only calculated for those patients in whom data were reported.

The method of editing and analysis of the recorded data has recently been described in detail[9]. In brief, the onset of an ST episode was defined as a change of ST amplitude in one or more leads of at least ± 100 µV from the baseline ST level, developing within a 10 min period and persisting for at least 1 min. The end was defined as a return of the ST level within ± 100 µV of the baseline ST level, again lasting for at least 1 min. Episodes had to be separated from each other by at least 1 min. If ≥ 100 µV ST change was present in more than one lead simultaneously, the episode onset was defined by the lead exhibiting the first significant ST change. Similarly, the end of an episode was defined by the lead exhibiting the latest return to baseline ST level. Postural ST changes were defined as a sudden change of the electrical axis or a sudden QRS amplitude shift in the precordial leads[9].

Statistical analysis and power calculation

Laboratory parameters were compared using analysis of variance and are expressed as medians and interquartile ranges (25th and 75th percentiles). Continuous non-parametric variables were compared using the Kruskal–Wallis test. Discrete variables are described with percentages and were compared using Fisher's exact test. A two-tailed *P* value was calculated in all instances. A *P* value of ≤ 0·05 was considered statistically significant. The Kaplan–Meier method was used for evaluation of event free survival and for evaluation of the time to the occurrence of a first ST episode or a recurrent ST episode, with censoring of data. Statistical difference was tested with the log rank test. Based on the data of the dose ranging group, we expected that approximately 75% of the heparin treated patients and 55% of the efegatran treated patients would exhibit ischaemic episodes during the 48 h continuous ECG ischaemia monitoring. Power calculations indicated that approximately 100 patients per treatment group were needed to achieve a power of 80% (*a*=0·05).

Results

A total of 432 patients were included: 132 patients in the dose ranging phase and another 300 patients in the parallel phase. Baseline patient characteristics are summarized in Table 1. The mean age of the patients was 60 years, 70% were male, and almost all were Caucasian (98%). There were no differences in the prevalence of previous myocardial infarction, diabetes mellitus, hypertension or smoking history among the treatment groups. Fifty-eight patients (13·4%) were enrolled as having unstable angina, but actually had a myocardial infarction at presentation which became evident from subsequent creatine kinase elevation.

Markers of coagulation and bleeding time

Infusion of efegatran was associated with an increase in the activated partial thromboplastin time, the pro-thrombin time as well as the thrombin time, which rapidly resolved following cessation of therapy (Fig. 1). The activated partial thromboplastin time increase appeared to be dose dependent. The increase in activated partial thromboplastin time associated with 1·2 mg . kg^{-1} . h^{-1} efegatran was comparable to that observed with heparin (*P*=0·89). The activated partial thromboplastin time was more stable when using efegatran as compared to using heparin.

With respect to the three major treatment groups, prothrombin time was mildly increased following administration of efegatran, with a significant difference between the 1·2 mg . kg^{-1} . h^{-1} efegatran and heparin
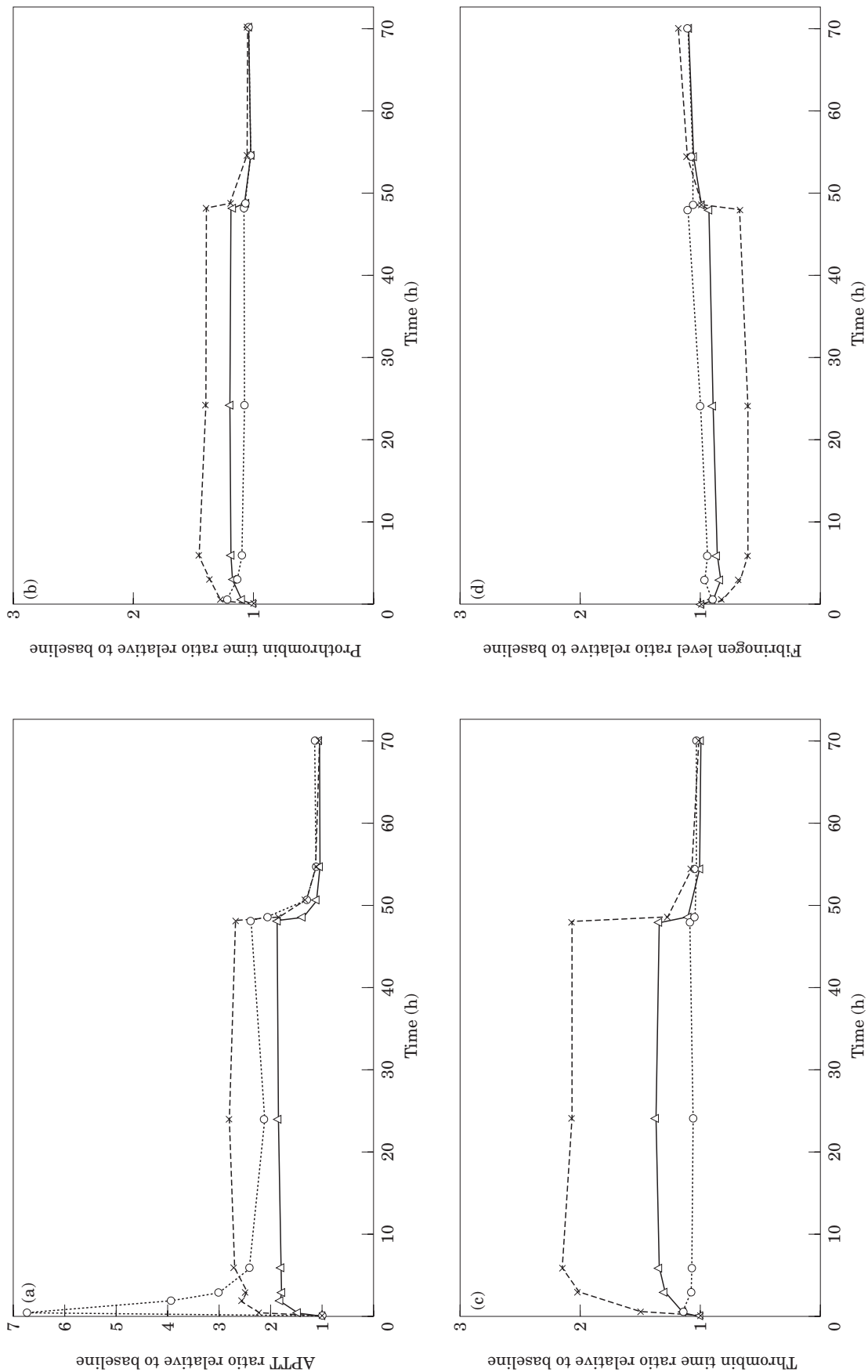
Figure 1 **Activated partial thromboplastin times (APTT), prothrombin times, thrombin times and fibrinogen levels of the three major treatment groups. (a) Ratio of median activated partial thromboplastin times relative to baseline value; (b) ratio of median prothrombin times relative to baseline; (c) ratio of median thrombin times relative to baseline; (d) ratio of median fibrinogen levels relative to baseline levels.** —×—=efegatran 1·2; —△—=efegatran 0·63; – –○– –=heparin.

Table 2   Number and duration of ischaemic episodes during continuous ECG ischaemia monitoring

	Efegatran 0·105	Efegatran 0·32	Efegatran 0·63	Efegatran 0·84	Efegatran 1·2	Heparin	All
Patients	7	21	115	18	124	120	405
Ischaemic episodes*							
≥1 ST episode	5 (71%)	17 (81%)	68 (59%)	10 (56%)	80 (65%)	77 (64%)	257 (64%)
≥2 ST episodes	4 (57%)	10 (48%)	53 (46%)	7 (39%)	55 (44%)	55 (46%)	184 (45%)
≥3 ST episodes	2 (29%)	7 (33%)	37 (32%)	5 (28%)	34 (27%)	34 (28%)	130 (32%)
Patients with ≥30 min ischaemia*	2 (29%)	7 (33%)	31 (27%)	2 (11%)	28 (23%)	39 (33%)	109 (27%)
Total duration/pt (min)*, **	11 (6, 14)	11 (4, 16)	8 (3, 16)	11 (3, 13)	8 (3, 16)	12 (5, 20)	10 (4, 17)
Time to first episode (h)**	13·7 (2·1, 22·1)	9·2 (4·0, 37·5)	9·1 (1·8, 21·5)	9·0 (2·9, 20·6)	10·9 (2·3, 20·4)	7·5 (1·9, 21·6)	9·2 (2·2, 21·3)

*Normalized to 24 h of recording
**Median, 25, 75 percentiles, patients with ischaemia only.

Table 3 *Clinical end-points at seven days from randomization*

	Efegatran 0·105 (n=10)	Efegatran 0·32 (n=25)	Efegatran 0·63 (n=122)	Efegatran 0·84 (n=24)	Efegatran 1·2 (n=128)	Heparin (n=123)	All (n=432)
Composite end-point reached*	7 (70%)	13 (52%)	77 (63%)	17 (71%)	84 (66%)	87 (71%)	285 (66%)
Death	—	—	2 (1·6%)	—	—	—	2 (0·5%)
Myocardial infarction/reinfarction	—	—	3 (2·5%)	—	3 (2·3%)	3 (2·4%)	9 (2·1%)
Recurrent angina	6 (60%)	13 (52%)	76 (62%)	17 (71%)	84 (66%)	85 (69%)	282 (65%)
PTCA	—	—	11 (9%)	—	10 (8%)	5 (4%)	26 (6%)
CABG	1 (10%)	—	1 (0·8%)	—	3 (2·3%)	4 (3·3%)	9 (2·1%)

*Composite end-point defined as the occurrence of either death, myocardial infarction, recurrent angina or need for revascularization.

groups ($P=0.006$). Prothrombin time returned rapidly to normal after discontinuation of therapy (Fig. 1b). Thrombin time was influenced in a strong and dose dependent manner by efegatran, while administration of heparin did not modify thrombin time (Fig. 1c). Efegatran 0·63 mg . kg^{-1} . h^{-1} was associated with an increase of thrombin time levels of approximately 40%, while thrombin time values doubled following the administration of efegatran 1·2 mg . kg^{-1} . h^{-1}. These differences were all highly significant ($P=0.0007$). Thrombin time levels returned to normal rapidly after cessation of efegatran.

Fibrinogen levels decreased following administration of efegatran, and returned to baseline levels immediately following discontinuation of therapy (Fig. 1d). The concentration of fibrinogen did not change under heparin.

Different methods were employed to measure bleeding times. Local measurements were abnormal at baseline in 9·1% of the patients. The number of abnormal values increased slightly during infusion of heparin and efegatran, but no consistent pattern emerged across the different treatment groups.

Markers of coagulation activation

Levels of activation markers were measured in the dose finding phase group only and were therefore available in a limited number of patients. It should be appreciated that the concentrations of all these parameters, with the exception of the fibrin degradation products, could have been affected artificially as a result of a traumatic vein puncture, although attempts were made to avoid this.

Levels of beta-thromboglobulin and platelet factor 4 showed wide variability at baseline, during treatment with heparin and efegatran, and following discontinuation of medication. No consistent changes were observed, and no differences between the treatment groups could be established. Also fibrinopeptide A, prothrombin fragment 1·2, thrombin-antithrombin complexes and fibrin degradation products did not change significantly during treatment with heparin or efegatran.

Recurrent ischaemia during computer-assisted continuous ECG ischaemia monitoring

Good quality ECG recordings were obtained in 405 patients (93%). One hundred and fourteen patients were randomized to one of the six treatment groups in the dose finding phase, and 291 to one of the three treatment groups of the parallel design phase. For all patients, the median (25–75 percentiles) total ECG monitoring time from the start of study drug until the end of monitoring was 51 (46–54) h. Total analysable ECG monitoring time was 46 (39–50) h and did not differ across treatment groups. The median ECG recording data loss was 6% (2–6).

Recurrent ischaemic episodes were observed in 64% of all patients. Symptomatic episodes occurred in 14% of patients. The median number of episodes (25–75 percentiles) per patient (normalized to 24 h) was 0·6 (0–3·4) and the total duration of ischaemic episodes per patient in those patients with ischaemia was 10 (4–17) min (Table 2). Ischaemia of ≥30 min duration was present in 27% of all patients. There was no significant difference between the number of patients with recurrent ischaemia or the number or duration of ischaemic episodes among the treatment groups, although there was a trend towards less prolonged ischaemia with the higher doses of efegatran compared to heparin ($P=0.068$).

Figure 2 demonstrates Kaplan–Meier estimates of the probability of remaining free of recurrent ischaemia during the course of the monitoring period for the three largest groups. Overall, the median time to the first episode in patients with recurrent ischaemia was 9·2 h. The risk of a first, second or third recurrent ischaemic episode was comparable among the three treatment groups. There was no evidence of a rebound of ischaemia following cessation of efegatran or heparin administration (data not shown).

Clinical outcomes

Recurrent angina was frequent in all groups, but only 2·1% and 0·5% of patients experienced a myocardial

infarction or death at 7 days follow-up, respectively (Table 3). The percentage of patients that reached the composite end-point (recurrent angina, myocardial infarction, ischaemia driven coronary intervention or death) at 7 days ranged from 52% to 71% in the efegatran treatment groups and was 71% in patients treated with heparin. Although the need for percutaneous interventions in the efegatran treated patients was slightly higher than in the heparin group (9%, vs 4%

in the heparin treated patients), no significant differences were observed among the treatment groups.

At 30 days follow-up, the percentage of patients that reached the composite end-point was 73% and 81% in the efegatran treatment groups, and 81% in those treated with heparin. Only 3·2% and 2·1% of patients experienced a myocardial infarction or death at 30 days follow-up, respectively (Fig. 3).

The relationship of ischaemic episodes during treatment with subsequent death and myocardial infarction was explored but the number of these complications was too low for a meaningful assessment of such an association.

Adverse events and bleedings

Patients receiving efegatran often developed a superficial thrombophlebitis that seemed to increase, although not significantly, in severity in the higher dose groups, the incidence ranging from 7·7% to 20%, which was significantly higher than with heparin ($P=0.0001$). For this reason the infusion rate in the highest dose group during the dose ranging phase was increased from 4 ml . h^{-1} to 40 ml . h^{-1} with a subsequent decrease in the concentration of efegatran administered. This regimen was also used for the subsequent phases of the study, and did reduce the severity of the events. However, it did not reduce the overall occurrence of phlebitis. In the second phase of the study, the number of patients with phlebitis in the 0·63 mg . kg^{-1} . h^{-1} dose group was 13%, compared to 25% in the 1·2 mg . kg^{-1} . h^{-1} dose group and 2% in the patients treated with heparin. In the great majority of patients, the severity of the phlebitis was only mild.

The incidence of minor bleeding events was significantly higher in patients treated with efegatran ($P=0.001$) ranging from 17% to 32%, against 11% in patients under heparin (Table 4). There were three major bleedings, two of which occurred in patients treated with heparin. Spontaneous gross haematuria was equally distributed and observed in three patients (0·7%). Most minor bleedings were associated with a previous puncture site, and did not require specific measures. There were no strokes associated with administration of trial medication.
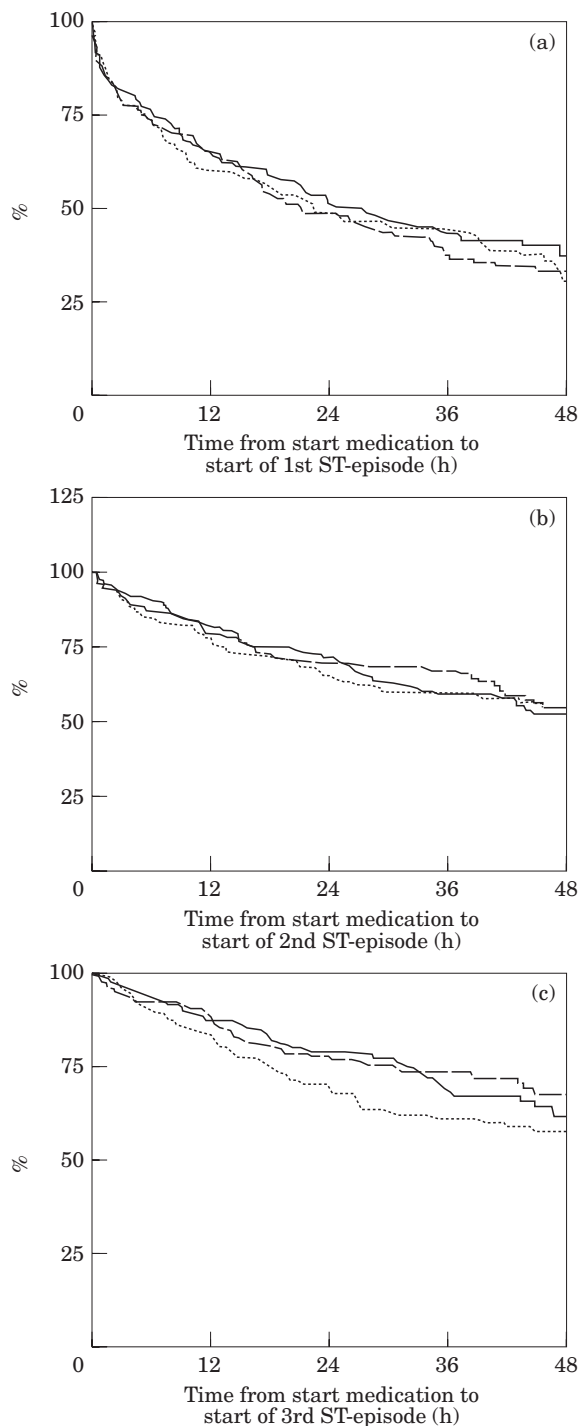
Figure 2 Kaplan–Meier estimate of the probability of remaining free of an ST-episode during the course of the monitoring period. (a) Probability of remaining free from a recurrent ST episode from the start of medication. The continuous curve represents the patients treated with efegatran 0·63 mg . kg^{-1} . h^{-1} (115), the broken curve the patients treated with efegatran 1·2 mg . kg^{-1} . h^{-1} (124) and the dotted curve the patients treated with heparin (120). (b) Probability of remaining free of a second ST episode from the start of medication. (c) Probability of remaining free of a third ST episode from the start of medication.
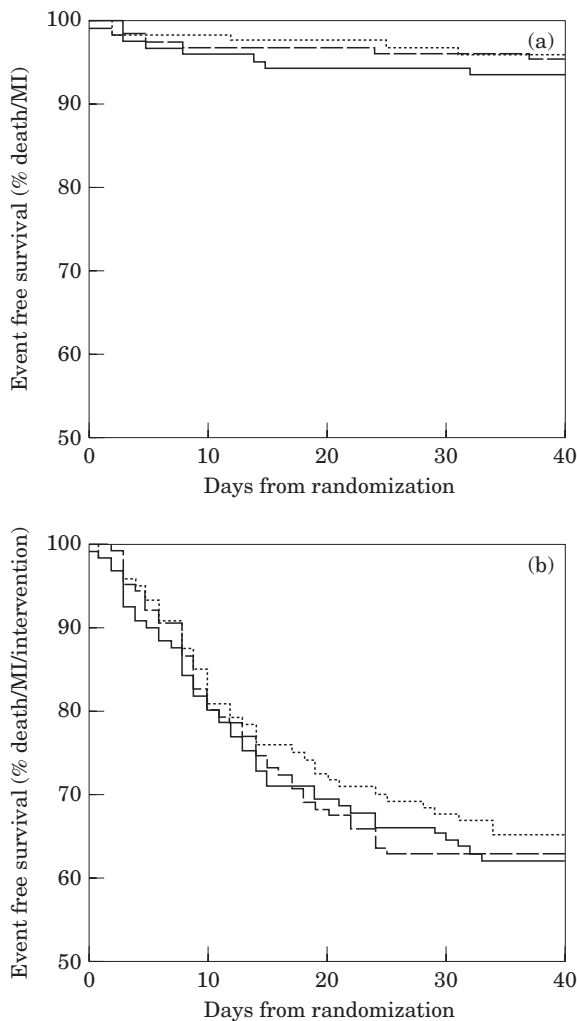
Figure 3 **Kaplan–Meier event free survival from the moment of randomization until 30 days follow-up. (a) Event-free survival from death or myocardial infarction (MI). (b) Event-free survival from death, myocardial infarction (MI) or coronary intervention. Abbreviations as in Fig. 2.**

Discussion

In this multi-centre single-blind dose finding study, the antithrombotic effects of the direct acting thrombin inhibitor efegatran sulfate were compared with heparin in patients with unstable angina. At similar levels of ex-vivo anticoagulation, activated partial thromboplastin times were more stable for the direct thrombin inhibitor. However, no clinical advantages for efegatran were apparent, while mild or moderate bleeding and thrombophlebitis were more frequent.

Anticoagulant effects

Efegatran demonstrated a dose-dependent anticoagulant activity, with the highest dose level of $1.2 \text{ mg . kg}^{-1} \text{ . h}^{-1}$ resulting in a steady state activated partial thromboplastin time value of about three times baseline. Furthermore, administration of efegatran was associated with a pronounced increase in thrombin time. Fibrinogen levels decreased in patients treated with efegatran. There were no demonstrable effects on the levels of coagulation activation markers.

The extent of thrombin inhibition as measured by the activated partial thromboplastin time appeared to be more stable with efegatran than with heparin, especially during the first hours following initiation of therapy during which activated partial thromboplastin time guided dose adjustments were made in the heparin treated patients. This may have been due to the effect of the relatively high initial dose of heparin, which has a pronounced effect on activated partial thromboplastin time. Similar observations have been reported for other direct thrombin inhibitors[10–14].

The incidence of minor bleeding was higher in patients treated with efegatran compared to patients treated with heparin. However, there was no excess in major bleeding for either dose of efegatran and there were no strokes associated with trial treatment. These results are similar to other studies in patients with acute coronary syndromes receiving anti-thrombin therapy, which reported no, or only a modest, increase in minor bleeding events compared to heparin[13,14,17]. A higher incidence of bleeding events was reported using thrombin inhibitors in combination with thrombolytic agents[11,12,15,16,18]. This led to interruption of three trials studying the effects of hirudin in patients with an acute myocardial infarction or acute coronary syndromes[15,16,18]. Two of these (TIMI 9b and GUSTO IIb) were restarted at lower

Table 4 **Bleeding events**

	Efegatran 0·105 (n=10)	Efegatran 0·32 (n=25)	Efegatran 0·63 (n=122)	Efegatran 0·84 (n=24)	Efegatran 1·2 (n=128)	Heparin (n=123)	All (n=432)
Major bleeding (total)	—	—	1 (0·8%)	—	—	2 (1·6%)	3 (0·69%)
Haematoma at puncture site	—	—	1 (0·8%)	—	—	—	1 (0·2%)
Gastro-intestinal bleeding	—	—	—	—	—	1 (0·8%)	1 (0·2%)
M. psoas bleeding	—	—	—	—	—	1 (0·8%)	1 (0·2%)
Minor bleeding (total)	2 (20%)	8 (32%)	35 (29%)	4 (17%)	39 (31%)	13 (11%)	101 (23%)
Haematoma at puncture site	1 (10%)	5 (20%)	16 (13%)	2 (8%)	17 (13%)	4 (3%)	45 (10%)
Other	1 (10%)	3 (12%)	19 (16%)	2 (9%)	22 (18%)	9 (8%)	56 (13%)

doses of hirudin, with activated partial thromboplastin time guided dosing regimens[11,12]. In GUSTO IIb, 25% of patients received concomitant thrombolytic therapy. Compared to heparin, the administration of low dose hirudin appeared to be associated with an increased major bleeding rate (7·9% vs 6·9%, $P=0.03$), with an excess of intracranial haemorrhages in patients without ST elevation, who had not received concomitant thrombolytic therapy (0·2% vs 0·02%, $P=0.06$). In TIMI 9b, all patients received concomitant thrombolytic therapy, and similar bleeding rates were observed for hirudin and heparin treated patients.

Efficacy and clinical outcome

Neither dose of efegatran suppressed recurrent myocardial ischaemia during 48 h continuous ECG ischaemia monitoring to a greater extent than that seen with heparin, and there were no differences in clinical outcome between the efegatran and heparin groups. Of note was the high incidence of patients with a myocardial infarction at the time of enrolment (58 patients, 13·4%) and the subsequent low incidence after enrolment into the study (14 patients, 3·2%). This was due to the selection process since the majority of patients was enrolled directly after admission to hospital, without knowledge of possibly elevated creatine kinase and creatine kinase-MB enzyme levels.

Our data confirm the results of other studies on direct thrombin inhibitors, which reported only equivalent or slightly improved outcome compared to heparin, sometimes at the cost of a higher incidence of bleeding[11–19]. Of all studies with direct thrombin inhibitors, only the OASIS study reported superiority of hirudin over heparin in preventing both short- (7 days) and long-term (180 days) ischaemic outcome in patients with acute myocardial ischaemia without ST-segment elevation[17]. As in our study, there was no significant increase of major bleedings, while the incidence of minor bleeding events was higher for hirudin compared with heparin. In the HELVETICA study, treatment with hirudin peri-PTCA was associated with fewer early cardiac events during the first month, without an increased risk of bleeding, but no apparent benefit was present at 7 months follow-up[19,20]. A similar study of hirulog vs heparin showed a reduction in immediate (in-hospital) ischaemic complications in a pre-defined group of patients with post-infarction angina only[14]. Again, this difference was no longer apparent after 6 months follow-up.

Dosing regimens and duration of treatment of both heparin and anti-thrombins varied widely across these studies, making comparisons difficult. As only one study demonstrated a persisting beneficial effect from these agents, it is possible that the duration of treatment (24 h to 5 days maximum) may have been too short to obtain long-term clinical benefit. Rebound effects may also have influenced long-term outcome, although these were not observed in the present study[17]. The lack of clinical

benefit may be related to the mechanism of action of direct antithrombins, which have a greater ability to decrease thrombin activity (also clot-bound thrombin) than heparin, while the latter has a greater ability to decrease thrombin generation, as it inhibits earlier steps in the coagulation cascade, which are not affected by direct thrombin inhibitors[21]. Such combined inhibition of both thrombin generation and thrombin activity may in fact be advantageous. However, no such effect was observed in the present study.

Conclusions

We compared the effect of efegatran, a direct thrombin inhibitor with heparin. Administration of efegatran sulphate at levels of at least $0.63\ \text{mg}\ .\ \text{kg}^{-1}\ .\ \text{h}^{-1}$ provided a pronounced increase in thrombin time, which is at least comparable to activated partial thromboplastin time adjusted heparin infusion. The level of thrombin inhibition by efegatran, as reflected by the activated partial thromboplastin time, appeared to be more stable than with heparin, especially during the first few hours following initiation of therapy, which may be due to the relatively high initial dose of heparin. This may reflect a more predictable dose response, suggesting that efegatran sulphate administration is probably easier to monitor than heparin.

As thrombin plays a key role in the coagulation cascade it was expected that the direct effects of efegatran would result in a more potent antithrombotic effect compared to heparin, which acts indirectly, requiring antithrombin III as a cofactor. However, no clinical benefit of efegatran over heparin was apparent whereas minor bleeding was more frequent. Our findings are in concert with other studies investigating direct thrombin inhibitors.

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Appendix

Steering Committee

The Steering Committee consisted of all investigators, the haematologist, and Lilly representatives.

Clinical End-point Committee

C. van der Zwaan, Department of Cardiology, Thoraxcenter, Erasmus University and University Hospital Dijkzigt, Rotterdam, The Netherlands. W. A. J. Bruggeling, Department of Cardiology, Pasteurziekenhuis Oosterhout, The Netherlands.

Participating clinics and collaborators

Thoraxcenter, Erasmus University and University Hospital Dijkzigt, Rotterdam, The Netherlands: M. L. Simoons; *Department of Cardiology, Havenziekenhuis, Rotterdam, The Netherlands*: C. M. Leenders; *Department of Cardiology, Medisch Spectrum Twente, Enschede, The Netherlands*: J. C. Poortermans; *Department of Cardiology, Zuiderziekenhuis, Rotterdam, The Netherlands*: W. J. Remme; *Department of Cardiology, St. Clara Ziekenhuis, Rotterdam, The Netherlands*: M. Scheffer; *Department of Cardiology, Schieland Ziekenhuis, Schiedam, The Netherlands*: H. A. Werner; *Department of Cardiology, Ziekenhuis Hilversum, Hilversum, The Netherlands*: P. A. R. de Milliano; *Department of Cardiology, Medisch Centrum Alkmaar, Alkmaar, The Netherlands*: V. A. W. M. Umans; *Department of Cardiology, Spaarne Ziekenhuis, Heemstede, The Netherlands*: E. J. Müller; *Department of Cardiology, Ikazia Ziekenhuis, Rotterdam, The Netherlands*: J. P. Kerker; *Department of Cardiology, Wilhelmina Ziekenhuis, Assen, The Netherlands*: M. J. de Leeuw; *Department of Cardiology, Reinier de Graaf Gasthuis, Delft, The Netherlands*: P. J. A. M. Withagen; *Department of Cardiology, Holy-Ziekenhuis, Vlaardingen, The Netherlands*: R. van der Heyden; *Department of Cardiology, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands*: R. W. Breedveld; *Department of Cardiology, Diakonessenhuis, Utrecht, The Netherlands*: J. M. Hartog; *Department of Cardiology, Maasziekenhuis, Boxmeer, The Netherlands*: W. C. G. Smits; *Department of Cardiology, Beatrixziekenhuis, Winterswijk, The Netherlands*: J. V. C. Stevens; *Department of Cardiology, Juliana Ziekenhuis, Apeldoorn, The Netherlands*: E. G. Faber; *Core laboratory for continuous ECG monitoring (Mortara) analysis, Cardialysis B.V., Rotterdam, The Netherlands*: P. Klootwijk, A. Spierings; *Data processing center Cardialysis B.V., Rotterdam, The Netherlands*: T. Lenderink, W. Groothuis, I. v. Oosterom, G.A. v. Es; *Cardiac enzymes*: C. M. Boersma-Cobbaert, *Erasmus University and University Hospital Dijkzigt, Rotterdam, The Netherlands*; *Chemistry, general: SciCor, S.A. Geneva, Switzerland*; *Efegatran sulphate plasma concentration: Simbec Research Limited, South Wales, United Kingdom*; *Haemostasis*: J. Stibbe; *Erasmus University and University Hospital Dijkzigt, Rotterdam, The Netherlands*.