Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction

A randomized, placebo-controlled, double-blind study (RUSSLAN)

V. S. Moiseyev[1], P. Põder[2], N. Andrejevs[3], M. Y. Ruda[4], A. P. Golikov[5], L. B. Lazebnik[6], Z. D. Kobalava[1], L. A. Lehtonen[7], T. Laine[2], M. S. Nieminen[8] and K. I. Lie[9] on behalf of RUSSLAN Study Investigators

[1]*Hospital No. 64, Russian University of People's Friendship, Moscow, Russia;* [2]*Orion Pharma, Research Center, Espoo, Finland;* [3]*P. Stradin's Research and Teaching Hospital, Latvian Medical Academy, Riga, Latvia;* [4]*A.L. Myasnikov Institute of Cardiology, Cardiology Research Center, Moscow, Russia;* [5]*Cardiology Clinic, Sklifosovsky Research Institute for Emergency Medicine, Moscow, Russia;* [6]*Department of Gerontology and Geriatrics of Russian Medical Academy for Postgraduate Training, Moscow, Russia;* [7]*Department of Clinical Pharmacology, University of Helsinki, Finland;* [8]*Helsinki University Central Hospital, Cardiology Division, Helsinki, Finland;* [9]*Academic Medical Center, University of Amsterdam, The Netherlands*

Aims To evaluate the safety and efficacy of levosimendan in patients with left ventricular failure complicating acute myocardial infarction.

Methods and Results Levosimendan at different doses ($0{\cdot}1$–$0{\cdot}4\ \mu g \cdot kg^{-1} \cdot min^{-1}$) or placebo were administered intravenously for 6 h to 504 patients in a randomised, placebo-controlled, double-blind study. The primary end-point was hypotension or myocardial ischaemia of clinical significance adjudicated by an independent Safety Committee. Secondary end-points included risk of death and worsening heart failure, symptoms of heart failure and all-cause mortality. The incidence of ischaemia and/or hypotension was similar in all treatment groups ($P=0{\cdot}319$). A higher frequency of ischaemia and/or hypotension was only seen in the highest levosimendan dose group. Levosimendan-treated patients experienced lower risk of death and worsening heart failure than patients receiving placebo, during both the 6 h infusion ($2{\cdot}0\%$ vs $5{\cdot}9\%$; $P=0{\cdot}033$) and over 24 h ($4{\cdot}0\%$ vs $8{\cdot}8\%$; $P=0{\cdot}044$). Mortality was lower with levosimendan compared with placebo at 14 days ($11{\cdot}7\%$ vs $19{\cdot}6\%$; hazard ratio $0{\cdot}56$ [95% CI $0{\cdot}33$–$0{\cdot}95$]; $P=0{\cdot}031$) and the reduction was maintained at the 180-day retrospective follow-up ($22{\cdot}6\%$ vs $31{\cdot}4\%$; $0{\cdot}67$ [$0{\cdot}45$-$1{\cdot}00$], $P=0{\cdot}053$).

Conclusions Levosimendan at doses $0{\cdot}1$–$0{\cdot}2\ \mu g \cdot kg^{-1} \cdot min^{-1}$ did not induce hypotension or ischaemia and reduced the risk of worsening heart failure and death in patients with left ventricular failure complicating acute myocardial infarction.
(Eur Heart J, 2002; 23: 1422–1432, doi:10.1053/euhj.2001. 3158)
© 2002 The European Society of Cardiology. Published by Elsevier Science Ltd. All rights reserved.

Key Words: Left ventricular failure, myocardial infarction, levosimendan, hypotension, ischaemia, mortality.

Introduction

The prognosis of patients with heart failure complicating acute myocardial infarction remains poor, despite current standard therapy with diuretics, vasodilators and angiotensin-converting-enzyme (ACE) inhibitors. Previous studies indicate a 20–40% annual mortality rate in this patient population, suggesting the need for additional therapeutic options[1–3]. Positive inotropic agents, including dobutamine and phosphodiesterase inhibitors, have also been studied in this patient population, but the data regarding their efficacy and safety is still limited[4–6]. In addition, the results of several clinical trials with various positive inotropic drugs in patients with heart failure have shown increased mortality[7–10].

Levosimendan is a novel drug developed for the treatment of decompensated heart failure. Levosimendan is a calcium sensitizer that increases the contractile force of the myocardium by enhancing the sensitivity of myofilaments to calcium without increasing intracellular calcium concentration at therapeutic doses[11–13]; the risk of cardiac arrhythmias is similar to placebo[14]. It improves cardiac contractility without increasing oxygen consumption[15,16] and, in theory, should not induce ischaemic episodes. Levosimendan has also vasodilatory and antiischaemic properties attributable to its effects on adenosine triphosphate (ATP)-dependent potassium channels[17–20].

Previous clinical trials have established the favourable haemodynamic effects of intravenously administered levosimendan in patients with moderate or severe heart failure[21–23]. Therapeutic options that improve cardiac function without detrimental effects are limited in heart failure complicating acute myocardial infarction. Levosimendan may confer clinical benefits in this setting due to its lack of detrimental effects on myocardial oxygen consumption. A previous open-label dose-controlled study with three different bolus doses of levosimendan has demonstrated the haemodynamic efficacy of levosimendan in patients with acute myocardial infarction[24]. However, the safety and efficacy of longer infusions had to be addressed in a large-scale placebo-controlled clinical trial in acute myocardial infarction patients. This study was therefore conducted to assess the short- and the long-term safety and efficacy of different 6-h infusions of levosimendan in patients with decompensated heart failure complicating acute myocardial infarction compared with placebo. This is the first clinical study to address the safety and efficacy of a calcium-sensitizing drug in this setting.

Methods

The RUSSLAN study (Randomised stUdy on Safety and effectivenesS of Levosimendan in patients with left ventricular failure due to an Acute myocardial iNfarct) was conducted according to the Declaration of Helsinki of the World Medical Assembly and its amendments. The protocol and any relevant amendments were reviewed and approved by local Ethics Committees. Written informed consent was obtained from all patients. The first patient was randomized to the study on 13 June 1996. The final 180-day mortality follow-up of the last patient was completed on 27 April 2000.

Study population

Study patients were recruited at 21 centres in Russia and Latvia. Inclusion criteria were: acute myocardial infarction (according to World Health Organization criteria) during the previous 5 days; evidence of left ventricular failure on chest X-ray (pulmonary venous congestion or pulmonary oedema); and a clinical need for inotropic therapy on the basis of symptomatic heart failure despite conventional therapy. Exclusion criteria comprised: right ventricular infarction; systolic blood pressure <90 mmHg; sustained ventricular tachycardia or frequent ventricular non-sustained tachycardias not related to thrombolysis; atrial fibrillation with a rapid ventricular response; immediate need for cardiac pacing, percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting; myocardial rupture, or severe mitral valve insufficiency; cardiac tamponade; use of beta-adrenergic agonists within 30 min of the start of the study; adult respiratory distress syndrome; septic shock; history of moderate or severe renal failure (serum creatinine >250 $\mu mol . l^{-1}$); clinically relevant hepatic failure; allergy requiring medication; and participation in another clinical trial within 1 month before study entry. Women with childbearing potential and patients with agonal status were ineligible for the study.

Study design

This was a randomized, placebo-controlled and double-blind study. A computer-generated randomization schedule, based on permuted blocks and balanced within each centre, was used to allocate patients to placebo or one of four dose regimens of levosimendan (SIMDAX®, Orion Pharma, Finland): $6 \mu g . kg^{-1}$ loading dose + $0.1 \mu g . kg^{-1} . min^{-1}$ continuous infusion; $12 \mu g . kg^{-1}$ loading dose + $0.2 \mu g . kg^{-1} . min^{-1}$ continuous infusion; $24 \mu g . kg^{-1}$ loading dose + $0.2 \mu g . kg^{-1} . min^{-1}$ continuous infusion; $24 \mu g . kg^{-1}$ loading dose + $0.4 \mu g . kg^{-1} . min^{-1}$ continuous infusion (Fig. 1). The loading dose was infused over a period of 10 min, and the continuous infusion was maintained for 5 h and 50 min. The placebo was identical in appearance to the active drug. All the formulations and vials were made to look identical and had either no active ingredient or different amounts of levosimendan. The volumes infused into the patients of the five different treatment arms were also identical. Study medications were introduced via a peripheral vein using a calibrated infusion pump.
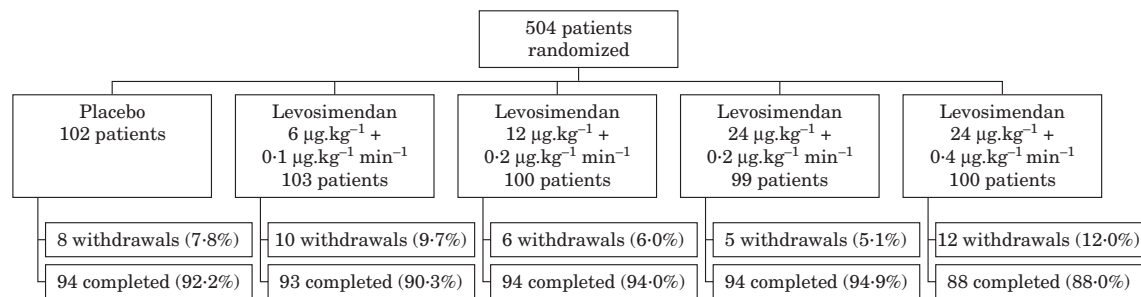
```
                          ┌─────────────────┐
                          │  504 patients   │
                          │   randomized    │
                          └─────────────────┘
```

Placebo 102 patients	Levosimendan 6 µg.kg^{-1} + 0·1 µg.kg^{-1} min^{-1} 103 patients	Levosimendan 12 µg.kg^{-1} + 0·2 µg.kg^{-1} min^{-1} 100 patients	Levosimendan 24 µg.kg^{-1} + 0·2 µg.kg^{-1} min^{-1} 99 patients	Levosimendan 24 µg.kg^{-1} + 0·4 µg.kg^{-1} min^{-1} 100 patients
8 withdrawals (7·8%)	10 withdrawals (9·7%)	6 withdrawals (6·0%)	5 withdrawals (5·1%)	12 withdrawals (12·0%)
94 completed (92·2%)	93 completed (90·3%)	94 completed (94·0%)	94 completed (94·9%)	88 completed (88·0%)

Figure 1 **Trial profile.**

Investigators were mandated to stop the infusion of the study medication if patients experienced: symptomatic hypotension, heart rate >130 beats . min^{-1} sustained for 10 min, or any serious adverse event. Baseline assessments included blood pressure (measured with a sphygmomanometer or with an automatic blood pressure measuring device), heart rate (determined from the ECG) and respiratory rate. Baseline assessments of dyspnoea, fatigue, anginal pain and physical signs of heart failure were also made. Patients were permitted to receive all appropriate therapy for the management of both acute myocardial infarction and heart failure. Patients developing persistent hypotension or refractory heart failure during infusion, were permitted intravenous dopamine (3–9 µg . kg^{-1} . min^{-1}).

Throughout the 6-h infusion period, patients were assessed for hypotension or myocardial ischaemia of clinical significance, symptoms of heart failure, haemodynamics, urinary output and adverse events. In addition to spontaneous reporting, an adverse event inquiry was undertaken by an investigator at the end of the infusion and at 24 h after the start of the infusion. Patient survival was evaluated at 14 days following the start of the infusion. An additional 180-day mortality follow-up was conducted after the end of the study. The information for the 180-day follow-up was obtained from Official Inhabitant Registries and patients' hospital files. Confirmation of survival was obtained through telephone contact with the patients.

Blood samples, drawn before the start of infusion and immediately after infusion, were used to determine serum creatine kinase-MB levels. A chest X-ray was repeated within 12–30 h after the start of the infusion.

End-points

The primary end-point was the proportion of patients developing hypotension or ischaemia of clinical significance adjudicated by an independent safety committee. Clinically significant hypotension was defined as: (1) symptomatic hypotension (obligatory) or (2) an asymptomatic drop in systolic blood pressure of more than 10 mmHg (at the discretion of the investigator). Clinically significant ischaemia was defined as: (1) aggravation or a new onset of anginal pain; or (2) further depression or elevation of the ST-segment by more than

1 mm in a 12-lead ECG. Clinically significant hypotension and/or ischaemia, reported by the investigator, were evaluated by the Safety Committee. For the evaluation, investigators provided the committee with case record forms, ECGs and copies of patients' hospital files. Committee meetings were held after every 100 patients recruited. Members of the Committee were unaware of patient treatment allocation at the time of assessment.

Secondary end-points included the combined risk of death and worsening heart failure during the first 6 and 24 h after the start of the infusion, a change in dyspnoea and fatigue at the end of the infusion and death for any reason over 14 days after the start of the infusion. Patients were considered to have worsening heart failure if they experienced onset or worsening of any following conditions: dyspnoea, fatigue, pulmonary congestion or oedema, heart failure or cardiogenic shock. The severity of dyspnoea and fatigue was assessed both by the patient and the investigator before and after the infusion as a score from 1 to 4, where 1 represented none and 4 disabling. An increase in score was categorized as 'worse', a decrease as 'better', and no 'change' as 'unchanged'. In the worst-rank symptom analysis, patients were considered to be worse if, in addition to the changes in actual dyspnoea and fatigue scores during the 6 h study infusion, they (1) died; (2) developed worsening heart failure; or (3) received a new drug for the treatment of heart failure.

Statistical analysis

Statistical analyses were based on the intention-to-treat principle, performed at a two-sided 0·05 level of significance. Analyses were carried out using SAS 6.12 statistical software (SAS Institute Inc., Cary, NC, US) for Windows.

In a separate pilot study, evaluating the effects of three bolus infusions of levosimendan in patients with acute myocardial infarction, levosimendan improved haemodynamics, but did not cause myocardial ischaemia in Holter-recordings and did not cause hypotension[24]. However, the regulatory authorities (FDA) required that a population of about 500 patients would be required to assess the risk/benefit ratio of levosimendan in patients with acute myocardial infarction. A placebo-controlled study with 6 h infusions was

therefore conducted and the incidence of clinically significant hypotension and ischaemia in the placebo group represents the spontaneous variation of the primary end-point in this patient population.

Baseline characteristics were summarized using appropriate descriptive statistics; values for each characteristic were compared among the five treatment groups using analysis of variance (ANOVA) with effects for treatment, centre and treatment by centre interaction or the non-parametric Cochran–Mantel–Haenszel (CMH) test, controlling for centre. In a primary analysis for a primary end-point, the differences between treatment groups in the proportions of patients experiencing clinically significant ischaemic and/or hypotensive events were tested using the CMH row means score test, controlling for centre. The same analysis was tested comparing the placebo group and the pooled levosimendan group. The relationship between dose and frequency of event(s) was evaluated using the CMH non-zero correlation test; the effects in each treatment arm were weighed according to the total quantity of drug (in mg . kg^{-1}) due over the 6 h infusion period.

The combined risk of death and worsening heart failure were expressed using a time-to-event model. The log-rank test was used for detecting differences between placebo and pooled levosimendan groups. Cumulative survival curves for placebo and pooled levosimendan groups were constructed by the Kaplan–Meier method and the differences between the curves were tested for significance using the Cox proportional hazards model. Survival time in the model was calculated as the difference in days from the start of infusion to the event or to the last follow-up date. The relationship between dose and frequency of event(s) was evaluated using the CMH non-zero correlation test, controlling for centre.

Changes in overall clinical status, symptoms of heart failure, anginal pain, jugular venous distension, peripheral oedema, urinary output, pulmonary congestion and creatine kinase-MB values were evaluated using ANOVA methods or by use of the CMH row mean scores test, controlling for centre. The frequency of adverse events in the five treatment groups was compared using Fisher's exact test. Dose-relations of adverse events were tested using the CMH non-zero correlation test, controlling for centre.

Results

Patient characteristics

The five treatment groups were well matched regarding baseline characteristics (Table 1) and concomitant medications (Table 2). Diabetes mellitus was more prevalent among levosimendan patients and cerebrovascular disease in the placebo group. All patients had pulmonary congestion or oedema on the chest X-ray despite conventional therapy (nitrates and diuretics) and were highly symptomatic (more than 90% of patients had

dyspnoea and about 90% had pulmonary rales at rest despite previous treatment).

Primary end-point

The safety committee considered that 65 patients had clinically significant ischaemia or hypotension (Table 3). No significant differences among the five treatment groups were observed in the proportion of patients who experienced the primary end-point ($P=0·319$). When all four levosimendan groups were combined and compared with placebo, the proportions of patients who experienced clinically significant hypotension and/or ischaemia in the placebo and levosimendan groups were similar (10·8% vs 13·4%, respectively, $P=0·456$). There was, however, a weak relationship between the dose of levosimendan and the risk of hypotension and/or ischaemia ($P=0·054$), which was attributable to a higher frequency (19·0%) of ischaemia and hypotension among patients who received the highest levosimendan infusion rate (24 μg . kg^{-1} + 0·4 μg . kg^{-1} . min^{-1}).

Secondary end-points

Death and worsening heart failure
The combined risk of death and worsening heart failure was lower among patients treated with levosimendan than among patients receiving placebo during both the 6 h infusion period (2·0% vs 5·9%, respectively; $P=0·033$), and 24 h after the start of infusion (4·0% vs 8·8%, respectively; $P=0·044$) (Fig. 2). There was no relationship between the dose of levosimendan and the combined risk of death and worsening heart failure during both the 6 h infusion and 24 h after start of infusion (Table 4). All-cause mortality among levosimendan-treated patients was significantly lower than with placebo for the 14-day period after the start of the treatment (11·7% vs 19·6%, respectively; 0·56 [95% CI 0·33–0·95]; $P=0·031$); this difference was also seen when the follow-up was extended to 180 days (22·6% vs 31·4%, respectively; 0·67 [0·45-1·00]; $P=0·053$) (Fig. 3). There was no relationship between the dose of levosimendan and all-cause mortality during both the 14-day and 180-day follow-up (Table 4).

Symptoms of heart failure
There were no differences among the treatment groups with respect to changes in dyspnoea or fatigue scores. In the worst rank analysis, however, patients treated with levosimendan were judged by the investigators to have experienced worsening dyspnoea less frequently than those receiving placebo (10·8% vs 17·0%, respectively, $P=0·042$). This treatment difference was also reflected in patient self-assessments (11·0% vs 16·7%, respectively, $P=0·056$). In the worst rank analysis patients treated with levosimendan experienced also worsening fatigue less frequently than patients receiving placebo in both

Table 1 *Baseline characteristics*

Variable	Placebo (n=102)	Levosimendan 6 μg . kg⁻¹ + 0·1 μg . kg⁻¹ . min⁻¹ (n=103)	Levosimendan 12 μg . kg⁻¹ + 0·2 μg . kg⁻¹ . min⁻¹ (n=100)	Levosimendan 24 μg . kg⁻¹ + 0·2 μg . kg⁻¹ . min⁻¹ (n=99)	Levosimendan 24 μg . kg⁻¹ + 0·4 μg . kg⁻¹ . min⁻¹ (n=100)	P-value*
Age (years)	68 ± 11	67 ± 12	68 ± 10	66 ± 11	67 ± 11	0·779
Sex (M/F)	57/45	52/51	44/56	53/46	54/46	0·968
Weight (kg)	76 ± 12	79 ± 14	78 ± 15	76 ± 12	78 ± 13	0·385
Time since AMI (days)	1·6 ± 1·2	1·9 ± 1·2	1·9 ± 1·3	1·8 ± 1·2	2·0 ± 1·3	0·148
Anginal pain (%)	3·9	5·8	4·0	7·1	5·1	0·803
Dyspnoea (%)	97·1	89·3	94·0	93·9	94·9	0·228
Fatigue (%)	54·9	49·5	52·0	53·5	49·5	0·816
Pulmonary rales (%)	89·2	89·3	86·0	89·9	92·0	0·744
S3 with tachycardia (%)	15·7	11·7	12·0	12·1	9·1	0·633
Signs of poor tissue perfusion (%)	61·8	58·3	55·0	55·6	57·0	0·545
Previous MI (%)	21·6	32·0	31·0	30·3	20·0	0·145
Hypertension (%)	60·8	73·8	72·0	64·6	66·0	0·256
Atrial fibrillation (%)	2·9	6·8	2·0	7·2	10·0	0·097
Peripheral vascular disease (%)	6·9	4·9	9·0	4·0	6·0	0·588
Gastrointestinal disease (%)	30·4	23·3	19·0	25·3	27·0	0·333
Pulmonary disease (%)	26·5	28·2	26·0	19·2	20·0	0·348
Diabetes mellitus (%)	9·8	16·5	26·0	22·0	22·0	0·038
Cerebrovascular disease (%)	17·6	7·8	20·0	10·1	16·0	0·033

*Comparison of levosimendan groups versus placebo based on CMH test (except ANOVA for age and weight).

Table 2 *Baseline and concomitant medication during 24 h after start of infusion*

	Placebo (n=102)	Levosimendan 6 $\mu g \cdot kg^{-1}$ + 0·1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n=103)	Levosimendan 12 $\mu g \cdot kg^{-1}$ + 0·2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n=100)	Levosimendan 24 $\mu g \cdot kg^{-1}$ + 0·2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n=99)	Levosimendan 24 $\mu g \cdot kg^{-1}$ + 0·4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (n=99)	P-value*
Thrombolytics (%)	15·7	17·5	22·0	14·1	16·2	0·487
Cardiac glycosides (%)	12·6	10·8	13·0	20·2	9·1	0·146
Dopamine (%)	13·6	14·7	8·0	9·1	6·1	0·226
Intravenous inotropes (others than cardiac glycosides and dopamine) (%)	6·8	9·8	7·0	7·1	4·0	0·624
Diuretics (%)	69·9	75·5	76·0	75·8	74·7	0·883
ACE-inhibitors (%)	44·7	46·1	48·0	47·5	48·5	0·991
Beta-blockers (%)	40·8	42·2	38·0	32·3	42·4	0·520
Calcium channel blockers (%)	14·6	10·8	12·0	14·1	14·1	0·881
Nitrates (%)	94·2	97·1	98·0	97·0	96·0	0·822
Antiarrhythmics (%)	30·1	22·5	29·0	20·2	26·3	0·385
Analgesics (%)	79·6	84·3	79·0	80·8	81·8	0·893
Acetylsalicylic acid (%)	88·3	90·2	88·0	85·9	86·9	0·920
Heparin/heparin analogues (%)	77·7	88·2	84·0	84·8	87·9	0·183

*CMH statistics (row mean score difference).

Table 3   Incidence of clinically significant ischaemia or hypotension, adjudicated by the Safety Committee

	Placebo (n=102)	Levosimendan 6 µg . kg^{-1}+ 0·1 µg . kg^{-1} . min^{-1} (n=103)	Levosimendan 12 µg . kg^{-1}+ 0·2 µg . kg^{-1} . min^{-1} (n=100)	Levosimendan 24 µg . kg^{-1}+ 0·2 µg . kg^{-1} . min^{-1} (n=99)	Levosimendan 24 µg . kg^{-1}+ 0·4 µg . kg^{-1} . min^{-1} (n=100)
Hypotension only	5 (4·9%)	7 (6·8%)	4 (4·0%)	5 (5·1%)	9 (9·0%)
Ischaemia only	4 (3·9%)	0 (0·0%)	7 (7·0%)	5 (5·1%)	8 (8·0%)
Hypotension and ischaemia	2 (2·0%)	4 (3·9%)	1 (1·0%)	2 (2·0%)	2 (2·0%)
Hypotension and/or ischaemia*†	11 (10·8%)	11 (10·7%)	12 (12·0%)	12 (12·1%)	19 (19·0%)§

*P=0·319 for comparison between all treatment groups (CMH row means score test).
†P=0·456 for comparison of combined levosimendan groups versus placebo (CMH row means score test).
§P=0·054 for dose–response relation (CMH non-zero correlation test).

investigator (10·6% vs 17·0%, respectively, P=0·047) and patient assessments (10·8% vs 16·7%, respectively, P=0·045).

Other indices of clinical status
There were no significant differences among the five treatment groups as regards change of overall clinical status, anginal pain, jugular venous distension, peripheral oedema, urinary output and pulmonary congestion.
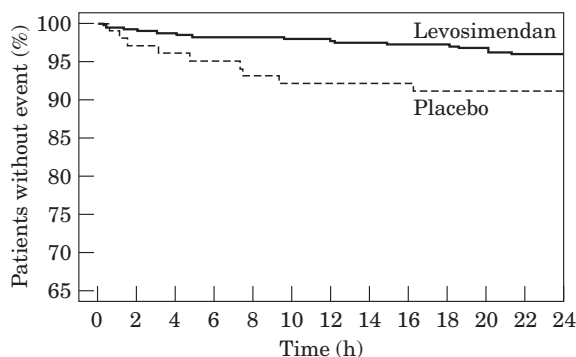
Figure 2   Combined risk of death and worsening heart failure during the first 24 h after start of infusion. The combined risk of death and worsening heart failure was 2·0% in levosimendan group and 5·9% in placebo group during the 6–h infusion period (P=0·033, log-rank) and 4·0% in levosimendan group and 8·8% in placebo group (P=0·044) during the first 24 h after start of infusion.

Fewer patients treated with levosimendan required a new vasodilator, diuretic or positive inotropic drug for the treatment of heart failure than with placebo (7·2% vs 13·7%, respectively, P=0·003) during the 6 h infusion.

Haemodynamic responses

Levosimendan produced dose-dependent decreases in systolic and diastolic blood pressure and increases in heart rate at the end of the 6 h treatment period (Table 5). The effect on blood pressure was most marked at the highest dose (24 µg . kg^{-1}+0·4 µg . kg^{-1} . min^{-1}) studied, where placebo-corrected decreases of up to 6 mmHg were noted. The effect on heart rate was small at the lower doses, but the highest dose produced a placebo-corrected increase of 11 beats . min^{-1}. The respiratory rate was unaffected.

Adverse events

During the 6 h infusion period, adverse events were recorded in 23·4% of patients receiving levosimendan compared with 17·6% in the placebo group (P=0·233). The only statistically significant differences between levosimendan and placebo were observed in the frequencies of sinus tachycardia and myocardial rupture (Table 6). Sinus tachycardia was most common
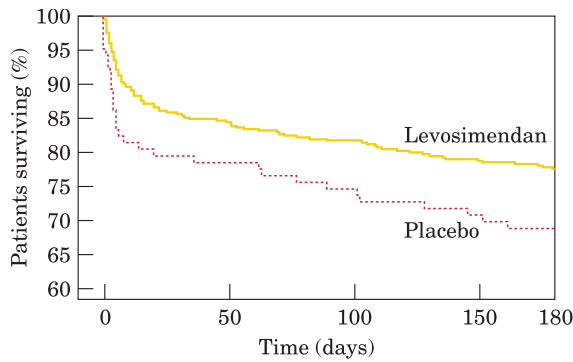
Table 4   Incidence of death and worsening heart failure and all-cause mortality in all dose groups

End-point	Placebo (n=102)	Levosimendan 6 µg . kg^{-1}+ 0·1 µg . kg^{-1} . min^{-1} (n=103)	Levosimendan 12 µg . kg^{-1}+ 0·2 µg . kg^{-1} . min^{-1} (n=100)	Levosimendan 24 µg . kg^{-1}+ 0·2 µg . kg^{-1} . min^{-1} (n=99)	Levosimendan 24 µg . kg^{-1}+ 0·4 µg . kg^{-1} . min^{-1} (n=100)	P-value*
Death or worsening heart failure at 6 h (%)	5·9	2·9	2·0	1·0	2·0	0·094
Death or worsening heart failure at 24 h (%)	8·8	5·8	3·0	3·0	4·0	0·089
Mortality at 6 h (%)	3·9	1·9	1·0	0·0	0·0	0·015
Mortality at 24 h (%)	4·9	3·9	1·0	1·0	2·0	0·127
Mortality at 14 days (%)	19·6	12·6	10·0	13·1	11·0	0·112
Mortality at 180 days (%)	31·4	26·2	16·0	27·3	21·0	0·088

*For dose-relation (CMH non-zero correlation test).

Figure 3 **Overall survival in 180 days after start of infusion. The mortality rates at 14 days were 11·7% in the levosimendan group and 19·6% in the placebo group (*P*=0·031, Cox Proportional Hazards); at 180 days the rates were 22·6% and 31·4%, respectively (*P*=0·053).**

in the highest levosimendan dose $(24 \,\mu g \cdot kg^{-1} + 0.4 \,\mu g \cdot kg^{-1} \cdot min^{-1})$ group (5·0%). Myocardial rupture occurred more frequently with placebo than with levosimendan (3·9% vs 0·25%, respectively, *P*=0·027). Of the 41 patients who experienced adverse events

leading to withdrawal from study infusion, eight were receiving placebo (7·8%) and 33 were receiving levosimendan (8·2%).

During the first 24 h after the start of the infusion, adverse events were recorded in 29·4% of patients receiving levosimendan compared with 26·5% in the placebo group (*P*=0·625). The incidence of adverse events was highest in the highest levosimendan dose $(24 \,\mu g \cdot kg^{-1} + 0.4 \,\mu g \cdot kg^{-1} \cdot min^{-1})$ group (36·0%).

Discussion

This study demonstrates that levosimendan is both well tolerated and effective in patients with left ventricular failure complicating acute myocardial infarction. The patients enrolled into the study were highly symptomatic. Of the 504 randomized patients, nearly all had either dyspnoea at rest, pulmonary rales or signs of peripheral hypoperfusion (Table 1). Earlier studies in post-acute myocardial infarction patients with similar clinical characteristics have identified them to be at very high risk of death[1–3]. In common with these earlier

Table 5   Mean changes in blood pressure and heart rate after 30 min and 6 h

	Placebo (n=102)	Levosimendan 6 µg . kg⁻¹ + 0·1 µg . kg⁻¹ . min⁻¹ (n=103)	Levosimendan 12 µg . kg⁻¹ + 0·2 µg . kg⁻¹ . min⁻¹ (n=100)	Levosimendan 24 µg . kg⁻¹ + 0·2 µg . kg⁻¹ . min⁻¹ (n=99)	Levosimendan 24 µg . kg⁻¹ + 0·4 µg . kg⁻¹ . min⁻¹ (n=100)
Systolic blood pressure (mmHg) baseline mean (SD)	123·5 (21·1)	123·3 (19·5)	128·0 (19·7)	125·0 (22·2)	125·5 (18·7)
Δ 30 min	− 1·6	− 3·0	− 1·7	− 2·1	− 3·0
Δ 6 h*	− 1·3	− 2·1	− 4·2	− 5·4	− 7·9
Diastolic blood pressure (mmHg) baseline mean (SD)	76·8 (13·2)	74·7 (11·4)	76·0 (12·8)	75·0 (12·4)	74·9 (12·9)
Δ 30 min	− 2·4	− 3·4	− 3·0	− 4·5	− 3·8
Δ 6 h†	− 2·5	− 3·1	− 4·3	− 4·6	− 8·0
Heart rate (beats/min) baseline mean (SD)	83·8 (16·0)	81·8 (13·9)	81·5 (17·8)	84·7 (16·9)	80·0 (17·2)
Δ 30 min	− 1·5	0·5	1·1	4·7	5·2
Δ 6 h†	0·0	2·0	3·7	3·9	11·4

*P=0·012 for dose-relation (CMH non-zero correlation test).
†P=0·001 for dose-relation (CMH non-zero correlation test).

Table 6   Adverse events during 6 h infusion

Adverse event	Placebo (n=102)	Levosimendan 6 µg . kg⁻¹ + 0·1 µg . kg⁻¹ . min⁻¹ (n=103)	Levosimendan 12 µg . kg⁻¹ + 0·2 µg . kg⁻¹ . min⁻¹ (n=100)	Levosimendan 24 µg . kg⁻¹ + 0·2 µg . kg⁻¹ . min⁻¹ (n=99)	Levosimendan 24 µg . kg⁻¹ + 0·4 µg . kg⁻¹ . min⁻¹ (n=100)	P-value*
Ventricular extrasystoles	1 (1·0%)	3 (2·9%)	1 (1·0%)	4 (4·0%)	9 (6·0%)	0·198
Atrial fibrillation	2 (2·0%)	1 (1·0%)	4 (4·0%)	3 (3·0%)	3 (3·0%)	0·653
Other atrial arrhythmia	1 (1·0%)	1 (1·0%)	1 (1·0%)	1 (1·0%)	2 (2·0%)	0·952
Sinus tachycardia	2 (2·0%)	0 (0·0%)	0 (0·0%)	3 (3·0%)	5 (5·0%)	0·028
Hypertension	1 (1·0%)	1 (1·0%)	3 (3·0%)	0 (0·0%)	0 (0·0%)	0·206
Nausea	0 (0·0%)	1 (1·0%)	1 (1·0%)	2 (2·0%)	1 (1·0%)	0·611
Headache	1 (1·0%)	2 (1·9%)	3 (3·0%)	1 (1·0%)	1 (1·0%)	0·796
Myocardial rupture	4 (3·9%)	1 (1·0%)	0 (0·0%)	0 (0·0%)	0 (0·0%)	0·027

*Fisher's exact test.

findings[1–3], the 14-day follow-up showed a 20% mortality in the placebo group; this rose to 31% at the 180-day follow-up. Compared with the recent large-scale observational studies in patients with acute myocardial infarction, there were no major differences between these and RUSSLAN-study regarding the use of concomitant medication, except for the lower usage of thrombolytics compared with Western Europe. This, however, was similar to that reported in the U.S.A.[25–27]. It is noteworthy that the study was performed without invasive haemodynamic monitoring, thus reflecting common clinical practice[28], which also helped to ensure that investigators' knowledge of the changes in haemodynamic parameters did not bias the assessments of symptoms of heart failure.

In post-acute myocardial infarction patients it is especially important not to increase the ischaemic burden. An improved cardiac contractility must not be obtained at the expense of an increase in oxygen demand and further ischaemic events. The study was therefore designed primarily as a randomized double-blind dose-safety trial with a placebo group. The end-points chosen for this study — hypotension and ischaemia, are relevant to both the study population and to the mechanisms of action of levosimendan — improved cardiac contractility and vasodilation[11–13,17–20,29]. The proportion of patients experiencing hypotension and/or ischaemia during the 6 h infusion was similar in the combined levosimendan groups and the placebo group. A higher risk of hypotension and/or ischaemia compared with placebo was observed only with the highest levosimendan dose ($24\,\mu g \cdot kg^{-1} + 0.4\,\mu g \cdot kg^{-1} \cdot min^{-1}$). These findings are consistent with the results of a previous dose-finding study in patients with congestive heart failure, excluding patients with acute myocardial infarction, that identified 0.05–$0.2\,\mu g \cdot kg^{-1} \cdot min^{-1}$ as the optimal infusion rate for levosimendan[21].

The effects of levosimendan on the improvement of symptoms of heart failure during the infusion period were small. Given the short duration of the study and the relatively insensitive methods used to appraise changes in symptom severity, this finding is not unexpected. There have been few studies in patients with left ventricular failure due to acute myocardial infarction; moreover, no published placebo-controlled double-blind study has reported significant improvement of symptoms in this patient population.

As clinical measures like symptom inquiry provide only subjective evidence of changes in clinical status, there was a need to provide more objective evidence, which would better characterize the change in clinical status[30]. Especially in the acute setting, the clinical stabilization of the patient (i.e. prevention of heart failure worsening) is also an important clinical goal. For this purpose, 'the combined risk of death and worsening heart failure' was used as a pre-defined end-point in our study. 'Worsening heart failure' included all possible adverse clinical events, indicating deterioration of clinical condition in this patient population. Levosimendan

was associated with a significant reduction in the combined risk of death and worsening heart failure and also in the need for new medications for heart failure during the infusion period. The treatment benefit on combined risk of death and worsening heart failure was still evident 24 h after the start of the treatment.

The continued mortality benefit up to 180 days after a 6-h infusion is noteworthy. It is evident, however, that the risk reduction attributable to levosimendan was achieved during the first 14 days of follow-up. After 14 days the Kaplan–Meier curves are parallel indicating no further additional survival benefit after that time (Fig. 3). Similar long-term results have also been seen in trials with short-term therapy with thrombolytic agents and beta-blockers[31–33]. However, this is the first time, that the decrease in mortality in this patient population was achieved by the use of an intravenous positive inotropic drug. This interesting finding is in accordance with previous pharmacological results. In a dog study levosimendan was found to reduce myocardial infarct size, suggesting cardioprotective effects[19]. In another, recently published study racemic simendan improved survival in rats with healed myocardial infarction[34]. It has also been shown that the haemodynamic benefits of a 6-h levosimendan infusion in patients with heart failure were not at the expense of increased sympathomimetic stimulation or autonomic imbalance, which are known to be associated with an increased proarrhythmic risk[35]. Thus levosimendan possesses a unique combination of antiischaemic and inodilatory properties and therefore favourable clinical results in patients with ischaemic pump failure are not surprising[36].

Given the similarity in patient populations, differences in mortality rates cannot be attributed to the differences in the baseline characteristics. Especially noteworthy is the finding that the prevalence of diabetes, a disease known to have an adverse effect on survival in patients with acute myocardial infarction[37–38], was higher among levosimendan-treated patients. However, when evaluating the mortality results, one should take into account that the study was not prospectively designed and powered to show a difference in mortality as an end-point. Nevertheless, the significant difference observed suggests that levosimendan may have favourable effects on long-term mortality outcomes in addition to its beneficial effects on haemodynamics (such as increased stroke volume and cardiac output, reduced pulmonary capillary wedge pressure)[21–23]. This possibility needs to be confirmed in a prospective mortality trial.

The combined risk of death and worsening heart failure and all-cause mortality at 24 h, 14 days and 180 days showed no dose-relation, and the frequency of events was lower in all the levosimendan groups than in the placebo group (Table 4). However, a dose-relation regarding all-cause mortality was seen during the 6 h infusion period. It is important that the highest levosimendan dose ($24\,\mu g \cdot kg^{-1} \cdot min^{-1} + 0.4\,\mu g \cdot kg^{-1} \cdot min^{-1}$), showing a higher incidence of ischaemia and/or hypotension during the 6 h infusion,
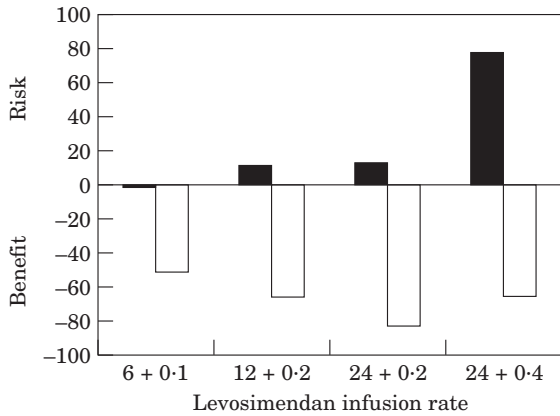
Figure 4 **Placebo–adjusted risk-benefit ratio of levosimendan. Placebo-adjusted means that the risk for each levosimendan group is expressed as a percentage of the corresponding risk in the placebo group. Black columns represent the risk of clinically significant hypotension or ischaemia and white columns represent the combined risk of death and worsening heart failure during 6 h infusion.**

was safe and effective in this respect, i.e. ischaemia and hypotension during infusion were not adversely affecting the short-term efficacy and long-term safety. However, combining the results of the primary end-point and the combined risk of death and worsening heart failure as the secondary end-point indicate that the risk–benefit ratio of a 6 h infusion of levosimendan was favourable up to $0.2 \, \mu g \cdot kg^{-1} \cdot min^{-1}$ due to a higher incidence of ischaemia and/or hypotension in the highest dose group (Fig. 4).

In conclusion, the RUSSLAN study shows that a 6 h infusion of levosimendan $(0.1-0.2 \, \mu g \cdot kg^{-1} \cdot min^{-1})$ did not increase clinically significant hypotension or ischaemia. Levosimendan also decreased the incidence of worsening heart failure and reduced both short- and longer-term mortality. Levosimendan offers a promising therapeutic option for the management of left ventricular failure complicating an acute myocardial infarction.

References

[1] Dwyer EM, Greenberg HM, Steinberg G and The Multicenter Postinfarction Research Group. Clinical characteristics and natural history of survivors of pulmonary congestion during acute myocardial infarction. Am J Cardiol 1989; 63: 1423–8.

[2] The Acute Infarction Ramipril Efficacy (AIRE) Study investigators. Effect of ramipril on mortality and morbidity in survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821–8.

[3] Mahon NG, O'Rorke CO, Codd MB, McCann HA, McGarry K, Sugrue DD. Hospital mortality of acute myocardial infarction in the thrombolytic era. Heart 1999; 81: 478–82.

[4] Gillespie TA, Ambos HD, Sobel BE, Roberts R. Effects of dobutamine in patients with acute myocardial infarction. Am J Cardiol 1977; 39: 588–94.

[5] Caldicott LD, Hawley K, Heppell R, Woodmansey PA, Channer KS. Intravenous enoximone or dobutamine for severe heart failure after acute myocardial infarction: a randomized double-blind trial. Eur Heart J 1993; 14: 696–700.

[6] Karlsberg RP, DeWood MA, DeMaria AN, Berk MR, Lasher KP for The Milrinone-Dobutamine Study Group. Comparative efficacy of short-term intravenous infusions of milrinone and dobutamine in acute congestive heart failure following acute myocardial infarction. Clin Cardiol 1996; 19: 21–30.

[7] Krell MJ, Kline EM, Bates ER et al. Intermittent, ambulatory dobutamine infusions in patients with severe congestive heart failure. Am Heart J 1986; 112: 787–91.

[8] Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM for the PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991; 325: 1468–75.

[9] Cohn JN, Goldstein SO, Greenberg BH et al. A dose-dependent increase in mortality with vesnarinone among patients with severe heart failure. N Engl J Med 1998; 339: 1810–6.

[10] O'Connor CM, Gattis WA, Uretsky BF, Kirkwood FA, McNulty SE, Grossman SH for the FIRST Investigators. Continuous intravenous dobutamine is associated with an increased risk of death in patients with advanced heart failure: Insights from the Flolan International Randomized Survival Trial (FIRST). Am Heart J 1999; 138: 78–86.

[11] Haikala H, Nissinen E, Etemadzadeh E, Levijoki J, Lindén I-B. Troponin C-mediated calcium sensitization induced by levosimendan does not impair relaxation. J Cardiovasc Pharmacol 1995; 25: 794–801.

[12] Lancaster MK, Cook SJ. The effects of levosimendan on $[Ca \, 2+]_i$ in guinea-pig isolated ventricular myocytes. Eur J Pharmacol 1997; 339: 97–100.

[13] Kristof E, Szigeti G, Papp Z et al. Cardiac responses to calcium sensitizers and isoproterenol in intact guinea pig hearts. Effects on cyclic AMP levels, protein phosphorylation, myoplasmic calcium concentration and left ventricular function. Ann N Y Acad Sci 1998; 853: 316–9.

[14] Singh BN, Lilleberg J, Sandell E-P, Ylönen V, Lehtonen L, Toivonen L. Effects of levosimendan on cardiac arrhythmias: electrophysiologic and ambulatory electrocardiographic findings in Phase II and Phase III clinical studies in cardiac failure. Am J Cardiol 1999; 83 (Suppl I): (I)16–(I)20.

[15] Ukkonen H, Saraste M, Akkila J et al. Myocardial efficiency during calcium sensitization with levosimendan: a noninvasive study with positron emission tomography and echocardiography in healthy volunteers. J Clin Pharmacol Ther 1997; 61: 596–607.

[16] Ukkonen H, Saraste M, Akkila J et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. J Clin Pharmacol Ther 2000; 68: 522–31.

[17] Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. The novel calcium sensitizer levosimendan activates the ATP-sensitive K^+ channel in rat ventricular cells. J Pharmacol Expt Ther 1997; 283: 375–83.

[18] Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. Levosimendan, a novel Ca^{2+}-sensitizer activates the glibenclamide-sensitive K^+ channel in rat arterial myocytes. Eur J Pharmacol 1997; 333: 249–59.

[19] Pataricza J, Hohn J, Petri A, Balogh A, Papp JG. Comparison of the vasorelaxing effect of cromakallim and the new inodilator, levosimendan, in human isolated portal vein. J Pharm Pharmacol 2000; 52: 213–17.

[20] Kersten JR, Montgomery MW, Pagel PS, Warltier DC. Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K (ATP) channels. Anesth Analg 2000; 90: 5–11.

[21] Nieminen MS, Akkila J, Hasenfuss G, Kleber FX, Lehtonen LA, Mitrovic V on behalf of the Study Group. Haemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000; 36: 1903–12.

[22] Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH, Haeusslein E, Hare J on behalf of the Study Investigators. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Circulation 2000; 102: 2222–7.

[23] Follath F, Hinkka S, Jäger D et al. Dose-ranging and safety with intravenous levosimendan in low-output heart failure: experience in 3 pilot studies and outline of the LIDO trial. Am J Cardiol 1999; 83 (Suppl I): (I)21–(I)25.

[24] Luotolahti M, Lammintausta O, Ukkonen H et al. Levosimendan, a calcium sensitizer and potassium channel opener, is safe and improves left ventricular function in acute myocardial infarction. Circulation 1998; 98 (Suppl I): (I)105–(I)106.

[25] European Secondary Prevention Group. Translation of clinical trials into practice: a European population-based study of the use of thrombolysis for acute myocardial infarction. Lancet 1996; 347: 1203–7.

[26] Chen J, Radford MJ, Wang Y, Marcinak TA, Krumholz HM. Do 'America's best hospitals' perform better for acute myocardial infarction? N Engl J Med 1999; 340: 286–92.

[27] Michaels AD, Maynard C, Every NR, Barron HV for the National Registry of Myocardial Infarction 2 participants. Early use of ACE inhibitors in the treatment of acute myocardial infarction in the United States: Experience from National Registry of Myocardial Infarction 2. Am J Cardiol 1999; 84: 1176–81.

[28] Zion MM, Balkin J, Rosenmann D et al. Use of pulmonary artery catheters in patients with acute myocardial infarction. Analysis of experience in 5841 patients in the SPRINT Registry. Chest 1990; 98: 1331–5.

[29] Gill JB, Cairns JA, Roberts RS et al. Prognostic importance of myocardial ischemia early after acute myocardial infarction. N Engl J Med 1996; 334: 65–70.

[30] Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. J Card Fail 2001; 7: 176–82.

[31] ISIS-1 (First International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous atenolol among 16027 cases of suspected acute myocardial infarction: ISIS 1. Lancet 1986; ii: 57–65.

[32] Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: Final Report of the GISSI study. Lancet 1987; ii: 871–4.

[33] ISIS-2. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17187 cases of suspected acute myocardial infarction. Lancet 1988; ii: 349–60.

[34] Levijoki J, Pollesello P, Kaheinen P, Haikala H. Improved survival with simendan after experimental myocardial infarction in rats. Eur J Pharmacol 2001; 419: 243–8.

[35] Binkley PF, Nunziata E, Hatton PS, Leier CV. The positive inotropic agent levosimendan mediates increased cardiac output without progression of sympathovagal imbalance in patients with heart failure. Circulation 2000; 102 (Suppl II): (II)720–(II)721.

[36] Lehtonen LA. Levosimendan: a parenteral calcium-sensitising drug with additional vasodilatory properties. Exp Opin Invest Drugs 2001; 10: 945–60.

[37] Karlson BW, Herlitz J, Hjalmarson Å. Prognosis of acute myocardial infarction in diabetic and non-diabetic patients. Diabet Med 1993; 10: 449–54.

[38] McGuire DK, Emanuelsson H, Granger CB et al. for GUSTO-IIb Investigators. Influence of diabetes mellitus on clinical outcomes across the spectrum of acute coronary syndromes. Findings from the GUSTO-IIb Study. Eur Heart J 2000; 21: 1750–8.

Appendix