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Troponin T Identifies Patients With Unstable Coronary Artery Disease Who Benefit From Long-Term Antithrombotic Protection

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Objectives. **We sought to evaluate whether troponin T might be used for identification of patients with unstable coronary artery disease in whom treatment with low molecular weight heparin is beneficial.**

Background. **Early identification of subgroups with differences in response to a certain treatment is important to optimize the utilization of different therapeutic approaches.**

Methods. **Nine-hundred seventy-one patients with unstable coronary artery disease who participated in a trial of the low molecular weight heparin dalteparin (Fragmin) and who provided blood samples were classified into subgroups according to troponin T level. In the short-term phase all patients received subcutaneous dalteparin/placebo twice daily for 6 days. During the long-term phase they continued with daltparin/placebo once daily for another 5 weeks.**

Results. **In the short-term phase, dalteparin reduced the incidence of death or myocardial infarction from 2.4% to 0% ($p = 0.12$) and from 6.0% to 2.5% ($p < 0.05$) in 327 and 644 patients with troponin T levels <0.1 and ≥0.1 μg/liter, respectively. During long-term treatment there was an increasing difference between the placebo and dalteparin group in those with troponin T levels ≥0.1 μg/liter, in whom the incidences at 40 days were 14.2% and 7.4%, respectively ($p < 0.01$). In contrast, no beneficial effect of the long-term treatment could be demonstrated in those with troponin T levels <0.1 μg/liter (4.7% vs. 5.7%).**

Conclusions. **Elevation of troponin T identifies a subgroup of patients in whom prolonged antithrombotic treatment (e.g., with dalteparin) is beneficial.**

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In patients with unstable coronary artery disease (CAD), i.e., unstable angina (UA) and non–Q wave myocardial infarction (MI), one of the main aims of treatment is prevention of new cardiac events, which are frequent during the subsequent weeks and months (1,2). In the Fragmin in Unstable Coronary Artery Disease (FRISC) study, inhibition of coagulation by the low molecular weight heparin, dalteparin (Fragmin), in addition to platelet inhibition by aspirin, was shown to reduce the event rate in unstable CAD in the short-term phase and possibly also during long-term treatment (3). However, the large population with unstable CAD is heterogeneous, regarding both the severity of the underlying CAD and the prognosis (4–6). Therefore, early risk stratification might be essential to select the most beneficial and cost-effective therapeutic approach for the individual patient. Several studies, including a previous report from the FRISC troponin T substudy, have shown that patients with even minor elevation of troponin T have an increased risk for subsequent cardiac events (7–9). We have speculated that there might be differences in the pathogenic mechanisms in unstable CAD patients with and without troponin T elevation, which might also affect the response to antithrombotic treatment. However, so far no study has demonstrated any difference in the effect of any therapeutic approach between subgroups of patients with unstable CAD. Accordingly, in the present prespecified substudy we evaluated prospectively whether the effect of low molecular weight heparin differed between patients with different levels of troponin T, and hence, if troponin T levels might be used to identify patients with unstable CAD who benefit from short- or long-term treatment, or both, with low molecular weight heparin.

Methods

Patients. This was a substudy of the FRISC trial—a double-blind, randomized, placebo-controlled trial of low molecular weight heparin (dalteparin sodium [Fragmin, Pharmacia AB, Sweden]) in patients with unstable CAD, including 1,506 patients at 23 hospitals in Sweden between May 1992 and October 1994. Details of the FRISC protocol have been reported (3). Eligible for inclusion were men >40 years or women 1 year after menopause who were admitted to the

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Abbreviations and Acronyms

CAD = coronary artery disease
CI = confidence interval
MI = myocardial infarction
RR = relative risk
UA = unstable angina

hospital because of chest pain, with their last episode within 72 h. All patients had to fulfil at least one of the following anamnestic criteria: newly developed or increased angina pectoris or angina at rest during the previous 2 months or ongoing chest pain suggestive of MI; and at least one of the following electrocardiographic (ECG) criteria: transient or persistent pathologic ST segment depression ≥0.1 mV or T wave inversion in at least two adjacent leads without pathologic Q waves, believed to indicate ischemia. Exclusion criteria were conditions with an increased risk of bleeding, indication for thrombolysis, new Q wave, left bundle branch block, pacemaker, suspected endomyopericarditis, cardiomyopathy, significant aortic valve disease, uncontrolled hypertension or hypotension, coronary artery bypass grafting or percutaneous transluminal coronary angioplasty planned or performed within the last 3 months, anemia, renal failure, hepatic failure, fever ≥39°C, serious intercurrent disease, hypersensitivity to heparin or low molecular weight heparin and unwillingness or inability to participate.

In 15 hospitals the protocol included a blood sampling schedule. The present substudy included all 971 patients in whom one blood sample for analysis of troponin T was obtained at inclusion.

Randomization and management. After admission all patients without a contraindication received oral aspirin (75 mg once daily), beta-blockers and organic nitrates and calcium antagonists as needed. The randomization was done in blocks within each center. Treatment was to start as early as possible after admission. Double-blind, placebo-controlled, randomized treatment with dalteparin/placebo was given as a subcutaneous injection twice daily at a dose of 120 U/kg body weight (maximal dose 10,000 U) for the first 5 to 7 days (short-term phase) and then once daily at a dose of 7,500 U for another 5 weeks (long-term phase). Heparin infusion, coronary angiography and revascularization were recommended in case of refractory or incapacitating angina despite medical treatment or after signs of severe ischemia on an exercise test. All therapeutic decisions were made without knowledge of the patients' troponin T levels.

The study was approved by the local ethics committee and all enrolled patients provided witnessed informed consent.

Evaluation of index event and end points. The episode that caused the enrollment in the study (index event) was retrospectively classified as MI or UA according to the maximal levels of available cardiac enzymes (serum creatine kinase [CK], serum CK-MB fraction or serum aspartate transaminase) obtained and analyzed at the local hospital immediately after the episode.

All patients were followed up while in the hospital and thereafter by outpatient visits after 6 weeks and 5 to 6 months. All primary end points (i.e., death and nonfatal MI) were classified by an independent end point committee. Myocardial infarction was defined by conventional World Health Organization criteria (10), satisfying two of the following three criteria: 1) severe ischemic chest pain of at least 20 min duration; 2) a diagnostic ECG; or 3) an increase in cardiac enzymes above the upper reference level at the local hospital in at least two consecutive samples.

Blood samples and laboratory methods. A venous blood sample for analyses of plasma troponin T was obtained at study inclusion. Blood was collected in an EDTA-containing tube and centrifuged, and plasma was frozen in aliquots and stored for subsequent analysis. Troponin T was determined by the Enzymun-Test system (Boehringer-Mannheim, Germany) (11). The lower detection limit is 0.04 μg/liter according to the manufacturer, and the upper reference level in healthy blood donors is 0.06 μg/liter (12). All analyses were done at one laboratory (Department of Clinical Chemistry, University of Uppsala, Sweden) and without knowledge of the patients' diagnosis and outcome. The between-day coefficient of variation over 4 months (n = 99) at our laboratory was 10.2% and 5.1% at a level of 0.28 and 6.10 μg/liter, respectively.

Statistical analysis. All analyses were performed according to the intention to treat principle. Differences in proportions were judged by the chi-square test. The relative risk (RR) ratio and the 95% confidence interval (CI) were calculated as appropriate. For nonparametric unrelated data, the Mann-Whitney U test was used. The cumulative hazard curves were constructed using the Kaplan-Meier method. The end points were death or nonfatal MI. Statistical assessment was performed using the log-rank test. Testing for an interaction between dalteparin/placebo treatment and troponin T level on the risk of death or MI was done by a multiple logistic regression analysis. A significant difference was considered to exist at the $p < 0.05$ level. All statistical analyses were performed by a computer utilizing the SPSS system 6.1 (Statistical Package for the Social Sciences, 1994).

Results

General findings. The clinical characteristics at inclusion of the 488 and 483 patients in the placebo and the dalteparin group, respectively, were very similar to those in the main study (3). There were no significant differences between the two groups, except for a slightly higher proportion of congestive heart failure in the dalteparin group (10% vs. 7%). The end point rates were also almost exactly the same as those in the main study (3). On day 6, after completion of the short-term phase of treatment, death or MI had occurred in 8 (1.7%) and 23 (4.7%) patients in the dalteparin and placebo groups, respectively (RR 0.35, 95% CI 0.16 to 0.78, $p < 0.01$). Immediately before the termination of the long-term phase of

Table 1. Clinical Characteristics of the Study Group (n = 971)

Baseline Variables	tn-T <0.1 μg/liter		tn-T ≥0.1 μg/liter	
	Placebo (n = 170)	Dalteparin (n = 157)	Placebo (n = 318)	Dalteparin (n = 326)
Male	96 (57)	86 (55)	221 (70)	224 (69)
Age (yr)	68 (62–75)	69 (62–75)	71 (64–76)	70 (63–75)
Previous heart failure	12 (7)	19 (12)	20 (6)	31 (10)
Previous stroke	4 (2)	7 (5)	10 (3)	18 (6)
Hypertension	53 (31)	58 (37)	106 (33)	103 (32)
Diabetes	20 (12)	16 (10)	35 (11)	51 (16)
Current smoking	30 (18)	24 (15)	61 (19)	68 (21)
Delay (h)*	22 (14–32)	24 (15–32)	25 (14–37)	24 (15–34)
History of CAD				
Previous MI	50 (29)	46 (29)	89 (28)	91 (28)
Rest angina the preceding week	75 (44)	65 (41)	163 (51)	169 (52)
Inclusion diagnosis				
UA/non–Q wave MI	162/7 (96/4)	156/1 (99/1)	137/181 (43/57)	136/190 (42/58)
Medication on admission				
Aspirin	65 (38)	70 (45)	97 (31)	103 (32)
Beta-blocker	61 (36)	63 (40)	122 (38)	113 (35)
Calcium inhibitor	39 (23)	42 (27)	70 (22)	68 (21)
Long-term nitrates	52 (31)	46 (29)	79 (25)	84 (26)
Diuretics	40 (24)	40 (26)	68 (21)	63 (19)
ACE inhibitor	17 (10)	20 (13)	19 (6)	29 (9)
Digoxin	11 (7)	19 (12)	12 (4)	17 (5)
Rest ECG at inclusion				
ST segment depression and T wave inversion	66 (39)	62 (40)	154 (49)	154 (48)
Only ST segment depression	21 (12)	20 (13)	59 (19)	58 (18)
Only T wave inversion	82 (49)	72 (47)	101 (32)	110 (34)
Troponin T at inclusion (μg/liter)	0.04 (0.04–0.06)	0.04 (0.04–0.06)	0.63 (0.25–1.6)	0.69 (0.25–1.7)

*Time from onset of chest pain until inclusion. Data presented are median values (25th to 75th percentile) or number (%) of patients. ACE = angiotensin-converting enzyme; CAD = coronary artery disease; ECG = electrocardiogram; MI = myocardial infarction; tn-T = troponin T; UA = unstable angina.

treatment, on day 40, the number of deaths or MIs was 33 (6.8%) in the dalteparin group and 53 (10.9%) in the placebo group (RR 0.63, 95% CI 0.41 to 0.95, $p < 0.05$). However, after 150 days no significant difference between the two groups remained—death or MI had occurred in 66 dalteparin-treated patients (13.7%) and 75 patients who received placebo (15.4%) (RR 0.89, 95% CI 0.65 to 1.21, $p = 0.45$).

Compliance with the study treatment was good, only 7.8% and 10.6% of the patients in the placebo and dalteparin groups, respectively, terminated the injections prematurely at their own request.

Effects of dalteparin treatment in relation to troponin T level. To study the treatment effect of dalteparin in relation to troponin T, the patients were classified into tertiles of the troponin T level at inclusion, i.e., below the 33rd percentile (<0.1 μg/liter), between the 33rd and 66th percentile (0.1 to 0.64 μg/liter) and above the 66th percentile (≥0.64 μg/liter). During the short-term phase of treatment, the occurrence of death or MI was lower in the dalteparin group compared with the placebo group in all troponin T tertiles—0% and 2.4% ($p = 0.12$), 1.9% and 6.9% ($p = 0.03$) and 3.0% and 5.0% ($p = 0.34$), in the lowest, middle and highest tertile, respectively. At the end of the long-term treatment, on day 40, there was no beneficial effect in the lowest troponin T tertile on the incidence of death or MI in the dalteparin compared with the placebo group—5.7% versus 4.7% ($p = 0.68$). However, there seemed to be a similar decrease in death or MI, from 12.6% to 5.7% ($p = 0.03$) and from 15.7% to 8.9% ($p = 0.06$), in the middle and highest tertiles, respectively. Thus, for all the further analyses the patients were classified according to troponin T level <0.1 and ≥0.1 μg/liter.

The clinical characteristics of the placebo and dalteparin groups, respectively, in patients with troponin T levels <0.1 and ≥0.1 μg/liter, respectively, are shown in Table 1. There were no significant differences in clinical characteristics between the placebo and dalteparin groups within each troponin T subset. In patients with a troponin T level ≥0.1 μg/liter, the difference in the end point rate between the placebo and dalteparin groups was already significant after the short-term phase, and seemed to further increase during the long-term treatment. In contrast, in patients with a troponin T level <0.1 μg/liter, there was no difference between the dalteparin and placebo groups during long-term treatment (Table 2, Fig. 1). The interaction between treatment and troponin T level and troponin T level alone, but not the treatment alone, remained as statistically significant indicators of the risk of death or MI

Table 2. Effect of Dalteparin on the Rate of Death or Myocardial Infarction in Relation to Troponin T Level <0.1 or ≥0.1 μg/liter at Inclusion (n = 971)

	Death/MI, Day 6			Death/MI, Day 40			Death/MI, Day 150		
Troponin T (placebo/dalteparin)	Placebo [no. (%)]	Dalteparin [no. (%)]	RR (95% CI)	Placebo [no. (%)]	Dalteparin [no. (%)]	RR (95% CI)	Placebo [no. (%)]	Dalteparin [no. (%)]	RR (95% CI)
<0.1 μg/liter (170/157)	4 (2.4)	0 (0)	p = 0.12	8 (4.7)	9 (5.7)	1.22 (0.48–3.1)	10 (5.9)	14 (8.9)	1.52 (0.69–3.31)
≥0.1 μg/liter (318/326)	19 (6.0)	8 (2.5)	0.41 (0.18–0.92)	45 (14.2)	24 (7.4)	0.52 (0.32–0.83)	65 (20.4)	52 (16.0)	0.78 (0.56–1.09)

CI = confidence interval; MI = myocardial infarction; RR = relative risk.

after 40 days in a multivariate logistic regression analysis (Table 3). The rate of revascularization in the placebo and dalteparin groups on day 40 in patients with a troponin T level ≥0.1 μg/liter was 18% and 12% ($p < 0.05$), respectively, and in patients with a troponin T level <0.1 μg/liter, 21% and 18% (NS), respectively. After termination of the randomized treatment the difference in deaths or MI between the dalteparin and placebo groups of patients with a troponin T level ≥0.1 μg/liter slowly decreased and was not statistically significant at the last follow-up visit, after 150 days (Table 2).

If the analysis was restricted to only those with UA as the inclusion event (n = 591) the relative risks for death or MI on day 40 with dalteparin compared with placebo were in the same range as in the whole population, although the confidence intervals were broader. In those with a troponin T level <0.1 μg/liter (n = 318), the rate of death or MI after 40 days was 5.8% and 4.3% in the dalteparin and placebo groups, respectively (RR 1.34, 95% CI 0.51 to 3.50). In those with a troponin T level ≥0.1 μg/liter (n = 273), the corresponding rate of death or MI was 7.4% and 10.9% (RR 0.67, 95% CI 0.31 to 1.44), respectively.

Discussion

Unstable CAD is an increasing reason for hospitalization in the Western world, and considerable resources are needed for evaluation and treatment of these patients (13). The syndrome still implies a high risk for subsequent cardiac events (1,2), despite considerable progress in treatment in the last decade (1,14–16). Because the unstable CAD population is heterogeneous, the treatment should ideally be tailored according to proper considerations about prognosis and underlying pathophysiology. Several noninvasive methods have been proposed for identification of subgroups with high and low risk, e.g., exercise test, Holter ST segment monitoring, thallium scintigraphy, stress echocardiography and biochemical markers (7–9,17–20). We have in a previous report shown that the troponin T level identified low, intermediate and high risk groups for death or MI during the subsequent 5 months in patients with unstable CAD (9). This probably mirrors differences in severity or underlying mechanisms of the disease, which might have importance for the effects of treatment in general and heparins in particular.

Table 3. Univariate and Multivariate Logistic Regression Analysis Evaluating the Effect of Randomized Treatment, Troponin T Level and Interaction Between Treatment and Troponin T Level on the Rate of Death or Myocardial Infarction During 40 Days of Follow-Up (n = 971)

	Myocardial Infarction or Death	
Variable Analyzed	Univariate (p value)	Multivariate (p value)
Treatment (placebo/dalteparin)	0.03	NS
Troponin T (<0.1/≥0.1 μg/liter)	0.004	0.003
Interaction term (treatment by troponin T)	0.0017	0.007

Heparins inhibit the generation of thrombin, low molecular weight heparin mainly by inhibiting factor Xa (21), thus preventing thrombus formation and, ultimately, the development of MI. A reactivation phenomenon after cessation of short-term heparin treatment has previously been demonstrated (22). The rationale for the prolonged treatment period in the FRISC trial was that treatment with a low dose dalteparin would give sufficient protection until the plaque fissure, which triggered the activation of the coagulation system, had healed. To obtain maximal benefit and compliance in relation to cost, it is important to be able to identify the target patients for this rather demanding treatment with self-administration of subcutaneous injections over several weeks or months. The results of the present study showed that troponin T determinations might contribute to the identification of patients in whom long-term dalteparin treatment would be beneficial.

Effects of dalteparin treatment in relation to troponin T level. The event rate in the total dalteparin group was reduced by ~65% during the short-term phase of treatment. During the long-term treatment phase the absolute reduction was maintained, but there was no further reduction. However, in the subgroup with troponin T levels ≥0.1 μg/liter, not only was there an effect of dalteparin treatment during the short-term treatment phase, but also an additive effect during the long-term treatment phase. In contrast, there seemed to be no protective effect of long-term dalteparin in patients with very low or undetected levels of troponin T (<0.1 μg/liter). Treatment with dalteparin reduced the risk of events in patients with a troponin T level ≥0.1 μg/liter almost to the same level as in

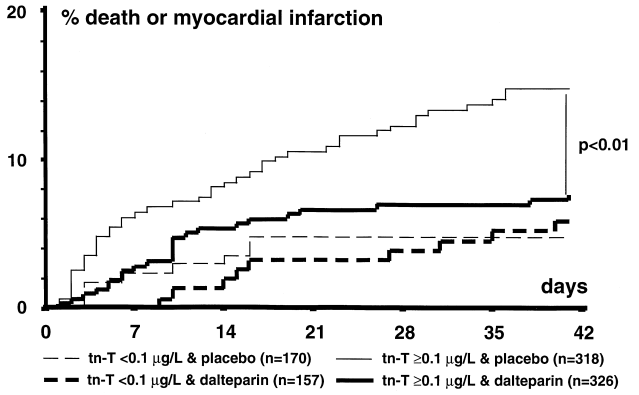

Figure 1. Cumulative hazard curves for death or myocardial infarction in patients with and without dalteparin treatment and with and without elevation of troponin T (tn-T).

the low risk patients with a troponin T level <0.1 μg/liter (Table 2, Fig. 1). There was no further relation between the effect of dalteparin and troponin T above the level of 0.1 μg/liter. There were no differences in clinical characteristics between the placebo and dalteparin groups within each troponin T subset that could explain these results (Table 1). The interaction analysis further supported that there was a real difference in effect of dalteparin treatment in patients with and without elevation of troponin T. Even if restricted to the UA group, a cut-off value of 0.1 μg/liter seemed to stratify the patients in the same way as in the total material. The inclusion samples of troponin T obtained in the present study might not be translated in clinical practice to admission samples, but rather to samples obtained during the first 24 h after admission since the median delay to inclusion (and first blood sample) from onset of the last episode of chest pain was 24 h, whereas the median delay to admission was only 5 h. Thus, a troponin T level ≥0.1 μg/liter during the first day seems to be a useful criterion for selecting potential candidates for long-term treatment with dalteparin in patients with unstable CAD. However, this stratification needs to be confirmed and also tested for its applicability to other medical or interventional therapies in unstable CAD in further studies.

How might the difference in the protective effect of long-term dalteparin in patients with "normal" and increased levels of troponin T be explained? It is more difficult to show a beneficial effect of any treatment in low risk groups. The lack of prophylactic long-term effect of dalteparin in the group of patients with a troponin T level <0.1 μg/liter might therefore be a play of chance, as evident from the broad confidence interval (Table 2). A substantially larger number of patients, versus the number included in the present study, is necessary to exclude a small beneficial effect. However, in such a low risk population it is doubtful that a small beneficial effect will outweigh the risks and costs. It might also be speculated that the lack of protective effect of long-term dalteparin in unstable CAD patients with normal troponin T levels might imply that other mechanisms, besides a thrombotic process, might cause the symptoms in these patients, e.g., coronary vasoconstriction due to impaired endothelial vasoactive function in the atherosclerotic coronary arteries (23,24). Thus, in patients with elevation of troponin T an embolizing or at least temporary occluding red thrombus might be the main mechanism that responds to low molecular weight heparin (5). In contrast, in patients without troponin T elevation this process might be less prominent and therefore less responsive to this kind of therapy.

Clinical implications. Analysis of troponin T during the first day after admission might identify patients with unstable CAD in whom prolonged antithrombotic treatment, e.g., with dalteparin, is beneficial. Any beneficial effect, at least of clinical significance, of long-term dalteparin treatment seemed to be restricted to patients with an elevation of troponin T ≥0.1 μg/liter. Thus, in the selection of a long-term treatment strategy for the individual patient with unstable CAD, this simple, inexpensive and rapid biochemical test might be useful.

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