Left Ventricular Thrombus Formation and Bleeding Complications during Continuous In-Hospital Anticoagulation for Acute Anterior Myocardial Infarction

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ABSTRACT: **Background:** The 20%–60% rate of acute anterior myocardial infarction (AAMI) patients with concomitant left ventricular thrombus (LVT) formation dropped to 10–20% when thrombolysis and primary percutaneous coronary intervention (PPCI) were introduced.

Objective: To test our hypothesis that prolonged anticoagulation post-PPCI will lower the LVT incidence even further.

Methods: Included in this study were all 296 inpatients with ST elevation AAMI who were treated with PPCI (from January 2006 to December 2009). Treatment included heparin anticoagulation (48 hours) followed by adjusted doses of low molecular weight heparin (3 more days). All patients underwent cardiac echocardiography on admission and at discharge. LVT and bleeding complications were reviewed and compared.

Results: LVT formation was present on the first echocardiogram in 6/296 patients. Another 8/289 patients displayed LVT only on their second echocardiogram (4.7%, 14/296). LVT patients had significantly lower LV ejection fractions than non-LVT patients at admission ($P < 0.003$) and at discharge ($P < 0.001$), and longer time to reperfusion ($P = 0.168$). All patients were epidemiologically and clinically similar. There were 6 bleeding episodes that required blood transfusion and 11 episodes of minor bleeding.

Conclusions: Five days of continuous anticoagulation therapy post-PPCI in inpatients with AAMI is associated with low LVT occurrence without remarkably increasing bleeding events.

IMAJ 2012; 14: 742-746

KEY WORDS: acute anterior myocardial infarction (AAMI), left ventricular thrombus (LVT), percutaneous coronary intervention (PPCI), anticoagulation, bleeding

Left ventricular mural thrombus is a well-known complication of acute anterior wall myocardial infarction. The incidence of LVT in acute anterior MI patients in the pre-thrombolytic era ranged from 20% to 40% and could reach as high as 60% among patients with large anterior wall infarcts [1,2]. Prospective studies have shown that the presence of an LVT is associated with poor early prognosis, probably related to the large infarct size rather than to the embolic events, which are reported in 10% of the patients [3,4]. The risk for LVT formation is increased in patients with an anterior location of the infarct, apical aneurysm, reduced left ventricular ejection fraction, advanced age, a hypercoagulable state and elevated C-reactive protein levels [5-7]. Early anticoagulation [8,9] and reperfusion therapy with either thrombolysis [10,11] or primary percutaneous coronary intervention [5,6,12] further decreased LVT, and the updated incidence now ranges between 10 and 15% [12,13]. Solheim et al. [14] recently reported an LVT incidence of 10% in the first week following an MI among patients with AAMI who had been treated with PPCI and dual antiplatelet therapy. Similarly, Osherov et al. [15] reported a 7.1% incidence of early LVT formation among AMI patients treated with PPCI.

In the pre-thrombolytic era, guidelines for the management of patients with ST-segment elevation myocardial infarction favored anticoagulation with heparin for 5 days following an AMI. These guidelines were revised over the years, and the current ones recommend that anticoagulation therapy be stopped following PPCI [16,17]. Continuous administration of anticoagulants is recommended for patients who are at high risk for systemic emboli (e.g., large or anterior MI, atrial fibrillation, previous emboli or known LVT). We evaluated whether continuous treatment with heparin contributes to a lower incidence of LVT in AAMI patients, and to what extent this treatment affects the tendency towards bleeding.

PATIENTS AND METHODS

The data for this retrospective observational study were retrieved from the records of all patients with an anterior STEMI admitted between January 2006 and December 2009 to the Cardiac Intensive Care Unit in the Tel Aviv Sourasky

LVT = left ventricular thrombus
MI = myocardial infarction

AAMI = acute anterior wall myocardial infarction
PPCI = primary percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

Medical Center. All patients were treated with dual antiplatelet therapy consisting of aspirin and clopidogrel (a loading dose of 300 mg followed by 75 mg/dl). The IIb/IIIa antagonist was administered during PPCI at the discretion of the operator. Our departmental policy for all patients who undergo PPCI for STEMI is to continue with the administration of heparin after PPCI by continuous intravenous drip adjusted to achieve a partial thromboplastin time of 45–60 seconds for 48 hours, followed by adjusted doses of subcutaneous low molecular weight heparin for an additional 3 days. All patients in the CICU undergo an echocardiogram within 24–48 hours from admission, and all those with evidence of an AAMI have a repeat echocardiogram before discharge from the hospital. Patients with an AAMI treated conservatively or with fibrinolysis and those who underwent an echocardiographic evaluation more than 48 hours from admission (mostly individuals admitted on weekends and holidays), as well as those with non-anterior wall MI were excluded from this study.

Echocardiography was performed with a Philips IG-33, GE and Vivid 3 models equipped with S5-1 transducers. Parasternal long and short axis, apical, and two- and four-chamber views were obtained using standard transducer positions. Special consideration was also given to apical and low parasternal echocardiographic windows. Echocardiograms were interpreted independently by two investigators. An LVT was defined as an echodense mass adjacent to an abnormally contracting myocardial segment. It had to be distinguishable from the underlying myocardium, have a clear thrombus-blood interface, and be visible in at least two transducer positions. The 16-segment model was used for scoring the severity of segmental wall motion abnormalities according to the American Society of Echocardiography [18]. LV wall motion was graded on a scale from 0 to 4 where 0 = normal motion, 1 = hypokinesia, 2 = akinesia, 3 = dyskinesia and 4 = signs of an LV aneurysm.

When available, the patients' records and laboratory results up to 30 days following admission were also reviewed for any change in hemoglobin levels or the need for a blood transfusion. Minor bleeding was defined as a ≤ 3 g/dl drop in hemoglobin, while major bleeding was defined as a > 3 g/dl drop in hemoglobin, an expanding groin or the presence of a retroperitoneal hematoma or bleeding requiring blood transfusion.

STATISTICAL ANALYSIS

Data are reported as mean ± SD. Categorical variables were compared by chi-square tests. Standard formulas for sensitivity, specificity, and positive and negative predictive values were used. All *P* values are two-tailed, and $P < 0.05$ was considered significant.

CICU = Cardiac Intensive Care Unit

RESULTS

A total of 296 consecutive patients (mean age 61 ± 13 years, range 29–92; 82% males) met the inclusion criteria of this study and their data were included in the analyses. Selected baseline characteristics of the study group are listed in Table 1. Twenty-seven of them (9%) had a past history of MI (14 anterior and 13 inferior), while this was the first MI for the other 269 study patients. Mean duration of time from symptom onset to hospital arrival was 189 ± 460 minutes (range 30–720). All patients underwent PPCI, and the mean door-to-balloon time was 44 ± 15 minutes (range 20–90). The median duration of hospitalization was 6.4 ± 2.8 days (range 5–33). A total of 175 patients (59%) received glycoprotein IIb/IIIa.

The first echocardiogram was performed within 1.2 ± 0.9 days of admission and the second after 5.8 ± 3.6 days. The mean admission LVEF for the entire cohort was 42 ± 7.0% (range 20–60%) and the mean hospital discharge LVEF 45 ± 8% (range 20–60%), representing a mean change in LVEF of 2.8% ($P < 0.0001$). LVT had been demonstrated on the admission echocardiogram of seven patients (2%) [Table 2] and again on the second echocardiogram in six of them. The second examination of the seventh patient showed no evidence of the LVT that had been suspected on the first echocardiogram. An LVT was found only on the second echocardiographic examination in another 8 patients (2%) [Table 3], totaling 14 patients whose second echocardiographic examination demonstrated an LVT (4.7%, 14/296). Wall motion abnormalities were identified in all 15 patients with LVT (100%). Of 281 patients without

LVEF = left ventricular ejection fraction

Table 1. Selected baseline characteristics of the study group (n=296)

	n	%
Males	231	82.2
Diabetes	61	20.6
Hyperlipidemia	140	47.3
Family history for ischemic heart disease	40	13.5
Current smoker	116	39.2
Past smoker	26	8.8
Hypertension	105	35.5
Treatment		
Aspirin	20	6.8
Clopidogrel	2	0.7
Beta blockers	18	6
Nitrates	2	0.7
Calcium channel blockers	11	3.7
Coumadin	4	1.4
ACE inhibitors/ARB	8	6.1
IIb/IIIa receptor blockers	175	59
Time interval		
Time from symptom onset to first medical contact (min)	189 ± 81	
Door-to-balloon time (min)	44 ± 15	

ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blockers

Table 2. Demonstration of a left ventricular thrombus on the first echocardiogram

	No thrombus (n = 289)	Thrombus (n = 7)	*P*
Age (yrs)	61 ± 13	60 ± 13	0.859
Admission LVEF	42 ± 7%	39 ± 2%	0.162
Discharge LVEF	45 ± 8%	39 ± 3%	0.003
Males	61 (21%)	2 (29%)	1.000
Diabetes mellitus	59 (22%)	2 (33%)	0.614
Dyslipidemia	137 (50%)	3 (50%)	1.000
Family history of ischemic heart disease	40 (15%)	0 (0%)	0.599
Current/past smoker	138 (50%)	3 (50%)	1.000
Hypertension	104 (38%)	1 (17%)	0.416
Treatment			
Chronic aspirin	20 (10%)	0 (0%)	1.000
Chronic clopidogrel	2 (1%)	0 (0 %)	1.000
IIb/IIIa receptor blockers	166 (58%)	9 (60%)	1.000
Beta blockers	17 (9%)	1 (25%)	0.312
Nitrates	2 (1%)	0 (0%)	1.000
Calcium channel blockers	11 (6%)	0 (0%)	1.000
Coumadin	3 (2%)	1 (25%)	0.077
ACE inhibitors/ARB	18 (9%)	0 (0%)	1.000

LVEF = left ventricular ejection fraction

Table 3. Demonstration of a left ventricular thrombus on the second echocardiogram

	No thrombus (n = 282)	Thrombus (n = 14)	*P*
Age (yrs)	62 ± 13	56 ± 10	0.130
Admission LVEF	42 ± 7%	39 ± 3%	0.001
Discharge LVEF	45 ± 8%	41 ± 5%	0.009
Male gender	60 (22%)	2 (14%)	0.741
Diabetes mellitus	59 (22%)	2 (15%)	0.741
Dyslipidemia	134 (50%)	7 (54%)	1.000
Family history of ischemic heart disease	38 (14%)	2 (15%)	1.000
Current/past smoker	134 (50%)	8 (61%)	0.602
Hypertension	102 (38%)	3 (23%)	0.383
Time interval			
Time from symptom onset to first medical contact (min)	215 ± 296	167±487	0.168
Door-to-balloon time (min)	41 ± 7	43 ± 4	0.268

thrombus, normal LV function without segmental wall motion abnormalities was demonstrated in 37 cases (12.5%)

Patients with an LVT had significantly lower LVEF than those without, both at admission (39 ± 2% vs. 42 ± 7% respectively, $P < 0.003$) and prior to hospital discharge (41 ± 5% versus 45 ± 8% respectively, $P < 0.001$). Importantly, all patients with LVT had an LVEF ≤ 40. No LVT was demonstrated in patients with mild (45–50%) or preserved (≥ 50%) LVEF. Patients with an LVT had longer time to reperfusion, related mainly to the time that had elapsed from onset of symptoms to first medical contact, compared with those without an LVT (median 215 ± 296 minutes vs. 167 ± 487 minutes, respectively), however, this difference did not reach a level of significance ($P = 0.168$). There was also no significant difference in door-to-balloon time between those with an LVT (41 ± 7 minutes) and those without (43 ± 4 minutes, $P = 0.26$). The use of IIb/IIIa receptor blockers had no effect on thrombus formation. There were no other significant epidemiological or clinical differences between the patients in the LVT and non-LVT groups. No LVT was detected in patients with a past history of anterior MI. The six patients who demonstrated an LVT on both their first and second echocardiographic examinations were older and had lower LVEF values compared with the eight patients in whom LVT was present only in the second examination. All 14 patients with an LVT on their second echocardiographic examination were started on oral anticoagulation therapy with warfarin and were advised to continue taking it for at least 6 months.

Seventeen patients (6%, 17/296) experienced access site-related bleeding, including 6 (2%, 6/296) major bleeding events that necessitated blood transfusions for expanding groin hematoma. Noteworthy, two of these six events occurred within the first 24 hours of admission. There were no cases of intracranial bleeding or of bleeding that required surgical intervention. Eleven patients (4%, 11/296) had minor bleeding events that resolved without any intervention.

Follow-up echocardiograms were available for 9 of the 14 patients who had demonstrated an LVT on the second in-hospital echocardiogram. They were performed within a mean of 130 days (range 15–220) following hospital discharge. There was evidence of an LVT in three of these patients. Anticoagulation treatment was continued in two of them but was stopped in the third patient after he suffered a hemorrhagic stroke. Anticoagulation was stopped in the other six patients when the echocardiographic examination ruled out the presence of an LVT. One of the five patients for whom there was no follow-up echocardiograph continued on anticoagulation treatment and the other four were lost to follow-up.

DISCUSSION

Previous reports have shown that an LVT characteristically continued to complicate the course of many patients post-acute STEMI, albeit much less frequently following the introduction of thrombolysis, PPCI and dual antiplatelet therapy [5,6,12-15]. This was especially true for large AMIs. In those trials, the use of IIb/IIIa receptor blockers had no direct influence on LVT formation early after the occurrence of an AMI [5,6,14].

The genesis of a thrombus is probably related to a combination of factors, such as stasis of blood in areas of akinetic or dyskinetic wall motion, and a hypercoagulable state during the peri-infarction period. Early reperfusion therapy by PPCI results in salvage of the myocardium and reduction in the infarct area, thus promoting early recovery of LV function.

The presence of an LVT is associated with overall worse prognosis, with about 10% of thrombi resulting in systemic embolization. Kontny et al. [9] reported that the addition of

a regimen of anticoagulation with LMWH throughout the period of hospitalization in patients with an AMI treated with thrombolysis led to a marked reduction in the formation of LVT compared to placebo. However, the effect of this therapeutic approach in patients undergoing PPCI for AMI has not been evaluated in depth.

With the exception of LVEF, there were no significant differences between the thrombus and non-thrombus groups in our cohort, including use of IIb/IIIa receptor blockers and all the other examined echocardiographic findings, such as regional hypo/akinesia, mitral regurgitation and LV end-diastolic diameter.

We tried to compare our findings with data retrieved from previous observational studies that examined the prevalence of LVT in AAMI patients who were treated with PPCI and standard anticoagulation therapy for 48 hours [14,15] [Table 4]. However, a statistical multivariate analysis would have been needed in order for comparisons with other reports to be of value, but that was not possible due to missing data in those reports.

The main drawback of continuous anticoagulation is the increased risk of hemorrhage. The recent HORIZONS-AMI trial demonstrated a direct relation between bleeding complications and adverse outcome in AAMI patients treated with various anticoagulation strategies [19]. This trend was demonstrated in a number of other studies [20,21]. Anemia developing post-PCI or in the setting of an MI is also associated with a worse outcome [22]. On the other hand, continuous prophylactic anti-coagulation with warfarin for LVT (recommended for 3–6 months) is associated with increased bleeding risk, with an estimated absolute rate of PPCI of 0.5% per year in the general population. The hemorrhagic episodes usually happen in the first months of anticoagulation, and the rate is markedly increased with concomitant dual antiplatelet therapy [22].

LMWH = low molecular weight heparin

Table 4. Selected baseline characteristics of the current study group compared to historical study groups

	Current group	Osherov et al. [15]	Solheim et al. [14]
Patients	296	297	100
Males	231 (82%)	242 (81%)	84 (84%)
Diabetes Previous infarction Current or past smoker	61 (20.6%) 27 (9%) 142 (48%)	76 (25%) Not reported 142 (48%)	8 (8%) 48 (48%) 44 (44%)
Ejection fraction (%)*	42 ± 7	42 ± 11	45 ± 5
Time to percutaneous coronary intervention (min)	233	Not reported	215
GP IIb/IIIa receptor blockers	175 (58%)	Not reported	49 (49%)
Left ventricular thrombus formation	14 (4.7%)	21 (7.1%)	10 (10%)

*In the first echocardiogram

The rate of bleeding events in our group was comparable with the rates of major and minor bleeding complications in trials where standard anticoagulation was used in patients with STEMI undergoing PPCI [19,23]. None of our reported patients had intracranial bleeding. Moreover, since two of the major bleeding episodes and four of the minor ones occurred within the first 24 hours of anticoagulative administration, they cannot be related to prolonged treatment.

Unlike the absence of published data on the effect of prolonged anticoagulation on the incidence of LVT in patients undergoing PPCI, the administration of anticoagulants for the duration of hospitalization in STEMI patients has been assessed in several clinical trials [23-25]. Nevertheless, there is no consensus on the optimal duration of anticoagulant treatment for various cardiac indications. The American College of Cardiology/American Heart Association guidelines for the management of patients with STEMI recommend the administration of anticoagulants for patients who are at high risk for systemic emboli (e.g., large or anterior MI, atrial fibrillation, previous emboli or known LVT) [16]. The 2008 update suggests anticoagulation therapy for the duration of the index hospitalization in patients not undergoing PPCI. The European Society of Cardiology guidelines recommend that anticoagulation therapy be stopped following PPCI [17]. Glick and colleagues [24] demonstrated that extending the anticoagulant effect of heparin by continuous treatment with LMWH for 25 days may prevent recurrent coronary events for at least 1 month among patients with a recently diagnosed STEMI who were treated by streptokinase. The ExTRACT TIMI 25 trial [25] demonstrated that the use of enoxaparin for the duration of hospitalization (median 7.0 days) lowered the 30 day incidence of recurrent MI as well as the need for urgent revascularization compared with 48 hours of unfractionated heparin administration. There was, however, an increased risk of major and minor bleeding, although not intracranial bleeding. The 1 year results from that trial suggested that the primary endpoint (a composite of death from any cause or non-fatal MI) was obtained, but there was no additional benefit beyond 30 days and enoxaparin was not associated with reduced mortality at 1 year. On the other hand, the OASIS 6 trial demonstrated that fondaparinux (a factor Xa antagonist) therapy for up to 8 days or hospital discharge was not better than unfractionated heparin given for 48 hours in terms of preventing death or reinfarction at 30 days among STEMI patients [23].

Our study has the usual limitations of a non-randomized retrospective observational analysis. We compared our findings with historical controls since our departmental policy is to administer prolonged anticoagulation treatment to all AAMI patients post-PPCI. This precluded our having a contemporary non-treated control group, which made it difficult to determine the precise contribution of the duration of treatment to the

prevention of LVT formation, as well as determine the relative risk of bleeding between the treated and non-treated groups. In addition, we did not follow all our patients to assess the prevalence of LVT formation after hospital discharge.

CONCLUSIONS

PPCI followed by continuous anticoagulation therapy for the ensuing 5 days of hospitalization was associated with a low (4.7%) incidence of LVT in patients who presented with AAMI. This regimen was not associated with a significant risk of bleeding complications. Determination of the exact contribution of prolonged in-hospital anticoagulation awaits large randomized prospective trials.

Acknowledgment

Esther Eshkol, the institutional medical and scientific copy editor, is thanked for editorial assistance

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References

1. Asinger RW, Mikell FL, Elsperger J, Hodges M. Incidence of left-ventricular thrombosis after acute transmural myocardial infarction. *N Engl J Med* 1981;305: 297-302.
2. Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular thrombus formation after first anterior wall acute myocardial infarction. *Am J Cardiol* 1988; 62: 31-5.
3. Keren A, Goldberg S, Gottlieb S, et al. Natural history of left ventricular thrombi: their appearance and resolution in the posthospitalization period of acute myocardial infarction. *J Am Coll Cardiol* 1990; 15: 790-800.
4. Keeley E, Hillis LD. Left ventricular mural thrombus after acute myocardial infarction. *Clin Cardiol* 1996; 19: 83-6.
5. Zielinska M, Kaczmarek K, Tylkowski M. Predictors of left ventricular thrombus formation in acute myocardial infarction treated with successful primary angioplasty with stenting. *Am J Med Sci* 2008; 335: 171-6.
6. Rabbani LE, Waksmonski C, Iqbal SN, et al. Determinants of left ventricular thrombus formation after primary percutaneous coronary intervention for anterior wall myocardial infarction. *J Thromb Thrombolysis* 2008; 25: 141-5.
7. Anzia T, Yoshikawa T, Kaneko H, et al. Association between serum C-reactive protein elevation and left ventricular thrombus formation after first anterior myocardial infarction. *Chest* 2004; 125: 384-9.
8. Turpie AG, Robinson JG, Doyle DJ, et al. Comparison of high-dose with low-dose subcutaneous heparin to prevent left ventricular mural thrombosis in patients with acute myocardial infarction. *N Engl J Med* 1989; 320: 352-7.
9. Kontny F, Dale J, Abildgaard U, Pedersen TR. Randomized trial of low molecular weight heparin (dalteparin) in prevention of left ventricular thrombus formation and arterial embolism after acute myocardial infarction: The Fragmin in Acute Myocardial Infarction (FRAMI) Study. *J Am Coll Cardiol* 1997; 30: 962-9.
10. Pizzetti G, Belotti G, Margonato A, et al. Thrombolytic therapy reduces the incidence of left ventricular thrombus after anterior myocardial infarction. Relationship to vessel patency and infarct size. *Eur Heart J* 1996; 17: 421-6.
11. Ileri M, Tadogan I, Kosar F, Yetkin E, Buyukasik Y, Kutuk E. Influence of thrombolytic therapy in the incidence of left ventricular thrombi after acute anterior myocardial infarction: role of successful reperfusion. *Clin Cardiol* 1999; 22: 477-80.
12. Kalra A, Jang IK. Prevalence of early left ventricular thrombus after primary coronary intervention for acute myocardial infarction. *J Thromb Thrombolysis* 2000; 10: 133-6.
13. Nayak D, Aronow WS, Sukhija R, McClung JA, Monsen CE, Belkin RN. Comparison of frequency of left ventricular thrombi in patients with anterior wall versus non-anterior wall acute myocardial infarction treated with antithrombotic and antiplatelet therapy with and without coronary revascularization. *Am J Cardiol* 2004; 93: 1529-30.
14. Solheim S, Seljeflot I, Lunde K, et al. Frequency of left ventricular thrombus in patients with anterior wall acute myocardial infarction treated with percutaneous coronary intervention and dual antiplatelet therapy. *Am J Cardiol* 2010; 106: 1197-200.
15. Osherov AB, Borovik-Raz M, Aronson D, et al. Incidence of early left ventricular thrombus after acute anterior wall myocardial infarction in the primary coronary intervention era. *Am Heart J* 2009; 157: 1074-80.
16. Funck-Brentano C, Hellemans I, Kristensen SD, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction – Executive Summary. *Circulation* 2004; 110: 588-636.
17. Van de Werf F, Bax J, Betriu A, et al; ESC Committee for Practice Guidelines (CPG). Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008; 29: 2909-45.
18. Schiller NB, Shah PM, Crawford M, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography: American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr* 1989; 2: 358-67.
19. Mhran R, Lansky AJ, Witzenbichler B, et al; HORIZONS-AMI Trial Investigators. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet* 2009; 374: 1149-59.
20. Manoukian SV. Predictors and impact of bleeding complications in percutaneous coronary intervention, acute coronary syndromes, and ST-segment elevation myocardial infarction [Review]. *Am J Cardiol* 2009; 104 (5 Suppl): 9C-15C.
21. Jani SM, Smith DE, Share D, et al. Blood transfusion and in-hospital outcomes in anemic patients with myocardial infarction undergoing percutaneous coronary intervention. *Clin Cardiol* 2007; 30 (10 Suppl 2): II49-56.
22. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. *Stroke* 2005; 36: 1588-93.
23. Yusuf S, Mehta SR, Chrolavicius S, et al; OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST- segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA* 2006; 295: 1519-30.
24. Glick A, Kornowski R, Michowich Y, et al. Reduction of reinfarction and angina with use of low-molecular-weight heparin therapy after streptokinase (and heparin) in acute myocardial infarction. *Am J Cardiol* 1996; 77: 1145-8.
25. Antman EM, Morrow DA, McCabe CH, et al; ExTRACT-TIMI 25 Investigators. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med* 2006; 354: 1477-88.

"It is in the character of very few men to honor without envy a friend who has prospered"

Aeschylus (524-456 BC), first of the three ancient Greek tragedians whose plays are still read and performed, the others being Sophocles and Euripides. He is often described as the father of tragedy