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The Use of Tissue-Type Plasminogen Activator for Acute Myocardial Infarction in the Elderly: Results From Thrombolysis in Myocardial Infarction Phase I, Open Label Studies and the Thrombolysis in Myocardial Infarction Phase II Pilot Study

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The impact of age on hospital mortality, incidence of major hemorrhagic events and transfusion requirements was examined in 756 patients with acute myocardial infarction enrolled in the Thrombolysis in Myocardial Infarction (TIMI) Phase I, open label studies and the TIMI Phase II pilot study. The mortality rate significantly increased with age and was 3.5%, 11.5% and 12% in patients <65, 65 to 69 and 70 to 76 years of age, respectively ($p < 0.001$). Logistic regression analyses selected female gender, diabetes mellitus, extensive coronary artery disease, history of congestive heart failure, continuing chest pain immediately after recombinant tissue-type plasminogen activator (rt-PA) administration, low systolic blood pressure at the time of admission and advanced age as variables predictive of in-hospital death.

The incidence of major hemorrhagic events among patients not undergoing cardiac surgery during hospitalization was 8.7%, 14.5% and 24.7% in patients aged <65, 65 to 69 and ≥70 years, respectively ($p < 0.001$). The majority of hemorrhages were secondary to cardiac catheterization or puncture wounds. Variables related to a major hemorrhagic event included protocol, age, rt-PA dose/kg body weight and elevated diastolic blood pressure on admission. Of five intracranial bleeding events, three occurred in patients >65 years. Transfusion requirements significantly increased with age ($p < 0.001$). Reperfusion status at 90 min in the TIMI Phase I and open label studies A to C was similar in the three age groups studied and ranged from 60% to 71%.

Thus, a strategy of early cardiac catheterization in older patients with acute myocardial infarction treated with thrombolytic therapy is associated with an increased hospital mortality rate and incidence of bleeding compared with findings in younger patients. A randomized placebo-controlled trial appears to be needed to determine safety and efficacy of rt-PA therapy in patients >76 years.

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Elderly patients with acute myocardial infarction represent a high risk subset with increased morbidity and mortality compared with those in younger patients (1–10). Thrombolytic therapy and coronary angioplasty improve perfusion in infarct-related vessels and have the potential to limit myocardial infarct size when initiated early after symptom onset (11–17). Recombinant tissue-type plasminogen activator (rt-PA) is superior to streptokinase in restoring patency of initially occluded infarct-related vessels (18–20). However, data on the use of thrombolytic therapy in elderly patients are limited because most thrombolytic trials exclude patients >75 years and increased hemorrhagic complications were noted in one observational study (6) that used streptokinase in older patients. There are limited data that describe the use of rt-PA as therapy for acute myocardial infarction in older patients (7,21).

*A list of TIMI investigators appears in J Am Coll Cardiol 1987; 10:51B–64B.

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This study was performed to evaluate the clinical experience with rt-PA for acute myocardial infarction in older patients enrolled in the Thrombolysis in Myocardial Infarction (TIMI) Phase I, open label studies and the TIMI Phase II pilot study and to compare morbidity and mortality with those observed in younger patients. The effect of age as an independent risk factor contributing to in-hospital mortality and hemorrhagic events was tested with multiple logistic regression analyses.

Methods

Study design. The patient selection and exclusion criteria in the TIMI study have been previously described (20, 22–24). To be eligible for treatment, patients were required to satisfy the following criteria: 1) chest pain characteristic of myocardial ischemia for ≥30 min; 2) ST segment elevation ≥0.1 MV in at least two electrocardiographic (ECG) leads, reflecting a singular vascular territory; and 3) elapsed time from onset of ischemic pain to recruitment <7 h in TIMI Phase I and open label studies A to C and <4 h in open label study D and the TIMI Phase II pilot study; 4) the TIMI Phase I study required angiographic entry criteria of a ≥50% obstruction in the infarct-related vessel, and open label studies A to C required complete or subtotal obstruction of the infarct-related vessel (TIMI grade 0 or 1 flow) before initiation of rt-PA administration. Patients were not eligible if the ECG at presentation could not be interpreted for acute myocardial infarction or if the patient had the potential for significant hemorrhagic complications.

Study groups. The TIMI Phase I study (19) was a randomized trial comparing intravenous streptokinase with intravenous rt-PA. The 143 patients in Phase I included in the present report were treated with rt-PA. In this trial, rt-PA G11021 (roller bottle preparation) was infused intravenously over 3 h in doses of 40, 20 and 20 mg in successive hours. The drug was administered at the time of cardiac catheterization after visualization of the coronary arteries. Systemic heparinization was employed for 7 to 10 days. The subsequent open label studies and the Phase II pilot study used suspension culture rt-PA. In the latter studies, the total dose and dose rate of rt-PA were evaluated to determine the optimal regimen to achieve early and late patency of the infarct-related vessel (Table 1).

In open label studies, A to C, rt-PA was administered in the cardiac catheterization laboratory after identification of an occluded infarct-related vessel, whereas in open label study D and the Phase II pilot study, cardiac catheterization was scheduled in most patients at 18 to 48 h after rt-PA therapy. In each open label study, patients received systemic heparinization for at least 5 days with the dosage adjusted to maintain the activated partial thromboplastin time at 1.5 to 2.5 times the upper limit of normal, 80 mg/day of aspirin and dipyridamole 75 mg four times daily. Aspirin was increased to 325 mg three times daily when the intravenous heparin infusion was stopped. Patients in the Phase II pilot study received systemic heparinization for at least 5 days, with the dosage adjusted as in the open label studies and aspirin increased to 325 mg when the heparin infusion was discontinued. In the open label study D and the Phase II pilot study, heparin therapy was decreased to half strength 4 h before cardiac catheterization. Each protocol was approved by the institutional review board at participating institutions, and written informed consent was obtained from each enrolled patient.

Table 1. Recombinant Tissue-Type Plasminogen Activator (rt-PA) Dosing Requirements: TIMI Phase I, Open Label A to D and TIMI Phase II Pilot Studies

Study	Date Trial Started	No.	rt-PA Dose (mg)/Duration of Infusion					
			1h	2h	3h	4h	5h	6h
Phase I*	08/20/84	143	40	20	20			
Open label								
A	08/05/85	48	40	20	20			
B	09/17/85	88	60	20	20			
C	12/09/85	65	9/81	20	10	10	10	10
D	02/08/86	42	9/81	20	10	10	10	10
TIMI II pilot†	03/17/86	370	9/81	20	10	10	10	10

*Roller bottle preparation of rt-PA. †Dosage used in 317 patients; 53 patients received a study dosage of 6/54,20,5,5,5,5 or 100 mg of rt-PA. 9/81 = 9 mg bolus followed by 81 mg infusion.

Classification of major hemorrhagic events. Hemorrhagic events were classified by the Hemorrhagic Event Review Committee, which reviewed case reports of all patients who had a blood transfusion, a decrease in hemoglobin ≥3.0 g/dl or an observed blood loss. A major hemorrhagic event was defined as a decrease in hemoglobin >5 g/dl (or >15% decrease in hematocrit), pericardial hemorrhage with tamponade or any intracranial bleeding. The Committee also noted the location, spontaneity and onset of the major hemorrhagic event.

Statistical analysis. Group differences in outcome were assessed by the chi-square test for categorical variables. The reported probability values are two-sided and not adjusted for multiple testing. Multiple stepwise logistic regression analyses were used to choose a subset of variables that were most predictive of events (25). The outcome variables tested were in-hospital mortality and major hemorrhagic events. Categorical variables used in the stepwise logistic regression analyses were: prior use of antiplatelet drugs or anticoagulants; gender; history of diabetes; history of hypertension; number of vessels with >60% stenosis; history of myocardial infarction or of gastrointestinal disease, transient ischemic attacks, congestive heart failure or angina; the presence of pulmonary rales at admission; continuing pain immediately after rt-PA administration; protocol phase; site of

Table 2. Patient Characteristics in TIMI Study Patients by Age Group

	≤65 yr (n = 577)		65 to 69 yr (n = 87)		≥70 to 76 yr (n = 92)		Total	
	No.	%	No.	%	No.	%	No.	%
No. of men	493	85.4	59	67.8	56	60.9	608	80.4
History								
Hypertension	226	39.2	39	44.8	38	41.3	303	40.1
Previous MI	71	12.3	18	20.7	19	20.6	108	14.3
CHF	6	1.0	1	1.2	4	4.4	11	1.5
Diabetes	61	10.6	13	14.9	14	15.2	88	11.6
Angina pectoris	236	40.9	36	41.4	43	46.7	315	41.7
GI disease	63	10.9	17	19.5	15	16.3	95	12.6
Transient ischemic attack*	13	2.3	3	3.4	5	5.4	21	2.7
Infarct location								
Anterior	306	53.0	44	50.6	47	51.1	397	52.5
Inferior	256	44.4	41	47.1	44	47.8	341	45.1
Lateral	15	2.6	2	2.3	1	1.1	18	2.4
Rales	97	16.8	15	17.2	24	26.1	136	18.0
Cardiac surgery during hospitalization	59	10.2	11	12.6	11	12.0	81	10.7
Systolic blood pressure (mm Hg)†		131.5		125.9		129.8		130.6
Diastolic blood pressure (mm Hg)†		84.9		75.2		96.3		85.2
Heart rate (beats/min)†		77.4		73.4		75.9		76.8
Time from onset of symptoms to initiation of treatment (min)†		216		206		223		216
Length of hospital stay (days)†		12.0		12.5		15.2		12.4

*As of August 22, 1986, because of potential risk of intracranial bleeding, patients with a history of transient ischemic attacks were excluded from entry into the TIMI Phase II pilot study. †Data reported as mean values. CHF = congestive heart failure. MI = myocardial infarction.

qualifying myocardial infarction; cardiac surgery during hospitalization, and age category. Continuous variables used in the stepwise logistic regression analysis were systolic and diastolic blood pressure, heart rate, dose of rt-PA per kilogram of body weight and time from onset of symptoms to treatment with rt-PA. All statistical analyses were performed using BMDP or SAS statistical software package programs (26,27). The data and analyses presented in this report are based on all data forms received by the TIMI Coordinating Center as of August 1988.

Results

Clinical characteristics. The clinical characteristics of the 756 patients studied are illustrated in Table 2. Patients were grouped according to age as follows: <65 (n = 577), 65 to 69 (n = 87) and 70 to 76 years (n = 92). The percent of women significantly increased with age ($p < 0.001$), and previous myocardial infarction was significantly more frequent in older patients ($p = 0.009$). We examined the age distribution among the TIMI Phase I, open label studies and the TIMI Phase II pilot study and found that age distribution of patients younger and older than age 65 years was comparable in the different protocols.

Hospital mortality. The mean (±SD) length of stay in the hospital was 12.4 ± 6.9 days. The average length of stay in the oldest age group was slightly longer than that in the two younger age groups (Table 2). There was a significant increase in the in-hospital mortality as age increased ($p < 0.001$) (Fig. 1). Variables associated with an increase in in-hospital mortality (logistic regression analysis) included female gender, diabetes mellitus, number of diseased coronary vessels with ≥60% stenosis history of congestive heart

Figure 1. The in-hospital mortality rate was significantly increased in patients >65 years of age ($p < 0.001$).

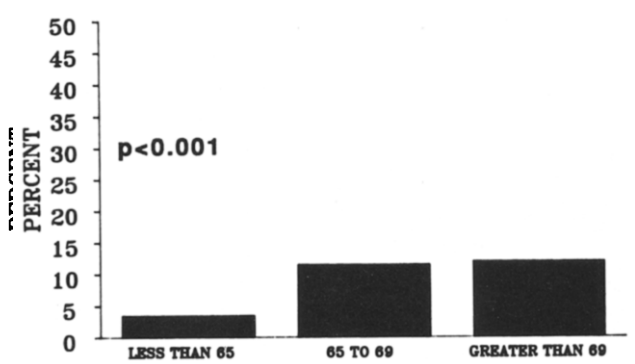

Table 3. TIMI Phase I and Open Label A to D and TIMI Phase II Pilot Patient Variables Significantly Related to In-Hospital Mortality as Determined by Logistic Regression

Categorical Variables	Group	% Dead	p (unadjusted)	p (adjusted)	Beta Coefficient
Gender	Male	4.1			
	Female	10.8	0.001	0.03	−1.16
History of diabetes	Yes	12.5			—
	No	4.5	0.002	0.06	1.10
No. of vessels with ≥60% stenosis	0	0			—
	1	2.3			2.62
	2	5.4			3.50
	3	14.3	<0.001	0.002	6.72
History of CHF	Yes	45.5			3.94
	No	4.8	<0.001	0.008	—
Continuing pain immediately after rt-PA administration	Yes	10.7			1.19
	No	3.8	<0.001	0.014	—
Age (yr)	<65	3.5			—
	65 to 69	11.5			1.51
	≥70	12.0	<0.001	0.034	0.22
Continuous variable systolic blood pressure				<0.001	−0.03

CHF = congestive heart failure.

failure, continuing chest pain immediately after rt-PA administration, low systolic blood pressure on admission, and age (Table 3). Age remained an important independent variable related to in-hospital mortality even after adjustment for the preceding covariates ($p = 0.034$). Of the 41 deaths observed, 2 (4.9%) were due to a hemorrhagic event (1 patient died from gastrointestinal bleeding, the other from intracranial bleeding).

Major hemorrhagic events. Every attempt was made to capture all potential bleeding events in the TIMI trial because the study employed a powerful thrombolytic drug. The incidence of major hemorrhagic events among patients not undergoing cardiac surgery during hospitalization increased with age ($p < 0.001$) (Fig. 2). When the 106 patients classified as having had a major hemorrhagic event were reviewed to determine the primary site of hemorrhage, some age trends were found among the three age groups, although the event numbers were too small to obtain any reliable inference for site-specific events (Table 4). The most common site of a major hemorrhagic event was the site of previous catheterization. Of five intracranial bleeding events, four occurred in the Phase II pilot study, with an assigned rt-PA dose of 150 mg administered over 6 h. The dose was subsequently reduced to 100 mg administered over 6 h in the last 53 patients of the TIMI Phase II pilot study (28,29).

The performance of cardiac surgery was associated with an increased likelihood of major hemorrhagic events. Because blood loss is a relatively common event in patients who have surgery, regardless of thrombolytic therapy, these events are confounded with the analysis of variables associated with increased bleeding risk after thrombolytic therapy. Therefore, all subsequent analyses were performed excluding patients who underwent cardiac surgery during hospitalization. The incidence of major hemorrhagic events in the TIMI Phase II pilot study, excluding those patients who underwent cardiac surgery during hospitalization, was

Figure 2. The incidence of major hemorrhagic events among patients not receiving cardiac surgery significantly increased with age ($p < 0.001$). The incidence of transfusions among those who had a major hemorrhagic event significantly increased with age. **Solid area** = transfusion; **cross-hatched area** = no transfusion.

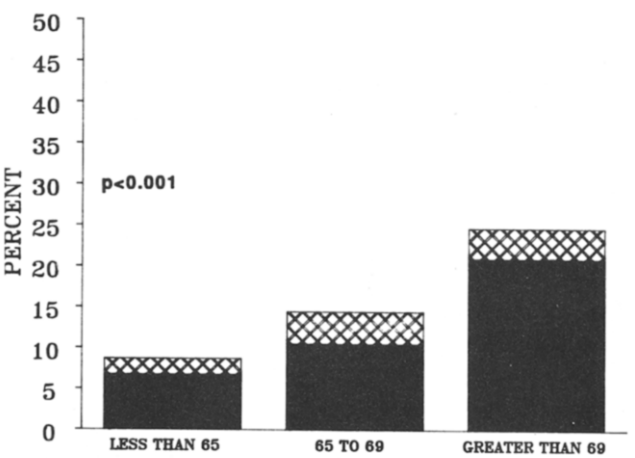

Table 4. Sources of Major Hemorrhagic Events by Age Group

	Age (yr)					
	<65 (n = 577)		65 to 69 (n = 87)		≥70 (n = 92)	
Site	No.	%	No.	%	No.	%
Intracranial	2	0.4	2	2.3	1	1.1
Gastrointestinal	7	1.2	1	1.1	4	4.3
Retroperitoneal	1	0.2	0	0.0	1	1.1
Catheterization site	31	5.4	5	5.7	12	13.0
Other puncture site	2	0.4	3	3.5	1	1.1
Other source	16	2.8	3	3.5	4	4.3
Multiple sites	4	0.7	0	0.0	1	1.1
Loss >5 g/dl Hb	3	0.4	2	2.3	0	0.0
Minor hemorrhage	74	12.8	13	14.9	19	20.6
No hemorrhage	437	75.7	58	66.6	49	53.3

Hb = hemoglobin

11.9% for patients receiving 150 mg of rt-PA and 10.6% for patients receiving <150 mg of rt-PA (p = 0.31).

Multiple logistic regression analysis selected protocol, age, dose of rt-PA per kilogram body weight and elevated diastolic blood pressure on admission as independent predictors of a major hemorrhagic event (Table 5).

The incidence of blood transfusions significantly increased with age and was 12.5%, 22.4% and 40.7% in patients <65, 65 to 69 and 70 to 76 years of age, respectively (p < 0.001). Transfusion requirements in the TIMI Phase II pilot and open label D studies were significantly less than in the TIMI Phase I and open label studies A to C (12.3% versus 21.7%, respectively; p < 0.001).

Reperfusion status. The reperfusion status at 90 min in TIMI Phase I and open label studies A to C was examined. The percent of patients with TIMI grade 2 or 3 flow at 90 min after rt-PA administration was 64.1%, 60.0% and 71% in patients <65, 65 to 69 and 70 to 76 years of age, respectively (p = 0.61).

Discussion

In-hospital mortality. Information on the prognosis of older patients with acute myocardial infarction treated with rt-PA is limited. We analyzed the TIMI Phase I, open label studies and Phase II pilot study to examine the incidence of in-hospital death and hemorrhagic events in older patients treated with rt-PA. Previously reported variables adversely affecting the mortality rate (such as a decreasing male/female ratio, previous myocardial infarction and pulmonary rales) were more common in the elderly, confirming previous reports (2,4,5) in the prethrombolytic era. Mortality was significantly increased in older patients, with an 11.5% to 12% in-hospital mortality rate for patients ≥65 years of age compared with 3.5% observed in patients <65 years. Multiple logistic regression analyses selected age as an independent prognostic variable, even after adjustment for multiple covariates known to influence in-hospital mortality. These data confirm previous reports (2) in the prethrombolytic era in older patients.

The explanation for an increased in-hospital mortality in older patients may be related to the greater extent of coronary artery disease and greater prevalence of previous myocardial infarction frequently found in older patients. Furthermore, older patients tend to present to the hospital later after symptom onset than do younger patients and may be denied therapeutic strategies that reduce myocardial infarct size and mortality (5). In this study, adjustment for these characteristics does not explain the relatively higher mortality rate in older compared with younger patients because these variables were either similar among the different age groups or did not remove the effect of age on observed mortality differences in adjusted analyses. The

Table 5. TIMI Phase I and Open Label A to D and TIMI Phase II Pilot Patient Variables Significantly Associated With Major Hemorrhage as Determined by Logistic Regression in 675 Patients*

	Group	% With Major Hemorrhage	p (unadjusted)	p (adjusted)	Beta Coefficient
Categorical variables					
Protocol	I	13.9			—
	II Pilot	8.1			−2.06
	Open A to D	14.6	0.035	0.008	0.56
Age (yr)	<65	8.7			—
	65 to 69	14.5			−0.28
	≥70	24.7	<0.001	<0.001	1.42
Continuous Variables					
Diastolic blood pressure				0.06	−0.346
Dose per kg body weight				0.006	0.90

*Patients undergoing cardiac surgery during hospitalization were excluded from this analysis.

normal aging process in humans includes brown atrophy of the myocardium, with focal amyloid deposits and calcific deposition in the aortic valve, mitral anulus and epicardial coronary arteries. Diastolic myocardial stiffness and the autonomic response to stress are altered in elderly patients, and it is possible that these characteristics in such patients reduce the tolerance to an acute myocardial ischemic insult as compared with that in younger patients (30,31).

Hemorrhagic complications. The incidence of bleeding complications after acute myocardial infarction is clearly related to the use of thrombolytic drugs, systemic heparinization and the performance of cardiac catheterization or cardiac surgery during or closely after the use of thrombolytic therapy. In previous studies (14) of patients treated without thrombolytic therapy or cardiac catheterization, the incidence rate of bleeding was reported to be as low as 0.2%. The incidence rate of bleeding complications associated with the use of intravenous streptokinase is reported to be 3.8% to 19% (3,15,16). When cardiac catheterization is associated with streptokinase therapy and the drug is administered by the intracoronary route, the incidence of bleeding is reported to be 25% to 53% (13,17). Continued bleeding after cardiac catheterization may be related to the use of systemic heparinization and antiplatelet drugs (32,33).

In the TIMI Phase I study, the incidence of major bleeding events after the administration of streptokinase or rt-PA was similar at 15.6% and 15.4%, respectively (33) and transfusion requirements were similar (33). Our data indicate that the incidence of hemorrhagic complications significantly increases in elderly patients and that major bleeding events may occur 2.8 times more frequently in patients >69 years of age as compared to those <65 years. Hemorrhage most commonly occurs at cardiac catheterization access sites or previous puncture wounds. Logistic regression analysis selected age as an independent predictor of a major hemorrhagic event, even after adjustments for other known prognostic factors. The incidence of major hemorrhagic complications was directly related to the dose of rt-PA used, and may indicate that dose adjustment per kilogram of body weight would reduce the incidence of hemorrhagic events.

Other thrombolytic trials. The Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) (3) and International Study of Infarct Survival (ISIS 2) (8) trials, which compared intravenous streptokinase and placebo, did not have an upper age limit in their patient inclusion criteria and did not require systemic heparinization or cardiac catheterization as part of the protocol design. The GISSI study did not show a significant treatment difference in mortality in patients >65 years, whereas the ISIS II study found a significant reduction in mortality with streptokinase in older patients. Neither study noted a significant difference in hemorrhagic events in older as compared with younger patients. The data are in contrast to those reported in the present study, where the strategy of thrombolytic therapy followed by systemic heparinization and urgent cardiac catheterization was employed.

In contrast to the current study in which rt-PA was used, the GISSI and ISIS II trials did not employ routine systemic heparinization after administration of streptokinase and treated a much larger sample of elderly patients with streptokinase. A larger sample size of elderly patients would provide more power to test the hypothesis that heparin has an effect on increased bleeding risk with age. The GISSI II trial, which is currently in progress, compares intravenous streptokinase with intravenous rt-PA and contains a second randomization sequence comparing systemic intravenous heparinization with placebo; the impact of concomitant use of heparin with rt-PA and impact of age is also being addressed. In the ASSET trial (7), where rt-PA therapy was compared with placebo, patients treated with rt-PA had a significant mortality reduction, even in the older age groups. The ASSET trial excluded patients >76 years of age. Lew et al. (6) examined mortality and morbidity in patients <75 and >75 years of age with acute infarction treated with intravenous streptokinase. Their data show a 25% incidence rate of major hemorrhagic complications in the >75 year old age group compared with 11% in patients <75 years. Mortality related to the hemorrhagic events was 17% versus 1% in the older and younger patients, respectively. There was no control group in that retrospective analysis, and the data do not permit evaluation of whether the risks of intravenous streptokinase in older patients outweigh the benefits.

When consecutive patient series of coronary care unit admissions for acute myocardial infarction are examined for potential candidates for thrombolytic therapy, as many as 30% of patients are ineligible because of age >75 years (7,34). The in-hospital mortality rate for these older patients in recent years is reported to be 21% (34). If rt-PA therapy can reduce this rate by 30% in patients >75 years, the expected in-hospital mortality rate in the treated group would be reduced to 14%. This reduction in in-hospital mortality might be offset if the risk of major bleeding events such as intracranial hemorrhage approaches the level of mortality reduction, and this issue requires additional investigation.

Conclusions. In a group of patients with acute myocardial infarction treated with rt-PA in whom a strategy of early catheterization is followed, in-hospital mortality significantly increases with age, confirming previous observations made before the thrombolytic era. Major hemorrhagic events are significantly increased in older patients. Reperfusion rates after rt-PA therapy in older patients are similar to those observed in younger patients. The incidence of hemorrhagic events observed in the TIMI Phase I and open label studies are relatively high because 1) urgent cardiac catheterization was required by protocol in all patients, and 2) an rt-PA dose of 150 mg was used in 49.9% of the total study group. We expect that hemorrhagic events will be significantly less

frequent with an rt-PA dose of 100 mg and with early cardiac catheterization in older patients being reserved for the subgroup of patients who demonstrate hemodynamic instability, recurrent myocardial ischemia or other well defined clinical indications. A randomized placebo-controlled study of rt-PA in patients >76 years of age with acute myocardial infarction would be of definite interest.

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