European Heart Journal (2000) **21,** 1944–1953
doi:10.1053/euhj.2000.2243, available online at http://www.idealibrary.com on IDEAL®

Combination reperfusion therapy with abciximab and reduced dose reteplase: results from TIMI 14

E. M. Antman[1], C. M. Gibson[2], J. A. de Lemos[1], R. P. Giugliano[1], C. H. McCabe[1], P. Coussement[3], I. Menown[4], C. A. Nienaber[5], T. C. Rehders[5], M. J. Frey[6], R. Van der Wieken[7], D. Andresen[8], J. Scherer[9], K. Anderson[10], F. Van de Werf[3] and E. Braunwald[1] for the Thrombolysis in Myocardial Infarction (TIMI) 14 Investigators*

[1]*Brigham and Women's Hospital, Boston, MA, U.S.A.;* [2]*University of California, San Francisco, CA, U.S.A.,* [3]*Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium,* [4]*Royal Victoria Hospital, Belfast, U.K.;* [5]*University Hospital Eppendorf, Hamburg, Germany;* [6]*Sarasota Memorial Hospital, Sarasota, FL, U.S.A.;* [7]*OLVG afdeling Cardiologie, Amsterdam, The Netherlands;* [8]*Krankenhaus am Urban, Berlin, Germany;* [9]*Eli Lilly, Inc., Indianapolis, IN, U.S.A.;* [10]*Centocor, Malvern, PA, U.S.A.*

Aims Abciximab has previously been shown to enhance thrombolysis and improve myocardial perfusion when combined with reduced doses of alteplase. The purpose of the reteplase phase of TIMI 14 was to evaluate the effects of abciximab when used in combination with a reduced dose of reteplase for ST-elevation myocardial infarction.

Methods and Results Patients (n=299) with ST-elevation myocardial infarction were treated with aspirin and randomized to a control arm with standard dose reteplase (10+10 U given 30 min apart) or abciximab (bolus of 0·25 mg . kg^{-1} and 12-h infusion of 0·125 μg . kg^{-1} . min^{-1}) in combination with reduced doses of reteplase (5+5 U or 10+5 U). Control patients received standard weight-adjusted heparin (bolus of 70 U . kg^{-1}; infusion of 15 U . kg^{-1} . h^{-1}), while each of the combination arms with abciximab and reduced dose reteplase received either low dose heparin (bolus of 60 U . kg^{-1}; infusion of 7 U . kg^{-1} . h^{-1}) or very low dose heparin (bolus of 30 U . kg^{-1}; infusion of 4 U . kg^{-1} . h^{-1}). The rate of TIMI 3 flow at 90 min was 70% for patients treated with 10+10 U of reteplase alone (n=87), 73% for those treated with 5+5 U of reteplase with abciximab (n=88), and 77% for those treated with 10+5 U of reteplase with abciximab (n=75). Complete (≥70%) ST resolution at 90 min was seen in 56% of patients receiving a reduced dose of reteplase in combination with abciximab compared with 48% of patients receiving reteplase alone.

Conclusions Reduced doses of reteplase when administered in combination with abciximab were associated with higher TIMI 3 flow rates than reported previously for reduced doses of reteplase without abciximab and were at least as high as for full dose reteplase alone
(Eur Heart J 2000; 21: 1944–1953, doi:10.1053/euhj.2000.2243)

Key Words: Thrombolysis, acute MI, glycoprotein IIb/IIIa inhibition, antiplatelet therapy.

See page 1913 for the Editorial comment on this paper

Introduction

Currently available regimens for pharmacological reperfusion in patients presenting with ST elevation myocardial infarction suffer from inadequate rates of restoration of normal flow in the infarct related artery and inadequate myocardial perfusion. As reported previously, abciximab in combination with reduced doses of alteplase facilitated the rate and extent of thrombolysis[1]. Among patients with TIMI 3 flow at 90 min,

Manuscript submitted 18 April 2000, and accepted 19 April 2000.

*Additional contributing authors were: E. Barnathan, M. Waller, and the TIMI 14 investigators and research coordinators (see Appendix).

Supported by a grant from Centocor, Malvern, PA and Eli Lilly, Inc, Indianapolis, IN, U.S.A.

Correspondence: Elliott M. Antman, MD., Cardiovascular Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, U.S.A.

0195-668X/00/211944+10 $35.00/0

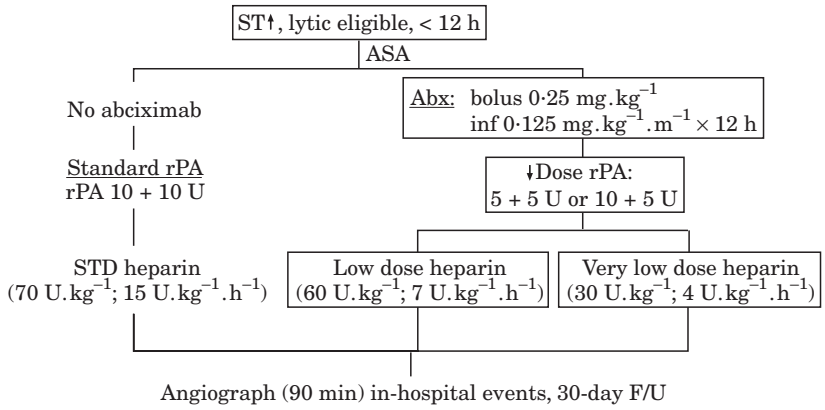

Figure 1 **Design of reteplase phase of TIMI 14. Eligible patients with ST-elevation myocardial infarction(ST↑) were randomized to a control group that did not receive abciximab and was treated with 10+10 U of reteplase (rPA), and two experimental reduced dose rPA groups each receiving abciximab as an initial bolus of 0·25 mg . kg^{-1} followed by a 12-h infusion (inf) of 0·125 µg . kg^{-1} . min^{-1}. The experimental rPA regimens used in combination with abciximab consisted of 5+5 U and 10+5 U. Control patients received standard (STD) heparin. Patients initially enrolled in the experimental groups received low dose heparin. After approximately 35 patients had been enrolled in the experimental groups, subsequent patients enrolled received very low dose heparin (see text for further discussion). F/U=follow-up.**

ST resolution was significantly greater when abciximab was administered, suggesting an additional benefit in terms of myocardial perfusion[2].

The dose of reteplase currently used in clinical practice was established by the RAPID I and RAPID II angiographic trials which reported that the double bolus regimen of 10+10 U was associated with TIMI 3 flow rates at 90 min of 63% and 60%, respectively[3,4]. A reduced dose regimen of 10+5 U of reteplase was found in RAPID I to be associated with only a 46% rate of TIMI 3 flow at 90 min[3]. The reteplase phase of the TIMI 14 trial was designed to examine whether abciximab facilitated thrombolysis in combination with reduced doses of reteplase.

Methods

The reteplase phase of TIMI 14 was conducted between July 1998 and April 1999 at 42 enrolling centres in Germany, the United States, the United Kingdom, The Netherlands, France and Canada.

Eligibility criteria

The enrollment criteria have been described previously[1]. Patients were eligible for inclusion if they were aged between 18 and 75 years, had a qualifying episode of ischaemic discomfort of at least 30 min duration within the previous 12 h and exhibited at least 0·1 mV ST segment elevation in two contiguous leads, as reported by the enrolling clinical centre. The major exclusion criteria consisted of an ECG pattern that obscured identification of the infarct related artery, increased bleeding risk due to neurological or haematological conditions, hypertension, or prior/concomitant therapy, or general administrative criteria such as an inability to undergo cardiac catheterization.

Study protocol

All patients were given aspirin (150–325 mg orally or 250–500 mg intraveneously) and were then randomized into the treatment groups described below (Fig. 1). The control group was treated with full dose reteplase (10+10 U) administered 30 min apart, and a standard dose of heparin consisting of a bolus of 70 U . kg^{-1} (maximum 4000 U) and an initial infusion of 15 U . kg^{-1} . h^{-1} (maximum 1200 U . h^{-1}). The experimental groups all received an initial bolus of abciximab of 0·25 mg . kg^{-1} followed by a 12-h infusion of 0·125 µg . kg^{-1} . min^{-1} and reduced dose reteplase (Table 1). Abciximab was to be administered prior to or concurrent with reteplase. The two reduced-dose reteplase regimens evaluated in combination with abciximab were 5+5 U and 10+5 U of reteplase as shown in Table 1. During the initial portion of the reteplase phase of TIMI 14, patients treated with abciximab and reduced-dose reteplase received low dose heparin using a bolus of 60 U . kg^{-1} (maximum 4000 U) and infusion of 7 U . kg^{-1} . h^{-1} (maximum 800 U . h^{-1}). Subsequently the heparin dose was reduced further in the experimental arms to a bolus of 30 U . kg^{-1} (maximum 2000 U) and initial infusion

Table 1 Baseline characteristics

Characteristic	Control	rPA+abciximab						All patients	Patients in ECG substudy
rPA (U)	10+10	5+5	5+5	Total 5+5	10+5	10+5	Total 10+5		
Abciximab									
Bolus	—	0·25	0·25	0·25	0·25	0·25	0·25		
Infusion ($\mu g \cdot kg^{-1} \cdot min^{-1} \times 12$ h)	—	0·125	0·125	0·125	0·125	0·125	0·125		
Heparin									
Bolus ($U \cdot kg^{-1}$)	70	60	30	All doses	60	30	All doses		
Infusion ($U \cdot kg^{-1} \cdot h^{-1}$)	15	7	4	All doses	7	4	All doses		
Number of patients	102	42	63	105	42	50	92	299	162
Age, years	59 (51, 66)	59 (45, 65)	61 (50, 67)	60 (50, 67)	59 (53, 67)	60 (56, 68)	60 (55, 68)	59 (51, 67)	60 (52, 68)
Sex: Male	81 (79)	33 (79)	48 (76)	81 (77)	33 (79)	39 (78)	72 (78)	234 (78)	128 (79)
Female	21 (21)	9 (21)	15 (24)	24 (23)	9 (21)	11 (22)	20 (22)	65 (22)	34 (21)
Race: White	90 (88)	36 (86)	59 (94)	95 (90)	34 (81)	47 (94)	81 (88)	266 (89)	149 (92)
Other	12 (12)	6 (14)	4 (6)	10 (10)	8 (19)	3 (6)	11 (12)	33 (11)	13 (8)
Diabetes	13 (13)	2 (5)	11 (18)	13 (12)	5 (12)	9 (8)	14 (15)	40 (13)	19 (12)
Hx hypertension	29 (28)	10 (24)	21 (33)	31 (30)	12 (29)	15 (30)	27 (29)	87 (29)	43 (27)
Current smoker	51 (50)	26 (62)	30 (48)	56 (53)	19 (45)	18 (36)	37 (40)	144 (48)	76 (47)
Prior MI:									
≤30 days	0 (0)	1 (2)	0	1 (1)	0	0	0	1 (0.3)	0 (0)
>30 days	8 (8)	1 (2)	5 (8)	6 (6)	3 (7)	9 (18)	12 (13)	26 (9)	12 (7)
MI location:									
Anterior	39 (38)	17 (41)	27 (43)	44 (42)	15 (36)	15 (30)	30 (33)	113 (38)	59 (36)
Time: Pain to Rx, h	3 (2, 4)	3 (2, 6)	3 (2, 6)	3 (2, 6)	3 (2, 5)	3 (2, 6)	3 (2, 5)	3 (2, 5)	3 (2, 5)
Randomization to Rx, min	16 (11, 20)	16 (13, 24)	17 (10, 29)	16 (11, 26)	24 (15, 29)	15 (11, 24)	19 (11, 28)	16 (11, 24)	16 (11, 23)
Abciximab to lytic, min	na	3 (1, 5)	1 (0, 4)	2 (0, 5)	3 (0, 5)	2 (0, 5)	2 (0, 5)	2 (0, 5)	2 (0, 5)
Abciximab given prior to/with lytic	na	40 (95)	53 (84)	93 (89)	37 (88)	43 (86)	80 (87)	173 (88†)	91 (84)

Data are shown as n (%) for dichotomous variables and median (27, 75th percentile) for continuous variables.
Rx=revascularization, MI=myocardial infarction.
†Denominator is 197 patients in experimental reperfusion arms.

of $4\ U\ .\ kg\ .\ h^{-1}$ (maximum $400\ U\ .\ h^{-1}$). For all groups, heparin infusions were adjusted according to a nomogram to a target aPTT of 50–70 s.

Angiographic procedures
For timing the performance of coronary angiograms, time 0 was considered to be the start of administration of the first drug of the assigned reperfusion regimen. Coronary angiography of the infarct related artery was performed as soon as possible after initiation of the reperfusion regimen but in no case later than 90 min (with a window of ± 15 min). Standardized views and techniques of injection were used by investigators[1].

Clinical procedures
Twelve-lead ECGs were obtained at baseline and at 90 and 180 min after reperfusion therapy. Creatine kinase (CK) and isoenzyme (CK-MB) levels were measured on admission and at 6, 12, and 24 h for the first 24 h and were repeated for episodes of recurrent ischaemic discomfort at rest ≥ 30 min in duration or following revascularization procedures during the index hospitalization. All patients were followed for clinical events during the index hospitalization and for the next 30 days.

Study end-points

Efficacy
The primary angiographic efficacy end-point was the achievement of TIMI grade 3 flow at 90 min in the infarct related artery. All angiograms were evaluated at the Angiographic Core Laboratory, which was unaware of the treatment assignment, using previously established procedures for determination of TIMI flow grade and TIMI frame count[5,6]. Patients were considered angiographically evaluable if they received the specified reperfusion regimen and had an evaluable 90-min angiogram. The angiographically evaluable cohort in patients receiving abciximab and reteplase was restricted to patients who received both abciximab and reteplase within 15 min of each other.

Clinical efficacy end-points during 30 days were analysed for all patients randomized (intention-to-treat cohort) by a Clinical Events Committee using standardized definitions. These end-points included all-cause mortality, recurrent myocardial infarction, recurrent ischaemia of ≥ 5 min, severe recurrent ischaemia requiring urgent revascularization, severe pump failure, the performance of rescue percutaneous coronary interventions, and coronary artery bypass grafting. The definitions of recurrent myocardial infarction, severe pump failure, and severe recurrent ischaemia were as previously described[1,7,8].

Safety
The primary safety end-point was major haemorrhage defined as any intracranial, retroperitoneal or intraocular haemorrhage or any clinically overt haemorrhage associated with a drop in haemoglobin level $\geq 5\ gm\ .\ dl^{-1}$. An additional end-point was confirmed thrombocytopaenia ($<100\,000$ cells $.\ \mu l^{-1}$ and a decrease of at least 25% from baseline). Severe thrombocytopaenia was defined as a platelet count $<50\,000$ cells $.\ \mu l^{-1}$. All patients who received any element of the assigned reperfusion regimen were included in safety analyses (safety-evaluable cohort); these events were also reviewed and classified by the Clinical Events Committee.

Two substudies were undertaken to explore the mechanism of benefit of combining abciximab with reduced doses of reteplase.

ST resolution substudy
The magnitudes of ST deviation on the baseline and 90-min ECGs were determined using previously described methods, and the percentage of ST resolution from baseline to 90 min was calculated[9–11]. ST resolution was categorized for each patient as complete ($\geq 70\%$), partial (30–70%), or none ($<30\%$). Two outcome measures were prospectively defined for the comparison of different treatment regimens: median ST resolution and the proportion of patients achieving complete ST resolution. Results were stratified according to TIMI flow grade and infarct location.

Myocardial perfusion substudy
Myocardial perfusion was evaluated according to a previously described TIMI myocardial perfusion grade, an independent predictor of mortality in a multivariate analysis of data from ST-elevation myocardial infarction patients[12]. Angiograms were classified as either perfusion grade 0/1 (dye either failed to enter the microvasculature or entered but failed to exit the microvasculature) or perfusion grade 2/3 (dye entered and exited the microvasculature either with a delayed time course or normal time course).

Statistical considerations

To guide the Operations Committee in identifying promising new regimens of reduced dose reteplase and abciximab, the rates of TIMI 3 flow in each of the treatment groups were monitored using a sequential probability ratio test (SPRT) described by Wald[13]. Statistical comparisons were made by Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

Because time from the onset of symptoms to treatment and location of the infarct related artery have been shown to influence the probability of achieving TIMI 3 flow, these two variables, along with a variable coding for whether the reperfusion regimen contained abciximab, were forced into logistic regression analyses assessing the likelihood of developing TIMI 3 flow at 90 min[14]. The same logistic regression models were used to assess the likelihood of achieving complete ($\geq 70\%$) ST-segment resolution at 90 min.

Table 2 Angiographic observations

	Control			rPA+abciximab			
rPA (U)	10+10	5+5	5+5	Total 5+5	10+5	10+5	Total 10+5
Abciximab							
Bolus	—	0·25	0·25	0·25	0·25	0·25	0·25
Infusion ($\mu g \cdot kg^{-1} \cdot min^{-1} \times 12$ h)	—	0·125	0·125	0·125	0·125	0·125	0·125
Heparin							
Bolus ($U \cdot kg^{-1}$)	70	60	30	All doses	60	30	All doses
Infusion ($U \cdot kg^{-1} \cdot h^{-1}$)	15	7	4	All doses	7	4	All doses
Number of patients	102	42	63	105	42	50	92
60 min							
Angio Eval Pts	26	13	17	30	15	12	27
TIMI 3	18 (69)	11 (85)	10 (59)	21 (70)	11 (73)	9 (75)	20 (74)
TIMI 2	3 (12)	1 (8)	1 (6)	2 (7)	1 (7)	1 (8)	2 (7)
TIMI 2/3	21 (81)	12 (92)	11 (65)	23 (77)	12 (80)	10 (83)	22 (82)
cTFC	31 (20, 58)	32 (24, 36)	39 (24, 100)	32 (24, 52)	34 (24, 46)	33 (22, 45)	34 (24, 46)
90 min							
Angio Eval Pts	87	35	53	88	34	41	75
TIMI 3	61 (70)	25 (71)	39 (74)	64 (73)	29 (85)	29 (71)	58 (77)
TIMI 2	9 (10)	7 (20)	8 (15)	15 (17)	3 (9)	6 (15)	9 (12)
TIMI 2/3	70 (81)	32 (91)	47 (89)	79 (90)	32 (94)	35 (85)	67 (89)
cTFC	32 (21, 50)	31 (18, 45)	32 (24, 48)	32 (22, 47)	29 (24, 38)	32 (23, 80)	30 (23, 44)
IRA							
LAD	34 (39)			42 (48)			23 (31)
Non-LAD	53 (61)			46 (52)			52 (69)
Pain to Rx							
0–6 h	73 (85)			69 (79)			59 (80)
>6–12 h	13 (15)			18 (21)			15 (20)

Angio Eval Pts=angiographically evaluable patients; cTFC=corrected TIMI frame count; IRA=infarct related artery; Rx=revascularization.
Data are shown as n (%) for dichotomous variables and median (27, 75th percentile) for continuous variables.

Due to the exploratory nature of the comparisons in the trial, nominal *P* values, without adjustment for multiple comparisons, were taken as an indicator of the statistical significance of comparisons between groups or trends among groups.

Results

A total of 299 consecutive patients were enrolled in the reteplase portion of TIMI 14. Baseline characteristics are shown in Table 1.

Impact of abciximab on epicardial flow

Of the 299 patients, 250 (84%) were considered angiographically evaluable at 90 min. The reasons for exclusion from the angiographically evaluable cohort at 90 min were failure to receive the reperfusion regimen as specified in the protocol (n=14 [5%]) and lack of a suitable angiogram due either to absence of angiography for clinical reasons, performance of the angiogram more than 15 min outside the 90-min timeframe or technically inadequate imaging (n=35 [12%]). Eighty-three patients (28%) were considered angiographically evaluable at 60 min.

Patients treated with 10+10 U of reteplase alone (n=87) achieved a 70% rate of TIMI 3 flow at 90 min (Table 2). The rate of TIMI 3 flow at 90 min was 73% among the 88 patients in the 5+5 U of reteplase plus abciximab group and 77% among the 75 patients in the 10+5 U of reteplase plus abciximab group (Table 2). No clinically important, directionally consistent difference in TIMI 3 flow rates was observed at 90 min when the reduced dose reteplase plus abciximab groups were analysed according to whether they received low dose or very low dose heparin (Table 2).

There tended to be differences among the treatment groups in the distribution of the infarct related artery and time from onset of symptoms to treatment with the assigned reperfusion regimen (see Table 2). While the likelihood of developing TIMI 3 flow at 90 min tended to be lower if the left anterior descending artery was the infarct related artery and decreased progressively as the delay in treatment increased, use of a regimen containing abciximab tended to be associated with an increase in the odds of developing TIMI 3 flow (see Table 4).

Table 3 Electrocardiographic observations during reteplase phase

	Control	rPA+abciximab		
rPA (U)	10+10	5+5	10+5	All reduced dose reteplase groups
Abciximab				
Bolus	—	0·25	0·25	0·25
Infusion (μg . kg^{-1}min^{-1} × 12 h)	—	0·125	0·125	0·125
Heparin				
Bolus (U . kg^{-1})	70	All doses	All doses	All doses
Infusion (U . kg^{-1} . h^{-1})	15	All doses	All doses	All doses
All patients n=	54	55	53	108
Complete (≥70%) ST resolution	26 (48%)	24 (44%)	36 (68%)*	60 (56%)
Partial (30–70%) ST resolution	19 (35%)	21 (38%)	11 (21%)	32 (30%)
No (≤30%) ST resolution	9 (17%)	10 (18%)	6 (11%)	16 (15%)
Median ST resolution	68%	63%	82%*	73%
Patients with TIMI 3 flow at 90 min	42	41	41	82
Complete (≥70%) ST resolution	23 (55%)	21 (51%)	32 (78%)**	53 (65%)
Partial (30–70%) ST resolution	14 (33%)	14 (34%)	5 (12%)	19 (23%)
No (≤30%) ST resolution	5 (12%)	6 (15%)	4 (10%)	10 (12%)
Median ST resolution	74%	71%	87%**	85%

*P=0·05 versus reteplase 10+10 U control group; **P<0·05 versus reteplase 10+10 U control group.

Table 4 Logistic regression analyses: angiographic and electrocardiographic observations at 90 min

Analysis/Variable	Multivariate analysis	
	β coefficient	OR (95 CI)
Angiographic analyses (n=250)		Development of TIMI 3 flow at 90 min
IRA (non-LAD=0, LAD=1)	−0·33	0·72 (0·40–1·27)
Pain to Rx (per hour)	−0·11	0·90 (0·82–0·99)*
Abciximab regimen (No=0, Yes=1)	0·31	1·36 (0·75–2·46)
Electrocardiographic analyses (n=162)		Development of complete ST resolution at 90 min
IRA (non-LAD=0, LAD=1)	−1·39	0·25 (0·12, 0·50)†
Pain to Rx (per hour)	−0·12	0·88 (0·78, 1·00)
Abciximab regimen (No=0, Yes=1)	0·42	1·52 (0 76, 3·08)

*P=0·03.
†P<0·001.
IRA=infarct-related artery; Rx=revascularization; LAD=left anterior descending artery.

Impact of abciximab on ST resolution

One hundred and sixty-two patients had interpretable baseline and 90-min ECGs and were enrolled in the ST resolution substudy. No significant differences in baseline characteristics were noted between the cohort of patients in the ST resolution substudy and the full cohort of patients in the reteplase phase of TIMI 14 (Table 1). The proportion of patients achieving complete ST resolution was 48% in the reteplase control group versus 44% in the 5+5 U of reteplase plus abciximab group and 68% in the 10+5 U of reteplase plus abciximab group (P=0·05 versus reteplase control) (Table 3). In an analysis restricted to patients with TIMI grade 3 flow at 90 min, the proportion of patients achieving complete ST resolution was 55% in the reteplase control group versus 51% in the 5+5 U of reteplase plus abciximab group and 78% in the 10+5 U of reteplase plus abciximab group (P<0·05 versus reteplase control).

It is important to note that imbalances in the distribution of the location of infarction were also seen in the ECG substudy cohort. The proportion of patients with anterior myocardial infarction was 37% in the 10+10 U of reteplase control group, 53% in the 5+5 U of reteplase plus abciximab group, and 28% in the 10+5 U of reteplase plus abciximab group. The multivariate analysis of the ECG data is shown at the bottom of Table 4. The odds of developing complete ST resolution at 90 min was significantly lower if the left arterior descending artery was the infarct artery. Patients treated

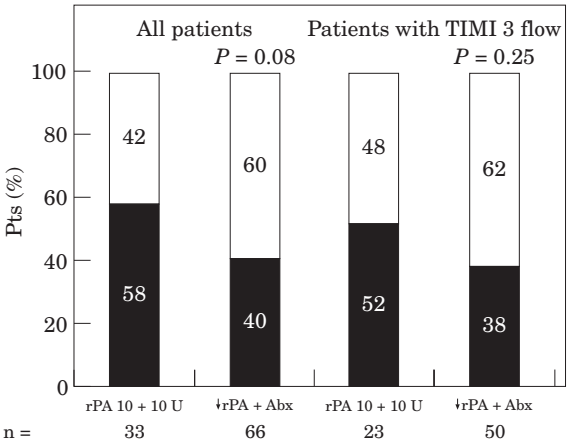

Figure 2 **TIMI Myocardial Perfusion Grade analysis from the reteplase phase of TIMI 14. Percentage of patients (% Pts) for whom the TIMI Myocardial Perfusion Grade (TMPG) was either 0/1 (■) or 2/3 (□) at 90 min in the reteplase (rPA) control group and the pooled reduced dose rPA plus abciximab (Abx) groups. The combination reperfusion groups tended to have a higher percentage of patients with TMPG 2/3 compared with the control group.**

later tended to have a lower chance of achieving complete ST resolution. Use of a reperfusion regimen containing abciximab tended to be associated with a greater chance of achieving complete ST resolution (Table 4).

Measurement of the TIMI Myocardial Perfusion Grade was introduced after the trial was underway and therefore the results were available in the subset of the final consecutive 99 patients with evaluable angiograms analysed in the Angiographic Core Laboratory. Of the 33 patients in the 10+10 U of reteplase control group, 14 (42%) had perfusion grade 2/3. Of the 66 patients receiving a regimen containing abciximab and a reduced dose of reteplase (either 5+5 U or 10+5 U), 40 (61%) had perfusion grade 2/3 (P=0·08 compared with control group). In an analysis restricted to 73 patients with TIMI 3 flow, a perfusion grade of 2/3 was observed in 11 (48%) patients in the reteplase control group and 31 (62%) patients receiving a regimen of reduced dose reteplase plus abciximab (Fig. 2).

Safety observations and other clinical events in reteplase phase

Safety observations along with other clinical events are summarized in Table 5. The overall rate of major haemorrhage was 6%; the majority of events were major bleeds at instrumented sites. The overall rates for intracranial haemorrhage, mortality, recurrent myocardial infarction, development of severe pump failure, and revascularization for severe recurrent ischaemia were 1·3%, 4%, 2%, 2% and 22%, respectively. No statistically significant differences in the events noted above were

Table 5 Clinical events during 30 days

	Control			rPA+abciximab				All patients
rPA (U)	10+10	5+5	5+5	Total 5+5	10+5	10+5	Total 10+5	
Abciximab								
Bolus	—	0·25	0·25	0·25	0·25	0·25	0·25	
Infusion (μg . kg^{-1} . min^{-1} × 12 h)	—	0·125	0·125	0·125	0·125	0·125	0·125	
Heparin								
Bolus (U . kg^{-1})	70	60	30	All doses	60	30	All doses	
Infusion (U . kg^{-1} . h^{-1})	15	7	4	All doses	7	4	All doses	
Number of patients	102	42	63	105	42	50	92	299
Major haemorrhage								
Total	4 (4)	1 (2)	3 (5)	4 (4)	6 (14)	5 (10)	11 (12)	19 (6)
Spontaneous	0 (0)	0 (0)	0 (0)	0 (0)	1 (2)	2 (4)	3 (3)	3 (1)
Instrumented	4 (4)	1 (2)	2 (3)	3 (3)	4 (10)	2 (4)	6 (7)	13 (4)
ICH	0 (0)	0 (0)	1 (2)	1 (1)	1 (2)	2 (4)	3 (3)	4 (1)
Death	3 (3)	0 (0)	2 (3)	2 (2)	4 (10)	4 (8)	8 (9)	13 (4)
Recurrent MI	2 (2)	2 (5)	2 (3)	4 (4)	1 (2)	0 (0)	1 (1)	7 (2)
Severe pump failure	2 (2)	0 (0)	1 (2)	1 (1)	2 (5)	1 (2)	3 (3)	6 (2)
Severe ischaemia→Urg revascularization	26 (26)	8 (19)	11 (18)	19 (18)	7 (17)	13 (26)	20 (22)	65 (22)
PTCA	63 (62)	26 (62)	51 (81)	77 (73)	21 (50)	28 (56)	49 (53)	189 (63)
Rescue	18 (18)	8 (19)	7 (11)	15 (14)	5 (12)	7 (14)	12 (13)	45 (15)
Other	45 (44)	18 (43)	44 (70)	62 (59)	16 (38)	21 (42)	37 (40)	144 (48)
CABG	12 (12)	1 (2)	2 (3)	3 (3)	2 (5)	6 (12)	8 (9)	23 (8)
Thrombocytopaenia	4 (4)	3 (17)	1 (2)	4 (4)	2 (5)	1 (2)	3 (3)	11 (4)
Severe thrombocytopaenia	1 (1)	0 (0)	1 (2)	1 (1)	2 (5)	1 (2)	3 (3)	5 (2)

Data are shown as n (%) for dichotomous variables and median (25, 75th percentile) for continuous variables. ICH=intra-cranial haemorrhage.

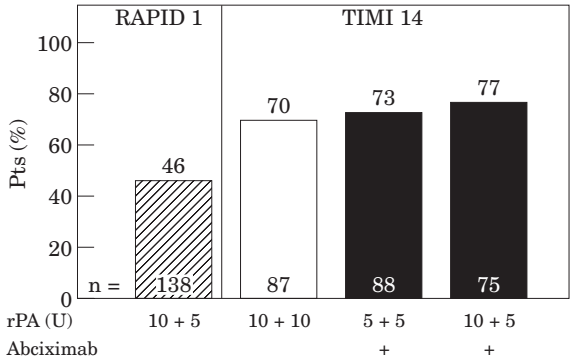

Figure 3 **Comparison of angiographic findings in RAPID I and TIMI 14. Percentage of patients (% Pts) achieving TIMI grade 3 flow at 90 min is shown for various doses of reteplase without abciximab in RAPID I (▨) and TIMI 14 (□). When reduced doses of reteplase were administered in combination with abciximab (■) the rate of TIMI 3 flow was higher than seen previously without abciximab and is similar to full dose reteplase (10+10 U) alone.**

seen across the dose groups. However, the patients receiving 10+5 U of reteplase plus abciximab had a numerically higher mortality rate as well as higher rates of haemorrhagic events compared with both the 10+10 U of reteplase control group and the 5+5 U of reteplase plus abciximab groups (Table 5).

Discussion

The reteplase phase of TIMI 14 supports the hypothesis that glycoprotein IIb/IIIa inhibition with abciximab facilitates reperfusion of thrombotically occluded coronary arteries. In earlier angiographic trials, the 10+10 U regimen of reteplase was associated with a higher rate of TIMI 3 flow at 90 min than a reduced dose regimen of 10+5 U[3,4]. As shown in Fig. 3, abciximab combined with reduced doses of reteplase was associated with TIMI 3 flow rates at least comparable full dose reteplase, and appeared to be higher than reported previously for 10+5 U of reteplase monotherapy. Despite the limitations of comparing angiographic results from different trials and Angiographic Core Laboratories, the magnitude of the difference suggests that this observation reflects a true difference. Furthermore, the multivariate analysis suggests that, after adjusting for infarct artery location and time to treatment, use of abciximab in combination with reduced doses of reteplase tends to increase the odds of achieving TIMI 3 flow.

It is interesting that the 90-min TIMI 3 flow rates in the combination arms of the alteplase and reteplase phases of TIMI 14 are similar (73–77%) underscoring the observation that abciximab enhances thrombolysis. This is particularly noteworthy since, as previously reported in a substudy from TIMI 14, platelet activation and aggregation are heightened in the setting of thrombolysis for acute myocardial infarction[15]. Despite enhanced platelet activity, the dose of abciximab used in TIMI 14 was associated with >80% inhibition of platelet aggregation to 20 μM ADP, a value comparable to that seen in a more elective setting such as percutaneous coronary intervention[15]. In addition to diminishing the mass of platelet aggregates, abciximab weakens the clot structure and permits greater penetration by the thrombolytic agent into the clot[16–21].

Additional important observations with respect to myocardial perfusion are found in the ST resolution and TIMI Myocardial Perfusion Grade analyses[22]. Despite restoration of normal flow in the infarct related epicardial coronary artery, many patients suffer from inadequate myocardial perfusion as evidenced by the microvascular 'no reflow' pattern. This finding is associated with poor recovery of left ventricular function[23]. Microvascular obstruction is the leading hypothesis for the no reflow phenomenon. Recent studies have shown that persistent ST elevation after primary percutaneous intervention in acute myocardial infarction is associated with no reflow seen on myocardial contrast echo and is an indicator of increased risk for cardiovascular morbidity and mortality[24,25]. We have previously reported that abciximab in combination with reduced dose alteplase improved both epicardial flow (TIMI 3 flow) and myocardial perfusion as reflected in a greater degree of ST-segment resolution[2]. The trend towards improved ST resolution when abciximab was combined with reduced dose reteplase is directionally consistent with the alteplase phase of the trial[2]. Additional support for a direct effect of abciximab on the myocardial microcirculation is provided by the improvements in TIMI Myocardial Perfusion Grade observed in the reteplase phase of the trial (Fig. 2)[12,22].

Clinical implications

The findings reported here extend our earlier obser vations on abciximab in several ways. Reduced doses of reteplase when administered in combination with abciximab were associated with higher TIMI 3 flow rates than reported previously without abciximab and were at least as high as those for full dose reteplase alone. The facilitation of thrombolysis with reteplase coupled with earlier observations with alteplase, supports the notion that there is an independent effect of abciximab on the thrombus in the infarct artery. Finally, the benefits of abciximab extend beyond facilitation of thrombolysis in the epicardial infarct artery to an improvement in myocardial perfusion. Although there was no important difference in the rate of TIMI 3 flow at 90 min with the 5+5 U of reteplase plus abciximab regimen compared with the 10+5 U of reteplase plus abciximab regimen, the latter was associated with higher rates of haemorrhagic events. These factors may have been taken into consideration when designing the GUSTO IV myocardial infarction study, a phase III trial comparing 10+10 U of reteplase alone versus 5+5 U of

reteplase plus abciximab with respect to 30-day mortality in patients with ST-elevation myocardial infarction.

References

[1] Antman EM, Giugliano RP, Gibson CM *et al*. Abciximab facilitates the rate and extent of thrombolysis: results of the thrombolysis in myocardial infarction (TIMI) 14 trial. The TIMI 14 Investigators. Circulation 1999; 99: 2720–32.

[2] de Lemos JA, Antman EM, Gibson CM *et al*. for the TIMI 14 Investigators. Abciximab Improves Both Epicardial Flow and Myocardial Reperfusion in ST Elevation Myocardial Infarction: Observations from the TIMI 14 Trial. Circulation 2000; 101: 239–43.

[3] Smalling RW, Bode C, Kalbafleisch J *et al*. and the Rapid Investigators. More rapid, complete, and stable coronary thrombolysis with bolus administration of reteplase compared with alteplase infusion in acute myocardial infarction. Circulation 1995; 91: 2725–32.

[4] Bode C, Smalling RW, Berg G *et al*. for the RAPID II Investigators. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. Circulation 1996; 94: 891–8.

[5] Chesebro JH, Knatterud G, Roberts R *et al*. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987; 76: 142–54.

[6] Gibson CM, Cannon CP, Daley WL *et al*. for the TIMI 4 Study Group. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996; 93: 879–88.

[7] Antman EM for the TIMI 9B Investigators. Hirudin in acute myocardial infarction: Thrombolysis and thrombin inhibition in myocardial infarction (TIMI) 9B trial. Circulation 1996; 94: 911–21.

[8] Cannon CP, McCabe CH, Henry TD *et al*. for the TIMI 5 investigators. A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. J Am Coll Cardiol 1994; 23: 993–1003.

[9] deLemos JA, Antman EM, Giugliano RP *et al*. for the Thombolysis in Myocardial Infarction (TIMI) 14 Investigators. ST-segment resolution and infarct related artery patency and flow after thombolytic therapy. Am J Cardiol 2000; 85: 299–304.

[10] Schröder R, Dissmann R, Bruggemann T *et al*. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol 1994; 24: 384–91.

[11] Schröder R, Wegscheider K, Schröder K *et al*. for the INJECT Trial Group. Extent of early ST segment elevation resolution: a strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens: a substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. J Am Coll Cardiol 1995; 26: 1657–64.

[12] Gibson CM, Cannon CP, Murphy SA *et al*. Relationship of TIMI myocardial perfusion grade to mortality following thrombolytic administration. Circulation 2000; 101: 125–30.

[13] Wald A. Sequential Analysis. Dover Publications, 1947: 88–105.

[14] Gibson CM, Murphy S, Menown IBA *et al*. for the TIMI Study Group. Determinants of coronary blood flowing following thombolytic administration. J Am Coll Cardiol 1999; 34: 1403–12.

[15] Coulter SA, Cannon CP, Ault KA *et al*. High levels of platelet inhibition with abciximab despite heightened platelet activation and aggregation during thrombolysis for acute myocardial infarction: results from TIMI (Thrombolysis in Myocardial Infarction) 14. Circulation 2000; 101: 2690–5.

[16] Carr ME Jr, Carr SL, Hantgan RR, Braaten J. Glycoprotein IIb/IIIa blockade inhibits platelet-mediated force development and reduces gel elastic modulus. Thromb Haemost 1995; 73: 499–505.

[17] Coller BS. Augmentation of thrombolysis with antiplatelet drugs. Overview. Coron Art Dis 1996; 6: 911–4.

[18] Coller BS. GPIIb/IIIa antagonists: pathophysiologic and therapeutic insights from studies of c7E3 Fab. Thromb Haemost 1997; 78: 730–5.

[19] Collet JP, Mirshahi M, Mishal Z, Montalescot G, Soria C, Soria J. A possible benefit of Reopro: modification of the clot structure. Thromb Haemost 1997; (June Suppl): 662.

[20] Cox AD, Devine DV. Factor XIIIa binding to activated platelets is mediated through activation of glycoprotein IIb-IIIa. Blood 1994; 83: 1006–16.

[21] Mascelli MA, Marciniak SJ, Weisman HF, Jordan R. In vitro characterization of dethrombosis by abciximab (Reopro). Thromb Haemost 1997; (June Suppl): 661.

[22] van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998; 97: 2302–6.

[23] Ito H, Maruyama A, Iwakura K *et al*. Clinical implications of the 'no reflow' phenomenon: A predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. Circulation 1996; 93: 223–8.

[24] Santoro GM, Valenti R, Buonamici P *et al*. Relation between ST-segment changes and myocardial perfusion evaluated by myocardial contrast echocardiography in patients with acute myocardial infarction treated with direct angioplasty. Am J Cardiol 1998; 82: 932–7.

[25] van't Hof AWJ, de Boer M-J, Zijlstra F for the Zwolle Myocardial Infarction Study. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Lancet 1997; 350: 615–9.

Appendix

TIMI 14 participants

Study Chairman's Office Harvard Medical School, Brigham and Women's Hospital, Boston, MA, U.S.A. Study Chairman, E. Braunwald; Principal Investigator, E. M. Antman; Project Director, C. H. McCabe; Coinvestigators, J. A. deLemos, R. P. Giugliano; Project Manager, K. Schuhwerk.

Leuven Coordinating Centre Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium. European Co-Chairman, F. van de Werf; Coinvestigator, P. Coussement.

Angiographic Core Laboratory Moffitt Hospital, University of California San Francisco, CA, U.S.A. Principal Investigator, C. M. Gibson; Quantitative Angiography Technician, K. Ryan; Data Manager, S. Murphy.

Sponsors Centocor, Malvern, PA, U.S.A.: K. Anderson, E. Barnathan, R. P. Schwartz Jr; Eli Lilly, Inc, Indianapolis, IN, U.S.A.: J. Scherer, S. Paddock, K. Hadley.

Data Coordinating Centre COVANCE, Princeton, NJ, U.S.A. Project Director, K. Vernarec; Director Statistics, R. Amatya; Programmer, L. Seifert.

Clinical centres in order of number of patients enrolled

Germany (113 patients)
Universitats-Krankenhous Eppendorf, Hamburg, Germany: Principal investigator, C. A. Nienaber; Research coordinator, T. Rehders. *Kardiologie Krankenhaus am Urban, Berlin, Germany:* Principal investigator, D. Andresen; Research coordinator, S. Hoffmann. *Medizinische Klinik II Universitatsklinik, Homburg, Germany:* Principal investigator, G. Berg; Research coordinator, B. Hammer. *CA der II. Medizinizschen Abteilung, Munchen, Germany:* Principal investigator, W. Doering; Research coordinator, F. Weiťhanner. *I. Medizinische Abteilung, Krankenhaus der Barmherzigen Brüder, Trier, Germany:* Principal investigator, K. E. Hauptmann; Research coordinator, B. Gestrich. *Städisches Klinikum Friedrichstadt, Dresden, Germany:* Principal investigator, E. Altmann; Research coordinators, A. Graf, J. Eberhard. *Kardiologie Kreiskrankenhaus, Traunstein, Germany:* Principal investigator, K. Schlotterbeck; Research coordinator, J. Schmid. *Kardiologie Kreiskrankenhaus 'an der Weser,' Hameln, Germany:* Principal investigator, H. Topp; Research coordinator, J. Tinnapel. *Innere Ev. Krankenhaus Kalk gGmbH, Koln, Germany:* Principal investigator, P. Wacker; Research coordinator, S. Bachman. *Kardiologie Zentralkrankanhaus 'Links der Weser', Bremen, Germany:* Principal investigator, H-J. Engel; Research coordinator, C. Hegeler. *CA der Kardiologie, Robert-Bosch-Krankenhaus, Stuttgart, Germany:* Principal investigator, U. Sechtem; Research coordinator, S. Hill. *Medizinische Klinik I Stadtisches Klinimkum, Fulda, Germany:* Principal investigator, T. R. Bonzel; Research coordinators, G. Strupp, G. Schreiner, R-O. Ibing. *Ltd. Arzt Herzkathederlabor Städtische Kliniken, Offenbeach, Germany:* Principal investigator, E. Girth; Research coordinators, N. Blees, N. Schuh. *Krankenhaus Leer, Leer, Germany:* Principal investigator, E. Stammwitz; Research coordinator, J. Könemann. *Innere Medizine II Krankenhaus Siloah, Hannover, Germany:* Principal investigator, E-R. von Lietner; Research coordinators, B. Hackenjos, T. Fürste.

United States of America (108 patients)
Sarasota Memorial Hospital and Doctor's Hospital, Sarasota, FL: Principal investigator, M. J. Frey; Research coordinators, J. Clark, M. Younger. *Montefiore Medical Center, Bronx, NY:* Coinvestigators, M. Greenberg, H. Mueller; Research coordinators, J. Cosico, K. Schneider. *Methodist Hospital, Houston, TX:* Principal investigator, N. S. Kleiman; Research coordinator, K. Maresh. *Columbia/JFK Medical Center, Atlantis, FL:* Principal investigator, J. Keival; Research coordinators, J. Kinley, J. Kosik. *Baystate Medical Center, Springfield, MA:* Principal investigator, M. J. Schweiger; Research coordinator, B. Burkott. *Iowa Heart Center/Mercy Hospital Medical Center, Des Moines, IA:* Principal investigator, M. G. H. Ghali; Research coordinator, T. Coulson. *Alta Bates Medical Center, Berkeley, CA:* Principal investigator, R. M. Greene; Research coordinators, E. Healy, V. Perry. *Bon Secours Saint Joseph Hospital and Fawcett Memorial Hospital, Port Charlotte, FL:* Principal investigator, J. Dulaney; Research coordinator, D. Landon. *St. Luke's-Roosevelt Hospital Center, New York, NY:* Coinvestigators, J. S. Hochman, J. Slater; Research coordinator, D. Burch. *Massachusetts General Hospital, Boston, MA:* Principal investigator, I.-K. Jang; Research coordinator, M. O'Connor. *The Mount Sinai Medical Center, New York, NY:* Principal investigator, S. Sharma; Research coordinators, E. Brown, T. King. *Rhode Island Hospital, Providence, RI:* Principal investigator, G. McKendall; Research coordinators, M. J. McDonald, J. Raymond, M. Grogan. *Broward General Medical Center, Ft. Lauderdale, FL:* Principal investigator, A. L. Niederman; Research coordinator, T. Kellerman. *Winthrop University Hospital, Mineola, NY:* Principal investigator, R. M. Steingart; Research coordinator, S. Bilodeau-Parker. *John L. McClellan Veteran's Memorial Hospital, Little Rock, AR:* Principal investigator, J. D. Talley; Research coordinators, M. Rawert, M. Dearen. *Utah Valley Regional Medical Center, Provo, UT:* Principal investigator, C. F. Dahl; Research coordinators, L. Merrill, J. Faulk. *University of Vermont, Burlington, VT:* Principal investigator, M. W. Watkins; Research coordinator, M. Rowen.

United Kingdom (42 patients)
Royal Victoria Hospital, Belfast, United Kingdom: Coinvestigators, A. A. J. Adgey, I. Menown; Research coordinators, B. Smith, L. Swailes. *Western Infirmary, Glasgow, United Kingdom:* Principal investigator, W. S. Hillis; Coinvestigators, D. Muir, G. McCann.

The Netherlands (19 patients)
OLVG afdeling Cardiologie, Amsterdam, Netherlands: Principal investigator, R. Van der Wieken; Coinvestigator, A. Scholte; Research coordinator, G. Kuiper.

France (14 patients)
Hopital Tenon, Paris, France: Principal investigator, A. Vahanian; Research coordinator, R. Farnoud. *Centre Hospitalier Universitaire Pontchaillou, Rennes, France:* Principal investigator, H. LeBreton; Research coordinator, J. F. Heautot.

Canada (4 patients)
University of Manitoba Health Sciences Centre, Winnipeg, MB: Principal investigator, J. Ducas; Research coordinator, U. Schick. *London Health Sciences Centre, Victoria Campus, London, ON:* Principal investigator, K. Sridhar; Research coordinator, J. White.