

A COMPARISON OF RETEPLASE WITH ALTEPLASE FOR ACUTE MYOCARDIAL INFARCTION

THE GLOBAL USE OF STRATEGIES TO OPEN OCCLUDED CORONARY ARTERIES (GUSTO III) INVESTIGATORS*

ABSTRACT

Background Reteplase (recombinant plasminogen activator), a mutant of alteplase tissue plasminogen activator, has a longer half-life than its parent molecule and produced superior angiographic results in pilot studies of acute myocardial infarction. In this large clinical trial, we compared the efficacy and safety of these two thrombolytic agents.

Methods A total of 15,059 patients from 807 hospitals in 20 countries who presented within 6 hours after the onset of symptoms with ST-segment elevation or bundle-branch block were randomly assigned in a 2:1 ratio to receive reteplase, in two bolus doses of 10 MU each given 30 minutes apart, or an accelerated infusion of alteplase, up to 100 mg infused over a period of 90 minutes. The primary hypothesis was that mortality at 30 days would be significantly lower with reteplase.

Results The mortality rate at 30 days was 7.47 percent for reteplase and 7.24 percent for alteplase (adjusted $P=0.54$; odds ratio, 1.03; 95 percent confidence interval, 0.91 to 1.18). The 95 percent confidence interval for the absolute difference in mortality rates was -1.1 to 0.66 percent. Stroke occurred in 1.64 percent of patients treated with reteplase and in 1.79 percent of those treated with alteplase ($P=0.50$). The respective rates of the combined end point of death or nonfatal, disabling stroke were 7.89 percent and 7.91 percent ($P=0.97$; odds ratio, 1.0; 95 percent confidence interval, 0.88 to 1.13).

Conclusions As compared with an accelerated infusion of alteplase, reteplase, although easier to administer, did not provide any additional survival benefit in the treatment of acute myocardial infarction. Other results, particularly for the combined end point of death or nonfatal, disabling stroke, were remarkably similar for the two plasminogen activators. (N Engl J Med 1997;337:1118-23.)

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RECENT trials have confirmed the importance of achieving early, complete, and sustained reperfusion after acute myocardial infarction.¹⁻³ In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) trial, an accelerated infusion of alteplase led to a relative reduction in 30-day mortality of 14.6 percent as compared with streptokinase, the previous standard therapy.^{1,2} The reason for the enhanced survival with tissue plasminogen activator (alteplase) proved to be a higher rate of complete patency of the in-

farcted vessel 90 minutes after therapy, as determined angiographically, but this was achieved in only 54 percent of patients.^{3,4} Accordingly, a major goal of myocardial reperfusion therapy is to improve this rate of early fibrinolysis.

Recombinant plasminogen activator (reteplase) is a mutant of wild-type tissue plasminogen activator that lacks the finger, epidermal growth factor, and kringle-1 domains.⁵ The slower clearance resulting from these changes in the molecule allows reteplase to be given as a bolus. In two angiographic trials, reteplase compared favorably with alteplase with regard to enhanced patency of the infarct-related vessel and the incidence of bleeding complications.^{6,7} In a previous randomized comparison with streptokinase, treatment with reteplase resulted in an absolute 0.5 percent reduction in mortality at 30 days and a 1.0 percent reduction at 6 months, which, although not statistically significant, established the safety profile of the drug.⁸ In the present trial, we tested the primary hypothesis that the mortality rate 30 days after acute infarction would be significantly lower with reteplase than with alteplase.

METHODS

Patient Population

Patients of any age who presented after 30 minutes of continuous symptoms but within 6 hours after the onset of symptoms of acute myocardial infarction and who had, on the basis of 12-lead electrocardiography, ST-segment elevation of at least 1 mm in two or more limb leads, ST-segment elevation of at least 2 mm in the precordial leads, or bundle-branch block were considered eligible. The exclusion criteria included active bleeding, a history of stroke or central nervous system damage, recent major surgery, systolic blood pressure greater than 200 mm Hg or diastolic blood pressure greater than 110 mm Hg at any time after arrival, recent noncompressible vascular puncture, or concomitant use of an oral anticoagulant with an international normalized ratio greater than 2. All patients provided informed consent for participation, and the protocol was approved by the institutional review board at each hospital.

Randomization and Drug Regimens

Investigators and study coordinators telephoned a central randomization center to receive a patient's treatment assignment. Patients were randomly assigned in a 2:1 ratio to receive reteplase

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Dr. Topol, as study chairman, assumes full responsibility for the overall content and integrity of the manuscript.

*The investigators and institutions participating in the GUSTO III trial are listed in the Appendix.

(Boehringer Mannheim, Gaithersburg, Md., and Mannheim, Germany), in two bolus doses of 10 MU given 30 minutes apart, or an accelerated infusion of alteplase (Genentech, South San Francisco, Calif., and Boehringer Ingelheim, Ingelheim, Germany), in a bolus dose of 15 mg, followed by the infusion of 0.75 mg per kilogram of body weight over a 30-minute period (not to exceed 50 mg) and the infusion of 0.5 mg per kilogram (up to 35 mg) over the next 60 minutes, on an open-label basis.¹

Aspirin (160 mg) was given as soon as possible and then in a daily dose of 160 to 325 mg. With the assigned fibrinolytic therapy, patients received a bolus dose of 5000 U of heparin given intravenously, followed by an infusion of 1000 U per hour. The initial rate of heparin infusion was reduced to 800 U per hour for patients who weighed less than 80 kg and was adjusted to maintain an activated partial-thromboplastin time of 50 to 70 seconds in all patients.⁹ Other medications, including beta-blockers and nitrates, were given at the discretion of the investigator.

Study End Points

The primary end point was mortality at 30 days of follow-up. Other prospectively defined secondary end points included net clinical benefit, defined as freedom from death or disabling stroke; death or nonfatal stroke; reinfarction; congestive heart failure; and mortality at 24 hours. All focal neurologic signs were evaluated by either computed tomographic or magnetic resonance imaging. Clinical features, images, and available autopsy results were reviewed by a stroke committee that was unaware of patients' treatment assignments to classify whether the stroke was hemorrhagic and whether it resulted in disability.¹ Bleeding complications were classified as severe or life-threatening if they resulted in substantial hemodynamic compromise requiring treatment. Moderate bleeding was defined by the need for transfusion, and minor bleeding was defined as bleeding that did not require transfusion or cause hemodynamic compromise.

Data Management and Quality Assurance

Case-report forms were used to collect the primary data and were forwarded to the coordinating centers (the Duke Clinical Research Institute in Durham, N.C., or the Nottingham Clinical Trials Data Centre in Nottingham, United Kingdom) so that the data could be entered and missing or inconsistent data could be identified. We used the methods of the GUSTO I trial to obtain data on vital status.¹ A random sample of 10 percent of the case-report forms was verified against source medical records, including at least one form at each enrolling site. The investigators had no access to the data until the trial was complete and the specified analyses had been performed by the two biostatisticians who coordinated the data analyses. An independent data and safety monitoring board reviewed the data after 7891 patients had been enrolled. The data reported herein are based on a 99.8 percent level of completeness for 30-day mortality outcomes.

Statistical Analysis

The study design required the enrollment of 15,000 patients in order to have at least 85 percent power to detect a 20 percent relative reduction in mortality with reteplase as compared with alteplase. Continuous data are summarized as medians with 25th and 75th percentiles unless otherwise stipulated. Selected baseline characteristics and clinical outcomes were compared between treatment groups by the chi-square test for discrete variables and by nonparametric analysis of variance for continuous variables. Mortality during the 30-day follow-up was characterized with Kaplan-Meier curves. Odds ratios and 95 percent confidence intervals were used to compare other major clinical outcomes between treatment groups. A logistic model that included adjustment for covariates was used to incorporate into the primary analysis base-line clinical predictors of mortality at 30 days: age, systolic blood pressure, heart rate, and location of infarction.¹⁰ The covariate-adjusted comparison of mortality in the two treat-

ment groups constituted the primary analysis, with the standard, unadjusted treatment comparison also provided.

The protocol specified the following categories for subgroup analysis: age, location of infarction, systolic blood pressure, heart rate, length of time from onset of symptoms to randomization, and site of enrollment (United States vs. elsewhere). All tests of significance were two-tailed, and treatments were compared according to the intention-to-treat principle.

RESULTS

A total of 15,059 patients were enrolled in 807 hospitals in 20 countries (see the Appendix) from October 13, 1995, to January 13, 1997. Both treatment groups had a very high rate of compliance: 97.3 percent with respect to the inclusion and exclusion criteria and 98.1 percent with respect to the initiation of study drug. Treatment with the study drug was terminated early in 0.8 percent of the patients treated with reteplase and 1.9 percent of those treated with alteplase, primarily because of early death or bleeding events. As expected, the base-line characteristics did not differ significantly between groups (Table 1).

The mortality rate at 30 days was 7.47 percent in the reteplase group and 7.24 percent in the alteplase group (odds ratio, 1.03; 95 percent confidence in-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	RETEPLASE (N = 10,138)	ALTEPLASE (N = 4921)
Median age — yr	62.9 (53, 71)	63.0 (53, 72)
Age >75 yr — %	13.6	13.5
Female sex — %	27.5	27.2
Prior hypertension — %	39.5	39.1
Diabetes — %	15.5	15.9
Current smoker — %	41.3	41.4
Hypercholesterolemia — %	34.4	34.8
Prior infarction — %	18.4	18.4
Prior bypass surgery — %	3.9	3.9
Median systolic blood pressure — mm Hg	135 (119, 150)	134 (119, 150)
Median diastolic blood pressure — mm Hg	80 (70, 90)	80 (70, 90)
Median heart rate — beats/min	73 (62, 86)	73 (62, 86)
Location of infarction — %†		
Anterior	47.4	47.7
Inferior	48.6	48.2
Other	3.3	3.3
None	0.7	0.9
Killip class — %†		
1	85.8	85.4
2	12.2	12.8
3	1.5	1.3
4	0.6	0.6
Median interval between onset of symptoms and treatment — hr	2.7 (1.8, 3.8)	2.7 (1.9, 3.9)

*Values in parentheses are the 25th and 75th percentiles.

†Because of rounding, not all percentages total 100.

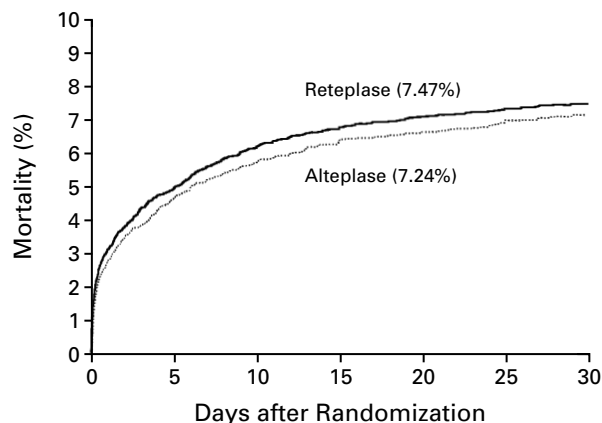


Figure 1. Kaplan-Meier Estimate of Mortality at 30 Days, According to Treatment Group.

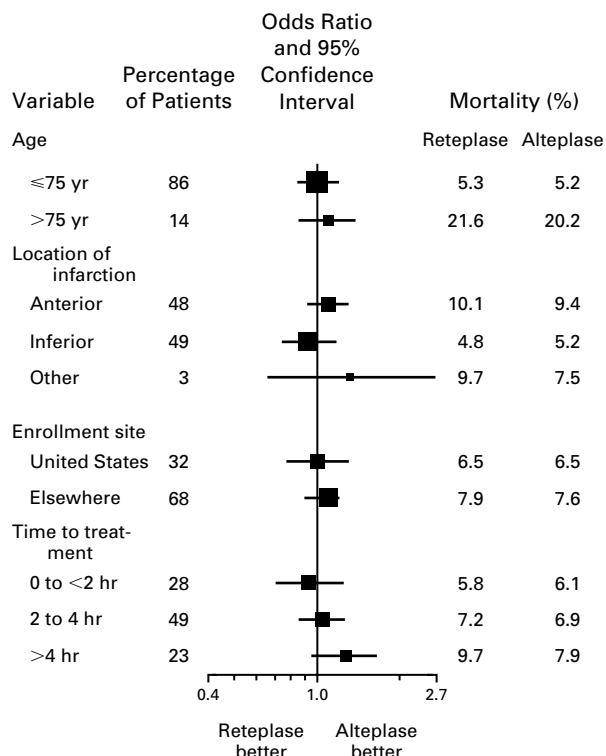


Figure 2. Odds Ratios and 95 Percent Confidence Intervals for Death within 30 Days, According to Age, Location of Infarction, Site of Enrollment, and Time from Onset of Symptoms to Treatment.

terval, 0.91 to 1.18; unadjusted $P=0.61$; covariate-adjusted $P=0.54$) (Fig. 1). At 24 hours, the mortality rate was 3.03 percent with reteplase and 2.72 percent with alteplase (odds ratio, 1.12; 95 percent confidence interval, 0.91 to 1.37). The 95 percent confidence interval for the absolute difference in 30-

day mortality was -1.11 to 0.66 percent. The similarity in the overall mortality data remained consistent across subgroups (Fig. 2). The patients who were at highest risk, such as elderly patients or those with anterior infarction, had a slightly higher mortality rate with reteplase than with alteplase. Only in the subgroup of patients who received treatment more than four hours after the onset of symptoms did the difference in mortality rates approach significance ($P=0.07$) (Fig. 2). However, there was a significant interaction between treatment assignment and time to treatment (adjusted $P=0.02$).

The rate of any stroke or hemorrhagic stroke was similar in the two treatment groups (Table 2), with a slightly but not significantly higher rate of hemorrhagic stroke after treatment with reteplase among patients over the age of 75 (2.5 percent vs. 1.7 percent; odds ratio, 1.55; $P=0.21$).

The overall incidence of death or disabling stroke was 7.89 percent with reteplase and 7.91 percent with alteplase (odds ratio, 1.0). Figure 3 shows the point estimates and 95 percent confidence intervals for the differences between the thrombolytic agents with respect to the primary and secondary end points of the trial. Serious or life-threatening bleeding was infrequent in the trial, occurring in 0.95 percent of the patients treated with reteplase and in 1.20 percent of the patients treated with alteplase. The rates of moderate bleeding were also similar (6.9 percent and 6.8 percent, respectively). Blood was transfused in 5.9 percent of the patients treated with reteplase, as compared with 6.2 percent of the patients treated with alteplase. The incidences of reinfarction, congestive heart failure, and arrhythmias were similar in the two groups (Table 3). Medication use was also similar in the two groups. Finally, the use of angiography, angioplasty, bypass surgery, and other major procedures did not differ significantly between the groups.

DISCUSSION

The chief finding of this trial is that reteplase is not superior to alteplase for the treatment of acute myocardial infarction. However, in terms of 30-day mortality, hemorrhagic stroke, the combined end point of death and stroke (be it nonfatal or disabling), and bleeding complications, the results of reteplase therapy were similar to those of alteplase therapy. Furthermore, because the long half-life of reteplase allows for bolus therapy, it is easier to administer. The results of the trial nonetheless raise questions about the reasons for the lack of superiority, the definition of equivalence in trials of reperfusion therapies, and the potential lack of meaningful progress in reducing key adverse end points since the early 1990s.

Our finding of the similar efficacy of reteplase and alteplase differs from the results of angiographic

TABLE 2. INCIDENCE OF STROKE IN THE TWO TREATMENT GROUPS.*

OUTCOME	RETEPLASE (N = 10,138)	ALTEPLASE (N = 4921)
	percent (95% CI)	
Any stroke	1.64 (1.39–1.89)	1.79 (1.42–2.16)
Intracerebral hemorrhage	0.91 (0.73–1.09)	0.87 (0.61–1.13)
Nonhemorrhagic stroke	0.60 (0.45–0.75)	0.75 (0.51–0.99)
Death or nonfatal, disabling stroke	0.79	0.79
Age ≤75 yr†		
Any stroke	1.3	1.5
Hemorrhagic stroke	0.7	0.8
Age >75 yr‡		
Any stroke	4.1	3.9
Hemorrhagic stroke	2.5	1.7

*Values are point estimates. CI denotes confidence interval.

†A total of 8760 patients in the reteplase group and 4257 patients in the alteplase group were 75 years of age or younger.

‡A total of 1378 patients in the reteplase group and 664 patients in the alteplase group were over 75 years of age.

studies^{6,7} that preceded the current trial. Although the rate of patency of the infarct-related vessel at 90 minutes had been shown to be higher with reteplase than with an accelerated infusion of alteplase, with a 30 percent increase in the incidence of complete reperfusion, patency at 30 minutes in a subgroup of patients who underwent very early angiography was lower with reteplase (27 percent, vs. 39 percent with accelerated alteplase).⁷ Furthermore, reteplase lacks the finger and kringle-1 domains, characteristics of wild-type tissue plasminogen activator that confer fibrin binding. Fibrin specificity may be a desirable feature of a plasminogen activator, and the potentially slower rate of initial lysis with reteplase may reflect its reduced fibrin affinity. Nonthrombolytic effects of reteplase, a protease with reduced fibrin specificity, may also account for its lack of an incremental mortality benefit. Other possible explanations for the difference in clinical and angiographic results include an overestimate of the patency advantage in the previous trial,⁷ differences in the rates of reocclusion, an underestimate of the survival benefit in the current trial, or simply the play of chance.

The absolute difference in mortality at 30 days between reteplase and alteplase was 0.23 percent, with a 95 percent confidence interval of -1.11 percent to 0.66 percent. In a trial of 6010 patients, designed to assess the equivalence of reteplase and streptokinase,⁸ the absolute difference in mortality at 30 days was 0.5 percent in favor of reteplase, with a 95 percent confidence interval of -1.98 percent to 0.96 percent. The results of these two trials raise the question of an appropriate boundary for the definition of equivalence. In the earlier trial, this was stipulated as an absolute difference of 1 percent, but 90

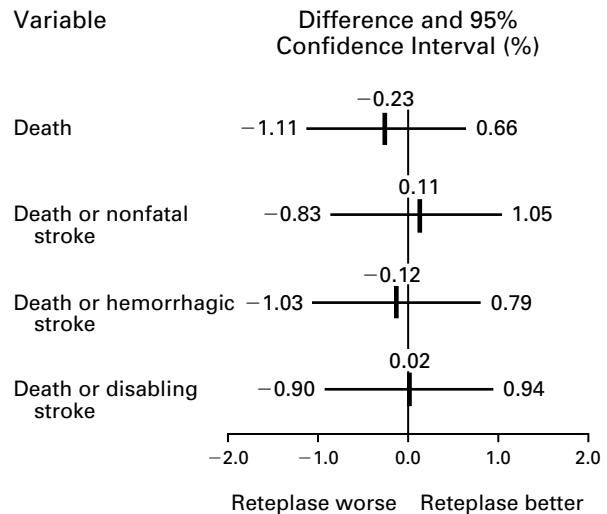


Figure 3. Point Estimates and 95 Percent Confidence Intervals for the Risk of Death within 30 Days, Stroke, and Net Clinical Benefit, Defined as Freedom from Death or Disabling Stroke.

With the use of a 1 percent lower boundary, reteplase was not equivalent to alteplase with respect to mortality at 30 days. For the end point of death or disabling stroke, the two treatments were equivalent.

TABLE 3. INCIDENCE OF COMPLICATIONS IN THE TWO TREATMENT GROUPS.

COMPLICATION	RETEPLASE (N = 10,138)	ALTEPLASE (N = 4921)
	percent	
Reinfarction	4.2	4.2
Recurrent ischemia	28.5	29.4
Congestive heart failure	17.2	17.5
Hypotension requiring therapy	20.6	19.5
Cardiogenic shock	4.6	4.4
Electromechanical dissociation	2.4	2.2
Tamponade or cardiac rupture	0.8	0.9
Second-degree atrioventricular block	2.3	2.2
Third-degree atrioventricular block	3.5	3.1
Atrial fibrillation	7.3	7.2
Asystole	4.2	4.2
Sustained ventricular tachycardia	4.0	4.1
Acute mitral regurgitation	0.6	0.4
Ventricular septal defect	0.2	0.3
Anaphylaxis	0.05	0.06
Pulmonary embolism	0.1	0.1

percent rather than 95 percent confidence intervals were used. This absolute difference of 1 percent, however, is the same as that between an accelerated infusion of alteplase and streptokinase,¹ and the use of alteplase would be associated with the prevention of one of every seven deaths that would otherwise

TABLE 4. CHANGES IN DEMOGRAPHICS AND MAJOR OUTCOMES IN THE GUSTO TRIALS OVER A SEVEN-YEAR PERIOD.*

CHARACTERISTIC	GUSTO I	GUSTO II†	GUSTO III
Years of the trial	1990–1993	1993–1995	1995–1997
No. of patients	41,021	3053	15,059
Median age — yr	62 (52, 70)	62.5 (53, 71)	63 (53, 71)
Age >75 years — %	10.5	11.8	13.6
Female sex — %	25.2	22.4	27.4
Median systolic blood pressure — mm Hg	130 (112, 144)	130 (115, 148)	135 (119, 150)
Median interval between onset of symptoms and treatment — hr	2.7 (1.9, 3.9)	2.8 (1.8, 4.2)	2.7 (1.8, 3.8)
Anterior infarction — %	39.1	40.9	47.5
Median length of hospitalization — days	9 (7, 13)	9 (6, 13)	7 (5, 12)
30-day mortality — %	7.0	6.2	7.4
All strokes — %	1.4	1.2	1.7
Hemorrhagic strokes — %	0.6	0.6	0.9

*Values in parentheses are the 25th and 75th percentiles.

†Only data on patients treated with thrombolytic agents are given.

have occurred with the established therapy. We used 95 percent confidence intervals, which exceed a definition of equivalence requiring a difference of less than 1 percent. Moreover, our study was not designed to assess equivalence, nor did it have adequate power to do so. Notwithstanding, for the secondary end point of death or disabling stroke, because the 95 percent confidence intervals are less than 1 percent, the equivalency of alteplase and reteplase is supported. As new approaches to reperfusion are attempted, we should be concerned that acceptance of broad statistical definitions of equivalence may compromise previously established benchmarks of therapy. Accordingly, the boundaries for equivalence deserve careful scrutiny with respect to the new plasminogen activators under development, including lanoteplase, recombinant staphylokinase, and TNK–tissue plasminogen activator.⁹

The types of patients who participate in thrombolytic trials have changed over the years (Table 4). For instance, in the GUSTO trials, there has been an increase in the numbers of elderly patients, with patients over 75 years of age accounting for nearly 14 percent of all patients in the current trial. There has also been increased representation of women and patients with hypertension. An important and unsettling finding is the lack of any reduction in the time to treatment during this extended period. After adjustment of the mortality and stroke models^{10,11} for differences in base-line features, including the increased proportion of anterior-wall infarctions, there has been no true increase in either the death rate or the rate of hemorrhagic stroke. However, an alternative interpretation is that mortality and stroke have not been reduced substantially during this period, as shown by longitudinal assessment of these successive

trials performed by the same network of investigators. The apparent increase in the incidence of hemorrhagic stroke in the current trial may be related to a more complete acquisition of data, through techniques such as the centralized, systematic review of all computed tomographic scans of the head and hospital-discharge summaries.

The search for more effective therapies for myocardial reperfusion will continue. The superior results of catheter-based strategies of reperfusion, as compared with thrombolytic therapy, although not entirely durable over the long term,¹² most likely relate to the fact that there is earlier and more complete restoration of myocardial blood flow than occurs with thrombolytic agents. For future thrombolytic strategies to have a clear survival advantage over established ones, substantial increases in the speed, quality, and persistence of reperfusion will be required. Such advances may rely not only on plasminogen activators, which until now have resulted in complete patency in less than 60 percent of patients (within 60 to 90 minutes after therapy), but also on better adjunctive agents such as direct antithrombins, which have markedly improved the results obtained with streptokinase,^{13,14} or inhibitors of platelet glycoprotein IIb/IIIa.^{15,16} It is equally as important to reduce the time to treatment, which remains considerably higher than the ideal of 30 minutes or less once the patient arrives at the hospital.

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APPENDIX*

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A. Capucci, P. Zardini, F. Sartori, G. Borello; France (453 patients): X. Tran Thanh, D. Barreau, J. Wolf, Boschat, Elhadad, Machecourt, J. Quiret, Slama, Coisne, A. Cohen, Furber, J. Dewilde, A. Vahanian Cazaux; Hungary (261 patients): I. Sárosi, S. Timár, K. Simon, L. Rudas, A. Katona, L. Vándor; Spain (236 patients): A. Betriu, A. Loma-Osorio, J. Bayón, J. Figueras, L. Bescos, X. Sabater; South Africa (215 patients): N. Ranjith, S. Cassim, G. Cassel, M. Baig, D. Duncan, J. Bennett; Portugal (159 patients): M. Carrageta, F. Caetano, R. Ferreira, C. dos Santos; Finland (149 patients): K. Pietilä, J. Melin, R. Kala, A. Kesäniemi, H. Koskivirta; Belgium (148 patients): H. Van den Bosch, D. El Allaf, P. Dejaegher, D. Koentges; Argentina (121 patients): L. Girotti, A. Sinisi, J. Badaraco; Austria (31 patients): J. Miczoch, K. Steinbach; Switzerland (31 patients): U. Münch, M. Vogt; the Netherlands (15 patients): P. Kalmthout, J. ten Kate.

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