

# Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: the GUSTO V randomised trial

The GUSTO V Investigators\*

## Summary

**Background** Plasminogen activator therapy for acute myocardial infarction is limited by lack of achievement of early, complete, and sustained reperfusion in a substantial proportion of patients. Many phase II trials have supported the potential of combined fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition for improving reperfusion. We did a randomised, open-label trial to compare the effect of reteplase alone with reteplase plus abciximab in patients with acute myocardial infarction.

**Methods** 16 588 patients in the first 6 h of evolving ST-segment elevation myocardial infarction were randomly assigned standard-dose reteplase (n=8260) or half-dose reteplase and full-dose abciximab (n=8328). The primary endpoint was 30-day mortality, and secondary endpoints included various complications of myocardial infarction. Analysis was by intention to treat.

**Findings** At 30 days, 488 (5.9%) of patients in the reteplase group had died, compared with 468 (5.6%) in the combined reteplase and abciximab group (odds ratio 0.95 [95% CI 0.83–1.08],  $p=0.43$ ). There were fewer deaths or non-fatal reinfarctions with the combination than with reteplase alone, and there was less need for urgent revascularisation and fewer major non-fatal ischaemic complications of acute myocardial infarction. On the other hand, there were more non-intracranial bleeding complications in the combination group. The rates of intracranial haemorrhage and non-fatal disabling stroke were similar.

**Interpretation** Although combined reteplase and abciximab was not superior to standard reteplase, the 0.3% absolute (5% relative) decrease in 30-day mortality fulfilled the criteria of non-inferiority. Combination therapy led to a consistent reduction in key secondary complications of myocardial infarction including reinfarction, which was partly counterbalanced by increased non-intracranial bleeding complications.

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## Introduction

Reperfusion therapy for acute myocardial infarction became the standard of care in the late 1980s,<sup>1,2</sup> and although there have been improvements in fibrinolytic therapy,<sup>3-5</sup> pharmacological treatment has many limitations. Compared with standard plasminogen-activator therapy, several pilot studies that combined low-dose plasminogen activator and platelet glycoprotein IIb/IIIa antagonists have suggested better speed, durability, and completeness of myocardial reperfusion.<sup>6-8</sup> To provide a meaningful assessment of combined therapy, a large-scale trial was necessary. GUSTO V was powered to detect a mortality difference between standard fibrinolytic therapy and the combination of reduced dose fibrinolytic and a IIb/IIIa receptor antagonist. Our aim was to find out whether the combination of half-dose reteplase and abciximab would be superior, or not inferior, to reteplase alone for mortality at 30 days after enrolment. Secondary endpoints included the composite of death and non-fatal disabling stroke, reinfarction, recurrent ischaemia, urgent revascularisation, intracranial haemorrhage and non-intracranial bleeding complications, and mortality at 1 year.

## Patients and methods

### Patients

820 hospitals in 20 countries participated in the trial, and the protocol was approved by each centre's institutional review board. Each patient provided informed consent to participate. The inclusion criteria were: continuous symptoms of chest discomfort for at least 30 min and fewer than 6 h from onset to the time of randomisation, along with electrocardiographic criteria of ST-elevation myocardial infarction or new left-bundle branch block.<sup>3-5</sup> Exclusion criteria were: age less than 18 years, planned catheter-based reperfusion, active bleeding or a non-compressible vascular puncture site, blood pressure higher than 180 mm Hg systolic and 110 mm Hg diastolic, warfarin therapy, stroke within the past 2 years, weight more than 120 kg, or platelet count less than 100 000 cells/ $\mu$ L.

### Methods

Patients were randomly assigned via a centralised institution to receive reteplase at the standard dose of two 10 U boluses, 30 min apart, or the combination of a standard abciximab infusion of 0.25 mg/kg bolus and 0.125  $\mu$ g/kg per min (maximum of 10  $\mu$ g/min) for 12 h plus half-dose reteplase (two boluses of 5 U, 30 min apart). The drug kits were not distinguishable before opening, but the medications were given on an open-label basis.

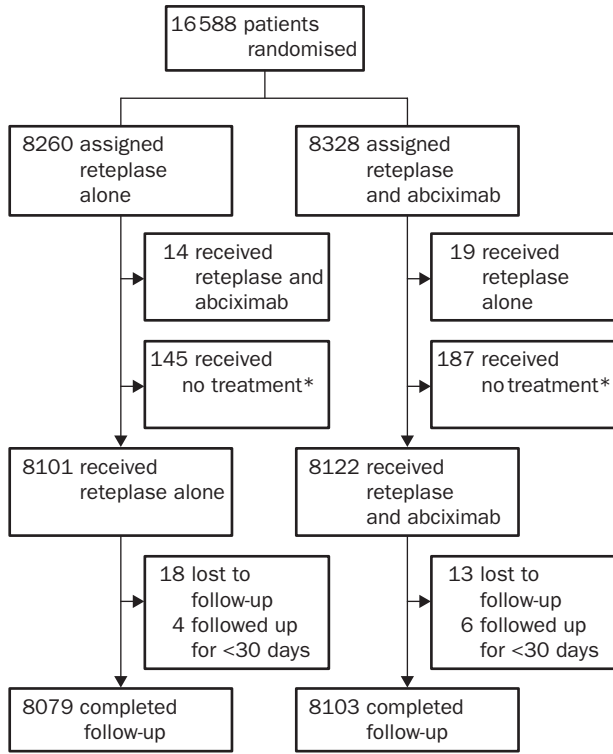


Figure 1: Trial profile

\*No treatment was given in some patients owing to death, non-fulfilment of entry criteria, or protocol violations.

All patients were also given aspirin (150–325 mg orally or 250–500 mg intravenously) at the time of randomisation, and 75–325 mg orally daily for the remainder of the study period. Heparin administration was adjusted by a nomogram to achieve an activated partial thromboplastin time of between 50 and 70 s, but because abciximab has an anticoagulant effect,<sup>9</sup> the dosing for heparin varied according to the random assignment. For patients on reteplase alone, the heparin dose was a 5000 U bolus followed by a 1000 U/h infusion (for those at least 80 kg) or an 800 U/h infusion for those less than 80 kg. In the combined group, patients received a 60 U/kg heparin bolus (maximum 5000 U) followed by an infusion of 7 U/kg per h. Besides aspirin and heparin, the use of all other adjunctive medications was left to the discretion of the participating investigator.

Coronary angiography and percutaneous coronary intervention were left to the discretion of the investigator on the basis of the clinical course of the patient. The use of abciximab for patients in the reteplase alone group was permitted if coronary intervention was done within 24 h and recommended if beyond 24 h of randomisation.

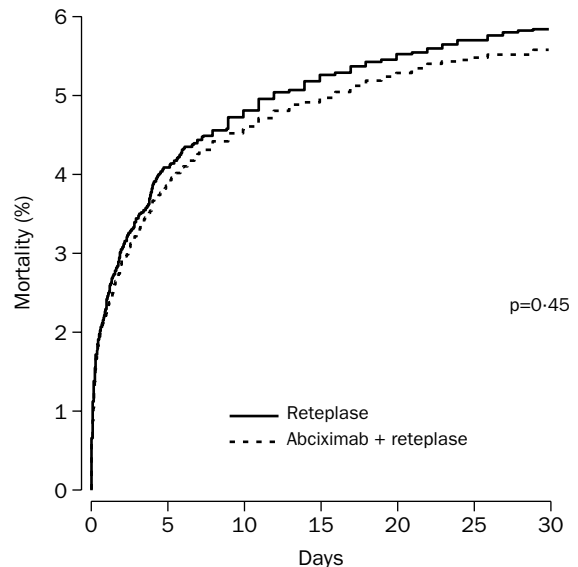
All-cause mortality was the primary endpoint. A central committee, masked to actual therapy assignment, reviewed all patients with a possible cerebrovascular event, with classification of whether a stroke had occurred, and the type of stroke. The disability status of surviving stroke patients was assessed between day 30 and 45 by a physician unaware of treatment assignment, with the modified Rankin scale. Definitions for all other events were provided to the investigators. Reinfarction required supportive evidence with either new significant electrocardiographic changes, an increase in cardiac enzyme concentration signifying myocardial necrosis, or both.<sup>10</sup> The endpoint of reinfarction was collated until 7 days after enrolment. 16 complications of acute myocardial infarction were prospectively defined

|  | Reteplase (n=8260) | Reteplase and abciximab (n=8328) |
|--|--------------------|----------------------------------|
| <b>Demographics</b>  |                    |                                  |
| Mean (SD) age (years)  | 61.1 (12.2)        | 61.6 (12.1)                      |
| Women  | 2026 (24%)         | 2064 (25%)                       |
| Diabetes   | 1299 (16%)         | 1334 (16%)                       |
| Smokers  | 3805 (46%)         | 3741 (45%)                       |
| <b>Previous events</b>   |                    |                                  |
| Myocardial infarction  | 1240 (15%)         | 1288 (16%)                       |
| Congestive heart failure                                       | 258 (3%)           | 224 (3%)                         |
| Hypertension   | 2733 (33%)         | 2866 (35%)                       |
| Raised cholesterol concentrations                              | 1325 (16%)         | 1420 (18%)                       |
| PTCA   | 561 (7%)           | 552 (7%)                         |
| CABG   | 273 (3%)           | 280 (3%)                         |
| <b>Drugs on entry</b>  |                    |                                  |
| β-blocker  | 1602 (19%)         | 1625 (20%)                       |
| ACE inhibitor  | 1088 (13%)         | 1182 (14%)                       |
| <b>Location of MI*</b>   |                    |                                  |
| Anterior   | 3071 (37%)         | 3126 (38%)                       |
| Inferior or posterior  | 4917 (59%)         | 4962 (60%)                       |
| Other  | 779 (9%)           | 760 (9%)                         |
| <b>Mean (SD) time from onset of symptoms to study drug (h)</b> |                    |                                  |
|  | 2.9 (1.6)          | 3.1 (2.2)                        |

ACE=angiotensin-converting enzyme; CABG=coronary-artery bypass graft; MI=myocardial infarction; PTCA=percutaneous transluminal coronary angioplasty. \*More than one myocardial infarction location was recorded in some patients.

Table 1: Baseline characteristics

and recorded for all patients until day 7 or hospital discharge (whichever was earlier). The timing of the performance of percutaneous coronary intervention was recorded, and urgent percutaneous revascularisation was recorded as defined by the investigator. Bleeding was classified as severe when associated with haemodynamic compromise, moderate when requiring transfusion without haemodynamic compromise, and mild without transfusion or haemodynamic compromise. Platelet counts were measured systematically 2–4 h and 24 h after administration of study drug.



Numbers at risk

|                       |      |      |      |      |      |      |      |
|-----------------------|------|------|------|------|------|------|------|
| Reteplase             | 8260 | 7917 | 7850 | 7812 | 7789 | 7768 | 7750 |
| Abciximab + reteplase | 8328 | 8000 | 7941 | 7906 | 7876 | 7857 | 7841 |

Figure 2: Kaplan-Meier mortality curves

|  | Reteplase (n=8260) | Reteplase and abciximab (n=8328) | Odds ratio (95% CI) | p     |
|--|--------------------|----------------------------------|---------------------|-------|
| <b>Non-fatal, disabling stroke</b>     | 26 (0.3%)          | 20 (0.2%)                        | 0.76 (0.43–1.37)    | 0.37  |
| <b>Stroke (any)</b>                    | 73 (0.9%)          | 81 (1.0%)                        | 1.10 (0.80–1.51)    | 0.55  |
| Intracranial haemorrhage               | 49 (0.6%)          | 52 (0.6%)                        | 1.05 (0.71–1.56)    | 0.79  |
| Non-haemorrhagic                       | 21 (0.3%)          | 21 (0.3%)                        | 0.99 (0.54–1.82)    | 0.98  |
| Non-haemorrhagic* with conversion      | 0                  | 0                                | ..                  | ..    |
| Unknown                                | 3 (0.04%)          | 8 (0.1%)                         | 2.65 (0.70–9.99)    | 0.15  |
| <b>Intracranial haemorrhage by age</b> |                    |                                  |                     |       |
| >75 years                              | 12 (1.1%)          | 24 (2.1%)                        | 1.91 (0.95–3.84)    | 0.069 |
| ≤75 years                              | 37 (0.5%)          | 28 (0.4%)                        | 0.76 (0.46–1.24)    | 0.27  |

\*Non-haemorrhagic with conversion refers to an initially bland stroke documented by imaging that was later associated with haemorrhage in the infarct zone, as documented by repeat imaging.

Table 2: **Stroke and intracranial haemorrhage**

### Statistical analysis

About 16 600 patients were required to detect a 15% relative mortality reduction from 7.4% to 6.3% with five interim analyses at 1000, 2500, 5000, 8300, and 12 450 patients, and one final analysis with an overall  $\alpha$  of 2.5% and 80% power with a one-sided  $\chi^2$  test. For non-inferiority, the upper limit of the 95% CI (1.11) was calculated by indirect estimation of the preservation of at least 75% of the benefit of streptokinase over placebo.<sup>11</sup> For the combination of half-dose reteplase and abciximab to be regarded as non-inferior, the upper bound of the 95% CI for the relative risk could be no greater than 1.10. Interim analyses were reviewed by the Safety and Efficacy Monitoring Committee with the Lan-DeMets method of stopping criteria.<sup>12</sup> All p values reported are two-sided, and analysis was by intention to treat.

### Results

16 588 patients were enrolled from July 7, 1999, until February 16, 2001 (figure 1). Table 1 shows the demographic characteristics of the two treatment groups. 1088 (13.2%) of the patients assigned reteplase and 1149 (13.8%) of those assigned reteplase and abciximab were older than 75 years. The use of conjunctive medications did not differ between the groups—at discharge, 6327 (77%) of those on reteplase and 6388 (77%) of those on reteplase and abciximab were receiving  $\beta$ -blockade; 4640 (56%) and 4714 (57%), respectively, received angiotensin-converting-enzyme inhibitors.

All-cause mortality at 30 days was 488 (5.9%) for the reteplase group, compared with 468 (5.6%) for the combined reteplase and abciximab group (test for superiority,  $p=0.43$ ; for non-inferiority, relative risk 0.95 [95% CI 0.84–1.08]). Figure 2 shows the Kaplan-Meier mortality curves. Mortality at 24 h after enrolment was 188 (2.3%) and 182 (2.2%), respectively (0.96 [0.78–1.18]), and at 7 days, it was 368 (4.5%) and 359 (4.3%), respectively (0.97 [0.83–1.12]).

There was no difference between the groups in terms of confirmed cerebrovascular events or non-fatal disabling stroke (table 2), or in terms of deaths or non-fatal disabling strokes (514 [6.2%] and 488 [5.9%], respectively). However, there was a significant ( $p=0.033$ ) interaction of treatment by age (<75 or  $\geq 75$  years) for intracranial haemorrhage. Figure 3 shows the complications of acute myocardial infarction.

For the composite of death or non-fatal reinfarction, the rate was 8.8% in the reteplase group compared with 7.4% in the combined group (0.83 [0.74–0.93],  $p=0.0011$ ). The use of percutaneous coronary intervention within 6 h was 8.6% in the reteplase group versus 5.6% in the combined group (0.64 [0.56–0.72],  $p<0.0001$ ); coronary-artery bypass grafting was done within 6 h in 0.1% of both groups. At 7 days, the use of percutaneous coronary intervention was 27.9% and 25.4%, respectively (0.88 [0.82–0.94],  $p<0.0001$ ), and coronary-artery bypass grafting was done in 3.7% and 3.0%, respectively (0.81 [0.68–0.96],  $p=0.013$ ). The reduction in the composite of death, reinfarction, or

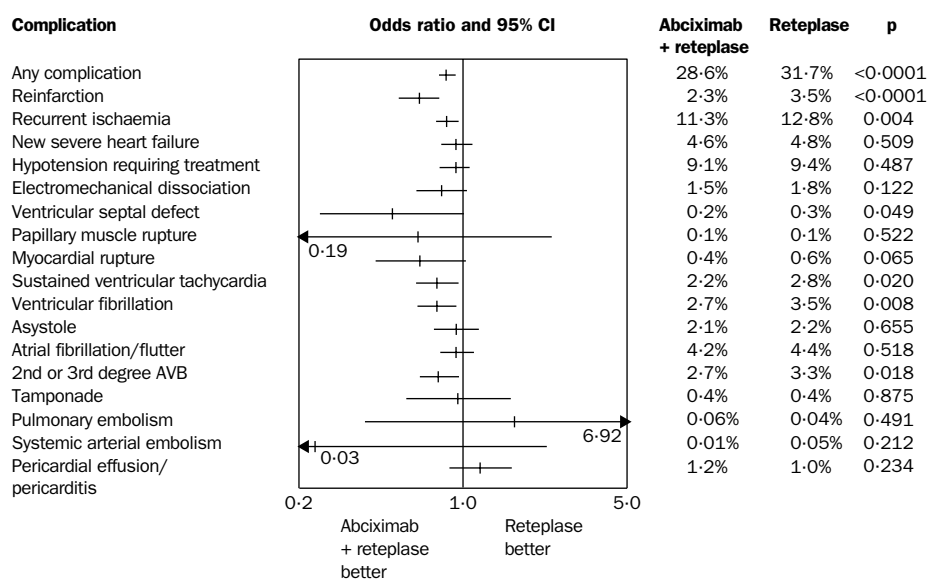


Figure 3: **Complications of myocardial infarction up to day 7**

AVB=atrioventricular block.

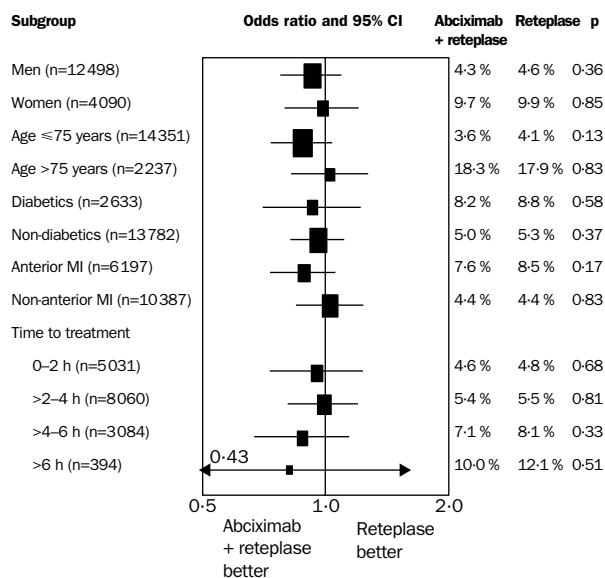


Figure 4: Subgroups and 30 day mortality

urgent percutaneous revascularisation until day 7 or discharge (whichever was earlier) was 20.6 versus 16.2% (0.75 [0.69–0.81],  $p < 0.0001$ ). Figure 4 shows the results for mortality in the main prespecified subgroups.

The data on non-intracranial bleeding complications and thrombocytopenia are summarised in table 3. The rate of bleeding associated with coronary-artery bypass grafting or cardiac catheterisation procedures was not higher in the group on combination therapy. In contrast, rates of spontaneous haemorrhage, predominately from gastrointestinal sources, were significantly higher among patients assigned abciximab and reteplase. Peak activated partial thromboplastin times (median) were 87.9 and 66.0 s in the reteplase and combination groups, respectively ( $p < 0.0001$ ).

## Discussion

Since fibrinolytic therapy became the standard of care for acute myocardial infarction in the 1980s, limitations have been recognised, including the relatively late time taken to re-establishing coronary blood, clinical instability with respect to recurrent ischaemia and reocclusion, and the lack of reperfusion at the myocardial tissue level in a large proportion of patients.<sup>13–15</sup> One of the obstacles to more effective reperfusion has been the known pivotal effect of platelets in responding to the plaque fissure or rupture of the diseased coronary artery. Beyond the role of platelet aggregation and the formation of “white clot” at the site of

vascular injury lies the potential for platelet-thrombus to embolise to the microcirculation and the release of vasoactive amines. Furthermore, plasminogen activators, by virtue of their ability to lyse fibrin from the fibrin-thrombin clot, expose free thrombin and, paradoxically, stimulate platelet aggregation.<sup>16</sup> Indeed, the use of aspirin in one of the classic trials of reperfusion led to an independent mortality reduction similar to and additive to fibrinolytic therapy.<sup>2</sup> Accordingly, the concept was fostered of more potent platelet inhibition as a driving feature for enhanced reperfusion. Many phase II trials that have assessed combined lowered doses of plasminogen activators and platelet glycoprotein IIb/IIIa inhibitors have provided mechanistic evidence for facilitating the velocity of reflow, diminishing recurrent ischaemic events, and augmenting tissue-level reperfusion.<sup>6–8</sup> However, whether this experimental approach would reduce mortality and whether it would prove to be safe, especially with the concern for the potential of increased intracranial haemorrhage, remained to be determined.

The results of our study show that combined reteplase and abciximab yields a mortality rate similar to that of standard fibrinolytic therapy with reteplase alone. Furthermore, there was no significant increase in intracranial haemorrhage or non-fatal disabling stroke. The rate of almost all of the prospectively defined non-fatal complications of myocardial infarction were lower with the combined therapy than with reteplase alone. Although a mortality benefit with combination therapy was not seen at 30 days, the reduced morbidity and reduced need for urgent revascularisation is encouraging, even if it is partly offset by higher rates of non-intracranial bleeding.

The explanation for the lack of superior survival benefit produced by the experimental therapy could lie, at least in part, in the unexpectedly low rate of mortality at 30 days. The 5.9% mortality in the reteplase group is substantially lower than the 7.5% in our previous GUSTO-III trial, which tested reteplase and alteplase,<sup>4</sup> and represents the lowest mortality rate of any large trial of acute myocardial infarction. Supporting this notion is the approximate 1% absolute difference in mortality in higher risk patients, such as those with anterior wall myocardial infarction, or patients receiving treatment late after symptom onset, favouring the combined therapy group. Whether the trial enrolled lower risk patients or whether there are secular trends for reduction of the mortality with evolving myocardial infarction remains unclear.

A second possible explanation for the lack of a reduction of mortality might relate to the dissociation between surrogate endpoints in smaller phase II trials and more definitive assessment in a large-scale trial. Even though combinations of lowered doses of fibrinolytics and IIb/IIIa

|  | Reteplase (n=8260) | Reteplase and abciximab (n=8328) | Odds ratio (95% CI) | p       |
|--|--------------------|----------------------------------|---------------------|---------|
| Severe bleeding                              | 42 (0.5%)          | 90 (1.1%)                        | 2.14 (1.48–3.09)    | <0.0001 |
| Moderate bleeding                            | 148 (1.8%)         | 289 (3.5%)                       | 1.97 (1.61–2.41)    | <0.0001 |
| Severe or moderate non-intracranial bleeding | 190 (2.3%)         | 379 (4.6%)                       | 2.03 (1.70–2.42)    | <0.0001 |
| Associated with CABG or procedure            | 34 (0.4%)          | 27 (0.3%)                        | 0.79 (0.48–1.31)    | 0.355   |
| Spontaneous                                  | 160 (1.9%)         | 357 (4.3%)                       | 2.27 (1.88–2.74)    | <0.0001 |
| Transfusion (any)                            | 329 (4.0%)         | 475 (5.7%)                       | 1.46 (1.26–1.69)    | <0.0001 |
| PRBC/whole blood (any)                       | 302 (3.7%)         | 414 (5.0%)                       | 1.38 (1.19–1.61)    | <0.0001 |
| PRBC/whole blood (≥2 units)                  | 239 (2.9%)         | 323 (3.9%)                       | 1.36 (1.14–1.61)    | 0.0005  |
| Platelets                                    | 69 (0.8%)          | 140 (1.7%)                       | 2.03 (1.52–2.71)    | <0.0001 |
| Mild bleeding                                | 945 (11.4%)        | 1664 (20.0%)                     | 1.93 (1.77–2.11)    | <0.0001 |
| Any bleeding                                 | 1135 (13.7%)       | 2043 (24.6%)                     | 2.04 (1.88–2.21)    | <0.0001 |
| Platelet count <100 000*                     | 55 (0.7%)          | 243 (2.9%)                       | 4.49 (3.34–6.02)    | <0.0001 |
| Platelet count <50 000                       | 10 (0.1%)          | 96 (1.2%)                        | 9.63 (5.02–18.48)   | <0.0001 |

PRBC=packed red blood cell. CABG=coronary-artery bypass graft. \*And 25% decreased from baseline.

Table 3: Bleeding complications and thrombocytopenia

inhibitors have been shown to improve the epicardial infarct vessel blood flow at 60 min into therapy (compared with fibrinolytic monotherapy), this effect might not, by itself, promote survival. Similarly, the improvement of electrocardiographic ST-segment resolution with combination therapy, which indicates augmented tissue-level reperfusion, might not be sufficient. Indeed, amelioration of all three surrogate endpoints, such as the 60-min angiographic restoration of coronary blood flow, the fluctuation of ST segments and recurrent ischaemia, and improved tissue perfusion, might not over-ride the extent of myocardial damage. The true benefit might only be realised at a later point, such that the 1-year follow up of survival could ultimately prove to be important. Of note, the patients in the current trial received reperfusion therapy an average of 2.7 h from the onset of symptoms. This almost 3-h delay from the onset of coronary occlusion to the start of therapy could be a critical determinant in improving survival and has not been notably reduced in the past decade of reperfusion trials.<sup>1-6</sup>

The question of equivalence or non-inferiority of combined reteplase and abciximab compared with fibrinolytic therapy deserves scrutiny. The non-inferiority criteria used were prespecified, and thus type I error for this conclusion should not be a cause for dispute.<sup>11,17</sup> Power for showing non-inferiority only reached 80% for the trial if there was an underlying 7% mortality reduction with combination therapy. Although the lower point estimate of 30-day mortality for the reteplase-abciximab group is encouraging, a 7% relative increase in mortality or a 15% relative decrease in mortality was not ruled out. Further support for potential benefit is lent by the lowered rate of reinfarction, need for urgent revascularisation, reduction of almost all of the non-fatal complications of acute myocardial infarction, and consistently lower point estimates for the combination group across all prespecified subgroups. This result was achieved with numerically less non-fatal disabling stroke and no notable increase in intracranial haemorrhage.

The use of an open-label design in large trials of acute myocardial infarction has been previously validated<sup>13,4</sup> with mortality as the primary endpoint. Incorporation of a triple-dummy placebo design in the current trial, which involved unequal doses of plasminogen activator, heparin, and the use of combination therapy, would have been extremely cumbersome and might have resulted in delay of active therapy in a large proportion of patients. In the current trial, the significant differences that emerged for treatment comparisons were in non-fatal outcomes. All of the neurological events were adjudicated by a committee masked to treatment assignments. The complications of myocardial infarction were each prospectively defined and were recorded by the treating physicians. Although bias in reporting non-fatal complications of myocardial infarction cannot be ruled out, the consistency across nearly all outcomes in such a large study population makes this possibility less likely.

Should combination therapy be incorporated into practice? This question will ultimately be decided by the clinical community and rests on another factor besides safety and efficacy: cost. If we assume that the price of combination therapy is not a consideration, our findings probably have an important application. First, the fewer complications of myocardial infarction and avoidance of reinfarction is certainly desirable. Second, for many patients who are to undergo immediate or early coronary angiography and possible coronary intervention, the combined therapy approach is attractive. Controlled trials of intravenous platelet glycoprotein IIb/IIIa inhibitors have

been uniformly supportive of the role of these agents in the setting of percutaneous coronary intervention.<sup>18-23</sup> Third, although bleeding complications and thrombocytopenia were increased with the combined therapy, the absolute rates are modest and clinicians can frequently assess a patient's risk of non-intracranial bleeding complications accurately.

The findings in this trial pertain to specific dosing schedules of one particular fibrinolytic and one IIb/IIIa inhibitor. Whether the optimum dose of these two agents was used, and whether other combinations with other agents in each class would yield the same findings, remains to be determined. Furthermore, the current trial emphasised the medical management of acute myocardial infarction, with only 7% of patients undergoing urgent percutaneous coronary revascularisation. The overall perspective of all of the trials of IIb/IIIa inhibitors so far indicates more substantial benefit when these agents are used with percutaneous coronary intervention. Future trials that encourage early angiography will be necessary to find out whether the combined therapy group provides a more definitive therapeutic advance than fibrinolytic therapy alone.

The results of the current trial have provided validation for an alternative reperfusion strategy that is very different from the one first introduced in the mid-1980s. The strategy of a combined reduced dose of a plasminogen activator and IIb/IIIa inhibitor provided similar 30-day survival outcomes with an improved profile of major, non-fatal ischaemic complications but an excess of transfusion use. Further analysis of our population, including 1-year follow-up, will be helpful in identifying those who gain particular benefit, as well as those subject to increased risk. These results represent a smaller net incremental advance than originally envisioned when the trial was designed, but sets the foundation for stepwise reduction of mortality and morbidity associated with the world's most important cause of death and disability.

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Gosford Hospital, Gosford (A Hill, B Conway); Box Hill Hospital, Box Hill (M Rowe, L Roberts); Dandenong Hospital, Dandenong (J Counsell, M Martin); Princess Alexandra Hospital, Brisbane (P Garrahy, C Hall); Cairns Base Hospital, Cairns (C Lim, B Cooke, Y Hodder); Prince Charles Hospital, Brisbane (N Bett, K McCosker); Royal Adelaide Hospital, Adelaide (M Kerruish, M Brown); Ashford Community Hospital, Ashford (R Lehman, H Morrison), Port Lincoln Hospital, Port Lincoln (R McLeay, A Dufek); Fremantle Hospital, Fremantle (R Hendricks, G Tulloch); The Canberra Hospital, Canberra (I Jeffery, A Kam, P Tavener); Coffs Harbour, Coffs Harbour (J Waites, P Cahill); Gippsland Base Hospital, Sale Victoria, (R Ziffer, J Dennett).

**Belgium (181 patients)**—AZ De Pelikaan, Temse (D Koentges); AZ St Erasmus, Borgerhout (W Smolders); AZ Stuyvenberg, Antwerpen (B Wallaert, DA Denie); Klinik Zusters van Barmhartigheid, Ronse (L Vanneste); Klinik Neerpelt, Neerpelt (A Van Dorpe); St Elisabeth Ziekenhuis, Turnhout (Lesseliers); Marie Ziekenhuis, Lommel (B Van Hauwaert); Hopital de la Citadelle, Leiege (J Boland, D Malmendier); Imelda Ziekenhuis, Bonheiden (L Janssens, C Muller); Jan Iepermanziekenhuis, Ieper (Roeland).

**Canada (1240 patients)**—Carleton Memorial Hospital, Woodstock, NB (J Milton, L McLellan); Clinique Invascor, Longueuil, QC (E Sabbah, J Lenis, J Roberge); Cowichan District Hospital, Duncan, BC (D Hilton, C Allen); General Hospital and Health Science Center, St John's, NF (B Rose, M Tobin, A Rideout); George L. Dumont Hospital, Moncton, NB (R Lee, M C Theriault); Grace General Hospital, Winnipeg, MB (J Wiatrowski, A Munoz, L Monteburno); Ottawa Hospital, Ottawa, ON (M Turek, T Seguin); Royal Alexandra Hospital (Edmonton Cardiology Associates), Edmonton, AB (W Hui, L Kvill); Royal Victoria Hospital, Barrie, ON (B Burke, M Sullivan); Sarnia General Hospital, Sarnia, ON (N Ali, C Degroot); Sudbury Regional Hospital, Sudbury, ON (Z Juma, J Bretzlaff-Michaud, D Cole); Thunder Bay Regional Hospital, Thunder Bay, ON (A Weeks, C Girard); University of Alberta Hospital, Edmonton, AB (W Tymchak, B Marple); Campbell River and District Hospital, Campbell River, BC (J Heath, L Saffarek); Concordia Hospital, Winnipeg, MB (H Smith, M Sokulski); Cornwall General Hospital, Cornwall, ON (P DeYoung, M Watt); Greater Niagara General Hospital, Niagara Falls, ON (Y K Chan, D Zanioli); Grey Nuns Community Hospital and Health Centre, Edmonton, AB (M Senaratne, M Goeres, K Heck); Hotel Dieu Grace Hospital, Windsor, ON (R Chetty, M Yakopich); Misericordia Community Hospital and Health Center, Edmonton, AB (P Greenwood, A Prosser); Montreal General Hospital, Montreal, QC (T Huynh, C Boudreau); Norfolk General Hospital, Simcoe, ON (S Chiu, C Verscheure-Hunt); North York General Hospital, North York, ON (B Lubelsky, D Dejewski); Pasqua Hospital-Regina Health, Regina, SK (V Deubardt, J Taylor); Penticton Regional Hospital, Penticton, BC (J Hernandez, D Pethybridge); Prince George Regional Hospital, Prince George, BC (D MacRitchie, J Fitzpatrick); Ridge Meadows Hospital, Maple Ridge, BC (F Ervin, H Coulson); Scarborough Centenary Health Centre, Scarborough, ON (F Halperin, B Bozek); Scarborough General Hospital, Scarborough, ON (T Davies, J Smith); St Michael's Hospital, Toronto, ON (D Fitchett, J Wawrzyniak); Sunnybrook Health Sciences Center, Toronto, ON (C Morgan, M A Chapel); Surrey Memorial Hospital, Surrey, BC (J Korner, M Perry); Southlake Regional Health Centre, Newmarket, ON (A Hess, S Webber, C Benke); Centre Hospitalier de Granby, Granby, QC (R Brossoit, C Robert); Centre Hospitalier de la Region de l'Amiante, Thetford-Mines, QC (G Pruneau, F Ouimet); Centre Hospitalier University de Quebec, Quebec, QC (J Audet, C Darveau); Centre Hospitalier Jonquiere, Jonquiere, QC (S Carrier, J Piche); Cite de la Sante de Laval, Laval, QC (M Montigny, R Major); Clinique de Cardiologie de Levis, Levis, QC (F Delage, F Dumont); William Osler Health Centre Etobicoke Hospital Campus, Rexdale, ON (K Kwok, J Gillett); Hospital Maisonneuve Rosemont, Montreal, QC (D Gossard, L Boutin); Hotel Dieu d'Arthabaska, Victoriaville, QC (P Chagnon, L Gauthier); Humber River Regional Hospital-Church St Site, Toronto, ON (R Bauer, J Parsons); Humber River Regional Hospital-Finch Site, Downsview, ON (T Bhesanian, K Caulfield); Huntsville District Memorial Hospital, Huntsville, ON (B Murat, H Featherstone); Centre Hospitalier de la Sanguanie, Chicoutimi, QC (G Tremblay, D Brassard); St Paul's Hospital, Saskatoon, SK (S Dhingra, L Kuspira); Sturgeon Community Hospital & Health Care, St Albert, AB (Z Lakhani, S Pysyk); Toronto East General Hospital, Toronto, ON (C Lefkowitz, M Thornley); Windsor Regional Hospital Western Campus, Windsor, ON (R Chetty, D Paltridge); York Central Hospital, Richmond Hill, ON (M Richmond, L Mighton, F Reinholdt); Le Centre Hospital Universitaire de Quebec, Ste-Foy, QC (L Desjardins, L St-Pierre); Sault Area Hospitals, Sault Ste Marie, ON (H Lee, K Barban, S McLean); Hotel Dieu Hospital, Cornwall, ON (P DeYoung, M Burrows); Lethbridge Regional Hospital, Lethbridge, AB (E Janzen, J Bigford, M McMurren); Royal Jubilee Hospital, Victoria, BC (W P Klinke, N Lounsbury); Saskatoon City Hospital, Saskatoon, SK (N Sharma, L Bergen); Seven Oaks Hospital, Winnipeg, MB (T Kesselman, A Munoz, L Monteburno); Medicine Hat Regional Hospital, Medicine Hat, AB (M Weigel, P Parekh, P Chisholm); St Joseph's Health Center, Toronto, ON (M DeVilla, J Sinclair); Victoria General Hospital (W P Klinke, N Lounsbury).

**Finland (107 patients)**—Lansi-Pohjan Keskussairaala, Kemi (Y K Jaaskelainen); Satakunnan Keskussairaala, Pori (A H Koskivirta); Kuopio University Hospital, Kuopio (K Peuhkurinen); Sisatautien Klinikka, Turku (L Voipio Pulkki); Sisatautien Klinikka, Turku (L Pahlama); Sisatautien Osastot, Espoo (A V Naukkarinen); Sisatautien Osastot, Jyväskylä (A J Melin); Sisatautien Osastot, Kajaani (Y J Juvonen); Kainuu Central Hospital, Kajaani (P Alasalmi); Sisatautien Osastot, Kotka (T E Koskela); Sisatautien Osastot, Vaasa (TH Kivela).

**France (404 patients)**—Centre Hospitalier, Nevers (B Vitoux); Centre Hospitalier, Lons-le-Saulnier (JD Berthou); Centre Hospitalier de Douai, Douai (J J Dujardin); Centre Hospitalier de Lagny Marne le Vallee, Marne (S El Hadad); Centre Hospitalier du Docteur Scheffner, Lens (B Berzin); Centre Hospitalier Dupuytren, Limoges (C Cassat); Centre Hospitalier General, Longjumeau (X T Thanh); Centre Hospitalier General, Valenciennes (J C Bodart); CHU-Hopital La Miletie, Poitiers (D Coisne); Hopital Cardiologique du Haut Leveque, Pessac (C Jais); Hopital du Bocage, Dijon (Zeller, JE Wolf); Hopital du Bon Secours, Metz (F Ben Ahmed); Hopital Tenon, Paris (E Garbarz); Centre Hospitalier Victor Provo, Roubaix (Y Haftel); Hopital Bichat, Paris (A Vahanian, PG Steg); Centre Hospitalier Victor Dupouy, Argenteuil (J Fruchaud); Hopital de Freyming, Merlebach (P Dambrine); Centre Hospitalier University de Grenoble, Grenoble (G Vanzetto); Centre Hospitalier Bretagne Sud, Lorient (P Cazaux); Hopital Robert-Ballanger, Aulnay-Sous-Bois (JP Maroni); CHU Lariboisiere, Paris (F Taragano); Hopital Pitie-Salpetriere, Paris (G Montalescot); Hopital Necker, Paris (P Cristofini); Centre Hospitalier Sud Francilien, Corbeil-Essonnes (M Habis); SAMU-Hopital Henri Mondor, Creteil (A Margenet); SAMU of Nord CHRU Lille, Lille (P Goldstein); SMUR Pitie-Salpetriere, Paris (P Ecollan); SMUR Lariboisiere, Paris (P Plaisance); Centre Hospitalier Docteur Schaeffner, Lens (N Ruold); CHU-Hopital Nord, Grenoble (P Menthonnex); SAMU-Hopital de la Source, Orleans (Chourar); Centre Hospitalier de Lagny sur Marne La Vallee (Y Guittard); SMUR Centre Hospitalier de Douai, Douai (B Averland).

**Germany (2511 patients)**—Agnes-Karil-Krankenhaus, Laatzen (Haun); Augusta-Krankenanstalt GmbH, Bochum (M Wehr); Borromaus-Hospital, Leer (R D Dannert); Caritas Krankenhaus, Mergentheim (Bundschu); DRK Krankenhaus Alzey-Worms, Alzey (J Schmidt); DRK-Krankenhaus, Neuwied (A Rieger); Ev. Elisabethkrankenhaus, Trier (Kronig); Ev. Krankenhaus, Witten (T Horacek); Ev. Krankenhaus Elisabethenstift, Darmstadt (W Schneider); Ev. Krankenhaus Herne, Herne (W Schnert); Evgl. Krankenhaus Kalk gGmbH, Köln (Wacher); Franziskus Krankenhaus, Aachen (Dienst); Klinik Oberstdorf, Oberstdorf (W Leupolz); Johanniter Krankenhaus Gronau gGmbH, Gronau (W Ziss); Wenckebach Krankenhaus, Berlin (H Kuckuck); Kath. Krankenhaus im Siebengebirge, Königswinter (Kummerhoff); Ketteler Krankenhaus, Offenbach (Nast); Klinik Memminger Strabe, Kempten (F Seidel); Klinikum Bernburg, Bernburg (F Odemar); Klinikum Ernst von Bergmann, Potsdam (Ohlmeier); Klinikum Hof, Hof (K Wette, T Podszus); Zentralkrankenhaus Links der Weser, Bremen (H J Engel); Klinikum Kreis Herford, Herford (U Schmitz-Hubner); Klinikum Leverkusen, Leverkusen (Jansen); Klinikum Nürnberg, Nürnberg (Gottwik); Klinikum Stralsund, Stralsund (T H Ittel); Krankenhaus am Urban, Berlin (Andresen); Krankenhaus Benrath, Düsseldorf (Schoppe); Krankenhaus Bietigheim, Beitzheim (M Wolf); Krankenhaus der Barmherzigen Brüder, Trier (K E Hauptmann); Krankenhaus Erlenbach am Main, Erlenbach (T Wielage); Krankenhaus Neukoelien, Berlin (F Forycki); Krankenhaus Porz am Rhein, Porz am Rhein (V Hossmann); Krankenhaus Reinickendorf Humboldt, Berlin (MM Menges); Krankenhaus Siloah, Hannover (von Leitner); Krankenhaus Spitalfond, Waldschüttlingen (C Kurth); Kreisklinik Langen, Langen (Grieshaber); Kreiskrankenhaus, Reutlingen, Reutlingen (M Hust); Kreiskrankenhaus, Traunstein (K Schlotterbeck); Kreiskrankenhaus Buchen, Buchen (G Gottfert); Kreiskrankenhaus Falkeneck, Braunfels (G Post); Kreiskrankenhaus Giben in Lich, Lich (G Goubeaud); Kreiskrankenhaus Leer, Leer (Stammwitz); Kreiskrankenhaus Ludenscheid, Ludenscheid (Henrichs); Kreiskrankenhaus Munchen Pasing, Munchen (Wonhas); Kreiskrankenhaus Rastatt, Rastatt (H Keller); Kreiskrankenhaus Trostberg, Trostberg (H G Biedermann); Kreiskrankenhaus Waldbrol GmbH, Waldbrol (K O Bischoff); Kreiskrankenhaus, Boblingen (H Nebelsieck); Kreiskrankenhaus, Ebersberg (Schneider); Kreiskrankenhaus, Eggenfelden (Gruber); Kreiskrankenhaus, Friedberg (J Meier); Kreiskrankenhaus, Gifhorn (Kreft); Kreiskrankenhaus, Grevenbroich (Holtmann); Kreiskrankenhaus, Kaltenkirchen (R Bernsmeier); Kreiskrankenhaus, Nauen (K F W Noga); Kreiskrankenhaus, Rudolstadt (Meier); Kreiskrankenhaus, Weinheim (F Holtermann); Lukas-Krankenhaus Altenkirchen, Altenkirchen (I Heck); Malteser Krankenhaus, Julich (Jebens); Marienkrankenhaus, Kassel (Koneremann); Marienkrankenhaus, Soest (Ochs); Mathias Spital, Rheine (H J Odenthal); Prosper Hospital, Recklinghausen (Tomsik); St Barbara-Hospital, Gladbeck (Graupner); St Carolus Krankenhaus, Gorlitz (HWM Breuer); St Franziskus-Hospital, Köln (F J Schneider); St Josef's-Krankenhaus, Linnich (Kuhrt-Lassay); St Josefs-Krankenhaus, Heidelberg (C Hasslacher); St Martinus Hospital, Olpe (G Muller); St Sixtus-Hospital, Haltern (RD Beythien); St-Vincenz-Krankenhaus,

Limburg (Neuss); Städtisches Klinikum Fulda, Fulda (T Bonzel); Städtisches Krankenhaus, Gutersloh, Gutersloh (Ditter); Städtisches Krankenhaus, Heilbronn, Heilbronn (J Cyran); Städtisches Krankenhaus, Nettetal, Nettetal (Appenrodt); Stadtklinik, Baden-Baden (Augustin); Stadtkrankenhaus, Hanau (W Pohlmann); Theresienkrankenhaus, Mannheim (Chorianopoulos); Universität Leipzig-Herzzentrum, Leipzig (Diederich); Universitätsklinikum Freiburg, Freiburg (C Bode, M Rave, A Van De Loo); Allgemeines Krankenhaus Celle, Celle (Terres); Burgfeld Krankenhaus, Kassel (Obst); DRK Klinik-Westend, Berlin (R Scholler); DRK Krankenhaus Koepenick 1, Berlin (H Voehringer); Ev. Waldkrankenhaus, Berlin (Justiz); Evangelisches Krankenhaus, Mulheim (Kotter); Klinikum Aschaffenburg, Aschaffenburg (R Uebis); Klinikum Lippe-Detmold, Detmold (U Tebbe); Klinikum Minden, Minden (Kratzsch); Krankenhaus Dresden-Friedrichstadt, Dresden (E Altmann); Krankenhaus St Joseph-Stift Bremen, Bremen (Caesar); Kreiskrankenhaus, Mosbach (Zipse); Kreiskrankenhaus an der Weser, Hameln (Topp); Kreiskrankenhaus Bergstrasse, Heppenheim (K Zolch); Kreiskrankenhaus Gummersbach, Gummersbach (C Kurz); Kreiskrankenhaus Schluchtern, Schluchtern (Beier); Kreiskrankenhaus Tuttingen, Tuttingen (Kauder); Marienhospital Stuttgart, Stuttgart (P Kratochvil); Paracelus-Klinik, Hemer (Riebeling); Robert Bosch Krankenhaus, Stuttgart (U Sechtem); St Josef-Hospital Cloppenburg, Cloppenburg (A Klaus); St Josef-Hospital, Wiesbaden (W Kasper); St Marien-Hospital, Köln (von Smekal); St Vincenz-Krankenhaus, Menden (Dundalek); Städtische Klinik Leipzig West, Leipzig (B Kottwitz); Städtische Kliniken Offenbach, Offenbach (Girth); Städtisches Krankenhaus, Darmstadt (Klingenbeck); Städtisches Krankenhaus Lebenstedt, Salzgitter (H Jablonowski); Stadtkrankenhaus Russelsheim, Russelsheim (von Mengden); Stadtkrankenhaus Wolfsburg, Wolfsburg (Engerberding); Universitätsklinik Tübingen, Tübingen (H M Hoffmeister); Zentralkrankenhaus, Bremerhaven (Dissmann); K H Lichtenberg Oskar-Zietheu-Krankenhaus, Berlin (H J Schulz, O Going); Kreiskrankenhaus Crailsheim, Crailsheim (H Bechtold); Medizinische Einrichtungen der Universität zu Köln, Köln (Griebenow); St Antonius Hospital gGmbH, Kleve (S Schuster); St Marienkrankenhaus Siegen, Siegen (P Schuster); Universitätskrankenhaus, Hamburg (C Nieuaber); Allgemeines Krankenhaus Eilbek, Hamburg (Heidemann); Clemens-August-Krankenhaus, Bitburg (Frelv); Ev Krankenhaus Holzminden, Holzminden (P Lowis of Menar); Ev Vereinskrankenhaus, Hann Munden (Kallmann); Harz Klinikum, Wernigerode (Hoffmann); Heidekreis-Klinikum Soltau, Soltau (Jacobs); Johanniter-Krankenhaus Rheinhausen, Duisburg (Reinhard); Josefs Hospital Warendorf, Warendorf (T Dorsel); Katholisches Krankenhaus Philippsstift, Essen (Dorwald); Kliniken des Main-Taunus-Kreises, Hofheim/Ts. (G Nissler); Klinikum der Ruprechts-Karl-Universität, Heidelberg (Ruf); Klinikum Erfurt GmbH, Erfurt (I Assmann); Klinikum Suhl, Suhl (M Kunze); Knappschaftskrankenhaus, Recklinghausen (Loos); Krankenhaus Bruchsal, Bruchsal (B Kohler); Krankenhaus, Itzehoe (Kentsch); Kreis Krankenhaus, Donaueschingen (E Walter); Kreis Krankenhaus, Herrenberg (Bierich); Kreis Krandenhaus, Kosching (Froböse); Maria-Hilf-Krankenhaus, Drefeld (U Peters); Marien Hospital, Osnabrueck (N Treese); St Elisabeth Krankenhaus, Mayen (Kilp); St Vincentius Krankenhaus, Karlsruhe (BD Gonska); Städtisches Krankenhaus Lüneburg, Lüneburg (Lankisch); Städtisches Krankenhaus, Pirmasens (K Stuby); Kreis Krankenhaus, Bautzen (Hempel); Kreis Krankenhaus, Heidenheim (A Schmidt); Sächsische Schweiz Klinik, Sebnitz (Radke); Kreisklinikum, Walsrode (K Wiese); Missionsärztliche Klinik, Würzburg (R Geiser); St Nikolaus Stifts Hospital, Andernach (H Degen); Unfallkrankenhaus Berlin Marzahn, Berlin (Thieme); St Ansgar Krankenhaus, Hoxter (Wilhelms); Klinikum Karlsbad Langensteinbach, Karlsbad (C Diehm); Universität Rostock, Rostock (Knorre); Allgemeines Krankenhaus Viersen, Viersen (G Linnart); St Elisabeth Krankenhaus, Badkissingen (K Pistel); Kreiskrankenhaus, Eschwege (H Kronert); Ev Diakoniekrankenhaus, Freiburg (Hockenjos); Städtisches Krankenhaus, Lubeck (J Stein); Krankenhaus Mecklenburg Strelitz, Neustrelitz (H Hemeling); Asklepios-ASB Klinik, Radeberg (Czech); Städtisches Krankenhaus, Sindelfingen (W Rupp); Krankenhaus Landshut-Achdorf, Landshut (R Bruckl); Städtisches Krankenhaus, Wismar (H Greiner-Leben); Krankenhaus, Bad Doberan (N Koeppling); Ostholstein Kliniken Klinikum, Eutin (O Freudenthaler); Klinikum, Schwerin (K Machill).

*Ireland (12 patients)*—Portiuncula Hospital, County Galway (J Barton); St James's Hospital, Dublin (P Crean, D Hughes); University College Hospital, Galway (K Daly, B Walsh).

*Israel (1973 patients)*—Asaf Harofeh, Yaacov (Z Vered); Bnei-Zion Medical Center, Haifa (E Abinader); Bikur Holim, Jerusalem (S Gottlieb); Carmel Medical Center, Haifa (H Schnieder); Chaim Sheba Medical Center, Tel-Hashomer (V Guetta, H Hod, Z Halevy); Hadasa-Ein Kerem Medical Center, Jerusalem (Y Hasin); Hadasa-Har Hazofim Medical Center, Jerusalem (T Weiss); Hillel-Yaffe, Hadera (B Pelled); Tel Aviv Sourasky Medical Center, Tel Aviv (A Roth); Laniado Hospital, Netanya (R Leor); Meir Hospital, Kfar Saba (D David); Rambam, Haifa (H Hammerman); Shaare Zedek, Jerusalem (J Balkin); Soroka Medical Center, Beer Sheva (H Gilutz); Barzilai

Medical Center, Ashkelon (L Reisin); Haemek Medical Center, Afula (T Rosenfeld); Joseftal Medical Center (T Zuabi); Kaplan Hospital, Rehovot (A Caspi); Western Galilee Hospital, Nahariya (N Roguin); Nazareth Hospital EMMS, Nazareth (M Omary); Poriah Hospital, Tiberias (L Rudnik); Rabin Medical Center, Petach Tikva (A Battler, Y Birenbaum); Sieff Government Hospital, Safed (A Marmor); Wolfson Medical Center, Holon (M Kriwisky); Carmel Medical Center, Haifa (A Palant).

*Italy (1231 patients)*—Policlinico San Matteo, Pavia (G DeFerrari); Istituti Ospitalieri, Verona (G Morando); Ospedale Ca' Foncello, Treviso (P Sritroni); Ospedale Civile, Chivasso (G Borello); Ospedale Civile, Caserta (G Corsini); Ospedale Civile, Senigallia (N Ciampini); Ospedale Civile E. Agnelli, Pinerolo (E Bellone); Ospedale Civile Santa Maria della Croce, Ravenna (A Maresto); Ospedale della Misericordia, Grosseto (S Severi); Ospedale Generale Provinciale, Gorizia (A Fontanelli); Ospedale Generale Regionale, Bolzano (W Pitscheider); Ospedale Maggiore, Lodi (M Orlandi); Ospedale Maggiore C.A. Pizzardi, Bologna (D Bracchetti); Ospedale Maggiore della Carità, Novaro (C Cernigliaro); Ospedale Mauriziano, Torino (N Gandolfo); Ospedale Niguarda Ca' Granda, Milano (R Fusco, S Savonitto); Ospedali Rivuti, Matera (L Tantalò); Ospedale S. Maria della Misericordia, Udine (A DiChiara); Ospedale Sant'Anna, Como (A Politi); Ospedale Santa Maria delle Grazie, Pozzuoli (E Murena); Ospedale SS Annunziata, Sassari (P Terrosu); Ospedale V Modaldi, Napoli (N Mininni); Policlinico D, Parma (D Ardissoni, A Finardi); Presidio Ospedaliero, Rovigo (P Zonzin); Spedali Civili, Brescia (C Cuccia); University of Padua, Padova (S Dalla Volta); Azienda Ospedale S Martino, Genova (E Borgo); Ospedale di Rho, Rho (G Rovelli); Ospedale di Treviglio e Caravaggio, Caravaggio (A Piti); Ospedale Silvestrini, Perugia (A Notaristefano); Presidio Ospedaliero di Fidenza, Fidenza (L Andreoli); Ospedale Curteri Mercato, Sau Severino (V Capuano); Ospedale Civile, Mirano, Mirano (G Pasquetto); Azienda Ospedaliera G. Brotzu, Cagliari (A Sanna); Ospedale Civile B Ramazzini, Carpi (S Ricci); Policlinico di Bari, Bari (I De Luca); Ospedale Bentivoglio, Bentivoglio (G Di Pasquale); Ospedale Maggiore di Crema, Crema (P Agricola); Ospedale Santi Antonio Biagio, Alessandria (D Medici); Cardiocentro Ticino, Lugano, Switzerland (A Rossi); Presidio Ospedaliero di Modena Sud-Ospedale Civile, Sasuolo (F Melandri); Ospedale Generale Provinciale di Monfalcone, Monfalcone (T Morgera); Ospedale Dei Pellegrini, Napoli (A Liguori); Ospedale di Desio, Desio (M DeMartini); Ospedale San Giovanni, Bellinzona, Switzerland (A Gallino); Azienda Ospedaliera M Mellini, Chiari (C Bellet); Ospedale Maggiore, Trieste (P Maras).

*Netherlands (1310 patients)*—Bosch Medicentrum, Den Bosch (AM van der Kraaij); Diaconessenhuis Eindhoven, Eindhoven (L Relik van Wely, B van Beers); Elkerliek Ziekenhuis, Helmond (M van Gent, PEF Bendermacher); Franciscus Ziekenhuis, Roosendaal (M van Straalen); Het Groene Hart Ziekenhuis, Gouda (EG Weijers, MA Hugo); Maastrandziekenhuis, Sittard (M van Daele); Medisch Centrum Haaglande, Den Haag (L Savalle); Oosterscheldeziekenhuis, Goes (A H Liem, M Goddrie); Schepersziekenhuis, Emmen (L F M van den Merkhof, W Veenstra); St Maartens Gasthuis, Venlo (H A Gratama, G M Dams); St Ziekenhuis de Heel, Zaandam (P N Bronzwaer, J Keasberry); Twenteborg Ziekenhuis, Almelo (R J Lionarons, L te Pas); Waterlandziekenhuis, Purmerend (F Slob, W Veenstra); Leyenburg Ziekenhuis, Den Haag (C De Jonge, R M Medina); Ziekenhuis Rijnstate, Arnhem (R M Tjon Joe Gin); Academisch Ziekenhuis Maastricht, Maastricht (F Bar, M Spanjers); Beatrix Ziekenhuis, Gorinchem (W van Dijk, P van Rossum); IJsselland Ziekenhuis, IJssel (W M Moer, I de Bruijn); Slingeland Ziekenhuis, Doetinchem (J H M Deppenbroek); Ziekenhuis Bernhoven, Oss (H J J Koorstra); Medisch Centrum Haaglande, Den Haag (C Dille); St Elisabeth Ziekenhuis, Venray (H A Gratama); St Joseph Ziekenhuis, Veghel (L Relik van Wely, J van Sterkenburg); Antonius Ziekenhuis, Sneek (D E P de Waard); Mesos Medisch Centrum Oudeneyn, Utrecht (K Van Leeuwen); St Anna Ziekenhuis, Geldrop (WAAJ van Ekelen); Ziekenhuiscentrum, Apeldoorn (L Cozijnsen, J van Remmen); Ziekenhuis Riverland, Tiel (van Loo, B van Beers); Albert Schweitzer Ziekenhuis Locatie Zwijndrecht (A H Herwijer, M Haasnoot); Albert Schweitzer Ziekenhuis Locatie Amstelveen (M Haasnoot, P W Fels); Albert Schweitzer Locatie Dordwijk (M J M Kofflard, M Haasnoot); Maasziekenhuis, Boxmeer (A Smits, WCG Smits); Medisch Centrum Rijnmond, Rotterdam (Galema, M van der Knaap); Ruwaard van Putten Ziekenhuis, Spijkenisse (van Beek).

*Norway (143 patients)*—Aker University Hospital, Oslo (F Kontny, T Dahl); Fylkeskyskehuset I Hagesunde, Hagesund (K Vaage); Gjøvik Fylkeskyskehuset, Gjøvik (T Indrebo); Kristiansund Sykehus, Kristiansund (I Blix); Lillehammer Fylkeskyskehuset, Lillehammer (H Dorum); Nordland Sentralsykehus, Bodo (A Hovland); Ost-Agder Sentralsykehus, Arendal (EH Andersen, IJ Gilberg, J Bo, T Gundersen, T Tverraan); Sentralsykehuset I Akershus, Nordbyhagen (F Sorgaard); Sentralsykehuset I Hedmark, Elverum (B Otterstad, B Larsen, E Hoye); Inherred Sykehus, Levanger (T Graven).

*Poland (1770 patients)*—Gornoslaskie Centrum Chorob Serca, Zabrze (S Pasyk); Collegium Medicum Uniwersytetu Krakowskiego, Krakow (K Janicki); Klinika Chorob Wewnetrznych AM, Gdansk (G Swiatecka);

Klinika Kardiologii, Poznan (M Wierchowicki); Instytut Kardiologii, Poznan (A Cieslinski); Instytut Kardiologii, Warsaw (Z Sadowski); Instytut Kardiologii, Warsaw (J Stepinska); Instytut Kardiologii, Szczecin (Z Kornaciewicz); Klinika Chorob Zawodowych, Gdynia (J Gorski); Klinika Hematologii, Poznan (K Zawilska); Klinika Kardiologii Akademii Medycznej, Białystok (W Musial); Prz Klinice Chorob Serca Akademii Medycznej, Gdansk (A Rynkiewicz); Szpital Brodnowski, Warsaw (J Kuch); Szpital im Marciniaka, Wrocław (K Lobo-Grudzien); Szpital IM Bieganskiego, Lodz (Z Bednarkiewicz, M Pakula); Szpital Miejski, Gdynian (P Miekus); Szpital Miejski, Milanówek (M Stopinski); Szpital Miejski, Swietokrzski (M Krzciuk); Szpital Wojewodzki, Szczecin (M Kurowski); Szpital Wojewodzki, Wloclawek (J Kopaczewski); Szpital Wojewodzki, Siedce (P Kolodziej); Szpital Wojewodzki, Plock (A Malinski); Szpital Wojewodzki, Zamosc (A Kleinrok); Szpital Wolski, Warsaw (D Wojciechowski); Wojewodzki Szpital Specjalistyczny, Wrocław (K Wrabec); Wojewodzki Szpital Zespólny, Kielce (M Janion); Wojewodzki Szpital Zespólny, Wrocław (W Prastowski); Wojewodzki Szpital Sespólny, Torun (K Jaworska); Szpital Wojewodzki, Rzeszow (J Kuzniar); Wojewodzki Medyczne, Opole (W Pluta); Wojewodzki Szpital, Radom (P Achremczyk); Wojewodzki Szpital, Lomza (R Krynicki).

*Portugal (88 patients)*—Hospital de Santa Cruz, Carnaxide (R Seabra Gomes, J Ferreira); UTIC Arsenio Codeiro, Lisbon (J Lopo Tuna); Hospital Pedro Hispano, Matosinhos (F Mouteiro, D Cunha); Hospital Fernando da Fonseca, Amadora (R Ferreira); Hospital Garcia de Orta, Almada (LM Oliveira, M Carrageta); Hospital Sao Joao, Porto (Cassiano); Hospital de S Bernardo, Setubal (A Forjao); Hospital de Santo Antonio, Porto (L Gomes); Hospital Distrital de Faro, Faro (V Gomes).

*South Africa (200 patients)*—Addington Hospital, South Beach (S Cassim, S Harripersadh); Glynnwood Hospital, Benoni (Tillet, D Fakude, R Jardine); Midlands Community Hospital, Pietermaritzburg (MNE Baig); Milpark Hospital, Johannesburg (G Harms, A Dalby, N Muller); Morningside Hospital, Gauteng (L Steingo, L Glaeser); St Dominic's Hospital, East London (F McKinley, D Duncan); Unitas Hospital, Pretoria (L Erasmus, P Blomerus); Vergelegen Medical Clinic, Somerset West (E Lock, J Roos); Pretoria Heart Hospital, Pretoria (A Ferreira, A Snyders); New Groote Schuur Hospital, Observatory (P Commerford, A Commerford); Panorama Medi-Clinic, Cape Town (J duPlooy, C Miller); Med Forum Hospital, Pretoria (E Maree, V Swart); Sunninghill Hospital, Johannesburg (E Klug, B Afonso); Wilgers Hospital, Pretoria (R Lubout, M Bennett); Entabeni Hospital, Durban (D Gillmer, K Muir).

*Spain (618 patients)*—Corporacion Sanitaria del Parc Tauli, Sabadell (A Artigas); Hospital Central de Asturias, Oviedo (Rodriguez-Llorian); Hospital Clinico Virgen de la Victoria, Malaga (JL Carpintero); Hospital Cruz Roja de Barcelona, Barcelona (J Masip); Hospital de Cruces, Vizcaya (G Froufe); Hospital de Girona Doctor Josep Trueta, Girona (R Masia); Hospital de la Santa Creu y Sant Pau, Barcelona (J Guindo); Hospital de Mutua de Terrassa, Terrassa (L Saenz); Hospital de San Juan, Alicante (C Climent); Hospital Peset, Valencia (V Valentin); Hospital Galdakao, Vizcaya (E Cantera); Hospital General de Alicante, Alicante (J Caturla); Hospital General Yague, Burgos (M Rodriguez); Hospital Marques de Valdecilla, Santander (J M Garagarza); Hospital Reine Sofia, Cordoba (N Martin); Hospital Son Dureta, Mallorca (M Fiol); Hospital Txagorritu, Vitoria (S Iribarren, A Loma-Osari); Hospital Universitario Clinico de Valladolid, Valladolid (F Aviles); Hospital Universitario Rio Hortega, Valladolid (J Blanco, J José); Hospital Universitario del Valle de Hebron, Barcelona (J Figueras); Ciutat Sanitaria de Bellvitge, Barcelona (X Sabate); University of Barcelona Hospital Clinic, Barcelona (M Heran); Hospital Clinico de Salamanca, Salamanca (C Martin Luengo); Hospital Nuestra Senora de Alarcos, Ciudad (J Ortega); Hospital General, Segovia (P Ancillo); Hospital Universitari Joan XXIII, Tarragona (S Alonso).

*Sweden (84 patients)*—Harnosand Sjukhus, Harnosand (L O Hemmingsson); Hudiksvall Sjukhus, Hudiksvall (K Haldar); Lycksee Lasarett, Lycksele (A Bjurman); Moindalsjukhus, Molndail (M Risenfors); Vrinnevisjukhuset, Norrköping (O Nilsson); Skelleftea Lasarett, Skelleftea (J Remmets); Medicinkliniken, Ystad (K Arnman); Sjukhuset, Kiruna (S Stalberg); Centralsjukhuset, Karlstad (C Abjorn); Ostar Sjukhuset, Goteborg (M Dellborg); Medicinkliniken plan 5, Helsingborg (L Ljungdal); Medicinkliniken, Visby (L Jacobsson).

*UK (1253 patients)*—Aberdeen Royal Infirmary, Aberdeen (K Jennings, M Jamieson); Addenbrooke's Hospital, Cambridge (P L Weissberg, S Blackwood); Blackburn Royal Infirmary, Lancashire (P Myers, A Myers); Cumberland Infirmary, Cumbria (R H Robson, A Graham); Glasgow Royal Infirmary, Glasgow (A P Rae, A Nasser); Hairmyres Hospital, Glasgow (K Oldroyd, T Young); King George Hospital, Essex (A Deaner, K Hughes); Monklands Hospital, Scotland (J C Rodger, J Anderson); Northwick Park Hospital, Middlesex (A Lahiri, L Chester); Pinderfields General Hospital, Wakefield (P Batin, C Taylor, B Durkin); Pontefract General Hospital, Pontefract (P Brooksby, J Beevers); The Royal Bournemouth Hospital, Dorset (A Rozkovec, A Whiting); Torbay Hospital, Torquay (P J Keeling, D Hughes); Trafford General Hospital, Manchester (J M S Trelawny, J Treadgold); University Hospital of Wales, Cardiff (P Groves, H Saunders, L Davies); University Hospital,

Nottingham (R G Wilcox, S Congreave); University of Leeds, Leeds (S G Ball, C Hague); Western General Hospital, Edinburgh (A Morrison, D Northridge); Wycombe General Hospital, Bucks (J Wilshire, C P Clifford); York District Hospital, York (M Pye, P Wathall); Blackpool Victoria Hospital, Blackpool (M Brack, L Radford); East Glamorgan General Hospital, Llantrisant (N Prasad, R Batton); Friarbridge Hospital, North Yorks (U Somanundram, J Johnson); Elderly Day Care Centre, Hartlepool (G Longstaff, A Khan); Hillingdon Hospital, Middlesex (S Dubrey, S McDonagh); Kent and Sussex Hospital, Tunbridge, Kent (C Lawson, D Kidman, J Highland); North Manchester General Hospital, Manchester (J Stuart, M Macaskill); North Tyneside General Hospital, North Shields (J C Doig, H Emmerson); Nottingham City Hospital, Nottingham (A J Ahsan, M Marriott); Peterborough District Hospital, Peterborough (D Rowlands, S Hennessy); Poole Hospital NHS Trust, Dorset (D Bruce, W Dickinson); Queen Margaret Hospital, Fife (DC MacLeod, R Stuart); St John's Hospital, Livingston (E White, AJ Jacob); Victoria Hospital, Fife (CM Francis, V Nicolson); West Suffolk Hospital, Suffolk (P Siklos); Southmead General Hospital, Bristol (J Dwight, B Durham); St Peter's Hospital, Surrey (D Fluck, M Wrigley); King's Mill Hospital, Notts (A Beal, J M Rowley); Princess of Wales Hospital, Wales (A Lloyd, J Goodfellow); Royal Infirmary of Edinburgh, Edinburgh (A D Flapan, M O'Donnell); Oldchurch Hospital, Ramford Essex (J D Stephens); Royal Devon and Exeter Hospital, Exeter (J W Dean, K James); Royal United Hospital, Bath (M Wicks, R D Thomas); Barnet General Hospital, Barnet (KE Gray, S McColgan); Broomfield Hospital, Essex (D Turner); Bromley Hospital, Kent (S Karwatowski, K Shears); County Hospital, Lincoln (R Andrews, S Heath); Princess Alexandra Hospital, Essex (G B Ambepitiya, R Rajesh); Craigavon Area Hospital, Portadown (AJ Moriarty, L Adair); Royal Victoria Hospital, Belfast (A A Adgey, G Scott); Ulster Hospital, Belfast (JDS Higginson, B McCullagh).

*USA (2918 patients)*—The Cleveland Clinic Foundation, Cleveland, Ohio (S Brenner, S Hejl); Advanced Medical Research, Inc, Covington, LA (V Mejia); Akron City Hospital, Akron, Ohio (R Jesephson, D Jasso); Alamance Regional Medical Center, Burlington, NC (B Carducci, D Isley); Alameda Hospital, Alameda, CA (S Raskin, C Irzyk); Arnot Ogden Medical Center, Elmira, NY (W DeLuccia, M Tuite); Austin Cardiovascular Associates, Austin, TX (M Jeffrey, M Pirasitz, S Crouch); Baptist Medical Center, Jacksonville, FL (J Schrank, D Hartley); Good Samaritan Hospital, Cincinnati, Oh (P Shea, K Loxterkamp); Brookdale University Hospital and Medical Center, Brooklyn, NY (H Chadow, R Hauptman, M Zema, S Veltri); Brookhaven Memorial Hospital Medical Center, Patchogue, NY (M Zema, S Veltri); Brunswick Hospital Center, Amityville, NY (M Chengot, C Morimando); Capital Health Systems, Trenton, NJ (L Glickman, R Williams); Cardiology Research Associates, Ormond Beach, FL (D Martin, J Carley); Norton Audubon Hospital, Louisville, KY (W Schmidt, M Hicks); MidAtlantic Cardiovascular Associates, Westminster, MD (S Jerome, S Little); Charlotte Heart Group, Port Charlotte, FL (M Lopez, R Dittenber, K Johnson); Christiana Care Health Services, Newark, DE (A Doorey, M Seador); Memorial Hospital, Jacksonville, FL (AA Seals, J Hartley-Mitchem); Broward Heart Group, Tamarac, FL (R Schneider, C Cutler); Creighton Cardiac Center, Omaha, NE (A Mooss, R Wurdeman, L Rasmussen); Danville Regional Medical Center, Danville, VA (G Miller, D Robinson); East Texas Medical Center, Tyler, TX (C N Israel, P Grove); Ellis Hospital, Schenectady, NY (M Saracco, R Parkes); Erlanger Medical Center, Chattanooga, TN (C Bell, J Steelman); Inova Fairfax Hospital, Falls Church, VA (P Dilonzo, E Pulsipher); Midatlantic Cardiovascular Associates, Bel Air, MD (M Drossner, D Roach); Falmouth Hospital, Falmouth, MA (D Urbach, T Bull); Free Memorial Hospital (B Patel, K Sopic); Frye Regional Medical Center, Hickory, NC (B Steg, L Lewis); Garden City Hospital, Garden City, MI (W Back, R Morgan, L Meharg); Adirondack Cardiology, Glens Falls, NY (J Layden, P Sehlmeier); Gnadon Huettner Memorial Hospital, Lehighton, PA (W Markson, M Alexander); Good Samaritan Hospital, Dayton, OH (G Broderick, C White); Grady Health System, Atlanta, GA (N Wenger, D Ander, V Jeffries); Greenwich Hospital, Greenwich, CT (H Seidenstein, M DeSteno); MidAtlantic Cardiovascular Associates, BelAir, MD (B Wohl, D Roach); Harton Regional Medical Center, Tullahoma, TN (D Gupta, R Rivers); Health Alliance Hospital, Leominster, MA (N Mercadante, C Cunningham); Health Central Hospital, Orlando, FL (M Gonzalez, L Jopperi); Heart and Vascular Institute of Texas, San Antonio, TX (K Kuri, S Wirebaugh, J Garrett); The Greater Fort Lauderdale Heart Research Group, Fort Lauderdale, FL (A Niederman, T Kellerman, P Rondino); Hermann Hospital, Houston, TX (R Smalling, C Underwood); Penn State Milton S Hershey Medical Center, Hershey, PA (I Gilchrist, H Zimmerman); The Heart Center, Kingsport, TN (R Santos, D Kerns); Inova Alexandria Hospital, Alexandria, VA (L Miller, A VanBreda); Integriss Southwest Hospital, Oklahoma City, OK (M Yasin, K Stilwell); Kaiser Permanente Medical Center, Los Angeles, CA (P Mahrer, P Scutella); Kent Hospital, Warwick, RI (K Salzsieder, D Horrocks); Krannert Institute of Cardiology, Indianapolis, IN (P Welker, E van der Lohe); Lake Forest Hospital, Lake Forest, IL (J Alexander, L Steckel, K Rodriguez);

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