The availability of RETAVASE® (Reteplase) marks an important advance in the thrombolytic treatment of acute myocardial infarction (AMI). RETAVASE possesses a unique molecular design and provides demonstrated reduction of mortality, a documented safety profile, and has been angiographically proven to achieve high rates of complete perfusion and patency. The correlation between patency and patient outcome has not been established. In addition, RETAVASE offers the convenience of a simple double-bolus dosing regimen.

This monograph is provided as a comprehensive informational reference to RETAVASE. It includes a complete review of preclinical and clinical pharmacology findings as well as clinical efficacy and safety data. The information presented has been designed to aid in the evaluation of RETAVASE for use in clinical practice.

RETAVASE is manufactured and distributed by Centocor, Inc.
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Please see full prescribing information on the last pages of this monograph.
RETAVASE is a modification of the tissue-type plasminogen activator (t-PA) protein that maintains the kringle-2 and protease domains of t-PA, but lacks its kringle-1, finger, and growth-factor domains. In contrast to t-PA, the RETAVASE molecule is nonglycosylated. These modifications result in a molecule with a longer half-life (13 to 16 minutes). RETAVASE lacks the high-affinity fibrin binding characteristic of t-PA, and is produced by recombinant DNA technology in Escherichia coli for use as a thrombolytic agent in the treatment of AMI. RETAVASE is a single-chain molecule consisting of 355 amino acids and can be converted to the two-chain form during fibrinolysis.

RETAVASE represents an important addition to the therapeutic options to treat patients with AMI. RETAVASE provides demonstrated reduction of mortality, a documented safety profile, and proven preservation of left ventricular function. Additionally, RETAVASE has been angiographically proven to achieve high rates of complete perfusion and patency, and offers a fast, convenient double-bolus dosing regimen. The correlation between patency and patient outcome has not been established.

Pursuing the ideal thrombolytic agent

It was observed in 1992 that none of the thrombolytic agents then available could be considered ideal. Each had limitations. Therefore, it is appropriate to define the characteristics of an ideal thrombolytic drug to help guide the direction of future research and development.®

Patient survival is the ultimate goal of thrombolytic therapy. An agent should produce rapid recanalization in patients with acute coronary thrombosis. Additional characteristics of an ideal agent are listed in Table 1.

It is noteworthy that RETAVASE possesses some of the attributes of the ideal agent: administration as an intravenous bolus, relative specificity for recent thrombi, and restoration of complete flow in a high percentage of patients. RETAVASE also has no effect on circulatory hemodynamics, is not antigenic, and has no known interactions with adjunctive therapies.

**Table 1.—Selected Characteristics of an Ideal Thrombolytic Agent**

- Rapid recanalization after administration
- Approaches 100% efficacy for recanalization
- Can be given as rapid IV bolus
- Specific for recent thrombi
- Assists in preventing reocclusion
  - Should result in sustained patency within the first 24 hours
  - Appropriate half-life if fibrin-specific
- Targets thrombus induced by plaque rupture
- No effect on circulatory hemodynamics
- No negative interactions with adjunctive therapies
- No antigenicity
- No significant side effects

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Adapted from Rapaport.®
Pharmacokinetic properties

Deletion of the three N-terminal domains and the absence of glycosylation present in native t-PA improves the pharmacokinetic properties of RETAVASE® (Retepase) without sacrificing its effectiveness as a plasminogen activator. These modifications to the molecule result in a plasma half-life of 13 to 16 minutes, which represents an increase over the 3- to 6-minute half-life of native t-PA. The longer half-life of RETAVASE permits fast, convenient double-bolus intravenous dosing, with the second dose given 30 minutes after the first.

Administration

The ease of administration afforded by bolus dosing may permit an earlier start of life-saving therapy in the hospital emergency department or intensive care unit. Bolus dosing may also eliminate the need for two intravenous lines during coadministration with heparin, since the heparin infusion can be interrupted during the injection of RETAVASE. The intravenous line should be flushed before and after administration of RETAVASE.

RETAVASE is supplied in glass vials as a sterile, preservative-free, lyophilized powder. The contents of the vial are reconstituted with Sterile Water for Injection, USP (without preservatives), and administered as an intravenous injection (10 U) over 2 minutes. The second bolus (10 U) is given 30 minutes after initiation of the first bolus injection. The dose of RETAVASE need not be adjusted for patient weight.

Clinical studies

The clinical benefits and safety profile of RETAVASE have been documented in well-controlled clinical trials in patients with AMI. The International Joint Efficacy Comparison of Thrombolytics (INJECT) trial was a randomized, double-blind, multicenter comparison of RETAVASE with Streptokinase in 6,010 AMI patients that was conducted in Europe. The study was powered to confirm that RETAVASE was safe and effective in reducing mortality in AMI patients.

Results demonstrated that RETAVASE is effective in reducing mortality in patients with AMI. Patients treated with RETAVASE had a significantly lower incidence of atrial fibrillation, asystole, cardiogenic shock, congestive heart failure (CHF), hypotension, and allergic reactions. Overall bleeding and stroke rates were similar for both agents. There was an increase in the incidence of in-hospital intracranial hemorrhage in patients treated with RETAVASE (0.77%) compared to those in the Streptokinase group (0.37%, P=0.04). The INJECT investigators concluded that RETAVASE is an effective agent for the treatment of AMI and has an acceptable safety profile.

In the Reteplase Angiographic Phase II International Dose-finding (RAPID 1) Study, infarct-related arteries were evaluated angiographically in 606 patients after therapy with RETAVASE administered by bolus injection (three different regimens) or Alteplase administered as a 3-hour infusion. In the Reteplase vs Alteplase Patency Investigation During Acute Myocardial Infarction (RAPID 2) Study, 324 patients received either RETAVASE or an accelerated-dose (90-minute) Alteplase infusion. Patients in both trials also received aspirin and heparin. In both angiographic trials, RETAVASE achieved high rates of complete perfusion and patency. The correlation between patency and patient outcome has not been established. These studies also demonstrated the efficacy of RETAVASE in preserving left ventricular function following AMI.

Low risk of antigenicity

RETAVASE is synthesized in transformed E. coli and is a modified endogenous protein with a low risk for antigenic activity. Antibodies to RETAVASE were not observed in any of approximately 2,400 patients tested for antibody formation.

The low risk of antigenicity with RETAVASE contrasts with that of Streptokinase and its derivatives. Since most patients have previously been exposed to hemolytic streptococcal infection, they may produce antibodies to Streptokinase, a protein derived from Lancefield group C strains of ß-hemolytic streptococci.
SECTION II

Thrombolysis in the management of acute myocardial infarction

Rationale for use of thrombolysis

Cardiovascular disease accounts for a large proportion of all deaths in both men and women in the United States. The age-adjusted death rate in 1991 was 186 per 100,000 individuals; for coronary heart disease, it was 99.1 per 100,000. Patients who survive the acute stage of a myocardial infarction are at two to nine times greater risk of subsequent cardiovascular morbidity and mortality than the general population.6

Three perfusion methods are currently available for the management of patients with AMI: thrombolysis with pharmacologic agents, percutaneous transluminal coronary angioplasty (PTCA), and revascularization by coronary artery bypass grafting (CABG). The effectiveness of thrombolytic therapy in reducing mortality in patients with AMI has been demonstrated in large, multinational clinical trials. PTCA is an invasive procedure that requires a catheterization laboratory and expert teams for implementation. PTCA is an option preferred by some physicians where facilities are available, especially in patients with contraindications to thrombolytic therapy or with infarction complicated by cardiogenic shock.

The era of thrombolysis

The nature of the infarction process was not well understood until comparatively recent years. In 1980, DeWood and colleagues provided definitive proof that thrombosis occurs early in the infarction process.7 These investigators angiographically visualized total occlusion of the infarct-related coronary artery within 4 hours of onset of symptoms in 110 of 126 patients (87%) with acute transmural (Q-wave) infarction. In addition, they found that thrombi were present in 88% of patients undergoing CABG. Since then, it has frequently been observed that the arterial lumen is considerably narrowed by dynamically changing atheromatous plaque, which enables relatively small thrombi to block antegrade flow and produce ischemia and hypoxia. More than 85% of myocardial infarctions result from formation of an acute thrombus obstructing an atherosclerotic, stenotic coronary artery.8 Thus, the development of selective coronary angiography proved to be a vital link in the development and acceptance of thrombolytic therapy.
Mechanisms of thrombolysis

Like native tissue plasminogen activators, all thrombolytic agents activate plasminogen into plasmin, which splits the fibrin in the clot into soluble fibrin degradation products; fibrinogen, a precursor of fibrin, is also degraded by plasmin. Plasminogen, which has high affinity for fibrin, is activated much more efficiently when bound than unbound because fibrin forms surface receptors that allow plasminogen and plasminogen activator to come into optimal contact (Fig 1). Thrombolytic agents differ in their affinity for fibrin; this is important because specificity for fibrin may result in lysis of hemostatic plugs not only in coronary thrombi but also elsewhere in the body, thus promoting bleeding.

Early history of thrombolytic therapy

The discovery in 1933 by Tillett and Garner that the streptococcal protein Streptokinase lyases blood clots did not translate into a tool for the cardiologist until decades later. The first clinical indications for Streptokinase were management of proximal deep-vein thrombosis and severe pulmonary embolism. The earliest attempt to treat AMI with coronary fibrinolysis was a pilot study in 1959 by Fletcher and colleagues, who infused Streptokinase intravenously for 30 hours, starting 6 to 72 hours after onset of symptoms. However, Streptokinase available at the time was pyrogenic, and treatment was sometimes delayed too long to salvage myocardium. Efficacy could not be adequately documented by coronary arteriography, left ventricular function (LVF) could not be assessed with noninvasive modalities, and even the correlation between infarct size and prognosis was not apparent.

Despite these obstacles, several investigators persisted with Streptokinase thrombolysis in the 1960s and 1970s. By 1983, Schröder and colleagues had shown that intravenous administration of Streptokinase could restore coronary blood flow in patients with AMI.

Early (exogenous) thrombolytic agents

Streptokinase. Rather than enzymatically cleaving plasminogen (the mechanism of action of t-PA, Alteplase, and RETAVASE® (Reteplase), Streptokinase forms a complex that produces a conformational change in the plasminogen molecule. The plasminogen complex then converts noncomplexed plasminogen molecules to plasmin. The half-life of Streptokinase is approximately 30 minutes, with much of the circulating Streptokinase catalyzed before it can bind to polymerized fibrin.

Fig 1.—Binding of plasminogen to endogenous tissue plasminogen activator (t-PA) and fibrin.

Fibrinolysis

[Diagram showing the binding of plasminogen to fibrin and t-PA]
Streptokinase indiscriminately binds to both circulating and thrombus-associated plasminogen; this may result in plasminemia. While some excess plasmin is inactivated by α2-antiplasmin, the rest remains active. Thus, Streptokinase generates a systemic lytic state by depleting concentrations of circulating fibrinogen, plasminogen, procoagulant proteins, and α2-antiplasmin while inducing high plasma concentrations of fibrin degradation products.

Equilibrium is normally reached between free and bound plasminogen. By converting circulating plasminogen into plasmin, Streptokinase may create a systemic plasminogen deficit that draws fibrin-associated plasminogen out of the clot. The hypothesis is that this “plasminogen steal” may attenuate plasmin formation at the site of the thrombus and hinder the reopening of obstructed coronary arteries. The clinical significance of plasminogen steal has not been established.

Streptokinase use is associated with side effects, allergic reactions, and circulating antistreptokinase antibodies that have been associated with patient reactions with repeat administration of this agent.

**Anistreplase.** Anistreplase is an anisoylated derivative complex prepared from plasminogen and purified Streptokinase. The anisoyl group blocks activity until released by acylation in aqueous solution (a first-order nonenzymatic reaction), after which the complex forms. Deacetylated Anistreplase cleaves plasminogen with greater catalytic efficiency within thrombi than in the circulation. Anistreplase is indicated for management of AMI. After reconstitution with sterile water, it is administered as a single intravenous dose of 30 mg (either directly into a vein or through an intravenous line) over 2 to 5 minutes. Antibody formation against the streptococcal protein may occur with Anistreplase.

**Endogenous thrombolytic agents and synthetic analogues**

**Alteplase.** Alteplase, a mixture of one-chain and two-chain t-PA, is produced by means of recombinant technology. Alteplase is activated in the presence of fibrin. Therefore, it may elicit little plasminogen from the clot to replenish plasma levels. Moreover, plasmin formed in the thrombus may be less accessible to inhibitors such as α2-antiplasmin. Alteplase reduces plasma fibrinogen levels only slightly. It was demonstrated angiographically and clinically in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) study that Alteplase recanalizes arteries more frequently than Streptokinase.

Effective thrombolysis requires that Alteplase doses result in plasma levels of unbound drug capable of saturating the endogenous inhibitors. Alteplase is cleared rapidly by the liver, resulting in a half-life of 3 to 6 minutes. The rapid clearance of Alteplase from plasma is mediated by two domains: the epidermal growth factor and kringle-1 domains. Binding of these domains to liver receptors promotes elimination of the agent. Therefore, infusion is usually utilized to sustain therapeutic plasma concentrations of Alteplase.
Other issues and considerations for current thrombolytic therapy

Adjunctive anticoagulation. The activity of thrombolytic agents can be potentiated by the concurrent administration of aspirin for its antiplatelet effect and heparin for its anticoagulant effect. Aspirin has been recommended for coadministration with thrombolytic therapy since the Second International Study of Infarct Survival (ISIS-2), which showed benefit for aspirin when administered alone, as well as concurrently with Streptokinase. Without heparin, ongoing coagulation may outpace thrombolysis and result in a lower patency rate.

Heparin in conventional doses has a narrow therapeutic range. Whether used as the sole antithrombotic agent, the initiating agent, or an adjunctive anticoagulant, it is associated with a risk of serious bleeding in 1% to 8% of patients. This risk is compounded by coadministration of antiplatelet agents.

The Heparin-Aspirin Reperfusion Trial (HART), which compared early intravenous heparin with low-dose oral aspirin as adjunctive treatment with recombinant tissue plasminogen activator during AMI, found that t-PA and heparin treatment resulted in a higher rate of arterial patency (82%) after 7 to 24 hours than t-PA and aspirin treatment (52%). These study results suggest that early systemic heparin treatment should be administered during thrombolytic therapy with t-PA.

The addition of intravenous heparin to Streptokinase in GUSTO-I produced results no better than those with subcutaneous heparin. In combination with either intravenous or subcutaneous heparin, Streptokinase produced a lower incidence of stroke without decreasing mortality compared to accelerated-dose Alteplase dosing with intravenous heparin. Aspirin, on the other hand, is a valuable addition to Streptokinase, as seen in ISIS-2. In ISIS-3, the addition of heparin to aspirin was associated with an excess of transfused or other major noncerebral bleeds and of definite or probable cerebral hemorrhage.

Cost-effectiveness of thrombolysis. Any analysis of the cost-effectiveness of thrombolysis must consider not only the price of the agent used but also the total cost of care and the gain in survival. Aggressive intervention, even with the most expensive thrombolytic agents, may reduce costs in the long run by lessening both short- and long-term risks of CHF and other cardiac complications.
The open-artery hypothesis in thrombolysis

Early reperfusion and reduction in mortality

According to the open-artery hypothesis, reperfusion of ischemic areas as early as possible after the appearance of symptoms of AMI (ie, within 3 hours) is crucial for limiting infarct size, preserving left ventricular function, and improving the odds of survival.25

The rationale for rapid reopening is based on animal experiments: a smaller area of infarction was observed in animals in which transiently induced coronary occlusion was relieved by early reperfusion than in animals subjected to permanent occlusion.26

As a corollary to the open-artery hypothesis, early thrombolysis (with adjunctive treatment such as aspirin, anticoagulants, or coronary angioplasty) may recanalize obstructed coronary arteries and salvage jeopardized myocardium, while reducing progression to chronic CHF.

The open-artery hypothesis suggests that the use of thrombolytic agents that reopen occluded coronary arteries earlier and more completely in patients with AMI may translate into lower mortality. However, the correlation between patency and patient outcome has not been established.

Early clinical trials

TIMI-1. The Thrombolysis in Myocardial Infarction (TIMI-1) Study27 in 1985 was the first trial to demonstrate that Alteplase is more effective than Streptokinase in reopening occluded coronary arteries. In this randomized trial, 90-minute angiography in 290 patients demonstrated that Alteplase achieved significantly higher rates of patency and complete perfusion than Streptokinase.27

ECSG-1. The European Cooperative Study Group (ECSG-1) observed a patency rate of 70% in 64 patients randomized to Alteplase and 55% in 65 patients randomized to Streptokinase (P=0.054).28 These data suggested that perfusion achieved late after the onset of the symptoms of AMI may not preserve ischemic myocardium, since prolonged ischemia damages not only the muscle but also the associated microvasculature.

Large-scale trials

GISSI-1. The Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI-1) was a milestone study that established the value of thrombolytic therapy for patients with AMI. GISSI-1 was the first large-scale (N=11,806) study to demonstrate a significant reduction in mortality achieved with Streptokinase thrombolysis compared to placebo.29

ISIS-2. In ISIS-2, another large-scale (N=17,187) trial, a combination regimen of Streptokinase and aspirin was shown to reduce cumulative vascular mortality (deaths from cardiac, cerebral, hemorrhagic, or other known vascular disease) in the first 35 days more effectively than either aspirin or Streptokinase monotherapy or placebo.21
Clinical megatrials: implications for the open-artery hypothesis

GISSI-2. The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI-2) study was the first large-scale trial to assess the comparative effects of Streptokinase 1.5 MU infused intravenously over 30 to 60 minutes and Alteplase 100 mg infused intravenously over 3 hours. In this multicenter, randomized, open trial in 12,490 patients with AMI admitted to coronary care units within 6 hours from onset of symptoms, half the patients were also randomized to receive 12,500 U of heparin subcutaneously twice daily, starting 12 hours after beginning thrombolytic therapy.

Fig 2.—Cumulative mortality (%) in days 0 to 35 in ISIS-3 and GISSI-2.

(A) Death in ISIS-3
SK: 1,455/13,780 (10.6%)
AP SAC: 1,448/13,773 (10.5%)

(B) Death in ISIS-3
SK: 1,455/13,780 (10.6%)
rt-PA: 1,418/13,746 (10.3%)

(C) Death in GISSI-2
SK: 958/10,396 (9.2%)
rt-PA: 993/10,372 (9.6%)

(D) Death in ISIS-3 and GISSI-2
SK: 2,413/24,176 (10.0%)
rt-PA: 2,411/24,118 (10.0%)

SK = Streptokinase; APSAC = Anistreplase; rt-PA = Alteplase/Duteplase.

(A) All patients allocated SK vs all allocated APSAC in ISIS-3 only; (B, C, D) all patients allocated SK vs all allocated rt-PA in (B) ISIS-3; (C) GISSI-2; (D) ISIS-3 and GISSI-2 combined.

– Adapted from ISIS-3.24
Atenolol (45.3%) and aspirin (87%) were administered to patients without contraindications. There was no significant difference in overall mortality in the Alteplase-treated patients (9%) and the Streptokinase group (8.6%). There was also no significant difference in the combined end point of death plus clinical CHF or extensive left ventricular damage in the absence of CHF.30

**International Study Group.** The International Study Group combined mortality data from the 12,490 patients in the GISSI-2 trial30 with data from 8,401 patients recruited in other countries. Again, no significant differences in hospital mortality were found between Alteplase (8.9%) or Streptokinase (8.5%) or between subcutaneous heparin (8.5%) and no heparin (8.9%) treatment.31

**ISIS-3.** In the Third International Study of Infarct Survival (ISIS-3), 41,299 patients entering 914 hospitals up to 24 hours after the onset of suspected AMI were randomized to Streptokinase, 1.5 MU infused over 1 hour; Duteplase (a double-chain t-PA), 0.04 MU/kg bolus over 1 minute, 0.36 MU/kg during the remainder of the first hour, and 0.067 MU/kg/h over the next 3 hours; or Anistreplase (30 U over 3 minutes).24 All patients received aspirin, and half also received 12,500 IU of calcium heparin, starting 4 hours after randomization and given subcutaneously twice daily for 7 days. Cumulative deaths during days 0 to 35 are shown in Fig 2. There were no significant differences in mortality between any two groups (10.6% Streptokinase, 10.5% Anistreplase, 10.3% Duteplase). There were also no significant differences in 35-day mortality between the aspirin only (10.6%) and aspirin plus heparin (10.3%) treated patients.24

**GUSTO-I.** The GUSTO-I study,17 the largest megatrial comparing the effect of Alteplase and Streptokinase on mortality (41,021 patients with confirmed AMI treated at 1,081 hospitals in 15 countries), differed in several important respects from the ISIS and GISSI trials.

In the GUSTO-I study, the accelerated-dose or “front-loaded” Alteplase regimen was given as an initial bolus, followed by a 90-minute infusion, with two thirds of the dose given in the first 30 minutes. This dosing regimen was designed to improve perfusion rates. In another departure from previous megatrials, heparin was given by bolus followed by intravenous infusion, rather than subcutaneously, and was continued for at least 48 hours to limit fibrin formation that might produce reocclusion. Similar to GISSI-2, patients in GUSTO-I were admitted within 6 hours after the onset of symptoms. In ISIS-2 and ISIS-3, however, patients were included up to 24 hours after onset of symptoms.

Patients in the GUSTO-I trial were randomized to one of four treatment regimens:

- Alteplase (bolus dose of 15 mg, followed by an infusion of 0.75 mg/kg over 30 minutes, not to exceed 50 mg, and 0.5 mg/kg, up to 35 mg, over the next 60 minutes) plus intravenous heparin
- Streptokinase and intravenous heparin
- Streptokinase and subcutaneous heparin
- Both thrombolytics together plus intravenous heparin

The primary clinical end point of 30-day mortality was 6.3% in patients receiving accelerated-dose Alteplase plus intravenous heparin, compared to 7.2% and 7.4% for the two Streptokinase groups (Table 2 and Fig 3).17 There was a significant reduction in mortality with accelerated-dose Alteplase compared with the two Streptokinase regimens (10 lives saved per 1,000 patients treated; risk reduction, 14%). The GUSTO-I trial adds to a growing body of evidence in support of the open-artery hypothesis.

In the GUSTO-I Angiographic Investigators substudy, 2,431 of the patients randomized to the four treatment regimens were assigned to undergo cardiac angiography at 90 minutes, 180 minutes, 24 hours, or 5 to 7 days after the initiation of thrombolytic therapy; angiography was repeated after 5 to 7 days in the 90-minute group.19 The rate
of patency of the infarct-related artery at 90 minutes was highest in the Alteplase plus heparin group (81%), compared with the Streptokinase and subcutaneous heparin group (54%, \( P < 0.001 \)), the Streptokinase and intravenous heparin group (60%, \( P < 0.001 \)), and the combination therapy group (73%, \( P = 0.032 \)). By 180 minutes, the four groups had similar patency rates and reocclusion rates. Left ventricular function, which paralleled patency rate at 90 minutes, was best in the Alteplase group and in patients with normal flow, regardless of treatment. Mortality at 30 days was lowest (4.4%) among patients with complete coronary flow at 90 minutes and highest (8.9%) among patients with no flow in the infarct-related artery (\( P = 0.009 \)). The investigators suggested that the mechanism by which accelerated-dose Alteplase therapy produced a superior outcome in the GUSTO-I trial was its more complete restoration of flow through the infarct-related artery than Streptokinase, which in turn resulted in improved ventricular performance and lower mortality due to AMI.18

### Table 2.—Major Clinical Outcomes in GUSTO-I

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Streptokinase and Subcutaneous Heparin (n = 9,796)</th>
<th>Streptokinase and IV Heparin (n = 10,377)</th>
<th>Accelerated-Dose Alteplase and IV Heparin (n = 10,344)</th>
<th>Both Thrombolytic Agents and IV Heparin (n = 10,328)</th>
<th>( P ) Value, Accelerated-Dose Alteplase vs Both Streptokinase Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hour mortality</td>
<td>2.8</td>
<td>2.9</td>
<td>2.3</td>
<td>2.8</td>
<td>0.005</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>7.2</td>
<td>7.4</td>
<td>6.3</td>
<td>7.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Or nonfatal stroke</td>
<td>7.9</td>
<td>8.2</td>
<td>7.2</td>
<td>7.9</td>
<td>0.006</td>
</tr>
<tr>
<td>Or nonfatal hemorrhagic stroke</td>
<td>7.4</td>
<td>7.6</td>
<td>6.6</td>
<td>7.4</td>
<td>0.004</td>
</tr>
<tr>
<td>Or nonfatal disabling stroke</td>
<td>7.7</td>
<td>7.9</td>
<td>6.9</td>
<td>7.6</td>
<td>0.006</td>
</tr>
</tbody>
</table>

– From GUSTO Investigators.17

### Fig 3.—Mortality (30 days) in the four treatment groups of GUSTO-I.
**SECTION IV**

**RETAVASE® (Retepase)**

**preclinical pharmacology**

**RETAVASE: a novel thrombolytic agent for acute myocardial infarction**

Various thrombolytic agents are in development for potential improvements in half-life, mode of administration, fibrin specificity, and proteolytic activity. RETAVASE is the first available agent using selected domains from the native t-PA molecule. The molecule consists of the kringle-2 and protease domains of native t-PA and shows predilection for fibrin-bound plasminogen. RETAVASE possesses important pharmacokinetic and mechanistic features that contribute to the feasibility of a double-bolus dosing regimen and restoration of flow in AMI patients.

**Description**

RETAVASE is a plasminogen activator whose design was based on naturally occurring t-PA and is produced by recombinant genetic technology in E coli. It is prepared as a white, sterile, lyophilized powder for intravenous bolus injection after reconstitution with Sterile Water for Injection, USP (without preservatives). The potency standard for RETAVASE, expressed in units (U), is not comparable to that for other thrombolytics. RETAVASE is supplied as a 10.8 U vial to ensure sufficient drug for administration of each 10 U dose. Each vial of the lyophilized product contains 18.8 mg of RETAVASE, along with arginine, phosphoric acid, and polysorbate 20 as inactive ingredients.

**Biochemistry: a recombinant plasminogen activator**

RETAVASE is a nonglycosylated recombinant plasminogen activator. It is a single-chain molecule that consists of 355 amino acids corresponding to coding sequences 1 to 3 and 176 to 527 of native t-PA. Expression in *E coli* results in a nonglycosylated protein, which accumulates inside cells as inactive inclusion bodies that must be refolded in vitro and purified to restore the native structure.

The RETAVASE gene lacks the complementary DNA sequence coding for the three N-terminal (finger, epidermal growth factor, and kringle-1) domains found in native t-PA but retains the kringle-2 and serine protease domains in a functional form. The domain structures of the Alteplase and RETAVASE molecules are shown in Fig 4 on page 18, and the structure-function relationships of these domains are shown in Table 3 on page 19.

Alteplase retains the kringle-1 and epidermal growth factor domains deleted from RETAVASE. Alteplase binds to liver receptors by means of these domains, thereby facilitating hepatic clearance. Oligosaccharide side chains retained by Alteplase and not by RETAVASE also influence clearance. These deletions from the RETAVASE molecule provide a longer half-life than that of Alteplase, with two consequences: (1) less drug is required to maintain therapeutic levels and (2) RETAVASE can be administered by intravenous bolus over a period of 2 minutes.
RETA V ASE differs further from Alteplase in that it lacks the finger domain, a fibronectin-like projection that promotes high-affinity fibrin binding. The RETA V ASE molecule is also specific for plasminogen bound to fibrin, but its affinity to fibrin is lower than that of Alteplase. RETA V ASE may activate plasminogen at the surface as well as in the interior of the thrombus.

In vitro catalytic activity and fibrin binding

RETA V ASE has approximately 20% to 30% of the in vitro plasminogenolytic potency of Alteplase as determined by a standard in vitro assay in which each activator is incubated with plasminogen in the presence of cyanogen bromide (CNBr) split products (fragments) of fibrinogen that serve as a stimulator. RETA V ASE, like Alteplase, is cleaved by plasmin specifically at the Arg\textsuperscript{275}-Ile\textsuperscript{276} bond, indicating that the protease and kringle-2 domains have the same structure as in native t-PA. Both RETA V ASE and Alteplase lose activity in a similar manner when incubated with increasing levels of PAI-1.
Besides its lower plasminogenolytic activity in the presence of a stimulator, RETAVASE* (Reteplase) does not bind to fibrin like Alteplase.32 In vitro fibrin binding was analyzed by adding RETAVASE or Alteplase to a newly forming clot in a test tube and measuring binding in response to increasing amounts of fibrin. As shown in Fig 5, Alteplase is nearly 100% bound by 200 µg of fibrin, while only 20% of RETAVASE is found in the clot fraction. The amount of RETAVASE in the clot fraction increases at higher fibrin concentrations, possibly because of a nonspecific protein-protein interaction. Thus, throughout the range of fibrin concentration from 0 to 1,000 µg, the binding of RETAVASE ranges from about 10% to 30% of that of Alteplase. The lower catalytic activity and fibrin binding of RETAVASE relative to Alteplase may be due to the missing finger domain. This leaves only the kringle-2 lysine-binding site as the focus of the interaction between RETAVASE and fibrin.20,32

**Table 3.—Structure-Function Relationships of Native t-PA Domains**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>F domain</td>
<td>High-affinity fibrin binding</td>
</tr>
<tr>
<td>(finger, fibronectin-like)</td>
<td></td>
</tr>
<tr>
<td>E domain (epidermal growth factor-like domain)</td>
<td>Receptor binding (liver)</td>
</tr>
<tr>
<td>K_1 domain (kringle-1)</td>
<td>Liver receptor binding(?) Fibrin binding(?)</td>
</tr>
<tr>
<td>K_2 domain (kringle-2)</td>
<td>Low-affinity interaction with fibrin (stimulation effect by fibrin)</td>
</tr>
<tr>
<td>P domains</td>
<td>Protease function (plasminogen specific)</td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Mediation of t-PA plasma clearance (half-life)</td>
</tr>
</tbody>
</table>

**Fig 5.—In vitro fibrin binding of RETAVASE* (Reteplase) and Alteplase in the presence of increasing fibrin concentrations.**
Fig 6 is a comparison of concentration-dependent in vitro clot lysis by RETAVASE, Alteplase, melanoma t-PA (which differs from Alteplase in carbohydrate side chains), and Urokinase, based on the method of Collen et al.35 Lytic activity is represented by the percentage of radioactivity released from iodine 125 (125I) radiolabeled fibrinogen plasma clots after 4 hours of incubation with RETAVASE or one of the three comparative agents.32 These data show that RETAVASE had the same maximal lytic activity as Alteplase at equipotent concentrations, despite a lower in vitro potency. RETAVASE is less active than Alteplase in lysis of platelet-rich plasma clots and aged clots.36 This diminished activity of RETAVASE toward old thrombi may reduce lysis of hemostatic plugs, which are thought to be older clots that seal small vessel wall injuries.37

**In vivo animal studies showed greater potency of RETAVASE than Alteplase**

**Jugular vein thrombolysis in rabbits.** The in vivo thrombolytic activity of RETAVASE was studied in rabbits and dogs. In the rabbit model of jugular vein thrombosis, the RETAVASE effective dose for 50% lysis (ED50) was 5.3-fold more potent per unit than the Alteplase ED50.32 The investigators attributed the greater in vivo potency of RETAVASE to its lower clearance rate. An important conclusion of this study is that the relative in vitro potencies of Alteplase and RETAVASE are reversed in animals.

---

**The paradox: in vivo and in vitro profile reversal**

- The in vitro potency (specific activity) of RETAVASE as determined by plasminogenolytic assay is lower than that of Alteplase by a factor of 2 or 3
- RETAVASE is significantly more potent than Alteplase in in vivo models
- The slower hepatic clearance and longer plasma half-life of RETAVASE may explain this reversal

---

Adapted from Martin et al.35
Greater activity in coronary thrombolysis in dogs. The activity of RETAVASE in inducing coronary reperfusion was investigated in open-chested anesthetized dogs in which electrical injury to the intima of the left circumflex coronary artery was used to simulate AMI. A double-bolus intravenous regimen of RETAVASE proved to be superior (*P* < 0.05) to a single bolus in stabilizing coronary artery blood flow and reducing reocclusion, but doubling the dose of a single bolus did not have this effect. The total plasma clearance rate of RETAVASE was at least three times lower than that of Alteplase, suggesting that this contributed to the greater thrombolytic potency of RETAVASE.

In another study utilizing the same canine model, RETAVASE was shown to induce reperfusion significantly more rapidly than Alteplase, Anistreplase, Streptokinase, and Urokinase when administered at clinically equivalent doses (Fig 7). Pharmacokinetics: clearance through liver and kidneys. The pharmacokinetic properties of RETAVASE were extensively studied in rats, rabbits, dogs, and nonhuman primates. Half-life and total plasma clearance parameters for RETAVASE in comparison with Alteplase in humans are shown in Table 4. Based on the mean liver uptake of the respective injected doses, hepatic clearance accounts for much less of the total plasma clearance of RETAVASE than for Alteplase in all species studied. RETAVASE is cleared mainly by the kidneys, although inhibitory proteins in the blood contribute to RETAVASE clearance through biochemical inactivation.

### Table 4.—Pharmacokinetic Properties of RETAVASE* (Reteplase) in Plasma Following Intravenous Bolus Injection

<table>
<thead>
<tr>
<th>Dose</th>
<th>N</th>
<th><em>t</em>&lt;sub&gt;½&lt;/sub&gt; (min)</th>
<th><em>t</em>&lt;sub&gt;β&lt;/sub&gt; (min)</th>
<th>CL (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 U (10.4 mg)</td>
<td>7</td>
<td>13.9 ± 0.7</td>
<td>173 ± 33</td>
<td>183 ± 15</td>
</tr>
<tr>
<td>10 U (18 mg)</td>
<td>4</td>
<td>19.2 ± 1.0</td>
<td>375 ± 34</td>
<td>104 ± 11</td>
</tr>
<tr>
<td>15 U (27 mg)</td>
<td>10</td>
<td>18.8 ± 0.8</td>
<td>377 ± 20</td>
<td>139 ± 21</td>
</tr>
</tbody>
</table>

Mean ± SEM. *t*<sub>½</sub> = half-life; CL = total plasma clearance. — From Martin et al. 32
Toxicology showed no internal bleeding, even at highest dose. The effect of RETAVASE® (Reteplase) on platelets, bleeding times, and plasma proteins was studied in rats, rabbits, and dogs. Pharmacologically effective doses produced a dose-dependent reduction in fibrinogen, plasminogen, and a2-antiplasmin 2 hours post-injection. In a 14-day subchronic toxicity study in cynomolgus monkeys, all dose levels induced unilateral focal hemorrhages that correlated with low red blood cell counts, but internal hemorrhaging did not develop, even at the highest dose.

Mutagenicity was not detectable in *Salmonella typhimurium* or in rat bone marrow erythrocytes tested in vivo for 2 weeks with daily intravenous administration of doses up to 1.4 U/kg. No adverse effects on reproduction or fetal development were seen at doses of 4.3 U/kg in rats. The minimum lethal dose of RETAVASE (from hemorrhage and/or hypotension) in rats, rabbits, and monkeys exceeds 8.4 U/kg given as a single injection; no deaths occurred in animals receiving 4.2 U/kg.

**Summary of preclinical findings.** The preclinical pharmacology studies demonstrate that RETAVASE has more potent in vivo thrombolytic activity than Alteplase on both a dose and molar basis, which contrasts with the results of in vitro studies. RETAVASE induces more rapid reperfusion than other thrombolytic agents in animal models of coronary thrombosis. Reperfusion is significantly more rapid after intravenous bolus injection than after infusion, and a double bolus is significantly more active in stabilizing coronary artery blood flow and preventing reocclusion.
SECTION V

RETAVASE® (Reteplase) clinical pharmacology

Well-tolerated hemostatic and fibrinolytic effects

The hemostatic and fibrinolytic properties of RETAVASE were investigated in a Phase I dose-ranging study in 18 healthy male volunteers. Intravenous bolus doses ranging from 0.11 U to 5.5 U given over 2 minutes did not alter plasma fibrinogen levels except at the higher doses. However, a 2-antiplasmin and fibrin D-dimers decreased in a dose-dependent fashion. RETAVASE was well tolerated, and antibodies to RETAVASE did not appear in plasma samples taken up to 1 year after the study.

A single intravenous bolus dose of 6 U (10.4 mg) of RETAVASE or placebo was given over 2 minutes to seven healthy male volunteers in another Phase I study, this time using a randomized, single-blind, placebo-controlled, crossover design. Fibrinogen levels were unchanged by RETAVASE. Plasminogen and a 2-antiplasmin levels, however, were reduced to 83% and 64%, respectively, of baseline values, probably reflecting a systemic activation of the fibrinolytic system. RETAVASE was well tolerated, and antibodies to RETAVASE were not detected.

Dose-response restoration of coronary flow in patients with AMI

The hemostatic and fibrinolytic effects of RETAVASE doses were evaluated in patients with AMI. The effects of RETAVASE on fibrinogen, plasminogen, a 2-antiplasmin, fibrin degradation products (FDP, as represented by fibrin-specific D-dimers), and fibrinogen degradation products (FgDP) in the two German Recombinant Plasminogen Activator Studies in patients with AMI (GRECO and GRECO-DB) are summarized in Table 5. At 2 hours after administration (2-hour values were chosen because they represent the strongest effects), mean values of fibrinogen were approximately 45% of baseline for the 15 U and 10 + 5 U regimens and 60% of baseline for the 10 U regimen. The higher doses used in the GRECO studies resulted in a greater reduction in plasminogen and a 2-antiplasmin and a greater increase in D-dimers and FgDP. The 15 U and the 10 + 5 U regimens had a greater effect on these parameters than the 10-U regimen, suggesting dose dependency.

Administration of RETAVASE in the GRECO-DB (double bolus) study caused the median fibrinogen level to decrease from a baseline of 286 mg/dL to 63% of this value at 24 hours (Fig 8).

Table 5.—Hemostatic and Fibrinolytic Parameters at 2 Hours in the GRECO and GRECO-DB Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>10 U RETAVASE (n = 38-41)</th>
<th>15 U RETAVASE (n = 66-99)</th>
<th>10 + 5 U RETAVASE (n = 43-49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>60</td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td>Plasminogen</td>
<td>55</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>α2-antiplasmin</td>
<td>30</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>D-dimers</td>
<td>2,940</td>
<td>5,709</td>
<td>5,986</td>
</tr>
<tr>
<td>FgDP</td>
<td>10,449</td>
<td>19,507</td>
<td>42,611</td>
</tr>
</tbody>
</table>

FgDP = fibrinogen degradation products. – Data on file.
Pharmacokinetics in healthy volunteers

The pharmacokinetics of RETAVASE were evaluated in three studies in healthy volunteers. Drug was administered by IV injection over 2 minutes in each study. Plasma concentrations of RETAVASE antigen, ie, protein, were measured using a monoclonal antibody enzyme-linked immunosorbent assay. A plasminogenolytic activity assay based on the method of Verheijen et al41 was used to measure the more relevant active concentrations.

In one of the studies, seven subjects received a single intravenous 6.0 U bolus dose of RETAVASE.20 The activity half-life was 11.2±0.4 min and the antigen half-life was 13.9±0.7 min (2.4 mL/min/kg), followed by a terminal antigen half-life of 173±33 min. Plasma clearance was 371±13 mL/min (4.9 mL/min/kg) for activity in plasma (ie, effect on fibrin) and 183±5 mL/min (2.4 mL/min/kg) for antigen. The half-life and clearance of RETAVASE activity were 3.3-fold longer and 3.3-fold lower, respectively, than in volunteers who received Alteplase in a study by Seifried et al.42 In addition, the half-life and clearance for antigen were 4.2-fold longer and 3.9-fold lower, respectively.42

In another study, 18 volunteers received sequential doses of RETAVASE between 0.11 U and 5.5 U.38 Plasma AUC and Cmax showed dose-dependent linear increases. Clearance was 406±40 mL/min (4 mL/min/kg), and half-life for the 5.5 U dose was 14.4±1 min.

Data from the studies in healthy subjects demonstrate that RETAVASE pharmacokinetics are linear over the dose range of 0.11 to 5.5 U. Plasma concentrations of RETAVASE antigen persist for a longer period of time than do those of activity.

Pharmacokinetics in AMI

The pharmacokinetics of RETAVASE in patients with AMI were evaluated using subsets of patients in two trials. In the GRECO study, doses were administered as single boluses of 10 U or 15 U;39 in MF4292, patients received a single bolus of 15 U or a double bolus of either 10 + 5 U or 10 + 10 U.34 The mean RETAVASE plasma concentrations (activity) for the two studies are shown in Fig 9 and Fig 10.
Linear pharmacokinetics

The pharmacokinetics of RETAVASE in patients with AMI as well as in healthy volunteers are linear over the dose range of 0.11 to 20 U and do not appear to be affected by the target disease. The effective half-life of RETAVASE is 13 to 16 minutes. Plasma antigen concentrations persist for a longer period than plasma activity. This is not unexpected, since the antigen assay measures all RETAVASE-related protein, not all of which is active RETAVASE.
RETAVASE® (Reteplase) clinical efficacy and activity

Six clinical trials of significance have identified the appropriate dose and demonstrated the efficacy and safety of RETAVASE as therapy for AMI. Three were Phase II dose-finding studies (without comparative agents) evaluating the activity of RETAVASE in restoring blood flow through the infarct-related artery (Table 6). Three comparative studies were performed to compare RETAVASE with Streptokinase (INJECT) or Alteplase (RAPID 1 and RAPID 2) (Table 7). Two of these, RAPID 2 and INJECT, were Phase III studies, while RAPID 1 was a Phase II study.

### Table 6.—Non-Comparative Studies in Patients With AMI

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Location</th>
<th>Study Design</th>
<th>Population</th>
<th>Dose Strength and Form</th>
<th>Frequency, Duration</th>
<th>Number of Patients</th>
<th>Primary Key</th>
<th>Key Entry Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRECO39</td>
<td>Germany</td>
<td>OL</td>
<td>AMI patients</td>
<td>10 U RP</td>
<td>Single bolus</td>
<td>42</td>
<td>90-minute ST segment patency and elevation</td>
<td>ST segment elevation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15 U RP</td>
<td>Single bolus</td>
<td>100</td>
<td>90-minute ST segment patency and TIMI 3 rates</td>
<td>Onset of ischemic pain within 6 hours</td>
</tr>
<tr>
<td>GRECO-DB40</td>
<td>Germany</td>
<td>OL</td>
<td>AMI patients</td>
<td>10 + 5 U RP</td>
<td>Double bolus</td>
<td>51</td>
<td>90-minute patency and TIMI 3 rates</td>
<td>ST segment elevation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Onset of ischemic pain within 6 hours</td>
<td>Onset of ischemic pain within 6 hours</td>
</tr>
<tr>
<td>MF429234</td>
<td>Germany</td>
<td>R, OL</td>
<td>AMI patients</td>
<td>15 U RP</td>
<td>Single bolus</td>
<td>9</td>
<td>90-minute patency and TIMI 3 rates, hemostasis parameters</td>
<td>ST segment elevation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 + 5 U RP</td>
<td>Double bolus</td>
<td>8</td>
<td>Onset of ischemic pain within 6 hours</td>
<td>Onset of ischemic pain within 6 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 + 10 U RP</td>
<td>Double bolus</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

OL = open label; R = randomized; RP = Reteplase.
The six studies evaluated four different dosage regimens of RETAVASE™ (Reteplaes):

- Single 10 U bolus
- Single 15 U bolus
- 10 U bolus followed by a 5 U bolus 30 minutes later (10 + 5 U)
- 10 U bolus followed by a 10 U bolus 30 minutes later (10 + 10 U).

Each bolus was administered as a slow intravenous injection over an interval not exceeding 2 minutes. Of the 3,805 patients treated with RETAVASE, 3,292 received the 10 + 10 U regimen.

Dose-finding trials determined patency of infarct-related arteries

GRECO. This was a sequential rising-dose study that enrolled 142 patients with AMI who presented less than 6 hours after the onset of symptoms.³⁹ RETAVASE was given as a single 10 U bolus to the first 42 patients and as a 15 U bolus to the next 100 patients. Patients also received an intravenous bolus of heparin immediately after the bolus dose of RETAVASE, and aspirin was given daily throughout the study. Nitroglycerin was administered intravenously unless hemodynamically contraindicated.
Activity was evaluated by means of angiographically determined patency of infarct-related arteries. Coronary arteriography of the presumed infarct-related artery was conducted 30 and 90 minutes after the bolus injection of RETAVASE™ (Reteplase, recombinant) and repeated at 24 to 48 hours and prior to discharge at 14 to 21 days. Patency was assessed by TIMI flow grade and had to be rated as grade 2 or 3 by two independent, experienced investigators.

The patency rate (TIMI 2 + 3 flow) at 90 minutes for the single-bolus 10 U dose group was 66%. Since the 66% was below the predetermined 70% lower limit of activity for Alteplase in the TIMI trial, the next 100 patients received a single bolus of 15 U. The 90-minute patency rate in these patients was increased to 75% and the TIMI 3 rate alone was 69% (Fig 11), a result similar to that associated with Alteplase thrombolysis.

**GRECO-DB.** A second bolus of RETAVASE maintained patency of coronary arteries. While the GRECO study demonstrated that single-bolus administration of RETAVASE could lead to high patency rates in patients with AMI, fluctuations were observed in the early angiograms. In some patients, infarct-related arteries that were patent at 30 or 60 minutes became reoccluded at 90 minutes.

In GRECO-DB, patients received an initial 10 U bolus of RETAVASE followed by 5 U of RETAVASE 30 minutes later. The purpose of this double bolus was to optimize perfusion of the infarct-related artery and maintain patency during the 24 to 48 hours and prior to discharge at 14 to 21 days.

### The TIMI flow grades

Since the TIMI trial, coronary flow after reperfusion therapy has been classified by TIMI angiographic grade.

- TIMI 0: no penetration of contrast medium beyond the thrombus
- TIMI 1: minimal penetration; no significant flow
- TIMI 2: restored but sluggish flow
- TIMI 3: brisk flow

---

Fig 11.—Patency of infarct-related arteries in the GRECO study.

- Adapted from Neuhaus et al.39
the early phase of thrombolysis by sustaining the RETAVASE™ (Reteplase, recombinant) plasma level. Otherwise, the protocol was similar to GRECO.

Fifty-one patients were treated with the 10 + 5 U RETAVASE regimen, and 50 underwent angiography (Table 8). The 90-minute patency rate (TIMI 2 + 3 flow) of 78% was slightly higher than the 75% observed with the 10 + 5 U regimen in GRECO; the TIMI 3 rate was 58%, compared with 69% in GRECO.

### Comparative clinical trials

The safety and efficacy of RETAVASE were evaluated in three controlled clinical trials in which RETAVASE was compared to other thrombolytic agents. INJECT compared RETAVASE to Streptokinase to assess the relative effects on 35-day mortality rates. RAPID 1 and RAPID 2 were both angiographic trials comparing the effect on coronary patency of RETAVASE and Alteplase (see Section VIII beginning on page 37).

**INJECT establishes efficacy of RETAVASE™ (Reteplase, recombinant) in reducing mortality**

INJECT was a randomized, double-blind, Phase III multicenter study designed to confirm that RETAVASE was effective in reducing mortality in AMI. In INJECT, RETAVASE was compared to Streptokinase, the standard thrombolytic agent in Europe. The trial was not powered, however, to statistically detect modest differences between the two agents. The goal of the study was to demonstrate the efficacy and safety of RETAVASE. The 35-day mortality rate of RETAVASE was compared to the standard Streptokinase regimen.

A total of 5,936 patients in nine European countries received thrombolytic therapy no later than 12 hours after the onset of symptoms of AMI. There was no upper age limit. A total of 2,965 patients randomized to RETAVASE 10 + 10 U (the second injection given 30 minutes after the first) and 2,971 patients randomized to a 1.5 MU infusion of Streptokinase over 60 minutes were assessable. All patients received intravenous heparin for at least 24 hours. Patients were given 250 mg to 350 mg aspirin, then 75 mg to 150 mg daily.

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**Table 8.—Patency of Infarct-Related Arteries in GRECO-DB**

<table>
<thead>
<tr>
<th>Patency Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiogram at 30 minutes (n = 48)</td>
</tr>
<tr>
<td>TIMI grade 2 or 3</td>
</tr>
<tr>
<td>TIMI grade 3</td>
</tr>
<tr>
<td>Angiogram at 60 minutes (n = 50)</td>
</tr>
<tr>
<td>TIMI grade 2 or 3</td>
</tr>
<tr>
<td>TIMI grade 3</td>
</tr>
<tr>
<td>Angiogram at 90 minutes (n = 50)</td>
</tr>
<tr>
<td>TIMI grade 2 or 3</td>
</tr>
<tr>
<td>TIMI grade 3</td>
</tr>
<tr>
<td>Angiogram at 24 to 48 hours (n = 50)</td>
</tr>
<tr>
<td>TIMI grade 2 or 3</td>
</tr>
<tr>
<td>TIMI grade 3</td>
</tr>
<tr>
<td>Angiogram at 14 to 21 days (n = 49)</td>
</tr>
<tr>
<td>TIMI grade 2 or 3</td>
</tr>
<tr>
<td>TIMI grade 3</td>
</tr>
</tbody>
</table>

TIMI = Thrombolysis in Myocardial Infarction trial. — From Tebbe et al.40
Results

The 35-day study mortality rates are shown in Fig 12, and the Kaplan-Meier survival curves over the 35-day interval are depicted in Fig 13. Mortality at day 35 in patients who received study medication was 8.90% in the RETAVASE group and 9.43% in the Streptokinase group, a difference of 0.53%.

These data provide confirmation that RETAVASE is effective in reducing mortality after AMI.

At 6 months, mortality rates (Kaplan-Meier estimate) were 11.02% for RETAVASE and 12.05% for Streptokinase, a difference of 1.03%. These results provide further evidence that RETAVASE is effective in reducing mortality after AMI.

---

Fig 12.—35-day mortality rates in the INJECT study.

![Bar chart showing 35-day mortality rates for RETAVASE and Streptokinase.]

- RETAVASE™ (Reteplase, recombinant) 10 U + 10 U (n = 2,965)
- Streptokinase 1.5 MU/60 min (n = 2,971)

Difference in mortality: RETAVASE – Streptokinase = −0.53% (90% CI: −1.76% to 0.71%).

---

Fig 13.—Kaplan-Meier survival curves from day 0 to 35 in INJECT.

![Kaplan-Meier curves showing mortality from day 0 to 35 for RETAVASE and Streptokinase.]

- RETAVASE
- Streptokinase

---

Adapted from INJECT.
**INJECT substudy demonstrates early resolution of ST segment elevation**

INJECT investigators conducted an exploratory substudy among the 1,909 patients in Germany to evaluate the prognostic power of early resolution of ST segment elevation.44

ST segment elevation was classified as achieving complete (≥70%), partial (30% to 70%), or no (0% to 30%) resolution after 3 hours of thrombolytic therapy.44

Results irrespective of therapy showed that the 35-day mortality rate in 1,398 patients with infarct age ≤6 hours for complete, partial, or no ST resolution was 2.5%, 4.3%, and 17.5%, respectively (P<0.0001).44 As can be seen in Table 9, RETAVASE™ (Reteplase, recombinant) achieved complete or partial ST segment resolution in 82% of patients at 3 hours.44 Although the authors concluded that resolution of ST segment elevation may correlate with mortality, the correlation with mortality and other patient outcomes was not established.

### Table 9.—Percentages of RETAVASE® (Reteplase) Patients in INJECT With Complete, Partial, or No ST Segment Elevation Resolution

<table>
<thead>
<tr>
<th>ST resolution (%)</th>
<th>All Patients</th>
<th>Anterior MI</th>
<th>Inferior MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>RETAVASE (n = 692)</td>
<td>RETAVASE (n = 318)</td>
<td>RETAVASE (n = 374)</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>51</td>
<td>36</td>
<td>65</td>
</tr>
<tr>
<td>Partial</td>
<td>31</td>
<td>43</td>
<td>22</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>22</td>
<td>14</td>
</tr>
</tbody>
</table>

MI = myocardial infarction. — From Schröder et al.44
GUSTO-III: a large-scale, mortality trial versus Alteplase

The accelerated-dose Alteplase regimen provided a 14% relative reduction in mortality from AMI over Streptokinase in the GUSTO (now known as GUSTO-I) trial in 1993. The most plausible explanation is that Alteplase achieved a higher TIMI 3 flow rate in infarct-related coronary arteries, thus supporting the open-artery hypothesis. Impressive as these results may seem, however, analysis of angiograms taken 90 minutes after the start of therapy reveals that only 54% of the Alteplase-treated patients actually attained TIMI 3 flow. This suggests that further increases in 30-day survival may be achieved if greater reopening of occluded arteries is also achieved. Moreover, once achieved, the patency should be sustained, since the initial benefit may be attenuated by subsequent reocclusion.

As discussed in Section VIII beginning on page 37, the RAPID 2 trial showed differences in patency between Reteplase™ (Reteplase, recombinant) and Alteplase. Direct comparison of these two agents for their effects on mortality was the logical next step.

In recognition of the need for additional study, the GUSTO-III (Global Use of Strategies to Open Occluded Coronary Arteries) trial was initiated in October 1995 with plans of enrolling approximately 15,000 patients of any age who present within 6 hours of the onset of symptoms of an AMI. Patients were randomized in a 2:1 ratio, 10,000 to the double-bolus Reteplase regimen and 5,000 to the accelerated-dose Alteplase regimen (Fig 14).

---

**Fig 14.—GUSTO-III protocol algorithm.**

Identify eligible patient

Aspirin 150-325 mg

2:1 Randomization

1

IV Reteplase
10 U bolus 32
30 min apart

2

Heparin
5,000 U bolus
For patients ≥ 80 kg: 1,000 U/hr
For patients < 80 kg: 800 U/hr
IV heparin 3 ≥ 24 hours

IV Alteplase
15 mg bolus
0.75 mg/kg over 30 min
not to exceed 50 mg
0.50 mg/kg over 60 min
not to exceed 35 mg
Total dose ≤ 100 mg

N = 15,000

Primary end point: 30-day mortality

Double-bolus safety profile established

The safety of RETAVASE was evaluated in 3,805 patients with AMI and 45 healthy volunteers. Most of the patients (3,296) participating in the clinical trials received the 10 + 10 U double-bolus regimen. These studies demonstrated that the safety profile of RETAVASE is similar to that of other available thrombolytic agents with respect to
- Cardiac events
- Allergic events
- Other adverse events

Bleeding

Bleeding is the most common complication encountered during the use of thrombolytics. Internal bleeding can occur at intracranial or retroperitoneal sites or in the gastrointestinal, genitourinary, or respiratory tracts. Superficial bleeding occurs mainly at sites of invasion or disturbance (eg, venous cutdowns, arterial punctures, or recent surgical incisions). Intracranial bleeding is the most important safety concern associated with the use of thrombolytic agents. The overall incidence for RETAVASE was 0.71%.

The incidence of bleeding varied widely among the clinical trials and was influenced by the use of arterial catheterization and other highly invasive procedures, and whether the study was performed in Europe or the United States. The overall incidence of bleeding in patients who received the RETAVASE 10 + 10 U double-bolus regimen in INJECT, RAPID 1, and RAPID 2 was 21.1%. This percentage was similar to that of Streptokinase and Alteplase. The rates of bleeding in the INJECT trial are summarized in Table 10.

Strokes

In-hospital stroke rates for the 10 + 10 U RETAVASE regimen in the INJECT trial is summarized in Table 11.

There were no significant differences in overall stroke rates between RETAVASE and Streptokinase in the INJECT study. Overall in-hospital stroke rates for the RETAVASE and Streptokinase treatment groups were 1.23% and 1.00%, respectively. There was an increase in the incidence of in-hospital intracranial hemorrhage for RETAVASE (0.77%) versus Streptokinase (0.37%, P = 0.04). The percentage of patients requiring transfusion was similar in the two groups (0.7% for RETAVASE and 1.0% for Streptokinase).

### Table 10.—Bleeding Incidence (%) in INJECT Trial

<table>
<thead>
<tr>
<th>Bleeding Site</th>
<th>RETAVASE (n = 2,965)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site</td>
<td>4.6</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2.5</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1.6</td>
</tr>
<tr>
<td>Anemia, site unknown</td>
<td>2.6</td>
</tr>
</tbody>
</table>

### Table 11.—In-Hospital Cerebrovascular Events (%) in INJECT Trial

<table>
<thead>
<tr>
<th>Event</th>
<th>RETAVASE (n = 2,965)</th>
<th>Streptokinase (n = 2,971)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All in-hospital strokes</td>
<td>1.21</td>
<td>1.01*</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.77</td>
<td>0.37*</td>
</tr>
<tr>
<td>Nonhemorrhagic stroke</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>Unknown etiology</td>
<td>0.13</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*P = 0.45; †P = 0.04.
No dosing adjustment is required based on patient’s weight

In low-weight (<65 kg) and higher-weight (>65 kg) RETAVASE® (Retepalase)-treated patients, the rates of cerebrovascular events, total strokes, and hemorrhagic strokes were similar. In the INJECT study, hemorrhagic stroke rates were 0.7% for both subgroups.

For hemorrhages of any type, combined data from INJECT and the RAPID studies showed that 25.8% of low-weight patients and 21.0% of higher-weight patients experienced at least one hemorrhage. For hemorrhages requiring a transfusion, the low-weight and higher-weight groups were more similar (3.8% vs 3.1%, respectively).

Because of these results, and particularly because the incidence of hemorrhagic strokes was similar in both low-weight and higher-weight patients, it was concluded that dose adjustment based on a patient’s weight is not necessary for RETAVASE use.

RETAVASE, therefore, can be administered rapidly in a convenient double-bolus dosing regimen, with no dosage adjustment necessary regardless of weight.

Congestive heart failure and cardiogenic shock in INJECT

As can be seen in Table 12, significantly fewer patients treated with RETAVASE in the INJECT trial had new or worsening CHF (P=0.004) and cardiogenic shock (P=0.03) than patients treated with Streptokinase. These results demonstrate that the rate of CHF reduced by Streptokinase can be further reduced by RETAVASE.

Other cardiovascular events in INJECT

The incidence of hypotension, pulmonary edema, atrial fibrillation or flutter, and asystole were all significantly lower for patients treated with RETAVASE. While a variety of additional cardiovascular events had similar rates for both agents, there were no cardiac complications for which the incidence rate was significantly lower in the Streptokinase group. Overall, 60.3% of RETAVASE-treated patients and 63.0% of Streptokinase-treated patients experienced at least one cardiovascular adverse event, while 20.0% and 22.2%, respectively, had at least one serious cardiovascular adverse event.

Allergic events

The incidence of allergic events in the INJECT study was lower in the RETAVASE group (1.1%) than in the Streptokinase group (2.0%). Serious events occurred more often in patients receiving Streptokinase (0.5%) than in those receiving RETAVASE (0.1%).

Across all studies, 42 of 3,288 RETAVASE-treated patients (1.3%) experienced an allergic event, compared to 59 of 2,971 Streptokinase-treated patients (2.0%).

Other adverse events

There were no major differences between RETAVASE and the control agents in the incidence of other events. The higher incidences of minor bleeding and other events in RAPID 1 and 2 than in INJECT are due to angiographic intervention and are consistent with rates in other angiographic trials. There was also a more detailed reporting scheme in the RAPID trials, since INJECT focused on major clinical end points (mortality, stroke, cardiovascular events, allergic reactions) appropriate for a mortality trial.

| Table 12.—Patients (%) Reported With CHF and Cardiogenic Shock in INJECT |
|---------------------------|---------------------------|---------------------------|---------------------------|
|                           | RETAVASE (n = 2,965)     | Streptokinase (n = 2,971) | P Value                  |
| Congestive heart failure  | 24.8                     | 28.1                      | 0.004                    |
| Cardiogenic shock         | 4.6                      | 5.8                       | 0.03                     |
**SECTION VIII**

**RETAVASE® (Reteplase) angiographic trials**

**RAPID 1 and RAPID 2 clinical trials establish activity of bolus dosing**

Both the RAPID 1 and RAPID 2 clinical trials were angiographic studies designed to test the hypothesis that bolus dosing of RETAVASE was superior to administration of Alteplase in achieving complete perfusion (TIMI 3 flow) and patency (TIMI 2 + 3 flow) of the infarct-related artery 90 minutes after initiation of thrombolytic therapy in patients with AMI.

Secondary end points in RAPID 1 and RAPID 2 were patency at 60 minutes after the initiation of therapy, patency prior to hospital discharge (in 5 to 14 days), and LVF prior to discharge.4,5

The correlation between patency and patient outcome has not been established. The angiographic trials were not designed or powered to compare RETAVASE and Alteplase with respect to the outcomes of mortality or stroke, consequently comparisons of mortality or stroke cannot be made.

**RAPID 1.** The RAPID 1 study compared three doses of RETAVASE to Alteplase in patients with AMI.4 A total of 606 patients treated within 6 hours of the onset of symptoms of AMI were randomized to one of four treatment groups:

- 146 had a 15 U single RETAVASE bolus
- 152 had a 10 + 5 U RETAVASE double-bolus dose
- 154 had a 10 + 10 U RETAVASE double-bolus dose
- 154 had a 3-hour infusion of Alteplase (100 mg)

**Fig 15.**—Summary of infarct-related artery patency rates in RAPID 1.

![Graph showing patency rates](image)

*P < 0.01 compared to Alteplase.

*P < 0.05 compared to Alteplase.

*P < 0.001 compared to Alteplase.

The *P*-values represent a comparison of the multiple RETAVASE groups to the single Alteplase group without adjustment for multiple comparisons.

– Adapted from Smalling et al.5
Aspirin was given at a dose of 200 to 325 mg immediately before administration of each thrombolytic agent and continued daily until hospital discharge. Heparin was started as an intravenous bolus just before the start of thrombolytic therapy and then infused at the rate of 1,000 U/hr for at least 24 hours.

Coronary arteriography was performed at 30 and 60 minutes after initiation of thrombolytic therapy (when possible) and at 90 minutes. Left ventriculography was also performed after coronary arteriography, and TIMI grade was estimated at 90 minutes. The complete angiographic procedure was repeated between 5 days after admission and discharge from the hospital.

**Results of RAPID 1.** Patency data in the RAPID 1 study are summarized in Fig 15 on page 37. The 10 + 10 U RETAVASE™ (Reteplase, recombinant) group achieved patency (TIMI 2 + 3 flow) in 85% of patients at 90 minutes compared to 77% of patients treated with Alteplase. This difference was not statistically significant. At 5 to 14 days after treatment, however, RETAVASE achieved significantly higher patency rates than the Alteplase group (95% vs 88%, \( P < 0.05 \)). Bolus administration of 10 + 10 U of RETAVASE resulted in improved complete flow, both at 90 minutes and before hospital discharge, compared with standard-dose Alteplase. These findings were associated with improved global and regional function at hospital discharge. Patients in the RETAVASE 10 + 10 U and Alteplase groups exhibited similar global ventricular function in the acute stage of treatment. There was, however, a significant difference in favor of RETAVASE at hospital discharge in left ventricular ejection fraction and regional wall motion. The bleeding risk of RETAVASE was similar to that associated with standard-dose Alteplase.

RAPID 1 provided dose-finding data that supported the use of the 10 + 10 U double-bolus regimen as the standard for subsequent studies. The correlation between patency and patient outcome has not been established. This trial was not designed or powered to make comparisons of mortality or stroke.

The need for coronary interventions within 6 hours of thrombolysis was also evaluated in RAPID 1. There were no significant differences in the incidence of early rescue PTCA (14.9% versus 22.1%), or the overall in-hospital incidences of PTCA (RETAVASE 46.8%, Alteplase 50.6%).

**RAPID 2.** In the RAPID 2 study, 324 patients treated within 12 hours of the onset of symptoms of AMI were randomized to receive either a 10 + 10 U double bolus of RETAVASE 30 minutes apart (n=169) or the accelerated (front-loaded) 90-minute Alteplase regimen (n=155). Patients also received aspirin and heparin. Angiographic procedures were conducted as in RAPID 1.

**Results of RAPID 2.** Patency (TIMI 2 + 3 flow) and complete perfusion (TIMI 3 flow) rates were significantly higher for the 10 + 10 U RETAVASE regimen than for Alteplase at 60 minutes and 90 minutes (Fig 16). At the primary time point of 90 minutes, the patency rate in the RETAVASE group was 10% higher and the complete perfusion rate (TIMI 3) was 15% higher (\( P = 0.011 \)) than in the Alteplase group.

In RAPID 2, patients who received treatment within 6 hours after onset of symptoms had better overall patency and complete perfusion in both groups than did patients who presented between 6 and 12 hours. Notably, patients treated with RETAVASE had better patency in all time-to-treatment categories. RETAVASE achieved 90-minute patency (TIMI 2 + 3 flow) in 86.5% and complete perfusion (TIMI 3 flow) in 62.4% of patients treated within 6 hours. The corresponding rates for Alteplase were 77.2% and 47.2%. The correlation between patency and patient outcome has not been established. This trial was not designed or powered to make comparisons of mortality or stroke.
The need for coronary interventions within 6 hours of thrombolysis was also evaluated in RAPID 2. There were significantly fewer early rescue PTCAAs for patients treated with RETAVASE compared to accelerated-dose Alteplase. There were no differences in the overall in-hospital incidences of PTCAAs (Fig 17).5

The correlation between patency and patient outcome has not been established. Due to different numbers of patients in the 60- and 90-minute groups and nonrandomization to these time points, no comparison can be made between 60- and 90-minute data.

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Fig 16.—Patency profile at 60, 90 minutes and 5 to 14 days in RAPID 2.

Fig 17.—Incidence of PTCA interventions in RAPID 2.
Summary of benefits of RETAVASE® (Reteplase)

**Demonstrated mortality reduction/ documented safety profile**

A double-blind mortality trial has demonstrated that RETAVASE is effective in reducing mortality following an AMI.\(^3\) Furthermore, patients treated with RETAVASE had a significantly lower incidence of atrial fibrillation, asystole, cardiogenic shock, CHF, and hypotension, and significantly fewer allergic reactions than patients treated with Streptokinase.\(^9\)

With the exception of intracranial hemorrhage in which the incidence with RETAVASE was higher, the incidence of serious complications, such as cerebrovascular and cardiovascular events, was similar to that of control agents.

**Restoration of coronary flow in more patients**

RETAVASE has been angiographically proven to achieve complete perfusion and patency in significantly more patients than the accelerated-dose Alteplase regimen.\(^5\) The correlation between patency and patient outcome has not been established. In addition, RETAVASE is proven to preserve left ventricular function.\(^4,5\)

The GUSTO-III trial with 15,000 patients was designed to study 30-day mortality with RETAVASE compared to Alteplase. Enrollment was completed in January 1997. Secondary end points included in-hospital rates of reinfarction, CHF, stroke, and intracranial hemorrhage.

**Simple, convenient administration**

The unique molecular structure of RETAVASE and its long therapeutic half-life permit a convenient double-bolus dosing regimen. Administration of RETAVASE as a double-bolus regimen—intravenous injections 30 minutes apart—may permit an earlier start of life-saving therapy in the hospital emergency department or intensive care unit, and the dose does not have to be adjusted for the patient’s weight. The greater ease of RETAVASE administration may reduce time and staff required for administration and may also obviate the need for two intravenous lines, since heparinization can be interrupted during RETAVASE bolus injections. Intravenous lines, however, should be flushed between administration of RETAVASE and other agents.
SECTION X

References


33. Data on file, Boehringer Mannheim Corporation–Therapeutics Division.


Retavase® (Reteplase) is a non-glycosylated deletion mutein of tissue plasminogen activator (tPA), containing the kringle 2 and the protease domains of human tPA. Retavase® contains 355 of the 527 amino acids of native tPA (amino acids 1-3 and 176-527). Retavase® is produced by recombinant DNA technology in E. coli. The protein is isolated as inactive inclusion bodies from E. coli, converted into its active form by an in vitro folding process and purified by chromatographic separation. The molecular weight of Retetapase is 39,570 daltons.

Potency is expressed in units (U) using a reference standard which is specific for Retavase® and is not comparable with the tissue plasminogen activator (tPA) used for other thrombolytic agents.

Retavase® is a sterile, white, lyophilized powder for intravenous bolus injection after reconstitution with sterile Water for Injection, USP (without preservatives) provided as part of a kit. After reconstitution, the pH is 6.0 ± 0.3. Retavase® is supplied as a 10.4 U vial to ensure sufficient drug for administration of each 10 U dose. Each single-use vial contains:

- 10.4 U (18.1 mg) Vial
- Retavase® 7.965 mg
- Streptokinase 2.971 mg
- Retavase®-Streptokinase difference (95% CI) Value
- 35 Day mortality 8.9% 9.4% -0.5 (2.0, 0.9) 0.49
- 6 Month mortality‡ 11.0% 12.1% -1.1 (-2.7, 0.6) 0.22
- Combined outcome of 35 day mortality or nonfatal stroke within 35 days 9.6% 10.2% -0.6 (-2.1, 0.9) 0.47
- Heart failure 24.8% 28.1% -3.3 (-5.5, -1.1) 0.004
- Cardiogenic shock 4.6% 5.8% -1.2 (-2.4, 0.1) 0.03
- Any stroke 1.4% 1.1% 0.3 (0.3, 0.8) 0.34
- Intracranial hemorrhage 0.8% 0.4% 0.4 (0.0, 0.8) 0.04

*p values represent one of multiple dose comparisons.

Approximately 70% (RAPID 1) and 78% (RAPID 2) of the patients in the antithrombotic studies underwent anticoagulation at 60 minutes following the administration of Alteplase and Retavase® with respect to the outcomes of interest. INDICATIONS AND USAGE Retavase® (Reteplase) is indicated for use in the management of acute myocardial infarction (AMI) in adults for the improvement of ventricular function following AMI, the reduction of the incidence of congestive heart failure and the reduction of mortality associated with AMI. Treatment should be initiated as soon as possible after the onset of AMI symptoms (see CLINICAL PHARMACOLOGY). CONTRAINDICATIONS Because thrombolytic therapy increases the risk of bleeding, Retavase® is contraindicated in the following situations: • Active internal bleeding • History of cerebrovascular accident • Recent intracranial or intraspinal surgery or trauma (see WARNINGS) • Intracranial neoplasm, arteriovenous malformation, or aneurysm • Known bleeding diathesis • Severe uncontrolled hypertension WARNINGS Bleeding The most common complication encountered during Retavase® therapy is bleeding. The sites of bleeding include both internal bleeding sites (intracranial, retroperitoneal, gastrointestinal, genitourinary, or respiratory) and superficial bleeding sites (including cutdowns, arterial punctures, sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to bleeding. In clinical trials some of the hemorrhage episodes occurred one or more days after the effects of Retavase® had dissipated, but while heparin therapy was continuing. If fibrin is lysed during Retavase® therapy, bleeding from recent puncture sites may occur. Therefore, thrombolytic therapy requires careful attention to all potential bleeding sites (including catheter insertion sites, arterial or venous puncture sites, cutdown sites, and sites of recent surgical intervention). The concomitant use of heparin anticoagulation may contribute to bleeding. In clinical trials some of the hemorrhage episodes occurred one or more days after the effects of Retavase® had dissipated, but while heparin therapy was continuing.

For mortality, stroke, and the combined outcome of mortality and stroke, the 95% confidence intervals in Table 2 reflect the range within which the true difference in outcomes probably lies and includes the possibility of no difference. The incidences of congestive heart failure and of cardiogenic shock were significantly lower among patients treated with Retavase® compared to Alteplase. The total incidence of stroke was similar between the groups. However, more patients treated with Retavase® experienced hemorrhagic strokes than patients treated with Streptokinase. An exploratory analysis indicated that the incidence of intracranial hemorrhage was higher among older patients or those with elevated blood pressure. The incidence of intracranial hemorrhage among the 698 patients treated with Retavase® who were older than 70 years was 2.2%. Intracranial hemorrhage occurred in 8 of the 332 (2.4%) patients treated with Retavase® and in 1 of 365 (0.3%) patients treated with Streptokinase. Intracranial hemorrhage is defined as blood pressure >160 mm Hg and in 15 of the 20 patients (65% of the 23 patients treated with Retavase® and 1 of 20 patients who had an initial systolic blood pressure <160 mm Hg).

Two antegrade studies (RAPID 1 and RAPID 2) were performed utilizing open-label administration of the study drug and a blinded review of the catheterograms. In RAPID 1, patients were treated within 6 hours of the onset of symptoms, and in RAPID 2, patients were treated within 12 hours of the onset of symptoms. Both studies evaluated coronary artery perfusion through the infarct-related artery at 1 hour following the administration of Retavase®. In RAPID 1, patients were treated within 6 hours of the onset of symptoms, and in RAPID 2, patients were treated within 12 hours of the onset of symptoms. Both studies evaluated coronary artery perfusion through the infarct-related artery at 60 minutes after the initiation of therapy. In RAPID 1, Retavase® (in doses of 10 + 10 U, 10 + 5 U, and 10 + 10 U) was compared to a 3 hour regimen of Alteplase (100 mg administered over 3 hours). In RAPID 2, Retavase® (10 + 10 U) was compared to an accelerated regimen of Alteplase (100 mg administered over 1.5 hours). The percentages of patients with partial or complete flow (TIMI grades 2 or 3) and complete flow (TIMI grade 3) were shown along with ventricular function assessments in Table 2. The follow-up arteriogram was performed at a median of 8 (RAPID 1) and 5 (RAPID 2) days following the administration of the thrombolytics. In RAPID 1 the best potency results were obtained with the 10 + 10 U dose. In RAPID 2, the percentage of patients with partial or complete flow and the percentage of patients with complete flow was significantly higher with Retavase® than with Alteplase at 90 minutes after the initiation of therapy. In both clinical trials the recollusion rates were similar for Retavase® and Alteplase. The relationship between coronary artery patency and clinical efficacy has not been established.

**Cholesterol Embolization**

Cholesterol embolization has been reported rarely in patients treated with thrombolytic agents; the true incidence is unknown. This serious condition, which can be lethal, is also associated with invasive vascular procedures such as catheterization, angiography, vascular surgery, and/or anticoagulant therapy. Clinical features of cholesterol embolization may include livedo reticularis, “purple toe” syndrome, acute renal failure, gangrenous digits, hypertension, pancreatitis, myocardial infarction, cerebral infarction, spinal cord infarction, renal artery occlusion, bone infarction, and/or aneurysmal change."

**Arrhythmias**

Coronary thrombosis may result in arrhythmias associated with reperfusion. These arrhythmias (such as sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, ventricular tachycardia) are not different from those often seen in the ordinary course of acute myocardial infarction and should be managed with standard antarrhythmic measures. It is recommended that antarrhythmic therapy for bradycardia and/or ventricular irritability be available when Retavase® is administered.
Retavase®

**WARNINGS**

**General**
Standard management of myocardial infarction should be implemented concomitantly with Retavase® treatment. Arterial and venous punctures should be minimized (see WARNINGS). In addition, the second bolus of Retavase® should not be given if the serious bleeding occurs before it is administered. In the event of serious bleeding, any concomitant heparin should be terminated immediately. Heparin effects can be reversed by protamine.

**Readadministration**
There is no experience with patients receiving repeat courses of therapy with Retavase®. Retavase® did not induce the formation of Retavase® specific antibodies in any of the approximately 2,000 patients who were tested for antibody formation in clinical trials. If an anaphylactic reaction occurs, the second bolus of Retavase® should not be given, and appropriate therapy should be initiated.

**Drug Interactions**
The interaction of Retavase® with other cardiovascular drugs has not been studied. In addition to bleeding associated with heparin and vitamin K antagonists, drugs that alter platelet function (such as aspirin, dipyridamole, and chloropropamide) may increase the risk of bleeding if administered prior to or after Retavase® therapy.

**Drug/Laboratory Test Interactions**
Administration of Retavase® may cause decreases in plasminogen and fibrinogen. During Retavase® therapy, if coagulation function tests or measurements of fibrinolytic activity are performed, the results may be unreliable unless specific precautions are taken to prevent in vitro artifacts. Retavase® is an enzyme that when present in blood in pharmacologic concentrations remains active under in vitro conditions. This can lead to degradation of fibrinogen in blood samples removed for analysis. Collection of blood samples in the presence of PPACK (chloromethylketone) at 2 µM concentrations was used in clinical trials to prevent in vitro fibrinolytic artifacts.

**Use of Antithrombotics**
Heparin and aspirin have been administered concomitantly with Retavase® in the management of acute myocardial infarction. Because heparin, aspirin, or Retavase® may cause bleeding complications, careful monitoring for bleeding is advised, especially at arterial puncture sites.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of Retavase®. Studies to determine mutagenicity, clastogenic action, gene mutations, and micronucleus induction were negative at all concentrations tested. Reproductive toxicity studies in rats revealed no effects on fertility at doses up to 15 times the human dose (4.31 µg/kg).

**Pregnancy Category C**
Retaplace has been shown to have an abortifacient effect in rabbits when given in doses 3 times the human dose (0.86 U/kg). Reproduction studies performed in rats at doses up to 15 times the human dose (4.31 µg/kg) revealed no evidence of fetal anomalies; however, Retaplace administered to pregnant rabbits resulted in hemorrhaging in the genital tract, leading to abortions in mid-gestation. There are no adequate and well-controlled studies in pregnant women. The drug is not likely to cause harm to the fetus when administered during pregnancy. The drug should, however, not be administered to a nursing woman.

**Nursing Mothers**
It is not known whether Retavase® is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Retavase® is administered to a nursing woman.

**Pediatric Use**
Safety and effectiveness of Retavase® in pediatric patients have not been established.

**ADVERSE REACTIONS**

**Bleeding**
The most frequent adverse reaction associated with Retavase® is bleeding (see WARNINGS). The types of bleeding events associated with thrombolytic therapy may be broadly categorized as either intracranial hemorrhage or other types of hemorrhage:

- **Intracranial hemorrhage** (see CLINICAL PHARMACOLOGY)
  - In the INJECT clinical trial the rate of intracerebral hemorrhage among all patients treated with Retavase® was 0.08% (23 of 29,365 patients). As seen with Retavase® and other thrombolytic agents, the risk for intracranial hemorrhage is increased in patients with advanced age or with elevated blood pressure.

- **Other types of hemorrhage**
  - The incidence of other types of bleeding events in clinical studies of Retavase® varied depending upon the use of arterial catheterization or other invasive procedures and whether the study was performed in Europe or the USA. The overall incidence of any bleeding event in patients treated with Retavase® in clinical studies (n = 3,805) was 21.1%. The rates for bleeding events, regardless of severity, for the 10 + 10 U Retavase® regimen from controlled clinical studies are summarized in Table 3.

**Table 3**

<table>
<thead>
<tr>
<th>Bleeding Site</th>
<th>INJECT</th>
<th>RAPID 1 and RAPID 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Europe</strong></td>
<td><strong>n = 2,965</strong></td>
<td><strong>USA</strong></td>
</tr>
<tr>
<td>Injection Site*</td>
<td>4.6%</td>
<td>48.6%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2.5%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>1.8%</td>
<td>9.5%</td>
</tr>
<tr>
<td>Anemia, site unknown</td>
<td>2.6%</td>
<td>1.4%</td>
</tr>
</tbody>
</table>

*Includes the arterial catheterization site (all patients in the RAPID studies underwent arterial catheterization).

In these studies the severity and sites of bleeding events were comparable for Retavase® and the comparison thrombolytic agent.

**Other Adverse Reactions**
Patients administered Retavase® as treatment for myocardial infarction have experienced many events which are frequent sequelae of myocardial infarction and may or may not be attributable to Retavase® therapy. These events include cardiacogenic shock, arrhythmias (e.g., sinus bradycardia, accelerated idioventricular rhythm, ventricular premature depolarizations, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation), AV block, pulmonary edema, heart failure, cardiac arrest, recurrent ischemia, reinfarction, myocardial rupture, mitral regurgitation, pericardial effusion, pericarditis, cardiac tamponade, venous thrombosis and embolism, and electromechanical dissociation. These events can be life-threatening and may lead to death. Other adverse events have been reported, including nausea and/or vomiting, hypotension, and fever.

**Dosage and Administration**
Retavase® (Reteplase) is for intravenous administration only. Retavase® is administered as a 10 + 10 U double-bolus injection. Each bolus is administered as an intravenous injection over 2 minutes. The second bolus is given 30 minutes after initiation of the first bolus injection. Each bolus injection should be given via an intravenous line in which no other medication is being simultaneously injected or infused. No other medication should be added to the injection solution containing Retavase®. There is no experience with patients receiving repeat courses of therapy with Retavase®.

**Heparin and Retavase® are incompatible when combined in solution. Do not administer heparin and Retavase® simultaneously in the same intravenous line. Each bolus of Retavase® is to be injected through an intravenous line containing heparin, a normal saline or 5% dextrose (DSW) solution should be flushed through the line prior to and following the Retavase® injection.**

**Reconstitution**
Reconstitution should be carried out using the dialyzer, syringe, needle and dispensing pin provided with Retavase®. It is important that Retavase® be reconstituted only with Sterile Water for Injection, USP (without preservatives). The reconstituted preparation results in a colorless solution containing Retavase® 1 U/mL. Slight foaming upon reconstitution is not unusual; allowing the vial to stand undisturbed for several minutes is usually sufficient to allow dissolution of any large bubbles. Because Retavase® contains no antibacterial preservatives, it should be reconstituted immediately before use. When reconstituted as directed, the solution may be used for 4 hours when stored at 2-30°C (36-86°F). Prior to administration, the product should be visually inspected for particulate matter and discoloration.

**References**

- Kohner U, Rudolph R, Verheugen JH. Biochemical properties of the kringle 2 and protease domains are maintained in the refolded t-PA deletion variant BM 06.022. Protein Engineering. 1992;5:93-100.