This reprint contains data from a Genentech-sponsored phase III clinical trial that led to the approval of Genentech's product Cathflo® Activase® (alteplase). The FDA has approved Cathflo® Activase® (alteplase) for the restoration of function to central venous access devices as assessed by the ability to withdraw blood.

This reprint contains information that is not contained in the approved product labeling, including history of catheter thrombolysis; rationale of the COOL-1 trial; additional information on materials, methods, and patients of the COOL-1 trial; and limitations of the COOL-1 trial.

Important Safety Information for Cathflo® Activase® (alteplase)

Contraindications
Cathflo Activase should not be administered to patients with known hypersensitivity to alteplase or any component of the formulation.

Precautions

General
Certain causes of catheter dysfunction should be considered before treatment with Cathflo Activase (e.g. catheter malposition, mechanical failure, constriction by a suture and lipid deposits or drug precipitates within the catheter lumen). These types of conditions should be considered before treatment with Cathflo Activase.

Excessive pressure should be avoided when Cathflo Activase is instilled into the catheter. Such force could cause rupture of the catheter or expulsion of the clot into the circulation.

Bleeding
The most frequent adverse reaction associated with all thrombolytics in all approved indications is bleeding. Cathflo Activase has not been studied in patients known to be at risk for bleeding events that may be associated with the use of thrombolytics. Caution should be exercised with patients who have any condition for which bleeding constitutes a significant hazard.

Should serious bleeding in a critical location (e.g., intracranial, gastrointestinal, retroperitoneal, pericardial) occur, treatment with Cathflo Activase should be stopped and the drug should be withdrawn from the catheter.

Infections
Cathflo Activase should be used with caution in the presence of known or suspected infection in the catheter. Using Cathflo Activase in patients with infected catheters may release a localized infection into the systemic circulation. As with all catheterization procedures, care should be used to maintain aseptic technique.

Hypersensitivity
Hypersensitivity, including urticaria, angioedema and anaphylaxis, has been reported in association with use of Cathflo Activase. Monitor patients treated with Cathflo Activase for signs of hypersensitivity and treat appropriately if necessary.

Drug Interactions and Drug/Laboratory Test Interactions
The interaction of Cathflo Activase with other drugs has not been formally studied. Concomitant use of drugs affecting coagulation and/or platelet function has not been studied.

Potential interactions between Cathflo Activase and laboratory tests have not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential or the effect on fertility.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Cathflo Activase should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Adverse Reactions
In clinical trials, the most serious adverse events reported after treatment were sepsis, gastrointestinal bleeding, and venous thrombosis.

You may report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at (888) 835-2555.

Please see accompanying full Prescribing Information for additional important safety information.

Recombinant Tissue Plasminogen Activator (Alteplase) for Restoration of Flow in Occluded Central Venous Access Devices: A Double-Blind Placebo-Controlled Trial—The Cardiovascular Thrombolytic to Open Occluded Lines (COOL) Efficacy Trial

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PURPOSE: Central venous access devices (CVADs) are a mainstay of current medical therapy but often become occluded by thrombus. Tissue plasminogen activator (alteplase), at a dose of 2 mg per 2 mL, has been shown to be effective in restoring flow to catheters proven by radiographic contrast injection to be occluded by thrombus. The purpose of this double-blind placebo-controlled multicenter trial was to determine the efficacy of alteplase in occluded catheters without earlier contrast injections or radiographic examinations.

MATERIALS AND METHODS: Patients were eligible for inclusion if blood could not be withdrawn from their catheter after a period of normal function of at least 48 hours. Single or multiple catheters, peripherally inserted central catheters, catheters with valves, and implanted ports were eligible; catheters used for hemodialysis were not included. Patients were randomly assigned to one of two groups. In one group, patients received a first dose of 2 mg alteplase followed, if needed, by a second dose of 2 mg alteplase and a third dose of placebo. The other group received placebo first followed by one 2-mg dose of alteplase and then a second, if needed. Each dose was allowed to dwell for 2 hours and ability to withdraw blood from the catheter was reassessed. The endpoint was restoration of the ability to withdraw and infuse through the catheter. One hundred forty-nine patients were randomized: 74 received placebo first, 75 received alteplase first.

RESULTS: After the first 2-hour treatment, function was restored to 74% in the alteplase arm and 17% in the placebo arm ($P < .0001$ compared to placebo). After one or two treatments, function was restored in 90% of patients. There were no serious study-drug–related adverse events, no intracranial hemorrhage, no major hemorrhage, and no embolic events.

CONCLUSION: Infusion of alteplase appeared to be safe and effective in restoring flow to occluded catheters without need for pretreatment radiographic evaluation.

Index terms: Central venous access • Thrombolysis • Tissue-type plasminogen activator • Urokinase

J Vasc Interv Radiol 2001; 12:951–955

Abbreviation: CVAD = central venous access device

CENTRAL venous access devices (CVADs) have become increasingly integral to modern medical therapy, and are used for infusion of chemotherapy, blood products, pain medication, nutritional support, pressors, and other treatments requiring central venous access. Unfortunately, these catheters become occluded as a result of thrombosis at a rate that has been estimated at 25% per year (1). Catheter thrombosis is quickly followed by clinical thrombosis (catheter-related venous thrombosis or obstruction) in a large number of patients (2).

Treatment of occluded CVADs had been performed with use of urokinase (3,4). Since the withdrawal of urokinase from the market, other treatment options have become necessary. Re-

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[1] These authors have disclosed the existence of a potential conflict of interest.

combinant tissue plasminogen activator (alteplase) has previously been shown to be very effective in restoring flow to dysfunctional catheters that were proven by radiographic contrast injection to be occluded by thrombus (5). However, almost 40% of dysfunctional catheters are not occluded by thrombus (6); rather, they are obstructed by mechanical problems such as migration and malposition of the intravascular segment or kinking of the subcutaneous segment of the catheter. Because clinical presentation is not specific for the cause of obstruction, radiographic contrast material injection is believed necessary to determine the cause of obstruction and the type of therapy necessary (thrombolytic or mechanical repositioning) (6). Unfortunately, contrast injection studies are often not readily available in clinical practice. Consequently, thrombolytic therapy is often administered empirically to dysfunctional catheters. Consequently, we evaluated the ability of alteplase to restore both infusion and withdrawal function in dysfunctional catheters without earlier radiographic contrast material injection.

MATERIALS AND METHODS

Trial Design

This trial was a multicenter, double-blind, placebo-controlled comparison of the rates of restoration of catheter function after treatment for 2 hours with either alteplase (2 mg in 2 mL) or placebo (patients weighing between 10 and 30 kg were given a dose equal to 110% of the internal catheter volume). The secondary goal of the study was to determine the rate of catheter function restoration after one or two treatments with alteplase. Safety endpoints of the study included the rates of study-drug–related intracranial hemorrhages, major hemorrhage, embolic events, and all drug-related serious adverse events.

Patient Population

Patients were eligible if they were clinically stable and had a dysfunctional indwelling long-term CVAD (peripherally inserted central catheters, catheters with valves, and implanted ports were allowed; catheters used for hemodialysis were not). Withdrawal dysfunction was defined as the inability to withdraw 3 mL of blood. Patients were excluded if it was not possible to infuse fluids at the volume necessary to infuse study drug into the CVAD, if the CVAD had been inserted less than 48 hours before randomization, or if the occlusion had been discovered more than 24 hours before randomization. Also excluded were patients younger than 2 years of age, who weighed less than 10 kg, who had catheters with any evidence of mechanical or nonthrombotic occlusion, or who had received any fibrinolytic agent within 24 hours of randomization. Subjects who, in the opinion of the investigator, were at high risk for bleeding events or embolic complications, or had a known condition for which bleeding constitutes a significant hazard, were also excluded at the discretion of the individual investigators.

Baseline studies consisted of a medical history, physical examination, and CVAD history, including the date of CVAD insertion and the date the CVAD was last known to function (withdrawal and infusion function). An assessment of CVAD function was performed and recorded at baseline. In subjects with multiple-lumen catheters, only one lumen of the catheter (chosen at the discretion of the investigator at the site) was used throughout the study for assessments of function. Withdrawal function was determined by the following method: An empty 10-mL syringe was attached to the catheter, forming an airtight seal. The syringe plunger was pulled back to the 5-mL mark to attempt to withdraw blood. The CVAD was considered to have withdrawal function if at least 3 mL of fluid (blood and any previously infused fluids) filled the syringe. Infusion function was determined by the following method: A 10-mL syringe with 5 mL normal saline solution was attached to the catheter to gently infuse the saline solution. The CVAD was considered to have infusion function if the entire contents of the syringe could be infused without significant resistance.

Baseline Characteristics

A total of 150 subjects were enrolled in the study (149 were randomized; one was treated without randomization); 74 in the placebo-first group and 75 in the alteplase-first group. One subject was treated (with alteplase first) but not formally randomized and was therefore not included in the intent-to-treat analysis but is included in the "as-treated" analysis. There were 10 patients randomized but not treated (four in placebo first and six with alteplase first). The catheter types randomized in the trial included 19 single-lumen catheters, 72 double-lumen catheters, 12 triple-lumen catheters, and 46 ports. A total of 26 sites enrolled patients in the trial (17 enrolled 1–4 patients, six enrolled 5–10, one enrolled 13, one enrolled 23, and one enrolled 25). Enrollment occurred from November 1999 through May 2000 with the last patient undergoing follow-up in June 2000. Baseline and demographic data are displayed in **Table 1.**

Study Procedure

Subjects were randomly assigned by an interactive voice randomization service to one of two groups. Each group had one opportunity to be treated with placebo and two opportunities to be treated with study drug (**Table 2**). In one arm, the first study drug vial contained placebo and the second and third vials contained active alteplase. In the other arm, the first and second study drug vials contained active alteplase and the third contained placebo.

After the first vial of study drug was instilled and allowed to dwell for 120 minutes, function was reassessed to determine if both withdrawal and infusion function were present. If function was successfully restored, the patient exited the study. Patients who did not have successful restoration of function were then treated by instillation of the second vial of study drug that was again allowed to dwell for 120 minutes. Function was again assessed at the end of the second 120-minute period. Patients who did not have successful restoration of function after the second treatment were then treated by instillation of the third vial of study drug that was again allowed to dwell for 120 minutes. Function was finally assessed at the end of the third 120-minute period.

All adverse events that met "good clinical practice" criteria for "serious"

Table 1
Selected Demographic and Baseline Characteristics of the Intent-to-treat Population

Characteristic	PAA (n = 74)	AAP (n = 75)
Sex		
Female	41 (55.4%)	41 (54.7%)
Male	33 (44.6%)	34 (45.3%)
Race		
White	51 (68.9%)	57 (76.0%)
Black	16 (21.6%)	8 (10.7%)
Asian/Pacific Islander	2 (2.7%)	6 (8.0%)
Hispanic	5 (6.8%)	3 (4.0%)
Other	0	1 (1.3%)
Age (y)*	49.6 (19)	50.5 (19)
Weight (kg)*	77.4 (27)	75.0 (20)
CVAD type		
Single	9 (12.2%)	10 (13.3%)
Double	36 (48.6%)	36 (48.0%)
Triple	5 (6.8%)	7 (9.3%)
Port	24 (32.4)	22 (29.3%)
Time from catheter insertion to treatment (d)†	35 (2–977)	39 (2–1678)
Time from last known function to treatment (d)†	1 (0–317)	3 (0–70)

Note.—Patient characteristics were not significantly different between groups. PAA = placebo, then two alteplase doses; AAP = two alteplase doses, then placebo (see **Table 2**).
* Values are provided as mean (SD).
† Values are provided as median (range).

Table 2
Specifications of Treatment Arms

Treatment Arm	Vial 1	Vial 2	Vial 3
PAA	Placebo (2 mL)	Alteplase (2 mg/2 mL)	Alteplase (2 mg/2 mL)
AAP	Alteplase (2 mg/2 mL)	Alteplase (2 mg/2 mL)	Placebo (2 mL)

Note.—P = placebo; A = alteplase.

were collected during the study period (which was defined as the time from the first treatment with study drug until successful restoration of catheter function or the final assessment after treatment with three vials of study drug). Additionally, all deaths and serious adverse events that were reported by the investigators as long as 30 days after the treatment with study drug were recorded.

The trial was conducted from November 1999 to June 2000 in 36 hospitals (see list of participants at the end of this article). The study was reviewed by the appropriate institutional review boards and was conducted in accordance with the Helsinki Declaration of 1975 (revised 1983).

Statistical Analysis

The primary endpoint of the study was the difference in rates of restoration of function in the alteplase-treated group compared with the placebo-treated group after 120 minutes. Cumulative rates of successful restoration of function were also determined after each of the treatment assessments. Primary analysis was by intent to treat regardless of early withdrawal or compliance. Analysis by actual treatment was also performed. Statistical analysis was performed with use of SAS statistical software (SAS, Cary, NC). Statistical comparisons of proportions were performed with use of the Fisher exact test. Exact confidence intervals were calculated with use of binomial distribution. Confidence intervals were also calculated with use of the binomial distribution. All statistical tests were two-sided and conducted at the 0.05 level of significance.

RESULTS

Efficacy

The primary endpoint of the study was the difference in rates of restoration of function in the alteplase-treated group compared with the placebo-treated group after 120 minutes in the intent-to-treat population. After the first 120-minute period, successful restoration of function was demonstrated in 73.9% (51 of 69) of alteplase-treated patients compared with only 17.1% (12 of 70) of placebo-treated patients. The difference in these rates was 56.8% (95% CI: 41.2%–70.8%), which was highly significant ($P < .0001$).

The cumulative rates of restoration of function are shown in the **Figure**. Successful restoration of function was achieved in 77.1% (54 of 70) of patients who received placebo as the first treatment and alteplase as the second treatment (in patients who did not have restoration of function after the first treatment). Successful restoration of function was achieved in 89.9% (62 of 69) of patients who received alteplase as the first treatment and alteplase as the second treatment (in those patients who did not have restoration of function after the first treatment). After treatment with either alteplase then placebo or placebo then alteplase, the rate of restoration of function was 89.9% (62 of 69). Similar results were achieved in the as-treated population when comparing alteplase against placebo after the first bolus.

Of the 150 patients enrolled in the trial, only five had a weight between 10 and 30 kg. Based on the dosing requirement of 110% of the internal catheter volume, all received a lower dose than the other patients in the trial (dose received: 1.30, 0.80, 0.88, 0.88, and 0.90 mL). Of the five patients, three received placebo first and two received alteplase first. None of the three receiving placebo had catheter function restored, and one of the two who received alteplase had clearance after first dose.

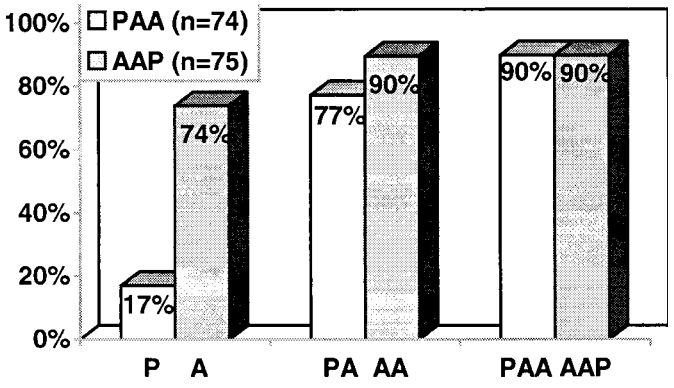

Figure. This graph shows the percentage of patients in whom normal catheter function was restored after a single 2-hour treatment with either placebo (*P*) or active drug (*A*) after treatment with placebo followed by active drug (*PA*), two active treatments (*AA*), placebo followed by active drug twice (*PAA*), or active drug twice followed by placebo (*AAP*).

Safety

In the as-treated population of 140 patients, there were no intracranial hemorrhages, no major hemorrhages, no embolic events, no drug-related serious adverse events, and no drug-related deaths during the study or 30-day follow-up. During the study, only one patient died (day 29 after study drug, from complications of bone marrow transplantation). No patient withdrew from the study because of an adverse event.

DISCUSSION

To our knowledge, this is the first double-blind, placebo-controlled assessment of the efficacy of alteplase in restoring function to unselected dysfunctional central catheters. Previous studies have been unblinded and/or selected catheters for enrollment that had been demonstrated by radiographic contrast material injection to be occluded by thrombus (5,7). The study demonstrated that alteplase, at a dose of 2 mg in 2 mL, is highly effective and appears safe for empiric use in restoring catheter flow without the requirement that thrombotic obstruction be documented radiographically. All types of central catheters were studied, including single-, double-, and triple-lumen, ports, Groshong catheters, Hickman catheters, apheresis catheters, and peripherally inserted central catheters.

The findings of this study are consistent with the initial report of the use of alteplase for clearing thrombosed catheters by Atkinson et al (7). The efficacy in the current trial is similar to that reported by Haire et al (5) in the 1994 comparison of the same treatment regimen and dose of alteplase (2 mg in 2 mL for 2 h) with urokinase used at twice its recommended dose. The study by Haire et al (5) reported that alteplase was statistically superior to urokinase and restored function to 89% of CVADs with angiographically proven thromboses. In the current study, angiograms or chest radiographs were not required for study participation. Patients could be selected based only on clinical assessment of the cause of catheter dysfunction. Therefore, we were unable to determine the position, type of occlusion (mural thrombus, fibrin sheath, or intraluminal occlusion), extent of occlusion, or cause of catheter malfunction. Based on our broader inclusion algorithm, we expected to observe a slightly lower efficacy rate after one or two doses of alteplase, presuming that as many as 40% of the dysfunctional catheters would be occluded by mechanical problems rather than thrombosis, as had been previously described (6). The fact that the current study observed similar or higher efficacy rates (90% after one or two doses) suggests that the rate of nonthrombotic obstruction in general clinical practice may be significantly lower than that reported from a single institution. This may be a result of statistical variation, differences in study populations, or varying clinical acumen of the investigators in excluding catheters with mechanical or nonthrombotic occlusions. However, the current study is likely to be representative of current clinical practices whereby patients with catheter dysfunction are often treated empirically and undergo angiographic evaluation only after initial treatment failures.

The dose of alteplase used in the study was chosen based on the study results of Haire et al (5). No information was collected on higher or lower doses. A number of nonrandomized studies have reported comparable efficacy rates at different (8) and similar (9) doses; however, it is unclear whether other doses would have similar efficacy if studied in a placebo-controlled double-blind study such as this.

The dwell time of 2 hours was also chosen based on the study results of Haire et al (5). The current study did not address shorter dwell times or the relationship of dose and dwell time. Although alteplase is the most rapidly acting thrombolytic drug currently or previously approved for noncardiac uses, time is needed for activation of plasminogen to plasmin and subsequent cleavage of clot-bound fibrin for successful thrombolysis to take place. Other studies (9,10) have reported successful restoration of function after shorter dwell times.

Because many catheters are flushed and maintained with heparinized saline and because alteplase mixing instructions recommend against mixing alteplase with heparin or heparinized saline solution, the question arises whether alteplase at this dose should be used in catheters that may retain residual heparin. The current study did not exclude patients based on previous heparin use, nor did it collect specific information on the flush solutions used. Based on reports of the current use of heparinized flush solutions, it is likely that the current study did include a large number of patients in whom heparin was previously used in their occluded lines. The safety and efficacy profile of the current study suggest that any effect of heparin is unlikely to be clinically important.

The fibrin binding and specificity of alteplase may be responsible for the high rates of efficacy demonstrated in this trial. Unlike with thrombolytic agents such as urokinase, with their lower or nonexistent fibrin binding, which may require prolonged constant infusions or administration of high, systematically thrombolytic doses, a brief instillation of alteplase is all that is necessary to achieve the high rates of patency shown in the current trial. By binding to fibrin and locally activating

plasminogen in the clot, systemic thrombolysis can be avoided. Additionally, because alteplase is not easily washed off clots, unlike non–fibrin-binding thrombolytic drugs, it is likely able to maintain a local effect and thereby require a lower (safer) total dose for successful restoration of catheter function.

The current study did not include catheters that were used for hemodialysis. However, catheters of similar type (tunneled 14-F apheresis catheters) were included in the trial and showed efficacy rates similar to those seen in the overall study. Although numerous reports suggest that alteplase may be safe and effective for restoration of function to catheters used in hemodialysis (11–14), no direct measure was made in the current study.

The safety of alteplase in the current study was encouraging. Although the doses of alteplase used in the current study are between only 2%–4% (2–4 mg) of the usual dose for the treatment of acute myocardial infarction, case studies are unclear as to whether there is a dose of alteplase below which there are no safety issues. Because of the limited number of subjects in the current study, only limited safety conclusions can be drawn. More detailed safety conclusions await the results of the ongoing COOL 2 safety trial.

The current study has several limitations. Because angiograms were not performed, no conclusions can be reached as to the efficacy of restoration of flow based on the cause of catheter malfunction. Additionally, catheters that had been occluded for less than 48 hours were not studied in the current study because they are more likely to be occluded as a result of mechanical problems. Finally, the safety of any thrombolytic therapy cannot be established with the limited number of patients treated in the current study; therefore, an additional study establishing the safety of 1,000 patients treated with 2 mg alteplase was conducted in parallel with this study and will be reported elsewhere.

In summary, this study has shown a profound benefit of alteplase (at a dose of 2 mg in 2 mL) compared to placebo for the restoration of flow to dysfunctional CVADs. This effect was seen in a clinically selected population of patients and did not require angiographic assessment of catheters. The treatment was well tolerated and no adverse safety events were reported. Therefore, alteplase appears to be safe and effective for restoration of flow to dysfunctional CVADs.

Acknowledgment: the participants in the COOL Efficacy Trial were: Jeffrey W. Andrey, MD, Scripps Clinic, La Jolla, CA; John F. Angle, MD, Department of Radiology, University of Virginia Health System, Charlottesville, VA; Joseph M. Carrucciu, MD, J.T. Mather Memorial Hospital, Port Jefferson, NY; Carlos M. de Castro III, MD, Duke University Medical Center, Morris Cancer Clinic, Durham, North Carolina; George A. Fisher, Jr, MD, PhD, Departments of Medicine and Oncology, Stanford University Hospital, Palo Alto, California; Paul S. Gaynon, MD, Children's Hospital Los Angeles, Los Angeles, California; Maria de Lourdes A.R. Gomes, MD, Department of Radiology, University of Minnesota Academic Health Center, Minneapolis, Minnesota; William D. Haire, MD, University of Nebraska Medical Center, Omaha, Nebraska; Bruce P. Himelstein, MD, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; David H. Irwin, MD, Alta Bates Comprehensive Cancer Center, Berkeley, California; Jan Jansen, MD, PhD, Indiana Blood and Marrow Transplantation, Indianapolis, Indiana; Sophie M. Lanzkron, Texas Transplant Institute at Southwest Texas Methodist Hospital, San Antonio, Texas; Jane L. Liesveld, MD, University of Rochester Medical Center, Rochester, New York; Steven P. Lipman, MD, Englewood Hospital and Medical Center, Englewood, New Jersey; John Lister, MD, Division of Hematology/Oncology, Western Pennsylvania Hospital, Western Pennsylvania Cancer Institute, Pittsburgh, Pennsylvania; Paul F. Mansfield, MD, The University of Texas M.D. Anderson Cancer Center, Houston, Texas; Geno J. Merli, MD, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; Gerald P. Miletello, MD, Hematology/Oncology Clinic, Baton Rouge, Louisiana; Hyman B. Muss, MD, Medical Center Hospital of Vermont, Burlington, Vermont; Ellis J. Neufeld, MD, PhD, Children's Hospital, Boston, Massachusetts; Michael L. Nieder, MD, Rainbow Babies and Children's Hospital, Cleveland, Ohio; Timothy J. O'Rourke, MD, Grand Rapids Clinical Oncology Program, Grand Rapids, Michigan; Donald J. Ponec, MD, Tri-City Medical Center Radiology Department, Oceanside, California; Dennis A. Priebat, MD, Washington Hospital Center, Washington, DC; Kanti R. Rai, MBBS, North Shore–Long Island Jewish Medical Center, New Hyde Park, New York.

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