First Experience With Direct Factor Xa Inhibition in Patients With Stable Coronary Disease

A Pharmacokinetic and Pharmacodynamic Evaluation

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Background—Thrombin generation is critical to the formation of an arterial thrombus after rupture of an atherosclerotic plaque. In patients with stable coronary disease receiving standard medical therapy, we evaluated the pharmacokinetics, pharmacodynamics, and safety profile of DX-9065a, a novel small-molecule anticoagulant that directly, selectively, and reversibly inhibits factor Xa.

Methods and Results—In a double-blind trial, 73 patients (median age, 63 years; 29% women) were randomly assigned to receive a fixed-dose intravenous bolus, followed by a 72-hour infusion of placebo or 1 of 4 weight-adjusted regimens of DX-9065a. Plasma samples were collected during infusion and a 24-hour elimination period. Only minor bleeding occurred, predominantly ecchymoses at infusion sites, and its incidence did not differ significantly among the groups, including placebo. Median hemoglobin, platelet count, serum creatinine level, and liver function tests did not change significantly from baseline during infusion or elimination. Significant predictors of pharmacokinetic response included infusion dose and weight. At 60 hours into the DX-9065a infusion, plasma drug levels correlated strongly with anti-factor Xa activity (r=0.97), prothrombin time (r=0.77), and international normalized ratio (r=0.72) but less so with activated partial thromboplastin time (r=0.56; all P<0.001).

Conclusions—This is the first study of a selective, reversible, and direct small-molecule factor Xa inhibitor in patients with stable coronary disease. These data lay the foundation for further investigation of factor Xa inhibitors in the treatment of patients with coronary atherothrombosis. (Circulation. 2002;105:2385-2391.)

Key Words: anticoagulants ■ coronary disease ■ pharmacokinetics ■ thrombin ■ thrombosis

Thrombin generation is a critical component of the coronary arterial thrombosis that follows atheromatous plaque disruption. In response to vascular injury, thrombin activates platelets, amplifies further thrombin generation, converts soluble fibrinogen to insoluble fibrin, stabilizes the fibrin meshwork, and initiates the cytokine-mediated inflammatory process. These actions provide a potent stimulus for perpetuation of the thrombotic milieu.

The attenuation of thrombus growth and distal embolization represents a logical, important objective for treatment strategies in acute coronary syndromes. Although the benefits derived from platelet inhibition with aspirin or a thienopyridine and intravenous glycoprotein IIb/IIIa receptor antagonists have been established, the success of antithrombotic therapies targeting factors within the coagulation cascade has varied.

Although the limitations of anticoagulants probably reflect a composite of pharmacokinetic and pharmacodynamic shortcomings, the comparatively favorable results achieved with low-molecular-weight heparin (LMWH) compared with unfractionated heparin suggest that factor Xa, proximally positioned at the confluence of the intrinsic and extrinsic coagulation pathways, may be a more biologically appealing therapeutic target. Enthusiasm for investigating factor Xa inhibitors in arterial disease was initially sparked by favorable trial results of indirect factor Xa inhibitors compared with enoxaparin in the treatment and prevention of venous thromboembolic disease. The results of two trials, Pentasaccharide as an Adjunct to Fibrinolysis in ST-Elevation Acute Myocardial Infarction (PENTALYSE) and Pentasaccharide in Unstable Angina (PENTUA) (M.L. Simoons, unpublished data, November 2001), extend the safety and preliminary...
efficacy experience of indirect factor Xa inhibitors to patients with ST-elevation acute myocardial infarction (MI) or an unstable coronary syndrome, respectively.

DX-9065a is the first in a class of small-molecule, direct factor Xa inhibitors. It specifically neutralizes factor Xa (K_i = 0.041 μmol/L) and exerts little effect on other proteases, particularly thrombin (K_i > 2000 μmol/L). DX-9065a inhibits both free and clot-bound prothrombinase, exerting an anticoagulant effect at plasma concentrations as low as 15 ng/mL (data on file, Daiichi Pharmaceutical Co, Ltd). Its antithrombotic efficacy has been shown in animal models of disseminated intravascular coagulation, venous thrombosis, arteriovenous shunt thrombosis, and vein graft thrombosis.

When given to healthy male volunteers, DX-9065a has been well tolerated, with no serious adverse events or clinically significant changes in routine laboratory assessments or bleeding time. DX-9065a exhibits renal clearance, and, in a study of single, increasing, intravenous doses of DX-9065a, peak plasma concentrations reached 1640 ng/mL in subjects receiving 30 mg over a period of 1 hour. At these levels, Xa clotting time increased 3.9-fold; prothrombin time (PT), 2.9-fold; and activated partial thromboplastin time (aPTT), 2.1-fold. DX-9065a exhibits renal clearance, particularly thrombin (K_i = 110 ng/mL), contraindicated to anticoagulant or antiplatelet agents, or assay measurements.

Initial phase I investigations with DX-9065a excluded women, subjects > 55 years of age, and those with mild renal insufficiency. Accordingly, the Xa Neutralization for Atherosclerotic Disease Understanding (XaNADU-IB) trial was designed to study DX-9065a in patients more representative of those likely to be treated in practice. Our purpose was to characterize the pharmacokinetic and pharmacodynamic effects and safety profile of intravenous DX-9065a in older men and women with coronary artery disease (CAD).

Methods

XaNADU was a randomized, double-blind, placebo-controlled, phase IB study evaluating a bolus and 72-hour continuous infusion of DX-9065a. Figure 1 displays the process for recruitment, screening, enrollment, and initial treatment of patients.

Dosing

Patients were randomly assigned to receive 1 of 4 DX-9065a dose regimens or placebo. All patients received a bolus injection (1 mg DX-9065a or placebo) over a period of 1 minute. Bolus injection was followed by a 72-hour continuous infusion of a fixed infusion rate of DX-9065a targeted to achieve 1 of 4 plasma concentration levels or placebo. The infusion rates were weight-adjusted to target the following 4 DX-9065a plasma concentrations: group 1: 15 ng/mL, group 2: 50 ng/mL, group 3: 100 ng/mL, and group 4: 200 ng/mL.

Clinical Assessments

Patients were monitored during infusion for major or minor bleeding events according to the Thrombolysis In Myocardial Infarction (TIMI) and Global Utilization of Streptokinase in TPA (alteplase) classification. External bruising was assessed every 24 hours and quantified by area measurement. All drug exposures were carefully recorded. Information about clinical, safety, adverse-event, and laboratory assessments was obtained during follow-up visits scheduled 7 and 10 days after random assignment.

Laboratory Assessments

Samples were drawn to measure plasma drug concentration, anti-factor Xa activity, PT, international normalized ratio (INR), and aPTT at baseline; 20 minutes into infusion; 1, 4, 16, 24, 36, 48, and 72 hours into infusion; and 1, 4, 12, 24, 96, and 168 hours after infusion. Safety assessments included daily local measurements of chemistry, complete blood count, and liver function as well as stool hemoccult and urinalysis with microscopic examination. Creatinine clearance was calculated from a 24-hour urine sample collected before random assignment.

Safety Assessments

The PT, INR, and aPTT were performed by routine methods of the Core Coagulation Laboratory (Fletcher-Allen Health Care, University of Vermont). Factor Xa inhibition by DX-9065a was measured (Colchester Research Facility, University of Vermont) with the Rotachrome anti–factor Xa assay (Diagnostica), following manufacturer specifications. Results of this assay were expressed in heparin anti–factor Xa units measured against the manufacturer’s heparin standard curve. DX-9065a was measured directly by means of liquid chromatography/mass spectrometry (Bioanalytical Systems).

Data and Safety Monitoring Committee

Adverse experiences, bleeding, serum creatinine, liver enzymes, platelet counts, and additional chemistry and hematology data were

Candidate Screening

- Complete history, physical examination, lab studies, bleeding questionnaire

Inclusion Criteria

- Age 55–75 years
- Stable CAD: prior infarction or revascularization, or CAD on angiography
- Ability to give informed consent

Exclusion Criteria

- Unstable CAD: MI < 3 months, new, increasing/resting angina at baseline, CCS class 4 heart failure
- Weight ≥ 100 kg
- Peptic ulcer disease; < 3 months of gastrointestinal or percutaneous bleeding; < 3 months
- Severe pre-existing hypertension (>180/110 mm Hg)
- Severe hypercoagulable state, coagulopathy, renal disease, liver disease, liver transplantation, ascites, or chronic obstructive pulmonary disease
- Severe dysrhythmia or atrial fibrillation
- Severe left ventricular systolic dysfunction (LVEF < 30%)
- Severe coagulopathy, abnormal liver function, or history of chronic active liver disease
- Severe hepatic impairment
- Severe renal impairment
- Severe peripheral vascular disease
- Active intracranial hemorrhage
- Neurosurgery
- Severe bleeding disorder
- Other serious concurrent medical conditions

Randomization

7:1:1:1, bolus + 72-hour infusion

Placebo

- Group 1: 15 ng/mL, n = 15
- Group 2: 50 ng/mL, n = 15
- Group 3: 100 ng/mL, n = 15
- Group 4: 200 ng/mL, n = 15

*Target plasma concentration of DX-9065a

Figure 1. Study design. CCU indicates coronary care unit; Cr, creatinine.
assessed throughout the study. An independent Data and Safety Monitoring Committee reviewed patient listings and summary tables after enrollment of 10, 15, 26, and 38 patients.

Statistical Analysis

The primary objective of the study was to describe the pharmacokinetic and pharmacodynamic dose-response relations of DX-9065a in patients with stable CAD. Treated patients were the analysis population. Baseline characteristics were summarized as percentages for categorical variables and medians with interquartile ranges (IQR) for continuous variables. Pearson correlation coefficients were calculated across the groups receiving DX-9065a to assess the correlation of coagulation assays at 3 hours (average of 1, 2, and 4 hours for anti–factor Xa activity; 1- and 4-hour average for coagulation assays) and at 60 hours (average of 48, 60, and 72 hours for anti–factor Xa activity; 48- and 72-hour average for coagulation assays) during drug infusion.

Drug concentration over time was plotted for each patient, as was the median drug concentration for each treatment arm. A 3-compartment pharmacokinetic model was used to fit individual drug concentrations over time (WinNonlin Software, Pharsight Corporation). Linear regression was used to explore the relation between peak drug concentration ($C_{\text{max}}$) and baseline clinical variables. Dose responses of coagulation assays (PT, INR, aPTT, and anti–factor Xa activity) and laboratory data (serum creatinine, liver enzymes, hemoglobin, and platelets) also were plotted.

Results

Overall, 73 patients with stable CAD were randomly assigned to treatment group or placebo, and all received the assigned treatment without interruption or early discontinuation. Women represented 30% of the cohort (Table 1). Most patients had a prior MI and had undergone coronary revascularization. No patient had class IV heart failure. All patients received aspirin; 71% also received a β-blocker, and 48% also received an ACE inhibitor. The high use of lipid-lowering agents (86%) reflected the high incidence of hypercholesterolemia.

Pharmacokinetic Measurements

Five minutes after the 1-mg bolus of DX-9065a was given, the median (IQR) plasma drug concentration was 67.9 (55.2 to 75.8) ng/mL (Figure 2). Thereafter, except in group 1, plasma concentrations decreased to nadir values below target levels. At 4 hours of infusion, group 1 had a median concentration 7% higher than the target concentration, group 2 was at 79% of target, group 3 was at 77% of target, and group 4 was at 68% of target. At 16 hours, the median concentrations approximated target concentrations: group 1, 16.6 (14.3 to 17.7) ng/mL; group 2, 48.8 (43.2 to 53.2) ng/mL; group 3, 95.2 (89.6 to 115.0) ng/mL; and group 4, 196.5 (133.9 to 225.2) ng/mL. Over the next 56 hours, concentrations gradually increased in all groups until the infusion was completed (72-hour values: 20.8 [17.1 to 24.3], 62.2 [60.2 to 73.3], 140.3 [120.5 to 154.8], and 271.9 [188.3 to 323.9] for groups 1 to 4, respectively). At 4 hours after infusion, DX-9065a levels were 50% of the 72-hour concentration in each group. At 24 hours after infusion, the plasma concentrations were 26% to 29% of the 72-hour values. Drug remained detectable 7 days after infusion: median concentrations of 2.2 (1.7 to 2.7), 6.1 (5.3 to 7.7), 11.6 (10.8 to 17.8), and 24.9 (21.0 to 28.0) ng/mL in groups 1 to 4, respectively.

![Figure 2. Median plasma concentration (dashed lines, 25th and 75th percentile) of DX-9065a for groups 1 through 4 during the infusion and elimination phases.](http://circ.ahajournals.org/DownloadedFrom)
The pharmacokinetic modeling estimates are presented in Table 2. The mean administered dose represents the bolus dose and weight-adjusted dose in each group. Three half-life ($t_{1/2}$) values were variables in the three compartments used in the pharmacokinetic model. The $t_{1/2}$ of the first compartment ($\alpha$) was rapid (range, 0.14 to 0.30 hours), followed by longer $t_{1/2}$ values in the second ($\beta$; range, 1.93 to 3.20 hours) and third compartments ($\gamma$; range, 76.57 to 98.86 hours).

Interindividual differences were increased at higher doses. Baseline predictors of pharmacokinetic response (using treatment dose, age, height, weight, sex, and baseline creatinine in the linear regression model) are presented in Table 3 (model 1, $r^2=0.957$). When translated back to the original units, it implies that the relative variation of the values from predicted is $\approx 18\%$ (1 SD). A second model was fitted that used only dose and weight as predictors. The estimated results are shown in Table 3 (model 2, $r^2=0.948$). When translated back to the original units, it implies that the relative variation of the values from predicted is $\approx 21\%$ (1 SD).

### Pharmacodynamic Measurements

All pharmacodynamic measurements increased with increasing drug concentration. The measures paralleled drug concentrations during both infusion and elimination of DX-9065a. Because the relation was dose dependent, group 4 had the most pronounced response in all pharmacodynamic measures of anticoagulation: anti-factor Xa (anti-Xa) activity level, PT, aPTT, and INR (Figure 3).

At baseline, anti-Xa activity level was undetectable for all groups receiving DX-9065a. Anti-Xa activity levels were scarcely detectable with the lowest DX-9065a infusion (group 1). The median value at 72 hours into the DX-9065a infusion was 0.01 IU (IQR, 0 to 0.04) and subsequently fell and remained 0.00 IU (0 to 0.01) 4 hours into the elimination phase. In group 2, peak anti-Xa activity levels were 0.11 IU (0.08 to 0.13) at 72 hours into infusion and were undetectable at 168 hours into elimination. In group 3, anti-Xa activity levels at 1 hour increased from 0.10 IU (0.08 to 0.11) to 0.23 IU (0.20 to 0.24) at 72 hours and decreased to 0.12 IU (0.09 to 0.16) at 4 hours. In the elimination phase, the levels for group 3 continued to decrease: 0.07 IU (0.05 to 0.09) at 24 hours and 0.03 IU (0.01 to 0.05) at 168 hours. The response in group 4 was similar to group 3 at 1 hour (0.13 IU, 0.11 to 0.16) but was higher at 4 hours: 0.22 IU (0.17 to 0.27) compared with 0.12 IU (0.11 to 0.19). Peak anti–Xa activity for group 4 was 0.38 IU (0.34 to 0.43) at 72 hours and decreased to 0.22 IU (0.18 to 0.31) 4 hours into elimination and 0.13 IU (0.09 to 0.17) by 24 hours. Levels were still measurable (0.06 IU, 0.04 to 0.08) 7 days after study drug discontinuation.

Peak response of PT in group 1 occurred after the DX-9065a bolus. At 1 hour into infusion, PT increased from 13 seconds (12.4 to 13.8) at baseline to 14 seconds (12.7 to 15.4). PT at 72 hours into infusion was 13.4 seconds (12.6 to 13.6) and returned to baseline 1 hour into elimination. PT for group 2 remained relatively constant from 1 hour to the end of infusion (baseline, 12.6 seconds [12.1 to 13.1] to 13.7 seconds [12.8 to 14]) at 1 hour and 13.9 seconds [13.6 to 14.5] at 72 hours. For group 3, PT increased from 13.1 seconds (12.6 to 14.3) at baseline to 16.1 seconds (14.8 to 16.9) at 72 hours of DX-9065a infusion. At 4 hours and 24 hours after infusion, PT measurements were 14.5 seconds (13.6 to 16) and 13.9 seconds (13 to 14.2), respectively. Median PT values were highest in group 4, reflecting the highest concentration of DX-9065a infusion. At 1 hour, PT was similar to all groups at 13.9 seconds (13.3 to 15.2) and increased to 16.5 seconds (15.2 to 17.4) at 24 hours of DX-9065a infusion. At 72 hours, PT was 17.4 seconds (16.2 to 18.7). After DX-9065a infusion, PT was 16.6 (15.8 to 17.5), 15.3 (14.8 to 15.9), and 14.2 (13.6 to 15) seconds at 1, 4, and 24 hours, respectively.

The response of aPTT to DX-9065a was more modest. No effect was seen in group 1 compared with baseline (27 seconds, 25 to 28). For groups 2 to 4, median aPTT values increased from 26 seconds at baseline (all groups) to 30, 31, and 33 seconds, respectively.

Anti–Xa activity correlated highly with drug concentration (Table 4) at both 3 hours of infusion ($r=0.92; P<0.0001$) and 60 hours of infusion ($r=0.97; P<0.0001$). PT and INR correlated less well ($r=0.33; P<0.01$) early into DX-9065a

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**TABLE 2. Pharmacokinetic Estimates**

<table>
<thead>
<tr>
<th>Group</th>
<th>DX-9065a Target, ng/mL</th>
<th>72-h Weight-Adjusted Dose, mg</th>
<th>$\alpha$-t$_{1/2}$, h</th>
<th>$\beta$-t$_{1/2}$, h</th>
<th>$\gamma$-t$_{1/2}$, h</th>
<th>72-h $C_{max}$, ng/mL</th>
<th>Area Under the Curve, ng*h/mL</th>
<th>Mean Residence Time, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>12.1±2.5</td>
<td>0.14 (0.02)</td>
<td>1.93 (0.18)</td>
<td>76.57 (19.57)</td>
<td>20.4±3.1</td>
<td>2219±403</td>
<td>64.2 (19.2)</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>37.8±9.2</td>
<td>0.24 (0.15)</td>
<td>2.54 (1.17)</td>
<td>81.46 (16.4)</td>
<td>64.8±11.0</td>
<td>6154±1094</td>
<td>63.1 (12.0)</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>78.9±15.2</td>
<td>0.25 (0.05)</td>
<td>2.67 (0.44)</td>
<td>96.68 (19.42)</td>
<td>138.6±24.6</td>
<td>14187±4568</td>
<td>80.4 (18.9)</td>
</tr>
<tr>
<td>4</td>
<td>200</td>
<td>150.6±29.5</td>
<td>0.30 (0.20)</td>
<td>3.20 (0.57)</td>
<td>82.95 (7.88)</td>
<td>266.9±77.1</td>
<td>24737±8940</td>
<td>66.8 (7.8)</td>
</tr>
</tbody>
</table>

Mean values±SD or (SEM). Area under the curve calculated by trapezoidal rule.

Mean values±SD or (SEM). Area under the curve calculated by trapezoidal rule.

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**TABLE 3. Predictors of Pharmacokinetic Response**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln (Dose)</td>
<td>0.961</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.008</td>
<td>0.0200</td>
</tr>
<tr>
<td>ln (Height)</td>
<td>-0.656</td>
<td>0.3301</td>
</tr>
<tr>
<td>ln (Weight)</td>
<td>0.271</td>
<td>0.0105</td>
</tr>
<tr>
<td>Baseline creatinine</td>
<td>0.404</td>
<td>0.0017</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.195</td>
<td>0.0102</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ln (Dose)</td>
<td>0.988</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ln (Weight)</td>
<td>-0.624</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

In indicates natural logarithm.
Figure 3. Relation of median DX-9065a concentration over time in group 4 to median anti-factor Xa activity (A), INR (B), and aPTT values (C).
infusion (3 hours) rather than later (60 hours, \( r=0.77 \) and 0.72, respectively; \( P<0.0001 \)). The correlation of aPTT also increased during later measurements compared with early measurements (3 hours, \( r=0.11 \), \( P=NS \); 60 hours, \( r=0.56 \), \( P<0.0001 \)).

**Clinical Data**

Overall, DX-9065a was well tolerated during infusion. No TIMI major or minor bleeding occurred, and no patient received a blood transfusion. By GUSTO-I criteria, the incidence of minor bleeding was 33% in the placebo group, 44% in group 1, 39% in group 2, 43% in group 3, and 60% in group 4 (\( P=0.6578 \) for overall difference and \( P=0.1610 \) for overall trend). Most minor bleeding consisted of ecchymosis at the infusion site.

No clinical laboratory measure changed significantly within or between groups during infusion or elimination. No serious adverse events were reported during infusion. One patient had a fatal MI >72 hours after infusion. Because it occurred early during enrollment, a chest pain safety summary form was developed and completed for every patient during each follow-up visit. No significant change in anginal pattern was identified in later patients.

**Discussion**

This is the first report of a direct, selective factor Xa inhibitor infused in patients with CAD. Accumulating experience in venous thromboembolic disease with indirect antagonists provides compelling support for factor Xa–targeted therapies. XaNADU-IB heightens the level of enthusiasm and extends the experience to include patients with arterial disease.

Enrollment in XaNADU-IB represented a typical CAD population. Most had had an MI and undergone coronary revascularization. As anticipated, XaNADU-IB enrolled older patients, a relatively large proportion of women, and patients with evidence of mild renal insufficiency. Concomitant medications reflected appropriate secondary prevention therapy, thereby allowing initial evaluation of cometabolism and potential interactions with DX-9065a. No interactions were identified.

Our primary objective was to delineate the pharmacokinetic and pharmacodynamic profiles of DX-9065a. The rationale for the range of plasma concentrations studied reflects investigations that showed an anticoagulant effect at doses as low as 15 ng/mL and a good safety profile at doses as high as 200 ng/mL. Targeted concentrations were modeled from phase I studies in young, healthy male volunteers. Median measured plasma concentrations were higher than target, with most of the variation in pharmacokinetic response attributed to dose and weight. Furthermore, although drug levels were halved 4 hours after infusion, DX-9065a remained measurable at 7 days. The clinical effect of a persistent, low level of factor Xa inhibition is unknown.

Traditional measures of coagulation (PT, INR, and aPTT) correlated less with plasma drug concentrations early during infusion compared with later time points, perhaps because of reduced sensitivities of these assays to low drug concentrations. The mechanism for a differing response in PT to direct factor Xa inhibition with DX-9065a versus the pentasaccharide is unknown but may reflect greater inhibition of thrombinase activity. Despite statistically significant correlations in all measures after reaching specified target concentrations, these assays appear less than ideal to monitor the anticoagulant effect of DX-9065a.

In contrast, anti-Xa activity correlated strongly with plasma DX-9065a concentrations, suggesting a potential role in determining anticoagulant response. In a separate analysis, calculations performed with the use of a chromogenic assay of anti-Xa activity reliably predicted plasma concentrations when compared with the actual direct measurement of drug concentration (\( r=0.99 \)).

Because this is the first clinical experience with a direct factor Xa inhibitor, the optimal method for determining anti-Xa activity still must be defined. The method chosen for this study (Rotachrom) uses LMWH to construct a standard curve. Because there are considerable differences in structure and activity between DX-9065a and LMWH, interpretation of heparin-based anti-Xa activity should be approached cautiously, particularly in light of existing variability between LMWH preparations and anti–factor Xa assays. To emphasize the point of distinction between coagulation measurements and antithrombotic response, a recent study that used an ex vivo flow chamber with plasma concentrations and anti–factor Xa activity levels similar to those observed in group 2 (50 mg/mL) showed significantly reduced thrombus formation with DX-9065a compared with enoxaparin (1 mg/kg) (J.J. Badimon, personal communication). Thus, the clinical response and antithrombotic potential based on measured anti–factor Xa activity may vary among compounds (as might the “therapeutic level”).

An essential component of drug development is safety and tolerability. DX-9065a was well tolerated in patients with stable CAD taking conventional cardiac medications (including aspirin), and there were no discernible adverse effects on renal or hepatic function, platelet count, or hemoglobin. There were no major bleeding complications and only a small, nonsignificant, dose-related increase in minor bleeding in group 4 versus placebo by the GUSTO-I criteria.

In conclusion, specific targeting of factor Xa is a biologically appealing consideration for pharmacological therapy in thrombotic disorders of the cardiovascular system. XaNADU-IB represents the first clinical experience in patients with CAD with the direct, selective factor Xa antagonist DX-9065a. Initial observations are encouraging and suggest that a broad range of plasma concentrations can be achieved reliably and safely. Further investigation of this compound is warranted in patients with coronary athero-
thrombosis to further refine the safety profile of DX-9065a and provide initial assessments of efficacy.

Appendix

Participants
The following investigators participated in the trial (numbers in parentheses are General Clinical Research Center National Center for Research Resources grant numbers): University of Alberta Hospital, Clinical Investigation Unit: V. Dzavik, R. Cornish; Baylor College of Medicine: N. Kleiman, K. Maresh; Boston University Medical Center (M01-RR00533): J. Ansell, M.E. McDonough; Duke University Medical Center (M01-RR00030): R.A. Harrington, V. Chadaram; University of Florida (M01-RR00082): C. Pepine, R. Cooper-DeHoff; The Johns Hopkins University School of Medicine (M01-RR00052): G. Gerstenblith, S. Townsend; Johns Hopkins Bayview Medical Center (M01-RR02719): M. Williams, L. Weinberg; Mount Sinai Medical Center (M01-RR00071): D. Vorchheimer, I. Guzman; Royal University Hospital: R. Herman, A. Buxton; Tulane University Medical Center (M01-RR05096): A. Tenaglia, E. Plaia.

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References
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