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ORIGINAL ARTICLE

Initial experience with factor-Xa inhibition in percutaneous coronary intervention: the XaNADU-PCI Pilot

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Summary. *Background*: Direct factor (F)Xa inhibition is an attractive method to limit thrombotic complications during percutaneous coronary intervention (PCI). *Objectives*: To investigate drug levels achieved, effect on coagulation markers, and preliminary efficacy and safety of several doses of DX-9065a, an intravenous, small molecule, direct, reversible FXa inhibitor during PCI. *Patients and methods*: Patients undergoing elective, native-vessel PCI ($n = 175$) were randomized 4 : 1 to open-label DX-9065a or heparin in one of four sequential stages. DX-9065a regimens in stages I–III were designed to achieve concentrations of $>100\,ng\,mL^{-1}$, $>75\,ng\,mL^{-1}$, and $>150\,ng\,mL^{-1}$. Stage IV used the stage III regimen but included patients recently given heparin. *Results*: At 15 min median (minimum) DX-9065a plasma levels were 192 (176), 122 (117), 334 (221), and 429 (231) $ng\,mL^{-1}$ in stages I–IV, respectively. Median whole-blood international normalized ratios (INRs) were 2.6 (interquartile range 2.5, 2.7), 1.9 (1.8, 2.0), 3.2 (3.0, 4.1), and 3.8 (3.4, 4.6), and anti-FXa levels were 0.36 (0.32, 0.38), 0.33 (0.26, 0.39), 0.45 (0.41, 0.51), and 0.62 (0.52, 0.65) $U\,mL^{-1}$, respectively. Stage II enrollment was stopped ($n = 7$) after one serious thrombotic event. Ischemic and bleeding events were rare and, in this small population, showed no clear relation to DX-9065a dose. *Conclusions*: Elective PCI is feasible using a direct FXa inhibitor for anticoagulation. Predictable plasma drug levels can be rapidly obtained with double-bolus and infusion DX-9065a dosing. Monitoring of DX-9065a may be possible using whole-blood INR. Direct FXa inhibition is a novel and potentially promising approach to anticoagulation during PCI that deserves further study.

Keywords: angioplasty, anticoagulant, factor Xa inhibition.

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Introduction

Catheter-induced atherosclerotic plaque rupture during percutaneous coronary intervention (PCI) activates platelets and initiates the extrinsic and intrinsic coagulation cascades. The resulting dynamic thrombotic process is the principal mechanism behind many early clinical complications of PCI. Unfractionated heparin remains the cornerstone of anticoagulation in PCI [1,2]. Its numerous limitations, however, have spawned the development of newer agents that offer pharmacokinetic, pharmacodynamic, and potential clinical advantages.

Factor (F)Xa, situated at the intersection of the intrinsic and extrinsic pathways, combines with factor Va and calcium to form the prothrombinase complex that converts prothrombin to thrombin. Because of its pivotal role in thrombosis, inhibition of FXa is an attractive method to limit thrombin generation and activity. Initial enthusiasm for inhibiting FXa followed the observation that low-molecular-weight (LMW) heparin, with relatively greater anti-FXa/IIa activity, appeared superior to unfractionated heparin in treatment of both venous and arterial thrombosis [3,4]. Promising results with the indirect FXa

inhibitor, fondaparinux, in venous and arterial thrombosis has generated further enthusiasm for therapeutic FXa inhibition [5–7].

DX-9065a (Daiichi Pharmaceuticals, Co., Ltd, Tokyo, Japan) is a small-molecule (571.07 Da), direct, selective, reversible FXa inhibitor that inhibits free FXa and FXa within the prothrombinase complex [8]. It has a three-compartment distribution [9] and is cleared primarily through renal mechanisms. Its antithrombotic activity, present at concentrations as low as 15 ng mL^{-1} [10], has been assessed in several animal models of thrombosis [11–14]. In an *ex vivo* model of thrombosis, DX-9065a concentrations of 50 ng mL^{-1} showed greater antithrombotic activity than therapeutic doses of enoxaparin [15]. In the Xa Neutralization for Atherosclerotic Disease Understanding (XaNADU) IB study, 72-h infusions of DX-9065a produced concentrations of 14–324 ng mL^{-1} and were well tolerated in patients with stable coronary disease [9].

The XaNADU-PCI Pilot is the first investigation of DX-9065a in patients undergoing percutaneous coronary intervention. The objectives of the XaNADU-PCI Pilot study were to describe the achieved drug levels and effect on coagulation markers of various doses of DX-9065a and to assess the feasibility and preliminary efficacy and safety of using DX-9065a as an anticoagulant in elective PCI.

Methods

The XaNADU-PCI Pilot was a Phase II, multicenter, randomized, patient-blinded, heparin-controlled, dose-finding study in patients undergoing elective native-vessel PCI. The trial was conducted in sequential stages, each investigating a different DX-9065a dosing regimen and enrolling up to 56 patients (Fig. 1). During regular teleconferences, the Steering Committee reviewed cumulative pharmacokinetic, pharmacodynamic, safety, and efficacy data. They then decided whether to continue recruitment into that stage and, as each stage approached completion, what DX-9065a regimen to study next. The Institutional Review Board or Ethics Board at each participating site approved the protocol, and all patients gave written informed consent. A list of participants is available at http://www.dcri.duke.edu/research/publications.html.

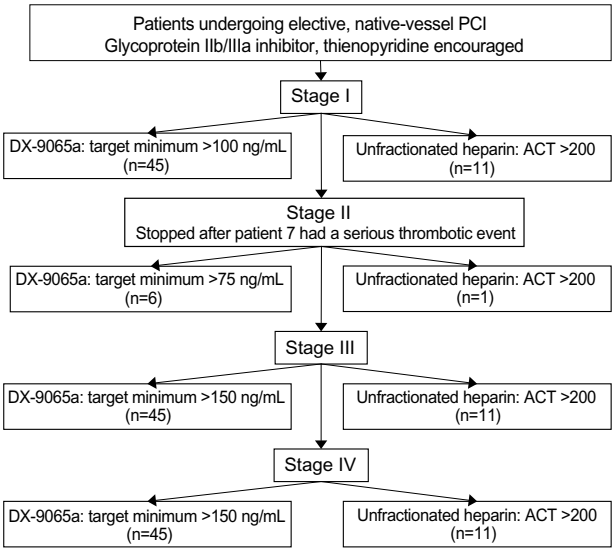

Fig. 1. Design of XaNADU-PCI Pilot.

Patients

Patients aged 18–75 years undergoing elective, native-vessel PCI were eligible. Exclusion criteria were weight >125 kg; sustained hypotension (<90 mmHg) or hypertension (>180/110 mmHg); severe pulmonary edema, dissecting aortic aneurysm, significant valve or congenital heart disease; prior intracranial aneurysm or stroke; hypercoagulable state, coagulopathy, or thrombocytopenia; recent trauma, prolonged cardiopulmonary resuscitation, major surgery, or biopsy of parenchymal organ; recent gastrointestinal or genitourinary bleeding; recent use of fibrinolytic therapy, heparin, or warfarin; hemoglobin <12.0 g dL^{-1}; platelets <100 000 mm^{-3} or >600 000 mm^{-3}; elevated activated partial thromboplastin time (APTT) or prothrombin time (PT); liver-function tests >1.5 times the upper limit of normal; serum creatinine >1.8 mg dL^{-1}; allergy to aspirin; or known or suspected pregnancy.

Stage IV was designed to investigate interactions between DX-9065a and heparin. Patients who had been on heparin for up to 72 h and who had activated clotting time (ACT) of 120–180 s or an APTT of 1.5–2.5 times the mean normal at the time of screening were eligible. Those with an ACT between 120 and 180 s or an APTT between 1.5 and 2.0 times the mean normal had study drug started 30–60 min after stopping heparin. Those with an APTT 2.0–2.5 times the mean normal had study drug started 1–2 h after stopping heparin. Patients getting LMW heparin with an estimated creatinine clearance [16] >40 mL min^{-1} had study drug started 12–18 h after stopping LMW heparin.

Randomization and treatment (Table 1)

Fifty-six patients were to be enrolled in each stage and randomized 4 : 1 to receive either DX-9065a or unfractionated heparin via central telephone randomization center.

In each stage, patients randomized to DX-9065a received two boluses (10 min apart) and a weight-adjusted, continuous infusion of DX-9065a started with the first DX-9065a bolus. Each regimen was developed by pharmacokinetic simulation to achieve or exceed a minimum specified DX-9065a concentration (WinNonlin software, version 3.0; Pharsight, Mountain View, CA, USA). Simulations were developed using pooled data from Phase I studies in volunteers with and without coronary artery disease [9]. We first investigated a minimum DX-9065a concentration of 100 ng mL^{-1}, then a lower dose (minimum DX-9065a concentration 75 ng mL^{-1}) and then, in stages III and IV, a higher dose (minimum DX-9065a concentration 150 ng mL^{-1}).

Patients randomized to unfractionated heparin received a 60–70-U kg^{-1} bolus with a goal ACT of 200–300 s [if also receiving

Table 1 DX-9065a dosing regimens

Stage	Mean predicted DX-9065a concentration (5th, 95th percentile)*	Bolus (×2)	Infusion <70 kg	Infusion 70–90 kg	Infusion >90 kg
I	154 ng mL^{-1} (113, 210)	2.5 mg	1.0 mg h^{-1}	1.5 mg h^{-1}	2.0 mg h^{-1}
II	112 ng mL^{-1} (83, 153)	1.0 mg	2.0 mg h^{-1}	3.0 mg h^{-1}	4.0 mg h^{-1}
III, IV	228 ng mL^{-1} (168, 310)	2.5 mg	5.0 mg h^{-1} × 30 min then 2.0 mg h^{-1}	5.0 mg h^{-1} × 30 min then 2.5 mg h^{-1}	10.0 mg h^{-1} × 30 min then 3.5 mg h^{-1}

*Fifteen minutes after the second DX-9065a bolus.

a platelet glycoprotein (GP)IIb/IIIa inhibitor] or a 100-U kg^{-1} bolus with a goal ACT of 250–350 s (without GPIIb/IIIa inhibition).

Study drug was stopped at completion of PCI. Arterial sheaths were removed after 1–2 h or with a recorded ACT <170 s.

Concomitant medications

All patients received aspirin 325 mg and clopidogrel 300 mg before PCI, and 325 mg and 75 mg daily for ≥30 days after PCI. GPIIb/IIIa inhibitors were strongly encouraged, but their use and the selection of a particular agent was up to the treating physician.

Drug concentrations

A subset of patients ($n = 25$) randomized to DX-9065a at select sites had samples collected for plasma drug concentrations at baseline; 1 and 5 min after the first DX-9065a bolus; 1, 5, 15, 30, 45, and 60 min after the second bolus; and at study-drug discontinuation. Samples were collected in 4.5 mmol L^{-1} EDTA and shipped on dry ice to Bioanalytical Systems, Inc. (West Lafayette, IN, USA). DX-9065a levels were measured by liquid chromatography/mass spectrometry.

Coagulation parameters

All patients had plasma PT/international normalized ratio (INR) and ACT measured locally at baseline, 15 min after the unfractionated heparin bolus or the second DX-9065a bolus, and at study-drug discontinuation.

A subset of patients randomized to DX-9065a at select sites also had additional coagulation markers assessed at 15 min after the second DX-9065a bolus. Bedside whole-blood INR was performed with the Hemochron Junior device (I.T.C., Edison, NJ, USA). Blood samples were collected in 3.2% sodium citrate, centrifuged, and placed on ice. Plasma was then transferred to 0.05-mL cryovials, stored at −70 °C, and batch-shipped to the core coagulation laboratory (University of Vermont) for analysis. Plasma APTT was assessed by routine methods. Anti-FXa levels were measured by Rotachrome anti-Xa assay (Diagnostica, Stago, France). Results are expressed as anti-FXa units measured against the manufacturer's unfractionated heparin standard curve.

Clinical assessments

The main clinical assessments were periprocedural thrombotic complications (abrupt closure, 'no reflow', thrombus formation, side-branch closure, distal embolization, major dissection) and clinical events [myocardial infarction (MI), urgent revascularization, stroke, bleeding]. The protocol mandated that all patients have creatine kinase-myocardial band levels measured every 8 h for 24 h. MI was defined as creatine kinase-myocardial band elevation three or more times the upper limit of normal (ULN) after PCI or two or more times the ULN and ≥50% above the previous nadir after new, symptomatic ischemia. Bleeding was categorized by the Thrombolysis In Myocardial Infarction (TIMI) criteria [17].

Statistical analysis

The number of patients assigned to DX-9065a in each stage ($n = 45$) was selected to exclude a major bleeding rate >5% [one-sided 90% confidence interval (CI)] based on a binomial distribution [18]. The primary efficacy endpoint was the composite of in-hospital death, MI, or urgent revascularization. As this was a Phase II, exploratory trial, no other efficacy or safety hypotheses were prespecified.

Data were summarized as percentages for categorical variables and as medians with interquartile ranges for continuous variables. Median drug levels were plotted over time for each stage. Coagulation markers (whole-blood INR, APTT, ACT, anti-FXa) at 15 min after the second DX-9065a bolus were also plotted by stage. Pearson correlation coefficients were calculated, and the Wilcoxon rank sum test was used to assess overall differences among stages I–III at this time point.

Results

In all, 175 patients were enrolled at 10 centers in the USA and Canada from February 2001 to September 2002.

Baseline and procedural characteristics (Table 2)

Recent MI and positive baseline troponin were more frequent in stage IV, consistent with the inclusion of patients recently given heparin. Procedures were brief, and most patients received a coronary stent, GPIIb/IIIa inhibitors, and clopidogrel.

Table 2 Baseline and procedural characteristics

	DX-9065a				
	Stage I ($n=45$)	Stage II ($n=6$)	Stage III ($n=45$)	Stage IV ($n=45$)	Combined heparin ($n=34$)
Age (years)	60 (55–70)	54 (49–60)	61 (54–69)	60 (52–68)	60 (53–66)
Male sex	80.0%	83.3%	77.8%	82.2%	85.3%
Caucasian	93.3%	50.0%	91.1%	93.3%	91.2%
Weight (kg)	86 (75–95)	81 (78–114)	87 (82–95)	89 (80–100)	90 (73–98)
Diabetes	24.4%	66.7%	15.6%	33.3%	14.7%
Hyperlipidemia	82.2%	66.7%	77.8%	71.1%	73.5%
Current smoking	13.3%	16.7%	24.4%	33.3%	8.8%
MI <3 months	15.6%	0%	4.4%	26.7%	17.7%
Positive baseline troponin	27.3%	0%	0%	51.7%	12.5%
Prior PCI	37.8%	50.0%	31.1%	22.2%	35.3%
Prior bypass surgery	8.9%	0%	8.9%	6.7%	17.6%
PCI duration (h)	0.4 (0.2–0.7)	0.3 (0.3–1.0)	0.3 (0.2–0.6)	0.3 (0.2–0.7)	0.3 (0.1–0.6)
Stent implantation	95.6%	83.3%	93.3%	93.3%	79.4%
Glycoprotein IIb/IIIa inhibitor	80.0%	83.3%	84.4%	95.6%	85.3%
Eptifibatide	35.6%	66.7%	18.8%	57.8%	29.4%
Abciximab	44.4%	16.7%	62.2%	17.8%	47.1%
Tirofiban	0%	0%	2.2%	20.0%	8.8%
Clopidogrel	100%	100%	100%	97.8%	100%

Data are medians (interquartile range) or percentages. PCI, Percutaneous coronary intervention; MI, myocardial infarction.

Drug concentrations (Fig. 2)

Actual DX-9065a concentrations were higher than those predicted by pharmacokinetic simulation. At 15 min after the second bolus, median (minimum–maximum) DX-9065a concentrations were 192 (176–252) ng mL^{-1} in stage I, 122 (117–126) ng mL^{-1} in stage II, 334 (221–450) ng mL^{-1} in stage III, and 429 (231–569) ng mL^{-1} in stage IV.

Coagulation markers (Figs 3 and 4)

Coagulation test results are shown for 15 min after the second DX-9065a bolus or the single unfractionated heparin bolus in Fig. 3. APTTs were modestly elevated above normal with DX-9065a in stages I–III and were higher in stage IV. The correlation between plasma DX-9065a concentration and APTT was poor ($r=0.26$; $P=0.27$). ACTs also were modestly elevated with DX-9065a in all stages, but the correlation again was poor ($r=0.35$; $P=0.14$). Median ACT in the unfractionated heparin group was within the expected range. Median plasma INRs (interquartile range) were slightly and similarly elevated above normal with DX-9065a [1.6 (1.3, 1.8), 1.5 (1.4, 1.6), 1.7 (1.5, 1.9), and 1.5 (1.4, 1.8) in stages I–IV] but not with unfractionated heparin. The correlation between DX-9065a concentration and plasma INR, however, was statistically significant ($r=0.66$; $P=0.006$). Whole-blood INR, on the other hand, was elevated in all stages with DX-9065a, showed an apparent dose–response, and correlated strongly with DX-9065a concentration ($r=0.82$; $P<0.0001$) (Fig. 4A). Median anti-FXa levels ranged from 0.33 anti-FXa U mL^{-1} in stage II to 0.62 anti-FXa U mL^{-1} in stage IV and also correlated strongly with DX-9065a concentration ($r=0.83$; $P=0.0001$) (Fig. 4B).

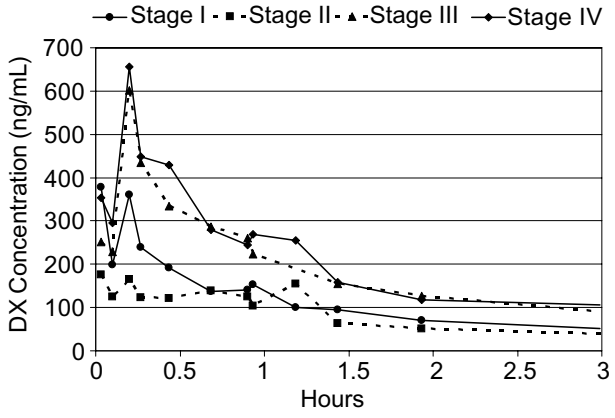

Fig. 2. Median plasma DX-9065a concentrations over time in stages I–IV. Samples at each time point are plotted at their median collection time.

Clinical assessments (Table 3)

There were no deaths or strokes. Ischemic complications were infrequent and within the range expected for elective PCI [19]. In stage I, three patients had side-branch closure after stent implantation resulting in MI, and two other patients had periprocedural MI. In stage II, one patient developed a large intracoronary thrombus that resulted in MI. Enrollment in stage II was terminated after this event. In stage III, two patients had major dissection, both successfully treated with stent implantation, and a third patient had thrombus present before PCI that extended distally without apparent adverse effect. In stage IV, one patient had thrombus present before PCI with downstream propagation, distal embolization, no reflow, and MI. A second patient had subacute stent thrombosis ~12 h after PCI, resulting in urgent revascularization and MI. Two patients had

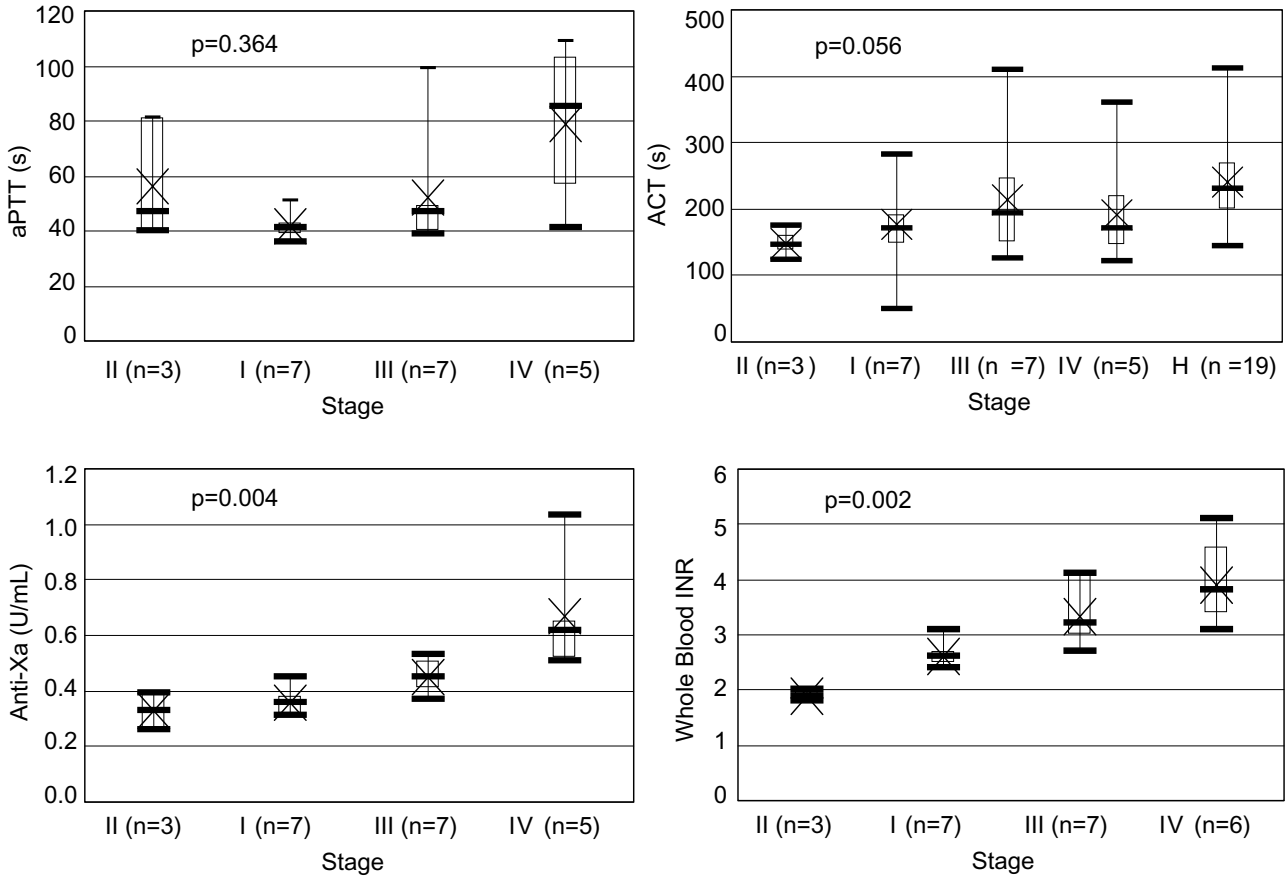

Fig. 3. Coagulation markers 15 min after the second DX-9065a bolus, by treatment. Vertical bars span the minimum and maximum, crosses are means; boxes are interquartile ranges; horizontal lines within boxes are medians. *P*-values test for an overall difference among stages I–III.

side-branch closure, both without adverse clinical effects, and four additional patients had MI. Among the unfractionated-heparin patients, one patient had major dissection successfully treated with stent implantation, and two patients had MI.

Bleeding rates were low and within the range expected for elective PCI; we saw no evidence of a dose–response or a difference by treatment assignment (Table 4). Two patients had TIMI major bleeding, one each in stages I and II; only one required transfusion. Thrombocytopenia was rare and typically mild (80 000–100 000 platelets mm^{-3}). One case of severe thrombocytopenia (platelet count $<20\,000$) occurred in a patient given DX-9065a and abciximab.

Discussion

This is the first report on the use of a direct FXa inhibitor as an anticoagulant in patients undergoing PCI. We found that native-vessel, elective PCI was feasible and safe using DX-9065a as an anticoagulant, at levels ranging from 100 to 400 ng mL^{-1}. Because of the central role of PCI in the management of acute coronary syndromes [20], it is critical to have an understanding of the dosing, safety, and efficacy of DX-9065a in PCI before examining its use in patients with acute coronary syndromes. These data are a valuable first stage towards understanding how these agents might be applied clinically.

Almost all patients in the trial received stents, and most received GPIIb/IIIa inhibitors. Whether such antiplatelet therapy is needed with adequate dosing of a direct FXa inhibitor that blocks the generation of thrombin is an intriguing question that requires further investigation [21].

We investigated doses of DX-9065a that achieved plasma drug levels of 100–400 ng mL^{-1}. The double bolus and infusion regimens used in the XaNADU-PCI Pilot achieve rapid target concentrations without a subsequent trough during the early period of PCI with marked vessel injury and thrombotic stress. This type of dosing regimen has been successfully used with other antithrombotic agents in PCI. Other DX-9065a dosing regimens may be appropriate for other clinical scenarios. These dosing regimens produced DX-9065a levels that were higher than those predicted by pharmacodynamic modeling. At 15 min after the second DX-9065a bolus, all patients had drug concentrations well above the targeted minimum for each stage. This discrepancy between predicted and observed DX-9065a levels may reflect that the model was developed partly from healthy volunteers and the kinetics of DX-9065a may differ in patients undergoing PCI. DX-9065a levels 15 min after the second bolus were higher in stage IV than in stage III, however, the overall pharmacokinetic curves appear similar (Fig. 2) and this finding is probably due to the play of chance. The incorporation of additional pharmacokinetic data, from this and other

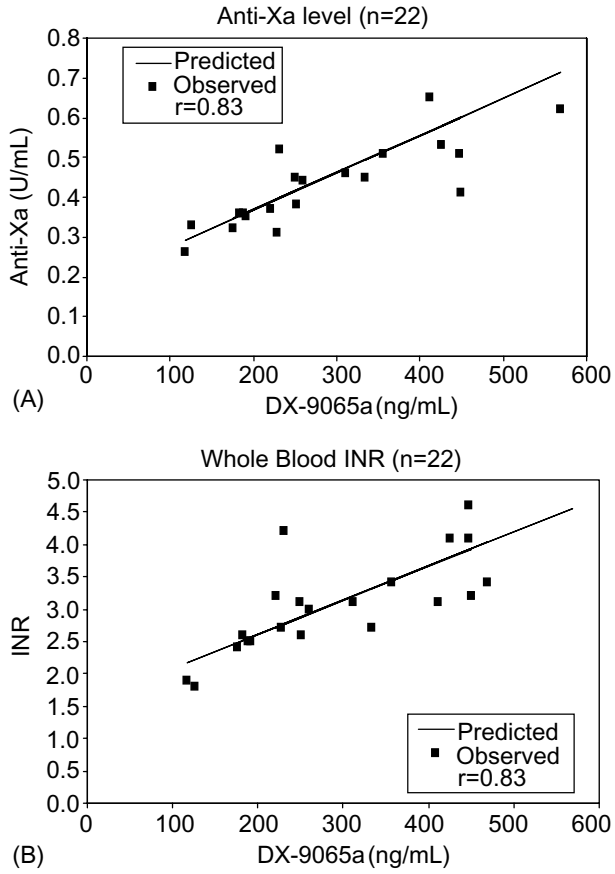

Fig. 4. Correlations between DX-9065a level and whole-blood international normalized ratio (INR) (A) and between DX-9065a level and anti-FXa level (B) 15 min after the second DX-9065a bolus.

ongoing trials, should improve the pharmacodynamic models of DX-9065a.

DX-9065a levels related strongly to both anti-FXa levels and whole-blood INR. The relations between DX-9065a and INR, APTT, and anti-FXa were consistent with those seen in patients with stable coronary disease in the XaNADU IB trial [9]. Either bedside anti-FXa testing or whole-blood INR could be used to monitor anticoagulation with DX-9065a [22]. The DX-9065a doses used in this study achieved whole-blood INR levels of 1.9–3.8. Unlike plasma-based INR, a whole-blood assay incorporates the potential impact of cellular elements on coagulation and may provide a more complete physiological assessment of the pharmacodynamic effects of DX-9065a. DX-9065a has no known direct or indirect effect on either white blood cells or red blood cells; however, there are several reasons to suspect that DX-9065a may have a greater effect on INR in the presence of platelets. First, by blocking FXa, DX-9065a inhibits prothrombinase formation on the platelet surface (M. Furman *et al*., unpublished work). Second, because DX-9075a inhibits FXa 'up-stream' in the coagulation cascade, it reduces the generation of thrombin, a potent platelet agonist. Additional work is required to define the 'optimal' whole-blood INR associated with the fewest ischemic and bleeding complications. The availability of a bedside assay that accurately reflects plasma DX-9065a concentrations may be an asset in the development and use of this agent in clinical care.

DX-9065a plasma levels as low as 15 ng mL^{-1} have been shown to have antithrombotic effect, and, in a flow chamber *ex vivo* model of thrombosis, concentrations of 40–80 ng mL^{-1} had antithrombotic efficacy superior to therapeutic doses of enoxaparin [11,16]. The anti-FXa levels achieved in this study (0.3–0.6 anti-FXa U mL^{-1}) are similar to those commonly achieved with unfractionated heparin (0.3–0.7 anti-FXa U mL^{-1}) [23]. Although the anti-FXa levels with DX-9065a appear to be lower than those achieved with enoxaparin (0.5–1.8 anti-FXa U mL^{-1}) [24], such a comparison is inappropriate because of the different standard curves used in the LMW heparin and unfractionated heparin anti-FXa assays.

Perhaps more important, the relation between anti-FXa level and anticoagulation may differ for indirect, antithrombin III-dependent inhibitors and direct, LMW inhibitors such as DX-9065a. Both DX-9065a and heparin act to inhibit prothrombin activation by the prothrombinase complex. However, prothrombin prevents the catalytic effect of heparin on

Table 3 Procedural and clinical outcomes

	DX-9065a				
Outcome	Stage I ($n=45\%$)	Stage II ($n=6\%$)	Stage III ($n=45$)	Stage IV ($n=45$)	Combined heparin ($n=34$)
Death	0	0	0	0	0
Myocardial infarction	5 (11.1%)	1 (16.7%)	0	6 (13.3%)	2 (5.9%)
Urgent revascularization	0	0	0	1 (2.2%)	0
Composite*	5 (11.1%)	1 (16.7%)	0	6 (13.3%)	2 (5.9%)
Stroke	0	0	0	0	0
Major dissection	0	0	2 (4.4%)	0	1 (2.9%)
Abrupt closure	0	0	0	0	0
No-reflow	0	0	0	1 (2.2%)	0
Thrombus formation	0	1 (16.7%)	1 (2.2%)	1 (2.2%)	0
Side-branch closure	3 (6.7%)	0	0	2 (4.4%)	0
Distal embolization	0	0	0	1 (2.2%)	0
Any ischemic event†	5 (11.1%)	1 (16.7%)	1 (2.2%)	6 (13.3%)	2 (5.9%)

*Death, MI, or urgent revascularization. †Death, MI, urgent revascularization, abrupt closure, no reflow, embolization, or thrombus formation.

Table 4 Bleeding events

Outcome	DX-9065a				Combined heparin ($n=34$)
	Stage I ($n=45$)	Stage II ($n=6$)	Stage III ($n=45$)	Stage IV ($n=45$)	
Any bleeding	18 (40.0%)	1 (16.7%)	6 (13.3%)	11 (24.4%)	11 (32.4%)
Major	1 (2.2%)	1 (16.7%)	0	0	0
Minor	1 (2.2%)	0	0	4 (8.9%)	0
Red-cell transfusion	1 (2.2%)	0	0	0	0
Thrombocytopenia*	0	1 (16.7%)	2 (4.4%)	1 (2.2%)	1 (2.9%)
Severe	1 (2.2%)	0	0	0	0

*Defined as $<100\,000$ platelets mm^{-3}; severe, $<20\,000$ platelets mm^{-3}.

antithrombin inhibition of FXa in the prothrombinase complex. Because DX-9065a acts independently of antithrombin, it remains active and inhibits FXa in the presence of prothrombin [8]. Caution is therefore needed in extrapolating clinical inferences from anti-FXa assays. Given the relatively infrequent bleeding and lack of dose–response in this regard, higher doses of DX-9065 may be well tolerated, could be more efficacious, and should be considered in future trials of DX-9065a in patients undergoing PCI.

In stage IV, we investigated potential interactions between unfractionated, or LMW heparin and DX-9065a. We saw some evidence of pharmacodynamic interaction with APTT, whole-blood INR, and anti-FXa level, but not with ACT. The heterogeneity of the patients and heparin dosing, both within stage IV and compared with other stages, complicates understanding these potential interactions. Further work is needed to understand possible pharmacodynamic interactions between DX-9065a and other currently available anticoagulants.

Given the small sample size and the fact that stages enrolled sequentially rather than simultaneously, differences between the stages, particularly regarding clinical events, should be interpreted with caution. That being said, the rates of both ischemic and bleeding complications were within the general ranges expected in this cohort undergoing elective PCI [19]. One serious thrombotic complication with extensive intracoronary thrombosis occurred, in a high-risk, diabetic, stage II patient during PCI. At the time, the patient had not received a GPIIb/IIIa inhibitor and had a DX-9065a concentration of $\sim 100\,ng\,dL^{-1}$. This level of DX-9065a may not provide adequate anticoagulation in some high-risk patients, but further investigation is warranted. Two other noteworthy thrombotic events occurred in stage IV. In one, thrombus that was present at baseline embolized distally during PCI. In the second, subacute stent thrombosis occurred ~ 12 h after PCI, when drug concentrations would be expected to be low. Patients treated with DX-9065a in the XaNADU-PCI pilot study all had DX-9065a concentrations that were higher than those shown to have efficacy in animal and preclinical models. Interpreting isolated events illustrates the challenge of developing new antithrombotics in patients in whom serious complications are known to occur.

Elective PCI is feasible using the direct, selective FXa inhibitor DX-9065a as an anticoagulant at the doses investigated in the XaNADU-PCI pilot study. The dose investigated in stage II may not provide adequate anticoagulation in some high-risk patients. Predictable plasma drug concentrations can be rapidly obtained using double-bolus and infusion DX-9065a dosing. Monitoring of DX-9065a may be possible with either whole-blood INR or anti-FXa activity level. Direct FXa inhibition is a novel and potentially promising approach to limiting thrombotic complications in patients with cardiovascular disease. Adequately powered, Phase III trials of DX-9065a in PCI and in acute coronary syndromes are warranted.

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