Iliac Venous Stenting
Antithrombotic Efficacy of PD0348292, an Oral Direct Factor Xa Inhibitor, Compared With Antiplatelet Agents in Pigs

Robert D. McBane II, Robert J. Leadley Jr, Sangita M. Baxi, Krzysztof Karnicki, Waldemar Wysokinski

Objective—The clinical use of venous stents is increasing dramatically. Although antiplatelet agents are required for arterial stent patency, optimal thrombo-prophylaxis after venous stenting remains undefined. To address this issue, PD0348292, a direct Factor Xa inhibitor, was compared with antiplatelet therapy in a porcine venous stent model.

Methods and Results—Four hours before stent deployment, pigs (n=5 to 6 per group) received oral PD0348292 at 0.4, 0.9, 4.3 mg/kg, or 0.4 mg/kg plus aspirin (325 mg). Aspirin, clopidogrel (75 mg), aspirin plus clopidogrel, or vehicle (n=10) were administered daily for 2 days before the procedure. Two hours after stent placement, thrombi were quantified by autologous 111In-platelet content and weights. Thrombus weight and platelet deposition were significantly reduced by PD0348292 at 0.4 (49±79 mg and 110±145×106/cm²), 0.9 (5±6 mg and 107±128×106/cm²), 4.3 mg/kg (0±0 mg and 87±125×106/cm²), and PD348292 plus aspirin (20±40 mg and 157±70×106/cm²) compared with vehicle (402±226 mg; 584±454×106/cm²). Despite prolonging bleeding times and inhibiting platelet aggregation, neither aspirin (567±683 mg and 533±622×106/cm²), clopidogrel (404±349 mg and 178±101×106/cm²), nor aspirin plus clopidogrel (247±261 mg and 231±266×106/cm²) significantly decreased stent thrombosis.

Conclusions—PD0348292 completely inhibited thrombosis after venous stenting. Platelet accretion in these venous thrombi appear to involve pathways distinct from arachidonate metabolism or ADP P2Y12 receptor activation.

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Key Words: coagulation factor Xa ■ aspirin ■ clopidogrel ■ stent ■ venous thrombosis

The clinical use of venous stents for the treatment of acute or chronic venous occlusive disease is increasing exponentially. Common clinical scenarios where venous stents are used include May Thurner syndrome, thoracic outlet syndrome, or dialysis fistulae malfunction. Other indications used include May Thurner syndrome, thoracic outlet syndrome. Common clinical scenarios where venous stents are used include May Thurner syndrome, thoracic outlet syndrome. The thienopyridines provide effective prophylaxis after arterial stent placement,13 and antiplatelet agents improve vein bypass graft patency after surgery.14 By comparison, vitamin K antagonists have not been effective in this area and are currently not recommended for this purpose.13 Therefore, one might hypothesize that the use of antiplatelet agents would provide effective thromboprophylaxis after venous
stenting. Alternatively, the nonpulsatile flow and vascular substrate of the venous system may predispose to thrombi specific for this system. Considerable histological differences distinguish iliac veins from muscular arteries such as the coronary artery. The iliac vein contains an intima, media, and adventitia, yet the boundaries between these layers are indistinct with poorly developed elastic components and more prominent connective tissue components. The intima contains endothelium, basal lamina, and reticular fibers yet no true elastic interna. The media is thin yet contains both circular and longitudinal smooth muscle cells and collagen fibers with few fibroblasts. The adventitia consists of collagen bundles and elastic fibers with few smooth muscle cells. In contrast, the muscular coronary arteries contain an elastic interna just beneath the endothelial cell layer with fenestrations. The media varies in thickness (from 3 to 40 layers of smooth muscle cells). The adventitia contains fibroblasts, collagen and elastic fibers, and dermatan and heparan sulfate. Exposure of the vascular substrate of veins and arteries to flowing blood might therefore be anticipated to yield different thrombotic stimuli. Although anticoagulants provide effective thromboprophylaxis against venous thromboembolism, the role of antiplatelet therapy in this setting is less clear. For these reasons, the impact of antiplatelet therapy on venous stent thrombosis requires further investigation.

The prevention of thrombin activation by factor Xa inhibition would be anticipated to inhibit thrombin generation and platelet activation. PD0348292 is a highly potent (Ki = 0.32 nmol/L versus human FXa), selective, and orally available coagulation Factor Xa inhibitor that has been evaluated in humans for the treatment and prevention of thromboembolic events.

We have developed a porcine model of venous thrombosis which uses placement of a Wallstent in the iliac vein. Within 2 hours of stent placement, a gross thrombus is present in 88% of stented segments and 80% are totally occluded in untreated animals. Examination of these thrombi reveals distinct variability comparing the histology of caudal to more cephalad regions. The caudal end of the thrombus is comprised primarily of leukocytes and platelets. Fibrin(ogen) and red cells with “Lines of Zahn” morphology typify the more prominent cephalad “tail” of the thrombus which is relatively devoid of platelets and extends throughout the length of the stent. We sought to use this new model to compare direct FXa inhibition to antiplatelet treatment with clopidogrel or aspirin for the prevention of early thrombosis after iliac venous stent placement in pigs.

Materials and Methods

Materials

PD0348292 [1,2-Pyrrolidinediacarbamoxime, N1-(4-chlorophenyl)-N2-(2-fluoro-4-(2-oxo-1(2H)-pyridinyl)phenyl)-4-methoxy- (2R,4R)-(9CI)], was obtained from Pfizer Global R&D. Clopidogrel was purchased from Bristol-Myers Squibb, and aspirin was obtained from Bayer Pharmaceuticals. Wallstents were a generous gift from Boston Scientific (Natick, Mass).

Animals

Four-month-old pre-estrus female pigs of the Babcock 4-way cross stock (a mixture of Landrace, Yorkshire, Hampshire, and Duroc breeds) were purchased through the Mayo Clinic’s section of Veterinary Medicine and housed at the Mayo Institute Hills Facility. The study was approved by the Mayo Clinic Animal Care and Use Committee and conformed to the National Institutes of Health and United States Department of Agriculture guidelines.

Induction of Thrombosis

Anesthesia of pigs and 111In-platelet labeling were performed as described previously. Twenty-seven hours before the procedure, pigs received clopidogrel (75 mg; n = 6), aspirin (325 mg; n = 6), clopidogrel plus aspirin (n = 6), or vehicle control (n = 10). These agents (or vehicle) were then readministered 4 hours before thrombus induction. Other treatment groups received oral PD0348292 at 0.4, 0.9, or 4.3 mg/kg (n = 5 to 6 each) or PD0348292 at 0.4 mg/kg plus aspirin (325 mg; n = 6) once, just 4 hours before thrombus induction. Doses were selected based on preliminary observations that PD0348292 at 4.3 mg/kg demonstrated maximum efficacy in this model with relatively small changes in routine coagulation parameters. Doses were titrated to cover a dose-proportional 10-fold range of plasma drug concentrations. Left femoral venous catheterization was accomplished percutaneously after a small stab incision at the left inguinal region. An 8 x 30 mm self expanding Wallstent was then deployed into the left common iliac vein and the delivery catheter removed. Two hours after stent deployment, each stented segment was retrieved surgically without ligation of either the proximal or distal ends and inspected both for placement accuracy and complete expansion. In all cases, placement and expansion were satisfactory. There were no cases of venous tear or perforation yet microscopic venous wall trauma with endothelial denudation is most assuredly part of this model. Harvested venous segments were placed in 2-methylbutane (liquid nitrogen (LN2)) and ultimately archived at −70°C. The 111In-Indium platelet content of harvested venous segments was measured in a scintillation counter (Minaxi Autogamma Counter 5000 series, Packard). Harvested segments were incised, assessed grossly for macroscopic thrombosis, and scored on a scale of 0 to 3 (0 = absent; 1 = small but detectable; 2 = large, but not occlusive; 3 = large and occlusive). Visible thrombi were then gently removed and weighed. Thirty minutes before venous stent placement, animals underwent carotid injury to examine the arterial antithrombotic effects of the agents tested in this study; the complete results of the arterial results are reported separately.

Clotting Assays

At 27 hours and 4 hours before the procedure, at baseline, and 15 and 30 minutes after thrombus initiation, blood samples were collected into 1.9 volume of 3.2% Na citrate and centrifuged for 20 minutes at 1500g. The plasma samples were then snap-frozen and stored in aliquots at −70°C. Whole blood activated clotting times were measured with the Hemachron ACT device (ITC). Prothrombin times and activated partial thromboplastin times were measured with the ACL9000 coagulation analyzer (Beckman Coulter).

The Factor Xa clotting assay was used to determine the inhibitory effect of PD0348292. Plasma samples were diluted 1:1 with Factor X–deficient human plasma (Helena Laboratories Corp), and then clotting was initiated with recombinant tissue factor (RecombiPlasTin, Instrumentation Laboratory). Clotting times were measured with the ACL 9000 coagulation analyzer and compared with untreated pig plasma diluted with varying amounts of Factor X deficient human plasma. Factor Xa activity was analyzed by complete activation of endogenous Factor X by RVV (DiaPharma) addition of CaCl2, and subsequent measurement of plasma activity by cleavage of a specific FXa paraaminanilide substrate (Spectrozyme FXa, American Diagnostica). Thrombin generation was assessed by using a fluorescent substrate specific for thrombin (Z-Gly-Gly-Arg-AMC, Bachem Bioscience Inc) mixed with Innovin (Dade Behring, Deerfield, IL).

Platelet Aggregation Assay

Platelet rich plasma (PRP) was prepared by centrifugation (700g for 10 minutes at room temperature) for platelet aggregometry testing.
Venous stent thrombus inhibition. Occlusive thrombi were noted in the majority of animals receiving aspirin, clopidogrel, or vehicle control. None of the animals receiving PD-0348292 had occlusive thrombi (Mean±SD; *P<0.05 compared with vehicle control or antiplatelet therapy).

Small, visible, but nonocclusive thrombi were noted in 50% of the stented segments taken from animals receiving lower doses of PD-0348292 with or without aspirin. In contrast, no visible or measurable thrombus was detected in the stented venous segments with vehicle control (Figure 1). No visible or measurable thrombus was detected in the stented venous segments with vehicle control (Figure 1). No visible or measurable thrombus was detected in the stented venous segments with vehicle control (Figure 1). No visible or measurable thrombus was detected in the stented venous segments with vehicle control (Figure 1). No visible or measurable thrombus was detected in the stented venous segments with vehicle control (Figure 1).

Thrombus size, venous thrombosis was significantly reduced on the thrombus scoring system for gross evaluation of thrombus deposition (Figure 2A) varied considerably in animals receiving vehicle control (range 2 mg to 540 mg; mean 402±226 mg). Nonetheless, compared with vehicle control, mean thrombus weights were significantly reduced for animals receiving PD-0348292 at 4.3 mg/kg (49±26 mg), PD-0348292 at 0.4 mg/kg plus aspirin (20±40 mg). Thrombus weights for animals receiving antithrombotic therapy with aspirin (567±683 mg); clopidogrel (404±349 mg); or clopidogrel plus aspirin (247±261 mg) were not statistically different than vehicle control.

Venous thrombus platelet content. A, Thrombus weights were decreased in animals receiving PD-0348292 (P<0.05) but not those receiving antiplatelet agents. B, Platelet deposition was also reduced in animals receiving PD-0348292 at all 3 doses (P<0.05). In contrast, antithrombotic therapy did not significantly reduce platelet content.

Ear Bleeding Time

After sedation, the ear was immersed in warm saline at 37°C for 5 minutes. Two small stab incisions were made at the ear margin using a #11 surgical blade. The incised ear was then placed back into warm saline and carefully observed for bleeding cessation. Results are reported as time to cessation of bleeding, representing an average of the 2 incisions. If bleeding persisted at 15 minutes, that value was recorded for bleeding time. Ear bleeding times were performed at baseline, 27 hours before the procedure, and again immediately before surgery.

Statistics

All values are presented as mean±SEM. Analysis of variance followed by Student t test was used to perform multiple comparisons between treatment groups. Paired Student t test was used to compare hemoglobin, hematocrit, and platelet counts before and after each surgery. Statistical significance was set at P<0.05.

Results

To compare the antithrombotic efficacy of Factor Xa inhibition to aspirin and clopidogrel, pigs received either 1 of 3 different doses of an oral factor Xa inhibitor, PD-0348292, low dose PD-0348292 plus aspirin, clopidogrel or aspirin alone or in combination before iliac venous stenting. Based on the thrombus scoring system for gross evaluation of thrombus size, venous thrombosis was significantly reduced in all animals receiving PD-0348292 at all 3 doses compared with vehicle control (Figure 1). No visible or measurable thrombus was detected in the stented venous segments harvested from animals receiving PD-0348292 at 4.3 mg/kg. Small, visible, but nonocclusive thrombi were noted in 50% of the stented segments taken from animals receiving lower doses of PD-0348292 with or without aspirin. In contrast, occlusive thrombi were noted in 80% or more of animals receiving aspirin, clopidogrel or vehicle control. In those animals receiving clopidogrel plus aspirin, 50% of venous segments were completely occluded. Thrombus weights (Figure 2A) varied considerably in animals receiving vehicle control (range 4 mg to 540 mg; mean 402±226 mg). Nonetheless, compared with vehicle control, mean thrombus weights were significantly reduced for animals receiving PD-0348292 at 4.3 mg/kg (0±0 mg); 0.9 mg/kg (5±6 mg); 0.4 mg/kg (49±79 mg) and PD-0348292 at 0.4 mg/kg plus aspirin (20±40 mg). Thrombus weights for animals receiving antithrombotic therapy with aspirin (567±683 mg); clopidogrel (404±349 mg); or clopidogrel plus aspirin (247±261 mg) were not statistically different than vehicle control.

Platelet deposition (×10⁶/cm²) within stented iliac venous segments was significantly reduced in animals receiving PD-0348292 at 4.3 mg/kg (87±125), 0.9 mg/kg (107±128), and 0.4 mg/kg (110±145), and PD-0348292 0.4 mg/kg plus aspirin (157±70) compared with vehicle control (584±454). In contrast, platelet deposition was not significantly reduced in animals receiving aspirin (533±622), clopidogrel (178±101), or clopidogrel plus aspirin (231±266) (Figure 2B).

Prolongation of clotting assays was observed after oral delivery of PD-0348292 (Table 1). These clotting tests were not altered by either of the antiplatelet agents. Inhibition of
factor X was noted by direct measures of factor X activity (ie, Heptest, RVV test, and FX Clotting test) and total thrombin generation was dose-dependently decreased with PD-0348292. Aspirin and clopidogrel had no significant effect on any of these parameters. Values were obtained from measurements using blood samples obtained just before stent placement. Percent changes represent the mean changes from the predrug sample for each animal.

Ear bleeding times remained stable throughout the experiment in the control animals (Table 2). Compared with the control group, ear bleeding times were significantly prolonged in the groups receiving PD-0348292 at 0.9 and 4.3 mg/kg and those receiving PD-0348292 plus aspirin or clopidogrel plus aspirin. No excessive surgical bleeding was noted irrespective of the antithrombotic agent or dose. The pre- and postprocedural mean hematocrit, hemoglobin, and platelet count values did not differ significantly in any treatment group.

Platelet aggregation response to ADP was significantly reduced by 35% to 43% in animals that received clopidogrel alone or in combination with aspirin.20 PD-0348292, alone or in combination with aspirin, had no effect on ADP-induced aggregation. PD0348292 had no consistent effect on arachidonate-induced aggregation.

Discussion
Identification of the optimal antithrombotic prophylaxis regimen for individuals receiving venous stents is an important clinical problem. Each year, 1 in 1000 Americans will experience venous thrombosis.21 At 10 years, more than 30% of these individuals will experience the ravages of the postphlebitic syndrome.22 Consequently, enthusiasm is growing for aggressively treating venous thrombosis with fibrinolytic therapy and mechanical thrombectomy to relieve venous obstruction and preserve valvular function. Placing a venous stent for residual venous stenosis in this setting is common. In the National Multicenter Venous Registry report, of the 221 iliofemoral deep venous thrombi receiving fibrinolytic therapy, 45% also received a stent. Patients undergoing iliofemoral angioplasty and stenting experience a high rate of recurrent stenosis or obstruction.23 Defining the ideal antithrombotic prophylaxis regimen to maximize stent patency therefore remains a priority.

The principal finding of the current study is that anticoagulant therapy with PD-0348292, an oral factor Xa inhibitor, provides effective acute antithrombotic prophylaxis after iliac venous stent placement in pigs. Even at the lowest dose, venous thrombus was markedly reduced compared with vehicle. In contrast, antiplatelet therapy with either clopidogrel or aspirin alone or in combination is ineffective. These findings are in agreement with those in the current study and thus provide a foundation for future investigations that would attempt to optimize antithrombotic prophylaxis regimens in this and other clinical settings.

Table 2. Clotting Assays

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<th>Parameter</th>
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<th>4.3 mg</th>
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<th>Clopidogrel ASA</th>
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<td>RVV, % inhibition</td>
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<td>48±7*</td>
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<td>Total TG, % inhibition</td>
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Table 2. Platelet Function Assays

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<td>Aggregations, % inhibition</td>
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<td>−12±7</td>
<td>−12±3</td>
<td>−26±23</td>
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keeping with the notion that venous thrombosis is primarily governed by thrombin generation and activity.17 By limiting prothrombin activation with a FXa inhibitor such as PD0348292, this process can be effectively inhibited.

The second finding of this study is that considerable platelet deposition occurs in the untreated stented venous segments. The mean platelet content of stented venous segments of control animals was less than observed for arterial thrombosis,10,11,19 but considerably higher than expected. Indeed, compared with whole blood, the platelet content of these venous stent thrombi is increased by more than 100-fold, implying considerable platelet accretion. This platelet accretion could only occur in the setting of flowing venous blood as opposed to venous stasis. Platelet detection with radiolabeled RGD mimetics12 indicates that platelets are activated in venous thrombosis and are likely playing a role in the propagation of these thrombi, either by secretion of procoagulant or vasoactive molecules, providing a surface for the colocalization of coagulation components, or by cross-bridging fibrin and trapping other cells which may contribute to the inflammatory or thrombogenic process.

The third finding of this study is that despite bleeding time prolongation and platelet aggregometry inhibition, currently available platelet antagonists, aspirin or clopidogrel, were ineffective at preventing platelet accumulation and stent thrombosis in this model. In those pigs which had pretreatment platelet responses to arachidonate, aspirin treatment completely eliminated subsequent ex vivo platelet responsiveness to this agonist, thereby demonstrating the effect of aspirin in these experiments. Clopidogrel also demonstrated an antiplatelet response (35% to 42% inhibition of ex vivo ADP-induced platelet aggregation) that was very similar to the response observed at steady-state in humans (35% inhibition of 20 μmol/L ADP after 30 days of dosing at 75 mg/d).20 Therefore, platelet accretion in these venous thrombi appears to involve pathways distinct from arachidonate metabolism or platelet ADP P2Y12 receptor activation.

Thrombin activity, either by fibrinogen cleavage or by platelet activation via protease activated receptors (PAR), appears to be the primary mechanism governing thrombus generation in this model. Inhibition of prothrombin activation by Xa inhibition limits both platelet deposition and thrombus formation in this model. PAR-1 agonists have been shown to promote platelet activation, venous constriction, arterial dilation, and tPA release both in vitro and in vivo.24,25 Further studies with a selective platelet PAR-1 antagonist would aid in elucidating the relative role of thrombin-mediated platelet activation compared with fibrin formation in thrombus generation in this model.26,27

There are several study limitations which should be acknowledged. First, the specific platelet ADP P2Y12 inhibitor, clopidogrel, was used in this study. There are now several new ADP receptor antagonists in phase III clinical trials. Whether these agents would effectively inhibit platelet depo- sition in venous stenting remains to be determined. Second, we have previously shown that the caudal end of these thrombi are both platelet and leukocyte rich.10 Whether other antiplatelet therapies such as integrin αIIbβ3 inhibitors would effectively inhibit venous thrombosis in this model is also not yet known. Testing the hypothesis that platelet inhibition alone will prevent venous thromboembolism remains a central pursuit of our laboratory. Third, the time-frame of thrombus initiation and propagation was limited to 2 hours. During this time interval, inhibition of Factor Xa prevented venous thrombosis. Further studies are needed to assess long term patency with these various antithrombotic agents. Fourth, whereas low molecular weight heparin and warfarin are the current standard for venous thromboembolism prophylaxis and treatment, future antithrombotic studies should include the use of these agents as comparators. Lastly, further studies are needed to determine whether oral direct factor Xa inhibitors will be effective when used in humans in this setting.

In summary, because effective antiplatelet doses of aspirin or clopidogrel did not significantly reduce platelet accretion in these venous thrombi, the mechanism involved in platelet accretion appears to be distinct from either arachidonate metabolism or ADP P2Y12 receptor occupation. PD0348292 at doses which produce modest changes in coagulation parameters and have comparable effects to clopidogrel and aspirin on bleeding time, promptly and completely inhibited thrombosis after iliac venous stenting. These results suggest that direct Xa inhibition with agents such as PD0348292 may be safe and effective in acute, and possibly chronic, prevention of venous stent thrombosis.

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Disclosures

Robert J. Leadley Jr and Sangita M. Baxi have been employed by Pfizer Global R&D.

References


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<td>FXC (% of normal)</td>
<td>86±5</td>
<td>31±12*</td>
<td>68±4</td>
<td>64±5*</td>
<td>77±10</td>
<td>78±7</td>
<td>89±7</td>
<td>77±6</td>
</tr>
<tr>
<td>RVV (% inhibition)</td>
<td>2±4</td>
<td>88±9*</td>
<td>62±3*</td>
<td>48±7*</td>
<td>35±10*</td>
<td>14±4</td>
<td>-3±4</td>
<td>6±7</td>
</tr>
<tr>
<td>Total TG (% inhibition)</td>
<td>-6±11</td>
<td>77±10*</td>
<td>48±5*</td>
<td>38±10*</td>
<td>33±4*</td>
<td>-1±30</td>
<td>15±6</td>
<td>1±21</td>
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<tr>
<td>PD 238292 (ng/mL)</td>
<td>BLQ</td>
<td>421±87</td>
<td>173±59</td>
<td>50±11</td>
<td>31±11</td>
<td>BLQ</td>
<td>BLQ</td>
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<tr>
<td>N</td>
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<tr>
<td>Variable</td>
<td>Control</td>
<td>4.3mg</td>
<td>0.9mg</td>
<td>0.4mg</td>
<td>0.4mg ASA</td>
<td>ASA</td>
<td>Clopidogrel</td>
<td>Clopidogrel ASA</td>
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<tr>
<td>BT (min)</td>
<td>2.4±0.7†</td>
<td>9.1±2.7*</td>
<td>6.7±1.7*</td>
<td>1.4±0.3</td>
<td>7.5±2.1*</td>
<td>5.0±1.2</td>
<td>3.6±0.7†</td>
<td>7.5±1.9*</td>
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<tr>
<td>ADP&lt;sub&gt;20&lt;/sub&gt;</td>
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<td>-12±7</td>
<td>-12±3</td>
<td>-26±23</td>
<td>-12±11</td>
<td>-28±16</td>
<td>43±13*</td>
<td>36±9*</td>
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<td>ADP&lt;sub&gt;10&lt;/sub&gt;</td>
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<td>-14±7</td>
<td>-30±21</td>
<td>-21±17</td>
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<td>42±13*</td>
<td>35±14*</td>
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<tr>
<td>AA</td>
<td>163±64</td>
<td>92±56</td>
<td>115±40</td>
<td>343±135</td>
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<td>5±46</td>
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