

Editorial Focus

Expanding the role of coagulation in arterial thrombosis: Evidence from animal models using a new factor Xa inhibitor

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Anticoagulants represent a mainstay in the current management of arterial thromboembolism. Heparins are recommended for virtually all forms of acute coronary syndromes (1, 2), whereas long-term oral anticoagulation is of proven benefit in the treatment of patients with atrial fibrillation at high risk of stroke, prosthetic mechanical heart valves, chronic heart failure, left ventricular thrombi and systemic lupus erythematosus (3, 4). For the prevention of vascular events in high-risk patients with non-valvular atrial fibrillation, warfarin is superior to aspirin alone and to aspirin plus clopidogrel (5). For the primary and secondary prevention of ischaemic heart disease, warfarin is as effective as aspirin and, added to aspirin, more effective than aspirin alone in reducing major adverse cardiovascular events, although at increased bleeding rates (3, 6). Indirect meta-analyses suggest that the protection by warfarin plus aspirin may not be inferior to that afforded by aspirin plus clopidogrel following an acute coronary syndrome (7). Fibrinolytic drugs, that degrade fibrin and fibrinogen, reduce early vascular mortality after acute myocardial infarction as well as aspirin (8). Finally, at least three hypercoagulable thrombophilic gene variants [prothrombin G20210A, factor V Leiden (G1691A), and plasminogen activator inhibitor type-1 (PAI-1)–6754G/5G], but none of the currently known platelet receptor gene polymorphisms, show a modest but consistent and significant association with the risk of ischaemic heart disease (9). These multiple lines of clinical evidence support a relevant role of coagulation in arterial thromboembolic diseases, equalling or even surpassing the role played by platelets.

Currently available anticoagulants include heparins, coumarins, direct thrombin inhibitors, and the indirect factor Xa (FXa) inhibitor, fondaparinux (10). Only coumarins are orally active and thus appropriate for extended therapy, despite their well-known hurdles. Limits of warfarin include delayed onset of anticoagulant effects, unpredictable dose response, interaction with food and drugs, need for frequent monitoring, difficult standardization of laboratory control, narrow therapeutic window – with its attending haemorrhagic risks – and poor patient compliance (11). Thus, there is a pressing demand for new simple, safe, and effective oral anticoagulants. FXa assembles with cofactor Va

and calcium on cellular and platelet surfaces leading to the crucial reaction that converts prothrombin into thrombin. Several inhibitors of FXa are currently under development or investigation (10), including a new group of orally available, competitive, reversible, direct FXa inhibitors: the pyrrolidine-1,2-dicarboxamides (12). Like other direct FXa inhibitors, these agents block both free and surface-bound FXa, bind to the active site of FXa with a 1:1 stoichiometry, and are independent from anti-thrombin (10). PD0348292 is a small, highly selective inhibitor belonging to this new drug series (13) (Fig. 1).

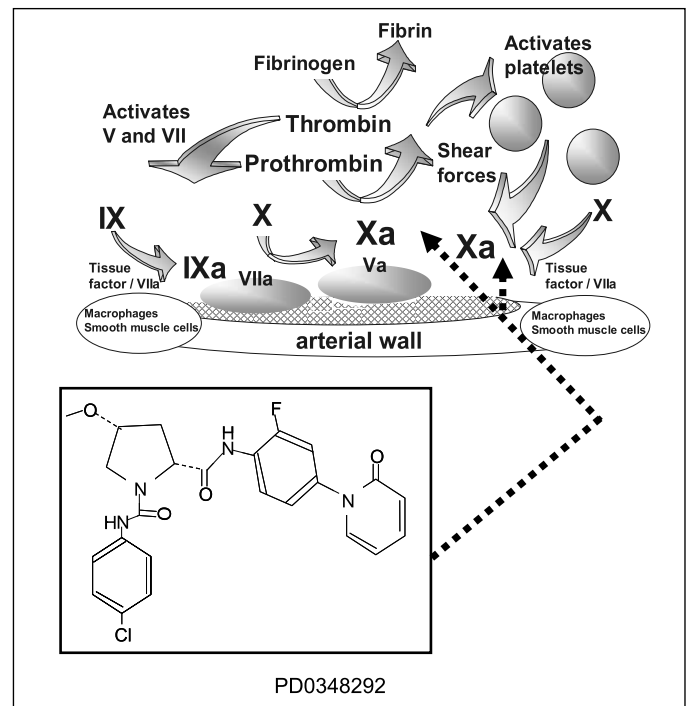


Figure 1: PD0348292 [(2R,4R)-N-(4-chlorophenyl)-N-(2-fluoro-4-(2-oxopyridinyl) phenyl)-4-methoxypyrrolidine-1,2-dicarboxamide] is a site-specific inhibitor of factor Xa that blocks the conversion of prothrombin to thrombin. Upper panel modified from reference 14.

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Given the wide array of responses induced by thrombin, ranging from fibrin generation and stabilization, to platelet and inflammatory activation, and indirect vasoconstriction, it is reasonable to ask whether inhibition of thrombin formation on its own may prevent the build-up of arterial thrombi to a similar extent as the widely recommended antiplatelet regimen based on aspirin and clopidogrel.

In this issue of *Thrombosis and Haemostasis*, Karnicki et al. compare the antithrombotic effects of oral PD0348292 (0.4, 0.9 and 4.3 mg/kg given 4 hours before injury) to the effects of pretreatment with aspirin (325 mg/day), clopidogrel (75 mg/day), both, or vehicle in four-month-old pigs subjected to crush injury of both carotid arteries (13). Radiolabelled platelet deposition, measured *in vivo* for 30 minutes after carotid injury and prior to vessel harvesting, was reduced to about one fourth of that found in vehicle-treated animals by all three PD0348292 doses and by clopidogrel alone. There was a tendency towards lower deposition with the two antiplatelet agents combined and towards higher deposition with aspirin alone (13). Interestingly, bleeding time – a measure of in-vivo platelet-mediated haemostasis – was prolonged equally in all treatment groups (including the group receiving FXa inhibitor) compared to baseline or vehicle controls. PD0348292, but none of the antiplatelet regimens, dose-dependently inhibited FXa activity and thrombin generation, and

prolonged activated clotting time, as well as tissue factor (prothrombin time) and contact phase (aPTT) reactions.

The well-designed and carefully conducted study by Karnicki et al. provides valuable information on the role of coagulation in arterial thrombosis using a model that approaches human atherothrombotic disease. Important messages include the evidence that the oral FXa inhibitor PD0348292 prevents arterial thrombus formation to a degree comparable to that of single or dual antiplatelet regimens. Moreover, the data indicate that anticoagulation affects arterial/arteriolar platelet-mediated processes (carotid platelet deposition and bleeding times), but the converse does not necessarily occur (as the antiplatelet regimens had no effect on clotting assays). Of course, safety, in particular bleeding risk, is a constant concern with all antithrombotic drugs. Indeed, excess bleeding rates halted the development of the long-acting indirect FXa inhibitor, idraparinux, and of the direct oral FXa inhibitor, razaxaban (10). Another potential limitation of FXa inhibitors is the lack of a known antidote (10). On the other hand, routine coagulation tests (prothrombin time and aPTT) as well as a FXa clotting assay exist to measure their inhibitory effects. It remains to be seen whether this new class of oral anticoagulants, the pyrrolidine-1,2-dicarboxamides, will prove safe in healthy subjects and additionally effective in the many clinical settings that benefit from long-term anticoagulation.

References

1. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *Lancet* 2000; 355: 1936–1942.
2. Eikelboom JW, Quinlan DJ, Mehta SR, et al. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. *Circulation* 2005; 112: 3855–3867.
3. Andreotti F, Testa L, Biondi-Zoccai G, et al. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. *Eur Heart J* 2006; 27: 519–526.
4. Andreotti F, Becker RC. Atherothrombotic disorders. New insights from hematology. *Circulation* 2005; 111: 1855–1863.
5. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006; 367: 1903–1912.
6. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet* 1998; 351: 233–241.
7. Testa L, Zoccai GB, Porto I, et al. Adjusted indirect meta-analysis of aspirin plus warfarin at international normalized ratios 2 to 3 versus aspirin plus clopidogrel after acute coronary syndromes. *Am J Cardiol* 2007; 99: 1637–1642.
8. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988; 2: 349–360.
9. Ye Z, Liu EH, Higgins JP, et al. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66,155 cases and 91,307 controls. *Lancet* 2006; 367: 651–658.
10. Hirsh J, O'Donnell M, Eikelboom JW. Beyond unfractionated heparin and warfarin. Current and future advances. *Circulation* 2007; 116: 552–560.
11. Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004; 126: 204–233.
12. Kohrt JT, Bigge CF, Bryant JW, et al. The discovery of (2R,4R)-N-(4-chlorophenyl)-N-(2-fluoro-4-(2-oxopyridin-1(2H)-yl)phenyl)-4-methoxy-pyrrolidine-1,2-dicarboxamide (PD 0348292), an orally efficacious factor Xa inhibitor. *Chem Biol Drug Des* 2007; 70: 100–112.
13. Karnicki K, Leadley RJ, Baxi S, et al. Comparison of PD0348292, a selective factor Xa inhibitor, to antiplatelet agents for the inhibition of arterial thrombosis. *Thromb Haemost* 2008; 99: 759–766.
14. Eisenberg PR. Novel antithrombotic strategies for the treatment of coronary artery thrombosis: A critical appraisal. *J Thromb Thrombolysis* 1995; 1: 237–249.