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, equaling 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 antithrombin (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-methoxy pyrrolidine-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.
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 pre-treatment 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 (pro-thrombin 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 atherosclerotic 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, razoxaban (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**