

ANTICOAGULATION ARMAMENTARIUM: UPDATE ON DRUGS AND MECHANISMS

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Anticoagulants have an essential role in the prophylaxis and treatment of thrombotic and cardiovascular disorders. For decades, two anticoagulants, heparin and warfarin, have been the principal drugs available. Warfarin has a very narrow therapeutic index, has interaction with medications and food, and needs close monitoring. Heparin requires parenteral administration and is associated with severe adverse reactions such as heparin-induced thrombocytopenia (HIT). These limitations make the case for the development of new anticoagulants.

An ideal anticoagulant should be effective, safe, simple to use, and widely applicable. Novel anticoagulants targeting specific steps in coagulation are in various stages of development. New anticoagulants can be classified into three groups: inhibitors of activation of coagulation, inhibitors of propagation of coagulation, and inhibitors of thrombin formation.

Agents currently under study include direct thrombin inhibitors, direct and indirect activated factor X inhibitors, activated protein C and soluble thrombomodulin, and inhibitors of tissue factor and activated factor VII. Although most of these are parenteral agents, several of the direct inhibitors of factor Xa and thrombin are orally active.

Two parenteral direct thrombin inhibitors, lepirudin and argatroban, have FDA approval for the management of HIT. Bivalirudin is a parenteral direct thrombin inhibitor that is licensed for patients undergoing percutaneous coronary interventions and for those with HIT who require percutaneous coronary interventions. Fondaparinux is a synthetic pentasaccharide, which binds to antithrombin, thereby indirectly and selectively inhibiting factor Xa. Fondaparinux demonstrated efficacy compared to low-molecular-weight heparin in randomized clinical trials and is FDA approved for the prevention and treatment of venous thromboembolism. Idraparinux, a long-acting synthetic pentasaccharide is given subcutaneously once a week. When compared to placebo, idraparinux is very effective in extended treatment of VTE but is associated with an increased risk of bleeding. Recent randomized trials confirm similar efficacy and safety when compared to standard therapy in treatment of DVT but not PE.

Of the new oral anticoagulants in development, the two agents in the most advanced stage are dabigatran etexilate (BIBR 1048) and rivaroxaban (BAY 59-7939), which inhibit factor IIa and factor Xa, respectively. Other agents in the early stages of development include several Xa inhibitors (LY-517717, YM150, DU-176b and apixaban [BMS-562247]), a factor IXa inhibitor (TTP889), and an orally active glycosaminoglycan enhancer (odiparcil [SB-424323]), which indirectly enhances thrombin inhibition via heparin cofactor II. A novel anticoagulation system (REG1) developed using a protein-binding oligonucleotide to factor IXa (drug, RB006) and its complementary oligonucleotide antidote (RB007), was recently evaluated in a phase I trial. A number of phase III studies have been initiated with the aim of finding potentially more effective, but primarily safer and more convenient therapies for the prevention and treatment of venous and arterial thrombosis.

Suggested reading:

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4. Fareed J, Hoppensteadt DA, Bick RL. Management of thrombotic and cardiovascular disorders in the new millenium. Clin Appl Thromb Hemost. 2003 Apr;9(2):101-8.