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NEW ORAL ANTICOAGULANTS – THE NEWEST UPDATE IN PATIENTS UNDERGO ORAL SURGERY

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INTRODUCTION: During the past 20 years, the approval of anticoagulants such as low-molecular-weight heparins (LMWHs), indirect factor Xa inhibitors and direct thrombin inhibitors has signaled a growing interest in antithrombotic compounds that have relatively discrete targets within the coagulation pathway.

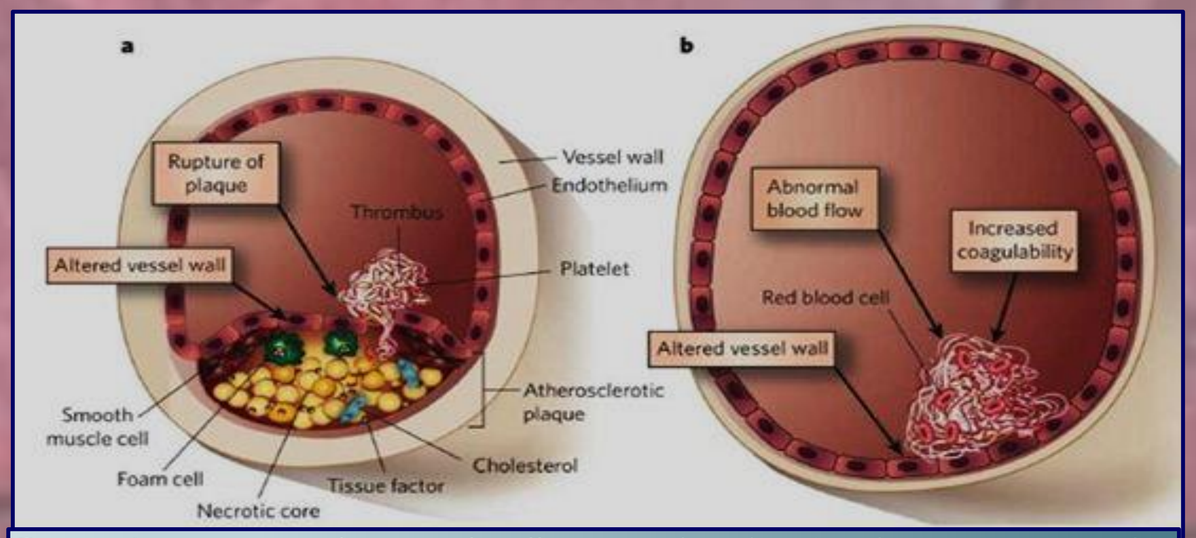

Figure 1. Injury to the vessel wall is considered to be the primary stimulus that sets coagulation in motion. Vessel injury may be mechanical, chemical, or electrical. In **arteries**, vessel injury is mainly due to the rupture of an atherosclerotic plaque, resulting in disruption of the endothelium and exposure of plaque constituents to the blood. In **veins**, vessel wall disruption is a less important trigger of coagulation, although vessel wall injury can occur in the setting of surgery or with indwelling central venous catheters. More common triggers are reduced blood flow (stasis), altered properties of the blood that render it more prone to clotting (thrombophilia), and/or alterations in the endothelium.

AIM: of this study is to review the evidence of different therapy approach, to highlight the areas of major concern, and to suggest specific oral surgery treatment for patients on new oral anticoagulants.

MATERIAL AND METHOD: A Medline and an extensive hand search were performed on English-language publications beginning in 1971 till now. The pertinent literature and clinical protocols of hospital dentistry departments have been extensively reviewed, presented and discussed.

RESULTS: Several evolving clinical practices in the last years have been detected:

- anticoagulants are generally not discontinued,
- oral surgery is performed despite laboratory values showing significant bleeding tendency,
- new effective local hemostatic modalities are used to prevent bleeding,
- patients at risk are referred to hospital-based clinics.

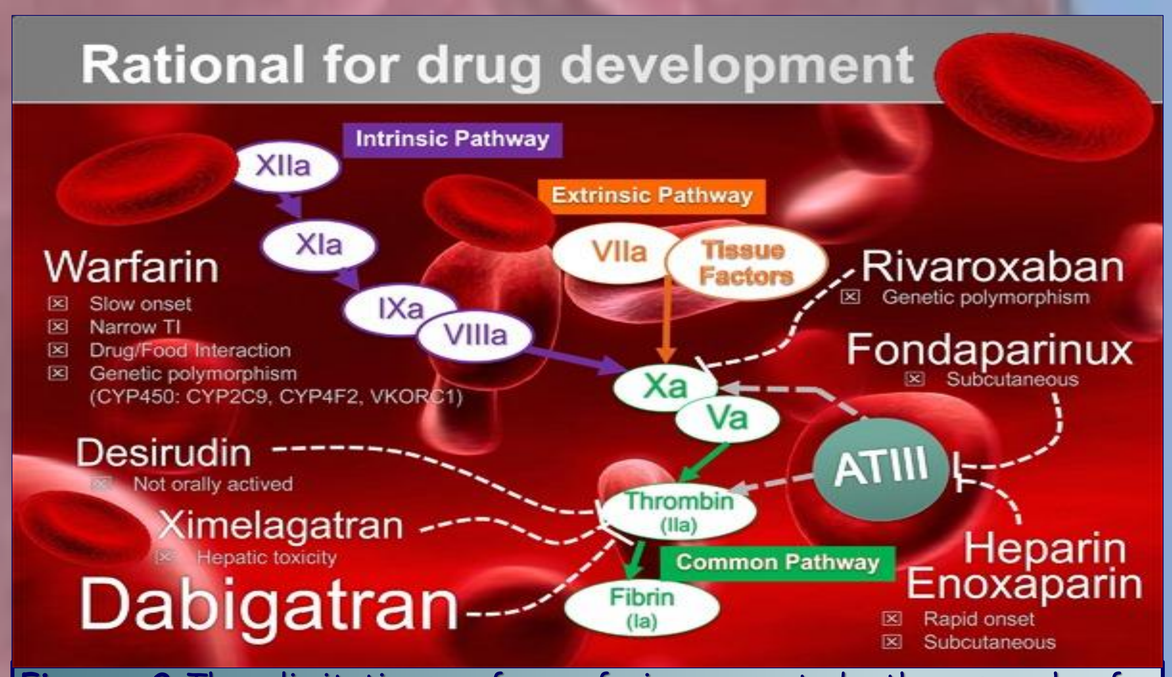

Figure 2. The limitations of warfarin prompted the search for **new oral anticoagulants** that can be given in fixed doses without the need for routine coagulation monitoring. The agents in most advanced stages of development target either thrombin or Fxa. Two such agents, **dabigatran etexilate** and **rivaroxaban**, have already been licensed in Europe and Canada (but not currently in the United States) for thromboprophylaxis after elective hip or knee replacement surgery. A third agent, apixaban, is under investigation for this indication.

Table 1. Pharmacologic Features of Dabigatran Etexilate, Rivaroxaban, and Apixaban

	Dabigatran Etexilate	Apixaban	Rivaroxaban
Target	Thrombin	Factor Xa	Factor Xa
Prodrug	Yes	No	No
Dosing	Fixed, once daily	Fixed, twice daily	Fixed, once daily
Bioavailability (%)	6	50	80
Monitoring	No	No	No
Half-life (h)	12-14*	12.7	7-11
Renal clearance (%)	80	25	65
Interactions	P-gp inhibitors**	Potent CYP3A4 inhibitors†	Combined P-gp inhibitors + CYP3A4 inhibitors†

*In healthy volunteers, 14-17 hours in patients undergoing major orthopaedic surgery.
**P-glycoprotein (P-gp) inhibitors include verapamil, clarithromycin, and quinidine. Quinidine is contraindicated in patients receiving dabigatran.
†Cytochrome P450 (CYP) 3A4 inhibitors include ketoconazole, macrolide antibiotics, and protease inhibitors.

Gross PL, et al. *Clin Pharmacol Ther*. 2009;86:139-146.

CONCLUSION:

- The currently available anticoagulant agents all target thrombin or FXa, either indirectly or directly. Thrombin is a logical target because of its multiple roles in coagulation.
- The management of oral surgery procedures on patients treated with new anticoagulants should be influenced by several factors: laboratory values, extent and urgency of the intervention, treating physician's recommendation, available facilities, dentist expertise, and patient's oral, medical, and general condition.