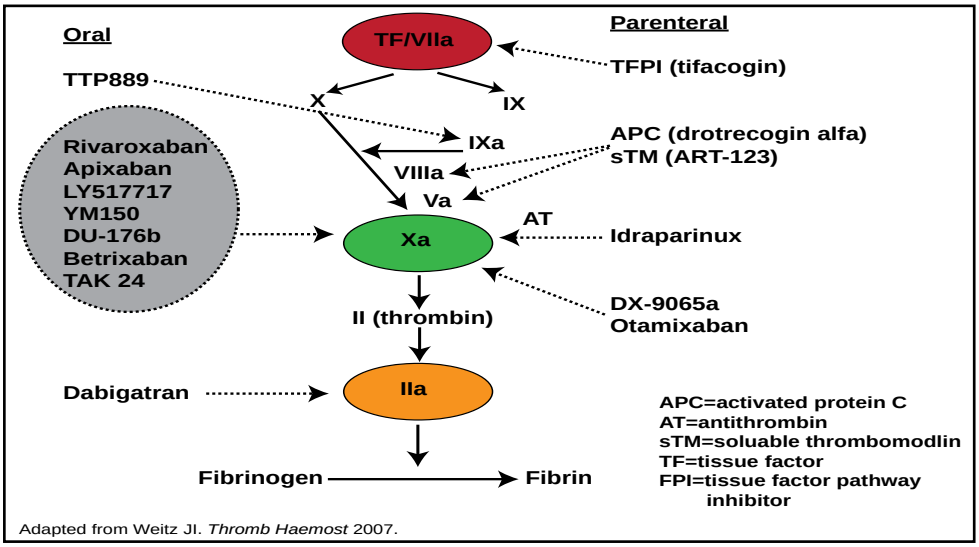
Novel Oral Anticoagulants

Jonathan L. Halperin, MD, Mount Sinai School of Medicine, New York, NY, discussed some of the novel targets for anticoagulants, the two most immediate of which are Factor Xa and Factor IIa (thrombin).

There are several potential targets for novel anticoagulants. "Factor IIa (thrombin) was the first target addressed, because it is the last step in the cascade before the formation of fibrin," said Dr. Halperin (Figure 1). It also has the advantage of potentially interfering with platelet-thrombin interactions, since thrombin is a potent activator of platelets. These platelet-thrombin interactions may be important not only in acute coronary syndromes (ACS) but also in the mechanism of stroke in atrial fibrillation (AF). Hepatoxicity led to the demise of the first oral thrombin inhibitor (ximelagatran) that was developed; however, an excess in hepatotoxicity was not observed in the clinical trial development with the second agent in this class, dabigatran.

Factor Xa, which acts more proximally in the coagulation cascade than Factor IIa, is also a logical target because of its amplification effect and the potential for a reversible action, which is not available at the level of thrombin. The major safety question for the development of the Factor Xa inhibitors is the potential for bleeding. While there is tremendous promise for excellent efficacy with a very low risk of bleeding with the Factor IX and XI inhibitors, they remain in very early development. Tissue factor (TF/VIIa) is also a very appealing target that is particularly attractive to those who deal with patients in the acute surgical setting, but no trials are currently ongoing in patients with AF or ACS.

Figure 1. Investigational Anticoagulant Targets.



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Robert P. Giugliano, MD, SM, Brigham & Women's Hospital, Boston, MA, presented an overview of the characteristics of five new anticoagulant agents and current studies that involve these agents (Table 1) and commented on how each might fit the definition of the "ideal anticoagulant" (Table 2).

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Table 1. Trial and Publication Status.

Dabigatran Trial Status: Completed 11 Phase 2 or 3 trials. Results have been reported for VTE prevention and treatment and for AF; ACS trial is recruiting.	
Ongoing Trials	**Important Publications**
NCT00329238 Phase 3 VTE secondary prevention NCT00558259 Phase 3 VTE long-term prevention NCT00808067 Phase 3 AF (RELY-ABLE) NCT00818753 Phase 2 elective PCI NCT00844415 Phase 2 VTE adolescents NCT00846807 * VTE post TKR or THR NCT00847301 * TKR/THR mod. renal impairment NCT01083732 Phase 2 VTE children	RE-NOVATE [Eriksson BL et al. *Lancet* 2007] RE-MODEL [Eriksson BL et al. *J Thromb Haemost* 2007] RE-MOBILIZE [*J Arthroplasty* 2009] RE-COVER [Schulman S et al. *N Engl J Med* 2009] RE-LY [Connolly SJ et al. *N Engl J Med* 2009] RE-DEEM [Oldgren J. AHA 2009]
Rivaroxaban Trial Status: Completed 20 Phase 2 or 3 trials. Results have been reported for VTE prevention and treatment; AF study enrollment is complete. ACS trial is recruiting.	
Ongoing Trials	**Important Publications**
NCT00403767 Phase 3 AF (ROCKET-AF) NCT00439777 Phase 3 PE NCT00440193 Phase 3 DVT NCT00571649 Phase 3 medically ill patients NCT00786422 Phase 2 DVT CYP3A4 NCT00809965 Phase 3 ACS	RECORD [Eriksson BL et al. *N Engl J Med* 2008; Kakkar AK et al. *Lancet* 2008; Lassen MR et al. *N Engl J Med* 2008; Turpie AG et al. *Lancet* 2009]
Apixaban Trial Status: Completed 9 Phase 2 or 3 trials. Results have been reported for VTE prevention. VTE treatment and ACS treatment studies are recruiting. AF study has completed enrollment.	
Ongoing Trials	**Important Publications**
NCT00412984 Phase 3 Stroke in AF (ARISTOTLE) NCT00457002 Phase 3 Acutely ill patients NCT00496769 Phase 3 AF NCT00633893 Phase 3 Long-term VTE/PE NCT00643201 Phase 3 DVT/PE NCT00831441 Phase 3 ACS NCT00852397 Phase 2 ACS	ADVANCE-1 [Lassen MR et al. *N Engl J Med* 2009] APPRAISE [*Circulation* 2009] ADVANCE-2 [Lassen MR et al. *Lancet* 2010]
Edoxaban (DU-176b) Trial Status: Completed 5 Phase 2 or 3 trials. Phase 2 VTE prevention study has completed enrollment; Phase 3 VTE treatment and AF studies are recruiting. No ACS studies announced.	
Ongoing Trials	**Important Publications**
NCT00781391 Phase 3 AF (ENGAGE AF-TIMI 48) NCT00986154 Phase 3 VTE	Fuji T et al. *Blood* 2008;112 ASH Abstract 34 Raskob Get al. *Eur Heart J* 2008 (ESC Suppl p 609) Weitz JL et al. *Blood* 2008; 112 ASH Abstract 33
Betrixiban Trial Status: Completed 2 Phase 2 trials. VTE Prevention study completed (not yet reported); VTE treatment study is planned. Phase 2 study in AF reported results March 2010 at ACC. A secondary preventions study is planned in ACS.	
Ongoing Trials	**Important Publications**
NCT00999336 Phase 2 PK/PD degrees of renal impairment	EXPERT [Turpie AG et al. *Thromb Haemost* 2009] EXPLORE-Xa [Ezekowitz M. ACC 2010]

ACS = acute coronary syndrome; AF=atrial fibrillation; DVT = deep vein thrombosis; PCI = percutaneous coronary intervention; PE = pulmonary embolism; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism; * Observational study

Table 2. PK/PD Properties of an Ideal Long-Term Oral Anticoagulant.

Property	Benefit	Agents in Development
Oral, once daily	Ease of administration	rivaroxaban, edoxaban, betrixaban
Rapid onset of action	No need for overlapping parenteral anticoagulant	All Factor IIa and Xa inhibitors
No food/drug interactions	Simplified dosing	All
Predictable anticoagulant effect	No routine coagulation monitoring	All Factor IIa and Xa inhibitors
Extrarenal clearance	Safe in patients with renal insufficiency	Betrixaban, apixaban, edoxaban (in order of most to least)
Rapid offset of action	Simplifies management in case of bleeding or intervention	All (betrixaban has the longest half-life at 19-20 hours)
Safe antidote	…in case of major bleeding	Potentially all Factor Xa inhibitors

"Compared with warfarin," said Dr. Giugliano, "the new anticoagulant therapies have more stable PK/PD profiles, no diet interaction, and fewer drug-drug interactions. They do not require monitoring of their anticoagulant effect and, so far, do not appear to be associated with off-target adverse events." Dabigatran is the only thrombin inhibitor among the new group. The time to action is short (1 to 4 hours) for those agents for which this information has been reported (all but betrixaban). The only agent that appears to have substantial interaction with the CYP 450 system is rivaroxaban. Bioavailability is good for all of the agents, with the exception of dabigatran, where it is rather low (7%). Protein binding is variable across the group, with rivaroxaban having the highest (>90%). This could be a disadvantage in patients with different levels of plasma proteins, a high state of acute phase reactance, or malnutrition. It could also mean that rivaroxaban is less likely to be successfully removed by dialysis. The half-life of the drugs varies 2-fold or more. Edoxaban has the shortest half-life (8 to 10 hours). Betrixaban has the longest (19 to 20 hours); thus, it would be suitable for once-daily dosing. Renal elimination varies markedly—80% for dabigatran and <5% for betrixaban—which means that there could be roles for more than one agent in this class in clinical practice to accommodate patients with varying renal and hepatic function.

Many excellent alternatives to vitamin K antagonists are on the horizon, and there are meaningful differences in the PK/PD properties of these agents. Trial results so far indicate that dose selection is a critical area for this class of drugs to identify the optimal balance of thrombotic protection and bleeding risk. It also appears advantageous to bring multiple doses forward from Phase II into Phase III testing (rather than the typical single dose that is selected for Phase III) to more thoroughly evaluate these novel agents.

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