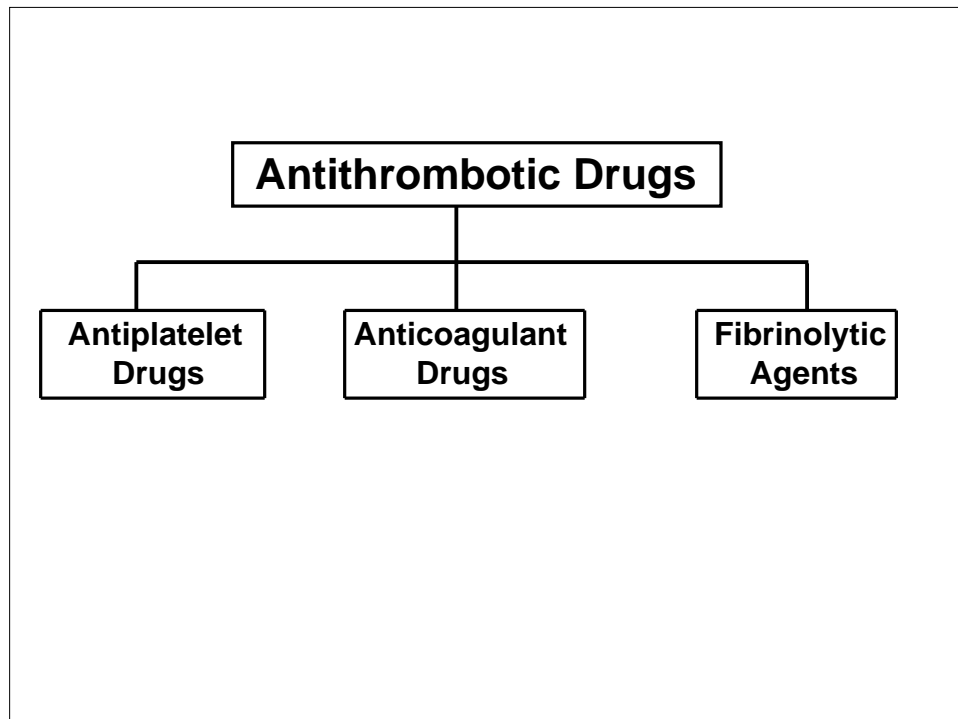


NEW ANTITHROMBOTIC DRUGS

Jeffrey I Weitz, MD, FRCP(C), FACP

**Professor of Medicine and Biochemistry
McMaster University
Canada Research Chair in Thrombosis
Heart & Stroke Foundation/ J.F. Mustard Chair
in Cardiovascular Research**

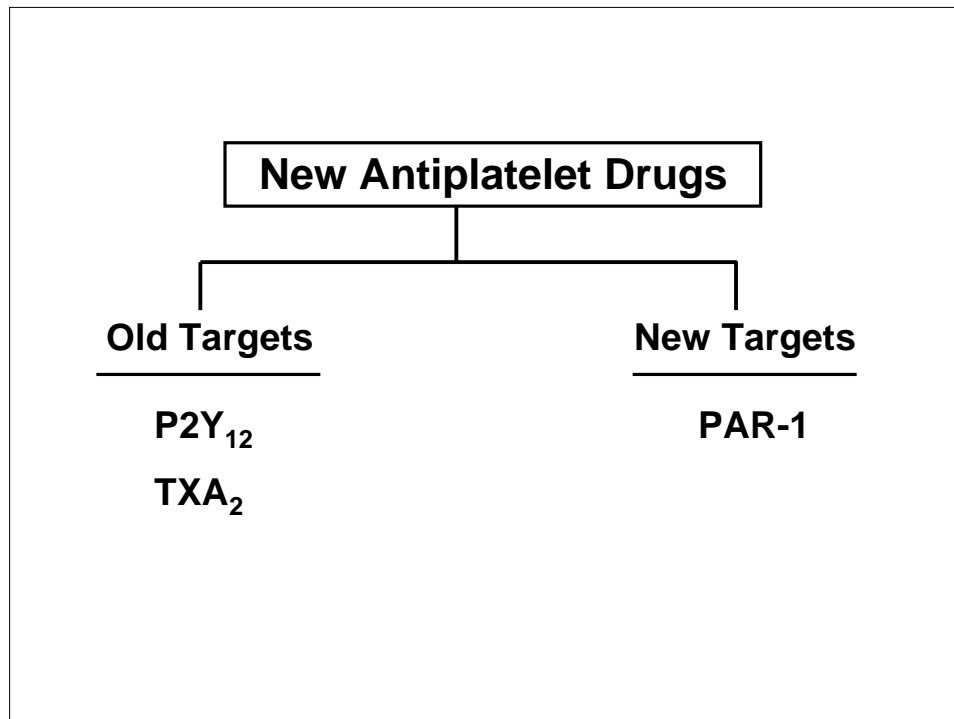


WHY DO WE NEED NEW ANTIPLATELET DRUGS?

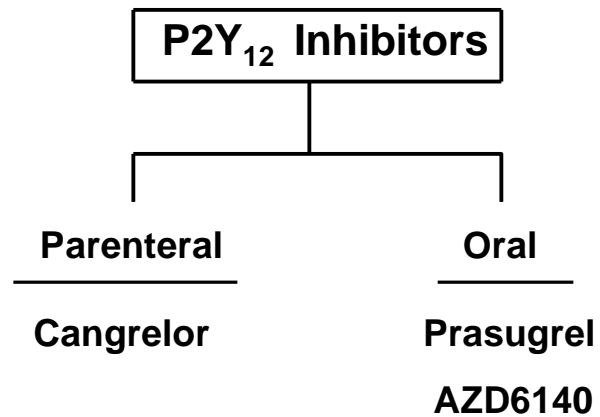
Platelets are central to arterial thrombosis

**Breakthrough cardiovascular events
occur despite aspirin and/or clopidogrel**

**Aspirin and/or clopidogrel “resistance”
may contribute to recurrent events**



NEW DRUGS, OLD TARGETS



New P2Y₁₂ Inhibitors

Indirect (prasugrel) or direct inhibitors (cangrelor and AZD6140)

Like clopidogrel, prasugrel requires metabolic activation, but prasugrel absorption and activation are more efficient

Direct inhibitors have rapid onset and offset because metabolic activation is unnecessary

Potential Advantages and Disadvantages of Prasugrel

More rapid onset of action than clopidogrel, but still delayed despite a loading dose

More effective and consistent inhibition of ADP-induced platelet aggregation

Slow offset of action

Results of TRITON/TIMI-38 trial will define role of prasugrel in PCI setting

Potential Advantages and Disadvantages of Direct P2Y₁₂ Inhibitors

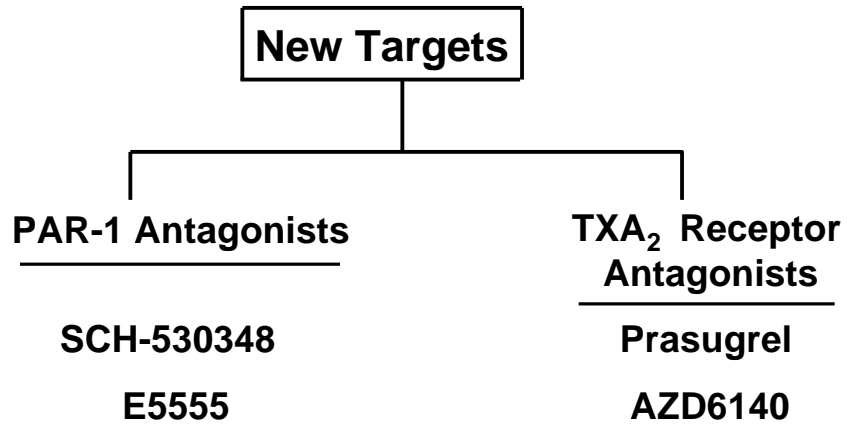
Rapid onset and offset of action

Dose-dependent inhibition of P2Y₁₂

More potent P2Y₁₂ blockade may increase risk of bleeding

Side effects of AZD6140 (dyspnea, bradycardia) are worrisome

NEW DRUGS, NEW TARGETS



NEW ANTICOAGULANTS

Current Anticoagulants

Parenteral

Heparin
LMWH
Fondaparinux

Oral

Warfarin

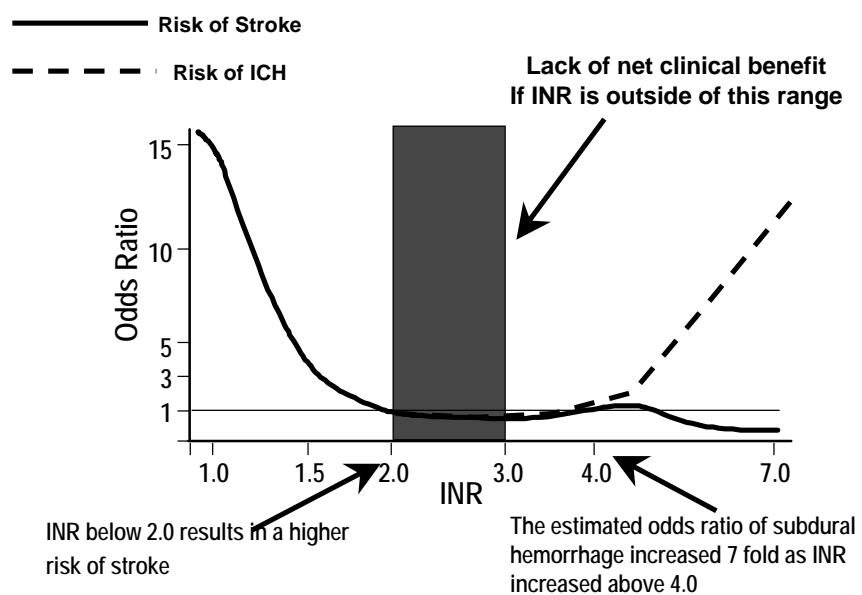
Why Do We Need New Anticoagulants?

Current anticoagulants are suboptimal

Properties of an Ideal Anticoagulant

Properties	Benefits
Orally active	Ease of administration
Rapid onset of action	Obviates need for overlap with a parenteral anticoagulant
No food or drug interactions	Simplified dosing
Predictable anticoagulant effect	No routine coagulation monitoring
Extra-renal clearance	Safe in patients with renal insufficiency
Rapid offset of action	Simplifies management in case of bleed or need for intervention
Safe antidote	Useful in case of major bleed
Favourable net clinical benefit	Treatment benefit outweighs risk

Therapeutic Range for Warfarin Therapy

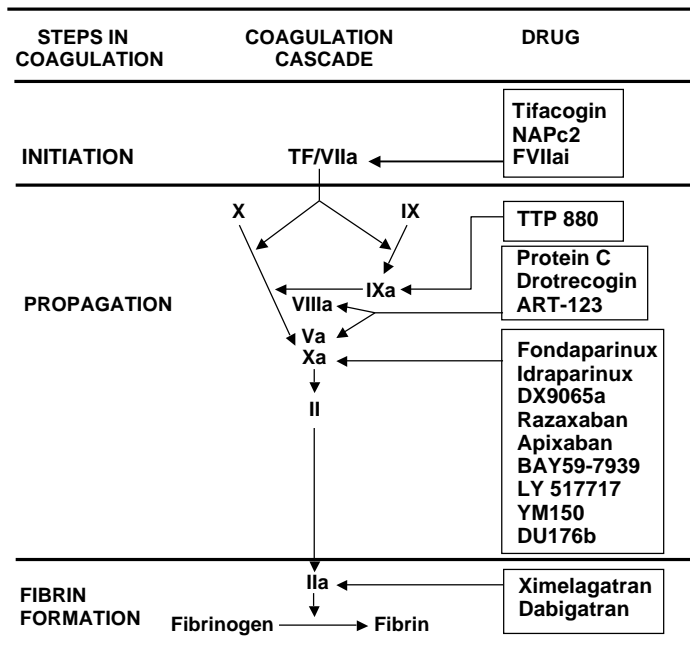


Hylek EM, et al. *N Engl J Med* 1996;335:540-546.

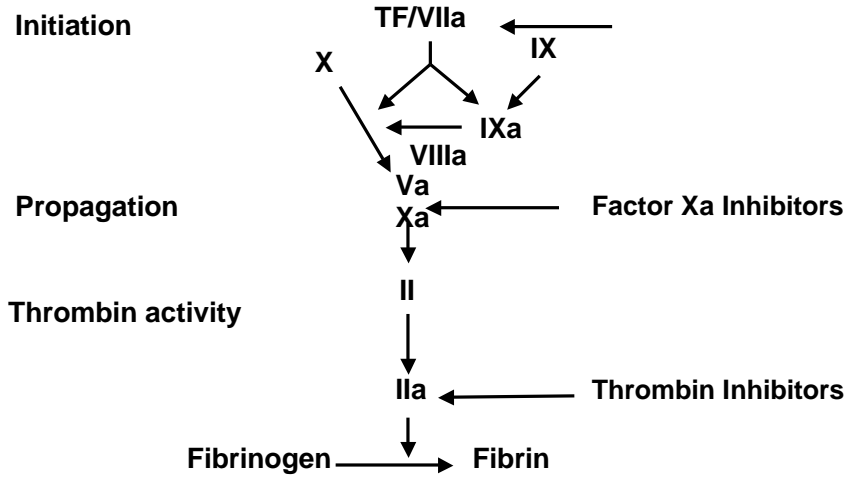
Properties of Currently Available Anticoagulants

Properties	Heparin	LMWH	Fondaparinux	Warfarin
Orally active	No	No	No	Yes
Rapid onset	Yes	Yes	Yes	No
No food/drug interactions	Yes	Yes	Yes	No
Predictable anticoagulant effect	No	Yes	Yes	No
Extra-renal clearance	Yes	No	No	Yes
Rapid offset	Yes	No	No	No
Antidote	Yes	Partial	No	Yes

TARGETS FOR NEW ANTICOAGULANTS



Targets of New Oral Anticoagulants in Development



Eikelboom JW, Weitz JI, A Replacement for Warfarin: The Search continues, *Circulation*, July 10, 2007, 131-133

Factor Xa Inhibitors

Indirect

Fondaparinux
Idraparinux

Direct

Apixaban
Rivaroxaban
LY517717
YM150
DU-176b
PRT054021

} Early Stage
Development

Direct vs. Indirect Factor Xa Inhibitors

Indirect Factor Xa Inhibitors

Fondaparinux
Idraparinux



Direct Factor Xa Inhibitors

Apixaban
Rivaroxaban



-
- | | |
|--|--|
| <ul style="list-style-type: none">• Parenteral• Require cofactor – ATIII• Bind PF4• Inhibit free Factor Xa only | <ul style="list-style-type: none">• Oral• No cofactor needed – reversible• Do not bind PF4 – no risk of HIT• Inhibit free Factor Xa and Factor Xa in prothrombinase complex – Better attenuation of thrombin generation |
|--|--|
-

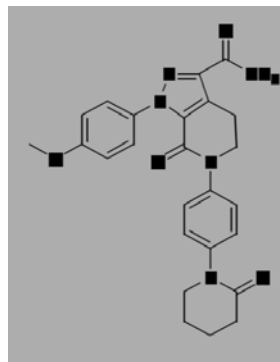
Evidence Supporting Factor Xa as a Target

At prophylactic doses, fondaparinux is:

- (a) superior to enoxaparin for VTE prevention after orthopedic surgery
- (b) as effective as enoxaparin for prevention of recurrent ischemia in non-ST-elevation ACS, but causes less bleeding

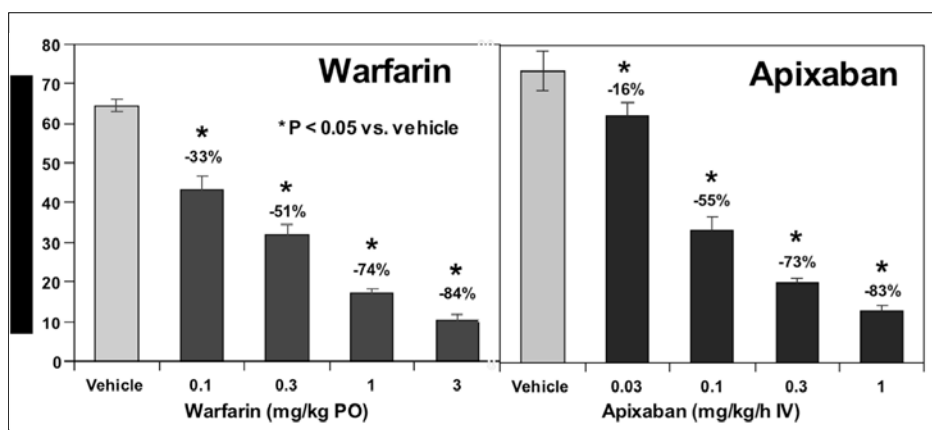
Features of Apixaban

- Oral, direct, highly selective Factor Xa inhibitor
- Produces concentration-dependent anticoagulation
- No reactive intermediates
- No organ toxicity or LFT abnormalities in chronic toxicology studies
- Low likelihood of drug interactions
- Good oral bioavailability
- No food effect
- Balanced elimination (~25% renal)
- Half-life ~12 hrs



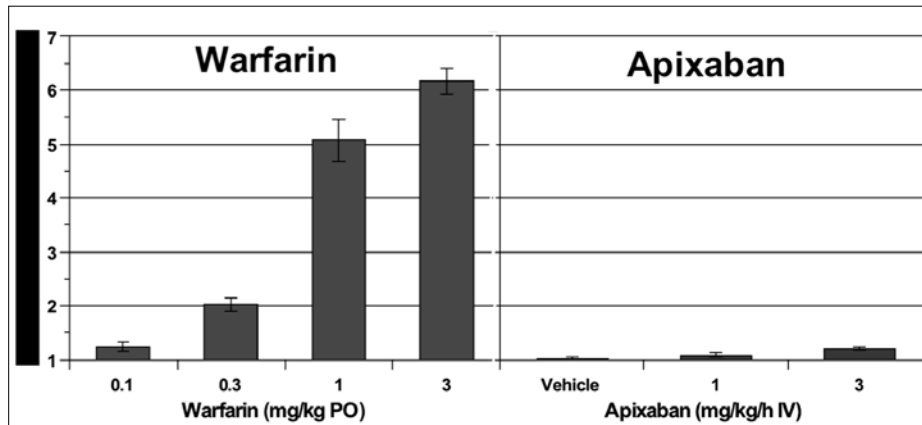
He et al., ASH, 2006, Lassen, et al ASH, 2006

Comparison of the Antithrombotic Effects of Warfarin or Apixaban in a Rabbit DVT Model



Wong et al., ASH, 2006

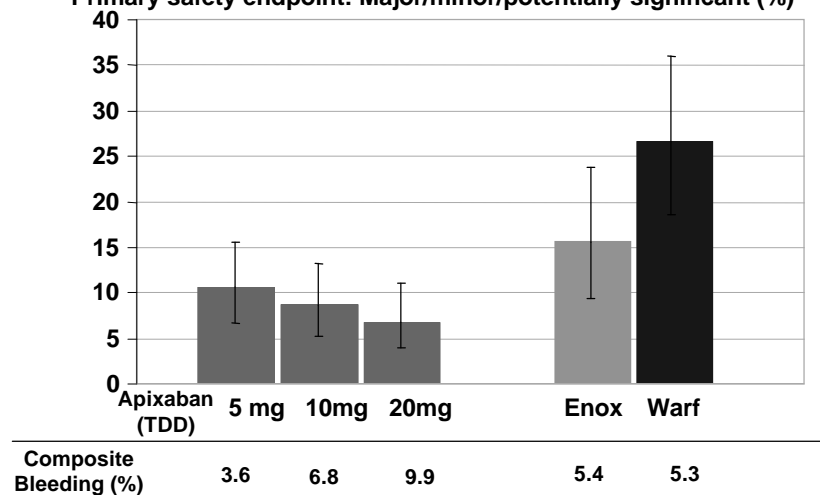
Comparison of the Effects of Warfarin or Apixaban on Cuticle Bleeding Time in Rabbits



Wong et al., ASH, 2006

Phase II APROPOS Trial – Apixaban PROphylaxis in Patients Undergoing Orthopedic Surgery

Primary efficacy endpoint: VTE/All Cause Death Event Rates (%)
 Primary safety endpoint: Major/minor/potentially significant (%)



Lassen, ASH 2006

Apixaban Clinical Development Program

Indication	Status
VTE Prevention in Major Orthopedic Surgery	Phase III
VTE Prevention in Acutely Ill Medical Patients	Phase III
Stroke Prevention in Atrial Fibrillation	Phase III
Acute & Extended VTE Treatment	Planning Phase III
Prevention of Thrombotic Events in Patients with Recent ACS	Phase II
VTE Prevention in Cancer Patients	Phase II

RECORD-3: A Comparison of Rivaroxaban and Enoxaparin For Thromboprophylaxis After Knee Replacement

Endpoint	Rivaroxaban (10 mg)	Enoxaparin (40mg)	P-value
<u>Efficacy (%)</u>			
DVT, non fatal PE and all-cause mortality	9.6	18.9	<0.001
<u>Safety (%)</u>			
Major bleeding	0.6	0.5	

Lassen, ISTH 2007

What About Thrombin as a Target?

Ximelagatran: Lessons Learned

- **Thrombin is a viable target for new anticoagulants**
- **Possible to develop an oral anticoagulant that can be given in fixed doses without routine coagulation monitoring**
- **Regulatory agencies require stringent monitoring to ensure there are no off-target side effects such as liver toxicity**

Dabigatran; A New Oral Direct Thrombin Inhibitor in Development

Results of RE-MODEL, RE-MOBILIZE, and RE-NOVATE Trials

Endpoint	Dabigatran (150 mg)	Dabigatran (220 mg)	Enoxaparin (40 mg/30 mg bid)
VTE+/-Mortality (%)			
Major bleeding (%)			
RE-MODEL	40.5 1.3	36.4 1.5	37.7 1.3
RE-MOBILIZE	33.7 0.6	31.1 0.6	25.3 1.4
RE-NOVATE	8.7 1.3	6.0 2.0	6.7 1.6

Caprini, ISTH, 2007,
Eriksson, ASH,
2006

Comparison of the Features of Dabigatran Etexilate and Ximelagatran

Features	Dabigatran Etexilate	Ximelagatran
Molecular weight	628	474
Double Prodrug	Yes	Yes
Bioavailability (%)	6	20
Formulation	Capsule	Tablet
Time to peak drug level (h)	2	2
Half-life (h)	12-17	4-5
Renal excretion (%)	80	80
Liver Toxicity	Undetermined	Yes

NEW FIBRINOLYTIC AGENTS

Alfimeprase

Desmoteplase



Summary

Several new antiplatelet and anticoagulant drugs in advanced stages of development

Major challenge with new antiplatelet drugs is whether efficacy advantages will outweigh bleeding risk

Emerging results with oral direct factor Xa and thrombin inhibitors are promising