DEVELOPMENT OF REVERSAL AGENTS FOR NOVEL ANTICOAGULANTS

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

Atrial Fibrillation: A Threat to the Brain

2.5 M people with atrial fibrillation

Atrial fibrillation associated with a 5-fold increased risk of stroke

Strokes with atrial fibrillation have a worse outcome and cost the healthcare system billions of dollars each year

Warfarin for Stroke Prevention in Atrial Fibrillation

Warfarin reduces the risk of stroke by 65%

Only 50% of patients with atrial fibrillation are receiving warfarin and when it is given the INR is often subtherapeutic

The inconvenience of warfarin is a major factor in its underuse

NOACs for Stroke Prevention in Atrial Fibrillation

At least as effective as warfarin and are associated with a 50% reduction in the risk of intracranial hemorrhage

More convenient than warfarin

Have the potential to increase the uptake of anticoagulants for stroke prevention

Unmet Medical Needs

- Despite the advantages of the NOACs over warfarin, the lack of reversal agents instills fear in patients and physicians and limits their uptake

Reversal Agents

Agent	Target
Idarucizumab	Dabigatran
Andexanet alfa	Rivaroxaban and apixaban
Aripazine	Edoxaban

Development of Reversal Agents

RCTs impossible because there is no standard of care

Addition of reversal agents to procoagulants (PCC or factor VIIa) may increase the risk of thrombotic complications

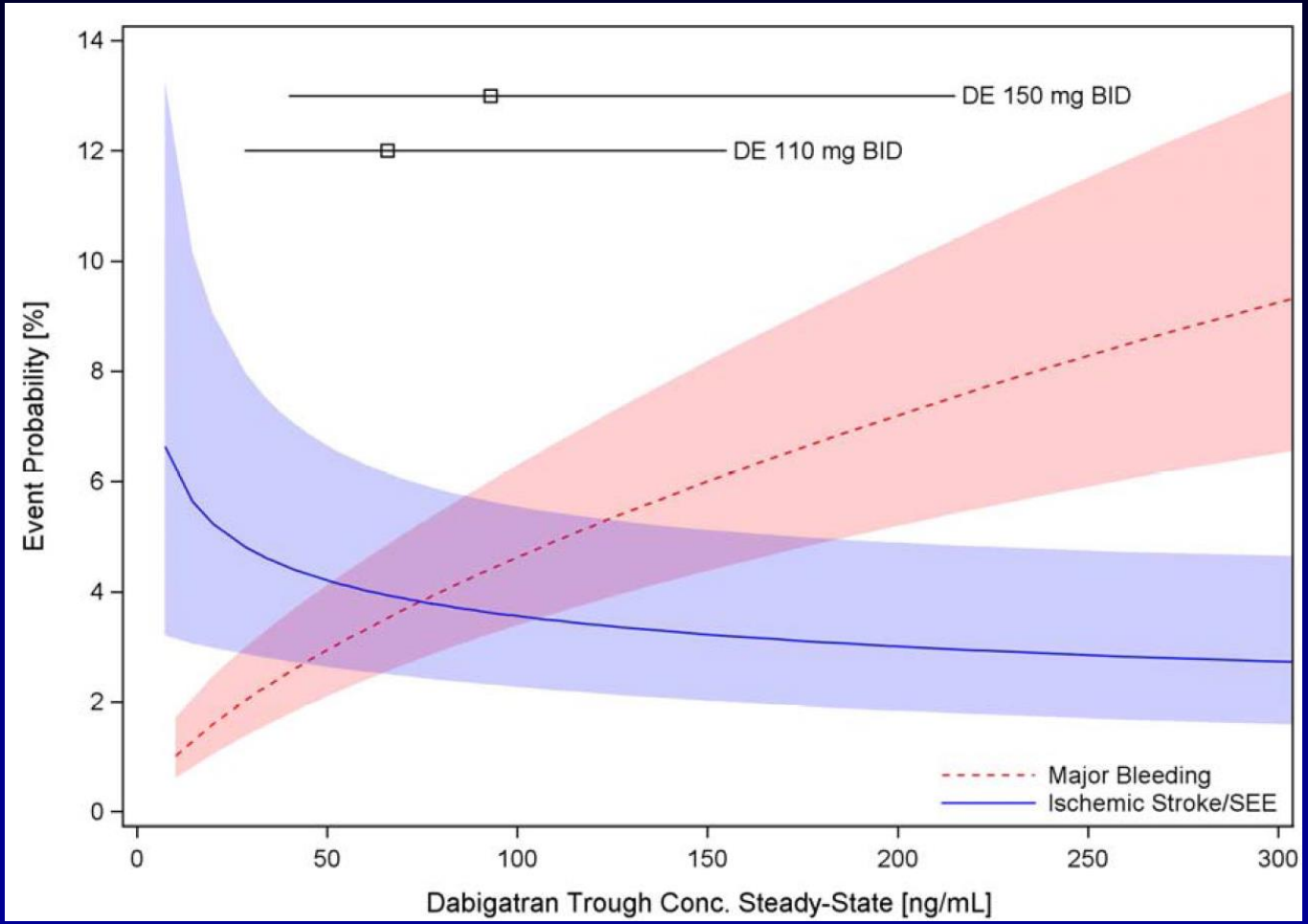
Solution

Safety and “efficacy” studies in volunteers

Cohort studies in patients with serious bleeding or requiring urgent surgery

Post-marketing surveillance

RE-LY
Dabigatran Concentrations and Outcome



DE, dabigatran etexilate; SEE, systemic embolic event

Reilly *et al. J Am Coll Cardiol* 2014;63:2885

Pharmacometric Approach

- Adjusting doses based on measurement of anticoagulant activity or drug levels, i.e., monitoring

NOAC therapy should NOT be routinely monitored

NOACs were introduced, in part, to avoid the need for routine coagulation monitoring

Results with unmonitored NOAC therapy are superior to those with warfarin

Although coagulation tests and drug levels can predict outcome, there is no evidence that dose adjustment based on test results improves outcome

Reilly PA, et al. *J Am Coll Cardiol* 2014; 63: 2885-6.

Variability in Dabigatran Levels

Large inter- and intra-patient variability in dabigatran levels (CV up to 60% and 40%, respectively)

Similar median and drug level distributions with 110 and 150 mg dose suggesting that dose adjustment based on clinical characteristics results in similar drug exposure

Up to 40% of patients with high and 80% with low trough levels at 1 month had subsequent levels in the middle quartiles

Chan NC et al. *J Thromb Haemost* 2014 [Epub ahead of print]

Monitoring versus Measuring Anticoagulant Effect of NOACs

We don’t need to monitor, we do need to measure

Conclusions

Reversal agents have the potential to increase uptake of NOACs

Breakthrough therapy designation will accelerate the approval of reversal agents

Post-marketing surveillance essential to ensure appropriate use of reversal agents and to assess their safety in the real world