Dose - Response - Anticoagulants

Robert Temple, MD

Deputy Director for Clinical Science,
Center for Drug Evaluation and Research

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NOAC Dosing is Complicated

1. Events of interest are relatively infrequent, 2-3%, so large studies are needed.
2. Not placebo-controlled; rather active-controlled, so differences being sought are a small part of overall effect.

   Coumadin gives 50-60% reduction. Although we used an NI margin of about 36%, realistically, the NOACs should be a lot closer than that, and indeed, one hopes for superiority.
3. Confusion of very different strokes; thromboembolic and hemorrhagic. Tend to be counted together, but a higher

   dose should lower TE strokes and might raise hemorrhagic stroke rate.
4. D/R may be very steep at low end of dosing for TE stroke (as it is for warfarin).

Dose Finding

Most dose-finding efforts focused on avoiding too much bleeding, which is more common than strokes, but it really does not tell you what dose to use.

Some sponsors used 2 doses:

Dabigatran: 110 mg b.i.d., 150 mg b.i.d.

Edoxaban: 30 or 60 mg o.d.

Some used only one dose:

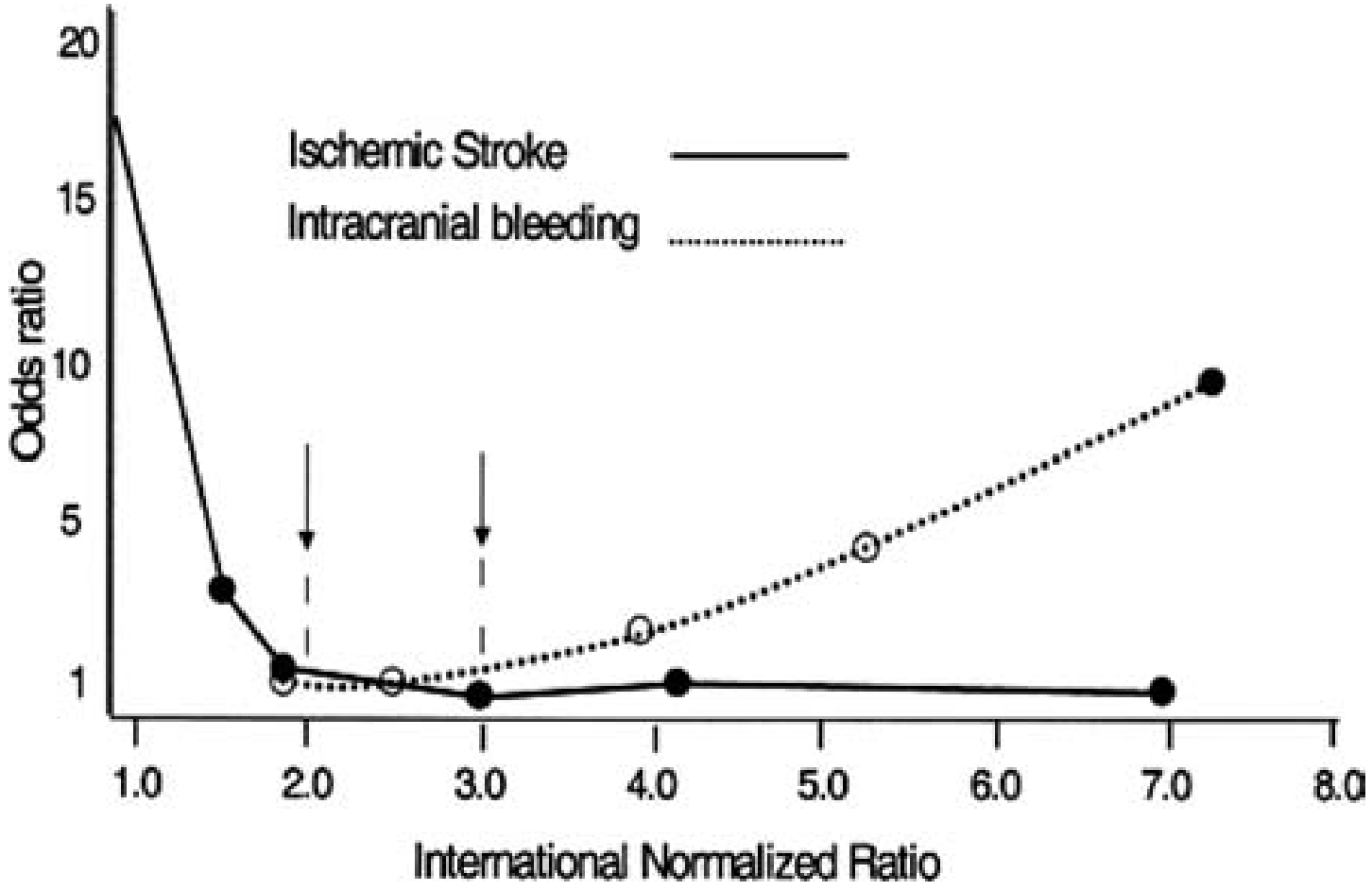
Apixiban

Riveroxiban

Does a single, fixed dose make sense?

Dose-Finding (continued)

For the warfarin control we do not use a fixed dose. We titrate to desired INR. This is perhaps because we know blood levels can be very variable, but we also know that dose matters to outcome.


Ischemic Stroke
Intracranial bleeding
Odds ratio
20
15
10
5
1
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
International Normalized Ratio

The slide shows relation of INR to thrombotic stroke and intracranial bleeding, but the total bleeding curve is similar to intracranial bleeding. We can see that INR <2 does not reduce stroke adequately and that beyond INR of 2 there is very little benefit BUT increased bleeding.

The “sweet spot” is an INR of about 2-3, perhaps 2-3.5.

So, for the previous of standard of care, warfarin, we do not use a fixed dose but always use a dose titrated to anticoagulant effect. Why are NOACs different?

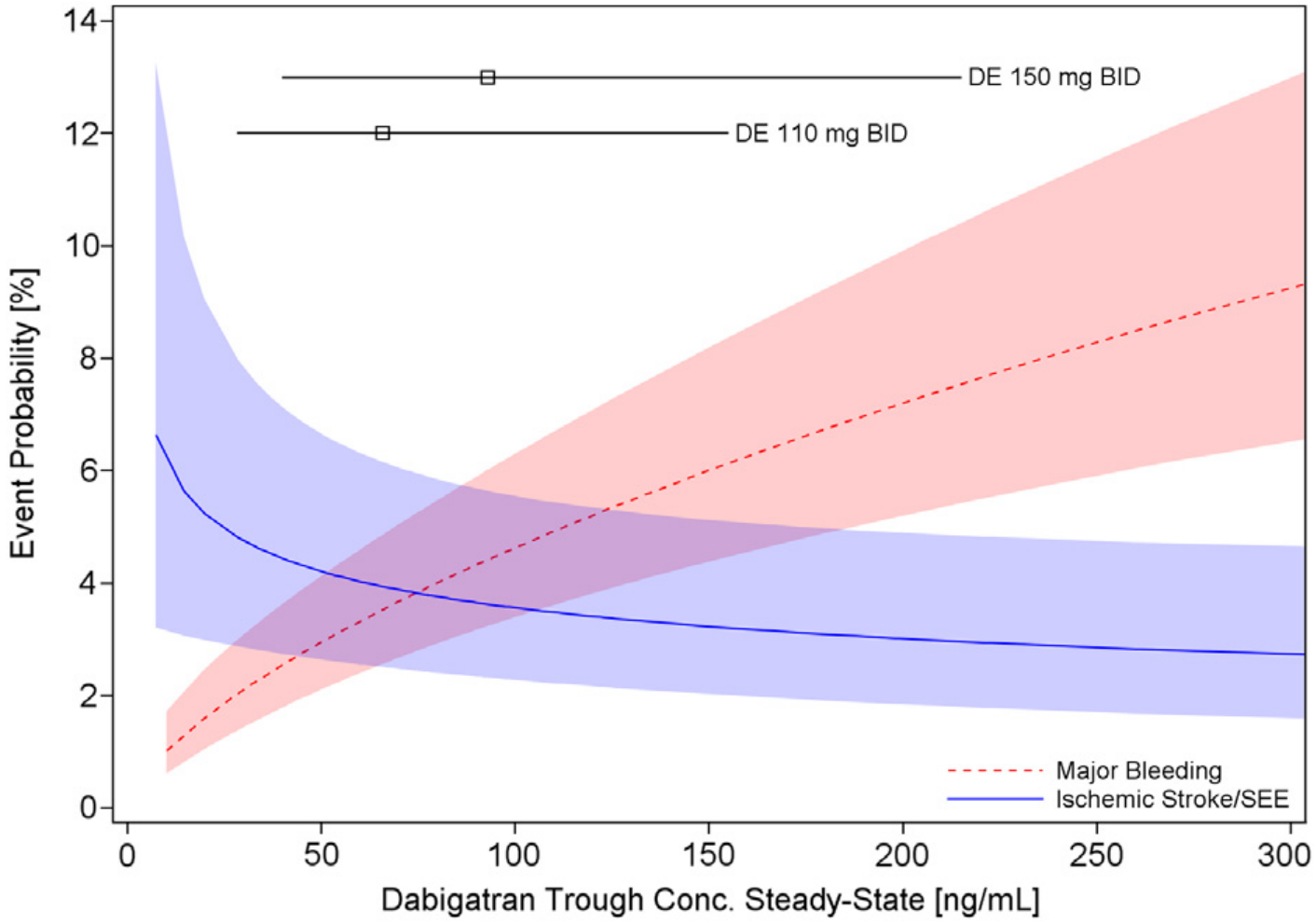
Maybe they shouldn’t be.

NOACs

1. Dabigatran: Substantial D/R from 35% increase

	Dabi 150	Dabi 110	Warfarin
n	6076	6015	6022
All Stroke	122 HR 0.64	171 HR 0.91	186
Ischemic Stroke	103 HR 0.75	152 HR 1.13	134
Hemorrhagic Stroke	12 HR 0.26*	14 HR 0.31*	4.5
Major Bleed	3.3%		3.6%

Only D150 numerically better on ischemic stroke; both superior on hemorrhagic stroke.
Good thing they used 2 doses.


DE 150 mg BID
DE 110 mg BID
Major Bleeding
Ischemic Stroke/SEE
Event Probability [%]
0
2
4
6
8
10
12
14
0
50
100
150
200
250
300
Dabigatran Trough Conc. Steady-State [ng/mL]

The curves, based on trough blood level, look a lot like coumadin. In particular, the full benefit on thromboembolic stroke is there at 75-150 ng/ml trough; but bleeding increases above that. Below 50 ng/ml strokes go up a lot.

Very few DB 150 patients were below 50 ng/ml, but a fair number on DB 110 were. On the other hand, DB 150 puts a fair number into bleeding range.

Why not adjust trough doses to get 75-150 or 75-100 in everyone?

NOACs

NOACs, even unmonitored, at doses studied, work well.

- All have lower hemorrhagic stroke rate and less intracranial bleeding, an unexpected but important finding.
- All have thrombotic stroke rates similar to warfarin, a large and valuable effect. BUT only dabigatran has a lower thrombotic stroke rate.

Could the others also give lower thromboembolic rates with somewhat increased dose, at least for “lower end” patients?

People like to avoid monitoring, but dabigatran C/R data suggest one blood level and adjustment could optimize stroke reduction and minimize bleeding.

Data

We have blood level data on dabigatran and edoxaban, but not riveroxiban or apixiban.

It is possible that if blood levels were not too variable a single dose could get most people into proper range. We know that is not true for dabigatran and edoxaban, and we also know that apixiban and riveroxiban did not reduce thromboembolic strokes compared to warfarin although they caused less bleeding.

Coagulation measures might do as well as, or better than, blood levels.

All this is under active consideration. With steep D/R for both benefit and risk, optimizing dose or blood level seems like a very good idea.