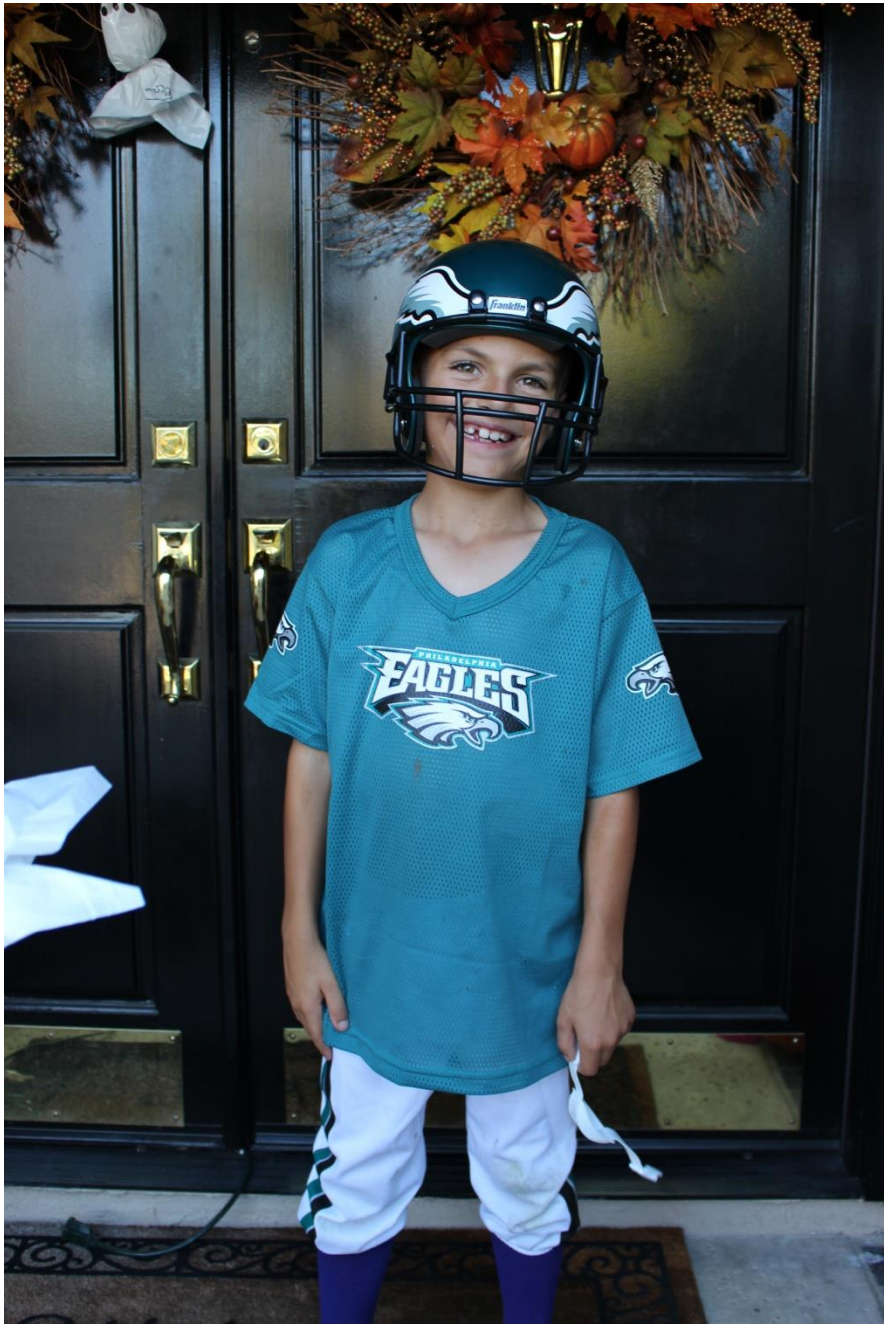
How Are Doctors Going to Make Use of NOAC PK/PD Information in Clinical Practice?

Peter R. Kowey, FACC, FAHA, FHRS
Lankenau Heart Institute
Jefferson Medical College
Philadelphia, PA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John Kenneth Galbraith

“It is a far, far better thing to have a firm anchor in nonsense than to put out on the troubled seas of thought.”

Disclosure

- Dr. Kowey has consulted for several companies involved in the development of NOACs and reversal agents including BI, J&J, BMS, Pfizer, Daiichi-Sankyo, Portola, Merck, AZ
- More importantly, Dr. Kowey prescribes anticoagulants and has had to deal with the consequences regularly

Case Example

- 75 year old man (CHADS-VASc 4) who was switched from warfarin to NOAC two months ago because of fluctuating INRs
- Cause of instability uncertain but requires lower dose because of impaired renal function
- After long period of SR on dofetilide, he lapses into AF with controlled VR
- Intended cardioversion
- Unclear adherence based on previous INR issues

Case Example

- 80 year old woman (CHADS-VASc 5) presents with monocular blindness that resolved in < 1 hour on the way to the hospital
- History of permanent AF with auto-controlled VR and no symptoms
- On NOAC for 6 months with supposedly good adherence although “I miss a dose occasionally.”
- Negative neurological examination and imaging

Doctor Attitudes about Anticoagulants

- Continue to believe (without reason) that anti-platelets have some value for SPAF
- Warfarin is the devil they know
- Deluged with information about NOACs
- Don’t understand the diverse pharmacology
- Like the idea of dosing convenience but…
- Want to be able to measure something
- Reassured by availability of an antidote but not sure why or how often they will need it
- Naïve to cost issues and other constraints

How do the antidotes fit in?

- They have (will) provided reassurance
- Unclear how they will be employed
- Cost will be a significant impediment
- Unreasonable to expect a mortality advantage and may only have small impact on morbidity

Clinical Scenarios in Which Measurements Might Make Sense

- Adherence concerns
- Cardioversion
- Ablation
- Surgical procedures
- Presentation with major bleeds or stroke (as an aid to decisions about subsequent Rx)
- Extremes of renal function, BMI, etc

Value Added

- Patients with CVA or major bleed on a NOAC
- Patients with renal impairment, especially those with wide fluctuations
- Patients on concomitant medications of concern
- Patients with very high stroke/bleed risk scores
- Switch/discontinuation

Challenges

- Usable metric (rapidly available, understandable, reliable, reproducible)
- Clear definition of therapeutic range
- Cost
- Guidelines for proper use
- Will be used as an excuse to underdose

Bill Watterson

“Sometimes I think the surest sign that intelligent life exists elsewhere in the universe is that none of it has tried to contact us.”

From a Referring Doctor

Peter,

Is there any data or recommendations on the novel agents with the morbidly obese. By morbidly obese, I mean a patient that weighs 638 lbs with a BMI of 120!

Thanks

REALITY

- NOACs did not require routine monitoring of coagulation to show superiority
- Neither the dose nor the dosing intervals should be altered in response to changes in laboratory coagulation parameters for the current registered indications
- When interpreting a coagulation assay in a patient treated with a NOAC, it is paramount to know exactly when the NOAC was administered relative to the time of blood sampling
  - The maximum effect of the NOAC on the clotting test will occur at its maximal plasma concentration, which is approximately 3 h after intake for each of these drugs

Conclusions

- Adding measurements to guide dosing is feasible but will require significant physician education (and they are already overwhelmed)
- Need to have clear parameters for utilization and relatively specific instructions for how to adjust the dose and reassess
- Cost may be substantial; will need to be offset by some tangible evidence that it improves NOAC safety and efficacy