CSRC Symposium: Is There a Role For Pharmacokinetic/Pharmacodynamics Guided Dosing For Novel Anticoagulants?

Session II: Is it possible that with better precision dosing we can do better in avoiding strokes and bleeds? What types of clinical evidence would be necessary to support PK/PD dosing? How do we ensure we are not hurting anyone?

Counterpoint: PK based dosing strategy is impractical and may not add value

a) Initial PK measurement—should we do it?
b) Is there a rationale for monitoring?
c) Is it possible to measure and/or monitor?

Scott D. Berkowitz, M.D.
Vice President and Head, Thrombosis Group
Global Clinical Development
Bayer HealthCare Pharmaceuticals

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Views and perspective expressed are mine and do not necessarily reflect those of Bayer HealthCare Pharmaceuticals

a) Initial PK (/PD) measurement - should we do it?

- Clinical value of a PK/PD measurement for NOAC dosing not proven nor as straightforward as with PT/INR for VKAs
  - Appropriateness of the measure
    - Routine coagulation tests (PT, aPTT) refined for VKA and heparin monitoring
      - Not originally designed for this purpose
    - Specialized, not readily available:
      - DTIs: dilute TT, ECT
      - FXa inhibitors: anti-FXa chromogenic assays require calibrators and controls specific for specific inhibitor
  - Appropriate time to measure
    - NOAC plasma concentrations can change rapidly over the dosing interval
    - Timing of the sample: peak or trough or mid-range
    - Time sample taken in relation to time of last dose (patient memory) are critical
  - Proof of the clinical worth of taking the measurement
    - PD effect of VKAs - more stable at time of measurement and clinical interpretation
    - Value of plasma concentration level for NOACs is more fleeting
      - Little lasting information beyond moment of testing
    - Despite extensive testing and modelling with edoxaban, no direct association found between reduction in concentration and reduction in anti-factor Xa activity[1,2]

[1]Ruff CT et al, Lancet 2015; 385: 2288–95.
[2]Patel & Washam, Lancet 2015;385:2232-33.

Rivaroxaban Plasma Levels Sensitive To Both Time Of Sampling And Time Of Last Dose Taken As Recalled By Patient

Indication and rivaroxaban dose	VTE prevention: 10 mg od	DVT treatment: 15 mg bid for 3 weeks followed by 20 mg od	Prevention of stroke in patients with AF and CrCl ≥50 ml/min: 20 mg od	Prevention of stroke in patients with AF and CrCl <50 ml/min: 15 mg od	Prevention of CV events in patients with ACS: 2.5 mg bid
Time after dosing (hours)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)
1	111 (75.1–177)	235 (164–361)	216 (152–316)	189 (134–281)	41.3 (23.5–65.9)
2	122 (90.6–195)	270 (189–419)	250 (177–361)	219 (157–317)	44.1 (26.7–69.5)
3	114 (82.3–186)	259 (180–405)	246 (172–361)	216 (153–317)	42.0 (25.9–66.4)
4	102 (75.8–164)	237 (161–369)	232 (157–349)	205 (141–309)	38.7 (23.3–63.3)
5	90.7 (62.2–143)	213 (145–339)	215 (140–333)	191 (127–297)	35.2 (20.2–59.1)
6	80.2 (51.8–125)	191 (123–311)	198 (123–318)	177 (111–286)	31.7 (17.4–55.5)
9	55.2 (30.5–96.0)	137 (71.3–240)	155 (81.9–276)	141 (74.9–254)	22.8 (10.4–45.2)
12	37.8 (15.2–76.1)	97.8 (42.9–190)	121 (53.4–242)	112 (50.0–225)	16.2 (6.11–36.6)
18	17.9 (4.85–49.9)	50.0 (16.0–124)	73.5 (22.0–187)	70.4 (21.9–180)	–
24	8.54 (1.36–37.2)	25.6 (5.93–86.9)	44.7 (9.02–147)	44.4 (9.42–143)	–

Plasma concentrations given as geometric mean values with 90% prediction intervals (5/95 percentiles). Values given to 3 significant figures.
ACS acute coronary syndrome, *AF* atrial fibrillation, *bid* twice daily, *CrCl* creatinine clearance, *CV* cardiovascular, *DVT* deep vein thrombosis, *od* once daily, *VTE* venous thromboembolism.

Ref: Mueck W, Schwers S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. Thromb J. 2013 Jun 28;11:10. doi: 10.1186/1477-9560-11-10.

a) Initial PK (/PD) measurement - should we do it?

- Value added (for the patient) by taking a measurement not clear
  - Outcome events (bleeding and thrombosis) are the culmination of a number of elements that may be present or changing over hours, days, weeks
  - Reduction in ICH with NOACs not directly dependent on drug concentration; probably related to mechanism of action of warfarin[4]
  - Patient clinical features are more valuable for dose adaptation
    - Relationship between drug levels and outcome is intertwined with patient characteristics[1,2,3]
    - Demographic and patient factors impart risks that are not fully captured by their effect on drug concentration and by coagulation tests that measure intensity of anticoagulation[3]
- A drug plasma concentration level does not provide information about the overall status of hemostasis in the patient in conjunction with that level
  - Hemostasis is dynamic

[1]Reilly PA et al. J Am Coll Cardiol 2014;63:2885
[2]Mueck W et al., Clin Pharmacokinet 2011; 50: 675-686
[3]Ruff CT et al, Lancet 2015; 385: 2288–95
[4]Patel & Washam, Lancet 2015;385:2232-33

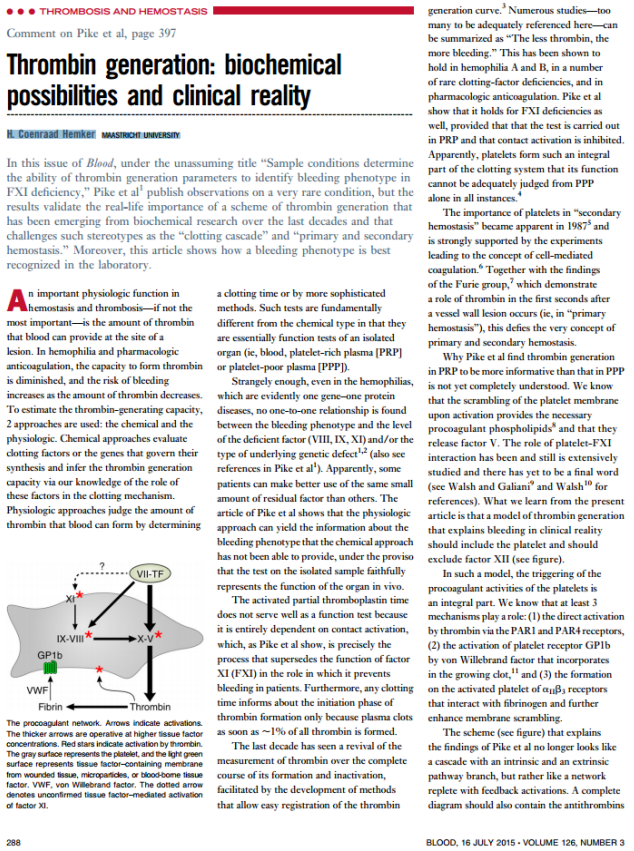
Hemostasis is dynamic

http://marketingland.com/wp-content/ml-loads/2012/07/shutterstock_92903281-dynamic.jpeg

- Hemostasis is a complex and delicate balance
- Dynamic
  - dy•nam•ic, adj. (Oxford Dictionaries)
    - (of a process or system) characterized by constant change, activity, or progress
- Interactive process involving coagulation and fibrinolytic proteins, activators and inhibitors, platelets, endothelium, rheology, microparticles, and WBCs/NETs
- A plasma drug concentration level (PK) or laboratory coagulation test (PD) cannot capture the dynamics of hemostasis over time

Thrombin at the site of vascular injury

- "An important physiologic function in hemostasis and thrombosis……is the amount of thrombin that blood can provide at the site of a lesion."
- "In hemophilia and pharmacologic anticoagulation, the capacity to form thrombin is diminished, and the risk of bleeding increases as the amount of thrombin decreases."
- "….even in the hemophilias, which are evidently one gene–one protein diseases, no one-to-one relationship is found between the bleeding phenotype and the level of the deficient factor (VIII, IX, XI) and/or the type of underlying genetic defect[1,2]…….Apparently, some patients can make better use of the same small amount of residual factor than others."



THROMBOSIS AND HEMOSTASIS

Comment on Pike et al, page 397

Thrombin generation: biochemical possibilities and clinical reality

H. Coenraad Hemker MAASTRICHT UNIVERSITY

In this issue of *Blood*, under the unassuming title "Sample conditions determine the ability of thrombin generation parameters to identify bleeding phenotype in FXI deficiency," Pike et al[1] publish observations on a very rare condition, but the results validate the real-life importance of a scheme of thrombin generation that has been emerging from biochemical research over the last decades and that challenges such stereotypes as the "clotting cascade" and "primary and secondary hemostasis." Moreover, this article shows how a bleeding phenotype is best recognized in the laboratory.

An important physiologic function in hemostasis and thrombosis—if not the most important—is the amount of thrombin that blood can provide at the site of a lesion. In hemophilia and pharmacologic anticoagulation, the capacity to form thrombin is diminished, and the risk of bleeding increases as the amount of thrombin decreases. To estimate the thrombin-generating capacity, 2 approaches are used: the chemical and the physiologic. Chemical approaches evaluate clotting factors or the genes that govern their synthesis and infer the thrombin generation capacity via our knowledge of the role of these factors in the clotting mechanism. Physiologic approaches judge the amount of thrombin that blood can form by determining a clotting time or by more sophisticated methods. Such tests are fundamentally different from the chemical type in that they are essentially function tests of an isolated organ (ie, blood, platelet-rich plasma [PRP] or platelet-poor plasma [PPP]).

Strangely enough, even in the hemophilias, which are evidently one gene–one protein diseases, no one-to-one relationship is found between the bleeding phenotype and the level of the deficient factor (VIII, IX, XI) and/or the type of underlying genetic defect[1,2] (also see references in Pike et al[1]). Apparently, some patients can make better use of the same small amount of residual factor than others. The article of Pike et al shows that the physiologic approach can yield the information about the bleeding phenotype that the chemical approach has not been able to provide, under the proviso that the test on the isolated sample faithfully represents the function of the organ in vivo.

The activated partial thromboplastin time does not serve well as a function test because it is entirely dependent on contact activation, which, as Pike et al show, is precisely the process that supersedes the function of factor XI (FXI) in the role in which it prevents bleeding in patients. Furthermore, any clotting time informs about the initiation phase of thrombin formation only because plasma clots as soon as ~1% of all thrombin is formed.

The last decade has seen a revival of the measurement of thrombin over the complete course of its formation and inactivation, facilitated by the development of methods that allow easy registration of the thrombin generation curve.[3] Numerous studies—too many to be adequately referenced here—can be summarized as "The less thrombin, the more bleeding." This has been shown to hold in hemophilia A and B, in a number of rare clotting-factor deficiencies, and in pharmacologic anticoagulation. Pike et al show that it holds for FXI deficiencies as well, provided that that the test is carried out in PRP and that contact activation is inhibited. Apparently, platelets form such an integral part of the clotting system that its function cannot be adequately judged from PPP alone in all instances.[4]

The importance of platelets in "secondary hemostasis" became apparent in 1987[5] and is strongly supported by the experiments leading to the concept of cell-mediated coagulation.[6] Together with the findings of the Furie group,[7] which demonstrate a role of thrombin in the first seconds after a vessel wall lesion occurs (ie, in "primary hemostasis"), this defies the very concept of primary and secondary hemostasis.

Why Pike et al find thrombin generation in PRP to be more informative than that in PPP is not yet completely understood. We know that the scrambling of the platelet membrane upon activation provides the necessary procoagulant phospholipids[8] and that they release factor V. The role of platelet-FXI interaction has been and still is extensively studied and there has yet to be a final word (see Walsh and Galiani[9] and Walsh[10] for references). What we learn from the present article is that a model of thrombin generation that explains bleeding in clinical reality should include the platelet and should exclude factor XII (see figure).

In such a model, the triggering of the procoagulant activities of the platelets is an integral part. We know that at least 3 mechanisms play a role: (1) the direct activation by thrombin via the PAR1 and PAR4 receptors, (2) the activation of platelet receptor GP1b by von Willebrand factor that incorporates in the growing clot,[11] and (3) the formation on the activated platelet of $\alpha_{IIb}\beta_3$ receptors that interact with fibrinogen and further enhance membrane scrambling.

The scheme (see figure) that explains the findings of Pike et al no longer looks like a cascade with an intrinsic and an extrinsic pathway branch, but rather like a network replete with feedback activations. A complete diagram should also contain the antithrombins

The procoagulant network. Arrows indicate activations. The thicker arrows are operative at higher tissue factor concentrations. Red stars indicate activation by thrombin. The gray surface represents the platelet, and the light green surface represents tissue factor–containing membrane from wounded tissue, microparticles, or blood-borne tissue factor. VWF, von Willebrand factor. The dotted arrow denotes unconfirmed tissue factor–mediated activation of factor XI.

ref: HC Hemker. Thrombin generation: biochemical possibilities and clinical reality. Blood 2015:126;288-9.

Hemostasis is dynamic

- Patients do not bleed simply due to the presence of an excess of antithrombotic drug in the circulation
  - There must be concurrently some pathology at the site of bleeding, vascular structural abnormality (e.g., AV malformation), or physiologic process put under stress (e.g., menses)
  - Must consider the concomitant presence of alterations of other coagulation and fibrinolytic proteins, activators and inhibitors, attenuated or disturbed platelet function, endothelial dysfunction, diseased blood vessels, and altered blood rheology
  - Antithrombotic medications exacerbate, but are not the underlying etiology
- Timepoint at which event becomes clinically apparent does not necessarily define when process began and for how long it has been present

b) Is there a rationale for monitoring?

- When is it valuable to monitor (routinely)?[1,2,3]
  - Test accurately and precisely measures drug levels
  - Target window validated and can be maintained
  - Test results predict clinical outcome
  - Modifying treatment on basis of test result improves outcome (e.g., survival, QOL)
- When is it valuable to measure?[3]
  - When we need to know drug levels (PK) or coagulation effects (PD)
    - Assess adherence
    - Detect overdose
    - Evaluate potential drug interactions
    - Disease of the metabolizing organs (hepatic/renal)
    - Plan timing of urgent surgery
    - Assess contribution to an event (stroke or bleeding)
    - Aid in decision on use of thrombolytics

Refs: [1]Woodcock J, et al. Clin Pharmacol Ther 2010; 88: 765-773. and [2]Chan N, et al. Blood 2014; 124: 689-699. [3]NOAC Reversal Agent Think Tank Follow-up: Post Approval Safety and Effectiveness. Clinical Perspective: What are the opportunities and challenges of using a pharmacometric approach? Jeffrey Weitz, MD (McMaster University). http://www.cardiac-safety.org/1374-2/

When it is not valuable to monitor (or measure)

- When
  - the test is not reliable, reproducible, accurate, precise
  - the test is not readily available to the physician
  - there is infrequent need
  - there is infrequent use
    - Insufficient to give the physician opportunity to learn how to use
  - plasma concentrations change rapidly over dosing interval
  - plasma concentrations vary to a wide range
    - implies that selection of specific thresholds in drug concentrations to guide dose changes will be challenging[1,2,3]
  - there is no proven correlation with the measurement and outcomes
  - there is not validation of how adjusting the dose with the measurement improves clinical outcomes

❑ No evidence to date for NOACs that dose adjustment based on PK or PD measurements results in improved outcomes

❑ Obtaining a level and taking a dose adjustment decision without clinical outcomes correlation is not evidence-based; risks harming patients and negating the proven benefit

[1]Reilly PA et al. J Am Coll Cardiol 2014;63:2885
[2]Mueck W et al., Mueck et al. Thromb J. 2013 Jun 28;11:10.
[3]Ruff CT et al, Lancet 2015; 385: 2288–95

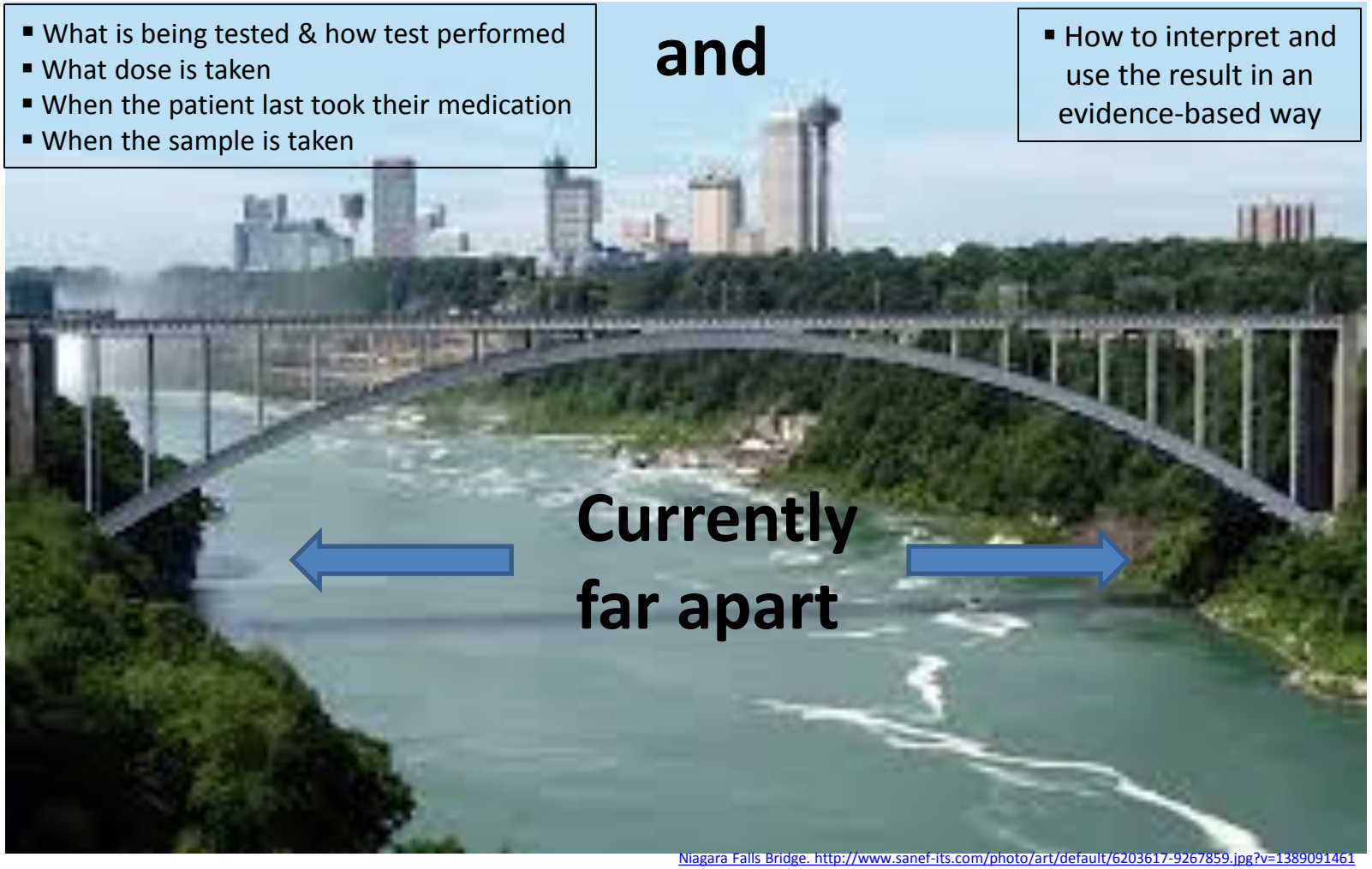
c) Is it possible to measure and/or monitor?

It is possible to measure but a link must be present between:

- What is being tested & how test performed
- What dose is taken
- When the patient last took their medication
- When the sample is taken

and

- How to interpret and use the result in an evidence-based way



Niagara Falls Bridge. http://www.sanef-its.com/photo/art/default/6203617-9267859.jpg?v=1389091461

❑ **Association of available lab tests with drug dose and concentration is complex and not direct[1]**

[1]Patel & Washam, Lancet 2015;385:2232-33

What we should do rather than monitor/measure a level

- Monitor the patient
  - Regular periodic visits to ask the litany of bleeding history questions, do a focused physical exam, and evaluate the patient for changing clinical status, just as we do with VKA patients
  - Value should be recognized by payors
- Know the label
  - Be aware of the predictive patient characteristics for the NOAC patient is on
  - Adapt the dose according to patient characteristics and clinical outcomes trials
- Emphasis on NOAC education
  - Pharma, Academics and Regulators
- Measure for the right reasons
- Treat the patient, not a level

PK based dosing strategy for NOACs is impractical at this time and may not add value

- Predictable PK/PD of developed NOACs and their large clinical outcome trial results precludes need to do so, and doing so diminishes value
- Therapeutic level, even as a range, not easy to define
- Reliable approved rapid assays not yet widely available
- A plasma drug concentration level (PK) or a laboratory coagulation test (PD) cannot capture the dynamics of hemostasis over time
- No evidence to date for NOACs that dose adjustment based on PK or PD measurements results in improved outcomes
- For an evidence-based evaluation, PK based dosing strategy would require assessment in clinical trial setting by indication and subpopulation, and then validation
- Obtaining a level and making a dose adjustment decision without clinical outcomes trial correlation is not evidence-based and risks harming patients while negating the proven benefit
- Demographic and patient characteristics, along with a thorough understanding of the label and clinical judgment, provide sufficient information to make a dose selection or adjustment
- We should monitor, but we should monitor the patient, not a level