Is the ideal anticoagulant a myth?

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"It is clear that the newer anticoagulants … are not more predictable than the older anticoagulant warfarin…"

The ideal anticoagulant does not exist. In all likelihood it will never exist. In 2011, Favaloro and Lippi described the important characteristics of the ideal anticoagulant [1]. Among the list of traits were high efficacy with a wide therapeutic and safe window, oral administration with a rapid onset of action, a predictable anticoagulant effect and, importantly, does not need to be monitored. In this article, I will explore theoretically why chronically administered oral anticoagulants cannot fulfil the wish list criteria proposed by Favaloro and Lippi. I will also highlight the need for appropriate consideration of dose individualization and monitoring in order to optimize patient care.

In 1999, Holford described the importance of identifying a target plasma concentration that can be used to guide drug therapy [2]. This concept can also be generalized to a target based on any biomarker related to drug response (e.g., clotting time). Importantly, when defining a target response, the probability that any given dosing regimen will be successful in achieving this target must be considered. This probability is related to the variability in the relationship between the concentration (or effect) of the drug and the chosen dosing regimen. This variability was attributed to 'population-parameter variability' and consisted of between-subject variability and within-subject variability. Like Favaloro and Lippi, Holford indicates that if the variability in response to a drug is less than a predefined safe level of variability, then the drug can be safely dosed without need for careful scrutiny of an individual's biomarker response. If, however, the variability in response exceeds a safe level, then the dosing regimen would need to be individualized.

A predictable anticoagulant

It is claimed that newer oral anticoagulants have predictable pharmacokinetics [3,4]. It is largely on this basis that newer agents are expected to be safer than existing oral agents, such as warfarin. The claim of predictability is testable on the basis of the unexplained variability in the concentration–time profile. For most drugs that are dosed chronically, this can be conservatively determined on the basis of the unexplained variability in clearance (CL) in the target population (a more accurate estimate would consider variability in all pharmacokinetic and pharmacodynamic parameters). The greater the unexplained variability, the less predictable the response. Various studies have quantified the variability in CL for a number of newer oral anticoagulants as well as for warfarin (Table 1). We see that the newer agents are not different in terms of unexplained between-subject variability and the typical coefficient of variation ranges from 30–50%. This level of unexplained variability is indeed typical for most drugs. It is clear that the newer anticoagulants (e.g., rivaroxaban and dabigatran) are not more predictable than the older anticoagulant warfarin, and indeed are not more or less predictable than most other drugs.

The question remains, however, as to whether this level of unpredictability exceeds some safe level of variability and in doing so mandates individualization.

Keywords: anticoagulants • anticoagulation • clinical pharmacology • modeling • multiscale pharmacology model • pharmacodynamics • pharmacokinetics

Table 1. Between-subject variability in clearance for oral anticoagulants.

Anticoagulant	Target	BSV CL (%CV)	Ref.
Rivaroxaban	Factor Xa	30–59	[12,13]
Warfarin†	VKOR	25–49	[14–16]
Dabigatran	Factor IIa	50	[17]
Argatroban	Factor Xa	37	[18]
Melagatran	Factor IIa	27 (BSV) + 23 (BOV)‡	[19]

†Values exclude studies enrolling healthy volunteers.
‡The variability within an individual from day to day. If BSV is not considered, then the apparent BSV is the sum of 27 and 23%.
BOV: Between-occasion variability; BSV: Between-subject variability; CL: Clearance; CV: Coefficient of variation; VKOR: Vitamin K oxide reductase.

Could the level of unpredictable variability in response be different for different anticoagulants?

Is there a wide therapeutic & safe window?

The coagulation system has been described as a cascade of events that flows inexorably from initiation to clot formation [5]. Initiation occurs via release of bound tissue factor (TF) that complexes with Factor VII, which following autocatalysis forms the TF: Factor VIIa complex, which initiates the coagulation process. This image of a cascade provides an effective method for perceiving the coagulation process as a series of steps which, if disrupted, could prevent clot formation. The process is, however, far from unidirectional and indeed rather than a cascade, is perhaps better thought of as a complex network of both positive and negative feedback and feedforward reactions (Figure 1), making prediction of clotting events from any given stimuli a difficult task [6]. Add to this typical (i.e., nonpathological) levels of variability in clotting factor concentrations (depicted in Table 2), then it should be expected that drugs that affect this system would yield highly unpredictable results even if the drugs themselves had predictable behavior in the body.

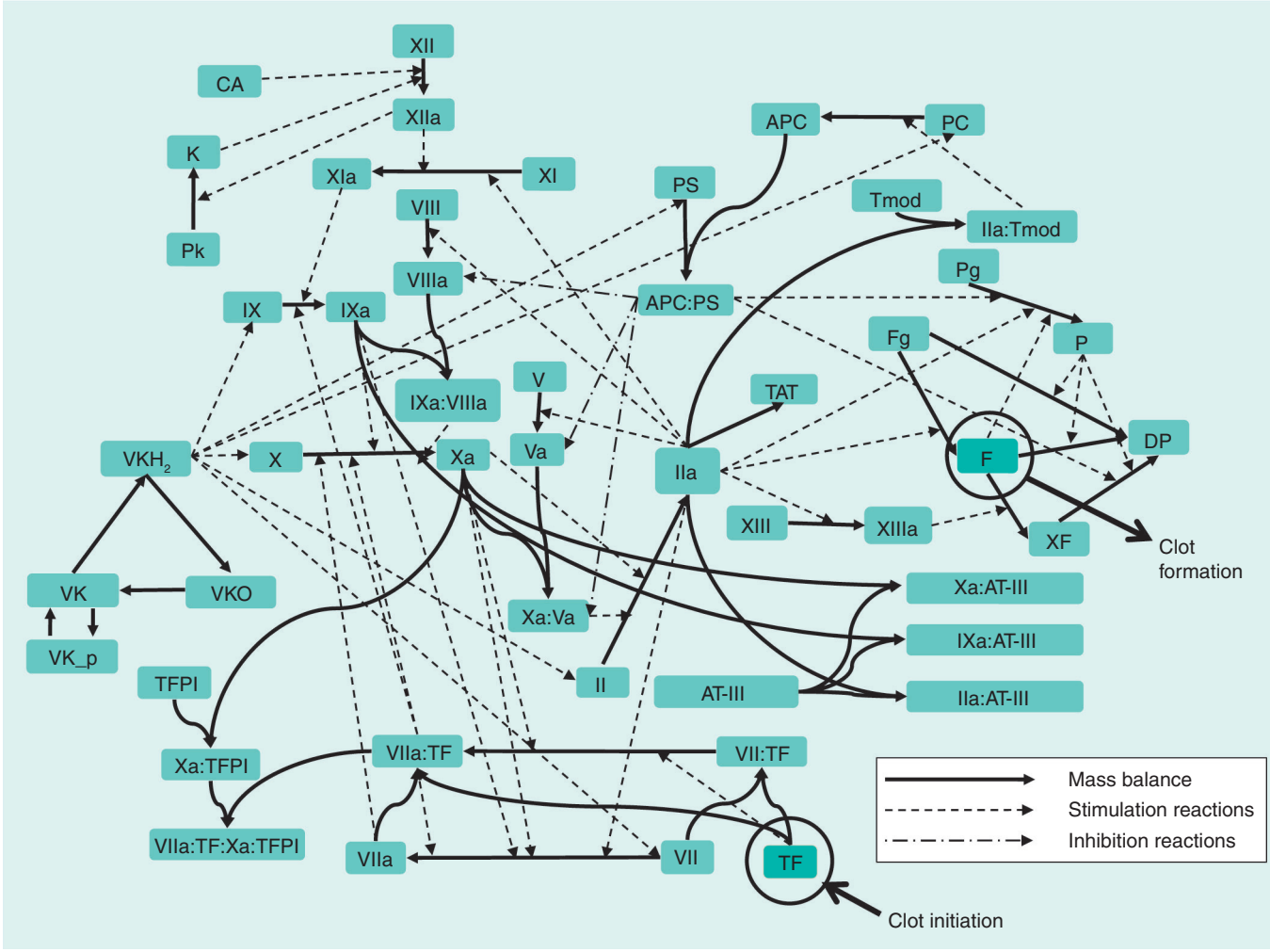

Figure 1. The coagulation network. Here the initiation of clot formation is shown via tissue-bound tissue factor and clot formation occurs when the cumulative production of fibrin reaches a threshold value. The coagulation network is described by a computer model that allows for *in vivo* interactions and application of *in vitro* clotting time tests.
APC: Activated protein C; AT-III: Antithrombin III; CA: Contact activator; F: Fibrin; PC: Protein C; PS: Protein S; TF: Tissue factor; Tmod: Thrombomodulin; VKO: Vitamin K epoxide; XF: Cross-linked fibrin.
Adapted with permission from [6].

Variability in response, however, can only be quantified in the presence of both an inhibitor as well as a stimulus mechanism. The former perturbs the system therapeutically. The latter is the measure we can use to generate a response from the coagulation system. Prior to quantifying the inherent variability in the system, it is necessary to establish what may be considered a safe level of variability given some predefined target.

The work of Hylek *et al.* provided clear evidence of functional relationships between the international normalized ratio (INR; a standardized measure of the prothrombin clotting time test, see [7] for a review of these tests for newer agents) and incidence rates of thrombotic stroke and intracranial hemorrhage (ICH) in patients with atrial fibrillation [8]. These data have previously been worked into a combined risk plot by Kurnik *et al.* [9]. In the current work, the incidence of thrombotic events has been rescaled to become the incidence of thromboses prevented and therefore becomes a benefit (assigned positive values) on the utility scale (Figure 2) while the ICH incidence is depicted as a loss (assigned negative values). E_{max} and power function models were chosen empirically and fitted by nonlinear regression to the benefits and loss data, respectively, to provide smoothed relationships. An E_{max} model is a hyperbolic model that is used to describe the increase in effect (in this case thrombotic events) with an increase in a substrate (in this case INR). It is termed E_{max} as the model asymptotes to a maximum effect. When the benefits (positive y-axis) of warfarin treatment are combined with the loss (negative y-axis) associated with ICH, a difference curve, termed a utility curve, is calculated. This utility curve was developed to help visualize the risk–benefit profile of anticoagulants and is not intended to be used clinically. The utility makes the simplifying assumption that one benefit (reduced thrombotic stroke) carries equal weight to one loss (ICH), and hence the utility is simply the difference between the two. The range of INR values where the utility curve is positive indicates the region of net benefit for warfarin and maximal benefits appear to be associated with INR values ranging between >1.5 and <3.5. This provides quantification of the safe level of variability around the target INR of 2.5.

For the purposes of the argument developed here, an additional assumption is made that a measure of clotting time (from any given test) once validated is sufficient in itself to completely describe the hemostatic benefits and risks of anticoagulants. In this sense, anticoagulants do not possess significant additional life-saving or risk-causing profiles that are not summarized in a clotting time test. That the clotting time test may be other than INR is simply a matter of the complexity of the coagulation network and the historic nature of how the tests were developed and applied, rather than an index that an anticoagulant that does not perturb INR must therefore be either of limited or greater benefit.

The question then arises: can we expect an anticoagulant to achieve a desired target effect safely?

Table 2. Unpredictable variability in clotting factors.

Factor	Reported normal variability
Fibrinogen	2–4 g/l
Factor II	50–165 mg/l
Factor VII	70–125%
Factor VIII	500–2000 U/l
Factor XI	65–140%
AT-III	75–128%
Factor V	54–155%
Factor XII	65–140%

AT-III: Antithrombin III.
Data taken from [20].

Assessing variability in anticoagulant response

Simulations were performed from a mathematical model of the coagulation network [6] to assess the expected variability in clotting time responses when different components of the network were inhibited. Four hypothetical drugs were proposed, each an inhibitor of one of the Factors IIa or Xa, the TF: Factor VIIa

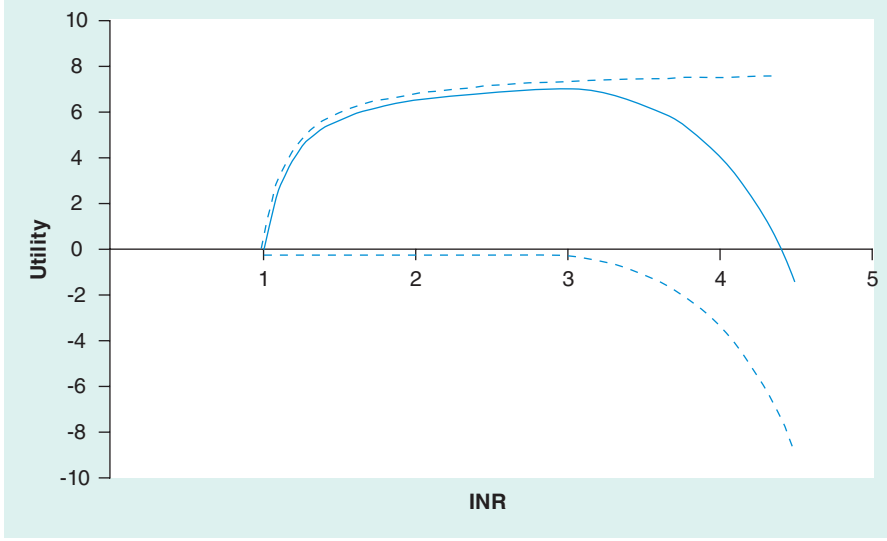

Figure 2. A pharmacological utility curve estimated for warfarin in the treatment of chronic atrial fibrillation. Here an E_{max} model is fitted to the thrombotic rates (expressed as thrombotic rate saved) and a power model to the intracranial hemorrhage rates. Positive values of this utility function describe net benefits of treatments; negative values describe net losses. The dashed lines are either thrombosis rates saved (positive utility) or intracranial hemorrhage caused (negative utility). The solid line is the difference of those rates under the simple assumption that a positive benefit is equally as good as a negative loss is bad.
INR: International normalized ratio.
Data taken from [8].

complex or vitamin K oxide reductase (a warfarin analogue that will inhibit the formation of the vitamin-K dependent Factors II, VII, IX and X). These are summarized in Figure 3. Each hypothetical drug had a half-life of 1 day, had high sensitivity and selectivity for the specified clotting factor and exhibited competitive binding causing reversible inactivation. Clotting time was assessed using an INR-like test (i.e., one that assessed time to clot formation by stimulating the system with TF). The initial dose was adjusted so that it provided a target INR of 2.5. Based on between-subject variability values presented in Table 1, a between-subject variability in CL was assumed to be 40% for the hypothetical drug. For this scenario a mean value of CL of 1 l/h would mean that 95% of the population would have a value of CL ranging from less than 0.5 l/h to greater than 2 l/h, assuming a log normal distribution of CL. In addition, variability in the clotting factors fibrinogen, and Factors II, V, VII, VIII, XI and XII was also included (from Table 2). No variability in the sensitivity of the binding of drug to the clotting factor was considered in these simulations.

Simulations were performed from the coagulation network model that incorporated variability in the concentrations of the hypothetical drug and variability in the coagulation factors. The resulting range of INR values are shown in Table 3. It is seen that even under a conservative level of variability for the coagulation factors (75–150% of normal) and typical variability in the between-subject variability of CL the INR values ranged from 1.5 to >3.4, indicating that none of the drugs (and therefore none of the targeted clotting factors) provided a safe level of variability. Simulations using a less conservative variability in the coagulation factors (50–200%) resulted in INR values ranging from 1.2 to 5.9. In addition, there was only minimal difference between the level of variability associated with the different hypothetical

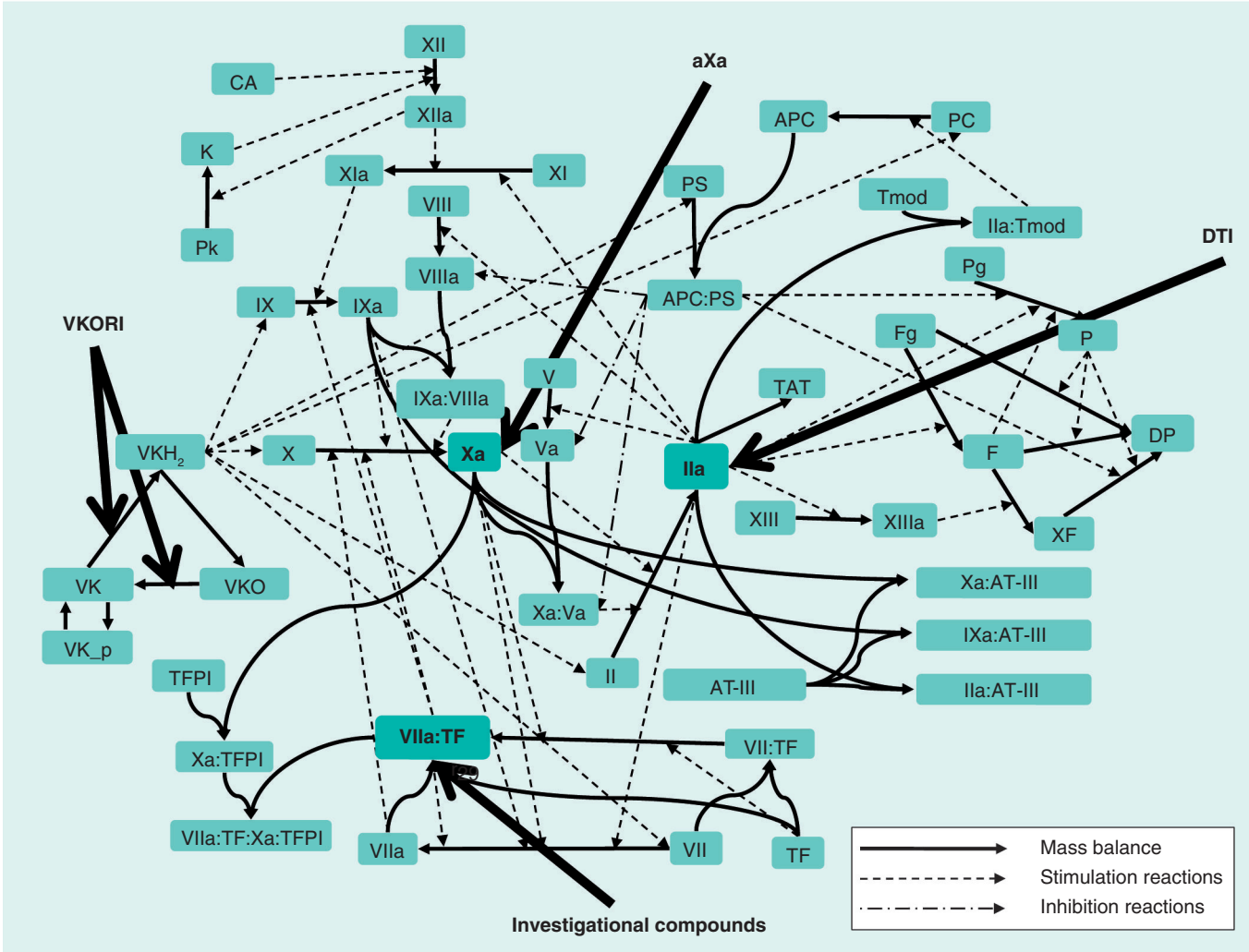

Figure 3. The coagulation network, highlighting potential or existing targets. Current targets include the VKORIs (e.g., warfarin), DTIs (e.g., dabigatran), aXa (e.g., rivaroxaban) and an investigational target depicting activity at TF:VIIa.
APC: Activated protein C; AT-III: Antithrombin III; aXa: Factor Xa antagonist; CA: Contact activator; DTI: Direct thrombin inhibitor; F: Fibrin; PC: Protein C; PS: Protein S; TF: Tissue factor; Tmod: Thrombomodulin; VKO: Vitamin K epoxide; VKORI: Vitamin K oxide reductase inhibitor; XF: Cross-linked fibrin.
Adapted with permission from [6].

Table 3. Ranges of international normalized ratio values for various drug targets.

Drug target	Therapeutic description	INR range for clotting factor activity range	
		75–150% †,‡	*50–200%* †,§
Factor IIa	Direct thrombin inhibitor	1.6–3.9	1.3–5.5
Factor Xa	Factor Xa inhibitor	1.6–3.6	1.3–5.2
TF:Factor VIIa	TF:Factor VIIa inhibitor	1.5–3.4	1.3–4.8
Vitamin K cycle	Vitamin K oxide reductase inhibitor	1.5–4.5	1.2–5.9

†Percent value of the baseline concentrations of fibrinogen, and Factors II, V, VII, VIII, XI and XII.
‡Conservative variability in the coagulation factors.
§Nonconservative variability in the coagulation factors.
INR: International normalized ratio; TF: Tissue factor.

novel drug targets (Factor IIa, Xa and TF:Factor VIIa inhibitors) compared with the warfarin analog (vitamin K oxide reductase inhibitor [VKORI]).

It should be noted that these simulations were performed on a theoretical basis, and did not include variability in all coagulation factors nor in the sensitivity of the system to the drug. The purpose of the simulations was to provide a feeling for the likely variability associated with anticoagulants. The simulations should not be viewed as exact. While it remains uncertain whether an INR-like test is an appropriate measure of clotting time for agents other than VKORIs, it provided a useful yardstick for these comparative simulations.

Routine monitoring & dose individualization of anticoagulants?

Routine monitoring of warfarin (and VKORIs) as well as unfractionated heparins is commonplace. Monitoring of the newer agents, such as rivaroxaban and dabigatran, is not readily available via INR or activated partial thromboplastin time [3]. There is some suggestion that ecarin clotting time may be of value for the DTIs due to its specific activity at thrombin [7]. There are, however, numerous new drug targets and agents becoming available [10] and a lack of currently available clotting-time tests for monitoring should not be construed to mean that monitoring is not necessary. Theoretical evidence from these simulations and empirical evidence from clinical studies (see a recent review [11]) does not support the notion that newer anticoagulants are markedly safer in terms of the risk of bleeding events.

It is logical to propose, therefore, that the expectation for all anticoagulants should be that it is mandatory to monitor a biomarker of patient response, such as a clotting time, in order to determine the dose that best meets the needs of our patients.

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