EMB-MED CHEM INTERFACE WARFARIN *vs* NOAC

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Some Essential Stats Tools

- EMB is based upon verifiable research and practical results.
- Parametric *vs* non-parametric: continuous numerals/values *vs* ranking/levels
- ANOVA, Forest Plots
- Kaplan Meier survival plots
- Linear vs Logistical regression
- Calculation of r and r^2 & significance
- Meta analysis

Parametric vs non-Parametric

- **Parametric** statistics is a branch of statistics which assumes that sample **data** comes from a population that follows a probability distribution based on a fixed set of parameters. Most well-known elementary statistical methods are **parametric**.
- **Nonparametric** tests are also called distribution-free tests because they don't assume that your *data* follow a specific distribution. Use nonparametric tests when *data* does not meet the assumptions of the *parametric* test, especially the assumption about **normally distributed** *data*.

ANOVA

- One-way ANOVA or student's T-test?
- Analysis of variance (*ANOVA*) tests the hypothesis that **the means** of two or more **populations** are equal.
- A *t-test* is any statistical hypothesis *test* in which the *test* statistic follows a *Student's t*-distribution under the **null hypothesis***. It can be used to determine if two sets of data are significantly different from each other. '**Student's' t Test** is one of the most commonly used techniques for **testing** a hypothesis on the basis of a difference between **sample means.**

Null Hypothesis & Errors

- Type I Error :- A type 1 error occurs when we reject the null hypothesis when it is in fact true. The smaller the p value the less the likelihood of a Type 1 error.

- Type II Error:- A type II error occurs when we do not accept the alternative hypothesis when it is true.

Forest Plots

- *Forest plots* are graphical representations of the meta-analysis.
- A *forest plot,* also known as a blobbogram, is a graphical display of estimated results from a number of scientific studies addressing the same question.
- (see handout for worked example).

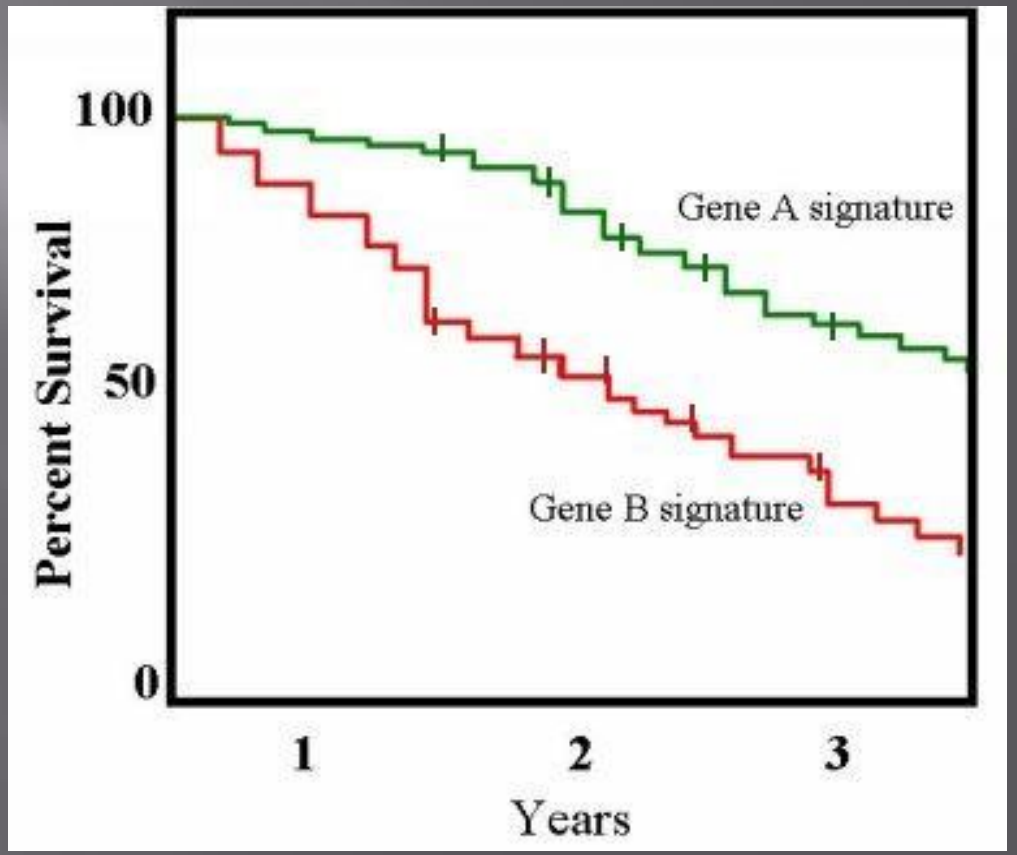
Kaplan Meier Plots

- The **Kaplan–Meier** estimator, also known as the product limit estimator, is a non-parametric statistic used to estimate the survival function from lifetime data.
- In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment.

- Log rank test & hazard ratios

Comparing the survival distributions of two samples

The graphical representation Survival Function.



Limits to Survival Analysis

- Censoring :- this happens when an observation is incomplete due to some random cause. The cause of the censoring must be independent of the event of interest if we are to use standard method of analysis.
- Truncation:- this is variant of censoring which occurs when the incomplete nature of the observations is due to a systematic selection process inherent in the study design.

Linear *vs* Logistical Regression

- Logistical regression is used when there is one nominal variable and one measurement variable.
- LR allows assessment of whether variation in the measurement variable causes variation in the nominal measurement.
- **Simple** LR:- *nominal* variable has 2 values e.g. male or female, dead or alive, present or not present. Also called *binary* logistical regression

Regression

- The *nominal* variable is the **dependent** variable and the *measurement* variable is the **independent** variable.
- **Multiple** LR:- has more than one **independent** variable.
- **Simple LR** is analogous to linear regression;
- But NB that nominal variable cannot be measured.
- Example:- Suzuki *et al* (2006) experiment. Absence or presence (nominal value) of spiders *vs* sand grain size (measurement value).

Hierarchy of Evidence Strength

- (i) Systematic reviews and meta analysis
- (ii) RCTs with definitive results (i.e. confidence intervals which do not overlap the threshold clinically significant effect)
- (iii) RCTs with non-definitive results (i.e. point estimate which suggests a clinically significant effect but with confidence intervals overlapping the threshold for this effect)
- (iv) cohort studies
- (v) case-controlled studies
- (vi)cross-sectional surveys
- (vii) case reports

A Case Study

- NICE guidelines for Warfarin
- NOACs
- Warfarin Vitamin K "antagonists"
- Scheme for Clotting
- Medicinal Chem basics:- agonist *vs* antagonist, receptors, dose response curves, measure of efficacy and affinity; significance.

NICE Guidelines Warfarin

- **Scenario: Warfarin** : covers the management of people receiving long-term anticoagulation with warfarin e.g. the treatment of deep vein thrombosis and the prevention of stroke and systemic embolism in adult patients with atrial fibrillation.

- **Scenario: Warfarin**
- Age from 18 years onwards
- **Contraindications and cautions**
- **What are the contraindications and cautions of warfarin?**
- **Contraindications for the use of warfarin include:**
  - Haemorrhagic stroke.
  - Bleeding disorders, such as:
    - Uncorrected major bleeding — avoid using warfarin until the bleeding has stopped and the cause healed.
    - Uncorrected major bleeding disorder — for example, thrombocytopenia, haemophilia, liver failure and renal failure.
  - Potential bleeding lesions — for example; active peptic ulcer; oesophageal varices; aneurysm; proliferative retinopathy; recent organ biopsy; recent trauma or surgery to head, orbit, or spine; recent stroke; confirmed intracranial or intraspinal bleed; or within 72 hours of major surgery with risk of severe bleeding, or within 48 hours postpartum.
  - Uncontrolled severe hypertension — for example, systolic blood pressure greater than 200 mmHg or diastolic pressure greater than 120 mmHg.
  - Pregnancy — due to the risk of teratogenicity with warfarin.
- **Cautions for the use of warfarin include:**
  - The person is uncooperative or unreliable — as there may be compliance and follow-up issues.
  - The person is prone to repeated falls or unstable gait — since there is an increased chance of injury and head trauma.
  - Concomitant use of antiplatelet drugs, nonsteroidal anti-inflammatory drugs, selective serotonin-reuptake inhibitors (SSRIs), venlafaxine, or duloxetine — there is an increased risk of gastrointestinal bleeding (see Drug interactions).
  - Protein C deficiency — a risk of skin necrosis on initiation of warfarin requires caution.

- **For more information, go to http://cks.nice.org.uk/anticoagulation-oral#!scenario:3**

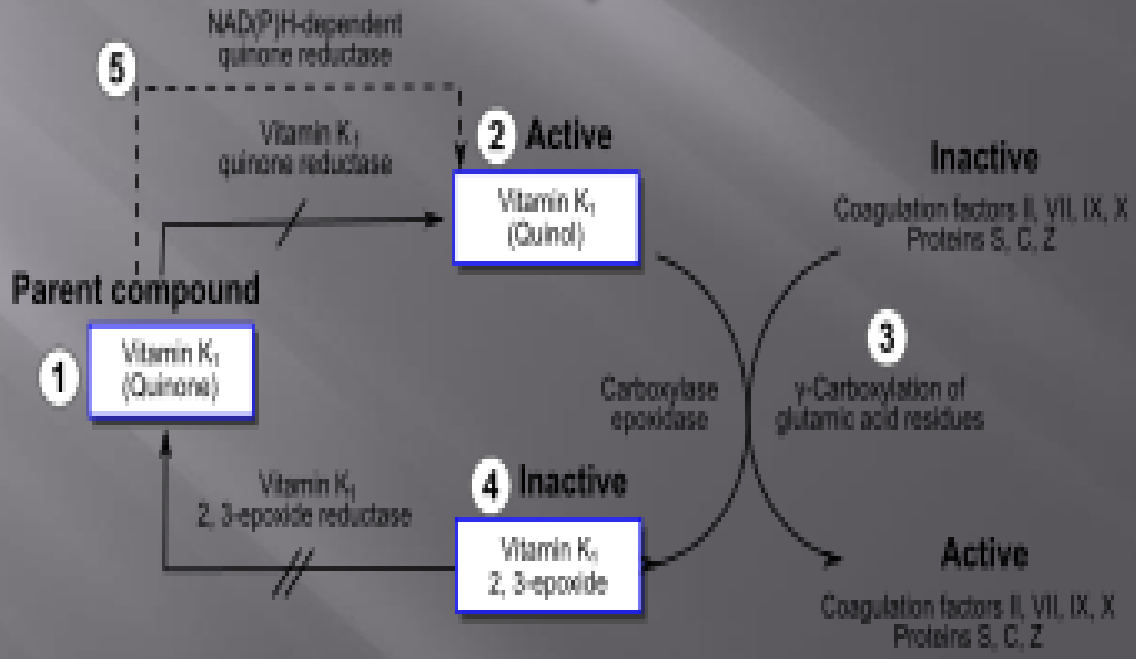
Warfarin

- **Warfarin is the main oral anticoagulant used in the UK. An anticoagulant is a medicine that stops blood clotting.**
- Clotting (thickening) is a ***complex process*** involving a number of substances called clotting factors.
- Clotting factors are produced by the liver and help control bleeding. They work with cells that trigger the clotting process (platelets) to ensure blood clots effectively.
- To produce some of the clotting factors, the liver needs a good supply of vitamin K.
- Warfarin blocks one of the enzymes (proteins) that uses vitamin K to produce clotting factors. This disrupts the clotting process, making it take longer for the blood to clot.

Vitamin K "Antagonist"

- **Vitamin K** is essential for the hepatic synthesis of Factors II (prothrombin), VII, IX, and X, as well as protein C and protein S.
- **Antagonists** of vitamin K have been used as anticoagulants for over 50 years.
- The most widely used medications for treating thrombosis* are heparins and **vitamin K antagonists** (VKAs).
- These medications have proven efficacy, but lack many properties of an ideal anticoagulant.

The Role of Vit K (Quinone);
step 1 *Vit K quinone reductase*,
step 2 *carboxylase epoxidase*,
step 3 *gamma carboxylation* of glutamic acid residues*,
step 4 *Vit K2,3 epoxide reductase*, step 1 etc…..
Step 5 *NADP (H-dependent) quinone reductase*, step 2 ..

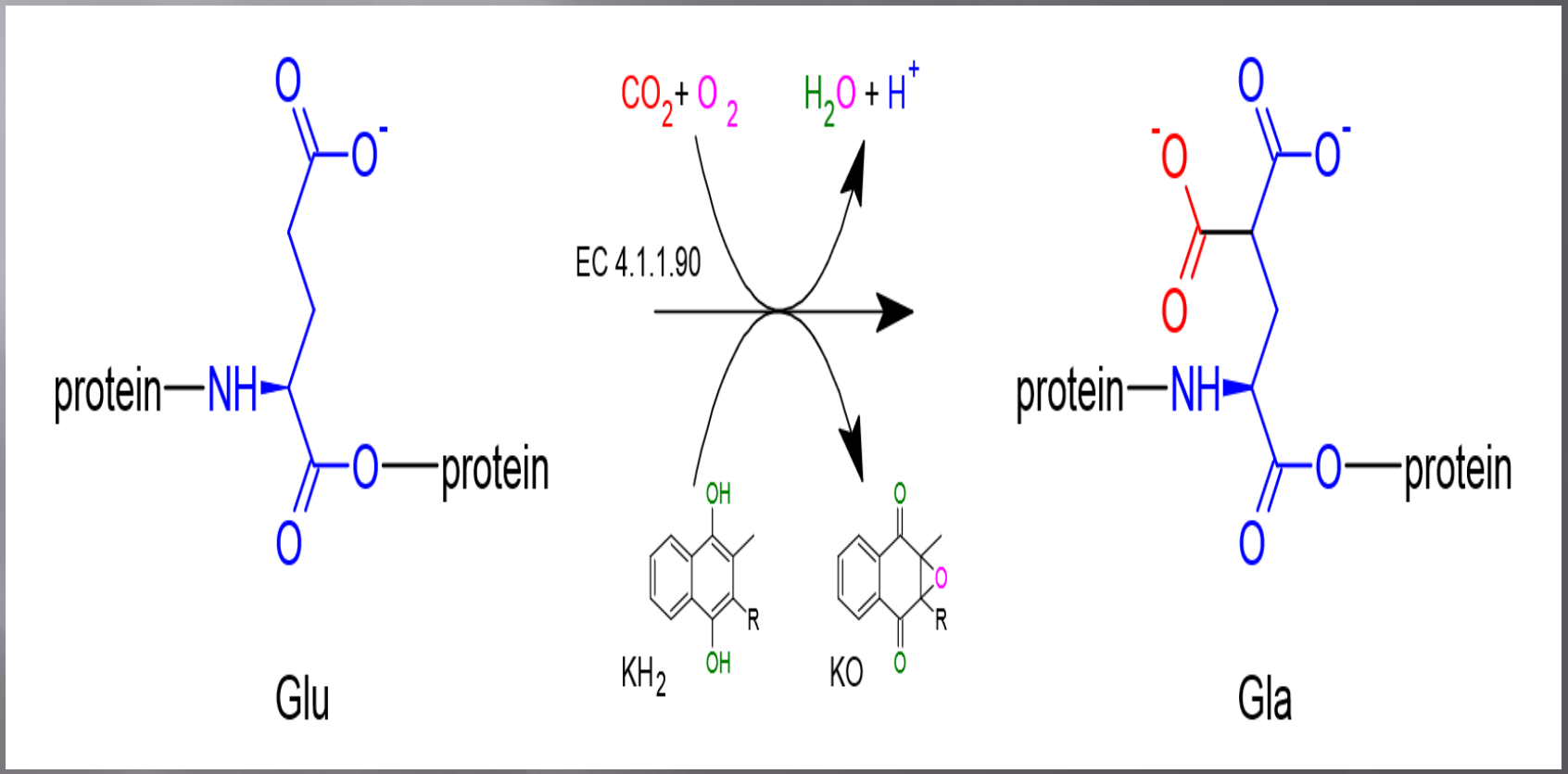


*Gla Domain

- **Vitamin K-dependent carboxylation/γ-carboxyglutamic (GLA) domain** is a protein domain that contains post-translational modifications of many glutamate residues by vitamin K-dependent carboxylation to form γ-carboxyglutamate (Gla).
- Proteins with this domain are known informally as **Gla proteins**. The Gla residues are responsible for the high-affinity binding of calcium ions.
- The GLA domain binds calcium ions by chelating them between two carboxylic acid residues.
- These residues are part of a region that starts at the N-terminal extremity of the mature form of Gla proteins, and that ends with a conserved aromatic residue.
- This results in a conserved Gla-x(3)-Gla-x-Cys motif that is found in the middle of the domain, and which seems to be important for substrate recognition by the carboxylase. i.e. substrate is Glu
- For anchoring of Coagulation Factor VIIa to the membrane through its Gla domain (see Vit K handout).

Glu to Gla

- Carboxylation reaction



*Gla Domain (contd)

- The 3D structures of several Gla domains have been solved. Calcium ions induce conformational changes in the Gla domain and are necessary for the Gla domain to fold properly. A common structural feature of functional Gla domains is the clustering of N-terminal hydrophobic residues into a hydrophobic patch that mediates interaction with the cell surface membrane.
- At present, the following human Gla-containing proteins (Gla proteins) have been characterized to the level of primary structure: the blood coagulation factors II (prothrombin), VII, IX, and X, the anticoagulant proteins C and S, and the factor X-targeting protein Z.
- The bone Gla protein osteocalcin, the calcification-inhibiting matrix Gla protein (MGP), the cell growth regulating "growth arrest specific gene 6" protein GAS6, periostin (a factor necessary for migration and adhesion of epithelial cells), two transmembrane Gla proteins (TMGPs), and two proline-rich Gla-proteins (PRGPs), the function of which at present are unknown.
- In all cases in which their function was known, the presence of the Gla residues in these proteins turned out to be essential for functional activity.

The Vitamin K-dependent carboxylation reaction

- Mol Cell Biochem. 1984;61(1):17-35. Vermeer C.
- **Abstract (Historical)**
- Gammacarboxyglutamic acid (Gla) is an abnormal amino acid, which occurs in a number of proteins. It was discovered about 10 years ago in the four vitamin K-dependent blood clotting factors and it could be demonstrated that Gla is formed in a post-translational modification step, which requires a carboxylating enzyme system (carboxylase) and vitamin K.

- Since at the time of this discovery the earlier mentioned clotting factors were the only proteins known to be synthesized in a vitamin K-dependent way, it has been assumed for many years that the blood clotting system was unique in this respect.

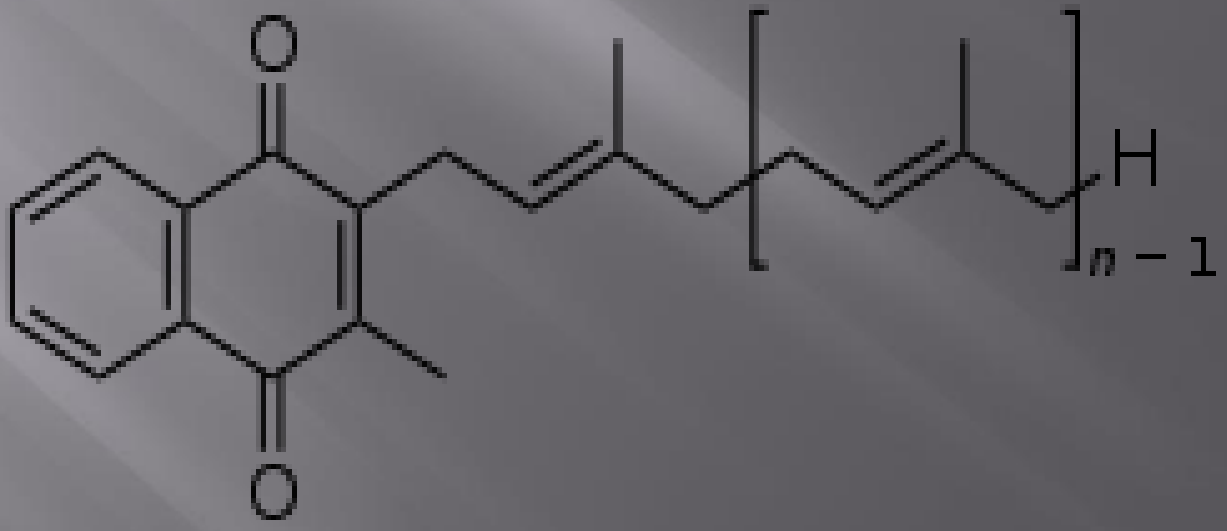
- Recently it has been demonstrated, however, that vitamin K-dependent carboxylase is not restricted to the liver (the place of synthesis of the clotting factors) but that it is also present in other tissues such as lung, kidney, spleen and testis. Moreover, numerous Gla-containing proteins have been detected, although in most cases their function is not wholly understood.

- It seems that (like for instance the glycosylation) the vitamin K-dependent carboxylation is a normal post-translational modification, which is required for the correct function of a certain class of Ca2+-binding proteins.

Warfarin Target

- Warfarin (& other 4 hydroxy coumarins) targets ***Vit K epoxide reductase (VKOR).***
- **Warfarin**, a synthetic derivative of coumarin, is the most commonly used vitamin K antagonist (VKA) in the United States.
- In some European countries, other coumarin derivatives (phenprocoumon and acenocoumarol) are used as an alternative to warfarin
- Vitamin K_2 (menaquinone). In menaquinone the side chain is composed of a varying number of isoprenoid residues.

Vitamin K_2 Menaquinone, (side chains composed of varying numbers of isoprenoid residues).



VKAs

- **Vitamin K antagonists** (VKA) are a group of substances that
- reduce blood clotting by
- reducing the action of vitamin K.
- They are used as anticoagulant medications in
- the prevention of thrombosis, and
- in pest control, as rodenticides.

Mechanism of action

- These drugs deplete the active form of the vitamin by *inhibiting* the enzyme vitamin K epoxide reductase
- and thus the recycling of the inactive vitamin K epoxide back to the active reduced form of vitamin K.
- The drugs are structurally similar to vitamin K and act as competitive inhibitors of the enzyme.
- The term "vitamin K antagonist" is a misnomer, as the drugs do not directly antagonise the action of vitamin K in the pharmacological sense, but rather the recycling of vitamin K.

Vit K's role

- Vitamin K is required for the proper production of certain proteins involved in the blood clotting process.
- For example, it is needed to carboxylate specific glutamic acid residues on prothrombin.
- Without these residues carboxylated, the protein will not form the appropriate conformation of thrombin, which is needed to produce the fibrin monomers that are polymerized to form clots.[1]

VKA “antagonists”

- The action of this class of anticoagulants may be reversed by administering vitamin K for the duration of the anticoagulant's residence in the body, and the daily dose needed for reversal is the same for all drugs in the class.
- However, in the case of the second generation "super warfarins" intended to kill warfarin resistant rodents, the time of vitamin K administration may need to be prolonged to months, in order to combat the long residence time of the poison.

Drawbacks

- The vitamin K antagonists can cause birth defects (teratogens).
- Coumarins (more accurately 4-hydroxycoumarins) are the most commonly used VKAs.
- In medicine, the most commonly used VKA is warfarin.
- Warfarin was initially used as a rodenticide, but made the transition to pharmaceutical. Eventually some rodents developed resistance to it.
- The "second generation" VKAs for dedicated use as rodenticides are sometimes called "super warfarins."
- These VKAs are enhanced to kill warfarin-resistant rodents.
- The enhancement to the molecule takes the form of a larger lipophilic group to enhance the fat solubility of the poison and greatly increase the time it acts within the animal's body (ADME properties)

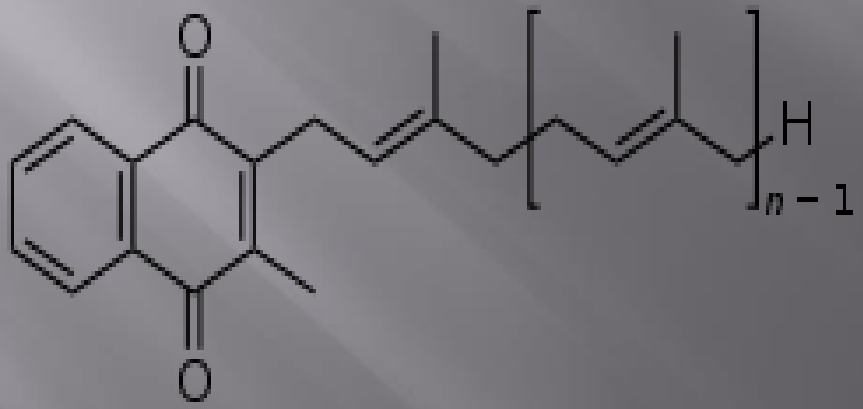
Medicinal Chem Terminology

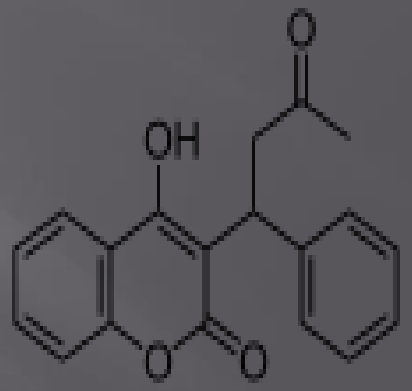
- Agonist vs antagonist and receptors
- Switch on vs switch-off:- ligand binding
- Activation of 2nd messengers → cascades.
- Efficacy and affinity of a drug molecule:- ability of a single molecule to switch on vs ability of a molecule to bind loosely or tenaciously.
- All the above are subject to mathematical calculations generating specific values.
- Dose response curves
- Competitive vs uncompetitive
- Enzyme Inhibitors and active sites.
- Selectivity & Potency

Vit K2 compared with Warfarin

(Coumadin) Active site recognition

the enzyme is “fooled” into accepting warfarin into its active site



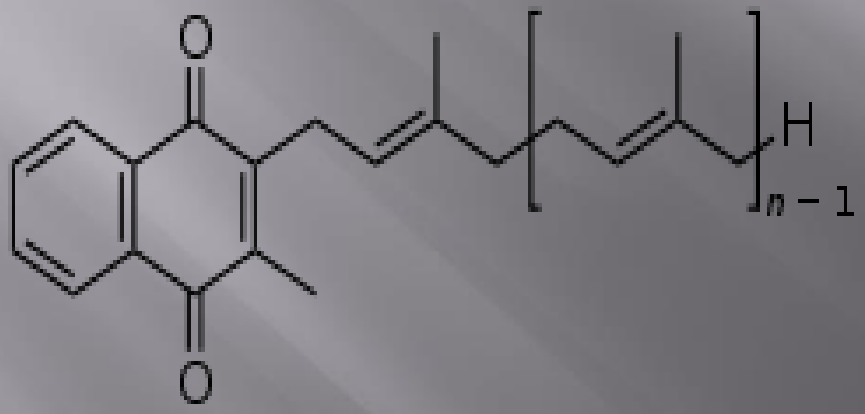


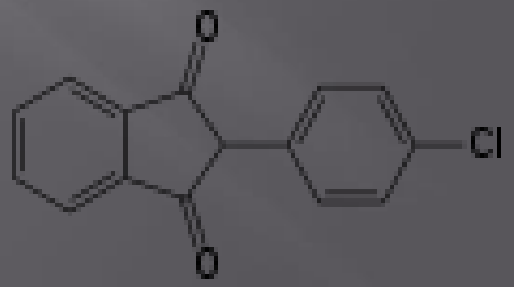
Other VKAs

- Not all VKAs are coumarins; many of the non-coumarin VKAs are 1,3-indandione derivatives.
- Such therapeutic agents may themselves be antagonized by administration of vitamin K.
- Examples include phenindione,Clorindione, diphenadione, and fluindione.

Vit K compared with Clorindione:-

structural similarities allow active site recognition





Review of mechanism

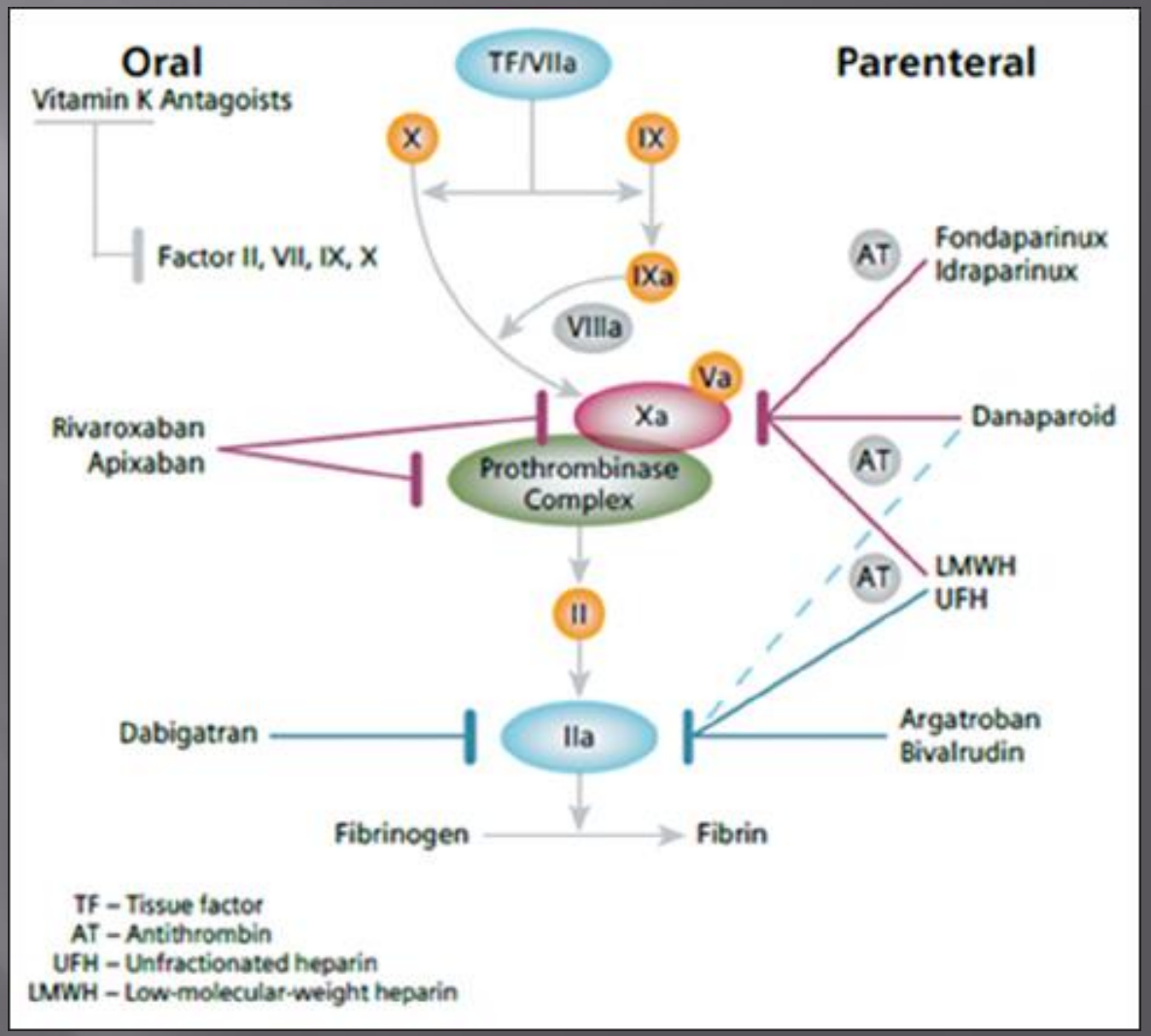
- Vitamin K is essential for the activation of certain clotting factors (II, VII, IX and X).
- In this process, vitamin K gets oxidised to vitamin K epoxide.
- There is a mechanism however, through which the vitamin
- K epoxide is recycled within the liver back to vitamin K.
- The enzyme involved is vitamin K epoxide reductase complex 1 (VKORC1) and
- This is the enzyme that is strongly inhibited by warfarin.
- Administration of large doses of exogenous vitamin K will overcome the need to recycle vitamin K epoxide within the liver i.e. inhibition is competitive
- and will therefore reverse the effects of warfarin.

NOACs

- What are NOACs? Direct thrombin inhibitors,
- And direct factor Xa inhibitors
- *Dabigatran* (*Pradaxa*) is currently the only direct *thrombin inhibitor* and was the first NOAC approved in 2010.
- Factor Xa inhibitors include *rivaroxaban* (*Xarelto*), *apixaban* (*Eliquis*), and edoxaban (Savaysa).
- Warfarin has been the anticoagulant of choice for the prevention of ischaemic stroke in patients with atrial fibrillation (AF).
- Novel oral anticoagulants (NOACs) are increasingly used as an alternative.

Mechanism NOAC

Three points of intervention in the clotting process.



Non-vitamin K antagonist oral anticoagulants (NOACs)

- NOACs are novel direct-acting medications that are selective for one specific coagulation factor, either thrombin (IIa) or activated factor X (Xa).
- Several NOACs, such as dabigatran (a direct inhibitor of FIIa) and rivaroxaban, apixaban and edoxaban (direct inhibitors of factor Xa), have been used for at least 5 years but possibly 10 years.
- Unlike traditional VKAs, which prevent the coagulation process by suppressing the synthesis of vitamin K-dependent factors, NOACs directly inhibit key proteases (factors IIa and Xa) involved in the *coagulation cascade*.

Coagulation Cascade

- The pathways are a series of reactions, in which a zymogen (inactive enzyme precursor) of a serine protease and its glycoprotein co-factor are activated to become active components that then catalyze the next reaction in the cascade, ultimately resulting in cross-linked fibrin.
- Coagulation factors are generally indicated by Roman numerals, with a lowercase *a* appended to indicate an active form.
- The coagulation factors are generally serine proteases (enzymes), which act by cleaving downstream proteins.
- There are some exceptions. For example, FVIII and FV are glycoproteins, and Factor XIII is a transglutaminase.[7]
- The coagulation factors circulate as inactive zymogens.
- The coagulation cascade is therefore classically divided into three pathways. The *tissue factor* and *contact activation* pathways both activate the "final common pathway" of factor X, thrombin and fibrin.

Pharmacokinetics of NOACs

- After administration, all 3 of the NOACs are rapidly absorbed and produce peak plasma concentrations between 0.5 and 4 hours.[6]
- Unlike warfarin, which has a slow onset of action and works on inactive forms of multiple vitamin K-dependant proteins in the plasma coagulation cascade,
- the NOACs work quickly to inhibit specific activated clotting enzymes involved in later stages of the coagulation process.
- Dabigatran selectively targets thrombin (factor IIa), while rivaroxaban and apixaban block factor Xa.

EBM-Med Chemistry Interface

Meta-analysis

Original research article

NOACs versus warfarin for stroke prevention in patients with AF: a systematic review and meta-analysis

Abstract

Background

Warfarin has been the anticoagulant of choice for the prevention of ischaemic stroke in patients with atrial fibrillation (AF). Novel oral anticoagulants (NOACs) are increasingly used as an alternative.

Meta Analysis

- **Objectives** The objective of this review was to evaluate the efficacy and safety of the NOACs versus warfarin in patients with AF.
- **Search methods** Medline, EMBASE and grey literature* search for all phase II and III randomised control trials.
- **Data collection/analysis** Two authors independently reviewed abstracts and performed data extraction of eligible full-text articles. Revman V.5 was used for meta-analysis.
- **Main results** 12 studies were identified with a total study population of 77 011. NOACs demonstrated a reduction in the composite of stroke or systemic embolic events OR 0.85 (95% CI 0.75 to 0.98), a 52% reduction in intracranial haemorrhage OR 0.48 (95% CI 0.40 to 0.57) and a 14% reduction in mortality OR 0.86 (0.82 to 0.91).
- The 30-day end of study switch to warfarin demonstrated an increase in stroke or systemic embolic events OR 2.60 (95% CI 1.61 to 4.18) and an increase in major bleeding OR 2.19 (95% CI 1.42 to 3.36).
- **Conclusions** NOACs are superior to warfarin for the prevention of the composite of stroke and systemic embolism in patients with AF and an additional risk factor for stroke. There is a significant reduction in intracranial haemorrhage, which drives the finding of significantly lower mortality. During the post-study switch from NOACs to warfarin there is an excess of the composite of stroke and systemic embolism as well as major bleeding events, which may be of significance in clinical practice.

Pros and Cons of Warfarin vs NOACs

- The availability of new oral anticoagulants (NOACs) targeting either thrombin (dabigatran etexilate) or factor Xa (rivaroxaban and apixaban) for the prevention and treatment of thrombosis has been highly anticipated.
- NOACs have major pharmacologic advantages over vitamin K antagonists (eg, warfarin), including rapid onset/offset of action, few drug interactions, and predictable pharmacokinetics, eliminating the requirement for regular coagulation monitoring.
- Regulatory agencies have approved several NOACs for specific indications based on the results of clinical trials demonstrating efficacy and safety that are at least as good, if not better, than warfarin (for stroke prevention in atrial fibrillation and treatment and secondary prevention of venous thromboembolism) or low-molecular-weight heparin, which is injectable (for initial treatment of venous thromboembolism and thromboprophylaxis in patients undergoing hip or knee arthroplasty).

Pros and Cons

- However, the adoption of this new therapeutic class into clinical practice has been slower than expected due to several factors including concerns regarding medication adherence without laboratory monitoring, uncertainty about dosing in some patient populations (eg, renal dysfunction, marked extremes of body weight), and higher drug costs compared with warfarin.
- Other issues are the current absence of specific antidotes for NOACs and assays to measure drug levels at most centers.
- The indications for NOACs on the market will expand and at least one additional agent (edoxaban) will likely gain approval within the next 2 years.
- As practitioners gain familiarity with the drugs and healthcare systems adapt to their use, NOAC use will increase substantially over time. Warfarin, however, will continue to be an appropriate anticoagulant choice for many patients.

However.....

- 18 Dec 2013 - Dr John Mandrola calculates the absolute risk reductions from recent meta-analyses comparing the *novel anticoagulants* with warfarin and ...
- **Novel Oral Anticoagulants vs Warfarin: The Truth is Relative**
- John Mandrola

Cons and Pros?

- The makers of novel anticoagulant (NOAC) drugs have done well. A neutral observer might think these drugs are the next **penicillin**. The ads are everywhere, no medium spared. Influential thought leaders are out in force, exerting their influence. Compared with **warfarin**, novel anticoagulants have been sold as both superior and more convenient—and oh, how Americans love easy.
- The problem, of course, is that when the free samples run out, patients and third-party payers are left asking *the question*: Are these drugs worth the added expense?
- The answer depends on how you define value and superiority.
- I had originally set out in this post to explain how two recently published meta-analyses of novel anticoagulant trials had once and for all demonstrated the drugs' superior safety and efficacy compared with warfarin.

Another point of view

- But that is not what I found. Not at all. Rather, I made a discovery:
- In the measures that matter for patients with atrial fibrillation, hard outcomes like stroke, bleeding, and mortality,
- **dabigatran** (Pradaxa, Boehringer Ingelheim), **rivaroxaban** (Xarelto, Bayer Pharma/Janssen Pharmaceuticals), **apixaban** (Eliquis, Pfizer/Bristol-Myers Squibb), and **edoxaban** (Lixiana, Daiichi-Sankyo) perform almost identically to warfarin.
- Yet the drugs are priced and promoted as if they are special, more valuable.

More.....

- Not only do I intend to prove that NOAC drugs are *clinically equivalent* to warfarin, I hope to convince you that the simple math that follows could be used to improve the quality of all evidence-based medical decisions.
- **The story begins with two recent meta-analyses:**
- **Dr Christian Ruff** (Brigham and Women's Hospital, Boston, MA) and colleagues culled together the four phase 3 randomized clinical trials of novel anticoagulants vs warfarin in patients with nonvalvular AF. Publishing in the *Lancet* (and summarized on **heart***wire*), these researchers report significant reductions in the *relative* risk of stroke, intracranial hemorrhage (ICH), and mortality. The authors emphasize a halving of the relative risk of ICH.
- **Dr Saurav Chatterjee** (Brown University, Providence RI) and colleagues studied the risk of ICH in AF patients treated with either novel anticoagulants or warfarin. They used the phase 3 randomized clinical trials that compared the three **FDA**-approved novel anticoagulants and warfarin (edoxaban is still investigational). Publishing in *JAMA Neurology*, they also reported that novel anticoagulant therapy reduced the *relative* risk of ICH by 50%.

Consider.....

- **The key word is relative:**
- It is true—not a lie—to say *relative* to the patients who had strokes or ICH, novel anticoagulants looked favourable. But that's not a useful way to explain the trade-offs to a patient in the exam room. It's not a useful way for doctors to interpret clinical evidence.
- An AF patient who has accepted the net benefits of anticoagulation (an important decision in and of itself) wants to know something simple: what is the risk of an event on a novel anticoagulant vs warfarin? That's how they *judge value*. It's also how payers judge value.
- Here, it is critical to look at absolute, not relative, risks and benefits of each drug. This is because most AF patients treated with either drug experience no effects.
- **Absolute numbers are truth**

Review articles

- According to both meta-analyses, the most significant relative risk reduction was observed for ICH. Let's look at the raw numbers from the *JAMA Neurology* paper. (Numbers from the *Lancet* paper and this 2012 meta-analysis are nearly identical.)
- From Figure 1: There were 31 830 patients treated with NOAC drugs and 25 661 treated with warfarin. There were 186 ICH events in the NOAC group and 317 in the warfarin group. The absolute risk for ICH was 0.58% with NOAC drugs and 1.24% with warfarin. The NOAC drugs prevented 131 ICHs. The absolute difference between the two groups was a mere 0.65%. Said another way: for 151 of 152 patients treated, there was no difference between NOAC drugs and warfarin.
- That means we can tell an AF patient similar to the 60 000+ enrolled in the three randomized clinical trials that he or she has a 99.4% chance of *not having* an ICH on a NOAC drug and a 98.8% chance of *not having* one on warfarin.

Conflict resolution?

- Is this clinically superior?
- You don't believe me yet. I know; this discovery had me running around like Archimedes, too. Let's perform the same simple math on the stroke-prevention numbers.
- From Figure 1 of the *Lancet* meta-analysis: There were 29 312 patients treated with NOAC drugs and 29 229 patients treated with warfarin.
- There were 911 stroke or systemic-embolism events in the NOAC group and 1107 in the warfarin group.
- The absolute risk of an event was 3.1% on a NOAC drug and 3.8% on warfarin. The reduction in absolute risk was 0.7%. In this case, 141 of 142 patients treated with a NOAC drug received no benefit over warfarin. Again, our AF patient has a 96.9% chance of *not having* an embolic event on a NOAC drug and a 96.2% chance of *not having* one on warfarin.

And so……..

- When asked to comment, Dr Chatterjee noted, "In a patient at high risk of ICH, an option of possibly cutting the risk by half will carry definite significance, and future research endeavors should be directed at identifying such patients." Dr Ruff concurred and cautioned against focusing on a single outcome. "What matters is what happens to patients overall. NOACs offer the potential of a more effective and safer anticoagulation option with reductions in stroke, ICH, and mortality. A net benefit would combine all of those outcomes."

Cost-Benefit Analysis

- I agree with Dr Chatterjee that ICH is perhaps the most serious complication of anticoagulation, and reducing it is important.
- But I reiterate: for the patient who is trying to decide whether to pay up to 50 times more for a drug purported to prevent devastating brain bleeding, the fact that there is a greater than 99% chance of no incremental benefit is central to decision making. My point in saying it that way is to be clear.
- When only relative risk reductions are emphasized in scientific writing, it would be easy to get the impression that one has a 50% lower risk of ICH on a NOAC drug. That's not the case.
- I live in the real world. Believe me: relative risk reductions confuse caregivers and patients alike.

Arguments for and against….

- Dr Ruff's emphasis of net clinical benefit is well founded. Patients with AF and risk factors for stroke are often burdened with other medical problems, like hypertension, diabetes, arthritis, immobility, dementia, and vascular disease. AF is only one of their problems.
- The trade-off of stroke reduction with an anticoagulant is accepting the risk of bleeding.
- In the *Lancet* meta-analysis, the risk of major bleeding was not significantly different, but the risk of gastrointestinal bleeding was higher for NOAC drugs by a factor of 0.5%.
- Though it is true a brain bleed is worse than a GI bleed, the larger point remains—less than 1% net difference.

Warfarin vs NOACs?

- **Summary:**
- The two approaches to anticoagulation in patients with AF have been studied head-to-head in thousands of patients in trials that measured hard outcomes. Strokes, bleeds, and deaths are easy to count. Division is easy. So is subtraction.
- In the outcomes that matter to the patient who sits across from us, the two classes of drugs perform nearly identically—that is, if you count greater than 99% the same.
- This doesn't mean novel anticoagulants are bad drugs or that I recommend stopping them. It simply means they are clinically equivalent to warfarin. And, therefore, at the current premium, these drugs are grossly overvalued.
- To be fair, NOAC drugs have some practical advantages, like convenience, lack of dietary interactions, and fewer drug-drug interactions. And not all patients do well with warfarin. For these patients, NOAC drugs may be an alternative. What's more, if one is willing to pay for convenience and absolute differences of less than 1%, then that is his or her choice.

Warfarin vs NOACs

- **The larger message:**
- This is not just an important story about atrial-fibrillation therapy. The NNT message extends to all evidence-based medical decision making. To achieve the highest-quality decisions, caregivers should understand and communicate absolute risks and benefits.
- Journal editors should look askance at studies that emphasize relative risk reductions.
- I challenge you to apply this method to all clinical studies. Such raw data are usually presented in the first or second table of published studies. All you need is a calculator and the strength to ignore the hype.

Cost-Benefit Analysis: GP Viewpoint

- The use of NOACs dispenses with the need for continual monitoring required when Warfarin is used.
- It is a cost saving to the NHS not to have to keep running warfarin-monitoring clinics.
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