OPTIMIZATION OF VITAMIN K ANTAGONISTS LABORATORY MONITORING AND TECARFARIN : TWO FUTURE SOLUTIONS FOR ORAL ANTICOAGULANT TREATMENT ?

TROMBOSI - ANTICOAGULANTI ORALI

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Abstract

Optimization of laboratory monitoring in the oral anticoagulant treatment with vitamin K antagonists is crucial to avoid the major possible amount of adverse events. In these review, different methods to optimize this laboratory monitoring will be discussed. If we are able to achieve a good Time in Therapeutic Range (TTR) and a low Variance Growth Rate (VGR) as described by Poller and collegues **(1) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1193-1195), (2) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1540-1546),** and by Van Leeuwen et al. **(3) (Journal of Thrombosis and Haemostasis 2008 vol. 6 pp. 451-456)** the rate of adverse events will decrease enormously and will also be less than the rate that occurs using new oral anticoagulants in some cases. Using some methodological cautions it is possible to achieve an optimized laboratory monitoring of treatment with vitamin K antagonists not only in specialized anticoagulation clinics, but in small laboratories too. " Warfarin treatment with a high TTR performs well, and should not be ruled out in favour of NOACs" **(4) (Thrombosis and Haemostasis 2015 vol. 113 pp. 1370-1377)** The efficacy and safety of self-testing, using a portable coagulometer CoaguChek XS at least every two weeks was shown in a large prospective cohort study (n=1140) in Switzerland. In this study the rate of thromboembolic event was 0.4 per 100 patient-years, the rate of major bleedings was 1.1 per 100 patient-years and in particular the rate of Intracranial bleedings was 0.2 per 100 patient-years with a trend towards a higher rate in patients older 50 years (0.2 versus 0.04 per 100 patients years). The median time within the intended therapeutic range was 80% (IQR 66-89%) and the median time in a safety range of 2.0 to 4.5 was 96% (IQR 89-99%). **(5) (PLOS One 2014 vol. 9 Issue 4 pp. e95761)** Remarkable is the low annual rate of intracranial bleedings which is equal to that achieved with some new oral anticoagulants and better than that achieved with rivaroxaban. The accuracy of Point-Of-Care Testing coagulometers is generally acceptable, and they can be used in a clinical setting, although these POCT tend to overstimate the INR when INR measurements are high, especially above 4.0. A tendency to understimate INR is found when the INR is within or below the therapeutic INR target range. **(6) (Journal of Thrombosis and Haemostasis 2012 vol. 10 pp. 251-260) ; (7) (Annals of Clinical & Laboratory Science 2008 vol. 38 pp. 905-910)** In another paper, regarding clinical accuracy, the INR measurements obtained with CoaguChek XS deviated by > / = 15% from the laboratory measurements in 40% of patients. A deviation of 15% with an INR measurements of 2.5 will provide a range of 2.125 - 2.875 (+/- 0.375 INR). This has probably no clinical consequence in terms of more thromboembolism and bleeding events in patients using the coagulometers. In this study only patients with mechanical aortic valve or atrial fibrillation were included to obtain a homogeneous population as possible, and thereby optimizing the external validity of the study. **(8) (Thrombosis and Haemostasis 2009 vol. 101 pp. 563-569)** Vitamin K supplementation can reduce variability in patients with unexplained unstable anticoagulation response through reducing the relative day-t--day variability in dietary vitamin K intake. **(9) (Blood 2007 vol. 109 (6) pp. 2419-2423)** A 25% point improvement in TTR was achieved with a system combining frequent INR **S**elf-**T**esting with

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Online **R**emote **M**onitoring and **M**anagement **(STORM$_2$)** and low-dose vitamin K supplementation (100 microgr./daily of vitamin K1). In this study, TTR improved from 56% achieved with laboratory monitoring to 81% achieved with this system. **(10) (Pharmacotherapy 2013 vol. 33 (11) pp. 1136-1146)** Some authors developed a modified PT that was sensitive only to reductions in factors II and X. This modified PT is called FiiX-PT (FiiX-INR) and correlated well with PT (INR) but the FiiX-INR fluctuated less than the INR in an anticoagulated patient reflecting its insensitivity to FVII. The rotational thromboelastomeric (ROTEM) results suggest that mild to moderate reductions in factors II or X are more important during clot formation than factors VII or IX. The FiiX-PT is a Platelet Poor Plasma (PPP) based test that more accurately reflect the anticoagulant effect of VKA than do the currently applied INR tests. It was done by correcting all deficiences other than those of factors II and X by mixing factor II and X-depleted plasma with the test sample prior to measuring the PT. **(11) (Thrombosis Research 2012 vol. 130 pp. 674-681)** The Fiix trial was a single centre, double-blind, prospective, non-inferiority, randomised controlled clinical trial in which patients were randomly assigned (1:1) to either the Fiix-PT monitoring group or the PT monitoring group by block randomisation without a stratification procedure. The patients enrolled between March 1, 2012 and February 28, 2014 were 573 assigned to the Fiix-PT, and 575 to PT-INR monitoring. Median follow-up was 1.7 years. In the primary analysis of thromboembolic events occurring during days 1-720, thromboembolism occurred in 10 patients in the Fiix-PT group (incidence of 1.2% per patient-year) versus 19 (2.3% per patient-year) in the PT group. Major bleeding occurred in 17 of 571 patients in the Fiix group (2.2% per patient-year) versus 20 of 573 patients in the PT group (2.5% per patient-year). With long term Fiix-PT monitoring (180-720 days), monitoring tests were reduced by 5.8%. The median per cent time in range in the control group was 81%, 80%, 81% and 79% during four consecutive 6-month observation periods, whereas in the Fiix monitoring group the median per cent time in range was 85%, 85%, 80% and 87% respectively. INR fluctuation measured as variance growth rate was significantly higher in the PT group than in the Fiix-PT group. Patients with major events had a higher variance growth rate than did those without major events. **(12) (Lancet Haematology 2015 vol. 2 pp. e231-240)**

Tecarfarin (ATI-5923) is a new oral vitamin K antagonist that, differently from warfarin, is metabolized by esterases and not by cytochrome P450 mixed-function oxidases and is specifically designed to avoid transport by transporter permeability protein (P-gp). For these reasons, it does not interfere with drugs which are moderate or strong inhibitors or inducers of CYP enzymes and of P-glycoprotein. This drug is not renally excreted and can be safely administered in patients with chronic renal dysfunction or failure (CRDF) because in these patients there is an impaired drug elimination mainly because of impaired glomerular filtration rate that has a direct effect on the elimination of drugs and because in addition, this drug it is not metabolized by cytochrome p450 and is not transported by the transporter permeability protein P-gp. In fact, the metabolic clearance (consisting mainly of hepatic CYP450 metabolism) of various substrates is reduced in patients with CRDF. In humans, decreased CYP2C9 and CYP3A4 activities have been reported in uremic patients. In addition, in patients with uremia associated with advanced kidney disease, P-glycoprotein (P-gp) appears to be down-regulated in the gastrointestinal tract, resulting in increased intestinal absorption of P-gp substrates, but is upregulated in hepatocytes, resulting in increased biliary elimination. Due to these characteristics, Tecarfarin could really be an important step in the oral

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anticoagulant treatment, better than Warfarin and much better than Direct Oral Anticoagulants (DOACs) because does not interfere with other drugs or food and very probably, patients in treatment with it will need much less laboratory controls by INR, compared with patients in treatment with other vitamin K antagonists. (see review on warfarin, acenocoumarol and tecarfarin) **(www.armatheon.com)** The drug is currently in Phase 3 development for the prevention and management of thrombosis. In the tecarfarin anti-coagulation trial (TACT), 3000 subjects with indications for chronic anticoagulation will be randomized to either tecarfarin or warfarin for at least one year (6 months for some VTE subjects). In this study will be enrolled 1200 subjects with a mechanical heart valve as the primary indication for chronic anticoagulation and 1800 subjects who are taking a chronic medication concomitantly which is known to interact with CYP2C9 and who have a CYP2C9 genetic variant allele.

https://clinicaltrials.gov/ct2/show/NCT02522221

Tecarfarin and the optimization of laboratory monitoring of vitamin K antagonists can really represent the solutions of oral anticoagulant treatment, considering that at the moment in patients with valve prostheses and in patients with antiphospholipid syndrome can only be used vitamin K antagonists, and also considering that Direct Oral Anticoagulants (DOACs) need to be monitored not only clinically but by laboratory monitoring too with appropriate tests, due to the high intra and inter-individual variability of their plasma concentrations, as recently demonstrated. **(13) (The American Journal of Cardiology 2014 vol. 63 pp. 321-328); (14) (Canadian Journal of Cardiology 2013 vol. 29 pp. S24-S33) ; (15) (Thrombosis Research 2015 vol. 136 pp. 148-153)** A high intra- and inter-individual variability of plasma concentrations of dabigatran, rivaroxaban and apixaban was observed in real life patients with atrial fibrillation. In particular for the inter-individual variability, the drug concentration levels varied more than 20-times among the patients for dabigatran, nearly 15-times for rivaroxaban and 7-times for apixaban. In addition this variability was considerably higher in patients treated with the lowest dose of DOAC. **(16) (Thrombosis Research 2016 vol. 137 pp. 178-183)**

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Optimization of INR testing and Tecarfarin

Tecarfarin is potentially a better orally active vitamin K epoxide reductase (VKORC1) inhibitor than warfarin because not only it does not interfere with other drugs or food but can really represents a great advantage for patients who have a genetic variant of metabolizing enzymes such as CYP2C9 and the other CYP enzymes, considering that CYP2C9 is the principal metabolizer of warfarin, of Acenocoumarol and for a less extent of Phenprocoumone because for the metabolism of this last vitamin K antagonist is very important the CYP3A4 enzyme too. This may mean that tecarfarin will need less monitoring than warfarin, potentially resulting in better patient compliance especially if used together with widely available self-monitoring system. **(1) (www.armetheon.com)** VKORC1, a hepatic microsomial enzyme, is a amino acid integral membrane protein associated with the endoplasmic reticulum and is responsible for the conversion of vitamin K epoxide to vitamin K, which is the rate limiting step in the physiological process of vitamin K recycling. The availability of reduced vitamin K is of particular importance for many coagulation factors that require it as a cofactor, including factor II, VII, IX and X. Tecarfarin like warfarin, acting as an inhibitor of VKORC1 leads to a reduced amount of vitamin K available to serve as a cofactor for clotting proteins. **(2) (Pharmacogenetics Genomics 2010 vol. 20 (10) pp. 642-644)** Vitamin K hydroquinone (KH_2) is a cofactor for gamma-glutamyl carboxylase (GGCX), which catalyzes the posttranslational carboxylation of specific glutamic acid residues to gamma-carboxyglutamic acid (gla) in many vitamin K dependent proteins. Gamma-glutamyl carboxylation is crucial for the biologic functions of vitamin K-dependent proteins involved in blood coagulation, bone metabolism, signal transduction and cell proliferation. During vitamin K-dependent carboxylation of glutamic acid to gamma-carboxyglutamic acid, the reduced form of vitamin K (KH_2) is oxidized to vitamin K 2,3-epoxide (KO) by gamma-glutamyl carboxylase (GGCX). KO is reduced to vitamin K by vitamin K-epoxide reductase (VKOR) using the enzyme's 2 active-site cysteine residues. This reaction is sensitive to warfarin inhibition. The subsequent reduction of vitamin K to KH_2 is carried out in 2 pathways. In one pathway is involved a warfarin-sensitive enzyme, another yet-to-definied reductase, that is different from VKOR and also involves 2 free cysteine residues in the enzyme active site. In the second pathway is involved a warfarin-resistant antidotal enzyme, a reductase that uses NADPH as a cofactor. In conclusion the main function of VKOR is to covert KO to vitamin K, not vitamin K to KH_2. **(3) (Blood 2011 vol. 117 (10) pp. 2967-2974)**

KH_2 (vitamin K hydroquinone, the reduced form of vitamin K)
I<----------gamma-glutamyl carboxylase (GGCX)
KO (vitamin K 2,3 epoxide)
I<---------VKOR <---------reaction sensitive to warfarin and tecarfarin inhibition
VITAMIN K
I<----one pathway which involves a warfarin sensitive enzyme different from
I VKOR and which uses 2 free cysteine residues in the enzyme active sites
I<----another pathway which involves a warfarin resistant antidotal enzyme, a
I reductase which uses NADPH as a cofactor
KH_2

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One of the major causes of unpredictable variability in warfarin anticoagulation response leading to bleeding complications or stroke is its metabolism by the enzyme CYP2C9. In addition, this variability is increased in patients who have a genetic variant of this enzyme. The advantage of tecarfarin, differently from not only warfarin but from Direct Oral Anticoagulants (DOACs) too, is that it is not metabolized by any CYP enzyme and avoids transport by transport permeability protein (P-gp). For this reasons it does not interfere with all drugs which are moderate or strong inhibitors or inducers of CYP enzymes and of P-glycoprotein. Genetic variants in the drug metabolizing enzymes CYP2C9 and CYP3A4 or transport related proteins such as a P-gp, could lead to unpredictable variability in plasma levels of drugs that are metabolized/eliminated through these pathways, particularly, as said before, if they are used with concomitant medications that may be inhibitors or inducers of these metabolic/elimination pathways. In addition, because tecarfarin is not excreted via the kidney and because is not metabolized by CYP2C9 and CYP3A4, can be administered with safety in patients with chronic renal impairment. Patients with Chronic Renal Dysfunction or Failure (CRDF) show impaired drug elimination mainly because of impaired glomerular filtration rate that has a direct effect on the elimination of drugs normally excreted by the kidneys. In addition, there are indirect factors of CDRF that significantly modify the transport and metabolism of drugs eliminated by the liver. In fact, several studies have demonstrated modifications in the hepatic functional expression of CYP450 enzymes in experimental models of uremia, and various uremic by-products, so called "uremic toxins" have been implicated, including urea, parathyroid hormone and indoxyl sulfate. The severity of the inhibition of hepatic drug metabolism in CRDF varies from 17% to 85% depending on the metabolic pathway involved, and depending on the severity of the disease, but drugs metabolized by hepatic cytochrome P450 (CYP450) are particularly vulnerable. For this reason, appropriate dosing of drugs in renal insufficiency is important to avoid an increased incidence of adverse effects. **(1) (www.armetheon.com)** In some papers it was demonstrated that patients with chronic renal dysfunction or failure have reduced or variable activity of CYP enzymes such as CYP2C9 and CYP3A4 as well as transporter permeability glycoprotein (P-gp). Studies conducted in rodent models of renal failure have shown decreased mRNA and protein expression of many members of the cytochrome P450 enzyme (CYP) gene family and the ATP-binding cassette (ABC) and solute carrier (SLC) gene families of drug transporters. Uremic toxins interfere with transcriptional activation, cause down regulation of gene expression mediated by proinflammatory cytokines, and directly inhibit the activity of the cytochrome P450 and drug transporters. **(4) (Kidney International 2014 vol. 85 pp. 522-528) (5) (Expert Opinion Drug Metabolism Toxicology 2008 vol. 4 (8) pp. 1065-1074)** In conclusion in uremia, decreased CYP2C9 and CYP3A4 activities could have significant clinical implications and this decrease appears to correlate with the severity of the disease.The P-glycoprotein (P-gp) has a decreased functional expression (is down-regulated) in the gastrointestinal tract, resulting in increased intestinal absorption of P-gp substrates, but has an enhanced expression (is up-regulated) in hepatocytes, resulting in increased biliary elimination and in more, less, or unchanged amount of drug in the body. These considerations may explain the suboptimal performance of warfarin in these patients. **(1) (www.armetheon.com)** For what concern Direct Oral Anticoagulants (DOACs), in case of **Dabigatran**, the cytochrome P450 plays no part in in the metabolism of dabigatran and there are no active metabolites. However it has

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interactions with drugs which are P-glycoproteins inhibitors and inducers. Important P-glycoprotein inhibitors which interfere with dabigatran are Verapamil, Amiodarone, Dronedarone and Quinidine. These drugs are very used in atrial fibrillation and nonvalvular atrial fibrillation is the principal indication for which DOACs were approved. Because dabigatran is a substrate of P-gp, when it is used with P-gp inhibitors, inhibition of dabigatran efflux is probably the mechanism of this interaction and its concentration will arise. Amiodarone increases dabigatran plasma concentrations of about 58% and Dronedarone of 73-100%. Other important inhibitors of P-gp are Ketoconazole, Itraconazole, Cyclosporine and Tacrolimus.If inhibitors of P-gp increase dabigatran plasma concentration, on the contrary, the concomitant use of dabigatran with P-gp inducers such as Rifampin, Dexamethasone, Carbamazepine, Phenytoin will reduce dabigatran bioavailability and for this, their concomitant use must be avoided. Another important interaction is the interaction of dabigatran with antiacids which decrease its plasma concentration, and therapy modification must be considered. Other minor interactions are with Atovarstatin, Dasanitib, Tibolone, Tipramavir that increase dabigatran concentrations. On the contrary, interaction with proton pump inhibitors, decreases dabigatran concentration of about 30% as it is written in the **Canadian product monograph.** About 20% of this drug is conjugated and excreted via the biliary system and the remaining 80% is excreted unchanged via the kidneys. For this reason a reduced kidney function results in elevated plasma concentrations and prolonged half life. Exposure to dabigatran is approximately 2.7 fold higher in patients with moderate renal insufficiency (creatinine clearance 30-50 ml/mn) and about 6 times higher in patients with severe renal insufficiency (creatinine clearance 10-30 ml/mn) than in those without renal insufficiency. **(6) (Essential Guide to Blood Coagulation 2013, second edition pp. 113)**

Rivaroxaban is metabolised by liver enzymes, principally cytochrome P450 3A4, and also by cytochrome -independent mechanisms. There are no active metabolites. Approximately 66% of the dose is excreted via the kidneys, 36% as rivaroxaban and 30% as inactive metabolites. The remainder is excreted by the fecal-biliary route. Intestinal excretion of rivaroxaban is mediated, at least in part, by P-glycoprotein transport protein and the renal excretion is mediated by P-glycoprotein and Breast Cancer Resistance Protein [BCRP (BCG2)] and for this, potent P-glycoprotein inhibitors will increase plasma concentrations of rivaroxaban and potent inducers of this glycoprotein on the contrary will reduce plasma concentrations of rivaroxaban. About 2/3 of the administered dose of rivaroxaban are metabolized mainly via oxidative degradation in the liver. Rivaroxaban is metabolized by several cytochrome P450 enzymes (CYP3A4/5, CYP2J2) and CYP-independent mechanism. CYP3A4 accounts for approximately 18% and CYP2J2 for approximately 14% of total rivaroxaban elimination. In addition to this oxidative biotransformation, non-CY--mediated hydrolysis of the amide bonds accounts for 14% of total rivaroxaban elimination. About 50% of rivaroxaban oral dose is cleared via hepatic biotransformation; CYP3A4 (18%), CYP2J2 (14%), CYP independent hydrolytic cleavage (14%). For these considerations, because rivaroxaban is a substrate of CYP3A4 and P-glycoprotein (P-gp),and its elimination is partially dependent on normal renal function, the interaction with inhibitors or inducers of CYP3A4 and P-gp is of greater severity and significance in patients with renal impairment. Rivaroxaban must not be used in patients in treatment with strong CYP3A4 and P-glycoprotein inhibitors such as azole antimycotics (Ketoconazole, Itraconazole, Voriconazole, Posaconazole) which are associated with a 160% increase

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in rivaroxaban AUC (area under the curve) and a 70% increase in rivaroxaban Cmax (maximum concentration) and HIV protease inhibitors such as ritonavir, indinavir, telaprevir which are associated with a 150% increase in rivaroxaban AUC and a 60% increase in rivaroxaban Cmax.
Caution must be used when rivaroxaban is administered in patients in treatment with P-glycoprotein inhibitors such as amiodarone, dronedarone, verapamil and quinidine beause they increase plasma rivaroxaban concentration. The administration of rivaroxaban with strong CYP3A4 and P-glycoprotein (P-gp) inducers such as carbamazepine, phenytoin, systemic dexamethasone, phenobarbital, rifampin and aminoglutethimide must be avoided because they decrease rivaroxaban AUC and Cmax. Elderly subjects exhibited higher plasma concentrations, with mean AUC values being 41% higher in elderly than in younger subjects. These changes were mainly attributed to the reduced rivaroxaban clearance in the elderly subjects, arising from reduced renal and non-renal clearance. Because approximately one-third of the administered rivaroxaban dose is escreted renally as unchanged drug, renal insufficiency is expected to affect drug elimination. The AUC increases by 44% with mild impairment (creatinine clearance 50-79 ml/mn), by 52% with moderate impairment (creatinine clearance 30-49 ml/mn) and by 64% with severe impairment (creatinine clearance < 30 ml/mn). In elderly people, because there is a decrease of creatinine clearance of about 7,5-8 ml/mn every decade after an age of thirty years, rivaroxaban plasma concentrations increase with increasing age. **(7) (Thrombosis Research 2011 vol. 127 pp. 497-504) (8) (Clinical Pharmacokinetics 2014 vol. 53 pp. 1-16) Apixaban** is recovered for about 50% in feces and about 25% in urine and over 50% of the administered dose of this drug is excreted unchanged. The oxidative metabolism of apixaban for the formation of all metabolites was predominantly catalyzed by CYP3A4/5, with minor contributions made by CYP1A2 and CYP2J2. The contributions of CYP2C8, CYP2C9, and CYP2C19 to the metabolism of apixaban were less important. For these considerations, the pharmacokinetics of apixaban may be altered by other drugs that are inhibitors or inducers of CYP3A4/5 such as statins, antiretrovirals, antihypertensive, antibiotics. **(9) (Drug Metabolism and Disposition 2010 vol. 38 pp.448-458)** The area under the plasma concentration-time curve (AUC) for apixaban was 32% higher in elderly subjects compared with young volunteers. **(10) (Journal of Thrombosis and Haemostasis 2009 vol. 7 (suppl. 2) Abstract PP-MO-407).** In individuals with mild, moderate, and severe renal impairment (creatinine clearance of 51-80, 30-50, and 15-29 ml/mn, respectively), plasma apixaban concentrations (as indicated by AUC) were increased by 16%, 29%, and 44% respectively, compared with values for individuals with normal creatinine clearance. **(11) (Summary of product characteristics)** The oxidative metabolism of apixaban by CYP3A4 and the fact that apixaban is a substrate for P-glycoprotein (P-gp) create the potential for drug interactions. For this reason the use of apixaban is not recommended in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp such as ketoconazole, itraconazole, voriconazole, posaconazole and protease inhibitors such as ritonavir, saquinavir, indinavir etc. because for example the concomitant administration of apixaban and ketoconazole led to a 2-fold increase in mean apixaban AUC and a 1.6 fold increase in mean apixaban maximum concentration. **(12) (Journal of Clinical Pharmacology 2009 vol. 49 pp. 1091-1130 Abstract)** On the contrary, the concomitant use of apixaban with strong CYP3A4 and P-gp inducers such as rifampicin, phenytoin, carbamazepine, phenobarbital, St. John's wort may lead to reduced plasma apixaban concentrations. In fact coadministration of apixaban with rifampicin, a

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strong inducer of both CYP3A4 and P-gp, leads to a decrease of 54% in mean apixaban AUC and a decrease of 42% in maximum plasma apixaban concentration. **(13) (Journal of Clinical Pharmacology 2009 vol. 49 pp. 1124 Abstract)** **Edoxaban,** differently from the other Xa inhibitors commercially available such as rivaroxaban and apixaban is metabolised by CYP3A4 for less than 4% but is a substrate of P-glycoprotein and for this, its plasma concentration may increase or decrease when used with the concomitant administration of strong inhibitors or strong inducers of P-gp respectively. **(14) (Hamostaseologie 2013 vol. 33 pp. 218-224)** In fact the concomitant administration of edoxaban and strong P-gp inhibitors such as Amiodarone (40% increase in Edoxaban AUC), Cyclosporine (73% increase in Edoxaban AUC), Dronedarone (85% increase), Erythromycin (85% increase), Ketoconazole (87% increase), Quinidine (76% increase), Verapamil (53% increase) increases edoxaban plasma concentration. Other P-gp inhibitors including diltiazem, itraconazole, clarithromycin, grapefruit jiuce, propafenone, and ritonavir will likely increase the AUC of edoxaban in a similar manner. Currently, the manufacturer of edoxaban does not recommend a dose adjustment when P-gp inhibitors are coadministered, even though the increases in edoxaban plasma concentrations may exceed the degree of increase that triggers a dose reduction recommendation in patients withy renal dysfunction. Strong P-gp inducers such as rifampin, carbamazepine and St.John's wort may reduce edoxaban plasma concentrations and may require an increase of edoxaban doses. In particular rifampin decreases the AUC of edoxaban by about 35%. Patients stabilized on edoxaban should be monitored for altered response (bleeding or loss of anticoagulant effect) if P-gp inhibitors or inducers are added or removed from their drug regimen. **(15) (www.hanstenandhorn.com/hh-article-August-2015) I**t is recommended to halve the dosage normally used in clinical trials. On the other hand, this dose reduction was used in all trials about edoxaban already published. In subjects with renal dysfunction (creatinine clearance between 30 and 50 ml/mn), the area under the concentration time curve (AUC) of edoxaban increased from 35% to 60%. **(16) (Journal of Clinical Pharmacology 2015 vol. 55 (11) pp. 1268-1279)** The manufacturer recommends to reduce the dose by 50% in patients with a CrCl between 50 and 15 ml/mn. Edoxaban is eliminated unchanged via renal (35%) and via biliary and intestinal (65%) **(17) (Drug Metabolism and Disposition 2012 vol. 40 (12) : 2250-2255)** Therefore the unchanged edoxaban detected in the feces was a result of both unabsorbed drug and hepatobiliary excretion of systematically absorbed drug.

This brief review about direct oral anticoagulants demonstrates that although DOACs have less drug interactions than warfarin, in any case they have important drugs interactions which may cause great variations in their plasma concentrations and consequently may cause bleeding or thrombotic events. For this reason tecarfarin, although be a vitamin K antagonist, has not interferences with other drugs or food and may really represent a turning point in the oral anticoagulant treatment. In addition, differently from vitamin K antagonists that we can easily monitor using the INR, in case of DOACs, although we can use other laboratory tests such as a Dilute Thrombin Time (Hemoclot) or the Ecarin Clotting Time to measure plasma concentrations of the Direct Thrombin Inhibitor Dabigatran, (in case of plasma concentrations below 50 ng/ml it is better to use a Hemoclot Thrombin Inhibitors (HTI) Low test) **(18) (Thrombosis and Haemostasis 2014 vol. 113 (4) pp. 862-869)** of or a calibrated anti FXa assay by the use of chromogenic substrates to monitor Direct Anti-Xa Inhibitors **(19) (Journal of Thrombosis and Haemostasis 2013 vol. 11 suppl. 1**

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pp.122-128) (20) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 579-580) (21) (Thrombosis and Haemostasis 2014 vol. 111 (2) pp. 240-248), at the moment we do not have cut-off values that can predict bleeding or thrombotic events or that can be used to decide if a patient may receive a major or minor surgery without bleeding, although a plasma concentrations < 30 ng/ml may be considered sure enough to receive a surgery. **(22) (Archives Cardiovascular Diseases 2013 vol. 106 pp. 382-393)** Another consideration is that in all the clinical trials which investigated the non-inferiority of DOACs versus warfarin, never was reached a mean Time in Therapeutic Range (TTR) > / = 70% in the warfarin group and, for this, the Intracranial haemorrhages (ICH) were much more in this group of patients. In the **RE-LY trial (Dabigatran versus Warfarin in patients with atrial fibrillation)** the mean TTR was 64% and ICH were 0.23% per year in the Dabigatran group treated with 110 mg. twice daily, 0.30% per year in the Dabigatran group treated with 150 mg. twice daily and 0.74% per year in the Warfarin group **(23) (NEJM 2009 vol. 361 pp. 1139-1151)**; in the **ROCKET AF trial (Rivaroxaban versus Warfarin in atrial fibrillation)** the mean TTR was 55% and ICH were 0.50% per year in the rivaroxaban group and 0.70% per year in the warfarin group **(24) (NEJM 2011; 365 : 883-891)**; in the **RE-COVER study (Dabigatran versus Warfarin in the treatment of acute venous thromboembolism)** the mean TTR was 60% and ICH were 0 in the Dabigatran group (n=1273) and were 3 in the Warfarin group (n=1266) **(25) (NEJM 2009 vol. 361 pp. 2342-2352)**; in the **RE-MEDY study (Extended use of Dabigatran, Warfarin or Placebo in venous thromboembolism)** the median TTR was 65.3% (in this study the mean TTR is not cited) and ICH were 2 in the Dabigatran group (n=1430) and 4 in the warfarin group (n=1426) **(26) (NEJM 2013 vol. 368 pp. 709-718)**; in the **ARISTOTLE trial (Apixaban versus Warfarin in patients with atrial fibrillation)** the mean TTR was 62.2% and ICH were 0.24% per year in the Apixaban group and 0.47% per year in the Warfarin group **(27) (NEJM 2011 vol. 368 pp. 981-992)**; in the **RE-COVER II study (Treatment of acute venous thromboembolism with Dabigatran or Warfarin and pooled analysis)** the mean TTR was 57% and ICH were 2 in the Dabigatran group (n=1279) and 6 in the Warfarin group (n=1289) **(28) (Circulation 2014 vol. 129 pp. 764-772)**; in the **EINSTEIN DVT (Oral Rivaroxaban for symptomatic venous thromboembolism)** study the mean TTR was 57.7% and the number or percentage of ICH were not cited **(29) (NEJM 2010 vol. 363 : 2499-2510)**; in the **EINSTEIN-PE study (Oral Rivaroxaban for the treatment of symptomatic pulmonary embolism)** the mean TTR was 62.7% and fatal ICH were 2 (<0.1% per year) in the Rivaroxaban group (n=2419) and 2 (<0.1% per year) in the standard therapy group (enoxaparin + VKA for 3, 6 or 12 months) (n=2413); nonfatal ICH were 1 (<0.1% per year) in the Rivaroxaban group and 10 (0.4% per year) in the standard therapy group **(30) (NEJM 2010 vol. 363 : 2499-2510)**; in the **AMPLIFY trial (Oral Apixaban for the treatment of acute venous thromboembolism)** the mean TTR was 61% and ICH were 3 (0.1% per year) in the Apixaban group and 6 (0.2% per year) in the Warfarin group **(31) (NEJM 2013 vol. 369 pp. 799-808)**; in the **Hokusai-VTE trial (Edoxaban versus Warfarin for the treatment of acute venous thromboembolism)** the mean TTR was 63.5% and fatal ICH were 0 in the Edoxaban group and 6 (0.1% per year) in the Warfarin group; nonfatal ICH were 5 (0.1% per year) in the Edoxaban group and 12 (0.3% per year) in the Warfarin group **(32) (NEJM 2013 vol. 369 : 1406-1415)**; in the **ENGAGE AF-TIMI 48 trial (Edoxaban versus Warfarin in patients with atrial fibrillation)** the mean TTR was 64.9% and ICH were 0.39% per year in the Edoxaban

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high-dose group (60 mg. die), 0.26% per year in the Edoxaban low-dose group (30 mg. die) and 0.85% per year in the Warfarin group. Of these ICH, 0.15% per year were fatal in the Edoxaban high-dose group, 0.08 were fatal in the Edoxaban low-dose group and 0.27% per year were fatal in the Warfarin group **(33) (NEJM 2013 vol. 369 pp. 2093-2104)**. As cited before, in all the studies in which patients treated with DOACs were compared with patients in treatment with warfarin, was never reached a mean TTR of about 70% that normally is considered a good TTR to avoid many bleeding or thrombotic events in patients in treatment with warfarin. Consequently we can deduce that the quality of anticoagulation in patients in treatment with warfarin was poor in all the cited studies.On the other hand, if patients in treatment with warfarin are referred to specialized anticoagulation clinics that are so numerous in all west european countries and in the US, it is possible to obtain in these patients a mean TTR > / = 70% with a great reduction of bleeding and thrombotic events as recently demonstrated by a swedish retrospective registry-based study Auricula in which was obtained a TTR of 75.6%. In this study the incidence of intracranial bleeding was 0.37% per treatment year in the whole population, and 0.38% among patients with atrial fibrillation in a population of unselected patients. Although the authors cannot exclude bias, the mere size of the cohort (77423 unselected patients), and the fact that the Auricula data represent a nationwide Swedish cohort, both from anticoagulation clinics and primary health care settings suggest that these results represent "real world" clinical practice in Sweden. The authors conclude that not only is possible to achieve a warfarin therapy with a high mean TTR in routine clinical practice, but in the same time "warfarin treatment with a high TTR performs well, and should not be ruled out in favour of NOACs". **(34) (Thrombosis and Haemostasis 2015 vol. 113 pp. 1370-1377)** (see also the review "The truth about new oral anticoagulants") TTR is normally calculated using the Rosendaal method **(35) (Thrombosis Haemostasis 1993 vol. 69 pp. 236-239)** For a more clear explanation how to calculate TTR, see the following website : **www.inrpro.com/rosendaal.asp** where it is possible to download an Excel spreadsheet where you can enter your patient's test dates and INR values, and it will calculate the results with the traditional and Rosendaal method. After all these considerations to state that DOACs have the two claimed commercial appeals, the absence of laboratory monitoring and the reduction of ICH compared with warfarin is not correct. The high intra-individual and inter-individual variability of their plasma concentrations was already demonstrated in many papers **(36) (Journal of the American College of Cardiology 2014 vol. 63 pp. 321-328); (37) (Thrombosis Research 2014 vol. 134 pp. 783-789); (38) (Canadian Journal of Cardiology 2013 vol. 29 pp.S24-S33); (39) (Thrombosis Research 2015 vol. 136 pp. 148-153);** and also the interferences they have with important drugs were also demonstrated (see above). As a consequence, DOACs plasma concentrations must be measured periodically using appropriate tests already commercially available for dabigatran, rivaroxaban and apixaban. For what concern the other claimed commercial appeal, the reduction of intracranial bleedings, there is not a reduction of these events in patients treated with DOACs compared with patients treated with warfarin, if warfarin laboratory monitoring is done correctly with a mean TTR > / = 70% that today is possible to obtain in small laboratories too, if managed by skilled physicians and skilled laboratory technicians. **(34) (Thrombosis and Haemostasis 2015 vol. 113 pp. 1370-1377)** In fact, differently from the recent non-inferiority trials in which DOACs were compared with warfarin, the annualized incidence of intracranial

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hemorrhage was lower in atrial fibrillation patients taking warfarin during other comparable trials. In particular in the SPORTIF III study, an open-label study (n=3407) that involved 259 centers in 23 countries in which the mean TTR for patients in treatment with warfarin was 66%, the annual incidence of hemorrhagic stroke was 0.20% per year (4 events in 1704 patients) in the ximelagatran group and 0.45% (9 events in 1703 patients) in the warfarin group. **(40) (Lancet 2003 vol. 362 : 1691-1698);** In the SPORTIF V study, a double-blind, randomized, multicenter trial 2000-2001 conducted at 409 North American sites,involving 3922 patients with nonvalvular atrial fibrillation and additional stroke risk factors, in which warfarin adjusted dosage, INR 2.0-3.0, was compared with a fixed oral dose of ximelagatran 36 mg. twice daily, the mean TTR was 68%. In this trial there were only 2 hemorrhagic stroke in the ximelagatran group (n=1960) and 2 in the warfarin group (n=1962) too (0.06% per year).Two fatal hemorrhagic stroke occurred in the ximelagatran group and no one occurred in the warfarin group. Five sud-dural hematomas (0.19%) occurred in the ximelagatran group and 7 (0.26%) occurred in the warfarin group **(41) (JAMA 2005 vol. 293 pp. 690-698);** In a pooled analysis of SPORTIF III and V trials, the risks of intracranial hemorrhage were only 0.19% and 0.11% per year in the warfarin and ximelagatran group respectively. **(42) (The American Journal of Managed Care 2004 vol. 10 pp. S462-S473)** In a post-hoc analysis of the SPORTIF III and SPORTIF V trials, event rates were strictly correlated with the mean TTR. Patients were divided in three groups : 1190 patients had an INR in the therapeutic range less than 60% of the time and were included in the poor control group, 1207 patients had an INR in the therapeutic range 60% to 75% of the time and were included in the moderate control group, 1190 patients had an INR in the therapeutic range more than 75% of the time and were included in the good control group. The annual mortality was 4.20% per year in the poor control group, 1.84% and 1.69% in the moderate and good control group respectively. The annual rate of major bleedings was 3.85% per year, 1.96% and 1.58% in the poor, moderate and good control group respectively. The annual rate of hemorrhagic stroke was 0.20% per year, 0.28% and 0.06% in the poor, moderate and good control group respectively. The annual rate of stroke + systemic embolic events was 2.1% per year, 1.34% and 1.07% in the poor, moderate and good control group respectively. The authors conclude that patients with poor INR control had increased rates of death, bleeding, MI, and stroke or Systemic Embolic Events (SEE) compared with patients with good INR control. **(43) (Archives Internal Medicine 2007 vol. 167 pp. 239-245)** In one Cochrane review the annual rate of Intracranial Hemorrhage (ICH) was 0.30% **(44) (Cochrane Database of Systematic Reviews 2005 issue 3 Art. No. CD001927);** In another Cochrane review was 0.45% **(45) (Cochrane Database of Systematic Reviews 2007 issue 3 Art. No. CD006186);** The incidence of stroke, major bleeding,minor bleeding and deaths per year was 0.30%, 0.86%, 2.70% and 0.75% per year respectively in the warfarin group (n=5939) of the international study by the European Action on Anticoagulation (EAA) in which was used a computer-assisted dosage, compared with an annual incidence of stroke, major bleeding, minor bleeding and deaths per year of 1.57%, 3.36%, 16.37% and 4.13% respectively, in the warfarin group (n=6022) of the RE-LY trial. In this trial the annual incidence of stroke, major bleeding, minor bleeding and deaths per year was 1.01%, 3.11%, 14.84% and 3.64% respectively in the dabigatran 150 mg. group and 1.44%, 2.71%, 13.16% and 3.75% per year respectively in the dabigatran 110 mg. group. In this very interesting paper Poller and collegues point out that although the TTR was marginally better in the EAA study than in RE-LY,

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(67% versus 64%) this is unlikely to account for its substantially greater success. In RE-LY two important assessments of INR control, local ISI calibration and external quality control of INR were not reported. The authors suggest that this may be one of the reasons explaining why the EAA warfarin group suffered considerably less thrombotic and bleeding episodes. Manufacturers' ISIs and INRs, cannot be guaranteed to reflect local values as, for example, coagulometer calibration ISIs are required and INRs often vary with coagulometers even of the same model and manufacturer used in the same laboratory. In RE-LY there was no method reported of checking the reliability of local ISIs and INRs and there was only a recruitment of 6.3 patients per centre against the EAA's 182. The larger number of centers participating in the RE-LY trial compared with the EAA study would result in greater between-centre evaluation in the quality of oral anticoagulant treatment and this could also be another reason for the lower number of thrombotic and bleeding events in the EAA study. The higher incidence of events in the RE-LY trial may have been at less experienced clinical centres and a subgroup analysis stratifying centres by size or proficiency may prove this. Poller and collegues suggest the use of two recent EAA developments in warfarin control : **(46) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1193-1195)** 1) The PT/INR line, based on a simple procedure using a selected set of only five certified EAA lyophilized test plasmas to derive a laboratory's local INR, was shown to provide closely similar INRs to the more time consuming FDA-approved simplified ISI calibration. The EAA PT/INR line test plasmas are now available internationally in a five-plasmas kit available internationally from Hart Biologicals (Hartlepool, UK) The simple Excel spreadsheet showing the procedure of INR derivation using the PT/INR Line is available from the following website : **www.anticoagulants.co.uk/** and does not require the complex linear regression analysis to derive INR. Users of the European Concerted Action on Anticoagulation (ECAA) plasmas can input their PT results (in seconds) and the PT/INR Line is determined for them. Subsequently, PT results of patients on oral anticoagulant treatment can also be entered on the spreadsheet and the INR obtained directly using their PT/INR Line. The PT/INR Line procedure can be incorporated into a software application or can also be incorporated into the user's automated instrumentation and using the plasmas, a direct calibration line can be measured and used for direct INR determination as an alternative to the more complicated local ISI calibration. With the PT/INR Line, the users would not require local ISI or MNPT to determine INR. **(47) (Journal Clinical Pathology 2011 vol. 64 pp. 930-932) (48) (Thrombosis Research 2011 vol. 128 pp. 101-102) (49) (American Journal of Clinical Pathology 2011 vol. 135 pp. 732-740)** This method was also advocated by the ESC Task Force on Anticoagulants in Heart Disease, and published in a position paper of the ESC Working Group on Thrombosis about vitamin K antagonists in heart disease. **(50) (Thrombosis Haemostasis 2013 vol. 113 pp. 1087-1107)** 2) A variable growth rate (VGR) analysis which was shown to be of greater value than the previously accepted "time in INR range", in predicting clinical events during warfarin treatment. Although TTR is generally reported in studies on the full follow-up of oral anticoagulation in patients, INR monitoring with a measure such as the VGR on a shorter-term basis (3 or 6 months before the current INR measurement) may help in detecting and isolating patients who may be at increased risk of possible adverse events. Because assisted dosage programs are now widely used in oral anticoagulant control, the authors suggest to incorporate VGR in such programs, thereby giving a "V-score" instantly to a clinician and offering the possibility of identifying accurate safety cut-off

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points for the VGR, which could provide an additional safety marker for adverse clinical events. This could potentially aid clinicians by identifyng patients who may be at increased risk of clinical events. **(51) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1540-1546)** Three methods to calculate VGR were described. Method A which combines variability and time in range, and methods B1 and B2 which purely look at variability. The authors suggest to use methods B1 and B2 to reflect pure variability of oral anticoagulant therapy. The method A because include both the aspects of instability, was principally associated with hemorrhagic events and on the contrary, thrombotic events were most clearly predicted by variability calculated with methods B1 and B2 which only include variability of the INR and not the time within the range. The optimal time window to determine these measures was 3 months. The variance growth rate by Fihn et al. (method A) reflects the degree to which a patient's INR deviates from his or her target INR over a prolonged period. Using this formula for variability, a patient is most stable when his or her INRs are close to the target INR. The variance growth rate by Cannegieter (method B1) reflects the degree to which a patient's INR deviates from the previous one. This formula is a reflection of the true variability, not taking into account the intensity of anticoagulation. With this formula, a patient is most stable if his or her INRs are around the same level even if this means that the INR is constantly above the upper limit of the target range. The second variance growth rate by Fihn et al. (method B2) is approximately the same as the formula used by Cannegieter, with minor differences in the denominator. The variability according to the method A was best associated with complications of oral anticoagulant therapy. However, this method is a composite of time in range and variability. When the authors combined the methods that only looked at variability with a measure of time in range, this predicted equally well. The importance of the association of risk of the methods that only look at the variability of the INR is that the authors showed this is a risk factor per se, added to the risk of under- and overanticoagulation. An INR within the therapeutic range in patients with high variability in INRs cannot be interpreted in the same way as in patients who constantly are in their INRs. The authors of this interesting paper conclude that although method A is best associated with complications, this method does not explain the reason for the increased risk. Because methods B1 and B2 in combination with the time spent at INR 2.5-4.0 are equally well associated, they prefer to disentangle the variability and the time in therapeutic range to target more directly either the instability or the inadequate level, hence possibly preventing these events. For this reason, they recommend to use the variance growth rate by methods B1 and B2 to reflect the variability of oral anticoagulant therapy. **(52) (Journal of Thrombosis and Haemostasis 2008 vol. 6 pp. 451-456)** For more clear explanation how to calculate VGR, see the following website : **www.4s-dawn.com/wp-content/uploads/2014/01/Introduction-to-Variance-Growth-Rate-VGR-4S-DAWN-Clinical-Software.pdf** In total, in the study of EAA were recruited 13219 patients from 32 centers, 6503 patients were randomized to medical staff and 6716 to computer assisted dosage. The number of clinical events with computer-dosage was lower (P=0.1) and the TTR was 67% in the warfarin group in which was used a computer-assisted dosage. **(53) (Journal of Thrombosis and Haemostasis 2008 vol. 6 pp. 935-943)** (see also the review "The true about New Oral Anticoagulants") In any case, improved TTRs translate into fewer strokes and hemorrhages and because there is no statistically significant randomized controlled trial (RCT) evidence to support the noninferiority of DOACs over well-managed warfarin at a mean TTR greater than 65%, some authors

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correctly suggest to switch to DOACs those patients in treatment with warfarin whose TTR is less than 65%, considering warfarin as the first-line oral anticoagulant in most patients, to see if they can achieve a TTR greater than 65%. "To initiate the NOACs without allowing these potentially well-managed patients to be identified, or switching well-managed patients from warfarin to an NOAC is a disservice to our patients and to our health care system" **(54) (Canadian Family Physician 2015 vol. 61 pp. 23-24)** I add that this would also be very unethical. At this point it is easy to understand that Tecarfarin which has not interferences with other drugs or food and that can be administered without any contraindication in patients with renal impairment and in patients with mechanical heart valves too, differently from DOACs which cannot be used in these two indications, represents really a key drug in the future of oral anticoagulant treatment. Tecarfarin was specifically designed to be non-oxidatively metabolized by human carboxylesterases (hCE) in order to yield more predictable metabolism and to decrease the likelihood of drug-drug interactions, especially with CYP450 inhibitors or inducers. Tecarfarin is converted by esterases to ATI-5900 that is essentially inactive with respect to human liver microsomial VKORC1 inhibition.The biotransformation of tecarfarin is completely independent of nicotinamide adenine dinucleotide phosphate (NADPH), the necessary cofactor for CYP450. In beagle dogs was demonstrated that Fresh Frozen Plasma (FFP) had an immediate effect on reversing INR back to a physiological value and that the main mechanism of action of tecarfarin is via inhibition of VKOR. In addition, co-administration of amiodarone had no measurable effect on the blood levels or on the anticoagulation induced by tecarfarin in adult beagle dogs **(55) (Drug Metabolism Reviews 2006 vol. 38 pp. 93)** Also in another more recent study was shown that like warfarin, oral tecarfarin administration to rabbit and dogs selectively reduces the levels of the vitamin K- dependent factors. **(56) (Thrombosis Research 2010 vol. 126 pp.e383-e388)** Tecarfarin has a mean terminal half-life of 119 hours (range, 107 to 140 hours), is highly protein bound (99)%), is a structural analogue of warfarin, but differently from warfarin is a single enantiomer and is not metabolized by the CYP450 system, but is metabolized by carboxylesterases in the hepatic microsomes, yelding a single inactive metabolite, ATI-5900. The mean plasma concentration of tecarfarin increased from day 5 to day 12 and then remained relatively constant. Plasma concentrations correlated with VKORC1 genotype, with the GG genotype having the highest concentration, GA having an intermediate concentration and AA having the lowest concentrations. In an open-label, multicenter, phase IIA study, tecarfarin was used in 66 patients with atrial fibrillation with a mild to moderate risk of stroke to determine the safety and tolerability of tecarfarin and to ascertain an optimal tecarfarin dosing regimen. Sixty-four subjects were taking warfarin at enrollment and were switched to tecarfarin. After 1 week of treatment with tecarfarin, 77% of patients reached a therapeutic INR, and after 2 weeks of treatment, 95% of patients had attained a therapeutic INR. After 3 weeks of treatment the mean TTR was 71.4%. The same group of patients on warfarin achieved a mean TTR of 59% over the year before enrollment. The authors reported that the proportion of patients with poorly controlled INR (< 45% TTR) was 10.9% (with the use of weeks 4 to 12 INR values).
The time spent significantly below therapeutic INR range (<1.5%) was 1.2%; the time spent significantly above the therapeutic INR range (>4.0%) was 1.2%. A stable maintenance dose was reached by 25% of patients at week 3, 56% of patients at week 6, and 81% of patients at week 9. The authors conclude that due to its lack of interferences with drugs or food because is not metabolized

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by the CYP450 system and because is not excreted via kidneys, tecarfarin may possess advantages over warfarin, by improving time in therapeutic range. Prospective trials are needed to compare tecarfarin with warfarin in clinical settings for which warfarin is indicated. **(57) (Circulation 2009 vol. 120 pp. 1029-1035)** Any new oral anticoagulant therapy must be evaluated establishing its efficacy, safety, and cost-effectiveness by an appropriate trial design. "Clearly, a therapy that removes many of the burdens of warfarin therapy would be greatly welcomed, but for this to become a clinical reality requires careful steps down a long and difficult road". **(58) (Circulation 2009 vol. 120 pp. 1024-1026)** Armetheon completed five Phase 1 clinical trials in 156 healthy volunteers. The trials showed no important adverse events, alterations of vital signs, of ECG, and unexpected laboratory tests alterations. There have been no frequent or consistent adverse events suggestive of off-target toxicity. Mild side effects typical of an anti-anticoagulant were experienced, including headache, gastrointestinal effects, bruising and nose bleeds. Phase 1 clinical trials also studied the impact of this potential drug on other medications such as fluxonazole, and found no affect on blood levels. In addition, well-known teratogenic effects of warfarin were not seen in reproductive toxicity studies.**(1) (www.armetheon.com)** As cited above, was also shown no interference of tecarfarin with amiodarone. A trial, the EmbraceAC trial, was conducted to evaluate whether tecarfarin is superior to optimized warfarin as measured by interpolated time in therapeutic range (TTR). EmbraceAC was a 6-9 month randomized, double-blind, multicenter study in which was used a dose control center and prospective genotyping in oral anticoagulation patients. Data from weekly INR monitoring was analyzed on an Intention To Treat (ITT) basis. A total of 612 patients from 47 sites were randomized (305 to warfarin and 307 to tecarfarin). Mean interpolated TTR was 73.2% for Warfarin and 74.0% for tecarfarin. Pre-specified subgroups analyses of warfarin experienced patients, wild-type CYP2C9 patients, and on-treatment analysis, all showed statistically significant superiority of tecarfarin over warfarin. For the 31% of patients taking drugs that inhibit CYP2C9, the observed TTR for warfarin decreased, whereas the TTR for tecarfarin remained steady. There was no significant difference in the composite of clinical outcomes (death, stroke, MI, DVT, PE, or major hemorrhage). Tolerability was good with both treatments and there were no differences in overall adverse events rate. The authors observed that TTR was exceptionally high, perhaps as a result of frequent monitoring, availability of accurate and timely genotype information, close surveillance by the Dose Control Center and early dose adjustment for potential interacting drugs. **(59) (Blood 2009 51st ASH Annual Meeting Abstract 3135)** There are some considerations to evaluate about this study. First of all, this trial was a superiority trial, the gold-standard to evaluate the efficacy and superiority of a new drug compared with another drug, differently from all the trials that compared DOACs with warfarin, which were non-inferiority trials. In addition, as pointed out by the authors, TTR in the warfarin group was exceptionally high (73.2%) especially if we consider that TTR in all the trials which involved DOACs, in the warfarin group, was included from 55%, the lowest value, in the ROCKET-AF trial, to 64.9%, the highest value, in the ENGAGE AF-TIMI 48 trial. On the other hand, in the United States, with the exceptions of specialized anticoagulation clinics, normally TTR is < 70%. Based on the results of this trial, because was not demonstrated a superiority of tecarfarin over warfarin, the FDA did not approve its clinical use. Its original owner, ARYx Therapeutics closed down for good in 2011. However the founder, Peter Milner, took the drug to a new company, Armetheon, in 2011, and this company now is starting a new phase 3 test that

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again will compare tecarfarin with warfarin. Armetheon and the FDA have negotiated a "special protocol assessment" for the study, an agreement up front about the key elements of a clinical trial, like the main goal and the statistical plan. The armetheon's task is to prove that tecarfarin is safer and more effective than warfarin in patients who have the worst response to warfarin. The Tecarfarin Anti-coagulation Trial (TACT) is a "real world" randomized controlled trial of tecarfarin versus warfarin. The quality of anticoagulation control will be compared for the two groups of subjects who require chronic oral anticoagulation for a broad panel of indications. Three thousands subjects with indications for chronic anticoagulation will be randomized to either tecarfarin or warfarin for at least one year (6 months for some VTE subjects). The study will include 1200 patients having a mechanical heart valve as the primary indication for chronic anticoagulation. The remaining 1800 patients will be required to be taking a chronic medication concomitantly, which is known to interact with CYP2C9. The primary endpoint of the study consists of a comparison of Time in the Therapeutic Range (TTR) for a nested group which is blinded to investigators and subjects. It consists of a subgroup of the overall population which takes at least one drug known to interact with CYP2C9 and who have at least one CYP2C9 variant allele. As secondary outcomes measures, TTR will be compared in the subgroup of the overall population who have a mechanical heart valve as the indication for chronic anticoagulation and in addition will be evaluated the reduction in embolic stroke in the tecarfarin group versus the warfarin group. **http://clinicaltrials.gov/ct2/shown/NCT02522221** The fact that the mean TTR is crucial in oral anticoagulant treatment was also demonstrated by a paper in which the authors showed that for every 10% increase in a patient's time out of the INR range, there is an increase in the likehood of death of 29.3% and an increase of a thromboembolic event by 12.4%. Since INR control was worst during the first three months after the initiation of warfarin and poor control was linked to an increased risk of events, it was likely that patients were at higher risk of events during their first months of treatment while an appropriate dose of warfarin was being established. The authors also found an association between INR values outside the target range and increased rate of hospitalization. **(60) (Heart 2005 vol. 91 pp. 472-477)** In one large study, the risk of stroke caused by a blood clot increased 3 to 4 times when the INR was between 1.4 and 1.7 and the risk of stroke caused by bleeding increased about 12 times when the INR was > 4.5. For this reason is crucial to avoid such extreme INR values. **(61) (Circulation Cardiovascular Quality Outcomes 2009 vol. 2 pp. 297-304)** The Atrial Fibrillation Clopidogrel Trial With Irbersartan for Prevention of Vascular Events (ACTIVE W) study data were used to calculate the mean TTR for each of 526 centers and 15 countries, to estimate the minimal TTR needed to confidently achieve a benefit compared with therapy with clopidogrel and aspirin. This estimate was based on comparing the outcomes of patients in ACTIVE W randomized to either Oral Anticoagulant Treatment (OAC) or clopidogrel plus aspirin. The analysis used stratification according to the TTR achieved by each clinical center in its OAC patients. Of the 6706 patients in ACTIVE W, 3371 were randomized to OAC and 3335 to clopidogrel plus aspirin. Only patients at centers with TTR above the study median of 65% benefited from OAC compared with clopidogrel plus aspirin with a marked reduction of stroke and total vascular events. An analysis by country was also carried out and a strong relationship was found between the TTR achieved by a country and the benefit of OAC.The estimate of the minimum TTR needed to achieve a benefit from OAC therapy was between 58% and 65%. The authors point

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out that centers that achieve an INR below this level cannot be confident that their patients are benefiting from OAC compared with antiplatelet therapy and conclude that providers of OAC need to achieve a minimum TTR of 58% to 65% and an optimal control of > 70% TTR that is achieved in some countries. The authors recommend that centers must "attempt to achieve the highest possible TTR". The success of INR control, as measured by TTR, is an important determinant of the benefit of OAC over antiplatelet therapy. **(62) (Circulation 2008 vol. 118 pp. 2029-2037)** (in the ROCKET AF trial, TTR was 55%) Self testing was demonstrated to be more effective than laboratory controls to achieve an improved TTR. In fact, in a large meta-analysis Bloomfield and collegues demonstrated that compared with usual care, Patient Self Testing with or without Patient Self Management is associated with significantly fewer deaths and thromboembolic events, without increased risk for a serious bleeding event and in particular the authors found a 26% lower risk of death and a 42% lower rate of major clotting events. **(63) (Annals of Internal Medicine 2011 vol. 154 pp. 472-482)** In a large prospective cohort study in Switzerland were examined data of 1140 patients with a median follow-up of 4.3 years. Twenty-two venous and arterial thromboembolic complications were reported during the observation period with a rate of 0.4 per 100 patient-years and 66 major bleedings with a rate of 1.1 per 100 patient-years. Nine intracranial bleedings were documented with a rate of 0.2 per 100 patient-years and with a trend towards a higher rate in patients older 50 years (0.2 versus 0.04 per 100 patient-years). INR data of 653 patients were available with a median observation period of 2.19 years. The median time within the intended therapeutic range was 80% (InterQuartileRange (IQR) 66-89%). Median time in a safety range of 2.0 to 4.5 was 96% (IQR 89-99). Efficacy was camparable to standard care and new oral anticoagulants. Remarkable is the low rate of intracranial bledings which is equal to that of some new oral anticoagulants and better than that obtained with rivaroxaban. **(64) PLOS One 2014 vol. 9 Issue 4 pp. e95761)** In a systematic review were analyzed 22 studies, of which 4 were characterized as high-quality studies. The authors concluded that the precision of the Point-Of-Care-Testing (POCT) coagulometers was acceptable for clinical use. For what concerns the internal quality control, CoaguChek uses electronic "onboard" quality control and for the external quality control the authors reported that it can be accomplished with different methods : 1) Comparing the INR obtained from venous samples analyzed in a laboratory with that of the POCT coagulometer (method dependent on the quality of the INR measured in the laboratory, and does not account optimally for imprecision or accuracy); 2) Comparing the INR of a reference POCT coagulometer with that of the POCT coagulometer (method that has the same drawbacks as method 1); 3) Comparing plasma with a known INR value sent from a central laboratory with the result of the POCT coagulometer (method developed by the UK NEQUAS, and does not estimate imprecision by using two samples, but does not estimate inaccuracy, as the deviation is based on a deviation from an overall performance. In addition, as the reporting of results is performed centrally, there is a time of delay.); 4) Comparing INR measured on a certified (calibrated) POCT coagulometer, using five sets of plasma. [method proposed by the EAA (European Action on Anticoagulation) which is, from a theoretical point of view, superior, as it takes imprecision and inaccuracy into account and the result is available to the patient without any delay. However, it has the drawback of requiring a considerable logistical set-up and substantial economic resources. **(65) (Journal of Thrombosis and Haemostasis 2012 vol. 10 pp. 251-260)** Furthermore, in a letter to the journal Clinical Chemistry, Kitchen and collegues criticized the use of

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plasma because the results obtained with this do not necessary reflect the performance of the test result on the native sample that is on whole blood. **(66) (Clinical Chemistry 2007 vol. 53 (8) pp. 1555-1556)** Poller and collegues replied that although Kitchen and collegues did not agree about the use of the EAA method which uses five sets of plasma whose ISI was calculated on the whole blood to certify the INR of EAA EQA plasmas, the whole blood ISI was preferred because of the small but constant difference in ISI between plasma and whole blood that persisted even with their modified recalcification. Thus adoption of the whole blood INR certification seemed preferable because the method gives less deviation from the certified values without affecting the underlying principles of EQA. The EAA implementation plan designed specifically for the EQA of the CoaguChek specifies that users of point-of-care testing monitors shoud test them with EQA plasmas at intervals of not > 6 months or whenever there is a change of the lot of test strips.] **(67) (Clinical Chemistry 2007 vol. 53 (8) pp. 1556-1557)**In terms of accuracy, the POCT coagulometers tend to overstimate the INR when INR measurements are high, especially above 4.0. On the contrary a tendency to understimate INR is found when the INR is within or below the therapeutic INR target range. **(65) (Journal of Thrombosis and Haemostasis 2012 vol. 10 pp. 251-260) ; (68) (American Journal of Clinical Pathology 2006 vol. 126 pp. 756-761) ; (69) (American Journal of Clinical Pathology 2014 vol. 141 pp. 878-883)** Christensen et al., regarding clinical accuracy found that INR measurements deviated by > / = 15% in 40% of all measurements obtained with CoaguChek. A deviation of 15% with an INR measurements of 2.5 will provide a range of 2.125 - 2.875 (+/- 0.375 INR). This deviation, although important in a clinical setting, has probably no clinical consequence in terms of more thromboembolism and bleeding events in patients using coagulometers. **(70) (Thrombosis and Haemostasis 2009 vol. 101 pp. 563-569)** Leichsenring et al. calibrated the CoaguChek XS PT test in agreement with WHO guidelines to obtain an ISI of 1.01, and the measuring range, using polynomial regression, was calibrated against the mean INRs obtained with the human recombinant reference thromboplastin rTF/95 and the rabbit reference thromboplastin AD149, between 0.8 and 8.0 INR. **(71) Thrombosis and Haemostasis 2007 vol. 97 pp. 856-861)** In a very interesting letter to the editor of Journal of Thrombosis and Haemostasis Tripodi and Moia pointed out that some recommendations of the American College of Chest Physicians published in 2012 are not correct. When discussing how and when vitamin K should be used to reverse over-anticoagulation, the guidelines recommended the following : "for patients taking VKAs with an INR between 4.5 and 10.0 and with no evidence of bleeding, we suggest against the routine use of vitamin K (Grade 2B); and "for patients taking VKAs with INR > 10.0 and with no evidence of bleeding, we suggest that oral vitamin K be administered" (Grade C). **(72) (Journal of Thrombosis and Haemostasis 2012 vol. 10 pp. 2207-2208)** According to the 1999 guidelines for thromboplastins and plasma used to control oral anticoagulant therapy issued by the World Health Organization (WHO), the INR scale for reporting prothrombin time (PT) results has well-defined limitations. The INR scale is most accurate within the interval of 1.5-4.5 because a working thromboplastin is calibrated using plasmas of 20 or more healthy subjects not taking anticoagulants and 60 or more patients stabilized on vitamin K antagonists (VKAs) for at least 6 weeks with their INRs included within the range of 1.5-4.5. On these plasmas PT is then determined with the working and standard thromboplastins, and paired PTs are plotted on a double-log scale putting the standard thromboplastin on the vertical axis. After cheking for linearity, the best-fit line that describes

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patients and normal data points is drawn, and the slope of the line is estimated by orthogonal regression analysis. The slope of the line after appropriate correction can be taken as the International Sensitivity index (ISI), which represents a measure of the responsiveness of the thromboplastin being calibrated relative to the international standard. Due to this procedure, the ISI and therefore the INR that is derived (i.e. INR=($[PT_{patient} / PT_{normal}]^{ISI}$) is accurate within the limits of INR from 1.5 to 4.5. In fact as shown above this is the range of the INRs of the patients selected for calibration. **(73) (WHO Technical Report Series no. 889. Geneva : WHO, 1999 : 64-93)** Tripodi and Moia point out that due to these considerations, the accuracy of INR values in excess of 4.5 is questionable because there is no assurance that the calibration line beyond that value is still linearly related to the increasing PT prolongation.In addition,it is possible that different thromboplastins, even if they have been calibrated correctely will display different INRs. For these reasons, grading the recommendation on the use of vitamin K to reverse anticoagulation on the basis of INR values from 4.5 to 10.0 or beyond 10.0, as stated in the ACCP recommendation, contrasts with the WHO guidelines. **(72) (Journal of Thrombosis and Haemostasis 2012 vol. 10 pp. 2207-2208)** In addition, the use of point-of-care coagulometers according to Leichsenring et al. reliably measure INR only up to 8.0, as cited above. **(71) (Thrombosis and Haemostasis 2007 vol. 97 pp. 856-861)** Tripodi and Moia recommend to use vitamin K administration when the INR is > 8.0 because although there is no assurance that an INR from 4.5 to 8.0 is accurate, it is certainly much more accurate than an INR of > /= 10.0. **(72) (Journal of Thrombosis and Haemostasis 2012 vol. 10 pp. 2207-2208)** The authors of these ACCP recommendations replied that they "suggest" rather than "recommend", as the quality of the evidence in the randomized trials was only moderate. The basis of their suggestion to abstain from reversal with vitamin K of asymptomatic INRs between 4.5 and 10 is derived from four randomized controlled trials. In three of those, the population studied had INRs of 4.5-10.0, whereas the smallest study included patients with INRs between 6.0 and 12.0. At the end of their reply, these authors state that the treating physician should make an individual judgement in these cases on whether to treat or not and in a future edition of the guidelines should be added the consideration by Tripodi and Moia that high INRs are inherently inaccurate. **(74) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 566-567)** In my opinion this happens because in some cases guidelines are based also on meta analysis studies and, unfortunately, many times meta analysis studies include individual studies that have important flaws that are overlooked. In a recent article, Biedermann and collegues evaluated the point-of-care INR monitoring on quality of treatment with vitamin K antagonists in non-self-monitoring patients of an unselected population. As point-of-care instrument was used a Coagucheck XS which uses a recombinant thromboplastin and for laboratory monitoring was used the STA-R Evolution (Hepato Quick test which uses a tissue-extract thromboplastin). (Clearly the use of another POC device or the use of a recombinant thromboplastin for laboratory INR measurements may lead to different results). They performed a retrospective cohort study using data from the anticoagulation clinic of the Star-Medical Diagnostic Center based in Rotterdam, (the Netherlands). In the study were included 1973 patients during the 1-year laboratory monitoring observation period and 1959 patients during the 1-year POC-monitoring observation period . The established therapeutic ranges were 2.0-3.5 for patients who received low intensity treatment and 2.5-4.0 for patients who received high intensity treatment, because in the Netherlands the target INR is set higher (2.5-3.5 and 3.0-

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4.0) to prevent inadequate anticoagulation. Patients included in this study were receiving acenocumarol or phenprocoumon, because warfarin is not used in the Netherlands. The TTR was calculated using the Rosendaal method and was classified in good (TTR > 75.0%), moderate (TTR 60-75%) and poor (TTR < 60.0%). The median TTR during POC monitoring was 77.9% and during laboratory INR monitoring was 81.0%. The incidence rate for major bleeding was 17.0 per 1000 patient years (95% Cl 11.9-24.3) during POC monitoring and 18.2 per 1000 patient years (95% Cl 12.9-25.6) during laboratory monitoring. Incidence rates for ischaemic stroke were 6.8 per 1000 patient years (95% Cl 3.9-11.9) during POC monitoring and 7.4 per 1000 patient years (95% Cl 4.3-12.6) during laboratory monitoring. Adjusted hazard ratios of POC monitoring as compared with laboratory monitoring were 0.93 (95% Cl 0.56-1.52) for major bleeding, 0.92 (95% Cl 0.42-2.02) for ischaemic stroke, 0.94 (95% Cl 0.79-1.12) for hospitalisation and 1.00 (95% Cl 0.78-1.29) for all cause mortality. Percentage of INR results within therapeutic range was lower during POC monitoring than during laboratory monitoring (66.8% vs. 70.1%, P < 0.001). INR testing frequency (21.0 vs. 19.7 per patient per year, P < 0.001) and percentage of INR followed by a significant adjustment in VKA dose (3.8% vs. 3.3%, P < 0.001) were higher during POC monitoring than during laboratory monitoring. Sensitivity analysis showed that TTR was lower during POC monitoring than with laboratory monitoring, as cited above, but the proportion of patients in treatment with phenprocoumon who achieved a good TTR (> 75%) during POC monitoring was higher than that obtained with laboratory monitoring, while other subgroups showed lower TTR during POC monitoring. The fact that in patients taking acenocoumarol TTR was lower during POC monitoring than during laboratory monitoring may be explained by the use of the current dosing algorithms, which are based on laboratory INR results rather than on POC INR results. The authors suggest that the effect of POC INR monitoring on the TTR may be better when the patient is taking a VKA with a longer half-life. The incidence of adverse events (see above), was not significantly increased after 1 year of follow-up during POC monitoring. The authors conclude that their results show that in non-self monitoring patients POC INR monitoring by professionals is a safe, effective, and adequate alternative to laboratory INR monitoring **(75) (Journal of Thrombosis and Haemostasis 2016 vol. 14 (4) pp. 695-703)** Using Self-Testing are possible more frequent controls than with laboratory-testing; in particular weekly INR testing helps keep INR values closer to the target range and prevents extremely low or high values. In an interesting paper are described all the information that may be useful to the clinician when managing warfarin therapy and all the tips that the patient must use when is doing an INR Self-Testing with the recommendation to repeat the test if the results are different than expected. The patient must let his physician know if he has missed or has taken extra doses of warfarin; if he has changed his diet, vitamins or food supplements, if he has changed his consumption of tobacco or alcohol or his physical activity; if he has been hill and had fever; if he had diarrhea or constipation; if he had some bleedings such as bruising, pink or brown urine, nose bleeds, gum bleeds, blood in his eye, coughing up blood, red or black stools, heavy vaginal bleeding; if he noticed any new symptoms that might suggest a milde stroke such as a change in vision, difficulties in speaking or balance, headache, numbness, tingling, right or left limbs weakness; if he had difficulty in breathing, chest pain or shortness of breath; if he was hospitalized for any reason. A repeat test may be done by using a point-of-care instrument or by a laboratory test. When the INR is within the usual therapeutic range, there is not discordance between the results obtained with the

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two different methods. On the contrary, regardless of the method used, the INR test becomes more variable at higher levels, so that repeat tests are likely to be some what different if the true INR is well above the therapeutic range. In other studies in which internet-based systems were combined with self-testing or self-dosing showed even better INR control, suggesting that even better outcomes are possible. **(76) (Circulation 2012 vol. 126 pp. e52-e54)** In fact in four trials was shown that by combining INR **S**elf **T**esting with **O**nline **A**utomated **M**anagement **(STOAM)** there was an improvement in the INR time in therapeutic range (TTR) of approximately 10-23%. In particular in the trial of Ryan and colleagues TTR improved from 60.2% to 71.4% and the automated online system used was INR Online (INR Online Ltd. Palmerston North, New Zeland) **(77) (Journal of Thrombosis and Haemostasis 2009 vol. 7 pp. 1284-1290)** ; in the trial of Harper et al. TTR improved from 71% to 80.4% and the automated system used was CoagCare (Zycare, Chapel Hill, NC) **(78) (Blood 2008 vol. 112 Abstract # 1278)** ; in the trial of Ferrando et al. TTR improved from 55.7% to 64.9% and the automated system used was Sintromac-Web (Grifols, Barcelona, Spain) **(79) (Thrombosis Haemostasis 2010 vol. 103 pp. 1091-1101)** ; in the trial of Bussey et al. TTR improved from 56.8% to 79.7% and the automated system used was ClotFree (Genesis Advanced Technologies, Inc., Lakehills, TX) **(80) (American heart association meeting on quality of care and outcomes research in cardiovascular disease and stroke 2010 meeting, poster # P260 ID#341,Washington, 21 May 2010)** . These reported improvements in TTR are considerably better than the less 4% improvement reported in two large trials that evaluated either weekly self-testing **(81) (New England Journal of Medicine 2010 vol. 363 pp. 1608-1620)** or computer dosing **(82) (Thrombosis Haemostasis 2010 vol. 101 pp. 487-494)** as methods to improve INR control. A total of 29,457 patients with multiple indications for warfarin therapy were included in a retrospective study (STABLE study) in which was evaluated the quality of anticoagulation control using point-of-care patients self-testing (PST) at home with the support of a health management service. The overall mean TTR achieved was 69.7%, higher than that observed for PST in randomized clinical trials (RCT). Interestingly, this large study confirmed that TTR improved increasing the test frequency and in particular, a high TTR, an early control of anticoagulant treatment and occurrence of low critical value were achieved with a weekly testing frequency. In addition the elderly, in particular patients who are 75 years and older, who are considered to be at higher risk of bleeding during warfarin therapy, in this STABLE study achieved a TTR above 73% using a weekly testing frequency. **(83) (American Journal of Managed Care 2014 vol. 20 (3) pp. 202-209)** As cited above, in a post-hoc analysis of the SPORTIF III and SPORTIF V trials, comparing the results of adverse events of the poor control group (TTR < 60%) with those of the good control group (TTR > 75%) there was a 50% reduction in major adverse events such as stroke, myocardial infarction, major hemorrhage, and death. **(43) (Archives of Internal Medicine 2007 vol. 167 : 239-245)** Daily low-dose vitamin K can improve an unexplained variability in patients in treatment with vitamin K antagonists. In a study, 70 patients in treatment with warfarin were randomly assigned in a double-blind fashion to receive a daily amount of 150 microgr. oral vitamin K or placebo orally for 6 months. Measures of stability of anticoagulation control in the 6-month study period were compared with those in the 6 months immediately prior to it. Vitamin K supplementation resulted in a significant greater decrease in standard deviation of international normalized ratio (INR) compared with placebo and a significantly

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greater increase in percentage time within target INR range. Anticoagulation control improved in 33 of 35 patients receiving vitamin K supplementation and of these, 19 fulfilled criteria for having stable control of anticoagulation. In this study the authors classified a patient as unstable if the SD of his/her INR values was greater than 0.5 and he/she had had at least 3 warfarin dose changes in the previous 6 months. Those patients whose instability was deemed to be due to poor adherence to warfarin therapy, changes in concurrent medication, comorbidity or irregular and excessive alcohol consumption were excluded. **(84) (Blood 2007 vol. 109 pp. 2419-2423)** Evidence suggests that alterations in the dietary intake of vitamin K can affect anticoagulation response to warfarin. It is possible that a low and irregular intake of dietary vitamin K is at least partly responsible for the variable response to warfarin in patients with unstable control of anticoagulation. In fact, in a study was demonstrated that the mean daily intake of vitamin K in unstable patients was considerably lower than that for stable patients during the study period. **(85) (Thrombosis and Haemostasis 2005 vol. 93 pp. 872-875)** In the above two studies by Sconce and collegues, was used vitamin K1 as supplementation. In a correspondence to the editor, Stafford and collegues on the contrary suggest the use of vitamin K2 because there is the danger that vitamin K1 administered with warfarin may increase the risk of arterial calcification and in the same time they say that there are several indications that the use of K2 may have at least the same ability to stabilize oral anticoagulation and appears to prevent arterial calcification. In addition, K1 has a relatively short half-life (1-2 hours), and for this reason a single day dose may result in substantial fluctuations of circulating and tissue K1 concentrations. Therefore, the stability of anticoagulation may be further improved by using vitamin K2 which has a longer half-life (about 3 days). Vitamin K1 is taken up preferentially by the liver so that extrahepatic tissues are more susceptible to vitamin K deficiency than the liver and this effect is exacerbated when K1 and warfarin are combined. On the contrary, a major advantage of K2 is that it is not preferentially targeted to the liver. A number of tissues, including the vessel wall, accumulate K2 at high levels. This results in protection by K2 but not by K1 against warfarin-induced calcification. In addition K2 can be used in the liver equally as well as K1. Doses as high as 45 mg/day of vitamin K2 seem to have no adverse effects. **(86) (Blood 2007 vol. 109 (8) pp. 3607)** Sconce and collegues replied that although warfarin inhibiting the recycling of vitamin K epoxide into its quinone form might interfere with the functioning of glutamate-containing proteins not associated with hemostasis, in particular matrix Gla-protein, the potent inhibitor of soft tissue calcification, and osteocalcin, promoter of bone formation, is necessary a robust trial to test the hypothesis that vitamin K2 through its longer half-life and greater arterial accumulation, has a greater benefit-risk ratio compared with vitamin K1. **(87) (Blood 2007 vol. 109 (8) pp. 3607-3608)** In a study the authors found data that suggest that uncarboxylated matrix Gla protein (ucMGP) may be a useful indicator of vitamin K status, but they found no evidence in older adults that is associated with Coronary Artery Calcification (CAC). The authors concluded that studies in populations at greater risk for nonatherosclerotic arterial calcification may identify novel associations between vitamin K, ucMGP, and pathologic calcification in certain disease populations, such as those with kidney disease or diabetes. **(88) (Nutritional Epidemiology 2011 vol. 141 pp. 1529-1534)** In a study in which were analyzed 45 aortic valves obtained after routine cardiac replacement surgery from patients treated with the vitamin K antagonist phenprocoumon for a period between 16 and 35 months, was shown a more than 2-fold difference between the treated and

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the untreated patients with a mean calcified area of 16% in the nontreated group and 37% in the OAC-treated group. Even low-dose OAC treatment combined with a relatively short period of treatment resulted in significantly more calcification. **(89) (Blood 2004 vol. 104 (10) pp. 3231-3232)** In a recent study, Knapen and collegues investigated long-term effects of menaquinone (MK, vitamin K2), administering MK-7 (180 microgr./day), on arterial stiffness in a double-blind, placebo-controlled trial in which 244 healthy post-menopausal women received either placebo (n=124) or MK-7 (n=120) for three years. Indices of local carotid stiffness (intima-media thickness IMT, Diameter end-diastole and Distension) were measured by echotracking. Regional aortic stiffness (carotid-femoral and carotid-radial Pulse Wave Velocity, cfPWV and crPWV, respectively) was measured using mechanotransducers. Circulating desphospho-uncarboxilated matrix Gla-protein (dp-ucMGP) and acute phase markers Interleukin-6 (IL-6), high-sensitive C-reactive protein (hsCRP), tumor necrosis factor-alfa (TNF-alfa) and markers for endothelial dysfunction Vascular Cell Adhesion Molecule (VCAM), E-selectin, and Advanced Glycation Endproducts (AGEs) were measured. After three years of MK-7 supplementation, cfPWV and the Stifness Index beta significantly decreased in the total group and distension, compliance, distensibility, and the local carotid PWV (cPWV) improved in women having a baseline Stifness Index beta above the median of 10.8.
Mk-7 decreased dp-ucMGP by 50% compared to placebo, but did not influence the markers for acute phase and endothelial dysfunction. MK-7 supplementation in this study lowered serum uncarboxylated osteocalcin (ucOC) levels, a marker for vitamin K status of bone, to a similar extent as circulating dp-ucMGP and this is indicative for comparable uptake of MK-7 by bone and arteries. The authors concluded that long-term use of MK-7 supplements improves arterial stifness in healthy postmenopausal women, especially in women having a high arterial stiffness. **(90) Thrombosis and Haemostasis 2015 vol. 113 pp. 1135-1144)** In a very interesting study, although a small study (55 patients), was evaluated warfarin management with INR **S**elf-**T**esting and **O**nline **R**emote **M**onitoring and **M**anagement **(STORM$_2$)** plus low-dose vitamin K. All patients performed weekly INR self-testing and received vitamin K 100 microgr./day and online anticoagulation management for 1 year. An analysis of warfarin dosing and INR stability by genetic polymorphisms subgroup (vitamin K epoxide reductase complex 1 [VKORC1] and cytochrome P450 2C9 isoenzyme) was performed and vitamin K product content was also analyzed. The percentage of time that the INR is within the time in therapeutic range (TTR) improved from 56% before the intervention to 81% after the intervention (25% improvement) and time spent at extreme INR values of lower than 1.5% or higher than 5 was reduced from 3.1% to 0.4%. Genetic polymorphisms did not correlate with INR stability or the increase in warfarin dose after vitamin K supplementation. The content of the vitamin K product was only 34-76% of the labeled amount. Patients with the GG VKORC1 genotype required a higher daily warfarin dose than the dose prescribed by the genomic-based chart included in the warfarin package.
The ClotFree system, used for patient management and data collection, is an online virtual clinic through which patients report their INR and warfarin dosage, and answer questions relating to signs and symptoms of bleeding or clotting, changes in medications or supplements, and changes in their lifestyle (diet, alcohol use, exercise). Information is communicated in writing and captured in a secure, encrypted progress note. ClotFree provides several color-coded alerts. For example , an increase in the dose of warfarin or the INR is displayed in red, whereas a decrease in either value is

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displayed in green. In this manner the clinician can quickly identify trends in either value and adjust the dose preemptively. Also interacting drugs are displayed in a color-code fashion to help identify the more significant drug interactions, and red-letter messages warn the clinician if he or she enters a dose change more than 20% or if the patient reports a dosing regimen different from the previously prescribed regimen. Analysis by genetic subgroups failed to show a correlation with either the change in warfarin dose after vitamin K supplementation or INR stability and this was probably due to the lower than intended dose of vitamin K supplementation. The exclusion criteria were a life expectancy of less than 1 year, a diagnosis of antiphospholipid antibody syndrome, pregnancy, or known human immunodeficiency virus or acquired immunodeficiency syndrome. Recent bleeding or thrombosis events were not exclusion criteria. **(91) (Pharmacotherapy 2013 vol. 33 (11) pp. 1136-1146)** Center-specific TTR (c-TTR) is a measure reporting the mean patient TTR within an anticoagulation clinic describing the quality of anticoagulant monitoring offered by that clinic. c-TTR has a considerable between-center variation, and this requires an effort to evaluate determinants of quality of anticoagulation clinics performance. For this reason, the Italian Federation of Anticoagulation Clinics (FCSA) endorsed a program of VKA treatment quality monitoring since 2009. In this study, the median c-TTR was 67.9% in the year 2013. Interestingly, also in this study which analyzed data from 832,204 individual patients followed for VKA therapy in 292 centers affiliated with the Italian Federation of Anticoagulation Clinics (FCSA) there was a trend toward an increase in c-TTR over the five-year study period, suggesting that participating in an external quality assessment of therapy may improve the Center performance. The authors showed that a significant improvement in Center performance is attained by reducing the time to the next control to 30% of the average interval, corresponding therefore to no more than one week. **(92) (PLoS ONE 2015 vol. 10 (12) pp. e0144314)** Prompt repeat testing after an out-of-range INR values is associated with better anticoagulation control at the site level and could be an important part of a quality improvement effort for oral anticoagulation. In particular follow-up within 1 week after a high or a low INR appears to be ideal. **(93) (Circulation Cardiovascular quality and outcomes 2011 vol. 4 (3) pp. 276-282)** To obtain optimal benefits of anticoagulation control, patients need to be mantained within their international normalized ratio reference range, which requires regular monitoring and appropriate modification of treatment. In anticoagulated atrial fibrillation patients, time in therapeutic range and percentage of international normalized ratios in range effectively predict international normalized ratio control, and data from retrospective studies support the use of time in therapeutic range to accurately predict reductions in adverse events across populations. A small increment in time in therapeutic range (6.9%) can be translated to approximately 10 less major haemorrhagic and 6 less thromboembolic events per 1000 patients per year with a significant impact on both morbidity and healthcare costs. The authors conclude that anticoagulation services should aim for a time in therapeutic range between 70% and 80% to optimize patient benefit and minimize harm. **(94) (Circulation Cardiovascular quality and outcomes 2008 vol. 1 (2) pp. 84-91)** In a study which evaluated the introduction of a computerised dosing assistance within the Swedish National quality register AuriculA significantly increased TTR from 64.3% to 71.3% in centre 1 and maintained a high TTR in centre 2 that already had a TTR of 73.6% before the implementation and after had a TTR of 74%. The introduction of AuriculA shortens the mean time period between the INRs taken at the centre significantly. In both

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centres, after the introduction of AuriculA, INR tests were prescribed significantly more frequent and in particular 20% more often at centre 1 and 21% more often at centre 2 corresponding to 6.8 and 4.2 more INR tests per treatment year. **(95) (European Journal of Medicine 2012 vol. 23 pp. 742-744)** In a large, nationally representative cohort of patients with atrial fibrillation, Lind and collegues showed that INR variability has a relationship with mortality, stroke, bleeding and hospitalization. Variability of INR is described by Standard Deviation (SD) of transformed INR (SDT_{INR}) and is a better predictor of clinically important outcomes than the time in the therapeutic range of INR 2.0-3.0 (TTR). The SDT_{INR} was a significantly better predictor for all four studied endpoints; mortality, stroke, bleeding and hospitalisations. The authors suggest that SDT_{INR} should have a role in monitoring patients with atrial fibrillation on warfarin therapy, as well as in assessing the quality and performance of anticoagulation clinics, and as a potential endpoint in clinical trials. (for details, how to calculate statistically the SDT_{INR} see the original article). The authors demonstrated that the predictive power of the SDT_{INR} for mortality is 8 times greater than that of the TTR. The SDT_{INR} was associated with 59% increase in the relative risk of mortality per one SD unit, whereas the TTR was associated with only 19% increase per one SD unit and for stroke it was associated with 30% increase per one SD unit and only 6% for the TTR. In addition , the strongest evidence for the superior performance of the SDT_{INR} as a predictor of clinical outcomes was the fact that TTR was no longer significant when both metrics were included in the same analysis, whereas the SDT_{INR} was highly significant. The SDT_{INR} is better than TTR in assessing whether the titration of warfarin dosing is successful in optimizing patient outcomes. Because the TTR and the SDT_{INR} are too complex to calculate in clinical practice, they need to be automatically computed using computer software, and then displayed to the clinician at regular clinical visits and if it is high, it indicates a need of more frequent monitoring of INR. The authors conclude that the SDT_{INR} is a more powerful predictor of clinical outcomes in patients with atrial fibrillation on warfarin therapy than the current standard TTR and can be reduced by more frequent (weekly) INR measurements. **(96) (Thrombosis Research 2012 vol. 129 pp. 32-35)** In a Danish study, Nielsen and collegues retrospectively validated a dynamic statistical method providing dosage suggestions to patients in warfarin treatment. The model was validated on a cohort of 533 patients achieving a TTR of 83%. Patients in the cohort were self-monitoring and managed by a highly specialised anticoagulation clinic. The predictive model consists of three parts : 1) INR history, 2) warfarin dosage and 3) biological noise. It takes warfarin intake and INR values as inputs, and uses an individual sensitivity parameter to model response to warfarin intake. The model is fully specified and discussed in details in a published paper. **(97) (Computer Methods and Program in Biomedicine 2013 vol. 110 Issue 3 pp. 380-388)** The authors point out that certain aspects of the potential performance of their model-suggested dosages cannot be evaluated, due to the retrospective study design. It should be investigated if replacing the currently used algorithm with the presently discussed algorithm would imply an increased number of possibly unnecessary dose changes, hereby risking oscillating warfarin and INR series. It is necessary to organize a well designed randomised clinical controlled trial comparing the existing algorithm with the presently discussed, keeping the administrative OAT set-up unchanged. **(98) (Thrombosis Research 2014 vol. 133 pp. 375-379)** The quality of treatment with vitamin K antagonists and clinical outcome during the 90 days after extreme overanticoagulation (EO) in a large cohort of patients with atrial fibrillation and with venous

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thromboembolism was evaluated in a study by a Dutch group. Extreme overanticoagulation (EO) was definied as international normalized ratio (INR) > / = 8.0 and/or unscheduled vitamin K supplementation. Of 14,777 initially stable patients, 800 patients developed EO. The authors compared the 90 days pre and post EO. The pre-period was characterised by frequent overanticoagulation, and half of EO patients had an inadequate iTTR(< 65%). After EO, underanticoagulation became more prevalent and although the mean time between INR-measurements decreased from 18.6 to 13.2 days, indequate iTTR became more frequent (62%). Compared to controls, patients with extreme overanticoagulation had a significantly lower iTTR despite intensified INR-monitoring, and a long-term increased risk for bleeding events, thrombotic events and VKA-related deaths after extreme overtanticoagulation. **(99) (Thrombosis and Haemostasis 2015 vol. 113 pp. 881-890)** A recent European consensus document recommends that an average individual time in therapeutic range (TTR) should be > 70% for optimal efficacy and safety outcomes whilst on Vitamin K Antagonists (VKA) treatment and this is also recommended in the European Guidelines. **(100) (European Heart Journal 2012 vol. 33 pp. 2719-2747)** In the National Institute for Health and Care Excellence (NICE) guidelines, a TTR of > 65% is recommended for patients with Atrial Fibrillation who are on VKA treatment. **(101) (http://guidanceniceorguk/CG180 2014)** As a consequence, poorly controlled VKA-therapy patients would beneficiate from switching to anticoagulant therapy with NOACs, especially if they were experienced VKA patients. For what concern anticoagulation-naive patients, normally is used a criterion that consists in a trial of VKA to see what the TTR value is at 6 months, with a NOAC only allowed if TTR < 65%. **(102) (Agencia Espanola de medicamentos y de productos sanitarios 2013) (54) (Canadian Family Physician 2015 vol. 61 pp. 23-24)** However it has been objected that in patients who initiate oral anticoagulant therapy with vitamin K antagonists, more INR fluctations occur during the first 3 months, resulting in a higher risk of thromboembolic and haemorrhagic events. In fact a number of studies have demonstrated that the risk of bleeding on anticoagulant therapy is highest during the period immediately warfarin is initiated. Similar to major hemorrhage, the incidence of stroke is also time-dependent. The highest risk of stroke exists at the time of initial presentation with atrial fibrillation. **(103) (Thrombosis and Haemostasis 2010 vol. 104 pp. 1099-1105)** In another paper published recently, patients initiating warfarin had a two-fold increased risk of stroke in the first 30 days of use suggesting the possibility of a hypercoagulable state at the start of treatment. On the contrary, warfarin was strongly associated with a decreased risk of ischemic stroke in patients who have used warfarin for more than 30 days. This paradoxical procoagulant effect of warfarin observed in the early days of the treatment is biologically plausible. While warfarin blocks the activation of clotting factors II, VII, IX, and X, it also deactivates protein C and protein S. Protein C has a short half-life (8 hours) and the rapid depletion of this protein can theorically lead to a transient hypercoagulable state. This hypothesis is supported by the increased risk observed in the first 7 days of treatment and this is also concordant with the time of onset of warfarin-induced skin necrosis. Additional well-conducted studies are needed to confirm these findings and to find out whether a heparin bridging strategy at the initial phase of the treatment reduces this risk. **(104) (European Heart Journal 2014 vol. 35 pp. 1881-1887)** In a recent published paper, a nationwide cohort study with the use of the French medico-administrative databases (SNIIRAM and PMSI) included patients with nonvalvular atrial fibrillation who initiated

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dabigatran or rivaroxaban between July and November 2012 or VKA between July and November 2011. The population was composed of 19713 VKA, 8443 dabigatran, and 4651 rivaroxaban new users. Patients were followed for up to 90 days until outcome, death, loss to follow-up, or December 31 of the inclusion year. All dabigatran, rivaroxaban, and their VKA-matched-treated patients, 55 and 122 and 31 and 68 bleeding events and 33 and 58 and 12 and 28 arterial thromboembolic events were observed during follow-up, respectively. After matching, no statistically significant difference in bleeding or thromboembolic risk was observed between dabigatran and VKA new users and between rivaroxaban and VKA new users during the early phase of therapy. The same level of caution is therefore required when initiating either NOACs or VKAs, particularly in view of the absence of a NOAC antidote commercial available for direct Xa inhibitors and objective monitoring of the extent of anticoagulation. **(105) (Circulation 2015 vol. 132 pp. 1252-1260)** To understand which AF patient will benefit of warfarin treatment reaching a TTR > 65%, Apostolakis et al. proposed and validated the SAMe-TT_2R_2 score [**S**ex (female) 1 point, **A**ge (< 60 years) 1 point, **M**edical history (definied as more than two of the following : hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), **T**reatment (interacting drugs such as amiodarone for rhythm control) (all 1 point), as well as current **T**obacco use (within 2 years) (2 points) and **R**ace (non-Caucasian : 2 points) ; Maximum points : 8. Patients who will obtain a good TTR will have a SAMe-TT_2R_2 score = 0-1 and conversely, those with a SAMe-TT_2R_2 score > / = 2 would be at risk of suboptimal anticoagulation control. **(106) (Chest 2013 vol. 144 (5) pp. 1555-1563)** This score was validated on retrospective cohorts. Poli and collegues applied it to 1,089 patients with AF on VKAs followed by two anticoagulation clinics. There was a significant decline in mean or median TTR in relation to the SAMe-TT_2R_2 . When the SAMe-TT_2R_2 scores were categorized, they found a TTR 74% for score < / = 2 and 68% for score > 2 . The rate of major bleeding events and stroke/TIA was 1.78 x 100 patient-years and 1.26 x 100 patients-years, respectively. No relationship exists between the SAMe-TT_2R_2 score and adverse events. The authors conclude that this score in AF patients, despite an overall good quality of anticoagulation, is able to identify the patients who are less likely to do well on VKA therapy. **(107) (Internal and Emergency Medicine 2014 vol. 9, Issue 4, pp. 443-447)** Lip and collegues evaluated a cohort comprised of 8,120 patients, among whom 4,637 patients were receiving VKA. A significantly higher mean SAMe-TT_2R_2 score was seen in patients with labile INR while taking VKA. A limitation of this study is that the criteria used for labile INR were based on physician diagnosis and not on traditional equation-based calculations of TTR, such as the Rosendaal method. In patients treated with a VKA, a higher mean SAMe-TT_2R_2 score was also found for patients in whom stroke/TE (P<.0001), severe bleeding (P<.0001), or Bleeding Academic Research Consortium (BARC)-definied major bleeding (P<.0001) developed and death occurred (P=.001) during follow-up. There were no significant differences in SAMe-TT_2R_2 score for these events among patients not treated with a VKA. Another limitation of this study is the fact that the dataset is based on a hospitalized cohort of patients with AF, and the data may not be generalizable to the wider nonhospitalized AF population. A comparison of patients taking VKAs with an SAMe-TT_2R_2 score of 0 to 2 (low-moderate risk) with those with a score > 2 (high risk of poor TTR) using Kaplan-Meyer analysis showed a significant increase in risk of severe bleeding events, and major BARC bleeding. The differences were nonsignificant for stroke/TE and death. Among the

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patients receiving VKAs, the SAMe-TT_2R_2 score was modestly predictive of labile INRs as well as of stroke/TE, severe bleeding, major BARC bleeding, and death. This did not happen for patients not taking VKAs.
In conclusion, the mean SAMeTT_2R_2 score was higher in patients who did have adverse events versus patients who did not have them, but only among those who were taking VKAs. This score predicts poor TTR, which leads to adverse events but does not otherwise directly predict adverse events. **(108) (Chest 2014 vol. 146 (3) pp. 719-726)** In a cohort of 972 consecutive patients with nonvalvular atrial fibrillation, treated with acenocumarol, who were clinically stable at study entry, with an INR between 2.0 and 3.0 during the previous 6 months, a high SAM2TT_2R_2 score, reflecting poor anticoagulation control with poor time-in-therapeutic range (TTR) was associated with more bleeding, adverse cardiovascular events, and mortality during follow-up. Clearly the fact that patients at study entry were clinically stable, so unstable patients who are more prone to have adverse events were excluded and, in addition, the selection of anticoagulation experienced patients with proven adherence and good anticoagulation control during the 6 months before inclusion, are important selection bias because patients with erratic anticoagulation were excluded from the analysis. In this cohort of patients the anticoagulation control was optimal, and therefore, only few major bleeding events occurred during follow-up with a rate of 3%/year. However, the authors found that the SAMe-TT_2R_2 score was still able to predict which patients were prone to subsequent instability and poor international normalized ratio control, even among previously anticoagulated patients, with good time in therapeutic range at inclusion. **(109) (The American Journal of Medicine 2014 vol. 127 pp. 1083-1088)** For what concerns the SAMe-TT_2R_2 score, Zhang and collegues observe that to develop and validate this score were used data of 2080 patients in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, such as sex female, age < 60 years, medical history (more than two comorbidities), treatment (interacting drugs such as amiodarone for rhythm control), tobacco use (2 points), race (2 points), but not other important parameters such as VKA inception status, alcohol abuse, and genotype, that have been identified as important predictors of quality of anticoagulation control. In addition, the AFFIRM cohort study included patients with valvular AF or patients with nonvalvular AF. However the quality of anticoagulation control in patients with valvular AF might be very different from those with nonvalvular AF. The other observation of these authors is that in the article by Apostolakis et al. about SAMeTT_2R_2 score, TTR was measured using the fraction of international normalized ratios (INRs) within the therapeutic range in the AFFIRM population, and by Rosendaal linear interpolation method in the external validation cohort, which would bias the SAMe-TT_2R_2 score. **(110) (Chest 2013 vol. 145 (2) pp. 418-419)** Some other variables not mentioned in the article, including whether INRs were obtained in the first month after VKA treatment **(111) (PLoS ONE 2012 vol. 7 (9) : e42269)** and whether there were gaps of > 56 days between INR tests, **(112) (Chest 2013 vol. 143 (3) pp. 751-757)** may also influence the results and bias the model. In addition, anticoagulation control varied extensively among different study settings and may be affected by different factors. **(113) (BMC Health Service Research 2013 vol. 13 : 85)** Zhang and collegues observe that in the article of Apostolakis et al., although the scheme was externally validated in a "real word" registry, the number of patients seems to be not large enough (n=286) to test performance of the score. For this reason these authors support a validation of the SAMe-TT_2R_2 score

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in a larger cohort in clinical practice and in different populations.Another consideration is that the score showed good discrimination performance for patients in the external validation cohort in the fifth TTR percentile, but poor performance for the 10th and 25th percentiles. **(110) (Chest 2013 vol. 145 (2) pp. 418-419)** Apostolakis et al. reply that they aimed to develop a simple user friendly tool to assist decision-making when oral anticoagulation is considered in patients with atrial fibrillation, but they agree that further work may be needed to validate their score in larger real-life databases. They write that their goal was not to consider all potential confounders that could affect TTR, but to identify those common clinical factors that were most influential, measurable, and accessible. In their study they want to consider long-term management of warfarin anticoagulation and not short term fluctuations that may occur in the first month. They conclude that until alternative efficient approaches are found, their score and clinical judgement are the only available options to decide to use VKA or alternative anticoagulant treatment. **(114) (Chest 2013 vol.145 (2) pp. 419)** Skoc and collegues applied the SAMe-TT_2R_2 score to patients with atrial fibrillation (n=182) in whom the average TTR was 76% in 1 year of follow-up. The average age was 70.2 years , and 54 patients were women. The population only included whites, resulting in a maximal SAMe-TT_2R_2 score of 6 points. A total of 77 patients had a SAMe-TT_2R_2 score of >/= 2. Interestingly, the TTRs of these patients were the same as those with a SAMeTT_2R_2 score of 0 to 1 (76%). A linear regression model of the variables included in the SAMe-TT_2R_2 score had a very low prediction of TTR in their study population, with only young age and amiodarone use reaching statistical significance. These and other two variables such as alcohol consumption and perceived stress seemed to be related to TTR. The authors conclude that in a high-quality setting, the SAMe-TT_2R_2 score was not predictive of TTR. The results from their study are limited by a small cohort from a single Danish center, and other multicenter studies of high-quality anticoagulation clinics are needed to identify better patient-related predictors of poor INR control. This score may be modified or expanded with additional variables, such as alcohol consumption or perceived stress, to become an important tool for allocating patients to the proper anticoagulant treatment. **(115) (Chest 2014 vol. 145 (1) pp. 187-188)** Apostolakis and collegues replied that first of all, the SAMeTT_2R_2 was not developed to predict TTR, as Skov et al. suggest, but was developed to identify anticoagulation control "outliers" within an anticoagulation population. In addition they write that in their cohort, the SAMeTT_2R_2 score performed well in identifyng patients with average TTRs below the fifth or the 10th percentile of the center's average and encourage Skov et al. to measure the predictive performance of the SAMeTT_2R_2 score in identifyng patients with TTR less than the fifth or the 10th percentile of their center's average, although their sample size is small. Also, the study by Skov et al. may not detect differences in TTR among subpopulations. **(116) (Chest 2014 vol. 145 (1) pp. 188-189)** In fact they suggest that female sex is associated with numerically better TTR, but similar to the study of Apostolakis et al., also in the Veterans Affairs Study to Improve Anticoagulation (VARIA) some investigators concluded that in a much larger cohort, female sex, minority status, and multiple comorbidities negatively affected TTR. **(117) (Journal of Thrombosis and Haemostasis 2010 vol. 8 (10) : 2182-2191)** Other studies (unpublished data) of Apostolakis et al. in substantially larger populations (N > 1000) show the utility of the SAMeTT_2R_2 score even in cohorts with overall median TTR of 73%,**(116) (Chest 2014 vol. 145 (1) pp. 188-189)** as well as the relation of a high SAMeTT_2R_2 score > 2 to thromboembolism and bleeding, reflecting a poor TTR. **(109) (The**

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American Journal of Medicine 2014 vol. 127 pp. 1083-1088) In conclusion, Apostolakis et al. agree with Skov et al. that in exceptionally efficient centers with average TTR of 75%, the use of SAMeTT2R2 score to help decision-making is probably less likely to be required. **(116) (Chest 2014 vol. 145 (1) pp. 188-189)** Although validation studies on the $SAMeTT_2R_2$ score have been performed on retrospective cohorts, this score needs validation in a contemporary prospective population of AF patients who were initiating OAC with a VKA. In addition, this score has only been evaluated in patients with AF and not in patients with venous thromboembolism (VTE), where rhythm control drugs did not play any role, and clinical risk factors may be different. If VKAs are used, all efforts should be directed to achieve and maintain a high TTR. On the other hand, all efforts should also be made in identifyng those patients who may benefit from NOACs treatment, avoiding the " trial of VKA" because of an increased risk of thromboembolism during the initial period whether TTRs are suboptimal **(118) (Thrombosis and Haemostasis 2015 vol. 113 (4) pp. 671-672)** although the French nationwide cohort study cited above, demonstrated that the same level of caution during the initial period of anticoagulation therapy must be observed with NOACs and with vitamin K antagonists because of the same incidence of bleeding and thrombotic events observed during this period with these two classes of therapeutic agents. **(105) (Circulation 2015 vol. 132 pp. 1252-1260)** For what concerns the PT, prior studies have indicated that the antithrombotic effect of FVII is of minor importance compared to the activity of FX and, in particular prothrombin. **(119) (Thrombosis and Haemostasis 1989 vol. 62 pp. 788-791)** In addition, factor VII does not start to prevent thrombin generation until levels are well below 5%. **(120) (Haemophilia 2004 vol. 10 pp. s180-183)** Since factor VII has the shortest half-life (4-6 hours), compared with prothrombin (42-72 hours) and factor X (27-48 hours), fluctuations in the PT may reflect FVII activity changes rather than a true change in antithrombotic effect. This consideration has important therapeutic implications because measuring prothrombin alone as native prothrombin antigen by ELISA, more accurately reflects the antithrombotic effect of VKA than does the PT. **(121) (Circulation 1993 vol. 88 pp. 454-460)** Some authors compared the effect of vitamin K dependent coagulation factors on PT and also on rotational thromboelastomeric (ROTEM) parameters. The PT was equally sensitive to reductions in factors II, VII or X but ROTEM parameters correlated poorly with the PT in anticoagulated patients' plasmas. ROTEM is a global coagulation assay usually done using whole blood. Whole blood ROTEM results are a function not only of coagulation factors but also of platelet function, proteases, inhibitors and fibrinolysis. ROTEM parameters were more affected by mild and moderate reductions in FII or FX than by FVII or FIX which had little influence except at very low coagulant activity. These authors developed a modified PT that was sensitive only to reductions in factors II and X. This modified PT obtained using factor II and X depleted plasma mixed into the test plasma to correct for any factor deficiency other than FII or FX is called Fiix-PT (Fiix-INR) and correlated well with PT (INR) but the Fiix-INR fluctuated less than the INR in an anticoagulated patient reflecting its insensitivity to FVII. The ROTEM results suggest that mild to moderate reductions in factors II or X are more important during clot formation than factors VII or IX. Reductions in FII and X may better reflect anticoagulation with VKA than FVII or IX. The prothrombin time is equally sensitive to a reduction in each of coagulation factors II, VII, and X, but not to reductions in factor IX that occur during vitamin K antagonist treatment. Rapid changes in factor VII activity during initiation and following dose changes of VKA, may exaggerate a fluctuation

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in prothrombin time (INR) that does not influence the antithrombotic effect or risk of bleeding. This may lead to unnecessary dose changes, too frequent monitoring tests and further fluctuation. This confounding effect of factor VII can be circumvented by monitoring VKAs treatment with the Fiix-PT which is not influenced by factor VII and is sensitive to reductions only in factors II and X. This Platelet Poor Plasma (PPP) based test more accurately reflects the anticoagulant effect of VKA than do the currently applied INR tests. It was done by correcting all deficiences other than those of factors II and X by mixing factor II and X-depleted plasma with the test sample prior to measuring the PT. **(122) (Thrombosis Research 2012 vol. 130 pp. 674-681)** The Fiix trial was a single centre, double blind, prospective, non-inferiority, randomised controlled clinical trial in an anticoagulation management centre at The National University Hospital of Iceland, Reykjavik, Iceland. Ambulatory adults on warfarin treatment with an INR target of 2-3, managed by an anticoagulation dosing service using software-assisted dosing (DAWN anticoagulation software, 4-S, Milnthorpe, UK) were eligible for inclusion in this study. Patients were randomly assigned (1:1) to either the Fiix-PT monitoring group or the PT monitoring group by block randomisation without a stratification procedure. A blinded research INR (R-INR) based on results of the respective test was reported to the dosing staff. Patients were contacted by a study nurse at 4-week intervals to know information about thromboembolism or bleeding events. The primary efficacy outcome was a composite of non-fatal and fatal arterial or venous thromboembolism, including myocardial infarction and transient ischemic attacks, assessed in all eligible patients who were randomised (intention-too-monitor population). The safety endpoint was major bleeding or other clinically relevant bleeding, assessed in the per-protocol population. The authors assumed a 3% annual thromboembolism incidence and a non-inferiority margin of 2.5%. The number of participants needed to show statistical non-inferiority of clinically important events for the test method with an 80% certainty per year observation was 576 patients in each group. The patients enrolled were 1156, between March 1, 2012, and February 28, 2014. 573 patients were assigned to Fiix-PT and 575 to PT-INR monitoring after exclusion of four patients from each group for various reasons. Median follow-up was 1.7 years. The average CHA_2DS_2-VASC scores were similar in patients with atrial fibrillation in both groups, mean 2.9 and median 3.0 in the Fiix-PT group and 3.0 and 3.0 in the control group, supporting a similar thromboembolism risk in both study groups. The automated STA-R Evolution coagulation analyser (Diagnostica Stago, Asnières, France) was used for both tests which used in-house standardisation of the thromboplastin sensitivity index (ISI) with ISI calibrators and control plasma (Danish Insitute for External Quality Assurance in Health Care, Glostrup, Denmark). The calibrator is designed for PT standardisation but not for Fiix-PT standardisation. The maximum recommended interval between monitoring tests was 6 weeks. **(123) (Lancet Haematology 2015 vol. 2 pp. e231-240)** The percentage of time that each individual spent within the INR target range was calculated using the Rosendaal formula. **(35) (Thrombosis and Haemostasis 1993 vol. 269 pp. 236-239)** The Variance Growth Rate (VGR) was calculated as an indicator of INR variability between tests (B2 method) **(51) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1540-1546)** In the primary analysis of thromboembolism events occurring during days 1-720, thromboembolism occurred in 10 patients in the Fiix-PT group (incidence of 1.2% per patient-year) versus 19 (2.3% per patient-year) in the PT group. The occurrence of ischaemic strokes (including transient ischaemic attacks) alone or myocardial

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infarction alone was also non-inferior. In a secondary analysis, that was not prespecified but based on the observation that a difference emerged after 6 months, the authors excluded the first 6 months after randomisation from analysis. In this analysis, Fiix-PT monitoring led to a significant long-term reduction in thromboembolism, 6 versus 15 cases (1.1% versus 2.2% per patient-year). Major bleeding occurred in 17 of 571 patients in the Fiix group (2.2% per patient year) versus 20 of 573 patients in the PT group (2.5% per patient year). Unlike thromboembolism, the incidence was consistent and showed no divergence after 6 months. In particular, despite the small number of events, Fiix-PT was also non-inferior to PT in the frequency of gastrointestinal bleeding, intracranial haemorrhage and intracerebral haemorrhage. Twelve patients died in the Fiix-PT group (1.45% per patient-year) versus 16 (1.92% per patient-year) in the control group. Composite major vascular events occurred in 27 patients in the Fiix group compared with 39 in controls. In the secondary post-hoc analysis beyond 6 months of Fiix-PT monitoring although significantly fewer major vascular events occurred in the Fiix-PT than in the PT group, the incidence of combined composite major vascular events and deaths from any cause did not differ significantly between the two groups. In a subgroup analysis of patients with atrial fibrillation, 10 arterial thromboembolic events (1.63% per patient-year) occurred in the Fiix-PT group versus 17 (2.7% events per patient-year) in the PT group. In the secondary analysis of thromboembolism beyond the first 6 months in participants with atrial fibrillation, 6 events occurred in the Fiix group (1.4% patient-year) versus 14 (3.2% per patient-year) in the PT group. Major bleeding occurred in 14 participants with atrial fibrillation in the Fiix-PT group (2.5% per patient year) and 15 (2.5% per patient year) in the PT group. Dose change frequency was reduced with Fiix-PT monitoring, particularly long term (after day 180), with no significant differences in the first 6 months. The median daily warfarin dose was identical in both groups (4.7 mg). With long term Fiix-PT monitoring (180-720 days), monitoring tests were reduced by 5.8%. Fewer tests with an INR less than 2.0 occurred in the Fiix-PT group. The median percent time in range in the control group was 81%, 80%, 81% and 79% during four consecutive 6-month observation periods, whereas in the Fiix-monitoring group the median percent time in range was 85%, 85%, 80% and 87%, respectively. INR fluctuation measured as variance growth rate was significantly higher in the PT group than in the Fiix-PT group. Patients with major events had a higher variance growth rate than did those without major events. When was used a new batch of the DEKS ISI calibrator the median Fiix-INR was 0.2 points higher than previously, despite control samples were within limits, whereas the PT-INR did not change. When the old batch DEKS calibrator was used again to recalibrate ISI, the median Fiix-INR returned to the previous levels. The authors correctly affirm that a special Fiix-INR calibrator will probably be needed. The fact that the clinical effect of improved anticoagulation stability only becomes evident after 6 months of Fiix-PT monitoring, could be explained by the lower variance growth rate (VGR) in the Fiix-PT group **(123) (Lancet Haematology 2015 vol. 2 pp. e231-240)** because a high variance growth rate has been retrospectively shown to be predictive of clinical events 3-6 months later. **(51) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1540-1546)** Onundarson and collegues correctly point out that in all trials that compared direct oral anticoagulants with warfarin the TTR was not high enough (58-65%) and this inevitably exaggerates the reported benefit of direct oral anticoagulants. Interestingly, the absolute incidence of total arterial thromboembolism in this study, in patients with atrial fibrillation monitored with Fiix-PT was lower than in the direct oral

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anticoagulation studies and the low major bleeding incidence, including intracranial haemorrhage incidence, compared favourably with direct oral anticoagulants. " Improved stability of warfarin management with Fiix-PT, with resulting improved long-term outcome and a low bleeding incidence could therefore lead to less impetus to switch patients to the unmonitored and more expensive direct oral anticoagulants". Because the protocol used for dosing warfarin in the Fiix-PT group was designed for the fluctuating PT-INR, may be that the dosing staff responded to the masked Fiix-INR with unnecessary dose adjustements that probably caused a bias in favour of the PT group. After this consideration,it is possible to suggest that even further improvements, better than those reported in this study, could be achieved with the Fiix-INR. **(123) (Lancet Haematology 2015 vol. 2 pp. e231-240)** Gudmundsdottir and collegues measured Vitamin K dependent coagulation factors (VKD) in plasma obtained from patients on stable warfarin anticoagulation and during the first days of warfarin treatment monitored either with the Fiix-PT or the PT. All the samples had been drawn from patients during very stable warfarin treatment (INR within range 2-3 for over 10 months by serial monitoring). Serial samples were also obtained from 10 patients in each group during days 1-30 of warfarin initiation. The median (95% range) VKD factors per cent coagulant activity was as follows in the stable Fiix-group vs the stable PT-group : FII 28 (19-40) vs 25 (18-40), FVII 48 (30-88) vs 42 (23-85), FIX 66 (41-85) vs 61 (36-79), and FX 15 (11-17) vs 15 (10-22). In patients starting on warfarin a stable Fiix-INR (definied as two INRs within target range) was reached on day 14 (median) in the Fiix group vs a stable PT-INR on day 11 in the PT controls. Following this, however, the PT-INR fluctuates more out of the INR target range than the FIIx-INR does. The FVII level decreases to a nadir of 20% in the Fiix group compared to a nadir of 30% in the PT monitoring group. Subsequently FII, FVII and FX fluctuate less in the Fiix-PT group than in the PT group. During the first 30 days 46% of Fiix-INRs in the Fiix-group were within target range vs 29% of INRs in the controls. Also during the initiation period FII was 47% vs 30% within the 95% stable range established for the PT method, FVII 60% vs 73%, FIX 41% vs 36%, and FX 51% vs 38% respectively. Interestingly, " the more fluctuating INR in the PT group is also reflected by a rollercoaster like pattern of warfarin dosing as opposed to the more cascade like pattern that is observed in the Fiix group". **(124) (56th ASH Annual Meeting December 6-9 2014, Blood)** Recently a single test, the dilute FiiX-Prothrombin Time (dFiiX-PT) (see above) using a single high Thromboplastin final dilution of about 1:1200 of the particular thromboplastin used can be used to determine the INR and also the concentrations of warfarin,dabigatran, rivaroxaban, apixaban, Unfractioned Heparin (UFH) and enoxaparin but not fondaparinux in plasma samples. Dabigatran and rivaroxaban plasma levels above 200 ng/ml have been shown to increase risk of bleeding. The dFiiX-PT assay provides an estimation of dabigatran, rivaroxaban and apixaban in the range of 30-200 ng/ml, but at higher concentrations are needed sample dilutions with normal plasma. The test can be easily automated using standard coagulation equipment and for this reason could be applied in clinical practice as a first screening test to evaluate plasma levels of the three DOACs analyzed and warfarin. The results could be reported either based on calibration curves or as seconds. Interestingly, the authors point out that measuring a simultaneous INR, a thrombin time (TT) and a repeat dFiiX-PT after mixing the test sample 1:1 with normal plasma could lead to easily identify the class of anticoagulant drug present when it is not possible to obtain a correct history. A prolonged TT would indicate the presence of a direct thrombin inhibitor and not of a direct Factor Xa inhibitor and an uncorrected

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mixing study would identify the presence of a direct acting inhibitor and not a factor deficiency. Knowing what drug the patient was taking and using separate calibration curves for dabigatran, rivaroxaban apixaban, UFH and enoxaparin it is possible to express the drug concentration in ng/mL or in IU/mL. **(125) (Journal of Thrombosis and Haemostasis published online on March 30, 2016)** In a recent interesting study, Beinema and collegues, considering that one of the major problems of VKA dosing is that INR does not present linearity because is a ratio, developed a new dosefinding algorithm based upon a novel bidirectional factor (BF). This BF is the linear transformation of the nonlinear INR.It is definied as : BF = - (1-Ln (INR)). The BF represents a linear scale for the interpretation of the level of anticoagulant activity. The range of the BF is -1 to 1, with the optimal value of BF = 0.0 (2.72). BF values > 1 are possible because they correspond with INR values > 8. The BF can be adjusted for different INR target values. The equation for the target INR value of 2.5 is : BF = - (0.92 - ln(INR)) and the equation for the target value of 3.0 is : BF = - (1.10 - ln(INR)). With the use of the BF, VKA dose finding can be calculated with the following formula : ND (the new dosage) = PD (the previous dosage) - PD * SF (a stability factor) * BF **(126) (Journal of Thrombosis and Haemostasis 2016 vol. 14 (3) pp. 479-484)** There is a nonlinear exponential relation between the INR and the plasma level of the vitamin K dependent coagulation factors II, VII and X. This exponential relation implies that to increase the INR level from 1.0 to 2.0 it is necessary to reduce the activity of these factors of about 80%, whereas the difference in activity level between 4.0 and 5.0 is only 1.5%. **(127) (Biomedicine & Pharmacotherapy 2010 vol. 64 pp. 130-132)** The SF is an individual measure for the stability of the VKA doses and INR values over a certain period of time. The SF can be calculated on base of BF values over a predefinied period of time before the latest INR (BF) measurement. SF has a range between 0.6 (no stability) and 0 (stable). Examples of dose finding calculators can be found at the following website : **www.oookoook.com** The interval to the next INR measurement depends on the SF and the current BF (INR value). The SF can be used to calculate the maximum interval and the BF adjusts this interval. This algorithm can be easily incorporated into existing Computerized Decision Support system (CDS) and can be used for patients on long term VKA therapy, but also for new patients soon after initiation of VKA therapy. It was validated comparing the outcomes of the algorithm with the dosage advices of three large Dutch anticoagulant centres. Patients were treated with acenocumarol or phenprocoumon because warfarin is not available in Holland. Datasets were obtained from three centres over a period from October 2012 to September 2013. A total of 20892 records were considered suitable for analysis. The outcomes of the BF-N algorithm showed a good linear correlation with VKA doses of the three centres for acenocumarol and for phenprocoumon. Interestingly, the rate of automated dosage proposals increased to 100% compared with the percentage of automated dosages proposals of the current CDCs (51-73%). Although the new algorithm presented a very good correlation with the dosages performed by the experienced anticoagulation clinics, a standard deviation of 3.8 found by the authors means that in 95% the difference between the new and the old dosage proposals is less than 7.6%. Correctly the authors affirm that although this difference is small, small differences in prescribed dosages can result in significant differences in achieved INR and for this reason their algorithm needs to be evaluated in a prospective trial. In addition the calculation of the interval to the next INR needs to be evaluated too. Because the algorithm was tested for the VKAs acenocoumarol and phenprocoumon, but not for

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warfarin, and performed well for both drug, validation by a warfarin dataset must be performed. The authors point out that there is the possibility of failure of the method if the patient has several previous INR values, but is a new patient in the system, where the prior INR values are not known. They conclude that,although this new algorithm increases the rate of automated dosage proposals from less than 50% to more than 90%, a randomized prospective study is needed to investigate if this algorithm improves VKA dosefinding to a higher level of evidence. **(126) (Journal of Thrombosis and Haemostasis 2016 vol. 14 (3) pp. 479-484)**

Genetic variation has a clinically important impact on warfarin dose too. In fact some authors in a meta-analysis which included 8000 patients demonstrated that carriers of the CYP2C9 *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3 genotypes require warfarin doses that are 19.6, 33.7, 36.0, 56.7, and 78.1% lower than in carriers of the wild-type CYP2C9 *1/*1 genotype respectively. **(128) (European Journal of Clinical Pharmacology 2009 vol. 65 (4) pp. 365-375)** For what concerns the impact of VKORC1 gene polymorphism on warfarin dosage, some authors found that the VKORC1 1173CT and 1639GA heterozygosities carriers required about 50% higher warfarin doses than 1173TT and 1639AA homozygosities carriers. **(129) (Thrombosis Research 2010 vol. 125 (4) pp. e159-166)** Caldwell and collegues found that patients with 2 TT alleles of CYP4F2 require about 1 mg/day more warfarin than patients with 2 CC alleles. **(130) (Blood 2008 vol. 111 (8) pp. 4106-4112)** In a recent meta-analysis some authors found that for what concerns the impact of gamma-glutamyl carboxylase gene (GGCX) polymorphisms on warfarin dose requirement, the GGCX rs11676382 polymorphism may be one of factors affecting the dose of warfarin requirement mainly in Caucasians, although the effect of GGCX polymorphisms was lower than that of CYP2C9 and VKORC1 in influencing warfarin maintenance dose. **(131) (Thrombosis Research 2015 vol. 135 issue 4 pp. p739-747)**

It has been suggested that the antithrombotic effect of warfarin mainly results from the reduction in factors II and X as opposed to factors VII and IX. The in vivo half-lives of factors II and X are about 60 and 40 hours, respectively. Any reduction in factors II and X that produce a clinically significant antithrombotic effect would take at least 96 hours to manifest. Early elevations in the INR are likely secondary to reductions in factor VII because of relatively short half-life of factor VII (2-6 hours). For transitioning heparin or a Direct Thrombin Inhibitor (DTI) to warfarin treatment, it is suggested an overlap of at least 4 to 5 days that allow levels of factor II and X to decrease into therapeutic ranges. In addition, a 4 to 5 day overlapping bridge to warfarin treatment provides prophylaxis for thrombosis during the period that vitamin K-dependent anticoagulant protein C is acutely decreased because of its short half-life (6-10 hours). The INR is invalid for patients with liver disease because of associated coagulopathies involving clotting factors that are not dependent on vitamin K. (This aspect will be discussed in a future review about coagulopathy in liver disease) In addition, a subset of patients with LAC, patients who are switched from a Direct Thrombin Inhibitor (DTI) to warfarin and rarely, patients with extrinsic pathway coagulation factor deficiences or dysfibrinogenemia may have elevated INRs. For this reason, the therapeutic effect of warfarin will be difficult to assess with PT testing. Because LACs are antibodies against protein-phospholipid complexes that interfere with phospholipid-dependent coagulation reactions in vitro, LACs are frequently associated with prolonged aPTT or DRVVT. It can also prolong the PT, leading to INRs that do not accurately reflect the true level of warfarin anticoagulation. **(132) (American Journal of Clinical Pathology 2013**

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vol. 40 pp. 623-634)
In a small study in which were evaluated 68 outpatients positive for lupus anticoagulant and 57 control patients receiving long-term warfarin therapy, concomitant INR and chromogenic factor X activity were measured. Of the 44 control patients, 4 (9%) had an INR above 3.0 and none had an INR above 4.0. In contrast, 18 (39%) of the 46 patients with lupus anticoagulant had an INR above 3.0, and 5 (11%) had an INR above 4.0. The authors conclude that at least 10% of patients with lupus anticoagulant receiving long-term warfarin therapy may have falsely high INR values, which could lead to inappropriate warfarin dosage reduction and monitoring warfarin therapy by chromogenic factor X activity in patients with lupus anticoagulant avoids this INR artifact. **(133) Pharmacotherapy 2004 vol. 24 pp. 838-842)**
These patients may have recurrent clots despite being treated with warfarin and having a therapeutic INR. In such patients, the INR cannot be relied on to accurately monitor warfarin therapy, and the Chromogenic Factor X (CFX) activity assay, which is insensitive to LAC, must be used to avoid subtherapeutic oral manticoagulation. As cited above, in the small study analyzed, 4 control patients (9%) (LAC-negative) receiving therapeutic warfarin show prolonged PT compared with CFX activity level. This group could represent patients with a transient LAC or an antiphospholipid antibody that prolongs the PT without being detected by the DRVVT or Staclot LAC assays. "Therefore, a patient who develops clots while receiving warfarin with a seemingly therapeutic PT should undergo at least one CFX activity measurement as part of a more extensive thrombophilia workup to rule out APLS". The CFX assay is also useful when patients in treatment with a DTI because of a heparin-induced thrombocytopenia (HIT), are switched to warfarin after the platelet count has returned to normal levels. Although the DTIs bivaluridin shows only minimal PT prolongation, argatroban significantly lengthens the PT and therefore the true INR value is not known. **(132) (American Journal of Clinical Pathology 2013 vol. 40 pp. 623-634)** The CFX assay can also be used in managing the syndrome of "warfarin resistance", described as the inability to obtain an INR in the therapeutic range despite the administration of warfarin at normally prescribed doses. The most common cause of warfarin resistance is noncompliance. Other causes of warfarin resistance include acquired causes (high vitamin K intake, poor warfarin absorption) and hereditary causes (hypersensitivity to vitamin K because of polymorphisms in VKORC1, rapid warfarin deactivation because of polymorphisms in CYP2C9). **(134) (Cleveland Clinic Journal of Medicine 2009 vol. 76 pp. 724-730)** In case of warfarin resistance, CFX levels provide a more precise assessment of the warfarin plasma level and should be included in the clinical evaluation algorithm. In general, when patients receiving a therapeutic warfarin dose are stable with an INR of 2.0 - 3.0, CFX levels are about 20-40%. However, each laboratory should establish its own CFX range to be used in patient management. **(132) (American Journal of Clinical Pathology 2013 vol. 140 pp. 623-634)** In a large study was compared the International Normalized Ratio with a chromogenic factor X (CFX) assay for monitoring patients on oral anticoagulant therapy using the DiaPharma CFX method on a STA-R Evolution Coagulation Analyzer. INR values were correlated with the CFX for determining normal, subtherapeutic, therapeutic and supratherapeutic ranges for these patients. Blood samples were analyzed and grouped as normal or patients on oral anticoagulant therapy with international normalized ratios of less than 2.0, 2.0-3.0, and more than 3.0. Three hundred and nine randomly selected oral anticoagulant therapy patients were tested.

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Results by group were as follows : **a)** normal (n=30), CFX range 72-132%, mean CFX 96%; **b)** INR less than 2.0 (n=70), CFX range 32-132%, mean CFX 53%; **c)** INR between 2.0 and 3.0 (n=135), CFX range 18-48%, mean CFX 28%; **d)** INR more than 3.0 (n=104), CFX range 9-46%, mean CFX 21%. Sensitivity and specificity crossed at a CFX of 35.5%, which yielded a sensitivity of 91.7% and a specificity of 91.9% for discriminating international normalized ratio of at least 2.0. In this randomly selected group of patients in treatment with vitamin K antagonists (VKA) and normal subjects at varying levels of anticoagulation, CFX correlated well with INR as determined by R=0.964. This data suggest that the CFX can be a useful tool for monitoring oral anticoagulation in patients in which confounders to INR may be present, such as some patients with antiphospholipid syndrome and patients who are switched from direct thrombin inhibitors (DTI), in particular argatroban, to warfarin. In this study were not assessed clinical outcomes. The authors conclude that further investigation is warranted in larger cohorts of patients on treatment with (VKA) to assess the feasibility of using CFX as the primary method of monitoring, and a study designed to assess clinical outcomes such as thromboembolic events and safety outcomes such as bleeding, should be undertaken to compare the INR values with the CFX. Future studies could include the comparison with INR in a population that was prospectively screened to eliminate confounding factors for INR. **(135) (Blood, Coagulation and Fibrinolysis 2008 vol. 19 pp. 513-517)**

In a recent interesting study, Efthymiou and collegues compared the degree of anticoagulation intensity in 50 patients with thrombotic antiphospholipd syndrome (APS) and 50 patients with non-APS by measurement of the INR with two available thromboplastins with instrument-specific values (Innovin, Siemens Healthcare Diagnostics, on a Sysmex CS-5100 analyser and a rabbit brain thromboplastin, PT Fibrinogen HS Plus (PT-Fib-HS+), on an ACL TOP500 analyser, IL) and investigated the potential role of amidolytic FX levels and thrombin generation testing (TG) in the assessment of anticoagulant intensity in thrombotic APS patients. As cited above, it has been suggested a CFX for monitoring warfarin in patients with APS whose INR is out of the established therapeutic range. In fact, patients with APS are characterized by the presence of antiphospholipid antibodies (aPL), in particular Lupus Anticoagulant (LA) and anti-prothrombin antibodies, and INR values may be over-estimated principally due to the variable sensitivity of thromboplastin reagents to LA. Of the 50 patients with APS included in this study, 27 had VTE alone, 15 Arterial Thromboembolism (AT), and 8 both VTE and AT. Of the non-APS patients, 40 had VTE and 10 both VTE and AT. The target INR ranges were : 2.5 (2.0-3.0); n=70; 32 APS and 38 non-APS, 3.0 (2.5-3.5) n=9; 3 APS and 6 non-APS, and 3.5 (3.0-4.0) n=21; 15 APS and 6 non-APS. The INR values obtained with Innovin and PT-Fib HS+ did not present significant differences, and 96% of the INR values obtained with the two reagents were within 0.5 INR units for non-APS patients, compared to 80% for APS patients; 10 of 12 patients showing >/= 0.5 INR unit difference between the reagents had LA and their INR values were consistenly higher using Innovin. All except two of these 10 APS patients were in the higher INR target ranges. Two non-APS patients had higher INR values using the PT-fib HS+ thromboplastin. FX levels did not show significant differences between the two patient groups for INR 2.0-3.0, and for what concerns their relation to the intensity of anticoagulation, in non-APS patients with INR 2.0-3.0 the corresponding FX levels (5-95th centile) were 18.1-33.4 IU/dL. For INR values between 3.1 and 4.0, the corresponding FX levels (5-95th centile) in the 6 non-APS patients were 12.7-18.4 UI/dL with similar levels in the 15 APS patients. Interestingly, there was no

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significant inverse correlation between FX levels and INR for patients with higher INR values, including up to 6.0, in both patient groups. FX levels were not useful when INR values exceeded approximately 3.5, possibly due to interference by acarboxy-FX when the level of fully functional FX becomes very low, < / = 12.0 IU/dL. Consequently, FX levels did not give useful information at higher anticoagulation intensity in 6 of 12 patients with >/= 0.5 INR unit discrepancy between thromboplastin reagents. For what concerns thrombin generation testing, which measures global hemostatic potential, both patient groups showed reduced Endogenous Thrombin Potential (ETP) and peak thrombin, and prolonged lag time when compared to Normal Controls (NC). The lag time was significantly prolonged in APS compared to non-APS patients. All APS patients with lag time outside the 95th centile established in non-APS patients, were LA positive. On the contrary, peak thrombin and ETP were similar in the two patient groups. Four APS patients had increased peak thrombin compared to non-APS patients (> 95th centile based on values in non-APS patients) and 2 of these also had sligthly increased ETP, despite having INR values in the desired target therapeutic range (INR 2.0-3.0). Three of these four patients showed similar INR with the two thromboplastin reagents, and agreement between FX levels and INR. One non-APS patient had peak thrombin value above the 95th centile and this patient had both VTE and AT prior to anticoagulation therapy. Differently from the FX levels, both ETP and peak thrombin showed good inverse correlations with INR and good sensitivity not only at INR values 3.1-4.0 but also at INR values > 4.0, despite wide variation in values in patients with the same INR target range, even between patients with similar INR values, although the reason for this remain unclear. All patient plasmas were also tested as a 1 : 1 mixture with Pooled Normal Plasma (PNP). After this correction, all TG parameters were normalised in non-APS patients (compared to 5-95th centile range of NC). However, in APS patients, the lag time remained significantly prolonged and both ETP and peak thrombin were significantly decreased when compared with non-APS patients and Normal Controls (NC). The high peak thrombin in the four APS patients persisted, suggesting a specific effect of aPL. All four patients were LA positive, 2 of them were triple aPL positive, and had a history of cerebral vein thrombosis, stroke, recurrent VTE, or multiple ischaemic brain lesions, respectively. The authors conclude that TG testing may be helpful in the determination of true anticoagulant intensity in APS patients, including those with INR values above 3.5. In this study, after the correction of warfarin-induced coagulation factors deficiencies with PNP, ETP values of APS patients normalised and were not suggestive of a hypercoagulable state. The prolongation of lag time in APS patients could be attributed to LA because the majority of APS patients were LA positive. Interestingly, TG testing showed in 4 APS patients an increased peak thrombin which persisted after mixing studies with PNP and for this reason it was not due to deficiency of vitamin K dependent factors. The INR values for each patient in this subgroup were within their target range (INR 2.0-3.0), and concordant with FX levels, suggesting that TG testing may be useful in identifying a prothrombotic state in patients who appear to have the desired anticoagulation intensity as assessed by INR. The authors describe the limitations of this study : 1) the study design was cross-sectional and not prospective; 2) the TG results may have been influenced by LA, because phospholipids are an essential component of this test; 3) the clinical outcome of these patients was not followed. For these reasons, are needed future prospective studies where anticoagulation is adjusted according to TG results to obtain information of the value of TG in the clinical setting. **(136) (Thrombosis Research 2015 vol. 135 pp. 1191-**

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1197)
The prolongation of INR principally depends on reductions in three of the vitamin K-dependent clotting factors that are Factor II, FVII and FX, whereas FIX dose not modify INR. Normally a PT-INR in the 2.0-3.0 therapeutic range corresponds to a FII plasmatic level of about 30%, to a FVII level of 30%, to a FX level of 15% and to a FIX level of 50%. Although FIX plasmatic levels do not affect INR, they can impact the risk of bleeding in patients during treatment with warfarin. **(137) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1043-1052)** Some individuals suffer recurrent serious bleeding episodes during warfarin anticoagulation, even although the INR is in the target range. This is probably due to mutations in the FIX propetide that cause an exaggerated response of FIX levels to warfarin, with FIX levels dropping to < 1% of normal, rather than the expected 50%. The propetide sequences of the vitamin K-dependent clotting factors serve as a recognition site for the enzyme gamma-glutamylcarboxilase, which catalyzes the carboxylation of glutamic acid residues at the NH_2 terminus of the mature protein. The described mutations in the propeptide of Factor IX result in warfarin sensitivity because of reduced affinity of the carboxylase for the Factor IX precursor. Direct sequencing of amplified genomic DNA from a patient's FIX gene disclosed a single-point mutation that results in the substitution of threonine for alanine at position -10 in the pre-pro leader sequence. **(138) (Journal of Clinical Investigation 1996 vol. 98 pp. 1619-1625);** In other three patients, analysis of the FIX gene revealed two different missense mutations affecting the ALA-10 residue in the propeptide coding region : Alanine to Valine in two patients and Alanine to Threonine in one patient. No further mutation was detected by screening 195 random blood donors for mutations at Ala-10, thus excluding a frequent polymorphism at this position. In all three patients coumarin therapy caused an unusually selective decrease of FIX activity to levels below 1-3%. Upon withdrawal of coumarin, FIX:C increased to subnormal or normal values of 55%, 85% and 125% respectively. **(139) (British Journal of Haematology 1997 vol. 98 pp. 240-244)** The FIX level can affect thrombin generation and hemostatic function in the setting of warfarin anticoagulation without an effect on the INR. Dargaud and collegues studying the in vitro effect of FIX levels on thrombin generation and PT-INR found no statistically significant correlation between the Endogenous Thrombin Potential (ETP) and INR when only considering the range of INR values from 2.0 to 3.0. This suggests that variables in addition to those reflected in the INR have an impact on thrombin generation in this range. Interestingly, some subjects on warfarin had surprisingly high FIX levels. Higher than expected FIX levels do not increase thrombin generation above that allowed by the prothrombin level. However, a lower than average FIX level could depress thrombin generation to a greater extent than it is reduced, due to the prothrombin level alone. The relative risk (RR) of clinical bleeding during well conducted warfarin therapy was calculated. Patients on warfarin in the target INR range of 2.0-3.0 and with a FIX activity below 50% have 2.89 times higher bleeding risk than warfarinized control patients having similar INR and FIX above 50%, confirming the potential role of FIX as a risk of bleeding, but suggesting that other factors also contribute to bleeding risk. Thrombin generation measurement may be better correlated with clinical bleeding or thrombosis risk than the activated partial thromboplastin time (aPTT) and PT-INR. Thrombin generation assays may be more useful to assess global hemostatic status than the common clinical coagulation tests (PT and aPTT) and probably provide a more sensitive measure of the level of anticoagulation. There is a significant inverse correlation between the INR and thrombin

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generation in patients on warfarin. However, there is also a significant interpatient variability in thrombin generation among warfarinized patients, that is not reflected in the INR. Dargaud et al. showed that the level of FIX is a determinant of the thrombin generation but not of the PT-INR. A very low FIX level during warfarin therapy can lead to bleeding complications in spite of INR values in the target range. Probably a direct assay of the FIX level would be useful in patients on warfarin treatment. In this study there was no patient with very low FIX levels (below 3%) like cases having the mutation in the propetide of FIX. However, a large degree of variability of FIX activity was observed in patients having identical INR values. Because normal ranges for most of the coagulation factors are between 50% and 150%, it is therefore very likely to find subjects with FIX levels of only 50-75% of the average at baseline. These subjects will have a proportionate reduction in FIX level during warfarin therapy and might need more careful follow-up or might be better managed by selecting a target INR that is based on their level of thrombin generation. The authors affirm that ideally a thrombin generation assay could be done on all patients at the time the INR stabilized after initiation of warfarin therapy. Patients with a discrepancy between the results of the PT-INR and thrombin generation assays could then be considered for dose adjustement and development of a personalized INR target. Warfarin treatment could be monitorized not only by PT-INR but also with occasional repeats of the thrombin generation assay. A target range for parameters of thrombin generation during warfarin therapy should be developed to use the thrombin generation assay in these patients. **(137) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1043-1052)**
In conclusion it is possible to suggest not only a determination of FX activity by a chromogenic test during the first week of warfarin treatment, to avoid wrong corrections of warfarin dosage, but also in case on unstable INR; in patients with antiphospholipid syndrome with a high INR or with a thrombotic event although their INR be in the therapeutic range. In addition, would also be useful a determination of factor IX in patients with INR in the target range, to avoid unpredictable bleeding events,and a thrombin generation test in all patients at the time the INR stabilized after initiation of warfarin treatment, to possibly avoid unpredictable thrombotic or bleeding complications. For what concerns the Thrombin Generation test, see **(140) (Thrombosis Research 2011 vol. 127 Suppl. 3 pp. S21-S25); (141) (Thrombosis Journal 2015 vol. 13 pp. 1); (142) (liu.diva-portal.org/smash/get/diva2:660831/FULLTEXT01.pdf)**
After all these considerations, it is possible to suggest that an optimization of laboratory monitoring of vitamin K antagonists treatment, coupled with the use of tecarfarin which very probable will require less laboratory monitoring than the other vitamin K antagonists, can really represent a breakthrough in the oral anticoagulant treatment also considering that at the moment, for patients with valve prostheses and with antiphospholipid syndrome, vitamin K antagonists still represent the only anticoagulant drugs that we can safely use, and considering that DOACs in patients with nonvalvular atrial fibrillation need to be monitored not only clinically, but by appropriate laboratory tests too, as recently demonstrated. **(143) (Journal of The American College of Cardiology 2014 Vol. 63 pp. 321-328); (144) (Canadian Journal of Cardiology 2013 vol. 29 S24-S33); (145) (Thrombosis Research 2015 vol. 136 pp. 148-153)** A high intra- and inter-individual variability was demonstrated for dabigatran, rivaroxaban and apixaban. In particular intra-individual variability, expressed as the coefficient of variation (CV) calculated for the three DOACs measured over time on 120 patients, was assessed from the data provided by one of the clinics at trough and

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peak. Dabigatran showed the greatest variability with a CV of 59% at trough and of 60% at peak for the 110 mg. dosage and of 49% at trough and 51% at peak for the 150 mg. dosage. Rivaroxaban variability was intermediate with a CV of 39% at trough and of 27% at peak for the 20 mg. dosage, and of 35% at trough and 31% at peak for the 15 mg. dosage. Apixaban variability was the smallest with a CV of 23% at trough and of 22% at peak for the 5 mg. dosage, and of 15% at trough and of 14% at peak for the 2.5 mg. dosage. For what concerns the inter-individual variability, on average the drug concentration levels varied more than 20-times among the patients for dabigatran, about 15-times for rivaroxaban and 7-times for apixaban. Variability was similarly high if assessed within each clinic or evaluated as a whole, suggesting that it cannot be accounted for by the variability of the different laboratory assays. In addition, variability was considerably higher in patients treated with the lowest dose of DOACs. Interestingly, the authors point out that this last obsertvation may have important clinical implications since on the one hand it supports the strategy of administering lower doses to patients with specific clinical characteristics, while on the other hand it shows that the same patient may have a greater variability of anticoagulation, regardless of the clinical criteria used to assign drug dosage. **(146) (Thrombosis Research 2016 vol. 137 pp. 178-183)**

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