

# THE TRUTH ABOUT NEW ORAL ANTICOAGULANTS

**TROMBOSI - ANTICOAGULANTI ORALI DIRETTI**

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Autore: Dr. Vincenzo Marottoli

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## Abstract

During these last years many papers about new oral anticoagulants have been published.

Drugs manufacturers invested a lot of money in the development of these drugs and clearly now they want to recover their money and eventually to earn other money. The pressure of these powerful pharmaceutical companies which naturally are profit organization, is really impressive. The money involved in the treatment of patients with these new oral anticoagulants is a very big amount, billion of dollars. It is easy to understand that when is involved such a big amount of money, “shadowy behaviours” on behalf of pharmaceutical companies, health Institutions and physicians who are “key opinion leaders” are very probable, especially when some health institutions receive an important percentage of their budget from donations from the medical industry. The fact that a drug is approved for the treatment of patients with a certain disease by regulatory agencies, does not mean that this drug must be used in all the patients with that disease. Probably that drug will be useful in a small amount of those patients with that disease as is the case of Non Vitamin K Antagonists Oral Anticoagulants (NOACs) or using a better definition, Direct Oral Anticoagulants (DOACs), but if we use correctly these drugs in selected cases in which they are really useful, clearly the pharmaceutical companies will not earn a lot of money. For this reason, the pressure of drug manufacturers is so impressive through sponsorizations of National and International Meetings, of Medical Societies, through consultancies of physicians who are key opinion leaders, through donations to well-known Medical Research Institutions, through sponsorship of clinical studies which in the majority of cases are non-inferiority trials and not superiority trials which are “the gold standard” to demonstrate without any doubt the superiority of a drug compared with another drug <sup>1</sup>. However, the pharmaceutical companies are not interested to demonstrate the superiority of new oral anticoagulants compared with vitamin K antagonists but just to try to demonstrate that they are more manageable principally because they do not need laboratory monitoring. Unfortunately for them and for their official and “non official employees” now we know that this is not true. For dabigatran we know from an internal report of Boehringer Ingelheim of 2011, that there is a reduction of 30-40% of bleeding events by laboratory monitoring and the analysis concluded that “Optimally used (=titrated) dabigatran has the potential to provide patients an even better efficacy and safety profile than fixed dose dabigatran and also a better safety and efficacy profile than a matched warfarin group” <sup>2</sup>, confirmed by two papers <sup>3,4</sup> and because of a marked intra- and inter-individual variability now demonstrated also for rivaroxaban <sup>5,6</sup>, apixaban <sup>6,7,8</sup> and very probably for edoxaban too. In a recent large study a high intra- and inter-individual variability for dabigatran, rivaroxaban and apixaban was demonstrated <sup>9</sup>. Their laboratory monitoring very probably will reduce adverse events, in particular bleeding events. For this, we need clinical studies in which should be compared patients in treatment with new oral anticoagulants without laboratory monitoring with patients in treatment with the same drugs but with laboratory monitoring by appropriate tests. Only by these studies we will be able to show the incidence of the adverse events, in particular bleeding events, in the two groups of patients and, as showed for dabigatran, if it will be

showed a significant reduction of bleeding events without an increase of stroke events in patients controlled by laboratory monitoring, will they continue to say that these drugs do not need laboratory monitoring ?. Why the pharmaceutical companies do not sponsor these studies ?

Because very probable they already know the favorable results which can be achieved by laboratory monitoring and clearly these direct oral anticoagulants would lose their principal commercial appeal. In fact, during litigation was revealed an internal mail discussion about the potential merit of dabigatran plasma monitoring in which one Boehringer employee, whose name has been redacted, said : “This may not be a onetime test and could result in a more complex message (regular monitoring) and a weaker value proposition” <sup>2</sup> .EMA documents from early 2010 show that Boehringer had “identified dabigatran concentrations not to be exceeded because of the increased risk of bleeding. The 200 ng/ml concentration is the value at trough not to be exceeded because of risk of bleeding”. A spokesperson for Boehringer said that the company “never told EMA or any regulatory authority that 200 ng/ml was a level not to be exceeded” <sup>2</sup> . In addition, internal emails released during US litigation show that Andreas Clemens, a medical leader for the drug dabigatran, stated that he was “phobic” and “not happy with the conclusion” that an optimal balance between benefit and risk occurs in a range of concentrations between 40 ng/ml and 215 ng/ml. Clemens also wrote “ The world is crying for this information but the tricky part is that we have to tailor the message smart” <sup>2</sup> . (For details see the abstract section of Dabigatran review)

Now what is really strange is that if for politicians in Europe and North America to avoid constant criticism is much better not have conflicts of interests, also because in some cases they can be forced to resign, in case of physicians this unwritten rule does not exist. As a consequence, physicians who received consultancy fees or other kind of honoraria for conferences, etc. from pharmaceutical companies and in some cases even if they are included in the board of these pharmaceutical companies, they can write and publish on leading medical journals papers about drugs manufactured by the companies from which they received honoraria and in addition in many cases the same publication is funded by the pharmaceutical companies. This is really unbelievable. Is it possible to be reliable just declaring the conflicts of interests at the end of the paper ? I think not. Transparency is essential , but is not sufficient to eliminate bias or perception of bias. Now I report exactly the words used by the authors in an article published by the British Medical Journal whose title is : Medical journals and industry ties. Zero tolerance on education articles with financial links to industry <sup>10</sup> . The words are : “This risk of bias is particularly important for clinical educational articles that are designed to guide patient care, when authors’ biases may be less visible to general medical readers. For some years we have sought to minimise as well as declare competing interests for these articles. Recently we introduced more active management of competing interests, requiring authors to complete a more detailed declaration and excluding authors with close ties. From the next year our clinical educational articles will be authored by experts without financial ties to industry. By industry we mean companies producing drugs, devices, or tests; medical education companies; or other companies with an interest in the topic of the article. We are phasing in this policy to start with editorials, clinical reviews, and most practice series. We hope that by the end of 2016, this will have extended to the rest of our education section : our specialist state of the art reviews and diagnostics and therapeutics series” <sup>10</sup> . The authors say that the principal reason for doing this is that “making clinical decisions based on information biased

by commercial interests can cause harm, as happened with cardiotoxicity from rosiglitazone and rofecoxib “<sup>10,11,12</sup> . Another medical journal, the American Family Physician, which primarily publishes clinical reviews, for over twenty years has not considered articles by authors who have financial ties with industry. I report the words written in the conflict of interest form of this journal : “ To avoid bias or the perception of bias, AFP will not consider manuscripts sponsored directly or indirectly by a pharmaceutical company, medical education company, or other commercial entity or those written by an author who has a financial relationship with or interest in any commercial entity that may have an interest in the subject matter of the article within the previous 36 months or in the foreseeable future. It also includes serving on a commercial speaker’s bureau or advisory board, or receiving commercial research support related to the subject matter of the article, as well as other relationships detailed in our conflict of interest policy”<sup>13</sup> . Considering the policies of these journals, all the articles about new oral anticoagulants should not have been accepted for publication. I hope that in the future all the leading medical journals will adopt the same policy adopted by these two journals to restore dignity to clinical medical research and to give our patients really the best of medical progress. Public and private research institutes should not forget their key role in the modern society and should adopt a strict ethical policy accepting funds from governmental institutions and from private donations only, refusing any kind of financial support from the medical industry. On the other hand, governmental institutions should start to fund all the clinical trials which involve the efficacy and safety of a new drug although this may be expensive, because the public money they will invest will return to the society in terms of improved public health. The health and life of only one patient, are much more important than the budget of many pharmaceutical companies.

## References :

- 1) Garattini Silvio, Bertelè Vittorio : Non-inferiority trials are unethical because they disregard patients’ interest. The Lancet 2007; 370 : 1875-1877
- 2) Cohen Deborah : Dabigatran : How the drug company withheld important analyses. British Medical Journal 2014; 349:g467023)
- 3) Douxflis J., Mullier R., Robert S. et al. : Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. Thrombosis Haemostasis 2012; 107 : 985-997
- 4) Reilly P.A., Lehr T., Haertter S. et al. : The effect of dabigatran plasma concentration and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients : The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). Journal of the American College of Cardiology 2014; 63: 321-328
- 5) Samama M.M., Guinet C., Le Flem L. et al. : Measurement of dabigatran and rivaroxaban in primary prevention of venous thromboembolism in 106 patients who have undergone major orthopedic surgery : an observational study. Journal of Thrombosis and Thrombolysis 2013; 35 : 140-146
- 6) Gong Inna Y. and Kim Richard B. : Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. Canadian Journal of

Cardiology 2013; 29: S24-S33

7) Freyburger Geneviève, Macouillard Gérard, Khennoufa Karim et al. : Rivaroxaban and apixaban in orthopaedics : is there a difference in their plasma concentrations and anticoagulant effects ? Blood, Coagulation and Fibrinolysis 2015; 26 : 925-933

8) Skeppholm Mika, Al-Aieshy Fadia, Berndtsson Maria et al. : Clinical evaluation of methods to monitor apixaban treatment in patients with atrial fibrillation. Thrombosis Research 2015; 136 : 148-153

9) Testa Sophie, Tripodi Armando, Legnani Cristina et al. : Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation : Results observed in four anticoagulation clinics. Thrombosis Research 2016; 137 : 178-183

10) Chew Mabel, Brizzel Catherine, Abbasi Kamran et al. : Medical journals and industry ties. Zero tolerance on education articles with financial links to industry. BMJ 2014; 349 : g7197 doi: 10.1136/bmj.g7197

11) Krumholz H., Ross JS, Presler AH et al. : What have we learnt from Vioxx ? BMJ 2007; 334 : 120

12) Moynihan R. : Rosiglitazone, marketing, and medical science. BMJ 2010; 340 : c1848

13) Conflict of interest form - American Family Physician  
[www.aafp.org/journals/afp/authors/guide/coi.html](http://www.aafp.org/journals/afp/authors/guide/coi.html)



## The true about New Oral Anticoagulants (NOACs)

Direct oral anticoagulants commercially available are dabigatran, a direct inhibitor of thrombin, and rivaroxaban, apixaban and edoxaban, which are direct inhibitors of activated factor X (FXa)<sup>1,2</sup>. Other direct oral anticoagulants are in development. These drugs were developed and introduced commercially after having been approved by the regulatory agencies, with the attempt to substitute the vitamin K antagonists such as warfarin, acenocumarol and phenprocoumon which is very used in Germany and the Netherlands in oral anticoagulant treatment. The benefits advertised of these drugs are the use in prefixed doses without a laboratory monitoring, a decrease of intracranial bleeding events and an interference with a less number of drugs compared with the vitamin K antagonists<sup>3,4</sup>. The truth, unfortunately, is that although these statements are expressed by many physicians who are "key opinion leaders" and published by prestigious international medical journals with high impact factors,<sup>5,6,7,8,9,10,11,12,13,14</sup> they are not correct.

Fortunately, there are other "key opinion leaders" who although be less numerous, have opinions that are not concordant with those expressed by their colleagues<sup>15,16,17,18,19,20,21,22</sup>. All the published clinical studies about new oral anticoagulants were sponsored by manufacturers of these drugs. It is well documented a marked intraindividual and interindividual variability of dabigatran plasma concentration correlated with ischemic stroke and bleeding outcomes. The median trough and post-dose concentrations were 55% and 36% higher, respectively, in the subjects with a major bleeding event than those in the subjects without bleeding events. Median (10th to 90th percentiles) trough concentrations in 323 patients with major bleeds were 116 ng/ml (46.7- 269 ng/ml) compared with 75.3 ng/ml (30.7-175 ng/ml) in 5,899 patients with no major bleed. Plasma concentrations of dabigatran were higher in subjects with hemorrhagic stroke (n= 11 with trough and 13 with peak measurements) than in subjects (n= 8,269 with trough and 8,971 with peak measurements) without hemorrhagic stroke (144 ng/ml vs. 78.4 ng/ml for trough and 241 ng/ml vs. 155 ng/ml for post-dose concentrations, respectively). The plasma concentration variability was about 5.5 folds with each dosage of dabigatran<sup>23,24</sup> used in the RE-LY study<sup>25</sup>. A marked intra and interindividual variability of rivaroxaban plasma concentration was also observed<sup>26,27,28</sup>. In addition, concentrations of rivaroxaban, a FXa inhibitor authorized for administration on a once-daily basis, were higher 12 hours after evening intake than 12 hours after morning intake. Evening intake of rivaroxaban leads to prolonged exposure to rivaroxaban concentration and better matches the morning hypofibrinolysis<sup>29</sup>. This variability is present with the other direct inhibitors of activated factor X, such as apixaban<sup>27,28,30</sup> and presumably with edoxaban, therefore to say that these new oral anticoagulants do not need a laboratory monitoring because they have a predictable pharmacokinetics and pharmacodynamics is not correct. In a recent paper Skeppholm and colleagues evaluated laboratory methods to monitor apixaban treatment in patients with atrial fibrillation and found that apixaban plasma concentrations determined by LC-MS/MS which is the "Gold Standard Method" varied more than 10-fold for the entire cohort, n=70) and similar patterns were observed in the two apixaban dosage groups both with a 6-fold difference between the lowest and highest plasma concentrations. More clearly, in this cohort of patients apixaban exposure varied 6-fold among patients within the same dose group. The range was between 15-83 ng/ml and 29-186 ng/ml

for the 2.5 mg twice daily and 5 mg. twice daily respectively. The apixaban plasma concentrations were increased 16 and 20% respectively in patients with mild (CrCl 51-80 mL/min) and moderate (CrCl 31-50 mL/min) renal impairment, compared to patients with normal CrCl. Correctly the authors observe that "taking into account also the pronounced variability of exposure, it may rather be that measurement of plasma concentrations could represent a future way to guide dosage in vulnerable groups of patients with a high risk of both thromboembolism and bleeding" <sup>30</sup>.

Skeppholm and colleagues also evaluated dabigatran plasma concentrations with different methods in another paper. They found that plasma concentrations of both free and total dabigatran determined by LC-MS/MS varied markedly, 20-fold with the 150 mg dose, and similar patterns were observed in the two dabigatran dosage groups <sup>31</sup>. The medians and the 10th to 90th percentiles of trough concentrations of total and free dabigatran were in the same range as those reported from the RE-LY trial in the paper by Reilly and colleagues <sup>24</sup> although somewhat lower in their patients treated with 150 mg twice daily. The authors conclude that "the considerable variability of dabigatran concentrations in plasma supports the contention that patients could benefit from a possibility to monitor dabigatran treatment and individualize dosages for optimal efficacy and safety. Such monitoring would, however, not need to be as intense as for warfarin treatment" <sup>31</sup>. In a recent study, the authors found a large heterogeneity in both peak and trough concentrations of rivaroxaban and dabigatran in patients after orthopaedic surgery <sup>32</sup>. Also in another recent collaborative study which involved four large Italian anticoagulation clinics for a total of 330 consecutive patients, of which 160 were on dabigatran (70 and 90 taking 150 mg or 110 mg twice-daily, respectively), 71 on rivaroxaban (37 and 34 taking 20 mg or 15 mg twice daily) and 99 on apixaban (73 and 26 taking 5 mg or 2.5 mg twice daily) the investigators showed a marked intra and inter-individual variability for all the three direct oral anticoagulants. In particular, for what concerns the intra-individual variability, expressed as the CV value calculated for the three DOAC measured over time on 120 patients, it was assessed from the data provided by one of the clinics, at trough and at peak. Dabigatran showed the greatest intra-individual variability with a CV of 59% at trough and 60% at peak for the 110 mg dosage and with a CV of 49% at trough and of 51% at peak for the 150 mg dosage. Rivaroxaban intra-individual variability was intermediate with a CV of 39% at trough and of 27% at peak for the 20 mg dosage, and with a CV of 35% at trough and of 31% at peak for the 15 mg dosage. Apixaban intra-individual variability was the smallest, with a CV of 23% at trough and of 22% at peak for the 5 mg dosage, and with a CV of 15% at trough and of 14% at peak for the 2.5 mg dosage. The inter-individual variability was expressed as CV for each drug. For dabigatran 110 mg, CV values ranged from 56% to 71% at peak and from 36% to 72% at trough. For dabigatran 150 mg, CV values ranged from 45% to 56% at peak and from 42% to 92% at trough. For apixaban 5 mg, CV values ranged from 31% to 33% at peak and from 29% to 49% at trough. For apixaban 2.5 mg, CV values ranged from 21% to 42% at peak and from 44% to 68% at trough. For rivaroxaban 20 mg, CV values ranged from 32% to 49% at peak and from 40% to 103% at trough. For rivaroxaban 15 mg, CV values ranged from 46% to 52% at peak and from 30% to 79% at trough. There were no major differences between clinics. Total inter-individual variability was expressed as overall CV, irrespective of the clinics. For dabigatran 110 mg, overall CV value was 69% at trough and 67% at peak. For dabigatran 150 mg, overall CV value was 78% at trough and 51% at peak. For rivaroxaban 20 mg, overall CV value was 61% at trough and 43% at peak. For rivaroxaban 15 mg,



overall CV value was 60% at trough and 43% at peak. For apixaban 5 mg, overall CV value was 49% at trough and 35% at peak. For apixaban 2.5 mg, overall CV value was 59% at trough and 39% at peak. As described above, overall CV values for all drugs were lower at peak than at trough. On average, the drug concentration levels varied more than 20-times among the patients for dabigatran, nearly 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. Variability was considerably higher in patients treated with the lowest dose of DOAC. The authors point out that this observation may have important clinical implications since on the one hand it supports the idea to treat with lower doses patients with specific clinical characteristics, while on the other hand it shows that the same patient may have a greater variability with respect to anticoagulation, regardless of the clinical criteria adopted to assign drug dosage. Patients taking the same oral dose of single DOAC may present with highly variable plasma concentrations and for the authors this can be explained by different DOAC metabolism patterns in individual patients. The authors of this study point out that there is an urgent need to establish drug-specific cut off levels about the occurrence of clinical events such as hemorrhagic or thrombotic events in treated patients. However, may be that due to the relatively high inter-individual variability, it will be difficult to set precise cut off values. In addition, there is a need to establish cut off drug levels to be applied to patients receiving treatment after stopping anticoagulation to undergo surgery or invasive procedures <sup>33</sup>. Analysing the results of these studies which demonstrate that NOAC, contrary to what stated in previous papers, do not have a predictable pharmacodynamics and pharmacokinetics, we can assume that new oral anticoagulants probably need less laboratory controls compared with vitamin K antagonists, but in any case these controls must be performed, using appropriate laboratory tests and in particular the diluted thrombin time (Hemoclot Thrombin Inhibitors, HTI Kit) and the ecarin time to evaluate dabigatran plasma concentration and the HTI LOW Kit or the STA-ECA II (ECA-II Kit), a chromogenic variant of the ecarin time, to measure low plasma concentrations of dabigatran < 50 ng/ml which are critical during the perioperative management of patients in treatment with dabigatran <sup>34</sup>. By an anti-activated factor X test using chromogenic substrates, it is possible to measure the rivaroxaban plasma concentration <sup>35</sup>, the apixaban plasma concentration <sup>36,37,30</sup>, and eventually can be used to measure the edoxaban plasma concentration too <sup>30,38</sup>. The rivaroxaban plasma concentration can also be evaluated using the PTRivaroxaban, expressed using the INRRivaroxaban calculated using the ISI (International Sensitivity Index) rivaroxaban and not the ISI of the thromboplastin that we are using <sup>39,40,41</sup>. These coagulation tests should be compared with a reference method and proficiency testing. Ultra-performance liquid chromatography - tandem mass spectrometry (UPLC-MS/MS) is a very suitable technique for assisting in this <sup>42</sup>. Some authors found that UPLC-MS/MS is also the method of choice to measure trough concentrations of dabigatran and rivaroxaban in patients after orthopaedic surgery. Current coagulation assays are not suited for this purpose although they seem to be suitable to exclude high concentrations of DOACs. However, they are all unsuitable to accurately measure low (Trough) concentrations.<sup>32</sup>. Differently from laboratory monitoring of vitamin K antagonists in which with an INR < / = 1.4 we can safely submit a patient to a surgical procedure, excluding for sure a medical bleeding naturally after having evaluated the absence of a bleeding risk of different nature, (an INR in the normal range is especially important in

patients undergoing surgery associated with a high bleeding risk such as intracranial, spinal, urologic surgery or if neuraxial anesthesia is to be used), <sup>43</sup> in case of patients in treatment with new oral anticoagulants we do not have a reference value of their plasmatic concentration that can surely rule out a probable bleeding, more clearly, there is currently no known "threshold" at which the haemorrhagic risk of patients on DOACs would be comparable to the non treated ones,<sup>44</sup> although a plasmatic concentration < 30 ng/ml of dabigatran or rivaroxaban has been proposed in case of an emergency surgical procedure with a certain haemorrhagic risk <sup>45</sup> . At the moment the only reversal agent approved by FDA in october 2015 with the commercial name Praxbind is Idarucizumab, a humanized mouse monoclonal antibody that antagonizes dabigatran. <sup>46,47,48</sup> Aziparine (PER977), a synthetic water soluble compound that antagonizes dabigatran, the direct inhibitors of activated factor X (rivaroxaban, apixaban, edoxaban), the unfractionated Heparin (UFH) and the low molecular weight heparins (LMWH) <sup>49,50</sup> and Andexanet alfa, a recombinant human protein made in Chinese hamster ovary cells which is a factor Xa protein modified by elimination of the gla residues and inactivation of its catalytic site by amino acid substitution and that antagonizes the direct inhibitors of activated factor X, <sup>51,52,53,54</sup> at the moment are not commercially available. For this, differently from vitamin K antagonists that can be antagonized in short times in case of important bleedings or in case of emergency surgical procedures using 4-Factors Prothrombin Complex Concentrates (PCCs) <sup>55</sup> , following a dose recommendation that varies according to the patient INR <sup>56</sup> , at the moment, in case of patients in treatment with the new oral anticoagulants we do not have a codified therapy that can stop a severe bleeding or can prepare the patient before an emergency surgical procedure <sup>44</sup> , with the exception of Idarucizumab (Praxbind) that antagonizes dabigatran, now approved also by the European Medical Agency (EMA). There are publications of anecdotal cases in which were used with a certain success Activated Prothrombin Complex Concentrates (FEIBA) in case of bleedings in patients in treatment with dabigatran <sup>57,58,59</sup> , 4-Factors Prothrombin Complex Concentrates in case of bleeding in patients in treatment with rivaroxaban or apixaban <sup>60,61</sup> . The next publications about the use of idarucizumab in bleeding patients in treatment with dabigatran will let us better understand the lag time of dabigatran neutralization by this drug, especially in bleeding patients who have an elevated dabigatran plasma concentration. Recently has also been described a greater correction of coagulation parameters in vitro altered by the addition of dabigatran, with Activated Prothrombin Complex Concentrates (FEIBA) and the recombinant activated Factor VII (rFVIIa), compared with the correction of coagulation parameters obtained using a 4-Factors Prothrombin Complex Concentrate without heparin (Cofact) <sup>62</sup> . On the other hand, the recombinant activated factor VII had already been used in a surgical patient with a severe bleeding due to dabigatran in whom had been performed a dialysis, which can be used in patients in treatment with dabigatran to reduce the drug plasma concentration and that, in patients with severe bleedings, in unstable hemodynamic equilibrium, can be very difficult to perform in the best emergency departments too. In addition, dialysis requires 4-6 hours minimum, a period of time that can be too much in case of severe bleedings that are life-threatening <sup>63</sup> . For what concerns the less incidence of intracranial bleeding, also this statement is not correct. In fact, as recently showed by a swedish study that has evaluated 77423 patients in treatment with warfarin and with a TTR (Time in Therapeutic Range) of 76.5% that is higher than the TTR evaluated in clinical studies that compared warfarin with new oral anticoagulants (TTR 55-64%), the annual incidence of intracranial bleeding

was 0.37% in the overall unselected population and 0.38% in patients with nonvalvular atrial fibrillation (NVAf) and was lower than the incidence obtained in clinical studies with new oral anticoagulants in which the annual incidence of intracranial bleeding in patients treated with warfarin was 0.70-0.80%. In addition, this incidence was lower than the incidence obtained with rivaroxaban (0.50%), not much higher of that obtained with apixaban (0,33%), with dabigatran 150 mg. (0.30%) and with dabigatran 110 mg. (0.23%). In addition, the annual incidence of TIA and of systemic embolism was 1.54% and was much lower of that obtained in patients treated with warfarin in clinical studies that evaluated dabigatran and rivaroxaban, in which was 1.74% and 2.42% respectively. The clinical results of this swedish study were amplified because patients were not selected and then included very old patients too, some with important impairment of their clinical conditions, and patients with prosthetic heart valves that had more bleeding events probably because in most cases were in a therapeutic range of 2.5-3.5 instead of 2.0-3.0 , differently from patients included in clinical studies investigating new oral anticoagulants that had inclusion and exclusion criteria and excluded very old patients and patients with prosthetic heart valves. These last patients were excluded because of unfavorable results obtained with the treatment of these patients with dabigatran <sup>64</sup> . In fact, the study that evaluated dabigatran in patients with prosthetic heart valves was interrupted prematurely because of a high major incidence of thrombotic and bleeding events compared with patients who were in treatment with warfarin <sup>65</sup> . The authors of the swedish study concluded the paper stating that it is possible to achieve an efficient therapy with warfarin with a TTR of 76.5% on a routine basis with unselected patients, and “warfarin should not be ruled out in favour of NOACs “ <sup>64</sup> . Favorable results were achieved with warfarin also in a study published by Poller in 2014 in which the results obtained in 5939 patients treated with warfarin, evaluated in the European Action on Anticoagulation (EAA) Study were compared with the results obtained in 6022 patients treated with dabigatran evaluated in the RE-LY study. The annual incidence of ictus, major bleedings, minor bleedings and death in patients treated with warfarin in the RE-LY study was 1.57%, 3.36%, 16.37% and 4.13% respectively. In patients treated with dabigatran 150 mg twice daily the annual incidence of ictus, major bleedings, minor bleedings and death was 1.01%, 3.11%, 14.84% and 3.64% respectively, and in patients treated with dabigatran 110 mg. twice daily was 1.44%, 2.71%, 13.16% and 3.75% respectively. On the contrary in the EAA study, the annual incidence of ictus, major bleedings, minor bleedings and death in patients treated with warfarin was 0.30%, 0.86%, 2.70% and 0.75% respectively <sup>66</sup> . In this last study the determination of the INR was optimized using a simple method described by Poller previously <sup>67</sup> . Recently has been described a monitoring method of warfarin treatment that is affected by plasma levels of factor II and of factor X only (FiiX-Prothrombin Time [FiiX-PT]) obtained using factor II and X depleted plasma (FiiX-depleted plasma) mixed into the test plasma to correct for any factor deficiency other than FII or FX. It seems to give a greater stability to the anticoagulant treatment with warfarin, demonstrated by a reduction of determinations number compared with the monitoring method performed using the PT-INR, by less dosage adjustments, by an increased time in therapeutic range and by a less variability of the INR <sup>68,69</sup> . In addition, was also recently described a diluted FiiX-Prothrombin Time (dFiiX-PT) using a single high thromboplastin final dilution of about 1:1200 of the particular thromboplastin used to determine the INR and the concentrations of dabigatran, rivaroxaban, apixaban, Unfractionated Heparin (UFH) and enoxaparin but not

fondaparinux. Of note, recombinant thromboplastins were less sensitive, particularly for measurement of rivaroxaban. The dFiiX-PT assay, which can easily be performed in automation using standard coagulation equipment, provided an estimation of drug concentrations in the range of 30-200 ng/ml for the three DOACs tested (dabigatran, rivaroxaban and apixaban), but at higher concentrations sample dilutions with normal plasma are needed,<sup>70</sup> considering that levels above 200 ng/ml have been shown to increase bleeding with both dabigatran and rivaroxaban<sup>71,72</sup>. In another paper that evaluated new oral anticoagulants, published in 2013, the authors concluded that "As the clinical use of NOACs increases, surveillance using therapeutic monitoring (measurement of plasma drug concentration or anticoagulation response) throughout the treatment period might be valuable in minimizing the risk of bleeding and lack of efficacy. Finally, because of the extent of interindividual variation in the metabolism and clearance of NOACs, it is likely that a greater range of NOAC doses will be needed to more precisely treat our patients"<sup>27</sup>. On the other hand, already in 2011 an internal report of dabigatran manufacturer showed that a laboratory monitoring of dabigatran treatment reduced the incidence of bleeding events of 30-40% with little or absent influence on the incidence of ischemic strokes, but this information was hidden not only to patients, but to the regulatory agencies too<sup>73</sup> [www.bmj.com/investigation/dabigatran](http://www.bmj.com/investigation/dabigatran). The documents were made public last week by a federal judge in Illinois who is overseeing thousands of lawsuits filed by patients and their families, who said that Pradaxa's manufacturer, the German company Boehringer Ingelheim, failed to properly warn them about the risks of taking the drug. Dabigatran was prescribed to 850,000 patients, but was linked to more than 1,000 deaths. The documents showed that Boehringer Ingelheim employees openly fretted when it appeared that the results of the research paper, written by Paul A. Reilly, a clinical program director at the company, indicated that some patients could benefit from monitoring of dabigatran plasma concentrations. One company supervisor, Dr. Jutta Heinrich-Nols, wrote in an email to other employees that she could not believe the company was planning to public research that would negate a decade's worth of work providing that patients taking Pradaxa would not need regular tests. Publishing the research results, she warned, could make it "extremely difficult" for the company to defend its long-held position to regulators that Pradaxa did not require testing. Another company leader, Dr. Andreas Clemens, questioned whether legal repercussions would arise if Dr. Reilly's paper detailed a specific range where the drug worked best. "Maybe I am phobic, but I am not happy with the conclusion", he wrote. "The world is crying for this information, but the tricky part is that we have to tailor the messages smart", Dr. Clemens wrote in a separate mail. Dr. Lisa Schwartz, a professor of medicine at the Dartmouth Institute for Health Policy and Clinical Practice said: "In these situations, where the stakes are really high, how crazy is it that it's in the hands of people who are so conflicted?". Dr. Reilly's paper was published in the Journal of the American College of Cardiology, and although many of the conclusions in the draft version remained, references to a patient's optimal blood-level range no longer appeared in the article. "The one-size-fits-all was a mistake for a drug with this kind of risk" said Thomas J. Moore, a senior scientist at the Institute for Safe Medication Practices, which keeps track of safety reports submitted to the FDA.<sup>74</sup> In one email, from June 2012, an employee wonders about the implications of internal research showing that blood levels of Pradaxa could vary significantly in a single patient. "This may be a onetime test and could result in a more complex message (regular monitoring), and a weaker value proposition...vs. competitors", wrote the



employee. Another employee said that such a test could be developed "in-house", but "2 years ago there was an informed decision not to develop this". "This would go against the no monitoring idea/claim". One email from a Boehringer Ingelheim employee expressed concern about safety risks in older patients, citing research showing that, in patients over 80, even a lower dose of Pradaxa, which is available in Europe but not in the United States, compared unfavorably to warfarin when it came to major bleeding. The employee said that "there may be a role" for one or two tests of Pradaxa levels in a patient's blood, and recommended that the company conduct a study to examine the issue.<sup>75</sup> In addition, the annual incidence of intracranial bleedings in patients who were in treatment with warfarin, was much lower than that obtained in patients in treatment with warfarin included in the clinical studies on new oral anticoagulants, already in the SPORTIF III Study (ICH of 0.53% with a TTR of 66%)<sup>76</sup> published in 2003, and in the SPORTIF V study (ICH of 0.28% with a TTR of 68%)<sup>77</sup> published in 2005. In these studies, patients with nonvalvular atrial fibrillation were randomised to receive oral anticoagulant treatment with warfarin or with ximelagatran, a direct inhibitor of thrombin, withdrawn from the market because of its hepatotoxicity. The annual incidence of intracranial bleedings was much lower than that obtained in the warfarin arm of NOACs trials also in 2 Cochrane reviews published in 2005 (0.30%)<sup>78</sup> and in 2007 (0.45%)<sup>79</sup>. After these considerations, it is possible to understand that if the laboratory monitoring of patients in treatment with vitamin K antagonists is good or optimal, clinical results are better than those obtained with new oral anticoagulants if these drugs are not monitored with appropriate laboratory tests<sup>64</sup>. Already in 2008 an interesting study showed for the first time the minimum TTR needed to achieve from Oral Anticoagulant Therapy (OAC) with warfarin a better clinical response than with dual antiplatelet therapy. The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE W) study data were used to develop an estimate of 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 OAC or clopidogrel plus aspirin. This posthoc analysis included 526 centers and 15 countries. Of the 6706 patients in ACTIVE W, 3371 were randomized to OAC and 3335 to clopidogrel plus aspirin. The mean TTR of each patient randomized to and receiving OAC was calculated, and each clinical center was characterized by the mean TTR of all its patients in OAC. Differences in TTR between centers and between countries affected the outcomes of OAC therapy. A marked benefit was found against stroke and against total vascular events for OAC patients treated at centers that had mean TTRs above the study median of 65% and no apparent benefit was found for the other half of OAC patients who were treated at centers achieving mean TTRs below 65%. This strong relationship between TTR and benefit of OAC was confirmed by the population-average analysis and by analysis of individual countries. These findings indicate that a threshold TTR exists below which the benefit of OAC over clopidogrel plus aspirin is questionable. The analysis based on quartiles of INR achieved by centers indicates a critical value for TTR of 65%. A population-average model showed that at TTR values > 58% it is reasonable to expect that a patient benefits significantly from being on OAC. At TTR values < 58%, one cannot confidently expect any net benefit from being on OAC compared with antiplatelet therapy. An even higher TTR (ie > 70%) is associated with even greater benefit from OAC and was achieved in some countries. These data indicate that providers of OAC therapy need to evaluate how well they deliver OAC to patients with atrial fibrillation, with the intent of achieving a minimum TTR

of 58% to 65% and an optimal control > 70% TTR.<sup>80</sup> In another very interesting paper, Gallagher et al. quantified the relationship between quality of INR control (TTR) and stroke risk in atrial fibrillation patients. Warfarin users with  $\geq 70\%$  of time spent within therapeutic range had the lowest risk of stroke while those with < 30% and 31-40% in range had the highest risks of stroke. Interestingly, they found that for TTR < 50% there was an increased risk of stroke in warfarin users compared with AF patients who were not in treatment with warfarin.<sup>81</sup> Fortunately in west countries it is possible to achieve a good or an optimal laboratory monitoring with a high TTR, referring patients in treatment with vitamin K antagonists to specialized centres of Haemostasis and Thrombosis, such as in Italy where there are centres which are members of the FCSA (Federation of Centres for the Diagnosis of Thrombosis and for the Surveillance of Antithrombotic Therapies) founded in Parma in 1989, and now widespread in all the Italian regions. [www.fcsa.it](http://www.fcsa.it) In Italy, the Center-specific TTR (cTTR), which is a measure reporting the mean patient TTR within an anticoagulation clinic describing the quality of anticoagulant monitoring offered by that clinic, was 67.9% in 2013<sup>82</sup>. In Germany the mean TTR was 68%<sup>83</sup>, in Sweden was 76%<sup>84,64</sup>, in Denmark was 83%<sup>85</sup>. On the other hand, also in the ROCKET AF trial was demonstrated an association between geographic regions and mean TTR that ranged from 36% in the small group of patients treated in India to 50% for patients treated in Eastern Europe and East Asia to 63 and 64%, respectively, for patients treated in Western Europe/similar and Canada/United States. Analyses excluding the first 90 days of follow-up resulted in improved regional mean TTRs, particularly in regions with a high proportion of patients naive to warfarin. Despite these changes, the regional- and country-level differences persisted. When these analyses were further stratified starting at 90 days by patients' previous exposure to warfarin and VKAs, the regional TTR patterns were preserved. Interestingly, the mean TTR was 47% in China and 38% in Taiwan but 66% in Hong Kong and 64% in Singapore. Ninety-nine percent of the patients in all 4 of these regions were identified as being of Asian race. The fact that the mean TTR for patients treated in Hong Kong and Singapore was much higher than the mean TTR in the remaining countries in East Asia indicates that medical care practices and not race determine anticoagulation control in this region. Geographic regional variation in mean TTR levels was largely due to time at INR < 2.0. For Canada/United States patients, the mean time at INR < 2.0 was 19.9%. In contrast, for Eastern European patients, the mean time at INR < 2.0 was 35.2%, and for patients in East Asia, the time at INR < 2.0 was 37.1%. The differences in mean time at INR > 3.0 were much smaller and contributed much less to the differences in TTR across regions.<sup>86</sup> In addition, in North America, in the ROCKET AF trial there was a higher incidence of 43% of major bleeding events in patients treated with rivaroxaban compared with patients treated with warfarin. Clearly this was due to the high TTR achieved in people treated with warfarin. " There was a statistically significant P value for interaction when comparing the HRs for major bleeding across regions, with the North American cohort having the highest overall rates, including a significantly higher frequency in the rivaroxaban-treated patients (7.1% vs. 5.0%; HR: 1.43; 95% CI: 1.12 to 1.82)."<sup>87</sup> On the basis of a comprehensive review of observational studies and randomized controlled trials of patients with AF receiving vitamin K antagonists, mostly warfarin, and reporting 1 or 2 measures of anticoagulant therapy such as TTR or percentage of INRs in range, Wan and colleagues found that TTR had a significant relationship with adverse outcomes in all studies, including major hemorrhage and thromboembolic rates. In retrospective studies, a strong negative correlation



existed between TTR and adverse clinical outcomes. As a consequence, assuming a linear relationship, a 7% improvement in TTR would lead to a reduction of 1 major hemorrhage per 100 patient-years, and a 12% improvement in TTR would lead to a reduction of 1 thromboembolic event per 100 patient-years. Interestingly, this inverse association was only evident in retrospective studies and was not observed in randomized controlled trials. The reason for the lack of relationship in RCTs is likely to be the relatively tight control of INR in the studies, which reduces the power of the linear relationship. They concluded their paper writing that : "TTR and percentage of INRs in range can be used to predict adverse events in anticoagulated AF patients and TTR and percentage of INRs in range should both be reported and used as predictors in studies of oral anticoagulation. Anticoagulation services should aim for a TTR between 70% and 80% to optimize benefits and reduce harm for patients. <sup>88</sup> (For other details, see review on "Optimization of vitamin K antagonists laboratory monitoring and tecarfarin, two future solutions for oral anticoagulant therapy ?" ) For what concerns the fact that new oral anticoagulants interfere with less drugs compared with warfarin, this is true, but in the same time they interfere with those drugs such as amiodarone, dronedarone, verapamil and quinidine which are very used in the main indication of these new oral anticoagulation, nonvalvular atrial fibrillation. In addition, they interfere with other important drugs such as antimycotics (ketoconazol, itraconazol, posaconazol, voriconazol), HIV protease inhibitors (rotonavir, indinavir,telaprevir), and with all the other inhibitors of P-glycoprotein which can increase the plasma concentration of new oral anticoagulants because these anticoagulants are substrates of P-glycoprotein. In addition, they interfere with carbamazepine, phenytoin, systemic dexamethasone, phenobarbital, rifampicin, aminoglutethimide and all the other inducers of P-glycoprotein which can significantly reduce plasma concentration of these direct oral anticoagulants <sup>89,90</sup> . In addition, because dabigatran and rivaroxaban are substrates of P-glycoprotein, the ABCB1 gene encoding the P-glycoprotein may have a role in the availability of these drugs. A clinical study, "New oral anticoagulants dabigatran etexilate and rivaroxaban: Influence of genetic factors in healthy volunteers" is currently underway. <http://clinicaltrials.gov/ct2/show/NCT01627665>

Another gene, the ABCG2 gene, encoding another efflux protein, the breast cancer resistance protein (BCRP) may also have a role in the rivaroxaban availability. Homozygous patients of BCRP variants who are in treatment with rivaroxaban and other inhibitors of P-glycoprotein and of CYP3A4 cytochrome, have the greatest bleeding risk. This must be considered especially in older patients with atrial fibrillation who have a renal function that decreases progressively and that rarely can avoid to take drugs that inhibit P-glycoprotein and CYP3A4 cytochrome <sup>91</sup> . In conclusion, new oral anticoagulants (NOACs), or it would be better to call them direct oral anticoagulants (DOACs), must not be used on a large scale but in selected cases only; in patients who cannot reach the specialized Haemostasis and Thrombosis Centres because of health or work problems or because they live very far from these centres, in patients in treatment with vitamin K antagonists with an unstable TTR, in patients who cannot achieve a TTR greater than 64% and in a recent paper of the Italian Federation of Thrombosis Centres (FCSA) evaluating 525 patients with nonvalvular atrial fibrillation in treatment with vitamin K antagonists, DOACs would cover 29% of the patients considering a TTR < 70% and this percentage falls to 10% if a TTR < 55% is considered <sup>92</sup> ; in patients who had an intracranial bleeding while they were in treatment with warfarin and after they must resume the oral anticoagulant therapy, because of a higher risk of recurrence if they resume warfarin as

demonstrated by an Italian study, the CHIRONE study published in 2014 <sup>93</sup>, although at the moment there are no data showing that NOAC are more effective or safer than VKA in patients with a history of intracranial, intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding, since these patients were excluded from the trials investigating the three NOAC dabigatran, rivaroxaban and apixaban <sup>94</sup>. In any case, patients in treatment with warfarin because they have prosthetic heart valves, should resume warfarin also after an intracerebral hemorrhage (ICH). Although be true that not every patient can be well-managed by using warfarin, a large percentage of patients can be. To initiate the NOACs without allowing these potentially well-managed patients to be identified or switching well-managed patients from warfarin to NOACs can be considering a disservice to our patients and to our health system. In the absence of non-inferiority at a TTR greater than 64%, the use of NOACs should be limited to patients who cannot achieve a TTR greater than 64% <sup>95</sup>. Although the first period of anticoagulation with VKA and in particular the first 90 days be associated with a higher rate of hemorrhagic events <sup>96,97</sup> due to occult lesions which can be unmasked at the beginning of anticoagulant therapy and/or to the dose adjustment which may be less adequate in that period <sup>98</sup>, and to concomitant prevalent medications such as antiplatelet therapy that increases bleeding risk and to period-specific factors that confer a transient increase in bleeding risk such as the immediate post-hospitalization period that might be characterized by increased use of heparin transition therapy, or dietary fluctuation or a higher prevalence of acute illness (e.g. gastrointestinal mucosal injury, stress-induced gastritis) associated with haemorrhage, <sup>99</sup> and although patients who initiate warfarin may be at an increased risk of stroke during the first 30 days of treatment, with the highest risk in the first week of therapy, probably due to a transient hypercoagulable state at the start of treatment <sup>100</sup>, a recent large French nationwide propensity-matched cohort study which included patients with nonvalvular atrial fibrillation who initiated dabigatran or rivaroxaban between July and November 2012 (8443 dabigatran and 4651 rivaroxaban new users) or VKA (19713 new users) between July and November 2011, followed for up to 90 days until outcome, death, loss to follow-up or December 31 of the inclusion year, using the French medico-administrative databases SNIIRAM and PMSI, showed that comparing NOAC with VKA, NOACs cannot be considered to be safer than VKA during the early phase of treatment. In particular in this large study there were no statistically significant difference between NOAC, dabigatran or rivaroxaban, and VKA in terms of hospitalizations for bleeding or for arterial thromboembolic events during the early phase of therapy among new users with nonvalvular atrial fibrillation. The authors conclude stating that the clinical implications of their study are that physicians must be just as cautious when initiating NOACs as when initiating VKAs, particularly in view of the absence of antidote commercially available (with the exception of idarucizumab for dabigatran) and of objective monitoring of the extent of anticoagulation. Similar analyses should be extended to other NOACs such as apixaban. Due to the observational study and to the two existing dosage regimens of NOAC, residual confounding by indication is a particular concern in this study. To reduce this bias the authors excluded patients with no NVAF or with contraindications to avoid artificially biasing the treatment effect by ineligible populations or inappropriate treatment indications <sup>101</sup>. Exclusion of these patients could partly explain the apparent discrepancy between their results and those of a recent study based on Medicare data, in which no exclusion were reported <sup>102</sup>. In addition, VKA-treated patients were selected in 2011, a period during which NOACs could not be prescribed in France for stroke

prevention in patients with NVA<sup>F</sup> and analyses were restricted to low and high doses with consistent results as previously described <sup>103</sup>. Since 2009 a new vitamin K antagonist has been developing, tecarfarin that, differently from warfarin and from the other vitamin K antagonists, because is not significantly metabolized by the microsomal enzymes of cytochrome P450, does not interfere with other drugs and food <sup>104,105</sup>. This drug should really be a remarkable progress in the treatment of patients with oral anticoagulant therapy because, as a result of the absence of these interferences, very probably patients in treatment with tecarfarin will need less laboratory controls compared with the other vitamin K antagonists. Very few papers about this drug have been published and after six years, only now it is in the design phase a clinical study of phase III to evaluate the efficacy and safety of this drug compared with warfarin ([armetheon.com/armetheon-announces-fda-agreement](http://armetheon.com/armetheon-announces-fda-agreement)). Although the manufacturer, a small company, emphasizes this drug only as a new step in the treatment of patients with prosthetic heart valves who, as is well known, cannot be treated with new oral anticoagulants, (<https://armetheon.com>) the truth is that very probably this drug could be used with success in all patients who need oral anticoagulant treatment and represent a better solution than the new oral anticoagulants, considered that these last drugs, as shown above, need a laboratory monitoring too because they do not have a "predictable pharmacodynamics and pharmacokinetics" differently from what many "Key opinion leaders" affirm at international meetings and publish on leading medical journals. In a review published by the European Heart Journal in 2014, whose title is "Edoxaban : a focused review of its clinical pharmacology", the authors in the introduction write that "warfarin is subject to a range of limitations in clinical practice. These include : a slow onset of action; a narrow therapeutic margin; inadequate anticoagulation; high discontinuation rates; frequent, complex dose adjustments; increased risk of bleeding, particularly in the elderly; variability in dose response; drug and food interactions; and lack of laboratory standardization in coagulation monitoring" <sup>106</sup>. As written above, with an optimal monitoring of warfarin treatment, with a TTR > / = 70% it is possible to achieve an adequate coagulation and few dose adjustments. The increased bleeding in the elderly people is not only present with warfarin but also with new oral anticoagulants <sup>107</sup>. As described above, the bleeding risk is greater with NOACs than with a skilled clinical and laboratory management of warfarin treatment. However, what is completely not correct is the last statement "lack of laboratory standardization in coagulation monitoring". At the moment not only laboratory monitoring of warfarin is very standardized <sup>66,67,68,69</sup> but it is much better standardized than laboratory tests used to evaluate plasma concentration of Direct Oral Anticoagulants. In addition, as reference of these statements in the introduction part of this paper about edoxaban, is cited a Position Paper of the ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease : "General mechanisms of coagulation and targets of anticoagulants (Section I)" <sup>108</sup>. However, in this paper is not mentioned any of those statements and, in addition, apart from "the slow onset of action" they are not mentioned even in another position paper of the ESC Working Group on Thrombosis-Task Force on Anticoagulants in Heart Disease : Vitamin K antagonists in heart disease : Current status and perspectives (Section III) <sup>109</sup>. In another paper published recently, the authors treat the management of bleeding in patients receiving new oral anticoagulants. Also in this paper are emphasized the great properties of new oral anticoagulants compared with warfarin. The authors write again that these drugs do not need laboratory monitoring because they have a predictable

anticoagulant response, that the incidence of intracranial bleedings is less compared with that obtained in warfarin treated patients, and “real-word studies have supported the efficacy and safety of these agents in routine clinical practice” . In this paper it is also treated a review of bleeding events occurred in clinical trials about new oral anticoagulants, all sponsored by drug manufacturers, and as is already known, in many cases their incidence is less compared with the incidence of bleeding events in patients treated with warfarin with the exceptions of gastrointestinal bleedings in dabigatran and rivaroxaban treated patients<sup>110</sup>. Several conflicts of interests are declared by the authors at the end of these two papers <sup>106,110</sup>. Whereas previous studies investigating the use of VKA for primary and secondary stroke prevention in atrial fibrillation were carried out by industry-independent institutions, all the large NOAC trials were sponsored by the manufacturers of the respective drugs. In addition, the majority of authors had either disclosures in relation to or were employees of the manufacturer. For this there is an urgent need for manufacturer-independent studies investigating NOACs. These manufacturer-independent studies would cost many million dollars. Due to the much higher price of NOAC compared with VKA and the increasing prevalence of AF patients due to the demographic development, governmental and non-governmental health care organisations should consider organization of such trials, preferably on an international level <sup>94</sup>. On the other hand in the past we already had some other examples such as the selective COX2 inhibitors, when the appearance of these drugs in the market was greeted enthusiastically and after thousands of adverse reactions such as myocardial infarction and stroke this enthusiasm disappeared <sup>111,112</sup> , and such as menopausal hormone replacement therapy that for many years was prescribed to about all women in menopause and now on the contrary is considered appropriate for menopausal symptoms management only in some women, <sup>113,114</sup> in particular in recently menopausal women who do not have contraindications, such as an excess risk of breast cancer or cardiovascular disease and who have a personal preference for such therapy <sup>115,116</sup> . I hope that also new oral anticoagulants in the future will be used in selected cases only. On the other hand dabigatran manufacturer is already facing more than 4,000 law suits in the United States and in January 2014 the New York Times reported that the employees were worried about publishing a research paper suggesting that patients taking dabigatran may require blood monitoring <sup>117</sup> . Just recently The British Medical Journal revealed that the Point-of-care device made by Alere, used to monitor the International Normalized Ratio (INR) of warfarin in the ROCKET AF trial was subject to a recall. In December 2014 a recall notice said that certain INRatio devices could deliver INR results that were “clinically significantly lower” than a laboratory INR method. It said that Alere had received 18924 reports of malfunctions, including 14 serious injuries. As a consequence, in the ROCKET AF trial, a falsely low reading could have led in the warfarin arm to unnecessary adjusted dosages which increased the risk of bleeding in patients in treatment with warfarin. In term of the trial results, it could make rivaroxaban seem better than it was at reducing the risk of bleeding. Even before the recall, the ROCKET AF trial had been criticized for the “poor” Time in Therapeutic Range (TTR). The criticism was that patients' use of warfarin was not adequately controlled, which, if correct, would have the effect of making rivaroxaban seem safer and more effective. When the Food and Drug Administration (FDA) approved rivaroxaban, one of the advisory committee members, the cardiologist Steven Nissen of the Cleveland Clinic, Cleveland, Ohio, said that the trial's approach to warfarin treatment “was a fatal flaw in the study design”. An FDA reviewer also said in a memo to



the FDA that the "poor warfarin control" in the ROCKET-AF trial biased the study in favor of rivaroxaban". Other FDA advisory committee members, however, commended the fact that ROCKET-AF used warfarin as it would be used in the real world<sup>118</sup>. However many investigators call "real world studies", studies in which patients in treatment with warfarin do not receive a correct laboratory monitoring that on the contrary, today is possible to achieve in routine clinical practice<sup>64</sup>, in small laboratories too. Robert Califf, President Barack Obama's nominee for the head of the FDA, who co-chaired the executive committee of the trial, said that the researchers "gave warfarin not only in an acceptable way, we gave it in a commendable way during this trial".<sup>118</sup> However the two primary clinical FDA reviewers cited above, also wrote in an FDA decisional memo about rivaroxaban approval that "ROCKET provides inadequate information to assess the relative safety and efficacy of Xarelto in patients whose warfarin administration can be well-controlled". In a letter submitted to the NEJM, not yet published and shown to the British Medical Journal, former FDA cardiovascular and renal drug reviewer, Thomas Marciniak, says: "The care for the warfarin control arm patients in the ROCKET-AF appears to have been compromised". In september 2015, The BMJ asked the investigators of the trial about the recall, but none of them responded. A spokesperson for Johnson and Johnson contacted the BMJ to say that they were "unaware of this recall" and they took the journal's concern "seriously", but it took months before the companies, world drug regulators, and Duke began to investigate the problem. When The BMJ contacted the European Medicine Agency (EMA) in April 2015 and the FDA, both said they did not know that the recalled device had been used in ROCKET-AF. In November the EMA told The BMJ it was investigating and after told journalists: "Due to the defect it is now thought that INR device may have impacted the clotting results in some patients in the warfarin group". Executive director of EMA, Guido Rasi, said: "It would be nice to have some independent study carried out to give confidence in the use of this medicine". Harlan Krumholz, professor of Cardiology at Yale University, says that the NEJM should place an "immediate expression of concern" on the paper to notify the medical community. He said that "the study should be considered of uncertain validity until a more thorough review can be done" and adding that should also be done "an investigation by an independent group of experts to quickly determine if there are grounds for retraction". At the moment there is little public information about which diagnostic point of care devices are used in any of the direct oral anticoagulant trials. They are not cited in the published phase III trials. In the letter sent to NEJM Dr. Marciniak wrote that "You should require that the devices used in trials are clearly and specifically identified in your publications". In 2005 a warning letter from the FDA to HemoSense, the company that owned the faulty device before Alere bought it, was written that there were "clinically significant erroneous" high and low INR results generated by the point of care device. "Both high and low test INR results have the potential to cause or contribute to a death or serious injury because they may result in erroneous dosing and thus improper control of coagulation". Despite these warning letters, the FDA approved subsequent iterations of the device through its regulatory system that requires makers of such devices to show only that the new version is "substantially equivalent", or similar, to one already on the market. This system has been criticised by the Institute of Medicine because does not provide enough evidence that a device is safe and effective. Alere told to The BMJ that the faulty device dates to 2002 and it may occur in all devices and not just in one batch. However, neither it nor the FDA responded to The BMJ why nothing had been done about this problem earlier. The BMJ

asked Johnson and Johnson, Bayer, and Duke if they validate the device at any point during the trial but none responded to the question. According to former FDA clinical pharmacologist, Bob Powell, the specificity and reproducibility of a diagnostic test or assay is vital to the performance of a trial. He said that "the fact that this was apparently not previously done nor reported in the primary publication is concerning as this is a basic principle in drug development". During the trial INR at 12 and 24 weeks was measured at a central laboratory as well as with the point of care device. Powell said that "a comparison should be made between the defective point of care readings and the two sets of gold standard central lab readings" as this would "determine whether this defective device undermined the integrity of the trial results". It is not clear that this has happened.<sup>119</sup> Recently has been published a letter in the New England Journal of Medicine in which the authors of the ROCKET AF trial report the results of their secondary analysis of the trial findings and state that the findings from the analysis are consistent with the results from the original trial and do not alter the conclusions of ROCKET AF and rivaroxaban is a reasonable alternative to warfarin and is non-inferior for the prevention of stroke and systemic embolism with less intracranial hemorrhage and fatal bleeding.<sup>120</sup> Dr. Marciniak said that he would not rely on any reanalysis done by Duke, Johnson and Johnson, or the FDA. He told The BMJ that "because they already missed the problems both in the trial and with the public marketing, I would not trust them to publish anything that is accurate or that provides any details". He added that datasets need to be released as "the only solution that would lead to unbiased analyses", however Bayer denied to Dr. Krumholtz the access to these data.

At the end of 2015, both the EMA and the FDA held meetings to discuss the need to measure blood levels of direct oral anticoagulants and adjust the dose accordingly to maximise benefit and minimise harm despite manufacturers claimed that this is not necessary.<sup>119</sup> The meetings were held after The BMJ revealed that Boehringer Ingelheim, manufacturer of dabigatran withheld analyses from the regulators that showed that 30-40% of major bleeding events could be prevented by monitoring anticoagulant activity and adjusting the dose.<sup>70</sup> A presentation to EMA last year by Robert Temple, deputy director for clinical science at the FDA's Center for Drug Evaluation and Research, suggests that the FDA believes that there is scientific evidence for measuring NOACs blood levels and adjusting the dose. He said that "being too low leads to a stroke, and being too high leads to major bleeds, so that early optimization of the dose seems worthwhile".<sup>118</sup> An article appeared in The New York Times on March 1, 2016 has revealed that lawyers for patients suing Johnson & Johnson and Bayer over the safety of the anticlotting drug Xarelto were claiming that the letter published in the NEJM<sup>120</sup> left out critical laboratory data that could have been used to evaluate the device's accuracy.

They claim the companies were complicit by staying silent, helping deceive the editors while the companies were in the midst of providing the very same data to regulators in the United States and Europe. Duke and Johnson & Johnson contend that they worked independently of each other. Bayer declined to comment. Asked to comment, a spokesperson for the NEJM said: "During the editing process....the editors told the authors that they would like to see a systematic evaluation of routinely obtained central laboratory INR data but assumed that such data did not exist. Only two data points existed for a subset of the study population. Without a substantial majority of paired values, a comparison between the two methods would not be clinically directive". "It just feels like it's a real ethical breach" said Dr. Lisa Schwartz, a professor of medicine at Dartmouth, of the failure to



include the lab data in the letter. "If you know the direct answer to this question, then how can you not provide it to be able to give insight?". Other researchers said that to correctly evaluate the device, it should be compared the device readings with test results that were done at a central laboratory. Investigators did that at two points in the trial, drawing blood from more than 5,000 of the patients who took warfarin and sending the samples for testing. The blood was taken 12 and 24 weeks after patients enrolled in the trial. However, the Duke researchers made no mention of the lab data in their letter. In an interview, journal editors said they did not know about the lab data until last Tuesday, when a reporter for The New York Times asked them about it. Lawyers in the case against Johnson & Johnson and Bayer filed a legal brief in federal court in New Orleans, asking a judge to unseal documents in the case, which involves more than 5,000 lawsuits filed by patients and their families who claim they were harmed by Xarelto. Of those, 500 involve patient deaths. In a footnote, the lawyers said that a peer reviewer asked about the existence of lab data that would allow a comparison with the device's readings. "Despite being provided this opportunity to respond to the peer reviewers" the lawyers said, the "defendants remained silent on this point, thereby misleading the NEJM". Duke said it had conducted its research separately from the two companies, but this fall, Bayer submitted an analysis to the European Medicines Agency that was nearly identical to the approach used by the Duke researchers, comparing the outcomes of patients who had specific medical conditions with outcomes of those who did not. Many researchers said they were surprised that Duke and the editors at the journal did not see value in comparing the lab data, especially since Bayer and Johnson & Johnson have submitted such information to regulators in Europe and the United States. "I think it's always important to make sure that you have all the information to answer the scientific question before publication" said Dr. Rita F. Redberg, a cardiologist who is also editor of JAMA Internal Medicine. Dr. Steven Nissen, a cardiologist at the Cleveland Clinic, who served on the FDA advisory panel that voted to approve Xarelto in 2011 and who was one of the two members who voted against the drug said: "Given the fact that the device was inaccurate, there is no way anybody can tell you what would have happened in the trial".<sup>121</sup>

The actual federal legislation in the US uses a national public registry that discloses physicians' financial relations with the pharmaceutical and medical device industry to tackle commercial conflicts of interest, known as Physician Sunshine Act (PSA). However, the disclosure of the commercial conflict of interests which became the governance option of choice on Wall Street, did not prevent further scandals and kept the biases in tact. A similar pattern was also seen in psychiatric medicine and has led to the call to go beyond transparency to combat bias. In medicine, isolating a bias and assessing its implications normally involves specialised training, knowledge and practice. The need for these tools and how to use them is especially important given that bias often functions in a self-serving unconscious way. Disclosure of conflicts of interests has been emphasized as a cure-all. However, transparency is clearly not a panacea or a magic weapon and cannot effectively combat bias as the evidence shows. The debate on how to mitigate the negative influences of bias has been focused mainly around the need to disclose commercial conflict of interests. As a consequence, our attention and that of governmental institutions has been diverted from the commercial conflict of interests themselves and their corrupting influence. Disclosure is insufficient to ensure the independent assessment of the integrity of data. However, a national registry that discloses commercial conflict of interests could play an important role. From such a

registry, experts who are free of commercial conflict of interests could serve on practice guidelines and oversight committees that assess the integrity of medical data. Members of such committees should have unfettered access to raw clinical trial data, past, present and future in order to better ensure public trust in a healthcare system in which commercial conflict of interests are so common<sup>122</sup> "As we apply new science to develop new medicines, we must not forget that our first job is to do no harm"<sup>123</sup>. At the moment prescription drugs are the third leading cause of death after heart disease and cancer. "The main reason we take so many drugs is that drug companies don't sell drugs, they sell lies about drugs. This is what makes drugs so different from anything else in life. If we wish to buy a car or a house, we may judge for ourselves whether it is a good or a bad buy, but if we are offered a drug, we have no such possibility. Virtually everything we know about drugs is what the companies have chosen to tell us and our doctors. The main problem with our healthcare system is that the financial incentives that drive it seriously impede the rational, economical and safe use of drugs. The drug industry prospers on this and exerts tight information control. The research literature on drugs is systematically distorted through trials with flawed designs and analyses, selective publication of trials and data, suppression of unwelcome results, and ghostwritten papers. Ghostwriters write manuscripts for hire without revealing their identity in the papers, which have influential doctors as authors, although they have contributed little or nothing to the manuscript. This scientific misconduct sells drugs. The patients do not realise that, although their doctors may know a lot about diseases and human physiology and psychology, they know very, very little about drugs that has not been carefully concocted and dressed up by the drug industry. Furthermore, they do not know that their doctors may have self-serving motives for choosing certain drugs for them, or that many of the crimes committed by the drug industry would not be possible if doctors did not contribute to them. Compared to other industries, the pharmaceutical industry is the biggest defrauder of the US federal government under the False Claims Act. Many people at senior levels in the drug industry have deliberately told lies to doctors, patients, regulators and judges".<sup>124</sup>

In conclusion, the truth is that at the moment vitamin K antagonists are still the drugs of first choice in the oral anticoagulant treatment in countries where it is possible to obtain a TTR about or higher than 65%. For a TTR  $\leq$  50%, it is even better not to treat NVAf patients with warfarin because, in this case, we will have a major incidence of stroke.

## References :

- 1) Asmis Lars M. : Direct oral anticoagulants (DOACs) versus "New" oral anticoagulants (NOACs) ? Seminars in Hematology 2014; 51 (2) : 87-88
- 2) Dempfle Carl-Erik : Direct oral anticoagulants-Pharmacology, drug interactions, and side effects. Seminars in Hematology 2014; 51 (2) : 89-97
- 3) Levy Jerrold H., Spyropoulos Alex C., Samama Charles M. et al. : Direct oral anticoagulants : new drugs and new concepts. Journal of the American College of Cardiology : Cardiovascular Interventions 2014; 7 (12) : 1333-1351
- 4) Fontana Pierre, Goldhaber Samuel Z., Bounameaux Henri : Direct oral anticoagulants in the treatment and long-term prevention of venous thrombo-embolism. European Heart Journal 2014; 35 (28) : 1836-1843

- 5) Eikelboom John W., Weitz Jeffrey I. : Update on antithrombotic therapy. New Anticoagulants. Circulation 2010; 121 : 1523-1532
- 6) van Es Nick, Coppens Michiel, Schulman Sam et al. : Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism : evidence from phase III trials. Blood 2014; 124 : 1968-1975
- 7) Yeh Calvin H. Gross Peter L., Weitz Jeffrey I. : Evolving use of new oral anticoagulants for treatment of venous thromboembolism. Blood 2014; 124 : 1020-1028
- 8) Vedovati M.C., Germini F., Agnelli G. et al. : Direct oral anticoagulants in patients with VTE and cancer : a systemic review and meta-analysis. Chest 2015; 147 (2) : 475-483
- 9) Ruff Christian T., Giugliano Robert P., Braunwald Eugene et al. : Comparison of efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation : a meta-analysis of randomised trials. The Lancet 2014; 383 (9921) : 955-962
- 10) Hart Robert G., Pogue Janice, Eikelboom John W. : Direct-acting oral anticoagulants. The brain gets a break. JAMA Neurology 2013; 70 (12) : 1483-1484
- 11) Lip Gregory Y.H. and Agnelli Giancarlo : Edoxaban : a focused review of its clinical pharmacology. European Heart Journal 2014; 35 : 1844-1855
- 12) Schulman Sam, Kakkar Ajay K., Goldhaber Samuel Z. et al. : Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation 2014; 129 : 764-772
- 13) Granger Christopher B., Armaganjian Luciana V. : Newer oral anticoagulants should be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. Circulation 2012; 125 : 159-164
- 14) Haas Sylvia, Turpie Alexander G.G. : Real-life studies : treating pulmonary embolism and/or deep vein thrombosis with novel oral anticoagulants in routine clinical practice. Thrombosis Adviser Newsletter. A Venous & Arterial Thrombosis Resource For Physicians. July 6, 2015
- 15) Ansell Jack : New oral anticoagulants should not be used as first-line agents to prevent thromboembolism in patients with atrial fibrillation. Circulation 2012; 125 : 165-170
- 16) ten Cate Hugo : New oral anticoagulants : discussion on monitoring and adherence should start now! Thrombosis Journal 2013; 11 : 8
- 17) Patel Jignesh P., Couchman Lewis, Chitongo Paradzai B. et al. : New oral anticoagulants : dosing and monitoring. British Medical Journal 2015; 350:h2655
- 18) Favaloro Emmanuel J., Lippi Giuseppe : Laboratory testing in the era of direct or non-vitamin K antagonist oral anticoagulants : A practical guide to measuring their activity and avoiding diagnostic errors. Seminars in Thrombosis and Hemostasis 2015; 41 : 208-227
- 19) Tripodi Armando : The laboratory and the new oral anticoagulants. Clinical Chemistry 2013; 59 (2) : 353-362
- 20) Chandler Wayne L. : Anticoagulation without monitoring. American Journal Clinical Pathology 2013; 140:606-607
- 21) Poller L., Jespersen J., Ibrahim S. et al. : Phase III studies on novel oral anticoagulants for stroke prevention in atrial fibrillation : a look beyond the excellent results : a rebuttal. Journal of Thrombosis and Haemostasis 2013; 11 (6) : 1203-1205
- 22) Bussey Henry I. : The future landscape of anticoagulation management. Pharmacotherapy 2011; 31 (12) : 1151-1155

- 23) Douxfils J., Mullier R., Robert S. et al. : Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate. *Thrombosis Haemostasis* 2012; 107 : 985-997
- 24) Reilly P.A., Lehr T., Haertter S. et al. : The effect of dabigatran plasma concentration and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients : The RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). *Journal of the American College of Cardiology* 2014; 63: 321-328
- 25) Connolly Stuart J., Ezekowitz Michael D., Yusuf Salim et al. : Dabigatran versus warfarin in patients with atrial fibrillation. *New England Journal of Medicine* 2009;361: 1139-11518
- 26) Samama M.M., Guinet C., Le Flem L. et al. : Measurement of dabigatran and rivaroxaban in primary prevention of venous thromboembolism in 106 patients who have undergone major orthopedic surgery : an observational study. *Journal of Thrombosis and Thrombolysis* 2013; 35 : 140-146
- 27) Gong Inna Y. and Kim Richard B. : Importance of pharmacokinetic profile and variability as determinants of dose and response to dabigatran, rivaroxaban, and apixaban. *Canadian Journal of Cardiology* 2013; 29: S24-S33
- 28) Freyburger Geneviève, Macouillard Gérard, Khennoufa Karim et al. : Rivaroxaban and apixaban in orthopaedics : is there a difference in their plasma concentrations and anticoagulant effects ? *Blood Coagulation and Fibrinolysis* 2015; 26 : 925-933
- 29) Brunner-Ziegler S., Jilma B., Schorgenhofer C. et al. : Comparison between the impact of morning and evening doses of rivaroxaban on the circadian endogenous coagulation rhythm in healthy subjects. *Journal of Thrombosis and Haemostasis* 2016, 14 : 316-323
- 30) Skeppholm Mika, Al-Aieshy Fadiea, Berndtsson Maria et al. : Clinical evaluation of laboratory methods to monitor apixaban treatment in patients with atrial fibrillation. *Thrombosis Research* 2015; 136 : 148-153
- 31) Skeppholm Mika, Hjemdahl Paul, Antovic Jovan P. et al. : On the monitoring of dabigatran treatment in "real life" patients with atrial fibrillation. *Thrombosis Research* 2014; 134 : 783-789
- 32) Schellings M.W.M., Boonen K., Schmitz E.M.H. et al. : Determination of dabigatran and rivaroxaban by ultra-performance liquid chromatography-tandem mass spectrometry and coagulation assays after major orthopaedic surgery. *Thrombosis Research* 2016; 139 : 128-134
- 33) Testa Sophie, Tripodi Armando, Legnani Cristina et al. : Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation : Results observed in four anticoagulation clinics. *Thrombosis Research* 2016; 137 : 178-183
- 34) Douxfils J., Lessire S., Dincq A.S. et al. : Estimation of dabigatran plasma concentration in the perioperative setting. *Thrombosis Haemostasis* 2015; 113 : 862-869
- 35) Samama M.M., Amiral J., Guinet C. et al. : An optimised, rapid chromogenic assay, specific for measuring direct factor Xa inhibitors (rivaroxaban) in plasma. *Thrombosis Haemostasis* 2010; 104 (5) : 1078-1079
- 36) Becker R.C., Yang H., Barrett Y. et al. : Chromogenic laboratory assays to measure the factor Xa inhibiting properties of apixaban-an oral, direct and selective factor Xa inhibitor. *Journal of Thrombosis and Thrombolysis* 2011; 32 (2) : 183-187

- 37) Gouin-Thibault I., Flaujac C., Delavenne X. et al. : Assessment of apixaban plasma levels by laboratory tests : suitability of three anti-Xa assays. *Thrombosis Haemostasis* 2014; 111 (2) : 240-248
- 38) Cuker Adam and Husseinzadeh Holleh : Laboratory measurement of the anticoagulant activity of edoxaban : a systematic review. *Journal of Thrombosis and Thrombolysis* 2015; 39 (3) : 288-294
- 39) Samama M.M., Martinoli J.L., LeFlem et al. : Assessment of laboratory assays to measure rivaroxaban-an oral, direct factor Xa inhibitor. *Thrombosis Haemostasis* 2010; 103 (4) : 815-825
- 40) Tripodi A., Chantarangkul V., Guinet C. et al. : The international normalized ratio calibrated for rivaroxaban has the potential to normalize prothrombin time results for rivaroxaban-treated patients : results of an in vitro study. *Journal of Thrombosis and Haemostasis* 2011; 9 (1) : 226-228
- 41) Harenberg J., Marx S., Kramer R. et al. : Determination of an international sensitivity index of thromboplastin reagents using a WHO thromboplastin as calibrator for plasma spiked with rivaroxaban. *Blood Coagulation and Fibrinolysis* 2011; 22 (8) : 637-641
- 42) Schmitz E.M.H., Boonen K., Van Den Heuvel D.J.A. et al. : Determination of dabigatran, rivaroxaban and apixaban by ultra-performance liquid chromatography- tandem mass spectrometry (UPLC-MS/MS) and coagulation assays for therapy monitoring of novel direct oral anticoagulants. *Journal of Thrombosis and Haemostasis* 2014; 12 : 1636-1646
- 43) Lip Gregory Y.H., Douketis James D., Leung Lawrence L.K. et al. : Perioperative management of patients receiving anticoagulants. [www.uptodate.com](http://www.uptodate.com) May 2015
- 44) Ferrandis Raquel, Castillo Jordi, de Andrés José et al. : The perioperative management of new direct oral anticoagulants : a question without answers. *Thrombosis Haemostasis* 2013; 110 : 515-522
- 45) Pernod G., Albaladejo P., Godier A. et al. : Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors : Proposals of the Working Group on Perioperative Haemostasis (GIHP)-March 2013. *Archives of Cardiovascular Diseases* 2013; 106 (6-7) : 382-393
- 46) Glund Stephan, Moschetti Viktoria, Norris Stephen et al. : A randomised study in healthy volunteers to investigate the safety, tolerability and pharmacokinetics of idarucizumab, a specific antidote to dabigatran. *Thrombosis Haemostasis* 2015; 113 : 943-951
- 47) Pollack Charles V., Reilly Paul A., Eikelboom John et al. : Idarucizumab for dabigatran reversal. *New England Journal of Medicine* 2015; 373 : 511-520
- 48) [www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/761025lbl](http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl)
- 49) Ansell Kack E., Bakhru Sasha H., Grosso Michael et al. : Use of PER977 to reverse the anticoagulant effect of edoxaban. *New England Journal of Medicine* 2014; 371 : 2141-2142
- 50) Lu G., Kotha J., Cardenas J.M. et al. : In vitro characterization of andexanet alfa (PRT064445), a specific FXa inhibitor antidote versus aripazine (PER977), a Non-specific reversal agent. *Circulation* 2014; 130 : A18218 Abstract
- 51) Lu G., DeGuzman F.R., Hollenbach S.J. et al. : A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nature Medicine* 2013 19 (4) : 446-451
- 52) Shah Neal, Rattu Mohammad A. : Reversal agents for anticoagulants : Focus on andexanet alfa. *American Medical Student Research Journal* 2014; 1 (1) : 16-28
- 53) Siegal Deborah M., Curnutte John T., Connolly Stuart J. et al. : Andexanet alfa for the reversal of factor Xa inhibitor activity. *New England Journal of Medicine* 2015; 373:2413-2424



- 54) Ansell Jack E. : Universal, class-specific and drug-specific reversal agents for the new oral anticoagulants. *Journal of Thrombosis and Thrombolysis* 2016; 41 : 248-252
- 55) Makris Mike, Van Veen Joost J., Tait Campbell R. et al. : Guideline on the management of bleeding in patients on antithrombotic agents. *British Journal of Haematology* 2012; 160 : 35-46
- 56) Barcellona Doris, Contino Laura, Erba Nicoletta et al. Guida alla terapia con anticoagulanti orali. Raccomandazioni della Federazione dei Centri per la diagnosi della Trombosi e la Sorveglianza delle Terapie Antitrombotiche (FCSA) 2014; 17 : 159-168
- 57) Dager William E., Gosselin Robert C., Roberts A. : Reversing dabigatran in life-threatening bleeding occurring during cardiac ablation with factor eight inhibitor bypassing activity. *Critical Care Medicine* 2013; 41 (5) : e42-e46
- 58) Schulmann Sam, Ritchie Bruce, Goy Jennifer K. Et al. : Activated complex concentrate for dabigatran-associated bleeding. *British Journal of Haematology* 2013; 64 : 308-310
- 59) Wong Henna and Keeling David : Activated prothrombin complex concentrate for the prevention of dabigatran-associated bleeding. *British Journal of Haematology* 2014; 166 : 152-153
- 60) Baumann Kreuziger Lisa M., Keenan Joseph C., Morton Colleen T. et al. : Management of bleeding patient receiving new oral anticoagulants : a role for prothrombin complex concentrates. *BioMed Research International* Volume 2014, Article ID 583794 <http://dx.doi.org/10.1155/2014/583794>
- 61) Siegal Deborah, M., Garcia David A. and Crowther Mark A. : How I treat target-specific oral anticoagulant-associated bleeding. *Blood* 2014; 123 (8) : 1152-1158
- 62) Lindhal T., Wallstedt M., Gustafsson K.M. et al. : More efficient reversal of dabigatran inhibition of coagulation by activated prothrombin complex concentrate or recombinant factor VIIa than by four-factor prothrombin complex concentrate. *Thrombosis Research* 2015; 135 : 544-547
- 63) Warkentin Theodore E., Margetts Peter, Connolly Stuart J. et al. : Recombinant factor VIIa (rVIIa) and hemodialysis to manage massive dabigatran-associated postcardiac surgery bleeding. *Blood* 2012; 119 (9) : 2172-2174
- 64) Sjogren Vilhelm, Grzymala-Lubanski Bartosz, Renlund Henrik et al. : Safety and efficacy of well managed warfarin. A report from the Swedish quality register Auricula. *Thrombosis Haemostasis* 2015; 113 : 1370-1377
- 65) Eikelboom John W., Connolly Stuart J., Brueckmann Martina et al. : Dabigatran versus warfarin in patients with mechanical heart valves. *New England Journal of Medicine* 2013; 369 : 1206-1214
- 66) Poller Leon, Jespersen J. and Ibrahim S. : Warfarin or dabigatran for treatment of atrial fibrillation. *Journal of Thrombosis and Haemostasis* 2014; 12 : 1193-1195
- 67) Poller Leon, Ibrahim Saied, Pattison Albert et al. : INR derivation with the PT/INR Line simplified using a spreadsheet from world wide web. *Journal of Clinical Pathology* 2011; 64 : 930-932
- 68) Onundarson Pall T., Francis Charles W., Indridason Olafur S. et al. : Fiix-prothrombin time versus standard prothrombin time for monitoring of warfarin anticoagulation : a single centre, double-blind, randomised, non-inferiority trial. *The Lancet Haematology* 2015; 2 (6) : e231-e240
- 69) Lippi Giuseppe, Favaloro Emmanuel : Laboratory monitoring of warfarin in the era of direct oral anticoagulants. *The Lancet Haematology* 2015; 2 (6) : e223-e224
- 70) Letertre L.R., Gudmundsdottir B.R., Francis C.W. et al. : A single test to assay warfarin, dabigatran, rivaroxaban, apixaban, unfractionated heparin and enoxaparin in plasma. *Journal of*



Thrombosis and Haemostasis published online, February 29, 2016 DOI: 10.1111/jth.13300

71) European Medicine Agency. Pradaxa Summary of product characteristics Ed. 2014

72) Pernod G., Albaladejo P., Godier A. et al. : Working Group on Perioperative Management of major bleeding complications and emergency surgery in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors : proposals of the working group on perioperative haemostasis (GIHP) March 2013. Archives of Cardiovascular diseases 2013; 106 : 382-393

73) Cohen Deborah : Dabigatran : How the drug company withheld important analyses. British Medical Journal 2014; 349:g4670

74) Thomas Katie : Study of drug for blood clots caused a stir, records show. New York Times, February 4, 2014

75) Thomas Katie : New emails in Pradaxa case show concern over profit. New York Times, February 7, 2014

76) Executive steering committee on behalf of the SPORTIF III investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with nonvalvular atrial fibrillation (SPORTIF III) : randomised controlled trial. Lancet 2003; 362 : 1691-1698

77) SPORTIF executive steering committee for the SPORTIF V investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. A randomised trial. JAMA 2005; 293 : 690-698

78) Aguilar M.I., Hart R. : Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. Cochrane Database of Systematic Reviews 2005; Issue 3 . Art. No. : CD001927. DOI: 10.1002/14651858.CD001927.pub2.

79) Aguilar M.I., Hart R., Pearce L.A. : Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No. : CD006186. DOI:10.1002/14651858.CD006186.pub.2

80) Connolly Stuart J., Pogue Janice, Eikelboom John et al. : Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of International Normalized Ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008; 118 : 2029-2037

81) Gallagher Arlene M., Setakis Efrosini, Plumb Jonathan M. et al. : Risks of stroke and mortality associated with suboptimal anticoagulation in atrial fibrillation patients. Thrombosis and Haemostasis 2011; 106 : 968-977

82) Tosetto Alberto, Manotti Cesare, Marongiu Francesco : Center-related determinants of VKA anticoagulation quality : A prospective, multicenter evaluation. PLOS ONE 10 (12) : e0144314.doi:10.1371/journal.pone.0144314

83) Mueller Sabrina, Pfannkuche Matthias, Breithardt Gunter et al. : The quality of oral anticoagulation in general practice in patients with atrial fibrillation. European Journal of Internal Medicine 2014; 25 (3) : 247-254

84) Wieloch M., Sjalander A., Frykman V. et al. : Anticoagulation control in Sweden : reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality

registry Auricula. European Heart Journal 2011; 32 : 2282-2289

85) Nielsen P.B., Lundbye-Christensen S., Rasmussen L.H. et al. : Improvement of anticoagulant treatment using a dynamic decision support algorithm : a Danish cohort study. Thrombosis Research 2014; 133 : 375-379

86) Singer Daniel E., Hellkamp Anne S., Piccini Jonathan P. et al. : Impact of global region on time in therapeutic range on warfarin anticoagulant therapy : Data from the ROCKET AF clinical trial. Journal of the American Heart Association 2013; 2 : e000067 doi:10.1161/JAHA.112.000067

87) Goodman Shaun G., Wojdyla Daniel M., Piccini Jonathan et al. : Factors associated with major bleeding events. Journal of The American College of Cardiology 2014; 63 : 891-900

88) Wan Yi, Heneghan Carl, Perera Rafael et al. : Anticoagulation control and prediction of adverse events in patients with atrial fibrillation. A systematic review. Circulation 2008; 1 : 84-91

89) Massicotte Anne : A practice tool for the new oral anticoagulants. Canadian Pharmacists Journal 2014; 147 (1) : 25-32

90) Nutescu Edith, Chuatrisorn Ittiporn, Hellenbart Erika : Drug and dietary interactions of warfarin and novel oral anticoagulants : an update. Journal of Thrombosis and Thrombolysis 2011; 31 (3) : 326-343

91) Gong Inna Y., Mansell Sara E. and Kim Richard B. : Absence of both MDR1 (ABCB1) and breast cancer resistance protein (ABCG2) transporters significantly alters rivaroxaban disposition and central nervous system entry. Basic & Clinical Pharmacology & Toxicology 2013; 112 : 164-170

92) Barcellona Doris, Luzzza Miro, Battino Luca et al. : The criteria of the Italian Federation of Thrombosis Centres on DOACs : A "real word" application in nonvalvular atrial fibrillation patients already on vitamin K antagonists. Internal and Emergency Medicine 2015; 10 (2) : 157-163

93) Poli D. Antonucci E., Dentali F. et al. : Recurrence of ICH after resumption of anticoagulation with vitamin K antagonists : CHIRONE study. Neurology 2014; 82 (12) : 1020-1026

94) Stollberger Claudia and Finsterer Josef : Contra : "New oral anticoagulants should not be used as 1<sup>st</sup> choice for secondary stroke prevention in atrial fibrillation". Thrombosis and Haemostasis 2013; 110 : 496-500

95) Trusler Murray : Well-managed warfarin is superior to NOACs. Canadian Family Physicians 2015; 61 : 23-24

96) Palareti G., Leali N., Coccheri S. et al. : Bleeding complications of oral anticoagulant treatment : an inception- cohort, prospective collaborative study (ISCOAT), Italian Study on Complications of Oral Anticoagulant Therapy). The Lancet 1996; 348 : 423-428

97) Hylek E.M., Evans M.C., Shea C. et al. : Major hemorrhage and tolerability of warfarin in the first year of therapy among elderly patients with atrial fibrillation. Circulation 2007; 115 : 2689-2696

98) Palareti Gualtiero and Cosmi Benilde : Bleeding with anticoagulant therapy - Who is at risk, and how best to identify such patients. Thrombosis and Haemostasis 2009; 102 : 268-278

99) Garcia David A., Lopes Renato D., Hylek Elaine M. : New-onset atrial fibrillation and warfarin initiation : High risk periods and implications for new antithrombotic drugs. Thrombosis and Haemostasis 2010; 104 : 1099-1105

100) Azoulay Laurent, Dell'Aniello Sophie, Simon Teresa A. et al. : Initiation of warfarin in patients with atrial fibrillation : early effects on ischaemic strokes. European Heart Journal 2014; 35 : 1881-1887

- 101) Géric Maura, Blotière Pierre-Olivier, Bouillon Kim et al. : Comparison of the short-term risk of bleeding and arterial thromboembolic events in nonvalvular atrial fibrillation patients newly treated with dabigatran or rivaroxaban versus vitamin K antagonists. A french nationwide propensity-matched cohort study. *Circulation* 2015; 132 : 1252-1260
- 102) Immaculada Hernandez, Baik Seo Hyon, Pinera Antonio et al. : Risk of bleeding with dabigatran in atrial fibrillation. *JAMA Internal Medicine* 2015; 175 (1) : 18-24
- 103) Psary B.M. and Siscovick D.S. : Minimizing bias due to confounding by indication in comparative effectiveness research : the importance of restriction. *JAMA* 2010;304:897-898
- 104) Ellis David J., Usman Mohammed Haris, Milner Peter G. et al. : The first evaluation of a novel vitamin K antagonist, tecarfarin (ATI-5923), in patients with atrial fibrillation. *Circulation* 2009; 120 : 1029-1035
- 105) Choppin A., Irwin I., Lach L. et al. : Effect of tecarfarin, a novel vitamin K epoxide reductase inhibitor, on coagulation in beagle dogs. *British Journal of Pharmacology* 2009; 158 : 1536-1547
- 106) Lip Gregoty Y.H. and Agnelli Giancarlo : Edoxaban : a focused review of its clinical pharmacology. *European Heart Journal* 2014; 35 : 1844-1855
- 107) Sardar Partha, Chatterjee Saurav, Chaudhari Shobhana et al. : New oral anticoagulants in elderly adults : evidence from a meta-analysis of randomized trials: *Journal of the American Geriatrics Society* 2014; 62 (5) : 857-864
- 108) De Caterina Raffaele, Husted Steen, Wallentin Lars et al. : General mechanisms of coagulation and targets of anticoagulants (Section I) Position Paper of the ESC Working Group on Thrombosis - Task Force on Anticoagulants in Heart Disease Thrombosis and Haemostasis 2013; 109 : 569-579
- 109) De Caterina Raffaele, Husted Steen, Wallentin Lars et al. : Vitamin K antagonists in heart disease : Current status and perspectives (Section III) Position Paper of the ESC Workingt Group on Thrombosis - Task Force on Anticoagulants in Heart Disease Thrombosis and Haemostasis 2013; 110 : 1087-1107
- 110) Weitz Jeffrey I., Pollack Charles V. Jr. : Practical management of bleeding in patients receiving non-vitamin K antagonist oral anticoagulants. *Thrombosis and Haemostasis* 2015; 114 : 1113-1126
- 111) Drazen Jeffrey M. : COX-2 Inhibitors - A lesson in unexpected problems. *New England Journal of Medicine* 2005; 352 : 1131-1132
- 112) Psaty Bruce M., Furberg Curt D. : COX-2 Inhibitors - Lesson in drug safety. *New England Journal of Medicine* 2005; 352 : 1133-1135
- 113) Manson JoAnn E., Chlebowsky Rowan T., Stefanick Marcia L. et al. : Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. *Journal of the American Medical Association* 2013; 310 : 1353-1368
- 114) Nelson Heidi D., Walker Miranda, Zakher Bernardette et al. : Menopausal hormone therapy for the primary prevention of chronic conditions : A systematic review to update the U.S. preventive services task force recommendations. *Annals of Internal Medicine* 2012; 157 : 104-113
- 115) Stuenkel C.A., Davis S.R., Gompel A. et al. : Treatment of symptoms of the menopause : an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology & Metabolism* 2015; 100 : 3975-4011
- 116) Manson JoAnn E. and Kaunitz Andrew M. et al. : Menopause management - Getting clinical

care back on track.

New England Journal of Medicine 2016; 374 : 803-806

117) O' Riordan Michael : Dabigatran bleeding analysis not disclosed to FDA, documents show. Medscape February 26, 2014 [www.medscape.com/viewarticle/821116](http://www.medscape.com/viewarticle/821116)

118) Cohen Deborah : Data on trial of anticoagulant is to be reanalyzed after discovery that investigators used faulty device. The British Medical Journal 2015; 351 : h6431

119) Cohen Deborah : Rivaroxaban : can we trust the evidence ? The British Medical Journal 2016; 352 : i575

120) Patel Manesh R., Hellkamp Anne S., Fox Keith A.A. : Point-of-care warfarin monitoring in the ROCKET AF trial. New England Journal of Medicine 2016; 374 : 785-788

121) Thomas Katie : Document claims drug makers deceived a top medical journal. New York Times March 2, 2016; page B1

122) Wilson Mark : Is transparency really a panacea ? Journal of the Royal Society of Medicine 2014; 107 (6) : 216-217

123 ) Drazen Jeffrey M. : COX-2 Inhibitors - A lesson in unexpected problems. New England Journal of Medicine 2005; 352 (11) : 1131-1132

124 ) Gotzsche Peter C. : Deadly medicines and organised crime. How big pharma has corrupted healthcare. CRC Press 2013