DABIGATRAN ETEXILATE

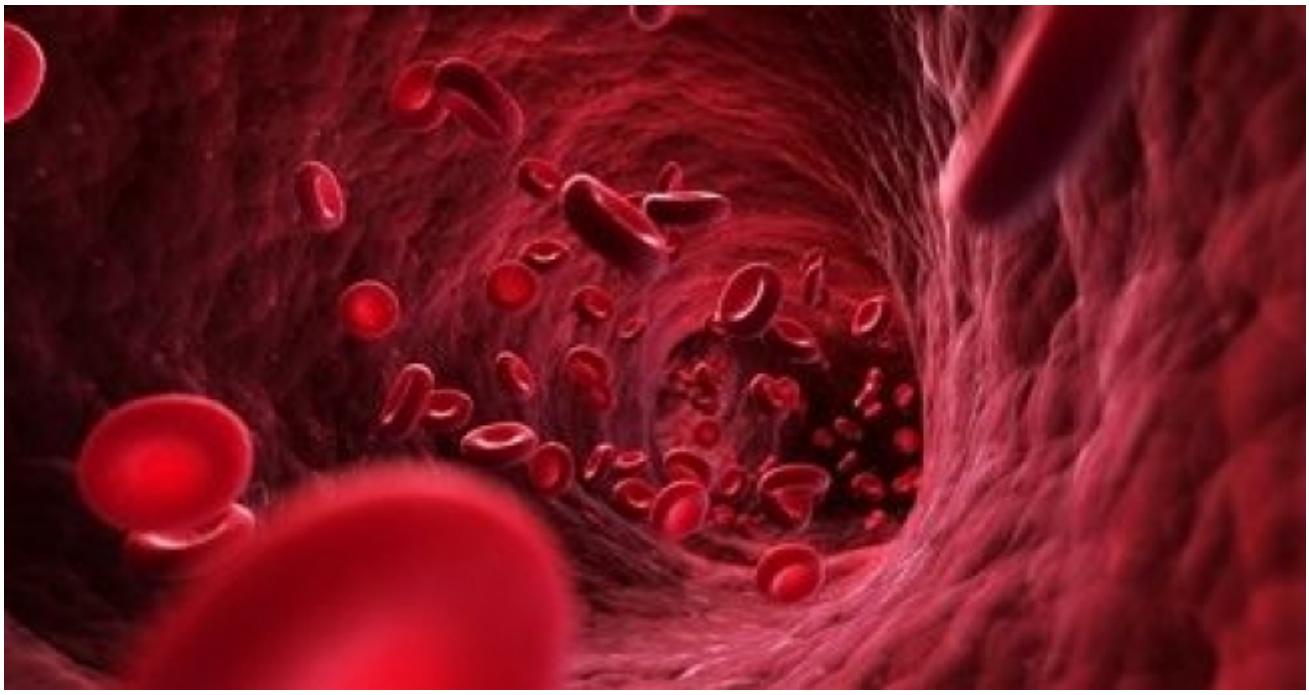
TROMBOSI - ANTICOAGULANTI ORALI DIRETTI

Ultimo aggiornamento: 22 Aprile 2015

Revisione letteratura: Aprile 2015

Autore: Dr. Vincenzo Marottoli

www.trombosiemostasi.it



Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Indice

Abstract
Mechanism of action
Indications
Absorption and metabolism
Dosage and drug interactions
Adverse reactions
Contraindications
Laboratory tests
Conclusions

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

Abstract

Initially conceived as an abstract, due to the enormous number of papers published continuosly, and due to the great controversy about laboratory monitoring of dabigatran, and probably of all other Direct Oral Anticoagulants (DOACs), this abstract has become day by day a chapter. The problem of laboratory monitoring is so an important issue because of the large number of patients who are involved, and of the tremendous impact that eventually its introduction may have on their health and their lives, that exceptionally deserves a large and detailed analysis of the most important papers published about this topic, also at the beginning of this review before all the other sections. For these considerations, this abstract could be called Chapter One : Increased evidence of the clinical utility of laboratory monitoring in dabigatran treatment.

Dabigatran etexilate is a direct thrombin inhibitor that has been approved for prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation in U.S.A., Canada and Europe,and for post-operative thromboprophylaxis in patients who have undergone a knee or a hip replacement surgery only in Europe. Recently at the end of march 2014, by the Food and Drug Administration (FDA) and after by European Medical Agency (EMA) dabigatran has been approved for treatment of deep vein thrombosis (DVT) and of pulmonary embolism (PE) and to prevent these conditions from reoccuring in adults. In the RE-LY trial, a non-inferiority trial, **(1) (NEJM 2009 vol.361 pp.1139-1151)** stroke and systemic embolism were 1.71% patients per year in the warfarin group and 1.11% patients per year in the group treated with 150 mg. of dabigatran etexilate twice daily and 1.54% patients per year in the group treated with 110 mg. twice daily. The rate of major bleeding in the warfarin group was 3.57% patients per year, and in the dabigatran etexilate group was 3.32% patients per year with a dosage of 150 mg.twice daily and 2.87% patients per year with a dosage of 110 mg. twice daily. The mortality rate was 4.13% patients per year in the warfarin group and 3.65% patients per year with 110 mg. of dabigatran and 3.75% patients per year with 150 mg of dabigatran always twice daily.**(2) (Thrombosis and Hemostasis 2013 vol 110 pp. 496-500)**
In patients with atrial fibrillation dabigatran at a dosage of 110 mg. twice daily was associated with similar rates of stroke and systemic embolism obtained with warfarin treatment but with lower rates of major hemorrhage. Dabigatran etexilate at a dosage of 150 mg twice daily was associated with lower rates of stroke and systemic embolism than warfarin but with similar rates of major hemorrhage. (RE-LY Trial) **(1) (NEJM 2009 vo.361 pp.1139-1151)** The RE-LY trial, a non-inferiority trial, sponsored by dabigatran etexilate manufacturer, is a large trial conducted in 44 different countries with different healths systems. Are non-inferiority trials unethical compared with superiority trials ? Some key leaders in the pharmacological research field, think they are unethical because they disregard patients' interests. Use of non-inferiority rather than superiority trials, implies the intention of not tryng to prove any additional value of new drugs. Drug

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

manufacturers argue that there is no reason to know whether a new drug is more effective than an older one. It is enough to show that they are similar. The added value is based on the probability of a better compliance. Non-inferiority trials allow new products to compete with older ones on the basis of small differences made to seem to benefit patients. In addition, non-inferiority trials expose patients to clinical experiments without any assurance that the experimental drug is not worse than the standard treatment, and without really exploring whether it is better.The subsequent statements of Garattini and Bertelé are so strong, so effective and so clear that I think to be obliged to use exactly their words : " We believe that non-inferiority studies have no ethical justification, since they do not offer any possible advantage to present and future patients, and they disregard patients' interests in favour of commercial ones. This situation betrays the agreement between patients and researchers set out in any fair informed consent form that presents randomised trials as the only ethical way to address clinical uncertainty. Non-inferiority trials claim minor advantages for the test drugs, but do not prove their efficacy compared with older products. Few patients would agree to participate if this message were clear in the informed consent form : as we said before, why should patients accept a treatment that, at best, is not worse, but could actually be less effective or less safe than available treatment ?. In conclusion we believe that non-inferiority trials fail to meet the commitments of good clinical research : Ask an important question, and answer it reliably ". **(3) (The Lancet 2007 vol. 370 pp. 1875-1877)** Others authors think they are useful and can be ethically justified in some cases. In addition, an author thinks that would be useful to ban the improper application of the non-inferiority design such as setting wide inferiority limits or using statistical rather than clinical difference as a basis for concluding that a drug is non-inferior, not the design itself. **(4) (The Lancet 2008 vol. 371 pp. 895-897)** It is undeniable that superiority trials are the gold standard in clinical trial research. Having difficulties to find more powerful drugs on the market, the pharmaceutical industry has been forced to look for drugs that may not improve the current efficacious treatments but may be better on other aspects of treatment such as adverse reactions. However, different definitions of non-inferiority may be a difficult obstacle for clinical decision maker to decide the true message of a non-inferiority trial. **(5) (Bullettin of the NYU Hospital for Joint Disease 2008 vol. 66 (2) pp. 150-154)** The noninferiority margin is taken into account in the formulation of the sample size calculation. The margin must be smaller than or equal to "the smallest value that would represent a clinically meaningful difference, or the largest value that would represent a clinically meaningless difference ". The determination of this margin must be based on both statistical reasoning and clinical judgement. For analysis, intent-to-treat (ITT) and per-protocol analyses should be performed. ITT analysis may lead to biased conclusions because protocol violations and withdrawals. In addition, dropouts and nonadherent participants from the 2 groups are potentially different, which may also bias a per-protocol analysis. Thus both analyses are required to draw a conclusion. Reporting the results of only one of the analyses may reflect a deliberate intention to mask some of the results, potentially modifying the interpretation of the results. **(6) JAMA 2006 vol. 295 (10) pp. 1147-1160)** For details see section on "Conclusions". At the moment, we do not have an antidote to neutralize the anticoagulant effect of dabigatran. PCC concentrates that are very useful in warfarin bleedings, and Recombinant Activated Factor VII are unsuccessfull in dabigatran bleedings, only FEIBA probably may reduce dabigatran anticoagulant effect as reported recently in anedoctal cases. **(7) (British Journal of Haematology**

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

2014 vol. 164 pp. 308-310) (8) (British Journal of Haematology 2014 doi: 10.1111/bjh.12831) Also tranexanic acid IV may be efficacious in reducing bleedings. The only procedure that reduces the anticoagulant effect of dabigatran removing it from plasma, is dialysis but, in patients with important bleeding that frequently are in unstable clinical conditions, performing this procedure can be very challenging also in the best emergency departments.

Less drug interactions compared with warfarin are described, but these few interactions are very important, considered that amiodarone and verapamil for example, are very used in atrial fibrillation and the approved principal use for dabigatran is to prevent stroke or systemic embolism in patients with non valvular atrial fibrillation.

The manufacturer of dabigatran is facing more than 4,000 law suits in the US, claiming dabigatran caused severe and fatal bleeding and in January 2014 the New York Times reported that the employees were worried about publishing a research paper suggesting that patients taking dabigatran might require blood monitoring. **(9) (www.medscape.com/viewarticle/821116)** (see section on "Discussion"). The FDA (Food and Drug Administration) has given the designation of breakthrough therapy to Idarucizumab, an experimental drug that is in evaluation as an antidote for the oral anticoagulant Dabigatran. In a study of phase 1, it has been demonstrated that Idarucizumab has produced an immediate, complete and prolonged reversal of the anticoagulation induced by Dabigatran in healthy people. A study of phase 3, RE-VERSE AD, is evaluating Idarucizumab in patients who are taking Dabigatran and are showing an uncontrolled bleeding or are undergoing an emergency surgery or other invasive procedures. Just recently, The New England Journal of Medicine published a human volunteer study of 80 individuals who received PER977 (Aziparine) which is a synthetic small molecule (D-arginine compound) which has broad activity against various old (heparin, low molecular weight heparin) and new oral anticoagulants (dabigatran, rivaroxaban, apixaban end edoxaban). **(10) (New England Journal of Medicine 2014 vol. 371 pp. 2141-2142)** see section on "Adverse reactions". At the moment there are not antidotes approved by FDA or EMA to reverse the effects of the new oral anticoagulants. More time passes and more questions about safety of Dabigatran raise. As it was pointed out in this review since last year, and in the reviews about rivaroxaban, apixaban and edoxaban, the fact that the new oral anticoagulants do not need laboratory monitoring is not correct, because probably they need less monitoring compared to warfarin, but in any case they do. It was emphasized that the new oral anticoagulants do not need laboratory monitoring because they have a predictable pharmacokinetics and pharmacodynamics but, in a new RE-LY substudy, was found that plasma dabigatran levels for either dose in RE-LY ranged over 5-fold for the 10th to 90th percentile **(11) (Journal of The American College of Cardiology 2014 vol. 63 pp. 321-328)** The authors concluded that considered that the primary analysis of the whole population, without consideration of plasma levels showed that the two doses of dabigatran in the RE-LY were safe and effective, this suggested that there is a wide therapeutic range. In 2010 was published a study in which the authors identified some sources of inter- and intra-individual variability, such as renal and/or hepatic function, advanced age, and certain clinically relevant drug-drug interactions. **(12) (Journal of Thrombosis and Haemostasis 2010 vol. 8 pp.621-626)** For details see section on "laboratory tests". On 23 july 2014, was published by the British Medical Journal an interesting article written by Dr. Deborah

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Cohen, the investigations editor at the BMJ, with the following title : **Dabigatran : how the drug company withheld important analyses.** I think that just the title do not need any comment, considered that Dabigatran achieved blockbuster status, with sales of over 1 billion US dollars by april 2012 and of 2 billions by 2014 despite increasing concerns about safety.
Boehringer Ingelheim, the maker of dabigatran,did not share with regulators information about the potential benefits of monitoring anticoagulant activity and adjusting the dose to make sure the drug is working as safely and effectively as possible. Analyses that calculated how many major bleeds dose adjustment could prevent were also withheld. The company replied that this information was not comunicated to the regulatory agencies because the analysis did not provide a reliable prediction of patient outcomes. Internal documents of Boehringer show that major bleeds with dabigatran may be reduced by 30-40% if the plasma levels of the drug were measured and the dose was adjusted accordingly. It has also identified the plasma level at which the dose adjustment should occur to reduce the risk of a major bleed. 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". During litigation was revealed an internal email discussions about the potential merits of drug plasma monitoring in which one Boehringer employee, whose name has been reducted, said : "This may not be a onetime test and could result in a more complex message (regular monitoring) and a weaker value proposition". On the contrary, in an FDA press statement in 2010 at the time of its US approval, Norman Stockbridge, director of the division of cardiovascular and renal products in the FDA's Center for Drug Evaluation and Research, said : "Unlike warfarin, which requires patients to undergo periodic monitoring with blood tests, such monitoring is not necessary for Pradaxa (dabigatran)". Differently EMA was concerned about the need to monitor the plasma levels of the drug to reduce the risk of bleeding; not just at the time of the decision to market the drug, but also later when widespread use of the drug led to safety concerns. As test to monitor drug level was chosen the Hemoclot test. EMA documents from early 2010 also 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 the increased risk of bleeding". A spokeperson for Boehringer said that the company "never told EMA or any regulatory authority that 200 ng/mL was a level not to be exceeded". When discussing how best to publish analyses of data from the RE-LY trial, Stuart Connolly,one of the principal investigators of the RE-LY trial, said in an email in July 2012 : "There is a very good reason to never go above 200 ng/mL. It is less clear at the low end due to the paucity of events but somewhere around 40-50 seems prudent for a lower boundary". A QuarterWatch report analysed all the adverse events submitted to the FDA's reporting system in 2011. The most commonly identified drugs reported to the FDA were the anticoagulants dabigatran and warfarin. For dabigatran alone this included 542 patient deaths and 2367 reports of haemorrhage. Warfarin accounted for 72 deaths in the same period. **(13) QuarterWatch 2012 Quarter 4)** Although the RE-LY protocol did not require monitoring of blood levels in patients taking dabigatran, the investigators collected drug plasma concentrations during the trial. Internal documents of the company in August 2011 show that employees completed a subgroup analysis of these data. Some of the conclusions of this analysis were published in the Journal of the American College of Cardiology as cited above. Internal emails released during US

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

litigation show that Andreas Clemens, a medical team leader for the drug, stated that he was "phobic" and "not happy with the conclusion" that an optimal balance between benefit and risk occurs in the range of concentrations between 40 ng/mL and 215 ng/mL. An email in October 2012 shows a company official saying that " The publication will do more harm than be useful for us, neither in the market but especially harmful in the discussion in the regulatory bodies". Clemens also wrote : "The world is crying for this information but the tricky part is that we have to tailor the message smart". Emails from February 2013 show that company employee Jutta Heinrich-Nols wrote to other employees to recommend that the company reconsider whether to publish this study. "This will make any defense of no monitoring to Health Authorities extremely difficult (i.e. Health Canada, TGA) and undermine our efforts to compete with other NOACs. As I am not empowered to release or stop any publications I would like to ask you to check once again whether this is really wanted". an email said. Publishing the research results, she warned, could make it "extremely difficult" for the company to defend its long-held position to regulators that dabigatran did not require monitoring. As the number of fatal bleeds accumulated, the EMA asked to Boehringer to "discuss and suggest appropriate monitoring frequency and laboratory tests". On 9 March 2012, Boehringer gave a presentation to the EMA committee. The EMA's minutes show that routine monitoring of anticoagulant activity was discussed "in depth" by the committee. However, most experts voted against it. Some of the analyses and conclusions pointed out in Reilly's 2011 paper, which was produced over six months before EMA's safety, were absent from the company's presentation to the committee. In particular there was not in the company's presentation a graph showing that beyond a certain plasma concentration of the drug major bleedings events continued to increase as the plasma levels increased with little effect on rates of stroke and systemic embolism. This graph was,however, published in 2013 in the Journal of the American College of Cardiology. Also absent from the presentation were data showing that some people taking dabigatran may have a suboptimal dose, putting them at "an appreciably higher" stroke risk. The company also chose to present statistics in which the plasma level variability seemed to be about 2.3 fold instead of 5.5 fold as documented in Reilly's paper. The BMJ asked to Boehringer if had comunicated to the EMA during the meeting that company analyses suggested "targeting a specific concentration range may optimize the benefit-risk" and that: "monitoring of plasma concentrations or antithrombotic activity woul be required to identify these patients. A dose adjustment could improve the benefit-risk ratio", as had been described in the draft publication. A company spokesperson said that the company did not comunicate to the EMA these information because they were "hypotheses in drafts of a paper that the authors of that paper rejected as they refined their analysis". However, Steve Nissen, department chair of cardiovascular medicine at the Cleveland Clinic and one of the members of the FDA's advisory committee considering dabigatran for use in non-valvular atrial fibrillation, told The BMJ :" If there is clinically useful information about the relationship between drug levels and the safety of dabigatran, it is the moral obligation of the company and its investigators to share this information with the medical community. Withholding such information for commercial purposes is unacceptable". Internal documents show that even though there had been deaths associated with major bleeds in the clinical trial and there was no antidote, a decision had been made not to support the development of a bedside monitoring device. An employee from the cardiology division of the company who wanted to develop such a device in a email said : " 2 years ago, (in 2008) there was an

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

informed decision NOT to develop this. As this would go against the "no monitoring" idea/claim ". At a certain point the company started to evaluate to prescribe monitoring for dabigatran therapy especially after that by an "intense effort" using data simulations and data from RE-LY, it found that by doing this, it "could preserve the effect on ischemic stroke prevention but with a reduction of major bleeding events compared to well controlled warfarin of perhaps up to 30-40%". The data also suggested that such an approach would even lead to fewer gastrointestinal bleeds with dabigatran compared to warfarin in such a setting". But after considering regulatory and other obstacles, the company decided to continue to support the position that dabigatran does not need laboratory monitoring. In their mid to long term strategy document, company officials also considered if patients who had low levels of dabigatran in their blood despite receiving the higher dose would have to stop treatment. And if so, What percentage of people with atrial fibrillation would this account for ?. Hugo ten Cate, medical director of the Maastricht thrombosis anticoagulation clinic and coeditor in chief of Thrombosis Journal, has been concerned about the lack of published studies on dose adjustment in the new oral anticoagulants for some time. "It is critical that pharmaceutical companies take their responsibilities and provide and publish all relevant data on drug levels and coagulation test responses so that it becomes clear what the approximate therapeutic and harmful ranges of laboratory test outcomes are, for each anticoagulant agent. There is no good reason not to be transparent in these matters, even if it would entail the small risk that doctors would want to optimise therapy based on lab test results", he said. **(14) (British Medical Journal 2014 vol. 349 pp. g4670)** Another article appeared on August 18, 2014 in the New York Times with the following title : **Weighing Pradaxa's risks.** For other comments and other articles about this very important problem, see section on " Adverse reactions" and " Discussion" .
On September 25, 2014, Chest Journal published on line an article in which the author points out that direct thrombin inhibitor anticoagulants, used for the treatment of cardiac and venous thromboembolism, have repeatedly associated with a significantly increased frequency of thrombosis on abnormal cardiac endothelium when compared with indirectly-acting therapeutic anticoagulants in studies of sufficient patients number and duration. The author concludes that " Although there is uncertainty as to mechanism, the weight of evidence as a class effect warrants prescribing effective anticoagulants other than direct thrombin inhibitors". **(15) (Chest 2015 vol. 147 (1) pp. 21-24)** For other comments, see section on " Adverse reaction" and section on "Conclusions".
Recently **(16) Circulation 2015 vol. 131 pp. 157-164** and **(17) JAMA November 3, 2014,** published two analyses of Medicare database to evaluate the efficacy and safety of dabigatran in clinical pratice, comparing it to warfarin in patients with nonvalvular atrial fibrillation.The studies attain divergent conclusions.The investigators of the first study published by Circulation conclude that dabigatran has a more favorable effect compared to warfarin. On the contrary, the investigators of the second study published by JAMA conclude that dabigatran should be prescribed with caution, especially among high risk patients. The two studies did not evaluate the quality of warfarin anticoagulation by TTR (Time in the therapeutic range). For details, see section on "Adverse reactions" and on "Conclusions". Also recently, on november 28, 2014, BMJ published an editorial about ties between medical journals and industry that can cause clinical decisions based on information biased by commercial interest. Its editors decided to start to accept in 2015 only clinical educational articles by experts without financial ties to companies producing drugs, devices, or test

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

and medical education companies. They hope to extend this policy to the state of the art reviews and diagnostic and therapeutic series by the end of 2016. For over two decades the journal American Family Physician which principally publishes clinical reviews, has not accepted articles by authors who have financial ties with industry. "Many clinical practice guidelines are little more than industry marketing tools because of the financial competing interests of their authors and sponsors". **(18) (British Medical Journal 2014 vol. 349 pp. g7197)** For details, see section on "Conclusions".
A very important paper which has practical clinical implications was published by Journal of Thrombosis and Haemostasis in July 2014, in which Poller and collegues compared the results obtained with warfarin and Dabigatran in the RELY study (6022 patients) with the results obtained with warfarin in the European Action on Anticoagulation (EAA) study (5939 patients). Morbidity and mortality were much higher in RE-LY in all three groups than with warfarin in the EAA study, and better results for stroke, major bleedings and minor bleedings were obtained in the EAA study, compared with patients treated with warfarin and with patients treated with both Dabigatran doses in the RE-LY study. In the RE-LY study, in warfarin patients, overall events (% per year) were 1.57, 3.36, 16.37, and 4.13 for stroke, major bleedings, minor bleedings and death respectively. In dabigatran patients were 1.44, 2.71, 13.16 and 3.75 in the 110 mg. group and 1.01, 3.11, 14.84 and 3.64 in the 150 mg. group. On the contrary, in the EAA study overall events (% per year) for stroke, minor bleedings, major bleedings and death were 0.30, 2.70, 0.86 and 0.75 per year respectively. These impressive results obtained in the EAA study although the "Time in INR range" was marginally better than in RE-LY may be explained by the lack in RE-LY of two important assessments of INR control, local ISI calibration and external quality control of INR. **(19) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1193-1195)** Now a precise local INR may be obtained easily using the prothrombin time/international normalized ratio (PT/INR) Line which is a simple method that uses only five certified European Concerted Action on Anticoagulation (ECAA) plasmas to derive local INR. The PT/INR Line does not require manual PT testing, an International Sensitivity Index (ISI) and Mean Normal Prothrombin Time (MNPT) and can be used in place of local ISI calibration. It can be performed with the assistance of a spreadsheet freely available online from www.anticoagulants.co.uk. **(20) (Journal of Clinical Pathology 2011 vol. 64 pp. 930-932)** In addition, in RE-LY there was only a recruitment of 6.3 patients per centre against a recruitment of 182 patients per centre in the EAA study. The larger number of centres participating in the RE-LY study, compared with the EAA study, would result in a greater between-centre variation in the quality of oral anticoagulation treatment and this could also be another reason for the impressive results obtained in the EAA study. In addition the higher incidence of events in the RE-LY study may be due to the participation of less experienced centres and a subgroup analysis stratifying centres by size or proficiency may prove this. **(19) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1193-1195)** see details in the sections "Indications" and "Conclusions". As more time passes, more papers are published by key physician opinion leaders too, emphasizing the tremendous advantage of the new oral anticoagulants in long term anticoagulation and in particular emphasizing the fact that can be given in fixed doses without routine coagulation monitoring, and that will replace warfarin for more and more indications. **(21) (Journal of thrombosis and thrombolysis 2015 vol. 39 pp. 264-272) (22) (ATVB 2015 DOI : 10.1161/ATVBAHA.115.303397) (23) (Blood 2014 vol. 124 (12) pp. 1968-1975)** Unfortunately, although the fact that they do not need

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

a laboratory monitoring would be really an important advantage over warfarin, this is not true. As written above, these new drugs need a laboratory monitoring, may be less times than warfarin, but in any case they do, and differently from vitamin K antagonists in which using the INR we can decide to let perform a surgery or not, with these drugs, we do not have a drug concentration that let us decide if a patient can receive or cannot receive a surgery, in particular a major surgery, although EMA marketing authorization holder informed that a dabigatran concentration below 48 ng/ml should be reached before an invasive procedure and although the "Groupe d'Intéret en Hémostase Périopératoire (GIHP) indicates a threshold at 30 ng/ml. **(24) (Archives of Cardiovascular Diseases 2013 vol. 106 pp. 382-393)** Also with low concentrations we cannot exclude a probable surgical bleeding. We will be sure that the patient can undergo a major surgical procedure safely only when the drug will be completely disappeared. In case of an emergency surgery, trying to antagonize the anticoagulant effect of these drugs using Prothrombin Complex Concentrates (PCCs) or FEIBA, are we able to say with certainty that the patient will not bleed ? Certainly not. Is this last aspect correctly explained to the patient before give him one of these drug? I hope yes. And if it is explained, how many patients do you think would be willing to take these drugs, considering that they could be in serious troubles in case of an emergency surgical procedure? Thomas Moore, senior scientist at the US Institute for Safe Medication Practices, and collegues raise concerns about the differences in how US and European regulatory agencies manage the safety problems of dabigatran and ask both FDA and EMA to think again and mandate plasma monitoring of dabigatran. In fact, they say that FDA pursued a policy making the new drug easier to use with just one primary dose, even though it would increase the risk of haemorrhage in older patients. But the FDA also believed its actions might slightly improve the efficacy of dabigatran in preventing stroke. On the contrary, EMA showed continuing concerns about reducing the risk of bleeding and pursued multiple risk reductions policies. Although results were not published until late 2013, the RE-LY trial had included a large sub-study (n= 9183) which showed that a fixed dose of dabigatran had a wide variability in plasma levels that were directly related to risk of bleeding. After a month of treatment, the 150 mg twice daily dose could produce peak levels as low as 2.3 ng/mL and as high as 1000 ng/mL. A conservative measure that omitted 20% patients at the extremes and used log transformed data indicated a 5.5 fold variability. They correctly affirm that "dabigatran's high variability was not a desirable characteristic for a drug where not enough anticoagulation means loss of benefit in stroke prevention and too much anticoagulation increases the risk of haemorrhage". Clearly the variability of dabigatran may be explained by its low bioavailability (3-7%), two metabolic steps to convert the pro-drug into the active drug and a single primary route of elimination, the kidneys. **(25) (BMJ 2014 vol. 349 pp. g4517)** Variability can also be explained by genetic variants that could contribute to interindividual variability in blood concentrations of the active metabolite of dabigatran and influence the safety and efficacy of dabigatran. **(26) (Stroke 2013 vol. 127 pp. 1404-1412)** These characteristics were not found in rivaroxaban and apixaban , which have much higher bioavailability (50-80%) and multiple routes of elimination. As the company stated, dabigatran showed a wide therapeutic range in effects on stroke, with about a similar efficacy from around 50 ng/mL through 300 ng/mL, but the probability of major bleeding rises rapidly from around 2-3% at 50 ng/mL to more than 9% for the typical patient around 300 ng/mL, and to more than 12% at the extremes. One member of the advisory committee of the FDA focused on the fact that with

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

high plasma level variability, did not dabigatran really need plasma level monitoring? " I am struck by what my eyeball tells me about a five-fold variability within the 90 percent confidence interval of the 150 mg. dose. That seems awfully big to me in a drug that we are proposing to use without therapeutic monitoring", said Darren McGuire, a cardiologist on the panel. But an agency pharmacologist told him, "We did not see a need for monitoring the concentration because we saw in a study, a favorable result in all subgroups". The FDA recommended the indication for any patient with nonvalvular atrial fibrillation and showed a strange narrow view in pursuing a reduction in stroke rate of a fraction of 1% on the basis of a single trial whose data quality the agency had already changed without caring of the bleeding risk. On the contrary, the EMA committee reviewed and expressed concern about the large variability in plasma levels and bleeding risk found in the then-unpublished RE-LY sub-study data. EMA requested, received and published a therapeutic range (48-200 ng/mL). It also ensured that an accurate assay was available and validated, the Hemoclot direct thrombin inhibitor assay, but did not oppose to Boehringer's will to market dabigatran as a drug that did not require blood level testing to establish the optimal level of anticoagulation. As of December 2011, the company summary cited 9049 reported bleeding events in its global experience, including 368 deaths. At least 10% of patients had peak plasma level concentrations >/= 383 ng/mL when taking the 150 mg. dose. This is about seven times (48-50 ng/mL) the minimum level needed for stroke prevention, according to Boehringer. The EMA on the other hand, considered whether to require plasma level testing for dabigatran.
As described above, EMA had already obtained a therapeutic range from Boehringer Ingelheim, 48-200 ng/mL, which was included in the European Union (EU) approved product information. However, at the end, the company position that routine monitoring of the anticoagulant activity is not necessary, was accepted. A review of the EMA meeting materials shows that the company slide presentation did not include all their relevant data on plasma level variability of dabigatran. **(24) (BMJ 2014 vol. 349 pp. g4517)** An internal document of Boehringer Ingelheim showed a significant reduction of bleeding events with dabigatran titration.There are some key documents referred to the BMJ investigation conducted by Deborah Cohen on how the company withheld important analyses, showing modelling which Boeringher Ingelheim carried out on dabigatran. **(www.bmj.com/investigation/dabigatran)** In 2012, a second risk of dabigatran become visible. At the low end of the variability range, plasma levels in some patients were insufficient to reduce the risks of stroke and other thromboembolic events. When Boehringer planned a new trial to study the effect of dabigatran on patients with mechanical heart valves decided to individualise the dose for each patient and selected a minimum of 50 ng/mL to be effective. The company revealed that 17% of RE-LY patients had ended up with plasma levels that were lower than 50 ng/mL. **(27) (American Heart Journal 2012 vol. 163 pp. 931-937)** The heart valve study using dose adjustment showed that at least 8% of participants had plasma levels below the 50 ng/mL target even when prescribed double the maximum approved dose up to 300 mg twice daily. The dabigatran study in mechanical heart valves was stopped for safety. A Boehringer unpublished simulation model compared the 150 mg. dose twice daily with a hypothetical treatment programme in which dose would be optimised for each patient to achieve a plasma concentration of 90-140 ng/mL. The model showed that only 45% of patients would receive the 150 mg. standard dose; 26% should be reduced to 75 mg and 30% to 110 mg.

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

The model projected that major bleeding could be reduced by 20% compared with the 150 mg dose without having a statistically significant effect on rates of ischemic stroke and serious embolism. Compared with warfarin the hypothetical reduction in risk of major bleeding was 40% and the risk of stroke or serious embolism was not statistically different. These results showed benefits in adjusting dose to optimise the level of anticoagulation in each patient.
Most patients could benefit from a lower dose and reduced bleeding risk with no loss of efficacy. Moore and collegues concluded that the manufacturer, the FDA, and EMA need to agree on a therapeutic range and recommend initial dose adjustment based on plasma measurements. **(25) (BMJ 2014 vol. 349 pp. g4517)** Hugo ten Cate argues that the safety of all the new oral anticoagulants can be potentially improved through documenting a therapeutic range for each agent, individualising dose in many patients subsets, and improving adherence. The title of his editorial is :"New oral anticoagulants : discussion on monitoring should start now ! ". The development and implementation in quantitative laboratory assays will enable further dose optimization and the conduction of the treatment by a patient centered manner would prevent non-adherence, especially in elderly patients. **(28) (Thrombosis Journal 2013 vol. 11 pp. 8)** Published data show the range in responses to dabigatran for the indication stroke prevention (150 mg bd), with average peak and trough levels of 175 and 91 ng/mL (assayed by TT-hemoclottest), with 25-75th percentile (ng/ml) of 117-275 and 61-143 ng/mL, respectively. **(29) (Pradaxa product monograph, revised 2012). (30) (Van Zuiden Communications BV; 2012, Dutch language)** Ten Cate concludes that for NOACs therapeutic ranges of each agent should become available based on concentrations and/or dose response effects in laboratory tests. This will ultimately provide a means of optimizing dose adjustment in individual patients, more so than by current algorithms.**(28) (Thrombosis Journal 2013 vol. 11 pp. 8)** In another paper published on BMJ in July 2014 **(31) (BMJ 2014 vol. 349 pp. g4747)** Deborah Cohen reported that academics who wrote the Therapeutics Letter expressed concern about RE-LY trial because it was an open label trial, meaning that clinicians and trial participants knew which drug was being given. This can lead to a risk of bias as was well demonstrated in the clinical trial of another direct thrombin inhibitor, ximelagatran, that did not receive regulatory approval. In an unblinded clinical trial similar to RE-LY, ximelagatran was associated with numerically fewer strokes and systemic emboli compared with warfarin. However, in a follow-up double blinded trial, there were more strokes and systemic embolisms with ximelagatran. All this leads to questions about the regulatory decision to licence a drug on the basis of a single open label trial when the regulators had identified serious concerns. A transcript of the FDA's advisory committe shows that the US agency found "that knowledge of treatment arm, by doctors and patients, may have led to important differences in the treatment of subjects. For example if a subject experienced an ischemic stroke, TIA (a non-end point event) or minor bleed, she was more likely to have her study medication permanently discontinued in the dabigatran than in the warfarin treatment arms". **(www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/)** The authors of the Therapeutic Letters correctly noted that the incidence of intracranial haemorrhage (ICH) observed with warfarin was higher (0.76% per year compared with 0.27% per year with dabigatran) than that observed in other trials such as SPORTIF III (0.53%), SPORTIF V (0.28%) and 0.3% or 0.45% in two Cochrane reviews. **(32) (Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No :**

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

CD001927) (33) (Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No : CD006186) These authors conclude that "Licensing of dabigatran 150 mg BID for atrial fibrillation is premature, pharmacologically irrational and unsafe for many patients. The optimal dose for non-valvular atrial fibrillation is not yet clear. An independent audit of RE-LY is needed to check for irregularities in conduct, sources of bias and the cause of the unusually high incidence of intracranial hemorrhage in the warfarin arm. An independently conducted double-blind RCT comparing dabigatran with warfarin in patients with non-valvular atrial fibrillation is required." **(34) (Therapeutics Letter 2011 vol. 80 www.ti.ubc.ca/letter80)** On 28 May 2014, the company announced that it had settled about 4000 cases for 650 million dollars, but denied wrongdoing saying that it had settled the lawsuit to avoid lengthy litigation. Two men who participated to RE-LY trial had major bleeds immediately before their deaths, but neither was counted as having had one in the company's original submission to the regulator when applying for approval in 2009. Nor were they identified in the FDA mandated review in 2010. In the cases of Barndt and Duncan, the two patients who died because major bleedings, the unblinded clinicians whose care they were under during the trial, listed them as having died from a cardiovascular event. Documents released during US litigation, however, showed that in neither case did clinicians fill in a major bleed case report form. Completion of the form, to be sent to the blinded adjudicator along with the patient's medical history, was required by the trial protocol, and both Duncan and Barndt were in the dabigatran arm of the trial. Three times the number of bleeds in the RE-LY trial had been evaluated, the first time during the trial itself , the second time in the FDA mandated review, and the third time in a recently "targeted" review prompted by information uncovered by lawyers acting for the families. The third evaluation found eight unreported fatal bleeds, three in the dabigatran 110 mg. arm of RE-LY, two in the 150 mg. arm, and three in the warfarin arm. Both the FDA and the EMA are aware of this review. It has also emerged, and Boehringer Ingelheim has confirmed it to the BMJ, that the FDA mandated review was conducted by company scientists and overseen by the company's most senior executive, Andreas Barner, who was spokeperson for the board of managing directors and responsible for research and development in medicine at that time. Deborah Cohen , the author of this paper published on BMJ, asks : "Why did the regulators allow this level of involvement from senior executives when so much was at stake? And is this acceptable?". Steve Nissen, department chair of cardiovascular medicine at the Cleveland Clinic and one of the members of the FDA's advisory committe considering dabigatran for use in non-valvular atrial fibrillation said to BMJ : "With regard to collection of cardiovascular event data, it is imperative that ascertainment of cardiovascular events be performed by a committe completely independent of the sponsor and fully blinded with respect to the assigned treatment group. Involvement by the sponsor in the adjudication process undermines the scientific integrity of any trial and can potentially result in inaccurate conclusions. Such involvement is not acceptable". **(31) (BMJ 2014 vol. 349 mpp. 4747)** Another consideration is the great difference of number of patients recruited in different cities in the RE-LY trial. For example Joué-Lès-Tours in France (Population of about 40000 people) ranks as the 1st by the number of patient recruitment centres (n=18) among RE-LY locations distributed across 43 countries (according to the clinical trials.gov.registry) or 44 Countries according to the RE-LY trial. A close city to Joué-Lés-Tours (Angers population about 300000 people) ranks 3rd by the number of locations (n=11) and only one patient recruitment centre was located in

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Paris. France also ranks 1st in Europe by number of RE-LY locations (clinicalTrials.gov) but the country is absent in the EudraCT registry. Israel is not a location of patient recruitment in the RE-LY registry but appears in the registry of their extension study RELY-ABLE (26 patient recruitment centres) and the NEJM 2009 publication (24 investigators recruited at least 12 patients). There are many other inconsinstencies in the ClinicalTrials.govlocations of RE-LY and RELY-ABLE. **(www.bmj.com/content/349/bmj.g4747/rapid-responses)** Another paper published always by BMJ in July 2014, described that analyses conducted by Boehringer Ingelheim showed that in August 2011 the company had calculated that there was an optimal plasma concentration range of the drug. In June 2012 another analysis showed that measuring blood dabigatran concentrations and changing the dose as needed could reduce major bleeds by 30-40% in comparison with well controlled warfarin. The analysis concluded : "Optimally used (=titrated) dabigatran has the potential to provide patients an even better efficacy and safety profile than fixed dose dabigatran and also better safety and efficacy profile than a matched warfarin group". But the results of these studies were not comunicated to the regulatory agencies and emails showed that Boehringer Ingelheim employees were reluctant to release the information as it could affect sales. Thomas Moore of the US Institute for Safe Medication Practices and collegues, already cited above, said that regulators should recommend plasma concentration testing in all new patients and eliminate the recommendation that dabigatran "does not in general require routine anticoagulant monitoring". **(35) BMJ 2014 vol. 349 pp.g4756)** Charlton Blake and Rita Redberg, professor of Medicine at the University of San Francisco, in a paper published in July 2014 by BMJ made some considerations. The RE-LY trial was the single pivotal trial for dabigatran. Boehringer Ingelheim applied for fast track approval premised on the novelty of fixed dose rather than an assessment after the completion of two randomised clinical trials as required under standard approval procedures. **(36) (BMJ 2014 vol. 349 pp. g4681)** In addition the FDA issued a reassuring "drug safety communication" after data from its pilot electronic programme **(Mini-Sentinel, www.mini-sentinel.org)** indicating that dabigatran's risks were less than warfarin's. However a meta-analysis of randomised controlled trials examining risk of gastrointestinal bleeding with dabigatran and warfarin obtained completely different results. In this study a total of 4 total Randomised Clinical Trials (RCTs) enrolling 26076 patients were included. On meta-analysis, dabigatran significantly increased the risk of GI tract bleeding, compared with warfarin and the results remained the same with the random-effects model. In this study there were 16074 GI tract bleeding events with dabigatran and 10002 events with warfarin. On the contrary, using the Mini-Sentinel Database, the FDA obtained a GI tract bleeding rate of 1.6 with dabigatran and 3.5 with warfarin (per 100,000 days at risk). With this analysis, the agency concluded that GI tract bleeding rates are not higher, and indeed lower with dabigatran, releasing a reassuring report about the bleeding risk of this drug. The discrepancy between these results is really wide. The meta-analytic results of the RCTs have very narrow confidence intervals and no heterogeneity, demonstrating the increased risk of GI tract bleeding with dabigatran compared with warfarin undoubtedly. However, the Mini-Sentinel Program reports a greater than 50% decrease in GI tract bleeding with dabigatran compared with warfarin. Observational studies like the Mini-Sentinel Program have several sources of bias and because of their limitations, the approval process of drugs is based on RCTs only. The authors conclude that in case of dabigatran, the results generated by this program are contradicted by the results obtained using RCTs which represent the

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

"gold standard" to evaluate the efficacy and safety of a drug. Examination of the reasons behind this contradiction by the FDA, may help to understand and improve the reliability of this program. **(37) (JAMA Internal Medicine 2014 vol. 174 (1) pp. 150-151)** In addition to bleeding risks identified in RE-LY, other methodological concerns include the fact that dabigatran was blinded while warfarin was not blinded and that RE-LY used an intention to treat analysis, which may bias it toward non-inferiority. Litigation revealed internal documentation that the company failed to disclose that monitoring might reduce risk of stroke and bleeding. The investigators conclude that a more transparent process of data collection and review would make important clinical data available without waiting for litigation as it happened with Boehringer in case of dabigatran and as it is also described in an article of The New York Times (February 7, 2014) **www.nytimes.com/2014/02/08/business/new-emails-in-pradaxa-case-show-concern-over-profit.html) (36) (BMJ 2014 vol. 349 pp. g4681)** Chan and collegues conducted a prospective observational study of 100 patients with atrial fibrillation (AF), peak and through levels of dabigatran were measured with the Hemoclot assay at baseline and every 2 months thereafter with a maximum of four visits. The results of their study showed that there is greater between-patient variability (gCV = 51-64%) than within-patient variability (gCV = 33-40%) in plasma dabigatran levels as measured by Hemoclot assay. They affirmed that the inter-patient variability was consistent with that observed in other studies including the RE-LY substudy **(11) (Journal of The American College of Cardiology 2014 vol. 63 pp. 321-328)** and was similar in magnitude to the variability reported with low-molecular-weight heparin and fondaparinux which are given in fixed doses like dabigatran. I think that we cannot compare variability of drugs that have different pharmacokinetics and pharmacodynamics and consequently the fact that LMWH and fondaparinux are given in fixed doses, this certainly does not mean that we can also use dabigatran in fixed doses without laboratory monitoring. They say that their findings are in contrast with those of RE-LY because in the RE-LY study, patients were randomly assigned to the two doses of 150 mg and 110 mg. and on the contrary, in their study informed physicians selected the lower dose based on known clinical characteristics of patients which could be correlated with increased bleeding risk and consequently with drug levels. In my opinion, it is not possible to obtain correct information on such an important issue like laboratory monitoring of a drug, affirming that were obtained similar levels of drug exposure in patients given dabigatran dose of 110 mg or 150 mg. because physicians correctely selected patients who, in their opinion, needed the lower dosage of 110 mg., due to the variability of physicians opinion in the so called "real world". I do not think that this is a correct scientific approach. On the other hand, I am really surprised by their other conclusion that because serial measurements of drug concentrations over a 6-month periods showed that up to 40% of patients whose baseline trough levels were in the upper 20th and 10th centiles had subsequent levels that no longer fell within these respective extremes and that an even 80% of patients with a single low trough measurement did not have subsequent levels in the low extremities, the use of a single Hemoclot measurement does not identify patients with extreme drug levels, considered the large variability related to the time of blood collection for trough levels (median of 13.3 +/- 4.7 hours after the last ingested dose). In any case I hope that in the future we will have more information on how and when correctely perform a laboratory monitoring of dabigatran, not only to identify high or low responders. After having emphasized the results of their study, they concluded that however there

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

were two limitations. The first was related to the intra-patient variability because only 50% of subjects underwent testing at all four time-points, and the second was due to the low sensitivity of the Hemoclot test (30 ng/mL) which was not able to distinguish between low drug levels and absence of the drug. Other objections about their study are well point out by a subsequent comment. **(38) (Journal of Thrombosis and Haemostasis 2015 vol. 13 pp. 353-359)** Douxfils and collegues commented that Chan and collegues revealed an impressive 17 fold variation in plasma concentrations (from < / = 30 to 510 ng/mL) at trough (median of 13.3 +/- 4.7 hours after the last drug intake) with an interpatient geometric coefficient of variation (gCV) of 63.8%. This variation was also important when plasma level was assessed at peak (median of 2.5 +/- 0.2 hours) after the drug intake) with an interpatient gCV of 50.9%. In addition they said that plasma levels were similar at baseline and 2, 4, and 6 months. **(39) (Journal of Thrombosis and Haemostasis 2015 DOI: 10.1111/jth.12880)** The greater variability observed at C trough is questionable as a study of Douxfils and collegues **(40) (Thrombosis and Haemostasis 2015 vol. 113 pp. 862-869)** and another study **(41) (Journal of Thrombosis and Haemostasis 2011 vol. 9 pp. 2168-2175)** showed lower variability in samples taken at trough. The variability of the median delay since the last drug intake is more important for blood taken at trough (4.7 h) than at peak (0.2 h), which certainly explains an important part of this discrepancy. This is a very important limitation of Chan and collegues' study. In addition Douxfils and collegues affirmed that results of the intraindividual variability are even more equivoque. Chan et al. found gCVs of 32.9% and 39.5% for trough and peak levels, respectively. Based on the 100 patients screened at baseline, they defined the upper 20th centiles (n = 20 patients) as equal to 129 ng/mL . Trough plasma levels remained above that threshold in 88.2%, 80.0%, and 70.0% of patients at the 2, 4, and 6 month visit, respectively. Similar analyses were performed for the upper 10th centiles (Plasma level of 180 ng(mL and n= 10 patients) and in the lower 20th percentiles (Plasma level of 38 ng/mL and n= 20 patients). Based on these results, they affirmed that "over the six months measurement of drug concentrations up to 40% of patients whose baseline trough level were in the upper 20th and 10th centiles had subsequent levels that no longer fell within these respective extremes. In addition about 80% of patients with a single low trough measurement did not have subsequent level in the low extreme and for this, as cited above, a single Hemoclot measurement does not identify patients with extreme drug levels. Douxfils and collegues believe that these conclusions must be interpreted with caution for many reasons. First, the lack of individual data does not let us make firm conclusions regarding the concept of a single Hemoclot Thrombin Inhibitor measurement. Namely, it is not possible to assert if it was the same patient who no longer fell within these respective extremes. In addition, from the 20 patients identified on the threshold of 129 ng/mL (the 20th centiles at baseline), data at 2, 4, and 6 months were available for only 17, 10, and 10 patients, respectively and the fact that 50% of patients were not included at all stages of follow-up is a limitation. Another important limitation, for trough plasma data, is the median value of the delay since the last drug intake had an impressive variation of +/- 4.7 hours. Thus, a patient initially identified above the threshold of 129 ng/mL can be normalized due to the fact that delay since the last intake is more important at the 2, 4, or 6 month visit. For the 20th lower percentiles, Chan and collegues said that the test used had a limit of quantitation of 30 ng/mL. **(39) (Journal of Thrombosis and Haemostasis 2015 DOI: 10.1111/jth.12880)** The recent study of Douxfils and collegues demonstrated that for

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

concentrations of < / = 30 ng/mL, it is more appropriate to use a test dedicated [Hemoclot Thrombin Inhibitors LOW (HTI LOW) kit or the STA -ECA II (ECA-II) kit, a chromogenic variant of the ecarin clotting time] to measure these low levels and probably not only < 30 ng/mL. **(41) (Thrombosis and Haemostasis 2015 vol. 113 pp. 862-869).** (see section on "Laboratory Tests"). Moreover, other preanalytical and analytical laboratory key information is still lacking. For example it is not possible to know if different batches of the Hemoclot Thrombin Inhibitor assay have been used, and also the delay between the blood sampling and the congelation is not stated. Douxfils conclude that these limitations clearly highlight that the conclusion of Chan and al. need to be "toned down". Several criteria should be taken into consideration when considering proper drug monitoring : 1) a high intraindividual and 2) high interindividual variability in drug level, both justifying identification of the optimal dose for each patient at the start of treatment; 3) a low variability and good reproducibility in the assay method; 4) a correlation between drug level and clinical event; 5) the demonstration of the value of the therapeutic drug monitoring.**(13) (Journal of Thrombosis and Haemostasis 2010 vol. 8 pp.621-628)** Although a previous simulated pharmacokinetic analysis from the RE-LY study stated that a 6 hours delay might put trough level outside the variability of a typical AF patient, **(42) (Journal of Thrombosis and Haemostasis 2011 vol. 9 pp. 2168-2175)** Douxfils and collegues concluded that a well designed study, assessing the plasma level with adequate coagulation tests and restricting the delay since the last drug intake for the trough measurement at 12 +/- max 1 hour, is required to obtain accurate information on the usefulness of a single measurement to identify high or low responders. **(39) (Journal of Thrombosis and Haemostasis 2015 DOI: 10.1111/jth.12880)** They pointed out that as cited above, the high intraindividual and interindividual variabilities in dabigatran plasma levels are clearly demonstrated. **(11) (Journal of the American College of Cardiology 2014 vol. 63 pp. 621-628)** Chan and collegues reply that the study by Douxfils et al. restricted inclusion to patients (n = 33) with plasma dabigatran levels < 200 ng/mL and they say that because they enrolled unselected clinic patients, their results are likely to be more representative of the variability in through level seen in clinical practice. In addition they say that Douxfils et al. propose that the differences in sampling times may have led to overstimation of interindividual and intraindividual variabilities in trough level and recommend that trough levels should be measured at 12 hours +/- max 1 hour. They found difficult to standardize trough sampling times (median time of collection was 13.3 + / - 4.7 hours after last dose) but they think that this did not affect their results because in the study of Liesenfeld et al. **(41) (Journal of Thrombosis and Haemostasis 2011 vol. 39 pp. 2168-2175)** sampling at 18 hours after dabigatran administration for a typical patient should not result in the pre-dose level falling outside the 80% confidence interval for a 12 hours trough level and similarly, sampling at 6 hours after administration should not result in a pre-dose level outside the 80% confidence interval for a 12 hours trough level. May this be considered a scientific approach ? Absolutely not. In addition they conclude saying that they wanted estimate variability in drug levels within and among patients over time, but not to examine clinical outcomes, as the correlation between drug levels and clinical outcomes were a secondary problem. Contrary to the assertions by Douxfils et al. they believe that their results for interindividual and intraindividual variabilities in dabigatran levels are robust but I absolutely do not think that their statement is correct. **(42) (Journal of Thrombosis and Haemostasis 2015 DOI: 10.1111/jth.12906)** Papers celebrating the advantages of new oral

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

anticoagulants also in thromboprophylaxis after elective hip and knee arthroplasty, continue to be published. **(43) (ATVB 2015 vol. 35 pp. 771-778)** (see also review on rivaroxaban) However dabigatran has been approved for thromboprophylaxis in patients undergoing a hip or knee replacement surgery in Europe and Canada but not in the United States. Although it seems that there is a certain advantage in the use of rivaroxaban and apixaban in these cases, considered the less incidence of the primary efficacy outcome, which was the composite of deep vein thrombosis (either symptomatic or detected by bilateral venography if the patient was asymptomatic), non fatal pulmonary embolism, or death from venous thromboembolism, this advantage is clear when as thromboprophylaxis is used a dosage of 40 mg. of enoxaparin daily on the basis of European guidelines, and is less clear when it is used a dosage of 30 mg. of enoxaparin twice daily on the basis of US guidelines. On the other hand, until an antidote will not be commercial available I do not think to use these drugs in these indications, considered the short period of thromboprophylaxis (14 days in case of knee replacement surgery and 35 days in case of hip replacement surgery) and the deep knowledge of enoxaparin that we have, due to many years of its clinical use.
Recently, Dr. Darlene Elias MD, Director, Anticoagulation Services, Division of Pulmonary and Critical Care Medicine, Scripps Clinic and Scripps Green Hospital, La Jolla, CA, USA, during **the 8th North American DAWN AC user group meeting, 21st november 2014,** showed an analysis of the percentage of adverse events by severity per patient year in their large patient base of about 3,000 patients. The percentage of major bleedings per patient year was much lower than the warfarin major bleed percentages reported by the DOACs trials such as RE-LY (TTR 64.0%), RECOVER (TTR 60.0%), ROCKET-AF (TTR 55.0%), EINSTEIN-DVT (TTR 57.7%), EINSTEIN-PE (TTR 62.7%), ARISTOTLE (TTR 62.2%), and AMPLIFY (TTR 61.0%). As can be seen, in none of these trial was reached an optimal TTR that can considerably reduce the incidence of all adverse events, notably major bleedings in patients in treatment with vitamin K antagonists. In conclusion, the dabigatran "saga" continues, but it is becoming increasingly difficult to hide the truth, and that is that dabigatran treatment and very probably treatments with all the other direct oral anticoagulants such as direct factor Xa inhibitors, need laboratory monitoring.

References :

1) Connolly Stuart J., Ezekowitz Michael D., Yusuf Salim et al. : Dabigatran versus warfarin in patients with atrial fibrillation.New England Journal Medicine 2009; 361 : 1139-1151
2) Stollberger Claudia, Finsterer Josef : Contra : " New oral anticoagulants should not be used as 1st choice for secondary stroke prevention in atrial fibrillation". Thrombosis and Haemostasis 2013; 110 : 496-500
3) Garattini Silvio, Bertele' Vittorio : Non-inferiority trials are unethical because they disregard patients' interest. The Lancet 2007; 370 : 1875-1877
4) Nunn Andrew J., et al., Gandjour Afschin, Soliman Elsayed Z, Chuang-Stein Christy et al. Menten Jaris et al. : The ethics of non-inferiority trials. Correspondence. The Lancet 2008; 371 : 895-897
5) Lesaffre Emmanuel : Superiority, Equivalence, and Non-inferiority Trials. Bullettin of the NYU Hospital for Joint Disease 2008; 66 (2) : 150-154
6) Le Henanff Anne, Giraudeau Bruno, Baron Gabriel et al. : Quality of reporting of noninferiority

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

and equivalence randomized trials. JAMA 2006; 295 (10) : 1147-1160
7) Schulman Sam, Ritchie Bruce, Goy Jennifer K. et al. : Activated prothrombin complex concentrates for dabigatran-associated bleeding. British Journal of Haematology 2013; 164 : 308-310
8) Wong Henna, Keeling David : Activated prothrombin complex concentrates for the prevention of dabigatran-associated bleeding. British Journal of Haematology 2014 doi: 10.1111/bjh.12831
9) Michael O' Riordan : Dabigatran bleeding analysis not disclosed to FDA, documents show. February 26, 2014
www.medscape.com/viewarticle/821116
10) Ansell Jack 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
11) 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
12) Mismetti P., Laporte S. : New oral antithrombotics : a need for laboratory monitoring. For. Journal of Thrombosis and Haemostasis 2010; 8 : 621-626
13) Moore T.J., Cohen M.R., Furber C.D. : Anticoagulants the leading reported drug risk in 2012. QuarterWatch 2012 Quarter 4. www.ismp.org/quarterwatch/pdfs/2011Q4.pdf
14) Cohen Deborah : Dabigatran: how the drug company withheld important analyses.British Medical Journal 2014; 349 : g4670
15) Davidson Bruce L. : The association of direct thrombin inhibitor anticoagulants with cardiac thromboses. Chest 2015; 147 (1) : 21-24
16) Graham David J., Reichman Marsha E., Wernecke Michael et al. : Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for nonvalvular atrial fibrillation. Circulation 2015; 131 : 157-164
17) Hernandez Immaculada, Baik Seo Hyon, Pinera Antonio et al. : Risk of bleeding with dabigatran in atrial fibrillation.
JAMA, Published on line November 3, 2014. Doi: 10.1001/jamainternmed.2014.5398
18) Chew Mabel, Brizzel Catherine, Abbasi Kamran et al. : Medical journals and industry ties. Zero tolerance on education articles with financial links to industry. British Medical Journal 2014; 349 : g7197 doi : 10.1136/bmj.g7197
19) Poller L., Jespersen J. and Ibrahim S. : Warfarin or dabigatran for treatment of atrial fibrillation. Journal of Thrombosis and Haemostasis 2014; 12 : 1193-1195
20) Poller Leon, Ibrahim Saied, Pattison Albert et al. : INR derivation with the PT/INR Line simplified using a spreadsheetfrom the world wide web. Journal of Clinical Pathology 2011; 64 : 930-932
21) Weits Jeffrey : Anticoagulation therapy in 2015 : where we are and where we are going. Journal of thrombosis and thrombolysis 2015; 39 : 264-272
22) Yehy Calvin H., Hogg Kerstin, Weitz Jeffrey I. : Overview of the new oral anticoagulants. Opportunities and challenges. Atherosclerosis Thrombosis Vascular Biology 2015; DOI : 10.1161/ATVBAHA.115.303397
23) van Es Nick, Coppens Michiel, Schulman Sam et al. : Direct oral anticoagulants compared with

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

vitamin K antagonists for acute venous thromboembolism : evidence from phase 3 trials. Blood 2014; 124 (12) : 1968-1975
24) Pernod G., Albaladejo P., Godier a. et al. : Management of major bleeding complications and emergency in patients on long-term treatment with direct oral anticoagulants, thrombin or factor-Xa inhibitors: proposal of the working group on perioperative haemostasis (GIHP) March 2013. Archives Cardiovascular Diseases 2013; 106 : 382-393
25) Moore Thomas J., Cohen Michael R., Mattison Donald R. et al. : Dabigatran, bleeding, and the regulators. British Medical Journal 2014; 349 : g4517
26) Paré Guillaume, Eriksson Niclas, Lehr Thorsten et al. : Genetic determinants of dabigatran plasma levels and their relation to bleeding. Stroke 2013; 127 : 1404-1412
27) Van de werf F., Brueckmann M., Connolly S.J. et al. : A comparison of dabigatran netexilate with warfarin in patients with mechanical heart valves : the randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN). American Heart Journal 2012; 163 : 931-937
28) Ten Cate H., New oral anticoagulants : discussion on monitoring and adherence should start now ! Thrombosis Journal 2013; 11 : 8
29) Pradaxa product monograph, revised 2012. http://www.boehringeringelheim.ca/content/dam/internet/opu/ca_EN/documents/humanhealth/product_monograph/Pradax-pm.pdf
30) Zakboek Rivaroxaban (Xarelto) : Table 4, page 28 (Dutch Language) Netherlands; Van Zuiden Communications BV, 2012
31) Cohen Deborah : Concerns over data in key dabigatran trial. British Medical Journal 2014; 349 : g4747
32) 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. : CD 001927. DOI: 10.1002/14651858.CD001927.pub2
33) 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.pub2
34) Therapeutics Initiative, The University of British Columbia, Department of Anesthesiology, Pharmacology & Therapeutics, Vancouver, BC Canada Therapeutics Letter 2011; 80 www.ti.ubc.ca/sites/ti/.ubc.ca/files/80.pdf
35) Zosia Kmietowic : Boehringer Ingelheim withheld safety analyses on new anticoagulant, the BMJ investigation finds. British Medical Journal; 349 : g4756
36) Charlton Blake and Redberg Rita : The trouble with dabigatran. British Medical Journal 2014; 349 : g4681
37) Sipahi Ilke, Celik Seden, Tozun Nordan : A comparison of results of the US Food and Drug Administration's Mini-Sentinel Program with ramdomized clinical trials. Jama Internal Medicine 2014; 174 (1) : 150-151
38) Chan N.C., Coppens M., Hirsch J. et al. : Real-word variability in dabigatran levels in patients with atrial fibrillation. Journal of Thrombosis and Haemostasis 2015; 13 : 353-359

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

39) Douxfils J., Chatelain B., Dogné M. et al. : Real-world variability in dabigatran levels in patients with atrial fibrillation : comment. Journal of Thrombosis and Haemostasis 2015; DOI: 10.1111/jth.12880
40) Douxfils Jonathan, Lessire sarah, Dincq Anne-Sophie et al. : Estimation of dabigatran plasma concentration in the perioperative setting. Thrombosis and Haemostasis 2015; 113 : 862-869
41) Liesenfeld K. H., Lehr T., Dansirikul C. et al. : Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. Journal of Thrombosis and Haemostasis 2011; 9 : 2168-2175
42) Chan N.C., Hirsh J., Ginsberg J.S. et al. : Real-world variability in dabigatran levels in patients with atrial fibrillation : reply. Journal of Thrombosis and Haemostasis 2015; DOI: 10.1111/jth.12906
43) Messerschmidt Cory, Friedman Richard J.:Clinical experience with novel oral anticoagulants for thromboprophylaxis after elective hip or knee arthroplasty. Atheriosclerosis, Thrombosis, Vascular Biology 2015; 35 : 771-778

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Mechanism of action

At the moment the new oral anticoagulants already investigated in clinical trials are Dabigatran, Rivaroxaban, Apixaban and Edoxaban.
Other drugs are under investigation in pre-clinical studies.

Dabigatran Etexilate is a competitive and reversible direct inhibitor of the active site of both free and clot-bound thrombin which is the molecule that at the end of the coagulation cascade converts fibrinogen into fibrin (figure 1) and activates factor XIII to activated factor XIII (Factor XIIIa) which crosslinks fibrin polymers solidifying the clot. (figure 2) and (figure 3)

Thrombin
Fibrinogen----------Fibrin monomers
(Figure 1)

Fibrin monomers----------Fibrin polymers
(Figure 2)
Factor XIIIa, activated by thrombin
Fibrin polymers----------crosslinked fibrin polymers
(Figure 3)

Fibrin with platelet aggregates will form the blood clot.
Thrombin has other functions. It activates platelets, factor V and factor VIII which are cofactors, to activated factor V and activated factor VIII (Factor Va and Factor VIIIa).
The cofactor is a molecule that binds to the enzyme and allows its action.
Enzymes are large and biological molecules that act on other molecules called substrates and convert them in different molecules called products. (figure 4)

Enzyme+Cofactor
A ----------B
(substrate) (product)
(figure 4)

Factor V binds to activated platelets and, activated by thrombin, is a cofactor of activated factor X (Factor Xa). In fact as you can see in figure 5, the activated factor X (Factor Xa) enzyme requires calcium, fosfolipids and activated factor V to convert prothrombin to thrombin.

(Enzyme) (Cofactor)
Factor Xa+Factor Va,+Calcium ions+phospholipids

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Prothrombin----------Thrombin
(Figure 5)

Factor VIII, also known as anti-hemophilic factor, is a cofactor for the activated factor IX (Factor IXa) that, in the presence of calcium ions and phospholipids, forms a complex which converts factor X to activated factor Xa (Factor Xa) as you can see in figure 6

(Enzyme) (Cofactor)
Factor IXa+Factor VIIIa,+Calcium ions+fosfolipids
Factor X ----------Factor Xa
(Figure 6)

By this way thrombin promotes coagulation. (see simplified coagulation cascade in rivaroxaban review)

In presence of a molecule called thrombomodulin produced by endothelial cells, thrombin acts on protein C and, in a reaction in which another protein called protein S is the cofactor, transforms protein C in activated protein C (see figure 7)

(Enzyme) (Cofactor)
Thrombin+Thrombomodulin+Protein S
Protein C----------Activated Protein C
(figure 7)

The cells which form endothelium are called endothelial cells. Endothelium is the thin layer of cells that coat the interior surface of blood vessels.
Activated protein C cleaves activated factor V (Factor Va) and activated factor VIII (Factor VIIIa), so they become inactive and the coagulation cascade slows down.
By this way thrombin decreases coagulation. (see figure 8)

Activated Protein C
Activated factor V (Factor Va)----------Factor V inactive

Activated Protein C
Activated factor VIII (Factor VIIIa)----------Factor VIII inactive
(figure 8)

Protein C also plays a fundamental role in endothelial injury by blocking the inflammatory reactions and the injury secondary to liberation of inflammatory peptides during coagulation,

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

fibrinolysis and complement activation.

Thrombin also regulates fibrinolysis through thrombin activated fibrinolysis inhibitor (TAFI). TAFI is activated when thrombin is bound on endothelial thrombomodulin. In this manner fibrinolysis, that is the process by which the blood clot dissolves spontaneously, slows down. By this way thrombin promotes coagulation.

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Indications

Dabigatran Etexilate has been approved for use in U.S.A. Canada and Europe for patients with non valvular atrial fibrillation who meet clinical and laboratory criteria for anticoagulation to prevent stroke and systemic embolism, and has been approved only in Europe for post-operative thromboprophylaxis in patients who have undergone a knee or hip replacement . Recently, at the end of march 2014, the FDA has approved dabigatran for the treatment of venous thromboembolism following therapy with a parenteral anticoagulant for 5 to 10 days and to reduce the risk of DVT/PE recurrence in patients who have been previously treated.
The criteria for clinical use are the same described in the non-inferiority RE-LY trial **(1) (New England Journal of Medicine 2009 vol. 361 pp.1139-1151)**. The patients must have a documented atrial fibrillation and at least one of the following characteristics : Previous stroke or transient ischemic attack, a left ventricular ejection fraction of less than 40%, a symptomatic heart failure, New York Heart Association (NYHA) =/> class 2 , an age of at least 75 years or an age between 65 and 74 years plus diabetes mellitus or hypertension, or coronary artery disease.
Criteria for exclusion were the presence of a severe heart valve disorder , stroke within 14 days or severe stroke within 6 months before screening , a creatinine clearance less than 30 ml/mn, active liver disease and pregnancy. Dosage in this case is 150 mg twice daily. The dosage can be modified when dabigatran etexilate is used with drugs that interfere with it and in patients with renal impairment. (See section on dosage and drug interactions).
In the RE-LY trial, a non-inferiority trial, stroke and systemic embolism were 1.71% per year in the warfarin group and 1.11% per year in the group treated with 150 mg. of dabigatran etexilate twice daily and 1.54% per year in the group treated with 110 mg. twice daily. The rate of major bleeding in the warfarin group was 3.57% per year, and in the dabigatran group was 3,32 per year with a dosage of 150 mg twice daily and 2.87% per year with a dosage of 110 mg twice daily. The mortality rate was 4.13% per year in the warfarin group and 3.65% per year with 110 mg. of dabigatran and 3.75% per year with 150 mg always twice daily. **(2) (Thrombosis and Haemostasis 2013 vol.110 pp. 496-500)**
In the post-operative thromboprophylaxis, dabigatran etexilate is indicated at a dosage of 110 mg twice daily. In case of knee replacement, therapy must be started 1-4 hours after surgery with just one capsule of 110 mg the first day, and 110 mg twice daily until 10-14 days. **(3) Journal of Thrombosis and Haemostasis 2007 vol. 110 pp. 496-500)**
In case of hip replacement, therapy must be started 1-4 hours after surgery, with just one capsule of 110 mg the first day, and 110 mg twice daily until 28-35 days. **(4) (The Lancet 2007 vol. 370 pp. 949-956)** (see section on dosage and drug interactions). Dabigatran etexilate can be used as initial treatment or in patients already in treatment with a parenteral anticoagulant, or with an antagonist of vitamin k as warfarin.
a) In the conversion from parenteral anticoagulants as low molecular weight heparins, (LMWH) is recommended to initiate dabigatran 2 hours prior to the time of the next scheduled dose .

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

In the conversion from a continuosly administered parenteral anticoagulant drug as intravenous heparin, it is recommended to initiate dabigatran at the of discontinuation of heparin.

b) In the conversion from warfarin, after having discontinued warfarin, dabigatran etexilate must be initiated when INR (International Normalized Ratio) is < 2 .
(We will explain what is INR when we will treat about warfarin)
But dabigatran can also be discontinued to treat patients with a parenteral anticoagulant or with a vitamin k antagonist as warfarin or acenocumarol.

c) In the conversion from dabigatran to a parenteral anticoagulant it is recommended to wait a minimum of 12 hours before initiating a parenteral anticoagulant (low molecular weight heparins or intravenous heparin)
In the conversion from dabigatran to warfarin the start time must be related to creatinine Clearance (Clcr).
If Clcr is > 50 ml/mn, initiate warfarin 3 days before discontinuation of dabigatran.
If Clcr is between 30-50 ml/mn, initiate warfarin 2 days before discontinuation of dabigatran
As already mentioned, if CLcr < 30 ml/mn, dabigatran use is contraindicated.
Also In these last two cases , (c and d) I recommend the use of a standardized diluted thrombin test (Hemoclot) before switching from dabigatran to a parenteral anticoagulant or to warfarin.
At the end on March 2014, Dabigatran has been approved by FDA and after by EMA for treatment of deep vein thrombosis, pulmonary embolism and to prevent these conditions from reoccuring in adults.

In a recent article published on the July number of Journal of Thrombosis and Haemostasis in 2014, Poller and collegues compared the results obtained in the RE-LY trial (6022 patients) in patients treated with warfarin and in those treated with the two doses of Dabigatran, 150 mg and 110 mg, with the results obtained in patients treated with warfarin in the European Action on Anticoagulation (EAA) study (5939 patients). Only in the EAA study was the reliability of reported INR at participant centres checked by centrally organized local ISI calibrations and by external quality control of reported INR. Clinical events in the EAA patients on warfarin were lower than for warfarin patients and for patients treated with both dose regimens of Dabigatran in the RE-LY study, although the reported "time in target INR range" was only marginally higher. Morbidity and mortality were much higher in RE-LY in all three groups than with warfarin in the EAA study and better results for stroke, major bleedings and minor bleedings were obtained in the EAA study compared with patients treated with warfarin and with patients treated with both Dabigatran doses in the RE-LY study. Overall events (% per year) in the RE-LY study for stroke, major bleedings, minor bleedings and death per year in warfarin patients were 1.57, 3.36,16.37 and 4.13 respectively; in dabigatran patients were 1.44, 2.71,13.16 and 3.75 in the 110 mg group and 1.01, 3.11,14.84 and 3.64 in the 150 mg group. On the contrary, in the EAA study overall events (% per year) for stroke, major bleedings, minor bleedings and death per year were 0.30, 0.86, 2.70 and 0.75 per year

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

respectively. The fact that the results obtained in the EAA study were really impressive although the "time in INR range" was marginally better than in RE-LY may be explained by the lack in RE-LY of two important assessments of INR control, local ISI calibration and external quality control of INR. In addition, in RE-LY there was only a recruitment of 6.3 patients per centre against a recruitment of 182 patients per centre in the EAA study. **(5) (Journal of Thrombosis and Haemostasis 2014; 12 : 1193-1195)** The larger number of centres participating in the RE-LY study, compared with the EAA study, would result in a greater between-centre variation in the quality of oral anticoagulation treatment and this could also be another reason for the impressive clinical results obtained in the EAA study. In addition the higher incidence of events in the RE-LY study may be due to the participation of less experienced centres. Two EAA developments should be further improve results obtained in patients treated with warfarin : 1) The PT/INR line, based on a simple effective procedure using a selected set of only five EAA lyophilised test plasmas to derive a laboratory's local INR, by which it is possible to obtain results similar to those obtained with the more demanding and time consuming FDA-approved simplified ISI calibration. **(5) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1193-1195)**
This last simple procedure has also been cited by the European Society of Cardiology (ESC) which stated that it achieves reliable INR without the need for local ISI calibrations. **(6) (Thrombosis and Haemostasis 2013 vol. 110 pp. 1087-1107)** The EAA PT/INR line test plasmas are now available internationally in a five-plasma kit. 2) A variable growth rate (VGR) analysis was shown in a 2013 EAA study to be of greater value than the previously accepted "time in INR range", in predicting clinical events during warfarin treatment, particularly in short-term oral anticoagulation. **(7) (Journal of THrombosis and Haemostasis 2013 vol. 11 pp. 1540-1546)** The investigators conclude that future studies which will compare a new oral anticoagulant with warfarin, should include the above two relatively simple control procedures introduced by the EAA to obtain a correct warfarin therapy. **(6) (Thrombosis and Haemostassis 2013 vol. 110 pp. 1087-1107)**

References :

1) Connolly Stuart J., Ezekowitz Michael D., Yusuf Salim et al. : Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal Medicine 2009; 361 : 1139-1151
2) Stollberger Claudia, Finsterer Josef : Contra : " New oral anticoagulants should not be used as 1st choice for secondary stroke prevention in atrial fibrillation". Thrombosis and Haemostasis 2013; 110 : 496-500
3) Eriksson B. I., Dahl O.E., Rosencher N. : Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement : the RE-MODEL randomized trial.
Journal of thrombosis and Haemostasis 2007; 5 : 2178-2185
4) Eriksson B.I., Dahl O.E., Rosencher N. : Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement : a randomised, double-blind, non-inferiority trial. The Lancet 2007; 370 : 949-956
5) Poller L., Jespersen J. and Ibrahim S. : Warfarin or dabigatran for treatment of atrial fibrillation. Journal of THrombosis and Haemostasis 2014; 12 : 1193-1195

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

6) ESC-Working Group on Thrombosis- Task Force on Anticoagulation in Heart Disease. Vitamin K antagonists in heart disease : current status and perspectives (section III). Thrombosis and Haemostasis 2013; 110 : 1087-1107
7) Ibrahim SW., Jespersen J., Poller L. : The clinical evaluation of INR variability and control in conventional oral anticoagulant administration using the variance growth rate. Journal of Thrombosis and Haemostasis 2013; 11 : 1540-1546

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Absorption and metabolism

After oral administration, dabigatran etexilate is rapidly absorbed and converted to its active forms dabigatran by enzymes called esterase in the gut, plasma and liver. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity. Dabigatran is approximately 35% bound to human plasma proteins. The bioavailability of dabigatran is only 6,5%, and peak plasma concentration occurs within about 2 hours after oral administration. With a dosage of 150 mg. twice daily, plasma concentrations measured after 2 hours were in a range of 117-275 ng/ml and measured after 12 hours were in a range of 61-143 ng/ml. With a dosage of 110 mg. twice daily, plasma concentrations measured after 12 hours were in a range of 60-130 ng/ml. The mean terminal half life, not affected by the dosage, is about 11 hours and duration of action is about 24 hours. After multiple doses the mean terminal half life is approximately 12-14 hours. Half-life of dabigatran is about 14 hours if creatinine clearance is > 50 ml/mn, is 18 hours for creatinine clearance between 30 and 50 ml/mn and 27 hours for creatinine clearance less than 30ml/mn. Only about 20% of dabigatran etexilate is converted into the active dabigatran form in the liver, and 80% is excreted unchanged by the kidneys. Because dabigatran is excreted principally by kidneys, it is easy to understand that reduced kidney function results in elevated plasma concentrations and prolonged half life. Kidney function is evaluated by creatinine clearance and is expressed in ml/mn. (milliter/minute). Normal values in men are in a range of 97-137 ml/mn and in women are in a range of 88-128 ml/mn. Creatinine clearance values normally go down by about 7,5 ml/mn every 10 years after the age of 30. For this reason, dabigatran must be given to patients older than 75 years very carefully. Exposure to dabigatran is approximately 2,7 fold higher in patients with moderate renal insufficiency (Creatinine Clearance 30-50 ml/mn) and about 6 times higher in patients with severe renal insufficiency (Creatinine Clearance 10-30 ml/mn) than in those without renal insufficiency. **(1)(Essential guide to blood coagulation 2013, second edition, pp.113)** Dabigatran is a prodrug that is supplied as dabigatran etexilate and converted to active dabigatran by hepatic esterases including CES1. The rs2244613 SNP intronic to the esterase gene CES1 was associated with decreased trough concentrations and decreased risk of bleeding. The CES1 SNP rs8192935 and ABCB1 SNP rs4148738 were associated with peak concentrations but not with clinical outcome. The ABCB1 gene encodes for P-glycoprotein, an ATP-dependent drug efflux transporter with broad substrate specificity. Dabigatran etexilate is an ABCB1 substrate however, and the active dabigatran is not. ABCB1 inhibitors increase dabigatran bioavailability by 10% to 20%. The ABCB1 SNP rs4148738 associated with peak concentration is in linkage disequilibrium with the C3435T SNP (rs1045642), widely reported to be associated with drug metabolism. The CES1 rs2244613 minor allele occurred in 32.8% of patients in RE-LY and was associated with lower exposure to active dabigatran metabolite. The presence of the polymorphism was associated with a lower risk of bleeding. In addition the genetic effect of CES1 rs2244613 was found to be greater than the effect of drug dosage (either 110 or 150 mg) in the RE-LY study. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. **(2) (Circulation 2013 vol.**

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

127 pp. 1404-1412)

References :

1) Antovic Jovan P., Blomback Margareta : Essential Guide to Blood Coagulation 2013; second edition : 113
2) Paré Guillame, Eriksson Niclas, Lehr Thorsten et al. : Genetic determinants of dabigatran plasma levels and their relation to bleeding. Circulation 2013; 127 : 1404-1412

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Dosage and drug interactions

For prevention of stroke and systemic embolism in patients with atrial fibrillation the dosage is 150 mg. twice daily. In the European labeling product it is written that also in case of patients with a mild or moderate renal insufficiency , creatinine clearance 50-80 ml/mn and creatinine clearance 30-50 ml/mn respectively, the recommended dosage of dabigatran etexilate is the same, 150 mg. twice daily, as in patients without renal insufficiency. I strongly disagree with this statement because, if we want to use dabigatran in these categories of patients, especially in case of moderate renal insufficiency, it would be better to calculate approximately dabigatran concentration after 2 hours and after 12 hours, using a simple standardized diluted thrombin test like Hemoclot (see section on monitoring and laboratory tests) when we use 150 mg. twice daily and after we will decide if to reduce or not the dosage.
In case of severe renal insufficiency creatinine clearance < 30 ml/mn, it is written to avoid use of dabigatran. In the European labeling it is also written to use 150 mg. twice daily when we use dabigatran with inhibitors of P-glycoprotein (P-gp) as amiodarone, and quinidine and to change the dosage to 110 mg. daily only when we use another P-gp inhibitor as verapamil. Canadian monographs also recommend to give oral dabigatran etexilate 2 hours prior to oral verapamil to obtain a minor charge in dabigatran concentrations. Intravenous verapamil is not expected to interact with dabigatran to any clinically significant degree. Because dabigatran is a substrate of P-gp, when it is used with P-gp inhibitors, inhibition of dabigatran efflux is probably the mechanism of this interaction and its therapeutic concentration will arise. We cannot assume that in every patient this interference will not be important without calculating approximately dabigatran concentration after 2 hours and after 12 hours with a dosage of 150 mg. twice daily, using also in this case a standardized diluted thrombin test. After the results of the tests, we will decide the correct dosage. Concomitant use of dabigatran and amiodarone results in a 58% increase of dabigatran concentration. When dabigatran is used with dronedarone , a potent P-glycoprotein (P-gp) inhibitors, U.S. labeling information recommends to use a lower dose of dabigatran etexilate, 75 mg. twice daily. Canadian labeling on the contrary, recommend to avoid concomitant use of dronedarone regardless of renal function. In fact interaction of dabigatran with dronedarone results in a 73-100% increase in dabigatran concentration.
If we consider that amiodarone, dronedarone and verapamil are the most used drugs in atrial fibrillation, and that non valvular atrial fibrillation is the principal indication for use of dabigatran etexilate, also if this drug has in general less drug interactions than vitamin K antagonists as warfarin or acenocumarol, this few interactions are very important clinically, especially because we are not able to measure the degree of anticoagulation as we normally do with vitamin k antagonists using INR. Other inhibitors of P-gp to avoid with concomitant use of dabigatran are ketoconazole, itraconazole, cyclosporine and tacrolimus. If inhibitors of P-gp increase dabigatran concentration, on the contrary, the concomitant use of dabigatran with P-gp inducers as rifampin, dexamethasone, carbamazepine, phenytoin will reduce dabigatran

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

bioavailability and so their concomitant use must be avoided.
Another important interaction is the interaction of dabigatran with antacids which decrease its plasma concentration, and therapy modification must be considered. Canadian product labeling recommends to avoid use with antacids for 24 hours after surgery and in other situations, to administer dabigatran 2 hours prior to antacids. U.S. product labeling does not show similar recommendations.
Other minor interactions are with atorvastatin, dasatinib, tibolone, tipramavir that increase dabigatran concentrations, on the contrary, interaction with proton pump inhibitors, decreases dabigatran concentration of about 30% as it is written in the Canadian product monograph.
For patients who are 80 years or older the recommended dosage is 110 mg. twice daily, but also in this case I strongly discourage use of dabigatran etexilate because these patients will have a certain degree of renal impairment. The majority will have a moderate renal insufficiency. If we consider that at this age there is a greater percentage of intracerebral hemorrhage and a very important percentage of traumatic events caused by falls, because we do not have an antidote to neutralize dabigatran, we can understand that the use of this drug in this category of patients must be avoided. The other very important consideration is that, at the moment, we do not have clinical trials on dabigatran use in patients older than 75 years. In fact the median age in the RE-LY trial was 71 **(1) (NEJM 2009 vol.361 pp. 1139-1151)**
For patients who are between 75 and 80 years old, in the European labeling is recommended a dosage of 150 mg. twice daily, and the dosage of 110 mg. twice daily must be decided on an individual base evaluating thrombotic and bleeding risk. Also in this category of patients, for the reasons I mentioned before, I do not recommend use of dabigatran.
Important drug interactions are bleeding events that we can have when we use dabigatran etexilate with antiplatelet agents (aspirin, clopidogrel, ticlopidine etc) and with non steroidal anti-inflammatory dugs (NSAIDs), especially if we consider that we cannot evaluate the degree of anticoagulation of dabigatran by laboratory examinations that, on the contrary, we can do using INR in case of vitamin K antagonists.

The other indication approved for dabigatran use, is post-operative thromboprophylaxis in patients who have undergone a knee or hip replacement (see indications). In this case, the treatment must start from 1-4 hours after surgery with only 110 mg. the first day and must continue from the second day for 10-14 days in knee replacement, and for 28-35 days in hip replacement surgery. In this prophylaxis, in patients with moderate renal insufficiency, (creatinine clearance 30-50 ml/mn), in patients who are 75 years or older, in patients who are treated in the same time with P-gycoprotein (P-gp) inhibitors such as amiodarone, quinidine and verapamil, the recommended dosage on labeling is 75 mg. twice a day.
In the first three studies that compared dabigatran etexilate 110 mg. twice daily with enoxaparin 40 mg. once a day, was found a " substantial equivalence between the two drugs in both the rates of total venous thromboembolism (VTE) and of major VTE and VTE

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

related mortality ".
Bleeding rates were similar. **(2) (Thrombosis and Haemostasis 2011 vol. 105 pp. 571-573)** In the RE-NOVATE trial **(3) (Thrombosis Haemostasis 2011 vol. 105 pp. 721-729)** for the first time was found a superiority of dabigatran etexilate compared to enoxaparin in major VTE plus VTE-related mortality, but this superiority was not statistically significant. Also this trial was sponsored by the dabigatran manufacturer.
After these considerations, because we have similar clinical results also with enoxaparin, I really do not understand why we must use a new drug which can give a bleeding very difficult to control, when on the contrary I can use a drug as enoxaparin that we have been using since many years, also considering that dabigatran is very sensitive to renal insufficiency, and that has a longer half life (12-14 hours) compared to enoxaparin that has an half life based on anti-Xa activity of about 7 hours. For patients very thin (< 50 kg) or very fat (> 110 kg) I strongly discourage the use of dabigatran, (see contraindications) because we use fixed doses with this drug, and we can have a supratherapeutic or a subtherapeutic level of dabigatran concentration respectively.
For patients with a body weight between 50-110 kg, if we want to use dabigatran etexilate, I recommend the use of a standardized diluted thrombin test (Hemoclot) after 2 hours and after 12 hours the administration of dabigatran etexilate 150 mg. twice daily, to know approximately the concentration of the drug. After the results of the tests, we will decide the dosage.

References :

1) Connolly Stuart J., Ezekowitz Michael D., Yusuf Salim et al. : Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal Medicine 2009; 361 : 1139-1151
2) Ageno Walter, Prandoni Paolo et al. : New insights on the role of direct thrombin inhibitors for the prevention of venous thromboembolism after major orthopaedic surgery. Thrombosis and Haemostasis 2011; 105 : 571-573
3) Eriksson B.I., Dahl O.E., Huo M.H., et al. : Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). Thrombosis and Haemostasis 2011; 105 : 721-729

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Adverse reactions

a) The most important reaction as for all anticoagulants is bleeding, but if we can reverse the anticoagulant effect of vitamin k antagonists (warfarin, acenocumarol) using vitamin k and PCC concentrates, and the effect of heparin using protamin, we cannot reverse the anticoagulant effect of dabigatran, because at the moment no commercial specific antidote exists. Well aware of this problem, scientists are trying to find an antidote, as it is shown in a scientific paper **(1) (Blood 2013 vol. 121 pp. 3554-3562)** where is described an antidote for dabigatran (aDabi-Fab) that reverses its anticoagulant effect in human plasma in vitro and in rats in vivo. The X-ray crystal structural of dabigatran in complex with the antidote reveals many structural similarities of dabigatran recognition compared with thrombin. By a tighter network of interactions,the antidote achieves an affinity for dabigatran that is about 350 times stronger than its affinity for thrombin. Despite the structural similarities in the mode of dabigatran binding, the antidote does not bind known thrombin substrates and has no activity in coagulation tests or platelet aggregation.
At the moment, the only procedure that can remove dabigatran from plasma, reducing its anticoagulant effect in a significant manner is dialysis. About 60% of its concentration is removed in 2-3 hours. However, the use of this procedure can be very challenging in patients with a massive hemorrhage who are clinically unstable also in the best emergency departments. PCC concentrates have been shown not to be very effective for dabigatran reversal. The manufacturer recommends use of Recombinant activated Factor VII (rFactor VIIa) or activated PCC (FEIBA) (Factor eight inhibitor bypassing activity) also if their use has not been evaluated in clinical trials. Recently FEIBA were reported to have been effective in rapidly reversing the anticoagulant effect of dabigatran in one case study. **(2) (Critical Care Medicine 2013 41 (5): e42-e46)** In another study, also published recently, 4 case of life-threatening bleedings in patients in treatment with dabigatran were reported. In these cases were used with success Activated Prothrombin Complex Concentrates (FEIBA) at a dosage of 50 U/Kg in 3 cases, and at a dosage of 100 U/Kg in a patient who after the insertion of a pace-maker needed a pericardiocentesis to drain blood from the pericardium. Two of these patients had a chronic renal insufficiency and all the four patients were between 81 and 85 years old. **(3) British Journal of Haematology 2014 vol. 164 pp. 308-310)** The mechanism of action is unclear but might entail boosting the prothrombinase complex on the platelet surface. Also recently has been reported a case of a patient who was 80 years old, in treatment with dabigatran, with a septic shock and acute renal failure in which was performed with success a percutaneous trans-hepatic drainage of a gallbladder empyema using FEIBA at a dosage of 40 U/Kg before the procedure. **(4) (British Journal of Haematology 2014 doi : 10.1111/bjh.12831)** Although in these cases the administration of FEIBA was effective to stop a life-threatening bleeding, because these patients had an age > / = 80 years and some of them had a chronic renal insufficiency, considering also that old people with an age > / = 80 present a mild or a moderate renal insufficiency due to the age, and considering that the mean age of patients in the RE-LY study was 71 years, and that at the moment there are not clinical studies about the use of dabigatran in very old patients, the use of this drug in this category

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

of patients must be avoid. Just recently, The New England Journal of Medicine, in November 2014, published a letter. The authors write that PER977 (Aripazine), developed by Perosphere, a small synthetic, water soluble, cationic molecule that is designed to bind specifically to unfractioned heparin (UF) and low molecular weight heparin (LMWH) through non-covalent hydrogen bonding and charge-charge interactions, binds in a similar way to the new oral factor Xa inhibitors, edoxaban, rivaroxaban and apixaban, and to the oral thrombin inhibitor dabigatran. In non clinical studies, PER977 did not bind to plasma proteins, including albumin, and showed no binding when tested against several common cardiovascular, antiepilectic, and anesthetic drugs. Pharmacokinetic and pharmacodynamic effets of escalating, single intravenous dose of PER977 (5 to 300 mg) administered alone and after a 60 mg oral dose of edoxaban were studied in a double blind, placebo controlled trial involving 80 healthy persons. As laboratory tests, a whole blood clotting time was used to measure the anticoagulant effect of edoxaban and its reversal by PER977. In clinical trials of PER977 (Aripazine), whole blood clotting time showed low variability and high reproducibility and correlated well with edoxaban plasma concentrations. After the administration of edoxaban, the mean whole blood clotting time increased by 37% over the baseline value. In patients receiving a single intravenous dose of PER977 (100 to 300 mg) 3 hours after the administration of edoxaban, the whole blood clotting time decreased to within 10% above the baseline value in 10 minutes or less, whereas in patients receiving placebo, the time to reach that level was much longer, approximately 12 to 15 hours. The whole blood clotting time remained within 10% above or below the baseline value for 24 hours after the administration of a single dose of PER977. There was no evidence of procoagulant activity after the administration of PER977, as assessed by measurement of levels of D-dimer. prothrombin fragment 1 + 2, and tissue factor pathway inhibitor and by whole blood clotting time. Baseline hemostasis was restored from the anticoagulated state within 10 to 30 minutes after administration of 100 to 300 mg of PER977 and was sustained for 24 hours. Clinical studies of phase 2 are ongoing. **(5) (New England Journal of Medicine 2014 vol. 371 pp. 2141-2142)** A report challenges that PER977 binds directly to anticoagulants, but indicates that it rather acts procoagulatory similar to polycationic molecules. **(6) (Circulation 2014 vol. 130 Abstracts A18218)** At the moment the biggest challenge for aripazine is its unclear mode of action. It is difficult to understand how this compund should show specificity for a broad range of structurally very different anticoagulants, while at the same time not interfering with other biologically relevant molecules or other drugs. Furthermore, an animal study comparing PER977 with andexanet alpha indicates that the molecule may reverse bleeding without reversing the altered clotting assay. This may become an issue for monitoring of reversal therapy. **(7) (Thrombosis and Haemostasis 2015 vol. 113 (5) pp. 931-942)**

Recently, on 23 july 2014, was published an interesting article by the British Medical Journal written by Dr. Deborah Cohen, the investigations editor at the BMJ, in which she writes that in an investigation she finds that recommendations for use of new generation oral anticoagulants may be flawed because regulators did not see evidence showing that monitoring drug plasma levels could improve safety. The maker of dabigatran has failed to share with regulators information about the potential benefits of monitoring anticoagulant activity and adjusting the dose to make sure the drug is working as safely and effectively as possible.**(8) (British Medical Journal 2014 vol. 349 pp. g4670)** In a published study, whose lead author was Paul Reilly, a Boehringer employee, in a RE-LY

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

substudy, analyzing blood samples from 9183 patients of the original RE-LY study, was found that there was a fivefold variation in blood plasma concentration of dabigatran with each dose. This paper also reported that renal function was the most important determinant of dabigatran concentration, and age is the most important covariate. It was first drafted in August 2011 and published in 2014. **(9) (Journal of The American College of Cardiology 2014 vol. 63 pp. 321-328)** The company also withheld analysis that calculated how many major bleeds could be prevented by dose adjustements. Internal documents of the company show how the company had produced extensive analyses that show how the bleeding risk may be reduced. The company found that if the plasma levels of the drug were measured and the dose was adjusted accordingly, major bleeds could be reduced by 30-40% compared with well controlled warfarin. **(8) (British Medical Journal 2014 vol. 349 pp. g4670)** This reduction of major bleeds is measured as Relative Risk Reduction (RRR). The rate of major bleeding in patients on the 150 mg dose of dabigatran in the RE-LY trial was 3.11% compared to 3.36% in the warfarin group with an Absolute Risk Reduction (ARR) of 0.25%. What it is important in these clinical studies is the absolute risk reduction and not the relative risk reduction. ARR is a way of measuring the size of a difference between two treatments. It simply tells you how much better or worse one treatment is at reducing a particular outcome in terms of the actual numbers (or rates) of people who experience the outcome compared with another treatment. The Relative Risk Reduction (RRR) is the difference between the likelihood of an event happening in two groups, expressed as a percentage of the risk for one of the groups. Using an example, if 4% of people taking placebo have a migraine, but only 2% of those taking the drug, the risk of migraine is 50% lower for people taking the drug. It is clear that 50% difference (RRR) sounds more impressive than a 2% difference (ARR), but both these numbers describe the same difference in effect, just in a different way. In all the clinical studies which want to study the efficacy of a drug compared to another drug, we must always consider the Absolute Risk Reduction (ARR) and not the Relative Risk Reduction (RRR) that create a bias in our results.
Randomized controlled trials are the gold standard in the assessment of a treatment effect. The magnitude of this effect can be presented in various ways, eg, Relative Risk Reduction (RRR), Absolute Risk Reduction (ARR) and Odds Ratio (OR). Reporting RRR alone may lead a reader to believe that a treatment effect is larger than it really is. Although these considerations, ARR is underused in the medical literature. **(10) (JAMA 2002 vol. 287 pp. 2813-2814)**
On the contrary, in all the clinical studies about new oral anticoagulants the results are emphasized as Relative Risk Reduction (RRR). As when we describe some events of our life we can emphasize some particulars, and speak less of other particulars without saying any lie, but altering the perception of the event, in the same manner in a clinical trial, we can emphasize some results and not other results, without saying any lie, but also in this case altering our perception of the true results of the clinical trial.

Management of bleeding patient anticoagulated with dabigatran (11) (Emergency Medical Journal 2014 vol. 31 pp. 163-168)

1) Coagulation screen to include APTT and TT (Thrombin Time) and if possible the dilute Thrombin Time (Hemoclot) that represent actually the "gold standard" to evaluate

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

anticoagulation in patients taking Dabigatran
2) Full blood cell count and evaluation of renal function by CrCl or better, by eGFR
I
If APTT and TT are normal, dabigatran levels are low or absent
I
If APTT and TT are prolonged, dabigatran anticoagulant effect may be present. (Consider oral charcoal if dabigatran ingestion < 2 hours) Repeat testing every 4-6 hours until bleeding has stopped.
I
In case of Mild Bleed Stop Dabigatran Use clinical judgement to hold or to continue dabigatran. Evaluate when the last dose of dabigatran was taken. Stopping the drug will decrease the continued bleeding risk, but the risk of stroke and the severity of the bleeding should be weighed. Consider additional factors, such as duration of the drug effects (1-2 days in patients with normal renal function, but can be > 5 days in patients with impaired renal function) and the onset of action when restarting (peak activity 2-4 hours).
I
a) Mechanical Compression
b) Tranexanic acid at the dosage of 10 mg/kg i.v. or at the dosage of 25 mg/kg per os
c) Delay next dabigatran dose or discontinue treatment
I
If the patient continues to bleed
I
a) Optimise tissue oxygenation
b)Control haemorrhage through mechanical compression or through surgical/radiological intervention
c) Tranexanic acid (1 gr i.v.)
d) Red cell transfusion to reach Hb > 8 g/dl
e) Platelet transfusion to reach Plt > 75,000/mm3, in case of CNS Bleed, reach Plt > 100,000/mm3
f) Identify bleeding source e.g. surgery, endoscopy, interventional radiology

In case of Major Bleed Stop Dabigatran Evaluate when the last dose was taken
I
Maintain BP and Urine Output (Dabigatran has 80% renal excretion)
I
a) Optimise tissue oxygenation
b)Control haemorrhage through mechanical compression or through surgical/radiological intervention
c) Tranexanic Acid (1 gr i.v.)
d) Red cell transfusion to reach Hb > 8 gr/dl
e) Platelet transfusion to reach Plt > 75,000/mm3, in case of CNS bleed reach Plt >

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

100,000/mm3
f) Identify bleeding source e.g. surgery, endoscopy, interventional radiology
I
Consider Haemodialysis or Haemostatic agent such as FEIBA/PPC/rVIIa

In case of Limb or Life threatening bleed
I
Consider use of Haemostatic agent such as FEIBA/PCC/rVIIa

Higher risk of thrombotic events with rVIIa (10-20%) compared to PCC (1-4%). Also with FEIBA the thrombotic risk is higher compared to PCC especially with doses above 200 U/kg or in patients with other risk factors for thromboembolic events.

Major bleedings in non-surgical patients are considered : (12) (Journal of Thrombosis and Haemostasis 2005 vol. 3 pp. 692-694)
1) Fatal bleeding and/or
2)Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or
3) Bleeding causing a fall in hemoglobin level of 2 gr/dl or more or leading to transfusion of two or more units of red cells

b) Gastrointestinal disorders
Abdominal discomfort and pain, epigastric discomfort in more than 10% are other adverse reactions . Dabigatran etexilate is associated with a modest but significantly higher risk of gastrointestinal l bleeding as described in a review this year **(13) (Gastroenterology 2013 vol. 145 pp. 105-112)** and also if in this study there are some limitations as the heterogenicity between studies, the problem is that in case of an important gastrointestinal bleeding , we do not have an antidote.

c) Myocardial infarction and acute coronary artery syndromes
Dabigatran etexilate is associated with an increased risk of myocardial infarction or acute coronary syndromes in a broad spectrum of patients. In the RE-LY trial was found a 38% increase in myocardial infarction, **(14) (New England Journal of Medicine 2009 vol. 361 (19) pp. 1139-1151)** but after a retrospective assessment, the incidence of MI remained at 27% but no longer reached statistical significance.**(15) (New England Journal of Medicine 2010 vol. 363 (19) pp. 1875-1876)**
In another scientific paper was found an increased risk of myocardial infarction or acute coronary syndromes with dabigatran etexilate compared with various control treatments that included adjusted-dose warfarin, enoxaparin or placebo. **(16) (Archives of Internal Medicine 2012 vol. 172 pp. 397-402)**
On September 25, 2014 was published an article in which the author writes that the apparent

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

paradoxical association of administering direct thrombin inhibitor anticoagulants with developing cardiac thromboses is being repeatedly reported.
A large data base from many comparative clinical trials in many indications is available for assessing the cardiac thrombosis risk associated with dabigatran, compared to well-controlled warfarin treatment, and the result is that patients who were taking dabigatran had more cardiac ischemic and thrombotic events. **(17) (Chest 2015 vol.147 (1) pp. 21-24)** In a review of individual patient data from atrial fibrillation and venous thromboembolism clinical trials, investigators from dabigatran manufacturer concluded that "the rate of myocardial infarction with well-controlled warfarin (for stroke prevention in patients with atrial fibrillation and acute VTE treatment or secondary VTE prevention) is lower than with dabigatran 150 mg. twice daily" **(18) (Vascular Health Risk Management 2013 vol. 9 pp. 599-615)**
Myocardial infarction during treatment with dabigatran occurred in 13 patients compared to 3 patients in treatment with warfarin for venous thromboembolism. This clinical trial investigated 1400 patients per treatment group. These differences (10 myocardial infarctions more than with warfarin) were not described in trials with fewer patients or when dabigatran was compared to placebo in a similar population. **(19) (New England Journal of Medicine 2013 vol. 368 (8) pp. 709-718)** Another clinical trial in which dabigatran was compared to warfarin for treatment of patients with mechanical heart valves was stopped prematurely because of a high rate of adverse thrombotic events in the dabigatran group. The investigators suggested that the higher cardiac thrombotic risk with dabigatran compared to warfarin, was due to the combination of tissue factor and contact activation-generated thrombin that might overwhelm a pharmacokinetically controlled dabigatran level.**(20) (New England Journal of Medicine 2013 vol. 369 (13) pp. 1206-1214)** Thrombin generation in plasma from 10 patients taking therapeutic doses of warfarin (mean INR 2.6) was compared with that in plasma containing 250 ng/mL dabigatran. Although lag times were similar when thrombin generation was induced by recalcification or with a range of tissue factor concentrations, there was a greater reduction in peak thrombin generation and endogenous thrombin potential in plasma from warfarin-treated patients than in dabigatran-containing plasma. Warfarin suppresses thrombin generation more efficiently than dabigatran. Greater suppression of normal hemostatic mechanisms in the brain and pathological thrombosis at sites of atherosclerotic plaque disruption may explain the higher rate of intracranial bleding and lower rate of myocardial infarction with warfarin compared to dabigatran. **(21) (Journal of Thrombosis and Thrombolysis 2013 vol. 35 (2) pp. 295-301)**
Recently, British Journal of Haematology published a study in which to 100 µl of plasma from patients in treatment with warfarin were added 100 µl of a cell suspension, derived from washed human mononuclear cells from the blood of healthy donors, incubated overnight at 37 °C with 1µg/ml lipopolysaccharide to induce maximal TF expression. The clot formation was then initiated by the addition of 100 µl of 20 mmol/l CaCl2.
The clotting time was evaluated manually, and the anticoagulant activity at each cell concentration was calculated as the ratio between the clotting time of patient plasma and the clotting time of control plasma. Warfarin plasma displayed a similar anticoagulant activity at all cell concentrations. On the contrary, the anticoagulant activity of dabigatran plasma was strongly influenced by cell number. Qualitatively similar results were obtained when the cells were replaced by thromboplastin,

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

indicating that the change in TF activity was indeed the cause of the different response of dabigatran plasma. Interestingly, the fact that warfarin displays the same anticoagulant effect regardless of TF concentrations, suggests that it will be able to inhibit the clotting process equally well during haemostasis and thrombosis. In contrast, the efficiency of dabigatran may vary depending on the local availability of TF. For these considerations, dabigatran might have a lower impact on the formation of a haemostatic plug within tissues, such as brain, where the concentration of TF is very high, and this might explain the lower incidence of intracranial hemorrhage in patients treated with dabigatran compared to patients treated with warfarin. On the other hand, this tissue factor dependent efficiency of dabigatran may explain the increased incidence of myocardial infarction in patients treated with this drug. **(22) (British Journal of Haematology 2015 vol. 168 pp. 911-913)** In fact, thrombosis within a coronary artery is triggered by the rupture of an atherosclerotic plaque, which is rich in TF-bearing cells, such as activated macrophages and smooth muscle cells, and cell-derived TF-positive microparticles. **(23) (Thrombosis Research 2012 vol. 129 pp. S38-S40)** Differently, the efficiency of dabigatran in preventing stroke and systemic embolism in patients with atrial fibrillation, may depend on the fact that thrombus formation within the atrial appendage is most likely to be caused by low TF concentration combined with stasis and other prothrombotic alterations, **(24) (Pathophysiology of Haemostasis and Thrombosis 2003 vol. 33 pp.282-289)** and both peak and through concentrations of dabigatran are likely to inhibit the thrombotic process. Just recently have been published two studies which attain divergent conclusions. The studies, analyzing Medicare database, have evaluated efficacy and safety of dabigatran in clinical practice compared with warfarin, in patients with nonvalvular atrial fibrillation. The first study has been published on line by Circulation on November 5, 2014 and evaluated patients who initiated dabigatran or warfarin for treatment of NVAF between October 2010 and December 2012. The primary outcomes of the study were ischemic stroke, major bleeding with specific focus on intracranial and gastrointestinal bleeding and acute myocardial infarction (AMI). Secondary outcomes were all hospitalized bleeding events and mortality. Major bleeding was defined as a fatal bleeding event, a hospitalized bleeding event requiring transfusion, or hospitalization with hemorrhage into a critical site (i.e. intracranial, intraspinal, intraarticular, intraocular, pericardial, retroperitoneal, or intramuscular with compartment syndrome). In this study, the increased risk of major gastrointestinal bleeding with dabigatran appeared to be restricted to women age 75 years or older and to men age 85 years and older, where there was a trend for a higher risk of death with dabigatran compared with warfarin. The investigators rightly write that their study has several limitations. It was observational and may be subject from factors not adjusted for in the analysis. In addition, correctly they write that because Medicare data do not capture laboratory results, they had no basis upon which to assess the quality of warfarin anticoagulation. " It is possible that the favorable effects of dabigatran on ischemic stroke and mortality and its adverse effect on major gastrointestinal bleeding in our study were at least partly due to low time in the therapeutic range with warfarin. However, this would not explain the reduced risk of intracranial hemorrhage with dabigatran". A possible explanation of more intracranial bleedings in patients treated with warfarin compared to patients treated with dabigatran may be due to the high TF concentration in the brain, and to the reduced efficiency of dabigatran in presence of high local avalability of TF as it is written above. The authors point out that warfarin management in

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

their study, independently if was or was not adequate, reflected the quality of anticoagulation experienced by patients treated with warfarin in the general practice setting in the U.S. They conclude that dabigatran was associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and mortality and an increased risk of gastrointestinal bleeding compared with warfarin principally with the dosage of 150 mg. With the dosage of 75 mg that is used in the U.S. was observed only a reduced risk of intracranial hemorrhage. **(25) (Circulation, published online October 30, 2014)** The second study has been published online by JAMA on November 3, 2014 and evaluated patients with NVAF who initiated dabigatran or warfarin treatment between October 2010 and December 2011. In this study the investigators evaluated in particular the risk of bleeding in these patients.
Bleeding events were divided in major and minor events. Major bleeding events included intracranial hemorrhage, hemoperitoneum, and inpatient or emergency department stays for gastrointestinal,hematuria, or not otherwise specified (NOS) hemorrhage; minor bleedings events included epistaxis, hemoptysis, vaginal hemorrhage, hemarthrosis and any outpatient claim for hematuria, gastrointestinal , and NOS hemorrhage. Any bleeding included major and minor bleeding events. Several claims for the same type of bleeding made within 1 week were considered as the same event to avoid double counting. They adjusted for two main categories of covariates : 1) demographic variables and 2) clinical characteristics. They found that the adjusted incidence of major bleeding was 9.0% for the dabigatran group and 5.9% for the warfarin group. Compared with warfarin, the hazard ratios (HRs) associated with dabigatran were 1.58 (95%CI, 1.36-1.83) for major bleeding and 1.30 (95%CI, 1.20-1.41) for any bleeding. Relative to warfarin, dabigatran for gastrointestinal bleeding had a hazard ratio (HR) of 1.85, for hematuria had a HR of 1.41, for vaginal bleeding a HR of 2.27, for hemarthrosis a HR of 2.78 and 1.49 for hemoptysis. Patients in treatment with dabigatran had a lower adjusted rate of intracranial bleeding of 0.6% compared with a rate of 1.8% among patients in treament with warfarin. However, hazard rates of intracranial bleeding for patients younger than 75 years and african americans were not different between the treatment groups. After adjusting for patient characteristics, dabigatran was associated with an increased risk of major or any bleeding events and gastrointestinal hemorrhage for all subgroups analyzed. The risk of major bleeding among patients taking dabigatran was especially high for blacks (HR 2,12) and for patients with chronic kidney disease (HR 2.58), both relative to warfarin. The investigators write that they had a maximum 14 month follow-up period because 2011 part D data were the most recently available data to them. They therefore could not evaluate the incidence of stroke,so their results cannot compare the benefit-risk ratio of treatments.Also in this study was not possible to assess the quality of warfarin treatment. The investigators conclude that physicians should prescribe dabigatran with caution, especially among African Americans and patients with renal impairment. The risk of gastrointestinal bleeding was consistenly higher for all subgroups of patients in treatment with dabigatran compared with patients who were taking warfarin. On the contrary, the risk of intracranial bleeding was lower in dabigatran users, compared with warfarin users. "Before more evidence is available, dabigatran should be prescribed with caution in high-risk patients".
(26) (JAMA Internal Medicine 2015 vol. 175 (1) pp. 18-24) As written in JAMA Internal Medicine, in the Editor's note, dabigatran was approved by the FDA in 2010 via the accelerated pathway after a 6 months review but the haste to approve new drugs gives more importance to

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

postapproval data to better understand risk and benefits. Although the Mini-Sentinel analysis from FDA shows less bleeding risk with dabigatran compared with warfarin, Hernandez et al., the authors of the previous paper, correctely note that the FDA has failed to adjust for differences in patient characteristics, which would bias the results. Redberg Rita, the author of the article, conclude that "This study reminds us of the importance of postmarketing data on risks and benefits to advise our patients accurately". **(27) (JAMA Internal Medicine 2015 vol. 175 (1) pp. 25)** On the other hand, although Healey and collegues observed no excess of bleeding in the RE-LY trial in patients who underwent a major or urgent surgical procedure **(28) (Circulation 2012 vol. 126 pp. 343-348)**, Hjemdahl et al. pointed out that differently from dabigatran, in case or warfarin treatment, a procedure-related bleeding may be prevented or handled with vitamin K and/or prothrombin complex concentrate treatment. In addition they note that in the RE-LY study the risk of major bleeding was greater with warfarin within 48 hours of discontinuation, but when study treatment was stopped > 72 hours before interventions, the risk was higher with dabigatran 150 mg twice daily and this may reflect accumulation of dabigatran in patients with renal impairment. **(29) (Circulation 2013 vol. 127 pp. e505)** David et al. at the end of their letter made an observation that is impossible to rebute. Although hemodialysis has been suggested to remove dabigatran in case of bleeding or urgent surgery, in certain situations of emergency, delaying the surgery, even for a few hours, may be strongly deleterious for the patient, and hemodialysis may not be feasible in all the hospitals. **(30) (Circulation 2013 vol. 2013 pp. e504)** Recently has been published a substudy of the RE-LY trial in which patients who interrupted dabigatran or warfarin for an elective surgery/procedure and received "bridging" were at increased risk for perioperative major bleeding more than those who did not receive "bridging", irrespective of interruption of dabigatran or warfarin. However, correctely the authors conclude that definitive conclusions about major bleeding and, especially thromboembolic outcomes and the periprocedural role of "bridging" need to await the results of the BRIDGE trial NCT00786474 which will determine whether "bridging" with dalteparin is helpful or harmful for people with atrial fibrillation who stop taking warfarin in preparation for a surgical procedure, and the result of the PERIOP-2 trial NCT00432796 which will determine the effectiveness and safety of LMWH postoperative bridging therapy (standard of care) versus postoperative placebo bridging therapy (experimental arm) for patients with mechanical heart valves or atrial fibrillation or atrial flutter who are at high risk for stroke when warfarin is temporarily interrupted for a procedure. **(31) (Thrombosis Haemostasis 2015 vol. 113 (3) pp. 625-632)** Also in other studies was observed an increase of bleeding events in patients who received a "bridging" treatment. These studies included a systematic review of observational studies that compared bridging versus no bridging periprocedural management **(32) (Circulation 2012 vol. 126 pp. 1630-1639)** and a randomised trial of warfarin continuation versus warfarin interruption with LMWH bridging in patients having pacemaker/defibrillator implantation. **(33) (NEJM 2013 vol. 368 pp. 2084-2093)**

Lindhal et al. found that in vitro there is a more efficient reversal of dabigatran inhibition of coagulation by activated prothrombin complex concentrate or recombinant factor VIIa than by four-factor prothrombin complex concentrate. The authors conclude affirming that based on their study and the few cases reports and in vitro and ex vivo studies, for a critically bleeding patient on dabigatran, their choice would be rFVIIa in the highest dosage used in this study to get maximal

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

effect or APCC in same dosage as for treatment of haemophilia patients with inhibitors. They also noted that rFVIIa and APCC in too high doses may induce excessive coagulation and eventually cause thrombotic complications.
The maximum dosage of rVIIa used in this study was from standard treatment of 90µg/kg to a tripled concentration corresponding to high-dose treatment. This represents a final concentrations in blood of 2.1 µg/ml and 6.3µg/ml respectively. **(34) (Thrombosis Research 2015 vol. 135 pp. 544-547)** In my opinion, based on reported anedoctal cases, the reversal of dabigatran anticoagulation activity must be evaluated on a case by case basis. In case of severe bleeding, the first agent which must be used is APCC (FEIBA) at a dosage between 50 and 100 unit/kg, depending on the severity of bleeding. As a second line treatment, recombinant Factor VIIa (rVIIa) at a dosage of 90 µg/kg, also if with these agents there is an increased risk of thromboembolic events especially with rVIIa. In case of a less severe bleeding is more convenient to use a PCC, due to a lower incidence of thrombotic complications. In a retrospective study of 73 patients treated by direct anticoagulant and admitted to an emergency room, 35 patients (47.8%) were treated by dabigatran and 38 (52.1%) were treated by rivaroxaban. The principal factors of hemorrhagic risk were male sex, an increased bleeding Beyth score, and a decreased creatinine clearance. **(35) (Journal des Maladies Vasculaires 2015 vol. 40 (1) pp. (1-9)** Recently Getta and collegues described an 84-year-old male who needed an urgent surgical procedure because of an ischaemic small bowel secondary to strangulated inguinal hernia. He was taking dabigatran at a dosage of 150 mg twice daily for chronic atrial fibrillation, with the last dabigatran dose being taken 12 hours prior admission. His past history included ischaemic heart disease, dilated cardiomyopathy and previous cardio-embolic stroke. Activated PTT was 57 sec., thrombin time > 150 sec. and dabigatran level was 260 ng/ml as measured by Hemoclot assay (Hyphen BioMed, Neuville-Sur-Oise, France) with an assay working range of 50-500 ng/ml. Renal and hepatic functions were impaired with creatinine 119 µmol/l (estimated glomerular filtration rate 48 ml/min), total bilirubin 42 µmol (< 21 µmol/l) and albumin 32 g/l (38-48 g/l). To remove dabigatran, 4 hours of haemodialysis was performed with a Fresenius 4008.S dialysis machine using a Fresenius FX60 CorDiax dialyser (both from Fresenius, Bad Homburg, Germany). The blood flow rate was 300 ml/min with no anticoagulant and no net ultrafiltration. Dialysis was well tolerated with no haemodynamic alterations. The dabigatran level was 105 ng/ml prior surgery, corresponding to a 60% reduction from the pre-dialysis level. Necrotic small bowel was resected during surgery and was uncomplicated. Immediate post-operative dabigatran level increased to 144 ng/ml probably due to the redistribution of dabigatran bound to plasma proteins and the shift out of the extravascular compartment. He remained oliguric post-operatively. Continuos veno-venous dialysis (CVVHD) was performed for about 48 hours post-operatively to reduce dabigatran concentration. A Prismaflex dialysis machine with a ST100 filter (Gambro, Stockholm, Sweden) was used, with Prismocitrate 18/0 dialysate (Gambro) at a flow rate of 500 ml/h, against a blood flow rate of 150 ml/h; 0.9% saline was used as replacement fluid at a rate of 200 ml/h. The dabigatran level after this procedure was below the laboratory quantifiable limit (< 40 ng/ml) and interestingly there was no rebound rise in dabigatran level. CVVHD could be continued intra-operatively if bleeding occurred during surgery. **(36) (British Journal of Haematology 2015 vol. 169 pp. 603-604)** A reduction of dabigatran plasma concentration of about 62-68% by 4 hours of haemodialysis was previously described by Chang et al. and these

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

authors also suggested continuation of dialysis in the form of CVVHD to reduce further dabigatran concentration. **(37) (American Journal of Kidney Diseases 2013 vol. 61 (3) pp. 487-489)**
Recently was published a paper in which idarucizumab, a fab fragment derived from a monoclonal antibody that binds dabigatran with a high affinity, was investigated in humans. In this first-i--human, single-rising-dose study, the authors investigated the pharmacokinetics, safety and tolerability of idarucizumab in 110 randomised healthy males (27 received a placebo and 83 received idarucizumab). Idarucizumab was safe and well tolerated after intravenous infusion. Its pharmacological profile met the requirement for rapid peak exposure followed by rapid elimination, with no effect on pharmacodynamic parameters when administered alone. In the absence of dabigatran, idarucizumab was safe and well tolerated at all administered doses, as either a 1 hour or 5 min. infusion. **(38) (Thrombosis and Haemostasis 2015 vol. 113 (5) pp. 943-951** A study of phase 1 has shown that idarucizumab has produced an immediate, complete and prolonged reversal of the anticoagulant effect of dabigatran in healthy people. A clinical trial of phase 3 is evaluating the reversal of the anticoagulant effects of dabigatran by IV administration of 5.0 gr idarucizumab in patients treated with dabigatran who have uncontrolled bleeding or require emergency surgery or procedures. **(NCT02104947) https://**
clinicaltrials.gov/ct2/show/NCT02104947 The fab fragment directly binds dabigatran with a very high affinity, which is about 350 times greater than that of thrombin. The complex of the Fab and dabigatran can no longer bind into the cleft of the active center of thrombin. Idarucizumab inhibits dabigatran very effectively within minutes in vitro as well as in vivo in animals and healthy volunteers. Sustained reversal of dabigatran was seen with the 2.5 gr., the 5 gr., and the 2 x 2.5 gr dosing regimens. Interestingly, within minutes after application of idarucizumab the intravasal concentration of total dabigatran rapidly increases and in parallel the anticoagulant activity measured using clotting time was normalised. This paradox can be explained by the fact that the gradient, which determines the diffusion velocity of dabigatran from the extravasal to the intravasal compartment involves primarily free (unbound) dabigatran. As all dabigatran, which redistributes into the intravasal compartment, is immediately neutralised by idarucizumab, a high diffusion gradient is maintained until all active dabigatran is inactivated. About 15% of normal individuals have natural antibodies binding to the cleavage site of fab fragments, and in this case probably, the complexes of dabigatran, idarucizumab and the anti-Fab antibody will no longer be filtered by the kidney, because too large. This may prolong the resistance to new doses of dabigatran. Another theoretical risk is the formation of anti-idiotype antibodies which bind to the variable region of an antibody and could thereby inactivate the dabigatran antidote, if this has to be given again. Anti-idiotype antibodies can sterically mimick the original antigen of the idiotype antibody although the risk is very low, especially if the antidote is given only once. Thus an anti-idiotype antibody against idarucizumab may mimick sterically dabigatran and could become an endogenous thrombin inhibitor. **(39) (Thrombosis and Haemostasis 2015 vol. 113 (5) pp. 931-942)**

References :

1) Schiele Felix, van Ryn Joanne, Canada Keith, et al. : A specific antidote for dabigatran : functional and structural characterization. Blood 2013; 121 : 3554-3562

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

2) Dager William, E., Gosselin Robert C., Roberts A. et al. : Reversing dabigatran in life-threatening bleeding occurring during cardiac ablation with factor eight inhibitor bypassing activity. Critical Care Medicine 2013; 41, issue 5 : e42-e46
3) Schulman Sam, Ritchie Bruce, Goy Jennifer K. et al. : Activated prothrombin complex concentrate for dabigatran-associated bleeding. British Journal of Haematology 2014; 164 : 308-310
4) Wong Henna, Keeling David : Activated prothrombin complex concentrate for the prevention of dabigatran-associated bleeding. British Journal of Haematology 2014; doi : 10.1111/bjh.12831
5) Ansell Jack 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
6) 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
7) Greinacher Andreas, Thiele Thomas, Selleng Kathleen : Reversal of anticoagulants : an overview of current developments. Thrombosis and Haemostasis 2015; 113 (5) : 931-942
8) Cohen Deborah: Dabigatran: how the drug company withheld important analyses.British Journal Medical 2014:349 : g4670
9) Reilly P.A., Lehr T., Haertter S. et al. : The effect of dabigatran polasma concentrations 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).The Journal of The American College of Cardiology 2014;63: 321-328
10) Nuovo Jim, Melnikow Joy, Chang Denise : Reportin Number Needed To Treat and Absolute Risk Reduction in Randomized Controlled Trials. Journal of the American Medical association (JAMA) 2002; 287 : 2813-2814
11) Alikhan Raza, Rayment Rachel, Keeling David et al. : The acute management of haemorrhage, surgery and overdose in patients receiving dabigatran. Emergency Medical Journal 2014; 31 : 163-168
12) Schulman S., Kearon C. : Definition of major bleeding in clinical investigation of hemostatic medicinal products in non-surgical patients. Journal of Thrombosis and Haemostasis 2005; 3 : 692-694
13) Holster Lisanne I., Valkhoff Vera E., Kuipers Ernst J. et Al. : New oral anticoagulants increase risk for gastrointestinal bleeding : A systematic review and meta-analysis. Gastroenterology 2013; 145 (1) : 105-112
14) Connolly S.J., Ezekowitz M.D., Yusuf S. et al. : Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine 2009; 361 (19) : 1139-1151
15) Connolly S.J., Ezekowitz M.D., Yusuf S. et al. : Newly identified events in the RE-LY trial. New England Journal of Medicine 2010; 363 (19) : 1875-1876
16) Uchino Ken, Hernandez Adrian V. : Dabigatran association with higher risk of acute coronary events. Archives of Internal Medicine 2012; 172 (5) : 397-402
17) Davidson Bruce L. : The association of direct thrombin inhibitor anticoagulants with cardiac thromboses. Chest 2015; 147 (1) : 21-24
18) Clemens A., Fraessdorf J., Friedman J. et al. : Cardiovascular outcomes during treatment with dabigatran : comprehensive analysis of individual subject data by treatment. Vascular Health Risk

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Management 2013: 9 : 599-615
19) Schulman S., Kearon C., Kakkar A.K. et al. : Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. New England Journal of Medicine 2013; 368 (8) : 709-718
20) Eikelboom J.W., Connolly S.J., Brueckmann M. et al. : Dabigatran versus warfarin in patients with mechanical heart valves. New England Journal of Medicine 2013; 368 (8) : 1206-1214
21) Lane D., Eikelboom J.W., Weitz J.L. et al. : Dabigatran attenuates thrombin generation to a lesser extent than warfarin : could this explain their differential effects on intracranial hemorrhage and myocardial infarction ? Journal of Thrombosis and Thrombolysis 2013; 35 (2) : 295-301
22) Ammollo Concetta T., Zaccaria Federica, Visino Fabrizio et al. : Influence of cell-associated tissue factor concentration on the anticoagulant activity of dabigatran. A possible explanation for the reduced incidence of intracranial bleeding. British Journal of Haematology 2015; 168 : 911-913
23) Tec Cate H. : Tissue factor-driven thrombin generation and inflammation in atherosclerosis. Thrombosis Research 2012; 129 : S38-S40
24) Choudhury A., Lip G.Y.P. : Atrial fibrillation and the hypercoagulable state : from basic science to clinical practice. Pathophysiology of Haemostasis and Thrombosis 2003; 33 : 282-289
25) Graham David J., Reichman Marsha E., Wernecke Michael et al. : Cardiovascular, bleeding, and mortality risks in elderly medicare patients treated with dabigatran or warfarin for non-valvular atrial fibrillation. Circulation, published online October 30, 2014, DOI: 10.1161/CIRCULATIONAHA.114.012061
26) Hernandez Immaculada, Baik Seo Hyon, Pinera Antonio, et al. : Risk of bleeding with dabigatran in atrial fibrillation.
JAMA Internal Medicine 2015; 175 (1) : 18-24
27) Redberg Rita F. : The importance of postapproval data for dabigatran. JAMA Internal Medicine 2015; 175 (1) : 25
28) Healey J.S., Eikelboom J., Douketis J. et al. : Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin : results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. Circulation 2012; 126 : 343-348
29) Hjemdhal Paul, Johnsson Hans, Wallen Hakan N. et al. : Letter by Hjendhal et al. Regarding article, "Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin : results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial. Circulation 2013; 127 : e505
30) David Jean Stephane, Piriou Vincent, Albaladejo Pierre : Letter by David et al. Regarding article, Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin : Results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial". Circulation 2013; 127 : e504
31) Douketis James D., Healey Jeff S., Brueckman Martina et al. : Perioperative bridging anticoagulation during dabigatran or warfarin interruption among patients who had an elective surgery or procedure. Substudy of the RE-LY trial. Thrombosis and Haemostasis 2015; 113 (3) : 625-632
32) Siegal Deborah, Yudin Jovana, Kaatz Scott et al. : Periprocedural heparin bridging in patients receiving vitamin K antagonists : Systematic review and meta-analysis of bleeding and thromboembolic rates. Circulation 2012; 126 : 1630-1639

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

33) Birnie David H., Healey Jeff S., Wells Geore A. et al. : Pacemaker or defibrillator surgery without interuption of anticoagulation. New England Journal of Medicine 2013; 368 : 2084-2093
34) Lindhal Tomas L., Wallstedt Maria, Gustafsson Kerstin 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
35) Moustafa F., Milhaud G., Dublanchet N. et al. : Retrospective study about 73 consecutive patients treated by direct oral anticoagulant and admitted to an emergency room. Journal des Maladies Vasculaires 2015; 40 (1) : 1-9
36) Getta Bartlomiej, Muller Niccolo, Motum Penelope et al. : Intermittent haemodialysis and continuos veno-venous dialysis are effective in mitigating major bleeding due to dabigatran. British Journal of Haematology 2015; 169 : 603-604
37) Chang Don N., Dager William E. and Chin Andrew I. : Removal of dabigatran by hemodialysis. American Journal of Kidney Diseases 2013; 61 (3) : 487-489
38) 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 and Haemostasis 2015; 113 (5) : 943-951
39) Greinacher Andreas, Thiele Thomas, Selleng Kathleen : Reversal of anticoagulants: an overview of current developments. Thrombosis and Haemostasis 2015; 113 (5) : 931-942

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

Contraindications

a) Use is contraindicated not only in patients with advanced liver disease with impaired clotting function, but also in patients with moderate liver impairment, in fact one of the exclusion criteria in the RE-LY trial **(NEJM 2009 vol.361 pp. 1139-1151)** was the elevation of transaminases or alkaline phosphatase twice of the upper limit of normal range.

b) In severe renal insufficiency (creatinine clearance < 30 ml/mn) dabigatran etexilate is contraindicated. (see section on dosage and drug interactions)

c) Use is not recommended in patients with bioprosthetic valves (at the moment there are not studies that evaluated this use) and is contraindicated in patients with a mechanical prosthetic heart valves as it has been demonstrated in a paper published recently **(NEJM 2013 vol.369 pp. 1206-1214)**

d) In patients with a history of myocardial infarction or coronary artery diseases dabigatran etexilate must not be used because the increased risk of MI or acute coronary disease. (see section on adverse reaction)

e) The concomitant use of P-glycoprotein (P-gp) inducers as rifampicin, dexamethasone, carbamazepine and phenytoin is absolutely contraindicated with dabigatran etexilate, because they dangerously reduce the plasma concentration of dabigatran.
The use with P-gp inhibitors may require dose adjustement, especially in case of moderate renal impairment. (see section on dosage and drug interactions) because on the contrary, they increase dabigatran plasma concentration.

f) I do not recommend use in patients > 80 years because the higher risk of bleeding especially in those with low body weight and moderate renal impairment and also because at the moment we do not have clinical trials in which dabigatran etexilate has been used in very elderly people. In fact, in the RE-LY trial, the mean age was 71. Also in patients with an age between 75 and 80 dabigatran etexilate must be used very carefully because after the age of 30 years there is a 7,5-8ml/mn reduction in glomerular filtration (GFR) rate every ten years. Creatinine clearance is used to assess GFR.

g) other containdications are patients with a bleeding diathesis, patients with a spontaneous or pharmacologic hemostatic impairment, patients with lesions at risk of significant bleeding within previous six months. In the RE-LY trial one exclusion criteria was a severe or hemorrhagic stroke within previous six months.

h) In case of invasive or surgical procedures, we must discontinue dabigatran for 1 or 2 days in patients with a creatinine clearance > 50 ml/mn and for 3 or 5 days in patients

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

with a creatinine clearance < 50 ml/mn before the procedures, to avoid bleeding. Longer times must be considered in case of major surgery, spinal puncture or insertion of a spinal or epidural catheter.
In any case, before any surgical procedure, the bleeding risk must be assessed by laboratory tests as the standardized diluted thrombin test (dTT) (Hemoclot) or the ecarin clotting time (ECT).
(these tests will be discussed in the section "Monitoring and laboratory tests")

i) In patients with a very low body weight < 50 kg. or on the contrary, with a very high body weight > 110 kg. dabigatran etexilate use is not recommended because it can be difficult to choose the optimal dosage without having an increase of adverse events as bleeding or thrombotic episodes respectively.

l) Dabigatran etexilate use in patients with severe hypertension not well controlled is contraindicated, but this happens with all anticoagulant drugs.

m) Dabigatran etexilate use in patients with active gastric or duodenal ulcer must be avoided.

n) The concomitant use of dabigatran etexilate in patients in treatment with dual antiplatelet therapy, must be avoided. In fact, dual antiplatelet therapy is also an esclusion criteria in the RE-LY trial.

o) For women in fertile age, before using dabigatran, a pregnancy must be excluded.

References :

1) Connolly Stuart J., Ezekowitz Michael D., Yusuf Salim et al. : Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal Medicine 2009; 361 : 1139-1151
2) Eikelboom John W., Connolly Stuart J., Brueckman Martina et al. : Dabigatran versus warfarin in patients with mechanical heart valves. New England Journal of Medicine 2013; 369 : 1206-1214

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Laboratory tests

There are many clinical circumstances in which the measurement of the anticoagulant effect of dabigatran is required. Such circumstances include cases of :

a) Suspected overdose

b) Unexplained bleeding

c) Thrombotic events during treatment, to assess patient's compliance

d) Patients with renal impairment

e) Patients with liver impairment

f) Before emergency surgery

g) Before non urgent surgery or invasive procedure when the patient has taken dabigatran in the previous 24 hours or longer, if the patient has moderate renal insufficiency (creatinine clearance 30-50 ml/mn)

h) Patients presenting in emergency with thrombotic or hemorrhagic events

i) Patients with traumatic bleeding,considered that trauma is the fourth leading cause of death in the United States.

l) Identification of supratherapeutic level in patients taking P-glycoprotein (P-gp) inhibitors as verapamil, amiodarone, dronedarone, quinidine.
The use of P-glycoprotein inducers as phenytoin, carbamazepine, rifampicine and dexamethasone that can result in a sub-therapeutic level is contraindicated with dabigatran etexilate.

m) Cases of reversal of anticoagulation

n) The perioperative management

o) Identification of supratherapeutic or sub-therapeutic level in very thin or very fat patients respectively, also if the use of dabigatran etexilate in these patients is not recommended.

p) Patients with a stroke taking dabigatran etexilate, we cannot do thrombolysis if

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

we do not know if they are or they are not anticoagulated.

o) Elderly patients, because they have more bleeding episodes, are more prone to fall, and normally have more renal impairment than younger people.

It is clear that laboratory results are dependent on when the last dose of drug was taken, in fact the peak of dabigatran concentration is reached after 2 hours and the lowest concentration after 12 hours. Plasma concentration of dabigatran after 2 hours with administration of 150 mg. twice daily was 175 ng/ml with a range of 117-275 ng/ml and after 12 hours was 91 ng/ml with a range of 61-143 ng/ml. **(1) (Journal of Thrombosis and Haemostasis 2013, vol. 11 pp. 756-760)**
The best laboratory test that can be easily available in many clinical laboratories to calculate dabigatran plasma concentration is the diluted thrombin clotting time (dTT) commercially available as the Hyphen Biomed Hemoclot Thrombin Inhibitor Kit with dabigatran calibrators and controls.
In fact, the normal thrombin clotting time (TT) presents excellent dose-response linearity, but excessive responsiveness. A ratio=(value of patient expressed in seconds/value of normal control espressed in seconds) of 15 corresponds to a plasma concentration from 200 to 300 ng/ml.
The diluted thrombin clotting time reduces significantly this excessive responsiveness and using it, we will find excellent linearity and excellent responsiveness. The other test that will give a good linearity and an excellent responsiveness is the ecarin clotting time (ECT).
Ecarin is an enzyme obtained from the venom of the viper echis carinatus. This venom converts prothrombin into meizothrombin, and because dabigatran inhibits meizothrombin, the ecarin clotting time (ECT) measures dabigatran activity.
A ratio of 4 corresponds to a dabigatran concentration from 200 to 300 ng/ml.
So these two tests are the easiest and fastest laboratory tests that can evaluate plasma dabigatran concentration . They can be considered quantitative tests. In fact , probably, the most specific test but not readily available to evaluate dabigatran concentration, is the anti-Factor IIa (thrombin) activity, that can be assessed by measuring with specific chromogenic substrates the residual Factor IIa (thrombin) activity, upon addition to plasma of excess amount of thrombin. **(2) (Thrombosis Research 2012 vol.130 pp. S95-S97)**
Now we consider the activated partial thromboplastin time (APTT) and the prothrombin time (PT) because are the most used laboratory tests to evaluate coagulation.
The APTT shows poor linearity and an intermediate responsiveness. A ratio of 2 has been obtained with dabigatran plasma concentration from 200 to 300 ng/ml. **(3)** (Thrombosis and Haemostasis 2011 vol.106 pp. 868-876) Because different results were obtained in different laboratories depending on the reagents used, it is necessary a standardization across laboratories.
The PT shows good linearity, but poor responsiveness. A ratio lower than 2 has been obtained with plasma concentration from 200 to 300 ng/ml. **(3) (Thrombosis and Haemostasis 2011 vol.106 pp.868-876)** We must not express the results in INR

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

(International Normalized Ratio). We will explain what INR is when we will treat oral anticoagulants which are antagonists of vitamin k, as warfarin or acenocumarol.
When patients are in treatment with dabigatran, we cannot measure fibrinogen because we will obtain false low results, we cannot measure coagulation factors, thrombin generation time, antithrombin with anti-factor IIa (thrombin) assays , Protein C by a clot-based assay, but the chromogenic assay will not be affected. Dabigatran has no effect on D-dimer assays but we must consider that we can obtain in some cases false low results because of suppression of D-dimer levels by inhibition of thrombin.

Since 2010, some investigators found some sources of inter- and intra-individual variability, such as renal and/or hepatic function, advanced age, and certain clinically relevant drug-drug interactions. These criteria concern patients at very high risk of clinical events and laboratory monitoring should be assessed for these patients. Drug monitoring should provide a very useful and clinically effective means of determining an optimal and effective dose regimen for each individual. **(4) (Journal of Thrombosis and Haemostasis 2010 vol. 8 pp. 621-626)** Others authors published in the same journal another paper in which they write that the evidence available does not support laboratory monitoring of the new oral anticoagulants because fixed-dosed, orally administered doses of rivaroxaban and dabigatran are highly predictable, and there is no evidence that the antithrombotic effect and/or risk of bleeding correlate with any related biologic activity, or drug concentration measured in plasma. **(5) (Journal of Thrombosis and Haemostasis 2010 vol. 8 pp. 627-630)** However, recently in a new RE-LY substudy was found that dabigatran concentration range achieved for either dose in RE-LY ranged over 5-fold for the 10th to 90th percentiles, with a large overlap of concentrations, approximately 70% between the two doses. Ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations. Age was the most important covariate. Significant factors affecting dabigatran plasma concentrations were age, CrCL, weight and sex. Renal function was the predominant patient characteristic that determined plasma concentrations. The investigators conclude that individual benefit-risk might be improved by tailoring dabigatran dose after considering selected patients characteristics.**(6) (Journal of the American College of Cardiology 2014 vol. 63 (4) pp. 321-328)** In a recent well done study Douxfils and collegues investigated the performance of the Hemoclot Thrombin Inhibitors LOW (HTI LOW) kit, a diluted thrombin time, and the STA-ECA II (ECA-II) kit, a chromogenic variant of the ecarin clotting time, that were developed to measure low dabigatran concentrations, compared to reference dabigatran analysis by liquid chromatography tandem mass-spectrometry (LC-MS/MS). In this study were included 33 plasma samples obtained from patients with dabigatran plasma concentrations < 200 ng/ml because the aim of the study was to evaluate laboratory tests that effectively can measure plasma concentrations < 50 ng/ml that are critical in the perioperative management of patients in dabigatran treatment. During the two years of follow-up in the RE-LY trial, about 25% of the patients received at least one invasive procedure. In fact, although compared with warfarin, dabigatran be associated with a similar rate of perioperative bleeding and thrombotic complications, even among patients having a major or urgent surgery, in patients who withdrew treatment > 3 days before the surgical procedure had more bleeds, probably due to accumulation of the drug in patients with poor renal function. In addition, the equality of outcomes should be viewed

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

in relation to how warfarin-related bleeds or risk of bleeding were managed in the study. **(7) (Thrombosis and Haemostasis 2015 vol. 113 (4) pp. 862-869)** The comparison of bleeding problems might have been less favourable for dabigatran if patients taking warfarin would more often have received treatments that are recommended by expert opinion. **(8) (Circulation 2013 vol. 127 pp. e505)** In an initial report of EMA, the marketing authorization holder informed that a dabigatran concentration below 48 ng/ml is equivalent to eliminate of at least 75% of dabigatran and should reached before invasive procedures.
The "Groupe d'Intéret en Hèmostase Pèriopératoire (GIHP)" put the threshold at 30 ng/ml.**(9) (Archives cardiovascular Diseases 2013 vol. 106 pp. 382-393)** The inaccuracy of HTI at low concentrations probably does not change the outcome in invasive procedures with low bleeding risk, but with high-risk surgery, such as neurosurgery, may be needed a more accurate assessment of dabigatran concentrations. The results of this study show that ECA-II provides less systematic deviation than HTI (4ng/ml versus 10 ng/ml) for assessments of plasma concentrations in the 0-200 ng/ml range. For concentrations below 50 ng/ml, HTI LOW correlates better with LC-MS/MS than HTI or ECA-II, which were equivalent at these low concentrations. Regarding the systematic deviation, both HTI LOW and ECA-II performed very well with a small preference for HTI LOW due to a narrower 95% CI. Regarding sensitivity, HTI LOW was the most sensitive assay followed by ECA-II and HTI. **(7) (Thrombosis and Haemostasis 2015 vol. 113 pp. 862.869)** Differently from other studies ECA-II did not perform better that HTI. **(10) (European Journal of Clinical Pharmacology 2013 vol.69 pp. 1875-1881) (11) Journal of THrombosis and Haemostasis 2013 vol. 11 pp. 1493-1502)** Both HTI LOW and ECA-II performed better than HTI in case of plasma dabigatran concentrations <50 ng/ml with a slightly preference for HTI LOW due to narrower confidence intervals. However, HTI LOW requires a new calibration curve and a new sets of control and this is not required for ECA-II which directly introduces a calibration curve for the low concentrations and an automatic re-dilution of the sample if the result exceeds 230 ng/ml. However, if the test is already calibrated on the coagulometer, it is possible to reduce time, choosing directly the right procedure to use between HTI and HTI LOW. Douxfils and collegues propose the following approach to measure dabigatran concentrations : For TT that exceeds the Upper Limit of Measurement (ULM) (i.e. a TT < 120 sec or + / - 6 times the upper limit of normal on a STA-R Evolution coagulometer using the recommendations of the manufacturer) they propose the use of a standard HTI assay which has demonstrated enough accuracy in estimating plasma concentrations above 50 ng/ml. If TT is between the baseline clotting time and the ULM, must be employed the HTI LOW or the ECA-II assay but HTI LOW is more accurate due to narrower CI. This procedure may avoid unnecessary costs and ensure the best estimation of the dabigatran concentrations. Interestingly, the authors, in case of heparin bridging in patients at high cardiovascular risk who need a major surgical procedure, because the anticoagulant effect is transiently affected by LMWH to the effect of dabigatran, correctely propose to use the ECA-II assay instead of HTI LOW because the main advantage of ECA-II assay is that in case of switching or bridging therapy, meizothrombin, the intermediate product released by ecarin from prothrombin, is unaffected by the presence of heparin and derivatives differently from HTI. This allows an accurate assessment of dabigatran in plasma. In fact, in their patients while LC-MS/MS and ECA-II revealed no residual dabigatran in plasma (0 ng/ml) the HTI LOW assay showed a dabigatran plasma concentration of 8 ng/ml because

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

HTI LOW may be influenced by the presence of heparin or LMWH. The authors point out that another advantage of the ECA-II assay is that is not necessary to choose between a "LOW" or a "normal" procedure since the test intended to perform both by itself on a Stago platform. The principal limitation of this study is the fact that LC-MS/MS method measures free dabigatran only and not the conjugated form. However, this conjugated form is only about the 20% of the total dabigatran concentration and the authors consider minimal its influence at these low concentrations. **(7) (Thrombosis and Haemostasis 2015 vol. 113 pp. 862-869)** In another study, samples were obtained from 70 atrial fibrillation patients treated with dabigatran etexilate. Plasma concentrations were measured using liquid chromatography-tandem mass spectometry (LC-MS/MS) and were compared with coagulation methods Hemoclot thrombin inhibitors (HTI) and Ecarin clotting assay (ECA), with prothrombin time-international normalized ratio (PT-INR) and activated partial thromboplastin time (aPTT). A wide range of dabigatran concentrations was determined by LC-MS/MS (<0.5-586 ng/ml). Correlations between LC-MS/MS results and estimated concentrations were excellent for both HTI and ECA overall, but the precision and variability of these assays were not fully satisfactory in the low range of dabigatran plasma concentrations, in which ECA performed better than HTI. aPTT performed poorly, and was normal (< 40 sec) even with dabigatran levels of 60 ng/mL. PT-INR was normal even at supratherapeutic dabigatran concentrations. LC-MS/MS is the gold standard for measurements of dabigatran in plasma. Alternatively, either HTI or ECA assays may be used, but neither of these assays is dependable when monitoring low levels or to infer total absence of dabigatran. The aPTT assay is relatively insensitive to dabigatran, and normal aPTT results may be observed even with therapeutic dabigatran concentrations. **(12) (European Journal of Clinical Pharmacology 2013 vol. 69 (11) pp. 1875-1881)**

References :

1) Baglin T., Hillarp A., Tripodi A., et al. : Measuring oral direct inhibitors of thrombin and factor Xa : a recommendation from the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Journal of Thrombosis and Haemostasis 2013; 11 : 756-760
2) Tripodi Armando : Laboratory tests and the new oral anticoagulants. Thrombosis Research 2012; 130 suppl. 1 : S95-S97
3) Pengo Vittorio, Crippa Luciano, Falanga Anna et al. : Questions and answers on the use of dabigatran and perpectives on the use of other new oral anticoagulants in patients with atrial fibrillation. Thrombosis and Haemostasis 2011; 106 : 868-876
4) Mismetti P., Laporte S. : New oral antithrombotics : a need for laboratory monitoring. For. Journal of Thrombosis and Haemostasis 2010; 8 : 621-626
5) Bounemaux H., Reber G. : New oral antithrombotics : a need for laboratory monitoring. Against. Journal of Thrombosis and Haemostasis 2010; 8 : 627-630
6) Reilly Paul A., Thorsten Lehr, Haertter Sebastian et al. : The effect of dabigatran plasma concentrations 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

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

Therapy).Journal of the American College of Cardiology 2014;63 (4) : 321-328
7) Douxfils Jonathan, Lessire Sarah, Dincq Anne-Sophie et al. : Estimation of dabigatran plasma concentration in the perioperative setting. An ex vivo study using dedicated coagulation assays.Thrombosis and Haemostasis 2015; 113 (4) : 862-869
8) Hjemdahl P., Johnsson H., Wallen N.H. et al. : regarding article, "Periprocedural bleeding and thromboembolic events with dabigatran compared with warfarin : results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) Randomized Trial". Circulation 2013; 127 : e505
9) Pernod G., Albaladejo P., Godier A. et al. : Management of major bleeding complications and 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
10) Antovic J.P., Skeppholm M., Eintrei J. et al. : Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma. European Journal of Clinical Pharmacology 2013; 69 : 1875-1881
11) Hawes E.M., Deal A.M., Funk-Adcock D. et al. : Performance of coagulation tests in patients on therapeutic doses of dabigatran : a cross-sectional pharmacodynamic study based on peak and trough plasma levels. Journal of Thrombosis and Haemostasis 2013; 11 : 1493-1502
12) Antovic Jovan P., Skeppholm Mika, Eintrei Jaak et al. : Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma. European Journal of Clinical Pharmacology 2013; 69 (11) : 1875-1881

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

Conclusions

Dabigatran has been approved for prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation and for post-operative thromboprophylaxis in patients who have undergone a knee or a hip replacement surgery. Recently, at the end of march 2014, the FDA has approved dabigatran for the treatment of venous thromboembolism following therapy with a parenteral anticoagulant for 5 to 10 days and to reduce the risk of DVT/PE recurrence in patients who have been previously treated.
In secondary prevention of stroke, there are not data showing that dabigatran is more effective or safer than vitamin k antagonists in patients with a history of intracranial, retroperitoneal , spinal and intraocular bleeding because these patients were excluded from the RE-LY trial. **(1) (Thrombosis and Haemostasis 2013 vol. 110 pp. 496-500)**
Many patients who suffered a stroke are prone to fall due to impaired mobility, and because these falls can result in traumatic bleeding, also in these cases, in secondary prevention of stroke, we cannot use dabigatran considered that we have no antidote to neutralize the anticoagulant effect of dabigatran. In the RE-LY trial, **(2) (New England Journal of Medicine 2009 vol. 361 pp. 1139-1151)** patients who suffered a severe stroke in the previous 6 months were excluded, so at the moment we have no clinical data on the use of dabigatran in this category of patients. On the contrary, based on imaging examinations, CAT or MNR, normally it is possible to start vitamin k antagonists as warfarin with less delay for secondary stroke prevention.
Stroke patients may take multiple drugs including antiepileptic drugs and the most used antiepileptic drugs as carbamazepine and phenytoin cannot be used with dabigatran because they are strong P-glycoprotein (P-gp) inducers and reduce dabigatran concentration, diminishing its anticoagulant effect. Also for primary prevention of stroke, our clinical data are based only on a single trial, also if very large, the RE-LY trial, which was conducted in many foreign countries (44 foreign countries) that have different health systems. The RE-LY trial, a non-inferiority trial, was sponsored by the manufacturer of dabigatran etexilate and what we really need are manufacturer independent studies, sponsored by governmental organizations to avoid any bias in the studies. In the RE-LY trial if there are less hemorrhagic strokes and less intracranial bleedings with the two dosages of dabigatran, (110 mg. and 150 mg. twice daily) compared to warfarin, there are also major gastrointestinal bleedings with the dabigatran dosage of 150 mg. twice daily. This can be life threatening for patients, considered that at the moment we have no antidote. For patients who miss a dose, if with warfarin, missing just one dose do not expose patients to a great thrombotic risk because warfarin has an half life of about 48-60 hours, on the contrary, missing one dose of dabigatran exposes patients to a great thrombotic risk because dabigatran has a half life of 12-14 hours. Moreover, warfarin is administered once daily and dabigatran twice daily , so the probability of missing doses is doubled with dabigatran. Also if use of dabigatran is recommended in patients using warfarin with a poor TTR, (Percent of time in therapeutic INR range) the advantage as safety, is limited only to patients who have a TTR

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

inferior to 59% when dabigatran 150 mg. twice daily is used. The advantage as efficacy of this dosage, and the advantage as safety of dabigatran 110 mg. twice daily disappears when patients using warfarin have a TTR =/> 68% with a superiority of warfarin for higher TTR. **(3) (Comment of SISET, Italian Society for the Study of Haemostasis and Thrombosis, on the "Concept Paper" of AIFA,Italian Agency of Drug)** If we consider that in Italy in the Thrombosis and Haemostasis Centers of the FCSA (Federation for the diagnosis of thrombosis and the surveillance of antithrombotic therapies) the majority of patients in anticoagulant therapy with antagonists of vitamin k have a TTR of about 70% , it is easy to understand that we cannot switch these patients to dabigatran, and in the same time, it is also not recommended to use dabigatran in naïve patients if these patients will be followed in these centers. For the minority of patients with a TTR < 65% in which probably we could use dabigatran etexilate, we must try to understand why these patients have a poor TTR. If some of them have a poor compliance, they will have the same problem with dabigatran etexilate. In other cases, it is important to understand if we can ameliorate the quality of controls performed in our center. This can be done for example with weekly ground rounds.

At the end, will remain few patients that could be switched to dabigatran etexilate. Also in many other european countries, in thrombosis and hemostasis centers, many patients have a TTR =/> 70%. For this reason, I see an advantage in the use of dabigatran etexilate only in the developing countries that have a poor quality of clinical and laboratory controls of patients on anticoagulant therapy with vitamin K antagonists.

In patients who have difficulty in arriving to hemostasis and thrombosis centers, because health problems, because they live in remote small towns or because they are old and they live alone, we must try to use point-of-care instruments that are precise until INR between 6 and 8. We can trainee the patient, or if this is not possible, we can trainee some nurses who will go to the patient's home with the point-of-care instrument. They, after having obtained the results, will call the doctor of the center who will give them the therapy that will be printed at patient's home. Also in these cases, the use of dabigatran can be avoided in the majority of cases. The most important adverse effect , (see section on "adverse reactions") as for vitamin k antagonists, is bleeding. With vitamin k antagonists as warfarin we can achieve a rapid reversal using PCC factor concentrates , also if there is an increased risk of thrombosis with these products. We will also use vitamin k that however, can take about one day to neutralize the effect of warfarin, but in the meantime, based on our clinical judgment and laboratory results, we can decide to repeat PCC concentrates infusion. Moreover, warfarin reversal can be easily monitored with laboratory or point-o--care tests.

On the contrary, at the moment, the only reversal procedure to reduce the anticoagulant effect of dabigatran, is emergency dialysis but, to perform dialysis in patients with important bleedings and very probably in unstable conditions, is very challenging , also in the best emergency departments.

Other therapeutic procedures as PCC concentrates and recombinant activated factor VII were used for reversal of dabigatran, but were unsuccessful. Only activated PCC

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati

concentrates, FEIBA, (factor eight inhibitor bypassing activity) were found to obtain in anecdotal reports, a marked reduction of the anticoagulant effect of dabigatran. **(4) (Critical Care Medicine 2013 vol. 41 pp. e42-e46) (5) (British Journal of Haematology 2014 vol. 164 pp. 308-310) (6) British Journal of Haematology 2014 doi:10.1111/bjh.12831)** Also tranexanic acid IV may be efficacious in reducing bleeding caused by dabigatran. For prevention of post-operative thromboprophylaxis in patients who have undergone a knee or a hip replacement, comparing dabigatran 110 mg twice daily with enoxaparin 40 mg once a day, has not been found a clinical advantage using dabigatran, considering the rates of total venous thromboembolism (VTE) and of major VTE and VTE related mortality. (see section on dosage and drug interactions) The only pratical advantage is the route of administration, oral for dabigatran, and subcutaneous for enoxaparin, but this advantage is just for a limited period of time, 10-14 days in case of knee replacement surgery, and 28-35 days for hip replacement surgery.

I do not think we must use a new drug in this indication without having a clinical advantage, when we have a drug as enoxaparin that we have been using since many years and that we know very well. As happened for selective COX2 inhibitors, when the appearance of these drugs in the market was greeted enthusiastically and, after thousands of adverse reactions as myocardial infarction and stroke this enthusiasm disappeared, **(7) (NEJM 2005 vol. 352 pp. 1131-1132) (8) (NEJM 2005 vol.352 pp. 1133-1135)** and again as happened for 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, **(9) (JAMA 2013 vol.319 pp.1353-1368) (10) (Annals of Internal Medicine 2012 vol.157 pp. 104-113)** I think this enthusiasm will disappear again for dabigatran etexilate that can be useful in a limited number of cases and cannot be used on a large scale, especially until we will not have an antidote commercially available.

So now the question is, can we rely our clinical judgement only on results obtained by statistical analysis in clinical trials ? I think not. We must rely our clinical judgement also on our particular category of patients and especially on the clinical context (country, health system, hospital, private practice) in which we work.

It is clear that if we say to a patient that we have a new anticoagulant drug that does not need laboratory monitoring, that does not interfere with food, that interferes with few drugs compared to warfarin, he will be very happy to take this drug. However, if we want to be honest, we must also say that this drug increases the risk of myocardial infarction, also if in a non significant manner, that increases dyspepsia in a significant manner and that in some particular circumstances (see section on “Laboratory tests”) it is necessary to perform laboratory tests. Again, we must say that if after a certain period after having taken dabigatran, he will want to know if he is well anticoagulated, we will replay to him that we do not know, until we will not perform a proper laboratory test. We must also say that in case of an important bleeding, we have no antidote, and the only procedure that can reduce the anticoagulant effect of dabigatran is emergency dyalisis that can take some hours, and can be very challenging in case of severe bleedings with patients in unstable conditions, also in the best emergency departments.On the other hand, we must say that in the RE-LY trial, the rate of

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

intracranial hemorrhages in the dabigatran group compared to warfarin group,(0,74% patients per year) was reduced using the dosage of 110 mg.(0,23% patients per year) and with the dosage of 150 mg.,(0,30% patients per year) but the rate of gastro-intestinal hemorrhages was increased with the dosage of 150 mg.(1,51% patients per year) compared to warfarin (1,02% patients per year) Until potential advantages of dabigatran over vitamin k antagonists will not be proven by other manufacturer-indipendent trials, and until an antidote will not be commercially available, I do not recommend use of dabigatran on a large scale in patients with non valvular atrial fibrillation to prevent stroke and systemic embolism, and as post-operative thromboprophylaxis in patients who will undergo a knee or a hip replacement surgery.
" As we apply new science to develop new medicines, we must not forget that our first job is to do no harm" . **(7) (NEJM 2005 vol. 352 pp. 1131-1132)** In a recent published paper, ischemic stroke and bleeding outcomes were correlated with dabigatran plasma concentrations. Age was the most important covariate. Individual benefit-risk might be improved by tailoring dose after considering selected patients characteristics. **(11) (Journal of the American College of Cardiology 2014 vol. 63 (4) pp. 321-328)** " The one-size-fits-all was a mistake for a drug with this kind of risk".The New York Times reported that unsealed court documents show that dabigatran manifacturer employees were worried about publishing research paper suggesting that patients taking dabigatran might require blood monitoring. According to the same documents unsealed as part of court proceedings, the manufacturer of dabigatran gave the FDA one analysis following the 2010 approval of the drug, showing that fatal bleeds postapproval were less than in RE-LY. But according to the internal documents now made public, the company did not share a second analysis that had a lower number of fatal bleeds in the actual RE-LY trial, putting the postapproval bleeding rates higher that what seen in the pivotal trial. News of the second analysis has emerged as part of court filings related to more than 2000 lawsuits the manufacturer is facing in the US, claiming dabigatran caused severe and fatal bleeding. **(12) (www.medscape.com February 26, 2014)** As it is written in the section on " Adverse reactions ", a new article has been published recently whose title is Dabigatran : how the drug company withheld important analyses. **(13) (British Medical Journal 2014 vol. 349 pp. g4670)** In this article, Dr. Cohen Deborah, the investigations editor at BMJ, says that the manufacturer of dabigatran did not disclose some results that showed that plasma dabigatran levels can vary up to fivefold, and it is likely that also the other new oral anticoagulants will exibit variability in blood concentrations. Hugo ten Cate, medical director of the Maastricht thrombosis anticoagulation clinic, is concerned about the lack of published studies on dose adjustement in the new oral anticoagulants and this, combined with the lack of an antidote has been a " major hurdle in the safe introduction of NOACs" , he wrote in March 2012. " It is critical that pharmaceutical companies take their responsibilities and provide and publish all relevant data on drug levels and coagulation test responses so that it becomes clear what the approximate therapeutic and harmful ranges of laboratory test outcomes are, for each anticoagulant agent. There is no good reason not to be transparent in these matters, even if it would entail the small risk that doctors would want to optimise therapy based on lab test results " he said. For other considerations about this article, see section on " Adverse reactions " **(13) (British Medical Journal 2014,349 : g4670)** In addition to bleeding risk identified in RE-LY, other methodological concerns include the fact that dabigatran was blinded while warfarin was non-blinded and that RE-LY used an intention to

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

treat analysis, which may bias it toward non-inferiority. These concerns, taken together with the observed evidence of major haemorrhage show the risk data are evolving and that the risks of dabigatran could be larger than previously reported. Additional data from recent US lawsuits alleges Boehringer did not adequately warn patients of the bleeding risks of dabigatran. **(14) (British Medical Journal 2014 vol. 349 pp. g4681)**
Another concern about dabigatran is that in another study, investigators did genomewide association analyses on 2944 patients from the RE-LY database and found nearly one in three patients carried a minor allele that was associated with lower exposure to the active dabigatran metabolite. Dabigatran is given as a prodrug and requires enzymatic conversion to active drug. The bioavailability of dabigatran turns on genetic determinants and in the best case is only 6% bioavailable. **(15) (Circulation 2013 vol. 127 pp. 1404-1412)** Just on September 25, 2014, was published an article on line on Chest Journal. **(16) (Chest 2015 vol. 147 (1) pp. 21-24)** see section on "Adverse reactions". Regarding direct thrombin inhibitors the author describes a significantly increased frequency of thrombosis on abnormal cardiac endothelium when compared head-to head with indirectly-acting therapeutic anticoagulants in studies of sufficient patients number and duration. The weight of evidence as a class effect warrants prescribing effective anticoagulants other than direct thrombin inhibitors. For 2013, dabigatran manufacturer reported 1.6 billion dollars net from dabigatran sales. About half of that was from the USA, with over 40,000 dabigatran USA prescriptions reported filled every week. **Revenue from these drugs support advertisements in many peer-reviewed medical journals, medical society annual meetings, smaller-scale educational activities, key physician opinion leaders, and clinical trial investigators.** The author concludes writing that " Young patients without risk for coronary disease may escape myocardial infarction during direct thrombin inhibitor treatment for acute venous thromboembolism, but unless important financial considerations tip the judgement that way, why should they face a possibly increased risk? Other than in exceptional circumstances, clinicians shoud avoid prescribing direct thrombin inhibitors" **(16) (Chest 2014 doi: 10.1378/chest.14-2028)** As time passes and more concerns raise about the use of dabigatran, and after the above considerations, we can sadly conclude that financial considerations overcome patients health in dabigatran use, and this attitude that will destroy many lives will continue until the "financial era" caused by "shadowy" behaviours will not be finished. Just recently have been published two studies which attain divergent conclusions.The studies have analyzed Medicare database and have evaluated efficacy and safety of dabigatran in clinical practice compared with warfarin, in patients with nonvalvular atrial fibrillation (NVAF). In the first study published online by Circulation on November 5, 2014, Graham and collegues of the Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, Food and Drug Administration, in patients treated with dabigatran found a reduction of 20% of ischemic stroke and a reduction of 66% of intracranial bleeding in patients treated with dabigatran compared with patients in treatment with warfarin. The mortality was inferior of 14% and gastrointestinal bleedings were superior of 28% in patients treated with dabigatran compared with patients who were taking warfarin. The investigators conclude that dabigatran was associated with a reduced risk of ischemic stroke, intracranial hemorrhage, and mortality and an increased risk of gastrointestinal bleeding compared with warfarin, principally with the dosage of 150 mg. With the dosage of 75 mg that is used in the U.S., was observed only a

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

reduced risk of intracranial hemorrhage. **(17) (Circulation, published online October 30, 2014)** In the second study, published online by JAMA on November 3, 2014, Hernandez and collegues found on the contrary an increase of 58% of major bleedings and of 85% of gastrointestinal bleedings in patients in treatment with dabigatran compared with patients in treatment with warfarin.The incidence of major bleedings was 9% in the dabigatran group and 5.9% in the warfarin group.The risk of intracranial bleeding was superior in patients treated with warfarin (Hazard Ratio 0.32) while the risk of major bleeding and of any bleeding was superior in patients treated with dabigatran with a HR of 1.58 and of 1.30 respectively. For details, see section on "Adverse reactions". The authors conclude that "before more evidence is available, dabigatran should be prescribed with caution in high-risk patients". **(18) (JAMA, published online November 3, 2014)** Interestingly,the two studies obtained analyzing Medicare database,did not assess the quality of warfarin anticoagulation. This is a very important issue, because we are not able to evaluate the incidence of adverse events in patients in treatment with warfarin with an optimal Time in the Therapeutic Range (TTR). Normally is considered optimal a TTR > 70% that is obtained in many specialized anticoagulation clinics in North America and Europe. In fact, correctly Graham and collegues write : " Medicare data do not capture laboratory results so we had no basis upon which to assess the quality of warfarin anticoagulation. It is possible that the favorable effects of dabigatran on ischemic stroke and mortality and its adverse effect on major gastrointestinal bleeding in our study were at least partly due to low time in the therapeutic range with warfarin". On the other hand they say that warfarin management in their study, was or was not adequate, reflects the quality of anticoagulation in the general practice in the U.S. About this last issue, we cannot accept that in general practice, not only in the U.S. but also in Europe the quality of warfarin management is not optimal. At the moment in many European countries and in North America there many specialized anticoagulation clinics where skilled physicians, skilled laboratory technicians and nurses are able to obtain an optimal TTR in many patients.

All the patients in treament with warfarin should be addressed to these clinics, but this does not happen for many reasons. The principal reason is that internists and cardiologists do not want to address their patients to these anticoagulation clinics normally located at Haemostasis and Thrombosis Centres, because they are afraid to loose the control of these patients and at the moment not only in North America, but also in Europe they are prescribing new oral anticoagulants, especially dabigatran, to about all patients with nonvalvular atrial fibrillation differently from physicians who are working in anticoagulation clinics who prescribe these drugs in selected cases only.The second reason is that in some cases patients are not able to reach the Centre because they live far from it or are old and live alone, but also in this case some nurses could evaluate their INR by point-of-care testing (POCT) devices and then could communicate the result to a healthcare professional of an anticoagulation clinic for interpretation and subsequent therapy.Evaluation of a POCT device will usually include an assessment of reproducibility and accuracy. For POCT devices to be considered acceptable in terms of precision and accuracy, performance should be comparable to that achievable with INR measurement systems in secondary care. Also quality assurance, composed of internal quality control (IQC) and external quality assessment (EQA) should be performed where possible. **(19) (British Journal of Haematology 2014 vol. 167 pp. 600-607)** It is undeniable that with dabigatran there are less intracranial bleedings compared with warfarin.

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

After this consideration, the principal indication in which can be useful to prescribe dabigatran or other new oral anticoagulants is in patients at risk of intracranial bleeding, or in patients in treatment with warfarin who had an intracerebral hemorrhage (ICH) and after they need to take anticoagulant therapy again, because of the high rate of recurrence, as demonstrated by the Italian Collaborative Study **CHIRONE (C**erebral **H**aemorrhage **I**n patients **R**estarting **O**ral a**N**ticoagulant th**E**rapy). **(20) (Neurology 2014 vol. 82 pp. 1020-1026)** The other indication in which to use new oral anticoagulants is in patients who are not able to obtain a good TTR or in patients who cannot reach the Centre. Certainly it is not correct to use dabigatran or new oral anticoagulants on a large scale. The fact that a drug has been approved for use in a disease by a regulatory agency such as FDA or EMA, does not mean that we must use that drug in about all patients with that disease. On the other hand, it is clear that drug manufacturers will not be happy if we will use their drugs only in a limited number of patients who really can have a benefit when treated with those drugs.
Another important consideration is the fact that some investigators consider non-inferiority trials such as RE-LY trial, unethical because they disregard patients' interest. The autors of this paper point out that "scientific community should ban non-inferiority and equivalence trials because they are unethical, whatever measures are taken to prevent their methodological pitfalls and inappropriate interpretation of results". **(21) (The Lancet 2007 vol. 370 pp. 1875-1877)**
First of all, non-inferiority is a kind of similarity within a limit. The limit is the degree of tolerable inferiority of the new drug compared with the standard treatment, and this arbitrary difference in efficacy, the non-inferiority margin or delta, is decided before doing the study. The crucial aspect is that non-inferiority trial exposes patients to clinical experiments without any assurance that the experimental drug is not worse than the standard treatment, and without really exploring whether it is better. The authors correctly write that in any informed consent, randomised trials are the only ethical way to address clinical uncertainty. Considered the aim of non-inferiority trials, they think that few patients would agree to participate in these trials if the information about this kind of trials were clear in the informed consent form. "Why should patients accept a treatment that, at best, is not worse, but could actually be less effective or less safe than available treatments?" They conclude writing that non-inferiority trials fail to meet the commitments of good clinical research : "Ask an important question, and answer it reliably". Randomisation should not even be allowed in such trials, since it is unethical to permit that a part of patients will receive a drug that is anticipated to provide no extra benefit, but could be less safe and less effective than existing treatment options. **(21) (The Lancet 2007 vol. 370 pp. 1875-1877)**
Would be interesting to know the opinion of these authors about the use of the new oral anticoagulant dabigatran, as a result of a non-inferiority trial, such as the RE-LY trial, considering also the absence at the moment of an antidote commercially available. On the other hand, in a corrispondence published by The Lancet, other investigators think that non-inferiority trials are useful and can be ethically justified, and that the risks to patients in a properly done non-inferiority trial are no greater than those in a superiority trial and although superiority trials remain the design of choice, circumstances do not always permit those options. Interestingly, an investigator writes that appropriate action would be to ban the improper application of the non-inferiority design, not the design itsef. **(22) (The Lancet 2008 vol. 371 pp. 895-897)** In any case, it is undeniable that superiority trials are the gold standard in clinical trial research and are the simplest regarding

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

interpretation. In fact a superiority trial, if well designed and well conducted, is entirely interpretable without further assumptions because the result speaks for itself and requires no further extra-study information. Due to the difficulty of founding more powerful drugs, the pharmaceutical industry has been forced to look for drugs that may not improve the current, most efficacious medications, but may be better on other aspects of treatment such as adverse reactions. However, different definitions of non-inferiority will make for clinical researchers and clinical decision-makers more difficult and harder to decide the true message of a non-inferiority trial. **(23) (Bullettin of the NYU Hospital for Joint Disease 2008 vol. 66 (2) pp. 150-154)** Le Henanff and collegues report an analysis of 162 trials (116 trials of noninferiority and 46 of equivalence) published between January 1, 2003, and December 31, 2004. They correctly write that for non-inferiority trials Intention-to-treat (ITT) analysis may lead to biased conclusions because of protocol violators and withdrawls. In addition, dropouts and nonadherent participants from the two groups are potentially different, which may also bias a per-protocol analysis. Thus both analysis are required and considered to have equal importance in drawing a conclusion because reporting the results of only one of the analysis may reflect either ignorance about noninferiority trials or a deliberate intention to mask some of the results and preventing readers from drawing definitive conclusions. However, they conclude that also when non-inferiority trials included both an intent-t--treat (ITT) analysis (all randomized patients are included in the analysis) or modified ITT analysis (patients who never received treatment are excluded) and per-protocol analysis (patients who did not complete the treatment are excluded), conclusions are sometimes misleading. **(24) (JAMA 2006 vol. 295 (10) pp. 1147-1151)** On november 28, 2014, BMJ published an editorial online in which the editors of the journal write that from the next year, the clinical education articles published by BMJ will be authored by experts without financial ties to companies producing drugs, device, tests, medical education companies, or other companies with an interest in the topic of the article. They hope that this policy will be applied to other articles about state of the art reviews, and about diagnosis and therapy by the end of 2016. They also explain that the first reason for doing this is that making clinical decisions based on information biased by commercial interests can cause harm, as already happened with cardiotoxicity from rosiglitazone and rofecoxib that destroyed thousands of lives and continues to happen with hydroxyethyl starch. In addition they write that readers consider articles written by authors with declared financial links to industry to be less important, rigorous and believable.

I am very impressed when they say that finally they want "to encourage a shift in the culture of medicine". At this point I will report exactly some sentences they have written in their article because I consider their words so strong and efficacious that any attempt to change these words would result in a loss of the strong and courageous meaning of their concepts. " Financial competing interests are endemic to the culture of medicine and are rarely driven by malign motives or actions. The mechanisms of influence are diverse. An author of a review article might be an advisory board member for companies selling drugs for that condition, a commentator might have received honorariums from industry for lectures on the topic, or an editorialist on a disease might be a patent holder for one of its diagnostic tests. Psychological research suggests that biases may operate subconsciounsly. Our decisions not to proceed with an article or an author are not made lightly. Nor are they intended to pass judgement on an author's integrity. However, we cannot ignore the

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

mounting evidence of systematic attempts by commercial interests to corrupt the literature and influence clinical decisions. Internal company documents revealed during litigation expose practices aimed at influencing clinicians such as funding medical meetings, dinners, studies, and articles. Many clinical practice guidelines are little more than industry marketing tools because of the financial competing interests of their authors and sponsors ". **(25) (BMJ 2014 vol. 349 pp. g7197)** It is undoubted that there is a conflict of interest in the design and in the conclusions of the clinical trials about new oral anticoagulants because all these trials were sponsored by drugs manufacturers and about all the authors have financial ties with pharmaceutical companies. Any possible bias cannot be avoided just because the authors of the article declare all relevant competing interests in the article. Another article published on the July number of the Journal of Thrombosis and Haemostasis in 2014, confirms the fact that the trials which compared new oral anticoagulants and in particular Dabigatran with warfarin did not evaluate new oral anticoagulants with a correct warfarin treatment. On the other hand, the statement that the laboratory monitoring of warfarin treatment, also if incorrect, is the monitoring used in "real life", could be rationale if the procedures to better implement the warfarin monitoring were complex and difficult to apply in many laboratories. At the moment, as specified in the section "Indications", using only two simple recommendations of the European Action on Anticoagulation (EAA) should improve laboratory monitoring of warfarin and consequently clinical results too. The two simple procedures are 1) the PT/INR line based obtained using a selected set of only five EAA lyophilized test plasmas to derive a laboratory's local INR **(26) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp.1193-1195)** and 2) A variable growth rate (VGR) analysis which has been shown to be of greater value than the previously accepted "time in INR range", in predicting clinical events during warfarin treatment. **(27) (Journal of Thrombosis and Haemostasis 2013 vol. 11 pp. 1540-1546)** see section on "Indications".

Due to the relatively easy feasibility to obtain a correct monitoring of warfarin therapy, at the moment it is not anymore possible to accept an incorrect monitoring of this treatment. In this study the authors compared morbidity and mortality events obtained in the RE-LY study (6022 patients) with those obtained in the EAA study (5939 patients) and the results of this last study were much better although the "time in INR range" was marginally better in the EAA study. The investigators correctly explain these results with the fact that RE-LY lack of two important assessments of INR control, local ISI calibrations and external quality control that were evaluated in the EAA study. The impressive results obtained in the EAA study add another important step to the use of new oral anticoagulants in selected cases only (as described above) and not on a large scale. **(27) (Journal of Thrombosis and Haemostasis 2014 vol. 12 pp. 1193-1195)**

On the other hand, although it was emphasized that new oral anticoagulants do not need laboratory monitoring because they have a predictable pharmacokinetics and pharmacodynamics, in a new RE-LY substudy was found that plasma dabigatran levels achieved for either dose in RE-LY ranged over five fold for the 10th to 90th percentiles, with a large overlap of concentrations, approximately 70% between the two doses. For details see section on "Laboratory Tests". The authors correctely conclude that individual-risk benefit might be improved by tailoring dabigatran dose after considering selected patients characteristics. **(28) (Journal of the American College of Cardiology 2014 vol. 63 (4) pp.321-328)**

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

References :

1) Stollberger Claudia, Finsterer Josef : Contra : “New oral anticoagulants should not be used as 1st choice for secondary stroke prevention in atrial fibrillation”. Thrombosis and Haemostasis 2013; 110 : 496-500
2) Connolly Stuart J., Ezekowitz Michael D., Yusuf Salim et al. : Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal Medicine 2009; 361 : 1139-1151
3) SISET (Società Italiana per lo Studio dell’Emostasi e delle Trombosi) commento sul “Concept Paper” dell’AIFA (Agenzia Italiana del Farmaco)
4) Dager William E., Gosselin Robert C., Roberts A. Joseph et al. : Reversing dabigatran in life-threatening bleeding occurring during cardiac ablation with factor eight inhibitor bypassing activity. Critical Care Medicine 2013; 41, issue 5 : e42-e46
5) Schulman Sam, Ritchie Bruce, Goy Jennifer K. et al. : Activated prothrombin complex concentrate for dabigatran-associated bleeding. British Journal of Haematology 2014; 164, issue 2 : 308-310
6) Wong Henna, Keeling David : Activated prrothrombin complex concentrates for the prevention of dabigatran-associated bleeding. British Journal of Haematology 2014; doi: 10.1111/bjh.12831
7) Drazen Jeffrey M. : COX-2 inhibitors - A lesson in unexpected problems. New England Journal of Medicine 2005; 352 : 1131-1132
8) Psaty Bruce M., Furberg Curt D. : COX-2 inhibitors – Lessons in drug safety. New England Journal of Medicine 2005; 352 : 1133-1135
9) Manson JoAnn E., Chlebowski 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
10) Nelson Heidi D., Walker Miranda, Zakher Bernadette 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
11) Reilly Paul A., Lehr Thorsten.,Haertter Sebastian et al. : The effect of dabigatran plasma concentration and patients characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients. Journal of the American College of Cardiology 2014; 63 (4) : 321-328
12) Shelley Wood : Dabigatran bleeding analysis not disclosed to FDA, documents showed. www.medscape.com February 26, 2014
13) Cohen Deborah : Dabigatran : how the drug company withheld important analyses. British Medical Journal 2014; 349 : g4670
14) Charlton Blake and Redberg Rita : The trouble with dabigatran. British Medical Journal 2014; 349 : g4681
15) Paré G., Eriksson N., Lehr T. et al. : Genetic determinants of dabigatran plasma levels and their relation to bleeding. Circulation 2013; 127 : 1404-1412
16) Davidson Bruce L. : The association of direct thrombin inhibitor anticoagulants with cardiac thromboses. Chest 2015; 147 (1) : 21-24
17) Graham David J., Reichman Marsha E., Wernecke Michael : Cardiovascular, bleeding, and

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.

mortality risks in elderly medicare patients treated with dabigatran or warfarin for non-valvular atrial fibrillation. Circulation, published online, October 30, 2014, DOI: 10.1161/CIRCULATIONAHA.114.012061
18) Hernandez Immaculada, Baik Seo Hyon, Pinera Antonio et al. : Risk of bleeding with dabigatran in atrial fibrillation. JAMA, published online, November 3, 2014, DOI: 10.1001/jamainternmed.2014.5398
19) Jennings Ian, Kitchen Dianne, Keeling David et al. : Patient self-testing and self-management of oral anticoagulation with vitamin K antagonists : guidance from the British Committee for Standards in Haematology. British Journal of Haematology 2014; 367 : 600-607
20) Poli D., Antonucci E., Dentali F. et al. : Recurrence of ICH after resumption of anticoagulation with vitamin K antagonists : CHIRONE study. Neurology 2014; 82 : 1020-1026
21) Garattini Silvio, Bertele' Vittorio : Non-inferiority trials are unethical because they disregad patients' interest. The Lancet 2007; 370 : 1875-1877
22) Nunn Andrew J., et al., Gandjour Afschin, Soliman Elsayed Z., Chuang-Stein Christy et al. : The ethics of non-inferiority trials. Correspondence. The Lancet 2008; 371 : 895-897
23) Lesaffre Emmanuel : Superiority, Equivalence, and Non-Inferiority Trials. Bullettin of the NYU Hospital for Joint Disease 2008; 66 (2) : 150-154
24) Le Henanff Anne, Giraudeau Bruno, Baron Gabriel et al. : Quality of reporting of noninferiority and equivalence randomized trials. JAMA 2006; 295 (10) : 1147-1151
25) Chew Mabel, Brizzel Catherine, Abbasi Kamran et al. : Medical journals and industry ties. Zero tolerance on education articles with financial links to industry. British Medical Journal 2014; 349 : g7197 doi : 10.1136/bmj.g7197
published online on november 28, 2014.
26) Poller L., Jespersen J. and Ibrahim S. : Warfarin or dabigatrab for treatment of atrial fibrillation. Journal of Thrombosis and Haemostasis 2014; 12 : 1193-1195
27) Ibrahim S., Jespersen J., Poller L. : The clinical evaluation of International Normalized Ratio variability and control in
conventional oral anticoagulant administration by use of the variance growth rate. Journal of Thrombosis and Haemostasis 2013; 11 : 1540-1546
28) Reilly Paul A., Thorsten Lehr, Haertter Sebastian et al. : The effect of dabigatran plasma concentrations 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 (4) : 321-328

Copyright © Trombosi-Emostasi 2026 - Tutti i diritti riservati
Ultima modifica Aprile 2015 - Tutti gli argomenti vengono aggiornati non appena nuovi elementi di prova diventano disponibili.