Questions and answers on the use of dabigatran and perpectives on the use of other new oral anticoagulants in patients with atrial fibrillation

A consensus document of the Italian Federation of Thrombosis Centers (FCSA)

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Summary

Dabigatran and other new oral anticoagulants (OAC) represent a step forward in stroke prevention in patients with atrial fibrillation (AF). They indeed have been shown to be an alternative to vitamin K antagonists (VKAs) without the burden of laboratory control. However, these new drugs compete with an effective and well-established therapy, thus bringing about a series of questions and doubts. In this report members of the board of the Italian Federation of Thrombosis Centers (FCSA) answer some questions every clinician might be confronted with.

Keywords

Clinical trials, oral anticoagulants, heart, prevention

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Introduction

The new oral anticoagulant (OAC) dabigatran (Pradaxa, Boehringer Ingelheim, Ingelheim, Germany) is as effective as vitamin K antagonists (VKAs) in stroke prevention in atrial fibrillation (AF) without increasing the risk of bleeding (1). At variance with VKAs, its special merit is that laboratory control is not needed. Since November 3rd, 2010 dabigatran has been available in both Canada and USA for stroke prevention in AF (2). In April 2011 it was approved for this indication by the European Medicines Agency (EMA). Other new OAC have been studied for stroke prevention in AF: rivaroxaban (Xarelto, Bayer AG, Leverkusen, Germany) was tested versus warfarin in a double- blind double dummy study showing non inferiority in stroke prevention without an increase of bleeding (3), apixaban (Eliquis, Pfizer, BMS, New York, NY, USA) was not directly compared to VKAs but was shown to be superior to aspirin in patients for whom VKAs were unsuitable (4). In a phase II study edoxaban (DU-176b, Daiichi Sankyo, Tokyo, Japan) once daily showed a similar safety profile to VKAs (5). The novel oral anticoagulants are classified according to their mechanism of action in direct thrombin inhibitors (dabigatran) and factor Xa (FXa) inhibitors (rivaroxaban, apixaban, edoxaban). Many physicians and patients have long waited for an alternative to VKAs; however, they now find themselves confronted by a switch that is not that straightforward. This report mainly refers to issues specifically related to the use of dabigatran (the only new OAC compared to warfarin with a full paper available in the literature (1) and represents a position document of the Italian Federation of Thrombosis Centers (FCSA). An update will follow when new data on the use of other new OAC in AF will become available.

Methods

Members of the steering committee of the Italian FCSA were assigned a specific issue related to the questions raised with the introduction of dabigatran and other new oral anticoagulants in clinical practice. For this purpose, they were asked to perform a systematic review of evidence.

MEDLINE, PubMed, CANCERLIT, Cochrane Library and EMBASE were systematically searched for publications in English from 2000 to 2010. Reference lists and articles from the authors' libraries and older references generated from initial papers were also

examined. Randomised clinical trials, longitudinal studies, case series and reports from regulatory agencies were considered if appropriate.

The quality of the evidence was graded according to the statements of the Scottish Intercollegiate Guidelines Network (SIGN) (6). Randomised studies or systematic reviews were graded 1; longitudinal studies were graded 2 and case series 3. We ranked recommendations according to the supporting level of evidence. Grade A recommendations were supported by level 1 studies or by statements from drug regulatory agencies, grade B by level 2 studies, grade C by level 3 studies and grade D by expert judgement.

In Milan in December 2010, members of the steering committee of FCSA presented their answers to some common questions raised with the introduction of these new drugs. In the following months each member of the committee addressed each specific issue, and a general discussion took place in Cremona on March 3–4, 2011. This procedure allowed the group to reach a consensus on each of the proposed issues. As most recommendations in this paper are Grade D, this ranking is not reported in the text.

Question 1: Which naïve patient should be treated with dabigatran?

- All the patients with characteristics similar to those of patients enrolled in the RE-LY study (**Grade A recommendation**).
- Patients with history of intracranial bleeding (**Grade A recommendation**).
  - *Remarks:* Dabigatran 110 mg bid may be prescribed as it showed equal efficacy and superior safety as compared to VKAs in RE-LY study (1).
- Patients at high risk of stroke (**Grade A recommendation**).
  - *Remarks:* Dabigatran 150 mg bid may be prescribed as it showed superior efficacy and comparable safety as compared to VKAs in RE-LY study (1).
- Patients willing to be prescribed the new drugs.
- Patients with logistic problems that interfere with laboratory monitoring, as those confined at home due to physical problems.

Question 2: In which patients should dabigatran be prioritised in replacing VKAs?

The following list of patients may be switched to the new anticoagulants:

- Patients on stabilised VKA treatment with a percentage of time spent in therapeutic range (TTR) below 55–50% (**Grade A recommendation**).
  - *Remarks:* This is because in the RE-LY study both the rates of stroke and thromboembolism as well as those of major bleeding are greater when the TTR is in that range (7).
- Patients either with a time-demanding work schedule or with important logistic problems.
- Patients with a history of cerebral bleeding. In both the RE-LY and the ROCKET AF study (1, 3), the rate of cerebral haemorrhage was lower in the new OAC-treated groups when compared to patients randomised to VKAs (**Grade A recommendation**).
  - *Remarks:* Every time a patient suffers from a cerebral haemorrhagic event, the kind (unprovoked or traumatic) and the extension of the lesion, the time elapsed from the event and the presence of other risk factors (hypertension, old age and concomitant anti-platelet agents) should be carefully considered.
- Patients concomitantly treated with interfering drugs proven to cause wide international normalized ratio (INR) fluctuations.
  - *Remarks:* A possible drug interaction with a new OAC should not limit the choice of this drug. However, we do believe that this condition is one of the conditions where laboratory control is indicated (as stated under question 8 of the manuscript).
- Patients who strongly wish to take the new OAC or are unwilling to perform frequent blood testing.
  - *Remarks:* Bleeding risk has been found to be higher in VKA-treated patients older than 75 years of age (8). It is still uncertain whether the new OAC are safer than VKA in very elderly patients.

Question 3: How to switch from warfarin to dabigatran?

- If the INR is 2 or less, you can switch the patient immediately to dabigatran. We recommend the medication to be taken with food.
- If the INR is between 2.0 and 3.0, stop warfarin and start the drug 48 hours (h) after the last tablet.
- If INR is >3.0 stop warfarin and re-check INR 48 h after the last tablet.

Question 4: When can surgery be safely performed after stopping dabigatran?

- Withhold two doses (stop the drug on day –1) in case of elective surgery and the patient has normal renal function.
- Withhold four doses (stop the drug on day –2) and check for laboratory tests on day 0 (aPTT, see below) in case of impaired renal function (creatinine clearance 30–50 ml/minute).
- Resume dabigatran at the same preprocedure dosage on day 1 (at least 12 h after the procedure) or day 2 according to the adequacy of haemostasis, as judged by the surgeon/interventionist.

Question 5: Which patients are definitely to remain on VKAs?

- Patients with both a stable INR and a low bleeding risk (**Grade A recommendation**).
- Patients with recurrent dyspepsia (including nausea, vomiting and diarrhoea).
  - *Remarks:* The RE-LY study has shown a greater percentage of patients with gastrointestinal discomfort in the dabigatran groups (**Grade A recommendation**).
- Patients with previous myocardial infarction.
  - *Remarks:* A significantly higher rate of myocardial infarction as compared to warfarin was reported in the dabigatran 150 mg bid arm of the RE-LY study (1). A revision of the events found this difference not significant. As VKAs are effective in secondary prevention of myocardial infarction, they may be considered as first choice in patients with previous myocardial infarction and low bleeding risk.
- Patients who prefer to continue with VKAs after having received complete information on the pros and cons of the new drugs.
- Patients with severe renal failure (**Grade A recommendation**).

Question 6: What is the compliance to treatment in the absence of a systematic laboratory control? How can we improve medication adherence and persistence?

Achieving optimal prevention of stroke in patients with AF using novel oral anticoagulants implies that patients take their medications not only properly (medication adherence) but also continue to do so throughout long-term treatment (persistence). Poor medication-taking behaviour is not a major problem among patients taking VKAs, as systematic laboratory control is the guarantee of a good adherence to treatment. Conversely, patients prescribed new OAC that do not need laboratory controls may behave in the same way as patients taking antihypertensive drugs (9), where poor medication-taking behaviour is the rule rather than the exception. Even after a dramatic event as an acute coronary syndrome, the continuous use of life-saving drugs after 6–12 months drops to 71% for aspirin, 46% for beta-blockers and 44% for statins, with the adherence to all the three medications being only 21% (10). This scenario may be worse in clinical condition such as AF which is often an asymptomatic chronic disease (11). Estimates of non-adherence in the elderly (defined as those aged >or=65 years) with such chronic conditions as AF vary from 40% to 75%. The problems caused by non-adherence in the elderly include residential care and hospital admissions, progression of the disease and increased costs to health care system (12).

Many interventions have been advocated:

- Specific education programs for subjects with hypertension have been shown to improve adherence (12).
- There is some evidence that telephone counseling concerning adherence by a nurse or pharmacist improves short- and long-term adherence (12).
- One of the consistent features of successful interventions has been regular follow-up with the healthcare system using a screening question on medication non-adherence on the occasion of each visit (11).
- Another intervention may involve hospital or community pharmacists as the refill frequency and the date of the last refill may also help in improving medication adherence (11).
  - *Remarks:* There are many unanswered questions about the most effective interventions for promoting adherence and more studies are needed.

Question 7: What can be practically done to improve adherence/persistence?

Systematic follow-up visits (**Grade B recommendation**) at least every six months (check for adverse events, renal function, dyspepsia) by either:

- Prescribing physician
- General practitioner
- Thrombosis center physician
- Community pharmacist (refill frequency)
  - *Remarks:* Community pharmacists are often the last point of contact in the healthcare chain for patients collecting their prescription(s). They are, therefore, well placed to screen for motivational problems, to assess any obstacles or lack of understanding and knowledge and to provide technical and motivational support tailored to the patients' needs. Open discussion between the pharmacist and patient regarding barriers to adequate medication adherence, followed by a multifaceted, personalised intervention to address these barriers, plays a key role in encouraging patients to adhere to the recommendations of the health care team.
- Caregivers

Alternatively, other less effective measures to improve compliance are:

- Phone call by nurses
- Log book to be filled by patients
- Broad education at time of prescription
- Specific education with pamphlets and questionnaire

Question 8: Is laboratory control ever indicated?

According to the results stemming from phase III clinical trials neither dabigatran nor rivaroxaban require laboratory control to adjust the dosage. However, it could be argued that in specific situations some sort of assessment of their anticoagulant effect may be useful.

The following situations might require laboratory control for patient management.

- Patients presenting in emergency with adverse events (thrombosis or haemorrhage)
- Immediate reversal of anticoagulation
- Renal failure
- Liver failure
- Suspicion or known interaction with other drugs

Question 9: Which test should be performed?

On the basis of the limited experience it could be argued that most of the global and some specific tests can be used to assess the anticoagulant effect of dabigatran (see ▶Table 1) and rivaroxaban (see ▶Table 2).

Dabigatran

Activated partial thromboplastin time (APTT)

Remarks: This test shows poor dose-response linearity and an intermediate responsiveness to increasing dose. A ratio (patient-to-normal clotting time) of 2.0 has been obtained with plasma concentrations ranging from 200 to 300 ng/ml (13). Different results have been reported depending on the reagents used for testing. Thus, it can be anticipated that standardisation across laboratories will be an issue and therefore management on the basis of the test results cannot be generalised.

Thrombin clotting time (TT)

Remarks: Excellent linearity, but excessive responsiveness. A ratio of 15.0 has been obtained with plasma concentration ranging from 200 to 300 ng/ml (13). Modified TT aimed at reducing responsiveness might be suitable. It can be anticipated that standardisation across laboratories will be difficult.

Prothrombin time (PT)

Remarks: Good linearity, but poor responsiveness. A ratio lower than 2.0 was obtained with plasma concentration ranging from 200 to 300 ng/ml. Standardisation will be an issue.

Ecarin clotting time (ECT)

Remarks: Good linearity and excellent responsiveness. A ratio of 4.0 was obtained with plasma concentrations ranging from 200 to 300 ng/ml. Here again standardisation can be an issue owing to the type/concentration of phospholipids and purity of the snake venom.

Others

Remarks: At least in theory the thrombin generation test could be useful, but it is presently too demanding for daily routine.

Rivaroxaban

Anti-FXa activity

Remarks: by definition it would be the test of choice. However, it is not readily available especially in emergency. From the experience gained from its use in monitoring low-molecular-weight heparin it can be anticipated that standardisation across laboratories will be far reaching.

Prothrombin time (PT)

Remarks: Good linearity and acceptable responsiveness. A ratio of 2.0 was obtained with plasma concentrations of 4 μg/ml (14). Although results are dependent on the type of thromboplastin used for testing, evidence was provided that standardisation across reagents is feasible by devising an international sensitivity index (ISI) based on plasma spiked with increasing doses of rivaroxaban (ISI-rivaroxaban). This index was successfully used to convert PT-ratio into INR-rivaroxaban and proved effective in minimizing between-thromboplastin results variability (15, 16).

Activated partial thromboplastin time (APTT)

Remarks: Excellent linearity, but poor responsiveness. A ratio close to 1.5 was obtained with concentrations of 0.4 μg/ml (14). Standardisation will be an issue. Drug concentrations needed to double the APTT clotting time ranged from 0.5 to 0.7 μg/ml depending on the reagent used for testing (14).

Table 1: Potentially useful tests for dabigatran and their characteristics.

Characteristics	Test			
	APTT	PT	ECT	TT
Linearity	-	+	+	+
Standardisation	-	-	– +	-
Responsiveness	+	-	++	++++

Table 2: Potentially useful tests for rivaroxaban and their characteristics.

Characteristics	Test			
	PT	APTT	HepTest	dRVVT
Linearity	+	+	-	-
Standardisation	-	-	?	?
Responsiveness	+	+	++	++

HepTest

Remarks: Good linearity and excellent responsiveness. A ratio of 4.0 was obtained with plasma concentrations of 4 μg/ml (14). Although no experience is available standardisation could be an issue.

Dilute Russell viper venom test (dRVVT)

Remarks: Good linearity and responsiveness. A ratio of 4.0 was obtained with plasma concentrations of 4 μg/ml (3). Standardisation might be an issue depending on the type of phospholipids and purity of snake venom used for testing.

Others

Remarks: Other tests such as point-of-care devices with test strips calibrated in terms of INR valid for patients on vitamin K antagonists (INR-VKAs) and thrombin generation tests have been proposed (13), but their advantages over the previous ones are to be investigated.

Recommendation

Based on the above considerations and present experience the ECT for dabigatran and PT for rivaroxaban should be recommended (**Grade C recommendation**). The ECT is simple, readily available and can be run in an ordinary coagulometer. The PT is simple and readily available. Results for both tests should be expressed as ratio (patient-to normal clotting time). For the PT, results should be expressed as PT-ratio or INR-rivaroxaban. Results expression as INR-VKAs is strongly discouraged as this dramatically magnifies the between-reagent variability (15). Whatever the choice, it is recommended to do testing after 2–3 months from the initiation of the therapy in order to have a steady-state laboratory value that may be useful in the future if adverse clinical events will occur.

Question 10: Is new OAC prescription safe in very elderly patients (>80 years of age)?

Older age is associated with high bleeding risk in patients treated with VKAs (17). In addition, older age is frequently associated with several co-morbid conditions such as renal failure, anaemia, hypertension or history of stroke that represent risk factors for bleeding (18). In the last few years studies concerning the bleeding risk of AF patients older than 75 years have been published, suggesting that the bleeding risk in elderly patients is not severe and not superior to the risk of aspirin treatment (19). The expected net clinical benefit of warfarin therapy is defined as the annualised rate of thromboembolic complication minus the annualised rate of cerebral haemorrhage. Based on this definition, Singer et al. found that it is highest among patients with the highest risk for stroke, which includes the oldest age category, suggesting a benefit for VKAs use in the elderly (20).

Safety of new OAC in very elderly patients is largely unknown as this population was poorly represented in published trial (mean age in RE-LY was 71 and mean age in ROCKET AF study was 73)

Remarks: A recent large prospective collaborative study has been conducted among centres affiliated to the Italian Federation of Thrombosis Centers (FCSA) to assess the adverse events of VKAs in patients who started treatment after 80 years of age (21). History of cancer, renal failure and history of falling were risk factors for bleeding.

We suggest that whenever the use of old and new OAC in very elderly patients is considered, renal function should also be taken into account (**Grade B recommendation**).

Question 11: Should renal function be monitored? If yes, when and in which patient?

After oral administration of a single dose of 150 mg dabigatran etexilate, its pharmacokinetic properties were clearly affected by renal failure (22, 23). Compared with the values in healthy subjects, the area under the plasma concentration-time curve from time zero to infinity (AUC(infinity)) values were 1.5-, 3.2– and 6.3-fold higher in subjects with mild (creatinine clearance 50–80 ml/min), moderate (creatinine clearance 30–50 ml/min) and severe renal impairment (creatinine clearance <30 ml/min). In subjects with severe renal impairment, the mean terminal elimination half-life was doubled (28 h vs. 14 h for control). The AUC for prolongation of pharmacodynamic parameters (the APTT and ECT) increased according to the pharmacokinetic changes. Of note, in patients with end-stage renal disease, dabigatran can be partly removed from the plasma by haemodialysis (23). Thus, exposure to dabigatran is increased by renal impairment and correlates with the severity of renal dysfunction. A reduction of the daily dose from 220 mg to 150 mg is recommended in patients with moderate renal failure and in those aged >75 years, considering the reduction of renal function with age (24). Importantly, in the elderly serum creatinine concentration may only increase slightly due to a concurrent decrease in muscle mass. Thus, many aged patients with AF who may be eligible to receive dabigatran may, unknowingly, have impaired renal function.

Estimating patients' renal function can be done easily with the Cockroft-Gault equation, as shown below:

$$\mathrm{CCr} = \frac{(140 - \mathrm{age}) \times \mathrm{weight}}{72 \times \mathrm{SCr}} \times (0.85 \text{ if female}),$$

where CCr is given in ml/min, SCr in mg/dl, weight in kg.

Dabigatran is contraindicated in patients with severe renal insufficiency (24) and, in fact, these patients were not included in the RE-LY study (1). Subgroup analyses of this trial showed that the rate of stroke and systemic embolism proportionally increased in patients with mild and moderate renal impairment as compared with those with normal renal function. Nevertheless, the efficacy and safety of dabigatran in patients with AF were independent of age and renal function (1, 25). Considering all these findings, the following indications for monitoring renal function in patients given dabigatran could be proposed:

- normal renal function: no monitoring;
- mild renal failure: periodic (every year) evaluation of renal function;
- moderate renal failure: dose reduction (**Grade A recommendation**) and periodic (every six months) evaluation;
- severe renal impairment: dabigatran contraindicated (**Grade A recommendation**).

Question 12: Should we expect significant drug interactions?

One of the limitations of VKA therapy is the extensive interactions with drugs and food. Therefore a low drug/food interaction is among the most important characteristics sought in the development of new anticoagulant molecules (26). In this respect, dabigatran, rivaroxaban, apixaban, and edoxaban are being evaluated. However, few long-term data are available and most interaction studies have been conducted with healthy volunteers (27).

Many of the warfarin interactions are due to its almost exclusive clearance via the liver, which is mediated by the CYP450 enzyme system (particularly the isoform CYP2C9), very vulnerable to competitive inhibition/activation.

There are two principal mechanisms by which anticoagulant drugs are metabolised and eliminated, one is the CYP450 isoenzyme system, and the other is the efflux transport operated by the P-glycoprotein, which is involved in the efflux regulation of many drugs (with the possibility of significant drug-drug interactions).

Dabigatran appears to be metabolized primarily in the plasma and liver without mediation by CYP450; however, it does act as a substrate for P-glycoprotein. Differently, rivaroxaban, apixaban and edoxaban are metabolised almost by two-thirds by the CYP450 isoform CYP3A4, involved in the metabolism of many other drugs, and also are a substrate of P-glycoprotein efflux transporter (28). Therefore the possibility exists that morbidities and drug interactions may interfere with the anticoagulant effect of these agents.

- Dabigatran can be susceptible to strong inhibitors or inducers of P-glycoprotein
- Rivaroxaban, apixaban, and edoxaban, can be sensitive to drugs that strongly inhibit or induce either CYP3A4, or P-glycoprotein, or both.

The currently acknowledged drug interactions for the new anticoagulants are listed in ▶Table 3.

Adverse interactions may be expected also with non-steroidal anti-inflammatory drugs (NSAIDs) and antiplatelet drugs, such as aspirin and clopidogrel (27).

At present, the documented food interactions associated with the new OAC are few, because there is limited clinical experience. One interaction of these drugs can be anticipated with the St. John's Wort, known to induce both P-glycoprotein and CYP4503A4.

Given the common long-term use of drugs for chronic disorders, the frequent use of over-the-counter medications, and the need for multiple treatments in special population, i.e. elderly

Table 3: Predictable drug interactions of the new oral anticoagulants according to the type of metabolism. CYP3A4= CYP450 isoenzyme; NSAIDs= nonsteroidal anti-inflammatory drugs.

	Dabigatran	Rivaroxaban, edoxaban, apixaban
P-glycoprotein inhibitors (amiodarone, phenotiazin, carboxylic acid, azole antifungals, verapamil, antimalarial, cyclosporine, thioxanthenes)	Yes	Yes
P-glycoprotein inducers (dexamethasone, rifampicin, St. John's Wort)	Yes	Yes
CYP3A4 inhibitors (phenotiazin, carboxylic acid, azole antifungals, verapamil, erythromycin, telithromycin, nefazodone, antimalarial, cyclosporine, thioxanthenes)	No	Yes
CYP3A4 inducers (carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, rifabutin, rifapentine, rifampicin, St. John's Wort, alcohol, eucalyptol)	No	Yes
NSAIDS (aspirin, naproxen, diclofenac)	Yes	Yes
Antiplatelet agents (clopidogrel)	Yes	Yes

people, we conclude that it is essential that the issue of drug/food interactions is properly evaluated for the new OAC. To this purpose, we propose that, whenever a concomitant therapy is ongoing with a drug likely to interfere with the new OAC, the laboratory control of anticoagulation should be performed.

Question 13: How should patients with major or life-threatening bleeding be treated?

Bleeding is the most common and worrying side effect of VKAs (29, 30). The anticoagulant effect of VKAs can be reversed by discontinuing treatment, administering vitamin K or replacing the vitamin K-dependent coagulation factors by fresh frozen plasma (FFP) or prothrombin complex concentrates (PCCs). PCCs are considered the treatment of choice for life-threatening haemorrhage in orally anticoagulated patients (31). PCC containing FVII may improve therapeutic performance with prompt reversal of anticoagulation in case of very high INR values.

The new oral anticoagulants dabigatran, rivaroxaban, apixaban and edoxaban have a half-life of 17 h, 9–12 h, 8–15 h and 9–11 h, respectively (32, 33). If a patient bleeds, the first step to take is to stop the medication because the blood levels of the agent drop fairly rapidly after stopping the medication. However the half-lives are not short enough to avoid problems in case of major haemorrhage.

In case of intracerebral haemorrhage, the haematoma volume is critical and related to mortality and functional outcome. A rapid reversal of anticoagulation is necessary in this situation.

The new oral anticoagulants do not have specific antidotes, and this could be an important limitation.

Safety and usefulness of FFP or PCC administration in reversal the effect of new antithrombotic drugs has not been established and recombinant activated FVII (rFVIIa) may be used off-label with a potential high risk for arterial thrombosis (34, 35).

Desmopressin acetate (DDAVP) has been proposed (36), but there are no efficacy and safety data in patients treated with dabigatran or rivaroxaban. Recombinant antidotes or modified plasma-derived protein have the potential to act as antidotes for reversal new OAC, but only experimental data are available (37).

In conclusion, novel anticoagulants will cause bleeding but in routine clinical practice lack effective antidotes. Reasonable approach to major-life threatening bleeding in these patients may vary according to the type of new OAC:

- Direct thrombin inhibitors are hardly counteracted by PCC or FFP. Dabigatran could be adsorbed via haemoperfusion over a charcoal filter. In case of major-life threatening bleeding, haemodialysis is a therapeutic option .
- Direct FXa inhibitors could be (partially) antagonised by non-activated four-factor PCCs. They contain factor II-VII-IX-X and dosage could be 50UI/Kg by one-shot administration.

Question 14: Is the comparison of cost-effectiveness favourable?

Typically the cost-effectiveness is expressed in terms of a ratio where the denominator is a gain in health from a measure and the numerator is the cost associated with the health gain. The effectiveness (and safety) of VKAs is adequate when INR is kept into therapeutic range for an appropriate time (TTR) (38, 39) and cost-effectiveness of VKAs is linked to this assumption. The operating costs of VKAs therapy is highly variable both in Italy and internationally; this stems from the different models used. A correct calculation of the economic management of VKAs therapy should consider the costs of drug, health care and INR determination.

The cost to the Italian National Health System is calculated on the basis of time (min) spent for each visit by each healthcare professional (this cost is increased by 15% considering holidays and sickness) with the total cost increased by 20% for overheads. The total cost is then multiplied by 16, which is the mean number of INR controls per year (data derived from FCSA 2010 therapeutic quality control): a total cost per patient/year of 151 Euro (~$207) is computed. However, indirect costs for INR monitoring (transportation, parking, time spent by accompanying persons) are not taken into account in this calculation.

In the U.S. the cost per year of the annual cycle of treatment, including clinical assessment, was estimated to be $2,884 for dabigatran and $1,761 for warfarin (40). Dabigatran annual cost is strictly dependent on the dabigatran price currently marketed in US (40).

Wallentin et al. in 2010 analysing the results of the RE-LY study in terms of TTR in the warfarin arm, showed that, compared to dabigatran, warfarin is superior in terms of cost-effectiveness when patients TTR is > 72% (41).

Recently Shan and Gage (42), in their study on cost-effectiveness on RE-LY data, state that dabigatran was cost-effective in the AF populations at high risk of haemorrhage or high risk of stroke unless INR control with warfarin was excellent. On the other hand, warfarin was cost-effective in moderate-risk AF populations unless INR control was poor.

Question 15: Which are the general recommendations before starting new OAC?

- New oral anticoagulants may be prescribed by specialists in cardiology, neurology, internal medicine, or by Thrombosis Centres. Before prescribing the following steps should be followed: Comply with the indications and contraindications of individual new OAC.
- Explain to the patient the characteristics of various available drugs.
- Take into account the patient preferences in the choice of treatment. Once the treatment is chosen then it is needed to make a correct and complete information and patient education.

  - *Remarks:* Each patient must receive complete information on: mode, duration of effect of the drug, method and timing of intake, possible interactions and side effects.
- Arrange personally the follow-up or through the support of Thrombosis Centres or by express agreement with the general practitioner (GP).
  - *Remarks:* Each patient must be informed of the future timing of follow-up checks, place of these controls and procedures for supplying of the drug. It must be stressed the need for full compliance with the requirements of treatment and follow-up (see below).
- Advise the patient to keep a personal identification card, containing personal information, the type of anticoagulant treatment in progress, an address reference with telephone number for contact by the patient in case of need or by another physician for any emergency.
- Check blood cell count, PT, APTT, liver function tests and the creatinine clearance in all subjects over 75 years of age.

Question 16: What is recommended for the follow-up of these patients?

- It is suggested that patients are entered into a registry collecting data of patient characteristics and treatment (demographic information, indication for treatment, personal risk factors, medical history, drugs, type of drug and dose used, information gathered during follow-up, side effects, bleeding or thrombotic events.
- In the initial phase of treatment it is appropriate a follow-up visit after three and six months and every six months thereafter. At the same time intervals inspections on the drug blisters for the new supply may be useful. In patients with moderate renal impairment or age> 75 years creatinine clearance should be checked at time of follow-up.
- The GP can usefully be involved in monitoring patients treated with new OAC, provided they are connected to the computerised registry for data collection.
- A timely reminder (telephone) of follow-up visits should be provided. For patients missing a scheduled visit it is necessary to find out his/her clinical status. Patients lost to follow-up (mentioning the causes) should be reported.

Conflict of interest
None declared.

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