Dabigatran etexilate: appropriate use in patients with chronic kidney disease and in the elderly patients

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Mauro Molteni, Mario Bo, Giovanni Di Minno, Giuseppe Di Pasquale, Simonetta Genovesi, Danilo Toni, Paolo Verdecchia

Abstract

Dabigatran etexilate (DE) is a direct thrombin inhibitor, which has been approved for the treatment of non-valvular atrial fibrillation (AF), and for the prevention and treatment of venous thromboembolism (VTE). Despite large randomized clinical trials and independent observational studies providing robust data concerning DE safety and efficacy, some physicians still perceive mild-to-moderate renal impairment and old age as a relative contraindication to its use. In this article, we review the available scientific evidence supporting the use of DE in these clinical situations. Patients with AF and chronic kidney disease (CKD) are per se at high risk of stroke, bleeding and mortality. Although there is evidence of clinical benefit of anticoagulation in these patients, anticoagulant therapy requires caution and demands careful clinical monitoring, regardless of the drug used. In patients with no contraindication to its use, the clinical benefit of DE versus warfarin is independent of renal function. The elderly with AF are frequently undertreated because of the perception of high bleeding risk and limited clinical benefit. However, the clinical benefit of anticoagulation is independent of patient age, and age per se should not represent a contraindication to anticoagulation. DE has been extensively studied in the elderly, both in randomized clinical trials and in observational studies: DE 150 mg BID should not be used in patients 80 years of age or older, while DE 110 mg BID is as safe as warfarin. Intracranial haemorrhages reduction by DE compared with warfarin is preserved in the elderly. Therefore, mild and moderate CKD and being elderly should not deter physicians from prescribing DE. Furthermore, the availability of a specific antidote is expected to improve the safety of the use of DE in clinical practice.

Introduction

Dabigatran etexilate (DE) is a direct thrombin inhibitor, which has been approved for stroke prevention in non valvular atrial fibrillation (AF), and for the treatment and prevention of venous thromboembolism (VTE) [1].

At nearly 6 years from its marketing, robust scientific evidence of DE safety and efficacy is available from randomized clinical trials and real-life observational

studies, but some uncertainties still exist in some prescribers, namely for its use in older people and in patients with moderate renal impairment [2, 3, 4, 5, 6, 7, 8].

Patients with AF and chronic kidney disease (CKD) are per se at high risk of stroke, bleeding, and mortality [9, 10, 11]. Although there is evidence of clinical benefit of anticoagulation in these patients, anticoagulant therapy requires caution and demands a careful clinical monitoring, regardless of the drug used [12, 13]. In patients with no contraindication to its use, the clinical benefit of DE versus warfarin is independent of renal function [14].

Despite the clinical benefit of anticoagulation being independent of patient age, and age per se not representing a contraindication to anticoagulation, the elderly patients with AF are often denied anticoagulant therapy because of the perception of a high bleeding risk [15]. In the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, the effects of both doses of DE in the prevention of stroke and systemic thromboembolism were consistent irrespective of patient age [7].

Hereafter, we analyse the current scientific evidence concerning these issues, trying to provide scientific background to support physician in the choice of anticoagulant therapy in these patients.

Dabigatran and chronic kidney disease

Chronic kidney disease and atrial fibrillation

Renal function is inversely related to the prevalence of AF [9], and its impairment is associated with a higher risk of stroke, bleeding, and mortality than in patients with preserved renal function [10]. However, AF patients with severe renal failure have often been excluded from clinical trials [11]. Renal impairment is usually perceived as a major bleeding risk factor, but bleeding risk per se should not be used to exclude patients from anticoagulant therapy [16]. As suggested by recent guidelines, bleeding risk calculation should allow clinicians to make an informed assessment of this risk, and to encourage them to modify correctable risk factors, such as uncontrolled blood pressure, concomitant use of aspirin, alcohol consumption etc [17].

In clinical practice, patients may have mild or moderate renal impairment, and have medical conditions or use concomitant drugs that can cause fluctuation of renal function. The NHANES study shows that nearly 40% of adults aged 70 years or older have an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2 [18]. Therefore, the definition of renal function is of paramount importance in patients with AF, both in those treated with vitamin K antagonists (VKAs) and those treated with direct oral anticoagulants (DOACs).

Estimation of renal function

Glomerular filtration rate (GFR) estimation has several limitations related to the variability of daily urine output. For many years, the Cockcroft–Gault (CG) equation has been used for the prediction of creatinine clearance from serum creatinine [19]. Currently, the most used and validated equations to estimate GFR are the Modification of Diet in Renal Disease Study (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI); however, they do not perform so well in all patient populations [20, 21]. In a population of the elderly patients (mean age 80.7 ± 6), Dowling and co-workers evaluated the performance of kidney function estimation equations, and determined the frequency of drug dose discordance relative to the measured 24-h creatinine clearance (mClcr). The study shows that all the equations, namely, CG, MDRD and CKD-EPI, provide a biased estimate of mClcr, but the CG equation was the least-biased estimate of mClcr. The MDRD and CKD-EPI equations significantly overestimate creatinine clearance (mClcr) in the elderly individuals, and this fact could lead to dose calculation errors for drugs requiring renal dosage adjustments, in patients with severe kidney disease. Median discordances relative to CG among the drugs tested are 28.6% (range 2.2–44.6%) for MDRD and 22.9% (range 2.2–36.4%) for CKD-EPI, with the highest discordance observed in patients with mClcr <50 ml/min [22]. Although CG formula could be an imperfect instrument to estimate eGFR and current guidelines suggest the use of other equations [23], it is still probably the best available tool, when considering DOACs prescription. Firstly, in phase III clinical trials of DE and DOACs for stroke prevention in AF, drug eligibility and dosing were determined using the CG equation to estimate GFR. Secondly, the MDRD equation for eGFR calculation in an elderly population could overestimate GFR. MacCallum et al. compared MDRD and CG equations to estimate GFR in 4120 AF patients, from a general practitioner-registered population. Of these patients, 2706 were aged <80 years, and 1414 were ≥80 years of age. Among those ≥80 years of age, 14.9% were ineligible for DE per CG equation, but would have been judged eligible when applying the MDRD method. For those <80 years of age, 0.8% would have been incorrectly judged eligible for DE, and 5.3% would have received a too high a dose [24].

Chronic kidney disease and atrial fibrillation: real-life data

A substantial proportion of the general population is affected by CKD [21]: its incidence increases with age, and it is associated with increased morbidity and mortality [25]. Bonde et al. assessed the risk associated with CKD in individual CHA_2DS_2-VASc strata and the net clinical benefit of warfarin in patients with AF and CKD in a nationwide Danish cohort. They identified more than 11,000 patients with non-end-stage CKD and 1700 patients with end-stage renal disease (ESRD), representing, respectively, 7.2 and 1.1% of all the identified AF patients. In patients with ESRD and CHA_2DS_2-VASc score ≥2, warfarin is associated with lower risk of all-cause death (HR 0.85, 95% CI 0.72–0.99). In non-end-stage CKD patients with CHA_2DS_2-VASc score ≥2, warfarin is associated with a lower risk of a composite outcome of fatal stroke/fatal bleeding (HR 0.71, 95% CI 0.57–0.88), a

lower risk of cardiovascular death (HR 0.80, 95% CI 0.74–0.88) and a lower risk of all-cause death (HR 0.64, 95% CI 0.60–0.69) [12].

In real practice, CKD, especially in the elderly patients, is a factor independently associated with a lower prescription of anticoagulant therapy. The REPOSI study shows that among patients with AF, higher values of eGFR are associated with a lower risk of mortality both in the hospital [odds ratio (OR) 0.96 (95% CI 0.94–0.99; $p = 0.011$)] and at 3 months after discharge (OR 0.97; 95% CI 0.94–1.00; $p = 0.038$). This study also shows an association between reduced eGFR and lower probability of oral anticoagulant prescription [26]. Therapy-related bleeding risk is particularly high in AF patients with ESRD, and there is no agreement on the use of anticoagulation in this setting. A recent survey of physicians treating ESRD patients with AF shows that a permanent AF is the only clinical factor directly associated with warfarin administration, while previous bleeding is inversely related to VKAs prescription. The $CHADS_2$score is not associated with warfarin prescription. This turns into a low prevalence of warfarin prescription (less than 50% of the patients) [27]. In this specific setting characterized by a very high mortality, anticoagulation seems to be associated with a better survival; furthermore, patients with the highest time of International Normalized Ratio (INR) in therapeutic range had the lowest bleeding rate [28].

Although the perceived high risk of bleeding very often hampers the use of anticoagulation [29], physicians should consider that there is a net clinical benefit with oral anticoagulation, which is associated with reduced mortality and vascular events, especially in perceived frail patients such as those with CKD [30]. The benefits in terms of efficacy are greater than the detrimental effects of increased bleeding risk.

Using direct oral anticoagulants in patients with chronic kidney disease

There is concern regarding the use of DOACs in patients with renal impairment, due to a significant impairment in the renal clearance of these drugs. However, current scientific evidence does not support this concern. Sardar et al. published a meta-analysis evaluating the efficacy and the safety in respect of DE, apixaban and rivaroxaban compared with conventional treatment in patients with renal insufficiency. The authors defined moderate renal insufficiency as eGFR of 30–49 ml/min, and mild renal insufficiency as eGFR 50–79 ml/min. They identified 40,693 patients with renal insufficiency in ten large phase III trials, and found that DOACs, compared with warfarin, significantly reduce major and clinically relevant non-major bleeding [OR 0.81; 95% confidence interval (CI) 0.72–0.90], and stroke or systemic embolism (OR 0.70; 95% CI 0.54–0.92) in patients with mild renal impairment. In patients with moderate renal impairment, DOACs, compared with warfarin, reduce stroke, or systemic embolism (OR 0.72; 95% CI 0.57–0.92) and have a favourable safety profile with a trend towards less major or clinically relevant non-major bleeding (OR 0.82; 95% CI 0.59–1.14). DE significantly reduces stroke or systemic embolism of about 30% (OR 0.71; 95% CI 0.50–0.99) [31].

After oral administration, DE is rapidly hydrolysed in vivo to the active form. Furthermore, DE is the only DOAC to be almost exclusively excreted by the kidney, nearly 80% of the absorbed DE being excreted through glomerular filtration, as an active drug [32]. DE has been extensively studied in patients with GFR 30 ml/min or higher [2, 3, 4, 5].

In a pre-specified sub-study of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RELY) trial, Hijazi et al. investigated the outcomes of DE compared with warfarin, in relation to renal function. GFR was estimated using CG, MDRD, and CKD-EPI formula. The rates of stroke or systemic embolism were lower with DE 150 mg BID and similar with 110 mg BID compared with warfarin, without significant heterogeneity in subgroups defined by renal function (interaction $p > 0.1$ for all). These data clearly show that the antithrombotic efficacy of DE versus warfarin in patients with AF is independent of renal function [14].

In the RE-LY trial, two different dosages of DE, 110 mg BID and 150 mg BID, were separately studied in a double-blind fashion in 6015 and 6076 patients, respectively, and this allows for a clear definition of the different profile of both dosages [2]. DE 110 mg is as effective as warfarin, with a lower bleeding risk, and this dosage applies to a significant proportion of patients in a real world setting [6]. The RE-LY trial included many patients ($N = 3554$) with an eGFR (CG formula) less than 50 ml/min. As shown in Fig. 1, the differences in the risk of primary outcome (composite of stroke/systemic embolism) between each dose of DE and warfarin did not change (i.e. did not show any significant interaction) with eGFR. Similarly, the differences in the risk of major bleeding between each dose of DE and warfarin did not change with eGFR (Fig. 2). Notably, the rates of major bleeding in patients with eGFR <50 ml/min are nearly identical with D110 mg, D150 mg and warfarin (i.e. 5.45, 5.50 and 5.49% per year, respectively). The above estimates show some differences when eGFR is measured, post hoc, with equations not pre-specified in the RE-LY protocol (i.e. CKD-EPI and MDRD) [14].

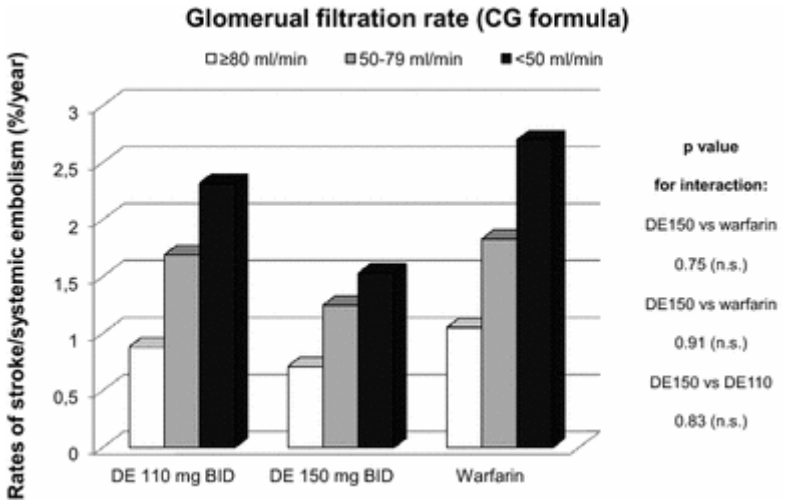

Fig. 1 Rates of stroke and systemic embolism with DE 110 mg/bid, DE 150 mg/bid and warfarin according to glomerular filtration rate in RE-LY population
Modified from Hijazi et al. [14]

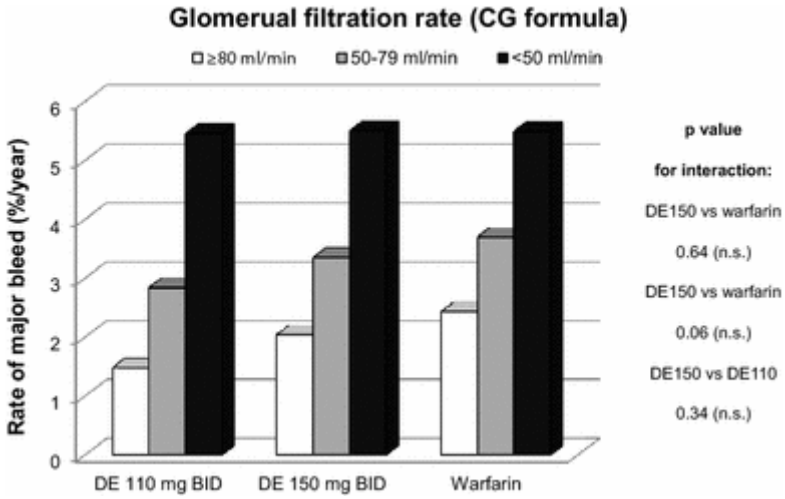

Fig. 2 Rates of major bleedings with DE 110 mg/bid, DE 150 mg/bid and warfarin according to glomerular filtration rate in RE-LY population;
Modified from Hijazi et al. [14]

We strongly discourage the off-label use of DOACs in patients who have clear contraindication, such as patients with ESRD treated with dialysis, also based on real-life experience that show detrimental effects compared with warfarin [8]. On the other hand, although the summary of product characteristics of apixaban and rivaroxaban admit use of these DOACs in patients with severe renal impairment (e.g. eGFR less than 30 ml/min), major guidelines discourage their use in these patients [32]. Although a recent meta-analysis finds that VKAs do not reduce stroke rate in ESRD patients on replacement therapy, and is associated with a 30% increase in major bleeding [13], some recent studies suggest that these patients with AF when treated with VKAs have a better survival compared with patients not anticoagulated. Warfarin benefit seems to be particularly evident in patients taking VKAs without interruption, and with an INR kept in therapeutic range [33, 34]. In case of DE overdose, and in case of life-threatening bleeding, haemodialysis can be used to reduce DE level, and stop bleeding [32]. In patients with acute renal failure, the availability of the monoclonal antibody fragment Idarucizumab makes it easier to antagonize the anticoagulation effect of DE in these situations and help the physician to stop it in case of bleeding.

Haemodialysis cannot be used for apixaban and rivaroxaban overdose, because of high protein binding [32].

Warfarin-related nephropathy

In recent years, a new complication of warfarin has been described, the so-called Warfarin-related Nephropathy (WRN) [35, 36, 37]. This condition consists in a rise of serum creatinine greater than 0.3 mg/dl, within one week of a supra-therapeutic international INR measurement in patients being treated with VKAs without overt bleeding. Recent scientific evidence reveals that WRN can occur in any VKAs-experienced patients, regardless of baseline renal function, and that it

can be associated to a higher risk of mortality, compared with patients without WRN [38]. Some authors hypothesized also the existence of a DE-related nephropathy [39]. Böhm et al., analysed changes in GFR during treatment with warfarin or DE in patients enrolled in the RE-LY trial. GFR declined in all treatment groups, but, after an average of 30 months, the mean decline in GFR was significantly greater with warfarin (−3.68 ± 0.24 ml/min) compared with DE 110 mg (−2.57 ± 0.24 ml/min; vs. warfarin, $p = 0.0009$) and DE 150 mg (−2.46 ± 0.23 ml/min; vs. warfarin, $p = 0.0002$). Patients with a poor INR control (i.e. time in therapeutic range <65%) exhibited the fastest decline in GFR [40]. The difference found between the two drugs, however, is not such as to have a clinical impact and is probably due to the large size of the sample and to the long-time follow-up. However, it shows that DE does not have a worse impact compared with warfarin in the progression of renal damage.

Anticoagulation in patients with chronic kidney disease: key points

Patients with CKD are per se at higher risk of stroke, bleeding and mortality

Renal function fluctuates in several patients owing to their medical conditions and concomitant drug use

In patients with CKD, anticoagulation requires caution and demands a careful clinical monitoring

Anticoagulation is worthwhile in patients with mild-to-moderate CKD and AF; net clinical benefit in patients with severe CKD is not fully proven

When choosing a DOAC, CG formula should be used to estimate GFR

In patients with AF and no contraindication to DE treatment (eGFR >30 ml/min), the benefit of DE versus warfarin for stroke prevention is independent of renal function. In these patients, the risk of intracranial bleed is lower with both doses of DE than with warfarin at all levels of renal function

Where clinically indicated, mild and moderate renal failures, (and their possible fluctuations), should not, per se, be considered as a barrier to the use of DE

In patients with ESRD, the use of DOACs is not recommended as per guidelines

Dabigatran in the elderly

Elderly, atrial fibrillation and anticoagulation

A large proportion of patients with AF are older than 75 years of age [15]. Although age is significantly associated with a high risk of stroke [41], old age itself is negatively associated with anticoagulant prescription [42]. Advanced age per se, physician's perceived high risk of age-related and fall-related bleeding, and difficulties in monitoring warfarin-based anticoagulant therapy have been reported among the main factors accounting for under-prescription of anticoagulant therapy in older patients with AF [41, 43, 44, 45]. Although several studies suggest that advanced age itself should not prevent prescription of oral anticoagulants in the elderly patients [46, 47, 48], under-prescription of anticoagulants among the oldest patients remains a common clinical practice in several contemporary medical settings [15, 45].

Among the perceived or actual barriers to warfarin use in older subjects with AF, the predisposition to falls represents an important issue [49]. Some authors show that patients subjected to VKA therapy, who are at high risk of falls, suffer ICH more frequently than the other subjects [50], but some other studies do not confirm these data [51]. A meta-analysis on antithrombotic therapy in the elderly patients at risk for falls concludes that the propensity for falling in the elderly patients should not be an important factor: considering the median stroke risk, an elderly patient treated with VKAs should fall nearly 300 times/year for the risk of bleeding to outweigh anticoagulation benefits [52]. Therefore, current guidelines do not require estimation of the risk of fall in bleeding risk evaluation [17].

Patient's age does not influence the relative benefit of anticoagulation versus placebo or antiplatelet therapy [53], this latter being commonly prescribed in the elderly with AF [15], and whose benefit for stroke prevention in AF decreases significantly as patient's age [53]. The BAFTA study demonstrates that warfarin is more effective than aspirin in preventing ischaemic stroke in older patients with AF [46]. Furthermore, compared with warfarin, antiplatelet therapy does not seem to be associated with a lower bleeding risk in the elderly [46, 47]. In the ATRIA study, the net clinical benefit of warfarin, expressed as thromboembolic events prevented minus the annualized rate of ICH, was better than aspirin net clinical benefit, and the benefit was the greatest in patients aged 85 years and over and in those at high cardioembolic risk [54].

A retrospective cohort study on nearly 32,000 veterans 75 years or older with AF treated with VKAs, who were new referrals to Veteran Affairs anticoagulation clinics, demonstrates a high incidence of traumatic ICH (4.80 per 1000 person-years). The factors associated with intracranial bleeding are: dementia (HR 1.76; 95% CI 1.26–2.46), anaemia (HR 1.23; 95% CI 1.00–1.52), depression (HR 1.30; 95% CI 1.05–1.61), anticonvulsant use (HR 1.35; 95% CI 1.04–1.75), and labile INR (HR 1.33; 95% CI 1.04–1.72), and there is no influence of CHA_2DS_2-VASc score. Furthermore, the rate of any ICH (traumatic or non-traumatic) is like that

of the rate of ischaemic stroke [55]. These data highlight the difficulties of VKAs management in the elderly patients with AF, although it is important to note that, when they are treated in a setting of Anticoagulation Clinics, the bleeding risk is low [56] as well as the rate of thromboembolic events [57].

Drug–drug interaction is a matter of concern in the elderly, but DE displays few significant drug interactions [32]. On the other hand, warfarin displays several drug–drug interactions, mainly with drugs of common use, potentially causing fluctuations of the anticoagulant effects and thereby exposing patients to the risk of under- and over-anticoagulation. Warfarin is responsible for one-third of the emergency hospitalizations for adverse drug events in the U.S. adult population 65 years of age or older, and nearly half of these hospitalizations are among the adults 80 years of age or older [58]. The results of the meta-analysis of Barco et al. confirm the robust data on DE in the elderly [59]. Accordingly, these data imply that age per se should not deter DE or DOACs prescription.

INR lability is maximal in the first weeks of treatment, thus conditioning the highest incidence of bleeding in the first 3 months [60, 61]. Due to their pharmacokinetics, DE and DOACs do not require laboratory monitoring and have a fixed dose–effect relationship [32]. This issue is of paramount importance, in settings such as the elderly, where dosing scheduling and blood sampling could be major barriers to a practical management of anticoagulation.

Dabigatran etexilate and the elderly

The RE-LY trial enrolled more than 7200 patients older than 75 years, and therefore reliable data are available for DE in this setting, regarding both dosages. There is a significant treatment-by-age interaction, such that DE 110 mg BID, compared with warfarin, is associated with a lower risk of bleeding in patients aged <75 years (1.89 vs. 3.04%; $p < 0.001$) and a similar risk in those aged ≥75 years (4.43 vs. 4.37%; $p = 0.89$; p for interaction <0.001). DE 150 mg BID is associated with a lower risk of bleeding in those aged <75 years (2.12 vs. 3.04%; $p < 0.001$) and a trend towards higher risk of major bleeding in the elderly (5.10 vs. 4.37%; $p = 0.07$; p for interaction <0.001) [7]. In patients aged >80 years, DE 150 mg BID is associated with a higher rate of major bleeding compared with warfarin (6.23 vs. 4.68%; p for interaction 0.002); see Fig. 3 for details [59]. Anyway, the interaction with age is not present for ICH, and DE is associated with a consistent reduction of ICH irrespective of age, compared with warfarin [7].

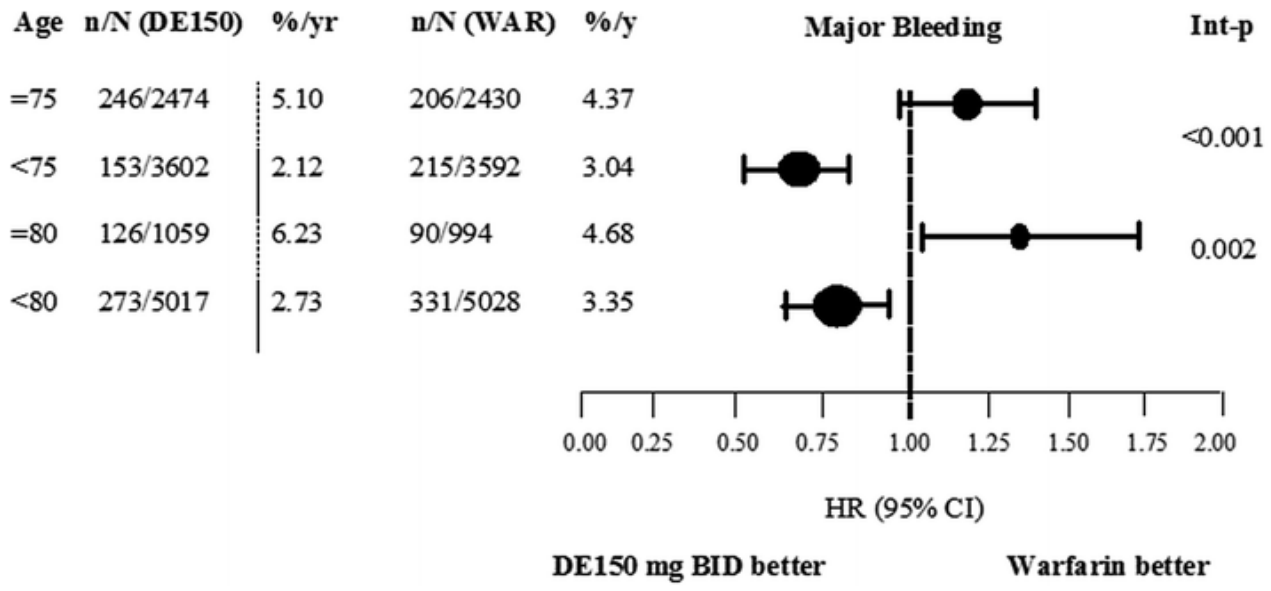

Fig. 3 Major bleeding in the RE-LY study, comparing DE 150 mg/bid with warfarin in patients with atrial fibrillation. *DE150* DE150 mg/bid, *WAR* warfarin, *n* number of patients with events, *N* the total number of patients in the subgroups, *%/yr* event-rate expressed as the number of events per 100-patient-years of follow-up, *Int-P p* value for interaction between age category and treatment, *HR* hazard ratio, *CI* confidence interval
Modified from Barco et al. [57]

Real-life data of the use of DE in the elderly are consistent with the RE-LY results. In a Medicare population of the elderly AF patients with the newly prescribed anticoagulation, the HRs of DE compared with warfarin are 0.80 (0.67–0.96) for ischaemic stroke, 0.34 (0.26–0.46) for ICH, 1.28 (1.14–1.44) for major gastrointestinal bleeding, 0.92 (0.78–1.08) for acute myocardial infarction and 0.86 (0.77–0.96) for death [62]. DE 110 mg BID is not available in the United States, while lower-dose DE (75 mg BID) has been approved by Food and drugs Administration, for patients with severe renal impairment (eGFR 15–30 ml/min) based on pharmacokinetic modelling [1]. Except for 16% of the patients who were treated with DE 75 mg BID, this Medicare population was treated with DE 150 mg BID. In the DE 150 mg BID group, the magnitude of effects for each outcome is even greater, compared to the overall results of this study [62].

In a post hoc analysis of the RE-LY evaluating patient outcomes using the European label for DE, the “European label simulated dabigatran treatment”, DE is associated with statistically significant reductions of stroke and systemic embolism (HR 0.74; 95% CI 0.60–0.91), haemorrhagic stroke (HR 0.22; 95% CI 0.11–0.44), death (HR 0.86; 95% CI 0.75–0.98), major bleeding (HR 0.85; 95% CI 0.73–0.98), life-threatening bleeding (HR 0.72; 95% CI 0.58–0.91), ICH (HR 0.28; 95% CI 0.17–0.45) and “any bleeds” (HR 0.86; 95% CI 0.81–0.92). There is a non-significant 20% increase of major gastrointestinal bleeding (HR 1.23; 95% CI 0.96–1.59) [63].

Anticoagulation in the elderly patients: key points

The elderly patients with AF are often denied anticoagulant therapy mainly because of misperceived high bleeding risk and underestimated net clinical benefit

The net clinical benefit of anticoagulation is largely independent of patient's age

Age per se should not represent a contraindication to anticoagulation

Aspirin or other antiplatelet therapy does not represent a reliable alternative to oral anticoagulation

DE is well studied in the elderly patients

DE 150 mg BID should not be used in patients 80 years of age or older

DE 110 mg BID is as safe as warfarin in the elderly patients (i.e. patients 80 years of age or older)

ICH risk reduction of DE, compared with VKAs, is better preserved in the elderly

DE displays only a few significant drug interactions, and this is important in the elderly, where polypharmacy is common

DE management is easy and should help overcome the problems associated to VKAs management; this should impact on implementation of anticoagulation prescription, as clinically indicated

There is no need to estimate the risk of fall in bleeding risk evaluation, and the perceived or actual risk of fall should not hamper the use of anticoagulation

Dabigatran etexilate and the antidote

Each year, 3–5% of patients treated with oral anticoagulants will experience major bleeding and about 10% will require invasive interventions [64]. While most of the bleeding events and surgical procedures can be managed without specific agents, the ability to quickly reverse anticoagulant activity is of paramount importance in life-threatening situations.

In the setting of a life-threatening bleeding in VKA-treated patients, rapid replacement of these coagulation factors is required [65]. Prothrombin complex concentrates (PCCs) are a reasonable option [66, 67]; nevertheless, data for PCCs are based almost exclusively on laboratory rather than clinical endpoints [68].

Reversing dabigatran etexilate bleeding

So far, DE-related bleeding has been managed with supportive measures and by temporarily withholding the drug. Use of PCCs for DOAC-related bleeding has been based on little scientific evidence and on the consensus of expert opinion

[32]. The scientific evidence includes pre-clinical studies [69], and studies on healthy volunteers [70, 71] or ex vivo addition of PCC or aPCC to patients receiving DE 150 mg BID [72]. Idarucizumab is a humanized antibody fragment that has been developed to specifically reverse the anticoagulant effects of DE, and recently, the preliminary results of a multicentre prospective cohort study (i.e. RE-VERSE AD) including DE-treated patients who had major bleeding or required urgent procedures have been published. The median maximum percentage reversal was 100% (95% confidence interval, 100–100). Coagulation test results are normalized in 88–98% of the patients, and the effect is evident within minutes [73].

Therefore, although DE displays a safer profile than warfarin, and most of the bleeding can be managed without reversing its anticoagulant effect, DE has now a specific antidote that can rapidly restore haemostasis in life-threatening situations.

Dabigatran compliance

DOACs do not require routine laboratory monitoring, thus potentially simplifying anticoagulation management. However, some physicians argue on compliance troubles, because INR measurement may reflect a patient's compliance.

Medication compliance is poor among patients on warfarin, which increases the risk of cardiovascular events [74, 75]. Although DOACs are easier to use than warfarin, poor medication compliance may have a negative impact on clinical outcomes [76].

As far as compliance itself is concerned, recent scientific evidence confirms that DE treatment persistence is good [77], and more in general, DOACs real-life data show greater persistence of anticoagulation compared with warfarin. One-year persistence rate of warfarin is nearly 50% [78], although some authors report even smaller numbers [75, 76]. However, contrasting results about this crucial issue have been published, demonstrating low compliance (namely <50%) also in patients treated with DE [79]. A greater number of data from real-life studies are needed to clarify this point.

DE, as well as apixaban, are dosed BID [32], which may represent for some patients a disadvantage compared to VKAs, and this could represent a limitation to switching from VKAs to DOACs in experienced patients. Anyway, some authors think that DOACs with BID dosing are potentially safer than those with QD dosing, because a single, missed dose should not lower vascular protection because drug plasmatic levels should not vary that much [80]. DOACs greatest implementation is the avoidance of need for constant laboratory monitoring. However, there are some settings in which laboratory testing could be useful. Beyond bleeding and emergency setting, measurement of residual drug concentration before surgery or invasive procedures could help to minimize the risk of bleeding in these clinical settings [81].

Conclusion

The safety and efficacy of DE result from robust evidences derived from randomized clinical trials and from real-life studies. Nevertheless, there are some clinical scenarios in which physicians still do not feel comfortable with its use, due to a misperceived high risk of bleeding, such as in patients with chronic kidney disease and the elderly.

The RE-LY study shows that the antithrombotic efficacy and the haemorrhagic risk of either dose of DE are independent of renal function. The higher thrombotic and haemorrhagic risks of patients with CKD are thus largely related to CKD itself. In this setting, the rates of major bleeding in patients with eGFR <50 ml/min are nearly identical to those with D110 mg, D150 mg and warfarin (i.e. 5.45, 5.50 and 5.49% per year, respectively) [14].

The elderly with AF, who are frequently undertreated, may derive a net clinical benefit from anticoagulation itself. DE 110 mg BID appears to be the dosage of choice because of its superior safety profile. In patients aged ≥75 years, the risk of major bleeding is almost identical with DE 110 mg and warfarin (4.43 vs. 4.37% per year; HR 1.01 (0.83–1.23) [7].

Compliance with anticoagulation is of paramount importance, and DE characteristics and management improve compliance compared with warfarin, for which long-term non-compliance is surely troublesome.

Therefore, mild and moderate CKD and old age should not deter physicians from prescribing DE. Furthermore, the availability of a specific antidote is expected to improve the safety of its management in clinical practice.

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Compliance with ethical standards

Conflict of interest

Dr. Mauro Molteni has received consultancy/lectures/research fees from Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi Sankyo, Novartis, Portola, and Sanofi. Dr. Mario Bo has received lectures fees from Bayer, BMS/Pfizer, Boehringer-Ingelheim, Giotto and Menarini. Dr. Giovanni Di Minno has no conflict of interests to disclose. Dr. Giuseppe Di Pasquale has no conflict of interests to disclose. Dr. Simonetta Genovesi has received consultancy/lectures/research fees from Boehringer-Ingelheim. Dr. Danilo Toni has received consultancy/lectures/research fees from Bayer, BMS/Pfizer and Boehringer-Ingelheim. Dr. Paolo Verdecchia has received consultancy/lectures/research fees from Bayer, BMS/Pfizer, Boehringer-Ingelheim and Daiichi Sankyo.

Statement of human and animal rights

This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent

For this type of study, formal consent is not required.

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