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## Review Article

## Diagnosis and management of pulmonary embolism in the elderly

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## ABSTRACT

Elderly patients are a population not only at particularly high risk of venous thromboembolism including pulmonary embolism (PE), but also at high risk of adverse clinical outcomes and treatment-related complications. Major progresses have been achieved in the diagnosis and treatment of PE over the last two decades. Nevertheless, some of elderly patients' specificities still represent important challenges in the management of PE in this population, from its suspicion to its diagnosis and treatment, and are discussed in this review. Perspectives for the future are from a diagnostic point of view the potential implementation of age-adjusted D-dimer cut-offs that will allow ruling out PE in a greater proportion of elderly patients without the need for thoracic imaging. From a therapeutic point of view, acquisition of post-marketing clinical experience with the use of new oral anticoagulants is still necessary, and in the meantime, these drugs should be prescribed with great caution in thoroughly selected elderly patients.

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## 1. Introduction

Elderly patients are known to be not only at increased risk of venous thromboembolism (VTE) including pulmonary embolism (PE) [1,2] but also at increased risk of adverse clinical outcomes such as VTE recurrence, anticoagulation (AC) related bleeding and death [2,3]. Despite major progresses in the diagnosis and treatment of PE, recent data from a Swiss national cohort on patients  $\geq 65$  years with objectively confirmed PE still show a high overall mortality rate of 9.4% at three months [4]. The objective of this review is to highlight some specific aspects and challenges in the management of PE in elderly patients.

## 2. Suspecting pulmonary embolism in the elderly: a real challenge

One of the major challenges in elderly patients lies in fact well upstream to the actual treatment of confirmed PE and consists of answering the following question: should I suspect PE in this patient? Indeed, ageing is associated with an increasing prevalence of cardiac or pulmonary comorbidities, and as none of the clinical symptoms and signs of PE is specific to PE, the initial assessment of patients can be really puzzling for the clinician. Whereas typical symptoms and signs suggestive of PE are found in the majority of patients with PE who do not have pre-existing cardiac or pulmonary diseases [5], this is not the case for elderly patients. In small retrospective series of elderly patients with confirmed PE, clinical presentation is shown to differ from younger

patients, syncope being more often present [6–8] whereas pleuritic chest pain is consistently less frequently reported than in younger patients [8–10].

The consequence of nonspecific clinical presentation can be a delay from onset of symptoms to diagnosis. As recently shown, almost 20% of patients with suspected PE included in large management outcome studies present with symptoms lasting for more than 7 days, with age identified as an independent determinant of delayed presentation on multivariate analysis [11]. On the other hand, because of increasing availability of imaging techniques, especially CT pulmonary angiogram (CTPA), it can be tempting to systematically add PE to a list of differential diagnoses without refining clinical assessment [12]. Such a strategy is obviously not acceptable not only in terms of costs but also because of the potential nephrotoxicity of the iodine contrast in a population with a high prevalence of renal insufficiency [13] and hence at higher risk for contrast-induced nephropathy [14]. Finding the balance between undersuspicion and oversuspicion of PE is therefore a particularly challenging issue in the elderly. Moreover, clinical presentation not always correlates with the extent of PE. A central PE can be almost asymptomatic in an elderly patient with limited mobility, whereas a small peripheral PE can cause severe dyspnoea in a patient with reduced cardio-respiratory reserve.

On physical examination, tachycardia ( $>100/\text{min}$ ), tachypnea ( $\geq 20/\text{min}$ ) and signs of deep vein thrombosis (DVT) are more frequently observed in patients with PE than in those without PE [9], but the strength of association of these signs with PE is weaker in elderly patients than in younger patients [15]. As an example, the positive likelihood ratio of lower limb pain on palpation and/or oedema is 5.4 (3.1–9.6) in patients  $<50$  years compared to only 2.0 (1.4–2.9) in patients  $>75$  years [15]. No single symptom or sign can therefore confirm

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or exclude PE, even less so in the elderly, but the presence of a given combination can raise its suspicion. As for clinical features, findings on the general first line tests such as oxygen saturation, electrocardiogram and chest X-ray are neither sensitive nor specific for the diagnosis of PE and can at best help to increase or decrease its probability [5].

A particular effort is thus needed to identify venous thromboembolic (VTE) risk factors that could increase the level of suspicion, as VTE events are less often “unprovoked” in elderly patients [16]. The most relevant risk factors to seek for in this age category are the presence of cancer, recent hospital stay or reduced mobility for any reason, and past history of VTE. At the end of this initial assessment, a certain percentage of patients will be identified as having suspected PE. The first step in the diagnostic strategy will then be to establish the clinical pre-test probability.

### 3. Diagnostic strategy of pulmonary embolism in the elderly

#### 3.1. First essential step: clinical probability assessment

Clinical probability assessment is a crucial step from which further diagnostic strategy and interpretation of some results depend. Indeed, the negative or positive predictive value of any diagnostic test depends not only on its intrinsic characteristics but also on the prevalence of disease in the tested population. Establishing a clinical pre-test probability corresponds to selecting a patient population in which the prevalence of disease will be lower or higher, therefore increasing the diagnostic performance of a test performed in that group of patients. Clinical probability can be assessed implicitly with a good discriminative power demonstrated in early clinical studies in the 1990s such as PIOPED [17] when performed by experienced or specifically trained physicians. Inter-observer reproducibility of this method is however poor with a kappa of 0.33 [18], which means that two different physicians are highly likely to classify a patient in different clinical probability categories. Over the last decade, clinical prediction rules have thus been developed to standardise the initial assessment of patients with suspected PE.

The Wells score separates patients into three different categories of low, intermediate and high clinical probability, and can also be used in a dichotomised manner, PE likely versus PE unlikely [19]. It has been widely validated in prospective management outcome studies [20,21]. The Geneva score in its original version needed arterial blood sample and chest X-ray [22] hence the development and validation of a revised Geneva score including only clinical characteristics [23–25]. None of the different scores can be considered superior to the others [26]. The important issues are first to apply the right score to the right population (i.e. Wells in outpatients and inpatients, Geneva score only in outpatients) and second to know the sensitivity of the D-dimer test that will be used (see below). Of note, increasing age has no significant impact on the performance of the Geneva and Wells scores, with similar area under the ROC curves in all age categories (0.69–0.78) [27].

#### 3.2. Performance of D-dimers in the elderly

The diagnostic utility of D-dimers lies in their high sensitivity and hence their capacity to exclude PE when below a certain cut-off (“negative D-dimers”) without further investigations [28]. In patients with “non-high” clinical probability (low and intermediate groups in a three category score or unlikely group in a dichotomic score), a highly sensitive negative D-dimer safely excludes PE without additional investigations [26]. Sensitive D-dimer tests include those performed by the ELISA technique (median sensitivity 99%; Vidas®, Stratus®, AxSYM®) and by quantitative latex methods (median sensitivity 96%; STA Liatest®, Tinaquant®) [29]. Lower sensitivity D-dimer tests by whole blood agglutination methods (Simpli-RED®) are semi-quantitative, and with a median sensitivity of 87% they can safely exclude PE only in patients with low clinical probability (low group of a three category score or unlikely group in a dichotomic score) [26]. In patients with

high clinical probability or likely PE, the negative predictive value of even a highly sensitive D-dimer test will be insufficient to exclude PE. D-Dimer measurement is thus skipped, and diagnostic work-up directly proceeds to imaging (see next section and Fig. 1).

D-Dimers are fibrin degradation products and their plasmatic level increases not only in the presence of a clot, but also in various other situations such as cancer, infectious or inflammatory states, pregnancy or during post-operative periods. They thus do not represent a specific marker of VTE. D-Dimer levels also increase with age, leading to a reduced specificity of the test in the elderly [30,31]. This means that the probability of having a negative test result is reduced and hence the number of patients needed to test to exclude one PE (NNT) without further testing is higher. Indeed, whereas PE can be ruled out in the presence of non-high clinical probability and negative D-dimers in one out of 3 outpatients presenting to the emergency room with suspected PE [28], it can be excluded in only one out of 9 patients with cancer [32] and one out of 20 patients >80 years [33]. As current diagnostic strategies for PE include imaging (most often CTPA) in patients with positive D-dimers, lack of specificity of D-dimers in the elderly leads to a high proportion of these patients undergoing CTPA.

The question of a higher D-dimer cut-off in elderly patients was raised a decade ago [34], but studies confirming the potential security of such a strategy by retrospectively applying age-adjusted cut-offs to large prospective cohorts of consecutive patients with suspected VTE were published between 2010 and 2012 [35–39]. A recent systematic review and meta-analysis of studies in patients with suspected VTE (PE and DVT) showed a dramatic decrease of the pooled specificity from 66.8% (95% CI 61.3–72) in patients <50 years to 14.7% (95% CI 11.3–18.6) in patients >80 years with the conventional D-dimer cut-off [40]. When an age-adjusted cut-off was used (age  $\times$  10  $\mu$ g/L in patients >50 years), specificity was higher in all age categories, the difference with conventional cut-off being most pronounced in patients >80 years with a specificity of 35.2% (95% CI 29.4–41.5). This increase in specificity was of course obtained at the expense of a decrease in sensitivity, which was however small (sensitivity remained above 97% in all age categories) and not statistically significant. A large multicentre prospective management outcome study validating age-adjusted D-dimer cut-offs (age  $\times$  10  $\mu$ g/L in patients > 50 years) in patients with suspected PE has just been published. This study showed that the use of age-adjusted D-dimer cut-offs instead of the 500  $\mu$ g/L cut-off increased the proportion of patients in whom PE could be excluded without further imaging. Among patients 75 years or older with non-high clinical probability, this proportion increased dramatically from 6.4% (95% CI, 4.8%–8.5%) with standard cut-off to 29.7% (95% CI, 26.4%–33.3%) with age-adjusted cutoffs. Moreover, this study confirmed the safety of such a strategy, with a very low 3-month thromboembolic event rate of 0.3% (95% CI, 0.1%–1.7%). REF: Righini M. et al. JAMA 2014; 311:1117–24. The use of age-adjusted D-dimer cut-offs could thus allow reducing the cost and burden of unnecessary imaging studies in a significant proportion of elderly patients.

#### 3.3. Imaging techniques in the elderly: how to choose the right one

A major progress over the last two decades in the diagnosis of PE has been the development of non-invasive alternatives to pulmonary angiography which was the only available imaging technique and still the gold standard [41]. Historically, ventilation/perfusion lung scintigraphy (V/Q scan) was the first imaging technique compared to pulmonary angiography in the PIOPED study in 1990 [17]. The main drawback of V/Q scan was a very high proportion of non-conclusive results. This led to the development of non-invasive diagnostic strategies (rather than a stand-alone test), including a sequential assessment of clinical probability, D-dimer level measurement and lower limb compression ultrasonography (CUS) in association with V/Q scan, allowing to confirm or exclude PE in 94% of patients without additional angiography [28,42].

Over the last ten years, CTPA has largely replaced V/Q scan. With the introduction of newer generation multidetector CT (MDCT), lower limb CUS has gradually been abandoned as a routine additional test. A multicentre randomised controlled study published by Righini et al. in 2008, demonstrated that excluding PE by MDCT without CUS was equally safe to the previously validated strategies including CUS, with a very low 3 month thromboembolic event rate of 0.3% (95% CI 0.1–1.2) [25]. The safety of CTPA was further confirmed in a meta-analysis by Mos et al. including more than 3000 patients [43].

Although MDCT has become the most widely performed imaging modality in patients with suspected PE, its use is not infrequently limited in elderly patients because of the high prevalence of renal insufficiency in this population. Recent diagnostic outcome studies with MDCT excluded patients with an estimated CrCl <30 mL/min because of the potential nephrotoxic effects of iodine contrast. This seems a safe strategy, as confirmed in the study by Righini et al. in which none of the included patients with a creatinine clearance  $\geq 30$  mL/min (calculated by the Cockcroft-Gault formula) developed acute renal failure or needed dialysis. Patients with suspected PE and severe renal failure, a group mainly represented by elderly patients, are however not rare. In the same study, for instance, 6.4% of the screened consecutive outpatients with suspected PE had a CrCl <30 mL/min. Lower limb CUS and V/Q scan are therefore still performed on a regular basis when renal failure is not rapidly reversible after hydration and MDCT remains contra-indicated.

In a patient with suspected PE, the presence of a proximal DVT is highly predictive of PE (positive likelihood ratio of 42) allowing to rule in the diagnosis of PE without further thoracic imaging [44]. Interestingly, data from two large prospective management outcome studies enrolling more than 1000 consecutive patients with suspected PE show a higher yield of CUS in elderly patients compared to younger patients. Proximal DVT was indeed found in 7% of patients <40 years and in 25% of those >80 years, corresponding to a NNT of only 4 in the older group to rule in one PE without further imaging [33]. It thus seems useful to perform CUS in elderly patients with severe renal failure as the first imaging test. However, an unfortunately often encountered reasoning mistake is to stop investigations after a normal CUS. This is of course not acceptable

as the absence of proximal DVT does not rule out PE, and further thoracic imaging with V/Q scan is necessary in this setting unless an alternative diagnosis has become obvious or PE is no longer suspected.

As mentioned earlier, the main limitation of V/Q scan is a significant proportion of nondiagnostic results, which increases with age (from 32% in patients <40 years to 58% in those >80 years) [33] due to a higher prevalence of cardio-pulmonary comorbidities and chest X-ray abnormalities [45]. V/Q scan results thus need to be interpreted in conjunction with clinical probability and CUS, the latter sometimes being repeated at a week's interval in order to safely exclude PE [46]. Whenever possible, CTPA should therefore be preferred, especially as age was shown to have no significant influence on the good diagnostic performances of this test [47].

Finally, magnetic resonance angiography (MRA) is currently not an option for the diagnosis of PE, mainly due to a high proportion (up to 25%) of poor quality examinations for technical reasons as well as a low sensitivity (only 78%) as shown in the PIOPE III study [48].

In summary, the performance of clinical probability scores is similar in elderly patients and in younger patients and their use should be highly encouraged. The major differences in elderly patients lie in the reduced specificity of D-dimers and the higher prevalence of severe renal insufficiency contra-indicating CTPA. The main perspective for improving the performance of diagnostic strategies of PE in the elderly in the near future is the introduction of age-adjusted D-dimer cut-offs that would increase the proportion of patients in whom PE could be ruled out without imaging, and extend the cost-effectiveness of sequential diagnostic strategies to this age group [49].

#### 4. Management of pulmonary embolism in the elderly

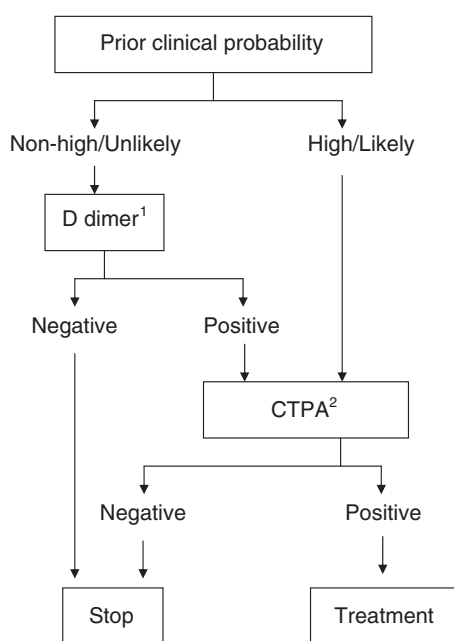
Once diagnosis has been confirmed, the initial management of an elderly patient with non-massive PE often differs from a younger patient. There is growing evidence that selected patients with non-massive PE can be treated safely on an outpatient basis, provided they are identified as being at low risk using validated prognostic scores [50,51]. The only prospective randomised controlled study available to date [52] is based on the PESI (Pulmonary Embolism Severity Index) score [53] that sets the threshold of low risk at  $\leq 85$  points. Considering the fact that each year of age gives one point and male gender 10 points (besides all the 9 other items assessed), it is easy to infer that most elderly patients are not classified at low risk and thus cannot be safely treated as outpatients, a finding which is in accordance with empirical clinical experience. In a Swiss national cohort of patients  $\geq 65$  years with PE, the simplified version of the PESI score classified a slightly higher proportion of patients as low risk (40% versus 36%) and had a good prognostic accuracy (area under the ROC curve 0.77) [4]. Despite its greater ease of use, the demonstration of its safety is however not as robust as for the original PESI score.

Besides the frequent need for hospitalisation and overall worse prognosis, another major difference between elderly and younger patients with PE is the greater difficulty in managing and higher complication rates of anticoagulant drugs as discussed below.

In unstable patients with acute PE, recent retrospective data suggest that thrombolytic therapy and inferior vena cava filter placement could be associated with lower mortality, even in the elderly [54,55].

##### 4.1. General considerations on therapeutic anticoagulation in elderly patients with PE

The aim of anticoagulation (AC) in the acute phase of PE is to prevent thrombus extension. As soon as the diagnosis is confirmed, therapeutic AC should thus be initiated without delay unless there is an absolute contra-indication (in which case an inferior vena cava filter should be placed) [56]. In patients with high probability and those with intermediate probability in whom diagnostic work-up will not be completed within 4 h, initiating therapeutic AC is also recommended [56]. Standard options



**Fig. 1.** Diagnostic algorithm for pulmonary embolism. 1) Highly sensitive D-dimer test. 2) Computed tomography pulmonary angiography. In patients with severe renal failure with contra-indication to CTPA, lower limb compression ultrasound +/- V/Q scan are performed sequentially (see text).



for the initial treatment of VTE consist of subcutaneous (sc) fondaparinux, sc low molecular weight heparins (LMWHs) and intravenous (iv) or sc unfractionated heparin (UFH), with a grade 1A level of recommendation for all these substances in the Evidence-Based Clinical Practice Guidelines of the American College of Chest Physicians (ACCP) [56]. Initial parenteral AC is then overlapped and followed by an oral vitamin K antagonist (VKA) with a target INR of 2.5 (2.0–3.0). A major concern when prescribing therapeutic AC in elderly patients is the higher risk of haemorrhage related to higher prevalence of co-morbidities and co-medication, altered pharmacokinetics and pharmacodynamics, and the risk of falls. However, data on nonagenarians with PE from the RIETE registry showed that if fatal outcomes are considered, the incidence of fatal PE by far exceeds fatal bleeding (5.9% versus 2.2%) [57].

The most significant age-related change with an impact on drug pharmacokinetics is the gradual decline in renal function even in the absence of any renal disease [58], and renal impairment is a true concern for many AC drugs including NOA as discussed below. Serum creatinine level is unreliable for the estimation of renal function in elderly patients [59], and a value within the “normal” range can already be associated with significantly impaired renal function. Routine calculation of estimated creatinine clearance (CrCl) is therefore recommended in all geriatric patients [60]. None of the most commonly used formulas such as the Cockcroft–Gault (CG) [61], Modification of Diet in Renal Disease (MDRD) [62] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [63] has been specifically validated in elderly patients, but it is well known that CrCl estimation is consistently higher with the latter two formulas compared to the CG formula in older adults [64,65]. For drug dosing, the CG formula is recommended [66], and most clinical trials testing AC in the therapeutic range excluded patients with a CrCl <30 mL/min estimated by the CG formula as follows:  $\text{CrCl} = [(140 - \text{age}) \times \text{weight in kg}] / (72 \times \text{serum creatinine in mg/dL})$  in males, and the same formula minus 15% in females [61].

Age-related pharmacodynamic changes are most prominent for VKAs, with a higher sensitivity of elderly patients to these drugs [67,68]. Finally, because of the higher prevalence of cardiovascular diseases in elderly patients, they are more likely to be on antiplatelet agents (APA) at the time of PE diagnosis. Unless there is an absolute indication to APA such as recent coronary stents, transient discontinuation of APA during the AC period should in our opinion be considered on a case-by-case basis in order to reduce haemorrhagic risk, as the benefit of such a combination in terms of cardiovascular outcomes has not been proven [69,70].

Duration of AC usually varies from 3 months in the case of a reversible provoking factor to extended therapy without limitation of duration in cases of recurrent unprovoked episodes [56]. In the latter situation, the benefit–risk balance and patient's preferences should be reassessed on a regular basis. In cases of cancer-associated VTE, AC is continued as long as the cancer is not considered in remission [56].

#### 4.2. Initiating therapeutic anticoagulation in elderly patients with PE

For initiating therapeutic AC in the acute phase, LMWHs or fondaparinux are always preferred to UFH whenever possible because of more predictable pharmacokinetics without the need for routine monitoring, an overall higher efficacy and safety and a lower incidence or absence of heparin-induced thrombocytopenia for LMWHs and fondaparinux, respectively [71].

The high prevalence of renal insufficiency in elderly patients, rising to more than 50–60% of adults >75 years living in long term facilities [72], limits the universal prescription of LMWH and fondaparinux in these patients. Evidence is lacking in the literature to define the optimal CrCl threshold under which LMWHs should be contra-indicated [73]. A meta-analysis of 12 studies including almost 5000 patients showed a higher rate of major bleeding on LMWHs in patients with CrCl <30 mL/min compared to  $\geq 30$  mL/min (5% versus 2.4%) [74], but the risk of major bleeding on LMWHs for patients with mild renal impairment (CrCl 30–60 mL/min) is less well documented. Nevertheless, at

therapeutic dosage, even mild decreases in CrCl have been shown to be associated with accumulation of LMWHs [75]. Great caution is thus needed, especially with LMWHs with the lowest molecular weight chains (whose clearance is mainly renal) even in patients with mild renal impairment, particularly in the frail, underweight, very old patients and if treatment is prolonged for more than a few days. Paucity of data does not allow strong recommendations in this setting, but early detection of overdosage by measuring anti-Xa activity or empirical LMWH dose reduction are two different strategies that have been suggested [71]. In the absence of sufficient safety data [76], fondaparinux (whose clearance is exclusively renal), should in our opinion be prescribed with even greater caution, especially in case of prolonged treatment, and preferably avoided in elderly patients with borderline values of CrCl close to 30 mL/min.

#### 4.3. Managing the switch to VKAs in elderly patients with PE

The initial parenteral AC phase is overlapped and followed by VKA, and the parenteral drug is continued for a minimum of 5 days and can be stopped when INR in the target range (2.0–3.0) has been achieved on 2 consecutive days. In clinical and pharmacogenetic models for predicting maintenance dose, age is associated with lower dose requirements [77]. Low dose VKA initiation algorithms have been suggested in the elderly to reduce bleeding complications [78] as the initial phase of AC is the period at highest haemorrhagic risk [79]. Several bleeding scores have been developed in the setting of VTE [80–83], but a recently published analysis on patients from the Swiss national VTE cohort showed poor performance of all these scores in patients >65 years (area under the ROC curves ranging from 0.49 to 0.6) [84].

An important practical issue in VKA management in elderly patients is to increase the frequency of INR controls as soon as an acute illness or changes in diet or concomitant medications occur. Intensity of AC is a major determinant of haemorrhagic complications [85], with an exponential increase in bleeding risk with INRs > 4.5 regardless of age [86]. A recent prospective study including more than 4000 elderly patients >80 years naïve to VKA in whom VKA was initiated (25% with VTE) showed a low rate of major bleeding (1.87 per 100 patient-years) in these patients followed-up in Italian anticoagulation clinics (median time in therapeutic range 62%) suggesting that careful monitoring can highly improve the security of VKAs even in very old patients [79]. Patient information is also essential and reduces AC-related haemorrhagic complications in elderly patients [87].

#### 4.4. The role of new oral anticoagulants (NOA) in elderly patients with PE

Recent phase III randomised trials comparing NOA to standard therapy in open-label or double-blind double-dummy designs in patients with acute VTE have all proven the non-inferiority of NOA compared to LMWH/VKA in terms of efficacy with better security profiles, and especially a consistently lower rate of intracranial haemorrhage (ICH). Current NOA can be divided in two classes: direct thrombin inhibitors (DTI) represented by dabigatran studied in VTE in the RECOVER trial [88] and direct factor Xa inhibitors represented by rivaroxaban (EINSTEIN studies) [89,90], apixaban (AMPLIFY study) [91] and edoxaban (HOKUSAI study) [92]. Many review articles have been written following publication of these phase III trials including a very recent review in this journal [93,94], so detailed results will not be discussed in this paper. We will rather focus on some important concerns that arise with the prescription of these drugs in elderly patients, who were moreover better represented in AF studies than in VTE studies.

The main preoccupation with dabigatran in the geriatric population is obviously its renal route of excretion (80%). Even in the AF study RE-LY, the proportion of patients with moderate renal insufficiency (30–49 mL/min) was only 19% and of patients <50 kg only 0.02%, characteristics that differ widely from those of frail elderly patients of real life [95].

Another obstacle to compliance with dabigatran could be the higher incidence of dyspepsia (11% versus 5.8% on warfarin in RE-LY). One potential advantage of factor Xa inhibitors is their predominantly extrarenal excretion, only one third of rivaroxaban in its active form, and one fourth of apixaban being eliminated by the kidneys. Nevertheless, according to manufacturers, exposure to these drugs may still be 30–50% higher in older patients [96] hence the reduced doses of NOA used in patients with advanced age and/or renal impairment in phase III AF studies. In VTE trials however, no reduced dose was studied (except for edoxaban). Interestingly, a pooled analysis of EINSTEIN-VTE studies showed a particularly higher safety profile of rivaroxaban compared to enoxaparin/warfarin in patients defined as fragile because of age, moderate or severe renal impairment or low body weight, with major bleeding rates of 1.3% versus 4.5% (HR 0.27; CI 0.13–0.54) in this subgroup [97]. Although a subgroup analysis, these data are derived from a large number of patients (1573 patients; 19% of all included patients). A possible disadvantage of factor Xa inhibitors is metabolism via the CYP-3A4 with the potential for drug–drug interactions in elderly patients with multiple co-medications.

Other more general concerns with NOA are the absence of any monitoring (which is a great advantage but at the same time raises the question about adherence), the higher cost of these medications and the absence of a specific antidote in case of acute bleeding.

In summary, although NOA seem to be promising alternatives for the treatment of VTE [98], data remain limited in elderly patients, as well as in patients with moderate renal impairment (CrCl 30–50 mL/min). In order to increase the safety of prescription of these new drugs, all physicians should be fully aware of the need to use the CG formula for estimation of CrCl to determine eligibility of patients for NOA. The use of the MDRD formula has recently been shown to make 15% of patients >80 years become incorrectly eligible [65] with the potential for serious haemorrhagic outcomes in these cases of unsuspected renal insufficiency. Particular vigilance is necessary in the frail geriatric population that was poorly represented in clinical trials, and acquiring a certain clinical experience with these new drugs is crucial before generalising their use to the geriatric population. Data from post-marketing registries will be very precious in this setting.

## 5. Conclusion

Awareness of elderly patients' specificities can be of great help in taking care of these patients in the setting of PE, from its clinical suspicion to diagnostic work-up and treatment. Despite major advances in diagnostic strategies and therapeutic options, many challenges remain. Perspectives for the future are the implementation of age-adjusted D-dimer cut-offs that will allow ruling out PE in a greater proportion of elderly patients without additional imaging, and acquisition of clinical experience in the use of new oral anticoagulants that in the meantime should in our opinion be prescribed with great caution in thoroughly selected patients in geriatrics.

## Learning points

- Elderly patients are not only at higher risk of VTE, but also at higher risk of unfavourable outcomes including anticoagulant-related haemorrhagic complications.
- As clinical symptoms and signs are aspecific, VTE risk factors should be actively searched for in the initial assessment to refine PE suspicion.
- With conventional cut-offs, the diagnostic performance of D-dimers is reduced in elderly patients, but new age-adjusted cut-offs increase the percentage of elderly patients in whom PE can be ruled out without imaging.
- The high prevalence of renal impairment in elderly patients limits the widespread prescription of some anticoagulants such as fondaparinux, LMWHs and NOA.

- Acquiring post-marketing clinical experience in the use of NOA in elderly patients is necessary, and these new drugs should in our opinion only be prescribed with great caution in thoroughly selected patients in geriatrics.

## Conflict of interests

The authors declare no conflicts of interest associated with this publication.

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