Diagnosis and Treatment of Pulmonary Embolism in Challenging Populations

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Abstract

Although the diagnostic and therapeutic approach to pulmonary embolism (PE) has been considerably improved and standardized in recent years, special populations such as pregnant patients and those with impaired renal function or cancer still represent a clinical challenge and a detailed knowledge about the available diagnostic and therapeutic alternatives is mandatory to provide best evidence-based care for these difficult-to-treat patients. Although this review aimed to summarize the most important aspects in this field, the reader is referred to the original studies cited here and dedicated guideline and guidance documents for more detailed information.

Keywords
- pulmonary embolism
- pregnancy
- cancer
- chronic kidney disease

Zusammenfassung

Obwohl in den letzten Jahren Diagnostik und Therapie der Lungenembolie deutlich verbessert und standardisiert wurden, stellen Patienten in der Schwangerschaft, mit eingeschränkter Nierenfunktion oder einer Krebserkrankung immer noch eine klinische Herausforderung dar, und ein detailliertes Wissen um verfügbare diagnostische und therapeutische Alternativen ist Voraussetzung, um eine gute evidenz-basierte Versorgung dieser schwer zu behandelnden Patienten zu gewährleisten. Wenngleich diese Übersichtsarbeit die wichtigsten Aspekte hierzu zusammenzufasst, wird der Leser für weitergehende Informationen auf Originalarbeiten sowie Leitlinien zu diesem Thema verwiesen.

Schlüsselwörter
- Lungenembolie
- Schwangerschaft
- Krebserkrankung
- chronische Nierenerkrankung

Introduction

Although pulmonary embolism (PE), as a manifestation of venous thromboembolism (VTE), is a common condition and evidence for diagnostic workup and treatment is extensive and summarized in dedicated guidelines,[1,2] some common clinical scenarios are especially challenging, because standard diagnostic approaches to suspected PE, i.e. pre-test probability, followed by D-dimer testing and/or imaging, may not be feasible (for instance, in pregnancy or cancer patients); because some PE patients may be at higher risk for thromboembolic or bleeding complications (such as cancer or patients witch chronic kidney disease [CKD]) or because standard anticoagulants may be contraindicated (such as vitamin K antagonists [VKAs] or direct, non-vitamin K affecting oral anticoagulants [NOACs] in pregnant PE patients). The following review will discuss the most common challenges of PE diagnosis and treatment in pregnancy, active cancer or CKD. For a more detailed guidance, the reader is referred to dedicated guideline and guidance documents.

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Diagnosis and Treatment of PE in Pregnancy

Special VTE Epidemiology in Pregnancy

Venous thromboembolism still is one of the leading causes of maternal death in the western world.[3] With an incidence of 1.2/1,000 pregnancies, VTE is a common complication of pregnancy, which translates into a fivefold risk compared with non-pregnant women.[4] A relevant proportion of VTE in pregnancy manifests as PE, which will affect both maternal and foetal health and the highest risk for thromboembolic complications is observed between the 38th gestational week and 6 weeks post-delivery, when the risk increase is up to 20-fold of that of non-pregnant women.[5] Of note, in pregnancies following in vitro fertilization (IVF), the risk of VTE is even higher: in a large cross-sectional study from Sweden, IVF was associated with an overall VTE risk of 4.2/1,000 women (vs. 2.5/1,000 in women with natural pregnancies; hazard ratio [HR] 1.77, 95% confidence interval [CI] 1.41–2.23) (Henriksson P, BMJ 2013; 346:e8632). Although this risk increase was observed during the whole pregnancy, it was particularly increased during the first trimester (HR, 4.22), during which VTE much more often manifested as PE (0.3/1,000 after IVF vs. 0.04/1,000; HR, 6.97, 95% CI, 2.21–21.96).

Although diagnosis and treatment of PE have seen important improvements over the last two decades, management of suspected or confirmed PE in pregnant patients is still challenging for various reasons, most of which are highlighted below.

Challenge 1: Overlap of Symptoms of Pregnancy and VTE and Failure of Diagnostic Algorithms

One of the major challenges in pregnancy relates to the physiological cardiopulmonary changes and their corresponding symptoms. As pregnancy progresses, lower extremity pain and oedema, exertional dyspnoea, tachycardia and palpitations are common. Consequently, established pre-test probability scores such as the Wells score[6,7] for suspected deep vein thrombosis (DVT) or the Geneva score for suspected PE[8] are of limited value in assessing the likelihood of VTE. Furthermore, D-dimer physiologically increase during pregnancy[9,10] so that established VTE diagnostic algorithms ('negative D-dimer can safely rule out VTE in patients with low pre-test probability scores') are of little help in pregnant patients with suspected VTE. Although this algorithm statement per se is also correct for pregnant patients with suspected PE, the clinical feasibility is impaired by the fact that negative D-dimer levels are rare in pregnant women. Pregnancy-specific algorithms or pregnancy-adjusted D-dimer cut-offs have been suggested[11] but, so far, they need further validation before their use can be recommended. Consequently, the approach to suspected PE in pregnant patients requires dedicated clinical experience.

Challenge 2: Potential Harm from Radiation or Contrast Media in Diagnostic Procedures

Due to the potential maternal and foetal harm, every suspicion of VTE needs immediate, safe and effective confirmation or exclusion. Because of the limitations of pre-test probability scores and D-dimer testing, imaging procedures are the mainstay of the diagnostic process. However, the accuracy of venous ultrasound is again limited, since only a relatively small proportion of VTE in pregnant patients manifest as infra-inguinal DVT which can be easily detected by compression ultrasound.[12,13] Iliac DVT is relatively common in pregnant women but ultrasound examination of iliac veins is challenging, also because of the pregnancy-related anatomical changes which may lead to venous compression.[13] Diagnostic alternatives include computed tomography (CT) or magnetic resonance (MR) venography for iliac vein imaging or CT pulmonary angiography or lung scintigraphy (ventilation–perfusion [VQ] scan) for pulmonary arteries. Although well established, these imaging procedures carry specific risks. CT scanning requires the use of contrast media with the risk of anaphylactic reactions, hyperthyroidism or renal injury. Furthermore, the radiation exposure to the pelvic region (for iliac vein imaging) or to the chest (for suspected PE) increases the risk for radiation embryopathy or breast cancer.[14,15] A lower maternal radiation exposure can be expected from VQ scanning but the foetal radiation exposure is higher, since radioactive tracers will pass the placenta. MR imaging does not carry the radiation risk but the most commonly used contrast media such as gadolinium cross the placenta and embryotoxicity cannot completely be ruled out.[16] Finally, MR imaging of the pulmonary vasculature has not been sufficiently validated in pregnant women with suspected PE.

As a consequence of all these challenges, the diagnostic approach to PE in pregnancy needs both standardization and an individualized, tailored approach based on clinical experience with this clinical scenario. Therefore, such patients should be referred to a specialist care setting because, in a pregnant patient with suspected PE, it is most important to definitively rule out (or confirm PE), since over- or under-treatment with anticoagulants may have deleterious implications for the mother and child. A specialized centre will also have CT protocols established that are dedicated to reduce CT-related radiation dosages for mother and foetus so that the fear of CT-related radiation exposure should no longer exclude a pregnant women from adequate PE diagnosis via CT.

Recommended Diagnostic Strategy for Suspected PE in Pregnancy

If PE is suspected in pregnant women, D-dimer testing (may still be negative in early stages of pregnancy to rule out PE), compression ultrasound (may establish the presence of DVT and, therefore, the indication for anticoagulant therapy without the need for lung scanning) and echocardiography (may be used to detect signs of otherwise unexplained right heart strain or pulmonary hypertension) should be applied first, before the exposure to radiation or contrast media is considered. If these tests remain inconclusive (which is often the case in suspected pregnancy related PE!) and the clinical suspicion justifies further evaluation, radiological imaging procedures should not be withheld. First, a standard chest X-ray should rule out non-PE pathologies such as pleural effusion, pneumonia or pneumothorax. After a normal X-ray result, lung perfusion scintigraphy is sufficient to safely rule out PE, since cardiopulmonary co-morbidities requiring classic VQ scan

are very rare in younger women and, by elimination the ventilation part, radiation exposure as well as examination times can be reduced. If lung perfusion scintigraphy is not readily available or the chest X-ray shows pathological findings, CT pulmonary angiography should be used as the next step. If dedicated test protocols are applied, both lung perfusion scintigraphy and CT pulmonary angiography carry a foetal radiation exposure considerably below 50 mSv, which is the commonly described threshold for radiation-related congenital abnormalities and miscarriages.[15] Of note, a higher cardiac output needs to be considered in CT protocols in late pregnancy to achieve adequate contrast in the pulmonary vasculature.

►Fig. 1 summarizes a feasible clinical pathway for pregnant women with suspected PE. Of note, this pathway is based on expert recommendation and, so far, has not been fully validated.

Recommended Therapy for Pregnancy-Associated PE

Although inconvenient and costly, anticoagulant therapy in pregnancy-associated VTE is usually performed with low-molecular-weight heparin (LMWH) or fondaparinux,[17] because these drugs have been used in pregnancy for nearly two decades with low rates of severe maternal or foetal complications,[18] whereas all oral anticoagulants have serious limitations, which mainly relate to the placenta-crossing of VKAs and direct acting, NOACs. In addition to placental and foetal haemorrhage, coumarin embryopathy is a reported complication especially with VKA exposure between 6 and 12 weeks after last menstrual period[19] and reported abnormalities include mid-face hypoplasia, ocular malformations and skeletal abnormalities.[20,21] Older studies suggested rates up to 30%[22] but more recent data estimate a 7% risk for coumarin embryopathy.

NOACs are rapidly becoming the standard of care in most VTE patients, because, compared with VKA, they offer a favourable efficacy/safety profile and better convenience. However, NOACs are small molecules that cross the placenta[23–25] and the clinical risk of NOAC embryopathy is currently unknown. NOAC exposure in animals indicated a risk of reproductive toxicity at therapeutic to toxic dosages, which manifested as a decrease in implantations, increased implantation loss, malformations, altered ossification and haemorrhagic complications.[23,24,26]

The available data on NOAC exposure in pregnant patients are very limited[23,24,26–28] and, although the risk of embryotoxicity seems to be rather low,[29] the use of NOAC during pregnancy or breastfeeding cannot be recommended.[30]

Because of these serious limitations of oral anticoagulants, LMWH are the treatment of choice for VTE during pregnancy.[18] Similar to the treatment of non-pregnant patients, LMWH dosing in pregnancy is adjusted to body weight. Measurement of anti-factor Xa plasma levels is not generally recommended (also, because target ranges are not well established and pharmacokinetics of LMWH change as pregnancy progresses, due to a change in distribution volume and kidney function) but may help to guide LMWH dosing in difficult situations such as extremely high or low body weights, hereditary antithrombin deficiency or renal impairment.

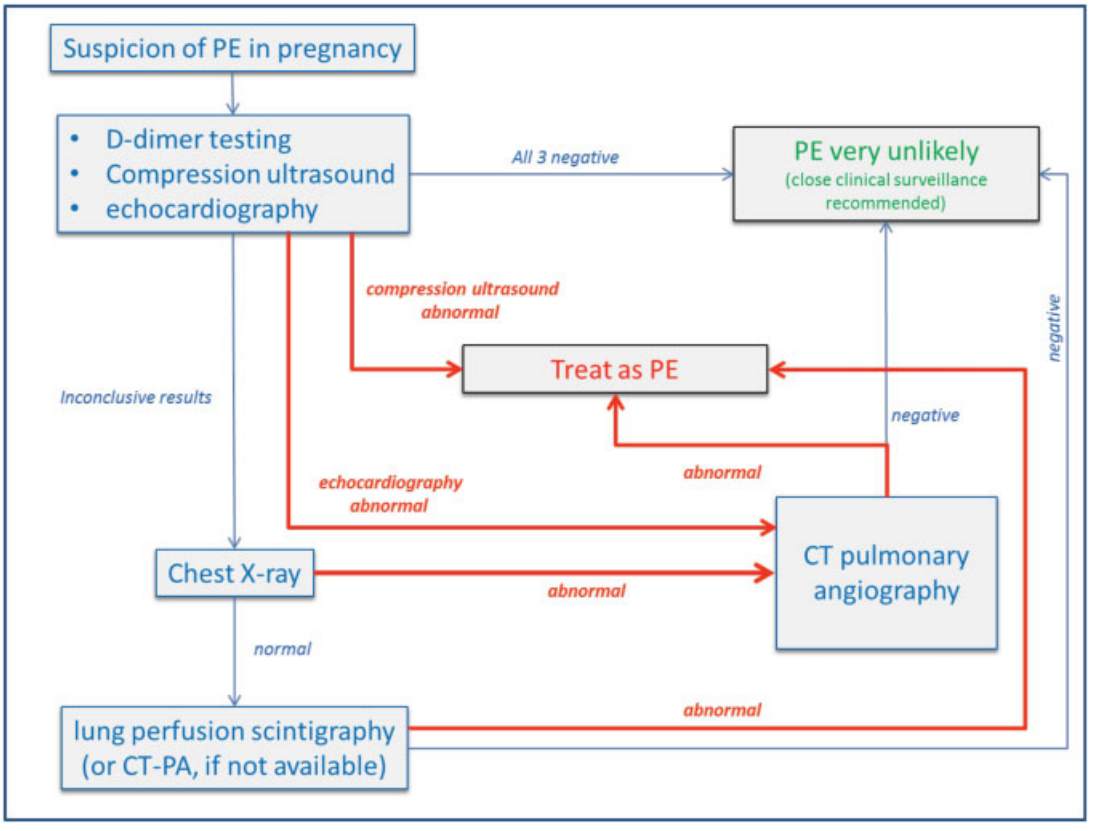

Fig. 1 Proposed diagnostic algorithm for suspected pulmonary embolism (PE) in pregnancy.

To treat pregnancy-associated VTE, LMWH should be administered in therapeutic dosages (175–200 aXa units/kg/day) for at least 3 months.[18] In case of VTE diagnosis in the early phases of pregnancy, LMWH should be continued until 6 weeks post-delivery but a dose reduction to 100 aXa units/kg/day may be considered after 3 months of therapeutic anticoagulation. If VTE is diagnosed after the 28th gestational week, LMWH should be administered in therapeutic dosages (175–200 aXa units/kg/day) until at least 6 weeks post-delivery or until 3 months of anticoagulation are completed (whichever is longer).

Around delivery, LMWH dosing regimen may be switched to twice daily (lower LMWH peak levels) and interrupted with the onset of labour. If no major bleeding occurs, LMWH can be restarted 6 to 12 hours post-delivery. In high-risk VTE patients, switch to unfractionated heparin infusions and induced delivery or caesarean section may be considered.

Anticoagulation in Cancer Patients with PE

Epidemiology of Cancer-Associated VTE

VTE is a significant contributor to morbidity and mortality in cancer patients,[31] since local vein compression, pro-coagulant effects of cancer and cancer therapies, immobility, medical and surgical interventions and the long-term use of central venous catheters increase the risk of VTE up to sevenfold.[32] At the same time, active cancer is a strong and independent risk factor for major bleeding, which makes the anticoagulant treatment of cancer-associated VTE (CAT) especially challenging.[33,34]

The incidence of CT is highly variable across different cancer types, with brain, pancreatic and gastric cancer as well as myeloma being associated with very high risk, colon, liver, rectum and lung cancer with high risk and prostate, cervix, uterus, breast and bladder cancer with comparatively low risk, respectively. At the same time, risk of CAT is increasing with advanced stages of cancer and metastatic disease.[35,36] As with the risk for a primary VTE event, risk of VTE recurrence is dependent on cancer type and stage,[37] which makes the decision to continue or discontinue anticoagulant therapy challenging.

Diagnosis of PE in Cancer Patients

Cancer patients with suspected PE should generally undergo objective testing, for which CT is the current standard. In contrast to patients without cancer, the use of clinical prediction models such as the Wells score or the Geneva score is of limited use in cancer patients, because the presence of cancer alone will increase the score.[6,8] Furthermore, even if these scores indicate a low probability of PE, this result needs to be complemented with low D-dimer values to safely rule out presence of PE, but D-dimer often is elevated in cancer patients.[38,39] Of note, a negative D-dimer test has the same diagnostic value as in non-cancer patients and there is evidence that raising the D-dimer cut-off level to 700 mg/L or using age-dependent cut-off levels may help to increase the proportion of cancer patients in whom PE could be ruled out without imaging with an acceptable failure rate.[38,39] Since the standard diagnostic algorithm of combining pre-test probability scores and D-dimer testing before imaging has limitations, CT scanning is currently the standard approach to establish or rule out PE in most cancer patients. However, many cancer patients also have silent or even bilateral lower extremity DVT at the time of PE suspicion so that a bilateral compression ultrasound of the lower extremities may streamline the diagnosis and treatment decisions in cancer patients, since the presence of DVT and the indication for anticoagulant therapy may reduce the need for CT scanning.

Special Risk for Recurrence and Bleeding

Cancer patients with PE are at an increased risk for VTE recurrence and major bleeding complications compared with non-cancer PE patients. The rate of recurrence is highest during the first 2 weeks after VTE diagnosis and declines thereafter and a failure to rapidly achieve therapeutic levels of anticoagulation has been shown to be an independent predictor of VTE recurrence.[40,41] Early mortality after VTE diagnosis is especially high in cancer patients. In the RIETE registry, all-cause 3-month mortality was as high as 26% for cancer patients and mostly related to active cancer.[42] However, poor outcome was also shown to be related to the increased bleeding risk during anticoagulation therapy and to the high rate of recurrence of VTE.[43] Unfortunately, bleeding complications in CAT patients, although a common clinical problem, are difficult to predict. The existing bleeding prediction scores for VTE patients are not well established yet and have included very few or no CAT patients in their derivatization or validation cohorts. The prognostic risk assessment for future bleeding risk in CAT patients thus remains an urgent but unmet clinical need.

However, although cancer patients with PE are at higher risk of thromboembolic and bleeding complications compared with non-cancer PE patients, the clinical approach to the acute phase of PE is independent from cancer status, because a dedicated assessment of PE severity immediately at the time or presentation is crucial to tailor the following treatment decisions in accordance with the short-term risk of right-heart failure. Therefore, PE patients with our without cancer who present in shock should undergo urgent revascularization, although mechanical revascularization may be more frequently considered in cancer PE due to the increased bleeding risk associated with both active cancer and fibrinolytic therapy. Similarly, in low to intermediate risk PE a more conservative approach, consisting of therapeutic anticoagulation and surveillance may be used, irrespective of cancer status. Of note, the risk assessment of PE severity should always be based on validated scores such as Pulmonary Embolism Severity Index (PESI) or simplified PESI (sPESI),[44,45] all of which include cancer as a prognostic factor. Therefore, the aforementioned risk-adjusted approach to high-, intermediate- or low-risk PE already accounts for the presence or absence of active cancer. On the other hand, the fact that presence of cancer will always result in an increased PESI or sPESI score, CAT patients would generally be excluded from outpatients PE treatment, if the eligibility check for outpatient therapy would solely be based on PESI or sPESI. It seems

reasonable to allow for outpatient PE treatment also in CAT patients, if no other risk factors are present.

Special Situation 'Incidental PE' in Cancer Staging Examinations

With the increased availability and sensitivity of CT and MR, scans are increasingly demonstrating asymptomatic DVT or PE ('clinically unsuspected PE' or 'incidental PE') in cancer patients undergoing routine staging examinations.[46,47] The prevalence of such incidental VTE events has been reported to be in a range of 2 to 6%[48,49] and ~40% of these events are found in lung scans.[50] Naturally, the prevalence is depending on the type of scan and higher in series that report findings from CT pulmonary angiography.[51]

Although asymptomatic, incidental PE is of clinical relevance. Several studies have demonstrated that patients with incidental VTE seem to be at a similar risk to develop symptomatic VTE or mortality as cancer patients with symptomatic VTE.[52,53] As a consequence, current guidelines suggest that incidental PE should be treated similarly as symptomatic CAT,[1,54] which would mean that all cancer patients with incidental PE would receive at least 6 months of anticoagulant therapy or indefinite treatment in case of non-curable cancer. However, no prospective studies have demonstrated a benefit from such a decision and the likelihood of false-positive scan results (especially in segmental and sub-segmental PE) as well as the increased risk of bleeding need to be taken into consideration.

Data for VKA and LMWH in CAT

Several studies have demonstrated that LMWH achieve superior efficacy over VKA in the treatment of cancer-associated VTE. Several smaller studies as well as the CLOT trial[55] and, more recently, the Comparison of Acute Treatments in Cancer Hemostasis (CATCH) trial[56] cumulatively demonstrated a 40% relative risk reduction for VTE recurrence[57] for LMWH compared with warfarin in the treatment of CAT with similar rates for major bleeding. However, at 6 months of therapy absolute rates of VTE recurrence with LMWH were still 7% for tinzaparin[56] and 8% for dalteparin,[55] which in a cancer population that demonstrated mortality rates between 30 and 40%, which was mainly driven by cancer-related death. Based on these data, guidelines currently recommend LMWH over VKA in the treatment of cancer-associated VTE but these recommendations have not been updated in the era of NOACs.

Data for NOAC in CAT

Over the last few years, NOAC have rapidly developed towards a standard therapy in VTE and evidence for NOAC use in CAT is increasing. Post hoc analyses of cancer patients from phase III NOAC trials were summarized in a network meta-analysis, which modelled an indirect comparison against LMWH from the aforementioned LMWH/VKA trials.[57] This indirect comparison suggested that NOAC could be as effective and safe as LMWH in CAT treatment. Over the last 2 years, real-world studies have provided first evidence for NOAC use in CAT and have demonstrated outcome rates for recurrent VTE and major bleeding that were not higher than the rates in the respective LMWH studies.[58–60]

Recently, two randomized controlled trials (RCTs) comparing NOAC against LMWH have reported outcomes for CAT treatment. The Hokusai Cancer[61] study was a large, multinational non-inferiority RCT comparing edoxaban versus dalteparin for CAT therapy. A total of 1,050 patients (mean age, 64 years; 98% active cancer, 53% metastatic disease) were included and followed-up for 12 months. Rate of recurrent VTE was 7.9 versus 11.3% (HR, 0.71, 95% CI, 0.48–1.06) for edoxaban versus dalteparin. Rate of major bleeding was 6.9 versus 4.0% (HR, 1.77, 95% CI, 1.03–3.04) for edoxaban versus dalteparin.

Another randomized trial in SELECT-D[62] cancer patients at risk of recurrence of VTE (SELECT-D) evaluated rivaroxaban versus dalteparin in 406 patients (mean age, 67 years; 59% metastatic disease) over a period of 6 months. Rate of recurrent VTE was 4 versus 11% for rivaroxaban versus dalteparin. Rate of major bleeding was 5 versus 3% for edoxaban versus dalteparin. Further RCTs comparing NOAC against LMWH in CAT treatment are currently on-going.

Recommendation for Anticoagulant Treatment in CAT

Although there is increasing evidence for NOAC use in CAT, it should be recognized that, so far, no direct head-to-head comparisons for NOAC versus LMWH are available and that the existing data are likely derived from less sick cancer patients for whom an alternative to daily LMWH injections was sought. Whereas LMWH can be easily dose-adjusted in case of declining body weight, renal impairment or thrombocytopenia, the fixed dosing of NOAC does not allow for such dedicated treatment tailoring in cancer patients. Furthermore, oral anticoagulation may not be feasible in cancer patients affected by nausea or vomiting. Finally, NOAC metabolism is affected by several drugs that are metabolized via CYP3A4 or p-GP, which includes several antibiotic, antimycotic and antiviral drugs,[63] which are commonly used in cancer patients. Consequently, LMWH offer advantages over oral anticoagulants that go beyond the comparative rates of VTE recurrence or major bleeding and it can be expected that the recommendation to use LMWH as a first line therapy in CAT will probably not change completely. However, based on the currently available evidence, edoxaban and rivaroxaban may be considered as alternatives for patients who are unable or unwilling to continue long-term LMWH therapy. Furthermore, no evidence supports a benefit of LMWH over oral alternatives in the CAT treatment beyond 6 months and a switch to oral anticoagulants may offer such long-term survivors a more convenient and less costly alternative.

Anticoagulation in Patients with Chronic Kidney Disease

Epidemiology of CKD-PE

VTE patients with CKD are especially challenging, since they exhibit a higher risk for VTE recurrence and bleeding complications, compared with patients without renal impairment.[64]

In a sub-study of the RIETE registry, patients with creatinine clearance (CrCl) < 30 mL/min were compared with patients with a CrCl of 30 and higher and were found to be at higher risk for fatal bleeding (0.2% for CrCl > 30 mL/min vs. 1.2% for CrCl < 30 mL/min), fatal PE (1.1 vs. 6.6%, respectively) and overall death (2.6 vs. 16) during the 3-month study period.[65] As a consequence, anticoagulant treatment options need to provide an optimal net clinical benefit.

Data for VKA and LMWH in CKD-PE

Most of the available data on VKA anticoagulation in CKD refer to atrial fibrillation patients and data on VTE are scarce. However, the limitations of VKA anticoagulation in advanced CKD stages can be expected to be similar in atrial fibrillation and VTE and mainly relate to high bleeding rates and unstable international normalized ratio (INR) values. Even though, VKA are still widely used in VTE treatment in CKD patients.

In recent years, warfarin was used as the standard of care comparator in all NOAC phase III trials in acute VTE treatment.[66–71] All these studies consistently reported increase of thromboembolic and bleeding complications for VKA as renal function was declining. Potential explanations for a higher incidence of thromboembolic and bleeding complications may include:

- More unstable INR courses with a higher risk of overdose, which increases the risk of bleeding in CKD.[72]
- Higher age and more complex co-morbidities of CKD patients.[73]
- Harmful side effects of VKA such as accelerated vascular calcification including additional renal decline.[74,75]

However, the evidence for these considerations is weak. In summary, VKA are not providing optimal net clinical benefit for VTE patients with CKD but the underlying pharmacological mechanisms for this established clinical observation are insufficiently understood.

Data for NOAC in CKD-PE

The pharmacological background of NOAC (fixed daily dosing, strong dose–response correlation, comparatively broad therapeutic window, well-defined interaction with coagulation cascade) suggests that this class of compounds may overcome the limitations of VKA therapy in VTE and CKD, although all NOACs are renal excreted to some extent, which introduces the risk of accumulation and relative overdosing. Pre-clinical data indicate that the rate of renal excretion of active NOAC varies from 27% (apixaban) over 35% (rivaroxaban) and 50% (edoxaban) to 80% (dabigatran).[63,76–78] While the high rate of renal excretion for dabigatran has clinical implications, the considerably lower renal excretion rates seen in direct Xa inhibitor (DXI) treatments carry a lower accumulation risk.

These pharmacological observations seem to translate into a profound clinical benefit from VTE treatment with DXI in CKD.

Rivaroxaban: In a dedicated post hoc analysis of the pooled EINSTEIN DVT/PE studies,[79,80] increasing rates of recurrent VTE were observed in CrCl cohorts of > 80; 50 to 79; 30 to 49; < 30 mL/min, which was observed in both rivaroxaban and VKA recipients to a similar degree. In contrast, with declining renal function rates of major bleeding dramatically increased from 1.0% (glomerular filtration rate [GFR] > 80) to 3.4% (GFR < 50 mL/min) in VKA recipients, but not in rivaroxaban-treated patients (0.8% with GFR > 80 compared with 0.9% with GFR < 50 mL/min).

Of note, impaired renal function was not a pre-defined criterion for rivaroxaban dose reduction so that these efficacy/safety findings were derived from standard dosing of rivaroxaban 15 mg twice a day, followed by 20 mg once a day throughout the study. As a consequence of this, the dosing label in the summary of product characteristics (SmPc) differs between VTE (no dose reduction in CrCl below 50 mL/min in the acute phase, but dose reduction to 15 mg once a day in the maintenance phase in CrCl below 30 mL/min is recommended for patients perceived to be at increased risk for bleeding complications) and atrial fibrillation treatment (dose reduction of rivaroxaban to 15 mg for CrCl below 50 mL/min). Rivaroxaban is not recommended for patients with a CrCl of < 15 mL/min in both indications.

Apixaban: In its phase III trial, apixaban was found to have similar efficacy and better safety compared with LMWH/VKA in patients treated for DVT and PE.[68] Although no dedicated post hoc analysis exist for CKD patients, the appendix of this publication also includes sub-group analyses on patients with renal impairment. Overall, apixaban efficacy was established across the evaluated spectrum of renal function (CrCl < 30 mL/min was an exclusion criterion) but a significant reduction of bleeding events by apixaban was only seen in patients with normal renal function, whereas bleeding rates similarly increased for apixaban and LMWH/VKA as renal function declined.[68,81]

A dose reduction of apixaban from 5 mg twice a day to 2.5 mg twice a day is recommended if two of the three following criteria are fulfilled: body weight < 60 kg, age > 80 years and/or creatinine level > 133 µmol/L or > 1.5 mg/dL.

Edoxaban: The third DXI, edoxaban, also demonstrated non-inferiority in the effectiveness of VTE therapy compared with LMWH/VKA with significantly reduced bleeding rates in edoxaban recipients.[69] No dedicated post hoc analysis for CKD stages exist but in the appendix of the original trial report, a comparison of patients with CrCl higher or lower than 50 mL/min is presented. Similar to the findings of the apixaban trial, edoxaban reached consistent efficacy with non-inferiority towards LMWH/VKA in both sub-groups, whereas a significant reduction in bleeding complications was observed only in patients with normal renal function. With declining renal function, bleeding rates numerically increased for edoxaban and LMWH/VKA.[69] In a sub-group analysis, therapy with 30 mg of edoxaban versus warfarin was compared for patients with a GFR 30 to 45 mL/min, a body weight < 60 kg or with accompanying therapy with P-glycoprotein inhibitors (pre-specified criteria for dose reduction of edoxaban; 733 vs. 719 patients). In the patient population for an edoxaban dose reduction, 30 mg of edoxaban administration showed comparable efficacy with improved safety over warfarin.[82] Based on these data, a dose

reduction of edoxaban is recommended for patients with one of the following conditions: renal impairment with GFR 15 to 50 mL/min or body weight < 60 kg or concomitant therapy with a P-gp inhibitor (ciclosporin, dronedarone, erythromycin, ketoconazole).

Of note, all DXI are recommended not be used in patients with a CrCl < 15 mL/min and should be used only with caution in patients with CrCl 15 to 29 mL/min. Only few data exist for DXI treatment in patients under haemodialysis.[83,84] Consequently, DXI should not be used in this population outside of dedicated registered clinical trials.

Dabigatran: Dabigatran is an orally available thrombin inhibitor. Two dedicated phase III studies in DVT and PE patients demonstrated non-inferiority of dabigatran versus LMWH/warfarin. In the pooled results of the RE-COVER 1 and 2 studies, a comparable effectiveness of dabigatran versus warfarin with improved safety profile was shown.[85] Although very limited information is available on the efficacy of dabigatran versus LMWH/VKA across different CKD stages, a sub-group analysis demonstrated a better safety profile of dabigatran in patients with a GFR > 50 mL/min compared with VKA with similar safety in patients with a GFR 30 to 49 mL/min.

A dose reduction is recommended for patients who are older than 80 years or when co-administered with verapamil. Due to the higher renal elimination rate, dabigatran should not be used in patients with a CrCl below 30 mL/min.

Conflict of Interest

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