Pulmonary embolism (PE) is a potential life-threatening condition and risk-adapted diagnostic and therapeutic management conveys a favorable outcome. For patients at high risk for early complications and mortality, prompt exclusion or confirmation of PE by imaging is the key step to initiate and facilitate reperfusion treatment. Among patients with hemodynamic instability, systemic thrombolysis improves survival, whereas surgical embolectomy or percutaneous intervention are alternatives in experienced hands in scenarios where systemic thrombolysis is not the best preferred thromboreduction measure. For patients with suspected PE who are not at high risk for early complications and mortality, the organized approach using a structured evaluation system to assess the pretest probability, the age-adjusted D-dimer cut-offs, the appropriate selection of imaging tools, and proper interpretation of imaging results is important when deciding the allocation of treatment strategies. Patients with PE requires anticoagulation treatment. In patients with cancer and thrombosis, low-molecular-weight heparin (LMWH) used to be the standard regimen. Recently, three factor Xa inhibitors collectively show that non-vitamin K oral anticoagulants (NOACs) are as effective as LMWH in four randomized clinical trials. Therefore, NOACs are suitable and preferred in most conditions. Finally, chronic thromboembolic pulmonary hypertension is the most disabling long-term complication of PE. Because of its low incidence, the extra caution should be given when managing patients with PE.
INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), represents a significant healthcare burden worldwide. Although DVT and PE occur at different vascular territories in the circulatory system, these two clinical conditions share a common pathogenesis centered on Virchow’s triad of blood flow stasis, vessel wall damage, and increased blood viscosity. The diagnostic work-up of both diseases requires high clinical awareness, an organized pathway including the use of a clinical decision rule and D-dimer testing, and the confirmatory imaging. After the timely verification of the diagnosis, DVT and PE are commonly managed with anticoagulants.

We have previously reported the consensus on the diagnosis and treatment of DVT. In this document, experts reviewed the information of PE and made recommendations for clinical practices in diagnostic and therapeutic approaches pertinent to PE and updated our recommendations for pharmacological management of VTE.

EPIDEMIOLOGY

The incidence rate of VTE in the Western countries is 100 or greater per 100,000 person-years. Although Asian populations, compared with Western populations, are subject to the similar acquired risk factors for VTE and have a higher prevalence of strong thrombophilia, the incidence estimates in Asia are approximately 15 to 20% of the levels reported in Western countries. Nevertheless, the incidences of both DVT and PE continue to rise in Asia.

Given the fact that the presentation of PE can range from a silent (asymptomatic) complication of DVT or an incident finding during diagnostic work-up for another disease(s) to syncope or sudden death, the true incidence of PE is difficult to determine. By estimation, the incidence of PE in East Asia is around 5 to 7 per 100,000 person-years. Even with anticoagulation treatment, the mortality rate related to PE remains high (12% at the first month and 24% at the first year).

DIAGNOSIS

The clinical assessment and diagnostic testing for PE are the same in Asian populations as they are in Western populations. Because PE may be fatal in the acute phase or leads to chronic disability that impairs physical performance and quality of life, careful history taking, risk factor identification, and distinguishing presentations associated with suspected PE from other medical emergencies are important. However, common symptoms reported by patients as dyspnea or signs found by physicians as tachycardia and tachypnea are non-specific. The clinical suspicion of PE must be confirmed by objective testing, including invasive pulmonary angiography, computed tomographic pulmonary angiography, or lung ventilation/perfusion scintigraphy, among the majority of PE-likely patients, whereas PE can be safely excluded by a validated algorithm among PE-unlikely patients without further imaging. Therefore, the accurate and timely diagnosis of PE depends on the combined use of clinical assessment, plasma D-dimer measurement, and imaging tests.

Clinical presentations

Although common symptoms suggestive of PE including acute dyspnea or deteriorating dyspnea, chest pain, and/or hemoptysis are not challenging to identify, they are non-specific for PE. Syncope is frequent but may occur without hemodynamic instability. The prevalence of PE in patients without an alternative explanation for syncope may reach up to a quarter. Furthermore, shock might be the central presentation of PE in around 5% of patients. Tachypnea is the most common sign followed by tachycardia. However, both are non-specific for PE. On contrary, about 70% of patients with symptomatic PE have concomitant DVT, in which up to a quarter is symptomatic. Therefore, symptoms suggestive of DVT, including leg edema, erythema, tenderness, and/or the palpable cord, may present. Physical examination may also identify signs of PE-associated pulmonary hypertension, such as elevated neck veins, a loud P2, a right-sided gallop, and a right ventricular lift.

Abnormalities on chest radiography, electrocardiography, or a blood gas analysis are neither specific for PE but useful in judging the differential diagnosis. Sinus tachycardia by electrocardiography is common.
cardia is associated with an increase in the risk of mortality even a cut-off of the heart rate from 86 beats/min is associated with an elevated risk of right ventricular dysfunction and the intermediate risk PE status. Other electrocardiographic markers that are useful in risk stratification for patients with PE include right bundle branch block and SIQIII-type patterns. But, the electrocardiogram is of limited diagnostic value in patients with suspected PE as those abnormalities found in suspected PE are equally prevalent in patients suspected of PE in whom PE is ultimately excluded. Hypoxia associated symptoms and signs are the cardinal presentation of PE. Hypoxemia by the blood gas analysis is a sensitive indicator of PE. Nevertheless, a normal alveolar-arterial oxygen gradient alone can not safely exclude the diagnosis of PE.

Clinical assessment

As with the diagnosis of DVT, a key step for diagnosing PE is to assess a patient’s clinical probability of PE based on medical history and physical examination before any testing. Although there are structured clinical probability scoring systems developed to stratify patients, the Wells scoring system, which incorporates medical history and physical examination, is the most widely used pretest tool stratifying patients with suspected PE. This scoring system generally has a high specificity across the prevalence of PE in the studied populations. Given the original Wells scoring system is complexed by assigning each item with a different weight, a simplified version has been created and widely validated. Because both versions of the Wells scoring system have similar performance for exclusion of PE, the simplified Wells scoring system, listed in Table 1, is recommended, using the acronym MI-SHE-PO as a convenient pretest tool.

When an extensive clinical history of the patient has been obtained, the physician can get confirmation of whether the presence of active malignancy, any recent instances leading to immobilization or surgery (within 4 weeks), or prior VTE. Those are factors predisposing patients to both DVT and PE. Upon physical examination, leg swelling, either confined to the calf or the entire leg, visible collateral venous circulation, and leg pain while palpat ing should alert physicians to DVT. Hemoptysis and tachycardia are common symptoms and signs other than findings on legs. If there is no other tentative diagnosis at least as likely as PE, the likelihood of PE is increased. Nonetheless, it should be noted that the item, any alternative diagnosis less likely than PE, is subjective and may reduce the inter-observer reproducibility of this clinical probability scoring system.

Table 1. MI-SHE-PO acronym for Wells prediction rules for diagnosing pulmonary embolism

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Original version*</th>
<th>Simplified version#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy, active</td>
<td>+1.0</td>
<td>+1</td>
</tr>
<tr>
<td>Immobilization or surgery within the past 4 weeks</td>
<td>+1.5</td>
<td>+1</td>
</tr>
<tr>
<td>Signs of DVT</td>
<td>+3.0</td>
<td>+1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+1.0</td>
<td>+1</td>
</tr>
<tr>
<td>Elevated heart rate (≥ 100 beats per minutes)</td>
<td>+1.5</td>
<td>+1</td>
</tr>
<tr>
<td>Prior VTE</td>
<td>+1.5</td>
<td>+1</td>
</tr>
<tr>
<td>Other diagnoses are less likely than PE</td>
<td>+3.0</td>
<td>+1</td>
</tr>
</tbody>
</table>

* Two-level clinical probability: unlikely, ≤ 4; likely, > 4. # Two-level clinical probability: unlikely, < 2; likely, ≥ 2.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.
linked fibrin. D-dimer levels are typically elevated in patients with VTE because of simultaneous activation of coagulation and fibrinolysis. However, it may be positive in patients with inflammatory states such as cancer and infection and in the elderly patients. Therefore, a positive D-dimer test is not confirmatory enough for the diagnosis of PE.

A number of D-dimer assays are available. The meta-analysis of 111 D-dimer test evaluations for suspected PE showed that the enzyme-linked immunofluorescence assay, microplate enzyme-linked immunosorbent assay, and latex quantitative assay had a greater sensitivity than did the whole-blood D-dimer assay, latex semi-quantitative assay, and latex qualitative assay (97%, 95%, and 95% versus 87%, 88%, and 75%).

Given its fair sensitivity and poor specificity, D-dimer testing is best considered together with the clinical probability. Overall, the assays with a higher sensitivity yield a higher negative predictive value and are preferable. The highly sensitive D-dimer assays (the quantitative enzyme-linked immunosorbent assay and its derived assays and immunoturbidimetric tests) are best used to exclude PE patients at a lower likelihood, whereas a negative D-dimer test by any less sensitive assays may not be safe to exclude the diagnosis. Finally, using the point-of-care D-dimer assays in the hospital setting for exclusion of PE requires extra cautions, especially for those qualitative assays that have a lower sensitivity.

Computed tomographic pulmonary angiography

Multidetector computed tomographic pulmonary angiography has been widely used for the diagnosis of PE. It has the advantage of making rapid diagnosis, visualizing thrombosis down to the segmental to subsegmental level of the pulmonary arteries, and providing alternative diagnoses for acute dyspnea and/or chest pain. Overall, the sensitivity and specificity of adequate computed tomographic pulmonary angiography is 83% and 96%, respectively, in symptomatic patients. However, the predictive value of the computed tomographic pulmonary angiography is modified by the clinical probability where physicians are required to utilize their clinical judgement and/or more tests when discordance between the clinical probability and the result of computed tomographic pulmonary angiography occurs.

In most patients with PE, routine imaging of the leg (either by ultrasound or computed tomography) does not substantially increase the diagnostic yield. Furthermore, the diagnostic validity of isolated subsegmental PE by multidetector computed tomographic pulmonary angiography is under debate, partially being contributed to beam-hardening attenuation, the partial volume effect, and poor contrast opacification.

Pulmonary angiography

Invasive pulmonary angiography has been the gold standard for the diagnosis or exclusion of PE. The prior reported procedure-related mortality rate and the rate of major non-fatal complications were 0.5 and 1%, respectively. Nevertheless, the interobserver agreement for isolated subsegment PE was achieved in only two third of patients. With the advancement of computed tomographic pulmonary angiography, nowadays, it is often used when non-invasive imaging modalities fail to confirm the diagnosis of PE or when the diagnosis of chronic thromboembolic pulmonary hypertension needs to be validated.

Lung ventilation/perfusion scintigraphy

The lung ventilation/perfusion scan is an alternative imaging modality to (computed tomographic) pulmonary angiography to verify the diagnosis of PE. However, its accessibility may be limited to time and institutes. The purpose of the ventilation scan is to increase specificity. Therefore, perfusion only scanning might be acceptable in patients with a normal chest x-ray. The reporting usually has three tiers where a normal scan excludes PE and a high probability scan is considered to be diagnostic. A nondiagnostic scan requires further testing. The clinical utility of the lung ventilation/perfusion scan is limited by the high frequency of nondiagnostic scans. Currently, the lung ventilation/perfusion scan still serves as an important early step in the diagnostic work-up of patients with suspected chronic thromboembolic pulmonary hypertension.

Other imaging modalities

Magnetic resonance angiography has been evaluated for the application in the diagnosis of PE for several years. Magnetic resonance angiography with or without enhancement or using various sequences has a similar
sensitivity and specificity comparing with early multi-
detector computed tomographic scanners.\textsuperscript{58-60} Although
being promising as being radiation free and less restr-
ained by the renal requirement, the proportion of tech-
nically inadequate images or inconclusive results was
high and the availability and accessibility was low in the
emergency settings. Those drawbacks prevent its wide
clinical application when managing patients with sus-
ppected PE.

When visualizing right-heart thrombi detected by ei-
ther transthoracic or transesophageal echocardiogra-
phy, PE is essentially confirmed. However, only a minor-
ity of patients with PE (\( \approx 4\% \)) had intracardiac thrombus,
mostly in the right atrium.\textsuperscript{19} PE may cause right ven-
tricular strain by acute pressure overload. Proposed echo-
cardiographic parameters signaling right ventricular
pressure overload are listed in Table 2. Although being
defined, they have not been widely validated in any pro-
spective clinical trials for exclusion or confirmation of
the diagnosis of PE.\textsuperscript{61} In addition, right ventricular strain
can be frequently seen in patients with cardiac or pul-
monary conditions other than PE. The modest sensitiv-
ity and the moderate to high specificity of right ven-
tricular dysfunction and dilatation or pulmonary hyper-
tension on echocardiography preclude the clinical utility
of echocardiography in the unselected populations.\textsuperscript{62-64}
Overall, using echocardiography in the diagnosis of PE
has a poor sensitivity and a fair specificity at \( \approx 80\% \).\textsuperscript{65}
Nevertheless, it is useful in the differential diagnosis of
acute dyspnea in patients with hemodynamic instability.

It has been expected that thromboemboli in the
pulmonary arteries originate from DVT in a lower limb.\textsuperscript{22}
In the early days when invasive angiography and veno-
graphy were routinely performed for diagnosing VTE,
DVT was present in 70\% of patients with PE.\textsuperscript{66} It had
been suggested to use leg compression ultrasound to
confirm the diagnosis of PE in patients with inconclusive
lung imaging or in those with clinical DVT.\textsuperscript{67} Data from
compression ultrasound of the proximal legs, the most
commonly used protocol, suggested DVT presented in
only 30\% of patients with PE.\textsuperscript{30,68} Both the positive and
negative predictive values of leg compression ultra-
sound for symptomatic proximal DVT were 100\%. How-
ever, it should be noted that the values decreased to
71\% and 94\%, respectively, in asymptomatic patients.\textsuperscript{4}
Currently when diagnosing PE, leg compression ultra-
sound should be reserved for patients with a contraindi-
cation for computed tomographic pulmonary angiogra-
phy or it may be the frontline option in those with signs
and symptoms suggestive of proximal DVT and greater
concerns for excessive radiation exposure.

**Diagnostic algorithm**

VTE is a serious condition that is potentially fatal
when being left untreated,\textsuperscript{69} whereas anticoagulation
treatment is usually effective but carries the risk for ma-
jor bleeding of \( \approx 2\% \), of which \( \approx 10\% \) is fatal.\textsuperscript{70} There-
fore, diagnostic certainty needs to be high enough to
start or to withhold anticoagulation treatment. Given
that currently there is no reliable stand-alone test that is
non-invasive, beginning with the assessment of the clin-
ical probability in the absence of hemodynamic instabil-
ity at presentation as for the diagnostic work-up before
allocating further imaging tests is the mainstream. In pa-
tients with hemodynamic instability in whom acute PE is
suspected, right ventricular dysfunction shown by the
echocardiography warrants further computed tomogra-
phic pulmonary angiography to search for PE.

The use of D-dimer testing in patients with the low
clinical probability safely excludes PE without further
imaging tests in \( \approx 40\% \) and the 3-month diagnostic fail-
ure rate is 0.5\%.\textsuperscript{43,71} The application of the age-adjusted
cut-offs (age \( \times 10\) \text{ug/L} above 50 years) has improved
the specificity of D-dimer testing (high sensitivity) in the
elderly patients without compromising patient safety.\textsuperscript{72}
Since 2014, the European guidelines have adopted the
age-adjusted D-dimer cut-offs for the exclusion of PE.\textsuperscript{61,73}
The original and simplified Wells scoring systems com-

<table>
<thead>
<tr>
<th>Echocardiographic parameters suggestive of right ventricular pressure overload\textsuperscript{61,65}</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV dilatation</td>
<td>76%</td>
<td>85%</td>
</tr>
<tr>
<td>RV/LV ratio</td>
<td>66%</td>
<td>79%</td>
</tr>
<tr>
<td>McConnell sign</td>
<td>81%</td>
<td>72%</td>
</tr>
<tr>
<td>Flattened interventricular septum</td>
<td>77%</td>
<td>66%</td>
</tr>
<tr>
<td>60/60 sign</td>
<td>72%</td>
<td>37%</td>
</tr>
<tr>
<td>Decreased TAPSE</td>
<td>61%</td>
<td>84%</td>
</tr>
<tr>
<td>Right-heart thrombus</td>
<td>100%</td>
<td>62%</td>
</tr>
</tbody>
</table>

LV, left ventricle; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.
bined with age-adjusted D-dimer testing have similar performances in exclusion of PE. Given its convenience in clinical practice, the combination of the simplified Wells score and the age-adjusted D-dimer cut-offs is preferred.\(^7\)

In other patients who are more likely to have PE by the clinical probability or have an elevated D-dimer level, the computed tomographic pulmonary angiography-based strategy is favored (Figure 1). In patients in whom computed tomographic pulmonary angiography is contraindicated or who are more susceptible to radiation and are managed in the hospital where timely scintigraphy is available, lung ventilation/perfusion scintigraphy plus leg compression ultrasound is a valid option.

**Other algorithms**

The pulmonary embolism rule-out criteria has been developed for emergency department patients with the purpose of selecting patients in whom diagnostic work-up should not be initiated. The criteria include: 1. an arterial oxygen saturation \(\leq 94\%\); 2. a pulse rate \(\geq 100\) beats per minute; 3. patient aged \(\geq 50\) years; 4. unilateral leg swelling; 5. hemoptysis; 6. recent trauma or surgery; 7. prior VTE; and 8. exogenous estrogen use. In patients who meet none of the above criteria, it appears safe to exclude PE without any further testing.\(^7\) It is estimated that computed tomographic pulmonary angiography could be avoided in 10% of patients. However, without D-dimer testing, the pulmonary embolism rule-out criteria might fail to capture subsegmental PE in those who are negative for all criteria when the prevalence of PE is expected to be > 3%.\(^7\)

The other diagnostic algorithm intended to simplify PE diagnosis and to minimize the use of computed tomographic pulmonary angiography is the YEARS rule, which consists of three clinical items of the Wells scoring system and the D-dimer level. The items from the Wells scoring system are signs of DVT, hemoptysis, and PE more likely than an alternative diagnosis. In addition, the D-dimer cut-off is set at < 1000 ng/mL in patients without any clinical items and < 500 ng/mL in patients with one or more clinical items. All other patients undergo computed tomographic pulmonary angiography. Compared with the current standard algorithm with the age-adjusted D-dimer threshold, the advantage of the YEARS rule is an absolute reduction of 14% of computed tomographic pulmonary angiography in those aged < 50 years with the 3-month diagnostic failure rate of 0.1%.\(^3\)

The pregnancy-adapted YEARS rule using leg compression ultrasound for women with signs of DVT as the initial step has high efficacy and potentially avoid computed tomographic pulmonary angiography in 39% of pregnancy women.\(^7\) Therefore, using the YEARS rule in the pregnant patients appears safe (Figure 2).

To use those new algorithms requires extra cautions as their purpose is to avoid “unnecessary” computed tomographic pulmonary angiography. The prevalence of PE in the management studies ranged between 3% and 14%. Therefore, whether the generalizability of their findings to a more prevalent cohort (e.g. the elderly population) and/or for patients in whom computed tomographic pulmonary angiography is contraindicated requires further studies.

**Recommendations**

- To diagnose PE requires a systematic assessment.
- An acronym of MI-SHE-PO for the Well score is the comprehensive initial to stratify patients.
- The combination of the Wells score and a D-dimer test, using the age-adjusted cut-offs, is validated in allocating further imaging studies.

![Figure 1. Diagnosis flowchart for patients with stable hemodynamic and suspected pulmonary embolism. * 500 ug/L if age is 50 years and less and age \(\times 10\) ug/L if age is above 50 years with D-dimer testing (high sensitivity). † Pulmonary embolism is confirmed if thrombosis visualized above the subsegmental level. ‡ Clinical judgement and/or more tests (e.g. lung ventilation/perfusion scintigraphy or leg compression ultrasound) are required in patients with a Wells score > 2. PE, pulmonary embolism.](image)
In patients who require further imaging studies, the computed tomographic pulmonary angiography-based strategy is favored. For patients in whom computed tomographic pulmonary angiography is deemed unfeasible, lung ventilation/perfusion scintigraphy plus leg compression ultrasound can be an alternative, provided local experience does exist.

**PROGNOSIS ASSESSMENT**

The prognosis of patients with PE varies substantially and is determined by patient hemodynamics, concomitant disease conditions, and right ventricular function. The clinical classification by PE severity based on the early mortality rate facilitates the proper allocation of the initial therapeutic approach.

A number of models have been derived and validated in PE over the past two decades. Nevertheless, the hemodynamic at the presentation when PE is suspected is one of the strongest determinants of early death. Consequently, both diagnostic and therapeutic strategies should be prioritized in those with pulselessness or sustained hypotension (systolic blood pressure < 90 mmHg for at least 15 minutes or requiring inotropic support).

**PE severity index**

The PE severity index which incorporates patient characteristics, comorbidities, and clinical conditions has been developed and extensively validated to assess the risk of early death (30-day mortality). The original version contains 11 differently weighted variables and its simplified version retains 6 fixed value items (Table 3). The performance of those two versions is similar and both have good sensitivity and poor specificity for early mortality. As the majority of patients with PE are hemodynamically stable at presentation, both versions have a high negative predictive value. Despite the development and application of the PE severity index, there was only one randomized trial that compared outpatient versus inpatient treatment of patients with PE who were at lower risk for early mortality by this model.

**Imaging markers**

Right ventricular failure due to acute pressure overload is considered to be the primary cause of early death in patients with PE. Among patients with PE, 40% reported to have right ventricular hypokinesis, which marked a higher mortality within 3 months. In addition to right ventricular dilatation (without hypertrophy),

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**Figure 2.** Diagnosis flowchart for pregnant patients with stable hemodynamic and suspected pulmonary embolism. DVT, deep vein thrombosis; PE, pulmonary embolism.
paradox septal systolic motion and/or pulmonary hypertension identifies normotensive patients who develops latent hemodynamic impairment and/or in-hospital mortality. Nevertheless, the predictive values of echocardiographic parameters are generally poor, reflecting the requirement for the standardized assessment. Currently, measuring right ventricular and left ventricular end-diastolic (defined by the electrocardiogram R-wave) diameters at the valvular level during late diastole and tricuspid annular plane systolic excursion in the M-mode presentation at peak systole are recommended.

Beyond the diagnostic role, computed tomographic pulmonary angiography provides additional prognostic information by showing right ventricular dysfunction.

The ratio of right ventricular end-diastolic diameter to left ventricular end-diastolic diameter at the valvular plane in the transverse images is used as an indicator of right ventricular dysfunction. Although the ideal cut-off for such the ratio is debatable, the increased ratio appears to rise prognostic specificity.

**Biomarkers**

The abrupt increase in pulmonary vascular resistance results in right ventricular dilatation, which is followed by ischemia and then dysfunction. Biomarkers of increased myocardial stretch and/or myocardial injury have been investigated for their prognostic values in patients with PE. An elevated cardiac troponin level (above

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**Table 3. Risk stratification models for patients with pulmonary embolism by the risk of 30-day mortality**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PESI</th>
<th>Simplified PESI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>10</td>
<td>1 if age &gt; 80 years</td>
</tr>
<tr>
<td>Male sex</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>30</td>
<td>Cancer</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>10</td>
<td>Chronic cardiopulmonary disease</td>
</tr>
<tr>
<td>SBP &lt; 100 mmHg</td>
<td>30</td>
<td>SBP &lt; 100 mmHg</td>
</tr>
<tr>
<td>Heart rate ≥ 110 beats per minute</td>
<td>20</td>
<td>Heart rate ≥ 110 beats per minute</td>
</tr>
<tr>
<td>Respiratory rate ≥ 30 breaths per minute</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Arterial oxygen saturation &lt; 90%*</td>
<td>20</td>
<td>Arterial oxygen saturation &lt; 90%*</td>
</tr>
<tr>
<td>Temperature &lt; 36°C</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Altered mental status*</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Risk category</td>
<td>Point</td>
<td>Mortality</td>
</tr>
<tr>
<td>Class I, very low</td>
<td>≤ 65</td>
<td>1.1%</td>
</tr>
<tr>
<td>Class II, low</td>
<td>66-85</td>
<td>3.1%</td>
</tr>
<tr>
<td>Class III, intermediate</td>
<td>86-105</td>
<td>6.5%</td>
</tr>
<tr>
<td>Class IV, high</td>
<td>106-125</td>
<td>10.4%</td>
</tr>
<tr>
<td>Class V, very high</td>
<td>&gt; 125</td>
<td>24.5%</td>
</tr>
</tbody>
</table>

* With and without the supplemental oxygen. * Defined as disorientation, lethargy, stupor, or coma. † Estimates in the derivation cohorts.

PESI, pulmonary embolism severity index; SBP, systolic blood pressure.
the normal thresholds dependent on the assay used) was associated with an increased risk of mortality, both in overall patients and in those who were hemodynamically stable at presentation. Similarly, an increased brain-type natriuretic peptide or N-terminal-pro-brain-type natriuretic peptide level at baseline was associated with right ventricular dysfunction and adverse clinical outcomes.

Other surrogate markers indicating low cardiac output and its complications, such as renal dysfunction or kidney injury, have been reported to be useful for risk stratification in patients with PE, including plasma lactate, copeptin, neutrophil gelatinase-associated lipocalin, and cystatin C in patients with normotensive.

Combined risk assessment model

Among patients with PE at low risk by the risk prediction models, 34% had evidence of right ventricular dysfunction by imaging and 26% had an elevated cardiac troponin level. Both were associated with an increased mortality in patients with PE who were classified as being at low risk by the risk prediction models. Since the prognostic information from the clinical, imaging, and laboratory findings is complementary, their integration provides better calibration in prediction of early death in patients with PE who are at the non-high risk categories. The accuracy for early mortality is better with the integrated model than with the clinical model, particularly in patients at intermediate risk by the PE severity index.

A 3-tier risk stratification model is recommended, in which patients at intermediate risk are further classified into two subcategories. For patients who are at high risk, prompt pulmonary artery reperfusion and intensive care are needed, whereas early discharge and outpatient or home treatment may be feasible in patients who are at low risk.

Recommendations

- The assessment of prognosis is essential after the diagnosis of PE is confirmed.
- Hemodynamic stability is the major determination for early outcomes in patients with PE.
- Right ventricular dysfunction by imaging and/or myocardial strain by biomarkers are markers signaling worse clinical outcomes.
- The PE severity index, a structured assessment combing patient characteristics, comorbidities, and clinical conditions, is a useful tool to evaluate the risk of early death in patients with stable hemodynamics.
- The clinical risk and imaging and/or biomarker levels are complimentary when assessing early outcomes.
- The therapeutic strategy should be prioritized in patients with pulselessness or sustained hypotension.

TREATMENT FOR PE

Thrombolysis and embolectomy

Thromboembolic obstruction of pulmonary arterial vasculature and subsequent elevation of right ventricular afterload hallmark the initiation of the vicious pathophysiologic cycle leading to the hemodynamic compromise and fatality. Either pharmacological or surgical removal of thrombus leads to faster improvements in pulmonary circulation and reductions in pulmonary hypertension and right ventricular dilatation. The early evidence suggested that systemic thrombolysis improved survival in patients with increased thrombus burden. In patients who are at intermediate risk for early mortality, systemic thrombolysis has been compared with heparin (Table 4). Although there was no difference in mortality, systemic thrombolysis reduced the need for emergent escalation of treatment due to hemodynamic decompensation within the first week of hospitalization when compared to anticoagulation alone in this patient population. In the PEITHO study, the largest trial of thrombolysis in pulmonary embolism to date, the risk of major bleeding and of hemorrhagic stroke was substantially higher with systemic thrombolysis. The catheter-directed pharmacological reperfusion could have been a promise for a balance between improvement in right ventricular function and the excessive risk of major bleeding. The early experience suggested that the local delivery of one tenth of the dose used for systemic thrombolysis over 15 hours improved early hemodynamic parameters and right ventricular function. Using a lower dose and shorter infusion duration may be feasible in selected patients with intermediate risk. Nevertheless, the catheter-directed treatment requires local expertise and a high institutional volume to ensure satisfactory outcomes. There is cer-
Certainly a need for a randomized trial comparing the catheter-directed treatment with systemic thrombolysis and with anticoagulation that is powered to evaluate clinical outcomes before the widely accepted utility of the catheter-directed pharmacological reperfusion strategy (Table 5). Therefore, in most patients with right ventricular dysfunction and the elevated level of cardiac biomarkers, a watchful waiting strategy is preferred over routine thrombolysis.\textsuperscript{117}

It has been reported that \( \approx 8\% \) of patients who underwent systemic thrombolysis failed to achieve clinical stability and restore right ventricular function.\textsuperscript{118} Although there is no randomized trials comparing surgical embolectomy with pharmacological thrombolysis, surgical embolectomy for patients with PE is as effective and as safe as pharmacological thrombolysis.\textsuperscript{119,120} According to local expertise, surgical embolectomy should be considered when thrombolysis is contraindicated or when thrombolysis fails to achieve hemodynamic improvement.

Non-vitamin K oral anticoagulants (NOACs)

Oral anticoagulants are the mainstay for VTE treatment and the duration of treatment should include at least 3 months. The development of four NOACs has changed the treatment pattern observed over the recent years.\textsuperscript{121}

There were six pivotal trials of four NOACs in the therapeutic area of VTE over the past decade.\textsuperscript{122-127} Although there was only one study specifically examining the efficacy of one of the NOACs in patients with PE,\textsuperscript{124} the general information of all four NOACs applied to patients with DVT and to patients with PE.\textsuperscript{128} With either well-managed vitamin K antagonists (VKAs) or NOACs,

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**Table 4. Randomized trials of systemic thrombolysis in patients with intermediate risk of pulmonary embolism\textsuperscript{111-114}**

<table>
<thead>
<tr>
<th>Publication year</th>
<th>MAPPET-3</th>
<th>MOPETT</th>
<th>TOPCOAT</th>
<th>PEITHO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient no.</td>
<td>2002</td>
<td>2013</td>
<td>2014</td>
<td>2014</td>
</tr>
<tr>
<td>Patient no.</td>
<td>256</td>
<td>121</td>
<td>83</td>
<td>1006</td>
</tr>
<tr>
<td>PE severity</td>
<td>RV dysfunction by echocardiograph, right heart catheterization, or electrocardiogram</td>
<td>RV strain by echocardiography or an elevated troponin or brain natriuretic peptide level</td>
<td>A single weight-based intravenous bolus of tenecteplase</td>
<td>A single weight-based intravenous bolus of tenecteplase</td>
</tr>
<tr>
<td>Thrombolysis regimen</td>
<td>Alteplase 100 mg over 2 hours (a 10-mg bolus, followed by a 90-mg intravenous infusion)</td>
<td>Alteplase 50 mg over 2 hours (a 10-mg bolus, followed by a 40-mg intravenous infusion) if weight ( \geq 50 ) kg or 0.5 mg/kg over 2 hours (a 10-mg bolus, followed by the reminder intravenous infusion) if weight &lt; 50 kg</td>
<td>Tenecteplase</td>
<td>Tenecteplase</td>
</tr>
<tr>
<td>Initial anticoagulation regimen</td>
<td>UFH adjusted to maintain the activated partial thromboplastin time at 2.0 to 2.5 times the upper limit of normal</td>
<td>UFH or enoxaparin</td>
<td>Low-molecular-weight heparin</td>
<td>UFH adjusted to maintain the activated partial thromboplastin time at 2.0 to 2.5 times the upper limit of normal</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>In-hospital death or clinical deterioration that required an escalation of treatment</td>
<td>The development of pulmonary hypertension at intermediate-term follow-up</td>
<td>Death, circulatory shock, intubation or major bleeding within 5 days or recurrent PE, poor functional capacity or an SF-36 Physical Component Summary &lt; 30 at 90-day follow-up</td>
<td>Death or hemodynamic decompensation within 7 days</td>
</tr>
<tr>
<td>Efficacy</td>
<td>14% absolute reduction in the primary endpoint</td>
<td>41% absolute reduction in the primary endpoint</td>
<td>No difference</td>
<td>3% absolute reduction in the primary endpoint</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>No difference</td>
<td>No difference</td>
<td>Not reported</td>
<td>9% absolute increase</td>
</tr>
</tbody>
</table>

PE, pulmonary embolism; RV, right ventricle; UFH, unfractionated heparin.
the overall recurrent rate of VTE was around 2% within 6 to 12 months. However, treatment with a NOAC significantly reduced the risk of major bleeding by 39%. Therefore, NOACs as a therapeutic class for VTE are as effective as but safer than well-managed VKAs (with the targeted international normalized ratio between 2.0 and 3.0).128

These NOACs are classified into two therapeutic strategies — one has a heparin lead-in phase and the other uses a single-drug approach with escalated doses in the first phase.5 The strategy of using no up-front heparin has been tested in the EINSTEIN program and in the AMPLIFY study.123-125 In the predefined safety analysis of the EINSTEIN-PE study, serial imaging suggested that there was no difference in clot resolution between the conventional heparin lead-in management and rivaroxaban after 3 weeks.129 As expected,130,131 most patients had complete (41%) or partial (47%) resolution after treatment. Therefore, the single-drug approach strategy with an initial escalation of therapeutic doses may be considered in selected patients in whom inpatient care can be shorten. Another aspect in PE treatment with NOACs is that there might be concerns of using NOACs in patients with more extensive PE or those with intermediate risk as the anatomical extent of PE is associated with the recurrent rate of PE regardless of treatment.132 Nevertheless, in the subanalysis from the Hokusai-VTE study, the efficacy and safety of edoxaban compared with well-managed VKAs were maintained in patients with evidence of right ventricular dysfunction.133

After the first 3 to 6 months, extending anticoagulation treatment is considered in patients without a transient reversible risk factor.4 Aspirin appears to reduce the risk of recurrence by 32% when compared with placebo,134 where either standard or low dose rivaroxaban further reduce the risk by 48%.135 Compared with standard-intensity VKAs, dabigatran and edoxaban appear to be as effective as but safer.136,137 Overall, current evidence from multiple clinical trials comparing different regimens suggests that standard-intensity VKAs and NOACs are preferred over aspirin when considering long-term secondary prevention of VTE with a higher risk of major bleeding observed with standard-intensity VKAs.138

Despite that NOACs are widely used in most of patients with PE, VKAs with a targeted international normalized ratio between 2.0 and 3.0 are used in patients when they have any contraindications to NOACs (e.g. those with renal dysfunction, rheumatic mitral stenosis, and/or a mechanical heart valve).

**Cancer-associated thrombosis**

By estimation, ≈ 20% of VTE is cancer-associated thrombosis.139 VTE is more common in patients with cancer as they have a several-fold increased risk of VTE compared with the general population.140 The occur-

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**Table 5. Recent trials of ultrasound-assisted catheter-directed thrombolysis in patients with pulmonary embolism**109,115,116

<table>
<thead>
<tr>
<th>Publication year</th>
<th>Patient no.</th>
<th>Design</th>
<th>PE severity</th>
<th>Thrombolysis regimen</th>
<th>Primary endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ULTIMA SEATTLE II</td>
<td>2014</td>
<td>59</td>
<td>Two arms comparing thrombolysis and no thrombolysis</td>
<td>Intermediate-risk PE defined by RV/LV diameter ratio ≥ 1.0 on imaging</td>
<td>The difference in RV/LV diameter ratio from baseline to 24 hours</td>
</tr>
<tr>
<td>OPTALYSE PE</td>
<td>2015</td>
<td>150</td>
<td>Single arm</td>
<td>No control group</td>
<td>The change in RV/LV diameter ratio from baseline to 48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Four arms comparing four thrombolytic regimens</td>
<td>Intermediate-risk PE defined by RV/LV diameter ratio ≥ 0.9 on imaging</td>
<td>The change in RV/LV diameter ratio from baseline to 48 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Either one of the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm 1: alteplase 2 mg/h per catheter for 24 hours if unilateral device placement and for 12 hours if bilateral device placement</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm 2: alteplase 1 mg/h per catheter for 48 hours.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm 3: alteplase 1 mg/h per catheter for 6 hours.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm 4: alteplase 2 mg/h per catheter for 6 hours.</td>
<td></td>
</tr>
</tbody>
</table>

LV, left ventricle; PE, pulmonary embolism; RV, right ventricle.
rence of VTE in patients with cancer usually signals an advanced disease stage and poor prognosis.\textsuperscript{141} The pathogenesis is not limited to cancer biology \textit{per se} but multifactorial, including patient characteristics and treatment side effects.\textsuperscript{142}

Treating cancer-associated thrombosis is challenging as the risk of recurrence and the risk of bleeding are both higher in patients with cancer than in those without cancer.\textsuperscript{143} Low-molecular-weight heparin (LMWH) has been the mainstay for the treatment of VTE in patients with cancer over the past decade.\textsuperscript{144,145} LMWH was more effective on treatment and secondary prevention of cancer-associated thrombosis than VKAs (with a targeted international normalized ratio between 2.0 and 3.0).\textsuperscript{146,147} The meta-analysis of six clinical trials in patients with cancer-associated thrombosis further showed that LMWH reduced the risk of recurrent VTE by 44% while sharing the similar rate of major bleeding when compared to VKAs.\textsuperscript{148}

Despite supportive evidence from multiple clinical trials and guidelines recommendations, the use of LMWH in patients with cancer and VTE is limited, whereas VKAs remain frequently adopted.\textsuperscript{149,150} In the pivotal trials of NOACs, there were only a small number of patients with cancer (5%) were enrolled. It appeared that the efficacy and safety of NOACs are comparable to those of VKAs in patients with cancer and VTE.\textsuperscript{151}

In the area of cancer-associated thrombosis, first and foremost, four open-label randomized clinical trials comparing NOACs with LMWH have completed and reported their results (Table 6). The first report came from the Hokusai VTE Cancer study,\textsuperscript{152} in which 1050 patients

| Table 6. Randomized trial of non-vitamin K oral anticoagulants for patients with cancer associated thrombosis\textsuperscript{152,154-156} |
|---|---|---|---|---|
| **Publication year** | 2018 | 2018 | 2020 | 2020 |
| **Patient no.** | 1050 | 406 | 300 | 1170 |
| **Study arm treatment** | Edoxaban 60 mg (30 mg in patients with CrCl of 30 to 50 mL/min or weight of 60 kg or less or in those receiving concomitant treatment with potent P-glycoprotein inhibitors) once daily after 5-day low-molecular-weight heparin lead-in | Rivaroxaban, 15 mg twice daily for the first 3 weeks followed by 20 mg once daily | Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily | Apixaban 10 mg twice daily for 7 days followed by 5 mg twice daily |
| **Control arm treatment** | Dalteparin 200 IU/kg once daily for 30 days then 150 IU/kg once daily | Dalteparin 200 IU/kg once daily for 30 days then 150 IU/kg once daily | Dalteparin 200 IU/kg once daily for the first month followed by 150 IU/kg | Dalteparin 200 IU/kg once daily for the first month followed by 150 IU/kg |
| **Study duration** | 12 months | 6 months | 6 months | 6 months |
| **Specific exclusion** | ECOG performance status > 2 | Weight < 40 kg | CrCl < 30 mL/min | ECOG performance status > 2 | CrCl < 30 mL/min | Concomitant use of strong CYP3A4 inducers | CrCl < 30 mL/min | Concomitant use of strong CYP3A4 inhibitors or inducers or P-glycoprotein inhibitors or inducers |
| **Thrombocytopenia (< 50000/cL)** | | | | | | | | |
| **Primary endpoint** | Recurrent VTE or major bleeding | Recurrent VTE | Major bleeding | Recurrent VTE |

CrCl, creatinine clearance; CYP, cytochrome P-450; ECOG, Eastern Cooperative Oncology Group; VTE, venous thromboembolism.
with active cancer and symptomatic or incidentally detected VTE were randomly allocated to either edoxaban or LMWH. For the primary composite endpoint of recurrent VTE or major bleeding, treatment with edoxaban (with a heparin lead-in phase) was noninferior to treatment with LMWH during 12 months after randomization regardless of treatment duration. When compared with LMWH, edoxaban marginally improved the rate of recurrent VTE [hazard ratio (HR), 0.71; 95% confidence interval (CI), 0.48-1.06; p = 0.09]. However, there was an increased risk of major bleeding (HR, 1.77; 95% CI, 1.03-3.04; p = 0.04). The excess of major bleeding was contributed to patients with gastrointestinal cancer (including upper and lower gastrointestinal tract and the pancreatic or hepatobiliary system). The second report came from the SELECT-D study, in which 406 patients with cancer and VTE were randomized to the single-drug approach with the escalated dose of rivaroxaban in the first 3 weeks followed by the standard dose or to LMWH. When compared with LMWH, the rate of recurrent VTE was lower with rivaroxaban (HR, 0.43; 95% CI, 0.19 to 0.99) at the cost of an increase in bleeding, occurring excessively in patients with gastrointestinal cancer. The evidence of the third NOAC also suggested that there was a trend of a lower rate of recurrent VTE favoring apixaban over LMWH. In the Caravaggio study, the rate of recurrent VTE was slightly lower with apixaban than with LMWH (HR, 0.63; 95% CI, 0.37 to 1.07; p = 0.09). Meanwhile, the rate of major or clinically relevant nonmajor bleeding was similar between two treatments. Being distinct from edoxaban and rivaroxaban, there was no excess of major gastrointestinal bleeding with apixaban when compared with LMWH. Collectively, NOACs have better efficacy than LMWH and balanced net clinical benefits (Figure 3). Furthermore, compared with subcutaneous LMWH injection, NOACs had better treatment adherence and overall satisfaction. Therefore, NOACs are effective for cancer patients with acute VTE, although caution is needed in patients at high risk of bleeding.

**Multidisciplinary management**

Treatment options for patients with PE, especially for patients who are at high risk of early complications and/or mortality, have been expanded and sometimes have controversy between medical practice. With limited comparable data, deciding which strategy is more appropriate than the others for each patient becomes challenging. The pulmonary embolism response team (PERT) consisting of local expertise in the field of diagnosis and treatment of PE can be set up to improve patient care. This particularly holds true for patients with PE and cardiac arrest, in whom immediate extracorporeal membrane oxygenation support in addition to cardiopulmonary resuscitation is often required. After cardiopulmonary resuscitation, thrombolysis, surgical embolectomy, and mechanical embolectomy are reasonable emergency treatment options. The standard contraindications to thrombolysis should be weighed against potentially lifesaving benefits.

The structure of a PERT can vary and often include members from emergency medicine, radiology, cardiology, vascular surgery, critical care medicine, and/or pulmonary medicine. The introduction of the PERT has facilitated the decision making, favoring more advanced and aggressive management for patients who are at intermediate risk. Although the scope of a PERT was largely intended to provide recommendations to patients who are or will be in need of thromboreduction strategies, the initial experience showed that the PERT was often consulted for patients who had low-risk PE and complex comorbidities. It is encouraging to form multidisciplinary dialogues and collaborations within the institution for PE management. Nevertheless, whether a PERT can improve patient outcomes requests more research.

**Recommendations**

- Systemic thrombolysis or its alternatives, surgical or percutaneous thromboreduction measures, is life-saving in patients with hemodynamic instability.
- Timely administration of anticoagulation is essential in treatment of PE.
- The single-drug approach using rivaroxaban or apixaban and the 2-phase approach using parenteral heparin bridged to dabigatran or edoxaban are preferred over VKAs in most of patients with acute VTE.
- When considering to extend anticoagulation treatment, NOACs are the preferable agents.
- In patients with cancer-associated thrombosis, three factor Xa inhibitors and LMWH have similar efficacy for secondary VTE prevention. However, cautions are required in patients at higher risk of bleeding (e.g. those...
with thrombocytopenia or unresectable gastrointestinal cancer) or at potential for drug-drug interactions.

**LONG-TERM COMPLICATIONS OF PE**

After acute PE, complete PE resolution occurs in $\approx 40\%$ after the first month treatment and in $\approx 80\%$ after six months.\(^{29,166}\) However, residual thrombi can be persistent and organized and later lead to the life-threatening complication known as chronic thromboembolic pulmonary hypertension (CTEPH) in a small proportion of patients. Functional deterioration, chronic dyspnea, and/or impaired quality of life are reported in $\approx 50\%$ of patients who have received effective anticoagulation for PE for more than 3 months.\(^{15}\) Clinical determinants for the exercise limitation include the female gender, younger age, a larger body mass index, and smoking history.\(^{167}\) However, there is no association between exercise impairment and right ventricular dysfunction or residual pulmonary vascular obstruction.\(^{167,168}\)

On the other hand, CTEPH occurs in $\approx 3\%$ of patients who survive from a first episode of PE. CTEPH is characterized by symptoms ranging from persistent dys-

<table>
<thead>
<tr>
<th>Recurrent VTE</th>
<th>DOAC</th>
<th>Dalteparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ADAM VTE</td>
<td>1</td>
<td>145</td>
</tr>
<tr>
<td>Caravaggio</td>
<td>32</td>
<td>576</td>
</tr>
<tr>
<td>Hokusai VTE cancer</td>
<td>34</td>
<td>522</td>
</tr>
<tr>
<td>SELECT-D</td>
<td>8</td>
<td>203</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.63</td>
<td>[0.43, 0.91]</td>
</tr>
</tbody>
</table>

$P = 29\%$

<table>
<thead>
<tr>
<th>Major bleeding</th>
<th>DOAC</th>
<th>Dalteparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ADAM VTE</td>
<td>0</td>
<td>145</td>
</tr>
<tr>
<td>Caravaggio</td>
<td>22</td>
<td>576</td>
</tr>
<tr>
<td>Hokusai VTE cancer</td>
<td>29</td>
<td>522</td>
</tr>
<tr>
<td>SELECT-D</td>
<td>11</td>
<td>203</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.31</td>
<td>[0.83, 2.07]</td>
</tr>
</tbody>
</table>

$P = 23\%$

<table>
<thead>
<tr>
<th>CRNM bleeding</th>
<th>DOAC</th>
<th>Dalteparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ADAM VTE</td>
<td>9</td>
<td>145</td>
</tr>
<tr>
<td>Caravaggio</td>
<td>52</td>
<td>576</td>
</tr>
<tr>
<td>Hokusai VTE cancer</td>
<td>64</td>
<td>522</td>
</tr>
<tr>
<td>SELECT-D</td>
<td>25</td>
<td>203</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.65</td>
<td>[1.19, 2.28]</td>
</tr>
</tbody>
</table>

$P = 29\%$

<table>
<thead>
<tr>
<th>Death</th>
<th>DOAC</th>
<th>Dalteparin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ADAM VTE</td>
<td>23</td>
<td>145</td>
</tr>
<tr>
<td>Caravaggio</td>
<td>135</td>
<td>576</td>
</tr>
<tr>
<td>Hokusai VTE cancer</td>
<td>140</td>
<td>522</td>
</tr>
<tr>
<td>SELECT-D</td>
<td>48</td>
<td>203</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.99</td>
<td>[0.83, 1.18]</td>
</tr>
</tbody>
</table>

$P = 37\%$

---

Figure 3. Pooled efficacy and safety of factor Xa inhibitors compared with low-molecular-weight heparin in patients with cancer associated thrombosis. CI, confidence interval; CRNM, clinically relevant nonmajor; VTE, venous thromboembolism.
pnea to evidence suggestive of right heart failure, elevated pulmonary artery pressure with normal or low wedge pressure, and imaging showing residual pulmonary vascular obstruction. In other patients who have characteristic symptoms and perfusion defects of CTEPH but normal pulmonary artery pressure at rest, chronic thromboembolic disease occurs.

The concept of post-PE syndrome is growing but its spectrum and the diagnosis criteria are still controversial at the present time. With regard to CTEPH and chronic thromboembolic disease, the relevant information has been updated in the 2018 Taiwan Society of Cardiology focused update on diagnosis and treatment of pulmonary arterial hypertension.

SUMMARY

PE is part of VTE continuum. It could bring fatal consequences within few days or even hours without appropriate management. Therefore, rapidly identifying patients at risk and implanting the comprehensive diagnostic algorithm facilitates the timely therapeutics in the appropriate patients. The diagnosis of PE requires a sophisticated evaluation from pretest probability assessment till the confirmation by the imaging, whereas the treatment focuses on the use of anticoagulation. In patients at high risk of early complications and mortality, immediate thromboreduction treatment, either with pharmacological, surgical, or percutaneous measures, can be life-saving. In the rest of patients, either a parenteral heparin lead-in versus the single-drug approach or once daily versus twice daily NOACs are preferred over warfarin in most of the scenarios. Now, in patients with cancer and VTE, three factor Xa inhibitors are collectively as effective as, if not better than, the standard regimen, LMWH. Finally, a minority of patients with PE will develop long-term disturbing complications that requires further surveys and management by pulmonary hypertension specialists.

DISCLOSURE

Kang-Ling Wang reports honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Novartis, and Pfizer. Other authors have no relevant conflict of interest.

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