Venous thromboembolism in the elderly
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Summary
Old age is an independent risk factor of venous thromboembolism. Nevertheless initial symp-
toms are often attributed to existing cardiac or pulmonary comorbidity. Once deep thromboem-
bolism (DTE) is in focus, the synopsis of clinical findings and anamnestic clues help to take
further steps to establish or rule out the diag-
nosis (e.g. Wells score). Treatment consists in
oral anticoagulation, either by vitamin-k-antag-
onists or by direct oral anticoagulants ("DOACs"). Strict compliance of patients or
main caregivers is essential in both cases. Simult-
aneous medication of platelet-inhibiting- or
nonsteroidal anti-inflammatory drugs – often
unknown self medication – results in a raised
bleeding risk and should be avoided. If longterm
anticoagulation is mandatory, a strategy of se-
quential dose-reduced anticoagulation can be
considered, especially in the case of increased
bleeding-risk. Systemic fibrinolysis of pulmonary
embolism goes along with a very high bleeding
risk in old age and should be performed only in
case of vital circulatory depression or failure.

Epidemiology and aetiology
Venous thromboembolism (VTE) is a dis-
ease associated with age. The incidence in
the under-35s is 0.07 % but increases with
age to at least 0.7 % in the over-80s. This
means that the condition affects almost one
in a hundred elderly persons. It is also a
known fact that the proportion of clinically
manifest pulmonary emboli increases con-
siderably with age, in relation to deep vein
thrombosis of the legs. One study in Min-
nesota found the annual incidence of iso-
lated deep vein thrombosis to be almost
0.2 % in patients over 80, while the inci-
dence of pulmonary embolism with or
without deep vein thrombosis was about
0.7 % (1).

Older inpatients have a VTE more often
than younger patients, with an increased
proportion of clinically manifest pulmonary
emboli (2). VTE mortality increases consid-
erably with advancing age. 30-day post pulmonary embolism mortality in
elderly patients is 15–30 %, as opposed to
2 % in the under-40s (3, 4), and at least 5 %
with deep vein thrombosis as the primary
manifestation. The risk of clinical recur-
rence also increases with age, going up by
15–20 % per decade of life (5). Pulmonary
embolism as the primary clinical manifesta-
tion carries a less favourable prognosis
than deep vein thrombosis of the legs.

The RIETE registry showed a significant
effect of age on mortality three months
after VTE (3.7 % in patients >80 years vs
1.1 % in patients ≤80 years; odds ratio (OR)
3.6) (6).

A French study systematically investi-
gated 852 elderly inpatients using compres-
sion ultrasound scanning. The prevalence of
thrombosis involving the thigh was almost
6 %, with an overall prevalence of
about 16 %. Half of these patients were
receiving thrombosis prophylaxis (7).
It can therefore be assumed that the consistently greater comorbidity in the elderly, especially in patients under the care of a geriatrician, is a major factor in the increase in VTE mortality. This has been demonstrated in patients with comorbid cardiopulmonary, neurological, and oncological conditions (4, 8).

Folsom et al. (9) identified the core geriatric syndrome of frailty as an independent risk factor. In a prospective cohort study (4859 participants >65 years of age), the relative risk of idiopathic VTE in persons with frailty syndrome was 1.71.

An Italian research team looked at the relationship between obesity, muscle weakness, and VTE in elderly patients (In-Chianti study). The OR for VTE was about 9.5% in patients with obesity alone, about 6.5% in those with poor muscle strength alone, and rose to 14.5% in those patients who were both obese and had poor muscle strength (10).

The role of genetic variants of haemostasis and inflammatory mediators is a further focus of research into the aetiology of age-associated VTE (11). The significance of circulating cell membrane fragments as the vehicle for inducing coagulation cascades has also been addressed (12).

### Clinical symptoms/signs and diagnostic investigations

In the case of elderly and infirm patients with an increased risk of VTE, we have to remember that the initial events may well be clinically silent. One research group (TA-DEUS project) showed that 17.8% of patients over the age of 80 who were being treated in hospital for another medical reason had an asymptomatic VTE (13).

Irrespective of age, it has long been recognised that individual clinical symptoms and findings taken in isolation have a very low specificity and sensitivity for the presence of VTE.

It is a different matter, however, when several indicative parameters are present at the same time. Scores based on these criteria (e.g. Wells’ scores for pulmonary embolism and deep vein thrombosis; ▶ table 1 and ▶ table 2) (14) can play a crucial role in assessing the clinical pre-test probability of VTE and allow a rational and efficient procedure for further diagnostic investigation. This is particularly valuable in the case of pulmonary embolism: given the comorbidity, clinical symptoms are more difficult to evaluate in elderly patients. Here, too, the summation of several indicative findings allows us to at least narrow the diagnosis down. Compression ultrasound scanning of the leg veins may be helpful in such cases. If the results are positive, further diagnostic investigations can be dispensed with, as the treatment of deep vein thrombosis and pulmonary embolism is identical in patients with a stable circulation (15). This presupposes, however, that the diagnosis of pulmonary embolism has even been considered, all the more so under the “pressure” to explain the symptoms on the basis of pre-existing disease.

A small Irish study has, in fact, provided evidence that collapse in elderly patients with pulmonary embolism occurs significantly more often than in younger patients (16), but this does not help us at all in the individual case.

Nor does the determination of D-dimers help in the diagnosis of exclusion in elderly patients, as advanced age alone usually leads to false positive results (17).

### Wells’ score for pulmonary embolism (simplified version)

**Tab. 1**

<table>
<thead>
<tr>
<th>Symptom/signs</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical symptoms or signs of deep vein thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Pulmonary embolism is the most likely diagnosis; no other diagnosis is more likely</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>1</td>
</tr>
<tr>
<td>Immobilisation (even only a few days) or surgery in the previous four weeks</td>
<td>1</td>
</tr>
<tr>
<td>Previous confirmed deep vein thrombosis or pulmonary embolism</td>
<td>1</td>
</tr>
<tr>
<td>Haemoptysis (coughing up blood)</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (treated in the previous six months or palliative care)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Wells’ score for deep vein thrombosis

**Tab. 2**

<table>
<thead>
<tr>
<th>Symptom/signs</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis or immobilisation of the suspect lower extremity</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden (for more than three days) and/or major surgery within the previous four weeks</td>
<td>1</td>
</tr>
<tr>
<td>Tenderness/hardening along the deep vein system</td>
<td>1</td>
</tr>
<tr>
<td>Swelling of the entire leg</td>
<td>1</td>
</tr>
<tr>
<td>Unilateral calf swelling, &gt;3 cm larger than the other leg (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting oedema</td>
<td>1</td>
</tr>
<tr>
<td>Presence of collateral non-varicose superficial veins in the affected leg</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as DVT</td>
<td>−2</td>
</tr>
</tbody>
</table>

Score <2: low probability of deep vein thrombosis (DVT)/pulmonary embolism (PE); Score ≥2: high probability of DVT/PE
In addition – at least in elderly patients who are in hospital – it is not unlikely that D-dimer measurement will give a false positive for other reasons (e.g. concomitant inflammation, bleeding, trauma etc.). A targeted work-up with compression ultrasound scanning or cross-sectional imaging is therefore required if we suspect VTE.

**Prophylaxis and treatment**

According to the current guidelines on the prophylaxis of venous thromboembolism (20), elderly and especially infirm patients in hospital for the treatment of underlying general medical, neurological or surgical conditions (exposure factors) usually require consistent pharmacological VTE prophylaxis.

However, the question arises concerning the procedure to be followed for immobile patients in need of long-term care, for example those in nursing homes. Pharmacological thrombosis prophylaxis is not the rule here. A small retrospective Israeli cohort study carried out over 10 years in patients with similar baseline medical parameters (n=26, mean age 85 ± 8.4) found no difference in the incidence of VTE between the mobile and immobile groups (18). The few other data available from the literature (19) also suggest that immobility and the need for long-term nursing care per se are of secondary importance as predisposing factors, as long as none of the previously mentioned factors with a considerably higher probability of thromboembolism is also present.

The treatment of choice in VTE is anticoagulation therapy. In the long term, the standard procedure consists of initial treatment with a low molecular weight heparin (LMWH) or fondaparinux, overlapping saturation with a vitamin K antagonist (VKA), and discontinuation of the LMWH or fondaparinux, overlapping with a low molecular weight heparin (LMWH) or fondaparinux, overlapping with a vitamin K antagonist (VKA) immediately on the first day of treatment was associated with a reduced risk of bleeding (hazard rate (HR) 0.37; confidence interval (CI) 0.20–0.71) but there was no difference in mortality or VTE recurrence rate between the strategies. Just under half (47%) of the bleeds occurred in the first month of treatment.

Emergency systemic fibrinolysis is the treatment of choice for pulmonary embolism with symptoms of shock. There is some controversy over fibrinolytic therapy for pulmonary embolism with significant right heart strain (atrial natriuretic peptide, troponin, echocardiographic findings) but no circulatory depression.

Investigations in the PEITHO study (27) indicated that routine systemic fibrinolysis in right heart strain without symptoms of shock, i.e. not life-threatening, is associated with a considerable risk of major bleeding in elderly patients >75 years, with a figure of 11.1% in comparison with 5.5% for patients up to the age of 75. The rate of cerebral haemorrhage was 2% in the fibrinolysis group and 0.2% in the placebo group.

The better strategy, at least in elderly patients, is to hold off fibrinolysis until there is a clear development of hemodynamic instability: in this study, only 17 of the 500 patients in the placebo group were given crossover treatment with fibrinolysis because of secondary symptoms of shock.

Apart from vitamin K antagonists, direct thrombin and factor Xa antagonists (known as direct oral anticoagulants [DOAC] or novel oral anticoagulants [NOAC]) are available for oral anticoagulation.

The great advantage of these substances is a stable dose-effect relationship with only slight interference from food and other medications, so that close laboratory monitoring is no longer required.

A meta-analysis looked at the efficacy and complications of direct oral anticoagulants in the elderly, used for the treatment of venous thromboembolism and stroke prevention in atrial fibrillation (28). All drugs (dabigatran, rivaroxaban, apixaban, edoxaban) were at least as effective as vitamin K antagonists for both indications. Although the statistical analysis in the treatment of VTE was limited by the small number of index events, it still showed non-inferiority to VKAs.

Apixaban (OR 0.63) and edoxaban 60 mg (OR 0.81) and 30 mg (OR 0.46) reduced the risk of major bleeding in elderly patients.

Dabigatran showed a non-significant higher risk of major bleeding (OR 1.15) with the 150 mg strength and a risk similar to that of VKAs with the 110 mg dose. In the total population, however, the risk of major bleeding was not significant (150 mg) or significantly reduced (110 mg).

Gastrointestinal (GI) bleeding occurred significantly more often in the elderly, not only at a dose of 150 mg twice daily (OR 1.78) but also at a dose of 110 mg twice daily (OR 1.40). According to the authors, data on the other substances had not been published or made available. Irrespective of age, the increased risk of GI bleeding in the total population was sustained with dabigatran 150 mg twice daily but not with the 110 mg dose, and was also seen with rivaroxaban (20 mg) and edoxaban (60 mg).
The lowered risk of intracranial bleeding in the elderly compared with VKAs for dabigatran (OR 0.43 for 150 mg twice daily; OR 0.36 for 110 mg twice daily) and apixaban (OR 0.38) was of particular note. The reduction of bleeding seen with rivaroxaban was not significant.

Data on fatal bleeding were limited by the small number of index events, but at least showed the non-inferiority of DOACs.

It is essential to ensure patient compliance or the reliable assistance of the main carer for all anticoagulants used for VTE.

It is also true for all anticoagulants that combinations with platelet aggregation inhibitors and non-steroidal anti-inflammatory drugs increase the risk of bleeding in elderly patients.

If long-term anticoagulation is necessary, stepping down the dose should be considered, such as the use of a lower INR target range of 1.5 to 2 when using VKAs in long-term prophylaxis in geriatric patients, for example, after idiopathic VTE. Ridker et al. showed that, compared with placebo, the VTE recurrence rate could be reduced by 64% (relative risk) with no increase in the risk of bleeding (29). The risk of bleeding was no higher than that with placebo. On the other hand, in a direct comparison, Kearon et al. found that full anticoagulation (INR 2–3) gave a relative risk reduction of 69% (30). Taken overall, it is worth considering a strategy of a lower target INR when weighing up the risks of bleeding and VTE in the individual case. Even so, the maintenance of a stable INR is still prerequisite.

The following procedure can also be used with the "novel" oral anticoagulants: A lower dose of the direct thrombin inhibitor apixaban has been shown to be effective for long-term treatment in comparison with placebo (AMPLIFY-EXT study). Lower doses of 5 mg and even 2.5 mg reduced the absolute risk of recurrent VTE by 7% and 7.2%, respectively, but not at the cost of an increased rate of bleeding (31). The EINSTEIN CHOICE study is currently testing a similar procedure for rivaroxaban against aspirin (32).

### Conflict of interest

The author declares that there is no conflict of interest.

### Ethical guidelines

Preparation of the manuscript did not involve any studies on humans or animals.

### References

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