

# Preventing Deep Vein Thrombosis After Stroke: Strategies and Recommendations

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## Opinion statement

The risk of deep vein thrombosis (DVT) after stroke is increased in patients with restricted mobility, a previous history of DVT, dehydration, or comorbidities such as malignant diseases or clotting disorders. Patients with an increased risk of DVT should receive prophylactic treatment. To reduce the chance of DVT, patients should be mobilized as soon as possible and should be kept well hydrated. Anti-embolism stockings cannot be recommended, because they have been demonstrated not useful for preventing DVT or pulmonary embolism in patients with stroke, and they are associated with a significantly increased risk of skin breaks. The usefulness of intermittent pneumatic compression is currently under study in a randomized clinical trial. Treatment with subcutaneously administered low-dose unfractionated heparin is preferred to unfractionated heparin and may be considered in patients with ischemic stroke if the risk of DVT is estimated to be higher than the risk of hemorrhagic complications. Aspirin may also be effective for patients with ischemic stroke who have contraindications to anticoagulants, although direct comparisons with anticoagulants are not available. In patients with intracerebral hemorrhage, low-dose subcutaneous low-molecular-weight heparin is probably safe after documentation of cessation of active bleeding, and may be considered on an individual basis after 3 to 4 days from stroke onset.

## Introduction

Patients with stroke have a relatively high risk of deep vein thrombosis (DVT) because of immobility and increased prothrombotic activity [1]. DVT in the paralyzed leg of a stroke patient was described as early as 1810 by Ferriar [1]. The clinical diagnosis of DVT may be difficult, as there are no reliable

clinical signs or symptoms that can be used for a definite diagnosis. Most cases of DVT detected with ancillary investigations is asymptomatic. The preferred method to diagnose DVT is currently Doppler ultrasonography, but <sup>125</sup>I fibrinogen scanning, venography, and MRI of the thrombus can also

be used. In patients with an ischemic stroke and a severe handicap, assessment of d-dimer on day 9 after stroke has been associated with an increased incidence of DVT [2]. Depending on the diagnostic methods, DVT has been said to occur in up to 80% of patients with ischemic stroke who did not receive prophylactic therapy [3]. Clinically relevant DVT has been reported in 1% to 5% of the patients [4]. DVT develops most often between days 2 and 7 after stroke onset; about 80% of all DVTs occur within the first 10 days [5••]. The incidence of clinically apparent DVT was studied in a large cohort of hospitalized patients with stroke from 1979 to 2003 [1]. DVT was reported in 0.74% of 1,410,000 patients with ischemic stroke and in 1.37% of 1,606,000 patients with hemorrhagic stroke [1]. These rates did not change over the 25-year period of observation. The difference between patients with ischemic and hemorrhagic stroke probably is the result of less rigid preventive management and of a generally more severe focal deficit in the second group. In the CLOTS-2 (Clots in Legs Or sTockings after Stroke), DVT also occurred about twice as often after hemorrhagic stroke than after ischemic stroke [6••].

DVT is associated with increased mortality and morbidity. In the International Stroke Trial (IST),

0.8% of patients who did not receive thrombosis prophylaxis developed a clinically apparent pulmonary embolism (PE) within the first 2 weeks after stroke onset [7]. PE accounts for 13% to 25% of early deaths after stroke [8]. Proximal thrombosis is considered to carry a higher risk for PE than thrombosis in the calves. The risk of DVT and PE for patients with an acute ischemic stroke resembles that of patients undergoing major surgical procedures. The combination of DVT and PE occurred in 1.17% of patients hospitalized with ischemic stroke and in 1.93% of patients with hemorrhagic stroke [1]. DVT also can lead to post-phlebotic leg and varicose ulcers, and it can delay rehabilitation.

There is no evidence-based method of predicting the occurrence of DVT after stroke. In the CLOTS-2 trial, the following items were associated with an increased risk of DVT: dependency before stroke (OR, 3.06; 95% CI, 1.70–5.51), inability to lift arms off bed (OR, 2.97; 95% CI, 1.68–5.26), inability to lift both legs (OR, 2.09; 95% CI, 1.93–3.40), and history of DVT or PE (OR, 2.92; 95% CI, 1.42–5.97). Non-stroke-related factors that increase the risk of DVT include increased age, obesity, hormone therapy, a prothrombotic state, and cancer. Genetic components probably also play a role.

## Treatment

### Nonpharmacologic treatment

#### Early mobilization

- Preliminary results suggest that early mobilization after stroke is not harmful [9]. The usefulness of early mobilization after acute ischemic stroke is currently tested in the multicenter A Very Early Rehabilitation Trial (AVERT).
- Although the results of AVERT must be awaited for a definite statement, early mobilization of patients with ischemic stroke can be recommended, because it probably lessens the likelihood not only of DVT and PE but also of pneumonia and pressure sores [10, Class IV].

#### Hydration

- Dehydration after ischemic stroke is independently associated with DVT [11]. In the context of DVT prophylaxis, fluid intake has not been evaluated in a clinical trial, but current guidelines advocate

specific attention to keep patients well hydrated in the early stage of ischemic stroke [12, Class IV].

### Graduated compression stockings

- A meta-analysis of 2,615 patients demonstrated that the use of graduated compression stockings was not associated with a reduction in risk of DVT (OR, 0.88; 95% CI, 0.72–1.08) or death (OR, 1.13; 95% CI, 0.87–1.47) [13]. This meta-analysis included the results of the CLOTS-1 trial, which randomized 2,518 immobile patients with acute stroke to thigh-length graduated compression stockings or no stockings [5••]. The results of the CLOTS-2 trial, which randomized 3,114 patients to thigh-length or below-knee stockings, were published after this meta-analysis [6••]. The CLOTS-1 trial showed that that full-length stockings did not significantly reduce the risk of DVT, as compared with no stockings; the absolute risk reduction was 0.5% (95% CI, -1.9 to 2.9) [5••]. In the CLOTS-2 trial, there was a trend towards increased DVT in the group that used knee-length stockings as compared with thigh-length stockings; the absolute risk increase was 2.5% (95% CI, 0.7–4.4) [6••]. Both types of stockings were associated with an increase in the risk of skin complications.
- The routine use of stockings cannot be recommended on the basis of current evidence [6••, 13, Class I].

### Intermittent pneumatic compression

- A meta-analysis of two trials with a total of 177 patients showed that the use of intermittent pneumatic compression within the first week after stroke onset was associated with a nonsignificant trend towards a lower risk of DVT (OR, 0.45; 95% CI, 0.19–1.10), with no evidence of an effect on deaths (OR, 1.04; 95% CI, 0.37–2.89) [13]. One of the studies in this meta-analysis has addressed the benefits of intermittent pneumatic compression in preventing DVT in 155 patients with intracerebral hemorrhage [14]. The combination of elastic stockings and intermittent pneumatic compression significantly decreased the occurrence of asymptomatic DVT, as compared with the use of elastic stockings alone (relative risk, 0.29; 95% CI, 0.08–1.00) [14].
- Another meta-analysis showed that in high-risk patients the combination of antithrombotic treatment and intermittent pneumatic compression significantly reduced the incidence of DVT as compared with intermittent pneumatic compression alone; the risk dropped from about 4% to 1% (OR, 0.43; 95% CI, 0.24–0.76) [15]. Compared with pharmacologic prophylaxis alone, the use of combined modalities also significantly reduced the incidence of DVT from 4.21% to 0.65% (OR, 0.16; 95% CI, 0.07–0.34) [15].
- Currently, in the multicenter randomized CLOTS-3 trial, the usefulness of intermittent pneumatic compression is being tested versus routine care including aspirin, hydration, and the possible use of

stockings. Pending the results of this trial, intermittent pneumatic compression for the prevention of DVT in patients with an acute stroke can only be recommended in the context of a clinical trial [13, Class I].

## Antithrombotic treatment in patients with ischemic stroke

### Unfractionated heparin

- In a Cochrane meta-analysis, the use of subcutaneous and intravenous unfractionated heparin, low-molecular-weight heparins, subcutaneous and intravenous heparinoids, oral vitamin K antagonists, and specific thrombin inhibitors was associated with a highly significant reduction in the risk of DVT in patients with ischemic stroke (OR, 0.21; 95% CI, 0.15–0.29), although the majority of DVTs detected were subclinical and asymptomatic [16]. However, the International Stroke Trial showed that the prevention of recurrent ischemic stroke by subcutaneous administration of unfractionated heparin (5000 U or 12,500 U twice daily) was offset by a proportional increase in the rate of intracranial hemorrhagic events, resulting in the absence of a net benefit from this preventive treatment [7]. Therefore, routine use of unfractionated heparin cannot be recommended to prevent DVT [7, Class I].

### Low-molecular-weight heparin

- A meta-analysis showed that low-molecular-weight heparin or heparinoid reduces the risk of DVT (OR, 0.27; 95% CI, 0.08–0.96) in patients with acute ischemic stroke as compared with placebo, but they are associated with a twofold increase in the risk of extracranial bleeding (OR, 2.17; 95% CI, 1.10–4.28) [17].
- Another meta-analysis showed that in patients with ischemic stroke, prophylaxis with low-molecular-weight heparin or heparinoid was associated with a significant reduction in the occurrence of DVT as compared with standard unfractionated heparin (OR, 0.55; 95% CI, 0.44–0.70) [18].
- The open-label, randomized PREVAIL study compared 10 days' treatment with prophylactic enoxaparin (40 mg once daily) with unfractionated heparin (5000 U twice daily) for the prevention of the combined end point of symptomatic or asymptomatic DVT or symptomatic PE after acute ischemic stroke [19•]. Enoxaparin reduced the risk of DVT or PE; the absolute risk reduction was 7.9% (95% CI, 4.2–11.6) [19•]. The composite of symptomatic intracranial and major extracranial hemorrhage occurred in 1% of both groups. It remains uncertain whether enoxaparin is also associated with a clinical benefit. When considering the total cost of events and drugs, enoxaparin was associated with cost-savings of \$895 per patient compared with unfractionated heparin (\$2,018 vs \$2,913) [20].
- Despite a small but definite risk of major hemorrhage, low-molec-

ular-weight heparin is the preferred medication for the prevention of DVT in patients with ischemic stroke [18, 19•, Class I].

### Antiplatelet therapy

- Information about antiplatelet therapy for the prevention of DVT is scarce. A Cochrane review of two small trials including 133 patients (fewer than 0.3% of the participants included in the overall review) showed that antiplatelet therapy did not reduce the risk of DVT (OR, 0.78; 95% CI, 0.36–1.67) [21]. However, aspirin in the acute stage of ischemic stroke is associated with a reduction in recurrent stroke and is not associated with an excess of intracerebral hemorrhages [7]. Therefore, it seems reasonable to conclude that routine use of aspirin alone in patients with acute ischemic stroke is safe. It remains unclear whether aspirin alone is as good as low-molecular-weight heparin for the prevention of DVT.
- Aspirin alone may be an adequate antithrombotic agent to be used for routine DVT prophylaxis in patients with acute ischemic stroke, but this has not been demonstrated in a clinical trial [21, Class IV].

### Antithrombotic treatment in patients with hemorrhagic stroke

- The role of anticoagulants in preventing DVT or PE following acute hemorrhagic stroke is uncertain. A meta-analysis of four studies (two randomized) involving 1,000 patients with acute hemorrhagic stroke showed that the use of unfractionated heparin, heparinoid, or low-molecular-weight heparin was associated with a nonsignificant reduction in the risk of DVT, from 4.2% to 3.3% (RR, 0.77; 95% CI, 0.44–1.34) [22]. The reduction in mortality (16.1% vs 20.9%) also was not significant (RR, 0.76; 95% CI, 0.57–1.03), and anticoagulants were associated with a nonsignificant increase in any hematoma enlargement (8.0% vs 4.0%; RR, 1.42; 95% CI, 0.57–3.53) [22].
- There are no clinical data on the usefulness of antiplatelet therapy for the prevention of DVT in patients with hemorrhagic stroke, and this type of therapy should be discouraged.
- After documentation of cessation of bleeding, low-dose subcutaneous low-molecular-weight heparin is probably safe in patients with intracerebral hemorrhage. It may be considered on an individual basis for patients with hemiplegia after 3 to 4 days from stroke onset [22, 23, Class IV].

### Disclosure

Conflict of interest: L.J. Kappelle: consulting fees from Boehringer Ingelheim, Bayer, Boston Scientific; speakers' fees from Boehringer Ingelheim and Bayer.

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