Should Patients With Stroke Wear Compression Stockings to Prevent Venous Thromboembolism?

Venous thromboembolism, including deep venous thrombosis and pulmonary embolism, is a common and preventable complication of acute stroke (1). Without the use of prophylaxis, asymptomatic deep venous thrombosis occurs in about 40% and symptomatic deep venous thrombosis or pulmonary embolism in about 5% of patients who are immobilized after stroke (1,2). Low-dose unfractionated heparin and low-molecular-weight heparin reduce venous thromboembolism by about two thirds, but these therapies may be associated with an increase in intracerebral hemorrhage in patients with ischemic stroke and are contraindicated in the approximately 20% of patients with stroke who have primary acute intracerebral hemorrhage (1).

Mechanical interventions to reduce venous stasis without increasing bleeding risk are an appealing method of thromboprophylaxis after stroke (3). These interventions include graduated compression stockings, which reduce the pooling of blood in the deep veins by applying greater pressure at the ankle than higher up the leg, and intermittent pneumatic compression devices, which cyclically inflate and deflate to promote venous return. Of these options, graduated compression stockings have the advantages of being less expensive and easier to use, and they also permit greater patient mobility. On the basis of evidence of their efficacy in patients who have had surgery (4), as well as a single small study (5) that suggests they are effective in patients with stroke, physicians often include graduated compression stockings in the acute care of patients after stroke (3, 6). However, 2 large randomized trials (2,7), including CLOTS (Clots in Legs Or sTockings after Stroke) Trial 2 in this issue (7), prompt a reevaluation of the role of graduated compression stockings for preventing venous thromboembolism in patients with acute stroke and, by extension, in other populations.

The CLOTS Trials are a series of 3 trials evaluating mechanical interventions to prevent venous thromboembolism in patients with acute stroke. CLOTS Trial 1 (2) compared thigh-length compression stockings with no stockings in about 2500 patients and found that thigh-length stockings were ineffective at preventing the combined outcome of asymptomatic, ultrasonography-detected, and symptomatic proximal deep venous thrombosis (odds ratio, 0.98 [95% CI, 0.76 to 1.27]). CLOTS Trial 2 compared thigh-length stockings with below-knee stockings in 3014 patients with acute stroke and found fewer cases of venous thromboembolism with thigh-length than with below-knee stockings (odds ratio, 0.69 [CI, 0.53 to 0.91]) (7). The ongoing CLOTS Trial 3 is comparing intermittent pneumatic compression with a control group.

Although interpretation of the findings of CLOTS Trials 1 and 2 in isolation might seem straightforward, interpreting the 2 studies together is more difficult. If thigh-length stockings are ineffective (CLOTS Trial 1), why are they more effective than below-knee stockings (CLOTS Trial 2)? One possibility raised by the CLOTS investigators is that below-knee stockings increase the risk for venous thromboembolism. However, in the few studies that assessed below-knee stockings in surgical patients and in studies of long-distance air travellers, below-knee stockings seemed to be more effective than no stockings (4,8). Another possible explanation for the findings of CLOTS Trials 1 and 2 is that thigh-length stockings result in a modest reduction of venous thromboembolism of about 20%. This modest reduction could have been missed in CLOTS Trial 1, and would be consistent with the findings of CLOTS Trial 2 if below-knee stockings neither increased nor decreased the risk for venous thromboembolism.

Could differences in study design explain the discrepant findings of CLOTS Trials 1 and 2? This does not seem to be the case. Although the clinical centers that enrolled patients in each trial differed, the patient populations in the 2 studies were very similar. Both studies also used the same type of thigh-length stockings, had similar follow-up procedures, defined the same primary outcome, and measured it similarly. Although patients and caregivers were not blinded to treatment in either study, it is unlikely that the lack of blinding negatively biased the assessment of efficacy of thigh-length stockings in CLOTS Trial 1 or positively biased it in CLOTS Trial 2. It is also unlikely that the early stopping of CLOTS Trial 2 in response to the results of CLOTS Trial 1 led to an overestimate of the efficacy of thigh-length stockings in CLOTS Trial 2. Similarly, ascertainment bias is unlikely to explain the discrepant findings because even if patients who wore shorter stockings were more likely to have ultrasonography performed because they had greater leg swelling, routine ultrasonography also detected a higher frequency of deep venous thrombosis in the below-knee stocking group.

Given the puzzling findings of CLOTS Trials 1 and 2, how should clinicians attempt to prevent venous thromboembolism in patients with acute stroke? Current evidence suggests that graduated compression stockings are, at best, modestly effective at preventing venous thromboembolism in patients with stroke and immobility, and their use is associated with skin breakdown in about 5% of patients (2,7). Whether intermittent pneumatic compression, which also avoids the risk for intracerebral bleeding that is associated with anticoagulants, is effective will not be known until the completion of CLOTS Trial 3, and we will still lack a direct comparison of pneumatic compression with graduated compression stockings. Despite some concerns that low-dose unfractionated heparin and low-molecular-
weight heparin increase intracerebral bleeding, the American College of Chest Physicians and the American Heart Association recommend these agents in patients with acute ischemic stroke and immobility who do not have additional contraindications to anticoagulant therapy (9, 10). The lack of a clearly effective mechanical alternative to unfractionated heparin and low-molecular-weight heparin lends support to the cautious use of these agents in patients with acute ischemic stroke. In patients with stroke for whom anticoagulant therapy is contraindicated, it is reasonable to use thigh-length stockings or intermittent pneumatic compression if caregivers are vigilant for signs of skin breakdown.

The unexpected findings that thigh-length stockings are not very effective at preventing venous thromboembolism and that below-knee stockings might increase incidence of thrombosis in patients with stroke should prompt a reevaluation of the role of graduated compression stockings in other groups of patients. Such studies should be large enough to assess the frequency of symptomatic venous thromboembolism, an outcome of clear importance to patients. The CLOTS investigators address several important clinical questions and raise others in their ongoing, rigorously performed studies. Clinicians need to realize that despite the ubiquity of graduated compression stockings in many settings, the net benefits and risks of this seemingly innocuous intervention remain uncertain.

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