Effective Prophylaxis for Deep Venous Thrombosis After Stroke
Both Low-Dose Anticoagulation and Stockings for Most Cases

Stephen M. Davis, MD, FRACP; Geoffrey A. Donnan, MD, FRACP

What are the factors that underline the benefits achieved by stroke unit care? Although incompletely understood, an increased adherence to a range of processes of care is important. Many of these processes are directed at the prevention of poststroke complications. Among the most important of these is prophylaxis against deep venous thrombosis (DVT) and pulmonary embolism. Although there have been a number of small trials in stroke patients demonstrating the relative safety and usefulness of low-dose anticoagulants, the evidence base is relatively small, as pointed out by Dennis. Both protagonists consider that in patients at very high risk, there is no debate, and low-dose heparin or low-molecular-weight heparin/heparinoids should be used. Nonetheless, it would appear that Adams would advocate anticoagulation more often. Interestingly, neither seems to favor stockings as routine. Although relatively uncommon in stroke, most of us will have managed patients who are about to go from acute care to a rehabilitation unit, and who suddenly deteriorate because of life-threatening pulmonary embolism.

The risk of low-dose anticoagulation, specifically the development of symptomatic hemorrhagic transformation, appears to be quite low. The accumulated evidence for this is now quite strong. Although Dennis draws attention to the discomfort and potential risks of stocking use, we find that they are generally well-tolerated. Systematic overview shows that graduated compression stockings are effective in diminishing the risk of DVT in hospitalized patients, even more so when combined with a form of antithrombotic therapy.

What do we do in our practice? We recognize the inadequacy of the evidence in guiding clinical practice and look forward to the completion of trials such as CLOTS and new DVT prevention trials using low-dose anticoagulation. At present, we routinely use below-knee stockings in most stroke patients in our Stroke Care Units and use this as a quality indicator of the unit performance. In patients at higher risk, particularly those who are difficult to mobilize or have major leg weakness, we use a combination of stockings and low-dose anticoagulation. We also apply these principles to patients with intracerebral hemorrhage, but only after their conditions have stabilized. There is also uncertainty about the type of anticoagulation. Following an earlier small trial, a larger study is comparing unfractionated heparin with a low-molecular-weight heparin. Direct thrombin inhibitors, such as ximelagatrin, might have a role in the future. On this occasion, while awaiting more evidence, we favor a more aggressive approach.

References

Key Words: deep vein thrombosis, heparin, pulmonary embolism, stroke
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Low-Dose Anticoagulation Rather Than Stockings Alone: For

Harold P. Adams, Jr, MD

Deep vein thrombosis (DVT) is an important cause of morbidity in its own right and it is complicated by pulmonary embolism, a potential cause of death after stroke.1 DVT occurs most commonly among seriously ill or elderly patients who have paralysis of the lower extremity, and it can develop in either an acute care or a rehabilitation setting.2 Because DVT can be prevented effectively, treatment guidelines rightly emphasize the importance of prophylactic measures.3

Treatment options include early ambulation, use of stockings supplemented by alternating pressure devices, and antithrombotic agents. Each option has limitations. Whereas early mobilization is recommended for mildly affected patients, seriously ill patients or those with severe motor impairments often cannot return to walking. Stockings can be used to treat bedridden patients who have an intracranial hemorrhage or another contraindication for antithrombotic agents, but data showing efficacy in the setting of stroke are limited. Any recommendation is inferred from the experience in other groups of patients.2,4 In addition, these interventions cannot be used on a long-term basis, and patients initially treated with compression stockings subsequently often need antithrombotic therapy.

Oral anticoagulants are the standard intervention for the long-term prevention of DVT, and they are effective in patients surviving stroke.5,6 Anticoagulants are the preferred therapy for patients considered to be at high risk for DVT. Their status is demonstrated by the design of clinical trials of other interventions; their usefulness is compared with the effectiveness of anticoagulation. Evidence for the efficacy of parenteral anticoagulants in preventing DVT, in a variety of settings, including for treatment of immobilized patients, is robust.5 Data from individual trials and meta-analyses demonstrate the efficacy of anticoagulants in preventing DVT after stroke.7–10 However, Kelly et al12 rightly note that the significance of the meta-analyses is muted by the heterogeneous nature of the included trials. Hillbom et al11 showed that low molecular weight heparin probably was superior to unfractionated heparin in preventing venous thromboembolic events following ischemic stroke.

Whereas anticoagulants are effective in preventing DVT after stroke, the real question is whether these medications can be administered with a reasonable degree of safety. Their safety partially relates to the timing of initiation of treatment. Even low-dose anticoagulants given to prevent DVT can be accompanied by bleeding. The issue is whether the risk of bleeding, including intracranial hemorrhage, outweighs the benefit of DVT prophylaxis. Presumably, patients with a primary intracranial hemorrhage or a large multilobar infarction might not tolerate early anticoagulation to prevent DVT. Still, the bleeding risk of parenterally administered anticoagulants used to prevent DVT is not known. For example, one small trial found that heparin could be started safely within 2 days of a spontaneous intracerebral hemorrhage.12 Most of the available information about the use of anticoagulants after ischemic stroke is inferred from clinical trials in which the primary indication for emergent anticoagulation was to improve neurological outcome.8

Using care, anticoagulants can be recommended for the reduction of the risk for DVT in many patients with recent stroke. Evidence to support their use is the stronger than that for either stockings or antiplatelet agents. Some patients probably can be safely treated within a few hours of stroke. Besides being effective, anticoagulant prophylaxis eliminates the necessity for the compression stockings and devices, which are cumbersome and often not tolerated well by patients. Anticoagulants remain a key component of ancillary care of patients with stroke. In carefully selected patients, these medications remain the best therapy to prevent DVT. The duration of treatment will depend on the needs of the patient and the perceived long-term risk of the medications. Maybe future studies will demonstrate that compression stockings or devices or antiplatelet agents are equal to or superior to anticoagulants. Until then, these measures should be reserved for treatment of those patients who might have a high bleeding risk associated with anticoagulation.

References
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Low-Dose Anticoagulation Rather Than Stockings Alone: Against

Martin S. Dennis, MD

Approximately 5% of hospitalized stroke patients have a clinically apparent deep vein thrombosis (DVT) and ≈2% will have a pulmonary embolus (PE) confirmed. However, prospective studies that systematically screen for DVT with, for example compression Doppler ultrasound or magnetic resonance imaging, identified DVT in up to 50% of patients. Some patients who are breathless because of aspiration pneumonia, chest infection, or heart failure may actually have had an undiagnosed pulmonary embolus. Autopsies often identify clinically unrecognized PEs that probably contributed to the patient’s death. Therefore, it seems sensible to offer patients prophylaxis against venous thromboembolism. However, a brief discussion with colleagues is likely to reveal wide variation in the approaches taken to prophylaxis.

In our unit, we aim to treat all patients with ischemic stroke with aspirin within 48 hours, because this has been shown to improve long-term outcomes and probably also reduces the risk of venous thromboembolism to some extent. In addition, we try to ensure that patients are adequately hydrated and mobilized as early as possible. These interventions will, we hope, reduce other complications as well, although we acknowledge the lack of direct evidence for the benefits of either of these interventions.

We reserve low-dose subcutaneous heparin (5000 U twice daily) for a small number of carefully selected patients. The systematic reviews of all the randomized controlled trials of heparin in acute ischemic stroke suggest that although heparin is likely to substantially reduce the risk of both DVT (at least that detected on isotope labeled fibrinogen) and of PE, it does not, on average, improve patients’ survival or their functional outcome. Any reduction in venous thromboembolism, and early recurrent cerebral ischemic events, appears to be completely offset by an increase in hemorrhagic complications (the most disabling being symptomatic intracranial hemorrhage). Thus, we only use heparin for DVT prevention in selected patients who we believe have a much greater than average risk for venous thromboembolism and a less than average risk for hemorrhagic complications. The criteria we use are based on “common sense” rather than hard evidence, which does not exist. Thus, we would consider low-dose heparin in an obese stroke patient with severe leg weakness and a history of previous venous thromboembolism, known disseminated malignancy, or some other prothrombotic state. We would avoid heparin in those with larger cerebral infarcts but would be less worried in patients with a lacunar infarct in which hemorrhagic transformation appears to be unusual. Today, we might, rightly or wrongly, avoid heparin if gradient echo magnetic resonance imaging has shown microhemorrhages.

Far more controversial than the use of heparin in our view is the assumption made in the title of this “controversy” that stockings should represent the standard approach. We currently do not routinely apply graduated compression stockings (GCS) to the legs of immobile stroke patients because we are uncertain that they are of net benefit. We do not believe that the available evidence is sufficient to justify their routine use.
The evidence that GCS stockings prevent DVT comes from meta analyses of \( \approx 19 \) small randomized control trials, which together suggest that they reduce the risk of DVT by approximately two-thirds.\(^5,6\) However, 17 of these trials were in surgical patients. In surgical patients, unlike those with stroke, GCS can be applied before the onset of paralysis; paralysis is usually brief and mobilization rapid. In patients with peripheral arterial disease, diabetes, and peripheral neuropathy (which are more common in stroke than the average surgical patient), GCS can cause skin necrosis, which may even lead to amputation. They have other less serious but nonetheless important disadvantages. Stroke patients, and especially those with urinary incontinence, find GCS uncomfortable. GCS are time-consuming to apply and monitor properly and the time nurses spend on this activity might be better spent in other ways if GCS are not effective. Only one randomized control trial has tested stockings in stroke patients, and this was far too small to provide a reliable estimate of effect.\(^5,7\)

Interestingly, although below-knee GCS are used, almost all the trial evidence is based on the full-length variety.

We enroll our patients in the CLOTS (Clots in Legs Or TEDS after Stroke) Trial, which is a family of 2 multicenter international randomized control trials funded by the UK Medical Research Council (www.clotstrial.com). Trial 1 aims to establish whether full-length GCS reduce the risk of DVT after stroke, and trial 2 aims to establish if full-length stockings are more effective than below-knee GCS. In the CLOTS trial, some patients get stockings and others avoid them, but all benefit from routine noninvasive screening for DVT, and thus the possibility of early treatment for occult DVT. We reckon this is the best management we can offer at this time.

**References**


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