European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke

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Abstract

Background: Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism is a frequent complication in immobile patients with acute ischemic stroke. This guideline document presents the European Stroke Organisation guidelines for the prophylaxis of VTE in immobile patients with acute ischaemic stroke. Guidelines for haemorrhagic stroke have already been published.

Methods: A multidisciplinary group identified related questions and developed its recommendations based on evidence from randomised controlled trials using the Grading of Recommendations Assessment, Development, and Evaluation approach. This guideline document was reviewed within the European Stroke Organisation and externally and was approved by the European Stroke Organisation Guidelines Committee and the European Stroke Organisation Executive Committee.

Results: We found mainly moderate quality evidence comprising randomised controlled trials and systematic reviews evaluating graduated compression stockings (GCS), intermittent pneumatic compression (IPC) and prophylactic anticoagulation with unfractionated (UFH) and low molecular weight heparins (LMWH) and heparinoids, but no randomised trials evaluating neuromuscular electrical stimulation (NES). We recommend that clinicians should use IPC in immobile patients, but that they should not use GCS. Prophylactic anticoagulation with UFH (5000U ×2, or ×3 daily) or LMWH or heparinoid should be considered in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of VTE is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use. Where a judgement has been made that prophylactic anticoagulation is indicated LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs and patient comfort associated single vs. multiple daily injections but these advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and risks in elderly patients with poor renal function associated with LMWH and heparinoids.

Conclusions: IPC, UFH or LMWH and heparinoids can reduce the risk of VTE in immobile patients with acute ischaemic stroke but further research is required to test whether NES is effective. The strongest evidence is for IPC. Better methods are needed to help stratify patients in the first few weeks after stroke onset, by their risk of VTE and their risk of bleeding on anticoagulants.

Keywords

Stroke, deep vein thrombosis, pulmonary embolism, guidelines

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Introduction

Recently, the European Stroke Organisation (ESO) updated its policy on preparation and publication of clinical guidelines.[1] There have been two major developments: First, it was decided that the ESO would implement the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system as a guide for the preparation of the guidelines because of its advantages over other systems.[2,3] Second, it was decided that guidelines would not be prepared and published as a single document but rather in several documents each one focusing on a specific topic of interest (called a 'module'); this approach allows us to address each module in greater detail and depth, and also provides more flexibility to the development and updating processes which in turn contributes to the aim of delivering up-to-date guidelines in a timely manner.

The authors were asked to develop guidelines on behalf of the ESO for the prophylaxis of venous thromboembolism (VTE) in patients with acute ischaemic stroke. The focus on ischaemic stroke, rather than all stroke, was dictated by the prior publication of ESO guidelines for the management of intracerebral haemorrhage which included prophylaxis of VTE.[4] Their recommendations for patients with ICH were:

> "We do not recommend short or long graduated compression stockings for the prevention of DVT. We recommend intermittent pneumatic compression to improve outcome and reduce the risk of DVT in immobile patients with ICH. (Quality of evidence: Moderate; Strength: Strong)"
>
> "There is insufficient evidence from RCTs to make strong recommendations about how, when, and for whom anticoagulation should be given to prevent DVT or improve outcome after intracerebral haemorrhage. (Quality of evidence: Low; Strength: Weak)"

VTE, a term encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common complication in patients with stroke. Estimates of its frequency in cohorts and trials vary widely and depend on the characteristics of patients, and the timing and method of screening. Severe strokes and those associated with immobility dehydration infection, co-morbidities (cancer, heart failure), obesity and prior history of thrombosis have been associated with higher rates of VTE.[5–7] The risk of VTE appears to be highest during the early post stroke phase and then falls over the next few weeks and months.[6,7] Although clinically overt DVTs occur in about 5% of hospitalised patients, if DVTs are screened for with different forms of imaging they can be detected in many more. Estimates of frequency of proximal or distal DVT vary: 20% with compression duplex ultrasound;[6] 73% with radiolabelled fibrinogen scanning[8,9] and 43% with magnetic resonance direct thrombus imaging.[10] Similarly, PEs are only diagnosed in clinical practice in 1–2% of hospitalized stroke patients but in those rare studies where PE has been screened for the frequency is much higher, 10% in one study.[10] Also, in earlier studies from an era where hospital autopsies were much more common, PE could be identified in about half of the patients dying after stroke.[11]

Despite the uncertainties about the frequency of the problem, it is generally accepted that VTE is an important cause of morbidity and death in hospitalised stroke patients. Since VTE is regarded as an important, and potentially preventable cause of death, clinicians caring for stroke patients are expected to assess their patients' risk of VTE and to provide the most effective and safe prophylaxis. This guideline aims to provide recommendations to achieve the best outcomes for ischaemic stroke patients.

Methods

The ESO Guidelines Committee invited the lead author (MD) to form and chair a working group. The working group initially consisted of MD, VC, LK and AP. It was later joined by PS who was the lead author on relevant Cochrane systematic reviews. The conflicts of interest of its members are presented at the end of this article and in Supplementary Appendix S1, (supplementary files can be found online with this article at ESO.sagepub.com). The working group consisted of neurologists and internists but members of nursing or other disciplines were not involved in writing these recommendations.

Briefly, the steps undertaken by the working group are summarized below:

1. Formulation of the population, intervention, comparator, outcome (PICO) questions suggested and concluded by consensus among the members of the working group.
2. Ranking of the importance of the outcomes selected and concluded by consensus among the members of the working group.
3. Identification of all relevant unconfounded randomised controlled trials (RCTs) and systematic reviews/meta-analyses. The Cochrane Stroke Group Information Specialist (Brenda Thomas) developed the search strategies for each database using a combination of controlled vocabulary and free text terms to describe each PICO topic and performed the literature searches in December 2014 (Supplementary Appendix S2).
4. Selection of eligible studies. Fortunately, for each PICO question a relevant Cochrane review was

Box 1. Grades of quality of evidence.

Grade	Definition	Symbol
High	Further research is very unlikely to change our confidence in the estimate of effect.	⊕⊕⊕⊕
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.	⊕⊕⊕
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.	⊕⊕
Very low	We are very uncertain about the estimate.	⊕

identified. Therefore only one author (MD) screened the titles and abstracts of the publications identified to identify any potentially relevant studies which were not included in the published reviews.

5. Checking of data in each Cochrane review and extraction of data from additional study reports was performed by MD for each PICO question. PS cross checked the results of the relevant systematic reviews and this manuscript.

6. Analysis of extracted data using the Review Manager 5. Analysis was performed on a random-effects basis, and results are summarized as odds ratios (OR) and 95% confidence intervals (CIs). An i^2 of > 50% was considered as indicating significant heterogeneity.

7. Grading of the quality of available evidence for each outcome was concluded by consensus among the members of the working group using the following criteria: the type of studies included, limitations in study design and methodology (i.e. risk of bias), inconsistency (or else: heterogeneity) of results, indirectness of evidence, imprecision, reporting bias, the magnitude of the treatment effect, evidence of a dose–response relationship and the effect of all plausible confounding. Quality of evidence was graded in four grades as high, moderate, low and very low (Box 1).[2,3] Minimally important differences are defined as the smallest effect size which would be regarded as clinically important. However, there is almost no published information on what effect sizes clinicians, patients or their families consider important with respect to VTE prophylaxis. The guideline group decided that any increase or decrease in the symptomatic outcomes would be of clinical importance and therefore elected not to base any judgement on minimally important differences.

8. Grading of the quality of evidence across several outcomes. When several outcomes were assessed for a clinical question, the grade for the overall quality of evidence was based on the grade for the most important outcome(s).[12,13]

9. Determination of the direction and the strength of the recommendation was concluded by consensus among the members of the working group. For each PICO question, according to the GRADE methodology, the direction of recommendation was either 'for' or 'against', and the strength of recommendation was defined as either strong or weak based on the balance between desirable and undesirable effects, taking into consideration the quality of the evidence, patient preferences and resource use (Box 2).[12,13] Where no randomised trials existed we elected not to make any recommendation for practice, other than to recommend that randomised trials should be carried out in the future.

10. Wording of recommendations was concluded by consensus among the members of the working group. For strong recommendations, we use the terminology '*we recommend…*', whereas for weak recommendations, we use the term '*consider…*', meaning that doctors and patients should consider more carefully whether this is the right choice for that particular patient…. This document was approved by consensus by the members of the working group for the preparation of the ESO Guidelines about VTE prophylaxis in acute ischemic stroke; it was then reviewed by two external reviewers who do not carry any responsibility for its integrity. It was submitted to and approved for publication by the ESO Guidelines Committee and the ESO Executive Committee.

Population

These recommendations refer to patients who have suffered an ischaemic stroke which has led to an acute hospital admission and which has reduced the patients' mobility. It specifically does not consider patients who have had intracerebral haemorrhage, patients who do not require hospital admission, fully ambulant patients, or those in the later phases of their hospital admission (after 14 days) when the risks of VTE are thought to be lower.[6,7] It was not essential for all patients to have computed tomography (CT) scanning before entry to the trials (we were interested in patients with confirmed or presumed ischaemic stroke) so we included those with mixed populations of patients, but we excluded

Box 2. Definitions of categories of strength of recommendation.

Strength of recommendation	Criteria	Symbol
Strong for an intervention	The desirable effects of an intervention clearly outweigh its undesirable effects.	↑↑
Weak for an intervention	The desirable effects of an intervention probably outweigh the undesirable effects.	↑?
Weak against an intervention	The undesirable effects of an intervention probably outweigh the desirable effects.	↓?
Strong against an intervention	The undesirable effects of an intervention clearly outweigh its desirable effects.	↓↓

trials which only included patients with definite haemorrhagic stroke.

Interventions

We have focused on both non-pharmacological and pharmacological interventions given with the primary objective of reducing the risk of VTE. These include: graduated compression stockings (GCS), intermittent pneumatic compression (IPC) and neuromuscular electrical stimulators (NES), unfractionated heparin (UFH), low molecular weight heparin (LMWH), heparinoids and oral anticoagulants and combinations of these interventions. For anticoagulants we only considered trials testing doses used for VTE prophylaxis since higher doses are likely to have a different balance of benefit and risk.

Comparators

We want to know whether intervening with the aim of reducing the risk of VTE achieves better outcomes for patients than providing standard care. Thus our comparators were care which did not include that specific VTE prophylactic intervention. We sought to identify all unconfounded randomised trials in which the interventions of interest were applied in the early phase of ischaemic stroke. Because treatment with antiplatelet medication is now standard for patients with acute ischaemic stroke the background treatment will usually include these. Therefore, we did not include trials which directly compared anticoagulants with antiplatelet medication. We did include trials which evaluated combinations of compatible prophylactic interventions, comparing the combination against either intervention alone (e.g. external compression plus anticoagulants vs. either alone). Also, we included evidence which compared two similar interventions (e.g. LMWH and UFH).

Outcomes

The GRADE methodology recommends that evidence based guidelines consider outcomes which are of importance to patients and/or their families and that more emphasis is placed on outcomes of greatest importance to them. Therefore, we did not simply focus on DVT and PE as outcomes but also on patients' chance of survival and functional outcome. We also considered the risks of adverse effects of prophylaxis (e.g. haemorrhage, skin breaks). For the purpose of this guideline we arrived at the following outcomes in the agreed priority order through discussion rather than by summing individuals' scores or ranks. Therefore the order is based on our judgement, and not those of patients or their families.

1. Death or dependency at follow up.
2. Survival (or its reciprocal – mortality) – including all cause mortality because it is too difficult to accurately identify which death results from VTE.
3. Functional status – quicker or more complete recovery due to avoidance of VTE, or slower or less complete recovery due to adverse effects of VTE prophylaxis, such as bleeds and pressure ulcers. Functional status was most often measured with the modified Rankin scale, the Oxford handicap scale, the International Stroke trial (IST) simple questions or the Barthel Index.
4. Intracranial haemorrhage – some interventions aimed at reducing VTE may increase symptomatic or asymptomatic intracranial haemorrhage, haemorrhagic transformation of the infarct, or bleeding into other intracranial compartments.
5. Symptomatic PE (fatal and non-fatal) –whilst PEs are clearly important, they are often not recognised. Fever, cough, breathlessness, neurological deterioration and sudden death have many other causes.[14] The clinical relevance of PE detected only on imaging or autopsy is unclear. No randomised trials routinely screened for PE with imaging. Most PEs were symptomatic or identified at autopsy.
6. Major (or serious) extracranial haemorrhages, for instance gastrointestinal or soft tissue bleeds which might arise due to or exacerbated by anticoagulants. These may lead to death, or simply interrupt rehabilitation.
7. Symptomatic DVT – these are frequently uncomfortable and often lead to patients feeling unwell. Their main impact is on the risk of recognised, or

unrecognised, PE. Longer term consequences such as post-phlebitis leg syndrome have not been recognised as frequent problems in stroke patients. Few studies distinguish DVTs which lead to these symptoms from those which were only detected by systematic screening with imaging (see below).

8. Any DVT including asymptomatic DVT – these will only be of importance to patients if they cause a PE, which of course may frequently not be recognised even if it leads to death. Proximal DVTs are considered more important than DVTs restricted to the calf veins since they are associated with a greater risk of PE. The importance of asymptomatic DVTs may also vary depending on the imaging modality used to detect them. For instance, the clinical relevance of a DVT identified on screening radiolabelled fibrinogen isotope scan may be less than one detected by compression duplex ultrasonography; the frequency of DVT detected on the former is often very high, and yet many positive scans are not confirmed on further imaging by ultrasound or contrast venography.

9. Fractures which may occur secondary to falls due to mechanical devices or even osteoporosis secondary to prolonged heparin use may impact on patients' recovery, their functional outcome and survival. They may also impact on patients' comfort.

10. Any haemorrhage including minor bruising. This is relevant to patients because it may impact on their comfort, predispose to skin breakdown and simply cause concern.

11. Skin breaks which may be caused by stockings and IPC sleeves might influence functional outcomes, especially in the patients with peripheral arterial disease since they may lead to the need for amputation. They may impact on patients comfort but are usually not serious.

Other outcomes were considered, including fatal PE and health related quality of life and quality (HRQOL) adjusted survival. However, we were aware that there was very little evidence relating to these outcomes. The lack of evidence relating specifically to fatal PE results from the practical difficulty in reliably ascertaining the cause of death in trials. Also, utilities derived from measures of HRQOL reflect the values of the general population rather than those of stroke patients or their families. Therefore, quality adjusted life years (QALY) may not reflect an outcome which is as relevant to patients as it might be to society in its decision making around use of resources. We also have not formally considered the effect that interventions might have on further cerebral ischaemic events, but some clinicians might take account of this in their decision making.

Search strategy

We limited our search to trials in stroke patients, or in mixed patient groups where information on stroke patients is given separately, since extrapolating from surgical patients and those with other medical conditions is of limited relevance because prophylaxis can be started before immobilisation in surgery, the risks of VTE are higher after stroke compared with many other medical conditions, the presence of a recent cerebral infarct increases the risk of intracranial bleeding, and because stroke patients have prolonged immobilisation, often with limb paralysis.

We did not include trials in which the method of allocation to treatment or control group was not adequately concealed (e.g. allocation by alternation, date of birth, hospital number, day of the week, or open random number list), since foreknowledge of treatment allocation might lead to biased allocation and hence to misleading estimates of treatment effect. We did not limit our search to English language. We only searched for published studies (papers, abstract and theses) but did include information from Cochrane systematic reviews which had searched for, and found, unpublished data. The search strategy in shown in Supplementary Appendix S1.

Results

Our literature search generated a large number of potentially eligible references

1. Cochrane Stroke Group Trials Register (using condition "deep venous thrombosis/pulmonary embolism" and ALL interventions) (searched 10 November 2014) ($N = 315$ refs).
2. Cochrane Stroke Group Trials Register (using conditions ischaemic or undefined stroke and interventions antiplatelet or anticoagulant) (searched 10 November 2014) ($N = 3134$ refs).
3. COCHRANE LIBRARY DATABASES (Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Reviews of Effects (DARE), Health Technology Database (HTA)) (The Cochrane Library 2014 Issue 10) ($N = 560$ refs).
4. MEDLINE (Ovid) 2008 to November 2014 ($N = 1110$ refs).
5. EMBASE (Ovid) 2008 to November 2014 ($N = 5984$ refs).
6. CINAHL (Ebsco) 1982 to November 2014 ($N = 696$ refs).

However, it identified several recent Cochrane systematic reviews of direct relevance to our PICO

question(s).[15–17] We cross referenced these with other published systematic reviews, existing guidelines and our search for individual randomised trials to ensure that all relevant studies had been included. We excluded some studies from the Cochrane reviews if they were not consistent with our PICO questions – specifically if they focused only on haemorrhagic stroke, or if they were trials of treatment dose, rather than prophylactic dose, anticoagulation.

The results of the meta-analyses of the RCTs testing GCS, IPC, anticoagulants and comparing LMWH/heparinoid and UFH are summarised in Table 1 and Figures 1.1–4.6 and the Evidence table in Supplementary Appendix S2. In Table 1, the statistically significant benefits and harms are highlighted in blue and red, respectively. The size of effect are indicated by ORs (95%CI), hazard ratio (95%CI) for survival in the IPC trial, and absolute differences for those statistically significant differences. When interpreting the absolute benefits and harms it is important to take account of the relative clinical importance of the different outcomes (see above).

Graduated compression stockings

In immobile patients hospitalized with acute ischaemic stroke does the use of GCS, compared with no GCS, improve survival, or functional status or reduce the risk of VTE without causing adverse effects?

The evidence is summarised in Table 1, evidence tables and Figures 1.1–1.5 (Supplementary Appendix S2). The meta-analysis included one large ($n = 2518$)[18] and one small trial ($n = 97$),[19] and indicated that GCS had no significant effect on death (during treatment period and follow up), death or dependency at six months, DVT (symptomatic or asymptomatic) or pulmonary embolism during treatment. The CLOTS trial evaluated a single type of thigh-length GCS, whereas the small trial evaluated two types of thigh-length stocking. The quality of this evidence was judged to be moderate because of a lack of power to demonstrate an effect on the most important outcomes, e.g. survival, functional status, symptomatic PE. The only statistically significant effect of GCS was an increase of the risk of a skin breaks in the patients allocated GCS, although this evidence was of low quality because of the lack of blinding of assessors of this outcome.

Recommendation

We recommend that graduated compression stockings should not be used in patients with ischaemic stroke.
Quality of evidence: Moderate ⊕⊕⊕
Strength of recommendation: Strong against ↓↓

Intermittent pneumatic compression

In immobile patients hospitalized with acute ischaemic stroke does the use of IPC, compared with no IPC, improve survival, or functional status or reduce the risk of VTE without causing adverse effects?

The evidence is summarised in Table 1, the evidence tables and Figure 2.1 to 2.6 (Supplementary Appendix S2). The meta-analysis included one large ($n = 2876$)[20,21] and two small trials.[22,23] This showed that IPC had no significant effect, despite a strong trend on deaths during treatment period (OR = 0.82 95%CI 0.66 to 1.02) but improved survival to six months (hazard ratio = 0.86) (95% CI 0.74 to 0.99). There was no statistically significant effect on functional status or pulmonary embolism or symptomatic DVT (OR = 0.73 95%CI 0.53 to 1.01). The quality of this evidence was judged to be moderate because of a lack of power to demonstrate an effect on the most important outcomes, e.g. survival, functional status and symptomatic PE. IPC significantly reduced the risk of any DVT (including asymptomatic DVT) (OR = 0.73 95%CI 0.61 to 0.88). The quality of this evidence was judged to be high. IPC also increased the risk of skin breaks (OR = 2.15 95%CI 1.31 to 3.59) but this was based on low quality evidence because of the lack of blinding of assessors of this outcome. However, the strength of recommendation was judged to be strong.

Recommendation

We recommend that intermittent pneumatic compression (IPC) (thigh-length, sequential) should be used for immobile patients with ischaemic stroke. It should not be used in patients with open wounds on the legs and should be used with caution in those with existing DVT, heart failure, severe peripheral vascular disease or confusion where attempts to mobilise when unsupervised could lead to falls and injury.

Quality of evidence: Moderate ⊕⊕⊕

Strength of recommendation: Strong for ↑↑

Neuromuscular electrical stimulation

In immobile patients hospitalized with acute ischaemic stroke does the use of NES, compared with no NES, improve survival, or functional status or reduce the risk of VTE without causing adverse effects?

We identified no relevant RCTs. There is no direct evidence that NES reduces the risk of VTE in ischaemic stroke patients so we have not made any recommendation, other than to suggest that electrical stimulation for VTE prophylaxis should only be used in the context of research.

Table 1. The pooled estimates of the effectiveness of VTE prophylaxis in stroke.

Outcome	No. of RCTs	Events/Patients	Control (%)	Absolute diff (%)	Heterogeneity I^2	p	Treatment effect OR < 1.0 indicates benefit Odds ratio	95% CI	p
Graduated compression stockings		GCS	Control						
Death or dependency at final follow up	1	865/1256 (68.9)	888/1262 (70.4)	−1.5	n/a		0.93	0.79–1.10	0.41
Death in treatment period	2	131/1321 (9.9)	114/1294 (8.8)	+1.1	0	1.0	1.13	0.87–1.47	0.39
Pulmonary emboli in treatment period	2	13/1321 (1.0)	20/1294 (1.6)	−0.6	n/a		0.65	0.33–1.30	0.23
DVT in treatment period	2	206/1321 (15.6)	228/1294 (17.6)	−2.0	79	0.03	0.88	0.72–1.08	0.23
Skin breaks in treatment period	1	64/1256 (5.1)	16/1262 (1.3)	+3.8	n/a		3.47	2.22–5.41	<0.001
Intermittent pneumatic compression		IPC	Control						
Death or dependency at final follow up	1	1126/1428 (78.9)	1127/1428 (78.9)	0	n/a		1.00	0.83–1.19	0.96
Death in treatment period	3	167/1502 (11.1)	199/1500 (13.3)	−2.2	21	0.28	0.82	0.66–1.02	0.07
Survival to 6 months	1	n/a	n/a	−2.8[a]	n/a		HR = 0.86	0.74–0.99	0.042
Pulmonary emboli in treatment period	1	29/1428 (2.0)	35/1428 (2.5)	−0.5	n/a		0.83	0.50–1.35	0.45
Symptomatic DVT in treatment period	2	67/1489 (4.5)	90/1487 (6.1)	−1.6	23	0.25	0.73	0.53–1.01	0.06
Any DVT (including asymptomatic) in treatment period	3	240/1500 (16.0)	310/1502 (20.6)	−4.6	0	0.48	0.73	0.61–0.88	<0.001
Skin breaks in treatment period	1	44/1428 (3.1)	20/1428 (1.4)	+1.7	n/a		2.15	1.31–3.53	0.002
Low dose anticoagulation		Anticoagulant	Control						
Death or dependency at final follow up	6	3281/5363 (61.2)	6300/10,197 (61.8)	−0.6	30	0.21	1.00	0.93–1.07	0.97
Death in treatment period	11	464/5234 (8.9)	934/10,075 (9.3)	−0.6	29	0.18	0.95	0.85–1.07	0.41

(continued)

Table 1. Continued

Outcome	No. of RCTs	Events/Patients	(%)	Absolute diff (%)	Heterogeneity		Treatment effect OR < 1.0 indicates benefit		
Intracranial haemorrhage in treatment period	9	49/5434 (0.9)	50/10,254 (0.5)	+0.4	0	0.76	1.68	1.11–2.55	0.01
Pulmonary emboli in treatment period	10	41/5501 (0.7)	102/10,322 (1.0)	−0.3	22	0.26	0.69	0.49–0.98	0.04
Significant extracranial bleed	9	31/5798 (O.5)	38/10,029 (0.40)	+0.1	0	0.74	1.65	1.0–2.72	0.05
Any DVT (including asymptomatic) in treatment period	9	66/392 (16.8)	195/393 (49.6)	−32.8	66	0.21	0.21	0.15–0.29	<0.001
		LMWH /Heparinoid	UFH						
Death or dependency at final follow up	1	450/876 (51.4)	437/870 ((50.2)	+1.2	n/a		1.05	0.87–1.26	0.63
Death in treatment period	7	193/1570 (12.3)	174/1442 (12.1)	+0.2	0	0.51	1.0	0.80–1.25	0.98
Intracranial haemorrhage in treatment period	7	13/1570 (0.8)	15/1442 (1.0)	−0.2	0	0.96	0.78	0.37–1.66	0.52
Pulmonary emboli in treatment period	6	8/686 (1.1)	12/564 (2.1)	−1.0	0	0.69	0.57	0.23–1.41	0.23
Significant extracranial bleed	7	12/1570 (0.8)	2/1442 (0.1)	+0.7	0	0.55	3.79	1.30–11.06	0.01
Any DVT (including asymptomatic) in treatment period	7	140/1352 (10.3)	206/1233 (16.7)	−6.4	0	0.52	0.55	0.44–0.70	<0.001

[a]The absolute difference was estimated from the proportions of patients alive at 6 months, although the statistical significance of the difference is based on a survival analysis which is a more sensitive tests than simply a comparison of proportions. The blue shading indicates statistically significant benefit, and the red, statistically significant harms from the interventions.

Anticoagulants

In immobile patients hospitalized with acute ischaemic stroke does the use of prophylactic dose anticoagulation, compared with no anticoagulation, improve survival, or functional status or reduce the risk of VTE without causing adverse effects?

The evidence is summarised in Table 1, and the evidence tables and Figure 3.1 to 3.6 (Supplementary Appendix S2). The meta-analysis included one very large trial ($n = 14,578$)[24] and four small trials of UFH,[8,9,25,26] eight small trials of LMWHs or heparinoids.[27–34] and one of a heparinoid.[35] Prophylactic anticoagulants were not associated with any significant effect on death during the treatment period or follow up, or functional status by final follow up. The quality of this evidence was judged to be high. However, it was associated with a statistically significant reduction in symptomatic pulmonary emboli (OR = 0.69) (95% CI 0.49 to 0.98). The quality of this evidence was judged to be moderate, because of a lack of blinding and imprecision with respect to this outcome. Anticoagulation was associated with a reduction in DVT (OR = 0.21) (95%CI 0.15 to 0.29) but the quality of the evidence was judged to be low because there was significant heterogeneity between trials, almost all DVTs were asymptomatic and the more positive trials based their diagnosis on isotope scanning only, which is of dubious reliability and limited clinical relevance. There were also statistically significant increases in symptomatic intracranial haemorrhage (OR = 1.68 95%CI 1.11 to 2.55) and symptomatic extracranial haemorrhages (OR = 1.65 95%CI 1.0 to 2.75). The quality of this evidence was judged to be moderate, because of the lack of blinding and imprecision.

Recommendation

Prophylactic anticoagulation with unfractionated heparin (UFH) (5000U ×2, or ×3 daily) or low molecular weight heparin (LMWH) or heparinoid should be considered in immobile patients with ischaemic stroke in whom the benefits of reducing the risk of venous thromboembolism is high enough to offset the increased risks of intracranial and extracranial bleeding associated with their use.

Quality of evidence: Moderate ⊕⊕⊕

Strength of recommendation: Weak for ↑?

LMWHs of heparinoids or UFH

In immobile patients hospitalized with acute ischaemic stroke does the use of LMWH or heparinoid compared with prophylactic dose UFH, improve survival, or functional status or reduce the risk of VTE without causing adverse effects?

The evidence is summarised in Table 1, and the evidence tables and Figure 4.1 to 4.6 (Supplementary Appendix S2). The meta-analysis included one large trial ($n = 1762$)[36] and two smaller trials comparing LMWHs with UFH[37,38] and four small trials comparing heparinoids with UFH.[39–42] There were no significant effects on death during follow up, death or disability. We judged the quality of this evidence to be moderate due to imprecision with respect to these outcomes. There were non-significant trends towards reduction in pulmonary emboli and symptomatic intracranial haemorrhage but there was a statistically significant increase in major extracranial haemorrhage (OR = 3.79) (95%CI 1.30 to 11.03) with LMWH. We judged the quality of this evidence to be moderate due to imprecision with respect to these outcomes. The use of LMWH was associated with a statistically significant reduction in DVTs (OR = 0.55) (95%CI 0.44 to 0.70) which were mostly asymptomatic. We judged the quality of this evidence to be high.

Recommendation

Where a judgement has been made that prophylactic anticoagulation is indicated LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs and patient comfort associated single daily dose vs. multiple daily injections but these advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and risks in elderly patients with poor renal function

Quality of evidence: Moderate ⊕⊕⊕

Strength of recommendation: Weak ↑?

We have not identified reliable evidence with regard to the following clinically relevant issues:

- How best to define which stroke patients are at high enough risk of VTE acutely, or during later phases of care, to warrant prophylaxis. The entry criteria for RCTs varied with respect to the degree of immobility or leg weakness. The patients were eligible for the largest trials (CLOTS 1 & 3) if the patients were unable to mobilise without the help of another person (but they could use walking aids) to the toilet regardless of the reason for that immobility; this is a simple and practical eligibility criterion for prophylaxis.[18,20]
- We do not have prediction tools which accurately define the balance of benefit (reduced risk of VTE) and harm (increased risk of adverse effects of prophylaxis), which might have value in targeting prophylaxis on patients who might have greater benefit.[43]
- The effectiveness of NES for VTE prophylaxis. In experimental settings this does increase blood flow

in the deep veins but has not yet been shown to reduce the risks of DVT or PE.

- The effectiveness of a strategy of screening for asymptomatic VTE, and treating patients who are found to have asymptomatic DVT as a means to improve outcome.

Discussion

We have identified mainly moderate quality evidence from randomised controlled trials and meta-analyses to guide what prophylaxis against VTE should be given to immobile patients with acute ischaemic stroke. GCS should not be used because they do not improve any important outcomes and increased the risk of skin breaks. We have made a strong recommendation to use IPC because it reduces the risk of DVT and improves overall survival, although it can cause skin breaks and some patients find it uncomfortable. Anticoagulation with prophylactic LMWH, heparinoids or UFH should be considered for selected patients, since their routine use reduces the risk of PE and DVT, but also increases the risk of serious bleeding. Overall, no net benefit with respect to survival and functional status has yet been demonstrated. However, we accept that any recommendation with respect to anticoagulation is bound to be controversial, in part because of its routine use, or routine avoidance, has been so long established in many health care systems. A systematic review suggested that acute anticoagulation may also reduce the risk of early cerebral and cardiac ischaemic events,[16] but we did not include this outcome in our considerations. It is still unclear whether the lack of improvement in survival or functional status is because the increased risk of bleeding offsets the benefits of reducing the risk of VTE and ischaemic recurrence. So far, it has not been possible to identify clinical factors that can be used to reliably identify a subgroup of patients who will gain more or less benefit from prophylactic anticoagulation.[43] The clinical features which are likely to indicate a very high risk of VTE, such as active malignancy, sepsis, previous VTE or coagulopathies were not consistently assessed in the randomised trials so there is no reliable evidence that patients with them gain greater benefit from anticoagulation. Some clinicians delay the start of anticoagulation in the belief that this will reduce the risk of intracranial bleeding but this may fail to protect the patients during the period of highest risk of VTE. The trials do not provide any reliable evidence on which to base this practice.

We have made no recommendations regarding the use of combinations of prophylactic measures (e.g. IPC plus anticoagulation) because the only available information on this topic comes from a subgroup analysis in the CLOTS 3 trial that did not demonstrate that background use of anticoagulants had any significant effect on the effectiveness of IPC as determined by the relative reduction in odds of a proximal DVT.[20] We have also made no recommendation regarding the use of NES because we identified no randomised controlled trials assessing its effectiveness in stroke patients. However, we would recommend that further research comparing NES with IPC would be justified.

The trials of prophylaxis did not include all admitted stroke patients, but rather selected patients who were regarded as having a high enough risk of VTE to justify prophylaxis. Therefore, before we apply these guideline recommendations to patients admitted to hospital with an acute stroke we need to assess their risk. Those who are unable to walk to the toilet without the help of another person are likely to be at high enough risk to justify prophylaxis. Among such patients on average 20% will develop any DVT (including asymptomatic DVT) within 30 days, 5% a symptomatic DVT and 2% a recognised PE.[6,7] However, even where the risk of VTE may be high enough to justify prophylaxis, the decision to apply prophylaxis in an individual patient should depend on the objectives of care. The clinical team, should take into account the patients' pre-stroke status, the severity of stroke and any co-morbidities, an assessment of the prognosis and an appreciation of the patients' and families' wishes and beliefs. The purpose of VTE prophylaxis is primarily to reduce the risk of VTE in order to optimise the patients' survival and reduce avoidable morbidity, which could interrupt or slow their recovery and ultimately affect functional outcomes. In patients for whom palliation or end of life care is the primary aim, VTE prophylaxis may not be appropriate.

Based on the pathophysiology of VTE, a number of other interventions which have not been considered here might be expected to reduce the incidence of VTE. These include use of antiplatelet medication, avoidance of dehydration and early mobilisation. However, these approaches are expected to have wider benefits such as avoiding further cardiac and cerebral ischaemic events and improved functional outcomes. Aspirin is given routinely in patients with acute ischaemic stroke because of a small but clinically useful reduction in the rate of recurrent stroke and improvement in functional outcomes.[44] Even though this Cochrane review demonstrated a small apparent reduction in PE, this is not the main object of giving aspirin to stroke patients.[44] Aspirin is therefore considered part of routine care for patients with ischaemic stroke and is not considered in these guidelines. Our detailed search strategies have not identified any randomised trials which have directly addressed the questions whether

avoiding dehydration[45] or early mobilisation would reduce the frequency of VTE. Trials of haemodilution might have some relevance to the question of hydration, but the purpose of haemodilution treatment was to improve cerebral blood flow with the hope of improving the neurological outcome. The randomised trials, and subsequent systematic reviews, indicated that haemodilution was ineffective in this respect, despite weak evidence that it might reduce the risk of VTE.[46] Since immobility is a major risk factor for post stroke VTE, then it would be expected that earlier mobilisation would reduce the risks. However, early mobilisation does not only include walking, but also sitting out, and the latter might actually increase venous pooling and could theoretically increase VTE risk. The only randomised controlled trial to evaluate early mobilisation, the AVERT trial, did not demonstrate a beneficial effect of a policy of early mobilisation in stroke on overall functional outcomes, will eventually report the effects on clinical VTE in the treatment and control groups.[47]

Further analyses of existing data, and further studies, are needed to establish better methods to target prophylaxis with IPC and anticoagulants to those patients who will gain most from the interventions.

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Informed consent

Not applicable since based on literature review

Ethical approval

N/A

Guarantor

MD

Contributorship

Martin Dennis chaired the working group, reviewed the literature, re-analysed the data and drafted the manuscript. Valeria Caso, L Jaap Kappelle, Aleksandra M. Pavlović and Peter Sandercock were members of the working group, reviewed the results of the literature review and analyses and critically reviewed the draft manuscript and approved the submitted version.

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