MODULE-2

BEST PRACTICES
FOR INITIAL MANAGEMENT OF STROKE

Dr. Reddy's Laboratories Ltd.
Global Genics - 7 1-27, Ameerpet, Hyderabad - 500 016, India
The **core purpose**
To upgrade practising physicians in the management of **Stroke** with the help of eminent Neurologists and to build a sustainable business relationship with the practising physicians of API

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| INDEX |
|---|---|
| **BLOOD GLUCOSE, BLOOD PRESSURE & INFECTION & PREVENTION OF ASPIRATION PNEUMONIA** |
| Burden of post-stroke | 1 |
| Blood glucose management | |
| - Hypoglycaemia | 2 |
| - Hyperglycaemia | 2 |
| - Glucose variability | 2 |
| - Current recommendations | 4 |
| Blood pressure management | |
| - Hypertension & acute ischaemic stroke | 5 |
| - BP and cerebral perfusion in acute stroke | 6 |
| - BP reduction and clinical outcome | 8 |
| - Current recommendations | 9 |
| Post stroke infection | |
| - Aspiration pneumonia | 10 |
| - Urinary tract infections | 10 |
| - Current recommendations | 10 |
| Stroke order set/charts | 11 |
| **MANAGEMENT OF PREVENTION OF DVT, TEMPERATURE MANAGEMENT AND NUTRITION** |
| Prevalence | 20 |
| Risk factors | 21 |
| Treatment approaches for prevention of stroke | 21 |
| Temperature management | |
| - Therapeutic hypothermia for acute ischaemic stroke | 34 |
| - Potential risks of different cooling methods | 36 |
| Nutrition | |
| - Screening and assessment for dysphagia in stroke patients | 37 |
| MCOs | 41 |
BLOOD GLUCOSE, BLOOD PRESSURE & INFECTION & PREVENTION OF ASPIRATION PNEUMONIA
POST-STROKE BURDEN

Age-wise stratification of number of deaths globally per year from different types of cardiovascular disease (CVD) shows that stroke is a major contributor for CVD mortality. Stroke results in 5.5 million deaths, while other CVDs, such as coronary heart disease, hypertensive heart disease, inflammatory heart disease, rheumatic heart disease and other forms of heart disease cause 7.2, 0.9, 0.4, 0.3 and 2.4 million deaths, respectively.

Post-stroke disability is caused due to complications such as urinary tract infections (UTIs), chest infection, bedsores, pain and depression. The factors associated with more complications include: stroke severity, limb weakness, anaemia, length of hospital stay and recurrent stroke.

Thrombolysis and endovascular therapy are the base for citadel of stroke recovery. Though thrombolysis improves clinical outcome, it does not affect mortality whereas stroke unit care does prevent mortality.

The key pillars for citadel of stroke recovery are:

- Blood glucose management
- Blood pressure management
- Infection management
- Venous thrombosis management
- Temperature management
- Nutrition management

Figure 1: Citadel of Stroke Recovery

(Revised from eStroke academy module: 2019 edition)
Management of hypoglycaemia, hyperglycaemia and glucose variability is included in this segment.

**Hypoglycaemia**
Hypoglycaemia, i.e., low blood glucose levels, can result in neurological symptoms, like stroke mimics. If untreated, severe and prolonged hypoglycaemia can cause permanent brain damage.⁶

Thus, blood glucose should be measured immediately in patients with acute ischaemic stroke, and treatment for hypoglycaemia should be initiated if blood glucose levels <60mg/dl.⁶

**Hyperglycaemia**
Forty percent of stroke patients present with hyperglycaemia, making it an important clinical problem.⁴ Stress that occurs in diabetes is one of the contributing factors for hyperglycaemia.⁸

Clinical studies have also demonstrated that persistent post-stroke hyperglycaemia is an independent determinant of infarct expansion and is correlated with worse clinical outcome.⁷ Additionally, in stroke patients treated with thrombolytics, hyperglycaemia can cause symptomatic intracerebral haemorrhage.⁹

**Glucose variability**
Glucose variability, i.e., fluctuation in blood glucose levels, is also associated with poor clinical outcomes in stroke patients. This statement is supported by two studies presented in the stroke conference held in 2015 and the neurology conference held in 2016.

In an abstract presented by Kubo S et al.,⁶ relationships between daily blood glucose variability and early neurological outcome in 329 acute ischaemic stroke patients with diabetes mellitus were examined. The study revealed independent association of increased blood glucose variability, but not blood glucose, with unfavourable outcome in stroke patients with diabetes.¹⁰

Similarly, a poster presented by Camara-Lemarroy C et al.¹¹ showed that elevated glycaemic variability was significantly associated with worse functional outcome in patients with ischaemic stroke. Therefore, glycaemic variability could be an important therapeutic target in the early management of acute ischaemic stroke.¹²

**Is tight blood glucose control a good idea?**
Gray CS et al. performed the UK Glucose Insulin in Stroke Trial (GIST-UK) to determine whether treatment with glucose-potassium-insulin (GIK) infusions to maintain euglycaemia immediately after the acute event reduces death at 90 days. Patients presenting within 24 hrs of stroke onset and with plasma glucose concentration at admission between 108-305mg/dl were randomly assigned to receive variable-dose insulin GIK (Intervention) or saline (control) as a continuous intravenous infusion for 24 hrs. The purpose of GIK infusion was to maintain capillary glucose at 72-126mg/dl with no glucose intervention in the control group. The result showed no significant reduction in mortality in GIK and control group at 90 days. In the GIK group, plasma glucose concentrations and BP were significantly reduced, however, this treatment was not associated with significant clinical benefit.¹³

The study had neutral results with a few key limitations which included unmatched blood glucose levels of the control group (mean glucose = 122mg/dl), 84% patients being non-diabetic and patients being enrolled after 13 hours of symptom onset.¹⁴

The design and study outcomes of an ongoing study called SHINE, were also highlighted. The trial aims to determine the safety and efficacy of standard vs. intensive glucose control with insulin in 1400 hyperglycaemic (blood glucose >150mg/dl or diabetes mellitus) acute ischaemic stroke patients. The randomized, blinded, multicenter phase III trial stratifies patients to receive either standard sliding scale subcutaneous insulin (blood glucose range 80-179mg/dl) or continuous intravenous insulin (target blood glucose 80-130mg/dl) for up to 72 hrs, starting within 12 hrs of stroke symptom onset.¹⁵
Current recommendations

The American Diabetes Association guidelines agree with American Heart Association and recommend maintaining the blood glucose level in the range 140-180mg/dL for majority of critically ill patients.3,4 The guideline also advocates frequent glucose level monitoring to review or change the treatment regimen to prevent/treat hypoglycaemia (blood glucose value <60mg/dL).5,6 The speaker also talked about avoiding oral hypoglycaemic agents, especially sulfonylureas, as they can affect endothelial function in acute stroke.7

Hypertension & acute ischaemic stroke

An acute hypertensive response occurs within 24 hours in up to 80% of patients with acute stroke.8 The causes underlying acute hypertensive response include untreated hypertension, damage to specific areas viz. prefrontal and insular cortices, increased sympathetic renal tone and reduced parasympathetic activity. Stress responses to hospitalization, headache, urinary retention, concomitant infection or dehydration can also contribute to the hypertensive response.9 The speaker also added that exacerbated factors such as diabetes mellitus and renal dysfunction can cause acute hypertensive response.10

Association of BP and clinical outcomes

In retrospective analysis from Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register, Ahmed N et al11 retrospectively determined the association of BP and antihypertensive therapy with clinical outcomes after stroke thrombolysis.12

For symptomatic haemorrhage rates, the association between systolic BP (SBP) increase and the odd ratio was almost linear; the higher the SBP, the greater the risk of symptomatic haemorrhage (Figure 2).13

**Figure 2: Association of symptomatic haemorrhage and BP**

(SICH - Symptomatic Intracranial Haemorrhage; SITS-MOST - Safe Implementation of Thrombolysis in Stroke Monitoring Study; RCT - Randomized Controlled Trial; NIHSS - National Institutes of Health Stroke Scale; SDHI per SITS-MOST: SICH score determination; all work within 24 hours plus intravenous thrombolysis Type A; SICH per RCT: mild haemorrhage plus worsening neurological deterioration, mortality, and/and/or independent functional scores less than 4.5 points)
For mortality and independence, the relationship was U-shaped with SBP 141 to 150 mmHg associated with the most favourable results though the rate of symptomatic haemorrhage declined at even lower SBP levels (Figure 3). The study also reported a strong association of high SBP after thrombolysis with worse outcome.17

Figure 3: Association of mortality and BP
![Graph showing association between mortality at 3 months and SBP]

**BP and cerebral perfusion in acute stroke**

Autoregulation depends on vasoactive tone and maintains a steady blood flow through normal brain tissue independent of the perfusion pressure, whereas blood flow in ischaemic brain tissue is proportional to the perfusion pressure. Figure 4 (A) represents cerebral blood flow (CBF) in normal and ischaemic brain tissue.18

![Graph showing blood flow in normal and ischaemic brain tissue]

**Effect of modest BP reduction**

The speaker shared the results from his study which evaluated the association of CBF with BP reduction. The study measured magnetic resonance (MR) perfusion and BP levels before administration of Labetalol in order to lower BP levels. After 15 minutes of drug administration, MR perfusion and BP levels were assessed for vasoparalysis. The result did not show a proportionate drop in BP in relation to CBF. Thus, in humans, autoregulation might be impaired but it does not result in vasoparalysis.19

Figure 4: Blood pressure and cerebral perfusion in acute stroke
![Graph showing association between BP and CBF]

**Figure 4(B):** Association of drop in CBF with ischaemia
![Graph showing association between drop in CBF and ischaemia]

![Graph showing association between CBF drop and BP]

**Mean Systolic Arterial Pressure**

CBF - Cerebral Blood Flow
Effect of BP reduction with clinical outcome

High BP is associated with poor outcome after stroke. Subsequently, after a stroke, management of BP is still a matter of debate. In an effort to resolve this controversy, several clinical trials have been conducted. A few of them are discussed here.

The ENOS Trial Investigators assessed outcomes in 4,011 patients after stroke randomized to antihypertensive therapy, initiated within 48 h of stroke onset. The study reported acceptable safety with no benefit in functional outcome with a BP reduction of 7 mmHg.

Similar results i.e. without any functional improvement were also reported by the CATIS (2014: 9 mmHg) and ATACH II (2016: 12 mmHg) trials, while the evidence of SCAT trial (2011) suggested harmful effect of Candesartan in stroke patients with high BP.

Conversely, INTERACT II trial (2013) showed favorable outcomes with intensive BP lowering. The trial was conducted to determine the safety and effectiveness of early intensive lowering of BP in patients with intracerebral hemorrhage. The study resulted in a 14 mmHg greater reduction in BP in the intensive-treatment group compared to the standard-treatment group. Though the study did not result in a significant reduction in the rate of death or major disability, it showed a favorable shift in functional outcome with intensive lowering of BP.

The speaker also highlighted the ongoing RIGHT II trial in UK which aims to test the safety and efficacy of lowering BP in the pre-hospital setting (ambulance) within <6 hours of stroke symptoms.

Current recommendations

According to the 2013 Guidelines of the American Heart Association (AHA) for the early management of patients with acute ischemic stroke, for patients eligible for intravenous (IV) tissue plasminogen activator (tPA), SBP should be lowered to <185 mmHg and diastolic BP (DBP) should be lowered to <110 mmHg before initiating fibrinolytic therapy. BP should be maintained <180/105 mmHg for at least the first 24 hours. The speaker stated similar principles for endovascular therapy.

For patients not receiving tPA, the guidelines advocate a reasonable goal of lowering BP by 15% during the first 24 h after onset of stroke and antihypertensive therapy initiation within 24 h of stroke (Class I recommendation). However, there is no data to guide selection of medications for the lowering of BP in the setting of acute ischemic stroke.
Aspiration pneumonia
Incidences of stroke-associated pneumonia in neurological intensive care units ranges from 41.1 to 56.6% and that in stroke units from 3.9 to 44%. It is associated with 2.2-fold increase in the risk of death. The most common causes for stroke-associated pneumonia include National Institutes of Health Stroke Scale (NIHSS) >15 points, anterior circulation stroke, use of nasogastric tube and mechanical ventilation. Stroke can contribute to the immunosuppressive state in the sub-acute phase of stroke, predisposing patients to pneumonia.

Preventive measures for stroke-associated pneumonia include a semi-recumbent position, positioning of airway suctioning, early mobility and shortened intubation. Exercises such as breathing exercises and treatment of nausea and vomiting are some other preventive measures. Moreover, for the prophylaxis of infection in stroke patients, Levofloxacin administration is not better than optimal care.

Urinary tract infections
About 15-60% of patients acquire UTIs after a stroke. These infections independently contribute to worse outcomes and can lead to bacteraemia or sepsis as a potential complication. Hence, the speaker advocated avoidance of indwelling catheters and removal of urinary catheters that are no longer necessary. Utilization of an external catheter, use of adult diapers and intermittent catheterization are useful techniques to treat UTI.

Current recommendations
AHA 2013 guidelines recommend treatment of suspected pneumonia or UTI with appropriate antibiotics (Class I recommendation). The guideline also advocates assessment of swallowing before the patient eats or drinks or takes oral medication in hospital (Class I recommendation). Early mobilization of less severely affected patients and measures to prevent sub-acute complications of stroke are also recommended (Class I recommendation). On the other hand, routine use of prophylactic antibiotics and routine placement of indwelling bladder catheters are not recommended.
Acute Stroke Admission
Ischemic Stroke (non-thrombolysed)

Intravenous (IV) 30 mL (0.4% w/v) bolus followed by 10 mL/hour

Deep Vein Thrombosis (DVT) and Pulmonary Embolism Prevention Measures for patient with restricted mobility
- Low Molecular Weight Heparin Enoxaparin 40mg SC daily
- Consider Dabigatran 2000 units SC q8h if there is renal impairment (eGFR)
- TED stockings for all patients provided there are no open wounds

Blood Sugar Monitoring
- Non-Diabetic: If fasting blood glucose is less than 130 mg/dL
- Fasting glucose 8 times a day for the first 24 hours (blood glucose >180 mg/dL, consider intravenous insulin)

Bladder Care
- Not applicable
- If unable to void do bladder scan and in and out catheterisation every 4 to 6 hours, reassess in 48 hours
- If patient voiding, drain residuals every shift until residual less than 100ml
- Indwelling catheter (urethral release) for 24 hours, then reassess
- In and out times record every 4 hours

Nutrition for Non-thrombolysed Patients
- Nothing by mouth (NPO) until swallow screen (e.g. TORTEST or full dysphagia screen completed)
- Nasogastric (NG) tube
- Interal fluids (pomegranate, tangerine)
- Avoid and offer oral carbohydrates 4 hours
- Heart Healthy Diet
- Glucose diet, number of calories
- Other diet (PA)

Activity
- Activity as tolerated
- Other ...

Investigations
- Order investigations based on location and likely etiology of stroke
- CT or MRI (PA) and LUMBAR if needed
- CT Head perfusion (for cases on intravenous stroke induced anticoagulation with full anticoagulation therapy)
- Angiography (CTA or MRA) (please review protocol before angiography)
- Carotid and Vertebrobasilar Doppler study
- ECG on admission
- Holter Monitor for all patients
- ECHO note: order only on patients with one of the following
  - Abnormal ECG, Abnormal Cardiac exam, Atrial Fibrillation
  - Strong clinical suspicion of cardiac source, multiple emboli in two vascular territories
  - TEE (please discuss with cardiologist) or TTE

Physician signature
Date
Time
**Acute Stroke Admission**

**Ischemic Stroke (non-thrombolysed)**

<table>
<thead>
<tr>
<th></th>
<th>others</th>
<th>Dose</th>
<th>Times</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Assess medications taken at home
- Consult
  - Neuroradiology after discussing with the admitting Neurologist.
  - Diabetologist
  - Occupational Therapist within 48 hours of admission
  - Physiotherapist within 48 hours of admission
  - Social Worker
  - Speech Pathology Team: Speech and swallowing
  - Speech Language Pathology (swallowing and language)
- Stroke Psychologist

**Additional Orders**
- Transfer to stroke/Stroke Obs. Unit as appropriate, as soon as bed is available

**Physician signature**

**Date:**

**Time:**

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**REFERENCES**

1. Adapted from the slides presented by Dr. Mahesh P Kate in the second module of second year of "e-stroke academy" in Chennai on 14th October, 2017.


MANAGEMENT OF PREVENTION OF DVT, TEMPERATURE MANAGEMENT & NUTRITION
**Introduction**

Deep vein thrombosis (DVT) is the formation of a blood clot in the deep veins of the body. DVT usually originates in the veins of the lower extremities. It starts at the calf vein and progresses proximally to involve popliteal, femoral, or iliac system. Over 80-90% of pulmonary embolism originate in the veins of the lower extremities.

**Prevalence**

Absolute risk of DVT in hospitalized stroke patients is up to 50% (Table 1), of which 5% develop clinically apparent DVT and 2% develop confirmed pulmonary embolism (PE). DVT after a stroke develops mostly between day 2 and 7. More precisely, 80% of all DVTs occur within the first 10 days. DVT is reported to be equally common in patients with ischaemic stroke and haemorrhagic stroke. However, data suggest DVT occurs twice as often after haemorrhagic stroke than after ischaemic stroke. The cause for this being less rigid preventive management and presence of more severe focal deficit in haemorrhagic stroke.

**Risk factors**

Acute stroke increases the risk of venous thromboembolism (VTE) by almost 30-75%. Other acute medical conditions that are considered as high risk include presence of myocardial infarction (24% VTE risk), decompensated congestive heart failure (40% VTE risk), medical intensive care unit admission (MICU, 33% VTE risk), spinal cord injury (up to 100% VTE risk), central venous catheters (46% VTE risk) and malignancy.

**Major risk factors of post-stroke DVT**

- High National Institutes of Health Stroke Scale (NIHSS) score in patients with acute intracerebral haemorrhage
- AF is an independent risk factor for DVT in stroke patients
- History of DVT or PE is associated with an increased risk of DVT
- Non-stroke-related factors such as increased age, obesity, hormone therapy, a prothrombotic state, and cancer
- Atrial fibrillation (AF) and limb paralysis
- Altered level of consciousness
- Genetic components also probably play a role

**Treatment approaches for prevention of stroke**

Treatment approaches for prevention of stroke include the non-pharmacological, mechanical and pharmacological approaches.
**Nonpharmacologic treatment/Mobilization/General Medical**

- Early mobilization - Early mobilization of patients with ischemic stroke can be recommended, as it lowers the likelihood of DVT and PE but also of pneumonia and pressure sores.

- Hydration/Improvement of hydration status - Current guidelines specifically advocate that attention should be paid to keeping the patient well hydrated in the early stage of ischemic stroke.

**Mechanical**

- Graduated compression stockings (GCS) and intermittent pneumatic compression (IPC) - The combination of elastic stockings and IPC significantly decreases the occurrence of asymptomatic DVT.

**Pharmacological**

- Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), antiplatelet and new oral anticoagulants (NOAC) therapies.

**Anticoagulant prophylaxis - needed or not needed for acute ischemic stroke?**

The relative effects of prophylactic dose anticoagulation for VTE prophylaxis in patients with acute ischemic stroke and restricted mobility were obtained using a meta-analysis. Heparin prophylaxis, in comparison with no heparin prophylaxis, resulted in 33 fewer symptomatic DVTs, five fewer pulmonary embolism, and five additional major haemorrhages (three intracranial and two extracranial) per 1,000 treated patients (Table 2).

### Table 2: Prophylactic-dose anticoagulation (LMWH or UFH) for VTE prevention compared with no anticoagulation in patients with acute ischemic stroke and restricted mobility

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studied Follow-up)</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With No Anticoagulant Dose Heparin</th>
<th>Risk Difference With Prophylactic Dose Heparin (UFH or LMWH) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>15,594 (8 studies) 2:26 wk</td>
<td>Moderate due to imprecision</td>
<td>RR: 0.88 (0.59-1.22)</td>
<td>82 deaths per 1,000</td>
<td>12 fewer deaths per 1,000 from 36 fewer to 19 more</td>
</tr>
<tr>
<td>PE (fatal and nonfatal)</td>
<td>10,681 (8 studies) 14:30 d</td>
<td>Moderate due to imprecision</td>
<td>RR: 0.7 (0.47-1.03)</td>
<td>16 PEVs per 1,000</td>
<td>5 fewer PEVs per 1,000 from 8 fewer to 0 more</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>714 (6 studies) 2:52 wk</td>
<td>Moderate due to inconsistency</td>
<td>RR: 0.51 (0.31-0.81)</td>
<td>48 DVTs per 1,000</td>
<td>33 fewer DVTs per 1,000 from 28 fewer to 38 fewer</td>
</tr>
<tr>
<td>Symptomatic intracranial haemorrhage</td>
<td>36 (6 studies) 14:30 d</td>
<td>Moderate, due to DVT</td>
<td>RR: 1.52 (0.96-2.39)</td>
<td>5 bleeding events per 1,000</td>
<td>3 more bleeding events per 1,000 from 0 fewer to 7 more</td>
</tr>
<tr>
<td>Symptomatic extracranial haemorrhage</td>
<td>36 (6 studies) 2:52 wk</td>
<td>Moderate, due to DVT</td>
<td>RR: 1.62 (0.93-2.81)</td>
<td>4 bleeding events per 1,000</td>
<td>2 more bleeding events per 1,000 from 0 fewer to 7 more</td>
</tr>
</tbody>
</table>

UFH - Unfractionated Heparin, VTE - Venous Thromboembolism, DVT - Deep Vein Thrombosis, PE - Pulmonary Embolism, CI - Confidence Interval, wk - Week, d - Day.
Table 3. Occurrence of MTE and DVT according to NIHSS score

<table>
<thead>
<tr>
<th>NIHSS Score</th>
<th>Occurrence of MTE</th>
<th>Occurrence of DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score 12-14 (n=146)</td>
<td>15% (n=22/146)</td>
<td>25% (n=36/146)</td>
</tr>
<tr>
<td>NIHSS score 15-19 (n=18)</td>
<td>0% (n=0/18)</td>
<td>0% (n=0/18)</td>
</tr>
<tr>
<td>NIHSS score 20-24 (n=36)</td>
<td>16% (n=6/36)</td>
<td>28% (n=10/36)</td>
</tr>
<tr>
<td>NIHSS score 25+ (n=40)</td>
<td>12.5% (n=5/40)</td>
<td>20% (n=8/40)</td>
</tr>
</tbody>
</table>

P-values: 0.01 (MTE) and 0.03 (DVT), respectively.

The efficacy and safety of Enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischemic stroke (PREVAIL Study): an open-label randomized comparison

Table 4. Occurrence of Hemorrhage according to NIHSS score

<table>
<thead>
<tr>
<th>NIHSS Score</th>
<th>Occurrence of Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS score 12-14 (n=146)</td>
<td>0% (n=0/146)</td>
</tr>
<tr>
<td>NIHSS score 15-19 (n=18)</td>
<td>0% (n=0/18)</td>
</tr>
<tr>
<td>NIHSS score 20-24 (n=36)</td>
<td>0% (n=0/36)</td>
</tr>
<tr>
<td>NIHSS score 25+ (n=40)</td>
<td>10% (n=4/40)</td>
</tr>
</tbody>
</table>

P-values: 0.09 (hemorrhage)
There was a higher incidence of major extracranial haemorrhages in the Enoxaparin group than in the UFH group. This difference was significant for patients with an NIHSS score ≥14 but not significant for those with an NIHSS score <14.15

**LMWH compared with UFH for VTE prevention in patients with acute ischaemic stroke and restricted mobility**

Compared with UFH, the use of LMWH in patients with restricted mobility reduced VTE events (eight fewer PE and seven fewer symptomatic DVTs per 1,000 patients treated) without an influence on mortality and bleeding complications (Table 5).15

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of Participants (Studies) Follow-up</th>
<th>Quality of the Evidence (GRADE)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk With Prophylactic Dose LMWH</th>
<th>Risk Difference With Prophylactic Dose UFH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality</td>
<td>2,506 (13 studies) 14-90 d</td>
<td>Moderate due to imprecision</td>
<td>RR 0.99 (0.72-1.2)</td>
<td>75 deaths per 1,000</td>
<td>3 fewer deaths per 1,000 (from 21 fewer to 15 more)</td>
</tr>
<tr>
<td>PE fatal and nonfatal</td>
<td>2,092 (12 studies) 14-90 d</td>
<td>Moderate due to imprecision</td>
<td>RR 0.26 (0.07-0.95)</td>
<td>11 PEs per 1,000</td>
<td>8 fewer PEs per 1,000 (from 1 fewer to 10 fewer)</td>
</tr>
<tr>
<td>Symptomatic DVT</td>
<td>2,092 (12 studies) 14-90 d</td>
<td>Moderate due to imprecision</td>
<td>RR 0.56 (0.4-0.77)</td>
<td>15 DVTs per 1,000</td>
<td>7 fewer DVTs per 1,000 (from 2 fewer to 9 fewer)</td>
</tr>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>1,740 (3 studies) 14-90 d</td>
<td>Moderate due to imprecision</td>
<td>RR 0.7 (0.26-1.83)</td>
<td>7 bleeding events per 1,000</td>
<td>2 fewer bleeding events per 1,000 (from 5 fewer to 6 more)</td>
</tr>
<tr>
<td>Symptomatic extracranial hemorrhage</td>
<td>2,506 (13 studies) 14-90 d</td>
<td>Moderate due to imprecision</td>
<td>RR 2.12 (0.09-13.28)</td>
<td>5 bleeding events per 1,000</td>
<td>6 more bleeding events per 1,000 (from 5 fewer to 214 more)</td>
</tr>
</tbody>
</table>

LMWH = Low Molecular Weight Heparin, UFH = Unfractionated Heparin, VTE = Venous Thromboembolism, DVT = Deep Vein Thrombosis, PE = Pulmonary Embolism, d = Day, RR = Relative Risk, CI = Confidence Interval
Graduated Compression Stockings

Some recent trials suggest that GCS may not be effective in preventing VTE.

In CLOTS 1, GCS did not reduce DVT after stroke when compared to no mechanical prophylaxis. Higher-risk groups, such as patients with leg weakness and patients not on concomitant anticoagulation, also did not benefit from GCS.

CLOTS 2 demonstrated increased proximal VTE with the use of below-the-knee stockings as compared with thigh-high stockings. While in the CLOTS 3 trial, rates of DVT were examined in immobile stroke patients randomized to treatment with or without IPC. DVT occurred less frequently in stroke patients treated with IPC, with an absolute risk reduction of 3.6%.

The CLOTS trials found no statistically significant benefit of GCS on VTE or survival.

Problems associated with GCS

GCS are challenging to fit and maintain properly. Moreover, they are costly and are associated with adverse skin effects. Common adverse effects are skin breakdown, including skin ulcers, breaks and necrosis.

In the CLOTS 1 trial, skin breaks and ulcers were 4 times more common in the group treated with GCS (6.4% vs. 16%). In the CLOTS 2 trial, skin breakdown occurred in 3.9% of patients treated with thigh-high stockings and 2.9% with below-the-knee stockings. Therefore, GCS should be monitored at least 3 times daily for skin breakdown and migration of the stockings.

Fondaparinux in DVT prophylaxis

Fondaparinux, a synthetic factor Xa inhibitor, has weight-independent once daily subcutaneous dosage with stable pharmacokinetic profile. Compared to UFH, Fondaparinux is not associated with increased hemorrhagic complications in patients with ischemic stroke. Expert consensus guidelines recommend low-dose UFH, LMWH or Fondaparinux (Grade B) for VTE prophylaxis in acutely ill medical patients.

ACCP guidelines: Antithrombotic and thrombolytic therapy for ischemic stroke

Table 6: Guideline recommendations in patients with ischemic events

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<thead>
<tr>
<th>Recommendation in patients with acute ischemic stroke and restricted mobility</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic-dose subcutaneous heparin (UFH or LMWH) or IPC devices suggested over no prophylaxis</td>
<td>Grade 2B</td>
</tr>
<tr>
<td>Prophylactic-dose LMWH suggested over prophylactic-dose UFH</td>
<td>Grade 2B</td>
</tr>
<tr>
<td>Elastic compression stockings not suggested</td>
<td>Grade 2B</td>
</tr>
</tbody>
</table>
ACCP guidelines antithrombotic and thrombolytic therapy for ischaemic stroke

Approximately one third of patients admitted with stroke will be hyperthermic (temperature >37.6°C) within the first hours after stroke onset. In the setting of acute ischaemic stroke, hyperthermia is associated with poor neurological outcome, possibly secondary to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production. Hyperthermia may be secondary to a cause of stroke, such as infective endocarditis, or may represent a complication, such as pneumonia, urinary tract infection (UTI) or sepsis. Because of the negative effects of hyperthermia, maintenance of normothermia or lowering of an acutely elevated body temperature has been hypothesized to improve the prognosis of patients with stroke.\textsuperscript{22}

Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke (Class I; Level of Evidence C).\textsuperscript{23}

Table 7: Guideline recommendations in patients with haemorrhagic events

<table>
<thead>
<tr>
<th>Recommendation in patients with acute primary intracerebral haemorrhage and restricted mobility</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic-dose subcutaneous heparin (UFH or LMWH) started between days 2 and 4 or IPC devices suggested over no prophylaxis</td>
<td>Grade 2C</td>
</tr>
<tr>
<td>Prophylactic-dose LMWH suggested over prophylactic-dose UFH</td>
<td>Grade 2B</td>
</tr>
<tr>
<td>Elastic compression stockings not suggested</td>
<td>Grade 2B</td>
</tr>
</tbody>
</table>

LMWH - Low Molecular Weight Heparin, UFH - Unfractionated Heparin, IPC - Intermittent Pneumatic Compression.
Important prospective, controlled pharmacologic treatment studies on fever, performed during the past 10 years are summarized in the table below.17

### Table 8: Prospective, randomized trials on pharmacologic antipyretic treatment of patients with acute stroke

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Intervention</th>
<th>N</th>
<th>Disease</th>
<th>Blinding</th>
<th>Number of study centers</th>
<th>Qualifying body temperature, °C</th>
<th>Duration of treatment, days</th>
<th>Measurement</th>
<th>Temperature reduction vs. control (24 h), °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Konrood et al., 2001</td>
<td>Paracetamol (oral) 4 g/day, Indomethacin (oral) 45 mg/day</td>
<td>44</td>
<td>IS</td>
<td>1</td>
<td>1</td>
<td>&lt;37.5</td>
<td>5</td>
<td>tympanic</td>
<td>n.a.</td>
</tr>
<tr>
<td>Kersen et al., 2002</td>
<td>Paracetamol 4 g/day (oral), Indomethacin 45 mg/day (oral)</td>
<td>39</td>
<td>IS, ICH</td>
<td>1:2</td>
<td>2</td>
<td>&lt;38.5</td>
<td>24</td>
<td>bladder</td>
<td>0.27 (95% CI: 0.08 to 0.61)</td>
</tr>
<tr>
<td>Dippel et al., 2003</td>
<td>Paracetamol 6 g/day or ibuprofen 2,400 mg/day (oral or rectal)</td>
<td>151</td>
<td>IS, ICH</td>
<td>1:2</td>
<td>3</td>
<td>36-39</td>
<td>5</td>
<td>rectal/ tympanic</td>
<td>0.27 (95% CI: 0.09-0.46)</td>
</tr>
<tr>
<td>Castillo et al. (unpublished), 2003</td>
<td>Metamizol 6 g/day (oral)</td>
<td>60</td>
<td>IS</td>
<td>1</td>
<td>2</td>
<td>37-38</td>
<td>3</td>
<td>tympanic</td>
<td>n.a.</td>
</tr>
<tr>
<td>Der et al., 2009</td>
<td>Paracetamol 6 g/day (oral/rectal)</td>
<td>1400</td>
<td>IS, ICH</td>
<td>1:2</td>
<td>29</td>
<td>36-39</td>
<td>3</td>
<td>tympanic/ rectal</td>
<td>0.26 (95% CI: 0.06-0.47)</td>
</tr>
</tbody>
</table>

n = Number of patients enrolled; IS = Ischemic Stroke; ICH = Intracerebral Hemorrhage; n.a. = not provided.

**Blinding:** 1 - Single Blind; 2 - Double Blind

### Table 9: Prospective randomized trials on combined (physical + pharmacologic) antipyretic regimens

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Intervention</th>
<th>N</th>
<th>Disease</th>
<th>Number of study centers</th>
<th>Qualifying body temperature, °C</th>
<th>Duration of treatment, days</th>
<th>Measurement</th>
<th>Prim. EP</th>
<th>Result (Prim. EP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayer et al., 2001</td>
<td>Cooling blanket (air-circulating) + Acetaminophen</td>
<td>220</td>
<td>SAH, ICH</td>
<td>1</td>
<td>&gt;38.3</td>
<td>1</td>
<td>tympanic</td>
<td>normal temperature at 24 h</td>
<td>negative 35.5 vs. 44.2%</td>
</tr>
<tr>
<td>Mayer et al., 2004</td>
<td>Cooling blanket (water-circulating) + Acetaminophen</td>
<td>47</td>
<td>SAH, IS</td>
<td>1</td>
<td>&gt;38.3</td>
<td>1</td>
<td>tympanic</td>
<td>fever burden within 24 h</td>
<td>positive 41.3 vs. 16.1%</td>
</tr>
<tr>
<td>Drüger et al., 2004</td>
<td>Endovascular cooling + Acetaminophen, Ilopredon, cooling blanket, ice packs, gastric lavage</td>
<td>296</td>
<td>TBI, ICH, IS</td>
<td>13</td>
<td>&gt;38.0</td>
<td>3</td>
<td>bladder</td>
<td>fever burden within 72 h</td>
<td>positive 2.97 vs. 7.02%</td>
</tr>
<tr>
<td>Brosser et al., 2009</td>
<td>Endovascular cooling + Acetaminophen, Ilopredon, Phenylephrine, cooling blanket</td>
<td>112</td>
<td>SAH, IS</td>
<td>2</td>
<td>&gt;35.5</td>
<td>7-14</td>
<td>bladder</td>
<td>fever burden (up to 14 days)</td>
<td>positive 4.0 vs. 4.3%</td>
</tr>
</tbody>
</table>

n = Number of patients enrolled; ICH = Intracerebral Hemorrhage; SAH = Subarachnoid Hemorrhage; IS = Ischemic Stroke; TBI = Traumatic Brain Injury; Prim. EP = Primary Endpoint.

Promising strategies for physical treatment of fever in stroke have been suggested, but reliable data are more limited than that for pharmacologic approaches.17
Therapeutic hypothermia for acute ischaemic stroke: Ready to start large randomized trials?

A systematic review and meta-analysis of animal studies of focal cerebral ischemia, included data obtained from a total of 3,353 animals. The results showed that hypothermia reduced the infarct size by 44%.\(^9\)

Figure 2: Effect of target temperature on the efficacy of hypothermia in improving infarct volume in animal models of stroke

Table 10: Clinical trials of therapeutic hypothermia for ischaemic stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Indication (time from stroke on set)</th>
<th>Target temp &amp; mean time to cool</th>
<th>Duration &amp; method of cooling</th>
<th>Complications or adverse events</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schwoerer et al. (1998)</td>
<td>Cerebral oedema (7-21 h)</td>
<td>33-0</td>
<td>48-72 h</td>
<td>Surface cooling</td>
<td>Rebound increase in ICP after rewarming, pneumonia 14/25 survived</td>
</tr>
<tr>
<td>Schwoerer et al. (2001)</td>
<td>Cerebral oedema (13-21 h)</td>
<td>32-6</td>
<td>34-72 h</td>
<td>Surface cooling</td>
<td>Thrombocytopenia, pneumonia, tachycardia, rebound increase in ICP Mean Barthel index at 3 months=65, mean mRS at 3 months=3.9, NIHSS at 4 weeks=29</td>
</tr>
<tr>
<td>Martin-Schild et al. (2009)</td>
<td>Neuroprotection (&lt;6 h)</td>
<td>33-35</td>
<td>24 h</td>
<td>Endovascular device 8 pts, surface cooling 10 patients</td>
<td>Pneumonia, 2 not cooled due to device malfunction, 5 did not reach target temperature 15/20 had improvement in NIHSS by day 5 or discharge</td>
</tr>
<tr>
<td>ICTUS-L (2011)</td>
<td>Neuroprotection (&lt;6 h)</td>
<td>33-67 min</td>
<td>Endovascular device</td>
<td>Pneumonia</td>
<td>No difference in outcome or mortality at 90 days</td>
</tr>
</tbody>
</table>

ICP: Intracranial Pressure, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale.
American Academy of Neurology recommendations: The utility of induced hypothermia for the treatment of patients with ischemic stroke is not well established, & further trials are recommended (Class IIIb; Level of Evidence B)³⁹

Potential risks of different cooling methods²⁸
- Ice-cold saline overload: Lacks precision in temperature control; volume overload
- Surface cooling: Increased shivering; skin necrosis and breakdown
- Endovascular cooling: Infections, bleeding, and venous thrombosis
- Cooling helmets: Slow rate and local cooling
- Nasal cooling devices: Slow rate and local cooling; intubation needed

Shivering
Shivering is an important clinical challenge that needs to be proactively anticipated and managed. It not only causes discomfort for the cooled patients, but also triggers vasoconstriction, hindering efforts to achieve the goal temperature. The anti-shivering protocol includes:²⁸

- Buspirone 30mg orally or nasogastrically, preferably before catheter insertion
- Meperidine 1 mg/kg intravenous bolus more than 10 min before initiation of cooling (maximum 100 mg)
- Meperidine 25 mg/h maintenance infusion
- Assess for signs of shivering with Bedside Shivering Assessment Scale
- Meperidine 10-15 mg slow intravenous push as needed for shivering and increase infusion rate by 5 mg/h

- Reassess for signs of shivering
- Total dose of Meperidine should not exceed 1500mg per day

In the acute stage of stroke 30 to 50% of patients suffer from dysphagia, while the incidence drops to around 10% six months later.²⁹

Dysphagia

Several studies show that the risk for aspiration pneumonia increases by 12-fold in dysphagic stroke patients and occurs up to 30% of patients in certain patient groups. Malnutrition is present in about 24% of stroke patients, with studies reporting prevalence of 8% to 48%, depending on patient cohort and assessment technique. Due to its prognostic importance, an early detection of stroke-related dysphagia and suitable nutritional management is therefore of utmost clinical importance.²⁹

Screening and assessment for dysphagia in stroke patients

Which methods should be used for dysphagia screening? And How should the risk of aspiration be evaluated?

The following three methods have been evaluated in acute stroke patients:²¹

- Water-Swallowing-Test (WST): Based on the SIGN guidelines, a 30 ml WST may be recommended for the use in daily routine. In case that clinical signs of aspiration occur during the testing, the WST is considered positive²¹
- Multiple-Consistency-Test: Dysphagia is graded in one of four categories (severe, moderate, mild or no dysphagia)²⁰
Swallowing-Provocation-Test (SPT): The SPT exclusively examines the involuntary swallowing reflex by bolus injection of 0.4ml of distilled water through a small nasal catheter into the oropharynx.\textsuperscript{12}

In which patients is assessment of dysphagia indicated?

All stroke patients failing the dysphagia screening should be evaluated with a more thorough assessment of swallowing function.\textsuperscript{11}

How often should the assessment of dysphagia be repeated?

During the first days of illness the clinical bedside assessment (CBA) can be repeated in dysphagic stroke patients on a daily basis. If dysphagia persists, CBA can be carried out thereafter at least twice per week and before discharge. If dysphagia persists after discharge, assessment can be done at least once per month for 6 months after stroke manifestation.\textsuperscript{11}

Should tube-fed patients with dysphagic stroke be advised to have additional oral nutrition?

The majority of conscious dysphagic stroke patients with tube feeding should have additional oral intake, according to the kind and severity of dysphagia.\textsuperscript{11}

Which patients should receive oral nutritional supplements (ONS, “Sip feeds”)?

Stroke patients, who are able to eat and who have been identified to be at risk of malnutrition, who are malnourished or who are at risk for pressure sores should receive oral nutritional supplements.\textsuperscript{11}

In which situation is parenteral nutrition indicated in stroke patients?

If sufficient hydration by oral or enteral nutrition is not possible, parenteral hydration should be applied immediately.\textsuperscript{11}

Is texture modified food or thickened fluid indicated in patients with dysphagia?

A dietician should be consulted and nutrition support should be initiated in cases of insufficient intake over a prolonged period of time.\textsuperscript{11}
REFERENCES


MCQs

1. The key pillars for cascade of stroke recovery are
   a. Blood glucose management
   b. Blood pressure management
   c. Venous thrombosis management
   d. All of the above

2. Post stroke disability is caused due to complications such as
   a. UTI
   b. Chest infections
   c. Bedsores
   d. All of the above

3. % of stroke patients are hyperglycaemic
   a. 80%
   b. 75%
   c. 40%
   d. 20%
4. Which of the below mentioned is not the risk factor for DVT?
   a. Atrial fibrillation
   b. Obesity
   c. Hormone therapy
   d. Allergic rhinitis

5. _____patients with stroke will be hyperthermic
   a. 1/3
   b. 2/4
   c. 2/3
   d. 3/4