# Medical Complications Post Stroke

Evidence Tables

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17.1 Frequency of Medical Complications Post Stroke

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<th>Author, Year Country Study Design Sample Size</th>
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| Dromerick & Reding (1994) USA Case Series N=100 | **Population:** Mean age= 69+/9-yr; Gender: Males=42, Females=58. **Intervention:** Reviewed inpatient discharge records. **Outcomes:** Number of medical complications observed; Number of neurological complications observed. | 1. No significant correlation between patient’s age or interval from stroke to rehabilitation hospital admission and number of complications.  
2. No significant differences were found between patients who had ischemic infarcts or hemorrhagic infarcts.  
3. There was a statistically significant association between complications and length of rehabilitation hospital stay (r=0.54, p<0.01).  
4. 96% of patients developed a medical or neurological complication that required a physician’s order for further evaluation or treatment.  
5. More than half (54%) of medical complications were accounted for by the following: urinary tract infection, depression, MSK pain, urinary retention, falls, fungal dermatitis, hypotension, diabetes mellitus, hypertension. |
| Kalra et al. (1995) England Observational N=245 | **Population:** Not reported. **Intervention:** Exploratory study investigating whether management of a particular setting impacts the frequency of complications among patients. **Outcomes:** Frequency of medical complications; Frequency of neurological complications; Institutionalization rates. | 1. Baseline demographic characteristics between patients on the stroke unit vs patients on general medical wards were comparable.  
2. The frequency of documented medical complications were not significantly different between the two settings (stroke unit vs general ward).  
3. The frequency of neurological complications were not significantly different between the two settings (stroke unit vs general ward).  
4. The total number of complications among patients managed on the stroke unit vs general ward was not significantly different.  
5. There were significant differences in the type of medical complications between stroke patients managed on the stroke unit vs general ward (i.e. aspiration and musculoskeletal pain)  
6. There was a statistically significant relationship between the frequency of complications, prognostic grouping and duration of hospital stay (p<0.01). Age, sex, or management setting were not statistically significant factors.  
7. Frequency of complication was not significantly associated with institutionalization rates. |
<table>
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<th>Study</th>
<th>Country</th>
<th>Case Series</th>
<th>N</th>
<th>Population:</th>
<th>Intervention:</th>
<th>Outcomes:</th>
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<tr>
<td><strong>Davenport et al. (1996)</strong></td>
<td>Scotland</td>
<td>Case Series</td>
<td>613</td>
<td>Median age=73 (IQR range: 65 to 81yr); Gender: Males=46%, Females=54%.</td>
<td>Reviewed case notes for patients and recorded type, timing, and frequency of complications.</td>
<td>Frequency of complications that occurred during the inpatient period; Reliability of complication identification from case note review from two observers.</td>
</tr>
<tr>
<td>1.</td>
<td></td>
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<td></td>
<td>62% of persons with complicated strokes experienced more than one complication</td>
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<td>2.</td>
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<td>The level of agreement between the two observers was moderately good in this study, kappa value was greater than 0.6.</td>
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<tr>
<td>3.</td>
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<td>Out of the 607 hospital admissions for acute stroke, at least one complication occurred in 59% of patients. These included the following:</td>
<td>Falls (22%)</td>
<td>Urinary tract infection (16%)</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td></td>
<td></td>
<td>From the 360 complicated strokes, 62% experienced more than one type of complication. These included the following:</td>
<td>Falls (48%)</td>
<td>Urinary tract infections (26%)</td>
</tr>
<tr>
<td>5.</td>
<td></td>
<td></td>
<td></td>
<td>Experiencing a complication was associated with an increased risk of death during admission (OR=1.9, 95% CI: 1.2 to 2.9)</td>
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<tr>
<td><strong>Johnston et al. (1998)</strong></td>
<td>USA</td>
<td>Case Series</td>
<td>279</td>
<td>Mean age= 69 +/- 13yr; Gender: Males=57%, Females=43%.</td>
<td>Patients received either tirilazad mesylate or vehicle (Sodium citrate) diluted with sodium chloride (either 0.9% or 0.45% concentration) for a total volume of 250 mL administered as a rapid intravenous infusion over 10 to 30 minutes.</td>
<td>Poor outcomes defined as a severe disability or death at 3 months.</td>
</tr>
<tr>
<td>1.</td>
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<td>95% of patients had at least one event, 32% had at least one serious event, and 14% of patients were dead at 3 months.</td>
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<td>2.</td>
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<td>Serious medical events were associated an increased odds of a poor outcome at 3 months, as measured by the Barthel Index: (OR=6.1, 95% CI: 2.5 to 15.1), and the Glasgow Outcome Scale (OR= 95% CI, 4.3 to 30.9), after adjusting for age, admission NIHSS score, and history of diabetes mellitus.</td>
<td></td>
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<tr>
<td>3.</td>
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<td>Serious neurological complications were associated with an increased odds of a poor outcome at 3 months as measured by the Barthel Index, (OR=11.3, 95% CI: 3.8 to 33.4), and the Glasgow Outcome Scale (OR= 9.4 (95% CI, 3.2 to 27.4), after adjusting for age, admission NIHSS score, and history of diabetes mellitus.</td>
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<tr>
<td>4.</td>
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<td>Specifically for the outcome of severe disability, serious medical events were associated with severe disability as measured by the BI (OR=1.2; 95% CI, 0.3 to 4.4)and GOS (OR=4.4; 95% CI, 1.3 to 14.8).</td>
<td></td>
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<tr>
<td>5.</td>
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<td>Specifically, for the outcome of severe disability, serious neurological complications were associated with severe disability as measured by the BI (OR, 6.1; 95% CI, 1.4 to 26.1) and the GOS (OR 4.6; 95% CI, 1.2 to</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>N</td>
<td>Population Description</td>
<td>Intervention</td>
<td>Outcomes</td>
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</table>
| Langhorne et al. (2000) | Scotland      | Observational| 311  | Median age=76yr (IQR: 70 to 82); Gender: Males=52%, Females=48%                       | Weekly functional assessments and observation of the occurrence of pre-specified complications were performed on patients on a weekly basis until discharge from hospital. | 1. There was a statistically significant relationship between complications, namely, infections, pressure sores, and anxiety, and stroke severity (p<0.05).  
2. 85% of patients experienced at least 1 pre-specified complication during their time in the hospital  
3. Observations showed that the majority of complications occurred following early onset of stroke, particularly for pressure sores, pain, and infections. |
| Roth et al. (2001)     | USA           | Observational| 1029 | Mean age=63.6 +/- 15.3yr; Gender: Males= 47%, Females=53%                             | Reviewed patient medical records and monitored occurrence of medical complications. | 1. Multivariable findings showed that three factors were significantly associated with the occurrence of any complication: hypoalbuminemia, history of hypertension and NIHSS (neurological impairment)  
2. Multivariable findings showed that elevated white blood cell count and low hemoglobin levels on admission to rehabilitation, greater impairment and a history of a cardiac arrhythmia were significantly associated with the occurrences of a transfer during rehabilitation to an acute care facility.  
3. Severity of neurological deficit on admission to rehabilitation was the strongest predictor of any medical complications and of complications that required a transfer.  
4. Results showed that the likelihood of complications generally increased with increasing severity of neurological impairment; for all severity groups, the most common complication was urinary tract infection. |
| Doshi et al. (2003)    | Singapore     | Case Series  | 140  | Mean age= 65.7 (40-90yr); Gender: Males=46.6%, Females=53.6%                          | Case notes review of the type and frequencies of complications after an acute stroke in an inpatient rehabilitation setting, and examined which complications required transfer of patient back to care of primary physician. | 1. 45.7% of patients in the study did not experience any complications, 22% had at least one complication and 17.9% experienced three or more complications each.  
2. The most commonly documented complication rates occurred for constipation (22.9%), acute retention urine (20.9%), and urinary tract infection (14.3%), depression (9.3%), and limb pain (8.6%).  
Results from the subgroup analysis:  
1. Complication rates between males and females were statistically significantly different for the following, in that females were more likely to have urinary tract infections (OR=3.0, 95%CI: 1.03 to 8.77), acute retention of urine (OR=4.0, 95% CI: 1.68 to 11.76), and depression (OR= 5.41, 95% CI: 95% 1.15 to 25.64). |
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Type</th>
<th>Sample Size</th>
<th>Population</th>
<th>Gender</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
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<td>McLean (2004)</td>
<td>Canada</td>
<td>Observational</td>
<td>N=133</td>
<td>Mean age: 68.6 +/- 13.1 (41-91yr); Gender: Males=52%, Females=48%</td>
<td>Assessment of stroke patients was undertaken for specific complications.</td>
<td>Presence or absence of specific medical complications.</td>
<td>Clinical diagnostic criteria may vary between studies; Certain patient characteristics may be able to predict complications post-stroke (i.e. older patients, disabilities that existed before a stroke occurred, those who have severe strokes).</td>
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<td>Hung et al. (2005)</td>
<td>Taiwan</td>
<td>Case Series</td>
<td>N=346</td>
<td>Mean age: 65.2 +/- 11.4yr; Gender: Males=53.8%, Females=46.2%</td>
<td>Review of patients’ medical charts.</td>
<td>Number of medical complications during rehabilitation; Frequency of medical complications that resulted in transfer to an acute care ward.</td>
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<td>Chalouhi et al. (2013)</td>
<td>USA</td>
<td>Case Series</td>
<td>N=508</td>
<td>Mean age=55.2±11.9yr; Gender: Males=15.4%, Females=84.6%</td>
<td>Neuroform and Enterprise stents were used to treat patients with aneurysms over a period of 5 years.</td>
<td>Procedural complications and recanalization were measured using the Glasgow outcome scale (GAS) (for degree</td>
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</table>

1. There were no significant differences between males and females for the following: complication rates of constipation and limb pain.

1. The overall complication rate was 67%, that is, 67% of stroke survivors had at least 1 complication and 25% had 2 or more complications.
2. The most frequently reported complications were depression (26%), shoulder pain (24%), falls (20%), and UTIs (15%).
3. Less common complications included back and hip pain (5%), gastrointestinal disturbances (4%), and pneumonia (2%).
4. Seizures, pressure ulcers and shoulder-hand syndrome were found to occur in 1.5% of the population.

1. 44% of patients experienced at least one medical complication.
2. The most frequently occurring medical complications included musculoskeletal pain (13.6%), depression (9.3%), upper gastrointestinal tract bleeding (4.9%), and pneumonia (4.9%).

1. 70.3% experienced at least one complication.
2. The most common complications included post-stroke depression (56.6%), musculoskeletal pain (28%), urinary tract infection (UTI) (17.8%), and complex regional pain syndrome (CRPS) type I (15.3%).
3. Less common complications included pneumonia (4.2%), cardiovascular complications (4.2%), falls (4.2%), upper GI bleeding (3.2%), seizure (2.5%), and pressure ulcer (1.7%).
4. Fourteen patients (11.8%) were referred to the acute care hospital because of severe medical complications.
5. History of myocardial infarction, low admission Barthel ADL Index, urinary incontinence, indwelling catheterization, and dysphagia were risk factors of complications (p < 0.05).

1. Complications occurred in 6.8% of patients.
2. Multivariable results showed that cutely ruptured aneurysms (odds ratio [OR]=2.8; 95% confidence interval [CI], 1.1–7; P=0.01), delivery of coils before stent placement (OR=5.2; 95% CI, 2–15; P=0.002), and carotid terminus/middle cerebral artery aneurysm locations (OR=3.2; 95% CI, 1.2–8.5; P=0.02)
of unfavorable outcomes).

3. Multivariable results showed that older age (OR=1.03; 95% CI, 1.0–1.1; P=0.03), previously coiled aneurysms (OR=3.4; 95% CI, 1.4–8.1; P=0.005), larger aneurysms (OR=1.1; 95% CI, 1.1–1.2; P<0.001), incompletely occluded aneurysms (OR=1.5; 95% CI, 1.1–6; P=0.04), Neuroform stent (OR=0.4; 95% CI, 0.2–1; P=0.05), and cavernous/posterior communicating/middle cerebral artery aneurysms/vertebral locations (OR=2.2; 95% CI, 1.1–6.1; P=0.03) were statistically significant independent predictors of recanalization.

4. 94% of patients achieved a favorable outcome (GOS IV and V).

5. Multivariable results showed that patient age (OR=0.9; 95% CI, 0.92–0.99; P=0.04), ruptured aneurysm status (OR=0.01; 95% CI, 0.002–0.07; P<0.0001), and procedural complications (OR=0.02; 95% CI, 0.004–0.1; P<0.001) were the only independent predictors of unfavorable outcome.

### Chao et al. (2013)
Taiwan Case Series
N=297

**Population:** Patients who received thrombolytic therapy were classified into two groups based on their estimated renal glomerular filtration rate (eGFR). Group 1 (eGFR>60): Mean age=62.8±12.9yr; Gender: Males=146, Females=86. Group 2 (eGFR<60): Mean age=70±118yr; Gender: Males=45, Females=20.

**Intervention:** Thrombolytic therapy.

**Outcomes:** Incidence of ICH; Functional dependence or death based on two main groups of the modified Rankin scale (mRS) scores at 1 month and 1 year.

1. Multivariable findings revealed that renal dysfunction was associated with an increased odds of developing ICH (OR=ICH) was more common in the renal dysfunction group (23 vs. 12.5%; 95%CI: 1.05 to 4.21), after adjusting for age. The odds of developing ICH was not high in the group with low eGFR, even after adjusting for age, sugar, and TG levels.

2. At discharge and 1-year after discharge, GFR values <60 ml/min/1.73 m² were not significantly associated with the odds of functional dependence or death at 1 month or 1 year post-stroke.

### Chen et al. (2013)
Taiwan Case Series
N=51

**Population:** Mean age=80.3+/8.2yr; Gender: Males=37, Females=14.

**Intervention:** To investigate the predictors of 30-day mortality in patients with pneumonia following stroke.

**Outcomes:** 30-day mortality.

1. The most common pathogen found to be responsible for post-stroke pneumonia was Kelbsiella Pneumoniae, followed by Pseudomononas aeruginosa and Escherichia coli.

2. Findings from the univariate analysis revealed that patients who died within 30 days had higher NIHSS scores, higher CURB-65 scores, elevated instability of hemodynamic status and lower Glasgow Coma Scale (GCS) scores.

3. The 30-day mortality rate was 23.5%.

4. Cox-regression analysis showed that a GCS score of less than 9 on the day of pneumonia onset was the only statistically significant
<table>
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<th>Study</th>
<th>Country</th>
<th>Type</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Fisher et al. (2013)**      | Australia        | Observational     | N=2228     |              | 1. The average annual incidence rate of HF among stroke survivors was 1.45 times higher than in the general population (631.3 vs. 436.5 per 100,000 person-years).  
2. The standardized annual post-stroke HF incidence rate in women was 1.7 times higher than that in men (18.9 vs. 11.1 per 100,000 person-years, p=0.008).  
3. The average annual post-stroke HF incidence rates as a percentage of the total stroke survivors incidence rate was 3.9%, for males 2.6% and for females 5.1%.  
4. The risk of post-stroke HF in females is significantly higher than in men (hazard ratio=1.96, 95% CI (1.15,3.32), p=0.013).  
5. The mean time of HF occurring after the stroke was 2.34±2.08yr and it did not differ significantly by age of stroke survivors neither in women, nor in men.  
6. Female gender was associated with time to post-stroke HF (HR=1.93, 95% CI 1.13,3.30, p=0.016).  
7. In women, the absolute number of post-stroke HF increased by 7.3% with each 10 years of age (p=0.001), and decreased by 15.7% (p=0.003) with each calendar year of stroke. |
| **Kilbourn et al. (2013)**    | USA              | Case Control      | N=299      |              | 1. Mortality was significantly higher in the NCM group compared to the non-NCM group (46.9% vs. 11.2%, p<0.001).  
2. At 3 and at 12 months, the NCM group had lower mBI scores compared to the non-NCM group (p=0.002, p=0.014).  
3. Age, history of hypertension, hypercholesterolemia, and chronic obstructive pulmonary disease were not associated with the development of NCM.  
4. Diabetes mellitus was associated with vasospasm (p=0.009), as was tobacco use (p<0.001).  
5. At 3 months, a Hunt-Hess Score of ≤2 was associated with better functional outcome (p=0.002) while at 12 months, a Hunt-Hess score of <2 was associated with improved outcome (p=0.007).  
6. NCM was associated with both death (p=0.047, CI (1.012,7.288) and vasospasm (p=0.008, CI (1.34,6.66)). |
| **Lanterna et al. (2013)**    | Italy            | Observational     | N=27       |              | 1. Hypocortisolism indicator for 30-day mortality (HR=6.72; 95% CI: 2.12 to 21.30; p=0.001).  
2. Cortisol increment after stimulation test was  

**Note:** All data and interpretations are based on the studies mentioned in the table.
### Ormstad et al. (2013) Norway Observational N=45

<table>
<thead>
<tr>
<th>Population: Mean Age=67.7 yr; Gender: Male=27, Female=18.</th>
<th>1. TRP level was significantly lower in stroke patients compared to healthy control (stroke=95.2±20.3 µM, p=0.004).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention: Conducted assessments on post stroke patients.</td>
<td>2. TYR level was significantly lower in stroke patients compared to healthy control (stroke=13.5, p&lt;0.001).</td>
</tr>
<tr>
<td>Outcomes: Presence of: tryptophan (TRP) metabolites, tyrosine (TYR) metabolites, quinolinic acid (QA), kynurenic acid (KA), cytokines and kynurenine (KYN).</td>
<td>3. KYN was significantly negatively correlated with the IL-1β cytokine in stroke patients (p=0.043).</td>
</tr>
<tr>
<td>1. TRP level was significantly lower in stroke patients compared to healthy control (stroke=95.2±20.3 µM, p=0.004).</td>
<td>4. KA and QA were significantly positively correlated with the IL-6 cytokine in stroke patients (p=0.046).</td>
</tr>
<tr>
<td>2. TYR level was significantly lower in stroke patients compared to healthy control (stroke=13.5, p&lt;0.001).</td>
<td>5. TYR levels were significantly negatively correlated with the IL-6 cytokine (p=0.041).</td>
</tr>
<tr>
<td>3. KYN was significantly negatively correlated with the IL-1β cytokine in stroke patients (p=0.043).</td>
<td>6. IL-10 cytokine in stroke patients:</td>
</tr>
<tr>
<td>4. KA and QA were significantly positively correlated with the IL-6 cytokine (p=0.046).</td>
<td>- Significantly positively correlated with KA (p=0.003) and TRP levels (p=0.047).</td>
</tr>
<tr>
<td>5. TYR levels were significantly negatively correlated with the IL-6 cytokine (p=0.041).</td>
<td>- Significantly negatively correlated with KYN/KA (p&lt;0.001).</td>
</tr>
<tr>
<td>6. IL-10 cytokine in stroke patients:</td>
<td>- Significantly negatively correlated with TYR and TRP levels (p=0.037).</td>
</tr>
<tr>
<td>7. TRP levels were significantly negatively correlated with glucose (p=0.011).</td>
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### Tang et al. (2013) China Case Series N=500

<table>
<thead>
<tr>
<th>Population: Post Stroke Fatigue (PSF, N=125): Mean Age=64.7 yr; Gender: Male=67, Female=58; No PSF (N=375): Mean Age=65.3 yr; Gender: Male=257, Female=118.</th>
<th>1. Severity of stroke, previous stroke and cognitive function were not significantly different between patients with and without PSF.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention: Assesses stroke patients admitted to multiple centers from June 2004 to October 2010.</td>
<td>2. Caudate infarcts were significantly more common in PSF patients (PSF=8.0%, No PSF=1.3%, p=0.001).</td>
</tr>
<tr>
<td>Outcomes: Location of infarcts; Geriatric Depression Scale (GDS); Stroke severity; Previous stroke; Barthel Index (BI); Cognitive function.</td>
<td>3. Putamen infarcts were significantly more common in PSF patients (PSF=19.2%, No PSF=12.0%, p=0.043).</td>
</tr>
<tr>
<td>1. Severity of stroke, previous stroke and cognitive function were not significantly different between patients with and without PSF.</td>
<td>4. Pons infarcts were significantly less common in PSF patients (PSF=13.6%, No PSF=22.2%, p=0.038).</td>
</tr>
<tr>
<td>2. Caudate infarcts were significantly more common in PSF patients (PSF=8.0%, No PSF=1.3%, p=0.001).</td>
<td>5. PSF was independently and significantly predicted by caudate infarcts, female sex and GDS scores.</td>
</tr>
</tbody>
</table>
6. GOS scores were significantly greater in PSF patients at 3mo follow-up (PSF=6.0±3.4, No PSF=3.8±3.1, p<0.001).
7. BI was significantly greater in patients without PSF at 3mo follow-up (PSF=18.9±2.3, No PSF=19.4±1.5, p=0.0012).

**Visser-Meily et al.** (2013) 
Netherlands Observational 
N=143

Population: Mean Age=62.5yr; Gender: Male=17, Female=77.  
Intervention: A questionnaire was distributed to patients 3yr post stroke. Patients were divided between those with post-traumatic stress disorder (PTSD, n=24) and those without PTSD (n=70).  
Outcomes: Glasgow Outcome Scale (GOS); Incidence of cognitive impairment; Impact of Event Scale; Stroke Specific Quality of Life Scale (SSQoL).

1. GOS scores showed good recovery in 63% of patients, independent disability in 32% of patients and dependent disability in 5% of patients.  
2. Cognitive impairments were present in 20 patients (22%).  
3. Impact of event scale scores showed post-traumatic stress disorder (PTSD) to be present in 24 patients (26%).  
4. SSQoL total (PTSD=3.5±1.1, Non-PTSD=4.4±1.0, p<0.001), physical (PTSD=4.2±0.8, Non-PTSD=4.7±0.8, p<0.001) and psychosocial scores (PTSD=2.9±1.7, Non-PTSD=4.2±1.4, p<0.001) were significantly lower in PTSD patients compared to non-PTSD patients.

**Behme et al.** (2014)  
Germany Case Series 
N=176

Population: Mean age=62±14yr; Gender: Males=67.5%, Females=32.5%.  
Intervention: Mechanical thrombectomy.  
Outcomes: Symptomatic intracranial hemorrhage (sICH), vessel dissection, emboli to new vascular territories, vasospasm, and stent dislocation/occlusion; Secondary: mTICI score, time from symptom onset to revascularization, time from groin puncture to revascularization, and early clinical outcome at discharge.

1. Complications occurred in 11% of patients comprising 23 adverse events at the following rates: sICH 8/176 (5 %), emboli to new vascular territories 4/176 (2 %); vessel dissection 3/176 (2 %); vasospasm of the access vessel 5/176 (3 %); stent dislocation in 1/42 (2 %); and stent occlusion in 2/42 (5%).  
2. Only 10% of patients suffered from two or more procedure-related complications.  
3. There was a statistically significant correlation of complications with time from groin puncture to revascularization, unfavorable revascularization results, and unfavorable clinical outcome.

**Chen et al.** (2014)  
Taiwan Observational 
N=586

Population: Patients were classified into three main age groups for comparison purposes: Group 1 (<65 years, young); Group 2(65 years to <75 years, younger old); and Group 3(≥75 years, older old).  
Further, clinical characteristics and comparison of complications was provided based on patients from Acute ward and Rehabilitation Ward.  
Acute Ward: Mean age=65.71+/−13.33yr; Gender: Males=283, Females=285.  
Rehabilitation Ward: Mean age=65.71+/−13.33; Gender: Males=285, Females=283.  
Intervention: Examining effect of age on complication rates in inpatient stroke rehab patients.  
Outcomes: Complication rates at different

1. In the acute ward, patients experienced less shoulder pain, neck pain, knee pain, and other musculoskeletal pain, dermatitis, and hyperkalemia than in the rehab ward. In all three age groups, constipation, shoulder pain, symptomatic urinary tract infection (UTI), and fever were found to be common complications during initial stay in the rehabilitation ward and the incidence was >10%.  
Results for patients who transferred from acute to rehab at initial stay:
2. The incidence of neurogenic bladder, dysphagia, UGIB, and symptomatic UTI was statistically significantly lower in the young group than the younger old and older old groups.  
Results for patients who underwent subsequent
disease (stroke) stages.

hospitalization (subsequent stay) in the rehabilitation ward (n=150).
3. The incidence of UGIB was statistically significantly lower in the Group 1 than in Groups 2 and 3 (differences were between Groups 1 and 2, and between Groups 2 and 3).
4. The incidence of symptomatic UTI was statistically significantly higher in Group 3 than in Groups 1 and 2.
5. The correlations between age and number of complication types in both acute (p=0.260; r=-0.047) and rehabilitation (first hospitalization; p=0.126; r=0.064) wards were not significant.

Chu-Hsu et al. (2014) Taiwan Observational N=145

Population: Participants in the study were divided into three groups according to TPS (<3m, 3m to 1yr, and ≥1yr), Groups 1 to 3, respectively. Group1: Mean age=68.4±12.0yr; Gender: Males=31, Females=29; Group2: Mean age=62.2±13.2yr; Gender: Males=12, Females=18; Group3: Mean age=55.2±10.9yr; Gender: Males=44, Females=11.

Intervention: Review various outcomes post-stroke.

Outcomes: Spontaneous pain intensity (verbally reported numerical rating scale) (VRS) and pressure pain threshold (PPT).

1. The prevalence of moderate to severe spontaneous muscle pain from at least one of the three MTePs tested in the hemiparetic side decreased as the stroke duration increased, including 48.3%, 26.6%, and 25.4% for the subjects in Groups 1, 2, and 3, respectively.
2. VRS scores at the MTePs of the hemiparetic side were higher than those of the healthy side despite different durations from onset of stroke. Pain intensity was highest in Group 1 subjects, followed by Group 3 and then Group 2.
3. Mean PPT was higher in the periosteum point than in the MTeP and the PPT for each MTeP in increasing order, MTeP1, MTeP3 and MTeP2, regardless of healthy or hemiparetic side.
4. There were no significant differences in muscle-periosteum PPT difference in percentages between bilateral MTePs. For subjects with moderate to severe pain at the MTePs of the hemiparetic side, the PPT or muscle-periosteum PPT difference of each MTeP
5. Results showed that VRS at each MTeP of either the healthy or hemiparetic side was positively associated with the VRS at the other MTeP in both healthy and hemiparetic sides.

Gattringer et al. (2014) Austria Case Series N=41619

Population: Myocardial Infarction (MI, n=421): Median Age=79.5yr; Gender: Male=204, Female=217; Non-MI (n=41198): Mean Age=73.6yr; Gender: Male=21833, Female=19365.

Intervention: Assessed stroke patients on the Austrian stroke registry from January 2007 to January 2013. Patients spent a median of 3d at the stroke unit after their initial stroke.

Outcomes: Prevalence of complications:

1. Mortality in the stroke unit was significantly greater in MI patients (MI=14.5%, Non-MI=2%, p<0.001).
2. NIHSS scores at discharge were significantly greater in MI patients median MI=8, Non-MI=4, p<0.001).
3. mRS scores showed poor functional outcomes (mRS 3-5) in a significantly greater proportion of MI patients (MI=63.2%, Non-MI=42.7%, p<0.001).
4. Associated complications were significantly
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>N</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Savic et al. (2014)                       | Serbia  | Observational | 106 | Mean Age=83.2yr; Gender: Male=107, Female=137 | Assess characteristics of stroke patients admitted between January 2002 and May 2003. | 1. Significantly more patients reported no fever (fever=22, no fever=81, p=0.000).  
2. Significantly fewer patients with fever reported having a previous stroke (fever=13, no fever=64, p=0.043).  
3. Glycaemia was significantly higher in fever patients (fever=8.10±3.28mmol/L, no fever=6.62±2.71mmol/L, p=0.010).  
4. Hematocrit levels were significantly decreased in fever patients (fever=37.32±7.77, no fever=29.89±3.63, p=0.028).  
5. NIHSS scores were significantly higher in fever patients (fever=18.27±6.60, no fever=10.06±5.56, p=0.000).  
6. Bamford scale distribution was significantly different between fever and no fever patients with more fever patients classified as total anterior circulation stroke (fever=68.2%, no fever=14.8%) and more no fever patients classified as partial anterior circulation syndrome (fever=13.6%, no fever=35.8%). |
| Tang et al. (2014)                        | China   | Case Series | 199 | Mean Age=68.4yr; Gender: Male=140, Female=59 | Assess stroke patients admitted to multiple centers from June 2004 to October 2010. | 1. Number of infarcts, volume of infarcts and location of infarcts were not significantly different patients with and without PSF.  
2. Cerebral microbleeds were not significantly more prevalent in PSF patients (PSF=6.2±9.8, No PSF=4.3±7.7, p=0.060).  
3. Deep cerebral microbleeds were significantly more prevalent in patients with PSF (PSF=66.0%, No PSF=48.7%, p=0.038).  
4. The number of white matter hyperintensities and acute infarcts was not significantly different between groups. |
| Van Dijk et al. (2014)                    | Netherlands | Case Series | 708 | Mean Age=62.5yr; Gender: Male=53, Female=59; Injury etiology: stroke=283, TIA=222, unknown=3 | Assessed patients from 1. Calcification of the aortic arch was significantly more prevalent in non-lacunar stroke patients (non-lacunar=73%, lacunar=62%, p<0.01).  
2. Calcification volume in the aortic arc was |
December 2005 to September 2010. Patients were divided between those having a lacunar stroke (n=343) or a non-lacunar stroke (n=365). **Outcomes**: Severity of stenosis; and prevalence and volume of calcifications: aortic arch, symptomatic extracranial carotid, and the symptomatic intracranial carotid. Significantly higher in patients with a non-lacunar stroke (median non-lacunar=62.2mm³, lacunar=10.5mm³, p<<0.001).

1. **Chan et al.** (2015) Australia Case Series N=103
   - **Population**: Anemic group: Mean age=72yr; Non-anemic group: Mean age=70yr. Gender ratio of male:female=41:59 (identical in both groups).
   - **Intervention**: Description of stroke patients’ characteristics based on whether they were anemic or not.
   - **Outcomes**: functional improvement (functional independence measure (FIM)); discharge destination, length of stay (LOS) and complication rates.

2. 28.2% of ischemic stroke patients were anemic and 71.8% were not anemic.
3. A statistically significantly higher rate of complications were found in the anemic group than in the non-anemic group (60% versus 39%, p=0.049).
4. Average FIM on discharge and average LOS were not significantly different between the two groups (p>0.05).
5. There was a statistically significant difference in the proportion of patients discharged home between the two groups (p=0.006).

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1. Incidence of pneumonia in the patient population was 44%.
2. There was a statistically significant difference in severity between patients who had acquired pneumonia and those who did not (NIHSS score: p=0.000).
3. Patients who had acquired pneumonia had a higher prevalence of decreased consciousness (p=0.002), endotracheal intubation (p=0.04), and severe facial palsy (p=0.02) compared to those without pneumonia.
4. Patients who developed pneumonia required a significantly longer duration of nasogastric tube insertion (p<0.000) than those who did not develop pneumonia.
5. Prevalence of dysarthria (p=0.4), aphasia (p=0.13), neglect (p=0.35) and hemiparesis (p=0.09) were not significantly associated with pneumonia.

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1. 5% patients had recurrent stroke, 7% myocardial infarction, 17% chest infection, 28% urinary tract infection, 13% had other...
N=244 stroke patients admitted between January 2002 and May 2003 90d post discharge. **Outcomes:** Incidence of complications; Modified Rankin Scale (mRS).

1. Other infections and falls were associated with a mRS score ≥3.
2. Recurrent stroke, myocardial infarction and chest infections were associated with a mRS score ≥3.
3. Infections, 29% had falls and 57% had pain.

**Shah et al.** (2015) Canada Case Series N=14293

**Population:** Mean Age=68yr; Gender: Male=9515, Female=4778. **Intervention:** Assesses stroke patients admitted to multiple centers from July 2003 to March 2008. Patients were divided between those with language barriers (n=1506) and those without language barriers (n=12787). **Outcomes:** Incidence of complications; Length of stay; Prescriptions at discharge; Type of assessments: occupational therapist, physiotherapist, speech language pathologist, social worker and nutritionist; Imaging: brain imaging and carotid imaging; Neurological deficits; Mortality rates.

1. Mortality was significantly lower for patients with language barriers at 7d (without=9.2%, with=7.0%, p=0.006) and 30d (without=15.7%, with=14.6%, p<0.001) but was significantly higher 1yr post discharge (without=25.6%, with=26.8%, p<0.001).
2. The prevalence of a moderate-to-severe residual neurological deficit at discharge was significantly greater in patients with language barriers (without=51.5%, with=65.9%, p<0.001).
3. Incidence of in-hospital complications was not significantly different between groups.
4. Length of stay was significantly longer in patients with language barriers (median without=8, with=9, p=0.002).
5. Brain imaging within 24hr of admission was conducted significantly more frequently in patients with language barriers (without=95.7%, with=96.0%, p=0.039).
6. Carotid imaging within 2wk was not significantly different between groups.
7. Assessments from an occupational therapist (without=72.0%, with=80.3%, p=0.001), physiotherapist (without=76.8%, with=82.8%, p=0.003), speech language pathologist (without=54.7%, with=65.6%, p<0.001), nutritionist (without=34.6%, with=42.0%, p=0.002) and a social worker (without=46.9%, with=58.7%, p<0.001) were significantly more common in patients with a language disorder.
8. Discharge prescriptions were not significantly different between groups.

### 17.2 Bladder Dysfunction Post Stroke

#### 17.2.1 Prevalence, Predictors, and Consequences of Urinary Incontinence

**Table 17.2.1 Prevalence of Urinary Incontinence Post Stroke**
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chou et al. (2013)</td>
<td>Taiwan</td>
<td>Case Series</td>
<td>N=15</td>
<td>Population: Patients with cerebellar stroke were classified according to the location of lesion (Group 1=Ischemic Stroke and Group 2=Hemorrhagic Stroke). Control subjects were placed into Group 3 (data not shown). Group 1 (N=8): Mean age= 77.0±6.0yr; Gender: Males=5, Females=3. Group 2 (N=7): Mean age= 72.7±19.1yr; Gender: Males=5, Females=2.</td>
<td>1. DO was found in eight (53 %) patients, dyssynergic urethral sphincter in six (40 %), and nonrelaxing urethral sphincter in seven (47 %). 2. There were no significant differences in VUDS parameters among the patients with different lesion locations or between patients with ischemic and hemorrhagic stroke. DO occurred in 75% of patients with ischemic stroke and in 28.6% of patients with hemorrhagic stroke. 3. DO was more frequently detected in patients after 2 or more months poststroke (late stage, p=0.007) 4. The five stroke patients in early stage had nonrelaxing sphincter function, while 4/5 (80 %) also had urinary retention. 5. 20% (two patients) in the late stage were found to have coordinated sphincter, while in 60% (six patients), dyssynergic sphincter was noted and in the remained 20% (two patients), nonrelaxing urethral sphincter was observed (p=0.014).</td>
</tr>
<tr>
<td>Ifejika-Jones et al. (2013)</td>
<td>USA</td>
<td>Case Series</td>
<td>N=4971</td>
<td>Population: SUTI patients (N=368): Mean age=67.44±16.20yr; Gender: Males=132, Females=236. No-SUTI patients (N=4603): Mean age=62.70±15.47yr; Gender: Males=2337, Females=2266.</td>
<td>1. Acute stroke patients with SUTI were on average significantly older than those with no SUTI (p&lt;0.0001), had higher NIHSS scores (p&lt;0.0001), were more likely to be female (p&lt;0.0001), had a history of urinary incontinence (p&lt;0.0001), and had a longer length of stay in ICU (p&lt;0.0001). 2. A significantly higher number of deaths was found in the stroke patients with no SUTI compared to those with SUTI (N=441 vs. N=22; p=0.0213). 3. Patients with SUTI were 57% less likely to be discharged home (p&lt;0.0001, odds ratio 0.430, 95% CI (0.303,0.609)). 4. Patients with SUTI were 37% less likely to be discharged to inpatient rehabilitation versus skilled nursing facility (p&lt;0.0058, odds ratio 0.626, 95% CI (0.449,0.873)). 5. A significant interaction between SUTI and NIHSS for discharge disposition to a skilled nursing facility versus long-term acute care facility was found (p=0.037).</td>
</tr>
<tr>
<td>Itoh et al. (2013)</td>
<td>Japan</td>
<td>Observational</td>
<td></td>
<td>Population: Experimental Group 1 (EG1, N=141): Mean age=73.0+10.1yr; Gender: Males=100, Females=41. Experimental Group 2 (EG2, N=359): Male patients reported significantly higher scores on the OABSS than females (p=0.022).</td>
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</table>
## N=500

Mean age=71.0±11.7yr; Gender: Males=211, Females=148.  
**Intervention:** Outcomes were measured.  
**Outcomes:** Overactive Bladder Symptom Score (OABSS); Modified Rankin Score (MRS); Short Form 8 Health Survey (SF-8: Physical Component Summary, Mental Component Summary); International Prostate Symptom Score (IPSS); International Consultation on Incontinence Questionnaire (ICIQ).

2. OABSS scores significantly were significantly higher with increasing age (p<0.001) and MRS (p=0.005).  
3. EG1 scored significantly lower on both the SF-8 Physical and Mental Component Summaries compared to EG2 (p<0.001 and p<0.002 respectively), suggesting a lower of quality of life.  
4. EG1 scored significantly higher on the IPSS compared to EG2 (p<0.001), indicating a greater number of cases for urinary dysfunction.  
5. EG1 scored significantly higher on the ICIQ compared to EG2 (p<0.001), indicating greater frequency of incontinence.

## Kuptniratsaikul et al. (2013) Thailand Observational N=214

**Population:** Mean age=62.1±12.5yr; Gender: Males=124, Females=90.  
**Intervention:** The incidence of morbidities after stroke were prospectively analyzed. Comparisons were made at discharge and at 12 months.  
**Outcomes:** Incidence of morbidities (musculoskeletal pain, neuropathic pain, pneumonia, deep vein thrombosis (DVT), pressure ulcer, spasticity, shoulder subluxation, joint contracture, dysphagia, urinary incontinence, anxiety and depression).

1. Nearly 60% of patients with complications at discharge still had the same complaints after one year.  
2. Among the patients with no complications at discharge, 20% developed complication during the first year.  
3. The most common complications found during the first year of stroke were musculoskeletal pain (50.7%), shoulder subluxation (29.3%), depression (21.2%), spasticity (18.3%) and joint contracture (15.7%)  
4. Among those with musculoskeletal pain, the shoulder was the most common site with an incidence of 33.9%.  
5. Joint contracture was not present at discharge but developed during the year post-stroke, with common sites including the shoulder, ankle, and the knee joints.  
6. Urinary incontinence was found in 14.4% of patients.  
7. Other complications less than 5% include dysphagia (3.5%), pressure ulcer (2.6%), infection (1.5%) and neuropathic pain (3.0%).

## Thomas et al. (2014) UK Pre-Post  
**N**\(_{\text{Start}}=43\)  
**N**\(_{\text{End}}=28\)

**Population:** Mean Age=75yr; Gender: Male=16, Female=27.  
**Intervention:** Patient received an individualized systematic voiding programme where cognitively competent patients practiced bladder training and pelvic floor muscle training and cognitively impaired patients practised prompted voiding. 28 patients received the systematic voiding programme while 15 patients received no intervention (not analyzed). The intervention period was 6wk or until discharge.

1. 6/28 (21%) of patients reported being continent post intervention, 20/28 (71%) were incontinent, 1 (4%) was catheterized and 1 (4%) was unknown.  
2. Number of urinary incontinence episodes in patients at discharge was a median of 5.  
3. Number of urinary incontinence episodes in patients with 8-17 episodes 5d post baseline was reduced by median of 7 episodes.
### Outcomes: Incontinence Severity Index (ISI); Number of incontinence episodes; Incontinence status.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>White et al. (2014) Australia Observational N=8</td>
<td>Age=69-88yr; Gender: Male=6, Female=2.</td>
<td>Semi-structured interviews were conducted for 30-60min.</td>
<td>Experience with urinary incontinence was reported as being inconvenient and uncontrollable by all patients. Experience with urinary incontinence was reported to vary on a daily basis in regards to frequency of urination, urination duration and extent of soiling. All patients experienced the onset or exacerbation of urinary incontinence during their initial hospitalization post stroke. The attention paid to urinary incontinence was reported to be lacking in 5 patients while 3 patients received advice. Engagement in rehabilitation components was reported to be affected by urinary incontinence in several patients. Independence was not negatively affected post discharge in all patients. Quality of life was lowered post discharge predominantly when urinary incontinence affected leisure occupations and social outings. Emotions expressed due to urinary incontinence post discharge most commonly involved confusion, restricted freedom, altered self-esteem, humiliation and low mood. The amount of time spent outside their home was reported to be limited in some patients due to urinary incontinence. Adjusting to urinary incontinence was supported by family, friends and having opportunities to discuss their experiences.</td>
</tr>
<tr>
<td>Pizzi et al. (2014) Italy PCT N=106</td>
<td>Mean Age=68yr; Gender: Male=65, Female=41.</td>
<td>All patients received rehabilitation treatment for urinary incontinence including behavioral, pharmacological and surgical</td>
<td>NIHSS scores were not significantly different between groups post intervention. FIM total (mean change incon=29, con=31, p=0.005), FIM motor (mean change</td>
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</table>
interventions decided by the urologist and rehabilitation team. Treatment was provided for 30d (no further details). Patients were divided into two groups according to urinary continency: continent (n=22) and incontinent (n=84).

**Outcomes:** National Institute of Health Stroke Scale (NIHSS); Barthel Index; Functional Independence Measure (FIM): total, motor and cognitive; and prevalence of incontinence.

1. Prevalence of incontinence (mean incon=25, con=29, p=0.05) and FIM cognitive (mean change incon=4, con=2, p=0.005) were significantly lower in incontinent patients compared to continent patients post intervention.
2. BI scores were not significantly different between groups post intervention.
3. BI scores significantly increased within both groups post intervention (mean change incon=38 p<0.001, con=37 p<0.001).
4. 24/84 incontinent patients became continent post intervention.

**Cai et al. (2015) China Observational N=711**

**Population:** Age Range: 18-44yr(n=46), 45-59yr(n=179), 60-74yr(n=302), >75yr(n=184); Gender: Male=464, Female=247.

**Intervention:** Participants from eight hospitals were interviewed and completed questionnaires regarding urine incontinence (UI).

**Outcomes:** UI Prevalence; Risk Factors.

1. Overall prevalence of UI was 44.3%
2. Significant risk factors for UI were Assisted Care (OR=3.935), Hemorrhagic Stroke (OR=3.541), Parietal Lobe Lesion (OR=1.737), Aphasia (OR=3.541), and Depression (OR=3.398).

### 17.2.3 Diagnosis and Management of Urinary Incontinence Post Stroke

**Table 17.2.3 Treatment of Urinary Incontinence Post Stroke**

<table>
<thead>
<tr>
<th>Author, Year Country Study Design PEDro Score Time Post Stroke Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wikander et al. (1998) Sweden RCT PEDro=4 N=34</strong></td>
<td>34 patients randomized to receive either rehabilitation based on Functional Independence Measure (FIM) or conventional rehabilitation based on Bobath technique to regain continence.</td>
<td>1. Significantly greater proportion of FIM group regained continence than in the Bobath group. Significantly greater improvement in Katz ADL in the FIM group and on Psychological Well-being Index. 2. FIM group showed significantly greater improvement in transferring form wheelchair to toilet, bed to wheelchair and in managing wheelchair compared to Bobath group.</td>
</tr>
<tr>
<td><strong>McDowell et al. (1999) USA RCT PEDro=5 N=105</strong></td>
<td>105 patients were randomly assigned to biofeedback-assisted pelvic floor training. The treatment group (24.5% stroke patients) received behavioral therapies over an 8-week period with weekly in-home visits from a nurse practitioner. The control group (28.8% stroke patients) underwent 8-weeks of observation and then crossed over to complete the treatment protocol. Outcome Measures included the OARS Physical and Instrumental Activities of Daily Living, Folstein Mini Mental State Examination,</td>
<td>1. There was a significant reduction in urinary accidents for the treatment group 75% compared to the control group 6.4% (p&lt;0.001). 2. After the control subjects crossed over to complete the treatment protocol the 85 total patients who completed treatment attained a 73.9% reduction in urinary incontinence. 3. All accidents were reduced by 73.9% for patients who completed the treatment.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Design</td>
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| **Engberg et al.** (2002) | USA     | RCT    | 6     | 19  | 19 older patients were randomized to a prompted voiding group (30% stroke patients) or a delayed attention control group (56% stroke patients) who participated in an 8-weeks observational period and then crossed over complete to the treatment protocol. Outcome Measures included the OARS Physical and Instrumental Activities of Daily Living scales, Folstein Mini Mental State Examination, Clock Drawing Test, Performance-Based Toileting Assessment, bladder diaries and physical examination. | 1. The treatment group significantly reduced their total incontinent episodes by 55% compared with a 27% reduction for the control group. (p=0.04).  
2. After the control subjects crossed over to complete the treatment protocol there was a 22% reduction in daytime incontinent episodes for all subjects completing the treatment (p=0.04). |
| **Tibaek et al.** (2004) | Denmark | RCT    | 7     | 26  | 26 women with urinary incontinence (UI), at a median of 12 months post stroke were randomized to a treatment or a control group in a single blinded study. The intervention included 12 weeks of standardized pelvic floor muscle training. Patients in the control group received standard rehabilitation only. The outcome measures were the Short Form 36 (SF-36) Health Survey Questionnaire and The Incontinence Impact Questionnaire (IIQ). (2004). A subsequent publication in 2005 reports on voiding frequency, the number of incontinent episodes and the number of incontinence pads used in a 24 hour period, assessed by 2 and 3 day voiding diary and vaginal palpation. | 1. 24 subjects completed the study. There were no significant differences in either the SF-36 or IIQ between the two groups at the end of follow-up.  
2. The median voiding frequency over 3 days was lower in the control group compared to the control group.  
3. Although there were significant improvements among patients in the treatment group, on vaginal palpation, the treatment group showed significant improvement in dynamic endurance compared to the control group, but not on any of the other three parameters measured (function, strength and static endurance). |
| **Gross et al.** (2007) | USA     | RCT    | 6     | 45  | The purpose of the study was to compare the effect of urinary catheter removal at 7:00 a.m. with removal at 10:00 p.m. on: (a) the length of time to first void after catheter removal, (b) the amount of the first void, (c) post-void-residual urine, and (d) the number of subjects requiring recatheterization. 45 subjects were enrolled: 26 in Group A (10:00 p.m. removal) and 19 in Group B (7:00 a.m. removal). | 1. No significant differences were identified between the two groups with regard to time to void, volume of first void, post-void residual urine, or the number of subjects requiring recatheterization. |
| **Tibaek et al.** (2007) | Denmark | RCT    | 7     | 26  | Six-month follow-up of 24 from 2004 study, assessing indicators of quality of life. | 1. There were no significant differences in either the SF-36 or IIQ between the two groups at the end of follow-up.  
2. The treatment group showed slight improvement in the role limitations due to emotional problems sub-scale of the SF-36 from baseline to follow-up.  
3. The impact of urinary incontinence in 2 sub-scales of the IIQ showed a tendency to decrease in the treatment group compared to the control group. |
Yun et al. (2007)  
Korea  
RCT  
PEDro=6  
N=39  
39 stroke patients with urinary symptoms were randomized to receive moxibustion therapy (MO group) (n=20) or to control group (n=19) which did not receive MO for 10 days. The effectiveness of urinary symptoms and activities of daily living were measured by International Prostate Symptom Score (IPSS) and Barthel Index (BI), respectively before treatment, and 10 days after therapy.  
1. At the end of treatment subjects in the MO group had significantly higher IPSS scores (5.45 vs. 2.16, p<0.001).  
2. There was a significant treatment effect for subjects with mild and moderate symptoms, but not for those with severe.  
3. There were no differences between the groups in BI scores (70 vs. 68, p=ns)

Gao et al. (2012)  
China  
RCT  
PEDro=8  
N=240  
240 ischemic stroke patients were randomized to receive either complete correspondence of Chinese herbal medicine prescriptions and TCM syndrome or incomplete correspondence of a prescription and TCM syndrome for 21 days. Herbal medicines consisted of a combination of Chinese herbal granules (Hua Tan Tong Luo, Xing Lou Cheng Qi, Yi Qi Hua Yu, Yu Ying Xi Feng), mimetic agents, western medicines, standard care and rehabilitation. NIHSS score and BI were used to evaluate effectiveness of treatment. NIHSS scores were classified as nearly normal (91-100%), obviously improved (46-90%), improved (18-45%), unchanged (17%), and deteriorated (<17%). BI score <75 were regarded as ineffective, and BI score >75 were regarded as effective.  
1. There was no statistical significance in NIHSS scores between groups (p>0.05).  
2. There was no significant difference in ADL between the two groups at follow up (p>0.05).  
3. Subjective symptoms of stroke were observed. There was a significant decrease in paruria (p=0.015) in experimental group compared with control group after 1 week.  
4. There was as significant decrease in night sweating (p=0.005) and dysdipsia (p=0.002) in control group when compared with experimental group.  
5. Difficulty in talking (p=0.012) and memory loss (p=0.009) were significantly less in experimental group when compared with control group after 2 weeks.  
6. Abnormal defecation was significantly less in experimental group than in control group (p=0.015).

Moon et al. (2012)  
Korea  
RCT  
PEDro=4  
N=60  
The purpose of the study was to investigate the effects of bladder reconditioning by IUC clamping before IUC removal. Sixty stroke patients were randomized to 0-, 1-, and 3-day IUC clamping groups. Patients in the 1-, and 3-day clamping groups were clamped 4hrs followed by 5min of urinary drainage for 24- and 72-hrs, respectively.  
1. There were no significant differences for time to first void (FV), FV-vol, residual urine volume after FV, voiding method, mean voided volume, and residual urine volume among the three groups.

Yu et al. (2012)  
Taiwan  
Pre-Post  
No Score  
N=8  
8 patients after acute stroke admitted to a rehabilitation ward received electroacupuncture for ten sessions (5 days/week for 2 weeks). Spontaneous voiding of the bladder and PVR urine volumes were recorded by portable ultrasonic bladder scanner or intermittent catheterization.  
1. 7 patients completed the study. A significant difference was found in the PVR urine volume of each patient after 10 sessions of electroacupuncture (p<0.05).

Liu et al. (2016)  
China  
RCT  
PEDro=7  
TPS = 65.96±9.39d  
Population: 20Hz TENS (E1; n=27): Mean age=66.3±10.84y; Gender: Male=22, Female=5. 75Hz TENS (E2; n=27): Mean age=63.75±8.92y; Gender: Male=19, Female=8. No TENS (CG; n=27): Mean 1. E1 showed significantly greater improvements after treatment in OBSS, BI, Urodynamic Values, and Voiding Diary Parameters compared to the E2 and CG groups (all p<0.05).  
2. E2 showed significantly greater improvements in
TPS_E2 = 71.01 ± 14.86d
TPS.CG = 67.82 ± 11.58d
N_Start = 81
N_End = 81

Intervention: Participants were randomized to receive Transcutaneous Electrical Nerve Stimulation at 20Hz (E1), 75Hz (E2) or no TENS (CG) for 30min/d over 90d. Outcomes were assessed before and after treatment.

Outcomes: Overactive Bladder Symptom Scores (OBSS); Barthel Index (BI); Urodynamic Values; Voiding Diary Parameters.

Shin et al. (2016)
Korea
RCT
PEDro = 6
TPS_E2 = 6.17 ± 1.53mo
TPS.CG = 5.17 ± 2.08mo
N_Start = 35
N_End = 31

Population: Pelvic Floor Muscle Training (EG; n=16): Mean age = 62.08 ± 3.32yr; Gender: Male = 0, Female = 16. Control Group (CG; n=15): Mean age = 62.92 ± 4.93yr; Gender: Male = 0, Female = 15.

Intervention: Participants were all female and randomized to receive Pelvic Floor Muscle Training (EG) in combination with traditional rehabilitation or traditional rehabilitation alone (CG) for 6wk. Outcomes were assessed before and after treatment.

Outcomes: Maximal Vaginal Squeeze Pressure (MVSP); Pelvic Floor Muscle Activity (PVMA); Bristol Female Urinary Symptoms Questionnaire (BFUSQ).

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venn et al. (1992)</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro = 3</td>
<td>N = 58</td>
<td>58 subjects on a stroke rehabilitation unit were randomly assigned to one of four treatments: i) morning bowel training with mandatory suppository, ii) morning bowel training with optional suppository, iii) evening bowel training with mandatory suppository and iv) evening bowel training with optional suppository.</td>
<td>1. Subjects assigned to the morning groups were more likely to establish effective bowel movement patterns. 2. There were no differences found between the groups, which required mandatory or optional suppository use.</td>
</tr>
<tr>
<td>Harari et al. (2004)</td>
<td>UK</td>
<td></td>
<td></td>
<td></td>
<td>146 mainly community-dwelling stroke patients (n=122) with constipation or fecal</td>
<td>1. Percentage of bowel movements (BM) per week graded as “normal” by participants in a prospective</td>
</tr>
</tbody>
</table>

17.3 Bowel Dysfunction Post Stroke

17.3.1 Treatment of Fecal Incontinence and Constipation Post Stroke

Table 17.3.1 Treatment of Fecal Incontinence and Constipation Post Stroke
RCT
PEDro=6
N=146
incontinence were identified and randomized to receive intervention or routine care (73 per group). The intervention consisted of a 1 time nursing assessment (history and rectal examination), followed by patient/carer education with booklet and provision of diagnostic summary and treatment recommendations (after consultation with geriatrician) to patient’s general practitioner (GP)+/-ward physician.

1. 1-week stool diary was significantly higher in intervention versus control patients at 6 months (72% vs. 55%), as was mean number of BMs per week (5.2 vs. 3.6).
2. There was no significant reduction in fecal incontinence, although numbers were small. At 12 months, intervention patients were more likely to be modifying their diets and fluid intake to control their bowels and to have visited their GP for their bowel problem.
3. GP prescribing of laxatives and suppositories was significantly influenced at 12 months.

### Lin et al. (2013)
Taiwan
Case Series
No Score
N=155

**Population:** Constipation present group (N=123): Mean age=62.8±12.99yr; Gender: Males=76, Females=47. Constipation absent group (N=32): Mean age=64.4±12.8yr; Gender: Males=18, Females=14.

**Intervention:** The incidence and clinical course of post-stroke constipation in a rehabilitation ward was retrospectively analyzed in patients admitted to the ward.

**Outcomes:** The effect of demographic data, presence of impairment, degree of disability (measured via Barthel Index (BI)), walking ability, medications taken and medical complications on the incidence of post-stroke constipation.

1. The risk of experiencing major complications was significantly higher in patients with post-stroke constipation than those without (22.76% vs. 6.25%, p=0.04).
2. Patients aged <55yr were more likely to discontinue oral laxatives at discharge (p=0.03).
3. There was no significant difference in the degree of disability at discharge between patients who continued the use of laxatives and those who did not (p=0.17).
4. Patients with lower BI scores on admission had higher rate of constipation (p=0.02).
5. Patients using rectal medications were more likely to need nasogastric tubes (p=0.04) and Foley catheters p=0.03). They had lower BI scores (p<0.01) and were less ambulatory (p=0.03).

### Numata et al. (2014)
Japan
RCT
PEDro=7
N=34

**Population:** Experimental Group (EG; N=17): Mean age=77.5±11.9yr; Gender: Males=8, Females=9. Control Group (CG; N=17): Mean age=78.7±12.1yr; Gender: Males=9, Females=8.

**Intervention:** The experimental group (EG) received traditional Japanese medicine Diakenchuto (DKT) 15g/d for 4wk and conventional therapy, while the control group (CG) underwent conventional therapy for constipation only, which included laxative administration, enemas, and disimpaction. Assessments were conducted before and after the intervention.

**Outcomes:** Constipation Scoring System (CSS); Gas Volume Score (GVS).

1. A significant difference was found between the two groups regarding the CSS scores (p<0.01), with the EG showing a significant improvement after the intervention (p<0.01), while the CG did not show any significant improvement.
2. There was a significant difference between the two groups (p=0.03), and the intragroup comparison revealed a significant decrease in the EG group (p<0.01), while the CG did not show any significant changes (p=0.61).

### Uraloğlu et al. (2014)
Turkey
Observational
No Score
N=112

**Population:** Mean Age=62.5yr; Gender: Male=53, Female=59.

**Intervention:** Assessed stroke patients enrolled in an inpatient rehabilitation program.

**Outcomes:** Use of defecation promoters; Gastrointestinal (GI) system problems: regurgitation, stomach pain,

1. Interval of intestinal emptying was significantly increased post stroke (pre=1.53±0.95d, post=3.27±1.96d, p<0.01).
2. Intestinal emptying time was significantly increased post stroke (pre=5.72±3.47min, post=11.74±7.36min, p<0.01).
3. GI problems were significantly increased post stroke in regards to regurgitation (pre=9.8%,
nausea/vomiting, abdominal pain, abdominal distension, rectal bleeding, difficulty with defecation, GI bleeding and hemorrhoids; Intestinal emptying: interval and frequency; Incidence of constipation; Incidence of fecal incontinence; Medication use; Functional Ambulation Scale (FAS); Functional Independence Measure (FIM); and Use of defecation promoters.

1. During hospitalization, 33% of patients from the stroke group and 27% from the orthopaedic group developed new-onset constipation.
2. 37.3% of patients were prescribed one or a combination of two or more prophylactic laxatives.
3. Patients who took prophylactic laxatives have their new-onset constipation risk reduced by more than 50% compared with those without prophylaxis (95% CI: 29.7-84.5%; p<0.01).
4. For every one point of morbidity gained in FIM score, the risk also decreased by 25.9% (95% CI: 12.7-47.0%; p<0.001).
5. For every 1 day increase in hospital stay, the risk of new-onset constipation would increase by 3.2% (95% CI: 0.6-6.0%; p<0.05).
6. Bedpan use increased the risk of developing new-onset constipation (95% CI: 1.172-3.614; p<0.05).

| Lim et al. (2015) Singapore Observational No Score N=110 | **Population:** Stroke group (N=55): Mean age=51.2±9.7yr; Gender: Males=33, Females=22. Orthopaedic group (N=55): Mean age=61.7±9.6yr; Gender: Males=33, Females=22. **Intervention:** The predictors associated with constipation during acute hospitalization were explored by comparing stroke patients with orthopaedic patients prospectively. **Outcomes:** The effect of length of hospital stay, medications, morbidity on the incidence of new-onset constipation. **Results:**

| Jhang (2016) China | **Population:** Tui-Pushing group (EG; n=35): Mean age=58.6±10.3yr; Gender: Male=20, Female=15. **Intervention:** The effect of length of hospital stay, medications, morbidity on the incidence of new-onset constipation. **Outcomes:** The effect of length of hospital stay, medications, morbidity on the incidence of new-onset constipation. **Results:** |

1. EG group showed a significantly shorter first defecation time compared to the CG group.
RCT PEDro=6
N=70

Female=15. Control Group (CG; n=35): Mean age=59.3±11.1 yr; Gender: Male=19, Female=16.

**Intervention:** Participants with post-stroke constipation were randomized to receive additional training of Tui-pushing the Large Intestine Meridian and point sticking at Tianshu (EG) or no additional treatment (CG) for 14d. Both groups received conventional treatment. Outcomes were assessed before and after treatment.

**Outcomes:** First Defecation Time; Constipation Incidence; Chinese Stroke Scale (CSS).

1. Following treatment (p<0.05).
2. EG group showed a significantly lower constipation incidence compared to the CG group following treatment (p<0.05).
3. Both groups showed improvement in CSS scores (all p<0.05); however, the EG group showed a significantly greater improvement (p<0.05).

17.4 Venous Thromboembolism Post Stroke

17.4.2 Prevalence of Venous Thromboembolism Post Stroke

**Table 17.4.2 Prevalence of Venous Thromboembolism Post Stroke**

<table>
<thead>
<tr>
<th>Author, Year Country Study Design Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warlow et al. (1976) UK Observational N=76</td>
<td>76 patients with hemiplegia admitted within 48 hours of acute stroke. DVT was diagnosed using radiolabeled 125I-fibrinogen, conducted daily for 10 days. No patients were treated with prophylactic heparin</td>
<td>1. 40 (53%) developed a DVT. Of these, clinical signs occurred in 24 of the 40 paralysed limbs. 2. Only the presence of varicose veins had a statistically significant association with the development of DVT in the nonparalyzed leg. 3. However, all patients presenting DVT in the nonparalyzed leg also presented DVT in the paralyzed leg.</td>
</tr>
<tr>
<td>Miyamoto &amp; Miller (1980) USA Observational N=141</td>
<td>141 stroke patients undergoing intensive rehabilitation were evaluated by 125I-fibrinogen uptake leg scans for the presence of DVT 10 days to 2 weeks following stroke.</td>
<td>1. 29% incidence of DVT identified by I-125-fibrinogen uptake leg scans.</td>
</tr>
<tr>
<td>Sioson et al. (1988) USA Observational N=105</td>
<td>Impedance plethysmography was performed on 105 consecutive stroke patients admitted to a rehabilitation hospital.</td>
<td>1. 32/98 patients had evidence of new DVT. 2. Weakness, male gender, interval between stroke and screening, edema and leg hyperpigmentation were associated with the development of DVT.</td>
</tr>
<tr>
<td>Landi et al. (1992) Italy Observational N=70</td>
<td>70 consecutive acute stroke patients were evaluated to identify the presence of DVT during the first 10 days of hospitalization. Serial venous dopplers and iodine 125-labelled fibrinogen uptake tests were used.</td>
<td>1. 20 patients (28.6%) developed a DVT following entry into the study. 15 of these patients died during hospitalization. 2. At autopsy, a pulmonary embolus was discovered in 8 of these patients</td>
</tr>
<tr>
<td>Oczkowski et al. (1992) 102 consecutive patients undergoing</td>
<td></td>
<td>1. Venous thromboembolism was</td>
</tr>
<tr>
<td>Country</td>
<td>Study Design</td>
<td>N</td>
</tr>
<tr>
<td>------------------</td>
<td>-----------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Canada</td>
<td>Observational</td>
<td>102</td>
</tr>
<tr>
<td>Kelly et al.</td>
<td>(2004)</td>
<td>102</td>
</tr>
<tr>
<td>Skaf et al.</td>
<td>(2005)</td>
<td>~15 million</td>
</tr>
<tr>
<td>Zorowitz et al.</td>
<td>(2005)</td>
<td>1161</td>
</tr>
</tbody>
</table>
| De Silva et al.  | (2006)                | 111        | Singapore Observational                                                   | 111 acute ischemic Asian stroke patients received 25hrembo ultrasound scans of the lower limbs performed at days 7-10 and 25-30 after stroke onset. Assessments were done at 6-months to evaluated functional status using the modified Rankin Scale. 1. At days 7-10 and days 25-30 there were 30% and 45% of patients detected with DVT respectively. 2. Distal thrombosis were most common. DVT was significantly more common in paretic lower limbs than nonparetic lower limbs at days 25-30 (p<0.0001). 3. Age and degree of weakness was
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chua et al. (2008)</td>
<td>Singapore</td>
<td>Observational</td>
<td>419 consecutively admitted rehabilitation inpatients with either ischemic or hemorrhagic stroke were prospectively evaluated for the development of DVT. The screening protocol included a quantitative D-dimer assay within 24 to 48 hours of rehabilitation admission, and hemiplegic/weaker lower-extremity venous duplex ultrasonography was performed if D-dimer assay level was elevated at 0.34 microg/mL or higher. Patients were admitted for rehabilitation a mean of 26 days post stroke. 247 (58.9%) patients had an elevated D-dimer assay, and all underwent venous duplex ultrasonography. There were 11 incident cases of lower-limb DVT (5.01%), including 11 proximal and 10 distal. No patients had clinical pulmonary embolism.</td>
</tr>
<tr>
<td>Hara (2008)</td>
<td>Japan</td>
<td>Observational</td>
<td>272 consecutively admitted rehabilitation inpatients who had experienced an ischemic stroke were prospectively evaluated for the development of DVT. Suspected cases of DVT were identified by imbalance in calf circumference + clinical symptoms. Diagnosis was confirmed using D-dimer assay and venous duplex ultrasonography. 24 confirmed DVTs were identified (8.8%) out of 54 symptomatic/suspected cases. Of the confirmed cases, 21 were distal and 3 were proximal. All DVTs occurred on the hemiparetic side. Bilateral DVTs were present in 3 patients. Diagnosis was confirmed an average of 233 days post stroke. Severe spasticity was an independent predictor of the development of DVT.</td>
</tr>
<tr>
<td>Dennis et al. (2011)</td>
<td>UK</td>
<td>Observational</td>
<td>5,632 immobile patients were recruited for the CLOTS I &amp; II trials. The incidence of DVT was compiled from this cohort, as evaluated using compression duplex ultrasound. 641 patients (11.4%) developed DVT within a median of 8 days. An additional 176 patients (3.1%) had a DVT by the time of the second scan, a median of 28 days. Of the 817 with DVTs, 289 (35%) were symptomatic and 39 (5%) had pulmonary embolism confirmed by imaging.</td>
</tr>
<tr>
<td>Pongmoragot et al. (2013)</td>
<td>Canada</td>
<td>Case Series</td>
<td>11 287 patients with acute ischemic stroke whose information was included in the Registry of the Canadian Stroke Network. 89/11 287 or (0.78%) were found to have PE.</td>
</tr>
</tbody>
</table>
| Ogata et al. (2013)          | Japan                        | Case Series                  | Population: Deep venous thrombosis (DVT, n=19): Mean Age=73.2yr; Gender: Male=7, Female=12; No DVT (n=39): Mean Age=68.6yr; Gender: Male=15, Female=24. Intervention: Analysis of patients admitted after stroke between June 2005 and September 2006. Data was recorded from admission and 2wk post admission. Patients were divided according to the presence of DVT. Outcomes: Incidence of DVT; and diameter of the posterior tibial veins (PTV) or peroneal veins (PV). In <2wk, 7 patients (14.3%) developed DVT in a PTV and 6 patients (12.2%) developed DVT in a PV. PTV diameter was not significantly different between groups at admission (DVT=3.8±1.0mm, No DVT=3.9±1.1mm, p=0.77). PV diameter was not significantly different between groups at admission (DVT=5.1±1.3mm, No DVT=4.7±0.9mm, p=0.37). PTV diameter was significantly larger in DVT patients post 2wk (DVT=5.4±0.9mm, No DVT=3.6±0.9mm, p<0.001). PV diameter was significantly larger in DVT patients post 2wk (DVT=6.5±1.0mm, No
17. Medical Complications Post Stroke

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**DVT = 4.3 ± 1.2 mm, p < 0.001.**

**Liu et al.** (2014)  
China  
Observational  
N = 862  
Population: Age ≥ 65 yr = 509; Gender: Males = 540, Females = 322.  
Intervention: Patients with acute stroke recruited in the study were evaluated for the presence of deep vein thrombosis (DVT) 14 days after admission to a unit with an acute stroke. Potential predictive variables were determined.  
Outcomes: Predictive variables (i.e. age, gender, body mass index (BMI), smoking, hypertension, diabetes, atrial fibrillation, trans ischemic attack (TIA), ischemic heart disease, malignancy, history of venous thromboembolism (VTE), treatment methods) of DVT occurrence.

1. The overall incidence rate of DVT after stroke within two weeks was 12.4% (95% CI (10.3, 14.7)).  
2. Age (≥ 65 yr), female gender, obesity (BMI ≥ 25 kg/m²), presence of active cancers, stroke subtype (cerebral hemorrhage), muscle weakness (≥ 2 in lower limb NIHSS) are highly predictive of 14-day risk of DVT (p < 0.001, 95% CI (0.59, 0.70)).

---

**Chalouhi et al.** (2016)  
USA  
Observational  
N = 95  
Population: Mean age = 57 ± 12 yr; Gender: Male = 57, Female = 38.  
Intervention: Participants who were underwent decompressive hemicraniectomy and received prophylactic unfractionated heparin were screened for deep-vein thrombosis (DVT).  
Outcomes: DVT Incidence; Predictors of DVT.

1. 35% of patients developed a DVT including 27% who developed above-knee DVT and required placement of an inferior vena cava filter.  
2. Significant predictors of DVT were a National Institute of Health Stroke Scale > 16 (p = 0.007), seizures (p = 0.003), hypertension (p = 0.03), and increasing length of stay (p = 0.01).

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### 17.4.3 Pharmacological Prevention of Venous Thromboembolism Post Stroke

#### Table 17.4.3 Pharmacotherapy for the Prevention of Venous Thromboembolism Post Stroke

<table>
<thead>
<tr>
<th>Author, Year Country Study Design PEDro Score Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>McCarthy et al.</strong> (1977) UK RCT PEDro=5 N=32</td>
<td>32 stroke patients diagnosed with a stroke in previous 24 hours were randomized to receive either low dose heparin every 8 hours for 14 days or to receive no heparin. All patients received potassium iodide daily for 14 days.</td>
<td>1. Treatment with heparin was associated with a significant reduction of positive isotope leg scans from 75% to 12.4%.</td>
</tr>
</tbody>
</table>
| **McCarthy & Turner** (1986) UK RCT PEDro=4 N=305 | 305 stroke patients with a diagnosis of stroke in previous 24 hours were randomized to receive either 5000 units of calcium heparin s.c. hourly for 8 hours for 14 days. Control group received no heparin. | 1. Incidence of DVT was significantly lower in the Heparin group than in the control.  
2. Reduction in DVT rate from 72.1% in control group to 22.2% in treatment patients was achieved. |
| **Turpie et al.** (1987) Canada RCT PEDro=7 N=75 | 75 patients assessed within 7 days post-stroke were randomized to receive either Orgaran (low molecular weight heparin) prophylaxis or placebo for 14 days or until discharge from hospital if earlier than 14 days. | 1. DVT occurred significantly less often in treatment group compared to placebo group (4% vs. 28%). |
| **Prins et al.** (1989) | 60 patients with acute ischemic stroke were | 1. Both treatment groups were comparable |
Netherlands
RCT
PEDro=6
N=60

randomized to receive either placebo or the LMWH, Fragmin, subcutaneously twice daily for 14 days. A fibrinogen scan was used daily to confirm the development of a DVT.

with regard to neurological status and general condition.
2. In the Fragmin group, there were 6 cases of (DVT) compared to 15 in the placebo group at the end of the follow up period (p = 0.05).
3. In the placebo group there were 4 deaths and 2 cases of cerebral bleeding compared to 9 and 4 respectively in the Fragmin treated group.
4. Neither of these results was statistically significant.

Sandset et al. (1990)
Norway
RCT
PEDro=8
N=103

103 stroke patients were randomized to receive either low molecular weight heparin once daily or to receive a saline placebo for 14 days or until discharge if earlier.

1. No significant difference between thrombosis, Motricity Index score and mortality between the two groups.

Desmukh et al. (1991)
USA
RCT
PEDro=2
N=101

101 stroke patients randomized to one of three treatment groups or to a control group. In addition to bilateral stockings, patients received one of 3 treatments for DVT prophylaxis (adjusted dose heparin, electrical muscle stimulation or external pneumatic compression) for 28 days or until discharge.

1. 10 patients developed DVT during the study period. One of these patients developed a pulmonary embolus.
2. No treatment group comparisons reported.
3. Patients were unable to tolerate electrical muscle stimulation.

Turpie et al. (1992)
Canada
RCT
PEDro=7
N=87

A double blind trial of 87 stroke patients assessed within 7 days post-stroke were randomized to receive either low-molecular heparin (Orgaran) or to unfractionated heparin subcutaneously twice daily for 14 days or until discharge if earlier.

1. Incidence of DVT was significantly lower in Orgaran group compared to heparin 9% vs. 31%

Dumas et al. (1994)
France
RCT
PEDro=8
N=179

A double blind trial of 179 stroke patients screened within 72 hours on onset were randomized to receive either Orgaran 10172 once daily or heparin sodium twice daily for a minimum of 9 days.

1. No significant difference in the number of patients developing DVT in each group.

Kay et al. (1995)
Hong Kong
RCT
PEDro=7
N=312

312 acute stroke patients were randomized to receive either 4100 U Fraxiparine 2 x daily for 10 days (high dose LMWH, n=102), 4100 U Fraxiparine once daily (low dose LMWH, n=101) or placebo (n=105).

1. During the study period there was only one occurrence of DVT (control group).
2. At the end of 6 months fewer subjects in the high and low dose groups had poor outcomes (death or dependence) 45% vs. 52% vs. 65%.
3. There was no difference among groups in the number of patients experiencing hemorrhagic transformation.

Pambianco et al. (1995)
USA
RCT
PEDro=5
N=360

360 stroke patients assessed within 24 hours of stroke onset were randomized to one of three treatment groups or to a control group. Patients received one of 3 treatments for DVT: 1) prophylaxis adjusted dose heparin, 2) electrical muscle stimulation or 3) external pneumatic compression for 28 days or until discharge.

1. 20 patients developed DVT during the study period. No significant difference in the development of DVT by treatment.

TOAST (1998)
1281 acute stroke patients from 36 centres were

1. During the treatment period no patients in
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>PEDro</th>
<th>N</th>
<th>Intervention</th>
<th>Major Outcomes</th>
</tr>
</thead>
</table>
| USA RCT PEDro=9 N=1281         |         |           |       |      | 1486 acute stroke patients were randomized to receive Orgaran (0.6-0.8 anti-Xa U/ml by continuous infusion (n=641) or placebo (n=634) for 7 days. | 1. The treatment group experienced a DVT while 2 did in the placebo group.  
2. At the end of 3 months fewer patients in the treatment group had suffered a DVT (2 vs. 10, p<0.05).  
3. There were significantly more occurrences of major bleeding in treatment group (37 vs. 18, p<0.05). |
| Bath et al. (2000) TAIST UK RCT PEDro=7 N=1486 |         |           |       |      | 449 acute stroke patients were randomized to receive LMWH (100 I/kg 2x/day dalteparin (n=224) or 160 mg of aspirin every day for 14 days (n=225) for the prevention of recurrent stroke in patients with atrial fibrillation. | 1. 1 patient in the dalteparin group and 5 patients in the aspirin group developed a DVT during the treatment period.  
2. The result was not statistically significant (p=0.22). |
| Berge et al. (2000) HAEST Norway RCT PEDro=9 N=449 |         |           |       |      | 102 rehabilitating stroke patients were randomized to receive 2 mg of daily warfarin (or dose adjusted to maintain INR of ≤2) or placebo and followed for 120 days or until an event (DVT) had occurred. Patients were stratified into two groups: bedridden or wheelchair bound or walking with assistance. | 1. In the warfarin group, three (8%) patients had DVT of which one (2%) had proximal DVT. In the placebo group, seven (20%) had DVT of which five (13%) had proximal DVT.  
2. The risk ratio for any DVT in warfarin-treated patients relative to placebo-treated patients was 0.39 (95% confidence interval (CI), 0.13-1.37).  
3. For proximal DVT, the risk ratio was 0.17 (95% CI, 0.01-1.4). No patients suffered major bleeding. |
| Ginsberg et al. (2002) Canada RCT PEDro=7 N=102 |         |           |       |      | Equivalency trial. 212 stroke patients were randomized within 48 hrs of onset of symptoms to receive either enoxaparin (n=106) or unfractionated heparin (UFH) (n=106) for 10 days. | 1. The rate of thromboembolic events (DVT and PE) after 3 mos. were lower in the enoxaparin group compared to UFH (19.7% vs. 34.7%, p=0.044). |
| Hillbom et al. (2002) Finland RCT PEDro=8 N=212 |         |           |       |      | Analysis of a historical cohort of 1506 rehabilitating stroke patients to determine the effectiveness of anticoagulant and antiplatelet agents in preventing venous thromboembolism (VTE) during stroke rehabilitation. The use of anticoagulants (warfarin or anticoagulant doses of heparin), heparin in prophylactic doses, and antiplatelet agents was documented. The occurrence of deep vein thrombosis (DVT) detected by ultrasound or venography or pulmonary embolism detected by ventilation perfusion scan, spiral computed tomography, or pulmonary angiography was recorded. | 1. Fifty-eight VTE events occurred (3.9% incidence or 1.36 events per 1000 patient days), with higher risk in patients with severe stroke.  
2. Only therapeutic anticoagulation had a statistically significant protective effect for VTE risk (OR=0.44; 95% CI, 0.20-0.98).  
3. After adjusting for multiple medication use and other factors, including age, stroke onset to admission interval, length of rehabilitation stay, cause of stroke, and stroke severity, therapeutic anticoagulation gave strong protection against VTE (OR=0.37; 95% CI, 0.15-
1. Medical Complications Post Stroke

### Diener et al. (2006)

**Germany**  
**RCT**  
**PEDro=9**  
**N=272**  

Equivalency trial. 272 acute stroke patients received 3000 U of certoparin (LMWH) once daily and 273 patients received 5000 UFH 3 x daily for 12 to 16 days.

- During the treatment period 17 patients in the certoparin group experienced DVT compared with 24 in the UFH group (p=0.29).
- No patient in either group experienced a PE.
- At the end of 3 months there was a non significant increase in mortality in the certoparin group (14 vs. 8).
- Bleeding complications were similar between groups.

### Sherman et al. (2007)

**PREVAIL**  
**USA**  
**RCT**  
**PEDro=7**  
**N=1762**  

1,762 patients with acute ischemic stroke unable to walk were randomized to receive either LMWH 40 mg enoxaparin once daily (n=844) or 5,000 U UFH twice daily (n=878) for 10 days. Open-label study.

- The incidence of symptomatic DVT was 1 in the LMWH group and 4 in the UFH group at the end of 14 days (p=0.18).
- There were fewer incidences of asymptomatic DVT in the LMWH group (66 vs. 114, p<0.0001).
- The occurrence of any bleeding events was similar between groups.

### Orken et al. (2009)

**Turkey**  
**RCT**  
**PEDro=2**  
**N=75**  

75 patients with primary intracerebral hemorrhage were randomized to receive subcutaneous LMWH (Enoxaparin sodium 40mg/d) or long compression stockings (CS, which was considered the control condition) after the first 48 hours. All patients had cranial computed tomography (CT) scan at admittance, 24th and 72nd hours, seventh and 21st days, CT pulmonary angiography and bilateral lower extremity venous Doppler at 7th day. Hematoma volumes were calculated on the initial and follow-up CTs.

- Following randomization there was no evidence of hematoma enlargement at 72 hours, 7 and 21st days in either groups. There were no other systemic bleeding complications in LMWH group.
- There was no difference in the incidence of asymptomatic DVT (3 in LMWH and 1 in CS group, p=1.0).

### Mukand & Mukand (2010)

**USA**  
**Case Control**  
**No Score**  
**N=54**  

A review of 54 stroke rehabilitation inpatients who had received either 40 mg enoxaparin or 2.5 mg of Fondaparinux subcutaneously daily until they were mobile (able to walk 150 ft). Patients had been assessed clinically on a daily basis for evidence of DVT and PE and received an ultrasound study if DVT was suspected.

- Patients received treatment for an average of 21 days.
- There were no PE in either group and a single DVT in the enoxaparin group.
- Episodes of major and minor bleeding were similar between the groups.

### Amin et al. (2013)

**USA**  
**Case Series**  
**No Score**  
**N=1524**  

**Population:** Mean age=62.20±12.23yr; Gender: males=869, Females=655.  
**Intervention:** Analysis of symptomatic DVT/PE rates and prophylaxis usage.  
**Outcomes:** Prophylaxis usage during index hospitalization and for 14 days post-discharge; DVT/PE rates during index hospitalization and up to 30 days post-discharge; length of hospitalization and prophylaxis duration were all described.

- Of the patients included in the study, 46.1% received pharmacological and/or mechanical prophylaxis in-hospital (28.3%, 11.4% and 12.3% received unfractionated heparin, enoxaparin and mechanical prophylaxis, respectively). 6.4% of patients received outpatient pharmacological prophylaxis; warfarin was most frequently prescribed (5.9%). Length of index hospitalization was 3.0 ± 2.5 days.
- Mean prophylaxis duration in all patients was
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Number of Participants</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasquini et al. (2014)</td>
<td>France</td>
<td>Observational</td>
<td>N=2138</td>
<td>Median Age=72yr.</td>
<td>Assess frequency of the use of antithrombotic drugs in post stroke patients across multiple centers.</td>
<td>Antithrombotic drug use: antiplatelet drugs, vitamin K antagonists or both; and adverse events.</td>
</tr>
<tr>
<td>Wu et al. (2014)</td>
<td>China</td>
<td>RCT</td>
<td>N=297</td>
<td>No demographic information available.</td>
<td>Patients were randomly assigned to receive either the combination of low molecular weight heparin (LMWH) + calcium 6000IU once daily + aspirin 100mg once daily, or aspirin 150 once daily for 10 days.</td>
<td>Mortality; Symptomatic intracranial hemorrhage; Major extracranial hemorrhage; Minor extracranial hemorrhage; Thrombocytopenia.</td>
</tr>
</tbody>
</table>

- Fatality rate was higher in patients taking antithrombotic drugs (36%) at 30d compared to patients not taking antithrombotic drugs (23%).
- Higher in patients taking antithrombotic drugs at admission (36%) compared to patients not taking antithrombotic drugs (23%).
- Lower in patients taking antiplatelet drugs (35%) compared to vitamin K antagonists (38%) and both antiplatelet and vitamin K antagonists (40%).
- 942 patients were administered antithrombotic drugs initially, 595 (63%) survived until hospital discharge.
- 96 patients (20%) restarted antithrombotic drugs at discharge.
- 236 patients took antiplatelet drugs initially, 32 (14%) restarted antiplatelet agents and 204 patients (86%) discontinued antithrombotic use.
- 206 patients took vitamin K antagonists initially, 29 (14%) restarted vitamin K antagonists, 23 (11%) restarted antiplatelet drugs and 1 (0.5%) restarted both drugs.
- 27 patients took both vitamin K antagonists and antiplatelet drugs initially, 8 (30%) restarted antiplatelet drugs, 2 (7%) switched to vitamin K antagonists and 1 (4%) restarted both drugs.
- Of patients who restarted antithrombotic drugs took 14% antiplatelet drugs initially, 26% took vitamin K antagonists and 41% took both.

- No patients experienced symptomatic intracranial hemorrhage or heparin-induced thrombocytopenia or died from hemorrhagic complications.
- The frequency of asymptomatic intracranial hemorrhage was similar between the two groups (aspirin group: 3.4%; combination group: 2.6%; p=0.12).
- There was no difference in the rate of minor intracranial hemorrhage between the two groups (p=0.12).
- Mortality rate was not significantly different.

0.9 ± 1.5 days in-hospital and 1.7 ± 6.9 days post-discharge.

Symptomatic DVT/PE occurred in 25 patients overall (1.64%), with an inpatient rate of 0.98% and an outpatient rate of 0.66%.
17.4.4 Mechanical Devices for Prevention of Venous Thromboembolism

Table 17.4.4 Mechanical Devices for the Prevention of Deep Vein Thrombosis Post Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasad et al. (1982)</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro=5</td>
<td>N=26</td>
<td>26 acute stroke patients with weakness in either one or both limbs were randomized to receive intermittent pneumatic calf compression for 9 days or to a no treatment control group. DVT was assessed by I-25 Fibrinogen test.</td>
<td>1. There were no significant differences in the development of DVT between the groups at day 10. Six patients in each group had a positive scan, although clinical signs of DVT were only noted in one person with a positive scan.</td>
</tr>
<tr>
<td>Muir et al. (2000)</td>
<td>UK</td>
<td>RCT</td>
<td>PEDro=7</td>
<td>N=98</td>
<td>98 stroke patients who were not independently ambulatory within 24 hours of admission were randomized to receive either standard care (control), which included aspirin or early mobilization (n=32) or standard care plus TED or Brevett (TX) brand stockings (n=65). The thighs and calves of both legs were examined at baseline and again at day 7, using Doppler ultrasound.</td>
<td>1. DVT was detected in 7/65 patients allocated stockings, and 7/32 controls, which was associated with an overall reduction in the odds of DVT (odds ratio 0.43, 95% CI 0.14-1.36). The absolute risk of developing proximal DVT was 6.25% in controls and 4.6% in the stocking group.</td>
</tr>
<tr>
<td>Lacut et al. (2005)</td>
<td>France</td>
<td>RCT</td>
<td>PEDro=7</td>
<td>N=151</td>
<td>151 acute patients with intracerebral 32aemorrhage were randomly assigned to treatment with TED brand stockings (n=77) or TED+ intermittent pneumatic compression (IPC) device.</td>
<td>1. At day 10 of treatment 11 patients in the TED group experienced an asymptomatic DVT (3 proximal, 8 distal) compared with 3 in the TED+ICP group. Absolute risk reduction was 11%. At the end of 3 months, 2 patients, one in each group experienced a symptomatic VTE. None of the 14 deaths were attributable to PE.</td>
</tr>
<tr>
<td>Dennis et al. (2009)</td>
<td>UK</td>
<td>RCT</td>
<td>PEDro=8</td>
<td>N=2518</td>
<td>2,518 patients, admitted to hospital within 1 week of an acute stroke and who were immobile were enrolled from 64 centres in the UK, Italy, and Australia. Patients randomized to either routine care plus thigh-length GCS (n=1256) or to routine care plus avoidance of GCS (n=1262). Doppler ultrasound of both legs was performed at about 7-10 days and, when practical, again at 25-30 days after enrolment. The primary outcome was the occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins.</td>
<td>1. DVT occurred in 126 (10.0%) patients allocated to thigh-length GCS and in 133 (10.5%) allocated to avoid GCS, resulting in a non-significant absolute reduction in risk of 0.5% (95% CI -1.9% to 2.9%). Adverse effects (skin breakdown, necrosis, ulcers) were significantly more common in the GCS group.</td>
</tr>
<tr>
<td>Dennis et al. (2011)</td>
<td>UK</td>
<td>RCT</td>
<td>PEDro=6</td>
<td>3,114 acute, immobile stroke patients from 112 centres were randomized to 1552 patients to wear thigh-length stockings (n=1552) or below-knee stockings (1562) while they were</td>
<td>1. The incidence of proximal DVT within 30 days was significantly higher in the below-knee stocking group compared with the above keen group (8.8% vs. 6.3%, p=0.008). The</td>
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</table>
in the hospital, in addition to routine routine care, which could have included early mobilization, anticoagulants etc. The primary outcome measure was symptomatic or asymptomatic proximal DVT, assessed by compression duplex ultrasonography at either first (days 7-10) or on a second scan at day 30. The associated odds reduction was 31% (CI, 9% to 47%). Seventy-five percent of patients in both groups wore the stockings for 30 days or until they were discharged, died, or regained mobility.

Dennis et al. (2013b) UK RCT PEDro=6 N=2876

**Population:** Experimental Group (EG; N=1438): Mean age= 74.2±12.3yr; Gender: Males=48%, Females=52%. Control Group (CG; N=1438): Mean age=74.9±11.9yr; Gender: Males=48%, Females=52%.

**Intervention:** Patients received either IPC or no IPC

**Outcomes:**
- Primary: Symptomatic or asymptomatic DVT in the popliteal or femoral (proximal) veins detected on a screening CDU or any symptomatic DVT in the popliteal or femoral veins.
- Secondary outcomes within 30 days: death, any DVT (including symptomatic or asymptomatic calf, popliteal, or femoral), symptomatic DVT, pulmonary embolism, complications of IPC (e.g. skin breaks, falls with injury, fractures and adherence).
- Secondary outcomes at 6 months: death from any cause, any confirmed symptomatic or asymptomatic DVT or pulmonary embolism occurring since randomization.

1. The primary outcome (proximal DVT) occurred in 8.5% of patients allocated to EG and in 12.1% of patients allocated to CG: OR=0.65 (95% CI: 0.51–0.84; p=0.001 after adjustment for baseline variables), with the corresponding absolute reduction risk (ARR)=3.6% (95% CI: 1.4–5.8%).
2. There were statistically significant reductions in the outcome of any DVT (symptomatic or asymptomatic involving proximal or calf veins) (EG: 16.2%; CG: 21.1%, ARR=-4.9 (95% CI: -7.8 to -2.1) and symptomatic DVT (EG: 4.6%, CG=6.3%, ARR=-1.7(95% CI: -3.3 to 0.0) (including proximal or calf).
3. Results showed that patients in the EG had significantly more skin breaks than did CG patients (EG: 3.1%, CG: 1.4%, ARR=1.7(95% CI: 0.6 to 2.7), however, the risk of falls with injury or fractures within 30 days did not differ between groups: (EG:2.3%, CG: 1.7%, ARR=0.6, 95% CI: -0.4 to 1.6).
4. For EG, there were fewer deaths from all causes within 30 days: ARR=-2.3 (95% CI: -4.7 to 0.1).

Dennis et al. (2013a) UK Cohort No Score N=5532

**Population:** Experimental Group (EG, N=1438): Mean age= 74.2+/12.3yr; Gender: Males=48%, Females=52%. Control Group (CG, N=1438): Mean age=74.9+/11.9yr; Gender: Males=48%, Females=52%

**Intervention:** In CLOTS Trial 1 patients were allocated to either routine care plus thigh-length stockings or routine care alone, and CLOTS trial 2 to either routine care plus thigh-length stockings or routine care plus below-knee stockings.

**Outcomes:** Prevention of Venous Thromboembolism (VTE) events; Survival outcomes in patients.

Note: this is a secondary analysis for purposes of reporting on important outcomes such as survival, functional outcomes, and health-related quality of life. The CLOTS trials were not originally powered to detect effects on these important outcomes so this study

1. This study compares survival in patients who were enrolled in CLOTS Trials 1 and 2. According to their Cox proportional hazards model and minimization algorithm, they reported that allocation to thigh-length graduated compression stockings was associated with a nonsignificant, increased hazard of death in the first 6 months (Trial 1: hazard ratio, 1.087; 95% confidence interval, 0.913–1.295; and Trial 2: hazard ratio, 1.037; 95% confidence interval, 0.892–1.205).
2. They also reported no statistically significant differences in venous thromboembolism events, Oxford Handicap Scale or EQ5D-3 L between the treatment groups in CLOTS Trials 1 or 2.
3. Of the 5532 patients in both trials combined, 494 (8.9%) had a proximal DVT, 816 (14.8%) any DVT, 288 (5.2%) a symptomatic DVT (proximal or distal), and 74 (1.3%) a pulmonary embolism confirmed on imaging.
predicts long-term outcomes of patients who were enrolled into CLOTS Trials 1 and 2. or autopsy within 30 days. If one subtracts the numbers of VTE events during the first 30 days from the total numbers occurring by the 6-month outcome assessment (Table 1), then only 31 (0.56%) had a symptomatic DVT and 41 (0.74%) a pulmonary embolism between 30 days and 6 months.

17.5 Seizures Post Stroke

17.5.1 Prevalence, Timing, and Risk of Post Stroke Seizures Post Stroke

Table 17.5.1 Prevalence, Timing, and Risk of Seizures Post Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Holmes et al.</strong> (1980)</td>
<td>USA</td>
<td>Case Series</td>
<td>N=250</td>
<td>A retrospective study of 250 stroke patients who had an EEG within a week of their cerebral infarction and at least a 2 year follow up. EEGs were reviewed and classified into 1 of 4 categories (I: normal, II: diffuse slowing, III: focal slowing, and IV: sharp waves) and seizures were classified as early (within 1 month post-stroke) or late (after 1 month).</td>
<td>1. 21% of patients had seizures at time of cerebral infarction or in the 2 year follow up. 8 out of 23 with early seizures and 6 of 20 with late seizures had initial EEGs in class IV. 2. All patients with periodic lateralizing epileptiform discharges (PLEDs) on their initial EEGs developed seizures. Only 2% of those seizure-free had EEGs in class IV.</td>
</tr>
<tr>
<td><strong>De Reuck et al.</strong> (1980)</td>
<td>Belgium</td>
<td>Case Series</td>
<td>N=240</td>
<td>Of 240 patients with cerebral infarcts at necropsy, during the years 1970 to 1979, 14 with clinical history of epilepsy were selected. Etiology of seizures was analyzed by comparing the clinical and pathological data.</td>
<td>1. Convulsive disorder was noted in 7.9% of patients with cerebral infarcts in study patients.</td>
</tr>
<tr>
<td>Black et al. (1983)</td>
<td>Canada</td>
<td>Observational</td>
<td>N=827</td>
<td>Clinical data was prospectively collected on 827 patients with completed stroke.</td>
<td>1. 10% of patients had seizures during their first admission or during 2 to 5 years follow-up. 2. Seizures occurred only in those patients with hemispheric lesions. 39% of seizures occurred by the first day, 57% occurred by the first week and 88% occurred by the first year.</td>
</tr>
<tr>
<td>Olsen et al. (1987)</td>
<td>Denmark</td>
<td>Observational</td>
<td>N=77</td>
<td>Development of epilepsy studied prospectively in a sample of 77 stroke patients less than 75 years old admitted within first 3 days of onset. Cerebral angiography, CT and EEG were performed in all patients clinically followed for 2 to 4 years.</td>
<td>1. 9% of patients developed epilepsy. Of 23 with lesions involving the cortex, 6 developed epilepsy and of the 54 patients that had no cortical involvement, only 1 developed epilepsy. 2. 50% of patients with persisting paresis and cortical involvement developed epilepsy.</td>
</tr>
<tr>
<td>Gupta et al. (1988)</td>
<td>USA</td>
<td>Case Series</td>
<td></td>
<td>Retrospectively studied 90 patients with post infarction seizures to determine the clinical features, prognosis and electroencephalographic</td>
<td>1. 33% of the 90 seizures appeared within 2 weeks after infarction and 90% of the early seizures appeared within 24 hours after</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Type</td>
<td>Sample Size</td>
<td>Findings</td>
<td></td>
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</table>
| N=90 | | computed tomographic findings. | | then infraction.  
2. 73% of seizures occurred within the first year and only 2% occurred after the 2 years.  
3. The most common electroencephalographic abnormality was focal slowing by recurrent seizures occurred in all patients with periodic lateralized epileptiform discharges and in 75% of patients with diffuse slowing.  
4. CT scan showed large infarctions were associated with early and multiple seizures. Deep infarctions on CT tended to cause recurrent seizures. |
| Viitanen et al. (1988) | Sweden | Observational | N=409 | Analyzed the risk of recurrent stroke, myocardial infarction and epilepsy in a population-based cohort of 409 stroke patients over 3.5 to 7 years.  
1. The risk of epilepsy was 3±2% at 1 year and 5±4% at 5 years. |
| Kotila & Waltimo (1992) | Finland | Case Series | N=200 | A retrospective follow-up of 200 stroke patients who were in need of ambulatory rehabilitation after stroke for a mean period of 40 months.  
1. Epilepsy developed in 33 (17%) patients. The occurrence of epilepsy was 14% in IBI, 15% in ICH and 35% in SAH. 15% of those developing seizures did so within first 2 weeks and 55% developed epilepsy in first 6 months post-stroke.  
2. 48% were generalized seizures and antiepileptic drug (AED) treatment was started in 28 of 33 patients. |
| Lancman et al. (1993) | USA | Observational | N=219 | Evaluated the development of seizures in 219 consecutive patients who had ischemic or hemorrhagic stroke for a period of 11.5 months.  
1. 22 of 219 patients had seizures. 54.55% were of early onset and 45.5% were of late onset.  
2. 27% of those patients who developed seizures experienced recurrence.  
3. Those patients with hemorrhagic stroke, cortical lesions and lesions involving more than one lobe were at higher risk of developing seizures. |
| So et al. (1996) | USA | Case Series | N=535 | Performed a population-based study determining the risk and factors predictive of developing seizures after stroke on 535 stroke patients without prior unprovoked seizures. Patients were followed until death or until migration out of the catchment area (Rochester, MN).  
1. 6% developed early seizures of which 78% occurred within first 24 hours after infarction.  
2. The only factor predictive of early seizures occurrence was anterior hemisphere location of infarct. 27 patients developed initial late seizures.  
3. Probability of developing initial late seizures was 3% by 1 year, 4.7 by 2 years, 7.4% by 5 years and 8.9% by 10 years. |
| Burn et al. (1997) | UK | Observational | N=675 | A cohort follow-up study on 675 first-time stroke patients.  
1. 52 patients had one of more post-stroke seizures; in 25 the seizures were recurrent.  
2. The relative risk of developing seizures in comparison with the general population was estimated at 35.2 in the first year after stroke and 19 in year 2. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>N</th>
<th>Main Findings</th>
</tr>
</thead>
</table>
| Paolucci et al. (1997) | Italy | Observational | 306 | 1. Post-stroke late seizures occurred in 15.03% of patients.  
2. Putaminal and lobar hemorrhages showed a significant positive association with the development of seizures, whereas high scores on the Canadian Neurological Scale (CNS) and increasing age were negatively associated. |
| Teasell et al. (1999) | Canada | Case Series | 563 | 1. 7.8% suffered from post-stroke seizures. Incidence of post-stroke seizures was significantly smaller in infarction patients than in hemorrhage patients.  
2. Seizures occurring within 24 hours occurred in 23.8% of patients, 52.4% within the first week, 66.7% in the first month and in 83.3% within the first 6 months and 88.1% in the first year.  
3. In the 43 patients with post-stroke seizures, 19 were focal in nature, 12 were generalized and 6 were focal with secondary generalization. |
2. Patients with hemorrhagic stroke were at significantly greater risk of seizures (P = .002), with an almost 2-fold increase in risk of seizure after stroke.  
3. Risk factors for seizures after ischemic stroke were cortical location of infarction and stroke disability.  
4. The only risk factor for seizures after hemorrhagic stroke was cortical location.  
5. Recurrent seizures (epilepsy) occurred in 47 (2.5%) of 1897 patients.  
6. Late onset of the first seizure was an independent risk factor for epilepsy after ischemic stroke but not after hemorrhagic stroke. |
| Lossius et al. (2002) | Norway | Observational | 550 | 1. 12 patients (2.5%) developed epilepsy between 4 weeks and one year following stroke.  
2. Severe stroke (Scandinavian Stroke Scale score < 30) was found to be a significant predictor. |
<p>| Vespa et al. (2003) | USA | Observational | 109 | 1. Electrographic seizures occurred in 18 of 63 (28%) patients with ICH, compared with 3 of 46 (6%) patients with ischemic stroke (OR = 5.7, 95% CI 1.4 to 26.5, p &lt; 0.004) during the initial 72 hours after admission. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>N</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordinnier et al. (2005)</td>
<td>France</td>
<td>Observational</td>
<td>202</td>
<td>Prospective systematic study of 202 consecutive stroke patients evaluated for dementia at 6 months follow-up and then every year for 3 years.</td>
</tr>
<tr>
<td>Alberti et al. (2008)</td>
<td>Italy</td>
<td>Observational</td>
<td>638</td>
<td>638 consecutive patients with first-ever stroke (543 ischemic, 95 hemorrhagic) admitted to an acute stroke unit were included and monitored for early seizures (ES). Patients with history of epilepsy were excluded. ES were defined as seizures occurring within 7 days from acute stroke.</td>
</tr>
<tr>
<td>Szaflarski et al. (2008)</td>
<td>USA</td>
<td>Case Series</td>
<td>6044</td>
<td>The incidence of seizure within 24 hours of event was determined among a population-based cohort of patients admitted to hospital for stroke during a 3-year period. Patients with a prior history of seizures/epilepsy were excluded.</td>
</tr>
<tr>
<td>Burneo et al. (2010)</td>
<td>Canada</td>
<td>Case Series</td>
<td>5027</td>
<td>The data from 5027 patients included in the Registry of the Canadian Stroke Network between 2003 and 2005 were examined to identify the incidence of seizure during inpatient stay. Patient with both ischemic and hemorrhagic stroke were included.</td>
</tr>
<tr>
<td>Krakow et al. (2010)</td>
<td>Germany</td>
<td>Case Series</td>
<td>58874</td>
<td>The incidence of seizure was obtained from a large hospital-based stroke registry in Germany. 58,874 patients with the diagnosis of TIA, ischemic stroke (IS) or intracerebral hemorrhage (ICH) were included.</td>
</tr>
<tr>
<td>Beghi et al. (2011)</td>
<td>Italy</td>
<td></td>
<td></td>
<td>714 patients with first stroke from 31 Italian centers were recruited. 609 (85.3%) patients had acute symptomatic seizures within 7 days.</td>
</tr>
</tbody>
</table>
### Observational N=714
- Cerebral infarction (32 cerebral infarction with hemorrhagic transformation [CIHT]) and 105 (14.7%) had primary intracerebral hemorrhage (PIH).

### Chen et al. (2012) Taiwan Case Series N=4126
- Of stroke onset, 24 with cerebral infarction (4.2%), 4 with CIHT (12.5%), and 17 (16.2%) with PIH.
2. The odds of early seizure were higher among patients with CIHT and PIH.
3. Seizures were most common during the first 24 hours following stroke.
4. 30-day mortality was higher among patients with seizure (6.3% vs. 2.6%, p<0.01).

### Procaccianti et al. (2012) Italy Case Series N=2053
- Among stroke patients, 72.2% had ischemic stroke, 14.7% had intracerebral hemorrhage (ICH), 2.3% had subarachnoid hemorrhage (SAH), 2.0% had other and unspecified intracranial hemorrhage (OIH), and 8.9% had multiple stroke subtypes.

### Alvarez et al. (2013) Switzerland Case Control N=128
- Population: Group1 (N=20): Mean age=71±17yr; Gender: males= 10, Females=10. Group 2 (N=100): Mean age=70.9±18.5yr; Gender: males=59, Females=41.
- Intervention: Participants were categorized according to whether they experienced seizures (Group 1: Seizure group) or not (Group 2: Seizure-free (control) group).
- Outcomes: mRS ≥3 at 7 days; mRS ≥3 at 3 months; death at 3 months; seizure occurrence.
1. The incidence of early seizure was 3.2%, the majority of which occurred within the first 24 hours.
2. Independent predictors of seizure were TACI, hemorrhagic transformation (HT), hyperglycemia and hyperglycemia x diabetes.
3. These same variables (excluding HT) in addition to female sex, >80 yrs, premorbid dependency and increasing stroke severity predicted mortality within 30 days.

1. Bivariate analyses revealed that cortical involvement was significantly associated with seizures (p<0.01) (unadjusted model), and thrombolysis was significantly associated with recombinant tissue plasminogen activator (rt-PA) (p<0.01).
2. In the subgroup of thrombolysed patients, mRS ≥3 at 3 months was significantly worse in the seizure group with 9/12 (75%) patients with mRS≥3, compared to 6/18 (33.3%) in the seizure-free group (p=0.03).
3. Backward linear regression including...
cortical involvement, NIHSS on admission, recanalization thrombolysis identified cortical involvement (OR=7.53, 95 % CI: 1.6–35.2, p<0.01) and thrombolysis (OR=4.6, 95 % CI: 1.6–13.4, p=0.01) as being independently associated with seizure occurrence.*Patients who seized at stroke onset were excluded from bivariate and multivariable analyses, for factors associated with seizure occurrence.

**Arntz et al.** (2013)
Netherlands
Observational
N=697

Prospective cohort study of 697 consecutive patients with a first-ever TIA, IS or ICH, aged 18-50 years, admitted to hospital between 1-1-1980 till 1-11-2010. The occurrence of epilepsy was assessed by standardized questionnaires and verified by a neurologist.

1. After mean follow-up of 9.1 years, 11.3% patients developed post-stroke epilepsy and 5.6% developed epilepsy with recurrent seizures.
2. Patients with an initial late seizure more often developed recurrent seizures than patients with an initial early seizure.
3. Cumulative risk of epilepsy was 31%, 16% and 5% for patients with an ICH, IS, and TIA respectively.
4. Cumulative risk of epilepsy with recurrent seizures was 23%, 8%, and 4% respectively.
5. High NIH Stroke Scale score was a significant predictor of both epilepsy and epilepsy with recurrent seizures (HR 1.07, 95% CI 1.03-1.11 and 1.08, 95% CI 1.02-1.14).

**Ji et al.** (2013)
China
Case Series
N=19923

**Population:** Intervention Group (N=19923): Mean age=64.1±12.9yr; Gender: Males=12338, Females=7585.

**Intervention:** Data was collected from the medical records of patients who were enrolled on the China National Stroke Registry from September 2007 to August 2008.

**Outcomes:** Prevalence of medical complications.

1. Among patients with an ischemic stroke, pneumonia (11.4%) was the most common in-hospital medical complication, followed by atrial fibrillation/flutter (7.4%) and urinary tract infection (UTI), 3.1%.
2. Patients with a hemorrhagic stroke experienced pneumonia (16.8%) most frequently, followed by urinary tract infection (5.6%), and gastrointestinal bleeding (4.7%).
3. In both ischemic and hemorrhagic patients, pneumonia was significantly associated with the development of gastrointestinal bleeding, decubitus ulcer, deep vein thrombosis, seizures, UTI, atrial fibrillation/flutter, and recurrent stroke (all p<0.001).

**Jungehulsing et al.** (2013)
Germany
Observational
N=1020

A cohort of 1020 patients with first-ever stroke, without pre-stroke epilepsy, from a prospective population-based study (ESPro-Erlangen Stroke Project) were examined prospectively, and follow-up at 3,12, and 24 months. Post-stroke epilepsy (PSE) was based on the revised epilepsy definition

1. 8.2 % developed PSE within 2 years after stroke. Univariate analysis demonstrated stroke severity (p<0.001) and hypertension (p<0.05) as predictors of PSE.
2. In multivariate analysis, stroke severity remained the only independent predictor
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Graham et al., (2013)</strong></td>
<td>UK</td>
<td>UK Case Series</td>
<td>N=3310</td>
<td>Population: Intervention Group (N=3310): Mean age=Unspecified; Gender: Males=1673, Females=1637.</td>
<td>1. The prevalence of epilepsy was noted in 6.4% (N=213) of patients. 2. Cumulative risk estimates at 3m and 1yr, 5yr, and 10yr were 1.5% (95% CI, 1.1–2.0), 3.5% (95% CI, 2.9–4.3), 9.0% (95% CI, 7.8–10.5), and 12.4% (95% CI, 10.8–14.3), respectively. 3. Younger age was significantly associated with epilepsy post stroke as there was a greater prevalence among patients aged &lt;45yr (15.6%) compared to patients aged &gt;85yr (4.4%) (p&lt;0.001). 4. Significant predictors of epilepsy included dysphagia, visual neglect, and visual field defect (all p&lt;0.001).</td>
</tr>
<tr>
<td><strong>Haapaniemi et al., (2014)</strong></td>
<td>Finland</td>
<td>Finland Case Series</td>
<td>N=1317</td>
<td>Population: Experimental Group 1 (EG1, N=993): Mean age=68yr; Gender: Males=570, Females=423. Experimental Group 2 (EG2, N=325): Mean age=71yr; Gender: Males=176, Females=149.</td>
<td>1. Early seizure (&lt;7d) post stroke was noted in 109 patients (11%), of which 48 experienced a seizure at stroke onset and 45 within 7d of onset. 2. A total of 70 patients (9.2%) experienced a late seizure with a median time of 0.5yr post stroke. 3. The cumulative risk of late seizures among surviving patients was 7.1% at 1yr post stroke, 10.0% at 2yr, 10.2% at 3yr, 11.0% at 4yr, and 11.8% at 5yr. 4. Younger age, higher alcohol consumption, and lower GCS score at admission were significantly associated with the prevalence of a late seizure (all p&lt;0.001). 5. Sensitivity of the CAVE Score was 0.97 (0.91-0.99). 6. Specificity of the CAVE Score was 0.23 (0.20-0.26). 7. PPV of the CAVE Score was 0.11 (0.09-0.14). 8. NPV of the CAVE Score 0.99 (0.96-1.00). 9. Likelihood ratio of the CAVE Score 1.26 (1.20-1.32).</td>
</tr>
<tr>
<td><strong>Tanaka et al., (2015)</strong></td>
<td>Japan</td>
<td>Japan Case Series</td>
<td>No Score TPS=1029d (352-2625.5) NStart=104 NEnd=104</td>
<td>Population: Mean age=74yr (63.3-81); Gender: Male=71, Female=33.</td>
<td>1. Significant risk factors associated with PSS valproic acid monotherapy or polytherapy with antiepileptic drugs, frontal cortical lesion, and a higher modified Rankin Scale score at discharge (all p&lt;0.05).</td>
</tr>
<tr>
<td><strong>Bryndziar et al., (2016)</strong></td>
<td>USA</td>
<td>USA Case Control</td>
<td>No Seizure group (NS; n=454): Mean age=77.0±13.0yr; Gender: Male=179, Female=275. Seizure Group (SG; n=35): Mean age=72.7±10.8yr;</td>
<td>Population: No Seizure group (NS; n=454): Mean age=77.0±13.0yr; Gender: Male=179, Female=275. Seizure Group (SG; n=35): Mean age=72.7±10.8yr;</td>
<td>1. There was no significant difference between NS and SG groups in stroke type or premorbid stroke risk factors, including:</td>
</tr>
</tbody>
</table>
17. Medical Complications Post Stroke

17.5.3 Prevention and Treatment of Seizures Post Stroke

Table 17.5.3 Prevention and Treatment of Seizures Post Stroke

<table>
<thead>
<tr>
<th>Author, Year Country Study Design PEDro Score Time Post Stroke Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alvarez-Sabin et al. (2002) Spain Post-Test No Score N=71</td>
<td>The long-term efficacy and tolerability of gabapentin (900 to 1,800 mg/day) was evaluated in 71 patients (ischemic stroke=48, hemorrhagic stroke=23) with a first post-stroke late seizure. The mean follow-up period was 30 months.</td>
<td>1. Seizure recurred in 13 (18.3%) patients over the study period. 7 patients died. Side effects were noted in 27 cases (38%), but only two (2.8%) required discontinuation or early withdrawal.</td>
</tr>
<tr>
<td>Rowan et al. (2005) USA RCT PEDro=9 N=593</td>
<td>593 elderly subjects with newly diagnosed seizures from 18 centres were randomly assigned to one of three treatment groups: lamotrigine (LTG) 150 mg/day, gabapentin (GBP) 1,500 mg/day, and carbamazepine (CBZ) 600 mg/day for up to 12 months. The most common etiology of seizure was ischemic stroke (51%). The primary outcome measure of this study was retention, a measure of both efficacy and tolerability.</td>
<td>1. 276 (46.8%) completed 1 year in trial. Patients in the CBZ group were more likely to terminate the study early compared with patients in the GBP or LTG groups. 2. At 3, 6 and 12 months, 63.2%, 58.6% and 53.3% patients remained seizure free. There were no differences across treatment groups in terms of efficacy.</td>
</tr>
<tr>
<td>Gilad et al. (2007) Israel RCT PEDro=3 N=64</td>
<td>64 patients with a first post episode of seizures were randomized to receive either lamotrigine (LTG) or carbamazepine (CBZ) treatment. Subjects were followed for up to 12 months to establish efficacy and tolerability of the drugs.</td>
<td>1. At 12 months more patients in the LTG group were seizure-free (72%) versus those in the CBZ group (44%), although the result was not statistically significant (p = 0.06). Fewer subjects withdrew due to side-effects in the LTG group (3%) compared with the CBZ group (31%; p = 0.02).</td>
</tr>
<tr>
<td>Gilad et al. (2011) Israel RCT PEDro=6 N=84</td>
<td>84 patients with intracerebral hemorrhage were randomized to receive valproic acid (VA)(n=36) or placebo (n=36) for one month and followed for one year. The primary outcome was seizure occurrence.</td>
<td>1. At 1 year, there were 15 (21%) cases of new seizure. There were no differences between treatment groups in all seizures (7 vs. 8, p=0.8), early seizure (1 vs. 4, p=0.4), late seizure (6 vs. 4, p=0.5) and mortality (6 vs. 5, p=0.7). 2. Mean NIHSS scores were lower among patients in the VA group (4.4 vs. 8.6, p=0.002)</td>
</tr>
<tr>
<td>Van Tuijl et al. (2011) Netherlands Stroke patients with a cortical syndrome and a modified Rankin score ≥3 or NIHSS ≥ 6 were</td>
<td>1. Recruitment began in 2005. Over 16 months, only 16 patients entered into the</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
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<tr>
<td>Guo et al. (2015)</td>
<td>China</td>
<td>Case Control</td>
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<tr>
<td>Huang et al. (2015)</td>
<td>Taiwan</td>
<td>Case Series</td>
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<tr>
<td>Inokuchi et al. (2015)</td>
<td>Taiwan</td>
<td>Case Control</td>
</tr>
</tbody>
</table>

### Outcome Association

1. Overall, statin use was associated with a lower risk of post-stroke early-onset seizure (p<0.001); reduced risk was seen mostly in the patients who used a statin only in the acute phase (p<0.001).
2. Overall, no significant association was found between statin use and post-stroke epilepsy (p=0.349); however, among the YS group, statin use was associated with reduced risk of post-stroke epilepsy (p=0.026).

### Study Design

1. Medical Complications Post Stroke

   - Neurological Events
   - Neurological Impairment
   - Cognitive Impairment
   - Depression
   - Dementia
   - Suicide

### Conclusion

- The trial had a number of difficulties including small numbers of eligible patients available, the use of anticonvulsant co-medication, ensuring compliance with the trial medication after discharge, and the evaluation of possible side effects of the trial medication.

- Overall, statin use was associated with a lower risk of post-stroke early-onset seizure (p<0.001); reduced risk was seen mostly in the patients who used a statin only in the acute phase (p<0.001).

- Overall, no significant association was found between statin use and post-stroke epilepsy (p=0.349); however, among the YS group, statin use was associated with reduced risk of post-stroke epilepsy (p=0.026).
17.6 Osteoporosis Post Stroke

17.6.3 Treatment of Osteoporosis Post Stroke

Table 17.6.3 Treatment of Osteoporosis Post Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato et al. (1997)</td>
<td>Japan</td>
<td>RCT</td>
<td>PEDro=8</td>
<td>N=84</td>
<td>84 patients randomized to receive either 1 μg 1- (OH)₃ daily with 300mg elemental calcium or an inactive placebo.</td>
<td>1. Bone Mineral Density (BMD) on the hemiplegic side decreased significantly less for those receiving treatment compared to 8.9% of the placebo patients (2.4% vs. 8.9%). 2. BMD on the intact side increased by 3.5 in the treated group while decreasing by 6.3% in the placebo group. 3. 4 of the placebo patients suffered a hip fracture compared to none in the treatment group.</td>
</tr>
<tr>
<td>Sato et al. (1998)</td>
<td>Japan</td>
<td>RCT</td>
<td>PEDro=5</td>
<td>N=108</td>
<td>108 outpatients recovering from a stroke of 2 years duration or less were randomized to receive 45 mg mannaquinone-4 (MK-4), a form of vitamin K₂ or no treatment, daily for 12 months. The results were compared with 35 healthy control patients Bone mineral density (BMD) was assessed in the 2nd metacarpus along with serum indicators of bone metabolism. Vitamin K is known to affect bone metabolism.</td>
<td>1. BMD on the hemiplegic side increased by 4.3% in the MK-4 group and decreased by 4.7% in the untreated group, while BMD on the intact side decreased by 0.9% in the MK-4 group and by 2.7% in the untreated group. 2. At baseline, patients of both stroke groups showed vitamin D and K₁ deficiencies, high serum levels of ionized calcium, and other serum indicators of bone metabolism. Both vitamins K₁ and K₂ increased by 97.6% and 666.9%, respectively, in the MK-4 group. 3. One patient in the untreated group suffered from a hip fracture, compared with none in the MK-4 group. The treatment with MK-4 can increase the BMD of disused and vitamin D- and K-deficient hemiplegic bone by increasing the vitamin K concentration, and it also can decrease calcium levels through inhibition of bone resorption, resulting in an increase in 1, 25-[OH]₂D concentration.</td>
</tr>
<tr>
<td>Uebelhart et al. (1999)</td>
<td>Switzerland</td>
<td>RCT</td>
<td>PEDro=5</td>
<td>N=34</td>
<td>34 stroke patients with hemiplegia were randomly allocated to receive either 100 IU of salmon calcitonin or placebo by nasal spray for 2 years. Patients were recruited within the first month of stroke and all patients received active rehabilitation + calcium supplementation of 1000 mg. A variety of markers of bone and connective tissue were measured.</td>
<td>1. 11 subjects, the majority from the calcitonin group, dropped out over the study period. Biochemical markers of bone formation, serum total alkaline phosphatase, osteocalcin and type I procollagen did not vary during the two years of follow-up. 2. No significant differences were reported</td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Type</td>
<td>PEDro</td>
<td>N</td>
<td>Summary</td>
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<tr>
<td>Ikai et al. (2001)</td>
<td>Japan</td>
<td>PCT</td>
<td>No Score</td>
<td>81</td>
<td>81 post menopausal women with hemiplegia secondary to first stroke received 200 or 400 mg/day of etidronate (n=40) for 2 weeks or to a control condition (n=41). Women were divided into a low ADL group (motor FIM ≤ 70) and a high ADL group (FIM &gt; 70). 1. Following a 3-month rehabilitation program, bone mineral densities (BMD) obtained at the lumbar spine and femoral neck was remeasured. 2. There were no differences in BMD changes between the control or treatment conditions in the high ADL group. There was significantly less bone loss on the paretic side of the femoral neck associated with treatment for the low ADL group (-4.0% vs. -9.6%, p&lt;0.05).</td>
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<tr>
<td>Poole et al. (2007)</td>
<td>UK</td>
<td>RCT</td>
<td>PEDro=9</td>
<td>27</td>
<td>27 patients with stroke onset of 35 days or less who were unable to ambulate were randomized to receive a single intravenous infusion of 4 mg zoledronate, a bisphosphonate, (n=14) or placebo (n=13). Patients in both groups received calcium and vit. D supplements. Bone mineral density (BMD) was assessed after one year. 1. Mean total hip BMD was unchanged in the hemiplegic hip of the zoledronate group (mean 0.0% change). 2. The corresponding change in the placebo group was -5.5%, with the greatest bone loss observed in the trochanteric subregion (mean, -8.1%). 3. On the unaffected side the mean change in total hip BMD was +1.0% with zoledronate versus a mean change of -2.7% without. 4. The differences between groups were statistically significant. There were no fractures during the study period. 5. The number of reported falls was similar between groups.</td>
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<tr>
<td>Sato et al. (2010)</td>
<td>Japan</td>
<td>RCT</td>
<td>PEDro=8</td>
<td>40</td>
<td>40 chronically hospitalized, disabled, elderly stroke patients were randomized to receive either 400 mg/day of oral etidronate or placebo for 2 weeks, followed by a 13-week period of no drug therapy. This sequence was repeated for 2 years. Primary outcome measure was the incidence of hip fracture. Secondary outcome was metacarpal bone mineral density (BMD). 1. At baseline, both groups had low BMD with high levels of serum ionized calcium and urinary deoxypyridinoline. 2. In the etidronate group, serum calcium and urinary deoxypyridinoline levels decreased significantly during the study period, whereas the levels in the placebo group were increased. 3. BMD on the hemiplegic side increased by 1.4% in the etidronate group and decreased by 2.2% in the placebo group (P &lt; .001). 4. Two patients sustained hip fractures in the placebo group, and no hip fracture occurred in the etidronate group (p=0.16).</td>
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<tr>
<td>Gommans et al. (2013)</td>
<td>New Zealand</td>
<td>RCT</td>
<td>PEDro=8</td>
<td>164</td>
<td>As part of the VITAmins To Prevent Stroke (VITATOPS) RCT, 8, 164 stroke patients were randomized to receive one table daily of either B-vitamins (folic acid, vitamin B6, and vitamin B12) or placebo. The vitamin B therapy was a postulated homocysteine-lowering therapy, a potentially reversible risk factor for osteoporosis and realted 1. At the end of the trial, there were no statistically significant clinically apparent osteoporotic fracture incidence differences between the treatment and placebo group.</td>
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</table>
fractures. Median duration of therapy was 2.8 years with a median follow-up time of 3.4 years.

### 17.7 Central Pain States Post Stroke

#### 17.7.1 Prevalence of Central Post-Stroke Pain

**Table 17.7.1 Prevalence, Incidence, and Clinical Presentation of Central Post-Stroke Pain**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boivie et al. (1989)</strong></td>
<td>Sweden</td>
<td>Observational</td>
<td>N=27</td>
<td>27 stroke patients with CPSP were evaluated clinically with neurological tests and quantitatively.</td>
<td>1. All patients demonstrated abnormal temperature and pain sensibility. 92% (25/27) of patients had raised thresholds to thermal pain and 96% (26/27) had abnormal sensibility to pin prick stimulus. 2. 80% patients demonstrated hyperpathia, 85% somatic stimuli evoked dysesthesia. Paraesthesias were reported in 11 patients, radiation of stimuli in 50%, after-sensations in 45% and allodynia in 23%.</td>
</tr>
<tr>
<td><strong>Andersen et al. (1995)</strong></td>
<td>Denmark</td>
<td>Observational</td>
<td>N=207</td>
<td>All consecutive patients less than 81 yrs with acute stroke admitted to hospital were examined within 7 days and followed at 1, 6 and 12 months post stroke. CPSP was considered present if the patient complained of pain and if sensibility to touch, temperature and pinprick were abnormal compared to the contralateral areas tested.</td>
<td>1. 267 patients entered the study. 207 patients survived for at least 6 months. CPSP was reported in 16 (8%) patients. 2. 15 patient’s also demonstrated evoked dysesthesia or allodynia. In patients with a single cerebral lesion there was no association between size or location of the lesion and CPSP. 3. Pain was reported as light in 6 (3%) patients and moderate to severe in 10 (5%).</td>
</tr>
<tr>
<td><strong>Vestergaard et al. (1995)</strong></td>
<td>Denmark</td>
<td>Observational</td>
<td>N=11</td>
<td>The sensory abnormalities in an unselected, consecutive group of 11 stroke patients with CPSP, surviving more than 1 year were examined.</td>
<td>1. Median present spontaneous pain intensity on a visual analogue scale was 3.3 (range:0-7.7). 2. Warmth detection threshold was higher in the pain area in all patients. 10 patients had an increased cold detection threshold. 3. A cold allodynia in the 10-15 °C range was present in 6 patients.</td>
</tr>
<tr>
<td><strong>Bowsher (2001)</strong></td>
<td>UK</td>
<td>Observational</td>
<td>N=1071</td>
<td>Questionnaires about stroke and subsequent pain were administered to 1,071 elderly subjects (median age 80 years, 537 female) by nurses.</td>
<td>1. Seventy-two patients (6.7%), median age of 74 had completed strokes. 2. At least 8 (11%) of the completed stroke subjects had what seemed to be central post-stroke pain (CPSP). 3. Their median age at the time of the stroke was 77.5 years; all had a motor deficit.</td>
</tr>
<tr>
<td><strong>Widar et al. (2002)</strong></td>
<td>Of 528 patients who had been admitted to a</td>
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<td>1. 185 (37%) patients had died within the 2-</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Type</td>
<td>N</td>
<td>Methodology and Findings</td>
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<tr>
<td>Jonsson et al. (2006)</td>
<td>Sweden</td>
<td>Observational</td>
<td>297</td>
<td>297 patients were followed over a one-year period following stroke (population based Lund Stroke Register). Worst pain intensity during the previous 48 hours was assessed on a 0-100 point visual analogue scale (VAS), where 0 to 30 was defined as no or mild pain; 40 to 100 as moderate to severe pain. Median pain intensity was 6/10. 6 patients reported that the pain was continuous. Cold and stress/anxiety were identified as factors contributing to increasing pain.</td>
<td></td>
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<tr>
<td>Klit et al. (2011)</td>
<td>Denmark</td>
<td>Observational</td>
<td>51</td>
<td>A questionnaire was sent out to all (n = 964) stroke patients identified through the Danish National Indicator Project Stroke Database, between March 2004 and February 2005. All surviving patients who fulfilled 4 questionnaire criteria for possible CPSP (n = 51) were selected for further clinical examination, and their pain was classified by using stringent and well-defined criteria and a detailed, standardized clinical examination. 608 questionnaires were completed. 35 (5.8%) patients had definite or probable CPSP and the prevalence of CPSP-like dysesthesia or pain was 1% of the total sample. Pinprick hyperalgesia was present in 57%, cold allodynia in 40%, and brush-evoked dysesthesia in 51% of patients with CPSP.</td>
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<tr>
<td>O'Donnell et al. (2013)</td>
<td>Canada</td>
<td>Observational</td>
<td>15754</td>
<td>Population: Mean age=65.8±8.4yr; Gender: Males=10345, Females=5409. Intervention: Patients taking part in the Prevention Regimen for Effectively Avoiding Second Stroke trial were prospectively analyzed. Outcomes: Prevalence of chronic poststroke pain (CPSP), Mini-Mental State Examination (MMSE), modified-Rankin scale (m-Rankin) score, risk factors. 1665 subjects (10.6%; 95% CI, 10.1%-11.0%) developed CPSP. Decline in MMSE occurred for 8.8% of patients without CPSP, compared with 10.7% of patients that developed CPSP. Decline in m-Rankin occurred in 8.7% of patients without CPSP, compared with 13.7% of patients that developed CPSP. Risk factors associated with all poststroke pain were: increased stroke severity, female sex, alcohol intake, previous depression, statin use or hyperlipidemia, diabetes mellitus, peripheral vascular disease, and random allocation to aspirin/dipyridamole.</td>
<td></td>
</tr>
<tr>
<td>Raffaeli et al. (2013)</td>
<td></td>
<td></td>
<td>11 CPSP patients reported mild pain, 29</td>
<td></td>
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</table>

17. Medical Complications Post Stroke
Male=327, Female=274.

**Intervention:** Assesses stroke patients admitted between 2008 and 2010. Patients were divided between those experiencing central post stroke pain (CPSP, n=66) and those not (n=535).

**Outcomes:** Short Form questionnaire (SF); and National Institute of Health Stroke Scale (NIHSS);

reported moderate pain and 20 reported severe pain.

2. 57.6% of CPSP patients reported that the pain started immediately post stroke, 19.7% reported pain starting post 1mo and 19.7% reported pain starting after several months.

3. Continuous pain was present in 59.6% of CPSP patients and intermittent pain was present in 36.5%.

4. 30.3% of total patients reported complete/partial motor palsy ipsilateral to the lesion, 13.6% reported motor issues contralateral to the lesion and 10.6% reported motor issues in both lower limbs.

5. 43.9% of CPSP patients had no walking ability, 39.4% had impaired walking and 15.2% could move without problems.

6. 50% of CPSP patients could sleep normally, 28.8% experienced difficulty with sleeping and 21.8% could not sleep.

7. 33.3% of CPSP patients took care of themselves normally, 13.6% could only do so partially and 50% could not.

8. 36.4% of CPSP patients reported a good social life, 12.1% reported a partially recovered social life and 48.5% reported no social life.

9. SF scores for the physical component (stroke=30.77±8.47, healthy=51.2±7.4, p<0.05) and mental component (stroke=37.93±8.64, healthy=47.8±10.1, p<0.05) were significantly lower than the average scores for the Italian population.

10. 43.3% of CPSP patients were prescribed analgesic or anti-inflammatory drugs, 10.1% were prescribed pregabalin, 4.8% opioids, 5.5% other and 29.3% were not given analgesic prescriptions.

---

**Chuang et al.** (2014)

Taiwan Observational

N=50

**Population:** Mean age=52.63±11.09yr; Gender: Males=36, Females=14.

**Intervention:** Test/retest to evaluate the relative and absolute reliability of a vertical numerical pain rating scale (NPRS).

**Outcomes:** Pain intensity.

1. There was no statistically significant difference in pain intensity between the test and retest assessments for participants who had a right vs left hemispheric stroke (p>0.05).

2. For relative reliability assessments results from all patients showed that the ICC for the NPRS-FPS was 0.82, indicating that the NPRS-FPS had good relative reliability in participants with right or left hemispheric stroke.

3. For absolute reliability assessments, results from all patients indicated there was no
significant systematic bias between the repeated measurements in participants with right-side or left-side brain lesions.

4. Overall, good relative and absolute reliabilities, high agreement, small measurement error, no systemic bias for assessment of pain after stroke.

**Harno et al.** (2014)
Finland
Cohort
N=824

**Population:** Experimental Group 1 (EG1, N=529): Mean age=40.2±8.2yr; Gender: Males=324, Females=205. Experimental Group 2 (EG2, N=246): Mean age=41.5±7.1yr; Gender: Males=148, Females=98. Experimental Group 3 (EG3, N=49): Mean age=41.3±7.3yr; Gender: Males=27, Females=22.

**Intervention:** Data was collected from the Helsinki Young Stroke Registry and questionnaires were sent to patients evaluating pain and quality of life. Patients suspected of experiencing chronic pain were invited to participate in a telephone interview followed by a clinical examination and further questionnaires if the telephone interview supported a chronic pain prognosis. Follow-ups were conducted up to a median of 8.5yr.

**Outcomes:** Prevalence and onset of chronic pain; National Institutes of Health Stroke Scale (NIHSS); Trial of Org in Acute Stroke Treatment (TOAST).

1. The EG1 had no sensory abnormalities nor chronic pain (5.9%), EG2 had sensory abnormalities but no chronic pain (29.9%), and EG3 were diagnosed with chronic pain (64.2%).
2. Onset of chronic pain was noted to be most prevalent within 1m post stroke.
3. EG3 patients reported significantly higher NIHSS scores than EG1 (p<0.001) and EG2 (p=0.004).
4. No significant differences were reported between groups on TOAST classification.

**Paolucci et al.** (2016)
USA
Case Control
No Score
TPS = 2.10±2.83d
TPS = 47.77±24.42d
TPS = 174.89±107.71d
N = 730
N = 546

**Population:** Acute group (E1; n=320): Mean age=67.16±14.08yr; Gender: Males=197, Females=123. Subacute group (E2; n=110): Mean age=67.60±14.18yr; Gender: Males=65, Females=45. Chronic group (E3; n=116): Mean age=66.59±14.73yr; Gender: Males=68, Females=48.

**Intervention:** All participants were retrospectively analyzed for post-stroke central pain by time post stroke.

**Outcomes:** Central Pain Prevalence; Medication Prevalence.

1. The prevalence of central post-stroke pain was higher in E2 and E3 than in the E1 group.
2. Fewer than 25% of the patients with central post-stroke pain received drug treatment.
3. The mean overall prevalence of pain was 29.56% (14.06% in E1, 42.73% in E2, and 31.90% in E3).

### 17.7.4 Treatment of Central Pain Post Stroke

**Table 17.7.4 Treatment of Central Post Stroke Pain**

<table>
<thead>
<tr>
<th>Author, Year Country Study Design PEDro Score Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leijon &amp; Boivie</strong> (1989a) Sweden</td>
<td>A double-blind, 3 phase crossover placebo controlled trial of 15 patients. Treatment was</td>
<td>Amitriptyline produced a significantly greater reduction of pain when compared</td>
</tr>
</tbody>
</table>
RCT  
PEDro=6  
N=15  
given in randomized order, for 4 weeks, separated by 1 week wash-out periods in which patients were administered amitriptyline, carbamazepine and placebo. 
to placebo at week 4.

<table>
<thead>
<tr>
<th><strong>Leijon &amp; Boivie (1989b)</strong></th>
<th>Sweden</th>
<th>Pre-Post</th>
<th>No Score</th>
<th>N=15</th>
<th>15 stroke patients received both high frequency and low frequency transcutaneous electrical nerve stimulation (TENS) 3x/day for 16 days. A 10-step verbal pain rating scale was used for the assessments (baseline, 60 and 120 minutes following stimulation). Final follow-up at 23-30 months.</th>
<th>1. 4 patients obtained at least a 20% reduction in baseline pain (mean=42%), 3 patients continued to use TENS and reported an improvement in their pain symptoms for 23, 24 and 30 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Awerbuch et al. (1990)</strong></td>
<td>USA</td>
<td>Post-Test</td>
<td>No Score</td>
<td>N=9</td>
<td>9 patients (8/9 with stroke) were administered 150 mg/day of mexiletine for 3 days followed by 300 mg/day for 3 days and thereafter at a dose of 10mg/Kg/day for one month.</td>
<td>1. Mexiletine produced a significant improvement in pain in 8 of the 9 patients.</td>
</tr>
<tr>
<td><strong>Bainton et al. (1992)</strong></td>
<td>UK</td>
<td>RCT</td>
<td>PEDro=5</td>
<td>N=20</td>
<td>20 stroke patients received both naloxone (up to 8 mg) and normal saline in a randomized crossover trial. Visual analogue scale and verbal pain scores were obtained immediately before and after injection. There was a 2 to 3 week washout period.</td>
<td>1. There were no immediate or long-term differences in pain relief between the 2 groups.</td>
</tr>
<tr>
<td><strong>Yamamoto et al. (1997)</strong></td>
<td>Japan</td>
<td>Post-Test</td>
<td>No Score</td>
<td>N=39</td>
<td>39 central post-stroke pain patients who had intractable hemibody pain associated with dysesthesias, and radiologically demonstrated lesions in the thalamic area (thalamic pain, n = 25) or suprathalamic area (suprathalamic pain, n = 14) underwent 3 pharmacological tests including the morphine, thiamylal and ketamine test to assess their sensitivity to various treatments. After tests were completed, 28 patients underwent surgery for chronic motor cortex stimulation. Pain was assessed at 1 year (follow-up).</td>
<td>1. A total of 13/28 (46%) achieved and maintained satisfactory pain relief at 1 year. A comparison of the long-term follow-up results of chronic motor cortex stimulation therapy revealed that thiamylal and ketamine-sensitive and morphine-resistant cases displayed long-lasting pain reduction with chronic motor cortex stimulation therapy, whereas the remaining cases did not show good results.</td>
</tr>
<tr>
<td><strong>Katayama et al. (1998)</strong></td>
<td>Japan</td>
<td>Post-Test</td>
<td>No Score</td>
<td>N=31</td>
<td>31 patients with post stroke pain were treated with motor cortex stimulation delivered through surgically implanted devices which delivered a pulse of 0.2 msec duration, frequency of 25-50 Hz and intensity of 2-8 V. Stimulation was applied for 10-20 min on each occasion. Pain was assessed using a visual analogue scale. Pain control of &gt;60% reduction was considered a satisfactory result.</td>
<td>1. Among the 31 patients satisfactory pain control was reported by 23 (74%) of patients. The stimulation system was internalized in all of these patients. In 15 patients (48%), excellent or good pain control (pain reduction &gt; 60%) was achieved for follow-up periods of more than 2 years by using MC stimulation at intensities below the threshold for muscle contraction. Satisfactory pain control was achieved in 74% of (23) patients during the first one-week period. After one year 48% of these patients 15 continued to achieve satisfactory pain control, while the effect gradually diminished over time in the remaining 8 patients and was no longer evaluated by the patients as being effective.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Methodology</td>
<td>Participants</td>
<td>Results</td>
<td></td>
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<tr>
<td>Tsubokawa et al. (1993)</td>
<td>Japan</td>
<td>Post-Test</td>
<td>N=11</td>
<td>Following implantation, 6 patients reported excellent levels of pain reduction and 2 reported good levels of reduction. At 2 years, 5/6 patients continued to experience excellent results, while 1 patient was experiencing poor pain control. Both patients who had initially achieved good results had deteriorated and described their result as poor. No patient experienced seizures.</td>
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<tr>
<td>Katayama et al. (2001)</td>
<td>Japan</td>
<td>Post-Test</td>
<td>N=45</td>
<td>Stimulation at higher levels produced more frequent satisfactory pain control (7% by SCS, 25% by DBS and 48% by MCS). Stimulation by VC, post-central, pre-central and pre-frontal cortices caused some painful sensation, but as the stimulation site was raised to higher levels the sensation was less frequent.</td>
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<tr>
<td>Lefaucheur et al. (2001a)</td>
<td>France</td>
<td>RCT</td>
<td>N=18</td>
<td>A significant decrease in the mean pain level of the series was obtained only after 10 Hz rTMS. Mean pain scores before and after treatment were: 7.7 -6.2 (10 Hz); 7.1-6.3 (0.5 Hz); 8.2-7.0 (sham). 7/18 patients experienced significant (at least 30%) reduction in pain following treatment with 10 Hz rTMS.</td>
<td></td>
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<tr>
<td>Lefaucheur et al. (2001b)</td>
<td>France</td>
<td>RCT</td>
<td>N=14</td>
<td>A significant pain decrease was observed up to 8 days after the 'real' rTMS session. 4/7 stroke patients experienced significant reductions in pain (at least 30%) with real rTMS while 2/4 experienced good/excellent pain relief (at least 50%).</td>
<td></td>
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<tr>
<td>Vestergaard et al. (2001)</td>
<td>Denmark</td>
<td>RCT</td>
<td>N=30</td>
<td>Lamotrigine 200 mg/d reduced the median pain score to 5, compared to 7 during placebo (p = 0.01). No significant effect was obtained at lower doses. Twelve patients (44%) responded to the treatment. Lamotrigine only had significant effects on some of the secondary outcome measures. Oral lamotrigine 200 mg daily is a well tolerated and moderately effective treatment for central post-stroke pain.</td>
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<tr>
<td>Attal et al. (2002)</td>
<td>France</td>
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<td></td>
<td>Morphine significantly reduced the intensity of brush-induced allodynia but</td>
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<tr>
<td>Study</td>
<td>Country</td>
<td>Design</td>
<td>PEDro</td>
<td>N</td>
<td>Patients</td>
<td>Intervention</td>
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<tr>
<td>RCT</td>
<td>Austria</td>
<td>RCT</td>
<td>8</td>
<td>15</td>
<td>crossover study of 15 patients with post stroke (6 patients) or spinal cord injury (9 patients) related pain. All of the patients subsequently received sustained oral morphine.</td>
<td>had no effect on other evoked pains (i.e., static mechanical and thermal allodynia/hyperalgesia). The effects of morphine on ongoing pain were not significantly different from those of the placebo, but 7 patients (46%) responded to morphine. There was a correlation between the effects of morphine on spontaneous pain and the decrease of the responses to suprathreshold thermal stimuli on the nonpainful contralateral side. Only 3 patients (20%) were still taking morphine after 1 year.</td>
</tr>
<tr>
<td>Lampl et al. (2002)</td>
<td>Austria</td>
<td>RCT</td>
<td>7</td>
<td>39</td>
<td>39 stroke patients were randomly assigned to receive either amitriptyline (n=20) or placebo (n=19) over 1 year for the management of central pain.</td>
<td>1. There were no differences in the occurrence, intensity, type, site or distribution of pain between the 2 groups.</td>
</tr>
<tr>
<td>Serpell et al. (2002)</td>
<td>UK</td>
<td>RCT</td>
<td>8</td>
<td>9</td>
<td>307 patients with a wide range of neuropathic pain syndromes (9 with post stroke pain) with at least two of the following symptoms: allodynia, burning pain, shooting pain, or hyperalgesia were randomized to receive either gabapentin (n=153) or placebo (n=152) for 8-weeks following a run-in period. Gabapentin was given in three divided doses, initially titrated to 900 mg/day over 3 days, followed by two further increases, to a maximum of 2400 mg/day if required by the end of week 5. The primary outcome measure was changed in average daily pain diary score (baseline versus final week) using a 0-10 Likert scale.</td>
<td>1. Over the 8 week study, pain scores decreased 1.5 (21%) in gabapentin treated patients and by 1.0 (14%) in placebo treated patients (P=0.048, rank-based analysis of covariance). Significant differences were shown in favour of gabapentin for the clinician and patient Global Impression of Change, and some domains of the Short Form-McGill Pain Questionnaire. Improvements were also shown in patient-reported outcomes in quality of life, as seen by significant differences in favour of gabapentin in several domains of the Short-Form-36 Health Survey.</td>
</tr>
<tr>
<td>Shimodozono et al. (2002)</td>
<td>Japan</td>
<td>Pre-Post</td>
<td>No Score</td>
<td>28</td>
<td>28 patients with central post-stroke pain received selective serotonin reuptake inhibitor (SSRI) fluvoxamine 50 mg/day divided into 2 weekly doses. Doses were either increased or maintained (maximum of 125 mg/day) depending on the symptoms of the patient with the treatment lasting 2 to 4 weeks. Evaluations took place before and after treatment. They included the visual analog scale (VAS) and Zung’s Self-rating Depression Scale (SDS).</td>
<td>1. Following treatment patients’ mean VAS and mean SDS significantly decreased (p&lt;0.01). After, patients were split up into 2 groups, the patients in whom the duration after stroke was less than 1 year post-stroke showed a significant reduction in VAS (p&lt;0.001), whereas patients who had longer than 1-year duration since stroke onset did not.</td>
</tr>
<tr>
<td>Rowbotham et al. (2003)</td>
<td>USA</td>
<td>RCT</td>
<td>7</td>
<td>81</td>
<td>81 patients suffering from neuropathic pain were randomized to 1 of 2 groups: 1) High-strength (0.75-mg) (5 CPSP patients) or 2) low-strength (0.15-mg) (5 CPSP patients) capsules of µ-opioid agonist levorphanol for a period of 8 weeks.</td>
<td>1. High-strength levorphanol capsules reduced pain by 36 percent, as compared with a 21 percent reduction in pain in the low-strength group (P=0.02).</td>
</tr>
<tr>
<td>Canavero &amp; Bonicalzi (2004)</td>
<td>Italy</td>
<td></td>
<td></td>
<td>44</td>
<td>44 patients with central pain (52%) stroke received a bolus injection of propofol (0.2 mg/kg) and placebo, in random order, up to one month</td>
<td>1. 24/44 (54%) patients reported a positive response to propofol vs. 6 (14%) with placebo. When positive, propofol usually</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Design</td>
<td>PEDro</td>
<td>N</td>
<td>Treatment</td>
<td>Outcome 1</td>
</tr>
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<tr>
<td>Lefaucheur et al. (2004)</td>
<td>France</td>
<td>RCT</td>
<td>PEDro=4</td>
<td>60</td>
<td>Right-handed patients, suffering from intractable pain secondary to one of the following types of lesion: thalamic stroke, brainstem stroke, spinal cord lesion, brachial plexus lesion, or trigeminal nerve lesion were randomly assigned, in a crossover design, to receive a single 20-min session of rTMS of the motor cortex at 10 Hz using a ‘real’ and a ‘sham’ coil. Treatments were separated by 3 weeks. Stimulation was targeted on the hand cortical area. Pain was assessed before and after treatment using a 10-point visual analogue scale.</td>
<td>1. The percentage pain reduction was significantly greater following real vs. sham rTMS (~22.9% v -7.8%, p = 0.0002). Pain level was reduced by rTMS in 65% of patients. The best results were obtained in patients with trigeminal nerve lesion or facial pain, followed by patients with thalamic stroke. The worst results were seen in patients with brainstem stroke.</td>
</tr>
<tr>
<td>Nuti et al. (2005)</td>
<td>France</td>
<td>Post-Test</td>
<td>No Score</td>
<td>31</td>
<td>Patients (22 with stroke) with medically refractory neuropathic pain were included in a prospective evaluation of motor cortex stimulation. Pain was assessed using a 0-10 visual analogue scale. Mean follow-up period was 4 years.</td>
<td>1. Pain relief was rated as excellent (&gt;70% pain relief) in 3 (10%) of cases, good (40-69%) 13 (42%) of cases, poor (10-39%) in 11 (35%) and negligible (0-9%) in 4 (13%) of cases. Intake of analgesic drugs was decreased in 52% of patients and unchanged in 45% (unavailable data in 3%), with complete withdrawal of analgesic drugs in 36% of patients. Neither preoperative motor status, pain characteristics, type or localisation of lesions, quantitative sensory testing, Somatosensory Evoked Potentials, nor the interval between pain and surgery were found to predict the efficacy of MCS.</td>
</tr>
<tr>
<td>Vranken et al. (2005)</td>
<td>Netherlands</td>
<td>RCT</td>
<td>PEDro=9</td>
<td>33</td>
<td>Patients with central pain (15 stroke) were randomized to receive 50, 75 mg S(+) -ketamine or placebo administered daily for 5 days by an iontophoresis-assisted transdermal drug delivery system. The primary outcome was pain score, measured by VAS at days 5 and 7. Other outcomes included the Pain Disability Index, the EQ-5D and the SF-36.</td>
<td>1. At baseline, and days 5 and 7, there were no statistically significant differences in mean pain VAS scores among the groups. There were significant differences in Pain Disability Index scores and EQ-5D scores at 7 days, favouring the 75 mg ketamine group.</td>
</tr>
<tr>
<td>Andre-Obadia et al. (2006)</td>
<td>France</td>
<td>RCT</td>
<td>PEDro=8</td>
<td>14</td>
<td>Randomized, double-blinded, 25 min sessions of focal rTMS (1 Hz, 20 Hz and sham) were performed at 2 weeks intervals on 14 (10 stroke) patients suffering from chronic pain for a mean of 6.9 years. Pain was assessed using a 10-point VAS for across 5 days before, and 6 days after each session.</td>
<td>1. Data from 12 patients were available for analysis. At 1 week following treatment the mean percentage reductions in pain were 11% (20 Hz), +2% (1 Hz) and -8% (sham).</td>
</tr>
<tr>
<td>Rasche et al. (2006)</td>
<td>Germany</td>
<td>Post-Test</td>
<td>No Score</td>
<td>17</td>
<td>Long-term data was retrieved from 17 patients who underwent a MCS procedure between 1 and 10 (mean 3.6) years prior. 10 patients had trigeminal neuropathic pain (TNP) and 7 had post-stroke pain (PSP).</td>
<td>1. 50% of the TNP patients and 43% of the PSP patients had &gt;50% reduction of pain at follow-up. No lasting complications or seizures were observed during the follow-up. One patient experienced infections at surgical site 6 years post-procedure.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>PEDro</td>
<td>N</td>
<td>Population Details</td>
<td>Results</td>
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<tr>
<td>-------------------------------------------</td>
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<tr>
<td>Vranken et al. (2008)</td>
<td>Netherlands</td>
<td>RCT</td>
<td>9</td>
<td>40</td>
<td>40 patients with central pain (12 with stroke) were randomized to receive a 4-week course of treatment with escalating doses of pregabalin (max 600 mg/day) or placebo. The primary outcome was pain relief, measured on a 10-point VAS and was based on an average of 3 measurements scored within the last 24 hours of treatment. Other outcomes included Pain Disability Index and EQ-5D and quality of life (SF-36).</td>
<td>1. By 4 weeks, patients in the pregabalin group experienced significantly greater pain relief (mean=7.4 to 7.3 vs. 7.6 to 5.1, p=0.01). There was no significant difference in Pain Disability Index scores between groups. Patients in the pregabalin group had significant improvement in EQ-5D scores and in the bodily pain domain of the SF36. In the other domains, more favourable scores were reported without reaching statistical significance.</td>
</tr>
<tr>
<td>Vranken et al. (2011)</td>
<td>Netherlands</td>
<td>RCT</td>
<td>9</td>
<td>48</td>
<td>48 patients with central pain were randomized to receive escalating doses of either duloxetine (60 and 120mg/day) or matching placebo capsules for 8 weeks. In both groups, patients started with 1 capsule per day. If pain relief was insufficient, patients were titrated to a higher dose. The primary outcome was pain relief assessed using a 10-point VAS.</td>
<td>1. A trend towards a decrease in mean pain score after eight weeks was observed for duloxetine treatment (7.2 to 6.1 vs. 7.1 to 5.0 p=0.05). There were no differences between groups in PDI or EQ-5D scores but patients in the duloxetine group reported better pain scores on the bodily pain subdomain of the SF-36.</td>
</tr>
<tr>
<td>Fagundes-Pereyra et al. (2010)</td>
<td>Brazil</td>
<td>Pre-Post</td>
<td></td>
<td>27</td>
<td>27 patients with chronic neuropathic pain. 10 patients with post-stroke pain received motor cortex stimulation following surgery to implant 4 electrodes. Pain was assessed before and after treatment using a 0-10 point VAS.</td>
<td>1. Mean VAS scores decreases significantly from 7.9 to 3.8 (p&lt;0.001). 15 patients experienced a 50% or more reduction in pain; while in ten patients (38.5%), more than 60% of the original pain was relieved.</td>
</tr>
<tr>
<td>Kim et al. (2011)</td>
<td>Korea</td>
<td>RCT</td>
<td>9</td>
<td>220</td>
<td>220 patients with CPSP were randomized to receive either 150-600 mg of pregabalin (n=110) or placebo (n=109) over 13 weeks. The primary endpoint was the mean pain score on the Daily Pain Rating Scale over the last 7 days on study drug up to week 12 or early termination visit.</td>
<td>1. The mean pain scores were reduced from 6.5 to 4.9 in the pregabalin group and from 6.3 to 5.0 in the placebo group. The difference was not statistically significant. (p=0.578). Treatment with pregabalin resulted in significant improvements, compared with placebo, on secondary endpoints including some aspects of sleep, anxiety (HADS-A), and clinician global impression of change (CGIC) P&lt;0.05. Adverse events were more frequent with pregabalin than with placebo and caused discontinuation in 9 (8.2%) of pregabalin patients versus 4 (3.7%) of placebo patients.</td>
</tr>
<tr>
<td>Lefaucheur et al. (2011)</td>
<td>France</td>
<td>Pre-Post</td>
<td></td>
<td>6</td>
<td>6 patients with CPSP resistant for more than 1 year to at least 3 analgesic medications were surgically implanted with an 8-contact lead for motor cortex stimulation. Pain was assessed using a 0-100 point VAS, the Brief Pain Inventory (BPI)(0-100) and the McGill Pain Questionnaire. Additional assessments included the Sickness Impact Profile and the Patient Global Assessment of Change scale. All assessments were conducted before implantation and at months 1,3,6 and 12.</td>
<td>1. Compared with preoperative baseline, 2 patients were totally relieved of central poststroke pain, 3 patients were very much relieved, and 1 patient remained unchanged at the final examination.</td>
</tr>
</tbody>
</table>

Case had post-operative speech arrest for 3 months which was then completely resolved.
10-point VAS. Additional outcomes included Patient Disability Index (PDI), EQ-5D, SF-36 and the Patients Global Impressions of Change (PGIC).

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>PEDro</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho et al. (2013)</td>
<td>Korea</td>
<td>RCT</td>
<td>6</td>
<td>16</td>
<td>16 inpatients with central post-stroke pain (VAS&gt;4) were randomized to receive either 0.005% bee venom diluted in saline (treatment group) or normal saline (control group) twice weekly for three weeks. VAS score of pain severity was assessed at baseline and after 3 weeks.</td>
</tr>
<tr>
<td>Jungehulsing et al. (2013)</td>
<td>Germany</td>
<td>RCT</td>
<td>8</td>
<td>42</td>
<td>42 patients with CPSP of at least 3 months duration and a pain score ≥ 4 on an 11-point Likert scale were treated over two 8-week periods with Levetiracetam (max dose 3000 mg) or placebo. The primary endpoint was a median pain lowering at least 2 points in the final treatment week compared with the last baseline week. Secondary outcome measures included additional pain ratings, depression, sleep quality, quality of life and patients’ global impression of change.</td>
</tr>
<tr>
<td>Kobayashi et al. (2015)</td>
<td>Japan</td>
<td>PCT</td>
<td>No Score</td>
<td>20</td>
<td>Population: Mean age: 63.0+/−9.9yr; Gender: Males=12, Females=6. Intervention: 12 patients received real focal 5Hz rTMS delivered to the scalp over the primary motor cortex of the affected hemisphere. Each rTMS session was repeated once per week for 12 weeks. 6 patients received sham rTMS was performed using the same stimulation parameters (noise, time, frequency) as real rTMS. Outcomes: Poststroke pain: Visual Analog Scale (VAS).</td>
</tr>
<tr>
<td>Hesami et al. (2015)</td>
<td>Iran</td>
<td>Pre-Post</td>
<td>No Score</td>
<td>84</td>
<td>Population: Age Range: &lt;40yr(n=4), 41-50yr(n=12), 51-60yr(n=26), 61-70yr(n=29), &gt;70yr(n=13); Gender: Males=44, Females=40. Intervention: All participants received gabapentin (300mg 2x/d over 1mo) for the treatment of central post-stroke pain. Outcomes were assessed at baseline and post treatment. Outcomes: Numeric Rating Scale (NRS).</td>
</tr>
</tbody>
</table>

1. There was significant decrease in VAS after three weeks in both groups when compared with baseline (p<0.05). Treatment group had a significant improvement in VAS scores when compared with the control group (p=0.009).

1. 33 patients completed the study. Side effects and withdrawals were more frequent in the treatment group (n = 5 vs. n = 1). At the end of the active treatment period there was no significant improvement in median pain scores between groups or in any of the secondary outcomes.

1. There was a statistically significant main effect of time on VAS score (p<0.001). This was indicative of the maintained effects of rTMS applied weekly, on relief of poststroke pain.

2. There was a statistically significant time x group interaction (p<0.01); post-hoc tests showed that there was a statistically significant decrease in VAS scores for the rTMS group. This suggested that 5-Hz rTMS procedure reduced VAS scores, whereas the sham procedure did not.

3. The maximum reduction of the VAS value ranged from 5 to 70 (mean 36.7 ± 21.1) from the 8th to 12th week.

17.8 Fatigue Post Stroke

17.8.1 Prevalence of Post-Stroke Fatigue

Table 17.8.1 Prevalence of Post-Stroke Fatigue

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>PEDro</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>10-point VAS. Additional outcomes included Patient Disability Index (PDI), EQ-5D, SF-36 and the Patients Global Impressions of Change (PGIC).</td>
</tr>
</tbody>
</table>

www.ebrsr.com
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schepers et al. (2006)</td>
<td>Netherlands</td>
<td>Observational</td>
<td>N=167</td>
<td>167 patients admitted with first-ever supratentorial stroke for inpatient rehabilitation were included. Fatigue was assessed at admission, 6 months and 1 year. The Fatigue Severity Scale was used. A score of ≥4 was considered positive.</td>
<td>1. At admission, 6 months and 1 year, fatigue was identified in 51.5%, 64.1% and 69.5% of patients.</td>
</tr>
<tr>
<td>Van De Port et al. (2007)</td>
<td>Netherlands</td>
<td>Observational</td>
<td>N=223</td>
<td>223 patients admitted for inpatient stroke rehabilitation from 4 centres were included. The Fatigue Severity Scale was used. A score of ≥4 was considered positive.</td>
<td>1. At 6, 12 and 36 months post stroke, fatigue was identified in 68%, 74% and 58% of patients.</td>
</tr>
<tr>
<td>Christensen et al. (2008)</td>
<td>Denmark</td>
<td>Observational</td>
<td>N=165</td>
<td>165 ischemic or hemorrhagic stroke patients admitted to 3 stroke units were included and a reference group of 1,069 people from the Civil Registration system were included. Fatigue was assessed at 10 days, 3 months, 1 year and 2 years following stroke onset. The Multidimensional Fatigue Inventory was used. Score of ≥12 was considered positive.</td>
<td>1. At 10 days, 3 months, 1 year and 2 years following stroke onset, fatigue was identified in 59%, 44%, 38% and 40% of the patients respectively. This was considerably higher than that reported in the sample from the general population.</td>
</tr>
<tr>
<td>Snaphaan et al. (2011)</td>
<td>Netherlands</td>
<td>Observational</td>
<td>N=108</td>
<td>108 ischemic stroke patients admitted acutely to a neurology department were screened for fatigue at 2 months and 1.5 years after stroke onset. Fatigue was assessed using the Checklist Individual Strength. A score below 36 was considered positive.</td>
<td>1. The prevalence of fatigue was 35% and 33%, at 2 months and 1.5 years respectively.</td>
</tr>
<tr>
<td>Feigin et al. (2012)</td>
<td>New Zealand</td>
<td>Observational</td>
<td>N=613</td>
<td>613 ischemic stroke patients from the population-based Auckland Regional Community Stroke study, who were enrolled and followed for 6 months. Fatigue was assessed using the SF-36 Vitality Score</td>
<td>1. Fatigue was identified in 183 (30%) of patients at 6 months.</td>
</tr>
<tr>
<td>Hoang et al. (2012)</td>
<td>France</td>
<td>Observational</td>
<td>N=32</td>
<td>32 stroke patients recruited from the outpatient department of a rehabilitation hospital were included. Fatigue was assessed using the Fatigue Severity Scale at an average of 40 months following stroke. A score of ≥4 was considered positive.</td>
<td>1. Fatigue was identified in 11 (66%) patients.</td>
</tr>
<tr>
<td>Naess et al. (2012)</td>
<td>Norway</td>
<td>Observational</td>
<td>N=337</td>
<td>377 stroke patients, at least 6 months post stroke onset responded to postal questionnaire which included Fatigue Severity Scale (FSS), HADS and Barthel Index.</td>
<td>1. 42.3% of responders reported having post stroke fatigue (defined as FSS score ≥5)</td>
</tr>
<tr>
<td>Parks et al. (2012)</td>
<td>Canada</td>
<td>Observational</td>
<td>N=228</td>
<td>522 patients in the prospective Stroke Outcome Study (SOS) were enrolled and followed up at 1 year post stroke. 228 of the initial cohort completed follow-up. An interview was performed to determine various aspects of functioning and quality of</td>
<td>1. 36.8% (84/228) participants reported fatigue at least once a month at 12 months post stroke. Younger age at the time of stroke was the only significant predictor of increased fatigue measure at 12 months.</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Study Design</td>
<td>N</td>
<td>Population</td>
<td>Intervention</td>
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<tr>
<td><strong>Radman et al.</strong> (2012)</td>
<td>Switzerland</td>
<td>Observational</td>
<td>99</td>
<td>99 stroke patients with non-disabling stroke (NIHSS ≤ 6 in acute, ≤ 3 after 6 months; mRS score ≤ 1 at 6 months) were assessed at acute, 6 months and 12 months. Fatigue was assessed using the Fatigue Severity Scale.</td>
<td>Fatigue was reported in 30.5% at 6 months, and 34.7% at 12 months.</td>
</tr>
<tr>
<td><strong>Van Eijssen et al.</strong> (2012)</td>
<td>Netherlands</td>
<td>Observational</td>
<td>250</td>
<td>250 stroke patients were enrolled and followed up for 24 week. Measurement of fatigue was assessed using the Fatigue Severity Scale.</td>
<td>Fatigue was reported by 58.3% at T0 (baseline) and 55% at T1 (24 weeks). Mean FSS was 4.1 (SD 1.7) at both measurements.</td>
</tr>
<tr>
<td><strong>Badaru et al.</strong> (2013)</td>
<td>Nigeria</td>
<td>Observational</td>
<td>65</td>
<td>Population: Age range=58 to 80 yr; Gender: males=37, Females=28. Intervention: Prevalence of poststroke cases of fatigue and depression. Outcomes: Poststroke Fatigue (PSF): Fatigue Severity Scale (FSS); Poststroke Depression (PSD): Geriatric Depression Scale-14 (GSD-15).</td>
<td>The total number of fatigue cases was 30 and the total number of depression cases was 36, and 21 patients had both depression and fatigue.</td>
</tr>
<tr>
<td><strong>Miller et al.</strong> (2013)</td>
<td>USA</td>
<td>Observational</td>
<td>77</td>
<td>Population: Mean age=64.1yr; Gender: Males=58, Females=19. Intervention: Patients with chronic stroke competed a one-time assessment consisting of a battery of self-report and performance tools to describe and quantify mobility issues post stroke. Subgroup comparisons were made between participants with and without coexisting fatigue and pain. Outcomes: 10 Meter Walk Test (10MWT); 6 Minute Walk Test (6MWT); Berg Balance Scale (BBS); Chronic Disease Self-Efficacy Scale (CDSE); Activity-Specific balance Confidence Scale (ABC); Fatigue Severity Scale (FSS); Short pain scale (PEG); ICF Measure of Participation and Activities (IMPACT-A, IMPACT-P).</td>
<td>66% of participants reported high fatigue levels, and 45% reported high pain levels. Significant correlations were found between high fatigue levels and CDSE (r=-0.445, p&lt;0.0001), IMPACT-A (r=0.49, p&lt;0.0001), IMPACT-B (r=0.325, p=0.004), and ABC (r=-0.497, p&lt;0.0001). Significant correlations were found between high pain levels and scores on the CDSE (r=-0.372, p=0.001), IMPACT-A (r=0.306, p=0.007), and ABC (r=-0.416, p&lt;0.0001). 34% reported coexisting high pain and fatigue levels, and 22% reported coexisting low pain and fatigue levels. 3% reported coexisting high pain and fatigue levels. Individuals with high coexisting pain and fatigue levels had significantly worse CDSE, (p=0.003), IMPACT-A (p=0.007) and ABC (p=0.0001) scores compared to those with low coexisting fatigue and pain levels.</td>
</tr>
<tr>
<td><strong>Muina-Lopez et al.</strong> (2013)</td>
<td>Ireland</td>
<td>Observational</td>
<td>55</td>
<td>Population: Fatigue group (N=27): Mean age=67.04±9.16yr; Gender: Males=16, Females=11. No Fatigue group (N=28): Mean age=70.80±10.15yr; Gender: Males=19, Females=9. Intervention: Participants were recruited from the community and the presence/absence of fatigue was evaluated</td>
<td>A significant difference in NEADL scores was found between the two groups, with the no fatigue group being more independent (p=0.005). A significant difference was found in SSEQ scores between groups, indicating that the fatigue group had lower self-efficacy beliefs (p=0.000).</td>
</tr>
</tbody>
</table>

17. Medical Complications Post Stroke www.ebrsr.com
### Outcomes: Multidimensional Fatigue Inventory (MFI; general fatigue, physical fatigue, activity-related fatigue, motivational fatigue, mental fatigue); Nottingham Extended Activities of Daily Living Scale (NEADL); Stroke Self-Efficacy Questionnaire (SSEQ).

#### Naess et al. (2013)
Norway Observational N=190

**Population:** Mean age=48yr; Gender: Males=109, Females=81.

**Intervention:** The relationship between post-stroke fatigue and depression and subsequent mortality was prospectively analyzed from ischaemic stroke patients. Subjects were investigated on average 6yr after index stroke, and subsequently after a mean of 12.4yr.

**Outcomes:** Fatigue Severity Scale (FSS); Montgomery-Asberg Depression Rating Scale (MADRS).

1. Mortality was associated with fatigue (p=0.005) after adjusting for age (p=0.06) and sex (p=0.19).
2. Mortality was associated with depression (p=0.006) after adjusting for age (p=0.10) and sex (p=0.11).

#### Young et al. (2013)
UK Observational N=10

**Population:** Mean Age=52yr; Gender: Male=6, Female=4.

**Intervention:** Open-ended interviews were conducted for 20-45min.

**Outcomes:** Qualitative analysis of interview responses.

1. Restriction due to fatigue was reported in several patients in regards to self-care and participating in activities.
2. Frustration was expressed by all patients most commonly due to poor coping, boredom or lack of control.
3. Signs of depression or low mood were reported in many patients.
4. A sense of achievement when engaging in activities, the use of goal setting and the control of fatigue were reported by many patients.

#### Duncan et al. (2014)
UK Observational N<sub>Start</sub>=157 N<sub>End</sub>=86

**Population:** Participants who completed all 3 assessments (N=86): Median age (range)=71.8yr (63.5-79.8); Gender: Males=53, Females=33.

**Intervention:** The frequency, severity, and time course of clinically significantly fatigue in the first 12 months of stroke onset was assessed longitudinally. Assessments were conducted at the first month, at six months, and at 12 months.

**Outcomes:** Fatigue Assessment Scale (FAS).

**a change of 4 points on the FAS indicates a clinically relevant change in fatigue status**

1. Of those who attended all 3 assessments, clinically significant fatigue was present in 28% at 1mo, in 23% at 6mo and in 21% at 12mo.
2. A significant difference between 1mo and 6mo was found on the FAS (median values: 23 vs. 21; p=0.025), but not between 6mo and 12mo (median values: 21 vs. 22.5; p=0.19).
3. Of 101 patients who attended at least the 1m and the 6m assessments, fatigue status did not change in 64%, with 9% fatigued throughout, and 55% non-fatigued throughout; 15% became non-fatigued, 9% became fatigued, and in 12% fatigue status fluctuated across the assessments.

#### Ormstad et al. (2014)
Norway Observational N=45

**Population:** Mean Age=67.7yr; Gender: Male=27, Female=18.

**Intervention:** Conducted assessments on patients 6, 12 and 18mo post stroke.

1. FSS ≥4 62.2% at 6mo, 53.3% at 12mo and 64.0% at 18mo.
2. TRP index was significantly lower in patients with FSS ≥4 compared to patients with FSS
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Presence of: tryptophan (TRP) and kynurenic acid (KA) metabolites; Fatigue Severity Scale (FSS); and Beck Depression Inventory (BDI).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 at 12mo (FSS ≥4=12.8±2.4, FSS &lt;4=14.5±2.6, p=0.039).</td>
<td>1. VSH Sleep Scale scores were not significantly associated with hypertension, hyperlipidemia, metabolic syndrome or stroke subtype.</td>
<td></td>
</tr>
<tr>
<td>3. KA level was significantly higher in patients with FSS ≥4 compared to FSS &lt;4 at 18mo (FSS ≥4=57.0±24.5nM, FSS &lt;4=41.3±18.1nM, p=0.026).</td>
<td>2. VSH Sleep Scale scores were significantly lower in patients with cortical lesions compared to patients with lesions in other areas (p=0.049).</td>
<td></td>
</tr>
<tr>
<td>4. No other significant differences were found between patients with FSS ≥4 and FSS &lt;4.</td>
<td>3. Sleep duration was significantly shorter in patients hospitalized &lt;5d compared to patients hospitalized &gt;5d (p&lt;0.001).</td>
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<tr>
<td>5. No significant differences were observed between patients with BDI ≥10 and patients with BDI &lt;10.</td>
<td>4. Sleep latency was significantly longer in patients with depression (p&lt;0.001).</td>
<td></td>
</tr>
<tr>
<td>Population: Mean Age=62.34yr; Gender: Male=166, Female=116.</td>
<td>5. Waking after sleep was significantly more frequent in patients with depression (p=0.023) and in patients with fatigue (p=0.010).</td>
<td>1. FAS scores did not significantly differ over time among the patients, though the distribution of fatigue scores varied.</td>
</tr>
<tr>
<td>Intervention: Assesses stroke patients admitted to multiple centers from March 2009 to February 2010.</td>
<td>6. Increased daytime sleepiness was significantly more prevalent in patients with subcortical lesions (p=0.005), fatigue (p&lt;0.001) and poorer quality of sleep (p&lt;0.001).</td>
<td>2. From the 39 patients, 36% had one copy and 20% had 2 copies of the C allele of the rs4251961 SNP in IL1RN.</td>
</tr>
<tr>
<td>Outcomes: Length of stay; Verran-Snyder-Halpem (VSH) Sleep Scale; and Sleep characteristics: sleep duration, sleep latency, waking after sleep, daytime sleepiness, daytime sleep, nighttime sleep, number of patients in room, sleep apnea and snoring.</td>
<td>7. Daytime sleep was significantly more frequent in patients with subcortical lesions (p=0.001), previous stroke (p=0.033) and fatigue (p&lt;0.001).</td>
<td></td>
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<tr>
<td></td>
<td>8. Duration of daytime sleep was significantly greater in patients with a previous stroke (p=0.036), depression (p=0.025) and fatigue (p=0.042).</td>
<td></td>
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<tr>
<td></td>
<td>9. Daytime sleep was not significantly related to length of stay and number of patients in the room.</td>
<td></td>
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<tr>
<td></td>
<td>10. Sleep apnea and snoring were not significantly related to night or day sleep.</td>
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</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Population</td>
</tr>
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</tr>
<tr>
<td><strong>Kuppuswamy et al.</strong> (2015) UK Observational</td>
<td>N=70</td>
<td>Mean age=60.36±12.4yr; Gender: Males=50, Females=20.</td>
</tr>
<tr>
<td><strong>Tang et al.</strong> (2015) China Case Series</td>
<td>N=441</td>
<td>Pain (n=167): Mean Age=66.1yr; Gender: Male=79, Female=88; No Pain (n=274): Mean Age=66.1yr; Gender: Male=178, Female=96.</td>
</tr>
<tr>
<td><strong>Elf et al.</strong> (2016) Sweden Case Series</td>
<td>N=102</td>
<td>Mean Age=62±14yr; Gender: Male=57, Female=45.</td>
</tr>
</tbody>
</table>
### 17.8.2 Treatment of Post-Stroke Fatigue

#### Table 17.8.2 Treatment of Post-Stroke Fatigue

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Choi-Kwon et al. (2007) | Korea | RCT | PEDro=6 | N=83 | 83 consecutive outpatients with post stroke fatigue (PSF) at an average of 14 months after the onset of stroke were randomized to receive 20 mg/day of fluoxetine (n = 40) or placebo (n = 43) for 3 months. PSF was assessed at baseline, and 3 and 6 months post stroke using a visual analogue scale (VAS) and Fatigue Severity Score (FSS). The presence of post-stroke depression, post-stroke emotional incontinence and post-stroke anger proneness were also evaluated. | 1. There were no differences in the number of patients with PSF between the fluoxetine group and the placebo group at 3 and 6 months after the treatment.  
2. The percent changes in VAS scores and FSS at all follow-up assessments were not significantly different either.  
3. Fluoxetine significantly improved post-stroke emotional incontinence (p < 0.05) and post-stroke depression (p = 0.05) in the patients with PSF. |
| Brioschi et al. (2009) | Switzerland | Pre-Post No Score | N=40 | 14 brainstem or diencephalic stroke (BDS) patients, 9 cortical stroke (CS) patients and 17 multiple sclerosis (MS) patients were included in this non-placebo controlled study which aimed to compare fatigue observed in different neurological pathologies, to evaluate the tolerability to modafinil, and to describe changes in subjective fatigue. The Fatigue Assessment Instrument severity scale was performed at baseline, after 3 months of modafinil and after 1 month of washout. Cognition, mood and somnolence were assessed. A subgroup of 14 patients underwent activity measures before and during treatment. | 1. Thirty-one patients completed the study (10 BDS, 9 CS, 12 MS). The responder profile is more frequent in MS than in CS (p = 0.04), and in BDS than in CS patients (p = 0.04).  
2. Actiwatch measures showed no changes in activity during, before and after therapy.  
3. Modafinil was tolerated in 75% of patients at small doses and seemed to improve the severity of fatigue in the MS and BDS groups but not in the CS group. |
<p>| Clarke et al. (2012) | New Zealand | RCT | PEDro=4 | N=16 | 16 individuals 3 to 18 months post incident stroke with PSF were allocated to a Fatigue Management Group (FMG) or General Stroke Education (GSE) control group. The treatment group received 6 psychoeducational sessions (60 minutes each) including sessions on sleep/relaxation, exercise and nutrition, mood and review of fatigue diaries. Patients in the control group also received 6 psychoeducational sessions (60 minutes each) that were not fatigue-focused. Assessments were conducted before and after treatment and at the 3-month follow-up. The primary outcome was the Fatigue Severity Scale. | 1. Both groups had significantly reduced FSS fatigue at the end of follow-up, but the mean FSS score of patients in the FMG was not significantly different than that of patients in the GSE group (5.69 to 4.548 vs. 5.16 to 4.62, p=0.71). |
| Johansson et al. (2012) | RCT | PEDro=9 | N=12 | 6 patients with stroke and 6 patients with traumatic brain injury were given monoaminergic stabiliser OSU-6162 or placebo for 4wk, followed by the alternate treatment for 4wk. Fatigue was measured using the Mental Fatigue Scale before and after each treatment. | 1. OSU-6162 showed significantly greater improvement in fatigue than placebo (F=5.27, p=0.031). |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Johansson et al. (2012)</strong></td>
<td>18</td>
<td>Modafinil</td>
<td>Fatigue Stroke Scale (FSS)</td>
</tr>
<tr>
<td><strong>Karaioskos et al. (2012)</strong></td>
<td>60</td>
<td>Duloxetine</td>
<td>Fatigue Stroke Scale (FSS)</td>
</tr>
<tr>
<td><strong>Zedlitz et al. (2012)</strong></td>
<td>73</td>
<td>Modafinil</td>
<td>Fatigue Stroke Scale (FSS)</td>
</tr>
<tr>
<td><strong>Costantini et al. (2014)</strong></td>
<td>N=3</td>
<td>Oral or parenteral therapy with high-dose thiamine</td>
<td>Fatigue Stroke Scale (FSS)</td>
</tr>
<tr>
<td><strong>Poulsen et al. (2015)</strong></td>
<td>N=41</td>
<td>Modafinil</td>
<td>Fatigue Severity Scale (FSS); Stroke Specific Quality of Life (QoL)</td>
</tr>
<tr>
<td><strong>Liu et al. (2016)</strong></td>
<td>N=64</td>
<td>Astragalus Membranaceus</td>
<td>Fatigue Severity Scale (FSS); Stroke Specific Quality of Life (QoL)</td>
</tr>
</tbody>
</table>

1. Statistically significant improvement was achieved in the self-assessment for mental fatigue.  
2. Statistically significant improvements were achieved in neuropsychological tests (Digit Symbol-Coding and Trail Making Test).

1. None of the medications showed significant improvements in fatigue over time.  
2. There were no significant differences in fatigue between groups.

1. The qualification period showed stable outcome measures.  
2. Both treatments showed significant beneficial effects on fatigue (CIS-f; ηp²=0.48, P<0.001) and other outcomes (except pain and anxiety) with intention-to-treat analyses.  
3. Gains for the COGRAT group exceeded those in the CO group with individuals showing clinical improvement on the CIS-f (≥8 points: 58% versus 24%) and on physical endurance (ηp²=0.20, P<0.001).

1. All patients showed an improvement (i.e., relief from fatigue and related symptoms), within a week of treatment initiation.  
2. For patient 1, the FSS score was 10 points (decrease of 74.4%); for patient 2, the FSS score was 14 points (decrease of 62.4%); for patient 3, the FSS score was 9 points (complete regression of the fatigue). Qualitative results indicated that the therapy led to an appreciable (subjective) level of fatigue improvement.

1. The EG group showed significantly greater improvements on FSS (p=0.02) and QoL (p<0.05) over time compared to the CG group.

1. The EG group showed a significantly greater improvement in BFI scores at both post treatment (p=0.01) and 85d follow-up (p=0.05) compared to the CG group.
to receive 2.8g of oral astragalus membranaceus 3x/d for 28d (EG) or a placebo for the same duration (CG). Outcomes were assessed at pre, post, and 85d follow-up after treatment.

**Outcomes:** Brief Fatigue Index (BFI).

### 17.9 Insomnia Post Stroke

**Table 17.9 Treatment of Post-Stroke Insomnia**

<table>
<thead>
<tr>
<th>Author, Year Country Study Design PEDro Score Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kim et al.</strong> (2004) Korea RCT PEDro=7 N=30</td>
<td>30 in-patients with stroke and persistent insomnia were randomized to either a treatment group that received real intradermal acupuncture or a control group that received sham acupuncture. Interventions were delivered for two days. The Morning Questionnaire (MQ), Insomnia Severity Index (ISI), and Athens Insomnia scale (AIS) were assessed at baseline, and at one and two days after treatment.</td>
<td>1. There was an improvement in insomnia (as measured by MQ, ISI and AIS) after 2 days in the treated group.</td>
</tr>
<tr>
<td><strong>Lee et al.</strong> (2009) Korea RCT PEDro=7 N=52</td>
<td>52 in-hospital patients with stroke and insomnia were randomized to either a treatment group that received intradermal acupuncture or a control group that received sham acupuncture. Interventions. Both treatments were delivered for three days. The Insomnia Severity Index (ISI), and Athens Insomnia scale (AIS) were assessed at baseline, and three days after treatment.</td>
<td>1. After treatment, there was a significantly greater decrease in ISI scores in the treatment group when compared with the control group (p&lt;0.001). 2. Similarly, there was a greater significant decrease in AIS scores in the treated group when compared with the control group (p&lt;0.001) after treatment.</td>
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<td><strong>Cai et al.</strong> (2015) China RCT PEDro=5 TPS=14-180d N=154</td>
<td><strong>Population:</strong> Acupoint+Music group [EG; n=77]: Mean Age=63.9±10.4yr; Gender: Male=40, Female=37. Acupoint group [CG; n=77]: Mean Age=64.5±12.6yr; Gender: Male=43, Female=34. <strong>Intervention:</strong> Participants with post-stroke insomnia were randomly allocated to receive a combination of auricular acupoint sticking and music therapy (EG) or auricular acupoint sticking alone (CG) for 30d. Outcomes were assessed at baseline, post treatment, and 30d follow-up. <strong>Outcomes:</strong> Total Effectiveness Rate.</td>
<td>1. The EG group had an effectiveness rate of 98.7% at post treatment and 90.9% at follow-up, whereas the CG group had an effectiveness rate of 89.6% at post treatment and 80.5% at follow-up. 2. There was a significantly greater improvement in the EG group compared to the CG group in Effectiveness rate at both post treatment and follow-up (all p&lt;0.05).</td>
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References


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