Medical Complications Post Stroke

Norine Foley MSc, Andreea Cotoi MSc, Norhayati Hussein MBBS, Ashna Jinah MSc, Emma A. Bateman MD, Robert Teasell MD

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Abstract

Medical complications post-stroke are defined as medical or neurological problems that necessitate a physician’s order and require close attention and monitoring by medical staff (Chen et al. 2014; Dromerick & Reding 1994). These complications are separate from issues related to secondary stroke prevention, occur relatively frequently, and contribute to poor health outcomes (Doshi et al. 2003). Although the number of potential medical complications can be extensive for a given patient, the focus of this review is five of the most common and clinically relevant medical complications in the short- and long-term: urinary incontinence, venous thromboembolism, seizures, osteoporosis, central pain states, and post-stroke fatigue. As such, an understanding of these disorders is critically important to stroke care and management.
Key Points

Medical Complications
- Medical complications are common post stroke, occurring in 44-96% of patients, and vary significantly between studies. Some of these complications include cardiovascular complications (i.e. myocardial infarction, recurrent strokes, venous thromboembolism), pulmonary complications (i.e. chest infections, pneumonia), mood disorders (i.e. depression and other mood disturbances), complex pain (i.e. hyperalgesia and abnormal sensations), urinary/bowel complications (i.e. incontinence, constipation, and urinary tract infections), seizures, pressure sores, ulcers, fractures, and falls.

Urinary and Fecal Incontinence
- Urinary incontinence is a common post-stroke complication. Additional research is required for the effectiveness of pharmacologic therapies, prompted voiding interventions, pelvic muscle training programs, complementary and alternative therapies, and functionally-oriented rehabilitation approaches.
- Indwelling urinary catheters (IUCs) may be helpful in cases of intractable urinary retention, continuous wetness or the need for fluid balance or urine output monitoring. IUCs should be removed if not absolutely needed due to their association with poorer patient outcomes. Further research examining the impact of IUCs on bladder reconditioning is required.
- There is limited research regarding treatments for fecal incontinence post stroke.

Venous Thromboembolism (VTE)
- Deep vein thrombosis (DVT) and pulmonary embolism (PE) are common and serious post-stroke complications. DVT is more likely to occur in patients who do not receive DVT prophylaxis.
- Several randomized, controlled clinical trials have assessed the efficacy and safety of heparinoid medications for VTE prophylaxis. However, these studies do not use a rehabilitative stroke population. Enoxaparin may be preferable to other heparinoids due to its lower risk of major bleeding.
- Evidence for the effectiveness of compression stockings on preventing DVT is unclear. However, evidence suggests that intermittent pneumatic calf compression devices may help prevent the occurrence of DVT.

Seizures
- The incidence of post-stroke seizures varies among studies.
- Insufficient evidence exists to guide selection of monotherapy for antiepileptic medications in patients with post-stroke seizures. Treating all stroke patients with anticonvulsants as primary seizure prophylaxis is not recommended. The decision to initiate antiepileptic therapy should be tailored to patients' individual needs.

Osteoporosis
• Treatment with bisphosphonates or vitamin D derivatives may help to preserve bone density post stroke. Further research is required to examine the effect of treatment with vitamin D derivatives and estrogen products on osteoporosis and associated fractures.

Central Pain States
• A broad range of drug treatments are available for the treatment of central pain post stroke; however, the majority of these require further study for their effectiveness on pain reduction.

Fatigue
• More research is needed to determine treatment options for post-stroke fatigue.

Insomnia
• Acupuncture may be effective at treating post-stroke insomnia; however, more research is required.

Dr. Robert Teasell
Parkwood Institute, 550 Wellington Road, London, Ontario, Canada, N6C 0A7
Phone: 519.685.4000 ● Web: www.ebrsr.com ● Email: Robert.Teasell@sjhc.london.on.ca
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17.1 Type and Frequency of Medical Complications Post Stroke

Medical complications are common after acute stroke and contribute to adverse patient outcomes, delayed functional recovery, morbidity, and mortality. Medical complications post stroke are defined as medical or neurological problems that necessitate a physician’s order and require close attention and monitoring by medical staff (Chen et al. 2014; Dromerick & Reding 1994). Reports of the percentage of patients experiencing one or more medical complications after acute stroke vary widely, from 44 to 95% (McLean 2004). Complications tend to occur more frequently in older patients and patients with more severe strokes (Davenport et al. 1996). These complications are separate from issues related to secondary stroke prevention, occur relatively frequently, and contribute to poor health outcomes despite being potentially treatable (Doshi et al. 2003). For instance, the development of medical complications in acute care may result in delayed transfer to inpatient stroke rehabilitation. Roth et al. (2007) reported that in a cohort of 2,457 consecutively admitted patients with acute stroke, medical complications arising after stroke was the single greatest factor in a model for determining the number of days until patients could enter rehabilitation after stroke onset, accounting for 17.3% of the variance. In this study, the most common complications contributing to the delay were pneumonia and urinary tract infections (UTI) (Roth et al. 2007).

Medical complications can affect one or many body systems, including but not limited to depression, delirium, constipation, gastrointestinal bleeding, falls, fractures, congestive heart failure, myocardial ischemia, urinary incontinence, and pneumonia and/or other infections. Although the number of potential medical complications can be extensive for an individual patient, this review focuses on five of the most common and clinically significant medical complications in the short- and long-term: urinary incontinence, venous thromboembolism, seizures, osteoporosis and central pain states. Understanding the complications after acute stroke is crucial to preventing, identifying, and treating them to reduce adverse patient outcomes.

Table 17.1.1 Summary of Incidence of Common Medical Complications

<table>
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<tr>
<th>Author, Year</th>
<th>Sample Size</th>
<th>Complication (%)</th>
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| Dromerick & Reding (1994) N=100 | Incidence of complications in inpatient stroke rehabilitation: | • Urinary tract infection (44%)  
• Urinary retention (25%)  
• Pneumonia (7%)  
• Pulmonary embolus (0%)  
• Deep vein thrombosis (4%)  
• Musculoskeletal pain (31%)  
• Fall (25%)  
• Average number of medical complications per patient: 3.6  
• At least one medical complication occurred in 96% of patients  
• 13% of patients required transfer to acute care due to medical complications  
• 1% of patients died |
| Kalra et al. (1995) N=245 N_stroke=124 N_ward=121 | Patients with acute stroke managed on a stroke unit vs general medical ward: | • Urinary tract infection (17% vs 33%, p<0.01)  
• Urinary catheterization (7% vs 18%, p<0.01)  
• Aspiration (33% vs 20%, p<0.01)  
• Chest infection (8% vs 16%, p<0.05)  
• Deep vein thrombosis (3% vs 7%, NS)  
• Musculoskeletal pain (38% vs 23%, p<0.05)  
• At least one medical complication occurred in 60% of patients  
• 7.8% of patients died |
| **Davenport et al.** (1996) | Complications after acute stroke in a single acute care hospital:  
N=613  
Urinary tract infection (16%)  
Chest infection (12%)  
Deep vein thrombosis (3%)  
Fall (22%)  
Fracture (3%)  
Epileptic seizure (4%)  
At least one medical complication occurred in 59% of patients  
22.1% of patients died in hospital |
| **Johnston et al.** (1998) | Most common serious medical events in patients with acute ischemic stroke:  
N=279  
Urinary tract infection (11%)  
Pneumonia (all types) (10%)  
Aspiration pneumonia (6%)  
Deep vein thrombosis (2%)  
Congestive heart failure (11%)  
Angina/myocardial infarct/cardiac ischemia (6%)  
Gastrointestinal bleed (5%)  
Seizure (3%)  
At least one medical complication occurred in 95% of patients  
14% of patients died within 3 months of stroke onset |
| **Langhorne et al.** (2000) | Incidence of complications in hospitalized patients with acute stroke:  
N=311  
Urinary tract infection (23%)  
Chest infection (22%)  
Pulmonary embolism (1%)  
Deep vein thrombosis (2%)  
Pain, shoulder (9%)  
Pain, non-shoulder (34%)  
Pressure sore (21%)  
Fall (25%)  
At least one medical complication occurred in 85% of patients  
19% of patients died in hospital |
| **Roth et al.** (2001) | Incidence of new or exacerbated medical complications during inpatient stroke rehabilitation, proportion requiring transfer to acute care:  
N=1029  
Urinary tract infection (30.5%, 3.2%)  
Pneumonia (4.0%, 47.6%)  
Deep vein thrombosis (4.1%, 83.3%)  
Pulmonary embolism (1.1%, 60%)  
Peptic ulcer disease and gastrointestinal bleed (3.1%, 48.4%)  
Seizure (1.5%, 80%)  
At least one medical complication occurred in 75% of patients  
19% of patients required transfer to acute care due to medical complications  
0.3% of patients died |
| **Doshi et al.** (2003) | Incidence of complications in inpatient stroke rehabilitation:  
N=140  
Urinary tract infection (14.3%)  
Urinary retention (20.9%)  
Deep vein thrombosis (0.7%)  
Pulmonary embolism (0%)  
Constipation (22.9%)  
Seizure (0.7%)  
At least one medical complication occurred in 54.3% of patients  
There were no reported deaths |
| **McLean** (2004) | Incidence of complications in inpatient stroke rehabilitation:  
N=133  
Urinary tract infection (15%) |
• Pneumonia (2%)
• Depression (26%)
• Fall (20%)
• Shoulder pain (24%)
• Shoulder-hand syndrome (1.5%)
• Seizure (1.5%)
• At least one medical complication occurred in 67% of patients
• 2.3% of patients died

**Hung et al.** (2005)  
N=346  
Incidence of complications in inpatient stroke rehabilitation:  
• Urinary tract infection (13.6%)
• Pneumonia (4.9%)
• Depression (9.3%)
• Pressure sore (1.5%)
• Seizure (1.2%)
• At least one medical complication occurred in 44% of patients
• 2.9% of patients required transfer to acute care due to medical complications
• 0.3% of patients died

**Kitisomprayoonkul et al.** (2010)  
N=118  
Incidence of complications in inpatient stroke rehabilitation:  
• Urinary tract infection (17.8%)
• Pneumonia (4.2%)
• Depression (56.6%)
• Musculoskeletal pain (28%)
• Complex Regional Pain Syndrome-1 (15.3%)
• At least one medical complication occurred in 70.3% of patients
• 11.8% of patients required transfer to acute care due to medical complications

**Rohweder et al.** (2015)  
N=244  
Frequency of pre-selected complications within the first 90 days of acute stroke:  
• Urinary tract infection (28%)
• Myocardial infarction (7%)
• Pulmonary embolism (1.2%)
• Chest infection (17%)
• Other infection (13%)
• Fall (29%)
• Pain (57%)
• The frequency of death was not reported

**Shah et al.** (2015)  
N=14293  
Frequency of complications after acute stroke or transient ischemic attack in patients with language barriers compared to those without language barriers:  
• 7-day mortality (7.0% vs 9.2%, p<0.001)
• 30-day mortality (14.6% vs 15.7%, p<0.001)
• 1-yr mortality (25.6% vs 26.8%, p<0.001)
• Pneumonia (6.5% vs 9.2%, NS)
• Thromboembolic complication (1.5% vs 1.4%, NS)
• 15.6% of patients died within 30 days of acute stroke

**Discussion**
Numerous studies—large and small, prospective and retrospective, cohort and observational—have investigated the incidence of medical complications after acute stroke of multiple etiologies in a variety of settings, including acute care, inpatient stroke rehabilitation, and after discharge. As summarized in Table 17.1.1, these studies report variable rates of medical complications. The discrepancies in medical complication rates is likely multifactorial, including different study designs, differences between the acute care and inpatient rehabilitation setting, varying diagnostic criteria for medical complications, pre-selection of complications to be studied, different patient selection methods, and inherent differences in the populations studied, such as country of origin. Moreover, potential sources of bias can confound
the accurate reporting of complications. Sicker patient populations have medical records that tend to be
more difficult to trace, they often over-represent complex clinical cases, and have an increased
likelihood of death compared to survivors, who may be in a better position to receive acute care and
rehabilitation (Davenport et al. 1996). Retrospective identification of complications, case note retrieval
bias (i.e. obtaining information about patients who may have deceased earlier), and inter-observer bias
(i.e. the ability of one or more observers to accurately retrieve medical information from patient
records) may be factors contributing to the variability of complication reporting (Davenport et al. 1996).

In a large, prospective, multicentre cohort study in Scotland, UK, Langhorne et al. (2000) reported that
that the majority of complications experienced during acute care hospital stay included pressure sores,
pain and infections. In this study, approximately 85% of patients experienced at least 1 pre-specified
complication during their time in hospital after acute stroke (Langhorne et al. 2000). In a randomized,
retrospective study comparing complication rates between general medicine ward and specialized
stroke unit in patients 2 weeks after acute stroke, Kalra et al. (1995) reported that patients admitted to
a specialized stroke unit within acute care had fewer chest infections, episodes of aspiration, UTIs, and
musculoskeletal pain compared with patients admitted to general wards.

In a single-centre prospective cohort study of 1029 patients in inpatient stroke rehabilitation in Chicago,
IL, USA, Roth et al. (2001) reported that 75% of patients experienced at least one medical complication
during their inpatient rehabilitation stay. UTIs, soft tissue pain, depression, falls and elevated blood
pressure were the most common complications; 19% of patients required transfer back to acute care for
the management of medical complications. In this study, patients most likely to experience a
complication post stroke were those with greater severity of stroke, hypoalbuminemia, and a history of
hypertension. Both McLean (2004) and Kitisomprayoonkul et al. (2010) found depression, UTIs, and
musculoskeletal pain to be common, but they reported much lower frequency of certain medical events
than in other studies, specifically pneumonia, gastrointestinal disturbances, seizures and pressure
ulcers. In a prospective study of 133 patients admitted to a single stroke rehabilitation centre in Nova
Scotia, Canada, McLean (2004) reported that 67% of patients experienced at least one complication post
stroke, and 25% experienced two or more complications. The most frequently reported complications in
their study were depression (26%), shoulder pain (24%), falls (20%) and UTIs (15%). The author also
suggested that certain patient characteristics such as age, disability before stroke onset, and stroke
severity may predict the likelihood of complications post stroke. In a prospective study of 118 patients
admitted to inpatient rehabilitation in Bangkok, Thailand, Kitisomprayoonkul et al. (2010) found that
70.3% of patients experienced at least one medical complication. Depression was the most commonly
reported complication, occurring in 56.6% of patients. The only consistent predictive factor for
complications post stroke between these studies was severity of initial stroke (Kitisomprayoonkul et al.
2010; McLean 2004; Roth et al. 2001).

Within acute care, medical complications in patients after acute stroke were frequent, ranging from 59%
to 95% (Davenport et al. 1996; Johnston et al. 1998). For patients admitted for inpatient stroke
rehabilitation in tertiary rehabilitation centres, the rates of medical complications post stroke were also
high, ranging from 44% to 96% (Dromerick & Reding, 1994; Hung et al. 2005). Of these patients, 2.9-19%
required transfer to an acute care hospital for diagnosis, treatment, or management (Hung et al. 2005;
Roth et al. 2001). Although the relative frequency of each complication differs between these two
settings, the high incidence of medical complications post stroke clearly has implications for attending
and progressing through rehabilitation to improve patients’ functional status.

Conclusions Regarding Frequency of Medical Complications Post Stroke
Medical complications are common post stroke, occurring in 44-96% of patients, and vary significantly between studies. Some of these complications include cardiovascular complications (i.e. myocardial infarction, recurrent strokes, venous thromboembolism), pulmonary complications (i.e. chest infections, pneumonia), mood disorders (i.e. depression and other mood disturbances), complex pain (i.e. hyperalgesia and abnormal sensations), urinary/bowel complications (i.e. incontinence, constipation, urinary tract infections), seizures, pressure sores, ulcers, fractures, and falls.

17.2 Urinary Dysfunction Following Stroke

17.2.1 Disorders of Voiding
Disorders of voiding, also known as voiding dysfunction, refers to bladder and urinary problems or abnormalities in the process of urination as a consequence of underlying nervous system pathology. In adults with stroke, voiding dysfunction is common (Marinkovic & Badlani 2001). Urinary incontinence has been reported to occur in 30 to 70% of patients post stroke, and is an independent predictor of death, disability, and discharge to a long-term care facility (Brittain et al. 1999; Sreeraj et al. 2012; van Kuijk et al. 2001). The prevalence of urinary retention has been reported in 21% to 47% of adults with stroke (Burney et al. 1996; Doshi et al. 2003). Given the high frequency of these two types of voiding dysfunction, clinicians must address and manage complications related to overactive bladder, incontinence, and retention in their post-stroke patients (Linsenmeyer 2012; McKenzie & Badlani 2012; Mehdi et al. 2013).

17.2.2 Prevalence of Urinary Incontinence Post Stroke
Urinary incontinence (UI) is a common problem following stroke: its incidence ranges from 21% to 79% (Brittain et al. 1999; Doshi et al. 2003; Sreeraj et al. 2012; van Kuijk et al. 2001). However, UI post stroke usually resolves spontaneously (without intervention or treatment) within 8 weeks of stroke onset (Borrie et al. 1986; Brocklehurst et al. 1985). Of all patients experiencing UI post stroke, 14-19% may develop UI that persists at 6 months post stroke (Barer 1989; Nakayama et al. 1997). UI tends to be most frequent in patients with more severe strokes and in patients with pre-morbid incontinence (Nazarko 2003; Brittain et al. 1999). Normal age-related changes in bladder function may also independently affect recovery (Marinkovic & Badlani 2001). In patients with previously normal bladder function, other risk factors for developing UI post stroke vary by study; Brittain et al. (1999) implicated persistent stroke-related motor weakness, ataxia, and/or sensory abnormalities, altered level of consciousness, and cognitive impairment, whereas Jorgensen et al. (2005) identified depression, lower extremity motor weakness, and cognitive impairment as risk factors for incontinence. Gariballa (2003) found that patients with UI at admission tended to be more undernourished and dehydrated, more impaired, at greater risk for infective complications, and older than patients without UI, underscoring the clinical significance of UI.

Discrepancies in the reported rates and contributing factors likely arise from differing definitions of incontinence, the timing of assessment for UI post stroke, survey methods, and populations under study. Furthermore, variable reporting may reflect the fact that UI is common even amongst healthy elderly persons, particularly women (Brooks 2004). The prevalence of UI in women is estimated at 1.3 to 4.5 times greater than in men (Jorgensen et al. 2005). In general, UI is divided into three types: urge urinary incontinence (UUI), stress urinary incontinence (SUI), and mixed urged and stress urinary incontinence. Estimates of the incidence of all types of pre-stroke UI range from 17-22% (Benbow et al. 1991; Borrie et al. 1986). After stroke, UUI, often a manifestation of abnormal volitional control of
bladder function, is the most common type (Brooks 2004; Brittain et al. 1999). However, a stroke can exacerbate pre-existing SUI (Brooks 2004).

A study of 935 acute stroke patients demonstrated that significant risk factors for post-stroke UI included age, severity of stroke, diabetes and comorbidity associated with other pre-existing disabling diseases (Nakayama et al. 1997). Recovery from post-stroke UI is associated with less disability and lower rates of institutionalization than persistent incontinence (Patel et al. 2001). Bean et al. (2003) noted an almost 2-fold difference in level of disability post stroke among those who were incontinent versus those who were continent (p<0.001). One study found that patients suffering from UI on admission had greater morbidity and mortality throughout their hospital stay and at 3 months post stroke (Gariballa 2003). As noted by several investigators (Jawad et al. 1999; Jongbloed 1986; Reding et al. 1987), recurring incontinence denotes a poor long-term prognosis for functional recovery.

Kolominsky-Rabas et al. (2003) examined the occurrence of UI and the long-term effect UI had on subjects’ prognosis and institutional status post stroke within a community-based population. Throughout the acute phase 41% of patients had full UI, 12% had partial UI and 47% had no UI (16%, 16% and 68% respectively at 12-months follow-up). In total, patients’ institutionalized at 12-months follow-up included 45% of patients with UI compared to only 5% of patients without UI. The authors concluded that the risk of institutionalization 1-year post stroke is a “fourfold higher” for stroke patients with UI in the acute phase of rehabilitation.

Few investigators have examined the prevalence of UI past the acute and sub-acute stage of stroke. Although the time since stroke onset was not stated, Brittain et al. (2000) reported that a significantly higher proportion of community-dwelling persons who experienced a stroke had more urinary symptoms compared to those that had never had a stroke (64% vs. 32%). The difference was statistically significant even after adjusting for differences in age and sex between groups. Stroke survivors were 1.77 times more likely to experience urinary symptoms than non-stroke persons. More stroke survivors reported a significant impact on lifestyle than did the non-stroke subjects. Twice as many stroke survivors than non-stroke persons reported that their urinary symptoms were moderate to severe. A study conducted by Ersoz et al. (2013) found a statistically significant difference with respect to age and marital status regarding the frequency of regaining spontaneous voiding (SV) in chronic stroke patients. Geriatric patients (> 65 years old) were less likely to experience SV compared to their younger stroke patient counterparts (50% versus 75.5%, respectively). In addition, once discharged home married stroke patients were found to have a statistically significant higher SV frequency compared to single/divorced patients (79% versus 47%, respectively).

Jorgensen et al. (2005) reported that among a sample of 242 community-dwelling stroke survivors, 17% were incontinent compared with a non-stroke control group, where the prevalence was 7%. The study tracked subjects an average of nine years post stroke. UI was associated with depression, poor leg motor function and impaired cognition. Williams et al. (2012) reported that increasing age, female sex, pre-stroke UI and severe stroke were independent predictors of UI at 12 months. It is important to note that 14.3% of patients in this population study had pre-stroke UI.

<table>
<thead>
<tr>
<th>Table 17.2.2.1 Summary of Prevalence of UI Post Stroke</th>
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<tbody>
<tr>
<td><strong>Author, Year</strong></td>
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<tr>
<td>Brocklehurst et al. (1985)</td>
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Normal Bladder Function

Normal bladder function requires a compliant bladder and competent urethral sphincters. The bladder is a predominantly muscular structure: the detrusor muscle relaxes to accommodate and store urine, and contracts to expel it via the urethra (Mehdi et al. 2013). The actions of the detrusor muscle must be coordinated with the urethral sphincter, two muscles that control the opening of the urethra, the outflow tract for urine (Borrie 1998). This coordination and the normal control of voiding involve complex interplay of the brain, brainstem, spinal cord, and peripheral sympathetic, parasympathetic,
motor, and sensory nerves. The next paragraph outlines a simplified explanation of normal bladder function.

The sympathetic nervous system relaxes the detrusor muscle to allow for bladder filling. During filling, the internal urethral sphincter is tonically active due to sympathetic innervation via alpha-receptors, closing the urethra to keep urine in the bladder. Normally, humans are unaware of bladder fullness until the bladder contains approximately 300 mL of urine. At this point, sensory afferent pelvic nerves relay the fullness sensation to the sacral spinal cord, where reflexes coordinate to strengthen the sympathetic input to the internal urethral sphincter and stimulate the contraction of the external urethral sphincter via the pudendal nerve. At the same time, these reflexes also inhibit parasympathetic activity, which is normally responsible for causing contraction of the detrusor muscle. Together, these actions mediate continence in the presence of a relatively full bladder.

Once that fullness reaches a critical level, the sensory afferent pelvic nerves intensify their signal to the spinal cord, which relays to the pontine micturition centre in the brainstem. The pontine micturition centre has the ability to inhibit the sympathetic nerves responsible for retaining urine while simultaneously activating the parasympathetic nerves responsible for contracting the detrusor muscle: the net effect is to stop bladder filling, relax the internal and external urethral sphincters to open the urethra to the flow of urine, and contract the bladder to actively expel urine. However, the pontine micturition centre is under higher levels of control, particularly via the pre-frontal cortex and other frontal lobe structures. When not socially acceptable or when not desired, the frontal lobe can prevent the pontine micturition centre from initiating urination. This higher level control has its limits, however, and when the bladder reaches absolute maximum stretch, the pontine micturition centre or spinal cord reflexes will empty the bladder, regardless of frontal lobe inputs, as a protective mechanism against tissue damage.

Pathophysiology of Incontinence Post Stroke
A stroke can contribute to UI by altering a number of the structures involved in the complex control of urination, particularly the frontal lobe and pontine micturition centres, or the communication between these two structures. 1) Urge urinary incontinence (UUI) and bladder hyperreflexia (detrusor muscle overactivity) caused by disrupted neuromicturition pathways; 2) Incontinence from stroke-related motor, cognitive and language deficits, despite normal bladder function; and 3) Overflow incontinence and bladder hyporeflexia due to concurrent neuropathy or medications, unrelated to the acute stroke.

In a systematic review of post-stroke UI literature, Mehdi et al. (2013) expanded the number of causes and types of UI post stroke to include six contributory mechanisms. 1) Direct damage to neuromicturition pathways due to the stroke lesion, particularly if it affects the frontal lobe, causes the detrusor muscle to contract without cortical inhibition, leading to UUI. These patients tend to present with urgency and involuntary leakage of urine. 2) Detrusor hyporeflexia, which may be due to initial loss of bladder tone, pre-existing neuropathy, or other non-stroke factors, leads to overflow incontinence. These patients present with dribbling or continuous leakage of urine in the setting of urinary retention or incomplete bladder emptying. 3) Reduced ability to identify bladder fullness, leakage, or both, leads to impaired awareness UI. These patients tend to have anterior circulation strokes with parietal or subcortical involvement, but without prominent frontal lobe involvement. 4) Consequences of stroke, such as communicative, cognitive, or motor abnormalities, indirectly cause incontinence despite intact bladder function by functionally limiting a patient’s ability to perform tasks required to maintain continence, such as ambulating or asking for assistance. 5) Pre-existing stress incontinence, caused by weak pelvic floor muscles, is exacerbated or persists post stroke. 6) Reversible causes of UI may be present in the post-stroke period, such as medications, fecal impaction, and delirium.
An additional type of voiding dysfunction, detrusor-sphincter dyssynergia, was not described above. When the detrusor muscle is hyperactive due to a loss of cortical inhibition of urination, voiding is usually complete. After stroke, however, detrusor muscle contraction may not always coincide with coordinated relaxation of the urethral sphincters. Detrusor-sphincter dyssynergia describes the detrusor contracting against closed urethral sphincters (Gelber et al. 1993). The intra-bladder pressure rises significantly when this occurs, which may lead to reflex bladder emptying (either complete or incomplete) to avoid tissue damage (Chou et al. 2013).

Few studies have used urodynamic studies to evaluate the prevalence of these different mechanisms of UI post stroke. Gelber et al. (1993) performed urodynamic studies in 19 patients with post-stroke UI. In this relatively small study, 37% of patients had bladder hyperreflexia, 37% had normal bladder function but incontinence indirectly caused by stroke, and 21% had bladder hyporeflexia, either due to medications or pre-existing conditions (Gelber et al. 1993). Gelber et al. (1993) found detrusor-sphincter dyssynergia occurred in 5% of patients post stroke. In a recent study of urodynamics in 15 patients after cerebellar stroke, Chou et al. (2013) identified detrusor overactivity in 53.5% of patients, normal detrusor function in 20% of patients, and detrusor hyporeflexia in 26.7% of patients. In addition, this study found much higher rates of detrusor-sphincter dyssynergia, occurring in 40% of studied patients, suggesting that cerebellar function may be important to ensure coordination of sphincter relaxation.

Identifying the pathophysiology leading to UI post stroke has significant clinical implications, as the management of these conditions varies. For instance, some patients with detrusor hyperreflexia due to damaged cortical inhibition of urination may be continent with conservative measures such as timed voiding (Gelber et al. 1993). The pathophysiology and management of UI are discussed in the next sections.

**Detrusor Hyperreflexia**

Gelber et al. (1993), Chou et al. (2013), and Medhi et al. (2013) identified detrusor muscle hyperreflexia or overactivity as a common cause of post-stroke urinary incontinence. When a stroke affects cortical or subcortical structures responsible for controlling the pontine micturition centre, signals from the bladder can trigger the reflexes that contract the detrusor muscle and relax the urethral sphincters. In this setting, bladder filling, even at volumes much lower than would cause urgency to void in a normal bladder, leads to contraction of the detrusor muscle and the flow of urine (Borrie 1998). The detrusor contracts with little or no warning; the sensation or urgency to void may happen only seconds before or as voiding occurs. Hence, patients often present with urgency to void accompanying their incontinence, and voiding that is more frequent because the bladder empties at smaller volumes. These patients are more likely to have strokes that affect the anterior circulation, and specifically, the frontal lobe and pre-frontal cortex (Medhi et al. 2013).

**Urinary Retention**

Although it is the most common pattern of voiding dysfunction identified in urodynamic studies post stroke, detrusor hyperreflexia is not inevitable after a stroke. Acute urinary retention due to inactivity or hyporeflexia of the detrusor muscle is commonly seen in the first 72 hours post stroke (Chou et al. 2013). After the first 72 hours, urinary retention is less common; in patients who experience it, other mechanisms for urinary retention predominate (Chou et al. 2013). Specifically, detrusor-sphincter dyssynergia leads to urinary retention and incomplete bladder emptying (Fader & Craggs 2003; Nazarko 2003). By the time patients enter stroke rehabilitation, Gelber et al. (1993) found detrusor-sphincter dyssynergia occurred in 5% of patients who were, on average, 20 days post stroke.
Incomplete bladder emptying leads to residual urine remaining in the bladder and is a significant risk factor for the development of urinary tract infections (Fader & Craggs 2003; Kim et al. 2012). It is therefore important to determine if complete bladder emptying is occurring to identify and treat the problem by evaluating the post-void residual (PVR) urine volume. Intermittent or in-and-out catheterization is considered the gold standard measure for determining PVR volume; however, portable bladder ultrasound devices are an alternative PVR measurement tool that is practical, non-invasive, and cost-effective (Chan 1993). These devices can also be used to detect urinary retention in patients who have not voided by measuring the volume of the bladder.

There is no consensus regarding what volume of residual urine is considered abnormal (Grosshans et al. 1993). In general, two consecutive PVR volumes >150 mL indicates incomplete bladder emptying that may warrant further management (Borrie 1998). Patients with bladder volumes >500 mL are usually considered to be in urinary retention, and often require in-and-out catheterization or other management to prevent negative sequelae associated with urinary retention if they are unable to void spontaneously (Chou et al. 2013). One study evaluated the effectiveness of a standardized bladder scan regimen using portable ultrasound devices to measure PVR in 52 sub-acute stroke patients with known PVR>100 mL (Kim et al. 2012). Patients were randomized to the protocol group or usual care. The study used two separate protocols, one for patients with urinary retention who could not urinary volitionally, and one for patients who could. Overall, the standardized scan protocol was effective for managing urinary retention post stroke, but did not demonstrate a reduction in other consequences during admission.

**Urinary Tract Infection**

Urinary tract infections (UTI) are the single most common medical complication in with stroke rehabilitation, affecting 13.6-44% of patients (Dromerick & Reding 1994; Hung et al. 2005; Roth et al. 2001). Risk factors for UTI post stroke include indwelling urinary catheter, age over 65 years, female sex, pre-morbid UI of any type, anterior circulation stroke, prior stroke, antidepressant use, and a post-void residual volume of greater than or equal to 100 mL (Dromerick & Edwards 2003; Ifejika-Jones et al. 2013; Kim et al. 2012; Sabanathan et al. 1985). Voiding dysfunction is thought to contribute significantly to the risk of developing a UTI, which has the potential for adverse patient outcomes (Kim et al. 2012). Ifejika-Jones et al. (2013) examined the impact of hospital-acquired symptomatic urinary tract infections in stroke patients and how symptomatic UTI affected discharge disposition. Symptomatic UTI was an independent predictor of a patient’s discharge destination: patients with symptoms of UTI were 57% less likely to be discharged home and 38% less likely to be discharged to inpatient stroke rehabilitation compared to long-term care or skilled nursing facilities.

**Other Factors**

Incontinence may not be due to the direct neurologic consequences of stroke. Motor, cognitive and language deficits, immobility, and dependency are all factors that may lead to incontinence, even in patients with normal bladders (Fader & Craggs 2003; Gelber et al. 1993; Linsenmeyer 2012; Nazarko 2003).

Mobility impairments, such as hemiplegia or cerebellar dysfunction, may prevent patients from ambulating independently. These patients may rely on caregivers to assist them to the bathroom or commode. Depending on the setting and availability of caregivers, patients may not be assisted in time to avoid incontinence. Moreover, language deficits, delirium, or depression may prevent patients from communicating voiding needs to others. Medications used for secondary stroke prevention or management of other comorbidities, such as diuretics for hypertension and sodium-glucose transport
inhibitors for diabetes, can increase urinary output and frequency. Anticholinergic medications may increase confusion or lead to urinary retention.

Discussion
UI is a common complication post stroke. The type of incontinence and its pathophysiology varies by patient. Several studies have demonstrated that UI is associated with more severe strokes and poorer functional outcomes (Itoh et al. 2013; Pizzi et al. 2014).

The risk factors for UI post stroke vary by study, which may reflect diverse patient populations, different time of UI evaluation post stroke, and different definitions of UI. However, some common themes emerge with regards to stroke and personal factors that increase risk of UI post stroke. In a prospective case-control study, Pizzi et al. (2014) studied 106 patients admitted to a neurorehabilitation service after ischemic stroke and found that incontinence developed in 79% of patients, and that incontinence was strongly associated with lower functional status or greater stroke area, as measured by the FIM total and cognitive scores. Similarly, Gelber et al. (1993) found that patients who were incontinent had lower Barthel index and Modified Barthel Index scores at admission and discharge, and were more likely to have aphasia. In a prospective study of 423 patients with ischemic or hemorrhagic stroke admitted to inpatient rehabilitation, UI was associated with worse FIM scores, the presence of dysphagia, and worse motor function (Ween et al. 1996). This study found that small vessel, also known as lacunar, strokes had the lowest rates of UI and that pre-existing comorbidities were not predictive of UI (Ween et al. 1996). Ween et al. (1996) also found that UI was strongly associated with slower and reduced extent of recovery post stroke compared to continent controls, which was statistically significant.

In a retrospective cohort study, The Overactive Bladder Symptom Score (OABSS) was used to examine the prevalence and risk factors of post-stroke overactive bladder in 500 patients with chronic stroke (Itoh et al. 2013). Patients were stratified by the presence or absence of symptoms of overactive bladder (OAB), and independent risk factors for OAB were examined using logistic regression methods. Patients with symptoms of OAB had significantly lower health-related quality of life compared to patients who did not report any symptoms of OAB. This study found that 73% of patients with symptoms of OAB had never been treated for their symptoms, despite relatively high OABSS scores (mean 7.1) indicating significant burden of symptoms. Unlike previous studies, Itoh et al. did not find that motor deficits or sensory disturbances were predictive of UI.

Several of the studies reviewed above outlined negative patient consequences associated with UI and its sequelae: urinary tract infections; higher risk of skin breakdown; higher risk of falls; poorer health-related quality of life; slower and reduced extent of recovery post stroke; likelier discharge to a skilled nursing or long-term care facility than home or to rehabilitation; and, prolonged hospitalization (Gelber et al. 1993; Ifejika-Jones et al. 2013; Mehti et al. 2013; Pizzi et al. 2014; Ween et al. 1996). Despite the negative effects on patients and their caregivers, Itoh et al. (2013) found that many patients with significant symptoms had never been treated for their UI. These negative consequences emphasize the importance of identifying and treating symptoms of UI post stroke. Table 17.2.2.2 outlines a very basic approach to the features suggestive of different UI types, and the subsequent section examines treatment options.

<table>
<thead>
<tr>
<th>Features on voiding history</th>
<th>Physical examination and/or other findings</th>
<th>Post-void residual volumes</th>
<th>Pathophysiology on urodynamic studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Urge:</strong> sudden urge to void +/- incontinence</td>
<td>Signs of central or peripheral neurologic disease, such as</td>
<td>Low</td>
<td>Detrusor hyperactivity</td>
</tr>
<tr>
<td>Stress: unexpected voiding of small volumes with change in position or increased intraabdominal pressure (cough, laugh, sneeze)</td>
<td>Incontinence is reproducible with maneuvers that increase pressure on the bladder, such as coughing</td>
<td>Low</td>
<td>(Genuine) stress incontinence</td>
</tr>
<tr>
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</tr>
<tr>
<td>Overflow: urinary retention, including difficulty initiating urination and/or emptying bladder; dribbling urine</td>
<td>Palpable bladder (large volume) Outflow obstruction: enlarged prostate, urethral stricture, or heightened sphincter tone Reduced anal sphincter tone +/- reduced anal sensation</td>
<td>High</td>
<td>Detrusor hyporeflexia +/- detrusor-sphincter dyssynergia Outlet obstruction possible</td>
</tr>
<tr>
<td>Mixed: features of urge and stress incontinence</td>
<td>Variable</td>
<td>Variable</td>
<td>Mixed</td>
</tr>
<tr>
<td>Functional: unable to perform tasks that would promote continence, such as ambulating to bathroom, dexterity to remove clothes or ability to ask for help</td>
<td>Impaired mobility, language, or cognitive status Environmental factors</td>
<td>Low</td>
<td>Bladder function may be normal</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Medications that may contribute to increased urinary output, frequency, or inability to void Restraints (limit patient function)</td>
<td>Variable</td>
<td>Bladder function may be normal</td>
</tr>
</tbody>
</table>

### 17.2.3 Management of Urinary Incontinence Post Stroke

**Diagnosis of the Type of Urinary Incontinence**

The presence of urinary incontinence (UI) is common, and although most patients will have resolution of UI by 6 months post stroke, many patients will continue to experience UI (Gelber et al. 1993; Mehdi et al. 2013). In patients who have persistent UI, or in patients for whom UI is causing reduced health-related quality of life, excessive caregiver burden, or impeding their progress in rehabilitation, management of UI is crucial. Diagnosing the type of UI will help guide management. In a set of evidence-based guidelines for stroke rehabilitation, Duncan et al. (2005) found that there was insufficient evidence to recommend for or against the use of urodynamic studies for the diagnosis of the type of UI post stroke. In a Cochrane Review of incontinence not limited to post-stroke patients, Clement et al. (2015) developed the same conclusion, finding that urodynamics may change clinical decision-making, but that there is not enough evidence to support its universal use. Therefore, diagnosis of UI should be made using history and physical examination; when needed, additional investigations, including urodynamic studies, can be pursued to guide diagnosis and management.

**Management of Urinary Incontinence**

Few high-quality studies have evaluated treatment options for UI in the post-stroke population, although many studies exist in other patient populations with UI. In the absence of robust research and evidence-based guidelines, management usually falls to clinical expertise of the treating medical team and is guided by the patient’s type of incontinence. In the absence of rigorous evidence, Borrie (1998) proposed that a stepwise approach is best, starting with behavioural intervention, and then progressing to medication if needed, and considering surgical interventions only as a last resort.

A 2008 Cochrane review investigating optimal methods for prevention and treatment of UI post stroke in adults evaluated results from 724 patients in 12 trials (Thomas et al. 2008). There was a wide range of
interventions: behavioural interventions such as timed voiding; specialized professional input interventions such as continence nurse practitioner care; complementary and alternative medicine interventions including acupuncture and moxibustion; pharmacotherapy with estrogen, oxybutynin, meclofenoxate; and physical therapy such as pelvic floor muscle training and sensory-motor feedback combined with timed voiding. A pooled analysis across all interventions was not performed. The findings were tempered by small sample sizes and suboptimal study methodology across the studies. Two trials (Brittain et al. 2000; Wikander et al. 1998) offered some evidence supporting input from specialized professionals using systematic methods to help evaluate, manage, and improve outcome of patients with continence complications. Brittain et al. (2000) suggested short- and long-term improvements in UI symptoms could be established through this specialized care. While complementary and alternative medicine interventions appeared to be effective compared with placebo, small sample sizes and limited reporting of methodological details reduce the generalizability or potential applicability of the findings. In a study of women with UI, estrogen therapy was effective in reducing the number of incontinence episodes in a week, but supplemental estrogen is generally contraindicated post stroke because of its detrimental effect on secondary stroke prevention. Limited evidence suggested that the acute stage of rehabilitation has the largest impact on UI post stroke. Overall, however, there is a paucity of evidence from all intervention studies for UI post stroke. The authors concluded that further research is required.

Dumoulin et al. (2005) conducted a systematic review investigating the benefits of behavioural therapies used to treat UI. The study included four RCTs, one cohort study, and recommendations from three clinical practice guidelines. There was limited evidence that using the combination of bladder retraining, urge suppression, and pelvic floor exercises reduced UI in male patients post stroke. The authors concluded that although there is increasing recognition of the benefits of using behavioral approaches as treatment for stroke patients with a high occurrence of continual UI, the evidence remains very limited for specific treatments used for stroke survivors with UI.

An uncontrolled, qualitative study evaluated a systematic voiding protocol in an acute stroke unit and found that the organizational context of the acute care setting was disadvantageous for continence programs, but that a systematic voiding program might be useful and could be implemented (Johnston et al. 2014). Once again, methodologic limitations and the qualitative nature of the study preclude generalizability of these results.

**Fluid Intake**

Borrie (1998) suggested that patients’ total measurable fluid intake should be approximately 1500 – 1800 mL per 24 hours for patients with UI post stroke. Fluid restriction is a common method of controlling urinary symptoms, including for patients with obstructive uropathy such as benign prostatic hypertrophy. However, there are no specific studies demonstrating the safety or efficacy of this technique in post-stroke UI. Care providers should be mindful that the use of intravenous fluids or a feeding tube may result in fluid loads greater than 2L per day, which will in turn compromise bladder continence by increasing urine output (Borrie 1998). A careful clinical assessment should be done to ensure fluid restriction aimed at improving UI does not compromise adequate hydration.

**Bladder Training**

Scheduled voiding programs follow a set schedule of voiding every 2-4 hours regardless of whether the patient has a sensation that he or she needs to void. Timed voiding can be useful for the management of multiple types of voiding dysfunction. For patients whose cortical control of voiding is impaired and who experience urgency due to detrusor hyperreflexia, timed urination reduces the chance that the bladder fills to the point that triggers reflexic bladder emptying. In patients whose awareness of bladder fullness is reduced, following a schedule of voiding prevents unexpected voids in much the same way, by
pre-emptively emptying the bladder (Borrie 1998). Initiation of toileting in response to urgency, while shown to promote continence, often does not provide enough time to void especially when mobility is limited. Gradually, bladder training may allow for lengthening of the voiding interval as the patient becomes consistently dry (Borrie 1998; Burgio & Burgio 1986).

Some research supports the use of bladder training in patients with stroke-related UI. In an RCT of 19 patients with post-stroke UI, Engberg (2002) demonstrated a statistically significant reduction in episodes of incontinence in the timed void group compared to usual care. In a set of evidence-based stroke rehabilitation guidelines, Duncan et al. (2005) recommended the use of prompted voiding in stroke patients with UI. Similar conclusions favouring prompted voiding were drawn in a Cochrane systematic review of 355 elderly persons with UI, although stroke was not a criteria and the benefit was mild. F. Duncan et al. (2005) recommended developing and implementing individualized bladder training programs. However, a feasibility study by Thomas et al. (2014) found that not all institutions would be able to smoothly integrate such a systematic voiding program.

Pharmacological Treatments
Although UI is common after stroke, few studies have evaluated pharmacotherapy options for UI post stroke. In a Cochrane review of randomized controlled or quasi-controlled trials of treatments for UI post stroke, Thomas et al. (2008) found that there was insufficient evidence to determine the optimal treatment in this population. Borrie (1998) suggested that drug therapy should be implemented only after an adequate trial of behavioural interventions because drugs, particularly in the elderly, often have significant side-effects.

Anticholinergic medications act by inhibiting detrusor contraction, and are frequently prescribed to patients with symptoms of overactive bladder or detrusor hyperreflexia (Borrie 1998). Medications in this class that exert their effect on the bladder and other systems include Flavoxate, oxybutynin, propantheline, and tolterodine. Flavoxate is a non-specific anticholinergic, anti-muscarinic compound that has antispasmodic properties. It is felt to have lower anticholinergic side effects, although its non-selective anti-muscarinic effects can produce gastrointestinal symptoms including nausea by exerting antispasmodic action on the gut. Poor compliance due to lack of efficacy in reducing UI symptoms has been noted (DeMaagd & Davenport 2012). Oxybutynin is another non-selective anticholinergic which is frequently used (Borrie 1998); in a small RCT, oxybutynin showed no benefit over timed voiding (Thomas et al. 2008). Propantheline is postulated to not cross the blood-brain barrier, which offers a theoretical advantage over other non-selective anticholinergic drugs that can lead to confusion or precipitate delirium (Borrie 1998). Tolterodine is another non-selective anticholinergic which is thought to have less influence on salivary gland function and therefore less likely to lead to dry mouth as a complication. One RCT demonstrated no benefit over timed voiding (Thomas et al. 2008). There are no RCTs evaluating the safety or efficacy of the remaining medications. These medications are anticholinergic, and therefore can have negative impact on the elderly in terms of falls risk, delirium, and cognition, all of which may have negative consequences for recovering from stroke (Feinberg 1993).

Newer, more selective anticholinergic agents have been shown to effectively treat UI in populations other than stroke (Basra & Kelleher 2008; DeMaagd & Davenport 2012). Solifenacin is an anti-muscarinic medication that selectively inhibits the M3 muscarinic receptor, which is thought to be the primary mediator of bladder contractility (Basra & Kelleher 2008). Its efficacy and tolerability in patients with detrusor hyperreflexia has been demonstrated in RCTs, including one trial demonstrating superiority over tolterodine, although none of these studies were specific to stroke patients with these symptoms (Basra & Kelleher 2008). Although this medication is more specific to the bladder, it still has side effects of dry mouth and constipation which may limit its use.
Mirabegron is a first-in-class medication that prevents detrusor contraction by inhibiting beta-3-adrenergic receptors (Sacco & Bientinesi 2012). This novel mechanism of action produces fewer anticholinergic side effects, such as dry mouth and blurred vision, and is thought to be less likely to precipitate delirium and confusion. Mirabegron has shown benefit for reducing the number of urinary episodes and the number of incontinence episodes in RCTs and in a systematic review of over 10 000 patients with urge urinary incontinence (UUI) (Sacco & Bientinesi 2012). However, this medication has not specifically been evaluated in the post-stroke population, and there is a risk of exacerbating hypertension, which may negatively impact secondary stroke prevention efforts.

Supplemental estrogen therapy is effective for post-menopausal women with UUI (Cody et al. 2009). However, oral estrogen supplementation is relatively contraindicated in patients with a history of stroke due to the strong association between supplemental estrogen and stroke and venous thromboembolism (Wassertheil-Smoller et al. 2003). Estrogen delivered via vaginal suppository results in lower systemic doses with comparable benefits for UUI (Cody et al. 2009), but should still be used with caution in patients who have had a stroke (ACOG 2013).

For patients with overflow incontinence or detrusor hyporeflexia, bethanecol may be effective. Bethanecol is a muscarinic agonist that improves detrusor muscle contractility, which may aid bladder emptying either on its own or as an adjunct to in-and-out or intermittent catheterization (Borrie 1998; Sonda et al. 1979).

Pharmacotherapy for UI post stroke should be evaluated for effect after initiation. Medications that are not providing measurable benefit—subjective improvement, such as less urgency, or objective improvement, such as decreased post-void residual volumes—should be discontinued. Medications providing benefit should be titrated to optimal effect, bearing in mind medication tolerability.

Table 17.2.3.1 Summary of RCTs Evaluating Non-Pharmacologic Treatment of UI Post Stroke

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>RCT (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gao et al. (2012)</td>
<td>RCT (8)</td>
<td>N=240</td>
<td>E: Complete “correspondence of Chinese herbal medicine prescriptions” and traditional Chinese medicine (TCM) syndrome C: Incomplete “correspondence of prescriptions” and TCM syndrome Study duration: 21 days</td>
<td>• NIHSS scores between groups (no benefit) • ADL (no benefit) • Paruria (reduced with “correspondence”) • Night sweating and dysdipsia (reduced with “correspondence”) • Talking (no benefit) • Memory loss (no benefit) • Abnormal defecation (no benefit)</td>
</tr>
<tr>
<td>Tibaek et al. (2004)</td>
<td>RCT (7)</td>
<td>N=26</td>
<td>E: Pelvic floor muscle training C: Standard rehabilitation</td>
<td>• 24 hr pad test (no benefit for pelvic floor muscle training) • Strength, endurance, function of pelvic floor muscle (no benefit of pelvic floor muscle training) • SF-36 (no benefit of pelvic floor muscle training) • IIQ (no benefit of pelvic floor muscle training)</td>
</tr>
<tr>
<td>Tibaek et al. (2005)</td>
<td>RCT (7)</td>
<td>N=45</td>
<td>E: Complete “correspondence of Chinese herbal medicine prescriptions” and traditional Chinese medicine (TCM) syndrome C: Incomplete “correspondence of prescriptions” and TCM syndrome Study duration: 21 days</td>
<td>• NIHSS scores between groups (no benefit) • ADL (no benefit) • Paruria (reduced with “correspondence”) • Night sweating and dysdipsia (reduced with “correspondence”) • Talking (no benefit) • Memory loss (no benefit) • Abnormal defecation (no benefit)</td>
</tr>
<tr>
<td>Gross et al. (2007)</td>
<td>RCT (6)</td>
<td>N=45</td>
<td>E1: 10:00pm removal of catheter E2: 7:00am removal of catheter</td>
<td>• Time to void (no benefit) • Volume on first void (no benefit) • Post-void residual (no benefit)</td>
</tr>
<tr>
<td>Yun et al. (2007)</td>
<td>RCT (6)</td>
<td>E: Moxibustion therapy (traditional Chinese medicine technique that burns mugwort, a</td>
<td>• IPSS (improvement with Moxibustion) • Barthel Index (no benefit with Moxibustion)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
</tr>
<tr>
<td>-----------------------</td>
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<td>----</td>
<td>-------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>McDowell et al. (1999)</td>
<td>RCT</td>
<td>105</td>
<td>Biofeedback-assisted pelvic floor training</td>
<td>Attention control group that was provided social interaction and observed by a nurse practitioner</td>
</tr>
<tr>
<td>Engberg et al. (2002)</td>
<td>RCT</td>
<td>19</td>
<td>Prompted voiding</td>
<td>Delayed attention control group</td>
</tr>
<tr>
<td>Moon et al. (2012)</td>
<td>RCT</td>
<td>60</td>
<td>Bladder recondition through indwelling urethral Catheter (IUC) clamping at 0-day clamping</td>
<td>Same as E1, offered at 1-day clamping</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Same as E1 offered at 3-day clamping</td>
</tr>
<tr>
<td>Wikander et al. (1998)</td>
<td>RCT</td>
<td>34</td>
<td>FIM-based rehabilitation program</td>
<td>Conventional rehabilitation using the Bobath technique</td>
</tr>
</tbody>
</table>

*No benefit indicates no statistically significant difference between treatment groups*

**Discussion**

A number of behavioural, and complementary and alternative treatment options have been studied for post-stroke incontinence. A single RCT examines each of the following non-pharmacologic treatments: moxibustion, biofeedback-assisted pelvic floor training, bladder reconditioning through IUC clamping, IUC use with variable times of removal, traditional Chinese herbal medicine, and a FIM-focused rehabilitation unit. Prompted bladder voiding was studied in an RCT of 19 patients post stroke; in this study, Engberg et al. (2002) demonstrated a benefit for reducing the number of incontinence episodes. Biofeedback training yielded similar benefits in one trial (McDowell et al. 1999) but these findings are tempered by an RCT of similar quality with fewer patients (Tibaek et al. 2007). In general, there is a paucity of available literature for any one of these treatments, and the variable methodology may limit widespread use. Furthermore, the pre-stroke continence status, small sample sizes and heterogeneity of treatments and outcomes assessed limit the generalizability of the findings.

Studies evaluating the use of pharmacologic treatments, such as anticholinergics and beta-3 adrenergic agonists, in the post-stroke population are lacking. However, many of these agents have been studied in non-stroke patients with UI and have shown to be of benefit, particularly solifenacin and mirabegron. Estrogens should be used with caution given their association with venous thromboembolism and stroke. Further research is needed to determine optimal therapies as well as the safety and efficacy of these medications, which may have significant adverse effects, in the stroke population.

**Conclusions Regarding the Management of Urinary Incontinence**

*There is level 1b evidence that prompted voiding may reduce the number of episodes of incontinence compared to usual care in patients with urge urinary incontinence.*

*There is level 1b evidence that biofeedback-assisted pelvic training may decrease the number of episodes of incontinence compared to standard rehabilitation.*

*There is level 1b evidence that pelvic floor muscle training does not reduce incontinence symptoms or outcomes compared to standard rehabilitation.*
There is level 1b evidence that complete correspondence compared to incomplete correspondence of Chinese herbal medicines may be helpful for paruria and symptoms of abnormal defecation; however, the methodology is not adequately described to reproduce this intervention.

There is level 1b evidence that catheter clamping protocols offered at 0-days, 1-day and 3-days may be as effective on bladder reconditioning outcomes such as time to first void, volume on first void, voiding method, and residual urine volume following the first void.

There is conflicting level 2 evidence regarding the effectiveness of functionally-oriented rehabilitation programs alone at improving incontinence when compared to a conventional Bobath approach.

There are no RCTs of urinary incontinence in post-stroke patients to guide pharmacological agent selection in this population.

Urinary incontinence is a common post-stroke complication. Additional research is required for the effectiveness of pharmacologic therapies, prompted voiding interventions, pelvic muscle training programs, complementary and alternative therapies, and functionally-oriented rehabilitation approaches.

17.2.4 Urinary Bladder Catheterization Post Stroke

Urinary catheter insertion is common in the first 48 hours of admission following stroke for indications including urinary incontinence, urinary retention, and management of fluid balance (Duncan et al. 2005; Gresham et al. 1995; Wu et al. 2013). In a study of the prevalence of indwelling urinary catheters (IUC) in 2803 post-stroke patients, Wu et al. (2013) found that 25% of patients with acute stroke had indwelling catheters placed at the time of admission; this was more likely in patients with intracerebral hemorrhage than in patients with ischemic stroke, occurring in 60% compared to 16%, respectively. Studies and stroke guidelines suggest removing indwelling catheters within 48 hours to reduce adverse outcomes such as urinary tract infections (UTI) (Duncan et al. 2005; Nazarko 2003). Moreover, chronic IUC use is associated with worse patient outcomes, such as UTI, inflammatory bladder wall changes, and mortality. Wu et al. (2013) used the Taiwan Stroke Registry to evaluate the relationship between IUC and patients with stroke; those patients with IUC for greater than or equal to 3 months were more likely to experience mortality (p<0.001), require ventilator use (p<0.001), any complication (p<0.001), and UTI (p<0.001) regardless of their stroke type. These patients were also more likely to be older in age and to have worse NIH stroke scores, suggesting that long-term IUC may be associated with more severe stroke at presentation as well as poorer recovery and prognosis. As outlined in section 17.2.2, UTIs alone have a profound and negative impact on patient outcomes post stroke. Given that approximately 40% of patients regain continence during the first two weeks post stroke, judicious use of IUCs should be standard of practice (Brocklehurst et al. 1985; Wu et al. 2013).

In a descriptive study that looked to identify key factors influencing doctors’, nurses’, and physiotherapists, decision to have an indwelling catheter inserted in acute stroke patients, clinical indicators (skin, integrity, urinary retention, etc.) was identified as the main reasons for catheterization, however, overall there was a lack of standardized consensus regarding the decision process (Cowey et al. 2012). Stroke severity also likely informs IUC decision-making, as inferred from the findings of Wu et al (2013).
As an alternative to IUC use, clean intermittent catheterization has been shown to safely manage urinary retention (Bennett & Diokno 1984; Maynard & Diokno 1984; Webb et al. 1990). Intermittent catheterization can be utilized when a stroke survivor is unable to pass urine and/or has a substantial amount of residual urine still in the bladder. To reduce the incidence of nosocomial UTIs, the use of silver alloy-coated urinary catheters has been recommended (Duncan et al. 2005). While the cost of these catheters is greater, they may be more cost-effective considering the reductions in cost associated with treating bacterial UTIs. However, the literature upon which this recommendation was based was not specific to stroke patients.

**Conclusions Regarding the Use of Indwelling Urinary Catheters**

*The use of indwelling urinary catheters (IUC) in stroke patients is common.*

*There is level 3 evidence that IUCs are associated with worse outcomes, including urinary tract infections.*

*There is level 5 evidence that IUCs should be limited to those patients with intractable urinary retention, skin breakdown, continuous wetness and the need for urinary monitoring.*

*Indwelling urinary catheters (IUCs) may be helpful in cases of intractable urinary retention, continuous wetness or the need for fluid balance or urine output monitoring. IUCs should be removed if not absolutely needed due to their association with poorer patient outcomes. Further research examining the impact of IUCs on bladder reconditioning is required.*

**17.3 Fecal Incontinence and Constipation Following Stroke**

Both fecal incontinence and constipation are common problems following stroke. The reported prevalence of some form of fecal incontinence post stroke ranges from 7% to 56%; most patients experience resolution of fecal incontinence within 2 weeks (Brookehurst et al. 1985). Kovindha et al. (2009) reported that incontinence of bowel and bladder (double incontinence) occurred in 33% of patients at admission to a rehabilitation unit and persisted in 15.1% at discharge. Brittain et al. (2006) reported that major fecal incontinence was 4.5-times more prevalent among stroke survivors compared with non-stroke controls. A variety of risk factors for fecal incontinence have been identified, including stroke territory, mobility and functional limitations, and severity of stroke. Total anterior infarction is an independent predictor of the presence of fecal incontinence (Barrett 2002). Harari et al. (2003) identified problems with toilet access and constipating drugs as modifiable risk factors post stroke. This group also found that the most powerful predictor of fecal incontinence in the first few days post stroke was the initial level of consciousness and stroke severity.

Constipation post stroke has not been well studied. The prevalence is unclear, likely due to high variability in the diagnostic criteria for constipation in stroke research. Harari et al. (2004) reported that 66% of patients screened for their interventional study suffered from constipation. A similar percentage of affected patients (66%) was reported by Robain et al. (2002) among 152 rehabilitating stroke patients. In general, constipation is thought to be a consequence of poor fluid intake, the use of constipation-inducing medications, poor dietary fiber intake, decreased mobility, and increased dependence, rather than as a direct effect of stroke (Winge et al. 2003). Mild cases can be treated by correcting some of these abnormalities, such as ensuring adequate hydration, and with stool softeners or pro-kinetic agents.
17.3.1 Treatment of Fecal Incontinence and Constipation Post Stroke
The management of both fecal incontinence and constipation has not been well studied in the stroke population. In terms of constipation, a multidisciplinary approach to diagnosis and treatment is warranted. An effective intervention strategy recognizes the importance of fiber and fluid intake, bowel habits and the use of medications (Winge et al. 2003). Bulk-forming laxatives, bisacodyl suppositories, stool softeners, osmotic agents and/or stimulant laxatives may be indicated or contra-indicated depending on the needs of the individual patient. If a patient has a fecal impaction, treatment with enemas or digital evacuation may be required (Winge et al. 2003). Only three RCTs have evaluated treatment strategies for constipation and fecal incontinence (Table 17.3.1.1).

Table 17.3.1.1 Summary of RCTs Evaluating Treatments of Fecal Incontinence/Constipation

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>RCT (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numata et al. (2014)</td>
<td>RCT (7)</td>
<td>N=34</td>
<td>Constipation  E: experimental group; C: control group  E: Traditional Japanese medicine Diakenchuto (DKT)  C: Conventional therapy for constipation only, which included laxative administration, enemas, and disimpaction</td>
<td>• Constipation Scoring System scores (improved with treatment)  •</td>
</tr>
<tr>
<td>Harari et al. (2004)</td>
<td>RCT (6)</td>
<td>N=146</td>
<td>Constipation  E: One-time nursing assessment (history and rectal examination), followed by patient/carer education with booklet and provision of diagnostic summary and treatment recommendations  C: Routine care  Fecal Incontinence  E: One-time nursing assessment (history and rectal examination), followed by patient/carer education with booklet and provision of diagnostic summary and treatment recommendations  C: Routine care</td>
<td>Constipation  • Percentage of bowel movements per week graded as “normal” by patient (increased with intervention)  • Mean number of bowel movements per week (increased with intervention)  Fecal Incontinence  • Episodes of fecal incontinence (no benefit with intervention)  •</td>
</tr>
<tr>
<td>Venn et al. (1992)</td>
<td>RCT (3)</td>
<td>N=58</td>
<td>Constipation  E1: Morning bowel training with mandatory suppository  E2: Morning bowel training with optional suppository  E3: Evening bowel training with mandatory suppository  E4: Evening bowel training with optional suppository</td>
<td>• Consistent use of suppositories (no difference between groups)  • Time of day scheduled for the bowel training program (no difference between groups)</td>
</tr>
</tbody>
</table>

Discussion
Treatment for constipation commonly involves drug therapy (i.e. use of laxatives or stimulant purgatives), and these methods are considered to be the primary means of reducing gastrointestinal discomfort for chronic constipation in patients (Numata et al. 2014). There is a paucity of research on bowel dysfunction within a stroke population; treatment options for constipation or fecal incontinence are therefore based on usual practice (Harari et al. 2004).

Findings reported by Venn et al. (1992) showed that bowel training protocols implemented under a mandatory, timed suppository use schedule (morning vs evening) did not result in improved outcomes, although patients in the morning bowel training group had more bowel movements at baseline. Harari et al. (2004) compared effects of routine care on the percentage of bowel movements per week to the effects of a nurse-led intervention that consisted of a generic education booklet for the patient and carer, a diagnostic summary, and patient-specific treatment recommendations for improved bowel functioning. Findings suggest that the intervention was significantly associated with a reduction in
the weekly number of uncomfortable bowel movements, and a significantly greater likelihood of making lifestyle changes helpful for bowel movement (i.e. modifications to dietary and fluid intake) compared to the control group. These improvements were sustained at 6 months but not at 12 months. A major strength of the study was the use of an educational approach that highlighted a major benefit of structured management strategies as means for providing longer-term solutions for bowel dysfunction, instead of focusing on the pharmacological approach by increasing laxative doses. This is particularly important as a major limitation of conventional drug therapy for constipation is the ability of a patient to develop tolerance (Numata et al. 2014).

Numata et al. (2014) evaluated a traditional Japanese medicine, Daikenchuto (DKT), for constipation post stroke and found that, when administered along with conventional treatment, DKT was associated with decreased constipation as indicated by the Constipation Scoring System and a reduction in the gas volume score (GVS) post stroke compared to conventional treatments alone. There were no adverse events reported.

**Conclusions Regarding the Treatment of Fecal Incontinence and Constipation Post Stroke**

*There is level 1b evidence that a traditional Japanese medicine, Diakenchuto, may be effective at reducing constipation.*

*There is level 1b evidence that a nursing evaluation program consisting of an assessment, provision of educational material for the patient, and a summary of the diagnostic results may be effective in reducing constipation long-term post stroke.*

*There is level 1b evidence that a morning bowel routine may be as effective as an evening bowel routine.*

*There is limited research regarding treatments for fecal incontinence post stroke.*

### 17.4 Venous Thromboembolism Post Stroke

#### 17.4.1 Diagnosis of Venous Thromboembolism Post Stroke

Deep vein thrombosis (DVT) is a potentially life-threatening condition in which blood clots form in the deep veins of the body. Venous thromboembolism (VTE) occurs when these clots embolize, or break free, and travel through the body’s circulatory system; VTE is life-threatening when it enters the lungs, at which point it is clinically recognized as pulmonary embolism (PE), or when it embolizes to other areas, leading to focal ischemia.

The signs and symptoms of PE are often nonspecific and can include sudden onset, pleuritic chest pain, tachycardia, hypoxia, shortness of breath, tachypnea, hemoptysis, and/or loss of consciousness (syncope). Due to its non-specific nature, diagnosis of PE often requires a high index of suspicion. This is particularly true in the stroke population, as patients may be unable to verbalize complaints due to physical and cognitive impairment. PE is often mistaken for pneumonia, which is relatively common post stroke, and can delay diagnosis or worsen patient outcomes (Kelly et al. 2001). The Wells Score is a clinical tool commonly used to identify the pre-test probability that a patient has a PE, to help guide decision-making about further testing. A similar tool exists for determining the pre-test probability that a patient has a DVT (Table 17.4.1.2).
Table 17.4.1.1 Wells Scoring System for PE (from Wells et al. 2000)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of DVT</td>
<td>+3</td>
</tr>
<tr>
<td>Tachycardia (heart rate &gt;100 beats per minute)</td>
<td>+1.5</td>
</tr>
<tr>
<td>Immobilization for ≥3 days OR major surgery in the previous 4 weeks</td>
<td>+1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+1</td>
</tr>
<tr>
<td>Presence of malignancy (or treatment within the last 6 months)</td>
<td>+1</td>
</tr>
<tr>
<td>Prior history of DVT or PE</td>
<td>+1.5</td>
</tr>
<tr>
<td>PE is the most likely diagnosis, or no alternative diagnosis better explains the patient’s illness</td>
<td>+3</td>
</tr>
</tbody>
</table>

Sum Score for Risk of PE: Low risk score 0-1 (1.3%); Moderate risk 2-6 (16.2%); High risk > 6 (40.6%)

Table 17.4.1.2 Wells Scoring System for DVT (from Wells et al. 1997)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralysis, paresis, or recent orthopaedic casting of lower extremity</td>
<td>+1</td>
</tr>
<tr>
<td>Recently bedridden for ≥3 days or major surgery in the previous 4 weeks</td>
<td>+1</td>
</tr>
<tr>
<td>Localized tenderness or pain in deep vein system</td>
<td>+1</td>
</tr>
<tr>
<td>Swelling of entire leg</td>
<td>+1</td>
</tr>
<tr>
<td>Calf swelling 3 cm greater than other leg (measured 10cm below tibial tuberosity)</td>
<td>+1</td>
</tr>
<tr>
<td>Pitting edema greater in the symptomatic leg</td>
<td>+1</td>
</tr>
<tr>
<td>Collateral non-varicose superficial veins</td>
<td>+1</td>
</tr>
<tr>
<td>Active cancer or cancer treated within the last 6 months</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative diagnosis is more likely than DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

Sum Score for Risk of DVT: Low risk score -2-0 (3.0%); Moderate risk 1-2 (16.6%); High risk ≥ 3 (74.6%)

Venous Doppler Ultrasound

Venous Doppler ultrasound is often used to diagnose a DVT, particularly in the deep veins of the legs. The sensitivity of the test is 95% in all patients with symptomatic proximal DVTs but falls to 73% for DVTs distal to the popliteal fossa (Zierler 2004). However, distal DVTs are considered less dangerous, as the risk of embolism from the clot is reduced compared to more proximal DVTs, although the risk may be as high as 20% as distal DVTs can extend proximally without changes in symptoms (Kelly et al. 2001; Zierler 2004).

Venography

Venography is considered the gold standard test for DVT; it is an invasive study whereby contrast dye is injected into the leg veins and imaged with fluoroscopy, which requires radiation. Diagnosis of DVT is made if an intraluminal-filling defect is noted. Due to the wide-spread availability, lower cost, high specificity, lack of radiation exposure, and non-invasive nature of venous Doppler ultrasonography, venography has largely fallen out of favour (Zierler 2004).

D-Dimer Assay

D-dimers are fibrin degradation products that circulate in the blood stream. Fibrin is the main component of clot formation; hypercoagulable states, conditions in which clot formation is heightened, tend to have higher circulating levels of D-dimer (Gill & Nahum 2000). The D-dimer assay is a rapid, non-invasive and inexpensive blood test with a high negative predictive value (Gill & Nahum 2000), meaning that negative D-dimer tests are effective for ruling out DVT (Wells et al. 2000). Positive D-dimer tests lack specificity for DVT: D-dimers are elevated in many other disease states, including cancer, congestive heart failure, and inflammatory conditions (Raimondi et al. 1993). Due to their high sensitivity, D-dimer assays have a high negative predictive value: when the D-dimer is negative, it is unlikely that the patient has a DVT. Akman et al. (2004) reported that the sensitivity and negative predictive values of the D-
dimer test were high, at 95.2% and 96.2%, respectively in a group of 68 rehabilitating patients admitted with a diagnosis of stroke, spinal cord injury, hip arthroplasty or traumatic brain injury. However, because the specificity of the D-dimer is low, the positive predictive value is, too. In the same group of 68 persons in inpatient rehabilitation, Akman et al. (2004) found the specificity and positive predictive value of D-dimer was 55.3% and 48.7%, respectively, for DVT.

**Diagnosis of Deep Vein Thrombosis**
A diagnosis of DVT is made with venous Doppler ultrasound demonstrating DVT in one or more proximal leg veins, or venogram demonstrating intraluminal filling defect. DVT can be ruled out if there is a negative venogram, a negative D-dimer test, or a normal venous ultrasound in the setting of low clinical suspicion or a negative D-dimer. If the diagnosis is in doubt after a negative venous Doppler ultrasound, the test should be repeated approximately one week later (Zierler 2004).

**Clinical Presentation of Pulmonary Embolism**
As previously mentioned, the clinical presentation of PE is non-specific, and often a high index of suspicion is required to make the diagnosis. There is a significant range in the severity of presentation with PE: patients with a massive PE may have profound cardiovascular collapse, including hypotension, coma, and death; smaller PE with less pulmonary infarction may be associated with tachycardia, tachypnea, hemoptysis, pleuritic chest pain, clinical signs of heart failure, signs of right heart strain on ECG, and even fever; subsegmental or small vessel Pes may be asymptomatic (Kelly et al. 2001; Zierler 2004). Although PE is often associated with DVT, many cases are cryptogenic or have no known DVT, with only 30% having the clinical features of a DVT and only 50% demonstrating a DVT on ultrasonography (Zierler 2004).

**Ventilation-Perfusion Scanning**
Ventilation-perfusion (VQ) scans are nuclear medicine tests frequently used to diagnose a PE by detecting reduced perfusion (blood flow) due to the presence of a blood clot in an area of otherwise normal, ventilated lung. The use of VQ scanning is limited in patients who are at risk of other lung abnormalities, such as pneumonia or aspiration, and therefore may not be ideal in stroke patients (Zierler 2004).

<table>
<thead>
<tr>
<th>Ventilation-Perfusion Scan Results</th>
<th>Clinical Suspicion of Pulmonary Embolism*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>High probability</td>
<td>56%</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>16%</td>
</tr>
<tr>
<td>Low probability</td>
<td>4%</td>
</tr>
<tr>
<td>Normal/near-normal probability</td>
<td>2%</td>
</tr>
</tbody>
</table>

* Percentage of patients with pulmonary embolism

Adapted from the PIOPED Investigators (Gill and Nahum 2000, PIOPED Investigators 1990)

The PIOPED investigators (1990) demonstrated that a low-probability or normal VQ scan with a low clinical suspicion of pulmonary embolism essentially excludes the diagnosis of pulmonary embolism with a negative predictive value of 96% and 98%, respectively (Gill & Nahum 2000; PIOPED Investigators 1990). When clinical suspicion is high and the scan indicates a high probability of pulmonary embolism, the positive predictive value is 96% (Gill & Nahum 2000; PIOPED Investigators 1990). General consensus is that treatment should be initiated in patients with positive V/Q scans in whom there is a moderate or
high index of suspicion for PE (Kelly et al. 2001; PIOPED Investigators 1990). However, the majority of VQ scans yield nondiagnostic results, requiring further testing (PIOPED Investigators 1990).

**Pulmonary Angiography**

Pulmonary angiography provides a definitive diagnosis for pulmonary embolism and is therefore considered the gold standard for diagnosis (Gill & Nahum 2000). Pulmonary angiography directly visualizes the pulmonary vessels by percutaneous catheterization of the pulmonary arteries and injection of contrast dye into a pulmonary artery branch (Gill & Nahum 2000). A negative pulmonary angiogram excludes clinically relevant pulmonary embolism (Gill & Nahum 2000; Tapson et al. 1999). This invasive test poses significant risk to patients, including stroke from arterial manipulation, contrast reactions, contrast-induced kidney injury, risk of bleeding from arterial puncture, and it is associated with a mortality rate of up to 0.5% (Newman 1989; Stein et al. 1992). Relative contraindications include significant bleeding risk, allergy to contrast medium, and renal insufficiency (Gill & Nahum 2000). The test is expensive and personnel-intensive. Due to the advent of non-invasive, lower risk methods of evaluating the pulmonary arterial tree, pulmonary angiography has largely fallen out of use for the detection of PE (Zierler 2004).

**CT Pulmonary Angiography**

In most secondary and tertiary care centres with CT scan capabilities, CT pulmonary angiography (CTPA) is the diagnostic test of choice in patients with suspected PE (Zierler 2004). In a systematic review and meta-analysis of CTPA for pulmonary embolism diagnosis, Safriel & Zinn (2002) found the sensitivity to be 74.1% and the specificity to be 89.5%. CTPA has become the diagnostic method of choice; however, there is no level 1 evidence to support this practice (Zierler 2004). Technological advancements have decreased the cost and increased the sensitivity and specificity of this test (Zierler 2004).

**17.4.2 Incidence of Venous Thromboembolism Post Stroke**

Deep venous thrombosis (DVT) and pulmonary embolism (PE) remain a significant cause of morbidity and mortality in stroke patients undergoing rehabilitation (Desmukh et al. 1991). Patients are at highest risk of developing a DVT between the second and seventh day after acute stroke (Brandstater et al. 1992). The incidence of DVT in stroke patients varies considerably by study, ranging from 22% and 73% (Izzo & Aquino 1986; Landi et al. 1992; Miyamoto & Miller 1980). Brandstater et al. (1992) reviewed 12 studies evaluating the incidence of DVT in ischemic stroke, hemorrhagic stroke, or both. The incidence of DVT ranged from 23% to 75% and, in most studies, was approximately 50% (Bornstein & Norris 1988; Czechanowski & Heinrich 1981; Denham et al. 1973; Dickmann et al. 1988; Gibberd et al. 1976; McCarthy & Turner 1986; Mellbring et al. 1986; Prasad et al. 1982; Prins et al. 1989; Turpie et al. 1987; Warlow et al. 1976). The vast majority of these studies did not include standardized protocols for DVT prophylaxis. In this review, Brandstater et al. (1992) cited several studies that noted that DVT and PE risk continues beyond the initial two weeks post stroke and into the phase of active rehabilitation.

The prevalence of DVT among patients admitted for rehabilitation is lower than in acute care, ranging from 12-40%, depending on the provision of anticoagulants, mobility status, and method of detection used (R. D. Wilson & Murray 2005). The incidence of DVT diagnosed during rehabilitation is lower still, ranging from 5% to 11% (Harvey et al. 2004). However, in the absence of DVT prophylaxis, one study found over 60% of dense hemiplegics develop DVTs and 9-15% have pulmonary emboli, with an associated 1-2% mortality rate (Sioson et al. 1988). Indeed, pulmonary embolism has been reported to be the fourth most common cause of death in the 30 days post stroke, and the risk of thromboembolism persists thereafter (Bounds et al. 1981). Features that increase a patient’s risk of DVT include lower limb paresis, reduced consciousness, obesity, and having a personal history of DVT (Imberti & Prisco 2005).
Prior to the use of DVT prophylaxis, Brandstater et al. (1992) evaluated two studies of 118 post-stroke patients admitted to inpatient rehabilitation who were screened for DVT on admission to rehab; they reported 31% of patients admitted to rehabilitation units had a DVT (Izzo & Aquino 1986; Sioson et al. 1988). The mean time between stroke onset and screening was 45 days. Similarly, Cope et al. (1973) reported a DVT prevalence of 31%, detected by venography, in patients admitted to a rehabilitation centre. Miyamoto and Miller (1980) screened stroke patients with I-125 fibrinogen, a precursor to D-dimer, an average of 9 days following admission to rehabilitation and found a 29% prevalence of DVT.

Venous thromboembolism (VTE) usually begins with a calf DVT (Cogo et al. 1993; Nicolaides et al. 1971; Philbrick & Becker 1988). Previously, distal (calf) DVTs were thought to rarely cause PEs and therefore were considered less worrisome (Kakkar et al. 1969); however, 20% of distal DVTs will go on to extend into the proximal veins, and therefore do put patients at increased risk (Brandstater et al. 1992; Kakkar et al. 1969; Kelly et al. 2001). When DVTs cause symptoms, over 80% of those involve the popliteal or more proximal veins (Kearon et al. 1998). However, clinical findings of DVT such as leg pain, swelling, and erythema may be present in less than half of patients, even when diagnostic tests are positive (Brandstater et al. 1992). On admission to a rehab center, clinical features of a DVT were present in only 5-10% of patients in whom diagnostic testing had demonstrated the presence of a DVT (Izzo & Aquino 1986; Miyamoto & Miller 1980; Sioson et al. 1988). Similar findings have been reported in more recent studies (Zierler 2004).

Like the incidence of DVT, the incidence of PE post stroke varies widely between studies; estimates range from 0.8% at 2 weeks (IST Group 1997) to 39% at 10 days post stroke (Dickmann et al. 1988). Kelly et al. (2004) identified advanced age and a Barthel Index score of 9 or less as the two major risk factors for the development of DVT two days post stroke using a multivariable regression model including 102 acute ischemic stroke patients. A recent review of the Registry of the Canadian Stroke Network in 2013 by the Stroke Outcomes Research Canada Working Group reports a similar incidence of PE (Pongmoragot et al. 2013). The registry contains information on 11 287 patients with acute ischemic stroke. PE was identified in 0.78% of acute ischemic stroke patients and was associated with higher risk of death at 30 days (25.8% vs. 13.6%; P<0.001) and at 1 year (47.2% vs. 24.6%; P<0.001) as well as disability at discharge (85.4% vs. 63.6%; P<0.001) (Pongmoragot et al. 2013).

Given the relatively high prevalence of DVT and PE post stroke, identifying patients who are at increased risk is crucial to direct clinical management. Gregory and Kuhlemeier (2003) investigated the prevalence of DVTs in both hemorrhagic and ischemic stroke, and identified the following risk factors: hemorrhagic stroke is an independent risk factor for DVT in acute care (p<0.0007), as is increased length of hospital stay (p<0.00001). Skaf et al. (2005) observed at the same increased rate of PE, DVT and VTE in hemorrhagic stroke patients in comparison to ischemic stroke patients. The higher rate of DVT in hemorrhagic stroke may reflect decreased use of DVT prophylaxis in this population due to the concerns for increased bleeding risk (Skaf et al. 2005).

**Conclusions Regarding the Incidence of Venous Thromboembolism Post Stroke**

*DVT and PE are common and serious post-stroke complications. DVT is more likely to occur in patients who do not receive DVT prophylaxis.*

### 17.4.3 Prophylaxis of Venous Thromboembolism Post Stroke

Prophylactic anticoagulant therapy is widely used for preventing deep vein thrombosis (DVT) and pulmonary embolism (PE) from occurring during acute hospitalization for a number of indications,
including stroke. Prophylaxis is aimed at reducing the occurrence of new thrombosis episodes, and requires lower doses than active treatment of a known or pre-existing thrombus. Even at lower doses, prophylactic anticoagulation can lead to serious complications related to increased risk of bleeding. To aid in clinical decision-making, the authors of the CLOTs trials attempted to develop a prediction model to identify immobile patients at higher risk of DVT (Dennis et al. 2011). While a few factors, including dependency before stroke, history of DVT/PE, inability to lift arms off the bed, and diabetes, were all identified as independent predictors for developing DVT, the resulting model did not discriminate well between patients who did and did not develop DVTs.

Guidelines for prophylactic anticoagulation vary. The European Stroke Organisation’s 2016 guidelines for venous thromboembolism (VTE) prophylaxis after acute ischemic stroke supports the use of intermittent pneumatic compression, low molecular weight heparin (LMWH), heparinoids, and unfractionated heparin in patients in whom clinical judgment indicates the risk of VTE outweighs the risk of intracranial and extracranial bleeding (Dennis et al. 2016). These guidelines recommend against graduated compression stockings and neuromuscular electrical stimulation, as studies of efficacy and safety are inadequate. The American College of Physicians’ clinical practice guideline for hospitalized non-surgical inpatients including acute stroke recommends against universal use of VTE prophylaxis, recommends heparin or heparinoid pharmacotherapy for VTE prophylaxis only in patients whose risk of VTE outweighs their risk of major bleeding, and recommends against the use of graduated compression stockings (Qaseem et al. 2011).

The Canadian Best Practice Recommendations for Stroke Care state that patients at high risk of VTE should be started on VTE prophylaxis immediately [Evidence Level A] (Lindsay et al. 2010).

- Low molecular weight heparin should be considered for patients with acute ischemic stroke at high risk of VTE; or unfractionated heparin for patients with renal failure [Evidence Level B].
- The sole use of anti-embolism stockings, such as graduated compression stockings, for post-stroke VTE prophylaxis is not recommended [Evidence Level A].

**Pharmacological Agents for VTE Prophylaxis**

**Unfractionated Heparin (UFH)**

Heparin acts as an anticoagulant by forming a complex with antithrombin, catalysing the inhibition of several activated blood coagulation factors: XIIa, Xla, IXa, Xa, and thrombin. UFH has an immediate onset of action. It is most often used in acute conditions, and must be given parenterally; it is typically given in IV or subcutaneous form. Although low molecular weight heparin has become more popular in the treatment of DVT, the effects of intravenous heparin can be reversed rapidly. Bleeding is the most common adverse effect of heparin. Osteoporosis is associated with the prolonged use of high doses of heparin, although its occurrence is infrequent. Thrombocytopenia is an uncommon but serious side effect of the treatment (Pineo 2004).

**Low Molecular Weight Heparin (LMWH) and Heparin Analogues**

LMWH is derived from standard heparin through chemical or enzymatic depolymerization. Whereas unfractionated heparin has a molecular weight of 5,000 to 30,000 Daltons, LMWH has a lower molecular weight, ranging from 1,000 to 10,000 Daltons, hence its name. LMWH has the same mechanism of action as UFH, but binds less strongly to protein, has enhanced bioavailability, interacts less with platelets, and yields a predictable dose response (Rydberg et al. 1999). The clinical advantages of LMWH include predictability, dose-dependent plasma levels, a long half-life and less bleeding for a given antithrombotic effect (Rydberg et al. 1999). Thrombocytopenia is not associated with short-term use of low-molecular-weight heparin, unlike unfractionated heparin (Pineo 2004). LMWH is administered once
or twice daily, both during the high-risk period when prophylaxis for DVT is recommended and also while waiting for oral anticoagulation to take effect in the treatment of DVT. The activated partial thromboplastin time (aPTT) does not need to be monitored, and the dosage does not need to be adjusted (Rydberg et al. 1999).

Danaparoid sodium (Orgaran) is an alternative anticoagulant for patients who develop heparin-induced thrombocytopenia from heparin therapy (Hull & Pineo 2004). Danaparoid is a low molecular weight heparinoid that inactivates thrombin. The major difference between danaparoid and other low molecular weight heparins is that danaparoid is devoid of heparin or heparin fragments, which are through to cause thrombocytopenia by cross-reactivity with platelets. Its active components consist of heparin sulfate, dermatan sulfate and chondroitin sulfate.

<table>
<thead>
<tr>
<th>Table 17.4.3.1 Types of Heparinoids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic Name</strong></td>
</tr>
<tr>
<td>Dalteparin</td>
</tr>
<tr>
<td>Danaparoid</td>
</tr>
<tr>
<td>Enoxaparin</td>
</tr>
<tr>
<td>Ardeparin</td>
</tr>
<tr>
<td>Parnaparin, Reviparin</td>
</tr>
<tr>
<td>Tinzaparin</td>
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<tr>
<td>Certoporain</td>
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</table>

**Warfarin (Coumadin)**
Warfarin is a vitamin K antagonist that inhibits the synthesis of clotting factors II, VII, IX, and X, as well as anticoagulation proteins C and S. Therapeutic doses of warfarin reduce the production of vitamin K-dependent clotting factors by approximately 30 to 50 percent (Horton & Bushwick 1999). The dose of warfarin is titrated to clinical effect by monitoring the International Normalized Ratio (INR), a measure of anticoagulation effect. Clinical evidence indicates that an INR of 2.0-3.0 is sufficient for prophylaxis and treatment of VTE while minimizing the risk of hemorrhage associated with higher INRs (Horton & Bushwick 1999). Because warfarin inhibits the synthesis of vitamin K-dependent clotting factors, its anticoagulation effect is not present until approximately the fifth day of therapy; during this time, however, anticoagulation proteins C and S are inhibited, and the risk of clot formation is heightened. Concomitant use of heparin or heparinoid therapy, which has immediate onset of action, may be required to bridge the patient during the time it takes warfarin to have effect. Continuous anticoagulation during this period usually requires heparin therapy to overlap with warfarin therapy for 4-5 days for therapeutic anticoagulation (if clots are already present), although there is insufficient evidence that this is required for VTE prophylaxis (Sandercock et al. 2015).

**Novel Oral Anticoagulants (NOACs)**
NOACs belong to a relatively new pharmacologic medication class of factor Xa inhibitors and direct thrombin inhibitors which may be taken orally instead of parenterally. In general, these medications offer a number of benefits over warfarin, including: standardized dosing without the need for monitoring or adjustment, predictable pharmacokinetics and bioavailability, ease of dosing on an inpatient and outpatient basis, and evidence of effectiveness. Unlike warfarin, however, these medications often lack an antidote, which can be problematic for patients who develop serious bleeding.

Few studies have examined the use of this class of medications for VTE prophylaxis. A recent Cochrane review found insufficient evidence to recommend the use of argatroban, an oral direct thrombin inhibitor, for VTE prophylaxis post stroke (Sandercock et al. 2015). However, due to their relative
convenience compared to warfarin and parenterally administered medications, the use of NOACs will become more widespread. Additional research is needed in the post-stroke population.

**Reviews of Pharmacotherapy for VTE Prophylaxis Post Stroke**

Bath et al. (2000) conducted a systematic review evaluating the safety and efficacy of LMWH, including dalteparin, danaparoid, mesoglycan, nadroparin and tinzaparin. The analysis included the results from 11 studies and 3,048 subjects. The treatment contrast assessed was LMWH compared with placebo. While treatment was associated with a significant reduction in the occurrence of DVT (OR: 0.27, 95% CI 0.08 to 0.96) it was accompanied by a significant increase in the risk of extracranial hemorrhage (OR: 2.17, 95% CI 1.10 to 4.28). The authors concluded that LMWH should not be used routinely after ischemic stroke.

An updated 2015 Cochrane review of 24 trials of VTE prophylaxis post stroke including 23,748 patients compared the effectiveness of various pharmacologic agents (Sandercock et al. 2015). Based on 11 trials including 22,776 patients, there was no evidence that initiating VTE prophylaxis within 14 days of stroke reduced all-cause mortality. Earlier initiation of therapy was associated with fewer ischemic strokes, but this finding is tempered by the concurrent increase in intracranial hemorrhages. Early therapy was also associated with a reduction in the frequency of symptomatic PE, but this finding was offset by increased risk of extracranial bleeding. As expected, the use of anticoagulation for VTE prophylaxis was associated with lower rates of VTE, including ischemic stroke, pulmonary embolism, and deep vein thrombosis, but was also associated with increased intracranial and extracranial hemorrhages. The authors concluded that the data does not support routine, widespread use of anticoagulation for VTE prophylaxis post stroke; this recommendation was unchanged from the previous review in 2008 (Sandercock et al. 2015; Sandercock et al. 2008).

In a systematic review, Gubitz et al. (2004) examined the effects of all forms of anticoagulation after ischemic stroke. One of the aims of the study was to assess the effectiveness of anticoagulation therapy on the reduction of DVT incidence. Anticoagulation included unfractionated heparins, low molecular weight heparins, heparinoids, and oral anticoagulants. Although the review included only 3.9% of patients included in the individual RCTs, the reduction in DVT risk associated with anticoagulation therapy, compared to control, was dramatic (OR=0.21, 95% CI 0.15-0.29). Most of the DVTs identified in the review were asymptomatic. The odd ratio of developing PE was reduced by 79% with anticoagulation compared to control (OR=0.60, 95% CI 0.44-0.81); the number needed to treat to avoid one PE was 250 patients, as the trial found per every 1,000 patients treated, 4 PEs were avoided. However, the risk of major extracranial hemorrhage was 9 per 1,000 patients treated, indicating significant risk. Although anticoagulation reduced DVT and PE, there was no associated reduction in death or dependency at the end of follow-up.

Kamphuisen and Agnellu (2007) conducted a review investigating the benefit/risk ratio from pharmacological prophylaxis for VTE in acute ischemic stroke patients. Sixteen randomized controlled trials were included (n=23,043). The studies included had small number of events and varied in anticoagulant treatment doses. High-dose UFH was associated with decreased incidence of PE, increased intracranial hemorrhage, and increased extracranial hemorrhage compared to control. High-dose LMWH reduced the incidence of DVT and PE, but increased the risk of bleeding, comparable to high-dose UFH. Low-dose LMWH decreased DVT and PE, and was not associated with a higher rate of hemorrhage. The authors concluded low-dose LMWH has the most favourable risk/benefit profile.

Laporte et al. (2011) analyzed patients-level data from 4 RCTs that compared the use of UHF (5000 units subcutaneous 2-3 times daily) and enoxaparin (4000 units subcutaneous once daily) in the prevention of
DVT. The analysis included the results from two trials restricted to acute stroke patients (Hillbom et al. 2002; Sherman et al. 2007). Compared with UFH, enoxaparin was superior for preventing DVT and PE. Enoxaparin use was associated with risk reductions of 37% for total VTE and 62% for symptomatic VTE at day 15. The incidence of major bleeding episodes was similar between UFH and enoxaparin. There was a trend towards reduced risk for mortality in patients receiving enoxaparin (RR 0.83, 95% CI 0.64-1.08), compared with UFH.

The use of anticoagulants to reduce the risk of DVT after intracerebral hemorrhage is controversial, due to the increased risk of bleeding. To clarify its safety and efficacy in hemorrhagic stroke, Paciaroni et al. (2011) conducted a meta-analysis including the results from 4 trials (2 RCTs & 2 controlled trials) evaluating LMWH or UFH compared to no treatment or compression stockings. Treatment was initiated within 6 days and continued for up to 14 days. Follow-up ranged from 10 days to 3 months after treatment; there was a non-significant decrease in DVT risk (RR: 0.77; 95% CI: 0.44 to 1.34) and death (RR: 0.76; 95% CI:0.57 to 1.03) favouring the LMWH and UFH compared to no treatment or compression stockings, but these treatments had a non-significant risk in hematoma enlargement (RR: 1.42; 95% CI: 0.57 to 3.53).

Table 17.4.3.1 Summary of RCTs Evaluating Heparinoids for VTE Prophylaxis

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>RCT (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOAST (1998)</td>
<td>RCT (9) N=1281</td>
<td></td>
<td>E: LMWH</td>
<td>Incidence of DVT (+)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Placebo</td>
<td>Major bleeding (+) (C&lt;E at 3 months)</td>
</tr>
<tr>
<td>Berge et al. (2000)</td>
<td>RCT (9) N=449</td>
<td></td>
<td>E: LMWH (100 I/kg 2x/day dalteparin)</td>
<td>Incidence of DVT (-)</td>
</tr>
<tr>
<td>Diener et al. (2006)</td>
<td>RCT (9) N=272</td>
<td></td>
<td>E: LMWH</td>
<td>Incidence of DVT (-)</td>
</tr>
<tr>
<td>Hillbom et al. (2002)</td>
<td>RCT (8) N=212</td>
<td></td>
<td>E:LMWH</td>
<td>Rate of thromboembolic events (+), LMWH</td>
</tr>
<tr>
<td>Dumas et al. (1994)</td>
<td>RCT (8) N=179</td>
<td></td>
<td>E: LMWH</td>
<td>Incidence of DVT (-)</td>
</tr>
<tr>
<td>Sandset et al. (1990)</td>
<td>RCT (8) N=103</td>
<td></td>
<td>E: LMWH</td>
<td>Motricity Index Score (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Standard</td>
<td>Mortality (-)</td>
</tr>
<tr>
<td>Bath et al. (2000)</td>
<td>RCT (7) N=3048</td>
<td></td>
<td>E1: High dose tinzaparin (175 anti-Xa IU/kg)</td>
<td>Frequency of DVT (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E2: Medium dose tinzaparin (100 anti-Xa IU/kg daily)</td>
<td>Intracranial hemorrhage (+) (high vs aspirin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E3: 300 mg of aspirin daily</td>
<td></td>
</tr>
<tr>
<td>Sherman et al. (2007)</td>
<td>RCT (7) N=1762</td>
<td></td>
<td>E: LMWH</td>
<td>Incidence of asymptomatic DVT (+), LMWH</td>
</tr>
<tr>
<td>Kay et al. (1995)</td>
<td>RCT (7) N=312</td>
<td></td>
<td>E1: High-dose LMWH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E2: Low-dose LMWH</td>
<td>Poor outcomes (death or dependence): E1 &amp; E2&gt;C (-)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C: Placebo</td>
<td>Number of patients experiencing a hemorrhagic transformation (-)</td>
</tr>
<tr>
<td>Turpie et al. (1992)</td>
<td>E: LMWH</td>
<td></td>
<td>Incidence of DVT (+), LMWH</td>
<td></td>
</tr>
</tbody>
</table>
RCT (7)  
N=87

Turpie et al. (1987)  
RCT (7)  
N=75

Prins et al. (1989)  
RCT (6)  
N=60

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

McCarthy et al. (1977)  
RCT (5)  
N=32

McCarthy and Turner (1986)  
RCT (4)  
N=305

Wu et al. (2014)  
RCT (3)  
N=297

<table>
<thead>
<tr>
<th>Intervention</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>UFH</td>
<td>2-10</td>
</tr>
<tr>
<td>LMWH (compared to placebo)</td>
<td>1-4</td>
</tr>
<tr>
<td>Warfarin (fixed low dose, 2mg)</td>
<td>9</td>
</tr>
<tr>
<td>Compression Devices</td>
<td>9-16</td>
</tr>
<tr>
<td>Aspirin</td>
<td>&gt; 300</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant difference between treatment groups  
- Indicates no statistically significant difference between treatment groups

Discussion
Seven RCTs investigated the efficacy of anticoagulation therapy in reduction of DVT incidence when compared to no treatment. McCarthy et al. (1986) found that subcutaneous heparin significantly reduced the likelihood of developing DVT when compared to a non-treatment control. Four studies compared LMWH to a placebo control group. The incidence of DVT was lower among patients receiving LMWH in three of these trials (Kay et al. 1995; McCarthy & Turner 1986; McCarthy et al. 1977; Sandset et al. 1990; TOAST investigators 1998) although the TOAST investigators noted that patients in the LMWH group experienced a significantly greater number of major hemorrhages. Two trials included aspirin as a treatment group (Bath et al. 2001; Berge et al. 2000). Both trials reported no differences in the incidence of DVT compared with LMWH. The TAIST investigators noted an increase in the risk of intracerebral hemorrhage in the LMWH group.

Andre et al. (2007) calculated the number needed to treat (NNT) to prevent one post-stroke DVT for various DVT prophylaxis methods. The results are presented in Table 17.4.3.3.

Table 17.4.3.3 NNT for DVT Prevention (from Andre et al. 2007)
In two equivalency trials, Hillbom et al. (2002) and Diener et al. (2006) compared LMWH with UFH for DVT prophylaxis post stroke. At 3 months, the incidence of DVT was lower among patients treated with enoxaparin (Hillbom et al. 2002); however, there was no difference between groups in the other trial. The authors of the PROTECT trial suggested that the study results are not comparable since patients in the Hillbom trial were more disabled, and therefore likelier to experience DVT. A recent meta-analysis evaluating the efficacy of LMWH and UFH included the results from these three trials (Shorr et al. 2008). The use of LMWH was associated with a significant risk reduction for either DVT or PE (OR: 0.54; 95% CI, 0.41 to 0.70; p < 0.001). Treatment with LMWH was also associated with a reduction in the incidence of proximal DVT (OR: 0.53; 95% CI, 0.37 to 0.75; p < 0.001) and PEs (OR: 0.26; 95% CI, 0.07 to 0.95; p = 0.042). There were no differences in rates of overall bleeding, intracranial hemorrhage, or mortality based on the type of agent employed.

A large international, multicenter study (PREVAIL) compared enoxaparin with twice daily UFH (Sherman et al. 2007). The authors concluded that enoxaparin is preferable to UFH in the prevention of DVT. The NNT with enoxaparin to prevent one episode of VTE was 13. The number needed to harm, a measure of the number of patients who need to be treated for one patient to develop a clinically significant hemorrhage, was 173.

Fondaparinux is a synthetic pentasaccharide that inhibits Factor Xa; it is chemically similar to LMWH. The risk of major bleeding has been postulated to be lower for fondaparinux than other heparinoids. Its use among stroke patients has been evaluated in a single retrospective study of 60 patients (Mukand & Mukand 2010). This study found no differences in safety or efficacy between the two therapies.

There are few studies evaluating the efficacy of DVT prophylaxis in inpatient rehabilitation post stroke. Guidelines are vague with respect to when to discontinue DVT prophylaxis after acute stroke for patients in the rehabilitation setting. Common practice is to continue DVT prophylaxis until the patient is ambulatory or until they are discharged from the rehab unit. Although clinically symptomatic DVTs are less common in the rehabilitation setting a review of patients admitted to a stroke rehabilitation unit on average 60 days post stroke demonstrated that 11% of patients had evidence of a DVT (Oczkowski et al. 1992). The odds of having a DVT were 17.6 times greater if the patient was bedridden or wheelchair bound.

**Conclusions Regarding the Prevention of Deep Venous Thromboembolism**

*There is level 1 evidence that the use of enoxaparin is effective for DVT prophylaxis after acute stroke and has lower risk of significant bleeding compared to unfractionated heparin.*

*There is level 1a evidence that low molecular weight heparin may reduce the incidence of DVT and PE. Its effectiveness may be comparable to that of aspirin for reducing the incidence of DVTs.*

*Several randomized, controlled clinical trials have assessed the efficacy and safety of heparinoid medications for VTE prophylaxis. However, these studies do not use a rehabilitative stroke population. Enoxaparin may be preferable to other heparinoids due to its lower risk of major bleeding.*
17.4.4 Mechanical Devices for Prevention of Deep Vein Thrombosis

External physical forms of deep vein thrombosis (DVT) prophylaxis include graduated compression stockings, intermittent pneumatic compression, or neuromuscular electrical stimulation. The use of these devices is tempting because of the lower risk of bleeding as no anticoagulation is required. The mechanism by which compression stockings reduce the risk of DVT is not well-understood (Amaragiri & Lees 2000). Graduated compression stockings compress the surface veins, keeping their diameter small, and forcing blood into the deep vein system, which is thought to increase blood flow in deep veins, reducing venous insufficiency (Amaragiri & Lees 2000). A Cochrane review by Amaragiri and Lee (2000) suggests that there is a significant decrease in DVT risk among post-surgical patients who wore the stockings, although an RCTs involving stroke patients was not included in this review (Muir et al. 2000). Although often considered a relatively benign intervention, their use was associated with serious side effects as serious as skin ulceration and necrosis.

A Cochrane review by Naccarato et al. (2010) examined the effectiveness of compression stockings and intermittent pneumatic compression devices among RCTs of post-stroke patients. The review included five RCTs, two assessing intermittent pneumatic compression devices in 177 post-stroke patients and 3 assessing graded compression stockings in 2615 post-stroke patients. Neither device significantly reduces the risk of DVT or death. The authors concluded that there was insufficient evidence to support the use of physical methods in routine DVT prophylaxis.

Since this Cochrane review, the CLOTS3 study, a large, multicenter trial, has investigated intermittent pneumatic compression for DVT prevention (Dennis et al. 2013). The 94 participating sites enrolled 2876 patients with acute stroke and resultant immobility; patients were randomly assigned to intermittent pneumatic compression (IPC) or no IPC within 3 days of stroke. Venous Doppler ultrasound of both legs at 7-10 days and again at 25-30 days or when symptomatic of DVT. The IPC was worn at all times for a minimum of 30 days (except for washing and therapy) or until the second screening. At the conclusion of the study, DVT was diagnosed in 122/1438 (8.5%) in the IPC group and 174/1438 (12.1%) in the no IPC group resulting in an absolute risk reduction of 3.6%. There was no significant difference between groups on secondary outcomes of death and falls with injury; however, there were more episodes of skin breakdown on the legs in the IPC group (3%) compared to no IPC (1%) patients (p=0.002). This large study provides some support for the use of IPC in DVT prevention, although there is an increased risk of skin breakdown.

Pambianco et al. (1995) and Muir et al. (2000) did not report a reduced risk of DVTs among patients receiving a variety of treatments including electrical muscle stimulation, pneumatic compression and graded compression stockings. The results of the studies evaluating the efficacy of various drug treatments are presented in Table 17.4.4.1.

In patients with contraindications to anticoagulation, or who develop DVT or venous thromboembolism (VTE) despite anticoagulation, invasive mechanical means of VTE prevention can be pursued. Inferior vena cava (IVC) filters are physical devices inserted percutaneously into the IVC to act as a physical barrier to the migration of blood clots from the deep veins of the legs into the lungs. These devices are therefore primarily for VTE prophylaxis, and do not prevent DVT.

IVC filters have been studied in 371 post-stroke patients for preventing pulmonary embolism in a retrospective cohort study (Somarouthu et al. 2011). At baseline, 42.9% of patients enrolled in the study had a pulmonary embolism (PE) on imaging prior to IVC filter placement. The most common indications for IVC filter in this study were contraindication to anticoagulation (68%), PE prophylaxis, and complication from or failure of anticoagulation (4%). The follow-up period was, on average, 1.7 years.
Symptomatic PE occurred in 15% of patients after IVC filter placement. In this study of very ill patients, 49% of patients died but only 0.8% of patient deaths were attributed to post-IVC filter PE. The authors concluded that IVC filters had an acceptable safety profile and were effective at preventing life-threatening PE.

Table 17.4.4.1. Summary of RCTs Evaluating the Physical Methods for the Prevention of DVT

<table>
<thead>
<tr>
<th>Author, Year (PEDro Score)</th>
<th>Intervention E: experimental group(s); C: control group</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dennis et al.</strong> (2009) RCT (8) N=2518</td>
<td>E1: Routine care plus thigh-length compression stockings C: Routine care plus</td>
<td>Occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins was reduced with compression stockings (+)</td>
</tr>
<tr>
<td><strong>Lacut et al.</strong> (2005) RCT (7) N=151</td>
<td>E: TED brand stockings + IPC C: TED brand stockings alone</td>
<td>TED + IPC reduced the risk of asymptomatic DVT compared to TED stockings alone (+)</td>
</tr>
<tr>
<td><strong>Muir et al.</strong> (2000) RCT (7) N=98</td>
<td>E1: Early mobilization E2: TED stockings + standard care C: Standard care</td>
<td>No difference in reduction in DVT incidence between groups (-)</td>
</tr>
<tr>
<td><strong>Dennis et al.</strong> (2010) RCT (6) N=3114</td>
<td>E: Thigh-length stockings C: Below-knee stockings</td>
<td>Thigh-length stockings reduced the incidence of proximal DVT within 30 days (+)</td>
</tr>
<tr>
<td><strong>Dennis et al.</strong> (2013) RCT (6) N=2876</td>
<td>E: IPC C: No IPC</td>
<td>IPC reduced the incidence of DVT within 30 days compared to no IPC (+)</td>
</tr>
<tr>
<td><strong>Prasad et al.</strong> (1982) RCT (5) N=26</td>
<td>E: IPC of calf C: No treatment control group</td>
<td>No benefit for development of DVT (-)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant difference between treatment groups
- Indicates no statistical significant difference between treatment groups

**Discussion**
Neither Muir et al. (2000) or Prasad et al. (1982) reported differences in the development of DVT between groups in their small studies evaluating two different treatment approaches. The results from the largest and most methodologically rigorous trial to date CLOTS 1 suggests that there is no decreased risk of developing a DVT within 30 days of stroke associated with use of thigh-length graduated compression stockings (Dennis et al. 2013a). In fact, there was an increase in the number of adverse events reported with the use of stockings. However, the results from the CLOTS 2 trial indicated that the incidence of DVT was higher among patients randomized to wear knee-length GCS compared with those who wore thigh-length stockings (Dennis et al. 2013a). Although the results of each of these studies are clear and simple to understand, when combined, they are hard to interpret. The authors suggested that the use of knee-length stocking may actually increase the risk of DVT or that the protective effect of thigh-length stockings may have been under-estimated in the CLOTS 1 trial.

The prevention of DVT among patients suffering from ICH can be problematic given that traditional anticoagulants are hazardous to patients already at increased risk for bleeding complications. For this reason, non-invasive mechanical means of DVT prophylaxis are tempting in this group, although the efficacy is likely poorer than anticoagulation. In patients with DVT or at very high risk who cannot have anticoagulation, IVC filters warrant consideration.

**Conclusions Regarding the Prevention of Deep Vein Thrombosis with Mechanical Devices**
There is level 1a evidence that the use of an intermittent pneumatic compression device may reduce the occurrence of DVT compared to no IPC.

There is level 1b evidence that compression stockings with intermittent pneumatic compression may reduce the occurrence of DVT as compared to compression stockings alone.

There is conflicting level 1a evidence regarding the use of graded compression stockings on the development of proximal DVT.

Evidence for the effectiveness of compression stockings on preventing DVT is unclear. However, evidence suggests that intermittent pneumatic calf compression devices may help prevent the occurrence of DVT.

17.4.5 Treatment of Venomous Thromboembolism Post Stroke

Heparinoids for Venomous Thromboembolism Treatment
Van Dongen et al. (2004) conducted a Cochrane review comparing the effects of fixed-dose subcutaneous LMWH and adjusted-dose intravenous or subcutaneous unfractionated heparin for initial treatment of acute deep vein thrombosis (DVT) or pulmonary embolism (PE) among patients with a range of diseases, not limited to stroke. Twenty-two studies were included (n = 8867). Thrombotic complications occurred in 3.6% of patients treated with low molecular weight heparin (LMWH) compared with 5.4% treated with unfractionated heparin (UFH) (OR= 0.68; 95% CI; 0.55 to 0.84). Major hemorrhages occurred in 1.2% of patients treated with LMWH, compared with 2.0% of patients treated with UFH (OR= 0.57, 95% CI; 0.39 to 0.83, 19 trials). Mortality was higher among patients treated with UFH. In subgroup analyses, there were statistically significant reductions in thrombotic complications and major hemorrhage, favouring LMWH. The authors concluded that LMWH is as good as UFH for the initial treatment of DVT and significantly reduced the occurrence of major hemorrhage, both during initial treatment and overall mortality at follow up.

Oral Anticoagulation for VTE Treatment: Warfarin & Novel Oral Anticoagulants (NOACs)
The oral direct thrombin inhibitor dabigatran was studied in a randomized, double-blind, non-inferiority trial compared to warfarin for the treatment of acute venous thromboembolism (Schulman et al. 2009). In this study, patients in both groups were initially treated with parenteral anticoagulation for a mean 10 days then either dabigatran 150mg twice daily or Warfarin dosed to the International Normalized Ratio between 2-3. There was no significant difference between groups with respect to recurrent DVT and both had similar safety profile with respect to major bleeding episodes and episodes of any bleeding. As a result, the study concluded that fixed dose dabigatran is as effective as warfarin for the treatment of acute venous thromboembolism and does not require laboratory monitoring.

The oral factor Xa inhibitor rivaroxaban has also been studied for the treatment of DVT (EINSTEIN Investigators 2010) as well as PE (EINSTEIN-PE Investigators 2013). To study rivaroxaban’s efficacy in the treatment of acute, symptomatic DVT, an open-labeled non-inferiority study was constructed comparing rivaroxaban (15mg twice daily for 3 weeks then 20mg once daily for a total of 6 months) to subcutaneous enoxaparin followed by a vitamin K antagonist (wither warfarin or acenocoumarol) for the same time frame. There was no difference in rate of recurrent DVT and risk of major bleeding between the groups (EINSTEIN Investigators 2010). Regarding treatment of PE, rivaroxaban (15mg twice daily for 3 weeks then 20mg once daily for a total of 6 months) was compared to subcutaneous enoxaparin
followed by a vitamin K antagonist (wither warfarin or acenocoumarol). Again, the two groups had similar rates of recurrence of PE however, the rivaroxaban group had fewer episodes of major bleeding than the control (1.1% vs. 2.2% respectively, hazard ratio, 0.49; 95% CI, 0.31 to 0.79; P=0.003) (EINSTEIN Investigators 2010).

The use of these agents would offer patients a safe and simple treatment alternative to vitamin K antagonist like warfarin with no need for regular laboratory investigations and the same risk of bleeding. The use of these agents for this indication will depend on the country in which the physician is practicing since this indication may not be accepted with the respective regulatory agencies.

17.5 Seizures Post Stroke
Seizures are episodes of abnormal electrical activity in the brain; Wiebe and Butler (1998) described them as “the clinical expression of excessive, hypersynchronous discharge of neurons in the cerebral cortex.” Seizures post stroke are a known phenomenon. In a review of case series, Wiebe and Butler (1998) found the incidence of seizures after ischemic or hemorrhagic stroke was variable, ranging from 7.7% to 42.8%. The timing of seizure post stroke is also variable. The majority of seizures are an isolated event post stroke, and may be partial or generalized (Ferro & Pinto 2004). Whether seizures worsen stroke outcomes is unclear. Vernino et al. (2003) reported new-onset seizure among patients with ischemic stroke was an independent risk factor for mortality (Relative risk 1.81; 95%CI 1.16-2.83). Bladin et al. (2000) also reported higher mortality among patients with seizures at 30 days and 1 year post stroke, compared to patients who were seizure free (25% vs. 7% and 38% vs. 16%). However, the authors did not control for the confounding effects of stroke severity or comorbidity. Hamidou et al (2013) found higher mortality risk at 30 days and 1 year was seen in patients with early seizures but the risk disappeared after adjusting for stroke severity and other confounding factors. Other studies have not supported an increased risk of mortality (Labovitz et al. 2001; Reith et al. 1997).

17.5.1 Incidence of Seizures Post Stroke
Wiebe and Butler (1998) observed that the incidence of seizures after ischemic or hemorrhagic stroke in earlier series is noted to be highly variable ranging from a low of 7.7% to a high of 42.8%. This variability is influenced by factors such as study design, patient population, diagnostic methods, and follow-up (Black et al. 1983; DeReuck et al. 1980; Dodge et al. 1954; Holmes et al. 1980; Louis & McDowell 1967; Meyer et al. 1971). Cordonnier et al. (2005) reported that pre-existing dementia increase the risk of seizures more than one week post stroke. In comparison to earlier studies, recent reports reveal less variability in the risk of post-stroke seizures (PSS). The average risk of seizures is 10% within 9-10 years post stroke (Table 17.5.1.1), and well-conducted prospective studies report a 5-year cumulative incidence of 11.5% (Burn et al. 1997). At least two studies suggest a higher incidence of PSS (15-17%) in patients in rehabilitation units (Kotila & Waltimo 1992; Paolucci et al. 1997). It is not certain whether this reflects seizure ascertainment bias, in which seizures are less likely to be missed in these closely observed patients, or a true increased seizure risk in this population, possibly related to greater severity of stroke in inpatient rehabilitation, or both.

Black et al. (1983) reported 10% of all stroke patients developed seizures. In this study, thirty-nine percent of seizures occurred within the first 24 hours of stroke onset, 57% within the first week and 88% within the first year. Sung and Chu (1989) found that seizure onset time was very similar in a study of patients after ICH: 30% in the first 24 hours, 60% in the first two weeks and 90% in the first year.
Sundaram and Chow (1986) found that 84% of PSS took place within the first 2 weeks after subarachnoid hemorrhage.

### Table 17.5.1.1 Summary of Risk of Seizures Following Stroke of All Types

<table>
<thead>
<tr>
<th>Author, Year Sample Size</th>
<th>Incidence or Prevalence of Epilepsy ($I_{EP}$ or $P_{EP}$) or Seizures ($I_{Sz}$ or $P_{Sz}$)</th>
<th>Duration of Follow-up and/or Occurrence of Episode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al. (1980) N=250</td>
<td>$P_{Sz}=21%$</td>
<td>2 years</td>
</tr>
<tr>
<td>de Reuck et al. (1980) N=240</td>
<td>$P_{Sz}=7.9%$</td>
<td>At necropsy</td>
</tr>
<tr>
<td>Black et al. (1983) N=827</td>
<td>$P_{Sz}=10%$ (57% in the first week)</td>
<td>2 to 5 years</td>
</tr>
<tr>
<td>Olsen et al. (1987) N=77</td>
<td>$I_{Sz}=9%$</td>
<td>2 to 4 years</td>
</tr>
<tr>
<td>Gupta et al. (1988) N=90</td>
<td>Initial seizures present in full sample of patients (with initial post-stroke seizure)</td>
<td>1 month to 13 years (mean=29.8mo)</td>
</tr>
<tr>
<td></td>
<td>· 39% recurrent seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· 33% early-onset seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>· 67% late-onset seizures</td>
<td></td>
</tr>
<tr>
<td>Viitanen et al. (1988) N=409</td>
<td>Risk $I_{EP}=3%+/-2%$ at 1 year</td>
<td>3 to 5 years</td>
</tr>
<tr>
<td>Kotila &amp; Waltimo (1992) N=200</td>
<td>$I_{Sz}=17%$</td>
<td>During follow-up, 17% developed epilepsy</td>
</tr>
<tr>
<td>Lancman et al. (1993) N=219</td>
<td>$I_{Sz}=10%$ Of these, 54.55% early onset, 45.45% late onset</td>
<td>Mean follow-up=11.5 months</td>
</tr>
<tr>
<td>So et al. (1996) N=235</td>
<td>$I_{Ev}=6%$ early seizures</td>
<td>Until death or migration out of Rochester, MI or until December 31, 1992.</td>
</tr>
<tr>
<td></td>
<td>$I_{Sz}=3%$ late seizure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$I_{Ev}=5.0%$ recurrent late seizure</td>
<td></td>
</tr>
<tr>
<td>Burn et al. (1997) N=675</td>
<td>$I_{Ev}=2%$ (patients with onset seizures, within 24 hours of onset of stroke)</td>
<td>2 years</td>
</tr>
<tr>
<td></td>
<td>$I_{Sz}=5%$ of patients with onset seizures who developed post-stroke seizures</td>
<td></td>
</tr>
<tr>
<td>Paolucci et al. (1997) N=306</td>
<td>$I_{Ev}=15%$</td>
<td>1 year</td>
</tr>
<tr>
<td>Teasell et al. (1999) N=536</td>
<td>$I_{Ev}=7.8%$</td>
<td>1 year</td>
</tr>
<tr>
<td>Bladin et al. (2000) N=1897</td>
<td>$I_{Ev}=8.9%$</td>
<td>9 months</td>
</tr>
<tr>
<td>Lossius et al. (2002) N=550</td>
<td>$I_{Ev}=3.3%$</td>
<td>1 year</td>
</tr>
<tr>
<td>Vespa et al. (2003) N=109</td>
<td>$I_{Ev}=27.8%$ in patients with ICH, $I_{Ev}=6%$ in patients with IS</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Cordonnier et al. (2005) N=202</td>
<td>$I_{Ev}=5.4%$ early onset seizure</td>
<td>At 6-months and then every year for 3 years</td>
</tr>
<tr>
<td></td>
<td>$I_{Ev}=6.9%$ late onset seizure</td>
<td></td>
</tr>
<tr>
<td>Alberti et al. (2008) N=638</td>
<td>4.8% with early seizures (range=2% to 6%)</td>
<td>No follow-up</td>
</tr>
<tr>
<td>Szafarski et al. (2008) N=6044</td>
<td>$I_{Ev}=3.1%$ overall incidence of seizures</td>
<td>No follow-up</td>
</tr>
</tbody>
</table>
The incidence of post-stroke seizures is highly variable; in more recent studies, the incidence hovers around 10% for ischemic and hemorrhagic strokes. Many factors contribute to the studied incidence, including research designs, stroke populations, diagnostic methods, and follow-up interval (Szaflarski et al. 2008). Compared to earlier studies, differences in stroke severity and increased survival may explain some of these differences (Lossius et al. 2002). It remains unclear whether or not seizures post stroke are truly associated with worse patient outcomes; certainly, the presence of seizures, especially if persistent, has a significant impact on patient care and management post stroke. Because it alters the brain parenchyma, stroke is a known structural risk factor for the development of seizures (Cordonnier et al. 2005). Based on limited research, patients who develop seizures post stroke are most likely to have at least one seizure within the first year post stroke (Black et al. 1983; Sung & Chu 1989).

**Early vs. Late Seizures**
Most seizures occur within the first year after a stroke; however, the exact timing varies considerably (Procaccianti et al. 2012). Some of the variability in timing is due to lack of consistent definitions of early and late seizures. Across studies, early seizures have been defined as those occurring within 24 hours of stroke onset to as late as one month post stroke, while late seizures are most commonly identified as those occurring after two weeks of stroke. The incidence of seizures grouped according to time post stroke is presented in Table 17.5.1.2

**Table 17.5.1.2 Timing of Seizures Post Stroke (expanded from Camilo & Goldstein 2004)**

<table>
<thead>
<tr>
<th>Time</th>
<th>Incidence of seizure</th>
</tr>
</thead>
</table>
| < 24 hours | 4.9% (So et al. 1996)  
|         | 2% (Burn et al. 1997); Increased to 3% after 24 hours (Burn et al. 1997)  
<p>|         | 3.1% (Szaflarski et al. 2008) |</p>
<table>
<thead>
<tr>
<th>Time Period</th>
<th>Seizure Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 48 hours</td>
<td>2.2% (Arboix et al. 2003)</td>
</tr>
<tr>
<td>&lt; 72 hours</td>
<td>19.2% (Vespa et al. 2003)</td>
</tr>
<tr>
<td>&lt; 1 week</td>
<td>6% (So et al. 1996); Decreased to 5% after 1 week (So et al. 1996)</td>
</tr>
<tr>
<td></td>
<td>3.1% (Labovitz et al. 2001)</td>
</tr>
<tr>
<td></td>
<td>2.4% (Lamay et al. 2003); Increased to 3.4% after 1 week (Lamay et al. 2003)</td>
</tr>
<tr>
<td></td>
<td>5.4% (Cordonnier et al. 2005)</td>
</tr>
<tr>
<td></td>
<td>4.8% (Alberti et al. 2008)</td>
</tr>
<tr>
<td></td>
<td>3.2% (Procaccianti et al. 2012)</td>
</tr>
<tr>
<td></td>
<td>3.9% (Pezzini et al. 2013)</td>
</tr>
<tr>
<td></td>
<td>1.2% (Alvarez et al. 2013)</td>
</tr>
<tr>
<td></td>
<td>11% (Haapaniemi et al. 2014)</td>
</tr>
<tr>
<td>&lt; 2 weeks</td>
<td>6.5% (Kilpatrick et al. 1990)</td>
</tr>
<tr>
<td></td>
<td>2.5% (Kotila &amp; Waltimo 1992)</td>
</tr>
<tr>
<td></td>
<td>4.2% (Reith et al. 1997)</td>
</tr>
<tr>
<td></td>
<td>33% (Gupta et al. 1998); Increased to 67% after 2 weeks (Gupta et al. 1998)</td>
</tr>
<tr>
<td></td>
<td>4.8% (Bladin et al. 2000); Decreased to 3.8% after 2 weeks</td>
</tr>
<tr>
<td></td>
<td>6.9% (Cordonnier et al. 2005)</td>
</tr>
<tr>
<td></td>
<td>4.8% (Alberti et al. 2008)</td>
</tr>
<tr>
<td></td>
<td>2.2% for ischemic stroke; 5.1% for hemorrhagic (Krakow et al. 2010)</td>
</tr>
<tr>
<td></td>
<td>3.1% (Hamidou et al. 2013)</td>
</tr>
<tr>
<td></td>
<td>9.2% (Haapaniemi et al. 2014)</td>
</tr>
<tr>
<td>1 month</td>
<td>5.5% (Lancman et al. 1993)</td>
</tr>
<tr>
<td>1 year</td>
<td>3% (Viitanen et al. 1988)</td>
</tr>
<tr>
<td></td>
<td>15% (Paolucci et al. 1997)</td>
</tr>
<tr>
<td></td>
<td>7.8% (Teasell et al. 1999)</td>
</tr>
<tr>
<td></td>
<td>3.3% (Lossius et al. 2002)</td>
</tr>
<tr>
<td>5 years</td>
<td>5% (Viitanen et al. 1988)</td>
</tr>
<tr>
<td></td>
<td>2.6% (Chen et al. 2012)</td>
</tr>
</tbody>
</table>

**Risk Factors Associated with Seizures Post Stroke**

As reviewed above, post-stroke seizures are common, occurring in 1.2 to 27.8% of patients post stroke (Alvarez et al. 2013; Vespa et al. 2003). Several studies have examined risk factors for stroke to aid in identifying patients who are at increased risk of developing seizures post stroke. Despite considerable variability in the definitions and methodology, common risk factors have emerged from the literature: cortical strokes, more severe strokes or more severe disability, and younger age. Stroke type likely also predicts seizure development, with hemorrhagic strokes being more likely than ischemic strokes (Alvarez et al. 2013).

In a prospective study of 1640 patients presenting with first stroke, Giroud et al. (1994) found that younger patients and male patients are at increased risk of post-stroke seizures. Arboix et al. (1997) had similar findings in a prospective study of 1220 patients with first presentation stroke, identifying younger and male patients as at higher risk of seizure. This study also found that confusion on presentation, larger strokes, strokes with cortical involvement (frontal, temporal, parietal or occipital lobe) were associated with seizures post stroke, but that only acute confusion and cortical involvement on neuroimaging studies were predictive of seizure development (Arboix et al. 1997). Lamy et al. (2003) also identified that cortical and large strokes were independent risk factors for seizures. In this study, cortical involvement, large strokes, and early seizures were associated with a 4.5- to 10-fold increase in the risk of late onset seizures (Lamy et al. 2003).
The Copenhagen Stroke Study, a community-based, prospective study of 1197 patients with acute stroke, Reith et al. (1997) identified stroke severity as the single biggest risk factor for early seizures. In two large population-based studies, younger age and increasing stroke severity were found to be predictors of seizures post stroke occurring within 24 hours (Krackow et al. 2010; Szaflarski et al. 2008). One of these studies also found acute, non-neurologic infection and history of previous TIA to be predictive of developing seizures post stroke in both hemorrhagic and ischemic stroke (Krackow et al. 2010).

Recently, thrombolysis has been identified as an independent risk factor for seizure. In a population-based case-control study including 2,327 ischemic stroke patients, the overall incidence of seizure was 1.2% (Alvarez et al. 2013). The odds of seizure among patients who had received thrombolytic therapy was significantly higher, with an odds ratio of 4.6 (OR=4.6, 95% CI 1.6 to 13.4) in multivariate analysis. Similar to previous findings, Alvarez et al. (2013) found cortical stroke location was also predictive of post-stroke seizures. In a cohort of Canadian stroke patients included in the Registry of the Canadian Stroke Network (Burneo et al. 2010), stroke severity, hemorrhagic stroke and neglect were found to be independent predictors of seizure during the initial period of hospitalization post stroke.

**Conclusions Regarding the Incidence of Seizures Post Stroke**

The incidence of post-stroke seizures is, on average, 10% but due to methodological variation and study population differences, the incidence reported in the literature has a wide range, from 1.2% to 27.8%.

The incidence of post-stroke seizures varies among studies.

17.5.2 Seizures Following Hemorrhagic Stroke

Stroke type likely plays a role in the risk of developing seizures. The incidence of seizure following hemorrhagic stroke is estimated to be between 4% and 27.8% (DeHerdt et al. 2011; Vespa et al. 2003). The results from some studies support that hemorrhagic stroke increases the risk of early seizure (Beghi et al. 2011; Burneo et al. 2010; Kilpatrick et al. 1990; Vespa et al. 2003). However, some studies have not found hemorrhage stroke to be a significant risk factor for seizures post stroke (Alberti et al. 2008; Black et al. 1983; Olsen et al. 1987; Shinton et al. 1988). Some authors propose that hemorrhagic strokes are often more severe, and thus stroke severity accounts for the increase risk; others have proposed that hemorrhagic strokes cause more direct toxicity and irritation to surrounding brain parenchyma, thereby increasing the risk.

Reith et al. (1997) found a higher frequency of early seizures (within 14 days of onset) in patients with intracerebral hemorrhages when compared to those with cerebral infarction. However, in multivariate analysis, initial stroke severity was the sole predictor of early PSS and the apparent increased frequency of PSS with intracerebral hemorrhage reflected a higher initial stroke severity in this group of patients. Bladin et al. (2000) noted that patients who had suffered from a hemorrhagic stroke had an almost 2-fold risk of developing a seizure compared to ischemic stroke. In this study, seizures after hemorrhagic stroke were more common in cortical lesions, but not specifically to stroke severity. Krakow et al. (2010) also demonstrated a two-fold increase in the incidence of seizure in hemorrhagic compared to ischemic strokes (p<0.0001) in a prospective study of 58874 patients with acute stroke in Germany. A retrospective, population-based study of post-stroke seizure in 6044 patients with no prior seizure history in Cincinnati, USA, also identified a statistically significant increase in seizure risk for patients with hemorrhagic strokes compared to all other stroke subtypes (p<0.0001) (Szaflarski et al. 2008).
et al. (2012) noted that the adjusted hazard ratio for developing post stroke seizure after 5 year follow-up of 4126 stroke patients was highest for patients with intracerebral hemorrhage, hazard ratio of 76.3 (95%CI: 17.1 to 329.5), compared to ischemic stroke, hazard ratio 6.8 (95% CI: 4.4 to 10.5).

17.5.3 Seizures in Cortical vs. Subcortical Strokes
The results of some studies showed that post-stroke seizures only occurred in patients with cortical involvement (Kilpatrick et al. 1990; Lancman et al. 1993). Olsen et al. (1987) found that a lesion involving the cerebral cortex, irrespective of size, was a prerequisite for the development of epilepsy. Kilpatrick et al. (1990) supported this concept by reporting an absence of seizure activity among 1,000 patients with subcortical vascular strokes. For patients with hemorrhagic strokes, cortical involvement appeared to be associated with the development of seizures, since deep-seated hemorrhages rarely cause seizures (Kilpatrick et al. 1990; Olsen et al. 1987; Sung & Chu 1989). Many recent studies have demonstrated that cortical lesions are an independent risk factor for seizure post stroke (Alvarez et al. 2013; Arboix et al. 1997; Bladin et al. 2000; Burneo et al. 2010; Lamy et al. 2003). Conceptually, cortical strokes as a risk factor seems plausible: cortical insults increase the risk of abnormal electrical activity, and seizures are the result of abnormal electrical activity in the cerebral cortex. However, not all studies have demonstrated this relationship (Gupta et al. 1988; Shinton et al. 1988). Alberti et al. (2008) reported, on univariate analysis, that early seizures occurred more frequently in patients with cortical involvement (58.1% vs. 33.2%, p=0.01) but the association disappeared when controlling for other variables. The exact nature of this relationship is not entirely clear, but research favours the finding that cortical stroke is a risk factor for seizure.

17.5.4 Seizure Type Post Stroke
Wiebe-Velazquez and Blume (1993) totalled the frequency of various seizure types post stroke from seven studies. From the combined 231 patients, 50% had simple partial seizures, 32% had primary generalized seizures, 15% had partial seizures with secondary generalization, and 2.5% had complex partial seizures. In a prospective study of 1640 patients presenting with first stroke, Giroud et al. (1994) found that 61% of patients had simple partial seizures; 28% had partial seizures with secondary generalization; 11% had generalized tonic-clonic seizures. In The Copenhagen Stroke Study, 40% of patients had only a single seizure; 68% of seizures were simple partial seizures (no loss of awareness), or partial seizures with secondary generalization (loss of awareness); 22% of seizures were primary generalized tonic-clonic seizures (Reith et al. 1997). Anticonvulsant therapy was initiated within 2 weeks of stroke onset in 86% of the patients who developed seizures in the post-stroke period (Reith et al. 1997).

17.5.5 Treatment of Seizures Post Stroke
Few studies have examined of the treatment of seizures post stroke. Evidence to support definitive recommendations is lacking; thus, clinical guidelines for seizure management are often based on established management of seizures in other types of seizure disorders and clinical judgment (Gilad 2012). Acutely, standard therapy for aborting seizures begins with lorazepam, diazepam, or another benzodiazepine given via intravenous, sublingual, buccal, or rectal route. Lorazepam may be more effective in terminating status epilepticus (59-89%) compared to diazepam (43-76%) (Bluvol et al. 2003). Additional management varies with the severity of the clinical situation and the institution in which the stroke occurs.
Antiepileptic or anticonvulsant medications are considered for seizure prophylaxis in patients with multiple or recurrent seizures, or who are at increased risk of seizure. Studies have documented the rates of antiepileptic medication initiation for seizure post stroke, with significant variability. For instance, Reith et al. (1997) reported that 86% of patients with seizures post stroke were started on an antiepileptic medication. This reflects the common practice of treating patients empirically if their seizure is in the setting of stroke, as this is a known risk factor for recurrent seizures. However, there is some concern that the use of antiepileptic agents may impair recovery post stroke (Camilo & Goldstein 2004), an important consideration given that few post-stroke seizures are likely to recur (Silverman et al. 2002).

RCTs of antiepileptic medications post stroke have yet to identify optimal therapy (Table 17.5.5.1). However, Gupta et al. (1988) found that 88% of patients with post-stroke seizure were adequately managed with monotherapy, meaning with only one antiepileptic medication. The selection of a patient’s antiepileptic should be tailored to his or her existing medications and medical comorbidities (Silverman et al. 2002). For instance, phenytoin interacts with warfarin, which many patients may use for anticoagulation post stroke. Benzodiazepines should not be used as long-term antiepileptic therapy in post-stroke seizures (Gilad 2012; Silverman et al. 2002).

The Early Treatment with Levetiracetam After Stroke (ETLAS) trial by van Tuijl et al. (2011) was initiated aiming to determine whether treatment with levatiracetam was superior to placebo for primary prevention of post stroke seizure. The trial did not meet the intended sample size due to various factors, and the authors concluded that a prophylactic trial in stroke patients was not feasible (van Tuijl et al. 2011). Three other RCTs have evaluated the efficacy of anticonvulsant therapy in the post-stroke population (Rowan et al. 2005; Gilad et al. 2007; Gilad et al. 2011). Rowan et al. (2005) compared gabapentin, lamotrigine, and carbamazepine in elderly patients with seizures; the majority, but not all, had cortical stroke as the etiology for seizures. Although seizure control was similar between the groups, compliance was best in the lamotrigine group (Rowan et al. 2005). In a 2007 RCT, Gilad et al. compared monotherapy with lamotrigine to carbamazepine in 64 patients with post-stroke seizure. There was a trend toward improved seizure control in the lamotrigine group, 72% seizure free compared to 44% in the carbamazepine group; however, this did not reach statistical significance (p=0.06) (Gilad et al. 2007). Similar to Rowan et al. (2005), the study authors found lamotrigine was better tolerated (Gilad et al. 2007). A subsequent RCT by Gilad et al. (2011) evaluated valproic acid compared to placebo for primary prevention of post-stroke seizures in 72 persons with hemorrhagic stroke. In total, 15 patients (21%) developed seizures; the study did not detect a difference between placebo and valproic acid.

In a Cochrane review, Sykes et al. (2014) sought to examine the efficacy of antiepileptic drugs for prevention or treatment of seizure post stroke. In this update to a previous review by Kwan and Wood (2010), the authors found only one study suitable for review: a prospective, randomized, double-blind, placebo-controlled trial for primary prevention of seizures post stroke; the study compared valproic acid to placebo in 72 patients with intracerebral hemorrhage (Gilad et al. 2011). Sykes et al. (2014) concluded that there is insufficient evidence to support the routine use of antiepileptic therapy for secondary prevention in patients with post-stroke seizures; they also found insufficient evidence to support primary prevention of post-stroke seizures in all patients post stroke. The evidence was also insufficient to aid in the selection of antiepileptic drugs for the management of post-stroke seizures.

Table 17.5.5.1 Summary of RCTs Evaluating Treatment and Prevention of Seizures Post Stroke

<table>
<thead>
<tr>
<th>Author, Year (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E: experimental group(s); C: control group</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
17.6 Osteoporosis Post Stroke

Osteoporosis is a disease of decreased bone mass, quantified as diminished bone mineral density (BMD). It is associated with significant complications, including hip fractures and mortality (Carda et al. 2009). Osteoporosis is a well-recognized complication post stroke, and has a distinct pathophysiology and clinical presentation in patients post stroke than in the non-stroke population. Specifically, in stroke patients, bones in paretic limbs are disproportionately affected (Beaupre & Lew 2006; De Brito et al. 2013; Demirbag et al. 2005; Hamdy et al. 1993; Jorgensen et al. 2000; Liu et al. 1999; Ramnemark et al. 1999; Sato et al. 1996; Yavuzer et al. 2002). Beaupre and Lew (2006) found that for some patients the loss of bone density in the affected arm within the first year post stroke is equal to more than 20 years of bone loss for similar aged healthy individuals.

This section reviews the pathophysiology of osteoporosis post stroke, its clinical implications, and the management.

17.6.1 Pathophysiology of Osteoporosis Post Stroke

During the first year post stroke, subjects can lose from 3.6% to 17% of their bone mineral density (Carda et al. 2009). Considerable evidence suggests that loss of BMD preferentially occurs in paretic limbs (Beaupre & Lew 2006; De Brito et al. 2013; Demirbag et al. 2005; Hamdy et al. 1993; Jorgensen et al. 2000; Liu et al. 1999; Ramnemark et al. 1999; Sato et al. 1996; Yavuzer et al. 2002), even when controlling for disuse (Pang et al. 2013). For instance, Hamdy et al. (1993) reported a significant difference BMD for the affected upper limb compared to the nonaffected upper limb (7.95%, p<0.0003); similarly, for the affected lower limb, BMD was 3.42% compared to the unaffected side (p=0.0028). This finding underscores the difference in clinical presentation of osteoporosis post stroke:
upper limbs are disproportionately affected compared to the usual osteoporosis pattern for non-stroke patients (Carda et al. 2009). Even in patients without lower limb paresis, the ability to ambulate independently and low BMD are closely linked (Schnitzer et al. 2012). Watanabe (2004) found that 40% of patients admitted for inpatient stroke rehabilitation already had osteoporosis. These findings in stroke patients highlight the importance for screening for bone loss in this high risk group. Unfortunately, few stroke management guidelines include recommendations regarding bone loss or osteoporosis post stroke (Borschmann 2012).

Several studies have examined determinants of bone loss post stroke: longer duration of immobility; severity of hemiplegia; lower vitamin D serum levels; advanced age; and time since menopause in women (Carda et al. 2009; Levendoglu et al. 2004; Poole et al. 2002; Sato et al. 1999). Of these, reduced mobility and length of immobilization are felt to be the most significant risk factors (Carda et al. 2009; Del Puente et al. 1996). Immobility is thought to trigger an increase in bone resorption, mediated by increased hyperparathyroidism (Massagli & Cardenas 1999). This theory is supported by findings that the serum concentrations of bone resorption markers such as intact parathyroid hormone and ionized calcium were significantly higher in patients with stroke than in control subjects (Sato et al. 1996). Vitamin D deficiency, due inadequate dietary intake and sunlight deprivation, is also thought to contribute to post-stroke osteoporosis (Sato et al. 1996). Sato et al. (1996) found that patients with a history of stroke had significantly lower serum vitamin D levels: the mean level for inpatients with stroke was 5.9ng/mL, for outpatients with stroke was 9.1%, compared to 21.6% in controls (p<0.001, Sato et al. 1996). However, in a retrospective, population-based study of 10255 patients, of whom 415 had a history of stroke, osteoporosis and vitamin D deficiency were both prevalent, but the authors did not identify a relationship between the two (Uluduz et al. 2014). This may be due to the very high rates of vitamin D deficiency (71%).

**17.6.2 Hip Fractures Post Stroke**

Hip fractures are a common problem post stroke, related to high rates of osteoporosis, poorer mobility, and increased falls risks (Saverino et al. 2006). The incidence of hip fracture as a late complication of stroke is between 4% and 15%, with the majority of fractures occurring on the hemiparetic side (Chiu et al. 1992; Mulley & Espley 1979; Peszczynski 1957; Poplingher & Pillar 1985). In a study of 1139 patients followed for a median of 2.9 years, Ramnemark et al. (1998) reported the risk of hip fracture to be 2-4 times higher among stroke survivors compared to the general. Most post-stroke fractures are caused by accidental falls and tend to occur on the paretic side, likely related to more significant osteoporosis associated with paretic limbs and possibly with poorer ability to break a fall using the ipsilateral hand (Poole et al. 2002).

The risk of hip fracture post stroke is independently associated with advanced age, female gender, low pre-stroke functional status, poorer cognition, and diabetes mellitus (Dennis et al. 2002; Ishida et al. 1985; Kanis et al. 2001). Additional risk factors include depression, poor balance, urinary incontinence, and medications (Eng et al. 2008). Hemineglect and attention deficits may also increase the risk of falling post stroke. Kanis et al. (2001) reported a 7-fold increase in hip fracture in the first year post stroke. This increased risk has been attributed to the development of disuse osteoporosis post stroke and to perceptual deficits and balance disorders that predispose patients to falling (Peszczynski 1956). In addition, Beaupre and Lew (2006) noted that patients with hip fracture had a considerable increase in risk of morbidity and mortality post stroke.

Although hip fractures are a major source of morbidity and mortality in post-stroke patients, other osteoporotic fractures can also impair function and/or have significant clinical consequences. For
instance, radial fractures, which are more common in patients with upper extremity osteoporosis, may impair a person’s ability to use his or her gait aid, leading to immobility and its associated adverse effects. Pang et al., (2013) found grip strength to be the strongest determinant of radius compressive bone strength index (cBSI; a measure of the strength of the bone segment against compressive forces in the distal end of long bones), offering an easy-to-administer assessment to screen stroke patients who may have compromised upper extremity bone health.

17.6.3 Treatment of Osteoporosis Post Stroke
A number of therapeutic interventions intended to reduce the risk of osteoporosis and subsequent risk of hip fracture have been evaluated in randomized controlled trials, many of them by the same group of investigators. These include: bisphosphonates, isofalavone, vitamins B, D and K, sunlight exposure, and calcium supplementation.

Table 17.6.3.1 Summary of RCTs Evaluating Pharmacological Treatments for Osteoporosis

<table>
<thead>
<tr>
<th>Author, Year (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention E: experimental group(s); C: control group</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sato et al. (2005) RCT (9) N=628</td>
<td>E: Folate and 1500ug cobalamin C: Placebo</td>
<td>Incidence of hip fracture (+)</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (2005b) RCT (9) N=280</td>
<td>E: Risedronate C: Placebo</td>
<td>BMD in men (+) Hip fracture in men (+)</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (2005a) RCT (9) N=96</td>
<td>E: Ergocalciferol (vitamin D2) C: Placebo</td>
<td>Falls (+) Muscle strength (+)</td>
<td></td>
</tr>
<tr>
<td>Poole et al. (2007) RCT (9) N=27</td>
<td>E: Intravenous zoledronate C: Placebo</td>
<td>BMD (+) Falls (-)</td>
<td></td>
</tr>
<tr>
<td>Gommans et al. (2013) RCT (8) N=164</td>
<td>E: Folic acid, vitamin B6 or vitamin B12 C: Placebo</td>
<td>Fractures (-)</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (1997) RCT (8) N=84</td>
<td>E: 1ug vitamin D + 300mg calcium C: Placebo + 300mg calcium</td>
<td>BMD (+) Hip fracture (+)</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (2003) RCT (6) N=258</td>
<td>E: Sunlight therapy C: No sunlight treatment (no therapy)</td>
<td>BMD (+) Hip fracture (+)</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (2005c) RCT (6) N=187</td>
<td>E: Risedronate C: Placebo</td>
<td>BMD in women (+) Hip fracture in women (+) Changes in urinary/serum markers (+)</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (1998) RCT (5) N=108</td>
<td>E: 45 mg manaquinone (vitamin K2) C: No treatment</td>
<td>BMD (+) Hip fracture (-) Changes in urinary/serum markers (+)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Outcome Measures</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Sato et al. (2000)</td>
<td>E: 400mg etidronate C: Placebo</td>
<td>• BMD (+) • Changes in urinary/serum markers (+)</td>
<td></td>
</tr>
<tr>
<td>Uebelhart et al. (1999)</td>
<td>E: 1ug salmon calcitonin C: Placebo</td>
<td>• Markers of bone metabolism (-)</td>
<td></td>
</tr>
<tr>
<td>Ikai et al. (2001)</td>
<td>E: Etidronate C: Placebo</td>
<td>• BMD (–)</td>
<td></td>
</tr>
</tbody>
</table>

+ Indicates statistically significant difference between treatment groups
- Indicates no statistical significant difference between treatment groups

**Discussion**

Diverse therapeutic options have been studied for post-stroke osteoporosis, including RCTs in bisphosphonates, isoflavone, vitamins B, K, and D, sunlight exposure, and calcium. Of all groups, bisphosphonates have been studied most extensively.

Bisphosphonates prevent osteoporosis by inhibiting bone resorption by osteoclasts. A meta-analysis by Iwamoto et al. (2008) reported a reduction in the risk of hip fracture associated with risedronate treatment (RR: 0.25, 95% CI 0.13–0.48, p<0.0001) in patients with one of three neurological diseases, stroke, Alzheimer’s disease, and Parkinson’s disease. Overall, the treatment effect was greater in men compared with women. Six RCTs evaluated bisphosphonates in patients with osteoporosis post-stroke. Sato et al. (2005b) found that risedronate improved BMD in men post stroke compared to control and improved BMD in women post stroke compared to control (2005c). In these trials, the NNT to prevent one hip fracture was 16 for men and 28 for women. The difference in effect and NNT may be explained by women’s increased risk of osteoporosis and fractures at baseline, even in non-stroke patients, or to other factors not elicited in the trial (Sato et al. 2005c).

In an earlier study, Sato et al. (2000) conducted a 56-week randomized trial to evaluate the efficacy of intermittent cyclical etidronate therapy in hemiplegic acute stroke patients. Compared to patients who received no therapy or placebo, patients randomized to the etidronate group experienced significant decreases in serum ionized calcium and significantly less BMD loss on the paretic side (Sato et al. 2000). Poole et al. (2007) noting that significant bone loss occurs early on post stroke when many patients have dysphagia, hypothesized that an intravenous bisphosphonate would be an effective means to provide the treatment compared with tablet form. Although treatment was effective in preventing BMD loss compared to placebo, its effect on reducing hip fractures is unknown given the absence of its occurrence in either group (Poole et al. 2007). Ikai et al. (2001) found that BMD for inpatient stroke rehabilitation patients with worse FIM scores was less likely to decline over 3 months in patients who received two weeks of etidronate therapy compared to patients who did not receive etidronate. Hip fracture and mortality outcomes were not assessed. In a more recent study, Sato et al. (2010) found that etidronate increased BMD on the hemiparetic side of patients with stroke by 1.4% over 2 years, compared with a decrease in BMD of 2.2% in patients receiving placebo (p<0.001). The event rate for hip fractures was too low to identify a definitive benefit for the bisphosphonate over control.

Vitamin D supplementation is recommended for preventing osteoporosis in areas, such as Canada, where exposure to sunlight is insufficient to generate adequate vitamin D in the skin (Brown & Josse 2002). Vitamin D increases calcium absorption from the gut, and promotes bone mineralization while inhibiting bone resorption. For a number of reasons, including decreased mobility and social isolation, low vitamin D levels are more common in patients with a history of stroke than in age-matched controls (Sato et al. 2001). Moreover, stroke patients with vitamin D deficiency were more likely to experience hip fracture than post-stroke patients with normal serum vitamin D levels (Sato et al. 2001). Two RCTs
have investigated vitamin D supplementation for the treatment of osteoposis post stroke. In an RCT comparing calcium and vitamin D supplementation to calcium with placebo, Sato et al. (1997), reported that stroke patients who were treated with vitamin D3 and calcium experienced significantly less loss of bone mineral density on both the paretic and non-paretic sides compared to patients who were treated with calcium supplement and placebo. No patients treated with vitamin D fractured their hip during the study period compared to four patients in the control group (Sato et al. 1997). A more recent RCT by the same research group compared 1000iu of vitamin D3 to placebo in post-stroke patients who were vitamin D deficient at baseline (Sato et al. 2005a). In this study, the authors attributed a 59% relative decrease in fall rate to vitamin D supplementation, and found associated muscular and hip fracture benefits (Sato et al. 2005a).

The same group of authors reported an increase in BMD associated with exposure to sunlight, which indirectly increases vitamin D serum levels by exposing patients to the ultraviolet light required to generate vitamin D in the skin, among a group of vitamin D deficient stroke patients (Sato et al. 2003). This is the only RCT that evaluated sunlight for improving BMD; however, epidemiologic data regarding the global prevalence of osteoporosis supports the association of better bone mineral density (less osteoporosis) with sunlight (Carda et al. 2009).

One RCT evaluated the efficacy of ipriflavone (a flavanoid compound) and vitamin D on preservation of bone mineral density post stroke (Sato et al. 1999). The authors reported that ipriflavone with vitamin D was significantly more effective than vitamin D alone in preventing bone mineral loss post stroke. Treatment with ipriflavone appeared to decrease serum calcium levels by inhibiting osteoclastic bone resorption while activating osteoblastic bone formation.

In Canada, the Scientific Advisory Council of Osteoporosis Canada released updated guidelines for the diagnosis and management of osteoporosis (Papaioannou et al. 2010). The guidelines do not offer stroke-specific guidelines, but do recommend screening for osteoporosis in all patients who have a disorder strongly associated with rapid bone loss, such as stroke. Pharmacological interventions including bisphosphonates and vitamin D are recommended as first line treatment for osteoporosis (Papaioannou et al. 2010) Because the guidelines are not specific to stroke, clinicians should exercise caution with other recommended therapies, such as supplemental estrogens, as these are not generally recommended in the post-stroke population.

Although they do not target osteoporosis directly, mechanical hip protectors have also been used successfully to reduce the incidence of hip fractures associated with falls (Kannus et al. 2000). However, the study authors noted poor compliance may limit the use of these devices. For patients with contraindications to other osteoporosis therapies, or who are at significant risk of falling, these should be considered.

**Conclusions Regarding the Treatment of Post-Stroke Osteoporosis**

*There is level 1a evidence that treatment with bisphosphonates (risedronate, etidronate, and zoledronate), may preserve bone mineral density post stroke compared to placebo.*

*There is level 1a evidence that treatment with vitamin D, including vitamin D2, vitamin D3, and sunlight therapy, may be helpful in preserving bone mass density.*
There is limited level 2 evidence that treatment with estrogen-like products such as manaquinone, salmon calcitonin, or isoflavone derivatives compared to a placebo or vitamin D may not result in significant benefits in bone density outcomes.

There is conflicting level 1a evidence regarding the effect of vitamin D derivatives on osteoporotic fractures post stroke; further research is required.

Treatment with bisphosphonates or vitamin D derivatives may help to preserve bone density post stroke. Further research is required to examine the effect of treatment with vitamin D derivatives and estrogen products on osteoporosis and associated fractures.

17.7 Central Pain States Post Stroke

Over a century ago, two French neurologists, Dejerine and Roussy, described an intractable and distressing pain disorder after thalamic stroke in “Le syndrome thalamique” (Dejerine & Roussy 1906; Segatore 1996; Henry et al. 2008). Since their initial description of pain after thalamic stroke, additional stroke-specific pain syndromes have been described, including central post-stroke pain (CPSP), complex regional pain syndrome, myofascial pain syndrome, hemiplegic shoulder pain, spasticity-related pain, persistent headache, and post-stroke back pain. This section of EBRSR focusses on CPSP, a syndrome estimated to affect 8% of persons post stroke (Schott 1996).

CPSP is a specific type of neuropathic pain that develops post stroke and is thought to be due to injury to pathways or brain centres involved in pain processing (De Oliveira et al. 2012; Henry et al. 2008). In this condition, pain and sensory abnormalities occur in the parts of the body that correspond to the stroke lesion (Klit et al. 2009). In 40-60% of patients, the onset of pain occurs more than one month after the stroke (Hansson 2004). This delayed onset, combined with language or cognitive impairments, prioritization of other medical complications, and depression have been postulated to contribute to underdiagnosis and undertreatment of this debilitating pain (Hansson 2004; Henry et al. 2008; Jensen & Lenz 1995; Segatore 1996).

17.7.1 Incidence of Central Post-Stroke Pain

The incidence of CPSP varies by study, occurring in 2-8% of patients with stroke (Henry et al. 2008; Mucke & Maciewicz 1987; Pagni 1976; Schott 1996; Tasker 1990). Although CPSP is generally considered rare, some authors argue that this incidence is not getting the attention it deserves (Bowsher 2001). Some authors report an incidence as high as 35% among stroke patients, with up to 5% reporting moderate to severe pain (Andersen et al. 1995; Widar et al. 2002). The largest prospective cohort study of chronic pain syndromes to date, the Prevention Regiment for Effectively avoiding Second Stroke (ProFESS) trial, reported that the incidence of new chronic post-stroke pain from total of 15 754 participants was 10.6% (O'Donnell et al. 2013). The authors further identified the incidence of post-stroke central pain subtypes: 2.7% for CPSP; 1.5% for peripheral neuropathic pain; 1.3% for spasticity-related pain; 0.9% for pain from shoulder subluxation; and, 4.7% for all other pain syndromes combined. Risk factors associated with any post-stroke pain condition included increased stroke severity, female sex, alcohol intake, previous depression, statin use or hyperlipidemia, diabetes mellitus, peripheral vascular disease, and prescription of aspirin/dipyridamole. The clinical features, incidence, and prevalence of CPSP are shown in Table 17.7.1.1.

Table 17.7.1.1. Summary of Incidence, Prevalence, and Clinical Presentation of CPSP

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Incidence (I\textsubscript{CPSP}) or Prevalence (P\textsubscript{CPSP}) and/or</th>
</tr>
</thead>
</table>

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<table>
<thead>
<tr>
<th>Sample Size</th>
<th>Clinical Presentation of CPSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boivie et al. (1989) N=27</td>
<td>• 92% (25/27) of patients had raised thresholds to thermal pain and 96% (26/27) had abnormal sensitivity to pinprick stimulus • Paraesthesias were reported in 11/27 patients, radiation of stimuli in 50%, allodynia in 45%</td>
</tr>
<tr>
<td>Andersen et al. (1995) N=267</td>
<td>P_{CPSP}= 8% • Abnormal sensory signs were found at least once in 42% of patients • Presence of CPSP was not related to age, size of stroke lesion, or side of stroke • Pain onset was within 1mo of stroke in 63%, at 1-6mo in 19%, after 6mos in 19% • Patients with sensory abnormalities were more likely to have acute onset extremity paresis with stroke (p&lt;0.05) and greater levels of disability (p&lt;0.001) at 1mo post-stroke compared to patients without sensory abnormalities</td>
</tr>
<tr>
<td>Vestergaard et al. (1995) N=11</td>
<td>• Median spontaneous pain intensity on a visual analogue scale was 3.3 (range: 0-7.7) • Warmth detection threshold was higher in the pain area in all patients • 90.9% of patients had an increased cold detection threshold</td>
</tr>
<tr>
<td>Bowsher et al. (2001) N=1071</td>
<td>P_{CPSP}=11% in community sample of elderly patients • 25% of CPSP patients had thermal pain • In CPSP patients, 25% had plegia and 75% had paresis in the painful limb</td>
</tr>
<tr>
<td>Widar et al. (2002) N=43</td>
<td>P_{CPSP}=35% of patients with pain post stroke P_{CPSP}=2.8% of all patients post stroke • Among patients who had central pain, the thermal sensitivity was significantly reduced on the symptomatic side • Sensory abnormalities (alldynia, hypoalgesia, hyperalgesia) were present in 93% of CPSP</td>
</tr>
<tr>
<td>Jonsson et al. (2006) N=297</td>
<td>P_{pain post stroke}=32% at 4 months; 21% at 16 months • Predictors of post-stroke pain were younger age (p=0.01), female (p=0.006), higher NIHSS (p&lt;0.001), higher HbA1c (p=0.001) at stroke onset • Predictors of more severe post-stroke pain were female (p=0.036), higher GDS-20 suggestive of depression (p&lt;0.001), higher MMSE score suggestive of better cognition (p=0.004), higher HbA1c (p=0.004) at 16 months</td>
</tr>
<tr>
<td>Klit et al. (2011) N=964</td>
<td>P_{CPSP}=4.4% definite CPSP; 7.3% probable CPSP; 8.9% CPSP-like dysesthesia or pain • 66% of CPSP patients had alldynia or hyperalgesia • 80% of CPSP had alldynia or evoked dysesthesia in at least one sensory modality • 40% of CPSP had allodynia to cold and 66% had dysesthesia to cold • 57% of CPSP had pinprick hyperalgesia</td>
</tr>
<tr>
<td>O'Donnell et al. (2013) NStart=20332 NEnd=15754</td>
<td>I_{pain post stroke}= 10.6%; I_{CPSP}=2.7% • For non-CPSP pain syndromes: 1.5% had peripheral neuropathy; 1.3% had spasticity-related pain, 0.9% had shoulder pain, and 4.7% had other pain syndromes</td>
</tr>
<tr>
<td>Raffaeli et al. (2013) N=601</td>
<td>P_{CPSP}=11% • Pain onset was immediately post stroke in 57.6%, 1mo post stroke in 19.7%, and several months post stroke in 19.7% • Continuous pain was present in 59.6% of CPSP patients and intermittent pain was present in 36.5%</td>
</tr>
<tr>
<td>Harno et al. (2014) N=824</td>
<td>P_{CPSP}=5.9% • 29.9% had sensory abnormality without CPSP; 64.2% had neither sensory abnormality nor CPSP • Strong or very strong pain and sensory symptoms included tingling pain (54%), electric shocks (29%), warm or cold allodynia (29%), numbness (46%) • Hypoesthesia to warm was prevalent in 62% of patients, to cold 43%, to pinprick in 28%, and to touch in 23% of patients • Hyperesthesia to pinprick was found 36%, to cold in 13%, and to warm in 13%</td>
</tr>
</tbody>
</table>
CPSP was associated with moderate to severe stroke symptoms (p<0.001) and lower quality of life (p<0.001).

As outlined above, there is considerable variability in the incidence and prevalence of CPSP in the literature. Many authors identified that underdiagnosis of CPSP is plausible, as patients may have other conditions that healthcare providers prioritize over pain or may not be able to describe their pain (Hansson 2004; Henry et al. 2008; Jensen & Lenz 1995; Segatore 1996.) This postulate is supported by some of the above studies, including one which allowed patients to self-identify as having post-stroke pain and found the prevalence of CPSP to be higher than previously thought (Bowsher 2001), and the exclusion of patients with cognitive or language difficulties in other studies (Andersen et al. 1995; Raffaeli et al. 2013). Several studies attempted to characterize which patients develop CPSP and found that women, younger patients, and patients with more severe strokes were more likely (Harno et al. 2014; Jonsson et al. 2006). Despite the limitations in determining the prevalence, CPSP is common post stroke, and warrants management.

17.7.2 Pathophysiology of Central Post-Stroke Pain
Given that it was initially described as a result of thalamic stroke, central pain resulting from a stroke is often referred to as thalamic pain; however, further understanding and evaluation has demonstrated that central neuropathic pain post stroke can arise from lesions outside of the thalamus (Agnew et al. 1983; Bowsher 1985; Fields & Adams 1974; Garcin & Lapresle 1969; Leijon et al. 1989; Loh et al. 1981). CPSP is invariably associated with a lesion involving the spino-thalamo-cortical pathway, which is responsible for pain and temperature processing at different levels within the central nervous system (CNS), resulting in a disturbance in temperature and pain sensation (Andersen et al. 1995). Leijon et al. (1989b) showed that central pain states occurred following brainstem, thalamic, and suprathalamic (cortical) cerebrovascular events.

At present, the pathophysiology of CPSP states remains unknown. It is becoming increasingly clear that damage to the spino-thalamico-cortical pathway is associated with CPSP, although not all patients with damage to this pathway will experience central pain post stroke (Andersen et al. 1995; Boivie et al. 1989; Dejerine & Roussy 1906; Jensen & Lenz 1995; Vestergaard et al. 1995). CPSP is always associated with impaired sensory perceptions to temperature (cold and/or warm) and painful stimuli, somatosensory functions mediated by the spinothalamic tract (Boivie 1992; Boivie et al. 1989; Vestergaard et al. 1995). However, touch, 2-point discrimination and vibration sense, generally regarded to be mediated by lemniscal pathways in the CNS may be intact (Boivie et al. 1989; Vestergaard et al. 1995).

Many cases of CPSP are associated with hyperalgesia and/or allodynia despite sensory deficits in the affected areas due to stroke. This paradoxical presence of a sensory deficit in combination with hyperalgesia in the part of the body affected by the stroke lesion suggests a central sensitization of third and fourth order neurons in the central nervous system as a result of loss of spino-thalamic or thalamo-cortical input (Vestergaard et al. 1995). The loss of normal cortical or thalamic inputs or modulation to spinal sensory inputs may exaggerate the perception of pain; for instance, lack of cortical modulation due to stroke may lead to hyperexcitability of intact thalamic neurons, evoking a perception of pain to a harmless stimulus. This hypothesis shares many features thought to be characteristic of other neuropathic pain syndromes associated with peripheral nerve lesions where spinal cord neurons that have lost their afferent input develop hyperexcitability, producing pain (Bennett & Laird 1992; Dubner 1991; Wall 1991).
17.7.3 Clinical Features of Central Post-Stroke Pain

Neuropathic pain has different qualities than nociceptive pain; it may be described as a "burning" sensation, an unpleasant sensation of tingling, pins and needles, or numbness, or terms such as ripping, tearing, pressing, twisting, aching, pricking, and lacerating (Andersen et al. 1995; Boivie et al. 1989; Leijon et al. 1989; Tasker 1990). Dysesthesia are defined as unpleasant sensations, either spontaneous or evoked (Andersen et al. 1995). Allodynia refers to a painful or unpleasant somatosensory experience, often poorly localized, elucidated by normally non-painful stimuli (Andersen et al. 1995). Hyperalgesia is defined as an increased pain response to a painful stimulus (Andersen et al. 1995). In CPSP, the pain is experienced within an area smaller than the total area of sensory impairment; the pain may be constant or occur in spontaneous paroxysms of pain (Boivie et al. 1989; Frese et al. 2006; Leijon et al. 1989; Tasker 1990). CPSP also can be exacerbated by physical movement, emotional stress, loud noises or voices, changes in the weather, cold, and light touch (Boivie et al. 1989; Leijon et al. 1989; Tasker 1990). Leijon et al. (1989), in their study of 23 patients with CPSP secondary to a known cerebrovascular lesion, did not find that stroke location reliably predicted the description of pain, with the exception that "burning" pain was more commonly described with brainstem and supratotal lesions while "lacerating" pain was seen more with the thalamic lesions. Andersen et al. (1995), in their study of 16 patients with CPSP, noted no relationship between size or location of the stroke and the presence of CPSP.

All patients with CPSP have some type of sensory abnormality on the affected side, almost always involving decreased perception of pain and temperature (Boivie et al. 1989). In addition to abnormalities of decreased sensory perception, nearly all patients with CPSP report spontaneous or evoked paraesthesias and/or dysaesthesias (Andersen et al. 1995; Leijon et al. 1989). Spontaneous dysaesthesias occur in the majority of CPSP patients while almost all demonstrate some hypersensitivity to external somatic stimuli (Leijon et al. 1989). Andersen et al. (1995) noted 9 of 16 CPSP patients (56%) reported allodynia to cold stimulation and 9 (56%) reported allodynia to touch.

While stroke-related sensory impairment is almost certain in CPSP, paralysis is variably present. The original thalamic pain syndrome described by Dejerine and Roussy (1906) was associated with thalamic stroke and was characterized by mild hemiplegia, abnormal sensation, hemiastereognosia, intolerable pain, and hemiataxia with choreoathetoid movements (Andersen et al. 1995). One study of 27 patients with CPSP found that 52% had no paresis, 37% had moderate paresis, and 11% had severe paresis (Leijon et al. 1989).

Central sensitization leading to pain post stroke has been thought to occur during neuronal recovery (Segatore 1996). Few studies have closely examined the time required for the development of CPSP, but research supports the idea that CPSP develops early post stroke in the majority of patients, when neuronal recovery is most pronounced. Andersen et al. (1995), in their review of 16 CPSP patients, noted 10 (63%) reported pain onset within one month of the stroke, 3 (19%) within 1-6 months, and 3 (19%) after more than 6 months. A more recent study of 66 patients with CPSP had very similar findings: Rafaelli et al. (2013) found that pain onset occurred immediately post stroke in 57.6% of patients, one month post stroke in 19.7%, and several months post stroke in 19.7%. In the Helsinki Young Stroke Registry, 5.9% of patients had CPSP; the majority developed pain within 1 month post stroke (Harno et al. 2014). Cumulatively, these studies favour early development of CPSP, but do not exclude the possibility of delayed symptom onset.

A significant proportion of patients may experience central, neuropathic pain as a consequence of stroke; specifically, CPSP may occur in as many as 2.8-11% of patients (Bowsher 2001; Widar et al. 2002). The vast majority of patients who experience CPSP have sensory abnormalities involving pain (pinprick)
and temperature, supporting the hypothesis that disruption to part of the spino-thalamic-cortical pathway is the etiologic mechanism for central pain post stroke (Andersen et al. 1995; Boivie et al. 1989; Boivie 1992; Vestergaard et al. 1995); these patients may also have abnormal proprioception or vibration sense, paralysis or paresis, and positive sensory phenomena such as spontaneous or provoked dysesthesias or paraesthesias (Andersen et al. 1995; Boivie et al. 1989; Leijon et al. 1989; Tasker 1990). The development of CPSP occurs within 1 month of acute stroke in the majority of patients, but may develop over a longer time course in others (Andersen et al. 1995; Harno et al. 2014; Rafaelli et al. 2013). Younger patients, female patients, and patients with greater stroke severity, diabetes, and depression may be more likely to develop CPSP than other patients (Harno et al. 2014; Jonsson et al. 2006).

17.7.4 Treatment of Central Post-Stroke Pain

Widar & Ahlstrom (2002) identified that “[p]ain after stroke is a symptom often forgotten…although it is reported to be a great problem in care.” In the preceding sections, concerns regarding underdiagnosis of CPSP have been prevalent. Indeed, diagnosis and identification of a clinical problem is crucial to its management. In addition to difficulty in ensuring healthcare providers identify CPSP as a clinical problem for patients, inadequately effective treatments pose a considerable challenge to the management of CPSP. Due to its complex and incompletely understood pathophysiology, a number of therapies, both non-pharmacologic and pharmacologic, have been investigated.

Motor cortex stimulation has been studied as a non-invasive, non-pharmacologic treatment option for CPSP, including in three RCTs. Lefaucheur et al. (2001) evaluated repetitive transcranial magnetic stimulation (rTMS) compared to sham in 14 patients with trigeminal neuralgia or post-stroke (thalamic) pain. The authors observed a 30% reduction in pain visual analogue scale up to 8 days after the 20-minute treatment, but not to the end of the 12-day follow-up period. The authors reported that no adverse events, including no seizures, were associated with treatment. In a larger study by the same group, 66 patients with pain after thalamic or brainstem stroke, spinal cord injury, brachial plexus injury, or trigeminal neuralgia, compared the same interventions, rTMS and sham (Lefaucheur et al. 2004). Both the sham and rTMS groups had a significant decrease in their pain visual analogue scale scores immediately after treatment, suggesting a significant placebo effect. There was no difference between the rTMS and sham groups. No adverse events were observed, including no seizures. Andre-Obadia et al. (2006) evaluated the effect of rTMS compared to sham at 6 days after treatment in 12 patients with CPSP or peripheral nerve injury as part of a study aimed at identifying patients who would benefit from invasive brain stimulation. There was no significant difference between rTMS and sham in this study, and no adverse events were observed.

Within the available literature on the treatment of CPSP, there is significant variability in recommendations. For instance, a Cochrane review concluded that lamotrigine was not an effective treatment for post-stroke pain, based on the results from only a single RCT (Wiffen & Rees 2007), whereas Kumar et al. (2009) concluded that amitriptyline and lamotrigine should be considered first-line drugs for CPSP following a recent review of the literature. Frese et al. (2006) conducted a systematic review of studies investigating pharmacologic treatment of CPSP. The review included seven small RCTs, six uncontrolled trials and one case series. The study reported that oral drugs effective in treating CPSP were amitriptyline, lamotrigine, and gabapentin. IV lidocaine, propofol, and ketamine were effective for short-term control of CPSP, but the authors found these options unsuitable for long-term use due to possible side effects and toxicity with use (Frese et al. 2006). By contrast, Mulla et al. (2015) recently conducted a systematic review and meta-analysis of RCTs for nonpharmacological and pharmacological therapies, including anticonvulsants, tricyclic antidepressants, opioid antagonists, repetitive transcranial
magnetic stimulation, and electroacupuncture, in 459 patients with CPSP. Treatment effects from eight RCTs were assessed using the GRADE approach. On repeat analysis, the authors found that none of the RCTs demonstrated benefit for pain reduction or other clinically important outcomes, even in therapies commonly used in practice or recommended in clinical practice guidelines, such as amitriptyline and anticonvulsants. These authors excluded trials with less than 2 weeks of follow-up, stating that even if these therapies are effective, such short demonstrated benefit is not worthwhile given the chronic nature of CPSP.

**Table 17.7.4.1 Summary of RCTs Evaluating Treatments of CPSP**

<table>
<thead>
<tr>
<th>Author, Year (PEDro Score)</th>
<th>Intervention E: experimental group(s); C: control group</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kim et al.</strong> (2011)</td>
<td>E: Pregabalin</td>
<td>• Daily Pain Rating Scale (-)</td>
</tr>
<tr>
<td>RCT (9)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=220</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vranken et al.</strong> (2011)</td>
<td>E: Duloxetine</td>
<td>• Visual Analog Scale (-)</td>
</tr>
<tr>
<td>RCT (9)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=48</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vranken et al.</strong> (2008)</td>
<td>E: Pregabalin</td>
<td>• Visual Analog Scale (+)</td>
</tr>
<tr>
<td>RCT (9)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=40</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vranken et al.</strong> (2005)</td>
<td>E: Ketamine</td>
<td>• Pain Disability Index (+)</td>
</tr>
<tr>
<td>RCT (9)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=33</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Jungehulsing et al.</strong> (2013)</td>
<td>E: Levetiracetam</td>
<td>• 11-point Likert scale (-)</td>
</tr>
<tr>
<td>RCT (8)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=42</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vestergaard et al.</strong> (2001)</td>
<td>E: Lamotrigine</td>
<td>• Median Pain Score (+)</td>
</tr>
<tr>
<td>RCT (8)</td>
<td>C: Placebo (8 wk cross-over study)</td>
<td></td>
</tr>
<tr>
<td>N=30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Attal et al.</strong> (2002)</td>
<td>E: IV morphine</td>
<td>• Visual Analog Scale (-)</td>
</tr>
<tr>
<td>RCT (8)</td>
<td>C: Saline (2 wk cross-over study)</td>
<td></td>
</tr>
<tr>
<td>N=15</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Andre-Obadia et al.</strong> (2006)</td>
<td>E1: 1Hz rTMS</td>
<td>• Pain Disability Index (+)</td>
</tr>
<tr>
<td>RCT (8)</td>
<td>E2: 20Hz rTMS</td>
<td></td>
</tr>
<tr>
<td>N=12</td>
<td>C: Sham</td>
<td></td>
</tr>
<tr>
<td><strong>Serpell et al.</strong> (2002)</td>
<td>E: Up to 2400 mg/day of gabapentin</td>
<td>• Visual Analog Scale (+)</td>
</tr>
<tr>
<td>RCT (8)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=9</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Canavero &amp; Bonicalzi</strong> (2004)</td>
<td>E: Propofol</td>
<td>• Visual Analog Scale (+)</td>
</tr>
<tr>
<td>RCT (7)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=44</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Lampl et al.</strong> (2002)</td>
<td>E: Amitriptyline treatment</td>
<td>• Visual Analog Scale (-)</td>
</tr>
<tr>
<td>RCT (7)</td>
<td>C: Placebo</td>
<td></td>
</tr>
<tr>
<td>N=39</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Rowbotham et al.</strong> (2003)</td>
<td>E: High-strength (0.75-mg) levorphanol</td>
<td>• Pain Reduction (+)</td>
</tr>
<tr>
<td>RCT (7)</td>
<td>C: Low-strength (0.15-mg) levorphanol</td>
<td></td>
</tr>
<tr>
<td>N=81 (10 CPSP patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cho et al.</strong> (2013)</td>
<td>E: Bee venom (0.005%)</td>
<td>• Visual Analog Scale (+)</td>
</tr>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>
Discussion

Although the evidence for optimal treatment is lacking, central pain is generally intractable to most therapeutic interventions. Narcotic and non-narcotic analgesics consistently failed to provide adequate pain relief (Nuzzo & Warfield 1985). Apo-morphine has been reported to be effective but associated with significant adverse effects and a tendency to lose its effectiveness over time (Miley et al. 1978).

The most commonly used medications for central neuropathic pain, such as CPSP, are tricyclic antidepressants and anticonvulsants. Tricyclic antidepressants have been shown to have a beneficial effect on central pain states (Koppel 1986; Tourian 1987). In one controlled study (PEDro = 6), amitriptyline was shown to reduce pain in 15 CPSP patients, although the benefits were lost at 4 months (Leijon & Boivie 1989) and repeat analysis in a systematic review showed no benefit (Mulla et al. 2015). Anticonvulsants, such as chlorpromazine (Margolis & Gianacol 1956), phenytoin (Cantor 1972; Mladinich 1974), and carbamazepine (Leijon & Boivie 1989) are reportedly minimally effective in reducing pain (Bowsher 1985). However, pregabalin, a different anticonvulsant, was effective in reducing pain in two RCTs (J. S. Kim et al. 2011; Vranken et al. 2008).

Transcutaneous electrical nerve stimulation was reported to be effective in some CPSP patients (Leijon & Boivie 1989a). Sympathetic blockade in the form of stellate ganglion and lumbar sympathetic blocks or local venous guanethidine blocks may provide some temporary relief of pain (Loh et al. 1981). In one RCT, diluted bee venom was found to reduce pain scores significantly more than saline alone when both were injected locally during acupuncture of areas of heightened pain (Cho et al. 2013). Although the results proved optimistic, the authors indicate that both interventions improved pain scores from baseline to post-intervention. Furthermore, the sample size included in the study is small and the study does not provide any information comparing bee venom to other more commonly used pharmacological drugs for treating central pain.

A variety of operative treatments have been tried for central pain states. These include neurosurgical brain lesioning (Davis & Stokes 1966; Mark et al. 1961; Nashold et al. 1969; White & Sweet 1969), brain stimulation (Meyerson 1979; Sweet 1982) and even stereotaxic chemical hypophysectomy (Levin et al. 1983). Overall, neurosurgical ablative procedures have been reported in uncontrolled studies to have a 25% effectiveness rate in permanently relieving central pain states but are associated with a significant risk of brain injury (Pagni 1976). These findings led to interest in transcranial (non-invasive) cortical stimulation using rTMS. 3 RCTs, two of which were by the same group of authors, reported significant short-term improvements in pain following a single treatment, although this was not sustained and was
not always different from sham treatment. Kobayashi et al. (2015) showed that weekly rTMS may have benefit in CPSP, but the study was open-label and uncontrolled.

The findings of Mulla et al. (2015) emphasize the lack of robust evidence on which to base guidelines for the management of CPSP and other post-stroke central pain conditions. However, tricyclic antidepressants, despite only one effective RCT of 15 patients, remain the first line recommendation for the treatment of CPSP. Pregabalin, more so than other anticonvulsants, should also be considered as a potential first line therapy. Other interventions require further research to confirm their safety and long-term efficacy.

**Conclusions Regarding the Treatment of Central Pain Post Stroke**

- There is conflicting level 1a evidence for the effectiveness of anticonvulsants on pain post stroke: pregabalin, gabapentin, and lamotrigine have been shown to be variably effective at reducing pain compared to placebo.

- There is level 1a evidence that there is no difference between amitriptyline and a placebo on improving central pain. There is limited level 1a evidence that there is no difference between duloxetine and placebo on improving central pain. However, further study is necessary.

- There is level 1b evidence that intravenous injections of morphine may not provide pain relief compared to a saline treatment; however, this has not been sufficiently studied and further research is required.

- There is level 1b evidence that intravenous injections of propofol may contribute to a significant difference in pain outcomes compared to a placebo.

- There is conflicting level 1a evidence that rTMS may help to reduce symptoms of post-stroke pain in the short term, but this may not be different to sham rTMS.

- There is level 1b evidence that high-strength μ-opioid agonist levorphanol may reduce pain in post-stroke patients.

A broad range of drug treatments are available for the treatment of central pain post stroke; however, the majority of these require further study for their effectiveness on pain reduction.

### 17.8 Post-Stroke Fatigue

Although fatigue following stroke is common and may negatively affect progress during inpatient rehabilitation, it has not been well-studied. Fatigue is a subjective term and there is no universally accepted definition (Choi-Kwon & Kim 2011; Van Eijsden et al. 2012). Abnormal or pathological fatigue has been characterized as a state of general tiredness or weariness unrelated to exertion levels that is usually not ameliorated by rest (De Groot et al. 2003).

A review by Choi-Kwon & Kim (2011) proposed that the predisposing factors to post-stroke fatigue (PSF) be classified into 3 main categories: physiological, including functional disability, pre-stroke fatigue, medical comorbidities, medication, sleep disturbances, and nutritional problems; psycho-cognitive including, depression and cognitive dysfunction; and organic including, damage to particular brain areas.
with consequent neurochemical alterations due to perfusion deficit in stroke. A variety of risk factors for PSF have been identified: chronic pain, depression, certain medications, sleep disorders, disability level, and neurological impairment (Feigin et al. 2012; Hoang et al. 2012; Mead et al. 2011). Female sex and age emerged most consistently as independent predictors of fatigue in predictions models. Controversy exists as to whether there is a causal relationship between depression and fatigue. Patients with post-stroke pain were reported to have higher fatigue scores, although pain is not required nor necessarily comorbid with PSF (Tang et al. 2015).

17.8.1 Prevalence of Post-Stroke Fatigue
Estimates of the prevalence of PSF vary widely, from 30-74%, depending on the measure used to assess it and the timing of assessment (Table 17.8.1.1). Many studies demonstrate that the patients continue to experience PSF without much fluctuation over time. There is also evidence that fatigue both increases and decreases in frequency over time post stroke (Duncan et al. 2012).

Table 17.8.1.1 Prevalence of Post-Stroke Fatigue

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>51.5% - 58.3%</td>
</tr>
<tr>
<td>10 days</td>
<td>59%</td>
</tr>
<tr>
<td>1 month</td>
<td>28%</td>
</tr>
<tr>
<td>2 months</td>
<td>35%</td>
</tr>
<tr>
<td>6 months</td>
<td>23% - 68%</td>
</tr>
<tr>
<td>1 year</td>
<td>21% - 74%</td>
</tr>
<tr>
<td>1.5 years</td>
<td>33% - 64%</td>
</tr>
<tr>
<td>2 years</td>
<td>40%</td>
</tr>
<tr>
<td>3 years</td>
<td>58%</td>
</tr>
</tbody>
</table>

In addition to being prevalent, mortality has been shown to be significantly associated with PSF, even after adjusting for age and sex, which may suggest that patients suffering from PSF are at a higher risk of mortality than non-fatigued individuals (Naess & Nyland 2013). The most common type of fatigue experienced by stroke survivors was reported to be physical fatigue (69.6%), followed by activity-related fatigue (67.9%), and mental fatigue (62.5%) (Muina-Lopez & Guidon 2013). The presence of fatigue was found to restrict participation in various activities including those involving self-care (Miller et al. 2013; Young et al. 2013), which can negatively affect functional recovery especially when comorbid depression exists (Badaru et al. 2013). Higher fatigue levels were also significantly associated with lower self-efficacy beliefs (Miller et al. 2013; Muina-Lopez & Guidon 2013).

17.8.2 Treatment of Post-Stroke Fatigue
Given its high prevalence and negative impact on patient outcomes, treatment of PSF is an often unmet need, both due to limited understanding of its pathophysiology and due to paucity of effective treatment options. The etiology of PSF is multifactorial and incompletely understood; therefore, the approach to treatment is varied. Pharmacological and non-pharmacological approaches have been investigated.

17.8.2.1 Pharmacological Treatment of Post-Stroke Fatigue
An updated Cochrane review of interventions for PSF found no evidence to support any of the studied interventions (Wu et al. 2015a). The review identified five RCTs of pharmacologic interventions. Gurak et al. (2005) compared enerion (synthetic vitamin B1 derivative) with usual outpatient stroke rehabilitation
to usual outpatient rehabilitation alone in 30 patients meeting criteria for PSF. After 30 days of treatment, Choi-Kwan et al. (2007) compared fluoxetine 20mg daily to placebo 20mg daily in 78 patients at least three months post stroke who self-identified as having significant PSF. Patients were treated for three months; there was no significant difference between placebo and fluoxetine in this trial for the primary outcome measure of the Fatigue Severity Scale (FSS) (Choi-Kwan et al. 2007). Guo et al. (2012) compared a proprietary combination of Chinese herbs to placebo Chinese herbs in 90 patients meeting diagnostic criteria for PSF. After 4 weeks, there was no significant difference between placebo and fluoxetine in this trial for the primary outcome measure of the Fatigue Severity Scale (FSS) (Choi-Kwan et al. 2007). Guo et al. (2012) compared a proprietary combination of Chinese herbs to placebo Chinese herbs in 90 patients meeting diagnostic criteria for PSF. After 4 weeks, there was no significant difference between placebo and fluoxetine in this trial for the primary outcome measure of the Fatigue Severity Scale (FSS) (Choi-Kwan et al. 2007).

In a cross-over RCT, Johansson et al. (2012) compared monoaminergic stabilizer (-)-OSU6162 to placebo in 12 patients with mental fatigue, 6 of whom had PSF. The drug did not demonstrate benefit for PSF. The previously mentioned RCTs evaluated fatigue as a primary endpoint. The remaining RCT, evaluating trilazad mesylate, evaluated fatigue as one of many secondary outcomes but did not find a statistically significant difference between treatment and placebo on PSF (Ogden et al. 1998). Several major limitations to the studies involved in the review are small sample sizes, high risk of bias, and lack of primary outcome of interest being PSF.

In the non-placebo controlled study by Brioschi et al (2009), patients with brainstem or diencephalic stroke showed positive response with modafinil compared to patients with cortical stroke. The authors concluded that fatigue in patients with brainstem-diencephalic strokes may be caused by dysfunctional reticular activating system (RAS) and that modafinil, a drug originally used to treat patients with hypersomnia or narcolepsy, benefits only those stroke patients whose lesions involve the RAS. Although promising, this study was neither placebo-controlled nor included an adequate sample size to apply these results broadly.

Few studies of robust quality have evaluated pharmacologic interventions for PSF, so there is inadequate evidence on which to base suggestions or guidelines for initiation of therapy (McGeough et al. 2009; Wu et al. 2015). Thus the management of PSF will be variable based on clinician experience and case-by-case treatment considerations.

### 17.8.2.2. Non-Pharmacological Treatment of Post-Stroke Fatigue

Few non-pharmacologic treatment options for PSF have been evaluated using vigorous methodology. Three RCTs are summarized below (Table 17.8.2.2.1).

**Table 17.8.2.2.1. Summary of RCTs Evaluating Non-Pharmacological Treatment of PSF**

<table>
<thead>
<tr>
<th>Author, Year (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Zedlitz et al. (2012)</strong></td>
<td>N=73</td>
<td>E: Cognitive therapy + graded activity training (COGRAT) C: Cognitive therapy (CO)</td>
<td>• Checklist Individual Strength (subscale fatigue) and self-observation list (fatigue) (+)</td>
</tr>
<tr>
<td><strong>Clarke et al. (2012)</strong></td>
<td>N=16</td>
<td>E: Fatigue management group C: General stroke education</td>
<td>• Fatigue Severity Scale (-)</td>
</tr>
<tr>
<td><strong>Johansson et al. (2012)</strong></td>
<td>N=18</td>
<td>E: Mindfulness-based stress reduction (MBSR) C: No active treatment</td>
<td>• Mental fatigue self-assessment (+)</td>
</tr>
</tbody>
</table>

+ Indicates statistically significant difference between treatment groups  
- Indicates no statistical significant difference between treatment groups

**Discussion**
The two RCTs outlined above have attempted to discern the effectiveness of non-pharmacological therapies for reducing PSF. Cognitive therapy in addition to graded activity training was found to improve PSF when compared to cognitive therapy alone (Zedlitz et al. 2012). On the other hand, taking part of a fatigue management group was as effective as receiving general education regarding PSF (Clarke et al. 2012). It is clear there is a lack of research being done in attempting to find non-pharmacological treatment options for PSF despite the high prevalence of fatigue in stroke survivors. Future research is encouraged to investigate other treatment options that may be advantageous at reducing other symptoms such as depression and pain which are often comorbidities to PSF.

Conclusions Regarding Pharmacological and Non-Pharmacological Treatment of Post-Stroke Fatigue

Treatment with pharmacological agents has not been sufficiently studied to determine their efficacy for reducing post-stroke fatigue.

The effectiveness of fatigue management programs compared to a general stroke education program requires further study.

More research is needed to determine treatment options for post-stroke fatigue.

17.9 Post-Stroke Insomnia

There is limited research on the prevalence of insomnia among stroke survivors; however, some research does suggest the disturbance of sleep following stroke (Suh et al. 2014). This may occur concurrent with depression or independent of it, and may be more common in patients with cortical lesions compared to other lesions (Suh et al. 2014). Two studies are summarized in Table 17.9.1.

<table>
<thead>
<tr>
<th>Author, Year (PEDro Score)</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Main Outcome(s) (Result)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al. (2009) RCT (7) N=52</td>
<td>E: Real Intradermal Acupuncture; C: Sham acupuncture</td>
<td>• Insomnia Severity Index (+) • Athens Insomnia Scale (+)</td>
<td></td>
</tr>
<tr>
<td>Kim et al. (2004) N=30</td>
<td>E: Real Intradermal Acupuncture; C: Sham acupuncture</td>
<td>• Morning Questionnaire (+) • Insomnia Severity Index (+) • Athens Insomnia scale (+)</td>
<td></td>
</tr>
</tbody>
</table>

+ Indicates statistically significant difference between treatment groups

- Indicates no statistical significant difference between treatment groups

Discussion

Two studies have examined effects of intradermal acupuncture aimed at the autonomic nervous system on post-stroke insomnia (Kim et al. 2004; Lee et al. 2009). Kim et al. (2004) reported that patients in the treatment group demonstrated a statistically significant improvement in sleep compared to the control group, as measured by the Morning Questionnaire, Insomnia Severity Index and Athens Insomnia Scale. Lee et al. (2009) also assessed post-stroke insomnia using similar scales and the results are similar to the findings from Kim et al. (2004).
There are several advantages of intradermal acupuncture over sham acupuncture, and other conventional treatments available for post-stroke insomnia. First, intradermal acupuncture is generally thought to be safer than medications such as benzodiazepines and other non-benzodiazepine drugs (e.g. zopiclone, zolpidem and zaleplon) because of adverse effects associated with drug therapy. Second, as a technique, intradermal acupuncture is thought to be more effective at stimulating acupoints compared to conventional acupuncture (Kim et al. 2004). While literature has suggested that these treatments may be helpful for treatment of post-stroke insomnia, there is a paucity of randomized clinical trials investigating effects of intradermal acupuncture compared to conventional acupuncture therapy. Further research is required to assess clinical effects of real intradermal therapy on insomnia using larger controlled trials.

**Conclusions Regarding Acupuncture for Post-Stroke Insomnia**

*There is level 1a evidence that acupuncture may improve insomnia compared to a sham acupuncture session.*

*Acupuncture may be efficient at treating post-stroke insomnia; however, more research is required.*
Summary

1. There is level 1b evidence that prompted voiding may reduce the number of episodes of incontinence compared to usual care in patients with urge urinary incontinence.

2. There is level 1b evidence that biofeedback-assisted pelvic training may decrease the number of episodes of incontinence compared to standard rehabilitation.

3. There is level 1b evidence that pelvic floor muscle training does not reduce incontinence symptoms or outcomes compared to standard rehabilitation.

4. There is level 1b evidence that complete correspondence compared to incomplete correspondence of Chinese herbal medicines may be helpful for paruria and symptoms of abnormal defecation; however, the methodology is not adequately described to reproduce this intervention.

5. There is level 1b evidence that catheter clamping protocols offered at 0-days, 1-day and 3-days may be as effective on bladder reconditioning outcomes such as time to first void, volume on first void, voiding method, and residual urine volume following the first void.

6. There is conflicting level 2 evidence regarding the effectiveness of functionally-oriented rehabilitation programs alone at improving incontinence when compared to a conventional Bobath approach.

7. There are no RCTs of urinary incontinence in post-stroke patients to guide pharmacological agent selection in this population.

8. The use of indwelling urinary catheters (IUC) in stroke patients is common.

9. There is level 3 evidence that IUCs are associated with worse outcomes, including urinary tract infections.

10. There is level 5 evidence that IUCs should be limited to those patients with intractable urinary retention, skin breakdown, continuous wetness and the need for urinary monitoring.

11. There is level 1b evidence that a traditional Japanese medicine, Diakenchuto, may be effective at reducing constipation.

12. There is level 1b evidence that a nursing evaluation program consisting of an assessment, provision of educational material for the patient, and a summary of the diagnostic results may be effective in reducing constipation long-term post stroke.

13. There is level 1b evidence that a morning bowel routine may be as effective as an evening bowel routine.

14. There is level 1 evidence that the use of enoxaparin is effective for DVT prophylaxis after acute stroke and has lower risk of significant bleeding compared to unfractionated heparin.

15. There is level 1a evidence that low molecular weight heparin may reduce the incidence of DVT and PE. Its effectiveness may be comparable to that of aspirin for reducing the incidence of DVTs.
16. There is level 1a evidence that the use of an intermittent pneumatic compression device may reduce the occurrence of DVT compared to no IPC.

17. There is level 1b evidence that compression stockings with intermittent pneumatic compression may reduce the occurrence of DVT as compared to compression stockings alone.

18. There is conflicting level 1a evidence regarding the use of graded compression stockings on the development of proximal DVT.

19. The incidence of post-stroke seizures is, on average, 10% but due to methodological variation and study population differences, the incidence reported in the literature has a wide range, from 1.2% to 27.8%.

20. There is level 1b and level 2 evidence that patients who have experienced seizures post stroke should receive monotherapy with an antiepileptic drug to prevent seizure reoccurrence.

21. There is level 1a evidence that prophylactic treatment with antiepileptic drugs may not be effective in preventing first seizures post stroke.

22. There is level 1a evidence that treatment with bisphosphonates (risedronate, etidronate, and zoledronate), may preserve bone mineral density post stroke compared to placebo.

23. There is level 1a evidence that treatment with vitamin D, including vitamin D2, vitamin D3, and sunlight therapy, may be helpful in preserving bone mass density.

24. There is limited level 2 evidence that treatment with estrogen-like products such as manauquinone, salmon calcitonin, or isoflavone derivatives compared to a placebo or vitamin D may not result in significant benefits in bone density outcomes.

25. There is conflicting level 1a evidence regarding the effect of vitamin D derivatives on osteoporotic fractures post stroke; further research is required.

26. There is conflicting level 1a evidence for the effectiveness of anticonvulsants on pain post stroke: pregabalin, gabapentin, and lamotrigine have been shown to be variably effective at reducing pain compared to placebo.

27. There is level 1a evidence that there is no difference between amitriptyline and a placebo on improving central pain. There is limited level 1a evidence that there is no difference between duloxetine and placebo on improving central pain. However, further study is necessary.

28. There is level 1b evidence that intravenous injections of morphine may not provide pain relief compared to a saline treatment; however, this has not been sufficiently studied and further research is required.

29. There is level 1b evidence that intravenous injections of propofol may contribute to a significant difference in pain outcomes compared to a placebo.

30. There is conflicting level 1a evidence that rTMS may help to reduce symptoms of post-stroke pain in the short term, but this may not be different to sham rTMS.
31. There is level 1b evidence that high-strength μ-opioid agonist levorphanol may reduce pain in post-stroke patients.

32. Treatment with pharmacological agents has not been sufficiently studied to determine their efficacy for reducing post-stroke fatigue.

33. The effectiveness of fatigue management programs compared to a general stroke education program requires further study.

34. There is level 1a evidence that acupuncture may improve insomnia compared to a sham acupuncture session.
References


