ERABI
EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY

11. Heterotopic Ossification and Venous Thromboembolism Post Acquired Brain Injury

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Diagram 11.1: Virchow's Triad

Abbreviations

ABI	Acquired Brain Injury
DVT	Deep Venous Thrombosis
EHDP	Etidronate Disodium (ethane-1-hydroxy-1, 1-diphosphonate)
GCS	Glasgow Coma Scale
HO	Heterotopic Ossification
LMWH	Low-Molecular Weight Heparin
PCT	Prospective Controlled Trial
PE	Pulmonary Embolism
PIOPED	Prospective Investigation of Pulmonary Embolism Diagnosis
SCD	Sequential Compression Devices
TBI	Traumatic Brain Injury
VTE	Venous Thromboembolism

Key Points

Forceful joint manipulation may prevent bony ankylosis post ABI and may increase range of motion in joints affected by heterotopic ossification.

Etidronate Disodium may prevent the development of heterotopic ossification in individuals with ABI.

Radiation therapy and shock wave therapy may be effective for the treatment of pain and/or range of motion associated with heterotopic ossification in ABI populations.

Surgical excision of heterotopic ossification may improve range of motion.

A delay in surgical excision may not increase the risk of further heterotopic ossification recurrence.

Combining surgical excision with etidronate disodium, indomethacin, and/or passive motion therapy may improve range of motion in individuals post-ABI.

Sequential compression devices may not reduce the risk of developing deep vein thrombosis or pulmonary embolism post ABI.

Intermittent compression devices do not aggravate intracranial hemodynamics in patients with severe ABI.

Administration of pharmacological deep vein thrombosis prophylaxis within the first 72 hours post ABI may be effective for reducing the risk of developing deep vein thrombosis.

Enoxaparin is effective for the prevention of Venous Thromboembolism development after elective neurosurgery and has not been found to cause excessive bleeding.

Compression stockings may be more effective at preventing venous thromboembolisms when combined with low-molecular weight heparin post ABI

Intermittent pneumatic compression devices and low molecular weight heparin may have a similar effect in terms of the prevention of deep vein thrombosis post ABI when compared to each other.

11. Heterotopic Ossification and Venous Thromboembolism Post Acquired Brain Injury

11.1 Introduction
This module aims to provide information regarding what is currently known about the etiology and treatment of heterotopic ossification (HO) and venous thromboembolism (VTE) following acquired brain injury (ABI). Additionally, it is worth noting that the majority of interventions discussed for HO and DVT are preventative measures, as there is limited evidence regarding available interventions for either complication in the setting of ABI. Information on diagnostic tools is also provided for both complications. The studies included in this module follow the same inclusion criteria as other modules and is outlined in Module 1.

11.2 Heterotopic Ossification (HO)
HO is the formation of pathologic bone within soft tissues, often muscle tissues, where bone formation does not usually occur (Watanabe & Sant, 2001). The incidence of HO in patients with traumatic brain injury (TBI) has been reported to range from 11% to 77% but is clinically relevant in 10-20% (Dizdar et al., 2013; Garland et al., 1980; Rogers, 1988; Sarafis et al., 1999; Sazbon et al., 1981; Zychowicz, 2013). Risk factors include skeletal trauma, spasticity, diffuse axonal injury, mechanical ventilation, prolonged immobilization, and injury severity (Moreta & de los Mozos, 2014). HO is often quite painful and limits joint mobility; the restricted joint range of motion may exacerbate disability and impede progress towards desired rehabilitation goals.

11.2.1 Formation of Heterotopic Ossification Post Head Injury
The pathophysiology of HO is not fully understood. Mesenchymal stem cells are pleuripotent cells that can differentiate into cells capable of generating cartilage, bone, muscle, tendons, ligaments, or fat (Pape et al., 2004). It is thought that they play a pivotal role in the development of HO (Williams et al., 1999). HO development begins with the formation of osteoid periarticularly and intramuscularly, and progresses to full calcification within a matter of weeks (Pape et al., 2001). Over the next few months, the calcified osteoid remodels into well-organized trabecular bone at which point it is considered to have matured (Pape et al., 2001). Several months after the initial trauma, patients with HO begin to experience restricted range of motion, pain, and ankylosis (Banovac & Gonzalez, 1997; Garland et al., 1980). The bony lesion has been found to have a high metabolic rate, with a rate of bone formation more than three times greater than that of normal bone, and an osteoclastic density of more than twice the density found in normal bone (Puzas et al., 1987).

It is believed that there is likely a neurogenic factor contributing to HO, although this mechanism is not yet understood ("Collaborative overview of randomised trials of antiplatelet therapy - III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients," 1994; Hurvitz et al., 1992; Pape et al., 2001; Pape et al., 2004). It has also been noted that circulating factors promoting HO may be present in patients with head injuries (Pape et al., 2004). Many studies have shown enhanced osteogenesis in patients sustaining TBI (Trentz et al., 2005). The presence of certain hormonal factors early post injury influences the stimulation of osteoprogenitors within skeletal muscles (Ivanhoe et al., 2012). Further, tissue hypoxia, sympathetic changes, immobilization, remobilization, and spasticity are additional risk factors (Ivanhoe et al., 2012). Accelerated fracture healing and HO are well documented phenomena in these patients (Bidner et al., 1990; Keret et al., 1990).

11.2.2 Clinical Presentation of Heterotopic Ossification

Among individuals with TBI, the most common sites of HO are the soft tissues around the hip, elbow, shoulder, and knee (Garland, 1991; Garland et al., 1980; van Kampen et al., 2011; Vanden Bossche & Vanderstraeten, 2005). The hip is the most frequent site of ossification (Dizdar et al., 2013; Vanden Bossche & Vanderstraeten, 2005), with total ankylosis of the joint occurring in 5-16% of affected hips (Stover et al., 1991). HO of the shoulder has been found to affect 5% of individuals with a brain injury (Cipriano et al., 2009), while the knee is a less common site for HO following a head injury (Sarafis et al., 1999). When HO is present in the knee, it is usually seen medially (Hosalkar et al., 2013). The distribution of HO around the elbow occurs most commonly either anteriorly in the flexor muscles or posteriorly in the extensors (Sarafis et al., 1999). Of the joints affected by HO after head injury, ankylosis is most likely to occur in the posterior elbow (Garland et al., 1980).

The onset of HO has been reported to vary between two and three weeks post injury (Watanabe & Sant, 2001). More recently, clinical signs and symptoms have been reported to develop 3-12 weeks post injury (Vanden Bossche & Vanderstraeten, 2005; Zychowicz, 2013). Pape and colleagues (2004) noted that clinical examination in the setting of HO may reveal a swollen, warm, painful joint which is often associated with decreased range of motion. The earliest sign is typically a loss of range of motion in the involved joint (Watanabe & Sant, 2001). Other indicators include erythema, palpation of a periarticular mass, and fever (Varghese, 1992). Because of the association with fever, it is sometimes difficult to differentiate HO from infection (Citta-Pietrolungo et al., 1992; Garland, 1991; Garland et al., 1980). Moreover, the clinical picture may be confused with DVT, local trauma, or fracture (Buschbacher, 1992; Jensen et al., 1987). HO will then progress from these initial symptoms into a mass with stiffness and induration (Zychowicz, 2013). Potential complications of HO include compression of blood vessels and nerves, breakdown of associated tissue, restricted motion, and loss of function (Zychowicz, 2013).

11.2.3 Diagnostic Testing for Heterotopic Ossification

During the initial presentation, plain radiographs may be negative and will usually remain normal until ossification begins at approximately 4-6 weeks post injury. Serum levels of alkaline phosphatase, a glycoprotein in the plasma membrane of osteoblasts, and the erythrocyte sedimentation rate may become elevated early on but are non-specific. The triple phase technicium-99 bone scan remains the diagnostic gold standard. The test is positive if there is increased uptake during the first and second phases of the study. It typically becomes positive when clinical features appear (i.e., before an x-ray would be positive).

In the HO literature there are several classification systems, with the Brooker classification system being one of the most widely used. The Brooker Classification system is typically used to classify ectopic-bone formation after total hip replacement. The system is based on anteroposterior radiographs of the pelvis and the categorization of the progression of HO into classes (Brooker et al., 1973). Brooker et al. (1973) define Class I as islands of bone within soft tissues about the hip; Class II as bone spurs from the pelvis or proximal end of the femur with at least 1cm between opposing bone surfaces; Class III as bone spurs from pelvis or proximal end of the femur, reducing space between opposing bone surfaces to less than 1cm; and Class IV as apparent bony ankylosis of hip. This classification system has been criticized and consequently has been modified (Della Valle et al., 2002; Mavrogenis et al., 2012; Toom et al., 2005; Wright et al., 1994)*.*

11.2.4 Prevention of Heterotopic Ossification

Prophylactic treatment options for HO include range of motion exercises, nonsteroidal anti-inflammatory medications, low-dose radiation, warfarin, and etidronate disodium (EHDP) (Watanabe & Sant, 2001). As surgical excision is the most effective intervention once HO has already occurred, the majority of the literature focuses on preventative treatment.

11.2.4.1 Non-Pharmacological Prophylaxis

Previous literature on range of motion therapy post ABI suggested that this actually contributed to the development of HO (Chantraine & Minaire, 1981; Crawford et al., 1986). Other literature demonstrated a shift in thinking and practice towards the utilization of range of motion exercises, and even joint manipulation under anesthesia, to help prevent ankylosis in patients with ABI (Garland, 1991; Garland et al., 1982). Pape et al. (2004) have noted that for HO, careful and judicious use of physiotherapy, involving assisted range of motion exercises and gentle stretching, are beneficial. However, it has been cautioned that care should be taken not to move the joint beyond its pain-free range of movement as this can exacerbate the condition (Evans, 1991; Pape et al., 2004).

Table 11.1 Non-Pharmacological Interventions for the Prevention of Heterotopic Ossification Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Garland et al. (1982) USA Case Series N=16	**Population:** TBI; Mean Age=24 yr; Gender: Male=8, Female=8; Mean Time Post Injury=3.6 mo. **Intervention:** Records of patients who received forceful manipulation under general anesthesia were reviewed. The 28 manipulated joints included: 11 hips, 13 elbows, and 4 shoulders. Mean follow-up time was 15 mo. **Outcome Measure:** Degree of motion.	1. Gains in range of motion were made in 23 joints (82%). 2. Eighteen joints (64%) maintained or gained further motion with rehabilitation after manipulation. 3. Seven hips (63%) gained an average of 52°, 8 elbows (62%) gained an average of 47°, 3 shoulders (75%) increased in degree of external rotation.

Discussion

Research in this area is limited; however, case study examples have shown physiotherapy with assisted range of motion to be beneficial (Ellerin et al., 1999). Garland et al. (1982) conducted a review of patients with TBI who underwent forceful manipulation of joints with pre-existing HO under anesthesia and reported that it was useful in maintaining and increasing range of motion. With 82% of joints having increased range of motion, the authors concluded that forceful manipulation is not only useful in maintaining motion but also aids in the prevention of bony ankylosis and did not appear to exacerbate the ossification process (Garland et al., 1982; Garland & Varpetian, 2003). Garland and Varpetian (2003) also noted that patients with ABI frequently suffer from spasticity, intolerance to pain, and voluntary muscle guarding. As a result, anesthesia may be needed to help differentiate between spasticity and ankylosis and to allow for sufficient muscle relaxation to perform the joint manipulation (Garland & Varpetian, 2003).

Conclusions

There is level 4 evidence that forceful manipulation under general anesthesia may increase range of motion and prevent bony ankylosis in patients with heterotopic ossification following brain injury.

Forceful joint manipulation may prevent bony ankylosis post ABI and may increase range of motion in joints affected by heterotopic ossification.

11.2.4.2 Pharmacological Prophylaxis

The evidence for nonsteroidal anti-inflammatory medications as prophylactic treatment for HO stems mostly from the use of indomethacin or ibuprofen in patients following total hip arthroplasty (Kjaersgaard-Andersen & Schmidt, 1986; Ritter & Sieber, 1985). Although it has been reported that the prophylactic use of these medications significantly decreases HO formation following total hip arthroplasty, it is not known if they have the same effect in the ABI population.

The use of EHDP, a bisphosphate, in the prophylaxis and treatment of HO is controversial (Watanabe & Sant, 2001). EHDP works by preventing the aggregation, growth, and mineralization of calcium hydroxyapatite crystals which are essential for bone formation. EHDP may potentially delay fracture healing, as long-term use has been associated with osteomalacia.

Table 11.2 Pharmacological Interventions for the Prevention of Heterotopic Ossification Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
[Spielman et al.](#) (1983) USA PCT N=20	**Population:** Head Injury; Gender: Male=16; Female=4. *Intervention Group (n=10):* Mean Age=31 yr; Mean GCS=5.2. *Control Group (n=10)*: Mean Age=27 yr; Mean GCS=5.5. **Intervention:** The prospective intervention group received EHDP (20 mg/kg/day for 12 wk, 10 mg/kg/day for next 12 wk) within 2-7 days post injury which continued for 6 mo. The control group was retrospective and did not receive EHDP. **Outcome Measure:** Presence of fractures, development of HO.	1. The EHDP treated group showed a significantly lower incidence of HO compared with controls (2 versus 7 patients, $p<0.025$). 2. Of the 9 that developed HO, 25 sites were affected; elbows (35%), shoulders (29%), hips (18%), and knees (18%) were most common. Seven individuals had restricted limb motion and 2 had ankylosis.

Discussion

Although EHDP has been shown to be effective in reducing HO in other populations, such as spinal cord injury, its effectiveness among individuals with brain injury is less well studied. In an ABI population, Spielman et al. (1983) found that patients treated with EHDP showed a significantly lower incidence of HO than the control group. However, due to the small sample size of the study and the research design, additional research assessing the benefit of EHDP for the prevention of HO following brain injury is needed.

Conclusions

There is level 2 evidence that etidronate disodium may reduce the incidence of heterotopic ossification compared to no etidronate disodium in patients with severe head injury.

> **Etidronate Disodium may prevent the development of heterotopic ossification in individuals with ABI.**

11.2.5 Treatment of Heterotopic Ossification

The vast majority of HO interventions include the surgical excision of the affected area. As HO can be challenging to initially diagnose and have high recurrence rates (Almangour et al., 2016), it is important to determine which interventions are successful for the direct treatment of HO. Unlike patients with spinal cord injury, the cognitive and functional status of ABI patients is not a predictor of recurrence (Almangour et al., 2016); therefore, it is more difficult to infer which patients are most likely to re-develop HO, reinforcing the need for effective interventions.

11.2.5.1 Non-Pharmacological Interventions

Recently, there has been a focus on non-pharmacological, non-surgical interventions for the treatment of HO in the literature. The majority of non-surgical treatments for HO aim to disrupt the bone formations through either radiation or vibration (Lee et al., 2016; Reznik et al., 2017a). The goal of radiation therapy is to disrupt mesenchymal stem cell differentiation into osteoblasts during the early phases of HO (Balboni et al., 2006); by doing so, additional bone formation on a specific site should be arrested. Shock wave/vibration therapy, in contrast, seeks to erode unwanted formations of bone (Reznik et al., 2017a). Regardless of the mechanism of action, the overall goal of non-pharmacological interventions for the treatment of HO is to provide a less invasive alternative to surgical excision.

Table 11.3 Non-Pharmacological Interventions for the Treatment of Heterotopic Ossification Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Lee et al. (2016) Korea Pre-Post N$_{initial}$=3, N$_{final}$=3	**Population:** TBI=1, meningioma=1, spontaneous intracranial hemorrhage=1; Mean Age=37 yr; Gender: Male=3; Mean Time Post Injury=4.5 yr. **Intervention:** Three cases of neurogenic HO were treated with radiation therapy (RT). Patients received 10 days of RT for a total dose of 20 Gray (Gy) in 2 Gy fractions to each affected joint. The results of 4-6 mo follow-up evaluation after brain injury are reported. **Outcome Measure:** Serum alkaline phosphatase (ALP) level; serum bone-specific ALP (BALP); HO involved joint range of motion (ROM); pain severity.	1. All 3 patients had decreased serum ALP, decreased BALP levels, decreased pain, and increased joint ROM immediately after RT. 2. No further growth of the HO was indicated by post-treatment imaging. 3. At 4 or 6 months after RT, all patients maintained clinical and laboratory improvements.
Resnik et al. (2017a) Australia Pre-Post N$_{initial}$=11, N$_{final}$=9	**Population:** TBI=11; Mean Age=41 yr; Gender: Male=9, Female=2. **Intervention:** Patients with TBI and chronic neurogenic heterotopic ossification (NHO) at the hip or knee received 4 applications of high-energy extracorporeal shock wave therapy (ESWT) delivered to the affected joint over 8 wk (one treatment every two wk). **Outcome Measure:** Faces Rating Scale (FRS) for pain; NHO size.	1. Patients receiving high-energy ESWT experienced a significant reduction in pain intensity from baseline to post-intervention as measured by the FRS ($p=0.002$). 2. There was no significant mean difference from baseline to post-intervention in NHO size.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Resnik et al. (2017b) Australia Pre-Post $N_{initial}$=11, N_{final}=11	**Population:** TBI=11; Mean Age=41 yr; Gender: Male=9, Female=2. **Intervention:** Patients with TBI and chronic neurogenic heterotopic ossification (NHO) at the hip or knee received 4 applications of high-energy extracorporeal shock wave therapy (ESWT) delivered to the affected joint over 8 wk. **Outcome Measure:** Range of motion (ROM); Functional Reach (FR); Modified Functional Reach (MFR).	1. Patients receiving high-energy ESWT showed significant improvement in ROM (flexion) of the NHO-affected knee (p=0.002, n=4) from baseline to post-treatment. No significant effect of treatment on knee extension was observed. No significant results were found for hip ROM. 2. Patients receiving high-energy ESWT showed significant improvement and FR (p=0.006, n=5) score from baseline to post-treatment. 3. No significant effect of treatment on MFR scores was observed.
Garland et al. (1982) USA Case Series N=16	**Population:** TBI; Mean Age=24 yr; Gender: Male=8, Female=8; Mean Time Post Injury=3.6 mo. **Intervention:** Records of patients who received forceful manipulation under general anesthesia were reviewed. The 28 manipulated joints included: 11 hips, 13 elbows, and 4 shoulders. Mean follow-up time was 15 mo. **Outcome Measure:** Degree of motion.	1. Gains in range of motion were made in 23 joints (82%). 2. Eighteen joints (64%) maintained or gained further motion with rehabilitation after manipulation. 3. Seven hips (63%) gained an average of 52°, 8 elbows (62%) gained an average of 47°, 3 shoulders (75%) increased in degree of external rotation.

Discussion

Recent studies have shown that there are potential alternatives to the treatment of HO other than surgery, which is invasive and can be inefficient in terms of recurrence rates (Lee et al., 2016). A study by Resnik et al. (2017a) demonstrated that extracorporeal shock wave therapy was successful in reducing pain associated with HO. Additionally, patients experienced a significant improvement in the flexion range of motion of affected knees, however, no significant effects were seen on knee extension or hip range of motions (Reznik et al., 2017b). A study examining the effects of radiation therapy on HO also suggested positive results in terms of reduced pain and blood plasma levels of HO markers (Lee et al., 2016). Furthermore, results demonstrated immediate beneficial effects of radiation therapy on range of motion, in addition to the cessation of HO formation post treatment.

Conclusions

There is level 4 evidence that radiation therapy may prevent further formation of heterotopic ossification in ABI populations.

There is level 4 evidence that radiation therapy may improve range of motion in joints affected by heterotopic ossification in ABI populations.

There is level 4 evidence that extracorporeal shock wave therapy may reduce pain associated with heterotopic ossification in ABI populations.

There is level 4 evidence that forceful manipulation under general anesthesia may increase range of motion and prevent bony ankylosis in patients with heterotopic ossification following brain injury.

> **Radiation therapy and shock wave therapy may be effective for the treatment of pain and/or range of motion associated with heterotopic ossification in ABI populations.**

11.2.5.2 Surgical Interventions

Surgical excision of the heterotopic bone is suggested as a possible option for those in whom HO has generated marked functional impairment or ulcers in the skin due to deformity (Watanabe & Sant, 2001). A recent systematic review found that as high as 55% of those diagnosed with neurogenic HO required surgery (Almangour et al., 2016). It had been recommended, based on expert opinion, that surgical intervention be considered only 12 to 18 months after HO initiation to ensure that the bone tissue has matured, and to reduce the likelihood of HO recurrence (Garland, 1991; Sazbon et al., 1981); however, trends toward even later surgical intervention are also emerging (Moreta & de los Mozos, 2014). There is some indication that EHDP and nonsteroidal anti-inflammatory medications may be useful in preventing HO recurrence following surgical excision (Watanabe & Sant, 2001). Further studies are needed to corroborate this. Watanabe and Sant (2001) have reported that recurrence of HO following surgical excision usually occurs post-operatively within three months.

Table 11.4 Surgical Excision for the Treatment of Heterotopic Ossification Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Pansard et al. (2013) France Case Series N=16	**Population:** TBI=11, Spinal cord injury=2, stroke=1, Cerebral anoxia=2; Mean Age=30.1 yr; Gender: Male=15, Female=1; Mean Time Post Injury=64 mo. **Intervention:** Participants were included in retrospective analysis after receiving surgery for shoulder HO. **Outcome Measure**: Range of Motion (ROM).	1. Mean ROM increased significantly for forward elevation (69°), abduction (60°), and external rotation (13°). 2. Surgical approaches were superolateral (15.8%), deltopectoral (26.3%), posterior (26.3%), posterior-deltopectoral (10.5%), superolateral-deltopectoral (5.3%), axillary (5.3%), and martini (10.5%). 1. No recurrence was reported for any of the participants.
Fuller et al. (2013) USA Case Series N=10	**Population:** TBI; Mean Age=30 yr; Gender: Male=6, Female=4, Mean Time Post Injury=46.54 mo. **Intervention:** Retrospective review of individuals who had resection of HO for restrictive shoulder HO. **Outcome Measure:** Range of Motion (ROM).	1. ROM improved in all 3 planes of motion ($p<0.001$). Specifically 85°, 59.1° and 66.9° for the sagittal, coronal and axial plane respectively. 2. Three of 11 shoulders had recurrence of HO. One patient developed osteoarthrosis and had avascular necrosis in the opposite shoulder, one had a greater predisposition due to multiple joint involvement, and the other patient had severe post-operative swelling.
Genet et al. (2012) France Case Control N=80	**Population:** TBI; Gender: Male=65, Female=15. *Recurrence Group (n=16):* Mean Age=30.8 yr; Mean Time Post Injury=25.3 mo. *No Recurrence Group (n=64):* Mean Age=30.3 yr; Mean Time Post Injury=31.7 mo. **Intervention:** Patients who had surgery for HO (hip, knee or shoulder) were examined for recurrence. **Outcome Measure: recurrence of HO**	1. There was no link between recurrence and timing of surgery ($p=0.54$). 2. Recurrence was not associated with ABI severity ($p=0.81$).

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
[Melamed et al](#). (2002) Israel Pre-Post N=9	**Population:** TBI; Mean Age=38 yr; Gender: Male=8, Female=1; Mean Time Post Injury=29 mo. **Intervention:** Surgical resection of HO (8 hips, 3 knees, 1 elbow). All patients received postoperative physical therapy and participated in a rehabilitation program. **Outcome Measure:** Functional Status, Range of Motion (ROM), radiographic evaluation, Brooker Classification.	1. The mean preoperative flexion-extension arc of hips was 33°; postoperatively it was 93°. 2. The mean preoperative and postoperative ROM in knees was 58° and 67° respectively. 3. Improved ROM was seen in 7 of 8 hips; 4 patients had marked improvement in gait, 2 of whom no longer required prosthetics. 4. For follow-up (n=8), 7 graded themselves as functionally improved and 7 reported improved ROM.

Discussion

Four studies examined the effects of surgical excision of HO; three studies focused on the shoulder (Fuller et al., 2013; Genet et al., 2012; Pansard et al., 2013), and two on the hip (Genet et al., 2012; Melamed et al., 2002).

In two studies, the recurrence of HO was evaluated months following the initial operation (Fuller et al., 2013; Fuller et al., 2005; Ippolito et al., 1999a, 1999b; Moore, 1993; Pansard et al., 2013). The majority of the studies did not specify what qualified as recurrence; however a study by Kolessar et al. (1996) found recurrence rates differed based on the classification system utilized (23.8% versus 4.8% using the Brooker classification and the Stover and colleagues classification, respectively). A systematic review conducted by Lee et al. (2013) focused specifically on the surgical excision of HO in the elbow and found improvements in motion, with low levels of recurrence (14.3%). However, complications such as fracture, infection, nerve palsies, wound complications and loss of motion without recurrence were found in 27.5% of cases (Lee et al., 2013).

Overall, the surgical excision of HO resulted in improved range of motion (Fuller et al., 2005; Pansard et al., 2013). Improvements in activities of daily living and ambulation were also found (Fuller et al., 2013; Ippolito et al., 1999a, 1999b; Melamed et al., 2002). It is worth noting that a study by Genet et al. (2012) found no relationship between operative delay and recurrence of HO post-surgery.

Conclusions

There is level 4 evidence that surgical excision of heterotopic ossification may improve range of motion in ABI populations.

There is level 3 evidence that a delay in heterotopic ossification surgical excision does not increase the risk of further heterotopic ossification recurrence in ABI populations compared to immediate surgical intervention.

Surgical excision of heterotopic ossification may improve range of motion.

A delay in surgical excision may not increase the risk of further heterotopic ossification recurrence.

11.2.5.3 Combination Therapies

Often, surgical excision of HO is not sufficient to remediate the loss of functionality caused by HO. Many studies incorporate a combination of interventions with the aim to help patients regain the maximum amount of function possible. Combination therapies most commonly include surgical excision together with passive motion therapy, pharmacological prophylaxis, or both.

Table 11.5 Combination Therapy for the Treatment of Heterotopic Ossification Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Fuller et al. (2005) USA Case Series N=17	**Population:** TBI=15, Anoxia=1, SCI=1; Mean Age=33 yr; Gender: Male=10, Female= 7; Mean Time Post Injury=25 mo. **Intervention:** A retrospective review of individuals who had surgical excision of HO of the knee. All patients then participated in an inpatient rehabilitation program (e.g., range of motion, passive stretching, weight bearing) and received 20 mg/kg of etidronate disodium for 2 mo. **Outcome Measure:** Passive range of motion, Five-level Ambulatory scale, sitting function scale.	1. There was a significant improvement in arc of motion (mean 65°, p<0.0001). 2. Extension and flexion significantly improved postoperatively (p<0.002 and p<0.0001, respectively). 3. Significant improvements were found in ambulation and sitting ability postoperatively (both p<0.0001). 4. There were no recurrences of HO by clinical or radiographic examinations at 2, 6, or 12 wk.
de Palma et al. (2002) Italy Case Series N=10	**Population:** TBI; Gender: Male=6, Female=4. **Intervention:** Surgical resection of HO of the elbow with Indomethacin (25 mg, 3x/day for 6 wk) administered postoperatively. Active mobilization of the elbow joint commenced 1 mo after surgery. **Outcome Measure:** Garland's Classification, Range of Motion (ROM).	1. All patients had improved ROM in the early postoperative period, especially in those who had the most severe restriction in joint mobility. 2. Improvement correlated with residual neurological damage. Class I and II (minimal physical/cognitive benefits) patients had the greatest improvements, achieving satisfactory ROM, while class III (more marked physical deficits) had only partial improvement in ROM.
Lazarus et al. (1999) USA Pre-Post N=24	**Population:** TBI; Mean Age=37.4 yr; Gender: Male=20, Female=7; Mean Time Post Injury=35.4 mo. **Intervention:** Patients had HO resection in a total of 27 elbows. All patients received indomethacin (25-50 mg, 2x/day) after surgery. Some patients (n=17) received continuous passive motion. **Outcome Measure:** Range of Motion (ROM).	1. Maximum flexion increased from 80.1° preoperatively to 111.9° postoperatively (p=0.0003). 2. Maximum extension increased from 58.9° preoperatively to 32.1° postoperatively (p=0.0005). 3. Twenty-three elbows gained motion and 4 lost a mean of 15°. 4. The patients with ankylosed elbows (n=17) preoperatively, made greater gains than the remaining patients (n=10), mean of 59.1° vs 23.2° (p=0.03). 5. Patients with longer injury to resection times had worse outcomes compared to those with shorter times (p=0.02). 6. Patients who had continuous passive motion after surgery had greater ROM gains than those who did not (57.9° vs 24.1°, p=0.04).

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Ippolito et al. (1999a) Italy Case Series N=12	**Population:** TBI; Mean Age=29 yr; Gender: Male=9, Female=3. **Intervention:** Surgical resection of hip HO (total of 13 hips). As an antibiotic prophylaxis, each patient received Cefazolin (800 mg, 3x/day for 2 wk). Indomethacin (50 mg, 2x/day for 6 wk) was also given after the operation. **Outcome Measure:** Walking capacity, hip range of motion (ROM).	1. All patients showed satisfactory ROM following the surgery. 2. Radiographs revealed remnants of HO following surgery; these remnants did not interfere with ROM. 3. At final follow up (mean 38 mo post-operative), 8 hips maintained initial gains in ROM, 2 had decreased ROM with no evidence of HO recurrence and 3 decreased ROM with partial or full recurrence of HO. 4. All patients who had a painful hip prior to operation (n=5) were pain free after. 5. Nine of 12 patients were non-ambulatory prior to surgery; post-operatively, 10/12 were able to ambulate (5 with braces or crutches).
Ippolito et al. (1999a) Italy Case Series N=14	**Population:** TBI; Mean Age=30.8 yr; Gender: Male=10, Female=4. **Intervention:** Surgical resection of HO in 16 elbows. Immediately after the surgery, a continuous passive motion machine was applied and was gradually increased until the joint regained the whole arc of motion (6wk). Patients assigned to one of two groups. Group 1: elbows ankylosed in position (ranged from 0-100°; n=11 elbows) or group 2: elbows in which 10–25° of flexion was available (n=5 elbows). **Outcome Measure:** Arc of elbow range of motion (ROM).	1. At the end of surgery, the arc of flexion attained ranged from 90-145° in group 1 and 115-140° in group 2. 2. At follow up (mean 30.7 mo), the arc of flexion (both active and passive) attained ranged from 30-135° in group 1 and 80-145° in group 2. 3. 9 joints lost ROM, 3 joints gained ROM and 4 joints retained the same ROM at follow-up, relative to post operation. 4. Partial recurrence was observed in 3 elbows. 5. The average arc of flexion for those who had surgery <18 mo (n=11) or >18mo (n=5) after coma, was 105° and 92°, respectively.
Ippolito et al. (1999b) Italy Case Series N=5	**Population:** TBI; Mean Age=26 yr; Gender: Male=3, Female=2. **Intervention:** Patients had surgical resection of HO in 7 knees. Post-surgery, a continuous passive motion machine was applied and used daily until the joint had regained the whole arc of motion that was seen at time of operation (approximately 6 wk). **Outcome Measure:** Arc of knee motion, recurrence of HO.	1. At baseline all knees were in a fixed flexed position (10-40°) with a painful arc of motion (20-70°). 2. At follow up (mean 34 mo) the arc of motion had improved in all of the knees (0–130° in 3 knees, 0–120° in 3 knees, and 10–120° in 1 knee). 3. At follow up, arc of flexion was 10-100° for 2 patients, 0-120° for another 2 patients, and 0-90°, 5-110°, and 0-130° for the remaining 3 patients. 4. None of the patients could walk before the operation; however, at follow up, all patients could walk and all knees were pain free. 5. Ossification did not recur in any of the knees.
Moore (1993) USA Case Series N=17	**Population:** TBI; Mean Age=26 yr; Gender: Male=17, Female=0; Mean Time Post Injury to Surgery=21 mo. **Intervention:** Retrospective study of patients who had surgical excision of HO (13 hips, 7 elbows). Patients received etidronate disodium (10 mg/kg per day for approximately 3 mo) post-surgery.	1. The average arc of motion obtained immediately after surgery was 85° in for the hips and 65° for the elbows. 2. Eleven hip joints and 6 elbow joints maintained sufficient ROM to achieve pre-operative functional goals (e.g., enhanced wheelchair sitting, improvement in bed to wheelchair

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
	Outcome Measure: Range of Motion (ROM).	transfers or improvements in activities of daily living. 3. Three of 20 joints had recurrence of HO.

Discussion

Many studies examining combination therapies for relief from HO have used passive motion therapy (Fuller et al., 2005; Ippolito et al., 1999b; Lazarus et al., 1999) and have found it to be effective in combination with surgery for improving range of motion. In Fuller et al. (2005), participants completed a rehabilitation program which included a series of passive measures such as stretching and weight bearing. There were no instances of recurrence at 12 weeks, and both extension and flexion range of motion significantly improved. These results are further supported by Ippolito et al. (1999b), who found similar results. Lazarus et al. (1999) specifically examined the additional benefits of adding passive motion therapy to surgical HO excision and found that those who received continuous passive motion therapy had significantly greater improvements in range of motion compared to those that did not receive passive motion therapy. The study conducted by Lazarus et al. (1999) found that patients who had continuous passive motion exercises post operatively made significantly greater gains compared to those individuals who did not (57.9° versus 24.1°, p=0.04).

Several studies combined surgical excision of HO with pharmacological treatment (de Palma et al., 2002; Ippolito et al., 1999a; Moore, 1993). Ippolito et al. (1999a) treated patients with indomethacin and found that at final follow-up (38 months) all patients were pain free and eight of twelve maintained initial gains in range of motion. Fuller et al. (2005) found that, with treatment of etidronate disodium for 2 months after surgery, patients demonstrated significant improvements in ambulation, sitting, and range of motion. Additionally, there were no instances of recurrence. Moore (1993) found similar results with minimal accounts of recurrence and improvement in overall range of motion.

It is worth noting that length of time between injury and surgical resection was found to be a significant predictor of outcome, as longer times were associated with less improvement (Lazarus et al., 1999). Lastly, another correlation of interest was reported by de Palma et al. (2002), who found that range of motion improvement was correlated with level of neurological damage, with lesser damage correlating to improved outcomes.

Conclusions

There is level 4 evidence that surgical excision in combination with passive motion therapy may improve range of motion affected by heterotopic ossification in ABI populations.

There is level 4 evidence that surgical excision in combination with etidronate disodium may improve range of motion affected by heterotopic ossification in ABI populations.

There is level 4 evidence that surgical excision in combination with indomethacin may improve range of motion affected by heterotopic ossification in ABI populations.

> **Combining surgical excision with etidronate disodium, indomethacin, and/or passive motion therapy may improve range of motion in individuals post-ABI.**

11.3 Deep Venous Thrombosis

Venous thromboembolism (VTE) occurs when blood clots form within the venous system. Deep venous thrombosis (DVT) may occur if the clot forms in a deep vein (i.e., in the leg). If the clot breaks off and travels to the lungs, causing partial or full occlusion, it can become a pulmonary embolism (PE) (Office of the Surgeon et al., 2008). VTE remains a common complication in patients who have sustained an ABI (Raslan et al., 2010; Scudday et al., 2011); however the scientific literature specific to ABI is quite limited. The following section presents ABI specific research regarding the prevention and treatment of DVT. Additional information on clinical presentation and testing practices is presented, however, it should be noted that not all in-text citations refer to research that meets the specific ERABI ABI inclusion criteria (mixed populations, age, mixed ABI severity, etc.) and therefore should be interpreted with caution when considering the application of any tests or indicators of DVT to an ABI population.

11.3.1 Risk Factors for DVT Post Head Injury

In a large sample study consisting of 38,984 individuals with TBI, the incidence of VTE at the time of admission was 1.31% (Olufajo et al., 2016). At one month post injury, the incidence for VTE increased to 1.87% and by one year it was 2.83% (Olufajo et al., 2016). The reported incidence of DVT among patients with TBI ranges from 11% to 54% (Carlile et al., 2010; Cifu et al., 1996; Denson et al., 2007; Geerts et al., 1994). The risk of developing a DVT or PE, in the absence of prophylaxis, is estimated to be approximately 20% post TBI (Haddad & Arabi, 2012) and severity of injury is found to be associated with incidence of VTE in isolated patients with TBI (Van Gent et al., 2014). Decisions on how to treat, and when, are often made on a case by case basis (Tang & Lobel, 2009). Experts recommend beginning pharmacological prophylaxis as early as 48 to 72 hours post injury (Norwood et al., 2001). Unless contraindicated, mechanical thromboprophlaxis and low-molecular weight heparin (LMWH) are recommened in the acute phase of recovery (Haddad & Arabi, 2012).

Cifu et al. (1996) screened 153 patients admitted to a tertiary care brain injury unit within 24 hours of admission for a lower extremity DVT with colour flow duplex Doppler ultrasonography. All patients had received prophylactic intervention with either subcutaneous heparin anticoagulation or intermittent compression devices. The overall incidence of DVTs in those patients with ABI was 13%, while individuals with TBI had an incidence rate of 20%. Most of the DVTs were asymptomatic. Another study found that DVT was present in 31.6% of individuals who sustained a head injury (Ekeh et al., 2010). The most recognized risk factors for VTE are venostasis, intimal damage of the vessel wall, and a hypercoagulable state (Virchow's triad - see Diagram 11.1) (Watanabe & Sant, 2001). Patients with a severe brain injury are commonly immobilized for periods of time as a result of extremity or spine fractures they experienced at the time of their injury (Vergouwen et al., 2008). The incidence of DVT appears to be impacted by length of stay in the intensive care unit and the number of days a patient is on a ventilator. There does not appear to be a correlation between DVT incidence and initial Glasgow Coma Scale (GCS) scores, Injury Severity Scale scores, or the Abbreviated Injury Scale score (Denson et al.,
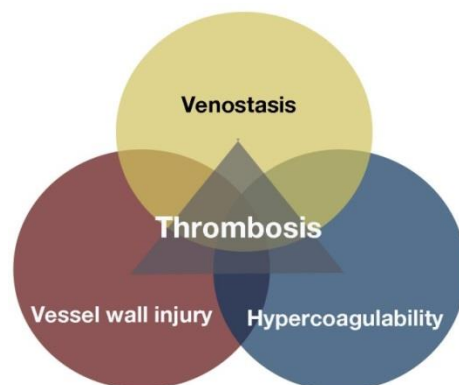

Diagram 11.1: Virchow's Triad

2007). Those at highest risk post injury are those who remain on a ventilator longer than 3 days (Olufajo et al., 2016; Raslan et al., 2010). At 1-year post injury, risk of VTE is greatest for those discharged to extended care facilities compared to home, and for individuals who undergo an operation (Olufajo et al., 2016). Patients involved in trauma that does not specifically involve vessel injury are still at increased risk of thromboembolism, suggesting a trauma-induced hypercoagulable state (Geerts et al., 1994; Geerts et al., 1996). Therefore, persons who have sustained a TBI appear to be at increased risk of developing VTE for multiple reasons.

11.3.2 Clinical Presentation of Deep Vein Thrombosis and Pulmonary Embolism
A recent study found that up to 91% of thrombi form below the iliac level (De Maeseneer et al., 2016), and that the most common symptoms reported when a DVT is present are pain, swelling of the legs, and discoloration of the region (Collins, 2009). The clinical presentation of PE is challenging. Many cases are clinically silent (66%) with only 30% having the clinical features of a DVT (Garcia-Fuster et al., 2014). Asymptomatic PE is discovered in 70% of patients with confirmed clinically symptomatic DVT (Browse, 1974; Corrigan et al., 1974; Hull & Hirsh, 1983). Clinically, PE presents with tachycardia, tachypnea, hemoptysis, pleuritic chest pain and fever. Radiographic findings might include signs of consolidation or pleural effusion (Worku et al., 2014). Massive PE may cause right heart failure, which can progress to cardiovascular collapse, coma, and death.

11.3.3 Diagnostic Testing for Deep Vein Thrombosis and Pulmonary Embolism
A positive diagnosis of DVT can only be made if a venogram is positive or there is a positive venous ultrasound at two or more sites of the proximal veins. The diagnosis of DVT can be ruled out if there is a negative venogram, a negative D-dimer test or a normal venous ultrasound, assuming the venous ultrasound is accompanied by one of the following findings: 1) low clinical suspicion for DVT, 2) negative D-dimer test, or 3) negative serial ultrasound performed one week later. In an email survey, 56% of respondents from acute centers reported the use of venous duplex ultrasonography (VDU) to screen for DVTs post ABI, whereas 13% of rehabilitation hospital responders use D-dimer along with venous duplex ultrasonography for routine screening of DVT post injury (Carlile et al., 2006).

Venous Ultrasound
Venous ultrasound is often used to diagnose a DVT. There are several types of venous ultrasonography. They include compression ultrasound, duplex ultrasound, and color Doppler imaging. Although these types of venous ultrasonography are sometimes used interchangeably, their sensitivities and specificities for detecting acute DVT vary (Zierler, 2004). The sensitivity and specificity of compression ultrasonography for detecting DVTs is 43% and 85%, respectively (Girard et al., 2005). The weighted mean sensitivity and specificity of venous ultrasonography for the diagnosis of symptomatic proximal DVT are 97% and 94%, respectively; the sensitivity falls to 73% for distal DVT (Kearon et al., 1998; Zierler, 2004). Importantly, distal DVTs do not confer the same risk of extension to PE as do proximal DVTs. Typically, if a distal clot is going to extend proximally, this occurs within one week of its development. Consequently, serial ultrasound could be used in symptomatic patients in whom the test is initially negative as the test would become positive with the clot extension.

Venography
Venography is considered a definitive test for DVT but it is an invasive test whereby contrast dye is injected into the leg veins. Diagnosis of DVT is made if an intraluminal-filling defect is noted.

D-dimer Assay

D-dimer assay is a rapid, non-invasive, and inexpensive test. Fibrin is the main component of thrombus formation and fibrin degradation products include D-dimers (Gill & Nahum, 2000). A positive D-dimer test is highly sensitive for the presence of a thrombus but lacks specificity since D-dimers are found in other disease states, including cancer, congestive heart failure, and inflammatory conditions (Raimondi et al., 1993). As a result, D-dimer assays have a high negative predictive value but a poor positive predictive value. To illustrate, 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 rehabilitation patients (stroke, spinal cord injury, TBI, hip arthroplasty). The specificity and positive predictive values were low at 55.3% and 48.7%, respectively.

Diagnostic Testing for Pulmonary Embolism

Ventilation/Perfusion Scanning
Nuclear ventilation/perfusion scans are often used to investigate possible PE. Palmowski et al. (2014) reported the sensitivity and specificity of ventilation/perfusion scanning as 95.8% and 82.6%, respectively, with false negative rates of 4.2% and false positive rates of 17.3%. Hence, a normal scan virtually excludes a PE (high negative predictive value). Identified perfusion defects are non-specific and only represent true PE in about one-third of cases. The probability that a perfusion defect represents a PE increases with the size, shape, and number of defects as well as the presence of a normal ventilation scan.

Table 11.6 Probability of Pulmonary Embolism Based on Ventilation-Perfusion Scan Results and Clinical Suspicion in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED Investigators) Study

Ventilation-Perfusion Scan Results	Clinical Suspicion of Pulmonary Embolism*		
	Low	Intermediate	High
High probability	56%	88%	96%
Intermediate probability	16%	28%	66%
Low probability	4%	16%	40%
Normal/near-normal probability	2%	6%	0%

* Percentage of patients with pulmonary embolism; Adapted from the PIOPED Investigators (Gill & Nahum, 2000; PIOPED Investigators, 1990).

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED Investigators) study demonstrated that a low-probability or normal ventilation-perfusion scan with a low clinical suspicion of PE essentially excludes the diagnosis of PE (negative predictive values of 96% and 98% respectively) (Gill & Nahum, 2000; PIOPED Investigators, 1990). When clinical suspicion is high and the scan indicates a high probability of PE, the positive predictive value is 96% (Gill & Nahum, 2000; PIOPED Investigators, 1990), and these patients should be treated. The majority of ventilation perfusion scans have non-diagnostic results, requiring further testing (PIOPED Investigators, 1990).

Pulmonary Angiography
Pulmonary angiography is the gold standard for diagnosis of PE (Gill & Nahum, 2000). It involves percutaneous catheterization and injection of contrast dye into a pulmonary artery branch (Gill & Nahum, 2000). Pulmonary angiography is most commonly used when ventilation-perfusion scanning is non-diagnostic but clinical suspicion remains high (Tapson et al., 1999). A negative pulmonary angiogram excludes clinically relevant PE (Gill & Nahum, 2000; Tapson et al., 1999). It is expensive and is

associated with the risk of significant complications. Relative contraindications include significant bleeding risk, allergy to contrast medium, and renal insufficiency (Gill & Nahum, 2000).

Spiral Computed Tomography (CT) Scan
A spiral computed tomography scan is a non-invasive test which can scan the entire thorax in one breath-hold. The sensitivity of a spinal computed tomography scan in diagnosing PE has been reported to range from 64% to 93%, with a specificity ranging between 89% and 100%. It is most accurate when the embolism is large. It actually visualizes the clot and has the added benefit of investigating other disease states in the differential diagnosis.

11.3.4 Prevention of DVT
Several interventions have been examined for the prevention of DVT after an ABI, including mechanical therapy, pharmaceuticals, or a combination of both. To date, the recommendation for treating those who sustain a DVT post ABI is the administration of preventative medication (Elliott et al., 2006; Scudday et al., 2011). However, there is no agreement on the administration of these medications in terms of timing, dose, and/or which medication.

11.3.4.1 Non-Pharmacological Prophylaxis
Non-pharmacological, mechanical interventions used to prevent the development of DVT post ABI include: the insertion of inferior vena cava filters, thromboembolism deterrent stockings, and intermittent pneumatic compression devices including arteriovenous foot pumps and sequential compression devices (SCDs). These devices operate primarily through two distinct mechanisms of action. The first is mechanical, in which the device increases the velocity of venous return to decrease venous stasis, thus reducing the opportunity for clot formation. The second, and perhaps more important mechanism, involves the systemic activation of the fibrinolytic system which, during compression, leads to the breakdown of fibrin clots associated with thromboembolism (Macatangay et al., 2008). The exception is vena cava filters, which operate by another method of mechanical VTE prevention (Watanabe & Sant, 2001). These filters are inserted into the inferior vena cava to prevent the passage of distal emboli into the lungs. Some reports have demonstrated success rates as high as 96% in the prevention of pulmonary emboli (Greenfield & Michna, 1988). However, the use of vena cava filters carries some associated risks. They can become blocked or dislodged which can increase the risk of an embolism. Some have also reportedly increased risks for repeated DVT compared with patients without such devices (Decousus et al., 1998).

Table 11.7 Mechanical Interventions for the Prevention of Deep Venous Thrombosis Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
Gersin et al. (1994) USA Cohort N=32	**Population:** TBI; *Group 1 (n=14)*: Mean Age=38.3 yr; Gender: Male=10, Female=4; Mean GCS Score=7.1. *Group 2 (n=18)*: Mean Age=36.1 yr; Gender: Male=14, Female=4; Mean GCS Score=6.8 **Treatment:** Patients admitted to the surgical Intensive care unit (ICU) either received (Group 1) or did not receive (Group 2) prophylactic sequential compression devices (SCDs). Technetium venoscans were conducted along with ventilation/perfusion (V/Q) lung scans	1. Of those who were given SCD prophylaxis, 4 developed PE and none developed DVT. 2. Of those who did not receive prophylactic SCD, 2 developed PE and 2 developed DVT. 3. The groups did not differ significantly in the development of DVT and PE (p=0.7).

Author/ Year/ Country/ Study Design/ N	Methods	Outcomes
	within 6 days of admission and repeated weekly for 1 mo. **Outcome Measure:** Incidence of DVT/PE.	
[Davidson et al.](#) (1993) USA Pre-Post N=24	**Population:** TBI=22, Other=2; Gender: Male=20, Female=4; Mean GCS Score=6. **Treatment:** Patients admitted to the surgical or trauma intensive care unit received intermittent sequential pneumatic leg compressions (11s compression phase, 60 sec of deflation). **Outcome Measure:** Mean Arterial Pressure (MAP), heart rate, central venous pressure, intracranial pressure, cerebral perfusion pressure. Measurements were obtained when the compression was initiated (time 0) and at 10, 20, and 30 min into therapy.	1. No significant changes in MAP, central venous pressure, intracranial pressure, or cerebral perfusion pressure occurred during the study period.

Discussion

Gersin et al. (1994) investigated the effectiveness of SCDs. Of 32 patients admitted to the surgical intensive care unit with severe TBI, a total of eight patients developed DVT or PE following injury, half of whom had received prophylactic SCDs (showing no significant difference between SCDs and no intervention). The effectiveness of prophylactic SCDs in the prevention of post-TBI DVT or PE thus remains questionable.

Davidson et al. (1993) conducted a study to evaluate the possibility that intermittent pneumatic compression could aggravate intracranial hemodynamics in severe brain injury patients. The authors reported that the use of intermittent compression devices to prevent the occurrence of DVT was not associated with any significant changes in intracranial pressure or cerebral perfusion pressure in stable patients in whom intracranial pressure was controlled by conventional measures (Davidson et al., 1993). These findings suggest that there is no contraindication to the use of pneumatic compression for the prevention of DVT in severe acute patients with brain injury who are responsive to conventional intracranial management measures.

Conclusions

There is level 2 evidence that sequential compression devices are not more effective for reducing the risk of developing deep vein thrombosis or pulmonary embolism compared to no sequential compression devices post ABI.

There is level 4 evidence that intermittent compression devices do not cause acute elevations in intracranial pressure in patients with severe ABI.

Sequential compression devices may not reduce the risk of developing deep vein thrombosis or pulmonary embolism post ABI.

Intermittent compression devices do not aggravate intracranial hemodynamics in patients with severe ABI.

11.3.4.2 Pharmacological Prophylaxis
Oral agents have been investigated for their prophylactic potential against DVT. Warfarin (Coumadin), a well-established anticoagulant with a predictable duration of action, is sometimes avoided as a prophylactic alternative for DVT due to its elevated bleeding side effects (Watanabe & Sant, 2001). Albrecht and colleagues (2014) report that warfarin use is associated with lower rates of DVT and PE, but comes at the cost of the risk of increased hemorrhagic bleeding. However, some experts felt the use of warfarin was advisable, especially for high risk patients due to its benefit in treating undetected thrombosis; the therapeutic concentration for prophylaxis and treatment of thromboembolism are the same (Hirsh et al., 1992; Hyers et al., 1992; Landefeld & Goldman, 1989).

In a study of DVT prophylaxis with a mixed population sample of 932 patients, 71% were given LMWH, 23% unfractionated heparin, 1% Coumadin, and 3% were given both LMWH and Low-dose unfractionated heparin, none of which were associated with increased intracranial or systemic hemorrhage (Carlile et al., 2010). The most recent guidelines, for those with ABI, on DVT prophylaxis recommend using LMWH or Low-dose unfractionated heparin in addition to mechanical prophylaxis (Elliott et al., 2006; Reiff et al., 2009). There is also evidence from a meta-analysis that aspirin has positive effects in the reduction of both DVT and PE, by 40% and 60% respectively ("Collaborative overview of randomised trials of antiplatelet therapy - III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients," 1994). Clinically, there remain concerns that chemical DVT prophylaxis may result in increased intracranial bleeding post ABI.

Overall, there is a lack of persuasive evidence to guide decisions about when to administer anticoagulant prophylaxis in those who sustain traumatic intracranial hemorrhage. Clinicians often make decisions based on their own assessments of the risks and benefits (Scales et al., 2010). To date no national standard of care exists for the administration of the pharmacological prophylaxis treatment of DVT post TBI (Phelan et al., 2012a).

Low Molecular Weight Heparin vs Low Dose Unfractionated Heparin
Subcutaneous heparin in low doses has been reported to be both safe and effective as prophylaxis against DVT development post ABI (Watanabe & Sant, 2001). The route of delivery may also affect the efficacy of anticoagulant prophylaxis (Watanabe & Sant, 2001). For this reason, intravenously delivered heparin may be more effective in the prevention of thromboembolism compared with subcutaneous administration, although this method of delivery might increase the risk of bleeding (Green et al., 1988). Low-molecular weight heparins, which are injected subcutaneously, have gained popularity due to the ease of administration and dosage adjustment. Of note, low-molecular weight variants of unfractionated heparin are significantly more expansive, and thus the risks, benefits, and costs need to be balanced out on an individual basis (Watanabe & Sant, 2001). Carlile et al. (2006) found that 15 of the 16 rehabilitation centers surveyed reported routinely initiating treatment with either LMWH or Low-dose unfractionated heparin. In a study with a mixed trauma population, low-dose unfractionated heparin was compared to enoxaparin (LMWH) for the treatment of DVT (Geerts et al., 1996). Of those receiving low-dose unfractionated heparin, 44% suffered a DVT compared to 31% of patients receiving enoxaparin (p=0.014) (Geerts et al., 1996).

Table 11.8 Pharmacological interventions for the Prevention of Deep Venous Thrombosis Post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Phelan et al. (2012b) USA RCT PEDro=8 N=62	**Population:** TBI; *Intervention Group (n=34):* Mean Age=40.7 yr; Gender: Male=22, Female=12. *Control Group (n=28):* Mean Age=42.6 yr; Gender: Male=16, Female=12. **Treatment:** The intervention group received enoxaparin (30 mg, 2x/day) within 24-96 hr after injury, whereas the control group received a placebo. **Outcome Measure:** Radiographic worsening of TBI, VTE, and extracranial hemorrhagic complications.	1. One DVT occurred in the control group; however, no mention of DVT occurrence was reported for the intervention group. 2. No clinical TBI progressions were found.
Byrne et al. (2016) USA Cohort N=3634	**Population:** ABI; Median Age=43 yr; Gender: Male=2798, Female=836; Median Time Post Injury=84 hr; Median GCS=3. **Treatment:** Participants were included in retrospective analysis after having received either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) as either early prophylaxis (<72 hr) or late prophylaxis (≥72 hr) for VTE. **Outcome Measure:** Risk of DVT, PE, late neurosurgical intervention and mortality; abbreviate head injury scale (AIS) and incidence of ischemic (ICH) stroke.	1. PE occurred in 1.7% of participants, and DVT in 6.5%. 2. Early prophylaxis was associated with lower odds of PE (OR=0.48) and DVT (OR=0.51) than late prophylaxis. 3. There was no significant difference in risk of late neurosurgical intervention or death between early and late prophylaxis. 4. LMWH was associated with lower odds of VTE (OR=0.6) and mortality (OR=0.59) than UFH. 5. Late prophylaxis group had significantly higher AIS score, ICH incidence, and early neurosurgical intervention rate than early prophylaxis group. **6.** The late group most commonly received LWMH and early group most commonly received UFH.
Dengler et al. (2016) USA Case Series N=155	**Population:** Gender: Male=119, Female=36. **Intervention:** Patients with severe TBI, intracranial hemorrhage (ICH), and invasive intracranial monitoring were retrospectively reviewed. Patient outcomes were correlated with prophylactic treatment (if any) for DVT that patients received. **Outcome Measure:** DVT: incidence, time to detection, time to starting prophylaxis; time to stable head computed tomography (CT); in-hospital mortality.	1. Twelve percent of the cohort experienced at least one DVT during the course of the study. 2. Following admission median time to stable head CT was 2 days, DVT prophylaxis was 4 days, and DVT detection was 8 days. 3. Among patients who did not receive anticoagulation treatment, the incidence of DVT (30.3%) was significantly greater than that of patients who received heparin (8.0%, p<0.01). 4. Among all patients, 28 (18%) experienced in-hospital mortality. 5. Those who did not receive anticoagulation treatment had a significantly increased risk of DVT and in-hospital death. 6. No significant association was observed between DVT formation, and the various doses of UH and LMWH.
Meyer et al. (2016) USA Case Series N=67	**Population:** TBI=67; *No Early VTC (n=35):* Mean Age=25.2 yr; Gender: Male=35; Mean GCS=8.3. *Early VTC (n=32):* Mean Age=24.9 yr; Gender: Male=32; Mean GCS=10.3.	1. The incidence of worsened ICH, DVT or PE, 30-day mortality, or non-elective reoperation were not significantly different between the treatment groups.

	Intervention: A retrospective analysis of patients with penetrating brain injury (PBI) was conducted. Patients were grouped by early venous thromboembolism chemoprophylaxis (VTC, occurring within 48 hr of injury) status. **Outcome Measure:** Intracranial hemorrhage (ICH) worsening; pulmonary embolism (PE); deep vein thrombosis (DVT); 30-day mortality; emergent reoperation; VTC: timing, agents used and dosage.	2. The mean time of first VTC dose was 24hr from admission. 3. The most commonly used early VTC agent was enoxaparin (30 mg subcutaneously, twice daily; 91%). The other 3 patients who received early VTC were given UFH (5000 units subcutaneously, 3 times daily).
Daley et al. (2015) USA Case Control N=271	**Population:** TBI; *Intervention Group (n=45):* Mean Age=42 yr; Gender: Male=38, Female=7; Mean GCS=10. *Control Group (n=226):* Mean Age=47 yr; Gender: Male=173, Female=53; Mean GCS=10. **Treatment:** Participants were categorized based on exposure (intervention) or lack of exposure (control) to enoxaparin during the acute phase after undergoing an emergency craniotomy, post-TBI. **Outcome Measure:** Rate of DVT and PE, days on ventilation (DOV), length of stay (LOS), mortality rate.	1. No significant differences between groups (intervention and control) were found in terms of rate of DVT (2% vs 3%, p=0.87) and PE (0% versus 1%, p=0.99), as well as LOS and DOV. 2. The intervention group had a significantly lower rate of mortality in hospital compared to the control group (4% vs 24%, p=0.01).
Kim et al. (2014) USA Case Control N=75	**Population:** TBI; Mean Age=44 yr; Gender: Male=59, Female=16; Mean GCS=4. **Treatment:** Participants received heparin prophylaxis at early (<3 days, n=22), intermediate (3-5 days, n=34), or late (>5 days, n=19) time intervals post injury. **Outcome Measure:** Rate of DVT, PE, and morality, number of ventilator and Intensive care unit (ICU) days, Glasgow Coma Scale (GCS), Abbreviated Injury Scale (AIS), Injury Severity Score (Ellerin et al.), Marshall CT), neurological improvement.	1. There was no significant difference between groups in mean rates of DVT, PE, or mortality; mean days on ventilator or in ICU; or mean scores on GCS, AIS, or Marshall CT. 2. There was a significant difference in mean ISS score between the early and intermediate groups (28 versus 35, p=0.02) and between the early and late groups (28 versus 36, p=0.007). 3. There was a significant difference in cumulative neurological improvement between the early and late groups (p<0.05), with greater improvement in the early group.
Lin et al. (2013) USA Case Series N=3812	**Population:** TBI, Abbreviated Injury Severity Scale>3. **Treatment:** Patient records were reviewed. Participants were grouped based on intervention without the heparin prophylaxis protocol (n=1970) and treatment after the implementation of a heparin prophylaxis protocol (n=1842). **Outcome Measure:** Rate of DVT and PE.	1. Rate of DVT was 0.97% without the protocol and 1.21% with the heparin prophylaxis protocol. 2. A single patient had PE in each group.
Farooqui et al. (2013) USA Case Control N=236	**Population:** TBI; Gender: Male=146, Female=90. *Group A (n=107):* Mean Age=53.3 yr. *Group B (n=129):* Mean Age=57.4 yr. **Treatment:** Group A had no routine administration of chemoprophylaxis and Group B received either Lovenox (30 mg, 2x/day) or Heparin (5000 U, 3x/day) 24 hr after stable CT. **Outcome Measure:** Rate of DVT and PE.	1. DVT rate was higher in group A than group B (5.6% versus 0%, p=0.008). 2. PE rate was 3.74% in group A and 0.78% in group B (p=0.18). 3. Progression of intracranial hemorrhage did not differ significantly between groups (p=0.33).

Kwiatt et al. (2012) USA Case Series N=1215	**Population:** TBI; Gender: Male=836, Female=379. *Control Group (n=995):* Mean Age=52.9 yr; Mean GCS=11.4. *LMWH Group (n=220):* Mean Age=46.2 yr; Mean GCS=8. **Treatment:** Retrospective comparison of patients who received LMWH for VTE prophylaxis and those who did not. **Outcome Measure:** Progression of intracranial hemorrhage.	1. Patients receiving LMWH were significantly older and had more severe injuries ($p<0.001$) than those who did not. 2. LMWH compared to the control had greater hemorrhage progression (42% versus 24%, $p<0.001$). 3. For those receiving LMWH, when it was initiated did not impact the rate of hemorrhage progression. 4. The LMWH compared to the control group had a greater number of VTE episodes (9.1% versus 3.1%, $p<0.001$).
Minshall et al. (2011) USA Case Series N=386	**Population**: TBI; Gender: Male=293, Female=93. **Treatment:** Chart review of patients receiving LMWH (30 mg, 2x/day; n=158), unfractionated heparin (UFH; 5000 IU 3x/day; n=171) or sequential compression devices alone (n=57). **Outcome Measure:** Rate of DVT, PE, and intracranial hemorrhage complications.	1. Mortality in the sequential compression devices alone group was higher (47%) compared to the LMWH (5%) and UFH (16%) groups. 2. Those in the UFH group had a significantly higher rate of DVT and PE than those in the LMWH group ($p<0.05$). 3. Five percent of those in the LMWH group and 12% in the UFH group had progression of their intracranial hemorrhage, compared to 25% in the untreated group.
Koehler et al. (2011) USA Cohort N=669	**Population:** TBI; Gender: Male=487, Female=182. *Early Group (n=268):* Mean Age=39.8 yr. *Late Group (n=401):* Mean Age=40.2 yr. **Treatment:** Enoxaparin (30 mg 2x/day) was administered to all patients. The early group received the VTE prophylaxis within 0-72 hr and the late group at 73 hr or later. **Outcome Measure:** Incidence of DVT and PE.	1. Those in the early group compared to the late group spent significantly fewer days on a ventilator ($p<0.001$), fewer days in ICU ($p<0.002$) and hospital ($p<0.004$). 2. Intracranial hemorrhage progression for the early vs late groups was 9.38% vs 17.41% ($p<0.001$) before prophylaxis and 1.46% vs 1.54% after ($p=0.912$). 3. The proportion of DVTs and PEs were not significantly different ($p=0.117$ and $p=0.49$, respectively).
Scudday et al. (2011) USA Case Control N=812	**Population:** TBI; Gender: Male=560, Female=252. *Intervention Group (n=402):* Mean Age=45.2 yr. *Control Group (n=410):* Mean Age=51.5 yr. **Treatment:** Retrospective review comparing patients that received chemical thromboprophylaxis (91% Heparin, 9% Enoxaparin) to an untreated control group. **Outcome Measure:** Incidence of VTE.	1. A lower incidence of VTE was found in the treated group compared to the untreated group (1% versus 3%, $p=0.019$).
Salottolo et al. (2011) USA Case Series N=480	**Population:** TBI; Mean Age=53 yr; Gender: Male=296, Female=184; Mean GCS=12.2. **Treatment:** Retrospective review of patients considered for thrombus prophylaxis (lovenox 30 mg 2x/day or heparin 5000 U, 2x/day), timing of administration, and whether or not the intervention was interrupted. **Outcome Measure:** Development of VTE or DVT.	1. Fifty-three percent of patients received pharmacological thromboprophylaxis (PTP); median time to start was 3d and it was continuous in 73.7%. 2. Medications began <72 hr post injury in 108 patients and >72 hr post injury in 147. 3. The no PTP group had 4 DVTs and 2 PEs compared to the PTP group which had 8 DVTs and 3 PEs. 4. Neither the administration of these medications ($p=0.29$) or the timing of

		administration (p=0.26) had any effect on the development of VTE.
Norwood et al. (2008) USA Case Series N=525	**Population:** TBI; Mean Age=39.6 yr; Gender: Male=387, Female=138; Abbreviated Injury Scale ≥2; Mean Time Post-Injury=36.2 hr. **Treatment:** Patients were given Enoxaparin sodium (30 mg, 2x/day). **Outcome Measure:** Incidence of DVT and PE, mortality rates.	1. Four percent of patients died. 2. Of 151 patients that underwent a lower extremity venous Doppler ultrasound, 6 patients were diagnosed with a DVT. 3. No patients within the study group were diagnosed with a PE.
Kleindienst et al. (2003) USA Case Series N=940	**Population:** Head Injury=344, Elective Surgery (tumors)=294, Intracranial Hemorrhage (ICH)=302; Mean Age=57.3 yr. **Treatment:** A retrospective review of patients either receiving 18 mg/day of Certoparin-sodium (3000 U anti-factor Xa) for prophylaxis on the evening prior to elective neurosurgery (ES) and within 24 hours after surgery, or admission whenever a CT showed an absence of a progressive haematoma. **Outcome Measure:** Incidence of bleeding complications, VTE events, and morbidity/mortality rates.	1. One hundred and fifty-five patients were excluded due to coagulation abnormalities or significant bleeding. 2. Intracranial bleeding was found in 1.5% of the total sample. 3. The incidence of VTE and PE was 0.2% and 0.1% of patients respectively, with no associated mortality. 4. No heparin induced thrombocytopenia was observed.
Norwood et al. (2002) USA Pre-Post N=150	**Population:** Traumatic Intracranial Hemorrhagic injuries (IHI); Mean Age=39.5 yr; Mean GCS=10. **Treatment:** Patients received Enaxoparin-sodium (30 mg, 2x/day) beginning 24 hr after initial evaluation. **Outcome Measure:** Incidence of DVT or PE, Progression of IHI, mortality, Glasgow Outcome Scale (GOS).	1. At discharge (n=106), 2% of patients had a DVT and no PE 2. Twenty-three percent of patients had CT progression of IHI pre-treatment. Rate of progression of IHI significantly decreased after initiation of the intervention (p=0.002). 3. Study group mortality was 7%. 4. On the GOS, the majority (76%) of patients showed good recovery.
Kim et al. (2002) USA Case Control N=64	**Population:** ABI; Gender: Male=49, Female=15. *Early Group (n=47):* Mean Age=37.7 yr; Mean GCS=9.1. *Late Group (n=17):* Mean Age=44 yr; Mean GCS=9.4. **Treatment:** Retrospective review of patients who received unfractionated heparin (UFH) within 72 hours of admission (Early Group) and those who received it after the third day (Late Group). **Outcome Measure:** VTE events, bleeding complications.	1. There was no increase in intracranial bleeding or deterioration on neurological examination due to UFH administration. 2. There was no statistical difference in VTE events between groups.

Discussion

Results indicate that early treatment (within the first 72 hours) may reduce the risk of developing DVT post injury (Byrne et al., 2016; Farooqui et al., 2013; Kim et al., 2002; Kim et al., 2014; Norwood et al., 2008; Salottolo et al., 2011; Scudday et al., 2011) without increasing the risk of intracranial hemorrhagic injury (Byrne et al., 2016; Koehler et al., 2011; Scudday et al., 2011) or deterioration on neurological examination (Kim et al., 2002). However, these results are in conflict with one study by Meyer et al. (2016) which similarly found no increased risk of ICH worsening, but found no benefit regarding VTE incidence either.

Patients with ABI who were started on unfractionated heparin within three days of injury onset, compared to those who started after this time period, did not differ significantly in terms of the number of thromboembolic events (Kim et al., 2002; Kim et al., 2014). However, those who received heparin earlier had greater cumulative neuro improvement and lower injury severity scale scores (Kim et al., 2014).

Norwood and colleagues conducted two studies examining the benefits of administering enoxaparin (LMWH) prophylaxis to those who sustain a severe ABI within the first 48 hours post injury (Norwood et al., 2008; Norwood et al., 2002). Results from both studies indicate that administering enoxaparin post ABI reduces the risk of developing DVT and PE, without increasing the risk of bleeding post injury. Scudday et al. (2011) also found that patients who received chemical prophylaxis within 72 hours of injury had a significantly lower incidence of developing VTE post ABI ($p<0.019$) compared to those not receiving chemical prophylaxis (Kim et al., 2014). Overall, a meta-analysis by Jamjoom and colleagues (2013) conclude that individuals who begin pharmacological thromboprophylaxis within 72 hours of injury have half the risk of VTE without significant risk of intracranial hemorrhage progression, compared to those who start prophylaxis more than 72 hours after their injuries.

On the contrary, a few studies have demonstrated that these medications may not be beneficial or superior treatments. In one study with individuals who underwent a craniotomy post ABI, no significant differences were reported for rate of DVT and PE when comparing those who received enoxaparin prophylaxis compared to those who did not (Daley et al., 2015). Further, Kwiatt et al. (2012) reported that patients receiving LMWH were at higher risk for hemorrhage progression and the risk of using LMWH may exceed its benefit. Similarly for heparin, Lin et al. (2013) did not find a reduction in DVT or PE once individuals with a severe TBI were administered a heparin prophylaxis protocol. Another study has demonstrated that heparin may not be as effective as other anticoagulant treatments (Dengler et al., 2016).

In conclusion, a systematic review of twelve studies reports that overall evidence supports the use of enoxaparin for reduction of DVT and UFH for decreased mortality rates compared to no chemoprophylaxis (Chelladurai et al., 2013).

Conclusions

There is level 1b evidence that enoxaparin is no more effective than placebo in reducing the risk of developing deep vein thrombosis in patients post-ABI.

There is level 2 evidence that the administration of low-molecular weight heparin within the first 72 hours post ABI reduces the risk of developing deep vein thrombosis and pulmonary embolism post injury compared to unfractionated heparin.

There is level 4 evidence that administering low molecular weight heparin (enoxaparin) or heparin post ABI does not increase the risk of intracranial bleeding compared to no treatment.

Administration of pharmacological deep vein thrombosis prophylaxis within the first 72 hours post ABI may be effective for reducing the risk of developing deep vein thrombosis.

> **Enoxaparin is effective for the prevention of Venous Thromboembolism development after elective neurosurgery and has not been found to cause excessive bleeding.**

11.3.4.3 Combination or Comparative Therapies

Compression stockings and pneumatic compression devices are among the most common non-pharmacological strategies used for the prevention of DVT in trauma patients (Watanabe & Sant, 2001). Such mechanical methods may be more advisable than the use of anticoagulants due to the increased risk of bleeding in patients with multiple fractures and injuries (Watanabe & Sant, 2001). These mechanical strategies have demonstrated positive results in the prophylaxis of DVT in neurosurgical patients (Turpie et al., 1989). There is some evidence that the effectiveness of these mechanical devices in the prevention of DVT could also be increased in combination with carefully selected low molecular weight anticoagulants that carry low bleeding risks (Agnelli et al., 1998).

Table 11.9 Combination Therapies for the Prevention of Deep Venous Thrombosis post ABI

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
Agnelli et al. (1998) USA RCT PEDro=6 N=307	**Population:** TBI=261, Other=46; *Intervention Group (n=153)*: Mean Age=55.1 yr; Gender: Male=69, Female=84. *Placebo Group (n=154)*: Mean Age=57.5 yr; Gender: Male=84, Female=70. **Treatment:** Patients received either enoxaparin (40 mg/day) or placebo administered subcutaneously for no less than 7 days, beginning within 24 hr following elective neurosurgery. All patients were fitted with thigh-length compression stockings, which were worn from the morning of surgery until discharge. **Outcome Measure:** Symptomatic, objectively documented VTE (DVT or PE) or DVT detected by bilateral venography performed at the end of the treatment period.	1. Eighty-four percent of patients receiving placebo and 85% of the patients receiving enoxaparin had venographic studies sufficient for analysis. 2. Thirty-two percent of patients in the placebo group and 17% in the intervention group had DVT, with a relative risk of 0.52 (p=0.004). 3. Six percent of patients in the placebo group had a clinically overt thromboembolic event compared to only 1% in the enoxaparin group. 4. The rates of proximal DVT were 13% in patients taking placebo and 5% in patients taking enoxaparin (p=0.04). 5. During the study period, death occurred in 4% and 3% of the placebo and intervention groups, respectively.
Praeger et al. (2012) Australia Cohort N=36	**Population:** TBI; Mean age=40.3 yr; Gender: Male=28, Female=8; Mean GCS=8. **Treatment:** Thromboprophylaxis included compression stockings and compression devices, and/or LMWH. **Outcome Measure:** Rate of DVT and PE assessed with compression ultrasound.	1. The rate of DVT was 6%, PE was 6%, and total VTE was 11%. 2. Among individuals with severe TBI the rates of DVT, PE, and total VTE were 10%, 10% and 19%, respectively.
Kurtoglu et al. (2004) Turkey PCT N=120	**Population:** TBI=103, Other=17; Median Age=37.1 yr; Gender: Male=47, Female=73. **Treatment:** Patients admitted to the intensive care unit (ICU) were allocated to receive either Intermittent Pneumatic Compression devices (IPC; n=60) placed below the knee or LMWH (n=60) (40 mg/day, enoxaparin sodium) for VTE prophylaxis. **Outcome Measure:** Rate of DVT, PE and mortality.	1. In the IPC group, there were 4 (6.6%) and 2 (3.3%) cases of DVT and PE, respectively. 2. In the LMWH group, there were 3 (5%) and 4 (6.6%) cases of DVT and PE, respectively. 3. Overall, 7 (11.6%) and 8 (13.3%) patients died in the IPC and the LMWH group, respectively.

Author/ Year/ Country/ Study Design/ N	Methods	Outcome
		4. There were no significant differences between groups in rates of DVT (p=0.04), PE (p=0.07), or mortality (p=0.08).

PEDro = Physiotherapy Evidence Database rating scale score (Moseley et al., 2002)

Discussion

In an RCT conducted by Agnelli et al. (1998), patients due to undergo elective neurosurgery within 24 hours were placed on LMWH or a placebo, and were also fitted with compression stockings. DVTs were more common in the placebo group than the intervention group (p<0.004). The combination of both the compression stockings and LMWH appeared to be more beneficial than the compression stockings alone (Agnelli et al., 1998). Agnelli et al. (1998) also reported an additive reduction in thromboembolism, without a significant increase in bleeding risks, in patients with brain injury treated with both enoxaparin and compression stockings compared with patients treated with mechanical compression alone. These conclusions have been supported by more recent literature (Praeger et al., 2012). However, when intermittent pneumatic compression devices were compared to prophylactic LMWH for the prevention of VTE, no significant differences in the development of PEs or DVTs were found between groups (Kurtoglu et al., 2004).

Conclusions:

There is level 1b evidence that low-molecular weight heparin combined with compression stockings is more effective than compression stockings alone for the prevention of deep vein thrombosis following elective neurosurgery post ABI, and that the use of low-molecular weight heparin in this setting does not cause excessive bleeding.

There is level 2 evidence that intermittent pneumatic compression devices alone are not more effective compared to low molecular weight heparin for the prevention of deep vein thrombosis post ABI.

Compression stockings may be more effective at preventing venous thromboembolisms when combined with low-molecular weight heparin post ABI

Intermittent pneumatic compression devices and low molecular weight heparin may have a similar effect in terms of the prevention of deep vein thrombosis post ABI when compared to each other.

11.4 Conclusions

When it comes to interventions which are used for the treatment HO and the prevention of DVT, combination therapies appear to have the best results. The evidence also tends to favour prophylactic treatments for both conditions. The most effective intervention for the treatment of HO overall is surgical excision. Unfortunately, research has not been able to delineate the etiology underlying neurogenic HO and as a result there has been a recent focus on prophylactic interventions. With regards to DVT, anticoagulation therapy, which reduces the risk of suffering a DVT without increasing the risk of

intracranial bleeding, is the most well studied intervention. LMWH used prophylactically appears to be effective in preventing DVTs without causing increased risk of intracranial bleeding. Unfortunately, due to the limited amount of research available that is directly related to the development of DVTs post ABI, the decision to begin pharmacological prophylaxis post ABI remains a subjective one (Norwood et al., 2008).

11.5 Summary

There is level 4 evidence that forceful manipulation under general anesthesia may increase range of motion and prevent bony ankylosis in patients with heterotopic ossification following brain injury.

There is level 2 evidence that etidronate disodium may reduce the incidence of heterotopic ossification compared to no etidronate disodium in patients with severe head injury.

There is level 4 evidence that radiation therapy may prevent further formation of heterotopic ossification in ABI populations.

There is level 4 evidence that radiation therapy may improve range of motion in joints affected by heterotopic ossification in ABI populations.

There is level 4 evidence that extracorporeal shock wave therapy may reduce pain associated with heterotopic ossification in ABI populations.

There is level 4 evidence that forceful manipulation under general anesthesia may increase range of motion and prevent bony ankylosis in patients with heterotopic ossification following brain injury.

There is level 4 evidence that surgical excision of heterotopic ossification may improve range of motion in ABI populations.

There is level 3 evidence that a delay in heterotopic ossification surgical excision does not increase the risk of further heterotopic ossification recurrence in ABI populations compared to immediate surgical intervention.

There is level 4 evidence that surgical excision in combination with passive motion therapy may improve range of motion affected by heterotopic ossification in ABI populations.

There is level 4 evidence that surgical excision in combination with etidronate disodium may improve range of motion affected by heterotopic ossification in ABI populations.

There is level 4 evidence that surgical excision in combination with indomethacin may improve range of motion affected by heterotopic ossification in ABI populations.

There is level 2 evidence that sequential compression devices are not more effective for reducing the risk of developing deep vein thrombosis or pulmonary embolism compared to no sequential compression devices post ABI.

There is level 4 evidence that intermittent compression devices do not cause acute elevations in intracranial pressure in patients with severe ABI.

There is level 1b evidence that enoxaparin is no more effective than placebo in reducing the risk of developing deep vein thrombosis in patients post-ABI.

There is level 2 evidence that the administration of low-molecular weight heparin within the first 72 hours post ABI reduces the risk of developing deep vein thrombosis and pulmonary embolism post injury compared to unfractionated heparin.

There is level 4 evidence that administering low molecular weight heparin (enoxaparin) or heparin post ABI does not increase the risk of intracranial bleeding compared to no treatment.

There is level 4 evidence that the use of chemoprophylaxis 24 hours after stable head computed tomography scan decreases the rate of deep vein thrombosis formation post ABI.

There is level 1b evidence that low-molecular weight heparin combined with compression stockings is more effective than compression stockings alone for the prevention of deep vein thrombosis following elective neurosurgery post ABI, and that the use of low-molecular weight heparin in this setting does not cause excessive bleeding.

There is level 2 evidence that intermittent pneumatic compression devices alone are not more effective compared to low molecular weight heparin for the prevention of deep vein thrombosis post ABI.

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