Intravascular Temperature Management Does Not Increase the Rate of Catheter-Related Deep Vein Thrombosis

Abstract
This whitepaper examines the risk factors for deep vein thrombosis (DVT) resulting from central venous catheter (CVC) placement. Therapeutic hypothermia via intravascular temperature management also uses the same CVC insertion sites, the same potential risks apply. Published literature shows that when IVTM cooled patients are compared to general critically ill patient populations who receive central lines, there is no difference in the rates of DVT and pulmonary embolism (PE). These results demonstrate that IVTM using a cooling catheter is not associated with an increased incidence of DVT.

Key Takeaways

1. The rate of thrombosis for critical care patients receiving CVCs ranges from 20 to 30%.
2. Patients with peripheral central catheters had a significantly higher incidence rate of DVT than patients with CVC (27.2% vs 9.6%, p=0.0012).
3. DVTs are common in the general neurosurgical population, as the rates of DVT range from 19 to 50%.
4. The rate of DVT in the patient population receiving IVTM for non-cardiac reasons is 5%.
5. The rate of DVT in the patient population receiving IVTM post-cardiac arrest is 1%.
6. Four randomized controlled clinical trials conducted in a total of 943 patients showed that there was no difference in the DVT rate when comparing ZOLL IVTM catheters to standard CVCs.
7. The rate of DVT in the patient population receiving surface cooling has been reported between 3 and 15%.
8. Timely administration of prophylactic anticoagulation is safe and significantly reduces DVT rates in high risk patient populations.

Abbreviations
CVC: Central Venous Catheter
DVT: Deep Vein Thrombosis
IVTM: Intravascular Temperature Management
PE: Pulmonary Embolism
PICC: Peripherally Inserted Central Venous Catheter
PTP: Pharmacological Thromboprophylaxis
PTS: Post-Thrombotic Syndrome
PTT: Partial Thromboplastin Time
TBI: Traumatic Brain Injury
VTE: Venous Thromboembolism

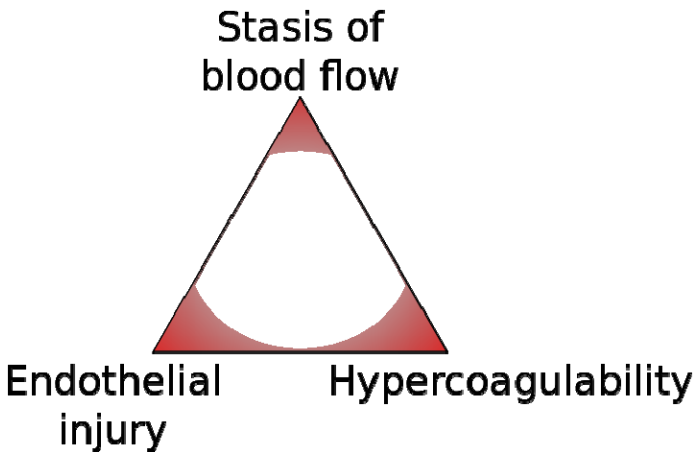
Introduction
Venous thromboembolism (VTE) is a common complication in critically ill patients which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTEs occur at a rate of approximately 100 per 100,000 persons in the United States per year[1], two-thirds of which are PE and one-third of which are DVT[1-2]. The distinction between DVT and PE is as follows: DVT is the formation of blood clots. Although the majority of DVTs occur in the lower extremities, other locations include the upper extremities and pelvic veins[3]. In some patients, DVT may still

occur even when the patient is on adequate therapy[4–6]. A DVT can either remain adherent to the vein wall where it undergoes the thrombus breakdown process of fibrinolysis and recanalization[7]. In contrast, PE is a potentially life-threatening disease involving pulmonary artery thrombosis or clot formation in one part of the body (often in the legs), which may then become clinically significant and travel to the lungs and block an artery. It can lead to the collapse of the respiratory or circulatory systems, resulting in death.

The mortality rate for the total VTE population has been reported as high as 32%[2,8]. The number of VTE in the United States is estimated to double to 1.82 million adults by 2050[9].

Risk Factors for DVT

The Virchow triad describes the 3 major risk factors that contribute to thrombosis, which are hypercoagulabililty, hemodynamic changes (stasis or turbulence), and endothelial injury or dysfunction[10].



In addition, previous studies have shown that inflammatory[7] status is associated with coagulation abnormalities due to increased procoagulant factors and inhibition of natural anticoagulant pathways[4] and may cause thrombotic tendencies and microvascular thrombosis. With inflammatory response, the properties of the endothelium may become dysfunctional with multiple outcomes, including the loss of anticoagulant, antiaggregant, and vasodilatory properties.[4] The following chart summarizes various DVT risk factors.

Patient-dependent DVT risk factors[6,11-12]	Illness or surgery-dependent DVT risk factors[6,11,13]
• Age over 40 years • Obesity • Critical illness with mechanical ventilation • Central venous catheter insertion • Hormonal therapy (estrogen, progesterone) • Using contraceptive pills • Deep vein thrombosis or pulmonary embolism in history • Thrombophilia, deficiency of antithrombin (AT) III factor, protein C, protein S and lupus anticoagulant, resistance to activated protein C, homocistinemia • Genetic predisposition	• Trauma or surgery: especially the pelvis, hip, leg • Malignant processes-particularly in the pelvis, abdomen, primary or metastatic • Lack of ambulation due to surgery • Heart failure • Recent myocardial infarction • Paraplegia • Severe infection • Intestinal inflammations o Polycythemia o Paraproteinemia o Behcet's disease o Paroxysmal nocturnal hemoglobinuria

DVT in the Neurosurgery Population

Thromboembolism is a common problem in neurosurgery and neurology patients[14-16]. As such, patients at substantial risk for DVT and PE include those with spinal cord injury, brain tumor, subarachnoid hemorrhage, head trauma, stroke, and patients undergoing a neurosurgical operation. The incidence of DVT in the general neurosurgical population ranges between 19 and 50% (Table 1, appendix). Stroke and spinal injury populations also have a high risk for DVT[17] (Tables 2 and 3, appendix).

In neurosurgical patients, a 2-fold increase in the risk of DVT has been associated with procedures that last longer than 4 hours[18]. Although the brain contains the highest concentration of thromboplastin in the human body, it is speculated that trauma, infarction, or surgery to the brain results in the release of tissue thromboplastin and activation of the coagulation cascade[19]. Some of the abnormalities of coagulation that may be associated with an increased risk of thrombosis include: 1) elevations of fibrinopeptide A and fibrinogen fragment B[beta][20]; 2) decreased activated partial thromboplastin time (PTT) and increased fibrinopeptide A levels[21-22], increased platelet count and plasma fibrinogen level with lowered platelet adhesiveness and plasminogen levels[23], and decreased fibrinolysis in the superficial veins of the paralyzed limbs of stroke patients[24]; 3) subclinical disseminated intravascular coagulation in patients with brain tumor[25-26]; and 4) increases in Factor VIII and platelet aggregation in patients with spinal cord injury[27]. Hypotheses regarding the mechanisms for these changes are less definite.

In a study of spinal cord injury, the DVT rate was at 41.4% (12/25) and detected as early as on postoperative day 3 (25%) with the peak of DVT formation occurring on day 7[28]. Risk for DVT increases with more severe paralysis; thus, early detection and treatment are essential. More

importantly, an awareness of the risk factors for the development of thromboembolic disease will allow for the initiation of adequate prophylactic measures[15].

Central Line Related Thrombosis in Critically Ill Patients

Central venous catheters (CVC) and interventional procedures are essential to manage patients who have been resuscitated from cardiac arrest or are critically ill, but catheters are not without risks. Studies have shown that thrombosis of the central venous system occurs in 20-30% of patients with indwelling catheters[29]. This is likely related to injury to the vessel endothelium from the catheter tip, antithrombotic properties of the catheter itself, and length of time the catheter is left in the vein[30].

The most common insertion sites for CVC are the subclavian, internal jugular, and femoral veins. In a study of 76 trauma patients who required unilateral femoral vein cannulation and had bilateral venous duplex sonography weekly for one month after cannulation, iliofemoral DVT was identified in 14% of the patients[31]. A hypothermia study of 80 consecutive patients admitted to a mixed medical/surgical ICU found that the incidence of catheter related femoral vein thrombosis, as detected with phlebography, was 8.5%[32]. However, fibrin sleeves, or fibrous, non-globular proteins involved in blood clots, were observed in 15.7% of the cases. The significance of this finding is that, although fibrin sleeves can consistently form around indwelling catheters regardless of catheter material, they may be associated with venous thrombosis even if they are not clinically apparent[33]. In another study of 124 mixed ICU patients who had femoral vein catheterization and were examined with duplex Doppler ultrasonography, 9.6% developed catheter related thromboses[34]. In that study, the incidence of thrombosis was not found to be related to duration of catheterization. Thus, the reported incidence of thrombosis with femoral central venous catheters ranges between 8.5 and 26.2% in critical care patients with a wide variety of medical and surgical diseases[31-32,34].

In addition, some venous insertion sites appear to be more prone to thrombosis than others. In a study with 239 patients randomized between CVC and peripherally inserted central venous catheters (PICC), patients with PICC had a significantly higher incidence rate of DVT than patients with CVC (27.2% vs 9.6%, p=0.0012)[14].

In a recent NEJM publication by Parienti et al., further details on the rates of complications reports for three CVC insertion sites (subclavian, jugular, and femoral)[35]. In this multicenter randomized trial, 2352 catheters were placed and randomly assigned in a three-choice, 1:1:1 scheme. The median number of days for catheterization is 5 days with the range of 2-9 days for 3 insertion sites. No differences in the rate of DVT were found between femoral vs. jugular sites, although femoral had a higher rate of symptomatic DVT. On the contrary, DVT occurrence was significantly higher in the jugular group compared to subclavian, although the symptomatic rate of DVT was the same. Although Parienti et al. found that the subclavian insertion site was associated with a lower risk of DVT compared to jugular and femoral sites, there are a number of key points of note in the results. First, the rates of DVT reported in this study should be interpreted with caution since data on asymptomatic DVTs were missing in 59.0% of the collected cases. Secondly, the overall rate of complications (summation of catheter-related

bloodstream infections, deep vein thrombosis, and mechanical events) for the three insertion sites in this trial was similar (subclavian 3.1%, jugular 3.8%, femoral 3.3%), and according to the authors, these results suggest that an ideal site for CVC insertion does not exist[35]. In choosing a CVC insertion site, it is important to consider the overall rate of complication, which has a greater impact than a single type of complication (i.e., mechanical complication such as pneumothorax). Lastly, the results show that femoral insertion site had the lowest rate of insertion failure (5.3%) compared to jugular (7.7%) and subclavian (14.7%) insertion sites. Thus, the ease of insertion should also be considered when selecting a CVC site.

Inferior Vena Cava Thrombosis

Thrombosis involving the inferior vena cava (IVC) is a rare event, and data on IVC thrombosis and its clinical presentation are scarce. In a registry of 1,470 consecutive patients with documented histories of DVT, 60 (0.4%) had thrombosis involving the IVC. The study showed that patients who suffered IVC thrombosis as the first thrombotic event were significantly younger: 58% experienced IVC thrombosis before age 40, 78% (47 patients) was first thrombosis. The most frequent location of IVC thrombosis was infrarenal[36]. In the majority of cases, IVC thrombosis extended to the iliac and lower-extremity veins. The most common initial symptom of IVC is lower back pain and abdominal pain. Among IVC thrombosis patients with malignant disease was more prevalent, followed by congenital anomalies of IVC.

IVC anomalies have a 0.5% incidence rate and could be associated with other congenital abnormalities. In later stages of the disease, trophic ulcers with or without DVT is a consistent finding. This condition is usually asymptomatic and thus is mostly an incidental finding. The incidence of IVC anomalies ranges from 0.3 to 0.5% in young healthy individuals, and increases to 5-6.7% in adults with spontaneous DVT[37]. In 2001, Ruggeri et al stated that congenital anomalies of the IVC might be a risk factor for DVT, because the azygous venous system does not drain the lower limbs adequately despite compensatory enlargement[38]. Some authors have referred to this condition as KILT syndrome (Kidney and IVC abnormalities with Leg Thromboses)[39]. Only a handful of cases where there is an absence of the inferior vena cava have been reported in the literature thus far[40-42].

Table 4 lists the distribution of established risk factors for IVC thrombosis versus isolated leg DVT[36]. Congenital IVC anomaly, inflammatory disease, malignant disease, and family history of VTE have a higher potential of IVC thrombosis.

Table 4. Distribution of established risk factors for IVC thrombosis and leg DVT[36]

	IVC Thrombosis (N=60)	Isolated LE-DVT (N=57)	p-value
	N (%)	N (%)	
Congenital IVC anomaly	8 (13)	0 (0)	0.006
Family history of VTE	12 (20)	20 (35)	0.096
Thrombophilia	32 (53)	35 (61)	0.455
Long-term travel	3 (5)	8 (14)	0.119
Immobilization	10 (17)	9 (16)	1.000
Previous surgery	13 (22)	7 (12)	0.223
Inflammatory disease	19 (32)	10 (18)	0.090
Malignant disease	16 (27)	5 (9)	0.015
Obesity (BMI ≥ 30kg/m^2)	15 (25)	14 (25)	0.832
Hormonal treatment (OC/HRT)	21 (58)*	20 (57)*	1.000
Pregnancy and post-partum period	1 (3)*	4 (11)*	0.199

OC=oral contraceptives; HRT=hormonal replacement therapy; LE=lower extremity;*percentage of women

Clinical Symptoms of DVT and PE

Typically, the symptoms of low extremity DVT are redness, unilateral leg swelling and pain. Less frequently, patients present with tenderness along the course of the deep veins or with a prominence of superficial veins functioning as collaterals, dilated blood vessels, varicosities and eventually stasis ulceration[43], also known as post-thrombotic syndrome (PTS). While the exact pathophysiology of PTS is unknown, it is thought to be a clinical manifestation of venous hypertension resulting from residual venous outflow obstruction or venous valvular incompetence secondary to valve damage following a DVT[43-44]. Extravasation of red blood cells, fibrin and inflammatory mediators occur as a result of the venous hypertension[45]. Severe DVT causes permanent damage to the leg. Only 10 to 17% of neurosurgical patients with documented DVT have clinical symptoms or sign of venous thrombosis[31,46].

In comparison to DVT, common symptoms of a PE include shortness of breath and a rapid heart rate, which may be accompanied by sharp chest pain under the breastbone or on one side, which might radiate to the neck, jaw, shoulder or arm. In many cases, however, the patient is asymptomatic prior to the PE.

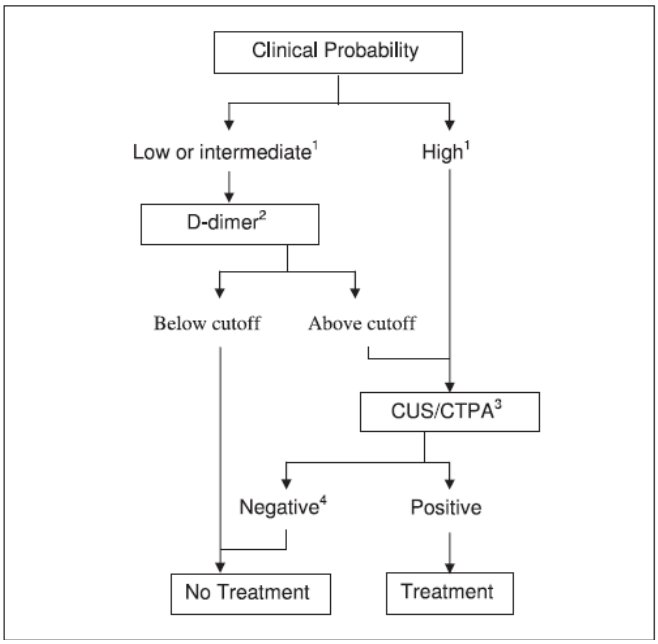
DVT Diagnostic Options

If a DVT is suspected, the doctor will take a full medical history and carry out a physical examination, and additional tests may be required. In patients with suspected DVT, venous ultrasound is the option of choice. In patients with suspected PE, computed tomography pulmonary angiography (CTPA) and ventilation-perfusion lung scan (V/Q scan) are the two recommended imaging tests. D-dimer, a highly sensitive biomarker, is useful for excluding acute DVT, it lacks the specificity necessary for diagnostic confirmation, therefore if D-dimer test is positive, the patient should go on to ultrasonography. Ultrasound remains the gold standard for DVT diagnosis, as it is an excellent method for noninvasive screening of DVT[47]. In a study where all possible detection modalities were available to clinicians, 91.4% of patients were screened using ultrasound and while 24.3% were screened with a venogram[48]. The sensitivity of

ultrasonography in detecting DVT is reported to be 98%-100% and its specificity to be 75%-100%[46,49-50].

Recent advances in the management of patients with suspected DVT have both improved diagnostic accuracy and made management algorithms safer, easier to use and well standardized. These diagnostic algorithms are mainly based on the assessment of clinical pretest probability, D-dimer measurement and imaging tests, mainly represented by compression ultrasound (CUS) for suspected DVT and computed tomography pulmonary angiography (CTPA) or lung ventilation-perfusion (V/Q) scan for PE. An example of validated diagnostic algorithm for both DVT and PE is displayed Figure 1[30].

*Figure 1: Diagnostic Strategy of venous thromboembolic disease. 1) when the clinical probability is low (or unlikely), a negative result from a highly sensitive D-diner rules out DVT or PE; 2) D-dimer measurement is a simple non-invasive blood test that allows to safely rule out VTE when below a certain cut-off (< 500 µg/l for most tests) in patients with a non-high or an unlikely clinical probability; 3) ultrasound in case of suspected DVT; CT pulmonary angiography in case of suspected PE; 4) in case of negative ultrasound or CTPA in high clinical probability patients, additional imaging, e.g. venography (suspected DVT) or lung ventilation/perfusion scintigraphy or pulmonary angiography (suspected PE) might be considered[30].



These diagnostic algorithms allow a safe and cost-effective diagnosis for most patients with suspected VTE. However, there are challenges in diagnosing VTE in special patient populations, such as elderly patients, pregnant, or patients with a prior VTE. For example, D-dimer level as a diagnosis of DVT and PE, is less sensitive and dependent on the timing of the measurement[28], especially in elderly and pregnant women and prior VTE in patients aged < 50 years[51]. D-dimer, a derivative of cross-linked fibrin, has been well studied and previously linked with both DVT and pulmonary embolism (PE)[52]. The sensitivity of D-dimer for the diagnosis of DVT is reported as 96% for the diagnosis of DVT, but serves as a poor biomarker for DVT given its low specificity

(40%) and low positive predictive value (PPV) (48%)[53-54]. However, a normal plasma D-dimer level serves as a test of exclusion for DVT.

Compression ultrasonography (CUS) might also be utilized in elderly patients in whom CTPA is contraindicated. Indeed, in a patient with suspected PE, the presence of a *proximal* DVT is highly predictive of PE allowing to rule in the diagnosis of PE without further thoracic imaging[55].

The main limitation of V/Q scan is an important proportion of non-diagnostic results, which increases with age (from 32 % in patients < 40 years to 58 % in those > 80 years)[51]. V/Q scan results thus need to be interpreted in conjunction with clinical probability, D-dimer and CUS, the latter sometimes being repeated at a week's interval in order to safely exclude PE[56].

Planar lung ventilation-perfusion (V/Q) scan and SPECT (Single Photon Emission Computed Tomography) V/Q scan have been developed to replace pulmonary angiography, the gold-standard test for PE [57], however there are some limitations such as a high proportion of non-conclusive tests and instances where further imaging is required. Studies published so far reported a high proportion of technically inadequate tests and a limited overall sensitivity[58-59]. This modality could be useful in patients with contraindications to CTPA (contrast-induced nephropathy, allergy) or in pregnant women.

Because of increasing availability of imaging techniques, it is possible to over-suspect VTE. Only 20% of patients clinically suspected to have DVT are found to have it[60]. Standard approach to surveillance for DVT and PE is based on the clinical symptoms. In absence of a standardized approach, reported DVT rates can be influenced by how often and how hard physicians look for these events. Surveillance bias is a type of selection or information bias that occurs when an exposure (ultrasound or imaging) may result in a higher probability of detection (of DVT) in exposed patients[15]. Several organizations have developed guidelines to make the diagnosis of DVT more specific and to reduce inefficient imaging. Clinical decision rules to establish pretest probability are recommended by, among others, the American College of Physicians and the American Academy of Family Physicians[61].

Treatment

Critically ill patients are at high risk for the development of VTE, so it is more cost effective to prevent than to treat DVT and subsequent PE[7,53,62-63]. With a well-structured program for thrombosis prophylaxis established as the standard of care for this high risk population, the incidence of DVT and PE will be dramatically reduced and considerable human life, health care energy, and health care dollars will be saved[64]. Without VTE prophylaxis the incidence of DVT ranges from 13 to 50%[65-66]; it has also been shown that DVT develops in one of every three patients old than 40 years of age undergoing elective general surgical procedure[5,9,37]. In a 100 patient study in general MICU, 61% received DVT prophylaxis, and the rate of DVT was 16%[61].

The basic principles for DVT prevention include the prevention of venous retention, stimulation of venous return, and anticoagulation. Thrombosis prophylaxis is undertaken with two basic methods, pharmacologic and mechanical, which can be used either alone or in combination.

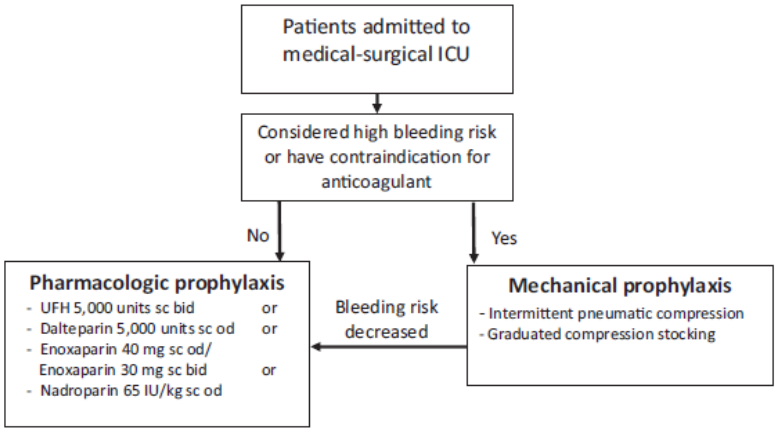
Pharmacologic prophylaxis with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) has been shown to decrease the incidence of DVT and PE in medical, surgical, and critically ill patients without increasing the risk of major bleeding or ICU mortality[67]. Over the past few decades, VTE prophylaxis had become a standard of preventive measure in the ICU. However, a failure rate as high as 5.1 to 15.5% has been reported[68-69]. This rate underscores the high risk of VTE in critically ill patients despite anticoagulation. In a prospective cohort study of 261 medical-surgical ICU patients given UFH 5,000 units subcutaneously twice a day, DVT developed in 9.6% of patients during hospitalization. Patients with DVT had a significantly longer duration of mechanical ventilation, ICU stay, and hospitalization than those without DVT[70]. A recent observational study, conducted in adult ICU patients in the United States, included 294,896 episodes of critical illness and reported that the group of patients who received prophylactic anticoagulation had a significantly lower risk of death than those not provided VTE prophylaxis[71]. LMWH is the preferred drug in critically ill patients because it demonstrates superior efficacy and has a reduced likelihood of heparin-induced thrombocytopenia. UFH can be an alternative if patients have impaired renal function[72-73].

Mechanical prophylaxis, or the use of graduated compression stockings (GCS) and intermittent pneumatic compression devices (IPC), should be considered for high risk patients. Studies have shown that IPC decreased the rate of VTE in the setting of ICU patients compared with no mechanical prophylaxis, but less is known about the effectiveness of GCS compared with other prophylaxis strategies[74-75].

For high risk patients, an extreme prophylactic treatment called an IVC filter can be considered. IVC filters are indicated in patients who have an absolute contraindication to anticoagulants and who have an active DVT, or PE with evidence of thrombosis below the level of the IVC at which the filter will be inserted. IVC filters can also be placed post-DVT detection in order to prevent PE.

In clinical practice, the rate of VTE prophylaxis varies and may be inadequate in some centers. Recent studies suggested prophylaxis administration rates of 33% in medical ICUs[76]. In comparison, prophylaxis administration rates in medical-surgical ICUs have been reported as 63-86%[77-78]. For surgical ICUs, the prophylaxis administration rate is 86.7%[32]. Low prophylaxis rates are attributable to fear of bleeding and low (and probably underestimated) perceived risk of VTE in critically ill patients among most physicians.

In one meta-analysis there was no evidence that pharmacologic prophylaxis increased the risk of major bleeding when heparin prophylaxis was compared with placebo[67]. A large observational study from International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) assessed in-hospital bleeding risk in acutely ill medical patients. The results showed that heparin prophylaxis was not the factor associated with a high bleeding risk[79]. Strategies to improve compliance include continual education strategies for physicians. The following is a decision tree on VTE prophylaxis[80].



American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines recommend prophylaxis of critically ill patients with LMWH or low-dose UFH over no prophylaxis[81] (Grade 2B), combined use of IPC (Grade 2C), combined use of IPC and stocking in cases where anticoagulants are contraindicated (Grade 1C+), and treatment with LMWH or an oral-dose vitamin K antagonist during rehabilitation (Grade 1C). Further, no difference has been detected in the incidence of DVT or hemorrhagic complications between patients receiving 5000 U of UFH every 8 hours and those receiving 30 mg LMWH every 12 hours, if treatment was started within 72 hours after injury[82].

Guidance Regarding Prophylaxis of Venous Thromboembolism in Neurocritical Care

As mentioned previously, VTE is a common problem in neurosurgery and neurology patients[14-16]. As such, patients who are at substantial risk for DVT and PE include those with spinal cord injury, brain tumor, subarachnoid hemorrhage, traumatic brain trauma, stroke, and patients undergoing a neurosurgical operation; thus, VTE prophylaxis is even more important in the neurocritical care population. The Neurocritical Care Society (NCS) and Society of Critical Care Medicine (SCCM) have issued guidelines for VTE prophylaxis in adult patients with Neurological/Neurosurgical diagnosis in the ICU based on scientific evidence[154].

Prophylaxis of VTE in the Traumatic Brain Injury Population

Patients with TBI are at an increased risk of developing VTE including DVT and PE due to their prolonged immobilization and hypercoagulable state[83-84]. Therefore early prophylaxis against VTE was warranted among TBI patients[85]. The incidence of VTE may be as high as 54% among patients with major head trauma not treated by mechanical or pharmacological thromboprophylaxis (PTP)[86]. However, there is difficulty in balancing PTP against VTE with the potential risk of intracranial hematoma (ICH) expansion. Published literature has not been consistent because TBI is not a homogeneous population; preinjury use of anticoagulation adds more controversy to management of TBI patients. Selection bias also exists in clinical practice where physicians tend to delay PTP for patients at a higher risk for ICH progression.

A recent metadata analysis by Shen et al. on the benefits and risks of anticoagulation following TBI reviewed 1026 unique studies, most of which were observational[87]. Only 23 studies had complete information on post-TBI anticoagulation use and outcome[87]. The analysis suggested that TBI is a heterogenic population and the need for crafting guidelines for the use of anticoagulation should be based on patients' risks for developing VTE and progression of existing injury. Hemorrhagic stability is commonly considered an important criterion for assessing risk of ICH progression. A study by Levy et al. stressed the importance of ensuring stability of hemorrhage patterns before initiating PTP demonstrated that PTP was safe among patients with a stable CT scan at 24 hours of admission[88]. These studies showed that PTP appears to be safe in TBI patients at a low risk of developing a new hemorrhage or experiencing progression of an existing hemorrhage.

It has been shown that the TBI population can develop VTE as early as the first 24 hours post-injury[88-89]. Therefore, there is value in commencing prophylactic anticoagulation early to help prevent the development of VTE. Reiff et al. compared the use of PTP in TBI when given within 24 hours, between 24 and 48 hours, and after > 48 hours. They found an increase in DVT rates from 3.6% when PTP was given within 24 hours to 15.4% when it was given after 48 hours[90]. Another systemic review and meta-analysis reporting on the timing of PTP in TBI showed that TBI patients who started PTP early had almost half the risk of developing VTE and without affecting progression of ICH[91]. The study recommended commencing PTP within 72 hours in the context of a stable follow-up CT.

In the context of clinical practice, many hospitals have incorporated PTP into their standard management in TBI population. For example, enoxaparin 30 mg administered subcutaneously every 12 hours is included into the University of Pittsburgh Medical Center (UPMC) standard severe traumatic brain injury admission protocol[155]. The medication is initiated 48 hours after admission.

In conclusion, the risks of intracranial and systematic bleeding have historically been the major concern of implementing prophylactic anticoagulation in patients with TBI[87,92]. However, studies have shown that prophylactic anticoagulation is safe and reduces the rate of VTE in patients with normal coagulation and stable intracranial hemorrhage patterns[93-95].

Intravascular Temperature Management

Therapeutic hypothermia using feedback-controlled patient temperature has become routinely used in the ICU setting for patients with a wide range of neurological injuries (cardiac arrest, acute ischemic stroke, traumatic brain injury, reduction of intracranial pressure, etc.). Therapeutic hypothermia can also be referred to as targeted temperature management (TTM). With promising results from various clinical studies, therapeutic hypothermia is increasingly recognized as an effective agent for treatment of several critical disease states. Therapeutic hypothermia is currently a Class I recommendation for the post-resuscitation treatment of patients who achieve return of spontaneous circulation but remain comatose after out-of-hospital cardiac arrest and for newborns with neonatal hypoxic ischemic encephalopathy[96-97].

Therapeutic hypothermia is also associated with a significant decrease in the incidence of intracranial hypertension[98-102].

Studies using hypothermia post-cardiac arrest, after neonatal hypoxia ischemia, and after traumatic brain injury have all suggested that reaching the target temperature sooner may allow for hypothermia to be even more beneficial than has already been demonstrated[96,103]. Given the unavoidable delays in the discovery, resuscitation, and transport of patients with cardiac arrest, stroke, or traumatic brain injury, it is very likely that significant secondary injury has already occurred by the time hypothermia is initiated. The sooner the patient is cooled to target temperature, the more likely he or she is to benefit from the therapy[104-106]. Importantly, it has been documented that precise control of target temperature can improve neurological outcome[107]. Cooling blankets, ice packs, gel pads, and other external methods are clinically inefficient, labor intensive, and hinder access to critically ill patients who require constant care[108-109]. In a study of therapeutic cooling using ice packs and cooling blankets, Holzer reported that target temperature was reached in only 30% of patients[110]. Another observational cohort study involving 1,036 patients reported similar findings[111]. Surface cooling failure (target temperature was not reached) occurred in nearly one-third of patients, the failure rate even higher with obese patients and patients who underwent percutaneous coronary intervention, both common among patients who have been resuscitated[111].

Compared to skin surface cooling, intravascular temperature management (IVTM) systems rapidly reach target temperature and precisely maintain patient core temperature. One recent publication showed that the target temperature (33°C) was reached in a mean time of 64 minutes[110], while another study found that 98% of patients cooled with an IVTM system were maintained at target temperature, compared with only 50% of patients cooled using surface methods[112]. IVTM not only provides ease of use but demonstrates good outcomes both short- and long-term[113].

It is a common assumption that patients are prone to thrombosis when CVC and interventional catheters are utilized, despite the use of prophylactic anticoagulants. Heparin is commonly used in hydrophilic coatings on catheters because it is anti-thrombogenic, although non-heparin coated catheters are also used in the clinical setting depending on the patient's situation. Studies have shown that heparin-bound catheter coatings reduce the incidence of DVT and PE and inhibit the formation of fibrin sleeves[33,67]. For the high risk population, thrombosis prophylaxis should routinely be considered.

As clinicians consider the use of therapeutic hypothermia or fever control, they must carefully weigh the risks as well as the potential benefits of the therapy. Like any interventional procedure, IVTM involves insertion of a catheter into the superior vena cava via the subclavian vein, internal jugular vein, or into the IVC via the femoral vein and therefore carries the potential for CVC-related complications. However, this potential is relative, since most patients who would be considered candidates for therapeutic hypothermia require central venous access anyway, by virtue of their critical medical condition.

Case Series on IVTM Looking at DVTs

Few publications have described thrombus related to the use of femoral IVTM on both severely brain-injured patients and post resuscitation. This section discusses all of the published case series reporting on DVT, listed in Table 5.

Table 5: IVTM Case Series Reporting on DVT

Case Series	Disease	Number of Patients
Simosa[114]	TBI	10
Furlan[115]	Spinal injury	35
Müller[116]	SAH	43
Reccius[117]	CA, TBI, ICH, SAH & CI	20
Maze[118]	CA	61
Lau[119]	CA	1

Simosa[114] reported duplex ultrasound evidence of thrombus in post severe brain trauma patients and found thrombi only in patients who had the catheter in place ranging from 4 to 8 days, which is greater than the approved dwell time of maximum 4 days given by the femoral catheter Instructions for Use (IFU). Hypercoagulable panels were not routinely checked, nor DVT prophylaxis provided to this high risk population. The presence of DVT did not increase the length of stay or affected outcome. No occurrence of PE was reported in this group.

Another study in 83 high risk patients with polytrauma or traumatic brain injury where IVTM was utilized in both core cooling or warming[120] showed that 10 patients were noted to have thrombus including 5 patients with IVC thrombus. Patients were either treated with anticoagulation or prophylactic IVC filter. The population in this report was at high risk for DVT and none received DVT prophylaxis. The DVT group had a higher injury severity score compared to the overall group (33 vs. 21, p= 0.039). This could indicate that the injury severity contributed to DVT formation. 60% of the study population had prophylactic IVC filters, which also indicates a high risk of DVT in this population.

Additional data from Furlan et al. showed that rates of DVT in the IVTM patient population were low[115]. In this study, 35 patients with complete spinal cord injury were cooled with IVTM, and 43% had improvement in ASA score by at least one grade at one year follow up (compared to 26% historical data). All patients underwent ultrasound to evaluate the possibility of DVT and DVT prophylaxis. Five events were observed including 2 DVTs (one seen in the subclavian vein, unrelated to the femoral catheter), 2 PE, and 1 clot in the inferior vena cava. Only three of these events were related to cooling catheters (2 PEs and 1 DVT not in the subclavian vein). The author also noted that the first 14 patients who received ***Lovenox*** had no DVT, and all DVTs were observed in the later patients who received ***Fragmin*** due to a hospital-wide change. Incidence of DVT and PE after spinal cord injury was varied and reported as high as 43%[17]. Despite the change to a different DVT prophylaxis medication, the overall DVT rate of 8.6% (3/35) with IVTM is still much lower than expected compared to published data[121].

Furthermore, a retrospective chart review was performed and reported in 43 severe subarachnoid hemorrhage (SAH) patients who received IVTM for fever management or therapeutic hypothermia[116]. A total of 16 patients were confirmed to have DVT (N=11) and PE (N=5) by ultrasound and CT scan. PE tended to occur more frequently in patients treated for fever, although without statistical significance. The median day for thrombosis occurrence was day 15. Patients in the IVTM group had a higher Hunt and Hess grade (3.6 vs 2.5, $p< 0.001$ compared to patients with standard CVC). The higher rate of thromboembolic events could be due to the severe SAH population because of the inflammatory response and the length of catheter indwelling time. In addition, the cooling catheters used in this study did not have covalently bonded heparin coating. It is important to note that the site continues to use IVTM catheters to manage SAH patients, as the benefits of better outcomes with IVTM continue to outweigh the low risk of DVT.

A small number of studies have been designed specifically to evaluate the rate of DVT in the IVTM and CVC populations. An article by Reccius et al. described a study of 20 patients in which the purpose was to detect thrombus in the inferior vena cava using two sensitive methods: invasive cavography and ultrasonography related to the use of IVTM in an ICU-based, critically ill patient population[117]. The patient population was at high risk for venous thrombus, with primary diseases such as severe traumatic brain injury, cardiac arrest, intracerebral hemorrhage, acute ischemic stroke and aneurysmal subarachnoid hemorrhage. It is important to note that no clinical evidence of DVT was reported in any of the 20 patients and that none of the thrombi produced stenosis with a significant hemodynamic effect.

Results showed that clinically asymptomatic thrombi were found in the IVC in 18 of 20 patients using invasive cavography; based on current literature, the rate of thrombi as detected by this method is not available for comparison. Thrombi were confirmed in only 3 of 20 patients using ultrasonography, which is comparable with the rates of DVT reported with CVC placement in the critically ill patient population[31]. No pulmonary embolism was identified in the case series. In addition, the dwell time of the catheters in most of the patients during this study was greater than the approved dwell time of maximum 4 days given by the catheter IFU. Although mechanical DVT prophylaxis measures were taken in every patient, LMWH prophylaxis was not given in the neuro patient population as they were thought to have a higher risk of brain bleeding.

Per direct communications with the principal investigator of the trial, the site has made improvements to patient care methods as a result of this trial, such as earlier delivery of DVT prophylaxis per 2011 guidelines[122]. Additionally, the site continues to use IVTM in 100% of its post-cardiac arrest patients undergoing coronary catheterization procedures, as the benefits of better outcomes with IVTM outweigh the low risk of DVT. In addition, the site's protocol is to deliver heparin, aspirin, and clopidogrel during catheterization procedures in order to lower the risk of thrombosis. The site also uses IVTM to manage neuro patients who are obese.

A second study reported the rates of DVT in patients receiving DVT prophylaxis[118]. In this retrospective cohort study[118] of 61 patients, 41 patients received DVT prophylaxis (subcutaneous heparin) and 20 patients received UFH. All patients were screened for DVT with ultrasound or phlebography regardless of the presence of symptoms. Catheter related thrombosis was found in 9 patients who received prophylactic dose heparin (DVT in 2 patients; IVC thrombus in 7 patients). Two patients with a thrombus on the catheter developed a symptomatic PE and confirmed with computed tomography. No DVT was detected in the full dose heparin group, nor were there increased bleeding complications. In this study, there was no difference in symptomatic events between the study groups (0 out of 20 patients on UFH regimen and 3 out of 41 patients on subcutaneous heparin regimen; p=0.54). Catheters used in this study did not have covalently bonded heparin coating. Cardiac arrest survivors undergoing TH are at high risk of complications given the high inflammatory physiological state and immobility due to an unconscious state. The choice of between subcutaneous heparin and UFH is dependent upon risk balance of both bleeding and clotting. In this study, the risk of catheter related thrombosis (CRT) was negated with a UFH regimen with no apparent increase in bleeding. The site continues to use IVTM to cool post cardiac arrest to 33°C per their standard practice.

Lau et al. also reported one case of a patient who received an IVTM catheter post-cardiac arrest[119]. The patient had a history of drug and alcohol abuse and TH was initiated after the patient was admitted comatose post-resuscitation from spontaneous ventricular fibrillation. On day 15 after TH was initiated, the patient was discovered to have a right femoral vein thrombosis near the area where the catheter had been placed. The authors state that it is not certain that the IVC thrombus is a consequence of the cooling catheter[119].

DVT Rates in Intravascular Temperature Management

Tables 6 and 7 summarize the rates of DVT/VCT and PE from studies of patients receiving IVTM for non-cardiac arrest and post-cardiac arrest, respectively. It is important to note that there was no mortality due to PE in any of these studies.

Table 6: IVTM in non- cardiac arrest population

Series	Disease	Number of Patients	Assessment	DVT/VCT(%)	PE (%)
Simosa[114]	TBI	10	Ultrasound	5	0
Keller[123]	SAH	90	Clinical	0	0
Diringer[124]	TBI, SAH, ICH, CI	154	Clinical	1	0
Horn[125]	Severe Stroke	20	Clinical	1	0
Levi[121]	Spinal injury	35	Ultrasound/CT	3	2
Hoedemaekers[112]	TBI	5	Clinical	0	0
Taylor E[126]	Polytrauma	12	Clinical	0	0
Sahuquillo[127]	TBI	24	Ultrasound	1	0
Allen[128]	OPCAB	38	Clinical	0	0
Müller[116]	SAH	43	Ultrasound	11	5
David[129]	Severe burn	23	Clinical	0	0
Fischer[130]	TBI	6	Clinical	0	0
Prunet[131]	Severe Burn	4	Ultrasound	0	0
Puccio[98]	TBI	21	Clinical	0	0
Georgiadis[132]	Stroke	6	Clinical	0	0
Guluma[133]	Stroke	10	Clinical	0	0
Gierman[120]	Polytrauma, TBI	83	Cavography or intravascular ultrasound	10	0
Hinz[134]	SAH, TBI	13	Clinical	0	0
Broessner[135]	SAH, stroke	102	Clinical	0	0
Reccius[117]	TBI, ICH, SAH & CI	14	Cavography or intravascular	14	0
Total		713		36	7
DVT Rate				5%	1%

Table 7: IVTM in post cardiac arrest population

Series	Disease	Number of Patients	Assessment	DVT/VCT(%)	PE (%)
Pichon[107]	CA	40	Ultrasound	0	0
Bruel[62]	CA	33	Clinical	0	0
Flemming[136]	CA	31	Clinical	0	0
Lopez-de-Sa[137]	CA	36	Ultrasound	1	1
Tømte[138]	CA	72	Clinical	0	0
Hoedemaekers[112]	CA	5	Clinical	0	0
Lundbye[139]	Nonshockable CA	52	Clinical	0	
Sunde[140]	CA	29	Clinical	0	0
Arrich[141]	CA	347	Clinical	0	0
Feuchtl[142]	CA	19	Clinical	0	0
Holzer[143]	CA	97	Clinical	0	0
Grimes[144]	CA	38	Clinical	0	0
Patel[63]	CA	115	Clinical	0	0
Maze R[118]	CA	61	Echocardiography	9	1
Waard[145]	CA	97	Clinical	0	0
Lau[119]	CA	1	Venogram	1	0
Pittl[146]	CA	40	Clinical	0	0
Kozinski[147]	CA	32	Clinical	0	0
Zobel[148]	Cardiogenic shock	20	Clinical	0	0
Deye[109]	CA	203	Clinical	0	0
Reccius[117]	CA	6	Ultrasound & cavography	4	0
Nielsen[149]	CA	228	Clinical	0	0
Total		1,596		15	2
DVT Rate				0.94%	0.13%

DVT Rates in Randomized Controlled Trials (RCTs) Comparing Surface Cooling to IVTM

Two multicenter, randomized controlled trials comparing surface cooling to IVTM showed that IVTM catheters are not associated with increased incidence of DVT[109,124]. In a trial by Diringer et al., 296 neuro ICU patients (TBI, SAH, ICH and Stroke) were randomized 1:1 to receiving fever control via a ZOLL IVTM catheter or surface cooling with a standard CVC[124]. Results showed 64% fever burden reduction in the IVTM group compared to surface cooling, and there was no difference in the rate of DVT occurrence between groups[124]. Another randomized controlled trial by Deye et al. was conducted in 400 post-cardiac arrest patients where therapeutic hypothermia was induced either with the ZOLL IVTM femoral catheter or surface cooling plus standard CVC. Trial results not only showed a better long term neurological outcome and 74% nursing workload reduction in the IVTM group, but also no difference was found in DVT rate compared to standard CVCs[109].

In addition, two single center randomized studies in 247 patients (Tomte & Pittl)[138,146] compared ZOLL IVTM to surface cooling using the Bard Arctic Sun system and found no difference in DVT or PE rate between two groups.

DVT rates with Surface Cooling Devices

Reporting on DVT from studies in temperature management in critically ill or resuscitated patients with surface cooling methods have been inconsistent and underreported, as many studies do not report DVT rates. Patients in these trials all received standard CVCs to deliver medication and withdraw blood due to vasoconstriction from peripheral vessels[150]. A randomized clinical trial compared Arctic Sun to Blanketrol surface cooling devices in post-cardiac arrest population showed a 3% DVT rate[151]. Another study in 40 Neuro ICU patients using fever control with Arctic Sun and Blanketrol showed a 15% DVT rate[152].

A summary of publications showed an overall low rate of DVT (2.2%) and PE (0.39%) with IVTM. Occurrence of DVT and PE were higher in the neurosurgical population with IVTM than in the cardiac arrest population (5.0% vs. 0.94% in DVT, 1.0% vs. 0.13% in PE), but both were below previously published DVT and PE rates (19 to 50% for neurosurgical population and 8.5-26.2% for standard CVC). The likely reasons for the lower rate of DVT with IVTM include short indwelling time and the use of DVT prophylaxis in critically ill populations at most institutions.

Product Surveillance Data

Post-market surveillance of IVTM catheters based on the manufacturer's internal complaint database shows a DVT rate of 63 out of 171,000 catheters sold between May 2009 and June 2015 (0.037%)[153]. Although underreporting of complaints from hospitals is possible, even an underreporting rate of 100x less than actual would show a DVT rate of less than the range of 1-5% in the IVTM patient population reported in Tables 5 and 6.

Conclusion

Critically ill patients admitted to the ICU are prone to DVT, mostly due to inflammatory[7] status post injury, abnormal coagulation, immobilization and catheterization. Institutions should follow guidelines in DVT prevention which include pharmacological and mechanical methods. Institutional implementation of standard protocols that incorporate these measures may have contributed to the reduction of DVT rate. Importantly, therapeutic hypothermia using a ZOLL IVTM cooling catheter placed in the femoral vein is not associated with increased incidence of DVT or PE. Four randomized controlled clinical trials (2 multicenter and 2 single center trials) conducted in a total of 943 patients showed that there was no difference in the DVT rate when comparing ZOLL IVTM catheters to standard CVCs[109,124]. When IVTM cooled patients are compared to general critically ill patient populations who receive central lines, there is no difference in the rates of DVT and PE. Therefore, the benefits of using IVTM in the critically ill patient population outweigh the potential risks of DVT and PE.

References

1. White RH. The Epidemiology of Venous Thromboembolism. Circulation. 2003;107:I4–I8.
2. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost 2005; 3: 1611–17.
3. Kucher N. Clinical practice. Deep-vein thrombosis of the upper extremities. N Engl J Med 2011;364:861-869.
4. Samad F, Ruf W. Inflammation, obesity, and thrombosis. Blood. 2013;122:3415–3422.
5. Eisenhardt SU, Thiele JR, Bannasch H, et al. C-reactive protein: how conformational changes influence inflammatory properties. Cell Cycle. 2009;8:3885–3892.
6. Goldhaber SZ, Visani L, De Rosa. Acute pulmonary thromboembolism. Clinical outcomes in the International Cooperative Pulmonary Registry (ICOPER). Lancet. 1999; 353: 1386
7. Zoller B, Li X, Sundquist J, et al. Risk of pulmonaryembolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. Lancet. 2012;379:244–249.
8. Heit JA, Silverstein MD, Mohr DN, et al. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med. 1999;159:445–453.
9. S.B. Deitelzweig, B.H. Johnson, J. Lin, K.L. Schulman Prevalence of clinical venous thromboembolism in the USA: current trends and future projections Am J Hematol, 86 (2) (2011), pp. 217–220
10. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol. 2008;143:180–190.
11. Stein PD, Terrin ML, Hales CA. Clinical, roendgenographic and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest. 1991; 100: 598-603.
12. Le Gal, Teztuz A, Righini M. Reproduction of chest pain by palpation: diagnostic accuracy in suspected pulmonary embolism. BMJ. 2005; 330: 452-455.
13. Cukić V, Maglajlić J, Konjić M. Postoperative pulmonary thromoboembolism. Med Arh. 1999; 53(suppl.3): 57-58.
14. Bonizzoli M: Peripherally inserted central cenous catheters and centrall venous catheters related thrombosis in post-critical patients. Intensive Care Med (2011) 37:284–289
15. Pierce C: Surveillance Bias and Deep vein thrombosis in the national trauma Data Bank: the more we look, the more we find. *The Journal of* TRAUMA_ *Injury, Infection, and Critical Care, 2007*
16. Swann KW, Black PM: Deep vein thrombosis and pulmonary emboli in neurosurgical patients: A review. J Neurosurg 61:1055–1062, 1984.
17. Hamilton MG, Russel H: Venous Thromboembolism in neurosurgery and neurology patients: a review. Neurosurgery 34, 1994
18. Valladares JB, Incidence of lower extremity deep vein thrombosis in neurosurgical patients. Neurosurgery 6:138-141, 1980
19. Powers SK, Edwards MSB: Prevention and treatment of thromboembolic complications in a neurosurgical patient, in Wilkins RH, Rengachary SS (eds): *Neurosurgery. New York, McGraw-Hill, 1985, pp 406–410*
20. Bostrom S, Holmgren E, Jonsson O, Lindstrom B, Stigendal L: Fibrinopeptide A and fibrinogen fragment B(beta)15-42 and their relation to the operative trauma and post-operative thromboembolism in neurosurgical patients. Acta Neurochir (Wien) 88:49–55, 1987.
21. Landi G, D'Angelo A, Boccardi E, Candelise L, Mannucci PM, Morabito A, Orazio EN: Venous thromboembolism in acute stroke. Prognostic importance of hypercoaguability. Arch Neurol 49:279–283, 1992.
22. Landi G, D'Angelo A, Boccardi E, Candelise L, Mannucci PM, Orazio EN, Morabito A: Hypercoagulability in acute stroke: Prognostic significance. Neurology 37:1667–1671, 1987.
23. Warlow CP, Rennie JAN, Ogston D, Douglas AS: Platelet adhesiveness and fibrinolysis after recent cerebrovascular accidents and their relationship with subsequent deep venous thrombosis of the legs. Thromb Haemost 36:127–132, 1976.
24. Menon IS, Dewar HA: Increased fibrinolytic activity in venous blood of hemiplegic limbs. Br Med J 2:613–615, 1967.
25. Sawaya R, Cummins CJ, Kornblith PL: Brain tumors and plasmin inhibitors. Neurosurgery 15:795–800, 1984.
26. Sawaya R, Zuccarello M, El-Kalliny M: Brain tumors and thromboembolism: Clinical, hemostatic, and biochemical correlations. J Neurosurg 70:314A, 1989 (abstr).
27. Rossi EC, Green D, Rosen JS, Spies SM, Jao JST: Sequential changes in factor VIII and platelets preceding deep vein thrombosis in patients with spinal cord injury. Br J Haematol 45:143–151, 1980.
28. Matsumoto S, et al: Prospective study of deep vein thrombosis in patients with spinal cord injury not receiving anticoagulant therapy. Spinal cord 2015 1-4
29. Seigel EL, Jew AC, Delcore R, Iliopoulos JI, Thomas JH: Thrombolytic therapy for catheter-related thrombosis. Am J Surg 166:716-718; discussion 718-719, 1993.
30. Righini et al. Diagnosis of venous thromboembolic disease: unresolved issues. Thrombosis and Haemostasis 113.3/2015. http://dx.doi.org/10.1160/TH14-06-0530.
31. Mian NZ, Bayly R, Schreck DM. Incidence of Deep Vein Thrombosis Associated with Femoral Venous Catheterization. Academic Emergency Medicine 1997. 4: 1118-1121.

32. Steinberg GK, Ogilvy CS, Shuer LM, Connolly ES, Jr., Solomon RA, Lam A, Kassell NF, Baker CJ, Giannotta SL, Cockroft KM, Bell-Stephens TE, Allgren RL: Comparison of endovascular and surface cooling during unruptured cerebral aneurysm repair. Neurosurgery 55:307-314; discussion 314-305, 2004.
33. Hoshal VL, Ause RG, Hoskins PA. Fibrin sleeve formation on indwelling subclavian central venous catheters. Arch Surg 1971; 102:353-358.
34. Joynt GM, Kew J, Gomersall CD, Leung VY, Liu EK: Deep venous thrombosis caused by femoral venous catheters in critically ill adult patients. Chest 117:178-183, 2000.
35. Parienti J, Mongardon N, Megarbane B, et al. Intravascular complications of central venous catheterization by insertion site. N Engl J Med 2015; 373:1220-9. DOI: 10.1056/NEJMoa1500964
36. Kraft C et al: Patients with inferior vena cava thrombosis frequently present with lower back pain and bilateral lower-extremity deep vein thrombosis. Vasa 2013; 42: 275-283
37. Lambert M, Marboeuf P, Midulla M, Trillot N, Beregi JP, Mounier-Vehier C, et al. Inferior vena cava agenesis and deep vein thrombosis: 10 patients and review of the literature. Vasc Med. 2010;15:451–9.
38. Ruggeri M, Tosetto A, Castaman G, Rodeghiero F. Congenital absence of the inferior vena cava: A rare risk factor for idiopathic deep-vein thrombosis. Lancet. 2001;357:441
39. Gayer G, Zissin R, Strauss S, Hertz M. IVC anomalies and right renal aplasia detected on CT: A possible link? Abdom Imaging. 2003;28:395–9.
40. Sakellaris G, Tilemis S, Papakonstantinou O, Bitsori M, Tsetis D, Charissis G. Deep venous thrombosis in a child associated with an abnormal inferior vena cava. Acta Paediatr. 2005;94:242–4
41. Hamoud S, Nitecky S, Engel A, Goldsher D, Hayek T. Hypoplasia of the inferior vena cava with azygous continuation presenting as recurrent leg deep vein thrombosis. Am J Med Sci. 2000;319:414–6.
42. Sitwala PS, Ladia VM, Brahmbhatt PB, Jain V, Bajaj K. Inferior vena cava anomaly: a risk for deep vein thrombosis. N Am J Med Sci. 2014 Nov;6(11):601-3.
43. M.J. Manco-Johnson. Postthrombotic syndrome in children Acta Haematol, 115 (2006), pp. 207–213.
44. S. Kuhle, B. Koloshuk, V. Marzinotto, M. Bauman, P. Massicotte, M. Andrew, *et al.* A cross-sectional study evaluating post-thrombotic syndrome in children. Thromb Res, 111 (2003), pp. 227–233.
45. R.B. Rutherford. Pathogenesis and pathophysiology of the post-thrombotic syndrome: clinical implications. Semin Vasc Surg, 9 (1996), pp. 21–25
46. Mattos MA, Melendres G, Sumner DS, Hood DB, Barkmeier LD, Hodgson KJ et al. Prevalence and distribution of calf vein thrombosis in patients with symptomatic deep venous thrombosis: a color-flow duplex study. JVascSurg 1996; 24:738-744.
47. Hirsh J, Guyatt G, Albers GW, Harrington R, Schünemann HJ. American College of Chest Physicians. Executive summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133:71S- 109S
48. Kumar R, Rodriguez V, Matsumoto JM, et al: Prevalence and risk factors for post thrombotic syndrome after deep vein thrombosis in children: A cohort study. Thromb Res. 2014 Dec 5.
49. Persson AV, Jones C, Zide R, Jewell ER. Use of the triplex scanner in diagnosis of deep venous thrombosis. Arch Surg 1989; 124 :593-596.
50. Comerota AJ, Katz ML, Greenwald LL, Leefmans E, Czeredarczuk M, White JV. Venous duplex imaging: should it replace hemodynamic tests for deep venous thrombosis? JVascSurg 1990; 11 :53- 59.
51. Righini M, Goehring C, Bounameaux H, et al. Effects of age on the performance of common diagnostic tests for pulmonary embolism. Am J Med 2000; 109:357–361.
52. Coleman DM, et al: Biomarkers for the diagnosis of deep vein thrombosis. Expert opin. Med Diagn. 2012 6(4)
53. Rectenwald JE, Myers DD, Hawley AE, et al. D-Dimer, P-Selectin, and microparticles: novel markers to predict deep venous thrombosis. Thromb Haemost 2005;94:1312-17
54. Wakefield TW, Myers DD, Henke PK. Mechanisms of venous thrombosis and resolution. Arterioscler Thromb Vasc Biol 2008;28:387-91
55. Le Gal G, Righini M, Sanchez O, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. Thromb Haemost 2006; 95: 963–966.
56. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. Ann Intern Med 2001; 135: 98–107.
57. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). J Am Med Assoc 1990; 263: 2753–2759.
58. Revel MP, Sanchez O, Couchon S, et al. Diagnostic accuracy of magnetic resonance imaging for an acute pulmonary embolism: results of the 'IRM-EP' study. J Thromb Haemost 2012; 10: 743–750.

59. Stein PD, Chenevert TL, Fowler SE, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). Ann Intern Med 2010; 152: 434–443, W142–143.
60. Hamper UM, DeJong MR, Scoutt LM. Ultrasound evaluation of the lower extremity veins. Radiol Clin North Am 2007;45(3):525–47. http://dx.doi.org/10. 1016/j.rcl.2007.04.013.
61. JAMA 1995 (4);274:335-7
62. Bruel C et al: Mild hypothermia during advanced life support: a preliminary study in out-of-hospital cardiac arrest. *Critical Care* 2008, 12:R31
63. Patel N, et al: Central Line Associated Blood Stream Infection Related to Cooling Catheter in Cardiac Arrest Survivors Undergoing Therapeutic Hypothermia by Endovascular Cooling. CONNECTICUT MEDICINE, JANUARY 2013, Vol 1
64. Cukic V. The pulmonary thromboembolism as a risk of surgical treatments and the role of anticoagulant prophylaxis. Mater Sociomed. 2014 Oct;26(5):303-5.
65. Moser KM, LeMoine JR, Nachtwey FJ, Spragg RG. Deep venous thrombosis and pulmonary embolism. Frequency in a respiratory intensive care unit. JAMA 1981;246(13):1422–1424
66. Geerts W, Cook D, Selby R, Etchells E. Venous thromboembolism and its prevention in critical care. J Crit Care 2002;17(2):95–104
67. Alhazzani W, Lim W, Jaeschke RZ, Murad MH, Cade J, Cook DJ. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. Crit Care Med 2013;41(9):2088–2098
68. Ribic C, Lim W, Cook D, Crowther M. Low-molecular-weight heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review. J Crit Care 2009;24(2):197–205
69. Khouli H, Shapiro J, Pham VP, et al. Efficacy of deep venous thrombosis prophylaxis in the medical intensive care unit. J Intensive Care Med 2006;21(6):352–358
70. Cook D, Crowther M, Meade M, et al. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. Crit Care Med 2005;33(7):1565–1571
71. Lilly CM, Liu X, Badawi O, Franey CS, Zuckerman IH. Thrombosis prophylaxis and mortality risk among critically ill adults. Chest 2014;146(1):51–57
72. Plott RT, Wagner RF Jr, Tyring SK. Iatrogenic contamination of multidose vials in simulated use. A reassessment of current patient injection technique. Arch Dermatol 1990;126(11):1441–1444
73. Bruguera M, Saiz JC, Franco S, et al. Outbreak of nosocomial hepatitis C virus infection resolved by genetic analysis of HCV RNA. J Clin Microbiol 2002;40(11):4363–4366
74. Zhang C, Zeng W, Zhou H, et al. [The efficacy of intermittent pneumatic compression in the prevention of venous thromboembolismin medical critically ill patients]. ZhongguoWei Zhong Bing Ji Jiu Yi Xue 2011;23(9):563–565
75. Arabi YM, Khedr M, Dara SI, et al. Use of intermittent pneumatic compression and not graduated compression stockings is associated with lower incident VTE in critically ill patients: a multiple propensity scores adjusted analysis. Chest 2013;144(1):152–159
76. Keane MG, Ingenito EP, Goldhaber SZ. Utilization of venous thromboembolism prophylaxis in the medical intensive care unit. Chest 1994;106(1):13–14
77. Ryskamp RP, Trottier SJ. Utilization of venous thromboembolism prophylaxis in a medical-surgical ICU. Chest 1998;113(1):162–164
78. Cook D, Attia J, Weaver B, McDonald E, Meade M, Crowther M. Venous thromboembolic disease: an observational study in medical- surgical intensive care unit patients. J Crit Care 2000;15(4): 127–132
79. Decousus H, Tapson VF, Bergmann JF, et al; IMPROVE Investigators. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. Chest 2011; 139(1):69–79
80. Boonyawat k, Crowther MA: Venous thromboembolism prophylaxis in critically ill patients. Seminars in thrombosis & hemostasis, 2014
81. Kahn SR, Lim W, Dunn AS, et al; American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2, Suppl):e195S–e226S
82. Spinal Cord Thromboprophylaxis Investigators. Prevention of venous thromboembolism in the acute traumatic phase after spinal cord injury: a randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin. J Trauma 2003; 54 : 1116-1124; discussion 1125-1126.
83. Rogers FB, Cipolle MD, Velmahos G, Rozycki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST Practice Management Guidelines Work Group. *J Trauma.* 2002;53(1):142–164.
84. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. *Ann Surg*. 2004;240(3):490–496; discussion 496–498.
85. Denson K, Morgan D, Cunningham R, et al. Incidence of venous thromboembolism in patients with traumatic brain injury. *Am J Surg.* 2007;193(3):380–383; discussion 383–384.

86. Geerts WH, Code KI, Jay RM, Chen E, Szalai JP. A prospective study of venous thromboembolism after major trauma. *New Engl J Med*. 1994;331(24):1601–1606.
87. Menaker, J., Stein, D. M., and Scalea, T. M. (2007). Incidence of early pulmonary embolism after injury. J. Trauma 63, 620–624.
88. Owings, J. T., Kraut, E., Battistella, F., Cornelius, J. T., and O'Malley, R. (1997). Timing of the occurrence of pulmonary embolism in trauma patients. Arch. Surg. 132, 862–867.
89. Reiff, D. A., Haricharan, R. N., Bullington, N. M., Griffin, R. L., McGwin, G., and Rue, L. W. (2009). Traumatic brain injury is associated with the development of deep vein thrombosis independent of pharmacological prophylaxis. J. Trauma 66, 1436–1440
90. Shen x et al: a systematic review of the benefits and risks of anticoagulation following traumatic brain injury. *JOURNAL OF HEAD TRAUMA REHABILITATION/JULY-AUGUST 2015*
91. Levy AS, Salottolo K, Bar-Or R, et al. Pharmacologic thromboprophylaxis is a risk factor for hemorrhage progression in a subset of patients with traumatic brain injury. *J Trauma.* 2010;68(4):886– 894.
92. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury, part v: deep vein thrombosis prophylaxis. *J Neurotrauma.* 2007;24(suppl 1):S32–S36.
93. Dudley RR, Aziz I, Bonnici A, et al. Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: risks and benefits. *J Neurotrauma.* 2010;27(12):2165–2172.
94. Koehler DM, Shipman J, Davidson MA, Guillamondegui O. Is early venous thromboembolism prophylaxis safe in trauma patients with intracranial hemorrhage. *J Trauma.* 2011;70(2):324– 329.
95. Scudday T, Brasel K, Webb T, et al. Safety and efficacy of prophylactic anticoagulation in patients with traumatic brain injury. *J AmColl Surg.* 2011;213(1):148–153; discussion 153–144
96. Peberdy MA et al: Part 9: Post_Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010;122;S768-S786
97. Higgins RD, Raju TN, Perlman J, Azzopardi DV, Blackmon LR, Clark RH, Edwards AD, Ferriero DM, Gluckman PD, Gunn AJ, Jacobs SE, Eicher DJ, Jobe AH, Laptook AR, LeBlanc MH, Palmer C, Shankaran S, Soll RF, Stark AR, Thoresen M, Wyatt J: Hypothermia and perinatal asphyxia: executive summary of the National Institute of Child Health and Human Development workshop. J Pediatr 148:170-175, 2006.
98. Puccio AM et al: Induced Normothermia Attenuates Intracranial Hypertension and Reduces Fever Burden after Severe Traumatic Brain Injury. Neurocrit Care (2009) 11:82–87
99. Takahashi I, Kitahara T, Endo M, Ohwada T: [Clinical analysis of hypothermia in children with severe head injury]. No Shinkei Geka 28:983-989, 2000.
100. Tateishi A, Soejima Y, Taira Y, Nakashima K, Fujisawa H, Tsuchida E, Maekawa T, Ito H: Feasibility of the titration method of mild hypothermia in severely head-injured patients with intracranial hypertension. Neurosurgery 42:1065-1069; discussion 1069-1070, 1998.
101. Tokutomi T, Morimoto K, Miyagi T, Yamaguchi S, Ishikawa K, Shigemori M: Optimal temperature for the management severe traumatic brain injury: effect of hypothermia on intracranial pressure, systemic and intracranial hemodynamics, and metabolism. Neurosurgery 52:102-111; discussion 111-102, 2003.
102. Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, Wisniewski SR, DeKosky ST: Treatment of traumatic brain injury with moderate hypothermia. N Engl J Med 336:540-546, 1997.
103. Guidelines for the Management of Severe Traumatic Brain Injury, 3rd Edition. J of Neurotrauma 24, Supplement 1:S-26 - S-31, 2007
104. Wolff B et al: Early achievement of mild therapeutic hypothermia and the neurologic, Int J Cardiol 2009
105. Mooney et al, Effects of variation in temperature management on cerebral performance category scores in patients who received therapeutic hypothermia post cardiac arrest. Resuscitation 2012 83 (2012) 829– 83
106. Howes D, Gray SH, Brooks SC, et al. Canadian Guidelines for the use of targeted temperature management (therapeutic hypothermia) after cardiac arrest: A joint statement from The Canadian Association of Emergency Physicians (CAEP), the Canadian Critical Care Society (CCCS), Canadian Neurocritical Care Society (CNCCS), and the Canadian Critical Care Trials Group (CCCTG). Resuscitation. http://dx.doi.org/10.1016/j.resuscitation.2015.07.052
107. Pichon N et al: Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. Critical Care Vol 11 No 3, 2007
108. Gillies MA et al: Therapeutic hypothermia after cardiac arrest: A retrospective comparison of surface and endovascular cooling techniques. Resuscitation 2010
109. Deye N, Cariou A, Girardie P, et al. Endovascular versus External Targeted Temperature Management for Out-of-Hospital Cardiac Arrest Patients: A Randomized Controlled Study. CIRCULATIONAHA.114.012805. Published online before print June 19, 2015, doi: 10.1161/CIRCULATIONAHA.114.012805
110. Holzer M, et al: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346:549-556, 2002

111. Ricome S: Predictors of external cooling failure after cardiac arrest Intensive Care Med DOI 10.1007/s00134-012-2794-7
112. Hoedemaekers CC, EzzahtiMM, et al: Comparison of different cooling methods to induce and maintain normo-and hypothermia in ICU patients: a prospective intervention study. Critical Care. 2007,11:R91
113. Zimmermann S: Mild Therapeutic Hypothermia After Out-Of-Hospital Cardiac Arrest Complicating ST-Elevation Myocardial Infarction: Long-term Results in Clinical Practice. Clin. Cardiol, 10.1002/clc.22131
114. Simosa HF, Petersen DJ, Agarwal SK, Burke PA, Hirsch EF: Increased risk of deep venous thrombosis with endovascular cooling in patients with traumatic head injury. Am Surg 73:461-464, 2007.
115. Furlan JC, Fehlings MG. Role of screening tests for deep venous thrombosis in asymptomatic adults with acute spinal cord injury: an evidence-based analysis. Spine(Phila Pa 1976) 2007; 32: 1908–1916.
116. Muller A: Risk of Thromboembolic Events with Endovascular Cooling Catheters in Patients with Subarachnoid Hemorrhage. Neurocrit Care (2014) 21:207–210
117. Reccius A, Mercado P, Vargas P, et al. Inferior Vena Cava Thrombosis Related to Hypothermia Catheter: Report of 20 Consecutive Cases. Neurocritical Care (Impact Factor: 2.44). 12/2014; 23(1). DOI: 10.1007/s12028-014-0069-6.
118. Maze R, et al: Endovascular cooling catheter related thrombosis in patients undergoing therapeutic hypothermia for out of hospital cardiac arrest. Resuscitation 85 (2014) 1354–1358
119. Lau E et al: Inferior vena cava thrombus associated with intravascular cooling catheter. Resuscitation *81 (2010) 1457–1458*
120. Gierman HL et al: Thermoregulatory catheter–associated inferior vena cava thrombus. *Proc (Bayl Univ Med Cent)* 2013;26(2):100–102
121. Levi AD: Systemic hypothermia in acute cervical spinal cord injury: a case-controlled study. Spinal Cord (2012)
122. Jobin S, Kalliainen L, Adebayo L, Agarwal Z, Card R, Christie B, Haland T, Hartmark M, Johnson P, Kang M, Lindvall B, Mohsin S, Morton C. Venous thromboembolism prophylaxis. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2012 Nov. 51.
123. Keller E: et al: theraputic hypothermia in patients with aneurysmal subarachnoid hemorrhage refractory intracranial hypertension, or cerebral vasospasm. Neurosurgery, 64:1. JANUARY 2009
124. Diringer MN, et al: Treatment of fever in the neurologic intensive care unit with a catheter based heat exchange system. Crit Care Med 2004 Vol. 32, No. 2
125. Horn CM, et al: Endovascular Reperfusion and Cooling in Cerebral Acute Ischemia (ReCCLAIM I). J NeuroIntervent Surg 2013;0:1-5.
126. Taylor EE et al: Active intravascular rewarming for hypothermia associated with traumatic injury: early experience with a new technique. *Proc (Bayl Univ Med Cent)* 2008;21(2):120–126
127. Sahuquillo J: Intravascular cooling for rapid induction of moderate hypothermia in severely head-injured patients: results of a multicenter study (IntraCool). Intensive Care Med, 2008
128. Allen G: Intraoperative Temperature Control Using the Thermogard System During Off-pump Coronary Artery Bypass Grafting. Ann Thorac Surg 2009;87:284–8
129. Davis J, et al: Use of a Warming Catheter to Achieve Normothermia in Large Burns. J Burn Care Res 2013;34:191–195)
130. Fischer M et al: Keep the Brain Cool—Endovascular Cooling in Patients With Severe Traumatic Brain Injury: A Case Series Study. Neurosurgery 68:867–873, 2011
131. Prunet B et al: Maintenance of normothermia during burn surgery with an intravascular temperature control system: A non-randomised controlled trial. njury, Int. J. Care Injured (2010)
132. Georgiadis D, Schwarz S, Kollmar R, Schwab S: Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. Stroke 32:2550-2553, 2001.
133. Guluma KZ, Hemmen TM, Olsen SE, Rapp KS, Lyden PD: A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: methodology. Acad Emerg Med 13:820-827, 2006.
134. Hinz J: Effectiveness of an Intravascular Cooling Method Compared With a Conventional Cooling Technique in Neurologic Patients. Neurosurg Anesthesiol. Volume 19, Number 2, April 2007
135. Broessner G et al: Influence of Prophylactic, Endovascularly Based Normothermia on Inflammation in Patients With Severe Cerebrovascular Disease. A Prospective, Randomized Trial. *Stroke* published online Oct 28, 2010.
136. Flemming K. SG, Ziegs E., Diewok C., Gildemeister R., Wunderlich C., Strasser R.: Comparison of external and intravascular cooling to induce hypothermia in patients after CPR. GMS Ger Med Sci 4, 2006.
137. Lopez-de-Sa E: Hypothermia in Comatose Survivors From Out-of-Hospital Cardiac Arrest : Pilot Trial Comparing 2 Levels of Target Temperature. Circulation December 18, 2012
138. Tømte o et al: A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors. Crit Care Med 2011 Vol. 39, No. 3
139. Lundbye JB, et al: Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms. Resuscitation, 2011
140. Sunde K, et al. Therapeutic hypothermia with Endovascular cooling. Intensive Care Med. 2004;12:1

141. Arrich J: Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med 35:1041-1047, 2007.
142. Feuchtl A. GB, Lawrenz T., Bartelsmeier M., Stellbrink C.: Endovascular cooling improves neurological short-term outcome after prehospital cardiac arrest. Intensivmed 44:37-42, 2007.
143. Holzer M, Mullner M, Sterz F, Robak O, Kliegel A, Losert H, Sodeck G, Uray T, Zeiner A, Laggner AN: Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and Bayesian approach. Stroke 37:1792-1797, 2006.
144. Grimes, Anderson, Horiuchi, Concha, Fleegler, Hurwitz et al. Resuscitative Hypothermia After Cardiac Arrest: Performance in a Community Hospital. CHEST / 128 / 4 / October, 2005 Supplement167S.
145. Waard MC et al: Intravascular versus surface cooling speed and stability after cardiopulmonary resuscitation. Emerg Med J 2014;0:1–6.
146. Pittl U: Invasive versus non-invasive cooling after in- and out-of-hospital cardiac arrest: a randomized trial. Clin Res Cardiol, March 2013
147. Kozinski M et al: ACS network-based implementation of therapeutic hypothermia for the treatment of comatose out-of-hospital cardiac arrest survivors improves clinical outcomes: the first European experience. Resuscitation and Emergency Medicine 2013, 21:22
148. Zobel C et al: Mild therapeutic hypothermia in cardiogenic shock syndrome. Crit Care Med 2012 Vol. 40, No. 6
149. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. N Engl J Med 2013; 369:2197-2206December 5, 2013DOI: 10.1056/NEJMoa1310519.
150. Bro-jeppesen et al: Hemodynamics and Vasopressor Support During Targeted Temperature Management at 33°C Versus 36°C After Out-of-Hospital Cardiac Arrest: A Post Hoc Study of the Target Temperature Management Trial. Critical Care Medicine. February 2015. Volume 43. Number 2
151. Heard K et al: A randomized controlled trial comparing the Arctic Sun to standard cooling for induction of hypothermia after cardiac arrest. Resuscitation, 2009
152. Lord A et al. Therapeutic Temperature Modulation for Fever After Intracerebral Hemorrhage. NeuroCritical Care, 2014, 21
153. ZOLL internal complaint database.
154. Nyquist P, Bautista C, Jichici D, et al. Prophylaxis of Venous Thrombosis in Neurocritical Care Patients: An Evidence-Based Guideline: A Statement for Healthcare Professionals from the Neurocritical Care Society. Neurocrit Care (2016) 24:47-60. DOI 10.1007/s12028-015-0221-y.
155. UPMC Physician Order Set.

Table 1. Thromboembolism and Neurological Disease (Neurosurgical Patient Population)[17]

Series	Patient No.	Assessment	DVT (%)	PE (%)	PE Mort (%)
General neurosurgical population					
Wetzel et al, 1960	599	Autopsy	NA	3	
Joffe, 1975	23	I-fibrinogen	43	0	0
Turpie et al, 1977	63	I-fibrinogen	19.1	0	0
Cerrato et al, 1978	50	I-fibrinogen	34		
Skillman et al, 1978	48	I-fibrinogen	25	4.2	50
Turpie et al, 1979	96	I-fibrinogen	20.8	0	0
Valladares et al, 1980	100	I-fibrinogen	29	1	0
Zelikovski et al, 1981	20	I-fibrinogen	50	5	100
Mark et al, 1986	101	Autopsy	NA	24.8	
Head injury					
Kaufman et al, 1983	23	I-fibrinogen	20		
Subarachnoid hemorrhage					
Black et al, 1985	56	Doppler	18		
Brain tumors					
Brisman and Mendell, 1973	238	Autopsy	NA	8.4	
Kayser-Gatchalian and Kayser, 1975	334	Autopsy	27.5		
Sawaya et al, 1989	46	I-fibrinogen	45		

*DVT=deep vein thrombosis; PE=pulmonary embolism; Mort=mortality; PE was diagnosed clinically except when screened for an autopsy

Table 2. Thromboembolism in Stroke Population[17]

Series	Patient No.	Assessment	DVT (%)	PE (%)	PE Mort (%)
Warlow et al, 1972	30	I-fibrinogen	60	13	25
Denham et al, 1973	47	I-fibrinogen	46.8		
Warlow et al, 1976	76	I-fibrinogen	53	15.8	71
Warlow et al, 1976	15	I-fibrinogen	53		
Gibberd et al, 1976	26	I-fibrinogen	50	3.8	0
McCarthy et al, 1977	16	I-fibrinogen	75		
Miyamoto and Miller, 1980	141	I-fibrinogen	29	0**	0
Bounds et al, 1981	100	Autopsy		13	
McCarthy and Turner, 1986	161	I-fibrinogen	72.2	19.8	100
Turpie et al, 1987	25	I-fibrinogen	28	8	0
Bornstein and Norris, 1988	49	I-fibrinogen and IPG	22.5	2	0
Scmidt et al, 1988	1538	Clinical		7.1	
		(573 Deaths first 3 wk		13.6)	
		(596 Deaths 3 wk-7 yr		5.2)	
Landi et al, 1992	70	I-fibrinogen and Doppler	28.6	11.4	40

Table 3. Thromboembolism in Spinal Injury Population[17]

Series	Patient No.	Assessment	DVT (%)	PE (%)	PE Mort (%)
Spinal cord injury					
Bors et al, 1954	99	Venogram	58.6		
Philipps, 1963	25	Venogram	12		
Tribe, 1963	28	Autopsy		21.4	
Todd et al, 1976	20	I-fibrinogen	10		
Brach et al, 1977	10	I-fibrinogen	70	10	0
Perkash et al, 1978	50	I-fibrinogen	16	8	50
Rossi et al, 1980	18	I-fibrinogen	72		
Frisbie and Sasahara, 1981	17	IPG	5.9		
Myllynen et al, 1985	23	I-fibrinogen	100	9	0
Mark et al, 1986	101	Autopsy		24.8	
Merli et al, 1988	17	I-fibrinogen	47		
DeVivo et al, 1989	459	Clinical		9	
Myllynen et al, 1989	54	Clinical		13	42.8
Petaja et al, 1989	9	I-fibrinogen	67		
Yelnik et al, 1991	127	Venogram	22.8	0.8**	0
Spinal fracture without cord injury					
Myllynen et al, 1985	14	I-fibrinogen	0	0	0
Petaja et al, 1989	12	I-fibrinogen	8.3		

*DVT=deep vein thrombosis; PE=pulmonary embolism; Mort=mortality; IPG=impedance plethysmography; PE was diagnosed clinically except when screened for an autopsy

** In this portion of the study, all patients with evidence of DVT underwent anticoagulation to prevent PE.