**Supplemental Digital Content 2. Research studies synthesis**

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| **Article** | **Title** | | **Citation** | | | **Study Methods** | | **Study Purpose/Results** | | | | **Conclusion/**  **Recommendation/**  **Nursing Implication** | | | **Study Limitations** | | | **Quality of Evidence** | |
| 1 | The Clots in Legs Or sTockings after Stroke (CLOTS) 3 trial: a randomized controlled trial to determine whether or not intermittent pneumatic compression reduces the risk of post-stroke deep vein thrombosis and to estimate its cost-effectiveness | | Dennis, M.,  Sandercock, P., Graham, C., Forbes, J.,  Smith, J.  (2015)  Health Technol Assess. 2015 Sep;19(76):1-90. DOI: 10.3310/htal19760. | | | Usage of a multicenter, parallel-group RCT which allocated patients via a centralized randomisation system to IPC or no IPC. A technician blinded to treatment allocation performed compression duplex ultrasound of both legs at 7-10 days and 25-30 days after enrolment. Follow-up was done after 6 months.  2876 patients in 94 UK hospitals participated. | | **Purpose:**  To establish whether or not the application of IPC to the legs of immobile stroke patients reduced their risk of deep vein thrombosis.  **Primary outcome:**  122 of 1267 IPC participants compared with 174 of 1245 non-IPC participants made an odds-ratio of 0.65 (95% of CI 0.51 to 0.84; p=0.001)  **Secondary outcome:**  156 (10.8%) death in IPC participants versus 189 \*13.1%) in non-IPC were p=0.058  Skin breaks in 44(3.1%) versus 20(1.4%) were p=0.002  Falls with injury in 33(2.3%) versus 24(1.7%) were p=0.221.  Among those on IPC, there is significant improvement in survival in 6 months (hazard ratio 0.86, 95% CI 0.73 to 0.99 were p=0.042, but no improvement in disability. | | | | **Conclusion:**  IPC is an effective and inexpensive method of reducing the risk of DVT and improving survival in immobile stroke patients.  **Recommendation:**  Further research should test whether or not IPC improves survival in other groups of high-risk hospitalized medical patients. In addition, research into methods to improve adherence to IPC might increase the benefits of IPC in stroke patients. | | | Excluded in the study were those with age of less than 16 years, cases of Subarachnoid Hemorrhage, those with leg ulcers, dermatitis, severe edema, severe peripheral vascular disease and congestive heart failure. | | | Evidence Level  9  Evidence Grade  Good | |
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| 2 | Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke: a randomized trial | | | CLOTS Trial Collaboration  (2010)  Ann Intern Med.2010 Nov 2;153(9):553-62. DOI: 10.7326/0003-4819-153-9-201011020-00280.Epub 2010 Sep 20. | | | Parallel-group trial with centralized randomization (minimization within centers) to ensure allocation concealment. The ultrasonographers who looked for DVT were blinded, but the patients and caregivers were not.  112 hospitals in 9 countries were included.  3,114 immobile patients with acute stroke between January 2002 to May 2009 were included. | | **Purpose:**  To compare the effectiveness of thigh-length stockings with that of below-knee stockings for preventing proximal DVT in immobile, hospitalized stroke patients.  **Results:**  The primary outcome occurred in 98 patients (6.3%) who received thigh-length stockings and 138 (8.8%) who received below-knee stockings, an odd reduction of 31%.  75% of patients in both groups wore the stockings for 30 days or until they were discharged, died, or regained mobility.  Skin breaks occurred in 61 patients who received thigh-length (3.9%) and 45 patients who received below-knee (2.9%). | | **Conclusion:**  Proximal DVT occurs most often in patients with stroke who wear below-knee stockings than in those who wear thigh-length stockings. | | Blinding was incomplete, 2 scans were not obtained for all enrolled patients, and the trial was stopped before the target accrual was reached. | | | | Evidence  Level  9  Evidence Grade  Fair | | |
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| 3 | Physical methods for preventing deep vein thrombosis in stroke | Naccarato, M., Chiodo Grandi, F.,  Dennis, M.,  Sandercock, P.,  (2010)  Cochrane Database Syst Rev.2010 Aug 4;(8):CD001922. DOI:10.1002/14651858.CD001922.pub3. | | | Unconfounded RCT comparing physical methods for reducing the risk of DVT with control and in which prophylaxis was started within seven days of the onset of stroke.  Two trials of GCS with 2,615 patients and two small studies of IPC with 177 patients were included. | | | **Purpose:**  To assess the effectiveness and safety of physical methods of reducing the risk of DVT, fatal or non-fatal PE and death in patients with recent stroke.  **Results:**  Physical methods were not associated with a significant reduction in DVT during the treatment period (odds ratio of 0.85 or 95%) (confidence interval of 0.70 to 1.04).  Use of graduated compression stockings was not associated with any significant reduction in risk of DVT (odd ratio of 0.88 or 95%) (confidence interval of 0.72 to 1.08). | | **Conclusion:**  Evidence from randomised trials does not support the routine use of graduated compression stockings to reduce the risk of DVT after acute stroke. There is insufficient evidence to support the routine use of IPC to reduce the risk of DVT in acute stroke and further larger RCT are needed. | | | |  | | Evidence  Level  9  Evidence Grade  Good | | |

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| 4 | Prevention of Deep Vein Thrombosis and Pulmonary Embolism in Patients With Stroke | | Field, S. & Hill, M. (2012)  DOI: 10.1177/1076029611412362 http://cath.sagepub.com | A literature search (PubMed) was performed to locate relevant articles and studies pertaining to the incidence of VTE in stroke and trials of thromboprophylaxis in stroke.  Total of 14,119,896 respondents were included from the study (1987 to 2007). | | | | **Purpose:**  To identify the various means of preventing DVT and pulmonary embolism after a stroke incident.  **Results:**  Use of antiembolic stockings is not effective in reducing DVT. CLOTS-1 & 2 trials yielded 98 (6.3%) DVT in the thigh-high group and 138 (8.8%) in the knee-high group.  IPC use was superb to placebo in preventing DVT (RR 0.41, 95% CI 0.21-0.78).  Patients enrolled in International Stroke Trial (0.7%) showed a decrease in PE than in the non-ASA group (0.9%). It is also supported by a Cochrane review.  LMWH and daparanoids were both effective in preventing DVT over heparin based on a Cochrane review. | | **Conclusion:**  Reported rates of VTE after stroke have decreased, possibly due to the implementation of stroke units, early mobilization, and increased early use of antiplatelets. IPC use has shown to decrease DVT in small trials underpowered to detect PE. Graduated compression stockings do not significantly reduce VTE and are associated with skin breakdown. Unfractionated heparin, LMWH, and daparanoids are acceptable options for chemoprophylaxis, though all are associated with an increased risk of bleeding. Cost may have an impact in the choice of agent: Unfractionated heparin versus LMWH. | | | | | Study is limited due to the spurt of new anticoagulants available now in the market.  It is also limited to cases of ischemic stroke excluding those with hemorrhagic stroke and subarachnoid haemorrhage. | | | | Evidence  Level  10  Evidence Grade  Good | | |
| **Article** | **Title** | | **Citation** | | | **Study Methods** | **Study Purpose/Results** | | | | **Conclusion/**  **Recommendation/**  **Nursing Implication** | | **Study Limitations** | | | | **Quality of Evidence** | | | |
| 5 | Venous thromboembolism prophylactic methods in acute stroke patients – current state of knowledge | | Bembenek, J. & Czlonkowska, A. (2013)  DOI: 10.5114/ninp.2013.39074 | | | An integrative review utilizing the different DVT prophylactic methods were tallied. Such includes use of heparin, LMWH, oral anticoagulants, NOAC(novel anticoagulants), dextrans, IPC(intermittent pneumatic compression) & GCS(graduated compression stockings). | **Purpose:**  To review literature and present state of knowledge regarding the effectiveness of each DVT and PE prevention methods in stroke patients and cite current Polish, European and American recommendations.  **Results:**  Heparins are the preferred method of VTE prophylaxis in both ischemic and hemorrhagic stroke patients.  LMWH are preferred over UFH.  graduated compression stockings are not recommended routinely in both ischemic and hemorrhagic stroke patients.  VTE prophylaxis in immobile patients with acute hemorrhagic stroke should be started in 2-4 days after stroke onset.  Adding IPC to heparins may provide additional benefit in preventing VTE in stroke patients. | | | | **Conclusion:**  Several methods were assessed aiming to reduce the risks of VTE. Heparins are recommended as a method of choice to prevent thromboembolic complications in stroke patients. However, there is no gold standard method for all post-stroke patients to prevent VTE. Variations in recommendations and clinical practice also exist. | |  | | | | Evidence  Level  10  Evidence Grade  Fair | | | |
| **Article** | **Title** | | **Citation** | | | **Study Methods** | **Study Purpose/Results** | | | | **Conclusion/**  **Recommendation/**  **Nursing Implication** | | | **Study Limitations** | | | | **Quality of Evidence** | |
| 6 | Preventing Deep Vein Thrombosis After Stroke: Strategies and Recommendations | | L. J. Kappelle (2011)  DOI: 10.1007/s11940-011-0147-4 | | | An integrative review utilizing four non-pharmacologic and three pharmacologic means of preventing VTE were compared. | **Purpose:**  To review which methods are useful in preventing VTE.  **Results:**  Early mobilization after stroke may reduce VTE and PE, but no conclusive results are yet published due to ongoing RCT like AVERT (A Very Early Rehabilitation Trial).  Fluid hydration has not been evaluated in RCT, but current guidelines advocate maintenance of well-hydrated status in the acute phase of stroke.  A meta-analysis of 2,615 patients showed that GCS was not associated with a reduction in risks of DVT  (OR, 0.88; 95% CI, 0.72-1.08).  A meta-analysis of 177 patients showed that IPC was associated with a nonsignificant trend towards a lower risk of DVT.  Another meta-analysis revealed that IPC plus antithrombotic medications reduced DVT from 4% to 1%, than IPC alone.  In a Cochrane meta-analysis, routine use of unfractionated heparin cannot be recommended due to risk of intracranial bleed, though it is beneficial in reducing DVT incidences in ischemic stroke.  A meta-analysis showed that LMWH reduces the risk of DVT in ischemic stroke patients.  (OR, 2.17; 95% CI, 1.10-4.28).  A meta-analysis showed that LMWH showed a significant reduction in DVT than with standard unfractionated heparin.  (OR, 0.55; 95% CI, 0.44-0.70).  A Cochrane review of two small trials of 133 patients showed that antiplatelet therapy did not reduce DVT  OR, 0.78; 95% CI, 0.36-1.67).  A meta-analysis of 1,000 patients in four studies showed that antithrombotic treatment in hemorrhagic stroke patients was associated with a nonsignificant reduction in DVT from 4.2% to 3.3%, and  nonsignificant increase in hematoma enlargement from 8.0% versus 4.0%. | | | | **Conclusion:**  Varied anti-DVT measures yielded different results. | | | Further study must be conducted in intracerebral haemorrhage patients. | | | | Evidence  Level  10  Evidence Grade  Good | |
| **Article** | **Title** | **Citation** | | | **Study Methods** | | **Study Purpose/Results** | | **Conclusion/**  **Recommendation/**  **Nursing Implication** | | | **Study Limitations** | | | | **Quality of Evidence** | | | |
| 7 | Prophylaxis of Venous Thrombosis in Neurocritical Care Patients: An Evidence-Based Guideline: A Statement for Healthcare Professionals from the Neurocritical Care Society | Nyquist, P., et.al  (2015)  DOI: 10.1007/s12028-015-0221-y | | | A multidisciplinary panel of experts were selected by Neurocritical Care Society based on their experience in neurocritical care and in VTE.  A representative from Society of Critical Care Medicine acted as liaison between the two organizations.  The panel was divided into topic-related working groups according to expertise.  Literatures from the past 30 years to Jan.2013 were reviewed.  RCT and meta-analyses were also included.  GRADE scale was used to analyzed data.  The recommendations underwent review by the general membership of NCS. | | **Purpose:**  To provide guidelines in VTE prevention in neurocritically ill patients including those who had stroke.  **Results:**  **1.Ischemic Stroke**  In the CLOTS 3 trial, there was an absolute risk of VTE reduction of 3.6% (95% CI 1.4-5.8%) with the use of IPC beginning 0-3 days post-stroke.  The PREVAIL study showed that LMWH reduced the risk of VTE by 43% compared with UFH (RR 0.57, 95% CI 0.44-0.76, p = 0.0001).  **2.Intracranial Bleed**  Small prospective randomized trials were conducted by Dickmann et.al and Boeer et.al. However, the quality is limited due to very small size and low frequency of VTE and hemorrhagic events.  A comprehensive meta-analysis by Pacarioni et.al demonstrated a significant reduction in PE associated with UFH or LMWH prophylaxis (RR 0.37, 95% CI 0.17-0.80, p = 0.001) compared with no pharmacoprophylaxis, but no differences for DVT, hematoma expansion, or mortality.  **3.Aneurysmal Subarachnoid Hemorrhage**  VTE is associated with nearly double the mean length of stay and an increased risk of pulmonary/cardiac complications (OR 2.8, 95% CI 2.4-3.3). | | **Conclusion:**  The panel encourages guideline users to consider their own clinical experience and the subtleties of the evidence presented as they use these recommendations in their practice.  **Recommendations:**  **1.Ischemic stroke**  Initiate VTE pharmacoprophylaxis as soon as it is feasible. LMWH is recommended than UFH.  Use of GCS is not recommended due to insufficient evidence, thou their use appears to be safe.  For those undergoing hemicraniectomy, it is suggested to use UFH, LMWH, and/or IPC in the immediate postsurgical or endovascular epoch except when patients received rTPA, in which prophylaxis should be delayed for 24-hours.  **2.Intracranial Bleed**  Use of IPC and/or GCS over no prophylaxis beginning at the time of admission is recommended.  Subcutaneous UFH or LMWH with stable hematomas and no ongoing coagulopathy beginning 48 hours of admission is suggested.  **3. Aneurysmal Subarachnoid Hemorrhage**  Use of UFH is recommended except in those with unsecured ruptured aneurysms expected to undergo surgery.  IPC at the beginning of admission is advisable.  Use of UFH 24-hours post-clipping or coiling is recommended. | | | The study is not limited to stroke. It also included other approaches to other neurologic cases.  Complexity of patients and rarity of VTE is challenging. | | | | Evidence  Level  10  Evidence Grade  Good | | | |

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| 8 | European Stroke Organization (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischemic stroke | Dennis, M., Caso,V., Kappelle, L.J., Pavlovic, A.,  Sandercock, P.  (2016)  DOI: 10.1177/2396987316628384 | A multidisciplinary group identified related questions and developed its recommendations based on evidence from RCT using GRADE approach. | **Purpose:**  To assess the varied methods available to prevent DVT in patients with ischemic stroke.  **Results:**  A meta-analysis of one large trial (2,518 patients) and one small trial (97 patients) revealed that the use of GCS has no significant effect in reducing VTE, and on death.  IPC significantly reduced DVT (OR 0.73, 95% CI 0.61-0.88).  There is no direct evidence that neuromuscular electrical stimulation reduces DVT. | **Conclusion:**  IPC, UFH, or LMWH and heparinoids can reduce the risk of VTE in immobile patients with acute ischemic stroke but further research is required to test whether neuromuscular electrical stimulation is effective. | Further analyses of existing data, and further study, are needed to establish better methods to target prophylaxis with IPC and anticoagulants to those who will gain most from the interventions. | Evidence  Level  10  Evidence Grade  Good |

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| 9 | Which stroke patients gain most from intermittent pneumatic compression: further analyses of the CLOTS 3 trial | Dennis, M.  Graham, C.  Smith, J.  Forbes, J.  Sandercock, P.  (2015)  Int J Stroke. 2015 Oct;10 Suppl A100:103-7  DOI: 10.1111/ijs.12598.Epub 2015 Aug 26 | A multicentre, parallel group, randomized trial enrolled immobile acute stroke patients and allocated them to IPC or no IPC.  The primary outcome was proximal DVT at 30 days.  Secondary outcomes at six-months included survival, disability, quality of life, and hospital costs.  The Six Simple Variable model was utilized.  2876 patients were enrolled in 94 UK hospitals. | **Purpose:**  To provide additional information which may help clinicians target IPC on the most appropriate patients by exploring the variation in its effects on subgroups defined by predicted prognosis.  **Results:**  IPC reduced DVT (odd reduction 34%) and improved survival 17% and significantly increased length of stay and hospital cost. | **Conclusion:**  IPC appears to reduce the risk of DVT and probably improves survival in all immobile stroke patients.  But, some decision should be based on individual prognosis.  In some, their prognosis for survival with an acceptable quality of life will be so poor that the use of IPC might be considered futile, while at the other end of the spectrum, patient’s risk of DVT, and of dying from VTE, may not be high enough to justify the modest cost and inconvenience of IPC use. | Minor methodology concern | Evidence  Level  9  Evidence Grade  Fair |

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| 10 | Timing of deep vein thrombosis formation after aneurysmal subarachnoid haemorrhage | Liang, C.  Su, K.  Liu, J.  Dogan, A.  Hinson, H.  (2015)  J Neurosurg.  2015 Oct;123(4):891-6  DOI: 10.3171/2014.12.jns.141288. Epub 2015 Jul 10 | 189 patients admitted at the Oregon Health & Science University Neurosciences ICU were included in the retrospective analysis.  Ultrasound was performed every 5.2 +/- 3.3 days between admission and discharge.  The chi-square test was used to compare DVT incidence during the time periods of interest.  Patient baseline characteristics as well as stroke severity and hospital complications were evaluated in univariate and multivariate analyses. | **Purpose:**  To identify the appropriate timing of using DVT prevention measures to reduce DVT in patients with aneurysmal SAH.  **Results:**  42/198 patients or 21% were diagnosed with DVT, and 2/198 or 2% were asymptomatic.  29 of the 42 cases of DVT or 69% were detected between Days 3 and 14.  7% occurred between Days 0 and 3.  24% had DVT after Day 14.  In the multivariate analysis, length of hospital stay and use of mechanical prophylaxis alone were significantly associated with DVT formation. | **Conclusion:**  DVT formation most commonly occurs in the first two weeks following aneurysmal subarachnoid haemorrhage, with detection in this cohort peaking between Days 5 and 9. Chemoprophylaxis is associated with a significantly lower incidence of DVT. | Needs a bigger population sample. | Evidence  Level  6  Evidence Grade  Fair |

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| 11 | Risk assessment of deep vein thrombosis after acute stroke: a prospective study using clinical factors | Liu, L. et.al  (2014)  CNS Neurosci Ther. 2014 May;20(5):403-10  DOI: 10.1111/cns.122227. Epub 2014 Feb 24. | Incidence of Deep Vein Thrombosis after Acute Stroke in China (INVENT-China) is a multicenter prospective cohort study.  It included a total of 862 hospital-based patients.  Ultrasound was used between Days 3 to 14.  Data were randomly assigned to either a training data set or a test data set.  Multivariate logistic regression analysis was used to develop risk scores to predict DVT in the training data set and the area under the receiver operating characteristic curve to validate the score in the test data set. | **Purpose:**  To assess the risk of developing DVT in acute stroke patients using a clinical score.  **Results:**  The overall incidence of DVT after acute stroke within two weeks was 12.4% (95% CI 10.3-14.7%).  A seven-point score derived in the training data set :  Age equal or more than 65 = 1  Female = 1  Obesity with BMI of 25 kg or more = 1  Active cancer = 2  Intracerebral bleed = 1  Muscle weakness with NIHSS of 2 or more = 1 | **Conclusion:**  Clinical scores may help identify acute stroke patients with high risk of DVT. | Needs a bigger population size.  It also must be tested on other sites/setting like in our country. | Evidence  Level  5  Evidence Grade  Good |

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| **Article** | **Title** | **Citation** | **Study Methods** | **Study Purpose/Results** | **Conclusion/**  **Recommendation/**  **Nursing Implication** | **Study Limitations** | **Quality of Evidence** |
| 12 | Venous thromboembolism in the Get With The Guidelines-Stroke acute ischemic stroke population: incidence and patterns of prophylaxis | Douds, G. et.al  (2014)  Stroke Cerebrovasc Dis. 2014 Jan;23(1):123-9  DOI: 10.1016/j.jstrokecerebrovasdis.2012.10.018 Epub 2012 Dec 14 | Data were analysed from 149,916 patients admitted and enrolled in GWTG-S from 1259 US hospitals. | **Purpose:**  To examine the incidence of VTE and the patterns of VTE prophylaxis in acute stroke patients in the GWTG-S study.  **Results:**  The overall rate of VTE prophylaxis in the analysis cohort was 93% (139,476/149,916) patients.  The median site prophylaxis rate was 95%, and prophylaxis rates ranged from 17% (1 site) to 100% (101 sites).  Factors associated with increased likelihood of VTE prophylaxis in the multivariable model included history of atrial flutter/fibrillation, receipt of intravenous or intra-arterial tissue plasminogen activator, and admission to an academic hospital.  Increasing age, black race, and a history of peripheral vascular disease, diabetes, or stroke were associated with lower likelihood of prophylaxis.  Patients receiving care in the Midwest were less likely to receive prophylaxis compared to other regions. | **Conclusion:**  VTE was found to occur in approximately 3% of patients.  Variables included the hospital region, hospital type, age, race, and other medical comorbidities. | Needs improvement in the methodology. | Evidence  Level  5  Evidence Grade  Fair |