EC PULMONOLOGY AND RESPIRATORY MEDICINE
Review Article

Prevention of Post-Traumatic Venous-Thromboembolism Complications in Intensive Care Unit

Mabrouk Bahloul*, Mariem Dlela and Mounir Bouaziz

Department of Intensive Care, Habib Bourguiba University Hospital, Faculty of Medicine of Sfax, Sfax University, Sfax, Tunisia

***Corresponding Author:** Mabrouk Bahloul, Professor, Department of Intensive Care, Habib Bourguiba University Hospital, Sfax, Tunisia.

Received: July 05, 2019 ; **Published:** September 13, 2019

Abstract

Background: Venous thromboembolism (VTE) is a well-established complication of trauma. However, up to now, no measures have been found to be both effective and safe in completely preventing VTE (in particular post-traumaticpulmonary embolism). In fact, it has been reported that up to three-quartersof trauma patients diagnosed with pulmonary thrombo-embolism are already receiving recommended prophylaxis

Aims: We have conducted this literature review in order to analyze all measures confirmed to have been found to be effective and safe in completely preventing VTE (in particular post-traumatic pulmonary embolism).

Results: VTE remains frequently observed in post-trauma patient requiring ICU admission. VTE prophylaxis seems to reduce the incidence of this complication. The Eastern Association for the Surgery of Trauma recognizes the importance of early initiating thrombo-prophylaxis. The efficacy of the various types of prophylaxis used is still vigorously debated. In comparison with LDUH, the use of LMWH reduced DVT risk. Although Guidelines lack specific recommendations regarding the timing, form and dosage of chemical prophylaxis, it was established that in the prevention of the events and mortality of VTE, Enoxaparin doses of 40 mg once daily or 30 mg twice daily was more effective than UFH 5,000 units three times daily. Moreover, the association between mechanical and pharmacological prophylaxis reduces significantly the risk of DVT. Future studies should evaluate the use of aspirin or other antiplatelet therapy, in conjunction with LMWH, for thrombo-prophylaxis in trauma patients.

Conclusion: Post-traumatic VTE is frequent in ICU.VTE prophylaxis seems to reduce the incidence of this complication. The association between mechanical and pharmacological prophylaxis reduces significantly the risk of DVT. Future studies should evaluate the use of aspirin or other antiplatelet therapy, in conjunction with LMWH, for thrombo-prophylaxis in trauma patients.

Keywords: *Post-traumatic Pulmonary Embolism; Prevention; Intensive Care Unit*

Introduction

Venous thromboembolism (VTE) is a well-established complication of trauma [1-3]. Traumatic events are nowadays known to increase the risk of VTE and were reported to be responsible for approximately 12% of VTE episodes occurring in the community [4]. Recently, it has been established that a transitory hypercoagulable state actually occurs early (in the first few days following injury) [5,6], leading to very early VTE complications after trauma [7-16]. Moreover, It has been well established, that the use of any type of mechanical and/or pharmacological prophylaxis reduces the risk of DVT in trauma patients [17]. Without prophylaxis, the reported incidence of VTE in patients with traumatic brain injury ranges from 10% to 90% [18-23].

The Eastern Association for the Surgery of Trauma (EAST) and the American College of Chest Physicians (ACCP) have developed and published guidelines for thrombo-prophylaxis in 2002 and 2012, respectively [23,24]. The ninth edition of Evidence-based Clinical Practice Guidelines from the ACCP suggests the use of low-dose unfractionated heparin (LDUH), low molecular weight heparin (LMWH), or mechanical prophylaxis for major trauma patients. For trauma patients at high risk of VTE, the combined use of mechanical and pharmacologic prophylaxis is a suggested guideline. However, if pharmacologic prophylaxis is contraindicated, mechanical prophylaxis is preferred over no prophylaxis. The guidelines, also, suggest that an IVC filter not be used for primary prevention of VTE [23].

However, up to now, no measures have been found to be both effective and safe in completely preventing VTE (in particular post-traumatic pulmonary embolism). In fact, it has been reported that up to three-quarters of trauma patients diagnosed with pulmonary thrombo-embolism are already receiving recommended prophylaxis [1]. On the other hand, screening and thrombo-prophylaxis can significantly reduce mortality of post-traumatic thrombo-embolic events [1].

Mechanical prophylaxis

It is well known, in the general surgery population, that early postoperative mobilization reduces the risk of VTE complications [22]. However, early mobilization might not be achievable in critically injured patients, with depressed mental status.

Therefore, mechanical prophylaxis is recommended to be used as soon as possible, after injury. Mechanical prophylaxis includes the use of elastic compression stockings and intermittent pneumatic compressive devices (IPCs).

IPCs work by sequentially inflating and deflating, compressing the lower extremities to provide an intermittent gradient of pressure, driving the flow of venous blood centrally and preventing blood stasis. They also have a systemic effect by activating the fibrinolytic pathway [23].

Both, the ACCP guidelines and the recent Cochrane review, recommend the use of mechanical prophylaxis. The main advantage, in addition to reducing the risk of DVT, is the fact they can be used in patients with active contraindications to pharmacological prophylaxis such as hemorrhage [21,23]. However, due to lower extremity injuries, these techniques, may not always be feasible in trauma patients. In fact, it is common for trauma patients to have anatomic contraindications to bilateral lower extremity IPC placement. These contraindications include soft tissue trauma to the lower extremity, and lower extremity fractures and recent lower extremity surgery. Moreover, the use of pharmacologic prophylaxis was found to be more effective than mechanical devices at reducing the risk of DVT [18,20-27]. In the recent Cochrane review [21], it was established that mechanical prophylaxis reduced the risk of DVT (RR = 0.43; 95%; CI 0.25 to 0.73). However, it was also established that in reducing the risk of DVT, pharmacological prophylaxis was more effective than mechanical methods (RR 0.48; 95% CI 0.25 to 0.95).

Chemical prophylaxis

According to the recent Cochrane review [21], a total of six trials including 1033 patients compared chemical prophylaxis to mechanical prophylaxis. Pharmacological prophylaxis was proven more effective than mechanical techniques at reducing the risk of DVT (RR 0.48). Although, it increased the risk of bleeding (RR:2.04), there was no evidence for a difference in effect on the risk of major bleeding [21].

Low dose unfractionated heparin (LDUH)

Low dose unfractionated heparin (LDUH) has been found to reduce the overall incidence of DVT in postoperative patients from 25% to 8% [24]. However, it was established in other reports, that in trauma populations, chemoprophylaxis with LDUH was not proven effective, and has been shown to be equivalent to no prophylaxis in high-risk trauma patients [24,25]. In 2017, Jacobs BN., et al. [25] had conducted an analysis of the Michigan Trauma Quality Improvement Program data from January 2012 to December 2014. Information contained in the data set include date, time, and drug type of the first dose of VTE prophylaxis. The time of administering the first dose of VTE prophylaxis in addition to standard covariates was entered into the model. The cohort analysis consisted of 18,010 patients. In this study, authors had found that patients administered LMWH had a decreased risk of mortality (odds ratio, 0.64; confidence interval, 0.49 - 0.83), VTE (odds ratio, 0.67; confidence interval, 0.53 - 0.84), pulmonary embolism (odds ratio, 0.53; confidence interval, 0.35 - 0.79) and deep vein thrombosis (odds ratio, 0.73; confidence interval, 0.57 - 0.95) when compared with UFH following risk adjustment and accounting for hospital effect. The conclusion of this study is LMWH was found to be moreeffective than UFH in reducing the incidenceof mortality and VTE events among trauma patients. Therefore, UFH should not be used for prophylaxis in trauma patients, unless a low molecular weight heparin (LMWH) is contraindicated.

Low molecular weight heparin (LMWH)

LMWH should be initiated when primary hemostasis has occurred, and it tends to be the method of choice to provide DVT prophylaxis in the high-risk trauma patient [23-26]. According to the latest Cochrane review, the use of LMWH appeared to decrease the risk of DVT compared to LDUH, with no statistically significant difference in the risk of bleeding between the two [21]. According to this review [21], Two trials involving 331 patients compared low molecular weight heparin (LMWH) with unfractionated heparin (UH). The risk of DVT was observed to be reduced by LMWH compared to UH (RR 0.68; 95% CI 0.50 to 0.94). According to Jacobs BN., et al. [25], in the prevention of the events and mortality of VTE, Enoxaparin doses of 40 mg once daily or 30 mg twice daily was more effective than UFH 5,000 units three times daily. Finally, according to the latest Cochrane review [21], Mechanical prophylaxis plus pharmacological prophylaxis have been compared with pharmacological prophylaxis alone in three trials involving 507 patients. The conclusion is that a lower risk of DVT was observed in patients who received both mechanical and pharmacological prophylaxis (RR 0.34; 95%CI 0.19 to 0.60).

Therefore, the use of LMWH should be preferred to LDUH for prophylaxis in trauma patients, unless a low molecular weight heparin (LMWH) is contraindicated.

Antiplatelet therapy

The rate of VTE in trauma patients remains high despite mechanical and pharmacologic thromboprophylaxis. Moreover, many studies [14-16,27-34] showed that a high proportion of VTE events occurred while patients were under either mechanical or chemical prophylaxis.

On the other hand, several studies revolving about trauma patientsshowed changes in coagulation profile associated with both, the change in platelet levels and the initiation of thromboprophylaxis [28,29,33,34]. They assume that platelet function is a dominant contributor to trauma induced hypercoagulability, and hypothesize that antiplatelet therapy may be indicated in the management of severely injured trauma patients [28,29,33,34]. Similarly, the study by Harr., et al. [34], clearly showed that after injury, the increase in platelet count increased fibrin production and thrombus generation and had the strongest correlation with clot strength. They postulate that heparin activates platelets, and antiplatelet therapy may play an important role in thromboprophylaxis in trauma [34].

Fondaparinux

Fondaparinux is a synthetic, non-heparin drug, acting as an anti-factorXa inhibitor that has shown promise in reducing VTE in orthopedic patients. The indications of its use include DVT prophylaxis postoperatively in orthopedic as well as abdominal surgery, acute DVT treatment and acute PE treatment [23,31]. However, it has been less studied in the trauma population, and is not currently, indicated for post-traumatic VTE prophylaxis. In one series, fondaparinux was found to be an effective prophylactic agent for VTE, in high-risktrauma patients [35]. In fact, among the 87 enrolled patients, only 1 of 80 patients who received fondaparinux (1.2%) had developed DVT [35]. As a consequence, the authors had concluded that protection against VTE in high-risk trauma patients appears to be offered by Fondaparinux [35]. Also, they concluded that once-daily dosing treatment of Fondaparinux can improve compliance, reduce cost, and eliminate the risk of heparin-induced thrombocytopenia.

Novel oral anticoagulants

The novel oral anticoagulants (NOACs) are a new class of anticoagulant drug that can be used in the prevention of stroke for people with non-valvular atrial fibrillation and can also be used in the management of VTE. Two classes of NOACs are currently available, the oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban). These drugs are known to block the activity of one single step in coagulation contrary to VKAs that block the formation of multiple dependent factors of vitamin K [14,35].

Compared to enoxaparin, several studies including a systematic review of randomized controlled trials, found NOACs to be as effective as LMWH for venous thromboembolism prophylaxis in elective orthopedic surgeries and can be considered an alternative to conventional thromboprophylaxis [36-38]. However, until now, there are no studies demonstrating the efficacy and safety of NOACs in critically ill post-traumatic population.

IVC filters

Controversies still exist regarding the prophylactic use of IVC filters, and their use varies widely [39]. The more recent ACCP guidelines do not recommend prophylactic placement of an IVC filter in trauma patients [23]. IVC filters may cause serious complications including insertion site thrombosis, IVC thrombosis, hematoma, and filter migration in up to 5% of patients [39-43].

A recent meta-analysis from Haut., et al. concluded that prophylactic IVC filter placement was associated with a lower incidence of pulmonary embolism and of fatal pulmonary embolism in trauma patients [42]. In fact, in the eight included controlled studies compared the effectiveness of no IVC filter vs IVC filter on PE, fatal PE, deep vein thrombosis, and/or mortality in trauma patients, there is a consistent reduction of PE (relative risk, 0.20 [95% CI, 0.06 - 0.70]; and fatal PE (0.09 [0.01 - 0.81]; with IVC filter placement, without any statistical heterogeneity. However, there is no significant difference in the incidence of deep vein thrombosis (relative risk, 1.76 [95% CI, 0.50 - 6.19]; or in the total mortality (0.70 [0.40 - 1.23]). Finally, the strength of evidence was low. And it was unclear whether patients experience benefit enough to outweigh the harms associated with IVC filter placement.

Intracranial hemorrhage (ICH) and TBI peculiarities

Patients with TBI have an increased risk of VTE [44]. The timing of initiating thromboprophylaxis and dosage is not universally agreed upon. The most up-to-date review assessing the timing of pharmacological thromboprophylaxis in TBI, was a meta-analysis published in 2013 [44], concluding that early chemical prophylaxis reduces VTE risks without significantly increasing the risk of ICH progression and recommending, as such, the use of pharmacological prophylaxis within 72 h in the context of a stable follow-up CT [44].

Obesity and VTE prophylaxis

In light of recent advances in understanding the underlying pathophysiology of obesity-related thrombosis, there is hope that new antithrombotic therapies may emerge. Given the central role of chronic inflammation, a potential target is pro-inflammatory [45-47]. Aspirin, which has anti-inflammatory as well as antiplatelet effects, could be used to reduce cardiovascular and thrombotic risk in obese patients [45].

In addition, statins, due to their anti-inflammatory, antithrombotic and lipoprotein modulatory effects, could help decrease thrombotic risk in obese patients [46]. PAI-1 as another attractive target for antithrombotic therapy in obese patients was the subject of a recent study by Fjellstrom., et al [47]. They reported the successful development of a small molecule inhibitor of PAI-1. There are few other studies actively working to develop PAI-1 inhibitors, but these new protocols have not yet been tested in patients [48,49].

Pharmacological therapies targeting adipokines with antithrombotic properties, such as adiponectin and apelin, is another potentially promising field of research [50,51]. Finally, the observation that microRNAs play a role in regulating the thrombotic pathway in obesity, suggests other potential therapeutic approaches for the future [51,52]. More investigation is acquired before any of these new strategies could be clinically efficacious.

Timing of VTE prophylaxis initiation

Up until now, there are no clear data regarding the timing and dosing protocols of LMWH in thromboprophylaxis of the injured patients [19,20]. One might argue that the delay to initiating VTE prophylaxis could be associated to a greater risk of venous thromboembolic events. However, reports in the literature regarding this issue are mixed [50-53].

Benns and colleagues [51] found that patients with early PE were less likely to have had a delay in the initiation of DVT prophylaxis. In contrast, Owings., et al. [54] found that patients who did not receive prophylaxis had their PE diagnosed earlier. However, Brakenridge and coworkers [52] found no relationship between the timing of PE and the timing or type of DVT prophylaxis.

Although its presence did not probably prevent the occurrence of emboli, it is possible that chemical prophylaxis contributed to a lower thrombus extension and respiratory and hemodynamic impact in these patients. Finally, Clinical practice guidelines developed by the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma recognize the importance of early initiating thrombo-prophylaxis.

Conclusion

In summary, VTE prophylaxis seems to reduce the incidence of PE. However, the recent Cochrane review concluded that, contrary to DVT, thrombo-prophylaxis did not affect the rate nor mortality in pulmonary embolism. Clinical practice guidelines developed by the American College of Chest Physicians and the Eastern Association for the Surgery of Trauma recognize the importance of early initiation of thrombo-prophylaxis. The efficacy of the various types of prophylaxis used is still vigorously debated. The use of LMWH appeared to decrease the risk of DVT compared with LDUH. Although Guidelines lack specific recommendations regarding the timing, form and dosage of chemical prophylaxis, it was established that Enoxaparin doses of 40 mg once daily or 30 mg twice daily were both better than UFH 5,000 units three times daily in the prevention events and mortality of VTE. Moreover, the association between mechanical and pharmacological prophylaxis reduces significantly the risk of DVT. Future studies should evaluate the use of aspirin or other antiplatelet therapy, in conjunction with LMWH, for thrombo-prophylaxis in trauma patients.

Conflicts of Interest

We have no conflicts of interest to disclose.

Bibliography

1. Shuster R., *et al*. “Variables associated with pulmonary thromboembolism in injured patients: A systematic review”. *Injury* 49.1 (2018): 1-7.

2. Ruskin KJ. “Deep vein thrombosis and venous thromboembolism in trauma”. *Current Opinion in Anesthesiology* 31.2 (2018): 215-218.

3. Lichte P., *et al*. “Post-traumatic thrombo-embolic complications in polytrauma patients”. *International Orthopaedics* 39.5 (2015): 947-954.

4. Bahloul M., *et al*. “Early post-traumatic pulmonary-embolism in patients requiring ICU admission: more complicated than we think!”. *Journal of Thoracic Disease* 10.33 (2018): S3850-S3854.

5. Liou DZ., *et al*. "Defining early trauma-induced coagulopathy using thromboelastography". *The American Surgeon* 80.10 (2014): 994-998.

6. Shaz BH., *et al*. "Pathophysiology of Early Trauma-Induced Coagulopathy: Emerging Evidence for Hemodilution and Coagulation Factor Depletion". *Journal of Trauma - Injury, Infection and Critical Care* 70.6 (2011): 1401-1407.

7. Benns M., *et al*. "Early pulmonary embolism after injury: A different clinical entity?" *Injury* 45.1 (2014): 241-244.

8. Coleman JJ., *et al*. "Factors Associated with Pulmonary Embolism Within 72 Hours of Admission after Trauma: A Multicenter Study". *Journal of the American College of Surgeons* 220.4 (2015): 731-736.

9. Gelbard RB., *et al*. "Immediate post-traumatic pulmonary embolism is not associated with right ventricular dysfunction". *The American Journal of Surgery* 212.4 (2016): 769-774.

10. Menaker J., *et al*. "Incidence of early pulmonary embolism after injury". *The Journal of Trauma* 63.3 (2007): 620-624.

11. Brakenridge SC., *et al.* "Predictors of early versus late timing of pulmonary embolus after traumatic injury". *The American Journal of Surgery* 201.2 (2011): 209-215.

12. KazemiDarabadi F., *et al*. "Prevalence and main determinants of early post-traumatic thromboembolism in patients requiring ICU admission". *European Journal of Trauma and Emergency Surgery* 44.1 (2018): 133-136.

13. Bahloul M., *et al*. "Pulmonary embolism in intensive care unit: Predictive factors, clinical manifestations and outcome". *Annals of Thoracic Medicine* 5.2 (2010): 97-103.

14. Bahloul M., *et al*. "Les complications thromboemboliques post-traumatique: incidence, facteurs de risques, physiopathologie et prevention". *Annales de Cardiologie et d'Angéiologie* 66.2 (2017): 92-101.

15. Bahloul M., *et al*. "Post-traumatic pulmonary embolism in the intensive care unit". *Annals of Thoracic Medicine* 6.4 (2011): 199-206.

16. Bahloul M., *et al*. "Pulmonary embolism following severe traumatic brain injury: incidence, risk factors and impact outcome". *Intensive Care Medicine* 43.9 (2017): 1433-1435.

17. "Guideline developed in collaboration with the American College of Radiology, the Society of Pediatric Radiology, the Society of Radiologists in Ultrasound. AIUM Practice Guideline for the Performance of Peripheral Venous Ultrasound Examinations". *Journal of Ultrasound in Medicine* 34.8 (2015): 1-9.

18. Heijboer H., *et al*. "A comparison of real-time compression ultrasonography with impedance plethysmography for the diagnosis of deep-vein thrombosis in symptomatic outpatients". *The New England Journal of Medicine* 329.19 (1993): 1365-1369.

19. Daniel KR., *et al*. "Utility of lower extremity venous ultrasound scanning in the diagnosis and exclusion of pulmonary embolism in outpatients". *Annals of Emergency Medicine* 35.6 (2000): 547-554.

20. Pomero F., *et al*. "Accuracy of emergency physician-performed ultrasonography in the diagnosis of deep-vein thrombosis: a systematic review and meta-analysis". *Thrombosis and Haemostasis* 109.1 (2013): 137-145.

21. Barrera LM., *et al*. "Thromboprophylaxis for trauma patients. Cochrane Injuries Group". *Cochrane Database of Systematic Reviews* 28.3 (2013): CD008303

22. Adams RC., *et al*. "Four Years of an Aggressive Prophylaxis and Screening Protocol for Venous Thromboembolism in a Large Trauma Population". *Journal of Trauma - Injury, Infection and Critical Care* 65.2 (2008): 300-308.

23. Guyatt GH., *et al*. "Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines". *Chest* 141.2 (2012): 7S-47S.

24. Rogers FB., *et al*. "Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group". *Journal of Trauma* 53.1 (2002): 142-164.

25. Jacobs BN1., *et al*. "Unfractionated heparin versus low-molecular-weight heparin for venous thromboembolism prophylaxis in trauma". *Journal of Trauma and Acute Care Surgery* 83.1 (2017): 151-158

26. Gudipati S., *et al*. "A cohort study on the incidence and outcome of pulmonary embolism in trauma and orthopedic patients". *BMC Medicine* (2014): 12-39.

27. Cassidy MR., *et al*. "Reducing Postoperative Venous Thromboembolism Complications with a Standardized Risk-Stratified Prophylaxis Protocol and Mobilization Program". *Journal of the American College of Surgeons* 218.6 (2014): 1095-1104.

28. DeMuro JP. "Prophylaxis of Deep Venous Thrombosis in Trauma Patients: A Review". *Journal of Blood Disorders and Transfusion* 4.4 (2013): 151.

29. Heit JA., *et al*. "Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study". *Archives of Internal Medicine* 159.5 (1999): 445-453.

30. Geerts WH., *et al*. "A Comparison of Low-Dose Heparin with Low-Molecular-Weight Heparin as Prophylaxis against Venous Thromboembolism after Major Trauma". *The New England Journal of Medicine* 335.10 (1996): 701-707.

31. Paffrath T., *et al*. "Venous thromboembolism after severe trauma: Incidence, risk factors and outcome". *Injury* 41.1 (2010): 97-101.

32. Kornblith LZ., *et al*. "Fibrinogen and platelet contributions to clot formation: Implications for trauma resuscitation and thromboprophylaxis". *Journal of Trauma and Acute Care Surgery* 76.2 (2014): 255-263.

33. Allen CJ., *et al*. "Coagulation Profile Changes Due to Thromboprophylaxis and Platelets in Trauma Patients at High-Risk for Venous Thromboembolism". *The American Surgeon* 81.7 (2015): 663-668.

34. Harr JN., *et al*. "Platelets are dominant contributors to hypercoagulability after injury:". *Journal of Trauma and Acute Care Surgery* 74.3 (2013): 756-765.

35. Lu J-P., *et al*. "Fondaparinux for Prevention of Venous Thromboembolism in High-Risk Trauma Patients: A Pilot Study". *Journal of the American College of Surgeons* 209.5 (2009): 589-594.

36. Hinojar R., *et al*. "New oral anticoagulants: a practical guide for physicians". *European Heart Journal - Cardiovascular Pharmacotherapy* 1.2 (2015): 134-145.

37. Yoshida R de A., *et al*. "Systematic Review of Randomized Controlled Trials of New Anticoagulants for Venous Thromboembolism Prophylaxis in Major Orthopedic Surgeries, Compared With Enoxaparin". *Annals of Vascular Surgery* 27.3 (2013): 355-369.

38. Rostagno C. "New Oral Anticoagulants in Prophylaxis of Venous Thromboembolic Disease in Major Orthopedic Surgery". *Cardiovascular and Hematological Disorders - Drug Targets* 15.3 (2016): 204-209.

39. Dossett LA., *et al*. "Unwarranted National Variation in the Use of Prophylactic Inferior Vena Cava Filters After Trauma: An Analysis of the National Trauma Databank". *Journal of Trauma - Injury, Infection and Critical Care* 70.5 (2011): 1066-1071.

40. Lentz SR. "Thrombosis in the setting of obesity or inflammatory bowel disease". *Blood* 128.20 (2016): 2388-2394.

41. Gould MK., *et al*. "Prevention of VTE in Nonorthopedic Surgical Patients". *Chest* 141.2 (2012): e227S-e277S.

42. Haut ER., *et al*. "The Effectiveness of Prophylactic Inferior Vena Cava Filters in Trauma Patients: A Systematic Review and Meta-analysis". *JAMA Surgery* 149.2 (2014): 194.

43. Reiff DA., *et al*. "Traumatic Brain Injury Is Associated With the Development of Deep Vein Thrombosis Independent of Pharmacological Prophylaxis". *Journal of Trauma - Injury, Infection and Critical Care* 66.5 (2009): 1436-1440.

44. Jamjoom AAB and Jamjoom AB. "Safety and efficacy of early pharmacological thromboprophylaxis in traumatic brain injury: systematic review and meta-analysis". *Journal of Neurotrauma* 30.7 (2013): 503-511.

45. Frantz B and O'Neill EA. "The effect of sodium salicylate and aspirin on NF-kappa B". *Science* 270.5244 (1995): 2017-2019.

46. Ridker PM., *et al.* "Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein". *The New England Journal of Medicine* 359.21 (2008): 2195-2207.

47. Fjellström O., *et al*. "Characterization of a Small Molecule Inhibitor of Plasminogen Activator Inhibitor Type 1 That Accelerates the Transition into the Latent Conformation". *The Journal of Biological Chemistry* 288.2 (2013): 873-885.

48. Fortenberry YM. "Plasminogen activator inhibitor-1 inhibitors: a patent review (2006 – present)". *Expert Opinion on Therapeutic Patents* 23.7 (2013): 801-815.

49. Norris AW and Sigmund CD. "A Second Chance for a PPARγ Targeted Therapy?" *Circulation Research* 110.1 (2012): 8-11.

50. Lau WB., *et al*. "Role of Adipokines in Cardiovascular Disease". *Circulation Journal* 81.7 (2017): 920-928.

51. Benns M., *et al*. "Early pulmonary embolism after injury: A different clinical entity?" *Injury* 45.1 (2014): 241-244.

52. Brakenridge SC., *et al*. "Predictors of early versus late timing of pulmonary embolus after traumatic injury". *The American Journal of Surgery* 201.2 (2011): 209-15.

53. Howard VJ., *et al*. "The Reasons for Geographic and Racial Differences in Stroke Study: Objectives and Design". *Neuroepidemiology* 25.3 (2005): 135-143.

54. Owings JT., *et al*. "Timing of the occurrence of pulmonary embolism in trauma patients". *Archives of Surgery* 132.8 (1997): 862-866.

Volume 8 Issue 10 October 2019