Critically ill patients commonly face coagulation abnormalities. A number of parameters involved in such abnormalities are easily measurable and include thrombocytopenia, prolonged global coagulation times, reduced coagulation inhibitor levels, and the high fibrin split product levels. Thus, a proper and prompt identification of the causes of these abnormalities is necessary since different disorders call for different therapeutic measures. This article is a meta-analysis on the reduction of the risks of severe bleeding with the utility of ultrasound in the guiding of insertion of a central line for adult patients with deranged or unknown clotting profile in the emergency department.

Different causes of thrombocytopenia exist for patients within the emergency department. The most common causes include:

- ***Sepsis***

  The severity of sepsis is in direct correlation with the reduced number of platelet count. The main factors leading to sepsis in critically ill patients are impaired production of platelet, sequestration, destruction or increased platelet consumption by the spleen (Pierrakos & Vincent, 2010). Despite the high circulation of platelet production-stimulation pro-inflammatory thrombopoietin and cytokines, the bone marrow producing platelets production of platelets from the bone marrow in septic patients may seem contradictory. Marked hemaphogocytosis may however occur in patients with sepsis (Pierrakos & Vincent, 2010). The respective pathological process consists of hematopoietic cells and active phagocytosis of megakaryocytes through macrophages and monocytes responding to high macrophage colony stimulated by factor in sepsis. The most potent activator in vivo is thrombin with or without the presence of disseminated intravascular coagulation (DIC) (Hagel & Brunkhorst, 2011).

- ***Disseminated intravascular coagulation***

  The platelet count in patients with DIC is low or fast decreasing. DIC may therefore complicate a number of underlying disease processes including cancer, trauma, sepsis, or obstetrical calamities such as absorption of the placenta (HHS, 2010).

- ***Thrombotic microangiopathy***

  Syndromes included in the category of thrombotic microangiopathies include thrombotic thrombocytopenic purpura, severe malignant hypertension, hemolytic-uremic syndrome and chemotherapy-induced microangiopathy (Oberlander, 2014). The common feature for these clinical conditions appears to be endothelial damage caused by platelet aggression and adhesion. The clinical consequences of these endothelial consequences include mechanical fragmentation of red cells with hemolytic anemia and blocking of the brain, kidney and other organs (RICE, 2012).

- ***Heparin-induced thrombocytopenia (HIT)***

  HIT is caused by antibodies that induce heparin and bind the heparin-platelet-factor-4 on the complex of the platelet. This results in massive activation of the platelets followed by arterial, venous, and consumptive thrombocytopenia (Prechel & Walenga, 2012). The HIT incidence can be as high as 5% on patients who are currently on heparin and depends on the dose and type of heparin and the duration of its administration. Critically ill patients who were observed continuously revealed a 1% occurrence

of the incidence in their present setting. Low molecular weight heparin carries less risk of HIT than unfractioned heparin (Greinacher, 2015). Further, the risk of patients diagnosed with HIT having thrombosis is 40 times higher than patients without HIT. Also, the risk of developing absolute thrombosis is 25-60% with the risk of developing fatal thrombosis at 4-5%. The diagnosis depends on the HIT antibodies detection and the occurrence of thrombocytopenia on patients getting heparin (Solomon & Greinacher, 2015).

A meta-analysis of researches conducted

America College of Cardiology or America Heart Association (ACC/AHA) produced a report that outlines the basic components of Non-Cardiac Surgery. The systems provide guidelines, which apply to every patient intending to go through Non-Cardiac Surgery and any other types of surgeries. It is as well applied in Cardiovascular Evaluation. Millions of people across the world encounter cardiac problems (Fleisher, 2014). These always come as a result, of the surgery they undergo. After the surgery almost 2% of these people attain cardiac complications. Another bigger percentage exhibit signs of myocardial injuries. The system of Perioperative Beta Blockade tried to act as a means of avoiding these problems. They actually achieved certain impressive results. ACC/AHA recommended perioperative beta blockade for certain surgical patients. They applied Clinical Practice Guidelines (CPGs). This system operated in a way that certain patients were referred to perioperative beta blockade and some untreated patients with hypertension like cardiac risks and even coronary heart diseases were referred to the CPGs (Hoffmann, T., Buchan, 2013)

Perioperative beta blockade showed a positive result in the RCTs (A. W. Wallace, Au, & Cason, 2010). However, with time, several conditions arose that made the strength and validity of the recommendations set to decline. As a result, the successive measures brought by the CPGs started diminishing. RCTs had a subsequent decline as it could not reveal the benefits that perioperative beta blockade attained (Irani, 2013). A trial using more than 8000 patient confirmed that most of them benefited from perioperative beta blockade. However, the benefit was not that significant since they were only protected from perioperative MI. This benefit was accompanied by bad happenings for instance, death of patients was experienced. Other complications increased as well, and among these complications were bradycardia, stroke, and hypertension. The trial faced certain criticism across different health organizations. They felt that it was conducted with increased doses according to the beta blockers (Poldermans & Devereaux, 2009). The results of the trial confirmed that there was a bigger risk in applying perioperative beta blockade.

It is believed that there was a scientific misconduct in the trial. For this reason, two perioperative beta-blockade RCTs have been looked at for more confirmation (Preckel, Poels, Wappler, Schlack, & Buhre, 2010). CPGs are advised to re-evaluate the results and to assert that the results are data without substance or rather evidence. ACC/AHA came up with a task force that was to develop better guidelines. The task force recommended that there was need to review and confirm the available RCTs. To carry out these they recommended for an Evidence Review Committee to be set. This committee must be independent and free from interference of other bodies. This committee was to inform ACC/AHA about certain prospective they applied in the year 2014. ERC took this chance to attend to certain clinical matters. The main issue it was to assert was whether having beta blockade 40 days before Non-Cardiac Surgery could lead to a decline in perioperative cardiovascular mobility and even mortality after thirty days (Bakker, Ravensbergen, & Poldermans, 2011). ERC main objective was to confirm the evidence of the trial and to come up with a certain conclusion.

The methods attained in this report contain recommendations and Meta-Analysis data of ACC/AHA. It majorly contains the clinical practices and the guidelines to be applied. Certain eligible criteria are applied and in it, RCTs are used to compare inactive control situations against perioperative beta blockade (Flier, Buhre, & van Klei, 2011). Placebo is a right example of inactive control especially in adults who are 18 years and above. These adults must have been going through Non-Cardiac Surgery. Perioperative beta blocked was like a process carried out 45 days before the surgery (A. et al. Wallace, 2013). After the surgery beta blocked is again conducted. The treatment of the patients proceeded even after the surgery till the hospital confirms

the patient's condition is good. This was referred to as 'beta blockade therapy'.

Certain strategies applied on April 2013 used a database that precisely contains all the measures ERC applied. They as well applied the abstracts for other scientific researches for different organizations. These scientific organizations include America Society of Anesthesiology, Society of Cardiovascular Anesthesiologists , European Society of Anesthesiology, AHA , ACC, and Anesthesia Research Society (Blumenfeld, 2003). This strategy did not look at certain aspects of the abstracts. For instance, there were no language restrictions and even the unpublished tests were not looked for. However, they contacted some of the authors of the abstracts.

This report had certain methods of review and in this, they confirm the sources of the information to be legit, perfect, and reliable. There were groups of reviewers paired like D. Duncan and C. Nkonde-Price (Curtis, Sheerin, & Vries, 2011). These groups independently perform various studies by having study quality evaluation, data abstraction, and right screening. The abstracted information was to be in rightly tested form to prove the contents. Certain previous reports were used to compare them. These reports were from different countries including Canada, Ontario, and Ottawa among others. Some partners like Indico Clinical Guideline Platform were as well used (Parker & Smith, 2015). There was some conflicting information that led to disagreements. This was settled by consensus and where necessary the third party mediation was used. The eligible criteria made ERC's work to be much easier.

The criteria were set in that different statistics were taken to avoid confusion (Brady Germain & Cummings, 2010). For example, the forms of surgery, number of participants, beta blocker form of treatment, and the characteristics of participants. Features of participants looked at include, sex, age, coronary heart disease cases, and current angina. There was certain period set for follow up, in that the patients were to have checkup at certain times till the end of the period. RCT was scrutinized thoroughly and the number of patients having long-term beta-blocker treatment was taken to the RCT in time (Littlewood, 2011). The different events occurring after the thirty days of the surgery were reviewed to ensure there were no casualties. This act is referred to as nonfatal MI and this because certain bad outcomes such as acute stroke, cardiovascular death, bradycardia, and hypertension.

The quality of this study was conducted to confirm its contents and verify every other source. ACC/AHA ensures that every statement in the report is accurate and that various ideas have evidence backing them up. Through this, the content of the report is not bias and the study questions can be set directly and accurately. It will be easy to identify the required guidelines in case there will be need to implement the study. The relevance of the study is emphasized to articulate its content uniformly. This enables different readers to access the answers to their questions easily. RCT operation was to award the findings of the report some ratings. The overall rating was on the basis of whether the ideas in the report risk being bias and unreliable. In case of high risk of bias, the quality of the study is questioned (Petticrew, Chalabi, & Jones, 2012). ACC/AHA has certain guidelines that address every clinical issue across the world.

Statistical Data Analysis

The studies conducted analyses using the statistical software STATA Version 13 defining the statistical significance by a P value of <0.05 without making any changes for multiple comparisons (StataCorp, 2015). The study analyzed various studies with different methodical approaches to determine the effectiveness of initiating a beta blockade within 45 days before Non-Cardiac surgery in reducing the 30 – day cardiovascular mortality and morbidity rates. The RCTs and cohort studies were therefore analyzed separately. After assessing the statistical heterogeneity across various studies, it was established that it was characterized with I2 statistics. This described the proportion of total variation using the between-study variation thus implying more heterogeneity between studies than other statistical approaches.

Moreover, the study employed the random-effect model of Laird and DerSimonian in computing the pooled relative risks at 95% confidence interval (Altman & Bland, 2011). Before making any conclusions, the study had to examine the influence of DECREASE-I (Dutch Echocardiographic Cardiac Risk Evaluation Applying

Stress Echocardiography), POISE-1 (Perioperative Ischemic Evaluation), and DECREASE-IV on the final results. This was done by comparing the treatment effect within the DECREASE-I with the rest of the RCTs trials and later on comparing the treatment effects of POISE –1 trial with the group results of the remainder of the tests (Morey, Hoekstra, Rouder, Lee, & Wagenmakers, 2015).

The second analysis of the POISE - 1 concerning the pooled effect was meant to establish the presence of any signal of treatment effect which is independent of the whole RCT trial used in the meta – analysis. Furthermore, the study employed the random – effects regression to test for the stochastic significance of any subset treatment effects. The study used ERC funnel plots to ensure that there was no any publication bias among the analyzed studies (Luukkonen, 2012). Furthermore, the study found it necessary to assess any asymmetry in the plot using Eager's, Peter's and Harbord's.

Results

The analysis was carried out using 17 studies, 16 of which were RCT studies and only one cohort study. However, despite being only one study, the group gave paramount information concerning 384 participants. The Sixteen RCTs provided information for about 12043 members. Apart from the DECREASE-DECREASE-IV, and I all the remaining RCTs studies began the beta – blocker treatment for the patients one day before the surgery was carried out. Eight of the RCTs trials shown low – intermediate risk bias while fourteen of the total had medium to high relevance of the outcome, treatment and the population measures among the trials analyzed in the study. However, the cohort study did not indicate consistent study quality as assessed by the Newcastle – Ottawa Scale.

Nonfatal MI

All the RCTs gave effects on the nonfatal MI for the 11963 patients with perioperative beta blockade projecting an overall moderate decrease in the nonfatal MI according to an RR of 0.68 (95% CI: 0.57 to 0.81; P<0.001) with negligible statistical heterogeneity (Goldberger et al., 2010). The statistical significance of (P=0.08) was observed between the DECREASE trials and the rest of the RCTs trials. Removing the DECREASE trials had no significant effect on the pooled RR at 0.72 (95% CI: 0.59 to 0.86) without any qualitative differences between the POISE –1 trial and other RCTs.

In 10 trials, it was observed that the beta blockade resulted in a significant increase in the frontal stroke risks at an RR of 1.79 (95% CI: 1.09 to 2.93; P=0.02). However, the statistical heterogeneity was no statistically significant. Without the DECREASE trial, the effect on the POISE – 1 test was qualitatively indifferent from the other trials at (RR: 1.72; 95% CI:

0.67 to 4.40).

All – cause Deaths

The subgroup difference between the remaining RCTs and the DECREASE trials was statistically significant at (P=0.02) indicating an effect on the rates of the all – cause deaths among the 11963 participants in the 16 RCTs trials analyzed (Binswanger, Blatchford, Lindsay, & Stern, 2011). The beta blockade intervention on the DECREASE trials was observed to result in a reduced risk of all – cause death (RR: 0.42; 95% CI: 0.15 to 1.22; P=0.11). However, the beta blocker had an effect of increasing the risk of all-cause death among the remaining RCTs trials with a negligible statistical heterogeneity. The effects of the intervention in the POISE – 1 trials (RR: 1.33; 95% CI: 1.03 to 1.73) were similar to those of the remaining RCTs trials (RR: 1.17; 95% CI: 0.70 to 1.94) after the exclusion of the DECREASE trial.

Cardiovascular Death

These types of deaths were observed in 13 out of 17 trials with 11607 participants with relevant statistically significant with the p-values of (P=0.004) between the DECREASE trials and other RCTs trials (Ray, Murray, Hall, Arbogast, & Stein, 2012). According to the results, it was observed that the beta blocker

interventions were more effective in reducing the deaths arising from cardiovascular death risks among the DECREASE trial patients (RR: 0.17; 95% CI: 0.05 to 0.64; P=0.008). however, this was not the case with the rest of RCTs trials which recorded an increase in cardiovascular death risks at (RR: 1.25; 95% CI: 0.92 to 1.71; P=0.16).

Perioperative Adverse Effects

The adverse effects in this study were used to refer to risks involving heart failure and hypertension. Heart failure was observed in 13 of the trials comprising of 11378 patients. In all these trials, the beta blockade had no significant effect on the risks of perioperative heart failures at (RR: 1.15; 95% CI: 0.91 to 1.45; P=0.23) and insignificant statistical heterogeneity. Hypertension was observed in ten trials excluding the DECREASE IV and I (Svanström, Pasternak, & Hviid, 2013). Nine of the trials reported effects on perioperative hypertension among the 10448 participants. The beta blockers intervention increased the risks of perioperative hypertension without any qualitative variation in results between the POISE – 1 trial (RR: 1.55; 95% CI: 1.38 to 1.74) and the remaining RCTs trials (pooled RR: 1.37; 95% CI: 1.20 to 1.56). Moreover, it was observed that the risks of bradycardia were significantly increased among the patients receiving the beta blockade intervention in both the POISE – 1 trial (RR: 2.74; 95% CI: 2.19 to 3.43) and the rest of RCTs trials.

Post-Hoc Analysis

The ERC excluded the DECREASE trials and only used the remaining tests in conducting the post hoc analysis. Moreover, the study applied pooled RRs from the remaining trials to compute the numbers of the excess nonfatal MI, all-cause death, and nonfatal strokes per thousand of the population (Weiss, Blumenthal, Sharrett, Redberg, & Mora, 2010). Considering the baselines of 6%, 2% and 0.5% for nonfatal MI, all – cause death and nonfatal stroke respectively, the analysis established that nonfatal MI was reduced by 17, all – cause deaths increased by 6 and an excess of 4 nonfatal strokes for every 1000 population (Maryland & Gonzalez, 2012).

In overall, the visual inspection of funnel plots indicated no evidence of publication bias in all the risks examined apart from all – cause death and cardiovascular death that had some publication bias (Bezruchka, 2010).