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Abstracts

☐ THERAPEUTIC VERSUS PROPHYLACTIC ANTICOAGULATION FOR PATIENTS ADMITTED TO THE HOSPITAL WITH COVID-19 AND ELEVATED D-DIMER CONCENTRATION (ACTION): AN OPEN-LABEL, MULTICENTER, RANDOMIZED, CONTROLLED TRIAL

LOPES RD, MELO DE BARROS E SILVA PG, FURTADO RM, ET AL. LANCASTER 2021; 297: 2253-2263

Increased arterial and venous thrombotic events have been reported in patients with COVID-19 compared to those with other respiratory viruses. These thrombotic events are thought to be related to a thromboinflammatory state brought about by the virus. Observational data has suggested that starting patients on therapeutic or prophylactic anticoagulation on admission to the hospital may lower in-hospital mortality for patients with COVID-19. However, there is currently not enough data to know the optimal strategy in terms of type, dose, and duration of anticoagulation treatment.

This study aimed to determine whether therapeutic anticoagulation is effective in preventing complications in patients hospitalized with COVID-19 and elevated d-dimer concentrations. It was an open-label multicenter, randomized controlled trial in patients hospitalized in Brazil with COVID-19 diagnosis, symptoms for up to 14 days prior to randomization and elevated d-dimer concentrations. Patients were randomized via a 1:1 ratio in permuted blocks of variable size, stratified based on clinical condition (stable vs unstable) to either receive therapeutic anticoagulation for 30 days (with rivaroxaban if clinically stable, or with enoxaparin if clinically unstable) or prophylactic anticoagulation (with either enoxaparin or unfractionated heparin). Neither patients nor investigators were blinded to group allocation. The clinically unstable group received subcutaneous enoxaparin 1mg/kg twice per day or unfractionated heparin dosed to achieve a target anti-Xa concentration (0.3-0.7IU/mL). Once stabilized, these patients were transitioned to oral rivaroxaban dosed at 20mg daily. All patients in the therapeutic group continued treatment with rivaroxaban to day 30. The prophylactic group received standard venous thromboembolism prophylaxis dosing. If patients developed an indication for therapeutic anticoagulation, they were allowed to receive it. The prophylactic group of patients was only kept on anticoagulation while inpatient. Follow up was performed at 30 and 60 days.

The primary outcome studied was a hierarchical composite of time to death, duration of hospitalization or duration of supplemental oxygen use through 30 days. The primary safety outcome was major or clinically relevant non-major bleeding. Intention-to-treat analysis was used, and the primary outcome was reported using a win ratio method. Each patient in the treatment group was incrementally compared to each control patient to determine the “winners” or “ties” in relation to time to death, length of stay, and days of oxygen-free support in escalating challenges if “ties” occurred. The win ratio was then reported.

There were 310 patients in the therapeutic group’s and 304 patients in the prophylactic group’s primary analysis. Baseline characteristics were similar between the therapeutic and prophylactic groups. The total number of wins between the groups was not statistically different (win ratio 0.86, p=0.40, 95% CI 0.59-1.22) with 28,899 (34.8%) wins in the therapeutic group versus 34,288 (41.3%) wins in the prophylactic group. There were 19,837 (23.9%) ties. There was no statistical difference between the 8-point ordinal scale at day 30, disease progression measured on day 7, 15, and 30, or duration of invasive mechanical ventilation at the end of 30 days. There was also no statistical difference between individual thrombotic events or composite VTE, myocardial infarction, stroke, systemic embolism, or major adverse limb events. Differences remained insignificant when comparing clinically stable and unstable patients in each group. As to safety outcomes, there were 26 (8%) major or clinically relevant bleeding events in the therapeutic group compared to 7 (2%) in the prophylactic group (RR 3.64, 95% CI 1.61-8.27, p=0.001).

The authors concluded that therapeutic anticoagulation did not result in clinically better outcomes than prophylactic anticoagulation in the specific population of patients studied, and that therapeutic was in fact associated with a higher risk of major or clinically relevant bleeding than was prophylactic anticoagulation. They therefore recommended against using therapeutic anticoagulation in this population unless specifically indicated for other clinical reasons. The authors do note limitations such as performing follow-up interviews and pill counts over a phone call may have influenced their results or that the open label type study may have introduced bias although possibly mitigated by blind adjudication process.

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Comment: Thus far, there is a limited collection of data regarding the best management of hospitalized COVID-19 patients especially when considering thrombotic events. This study provides moderate quality evidence that therapeutic anticoagulation likely provides more harm than benefit and should not be used for patients with COVID-19 unless they are being treated for another indication. There is still much work to be done before we can definitively create high quality evidence practice guidelines on the role of anticoagulation in COVID-19 patients.

HYPOTHERMIA VERSUS NORMOTHERMIA AFTER OUT-OF-HOSPITAL CARDIAC ARREST
DANKIEWICZ J, CRONBERG T, LILJA G, ET AL. N ENGL J MED 2021;384:2283-94

Target temperature management (TTM), often defined as maintaining temperatures between 32°C and 36°C, is performed in an attempt to prevent adverse neurologic outcomes following cardiac arrest. This is currently recommended based on the existing evidence, but the current studies are of low methodologic quality with concern of bias and random error. There is a need for more robust analysis on the long-term effects of TTM.

The purpose of this randomized controlled trial is to determine if targeted hypothermia after out-of-hospital cardiac arrest affects outcomes at 6 months when compared with targeted normothermia. Between November 2017 and January 2020, enrollment was able to include 1,900 patients after screening. Inclusion criteria were age of 18 years or greater, hospital admission following out-of-hospital cardiac arrest (presumed cardiac or unknown in origin), unconscious, not following verbal commands, not verbally responding to painful stimuli, and at least 20 minutes of spontaneous circulation after successful resuscitation. Exclusion criteria comprised of time from return of spontaneous circulation (ROSC) to screening of 3 hours or greater and unwitnessed arrest with asystole as the initial recorded rhythm. The primary outcome of interest was all-cause mortality 6 months after cardiac arrest and ROSC. The main secondary outcome was a poor functional outcome at 6 months. This was measured utilizing the modified Rankin scale (0-6, with 0 being asymptomatic and 6 being death). Of note, this scale was made binary with 0-3 defined as “good” and 4-6 defined as “poor” for patients in which a more detailed assessment could not be performed secondary to the SARS CoV-2 pandemic. Additional secondary outcomes included number of days alive out of the hospital and health-related quality of life as measured using a visual-analogue scale.

A total of 1,850 patients were included in measurement of the study’s primary outcome: 925 in each group. In the hypothermia group, 465 patients (50%) had died by 6 months. In the normothermia group, 446 patients (48%) had died by 6 months (relative risk of 1.04; 95% CI 0.94 to 1.14). Per the modified Rankin scale, 54% of those in the hypothermia group were determined to have a poor functional outcome at 6 months (relative risk of 1.00; 95% CI 0.91 to 1.08). This is similar to the normothermia group, with 54% having a poor functional outcome. Quality of life and number of days alive out of the hospital were similar between the two groups. Additional reported data noted that hypothermia group had an increased frequency of arrhythmia but did not see an increased rate of pneumonia, sepsis, or bleeding.

The authors concluded that no significant difference existed between the hypothermia group and normothermia group with regards to death and functional outcome 6 months from the initial cardiac arrest. They state that these findings are less biased and more reproducible when compared with contrasting papers from prior studies. Limitations of this study include that additional treatment was similar between the groups which opens up the possibility of introducing confounding variables, knowledge of clinicians as to which group the patients belonged, lack of control group without target temperature management, and not assessing for causes of cardiac arrest other than out-of-hospital with presumed cardiac cause. Additionally, approximately half of patients that were in the normothermia group received some form of cooling during the course of their treatment which is still a form of TTM in the form of fever management. The use of TTM with cooling is coming under more scrutiny as a result of this and similar recent studies, and its use may need reconsideration.

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Comment: The study provides moderate quality evidence that the risks and costs outweigh the benefits of hypothermic TTM for this specific population of out of hospital cardiac arrest patients. This therapy does confer risk of clinically significant arrhythmias in patients undergoing TTM and is not benign in scope. The results of this study, when paired with similar recent studies, challenges the currently accepted standard of care for the treatment of out-of-hospital cardiac arrest using TTM.