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Editorial

What Primary Care Physicians Need to Know About Outpatient Anticoagulation Prophylaxis in Symptomatic but Stable Covid-19 Infection

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COVID-19 is a viral infection very well known to causes systemic inflammatory response. Hypercoagulable state with elevated levels of D dimer, fibrinogen and fibrin degradation products is thought secondary to this systemic inflammation [1]. Several observational studies have shown that these elevated markers correlate with increased rates of thromboembolic events and mortality rates [2]. However, no clear data available to compare outpatient stable and inpatient critically ill patients and guide appropriate treatment with anticoagulation.

As per CDC data, US recently surpassed 50 million covid cases and 800,000 deaths since the start of the pandemic. Most cases of COVID-19 infection are treated on an outpatient basis and very few limited treatment options are available at this time except for the monoclonal antibody treatment to prevent severe disease and hospitalizations.

In a trial by Goligher EC., *et al.* done in critically ill patients, therapeutic doses of heparin did not improve clinical outcomes and was associated with major bleeding when compared to routine prophylactic anticoagulation [3]. In a randomized clinical trial with data from ACTIV-4a, REMAP-CAP and ATTACC studies therapeutic dose anticoagulation showed improved survival until hospital discharge with decreased need for organ support. However, in contrast ACTION, INPIRATION and RAPID trials did not find any difference in outcomes [4]. Also, findings from RECOVERY trial showed that aspirin did not show any survival benefits in patients who are hospitalized with Covid-19 [6].

Very few studies are available currently to guide anticoagulation in outpatient treatment of Covid-19. ACTIV-4B Outpatient Thrombosis Prevention Trial is a randomized double blinded study done by National Heart, Lung, and Blood Institute (NHLBI) in 657 participants [5]. The study participants were randomized in a 1:1:1:1 ratio to aspirin (81 mg orally twice daily), therapeutic dose of apixaban (5mg orally twice daily), prophylactic dose of apixaban (2.5 mg orally twice daily) and placebo for 45 days [5]. The primary adjusted outcomes measured were all cause mortality, symptomatic venous and arterial thrombosis, stroke, myocardial infarction, and cardiovascular and pulmonary complications leading to hospitalization.

The absolute risk reduction compared with placebo for primary outcome were 0.0% in aspirin, 0.7% (95%CI -2.1 to 4.1) in the prophylactic dose of apixaban,1.4% (95% CI -1.5 to 5.1%) in the therapeutic apixaban group. No major bleeding events were reported in the trial [5].

Randomization remains the biggest strength of the trial, but the limited number of participants give us limited statistical power. Also, several factors such as participants who were vaccinated and got infected were also included and some infected with newer strains such as delta variant. Although, the interpretation of the study results is limited due to the above-mentioned facts, it still gives us some guidance in making an informed decision making with outpatient symptomatic patient population infected with Covid-19. Given that the study did not show any major improved outcomes in vascular and pulmonary events it is justifiable not to use aspirin or apixaban in treatment of these patient on an outpatient basis.

Early in the pandemic several observational studies have led several physicians to use anticoagulation in a variety of Covid-19 patients. Several randomized clinical trials gave us a better insight in the understanding of outcomes and yet, a lot of factors remain challenging such as new variants, vaccination status etc.

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