Letter to the Editor

An Update of Anticoagulant Strategies in Noncritically Ill Patients Hospitalized with COVID-19

Dear Editor,

Three years after the COVID-19 pandemic onset, the World Health Organization declared an end to the COVID-19 global public health emergency in May 2023. Given the hypercoagulable state associated with the disease, numerous studies have investigated the role of prophylactic or therapeutic anticoagulants in reducing mortality and thromboembolic events. However, optimal anticoagulation strategies for noncritically ill hospitalized patients with COVID-19 remain uncertain.

Previous large-scale studies have supported therapeutic-dose anticoagulation strategies in noncritically ill patients with COVID-19. In a 2021 study, the ATTACC, ACTIV-4a, and REMAP-CAP investigators demonstrated that therapeutic-dose anticoagulation improved survival to hospital discharge and reduced the need for cardiovascular or respiratory organ support compared with prophylactic-dose anticoagulation in noncritically ill patients (probability of therapeutic-dose anticoagulation superiority: 98.6%; adjusted odds ratio=1.27; 95% credible interval [CI], 1.03 to 1.58).[1]

At the beginning of 2023, a systematic review and meta-analysis was published, examining anticoagulation strategies in noncritically ill hospitalized patients with COVID-19.[2] In that study, which investigated 6 multicenter randomized controlled trials (RCTs), all-cause mortality and thrombotic events were significantly lower in patients treated with full-dose heparin-based anticoagulation than in those treated with prophylactic-dose anticoagulation (all-cause mortality: 6.2% vs 7.7%; risk ratio=0.76; 95% CI, 0.59 to 0.98; *P*=0.037 and thrombotic events: 1.5% vs 3.9%; risk ratio=0.41; 95% CI, 0.26 to 0.64; *P*<0.001, respectively).

One of the most recent studies on anticoagulation strategies for acute COVID-19 is the FREEDOM COVID-19 trial.[3] Its results may be pivotal in modifying anticoagulation strategies for noncritically ill hospitalized patients with COVID-19, as they contrast with previous studies. In that multicenter RCT, noncritically ill patients hospitalized with COVID-19 were assigned to 1 of 3 groups: prophylactic-dose enoxaparin, therapeutic-dose enoxaparin, or therapeutic-dose apixaban. After 30 days, there was no significant difference in the primary composite outcome of all-cause mortality, ICU requirement, and thromboembolic events between patients receiving prophylactic-dose anticoagulation and those receiving therapeutic-dose anticoagulation (13.2% in the prophylactic-dose group and 11.3% in the combined therapeutic-dose groups; hazard ratio: 0.85, 95% CI, 0.69 to 1.04; *P*=0.11). Moreover, subgroup analyses, including patients with diabetes mellitus, hypertension, and higher D-dimer levels, showed no significant difference in the primary outcome between the groups. The contrasting results of the FREEDOM COVID study with previous studies may be attributed to several factors. These include increased acceptance, availability, and use of vaccination and various anti-inflammatory and antiviral treatments during the second and third years of the pandemic, when the FREEDOM study was conducted. Previous studies primarily focused on the first year and early second year of the pandemic, when patients faced higher mortality and morbidity risks.

References

1. ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators; Lawler PR, Goligher EC, Berger JS, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med 2021;385:790-802.
2. Pilia E, Belletti A, Fresilli S, Lee TC, Zangrillo A, Finco G, Landoni G; full anticoagulation. The Effect of Heparin Full-Dose Anticoagulation on Survival of Hospitalized, Non-critically Ill COVID-19 Patients: A Meta-analysis of High Quality Studies. Lung 2023;201:135-147.
3. Stone GW, Farkouh ME, Lala A, Tinuoye E, Dressler O, Moreno PR, Palacios IF, Goodman SG, Esper RB, Abizaid A, Varade D, Betancur JF, Ricalde A, Payro G, Castellano JM, Hung IFN, Nadkarni GN, Giustino G, Godoy LC, Feinman J, Camaj A, Bienstock SW, Furtado RHM, Granada C, Bustamante J, Peyra C, Contreras J, Owen R, Bhatt DL, Pocock SJ, Fuster V; FREEDOM COVID Anticoagulation Strategy Randomized Trial Investigators. Randomized Trial of Anticoagulation Strategies for Noncritically Ill Patients Hospitalized With COVID-19. J Am Coll Cardiol 2023;81:1747-1762.

Mohammadreza Iranian, MD*

Iran University of Medical Sciences,

School of Medicine,

Rajaie Cardiovascular Medical and Research Center,

Vali-e-Asr Street,

Tehran,

Iran.

1995614331.

Tell: +98 21 23921.

Fax: +98 21 22042026.

E-mail: dr.m.iranian@gmail.com;

driranian@yahoo.com

Seyed Shahab Rostamkolaei, MD
Iran University of Medical Sciences,
School of Medicine,
Rajaie Cardiovascular Medical and Research Center,
Vali-e-Asr Street,
Tehran,
Iran.
1995614331.
Tell: +98 21 23921.
Fax: +98 21 22042026.
E-mail: S.rostamkolaei@gmail.com