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# EFFICACY AND SAFETY OF APIXAN (APIXABAN) COMPARED WITH RIVAROXABAN IN COVID PATIENTS

**Pathophysiology**

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## ABSTRACT

**Background:** Increased risk of thromboembolic manifestations associated with COVID-19 shown in recent literature. Several hypotheses have been suggested to understand the underlying pathophysiology behind development of a prothrombotic state in COVID-19 such as exaggerated inflammatory response resulting in activation of the coagulation cascade and endothelial injury. **Methods And Materials:** It was a prospective observational study, conducted in three tertiary care Private Hospitals of Chattogram City in Bangladesh. The study enrolled 253 consecutive outpatients from June 01, 2021 to May 31, 2022 due to Covid-19 disease on the basis of presentation of signs and symptoms severity. Upon admission, routine investigations, treatment and follow-up were carried out. Study population divided into two groups. In Apixan group, used only one brand drug tab. Apixan 5 mg twice daily and in Rivaroxaban group, used different brand of drugs 10 mg daily. **Results:** Mean age of the patients was 54.3±7.3 years. Between two groups, the predominant co-morbidity among patients was hypertension (74.0% vs 73.8%), followed by diabetes mellitus (53.5% vs 60.3%). Cough (95.2% vs 94.4%) was the most common symptom at presentation, followed by fever (86.6% vs 88.0%) and Fatigue (30.7% vs 30.2%), among cases of COVID patients. Maximum patients were mild illness 81.1 % vs 76.9% and severe cases 3.1% vs 7.1% which were statistically significant (p=0.046). Patients Apixan group received more ACEi/ARB (74% vs 73.8%), antiplatelet (22% vs 20.6%) and Rivaroxaban group received more anti-diabetic (60.3% vs 53.5%), Beta Blocker (56.3% vs 50.3%). All event rates were numerically higher in the rivaroxaban group of COVID-19 patients compared with apixan group. In the unmatched analysis, hypoxia/ Oxygen used 9 cases of Apixan group compared with Rivaroxaban group 24 cases (7.1% vs 19%, p- 0.005), Lower limb swelling (DVT) (3.9% vs 11.1%, p- 0.03) and others bleeding events (16.5% vs 26.1%, p-0.047) which were significant. In the term of primary outcome after propensity score matching (PSM), there were no significant differences in the risks of all-cause mortality (0.8% vs 1.6%, p-0.62), muscle spasm (47.2% vs 46%, p-0.847), fatigue (37% vs 43.7%, p-0.28) and hospital admission (6.3% vs 9.5%, p- 0.34). Likewise, there were no significant differences in the risk of myocardial infarction (MI) between both groups (1.5% vs 2.3%, p-0.85) and major bleeding (ICH/GI bleeding) (1.6% vs 3.9%, p-0.42). The risk of suffering an ischemic stroke/TIA at 90-days after medication was higher in Rivaroxaban group (0.8% vs 6.3%, p-0.02) which was clinically significant. **Conclusion:** In conclusion Rivaroxaban may be associated with an elevated bleeding risk and Apixan (Apixaban) may be associated with a lower bleeding risk with lower other events.

## KEYWORDS

%- Percentage, ACEi/ARB- Angiotensin converting enzyme inhibitor/ angiotensin receptor blocker, DVT- deep vein thrombosis, PSM- propensity score matching, ICH/TIA- intracranial haemorrage/transient ischaemic attack, GI- gastro-intestinal.

## INTRODUCTION

Rising incidence of thromboembolism secondary to COVID-19 has become a global concern, with several surveys reporting increased mortality rates. Thrombogenic potential of the SARS-CoV-2 virus has been hypothesized to originate from its ability to produce an exaggerated inflammatory response leading to endothelial dysfunction. Anticoagulants have remained the primary modality of treatment of thromboembolism for decades.[1]

The novel beta-coronavirus, appropriately named SARS-CoV-2 is associated with a broad spectrum of clinical respiratory illness, ranging from mild variety of upper respiratory tract infection to the severe form of disease such as, severe life-threatening pneumonia, acute respiratory distress syndrome (ARDS), sepsis, coagulopathy and death in a substantial proportion of patients.[2] Apart from the characteristic respiratory illness, it has also seen to be associated with florid extra-pulmonary manifestations.[3]

Over the past several months, an overwhelming amount of literature suggests an increased risk of thromboembolic manifestations associated with COVID-19.[4] Several hypotheses have been suggested to understand the underlying pathophysiology behind development of a prothrombotic state in COVID-19 such as exaggerated inflammatory response resulting in activation of the coagulation cascade and endothelial injury.[5-6]

Oral anticoagulants (OACs), including vitamin K antagonists (VKAs) and direct-acting OACs (DOACs), have been used for thrombo-prophylaxis in different clinical scenarios. In the pivotal clinical trials of stroke prevention in atrial fibrillation (AF), DOACs were non-inferior to warfarin for preventing stroke/systemic embolism (SE), with lower rates of intracranial hemorrhage (ICH) in comparison with warfarin. Similarly, in venous thromboembolism (VTE), dabigatran, rivaroxaban, apixaban and edoxaban were non-inferior to conventional therapy in terms of efficacy and caused less bleeding in a broad spectrum of patients. These trials evidences are supported by data from real world and observational studies, where DOACs have demonstrated significantly lower rates for major bleeding and a positive net clinical benefit compared to VKAs. In VTE patients, the use of DOACs has also been associated with a lower risk of VTE recurrence even after anticoagulant discontinuation.[7]

Coronavirus Disease 2019 (COVID-19) has shown to trigger endothelial dysfunction, inflammatory and hypercoagulable states. The risk of thrombosis is increased, and thromboembolic complications are relatively frequent in these patients, particularly in those patients with intensive care unit (ICU) admission. Thus, anticoagulation is now well-established for the management of COVID-19 patients.[7] However, a common limitation is that most of the evidence to date refers to the hospitalization context. Thus, it remains uncertain if prior OAC therapy in outpatients, especially amongst patients with multimorbidity, would potentially influence the severity and clinical outcomes after COVID-19 diagnosis.[7]

The aim of this study was to compare clinical outcomes after COVID-19 diagnosis between outpatients on DOAC (Apixan and Rivaroxavan) therapy at time of COVID-19 diagnosis, using a propensity score matching (PSM) approach

## METHODS

### Study Subjects And Design

The study was conducted in three tertiary care Private Hospitals of Chattogram division of Bangladesh includes- CSCR Hospital, Delta Health Care Chittagong Ltd. & Chevron Clinical Laboratories (pte) Ltd. The study enrolled 253 consecutive outpatients from June 01, 2021 to May 31, 2022 due to Covid-19 disease on the basis of presentation of signs and symptoms severity. All patients were diagnosed and graded as per the National guideline.[15] The diagnosis of COVID-19 was confirmed with real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Clinical data was collected by the attending physician during 1st visit and follow up time of patients within 3 months. Written informed consent was taken from the attendants and stable patients.

We divided all patients in two groups, Apixan (Apixaban) and Rivaroxaban group. In Apixan group, used only one brand drug tab. Apixan 5 mg twice daily and in Rivaroxaban group, used different brand of drugs 10 mg daily.

We compared persons older than 18 years of COVID-19 patients and received a new prescription for Apixan (Apixaban) 5 mg or rivaroxaban 10 mg between above study period. Lower dosages of either medication were not included, and we assumed that the dosing was twice daily for apixaban and once daily for rivaroxaban on the basis of their product monographs

The clinical data of patients were collected including demographics, clinical symptoms, and signs, co-existing conditions, imaging findings, laboratory results as per case record form.

### Patients Follow-up

Follow-up began the day after data entry and continued up to three months, the end of continuous health plan enrollment, the occurrence of a study outcome, discontinuation of the initial medication, a switch to the comparator, or death.

All baseline covariates were assessed by using information from up to three months preceding the date of entry. For each patient, data were collected reflecting diagnoses and procedures recorded during health encounters, including chronic medical conditions (such as hypertension and coronary artery disease), overall health care use (such as a recent hospitalization or an emergency department visit), and medications (such as anti-hypertensive and diuretics).

### Clinical Outcomes

Primary clinical outcomes included all-cause mortality, ICU admission/mechanical ventilation (MV) necessity, ICH/ gastrointestinal bleeding, and the composite of any arterial or venous thrombotic event (any of the following: myocardial infarction, other arterial thrombosis, VTE, or ischemic stroke/transient ischemic attack [TIA]/SE). The secondary outcomes were hospital admission, myocardial infarction, VTE, ischemic stroke/ TIA/SE, and all bleeding.

Our primary safety and effectiveness outcomes were defined by using the primary diagnosis code alone.

### Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD), and tested for differences with independent-sample t tests. Categorical variables were expressed as absolute frequencies and percentages, and tested for differences with chi-squared test. The TriNetX platform was used to run 1:1 PSM using logistic regression. The platform uses 'greedy nearest-neighbour matching' with a caliper of 0.1 pooled standard deviations and difference between propensity scores≤0.1. We assessed covariate balance between groups using standardized mean differences (SMDs). Any baseline characteristic with a SMD between cohorts lower than 0.1 is considered well matched [28]. Cox proportional Hazard Ratios (HRs) with 95% confidence intervals (CI) for 30-days outcomes were calculated following PSM. Kaplan–Meier survival curves were also produced with Log-Rank tests after PSM. No imputations were made for missing data. Two-sided p-values <0.05 were accepted as statistically significant. Analysis will be performed with SPSS, version 24.0 with 0.05 as a level of significance.

## RESULTS

Patients newly prescribed Apixan (apixaban) (n = 127) were slightly older, were more likely to have a diagnosis of hypertension or cardiovascular disease, and were receiving slightly more medications at baseline (Table I, IV). Patients newly prescribed rivaroxaban (n = 126) were likely to have a history of diabetes, smoking or hyperlipidemia and asthma/ COPD. (Table-1).

The study included 253 patients with a mean age of 54.3±7.3 years. Majority of them were male 178 (70.3%) with COVID patients. Both two group Apixan (Apixaban) and Rivaroxaban, male were predominant (75.6% vs 73.0%). About 38.7% (n=98) of the cases had co-morbidities. The predominant co-morbidity among patients was hypertension (74.0% vs 73.8%), followed by diabetes mellitus (53.5% vs 60.3%). Cough (95.2% vs 94.4%) was the most common symptom at presentation, followed by fever (86.6% vs 88.0%) and Fatigue (30.7% vs 30.2%), among cases of COVID patients. However, patients with severe disease had breathlessness (19.3%) as their principal presenting complaint. The demographic and clinical characteristics of the patients status are depicted in Table- 1.

**Table 1: Demographic and clinical characteristics of patients (n=253) with COVID-19 by outcome.**

| Characteristics | | Apixaban Group (n=127) | Rivaroxaban Group (n=126) | P value |
|---|---|---|---|---|
| Age, years Mean ±SD | | 52.9±16.2 | 54.6±16.2 | 0.398 |
| Sex | | | | |
| | Male | 96 (75.6) | 92 (73.0) | 0.639 |
| | Female | 31 (24.4) | 34 (27.0) | |
| BMI, ≥25Kg/m2 | | 68 (53.5) | 69 (54.8) | 0.898 |
| Comorbidity | | | | |
| | Any comorbidity | 102 (80.3) | 106 (84.1) | 0.428 |
| | Hypertension | 94 (74.0) | 93 (73.8) | 0.970 |
| | Diabetes mellitus | 68 (53.5) | 76 (60.3) | 0.277 |
| | COPD/Asthma | 40 (31.5) | 40 (31.7) | 0.966 |
| | IHD | 28 (22.0) | 26 (20.6) | 0.784 |
| | CVA | 3 (2.4) | 4 (3.2) | 0.694 |
| Currant smoker | | 16 (12.6) | 21 (16.7) | 0.298 |
| Symptoms | | | | |
| | Cough | 121 (95.2) | 119 (94.4) | 0.988 |
| | Fever | 110 (86.6) | 111 (88.0) | 0.435 |
| | Fatigue | 39 (30.7) | 38 (30.2) | 0.924 |
| | Sore throat | 33 (26.0) | 28 (22.2) | 0.484 |
| | Muscle ache | 36 (28.3) | 48 (38.1) | 0.100 |

*p<0.05, **p<0.01 (statistically significant)

Laboratory parameters focused on severity of diseases. Most of inflammatory parameter increased in moderate to severe cases of both groups (Apixan vs Rivaroxaban) like raised CRP (78.7% vs 79.4%), raised lymphocyte (60.6% vs 56.3%), increased Ferritin (68.5% vs 65.9%), D-dimer (60.6% vs 62.7%) and abnormal X-ray chest (44.1% vs 40.5%).

**Table II depicts that, significantly higher proportion of patients with abnormal laboratories parameter of both groups-.**

| Laboratory parameters | | Apixaban Group (n=127) | Rivaroxaban Group (n=126) | P value |
|---|---|---|---|---|
| | Raised lymphocyte | 77 (60.6) | 71 (56.3) | 0.490 |
| | Raised ESR | 49 (36.6) | 53 (42.1) | 0.573 |
| | Hemoglobin | 58 (45.7) | 57 (45.2) | 0.944 |
| | Platelet | 34 (26.8) | 28 (22.2) | 0.400 |
| | CRP | 100 (78.7) | 100 (79.4) | 0.903 |
| | Ferritin | 87 (68.5) | 83 (65.9) | 0.657 |
| | D-dimer | 77 (60.6) | 79 (62.7) | 0.735 |
| | SGPT | 58 (45.7) | 58 (46.0) | 0.954 |
| | Abnormal Chest X-ray | 56 (44.1) | 51 (40.5) | 0.560 |
| | Raised troponin-I | 61 (48.0) | 71 (56.3) | 0.185 |
| | Ischemia/MI on ECG | 35 (27.6) | 26 (20.6) | 0.198 |

*p<0.05, **p<0.01 (statistically significant)

Patients are categorized according to guidelines- mild, moderate and severe cases. Maximum patients were mild illness 81.1 % vs 76.9% and severe cases 3.1% vs 7.1% which were statistically significant (p=0.046). Table-III

**Table-III: Clinical severity of diseases in both groups of COVID patients-**

| Disease category | | Apixaban Group (n=127) | Rivaroxaban Group (n=126) | P value |
|---|---|---|---|---|
| | Mild | 103 (81.1) | 97 (76.9) | 0.046 |
| | Moderate | 18 (14.1) | 20 (15.8) | |
| | Severe | 06 (3.1) | 9 (7.1) | |

Table-III: Clinical severity :*p<0.05, **p<0.01 (statistically significant)

Patients have taken medicine according to their clinical diagnosis and complications. Most of patients need multiple drugs for clinical managements. Patients Apixan group received more ACEi/ARB (74% vs 73.8%), antiplatelet (22% vs 20.6%) and Rivaroxaban group received more anti-diabetic (60.3% vs 53.5%), Beta Blocker (56.3% vs 50.3%).

**Table IV: Treatment And Medication Of The Covid-19 Patients In Both Groups At Baseline**

| Characteristics | Apixaban Group (n=127) | Rivaroxaban Group (n=126) | P value |
|---|---|---|---|
| Antiplatelet | 28 (22.0) | 26 (20.6) | 0.619 |
| ACEi/ARB | 94 (74.0) | 93 (73.8) | 0.688 |
| Beta Blockers | 64(50.3) | 71 (56.3) | 0.047 |
| Statins | 36 (28.3) | 41 (32.5) | 0.940 |
| Blood Glucose regulation agents (including oral anti-diabetics and insulin) | 68 (53.5) | 76 (60.3) | 0.759 |

**Comparisons of clinical outcomes/events**

In the study populations, all event rates were numerically higher in the rivaroxaban group of COVID-19 patients compared with apixan group. In the unmatched analysis, hypoxia/ Oxygen used 9 cases of Apixan group compared with Rivaroxaban group 24 cases (7.1% vs 19%, p- 0.005), Lower limb swelling (DVT) (3.9% vs 11.1%, p- 0.03) and others bleeding events (16.5% vs 46%, p-0.04) which were significant. In the term of primary outcome after propensity score matching (PSM), there were no significant differences in the risks of all-cause mortality (0.8% vs 1.6%, p-0.62), muscle spasm (47.2% vs 46%, p-0.847), fatigue (37% vs 43.7%, p-0.28) and hospital admission (6.3% vs 9.5%, p- 0.34).

**Table V: Clinical and secondary outcome/adverse events observed in the follow-up period of the COVID-19 patients received anti-coagulant**

| Characteristics | Apixaban Group (n=127) | Rivaroxaban Group (n=126) | P value |
|---|---|---|---|
| All-cause mortality | 1 (0.8) | 2 (1.6) | 0.622 |
| Stroke/TIA | 1 (0.8) | 8 (6.3) | 0.020 |
| Lower limb Swelling (DVT) | 5 (3.9) | 14 (11.1) | 0.030 |
| Hospital admission | 8 (6.3) | 12 (9.5) | 0.342 |
| Myocardial Infarction (MI) | 2(1.5) | 3(2.3) | 0.857 |
| Hypoxia/ Oxygen use | 9 (7.1) | 24 (19.0) | 0.005 |
| Major Bleeding (ICH/GI) | 2(1.6) | 5 (3.9) | 0.427 |
| Other bleeding events (Coughed up/nasal/gum/bloody spot stool etc) | 21(16.5) | 33 (26.1) | 0.047 |
| Muscle spasm | 60 (47.2) | 58 (46.0) | 0.847 |
| Fatigue | 47 (37.0) | 55 (43.7) | 0.281 |

**Secondary Outcomes**

Hospital admission was not similar in Apixan and Rivaroxaban group of patients (6.3% vs 9.5%, p-0.34). Likewise, there were no significant differences in the risk of myocardial infarction (MI) between both groups (1.5% vs 2.3%, p-0.85) and major bleeding (ICH/GI bleeding) (1.6% vs 3.9%, p-0.42). (Fig. 1).

The risk of suffering an ischemic stroke/TIA at 30-days after medication was higher in Rivaroxaban group (0.8% vs 6.3%, p-0.02) which was clinically significant. (Fig. 1).

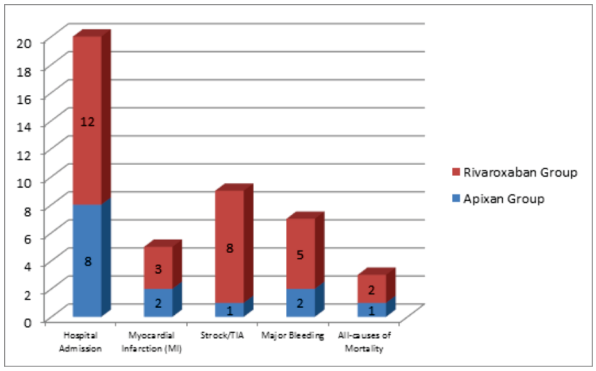


**Figure-1: Secondary outcomes comparison of both groups.**

## DISCUSSION

COVID-19 has been shown to cause cardiovascular morbidity by direct myocardial injury as a result of the inflammatory cascade or cytokine release, microvascular damage due to disseminated intravascular coagulation and thrombosis, direct entry of SARS-CoV-2 into myocardial cells via binding to ACE2 receptors, and hypoxemia combined with increased metabolic demands of acute illness leading to myocardial injury [8].

In this study including 253 outpatients, patients taking DOAC after COVID19 diagnosis and follow up for three months to see risk of any arterial/venous thrombotic event and ischemic stroke/ TIA/SE, compared to patients taking Apixan or Rivaroxaban, adjusting for comorbidities using PSM.

It is well established that COVID-19 increases the risk of arterial and venous thrombosis, leading to the research focus on thrombo-inflammation and antithrombotic therapy, particularly in anticoagulation therapy [7, 9, 10]. Many patients had preexisting cardiovascular diseases and were already on OAC therapy when they were diagnosed of COVID-19 [11]. Hence, the role of prior OAC therapy in the context of COVID-19 is gaining interest. For example, a recent study concluded that prior use of therapeutic anticoagulation was not associated with improved survival in hospitalized COVID-19 patients [12]. Similarly, a small study found that regular VKA use in hospitalized frail older patients with COVID-19 was associated with increased mortality during the frst week [13]. On the contrary, a retrospective study concluded that COVID-19 patients on OAC at the time of infection and throughout their disease course had signifcantly lower risk of all-cause mortality at 21 days [14]. Indeed, OAC therapy was associated with lower risk of all-cause mortality in elderly AF patients with COVID-19 [15], and more recently, the ACTION trial showed that among patients admitted with COVID-19 and elevated D-dimer, therapeutic anticoagulation was not superior to prophylactic anticoagulation; and rivaroxaban for stable patients and enoxaparin for unstable patients increased major bleeding without improving clinical outcomes [16,17].

In our study, Apixan group showed less major bleeding (1.6% vs 3.9%, p-0.42) and other bleeding events (16.5% vs 26.1%, p 0.047) than rivaroxaban group.

Several observational studies indirectly compared apixaban with rivaroxaban through a common comparator group that received warfarin [18–23]. Other observational studies directly compared patients receiving apixaban with those receiving rivaroxaban. One study found a decreased risk for major bleeding with apixaban relative to rivaroxaban. It did not identify a difference in the rate of stroke or systemic embolism; however, the study's small sample size (n = 6565 receiving apixaban) may have resulted in it being underpowered to detect this difference[24]. An industry-funded observational study of patients covered by Medicare or private insurance also reported a decreased risk for major bleeding with apixaban, as well as a decreased risk for stroke, with a point estimate similar to our findings[25]. Finally, a study of patients covered by Medicare identified a lower risk for bleeding with apixaban versus rivaroxaban but a similar risk for thromboembolic stroke [26].

In our study, apixan group showed less lower limb swelling (DVT) (3.9% vs 11.1%, p-0.03) and stroke or TIA (0.8% vs 6.3%, p-0.02) which was clinically significant.

Despite the possibility for unmeasured confounding in previous studies, our results are generally consistent with other cohort studies of bleeding risk with rivaroxaban and apixaban when used for stroke prevention in AF.[27–29,30,31] A meta-analysis of registry-based studies that compared bleeding risk with apixaban versus rivaroxaban, showed a 48% lower risk of bleeding with apixaban compared with rivaroxaban.5 Network meta-analyses using extrapolation of data from trials with warfarin as comparator, also showed increased risk of bleeding with rivaroxaban versus apixaban,[32,33] but different inclusion criteria and differences in quality of anticoagulation control with warfarin between the NOAC trials makes these analyses difficult.

In our study, Rivaroxaban group showed more all-cause mortality (0.8% vs 1.6%, p-0.62), myocardial infarction (MI) (1.5% vs 2.3%, p-0.5) and hospital admission (6.3% vs 9.5%, p-0.34) than apixan group which was not clinically significant.

Apixaban and rivaroxaban both act through direct, selective, and reversible inhibition of free and clotbound factor Xa. Anti–factor Xa levels may be used to estimate the plasma concentration of rivaroxaban or apixaban, with higher levels indicating higher drug concentrations[34]. A randomized study of healthy participants found that apixaban (5 mg twice daily), compared with rivaroxaban (20 mg once daily), was associated with more consistent and stable anti–factor Xa activity (that is, higher trough anti–factor Xa activity and lower peak anti–factor Xa activity). The lower peak anti–factor Xa levels in patients receiving apixaban might account for the lower rates of major bleeding, whereas the higher trough levels may explain the lower rates of stroke and systemic embolism. These proposed mechanisms are supported further by a recent study of patients with nonvalvular atrial fibrillation that showed lower peak prothrombin time (a measure associated with anticoagulant activity) and higher trough prothrombin time with apixaban compared with rivaroxaban[34].

### Limitations

The study had some limitations inherent to its design. As patients were selected purposively from selected outpatients their might be a chance of selection bias.

## CONCLUSION

In conclusion Rivaroxaban may be associated with an elevated bleeding risk and Apixan (Apixaban) may be associated with a lower bleeding risk with lower other events.

### Recommendations

The study findings could be used for early prescribing oral anticoagulant to prevent or lower thrombo-embolic complications of COVID19 patients. Close examination should be taken on clinical outcomes or events during managing such patients.

**Conflict Of Interest:** Nothing to declare.

## REFERENCES


1. Anticoagulation in COVID-19: current concepts and controversies, Atanu Chandra ,1 Uddalak Chakraborty ,2 Shrestha Ghosh,1 Sugata Dasgupta3 Postgrad Med J. 2022 May; 98(1159) :395-402. doi: 10.1136/postgradmedj-2021-139923. Epub 2021 Apr 13. (Link: https://pubmed.ncbi.nlm.nih.gov/33850011/).
2. Tu H, Tu S, Gao S, et al. Current epidemiological and clinical features of COVID-19; a global perspective from China. J Infect 2020;81:1–9.
3. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nat Med 2020;26:1017–32.
4. Miesbach W, Makris M. COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb Hemost 2020;26:107602962093814.
5. Ahmed S, Zimba O, Gasparyan AY. Thrombosis in Coronavirus disease 2019 (COVID-19) through the prism of Virchow's triad. Clin Rheumatol 2020;39:2529–43.
6. Bourgonje AR, Abdulle AE, Timens W, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol 2020;251:228–48.
7. Efficacy and safety of direct-acting oral anticoagulants compared to vitamin K antagonists in COVID-19 outpatients with cardio metabolic diseases José Miguel Rivera-Caravaca1,2,3, Stephanie L. Harrison1,4, Benjamin J. R. Buckley1,4, Elnara Fazio-Eynullayeva5 , Paula Underhill6 , Francisco Marín2 and Gregory Y. H. Lip1,4,7* Cardiovascular Diabetology volume 20, Article number: 176 (2021). Link:
8. Original Article Prognostic Value of Electrocardiographic Abnormalities and Troponin-I Elevation in Hospitalized COVID-19 Patients. Anisul Awal[1] , Kazi Shamim Al Mamun[2] , Mohammed Rezaul Karim[3] , Md Saif Uddin Azad[4] , Farid Uddin Ahmed[5]. link: https://www.banglajol.info/index.php/BHJ/article/view/56036
9. McBane RD 2nd, Torres Roldan VD, Niven AS, Pruthi RK, Franco PM, Linderbaum JA, et al. Anticoagulation in COVID-19: a systematic review, meta-analysis, and rapid guidance from Mayo Clinic. Mayo Clin Proc. 2020;95(11):2467–86.
10. Patell R, Chiasakul T, Bauer E, Zwicker JI. Pharmacologic thromboprophy- laxis and thrombosis in hospitalized patients with COVID-19: a pooled analysis. Thromb Haemost. 2021;121(1):76–85.
11. Gerotziafas GT, Catalano M, Colgan MP, Pecsvarady Z, Wautrecht JC, Fazeli B, et al. Guidance for the management of patients with vascular disease or cardiovascular risk factors and COVID-19: position paper from VAS-European Independent Foundation in angiology/vascular medicine. Thromb Haemost. 2020;120(1):1597–628.
12. Spiegelenberg JP, van Gelder M, Maas ML, Hovens MMC, Esselink A, Doferhof ASM, et al. Prior use of therapeutic anticoagulation does not protect against COVID-19 related clinical outcomes in hospitalized patients: a propensity score-matched cohort study. Br J Clin Pharmacol. 2021. https://doi.org/10.1111/bcp.14877.
13. Ménager P, Brière O, Gautier J, Riou J, Sacco G, Brangier A, et al. Regular use of VKA prior to COVID-19 associated with lower 7-day survival in hos- pitalized frail elderly COVID-19 patients: the GERIA-COVID cohort study. Nutrients. 2020;13(1):39.
14. Harrison RF, Forte K, Buscher MG Jr, Chess A, Patel A, Moylan T, et al. The association of preinfection daily oral anticoagulation use and all-cause in hospital mortality from novel coronavirus 2019 at 21 days: a retrospective cohort study. Crit Care Explor. 2021;3(1):e0324.
15. Denas G, Gennaro N, Ferroni E, Fedeli U, Lorenzoni G, Gregori D, et al. Reduction in all-cause mortality in COVID-19 patients on chronic oral anticoagulation: a population-based propensity score matched study. Int J Cardiol. 2021;329:266–9.
16. Lopes RD, de Barros ESPGM, Furtado RHM, Macedo AVS, Ramacciotti E, Damini LP, et al. Randomized clinical trial to evaluate a routine full anti- coagulation strategy in patients with coronavirus infection (SARS-CoV2) admitted to hospital: rationale and design of the ACTION (AntiCoagulaT- Ion cOroNavirus)-Coalition IV Trial. Am Heart J. 2021;238:1–11.
17. Lopes RD, Alexander JH. Coalition ACTION Trial: Randomized Clinical Trial To Evaluate A Routine Full Anticoagulation Strategy In Patients With Coro- navirus Infection (SARS-CoV-2) Admitted To Hospital. American College of Cardiology (ACC) meeting - ACC212021.
18. Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. J Am Heart Assoc. 2016;5. [PMID: 27412905] doi:10.1161/JAHA.116.003725
19. Martinez BK, Sood NA, Bunz TJ, et al. Effectiveness and safety of apixaban, dabigatran, and rivaroxaban versus warfarin in frail patients with nonvalvular atrial fibrillation. J Am Heart Assoc. 2018;7. [PMID: 29654196] doi:10.1161/JAHA.118.008643
20. Vinogradova Y, Coupland C, Hill T, et al. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. BMJ. 2018;362:k2505. [PMID: 29973392] doi:10.1136/bmj.k2505
21. Larsen TB, Skjøth F, Nielsen PB, et al. Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2016;353:i3189. [PMID: 27312796] doi:10 .1136/bmj.i3189
22. Amin A, Keshishian A, Trocio J, et al. Risk of stroke/systemic embolism, major bleeding and associated costs in non-valvular atrial fibrillation patients who initiated apixaban, dabigatran or rivaroxaban compared with warfarin in the United States Medicare population. Curr Med Res Opin. 2017;33:1595-1604. [PMID: 28635338] doi:10.1080/03007995.2017.1345729
23. Lip GYH, Skjøth F, Nielsen PB, et al. Effectiveness and safety of standard-dose nonvitamin K antagonist oral anticoagulants and warfarin among patients with atrial fibrillation with a single stroke risk factor: a nationwide cohort study. JAMA Cardiol. 2017;2:872-881. [PMID: 28614582] doi:10.1001/jamacardio.2017.1883
24. Noseworthy PA, Yao X, Abraham NS, et al. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. Chest. 2016;150:1302-1312. [PMID: 27938741] doi:10.1016/j.chest.2016.07.013
25. Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among nonvalvular atrial fibrillation patients. Stroke. 2018;49:2933-2944. [PMID: 30571400] doi:10.1161/STROKEAHA.118.020232
26. Graham DJ, Baro E, Zhang R, et al. Comparative stroke, bleeding, and mortality risks in older Medicare patients treated with oral anticoagulants for nonvalvular atrial fibrillation. Am J Med. 2019;132: 596-604.e11. [PMID: 30639551] doi:10.1016/j.amjmed.2018.12.023
27. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke. 2018;49:98–106. doi: 10.1161/STROKEAHA.117.018395
28. Staerk L, Gerds TA, Lip GYH, Ozenne B, Bonde AN, Lamberts M, Fosbøl EL, Torp-Pedersen C, Gislason GH, Olesen JB. Standard and reduced doses of dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation: a nationwide cohort study. J Intern Med. 2018;283:45–55. doi: 10.1111/joim.12683
29. Noseworthy PA, Yao X, Abraham NS, Sangaralingham LR, McBane RD, Shah ND. Direct comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in nonvalvular atrial fibrillation. Chest. 2016;150:1302–1312. doi: 10.1016/j.chest.2016.07.013
30. Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, Stein CM. Association of oral anticoagulants and proton pump inhibitorcotherapy with hospitalization for upper gastrointestinal tract bleeding. JAMA. 2018;320:2221–2230. doi: 10.1001/jama.2018.17242
31. Graham DJ, Reichman ME, Wernecke M, Hsueh YH, Izem R, Southworth MR, Wei Y, Liao J, Goulding MR, Mott K, Chillarige Y, MaCurdy TE, Worrall C, Kelman JA. Stroke, bleeding, and mortality risks in elderly medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation. JAMA Intern Med. 2016;176:1662–1671. doi: 10.1001/jamainternmed.2016.5954
32. López-López JA, Sterne JAC, Thom HHZ, Higgins JPT, Hingorani AD, Okoli GN, Davies PA, Bodalia PN, Bryden PA, Welton NJ, Hollingworth W, Caldwell DM, Savović J, Dias S, Salisbury C, Eaton D, Stephens-Boal A, Sofat R. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ. 2017;359:j5058. doi: 10.1136/bmj.j5058
33. Lip GY, Larsen TB, Skjøth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60:738–746. doi: 10.1016/j.jacc.2012.03.019
34. Effectiveness and Safety of Apixaban Compared With Rivaroxaban for Patients With Atrial Fibrillation in Routine Practice A Cohort Study Michael Fralick, MD, PhD, SM; Michael Colacci, MD; Sebastian Schneeweiss, MD, ScD; Krista F. Huybrechts, MS, PhD; Kueiyu Joshua Lin, MD, ScD, MPH; and Joshua J. Gagne, PharmD, ScD. Ann Intern Med. 2020 Apr 7;172(7):463-473. doi: 10.7326/M19-2522. Epub 2020 Mar 10.