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ORIGINAL RESEARCH

Effect of Ticagrelor Compared to Clopidogrel on Short-term Outcomes of COVID-19 Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention; a Randomized Clinical Trial

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Abstract: **Introduction:** Acute COVID-19 infection is associated with increased adverse clinical outcomes in patients with acute coronary syndromes (ACS). Given that some studies suggested improved pulmonary function with Ticagrelor, this clinical trial aimed to compare the effects of Ticagrelor versus Clopidogrel on the short-term outcomes of these patients. **Methods:** In this multicenter clinical trial, 180 COVID-19 patients with ACS who underwent urgent percutaneous coronary intervention (PCI) were randomized to receive Ticagrelor (180mg loading dose followed by 90mg twice daily, n=90) or Clopidogrel (600mg loading dose with 75mg daily, n=90), and then followed for one month after their procedure. The primary composite endpoint was a combination of all-cause mortality, myocardial infarction, and early stent thrombosis within the first month after stent implantation. **Results:** After thirty days of follow-up, the primary composite endpoint was non-significantly lower in the Ticagrelor compared to the Clopidogrel group (18.5% vs 23.5% respectively, p = 0.254). Based on the time-to-event analysis, the mean survival rate was 26.8 ±7.7 and 24.7 ±9.9 days, respectively, for the Ticagrelor and the Clopidogrel arms (Log-rank p = 0.275). Secondary endpoints were similar in the two trial arms, except for the mean oxygen saturation, which was higher in the Ticagrelor group (95.28 ±2.68 % vs. 94.15 ± 3.55 %, respectively; p = 0.021). **Conclusion:** Among COVID-19 patients with concomitant ACS, who were treated with urgent PCI, the composite outcome of death, myocardial infarction, and early stent thrombosis was not different between Ticagrelor and Clopidogrel groups. However, administration of Ticagrelor was associated with a slight but statistically significant increase in oxygen saturation compared to Clopidogrel, but this difference wasn't clinically important.

Keywords:COVID-19; Myocardial infarction; Percutaneous coronary intervention; Ticagrelor

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1. Introduction

The novel coronavirus disease, known as COVID-19 (coronavirus disease of 2019), is caused by the SARS-Cov-2 virus. It supposedly originated in Wuhan, China in December 2019, and since then, has led to a pandemic in the whole world, with significant medical, social, economic, and political consequences for almost all countries (1). COVID-19 mainly affects the lungs and leads to interstitial pneumonitis, which may be followed by respiratory distress syndrome. However, in more severe cases, it may lead to multi-organ failure and death (2).

The cardiovascular system has demonstrated an important role in the disease course. While preexisting cardiovascular disease worsens the outcomes of the COVID-19 infection and increases its morbidity and mortality rates, it can also result in serious cardiovascular problems by itself, such as acute coronary syndrome (ACS), cardiac arrhythmia, heart failure,

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myocarditis, etc. (3, 4).

Among these, ST-elevation myocardial infarction (STEMI) is specifically important due to its high burden of adverse outcomes. According to studies in many countries, during the pandemic, different aspects of STEMI, including time from symptoms to arrival at the hospital, first medical contact to wiring time, periprocedural complications, and short-term and long-term cardiovascular outcomes have changed (5-11). Multiple studies have shown that COVID-19 increases hypercoagulability in both arterial and venous systems (12-15). Stent thrombosis, a serious post-percutaneous coronary intervention (PCI) complication with a high rate of cardiac events and mortality, is frequently reported in these studies. Therefore, the selection of the P2Y12 inhibitor agent (a drug that inhibits the adenosine diphosphate receptor in the platelet membrane) in such circumstances would be a crucial factor. As shown in the PLATO trial, in ACS patients, subjects who were treated with ticagrelor, had significantly lower rates of death, myocardial infarction, and cerebrovascular events in comparison with clopidogrel, without an increased rate of major bleeding (16). These results were also demonstrated in a study of the SWEDEHEART registry (17).

Furthermore, in a subgroup analysis of the PLATO trial, performed on the patients with pulmonary events and sepsis, the authors concluded that mortality risk after pulmonary events and sepsis in ACS patients tends to be lower in the Ticagrelor group compared to the Clopidogrel group (18). Since COVID-19 mainly affects the lungs and in severe cases, leads to pulmonary-related sepsis, this interesting result encouraged us to design a randomized clinical trial to investigate the potential benefits of ticagrelor over clopidogrel, including lower rates of mortality and morbidity (myocardial infarction, stent thrombosis, hospitalization duration) and also improved pulmonary function parameters such as arterial oxygen saturation, in concomitant ACS and COVID-19 patients. Based on this, we decided to conduct a study to compare cardiovascular outcomes, especially stent thrombosis, after PCI for ACS patients with concomitant COVID-19, between groups that took clopidogrel, versus ticagrelor as P2Y12 inhibitors.

2. Methods

2.1. Study design and setting

This randomized controlled trial was designed to compare dual antiplatelet therapy after PCI in subjects who had COVID-19 infection at the time, and presented to the emergency departments of Artesh 501, Artesh 502, and Be'sat Hospitals, affiliated to Aja University of Medical Sciences, Tehran, Iran. Subjects were randomized with a 1:1 ratio to receive either Ticagrelor or Clopidogrel, as their second antiplatelet drug. During the study, patients were aware of the prescribed drugs, but the physicians and investigators who analyzed the data were blinded to the trial groups and interventions. The scheme of this trial was approved by the Research Ethics Committee of the School of Medicine, Aja University of Medical Sciences (IR.AJAUMS.REC.1400.233). Written informed consent was obtained for participation in the study. The study protocol and design have been registered in the Iranian Registry of Clinical Trials (IRCT20220813055675N1).

2.2. Participants

Subjects with the diagnosis of ACS (ST-elevation MI or Non-ST-elevation MI) who were scheduled for emergent invasive strategy treatment (coronary angiography and angioplasty), and had concurrent active COVID-19 infection, were enrolled in the study. The COVID-19 disease was confirmed either by a positive CT scan of the lungs, or a positive PCR test. The exclusion criteria of the participants were: 1- Age<18 years, 2- Lack of patient consent to perform coronary angiography, 3- Severe heart failure (Left ventricular Ejection Fraction<30%), 4- Severe renal failure (glomerular filtration rate (GFR)<15), 5- Severe liver failure, 6- History of any malignancy, chemotherapy, or radiotherapy, 7- History of any intracranial or intraspinal hemorrhage, 8- Pregnancy or suspicion of pregnancy, 9- Chronic consumption of any anticoagulation drug by the patient, and 10- Critical COVID-19 disease, which inhibits us to perform invasive treatment due to moribund condition. Since this was the first trial to compare the differences between ticagrelor and clopidogrel in the setting of ACS and COVID-19 and specially to investigate the potential benefits of ticagrelor in acute pulmonary-induced sepsis, it was designed based on a pilot study and conducted with a sample size of 80 subjects in each group. Regarding possible missing data or patient loss to follow-up, a safety margin of 10% was adopted, so eventually, a total of 176 patients (88 in each trial arm) were considered to enroll in the study.

In terms of the COVID-19 status, the determination of pulmonary disease severity was based on the 2022 CDC COVID-19 guidelines, which define severe illness as having arterial oxygen saturation < 94% on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PiO2/FiO2) < 300 mmHg, a respiratory rate > 30 /min, or lung infiltrate > 50%. In the absence of all of these criteria, the disease status was rated as a non-severe illness.

2.3. Interventions

Except for the P2Y12 inhibitor drug, all individuals regardless of their group received the standard guideline-directed medical treatment for ACS, and the coronary interventions were done in the same way for both groups. Two arms of the trial consisted of one group who were taking 180 milligrams of Ticagrelor (BRILAVUS®, Abidi Pharmaceutical Co.) at the

time of admission, followed by a daily dose of 90 milligrams every 12 hours for one year; and the other group who received 600 milligrams of Clopidogrel (PLAVIX®, Abidi Pharmaceutical Co., licensed by Sanofi) for loading dose, followed by a maintenance dose of 75 milligrams every 24 hours for one year. All the other prescription drugs and interventions were identical in both trial groups. All medications were administered in the emergency department by an expert nurse under the supervision of an emergency medicine specialist. Therefore, patients were divided into their groups before the entrance to the catheterization laboratory, and the interventional cardiologist who performed PCI procedures was unaware of the premedication drugs, also the person who was in charge of statistical analysis was blind to the type of drugs used. The Simple randomization process was done using a random numbers table, that was generated via the Research Randomizer website "https://www.randomizer.org/".

2.4. Study protocol

Participants in placebo (n=42) and Citrulline (n=40) groups received 10 gram/day Microcrystalline cellulose and L-Citrulline powder (Karen Pharma & Food Supplement Co., Iran) for 7 days, respectively. Blood samples were drawn before and after the 7-day intervention. Acute-phase proteins (APPs) as immunology factors, complete blood count (CBC), blood urea nitrogen (BUN), creatine, albumin, glycemic status, lipid profile, and liver function were determined before and after the intervention.

Demographic characteristics, physiological variables, and other clinical and laboratory data were collected. Data on the days with mechanical ventilation were collected within 28 days.

Enteral feeding started for all patients within 24-48 hours of admission in hospital. All subjects received the same Hospital Prepared Enteral Formulation (HPF), which contained 42.8% carbohydrates, 16.6% protein, and 34.2% fat.

2.5. Outcomes

The primary efficacy endpoint was the composite of all-cause mortality, the occurrence of myocardial infarction, or stent thrombosis during the index hospitalization or follow-up period (one month). The secondary efficacy endpoints were death from any cause alone, the occurrence of myocardial infarction alone, acute or subacute stent thrombosis (defined as occurring 0-24 hours and within 30 days after PCI, respectively), the duration of the patient's hospitalization, the mean of arterial oxygen saturation during the main admission, the "neutrophil-to-lymphocyte ratio" (NLR) and the "platelet-to-lymphocyte ratio" (PLR), two indices that are considered to be related with COVID-19 infection severity. Subjects were followed for one month after their hospital admission.

2.6. Blinding

In this clinical trial, blinding was applied on two levels: the researchers and the data analyzer. The researchers included an interventional cardiologist who performed PCI procedures and a general cardiologist who was in charge of the randomization process and assigned participants to the interventions. The patients were aware of the types of drugs that were prescribed because they used them at least for one year on a daily basis. The data processor was blind to the type of drug administered for each trial arm.

2.7. Statistical Analysis

The statistical analysis was done based on the intention-to-treat method and applied to all the subjects who were initially randomized, but also, performed a per-protocol analysis, which had the same findingss, because of the small number of total missed subjects. The Kolmogorov-Smirnov test was used to evaluate the distribution of the continuous numerical variables. The normally distributed variables were reported as the mean and standard deviation and non-normal variables as the median with 25th, and 75th quartiles. To examine the difference of continuous variables between the two groups, the student's t-test, and the non-parametric two independent samples test were used, respectively, for the normal and the skew-distributed variables. Qualitative variables were reported as frequencies in their related group, and the Chi-Square or Fisher's exact tests were performed to analyze their inter-group differences.

The Mann-Whitney U test was applied to compare the primary composite endpoint between two trial arms. The time to death was reported using the Kaplan-Meier method and the difference was evaluated via the log-rank test. All of the statistical analyses were performed with the IBM SPSS Statistics Software for Windows, version 26. The significance level was determined at a p-value<0.05.

3. Results

3.1. Trial population

A total of 256 patients were considered to enroll in this study, from June 2022 to September 2022, of whom 76 individuals had the exclusion criteria, and finally, 180 patients were assigned to randomized trial groups (Figure 1). During follow-up, ten subjects were excluded from the study due to loss to follow (one in the Clopidogrel group and nine in the Ticagrelor group). The baseline and procedural characteristics of the patients are shown in Table 1. The mean age of the participants was 59.4±12.5 and 60.9±12.4 years in the clopidogrel and ticagrelor groups, respectively. There was a male predominance in both groups, with 73% of patients in the clopidogrel and 79% of people in the ticagrelor group being

Table 1: Baseline characteristics of the total population

Age (years)	59.4 ± 12.5	60.9 ± 12.4	0.460
Gender			
Male	65 (73.0)	64 (79.0)	0.363
BMI (kg/m^2)	28.6 ± 4.9	27.6 ± 4.3	0.179
Ejection Fraction (%)	37.4 ±5.9	39.0 ± 6.5	0.158
COVID-19 Status			
Non-Severe disease	68 (76.4)	62 (76.5)	0.983
Severe disease	21 (23.6)	19 (23.5)	
Cardiovascular Risk Factor			
Diabetes	40 (44.9)	46 (56.8)	0.123
Hypertension	44 (49.4)	37 (45.7)	0.624
Dyslipidemia	45 (50.6)	41 (50.5)	0.994
Family History	43 (48.3)	45 (55.6)	0.345
Cigarette Smoker	33 (37.1)	31 (38.3)	0.873
Opium Addiction	13 (14.6)	18 (22.2)	0.199
Laboratory Tests			
Triglyceride (mg/dL)	129.2 ± 73.4	151.4 ± 104.2	0.132
Total Cholesterol (mg/dL)	155.6 ± 43.0	158.5 ± 45.3	0.668
HDL Cholesterol (mg/dL)	40.1 ± 10.4	40.4 ± 9.4	0.873
LDL Cholesterol (mg/dL)	96.8 ± 34.0	97.0 ± 35.0	0.960
Fasting BS (mg/dL)	141.1 ± 77.8	155.6 ± 73.6	0.190
Creatinine (mg/dL)	1.2 ± 0.7	1.1 ± 0.2	0.519
Hemoglobin (g/dL)	14.70 ± 2.0	14.75 ± 1.8	0.849
White Blood Cells ($*10^6$/L)	11937.6 ± 3487.3	10941.1 ± 3503.2	0.065
Lymphocyte (%)	21.7 ± 11.5	23.1 ± 12.7	0.555
Platelet ($*10^6$/L)	247321.3 ± 61704.3	234839.5 ± 65281.4	0.116
Physical Examination			
Systolic BP (mmHg)	135.4 ± 27.9	138.2 ± 25.9	0.505
Diastolic BP (mmHg)	86.0 ± 16.9	88.1 ± 18.8	0.447
Heart Rate (beat/min)	83.8 ± 16.5	86.7 ± 18.2	0.398
Procedural Properties			
Stent Length (mm)	32.8 ± 9.9	30.4 ± 8.8	0.304
IIb/IIIa Inhibitors	58 (65.2)	44 (54.3)	0.149
Slow Flow CAD	25 (28.1)	18 (22.2)	0.379
Thrombo-suction	10 (11.2)	6 (7.4)	0.393
Baseline TIMI			
0	60 (67.4)	54 (66.7)	
1	1 (1.1)	2 (2.5)	0.312
2	10 (11.2)	15 (18.5)	
3	18 (20.2)	10 (12.3)	
Final TIMI			
0	1 (1.1)	1 (1.2)	
1	2 (2.2)	4 (4.9)	0.713
2	22 (24.7)	16 (19.8)	
3	64 (71.9)	60 (74.1)	
Blush Grade			
0	6 (6.7)	8 (9.9)	
1	18 (20.2)	14 (17.3)	0.873
2	31 (34.8)	28 (34.6)	
3	34 (38.2)	31 (38.3)	
Thrombus Burden			
0	9 (10.1)	4 (4.9)	
1	13 (14.6)	13 (16.0)	
2	14 (15.7)	21 (25.9)	0.502
3	26 (29.2)	22 (27.2)	
4	4 (4.5)	2 (2.5)	
5	23 (25.8)	19 (23.5)	

Data are presented as mean ± standard deviation or frequency (%). BMI: body mass index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; BS: blood sugar; BP: blood pressure; CAD: coronary artery disease; TIMI: thrombolysis in myocardial infarction.

Table 2: Rates of the primary and secondary endpoints during follow-up

Outcomes	Clopidogrel (N=89)	Ticagrelor (N=81)	P-value
Primary Composite Endpoint*			
Frequency (%)	23 (25.8)	15 (18.5)	0.254
Secondary Endpoints			
All-cause mortality	21 (23.6)	14 (17.3)	0.309
Myocardial infarction	3 (3.4)	1 (1.2)	0.359
Stent thrombosis	3 (3.4)	1 (1.2)	0.359
Hospitalization duration (days)	4.84 ± 2.34	4.30 ± 2.08	0.161
Oxygen saturation (%)	94.15 ± 3.55	95.28 ± 2.68	0.021
NLR	4.98 ± 4.31	4.54 ± 3.65	0.585
PLR	133.02 ± 91.4	135.70 ± 97.16	0.904

Data are presented as mean ± standard deviation or frequency (%). *: All-cause mortality, myocardial infarction, or stent thrombosis; NLR: neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio.

male. About 76.5% of all subjects in both groups were at the non-severe stage of COVID-19 disease at the time of randomization. As illustrated in Table 1, there was no statistical difference between trial arms in any of the characteristics.

3.2. Primary endpoint

As seen in Table 2, at 30 days of follow-up, the primary endpoint (composite of all-cause mortality, myocardial infarction, or stent thrombosis) occurred in 24 (25.8%) subjects in the Clopidogrel arm, compared to 15 (18.5%) cases in the Ticagrelor arm (p = 0.254). Furthermore, the mean survival rate during the first month after the patient's admission was 24.7 (95% CI=22.6, 26.7) and 26.8 (95% CI= 25.1, 28.5) days, respectively, for the Clopidogrel and the Ticagrelor groups (figure 2; p = 0.275).

3.3. Secondary endpoints

According to Table 2, all-cause mortality occurred more frequently in the Clopidogrel arm than in the Ticagrelor arm (23.6% versus 17.3%, p=0.309). Moreover, the occurrence of myocardial infarction was lower in the Ticagrelor group (1.2% versus 3.4%, p=0.359). Since all myocardial infarctions in both trial arms were due to stent thrombosis, the results for stent thrombosis were the same as the results of myocardial infarction. Yet, all these inter-group differences were not statistically significant. This also applies to the other secondary endpoints including the duration of hospitalization (p=0.161), the NLR (p=0.585), and the PLR (p=0.904) indices. However, the arterial oxygen saturation differed, as patients in the Ticagrelor group had a statistically significant higher mean oxygen saturation during their hospitalization compared to the Clopidogrel group, nevertheless, the difference wasn't clinically remarkable (95.28 ± 2.68 % versus 94.15 ± 3.55 %, respectively, p=0.021).

4. Discussion

In this randomized clinical trial, we found that in patients who presented with ACS and had been treated with PCI, while concomitantly having active COVID-19 infection, Ticagrelor was associated with statistically non-significant lower rates of combined all-cause mortality, myocardial infarction, and stent thrombosis one month after the procedure. However, despite individuals in the Ticagrelor group having statistically significant higher mean arterial oxygen saturation during the index hospitalization, this difference was not clinically important. Many reports indicate early (within the first month), late (30 days to one year), and very late (beyond the first year) stent thrombosis after PCI in patients with concomitant COVID-19 disease (15, 19-27). A study by Hamadeh et al. showed that early stent thrombosis occurred in 21% (5 out of 24) of STEMI patients who were treated with primary PCI (28). Hypothetically, the higher incidence of thrombotic events during systemic viral inflammatory states may be related to hypercoagulability mechanisms such as immune-mediated thrombotic conditions, macrophage activation, complement activation, anti-phospholipid syndrome, and dysregulation of the renin-angiotensin-aldosterone system (13). However, stent thrombosis could lead to an increased rate of morbidity and mortality. In our study, one of the three patients who had early stent thrombosis in the Clopidogrel arm died due to unsuccessful revascularization and following persistent cardiogenic shock; the two other patients and one subject with stent thrombosis in the Ticagrelor group underwent successful urgent coronary angioplasty and survived. Even though Ticagrelor decreased early stent thrombosis in our study, it was not statistically significant, maybe due to the small number of events.

COVID-19 patients experience flu-like symptoms such as fever, fatigue, and cough. As the disease progresses, shortness of breath, dyspnea, and in severe cases, decreased arterial oxygen saturation, lymphopenia, and ground glass opac-

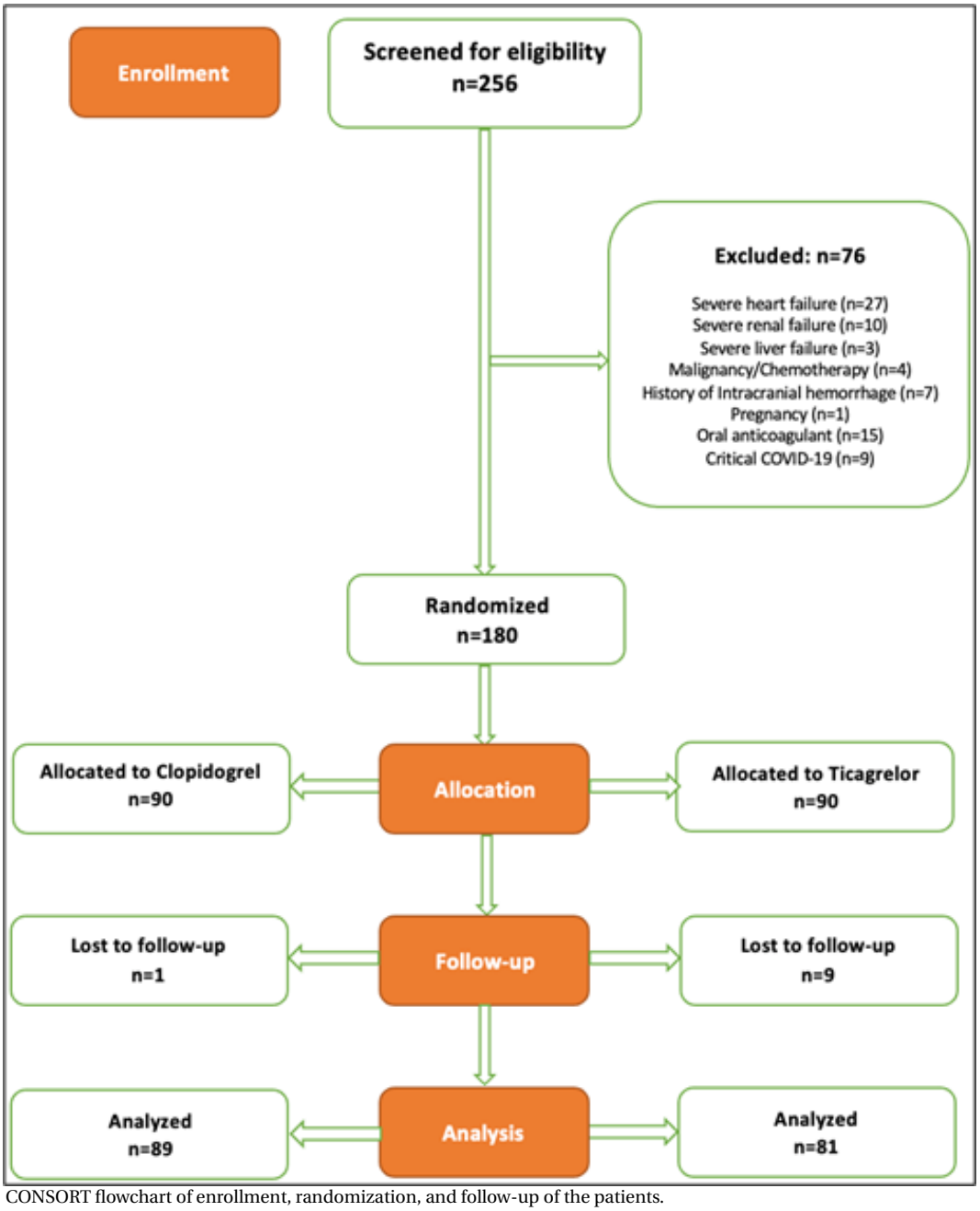

Figure 1: CONSORT flowchart of enrollment, randomization, and follow-up of the patients.

ities in chest CT scans may occur, eventually leading to acute respiratory distress syndrome (ARDS) (29). An important aim of this trial was to investigate if Ticagrelor could improve pulmonary function in our patients or not. In a study by Storey et al. on the results of the previous large PLATO clinical trial, they compared the incidence of pulmonary adverse events or mortality in 18,421 patients with ACS, between two groups of Ticagrelor and Clopidogrel. The adverse events in the Ticagrelor group occurred less than in the Clopidogrel group (275 versus 331; p= 0.019), also deaths were significantly fewer in Ticagrelor than in Clopidogrel group (33 versus 71; p<0.001). Eventually, they concluded that the mortality related to pulmonary adverse events in patients with ACS decreases when the patients were on Ticagrelor compared to Clopidogrel treatment (18). Sexton and colleagues developed a study to investigate whether Ticagrelor has possible beneficial effects on pneumonia patients. Finally, they showed that Ticagrelor improved pulmonary function during pneumo-

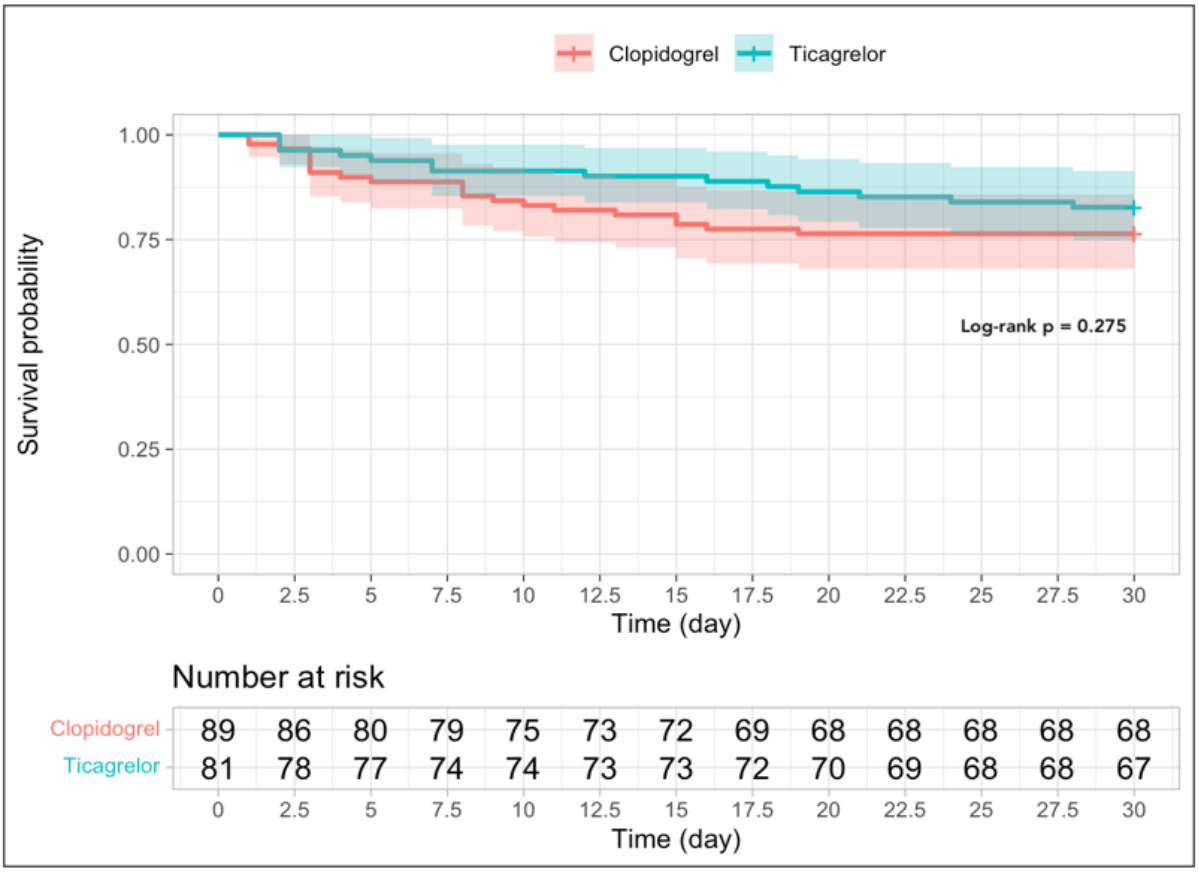

Figure 2: Kaplan-Meier curve comparing survival rates between the two trial arms during follow-up.

sepsis compared to placebo (free from supplemental oxygenation period: OR=1.08; 95% CI= 1.01 to 1.15) (30). They also realized that Ticagrelor administration in patients with pneumonia and sepsis lowered platelet-leukocyte aggregation and reduced interleukin-6 levels, which are associated with an anti-inflammatory effect. As mentioned before, in our clinical trial, we found that individuals in the Ticagrelor arm had significantly higher mean oxygen saturation in comparison with those in the Clopidogrel arm. (95.26±2.68% versus 94.29±3.55%, p=0.028). Xie et al. studied the association between hypoxemia and COVID-19 mortality. They found that hypoxemia is independently related to higher in-hospital mortality, and an oxygen saturation cut-off value of 90.5%, had 84.6% sensitivity and 97.2% specificity in the prediction of survival (31). Thus, our findings could lead to conducting further studies that survey the potential beneficial effects of ticagrelor on COVID-19 patients to decrease overall mortality.

Solano-López et al., demonstrated that in patients with acute STEMI, all-cause mortality, and cardiovascular mortality are remarkably increased when the concomitant COVID-19 infection is present, compared to COVID-19-negative individuals (25% versus 3.8% (P < 0.001), and 15.2% versus 1.8% (P = 0.001), respectively) (32). In the study by Mohsenizadeh et al., the presence of COVID-19 in patients undergoing primary PCI was associated with significantly higher duration of hospitalization and in-hospital mortality (33, 34). In our study, the overall 30-day mortality in the total population was 20.58% (35 out of 170), while people in the Ticagrelor group died less than those in the Clopidogrel group, the difference was not statistically significant. Furthermore, the overall period of hospitalization was not different between the two trial arms.

5. Limitations

Although this study was designed based on a clinical trial, some limitations should be considered when interpreting the results. Since this was the first trial that compared the therapeutic effects of Ticagrelor on COVID-19 outcomes in ACS patients, the total sample size and follow-up duration were limited. A study with a larger sample size and a longer follow-up duration might be more confidently conclusive.

To the best of our knowledge, this was the first trial devel-

oped to investigate the beneficial effects of Ticagrelor compared to Clopidogrel, in patients with concomitant ACS and COVID-19 infection who had undergone urgent coronary angioplasty. As previously said, we assessed the early (acute and subacute) stent thrombosis, while it's shown that COVID-19 could be associated with late (within the first year after PCI) and even very late (beyond the first year) stent thrombosis, so future studies should be designed with longer follow-up duration and include more subjects so it would be possible that the non-significant results from this study become statistically significant and indicate the administration of Ticagrelor in such patients with more emphasis.

6. Conclusions

We found that in patients who presented with acute coronary syndromes and active COVID-19, who were treated with urgent coronary angioplasty, Ticagrelor in comparison with Clopidogrel did not significantly decrease all-cause mortality, myocardial infarction, or early stent thrombosis in 30-day follow-up. Although Ticagrelor administration was associated with a statistically significant higher mean arterial oxygen saturation during admission, but this difference was not clinically remarkable. However, this finding might be indicative of Ticagrelor's potential benefits for improving pulmonary function in such patients.

7. Declarations

7.1. Acknowledgments

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7.2. Conflict of interest

The authors declare no potential conflict of interest regarding this manuscript's study design, writing, or publication.

7.3. Fundings and supports

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7.4. Authors' contribution

Reza Arefizadeh: the concept and design of the clinical trial, and patient allocation.
Seyed Hossein Moosavi: the patient allocation and supervising of the team.
Sayiied Tufeeqee: patient follow-up and writing the manuscript.
Seyed Abolfazl Mohsenizadeh: statistical analysis and writing the manuscript.
Mehdi Pishgahi: trial design and analysis of the results.
All authors read and approved final version of manuscript.

References

1. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3.
2. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. Cardiovasc Res. 2020;116(10):1666-87.
3. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular considerations for patients, health care workers, and health systems during the COVID-19 pandemic. J Am Coll Cardiol. 2020;75(18):2352-71.
4. Bansal M. Cardiovascular disease and COVID-19. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14(3):247-50.
5. Tomasoni D, Adamo M, Italia L, Branca L, Chizzola G, Fiorina C, et al. Impact of COVID-2019 outbreak on prevalence, clinical presentation and outcomes of ST-elevation myocardial infarction. J Cardiovasc Med. 2020;21(11):874-81.
6. Wu J, Mamas MA, Mohamed MO, Kwok CS, Roebuck C, Humberstone B, et al. Place and causes of acute cardiovascular mortality during the COVID-19 pandemic. Heart. 2021;107(2):113-9.
7. Jain V, Gupta K, Bhatia K, Bansal A, Arora S, Khandelwal AK, et al. Management of STEMI during the COVID-19 pandemic: Lessons learned in 2020 to prepare for 2021. Trends Cardiovasc Med. 2021;31(3):135-40.
8. Chew NW, Sia C-H, Wee H-L, Jia-Da Benedict L, Rastogi S, Kojodjojo P, et al. Impact of the COVID-19 Pandemic on Door-to-Balloon Time for Primary Percutaneous Coronary Intervention—Results From the Singapore Western STEMI Network—. Circ J. 2021;85(2):139-49.
9. De Luca G, Cercek M, Jensen LO, Vavlukis M, Calmac L, Johnson T, et al. Impact of COVID-19 pandemic and diabetes on mechanical reperfusion in patients with STEMI: insights from the ISACS STEMI COVID 19 Registry. Cardiovasc Diabetol. 2020;19(1):215.
10. Rodriguez-Leor O, Cid-Álvarez B, Ojeda S, Martín-Moreiras J, Rumoroso JR, López-Palop R, et al. Impact of the COVID-19 pandemic on interventional cardiology activity in Spain. REC Interv Cardiol. 2020;2(2):82-9.
11. Scholz KH, Lengenfelder B, Thilo C, Jeron A, Stefanow S, Janssens U, et al. Impact of COVID-19 outbreak

on regional STEMI care in Germany. Clin Res Cardiol. 2020;109(12):1511-21.
12. Choudhary R, Kaushik A, Sharma JB. COVID-19 pandemic and stent thrombosis in a post percutaneous coronary intervention patient-a case report highlighting the selection of P2Y12 inhibitor. Cardiovascular Diagnosis and Therapy. 2020;10(4):898.
13. Hanff TC, Mohareb AM, Giri J, Cohen JB, Chirinos JA. Thrombosis in COVID-19. Am J Hematol. 2020;95(12):1578-89.
14. Miesbach W, Makris M. COVID-19: coagulopathy, risk of thrombosis, and the rationale for anticoagulation. Clin Appl Thromb Hemost. 2020;26:1076029620938149.
15. Prieto-Lobato A, Ramos-Martínez R, Vallejo-Calcerrada N, Corbí-Pascual M, Córdoba-Soriano JG. A case series of stent thrombosis during the COVID-19 pandemic. Case Reports. 2020;2(9):1291-6.
16. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361(11):1045-57.
17. Sahlén A, Varenhorst C, Lagerqvist B, Renlund H, Omerovic E, Erlinge D, et al. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. Eur Heart J. 2016;37(44):3335-42.
18. Storey RF, James SK, Siegbahn A, Varenhorst C, Held C, Ycas J, et al. Lower mortality following pulmonary adverse events and sepsis with ticagrelor compared to clopidogrel in the PLATO study. Platelets. 2014;25(7):517-25.
19. Skorupski WJ, Grygier M, Lesiak M, Kałużna-Oleksy M. Coronary stent thrombosis in COVID-19 patients: a systematic review of cases reported worldwide. Viruses. 2022;14(2):260.
20. Hinterseer M, Zens M, Wimmer RJ, Delladio S, Lederle S, Kupatt C, et al. Acute myocardial infarction due to coronary stent thrombosis in a symptomatic COVID-19 patient. Clin Res Cardiol. 2021;110(2):302-6.
21. Kunal S, Pathak V, Pathak K, Mishra M, Sharma SM, Bhandari S. Very late stent thrombosis associated with COVID-19 infection: a case report and review of the literature. Monaldi Archives for Chest Disease. 2022;92(2):1960.
22. Ayan M, Kovelamudi S, Al-Hawwas M, editors. Subacute stent thrombosis in a patient with COVID-19 pneumonia. Baylor University Medical Center Proceedings; 2021;34(1):175-177. Taylor & Francis.
23. Kermani-Alghoraishi M. A review of coronary artery thrombosis: a new challenging finding in COVID-19 patients and ST-elevation myocardial infarction. Curr Probl Cardiol. 2021;46(3):100744.
24. Elkholy KO, Khizar A, Khan A, Hakobyan N, Sahni S. Subacute stent thrombosis in a patient with COVID-19 despite adherence to antiplatelets. Cureus. 2021;13(2): e13194.
25. Antuña P, Rivero F, Del Val D, Cuesta J, Alfonso F. Late coronary stent thrombosis in a patient with coronavirus disease 2019. JAMA cardiology. 2020;5(10):1195-8.
26. Galeazzi GL, Loffi M, Di Tano G, Danzi GB. Severe COVID-19 pneumonia and very late stent thrombosis: a trigger or innocent bystander? Korean Circulation Journal. 2020;50(7):632.
27. Montaseri M, Golchin Vafa R, Attar A, Ali Hosseini S, Kojuri J. Stent thrombosis during COVID-19 pandemic: A case series. Clinical Case Reports. 2022;10(5):e05872.
28. Hamadeh A, Aldujeli A, Briedis K, Tecson KM, Sanz-Sánchez J, Al-Obeidi A, et al. Characteristics and outcomes in patients presenting with COVID-19 and ST-segment elevation myocardial infarction. The American journal of cardiology. 2020;131:1-6.
29. Batah SS, Fabro AT. Pulmonary pathology of ARDS in COVID-19: a pathological review for clinicians. Respir Med. 2021;176:106239.
30. Sexton TR, Zhang G, Macaulay TE, Callahan LA, Charnigo R, Vsevolozhskaya OA, et al. Ticagrelor reduces thromboinflammatory markers in patients with pneumonia. JACC: Basic to Translational Science. 2018;3(4):435-49.
31. Xie J, Covassin N, Fan Z, Singh P, Gao W, Li G, et al., editors. Association between hypoxemia and mortality in patients with COVID-19. Mayo Clin Proc; 2020:95(6): 1138-1147 Elsevier.
32. Solano-López J, Zamorano JL, Sanz AP, Amat-Santos I, Sarnago F, Ibañes EG, et al. Risk factors for in-hospital mortality in patients with acute myocardial infarction during the COVID-19 outbreak. Revista Española de Cardiología (English Edition). 2020;73(12):985-93.
33. Mohsenizadeh SA, Alidoosti M, Jalali A, Tofighi S, Salarifar M, Poorhosseini H, et al. Comparison of Angiographic and Clinical Outcomes After Primary Percutaneous Coronary Intervention for ST-elevation Myocardial Infarction Between Patients With and Without Concomitant COVID-19 Infection. Crit Pathw Cardiol. 2022;21(3):141-6.
34. Namazi MH, Saemifard F, Pishgahi M. One-Month Outcomes of Cases Receiving Ticagrelor after Percutaneous Coronary Intervention; a Case Series. Arch Acad Emerg Med [Internet]. 2020;8(1):e42.