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**ORIGINAL ARTICLE**

# Coronary Artery Bypass Surgery in Patients Receiving Dual Antiplatelet Therapy and the Impact of Preoperative Vitamin D Levels During COVID-19 Pandemic: An Observational Single Center Study

# COVID-19 Pandemi Döneminde Koroner Bypass Cerrahisi Uygulanan Hastalarda Preoperatif İkili Antiplatelet Tedavi Kullanımı ve D Vitamini Düzeylerinin Postoperatif Sonuçlara Etkisi: Gözlemsel Tek Merkezli Çalışma

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**ABSTRACT**

Objective: The COVID-19 pandemic has led to a surge in catheter-based interventions as elective surgeries were postponed. However, there has been a simultaneous rise in emergency CABG surgeries due to stent thrombosis or catheter-related complications. The potential impact of vitamin D on the immune system has also gained attention during the pandemic. We aimed to investigate the impact of preoperative dual anti-platelet (DAPT) usage and vitamin D levels of those patients who underwent CABG on postoperative outcomes.
Materials and methods: This retrospective study was conducted between March 23, 2020, and December 30, 2021. The study included 63 patients who underwent elective and emergency CABG while on dual antiplatelet therapy. D vitamin levels were obtained from all the patients preoperatively.
Results: Fifty-one of the 63 patients were males and 12 were females. The mean age was 62.69 ± 8.43 years. 15 patients (24%) were on Clopidogrel and Acetylsalicylic acid (ASA) and 48 patients (76%) were on Ticagrelor and ASA preoperatively. Off-pump CABG was performed in 21 patients (33%). One patient had a stroke (1.6 %). The amount of drainage was significantly higher in patients using Ticagrelor and (ASA) (p = 0.015). The mean vitamin D level was 13.94 ± 5.24 ng/mL ranging from 3.38 ng/mL to 24.99 ng/mL, Vitamin D levels were significantly lower in female patients compared to males (p = 0.004).
Conclusion: CABG surgery in patients receiving DAPT presents unique challenges and requires careful management to minimize bleeding complications. Additionally, maintaining adequate vitamin D levels preoperatively may improve postoperative outcomes.

**Keywords:** COVID-19, Coronary Artery Disease, Dual Anti-platelet Therapy.

**ÖZ**

Amaç: COVID-19 salgını, elektif cerrahi girişimLer ertelendikçe kateter bazlı müdahalelerde artışa neden oldu. Bununla birlikte, stent trombozu veya kateter ilişkili komplikasyonlar nedeniyle acil koroner bypass ameliyatlarında da eş zamanlı bir artış olmuştur. D vitamininin bağışıklık sistemi üzerindeki potansiyel etkisi de pandemi sırasında dikkatleri üzerine çekmiştir. Koroner bypass uygulanan hastalarda preoperatif ikili antiplatelet tedavisinin (DAPT) kullanımının ve D vitamini düzeylerinin postoperatif sonuçlara etkisini araştırmayı amaçladık.
Gereç ve yöntem: Bu retrospektif çalışma, 23 Mart 2020 ile 30 Aralık 2021 tarihleri arasında gerçekleştirildi. Çalışmaya elektif ve acil KABG uygulanan ve ikili antiplatelet tedavi alan 63 hasta dahil edildi, tüm hastalardan ameliyat öncesi d vitamini seviyeleri ölçüldü.
Bulgular: altmış üç hastanın 51'i erkek, 12'si kadındı. Ortalama yaş 62.69 ± 8.43 idi. Ameliyat öncesi 15 hasta (%24) Klopidogrel ve Asetilsalisilik asit (ASA), 48 hasta (%76) Ticagrelor ve ASA kullanıyordu. 21 hastaya (%33) pompasız koroner bypass uygulandı. Bir hastada serebrovasküler olay gelişti (%1.6). Ticagrelor ve (ASA) kullanan hastalarda drenaj miktarı anlamLı olarak fazlaydı (p = 0,015). Ortalama D vitamini düzeyi 13,94 ± 5,24 ng/mL idi (3,38 ng/mL-24,99 ng/mL), D vitamini düzeyi kadın hastalarda erkeklere göre anlamLı olarak düşüktü (p = 0,004).
Sonuç: İkili antiplatelet tedavisi alan hastalarda korroner bypass cerrahisi eşsiz zorluklar taşımaktadır ve kanama komplikasyonlarını en aza indirmek için dikkatli bir yönetim gerektirir. Ek olarak, ameliyat öncesi yeterli D vitamini düzeylerinin korunması ameliyat sonrası sonuçları iyileştirebilir.

**Anahtar kelimeler:** Kovid-19, koroner arter hastalığı, ikili antiplatelet tedavi.

## Introduction

Until the 21st century, coronaviruses were considered insignificant agents of mild cold and received relatively little attention due to their mild phenotype in humans. However, there had been worrisome outbreaks of coronaviruses in the early twentieth century. The first was the severe acute respiratory syndrome (SARS-CoV) outbreak in China in 2002, the second was the Middle-East respiratory syndrome coronavirus (MERS-CoV) epidemic that occurred in Saudi Arabia in 2012, and the third is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a new coronavirus isolated from respiratory epithelial cells for the first time in the last month of 2019 in the Wuhan region of China and continues to spread (1). The disease caused by

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SARS-CoV-2 was named COVID -19. On March 11, 2020, the World Health Organization (WHO) declared COVID -19, a highly contagious zoonotic disease, as a pandemic (2).

During the pandemic period, catheter-based procedures were preferred over surgical procedures. However, there has also been an increase in the number of patients requiring emergency coronary artery bypass grafting (CABG) because of stent thrombosis or catheter-related complications. Dual antiplatelet therapy (DAPT) is a standard therapy used in patients with acute coronary syndrome or those who have undergone coronary stenting (3). It typically involves the use of (acetyl salicylic acid) ASA and a P2Y12 receptor inhibitor, such as clopidogrel or ticagrelor. In patients undergoing CABG surgery, DAPT has been shown to reduce the risk of postoperative complications, such as stroke, myocardial infarction, and graft occlusion (4). However, there is also evidence to suggest that DAPT can increase the risk of bleeding, which can be a serious concern during surgery. The hypercoagulability state during Covid-19 infection has raised concerns about the impact of DAPT(5). The COVID-19 pandemic has also brought attention to the role of vitamin D in the immune system, and its potential impact on patients undergoing CABG surgery. All of our patients underwent surgery without discontinuation of dual antiplatelet therapy. We aimed to study the clinical outcomes of continued DAPT and preoperative vitamin D levels in our patients.

**Materials and methods**

We conducted a retrospective study during the lockdown period of the COVID-19 pandemic between March 23, 2020, and December 30, 2021. Sixty-three patients who underwent acute or emergency CABG while under dual anti-platelet therapy were included in the study.

Since our study was conducted during the COVID-19 pandemic, preoperative chest radiography, chest computed tomography (CT), and reverse transcription-polymerase chain reaction (RT-PCR) tests were performed in all patients. In addition to routine laboratory and imaging tests required for CABG procedures, 25 (OH) vitamin D level was also measured in all patients. Due to both hemodynamic instability and poor collateral circulation, it was decided to operate on our patients without delay.

In all patients, a standard median sternotomy incision was made, and the left internal mammary artery (LIMA) was mobilized with a pedicle. In the same session, saphenous vein grafts were harvested. Although off-pump CABG was considered in all patients, purse string sutures were placed on the aorta and right atrium considering the possibility of establishing cardiopulmonary bypass (CPB).

The study was approved by our university Clinical Research Ethics Committee in accordance with the Declaration of Helsinki (no: 2017-KAEK-189_2023.02.17_7, date: 17.02.2023).

**Statistical analysis**

Descriptive statistics are presented as mean with SD or median with İQR for numerical variables while frequencies and percentages are used for the categorical variables. The distribution of variables was assessed by Kolmogorov-Smirnov and Shapiro-Wilk's tests. For analytical statistics, independent sample t-test, and Mann-Whitney Test were used to compare numerical variables between two groups based on the normality assumption while Pearson Chi-Square test or Fisher's Exact test were used to compare two categorical variables. The data were analyzed using IBM SPSS statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). P-value <0.05 was considered statistically significant.

**Results**

Twelve out of 63 patients were females (19%). The mean age was 62.69 ± 8.43 years ranging from 40 to 77 years. The most common risk factors were hypertension in 16 (25%) patients, diabetes in 27 (43%) patients, chronic pulmonary obstructive disease (COPD) in 5 patients (8%) patients and tobacco use in 46 patients (73%). Among the patients scheduled for CABG, 11 patients had a single vessel disease, 23 patients had two-vessel disease and the remaining 29 patients had three-vessel disease. Following coronary angiography, 48 (76%) patients were treated with clopidogrel and ASA and 15 (24%) with ticagrelor and ASA. CABG was required from 3 to 30 hours after angiography to avoid life-threatening complications. (Table 1).

Postoperative morbidities are shown in Table 2. Although off-pump CABG was planned in all patients, we were able to perform off-pump CABG in only 21 patients. The remaining 42 patients required cardiopulmonary bypass due to hemodynamic deterioration. Myocardial protection was provided with combined antegrade and retrograde blood cardioplegia in patients requiring on-pump CABG. Left internal mammary artery (LIMA) graft was anastomosed to the left anterior descending artery (LAD) in all patients except two. The median cross-clamp time was 85 minutes ranging between 45 to 180 minutes, the median CPB time was 130 minutes ranging between 55 and 357 minutes.

Vitamin D levels ranged from 3.38 ng/mL to 24.99 ng/mL, and the mean vitamin D level was 13.94 ± 5.24 ng/mL. Overall, 53 (84%) of the study patients had vitamin D deficiency, 25 of whom (40%) had severe vitamin D deficiency (Table 3). We did not have any patients with adequate vitamin D levels. Vitamin D levels were significantly lower in female patients compared to males (10.16 ± 5.80 vs 14.85 ± 4.72; p=0.04).

Postoperatively, all patients required blood products to mitigate blood drainage. In addition, platelet suspension transfusion was administered to 10 patients who needed intra-aortic balloon pumping (IABP) support to wean from CPB. These 10 patients received Ticagrelor and ASA in the preoperative period. Vitamin D levels of these patients were critically deficient and

**Figure 1.** The postoperative thoracic computed tomography of the patients with COVİD- 19 shows bilateral ground-glass opacities and bronchiectasis areas. The red arrows indicate the location of the abnormalities.

**Table 1:** Perioperative characteristics of the patients.

| | (n = 63) |
|---|---|
| Age, (years), mean (±SD) | 62.69 ± 8.43 |
| Sex, n (%) | |
| Male | 51 (81) |
| Female | 12 (19) |
| Comorbidities | n (%) |
| Diabetes Milletus | 27 (43) |
| Hyperlipidemia | 20 (32) |
| Hypertension | 16 (25) |
| Smoking | 46 (73) |
| Obesity | 12 (19) |
| Chronic renal disease | 1 (1.6) |
| COPD | 5 (8) |
| Asthma | 2 (3.2) |
| Positive COVİD-19 (RT-PCR) test | 3 (5) |
| Left ventricular EF (%), median (range) | 55 (29-62) |
| Level of priority, n (%) | n (%) |
| Elective | 42 (67) |
| Urgent | 8 (13) |
| Emergency | 13 (21) |
| Preoperative use of dual-antiplatelet therapy, n (%) | |
| Clopidogrel +ASA | 15 (24%) |
| Ticagrelol+ASA | 48 (76%) |
| Extension of coronary lesions, n (%) | |
| 1 vessel disease | 11 (17.5) |
| 2 vessel disease | 23 (36.5) |
| 3 vessel disease | 29 (46) |
| İndication for surgery, n (%) | |
| LMCA | 7 (11) |
| LMCA equivalent | 11 (17.5) |
| Severe LAD stenosis ( >90%) | 23 (36.5) |
| LAD stent thrombosis | 11 (17.5) |
| Euroscore II (%), median (range) | 1,2 (0.55-6.15) |

Abbreviations: COPD: chronic obstructive pulmonary disease ; EF: ejection fraction;LMCA, left main coronary artery; LAD: left anterior descending.

**Table 2:** Postoperative characteristics of the patients and surgical details.

| | (n=**63**) |
|---|---|
| Type of operation, n (%) | |
| On-pump | 42 (67) |
| Off-pump | 21 (33) |
| Complications | n (%) |
| Stroke | 1 (1.6) |
| Re-opening for bleeding | 1 (1.6) |
| Renal failure requiring dialysis | 2 (3.1) |
| Wound infection | 2 (3.1) |
| Mediastenit | 1 (1.6) |
| New onset Atrial fibrillation | 9 (14.3) |
| Pulmonary embolism | 1 (1.6) |
| Respiratory failure | 1 (1.6) |
| İnotrope support, n (%) | 37 (59) |
| İntraaortic balloon pump support, n (%) | 10 (16) |
| Mechanical ventilation time (hour), median (range) | 10 (6-120) |
| Cross clamp time (minute), median (range) | 85 (45-180) |
| CPB time (minute), median (range) | 130 (55-357) |
| Postop. Platelets (×$10^9$ L), mean (±SD) | 80 (±50) |
| Total blood drainage (mL). p.o. 24. hour | 868.2 (333) |
| PRBC transfusion (unit), median (range) | 3(0-40) |
| FFP transfusion (unit), median (range) | 5 (0-40) |
| Platelet transfusion (unit), median (range) | 5 (0-40) |
| Length of hospital stay, (day), median (range) | 9 (1-60) |
| Hospital mortality, n (%) | 1 (1.6) |

Abbreviations: CPB: cardiopulmonary bypass; PRBC: packed red blood cell; FFP: fresh frozen plasma

**Table 3:** Distribution of D vitamin levels according to gender.

| | Mean (± SD) | | |
|---|---|---|---|
| | Male 51 (81%) | Female 12 (19%) | P -Value |
| Vitamin D levels (ng/mL), (mean ± SD) | 14.85±4.72 | 10.16±5.80 | 0.004 |
| patients with low vitamin D levels, n (%) | 43 (84%) | 10 (83%) | 0.933 |

their mean platelet counts were 80×109 L (±50). The mean amount of blood drainage in the first 24 hours postoperatively in patients treated with Ticagrelor and ASA was higher than those who received Clopidogrel and ASA preoperatively [1033 mL (±121) vs. 868 mL (±238), P = 0.015], respectively. The amount of blood drainage was significantly higher in patients using Ticagrelor and ASA and requiring IABP support [1500 mL (±646) vs. 850 mL (±456), p = 0.0001). A reopening due to hemodynamic instability and tamponade was required in one patient who received Ticagrelor and ASA preoperatively.

### COVID-19 infections

Three patients tested positive for COVİD-19, and one of them underwent CABG in the incubation period and tested positive postoperatively despite being tested negative at admission. The patient started developing symptoms of fever and pulmonary infiltration on x-ray

(figure 1) and died on the 4th postoperative day due to severe respiratory failure. Two patients who needed an elective CABG procedure tested positive on RT-PCR and were sent to the isolation unit for treatment. One week later, they were operated on after two subsequent negative nasopharyngeal swabs, and the postoperative course of those patients was uneventful.

All patients were discharged with good recovery, except for one patient who tested positive for COVID-19 as mentioned previously.

**Discussion**

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new coronavirus that was first isolated from respiratory epithelial cells in the Wuhan region in the last month of 2019 and continues to spread. COVID-19 is an extremely contagious disease and was declared a pandemic by WHO on March 11, 2020(6). Since then, the pandemic has continued to drain healthcare and economic resources. The outbreak had a particularly negative impact on cardiac surgery, as critical care resources in hospitals were limited resulting in elective procedures being postponed, and even patients requiring urgent or emergent procedures faced challenges due to increasing resource shortages.

The SARS-CoV-2 virus spread rapidly in hospitals, with transmission rates reaching 40% (7). As a result, elective surgical procedures were postponed worldwide. Several observational studies reported that patients with left ventricular dysfunction and severe angina had higher mortality and nonfatal myocardial infarction while waiting for CABG or percutaneous coronary intervention (8). Therefore, surgical interventions had to be performed without delay in patients with severe coronary artery disease who required acute or urgent CABG.

In the present study, a total of 63 patients underwent CABG procedure during the lockdown period at our department. We identified a considerable decrease in surgical procedures during this period, which is consistent with what has been observed elsewhere (9). The COVID-19 pandemic has made significant changes in the practice of cardiovascular surgery in our department. The fact that even coronary artery patients did not come to the hospital for fear of COVID-19 contamination and that cardiologists preferred thrombolytic therapy over catheter-related revascularization may have played a role in the decrease in patients requiring CABG.

DAPT is commonly used to reduce the risk of blood clots and subsequent heart attacks or strokes in patients with CAD. However, the use of DAPT in patients undergoing CABG surgery is controversial, as it may increase the risk of bleeding complications during and after surgery. Several studies have investigated the optimal timing of discontinuing DAPT before CABG surgery. A meta-analysis of 12 randomized controlled trials found that discontinuing DAPT 5 to 7 days before CABG surgery reduced the risk of bleeding complications without increasing the risk of cardiovascular events (4). However, the timing of DAPT discontinuation may depend on individual patient factors and should be determined on a case-by-case basis.

Coronary collateral circulation is poorly developed in patients with coronary artery disease and low vitamin D levels. Therefore, it is suggested that inadequate angiogenesis might be one of the mechanisms that cause higher cardiovascular risk in patients with low vitamin D levels (10). Vitamin D deficiency has been reported to be associated with both increased risk of coronary artery disease and poor postoperative outcomes and increased operative mortality after CABG (11).

The tendency to thrombosis increases in COVID -19 patients due to increased inflammation, platelet activation, endothelial dysfunction, and congestion from immobilization [9]. Given that respiratory infections are associated with an increased risk of vascular disease, including thrombosis, it is not surprising that COVID-19 may eventually be complicated by coagulation changes leading to thrombosis (12). In addition, we believe that vitamin D deficiency resulting from patients not receiving adequate sunlight due to lockdown, may play a role in stent thrombosis or predispose to graft thrombosis in patients undergoing CABG. Therefore, we may assume that the risk of stent thrombosis increases in patients undergoing coronary stenting despite antithrombotic therapy during the lockdown period.

Surgery was not postponed due to the use of preoperative antiplatelet agents, especially in patients who required emergency CABG due to life-threatening complications and hemodynamic instability after percutaneous coronary intervention. We believe that early surgery should be performed regardless of possible COVID -19 infection despite the increased risk of bleeding and the need for transfusions. In such cases, we also performed off-pump CABG when possible, which is associated with a lower blood transfusion rate compared with on-pump procedures (11). In our cases, we did not discontinue antiplatelet agents, and only one patient who developed severe thrombocytopenia associated with Intra-aortic balloon pump and heparinization required reopening for bleeding. Antiplatelet therapy has been reported to be associated with higher blood loss and blood product requirements and a higher incidence of reopening in patients undergoing CABG (13). However, we believe that urgent or elective CABG can be performed by discontinuing antiplatelet treatment before the times recommended in the current guidelines.

**Conclusion**

considering the tendency of COVID -19 to thrombosis, emergency or elective CABG can be performed without discontinuing preoperative dual antiplatelet therapy. However, as in our series, it should be noted that blood products, including platelet transfusion,

may be required more frequently in patients treated with Ticagrelor and ASA who receive IABP support. In addition, risk factors such as vitamin D deficiency should be avoided to reduce the risk of thrombosis in coronary stents and bypass grafts; however, our study should be supported by further studies.

**Author Contributions**

Study design: S.A., Data collection and analyzing: S.A, Writing the original draft: S.A., Literature review: M.E., Scientific advisors: M.E.

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