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# Recurrent Coronary Artery Thrombosis on Triple Anti-Thrombotic Therapy, Is There a Possible Association with ChAdOx1 nCoV-19 Vaccination?

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## Abstract

**Background:** Vaccines remain the only viable and safe option to control transmission and minimise disease sequelae during the COVID-19 pandemic. Whilst multiple vaccines are available, evidence has emerged regarding the association between the ChAdOx1 nCoV-19 vaccine, platelets and thrombosis, manifesting in thrombotic thrombocytopaenia. **Case Summary:** We report a case of recurrent coronary artery thrombosis on triple antithrombotic therapy, namely aspirin, clopidogrel, and continuous intravenous heparin, nine days after the ChAdOx1 nCoV-19 vaccine, in a 63-year-old female with no significant history of cardiovascular disease. **Conclusion:** This case may suggest that the association between platelets, SARS-CoV-2, the ChAdOx1 nCoV-19 vaccine, and coronary thrombosis may remain incompletely understood and warrants further study. Clinicians should remain on high alert if presented with similar circumstances.

## Keywords

ST-Elevation Myocardial Infarction, Stent Thrombosis, ChAdOx1 nCoV-19, AstraZeneca, COVID-19, SARS-CoV-2

## 1. Introduction

The SARS-CoV-2 vaccinations are continuing to play a vital role in controlling the global pandemic. While ongoing compliance with the vaccination programs is of paramount importance, the rare side effects of these new vaccinations need to be recognised and treated appropriately to ensure patient safety. Evidence has

emerged of the risk of acute thrombosis in the setting of ChAdOx1 nCoV-19 (AstraZeneca) vaccination. This has led to updated guidelines from the Australian Technical Advisory Group on Immunisation recommending ChAdOx1 nCoV-19 (AstraZeneca) for those over 50 years, in line with recommendations from the United Kingdom Medicines and Healthcare Products Regulatory Agency. We present a case of coronary artery thrombosis without thrombocytopaenia whilst on dual antiplatelets and intravenous anticoagulation post initial thrombolytic therapy, nine days after ChAdOx1 nCoV-19 vaccination. Whilst the known thrombotic risk associated with the ChAdOx1 nCoV-19 vaccination remains incredibly rare, the thrombotic risk for patients with acute coronary syndromes may be increased, particularly given that the ChAdOx1 nCoV-19 vaccination is the recommended vaccine for patients over 50 years, those patients most at risk for acute coronary events.

## 2. History of the Case

We present the case of a 63-year-old female who developed severe retrosternal chest pain nine days after receiving her first dose of the ChAdOx1 nCoV-19 vaccination. Following acute onset of chest pain and dyspnoea she was transferred to her local regional hospital via emergency services. The time from chest pain onset to first medical contact was 59 minutes. On arrival, she had ongoing severe pain, yet was haemodynamically stable, with a blood pressure of 128/65 mmHg and a heart rate of 71 beats per minute, was afebrile at 37.4 degrees Celsius, with normal oxygen saturations and respiratory rate. Her clinical exam was normal. Given the absence of symptoms and the regional epidemiological profile at the time of presentation, she was not tested for SARS-CoV-2 virus infection.

Past medical history included ulcerative colitis, which was quiescent on azathioprine and mesalazine, and gastroesophageal reflux disease. She had a family history of ischaemic heart disease, with no other cardiovascular risk factors. She had no known clotting disorders or history of thromboembolic disease. Her vaccine status was not known at the time of presentation.

## 3. Investigations and Management

Her initial 12-lead electrocardiograph (ECG) demonstrated 11 mm ST-segment elevation in the anterolateral leads with reciprocal ST-segment depression (**Figure 1(A)**). Following prompt recognition of anterolateral ST-segment elevation myocardial infarction (STEMI), she was administered 300 mg loading doses of aspirin and 600 mg of the $P2Y_{12}$-inhibitor clopidogrel. Given the travel time to the nearest percutaneous coronary intervention (PCI) centre was greater than 120 minutes, she also underwent pharmacological fibrinolysis with tenecteplase which was followed by a continuous infusion of intravenous heparin. Her pain onset to fibrinolysis time was 135 minutes. Thirty minutes post fibrinolysis, she was pain free with near complete resolution of STEMI on serial ECG (**Figure 1(B)**). She was subsequently transferred the 230 kilometres by road to our PCI

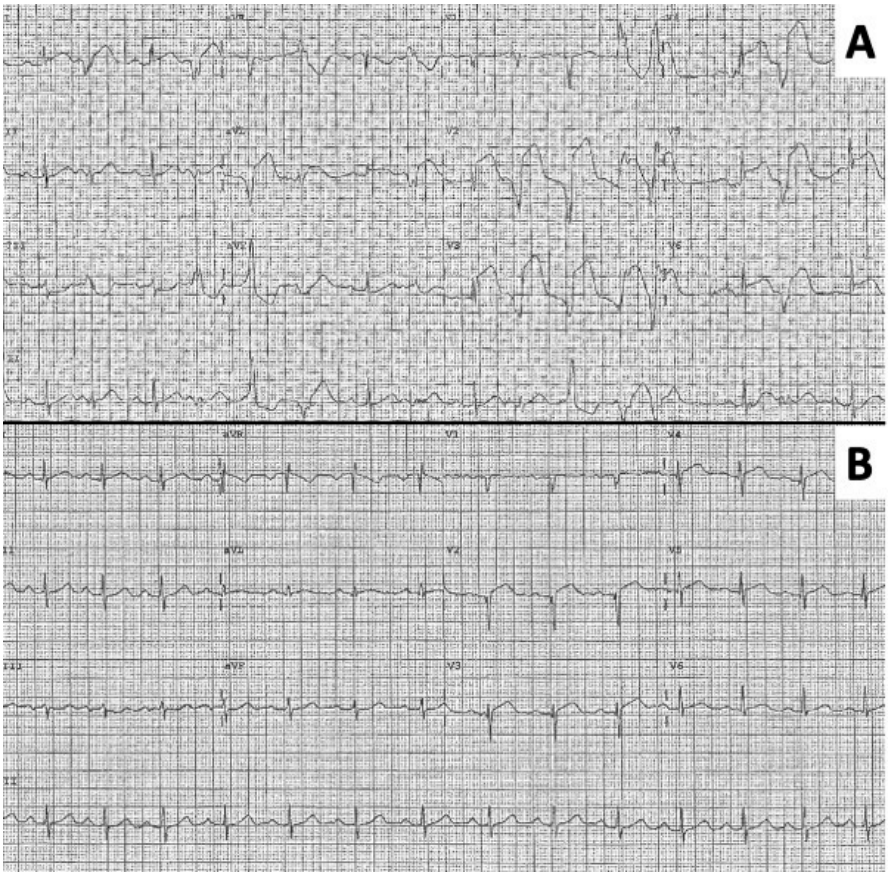


**Figure 1.** Anterolateral ST-segment Myocardial Infarction. 12-lead ECG pre (A) and post (B) thrombolysis.

capable tertiary hospital.

Upon arrival, she remained haemodynamically stable and pain free. Her admission ECG demonstrated sinus rhythm with anterior q waves, without evidence of acute ischaemia (**Figure 2(A)**). Her laboratory findings were unremarkable, with the exception of an elevated cardiac troponin I of 116,013 ng/L (reference value, <26 ng/L). Of note, her platelet count was normal at 291,000/mm$^3$ (reference value, 150,000 - 400,000/mm$^3$). Within two hours of arrival, day 10 post ChAdOx1 nCoV-19 vaccination and four hours post thrombolysis, she experienced recrudescence of severe chest pain with corresponding 5 mm anterior ST-segment elevation on her ECG (**Figure 2(B)**) and was promptly taken for emergency coronary angiography.

Coronary angiography, via right radial access, demonstrated mid-vessel occlusion of the left anterior descending artery (LAD) (**Figure 3**). Occlusion was predilated and treated with a 2.75 × 34 mm Resolute Onyx (R-Onyx, Medtronic, CA, USA) zotarolimus-eluting stent and post-dilated with 3.0 NC balloon at high pressure achieving a good angiographic result (**Figure 4**), however slow antegrade flow was noted in the distal artery after the post-dilatation (Thrombolysis in Myocardial Infarction (TIMI) Grade II). She was therefore maintained on a continuous infusion of intravenous heparin. Intravascular imaging was not

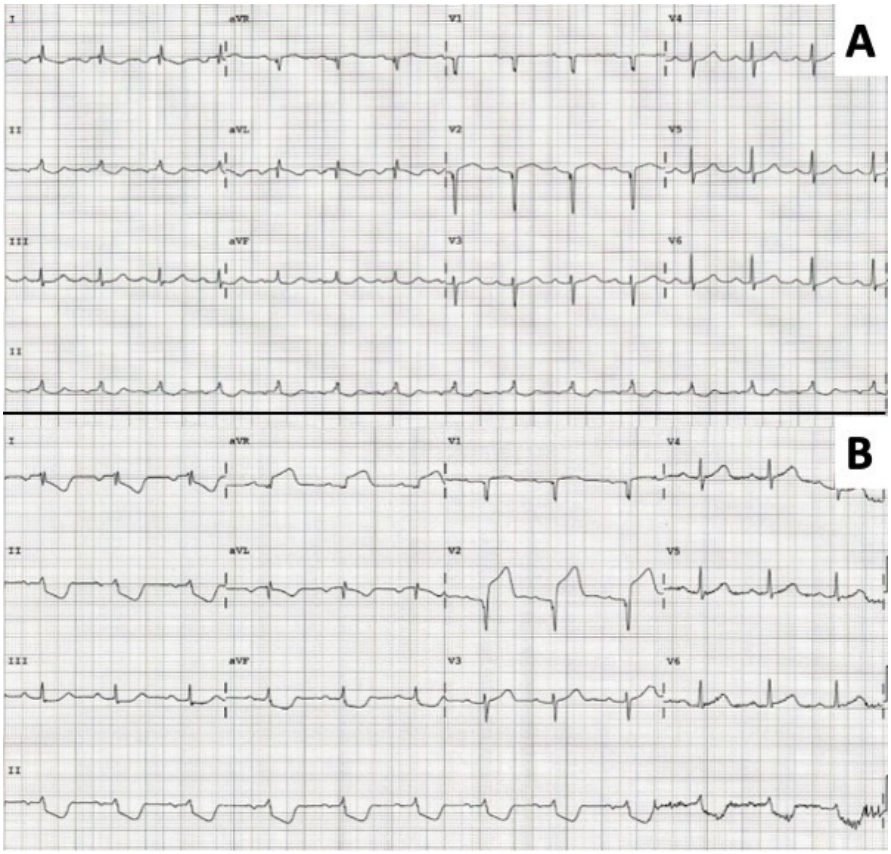


**Figure 2.** Failed thrombolysis. Arrival 12-lead ECG (A) without acute ischaemic changes, and following onset of chest pain (B) on dual anti-platelet and heparin infusion.

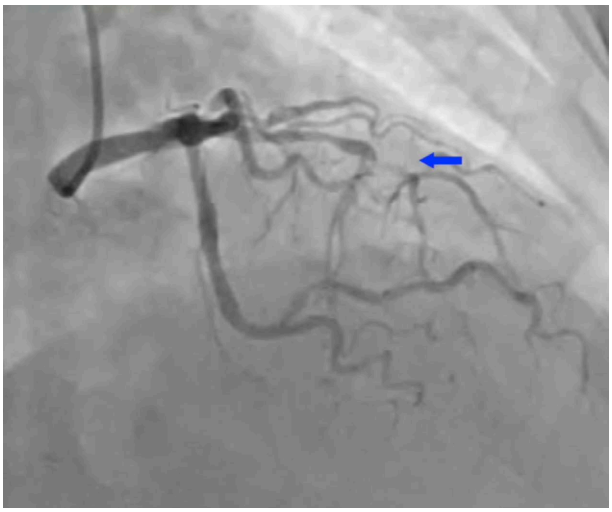

**Figure 3.** Coronary angiogram. Mid-vessel occlusion (blue arrow) of the LAD.e.

undertaken due to the lack of availability within the regional setting.

Post coronary angiogram she remained pain free for two hours. Whilst on triple antithrombotic therapy, her chest pain returned with ECG demonstrating acute change from sinus rhythm with anterior q-waves post PCI (**Figure 5(A)**) to a new right bundle branch block with concurrent 3 mm anterior ST-segment

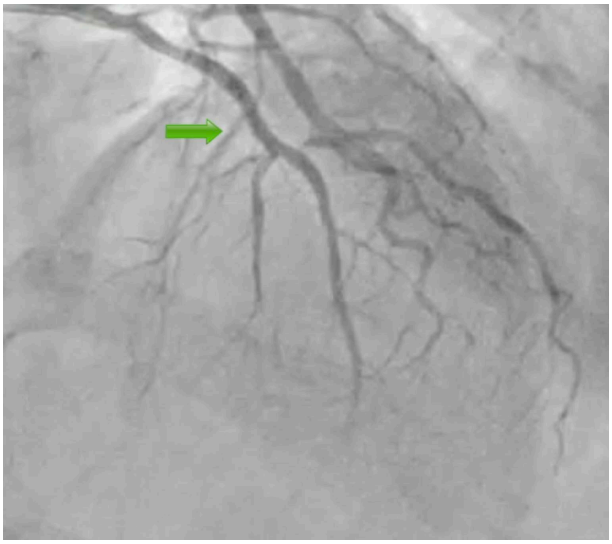

**Figure 4.** Coronary angiogram and PCI. Post PCI and stent insertion (green arrow) of the LAD occlusion with distal TIMI II flow.

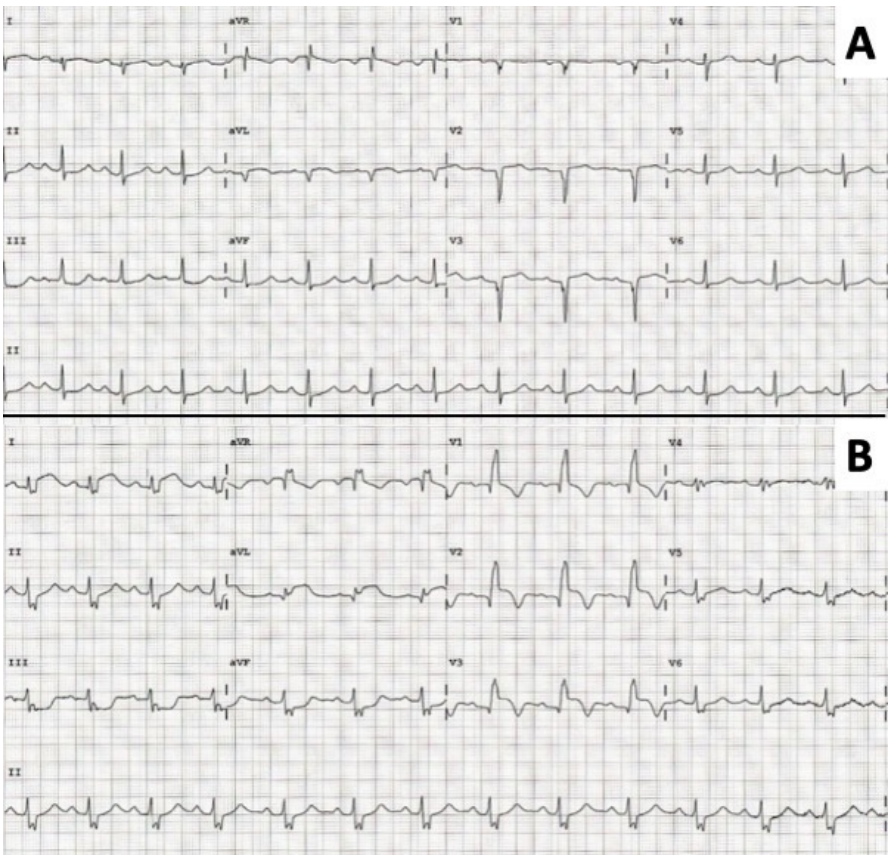


**Figure 5.** Anterior ST-segment myocardial infarction post PCI. 12-lead ECG post recent left anterior descending artery stent (A) and upon return of chest pain (B).

elevation (**Figure 5(B)**). She was commenced on a glyceryl trinitrate infusion and urgently transferred for repeat coronary angiography, which revealed occlusive, acute stent thrombosis (**Figure 6**). Following intracoronary thrombectomy

via an export aspiration catheter (MedtronicAVE, Santa Rosa, CA), further prolonged balloon angioplasty at low and intermediate pressures was performed for the residual thrombus, achieving improved flow albeit some distal embolization (Figure 7). She was commenced on an infusion of glycoprotein IIb/IIIa antagonist, tirofiban.

## 4. Outcome and Follow Up

Our patient remained pain free and stable post repeat coronary angiogram and was transferred to the intensive care unit for monitoring. Her platelets remained stable and within the normal range throughout her admission and a heparin-induced-thrombocytopaenia test was negative. She was subsequently discharged home day four post presentation.

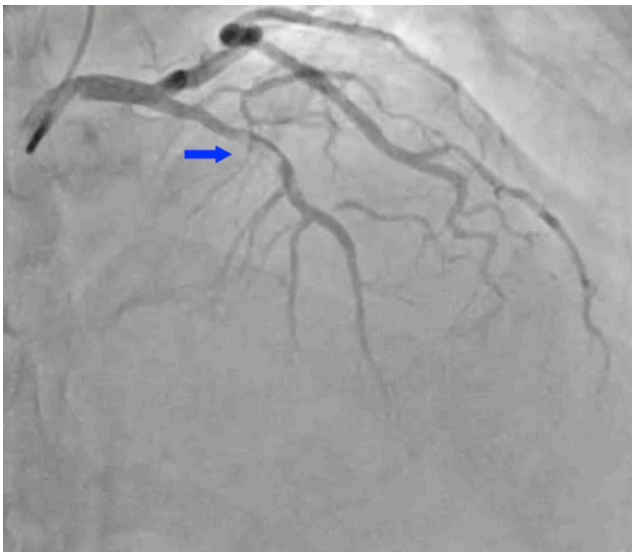

Figure 6. Acute stent thrombosis. Repeat angiography demonstrating acute stent thrombosis (blue arrow).

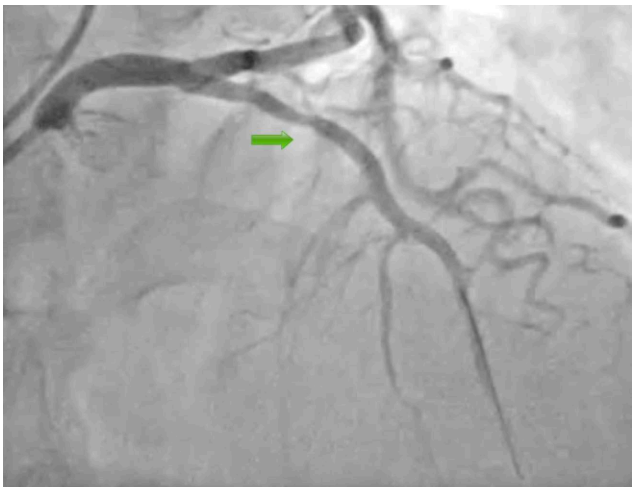

Figure 7. Acute stent thrombosis. Resolution of stent thrombosis post thrombectomy and balloon angioplasty (green arrow) with improved LAD flow.

## 5. Discussion

This case represents recurrent coronary thrombosis due initially to failed thrombolysis and subsequently to acute stent thrombosis. Whilst failed thrombolysis is not uncommon, occurring in up to 40% of patients [1], acute stent thrombosis, within 24 hours, is exceedingly rare, occurring in 0.8% of patients [2]. What is particularly unusual in this case is the consecutive occurrence of outcomes whilst on triple antithrombotic therapy, namely that of aspirin, clopidogrel and continuous heparin infusion. Procedural or device related causes of acute stent thrombosis cannot be completely ruled out in the absence of intravascular imaging, which was unfortunately unavailable within the regional facility.

Clopidogrel resistance must also be considered as a possible cause for acute stent thrombosis. Whilst stent thrombosis on clopidogrel is reported in both the PLATO, at 1.9% [3], and TRITON-TIMI 38, at 2.4% [4], trials, it is important to consider that these outcomes did not occur whilst on a continue heparin infusion, and related to subacute, late and very late stent thrombosis, as per Academic Research Consortium [5], at twelve and fifteen month follow up respectively, rather than the acute stent thrombosis seen in our patient. Whilst clopidogrel resistance has been suspected in acute stent thrombosis [6], these also have occurred on dual rather than triple antithrombotic therapy.

Furthermore, the management of acute stent thrombosis, in addition to invasive thrombectomy and stent balloon angioplasty, includes triple antithrombotic therapy [7], so the development of acute stent thrombosis within two hours of stenting in our patient is noteworthy. A single similar case report exists, that of failed thrombolysis, rescue PCI, followed by sequential acute and subacute stent thrombosis, whilst on triple antithrombotic therapy, occurring in an asymptomatic SARS-CoV-2 positive patient [8].

As the SARS-CoV-2 pandemic has progressed, evidence has emerged of the increased cardiovascular complications of infection, including that of acute coronary syndrome [9], yet the pathogenesis remains incompletely understood. Hypotheses for coronary complications include inflammatory mediated cytokine excess and decreased activation of platelet Mas receptors, with resultant platelet activation, aggregation and thrombosis [10]. Recent interest has also included SARS-CoV-2 vaccinations, particularly ChAdOx1 nCoV-19, an adenovirus vectored vaccine, and its rare side-effect on platelets resulting in thrombotic thrombocytopaenia [11]. Whilst these adverse events are well described and recognised in the clinical setting, reports of patient presenting with acute coronary syndromes post SARS-CoV-2 vaccinations, without thrombocytopenia [12] [13] [14], when considered with the demonstrated activation and aggregation of platelets by adenovirus vaccine vectors via unknown platelet receptors [15], suggest further research is required to ensure patient safety.

Whilst the overall safety and efficacy of the ChAdOx1 nCoV-19 vaccine is well documented [16], the occurrence of rare sequential platelet associated complications in our patient whilst on triple antithrombotic therapy, only previously do-

cumented in a SARS-CoV-2 positive patient, may suggest the association between platelets, SARS-CoV-2, the ChAdOx1 nCoV-19 vaccine, and coronary thrombosis remains to be elucidated. Causality to the ChAdOx1 nCoV-19 vaccine is not claimed in this case and authors acknowledge the possible procedural, device and pharmaceutical causes that may have contributed to our patients' outcomes. This case however highlights possible avenues for further research.

The importance of SARS-CoV-2 vaccinations in controlling the global pandemic cannot be understated. It is vital to recognise that these vaccines are not only efficacious but safe [16]. This case of recurrent coronary artery thrombosis whilst on triple antithrombotic therapy and without clinical or serological evidence of heparin induced thrombocytopaenia, demonstrates the need for ongoing investigation, and for clinicians to remain on high alert if presented with similar circumstances.

## 6. Learning Points

- Fibrinolysis remains first line treatment of STEMI in healthcare setting greater than 120 minutes from PCI capable centres. Transfer to PCI capable centres should be initiated post fibrinolysis due to the risk of failed therapy.
- Recurrent chest pain and ST-segment elevation post thrombolysis and PCI always require prompt management, however increased suspicion for recurrent thrombosis post ChAdOx1 nCoV-19 vaccination may be prudent.
- Whilst stent thrombosis is relatively rare in the modern era, patient, device, and procedural related factors can be contributing factors and require appropriate assessment.
- Further investigation may be required to completely understand the relationship between platelets, SARS-CoV-2, the ChAdOx1 nCoV-19 vaccine, and thrombotic events.
- ChAdOx1 nCoV-19 vaccine remains a safe vaccination and is vital in the SARS-CoV-2 pandemic response.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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