



Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Research Brief

Coronary thrombo-embolic events after Covid-19 vaccination- a single centre study

Refai Showkathali^{*}, Radhapriya Yalamanchi, Lavanya Narra, Nandhini Vinayagamoorthy, Sengottuvelu Gunasekaran, Rajeshwari Nayak, Y. Vijayachandra Reddy, Asha Mahilmaran, Kanthallu Narayanamoorthy Srinivasan, Abraham Oomman, Dhamodaran Kaliyamoorthy

Department of Cardiology, Apollo Main Hospital, Chennai, India

ARTICLE INFO

Article history:

Received 25 August 2021

Received in revised form

7 November 2021

Accepted 26 January 2022

Available online xxx

Keywords:

Thrombo-embolic

COVID-19 vaccine

Acute Coronary syndrome

Thrombus

Coronary Thrombosis

Vaccine

ABSTRACT

Thrombo-embolic complications after Corona virus disease-19 (COVID-19) vaccination have been previously reported. We aimed to study the coronary thrombo-embolic complications (CTE) after COVID-19 vaccination in a single centre during the initial 3 months of vaccination drive in India. All patients admitted to our hospital between 1st March 2021 and 31st May 2021 with Acute coronary syndrome (ACS) were included.

Of the 89 patients [Age 55 (47–64)y, 13f] with ACS and angiographic evidence of coronary thrombus, 37 (42%) had prior vaccination history. The timing from last vaccination dose to index event was <1, 1–2, 2–4 and >4 weeks in 9(24%), 4(11%), 15(41%) and 9 (24%) respectively. ChAdOx1 nCoV-19/AZD1222 (Covishield) was the most used vaccine- 28 (76%), while 9 (24%) had BBV152 (Covaxin). Baseline characteristics were similar in both vaccinated (VG) and non-vaccinated group (NVG), except for symptom to door time [8.5 (5.75–14) vs 14.5 (7.25–24) hrs, $p = 0.003$]. Thrombocytopenia was not noted in any of the VG patients, while 2 (3.8%) of NVG patient had thrombocytopenia ($p = 0.51$). The pre- Percutaneous Coronary Intervention (PCI) Thrombolysis in Myocardial Infarction (TIMI) flow was significantly lower [1 (0–3) vs 2 (1–3), $p = 0.03$] and thrombus grade were significantly higher [4 (2.5–5) vs 2 (1–3), $p = 0.0005$] in VG. The in-hospital (2.7% vs 1.9%, $p = 1.0$) and 30-day mortality were also similar (5.4% vs 5.8%, $p = 1.0$).

This is the first report of CTE after COVID-19 vaccination during the first 3 months of vaccination drive in India. We need further reports to identify the incidence of this rare but serious adverse events following COVID-19 vaccination.

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1. Introduction

Various types of vaccines have been developed for Corona virus disease 2019 (COVID - 19) caused by SARS-CoV-2 across the world and as of 28th May 2021, 817 million people (10.5%) were vaccinated in the world.¹ Vaccine related thrombo-embolic (TE) complications, though rare, have been reported with ChAdOx1 nCoV-19/AZD1222 (University of Oxford/AstraZeneca and Serum Institute of India) and Ad26.COV2.S (Janssen) vaccines, mostly from Europe and North America.^{2–4} ChAdOx1 nCoV-19/AZD1222 has also been temporarily suspended in Austria, Denmark and several

other European countries on March 11th after few cases of thrombosis have been reported until further investigation and resumed after thorough analysis of risk-benefit assessment on March 19th 2021 by the European Medicine Agency (EMA).⁵ In India, until 31st May 2021, two vaccines for COVID- 19 have been used- ChAdOx1 nCoV-19/AZD1222 (called Covishield- Serum Institute, India) and inactivated BBV152 vaccine- Covaxin (Bharat Biotech, India). Vaccination for general public started on 1st of March, 2021 in various phases in India. As of 28th May 2021, 161 million Indians (11.6% of population) had at-least one dose of vaccine.¹ The ministry of health and family welfare (MOHFW) of India released a document on 17th May 2021 reporting the National adverse events following Immunisation (AEFI) committee analysis of the data related to the TE risk post vaccination in India. According to this report, as of 3rd April 2021 approximately 68.7 and 6.8

^{*} Corresponding author. Professor, Apollo Hospitals and Educational Research Foundation, Chennai.

E-mail address: refais@gmail.com (R. Showkathali).

<https://doi.org/10.1016/j.ihj.2022.01.002>

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million doses of Covishield and Covaxin respectively were administered in India. The potential TE complication following Covishield vaccination was reported to be 0.61 cases/million doses, while none was reported with Covaxin administration.⁶ We aimed to look at the coronary TE events in subjects who underwent COVID-19 vaccination during the first 3 months period of vaccination drive.

2. Methods

All patients who were admitted to our hospital between 1st March 2021 and 31st May 2021 (inclusive) with Acute coronary syndrome (ACS) were included and their angiographic images were analysed by qualified cardiologists (RS and RY). Patients who had angiographic evidence of coronary thrombus were included for further analysis and all others were excluded for this study. A detailed COVID-19 vaccination history including the type, dose and date of vaccine were taken as a part of history taking at the time of hospital admission. The study has been approved by our Institutional Ethics committee and the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation. All patients were followed up for a period of 30 days. TIMI flow grade and TIMI thrombus grade were used as per definition.

Categorical variables are expressed as numbers and percentages. Normally distributed continuous variables are expressed as median (IQR), unless mentioned otherwise. Comparison between two groups was performed using Fisher's Exact test for categorical variables and the paired two-tailed 't' test for normally distributed variables. A *p* value of <0.05 is considered significant.

3. Results

Out of the total of 146 patients [ST elevation myocardial infarction (STEMI)- 79, Non-ST elevation myocardial infarction (NSTEMI)- 48, Unstable angina (UA)- 19] admitted with ACS, 130 patients (89%) underwent coronary angiography. Of these, 89 [Age 55 (47–64)y, 13 F] patients (68.5%) were identified to have thrombus on coronary angiography and included for analysis (Fig. 1). Of these, 37 (42%) had history of COVID-19 vaccination prior to this episode. The timing from the last COVID-19 vaccination dose and the index event was <1 week in 9 (24%), 1–2 weeks in 4 (11%), 2–4 weeks in 15 (41%) and >4 weeks in 9 (24%) patients respectively. Covishield was the most commonly used vaccine - 28 (76%), while 9 patients (24%) had Covaxin. The index event happened after the first dose and second dose of vaccine in 24 (65%) patients and 13 (35%) patients respectively. The baseline characteristics of those who had vaccination (VG) and no vaccination (NVG) are compared in Table 1. The symptom to door time was shorter in the VG compared to NVG [8.5 (5.75–14) vs. 14.5 (7.25–24) hrs, *p* = 0.003]. In NVG, 4 (7.7%) had COVID RTPCR positive prior to this index event, while one patient (2.7%) in VG had positive RTPCR, more than a month before the vaccination. Two patients (5.4%) in VG developed RTPCR positivity during this index hospital stay. Thrombocytopenia was not noted in any of the VG patients, while 2 (3.8%) of NVG patient had thrombocytopenia. All patients had loading dose of at least one anti-platelet on admission prior to angiogram - Aspirin (100%), Clopidogrel (62.9%), Ticagrelor (25.8%), Prasugrel (4.5%) (Table 2). The Pre-Percutaneous Coronary Intervention (PCI) Thrombus in Myocardial Infarction (TIMI) flow was significantly

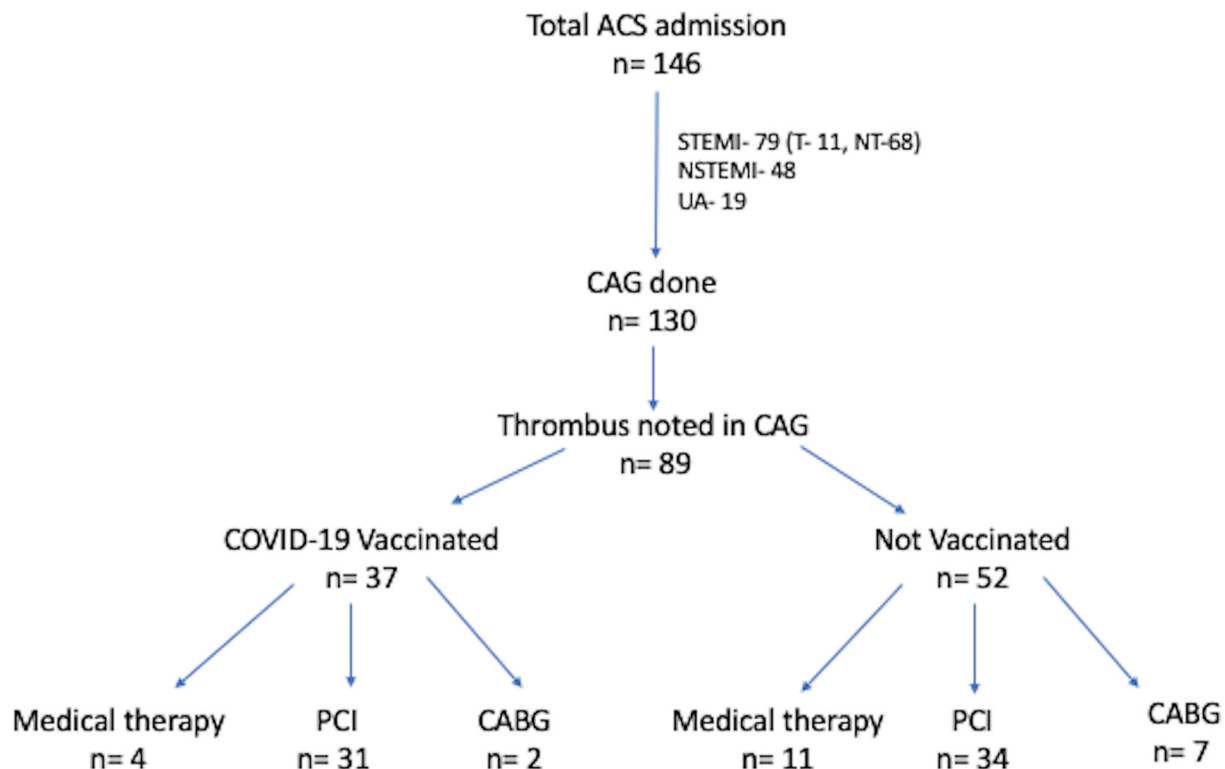


Fig. 1. Flow chart of patients admitted with Acute Coronary Syndrome

Abbreviations- ACS- Acute Coronary Syndrome, STEMI- ST elevation myocardial infarction, NSTEMI- Non-ST elevation myocardial infarction, UA- Unstable angina, CAG- Coronary angiography, PCI- Percutaneous Coronary Intervention, CABG- Coronary artery bypass surgery.

Table 1
Baseline Characteristics of patients.

n (%)	All patients n = 89	VG n = 37	NVG n = 52	P value
Age (y)	55 (47–64)	57 (49–67)	55 (44–64)	0.20
Male	76 (85.4)	32 (86.5)	44 (84.6)	1.0
Diabetes	53 (59.6)	24 (64.9)	29 (55.8)	0.5
Hypertension	45 (50.6)	19 (51.4)	26 (50)	1.0
Dyslipidemia	38 (42.7)	16 (43.2)	22 (42.3)	1.0
Smoker	3 (3.4)	1 (2.7)	2 (3.8)	1.0
Previous Anti-platelet use	10 (11.2)	5 (13.5)	5 (9.6)	0.74
NOAC	1 (1.1)	1 (2.7)	0	0.41
Previous CAD	10 (11.2)	5 (13.5)	5 (9.6)	0.74
Previous CVA	2 (2.2)	1 (2.7)	1 (1.9)	1.0
Previous COVID-19 infection	5 (5.6)	1 (2.7)	4 (7.7)	0.40
Renal impairment (e GFR<60)	9 (10.1)	4 (10.8)	5 (9.6)	1.0
Symptom to door time (hrs)	12 (6–18)	8.5 (5.75–14)	14.5 (7.25–24)	0.003
Cardiogenic Shock	4 (4.5)	1 (2.7)	3 (5.8)	0.64
Platelet count*	292 (225–364)	275 (217–346)	308 (243–390)	0.21
Thrombocytopenia (<150*)	2 (2.2)	0	2 (3.8)	0.51

VG- Vaccinated group, NVG- Non-Vaccinated group, NOAC- Novel Oral Anti-coagulants, CAD-coronary artery disease, CVA- Cerebrovascular event, COVID – 19- Corona virus disease – 19, GFR- Glomerular filtration rate.

*- times 1000/dl of blood.

Table 2
Clinical and Procedural Characteristics of patients.

	All patients n = 89	Vaccinated n = 37	Non-vaccinated n = 52	P value
STEMI	56 (63)	27 (73)	29 (55.8)	0.12
NSTEMI	23 (25.8)	8 (21.6)	15 (28.8)	0.47
UA	10 (11.2)	2 (5.4)	8 (15.4)	0.18
Prior Thrombolysis	8 (9)	2 (5.4)	6 (11.5)	0.46
Loading dose				
Aspirin	89 (100)	37 (100)	52 (100)	1.0
Clopidogrel	56 (62.9)	22 (59.5)	34 (65.4)	0.66
Ticagrelor	23 (25.8)	11 (29.7)	12 (23.1)	0.62
Prasugrel	4 (4.5)	4 (10.8)	0	0.03
Culprit vessel:				
LAD	49 (55.1)	22 (59.5)	27 (51.9)	0.50
RCA	26 (29.2)	10 (27.0)	16 (30.8)	0.77
Cx	14 (15.7)	5 (13.5)	9 (17.3)	0.81
Pre-PCI TIMI flow	2 ^{1–3}	1 (0–3)	2 ^{1–3}	0.03
TIMI 0/1 flow	43 (48.3)	22 (59.5)	21 (40.4)	0.09
Thrombus grade	3 ^{2–4}	4 (2.5–5)	2 ^{1–3}	0.0005
PCI done	65 (73)	31 (83.8)	34 (65.4)	0.09
Stent diameter	2.75 (2.5–3)	2.75 (2.5–3)	3 (2.7–3)	0.44
Stent length	26 (23–32.5)	26 (23–33)	26 (23–32)	0.59
Post PCI TIMI flow	3 (3–3)	3 (3–3)	3 (3–3)	0.62
Gp2b3a inhibitor use	10 (11.2)	7 (18.9)	3 (5.7)	0.09

VG- Vaccinated group, NVG- Non-Vaccinated group, LAD- Left anterior descending artery, RCA- Right coronary artery, Cx- Circumflex artery, PCI – Percutaneous coronary intervention, TIMI- Thrombolysis in myocardial infarction, GP2b3a- Glycoprotein 2b3a.

lower [1 (0–3) vs 2, ^{1–3} $p = 0.03$], and thrombus grade were significantly higher [4 (2.5–5) vs. 2, ^{1–3} $p = 0.0005$] in the VG patients (Table 2). There were numerically more patients who had TIMI 0/I flow in VG group, but this did not reach statistical significance [22 (59.5%) vs. 21 (40.4%), $p = 0.09$]. There was no difference in the management of patients between the two groups - VG vs. NVG- PCI [31 (83.7%) vs. 34 (65.4%), $p = 0.09$], Coronary artery bypass surgery (CABG) referral [2 (5.4%) vs. 7 (13.5%), $p = 0.3$] and medical management [4 (10.8%) vs. 11 (21.2%), $p = 0.26$]. The procedural characteristics of the patients in both groups are shown in Table 2. The post-PCI TIMI flow was similar in both groups (Table 2). In those who underwent primary PCI for STEMI, there was no significant difference in “door to wire crossing time” (53 ± 20 vs. 51 ± 20 min, $p = 0.31$). The in-hospital (VG 2.7% vs. NVG 1.9%, $p = 1.0$) and 30 day mortality were also similar (VG 5.4% vs. NVG 5.8%, $p = 1.0$).

4. Discussion

This is the first report of coronary thrombotic events in COVID-19 vaccinated subjects during the first 3 months of vaccination drive in India. The previous reported cases of TE events post vaccination from other parts of the world are mostly associated with autoantibodies directed against the platelet factor 4 (PF4) antigen leading to severe thrombocytopenia.^{3,4} This syndrome was designated as Vaccine-induced immune thrombotic thrombocytopenia (VITT) or Thrombosis with thrombocytopenia syndrome (TTS). The syndrome likely begins in a narrow window of 5–10 days post-vaccination, leading to identification of cases typically between 5 and 30 days post-vaccination. None of our patients in the VG had thrombocytopenia suggesting they did not fit into this syndrome. The occurrence of VITT was more commonly associated with adenoviral vector vaccine like Covishield and Ad26. COV2. Sjaanssen.^{3–5} However, TE complications were also noted with mRNA vaccines like m-RNA Pfizer–BioNTech vaccine (Pfizer, New

York) and m-RNA-1273 (Moderna), suggesting there may be a different mechanism than VITT. There has also been a case report of coronary tree thrombosis in a patient within few hours of having the m-RNA Pfizer–BioNTech vaccine.⁷ Even though causality of vaccine to the thrombotic episode could not be confirmed, the occurrence of this event needs to be analysed and reported. In our study, it is important to note that the thrombus burden is significantly high and TIMI flow is significantly low in vaccinated patients suggesting vaccine may have a contributing element for the TE events. However, relatively low number of patients in the vaccinated group had thrombolysis, though statistically not significant, could have contributed to the high thrombus burden seen in the group. It is well established that COVID-19 disease itself is a high prothrombotic state and an immune response with the vaccine can also lead to a high thrombotic state, irrespective of thrombocytopenia. The shorter symptom to door time in the VG group suggests that the patients were well informed about the risks associated with the vaccine and to get medical help sooner, if any new symptoms appear.

The incidence of coronary thrombosis in vaccinated patients in our region cannot be interpreted from this report, as this is a single centre study, while vaccine have been given in many centres in the city. Also, until 31st May 2021, very few under the age of 45 years have been vaccinated, as the vaccine drive was in different phases according to the age. According to the Indian government database, as of 8th June 2021 around 2.24 million vaccine doses have been administered in Chennai, India with Covishield in 1.66 million and Covaxin in 0.58 million people.⁸ Our report with 76% and 24% of patients post-Covishield and Covaxin respectively may be a reflection of the proportionate usage of vaccine rather than an increased incidence with Covishield. This is also the first report about the incidence of coronary thrombosis after vaccination with Covaxin, the full phase III trial of which is not fully published in a peer-review medical journal yet.

5. Conclusion

This single centre study showed that 42% of patients admitted with ACS and found to have coronary thrombosis had recent COVID-19 vaccination. Both types of vaccine (Covishield and Covaxin) were associated with coronary TE events. We need further

studies to identify the incidence of this rare, but serious adverse events following COVID-19 vaccination and to identify if causality can be confirmed or not. Considering more younger people are going to be vaccinated in the coming few months, this needs to be addressed as a matter of urgency and to consider ways to prevent this.

Funding

None.

What is already known?

Vaccine related thrombo-embolic (TE) complications, though rare, have been reported with COVID-19 vaccines, mainly from Europe and North America.

What this study adds?

In patients admitted with Acute Coronary Syndrome and angiographic evidence of coronary thrombosis, 42% had prior COVID-19 vaccination.

Declaration of competing interest

None.

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