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CORONARY INTERVENTIONS

INTERMEDIATE

CASE REPORT: CLINICAL CASE SERIES

A Case Series of Stent Thrombosis During the COVID-19 Pandemic

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ABSTRACT

Coronavirus disease-2019 (COVID-19) triggers a hypercoagulable state with a high incidence of thrombotic complications. We have noted a higher than expected incidence of stent thrombosis in these patients. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:1291–6) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

INTRODUCTION

Advances in percutaneous coronary intervention (PCI) techniques, improvement in coronary stent designs, and more effective antithrombotic therapies have made coronary stent thrombosis a rare complication. The incidence at 30 days is <1%, whereas rates of late and very late stent thrombosis are 0.5% to 1% and 0.2% to 2% per year, respectively (1). Coronavirus disease-2019 (COVID-19) has modified the usual presentation of many diseases as we know them. This disease promotes a sustained prothrombotic state, triggered by interactions among proinflammatory cytokines, procoagulant factors, and platelets. We have recently observed an increase in stent thrombosis during the COVID-19 pandemic peak in our center, the Complejo Hospitalario Universitario de Albacete in Albacete, Spain.

LEARNING OBJECTIVES

- COVID-19 increases both arterial and venous thrombogenicity.
- The SARS-CoV-2 hypercoagulable state may lead to a stent thrombosis trigger in the presence of other mechanical and biological risk factors.
- Recommendations on antithrombotic treatment and PCI for acute coronary syndromes should be maintained during COVID-19 treatment.

CASE REPORTS

CASE 1. A 49-year-old man underwent primary angioplasty for a lateral ST-segment elevation myocardial infarction (STEMI) 6 h after the onset of symptoms (**Figures 1A to 1F**). Balloon angioplasty in a small ramus intermedius was performed. To decrease hospital length of stay, ad hoc PCI was performed in the circumflex artery with 2 overlapped drug-eluting stents (DES) (Videos 1 and 2). Thirty minutes later, there was new onset of more intense chest pain with marked ST-segment depression in the precordial leads. Acute circumflex artery stent thrombosis was confirmed by repeat angiography (Video 3). Optical coherence tomography demonstrated in-stent mixed thrombus with mild proximal stent underexpansion and a nonsignificant dissection of the distal stent edge. Intracoronary tirofiban was effective in

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ABBREVIATIONS AND ACRONYMS

ASA = acetyl salicylic acid

COVID-19 = coronavirus disease-2019

DES = drug-eluting stent

LAD = left anterior descending

PCI = percutaneous coronary intervention

SARS-CoV-2 = severe acute respiratory syndrome-coronavirus-2

STEMI = ST-segment elevation myocardial infarction

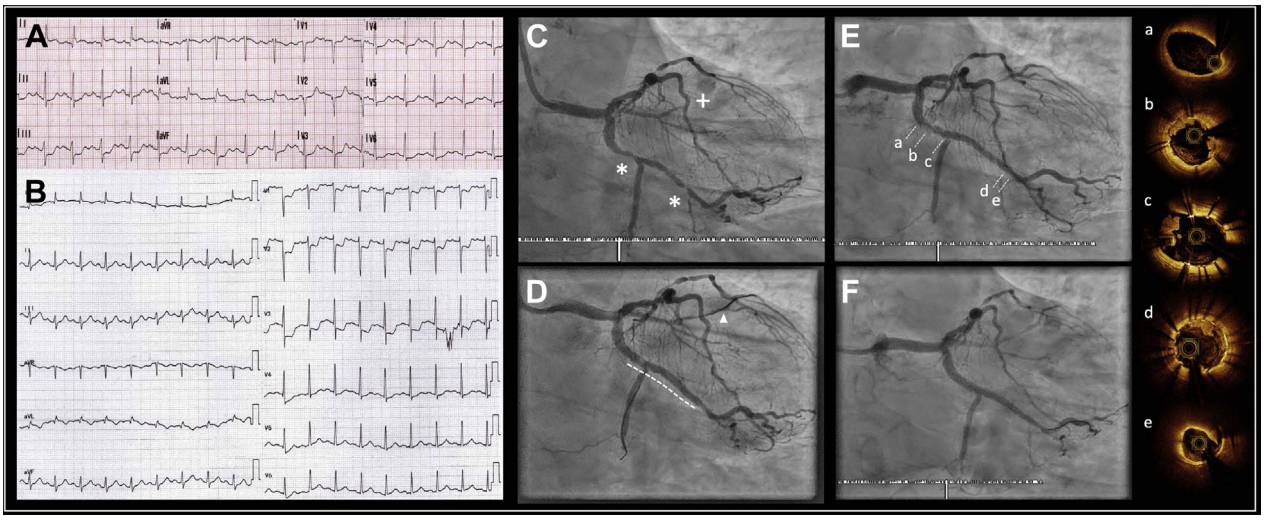
reducing thrombus burden, and proximal overexpansion of the stent was performed (Videos 4 and 5). The patient received acetyl salicylic acid (ASA), ticagrelor, and a 24-h continuous infusion of tirofiban after the procedure. He had dry cough with a chest radiograph compatible with COVID-19 infection, but no tests were performed because we were at the early stage of the pandemic and the threshold of suspicion was high. The patient was discharged at 4 days. Serological testing 23 days later confirmed that immunoglobulin G was positive for severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).

CASE 2. A 71-year-old man was admitted in 2007 for an inferior STEMI that was treated with right coronary artery DES. He presented with a high-risk non-STEMI resulting from very late right coronary artery stent thrombosis. Thrombectomy, tirofiban, and 2 DESs restored flow. The patient reported fever and cough some days before admission; blood testing and chest radiograph showed COVID-19-compatible findings. The patient remained asymptomatic, and no confirmatory tests were performed for the same reason as in the first patient.

CASE 3. An 86-year-old man with history of non-STEMI in 2018 that was treated with left anterior descending (LAD) artery DES underwent primary angioplasty for 6 h of chest pain and an anterior STEMI. Very late LAD artery stent thrombosis was found, and a new DES was implanted. The patient was asymptomatic, but because the COVID-19 pandemic had reached its peak, a pre-admission polymerase chain reaction test was performed, with a positive result. The patient had a favorable course and was discharged 5 days later.

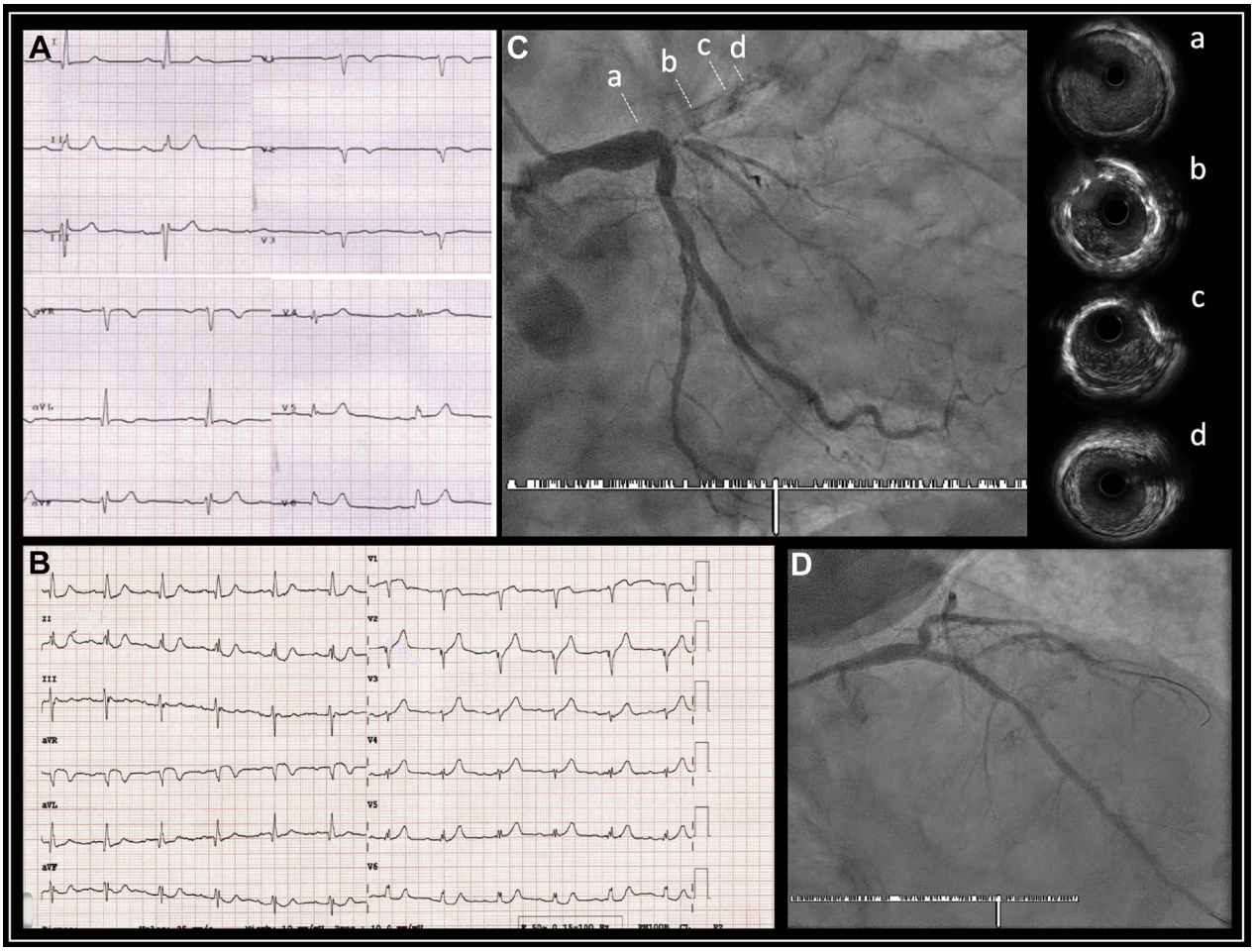
CASE 4. An 85-year old man underwent PCI with ostial LAD artery DES implantation in 2005. He presented at the pandemic peak with chest pain, a left ventricular ejection fraction of 30%, and anterior ST-segment elevation with prior Q waves (**Figures 2A to 2D**). The result of immunoglobulin M serological testing was positive despite the absence of respiratory symptoms. Angiography demonstrated very late LAD artery stent thrombosis (Video 6), which was treated with balloon angioplasty, thrombectomy, and tirofiban (Video 7). Intravascular ultrasound was performed and showed in-stent thrombus, appropriate stent expansion, and nonsignificant neoatherosclerosis (Video 8). The patient was treated with combined lopinavir and ritonavir, and despite his age, received ASA and prasugrel

FIGURE 1 Case 1: Acute Stent Thrombosis



(A) Electrocardiogram at admission showing lateral ST-segment elevation myocardial infarction. **(B)** Electrocardiogram 30 min after circumflex percutaneous coronary intervention showing posterior ST-segment elevation myocardial infarction. **(C)** Ramus occlusion **(+)** and 2 critical lesions **(asterisks)** in the proximal circumflex artery and first marginal branch. **(D)** Final result after percutaneous coronary intervention of ramus **(arrowhead)** and circumflex arteries (**dotted line** indicates the position of 2 overlapped drug-eluting stents). **(E)** Stent thrombosis, with haziness at the **(a)** proximal and **(d)** distal edge, as well as **(c)** at the bifurcation. **(F)** Final result after stent thrombosis treatment, with complete flow restored. **(a to d),**optical coherence tomography imaging showing **(a)** no compromise of the proximal edge, **(b)** mild proximal underexpansion of stent with mixed thrombus, which can also be observed **(c)** in the origin of the second marginal branch and **(d)** near the distal edge, which has **(e)** mild dissection.

FIGURE 2 **Case 4: Very Late Stent Thrombosis**



(A) Baseline electrocardiogram showing anterior Q waves with negative T waves in the precordial leads. **(B)** Electrocardiogram on admission, with ST-segment elevation in the precordial leads and reciprocal changes in the inferior leads. **(C)** Complete ostial left anterior descending artery stent thrombosis; **(a to d)** indicate the level of the images obtained with intravascular ultrasound. **(D)** Left anterior descending artery flow restored after percutaneous coronary intervention. Intravascular ultrasound images: **(a),** left main coronary artery immediately proximal to stent; **(b)** and **(c),** correct expansion without malapposition or neoatherosclerosis and with thrombus adhered to the stent; **(d),** distal edge of the stent, without complications.

as antiplatelet therapy. Ten days later, prasugrel was replaced by clopidogrel (after antiviral treatment was completed), and the patient was discharged.

DISCUSSION

The COVID-19 pandemic has significantly decreased worldwide interventional cardiology activity. In Spain, cardiac catheterization procedures have been reduced by 48%, with a reduction of 40% for primary angioplasty (2). Similar data have been reported in the United States (3). Compared with the immediate period before the pandemic peak (February 1 to 23, 2020), we experienced a 38% decrease in PCIs at our center between March 15, 2020 and April 5, 2020 (31 vs. 50). Moreover, we had an increase in the incidence of stent thrombosis (4 vs. 0; 13% of PCIs performed during this period). In 2019, we performed 899 PCIs, with 11 (1.2%) cases of stent thrombosis. Given the perception of a high rate of stent thrombosis among COVID-19 cases in other centers in Spain, a prospective registry is being conducted.

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TABLE 1 Summary of Cases of Stent Thrombosis Presented During the COVID-19 Pandemic

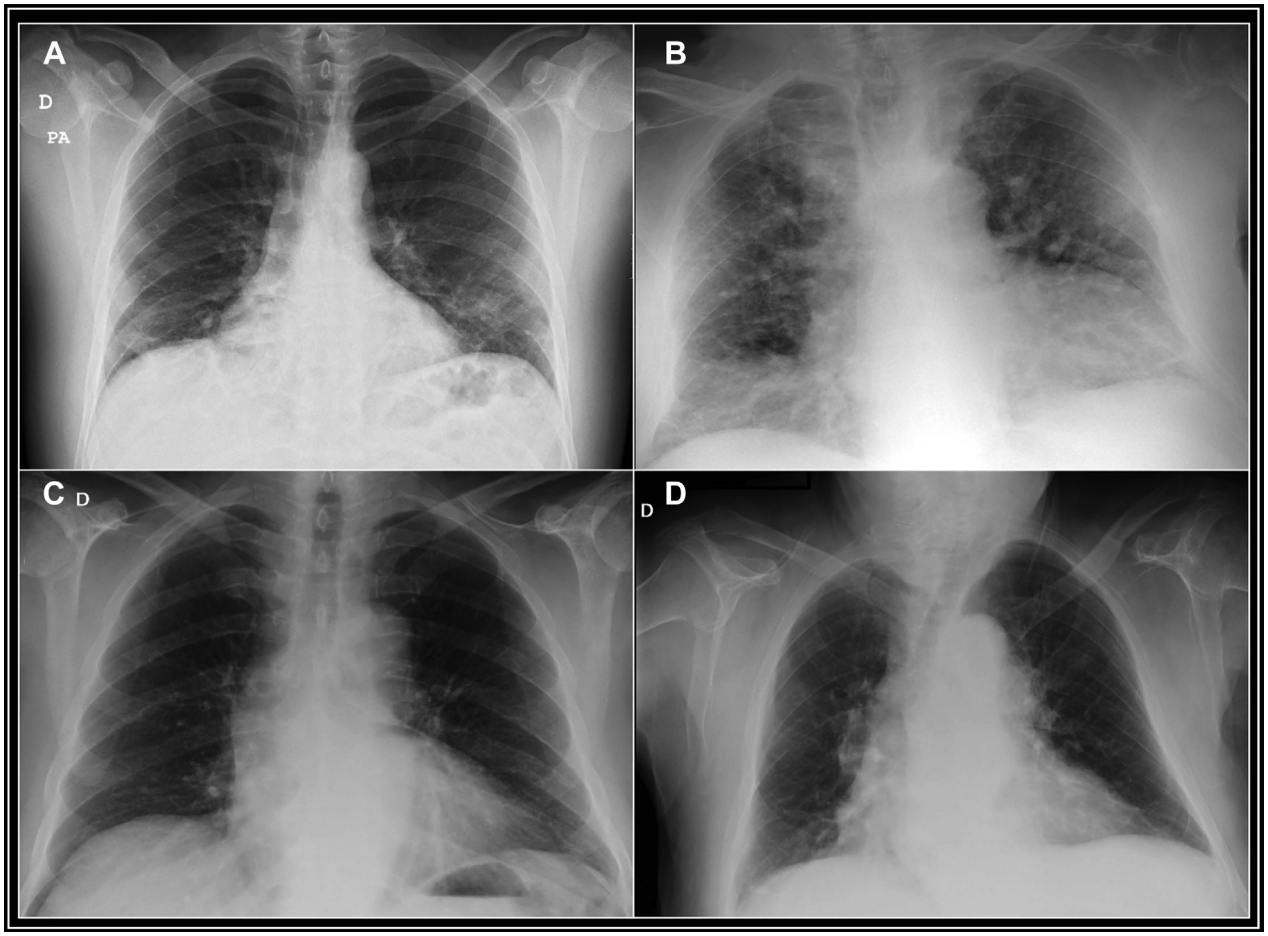
	Case 1	Case 2	Case 3	Case 4
Age, yrs	49	71	86	85
Sex	Male	Male	Male	Male
COVID-19 status	IgG +	Suspicion	PCR +	IgM +
COVID-19 presentation	Cough, bilateral ground-glass infiltrates	Cough, fever, bilateral ground-glass infiltrates	Asymptomatic, bilateral ground-glass infiltrates	Asymptomatic, bilateral ground-glass infiltrates.
COVID19 treatment	No	No	Hydroxychloroquine Acetylcysteine	Hydroxychloroquine Azithromycin Lopinavir-ritonavir Ceftriaxone
Presentation	STEMI	NSTEMI	STEMI	STEMI
Physical examination	Rales up to $^1/_2$ lung fields	Normal	Normal	Peripheral edema
Heart rate (beats/min)	110	53	75	80
Blood pressure (mm Hg)	150/86	150/85	160/80	110/60
So_2 (%)	90	96	95	95
Temperature (°C)	36.5	37.5	36	35.6
Vessel responsible	Proximal circumflex - OM (90% stenosis)	Mid-RCA (occluded)	Proximal LAD (occluded)	Proximal LAD (occluded)
Stent thrombosed	DES ×2 (Ultimaster 3 × 15 mm)	BMS (Driver 3.5 × 18 mm)	DES (Cypher 3 × 18 mm)	DES (Synergy 3.5 × 32 mm)
Timing	Acute (30 min)	Very late (13 yrs)	Very late (2 yrs)	Very late (4 yrs)
APT before admission	None	ASA	ASA	ASA
APT during PCI	ASA + clopidogrel	ASA+ clopidogrel	ASA + clopidogrel	ASA+ prasugrel
Anticoagulation during PCI	UFH 8,000 IU	UFH 5,000 IU	UFH 8,000 IU	UFH 7,000 IU
Vascular approach	Right radial	Left radial	Left radial	Left radial
PCI technique	GPI BA OCT guidance	Thrombectomy DES (Synergy 4 × 28 mm) GPI	DES (Ultimaster 3 × 15 mm)	Thrombectomy BA IVUS guidance
APT discharge	ASA + ticagrelor	ASA+ ticagrelor	ASA + clopidogrel	ASA + clopidogrel
LVEF (%) at discharge	45%	55%	45%	30%
Risk factors for stent thrombosis				
Patient	DM LVD ACS	CKD ACS	Age DM LVD CKD ACS PAD	Age LVD ACS
Lesion	Bifurcation	No	No	Ostial lesion
Procedural	Primary PCI Multivessel PCI Malapposition Underexpansion Dissection	No	First-generation DES Overlapped stents	Long stent

ACS = acute coronary syndrome; APT = antiplatelet therapy; ASA = acetyl salicylic acid; BA = balloon angioplasty; BMS = bare metal stent; CKD = chronic kidney disease; COVID-19 = coronavirus disease-2019; DES = drug-eluting stent; DM = diabetes mellitus; GPI = glycoprotein IIb-IIIa inhibitor; IU = international units; IVUS = intravascular ultrasound; NSTEMI = non-ST-segment elevation myocardial infarction; OCT = optical coherence tomography; OM = obtuse marginal branch; RCA = right coronary artery; LAD = left anterior descending; LVEF = left ventricular ejection fraction; LVD = left ventricular dysfunction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; So_2 = oxygen saturation; STEMI = ST-segment elevation myocardial infarction; UFH = unfractionated heparin.

A greater thrombogenic predisposition, both arterial and venous, during COVID-19 has been established. Pathophysiologically, the cytokine storm that occurs 5 to 7 days after the onset of symptoms promotes the coagulation cascade, as well as platelet activation mediated by interleukin-6 and tissue factor. The latter induces an increase in thrombin and fibrin synthesis, as well as platelet production. Thrombocytosis can occur, as can high levels of D-dimer and fibrinogen, with intravascular disseminated coagulation criteria often fulfilled (4,5). Additionally, endothelial damage, which could be caused by the virus binding to the angiotensin-converting enzyme receptor and the stasis promoted by the permanent inflammation, would complete the Virchow triad criteria (6).

We present 1 case of acute stent thrombosis and 3 very late stent thrombosis cases (Table 1). Despite no initial COVID-19 testing in 2 cases, symptoms and subsequent testing (Figures 3A to 3D) supported that the patients were infected at the time of stent thrombosis (Table 2).

FIGURE 3 Chest Radiographs of Patients



(A) Case 1, peripheral interstitial infiltrates, mainly affecting the left base and subpleural regions. **(B)** Case 2, both central and peripheral alveolointerstitial infiltrates, probably from mixed heart failure. **(C)** (Case 3) and **(D)** (Case 4), mild infiltrates, mainly central and resulting from mild heart failure. D = right; PA = posteroanterior.

Very late stent thrombosis with a first-generation DES occurs in the presence of a sustained inflammatory response. Other factors such as delayed endothelialization, late malapposition, or neoatherosclerosis plaque rupture can sometimes be implicated (7). Two of our patients had chronic kidney disease, which can induce a permanent inflammatory response, and 1 patient had a first-generation DES. The patient with acute stent thrombosis had mild proximal stent underexpansion detected by optical coherence tomography. All patients were receiving appropriate antiplatelet therapy at the time of stent thrombosis; the patient with acute thrombosis was following an ASA-clopidogrel regimen, whereas the 3 patients with very late stent thrombosis were taking ASA therapy. We think that SARS-CoV-2 infection triggered stent thrombosis in these patients.

TABLE 2 Summary of Laboratory Testing

	Case 1	Case 2	Case 3	Case 4
COVID-19 tests	IgM−/IgG +	Not performed	PCR +	IgM+/IgG−
D-dimer (45-500 μg/l)	630	539	662	1,251
Fibrinogen (150-450 mg/dl)	443	271	263	263
Partial thromboplastin time (25-39 seg)	32.7	28.3	29.4	31.1
Prothrombin time (70%-120%)	67	93	93	55
Platelets (140-400 × 10^3/μl)	175	127	167	165
C-reactive protein (0-5 mg/l)	12	24	9.6	40.5
Ferritin (30-400 ng/ml)	1,233	1,010	72	2,411
Lymphocyte count (1-4 × 10^3/μl)	1,590	930	2,240	790
High-sensitivity T troponin peak (0-14 pg/ml)	2,404	3,324	2,406	7,782
Creatine kinase peak (38-174 U/l)	874	634	523	1,276
GFRe (ml/min)	110	56	68	44

COVID-19 = coronavirus disease-2019; GFRe = estimated glomerular filtration rate; IgG = immunoglobulin G; IgM = immunoglobulin M; PCR = polymerase chain reaction; seg = segmented.

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Finally, the latest official statements for COVID-19 patients recommend following current PCI guidelines (8). Expert recommendations have been published on antithrombotic therapy management, with special consideration given to possible interactions with the drugs used for COVID-19 (9). This is especially important with drugs metabolized through CYP3A4, such as clopidogrel or ticagrelor, which could interact with antiviral agents such as lopinavir combined with ritonavir or darunavir combined with cobicistat. Therefore, prasugrel could be the drug of choice in patients without contraindications (prior stroke) but who are >75 years of age or have a weight <60 kg if antiviral agents are considered indispensable. Because of the low evidence on the effectiveness of these antiviral agents against SARS-CoV-2, antiplatelet therapy should be prioritized for COVID-19 patients in the setting of acute coronary syndromes.

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KEY WORDS coronary artery, COVID-19, SARS-CoV-2, stent thrombosis

APPENDIX For supplemental videos, please see the online version of this paper.