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Acute coronary syndromes following COVID-19 vaccine application: Kounis syndrome or chance?

Arguably, the management of the COVID-19 pandemic from all disciplines of the biomedical sciences has been the greatest challenge to date in the 21st century. The constant work by the basic sciences to create immuno-virological prototypes, the approach and support of the clinical sciences to reduce the number of complications and deaths, the strategies of primary care groups to prevent contagion and alteration of daily life activities, and the behaviour of the general population, have been the determining factors in the course of the pandemic. One of the biggest challenges at present is the acceptance and tolerance of prototype vaccines against this disease, due to mistrust and misinformation, despite the solid evidence of the safety and efficacy of the available vaccines. Phase III clinical trials have shown that the most commonly used prototypes have a minimum efficacy of 80% (p < 0.0001) and that the frequency of adverse events of the intervention groups vs. the placebo group does not show significant differences, with few fatalities or grade 4 adverse events [1]. Post-vaccine allergic reactions correspond to less than 0.1% [1]. The Johns Hopkins COVID-19 data centre states that as of June 27, 2022, 11,652,164,034 doses have been administered [2] and, to date, a non-systematic search in PubMed with the keywords “SARS-CoV-2 vaccine” and “Allergic Reactions,” plus synonyms, finds less than 200 results for this type of event globally.

In cardiology, an adverse event of interest in this situation is Kounis syndrome, which is defined as the occurrence of an acute coronary event secondary to a hypersensitivity reaction caused by vasoconstrictor mediators versus an allergic reaction [3]. It has been described that drugs, environmental agents or even some diseases are associated with this syndrome [3]. Considering that the physiopathology and specifically the agents involved in this pathological process are not clearly known, there is divergence in terms of its management and prevention, since patients with no history of allergies or other particular comorbidity may present it [3–5]. This represents a therapeutic and health education challenge, since it can generate misunderstandings about the safety of pharmacological agents and, as in this case, vaccine prototypes.

Currently, there are almost no case reports that have demonstrated the relationship between the application of any prototype vaccine against COVID-19 and the development of this syndrome (Table 1) [3–5]. There are even reports between the use of antibiotics for the management of COVID-19 and the development of coronary spasms [6]. Coincidentally, none of the reported cases coincided with the administration of the same vaccine, which is the main aspect to highlight. There is also a significant difference between ages, time since vaccination and presentation of acute symptoms, presence of comorbidities, pharmacological treatment for their underlying diseases and electrocardiographic and cardioimaging findings [3–5]. The first case, reported by Ozdemir et al. [3], corresponds to a 46-year-old woman, with no cardiovascular risk factors, who developed chest pain 15 minutes after the first dose of the vaccine was administered [3]. She was not taking any medication and had no history of allergic reactions. Electrocardiogram and echocardiogram showed compromise of the left ventricular wall and coronary angiography showed no signs of atherosclerosis. The second case, reported by Maadarani et al. [4], corresponds to a 62-year-old woman with a history of diabetes mellitus, hypertension and dyslipidemia, who developed chest pain 1.5 hours after the application of the vaccine. She had no history of diagnosed coronary artery disease or allergic reactions. He was taking Lisinopril 10 mg once daily, atorvastatin 40 mg once daily and insulin glargine. Coronary angiography showed a critical stenosis of middle segment of right coronary artery, and both electrocardiogram and echocardiogram showed compromise of the inferior cardiac wall [4]. The last case corresponds to an 86-year-old patient, with a history of prostate cancer and radiotherapy for approximately 15 years, and paroxysmal atrial fibrillation, under treatment with enalaprilamide and apixaban [5]. He had no history of allergic reactions. 15 minutes after the application of the vaccine, he collapsed. The electrocardiogram showed compromise of the inferior wall and coronary angiography showed occlusive/embolic involvement in three vessels [5]. Of the three patients described, only the latter died.

Although heterogeneity among cases is evident, these events raise concerns for the general population about the danger of a major adverse cardiovascular event, especially in groups with numerous cardiometabolic risk factors. Some authors have attempted to explain the causal relationship between COVID-19 and Kounis syndrome, claiming that cytokine storm and anaphylaxis share mediators that can generate coronary vasospasm [7]. However, not all of these arguments can be extrapolated to explain the presence of this syndrome due to the application of vaccines composed of attenuated viral structures or RNA [8]. Secondary allergic reactions to vaccines can be either to the vaccine compound itself or to the excipients (egg protein, gelatin, formaldehyde, thimerosal, or neomycin), which can generate immediate IgE-dependent reactions [8]. However, many of these excipients exist in other drugs, and among the cases described, two had established pharmacological treatment and a history of diseases, which could have been treated with drugs other than those described previously. Considering that different pathophysiological mechanisms have been characterized by which an allergic reaction secondary to a vaccine can be generated: 1) Reactions via the pathway of mast cell activation and degranulation as IgE/antigen through cross-linking of FcεRI on mast cells, 2) Non-IgE-mediated mast cell degranulation via activation of the complement system, 3) Life-threatening allergic reactions mediated via direct activation of the Mas-related G protein-coupled receptor X2, 4) Type IV hypersensitivity or delayed reactions [8]; it is difficult to determine precisely whether causation actually exists, especially in the absence of a history of allergies or other conditions associated with immune disorders.

The available evidence on this topic is scarce and unpecific. Actually, it cannot be determined with certainty that an acute coronary...
syndrome following the application of the COVID-19 vaccine corresponds to Kounis syndrome or if it is an incidental event due to subclinical coronary artery disease or decompensation of previous disease. New research on cardiac injury in COVID-19, both in the acute phase and during the post-COVID-19 syndrome, continues to emerge [9–12]. Further research is needed to investigate whether there is a possibility of silent myocardial injury [12], either by administration of vaccine doses or as a mechanism derived from SARS-Cov-2 infection.

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It is not necessary.

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### Author contribution

All authors equally contributed to the analysis and writing of the manuscript.

### Trial registry number

1. Name of the registry: Not applicable.
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### Table 1

Summary of studies reporting Kounis syndrome following administration of COVID-19 vaccine.

| Author            | Type of study | Vaccine administered | Description | Final outcome |
|-------------------|---------------|----------------------|-------------|---------------|
| Özdemir et al., 2021 [3] | Case report | CoronaVac (Sinovac Life Sciences, Beijing, China) | 41-year-old woman with no cardiovascular risk factors with flushing, palpitation, dyspnea, and chest pain 15 min after the first dose of vaccine. Electrocardiogram showed V4-6 T wave inversion, and echocardiography revealed left ventricular wall motion abnormalities. Troponin-I level on arrival was elevated. Coronary angiography showed no sign of coronary atherosclerosis. She was diagnosed with type 1 KS. | Alive |
| Maadarani et al., 2021 [4] | Case report | AZD1222 (Oxford University and AstraZeneca) | 62-year-old woman with a medical history of diabetes mellitus, hypertension and dyslipidaemia with central chest pain that started approximately 1.5 hours after receiving her first dose of vaccine. She denied loss of consciousness, headache, nausea or vomiting. No previous history of coronary artery disease or allergic reaction to any substances. Her medications included Lisinopril 10 mg once daily, atorvastatin 40 mg once daily and insulin glargine. Electrocardiogram showed ST elevation in inferior leads (II, III and AVF) and reciprocal ST segment depression in lead I and AVL. Bedside echocardiography showed an inferior wall motion abnormality and preserved systolic function of left ventricle. Coronary angiography showed a critical stenosis of middle segment of right coronary artery. Drug eluting stent was deployed with Thrombolysis In Myocardial Infarction III flow (TIMI III flow). | Alive |
| Tajstra et al., 2021 [5] | Case report | Pfizer – BioNTech vaccine (Pfizer, New York, USA) | An 86-year-old man with history of prostate cancer treated with prostatectomy and radiotherapy in 2006, until recently, with enzalutamide (androgen receptor inhibitor), had paroxysmal atrial fibrillation (treated with apixaban 2.5 mg twice a day), without any previous allergies to drugs or vaccines. Approximately 30 min after the injection of first dose of vaccine, the patient collapsed. Electrocardiogram showed acute ST-segment elevation myocardial infarction of the inferior wall. Coronary angiography revealed occlusions/distal embolization in the distal part of the left anterior descending coronary artery, in the first diagonal branch, and in the distal part of the dominant right coronary artery, with large thrombus. The patient developed cardiogenic shock and bradyarrhythmia. | Dead |

### Table 1 (continued)

| Author            | Type of study | Vaccine administered | Description | Final outcome |
|-------------------|---------------|----------------------|-------------|---------------|
| Maadarani et al., 2021 [4] | Case report | AZD1222 (Oxford University and AstraZeneca) | 62-year-old woman with a medical history of diabetes mellitus, hypertension and dyslipidaemia with central chest pain that started approximately 1.5 hours after receiving her first dose of vaccine. She denied loss of consciousness, headache, nausea or vomiting. No previous history of coronary artery disease or allergic reaction to any substances. Her medications included Lisinopril 10 mg once daily, atorvastatin 40 mg once daily and insulin glargine. Electrocardiogram showed ST elevation in inferior leads (II, III and AVF) and reciprocal ST segment depression in lead I and AVL. Bedside echocardiography showed an inferior wall motion abnormality and preserved systolic function of left ventricle. Coronary angiography showed a critical stenosis of middle segment of right coronary artery. Drug eluting stent was deployed with Thrombolysis In Myocardial Infarction III flow (TIMI III flow). | Alive |

Further research is needed to investigate whether there is a possibility of silent myocardial injury [12], either by administration of vaccine doses or as a mechanism derived from SARS-Cov-2 infection.
Declaration of competing interest

None.

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