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COVID-19 Vaccine-Related Cardiovascular Long-Term Complications

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مضاعفات القلب والأوعية الدموية طويلة المدى المرتبطة بلقاح كوفيد-19

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Abstract:
Numerous evaluations exist about the cardiovascular implications of COVID-19 across various populations; nevertheless, there is a paucity of research concerning the cardiovascular adverse effects of COVID vaccinations. This research aimed to examine the cardiac problems associated with different types of COVID-19 vaccinations: mRNA, vector-based, and inactivated vaccines. A comprehensive search was conducted on PubMed for English case reports and case-series studies, resulting in the inclusion of 60 papers. In conclusion, the individual and communal health advantages of COVID-19 immunization far above the negligible cardiac risks. Reporting bias over the greater availability of mRNA vaccinations in affluent nations may compromise our findings.

Keywords: COVID-19, Myocarditis, Takotsubo Cardiomyopathy, Myocardial Infarction, VITT, COVID-19 vaccines.

الملخص
توجد العديد من التقييمات حول الآثار القلبية الوعائية لكوفيد-19 بين مختلف المجموعات السكانية؛ ومع ذلك، هناك ندرة في الأبحاث المتعلقة بالآثار الضارة على القلب والأوعية الدموية للقاحات كوفيد. يهدف هذا البحث إلى فحص مشاكل القلب المرتبطة بأنواع مختلفة من لقاحات كوفيد-19: mRNA، واللقاحات القائمة على ناقلات الأمراض، واللقاحات المعطلة. تم إجراء بحث شامل على PubMed لتقارير الحالة الإنجليزية ودراسات سلسلة الحالات، مما أدى إلى إدراج 60 ورقة. في الختام، فإن المزايا الصحية الفردية والمجتمعية للتحصين ضد فيروس كورونا (كوفيد-19) أعلى بكثير من المخاطر القلبية التي لا تذكر. إن الإبلاغ عن التحيز حول زيادة توافر لقاحات mRNA في الدول الغنية قد يضر بالنتائج التي توصلنا إليها.

الكلمات المفتاحية: لقاحات كوفيد-19، التهاب عضلة القلب، اعتلال عضلة القلب تاكوتسوبو، احتشاء عضلة القلب، *VITT*، لقاحات كوفيد-19.

Introduction

The unprecedented development and deployment of COVID-19 vaccines has been critical in alleviating the burden of the global SARS-CoV-2 pandemic. However, there are worries about possible long-term cardiovascular side effects that require careful and continued scrutiny. Here, this review provides an update on the available evidence on cardiovascular complications related to COVID-19 vaccination with special emphasis on the incidence of myopericarditis and thromboembolic events due to COVID-19 vaccination [1]. Although infrequent, myocarditis and pericarditis have been observed primarily in younger males after mRNA-based vaccines, including BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). These cases are mild, self-limited and typically have a good prognosis. Thromboembolic

complications, including vaccine-induced immune thrombotic thrombocytopenia (VITT), have been associated with adenoviral vector vaccines, including ChAdOx1 nCoV-19 (AstraZeneca) and Ad26. COV2. S (Johnson & Johnson). New information indicates that the events described previously may be much less common than the cardiovascular hazards presented by COVID-19 infection itself. Additional long-term follow-up studies are needed to examine the durability of these effects and the potential public health implications. For example, a study by Patone et al. (2022) illustrates the relative risk of myocarditis attributable to vaccination as compared with SARS-CoV-2 infection, showing that when discussing vaccine safety, we should compare it with the other cardiovascular dangers we encounter during the pandemic [2]. In summary, the net benefit of COVID-19 vaccination in terms of severe disease and mortality far exceeds the rare cardiovascular reactions and highlights the importance of ongoing surveillance and open communication to sustain the public trust.

But the risk of long-lasting neurological side effects has raised questions about their safety profiles. Cardiovascular and neurological complications due to COVID-19 vaccination: How strong is the evidence? A rapid review Very rare cases of GBS have been reported after vaccination with adenoviral vector vaccines, such as ChAdOx1 nCoV-19 (AstraZeneca) and Ad26. COV2. S (Johnson & Johnson), at slightly above baseline incidence. Demyelinating disorders, including transverse myelitis, have been reported but the causality is still being evaluated. Also, cases of small fiber neuropathy and other (but rare) forms of peripheral neuropathy have been described, but they seem to be very infrequent and are often a confusing issue because patients may have pre-existing disease or other infections. Crucially, the risk of neurological effects after SARS-CoV-2 infection itself is much greater than that from vaccination. For instance, a study by Frontera et al. (2022) compared the risks of neurological sequelae from infection with SARS-CoV-2 against the risks from COVID-19 vaccination, with the conclusion that infection is riskier than vaccination and that vaccines offer protection against severe neurological outcomes [3]. Long-term follow-up studies are needed to further characterize these rare adverse events and the mechanisms that underlie their persistence. Overall, the risk of severe disease and neurological complications from SARS-CoV-2 infection greatly exceeds the risk of rare vaccine-associated neurological side effects, highlighting the need for ongoing monitoring and public health education [4].

Myocarditis

COVID-19 vaccines have played a fundamental role in controlling the global burden of the SARS-CoV-2 pandemic, by means of their rapid development and deployment. In contrast, vaccines in particular mRNA vaccines like Pfizer-BioNTech (BNT162b2) and Moderna (mRNA-1273) have shown high efficacy against severe disease and mortality. However, like any medical intervention, there have been adverse events after MRNA COVID-19 vaccination, including myocarditis, pericarditis, and myopericarditis. A rare number of cases of these heart and associated structure inflammatory conditions have reportedly occurred after COVID-19 vaccination, mainly among younger individual populations [5]. In this review, we outline the incidence, pathophysiology, clinical presentation, management, and risk-benefit analysis of myocarditis, pericarditis, and myopericarditis related to COVID-19 vaccines as supported by current evidence.

Myocarditis depicts irritation of the heart muscle and pericarditis – aggravation of the sac enveloping the heart. When both conditions occur together, it is called myopericarditis. Cases of post-vaccination myocarditis and pericarditis have been reported mainly in young males, especially after the second dose of mRNA vaccines. A study has been done by Mevorach et al. Myocarditis rates post-mRNA vaccination was about 1 in 50,000 in males aged 16–29 years (2021) In the case of males aged 12–17 years, data from the Vaccine [6]. Adverse Event Reporting System (VAERS) in the USA showed the highest rate of myocarditis, with an estimated incidence of 10.7 (95% confidence interval 6.4–19) cases per 100000 doses of the Pfizer-BioNTech vaccine received [7]. These results show a strong age and gender favoritism, identifying younger males to be the primary population that gets affected.

Exact pathways for the myocarditis and pericarditis associated with vaccines are still under study. A possible mechanism being proposed is an exaggerated immune reaction against the mRNA vaccines. Such response may involve molecular mimicry whereby, due to the similarities of the SARS-CoV-2 spike protein that was encoded by the vaccine and cardiac antigens, the immune system may be activated to mistakenly target and attack cardiac antigens [8]. Another explanation points to the lipid nanoparticles deployed in mRNA vaccines, which could trigger an inflammatory response in people who are predisposed to such a reaction. These mechanisms are important to note because they are significantly different from direct viral invasion of cardiac tissue, whereas this is seen in myocarditis following SARS-CoV-2 infection. Although the immune-mediated hypothesis has gained wide acceptance, studies are required to understand the precise mechanisms involved.

The majority of patients with myocarditis or pericarditis occurring after COVID-19 vaccination present with chest pain, dyspnea and palpitations. These symptoms generally appear two to three days after

the vaccination, and they typically occur after the second dose. An elevated cardiac biomarker like troponin, which indicates myocardial injury, can often be seen upon diagnostic evaluation. Patients often present with electrocardiographic (ECG) changes, such as ST-segment elevation or T-wave changes. CMR is useful in confirming the diagnosis due to the presence of myocardial inflammation and edema [9], The disease is generally mild and with proper management the patient recovers fully.
Supportive care remains the mainstay for management of myocarditis and pericarditis following COVID-19 vaccination. NSAIDs are often used to relieve symptoms, and corticosteroids or intravenous immunoglobulin (IVIG) can be used for severe cases. Admission is usually needed for monitoring, especially in those who have marked ECG changes or high troponin levels. The clinical course in vaccine-associated myocarditis and pericarditis is often favorable and the vast majority of patients have resolution of symptoms within weeks. Nonetheless, the potential for sequelae, such as arrhythmias or diminished cardiac function, requires long-term follow-up studies.
Myocarditis and pericarditis are serious adverse events of interest, but they should also be interpreted in the context of the extensive benefits of COVID-19 vaccination. Myocarditis risk after SARS-CoV-2 infection is much higher than the risk from vaccination. A study created a model where they estimated the risk of developing myocarditis as being about four times higher among those infected with SARS-CoV-2 as among those who got an mRNA vaccine [10]. In addition, people who are vaccinated are at far lesser risk of severe outcomes (hospitalization and death). These results highlight the protective role of vaccination against severe COVID-19 and its complications, even in vaccinated individuals with an increased risk of myocarditis after vaccination.

- **mRNA vaccines**

Research by Abu Mouch et al. documented 6 instances of myocarditis (5 following the second dosage and 1 after the first dose) without any indication of COVID-19 infection, occurring quickly after the administration of the mRNA vaccine Pfizer/BioNTech BNT162b2 [11]. The diagnosis of myocarditis in the research was confirmed using cardiac MRI, and all six instances were male subjects. Further research conducted by Al-Rasbi et al. in Oman documented a case involving a 37-year-old male with myocarditis, who had pulmonary oedema [12]. He had significant multisystem involvement, including thrombocytopenia, rhabdomyolysis, pulmonary hemorrhage, and non-oliguric acute renal damage following the BNT162b2 mRNA vaccination. Alania-Torres et al. documented an additional instance of myocarditis in individuals with arrhythmogenic left ventricular cardiomyopathy (ALVC) following mRNA immunization for COVID-19 [13]. A case of fatal fulminant necrotizing myocarditis has been documented in New Zealand involving a 57-year-old female subsequent to her initial dosage of the Pfizer-BioNTech vaccine [14]. Research from Korea documented a 22-year-old male who got myocarditis five days post-administration of the BNT162b2 mRNA vaccination and subsequently died seven hours later [15]. Myocarditis has also been documented following mRNA COVID vaccinations in pediatric cases, including a 17-year-old boy and a 14-year-old male patient. Tampoulouoglou et al. described a series of nine instances of peri-myocarditis, five cases of myocarditis, and three cases of pericarditis [16]. A separate case series investigation documented 9 instances of acute pericarditis, of which seven individuals were administered mRNA vaccines BNT162b2 and mRNA-1273, while two people got AZD1222 [17]. Numerous other case-report studies have recorded myocarditis or the return of acute myocarditis following mRNA immunization for COVID-19 infection.
Myocarditis was seen to be more prevalent in patients who got the COVID-19 mRNA vaccination compared to those who received a non-mRNA vaccine, and it was also more frequent in those who received the vaccine for the second time. It was also determined to be more prevalent among men and those aged 16 to 39 years [18].

- **Non-mRNA vaccines (vector-based vaccines/inactivated vaccines)**

A recent systematic study of myocarditis following COVID-19 immunization documented one case after AstraZeneca, one case after Sputnik V, and one case after Johnson & Johnson vector vaccination, from a total of 277 cases [19]. A 32-year-old female patient experienced myocarditis three days after getting the first dosage of AstraZeneca. The patient began to exhibit inappropriate exertional tachycardia and dyspnea during physical activity. A case report of myocarditis subsequent to the injection of the Janssen vaccination in a healthy young boy has also been documented. A Brazilian investigation documented a 47-year-old African-American male patient diagnosed with type 2 diabetes and a prior history of COVID-19 infection. He experienced cardiac failure due to myocarditis following the second dosage of an inactivated COVID-19 vaccination. Other investigations indicated no incidence of myocarditis in an individual administered an inactivated COVID-19 vaccination. A population-based analysis indicated that primarily, two mRNA vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer-BioNTech), were more closely linked to elevated risks of myocarditis/pericarditis compared to all other vaccination types, including the viral vector vaccines Ad26.COV2.S (Janssen) and AstraZeneca [20].

- **Proposed mechanisms for COVID-19 vaccines induced-Myocarditis**

Residual amounts of double-strand RNA (dsRNA) in mRNA COVID-19 vaccination formulations have been found. Double-strand RNA (dsRNA) is recognized for eliciting immune-inflammatory responses. The inclusion of dsRNA in vaccine nanoparticles may be the cause of the unresolved cases of myocarditis. Patients with a history of myocarditis, whether current or historical, represent a potential "susceptible" cohort that presents a therapeutic challenge [21]. In this demographic, patients are advised against receiving COVID-19 vaccination during the initial six months following the beginning of sickness or in cases of chronic or relapsing troponin release. The majority of patients treated for myocarditis or pericarditis exhibited favorable responses to pharmacological intervention and rest, resulting in a benign clinical trajectory. The individual and public health benefits of COVID-19 vaccination significantly surpass the little risk of myocarditis, which often resolves within days or weeks [22].

Takotsubo cardiomyopathy (TTC)

Takotsubo cardiomyopathy (TTC) is an acute, temporary impairment of left ventricular systolic function that occurs during physical or mental stress and is differentiated from myocardial infarction. Adrenergic stimulation, coronary vasospasm, microvascular dysfunction, inflammation, and changes in cellular metabolism have been suggested as contributing factors to this condition [23].

- **mRNA vaccines**

Case reports and small studies have reported cases of TTC after mRNA vaccination7,8. Case Report A report by Singh et al. Case reports: (2021)–reported a 63-year-old woman who developed TTC within 24 hours of receiving the Pfizer-BioNTech vaccine. Introduction The patient was presented with acute chest pain and dyspnea with imaging showing the classical left ventricle apical ballooning. Jabri et al. A small cluster of TTC cases occurring temporally associated with mRNA vaccination has been identified [24].

We refer to a systematic review performed by Abou Saleh et al. In a review of 15 cases of TTC following COVID-19 vaccination, Giustino et al. (2023) reported that most patients were older women with no history of cardiovascular disease. Symptoms usually appeared in 1–3 days after vaccination, and all cases were self-limiting and resolved with symptomatic management. These findings indicate a temporal association, however, the incidence of TTC after vaccination is overall very rare, with estimates of about 1 case per million doses [25].

There are substantial implications for vaccine safety in vulnerable populations from the proposed association between TTC and mRNA vaccines. Nevertheless, it should be stressed that the advantages of vaccination far exceed the hazards. TTC after vaccination is an extremely rare occurrence, and the disorder is mostly transient. On the other hand, the cardiovascular complication risk in the failure of COVID-19 is multifold greater than that of myocarditis/MI/heart failure.

Unfortunately, clinicians should at least keep the possibility of TTC in mind when patients come to the ED after vaccination, especially if the patient is an older woman or has a history of anxiety or stress-related disorders. The key to achieving a good outcome is early diagnosis and management. Studies are warranted to dissect the mechanism of TTC as well as risk factors for TTC after mRNA vaccination [26].

- **Non mRNA vaccines**

Several case reports and small studies have documented instances of TTC following non-mRNA COVID-19 vaccination. For example, a case report by Kounis et al. (2021) described a 62-year-old woman who developed TTC shortly after receiving the AstraZeneca ChAdOx1-S vaccine. The patient presented with chest pain and dyspnea, and imaging revealed the characteristic apical ballooning of the left ventricle. The authors hypothesized that the vaccine-induced immune response, combined with the stress of vaccination, may have triggered the condition [27].

Similarly, a study by Abou Saleh et al. (2022) reviewed 10 cases of TTC following COVID-19 vaccination, including both mRNA and non-mRNA vaccines. Among the cases associated with non-mRNA vaccines, most patients were older women with no prior history of cardiovascular disease. Symptoms typically developed within 1–3 days of vaccination, and all cases resolved with supportive care. These findings suggest a temporal association between non-mRNA vaccines and TTC, although the overall incidence remains extremely low [28].

In another case report, a 70-year-old man developed TTC after receiving the Sinovac CoronaVac vaccine [29]. The patient experienced chest pain and shortness of breath within 48 hours of vaccination. Echocardiography confirmed apical ballooning, and the patient recovered fully with conservative management. The authors noted that the inflammatory response to the inactivated vaccine, combined with the patient's underlying anxiety, may have contributed to the development of TTC.

The potential link between non-mRNA vaccines and TTC raises important questions about vaccine safety, particularly in vulnerable populations. However, it is crucial to emphasize that the benefits of vaccination far outweigh the risks. The incidence of TTC following vaccination is exceedingly rare, and the condition is generally self-limiting. In contrast, COVID-19 itself is associated with a significantly higher risk of cardiovascular complications, including myocarditis, myocardial infarction, and heart failure.

Healthcare providers should be aware of the possibility of TTC in patients presenting with chest pain after vaccination, particularly in older women or those with a history of anxiety or stress-related disorders. Early recognition and appropriate management are essential to ensure favorable outcomes [30]. Further research is needed to elucidate the mechanisms underlying TTC in the context of non-mRNA vaccination and to identify potential risk factors.

- **Recommended mechanisms for COVID-19 vaccines induced-TTC**

Takotsubo cardiomyopathy (TTC), also known as stress induced cardiomyopathy or "broken heart syndrome" is a transient cardiac condition characterized by left heart ventricle dysfunction, frequently mimicking acute coronary syndrome (ACS). Although most commonly linked to physical or psychological stress, TTC has recently been described after medical treatments such as vaccination. COVID-19 vaccines (mRNA and non-mRNA [vector-based and inactivated vaccines]) have appeared with rare reports of TTC [31]. While the number of cases of vaccine induced TTC are extremely rare, understanding how this could happen is important in terms of making these vaccines safer and for identifying populations at risk. This essay describes potential mechanisms by which COVID-19 vaccines can trigger TTC, with particular attention on immune, inflammatory, and neuroendocrine pathways [26].

i. Catecholamine Surge and Sympathetic Overactivation

An overstimulation hypothesis IX, which is one of the most widely accepted mechanisms in TTC, states that excessive catecholamines, including adrenaline and noradrenaline, lead to myocardial stunning along with transient left ventricular dysfunction. A sympathetic hyperactivity in response to COVID-19 vaccines may occur, especially in those with a higher threshold of anxiety or stress toward VACCINATION. This mechanism might be mediated by either the stress induced by the vaccination process itself (e.g., needle fear, side effects) or the immune response triggered by the vaccine [32].

Through multiple mechanisms, catecholamine surges can thus exert direct cardiotoxicity:

Myocardial stunning — Excessive catecholamines may impair myocardial contractility, especially at the apex of the left ventricle, resulting in classic "apical ballooning" observed in TTC.

Coronary microvascular dysfunction — Catecholamines may also cause coronary microvascular spasm or dysfunction, which decreases myocardial blood flow and may lead to myocardial stunning.

Oxidative stress: Increased catecholamines can cause production of ROS, potentially aggravating myocardial injury.

ii. Inflammatory and Cytokine-Mediated Pathways

COVID19 vaccines are intended to activate a strong immune response, which includes activating both the innate and adaptive immunity. This immune activation occurs with the release of pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β). Cytokines are a crucial contributor to TTC pathogenesis by inducing endothelial dysfunction in addition to elevating sympathetic activity and reducing myocardial function. Endothelial dysfunction: Pro-inflammatory cytokines can compromise integrity of the endothelium and reducing nitric oxide bioavailability and impairing vasodilation. This can also lead to coronary microvascular dysfunction, a major aspect of TTC. Sympathetic activation by cytokine: IL-6 and cytokines can induce HPA axis activation which increases catecholamine release, resulting in increased sympathetic tone. Direct myocardial effects: For example, cytokines such as TNF-α can exert direct negative inotropic effects on the myocardium, which may lead to left ventricular dysfunction [33]. Booster injection triggers an inflammatory response that is usually transient and self-limiting, but may serve as a trigger for TTC in predisposed individuals.

iii. Molecular Mimicry and Autoimmune Mechanisms

Molecular mimicry is another potential mechanism that we suspect could lead to TTCC because antibodies developed against vaccine antigens can cross-react with host tissues by virtue of structural similarities to endogenous proteins. COVID-19 vaccines, mainly those that encoding SARS-CoV-2 spike protein, could theoretically elicit myocardial or coronary vasculature autoimmune response during immune reaction. This mechanism is usually described more for myocarditis or pericarditis, although it may also contribute to TTC aggravating the inflammatory and endothelial dysfunction [34]. Cross-reactivity to myocardial antigens: Targeted antibodies raised by the vaccine may inadvertently cross-react with myocardial or vascular antigens, resulting in local inflammation and dysfunction. Immune complex formation: Immune complexes containing vaccine antigens and antibodies may deposit in the coronary microvasculature, promoting inflammation and microvascular dysfunction. Molecular mimicry

is a hypothetical mechanism, but it highlights the importance of studying the immunological effects that COVID-19 vaccines might have.

iv. Hypersensitivity and Anaphylactoid Reactions

Additionally, hypersensitivity reactions to components of the vaccines (e.g., PEG in mRNA vaccines and adenoviral vectors in vector-based vaccines) might also contribute to TTC [35]. These reactions may produce histamine and other vasoactive mediators causing coronary vasospasm and myocardial dysfunction. Moreover, hypersensitivity reactions might initiate a systemic inflammatory response, which would again result in increased TTC susceptibility.

Effects mediated by histamine: In an allergic reaction, histamine is released contributing to coronary vasospasm that decreases blood supply to the myocardium and can contribute to TTC. Systemic inflammation: Hypersensitivity reactions may potentiate the inflammatory response to vaccine and thus enhance the risk for endothelial dysfunction and sympathetic overactivation [36].

v. Stress and Psychological Factors

Psychological stress (as identified by the hypothesis) of vaccination, especially during a global pandemic, may be a major factor in TTC. The HPA axis may be triggered by fear of negative effects, fear of lack of vaccine efficaciousness, or general stress due to the pandemic, resulting in increases in catecholamines/epinephrine and norepinephrine. This mechanism may be more applicable to people with anxiety disorders and histories of stress-related disorders [37]. Interestingly, psychological stress can also activate the hypothalamic-pituitary-adrenal (HPA) axis, which can stimulate the secretion of the corticotropin-releasing hormone (CRH), and consequently the overproduction of both cortisol and catecholamines. Hormonal and autonomic factors mean that older women, who are at greater risk of TTC, may be more vulnerable to stress triggers [38].

vi. Microvascular Dysfunction and Coronary Vasospasm

TTC is characterized by microvascular dysfunction and coronary vasospasm that may be amplified by COVID-19 vaccines. The vaccine-related inflammatory response, associated with catecholamines spikes, can also negatively affect the coronary microvascular function leading to myocardial hypoperfusion and left ventricular dysfunction [39].

Vasospasm: Spasm of coronary arteries may occur through catecholamines and inflammatory mediators, thereby decreasing blood flow into the myocardium

Microvascular ischemia: Impairment of the coronary microcirculation may lead to regional ischemia, which can be a cause in the formation of TTC.

Myocardial Infarction Induced by COVID-19 Vaccination

The widespread deployment of COVID-19 vaccines was an essential milestone in the fight against SARS-CoV-2, proven to significantly decrease severe disease, hospitalization, and mortality rates. But, as is the case with any medical procedure, there are also risks with vaccines. Although most of the reported adverse events following COVID-19 vaccination are mild and self-limiting, serious cardiovascular events such as myocardial infarction (MI) has rarely been reported. Myocardial infarction is better known as a heart attack; it occurs with disruption of blood flow to the myocardium, causing ischemia and necrosis of myocardial tissue. Despite the fact that the incidence of MI after COVID-19 vaccination is very low [40], grasping the possible mechanisms, clinical evidence and implications is important for maintaining vaccine safety profile and addressing public concerns. The purpose of this essay is to discuss current evidence linking COVID-19 vaccination to MI, including potential mechanisms, clinical aspects, and implications for public health.

Myocardial infarction is defined as a marked decrease or total arrest of blood flow to a segment of myocardium, most commonly due to rupture of an atherosclerotic plaque and the formation of a thrombus in a coronary artery. MI may also secondarily cause like pathological mechanisms involving coronary artery spasm, microvascular dysfunction, or embolism. There are two main types that fall under the condition [41]:

Type 1 MI: secondary to rupture or erosion of atherosclerotic plaque, resulting in thrombus formation and occlusion of coronary arteries.

Type 2 MI: due to supply-demand imbalance often not caused by acute plaque rupture

It is hypothesized that direct and indirect mechanisms including immune-mediated inflammation, endothelial dysfunction, and prothrombotic states contributing to the development of MI may mediate the link between COVID-19 vaccination and MI [42].

1. mRNA vaccines

In Case-series research in the UK indicated an elevated risk of myocardial infarction following BNT162b2 (Pfizer-BioNTech) mRNA immunization. [44] Sung et al. [43] and Kunis et al. [27] documented 2 instances and 1 case of myocardial infarction, occurring 24 hours post-vaccination with mRNA vaccines, respectively. Population-based research indicated the short-term risk of serious

cardiovascular events, including myocardial infarction, in individuals aged 75 years or older after receiving the BNT162b2 mRNA COVID-19 vaccine. WHO research verified that vaccinations associated with myocardial infarction, cardiac arrest, and circulatory collapse were seen in individuals over 75 years of age [45].

2. Non-mRNA vaccines (vector-based vaccines/inactivated vaccines)

A 40-year-old male with no prior cardiovascular illness presented with retrosternal chest pain 8 days post-administration of the ChAdOx1 nCov-19 vaccine for COVID-19, exhibiting ST elevation on the ECG and regional wall motion abnormalities on echocardiography. The blood tests indicated elevated D-dimer levels, a troponin concentration of 3185 ng/L, and a significantly positive platelet factor-4 (PF-4) antibody test. Coronary angiography revealed a blockage in the left anterior descending coronary artery. His platelet counts rose after six days, while his PF-4 antibody, D-dimer, and troponin levels diminished. He was successfully discharged after 14 days [46]. Hsu et al. documented a case of a 33-year-old male who experienced acute ST-segment elevation myocardial infarction subsequent to receiving the ChAdOx1 nCoV-19 vaccine in Taiwan [46].

3. Proposed Mechanisms of Myocardial Infarction Following COVID-19 Vaccination

Here are several plausible pathways by which COVID-19 vaccines could theoretically contribute to MI, although their precise mechanisms remain unclear:

A. Immune-Mediated Inflammation

These types of response are triggered by the immune-stimulating COVID-19 vaccines, which imply the activation of both innate and adaptive immunity. Activation of the immune system and secretion of pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) [47]. These cytokines can:

- Induce endothelial dysfunction, compromising the vascular endothelium and increasing the likelihood of plaque rupture.
- Upregulate prothrombotic agents (for example, tissue factor production, which can initiate clotting)
- Worsen established atherosclerosis, with possible precipitation of acute coronary events.

B. Prothrombotic State

Vector-based COVID-19 vaccines (e.g., ChAdOx1-S from AstraZeneca and Ad26. COV2. However, in rare cases, the vaccination has been associated with early issuance of abnormal blood clots (V), which are called vaccine-associated immune immobility (VITT). VITT is associated with the development of antibodies that activate platelets, resulting in thrombosis in arterial as well as venous systems. Although the platelet activation mechanism associated VITT is most frequently reported to produce cerebral venous sinus thrombosis (CVST) and deep vein thrombosis (DVT), there is no reason to suspect it could not also cause coronary artery thrombosis and myocardial infarction (MI) [48].

C. Endothelial Dysfunction

COVID-19 vaccines encode the spike protein of SARS-CoV-2, and it has been hypothesized that the spike protein interacts with the angiotensin-converting enzyme 2 (ACE2) receptor on endothelial cells. Such an interaction can trigger endothelium activation and dysfunction, predisposing the vascular wall to inflammatory processes, plaque erosion and subsequent thrombus generation [49].

D. Stress and Sympathetic Activation

Vaccination stresses the individual and can cause sympathetic overactivation, especially in patients with pre-existing anxiety or cardiovascular risk factors. This may lead to an elevated heart rate, blood pressure, and myocardial oxygen demand and cause a Type 2 MI in at-risk patients [50].

E. Hypersensitivity Reactions

Systemic inflammation and consequent histamine release induced by hypersensitivity reactions against different vaccine components, for example PEG in mRNA vaccines or adenoviral vectors in vector-based vaccines could also trigger this type of reaction. These reactions may lead to coronary vasospasm, decrease myocardial perfusion, and increase the risk of MI [51].

Although rare, the occurrence of MI after COVID-19 vaccination has important implications for vaccine safety and how we should risk stratify individuals who receive the vaccine. That said, it cannot be overstated that the risks of vaccination are outweighed by the benefits. MI after vaccination occurrence is very rare and related to pre-existent cardiovascular risk factors. On the other hand, the risk of MI, myocarditis, and heart failure associated with COVID-19 infection itself is at least an order of magnitude larger.

Physicians should keep MI as a possible diagnosis in patients that show up with chest pain after vaccination, especially the high-CV risk patients. It is critical to diagnose and manage these conditions early to achieve positive outcomes. Public health messaging should focus on the very low rate of MI, even if these rare cases are related to vaccination, and underline that the benefits of vaccination always

far outweigh possible risks, which include MI, through at least several mechanisms–for example, reduction of the risk of severe COVID-19 and its related complications [52].

Pulmonary hemorrhage/pulmonary embolism/thrombotic thrombocytopenia (VITT)

The design and administration of COVID-19 vaccines have played a central role in alleviating the worldwide effects of the SARS-CoV-2 pandemic. Although these vaccines have proven extremely effective against severe disease, hospitalization and death, rare adverse events have occurred. Of these, vaccine-induced immune thrombotic thrombocytopenia (VITT) has been reported as a rare but potentially life-threatening complication predominantly following adenoviral vector-based COVID-19 vaccines (AstraZeneca's ChAdOx1-S (Vaxzevria) and Johnson & Johnson's Ad26). COV2. S (Janssen). Vitt is defined by thrombosis at unusual sites (e.g., cerebral venous sinuses and splanchnic veins) in association with thrombocytopenia and platelet-activating antibodies [53]. This essay reviews the pathophysiology, clinical characteristics, diagnosis, and treatment of VITT and discusses its public health impact.

Clinical Features of VITT

The onset of VITT after vaccination is usually in a range of 4 to 30 days, with a median time to onset of 10-14 days. VITT has the following clinical features [54]:

Thrombosis

- Cerebral Venous Sinus thrombosis (CVST): Patients can appear with severe headache, visual changes, seizures, or focal neurological deficits.
- Splanchnic vein thrombosis: Abdominal pain, nausea, and vomiting
- DVT and PE: leg swelling; chest pain; dyspnea
- Arterial thrombosis: VITT can sometimes cause arterial thrombosis but this is rare and it can cause ischemic stroke or limb ischemia.

Thrombocytopenia

Thrombocytopenia, typically marked and possibly extreme (with a platelet count lower than 150×10^9/L), is a distinctive element of VITT; it is the result of platelet consumption due to systemic activation and aggregation of platelets.

- **Systemic Symptoms**

In the first few hours of hospitalization, fever, fatigue and malaise which are nonspecific but can be present with thrombotic and hematologic manifestations may develop in patient.

- **Diagnostic Criteria for VITT**

The diagnosis of the VITT is mainly based on the clinical, laboratory and imaging findings 54. The following criteria are most often used:

- **Temporal Association with Vaccination**

Adenoviral vector-based COVID-19 vaccines normally symptoms emerge 4 to 30 days later.

- **Thrombosis**

Tests also demonstrate the presence of thrombosis at atypical sites, for example, the cerebral venous sinuses or the splanchnic veins, or in more standard locations such as the deep veins or the pulmonary arteries.

- **Thrombocytopenia**

Diagnostically, platelet numbers are very low, typically less than 150×10^9/L.

- **Positive PF4 Antibodies**

PF4-reactive antibodies are detected by enzyme-linked immunosorbent assay (ELISA) in laboratory testing.

- **Exclusion of Other Causes**

Differential diagnoses should also rule out other triggers for thrombosis and thrombocytopenia, most notably heparin-induced thrombocytopenia (HIT).

1. **mRNA vaccines**

Al-Rasbi et al. reported a 37-year-old male who had myocarditis, pulmonary oedema, and pulmonary hemorrhage 12 days following the initial dose of the Pfizer mRNA COVID-19 vaccine. He exhibited a positive response to a 5-day regimen of intravenous methylprednisolone and immunoglobulin [12]. A case-series investigation indicated a short-term risk of pulmonary embolism (PE) in French citizens aged 75 years or older following administration of the BNT162b2 mRNA vaccine. 11 An Italian investigation documented a case of acute aggravation of interstitial lung disorders and pulmonary embolism in an elderly patient following booster mRNA immunization for COVID-19 [55]. Research in Saudi Arabia documented a case of pulmonary embolism in a 78-year-old individual occurring one day after the administration of the second dose of the Pfizer vaccine. Another instance involving a healthy 24-year-old male with pulmonary embolism attributed to the Pfizer vaccination indicated that his symptoms began six hours post-administration of the second dosage. Idiopathic pulmonary fibrosis

was also observed following the Pfizer vaccination, which was effectively managed with a brief regimen of glucocorticoids [56].

2. Non-mRNA vaccines

VITT has surfaced as an uncommon adverse effect of adenoviral vector-based vaccinations for coronavirus illness 2019 (COVID-19) and is most commonly observed following the administration of the Vaxzevria (AstraZeneca) vaccine. A 73-year-old instance of pulmonary embolism was reported two weeks following the administration of an inactivated COVID-19 vaccination [57]. Research in Germany documented a case of life-threatening bilateral pulmonary embolism as a consequence of vaccine-induced thrombotic thrombocytopenia (VITT) following the initial dosage of the Oxford AstraZeneca vaccine. A rare instance of minor segmental pulmonary embolism and vaccine-induced thrombotic thrombocytopenia was documented in a 47-year-old woman zero days post-administration of the AstraZeneca vaccine. A case of VITT and PE was documented 13 days following the administration of a single dose of the Janssen vaccine. Following first clinical suspicion, the patient received corticosteroids and intravenous immunoglobulin, leading to a fast elevation in platelet count, so facilitating the timely administration of full-dose anticoagulation [58]. Intravenous immunoglobulin therapy may obscure the capacity of anti-platelet factor 4-heparin antibodies to bind and activate platelets in the presence of heparin, leading to false-negative findings in immunoassay functional tests.

3. Proposed Mechanisms of VITT Following COVID-19 Vaccination

VITT pathogenesis is a multifactorial and biphasic process with high level immune activation and platelet dysfunction followed by prothrombotic states in some patients. In this essay, we discuss the pathophysiological basis of VITT due to PF4–reactive antibodies, adenoviral vector-induced immune responses and the prothrombotic milieu induced by vaccination [59],[60].

A. Platelet Factor 4 (PF4)-Reactive Antibodies

Platelet-activating antibodies against platelet factor 4 (PF4), which is an abundant protein released from activated platelets, are a signature of VITT. They are considered as playing a key role in the pathogenesis of VITT through immune complexes activating platelets and leading to thrombosis [59],[60].

A.1 Formation of PF4-Antibody Complexes

- PF4 is a positively charged protein that binds negatively charged molecules like heparin or polyanions. In VITT, we believe that the vaccine components (e.g., adenoviral particles or induced polyanions) bind PF4 in a way that changes its structure, which then renders it immunogenic.
- IgG antibodies against the PF4-polyanion complex are generated in the immune system. Such antibodies bind to PF4, forming immune complexes that activate platelets through the FcγIIa receptor.

A.2 Platelet Activation and Aggregation

- Platelet activation and aggregation occur as a result of PF4-antibody immune complex binding to FcγIIa receptors on platelets. As a result, procoagulant factors like thromboxane A2 and ADP become released, contributing to the thrombotic response.
- When platelets are activated, they also release more PF4, and this potentiates positive feedback of platelet activation and consumption.

A.3 Thrombocytopenia

- The activation and aggregation of platelets in large numbers and the consumption of platelets leads to thrombocytopenia. One of the hallmarks of VITT is this paradoxical mixture of thrombosis and thrombocytopenia.

B. Adenoviral Vector-Induced Immune Activation

Adenoviral vector-based vaccines (ii) ChAdOx1-S, Ad26. COV2. S, which is believed to be integral in initiating the immune response culminating in VITT. While the precise mechanism by which adenoviral vectors contribute to VITT has not been elucidated [59],[60], several hypotheses have been suggested:

B.1 Interaction with Platelets and Endothelial Cells

- Adenoviral particles could directly activate platelets and endothelial cells to release PF4. These interactions could take place by the binding between the adenoviral particles to the cell surface receptors like integrins or heparan sulfate proteoglycans.
- In addition to that, activated endothelial cells might also enhance the expression of tissue factor, an important procoagulant that initiates the coagulation cascade, facilitating thrombosis as well.

B.2 Vaccine-Induced Inflammation

- Adenoviral vector-based vaccines activate innate immunity and induce the expression of pro-inflammatory cytokines (IL-6; TNF-α). These cytokines can:
- ❖ Increase activation and aggregation of platelets
- ❖ Endothelial dysfunction is encouraged, and the risk of thrombus increases.

- ❖ Expand production of PF4-reactive antibodies.

B.3 Polyanion-Like Properties of Adenoviral Components

- Adenoviral vector components (DNA or capsid proteins) can be polyanions that associate with PF4, changing its structure and immunogenicity. This mechanism resembles that of heparin in HIT, only differs by occurring in the absence of heparin exposure.

C. Prothrombotic State and Coagulation Activation

Vaccination-induced immune and inflammatory responses establish a prothrombotic milieu that renders thrombosis-prone [59],[60]. Some main drivers of this hypercoagulable process are:

C.1 Tissue Factor Expression

- The immune response could activate and damage endothelial lining and contribute to the upregulation of tissue factor, a major trigger of extrinsic coagulation pathway. Tissue factor initiates thrombin production, which is the central enzyme of the coagulation cascade that causes fibrin clot formation.

C.2 Platelet-Derived Microparticles

- Platelets activated in response to the local formation of the clot release microparticles enriched in procoagulant phospholipids, including phosphatidylserine. These microparticles serve as a platform for the assembly of clotting complexes, which additionally enhance thrombin generation.

C.3 Complement Activation

- PF4-antibody complexes could be potential activators of complement system from innate immunity. Activation of complement can lead to amplified activation of platelets and inflammation, thereby enhancing the prothrombotic milieu.

C.4 Cytokine Storm

- Immune reaction in response to vaccination releases pro-inflammatory cytokines which may reinforce the prothrombotic state via development of endothelial dysfunction, activation of platelets, and activation of coagulation.

D. Thrombosis in Unusual Sites

- Vaccine-induced thrombosis with thrombocytopenic syndrome (VITT) has certain unique patterns of thrombotic occurrence that clearly differentiate it from other, better-known forms of thrombocytopenic thromboembolism, especially the predisposition to thrombosis at odd sites including the cerebral venous sinuses (cerebral venous sinus thrombosis, CVST) and splanchnic veins 3 [59],[60]. The mechanisms behind this preference for atypical sites are not clearly elucidated but could involve:

D.1 High PF4 Concentrations in Venous Sinuses

- PF4 levels can be elevated in some venous beds like the cerebral venous sinuses, which may be at particular risk of immune complex development and thrombosis.

D.2 Endothelial Activation in Specific Vascular Beds

- One possible mechanism is that the adenoviral vector or the immune response to it might preferentially activate endothelial cells in certain vascular beds, thereby promoting specific thrombosis.

D.3 Stasis and Low Shear Stress

- In concert with a prothrombotic state, low shear stress and blood flow stasis in venous sinuses and splanchnic veins may predispose to thrombus formation.

E. Genetic and Individual Susceptibility

However, many people who get adenoviral vector-based vaccines do not develop VITT, indicating that genetics and individual characteristics may be at play [59],[60]. Potential factors include:

E.1 HLA Genotype

- Some human leukocyte antigen (HLA) genotypes might be predisposed to the production of PF4-reactive antibodies.

E.2 Prior Inflammatory or Autoimmune Disease

- The risk of VITT may also increase when the vaccine trigger an exaggerated immune response that is more likely in vaccinated patients with a pre-existing inflammatory or autoimmune condition.

E.3 Age and Sex

- clinical VITT primarily in younger population and women, for unexplained reasons.

Conclusion

Our research indicated that myocarditis was the most often reported cardiac incident following COVID-19 immunization. All documented cardiac effects, including myocarditis, Takotsubo cardiomyopathy, myocardial infarction, and vaccine-induced thrombotic thrombocytopenia, were more prevalent

following administration of mRNA vaccines (Moderna and Pfizer-BioNTech). The incidence of myocarditis and TTC was decreased in the context of vector-based and/or inactivated vaccinations. Myocarditis was more prevalent in males aged 16 to 39. Myocardial infarction/cardiac arrest was recorded in individuals beyond 75 years of age and was exceedingly uncommon. No instances of TTC have been reported following the administration of inactivated COVID-19 vaccinations. The personal and public health benefits of COVID-19 vaccination significantly surpass the minor cardiac risks, which often resolve within days or weeks. Reporting bias over the greater availability of mRNA vaccinations in affluent nations may distort these findings.

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