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RNA Vaccines and Prevalence of Heart Disorders

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Abstract

RNA vaccines are appealing because they share traits with live-attenuated vectors and subunit vaccines, such as flexible manufacturing and generating humoral and cellular resistance. In recent years, vaccine production employing ribonucleic acid (RNA) has emerged as the most promising and explored strategy for producing safe and effective novel vaccines, not just for prevention but also as a therapy. Compared to conventional vaccines, using messenger RNA (mRNA) as an immunogen offers various benefits in vaccine production, including a cheaper cost, the absence of cell cultures, and the ability to mix diverse targets.

Most significantly, mRNA-based vaccines have the potential to bridge the gap between growing pandemic infectious illnesses and an ample supply of effective vaccinations. Despite its advantages for vaccine application, mRNA technology confronts numerous critical hurdles, including worries about mRNA enzyme degradation, permeability, vaccine stability or inflammation, autoimmune problems, and cardiovascular problems. A recent report by the Centers for Disease Control and Prevention (CDC) advisory group on vaccination policies found that there is probably a link between cardiovascular (CV) diseases and the COVID-19 mRNA vaccine. According to research from the United States, the United Kingdom, and Switzerland, myocarditis and pericarditis are the most common cardiovascular complications in teenage boys following COVID-19 mRNA vaccination. Treatment of vaccine-induced CV disorders includes corticosteroids, NSAIDs, colchicine, and, in severe cases, IVIG. Corticosteroids and percutaneous coronary intervention (PCI) with guideline-directed medical therapy (GDMT) have also been proposed to treat vaccine-induced myocarditis. Complementary and alternative medicine (CAM) may assist patients with CV disease, but physicians and patients may overlook its use.

This study aims to review the history, investigate, summarize, and simplify the understanding of the association between RNA vaccines and heart disorders.

Keywords: *Autoimmune Disorders; Complementary and Alternative Medicine; Enzyme Degradation; Vaccine-Induced Disorders*

Abbreviations

ACE: Angiotensin-Converting Enzyme Inhibitor; ACEi: ACE Inhibitor; ATTP: Acquired Thrombotic Thrombocytopenic Purpura; ALC: Acetyl-L-Carnitine; CDC: Centers for Disease Control and Prevention; CHF: Congestive Heart Failure; cMRI: Cardiac Magnetic Resonance Imaging; CRP: C-Reactive Protein; HR: Heart Rate; MI: Myocardial Infarction; NSAID: Nonsteroidal Anti-Inflammatory Drug; PAD: Peripheral Artery Disease; PCI: Percutaneous Coronary Intervention; PLC: Propionyl-L-Carnitine; STE: Speckle Tracking Echocardiography; TLR: Toll-Like Receptor; TTS: Thrombocytopenia Syndrome; UTR: Untranslated Regions; VAERS: Vaccine Adverse Event Reporting System; VITT: Vaccine-Induced Immune Thrombotic Thrombocytopenia

Introduction

Over the last two centuries, vaccines have been a critical factor in transforming human well-being and community. Their development in the late 1800s resulted from years of groundbreaking immunology and germ theory research, which helped drastically lower the burden of many severe infectious diseases [1]. Louis Pasteur's standard 3Is paradigm of "isolating, inactivating, and injecting" the pathogenic microbe serves as the foundation for the production of vaccines [2].

Vaccines can be either preventative or therapeutic and are generally characterized as inactivated vaccinations, subunit vaccines, live attenuated vaccines, or toxoid vaccines [2]. These vaccines function by simulating an infectious agent, which teaches the body to react more quickly and efficiently [3]. Despite this accomplishment, considerable challenges remain in creating vaccines against various infectious diseases, particularly those that can better resist the adaptive immune response [4]. Conventional vaccination techniques are unsuccessful against quickly changing pathogens such as influenza and new disease threats such as the Ebola and Zika viruses [5].

DNA (as plasmids) and RNA (as messenger RNA (mRNA))-based vaccines open the door for safe and effective biologics that imitate receiving a live-organism-based vaccination, notably for the induction of cell-mediated immunity. This method has remarkable promise for treating various indications and illnesses, ranging from prevention to therapies for cancer, autoimmune disorders, hypersensitivities, and infectious diseases. RNA-based vaccines, compared to DNA-based ones, might significantly influence these fields because of their quicker manufacturing processes and higher efficacy [2,3].

The concept of mRNA first came into existence in the late 1950s and is connected to Francis Crick's presentation of his "Central Dogma of Molecular Biology," according to which DNA causes the production of RNA, which then triggers the synthesis of proteins [6]. In 1961, Brenner and colleagues reported the presence of an unstable intermediary molecule that duplicates the data contained by the DNA and controls the production of proteins. This discovery led to the identification of mRNA. The first instance of mRNA translation in a lab took place in 1969. Lockard and Lingrel demonstrated the first instance of *in-vitro* mRNA translation. Liposomes were first used in 1978 to transfer mRNA to eukaryotic cells. By the end of the next decade, the cationic liposome mRNA delivery system DOTMA had been characterized and commercialized [7].

Krieg and other team members utilized an RNA synthesis enzyme (derived from a virus) and other tools in 1984 to create physiologically active mRNA in the laboratory. The team was directed by developmental biologist Douglas Melton and molecular scientists Tom Maniatis and Michael Green. The mRNA was then administered to frog eggs, where Krieg demonstrated that it functioned identically to naturally produced [8].

Nonetheless, Robert Malone, Wolff J., and others laid the groundwork for the concept of mRNA as a medicinal agent in 1990. The researchers inserted naked RNA into the muscles of mice to demonstrate the feasibility of direct gene delivery *in vivo* [7,9]. In a subsequent investigation in 1992, researchers discovered that injecting vasopressin-encoding mRNA into the hypothalamus may induce a physiological reaction in rats [10].

Sahin., *et al.* (2014) reported the first evidence that mRNA stability might be increased by optimization and formulation in 1995. Additionally, it was shown in 1995 that intramuscular injection of naked RNA expressing carcinoembryonic antigen-induced antigen-specific

antibody responses. A year later, it was revealed that DCs supplied subcutaneously to tumor-bearing mice or exposed to total mRNA retrieved from tumor cells or mRNA coding for particular antigens activated T-cell immune function and prevented the development of existing tumors. These results hastened the development and practical use of the mRNA-transfected DC method and the growing availability of vaccine targets due to cloning new tumor antigens [11]. Table 1 highlights the historic research done in RNA vaccine development [7,9,12].

Year	**Researchers**	**Research**
1961	Sydney Brenner	Discovery of mRNA
1969	Jerry B. Lingrel	First evidence of in vitro translation of mRNA
1984	Paul A. Krieg	First evidence of in vitro transcription using SP6 polymerase
1990	Jon A. Wolff	First demonstration of translation of mRNA injected into mice
1992	Gustav Jirikowski	mRNA injected into rat brains reverses diabetes insipidus
1995	Robert M. Conry	Designed the first mRNA vaccine encoding cancer antigens
2005	Katalin Kariko and Dr. Drew Weissman	Nucleoside-modified, non-immunogenic mRNA transcript is designed
2009	Benjamin Weide	First trial of cancer immunotherapy using mRNA-based vaccines in human subjects was conducted
2010s	Pieter Cullis and his team with Dr. Drew Weissman and Dr. Katalin Karikó	Worked on vaccines that could use mRNA + lipid nanoparticles
2014+	Kizzmekia Corbett	Begins work on coronavirus biology and vaccine development
2020+	Dr. Corbett's team (under the direction of Dr. Barney Graham)	Develop a COVID-19 vaccine using mRNA

Table 1: *Historical research in RNA vaccine development [7,9,12]*

Infectious illness prevention, management, and eradication typically regard vaccinations as one of the most successful approaches. However, occasional adverse effects of vaccines have been observed in research [13]. The adverse reactions that have been recorded (fatigue, fever, chills, headache, myalgia, nausea, and pain) are often mild or moderate in severity (> 80%), and they are generally comparable to side effects from other vaccination classes [14].

The published evidence on mRNA vaccines is primarily restricted to serological studies. Most syndromes or isolated symptoms have been described in multicenter or nationwide longitudinal cohort studies and case series [15]. Although mRNA vaccines are highly preventative, their cardiovascular adverse effects should be considered. Acute myocarditis, pericarditis, and perimyocarditis are serious side effects of mRNA immunization, particularly in males [15,16]. Some vaccine-related adverse effects were observed to increase with age (e.g., myocardial infarction (MI), Takotsubo cardiomyopathy, Guillain-Barré syndrome), whereas others (e.g., anaphylaxis, appendicitis) were more prevalent in younger persons.

Other less commonly observed adverse effects of mRNA vaccination include Bell's palsy, Guillain-Barré syndrome, appendicitis, herpes zoster reactivation, neurological problems, and autoimmunity (e.g., hepatitis and peripheral neuropathies) [15].

Discussion

RNA vaccines

RNA vaccines are a new class of immunizations composed of mRNA sequences that encode pathogen-specific proteins [13]. Due to the activation of various pattern-recognition receptors, RNA vaccines have proven to have high immunogenicity and the ability to quickly induce antibody responses against several new diseases due to the activation of numerous pattern-recognition receptors. Since their inception, nucleic acid vaccines given virally, such as using viral replicon particles or similar methods, have held promise as an efficient means to generate T-cell immunity by simulating vaccination with a live vaccine [17]. Products made from RNA can take a variety of

shapes. The most sophisticated clinical candidate vaccines are mRNA molecules that encode the target antigen. However, nucleases can degrade mRNA. Therefore, the most sophisticated mRNA candidate vaccines are designed in lipid nanoparticles, which promote stability and delivery [18].

In RNA vaccines, the human body is not directly exposed to a live or inactivated pathogen or a pathogen-specific antigen. Instead, the body receives an mRNA sequence containing the genetic makeup of a pathogen-specific antigen. The host cell's protein-synthesis machinery subsequently creates the target antigen using this mRNA sequence as a template. Once made, the target antigen is presented on the cell's surface, so trained immune cells can detect it and trigger immunological reactions tailored to the particular pathogen. Because these vaccinations do not contain infectious organisms, they are safe even in immunocompromised people [19]. The five functional sections of mRNA—the 5′ cap, the 3′ poly(A) tail, the ORF flanking, and the 3′ untranslated regions (UTRs)—mediate the efficiency of mRNA translation and its rate of degradation. Notably, highly physiologically active RNA production depends on consistent design and preparation [20].

RNA vaccinations come in three primary forms: self-replicating mRNA vaccines, *in vitro* dendritic cell non-replicating mRNA vaccines, and non-replicating mRNA vaccines (Figure 1) [19].

The traditional vaccines use pathogens, their components (recombinant proteins, subunits, polysaccharides, or conjugates), or toxins

Figure 1: *Types of RNA vaccines [19]*

to elicit host immune responses. Although these approaches provide durable protection against various diseases and have had significant public health benefits, their major limitation in the global pandemic (COVID-19 pandemic) is that they can be challenging to develop and manufacture at scale quickly.

RNA vaccines, in contrast, provide a platform that can be designed and mass-produced rapidly [14]. mRNA vaccines teach cells how to make a protein that triggers an immune response if someone gets infected. The advantages of mRNA over other vaccines are shown in Figure 2 [14,21-23]. Figure 3 shows the limitations of mRNA vaccination [5,14,23-26].

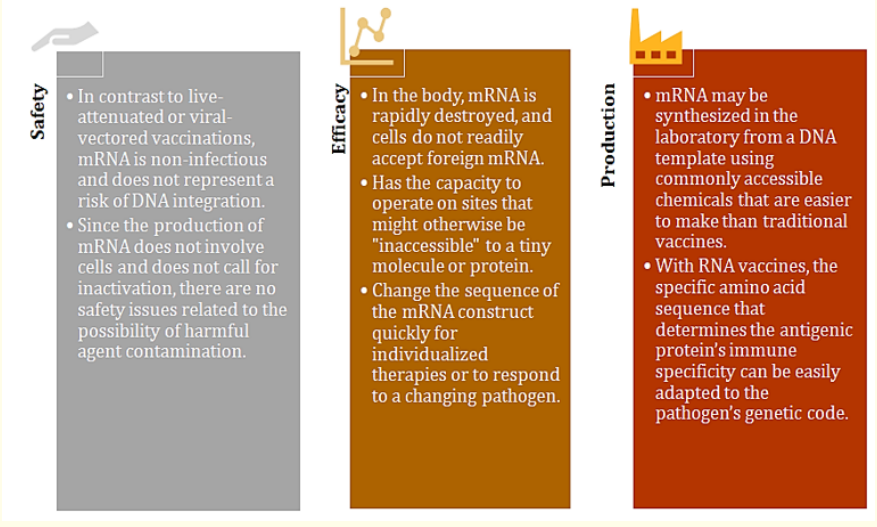

Figure 2: *Advantages of RNA over other vaccine strategies [14,21-23]*

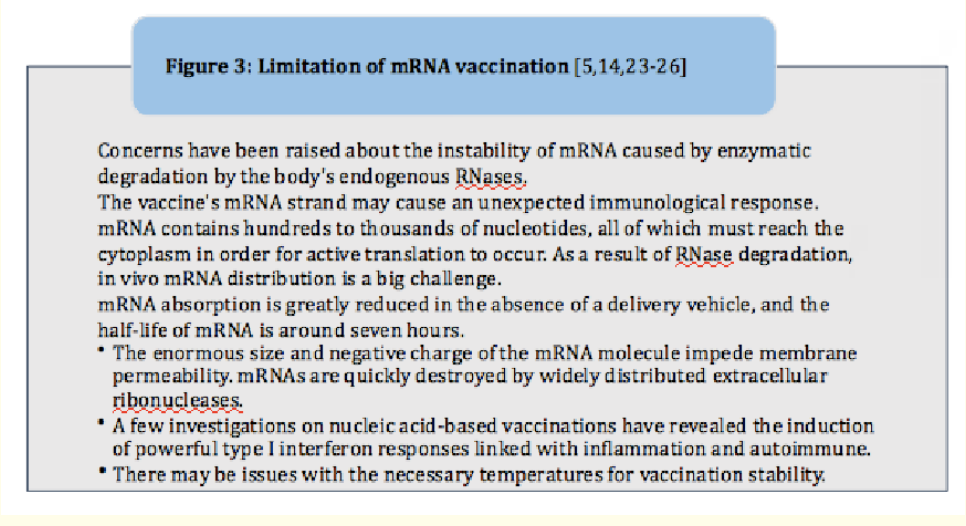

Figure 3: *Limitation of mRNA vaccination [5,14,23-26]*

Association of RNA vaccines and cardiovascular effects

The method through which mRNA vaccines generate cardiovascular effects is uncertain. It has been proposed that the lipid nanoparticle and RNA components of the COVID-19 vaccines might trigger excessive innate immune activation, which can result in myocarditis.

Endosomal toll-like receptors (TLR) TLR3, TLR7, and TLR8 in immune cells and RIG-I and MDA5 in nonimmune cells provide a natural defense against foreign RNA but can cross-react with IVT RNA. When these receptors are activated, an inflammatory cascade is initiated, which includes the formation of an inflammasome platform, the generation of type I interferons, and the nuclear translocation of NK-kB. Inflammasomes are multiprotein complexes that respond to pathogens and stress-related cellular damage. Inflammasomes yield the pleiotropic IL-1 family (IL-1 and IL-18) to be secreted, as well as pyroptosis [27]. Interleukin-1 (IL-1) receptor antagonist, interleukin-5 (IL-5), and interleukin-16 (IL-16) levels were elevated in one case report of individuals with vaccine-induced myocarditis [28].

According to specific reports, mRNA vaccinations are generally well tolerated, with meager rates of related severe postimmunization AEs. Although rare, AEs include serious clinical manifestations such as acute MI, MI with non-obstructive coronary arteries (MINOCA), cerebral venous sinus thrombosis, myocarditis/pericarditis (mostly in younger ages), pulmonary embolism, stroke, thrombosis, acquired thrombotic thrombocytopenic purpura (ATTP), thrombocytopenia, thrombosis with thrombocytopenia syndrome (TTS), vaccine-induced immune thrombotic thrombocytopenia (VITT), isolated tachycardia, and lymphadenopathy [15, 27,29,30]. Recently, the two COVID-19 mRNA vaccines from Pfizer-BioNTech and Moderna were linked to instances of myocarditis and pericarditis, according to the Centers for Disease Control and Prevention's (CDC) advisory committee on vaccination practices [31-33]. Patients who got the BNT162b2 mRNA COVID-19 vaccination experienced 4863 adverse events in the cardiovascular system. Tachycardia (16.41%), flushing (12.17%), elevated heart rate (HR) (9.03%), hypertension (5.82%), and hypotension (3.6%) were typical results with vaccinations under study [34].

Symptoms and diagnostic findings of vaccine-caused CV disorders

Patients with vaccine-induced CV problems might present differently clinically and have varying degrees of severity. The most common symptoms are syncope, palpitations, dyspnea, chest pressure, discomfort, and breathing pain. An ECG or cardiac magnetic resonance imaging (cMRI) examination may disclose an aberrant result (Figure 4) [35]. Due to the moderate clinical signs of suspected vaccine-induced myocarditis, a conventional echocardiogram may not be the best diagnostic method in these individuals, yet, conventional echocardiography seemed normal.

Condition	Definition	
Myocarditis	Presence of 1 new or worsening clinical symptom from the list below: chest pain, pressure, or discomfort; dyspnea, shortness of breath, or trouble with breathing; palpitations; as well as syncope.	Infants and children under the age of 12 years may experience two of the following symptoms: irritability, vomiting, poor eating, tachypnoea, and lethargy.
	≥1 new finding of • Troponin level > upper limit of normal • abnormal electrocardiogram (ECG or EKG) or rhythm monitoring findings consistent with myocarditis • abnormal cardiac function or wall motion abnormalities on echocardiogram • cMRI findings consistent with myocarditis	
Pericarditis	The presence of two new or worsening clinical features: • acute chest discomfort • pericardial rub on exam • new ST-elevation or PR-depression on EKG • new or worsening pericardial effusion on echocardiography or MRI	
Myopericarditis	Patients that fulfill myocarditis and pericarditis criteria.	

Figure 4: *Case definitions of probable myocarditis, pericarditis, and myopericarditis [35]*

The strain and strain-rate parameters of speckle tracking echocardiography (STE) are excellent diagnostic tools with high sensitivity for detecting subclinical ventricular dysfunction [36], and cardiac MRI may be the best technique to confirm a diagnosis of myocarditis in the majority of patients.

Multiple biomarkers from various pathophysiological pathways have been shown to predict cardiovascular events, and the use of biomarkers in risk assessment may improve prognostic information in secondary prevention. Elevated levels of circulating biomarkers, including high sensitivity C-reactive protein (CRP), CK, CK-MB, BNP, inflammatory markers, ESR, and cardiac troponin, are critical for the diagnosis, risk assessment, and treatment of individuals with a variety of CV illnesses. Additionally, research has shown that combining many biomarkers has effectively determined CVD risk classification [37,38].

Epidemiology of RNA vaccine-induced cardiovascular disorders

Vaccination promotes public health, but there are potentially some side effects [39]. Myocarditis and pericarditis have been identified as the most common cardiovascular problems following COVID-19 mRNA vaccination in studies conducted in the United States and the United Kingdom [40,41]. However, this is not the first occurrence of post-vaccine myocarditis; cases of myocarditis have been linked to other vaccines [42]. Myocarditis/pericarditis rates are ≈12.6 cases per million doses of second-dose mRNA vaccination among people aged 12 to 39, according to the US Centers for Disease Control and Prevention [43].

Li., *et al.* (2021)—in an international network cohort that comprised more than 126 million individuals—analyzed the overall background rate of 15 adverse events related to COVID-19 mRNA vaccinations and discovered that myocarditis or pericarditis was more prevalent among men, with the highest frequency occurring in the 75 - 84 age range (54 and 39 per 100,000 person-year incidence rates in males and females, respectively) [44]. Similarly, Oster., *et al.* (2022) investigated myocarditis reports to the Vaccine Adverse Event Reporting System (VAERS) and discovered that the incidence of myocarditis after getting mRNA-based vaccinations was highest after the second vaccination dose in adolescent males. The crude reporting rates for instances of myocarditis within 7 days after immunization outperformed the predicted rates across different age and gender strata. Teenage boys aged 12 to 15 years (70.7 per million doses of the BNT162b2 vaccine), adolescent males aged 16 to 17 years (105.98 per million doses of the BNT162b2 vaccine), and young men aged 18 to 24 years had the most significant incidences of myocarditis following the second immunization dose (52.45 and 565.3 per million doses of the BNT162b2 vaccine and the mRNA-1273 vaccine, respectively).

Furthermore, white people (69%) and Hispanic people (of all races; 17%) had the highest prevalence of myocarditis cases. There were 826 cases of myocarditis among persons younger than 30 years old with comprehensive clinical information available; of these cases, 792 of 809 (98%) had increased troponin levels, 569 of 794 (72%) had abnormal ECG data, 223 of 312 (72%) had abnormal cMRI results [39].

Wong., *et al.* (2022) found higher than predicted rates of myocarditis (and pericarditis) in persons younger than 35 years old, with the highest risk among males aged 18 - 25 years following their second COVID-19 mRNA vaccination dosage. For males aged 18 - 25 years following a second vaccination dose, the absolute risk of myocarditis or pericarditis was 2.17 (95% CI 1.55 - 3.04) cases per 100,000 person-days for the Moderna vaccine, mRNA-1273, and 1.71 (1.31 - 2.23) instances per 100 000 person-days for the Pfizer-BioNTech vaccine, BNT162b2 [45].

Additionally, among the 10.4 million people who had received the mRNA immunization, the Israeli Ministry of Health recorded 148 incidences of myocarditis, most of which occurred after a second dosage and predominantly affected men between the ages of 16 and 30. The frequency of myocarditis was 1/20,000 in the 16- to 30-year-old age range, compared to 1/100,000 in the overall population receiving the same vaccination.

In investigations from Switzerland and the United States, which compared the incidence with post-COVID-19 myocarditis, cases of post-vaccination pericarditis were also reported [46,47]. A total of 40 pericarditis cases were documented, with 75% of the patients being male, and the median age is 59 - 60 years old. Despite having symptoms that are similar to those of myocarditis, pericarditis is more common in older men. The top three comorbidities were high blood pressure, diabetes, and a history of coronary artery disease [47].

Aye., *et al.* (2021) [48] in a pooled analysis (n = 30), and Sung., *et al.* (2021) [49] in a case study (n = 2) evaluated MI complications associated with COVID-19 mRNA vaccination. In one of the studies, the median time between vaccination and the onset of symptoms was

approximately 1 - 2 days, with 33% of documented cases occurring post-second vaccination. Most patients (78% of all cases) were male, with a mean age of 55 in one study and 65 in the other. The most important risk factors for MI complications were all present as comorbidities in the two investigations, including hypertension (62%), hyperlipidemia (57%), diabetes mellitus (51%), and active smoking (35%).

Specific studies have also revealed that more than 80% of patients with myocarditis caused by the COVID-19 vaccination will recover spontaneously. Still, those hospitalized for myocarditis have a 4 - 5% chance of dying or requiring a heart transplant within a year of diagnosis [50]. Typically, following a chest pain condition, > 90% of individuals with COVID-19 mRNA-vaccine-associated myocarditis will functionally fully recover [51].

Treatment of RNA vaccine-induced CV disorders

Colchicine, nonsteroidal anti-inflammatory medications (NSAIDs), and steroids may be options for individuals with moderate chronic symptoms but no hemodynamic instability, arrhythmia, substantial LV dysfunction, or HF. Intravenous steroids, intravenous immunoglobulin, and other cardiac or circulatory supportive therapies might be considered in individuals with LV dysfunction, HF, new-onset arrhythmia, or hemodynamic instability. Guideline-directed treatment should be commenced in patients with LV systolic dysfunction, including β-blockers, angiotensin-converting enzyme inhibitors (ACEi), and diuretics. A further recommendation is to refrain from intense exercise for three to six months [52]. A cardiologist should be involved in the early assessment, examination, management, and follow-up, and an infectious disease specialist should provide advice on ongoing vaccination plans [44,53]

Sawalha., *et al.* (2021) showed that glucocorticoids (58%), immunoglobulin therapy (17%), and colchicine (17%) were the most common medical therapies for COVID-19-related myocarditis. In addition, inotropes, mechanical support, and anti-inflammatory drugs (e.g., tocilizumab and interferon) were commonly used [54]. Therapy may be deferred among patients with rapid resolution of symptoms, with preserved cardiac function and standard biomarkers, or with resolving cardiac biomarker abnormality [44].

Diaz., *et al.* (2021) treated post-mRNA vaccination myocarditis or pericarditis with NSAIDs, colchicine, and steroids. Only 18.9% of pericarditis cases had complete symptom relief [47].

Marshall., *et al.* (2021) looked into 7 cases of acute myocarditis or myopericarditis in healthy male teenagers who complained of chest pain within 4 days of receiving the second dose of COVID-19 immunization. Six individuals were given NSAIDs. Four patients received IVIG and oral prednisone; one received high-dose methylprednisolone at first. All seven individuals in the case study had their symptoms alleviated. Notably, three individuals healed only on NSAID medication [55].

Istampoulouoglou., *et al.* (2021) studied 9 patients with perimyocarditis (median age = 57 years).

The average period between vaccination and the beginning of symptoms was 4.7 days, with seven (78%) cases appearing after the second dose. Five patients (56%) had chest discomfort, and two (22%) had nonspecific symptoms such as myalgia, fever, and other flu-like symptoms). Eight patients (89%) had abnormal troponin levels, seven (77%) had substantial ECG signs, and six (67%) had notable MRI findings.

The recommended course of treatment for these instances was the administration of an ACE inhibitor to four patients or a beta-blocker to four patients, followed by combination therapy using an ACE inhibitor and a beta-blocker or ibuprofen as an anti-inflammatory drug. Notably, just three patients (or 33%) had symptoms disappear entirely, and their average duration of stay was six days [46].

Percutaneous coronary intervention (PCI) to the LC artery and medical therapy that follows established guidelines can aid in relieving chest discomfort in post-mRNA-vaccinated MI patients, according to Sung., *et al.* (2021) [49].

Complementary and alternative medicine (CAM) in CV disorders

Complementary and alternative medicine (CAM) is a broad category of healthcare treatments and therapies created outside mainstream allopathic medicine, focusing on health behavior modification. It plays a significant role in many aspects of healthcare worldwide,

including cardiovascular disease (CVD) [56]. Herbs, nutritional supplements, meditation, Ayurveda, homeopathy, naturopathy, Chinese medicine, chiropractic, massage, tai chi, yoga, reiki, and qigong are all examples of CAM [57].

One study analyzed data on CAM usage among CVD patients from the 2002 NHIS. The research revealed that 36% of CVD patients had used CAM in the preceding 12 months. Herbal medications and mind-body therapies (deep-breathing activities and yoga) were the most commonly utilized therapies, with 18% and 17% of patients using them, respectively [58].

Similarly, Grant., *et al.* (2012) discovered in a comprehensive analysis that CAM usage varied from 4% to 61% among persons with CVD (biologically-based treatments 22% - 68%, herbal medicine 2% - 46%, vitamins/minerals/dietary supplements 3% - 54%, and mind-body therapies 2 - 57%). The study also discovered that the use of CAM to treat CVD ranged from 7% to 82% [59].

A recent randomized clinical study discovered that tai chi might enhance the quality of life, happiness, and exercise self-efficacy in persons with chronic HF, despite the lack of difference in improvement in peak oxygen intake and the 6-minute walk test compared to education alone [58].

Omega-3 fatty acids have been suggested by the American Heart Association (AHA) as a supplemental cardiovascular disease prevention strategy [60]. Fish oil supplements are widely used to treat high blood triglycerides and preserve arterial wall health [61]. The FDA has authorized L-carnitine as a replacement medication for primary and secondary L-carnitine deficits. Many clinical investigations have shown that acetyl-L-carnitine (ALC) and propionyl-L-carnitine (PLC), two naturally occurring carnitine derivates, might be used to treat peripheral artery disease (PAD), heart and cerebral ischemia, and congestive heart failure (CHF) [62-64].

Several herbal medications appear to benefit individuals with suspected viral myocarditis. Astragalus membranaceus combined with supportive treatment reduced symptoms, myocardial enzymes, aberrant electrocardiograms, and heart function. The Shengmai injection was successful in alleviating symptoms. "Shortscape Fleabane, Xinshu Capsule, Compound Qiangqi pill, Qi Lu Decoction, Shengyangyixin Decoction, and Qingxinhuoming Decoction all improved symptoms as well as heart function, ECG, and myocardial enzymes [65]".

Several studies claim that Ginkgo biloba has cardioprotective benefits due to its antioxidant, antiplatelet, antithrombotic, vasodilatory, and antihypertensive activities [56]. However, due to the poor methodological quality of the studies, there currently needs to be more data to support the use of any of these herbal remedies in the management of viral myocarditis [64].

According to observational research, low serum ascorbic acid has been linked to increased cardiovascular disease in people [65]. Ascorbic acid can minimize the relative risk of cardiovascular events and avoid cardiotoxic events following COVID-19 immunization [66].

The use of CAM has increased in both developed and developing countries. However, they are not as helpful or safe as advertised since their usage may incur high financial or other costs (e.g., by delaying treatment or causing death). Its use may have substantial consequences for individuals and society by instilling false optimism, exacerbating bad symptoms, delaying CM treatment, and wasting resources that might be used toward evidence-based interventions [67].

The overuse of CAM can jeopardize effective medical care due to interactions with prescription medications or contraindications. Proper medication management is critical for cardiovascular disease patients [60]. Omega-3 polyunsaturated fatty acid supplementation was not linked to a lower risk of all-cause mortality, cardiovascular mortality, sudden cardiac arrest, MI, or stroke, according to a recent meta-analysis [68].

In cardiac patients, herb-drug interactions are a problem [69]. Herb-drug interactions can alter the activities of medications with a restricted therapeutic index (e.g., digoxin) or other regularly used pharmaceuticals like diuretics, β-blockers, cholesterol-lowering drugs, and amiodarone [67,70]. When medications with a restricted therapeutic range, such as digoxin or warfarin, are provided with herbs, herb-drug interactions might cause arrhythmias or enhance toxicity. Patients and CAM practitioners must be aware of the increased risk

of bleeding while using ginkgo and garlic, which cardiac patients use, especially if these herbs are used with blood-thinning drugs [67].

Nonetheless, improved patient and medical practitioner education is required to raise awareness of the risks and benefits of CAM use in CVD patients [61].

Future approaches and research to reduce potential adverse effects of RNA vaccines

In both scientific and clinical research, RNA vaccines are now undergoing a boom [71]. With hundreds of RNA-based vaccine candidates now in preclinical and clinical development, it is clear that mRNA-based vaccine technology is a potential tool for creating innovative therapeutic and preventive vaccinations against various diseases. However, it is difficult to translate mRNA-based treatments from the bench to the bedside because of the challenges brought on by mRNA's considerable size, charge, inherent instability, and high vulnerability to enzyme destruction. As a result, the broader application of mRNA-based treatments is hindered by the need for better vectors or drug delivery vehicles [2].

Advanced delivery techniques can be deployed to address naked mRNA's low stability, cell targeting, and translational efficiency. Many clinically evaluated mRNA vaccine candidates are constructed without a delivery method, implying that mRNA vaccine delivery technologies need further improvement. Expanding the use of mRNA for the diagnosis, treatment, and prevention of disease can be improved by enhancing mRNA formulation and delivery by employing various nanomaterials [2]. Further research is required to determine the prevalence, risk factors, prognosis, putative causes, clinical course, therapeutic options, sex- and age-related variations, and the long-term effects of CV problems following mRNA immunization. Molecular mimicry, autoantibody production, mRNA immune reactivity, and a trigger of already present dysregulated immunological processes are only some potential pathways for developing CV diseases linked to mRNA vaccination that should be explored in further research. Determining if these variables are unique to spike delivery using mRNA technology or if they may be an uncommon occurrence from mRNA immunizations is also crucial [43].

Conclusion

mRNA-based vaccines are a potential new adaptable, scalable, and affordable platform, as demonstrated by many papers. Numerous preclinical and clinical studies have made significant advancements in using mRNA vaccines. They have provided evidence that mRNA-based prevention and treatment may be applied to human applications. There are, however, a few sparse case reports of various local and systemic side effects linked to mRNA vaccines. Some cardiac issues associated with mRNA vaccinations include pericarditis, myocarditis, and myocardial infarction. Cases are often mild and require no specific treatment, but sometimes treatment is needed to relieve symptoms.

The treatment plan may include supportive care, NSAIDs, steroids, and colchicine. In extreme situations, intravenous immune globulins, corticosteroids, and biological immune-modulating substances may be explored. People with CVD may also benefit from CAM therapy, but there are risks. Dietary supplements are one of the most widely utilized therapeutic strategies in CVD patients. Nevertheless, data are needed to assess CAM usage's effects on CVD patients, particularly the clinical and prognostic effects when combined with prescription medications.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

References

1. Jain S., *et al*. "Messenger RNA-based vaccines: Past, present, and future directions in the context of the COVID-19 pandemic". *Advanced Drug Delivery Reviews* 179 (2021): 114000. https://pubmed.ncbi.nlm.nih.gov/34637846/

2. Wadhwa A., *et al*. "Opportunities and challenges in the delivery of mRNA-based vaccines". *Pharmaceutics* 12.2 (2020): 102. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7076378/

3. SITNFlash. "RNA vaccines: a novel technology to prevent and treat disease". *Science in the News* (2022). https://sitn.hms.harvard.edu/flash/2015/rna-vaccines-a-novel-technology-to-prevent-and-treat-disease/

4. Pardi N., *et al*. "mRNA vaccines-a new era in vaccinology". *Nature Reviews Drug Discovery* 17.4 (2018): 261-279. https://www.nature.com/articles/nrd.2017.243

5. RNA vaccines: an introduction. PHG Foundation (2022). https://www.phgfoundation.org/briefing/rna-vaccines

6. Lakhotia SC. "Central dogma, selfish DNA and noncoding RNAs: A historical perspective". *Proceedings of the Indian National Science Academy* 97 (2018). https://www.researchgate.net/publication/323175957_Central_Dogma_Selfish_DNA_and_Noncoding_RNAs_a_Historical_Perspective

7. Ebertz A. "The history of mRNA applications". *The DNA Universe BLOG* (2022). https://www.googleadservices.com/pagead/aclk?sa=L&ai=DChcSEwiK8a-1lvH9AhVUmWYCHY3sDRIYABAAGgJzbQ&ohost=www.google.com&cid=CAASJORoAHVQfBOb9N6jZiVBjbNhPBj72lvnGgf5PniR_UDZWV0juw&sig=AOD64_1wnBeZH_iDsFQbNiPLMAIm5MPQag&q&adurl&ved=2ahUKEwiR9qi1lvH9AhXsXmwGHYUfAMAQ0Qx6BAgHEAE

8. Dolgin E. "The tangled history of mRNA vaccines". *Nature* 597.7876 (2021): 318-324. https://www.nature.com/articles/d41586-021-02483-w

9. Schlake T., *et al*. "Developing mRNA-vaccine technologies". *RNA Biology* 9.11 (2012): 1319-1330. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3597572/

10. Jirikowski GF., *et al*. "Reversal of diabetes insipidus in Brattleboro rats: intrahypothalamic injection of vasopressin mRNA". *Science* 255.5047 (1992): 996-998. https://pubmed.ncbi.nlm.nih.gov/1546298/

11. Sahin U., *et al*. "mRNA-based therapeutics-developing a new class of drugs". *Nature Reviews Drug Discovery* 13.10 (2014): 759-780. https://pubmed.ncbi.nlm.nih.gov/25233993/

12. Government of Canada, Canadian Institutes of Health Research. The long road to mRNA vaccines (2022). https://cihr-irsc.gc.ca/e/52424.html

13. Machado BAS., *et al*. "The importance of RNA-based vaccines in the fight against COVID-19: An overview". *Vaccines* 9.11 (2021): 1345. https://pubmed.ncbi.nlm.nih.gov/34835276/

14. Lin CJ., *et al*. "RNA vaccines for COVID-19: 5 things every cardiologist should know". *JACC: Basic to Translational Science* 5.12 (2020): 1240-1243. https://pubmed.ncbi.nlm.nih.gov/33251385/

15. Trougakos IP., *et al*. "Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis". *Trends in Molecular Medicine's* 28.7 (2022): 542-554. https://pubmed.ncbi.nlm.nih.gov/35537987/

16. Habib MB., *et al*. "Acute myocarditis following administration of BNT162b2 vaccine". *ID Cases* 25 (2021): e01197. https://pubmed.ncbi.nlm.nih.gov/34189042/

17. Duthie MS., *et al*. "Leishmaniasis vaccines: Applications of RNA technology and targeted clinical trial designs". *Pathogens* 11.11 (2022): 1259. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9695603/

18. World Health Organization. Evaluation of the Quality, Safety and Efficacy of RNA-Based Prophylactic Vaccines for Infectious Diseases: Regulatory Considerations (2020): 1. https://www.who.int/docs/default-source/biologicals/ecbs/reg-considerations-on-rna-vaccines_1st-draft_pc_tz_22122020.pdf?sfvrsn=c13e1e20_3

19. Coveney S. "What is an RNA vaccine? News-medical (2022). https://www.news-medical.net/health/What-is-an-RNA-Vaccine.aspx

20. Qin S., *et al*. "mRNA-based therapeutics: powerful and versatile tools to combat diseases". *Signal Transduction and Targeted Therapy* 7.1 (2032): 166. https://pubmed.ncbi.nlm.nih.gov/35597779/

21. What's different about messenger RNA (mRNA) vaccines for COVID-19? Memorial Sloan Kettering Cancer Center (2022). https://www.mskcc.org/coronavirus/what-s-different-about-messenger-rna-vaccines-covid-19

22. How does a mRNA vaccine compare to a traditional vaccine? Vumc (2022). https://www.vumc.org/viiii/infographics/how-does-mrna-vaccine-compare-traditional-vaccine

23. Damase TR., *et al*. "The limitless future of RNA therapeutics". *Frontiers in Bioengineering and Biotechnology* 9 (2021): 628137.

24. Gupta SK., *et al*. "The mammalian secreted RNases: mechanisms of action in host defence". *The Innate Immune* 19.1 (2013): 86-97. https://pubmed.ncbi.nlm.nih.gov/22627784/

25. Hussain A., *et al*. "mRNA vaccines for COVID-19 and diverse diseases". *Journal of Controlled Release* 345 (2022): 314-333. https://pubmed.ncbi.nlm.nih.gov/35331783/

26. Understanding mRNA vaccine technologies. The Pharmaceutical Journal (2022). https://pharmaceutical-journal.com/article/ld/understanding-mrna-vaccine-technologies

27. Mansanguan S., *et al*. "Cardiovascular manifestation of the BNT162b2 mRNA COVID-19 vaccine in adolescents". *Tropical Medicine and Infectious Disease* 7.8 (2022). https://www.mdpi.com/2414-6366/7/8/196

28. Muthukumar A., *et al*. "In-depth evaluation of a case of presumed myocarditis after the second dose of COVID-19 mRNA vaccine". *Circulation* 144.6 (2021): 487-498. https://pubmed.ncbi.nlm.nih.gov/34133883/

29. Fazlollahi A., *et al*. "Cardiac complications following mRNA COVID-19 vaccines: A systematic review of case reports and case series". *Reviews in Medical Virology* 32.4 (2022): e2318. https://pubmed.ncbi.nlm.nih.gov/34921468/

30. Liu R., *et al*. "Cardiovascular complications of COVID-19 vaccines". *Frontiers in Cardiovascular Medicine* 9 (2022): 840929. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8971371/

31. Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practice (ACIP). Coronavirus Disease 2019 (COVID-19) Vaccines (2022). https://www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html

32. Kuntz J., *et al*. "Myocarditis and pericarditis are rare following live viral vaccinations in adults". *Vaccine* 36.12 (2018): 1524-1527. https://pubmed.ncbi.nlm.nih.gov/29456017/

33. García JB., *et al*. "Acute myocarditis after administration of the BNT162b2 vaccine against COVID-19". *Revista Espanola De Cardiologia* 74.9 (2021): 812. https://pubmed.ncbi.nlm.nih.gov/33994339/

34. Shimabukuro TT., *et al*. "Safety monitoring in the vaccine adverse event reporting system (VAERS)". *Vaccine* 33.36 (2015): 4398-4405. https://pubmed.ncbi.nlm.nih.gov/26209838/

35. Gargano MW., *et al*. "Oliver Sara E. Morbidity and Mortality Weekly Report. 2021. Use of mRNA COVID-19 Vaccine After Reports of Myocarditis Among Vaccine Recipients: Update from the Advisory Committee on Immunization Practices - United States (2021): 977-982.

36. Hsiao JF., *et al*. "Speckle tracking echocardiography in acute myocarditis". *The International Journal of Cardiovascular Imaging* 29.2 (2013): 275-284. https://pubmed.ncbi.nlm.nih.gov/22736428/

37. Wong YK and Tse HF. "Circulating biomarkers for cardiovascular disease risk prediction in patients with cardiovascular disease". *Frontiers in Cardiovascular Medicine* 8 (2021): 713191. https://pubmed.ncbi.nlm.nih.gov/34660715/

38. Behers BJ., *et al*. "Focus: Vaccines: Myocarditis Following COVID-19 Vaccination: A Systematic Review of Case Reports". *The Yale Journal of Biology and Medicine* 95.2 (2022). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9235262/

39. Oster ME., *et al*. "Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021". *The Journal of the American Medical Association* 327.4 (2022): 331-340. https://jamanetwork.com/journals/jama/fullarticle/2788346

40. Patone M., *et al*. "Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection". *Nature Medicine* 28.2 (2022): 410-422. https://www.nature.com/articles/s41591-021-01630-0

41. Boehmer TK., *et al*. "Association between COVID-19 and myocarditis using hospital-based administrative data-United States". *Morbidity and Mortality Weekly Report* 70 (2020): 1228-1232. https://pubmed.ncbi.nlm.nih.gov/34473684/

42. Almas T., *et al*. "Epidemiology, clinical ramifications, and cellular pathogenesis of COVID-19 mRNA-vaccination-induced adverse cardiovascular outcomes: A state-of-the-heart review". *Biomedicine and Pharmacotherapy* 149.112843 (2022): 112843. https://pubmed.ncbi.nlm.nih.gov/35325848/

43. Bozkurt B., *et al*. "Myocarditis with COVID-19 mRNA vaccines". *Circulation* 144.6 (2021): 471-484. https://pubmed.ncbi.nlm.nih.gov/34281357/

44. Li X., *et al*. "Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study". *British Medical Journal* 373 (2021): n1435. https://pubmed.ncbi.nlm.nih.gov/35727911/

45. Wong HL., *et al*. "Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases". *Lancet* 399.10342 (2022): 2191-2199. https://pesquisa.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/resource/fr/covidwho-2115496

46. Istampoulouoglou I., *et al*. "Myocarditis and pericarditis in association with COVID-19 mRNA-vaccination: cases from a regional pharmacovigilance centre". *Global Cardiology Science and Practice* 3 (2021). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8587334/

47. Diaz GA., *et al*. "Myocarditis and pericarditis after vaccination for COVID-19". *The Journal of the American Medical Association* 326.12 (2021): 1210. https://pubmed.ncbi.nlm.nih.gov/34347001/

48. Aye YN., *et al*. "Acute myocardial infarction and myocarditis following COVID-19 vaccination". *QJM: An International Journal of Medicine* (2021). https://pubmed.ncbi.nlm.nih.gov/34586408/

49. Sung JG., *et al*. "Acute myocardial infarction within 24 hours after COVID-19 vaccination". *The American Journal of Cardiology* 156 (2021): 129-131. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8541841/

50. Greulich S., *et al*. "Predictors of mortality in patients with biopsy-proven viral myocarditis: 10-year outcome data". *Journal of the American Heart Association* 9.16 (2020): e015351. https://pubmed.ncbi.nlm.nih.gov/32787653/

51. Heymans S and Cooper LT. "Myocarditis after COVID-19 mRNA vaccination: clinical observations and potential mechanisms". *Nature Reviews Cardiology* 19.2 (2022): 75-77. https://www.nature.com/articles/s41569-021-00662-w

52. Writing Committee Gluckman TJ., *et al*. "2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: Myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: A report of the American college of cardiology solution set oversight committee". *Journal of the American College of Cardiology* 79.17 (2022): 1717-1756. https://pubmed.ncbi.nlm.nih.gov/35307156/

53. Luk A., *et al*. "Myocarditis and pericarditis after COVID-19 mRNA vaccination: Practical considerations for care providers". *Canadian Journal of Cardiology* 37.10 (2021): 1629-1634. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8349442/

54. Sawalha K., *et al*. "Systematic review of COVID-19 related myocarditis: Insights on management and outcome". *Cardiovascular Revascularization Medicine* 23 (2021): 107-113. https://pubmed.ncbi.nlm.nih.gov/32847728/

55. Marshall M., *et al*. "Symptomatic acute myocarditis in 7 adolescents after Pfizer-BioNTech COVID-19 vaccination". *Pediatrics* 148.3 (2021): e2021052478. https://publications.aap.org/pediatrics/article/148/3/e2021052478/179728/Symptomatic-Acute-Myocarditis-in-7-Adolescents

56. Rabito MJ and Kaye AD. "Complementary and alternative medicine and cardiovascular disease: an evidence-based review". *Evidence-Based Complementary and Alternative Medicine* (2013): 672097. https://pubmed.ncbi.nlm.nih.gov/23710229/

57. National Center for Complementary and Alternative Medicine (NCCAM). Strategic object 3: increase understanding of 'real world' patterns and outcomes of CAM use and its integration into health care and health promotion (2022). https://files.nccih.nih.gov/exploring-the-science-of-complementary-and-alternative-medicine-strategic-plan-2011-2015.pdf

58. Yeh GY., *et al*. "Use of complementary therapies in patients with cardiovascular disease". *The American Journal of Cardiology* 98.5 (2006): 673-680. https://pubmed.ncbi.nlm.nih.gov/16923460/

59. Grant SJ., *et al*. "The use of complementary and alternative medicine by people with cardiovascular disease: a systematic review". *BMC Public Health* 12.1 (2012): 299. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3444368/

60. Okoli C., *et al*. "Use of complementary and alternative medicine among people with cardiovascular diseases in southeast Georgia". *The Journal of the Georgia Public Health Association* 7.2 (2019). https://www.researchgate.net/publication/336814459_Use_of_Complementary_and_Alternative_Medicine_Among_People_With_Cardiovascular_Diseases_in_Southeast_Georgia

61. Qidwai W., *et al*. "Role of complementary and alternative medicine in cardiovascular diseases". *Evidence-Based Complementary and Alternative Medicine* (2013): 142898. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3703383/

62. Miller KL., *et al*. "Complementary and alternative medicine in cardiovascular disease: a review of biologically based approaches". *American Heart Journal* 147.3 (2004): 401-411. https://pubmed.ncbi.nlm.nih.gov/14999187/

63. Mingorance C., *et al*. "Critical update for the clinical use of L-carnitine analogs in cardiometabolic disorders". *Vascular Health and Risk Management* 7 (2011): 169-176. https://pubmed.ncbi.nlm.nih.gov/21490942/

64. Liu ZL., *et al*. "Herbal medicines for viral myocarditis". *Cochrane Database of Systematic Reviews* 7 (2010): CD003711. https://pubmed.ncbi.nlm.nih.gov/15266498/

65. Ashor AW., *et al*. "Effect of vitamin C on endothelial function in health and disease: A systematic review and meta-analysis of randomized controlled trials". *Atherosclerosis* 235 (2014): 9-20. https://pubmed.ncbi.nlm.nih.gov/24792921/

66. Berretta M., *et al*. "Multiple effects of ascorbic acid against chronic diseases: Updated evidence from preclinical and clinical studies". *Antioxidants* 9.12 (2020): 1182. https://pubmed.ncbi.nlm.nih.gov/33256059/

67. Bahall M. "Complementary and alternative medicine usage among cardiac patients: a descriptive study". *BMC Complementary Medicine and Therapies* 15.1 (2015): 100. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4394556/

68. Rizos EC., *et al*. "Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events: a systematic review and meta-analysis: A systematic review and meta-analysis". *The Journal of the American Medical Association* 308.10 (2012): 1024-1033. https://pubmed.ncbi.nlm.nih.gov/22968891/

69. Xu H and Chen KJ. "Herb-drug interaction: an emerging issue of integrative medicine". *Chinese Journal of Integrative Medicine* 16.3 (2010): 195-196. https://pubmed.ncbi.nlm.nih.gov/20694770/

70. Tachjian A., *et al*. "Use of herbal products and potential interactions in patients with cardiovascular diseases". *Journal of the American College of Cardiology* 55.6 (2010): 515-525. https://pubmed.ncbi.nlm.nih.gov/20152556/

71. Pardi N., *et al*. "mRNA vaccines-a new era in vaccinology". *Nature Reviews Drug Discovery* 17.4 (2018): 261-279. https://www.nature.com/articles/nrd.2017.243

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