

The Incidence of Myocardial Infarction after Vaccination against COVID-19: a Meta-Analysis and Systematic Review

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ABSTRACT

Background: Vaccines were developed to stop the pandemic stage of COVID-19. A wide range of adverse effects, including vascular complications, has been reported after vaccination. Up to now, various studies have reported different rates of myocardial infarction (MI) after COVID-19 vaccination. So, this meta-analysis and systematic review study was designed to estimate the pooled incidence of MI after COVID-19.

Methods: Two experienced researchers conducted searches in various databases and sources such as EMBASE, Scopus, Web of Science, Google Scholar, PubMed and gray literature, including references from studies published before March 2023. They collected information on participant count, the number of individuals who experienced MI after vaccination, average age, vaccine type, primary author, publication year and country of origin.

Results: A total of 385 articles were revealed by a literature search, and for further evaluation, 248 studies remained after removing duplicates. Seven articles remained for meta-analysis. Three studies provided the number of controls and the incidence of MI in both vaccinated and non-vaccinated groups. The incidence of MI after COVID-19 vaccines was ignorable (0%, $P=99\%$, $P<0.001$). After COVID-19 vaccines, the odds of MI were 0.99 (95% CI 0.84-1.18) ($P=0$, $p=0.9$).

Conclusion: As shown by the results of the present meta-analysis and systematic review, the incidence of MI after COVID-19 vaccination can be ignorable and the risk was not increased by vaccination.

Keywords: myocardial infarction, vaccine, COVID-19.

ABBREVIATIONS

AZD: AstraZeneca vaccine
CABG: coronary artery bypass graft
ICVT: intracranial venous thrombosis
MI: myocardial infarction
MOD: moderna vaccine
NOS: Newcastle-Ottawa quality assessment scale
PFR: Pfizer

INTRODUCTION

The lives of many people were affected by the SARS-CoV-2 pandemic globally. The new virus was observed in late 2019 in the sprawling capital of Central China's Hubei province, Wuhan, and disseminated quickly throughout the world. Therefore, different vaccines were developed to control COVID-19. Nowadays, vaccination against COVID-19 is among health priorities in all nations, and individuals are encouraged to have the vaccination to end the pandemic as soon as possible.

A wide range of adverse effects has been reported after vaccination, including neurological complications, thrombotic thrombocytopenic purpura (TTP), neuromuscular complications, cardiovascular events such as pericarditis, myocarditis, arrhythmia, myocardial infarction (MI) and stroke (1-4). Different hypothesis are found for postvaccination MI such as an autoimmune

response against the platelets which cause prothrombotic state after vaccination (5, 6). Alternatively, postvaccination stress may lead to request ischemia and finally, to MI (7). On the other hand, allergic vasospasm after vaccination (Kounis syndrome), which is associated with increased IgE levels, could cause postvaccination MI (8, 9).

Up to now, various studies reported different rates of MI after COVID-19 vaccination. So, this meta-analysis and systematic review study was designed to estimate the pooled incidence of MI after COVID-19. □

METHODS

PubMed, Scopus, EMBASE, Web of Science, Google Scholar and gray literature, including references to the included studies published before March 2023, were searched by two expert researchers. After deleting duplicates, the titles and abstracts of potential studies were screened. Then, the full texts of remaining studies were evaluated and data were extracted.

The search terms were as follows: ("COVID-19 Vaccines" OR "COVID 19 Vaccines" OR (Vaccines AND COVID-19) OR "COVID-19 Virus Vaccines" OR "COVID 19 Virus Vaccines" OR (Vaccines AND "COVID-19 Virus") OR ("Virus Vaccines" AND COVID-19) OR "COVID-19 Virus Vaccine" OR "COVID 19 Virus Vaccine" OR

(Vaccine AND "COVID-19 Virus") OR ("Virus Vaccine" AND COVID-19) OR "COVID19 Virus Vaccines" OR (Vaccines AND "COVID19 Virus") OR ("Virus Vaccines" AND COVID19) OR "COVID19 Virus Vaccine" OR (Vaccine AND "COVID19 Virus") OR ("Virus Vaccine" AND COVID19) OR "COVID19 Vaccines" OR (Vaccines AND COVID19) OR "COVID19 Vaccine" OR (Vaccine AND COVID19) OR "SARS-CoV-2 Vaccines" OR "SARS CoV 2 Vaccines" OR (Vaccines AND SARS-CoV-2) OR "SARS-CoV-2 Vaccine" OR "SARS CoV 2 Vaccine" OR (Vaccine AND SARS-CoV-2) OR "SARS2 Vaccines" OR (Vaccines AND SARS2) OR "SARS2 Vaccine" OR (Vaccine AND SARS2) OR "Coronavirus Disease 2019 Vaccines" OR "Coronavirus Disease 2019 Vaccine" OR "Coronavirus Disease 2019 Virus Vaccine" OR "Coronavirus Disease 2019 Virus Vaccines" OR "Coronavirus Disease-19 Vaccines" OR "Coronavirus Disease 19 Vaccines" OR (Vaccines AND "Coronavirus Disease-19") OR "Coronavirus Disease-19 Vaccine" OR "Coronavirus Disease 19 Vaccine" OR (Vaccine AND "Coronavirus Disease-19") OR "COVID 19 Vaccine" OR (Vaccine AND "COVID 19") OR "2019-nCoV Vaccine" OR "2019 nCoV Vaccine" OR (Vaccine AND 2019-nCoV) OR "2019 Novel Coronavirus Vaccines" OR "2019 Novel Coronavirus Vaccine" OR "2019-nCoV Vaccines" OR "2019 nCoV Vaccines" OR (Vaccines AND 2019-nCoV) OR "COVID-19 Vaccine" OR (Vaccine AND COVID-19) OR "SARS Coronavirus 2 Vaccines" OR "2019-nCoV vaccine" OR "2019-nCoV virus vaccine" OR "coronavirus disease 2019 vaccine" OR "COVID 19 vaccine" OR "COVID-19 vaccine" OR "COVID-19 vaccines" OR "COVID-19 virus vaccine" OR "COVID19 vaccine" OR "COVID19 virus vaccine" OR "HCoV-19 vaccine" OR "HCoV-19 virus vaccine" OR "Human coronavirus 2019 vaccine" OR "inactivated SARS-CoV-2 vaccine" OR "nCoV-2019 vaccine" OR "nCoV-2019 virus vaccine" OR "novel 2019 coronavirus vaccine" OR "novel coronavirus 2019 vaccine" OR "SARS Coronavirus 2 vaccine" OR "SARS-CoV-2 inactivated vaccine" OR "SARS-CoV-2 recombinant protein vaccine" OR "SARS-CoV-2 virus vaccine" OR "SARS2 vaccine" OR "SARS2 virus vaccine" OR "severe acute respiratory syndrome 2 vaccine" OR "severe acute respiratory syndrome coronavirus 2 vaccine" OR "Wuhan coronavirus vaccine")

AND ("Myocardial Infarction" OR (Infarction AND Myocardial) OR (Infarctions AND Myocardial) OR "Myocardial Infarctions" OR "Cardiovascular Stroke" OR "Cardiovascular Strokes" OR (Stroke AND Cardiovascular) OR (Strokes AND Cardiovascular) OR "Myocardial Infarct" OR (Infarct AND Myocardial) OR (Infarcts AND Myocardial) OR "Myocardial Infarcts" OR "Heart Attack" OR "Heart Attacks" OR "heart infarction" OR "cardiac infarct" OR "cardiac infarction" OR "cardial infarct" OR "heart infarct" OR "heart micro infarction" OR "heart muscle infarction" OR (infarction AND heart) OR "myocardium infarct" OR "myocardium infarction" OR "premonitory infarction sign" OR "second heart attack" OR "subendocardial infarction" OR "transmural cardiac infarction" OR "transmural heart infarction" OR ("transmural infarction" AND heart))

Cohort studies that reported the number of patients who had MI after COVID-19 vaccination and studies which described at least 10 cases were all included only if they were published in English.

Letters to the editor, reviews, case-control, case reports and cross-sectional studies were all excluded.

We extracted data regarding the total number of participants, first author, publication year, country of origin, mean age, vaccine type and number of patients who developed MI after vaccination.

Risk of bias assessment

The Newcastle-Ottawa quality assessment scale (adapted for cohort studies) was used for assessing the bias risk (10).

Statistical analysis

STATA (Version 14.0; Stata Corp LP, College Station, TX, USA) was used for performing all statistical analyses. Inconsistency (I^2) was calculated to determine heterogeneity. A random-effects model was used for meta-analysis because the heterogeneity between study results (I^2) was greater than 50%. $\square$

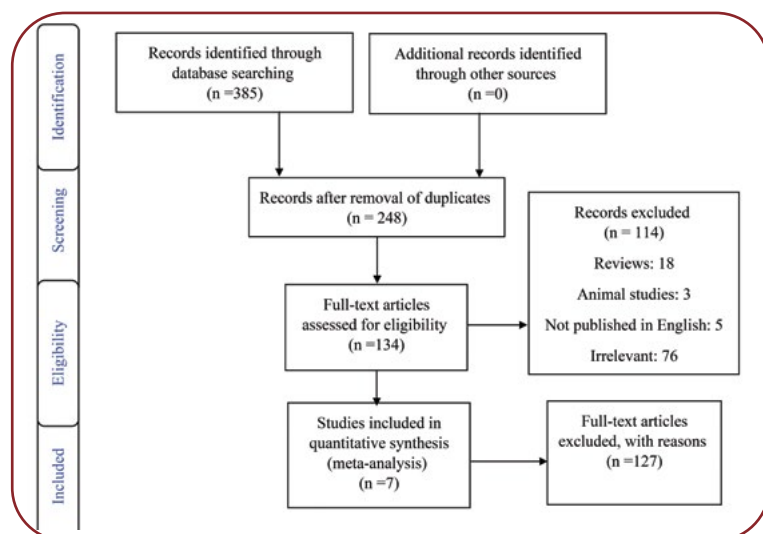
RESULTS

A total of 385 articles were found during the literature search, and after removing dupli-

TABLE 1. The country of origin, the number of controls, and the incidence of MI in both vaccinated and non-vaccinated groups

Author/year/country	All vaccines	Male/female/All vaccines	Vaccine type/dose	Vaccine-related MI	MI incidence male/female	Vaccine type/dose MI	All controls	Controls MI	Quality
Barbara H. Bardenheier/2021/USA	8275	NA	PFR: 5842 MOD: 2433	1	1/0	PFR: 1 1 st = 0 2 nd = 1 MOD: 0	11072	0	8
Anton Pottg�rd/2021/ Denmark, Norway	281264	59297/221967	AZD 1 st	20	NA	AZD 1 st =0	NA	NA	7
William N. Whiteley/2022/ UK	21193814	NA	PFR: 8712477 1 st AZD: 2481337 1 st	13609	NA	PFR: 7745 AZD: 5864 1 st =0	NA	NA	7
Julia Hippisley-Cox/2021/ UK	29121633	12657167/15265867/1198598	PFR: 9513625 1 st AZD: 9608008 1 st	14446	NA	PFR: 6545 AZD: 7901 1 st =0	NA	NA	7
Noam Barda/2021/ Israel	884828	461590/423238	PFR	59	NA	PFR=0	884828	60	8
Nicola P. Klein/2021/ USA	6175813	2830791/3345022	PFR: 539611 1 st =3539611 2 nd =3214737 MOD: 2636202 1 st =2636202 2 nd =2454578	613	NA	mRNA (PFR/MOD) =0	NA	NA	7
L.R. Baden/2021/USA	15181	7923/7258	MOD 1 st =15181 2 nd =14711	7	NA	MOD=0	15170	7	8

MOD: Moderna; PFR: Pfizer; AZD: AstraZeneca

**FIGURE 1.** Flow diagram of the included studies

cates, 248 studies remained pending for further evaluation.

Seven articles remained for meta-analysis after careful evaluation of their full text (Figure 1).

The country of origin was the USA in four studies, while one study was conducted in the UK, another one in Israel and the remaining one in Norway. Three studies provided the number

of controls and the incidence of MI in both vaccinated and non-vaccinated groups (Table 1).

After COVID-19 vaccines, the MI incidence was insignificant (0%, $I^2=99\%$, $P<0.001$) (Figure 2).

After COVID-19 vaccines, the MI odds were 0.99 (95% CI 0.84-1.18) ($I^2=0$, $p=0.9$) (Figure 3). ■

DISCUSSION

The results of the present study show that the pooled MI incidence is ignorable following COVID-19 vaccination and the COVID-19 vaccine administration does not increase the risk of MI. We gathered information of 57,680,808 patients who received one of three most common types of COVID-19 vaccines (Moderna, Pfizer, AstraZeneca), among whom 28,755 had a MI attack.

Boivin and Martin reported a case of MI in a 96-year-old woman who had a cardiac attack a few hours after the Moderna vaccine. She refused intervention and was treated medically (11).

In another case series, Sung *et al* reported two cases of MI within 24 hours of the Moderna vaccine (12). Bardenheier *et al* evaluated 8275 vaccinated cases who received mRNA vaccines

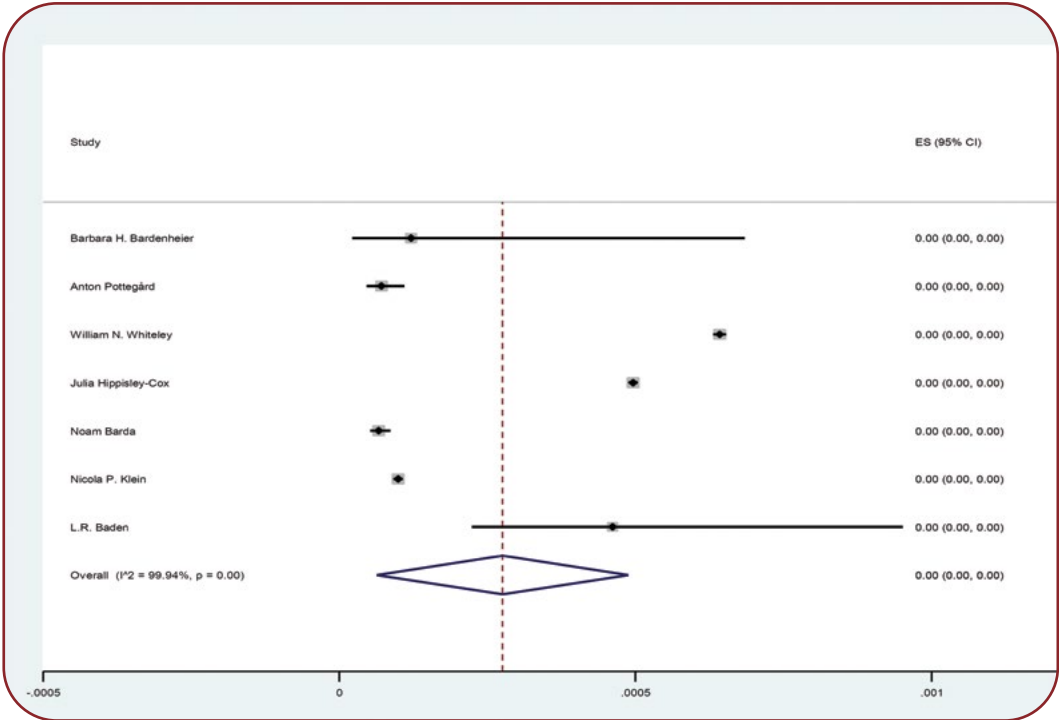


FIGURE 2. The MI incidence after COVID-19 vaccines

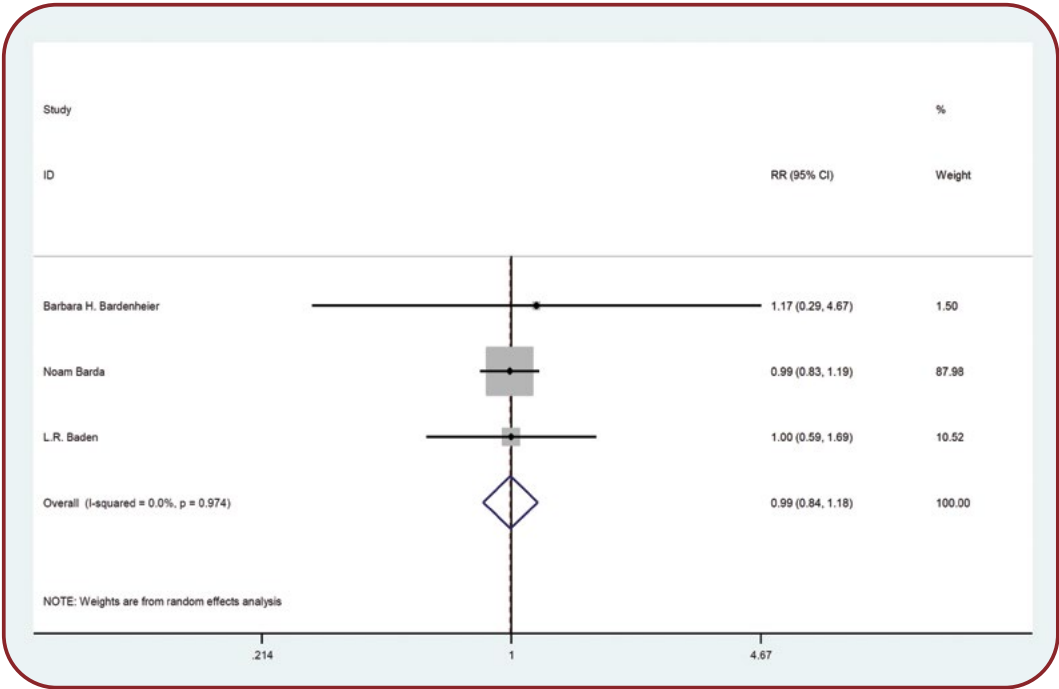


FIGURE 3. The odds of MI after COVID-19 vaccines

and reported an acute extensive MI in a 56-year-old man two days after the administration of the second dose. He had a past medical history of diabetes, hypertension, hypothyroidism and coronary artery bypass graft (CABG) (13).

Most thromboembolic events after COVID-19 vaccination were reported after administration of the Oxford-AstraZeneca COVID-19 vaccine (ChAdOx1-S). Pottegard *et al* found an increased rate of venous thromboembolic events and cerebral venous thrombosis following ChAdOx1-S by

assessment of 281 264 individuals, but they detected no increased risk of arterial events, and MI was reported in 20 cases (14).

In a large cohort study in England, Whiteley *et al* enrolled 21 193 814 individuals who had received the first dose of Pfizer or ChAdOx1-S vaccines. They investigated that receiving the ChAdOx1-S vaccine, rather than the BNT162b2 vaccine, was linked to a twofold increase in the likelihood of developing intracranial venous thrombosis (ICVT) in people aged under 70 years. They reported the incidence rate of late postvaccination MI (more than 28 days) as 740.7 and early postvaccination (less than 28 days) as 558.5 (15).

A recent systematic review, which included 20 studies, demonstrated that, after COVID-19 vaccination, venous thrombosis was more common than arterial thrombosis, and MI was more prevalent in cases with arterial thrombosis followed by an ischemic stroke (16).

Tajstra *et al* reported a case of MI who was treated with an androgen receptor inhibitor (enzalutamide) for prostate cancer. He collapsed 30 minutes after administration of the first dose of the Pfizer–BioNTech vaccine. Electrocardiogram findings showed MY of the inferior wall, while angiography revealed occlusion of the left anterior descending coronary artery, first diagonal branch and the distal part of the dominant right coronary artery (17).

There is no evidence regarding the relationship between COVID-19 vaccination and cardiac events as the exact mechanism of thrombotic events is poorly understood.

To control the pandemic stage of COVID-19, different vaccines have been developed worldwide with different mechanisms of action. Most adverse effects include injection site reactions such as pain and swelling. For the first time, thromboembolic events after vaccination were reported after administration of Astra Zeneca ChAdOx1 nCoV-19 vaccine (18). Although the rate is not too high, due to the risk of mortality, thromboembolic events should be carefully monitored especially in patients with higher risk thrombophilia or those with previous thrombotic events.

There are several notable strengths in this study. Primarily, it stands out as the inaugural systematic review conducted in this particular field. Secondly, different types of vaccines were evaluated.

Also, the present study had some limitations. Firstly, all eligible studies did not have control groups (people who did not receive vaccine) to compare the rate of MI in both groups. Secondly, the duration of follow-up after administration of vaccines was not similar for all studies.

CONCLUSION

The findings of the present study indicate that the occurrence of myocardial infarction following COVID-19 vaccination is negligible and there is no heightened risk associated with vaccination. □

Conflicts of interest: none declared.

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