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## Review

# No apparent association between mRNA COVID-19 vaccination and venous thromboembolism

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## ABSTRACT

By January 2022 over ten billion doses of COVID-19 vaccines had been administered worldwide. Concerns about COVID-19 vaccine-associated thrombosis arose after the characterization of a rare prothrombotic condition associated with adenoviral vector-based COVID-19 vaccines known as vaccine-induced immune thrombotic thrombocytopenia (VITT). Although mRNA COVID-19 vaccines have not been linked to VITT, concerns about thrombosis after vaccination persist despite safety data from hundreds of millions of recipients of mRNA COVID-19 vaccines. With widespread vaccination some VTE will occur shortly after vaccination by chance alone because VTE is a common condition that affects 1 to 2 in 1000 persons each year. Detailed analysis is required to determine whether these VTE events are coincidental or associated when they occur in close proximity to mRNA vaccine administration. This paper will review what is currently known about rates of VTE after mRNA vaccination in adults, discuss the reasons why uncertainty on this topic persists, and briefly review the implications of these findings for clinical practice and health policy.

## 1. Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is common in the general population with an incidence of about 1 per 1000 individuals per year. With the widespread administration of mRNA-based COVID-19 vaccines, large datasets have been analyzed to determine whether there is an association between mRNA COVID-19 vaccination and the occurrence of VTE among vaccinated individuals. Large randomized controlled trials evaluating mRNA COVID-19 vaccines including the BNT162b2 Pfizer–BioNTech [1] and mRNA-1273 Moderna [2,3] vaccines reported similarly low rates of VTE events in both the vaccine or placebo arms but these studies were designed to assess vaccine efficacy and had limited statistical power to detect differences between treatment arms with respect to rare but serious adverse events such as VTE. These vaccines have been instrumental in ameliorating the most profound consequences of the COVID-19 pandemic wherever they have been made available [4–9]. Since the use of these vaccines became widespread, surveillance and reporting systems for adverse events related to vaccines have been vital in detecting extremely rare adverse events not found in

the original trials.

A rare but serious thrombotic disorder known as Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) has been linked with the adenoviral vector-based COVID-19 vaccines AstraZeneca/COVISHIELD and Janssen/Johnson & Johnson vaccines. This clotting disorder was widely reported in the medical literature and the media and introduced uncertainty for healthcare practitioners and the public with regard to the risk of blood clots after all types of vaccination. The pathogenesis of VITT is linked to antibodies that bind to and activate platelet factor-4 and is similar to the mechanism of heparin-induced thrombocytopenia and thrombosis (HITT) but without heparin exposure. Although adenoviral vector-based vaccine components linked to the development of VITT are not shared by mRNA vaccines [10–12], concerns about thrombosis persist with mRNA vaccines. Case reports of VTE after mRNA vaccination, and studies that group several types of vaccines together when assessing thrombotic outcomes, may implicitly suggest a shared causal association where none exists [13]. In addition, venous thrombotic events secondary to VITT were found disproportionately at uncommon sites such as cerebral venous sinus thrombosis (CVST) and abdominal vein thrombosis. Concerns that these events

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could be common to all COVID-19 vaccine subtypes have led to increased scrutiny of all vaccine formulations and this review is partly a response to those concerns. Negative perceptions surrounding vaccine safety are a major contributor to vaccine hesitancy, and increased public communication about the safety of available vaccines would be expected to decrease vaccine hesitancy [14].

Answering the question of whether mRNA vaccines increase the risk of VTE is a complex endeavor. For many conditions, the absence of adverse events during a randomized controlled trial is sufficient to rule out a significant association. With preventative treatments including vaccines, expectations for safety are understandably extremely high, and the public demands a high degree of confidence in the security of these interventions. A randomized controlled trial with sufficient power to detect rare but serious adverse effects would be the “gold standard.” This approach would not be feasible because it would require a very large population. In theory, reported VTE event rates after vaccination could be compared to previously identified background rates, but this approach has the usual limitations of observational studies including confounding, imbalances in population characteristics, and the presence of secular trends over time. Background rates of VTE are heavily dependent on the characteristics of the population studied. Incidence of VTE rises exponentially with age and can be influenced by hereditary thrombophilia and acquired risk factors including a personal or family history of VTE, exogenous estrogen supplementation, malignancy, and the competing risk of VTE from COVID-19 infection [15–17]. Incidence rates of VTE approximate 1 per 1000 person-years across the entire population but can be as high as 4 per 1000 person-years in those over age 70, or as low as 1 in 10,000 person-years in those under 30 [18–21]. In addition, VTE incidence varies significantly by region [22]. Therefore, to formally compare observed rates of VTE after mRNA vaccines to background incidence rates the comparative population should be matched as closely as possible to the vaccinated group.

Over the last year researchers in the United States, United Kingdom, France, and Israel have compared VTE rates after mRNA vaccination with adjusted base rates of VTE occurring over a control period in matched individuals who did not undergo vaccination. A variety of study designs including randomized trials, case-control series, prospective cohort series, and analyses of active vaccine safety surveillance programs have not revealed an increased risk of VTE in recipients of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccines. This paper will review the available evidence on VTE after mRNA vaccines and discuss the implications of these findings in the management of VTE that occur in close proximity to mRNA vaccine administration.

### 1.1. Methods

To identify eligible studies, a systematic literature search was performed in electronic databases, including EmBASE, PubMed, Google Scholar, and Scopus. The search strategy was built based on the following keywords and MeSH terms: “BNT162b2”, “Pfizer”, “BioNTech”, “mRNA-1273”, “Moderna”, “Comirnaty”, “Elasomeran”, “RNA vaccine”, “mRNA vaccine”, “mRNA vaccination”, and any of “venous thromboembolism”, “thromboembolism”, “deep vein thrombosis”, “pulmonary embolism”, “cerebral sinus thrombosis”, “vein thrombosis”. The reference lists of relevant articles were also reviewed to retrieve additional studies. All relevant studies up to January 14th, 2022, were included. Studies that did not report on venous thromboembolism were not considered. Any calculations and figures were constructed using GraphPad Prism version 9.3.1 for Windows, GraphPad Software, San Diego, California USA, [www.graphpad.com](http://www.graphpad.com)”.

## 2. Results

We identified eight studies (two randomized controlled trials with extended follow-up, five large case-control series, and one large prospective cohort study) that provide data on VTE incidence and the

association between VTE and mRNA vaccines. We also discuss data from several small observational studies and analyses of events reported to pharmacovigilance databases including VAERS, FAERS, Eudravigilance, Vigibase. Additionally, a meta-analysis of randomized controlled trials for eight different COVID-19 vaccines, and a systematic review and meta-analysis of autopsy studies are reviewed. All available case series and case reports in publication or abstract were reviewed to identify unique characteristics or clinical events. A single report of upper extremity DVT and a single report of thrombosis with thrombocytopenia syndrome (TTS) and possible VITT are discussed. Due to the availability of higher quality data other case series and case reports detailing classical VTE presentation (leg DVT or PE) after mRNA vaccinations have not been included.

### 2.1. Randomized controlled trials (RCTs) and extended follow-up

The original randomized controlled trial of BNT162b2 (Pfizer-BioNTech) was reported in December 2020 [1]. The trial reported the results of safety and efficacy over a median follow-up of two months. Participants received either two doses of BNT162b2 or a saline placebo 21 days apart. The trial involved 45,548 participants and 37,416 doses of vaccine. There was no reporting of venous thromboembolic events in the original publication, but after the trial adverse events were monitored and reported during six months of follow-up. No thrombotic events were detected, and no deaths were attributable to thrombosis in those who received BNT162b2 [23].

A randomized controlled trial of mRNA-1273 (Moderna) was reported in January 2021. The trial reported the results of safety and efficacy mRNA-1273 over a median follow-up of two months [2,24]. Participants received either two doses of mRNA-1273 or a saline placebo 21 days apart. The trial involved 30,420 participants and 28,268 doses of vaccine. During initial follow-up, two events of deep vein thrombosis were seen in the vaccination group and no DVTs were seen in the placebo arm.

A follow-up study reported efficacy and safety at the completion of the blinded phase for mRNA-1273 (median 5.3 months after the second dose). The mean age of trial participants was 51 (18–95) years and trial discontinuations in the placebo group (4.5%) and the mRNA-1273 group (2.9%) were most commonly due to protocol deviations, withdrawal of consent, or loss to follow-up. At the completion of the open-label phase, four episodes of DVT, one axillary vein thrombosis, and one pulmonary embolism were seen in the mRNA-1273 arm, therefore <0.001% of those randomized to the treatment arm experienced a VTE event over the extended study period. In the placebo arm, one DVT, one superficial vein thrombosis, and no events of PE were reported [3].

### 2.2. Observational studies reporting on incidence of PE and leg DVT

Multiple large case-control series observed rates of VTE after mRNA vaccines and used self-control methods to explore whether VTE or other serious outcomes occur more commonly after mRNA vaccines. Self-controlled case series is a study design that reduces confounding by using participants as their own control by measuring outcomes after both an exposure of interest and a matched period without that exposure. The largest self-control case series was by Hippisley-Cox et al. through the National Immunisation Management System in England and the QResearch database representing approximately 20% of the national population [16]. The study examined the incidence rate of serious adverse events in the 28 days following the first dose of BNT162b2 vaccination as compared with baseline rates of disease in the same population and a control period of 28 days within the interval prior to vaccination. The mean age was 61.5 years and 0.3% had a prior history of VTE. They found no association between first dose BNT162b2 and the incidence of VTE across any 7-day interval or the full 28-day period. Subgroup analyses by age and gender did not reveal an increased incidence of VTE after mRNA vaccination.

Interim results from an active surveillance program in the United States provided unique insight into mRNA-1273 safety signals which are not otherwise well reported in the literature [25]. In this American series of from Klein et al. 43% of participants received mRNA-1273 and 57% received BNT162b2. Using a matched population of vaccinated individuals at 22 to 42 days after vaccination there was no increased risk of VTE with a risk ratio of 1.16 (95% CI 1.00–1.34) or Pulmonary Embolism with a risk ratio of 1.01, (95% CI 0.86–1.19) within the first 21 days after mRNA vaccine administration. In the study population with a mean age of 49, the absolute risk of VTE was 0.952 per 1000 person-years (in the risk interval) and 0.895 per 1000 person-years (in the control interval) which are similar to contemporary estimates of VTE incidence in this population [19,20,25]. Numerically more CVST events were seen in the vaccine group, but the results was not statistically significant (RR 1.55, 95% CI 0.37–8.17) [25].

Health data from a representative population of Israeli citizens were matched between those with mRNA vaccinations and those without (controls) over 42 days of follow-up [15]. The risk ratio for DVT after mRNA vaccination was 0.87 (95% CI, 0.55 to 1.40), the risk ratio for PE was 0.56 (95% CI, 0.21 to 1.15). Rates of VTE were 0.459 per 1000 person-years in the vaccinated group and 0.59 per 1000 person-years in the control group which are similar to contemporary estimates of VTE in this study with a mean age of 38 in both groups [15,19,20]. In the same study, a comparison between confirmed cases of COVID-19 infection and controls demonstrated a risk ratio for PE of pulmonary embolism of 12.14 (95% CI, 6.89 to 29.20) with a risk difference of 61.7 additional events per 100,000 persons (95% CI, 48.5 to 75.4).

A self-controlled case series from France examined older individuals at elevated risk of arterial and venous thromboembolic events within 14 days of the first or second dose of BNT162b2 [26]. In this population limited to age > 75 the relative incidence of pulmonary embolism after the first dose was 0.85 (95% CI 0.75–0.96) and after the second dose, 1.10 (95% CI, 0.95–1.26) indicating the risk of VTE is not increased in elderly populations after BNT162b2.

A recent abstract explored doppler ultrasound use and detection of VTE in the 90 days before and after vaccination [27]. Their population included a small number of patients who received the Janssen Adenoviral-vector vaccine (4.3% of those analyzed), but results were reported separately. The hazard ratio for VTE in the 90 days after vaccination was 0.68 (95% CI 0.34–1.38) for Janssen, 1.08 (95% CI 0.86–1.35) for Moderna, and 1.20 (95% CI 0.99–1.46) for Pfizer. They found the overall rate of VTE was 1.86 per 1000 patients, consistent with expected background rates given the demographics of the patients studied. More patients underwent duplex ultrasound in the 90 days after vaccination and the rate of detection was broadly similar with 11.6% of pre-vaccination ultrasounds showing DVT compared to 10.8% post-vaccination.

A prospective cohort study by Simpson et al. explored thromboembolic events and thrombocytopenia after BNT162b2 and ChAdOx1 nCoV-19 vaccination and compared event rates to matched patients who did not receive a vaccine [28]. Rates of VTE, including CVST, were reduced after BNT162b2 with a relative risk for VTE of 0.50 (95% CI, 0.47–0.62) over the first 28 days after vaccination as compared to unvaccinated individuals. Separate analysis of BNT162b2 for DVT revealed an adjusted risk ratio of 0.79 (95% CI, 0.56–1.11) and for PE an adjusted risk ratio of 0.35 (95% CI, 0.26–0.48).

The results of these six largest observational and prospective studies are represented in both Table 1 and Fig. 1, and in each case, the studies find incidence rate ratios for VTE after the exposure of interest (mRNA vaccine) clustering at or below 1.0 indicating no increased risk of VTE after these vaccines are given.

A smaller prospective study of nursing home residents vaccinated with BNT162b2 in the United States monitored for adverse events for 15 days after vaccination and utilized the staggered rollout of vaccines in similar nursing homes to generate a matched control group across 147 linked facilities. After 16,924 doses one case of DVT and one case of PE

**Table 1**

Summary of post-marketing studies investigating association between mRNA vaccines (BNT162b2 [Pfizer] and mRNA-1273 [Moderna]) and VTE.

	Total doses analyzed	Vaccine studied	Follow-up interval	Incidence rate ratio for VTE (95% CI)	Methods (abridged)
Hippisley-Cox et al 2021	9,513,625	BNT162b2	28 days	0.93 (0.84–1.02)	Self Control Case Series
Klein et al 2021	6,754,348	57% BNT162b2 43% mRNA-1273	21 days	1.16 (1.00–1.34)	Interim Analysis of Prospective Case-Control Surveillance
Jabagi et al 2021	3,900,000	BNT162b2	14 days	1.10 (0.95–1.26)	Self Control Case Series Limited to Age > 75
Barda et al 2021	884,828	BNT162b2	42 days	0.87 (0.55–1.40)	Case-Control Series
Simpson et al 2021	820,000	BNT162b2	27 days	0.50 (0.47–0.62)	National Prospective Cohort
Houghton et al 2021	245,572	64.2% BNT162b2 31.6% mRNA-1273	90 days	1.20 (0.99–1.46) 1.08 (0.86–1.35)*	Self Control Case Series

\* 4.3% of the studied population received the Janssen vaccine, RR shown are for BNT162b2 alone (top) and mRNA-1273 alone (bottom).

were detected in the vaccinated group, compared to one PE in the unvaccinated group [29].

### 2.3. Systematic reviews and analyses of pharmacovigilance database data

A systematic review and meta-analysis of thrombotic events which combined outcomes across different vaccine formulations did not find a significant association between a combination of arterial and venous thrombosis and vaccine use [13]. A recent meta-analysis of autopsy studies after COVID vaccination reviewed all published autopsies related to COVID vaccination. They found a total of 14 reported cases where an autopsy was performed after mRNA vaccine administration (10 with BNT162b2 and 4 with mRNA-1273) to determine whether the vaccine was implicated [30]. One case was classified as having a “possible” relationship with BNT162b2, and one death was determined to have a causal relationship to the COVID vaccine in association with myocarditis. In the case of mRNA-1273, the causality relationship was established in one case of mRNA-1273 vaccination out of four. In each of these cases the cause of death was related to non-thrombotic cardiac complications. Available autopsy series did not identify any cases with a causal relationship implicating thrombotic events after vaccination [30].

In March 2021, an analysis by Sessa et al. looked at all cases of thrombosis reported to the Vaccine Adverse Event Reporting System (VAERS) and the FDA Event Reporting System (FAERS) in women under age 50 [31]. Out of 13.6 million mRNA vaccinations administered at that time, they found 61 total reported cases of VTE, for a rate of 1 case of VTE per 222,951 vaccinated individuals. Four individuals with VTE in this group were also diagnosed with COVID-19 infection. In Europe, an early report explored rates of arterial thromboembolism and VTE reported to Vigibase after vaccination [32]. With BNT162b2 and mRNA-1273 the rates of reported arterial events outnumber venous events approximately 3:1, crudely in keeping with what is seen in the general population [32–35]. Interestingly after ChAdOx1 nCoV-19 vaccination a greater number of venous events than arterial events were reported

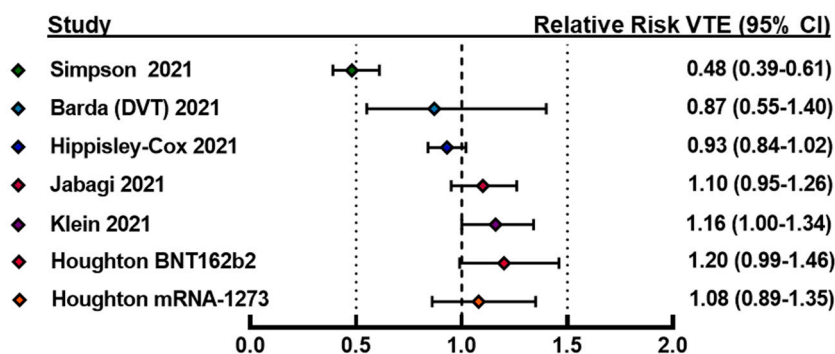


Fig. 1. Forest plot relative risk of VTE after mRNA vaccine administration.

indicating a change from the expected background rates of these conditions [32].

One paper compared rates of reported adverse events after BNT162b2 and ChAdOx1 nCoV-19 vaccination in the EudraVigilance database up to June 2021. They found the frequency of thromboembolic events was the same, or reduced, in those with BNT162b2 vaccination as compared to the base frequency in the population and significantly reduced compared to those with ChAdOx1 nCoV-19 vaccine [36]. A self-reported questionnaire in Saudi Arabia revealed one case of DVT after 2601 doses of BNT162b2 [37].

#### 2.4. Studies reporting on cerebral vein thrombosis (CVT)

Several studies have been dedicated specifically to examining whether vaccination is associated with cerebral venous sinus thrombosis (CVST). CVST is approximately two orders of magnitude less common than VTE with an annual incidence of approximately 1 per 100,000 across the general population, and approximately 2 per 100,000 in women aged 30–50 [38–40]. Even a significant increase in the relative risk would be expected to generate a minor increase in absolute risk. While this is reassuring from a public health perspective, it does make the question of whether mRNA vaccines increase the risk of CVST particularly challenging due to the low event rate. One analysis of the Eudravigilance database found rates of CVST 0.96–1.92 CVST cases per 100,000 persons after BNT162b2 vaccination in keeping with expected background rates [36]. In the American study more CVST events were seen in the vaccine group, but the result was not statistically significant with an incidence rate ratio of 1.55, (95% CI 0.37–8.17) after analysis of data from 6.7 million doses of either BNT162b2 or mRNA-1273 [25].

The British surveillance data assessed for CVST in the same manner as VTE [16]. No statistically significant association was found between BNT162b2 and CVST across 3 out of 4 of the pre-specified 7-day intervals, and there was no association for the full period of 28 days after vaccination. A positive association between BNT162b2 and CVST was found on days 15–21 after vaccination with an incidence rate ratio (IRR) of 3.58 (1.39 to 9.27) based on six episodes of CVST reported in this interval. For comparison after a positive COVID-19 test the incidence rate ratios for CVST were higher at 1–7 days IRR 12.90 (1.86 to 89.64), at 8–14 days IRR 13.43, (1.99 to 90.59), and at 15–21 days IRR 6.33 (0.63 to 63.67) but the absolute risk of CVST was low in this population as well [16]. However, the study has limitations. The statistically significant results were fragile in view of the limited number of events and the possibility of type 1 error with multiple comparisons. In the study, seven unique thrombotic outcomes were studied across 4 predetermined 7-day intervals to generate 28 incidence rate ratios, and one fewer CVST event in the 15–21 day interval would lead to a statistically null result. Subgroup analyses by age and gender found no association between BNT162b2 mRNA and CVST.

In the same dataset ChAdOx1 nCoV-19 vaccination was statistically associated with CVST in those younger than 50 years old with an

incidence rate ratio of 6.36, (95% CI 2.61 to 15.46) and an increased risk of arterial thrombosis and thrombocytopenia across the population studied [16]. The national prospective cohort from Scotland also found suggestive evidence for an association between ChAdOx1 nCoV-19 vaccination and arterial thrombosis and thrombocytopenia [28]. These findings are in keeping with what is now understood about the incidence of VITT following the ChAdOx1 nCoV-19 vaccine. The ability of the same methodology and dataset to detect an increase in risk for both CVST and arterial thrombosis provides some additional reassurance in interpreting a null result with regard to VTE or CVST after BNT162b2, but the statistical power to detect these rare events was greater with ChAdOx1 nCoV-19 since nearly twice as many doses were analyzed in the studies that found these associations.

Ongoing monitoring will help to determine whether CVST or other rare sites of venous thrombosis are associated with mRNA vaccines. The absolute risk of developing these conditions is so low that an increased risk has not been definitively captured despite the analysis of millions of doses of mRNA vaccines. A smaller study prospectively followed 62 patients with a history of CVST for thrombotic events after vaccination including 50 patients after mRNA vaccines and there were no thrombotic events within 30 days [41]. As it pertains to patient counseling and individual decision-making the highest available estimate of excess CVST events after mRNA vaccines is 20 per 10 million doses, or 1 per 500,000 doses [16], in contrast to other studies which show no statistical increase in the risk of CVST [25,36,40] and studies showing a significant increase in CVST after ChAdOx1 nCoV-19 vaccination and COVID-19 infection [16,28,36]. Therefore, if mRNA vaccines carry any increased risk of CVST the absolute risk is extremely low, the risk is lower than after ChAdOx1 nCoV-19 vaccination, and the risk is much lower than after COVID-19 infection [28,42]. Further study will help to clarify this important issue. Health practitioners seeing patients with unexplained headache or neurologic symptoms after vaccination may consider an increased index of suspicion for CVST.

#### 2.5. Studies reporting on thrombosis with thrombocytopenia syndrome (TTS)

While it was not the primary focus of this review an important related question is whether the incidence of TTS increase after mRNA vaccination. A single case of thrombosis with thrombocytopenia syndrome (TTS) and possible VITT was reported in the literature following vaccination with mRNA-1273 in October 2021 [43]. The accompanying editorial [44] calls attention to the difficulty in distinguishing VITT from autoimmune HIT or an early reaction to the heparin which was used to treat the patient prior to HIT testing being performed in that case. No other cases of possible VITT induced by mRNA vaccines have been reported in the literature.

The UK Yellowcard system is an active reporting system for adverse events after medicines or vaccinations. Prior to December 22nd, 2021, the UK Yellowcard system captured 29 cases of TTS after BNT162b2 and

3 after mRNA-1273. Over the same timeframe, the UK Yellowcard system reported 433 cases of TTS following ChAdOx1 nCoV-19 vaccination. One analysis of the Eudravigilance reporting system examined 26 cases of CVST after a messenger RNA (mRNA) vaccination (25 with BNT162b2 and one with mRNA-1273) and 187 cases of CVST following ChAdOx1 nCoV-19 vaccination. Concurrent thrombocytopenia occurred in 57% of the ChAdOx1 nCoV-19 vaccine group and 0% of the mRNA recipients [45]. Like most active reporting systems, the goal is to generate hypotheses using active reporting of all major adverse events after vaccination and reported cases do not establish causality.

A similar case-control approach can help inform whether these events are coincidental, representing a background rate of TTS unrelated to vaccines, or whether the rate of TTS is increased after mRNA vaccines. The two largest case-control series we reviewed investigated the incidence of TTS after BNT162b2 and found no association [16,25]. In the British series combinations of thrombocytopenia and venous thromboembolism and thrombocytopenia with arterial thromboembolism were analyzed across each 7-day interval after BNT162b2 and in all cases the incidence rate ratio for TTS was not statistically significant [16]. The available evidence strongly suggests that TTS, VITT, and CVST following ChAdOx1 nCoV-19 vaccination is due to a distinct mechanism [10–12] and clinical syndrome which are not shared by available mRNA vaccines.

We make no attempt to minimize systemic adverse reactions, stroke, myocardial complications, or autoimmune complications of mRNA vaccination including reports of ITP and TTP, but these issues fall outside the scope of this review.

### 3. Discussion

#### 3.1. Data in context – are available mRNA COVID-19 vaccinations associated with venous thromboembolism?

Well conducted randomized trials provide an unbiased assessment of the benefits and harms of interventions but may have limited generalizability. In the mRNA vaccine trials, rates of VTE were very low which is likely due, in part, to the relatively healthy populations studied. Observational studies, although inherently limited by bias and confounding, can be useful for measuring rare events in large populations over time.

Results of large case-controlled series, analysis of post-marketing surveillance data, and a large prospective cohort study found similar point estimates of risk which cluster at, or below, an incidence rate ratio of 1.0 after vaccination indicating no difference. To date, no studies have shown a significant increase in the incidence of VTE after mRNA vaccination.

These studies used designs and/or statistical methods to reduce confounding (e.g. self-controlled design), and subgroup analyses to explore variation within key subgroups (e.g. by age, race, and sex). However, the presence of residual confounding factors remains an important methodological limitation when interpreting results. Reliable ascertainment of vaccination status and clinical events may be a challenge for large retrospective administrative database cohorts. The control period of 22–42 days after vaccination used in the American study [25] may not be ideal, as thrombotic events have been reported more than 21 days after adenoviral vector vaccines, a limitation which is acknowledged in the study. Using identical methods the two large datasets also looked at adenoviral-vector-based ChAdOx1 nCoV-19 vaccine and detected an increased risk of VTE, CVST, and thrombocytopenia [16] and an increased risk of arterial thrombosis, immune thrombocytopenia (ITP), and hemorrhagic events [28]. In a single study BNT162b2 was associated with an increased risk of arterial ischemic stroke [16]. The presence of positive associations using identical methods in these studies may suggest a lower risk that these studies were underpowered to detect rare but serious adverse events.

In all studies only outcomes in which medical attention was sought

were considered in the final analysis, which may result in an underestimation of event rates. However, previously reported age-specific rates of VTE are similar to those reported in these studies [15,20,25,27,34].

Individual studies should be interpreted cautiously due to the non-randomized nature of the analysis but taken together these consistent results should be interpreted as confidently refuting a significant relationship between mRNA vaccination and VTE. Vaccination with BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) does not appear to be associated with an increased incidence of VTE.

#### 3.2. Clinical management of VTE after mRNA vaccines

These findings are directly relevant to clinical decision-making. Some episodes of VTE will be diagnosed shortly after the administration of mRNA vaccines by chance alone. When this happens clinicians should be skeptical of a causal relationship between these two events. Two specific points from this review will help avoid *post hoc ergo propter hoc* informal fallacy and attribution of these VTE events to the vaccine. First, the data acquired over the last confirm that an equal number of VTE events occur in the days leading up to vaccine administration as occur in the days following. The second is that 25–60% of VTE events are not associated with any identifiable provoking factor and the incidence of unprovoked VTE increases with age [46–48].

In clinical practice, we recommend a comprehensive history to identify other provoking factors for VTE. Where no other provoking factors are identified we recommend risk counseling and consideration for extended duration anticoagulation similar to patients with unprovoked VTE events [49–51] including risk-benefit assessment and consideration of patient preferences.

For every common clinical scenario there exist rare exceptions. Our local institutions have seen rare cases of ipsilateral upper extremity deep vein thrombosis which appear to result from local venous compression by swollen lymph nodes after vaccination or local inflammatory factors in the days following vaccination. A similar case report was found in the literature [52]. These cases of ipsilateral upper extremity DVT must be exceptionally rare such that they do not lead to a statistical increase in the number of VTE events after mRNA vaccines. Upper extremity DVTs have a low rate of embolization and death [53]. Treatment with a direct oral anticoagulant (DOAC) [54] for a duration of three months is appropriate for rare upper extremity DVTs occurring ipsilateral to mRNA vaccination when these events are determined to be provoked by resulting local inflammation or compressive lymphadenopathy.

#### 3.3. Unintended misinformation and association fallacy

Despite these reassuring results the misconception that vaccination causes blood clots has become commonplace. The clinical syndrome of VITT occurring after Adenoviral-vector vaccines may contribute to this misunderstanding through association fallacy. Additionally, media and medical literature reports that broadly link vaccines and VTE may cause readers to falsely associate blood clots as a side effect with all available vaccines [55]. Concerns regarding side effects and the perceived safety of available vaccines weigh heavily in decisions to get vaccinated [55,56], and studies suggest increasing the availability of information about vaccine safety may be among the most important factors in decreasing vaccine hesitancy. A poll from the United States in April 2021 during the investigation of VITT revealed that 76% of those surveyed felt were “very or somewhat concerned” they “might experience serious side effects” and 70% felt “The COVID-19 vaccines are not as safe as they are said to be” [57].

To avoid inadvertently inferring an association between all vaccines and VTE we suggest increasing the specificity of scientific and media communication in this area. Specifically, when VITT or other vaccine complications are discussed, authors should specify which vaccines are being discussed in the title or header rather than refer to vaccines as a broad category.

### 3.4. Future considerations

When a new drug or vaccine is first put into wider usage the publication of case reports detailing serious adverse events can be critical in identifying rare but important clinical concerns. These same reports run the risk of inferring causality where no such relationship exists. Evidence from large datasets do not support an association between VTE and mRNA vaccine, suggesting that case reports detailing events occurring shortly after mRNA vaccines are likely to be coincidental. A few reports involve a concurrent diagnosis of thrombophilia, and at this time data are insufficient to confirm or refute an association between hereditary thrombophilia and risk of VTE after mRNA vaccination. Ongoing collection of safety data is encouraged and could provide more information about unexpected thrombotic conditions or individual characteristics that predispose to VTE.

Most of the available evidence focuses on BNT162b2 rather than mRNA-1273, and confidence in these conclusions is higher for BNT162b2 mRNA-1273 due to the greater volume of data and analysis. There is no available evidence to suggest mRNA-1273 increases VTE risk in those studies that analyze this formulation separately [25,27]. Whether rates of CVST or abdominal vein thrombosis are increased after mRNA vaccination is also not a question that is definitively answered by the current data, but if such an association exists the absolute increase in the risk must be sufficiently small that it could not be captured across the analysis of over 27 million doses of mRNA vaccination. At least one of the studies discussed in this review is planned for further analysis in the future [25].

## 4. Conclusions

Over the last year post-marketing surveillance of vaccination safety has been critical to ensuring public trust during the widespread use of vaccines against COVID-19 infection. The rapid dissemination of information is crucial to the effective management of a viral pandemic, but the volume of information can also mean that important results are missed, and adverse events related to mRNA vaccines remain an area of concern for patients and practitioners. This review attempts to summarize the available evidence around a key question: is there any evidence to suggest an association between the most widely used COVID-19 vaccine formulations and VTE? At least six robust studies including analysis of over 27 million doses of mRNA vaccines have sought to answer this question. The consistent result is that mRNA vaccines are not statistically associated with VTE. Confidence in these findings is high due to the consistency of the null finding across different age groups, geographic regions, research methodologies, and risk intervals that have been studied. This finding may inform policy, scientific communication, and clinical decision-making.

Because both mRNA vaccine use and VTE are common in the general population VTE events will continue to be detected shortly after vaccine administration. The findings of this review should increase our collective confidence that such events are coincidental rather than causal. Where no other provoking factors can be identified, clinicians should counsel and treat these events as they would other VTE without an identifiable provoking factor. Further research will be useful in clarifying the risk of VTE in those with hereditary thrombophilia or prior VTE but there is no current evidence to suggest an association in these groups. Ongoing monitoring will help to determine whether CVST, unusual site thrombosis, or thrombosis with thrombocytopenia are associated with mRNA vaccines, but the available data do not suggest an increase in risk. The absolute risk of developing these conditions is either unchanged by mRNA vaccination or minimally affected such that an increased risk has not been definitively captured despite the analysis of millions of doses of mRNA vaccine. This fact stands in contrast to the increased risk of thrombosis with ChAdOx1 nCoV-19 vaccination and COVID-19 infection. The availability of robust real-world data refuting an association between vaccination and VTE is a testament to the

comprehensiveness and efficacy of vaccine post-marketing surveillance systems. These findings may increase public confidence in the safety of mRNA vaccine technology and our collective ability to identify rare but serious adverse events after vaccination.

## Practice points

- Available mRNA vaccines are not associated with an increased risk of venous thromboembolism
- Available mRNA vaccines are not known to be associated with vaccine induced thrombocytopenia with thrombosis (VITT)
- For VTE occurring after BNT162b2 or mRNA-1273 with no additional provoking factors we recommend risk counseling and consideration for extended duration anticoagulation including risk-benefit assessment and consideration of patient preferences similar to patients with unprovoked VTE

## Research agenda

- Further development and wider implementation of vaccine surveillance systems to monitor for rare but serious adverse events after vaccination
- Additional studies are required to clarify the risk of CVST after mRNA vaccines

## Author contributions

MN conceived the review, methods, and primary literature search. All authors wrote sections of the manuscript and reviewed the study design, clinical findings, and the manuscript's clinical and health policy implications.

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