Thromboembolic and Hemorrhagic Risks After Vaccination Against SARS-CoV-2: a Systematic Review and Meta-analysis of Randomized Controlled Trials

Noppacharn Uaprasert (✉ dmoppacharn@yahoo.com)

Chulalongkorn University Faculty of Medicine <https://orcid.org/0000-0003-4562-9139>

Krissana Panrong

Chulalongkorn University Faculty of Medicine

Ponlapat Rojnuckarin

Chulalongkorn University Faculty of Medicine

Thita Chiasakul

Chulalongkorn University Faculty of Medicine

Research

Keywords: thromboembolism, hemorrhage, vaccine, SARS-CoV-2

Posted Date: September 21st, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-903254/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at Thrombosis Journal on November 13th, 2021. See the published version at <https://doi.org/10.1186/s12959-021-00340-4>.

Abstract

Background: Thromboembolic and bleeding events after vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are major public concerns leading to vaccine hesitancy. Due to low incidence, an individual randomized controlled trial (RCT) is underpowered to determine whether SARS-CoV-2 vaccines increase the risks of thromboembolism and hemorrhage.

Methods: We performed a literature search using PubMed, EMBASE, Cochrane, medRxiv databases, and reference lists of relevant articles to identify RCTs that reported thromboembolic and hemorrhagic events and thromboembolism/hemorrhage-related death after SARS-CoV-2 vaccination. The primary aim of this systematic review and meta-analysis was to estimate the pooled thromboembolic risk related to SARS-CoV-2 vaccines compared to placebo. The secondary outcomes included estimating the risks of arterial thromboembolism (ATE), venous thromboembolisms (VTE), hemorrhage, and thromboembolism/hemorrhage-related death.

Results: Eight RCTs of 4 vaccine platforms comprised of 195,196 participants were retrieved. SARS-CoV-2 vaccines were not associated with an increased risk of overall thromboembolism (risk ratio [RR], 1.14; 95%CI [confidence interval], 0.61-2.14; $I^2 = 35\%$), ATE (RR, 0.97; 95%CI, 0.46-2.06; $I^2 = 21\%$), VTE (RR, 1.47; 95%CI, 0.72-2.99; $I^2 = 0\%$), hemorrhage (RR, 0.97; 95%CI, 0.35-2.68; $I^2 = 0$), and thromboembolism/hemorrhage-related death (RR, 0.53; 95%CI, 0.16-1.79; $I^2 = 0$). Compared to the baseline estimated risk of these outcomes in participants administered placebos, the risk differences with vaccines were very small and not statistically significant. These findings were consistent in the subgroup analysis across 4 vaccine platforms.

Conclusion: Vaccines against SARS-CoV-2 are not associated with an increased risk of thromboembolism, hemorrhage, and thromboembolism/hemorrhage-related death.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as a causative agent of an emerging cluster of pneumonia in China in December 2019. Its outbreak has been declared as a pandemic leading to a global health crisis since March 11, 2020 [1]. As of August 2021, SARS-CoV-2 has infected more than 200 million individuals and caused over 4 million deaths worldwide [2]. Vaccines against SARS-CoV-2 were developed at unparalleled speeds to end the coronavirus disease 2019 (COVID-19) pandemic by controlling the viral spread.

To date, there are at least 4 vaccine platforms including mRNA, adenoviral vector, inactivated, and protein subunit vaccines that have demonstrated effectiveness in the prevention of symptomatic infection and reduction in hospitalization and mortality from COVID-19 [3–10]. Although these SARS-CoV-2 vaccines had acceptable safety profiles in phase 3 randomized controlled trials (RCTs), concerns regarding potential rare side effects including the risk of thromboembolism remain a reason for vaccine hesitancy [11]. A distinctive syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT) associated with pathogenic anti-platelet factor 4 antibodies (anti-PF4 Abs) has been reported after two adenoviral vector vaccines against SARS-CoV-2, ChAdOx1 nCoV-19 and Ad26.COV2.S [12–15]. However, this thrombotic complication linked to SARS-CoV-2 vaccines is extremely rare with an estimated incidence of 0.73 per 100,000 doses of the ChAdOx1 vaccine [16]. Most thromboembolic and hemorrhagic events after vaccination against SARS-CoV-2 are independent of anti-PF4 Abs. The risks of thromboembolism and hemorrhage after vaccination against SARS-CoV-2 remain largely unknown and have never been comprehensively evaluated in phase 3 RCTs.

Due to the rarity of thrombotic and hemorrhagic events reported in individual studies, a single RCT is underpowered to determine whether SARS-CoV-2 vaccines increase the risks of thromboembolism and hemorrhage. We conducted a systematic review and meta-analysis of phase 3 RCTs to estimate the risks of thromboembolism, hemorrhage, and death related to thrombosis or hemorrhage after vaccination against SARS-CoV-2.

Methods

The protocol for this review was pre-specified and registered in PROSPERO (CRD42021253193). The study was subsequently conducted following Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [17]. The primary objective of this study was to estimate the risk of overall thromboembolism including arterial and venous thromboembolism of SARS-CoV-2 vaccines compared to placebo.

Data source, search strategy and study selection

A systematic search of electronic databases was performed using PubMed, EMBASE, and Cochrane Library Database from inception to the last update on June 30, 2021 to identify RCTs reporting thromboembolic and hemorrhagic events or death related to thromboembolic and hemorrhagic events after SARS-CoV-2 vaccination. The following search terms were used: vaccine, vaccination, immunization, thromboembolism, thromboembolic, thrombosis, infarct, stroke, ischemia, ischemic, bleeding, hemorrhage, hemorrhagic, platelet, thrombocytopenia, thrombocytopenic, coagulation, coagulopathy, safety, novel coronavirus 2019, COVID-19, SARS-CoV-2, and 2019-nCoV. Additionally, studies published on the preprint server (medRxiv) and reference lists of relevant articles were manually reviewed. The inclusion criteria for eligible studies were as follows: (1) RCTs with at least 100 participants in both the vaccine and control arms, (2) reported safety outcomes which specified thromboembolic and hemorrhagic events and/or death related to thromboembolism and hemorrhage. Non-original articles (such as reviews, commentaries, or guidelines) and duplicate studies were excluded. Two authors (N.U. and K.P.) independently searched the literature, screened titles and abstracts, and reviewed full texts to identify potentially eligible studies. Disagreements were resolved by consensus or a third reviewer (T.C.) when necessary. The selection result was reported according to the PRISMA flowchart.

Data extraction

Two authors (N.U. and K.P.) independently reviewed data from selected studies including supplementary materials and independently extracted pre-specified data. Disagreements of extracted data were resolved by consensus or a third reviewer (T.C.) when necessary. The primary outcome was the risk of arterial and/or venous thromboembolism after vaccination against SARS-CoV-2 compared to controls. The secondary outcomes included the risks of arterial thromboembolism (ATE), venous thromboembolisms (VTE), bleeding, thrombocytopenia, and death related to thromboembolism and hemorrhage after vaccination against SARS-CoV-2.

For each study, the following data were extracted: study design, phase of clinical trials, vaccine platform (mRNA, viral vector, inactivated, or protein subunit), treatment allocation, study population, number of participants, baseline characteristics of participants (age, sex, and ethnicity), thromboembolic events, hemorrhagic events, and death related to thromboembolism or hemorrhage. Corresponding authors of the BNT162b2 study were contacted twice to request additional outcome data that were not reported. However, we were unable to obtain data from the BNT162b study.

Quality Assessment

An assessment of the methodological quality of included studies for meta-analysis was performed independently by two authors (N.U. and K.P.) using the revised version of the Cochrane risk-of-bias tool in RCTs [18]. Bias was assessed in the domains of randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcomes, and selection of the reported results. Data on study characteristics and outcomes were extracted by using a standardized form. The risk of bias was graded as low, some concerns, or high. Discrepancies were resolved by consensus or contact with a third reviewer (T.C.).

Data analysis

The meta-analysis was performed using Comprehensive Meta-Analysis software (Version 3; Biostat, Englewood, NJ, USA). The risk ratio (RR) and the risk difference of each outcome were calculated using the Mantel-Haenszel method with random-effects model and were reported as RR and risk difference (per 100,000 persons) with 95% confidence interval (95%CI). The pre-specified subgroup analyses including the risks of thromboembolism and hemorrhage across vaccine platforms (mRNA, virus vector, inactivated, or protein subunit vaccines), age groups, sex, and races would be performed if there were sufficient data. Statistical heterogeneity was assessed using I^2 statistic which measures the inconsistency across study results. Inter-study heterogeneity was assigned as insignificant ($I^2 = 0-25\%$), low ($I^2 = 26-50\%$), moderate ($I^2 = 51-75\%$), or high ($I^2 > 75\%$) [19]. Publication bias was explored by visual inspection of the funnel plots. No formal tests for publication bias were performed as they lacked statistical power due to the low number of studies included in the meta-analysis (less than 10 studies).

Results

The study report was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidance (**Supplementary Table S1**) [17]. The PRISMA flow diagram is shown in **Supplementary Figure S1**. The literature search yielded 4,999 articles. After 1,568 duplicates removed, a total of 3,447 unique studies were screened by titles and abstracts. Of these, 3,816 were excluded, and 31 full texts were screened for eligibility. Eventually 8 studies [3–10] met the eligibility criteria and were included in the qualitative and quantitative synthesis. The risk of bias in each study was individually assessed. All studies [3–10] were assigned as low risk of bias (**Supplementary Figure S2**).

Study Characteristics

The main characteristics of the 8 included studies (7 published full-texts and 1 full-preprint report) are summarized in Table 1 [3–10]. The 8 studies contained 195,196 participants. A total of 104,779 participants were administered SARS-CoV-2 vaccines, and a total of 90,417 were administered placebos. There were 4 vaccine platforms including 2 mRNA vaccines (BNT162b2 and mRNA-1273) [3, 4], 3 adenoviral vector vaccines (Ad26.COV.2S, ChAdOx1 and rAD26/rAD5) [5–7], 1 inactivated vaccine (2 studies of CoronaVac) [8, 9], and 1 protein subunit vaccine (NVX-CoV23) [10]. The majority of participants were younger than 60 years and predominantly Caucasian. Baseline characteristics including age groups, sex, races, and coexisting conditions among participants in the vaccine and the placebo groups were similar. The BNT162b2 study reported only death related to thromboembolism and hemorrhage, while the primary and other secondary outcomes were not reported. Detailed thromboembolic and hemorrhagic events of each study are summarized in **Supplementary Table S2**.

Table 1
Baseline characteristics of included randomized controlled trials

Study name	Vaccine platform	Study characteristics	Treatment allocation	Number of participants (safety data)	Age (years)	Sex (male)	Race (white, black, Asian)	Countries	Comorbidities
Polack, 2020 [3]	mRNA	Primary analysis of safety and efficacy from the phase 2/3 part of BNT162b2 in preventing symptomatic COVID-19 in persons ≥ 16 years	BNT162b2 (30 μ g), 2 doses 21 days apart	18860 (21621)	52 ^a (Range; 16–89)	51.1%	82.9%, 9.2%, 4.2%	US 76.7%, Argentina 15.3%, Brazil 6.1%	Diabetes 8.3%, chronic lung disease 7.8%, cancers 3.9%
			Saline	18846 (21631)	52 ^a (Range; 16–91)	50.1%	82.9%, 9.4%, 4.3%	US 76.7%, Argentina 15.3%, Brazil 6.0%	Diabetes 8.4%, chronic lung disease 7.7%, cancers 3/5%
Baden, 2020 [4]	mRNA	Primary analysis of safety and efficacy of phase 3 RCT in preventing COVID-19 in persons ≥ 18 years	mRNA-1273 (100 μ g), 2 doses 28 days apart	15170 (15166)	51.3 ^b (Range; 18–95)	52.2%	79.2%, 10.3%, 4.3%	US 100%	Diabetes 9.5%, severe obesity 6.8%, cardiac disease 5%, chronic lung disease 4.7%
			Saline	15181 (15185)	51.4 ^b (Range; 18–95)	53.1%	79.1%, 10.1%, 4.8%	US 100%	Diabetes 9.5%, severe obesity 6.7%, cardiac disease 4.9%, chronic lung disease 4.9%
Sadoff, 2021 [5]	Adenoviral vector	Primary analysis of safety and efficacy of phase 3 RCT in preventing COVID-19 in persons ≥ 18 years	Ad26.COVS.S (A single dose of 5×10^{10} viral particles)	21895	52 ^a (Range; 19–100)	55.1%	58.7%, 19.4%, 3.4%	US 44.1%, Latin America 40.9%, South Africa 15.0%	Obesity 28.7%, hypertension 10.2%, diabetes 7.8%
			Saline	21888	52 ^a (Range; 18–94)	54.7%	58.7%, 19.5%, 3.1%	US 44.1%, Latin America 40.9%, South Africa 15.0%	Obesity 28.4%, hypertension 10.5%, diabetes 7.7%
Voysey, 2021 [6]	Adenoviral vector	Interim analysis of 4 cohorts of phase 1/2/3 RCT parts in preventing COVID-19 in persons ≥ 18 years	ChAdOx1 nCoV-19 (2.2–6.5 $\times 10^{10}$ viral particles, 2 doses 4– ≥ 12 weeks apart)	12021	Age (18–55 years) 81.5%	44.2%	75.1%, 10.0%, 3.7%	UK 50.0%, Brazil 41.6%, South Africa 8.4%	Cardiovascular disease 12.6%, respiratory disease 9.9%, diabetes 2.8%
			Meningococcal group A, C, W, and Y conjugate vaccine or saline	11724	Age (18–55 years) 83.5%	44.1%	75.4%, 10.2%, 3.3%	UK 48.8%, Brazil 42.7%, South Africa 8.5%	Cardiovascular disease 12.0%, respiratory disease 10.0%, diabetes 2.5%
Logunov, 2021 [7]	Adenoviral vector	Preliminary efficacy and safety analysis of phase 3 RCT in preventing COVID-19 in persons ≥ 18 years	rAd26 (1st dose) and rAd5 (2nd dose) containing 1×10^{11} viral particles, 2 doses 21 days apart	14964 (16427)	45.3 ^b (SD 12.0)	61.1%	98.5%, NA, 1.5%	Russia 100%	Diabetes, hypertension, ischemic heart disease, obesity 24.7%
			Excipients	4902 (5435)	45.3 ^b (SD 11.9)	61.5%	98.5%, NA, 1.5%	Russia 100%	Diabetes, hypertension, ischemic heart disease, obesity 25.2%

^aMedian; ^bMean; COVID-19, coronavirus disease 2019; RCT, randomized controlled trial; US, United States; UK, United Kingdom

Study name	Vaccine platform	Study characteristics	Treatment allocation	Number of participants (safety data)	Age (years)	Sex (male)	Race (white, black, Asian)	Countries	Comorbidities
Tanriover, 2021 [8]	Inactivated	Interim analysis of efficacy and safety of phase 3 RCT in preventing COVID-19 in persons aged 18–59 years	CoronaVac (3 µg of SARS-CoV-2 virions), 2 doses 14 days apart	6646 (6648)	45 ^a (IQR; 35–51)	57.4%	NA	Turkey 100%	Hypertension 11.8%, diabetes 4.9%, chronic lung disease 2.9%
			Aluminium hydroxide diluent	3568 (3568)	45 ^a (IQR;37–51)	58.65	NA	Turkey 100%	Hypertension, 11.6%, diabetes 4.5%, chronic lung disease 2.9%
Palacios, 2021 [9] (preprint)	Inactivated	Interim analysis of efficacy and safety of phase 3 RCT in preventing COVID-19 in healthcare workers ≥ 18 years	CoronaVac (3 µg of SARS-CoV-2 virions), 2 doses 14 days apart	6195 (6202)	39.4 ^b (SD 10.7)	36.6%	75.8%, 5.3%, 2.4%	Brazil 100%	Obesity 22.4%, cardiovascular disease 12.8%, diabetes 3.5%
			Aluminium hydroxide diluent	6201 (6194)	39.6 ^b (SD 10.8)	35.0%	74.8%, 5.2%, 2.6%	Brazil 100%	Obesity 22.6%, cardiovascular disease 12.5%, diabetes 3.2%
Heath, 2021 [10]	Protein subunit	Interim analysis of efficacy and safety of phase 3 RCT in preventing COVID-19 in persons ≥ 18 years	NVX-CoV2373 (5 µg), 2 doses 21 days apart	7020 (7569)	56 ^a (18–84)	51.4%	94.4%, 0.4%, 2.9%	UK 100%	Chronic lung, cardiac, renal, neurologic, hepatic, immunocompromising conditions, and obesity 44.4%
			Saline	7019 (7570)	56 ^a (18–64)	51.7%	94.5%, 0.4%, 3.0%	UK 100%	Chronic lung, cardiac, renal, neurologic, hepatic, immunocompromising conditions, and obesity 44.8%
^a Median; ^b Mean; COVID-19, coronavirus disease 2019; RCT, randomized controlled trial; US, United States; UK, United Kingdom									

The risk of thromboembolism after vaccination against SARS-CoV-2

The estimated risk of thromboembolism including arterial and/or venous thrombosis was estimated from 7 of the 8 studies, while omitting the BNT162b study [4–10]. A total of 85,915 and 71,571 participants received either a vaccine or placebo, respectively. The pooled RR of thromboembolism after vaccination was 1.14 (95%CI, 0.61 to 2.14; $I^2 = 35\%$) (Fig. 1). With a baseline estimated risk of thromboembolism in the placebo group of 52 events per 100,000 persons (95%CI, 33 to 83; $I^2 = 37\%$), the risk difference with the vaccine group was 7.8 events per 100,000 persons (95%CI, -20 to 36; $I^2 = 33\%$). The subgroup analysis did not demonstrate an increased risk of thromboembolism in any vaccine platform. There were no significant differences of thromboembolism across vaccine platforms ($P = 0.80$) (Supplementary Figure S3).

The risks of arterial thromboembolism and venous thromboembolism after vaccination against SARS-CoV-2

The risks of ATE and VTE after SARS-CoV-2 vaccination were estimated from the same 7 studies, again excluding the BNT162b2 study [4–10]. No VTE events occurred in one inactivated vaccine study (Tanriover) [8]. The pooled RR of ATE after SARS-CoV-2 vaccination was 0.97 (95%CI, 0.46 to 2.06; $I^2 = 21\%$) (Fig. 2). With an estimated risk of ATE from 7 studies [4–10] in the placebo group of 38 events per 100,000 persons (95%CI, 23 to 63; $I^2 = 20\%$), the risk difference with the vaccine group was -1.8 events per 100,000 persons (95%CI, -20 to 17; $I^2 = 27\%$).

The RR of VTE after SARS-CoV-2 vaccination (6 studies [4–7, 9, 10]; $N = 79,273$ in the vaccine group and $N = 68,003$ in the placebo group) was 1.47 (95%CI, 0.72 to 2.99; $I^2 = 0\%$) (Fig. 3). The risk of VTE after SARS-CoV-2 vaccination was increased only in the Ad26.COV2.S study (RR = 3.67; 95%CI, 1.02 to 13.14). With an estimated risk of VTE from 7 studies [4–10] in the placebo group of 21 events per 100,000 persons (95%CI, 13 to 36; $I^2 = 0\%$), the risk difference with the vaccine group was 6.3 events per 100,000 persons (95%CI, -8.5 to 21; $I^2 = 0\%$). The subgroup analysis did not demonstrate an increased risk of either ATE or VTE in any vaccine platform. There were no statistical differences across vaccine platforms ($P = 0.23$ and $P = 0.81$, respectively) (Supplementary Figure S4 and Figure S5).

The risks of hemorrhage and thrombocytopenia after vaccination against SARS-CoV-2

The risk of hemorrhage was estimated from 7 studies while excluding the BNT162b2 study ($N = 85,919$ in the vaccine group and $N = 71,751$ in the placebo group) [4–10]. No bleeding events occurred in one inactivated vaccine study (Palacios) [9]. The RR of hemorrhage after SARS-CoV-2

vaccination (6 studies [4–8, 10] included 79,724 participants in the vaccine group and 65,370 participants in the placebo group) was 0.97 (95%CI, 0.35 to 2.68, $I^2 = 0\%$) (Fig. 4). With an estimated risk of bleeding from 7 studies [4–10] in the placebo group of 18 events per 100,000 persons (95%CI, 8 to 35; $I^2 = 0$), the risk difference with the vaccine group was 4.1 events per 100,000 persons (95%CI, -5.3 to 13.5; $I^2 = 0$). The subgroup analysis did not demonstrate an increased risk of bleeding in any vaccine platform. There were no statistical differences across vaccine platforms ($P = 0.68$) (Supplementary Figure S6).

The risk of thrombocytopenia after SARS-CoV-2 vaccination was not analyzed because no events were reported in the included studies.

The risk of death related to thromboembolic and hemorrhagic events after vaccination against SARS-CoV-2

The risk of death related to thromboembolism and hemorrhage was estimated from all 8 studies [3–10] ($N = 104,779$ in the vaccine group and $N = 90,417$ in the placebo group). No deaths related to thromboembolism or bleeding occurred in the ChAdOx1 study, one CoronaVac study (Tanriover) and the NVX-CoV23 study [6, 8, 10]. The RR of death from thromboembolism or hemorrhage after SARS-CoV-2 vaccination (5 studies [3–5, 7, 9] included 78,543 participants in the vaccine group and 67,555 participants in the placebo group) was 0.53 (95%CI, 0.16 to 1.79; $I^2 = 0\%$) (Fig. 5). With an estimated risk of thromboembolism/hemorrhage-related death from 8 studies [3–10] in the placebo group of 9 events per 100,000 persons (95%CI, 5 to 19; $I^2 = 0$), the risk difference with the vaccine group was -3.7 events per 100,000 persons (95%CI, -12.2 to 4.8; $I^2 = 0$). The subgroup analysis did not demonstrate an increased risk of death related to thromboembolism and hemorrhage in any vaccine platform. There were no also statistical differences across vaccine platforms ($P = 0.48$) (Supplementary Figure S7).

Discussion

In this systematic review and meta-analysis of 8 RCTs involving nearly 200,000 participants, the risks of overall thromboembolism, ATE, VTE, hemorrhage, and death related to thromboembolism and hemorrhage were not found significantly increased after vaccination against SARS-CoV-2. An increased risk of VTE was observed only with the Ad26.COV2.S vaccine. The absolute risk differences of all outcomes were less than 0.01% or less than 10 per 100,000 persons. This meta-analysis confirmed the rarity of thromboembolic and hemorrhagic events after SARS-CoV-2 vaccines observed in phase 3 RCTs across all vaccine platforms.

In our systematic review, there were no thrombocytopenia events reported in the included studies suggesting the rarity of significant thrombocytopenia after SARS-CoV-2 vaccination. Of note, mild asymptomatic thrombocytopenia may be undetected and underreported in clinical trials. According to population-based studies, the estimated risk of thrombocytopenia after ChAdOx1 vaccination was correspondent to 2.9 excess events per 100,000 vaccinations in Denmark and Norway [20], while the estimated incidence of immune thrombocytopenia after ChAdOx1 vaccination was 1.13 (0.62–1.63) per 100,000 doses in Scotland [21]. Due to very low prevalence, this meta-analysis remained underpowered to detect the risk of thrombocytopenia after SARS-CoV-2 vaccination.

The subgroup analysis to determine the risks of thromboembolism and hemorrhage across vaccine platforms was performed. Compared to placebo, each vaccine platform did not show an increase in the risks of thromboembolism and hemorrhage in all analyses. These findings support the general safety among different SARS-CoV-2 vaccine platforms. There were insufficient data to perform other pre-specified subgroup analysis including age, gender and race.

COVID-19 is associated with the risks of systemic coagulopathy, thrombosis, and bleeding, especially in critically ill patients [22–26]. Since SARS-CoV-2 vaccines can effectively prevent symptomatic infection, hospitalization, and mortality [3–10], the risks of thromboembolism, hemorrhage, and death related to thromboembolism and hemorrhage from COVID-19 may also be reduced in vaccinated participants. However, in most studies, the SARS-CoV-2 infection status was not specified in participants who experienced thromboembolic or hemorrhagic events. A contributing risk of COVID-19 associated thromboembolism and hemorrhage could not be totally excluded.

The risks of thromboembolism and hemorrhage were also assessed in large national cohort studies. The population-based studies from Denmark and Norway, which included 281,264 people vaccinated with the ChAdOx1 vaccine, demonstrated an increased rate of VTE, but not for ATE, and a small increased risk of unspecified thrombocytopenia among recipients of the ChAdOx1 vaccine [20]. VITT cases may have been included in this cohort because of an unusually high incidence of cerebral vein thrombosis after ChAdOx1 vaccination. From a recent meta-analysis, the estimated incidence of VITT was highest in Scandinavian countries [16]. It remains uncertain whether the risks of VTE and thrombocytopenia would be higher in Scandinavian people vaccinated with the ChAdOx1 vaccine if VITT cases were excluded. The Scottish population-based study which included 1.71 million people vaccinated with the ChAdOx1 vaccine and 0.82 million people vaccinated with the BNT162b2 vaccine demonstrated an increased risk of immune thrombocytopenia and a minimally increased risk of ATE among recipients of the ChAdOx1 vaccine but not for those who received the BNT162b2 vaccine. In contrast, there was no association between ChAdOx1 vaccination and VTE including cerebral vein thrombosis [21]. In Scotland, the highest uptake for the BNT162b2 vaccine was found in people younger than 65 years, whereas for the ChAdOx1 vaccine, the highest vaccine uptake was found in people aged ≥ 65 years [27]. Therefore, a marginally increased risk of ATE after ChAdOx1 vaccination may be confounded by asymmetrical age distributions and potentially incomplete adjustment for covariates, especially cardiovascular comorbidities. In comparison, the population-based study from Israel, where the majority of vaccine recipients were young adults, demonstrated no increased risks of thromboembolism, hemorrhage, and thrombocytopenia after BNT162b2 vaccination [22]. There were also very few thromboembolic events observed among 288,368 recipients of the Ad26.COV2.S vaccine in South Africa [28]. No VITT or thrombocytopenia were documented in the South African cohort. Whether the

risks of thromboembolism and thrombocytopenia might be increased after vaccination against SARS-CoV-2 remains undetermined due to the conflicting findings among national cohort studies. One should also be cautious to generalize the risks of thromboembolism, hemorrhage, and thrombocytopenia after SARS-CoV-2 vaccination due to different genetic and thromboembolic risks among populations.

The strength of a meta-analysis of large multinational phase 3 RCTs is its inherent advantage to have even distribution of demographic characteristics, comorbidities, especially thrombotic and bleeding risk factors, and other unmeasured covariates. All RCTs included in this meta-analysis were assessed to have low risk of bias. The included studies had insignificant or low statistical heterogeneity suggesting that the effects can reasonably be combined in a meta-analysis.

There are some limitations of this study. Although it aggregated approximately 100,000 vaccinated participants, it may be insufficient to document extremely rare events such as significant thrombocytopenia. Additionally, despite our attempts to contact the authors, we were not able to obtain the data from the BNT162b2 study, and therefore this study was not included in most analyses. Consequently, there was only one type of vaccine in the mRNA, inactivated, and protein subunit platform in subgroup analysis. The lack of detailed descriptions of participants who experienced thromboembolic or hemorrhagic events also precluded evaluation of several other important subgroups analysis such as age, sex, race, coexisting comorbidities, and COVID-19 status. It may require the pooled analysis of large national cohorts to have sufficient power to determine the risks of thromboembolism and hemorrhages after vaccination against SARS-CoV-2 and risks among different vaccine platforms. Incomplete data entry and a lack of adequate adjustment for baseline confounders would potentially make such analysis very challenging.

Conclusions

This meta-analysis demonstrated no increased risks of thromboembolism, hemorrhage, and death from thromboembolism and hemorrhage after vaccination against SARS-CoV-2 across all vaccine platforms. These findings provide information that may assist global vaccination campaigns in order to reduce vaccine hesitancy. Although marginal risks of thromboembolism and hemorrhage in some subgroup populations may not be excluded, the estimated incidence of these events was very low. The absolute risks of thromboembolism and hemorrhage of SARS-CoV-2 vaccines were very small in the context of the proven benefits of vaccination against SARS-CoV-2 and the globally high incidence of severe and fatal cases of SARS-CoV-2 infection.

List Of Abbreviations

ATE, arterial thromboembolism; CI, confidence interval; COVID-19, coronavirus disease 2019; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomized controlled trial; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VITT, vaccine-induced immune thrombotic thrombocytopenia; VTE, venous thromboembolism

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors (NU, KP, PR and TC) declare that they have no known competing financial interests or personal relationships that could influence the work reported in this paper.

Funding

Not applicable

Authors' contribution

Contribution: N.U. was involved in conceptualization, database search, screening of abstracts and full texts, data extraction and analysis, quality appraisal, and writing the manuscript; K.P. was involved in conceptualization, database search, screening of abstracts and full texts, and editing of the manuscript; P.R. was involved in data analysis, appraisal and editing of the manuscript; and T.C. was involved in conceptualization, adjudication, data analysis and editing of the manuscript.

Acknowledgements

Not applicable

References

1. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA*. 2020;324(8):782-93.
2. Worldometer. COVID-19 coronavirus pandemic. 2020. <https://www.worldometers.info/coronavirus/> (accessed August 12, 2021)
3. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-15.
4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med*. 2021;384(5):403-16.
5. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med*. 2021;384(23):2187-201.
6. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet*. 2021;397(10269):99-111.
7. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet*. 2021;397(10275):671-81.
8. Tanriover MD, Doğanay HL, Akova M, Güner HR, Azap A, Akhan S, et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomised, placebo-controlled, phase 3 trial in Turkey. *Lancet*. 2021;398(10296):213-22.
9. Palacios R, Batista AP, Albuquerque CSN, Patino EG, Santos JDP, Conde MTRP, et al. Efficacy and safety of a COVID-19 inactivated vaccine in healthcare 3 professionals in Brazil: The PROFISCOV study (April 11, 2021). Available at SSRN: <https://ssrn.com/abstract=3822780> or <http://dx.doi.org/10.2139/ssrn.3822780>.
10. Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, et al. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. *N Engl J Med*. 2021 Jun 30; NEJMoa2107659. doi: 10.1056/NEJMoa2107659. PMID: 34192426. (Online ahead of print).
11. Razai MS, Chaudhry UAR, Doerholt K, Bauld L, Majeed A. Covid-19 vaccination hesitancy. *BMJ*. 2021 May 20;373:n1138.
12. Schultz NH, Sørvoll IH, Michelsen AE, Munthe LA, Lund-Johansen F, Ahlen MT, et al. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med*. 2021;384(22):2124-30.
13. Greinacher A, Thiele T, Warkentin TE, Weisser K, Kyrle PA, Eichinger S. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med*. 2021;384(22):2092-101.
14. Scully M, Singh D, Lown R, Poles A, Solomon T, Levi M, et al. Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination. *N Engl J Med*. 2021;384(23):2202-11.
15. See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, et al. US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021. *JAMA*. 2021;325(24):2448-56.
16. Chan BTB, Bobos P, Oduyayo A, Pai M. Meta-Analysis of Risk of Vaccine-Induced Immune Thrombotic Thrombocytopenia Following ChAdOx1-S Recombinant Vaccine. <https://www.medrxiv.org/content/10.1101/2021.05.04.21256613v1>.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019 Aug 28;366:l4898. doi:10.1136/bmj.l4898.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring in consistency in meta-analyses. *BMJ*. 2003;327:557-60.
20. Pottegård A, Lund LC, Karlstad Ø, Dahl J, Andersen M, Hallas J, et al. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study. *BMJ*. 2021;373:n1114.
21. Simpson CR, Shi T, Vasileiou E, Katikireddi SV, Kerr S, Moore E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. *Nat Med*. 2021; 27(7):1290-7.
22. Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Setting. *N Engl J Med*. 2021 doi: 10.1056/NEJMoa2110475. PMID: 34432976. (Online ahead of print).
23. Uaprasert N, Moonla C, Sosoithikul D, Rojnuckarin P, Chiasakul T. Systemic coagulopathy in hospitalized patients with coronavirus disease 2019: A systematic review and meta-analysis. *Clin Appl Thromb Hemost*. Jan-Dec 2021;27:1076029620987629.
24. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. 2020;136(4):489-500.

25. Jiménez D, García-Sánchez A, Rali P, Muriel A, Bickdeli B, Ruiz-Artacho P, et al. Incidence of VTE and bleeding among hospitalized patients with Coronavirus disease 2019: A systematic review and meta-analysis. *Chest*. 2021;159(3):1182-96.
26. Tan BK, Mainbourg S, Friggeri A, Bertolotti L, Douplat M, Dargaud Y, et al. Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis. *Thorax*. 2021 doi: 10.1136/thoraxjnl-2020-215383. PMID: 33622981. (Online ahead of print).
27. Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet*. 2021;397(10285):1646-57.
28. Takuva S, Takalani A, Garrett N, Goga A, Peter J, Louw V, et al. Thromboembolic Events in the South African Ad26.COVS.S Vaccine Study. *N Engl J Med*. 2021;385(6):570-1.

Figures

Figure 1

Figure 1

The pooled risk ratio of overall thromboembolism between the SARS-CoV-2 vaccine and the placebo groups

Figure 2

Figure 2

The pooled risk ratio of arterial thromboembolism between the SARS-CoV-2 vaccine and the placebo groups

Figure 3

Figure 3

The pooled risk ratio of venous thromboembolism between the SARS-CoV-2 vaccine and the placebo groups

Figure 4

Figure 4

The pooled risk ratio of hemorrhage between the SARS-CoV-2 vaccine and the placebo groups

Figure 5

Figure 5

The pooled risk ratio of death related to thromboembolism and hemorrhage between the SARS-CoV-2 vaccine and the placebo groups

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarymaterials.pdf](#)