# Epidemiological assessment of the risks of VITT with ChAdOx1-S

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DES, Nyborg, 2021

WE 

DRUGS

FAST TRACK

# Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study

Anton Pottegård,[1] Lars Christian Lund,[1] Øystein Karlstad,[2] Jesper Dahl,[2] Morten Andersen,[3] Jesper Hallas,[1] Øjvind Lidegaard,[4,5] German Tapia,[2] Hanne Løvdal Gulseth,[2] Paz Lopez-Doriga Ruiz,[2] Sara Viksmoen Watle,[2] Anders Pretzmann Mikkelsen,[4,5] Lars Pedersen,[6,7] Henrik Toft Sørensen,[6,7] Reimar Wernich Thomsen,[6,7] Anders Hviid[3,8]

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Accepted: 28 April 2021

## ABSTRACT

### OBJECTIVE

To assess rates of cardiovascular and haemostatic events in the first 28 days after vaccination with the Oxford-AstraZeneca vaccine ChAdOx1-S in Denmark and Norway and to compare them with rates observed in the general populations.

### DESIGN

Population based cohort study.

### SETTING

Nationwide healthcare registers in Denmark and Norway.

### PARTICIPANTS

All people aged 18-65 years who received a first vaccination with ChAdOx1-S from 9 February 2021 to 11 March 2021. The general populations of Denmark (2016-18) and Norway (2018-19) served as comparator cohorts.

### MAIN OUTCOME MEASURES

Observed 28 day rates of hospital contacts for incident arterial events, venous thromboembolism

### RESULTS

The vaccinated cohorts comprised 148 792 people in Denmark (median age 45 years, 80% women) and 132 472 in Norway (median age 44 years, 78% women), who received their first dose of ChAdOx1-S. Among 281 264 people who received ChAdOx1-S, the standardised morbidity ratio for arterial events was 0.97 (95% confidence interval 0.77 to 1.20). 59 venous thromboembolic events were observed in the vaccinated cohort compared with 30 expected based on the incidence rates in the general population, corresponding to a standardised morbidity ratio of 1.97 (1.50 to 2.54) and 11 (5.6 to 17.0) excess events per 100 000 vaccinations. A higher than expected rate of cerebral venous thrombosis was observed: standardised morbidity ratio 20.25 (8.14 to 41.73); an excess of 2.5 (0.9 to 5.2) events per 100 000 vaccinations. The standardised morbidity ratio for any thrombocytopenia/coagulation disorders was 1.52 (0.97 to 2.25) and for any bleeding was 1.23 (0.97 to 1.55). 15 deaths were observed in the vaccine cohort compared with 44 expected.

# Prologue?


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PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3942

ORIGINAL REPORT

# Generic switching of warfarin and risk of excessive anticoagulation: a Danish nationwide cohort study†

Maja Hellfritzsch[1]*, Jette Rathe[2], Tore Bjerregaard Stage[1], Steffen Thirstrup[3,4], Erik L. Grove[5], Per Damkier[1,2] and Anton Pottegård[1]

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## ABSTRACT

**Purpose** Generic switching of warfarin was recently repealed in Denmark, as adverse drug reaction (ADR) reports suggested risk of excessive anticoagulation following switches from branded to generic warfarin. We investigated this putative association in a formalized pharmacoepidemiological analysis.

**Methods** We conducted a nationwide cohort study based on Danish healthcare registries, including data from the introduction of generic warfarin until the repeal (January 2011–April 2015). We followed Danish warfarin users over time and compared the rate of incident hospitalizations due to excessive anticoagulation (i.e. increased INR or any bleeding requiring hospitalization) in periods following a recent switch to generic warfarin to the rate in periods without a recent switch.

**Results** We included 105 751 warfarin users, filling a total of 1 539 640 prescriptions for warfarin (2.5% for generic warfarin). This constituted 89.0% of all warfarin prescriptions in Denmark during the study period. We observed 19 362 switches to generic warfarin during the study period. The adjusted hazard ratio for excessive anticoagulation following a recent switch from branded to generic warfarin was 1.1 (95%CI, 0.8–1.4). The result was robust within subgroups and several sensitivity analyses.

**Conclusion** Switching from branded to generic warfarin is not associated with an increased risk of hospitalization with excessive anticoagulation. However, a minor excess risk of transient INR increase cannot be excluded. Pharmacoepidemiological studies provide an effective method for swift evaluation of hypotheses generated by ADR-reports. 

KEY WORDS—oral anticoagulants; warfarin; generic drugs; adverse drug reaction reports; excessive anticoagulation; pharmacoepidemiology; Denmark

*Received 27 August 2015; Revised 21 November 2015; Accepted 23 November 2015*

| Outcome measure | Events | Follow-up (PY) | Rate (/1000 PY) | Adjusted HR (95%CI) |
|---|---|---|---|---|
| *Excessive anticoagulation*‡ | | | | |
| Cont. use of branded | 5665 | 224 282 | 25 | 1.0 (ref.) |
| Cont. use of generic | 36 | 1349 | 27 | 1.1 (0.8–1.5) |
| Switch TO generic | 53 | 1940 | 27 | 1.1 (0.8–1.4) |
| Switch FROM generic | 11 | 375 | 29 | 1.2 (0.7–2.2) |


*Received 27 August 2015; Revised 21 November 2015; Accepted 23 November 2015*

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016; **25**: 344–345
Published online 22 January 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3969

COMMENTARY

# Automatic generic switching of warfarin: to do or not to do?

Jens Heisterberg*

*Danish Medicines Agency, Copenhagen, Denmark*

The cohort study by Hellfritzsch *et al.* addresses the clinical consequences of automatic generic switching of a narrow therapeutic index medicine, *in casu* warfarin.[1]

First, a striking feature of the study is the speed with which it was reported. Automatic generic switching with Warfarin "Orion"® (Orion Pharma Danmark, Copenhagen, Denmark) was introduced in Denmark in January 2015. It was repealed in April 2015 following five spontaneous reports (later, another two cases were reported) of increases in international normalized ratio (INR) levels after switching from branded warfarin to Warfarin "Orion"®. Here, still within the very same year, a thorough and well-conducted pharmacoepidemiological study investigating the clinical consequences has been completed and reported. This is a testimony to the strengths of healthcare registries and a well-established infrastructure for linking them together for pharmacoepidemiological research.

Licensing or marketing authorization of generic for generic switching vary across the EU. An analogous situation exists in the USA, where licensing of generic medicines is undertaken at the federal level (by the Food and Drug Administration (FDA)), while decisions on generic switching is determined by the individual state legislation.

The Danish Medicines Agency publishes criteria for automatic generic switching on its website.[3] We are currently reviewing the criteria across all therapeutic classes, so they are likely to change in the nearby future. Considering the results of the study by Hellfritzsch *et al.*, one may ask: Will we allow automatic generic switching for warfarin generics in the future? Alternatively, will we maintain our current abolishment (not evident from our website) of automatic switches between warfarin generics and branded warfarin?

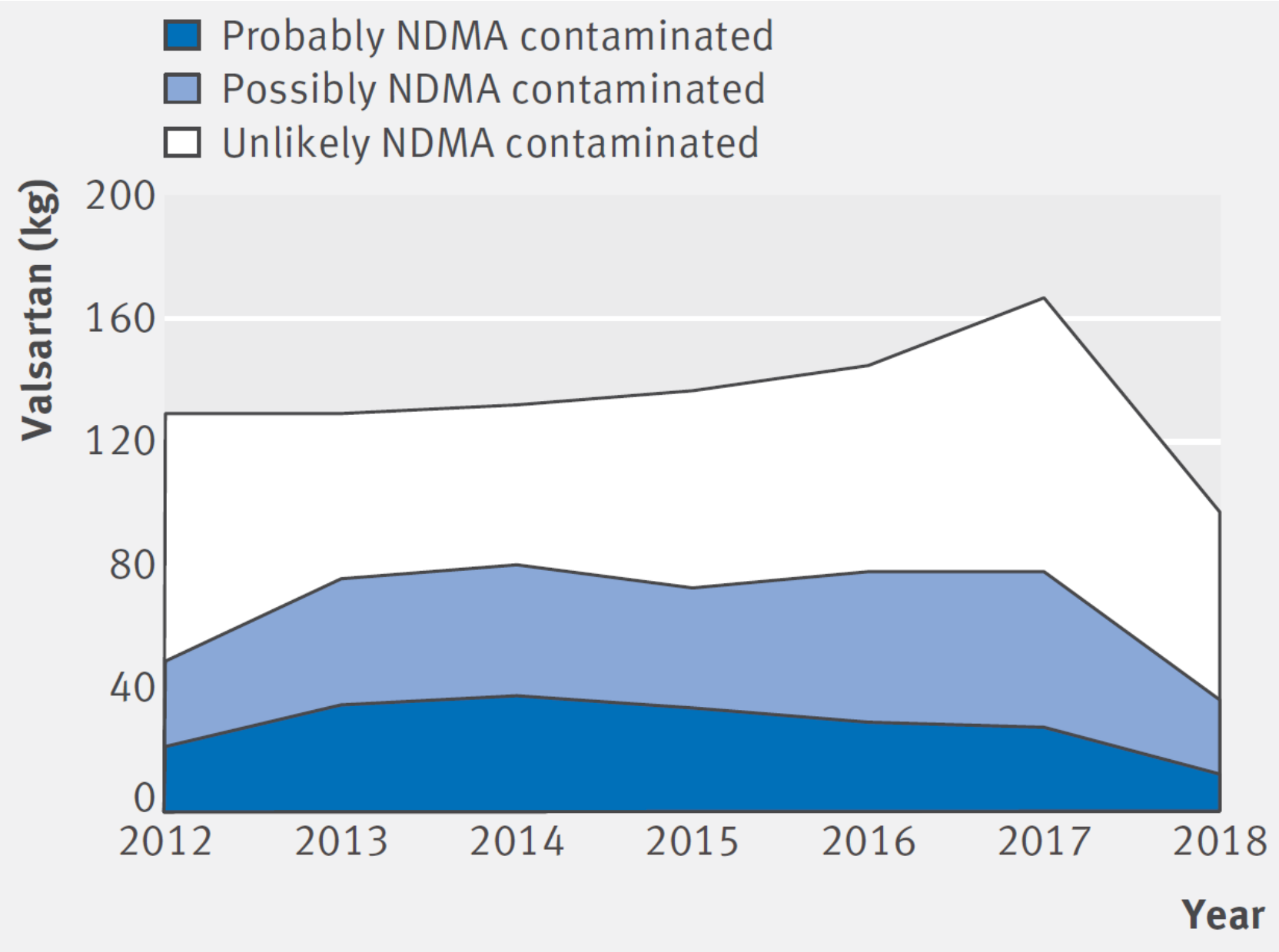
In the case of Warfarin "Orion"®, it may be worthwhile to look at the actual results of the bioequivalence trial supporting the marketing authorization.[4] The point

Time passes…

WORLDWIDE

# The contamination of a popular blood-pressure medicine is now a global problem

By Chase Purdy in New York • August 7, 2018




Pottegård et al. BMJ 2018 Sep 12

FAST TRACK

# Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study

Anton Pottegård,[1] Kasper Bruun Kristensen,[1] Martin Thomsen Ernst,[1] Nanna Borup Johansen,[2] Pierre Quartarolo,[3] Jesper Hallas[1]

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**Accepted:** 09 September 2018

## ABSTRACT

### OBJECTIVE

To perform an expedited assessment of cancer risk associated with exposure to N-nitrosodimethylamine (NDMA) through contaminated valsartan products.

### DESIGN

Nationwide cohort study.

### SETTING

Danish health registries on individual level prescription drug use, cancer occurrence, and hospital diagnoses.

### PARTICIPANTS

5150 Danish patients with no history of cancer, aged 40 years or older, and using valsartan at 1 January 2012 or initiating use between 1 January 2012 and 30 June 2017. Participants were followed from one year after cohort entry (lag time period) until experiencing a cancer outcome, death, migration, or end of study period (30 June 2018). Each participant's exposure to NDMA (ever exposure and predefined categories of cumulative valsartan exposure) was mapped out as a time varying variable while also applying a one year lag.

### MAIN OUTCOME MEASURES

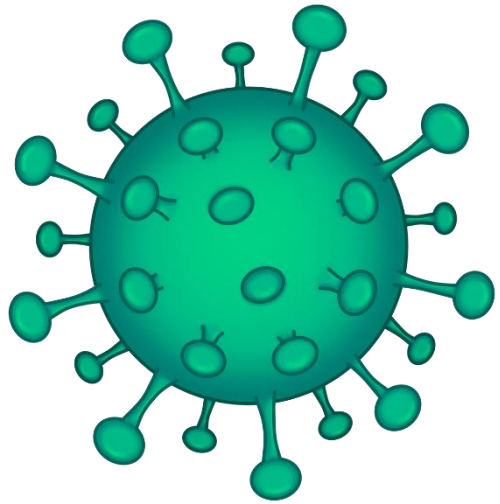
Association between NDMA exposure and a primary composite endpoint comprising all cancers except non-melanoma skin cancer, estimated using Cox of a dose-response relation (P=0.70). For single cancer outcomes, increases in risk were observed for colorectal cancer (hazard ratio 1.46, 95% confidence interval 0.79 to 2.73) and for uterine cancer (1.81, 0.55 to 5.90), although with wide confidence intervals that included the null.

### CONCLUSIONS

The results do not imply a markedly increased short term overall risk of cancer in users of valsartan contaminated with NDMA. However, uncertainty persists about single cancer outcomes, and studies with longer follow-up are needed to assess long term cancer risk.

## Introduction

Valsartan is an angiotensin II receptor antagonist used to treat hypertension and heart failure.[1 2] In July 2018, some valsartan products were discovered to have been contaminated with N-nitrosodimethylamine (NDMA).[3] This contamination, which far exceeded regulatory exposure limits, was specific to drug products manufactured by Zhejiang Huahai Pharmaceuticals, a company in Linhai, China, and seems to be related to a change in the manufacturing process that was implemented in 2012. Consequently, medical agencies across Europe as well as the US Food and Drug Administration have withdrawn all affected valsartan



# DACCOVID

Steering committee

Danish Medicines Agency

Danish Health Authority

Statens Serum Institut

Danish Health Data Authority

Danish Patients

Danish Regions

Danish Regions Clinical Quality Program

Danish Faculties of Health Science

Clinical Epidemiology

Dovepress
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ORIGINAL RESEARCH

# Existing Data Sources in Clinical Epidemiology: The Danish COVID-19 Cohort

This article was published in the following Dove Press journal:
*Clinical Epidemiology*

Anton Pottegård[1]
Kasper Bruun Kristensen[1]
Mette Reilev[1]
Lars Christian Lund[1]
Martin Thomsen Ernst[1]
Jesper Hallas[1,2]
Reimar Wernich Thomsen[3]
Christian Fynbo Christiansen[3]
Henrik Toft Sørensen[3,4]
Nanna Borup Johansen[5]
Henrik Støvring[1,6]
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Jesper Kjær[11]
Nikolai C Brun[5]

[1]Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark; [2]Department of Clinical Biochemistry and Clinical Pharmacology, Odense University Hospital, Odense, Denmark; [3]Department of Clinical

**Background:** To facilitate research on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a prospective cohort of all Danish residents tested for SARS-CoV-2 in Denmark is established.

**Data Structure:** All Danish residents tested by reverse transcriptase polymerase chain reactions (RT-PCR) for SARS-CoV-2 in Denmark are included. The cohort is identified using the Danish Microbiology Database. Individual-level record linkage between administrative and health-care registries is facilitated by the Danish Civil Registration System. Information on outcomes related to SARS-CoV-2 infection includes hospital admission, intensive care unit admission, mechanical ventilation, and death and is retrieved from the five administrative Danish regions, the Danish National Patient Registry, and the Danish Register of Causes of Death. The Patient Registry further provides a complete hospital contact history of somatic and psychiatric conditions and procedures. Data on all prescriptions filled at community pharmacies are available from the Danish National Prescription Registry. Health-care authorization status is obtained from the Danish Register of Healthcare Professionals. Finally, selected laboratory values are obtained from the Register of Laboratory Results for Research. The cohort is governed by a steering committee with representatives from the Danish Medicines Agency, Statens Serum Institut, the Danish Health Authority, the Danish Health Data Authority, Danish Patients, the Faculties of Health Sciences at the Danish universities, and Danish regions. The steering committee welcomes suggestions for research studies and collaborations. Research proposals will be prioritized based on timeliness and potential clinical and public health implications. All


1
3
1
2
3

**5 preparatory studies**

(all published)

**11 hypothesis evaluating studies**

1 under review

10 published

## Preparatory studies

| | | | |
|---|---|---|---|
| Methods review (ISPE) | Pottegård et al. | Considerations for pharmacoepidemiological analyses in the SARS-CoV-2 pandemic | Pharmacoepidemiol Drug Saf (LINK) |
| Description of DACCOVID | Pottegård et al. | Existing Data Sources in Clinical Epidemiology: The Danish COVID-19 Cohort | Clin Epi (LINK) |
| Baseline characteristics | Reilev et al. | Characteristics and predictors of hospitalization and death in the first 11 122 cases with a positive RT-PCR test for SARS-CoV-2 in Denmark: a nationwide cohort | Int J Epidemiol (LINK) |
| NSAID og influenza | Lund et al. | Association of Nonsteroidal Anti-inflammatory Drug Use and Adverse Outcomes Among Patients Hospitalized With Influenza | JAMA Netw Open (LINK) |
| ACE/ARB in influenza | Christiansen et al. | Renin–Angiotensin System Blockers and Adverse Outcomes of Influenza and Pneumonia: A Danish Cohort Study | J Am Heart Assoc (LINK) |

## COVID-19 studies

| | | | |
|---|---|---|---|
| ABO bloodtype | Barnkob et al. | Reduced prevalence of SARS-CoV-2 infection in ABO blood group O | Blood Adv (LINK) |
| ACE/ARB exposure | Christiansen et al. | SARS-CoV-2 infection and adverse outcomes in users of ACE inhibitors and angiotensin-receptor blockers: a nationwide case-control and cohort analysis | Thorax (LINK) |
| NSAIDs exposure | Lund et al. | Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study | PLOS Med (LINK) |
| Risk of VTE | Dalager-Pedersen et al. | Venous Thromboembolism and Major Bleeding in Patients With Coronavirus Disease 2019 (COVID-19): A Nationwide, Population-Based Cohort Study | Clin Infect Dis (LINK) |
| Inhaled steroids exposure | Husby et al. | Association between inhaled corticosteroid use and COVID-19 outcomes | Pharmacoepidemiol Drug Saf (LINK) |
| Immunsuppressant exposure | Ward et al. | The effect of immunosuppressants on the prognosis of SARS-CoV-2 infection | Eur Respir J (LINK) |
| PPI exposure | Israelsen et al. | Proton Pump Inhibitor Use Is Not Strongly Associated With SARS-CoV-2 Related Outcomes: A Nationwide Study and Meta-analysis | Clin Gastroenterol Hepatol (LINK) |
| Antidiabetic exposure | Israelsen et al. | Comparable COVID-19 outcomes with current use of GLP-1 receptor agonists, DPP-4 inhibitors or SGLT-2 inhibitors among patients with diabetes who tested positive for SARS-CoV-2 | Diabetes Obes Metab (LINK) |
| Thyroid function | Brix et al. | Risk and course of SARS-CoV-2 infection in patients treated for hypothyroidism and hyperthyroidism | Lancet Diab Endocrinol (LINK) |
| Psychotropics | Gasse et al. | - | Undergoing peer review |
| Late effects | Lund et al. | Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study | Lancet Infect Dis (LINK) |

FAST TRACK

# Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study

Anton Pottegård,[1] Lars Christian Lund,[1] Øystein Karlstad,[2] Jesper Dahl,[2] Morten Andersen,[3] Jesper Hallas,[1] Øjvind Lidegaard,[4,5] German Tapia,[2] Hanne Løvdal Gulseth,[2] Paz Lopez-Doriga Ruiz,[2] Sara Viksmoen Watle,[2] Anders Pretzmann Mikkelsen,[4,5] Lars Pedersen,[6,7] Henrik Toft Sørensen,[6,7] Reimar Wernich Thomsen,[6,7] Anders Hviid[3,8]

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Additional material is published online only. To view please visit the journal online.

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http://dx.doi.org/10.1136/bmj.n1114

Accepted: 28 April 2021

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Population based cohort study.

### SETTING

Nationwide healthcare registers in Denmark and Norway.

### PARTICIPANTS

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### MAIN OUTCOME MEASURES

Observed 28 day rates of hospital contacts for incident arterial events, venous thromboembolism

### RESULTS

The vaccinated cohorts comprised 148 792 people in Denmark (median age 45 years, 80% women) and 132 472 in Norway (median age 44 years, 78% women), who received their first dose of ChAdOx1-S. Among 281 264 people who received ChAdOx1-S, the standardised morbidity ratio for arterial events was 0.97 (95% confidence interval 0.77 to 1.20). 59 venous thromboembolic events were observed in the vaccinated cohort compared with 30 expected based on the incidence rates in the general population, corresponding to a standardised morbidity ratio of 1.97 (1.50 to 2.54) and 11 (5.6 to 17.0) excess events per 100 000 vaccinations. A higher than expected rate of cerebral venous thrombosis was observed: standardised morbidity ratio 20.25 (8.14 to 41.73); an excess of 2.5 (0.9 to 5.2) events per 100 000 vaccinations. The standardised morbidity ratio for any thrombocytopenia/coagulation disorders was 1.52 (0.97 to 2.25) and for any bleeding was 1.23 (0.97 to 1.55). 15 deaths were observed in the vaccine cohort compared with 44 expected.

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UNTERSUCHUNG NACH IMPFUNG

**Corona: Krankenschwester stirbt, Kollegin schwer erkrankt - Österreich stoppt vorsichtshalber AstraZeneca-Charge**

von Martina Lippl

*Eine Krankenschwester ist nach einer Corona-Impfung verstorben, eine Kollegin soll mit einer Lungenembolie im Krankenhaus liegen. Bisher hat sich ein Zusammenhang mit dem Impfstoff nicht bestätigt.*

**Update vom 11. März:** Die Europäische Arzneimittelagentur (EMA) gab nun eine erste Entwarnung. Es gebe derzeit keine Hinweise darauf, dass der Tod der Krankenschwester oder die Lungenembolie ihrer Kollegin durch die Corona-Impfung mit dem Vakzin von AstraZeneca verursacht wurden.

# COVID-19 Vaccine AstraZeneca: PRAC preliminary view suggests no specific issue with batch used in Austria



News 10/03/2021

The Austrian national competent authority has suspended the use of a batch of Vaxzevria (previously COVID-19 Vaccine AstraZeneca) (batch number ABV5300) after a person was diagnosed with multiple thrombosis (formation of blood clots within blood vessels) and died 10 days after vaccination, and another was hospitalised with pulmonary embolism (blockage in arteries in the lungs) after being vaccinated. The latter is now recovering. As of 9 March 2021, two other reports of thromboembolic event cases had been received for this batch.

There is currently no indication that vaccination has caused these conditions, which are not listed as side effects with this vaccine.

Batch ABV5300 was delivered to 17 EU countries[1] and comprises 1 million doses of the vaccine. Some EU countries[2] have also subsequently suspended this batch as a precautionary measure, while a full investigation is ongoing. Although a quality defect is considered unlikely at this stage, the batch quality is being investigated.

EMA's safety committee PRAC is reviewing this issue; it is investigating the cases reported with the batch as well as all other cases of thromboembolic events, and other conditions related to blood clots, reported post-vaccination. The information available so far indicates that the number of thromboembolic events in vaccinated people is no higher than that seen in the general population. As of 9 March 2021, 22 cases of thromboembolic events had been reported among the 3 million people vaccinated with COVID-19 Vaccine AstraZeneca in the European Economic Area.

PRAC will continue its assessment of any potential issue with the batch as well as its review of thromboembolic events and related conditions.

EMA will further communicate as the assessment progresses.

UNTERSUCHUNG NACH IMPFUNG

# Corona: Krankenschwester stirbt, Kollegin schwer erkrankt – Österreich stoppt vorsichtshalber AstraZeneca-Charge

artina Lippl

*ung verstorben, eine Kollegin soll mit*
*r hat sich ein Zusammenhang mit dem*

ttelagentur (EMA) gab nun eine erste
dass der Tod der Krankenschwester
rona-Impfung mit dem Vakzin von

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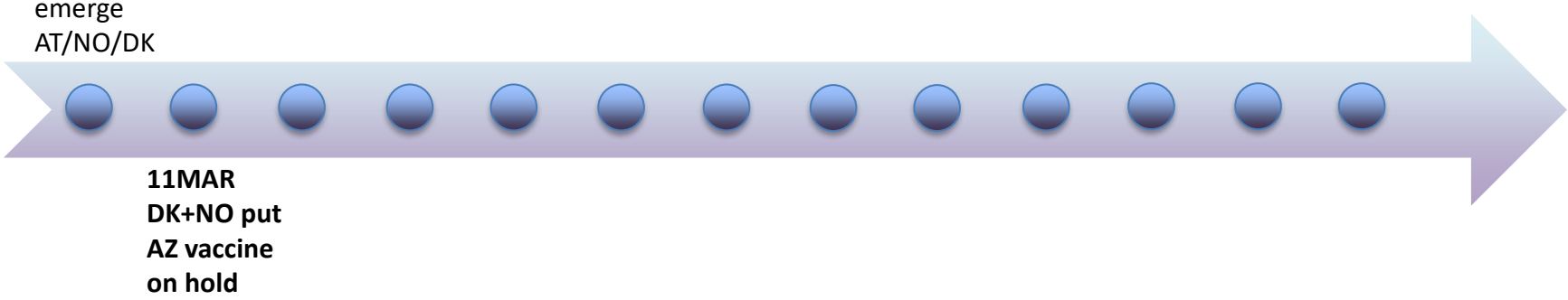
# Helsearbeider som ble innlagt etter AstraZeneca-vaksinering er død - undersøker om det er sammenheng

**En kvinnelig helsearbeider som ble innlagt på sykehus med en spesiell blodpropp-tilstand etter vaksinasjon, er død.**

Av LINE FAUSKO, MARTHA C. S. HOLMES, ODA ORDING, YASMIN SFRINTZERIS og EIRIK RØSVIK
Oppdatert 15. mars

*The casus of the Oxford-AstraZeneca jab:*
The story and the study leading to our *BMJ* publication
[Pottegård A et al. *BMJ* 2021 May 5;373:n1114]



DANISH HEALTH AUTHORITY

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NEWS

# Vaccination with the COVID-19 vaccine from AstraZeneca is put on hold until further notice

**Reports of severe cases of blood clots in people who have been vaccinated with the COVID-19 vaccine from AstraZeneca has caused the European Medicines Agency and other drug regulatory authorities in Europe to launch an investigation into the vaccine. One such report concerns the death of a person in Denmark. At this stage, it is too early to conclude whether there is a link between the vaccine and the blood clots.**

11 MAR 2021

Based on a precautionary principle and concerns raised by the pharmaceutical authorities, the Danish Health Authority has decided to stop vaccination with the COVID-19 vaccine from AstraZeneca for the next 14 days. The Danish Health Authority and the Danish Medicines Agency will re-evaluate this decision in week 12.

"We are engaged in the largest and most important vaccination rollout in Danish history. And right now, we need all the vaccine doses we can get. It is, therefore, not an easy decision to pause vaccination with one of the vaccines. However, because we vaccinate so many people, we also need to react with due diligence when we learn of possible and severe side effects. We need clarification before we can continue to use the vaccine from AstraZeneca," says Søren Brostrøm, Director General of the Danish Health Authority.

This page

Vaccination m
AstraZeneca s
videre

Statens legemiddelverk

Søk i alt innhold

Forside → Nyheter

# Vaksinering med Covid-19 Vaccine AstraZeneca settes på pause etter melding om ett dødsfall i Danmark

Folkehelseinstituttet (FHI) setter all vaksinering med koronavaksinen fra AstraZeneca på pause. Det undersøkes om det er en sammenheng mellom vaksinen og et dødsfall som følge av blodpropp i Danmark.

Publisert: 11.03.2021

Det er ikke konkludert med at det er en sammenheng mellom vaksinasjon og dødsfallet i Danmark, og pausen innebærer ikke at vaksinen frarådes i fremtiden. Legemiddelverket vurderer fortsatt at vaksinens nytte overstiger risikoen for bivirkninger.

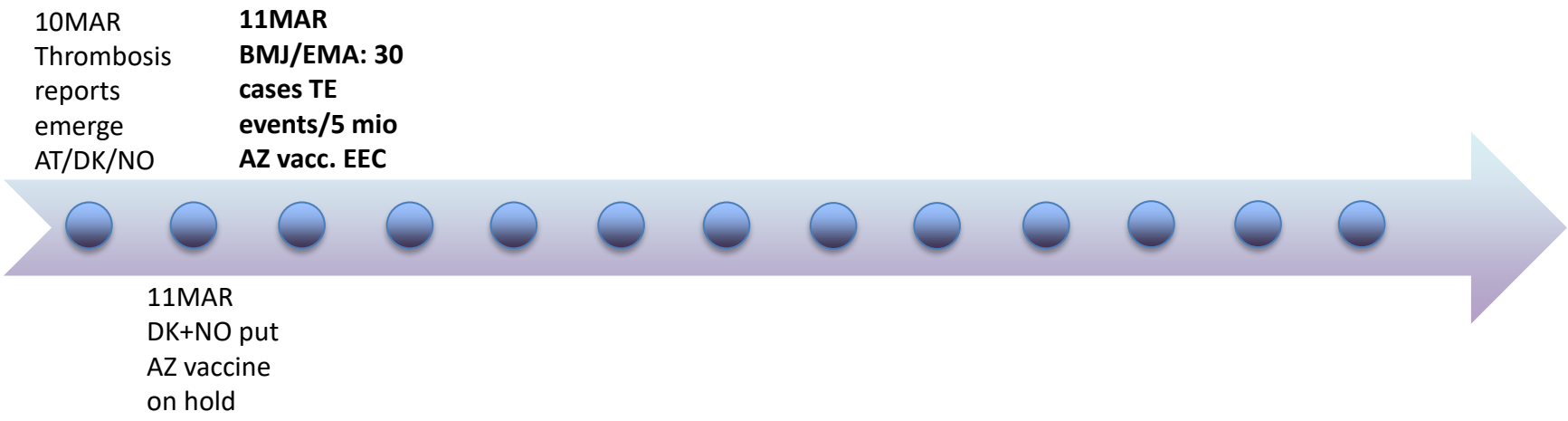
## Iverksetter undersøkelser

Når vaksineringen settes på pause er det for å være på den sikre siden. Vi vil nå vurdere disse alvorlige bivirkningsmeldingene sammen med europeiske legemiddelmyndigheter.

– Dette er sjeldne, men alvorlige bivirkninger, som vi tar på høyeste alvor. Det er viktig at vi tar oss tid til å vurdere ny informasjon grundig og avgjøre om vaksinen skal tas i bruk igjen, sier medisinsk fagdirektør Steinar Madsen.

Per 10. mars 2021 har det blitt rapport om 30 tilfeller av blodpropp blant de 5 millioner menneskene som har blitt vaksinert med Covid-19 Vaccine AstraZeneca i EU/EØS-området.

*The casus of the Oxford-AstraZeneca jab:*
The story and the study leading to our *BMJ* publication
[Pottegård A et al. *BMJ* 2021 May 5;373:n1114]



London

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Published: 11 March 2021

# Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots

Jacqui Wise

Denmark has temporarily suspended use of the Oxford-AstraZeneca covid-19 vaccine as a precautionary move after reports of blood clots and one death. However, the European Medicines Agency (EMA) and the UK's regulatory body have said that there is no indication that vaccination is linked to thromboembolic events.

Eight other countries—Norway, Iceland, Austria, Estonia, Lithuania, Luxembourg, Italy, and Latvia—have also suspended use of AstraZeneca's vaccine. The decisions are a further setback for Europe's vaccination campaign, which has struggled to pick up speed, partly because of delays in delivering the AstraZeneca vaccine.

The Danish Health Authority said that one person in Denmark had died after receiving the AstraZeneca vaccine and that it would suspend the drug's use for two weeks while the case was investigated. "It is important to point out that we have not terminated the use of the AstraZeneca vaccine—we are just pausing its use," said the Danish Health Authority's director, Soren Brostrøm.

On 10 March the EMA said that Austria had suspended the use of a batch of AstraZeneca vaccines after one person had multiple thrombosis diagnosed and died 10 days after vaccination. Another person was admitted to hospital with pulmonary embolism after being vaccinated and is now recovering. The EMA said that two other reports of thromboembolic event cases had also been received from that batch, which was delivered to 17 EU countries and comprised a million doses.

## Close review

The EMA's safety committee is reviewing the issue but said that there was currently no indication that vaccination has caused these conditions, which are not listed as side effects. It said that the information available so far showed that the number of thromboembolic events in vaccinated people was no higher than that seen in the general population. It said that, as of 10 March, 30 cases of thromboembolic events had been reported among the five million people given the AstraZeneca vaccine in the European Economic Area.

A spokesperson for AstraZeneca said, "Patient safety is the highest priority for AstraZeneca. Regulators have clear and stringent efficacy and safety standards for the approval of any new medicine, and that includes Covid-19 Vaccine AstraZeneca.

"An analysis of our safety data of more than 10 million records has shown no evidence of an increased risk of pulmonary embolism or deep vein thrombosis in any defined age group, gender, batch or in any particular country with Covid-19 Vaccine AstraZeneca. In fact, the observed number of these types of events is significantly lower in those vaccinated than what would be expected among the general population."

## Disease related clotting

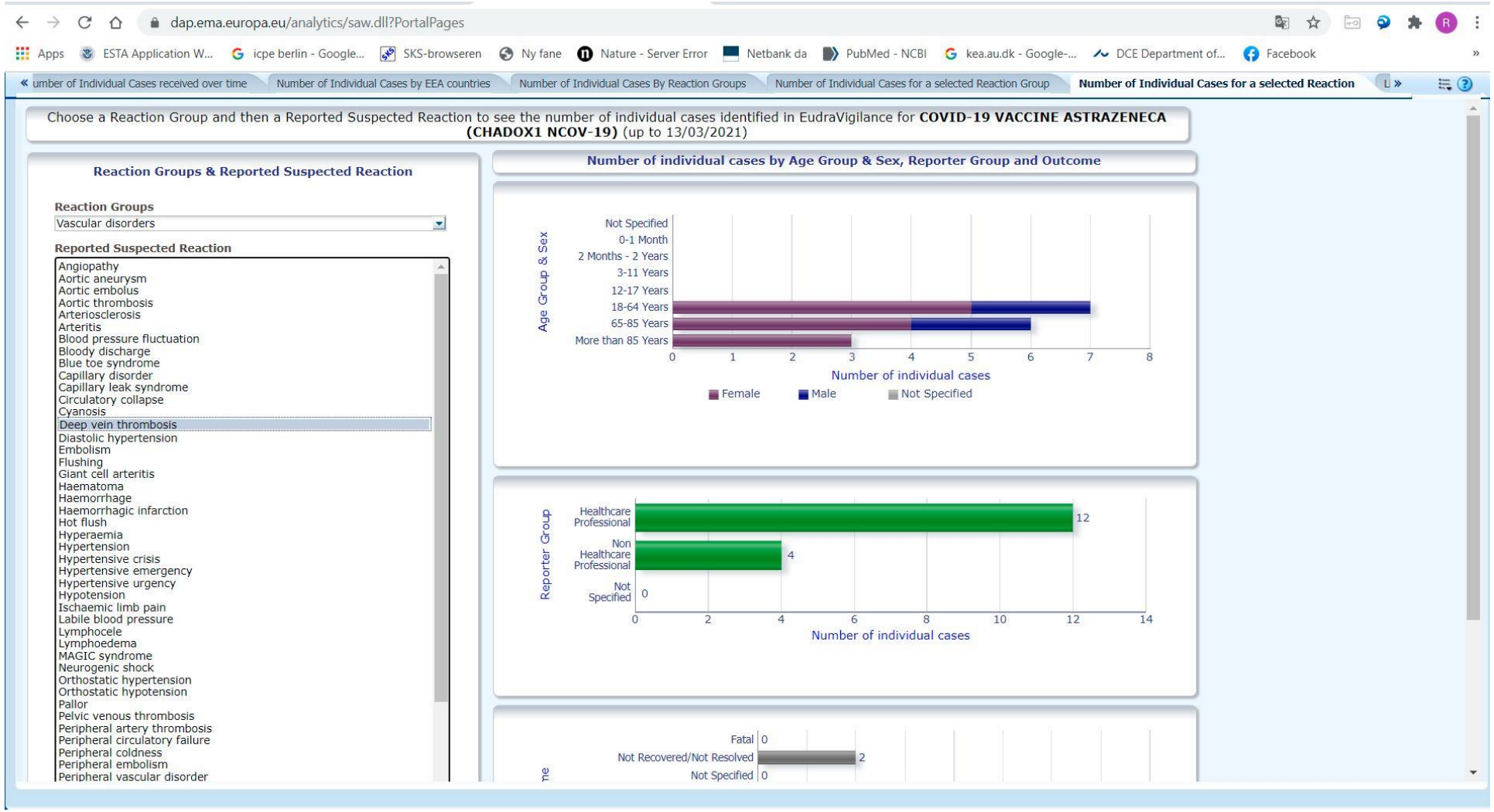
Commenting on the decisions, Stephen Evans, professor of pharmacoepidemiology at the London School of Hygiene & Tropical Medicine, said, "The problem with spontaneous reports of suspected adverse reactions to a vaccine [is] the enormous difficulty of distinguishing a causal effect from a coincidence." He highlighted that covid-19 disease was very strongly associated with blood clotting and that there had been hundreds, if not many thousands, of deaths caused by blood clotting as a result of covid-19.

Adam Finn, professor of paediatrics at the University of Bristol, said, "The position with the Oxford-AstraZeneca vaccine at the moment is that there is no sign anywhere, including the UK where very large numbers of doses have now been given, that blood clot related illnesses are happening any more frequently than usual.

"That's reassuring, because it means either that the vaccine doesn't cause blood clots at all or, at the very worst, that it's an extremely rare event."

***Addendum: We amended this article on 12 March 2021 to add Italy to the list of countries mentioned in paragraph 2 and to include an updated statement from AstraZeneca in paragraphs 7 and 8. Paragraph 8 replaces the original sentence, "The safety of the vaccine has been extensively studied in phase III clinical trials, and peer reviewed data confirms the vaccine has been generally well tolerated."***

# EMA 13MAR: Spontaneous Adverse Event Reporting



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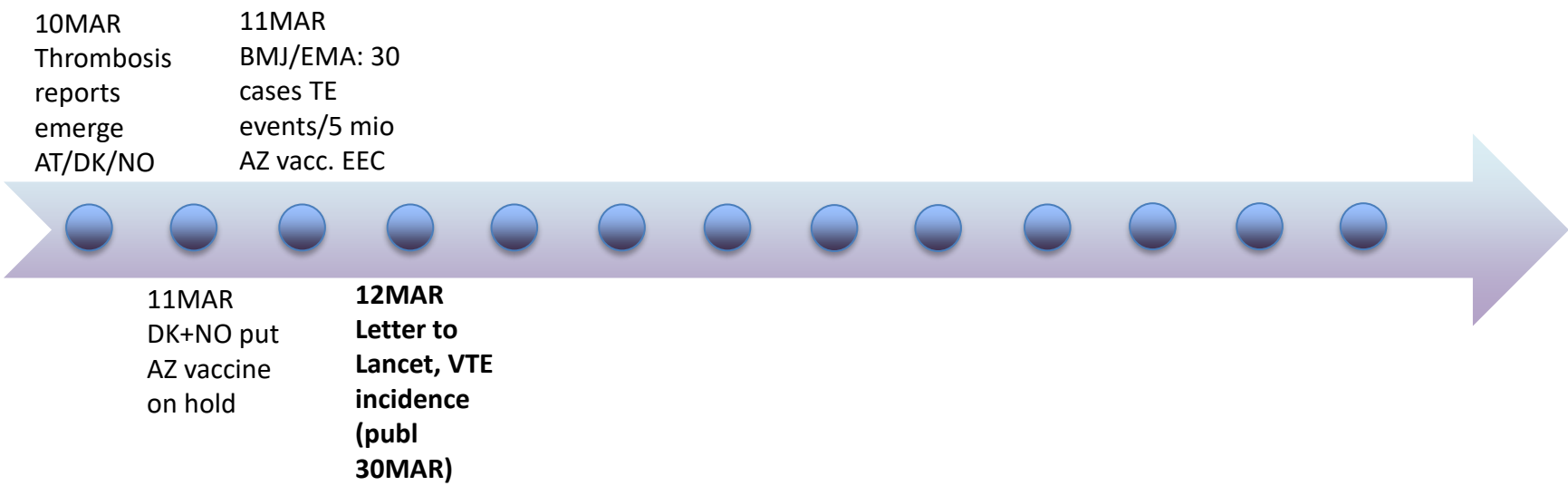

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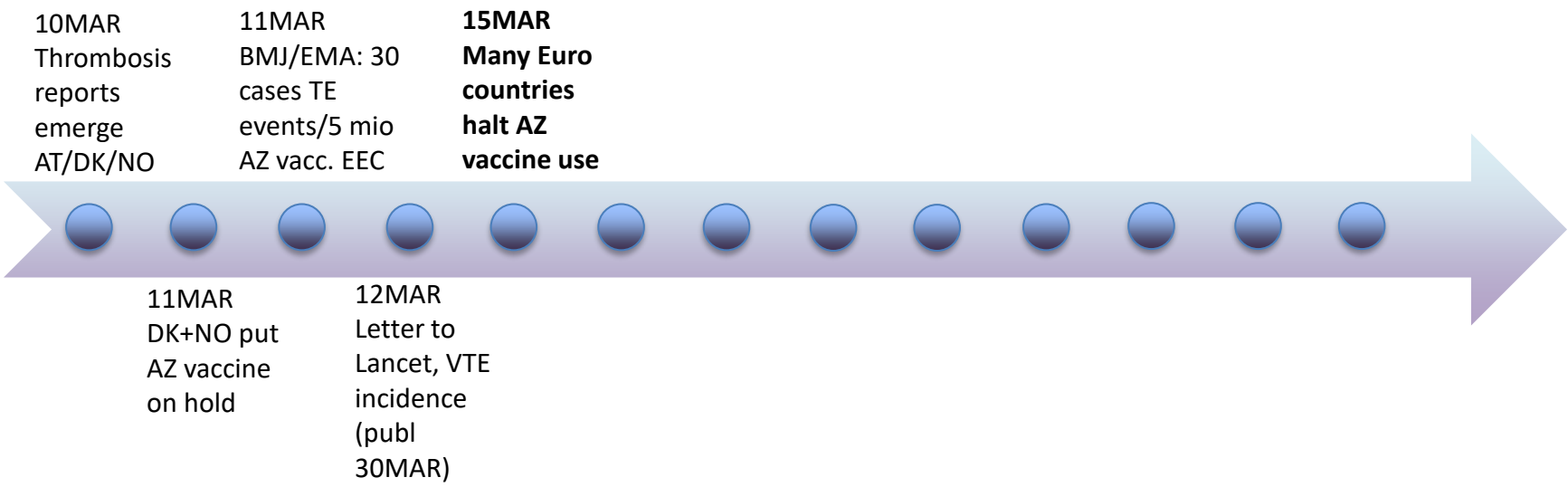

A nurse vaccines a student with the AstraZeneca Covid-19 vaccine in Brest, western France. [File: Fred Tanneau/AFP]

15 Mar 2021 | Updated: 16 Mar 2021 02:48 PM (GMT)

More than a dozen countries, mostly in Europe, have suspended the use of AstraZeneca's COVID-19 vaccine over fears the shot may have caused some recipients to develop blood clots.

Sweden and Latvia on Tuesday became the latest nations to halt the rollout, following moves by Germany, Italy, France, Spain, Denmark, Norway, and The Netherlands, among others.

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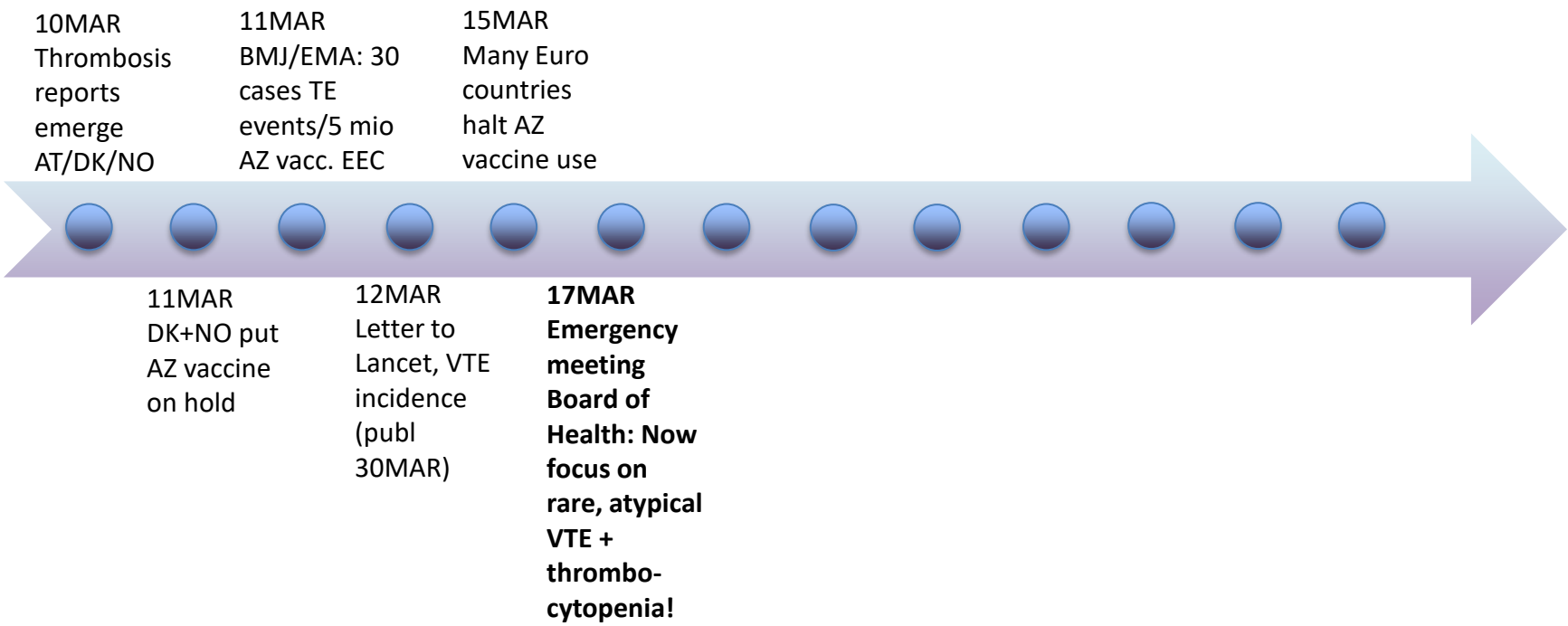
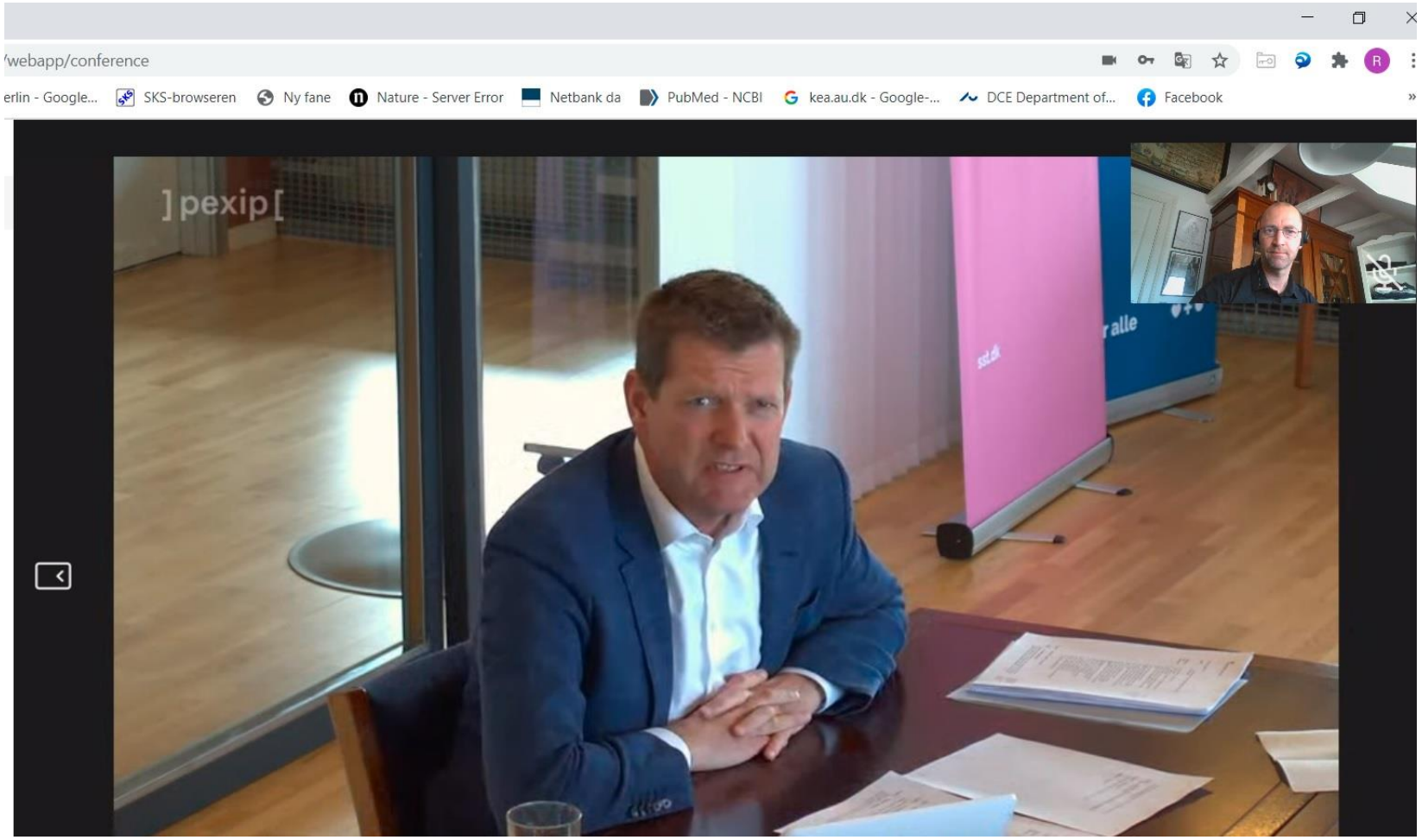


# Are we facing a new vaccine-induced syndrome??



A doctor administers a dose of the AstraZeneca vacc
March—the day the German government said it would
concerns. JENS SCHLUETER/GETTY IMAGES

## 'It's a very special picture.' put the brakes on AstraZe

By Gretchen Vogel, Kai Kupferschmidt | Mar. 17, 2021 , 1:3

German officials said Monday they had received seven reports of cerebral venous thrombosis (CVT), three of them fatal (…) All of the patients also had low levels of platelets (…) One affected patient had blood clots "from head to toe," (…) The symptoms remind Wendtner of a syndrome called disseminated intravascular coagulation (DIC)

Germany, Italy, Austria, Norway, and Denmark have all reported cases of people who developed widespread blood clots, low platelet counts, and internal bleeding; at least seven have died.

"It's a very special picture" of symptoms, says Steinar Madsen, medical director of the Norwegian Medicines Agency. "Our leading hematologist said he had never seen anything quite like it.""

[Science, 17MAR, 26MAR]

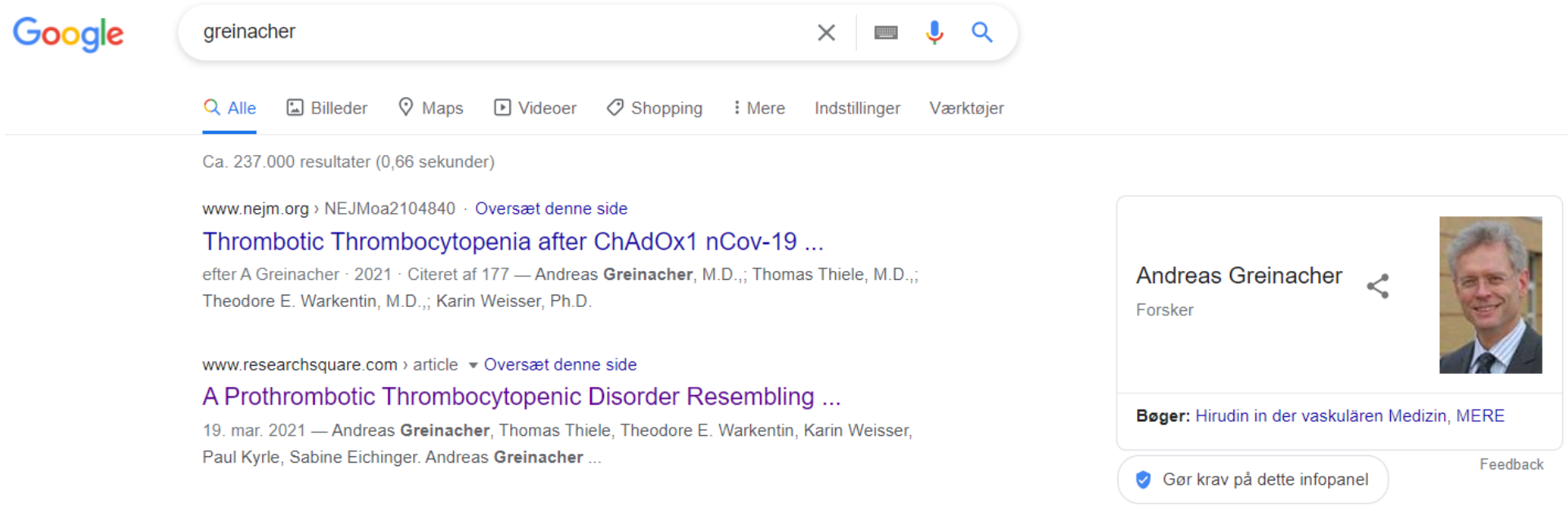


The decision this week by more than 20 European countries to temporarily stop using AstraZeneca's COVID-19 vaccine has opened a rift between vaccine safety experts, who say the cases of serious clotting and bleeding that triggered the pause are alarming and unusual, and public health officials concerned that the immunization pause on a continent in the grip of the pandemic's third wave could take a heavy toll.

# Thrombocytopenia

72y old patient with low platelet count after Covid-19 vaccination.

# A new syndrome?



# A Prothrombotic Thrombocytopenic Disorder Resembling Heparin-Induced Thrombocytopenia Following Coronavirus-19 Vaccination

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**Thomas Thiele**
Universitätsmedizin Greifswald

**Theodore E. Warkentin**
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**Paul Kyrle**
Medical University of Vienna

**Sabine Eichinger**
Medical University of Vienna

**Research Article**

**Keywords:** SARS-CoV-2; vaccine, thrombosis, cerebral vein thrombosis

**DOI:** https://doi.org/10.21203/rs.3.rs-362354/v1

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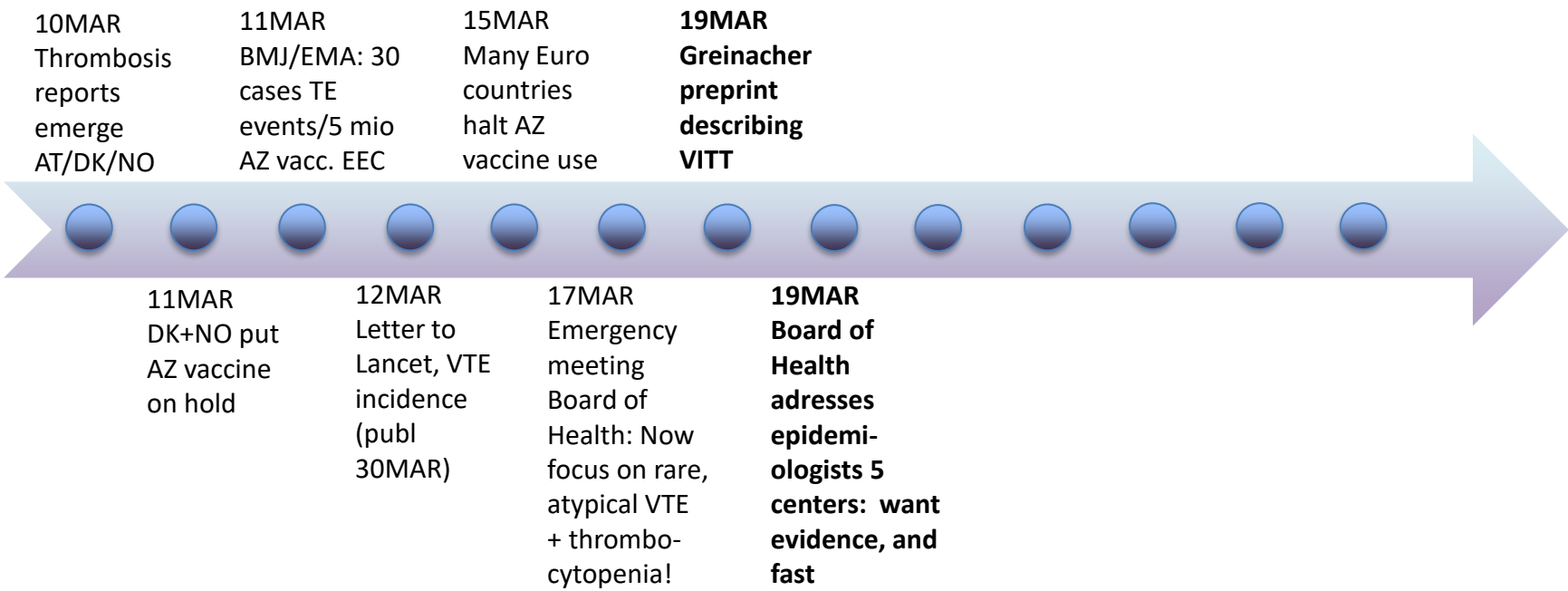
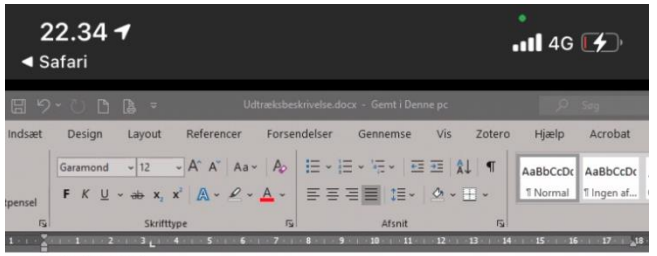


# Me, Friday March 19…

# What I dreamt of doing…

# What I ended up doing…




**Behandlingssted**

Forskermaskinen

**Population**

Populationen består af personer der er i live efter 1. januar 2010.

**Data der vil blive indsendt fra forskeren**

Det Danske Vaccineregister (all registrations; 2010-)

**Registre og overordnet afgrænsning**

| | |
|---|---|
| Lægemiddelstatistikregistret | År 2010 og frem, alle ATC-koder |
| Landspatientregistret (inkl. lpr-psyk + LPR3) | År 1995 og frem, alle kontakter |
| Dødsårsagsregistret | År 2010 og frem |
| Sygesikringsregistret | År 2000 og frem |
| CPR-registret | Hele registrets løbetid. Køn, fødselsdato, migration, indvandrer/efterkommer |
| MiBa | År 2020 og frem |
| Laboratoriedatabasen | År 2015 og frem |

**Specifikation af tabeller og variable**

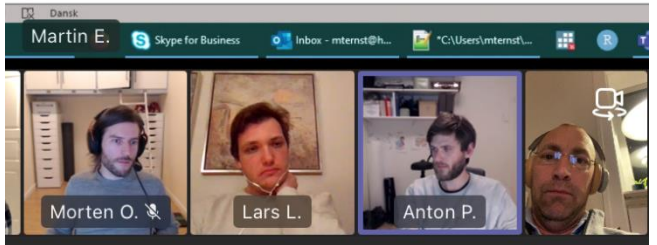
**CPR-register**

Tabeller:

T_Person

**MiBa**

Casedefinition
SampleDate
CPR
Region
KMA
Travel
CountryOfTravel



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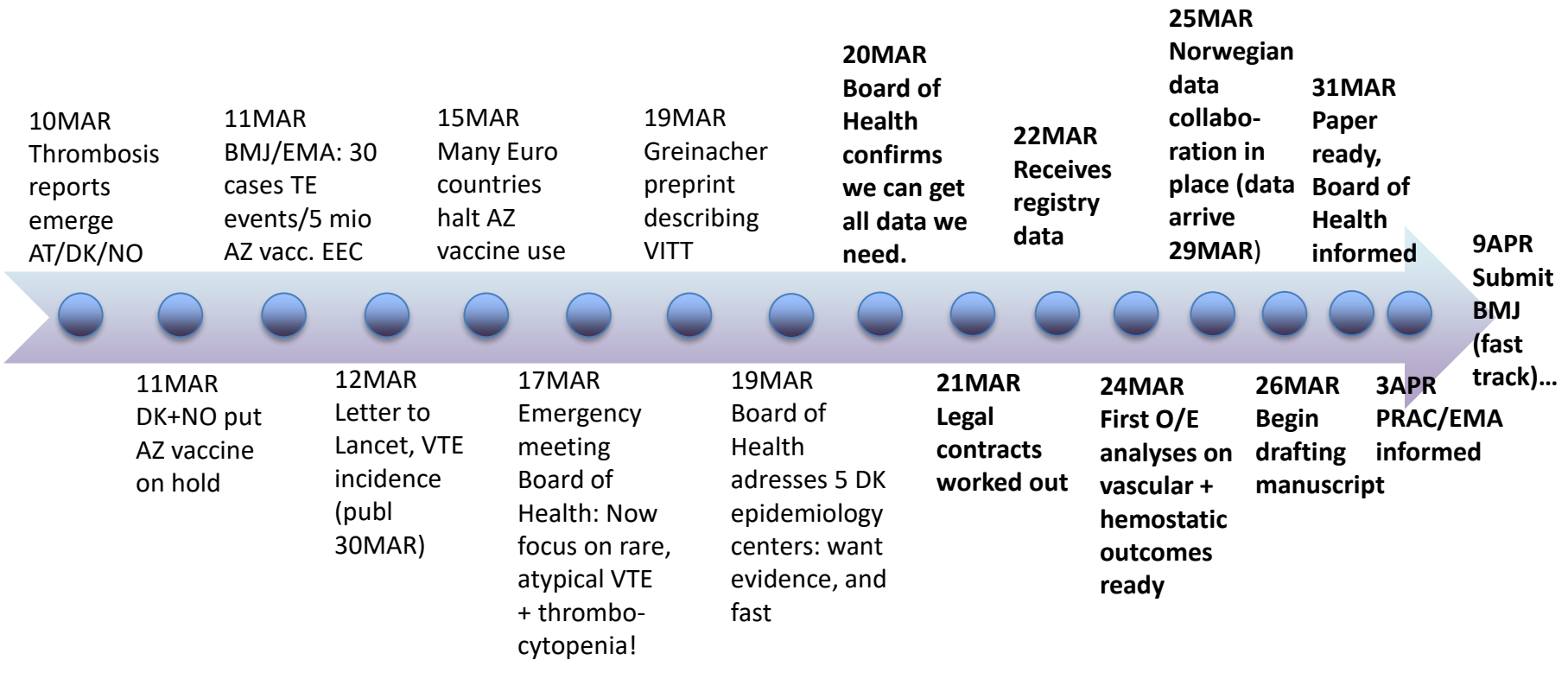

FAST TRACK

# Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study

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Accepted: 28 April 2021

## ABSTRACT

### OBJECTIVE

To assess rates of cardiovascular and haemostatic events in the first 28 days after vaccination with the Oxford-AstraZeneca vaccine ChAdOx1-S in Denmark and Norway and to compare them with rates observed in the general populations.

### DESIGN

Population based cohort study.

### SETTING

Nationwide healthcare registers in Denmark and Norway.

### PARTICIPANTS

All people aged 18-65 years who received a first vaccination with ChAdOx1-S from 9 February 2021 to 11 March 2021. The general populations of Denmark (2016-18) and Norway (2018-19) served as comparator cohorts.

### MAIN OUTCOME MEASURES

Observed 28 day rates of hospital contacts for incident arterial events, venous thromboembolism

### RESULTS

The vaccinated cohorts comprised 148 792 people in Denmark (median age 45 years, 80% women) and 132 472 in Norway (median age 44 years, 78% women), who received their first dose of ChAdOx1-S. Among 281 264 people who received ChAdOx1-S, the standardised morbidity ratio for arterial events was 0.97 (95% confidence interval 0.77 to 1.20). 59 venous thromboembolic events were observed in the vaccinated cohort compared with 30 expected based on the incidence rates in the general population, corresponding to a standardised morbidity ratio of 1.97 (1.50 to 2.54) and 11 (5.6 to 17.0) excess events per 100 000 vaccinations. A higher than expected rate of cerebral venous thrombosis was observed: standardised morbidity ratio 20.25 (8.14 to 41.73); an excess of 2.5 (0.9 to 5.2) events per 100 000 vaccinations. The standardised morbidity ratio for any thrombocytopenia/coagulation disorders was 1.52 (0.97 to 2.25) and for any bleeding was 1.23 (0.97 to 1.55). 15 deaths were observed in the vaccine cohort compared with 44 expected.

Risk : Benefit

**Objectives.** To assess rates of cardiovascular and haemostatic events during the first 28 days following administration of Oxford-AstraZeneca COVID-19 vaccine.

# Observed vs. Expected

Observed number of prespecified outcomes among Danish and Norwegian vaccine recipients age 18-65 years (n=281,264) within 28 days of first vaccination

compared to

Expected number of outcomes, based on incidence rates among the general population 2016-2018 (Denmark) and 2018-2019 (Norway), standardized on age, sex, and country to the vaccine cohort.

| | **Denmark** (n=148,792) | **Norway** (n=132,472) |
|---|---|---|
| Female sex | 119,119 (80) | 102,848 (78) |
| Age, median (IQR) | 45 (33-55) | 44 (32-55) |

Almost exclusively health care professionals or social service workers!

**Arterial events**

SMR 0.97 (95% CI 0.77 to 1.20)

**Venous thromboembolism**

SMR 1.97 (95% CI 1.50 to 2.54)

**Thrombocytopenias and coagulative disorders**

SMR 1.52 (0.97 to 2.25)

**Bleeding events**

SMR 1.23 (95% CI 0.97 to 1.55)

**Cerebral venous thrombosis**

SMR 20.25 (95% CI 8.14 to 41.73)

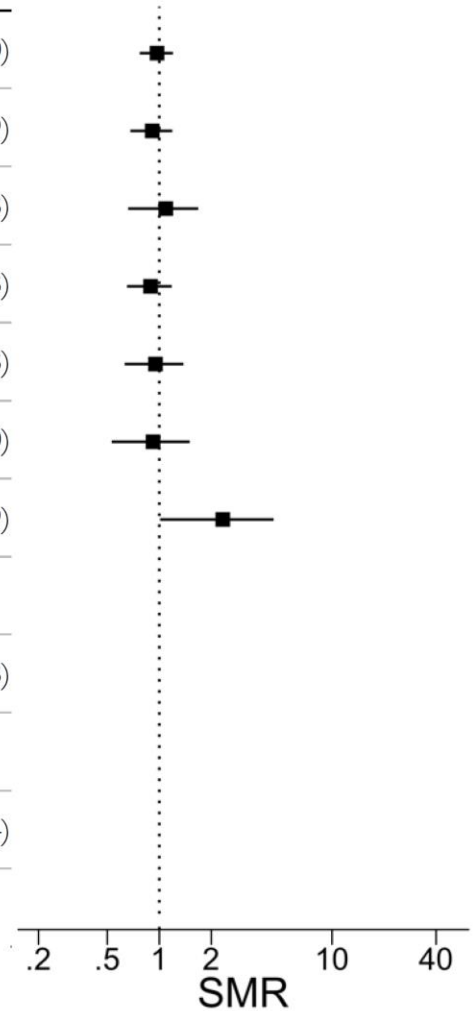
**Cerebral venous thrombosis**

+2.5 (0.9-5.2) / 100 000

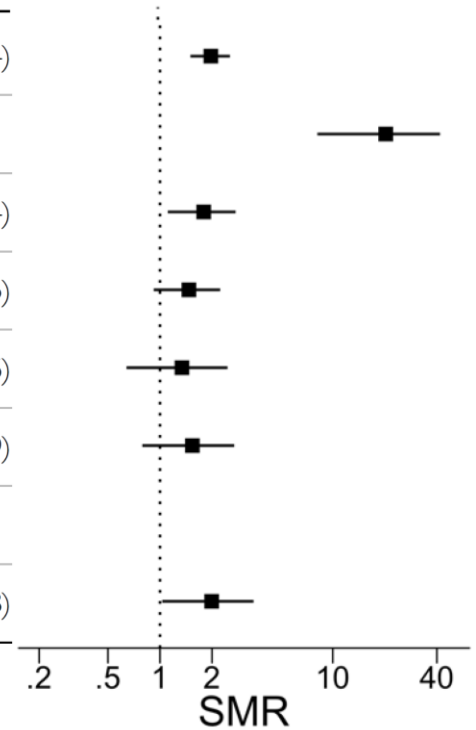
**Venous thromboembolism**

+10.8 (5.6-17.1) / 100 000

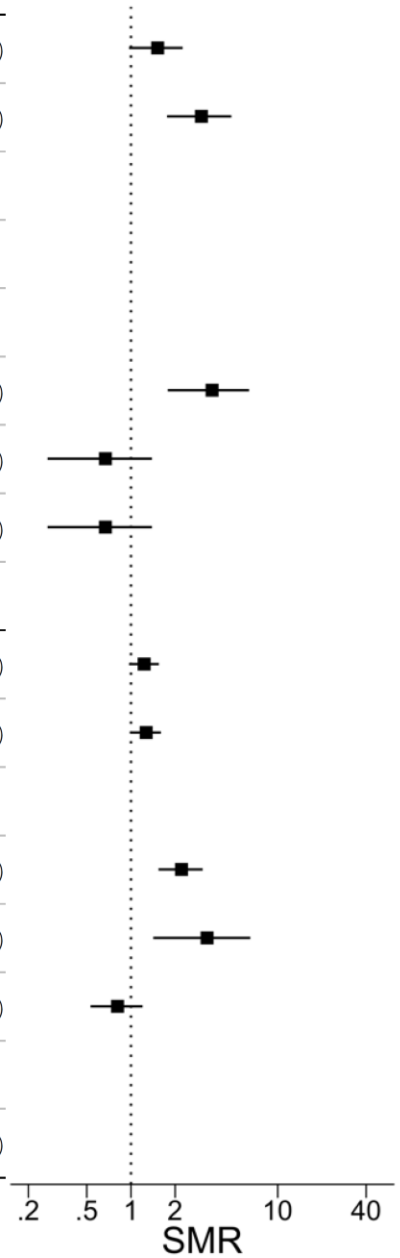
| Outcome | Incidence rate DK / NO | Observed | Expected | Standardised morbidity difference /100,000 (95% CI) | Standardised morbidity ratio (95% CI) |
|---|---|---|---|---|---|
| **ARTERIAL EVENTS** | 4.52 /4.71 | 83 | 86 | -1.0 (-7.2 to 6.4) | 0.97 (0.77 to 1.20) |
| **Cardiac events** | 2.93 / 3.56 | 52 | 57 | -1.9 (-6.8 to 4.1) | 0.91 (0.68 to 1.19) |
| Acute myocardial infarction (AMI) | 1.04 /1.21 | 20 | 18 | 0.6 (-2.3 to 4.6) | 1.09 (0.66 to 1.68) |
| Ischaemic heart disease without AMI | 2.58 / 3.35 | 46 | 52 | -2.2 (-6.8 to 3.5) | 0.89 (0.65 to 1.18) |
| **Cerebrovascular events** | 1.62 / 1.21 | 27 | 28 | -0.5 (-3.9 to 4.0) | 0.95 (0.63 to 1.38) |
| Cerebral infarction | 1.03 / 0.75 | 16 | 17 | -0.5 (-3.0 to 3.2) | 0.92 (0.53 to 1.50) |
| Intracerebral haemorrhage (ICH) | 0.20 / 0.14 | 8 | 3 | 1.7 (0.0 to 4.6) | 2.33 (1.01 to 4.59) |
| Occlusion and stenosis not resulting in cerebral infarction [d] | 0.07 / 0.21 | n<5 | 3 | NR | NR |
| Stroke, unspecified | 0.40 / 0.06 | 0 | 5 | -1.8 (-1.8 to -0.4) | 0.00 (0.00 to 0.78) |
| Subarachnoid haemorrhage (SAH) | 0.14 / 0.09 | n<5 | 3 | NR | NR |
| Transitory cerebral ischemic attack | 0.07 / 0.09 | 0 | 2 | -0.6 (-0.6 to 0.8) | 0.00 (0.00 to 2.24) |
| **Other arterial events** [e] | 0.11 / 0.10 | n<5 | 3 | NR | NR |



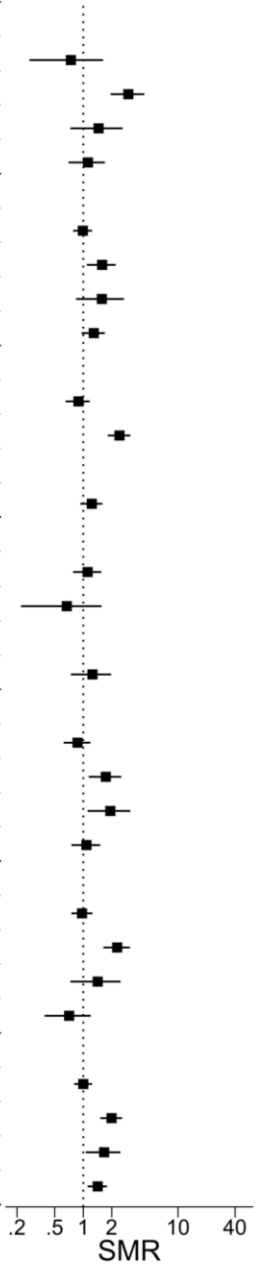
| Outcome | Incidence rate DK / NO | Observed | Expected | Standardised morbidity difference /100,000 (95% CI) | Standardised morbidity ratio (95% CI) |
|---|---|---|---|---|---|
| **VENOUS THROMBOEMBOLISM** | 1.58 / 1.26 | 59 | 30 | 10.8 (5.6 to 17.1) | 1.97 (1.50 to 2.54) |
| **Cerebral venous thrombosis** | 0.02/ 0.01 | 7 | 0 | 2.5 (0.9 to 5.2) | 20.25 (8.14 to 41.73) |
| **Pulmonary embolism (PE)** | 0.57/ 0.57 | 21 | 12 | 3.4 (0.5 to 7.5) | 1.79 (1.11 to 2.74) |
| **Lower limb venous thrombosis** | 0.94 / 0.48 | 22 | 15 | 2.6 (-0.4 to 6.8) | 1.47 (0.92 to 2.23) |
| Deep thrombophlebitis of veins in legs | 0.35 / 0.38 | 10 | 7 | 0.9 (-1.0 to 4.0) | 1.34 (0.64 to 2.46) |
| Unspecified deep thrombophlebitis in lower limb | 0.66 / 0.05 | 12 | 8 | 1.6 (-0.6 to 4.9) | 1.54 (0.79 to 2.69) |
| **Splanchnic thrombosis** | 0.04 / 0.06 | n<5 | 1 | NR | NR |
| **Other venous thrombosis** [f] | 0.22 / 0.36 | 12 | 6 | 2.2 (0.1 to 5.5) | 1.99 (1.03 to 3.48) |



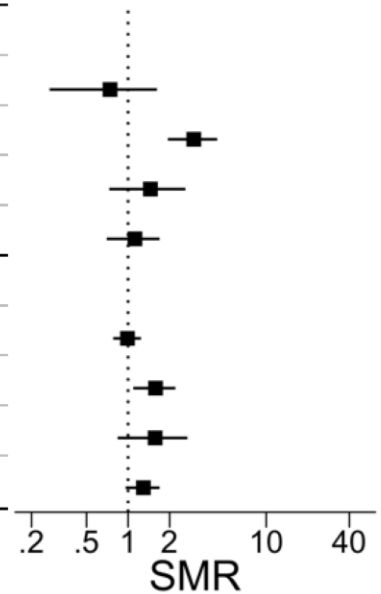
| Outcome | Incidence rate DK / NO | Observed | Expected | Standardised morbidity difference /100,000 (95% CI) | Standardized morbidity ratio (95% CI) |
|---|---|---|---|---|---|
| **THROMBOCYTOPENIA AND COAGULATIVE DISORDERS** | 0.60 / 0.75 | 24 | 16 | 3.0 (-0.2 to 7.4) | 1.52 (0.97 to 2.25) |
| **Thrombocytopenia** | 0.15 / 0.38 | 17 | 6 | 4.2 (1.6 to 8.0) | 3.02 (1.76 to 4.83) |
| Idiopathic thrombocytopenic purpura | 0.07 / 0.06 | n<5 | 1 | NR | NR |
| Other primary thrombocytopenia | 0.00 / 0.01 | 0 | 0 | -0.0 (-0.0 to 1.3) | 0.00 (0.00 to 35.70) |
| Secondary thrombocytopenia | 0.01 / 0.18 | NR | 2 | NR | NR |
| Thrombocytopenia unspecified | 0.09 / 0.20 | 11 | 3 | 2.9 (0.9 to 6.1) | 3.57 (1.78 to 6.38) |
| **Coagulative disorders** | 0.45 / 0.38 | 7 | 10 | -1.3 (-2.8 to 1.5) | 0.67 (0.27 to 1.39) |
| Coagulative disorders, purpura | 0.45 / 0.38 | 7 | 10 | -1.3 (-2.8 to 1.5) | 0.67 (0.27 to 1.39) |
| Disseminated intravascular coagulation (DIC) | 0.01 / 0.02 | 0 | 0 | -0.1 (-0.1 to 1.3) | 0.00 (0.00 to 12.20) |
| **BLEEDING EVENTS** | 2.75 / 3.04 | 74 | 60 | 5.1 (-0.7 to 12.2) | 1.23 (0.97 to 1.55) |
| **Bleedings** | 2.67 / 2.96 | 74 | 58 | 5.9 (0.0 to 12.9) | 1.27 (1.00 to 1.60) |
| Anemia from bleeding | 0.11 / 0.60 | n<5 | 8 | NR | NR |
| Bleeding from respiratory tract | 0.85 / 0.87 | 35 | 16 | 7.1 (3.2 to 12.2) | 2.21 (1.54 to 3.08) |
| Bleeding, not specified | 0.15 / 0.05 | 8 | 2 | 2.1 (0.4 to 4.9) | 3.30 (1.42 to 6.50) |
| Hematuria | 1.43 / 1.50 | 25 | 31 | -2.1 (-5.4 to 2.3) | 0.81 (0.53 to 1.20) |
| Intestinal bleeding | 0.18 / - [d] | n<5 | 2 | NR | NR |
| **Hemolytic anemias** [e] | 0.09 / 0.09 | 0 | 2 | -0.8 (-0.8 to 0.5) | 0.00 (0.00 to 1.66) |



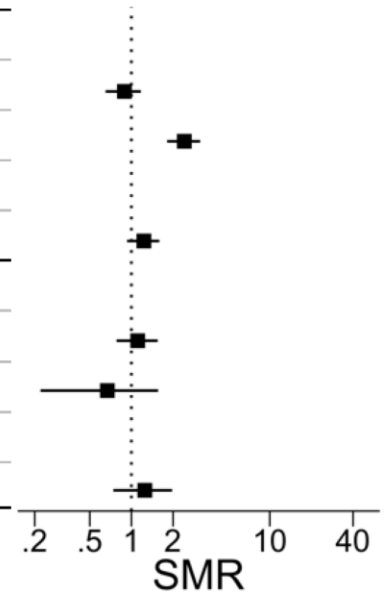
| | Observed | Expected | Standardised morbidity difference /100,000 (95% CI) | Standardised morbidity ratio (95% CI) |
|---|---|---|---|---|
| **AGE 18-44 YEARS** | | | | |
| Arterial events | 6 | 8 | -1.6 (-4.4 to 3.8) | 0.74 (0.27 to 1.62) |
| Venous thromboembolism | 25 | 8 | 12.6 (5.9 to 21.5) | 2.99 (1.94 to 4.42) |
| Thrombocytopenia and coagulative disorders | 11 | 8 | 2.6 (-1.6 to 9.1) | 1.45 (0.73 to 2.60) |
| Bleeding events | 22 | 20 | 1.8 (-4.4 to 10.3) | 1.12 (0.70 to 1.69) |
| **AGE 45-65 YEARS** | | | | |
| Arterial events | 77 | 78 | -0.4 (-12.3 to 13.7) | 0.99 (0.78 to 1.24) |
| Venous thromboembolism | 34 | 22 | 9.1 (1.5 to 18.9) | 1.58 (1.09 to 2.20) |
| Thrombocytopenia and coagulative disorders | 13 | 8 | 3.4 (-1.0 to 10.1) | 1.57 (0.84 to 2.69) |
| Bleeding events | 52 | 40 | 3.4 (-1.0 to 10.1) | 1.29 (0.96 to 1.69) |
| **FEMALES ONLY** | | | | |
| Arterial events | 48 | 54 | -2.9 (-8.8 to 4.4) | 0.89 (0.65 to 1.17) |
| Venous thromboembolism | 54 | 22 | 14.8 (8.5 to 22.5) | 2.41 (1.81 to 3.14) |
| Thrombocytopenia and coagulative disorders | NR | 13 | NR | NR |
| Bleeding events | 56 | 46 | 4.8 (-1.6 to 12.7) | 1.23 (0.93 to 1.59) |
| **MALES ONLY** | | | | |
| Arterial events | 35 | 31 | 6.5 (-12.6 to 31.0) | 1.11 (0.78 to 1.55) |
| Venous thromboembolism | 5 | 7 | -4.4 (-10.4 to 7.4) | 0.67 (0.22 to 1.56) |
| Thrombocytopenia and coagulative disorders | n<5 | 3 | NR | NR |
| Bleeding events | 18 | 14 | 6.3 (-6.7 to 24.9) | 1.25 (0.74 to 1.97) |
| **14-DAY FOLLOW-UP** | | | | |
| Arterial events | 39 | 45 | -4.3 (-12.3 to 6.0) | 0.87 (0.62 to 1.19) |
| Venous thromboembolism | 27 | 16 | 8.1 (1.6 to 16.9) | 1.73 (1.14 to 2.52) |
| Thrombocytopenia and coagulative disorders | 16 | 8 | 5.5 (0.6 to 12.6) | 1.93 (1.11 to 3.14) |
| Bleeding events | 34 | 31 | 1.8 (-5.6 to 11.5) | 1.08 (0.75 to 1.51) |
| **EXCLUDING. BRIEF HOSPITAL CONTACTS** | | | | |
| Arterial events | 62 | 64 | -0.7 (-6.0 to 5.8) | 0.97 (0.75 to 1.25) |
| Venous thromboembolism | 40 | 18 | 8.3 (4.1 to 13.7) | 2.28 (1.63 to 3.11) |
| Thrombocytopenia and coagulative disorders | 12 | 8 | 1.3 (-0.8 to 4.6) | 1.42 (0.73 to 2.48) |
| Bleeding events | 14 | 20 | -2.1 (-4.4 to 1.4) | 0.71 (0.39 to 1.20) |
| **USING A MORE RECENT GENERAL POPULATION COMPARISON COHORT** | | | | |
| Arterial events | 83 | 83 | 0.1 (-6.2 to 7.5) | 1.00 (0.80 to 1.24) |
| Venous thromboembolism | 59 | 30 | 10.9 (5.6 to 17.2) | 1.99 (1.51 to 2.57) |
| Thrombocytopenia and coagulative disorders | 24 | 14 | 3.5 (0.3 to 7.9) | 1.66 (1.06 to 2.47) |
| Bleeding events | 74 | 52 | 8.1 (2.2 to 15.1) | 1.42 (1.11 to 1.78) |



| | Observed | Expected | Standardised morbidity difference /100,000 (95% CI) | Standardised morbidity ratio (95% CI) |
|---|---|---|---|---|
| **AGE 18-44 YEARS** | | | | |
| Arterial events | 6 | 8 | -1.6 (-4.4 to 3.8) | 0.74 (0.27 to 1.62) |
| Venous thromboembolism | 25 | 8 | 12.6 (5.9 to 21.5) | 2.99 (1.94 to 4.42) |
| Thrombocytopenia and coagulative disorders | 11 | 8 | 2.6 (-1.6 to 9.1) | 1.45 (0.73 to 2.60) |
| Bleeding events | 22 | 20 | 1.8 (-4.4 to 10.3) | 1.12 (0.70 to 1.69) |
| **AGE 45-65 YEARS** | | | | |
| Arterial events | 77 | 78 | -0.4 (-12.3 to 13.7) | 0.99 (0.78 to 1.24) |
| Venous thromboembolism | 34 | 22 | 9.1 (1.5 to 18.9) | 1.58 (1.09 to 2.20) |
| Thrombocytopenia and coagulative disorders | 13 | 8 | 3.4 (-1.0 to 10.1) | 1.57 (0.84 to 2.69) |
| Bleeding events | 52 | 40 | 3.4 (-1.0 to 10.1) | 1.29 (0.96 to 1.69) |



| | Observed | Expected | Standardised morbidity difference /100,000 (95% CI) | Standardised morbidity ratio (95% CI) |
|---|---|---|---|---|
| **FEMALES ONLY** | | | | |
| Arterial events | 48 | 54 | -2.9 (-8.8 to 4.4) | 0.89 (0.65 to 1.17) |
| Venous thromboembolism | 54 | 22 | 14.8 (8.5 to 22.5) | 2.41 (1.81 to 3.14) |
| Thrombocytopenia and coagulative disorders | NR | 13 | NR | NR |
| Bleeding events | 56 | 46 | 4.8 (-1.6 to 12.7) | 1.23 (0.93 to 1.59) |
| **MALES ONLY** | | | | |
| Arterial events | 35 | 31 | 6.5 (-12.6 to 31.0) | 1.11 (0.78 to 1.55) |
| Venous thromboembolism | 5 | 7 | -4.4 (-10.4 to 7.4) | 0.67 (0.22 to 1.56) |
| Thrombocytopenia and coagulative disorders | n<5 | 3 | NR | NR |
| Bleeding events | 18 | 14 | 6.3 (-6.7 to 24.9) | 1.25 (0.74 to 1.97) |



**Main strength**

Population-based

**Main weaknesses**

'Healthy vaccinee' effect

Potential increased surveillance

**Limitations**

No data on individuals >65 years

No data on risks after second jab

Insufficient data on non-Caucasian individuals

# Risk : Benefit

## CONCLUSIONS

Among recipients of ChAdOx1-S, increased rates of venous thromboembolic events, including cerebral venous thrombosis, were observed. For the remaining safety outcomes, results were largely reassuring, with slightly higher rates of thrombocytopenia/coagulation disorders and bleeding, which could be influenced by increased surveillance of vaccine recipients. The absolute risks of venous thromboembolic events were, however, small, and the findings should be interpreted in the light of the proven beneficial effects of the vaccine, the context of the given country, and the limitations to the generalisability of the study findings.

A few ~~pharmacological~~ frustrations…

~~methodological~~

philosophical

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# Thromboembolism and the Oxford-AstraZeneca vaccine

## New study finds a link, but vaccination remains overwhelmingly the safest option

Rafael Perera, [1] John Fletcher[2]

Medicine regulators, health professionals, and the public are anxious to know whether the available vaccines against covid-19 are safe, and in particular whether the Oxford-AstraZeneca vaccine causes unusual thromboembolic events. In a linked paper, Pottegård and colleagues (doi:10.1136/bmj.n1114) compared observed rates of vascular and thromboembolic events in large cohorts of adults who received the Oxford-AstraZeneca vaccine in Denmark and Norway, with expected rates derived from the general populations of the same countries.[1]

They found that for arterial events, the number of observed outcomes was similar to that of expected (83 observed events *v* 86 expected), but people given the vaccine experienced more venous thromboembolic events than expected (59 observed *v* 30 expected). Seven of these events were cerebral venous thrombosis, a life threatening condition identified in recent weeks as a potential complication of the Oxford-AstraZeneca vaccine. Seven cases among 281 264 people vaccinated is a low absolute rate, but still 20 times the rate expected in the general population, and equivalent to an estimated 2.5 extra cases for every 100 000 people vaccinated.

Faced with an association of this relative magnitude that appears to confirm a previous safety signal, prompts three important questions. Is this association likely to be real? How should we interpret Pottegård and colleagues' findings? What more do we need to know?

It seems quite likely that thromboembolic events were

control group is almost impossible in a study such as this, since important differences between vaccinated and unvaccinated cohorts will exist simply because of the selection process for vaccination.

The authors acknowledge that the lower than expected mortality observed in vaccinated cohorts is likely to be a consequence of selection bias, and they suggest that the association with venous thromboembolism may not be. It is a strength that this study was conducted specifically to investigate a possible association between vaccination and cerebral venous thrombosis—and found one.

The interpretation of Pottegård and colleagues' findings as either reassuring or concerning depends critically on the type of comparisons. While the rate of venous thromboembolism in vaccinated cohorts was higher than the background rate, we know that all vaccines against covid-19, including the Oxford-AstraZeneca vaccine, reduce mortality from covid-19 substantially. The absolute magnitude of this benefit varies with the proportion of people exposed to infection over time, but we do know from vaccine trials that mortality reduction far outweighs any risk of adverse events. We also know that covid-19 is itself associated with cerebral venous thrombosis—an estimated 4.3 events per 100 000 infections, which is higher than the 2.5 per 100 000 reported by Pottegård and colleagues.[2]

Comparing vaccine adverse event rates to background population rates is appropriate for rare diseases, since most people are never exposed to the disease but are

we do know from vaccine trials that mortality reduction far outweighs any risk of adverse events. We also know that covid-19 is itself associated with cerebral venous thrombosis—an estimated 4.3 events per 100 000 infections, which is higher than the 2.5 per 100 000 reported by Pottegård and colleagues.[2]

2 Taquet M, Husain M, Geddes JR, Luciano S, Harrison PJ. Cerebral venous thrombosis: a retrospective cohort study of 513 284 confirmed COVID-19 cases and a comparison with 489 871 people receiving a COVID-19 mRNA vaccine. https://osf.io/a9jdq/


**Professor bag AstraZeneca-rapport er bekymret for at skabe vaccine-skepsis**

Synes godt om · Kommenter · Del

Alaa Burqhle og 60 andre · 37 kommentarer · 7,2 tusind visninger

Signal?

Process

Decision

RESEARCH

OPEN ACCESS

FAST TRACK

Use of N-nitrosodimethylamine (NDMA) contaminated valsartan products and risk of cancer: Danish nationwide cohort study

Anton Pottegård,[1] Kasper Bruun Kristensen,[1] Martin Thomsen Ernst,[1] Nanna Borup Johansen,[2] Pierre Quartarolo,[3] Jesper Hallas[1]

RESEARCH

OPEN ACCESS

Check for updates

FAST TRACK

Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population based cohort study

Anton Pottegård,[1] Lars Christian Lund,[1] Øystein Karlstad,[2] Jesper Dahl,[2] Morten Andersen,[3] Jesper Hallas,[1] Øjvind Lidegaard,[4,5] German Tapia,[2] Hanne Løvdal Gulseth,[2] Paz Lopez-Doriga Ruiz,[2] Sara Viksmoen Watle,[2] Anders Pretzmann Mikkelsen,[4,5] Lars Pedersen,[6,7] Henrik Toft Sørensen,[6,7] Reimar Wernich Thomsen,[6,7] Anders Hviid[3,8]

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ORIGINAL REPORT

Generic switching of warfarin and risk of excessive anticoagulation: a Danish nationwide cohort study[†]

Maja Hellfritzsch[1,*], Jette Rathe[2], Tore Bjerregaard Stage[1], Steffen Thirstrup[3,4], Erik L. Grove[5], Per Damkier[1,2] and Anton Pottegård[1]

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