Study Report

P2-C3-001

DARWIN EU® - EHDS Use Case: Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the OMICRON variant

03/09/2024

Version 3.0

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Study Title	DARWIN EU® - EHDS Use Case: Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the OMICRON variant
Study Report Version	V3.0
Date	03/09/2024
EU PAS number	EUPAS106679
Active substance	COVID-19 vaccines
Medicinal product	ChAdOx1, BNT162b2, Ad26.COV2.S, mRNA-1273
Research question and objectives	Research question: The aim of the study was to contextualise the risk of venous and arterial thromboembolic events associated with COVID-19, during the Omicron period, and SARS-CoV-2 vaccination. The research objectives which were addressed incrementally to support the project aim were: 1. To estimate the background incidence rate of venous and arterial thromboembolic events among the general pre-pandemic population. 2. To estimate the incidence rate of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, and 90- and 180-days during the Omicron period, stratified by prior SARS-CoV-2 vaccination and prior infection status. 3. To estimate the incidence rate of venous and arterial thromboembolic events among patients with SARS-CoV-2 vaccination within 30-, 60-, 90- and 180-days, stratified by prior infection status. 4. To estimate a) the association between clinical risk factors and prior SARS-CoV-2 vaccination on the incidence rate of venous and arterial events among patients with COVID-19 and b) the impact that thromboembolic events have on worsening severity of COVID-19 during the Omicron period. 5. To estimate incidence rate ratios for venous and arterial thromboembolic events among patients with COVID-19 and people vaccinated against SARS-CoV-2, compared to the background population using incidence rates estimated in objectives 1 to 3.
Countries of study	Spain, The UK, Germany, The Netherlands, and Estonia
Author	Xintong Li, Martí Català Sabaté, Annika Jödicke

1. DESCRIPTION OF STUDY TEAM

Study Team role	Names	Organisation
Principal Investigators	Martí Català Sabaté Xintong Li	*University of Oxford*
Data Scientist/Statisticians	Martí Català Sabaté Edward Burn	*University of Oxford*
Epidemiologists	Xintong Li Annika Jödicke	*University of Oxford*
Clinical Domain Expert	Albert Prats-Uribe	*University of Oxford*
Data partner name*	**Data Partner member name(s)**	**Organisation(s)**
IQVIA Germany	James Brash	*IQVIA*
SIDIAP	Talita Duarte Salles	*IDIAP JGol*
Estonian Biobank	Raivo Kolde	*University of Tartu*
IPCI	Mees Mosseveld	*Erasmus MC*
CPRD GOLD	Antonella Delmestri	*University of Oxford*

*Data partners' role is only to execute code at their data source, review and approve their results. These people do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for these people is not needed.

2. DATA SOURCES

This study was conducted using routinely collected data from 5 databases in 5 European countries. All databases were previously mapped to the OMOP CDM.

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
3. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. Estonian Biobank (EBB), Estonia*
5. Clinical Practice Research Datalink (CPRD) GOLD

*Estonian Biobank (EBB) only contributed to Objective 1

3. ABSTRACT

Title

DARWIN EU® - EHDS Use Case: Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the Omicron variant.

Rationale and Background

Coronavirus disease-2019 (COVID-19) patients are at increased risk of venous and arterial thromboembolic events. SARS-CoV-2 variants have evolved during the COVID-19 pandemic with Omicron being the dominant variant (as of December 2021). There is a need to better understand the risks of thromboembolic events

among patients with COVID-19 associated with the Omicron variant, their impact on prognosis, and whether risk factors for such events remain the same, overall and in the context of prior COVID-19 infection, prior SARS-CoV-2 vaccination and among certain subgroups.

This study was one of the five use cases selected in the pilot project to test and inform HealthData@EU frameworks. HealthData@EU pilot project is the European Health Data Space (EHDS) Pilot project that aims to investigate and establish an infrastructure and data ecosystem for the secondary use of health data to facilitate research, innovation and better policy making; and assess the ability to scale towards a Union-wide infrastructure, as a core component of the EHDS.

Objectives

1. To estimate the background incidence rate of venous and arterial thromboembolic events among the general pre-pandemic population.
2. To estimate the incidence rate of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, 90- and 180-days during the Omicron period, stratified by prior SARS-CoV-2 vaccination and prior infection status.
3. To estimate the incidence rate of venous and arterial thromboembolic events among patients with SARS-CoV-2 vaccination within 30-, 60-, 90- and 180-days, stratified by prior infection status.
4. To estimate a) the association between clinical risk factors and prior SARS-CoV-2 vaccination on the incidence rate of venous and arterial events among people with COVID-19 and b) the impact that thromboembolic events have on worsening severity of COVID-19 during the Omicron period.
5. To estimate incidence rate ratios for venous and arterial thromboembolic events among patients with COVID-19 and different SARS-CoV-2 vaccine doses compared to the background population, using incidence rates estimated in objectives 1 to 3.

Research Methods

Study type: Population-level cohort.

Data sources: The study included data from the following DARWIN EU data partners available at the time of study execution: CPRD GOLD (UK), IQVIA Germany (Germany), IPCI (Netherlands), SIDIAP (Spain), Estonian Biobank (Estonia). Databases contributed to the analysis of one or more of the objectives depending upon data component availability. A random sample of one million individuals was used in SIDIAP.

Study population

We included the pre-pandemic cohort from years 2017 through 2019; People with COVID-19 during the time when Omicron was the dominant variant; and people vaccinated against SARS-CoV-2. All participants were required to be visible in the data source since 1st January 2020 to have full records on infection and vaccination history.

Analyses

We calculated background incidence rates of venous and arterial thromboembolic events among the general pre-pandemic population (Objective 1), incidence rates of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, 90- and 180-days of diagnosis during the Omicron period (Objective 2), and incidence rates of venous and arterial thromboembolic events among patients within 30-, 60-, 90- and 180-days of SARS-CoV-2 vaccination (Objective 3).

We used cause-specific Cox models to calculates hazard ratios for the association between potential risk factors and developing venous and arterial thromboembolic events (VTE and ATE) after COVID-19 infection

during the Omicron period (Objective 4a). We used cause-specific Cox model within multistate framework to estimate the hazard ratios associated with having ATE or VTE and worsening COVID-19. (Objective 4b)

We calculated crude incidence rate ratios (IRR) using the rates estimated from objectives 1 to 3, and standardized incidence rate ratios (SIR) compared to the background population using indirect standardization with age and sex (Objective 5).

Analyses were stratified by prior COVID-19 infection occurrence and prior SARS-CoV-2 vaccination (COVID-19 and vaccine cohorts only), age, sex, and by whether patients are immunocompromised on the index date.

Results

CPRD GOLD, IPCI, IQVIA Germany contributed to all study objectives whilst Estonian Biobank contributed to Objective 1 only, and SIDIAP to Objectives 1 and 2 only. The background cohort included over 24 million individuals (CPRD GOLD: 5,278,189, IPCI: 1,589,237, IQVIA DA Germany: of 16,667,650, SIDIAP 746,737 and Estonia Biobank: 207,657). A total of 1,478,876 individuals with a COVID-19 infection during the Omicron period were included in the "COVID-19" cohort in this study (CPRD GOLD: 248,847, IPCI: 330,200, IQVIA DA Germany: 696,094, SIDIAP: 200,563). In addition, 4,901,863 individuals who received at least one dose of a COVID-19 vaccine since the pandemic were included in the "vaccinated" cohort this study (CPRD GOLD: 2,374,109, IPCI: 656,664, IQVIA DA Germany: 1,311,394, SIDIAP: 559,696).

Age, sex specific background incidence rates were heterogeneous between the included databases. For example, the background rates of VTE among females aged 75–84 years old ranged from 411 [95% confidence interval: 400-423] per 100,000 person-years (pys) in IQVIA DA Germany to 1234 [1084-1400] in Estonia Biobank. We also observed between database heterogeneity of incidence rates among the infected and vaccinated cohorts, however, the extent of this heterogeneity was smaller. For example, among the 75-84 years old group, incidence rates of VTE per 100,000 pys during the first 30 days infection ranged from 2101 [1332-3153] in CPRD GOLD, to 2292 [1696-3030] in IQVIA DA Germany. Use of corticosteroids or antithrombotics, presence of comorbidities (including obesity and diabetes), and having a prior history of ATE or VTE events were associated with a higher hazard of developing ATE or VTE events among people with COVID-19 during the period when Omicron was the dominant variant. The multistate model showed that having VTE on or after COVID-19 hospitalisation was associated with higher hazard ratio of death.

Crude IRRs varied between age, sex, infection history, and vaccination status within each database. Compared with the background population, the COVID-19 infected cohort showed higher SIR for both ATE and VTE after age-sex standardisation, which persisted up to 180 days following diagnosis of COVID-19 infection during the Omicron period. Increased SIR were also observed for individual conditions included in the composite outcomes, including pulmonary embolism and heart failure. Among people in the vaccinated cohort, those individuals who received a first or second dose of the ChAdOx1 vaccine showed higher SIR of ATE when using a longer follow-up window. We observed increased SIR of VTE among those who received a first dose ChAdOx1 vaccine within 90 or 180 days after vaccination but not in shorter period. No increased SIR of VTE were seen in other brand-dose stratification in both CPRD GOLD and IPCI data compared to the background population in the main analysis.

Conclusion

As one of the use cases of the EHDS pilot project, this study aimed to contextualise coagulopathy risk among people infected with COVID-19 during the Omicron period compared to the background population risk using simple standardisation for age and sex. Risk factors for coagulopathic events associated with COVID-19 during the omicron period remained similar and infection was associated with a higher standardised incidence ratio of arterial and venous events compared to the background population and people vaccinated. Heterogeneity in the absolute rate of events between data sources may be related to different factors such as the inclusion

of populations with different baseline risk, whether data sources had a primary care and secondary care data linkage, and coding practices by health care professionals. The use of routinely-collected health data mapped to the OMOP common data model analysed through a federated approach for DARWIN EU allowed for a faster generation of real-world evidence. .

4. LIST OF ABBREVIATIONS

Abbreviation	Name
ATC	Anatomical Therapeutic Chemical Classification
EHDS	European Health Data Space
CDM	Common Data Model
COVID-19	Coronavirus disease-2019
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
EHR	Electronic Health Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICU	Intensive care unit
LPD	Longitudinal Patient Data
MACE	Major cardiovascular events
OMOP	Observational Medical Outcomes Partnership
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VTE	Venous thromboembolic events
ATE	Arterial thrombotic events
RT-PCR	Reverse transcription polymerase chain reaction
IRR	Incidence rate ratio
SIR	Standardized incidence rate ratio
HR	Hazard ratio
CPRD	Clinical Practice Research Datalink
IPCI	Integrated Primary Care Information
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine
HIV/AIDS	Human immunodeficiency virus/ acquired immunodeficiency syndrome

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Draft Study Protocol	June 2023	
Final Study Protocol	July 2023	18/07/2023
Creation of Analytical code	October 2023	01/10/2023
Execution of Analytical Code on the data	December 2023	01/12/2023
Draft Study Report submitted to EMA	January 2023	15/01/2023
Final Study Report approved by EMA		14/02/2024
Final Study Report for archiving		22/05/2024

7. RATIONALE AND BACKGROUND

European Health Data Space

The HealthData@EU pilot project is the European Health Data Space (EHDS) Pilot project that aims to investigate and provide recommendations on an infrastructure and data ecosystem for the secondary use of health data in Europe for research, innovation and better policy making. The HealthData@EU pilot will assess the ability to scale towards a Union-wide infrastructure as a core component of the EHDS. The present study was one of the five use cases selected to test and inform HealthData@EU pilot frameworks.[1]

Occurrence of venous and arterial thromboembolic events among people with COVID-19

Coronavirus disease-2019 (COVID-19) may cause both venous and arterial thromboembolic events due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[2] A number of observational studies and case series conducted in the early phase of the pandemic have reported high rates of venous and arterial thromboembolic events among patients hospitalised with COVID-19. In a case series of COVID-19 patients admitted to ICU in the Netherlands, the incidence of thrombotic complications was found to be 31%,[3] while a similar case series from a hospital in Italy found the incidence of thromboembolic events to be 28%.[4] Meanwhile, the rate of venous thromboembolism was found to be as high as 69% for a case series from two French intensive care units (ICU).[5]

Studies assessing the incidence of thromboembolic events among people with COVID-19 during the early period of the pandemic were conducted in relatively small study populations, partly constrained by data availability at the time, and predominantly focused on hospitalised populations. Consequently, uncertainty

remained around the incidence of thromboembolic events among patients with COVID-19. Several larger studies examining coagulopathy risk have since been conducted using routinely collected health data. One study from Sweden demonstrated an increased risk of deep vein thrombosis (DVT) up to 70 days post-COVID-19 diagnosis and an increased risk of pulmonary embolism up to 110 days post-COVID-19 diagnosis.[6] Meanwhile, another study from England reported an increased risk of venous thromboembolism up to 49 weeks post-COVID-19.[7] Studies have also observed that the elevated risk of thromboembolic events associated with COVID-19 infection may be attenuated following SARS-CoV-2 vaccination.[8]SARS-CoV-2 variants have changed over time, with Omicron now widely established as the dominant SARS-CoV-2 variant. On 26 November 2021, the European Centre for Disease Prevention and Control classified the Omicron B.1.1.529 variant as a variant of concern due to concerns regarding immune escape and potentially increased transmissibility compared to the SARS-CoV-2 delta variant.[9] However, existing studies largely examined COVID-19 during the period when Omicron was not the dominant variant. The risk of venous and arterial thromboembolic events with Omicron COVID-19 is therefore less well studied, particularly in the context of exposure to either prior COVID-19 infection or prior SARS-CoV-2 vaccinations.

Thromboembolic events and worsening of COVID-19 during the Omicron period

COVID-19 patients with thromboembolic events are at increased risk of worse outcomes, with a systematic review finding a strong association between cardiovascular and thromboembolic events and poor prognosis among people with COVID-19.[10] However, it has been suggested that the Omicron variant has a milder course and therefore, subsequent coagulopathy risk may differ. This may be further influenced by prior SARs-CoV-2 vaccination. As with measuring the incidence of thromboembolic events themselves, routinely collected data may also be used to describe the risks of worsening among people with COVID-19 during the period when Omicron was the dominant variant.

Risk factors for thromboembolic events among people with COVID-19 during the Omicron period

Various patient factors have been associated with worse outcomes among people with COVID-19 that occurred during the early stages of the pandemic when Omicron was not the dominant variant. Older age, male sex, hypertension, diabetes, and being overweight or obese have all been reported to be associated with an increased risk of hospitalisation and mortality among people with COVID-19.[11–17] Many of these same factors have also previously been seen to predispose individuals to thromboembolic events.[18,19] In one study a set of pre-existing cardiovascular risk factors were associated with increased mortality among people with COVID-19, independent of patients´ age and sex.[20] Whilst the associations between such risk factors and thromboembolic events among patients with SARS-CoV-2 variants has been studied, this largely included data on COVID-19 during the early stages of the pandemic when Omicron was not the dominant variant. Information is limited on whether risk factors for venous and arterial thromboembolic events remain the same for COVID-19 associated with the Omicron variant, and to what degree this may be influenced by prior SARs-CoV-2 vaccination and the impact of immunosuppression.

Contextualising incidence rates for thromboembolic events with COVID-19 during the Omicron period

Two studies have compared incidence rates of thrombosis and thrombocytopenia after vaccination against SARS-CoV-2 and with COVID-19 using data from the United Kingdom and Spain. These studies calculated incidence rates of thromboembolic events in people vaccinated against SARS-CoV-2 and in people with COVID-19 infection and compared them to pre-pandemic rates in a historic background cohort.[21,22] Compared to pre-pandemic rates, standardised incidence ratios were elevated for venous thromboembolism shortly following both initial vaccination against SARS-CoV-2 and for COVID-19 infection, although to a much greater extent with COVID-19 infection. It is uncertain however to what extent evidence generated by these studies is generalisable to COVID-19 infection during the Omicron period.

Therefore, understanding the risks of arterial and venous thromboembolic events among patients with COVID-19 associated with the Omicron variant, their impact on prognosis, and whether risk factors for such events remain the same may support public health decision making.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of the study was to contextualise the risk of venous and arterial thromboembolic events associated with COVID-19, during the Omicron period and in the context of SARS-CoV-2 vaccination. To do so, the research objectives were:

1. To estimate the background incidence rate of venous and arterial thromboembolic events among the general pre-pandemic population.
2. To estimate the incidence rate of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, and 90- and 180-days during the Omicron period, stratified by prior SARS-CoV-2 vaccination and prior infection status.
3. To estimate the incidence rate of venous and arterial thromboembolic events among patients with SARS-CoV-2 vaccination within 30-, 60-, 90- and 180-days, stratified by prior infection status.
4. To estimate a) the association between clinical risk factors and prior SARS-CoV-2 vaccination on the incidence rate of venous and arterial events among people with COVID-19 and b) the impact that thromboembolic events have on worsening severity of COVID-19 during the Omicron period.
5. To estimate incidence rate ratios for venous and arterial thromboembolic events among patients with COVID-19 and different SARS-CoV-2 vaccine doses compared to the background population, using incidence rates estimated in objectives 1 to 3.

9. RESEARCH METHODS

9.1 Study Type and Study Design

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Drug/Vaccine Safety Studies	New User Cohorts	Complex

9.2 Study Setting and Data Sources

The selection of databases for this study was performed based on data reliability and relevance for the proposed research question among those databases onboarded and available within DARWIN EU. The selected databases fulfil the criteria required for the availability of key information on exposures, outcomes, and covariates, while covering different settings and regions of Europe. Databases contributed to the analysis of one or more of the objectives depending upon data component availability.

Records on COVID-19 infection and vaccination (needed for objectives 2 to 5) were available in all purposed databases except Estonia Biobank. Previously published studies showed that these databases can generate reliable evidence on COVID-19 research. [21,22] Specifically, the availability of COVID-19 tests results, and linked vaccination records through national/regional immunisation program (CPRD GOLD, SIDIAP) increased the reliability of the identified study exposures. Inpatient admission and intensive care use (needed for objective 4) were available in SIDIAP only, which provides primary care records with linked hospitalisation information.

Table 1. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (if relevant)*	Feasibility count of disease (if relevant)*	Calendar period covered (y-m-d)
UK	CPRD GOLD	Complete records on SARS-CoV-2 infection, COVID-19 vaccination, and outcome events of interest (objectives 1 to 5, exclude 4b on worsening COVID-19)	primary care	EHR	3M	COVID-19: 360198, ChAdOx1: 2360815, Ad26.COV2.S: 3034, ChAdOx1: 2822947, mRNA -1273: 311069	VTE as example for all databases: 219844	2022-12-15
Germany	IQVIA Germany	Complete records on SARS-CoV-2 infection, COVID-19 vaccination, and outcome events of interest (objectives 1 to 5, exclude 4b on worsening COVID-19)	outpatient visits of primary care physicians and a sample of specialists	EHR	8.5M	COVID-19: 1723895, ChAdOx1: 189261, Ad26.COV2.S: 83771, ChAdOx1: 2614482, mRNA -1273: 428057	392674	2023-04-01
The Netherlands	IPCI	Complete records on SARS-CoV-2 infection, COVID-19 vaccination, and outcome events of interest (objectives 1 to 5, exclude 4b on worsening COVID-19)	Primary care	EHR	1.39M	COVID-19: 941329, AstraZeneca: 178192, Ad26.COV2.S: 19645, ChAdOx1: 1173104, mRNA -1273: 463315	57087	2023-06-30
Estonian	Estonian Biobank	Geographic representative (objective 1 only)	Biobank	EHR	0.2M	79411 (COVID-19)	25766	2022-12-31
Spain	SIDIAP	Complete records on SARS-CoV-2 infection, Covid-19 vaccination, and outcome events of interest; Include inpatient admission information. (objectives 1 to 5)	primary care database + linkage to hospital data	EHR	5.8M	Covid-19: 3865976, AstraZeneca: 1152432, Janssen: 257806, Pfizer: 6548545, Moderna:3371395	101966	2023-06-30

**Feasibility counts were estimated at the feasibility assessment stage of this study.*

9.3 Study Period

The start of the study period was the time of when the Omicron variant became the dominant variant across Europe, commencing from 1st December 2021. The end of the study period was the last available date of data collection for each contributing dataset.

9.4 Follow-up

An overview of each cohort is presented in **Table 2** with further details described in Section 9.5. For cohort 1, follow-up began on January 1st, 2017, and continued up until the first of any of the following: outcome of interest, end of observation period/ data availability, death or December 31st 2019.

For cohorts 2 to 5, follow-up began on a person's respective index date and continued up until the first of any of the following: outcome of interest, end of observation period/ data availability, death, or either 30-, 60-, 90- or 180-days after the index date (depending upon the follow-up time period of interest).

Table 2. Operational Definition of Time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting1	Code Type	Diagnosis position	Incident with respect
Background population (cohort 1*)	January 1st 2017 or after when individuals have 365 days of prior history	Multiple	General pre-pandemic population	n/a	n/a	n/a	n/a	n/a
SARS-CoV-2 infection cohort (cohort 2*)	Test date of the positive test result for SARS-CoV-2, or date of clinical recorded coded diagnosis of COVID-19	Multiple	Incident within the Omicron period	No COVID-19 infection within 3 months prior	OP	SNOMED codes (see appendix)		
Hospitalised with COVID-19 cohort (cohort 3*)	Date the date of hospital admission	Multiple	Incident within the Omicron period	No hospitali-sation within 3 months prior	IP	SNOMED codes (see appendix)		
Intensive care service cohort (cohort 4*)	Date of the following depends on availability in data, in descending priority: 1.) Date of intensive care service (mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation (ECMO)). 2.) Date of ICU admission. 3.) Date of hospital admission.	Multiple	Incident within the Omicron period	n/a	IP	SNOMED (see appendix)	n/a	COVID-19 hospitalized
Vaccinated cohort (cohort 5*)	Date of vaccination record	Multiple	n/a	21 days	OP	RxNorm codes (see appendix)		

**Cohorts number as described in 8.5 study population with inclusion and exclusion criteria.*
1 IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

9.5 Study Population with inclusion and exclusion criteria

Five non-mutually exclusive study cohorts for the analyses were defined:

1. **General population cohort for the estimation of pre-pandemic background rates**
    - Individuals started contributing as of 1st January 2017, or when they had at least 365 days of data availability.
    - Follow-up for this cohort ran up to 31 December 2019.
2. **Persons tested positive for SARS-CoV-2 or with a clinical diagnosis of COVID-19 during the Omicron period**
    - had either a positive test result for SARS-CoV-2 or a clinical coded diagnosis of COVID-19 on or after 1st December 2021 (with the index date being whichever date comes first if both occur)
    - had no positive test result for SARS-CoV-2 or clinical diagnosis of COVID-19 within 3 months prior to the index date.
    - had at least 365 days of data availability prior to index date
3. **Persons hospitalised with COVID-19 during the Omicron period**
    - had a hospitalisation on or after 1st December 2021 (with the index date the date of hospital admission),
    - had a record of a clinical coded diagnosis of COVID-19 or a positive test result for SARS-CoV-2 in the period between 3 weeks prior to and up to 3 days following the index date.
    - had no diagnosis of COVID-19 or a positive test result for SARS-CoV-2 between 3 months and 3 weeks prior to index date.
    - had no COVID-19 hospitalisation within 3 weeks prior to the index date.
    - had at least 365 days of data availability prior to index date
4. **Persons requiring intensive services during a hospitalisation with COVID-19 during the Omicron period**
    - had intensive services initiated during a hospitalisation as described in cohort 3 (with the index date the date at which intensive services were initiated as described in **Table 2**)
    - patients had a confirmatory coded diagnosis or positive test result of COVID-19 (both as defined above) within a time window from 3 weeks to their index date up to three days following their index date.
    - had at least 365 days of data availability prior to index date
5. **Persons vaccinated against SARS-CoV2 infection**
    - had a vaccination record identified by brand (with the index date the date of vaccination record)
    - had no record of vaccination during the 21 days prior to index date of each dose. A 21-day gap between two consecutive records of vaccine was required to avoid repeated records of the same vaccine. The 21-days period was chosen based on the minimal recommended dosing schedule of the primary vaccine course in participated databases (Spain).

- have at least 365 days of data availability prior to index date

Cohorts 2 to 5 were stratified by prior COVID-19 infection status and for cohorts 2 to 4 also by prior SARS-CoV-2 vaccination status. All cohorts were additionally stratified by whether patients were immuno-compromised on the index date. People in each of the five cohorts were required to have at least a year of observed history in the database prior to their index date. This was to ensure a sufficient time period to identify health conditions and medication use prior to individuals´ index dates.

Table 3. Operational Definitions of Inclusion Criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations	Measurement characteristics validation	Source for algorithm
Observation period of 365 days prior entry (all 5 cohorts)	Study participants were required to have 365 days prior history observed before contributing observation time	before	[-365,0]	n/a	n/a	n/a	All individuals within the selected databases	n/a	n/a
COVID-19 infection (cohort 2)	A positive test result for SARS-CoV-2 or a clinical coded diagnosis of COVID-19 on or after 1st December 2021 (with the index date being whichever date comes first if both occur)	before	n/a	Primary care	SNOMED	n/a	All individuals within the selected databases	n/a	n/a
COVID-19 hospitalized (cohort 3)	A hospitalisation on or after 1st December 2021 (with the index date the date of hospital admission), a record of a clinical coded diagnosis of COVID-19 or a positive test result for SARS-CoV-2 in the period between 3 weeks prior to and up to 3 days following the index date	before	[-21, 3]	Primary care, secondary care	SNOMED	n/a	All individuals within the selected databases	n/a	n/a
COVID-19 intensive care use (cohort 4)	Intensive services initiated during a hospitalisation as described in the "COVID-19 hospitalized" criterion	before	During hospitali-sation	Intensive care	SNOMED	n/a	Individuals who met the "COVID-19 hospitalized" criteria	n/a	n/a

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations	Measurement characteristics validation	Source for algorithm
COVID-19 vaccinated (cohort 5)	A vaccination record identified by brand (with the index date the date of vaccination record)	before	n/a	Primary care	RxNorm	n/a	All individuals within the selected databases	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table 4. Operational Definitions of Exclusion Criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations	Measurement characteristics validation	Source for algorithm
Prior COVID-19 (cohort 2-4)	. Individuals were excluded if they had positive test result or clinical coded diagnosis of COVID-19 within 3 months prior to the index date (date of COVID-19 in Omicron).	After	[-91,-1]	OP, IP	SNOMED, RxNorm	n/a	SARS-CoV-2 infected, hospitalized (cohorts 2, 3, 4)	n/a	n/a
Hospitalisation (cohort 3)	Individuals were excluded if they had positive test result or clinical coded diagnosis of COVID-19 between 3 months and 3 weeks prior to index date (date of date of hospital	After	COVID-19 [-91, -21]; Hospitalisation [-21,0]	IP	SNOMED	n/a	COVID-19 hospitalized (cohorts 3, 4)	n/a	n/a

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations	Measurement characteristics validation	Source for algorithm
	admission). Individuals were excluded if they had COVID-19 hospitalisation within 3 weeks prior to the index date.								
Vaccinated (cohort 5)	No vaccine records in the 21 days prior to index vaccine	After	[-21, -1]	OP	RxNorm	n/a	Vaccinated (cohort 5)	n/a	n/a
Prior outcomes (all cohorts)	Exclude people with the outcome of interests during the 183-day prior to index (primary analysis, different washout period will be applied in sensitivity analysis)	After	[-183, 0]	IP, OP	SNOMED	n/a	(cohorts 1-5)	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6 Variables

9.6.1 Exposures

Positive test result for SARS-CoV-2

RT-PCR tests have high sensitivity and specificity for SARS-CoV-2. However, as a result of changes in the availability of population wide RT-PCR and home self-reported lateral flow tests during the Omicron period, it may not be possible to exclusively use RT-PCR tests when identifying positive test results in all datasets.[23] All positive test results for SARS-CoV-2 observable in the database were therefore included for the primary analysis, with documentation of what type of test it was to allow sensitivity analysis restricted to RT-PCR diagnosed patients as needed.

Clinical diagnosis of COVID-19

Whilst testing for SARS-CoV-2 was commonly performed in some of the countries represented in this study, clinical diagnoses of COVID-19 were also made for many individuals. Diagnostic codes compatible with COVID-19 were therefore identified, with the recorded date being used in the analyses.

Hospitalisation with COVID-19

Patients hospitalised with COVID-19 were identified based on having a hospitalisation along with a confirmatory diagnosis or test result of COVID-19 (both as defined above) within a time window from 21 days prior to admission up to three days following their admission. This time window has been chosen to include those who had the diagnosis made prior to their hospitalisation and to allow for a delay in test results or diagnoses to be made or recorded, while excluding individuals with hospital-acquired COVID-19.

Intensive care services during a hospitalisation with COVID-19

Patients who received intensive care services during a hospitalisation with COVID-19 were identified based on having a hospitalisation where they were admitted to the intensive care unit, received mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation (ECMO). If the date at which the intervention was initiated was observable in the database, this date was used as the index date. If the date at which the intervention was initiated is not observed (for example, if such interventions are recorded at time of discharge) then the date of ICU admission, or hospital admission if ICU admission is not recorded, was used as the index date.

Vaccination against SARS-CoV-2

COVID-19 vaccine exposure was defined as the date of a vaccination record. Vaccination exposures was defined by dose (1st, 2nd, 3rd, 4th etc.) and brand. The standard concepts used to define vaccine are available in the appendix.

Table 5. Operational Definitions of Exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics	Source of algorithm
Positive test result for SARS-CoV-2	All positive test results for SARS-CoV-2 observable in the database, including test type.	3 months	n/a	OP, IP	SNOMED, LOINC, or OMOP extended vocabulary	n/a	All meet observation period criteria	n/a	n/a	n/a
Clinical diagnosis of COVID-19	Diagnostic codes compatible with COVID-19 were identified in addition	3 months	n/a	OP, IP	SNOMED	n/a	All meet observation period criteria	n/a	n/a	n/a
COVID-19 hospitalisation	Hospitalisation along with a confirmatory diagnosis or test result of COVID-19 (both as defined above) within a time window from 21 days prior to admission up to three days following their admission.	3 months	n/a	IP	SNOMED		All meet observation period criteria	n/a	n/a	n/a
COVID-19 intensive care services	Intensive care services received during a hospitalisation with COVID-19 were identified based on having a hospitalisation where people were admitted to the intensive care unit, received mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation (ECMO).	n/a	During hospitalisation	IP	SNOMED	n/a	All patients meet the COVID-19 hospitalisation criteria	n/a	n/a	n/a

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics	Source of algorithm
Vaccination against SARS-CoV-2	COVID-19 vaccine exposure was identified by the date of a vaccination record. Vaccination exposures were defined by dose (1st, 2nd, 3rd, 4th etc.) and brand.	21 days	n/a	OP	SNOMED	n/a		n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient, [2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter

9.6.2 Outcomes

Venous thromboembolic events

In the primary analysis, venous thromboembolic events were identified by diagnostic codes for pulmonary embolism or deep vein thrombosis. In a secondary analysis pulmonary embolism and deep vein thrombosis were assessed separately. We also assessed portal vein thrombosis, splanchnic venous thrombosis (SVT) and cerebral venous sinus thrombosis separately.

Arterial thromboembolic events

In the primary analysis, arterial thromboembolic events were identified by an acute myocardial infarction or acute ischemic stroke. In a secondary analysis acute myocardial infarction and acute ischemic stroke assessed separately. We also identified stroke in general, for which we included both ischemic, haemorrhagic and non-specifically recorded stroke.

Cardiovascular events

Instances of heart failure, cardiac arrhythmia, and angina were identified. In addition, major cardiovascular events (MACE) were identified by heart failure, acute myocardial infarction, or stroke, or the occurrence of sudden cardiac death. As a sensitivity analysis, we required that events were identified by hospitalisation admission or discharge records.

Table 6. Operational Definitions of Outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study:	Measurement characteristics validation	Source of algorithm
Venous thromboembolic events	Venous thromboembolic events were identified by diagnostic codes for pulmonary embolism or deep vein thrombosis	Yes	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Arterial thromboembolic events	Arterial thromboembolic events were identified by diagnostic codes for acute myocardial infarction or acute ischemic stroke	Yes	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Cardiovascular events	Heart failure, cardiac arrhythmia, and angina were identified by diagnostic codes	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Major cardiovascular events (MACE)	MACE were identified by diagnostic codes for heart failure, acute myocardial infarction, or stroke, or the occurrence of sudden cardiac death.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Pulmonary embolism	Incident case of pulmonary embolism defined with washout window.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Deep vein thrombosis	Incident case of deep vein thrombosis defined with washout window.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Portal vein thrombosis	Incident case of portal vein thrombosis defined with washout window.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Splanchnic venous thrombosis (SVT)	Incident case of SVT defined with washout window.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Cerebral venous sinus thrombosis (CVST)	Incident case of CVST defined with washout window.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study:	Measurement characteristics validation	Source of algorithm
Acute myocardial infarction	Incident case of acute myocardial infarction defined with washout window.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Acute ischemic stroke	Incident case of acute ischemic stroke defined with washout window.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a
Stroke in general	Stroke in general was identified by diagnostic codes for ischemic, haemorrhagic or non-specifically recorded stroke.	No	Binary, time-to-event	[-183, -1]	IP, OP	SNOMED	n/a	All included cohorts	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable, [2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

9.6.3 Other covariates, including confounders, effect modifiers and other variables

Location at index date

For cohort 2 (persons tested positive for SARS-CoV-2 or with a clinical diagnosis of COVID-19) and cohort 5 (persons vaccinated against SARS-CoV2 infection) we identified whether individuals were currently hospitalised on their index date. By definition, all people in cohort 3 (persons hospitalised with COVID-19) and cohort 4 (persons requiring intensive services during a hospitalisation with COVID-19) were hospitalised on their index date.

Demographics

Patients´ age at index date and sex were identified. Age groups were also categorised using the following groupings: <20; 20-44; 45-54; 55-64; 65-74; 75-84; ≥85 years. For those databases where such information was available, individual or area level socioeconomic status and whether individuals were living in the community or were a nursing home resident were also identified.

Health conditions pre-index date

Individuals´ history of the study outcomes was identified over three time periods prior to the index date:

1) 30 days prior to one day prior index date,
2) 365 days prior to one day prior index date,
3) All available days observed up to one day prior to index date.

A range of health conditions, including whether a patient was immunocompromised prior to the index date, was identified using the same time windows. Among these, the following conditions were identified: antiphospholipid syndrome, asthma, chronic obstructive pulmonary disease, atrial fibrillation, cancer (excluding non-melanoma skin cancers), venous thromboembolism, myocardial infarction, stroke, transient ischaemic attack (TIA), heart failure, diabetes, chronic kidney disease, chronic liver disease, hypertension, rheumatoid arthritis, thrombophilia, inflammatory bowel disease (Crohn's disease or ulcerative colitis), dementia, alcohol or drug substance misuse and obesity. Venous thromboembolism, myocardial infarction and stroke are also outcomes of interest. Therefore, the number of events for venous thromboembolism, myocardial infarction and stroke in the patient's history only represented events identified prior to the washout period used to identify outcomes (Section 8.6.2 and **Table 6**).

Medications pre-index date

Pre-existing medication use were identified using two-time windows, defined as 183 days to one day prior to index date, and 30 days to 1 day prior to index date. Medications of interest were identified on the basis of Anatomical Therapeutic Chemical (ATC) codes, with use of the following medications identified:

- COVID-19 medications (ATC code: J05AB18 molnupiravir, J05AE30 nirmatrelvir ritonavir, J06BD05 sotrovimab)
- Non-steroidal anti-inflammatory drugs (ATC group: M01A, with all descendant codes included)
- Cox2 inhibitors (M01AH)
- Systemic corticosteroids (H02AB and H02BX), antithrombotic and anticoagulant therapies (B01A)
- lipid modifying agents (C10)
- Agents acting on the renin-angiotensin system (C09)

- antineoplastic and immunomodulating agents (L)
- Hormonal contraceptives for systemic use (G03A)
- Tamoxifen (L02BA01)
- ex hormones and modulators of the genital system (G03).

Immunocompromised at the index date

People who were immunocompromised at the index data were defined by the recording of certain conditions or certain conditions plus treatments prior to index date. People were considered immunocompromised if they had one or more of the following conditions recorded within 365 days prior to index date:

- HIV/AIDS,
- Hematological malignancies
- Solid malignancies
- Other intrinsic immune conditions

People were defined as being immunocompromised if they were treated with antineoplastic and immunomodulating agents between 183 days to one day prior to index date. People were also defined as being immunocompromised if they were treated with systemic corticosteroids between 183 days to one day prior to index date and have a recording of the following within 365 days prior to index date:

- Organ transplantations
- Rheumatologic/inflammatory conditions (rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus)

Smoking status pre-index date

Individuals´ smoking status (current smoker, ex-smoker, or non-smoker) was identified when available. All available history for an individual was used to identify records of their smoking status, with the most recent record included in the analysis.

Medications on or post-index date

We also identified medication use on or after the index date first up to 30-days. For each medication of interest, we grouped users into prevalent and new users. The following medications were identified where available: anticoagulants, anti-platelet drugs, thrombolytic agents, transfusion with blood products or immunoglobulins, and COVID-19 medications (molnupiravir, nirmatrelvir ritonavir, sotrovimab).

Table 7. Operational Definitions of Covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Measurement characteristics	Source for algorithm
Location at index date	COVID-19 hospitalized and the intensive care cohorts were identified in hospital setting	Binary	[0]	IP, intensive care	SNOMED	n/a	COVID-19 infected or hospitalized	n/a	n/a
Comorbidity	Check for conditions of interest before the start of follow-up	Binary	All history	Primary and secondary care	SNOMED	n/a	All cohort	n/a	n/a
Medication pre-index	Check for medications exposures prior to the index date	binary	[-183, -1] [-31, -1]	Primary and secondary care	ATC, RxNorm	n/a	All cohort	n/a	n/a
Immunocompromised	People who were immunocompromised at the index data were defined by the recording of certain conditions or certain conditions plus treatments prior to index date.	binary	[-365, 0] for condition, [-183, -1] for treatment	Primary and secondary care	SNOMED, ATC, RxNorm	n/a	All cohort	n/a	n/a
Smoking status	Individuals´ smoking status (current smoker, ex-smoker, or non-smoker) were identified when available.	Binary	All records	Primary care and secondary care	SNOMED and LOINC	n/a	All cohort	n/a	n/a
Measurements	Check for measurements factors prior to the index date	Continuous	[-12 months, 0]	Primary and secondary care	SNOMED and LOINC	n/a	All cohort	n/a	n/a
Medication during follow-up	The following medications were identified where available: anticoagulants, anti-platelet drugs, thrombolytic agent, or transfusion with blood products or immunoglobulins, and COVID-19 medications (molnupiravir, nirmatrelvir ritonavir, sotrovimab).	Binary	[0, 30]	Primary and secondary care	ATC, RxNorm	n/a	All cohort	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

9.7 Study size

In SIDIAP data, for objective 1,2,3, 4a and 5, we used a random sample of 1,000,000 people due to limited computing resource issue at the data partners' site.

For other included databases, all individuals that met the eligibility criteria for a study cohort were included.

9.8 Data transformation

All analyses were conducted separately for each database. Before study initiation, test runs of the analytics were performed on a subset of the data sources and quality control checks were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results.

The study results of all data sources were checked after which they were made available to the team in the Digital Research Environment and the Dissemination Phase started. All results were locked and timestamped for reproducibility and transparency.

9.9 Statistical Methods

9.9.1 Main Summary Measures

We report the observed characteristics of each study population overall, and stratified by age, sex, prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, whether patients were hospitalised or whether patients were immunocompromised on their index date. The time at risk observed along with the number of events during follow-up were summarised for each study population overall and by the covariates mentioned above.

9.9.2 Main Statistical Methods

Incidence of study outcomes

The incidence of each study outcome was estimated during 30-, 60-, and 90- and 180-days following the index date for the COVID-19 and vaccination cohorts of interest with 95% confidence intervals in each database. The 90-day cumulative incidence of study outcomes was estimated. Given the risk of mortality among patients with COVID-19, particularly among those hospitalised, the competing risk of mortality was accounted for by estimating cumulative incidence functions. If death was not available, cumulative incidence was estimated using the Kaplan-Meier approach. As well as estimating the incidence of outcomes for each study cohort as a whole, incidence was estimated by age group stratified by sex. Other stratifications by prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, whether patients were hospitalised on the index date or were immunocompromised on the index date were also performed.

Assessing the association between risk factors for thromboembolic events and COVID-19 during the Omicron period

To assess the association between potential risk factors on the incidence of venous and arterial thromboembolic events among patients with COVID-19 during the Omicron period, cause-specific Cox

models were used to calculate hazard ratios for the incidence of venous and arterial thromboembolic events for each of the COVID-19 cohorts. Adjusted models evaluated potential predictors including age, sex, prior COVID-19 infection status, prior vaccination status, cancer, whether patients were immunocompromised on the index date, prior use of antithrombotics, prior use of corticosteroids, and pre-index comorbidities listed in the covariate section.

Risks of COVID-19 "worsening" (hospital admission or death) stratified by thromboembolic event occurrence during the Omicron period

A multistate-type modelling approach was used to assess risks of COVID-19 worsening during the period when Omicron was the dominant variant, stratified by thromboembolic event occurrence. Multistate models allow for a consideration of individuals progression to multiple events of interest, extending on competing risk models by also describing transitions to intermediate events.[24] In the context of COVID-19, use of intensive care services during a hospitalisation can be considered as key intermediate events between testing positive for SARS-COV-2 or having a clinical diagnosis of COVID-19 in an outpatient setting on the one end to a COVID-19-related death on the other.

Venous thromboembolism and arterial thromboembolism were assessed separately, as time-dependent exposures for the following transitions:

(1) from outpatient COVID-19 diagnosis or PCR test positive to hospitalised with COVID-19
(2) from outpatient COVID-19 diagnosis or PCR test positive to death (without a COVID-19 hospitalisation in between)
(3) from being hospitalised with COVID-19 to death

When the study outcomes were recorded on the same date as hospital admission, we assume the event happened after people were hospitalised with COVID-19.

Cause-specific Cox models within the multistate framework were used to estimate hazard ratios associated with the risk factors of interest. This approach allowed for the factors of interest to have a different effect by the transition of interest and, where the model included a state representing deaths, to account for the competing risk of mortality. Models were adjusted for age and sex.

Contextualising incidence rates for thromboembolic events in COVID-19 during the period when Omicron was the dominant variant

We calculated crude incidence rate ratios (IRRs) for each event with 95% confidence intervals, for the vaccinated and COVID-19 cohorts compared against the background general population cohort. This was done both overall and stratified by key factors including age, sex, prior COVID-19 diagnosis, prior vaccination status and immunosuppressed status. We estimated the number of events expected among the vaccinated and COVID-19 cohorts using indirect standardisation by age and sex (with 10-year age bands), using the general population cohort as the standard population. We calculated standardized incidence rate ratios (SIRs) and 95% confidence intervals comparing observed and expected rates. A standardized incidence rate ratio above 1 indicates that the observed rate for a specific outcome is higher than what is expected in the general background population.

Table 8. Primary, secondary, and subgroup analysis specification

A. Primary analysis	
Hypothesis:	Objective 1 -3: Not applicable, descriptive incidence rate. Objective 4: Use of intensive care services during a hospitalisation can be considered a an intermediate event between testing positive for SARS-COV-2, or having a clinical diagnosis of COVID-19 in an outpatient setting, and COVID-19-related death. Objective 5: Prior COVID-19 infection or vaccination may change the incidence rate of study events in the cohorts.
Exposure contrast:	Objective 1 -3: Not applicable, descriptive incidence rate. Objective 4: Not applicable, risk factor analysis Objective 5: Infected or vaccinated vs. the non-infected or non-vaccinated population
Outcome:	Objective 1 -3: Incidence rates of VTE, ATE Objective 4: VTE, ATE, death Objective 5: Incidence rates of VTE, ATE
Analytic software:	R
Models:	Objective 1 -3: We used Poisson models to estimate incidence rates and 95% confidence interval. Overall, age group, and sex specific rates were reported. Within each age-sex strata, rates by prior COVID-19 diagnosis, prior vaccination status and vaccine brand, and whether patients were immunosuppressed was reported as well provided the event number was larger than 5 within the strata to meet data governance requirements. Objective 4a: To assess the association between potential risk factors on the incidence of venous and arterial thromboembolic events among patients with COVID-19 during the Omicron period. Cause-specific Cox models were used to calculate hazard ratios for the incidence of venous and arterial thromboembolic events for each of the COVID-19 cohorts. Adjusted models evaluated potential predictors including age, sex, prior COVID-19 infection status, prior vaccination status and vaccine brand, cancer, whether patients were immunocompromised on the index date, prior use of antithrombotics, prior use of corticosteroids, and pre-index comorbidities. Objective 4b: Cause-specific Cox models within the multistate framework were used to estimate hazard ratios associated with the risk factors of interest. This approach allowed for the factors of interest to have a different effect by the transition of interest and, where the model included a state representing deaths, accounted for the competing risk of mortality. Models were adjusted for age and sex. Objective 5: Crude incidence rate ratios (IRRs) for each event with 95% confidence intervals were calculated for the vaccinated and COVID-19 cohorts compared against the background general population cohort. This was done both overall and stratified by key factors including age, sex, prior COVID-19 diagnosis, prior vaccination status and brand, and whether patients were immunosuppressed. We estimated the number of events expected among the vaccinated and COVID-19 cohorts using

	indirect standardisation by age and sex (with 10-year age bands), using the general population cohort as the standard population. We calculated standardized incidence rate ratios (SIRs) and 95% confidence intervals comparing observed and expected rates. Rates were reported overall, and r age bands, by sex, by prior COVID-19 diagnosis, by prior vaccination status and brand, and whether patients were immunosuppressed. A standardized incidence rate ratio above 1 indicates that the observed rate for a specific outcome is higher than what is expected in the general background population.
Confounding adjustment method	
	For incidence rates, we estimated the rates with stratification. For incidence rate ratios, standardized incidence rate rations (SIRs) were calculated. No other methods were used to control for confounding.
Missing data methods	
	For cohort 2-5, we only included individuals with complete exposure (COVID-19 or vaccination) information.
Subgroup Analyses	
	All analysis were stratified by age, sex, prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, whether patients were hospitalised or whether patients were immunocompromised on their index date was reported, when sample size allowed.
B. Secondary Analysis	
	The only difference between the primary and secondary analysis related to the type of outcomes of interest considered for the analysis.
Outcome:	1. Venous thromboembolic events: In a secondary analysis, pulmonary embolism and deep vein thrombosis were assessed separately. We also assessed portal vein thrombosis, splanchnic venous thrombosis (SVT) and cerebral venous sinus thrombosis separately. 2. Arterial thromboembolic events: In a secondary analysis, acute myocardial infarction and acute ischemic stroke were assessed separately. We also identified stroke in general, for which we included both ischemic, haemorrhagic and non-specifically recorded stroke. 3. Cardiovascular events: Instances of heart failure, cardiac arrhythmia, and angina were identified. In addition, major cardiovascular events (MACE) were identified comprising heart failure, acute myocardial infarction, or stroke, or the occurrence of sudden cardiac death. As a sensitivity analysis, we required that events were identified by hospitalisation admission or discharge records. This sensitivity analysis was only conducted in SIDIAP, where hospitalisation data was available.

9.9.3 Missing Values

We did not include individuals with missing age or sex information. For cohort 2-5, we only included individuals with a recorded exposure of interest (Covid-19 or vaccination). As we identified health conditions through diagnostic codes, we assumed that absence of a diagnostic code corresponded to absence of disease.

9.9.4 Sensitivity Analysis

Table 9. Sensitivity analyses – rationale, strengths and limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Require inpatient cardiovascular events only	In the outcome definition of cardiovascular events, restrict to hospitalisation admission or discharge record. [only in SIDIAP]	Cardiovascular events are acute and usually lead to inpatient admission	Increase specificity of exposure definition.	Loss in sensitivity.
Washout period for outcome events	In the main analysis, we excluded patients with VTE or ATE within 183 days prior to the index date. Here, we varied this in two way 1.) reduced the exclusion period to 91 days. and 2.) excluded people with any VTE or ATE history	The choice of washout period may impact on the included study population, therefore impact on the generalisability of the rate for the vaccine cohort vs the risk of misclassification with prior event recording.	1.) Can reduce the risk of survival bias; 2.) Increase the specificity of incident event.	1.) May include recurrent events. 2.) Increase the risk of survival bias as people need to have no VTE or ATE after prior vaccines to be included in the later vaccine cohorts.

9.10 Deviations from the protocol

Analyses conducted in SIDIAP: While we planned to include all eligible people in each of the participating databases to maximise the sample size, in the analysis of objectives 1, 2, 3, 4a and 5, we used a 1,000,000 random sample of people in SIDIAP due to limited computing resources.

Meta analyses: We observed high heterogeneity in the incidence rate estimates between databases. The included data sources were of different characteristics in terms of data collection type and data period. While in the original protocol we had planned to pool the results from all participated databases with meta-analysis, the individual results from each data source suggested that the results of pooling the estimates will be mainly driven by the heterogeneities between databases. Therefore, no meta-analyses were performed.

10. DATA MANAGEMENT

10.1 Data management

All databases have previously mapped their data to the OMOP common data model (v5.3 for CPRD GOLD, IQVIA DA Germany, and SIDIAP, v5.4 for Estonia Biobank and IPCI). This enabled the use of standardised analytics and tools across the network since the structure of the data and the terminology system is

harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org.

This analytic code for this study was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then be combined in tables and figures for this study report.

10.2 Data storage and protection

For this study, participants from various EU member states and from the UK processed personal data from individuals which was collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study were already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses were run, which generated non-identifiable aggregate summary results. All and any results with n<5 participants were suppressed using cell suppression to minimise risk of reidentification as per data governance requirements.

The output files were stored in the DARWIN EU Data transfer zone. These output files do not contain any data that allow identification of subjects included in the study. The DTZ implemented further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, data partners have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

The *CohortDiagnostics* R package (https://github.com/OHDSI/CohortDiagnostics) was run prior to results generation to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This allowed for consideration of the validity of the outcome cohorts in each of the databases, and informed decisions around whether multiple definitions were required. Other

R package being used including: IncidencePrevelance (https://darwin-eu.github.io/IncidencePrevalence/) [25], and CohortSurvival (https://darwin-eu-dev.github.io/CohortSurvival/) which have been developed for DARWIN EU and were extensively tested.

12. RESULTS

All study results are available in the interactive web application ("Shiny App"): https://data-dev.darwin-eu.org/EUPAS106679/

12.1 Participants

The background cohort included a total of 24,489,574 individuals across included databases (CPRD GOLD: 5,278,189, Estonia Biobank: 207,657, IPCI: 1,589,237, IQVIA DA Germany: 16,667,650, SIDIAP: 746,737).

We identified a total of 1,478,876 people with COVID-19 during the Omicron period. (CPRD GOLD: 248,847; IPCI: 330,200; IQVIA DA Germany: 696,094; SIDIAP: 559,696) that contributed to 1,558,250 cases during the Omicron period.

After applying the exclusion criteria, a total of 4,901,863 eligible patients with at least one dose of SARS-CoV-2 vaccination were identified in the study (CPRD GOLD: 2,374,109, IPCI: 656,664, IQVIA DA Germany: 1,311,394, SIDIAP: 559,696).

Table 12.1. Cohort attrition by database.

	Number of Records	Person years	Reason	Excluded Records	Excluded Subjects
CPRD GOLD					
COVID-19	660575	567802	Qualifying initial records	0	0
COVID-19	596133	567802	No prior covid 90 days before	64442	0
COVID-19	270753	268992	covid records after2021-12-01	325380	298810
COVID-19	250463	248847	At least 365 of prior observation time (days)	20290	20145
Vaccinated	7339823	2523216	Qualifying initial records	0	0
Vaccinated	7324394	2523216	No prior vaccine 21 days before	15429	0
Vaccinated	6946736	2374109	At least 365 of prior observation time (days)	377658	149107
IPCI					
COVID-19	947180	504954	Qualifying initial records	0	0
COVID-19	554274	504954	No prior covid 90 days before	392906	0
COVID-19	380712	370011	covid records after2021-12-01	173562	134943
COVID-19	339552	330200	At least 365 of prior observation time (days)	41160	39811
Vaccinated	1853124	720228	Qualifying initial records	0	0
Vaccinated	1822920	720228	No prior vaccine 21 days before	30204	0
Vaccinated	1653493	656664	At least 365 of prior observation time (days)	169427	63564
IQVIA DA Germany					
COVID-19	752485	696094	At least 365 of prior observation time (days)	193783	186128
COVID-19	1983532	1348938	Qualifying initial records	0	0
COVID-19	1597985	1348938	No prior covid 90 days before	385547	0
COVID-19	946268	882222	covid records after2021-12-01	651717	466716
Vaccinated	3686879	2033477	Qualifying initial records	0	0
Vaccinated	3601423	2033477	No prior vaccine 21 days before	85456	0
Vaccinated	2480105	1311394	At least 365 of prior observation time (days)	1121318	722083
SIDIAP					
COVID-19	4115884	2434424	Qualifying initial records	0	0
COVID-19	3964975	2434424	No prior covid 90 days before	150909	0
COVID-19	2410638	1753407	covid records after2021-12-01	1554337	681017
COVID-19	212578	200563	1M Sample + At least 365 of prior observation	2198060	1552844
Vaccinated	13020107	4873223	Qualifying initial records	0	0
Vaccinated	12807026	4873223	No prior vaccine 21 days before	213081	0
Vaccinated	1500713	559696	1M Sample + At least 365 of prior observation	11306313	4313527

12.2 Descriptive Data

Baseline characteristics for people included in the background population, COVID-19 cohort and vaccinated cohort are provided for all databases in **Tables 12.2.1 – 12.2.4**. Characteristics of each study population stratified by age, sex, prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, and immunocompromised on their index date are reported in the interactive web application ("shiny app").

CPRD GOLD: The background population consisted of 5,278,189 people, with a median age of 38 years and 51% of female. The most common condition observed was obesity (17%), followed by hypertension (8%) and asthma (7%).

Among the 248,847 COVID-19 patients in CPRD GOLD, 57% were female. The median age of COVID-19 participants was 37 years. 9% of COVID-19 participants had a previous COVID-19 infection (more than 90 days before index date), and 80% had received at least one dose of a COVID-19 vaccine. 1% of eligible COVID-19 cases were classified as immunocompromised at index date. Among eligible people in the COVID-19 vaccinated cohort, 33% had received one dose, 31% had received 2 doses, 25% three doses, and 11% had received 4 or more doses. The most commonly observed conditions during the year prior to infection was obesity (23%), followed by cancer (3%) and asthma (2%). During the one-month time before COVID-19, 13% of the people received anti-inflammatory medication.

IPCI: The background cohort included 1,589,237 individuals. The median age was 39 years, 51% were female and the most common conditions observed before index were obesity and hypertension.

Among 330,200 individuals included in the COVID-19 cohort, 55% were female. The median age of COVID-19 participants was 37 years, 12% of COVID-19 participants had previous COVID-19 infection, and 61% had received at least one prior dose of a COVID-19 vaccine at index date. 1% of eligible COVID-19 cases were classified as immunocompromised at index date. Among eligible people in the COVID-19 vaccinated cohort, 38% had received one dose, 31% had received 2 doses, 19% three doses, and 13% had received 4 or more doses. The most observed conditions during the year prior to infection was obesity (9%), followed by cancer (4%) and hypertension (4%). During the one-month time before COVID-19, 7% of the people received lipid-lowering medication.

IQVA DA Germany: A total of 16,667,650 persons were included in the background cohort, with a median age of 49 and 56% of them were female. Hypertension was the most common condition, with 9% of the cohort had hypertension before the index.

Among 696,094 individuals in the COVID-19 cohort, 53% were female. The median age of COVID-19 participants was 42 years. 24% of COVID-19 participants had previous COVID-19 infection, and 34% had received at least one prior dose of a COVID-19 vaccine at index date. 3% of eligible COVID-19 cases were classified as were immunocompromised at index date. Among eligible people in the COVID-19 vaccinated cohort, 52% had received one dose, 32% had received 2 doses, 14% three doses and 3% had received 4 or more doses. The most observed conditions during the year prior to infection was obesity (14%), followed by hypertension (12%). During the one-month time before COVID-19, 10% of the people received anti-inflammatory medication and 14% received agents acting on the renin-angiotensin system.

SIDIAP: The background cohort included 746,737 individuals. The median age was 40 years, 50% were female and the most common conditions observed before index date were obesity and hypertension.

Among 200,563 individuals included in the Omicron COVID-19 cohort, 56% were female. The median age of people in the COVID-19 cohort was 43 years, 18% had previous COVID-19 infection, and 61% had received at least one prior dose of a COVID-19 vaccine at index date. There were 2% of eligible COVID-19 cases classified as having immunocompromised status at index date. By the time of infection with SARS-CoV-2 during the Omicron period, 40% of the participants received 2 doses of vaccines, and 34% received 3 doses. The most commonly observed conditions during the year prior to infection was obesity (24%), followed by cancer (6%). During the one month before COVID-19, 33% of the people received anti-inflammatory medications. Among eligible people in the COVID-19 vaccinated cohort, 37% had received one dose, 34% had received 2 doses, 21% three doses, and 8% had received 4 or more doses.

Estonia Biobank: The background cohort included 207,657 individuals. The median age was 44 years old, and 66% of the cohort were female. Hypertension was the most common comorbidity, observed among 31% of the cohort members, followed by obesity (12%), asthma (11%), and heart failure (11%).

Table 12.2.1 Cohort characteristics of CPRD GOLD.

Variable	Level	Format	Background population	Covid	Vaccinated
Number subjects		N	5,278,189	248,847	2,374,109
Number records		N	5,278,189	250,463	6,946,736
Age		median [q25 - q75]	38 [21 - 57]	37 [23 - 52]	54 [37 - 69]
		mean (sd)	39 (24)	38 (20)	53 (20)
Sex	Female	N (%)	2,673,727 (51%)	142,704 (57%)	3,650,878 (53%)
	Male	N (%)	2,604,462 (49%)	107,759 (43%)	3,295,858 (47%)
Prior observation time (days)		median [q25 - q75]	3,218 [626 - 5,147]	5,120 [2,325 - 6,881]	6,245 [3,091 - 7,021]
		mean (sd)	3,202 (2,566)	4,763 (2,655)	5,342 (2,598)
Future observation time (days)		median [q25 - q75]	1,663 [842 - 2,161]	306 [255 - 336]	457 [330 - 588]
		mean (sd)	1,457 (746)	281 (76)	428 (190)
Age group	0 to 19	N (%)	1,243,130 (24%)	46,814 (19%)	460,869 (7%)
	20 to 44	N (%)	1,813,022 (34%)	111,723 (45%)	1,943,306 (28%)
	45 to 54	N (%)	720,619 (14%)	38,214 (15%)	1,082,309 (16%)
	55 to 64	N (%)	603,147 (11%)	29,856 (12%)	1,256,499 (18%)
	65 to 74	N (%)	476,148 (9%)	13,972 (6%)	1,075,550 (15%)
	75 to 84	N (%)	284,160 (5%)	6,834 (3%)	823,499 (12%)
	85 to 150	N (%)	137,960 (3%)	3,050 (1%)	304,704 (4%)
	None	N (%)	<5 (NA%)	NA	NA
Immunocompromised status	Yes	N (%)	NA	3,730 (1%)	126,441 (2%)
Number of vaccine doses	0	N (%)	NA	50,641 (20%)	NA
	1	N (%)	NA	14,127 (6%)	2,307,414 (33%)
	2	N (%)	NA	64,828 (26%)	2,167,822 (31%)
	3	N (%)	NA	116,775 (47%)	1,716,405 (25%)

Variable	Level	Format	Background population	Covid	Vaccinated
	>=4	N (%)	NA	4,092 (2%)	755,095 (11%)
Previous COVID-19	No	N (%)	NA	227,484 (91%)	6,419,057 (92%)
	Yes	N (%)	NA	22,979 (9%)	527,679 (8%)
Vaccine brand	ChAdOx1	N (%)	NA	NA	2,232,528 (32%)
	Ad26.COV2-S	N (%)	NA	NA	572 (0%)
	mRNA-1273	N (%)	NA	NA	1,035,636 (15%)
	BNT162b2	N (%)	NA	NA	3,672,434 (53%)
	Unknown	N (%)	NA	NA	5,566 (0%)
Conditions (anytime to 1 day before index date)	Acute myocardial infarction	N (%)	5,546 (0%)	321 (0%)	15,180 (0%)
	Alcohol misuse	N (%)	8,192 (0%)	243 (0%)	8,848 (0%)
	Antiphospholipid syndrome	N (%)	855 (0%)	91 (0%)	2,405 (0%)
	Asthma	N (%)	91,601 (2%)	4,327 (2%)	110,153 (2%)
	Atrial fibrillation	N (%)	72,407 (1%)	3,164 (1%)	225,493 (3%)
	Cancer	N (%)	123,236 (2%)	6,351 (3%)	374,290 (5%)
	Chronic kidney disease	N (%)	18,517 (0%)	633 (0%)	36,026 (1%)
	Chronic liver disease	N (%)	1,678 (0%)	88 (0%)	3,689 (0%)
	Chronic Obstructive Pulmonary Disease	N (%)	24,732 (0%)	913 (0%)	34,222 (0%)
	Dementia	N (%)	8,626 (0%)	355 (0%)	19,151 (0%)
	Diabetes	N (%)	28,206 (1%)	1,560 (1%)	58,682 (1%)
	Haemorrhagic stroke	N (%)	604 (0%)	38 (0%)	1,627 (0%)
	Heart failure	N (%)	6,746 (0%)	384 (0%)	18,250 (0%)
	Hypertension	N (%)	36,085 (1%)	1,782 (1%)	61,218 (1%)
	Inflammatory bowel disease	N (%)	3,495 (0%)	266 (0%)	6,215 (0%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Ischemic stroke	N (%)	1,204 (0%)	52 (0%)	2,897 (0%)
	Obesity complex	N (%)	894,021 (17%)	58,801 (23%)	2,126,056 (31%)
	Rheumatoid arthritis	N (%)	3,276 (0%)	178 (0%)	6,571 (0%)
	Substance misuse dependence	N (%)	11,236 (0%)	443 (0%)	11,976 (0%)
	Thrombophilia	N (%)	2,113 (0%)	204 (0%)	5,217 (0%)
	TIA	N (%)	33,939 (1%)	1,491 (1%)	100,930 (1%)
	VTE (narrow definition)	N (%)	6,433 (0%)	412 (0%)	15,872 (0%)
Conditions (within 1 year before index date)	Acute myocardial infarction	N (%)	43,388 (1%)	2,175 (1%)	134,165 (2%)
	Alcohol misuse	N (%)	58,713 (1%)	3,147 (1%)	129,071 (2%)
	AntiphosphoLipid-lowering drugs syndrome	N (%)	855 (0%)	91 (0%)	2,405 (0%)
	Asthma	N (%)	362,427 (7%)	26,857 (11%)	717,483 (10%)
	Atrial fibrillation	N (%)	72,407 (1%)	3,164 (1%)	225,493 (3%)
	Cancer	N (%)	123,236 (2%)	6,351 (3%)	374,290 (5%)
	Chronic kidney disease	N (%)	161,630 (3%)	5,031 (2%)	380,571 (5%)
	Chronic liver disease	N (%)	8,129 (0%)	555 (0%)	25,437 (0%)
	Chronic Obstructive Pulmonary Disease	N (%)	82,804 (2%)	3,830 (2%)	227,495 (3%)
	Dementia	N (%)	27,380 (1%)	1,069 (0%)	70,190 (1%)
	Diabetes	N (%)	190,935 (4%)	10,472 (4%)	525,879 (8%)
	Haemorrhagic stroke	N (%)	4,224 (0%)	267 (0%)	13,313 (0%)
	Heart failure	N (%)	33,063 (1%)	1,487 (1%)	98,470 (1%)
	Hypertension	N (%)	430,557 (8%)	18,608 (7%)	1,098,904 (16%)
	Inflammatory bowel disease	N (%)	21,453 (0%)	1,786 (1%)	57,258 (1%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Ischemic stroke	N (%)	9,662 (0%)	413 (0%)	27,156 (0%)
	Obesity complex	N (%)	894,021 (17%)	58,801 (23%)	2,126,056 (31%)
	Rheumatoid arthritis	N (%)	20,926 (0%)	1,342 (1%)	64,206 (1%)
	Substance misuse dependence	N (%)	72,000 (1%)	3,632 (1%)	131,751 (2%)
	Thrombophilia	N (%)	2,113 (0%)	204 (0%)	5,217 (0%)
	TIA	N (%)	33,939 (1%)	1,491 (1%)	100,930 (1%)
	VTE (narrow definition)	N (%)	40,531 (1%)	2,381 (1%)	114,472 (2%)
Outcomes of interest recorded between 183 and 1 day(s) before index	ATE, myocardial infarction, ischemic heart disease, stroke	N (%)	3,461 (0%)	196 (0%)	9,182 (0%)
	VTE, incl. Pulmonary embolism	N (%)	3,599 (0%)	239 (0%)	8,686 (0%)
Medications (prescription record within -183 to -1 days before index date)	Anti-inflammatory drugs	N (%)	1,108,251 (21%)	64,565 (26%)	1,996,783 (29%)
	Antineoplastic drugs	N (%)	235,013 (4%)	18,227 (7%)	419,991 (6%)
	Antithrombotics	N (%)	339,680 (6%)	13,873 (6%)	911,023 (13%)
	Contraceptives	N (%)	288,739 (5%)	26,610 (11%)	455,535 (7%)
	COVID-19 medicines	N (%)	18 (0%)	<5 (NA%)	15 (0%)
	Coxibs	N (%)	11,706 (0%)	1,001 (0%)	31,969 (0%)
	Glucocorticoids	N (%)	652,311 (12%)	35,228 (14%)	1,209,794 (17%)
	Lipid-lowering drugs	N (%)	522,394 (10%)	20,460 (8%)	1,413,733 (20%)
	RAAS-inhibitors	N (%)	471,628 (9%)	19,975 (8%)	1,194,996 (17%)
	Sex hormones	N (%)	346,404 (7%)	31,792 (13%)	632,167 (9%)
	Tamoxifen	N (%)	6,502 (0%)	362 (0%)	15,459 (0%)
Medications (prescription record within -30 to -1 days before index date)	Anti-inflammatory drugs	N (%)	582,900 (11%)	32,003 (13%)	1,218,990 (18%)
	Antineoplastic drugs	N (%)	177,007 (3%)	13,459 (5%)	327,464 (5%)
	Antithrombotics	N (%)	307,398 (6%)	12,226 (5%)	848,813 (12%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Contraceptives	N (%)	200,768 (4%)	18,476 (7%)	335,509 (5%)
	COVID-19 medicines	N (%)	<5 (NA%)	<5 (NA%)	<5 (NA%)
	Coxibs	N (%)	7,551 (0%)	631 (0%)	22,180 (0%)
	Glucocorticoids	N (%)	346,575 (7%)	16,295 (7%)	718,669 (10%)
	Lipid-lowering drugs	N (%)	484,141 (9%)	18,998 (8%)	1,341,722 (19%)
	RAAS-inhibitors	N (%)	444,895 (8%)	18,738 (7%)	1,141,130 (16%)
	Sex hormones	N (%)	239,839 (5%)	22,565 (9%)	468,394 (7%)
	Tamoxifen	N (%)	5,801 (0%)	318 (0%)	13,483 (0%)

* Future observation time (days) refers to the time that individual remains visible in the database.

Outcomes of interest recorded between 183 and 1 day(s) before index: In the analysis, these people were excluded based on the pre-defined washout window. E.g. Individuals with VTE during this window were excluded from the analysis of VTE but may be included in the analysis of other outcomes.

Table 12.2.2 Cohort characteristics of IPCI.

Variable	Level	Format	Background population	Covid	Vaccinated
Number subjects		N	1,589,237	330,200	656,664
Number records		N	1,589,237	339,552	1,653,493
Age		median [q25 - q75]	39 [20 - 58]	37 [20 - 53]	59 [41 - 70]
		mean (sd)	39 (24)	38 (21)	55 (20)
Sex	Female	N (%)	810,595 (51%)	185,924 (55%)	843,558 (51%)
	Male	N (%)	778,642 (49%)	153,628 (45%)	809,935 (49%)
Prior observation time (days)		median [q25 - q75]	853 [31 - 1,827]	2,623 [1,291 - 3,735]	2,578 [1,518 - 3,511]
		mean (sd)	1,063 (975)	2,585 (1,394)	2,493 (1,214)
Future observation time (days)		median [q25 - q75]	1,856 [1,307 - 2,371]	476 [325 - 514]	539 [266 - 719]

Variable	Level	Format	Background population	Covid	Vaccinated
		mean (sd)	1,713 (716)	404 (152)	491 (241)
		q05	273	49	49
		q95	2,371	550	805
Age group	0 to 19	N (%)	384,036 (24%)	80,763 (24%)	108,282 (7%)
	20 to 44	N (%)	508,741 (32%)	127,347 (38%)	365,901 (22%)
	45 to 54	N (%)	226,490 (14%)	51,360 (15%)	216,807 (13%)
	55 to 64	N (%)	195,946 (12%)	39,273 (12%)	361,494 (22%)
	65 to 74	N (%)	159,007 (10%)	22,965 (7%)	323,458 (20%)
	75 to 84	N (%)	84,893 (5%)	13,166 (4%)	214,669 (13%)
	85 to 150	N (%)	30,124 (2%)	4,678 (1%)	62,882 (4%)
Immunocompromised status	Yes	N (%)	NA	4,967 (1%)	39,326 (2%)
Number of vaccine doses	0	N (%)	NA	185,861 (55%)	NA
	1	N (%)	NA	33,994 (10%)	620,134 (38%)
	2	N (%)	NA	68,010 (20%)	514,760 (31%)
	3	N (%)	NA	43,820 (13%)	310,604 (19%)
	>=4	N (%)	NA	7,867 (2%)	207,995 (13%)
Previous COVID-19	No	N (%)	NA	298,346 (88%)	1,474,702 (89%)
	Yes	N (%)	NA	41,206 (12%)	178,791 (11%)
Vaccine brand	ChAdOx1	N (%)	NA	NA	127,733 (8%)
	Ad26.COV2-S	N (%)	NA	NA	17,313 (1%)
	mRNA-1273	N (%)	NA	NA	331,940 (20%)
	BNT162b2	N (%)	NA	NA	903,793 (55%)
	Unknown	N (%)	NA	NA	272,714 (16%)
Conditions (anytime to 1 day before index date)	Acute myocardial infarction	N (%)	7,267 (0%)	1,537 (0%)	11,483 (1%)
	Alcohol misuse	N (%)	3,212 (0%)	629 (0%)	3,911 (0%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Antiphospholipid syndrome	N (%)	0 (0%)	0 (0%)	0 (0%)
	Asthma	N (%)	25,273 (2%)	6,390 (2%)	22,086 (1%)
	Atrial fibrillation	N (%)	18,255 (1%)	5,058 (1%)	54,669 (3%)
	Cancer	N (%)	42,581 (3%)	12,597 (4%)	115,690 (7%)
	Chronic kidney disease	N (%)	305 (0%)	79 (0%)	243 (0%)
	Chronic liver disease	N (%)	508 (0%)	104 (0%)	582 (0%)
	Chronic Obstructive Pulmonary Disease	N (%)	14,613 (1%)	2,209 (1%)	17,490 (1%)
	Dementia	N (%)	3,589 (0%)	654 (0%)	6,676 (0%)
	Diabetes	N (%)	40,811 (3%)	8,264 (2%)	62,778 (4%)
	Haemorrhagic stroke	N (%)	248 (0%)	42 (0%)	245 (0%)
	Heart failure	N (%)	5,497 (0%)	1,127 (0%)	10,035 (1%)
	Hypertension	N (%)	73,595 (5%)	13,058 (4%)	102,993 (6%)
	Inflammatory bowel disease	N (%)	2,556 (0%)	911 (0%)	3,314 (0%)
	Ischemic stroke	N (%)	2,484 (0%)	502 (0%)	3,947 (0%)
	Obesity	N (%)	85,117 (5%)	28,986 (9%)	228,121 (14%)
	Rheumatoid arthritis	N (%)	3,918 (0%)	935 (0%)	4,890 (0%)
	Substance misuse dependence	N (%)	15,215 (1%)	3,472 (1%)	18,449 (1%)
	Thrombophilia	N (%)	0 (0%)	0 (0%)	0 (0%)
	TIA	N (%)	11,124 (1%)	3,215 (1%)	30,902 (2%)
	VTE (narrow definition)	N (%)	3,034 (0%)	788 (0%)	5,576 (0%)
Conditions (within 1 year before index date)	Acute myocardial infarction	N (%)	12,804 (1%)	3,323 (1%)	31,431 (2%)
	Alcohol misuse	N (%)	7,833 (0%)	2,192 (1%)	15,563 (1%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Antiphospholipid syndrome	N (%)	0 (0%)	0 (0%)	0 (0%)
	Asthma	N (%)	55,858 (4%)	21,226 (6%)	79,261 (5%)
	Atrial fibrillation	N (%)	18,255 (1%)	5,058 (1%)	54,669 (3%)
	Cancer	N (%)	42,581 (3%)	12,597 (4%)	115,690 (7%)
	Chronic kidney disease	N (%)	706 (0%)	238 (0%)	1,214 (0%)
	Chronic liver disease	N (%)	1,200 (0%)	324 (0%)	2,124 (0%)
	Chronic Obstructive Pulmonary Disease	N (%)	23,359 (1%)	4,682 (1%)	45,806 (3%)
	Dementia	N (%)	5,767 (0%)	1,092 (0%)	13,453 (1%)
	Diabetes	N (%)	55,408 (3%)	13,290 (4%)	115,661 (7%)
	Haemorrhagic stroke	N (%)	614 (0%)	152 (0%)	1,033 (0%)
	Heart failure	N (%)	10,241 (1%)	2,554 (1%)	25,490 (2%)
	Hypertension	N (%)	125,353 (8%)	28,903 (9%)	268,676 (16%)
	Inflammatory bowel disease	N (%)	5,403 (0%)	2,283 (1%)	11,218 (1%)
	Ischemic stroke	N (%)	4,433 (0%)	1,098 (0%)	11,565 (1%)
	Obesity	N (%)	85,117 (5%)	28,986 (9%)	228,121 (14%)
	Rheumatoid arthritis	N (%)	8,288 (1%)	2,637 (1%)	17,322 (1%)
	Substance misuse dependence	N (%)	44,486 (3%)	16,082 (5%)	91,831 (6%)
	Thrombophilia	N (%)	0 (0%)	0 (0%)	0 (0%)
	TIA	N (%)	11,124 (1%)	3,215 (1%)	30,902 (2%)
	VTE (narrow definition)	N (%)	7,506 (0%)	2,835 (1%)	21,819 (1%)
Outcomes of interest recorded between 183 and 1 day(s) before index	ATE, myocardial infarction, ischemic heart disease, stroke	N (%)	6,369 (0%)	1,391 (0%)	10,392 (1%)

Variable	Level	Format	Background population	Covid	Vaccinated
	VTE, incl. Pulmonary embolism	N (%)	1,927 (0%)	471 (0%)	3,325 (0%)
Medications (prescription record within -183 to -1 days before index date)	Anti-inflammatory drugs	N (%)	202,010 (13%)	48,792 (14%)	304,492 (18%)
	Antineoplastic drugs	N (%)	81,081 (5%)	28,906 (9%)	137,507 (8%)
	Antithrombotics	N (%)	99,955 (6%)	22,141 (7%)	269,403 (16%)
	Contraceptives	N (%)	69,277 (4%)	26,343 (8%)	89,942 (5%)
	COVID-19 medicines	N (%)	106 (0%)	<5 (NA%)	77 (0%)
	Coxibs	N (%)	9,006 (1%)	1,957 (1%)	16,207 (1%)
	Glucocorticoids	N (%)	178,871 (11%)	44,973 (13%)	313,340 (19%)
	Lipid-lowering drugs	N (%)	129,285 (8%)	25,661 (8%)	325,345 (20%)
	RAAS-inhibitors	N (%)	125,977 (8%)	26,288 (8%)	313,171 (19%)
	Sex hormones	N (%)	78,867 (5%)	29,489 (9%)	110,848 (7%)
	Tamoxifen	N (%)	1,562 (0%)	301 (0%)	3,145 (0%)
Medications (prescription record within -30 to -1 days before index date)	Anti-inflammatory drugs	N (%)	83,631 (5%)	17,474 (5%)	124,998 (8%)
	Antineoplastic drugs	N (%)	60,368 (4%)	21,334 (6%)	105,528 (6%)
	Antithrombotics	N (%)	84,652 (5%)	18,929 (6%)	242,327 (15%)
	Contraceptives	N (%)	49,654 (3%)	18,703 (6%)	70,289 (4%)
	COVID-19 medicines	N (%)	83 (0%)	<5 (NA%)	62 (0%)
	Coxibs	N (%)	4,573 (0%)	999 (0%)	9,127 (1%)
	Glucocorticoids	N (%)	92,790 (6%)	21,006 (6%)	179,302 (11%)
	Lipid-lowering drugs	N (%)	114,809 (7%)	23,033 (7%)	300,302 (18%)
	RAAS-inhibitors	N (%)	113,471 (7%)	23,651 (7%)	290,180 (18%)
	Sex hormones	N (%)	56,044 (4%)	20,906 (6%)	84,433 (5%)
	Tamoxifen	N (%)	1,251 (0%)	240 (0%)	2,541 (0%)

* Future observation time (days) refers to the time that individual remains visible in the database. Outcomes of interest recorded between 183 and 1 day(s) before index: In the analysis, these people were excluded based on the pre-defined washout window. E.g. Individuals with VTE during this window were excluded from the analysis of VTE but may be included in the analysis of other outcomes.

Table 12.2.3. Cohort characteristics of IQVIA DA Germany.

Variable	Level	Format	Background population	Covid	Vaccinated
Number subjects		N	16,667,650	696,094	1,311,394
Number records		N	16,667,650	752,485	2,480,105
Age		median [q25 - q75]	49 [28 - 64]	42 [26 - 56]	60 [42 - 72]
		mean (sd)	46 (23)	41 (21)	56 (21)
Sex	Female	N (%)	9,304,816 (56%)	401,432 (53%)	1,313,358 (53%)
	Male	N (%)	7,347,088 (44%)	350,535 (47%)	1,164,749 (47%)
	None	N (%)	15,746 (0%)	518 (0%)	1,998 (0%)
Prior observation time (days)		median [q25 - q75]	89 [0 - 1,899]	2,666 [1,481 - 4,521]	3,345 [1,741 - 5,379]
		mean (sd)	1,160 (1,743)	3,252 (2,282)	3,727 (2,459)
Future observation time (days)		median [q25 - q75]	946 [58 - 1,857]	208 [54 - 346]	446 [268 - 583]
		mean (sd)	1,007 (859)	206 (150)	410 (207)
Age group	0 to 19	N (%)	2,577,831 (15%)	131,833 (18%)	185,709 (7%)
	20 to 44	N (%)	4,787,053 (29%)	275,959 (37%)	483,646 (20%)
	45 to 54	N (%)	2,552,932 (15%)	126,451 (17%)	319,735 (13%)
	55 to 64	N (%)	2,587,140 (16%)	132,744 (18%)	508,150 (20%)
	65 to 74	N (%)	1,947,721 (12%)	43,135 (6%)	492,539 (20%)
	75 to 84	N (%)	1,753,189 (11%)	27,588 (4%)	358,550 (14%)
	85 to 150	N (%)	461,784 (3%)	14,775 (2%)	131,776 (5%)
Immunocompromised status	Yes	N (%)	NA	24,359 (3%)	113,577 (5%)
Number of vaccine doses	0	N (%)	NA	498,065 (66%)	NA
	1	N (%)	NA	106,303 (14%)	1,282,410 (52%)
	2	N (%)	NA	86,674 (12%)	782,663 (32%)

Variable	Level	Format	Background population	Covid	Vaccinated
	3	N (%)	NA	56,283 (7%)	344,596 (14%)
	>=4	N (%)	NA	5,160 (1%)	70,436 (3%)
Previous COVID-19	No	N (%)	NA	568,358 (76%)	2,213,168 (89%)
	Yes	N (%)	NA	184,127 (24%)	266,937 (11%)
Vaccine brand	ChAdOx1	N (%)	NA	NA	144,984 (6%)
	Ad26.COV2-S	N (%)	NA	NA	48,566 (2%)
	mRNA-1273	N (%)	NA	NA	313,633 (13%)
	BNT162b2	N (%)	NA	NA	1,972,112 (80%)
	Unknown	N (%)	NA	NA	810 (0%)
Conditions (anytime to 1 day before index date)	Acute myocardial infarction	N (%)	12,668 (0%)	2,059 (0%)	14,330 (1%)
	Alcohol misuse	N (%)	15,104 (0%)	1,886 (0%)	10,985 (0%)
	Antiphospholipid syndrome	N (%)	0 (0%)	0 (0%)	0 (0%)
	Asthma	N (%)	129,349 (1%)	27,417 (4%)	79,685 (3%)
	Atrial fibrillation	N (%)	91,381 (1%)	11,433 (2%)	93,226 (4%)
	Cancer	N (%)	527,144 (3%)	48,441 (6%)	320,924 (13%)
	Chronic kidney disease	N (%)	77,990 (0%)	9,986 (1%)	70,624 (3%)
	Chronic liver disease	N (%)	7,136 (0%)	875 (0%)	6,208 (0%)
	Chronic Obstructive Pulmonary Disease	N (%)	119,891 (1%)	17,599 (2%)	82,861 (3%)
	Dementia	N (%)	41,506 (0%)	3,907 (1%)	26,599 (1%)
	Diabetes	N (%)	209,981 (1%)	27,278 (4%)	190,201 (8%)
	Haemorrhagic stroke	N (%)	3,117 (0%)	461 (0%)	2,796 (0%)
	Heart failure	N (%)	68,475 (0%)	8,215 (1%)	69,124 (3%)
	Hypertension	N (%)	557,402 (3%)	87,828 (12%)	541,498 (22%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Inflammatory bowel disease	N (%)	15,413 (0%)	2,790 (0%)	10,475 (0%)
	Ischemic stroke	N (%)	11,502 (0%)	1,703 (0%)	13,793 (1%)
	Obesity	N (%)	691,266 (4%)	102,998 (14%)	456,038 (18%)
	Rheumatoid arthritis	N (%)	37,113 (0%)	4,821 (1%)	24,205 (1%)
	Substance misuse dependence	N (%)	72,211 (0%)	9,982 (1%)	43,324 (2%)
	Thrombophilia	N (%)	6,708 (0%)	2,009 (0%)	6,656 (0%)
	TIA	N (%)	46,375 (0%)	7,968 (1%)	53,115 (2%)
	VTE (narrow definition)	N (%)	16,202 (0%)	3,401 (0%)	17,766 (1%)
Conditions (within 1 year before index date)	Acute myocardial infarction	N (%)	49,538 (0%)	7,472 (1%)	56,552 (2%)
	Alcohol misuse	N (%)	56,975 (0%)	8,441 (1%)	55,510 (2%)
	Antiphospholipid syndrome	N (%)	0 (0%)	0 (0%)	0 (0%)
	Asthma	N (%)	414,563 (2%)	95,296 (13%)	287,491 (12%)
	Atrial fibrillation	N (%)	91,381 (1%)	11,433 (2%)	93,226 (4%)
	Cancer	N (%)	527,144 (3%)	48,441 (6%)	320,924 (13%)
	Chronic kidney disease	N (%)	198,550 (1%)	32,197 (4%)	228,891 (9%)
	Chronic liver disease	N (%)	24,021 (0%)	3,347 (0%)	22,969 (1%)
	Chronic Obstructive Pulmonary Disease	N (%)	344,159 (2%)	69,639 (9%)	288,514 (12%)
	Dementia	N (%)	86,640 (1%)	9,922 (1%)	73,141 (3%)
	Diabetes	N (%)	595,985 (4%)	72,948 (10%)	484,770 (20%)
	Haemorrhagic stroke	N (%)	11,127 (0%)	1,936 (0%)	12,601 (1%)
	Heart failure	N (%)	177,841 (1%)	21,525 (3%)	185,520 (7%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Hypertension	N (%)	1,465,313 (9%)	191,630 (25%)	1,106,023 (45%)
	Inflammatory bowel disease	N (%)	51,757 (0%)	9,468 (1%)	34,613 (1%)
	Ischemic stroke	N (%)	34,830 (0%)	5,370 (1%)	45,166 (2%)
	Obesity	N (%)	691,266 (4%)	102,998 (14%)	456,038 (18%)
	Rheumatoid arthritis	N (%)	111,297 (1%)	17,916 (2%)	91,850 (4%)
	Substance misuse dependence	N (%)	282,461 (2%)	50,683 (7%)	232,691 (9%)
	Thrombophilia	N (%)	6,708 (0%)	2,009 (0%)	6,656 (0%)
	TIA	N (%)	46,375 (0%)	7,968 (1%)	53,115 (2%)
	VTE (narrow definition)	N (%)	56,578 (0%)	12,062 (2%)	66,072 (3%)
Outcomes of interest recorded between 183 and 1 day(s) before index	ATE, myocardial infarction, ischemic heart disease, stroke	N (%)	15,577 (0%)	2,528 (0%)	19,173 (1%)
	VTE, incl. Pulmonary embolism	N (%)	10,252 (0%)	2,165 (0%)	11,765 (0%)
Medications (prescription record within -183 to -1 days before index date)	Anti-inflammatory drugs	N (%)	878,972 (5%)	176,333 (23%)	514,273 (21%)
	Antineoplastic drugs	N (%)	227,115 (1%)	13,821 (2%)	61,442 (2%)
	Antithrombotics	N (%)	261,766 (2%)	46,265 (6%)	384,008 (15%)
	Contraceptives	N (%)	185,795 (1%)	9,520 (1%)	29,091 (1%)
	COVID-19 medicines	N (%)	213 (0%)	11 (0%)	80 (0%)
	Coxibs	N (%)	32,229 (0%)	8,085 (1%)	41,516 (2%)
	Glucocorticoids	N (%)	397,581 (2%)	63,651 (8%)	334,373 (13%)
	Lipid-lowering drugs	N (%)	265,772 (2%)	55,428 (7%)	460,509 (19%)
	RAAS-inhibitors	N (%)	545,235 (3%)	116,500 (15%)	789,441 (32%)
	Sex hormones	N (%)	244,068 (1%)	11,473 (2%)	41,709 (2%)
	Tamoxifen	N (%)	5,331 (0%)	358 (0%)	2,663 (0%)

Variable	Level	Format	Background population	Covid	Vaccinated
Medications (prescription record within -30 to -1 days before index date)	Anti-inflammatory drugs	N (%)	344,566 (2%)	72,303 (10%)	220,280 (9%)
	Antineoplastic drugs	N (%)	159,249 (1%)	8,281 (1%)	41,818 (2%)
	Antithrombotics	N (%)	201,723 (1%)	36,997 (5%)	322,315 (13%)
	Contraceptives	N (%)	138,174 (1%)	6,394 (1%)	21,117 (1%)
	COVID-19 medicines	N (%)	158 (0%)	8 (0%)	69 (0%)
	Coxibs	N (%)	13,821 (0%)	3,158 (0%)	18,958 (1%)
	Glucocorticoids	N (%)	216,230 (1%)	33,449 (4%)	219,755 (9%)
	Lipid-lowering drugs	N (%)	221,367 (1%)	47,565 (6%)	403,849 (16%)
	RAAS-inhibitors	N (%)	475,586 (3%)	103,012 (14%)	709,803 (29%)
	Sex hormones	N (%)	170,422 (1%)	7,362 (1%)	28,211 (1%)
	Tamoxifen	N (%)	4,320 (0%)	250 (0%)	2,106 (0%)

* Future observation time (days) refers to the time that individual remains visible in the database.

Outcomes of interest recorded between 183 and 1 day(s) before index: In the analysis, these people were excluded based on the pre-defined washout window. E.g. Individuals with VTE during this window were excluded from the analysis of VTE, but may be included in the analysis of other outcomes.

Table 12.2.4 Cohort characteristics of SIDIAP.

Variable	Level	Format	Background population	Covid	Vaccinated
Number subjects		N	746,737	200,563	559,696
Number records		N	746,737	212,578	1,500,771
Age		median [q25 - q75]	40 [23 - 57]	43 [25 - 59]	52 [36 - 68]
		mean (sd)	41 (23)	43 (23)	51 (21)
Sex	Female	N (%)	376,562 (50%)	118,509 (56%)	783,261 (52%)
	Male	N (%)	370,175 (50%)	94,069 (44%)	717,510 (48%)
Prior observation		median [q25 - q75]	4,018 [3,075 - 4,018]	5,859 [5,485 - 5,968]	5,650 [5,566 - 5,812]

Variable	Level	Format	Background population	Covid	Vaccinated
		mean (sd)	3,239 (1,388)	5,209 (1,463)	5,276 (1,197)
Future observation		median [q25 - q75]	2,371 [2,371 - 2,371]	518 [385 - 535]	700 [548 - 756]
Age group	0 to 19	N (%)	161,407 (22%)	40,466 (19%)	138,495 (9%)
	20 to 44	N (%)	264,623 (35%)	72,581 (34%)	414,036 (28%)
	45 to 54	N (%)	107,638 (14%)	35,559 (17%)	263,008 (18%)
	55 to 64	N (%)	82,670 (11%)	23,931 (11%)	241,325 (16%)
	65 to 74	N (%)	64,434 (9%)	17,261 (8%)	210,655 (14%)
	75 to 84	N (%)	43,216 (6%)	13,479 (6%)	153,647 (10%)
	85 to 150	N (%)	22,749 (3%)	9,301 (4%)	79,605 (5%)
Immunocompromised	Yes	N (%)	NA	4,249 (2%)	25,842 (2%)
		N (%)	7,009 (1%)	NA	NA
Vaccine doses	0	N (%)	NA	31,276 (15%)	NA
	1	N (%)	NA	18,227 (9%)	556,518 (37%)
	2	N (%)	NA	84,017 (40%)	513,619 (34%)
	3	N (%)	NA	73,108 (34%)	316,406 (21%)
	>=4	N (%)	NA	5,950 (3%)	114,228 (8%)
Previous covid	No	N (%)	NA	174,353 (82%)	1,284,112 (86%)
	Yes	N (%)	NA	38,225 (18%)	216,659 (14%)
Brand	ChAdOx1	N (%)	NA	NA	139,610 (9%)
	Ad26.COV2-S	N (%)	NA	NA	30,618 (2%)
	mRNA-1273	N (%)	NA	NA	406,511 (27%)
	BNT162b2	N (%)	NA	NA	924,032 (62%)
Conditions (within 1 year before index date)	Acute myocardial infarction	N (%)	758 (0%)	442 (0%)	2,978 (0%)
	Alcohol misuse	N (%)	2,666 (0%)	802 (0%)	6,310 (0%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Antiphospholipid syndrome	N (%)	114 (0%)	195 (0%)	1,150 (0%)
	Asthma	N (%)	3,820 (1%)	1,981 (1%)	9,847 (1%)
	Atrial fibrillation	N (%)	15,337 (2%)	6,564 (3%)	58,070 (4%)
	Cancer	N (%)	30,603 (4%)	12,998 (6%)	114,049 (8%)
	Chronic kidney disease	N (%)	6,833 (1%)	3,204 (2%)	21,214 (1%)
	Chronic liver disease	N (%)	972 (0%)	382 (0%)	2,782 (0%)
	Chronic Obstructive Pulmonary Disease	N (%)	4,411 (1%)	1,906 (1%)	13,041 (1%)
	Dementia	N (%)	2,370 (0%)	1,299 (1%)	7,955 (1%)
	Diabetes	N (%)	9,198 (1%)	3,853 (2%)	29,274 (2%)
	Haemorrhagic stroke	N (%)	291 (0%)	119 (0%)	806 (0%)
	Heart failure	N (%)	4,655 (1%)	2,159 (1%)	13,673 (1%)
	Hypertension	N (%)	21,503 (3%)	9,261 (4%)	71,114 (5%)
	Inflammatory bowel disease	N (%)	480 (0%)	262 (0%)	1,516 (0%)
	Ischemic stroke	N (%)	1,261 (0%)	762 (0%)	4,909 (0%)
	Obesity	N (%)	139,689 (19%)	50,204 (24%)	426,160 (28%)
	Rheumatoid arthritis	N (%)	457 (0%)	245 (0%)	1,691 (0%)
	Substance misuse dependence	N (%)	9,417 (1%)	3,019 (1%)	22,408 (1%)
	Thrombophilia	N (%)	318 (0%)	383 (0%)	2,237 (0%)
	TIA	N (%)	4,350 (1%)	1,940 (1%)	16,545 (1%)
	VTE (narrow definition)	N (%)	1,085 (0%)	624 (0%)	4,465 (0%)

Variable	Level	Format	Background population	Covid	Vaccinated
Conditions (anytime to 1 day before index date)	Acute myocardial infarction	N (%)	5,437 (1%)	2,416 (1%)	22,002 (1%)
	Alcohol misuse	N (%)	14,753 (2%)	5,034 (2%)	47,534 (3%)
	Antiphospholipid syndrome	N (%)	114 (0%)	195 (0%)	1,150 (0%)
	Asthma	N (%)	29,742 (4%)	15,192 (7%)	88,476 (6%)
	Atrial fibrillation	N (%)	15,337 (2%)	6,564 (3%)	58,070 (4%)
	Cancer	N (%)	30,603 (4%)	12,998 (6%)	114,049 (8%)
	Chronic kidney disease	N (%)	24,331 (3%)	10,691 (5%)	95,465 (6%)
	Chronic liver disease	N (%)	5,481 (1%)	1,752 (1%)	15,724 (1%)
	Chronic Obstructive Pulmonary Disease	N (%)	17,732 (2%)	6,774 (3%)	63,542 (4%)
	Dementia	N (%)	8,633 (1%)	4,154 (2%)	27,664 (2%)
	Diabetes	N (%)	46,219 (6%)	17,436 (8%)	162,925 (11%)
	Haemorrhagic stroke	N (%)	1,690 (0%)	745 (0%)	6,307 (0%)
	Heart failure	N (%)	13,279 (2%)	5,819 (3%)	46,231 (3%)
	Hypertension	N (%)	108,680 (15%)	38,901 (18%)	381,778 (25%)
	Inflammatory bowel disease	N (%)	2,485 (0%)	1,344 (1%)	9,304 (1%)
	Ischemic stroke	N (%)	8,135 (1%)	3,532 (2%)	30,703 (2%)
	Obesity	N (%)	139,689 (19%)	50,204 (24%)	426,160 (28%)
	Rheumatoid arthritis	N (%)	2,628 (0%)	1,167 (1%)	9,738 (1%)
	Substance misuse dependence	N (%)	84,944 (11%)	30,712 (14%)	241,559 (16%)
	Thrombophilia	N (%)	318 (0%)	383 (0%)	2,237 (0%)
	TIA	N (%)	4,350 (1%)	1,940 (1%)	16,545 (1%)

Variable	Level	Format	Background population	Covid	Vaccinated
	VTE (narrow definition)	N (%)	3,178 (0%)	2,142 (1%)	16,390 (1%)
Outcomes of interest recorded between 183 and 1 day(s) before index	ATE, myocardial infarction, ischemic heart disease, stroke	N (%)	1,037 (0%)	670 (0%)	4,345 (0%)
	VTE, incl. Pulmonary embolism	N (%)	754 (0%)	400 (0%)	3,082 (0%)
Medications (prescription record within -183 to -1 days before index date)	Anti-inflammatory drugs	N (%)	239,730 (32%)	100,171 (47%)	600,814 (40%)
	Antineoplastic drugs	N (%)	20,978 (3%)	10,063 (5%)	64,367 (4%)
	Antithrombotics	N (%)	63,219 (8%)	23,848 (11%)	209,565 (14%)
	Contraceptives	N (%)	13,166 (2%)	7,299 (3%)	37,301 (2%)
	COVID-19 medicines	N (%)	0 (0%)	0 (0%)	0 (0%)
	Coxibs	N (%)	4,225 (1%)	2,157 (1%)	16,058 (1%)
	Glucocorticoids	N (%)	80,674 (11%)	33,108 (16%)	231,456 (15%)
	Lipid-lowering drugs	N (%)	95,667 (13%)	31,592 (15%)	286,064 (19%)
	RAAS-inhibitors	N (%)	93,870 (13%)	30,982 (15%)	321,007 (21%)
	Sex hormones	N (%)	17,316 (2%)	9,206 (4%)	49,484 (3%)
	Tamoxifen	N (%)	803 (0%)	312 (0%)	2,238 (0%)
Medications (prescription record within -30 to -1 days before index date)	Anti-inflammatory drugs	N (%)	133,358 (18%)	69,840 (33%)	407,749 (27%)
	Antineoplastic drugs	N (%)	16,973 (2%)	8,552 (4%)	54,571 (4%)
	Antithrombotics	N (%)	55,476 (7%)	20,948 (10%)	188,551 (13%)
	Contraceptives	N (%)	10,617 (1%)	6,164 (3%)	31,709 (2%)
	COVID-19 medicines	N (%)	0 (0%)	0 (0%)	0 (0%)
	Coxibs	N (%)	1,937 (0%)	1,154 (1%)	9,054 (1%)

Variable	Level	Format	Background population	Covid	Vaccinated
	Glucocorticoids	N (%)	52,996 (7%)	22,763 (11%)	173,878 (12%)
	Lipid-lowering drugs	N (%)	82,895 (11%)	27,427 (13%)	266,868 (18%)
	RAAS-inhibitors	N (%)	90,573 (12%)	29,902 (14%)	313,276 (21%)
	Sex hormones	N (%)	13,376 (2%)	7,495 (4%)	40,839 (3%)
	Tamoxifen	N (%)	715 (0%)	282 (0%)	2,037 (0%)

* Future observation time (days) refers to the time that individual remains visible in the database.

Outcomes of interest recorded between 183 and 1 day(s) before index: In the analysis, these people were excluded based on the pre-defined washout window. E.g. Individuals with VTE during this window were excluded from the analysis of VTE but may be included in the analysis of other outcomes.

Table 12.2.5 Cohort characteristics of Estonia Biobank.

Variable	Level	Format	Background population
Number subjects		N	207,657
Number records		N	207,657
Age		median [q25 – q75]	44 [32 – 57]
		mean (sd)	45 (16)
Sex	Female	N (%)	136,377 (66%)
	Male	N (%)	71,280 (34%)
Prior observation time (days)		Median [q25 - q75]	4,749 [4,749 - 4,749]
		mean (sd)	4,749 (1)
Future observation time (days)		median [q25 - q75]	2,190 [2,190 - 2,190]
		mean (sd)	2,168 (168)
Age group	0 to 19	N (%)	6,957 (3%)
	20 to 44	N (%)	99,341 (48%)
	45 to 54	N (%)	39,392 (19%)
	55 to 64	N (%)	32,029 (15%)

Variable	Level	Format	Background population
	65 to 74	N (%)	19,610 (9%)
	75 to 84	N (%)	8,730 (4%)
	85 to 150	N (%)	1,598 (1%)
Immunocompromised status	Yes	N (%)	6,230 (3%)
Conditions (anytime to 1 day before index date)	Acute myocardial infarction	N (%)	480 (0%)
	Alcohol misuse	N (%)	947 (0%)
	Antiphospholipid syndrome	N (%)	0 (0%)
	Asthma	N (%)	8,555 (4%)
	Atrial fibrillation	N (%)	0 (0%)
	Cancer	N (%)	13,311 (6%)
	Chronic kidney disease	N (%)	1,663 (1%)
	Chronic liver disease	N (%)	909 (0%)
	Chronic Obstructive Pulmonary Disease	N (%)	2,074 (1%)
	Dementia	N (%)	279 (0%)
	Diabetes	N (%)	8,570 (4%)
	Haemorrhagic stroke	N (%)	56 (0%)
	Heart failure	N (%)	9,499 (5%)
	Hypertension	N (%)	45,197 (22%)
	Inflammatory bowel disease	N (%)	542 (0%)
	Ischemic stroke	N (%)	597 (0%)
	Obesity complex	N (%)	24,342 (12%)
	Rheumatoid arthritis	N (%)	2,415 (1%)
	Substance misuse dependence	N (%)	1,397 (1%)
	Thrombophilia	N (%)	0 (0%)
	TIA	N (%)	6,142 (3%)
	VTE (narrow definition)	N (%)	721 (0%)

Variable	Level	Format	Background population
Conditions (within 1 year before index date)	Acute myocardial infarction	N (%)	2,471 (1%)
	Alcohol misuse	N (%)	6,133 (3%)
	Antiphospholipid syndrome	N (%)	0 (0%)
	Asthma	N (%)	21,873 (11%)
	Atrial fibrillation	N (%)	0 (0%)
	Cancer	N (%)	13,311 (6%)
	Chronic kidney disease	N (%)	4,300 (2%)
	Chronic liver disease	N (%)	3,113 (1%)
	Chronic Obstructive Pulmonary Disease	N (%)	7,296 (4%)
	Dementia	N (%)	885 (0%)
	Diabetes	N (%)	14,261 (7%)
	Haemorrhagic stroke	N (%)	378 (0%)
	Heart failure	N (%)	22,929 (11%)
	Hypertension	N (%)	63,627 (31%)
	Inflammatory bowel disease	N (%)	1,919 (1%)
	Ischemic stroke	N (%)	2,119 (1%)
	Obesity	N (%)	24,342 (12%)
	Rheumatoid arthritis	N (%)	10,562 (5%)
	Substance misuse dependence	N (%)	6,719 (3%)
	Thrombophilia	N (%)	0 (0%)
	TIA	N (%)	6,142 (3%)
	VTE (narrow definition)	N (%)	2,890 (1%)
Outcomes of interest recorded between 183 and 1 day(s) before index	ATE, myocardial infarction, ischemic heart disease, stroke	N (%)	742 (0%)
	VTE, incl. Pulmonary embolism	N (%)	529 (0%)

Variable	Level	Format	Background population
Medications (prescription record within -183 to -1 days before index date)	Anti-inflammatory drugs	N (%)	54,346 (26%)
	Antineoplastic drugs	N (%)	20,810 (10%)
	Antithrombotics	N (%)	4,966 (2%)
	Contraceptives	N (%)	20,252 (10%)
	COVID-19 medicines	N (%)	58 (0%)
	Coxibs	N (%)	9,460 (5%)
	Glucocorticoids	N (%)	19,851 (10%)
	Lipid-lowering drugs	N (%)	12,548 (6%)
	RAAS-inhibitors	N (%)	29,807 (14%)
	Sex hormones	N (%)	23,733 (11%)
	Tamoxifen	N (%)	244 (0%)
Medications (prescription record within -30 to -1 days before index date)	Anti-inflammatory drugs	N (%)	23,189 (11%)
	Antineoplastic drugs	N (%)	12,649 (6%)
	Antithrombotics	N (%)	3,416 (2%)
	Contraceptives	N (%)	12,603 (6%)
	COVID-19 medicines	N (%)	24 (0%)
	Coxibs	N (%)	3,403 (2%)
	Glucocorticoids	N (%)	7,381 (4%)
	Lipid-lowering drugs	N (%)	8,429 (4%)
	RAAS-inhibitors	N (%)	21,475 (10%)
	Sex hormones	N (%)	14,271 (7%)
	Tamoxifen	N (%)	140 (0%)

* Future observation time (days) refers to the time that individual remains visible in the database.

Outcomes of interest recorded between 183 and 1 day(s) before index: In the analysis, these people were excluded based on the pre-defined washout window. E.g. Individuals with VTE during this window were excluded from the analysis of VTE, but may be included in the analysis of other outcomes.

12.3 Outcome Data

In CPRD GOLD, a total of 19,931 ATE and 19,009 VTE events were observed in the background population. A total of 146 ATE events and 238 VTE events were observed in individuals within 180 days after COVID-19 infection during Omicron period. In the vaccinated cohort, 6,927 ATE events and 5,874 VTE events were observed during the 180 days post vaccination.

In IPCI, a total of 34,294 ATE and 9,007 VTE events were observed in the background population. A total of 970 ATE events and 391 VTE events were observed in individuals within 180 days after COVID-19 infection during Omicron period. In the vaccinated cohort, 5,109 ATE events and 1,651 VTE events were identified during the 180 days following vaccination.

In IQVIA DA Germany, a total of 43,648 ATE and 61,776 VTE events were observed in the background population. A total of 1,374 ATE events and 1,508 VTE events were observed in individuals within 180 days after COVID-19 infection during Omicron period. In the vaccinated cohort, 7,787 ATE events and 5,408 VTE events were identified during the 180 days following vaccination.

In SIDIAP, 7,647 ATE and 2,730 VTE events were observed in the background population. A total of 610 ATE events and 295 VTE events were observed in individuals within 180 days after COVID-19 infection during Omicron period.

In Estonia Biobank, 3,673 ATE and 2,077 VTE events were observed in the background population.

12.4 Main Results

Objective 1 – Incidence rates in the background pre-pandemic population

The overall crude incidence rates (without any stratification) of the study outcomes for the background pre-pandemic population are shown in table 12.4.1 and figure 12.4.1 below for CPRD GOLD, the Estonian Biobank, IPCI, IQVIA DA Germany and SIDIAP. Crude incidence rates in the pre-pandemic population varied by condition, definition, and database. For example, the crude incidence per 100,000 person years (pys) for venous thromboembolism was 136 in SIDIAP, 167 in CPRD GOLD, 189 in IQVIA Germany, 264 in IPCI and 335 in Estonia biobank, whilst the crude incidence for arterial thromboembolism was 175 in CPRD GOLD, 268 in IQVIA Germany, 381 in SIDIAP, 592 in Estonia biobank and 1001 in IPCI. Crude rates similarly varied for individual conditions. For example, the crude incidence of pulmonary embolism (PE) was 62 in SIDIAP, 77 in CPRD GOLD, 106 in IQVIA Germany, 134 in IPCI and 177 in Estonia biobank, whilst the crude incidence for stroke (any) was 133 in CRPD GOLD, 247 in Estonia biobank, 262 in IQVIA Germany, 267 in SIDIAP and 557 in IPCI.

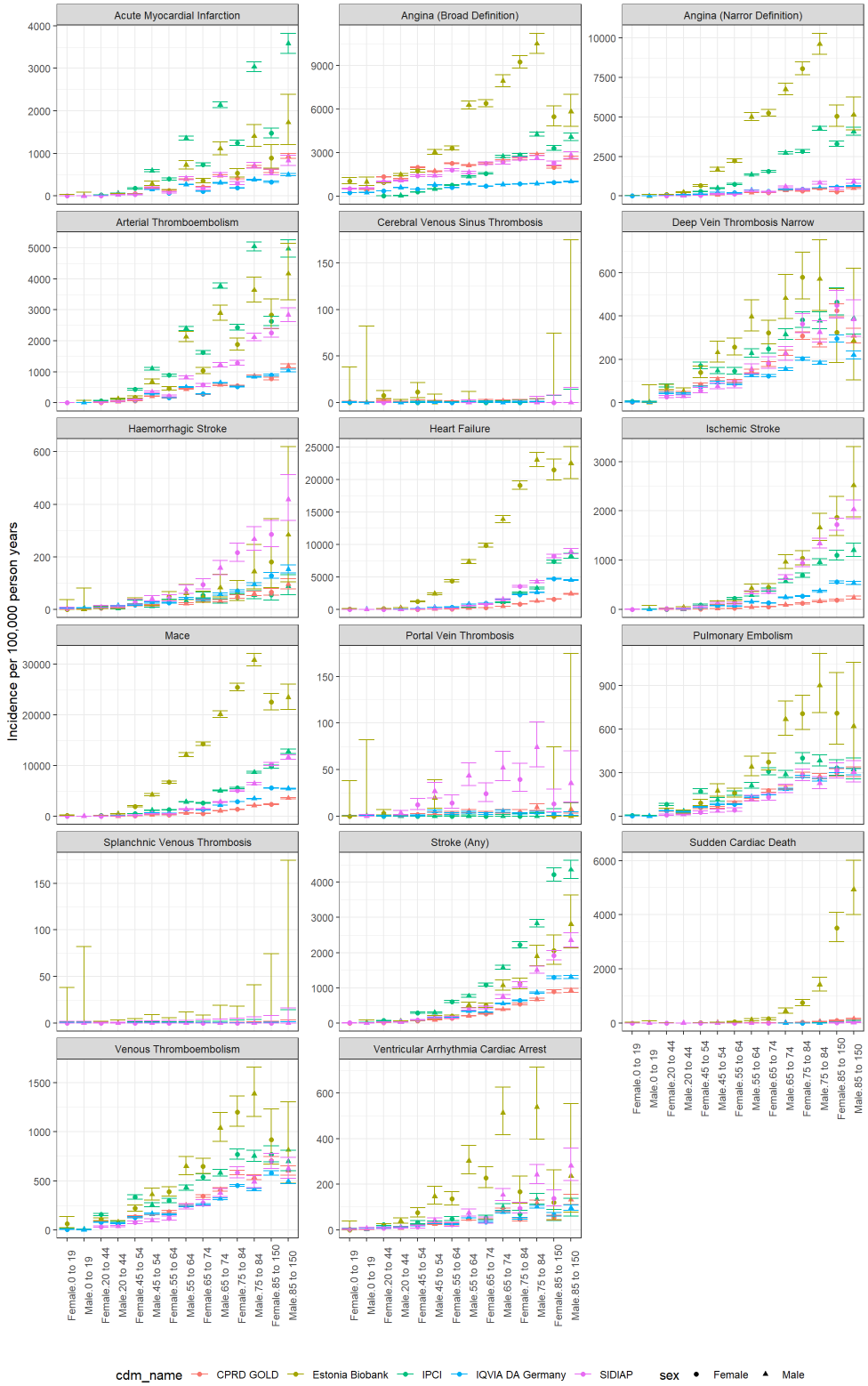
Age-sex specific rates are presented in **Figure 12.4.1**, and the number of events, person-time, and IRs are available in the online web application. We observed that the incidence rates of most of the study events increased with age and were similar between male and female individuals in most included datasets.

Table 12.4.1 Crude incidence rates per 100,000 person-years and 95% confidence interval among background population of each outcome by database.

Outcome	CPRD GOLD	Estonia Biobank	IPCI	IQVIA DA Germany	SIDIAP
Acute Myocardial Infarction	143 [140-145]	193 [182-204]	529 [521-537]	119 [118-121]	137 [132-142]
Angina (Broad Definition)	1527 [1520-1534]	2890 [2848-2933]	763 [754-773]	596 [593-599]	1346 [1330-1362]
Angina (Narrow Definition)	94 [92-95]	1808 [1775-1842]	763 [754-773]	213 [211-214]	138 [133-143]
Arterial Thromboembolism	175 [173-177]	592 [573-611]	1001 [991-1012]	268 [266-270]	381 [372-389]
Cerebral Venous Sinus Thrombosis	1 [1-2]	5 [3-7]	0 [0-0]	1 [0-1]	1 [0-1]
Deep Vein Thrombosis (Narrow Definition)	96 [94-98]	187 [176-198]	137 [133-141]	94 [93-96]	91 [87-95]
Haemorrhagic Stroke	17 [16-18]	32 [28-36]	20 [19-22]	34 [33-34]	55 [52-58]
Heart Failure	185 [183-188]	3468 [3422-3515]	513 [505-520]	771 [768-775]	704 [692-715]
Ischemic Stroke	30 [29-31]	213 [202-225]	189 [184-193]	113 [112-115]	228 [222-235]
MACE	365 [361-368]	5056 [5001-5111]	1579 [1566-1592]	1058 [1054-1062]	1097 [1082-1111]
Portal Vein Thrombosis	2 [2-2]	6 [5-9]	0 [0-0]	2 [2-3]	15 [14-17]
Pulmonary Embolism	77 [75-78]	177 [167-188]	134 [130-138]	106 [105-108]	62 [58-65]
Splanchnic Venous Thrombosis	0 [0-0]	0 [0-1]	0 [0-0]	0 [0-0]	0 [0-0]
Stroke (Any)	133 [131-135]	247 [235-260]	557 [550-565]	262 [260-264]	267 [260-274]
Sudden Cardiac Death	8 [8-9]	182 [171-193]	2 [1-2]	1 [1-1]	1 [1-2]
Venous Thromboembolism	167 [164-169]	335 [321-350]	264 [259-270]	189 [188-191]	136 [131-141]
Ventricular Arrhythmia Cardiac Arrest	25 [24-26]	112 [104-120]	34 [32-36]	33 [32-34]	39 [36-42]

Figure 12.4.1. Age-sex specific incidence rates of study events among the background population.

Figure 12.4.1: Age-sex specific lincidence rates of study events among the background population.



Objective 2 – Incidence rates of VTE and ATE in patients with Covid-19

Among the overall population, the crude incidence rate of VTE and ATE among patients with COVID-19 within 30-, 60-, and 90- and 180-days are presented in **Table 12.4.2** and **Figure 12.4.2-12.4.3**. The crude incidence rate per 100,000 py for venous thromboembolism fell over time in all datasets: in CPRD GOLD 461 [374-562] within 30 days of COVID-19 infection vs 230 [201-261] within 180 days; in IPCI 452 [377-538] within 30 days of COVID-19 infection vs 257 [232-284] within 180 days; in IQVIA DA Germany from 818 [742-899] within 30 days vs 595 [565-626] within 180 days; and in SIDIAP from 577 [471-700] within 30 days vs 305 [271-342] within 180 days. The crude incidence rate per 100,000 py for arterial thromboembolism: in CPRD GOLD fell from 204 [148-275] within 30 days of COVID-19 infection to 141 [119-166] within 180 days; in SIDIAP fell from 931 [795-1084] within 30 days to 631 [582-683] within 180 days; whilst in IPCI and IQVIA DA Germany changes in crude incidence rates at 30- and 180- days were more modest (IPCI 660 [568-762] within 30 days vs 639 [600-681] within 180 days; IQVIA DA Germany 585 [522-654] within 30 days vs 542 [514-572] within 180 days). A similar pattern of changes was observed for individual conditions of venous thromboembolism and arterial thromboembolism.

We stratified the crude incidence rates by the number of SARS-CoV-2 vaccination received prior to index, as well as by prior COVID-19 infection status in each database. Crude incidence rates per 100,000 py appeared to be lower among individuals with a history of prior COVID-19 infection for arterial thromboembolism compared to those with no history in most databases except in SIDIAP (figure 12.4.2). For example, within 90 days after infection, the incidence rate of arterial thromboembolism was 584 [442-756] among individuals with a history of prior COVID-19 infection and 867 [800-939] among those without in IPCI, 514 [442-594] among individuals with a history of prior COVID-19 infection and 612 [566-660] per 100,000 py among those without prior infection in IQVIA DA Germany. In SIDIAP, the crude incidence rate was 913 [726-1134] among individuals with a history of prior COVID-19 infection and 764 [683-853]among those without prior infection.

Crude incidence rates of venous thromboembolism were lower among individuals with a history of prior COVID-19 infection in CPRD GOLD and IPCI up to 90 days after infection, but opposite in IQVIA DA Germany. Within 30 days, the incidence rates were 471 [378-578] per 100,000 py in CPRD GOLD, 486 [403-582] in IPCI, 641 [518-784] in SIDIAP, and 792 [707-885] in IQVIA DA Germany among those without history of prior COVID-19 infection, whilst the 364 [146-750] in CPRD GOLD and 205 [82-422] in IPCI, and 283 [129-537] in SIDIAP, 894 [741-1070] IQVIA DA Germany among those previous infected with COVID-19.

Crude incidence rates per 100,000 py of arterial and venous thromboembolism after COVID-19 infection appeared to be higher among those with a prior history of one, two or three vaccine doses compared to those people with no prior history of vaccination in IQVIA DA Germany only (figure 12.4.3). For example, in IQVIA DA Germany, the 90-day incidence rate of ATE was 389 [350-432] per 100,000 py among people with no prior history of vaccination, and 1003 [830-1202] among people who received three doses before COVID-19 infection. In SIDIAP, the 90-day incidence rate of ATE was 392 [265-560]among people with no prior history of vaccination, and 1084 [890-1308]among people who received three doses before COVID-19 infection. In IPCI, the corresponding rates were 892 [806-984] and 501 [374-656] respectively.

Details on age-sex specific rates for individual outcomes are available in the interactive web applications.

Table 12.4.2. Crude incidence rates of study outcomes among patients with COVID-19 within 30-, 60-, and 90- and 180-days after infection.

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
CPRD GOLD				
Acute Myocardial Infarction	33	21 056,7	30	157 [108-220]
Acute Myocardial Infarction	55	39 793,6	60	138 [104-180]
Acute Myocardial Infarction	69	57 223,6	90	121 [94-153]
Acute Myocardial Infarction	118	103 700,9	180	114 [94-136]
Angina (Broad Definition)	443	20 904,1	30	2119 [1926-2326]
Angina (Broad Definition)	778	39 500,4	60	1970 [1834-2113]
Angina (Broad Definition)	1077	56 798,9	90	1896 [1785-2013]
Angina (Broad Definition)	1675	102 887,7	180	1628 [1551-1708]
Angina (Narrow Definition)	13	21 064,9	30	62 [33-106]
Angina (Narrow Definition)	28	39 809,5	60	70 [47-102]
Angina (Narrow Definition)	39	57 245,9	90	68 [48-93]
Angina (Narrow Definition)	62	103 738,9	180	60 [46-77]
Arterial Thromboembolism	43	21 054,0	30	204 [148-275]
Arterial Thromboembolism	72	39 788,4	60	181 [142-228]
Arterial Thromboembolism	90	57 215,8	90	157 [126-193]
Arterial Thromboembolism	146	103 686,9	180	141 [119-166]
Cerebral Venous Sinus Thrombosis	0	21 074,1	30	0 [0-18]
Cerebral Venous Sinus Thrombosis	0	39 827,2	60	0 [0-9]
Cerebral Venous Sinus Thrombosis	0	57 271,7	90	0 [0-6]
Cerebral Venous Sinus Thrombosis	0	103 787,8	180	0 [0-4]
Deep Vein Thrombosis (Narrow Definition)	28	21 061,9	30	133 [88-192]
Deep Vein Thrombosis (Narrow Definition)	44	39 802,8	60	110 [80-148]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Deep Vein Thrombosis (Narrow Definition)	61	57 235,9	90	107 [82-137]
Deep Vein Thrombosis (Narrow Definition)	84	103 723,4	180	81 [65-100]
Haemorrhagic Stroke	9	21 072,0	30	43 [20-81]
Haemorrhagic Stroke	12	39 822,9	60	30 [16-53]
Haemorrhagic Stroke	14	57 265,4	90	24 [13-41]
Haemorrhagic Stroke	22	103 776,0	180	21 [13-32]
Heart Failure	50	21 049,7	30	238 [176-313]
Heart Failure	79	39 782,4	60	199 [157-248]
Heart Failure	106	57 209,8	90	185 [152-224]
Heart Failure	155	103 689,9	180	150 [127-175]
Ischemic Stroke	6	21 071,1	30	28 [10-62]
Ischemic Stroke	10	39 821,1	60	25 [12-46]
Ischemic Stroke	13	57 262,7	90	23 [12-39]
Ischemic Stroke	19	103 771,8	180	18 [11-29]
MACE	101	21 029,2	30	480 [391-584]
MACE	164	39 743,6	60	413 [352-481]
MACE	213	57 154,2	90	373 [324-426]
MACE	323	103 588,0	180	312 [279-348]
Portal Vein Thrombosis	0	21 074,3	30	0 [0-18]
Portal Vein Thrombosis	NA	39 827,6	60	NA [NA-NA]
Portal Vein Thrombosis	NA	57 272,2	90	NA [NA-NA]
Portal Vein Thrombosis	NA	103 788,3	180	NA [NA-NA]
Pulmonary Embolism	70	21 058,0	30	332 [259-420]
Pulmonary Embolism	98	39 793,9	60	246 [200-300]
Pulmonary Embolism	117	57 222,8	90	204 [169-245]
Pulmonary Embolism	164	103 697,5	180	158 [135-184]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Splanchnic Venous Thrombosis	0	21 074,5	30	0 [0-18]
Splanchnic Venous Thrombosis	0	39 827,9	60	0 [0-9]
Splanchnic Venous Thrombosis	0	57 272,7	90	0 [0-6]
Splanchnic Venous Thrombosis	0	103 789,6	180	0 [0-4]
Stroke (Any)	33	21 059,0	30	157 [108-220]
Stroke (Any)	51	39 797,3	60	128 [95-168]
Stroke (Any)	70	57 228,7	90	122 [95-154]
Stroke (Any)	112	103 709,0	180	108 [89-130]
Sudden Cardiac Death	NA	21 074,3	30	NA [NA-NA]
Sudden Cardiac Death	NA	39 827,5	60	NA [NA-NA]
Sudden Cardiac Death	NA	57 272,3	90	NA [NA-NA]
Sudden Cardiac Death	NA	103 789,0	180	NA [NA-NA]
Venous Thromboembolism	97	21 046,4	30	461 [374-562]
Venous Thromboembolism	138	39 770,9	60	347 [292-410]
Venous Thromboembolism	171	57 189,5	90	299 [256-347]
Venous Thromboembolism	238	103 639,0	180	230 [201-261]
Ventricular Arrhythmia Cardiac Arrest	5	21 071,9	30	24 [8-55]
Ventricular Arrhythmia Cardiac Arrest	8	39 822,6	60	20 [9-40]
Ventricular Arrhythmia Cardiac Arrest	12	57 264,8	90	21 [11-37]
Ventricular Arrhythmia Cardiac Arrest	17	103 774,2	180	16 [10-26]
IPCI				
Acute Myocardial Infarction	90	28 041,9	30	321 [258-394]
Acute Myocardial Infarction	191	54 461,7	60	351 [303-404]
Acute Myocardial Infarction	261	80 358,7	90	325 [287-367]
Acute Myocardial Infarction	420	151 757,0	180	277 [251-304]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Angina (Broad Definition)	153	28 050,5	30	545 [462-639]
Angina (Broad Definition)	306	54 482,2	60	562 [500-628]
Angina (Broad Definition)	455	80 395,7	90	566 [515-620]
Angina (Broad Definition)	692	151 826,8	180	456 [422-491]
Angina (Narrow Definition)	153	28 050,5	30	545 [462-639]
Angina (Narrow Definition)	306	54 482,2	60	562 [500-628]
Angina (Narrow Definition)	455	80 395,7	90	566 [515-620]
Angina (Narrow Definition)	692	151 826,8	180	456 [422-491]
Arterial Thromboembolism	185	28 020,2	30	660 [568-762]
Arterial Thromboembolism	445	54 434,9	60	818 [743-897]
Arterial Thromboembolism	669	80 338,2	90	833 [771-898]
Arterial Thromboembolism	970	151 712,8	180	639 [600-681]
Cerebral Venous Sinus Thrombosis	0	28 131,5	30	0 [0-13]
Cerebral Venous Sinus Thrombosis	0	54 631,9	60	0 [0-7]
Cerebral Venous Sinus Thrombosis	0	80 606,4	90	0 [0-5]
Cerebral Venous Sinus Thrombosis	0	152 209,1	180	0 [0-2]
Deep Vein Thrombosis (Narrow Definition)	41	28 113,7	30	146 [105-198]
Deep Vein Thrombosis (Narrow Definition)	79	54 596,7	60	145 [115-180]
Deep Vein Thrombosis (Narrow Definition)	106	80 553,8	90	132 [108-159]
Deep Vein Thrombosis (Narrow Definition)	172	152 106,4	180	113 [97-131]
Haemorrhagic Stroke	NA	28 129,1	30	NA [NA-NA]
Haemorrhagic Stroke	NA	54 627,3	60	NA [NA-NA]
Haemorrhagic Stroke	6	80 600,0	90	7 [3-16]
Haemorrhagic Stroke	15	152 198,9	180	10 [6-16]
Heart Failure	107	28 065,7	30	381 [312-461]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Heart Failure	209	54 506,2	60	383 [333-439]
Heart Failure	307	80 422,1	90	382 [340-427]
Heart Failure	524	151 892,1	180	345 [316-376]
Ischemic Stroke	34	28 103,5	30	121 [84-169]
Ischemic Stroke	66	54 579,6	60	121 [94-154]
Ischemic Stroke	87	80 530,2	90	108 [86-133]
Ischemic Stroke	135	152 070,4	180	89 [74-105]
MACE	324	27 962,0	30	1159 [1036-1292]
MACE	777	54 335,6	60	1430 [1331-1534]
MACE	1194	80 208,1	90	1489 [1405-1576]
MACE	1714	151 471,7	180	1132 [1079-1186]
Portal Vein Thrombosis	0	28 131,5	30	0 [0-13]
Portal Vein Thrombosis	0	54 631,9	60	0 [0-7]
Portal Vein Thrombosis	0	80 606,4	90	0 [0-5]
Portal Vein Thrombosis	0	152 209,1	180	0 [0-2]
Pulmonary Embolism	89	28 105,0	30	317 [254-390]
Pulmonary Embolism	130	54 578,2	60	238 [199-283]
Pulmonary Embolism	159	80 525,8	90	198 [168-231]
Pulmonary Embolism	232	152 064,3	180	153 [134-174]
Splanchnic Venous Thrombosis	0	28 131,5	30	0 [0-13]
Splanchnic Venous Thrombosis	0	54 631,9	60	0 [0-7]
Splanchnic Venous Thrombosis	0	80 606,4	90	0 [0-5]
Splanchnic Venous Thrombosis	0	152 209,1	180	0 [0-2]
Stroke (Any)	106	28 051,2	30	378 [309-457]
Stroke (Any)	200	54 478,0	60	367 [318-422]
Stroke (Any)	278	80 383,8	90	346 [306-389]
Stroke (Any)	460	151 809,2	180	303 [276-332]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Sudden Cardiac Death	0	28 131,5	30	0 [0-13]
Sudden Cardiac Death	0	54 631,9	60	0 [0-7]
Sudden Cardiac Death	0	80 606,4	90	0 [0-5]
Sudden Cardiac Death	NA	152 209,1	180	NA [NA-NA]
Venous Thromboembolism	127	28 087,9	30	452 [377-538]
Venous Thromboembolism	204	54 544,4	60	374 [324-429]
Venous Thromboembolism	256	80 474,6	90	318 [280-360]
Venous Thromboembolism	391	151 965,2	180	257 [232-284]
Ventricular Arrhythmia Cardiac Arrest	8	28 125,8	30	28 [12-56]
Ventricular Arrhythmia Cardiac Arrest	20	54 620,5	60	37 [22-57]
Ventricular Arrhythmia Cardiac Arrest	24	80 588,4	90	30 [19-44]
Ventricular Arrhythmia Cardiac Arrest	35	152 173,2	180	23 [16-32]
IQVIA DA Germany				
Acute Myocardial Infarction	157	52 912,7	30	297 [252-347]
Acute Myocardial Infarction	272	99 440,2	60	274 [242-308]
Acute Myocardial Infarction	380	143 287,6	90	265 [239-293]
Acute Myocardial Infarction	604	253 862,5	180	238 [219-258]
Angina (Broad Definition)	1518	52 472,7	30	2893 [2749-3042]
Angina (Broad Definition)	2551	98 573,6	60	2588 [2488-2690]
Angina (Broad Definition)	3403	141 996,2	90	2396 [2317-2478]
Angina (Broad Definition)	5368	251 402,0	180	2135 [2078-2193]
Angina (Narrow Definition)	271	52 892,5	30	512 [453-577]
Angina (Narrow Definition)	474	99 398,2	60	477 [435-522]
Angina (Narrow Definition)	683	143 224,5	90	477 [442-514]
Angina (Narrow Definition)	1185	253 734,3	180	467 [441-494]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Arterial Thromboembolism	309	52 813,5	30	585 [522-654]
Arterial Thromboembolism	575	99 254,3	60	579 [533-629]
Arterial Thromboembolism	840	143 028,2	90	587 [548-628]
Arterial Thromboembolism	1374	253 423,8	180	542 [514-572]
Cerebral Venous Sinus Thrombosis	NA	53 036,8	30	NA [NA-NA]
Cerebral Venous Sinus Thrombosis	NA	99 681,1	60	NA [NA-NA]
Cerebral Venous Sinus Thrombosis	5	143 641,2	90	4 [1-8]
Cerebral Venous Sinus Thrombosis	6	254 509,0	180	2 [1-5]
Deep Vein Thrombosis (Narrow Definition)	155	52 942,1	30	293 [248-343]
Deep Vein Thrombosis (Narrow Definition)	274	99 498,4	60	275 [244-310]
Deep Vein Thrombosis (Narrow Definition)	409	143 372,3	90	285 [258-314]
Deep Vein Thrombosis (Narrow Definition)	719	254 008,3	180	283 [263-304]
Haemorrhagic Stroke	42	53 010,2	30	79 [57-107]
Haemorrhagic Stroke	82	99 630,1	60	82 [66-102]
Haemorrhagic Stroke	109	143 565,9	90	76 [62-92]
Haemorrhagic Stroke	203	254 381,1	180	80 [69-92]
Heart Failure	642	52 501,1	30	1223 [1130-1321]
Heart Failure	1145	98 660,3	60	1160 [1094-1230]
Heart Failure	1668	142 177,1	90	1173 [1118-1231]
Heart Failure	2961	252 027,8	180	1175 [1133-1218]
Ischemic Stroke	141	52 931,6	30	266 [224-314]
Ischemic Stroke	252	99 478,5	60	253 [223-287]
Ischemic Stroke	337	143 344,0	90	235 [211-262]
Ischemic Stroke	540	253 978,6	180	213 [195-231]
MACE	998	52 289,9	30	1909 [1792-2031]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
MACE	1851	98 269,7	60	1884 [1799-1971]
MACE	2729	141 635,0	90	1927 [1855-2000]
MACE	4564	251 077,3	180	1818 [1765-1871]
Portal Vein Thrombosis	8	53 034,0	30	15 [6-30]
Portal Vein Thrombosis	14	99 675,8	60	14 [8-24]
Portal Vein Thrombosis	15	143 633,3	90	10 [6-17]
Portal Vein Thrombosis	26	254 496,2	180	10 [7-15]
Pulmonary Embolism	316	52 912,2	30	597 [533-667]
Pulmonary Embolism	461	99 436,6	60	464 [422-508]
Pulmonary Embolism	578	143 283,1	90	403 [371-438]
Pulmonary Embolism	903	253 883,3	180	356 [333-380]
Splanchnic Venous Thrombosis	0	53 037,4	30	0 [0-7]
Splanchnic Venous Thrombosis	0	99 682,3	60	0 [0-4]
Splanchnic Venous Thrombosis	0	143 643,0	90	0 [0-3]
Splanchnic Venous Thrombosis	0	254 513,0	180	0 [0-1]
Stroke (Any)	265	52 825,6	30	502 [443-566]
Stroke (Any)	465	99 276,1	60	468 [427-513]
Stroke (Any)	638	143 050,1	90	446 [412-482]
Stroke (Any)	1092	253 469,5	180	431 [406-457]
Sudden Cardiac Death	NA	53 037,1	30	NA [NA-NA]
Sudden Cardiac Death	6	99 681,6	60	6 [2-13]
Sudden Cardiac Death	8	143 642,1	90	6 [2-11]
Sudden Cardiac Death	11	254 511,6	180	4 [2-8]
Venous Thromboembolism	432	52 831,5	30	818 [742-899]
Venous Thromboembolism	677	99 281,3	60	682 [632-735]
Venous Thromboembolism	912	143 055,0	90	638 [597-680]
Venous Thromboembolism	1508	253 465,7	180	595 [565-626]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Ventricular Arrhythmia Cardiac Arrest	33	53 006,9	30	62 [43-87]
Ventricular Arrhythmia Cardiac Arrest	76	99 623,5	60	76 [60-96]
Ventricular Arrhythmia Cardiac Arrest	111	143 557,4	90	77 [64-93]
Ventricular Arrhythmia Cardiac Arrest	209	254 369,7	180	82 [71-94]
SIDIAP				
Acute Myocardial Infarction	57	17 867,7	30	319 [242-413]
Acute Myocardial Infarction	95	34 761,8	60	273 [221-334]
Acute Myocardial Infarction	129	51 083,9	90	252 [211-300]
Acute Myocardial Infarction	200	96 850,2	180	206 [179-237]
Angina (Broad Definition)	411	17 721,6	30	2319 [2100-2555]
Angina (Broad Definition)	772	34 467,6	60	2240 [2085-2404]
Angina (Broad Definition)	1104	50 639,7	90	2180 [2053-2313]
Angina (Broad Definition)	1857	95 940,2	180	1936 [1848-2026]
Angina (Narrow Definition)	53	17 873,9	30	296 [222-388]
Angina (Narrow Definition)	97	34 773,3	60	279 [226-340]
Angina (Narrow Definition)	131	51 101,5	90	256 [214-304]
Angina (Narrow Definition)	205	96 883,0	180	212 [184-243]
Arterial Thromboembolism	166	17 827,7	30	931 [795-1084]
Arterial Thromboembolism	288	34 686,4	60	830 [737-932]
Arterial Thromboembolism	403	50 978,8	90	790 [715-872]
Arterial Thromboembolism	610	96 651,4	180	631 [582-683]
Cerebral Venous Sinus Thrombosis	0	17 895,0	30	0 [0-21]
Cerebral Venous Sinus Thrombosis	NA	34 813,9	60	NA [NA-NA]
Cerebral Venous Sinus Thrombosis	NA	51 160,8	90	NA [NA-NA]
Cerebral Venous Sinus Thrombosis	NA	96 994,9	180	NA [NA-NA]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Deep Vein Thrombosis (Narrow Definition)	45	17 869,3	30	252 [184-337]
Deep Vein Thrombosis (Narrow Definition)	78	34 762,8	60	224 [177-280]
Deep Vein Thrombosis (Narrow Definition)	109	51 085,5	90	213 [175-257]
Deep Vein Thrombosis (Narrow Definition)	169	96 850,5	180	174 [149-203]
Haemorrhagic Stroke	23	17 887,6	30	129 [82-193]
Haemorrhagic Stroke	34	34 799,2	60	98 [68-136]
Haemorrhagic Stroke	44	51 139,2	90	86 [62-116]
Haemorrhagic Stroke	78	96 953,3	180	80 [64-100]
Heart Failure	390	17 744,0	30	2198 [1985-2427]
Heart Failure	600	34 533,4	60	1737 [1601-1882]
Heart Failure	781	50 763,8	90	1538 [1432-1650]
Heart Failure	1195	96 326,7	180	1241 [1171-1313]
Ischemic Stroke	83	17 850,2	30	465 [370-576]
Ischemic Stroke	136	34 726,0	60	392 [329-463]
Ischemic Stroke	182	51 030,9	90	357 [307-412]
Ischemic Stroke	311	96 755,7	180	321 [287-359]
MACE	580	17 696,1	30	3278 [3016-3556]
MACE	969	34 454,5	60	2812 [2638-2995]
MACE	1305	50 663,7	90	2576 [2438-2719]
MACE	1929	96 130,3	180	2007 [1918-2098]
Portal Vein Thrombosis	8	17 892,6	30	45 [19-88]
Portal Vein Thrombosis	13	34 809,2	60	37 [20-64]
Portal Vein Thrombosis	17	51 153,9	90	33 [19-53]
Portal Vein Thrombosis	22	96 982,4	180	23 [14-34]
Pulmonary Embolism	76	17 873,5	30	425 [335-532]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Pulmonary Embolism	107	34 771,4	60	308 [252-372]
Pulmonary Embolism	132	51 097,3	90	258 [216-306]
Pulmonary Embolism	169	96 876,5	180	174 [149-203]
Splanchnic Venous Thrombosis	0	17 895,2	30	0 [0-21]
Splanchnic Venous Thrombosis	0	34 814,4	60	0 [0-11]
Splanchnic Venous Thrombosis	0	51 161,6	90	0 [0-7]
Splanchnic Venous Thrombosis	0	96 996,8	180	0 [0-4]
Stroke (Any)	98	17 846,0	30	549 [446-669]
Stroke (Any)	156	34 717,7	60	449 [382-526]
Stroke (Any)	209	51 018,8	90	410 [356-469]
Stroke (Any)	361	96 732,9	180	373 [336-414]
Sudden Cardiac Death	NA	17 895,2	30	NA [NA-NA]
Sudden Cardiac Death	NA	34 814,4	60	NA [NA-NA]
Sudden Cardiac Death	NA	51 161,6	90	NA [NA-NA]
Sudden Cardiac Death	NA	96 996,8	180	NA [NA-NA]
Venous Thromboembolism	103	17 852,8	30	577 [471-700]
Venous Thromboembolism	156	34 730,6	60	449 [382-525]
Venous Thromboembolism	204	51 037,4	90	400 [347-458]
Venous Thromboembolism	295	96 762,9	180	305 [271-342]
Ventricular Arrhythmia Cardiac Arrest	18	17 888,4	30	101 [60-159]
Ventricular Arrhythmia Cardiac Arrest	32	34 801,0	60	92 [63-130]
Ventricular Arrhythmia Cardiac Arrest	43	51 141,8	90	84 [61-113]
Ventricular Arrhythmia Cardiac Arrest	61	96 960,7	180	63 [48-81]

Figure 12.4.2 Age-sex specific incidence rates for ATE and VTE among COVID-19.

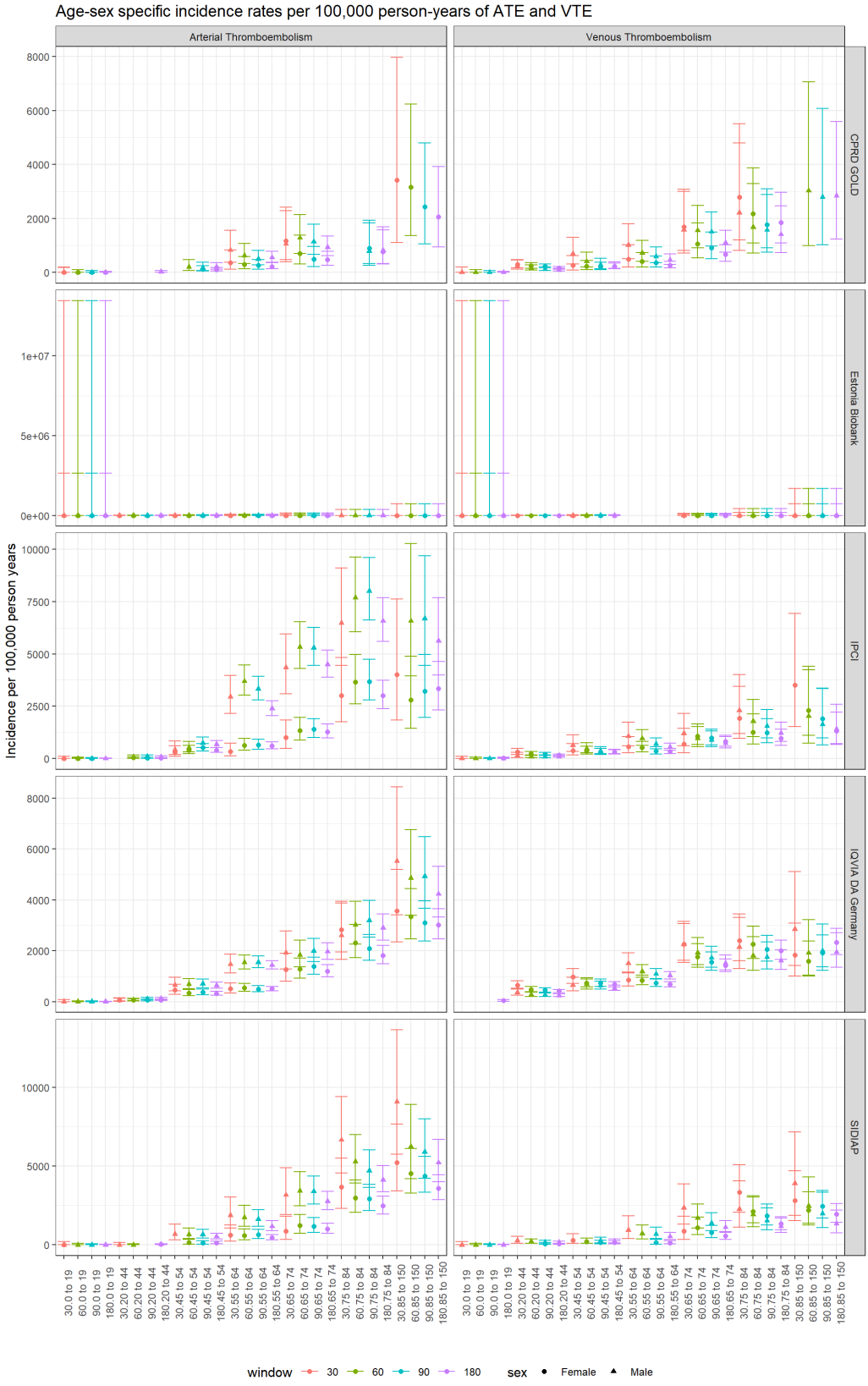
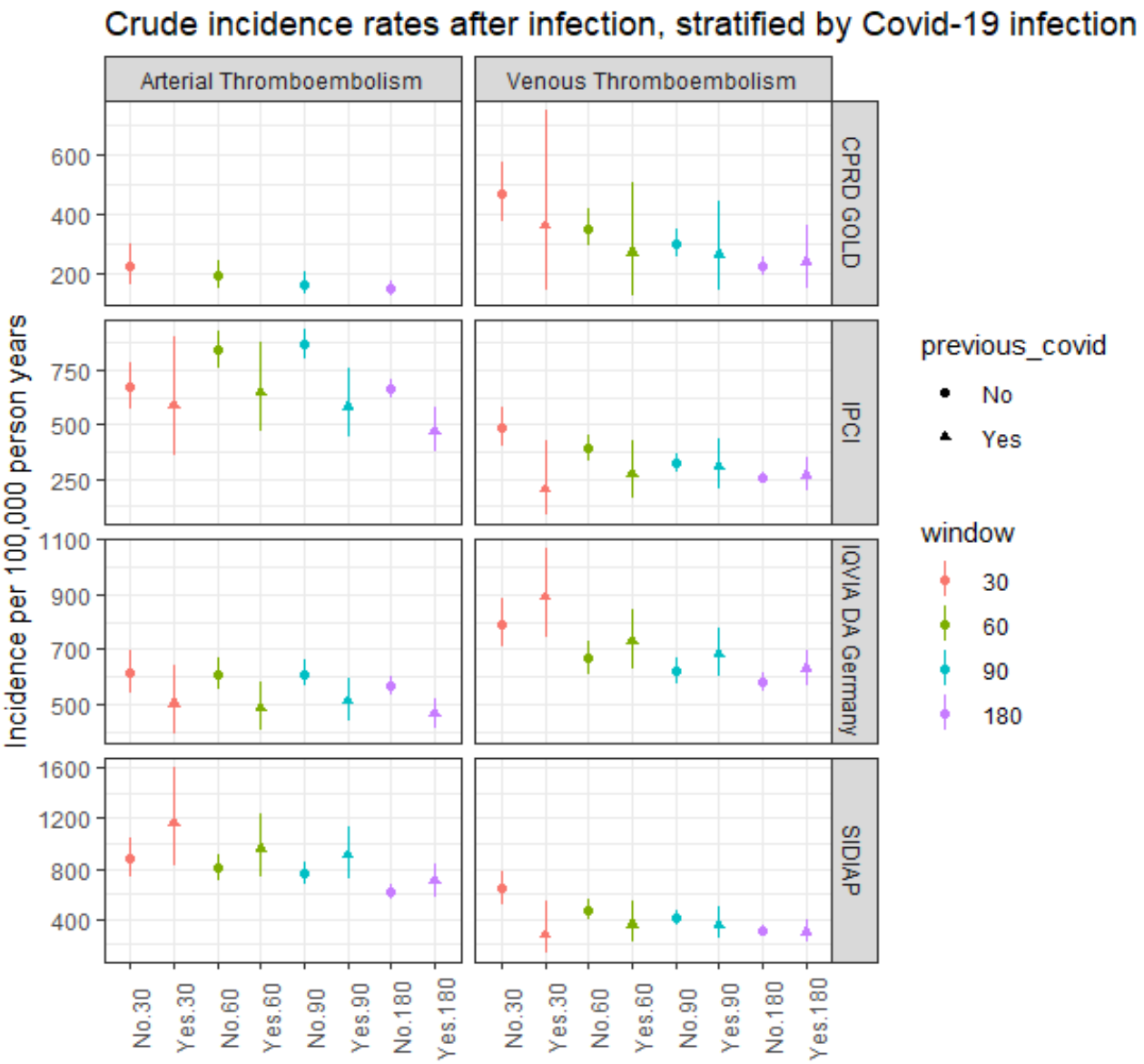
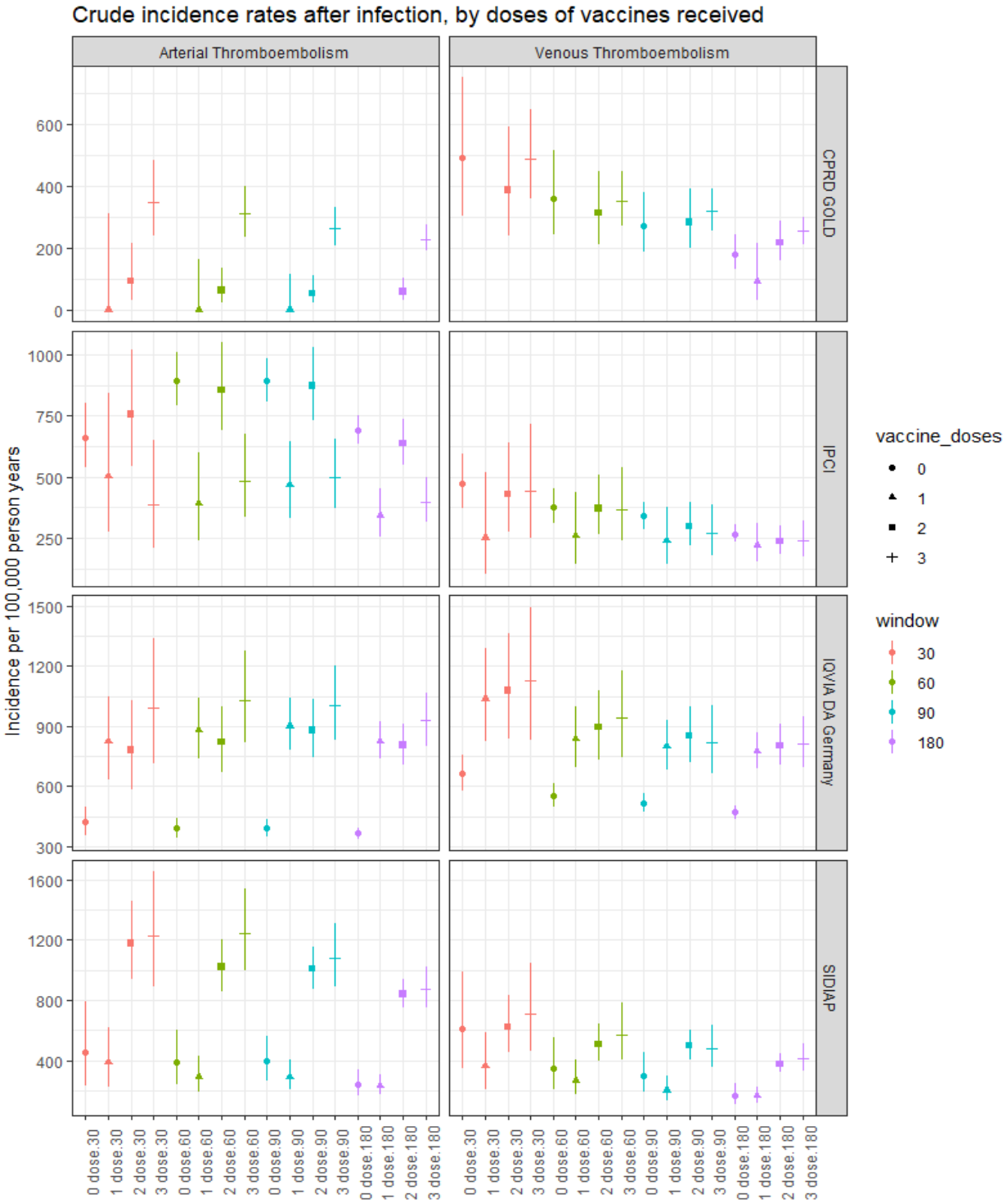


Figure 12.4.3 Crude incidence rates within 90 days after infection, stratified by Covid-19 infection history.



* number of events among people with Covid-19 history in CPRD GOLD was below 5 thus not shown here.

Figure 12.4.4 Incidence rates after infection, stratified by number of doses of vaccines received prior to infection.



Objective 3 – Incidence rates of VTE and ATE after Covid-19 vaccination

The crude incidence rate of VTE and ATE during the 30-, 60-, and 90- and 180-days after COVID-19 vaccination are presented in the table 12.4.3 below. Among the overall population, the crude incidence rate per 100,000 py for venous thromboembolism following COVID-19 vaccination was 215 [204-228] within 30 days vs 242 [236-248] within 180 days in CPRD GOLD; in IPCI it was 304 [275-334] within 30 days vs 292 [278-307] within 180 days; in IQVIA Germany it was 542 [510-576] within 30 days vs 645 [628-663] within 180 days; and in SIDIAP it was 240 [212-269] within 30 days and 257 [243-271] within 180 days. Among the overall population, the crude incidence rate per 100,000 py for arterial thromboembolism following COVID-19 vaccination was 258 [245-271] within 30 days vs 285 [278-292] within 180 days in CPRD GOLD; in IPCI it was 879 [830-931] within 30 days vs 906 [882-932] within 180 days; in IQVIA Germany it was 704 [667-742] within 30 days vs 932 [912-953] within 180 days; and in SIDIAP it was 794 [744-847] within 30 days and 858 [833-884] within 180 days. In general, crude incidence rates for arterial and venous thromboembolism events modestly increased or remained similar with increasing time windows. A similar pattern was observed for individual conditions.

Table 12.4.3 Crude incidence rates of study outcomes after COVID-19 vaccination within 30-, 60-, and 90- and 180-days.

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
CPRD GOLD				
Acute Myocardial Infarction	1187	580 327,6	30	204 [193-216]
Acute Myocardial Infarction	2371	1 106 527,8	60	214 [206-223]
Acute Myocardial Infarction	3345	1 510 478,0	90	222 [214-229]
Acute Myocardial Infarction	5450	2 430 333,5	180	224 [218-230]
Angina (Broad Definition)	7951	577 140,9	30	1378 [1348-1408]
Angina (Broad Definition)	15594	1 100 500,2	60	1417 [1395-1439]
Angina (Broad Definition)	21623	1 502 301,0	90	1439 [1420-1459]
Angina (Broad Definition)	34613	2 417 026,4	180	1432 [1417-1447]
Angina (Narrow Definition)	733	580 613,2	30	126 [117-136]
Angina (Narrow Definition)	1546	1 107 115,0	60	140 [133-147]
Angina (Narrow Definition)	2170	1 511 336,0	90	144 [138-150]
Angina (Narrow Definition)	3605	2 431 927,4	180	148 [143-153]
Arterial Thromboembolism	1497	580 227,2	30	258 [245-271]
Arterial Thromboembolism	3028	1 106 334,7	60	274 [264-284]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Arterial Thromboembolism	4305	1 510 209,5	90	285 [277-294]
Arterial Thromboembolism	6927	2 429 827,4	180	285 [278-292]
Cerebral Venous Sinus Thrombosis	8	581 020,9	30	1 [1-3]
Cerebral Venous Sinus Thrombosis	19	1 107 909,5	60	2 [1-3]
Cerebral Venous Sinus Thrombosis	28	1 512 450,7	90	2 [1-3]
Cerebral Venous Sinus Thrombosis	53	2 433 916,5	180	2 [2-3]
Deep Vein Thrombosis (Narrow Definition)	642	580 650,5	30	111 [102-120]
Deep Vein Thrombosis (Narrow Definition)	1264	1 107 170,9	60	114 [108-121]
Deep Vein Thrombosis (Narrow Definition)	1825	1 511 396,2	90	121 [115-126]
Deep Vein Thrombosis (Narrow Definition)	3057	2 432 032,0	180	126 [121-130]
Haemorrhagic Stroke	114	580 949,3	30	20 [16-24]
Haemorrhagic Stroke	242	1 107 766,1	60	22 [19-25]
Haemorrhagic Stroke	376	1 512 242,8	90	25 [22-28]
Haemorrhagic Stroke	650	2 433 527,2	180	27 [25-29]
Heart Failure	1728	580 122,6	30	298 [284-312]
Heart Failure	3502	1 106 131,4	60	317 [306-327]
Heart Failure	4882	1 509 914,7	90	323 [314-332]
Heart Failure	8146	2 429 404,5	180	335 [328-343]
Ischemic Stroke	229	580 890,9	30	39 [34-45]
Ischemic Stroke	452	1 107 645,3	60	41 [37-45]
Ischemic Stroke	650	1 512 069,4	90	43 [40-46]
Ischemic Stroke	1091	2 433 212,1	180	45 [42-48]
MACE	3357	579 337,9	30	580 [560-599]
MACE	6867	1 104 626,6	60	622 [607-636]
MACE	9750	1 507 825,5	90	647 [634-660]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
MACE	15748	2 425 711,4	180	649 [639-659]
Portal Vein Thrombosis	17	581 015,9	30	3 [2-5]
Portal Vein Thrombosis	46	1 107 899,2	60	4 [3-6]
Portal Vein Thrombosis	65	1 512 436,2	90	4 [3-6]
Portal Vein Thrombosis	115	2 433 888,4	180	5 [4-6]
Pulmonary Embolism	643	580 619,6	30	111 [102-120]
Pulmonary Embolism	1276	1 107 108,4	60	115 [109-122]
Pulmonary Embolism	1830	1 511 303,2	90	121 [116-127]
Pulmonary Embolism	3016	2 431 871,9	180	124 [120-128]
Splanchnic Venous Thrombosis	0	581 026,7	30	0 [0-1]
Splanchnic Venous Thrombosis	0	1 107 921,2	60	0 [0-0]
Splanchnic Venous Thrombosis	0	1 512 467,6	90	0 [0-0]
Splanchnic Venous Thrombosis	0	2 433 948,5	180	0 [0-0]
Stroke (Any)	1104	580 407,3	30	190 [179-202]
Stroke (Any)	2206	1 106 678,4	60	199 [191-208]
Stroke (Any)	3150	1 510 684,0	90	208 [201-216]
Stroke (Any)	5134	2 430 685,8	180	211 [206-217]
Sudden Cardiac Death	37	581 024,1	30	6 [4-9]
Sudden Cardiac Death	90	1 107 916,1	60	8 [6-10]
Sudden Cardiac Death	132	1 512 460,9	90	9 [7-10]
Sudden Cardiac Death	245	2 433 937,6	180	10 [9-11]
Venous Thromboembolism	1250	580 268,9	30	215 [204-228]
Venous Thromboembolism	2458	1 106 414,6	60	222 [214-231]
Venous Thromboembolism	3536	1 510 323,0	90	234 [226-242]
Venous Thromboembolism	5874	2 430 154,3	180	242 [236-248]
Ventricular Arrhythmia Cardiac Arrest	150	580 945,7	30	26 [22-30]
Ventricular Arrhythmia Cardiac Arrest	304	1 107 756,8	60	27 [24-31]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Ventricular Arrhythmia Cardiac Arrest	447	1 512 232,4	90	30 [27-32]
Ventricular Arrhythmia Cardiac Arrest	733	2 433 515,8	180	30 [28-32]
IPCI				
Acute Myocardial Infarction	666	136 980,3	30	486 [450-525]
Acute Myocardial Infarction	1193	241 748,3	60	494 [466-522]
Acute Myocardial Infarction	1711	334 645,6	90	511 [487-536]
Acute Myocardial Infarction	2720	563 912,1	180	482 [464-501]
Angina (Broad Definition)	962	137 033,4	30	702 [658-748]
Angina (Broad Definition)	1817	241 852,2	60	751 [717-787]
Angina (Broad Definition)	2554	334 801,9	90	763 [734-793]
Angina (Broad Definition)	3875	564 145,8	180	687 [665-709]
Angina (Narrow Definition)	962	137 033,4	30	702 [658-748]
Angina (Narrow Definition)	1817	241 852,2	60	751 [717-787]
Angina (Narrow Definition)	2554	334 801,9	90	763 [734-793]
Angina (Narrow Definition)	3875	564 145,8	180	687 [665-709]
Arterial Thromboembolism	1203	136 790,4	30	879 [830-931]
Arterial Thromboembolism	2309	241 455,6	60	956 [918-996]
Arterial Thromboembolism	3388	334 316,9	90	1013 [980-1048]
Arterial Thromboembolism	5106	563 403,6	180	906 [882-932]
Cerebral Venous Sinus Thrombosis	0	137 640,4	30	0 [0-3]
Cerebral Venous Sinus Thrombosis	0	242 887,0	60	0 [0-2]
Cerebral Venous Sinus Thrombosis	0	336 166,6	90	0 [0-1]
Cerebral Venous Sinus Thrombosis	0	566 395,9	180	0 [0-1]
Deep Vein Thrombosis (Narrow Definition)	205	137 501,4	30	149 [129-171]
Deep Vein Thrombosis (Narrow Definition)	375	242 641,6	60	154 [139-171]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Deep Vein Thrombosis (Narrow Definition)	518	335 824,2	90	154 [141-168]
Deep Vein Thrombosis (Narrow Definition)	831	565 785,9	180	147 [137-157]
Haemorrhagic Stroke	13	137 628,2	30	9 [5-16]
Haemorrhagic Stroke	35	242 865,4	60	14 [10-20]
Haemorrhagic Stroke	46	336 136,7	90	14 [10-18]
Haemorrhagic Stroke	75	566 348,1	180	13 [10-17]
Heart Failure	844	137 082,8	30	616 [575-659]
Heart Failure	1614	241 888,9	60	667 [635-701]
Heart Failure	2338	334 786,1	90	698 [670-727]
Heart Failure	3962	564 062,0	180	702 [681-725]
Ischemic Stroke	269	137 413,2	30	196 [173-221]
Ischemic Stroke	488	242 492,3	60	201 [184-220]
Ischemic Stroke	655	335 635,3	90	195 [180-211]
Ischemic Stroke	1016	565 524,8	180	180 [169-191]
MACE	2237	136 288,8	30	1641 [1574-1711]
MACE	4514	240 607,6	60	1876 [1822-1932]
MACE	6683	333 206,7	90	2006 [1958-2054]
MACE	10040	561 485,6	180	1788 [1753-1823]
Portal Vein Thrombosis	0	137 640,4	30	0 [0-3]
Portal Vein Thrombosis	0	242 887,0	60	0 [0-2]
Portal Vein Thrombosis	0	336 166,6	90	0 [0-1]
Portal Vein Thrombosis	0	566 395,9	180	0 [0-1]
Pulmonary Embolism	218	137 489,1	30	159 [138-181]
Pulmonary Embolism	374	242 617,9	60	154 [139-171]
Pulmonary Embolism	507	335 792,4	90	151 [138-165]
Pulmonary Embolism	850	565 741,5	180	150 [140-161]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Splanchnic Venous Thrombosis	0	137 640,4	30	0 [0-3]
Splanchnic Venous Thrombosis	0	242 887,0	60	0 [0-2]
Splanchnic Venous Thrombosis	0	336 166,6	90	0 [0-1]
Splanchnic Venous Thrombosis	0	566 395,9	180	0 [0-1]
Stroke (Any)	886	137 001,9	30	647 [605-691]
Stroke (Any)	1593	241 755,1	60	659 [627-692]
Stroke (Any)	2172	334 608,1	90	649 [622-677]
Stroke (Any)	3599	563 747,2	180	638 [618-660]
Sudden Cardiac Death	0	137 640,4	30	0 [0-3]
Sudden Cardiac Death	NA	242 887,0	60	NA [NA-NA]
Sudden Cardiac Death	NA	336 166,6	90	NA [NA-NA]
Sudden Cardiac Death	7	566 395,9	180	1 [0-2]
Venous Thromboembolism	417	137 355,5	30	304 [275-334]
Venous Thromboembolism	738	242 383,3	60	304 [283-327]
Venous Thromboembolism	1007	335 466,5	90	300 [282-319]
Venous Thromboembolism	1651	565 167,4	180	292 [278-307]
Ventricular Arrhythmia Cardiac Arrest	57	137 602,3	30	41 [31-54]
Ventricular Arrhythmia Cardiac Arrest	91	242 817,6	60	38 [30-46]
Ventricular Arrhythmia Cardiac Arrest	122	336 067,2	90	36 [30-43]
Ventricular Arrhythmia Cardiac Arrest	198	566 222,9	180	35 [30-40]
IQVIA DA Germany				
Acute Myocardial Infarction	698	194 518,8	30	359 [333-386]
Acute Myocardial Infarction	1354	350 855,7	60	386 [366-407]
Acute Myocardial Infarction	1935	489 088,2	90	396 [378-414]
Acute Myocardial Infarction	3388	838 422,9	180	404 [391-418]
Angina (Broad Definition)	3053	193 540,3	30	1577 [1522-1634]
Angina (Broad Definition)	5721	349 075,9	60	1639 [1597-1682]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Angina (Broad Definition)	8083	486 588,0	90	1661 [1625-1698]
Angina (Broad Definition)	13684	833 889,7	180	1641 [1614-1669]
Angina (Narrow Definition)	1025	194 621,9	30	527 [495-560]
Angina (Narrow Definition)	2064	351 042,7	60	588 [563-614]
Angina (Narrow Definition)	2962	489 355,0	90	605 [584-628]
Angina (Narrow Definition)	5180	838 876,8	180	618 [601-634]
Arterial Thromboembolism	1364	193 743,5	30	704 [667-742]
Arterial Thromboembolism	2816	349 448,2	60	806 [776-836]
Arterial Thromboembolism	4213	487 135,0	90	865 [839-891]
Arterial Thromboembolism	7787	835 154,3	180	932 [912-953]
Cerebral Venous Sinus Thrombosis	7	195 392,0	30	4 [1-7]
Cerebral Venous Sinus Thrombosis	10	352 472,8	60	3 [1-5]
Cerebral Venous Sinus Thrombosis	13	491 386,4	90	3 [1-4]
Cerebral Venous Sinus Thrombosis	20	842 480,3	180	2 [2-4]
Deep Vein Thrombosis (Narrow Definition)	520	194 932,0	30	267 [244-291]
Deep Vein Thrombosis (Narrow Definition)	1019	351 619,4	60	290 [272-308]
Deep Vein Thrombosis (Narrow Definition)	1467	490 168,5	90	299 [284-315]
Deep Vein Thrombosis (Narrow Definition)	2726	840 333,3	180	324 [312-337]
Haemorrhagic Stroke	169	195 242,2	30	87 [74-101]
Haemorrhagic Stroke	341	352 198,3	60	97 [87-108]
Haemorrhagic Stroke	516	490 999,5	90	105 [96-115]
Haemorrhagic Stroke	1034	841 811,7	180	123 [116-131]
Heart Failure	3539	191 038,1	30	1852 [1792-1915]
Heart Failure	6994	344 425,3	60	2031 [1983-2079]
Heart Failure	10346	480 027,0	90	2155 [2114-2197]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Heart Failure	19739	823 315,4	180	2398 [2364-2431]
Ischemic Stroke	617	194 567,4	30	317 [293-343]
Ischemic Stroke	1288	350 952,9	60	367 [347-388]
Ischemic Stroke	1880	489 225,5	90	384 [367-402]
Ischemic Stroke	3484	838 666,9	180	415 [402-429]
MACE	4980	189 521,5	30	2628 [2555-2702]
MACE	10178	341 722,1	60	2978 [2921-3037]
MACE	15233	476 344,5	90	3198 [3147-3249]
MACE	28034	817 128,8	180	3431 [3391-3471]
Portal Vein Thrombosis	13	195 378,3	30	7 [4-11]
Portal Vein Thrombosis	33	352 448,1	60	9 [6-13]
Portal Vein Thrombosis	50	491 351,4	90	10 [8-13]
Portal Vein Thrombosis	97	842 419,3	180	12 [9-14]
Pulmonary Embolism	588	194 777,0	30	302 [278-327]
Pulmonary Embolism	1150	351 339,8	60	327 [309-347]
Pulmonary Embolism	1648	489 778,4	90	336 [320-353]
Pulmonary Embolism	3091	839 726,4	180	368 [355-381]
Splanchnic Venous Thrombosis	0	195 394,2	30	0 [0-2]
Splanchnic Venous Thrombosis	0	352 477,1	60	0 [0-1]
Splanchnic Venous Thrombosis	0	491 392,7	90	0 [0-1]
Splanchnic Venous Thrombosis	0	842 491,4	180	0 [0-0]
Stroke (Any)	1359	193 814,0	30	701 [664-740]
Stroke (Any)	2650	349 564,4	60	758 [730-788]
Stroke (Any)	3862	487 260,8	90	793 [768-818]
Stroke (Any)	7061	835 239,6	180	845 [826-865]
Sudden Cardiac Death	7	195 394,0	30	4 [1-7]
Sudden Cardiac Death	13	352 476,4	60	4 [2-6]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Sudden Cardiac Death	17	491 391,4	90	4 [2-6]
Sudden Cardiac Death	37	842 488,2	180	4 [3-6]
Venous Thromboembolism	1054	194 375,9	30	542 [510-576]
Venous Thromboembolism	2028	350 595,9	60	578 [554-604]
Venous Thromboembolism	2914	488 722,3	90	596 [575-618]
Venous Thromboembolism	5408	837 868,0	180	645 [628-663]
Ventricular Arrhythmia Cardiac Arrest	158	195 236,7	30	81 [69-95]
Ventricular Arrhythmia Cardiac Arrest	317	352 188,6	60	90 [80-100]
Ventricular Arrhythmia Cardiac Arrest	443	490 987,3	90	90 [82-99]
Ventricular Arrhythmia Cardiac Arrest	805	841 797,7	180	96 [89-102]
SIDIAP				
Acute Myocardial Infarction	314	118 655,4	30	265 [236-296]
Acute Myocardial Infarction	555	207 377,2	60	268 [246-291]
Acute Myocardial Infarction	774	291 446,7	90	266 [247-285]
Acute Myocardial Infarction	1415	519 761,4	180	272 [258-287]
Angina (Broad Definition)	2002	117 753,8	30	1700 [1626-1776]
Angina (Broad Definition)	3686	205 777,5	60	1791 [1734-1850]
Angina (Broad Definition)	5321	289 164,5	90	1840 [1791-1890]
Angina (Broad Definition)	9553	515 372,4	180	1854 [1817-1891]
Angina (Narrow Definition)	268	118 667,3	30	226 [200-255]
Angina (NarrowDefinition)	516	207 404,1	60	249 [228-271]
Angina (NarrowDefinition)	734	291 490,4	90	252 [234-271]
Angina (Narrow Definition)	1308	519 839,5	180	252 [238-266]
Arterial Thromboembolism	941	118 445,9	30	794 [744-847]
Arterial Thromboembolism	1793	207 022,4	60	866 [826-907]
Arterial Thromboembolism	2595	290 962,7	90	892 [858-927]
Arterial Thromboembolism	4453	518 807,2	180	858 [833-884]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Cerebral Venous Sinus Thrombosis	2	118 792,9	30	2 [0-6]
Cerebral Venous Sinus Thrombosis	3	207 630,7	60	1 [0-4]
Cerebral Venous Sinus Thrombosis	6	291 816,2	90	2 [1-4]
Cerebral Venous Sinus Thrombosis	7	520 473,7	180	1 [0-3]
Deep Vein Thrombosis (Narrow definition)	175	118 628,1	30	148 [126-171]
Deep Vein Thrombosis (Narrow definition)	301	207 334,7	60	145 [129-162]
Deep Vein Thrombosis (Narrow definition)	434	291 389,4	90	149 [135-164]
Deep Vein Thrombosis (Narrow definition)	809	519 649,7	180	156 [145-167]
Haemorrhagic Stroke	78	118 757,5	30	66 [52-82]
Haemorrhagic Stroke	158	207 565,6	60	76 [65-89]
Haemorrhagic Stroke	228	291 720,3	90	78 [68-89]
Haemorrhagic Stroke	432	520 281,5	180	83 [75-91]
Heart Failure	1270	118 090,4	30	1075 [1017-1136]
Heart Failure	2392	206 402,5	60	1159 [1113-1206]
Heart Failure	3511	290 104,3	90	1210 [1170-1251]
Heart Failure	6747	517 480,6	180	1304 [1273-1335]
Ischemic Stroke	459	118 558,2	30	387 [352-424]
Ischemic Stroke	872	207 207,3	60	421 [393-450]
Ischemic Stroke	1252	291 200,0	90	430 [406-454]
Ischemic Stroke	2404	519 293,1	180	463 [445-482]
MACE	2316	117 861,1	30	1965 [1886-2047]
MACE	4505	206 047,6	60	2186 [2123-2251]
MACE	6690	289 684,3	90	2309 [2254-2365]
MACE	11833	516 737,3	180	2290 [2249-2332]
Portal Vein Thrombosis	29	118 783,0	30	24 [16-35]

Outcome	Number of Events	Person years	Window	Incidence rate per 100,000 person-years, 95% CI
Portal Vein Thrombosis	45	207 613,3	60	22 [16-29]
Portal Vein Thrombosis	65	291 792,4	90	22 [17-28]
Portal Vein Thrombosis	114	520 435,3	180	22 [18-26]
Pulmonary Embolism	143	118 686,9	30	120 [102-142]
Pulmonary Embolism	270	207 439,8	60	130 [115-147]
Pulmonary Embolism	391	291 540,1	90	134 [121-148]
Pulmonary Embolism	685	519 946,3	180	132 [122-142]
Splanchnic Venous Thrombosis	0	118 793,8	30	0 [0-3]
Splanchnic Venous Thrombosis	0	207 632,4	60	0 [0-2]
Splanchnic Venous Thrombosis	0	291 818,2	90	0 [0-1]
Splanchnic Venous Thrombosis	0	520 477,7	180	0 [0-1]
Stroke (Any)	514	118 537,0	30	434 [397-473]
Stroke (Any)	982	207 170,3	60	474 [445-505]
Stroke (Any)	1407	291 146,4	90	483 [458-509]
Stroke (Any)	2695	519 192,5	180	519 [500-539]
Sudden Cardiac Death	4	118 793,8	30	3 [1-9]
Sudden Cardiac Death	8	207 632,4	60	4 [2-8]
Sudden Cardiac Death	10	291 818,2	90	3 [2-6]
Sudden Cardiac Death	19	520 477,7	180	4 [2-6]
Venous Thromboembolism	284	118 542,4	30	240 [212-269]
Venous Thromboembolism	513	207 181,8	60	248 [227-270]
Venous Thromboembolism	738	291 170,2	90	254 [236-272]
Venous Thromboembolism	1334	519 237,9	180	257 [243-271]
Ventricular Arrhythmia Cardiac Arrest	59	118 761,9	30	50 [38-64]
Ventricular Arrhythmia Cardiac Arrest	128	207 573,5	60	62 [51-73]
Ventricular Arrhythmia Cardiac Arrest	187	291 732,5	90	64 [55-74]
Ventricular Arrhythmia Cardiac Arrest	387	520 302,7	180	74 [67-82]

Age-sex specific incidence rates are presented in **Figure 12.4.5** and the interactive web application. The incidence rates of ATE were higher among male than female in all age groups for all participated databases. Incidence rates of VTE were higher for male than female as well but was of a smaller difference. Incidence rates of both ATE and VTE increased with age.

Incidence rates stratified by vaccines doses and brand are presented in **Figure 12.4.6**. Crude incidence rates of arterial and venous thromboembolism after vaccination were greater with AstraZeneca vaccine in CPRD GOLD and IPCI but not in IQVIA Germany. For example, the incidence rates of ATE within 90 days after vaccination were 376 [359-393] per 100,000 py after any dose of ChAdOx1 and 234 [223-245] for BNT162b2 in CPRD GOLD, 2213 [2039-2398] after ChAdOx1 and 859 [816-904] after BNT162b2 in IPCI, and 878 [773-993] after ChAdOx1 and 851 [822-881] after BNT162b2 in IQVIA DA Germany. In CPRD GOLD, we observed that the crude incidence rates of both VTE and ATE were higher among third dose BNT162b2 cohort compared to first and second dose BNT162b2 cohorts, but not in other datasets.

Figure 12.4.5. Age-sex specific incidence rates of ATE and VTE after vaccination.

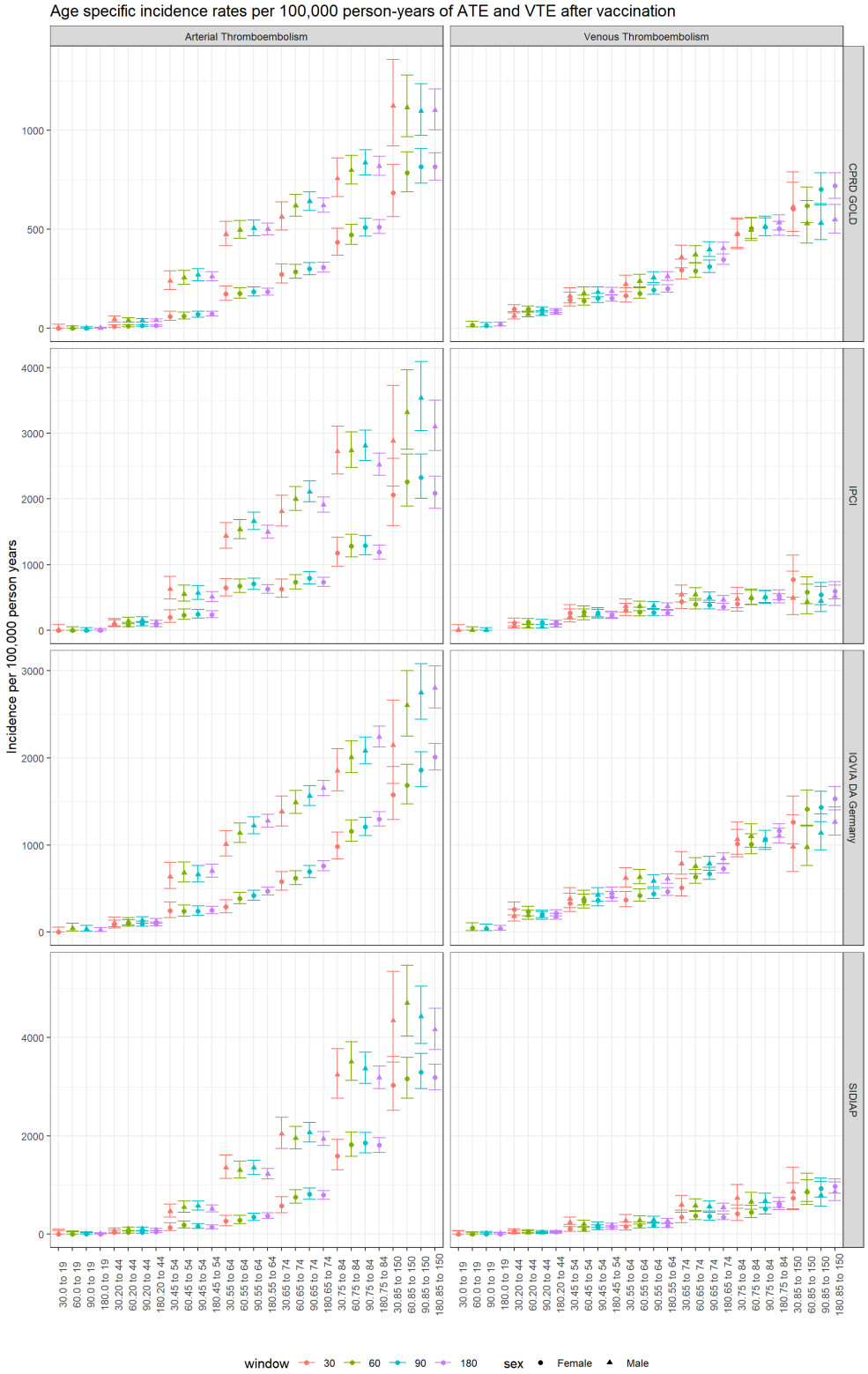
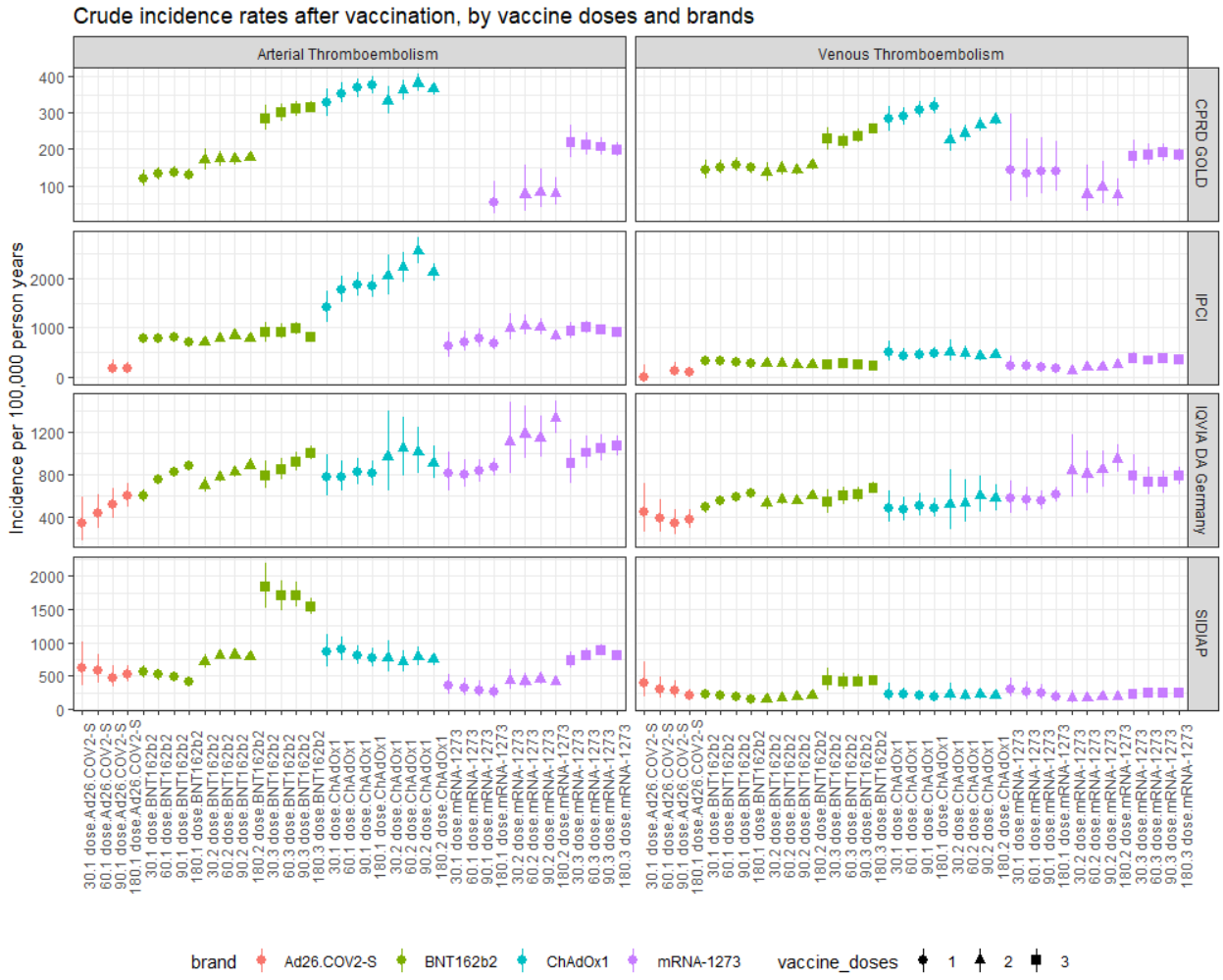


Figure 12.4.6. crude incidence rates within 90 days after vaccination, stratified for number of vaccine doses and brands.



Objective 4

Objective 4A - Risk factors for developing VTE and ATE with COVID-19 infection during the omicron period.

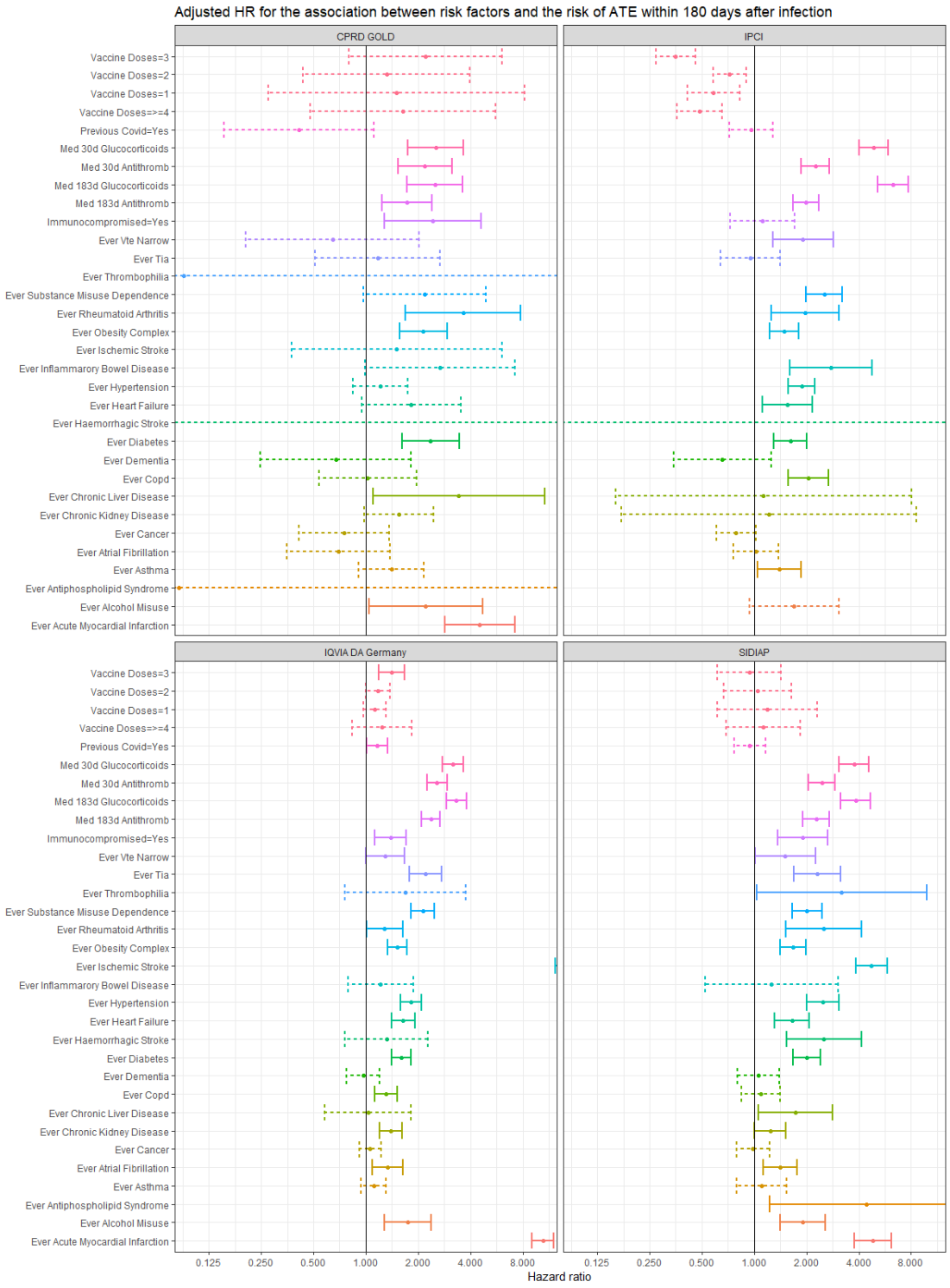
Objective 4 focused on potential risk factors for developing arterial and venous thromboembolic events with COVID-19 infection during the omicron period. We calculated the hazard ratios of risk factors for developing ATE (**Figure 12.4.7**) or VTE (**Figure 12.4.8**) within 180 days after COVID-19 infection.

After adjusting for age and sex, risk factors associated with a significantly increased hazard ratio for ATE within 180 days after COVID-19 infection during the omicron period across all databases included having any history of diabetes, obesity, and rheumatoid arthritis, and prior use of antithrombotic drugs or systemic glucocorticoids. Other comorbidities associated with an increased hazard ratio for developing ATE within 180 day of COVID-19 infection during the omicron period included chronic liver disease (CPRD GOLD, SIDIAP), chronic kidney disease (IQVIA DA Germany, SIDIAP), COPD (IPCI), hypertension (IPCI, IQVIA DA Germany, SIDIAP), and a history of substance misuse or dependence (IPCI, IQVIA Germany, SIDIAP). A prior history of cancer, and prior COVID-19 vaccines were not associated with an increased hazard of ATE with the exception of people with a prior history of 3 vaccine doses in IQVIA Germany.

In the analyses of risks factor for developing VTE events after COVID-19 infection during the omicron period, history of cancer, obesity, immunocompromised and prior use of systemic glucocorticoids was associated with an increased hazard in all databases. Other conditions including asthma, chronic kidney disease, COPD, diabetes, rheumatoid arthritis, and heart failure, and prior antithrombotics use were associated with significantly increased hazard in at least two databases.

Results of the risk factor analyses for each individual outcomes are available in the online web application. The results of individual outcomes were in line with the composite ATE and VTE outcomes, while the statistical significances of some estimates were no longer observed due to wider confidence intervals.

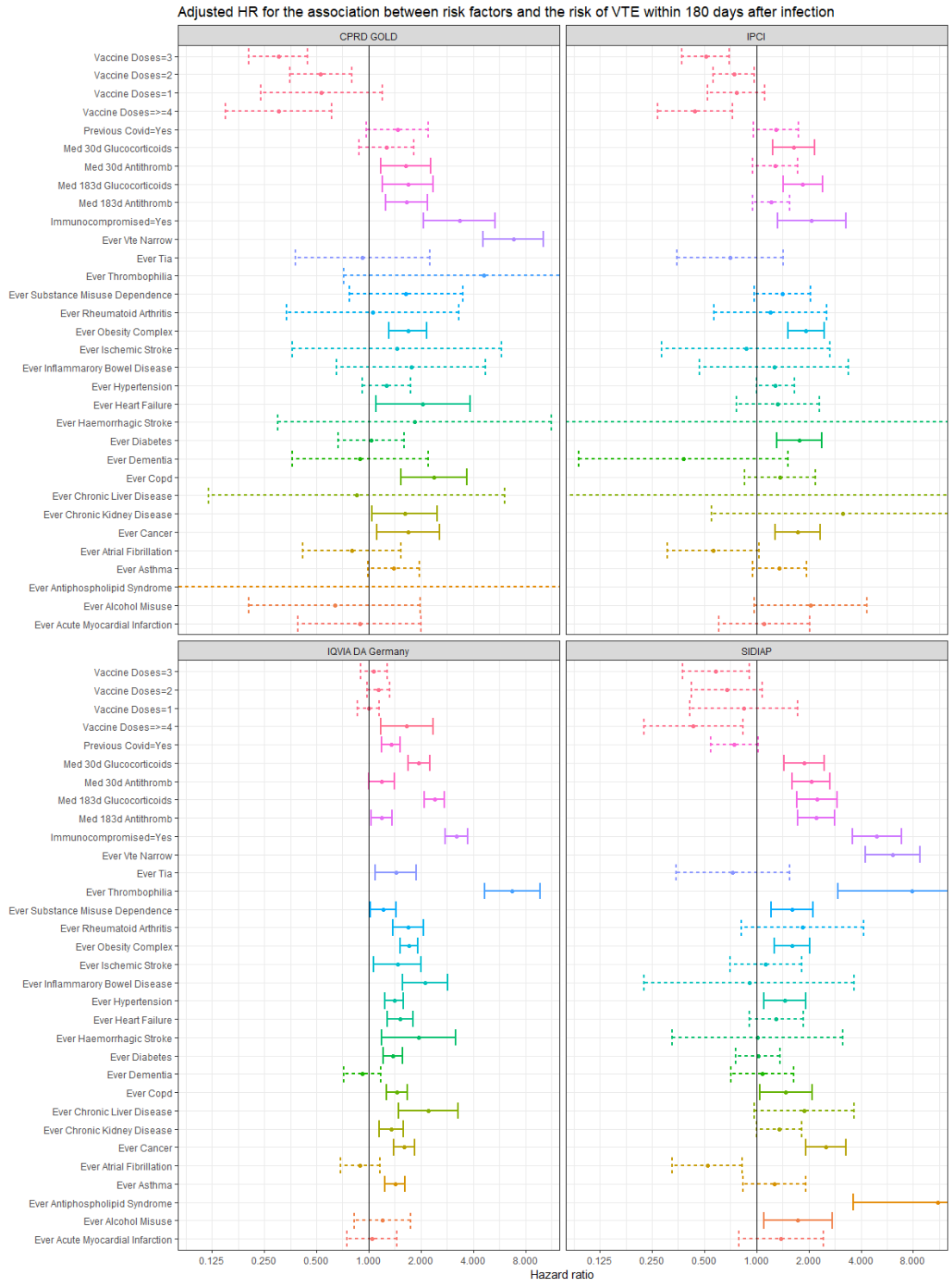
Figure 12.4.7. Adjusted hazard ratios of history of potential risk factors and the occurrence of any ATE events within 180 days after Covid-19 infection, by database.



Dashed lines indicate no significant association with confidence intervals including HR of 1.

Med 30d: medication use during the 30 days to 1 day prior to index date; Med 183d: medication use during the 183 days to 1 day prior to index date. Conditions were defined using all available data prior to index date.

Figure 12.4.8. Adjusted hazard ratio of risk factors for having any VTE events within 180 days after Covid-19 infection, by database.



Dashed lines indicate no significant association with confidence intervals including HR of 1

Objective 4B - impact that thromboembolic events have on worsening severity of COVID-19.

This analysis was only conducted in SIDIAP, where information on hospitalisation was available. The whole database rather than the 1 million sample was used for this analysis.

In the multistate model of ATE, a total of 1,731,019 individuals were included in the state of having COVID-19 during the Omicron period. Among these people, 52 with ATE prior to a COIVD-19 hospitalisation were identified. Of the 23,829 persons hospitalized with COVID-19, 776 had an ATE identified on the day of admission or after. The model of ATE prior to COVID-19 hospitalisation was underpowered. After adjustment for age and sex, ATE on or after date of hospital admission was associated with a hazard ratio of 1.08 (95% CI: 0.65 to 1.81) for death.

In the multistate model of VTE, 44 with VTE prior to a COIVD-19 hospitalisation were identified. Of the 23,833 persons hospitalized with COVID-19, 773 had an VTE identified on the day of admission or subsequently. The model of VTE prior to COVID-19 hospitalisation was also underpowered. After adjusted for age and sex, we found that VTE on or after date of hospital admission was associated with an increased risk of death, with an adjusted hazard ratio of 1.81 (1.21 to 2.70).

Objective 5

Crude incidence rate ratios

We calculated the crude incidence rate ratios (IRRs) within 30-, 60-, 90-, and 180- days after index for each event with 95% confidence intervals for both the COVID-19 and vaccinated cohorts compared against the background general population.

COVID-19 cohort

Incidence rate ratios for ATE and VTE among people with COVID-19 infection during the omicron period stratified by age and sex, by database are presented in figures 12.4.9-12.4.10. In IQVIA Germany, incidence rate ratios for ATE following COVID-19 infection during the omicron period was elevated in men and women for most age groups apart from those in the 0-19 age category across the different time windows. In SIDIAP, most of the age groups below 45 years had event counts below 5 and incidence rates were not estimated. The incidence rate ratios were elevated for male and female aged over 45. In IPCI, incidence rate ratios for ATE following COVID-19 infection during the omicron period were generally elevated in men and women in the older age groups (from age 55 and greater depending upon sex) across the different time windows. In CPRD GOLD, there was a pattern for incidence rate ratios to be increased in older age groups and in women however 95% confidence intervals were wide and often crossed 1.

In IQVIA Germany, incidence rate ratios for VTE following COVID-19 infection during the omicron period were almost consistently elevated in men and women for most age groups across the different time windows. In SIDIAP, age-sex specific incidence rate ratios were generally elevated among male across all age groups, and among females aged 65 or older. In IPCI, incidence rate ratios for VTE following COVID-19 infection during the omicron period were generally elevated in men and women in the older age groups (from age 55 and greater depending upon sex) across the different time windows but were greater in the 30- and 60-day time windows. In CRPD GOLD, incidence rate ratios for VTE within 30 days of COVID-19 infection during the omicron period were elevated for men and women across most age groups. Incidence rate ratios were

attenuated in younger age groups as time windows since COVID-19 infection increased but still generally remained above 1.

IRRs stratified by prior COVID-19 diagnosis, prior vaccination status and whether patients are immunosuppressed are available in the online web application.

Figure 12.4.9. Age-sex specific incidence rate ratios of ATE among people with COVID-19 infection stratified by age and sex, by database.

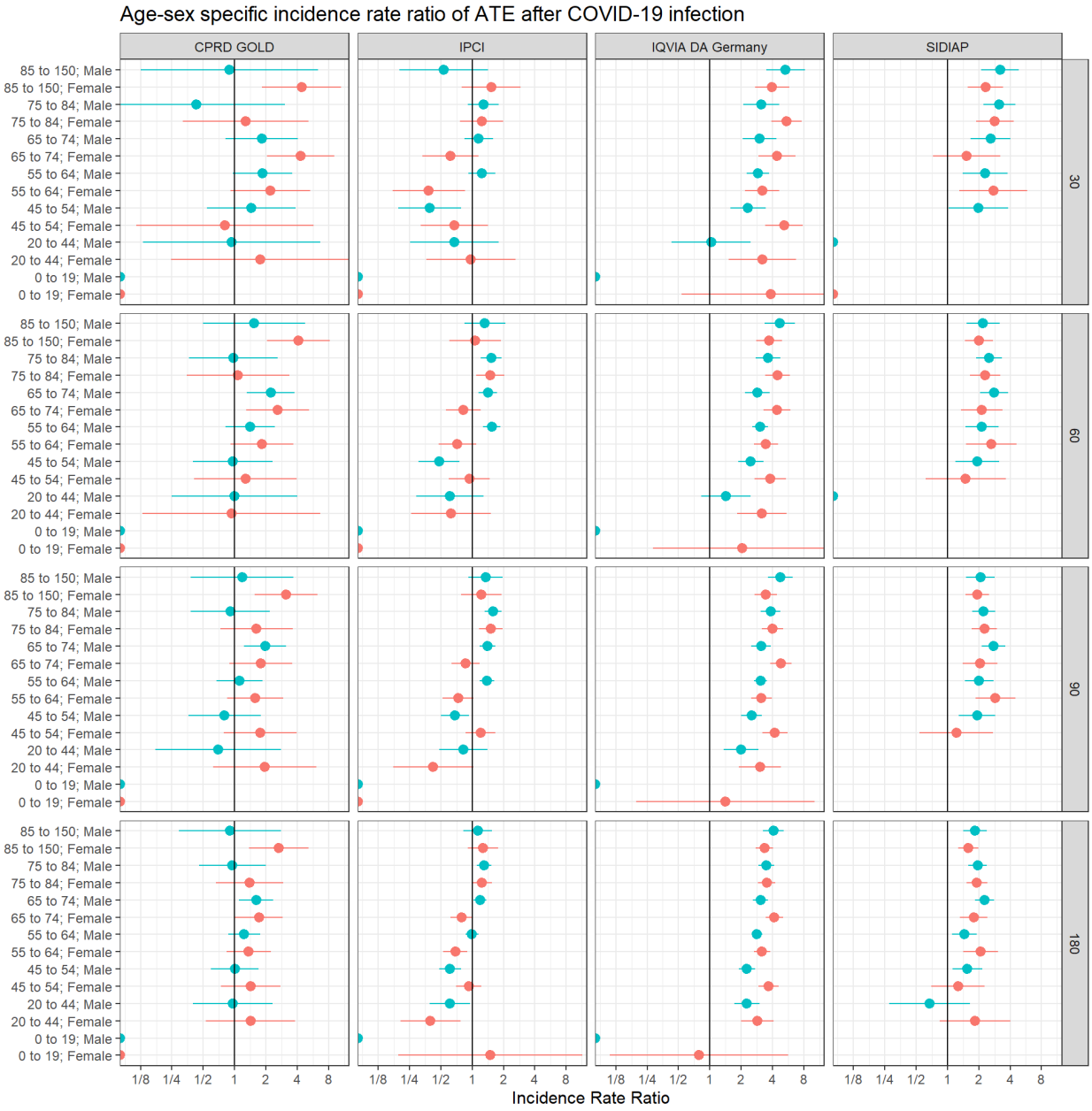
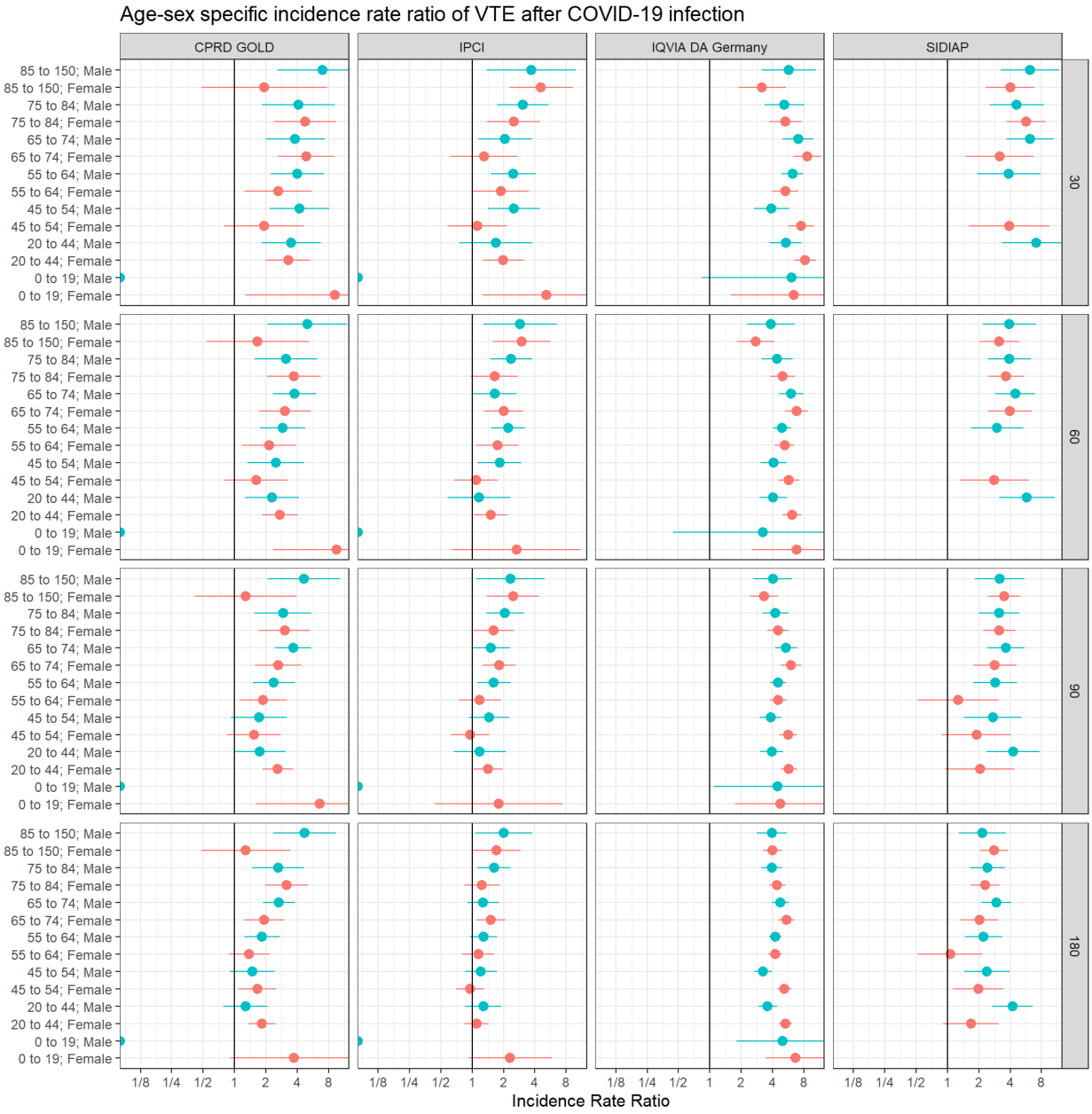


Figure 12.4.10. Age-sex specific incidence rate ratios of VTE among people with COVID-19 infection stratified by age and sex, by database.



Vaccinated cohort

Incidence rate ratios for ATE and VTE among people with COVID-19 vaccination stratified by age and sex, by database are presented in **Figures 12.4.11-12.4.12**. In IQVIA Germany and SIDIAP, incidence rate ratios for ATE following COVID-19 vaccination were elevated in men and women for most age groups across the different time windows. In CPRD GOLD, compared to the background population, the age-sex stratified incidence rate of ATE was higher than the background population among 20 to 44 years old men in all time windows. No increased IRR for ATE following COVID-19 vaccination was observed in the IPCI data, whereby lower IRRs were observed generally among individuals aged 45 years and older across the different time windows.

In IQVIA Germany, crude incidence rate ratios for VTE following COVID-19 vaccination were also elevated in men and women for most age groups across the different time windows. In CPRD GOLD there was no increase in the IRR across the time windows except in women in the 0-19 age group. IRR for VTE following COVID-19 vaccination in IPCI showed a similar pattern to the one observed for ATE although the lower IRR was more attenuated among older age groups.

IRRs stratified by prior COVID-19 diagnosis, vaccination doses and brands, and whether patients are immunosuppressed are available in the online web application.

Figure 12.4.11. Age-sex specific incidence rate ratios of ATE after vaccination, stratified by age, sex, and database.

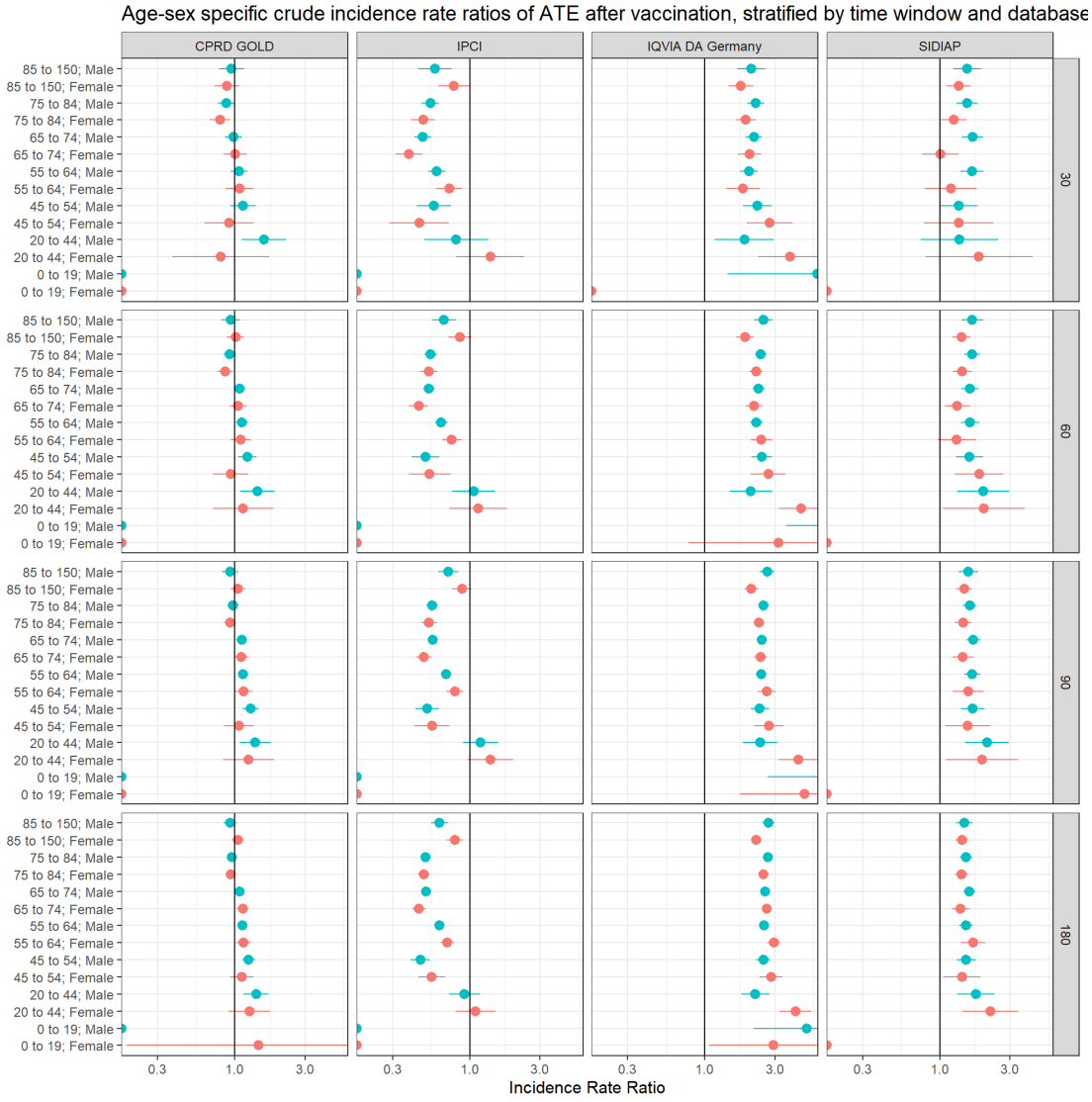
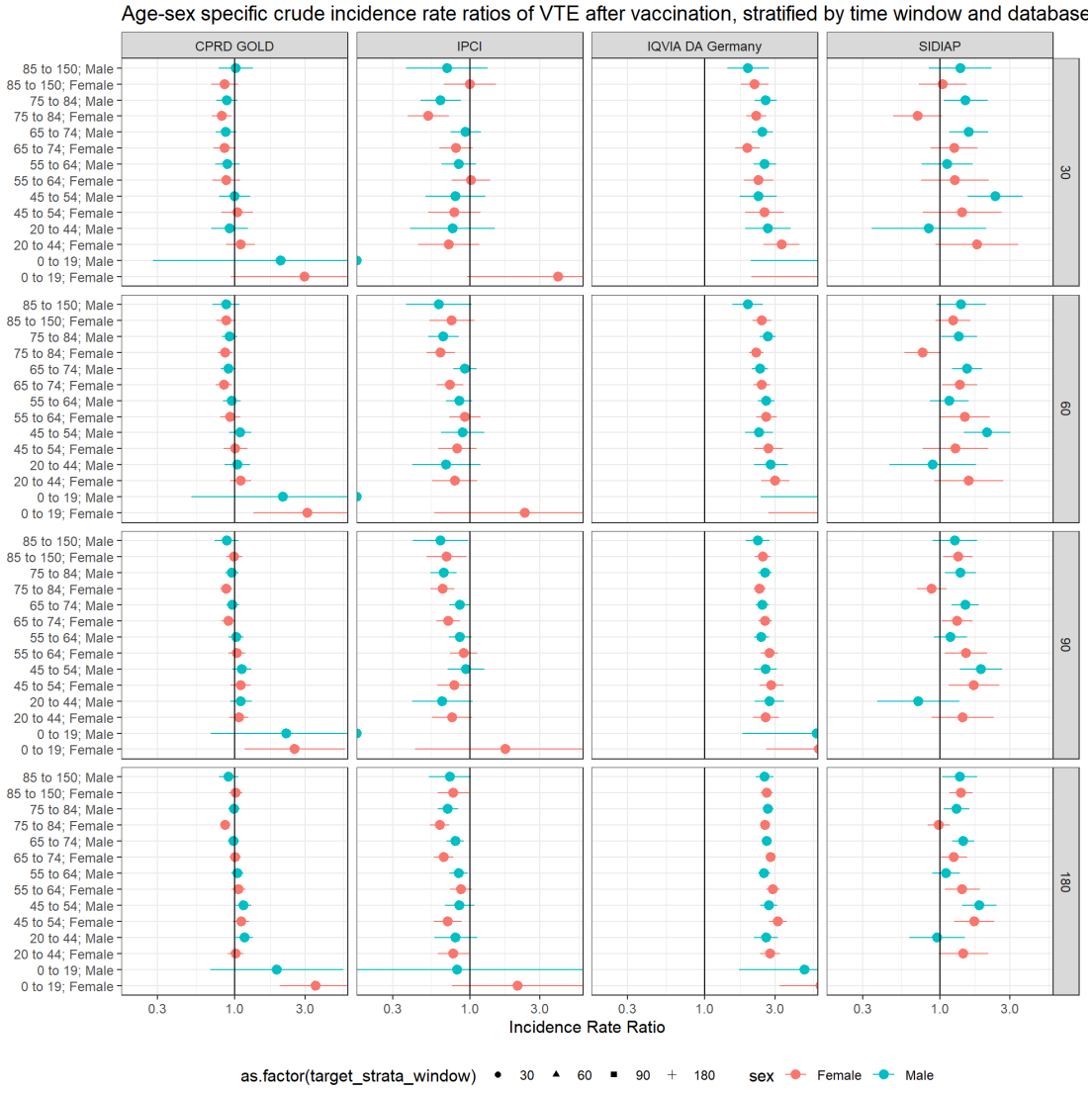


Figure 12.4.12. Age-sex specific incidence rate ratios of VTE after vaccination, stratified by age, sex, and database.

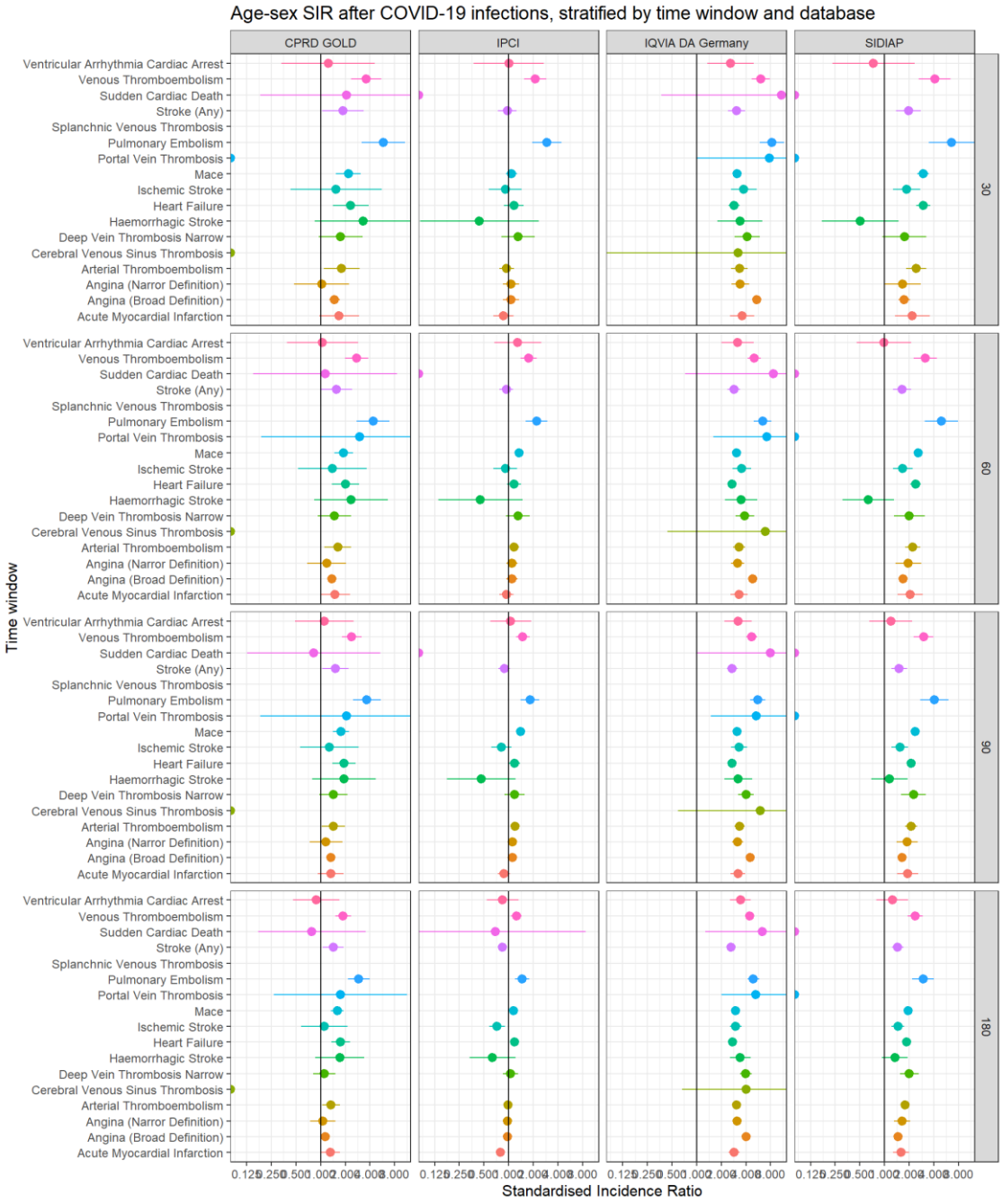


Age-sex standardised incidence ratio (SIR)

COVID-19 cohort (Figure 12.4.13)

In CPRD GOLD, the age-sex standardised incidence ratios showed that during the 30 days after COVID-19 infection during the omicron period, there were higher SIR of VTE and ATE. Secondary analysis of individual events showed higher than expected rates in pulmonary embolism, heart failure, and stroke. In IPCI, higher SIR of VTE, ATE, and pulmonary embolism were observed. SIR for individual events in IQVIA Germany showed a similar pattern as with ATE and VTE. In SIDIAP, higher SIRs were observed for most of the study outcomes except arrhythmia and haemorrhagic stroke.

Figure 12.4.13. Age-sex standardised incidence ratios of study events after COVID-19 infections.



Vaccinated cohort (Figure 12.4.14)

The 1st dose ChAdOx1 showed a higher SIR of ATE in CPRD GOLD (60-, 90- and 180-day), SIDIAP (all time windows), and IQVIA Germany (all time windows) but not in IPCI, while 2nd dose of ChAdOx1 vaccine showed higher SIR of ATE during the 90-, and 180 days after vaccination in all databases. No increased SIR was observed for Ad26.COV2-S, BNT162b2 or mRNA-1273 vaccines in CPRD GOLD or IPCI for any time window or dose, as opposed to SIRs in SIDIAP and IQVIA Germany which were elevated for all vaccines and doses.

In CPRD GOLD, only the 1st dose ChAdOx1 showed a higher SIR of VTE that was observed within 60-, 90- and 180- days post-vaccination. No increased SIR of VTE was observed for any vaccine or dose in IPCI. The calculated SIR was almost consistently increased for VTE for all vaccines and doses in IQVIA Germany. In SIDIAP, there were increased SIRs after 1st dose (all time window) and 2nd dose mRNA -1273 (90- and 180-days).

Figure 12.4.14. Age-sex standardised incidence ratios of ATE after vaccination, stratified by vaccine brand and doses, by database.

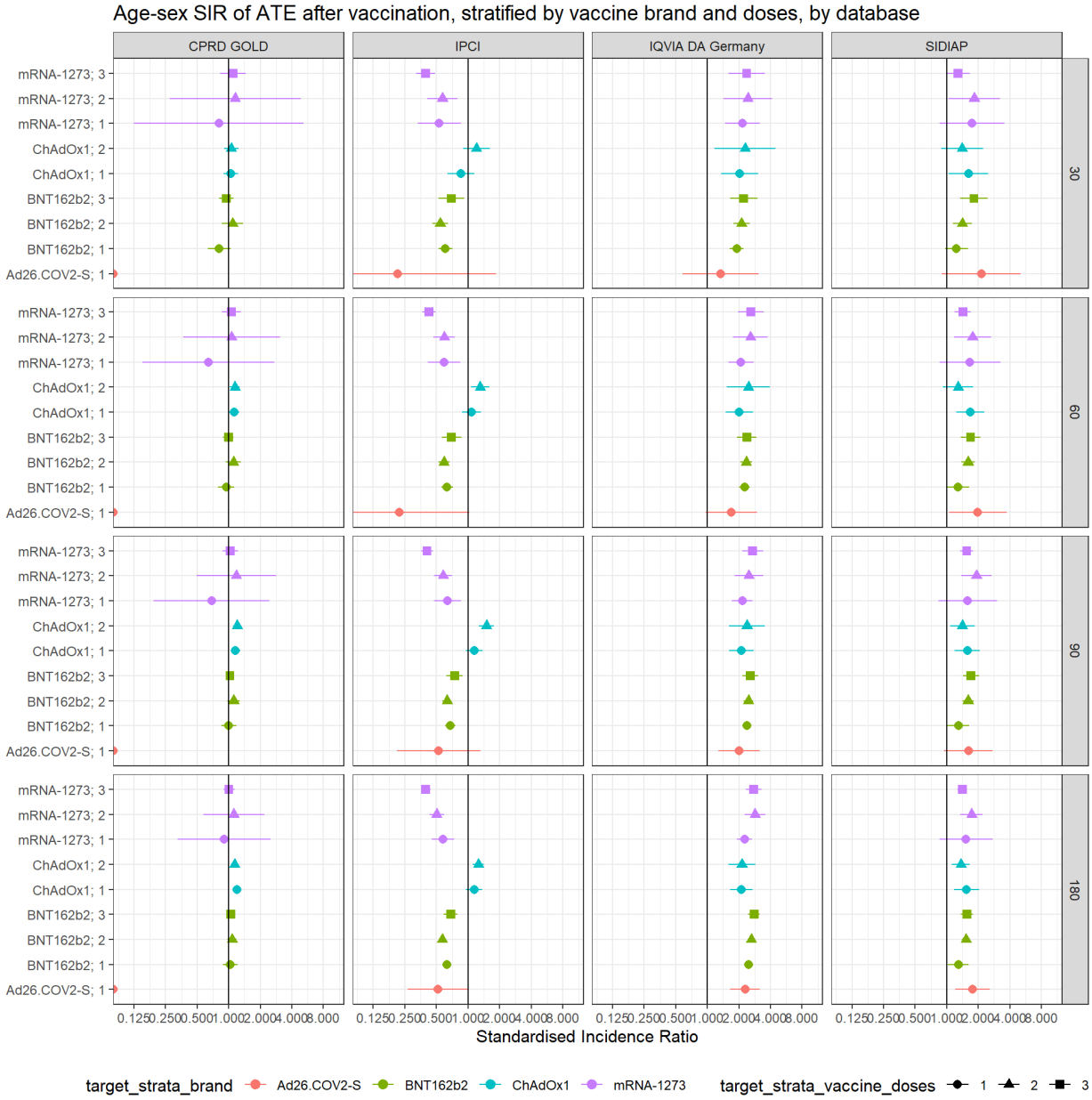
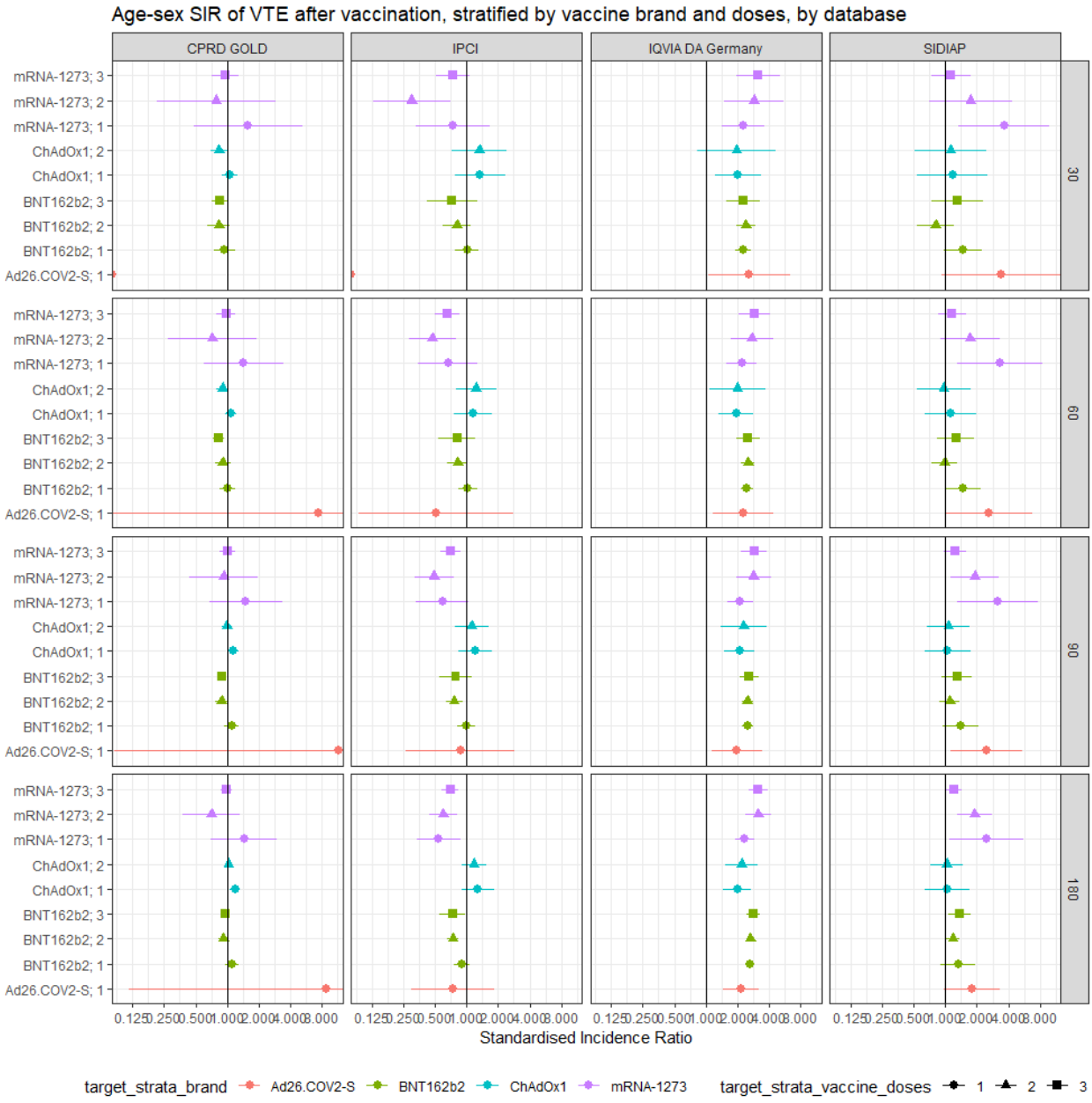


Figure 12.4.15. Age-sex standardised incidence ratios of VTE after vaccination, stratified by vaccine brand and doses, by database.



12.5 Other Analyses

Sensitivity analyses:

The first sensitivity analysis planned to restrict the exposure definition of "Positive test result for SARS-CoV-2" to RT-PCR test. At the cohort Diagnostic stage, in CPRD GOLD data for the cohort of "any COVID-19 infection during Omicron period", which was defined by having a diagnosis or positive test result, 78.1% of cases had a Read code "4J3R100: 2019-nCoV (novel coronavirus) RNA detected", and 25.8% had a diagnosis code for COVID-19. Type of test was therefore not further distinguishable in the source data.

In IPCI, 99.4% had COVID-19 condition code on index date, 49.9% had a RT-PCT test, and only 0.8% had an antigen test.

Results considering different washout periods were presented in the interactive web application.

The background rates were smaller when restricted to the first-ever event in all databases with a bigger impact in ATE in IPCI. For example, the IRs of myocardial infarction were 143 [140-145] and 128 [126-130] per 100,000 py in the main and sensitivity analysis in CPRD GOLD respectively, and 529 [521-537] and 262 [257-268] in IPCI respectively.

When restricted to first-ever events, we observed that SIR estimates moved away from the null in all included databases, the magnitude of which differed by outcome and database. For example, the SIR of ischemic stroke within 60 days after first dose Chadox1 vaccine was 1.18 [0.91-1.54] when using the 183 days washout period in the main analysis, and 1.24 [0.95-1.63] when limited to first ever event in CPRD GOLD. In IPCI, the SIR in the main analysis of ischaemic stroke after first dose Chadox1 vaccine was 1.16 [0.71-1.90], and 2.35 [1.27-4.34] when limited to first ever event. When restricted to the first ever event, the SIRs of ATE were higher after BNT162b2 vaccination when using a longer window (SIR of 1.26 [1.10-1.46] in CPRD GOLD and 1.15 [1.03-1.28] in IPCI within 90 days after second dose BNT162b2; and SIR 1.18 [1.07-1.30] in CPRD GOLD and 1.36 [1.10-1.67] in IPCI within 90 days after third dose BNT162b2).

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, did not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there would have been a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

14. DISCUSSION

14.1 Key Results

As one of the pilot projects of EHDS, this study aimed to contextualise coagulopathy event rates among people infected with COVID-19 during the Omicron period.

The estimation of age and sex specific background rates showed high heterogeneity between included databases. We also observed heterogeneity of incidence rates among the infected and vaccinated cohorts, however, the extent of that heterogeneity was smaller. We examined the potential risk factors, and found usage of corticosteroids and antithrombotics, presence of comorbidities such as obesity or diabetes, and having a history of ATE or VTE events to be associated with higher hazard ratio of developing ATE or VTE events among people with COVID-19. The multistate model showed that having VTE on or after COVID-19 hospitalisation was associated with higher risk of death.

Compared with the background population, the COVID-19 cohort showed higher SIR for both ATE and VTE after age-sex standardisation up to 180 days following infection. Higher SIRs were also observed for individual conditions included in the composite outcomes, including pulmonary embolism and heart failure.

Among the vaccinated cohort, people who received a first or second dose of ChAdOx1 vaccine showed higher SIR of ATE when using a longer follow-up window. No higher SIR of VTE in any brand-dose stratification was seen in both CPRD GOLD and IPCI data.

14.2 Limitations of the research methods

The study was informed by routinely collected health care data that was available through existing governance and infrastructure, so data access and quality issues must be considered, and these were documented to inform the HealthData@EU pilot. For example, cohorts of individuals with COVID-19 were identified; however, outpatient positive-tested- cohorts cannot capture all infected individuals, given the variable availability of testing in outpatient settings and between databases. People who were asymptomatic may not receive a test and therefore would not be identified. During the pandemic, the government national/regional regulations, recommendations, and clinical practice of testing changed over time. Therefore, we used the inclusion of a study cohort identified by both test results and clinical diagnoses to address some of these limitations.

The included databases varied in the data elements that they capture and in their current duration of follow-up. Depending on the dataset, not all study populations were observed. For example, identifying the intensive services cohort was not possible where inpatient hospital interventions were not observed such as in the CPRD GOLD data, where inpatient information was only available until March 2021. Similarly, not all outcomes were available in all databases e.g. deaths that were only reliably observed in CPRD GOLD and IPCI. For example, a study showed that the death date recorded in CPRD GOLD were 98.8% in agreement with the national data from the Office for National Statistics.[26] Only the cohorts and outcomes that could reliably be identified were assessed in the analyses. Since the vaccination programs changed over time (e.g. the primary vaccine courses targeted the general population, while the 4th dose was offered to more vulnerable people), the characteristics of patients receiving different doses were expected to be different. However, we stratified our analyses by vaccine status whenever sample size allows. We assumed that vaccination recording is

complete. In CPRD GOLD and IPCI, vaccine records were linked from national immunisation program, and all individuals received the vaccines through national health program. We believe that the records in these datasets were relatively complete. However, in other data source such as IQVIA DA Germany, vaccine records may be incomplete.

The contextualisation of incidence rates using a historical background period assumes that coding practices and data recording did not change over time, which cannot be ruled out. However, this method has been used in previous studies focussing on the 1st wave of covid, contracted by the same research group. [21,22]

The analyses calculated crude incidence rates and standardised incidence rates accounting for age and sex only. Although the characteristics of each cohort and stratification group was inspected, we did not account for other possible confounders including comorbidity or use of medicines in the analyses. Therefore, the observed rate ratios should be interpreted with caution and may not represent causal effects. The multiple analyses performed and stratification by age and sex can lead to spurious findings. No adjustment for multiple testing has been conducted.

While outcome definitions have been used in previous studies and quality control using R package CohortDiagnostics (https://github.com/OHDSI/CohortDiagnostics, a tool to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. Results included patient characteristics (e.g. demographics, comorbidities and previous comedication) which were reviewed by clinical experts.) have been conducted to assess their suitability in all databases participating in this study, outcome misclassification cannot completely be ruled out. We acknowledge the different level of ascertainment bias of study outcomes in each database.

14.3 Results in context

In late 2021, the study "Natural history of coagulopathy and use of anti-thrombotic agents in COVID-19 patients and persons vaccinated against SARS-CoV-2" was conducted under EMA's ROC13 tender (EUPAS40414) [27], using data from 5 European countries (the Netherlands (IPCI), Italy (IQVIA LPD Italy), France (IQVIA LPD France), Germany (IQVIA DA Germany), Spain (SIDIAP), and the UK (CPRD GOLD, CPRD Aurum)). In the main analysis of that study, a similar background population during year 2017-2019 was constructed without the requirement of 1 year visibility in the database before index. The sensitivity analysis restricted to people with a 1-year data visibility. In the current study, the 1-year visibility requirement was applied to all study cohorts. In the previous study, a 365-day washout window was applied to study outcomes, whilst the current study used 183 days in main analysis, and first-ever event in the sensitivity analysis. The background incidence rates estimated from both studies were overall similar, with some differences in IPCI. For example, the IR of ATE from the main analysis of current study was 1001 [991-1012] per 100,000 py, 628 [619-636] in the sensitivity analysis, and 319[313-326] in the previous study in IPCI. In CPRD GOLD, the IRs were 175 [173-177] and 172[170-175] from current and previous study, respectively.

This discordance in background rates could result from the changes of phenotyping of study outcomes, changes in the source codes which lead to changes in mapping of standardized vocabulary, differences in the way that the analytical codes were programmed, and a combination of all the above.

In the previous ROC13 study, a similar study design was used to estimate the incidence of coagulopathy events, but the data period was different, and CPRD Aurum and SIDIAP data were included. Individuals with

first or second dose ChAdOx1 or BNT162b2 December 2020 and mid 2021 were included and followed for up to 28 days after vaccination. A COVID-19 cohort was also constructed using data from September 2020 to mid-2021 and followed for up to 90 days to estimate the cumulative incidence of study outcomes. The participants were restricted to age over 20 years and were excluded if they had the same event recorded in the year before their index date.

The study identified a potential but small 10%-30% relative increase in risk of VTE following both BNT162b2 (SIR of 1.12 (1.03 to 1.21) after first dose, CPRD Aurum) and ChAdOx1 (SIR of 1.12 (1.05 to 1.20) after first dose, CPRD Aurum) vaccines, driven by a higher-than-expected rate of PE following vaccination. In the current study, we did not observe increased SIR among first dose BNT162b2 or ChAdOx1 users within 30 days after vaccination. In the sensitivity analysis where we restricted to first-ever event, the SIR for first dose ChAdOx1 was 1.32 [1.04-1.70] for PE and 1.25[1.04-1.49] for VTE.

The previous ROC13 study also found that following COVID-19 diagnosis or positive test, there were more than 7-fold increase in risk of VTE (SIR 7.27 (6.86 to 7.72) within 90 days after COVID-19) and a 12-fold excess risk of pulmonary embolism (SIR 12.77 (11.95 to 13.64)). In current study, we estimated SIR of 3.67 [2.48-5.43] for pulmonary embolism and 2.34[1.81-3.15] for VTE within 90 days following COVID-19 during the Omicron period.

Background rates

There was substantial heterogeneity in the background rates of both VTE and ATE events across databases. This has been seen in previous multi-database studies, which can result from the heterogeneity in source coding, healthcare settings included, and linkage availability. [28,29]

COVID-19 infected cohort

Incidence

Cardiovascular complications have been described after infection during the first and second waves of Covid-19. While most studies examined the risk during the acute phase after infection[30,31], some studies followed people with COVID-19 for a longer-term, from 90 days after infection [22], to 180 days or 12-months. [6,32,33]

In the current study, we found that the incidence rates of some of the included thromboembolic events, while numerically lower than the acute phase, was still significantly higher than the background population after 6-months during the Omicron period. In a self-controlled case series study using national registries from Sweden before the Omicron variant, risk of deep vein thrombosis and pulmonary embolism were estimated during the 180 days after COVID-19. The study found an increased risk of deep vein thrombosis up to 90 days after COVID-19 infection, pulmonary embolism up to 180 days.[6] The incidence rate ratio decreased after the first 30 days for both outcomes. Another study used electronic health records up to December 2020 from the UK showed the highest risk of VTE in first week after infection. While the risk decreased over time, they still observed an increased hazard ratio of 1.80 (95% CI, 1.50–2.17) during weeks 27 to 49. [7]

In our study, the stratified analysis of SIR showed higher rates of VTE, PE, heart failure, ATE (CPRD GOLD) among people without previous COVID-19 infection history, but not among those with prior COVID-19 infection . However, the number of people with prior COVID-19 infection was much smaller, thus the 95% confidence interval of the rate ratio was large and imprecise. In CPRD GOLD, there was higher rate ratio of acute myocardial infarction, heart failure, ATE, and MACE among COVID-19 patients who received 3 doses

vaccines. Estimates from other vaccine strata lacked precision because by the time of Omicron variant, a large portion of the population have received three doses.

Risk factors

The identified risk factors associated with thromboembolic events following COVID-19 infection during the Omicron period in the current study were similar to the previous study focused on the first and second waves of the pandemic. For example, both studies found comorbidities such as diabetes mellitus, history of heart disease, obesity, and kidney disease were associated with ATE amongst COVID-19 patients. [34]

The current study reports patients with comorbidities including asthma (90 days risk window), cancer, obesity, COPD, kidney disease, previous use of antithrombotics and glucocorticoids had a higher rate ratio of VTE, which were also identified in ROC13. Additionally, this study found that immunocompromised status at index was associated with higher hazard ratio of VTE at both 90- and 180- days.

A study by FDA used the Rapid Sentinel Distributed Database to evaluate patient characteristics prior to COVID-19 diagnosis as risk factors for arterial and venous thrombotic events during the first wave of the pandemic. Other comorbidities such as pregnancy, polycythemia, thrombocytosis, and use of antiplatelet drugs were also identified as risk factors of ATE or VTE in Covid-19. [35]

In the current analysis, we only adjusted for age and sex in the multivariable regression, as pre-specified in the protocol. These results are merely descriptive in nature, and no causal interpretation should be made.

Vaccinated cohort

Multiple observational studies with data from Europe, the UK, and the US have examined the association between thromboembolic events and both vector based and mRNA vaccines.[30,36–40] While the findings were inconsistent between studies, most studies used a risk period of 28-days following vaccination. In this study, we identified the incidence of study events from 30 days up to 180 days after vaccination.
In the previous study where people were followed up to 28 days after vaccination, an increased risk of venous thromboembolism was seen after first dose of ChAdOx1 and BNT162b2.[22] Another study used UK-based electronic health records studied the incidence of venous events after vaccination, and showed that the crude incidence rates higher in >= 28 days period, compare to within 28 days for both ChAdOx1 and BNT162b2.

We observed that in some datasets, higher than expected rates were only observed with longer follow-up windows but not shorter period. For example, in CPRD GOLD, the 90- and 180- days rates of VTE and ATE after first-dose ChAdOx1 were higher than expected, but not in 30- or 60-days after vaccination.

This can be partially explained by the “health user bias” where people with better condition were more likely to get vaccinated.

14.4 Generalisability

The results of this study need to be interpreted with caution, and findings should not be generalised beyond the databases included in this study.

During the pandemic, the national/regional regulations, recommendations, and clinical practice of testing changed over time. For example, in the UK, after January 2022, people who tested positive using a lateral

flow test were not long required to take a PCR test to confirm the result. Although reporting to the UK NHS was recommended, it was difficult to estimate what proportion of these home test results were reported. Even reported, the bias from self-reported data cannot be neglected. Moreover, different vaccines were approved and rolled out with various speed and priority groups as per country-specific schedules. Therefore, findings reported from this study should also not be generalized beyond the specific study period.

14.5 Other information

In the context of EHDS, our study was conducted using the OMOP common data model with standard analytics and code used to analyses included databases in a federated manner. This has the potential to improved efficiency and reduced the time taken to conduct studies compared to other approaches. However, this approach still met some challenges. For example, there was variation in the time required to obtain study approvals with different processes required for different databases. There were also differences in the process for running analytics scripts due to the size of the population studied, which required large amounts of data to be processed, highlighting the need to pay more attention to infrastructure requirements as databases increasingly grow in size. For example, the study codes (in R package format) could not be run on the full SIDIAP data cut due to the data partner's infrastructure constrains and the large cohort size for vaccinated people. We therefore used a random sample of 1 million people from the database to conduct this study.

We collected information related to hardware and software from the data partners as show in the table below.

	CPRD	IPCI	Estonia biobank	SIDIAP
Total hard disk capacity and types (SSD or HDD)	SSD, 10TB	SSD: 4x 8TB M.2 NVMe (Corsair Force MP400)	3TB of SSD	Disk 3,6TB, used 2TB
RAM memory (total size)	400GB	512 GB (8x HPE 64GB QR x4 DDR4-2933-21 LRDIMM ECC)	64GB	RAM 512GB
CPU	48 virtual processors	2x INTEL XEON SILVER 4214 2.2GHZ 16.5MB	16 CPU-s	2 x Intel(R) Xeon(R) CPU E5-2637 v4 @ 3.50GHz (Cores per socket 4 / Sockets 2)
Database size (not in people but in GB/TB)	2.16TB	900 GB	1.7TB (this full database size ohdsi_cdm schemas + all necessary etl-schemas for our workflows)	The last instance uses 775GB
Database management system and version used	PostgreSQL v15.3	PostgreSQL 12.9	PostgreSQL 12.16	
Other information		OS: Linux Ubuntu 20.04		HP ProLiant DL380 Gen9

Linked hospital data was not available for all the primary care databases in our study, limiting the possibility to address some aspects of our research questions. The ability to perform routine data linkage between healthcare settings would further support the secondary use of health data for public health decision making.

For the IQVIA DA Germany data, while the estimated incidence rates of study outcomes were much higher among the vaccinated cohort and the COVID-19 cohort, the estimated background rates were similar when comparing with other data. This resulted in increased IRRs and SIRs in the both the vaccinated cohort and the COVID-19 cohort. These increased IRRs and SIRs are partially impacted by how the observation period was defined in this data source. In the IQVIA DA Germany data, an individual's observation period end date was defined by the latest health care utilization activity of the individual. This also explains that the future observation time after index of the study participants were lower comparing with the other data sources. Therefore, the denominator population near the end of the data cut is less "reliable", as it only captured those with health care encounter, and might be of different risk profile comparing the general population. This should be taken into account when interpreting the results from the IQVIA DA Germany data.

15. CONCLUSION

As one of the pilot projects of EHDS, this study aimed to contextualise coagulopathy risk among people infected with COVID-19 during the Omicron period. Risk factors for coagulopathic events associated with COVID-19 during the omicron period remained similar and infection was associated with a higher standardised incidence ratio of arterial and venous events compared to the background population and people vaccinated.

The use of readily available data mapped to the OMOP common data model onboarded to DARWIN EU allowed for faster generation of real-world evidence providing sufficient infrastructure is available.

Heterogeneity was observed in the absolute rate of events across data sources, which may be related to different factors such as the inclusion of populations with different baseline risk, whether data sources had a primary care and secondary care data linkage, phenotypes and coding practices by health care professionals. These differences made it challenging to meta-analyse results into single values to facilitate interpretation and contextualisation. Further harmonization in some of these areas could therefore also contribute to increasing the impact of secondary use of health data.

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17. ANNEXES

Appendix I: List of concepts used for exposure and outcome definition

Appendix I, Table 1: concepts for exposure

Concept Id	Concept name		domain
3661405	Acute bronchitis caused by SARS-CoV-2	COVID Diagnosis	Condition
3655976	Acute hypoxemic respiratory failure due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
3661748	Acute kidney injury due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
3661406	Acute respiratory distress syndrome due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
3662381	Asymptomatic SARS-CoV-2	COVID Diagnosis	Condition
756031	Bronchitis caused by COVID-19	COVID Diagnosis	Condition
3656667	Cardiomyopathy due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
3656668	Conjunctivitis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
439676	Coronavirus infection	COVID Diagnosis	Condition
37311061	COVID-19	COVID Diagnosis	Condition
4100065	Disease due to Coronaviridae	COVID Diagnosis	Condition
3656669	Dyspnea caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
37310284	Encephalopathy due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
3661885	Fever caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
37310283	Gastroenteritis caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)	COVID Diagnosis	Condition
37310286	Infection of upper respiratory tract caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
3663281	Lower respiratory infection caused by SARS-CoV-2	COVID Diagnosis	Condition
3661631	Lymphocytopenia due to Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
37310287	Myocarditis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
37310254	Otitis media due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
704995	Patient meets COVID-19 clinical diagnostic criteria	COVID Diagnosis	Observation
700297	Patient meets COVID-19 laboratory confirmation criterion (detection of specific RNA in a clinical specimen using a molecular amplification detection test)	COVID Diagnosis	Observation
704996	Patient meets COVID-19 laboratory diagnostic criteria	COVID Diagnosis	Observation
700296	Patient meets COVID-19 presumptive laboratory evidence criteria (detection of specific antigen in a clinical specimen, OR detection of specific antibody in serum, plasma, or whole blood indicative of a new or recent infection)	COVID Diagnosis	Observation

37016927	Pneumonia caused by Human coronavirus	COVID Diagnosis	Condition
3661408	Pneumonia caused by SARS-CoV-2	COVID Diagnosis	Condition
40479642	Pneumonia due to Severe acute respiratory syndrome coronavirus	COVID Diagnosis	Condition
756039	Respiratory infection caused by COVID-19	COVID Diagnosis	Condition
3655977	Rhabdomyolysis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
3655975	Sepsis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
320651	Severe acute respiratory syndrome	COVID Diagnosis	Condition
37396171	Severe acute respiratory syndrome of upper respiratory tract	COVID Diagnosis	Condition
37311060	Suspected COVID-19	COVID Diagnosis	Observation
3661632	Thrombocytopenia due to Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition
45763724	Suspected coronavirus infection	COVID Diagnosis	Observation
40218804	2019-ncov coronavirus, sars-cov-2/2019-ncov (covid-19), any technique, multiple types or subtypes (includes all targets), non-cdc	COVID19 positive test	Measurement
40218805	Cdc 2019 novel coronavirus (2019-ncov) real-time rt-pcr diagnostic panel	COVID19 positive test	Measurement
44789510	Coronavirus nucleic acid detection	COVID19 positive test	Measurement
44811805	Coronavirus nucleic acid detection assay	COVID19 positive test	Measurement
45770687	Coronavirus RNA (ribonucleic acid) detection assay	COVID19 positive test	Measurement
44807536	Coronavirus RNA (ribonucleic acid) measurement by NAAT (nucleic acid amplification test)	COVID19 positive test	Measurement
3667069	Detection of ribonucleic acid of Severe acute respiratory syndrome coronavirus 2 using polymerase chain reaction	COVID19 positive test	Observation
36660491	Human coronavirus 229E RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement
36659667	Human coronavirus HKU1 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement
36660329	Human coronavirus NL63 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement
36660364	Human coronavirus OC43 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement
742224	Infectious agent antigen detection by immunoassay technique, qualitative or semiquantitative, multiple-step method; severe acute respiratory syndrome coronavirus (eg, SARS-CoV, SARS-CoV-2 [COVID-19]) (Coronavirus disease [COVID-19])	COVID19 positive test	Measurement
700360	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique	COVID19 positive test	Measurement
742218	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	COVID19 positive test	Measurement

742219	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	COVID19 positive test	Measurement
36661384	Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
36661375	Influenza virus A and B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
36661376	Influenza virus A and B RNA and SARS-CoV-2 (COVID-19) N gene panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
705104	Measurement of Coronavirus (Coronavirinae subfamily species)	COVID19 positive test	Measurement
705105	Measurement of Coronavirus (Coronavirinae subfamily species) antigen	COVID19 positive test	Measurement
37310257	Measurement of Severe acute respiratory syndrome coronavirus 2 antigen	COVID19 positive test	Measurement
756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	COVID19 positive test	Measurement
586310	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Genetic material using Molecular method	COVID19 positive test	Measurement
704991	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Blood	COVID19 positive test	Measurement
756029	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Respiratory specimen	COVID19 positive test	Measurement
586307	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Saliva	COVID19 positive test	Measurement
705107	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from nose	COVID19 positive test	Measurement
704976	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from oropharynx	COVID19 positive test	Measurement
586309	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Specified specimen	COVID19 positive test	Measurement
756065	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Unspecified specimen	COVID19 positive test	Measurement
702834	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific cell-mediated immune response in Blood	COVID19 positive test	Measurement
704992	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Culture method	COVID19 positive test	Measurement
705001	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique	COVID19 positive test	Measurement
705000	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Blood	COVID19 positive test	Measurement
756085	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Respiratory specimen	COVID19 positive test	Measurement

586308	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Saliva	COVID19 positive test	Measurement
705106	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from nose	COVID19 positive test	Measurement
704975	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from oropharynx	COVID19 positive test	Measurement
756084	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Unspecified specimen	COVID19 positive test	Measurement
704993	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Sequencing	COVID19 positive test	Measurement
723477	SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	COVID19 positive test	Measurement
706167	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
706157	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Measurement
706155	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Measurement
715272	SARS-CoV-2 (COVID-19) N gene [Presence] in Nasopharynx by NAA with probe detection	COVID19 positive test	Measurement
757678	SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with probe detection	COVID19 positive test	Measurement
706161	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
586524	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Measurement
586525	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Measurement
36661378	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by NAA with probe detection	COVID19 positive test	Measurement
586520	SARS-CoV-2 (COVID-19) N gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement
706175	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
706156	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Measurement
706154	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Measurement
723469	SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
706168	SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement

723478	SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
723464	SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
586516	SARS-CoV-2 (COVID-19) [Presence] in Unspecified specimen by Organism specific culture	COVID19 positive test	Measurement
723471	SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
723470	SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
706160	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
706173	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
586528	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
586529	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
715262	SARS-CoV-2 (COVID-19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
706158	SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
706169	SARS-CoV-2 (COVID-19) RNA panel - Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
723476	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	COVID19 positive test	Measurement
586526	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection	COVID19 positive test	Measurement
757677	SARS-CoV-2 (COVID-19) RNA [Presence] in Nose by NAA with probe detection	COVID19 positive test	Measurement
706163	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
36661377	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by Sequencing	COVID19 positive test	Measurement
715260	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	COVID19 positive test	Measurement
715261	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by Sequencing	COVID19 positive test	Measurement
723463	SARS-CoV-2 (COVID-19) RNA [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement
706170	SARS-CoV-2 (COVID-19) RNA [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
723467	SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
723468	SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
723465	SARS-CoV-2 (COVID-19) S gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
586519	SARS-CoV-2 (COVID-19) S gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement
723466	SARS-CoV-2 (COVID-19) S gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement

586517	SARS-CoV-2 (COVID-19) whole genome [Nucleotide sequence] in Isolate by Sequencing	COVID19 positive test	Measurement
757685	SARS-CoV+SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	COVID19 positive test	Measurement
706172	SARS-like coronavirus N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
706171	SARS-like coronavirus N gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
706166	SARS-related coronavirus E gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
586523	SARS-related coronavirus E gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
586518	SARS-related coronavirus E gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement
706174	SARS-related coronavirus E gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
706159	SARS-related coronavirus+MERS coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
706165	SARS-related coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement
723472	SARS-related coronavirus RNA [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement
739902	SARS-COV-2 (COVID-19) vaccine, vector non-replicating	covid-19 vaccine	drug
739903	SARS-COV-2 (COVID-19) vaccine, vector - Ad26 100000000000 UNT/ML	covid-19 vaccine	drug
739905	SARS-COV-2 (COVID-19) vaccine, vector non-replicating Injectable Suspension	covid-19 vaccine	drug
739906	SARS-COV-2 (COVID-19) vaccine, vector - Ad26 100000000000 UNT/ML Injectable Suspension	covid-19 vaccine	drug
37003432	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein	covid-19 vaccine	drug
37003433	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML	covid-19 vaccine	drug
37003435	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Suspension	covid-19 vaccine	drug
37003517	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML	covid-19 vaccine	drug
37003518	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	covid-19 vaccine	drug
37003436	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	covid-19 vaccine	drug
35894915	COVID-19 vaccine	covid-19 vaccine	drug
35897994	COVID-19 vaccine Injectable Solution	covid-19 vaccine	drug
36118948	COVID-19 vaccine, whole virus, inactivated, adjuvanted with Alum and CpG 1018	covid-19 vaccine	drug
36118949	COVID-19 vaccine, recombinant, full-length nanoparticle spike (S) protein, adjuvanted with Matrix-M	covid-19 vaccine	drug
36119720	COVID-19 vaccine, whole virus, inactivated, adjuvanted with Alum and CpG 1018 Injectable Suspension	covid-19 vaccine	drug

36119721	COVID-19 vaccine, recombinant, full-length nanoparticle spike (S) protein, adjuvanted with Matrix-M Injectable Suspension	covid-19 vaccine	drug
36119722	COVID-19 vaccine, recombinant, plant-derived Virus-Like Particle (VLP) spike (S) protein, adjuvanted with AS03 Injectable Suspension	covid-19 vaccine	drug
36126197	COVID-19 vaccine, recombinant, plant-derived Virus-Like Particle (VLP) spike (S) protein, adjuvanted with AS03	covid-19 vaccine	drug
724905	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL	covid-19 vaccine	drug
724904	SARS-COV-2 (COVID-19) vaccine, UNSPECIFIED	covid-19 vaccine	drug

Appendix I, Table 2: concepts for study outcomes

Concept ID	Concept name
Outcome	**Cerebral venous sinus thrombosis (CVST)**
4102202	Cerebral venous sinus thrombosis
4048786	Cerebral venous thrombosis of sigmoid sinus
4043735	Cerebral venous thrombosis of straight sinus
4111713	Non-pyogenic venous sinus thrombosis
314667	Nonpyogenic thrombosis of intracranial venous sinus
4116206	Septic thrombophlebitis of cavernous sinus
4121335	Septic thrombophlebitis of lateral sinus
4119136	Septic thrombophlebitis of sagittal sinus
4041680	Septic thrombophlebitis of sigmoid sinus
4100225	Thrombophlebitis lateral venous sinus
4217471	Thrombophlebitis of basilar sinus
4104695	Thrombophlebitis of cavernous sinus
4167985	Thrombophlebitis of inferior sagittal sinus
764714	Thrombophlebitis of sigmoid sinus
4100224	Thrombophlebitis of superior longitudinal venous sinus
4098706	Thrombophlebitis of superior sagittal sinus
4277833	Thrombophlebitis of torcular Herophili
764710	Thrombophlebitis of transverse sinus
4228209	Thrombosis of basilar sinus
4234264	Thrombosis of cavernous venous sinus
4048890	Thrombosis of inferior sagittal sinus
4057329	Thrombosis of lateral venous sinus
4102203	Thrombosis of superior longitudinal sinus
4290940	Thrombosis of superior sagittal sinus
4079905	Thrombosis of torcular Herophili
4105338	Thrombosis transverse sinus
Outcome	**DVT**

762047	Acute bilateral thrombosis of subclavian veins
762148	Acute deep vein thrombosis of bilateral iliac veins
761444	Acute deep vein thrombosis of bilateral lower limbs following coronary artery bypass graft
35616028	Acute deep vein thrombosis of left iliac vein
35615035	Acute deep vein thrombosis of left lower limb following procedure
761416	Acute deep vein thrombosis of left upper limb following coronary artery bypass graft
35615031	Acute deep vein thrombosis of left upper limb following procedure
43531681	Acute deep vein thrombosis of lower limb
35616027	Acute deep vein thrombosis of right iliac vein
35615034	Acute deep vein thrombosis of right lower limb following procedure
761415	Acute deep vein thrombosis of right upper limb following coronary artery bypass graft
35615030	Acute deep vein thrombosis of right upper limb following procedure
44782746	Acute deep venous thrombosis
44782751	Acute deep venous thrombosis of axillary vein
762008	Acute deep venous thrombosis of bilateral axillary veins
760875	Acute deep venous thrombosis of bilateral calves
765155	Acute deep venous thrombosis of bilateral ileofemoral veins
762017	Acute deep venous thrombosis of bilateral internal jugular veins
762417	Acute deep venous thrombosis of bilateral legs
762020	Acute deep venous thrombosis of bilateral popliteal veins
765546	Acute deep venous thrombosis of bilateral tibial veins
762004	Acute deep venous thrombosis of both upper extremities
44782742	Acute deep venous thrombosis of calf
44782747	Acute deep venous thrombosis of femoral vein
762015	Acute deep venous thrombosis of ileofemoral vein of left leg
765541	Acute deep venous thrombosis of ileofemoral vein of right lower extremity
44782748	Acute deep venous thrombosis of iliofemoral vein
44782752	Acute deep venous thrombosis of internal jugular vein
762009	Acute deep venous thrombosis of left axillary vein
760876	Acute deep venous thrombosis of left calf
765540	Acute deep venous thrombosis of left femoral vein
765922	Acute deep venous thrombosis of left internal jugular vein
762418	Acute deep venous thrombosis of left lower extremity
765537	Acute deep venous thrombosis of left upper extremity
44782767	Acute deep venous thrombosis of lower extremity as complication of procedure
46270071	Acute deep venous thrombosis of lower limb due to coronary artery bypass grafting
762022	Acute deep venous thrombosis of politeal vein of right leg
44782743	Acute deep venous thrombosis of popliteal vein
762021	Acute deep venous thrombosis of popliteal vein of left leg
762010	Acute deep venous thrombosis of right axillary vein
760877	Acute deep venous thrombosis of right calf
762013	Acute deep venous thrombosis of right femoral vein

762018	Acute deep venous thrombosis of right internal jugular vein
762419	Acute deep venous thrombosis of right lower extremity
762005	Acute deep venous thrombosis of right upper extremity
44782745	Acute deep venous thrombosis of thigh
44782744	Acute deep venous thrombosis of tibial vein
762026	Acute deep venous thrombosis of tibial vein of left leg
765156	Acute deep venous thrombosis of tibial vein of right leg
44782421	Acute deep venous thrombosis of upper extremity
764016	Acute deep venous thrombosis of upper extremity after coronary artery bypass graft
44782766	Acute deep venous thrombosis of upper extremity as complication of procedure
762048	Acute thrombosis of left subclavian vein
45757410	Acute thrombosis of mesenteric vein
762049	Acute thrombosis of right subclavian vein
36712892	Acute thrombosis of splenic vein
44782762	Acute thrombosis of subclavian vein
37109253	Bilateral acute deep vein thrombosis of femoral veins
40478951	Bilateral deep vein thrombosis of lower extremities
4046884	Deep vein thrombosis of leg related to air travel
4133004	Deep venous thrombosis
4181315	Deep venous thrombosis associated with coronary artery bypass graft
45773536	Deep venous thrombosis of femoropopliteal vein
763942	Deep venous thrombosis of left lower extremity
761980	Deep venous thrombosis of left upper extremity
443537	Deep venous thrombosis of lower extremity
4133975	Deep venous thrombosis of pelvic vein
40480555	Deep venous thrombosis of peroneal vein
4322565	Deep venous thrombosis of profunda femoris vein
763941	Deep venous thrombosis of right lower extremity
761928	Deep venous thrombosis of right upper extremity
4207899	Deep venous thrombosis of tibial vein
4028057	Deep venous thrombosis of upper extremity
193512	Embolism and thrombosis of the renal vein
435565	Embolism and thrombosis of the vena cava
4119760	Iliofemoral deep vein thrombosis
4124856	Inferior mesenteric vein thrombosis
4281689	Phlegmasia alba dolens
4284538	Phlegmasia cerulea dolens
4309333	Postoperative deep vein thrombosis
46285905	Provoked deep vein thrombosis
4033521	Splenic vein thrombosis
4055089	Superior mesenteric vein thrombosis
42538533	Thrombosis of iliac vein

44811347	Thrombosis of internal jugular vein
765049	Thrombosis of left peroneal vein
4317289	Thrombosis of mesenteric vein
4203836	Thrombosis of subclavian vein
4175649	Thrombosis of the popliteal vein
4153353	Traumatic thrombosis of axillary vein
46285904	Unprovoked deep vein thrombosis
4221821	Thrombophlebitis of deep veins of lower extremity
46271900	Recurrent deep vein thrombosis
4189004	Deep vein thrombosis of leg related to intravenous drug use
Outcome	**SVT**
4033521	Splenic vein thrombosis
36712892	Acute thrombosis of splenic vein
4033521	Splenic vein thrombosis
196715	Budd-Chiari syndrome
199837	Portal vein thrombosis
4317289	Thrombosis of mesenteric vein
4092406	Portal thrombophlebitis
36712892	Acute thrombosis of splenic vein
4173167	Mesenteric embolus
4144032	Mesenteric thrombus and/or embolus
45757410	Acute thrombosis of mesenteric vein
45757409	Chronic thrombosis of mesenteric vein
4318407	Thrombophlebitis of mesenteric vein
4124856	Inferior mesenteric vein thrombosis
4055089	Superior mesenteric vein thrombosis
199837	Portal vein thrombosis
36717492	Acute occlusion of mesenteric vein
45757410	Acute thrombosis of mesenteric vein
4124856	Inferior mesenteric vein thrombosis
4055089	Superior mesenteric vein thrombosis
4317289	Thrombosis of mesenteric vein
45757409	Chronic thrombosis of mesenteric vein
4318407	Thrombophlebitis of mesenteric vein
4173167	Mesenteric embolus
4144032	Mesenteric thrombus and/or embolus
36717492	Acute occlusion of mesenteric vein
36712892	Acute thrombosis of splenic vein
196715	Budd-Chiari syndrome
35624285	Complete obstruction of hepatic portal vein
4301208	Hepatic vein thrombosis
37110194	Hepatic veno-occlusive disease with immunodeficiency syndrome

37109927	Obstruction of visceral vein
4238060	Portal vein obstruction
4033521	Splenic vein thrombosis
4277276	Veno-occlusive disease of the liver
37111372	Visceral venous thrombosis
36712891	Chronic thrombosis of splenic vein
Outcome	**Pulmonary embolism**
4120091	Acute massive pulmonary embolism
45768439	Acute pulmonary embolism
45768888	Acute pulmonary thromboembolism
4309039	Hemorrhagic pulmonary infarction
762808	Infarction of lung due to embolus
40480461	Infarction of lung due to iatrogenic pulmonary embolism
4108681	Postoperative pulmonary embolus
4091708	Pulmonary air embolism
440417	Pulmonary embolism
37109911	Pulmonary embolism due to and following acute myocardial infarction
37016922	Pulmonary embolism on long-term anticoagulation therapy
43530605	Pulmonary embolism with pulmonary infarction
4119608	Pulmonary fat embolism
254662	Pulmonary infarction
4253796	Pulmonary microemboli
45766471	Pulmonary oil microembolism
4121618	Pulmonary thromboembolism
4119610	Pulmonary tumor embolism
4119607	Subacute massive pulmonary embolism
4119609	Subacute pulmonary fat embolism
4236271	Recurrent pulmonary embolism
Outcome	**Myocardial infarction**
4119457	Acute Q wave infarction - anterolateral
4119943	Acute Q wave infarction - anteroseptal
4121464	Acute Q wave infarction - inferior
4121465	Acute Q wave infarction - inferolateral
4124684	Acute Q wave infarction - lateral
4119948	Acute Q wave infarction - widespread
4126801	Acute Q wave myocardial infarction
4296653	Acute ST segment elevation myocardial infarction
46270162	Acute ST segment elevation myocardial infarction due to left coronary artery occlusion
761737	Acute ST segment elevation myocardial infarction due to occlusion of circumflex coronary artery
46270163	Acute ST segment elevation myocardial infarction due to right coronary artery occlusion
43020460	Acute ST segment elevation myocardial infarction involving left anterior descending coronary artery
45766076	Acute ST segment elevation myocardial infarction of anterior wall involving right ventricle

761736	Acute ST segment elevation myocardial infarction of anteroapical wall
46270159	Acute ST segment elevation myocardial infarction of anterolateral wall
46270160	Acute ST segment elevation myocardial infarction of anteroseptal wall
45766116	Acute ST segment elevation myocardial infarction of inferior wall
45766151	Acute ST segment elevation myocardial infarction of inferior wall involving right ventricle
35611570	Acute ST segment elevation myocardial infarction of inferolateral wall
35611571	Acute ST segment elevation myocardial infarction of inferoposterior wall
46274044	Acute ST segment elevation myocardial infarction of lateral wall
46270161	Acute ST segment elevation myocardial infarction of posterior wall
46273495	Acute ST segment elevation myocardial infarction of posterobasal wall
46270158	Acute ST segment elevation myocardial infarction of posterolateral wall
46270164	Acute ST segment elevation myocardial infarction of septum
45766075	Acute anterior ST segment elevation myocardial infarction
4178129	Acute anteroapical myocardial infarction
4267568	Acute anteroseptal myocardial infarction
312327	Acute myocardial infarction
44782769	Acute myocardial infarction due to left coronary artery occlusion
44782712	Acute myocardial infarction due to right coronary artery occlusion
45766115	Acute myocardial infarction during procedure
434376	Acute myocardial infarction of anterior wall
45766150	Acute myocardial infarction of anterior wall involving right ventricle
438438	Acute myocardial infarction of anterolateral wall
4243372	Acute myocardial infarction of apical-lateral wall
4108669	Acute myocardial infarction of atrium
4151046	Acute myocardial infarction of basal-lateral wall
4275436	Acute myocardial infarction of high lateral wall
438170	Acute myocardial infarction of inferior wall
45771322	Acute myocardial infarction of inferior wall involving right ventricle
438447	Acute myocardial infarction of inferolateral wall
441579	Acute myocardial infarction of inferoposterior wall
436706	Acute myocardial infarction of lateral wall
4324413	Acute myocardial infarction of posterobasal wall
4051874	Acute myocardial infarction of posterolateral wall
4303359	Acute myocardial infarction of septum
4147223	Acute myocardial infarction with rupture of ventricle
4145721	Acute non-Q wave infarction
4119944	Acute non-Q wave infarction - anterolateral
4119456	Acute non-Q wave infarction - anteroseptal
4119945	Acute non-Q wave infarction - inferior
4119946	Acute non-Q wave infarction - inferolateral
4121466	Acute non-Q wave infarction - lateral
4124685	Acute non-Q wave infarction - widespread

4270024	Acute non-ST segment elevation myocardial infarction
35610091	Acute nontransmural myocardial infarction
319039	Acute posterior myocardial infarction
444406	Acute subendocardial infarction
35610093	Acute transmural myocardial infarction
4119947	Acute widespread myocardial infarction
37109912	Arrhythmia due to and following acute myocardial infarction
438172	Atrial septal defect due to and following acute myocardial infarction
4124687	Cardiac rupture due to and following acute myocardial infarction
4215259	First myocardial infarction
4108678	Hemopericardium due to and following acute myocardial infarction
4173632	Microinfarct of heart
45771327	Mitral valve regurgitation due to acute myocardial infarction with papillary muscle and chordal rupture
45766214	Mitral valve regurgitation due to acute myocardial infarction without papillary muscle and chordal rupture
45766212	Mitral valve regurgitation due to and following acute myocardial infarction
4323202	Mixed myocardial ischemia and infarction
4329847	Myocardial infarction
37309626	Myocardial infarction due to demand ischemia
4170094	Myocardial infarction in recovery phase
4200113	Non-Q wave myocardial infarction
4030582	Postoperative myocardial infarction
35610087	Postoperative nontransmural myocardial infarction
4206867	Postoperative subendocardial myocardial infarction
35610089	Postoperative transmural myocardial infarction
4207921	Postoperative transmural myocardial infarction of anterior wall
4209541	Postoperative transmural myocardial infarction of inferior wall
37109911	Pulmonary embolism due to and following acute myocardial infarction
4108679	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction
4108219	Rupture of chordae tendinae due to and following acute myocardial infarction
4124686	Silent myocardial infarction
765132	Subendocardial myocardial infarction
45766114	Subsequent ST segment elevation myocardial infarction
45766113	Subsequent ST segment elevation myocardial infarction of anterior wall
45773170	Subsequent ST segment elevation myocardial infarction of inferior wall
4108217	Subsequent myocardial infarction
4108677	Subsequent myocardial infarction of anterior wall
4108218	Subsequent myocardial infarction of inferior wall
45766241	Subsequent non-ST segment elevation myocardial infarction
4108680	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction
439693	True posterior myocardial infarction

37109910	Ventricular aneurysm due to and following acute myocardial infarction
Outcome	**Heart failure**
44782718	Acute combined systolic and diastolic heart failure
4023479	Acute congestive heart failure
312927	Acute cor pulmonale
40481042	Acute diastolic heart failure
44782655	Acute exacerbation of chronic congestive heart failure
442310	Acute heart failure
764877	Acute heart failure co-occurrent with normal ejection fraction
4108245	Acute left ventricular failure
4327205	Acute left-sided congestive heart failure
4267800	Acute left-sided heart failure
44782733	Acute on chronic combined systolic and diastolic heart failure
40481043	Acute on chronic diastolic heart failure
764874	Acute on chronic heart failure co-occurrent with normal ejection fraction
37309625	Acute on chronic right-sided congestive heart failure
40480602	Acute on chronic systolic heart failure
4215446	Acute right-sided congestive heart failure
4233424	Acute right-sided heart failure
40480603	Acute systolic heart failure
4193236	Ayerza's syndrome
439698	Benign hypertensive heart disease with congestive cardiac failure
4030258	Bernheim's syndrome
4242669	Biventricular congestive heart failure
4215802	Cardiac asthma
4177493	Cardiac insufficiency due to prosthesis
4233224	Cardiac insufficiency during AND/OR resulting from a procedure
4264636	Cardiac insufficiency following cardiac surgery
4259490	Cardiorespiratory failure
44782719	Chronic combined systolic and diastolic heart failure
4229440	Chronic congestive heart failure
4195892	Chronic cor pulmonale
40479576	Chronic diastolic heart failure
444031	Chronic heart failure
764876	Chronic heart failure co-occurrent with normal ejection fraction
4206009	Chronic left-sided congestive heart failure
4009047	Chronic left-sided heart failure
4284562	Chronic right-sided congestive heart failure
4014159	Chronic right-sided heart failure
40479192	Chronic systolic heart failure
4108244	Compensated cardiac failure
319835	Congestive heart failure

44784345	Congestive heart failure as early postoperative complication
762002	Congestive heart failure as post-operative complication of cardiac surgery
762003	Congestive heart failure as post-operative complication of non-cardiac surgery
44782428	Congestive heart failure due to cardiomyopathy
4139864	Congestive heart failure due to left ventricular systolic dysfunction
4142561	Congestive heart failure due to valvular disease
36713488	Congestive heart failure stage B
36712928	Congestive heart failure stage B due to ischemic cardiomyopathy
43021826	Congestive heart failure stage C
36712927	Congestive heart failure stage C due to ischemic cardiomyopathy
43021825	Congestive heart failure stage D
44782713	Congestive heart failure with right heart failure
4307356	Cor pulmonale
4111554	Decompensated cardiac failure
4311437	Decompensated chronic heart failure
443587	Diastolic heart failure
43530643	Diastolic heart failure stage B
43021842	Diastolic heart failure stage C
43021841	Diastolic heart failure stage D
43022068	Exacerbation of congestive heart failure
316139	Heart failure
4124705	Heart failure as a complication of care
37311948	Heart failure with mid range ejection fraction
40486933	Heart failure with normal ejection fraction
45766164	Heart failure with reduced ejection fraction
45766167	Heart failure with reduced ejection fraction due to cardiomyopathy
45766165	Heart failure with reduced ejection fraction due to coronary artery disease
45773075	Heart failure with reduced ejection fraction due to heart valve disease
45766166	Heart failure with reduced ejection fraction due to myocarditis
4004279	High output heart failure
44782728	Hypertensive heart AND chronic kidney disease with congestive heart failure
439696	Hypertensive heart and renal disease with (congestive) heart failure
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
314378	Hypertensive heart disease with congestive heart failure
444101	Hypertensive heart failure
439846	Left heart failure
4185565	Low cardiac output syndrome
4103448	Low output heart failure
316994	Malignant hypertensive heart disease with congestive heart failure
4141124	Postvalvulotomy syndrome
764873	Reduced ejection fraction co-occurrent and due to acute heart failure
764871	Reduced ejection fraction co-occurrent and due to acute on chronic heart failure

764872	Reduced ejection fraction co-occurrent and due to chronic heart failure
4199500	Refractory heart failure
4138307	Right heart failure due to pulmonary hypertension
4195785	Right heart failure secondary to left heart failure
4273632	Right ventricular failure
35615055	Saddle embolus of pulmonary artery with acute cor pulmonale
4079695	Sepsis-associated left ventricular failure
4079296	Sepsis-associated right ventricular failure
44784442	Symptomatic congestive heart failure
443580	Systolic heart failure
43530642	Systolic heart failure stage B
36717359	Systolic heart failure stage B due to ischemic cardiomyopathy
43020421	Systolic heart failure stage C
36712929	Systolic heart failure stage C due to ischemic cardiomyopathy
43021840	Systolic heart failure stage D
40482857	Cardiorenal syndrome
4153875	Cardiac insufficiency as a complication of care
4215511	Emergency hospital admission for heart failure
4215689	Heart failure confirmed
4173819	Impaired left ventricular function