ASSOCIATION BETWEEN THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME (TTS) OR THROMBOEMBOLIC EVENTS, AND COVID-19 VACCINES: PROGRESS REPORT INCLUDING RESULTS FROM OBJECTIVES 3 AND 4

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Country(-ies) of study	France, Germany, Netherlands, Spain, United Kingdom, and United States of America
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2 List of abbreviations

Abbreviation	Name
ATE	Arterial thromboembolism
ASMD	Absolute standardised mean difference
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
COVID-19	Coronavirus disease-2019
CPRD	Clinical Practice Research Datalink
CVST	Cerebral venous sinus thrombosis
DA	Disease Analyzer
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
EHR	Electronic Health Record
HES APC	Hospital Episode Statistics Admitted Patient Care
HM	Hospital de Madrid
IPCI	Integrated Primary Care Information
IRR	Incidence Rate Ratio
LPD	Longitudinal Patient Data
MACE	MAjor Cardiovascular Events
MDRR	Minimum Detectable Relative Risk
OMOP	Observational Medical Outcomes Partnership
OR	Odd Ratio
PE	Pulmonary Embolism
PS	Propensity Score
RR	Relative Risk
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SVVT	Splanchnic and Visceral Vein Thrombosis
TTS	Thrombosis with Thrombocytopenia Syndrome/s
TE	Thromboembolic Events
VTE	Venous ThromboEmbolism

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4 Abstract

Rationale and background:

Thrombosis and TTS are being investigated as adverse effects of some COVID-19 vaccines. There is a lack of data on the determinants of post-vaccine thrombosis and TTS, and its management in real world settings.

Research question and objectives

This report includes results of **Objectives 3 and 4**:

3) To study the **association** between potential **risk factors and TTS/VTE/ATE** in people receiving COVID-19 vaccine/s;
4) To characterize the **treatments** used in patients with **TTS/TE**, including the use of anticoagulants and other therapeutic products

Study design

International network cohort study using data mapped to the Observational Medical Outcomes Partnership (OMOP) common data model.

Population

For Objective 3, all people exposed to any COVID-19 vaccine were included, stratified by dose, type, and brand. Historical, and post vaccination VTE/ATE/TTS were included for Objective 4.

Variables

Objective 3 outcomes included venous (VTE) and arterial (ATE) thromboembolism, and TTS defined based on VTE/ATE with concurrent thrombocytopenia. Risk factors including pre-specified health conditions and medication use were identified.

For Objective 4, a pre-specified list of medicines was studied based on existing guidelines for post-vaccination VTE/ATE/TTS.

Data sources

Data sources included primary care records from Netherlands, Spain, and UK; outpatient records from France and Germany, health claims from the US, and hospital records from Spain and the US.

Study size

All the individuals satisfying the eligibility criteria were included.

Data analysis

Logistic regression was used to identify risk factors associated with TTS/VTE/ATE post vaccination, adjusted for age, sex, and calendar month. Post-TTS/VTE/ATE treatment pathways were examined.

Results

Objective 3: In total, 9,535,996 persons with a first-dose were included. Of the first doses, 48% were BNT162b2, 47% were ChAdOx1, 3% were mRNA-1273, and 2% were Ad26.COV2-S. Median age ranged from 58 to 63 years old. Persons with post-vaccine VTE/ATE, thrombocytopenia, and TTS were typically older men with health conditions and prior use of medications.

Objective 4: Post-vaccine TTS was treated with any of the pre-specified medicines between 42% and 100% in hospital records, and from 6% to 34% in outpatient data. Most common first inpatient treatments included heparin and combination therapy; in outpatient, antiplatelet, heparin, and thrombolitics were the three most common treatments in Spain, whilst heparin, direct Xa inhibitors and antiplatelet were the top 3 treatments in the US. The most common post-VTE treatment was heparin whilst inpatient and in Spanish outpatient data, and direct Xa inhibitors elsewhere. Finally, the most common treatment for post-vaccine ATE was antiplatelet therapy everywhere except in US hospitals, where heparin was most common.

Conclusions

Although initial case reports indicated that thrombosis and thrombocytopenia concentrated among young women, our large multinational data show persons affected after vaccination to be similar to those typically observed with VTE/ATE/TTS in the general population. Additionally, we demonstrate heterogeneity in the management of post-vaccine VTE/ATE/TTS, mostly in line with scarce treatment guidelines.

5 Amendments and updates

There have been no formal amendments to the report so far.

Number	Date	Amendment or update	Reason
...			

6 Milestones

Milestone	**Planned date**
Approval Study Protocol by EMA	Aug 2021
<Registration in the EU PAS register>	Aug 2021
Start of data collection	No data collection is required.
End of data collection	No data collection is required.
Draft report	Jan 2022
Final study report accepted by EMA	Feb 2022
Manuscript to be provided to EMA	Feb 2022

7 Rationale and background

As of May 2021, four different COVID-19 vaccines were granted conditional marketing authorisation by the European Medicines Agency (EMA) after showing high efficacy and safety in phase-3 clinical trials [1-3]. These vaccines are classified into either viral vector-based including Vaxzevria (previously AstraZeneca or ChAdOx1) and COVID-19 Vaccine Janssen, or mRNA including Comirnaty (previously BNT162b2) and Spikevax (previously Moderna). After millions of vaccine doses were administered in large-scale immunization campaigns, spontaneous case reports of **thrombosis with thrombocytopenia syndrome (TTS)** usually within 2 weeks following the first dose of **viral vector-based vaccines** emerged [4-6]. As of 7th July 2021, 405 reports of major thromboembolic events with concurrent thrombocytopenia had been documented following 44.3 million first doses and 33.9 million second doses of the Vaxzevria vaccine in the UK[7]. Although fewer concerns have been raised about safety signals for Comirnaty (mRNA COVID-19 vaccine), instances of immune thrombocytopenia have also been observed among recipients of this vaccine[8].

Causal relationship was considered possible by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), leading to an update of the respective product information to include TTS as a **very rare** side effect [link]. As these unusual blood clots in combination with low thrombocyte counts were reported pre-dominantly among women aged <60 years, several European countries restricted the use of viral vector-based vaccines in younger age groups as a pre-cautionary measure. While the pathogenesis is not yet fully understood, an immune response leading to the development of pathologic platelet-activating antibodies is suggested (vaccine-induced immune thrombotic thrombocytopenia)[6, 9]. Although these events are very rare, based on the worldwide roll-out of these vaccines absolute numbers of affected patients may accumulate fast.

To further monitor COVID-19 vaccine safety and complement pharmacovigilance measures, multi-national observational studies have been requested by the EMA: Incidences of patient-reported side effects after COVID-19 vaccination [10] and adverse events of special interest [11, 12] are closely being monitored. The Covid-Vaccine-Monitor [13] project will facilitate the rapid signal assessment of emerging safety concerns. While these studies are designed to identify a broad range of new potential safety signals, one ongoing EMA project already focusses on cardiovascular and thromboembolic risk in both COVID-19 patients and COVID-19 vaccinated people [14]. The study is assessing incidences of thromboembolic events and their consequences, as well as risk factors for thromboembolism in COVID-19 patients and vaccinated people. Background incidence rates of five TTSs of special interest [15] were calculated based on records from over 20 million people in 6 European countries, ranging from 0.1 events per 100,000 person-years for cerebral venous sinus thrombosis/thrombocytopenia to 0.2-4.4 events per 100,000 person-years for stroke/thrombocytopenia. The study found TTS in unvaccinated people to be more common in men and older age groups, which differs from characteristics of the patient group reporting vaccine-related TTS. Preliminary findings from this study also showed larger than expected VTE (predominated by PE) in the 28 days following vaccination with either Vaxzevria or Comirnaty in UK and Spain; increasing rate of thrombocytopenia was seen among people vaccinated with Vaxzevria. In another study based on Danish and Norwegian data, increasing rates of VTE, PE and CVST were also found [16]. These studies provide important data on the incidence of adverse outcomes reported after vaccination and on potential risk factors for thromboembolic events in COVID-19 vaccinated patients. They will not, however, quantify the association between COVID-19 vaccines and the occurrence of these events taking into account possible risk factors. More recently, a nested case-control study from Scotland has suggested no increasing risk of VTE with either vaccines [17]. However, case-control analyses have been recently criticized for increasing bias and incapability of controlling for confounding [18]. In the light of important public-health decisions being based on TTS-risk for COVID-19 vaccines in different countries, insight to the magnitude of TTS risk related to COVID-19 vaccination at a large scale is urgently needed. Therefore, the EMA recently launched an invitation to tender under EMA/2017/09/PE Lot 3 – "Association between thrombosis with thrombocytopenia syndrome (TTS) or thromboembolic events, and COVID-19 vaccines", which was the basis for this study.

To our knowledge, there is no data available on the determinants of post-vaccine VTE, ATE, or TTS. Similarly, there is no information on the routine management of these conditions in real world clinical settings.

8 Research question and objectives

The current report covers Objectives 3 and 4 out of these:

1a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **TTS** within pre-specified risk periods, stratified by vaccine brand, age and gender, while controlling for relevant confounding factors.

1b) To quantify the comparative association of developing TTS among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.

2a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **venous or arterial thromboembolic events (VTE or ATE)** within pre-specified risk periods, stratified by vaccine brand, age and gender, while controlling for relevant confounding factors.

2b) To quantify the comparative association of developing VTE/ATE among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.

3) To study the association between potential risk factors and VTE, ATE or TTS in people receiving COVID-19 vaccine/s

4) To characterize the treatments used in patients with VTE, ATE or TTS, including the use of anticoagulants and other therapeutic products

9 Research methods

9.1 Study design

We conducted an international network cohort study using routinely collected health care data mapped to the OMOP common data model (CDM).

9.2 Setting

9.2.1 Countries

Datasets from France, Germany, Netherlands, Spain, the United Kingdom and the United States of America were used (see section 9.4 Data Sources below for more details).

9.2.2 Study period

The study period to identify exposure and outcomes covered from Dec 2020 (first vaccine users) until the latest data release available in each of the contributing databases (see Section 9.4 Data source below for more details).

For each objective and data source the study period was unique and went from cohort-specific index date to the latest data available. Cohort-specific index dates are:

- For vaccinated people [*Objective* 3]: date of first dose vaccine
- For TE and TTS cohorts [*Objective 4*]: date of TE/TTS diagnosis

Background cohorts were also built for Objective 3 and 4 for benchmark comparison. For Objective 3, the background cohort included people present in a database as of 1st January 2017 who had one year prior data visibility. The background cohort for Objective 4 was made up of all TE/TTS cases from 1st Jan 2016 to 30th November 2020.

Specific time windows for each of the objectives is specified in Section 9.2.4.

9.2.3 Study cohorts

All adult persons (aged >=18 at the start date of database) registered in any of the contributing databases within the study period and with at least one year of database history before the index date were included in the target population.

- **Study population for Objective 3**: Those with at least one exposure to any COVID-19 vaccine in the study period were included. In each contributing database, the following cohorts were built, with cohort-specific index dates:
    - Persons who received at least one dose of vaccine (any brand).
    - Persons who completed full doses of vaccine (any brand).
    - Persons who received at least one dose of any viral vector-based vaccine.
    - Persons who received at least one dose of any mRNA vaccine.
    - Persons who completed full doses of viral vector-based vaccines.
    - Persons who completed full (two) doses of any mRNA vaccine.
    - Brand-specific vaccine cohorts (one- and two-dose).
    - All individuals present in a database as of 1st January 2017.

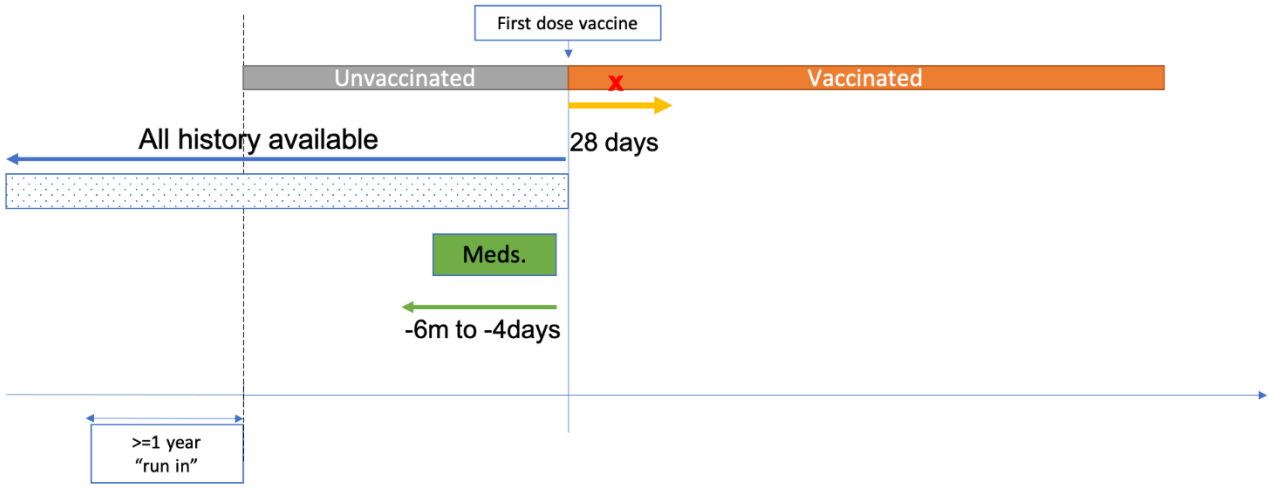
- **Study population for Objectives 4:** Those with a VTE, ATE or TTS from Dec 2020 were included in the **main cohort**. An additional **vaccinated cohort**, including all subjects with a VTE, ATE or TTS recorded after a first dose of any COVID-19 vaccine was included. Finally, a **background cohort** was made up of all individuals with VTE/ATE/TTS from Jan 2017 to Nov 2020. Besides the one year prior data visibility, participants in all three cohorts were also required to have at least one day post event of interest for this analysis. Details on the definition/s of vaccine exposure/s are provided in Section 9.3.1, whilst VTE/ATE and TTS definitions are provided in Section 9.3.2.

9.2.4 Follow-up

9.2.4.1 Risk factors time window (Objective 3)

For Objective 3, only vaccinated people were included, and studied for the identification of potential risk factors prior to the 1st dose date. Vaccinated people were followed for the outcome of interest, either TTS, VTE, or ATE, ascertained for up to 28 days or censored at the date of the 2nd dose, if this happened before 28 days (**Figure 1**). All available past medical history in the pre-vaccination time window was used to identify pre-vaccination risk factors related to comorbidity. Medication use was assessed from 6 months prior to 4 days before the 1st vaccination date.

Figure 1. Follow-up periods for risk factor and outcome ascertainment in vaccinated people.



9.2.4.2 Inpatient and outpatient treatments follow-up time for TE or TTS patients

For **Objective 4**, only people diagnosed with VTE, ATE or TTS were included. Participants in the related cohorts were followed up from the time of the VTE/ATE/TTS event until the last available date in the respective database. Inpatient and outpatient treatment/s were explored in different databases (described in Section 9.4) as there is no single database with both data available.

9.3 Variables

9.3.1 Exposures-vaccination against SARS-CoV-2

Each vaccine brand was defined based on standard concepts in the OMOP utilization vocabularies. A R cohort diagnostic package was used to identify "orphan source codes", to be included in future definitions/algorithms for the identification of COVID vaccine exposure/s. *Cohort diagnostics* is a tool that runs on the OMOP CDM to provide key features of patients eligible for a specific cohort or set of cohorts (see link). The analysis package provided the final exposure cohort definitions, concept sets and associated source codes.

9.3.2 Study outcomes

9.3.2.1 Thromboembolism (TE)

The following thromboembolic events (TE) of interest were included for Objective 3 analyses, with preliminary code lists available in Annex 4:

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Venous thromboembolism (VTE) as a composite of DVT or PE
- Cerebral venous sinus thrombosis (CVST)
- Splanchnic and visceral vein thrombosis (SVT)
- Ischemic stroke
- Myocardial infarction
- Arterial thromboembolism (ATE) as a composite of the two above and other rare arterial thromboembolisms defined in Annex 4.

VTE and ATE were assessed as composite outcomes separately.

9.3.2.2 TE and thrombosis with thrombocytopenia syndrome (TTS)

Our definition of TTS was based on the one proposed by the Brighton collaboration (**link**), and encompassed the occurrence of one of the TE of interest above (9.3.2.1) with concurrent thrombocytopenia within 10 days before/after the thromboembolic event date after the vaccination.

Thrombocytopenia was identified by a diagnostic code or a platelet count <150,000 per microliter of blood as proposed by the Brighton collaboration. This definition has been implemented in the OMOP CDM as part of a previous study [19] and can be seen in Annex 4. Separate TTS outcomes were ascertained, including the combination of thrombocytopenia with DVT, PE, VTE, SVT, MI, ischemic stroke, or ATE.

9.3.2.3 Risk factors for TTS (Objective 3)

The variables below were studied as potential risk factors for post-vaccine TTS and all the proposed events, in line with EUPAS40414 [19].

9.3.2.3.1 Medications of interest

The following medications were identified based on the WHO's Anatomical Therapeutic Chemical (ATC)

classification codes:

- Non-steroidal anti-inflammatory drugs (M01A)
- Cox2 inhibitors (M01AH)
- Systemic corticosteroids (H02AB and H02BX)
- Antithrombotic and anticoagulant therapies (B01A)
- Heparin (B01AB)
- Lipid modifying agents (C10)
- Agents acting on the renin-angiotensin system (C09)
- Antineoplastic and immunomodulating agents (L)
- Tamoxifen (L02BA01)
- Sex hormones and modulators of the genital system (G03)
- Hormonal contraceptives for systemic use (G03A)
- Selective estrogen receptor modulators(G03XC)

9.3.2.3.2 Health conditions of interest

Comorbidities were identified based on pre-specified SNOMED codes in all available history prior to index date, and included: autoimmune disease, antiphospholipid syndrome, thrombophilia, asthma, atrial fibrillation, malignant neoplastic disease, diabetes mellitus, obesity, heart disease, hypertensive disorder, renal impairment, chronic obstructive pulmonary disease (COPD), and dementia.

9.3.2.4 Medications of interest for treating TTS (Objective 4)

We identified the following medication via ATC/RxNorm + descendants in the OMOP CDM from the date of TTS/TE diagnosis to the last data available:

- Systemic corticosteroids (H02AB and H02BX)
- Anti-thrombotic agents
    - Anticoagulants (non-heparin)
        - Vitamin K antagonists (B01AA)
        - Direct Xa inhibitors (B01AF)
        - Direct Thrombin inhibitors(B01AE)
        - Other anticoagulants: (B01Axmostly fondaparinux)
    - Heparins (B01AB)
    - Platelet aggregation inhibitors (B01AC)

      This includes low-dose aspirin/ clopidogrel etc. as well as Glycoprotein Iib/IIIa inhibitors

      (i.v. specialist use only: tirofiban, eptifibatide, and abciximab)

    - Thromobolytic/fibrinolytic drugs (“Enzymes”)
    - thrombolytic therapy procedures
- Rituximab (L01XC)
- Fibrinogen (B02BB)
- Immunoglobulins (J06B)
- Plasma exchange/ platelet transfusion (B05AX)

9.4 Data sources

Data was obtained from primary care, outpatient, and inpatient databases across five countries in Europe. In addition, one US health claims and one large US hospital database were accessed to maximise sample size and exposure to vaccines under-represented in European data. A summary of key features of the proposed data sources was reported in Table 1.

Specifically, for the countries where general practitioners act as gatekeepers to the system, primary care databases are best positioned to identify COVID-19 vaccines and to provide information on health outcomes including the study events. This included CPRD AURUM (UK), IPCI (NL) and SIDIAP linked to hospital records from the official inpatient registry CMBD-AH for its acronym in Catalan language (ES). For European countries where general practitioners do not act as gatekeepers to the system (France and Germany), outpatient records (IQVIA DA France and Germany) including general practice and ambulatory specialist data were used for all analyses. A university hospital database from Barcelona, Spain (FIMIM, for Mar Institute of Medical Research Foundation in Catalan language) was also used. Finally, unadjudicated health claims (IQVIA Open Claims) and hospital records (Hospital Charge Data Master CDM) from the US were used.

Vaccine exposure was complete (fully recorded) in CPRD AURUM and SIDIAP, as these databases were linked to vaccination registries in origin. In all other data sources, exposure to vaccines was incomplete because vaccine exposure information was not embedded into the system. Here, the presence of a vaccine record was assumed to equate to a vaccine administration.

All primary care, outpatient records and the US Hospital CDM databases were used to define risk factors of post-vaccine TTS (**Objective 3).**

All databases available were used to identify treatment patterns in patients with TTS/VTE/ATE. Outpatient and inpatient databases provide complementary information on the management of post-vaccine and background (historical) VTE/ATE/TTS, which typically starts with a hospital admission but can continue in outpatient settings, mostly for secondary prevention purposes.

Table 1. Data sources contributing to the current report of results for Objectives 3 and 4

I = Incomplete

Database	**Country**	**Key data available**				
		COVID vaccine/s	**Hospital treatments**	**Hospital outcome/s**	**Outpatient treatments**	**Platelet counts**
CPRD AURUM	UK	Complete	No	I	Yes	Yes
SIDIAP-CMBD	ES	Complete	No	Yes	Yes	Yes
IPCI	NL	Incomplete	No	I	Yes	Yes
LPD France	FR	Incomplete	No	I	Yes	Yes
DA Germany	DE	Incomplete	No	I	Yes	Yes
OpenClaims	US	Incomplete	I	I	Yes	Yes
Hospital CDM	US	Incomplete	Yes	Yes	I	I
FIMIM	ES	Incomplete	Yes	Yes	No	Yes

9.5 Study size

For each database, all individuals that satisfied the eligibility criteria for any of the listed study cohorts were included. The number of people eligible in the primary cohorts are reported in the Results section.

9.6 Data management

All databases used in this study were standardised to the OMOP CDM. This enabled the use of standardised analytics and tools across all of them. The OMOP CDM is 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
Analytical 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 results containing only aggregated data. The results from each of the contributing data sites were combined for the study report. The analytical code is available for review and replication here:

- **Objective 3**: https://github.com/oxford-pharmacoepi/CoagulopathyInVaccinated
- **Objective 4**: https://github.com/oxford-pharmacoepi/TreatmentPatternsDUS

9.7 Data analysis

9.7.1. Objective 3.- Identification of key risk factors for VTE/ATE/TTS

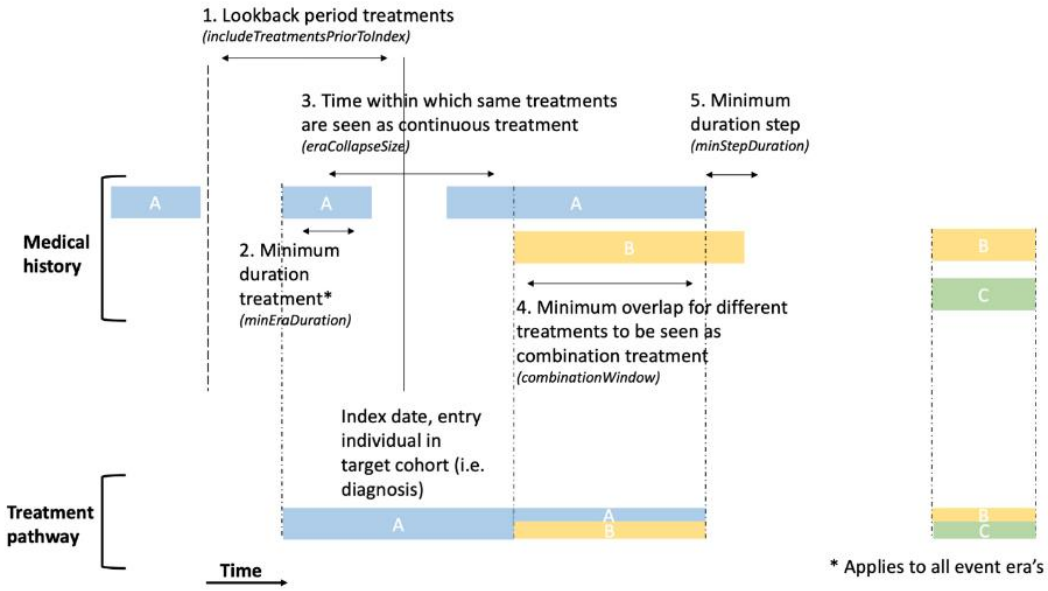
For each pre-identified risk factor, a logistic regression model adjusted for age, sex and calendar month was fitted. All analyses were conducted for each of the included cohorts and per database separately. We reported adjusted odd ratios and 95% confidence intervals.

9.7.2. Objective 4.- Drug utilization in patients with post-vaccine VTE/ATE/TTS

For each of the TTS/VTE/ATE event cohorts, all people with continuous observation of 365 days before and at least one day after event were included and the event date is the index date. The R package TreatmentPatterns was used to describe treatment pathways. Sunburst plots and Sankey diagrams were used to visualize treatment pathways.
Settings of treatment period, continuous treatment and combination treatment were (Figure 2):

1. Lookback period treatment: 0 days prior to the index date. We only looked at the treatment after an incidence case of VTE/ATE/TTS
2. Minimum duration treatment: all treatments recorded were included, regardless of their duration. This was done to allow for the study of one-off infusions e.g. plasma or intravenous glucocorticoids.
3. Continuous treatment: two periods of a same treatment with a gap of <=7 days was defined as a continuous treatment episode.
4. Combination treatment: two different treatments having a minimum of 1 day overlap
5. Minimum duration of two drug era durations before and after a combination treatment is generated: we define 1 day for two drug era

Figure 2. Diagram of follow-up windows used for the study of treatment patterns (Objective 4)


1. Lookback period treatments
(includeTreatmentsPriorToIndex)
3. Time within which same treatments are seen as continuous treatment
(eraCollapseSize)
5. Minimum duration step
(minStepDuration)
Medical history
2. Minimum duration treatment*
(minEraDuration)
4. Minimum overlap for different treatments to be seen as combination treatment
(combinationWindow)
Index date, entry individual in target cohort (i.e. diagnosis)
Treatment pathway
Time
* Applies to all event era's

10 Results

10.1 Results for Objective 3

A total of 9,535,996 persons with a first-dose of a vaccination against SARS-CoV-2 were included: 5,551,600 million from CPRD AURUM UK, 526,622 from IQVIA DA Germany, 275,417 from IPCI NL, 2,823,806 from SIDIAP ES, and 358,551 from IQVIA Hospital CDM US. Of these first doses, 4,554,027 (48%) BNT162b2, 4,493,233 (47%) ChAdOx1, 330,564 (3%) mRNA-1273, and 158,172 (2%) Ad26.COV2-S.

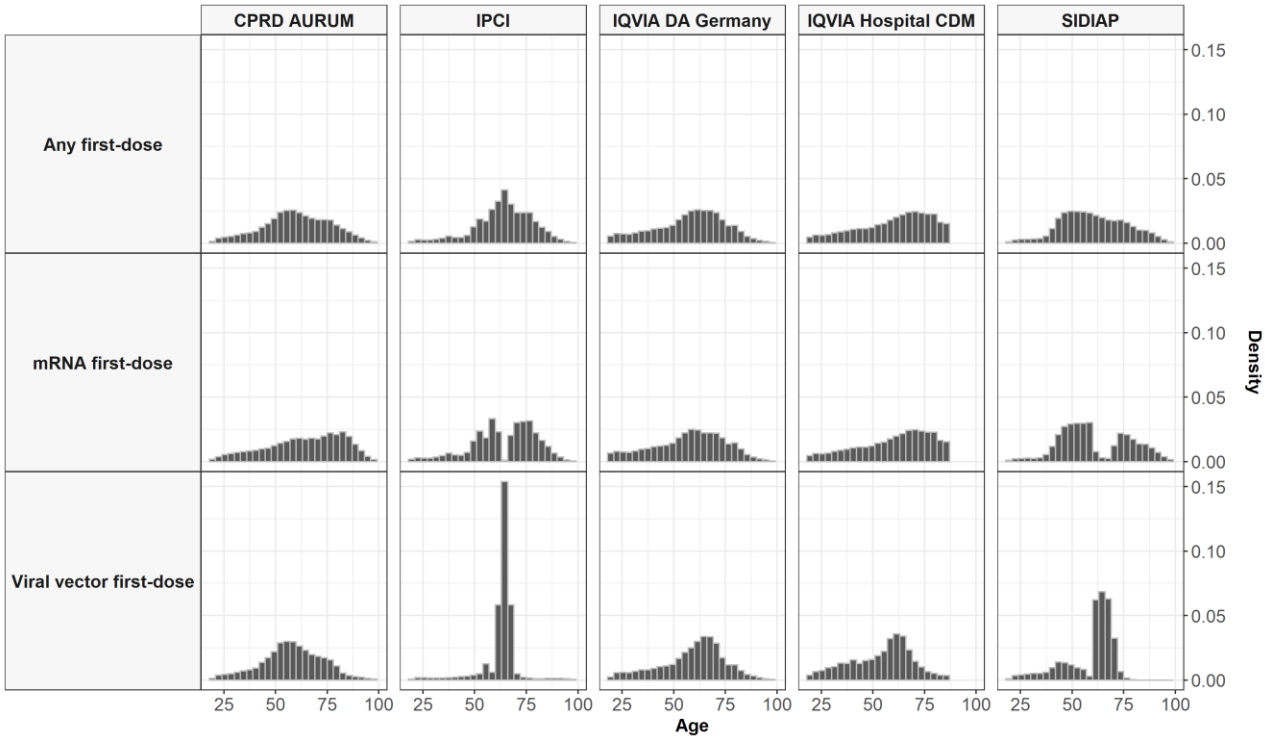
Baseline characteristics for some of the study cohorts are reported in full in Table 2. Additional cohorts (including 2-dose vaccinees) are available in the accompanying interactive web application. Median age ranged from 58 in SIDIAP to 63 in IPCI, while the proportion of males ranged from 41% in IQVIA Hospital CDM to 49% in IPCI. Between 41% (CPRD AURUM) and 56% (SIDIAP) of first-dose recipients had at least one health condition or medication of interest. The age distribution for first-dose cohorts, along with those for the viral vector and mRNA first-dose cohorts, are shown in Figure 3.

Table 2. Baseline characteristics of study participants at the time of their first dose vaccination

	CPRD AURUM	IQVIA DA GERMANY	IPCI	SIDIAP	IQVIA Hospital CDM
N	5,551,600	526,622	275,417	2,823,806	358,551
Earliest index date	02/12/2020	04/01/2021	28/12/2020	27/12/2020	15/12/2020
Latest index date	01/05/2021	20/09/2021	22/06/2021	22/06/2021	26/07/2021
Vaccinated with ChAdOx1	3,718,274 (67.0%)	98,354 (18.7%)	70,558 (25.6%)	606,047 (21.5%)	0 (0.0%)
Vaccinated with Ad26.COV2-S	0 (0.0%)	37,620 (7.1%)	1,664 (0.6%)	112,699 (4.0%)	6,189 (1.7%)
Vaccinated with BNT162b2	1,833,326 (33.0%)	389,929 (74.0%)	187,782 (68.2%)	1,861,526 (65.9%)	281,464 (78.5%)
Vaccinated with mRNA-1273	0 (0.0%)	719 (0.1%)	15,413 (5.6%)	243,534 (8.6%)	70,898 (19.8%)
Age	58 [48 to 71]	59 [45 to 68]	63 [55 to 72]	58 [47 to 71]	62 [47 to 73]
Sex: Male	2,562,150 (46.2%)	256,172 (48.6%)	134,345 (48.8%)	1,295,465 (45.9%)	147,288 (41.1%)
Years of prior observation time	17.0 [7.1 to 28.8]	9.4 [4.9 to 14.9]	7.1 [5.4 to 9.4]	15.3 [15.2 to 15.4]	7.3 [3.3 to 11.3]
Covid in year prior	345,405 (6.2%)	41,799 (7.9%)	17,884 (6.5%)	194,917 (6.9%)	6,810 (1.9%)
Autoimmune disease	172,228 (3.1%)	43,360 (8.2%)	9,669 (3.5%)	78,578 (2.8%)	14,049 (3.9%)
Antiphospholipid syndrome	3,846 (0.1%)	0 (0.0%)	0 (0.0%)	2,340 (0.1%)	400 (0.1%)
Thrombophilia	9,580 (0.2%)	1,458 (0.3%)	0 (0.0%)	4,524 (0.2%)	1,557 (0.4%)
Asthma	843,301 (15.2%)	62,326 (11.8%)	35,452 (12.9%)	191,473 (6.8%)	31,218 (8.7%)
Atrial fibrillation	231,702 (4.2%)	16,712 (3.2%)	0 (0.0%)	133,103 (4.7%)	20,168 (5.6%)
Malignant neoplastic disease	595,876 (10.7%)	64,663 (12.3%)	49,806 (18.1%)	348,375 (12.3%)	41,123 (11.5%)
Diabetes mellitus	665,579 (12.0%)	105,894 (20.1%)	37,080 (13.5%)	400,293 (14.2%)	61,011 (17.0%)
Obesity	293,144 (5.3%)	82,100 (15.6%)	16,684 (6.1%)	745,594 (26.4%)	53,785 (15.0%)
Heart disease	774,278 (13.9%)	153,765 (29.2%)	56,523 (20.5%)	535,756 (19.0%)	79,901 (22.3%)
Hypertensive disorder	1,572,072 (28.3%)	234,290 (44.5%)	93,536 (34.0%)	993,188 (35.2%)	145,714 (40.6%)
Renal impairment	485,164 (8.7%)	38,295 (7.3%)	17,861 (6.5%)	235,433 (8.3%)	31,735 (8.9%)
COPD	216,683 (3.9%)	59,254 (11.3%)	15,624 (5.7%)	154,274 (5.5%)	19,549 (5.5%)

Dementia	81,377 (1.5%)	11,538 (2.2%)	2,661 (1.0%)	57,538 (2.0%)	3,881 (1.1%)
Antiinflamatory and antirheumatic	603,267 (10.9%)	87,490 (16.6%)	46,550 (16.9%)	651,915 (23.1%)	22,089 (6.2%)
Coxibs	4,009 (0.1%)	6,698 (1.3%)	1,952 (0.7%)	22,251 (0.8%)	867 (0.2%)
Corticosteroids	266,058 (4.8%)	26,283 (5.0%)	32,937 (12.0%)	159,035 (5.6%)	15,085 (4.2%)
Antithrombotic	119,201 (2.1%)	32,711 (6.2%)	14,771 (5.4%)	84,348 (3.0%)	13,320 (3.7%)
Lipid modifying	211,308 (3.8%)	37,376 (7.1%)	15,881 (5.8%)	56,420 (2.0%)	5,812 (1.6%)
Antineoplastic immunomodulating	53,960 (1.0%)	8,112 (1.5%)	8,260 (3.0%)	28,594 (1.0%)	4,999 (1.4%)
Hormonal contraceptives	68,944 (1.2%)	3,703 (0.7%)	2,863 (1.0%)	11,731 (0.4%)	407 (0.1%)
Tamoxifen	1,608 (0.0%)	256 (0.0%)	208 (0.1%)	751 (0.0%)	19 (0.0%)
Sex hormones modulators	133,498 (2.4%)	5,673 (1.1%)	5,176 (1.9%)	17,528 (0.6%)	505 (0.1%)
Immunoglobulins	4,777 (0.1%)	80 (0.0%)	44 (0.0%)	440 (0.0%)	87 (0.0%)
One or more condition of interest	1,804,627 (32.5%)	228,318 (43.4%)	101,561 (36.9%)	1,248,913 (44.2%)	141,614 (39.5%)
One or more medication of interest	820,420 (14.8%)	102,437 (19.5%)	67,737 (24.6%)	713,891 (25.3%)	25,906 (7.2%)
One or more condition/ medication of interest	2,266,085 (40.8%)	275,195 (52.3%)	138,588 (50.3%)	1,581,944 (56.0%)	149,867 (41.8%)

Figure 3. Age distribution of first-dose cohorts



A total of 4,912,524 were included and analysed after receiving a full dose: 2,343,880 million from CPRD AURUM, 434,137 from IQVIA DA Germany, 107,221 from IPCI, 1,732,230 from SIDIAP, and 295,056 from IQVIA Hospital CDM. Of these, 3,209,233 (65%) were BNT162b2, 1,328,204 (27%) were ChAdOx1, 216,871 (4%) were mRNA-1273, and 158,216 (3%) were Ad26.COV2-S Baseline characteristics are detailed in Table 3. Participants in full-dose cohorts were overall older and with more co-morbidity and medicine/s use than those in the first-dose populations.

Table 3. Baseline characteristics of study participants at the time of their full-dose vaccination

	CPRD AURUM	IQVIA DA GERMANY	IPCI	SIDIAP	IQVIA Hospital CDM
N	2,343,880	434,137	107,221	1,732,230	295,056
Earliest index date	23/12/2020	01/04/2021	29/01/2021	28/12/2020	04/01/2021
Latest index date	01/05/2021	20/09/2021	22/06/2021	22/06/2021	26/07/2021
Vaccinated with ChAdOx1	1,056,694 (45.1%)	31,113 (7.2%)	27,106 (25.3%)	213,291 (12.3%)	0 (0.0%)
Vaccinated with Ad26.COV2-S	0 (0.0%)	37,620 (8.7%)	1,668 (1.6%)	112,729 (6.5%)	6,199 (2.1%)
Vaccinated with BNT162b2	1,287,186 (54.9%)	365,046 (84.1%)	75,858 (70.7%)	1,251,233 (72.2%)	229,910 (77.9%)
Vaccinated with mRNA-1273	0 (0.0%)	358 (0.1%)	2,589 (2.4%)	154,977 (8.9%)	58,947 (20.0%)
Age	71 [56 to 78]	59 [47 to 69]	67 [62 to 74]	63 [52 to 76]	62 [47 to 73]
Sex: Male	974,753 (41.6%)	211,750 (48.8%)	51,981 (48.5%)	749,985 (43.3%)	122,205 (41.4%)
Years of prior observation time	20.2 [8.3 to 32.1]	9.6 [5.1 to 15.2]	7.1 [6.0 to 9.4]	15.4 [15.2 to 15.4]	7.7 [3.5 to 11.5]
Covid in year prior	123,816 (5.3%)	26,814 (6.2%)	4,843 (4.5%)	111,289 (6.4%)	5,404 (1.8%)
Autoimmune disease	96,355 (4.1%)	36,822 (8.5%)	4,103 (3.8%)	58,262 (3.4%)	11,853 (4.0%)
Antiphospholipid syndrome	1,699 (0.1%)	0 (0.0%)	0 (0.0%)	1,669 (0.1%)	342 (0.1%)
Thrombophilia	3,913 (0.2%)	1,243 (0.3%)	0 (0.0%)	3,103 (0.2%)	1,305 (0.4%)
Asthma	349,754 (14.9%)	52,546 (12.1%)	13,694 (12.8%)	122,004 (7.0%)	25,756 (8.7%)
Atrial fibrillation	173,441 (7.4%)	14,461 (3.3%)	0 (0.0%)	117,830 (6.8%)	16,853 (5.7%)
Malignant neoplastic disease	403,785 (17.2%)	56,162 (12.9%)	22,770 (21.2%)	277,926 (16.0%)	34,111 (11.6%)
Diabetes mellitus	363,471 (15.5%)	91,222 (21.0%)	16,612 (15.5%)	297,324 (17.2%)	50,956 (17.3%)
Obesity	131,200 (5.6%)	70,132 (16.2%)	7,444 (6.9%)	506,417 (29.2%)	44,735 (15.2%)
Heart disease	503,188 (21.5%)	131,434 (30.3%)	25,427 (23.7%)	429,304 (24.8%)	66,852 (22.7%)
Hypertensive disorder	946,616 (40.4%)	200,395 (46.2%)	42,692 (39.8%)	754,528 (43.6%)	121,535 (41.2%)
Renal impairment	354,314 (15.1%)	33,107 (7.6%)	7,672 (7.2%)	210,053 (12.1%)	26,333 (8.9%)
COPD	152,720 (6.5%)	51,078 (11.8%)	7,270 (6.8%)	121,277 (7.0%)	16,294 (5.5%)
Dementia	59,712 (2.5%)	9,571 (2.2%)	1,050 (1.0%)	55,621 (3.2%)	3,252 (1.1%)
Antiinflamatory and antirheumatic	314,235 (13.4%)	72,179 (16.6%)	18,404 (17.2%)	416,686 (24.1%)	17,530 (5.9%)
Coxibs	1,889 (0.1%)	5,424 (1.2%)	760 (0.7%)	14,438 (0.8%)	707 (0.2%)
Corticosteroids	139,424 (5.9%)	21,943 (5.1%)	13,765 (12.8%)	113,188 (6.5%)	11,944 (4.0%)
Antithrombotic	81,545 (3.5%)	26,715 (6.2%)	6,461 (6.0%)	63,545 (3.7%)	10,535 (3.6%)
Lipid modifying	128,245 (5.5%)	30,904 (7.1%)	7,293 (6.8%)	38,428 (2.2%)	4,669 (1.6%)
Antineoplastic immunomodulating	27,628 (1.2%)	6,474 (1.5%)	3,029 (2.8%)	20,395 (1.2%)	3,984 (1.4%)
Hormonal contraceptives	22,548 (1.0%)	2,854 (0.7%)	626 (0.6%)	6,916 (0.4%)	320 (0.1%)
Tamoxifen	722 (0.0%)	203 (0.0%)	67 (0.1%)	521 (0.0%)	9 (0.0%)
Sex hormones modulators	51,934 (2.2%)	4,436 (1.0%)	1,532 (1.4%)	10,636 (0.6%)	390 (0.1%)
Immunoglobulins	1,512 (0.1%)	49 (0.0%)	18 (0.0%)	154 (0.0%)	63 (0.0%)
One or more condition of interest	1,058,637 (45.2%)	194,969 (44.9%)	45,306 (42.3%)	890,998 (51.4%)	117,988 (40.0%)
One or more medication of interest	412,889 (17.6%)	84,545 (19.5%)	26,733 (24.9%)	460,246 (26.6%)	20,639 (7.0%)
One or more condition/ medication of interest	1,247,750 (53.2%)	232,776 (53.6%)	58,675 (54.7%)	1,077,499 (62.2%)	124,536 (42.2%)

Finally, we included 39,888,955 persons in background/general population cohorts: 11,933,568 million from CPRD AURUM, 7,251,247 from IQVIA DA Germany, 1,106,793 from IPCI, 5,658,803 from SIDIAP, and 13,938,544 from IQVIA Hospital CDM. Table 4 summarizes baseline characteristics of the background cohorts at the time of their inclusion. Participants in these cohorts were typically younger and healthier than the vaccinated ones characterised in Tables 2-3 above.

Table 4. Baseline characteristics of background cohorts.

	CPRD AURUM	IQVIA DA GERMANY	IPCI	SIDIAP	IQVIA Hospital CDM
N	11,933,568	7,251,247	1,106,793	5,658,803	13,938,544
Earliest index date	01/01/2017	01/01/2017	01/01/2017	01/01/2017	01/01/2017
Latest index date	01/01/2017	01/01/2017	01/01/2017	01/01/2017	01/01/2017
Age	41 [23 to 59]	53 [34 to 68]	45 [23 to 61]	42 [26 to 59]	49 [29 to 64]
Sex: Male	5,997,319 (50.3%)	3,053,972 (42.1%)	543,280 (49.1%)	2,791,700 (49.3%)	5,502,781 (39.5%)
Years of prior observation time	10.4 [4.3 to 20.8]	5.9 [3.2 to 9.8]	3.8 [2.3 to 5.8]	11.0 [11.0 to 11.0]	5.3 [3.2 to 7.2]
Covid in year prior	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Autoimmune disease	211,058 (1.8%)	221,122 (3.0%)	21,664 (2.0%)	84,429 (1.5%)	331,635 (2.4%)
Antiphospholipid syndrome	4,152 (0.0%)	0 (0.0%)	0 (0.0%)	1,005 (0.0%)	4,109 (0.0%)
Thrombophilia	11,027 (0.1%)	6,077 (0.1%)	0 (0.0%)	2,782 (0.0%)	16,482 (0.1%)
Asthma	1,480,712 (12.4%)	383,991 (5.3%)	119,652 (10.8%)	351,825 (6.2%)	1,210,084 (8.7%)
Atrial fibrillation	231,384 (1.9%)	83,541 (1.2%)	0 (0.0%)	137,325 (2.4%)	420,090 (3.0%)
Malignant neoplastic disease	608,499 (5.1%)	497,905 (6.9%)	94,030 (8.5%)	341,321 (6.0%)	816,091 (5.9%)
Diabetes mellitus	690,019 (5.8%)	552,374 (7.6%)	76,657 (6.9%)	466,799 (8.2%)	1,730,400 (12.4%)
Obesity	355,804 (3.0%)	495,163 (6.8%)	35,742 (3.2%)	924,632 (16.3%)	1,330,372 (9.5%)
Heart disease	851,382 (7.1%)	867,430 (12.0%)	112,713 (10.2%)	588,931 (10.4%)	2,153,439 (15.4%)
Hypertensive disorder	1,762,152 (14.8%)	1,319,467 (18.2%)	193,380 (17.5%)	1,141,212 (20.2%)	3,986,104 (28.6%)
Renal impairment	513,516 (4.3%)	156,395 (2.2%)	24,089 (2.2%)	230,179 (4.1%)	695,033 (5.0%)
COPD	233,580 (2.0%)	332,072 (4.6%)	34,709 (3.1%)	166,447 (2.9%)	585,805 (4.2%)
Dementia	96,458 (0.8%)	81,598 (1.1%)	6,894 (0.6%)	72,278 (1.3%)	123,569 (0.9%)
Antiinflamatory and antirheumatic	5,604 (0.0%)	644 (0.0%)	325 (0.0%)	28,961 (0.5%)	7 (0.0%)
Coxibs	86 (0.0%)	46 (0.0%)	50 (0.0%)	270 (0.0%)	0 (0.0%)
Corticosteroids	594 (0.0%)	441 (0.0%)	141 (0.0%)	3,781 (0.1%)	<5
Antithrombotic	8,802 (0.1%)	4,706 (0.1%)	2,158 (0.2%)	16,696 (0.3%)	6 (0.0%)
Lipid modifying	19,788 (0.2%)	6,292 (0.1%)	3,511 (0.3%)	23,973 (0.4%)	0 (0.0%)
Antineoplastic immunomodulating	2,399 (0.0%)	1,129 (0.0%)	1,069 (0.1%)	6,127 (0.1%)	25 (0.0%)
Hormonal contraceptives	2,694 (0.0%)	719 (0.0%)	863 (0.1%)	2,567 (0.0%)	0 (0.0%)
Tamoxifen	122 (0.0%)	60 (0.0%)	16 (0.0%)	322 (0.0%)	0 (0.0%)
Sex hormones modulators	3,198 (0.0%)	1,013 (0.0%)	996 (0.1%)	3,657 (0.1%)	<5
Immunoglobulins	0 (0.0%)	<5	0 (0.0%)	0 (0.0%)	0 (0.0%)
One or more condition of interest	1,989,494 (16.7%)	1,535,705 (21.2%)	205,024 (18.5%)	1,533,605 (27.1%)	3,667,842 (26.3%)
One or more medication of interest	9,396 (0.1%)	2,143 (0.0%)	1,462 (0.1%)	35,110 (0.6%)	8 (0.0%)
One or more condition/ medication of interest	1,995,402 (16.7%)	1,536,864 (21.2%)	206,151 (18.6%)	1,547,103 (27.3%)	3,667,845 (26.3%)

Participants with ATE or VTE after a first-dose vaccination were typically older than the overall vaccinated cohorts (Table 5).

Table 5. Baseline characteristics of outcome cohorts after any first-dose vaccination

	N	Age	Sex: Male	One or more condition/ medication
Arterial thromboembolism				
CPRD AURUM	1,291	72 [61 to 80]	838 (64.9%)	778 (60.3%)
IQVIA DA Germany	236	68 [61 to 77]	166 (70.3%)	169 (71.6%)
IPCI	141	67 [62 to 80]	97 (68.8%)	85 (60.3%)
SIDIAP	1,205	72 [62 to 82]	725 (60.2%)	966 (80.2%)
IQVIA Hospital CDM	189	70 [61 to 77]	102 (54.0%)	145 (76.7%)
Cerebral venous sinus thrombosis				
CPRD AURUM	17	49 [35 to 61]	9 (52.9%)	<5
IQVIA DA Germany	6	44 [35 to 56]	<5	<5
SIDIAP	6	62 [49 to 64]	<5	5 (83.3%)
Splanchnic vein thrombosis				
CPRD AURUM	23	65 [56 to 70]	15 (65.2%)	15 (65.2%)
SIDIAP	34	62 [54 to 72]	19 (55.9%)	28 (82.4%)
IQVIA Hospital CDM	5	44 [43 to 69]	<5	5 (100.0%)
Venous thromboembolism				
CPRD AURUM	1,489	70 [57 to 78]	743 (49.9%)	931 (62.5%)
IQVIA DA Germany	218	68 [59 to 76]	96 (44.0%)	175 (80.3%)
IPCI	85	68 [63 to 75]	34 (40.0%)	60 (70.6%)
SIDIAP	518	72 [61 to 81]	240 (46.3%)	442 (85.3%)
IQVIA Hospital CDM	124	68 [58 to 76]	61 (49.2%)	98 (79.0%)
Thrombocytopenia				
CPRD AURUM	4,370	71 [58 to 79]	2,801 (64.1%)	3,026 (69.2%)
IQVIA DA Germany	376	67 [58 to 77]	220 (58.5%)	271 (72.1%)
IPCI	101	73 [64 to 82]	57 (56.4%)	73 (72.3%)
SIDIAP	5,168	72 [61 to 80]	3,198 (61.9%)	4,152 (80.3%)
IQVIA Hospital CDM	205	71 [62 to 77]	102 (49.8%)	170 (82.9%)
TTS ATE				
CPRD AURUM	13	79 [64 to 86]	9 (69.2%)	6 (46.2%)
SIDIAP	86	77 [65 to 85]	57 (66.3%)	75 (87.2%)
IQVIA Hospital CDM	15	71 [64 to 76]	8 (53.3%)	14 (93.3%)
TTS VTE				
CPRD AURUM	20	62 [49 to 73]	12 (60.0%)	11 (55.0%)
SIDIAP	54	74 [63 to 79]	35 (64.8%)	51 (94.4%)
IQVIA Hospital CDM	10	70 [64 to 72]	<5	10 (100.0%)

Meanwhile, thrombocytopenia was also more common in older recipients of a first-dose vaccination. In CPRD AURUM the median age of those with thrombocytopenia after first-dose vaccination was 71, Table 5.

As with VTE and ATE, a non-linear relationship was seen between age and risk of thrombocytopenia. For thrombocytopenia, however, this increase in risk was more pronounced for men, Figure 6.

These observed trends with age were similar for the background (general population) and for all the vaccinated cohorts.

Figure 4. Association between age and ATE in the general population and after first- and full-dose vaccination

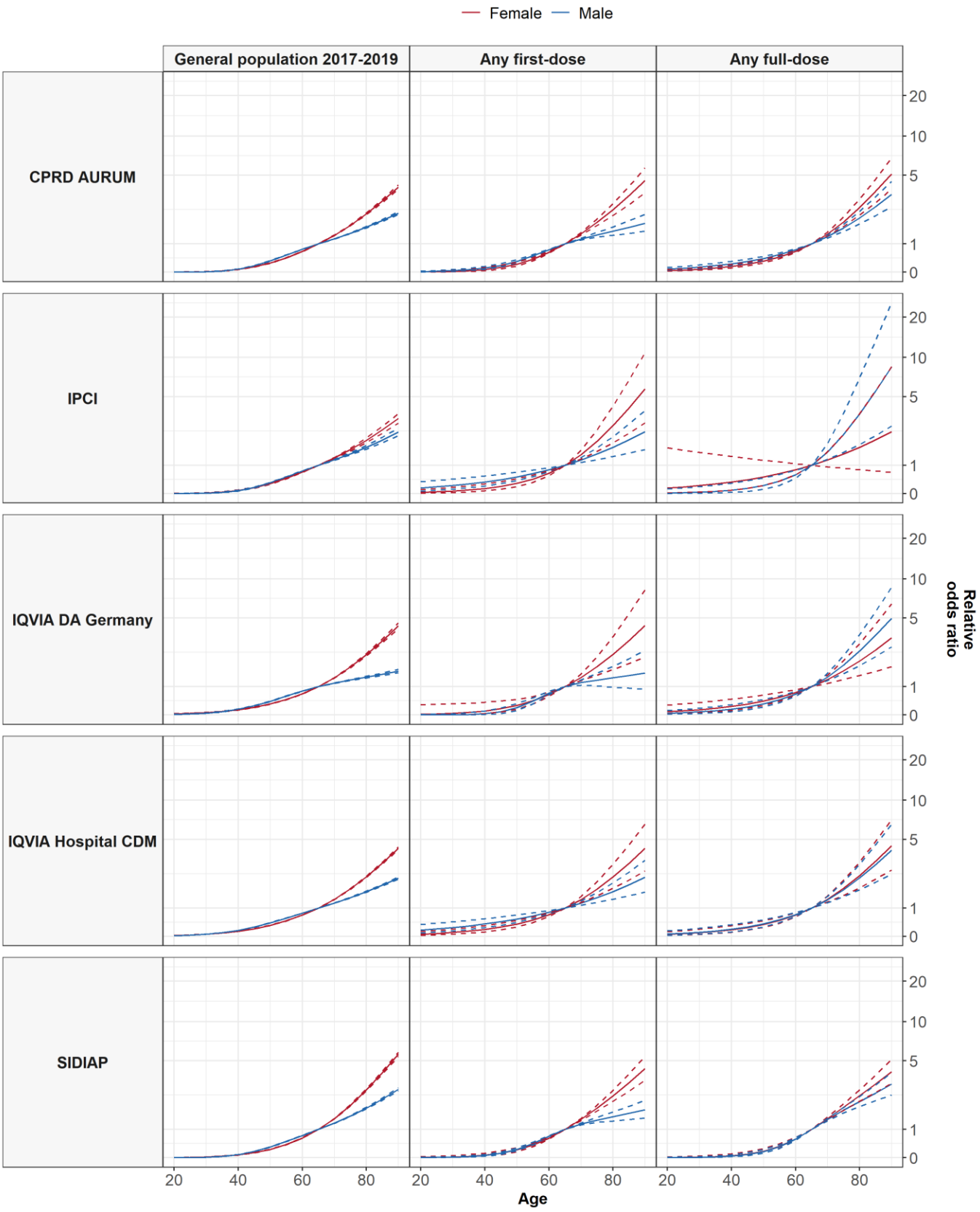


Figure 5. Association between age and VTE in the general population and after first- and full-dose vaccination

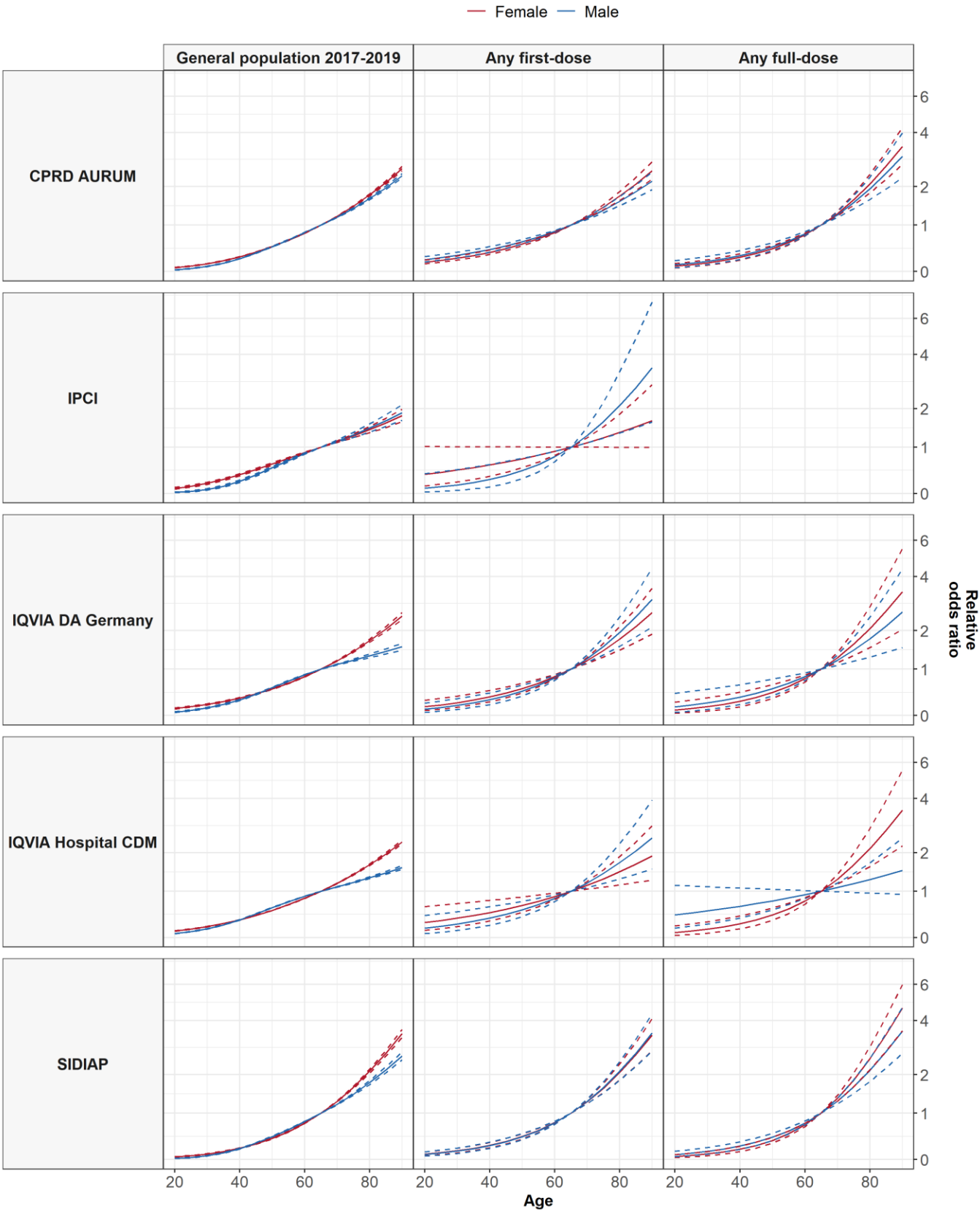
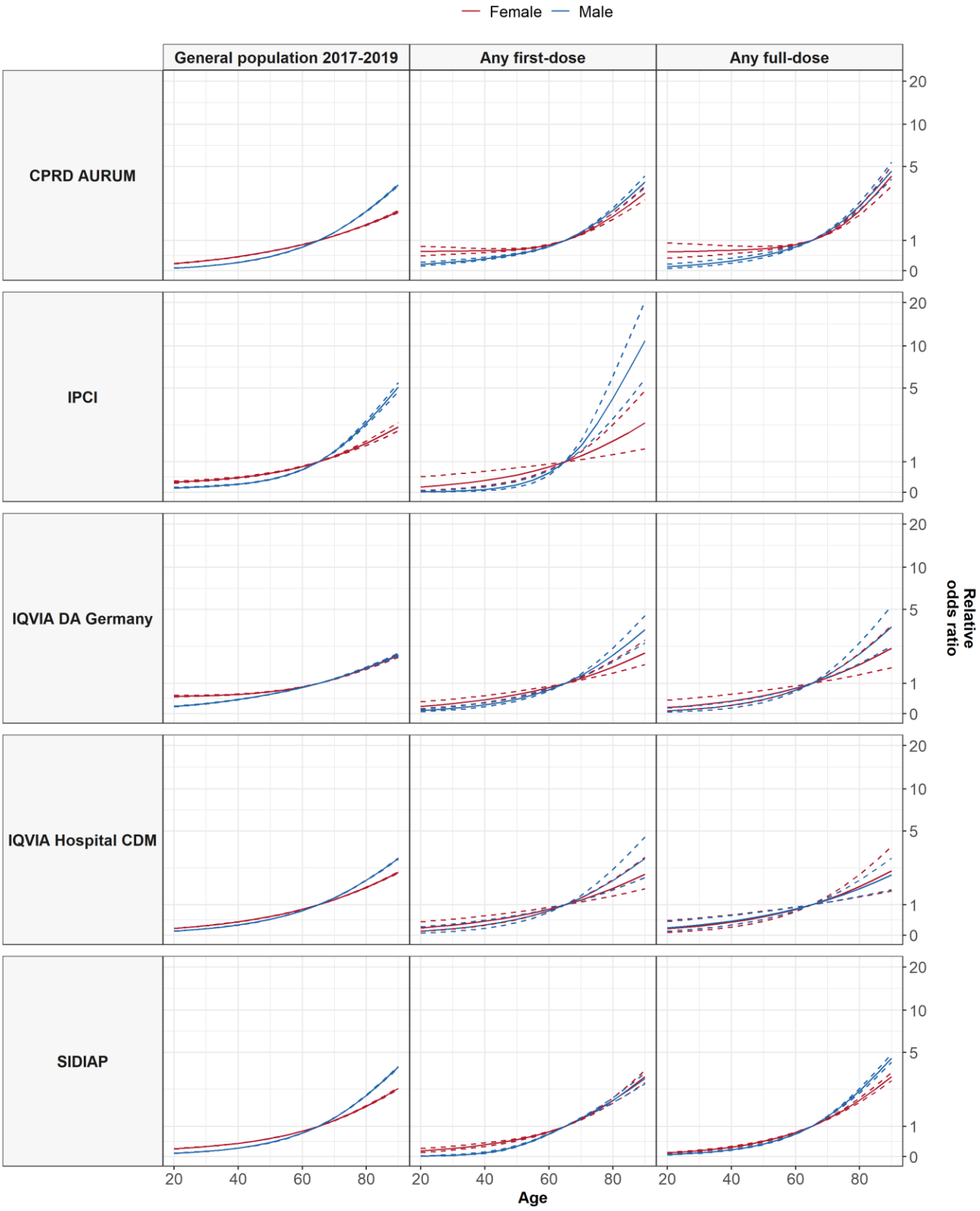


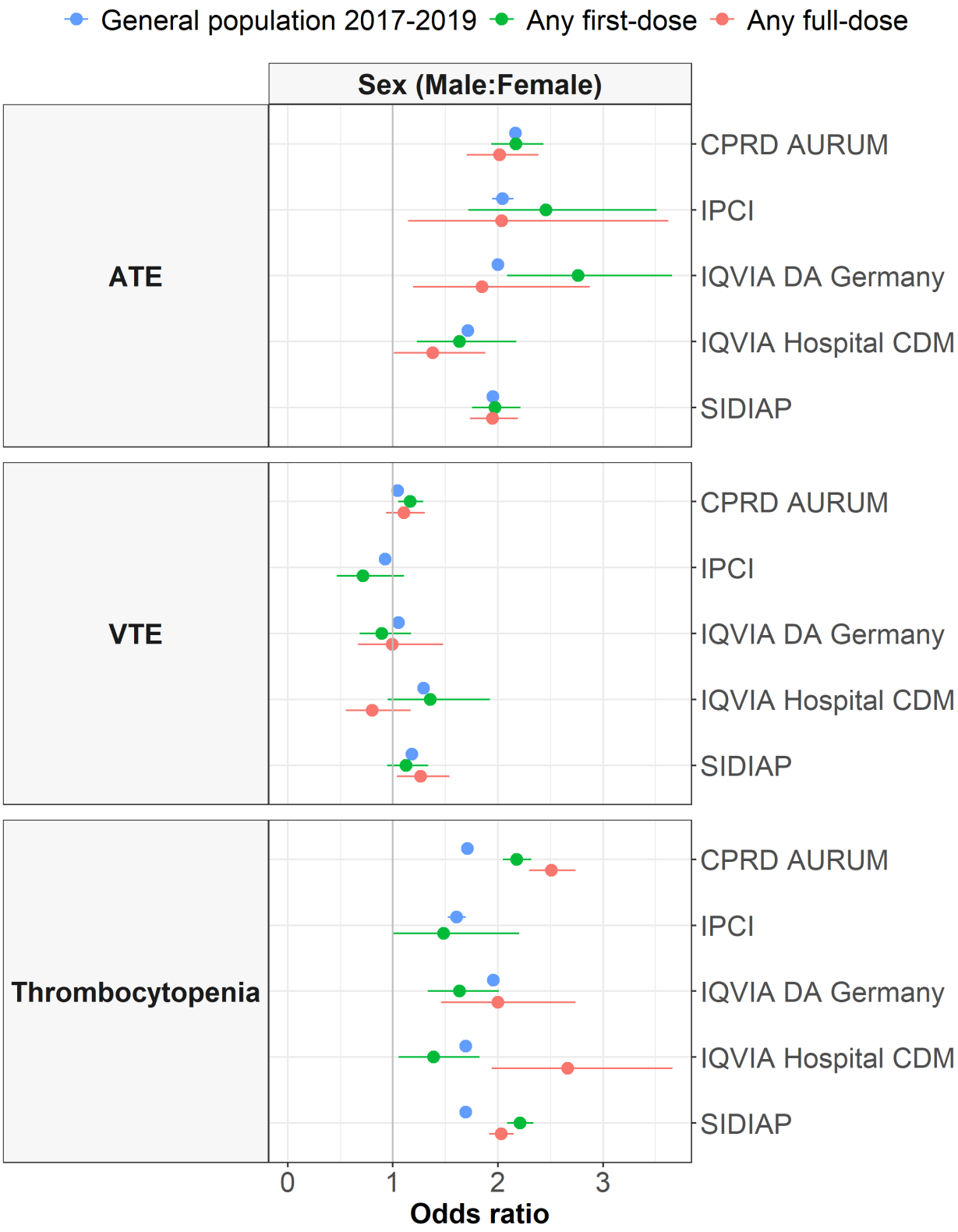
Figure 6. Association between age and thrombocytopenia in the general population and after vaccination



Regarding associations with sex, ATE, VTE, and thrombocytopenia were all more common among male first dose recipients across all databases. Similar patterns were seen for the full dose and general population

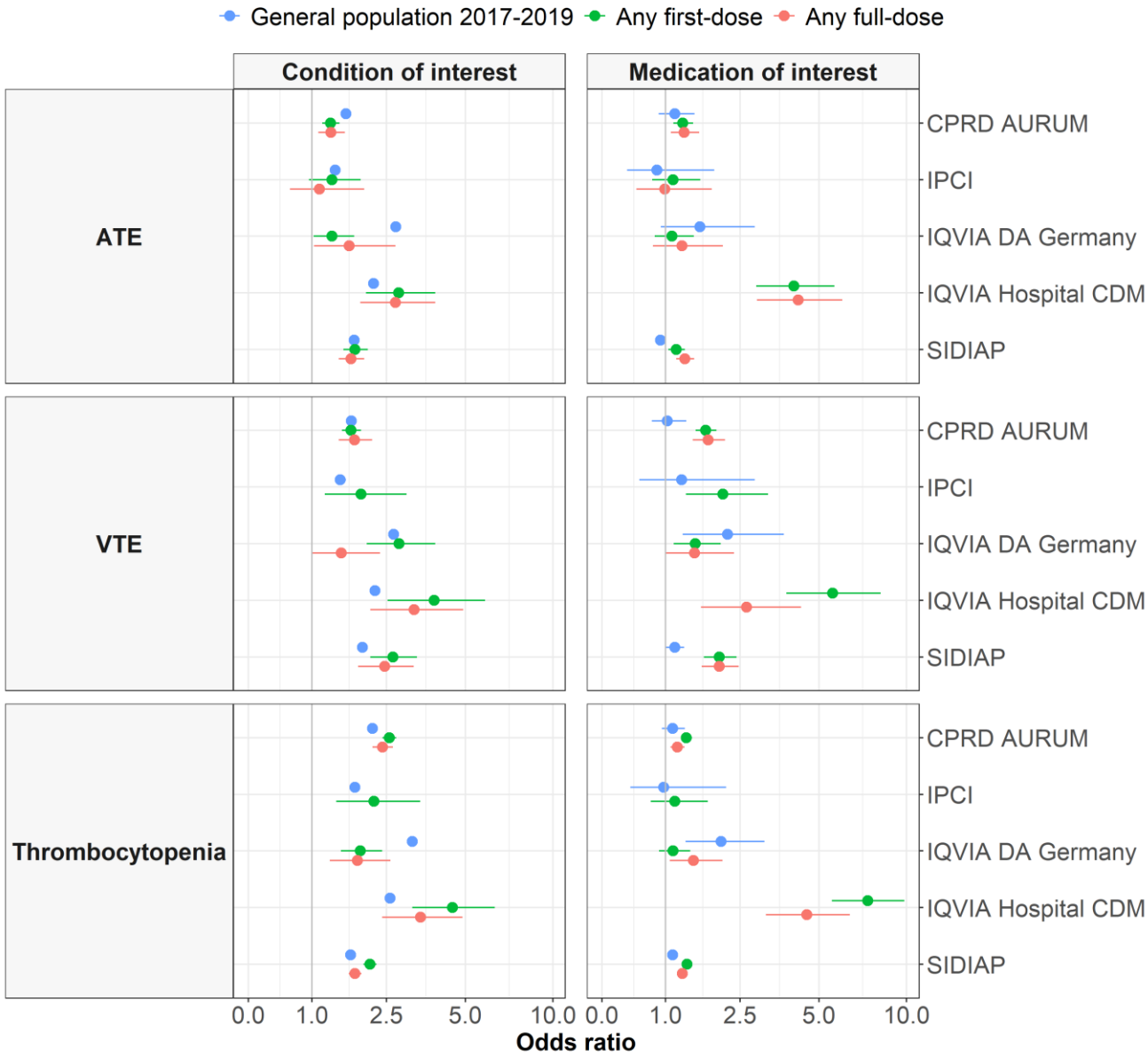
cohorts and when considering mRNA and viral vector vaccines separately. After adjustment for age, being male was generally associated with an increased risk for each of these events, see Figure 7. This increased risk for males was also seen when assessing mRNA and viral vector vaccines separately (see interactive web app).

Figure 7. Association between sex and the study outcomes after adjustment for age



ATE, VTE, and thrombocytopenia were more common among first dose recipients with one or more condition or medication of interest. In CPRD AURUM, while 41% of the whole first dose cohort had one or more condition or medication of interest, 60%, 63%, and 69% of those with ATE, VTE, or thrombocytopenia after first dose, respectively, did. After adjustment for age and sex, conditions and medications of interest were consistently associated with an increased risk of each of these events, Figure 8. Again, findings were generally similar when assessing mRNA and viral vector vaccines separately (see interactive web app).

Figure 8. Association between prevalent use of medicines of interest or history of condition/s of interest and study outcomes in the background population, those vaccinated with one dose, and those fully vaccinated against SARS-CoV-2



CVST, SVT, ATE with thrombocytopenia, and VTE with thrombocytopenia were extremely rare events after vaccination. The maximum cohort size for CVST and SVT were 17 (in CPRD AURUM) and 34 respectively (in SIDIAP). Meanwhile the maximum cohort size for ATE and VTE with thrombocytopenia were 86 and 54 (both in SIDIAP) respectively. The average age of those with ATE and VTE with thrombocytopenia in

SIDIAP after vaccination was 77 and 78 years, respectively, and both were also majority male. This small sample size limited our ability to model association with risk factors. All results for individual risk factors and outcomes and in each of the modelled cohorts are reported in our interactive web app.

10.2 Results for Objective 4

Detailed results are shown in https://dpa-pde-oxford.shinyapps.io/ROC22_TreatmentPatterns/. The interactive application includes granular and detailed information on the included cohorts (**Characterization** tab), Sunburst plots allowing for the comparison of different data sources and of different cohorts/settings (**Sunburst plots** tab), Sankey diagrams, and downloadable tables of proportion/s treated in different cohorts (**Treated patients** tab). The most relevant information and figures are summarized below.

10.2.1 Treatment patterns in patients with TTS

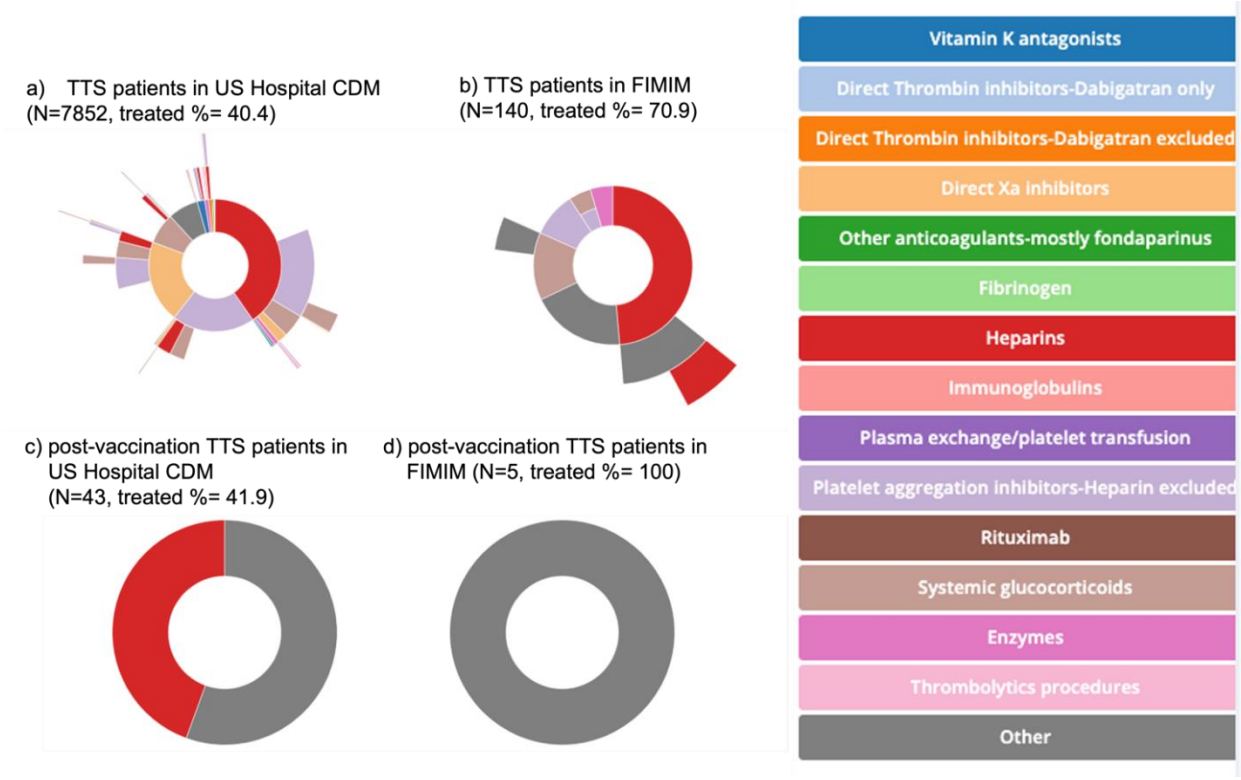
The number of TTS cases in each cohort for each database are detailed in Table 6. TTS in this section was defined as a composite outcome of any TE in addition to thrombocytopenia diagnosis or a measurement of <150,000 platelets per microliter of blood within 10 days of the TE event date. We did not report treatment patterns in patients with venous or arterial TTS separately because of limited sample size and cell suppression rules for < 5 counts in most databases.

Table 6.- TTS cohort size and proportion treated with any of the drugs of interest, stratified by database

	N of background TTS events	% of people with outcome treated	N of post-vaccine TTS events	% of people with outcome treated
FIMIM	140	77.9%	5	100%
US Hospital CDM	7,852	40.4%	43	41.9%
CPRD AURUM	218	7.3%	50	6%
SIDIAP	1,440	34%	258	33.7%
IPCI	8	37.5%	0	n/a
Germany DA	126	20.6%	8	12.5%
France LPD	8	62.5%	0	n/a
US Open Claims	36,005	40.4%	1,220	9.3%

Figure 9 illustrates the inpatient treatment patterns following TTS before Dec 2020 (previous to COVID-19 vaccination), and following post-vaccination TTS in two hospital records databases. The innermost circle represents the first line of treatment, with a combination therapy depicted as a sliced portion with two different colours. We do not show any treatment received by less than 5 patients due to cell suppression rules and information governance; these individual treatment patterns were aggregated into one slice called "other", depicted in grey in the sunburst plots.

Figure 9.- Sunburst plots of patients with historical/background TTS (top) and post-vaccination TTS (bottom) in hospital data from the US Hospital CDM (a & c, left) and FIMIM (b & d, right) databases



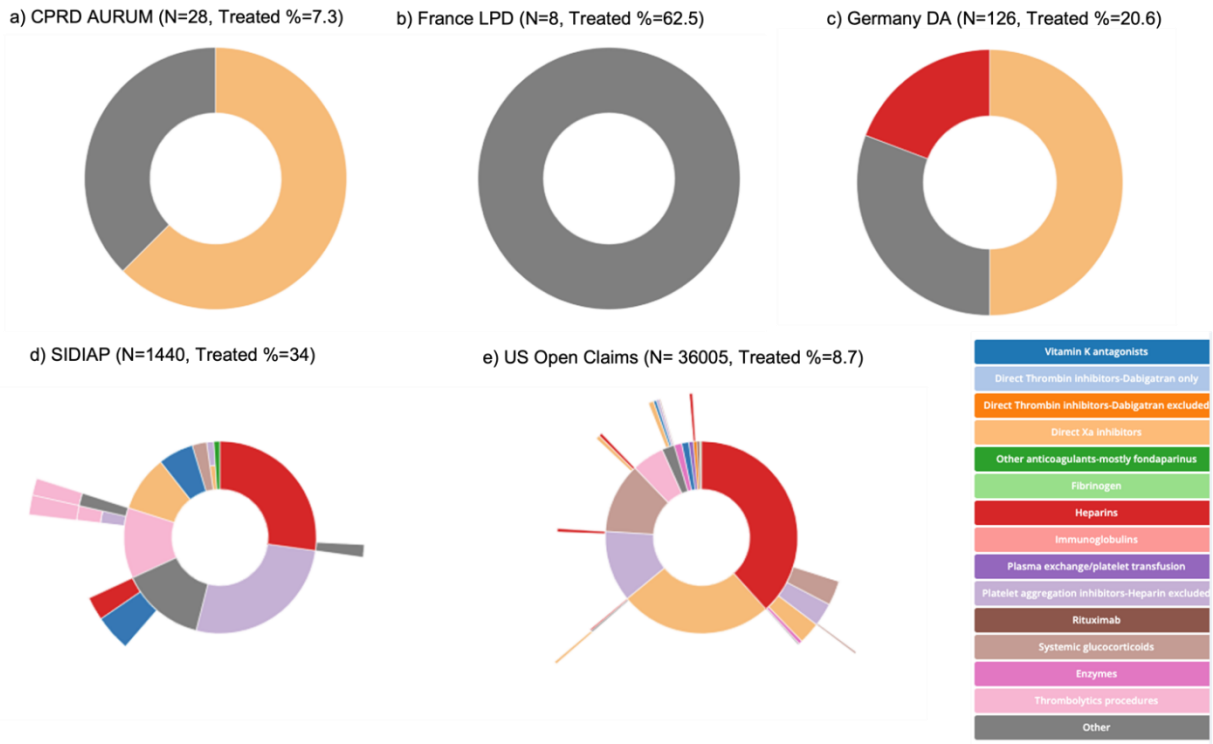
Among 109/140 historical TTS patients receiving any of the treatments of interest in FIMIM, 49% of them had their first treatment with heparin for an average duration of 4.8 days. Out of those started with heparin, 74% did not switch to another treatment during the study period. A further 18% of patients had systemic corticosteroids as their first treatment/s, either in monotherapy or in combination with platelet aggregation inhibitors. Only 4.6% of these patients initiated treatment with thrombolytic enzymes. The rest (19%) received less common treatments, used by <5 patients (Figure 9b). Only 5 patients in FIMIM had a TTS after vaccination. Although all of them were treated, limited sample size did not allow to characterise these due to information governance rules.

A total of 3,176/7,852 people with a historical TTS event in US Hospital CDM data received treatment with at least one of the medicines of interest (Figure 9a). Heparin, platelet aggregation inhibitors and systemic corticosteroids were frequent first-line treatments, used by 40%, 20% and 8% of the treated TTS patients respectively. Direct Xa inhibitor drugs was an additional common first line treatment in US Hospital CDM (20%). A 60% of TTS patients in US Hospital CDM switched to another treatment of interest during the study period. Only 43 patients had a post-vaccination TTS identified in US hospital CDM. Heparin was the most frequently used therapy amongst them (Figure 9c).

As for outpatient therapies, various proportions of TTS patients, ranging from 7.3% in CPRD AURUM to 62.5% in France LPD, received some of the proposed medicines in primary care or outpatient/ambulatory or health claims data (see Table 6). As shown in Figure 10, Direct Xa inhibitors were the most common first-line treatment in patients with historical TTS observed in CPRD AURUM and Germany DA. Heparin was the second most commonly used first-line treatment in Germany DA. More and various treatments were prescribed to historical TTS patients in SIDIAP and US Open Claims. Most patients in both databases did

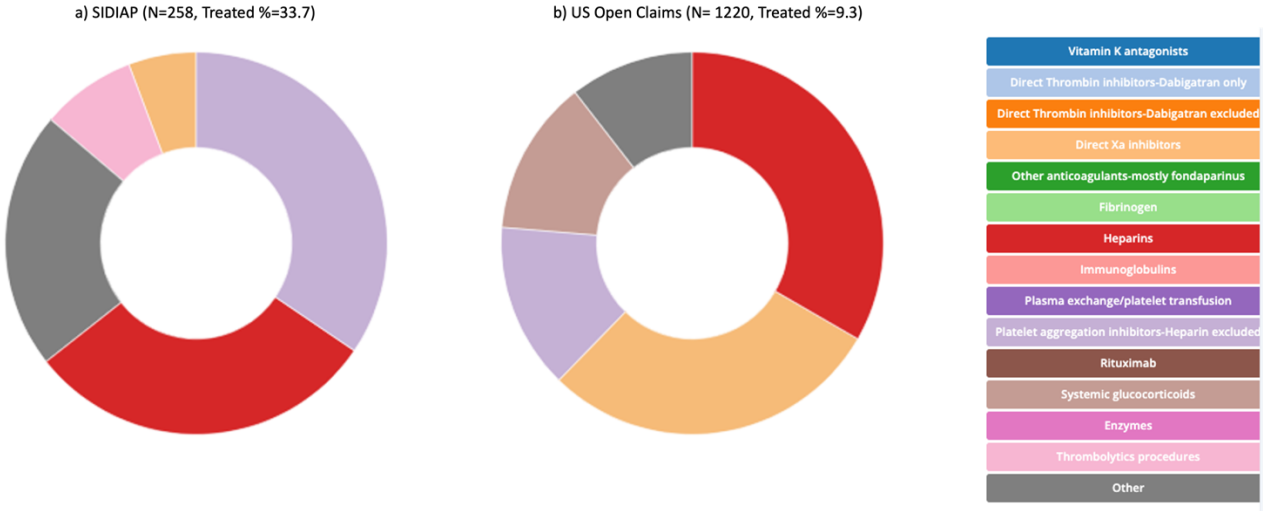
not switch to a second treatment during the study period, though 4% and 11% did switch in SIDIAP and US Open Claims, respectively. Heparin was the most frequently prescribed treatment seen in both SIDIAP (27.2%) and US Open Claims (38.3%), with an average duration of 34.4 (SIDIAP) and 2.2 (US Open Claims) days. Among TTS patients first treated with heparin (N=1,203), 21.9% switched to either direct Xa inhibitors, systemic corticosteroids, or platelet aggregation inhibitors. A 1.8% of patients in SIDIAP and US Open Claims initiated vitamin K antagonist treatment, which was not observed in any of the inpatient databases above. In SIDIAP, thrombolytic therapy was the treatment given for the longest period, an average day of 64.1 overall. In US Hospital CDM, it was the second longest treatment with an overall average day of 140.7 by 170 patients (5%).

Figure 10.- Sunburst plots of outpatient treatment patterns following historical/background TTS



No sunburst plots were depicted in post-vaccination TTS patients in CPRD AURUM, Germany DA, France LPD and IPCI because no treatment was given to more than 5 people. In both SIDIAP and US Open Claim databases, heparin was the most frequently initiated treatment following post-vaccination TTS (Figure 11), with an average duration of 26.2 (SIDIAP) and 1.8 days (US Open Claims). Platelet aggregation inhibitors and direct Xa inhibitors were also used in these patients in both SIDIAP and US Open Claims, whereas thrombolytic therapy was only used in SIDIAP (N=7, 8%) and systemic corticosteroids was only seen in US Open Claims participants (N=15, 13%).

Figure 11.- Sunburst plots of outpatient treatments prescribed following post-vaccine TTS



10.2.2 Treatment patterns in patients with VTE

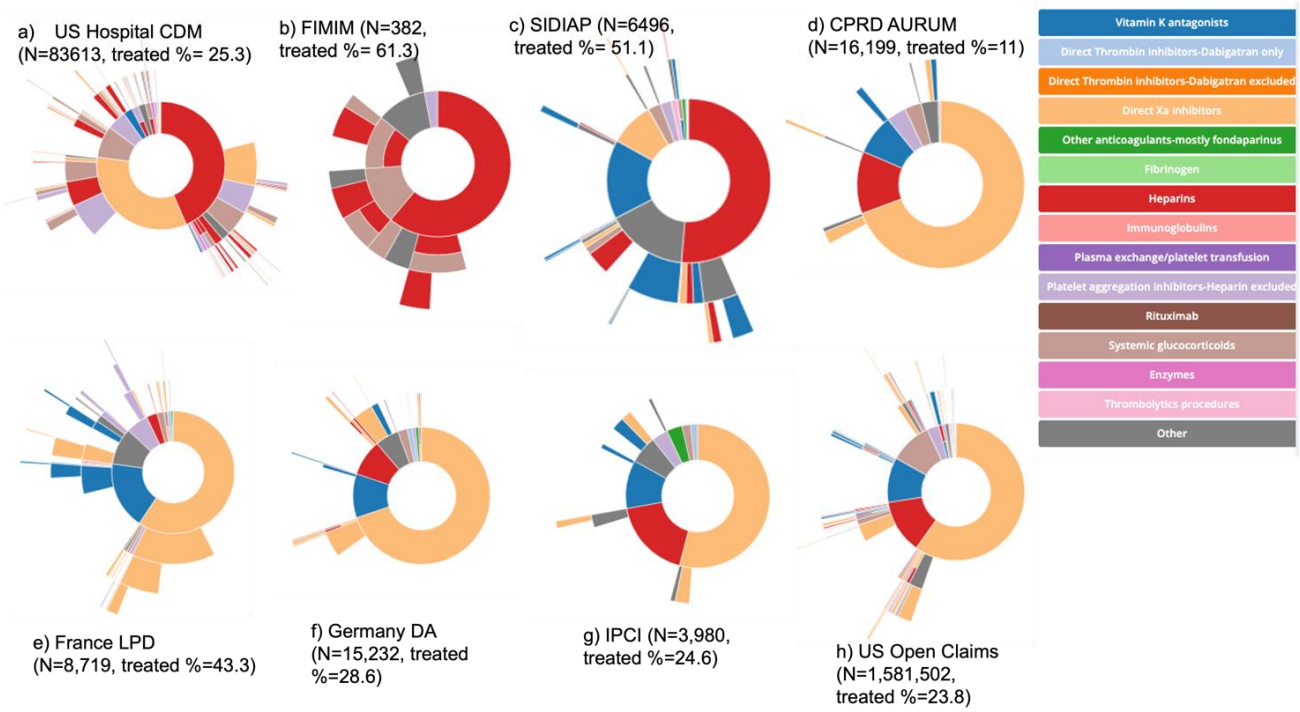
As seen in Table 7, there was a large difference in the proportion of people with background VTE treated with any of the medicines of interest, ranging from 11% (CPRD AURUM) to 61.3% (FIMIM). The proportions of VTE people treated following post-vaccine VTE were also heterogeneous but overall higher than the proportion treated following historical VTE events.

Table 7.- Number of historical and post-vaccine TTS, and % treated with medicines under study, stratified by data source

	VTE cohort	% of people with outcome treated	Post-vaccinated cohort	% of people with outcome treated
FIMIM	382	61.3%	10	70%
US Hospital CDM	83,613	25.3%	784	16.8%
CPRD AURUM	16,199	11%	3,800	9.5%
SIDIAP	6,496	51.1%	1,051	45.2%
IPCI	3980	24.6%	346	25.1%
Germany DA	15,232	28.6%	724	28.6%
France LPD	8,719	43.3%	140	60%
US Open Claims	1,581,502	23.8%	81,150	23.4%

Starting with inpatient treatments, approximately 75% of the treated VTE patients in FIMIM were given heparin or systemic corticosteroids as a monotherapy as the first line treatment. The average durations of heparin and systemic corticosteroids in FIMIM were 5.7 and 1.8 days respectively. Over 80% of patients treated with systemic corticosteroids as the first line received either heparin as a monotherapy or a combination therapy with heparin and systemic corticosteroids as a second line. By contrast, only 27% of patients started with heparin switched to another treatment, most frequently systemic corticosteroids.

Figure 12.- Sunburst plots of patients with 'historical' VTE patients in US Hospital CDM (a), FIMIM (b), SIDIAP (c), CPRD AURUM (d), France LPD (e), Germany DA (f), IPCI (g) and US Open Claims (h).

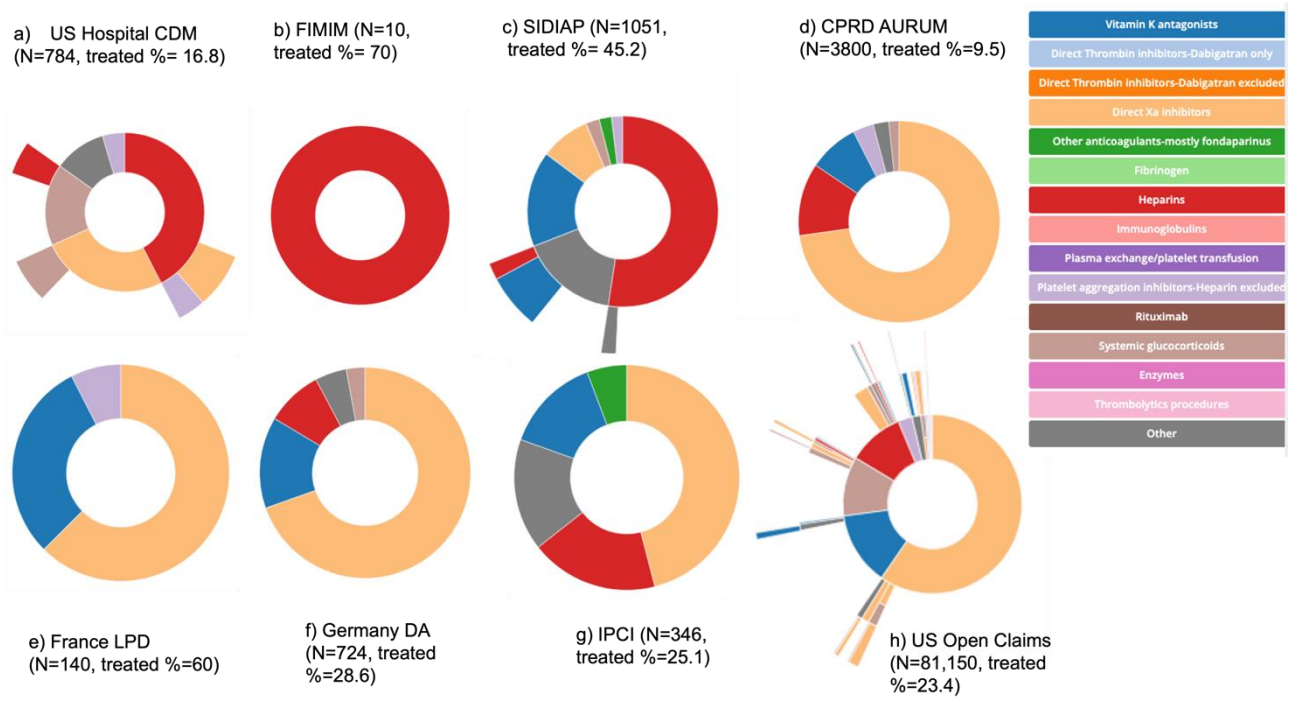


Heparin was also the most frequently used first line treatment in US Hospital CDM (43.7%), followed by direct Xa inhibitors (33.4%). Approximately 50% of those treated initially with heparins or direct Xa inhibitors switched to an alternative second line treatment.

Regarding outpatient treatments, Direct Xa inhibitors were the most frequently prescribed first line therapy in most of the contributing databases except for SIDIAP, where heparin (51.8%) and vitamin K antagonist treatments (15.7%) were the most two commonly used therapies.

Treatment patterns in patients with post-vaccination VTE were also similar to those seen in patients historical VTE. Smaller numbers of events in general meant however less second and third line treatments were observed following a post-vaccination vs historical VTE (Figure 13).

Figure 13.- Sunburst plots of patients with post-vaccination VTE including inpatient (US Hospital CDM (a), FIMIM (b)), and outpatient treatment (SIDIAP (c), CPRD AURUM (d), France LPD (e), Germany DA (f), IPCI (g) and US Open Claims (h))



Similar patterns were also observed after PE or DVT, with similar duration of treatment length (data shown in the shiny app).

10.2.3 Treatment patterns in patients with ATE

Similar to VTE and TTS, great variability was observed across databases in the proportion of people with ATE treated with at least one of the medicines of interest (Table 8). The proportion receiving any of the medicines under study following a historical ATE went from 3.8% (CPRD AURUM) to 58.9% (FIMIM), and after a post-vaccine ATE the range went from 3.7% (CPRD AURUM) to 55.9% (France LPD).

Table 8.- Number of ATE events and % treated with 1+ drugs of interest, stratified by data source

	Historical ATE	% treated	Post-vaccine ATE	% treated
FIMIM	732	58.9%	21	47.6%
US Hospital CDM	156,863	26.7%	1,334	17.5%
CPRD AURUM	17,832	3.8%	3,841	3.7%
SIDIAP	15,933	33.4%	2,820	32.8%
IPCI	19,207	7.5%	1,408	9.4%
Germany DA	28,415	10.6%	1,446	10.8%
France LPD	38,320	38.4%	639	55.9%
US Open Claims	4,745,099	7.3%	197,811	7.6%

Regarding inpatient therapies, 85.5% of the patients treated following background (pre-vaccination) ATE identified in US Hospital CDM received monotherapy, with heparin and platelet aggregation inhibitors being the two most common treatments. Those started with heparin were more likely to switch to platelet aggregation inhibitors, whereas more than 50% of those started with platelet aggregation inhibitors in both databases did not receive further therapies (Figure 14a). Results were very similar in the other inpatient database (FIMIM), where 75.5% received monotherapy, again with heparin and platelet aggregation inhibitors being the most common treatments (Figure 14b).

All outpatient databases showed a majority of background ATE patients firstly treated with platelet aggregation inhibitors. In fact, all except for Germany DA and US Open Claims showed over 70% of patients receiving platelet aggregation inhibitors as a first line therapy. In both Germany DA and US Open Claims, approximately 50% started their first-line treatment with alternative therapies: direct Xa inhibitors (26.3%) and vitamin K antagonists (6%) were the two most common first-line treatments in DA Germany; whilst heparin (15.7%) and systemic glucocorticoids (8.4%) were seen often in US Open Claims data. Platelet aggregation inhibitors and direct Xa inhibitors appeared as two of the most common second line outpatient treatments following a historical ATE event in our treatment pattern analysis (see Figures 14c, 14d, 14e, 14f, 14g, and 14h).

Treatments used following a post-vaccine ATE were similar to those used in historical ATE, with heparin and platelet aggregation inhibitors being the most common treatments (Figure 15).

Figure 14.- Sunburst plots of treatment patterns following background ATE in hospital (US Hospital CDM (a), FIMIM (b)), and outpatient data (SIDIAP (c), CPRD AURUM (d), France LPD (e), Germany DA (f), IPCI (g) and US Open Claims (h))

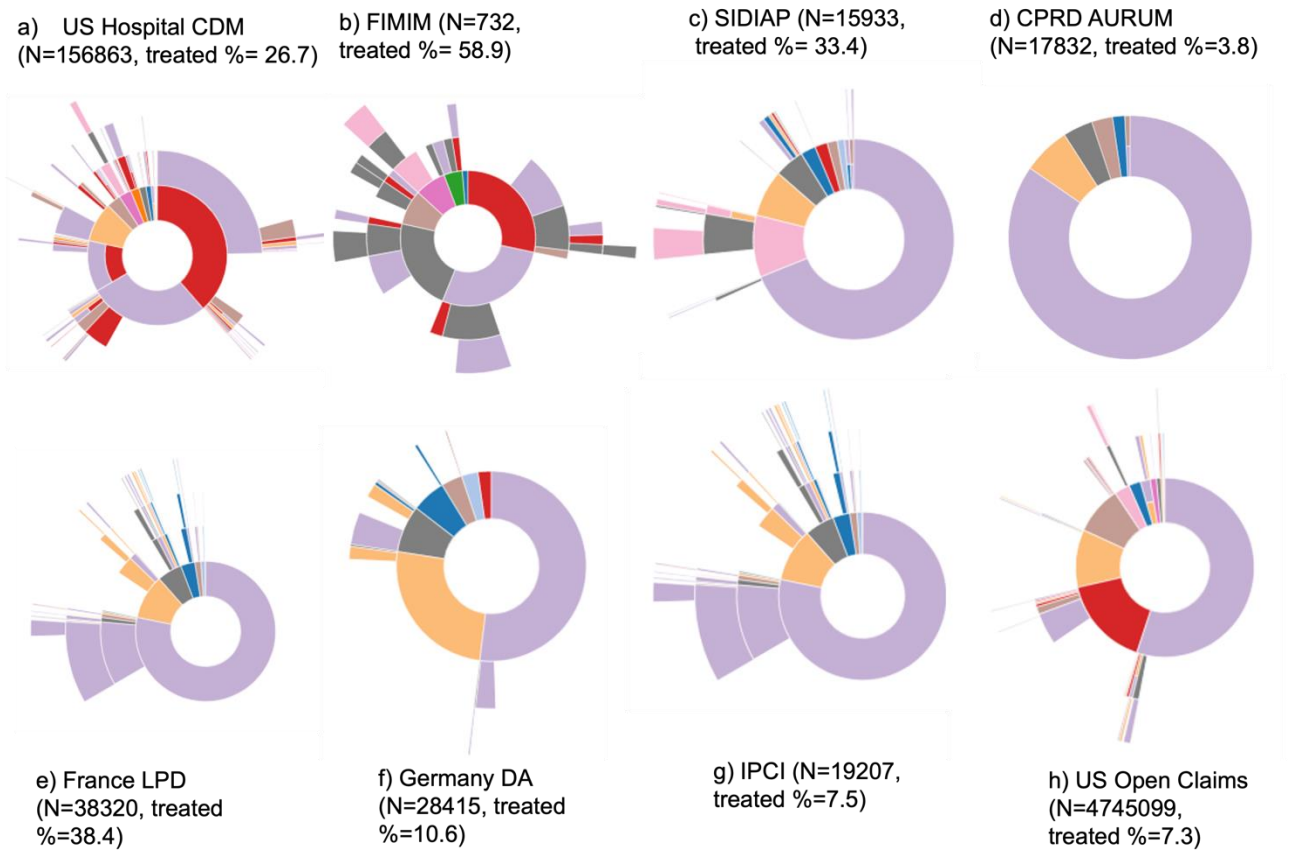
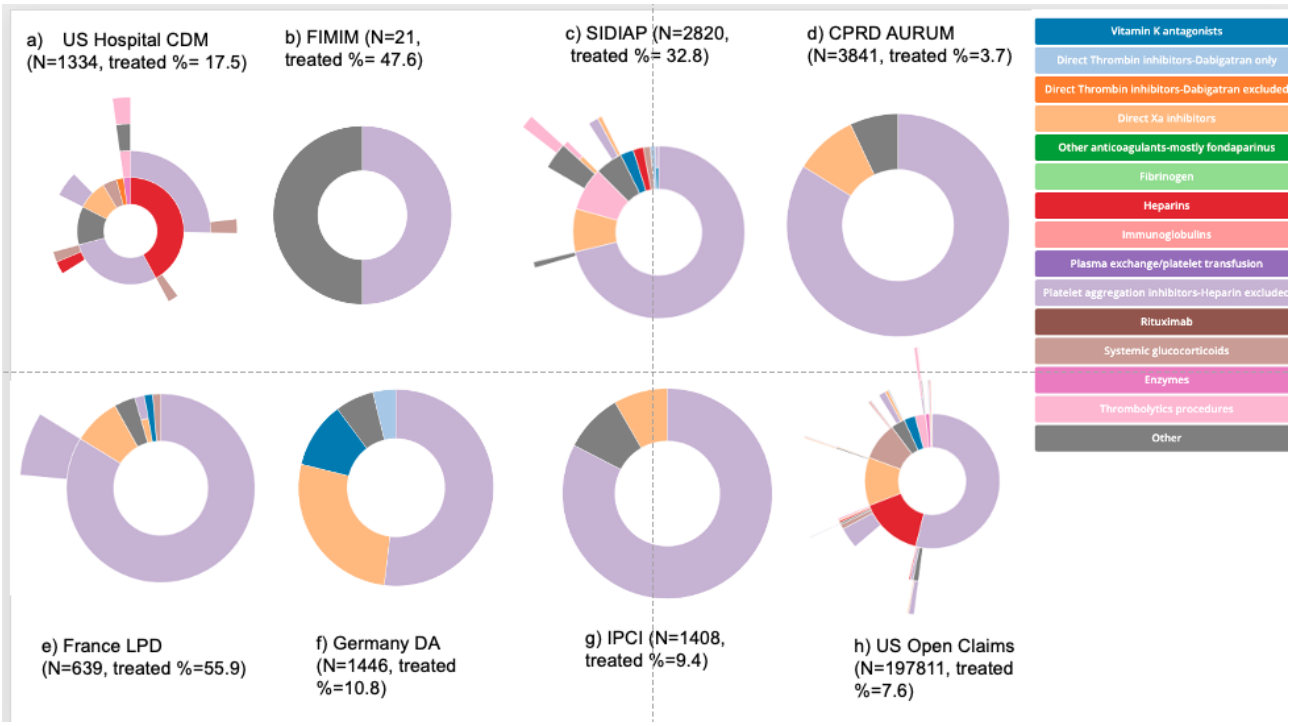


Figure 15.- Sunburst plots of treatment patterns following post-vaccine ATE in hospital (US Hospital CDM (a), FIMIM (b)), and outpatient data (SIDIAP (c), CPRD AURUM (d), France LPD (e), Germany DA (f), IPCI (g) and US Open Claims (h))



11 Discussion

11.1 Risk factors for post-vaccine thrombosis and thrombocytopenia (Objective 3)

11.1.1 Summary of main results

Using data from more than 9.5 million people across five countries, we describe the profiles of people with thrombosis, thrombocytopenia, and thrombosis with thrombocytopenia after vaccination against SARS-CoV-2. Risks for thrombosis and thrombocytopenia among those vaccinated against ARS-CoV-2 generally increased with age, and were higher for males and people with known risk factors including certain health conditions and prior medication use. This picture differs from the reported cases of VITT (see 11.1.2), which should be a much less common subset of TTS events with a different aetiology.

11.1.2 Results in context

The initial safety signals for thrombosis and thrombocytopenia after vaccination against SARS-CoV-2 have predominantly been concentrated on viral vector vaccines, and initial studies most often presented the cases of people with TTS after vaccination who were aged under 60, more often female, and with relatively few comorbidities described[20-22]. This safety signal led to various changes in the provision of COVID-19 vaccines, with a number of countries suspending its use or restricting its use to older age groups. Indeed the current interim guidance from the World Health Organisation states that the main risk factors for thrombosis and thrombocytopenia after vaccination are the use of non-replicant adenovirus vector-based vaccines and younger age, with no evidence that traditional risk factors for thrombosis or thromboembolisms increase risks[23].

Subsequent population based studies have, however, found that the majority of cases of thrombosis and thrombocytopenia after vaccination with both viral vector and mRNA vaccines have been among older patients. In the England, for example, while the mean age of those vaccinated was 56 and 62 for ChAdOx1 and BNT162b2 in one study of close to 30 million vaccine recipients, the average age of those who went on to have thrombocytopenia was 66 and 73, was 69 and 74 for those with venous thrombolism, and 72 and 77 for those with arterial thrombosis[24]. Furthermore, and in line with our findings, the vaccine recipients who went on to have thrombosis or thrombocytopenia were more often male. Similarly, a population based study using data from close to the 3 million vaccine recipients from Scotland, found older age, being male, and certain comorbidities (such as heart failure and diabetes) to be associated with an increased risk of idiopathic thrombocytopenic purpura, haemorrhage or arterial thromboembolic event after vaccination. This profile of patient is similar to those with such events in previous years with, for example, risks for both arterial and venous thromboembolism often seen to increase with age and for males in the general population[25-27].

The discrepancy between the patient profiles described in case reports of thrombosis and thrombocytopenia and those reported in population-based studies such as ours is notable. On the one hand, this may in part be explained by the selection of patients in the presented case series of thrombosis and thrombocytopenia, with the way in which cases where identified resulting in study populations that are not representative of all persons with thrombosis or thrombocytopenia after vaccination. On the other hand, however, population-based studies may be more prone to including broader cohorts from using outcome definitions with lower

specificity, thus including both "routine" thrombosis and thrombocytopenia (i.e. non-vaccine induced) events along with vaccine-induced events. In our study, events were identified over the 28 days following vaccination and so all included outcome events satisfied the proposed diagnostic criteria. However, not all of the included events can be considered attributable to the receipt of the vaccine.

11.2 Medicines use and treatment patterns following thrombosis and thrombocytopaenia (Objective 4)

11.2.1 Summary of main results

We observed great heterogeneity in the management of TTS in all the contributing databases. Historically, before COVID-19 vaccines were available, most patients were treated whilst inpatient with a combination of heparin, platelet aggregation inhibitors, and systemic glucocorticoids, either alone or in combination with each other. Less often, direct Xa inhibitors were also used in US data. Post-vaccine TTS was a very rare event, with only 5 and 43 events seen in Spanish and US hospital records available to us. This precluded a detailed analysis of treatments due to information governance rules. As for outpatient therapies, historical TTS was treated mostly with direct Xa inhibitors, heparin, and platelet aggregation inhibitors, and/or systemic glucocorticoids. Thrombolytic procedures were also observed in Spanish and US data, and Vitamin K antagonists were also commonly used in Spanish primary care. Patients with post-vaccine TTS received heparins, platelet aggregation inhibitors, direct Xa inhibitors, and systemic glucocorticoids according to US health claims. Similar treatments were dispensed according to Spanish data, with the addition of thrombolytic procedures.

VTE was a much more common event. Common treatments after a historical VTE included heparins in inpatient data (US Hospital CDM and FIMIM) and SIDIAP, and direct Xa inhibitors in all other outpatient records and health claims databases. Vitamin K antagonists were also commonly used as a first line treatment in all outpatient data, with platelet aggregation inhibitors used less commonly but still seen in all the proposed databases except for DA Germany. Post-vaccination VTE was treated similarly, with only a few differences when compared to historical VTE events: heparin and vitamin K antagonists were more commonly used post-vaccine compared to historical VTE in the hospital data, and in primary care records from the Netherlands, Spain, and the UK.

As for ATE, historical and post-vaccine events were treated very similarly and quite consistently across the study databases. Platelet aggregation inhibitors dominated the picture, whilst inpatient and health claims data also showed substantial use of heparins. Direct Xa inhibitors, systemic glucocorticoids and Vitamin K antagonists were also common after a historical ATE event, and some databases (mostly inpatient and SIDIAP) also showed the use of thrombolytic procedures. Post-vaccine ATEs were treated very similarly to historical events.

11.2.2 Results in context

To our knowledge, this is the first study on the use of medicines following VTE/ATE or TTS observed after a COVID vaccine. Our data suggest a more homogeneous use of medicines following VTE and ATE compared to TTS, probably due to the difficulties associated with the management of the latter. This could also be due to difficulties with the diagnosis of VITT, and misclassification of TTS/VITT events in our data. Various clinical guidelines have been issued on the management of post-vaccination thrombosis and TTS. German guidelines were published in April 2021[28], and suggested the use of heparin-induced thrombocytopenia (HIT) screening using PF4/heparin antibodies. Where positive, heparins should be avoided, and iv immunoglobulins to be used in case of severe thromboembolic complications together with HIT-compatible anticoagulants: danaparoid, argatroban, direct oral anticoagulants (DOACs), and possibly fondaparinux. German outpatient data was available in our study, but did not include post-vaccination TTS cases. Italian guidelines were also published in 2021[29], and were overall in line with the German ones. However, systemic corticosteroids were also mentioned in patients with lower platelet counts. UK NICE guidelines[30] mentioned similar treatments, and mentioned rituximab in additional to the previously mentioned treatments. The only European data with post-vaccine TTS cases available was SIDIAP (ES). In there, platelet aggregation inhibitors were most common, followed by heparin, thrombolytic procedures, and direct Xa inhibitors. It is likely that the proportion treated with heparin were PF4 antibody negative, although this level of detail was not available in our data.

A more recent publication from the US[31] updated diagnostic criteria, and added more nuanced treatments including a preference for direct Xa inhibitors over Vitamin K antagonists. Data from US Open Claims showed most patients with post-vaccine TTS treated with heparin, followed by direct Xa inhibitors, and systemic glucocorticoids. While the two latter are in line with VITT guidelines, heparins were probably used in the group of patients with negative PF4.

11.3 Study limitations

This study relies on routinely-collected health care data and so, as ever, there is concerns around data quality. Previous research has shown the heterogeneity across databases in estimates of the incidence of the events of interest included in this study, particularly thrombocytopenia where results vary considerably depending on the degree to which platelet measurements are captured. Also, timing of platelet count measurement could result in misclassification of the study event, as thrombocytopenia could potentially precede vaccination [32, 33]. Consequently, a degree of measurement error can be expected. In addition, the degree to which thrombotic and thrombocytopenic events observed after vaccination are comparable to events seen in the general population remains unclear. In particular, case reports have indicated that the location of thrombosis after vaccination has been atypical. Taking this into account, we have purposefully analysed constituent events, rather than focusing only on a single broad definition of thrombosis. However, even within these events differences may well exist between their presentation after vaccination as compared to among the general population.

A key limitation of our study is the inability to correctly classify Vaccine-Induced Thrombosis with Thrombocytopenia (VITT). Although Brighton criteria were implementable in our data, it remains true that clinical guidelines request the measurement of highly specific antibodies (PF4) to reach a diagnosis of VITT. Unfortunately, such measurements were not available in our data. This could explain why a proportion of the observed post-vaccination TTS were still treated with heparin despite guidelines contraindicating this. It is likely that those patients were indeed tested but had a negative results for PF4 antibodies and were therefore classified as TTS without VITT.

Finally, it is worth mentioning that our analyses of risk factors for VTE, ATE, and TTS (Objective 3) were an attempt at characterising the determinants of these events, but not designed to answer causal inference questions. Therefore, it is highly likely that residual confounding can partially explain the observed associations, which should not be interpreted as causal.

11.4 Conclusions

Our data suggest that post-vaccine VTE, ATE and TTS are more common amongst elderly men with specific comorbidities and medicines use. This picture differs from spontaneous reports of VITT and/or cranial venous sinus thrombosis (CVST), which appeared to affect predominantly young and middle age women.

The management of post-vaccine VTE, ATE and TTS appeared similar to that seen in historical events, and overall in line with VITT guidelines.

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

Annex 3. Concept set for persons vaccinated against SARS-CoV-2

Please note, these concept sets will be updated as and when the OHDSI vocabularies are updated. Excluded indicates that the related codes will not be used in the definition, while descendants indicates whether terms below the code in the hierarchy will be included in the definition. (Please see https://ohdsi.github.io/TheBookOfOhdsi/Cohorts.html#conceptSets for more details on how these concept sets are operationalised).

Sub concept sets for each type as well as brand of COVID-19 vaccine will be created from the relevant concept ID below.

Concept ID	Name	Vocabulary
59267100003	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
59267100002	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
592671000	bnt162b2 .23mg/1.8mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
80777027310	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	NDC
2470234	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	RxNorm
2470233	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML	RxNorm
2470232	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273	RxNorm
2468235	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	RxNorm
2468234	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Suspension	RxNorm
2468233	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Product	RxNorm
2468232	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML	RxNorm
2468231	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein	RxNorm
2468230	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2	RxNorm
80777027399	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	NDC
807770273	cx-024414 .2mg/mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
39214411000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) 1170 dose	dm+d
39326611000001100	Generic COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials 100 dose	dm+d
39326811000001100	Generic COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials	dm+d
39214511000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) (Pfizer-BioNTech) 1170 dose 195 x 6 dose vials	dm+d
39327011000001100	COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials (Moderna, Inc) 100 dose 10 x 10 dose vials	dm+d
39326911000001100	COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials	dm+d

Concept ID	Name	Vocabulary
39115611000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech)	dm+d
39115311000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) 6 dose	dm+d
39115711000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) (Pfizer-BioNTech) 6 dose	dm+d
39116111000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech)	dm+d
59676058005	Janssen COVID-19 vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x1010 viral particles/0.5mL dosage, for intramuscular use	NDC
310122210	AZD1222 Astrazeneca COVID-19 vaccine, DNA, spike protein, chimpanzee adenovirus Oxford 1 (ChAdOx1) vector, preservative free, 5x1010 viral particles/0.5mL dosage, for intramuscular use	NDC
310122215	azd1222 50000000000[VP]/.5mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
59267100001	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
91303	Janssen Covid-19 Vaccine	CPT4
91302	AstraZeneca Covid-19 Vaccine	CPT4
91301	Moderna Covid-19 Vaccine	CPT4
91300	Pfizer-Biontech Covid-19 Vaccine	CPT4
0022A	AstraZeneca Covid-19 Vaccine Administration - Second Dose	CPT4
0021A	AstraZeneca Covid-19 Vaccine Administration - First Dose	CPT4
0031A	Janssen Covid-19 Vaccine Administration	CPT4
0012A	Moderna Covid-19 Vaccine Administration - Second Dose	CPT4
0011A	Moderna Covid-19 Vaccine Administration - First Dose	CPT4
0002A	Pfizer-Biontech Covid-19 Vaccine Administration - Second Dose	CPT4
0001A	Pfizer-Biontech Covid-19 Vaccine Administration - First Dose	CPT4
208	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose	CVX
207	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg/0.5mL dose	CVX
210	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL	CVX
212	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL	CVX

Annex 4. Lists of included concepts for study outcomes

Please note, these concept set will be updated as and when the OHDSI vocabularies are updated. Excluded indicates that the related codes will not be used in the definition, while descendants indicates whether terms below the code in the hierarchy will be included in the definition. (Please see https://ohdsi.github.io/TheBookOfOhdsi/Cohorts.html#conceptSets for more details on how these concept sets are operationalised).

A4.1. Cerebral venous sinus thrombosis (CVST)

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4102202	Cerebral venous sinus thrombosis	SNOMED	FALSE	FALSE
4048786	Cerebral venous thrombosis of sigmoid sinus	SNOMED	FALSE	FALSE
4043735	Cerebral venous thrombosis of straight sinus	SNOMED	FALSE	FALSE
4111713	Non-pyogenic venous sinus thrombosis	SNOMED	FALSE	FALSE
314667	Nonpyogenic thrombosis of intracranial venous sinus	SNOMED	FALSE	FALSE
4116206	Septic thrombophlebitis of cavernous sinus	SNOMED	FALSE	FALSE
4121335	Septic thrombophlebitis of lateral sinus	SNOMED	FALSE	FALSE
4119136	Septic thrombophlebitis of sagittal sinus	SNOMED	FALSE	FALSE
4041680	Septic thrombophlebitis of sigmoid sinus	SNOMED	FALSE	FALSE
4100225	Thrombophlebitis lateral venous sinus	SNOMED	FALSE	FALSE
4217471	Thrombophlebitis of basilar sinus	SNOMED	FALSE	FALSE
4104695	Thrombophlebitis of cavernous sinus	SNOMED	FALSE	FALSE
4167985	Thrombophlebitis of inferior sagittal sinus	SNOMED	FALSE	FALSE
764714	Thrombophlebitis of sigmoid sinus	SNOMED	FALSE	FALSE
4100224	Thrombophlebitis of superior longitudinal venous sinus	SNOMED	FALSE	FALSE
4098706	Thrombophlebitis of superior sagittal sinus	SNOMED	FALSE	FALSE
4277833	Thrombophlebitis of torcular Herophili	SNOMED	FALSE	FALSE
764710	Thrombophlebitis of transverse sinus	SNOMED	FALSE	FALSE
4228209	Thrombosis of basilar sinus	SNOMED	FALSE	FALSE
4234264	Thrombosis of cavernous venous sinus	SNOMED	FALSE	FALSE
4048890	Thrombosis of inferior sagittal sinus	SNOMED	FALSE	FALSE
4057329	Thrombosis of lateral venous sinus	SNOMED	FALSE	FALSE
4102203	Thrombosis of superior longitudinal sinus	SNOMED	FALSE	FALSE
4290940	Thrombosis of superior sagittal sinus	SNOMED	FALSE	FALSE
4079905	Thrombosis of torcular Herophili	SNOMED	FALSE	FALSE
4105338	Thrombosis transverse sinus	SNOMED	FALSE	FALSE

A4.2. Deep vein thrombosis - narrow

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

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
760877	Acute deep venous thrombosis of right calf	SNOMED	FALSE	FALSE
762013	Acute deep venous thrombosis of right femoral vein	SNOMED	FALSE	FALSE
762018	Acute deep venous thrombosis of right internal jugular vein	SNOMED	FALSE	FALSE
762419	Acute deep venous thrombosis of right lower extremity	SNOMED	FALSE	FALSE
762005	Acute deep venous thrombosis of right upper extremity	SNOMED	FALSE	FALSE
44782745	Acute deep venous thrombosis of thigh	SNOMED	FALSE	FALSE
44782744	Acute deep venous thrombosis of tibial vein	SNOMED	FALSE	FALSE
762026	Acute deep venous thrombosis of tibial vein of left leg	SNOMED	FALSE	FALSE
765156	Acute deep venous thrombosis of tibial vein of right leg	SNOMED	FALSE	FALSE
44782421	Acute deep venous thrombosis of upper extremity	SNOMED	FALSE	FALSE
764016	Acute deep venous thrombosis of upper extremity after coronary artery bypass graft	SNOMED	FALSE	FALSE
44782766	Acute deep venous thrombosis of upper extremity as complication of procedure	SNOMED	FALSE	FALSE
762048	Acute thrombosis of left subclavian vein	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
762049	Acute thrombosis of right subclavian vein	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
44782762	Acute thrombosis of subclavian vein	SNOMED	FALSE	FALSE
37109253	Bilateral acute deep vein thrombosis of femoral veins	SNOMED	FALSE	FALSE
40478951	Bilateral deep vein thrombosis of lower extremities	SNOMED	FALSE	FALSE
4046884	Deep vein thrombosis of leg related to air travel	SNOMED	FALSE	FALSE
4133004	Deep venous thrombosis	SNOMED	FALSE	FALSE
4181315	Deep venous thrombosis associated with coronary artery bypass graft	SNOMED	FALSE	FALSE
45773536	Deep venous thrombosis of femoropopliteal vein	SNOMED	FALSE	FALSE
763942	Deep venous thrombosis of left lower extremity	SNOMED	FALSE	FALSE
761980	Deep venous thrombosis of left upper extremity	SNOMED	FALSE	FALSE
443537	Deep venous thrombosis of lower extremity	SNOMED	FALSE	FALSE
4133975	Deep venous thrombosis of pelvic vein	SNOMED	FALSE	FALSE
40480555	Deep venous thrombosis of peroneal vein	SNOMED	FALSE	FALSE
4322565	Deep venous thrombosis of profunda femoris vein	SNOMED	FALSE	FALSE
763941	Deep venous thrombosis of right lower extremity	SNOMED	FALSE	FALSE
761928	Deep venous thrombosis of right upper extremity	SNOMED	FALSE	FALSE
4207899	Deep venous thrombosis of tibial vein	SNOMED	FALSE	FALSE
4028057	Deep venous thrombosis of upper extremity	SNOMED	FALSE	FALSE
193512	Embolism and thrombosis of the renal vein	SNOMED	FALSE	FALSE
435565	Embolism and thrombosis of the vena cava	SNOMED	FALSE	FALSE
4119760	Iliofemoral deep vein thrombosis	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4281689	Phlegmasia alba dolens	SNOMED	FALSE	FALSE
4284538	Phlegmasia cerulea dolens	SNOMED	FALSE	FALSE
4309333	Postoperative deep vein thrombosis	SNOMED	FALSE	FALSE
46285905	Provoked deep vein thrombosis	SNOMED	FALSE	FALSE
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
42538533	Thrombosis of iliac vein	SNOMED	FALSE	FALSE
44811347	Thrombosis of internal jugular vein	SNOMED	FALSE	FALSE
765049	Thrombosis of left peroneal vein	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4203836	Thrombosis of subclavian vein	SNOMED	FALSE	FALSE
4175649	Thrombosis of the popliteal vein	SNOMED	FALSE	FALSE
4153353	Traumatic thrombosis of axillary vein	SNOMED	FALSE	FALSE
46285904	Unprovoked deep vein thrombosis	SNOMED	FALSE	FALSE
4221821	Thrombophlebitis of deep veins of lower extremity	SNOMED	FALSE	FALSE
46271900	Recurrent deep vein thrombosis	SNOMED	FALSE	FALSE
4189004	Deep vein thrombosis of leg related to intravenous drug use	SNOMED	FALSE	FALSE

A4.3. SVT

- **Splenic vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE

- **Splanchnic Vein Thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
196715	Budd-Chiari syndrome	SNOMED	FALSE	FALSE
199837	Portal vein thrombosis	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4092406	Portal thrombophlebitis	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE

- **Portal vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
199837	Portal vein thrombosis	SNOMED	FALSE	FALSE

- **Mesenteric vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
36717492	Acute occlusion of mesenteric vein	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE

- **Visceral venous thrombosis or obstruction**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
36717492	Acute occlusion of mesenteric vein	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
196715	Budd-Chiari syndrome	SNOMED	FALSE	FALSE
35624285	Complete obstruction of hepatic portal vein	SNOMED	FALSE	FALSE
4301208	Hepatic vein thrombosis	SNOMED	FALSE	FALSE
37110194	Hepatic veno-occlusive disease with immunodeficiency syndrome	SNOMED	FALSE	FALSE
37109927	Obstruction of visceral vein	SNOMED	FALSE	FALSE
4238060	Portal vein obstruction	SNOMED	FALSE	FALSE

4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
4277276	Veno-occlusive disease of the liver	SNOMED	FALSE	FALSE
37111372	Visceral venous thrombosis	SNOMED	FALSE	FALSE
36712891	Chronic thrombosis of splenic vein	SNOMED	FALSE	FALSE

A4.4. Pulmonary embolism

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4120091	Acute massive pulmonary embolism	SNOMED	FALSE	FALSE
45768439	Acute pulmonary embolism	SNOMED	FALSE	FALSE
45768888	Acute pulmonary thromboembolism	SNOMED	FALSE	FALSE
4309039	Hemorrhagic pulmonary infarction	SNOMED	FALSE	FALSE
762808	Infarction of lung due to embolus	SNOMED	FALSE	FALSE
40480461	Infarction of lung due to iatrogenic pulmonary embolism	SNOMED	FALSE	FALSE
4108681	Postoperative pulmonary embolus	SNOMED	FALSE	FALSE
4091708	Pulmonary air embolism	SNOMED	FALSE	FALSE
440417	Pulmonary embolism	SNOMED	FALSE	FALSE
37109911	Pulmonary embolism due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
37016922	Pulmonary embolism on long-term anticoagulation therapy	SNOMED	FALSE	FALSE
43530605	Pulmonary embolism with pulmonary infarction	SNOMED	FALSE	FALSE
4119608	Pulmonary fat embolism	SNOMED	FALSE	FALSE
254662	Pulmonary infarction	SNOMED	FALSE	FALSE
4253796	Pulmonary microemboli	SNOMED	FALSE	FALSE
45766471	Pulmonary oil microembolism	SNOMED	FALSE	FALSE
4121618	Pulmonary thromboembolism	SNOMED	FALSE	FALSE
4119610	Pulmonary tumor embolism	SNOMED	FALSE	FALSE
4119607	Subacute massive pulmonary embolism	SNOMED	FALSE	FALSE
4119609	Subacute pulmonary fat embolism	SNOMED	FALSE	FALSE
4236271	Recurrent pulmonary embolism	SNOMED	FALSE	FALSE

A4.5. Thrombocytopenia

- Platelet measurement

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
3007461	Platelets [#/volume] in Blood	LOINC	FALSE	TRUE
3031586	Platelets [#/volume] in Blood by Estimate	LOINC	FALSE	TRUE
3024929	Platelets [#/volume] in Blood by Automated count	LOINC	FALSE	TRUE
3039827	Platelets [#/volume] in Body fluid by Automated count	LOINC	FALSE	TRUE
3024386	Platelet mean volume [Entitic volume] in Blood by Rees-Ecker	LOINC	FALSE	TRUE
4267147	Platelet count	SNOMED	FALSE	TRUE
37393863	Platelet count	SNOMED	FALSE	TRUE

- Thrombocytopenia diagnosis

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
37397537	Beta thalassemia X-linked thrombocytopenia syndrome	SNOMED	FALSE	FALSE
432870	Thrombocytopenic disorder	SNOMED	FALSE	FALSE
46272950	Thrombocytopathy, asplenia and miosis	SNOMED	FALSE	FALSE
44782445	Thrombocytopenia due to alcohol	SNOMED	FALSE	FALSE
42536958	Pancytopenia caused by medication	SNOMED	FALSE	FALSE
40321716	Secondary thrombocytopenia	SNOMED	FALSE	FALSE
37312165	Atypical hemolytic uremic syndrome	SNOMED	FALSE	FALSE
37209558	Pancytopenia caused by immunosuppressant	SNOMED	FALSE	FALSE
37204551	Hereditary isolated aplastic anemia	SNOMED	FALSE	FALSE
37204548	Hereditary thrombocytopenia with normal platelets	SNOMED	FALSE	FALSE
37204520	Bleeding diathesis due to thromboxane synthesis deficiency	SNOMED	FALSE	FALSE
37204478	Pancytopenia due to IKZF1 mutations	SNOMED	FALSE	FALSE
37117164	Revesz syndrome	SNOMED	FALSE	FALSE
37116398	Thyrocerebrorenal syndrome	SNOMED	FALSE	FALSE
37110394	Isolated thrombocytopenia	SNOMED	FALSE	FALSE
37019055	Aplastic anemia co-occurrent with human immunodeficiency virus infection	SNOMED	FALSE	FALSE
37018663	Thrombocytopenia co-occurrent and due to alcoholism	SNOMED	FALSE	FALSE
37017607	Antibody mediated acquired pure red cell aplasia caused by erythropoiesis stimulating agent	SNOMED	FALSE	FALSE
37017165	GATA binding protein 1 related thrombocytopenia with dyserythropoiesis	SNOMED	FALSE	FALSE
37016797	MYH9 related disease	SNOMED	FALSE	FALSE
37016151	Aplastic anemia caused by antineoplastic agent	SNOMED	FALSE	FALSE
36717326	DK phocomelia syndrome	SNOMED	FALSE	FALSE
36716406	Severe fever with thrombocytopenia syndrome virus	SNOMED	FALSE	FALSE
36716047	Radioulnar synostosis with amegakaryocytic thrombocytopenia syndrome	SNOMED	FALSE	FALSE
36715586	Refractory thrombocytopenia	SNOMED	FALSE	FALSE
36715053	Autosomal dominant macrothrombocytopenia	SNOMED	FALSE	FALSE
36713970	WT limb blood syndrome	SNOMED	FALSE	FALSE
36713443	MYH9 macrothrombocytopenia syndrome	SNOMED	FALSE	FALSE
36713112	Pancytopenia due to antineoplastic chemotherapy	SNOMED	FALSE	FALSE
36674972	Macrothrombocytopenia with mitral valve insufficiency	SNOMED	FALSE	FALSE
36674474	Pancytopenia with developmental delay syndrome	SNOMED	FALSE	FALSE
35625536	Ataxia pancytopenia syndrome	SNOMED	FALSE	FALSE
35623407	Adult pure red cell aplasia	SNOMED	FALSE	FALSE
4345236	Parvoviral aplastic crisis	SNOMED	FALSE	FALSE
4338386	Thrombocytopenia due to non-immune destruction	SNOMED	FALSE	FALSE
4316372	HELLP syndrome	SNOMED	FALSE	FALSE
4314802	Kasabach-Merritt syndrome	SNOMED	FALSE	FALSE
4311682	Radial aplasia-thrombocytopenia syndrome	SNOMED	FALSE	FALSE
4305588	Doan-Wright syndrome	SNOMED	FALSE	FALSE
4301602	Thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4301128	Thrombocytopenia due to diminished platelet production	SNOMED	FALSE	FALSE

4300464	Wiskott-Aldrich autosomal dominant variant syndrome	SNOMED	FALSE	FALSE
4299560	Thrombocytopenic purpura due to defective platelet production	SNOMED	FALSE	FALSE
4298690	Immunologic aplastic anemia	SNOMED	FALSE	FALSE
4292531	Thrombocytopenic purpura due to platelet consumption	SNOMED	FALSE	FALSE
4292425	Sex-linked thrombocytopenia	SNOMED	FALSE	FALSE
4272928	Thrombocytopenia due to hypersplenism	SNOMED	FALSE	FALSE
4264464	Mediterranean macrothrombocytopenia	SNOMED	FALSE	FALSE
4258261	Drug induced thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4247776	Posttransfusion purpura	SNOMED	FALSE	FALSE
4239484	Acquired pancytopenia	SNOMED	FALSE	FALSE
4235220	Hereditary thrombocytopenic disorder	SNOMED	FALSE	FALSE
4234973	Chronic acquired pure red cell aplasia	SNOMED	FALSE	FALSE
4233407	Megakaryocytic aplasia	SNOMED	FALSE	FALSE
4230266	Autoimmune thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4226905	Thrombocytopenia associated with AIDS	SNOMED	FALSE	FALSE
4225810	Aplastic anemia associated with AIDS	SNOMED	FALSE	FALSE
4219476	Thrombocytopenia due to defective platelet production	SNOMED	FALSE	FALSE
4218171	Uremic thrombocytopenia	SNOMED	FALSE	FALSE
4214947	Thrombocytopenic purpura associated with metabolic disorder	SNOMED	FALSE	FALSE
4211348	Aplastic anemia associated with pancreatitis	SNOMED	FALSE	FALSE
4204900	Acquired thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4197574	Dilutional thrombocytopenia	SNOMED	FALSE	FALSE
4188208	Estren-Dameshek anemia	SNOMED	FALSE	FALSE
4186108	Aplastic anemia associated with metabolic alteration	SNOMED	FALSE	FALSE
4185078	Bernard Soulier syndrome	SNOMED	FALSE	FALSE
4184758	Acquired aplastic anemia	SNOMED	FALSE	FALSE
4184200	Secondary aplastic anemia	SNOMED	FALSE	FALSE
4177177	Cellular immunologic aplastic anemia	SNOMED	FALSE	FALSE
4173278	Thrombocytopenia due to blood loss	SNOMED	FALSE	FALSE
4172008	Cyclic thrombocytopenia	SNOMED	FALSE	FALSE
4166754	Perinatal thrombocytopenia	SNOMED	FALSE	FALSE
4159966	Upshaw-Schulman syndrome	SNOMED	FALSE	FALSE
4159749	Idiopathic maternal thrombocytopenia	SNOMED	FALSE	FALSE
4159736	Radiation thrombocytopenia	SNOMED	FALSE	FALSE
4156233	Thrombocytopenia due to sequestration	SNOMED	FALSE	FALSE
4148471	Fanconi’s anemia	SNOMED	FALSE	FALSE
4147049	Thrombocytopenia due to extracorporeal circulation	SNOMED	FALSE	FALSE
4146088	Aplastic anemia due to drugs	SNOMED	FALSE	FALSE
4146086	Constitutional aplastic anemia with malformation	SNOMED	FALSE	FALSE
4145458	Thrombocytopenia due to hypothermia	SNOMED	FALSE	FALSE
4140545	Post infectious thrombocytopenic purpura	SNOMED	FALSE	FALSE
4139555	Thrombocytopenia due to massive blood transfusion	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4133984	Alloimmune thrombocytopenia	SNOMED	FALSE	FALSE

4133983	Secondary autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133981	Benign gestational thrombocytopenia	SNOMED	FALSE	FALSE
4125496	Pure red cell aplasia, acquired	SNOMED	FALSE	FALSE
4125494	Pancytopenia with pancreatitis	SNOMED	FALSE	FALSE
4123076	Montreal platelet syndrome	SNOMED	FALSE	FALSE
4123075	May-Hegglin anomaly	SNOMED	FALSE	FALSE
4123074	Megakaryocytic thrombocytopenia	SNOMED	FALSE	FALSE
4121265	Mediterranean thrombocytopenia	SNOMED	FALSE	FALSE
4121264	Epstein syndrome	SNOMED	FALSE	FALSE
4120620	Amegakaryocytic thrombocytopenia	SNOMED	FALSE	FALSE
4119134	Thrombocytopenic purpura	SNOMED	FALSE	FALSE
4103532	Immune thrombocytopenia	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4101603	Thrombocytopenia due to extracorporeal circulation of blood	SNOMED	FALSE	FALSE
4101583	Aplastic anemia due to infection	SNOMED	FALSE	FALSE
4101582	Aplastic anemia due to chronic disease	SNOMED	FALSE	FALSE
4100998	Aplastic anemia due to toxic cause	SNOMED	FALSE	FALSE
4098148	Thrombocytopenia due to drugs	SNOMED	FALSE	FALSE
4098145	Idiopathic aplastic anemia	SNOMED	FALSE	FALSE
4098028	Transient acquired pure red cell aplasia	SNOMED	FALSE	FALSE
4098027	Aplastic anemia due to radiation	SNOMED	FALSE	FALSE
4082738	Autoimmune pancytopenia	SNOMED	FALSE	FALSE
4077348	Pancytopenia-dysmelia	SNOMED	FALSE	FALSE
4031699	Humoral immunologic aplastic anemia	SNOMED	FALSE	FALSE
4028065	Autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4027374	Alloimmune platelet transfusion refractoriness	SNOMED	FALSE	FALSE
4009307	Heparin-induced thrombocytopenia with thrombosis	SNOMED	FALSE	FALSE
4000065	Drug-induced immune thrombocytopenia	SNOMED	FALSE	FALSE
441264	Primary thrombocytopenia	SNOMED	FALSE	FALSE
440982	Wiskott-Aldrich syndrome	SNOMED	FALSE	FALSE
440372	Acquired thrombocytopenia	SNOMED	FALSE	FALSE
436956	Evans syndrome	SNOMED	FALSE	FALSE
433749	Heparin-induced thrombocytopenia	SNOMED	FALSE	FALSE
432881	Pancytopenia	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
140681	Constitutional aplastic anemia	SNOMED	FALSE	FALSE
138723	Acquired red cell aplasia	SNOMED	FALSE	FALSE
137829	Aplastic anemia	SNOMED	FALSE	FALSE

- Thrombocytopenic purpura

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4119134	Thrombocytopenic purpura	SNOMED	FALSE	FALSE

4301602	Thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4299560	Thrombocytopenic purpura due to defective platelet production	SNOMED	FALSE	FALSE
4292531	Thrombocytopenic purpura due to platelet consumption	SNOMED	FALSE	FALSE
4258261	Drug induced thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4247776	Posttransfusion purpura	SNOMED	FALSE	FALSE
4230266	Autoimmune thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4214947	Thrombocytopenic purpura associated with metabolic disorder	SNOMED	FALSE	FALSE
4204900	Acquired thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4159966	Upshaw-Schulman syndrome	SNOMED	FALSE	FALSE
4140545	Post infectious thrombocytopenic purpura	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
313800	Thrombotic microangiopathy	SNOMED	FALSE	FALSE

- Immune thrombocytopenia

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4103532	Immune thrombocytopenia	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4133984	Alloimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133983	Secondary autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4028065	Autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4027374	Alloimmune platelet transfusion refractoriness	SNOMED	FALSE	FALSE
4009307	Heparin-induced thrombocytopenia with thrombosis	SNOMED	FALSE	FALSE
4000065	Drug-induced immune thrombocytopenia	SNOMED	FALSE	FALSE
436956	Evans syndrome	SNOMED	FALSE	FALSE
433749	Heparin-induced thrombocytopenia	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE

A4.6. Ischemic stroke

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4045735	Anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
4031045	Anterior choroidal artery syndrome	SNOMED	FALSE	FALSE
761110	Bilateral cerebral infarction due to precererbral arterial occlusion	SNOMED	FALSE	FALSE
4110189	Cerebral infarct due to thrombosis of precerebral arteries	SNOMED	FALSE	FALSE
443454	Cerebral infarction	SNOMED	FALSE	FALSE
762951	Cerebral infarction due to anterior cerebral artery occlusion	SNOMED	FALSE	FALSE
765515	Cerebral infarction due to basilar artery stenosis	SNOMED	FALSE	FALSE

43530683	Cerebral infarction due to carotid artery occlusion	SNOMED	FALSE	FALSE
762933	Cerebral infarction due to cerebral artery occlusion	SNOMED	FALSE	FALSE
762937	Cerebral infarction due to cerebral venous thrombosis	SNOMED	FALSE	FALSE
4111714	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic	SNOMED	FALSE	FALSE
4108356	Cerebral infarction due to embolism of cerebral arteries	SNOMED	FALSE	FALSE
45772786	Cerebral infarction due to embolism of middle cerebral artery	SNOMED	FALSE	FALSE
4110190	Cerebral infarction due to embolism of precerebral arteries	SNOMED	FALSE	FALSE
762935	Cerebral infarction due to internal carotid artery occlusion	SNOMED	FALSE	FALSE
763015	Cerebral infarction due to middle cerebral artery occlusion	SNOMED	FALSE	FALSE
46273649	Cerebral infarction due to occlusion of basilar artery	SNOMED	FALSE	FALSE
35610084	Cerebral infarction due to occlusion of cerebral artery	SNOMED	FALSE	FALSE
46270031	Cerebral infarction due to occlusion of precerebral artery	SNOMED	FALSE	FALSE
762934	Cerebral infarction due to posterior cerebral artery occlusion	SNOMED	FALSE	FALSE
43531607	Cerebral infarction due to stenosis of carotid artery	SNOMED	FALSE	FALSE
35610085	Cerebral infarction due to stenosis of cerebral artery	SNOMED	FALSE	FALSE
46270381	Cerebral infarction due to stenosis of precerebral artery	SNOMED	FALSE	FALSE
4110192	Cerebral infarction due to thrombosis of cerebral arteries	SNOMED	FALSE	FALSE
45767658	Cerebral infarction due to thrombosis of middle cerebral artery	SNOMED	FALSE	FALSE
44782773	Cerebral infarction due to vertebral artery occlusion	SNOMED	FALSE	FALSE
46270380	Cerebral infarction due to vertebral artery stenosis	SNOMED	FALSE	FALSE
37110678	Cerebral ischemic stroke due to occlusion of extracranial large artery	SNOMED	FALSE	FALSE
37110679	Cerebral ischemic stroke due to stenosis of extracranial large artery	SNOMED	FALSE	FALSE
4043731	Infarction - precerebral	SNOMED	FALSE	FALSE
4131383	Infarction of basal ganglia	SNOMED	FALSE	FALSE
4046237	Infarction of optic radiation	SNOMED	FALSE	FALSE
4119140	Infarction of visual cortex	SNOMED	FALSE	FALSE
4141405	Left sided cerebral infarction	SNOMED	FALSE	FALSE
37116473	Multifocal cerebral infarction due to and following procedure on cardiovascular system	SNOMED	FALSE	FALSE
4077086	Occipital cerebral infarction	SNOMED	FALSE	FALSE
4046359	Partial anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
4319146	Pituitary infarction	SNOMED	FALSE	FALSE
4146185	Right sided cerebral infarction	SNOMED	FALSE	FALSE
36717605	Silent cerebral infarct	SNOMED	FALSE	FALSE
4142739	Thalamic infarction	SNOMED	FALSE	FALSE
4046358	Total anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
372924	Cerebral artery occlusion	SNOMED	FALSE	FALSE

A4.7. Myocardial infarction

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4119457	Acute Q wave infarction - anterolateral	SNOMED	FALSE	FALSE
4119943	Acute Q wave infarction - anteroseptal	SNOMED	FALSE	FALSE

4121464	Acute Q wave infarction - inferior	SNOMED	FALSE	FALSE
4121465	Acute Q wave infarction - inferolateral	SNOMED	FALSE	FALSE
4124684	Acute Q wave infarction - lateral	SNOMED	FALSE	FALSE
4119948	Acute Q wave infarction - widespread	SNOMED	FALSE	FALSE
4126801	Acute Q wave myocardial infarction	SNOMED	FALSE	FALSE
4296653	Acute ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
46270162	Acute ST segment elevation myocardial infarction due to left coronary artery occlusion	SNOMED	FALSE	FALSE
761737	Acute ST segment elevation myocardial infarction due to occlusion of circumflex coronary artery	SNOMED	FALSE	FALSE
46270163	Acute ST segment elevation myocardial infarction due to right coronary artery occlusion	SNOMED	FALSE	FALSE
43020460	Acute ST segment elevation myocardial infarction involving left anterior descending coronary artery	SNOMED	FALSE	FALSE
45766076	Acute ST segment elevation myocardial infarction of anterior wall involving right ventricle	SNOMED	FALSE	FALSE
761736	Acute ST segment elevation myocardial infarction of anteroapical wall	SNOMED	FALSE	FALSE
46270159	Acute ST segment elevation myocardial infarction of anterolateral wall	SNOMED	FALSE	FALSE
46270160	Acute ST segment elevation myocardial infarction of anteroseptal wall	SNOMED	FALSE	FALSE
45766116	Acute ST segment elevation myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45766151	Acute ST segment elevation myocardial infarction of inferior wall involving right ventricle	SNOMED	FALSE	FALSE
35611570	Acute ST segment elevation myocardial infarction of inferolateral wall	SNOMED	FALSE	FALSE
35611571	Acute ST segment elevation myocardial infarction of inferoposterior wall	SNOMED	FALSE	FALSE
46274044	Acute ST segment elevation myocardial infarction of lateral wall	SNOMED	FALSE	FALSE
46270161	Acute ST segment elevation myocardial infarction of posterior wall	SNOMED	FALSE	FALSE
46273495	Acute ST segment elevation myocardial infarction of posterobasal wall	SNOMED	FALSE	FALSE
46270158	Acute ST segment elevation myocardial infarction of posterolateral wall	SNOMED	FALSE	FALSE
46270164	Acute ST segment elevation myocardial infarction of septum	SNOMED	FALSE	FALSE
45766075	Acute anterior ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
4178129	Acute anteroapical myocardial infarction	SNOMED	FALSE	FALSE
4267568	Acute anteroseptal myocardial infarction	SNOMED	FALSE	FALSE
312327	Acute myocardial infarction	SNOMED	FALSE	FALSE
44782769	Acute myocardial infarction due to left coronary artery occlusion	SNOMED	FALSE	FALSE
44782712	Acute myocardial infarction due to right coronary artery occlusion	SNOMED	FALSE	FALSE
45766115	Acute myocardial infarction during procedure	SNOMED	FALSE	FALSE
434376	Acute myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
45766150	Acute myocardial infarction of anterior wall involving right ventricle	SNOMED	FALSE	FALSE
438438	Acute myocardial infarction of anterolateral wall	SNOMED	FALSE	FALSE
4243372	Acute myocardial infarction of apical-lateral wall	SNOMED	FALSE	FALSE
4108669	Acute myocardial infarction of atrium	SNOMED	FALSE	FALSE

4151046	Acute myocardial infarction of basal-lateral wall	SNOMED	FALSE	FALSE
4275436	Acute myocardial infarction of high lateral wall	SNOMED	FALSE	FALSE
438170	Acute myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45771322	Acute myocardial infarction of inferior wall involving right ventricle	SNOMED	FALSE	FALSE
438447	Acute myocardial infarction of inferolateral wall	SNOMED	FALSE	FALSE
441579	Acute myocardial infarction of inferoposterior wall	SNOMED	FALSE	FALSE
436706	Acute myocardial infarction of lateral wall	SNOMED	FALSE	FALSE
4324413	Acute myocardial infarction of posterobasal wall	SNOMED	FALSE	FALSE
4051874	Acute myocardial infarction of posterolateral wall	SNOMED	FALSE	FALSE
4303359	Acute myocardial infarction of septum	SNOMED	FALSE	FALSE
4147223	Acute myocardial infarction with rupture of ventricle	SNOMED	FALSE	FALSE
4145721	Acute non-Q wave infarction	SNOMED	FALSE	FALSE
4119944	Acute non-Q wave infarction - anterolateral	SNOMED	FALSE	FALSE
4119456	Acute non-Q wave infarction - anteroseptal	SNOMED	FALSE	FALSE
4119945	Acute non-Q wave infarction - inferior	SNOMED	FALSE	FALSE
4119946	Acute non-Q wave infarction - inferolateral	SNOMED	FALSE	FALSE
4121466	Acute non-Q wave infarction - lateral	SNOMED	FALSE	FALSE
4124685	Acute non-Q wave infarction - widespread	SNOMED	FALSE	FALSE
4270024	Acute non-ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
35610091	Acute nontransmural myocardial infarction	SNOMED	FALSE	FALSE
319039	Acute posterior myocardial infarction	SNOMED	FALSE	FALSE
444406	Acute subendocardial infarction	SNOMED	FALSE	FALSE
35610093	Acute transmural myocardial infarction	SNOMED	FALSE	FALSE
4119947	Acute widespread myocardial infarction	SNOMED	FALSE	FALSE
37109912	Arrhythmia due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
438172	Atrial septal defect due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4124687	Cardiac rupture due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4215259	First myocardial infarction	SNOMED	FALSE	FALSE
4108678	Hemopericardium due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4173632	Microinfarct of heart	SNOMED	FALSE	FALSE

45771327	Mitral valve regurgitation due to acute myocardial infarction with papillary muscle and chordal rupture	SNOMED	FALSE	FALSE
45766214	Mitral valve regurgitation due to acute myocardial infarction without papillary muscle and chordal rupture	SNOMED	FALSE	FALSE
45766212	Mitral valve regurgitation due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4323202	Mixed myocardial ischemia and infarction	SNOMED	FALSE	FALSE
4329847	Myocardial infarction	SNOMED	FALSE	FALSE
37309626	Myocardial infarction due to demand ischemia	SNOMED	FALSE	FALSE
4170094	Myocardial infarction in recovery phase	SNOMED	FALSE	FALSE
4200113	Non-Q wave myocardial infarction	SNOMED	FALSE	FALSE
4030582	Postoperative myocardial infarction	SNOMED	FALSE	FALSE
35610087	Postoperative nontransmural myocardial infarction	SNOMED	FALSE	FALSE
4206867	Postoperative subendocardial myocardial infarction	SNOMED	FALSE	FALSE
35610089	Postoperative transmural myocardial infarction	SNOMED	FALSE	FALSE
4207921	Postoperative transmural myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
4209541	Postoperative transmural myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
37109911	Pulmonary embolism due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4108679	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction	SNOMED	FALSE	FALSE
4108219	Rupture of chordae tendinae due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4124686	Silent myocardial infarction	SNOMED	FALSE	FALSE
765132	Subendocardial myocardial infarction	SNOMED	FALSE	FALSE
45766114	Subsequent ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
45766113	Subsequent ST segment elevation myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
45773170	Subsequent ST segment elevation myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
4108217	Subsequent myocardial infarction	SNOMED	FALSE	FALSE
4108677	Subsequent myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
4108218	Subsequent myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45766241	Subsequent non-ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE

4108680	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
439693	True posterior myocardial infarction	SNOMED	FALSE	FALSE
37109910	Ventricular aneurysm due to and following acute myocardial infarction	SNOMED	FALSE	FALSE

A4.8. Other arterial thromboembolism

- Intestinal infarction

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4195665	Gastrointestinal tract vascular insufficiency	SNOMED	FALSE	FALSE
4148299	Ischemic colitis	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4319280	Acute bowel infarction	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
44811741	Acute ischaemia of large intestine	SNOMED	FALSE	FALSE
44811740	Acute ischaemia of small intestine	SNOMED	FALSE	FALSE
37117790	Insufficiency of mesenteric artery	SNOMED	FALSE	FALSE
37016198	Epiploic appendagitis	SNOMED	FALSE	FALSE
35622081	Nongangrenous ischemic colitis	SNOMED	FALSE	FALSE
35622080	Gangrenous ischemic colitis	SNOMED	FALSE	FALSE
4345926	Abdominal angina	SNOMED	FALSE	FALSE
4342767	Transient ischemic colitis	SNOMED	FALSE	FALSE
4341648	Hemorrhagic infarction of intestine	SNOMED	FALSE	FALSE
4341646	Occlusive mesenteric ischemia	SNOMED	FALSE	FALSE
4340939	Non-occlusive mesenteric ischemia	SNOMED	FALSE	FALSE
4340378	Transmural infarction of intestine	SNOMED	FALSE	FALSE
4340375	Focal segmental ischemia of small intestine	SNOMED	FALSE	FALSE
4318537	Large bowel gangrene	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE
4240850	Acute ischemic enterocolitis	SNOMED	FALSE	FALSE
4239942	Embolic mesenteric infarction	SNOMED	FALSE	FALSE
4237654	Ischemic enterocolitis	SNOMED	FALSE	FALSE

4215949	Nonocclusive intestinal infarction	SNOMED	FALSE	FALSE
4214720	Thrombotic mesenteric infarction	SNOMED	FALSE	FALSE
4192856	Acute ischemic colitis	SNOMED	FALSE	FALSE
4188336	Chronic ischemic enterocolitis	SNOMED	FALSE	FALSE
4174014	Inferior mesenteric artery embolus	SNOMED	FALSE	FALSE
4149013	Mesenteric infarction	SNOMED	FALSE	FALSE
4148257	Chronic gastrointestinal tract vascular insufficiency	SNOMED	FALSE	FALSE
4148256	Acute GIT vascular insufficiency	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055025	Superior mesenteric artery embolus	SNOMED	FALSE	FALSE
4045408	Ischemic stricture of intestine	SNOMED	FALSE	FALSE
201894	Acute vascular insufficiency of intestine	SNOMED	FALSE	FALSE
192673	Vascular insufficiency of intestine	SNOMED	FALSE	FALSE

A4.9. Medications of interest

Concept ID	Code	Concept Name	Domain	Vocabulary

21603933	M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	Drug	ATC
21601386	L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Drug	ATC
21600961	B01A	ANTITHROMBOTIC AGENTS	Drug	ATC
21602722	H02	CORTICOSTEROIDS FOR SYSTEMIC USE	Drug	ATC
21603991	M01AH	Coxibs	Drug	ATC
21602472	G03A	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE	Drug	ATC
21601853	C10	LIPID MODIFYING AGENTS	Drug	ATC
21602471	G03	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	Drug	ATC
21603831	L02BA01	tamoxifen; oral	Drug	ATC

Annex 5. Preliminary list of negative control outcomes

- *Negative outcome Concept ID*

Concept Id	Outcome Name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia
193530	Follicular cyst of ovary
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi
135215	Hashimoto thyroiditis

Concept Id	Outcome Name
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung's disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland
194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence

Concept Id	Outcome Name
314962	Raynaud’s disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor’s bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets