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Thrombosis with thrombocytopenia after AZD1222 (ChAdOx1 nCov-19) vaccination: Case characteristics and associations

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ABSTRACT

Background: Post-marketing surveillance for COVID-19 vaccines during the pandemic identified an extremely rare thrombosis with thrombocytopenia syndrome (TTS) reported post-vaccination, requiring further characterisation to improve diagnosis and management.
Methods: We searched the AstraZeneca Global Safety Database (through April 26, 2021) for cases with co-reported thrombocytopenia and thrombosis (using standardised MedDRA queries/high-level terms) following AZD1222 (ChAdOx1 nCoV-19). Cases were adjudicated by experts as 'typical','possible', 'no' or 'unknown' according to available TTS criteria. Additional confirmatory datasets (May 20–June 20, October 1–December 28) were evaluated.
Findings: We identified 573 reports, including 273 (47.6 %) 'typical' and 171 (29.8 %) 'possible' TTS cases. Of these 444 cases, 275 (61.9 %) were female, median age was 50.0 years (IQR: 38.0–60.0). Cerebral venous sinus thrombosis was reported in 196 (44.1 %) cases, splanchnic venous thrombosis in 65 (14.6 %) and thromboses at multiple sites in 119 (26.8 %). Median time to onset was 12.0 days (IQR: 9.0–15.0). Comparison with a pre-pandemic reference population indicated higher rates of autoimmune disorders (13.8 %, 4.4 %), previous heparin therapy (7.4 %, 1.2 %), history of thrombosis (5.5 %, 1.4 %), and immune thrombocytopenia (6.1 %, 0.2 %). Fatality rate was 22.2 % (127/573) overall and 23.6 % (105/444) in 'typical'/'possible' TTS, which decreased from 39.0 % (60/154) in February/March to 15.5 % (45/290) in April. Overall patterns were similar in confirmatory datasets.
Conclusions: The reporting rate of 'typical'/'possible' TTS post first-dose vaccination in this dataset is 7.5 per million vaccinated persons; few cases were reported after subsequent doses, including booster doses. Peak reporting coincided with media-driven attention. Medical history differences versus a reference population indicate potentially unidentified risk factors. The decreasing fatality rate correlates with increasing awareness and publication of diagnostic/treatment guidelines. Adjudication was hindered

Abbreviations: CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; EU, European Union; EEA, European Economic Area; IQR, interquartile range; MI, myocardial infarction; PE, pulmonary embolism; PF-4, platelet factor 4; TTS, thrombosis with thrombocytopenia syndrome.

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by unreported parameters, and an algorithm was developed to classify potential TTS cases; comprehensive reporting could help further improve definition and management of this extremely rare syndrome.

1. Introduction

The safety and reactogenicity of AZD1222 (ChAdOx1 nCoV-19), a replication-deficient simian adenovirus-vectored vaccine encoding the full-length SARS-CoV-2 spike protein, has been extensively demonstrated in a global clinical development programme involving > 56,000 participants (of whom approximately half received AZD1222) [1–3]. Since initial authorisation for emergency supply in the UK on December 30, 2020, it has been used in >180 countries, with studies demonstrating its real-world effectiveness [4]. AZD1222 is a key component of the global COVID-19 pandemic vaccination effort, with > 2 billion doses distributed worldwide as of November 17, 2021 [5].

As population-level vaccination progressed in response to the pandemic, post-marketing surveillance identified a safety signal of extremely rare events of thrombosis with thrombocytopenia (syndrome; TTS) following COVID-19 vaccination [6–10], which was not seen in large clinical trials of AZD1222 [1–3]. The background rate of thrombosis alongside thrombocytopenia in a pre-pandemic population has been estimated as 3.75–7.16 events per 1 million persons per 14 days [11]. However, multiple studies suggest SARS-CoV-2 infection may itself be associated with an increased risk of coagulopathy [12–14], with one study finding 3.94–14.04-fold increased risk of thrombocytopenia, venous thromboembolism, arterial thromboembolism, cerebral venous sinus thrombosis (CVST), ischaemic stroke, rare arterial thrombotic events, and co-occurrence of thrombocytopenia with venous/arterial thromboembolism within 7 days post-infection [13]. Prior estimates of TTS rates within 14 days of first and second doses of AZD1222 are 8.1 and 2.3 per million vaccinees, respectively [11]. Understanding of the clinical features and characterisation, classification and management of TTS has evolved substantially since initial case reports. This has led to identification of key clinical and laboratory phenotypes that mark vaccine-associated TTS as a specific syndrome, the development of diagnostic guidelines and clinical care recommendations [15–18] as well as specialised case diagnostic criteria for use in clinical analyses [19,20]. However, in the context of the ongoing global vaccination campaign and given the continuing exposure of large and diverse populations, it is important to define clearly the characteristics and mechanism of this specific syndrome and identify individuals at increased risk.

Since regulatory authorisation, all reports of adverse events occurring after vaccination with AZD1222 have been captured in the AstraZeneca Global Safety Database. We aimed to comprehensively describe reported cases of TTS and its associated clinical characteristics and to develop an algorithm that would facilitate the accurate characterisation of spontaneously reported cases in the future. We searched for and analysed all cases of thrombosis with thrombocytopenia within the AstraZeneca Global Safety Database, using an expert review and adjudication process to mitigate the problem of evaluating often-incomplete data from spontaneous case reports. Additionally, we developed an algorithm specific to classification of potential TTS cases from post-marketing safety surveillance datasets to facilitate further large-scale surveillance.

2. Methods

2.1. Study design

This study was a retrospective analysis of potential TTS cases identified from spontaneous adverse event reports captured in the AstraZeneca Global Safety Database. Cases were identified via database searches using Medical Dictionary of Regulatory Activities (MedDRA) terms and queries for thrombocytopenia and thrombosis (Supplementary Appendix, p4) and provided to clinical experts for evaluation and then were adjudicated based on their consistency with known TTS clinical case criteria. Subsequent to adjudication, case characteristics were described and summarised for all reported cases, over time and according to adjudication status. Analyses included a primary analysis of the earliest reported cases through to the period of peak reporting, as well as confirmatory analyses involving datasets from later time periods to detect any changes, or stabilisation, in TTS case report characteristics over time.

2.2. Data source

The AstraZeneca Global Safety Database collates adverse events observed following AZD1222 vaccination as spontaneously reported to AstraZeneca from real-world use worldwide, regardless of source, clinical severity, or determination of causality. The database includes data from all available sources; duplicate case reports are identified and excluded (Supplementary Appendix p3). All known events in the database at the time of data cut-off (April 26, 2021) are included in the primary analysis.

2.3. Data extraction

A search of the database was conducted to identify potential cases of TTS by collating reports in which thrombocytopenia and thrombosis events were co-reported in association with the use of AZD1222, using previously described methodology (Supplementary Appendix p3–4) [11]. All data associated with identified reports up to a primary data cut-off of April 26, 2021, were extracted, including data on co-reported adverse events; available data from follow-up were incorporated until completion of expert review (Supplementary Appendix p3–4). Additional confirmatory datasets from later time-windows, May 20–June 20 and October 1–December 28, 2021, were analysed similarly, with similar data follow-up (Supplementary Appendix p3–4).

2.4. Expert review

The known details of each case were provided to clinical experts in haematology and thrombosis and in pharmacovigilance (authors MAL and SR) for manual adjudication in the context of evolving clinical understanding of TTS [6–9,21,22]. Cases were adjudicated in batches, including re-review for consistency and follow-up information, into four categories: 'Typical' – case aligned with typical TTS; 'Possible' – available data consistent with TTS, but insufficient for definitive alignment; 'No' – data inconsistent with

typical TTS; and 'Unknown' – insufficient data to draw any conclusion. All cases identified in the database search are presented here, regardless of adjudication status, along with a focused analysis on cases adjudicated as 'typical'/'possible' TTS and changes in cases reported over time.

As there was no consensus at the time of initial expert review (April/May 2021) regarding the spectrum of TTS, and in the context of incomplete patient datasets from spontaneous surveillance reporting, the adjudication process was not fully systematic. Characteristics evaluated (where provided) are listed in the Supplementary Appendix (p4). Based on adjudicated cases in the primary analysis and published data [19], a score-based algorithm utilising these parameters was developed for classifying suspected cases of TTS, which accommodated incomplete data from reporting. This algorithm was independently evaluated for concordance with expert adjudication in a subset of cases from the confirmatory May/June cohort (Supplementary Appendix p5).

2.5. Comparison of medical history and concomitant medications in a US population

The IBM MarketScan® Commercial Claims and Encounters and Medicare Supplemental databases were analysed to estimate prevalence of medical events and concomitant medication use in a US population with employer-sponsored commercial or supplemental Medicare insurance coverage in 2019 (i.e. pre-pandemic) (Supplementary Appendix p5).

2.6. Statistical analyses

All analyses in this study were descriptive and are reported using summary statistics, including numbers and percentages, medians, ranges, and interquartile ranges, as appropriate.

3. Results

3.1. Case report identification and adjudication

Between February 4, 2021 (first potential TTS case report received in the AstraZeneca Global Safety Database) and April 26, 2021, 573 case reports of thrombosis and thrombocytopenia were identified. Cases were adjudicated as 'typical' (n = 273, 47.6 %), 'possible' (n = 171, 29.8 %), 'no' (n = 83, 14.5 %), or 'unknown' (n = 46, 8.0 %) (Table 1, Fig. S1). During this period, 27,713,147 doses of AZD1222 were administered in the UK, 27,328,201 in the European Union (EU)/European Economic Area (EEA), 1,446,181 in Australia and 2,030,864 in Canada (Fig. S2). Based on these findings and the number of known administered doses in reporting countries at data cut-off (52.7 million first doses), the reporting rate of 'typical'/'possible' TTS cases post-first-dose vaccination in this dataset is 7.5 per million vaccinated persons.

3.2. Case report characterisation

Demographics and clinical characteristics of all case reports are summarised in Supplementary Appendix Tables S1 and S2, respectively. Median age was 52.0 years, and 335 (58.5 %) individuals were female; 375 (65.4 %) reports were received from the UK and 184 (32.1 %) from the EU; case reports and doses administered per time period are shown in Table S1 and Fig. S2.

Among 444 individuals with 'typical'/'possible' TTS, median age was 50.0 years, and 275 (61.9 %) were female (Table 1). Specific information on venous and/or arterial thrombosis sites was available for 371 (83.6 %) and 94 (21.2 %) cases, respectively; 119 (26.8 %) cases involved thromboses at multiple sites (Table 1). CVST was reported in 196 (44.1 %) cases, splanchnic venous thrombosis in 65 (14.6 %), pulmonary embolism (PE) in 134 (30.2 %) and deep vein thrombosis (DVT) in 61 (13.7 %). Excluding events of intracerebral haemorrhage, which were usually secondary to CVST, stroke was the most frequently reported arterial event (n = 39, 8.8 %;). Time to onset was within 21 days post-vaccination in 393 (88.5 %) cases; median time to onset was 12.0 days (Table 1).

Precise platelet counts were recorded in 443/573 (77.3 %) cases overall (Table S2), and in 361/444 (81.3 %) of 'typical'/'possible' TTS cases (Table 1). Of the latter, 208/444 (46.8 %) had a platelet count at presentation of $< 50 \times 10^9$/L (grade ≥ 3 severity), of whom 94 (45.2 %) had a bleeding event, compared to 71 (30.1 %) of the remaining 236 cases.

3.3. Changes in case report characterisation over time

Clinical characteristics of reported cases evolved over time. Among all 573 cases, 154/182 (84.6 %), 151/195 (77.4 %) and 139/196 (70.9 %) were adjudicated as 'typical'/'possible' in the February/March, early April and late April cohorts, respectively (Table S2). The proportions of cases that were missing laboratory data on platelet count, D-dimer level and fibrinogen level were also lower in the April cohorts versus the February/March cohort (Table S2).

Among 'typical'/'possible' TTS cases (Table S3), the proportion of females decreased from 74.0 % in February/March to 56.3 % and 54.7 % in early and late April, respectively. The proportion of cases with CVST decreased from 54.5 % in February/March to 41.1 % and 36.0 % in early and late April, respectively, whereas the proportion of cases with DVT/PE increased from 9.7 %/29.2 % in February/March to 16.6 %/21.9 % and 15.1 %/40.3 % in early and late April. The proportions of 'typical'/'possible' TTS cases that were missing D-dimer and fibrinogen level data were lower in the April cohorts versus the February/March cohort, whereas the proportions of cases missing platelet count and anti-platelet factor-4 (PF4) antibody data remained similar across the time periods (Table S3).

Overall patterns in clinical characteristics of reported cases and 'typical'/'possible' TTS cases were similar in the confirmatory May–June (Table S4) and October–December (Table S5) cohorts of adjudicated case reports.

3.4. Score-based classification algorithm for real-world reports of potential TTS

Based on the results from expert adjudication of the initial 573 case reports (Fig. S1), a score-based classification algorithm was developed for spontaneous surveillance reports (Fig. S3). This algorithm categorises cases as 'TTS', 'possible TTS', and 'not TTS', for alignment with recent UK Expert Haematology Panel case definition criteria of 'definite/probable', 'possible', and 'unlikely' [19], as well as 'unknown'. The algorithm was used to classify a subset of the secondary confirmatory cohort of case reports (Table S4); agreement between expert adjudication as 'typical' or 'possible' TTS and algorithm classification as 'TTS' or 'possible TTS' was 99.0 % (full concordance analysis provided in the Supplementary Appendix Results (p6), and Table S6).

3.5. Associated factors

Data were available on medical history and concomitant medications for 395/573 cases and for 311/444 'typical'/'possible' TTS cases (Fig. 1) for comparison with a pre-pandemic population. Median ages in these 395 and 311 cases were 53.0 years (IQR: 40.0–63.0) and 51.0 years (38.0–60.0), respectively; median age

Table 1
Clinical characteristics of the case reports of thrombosis with thrombocytopenia according to adjudicated TTS category– primary analysis, through April 26, 2021.

Characteristic	'Typical'/'Possible' cases			No*	Unknown*
	All	**Typical***	**Possible***	(n = 83)	(n = 46)
	(n = 444)	**(n = 273)**	**(n = 171)**		
Age, years, median†	50	48	55	62	56
(IQR, range)	(38.0–60.0, 18–93)	(33.8–57.3, 18–80)	(44.0–63.5, 21–93)	(49.0–74.3, 23–95)	(41.0–63.0, 19–87)
Sex					
Female	275 (61.9)	175 (64.1)	100 (58.5)	45 (54.2)	15 (32.6)
Male	166 (37.4)	97 (35.5)	69 (40.4)	37 (44.6)	24 (52.2)
Missing	3 (0.7)	1 (0.4)	2 (1.2)	1 (1.2)	7 (15.2)
Region					
United Kingdom	295 (66.4)	180 (65.9)	115 (67.3)	59 (71.1)	21 (45.6)
European Union	142 (32.0)	90 (33.0)	52 (30.4)	22 (26.5)	20 (43.5)
Other	7 (1.6)	3 (1.1)	4 (2.3)	2 (2.4)	5 (10.9)
Thrombosis site‡					
Cases with specified venous thromboses	**371 (83.6)**	**254 (93.0)**	**117 (68.4)**	**43 (51.8)**	**27 (58.7)**
Venous thrombosis site not specified	73 (16.4)	19 (7.0)	54 (31.6)	40 (48.2)	19 (41.3)
Venous events					
CVST	196 (44.1)	178 (65.2)	18 (10.5)	9 (10.8)	9 (19.6)
PE	134 (30.2)	70 (25.6)	64 (37.4)	19 (22.9)	9 (19.6)
Splanchnic	65 (14.6)	58 (21.2)	7 (4.1)	2 (2.4)	5 (10.9)
DVT	61 (13.7)	25 (9.2)	36 (21.1)	13 (15.7)	5 (10.9)
Abdominal	15 (3.4)	14 (5.1)	1 (0.6)	1 (1.2)	1 (2.2)
Other	10 (2.3)	2 (0.7)	8 (4.7)	7 (8.4)	1 (2.2)
Cases with specified arterial thromboses	**94 (21.2)**	**45 (16.5)**	**49 (28.7)**	**16 (19.3)**	**5 (10.9)**
Arterial thrombosis site not specified	350 (78.8)	228 (83.5)	122 (71.3)	67 (80.7)	41 (89.1)
Arterial events					
Stroke	39 (8.8)	15 (5.5)	24 (14.0)	10 (12.0)	4 (8.7)
MI	28 (6.3)	15 (5.5)	13 (7.6)	1 (1.2)	0
Limb	26 (5.9)	13 (4.8)	13 (7.6)	2 (2.4)	1 (2.2)
Abdominal	9 (2.0)	8 (2.9)	1 (0.6)	2 (2.4)	1 (2.2)
Other	2 (0.5)	1 (0.4)	1 (0.6)	1 (1.2)	0
Cases with thromboses at multiple specified sites	**119 (26.8)**	**97 (35.5)**	**22 (12.9)**	**6 (7.2)**	**4 (8.7)**
Both venous and arterial sites specified	31 (7.0)	27 (9.9)	4 (2.3)	2 (2.4)	0
Cases with bleeding events	**165 (37.2)**	**129 (47.3)**	**36 (21.1)**	**19 (22.9)**	**6 (13.0)**
Intracerebral	125 (28.2)	103 (37.7)	22 (12.9)	10 (12.0)	6 (13.0)
Other	43 (9.7)	28 (10.3)	15 (8.8)	10 (12.0)	1 (2.2)
AZD1222 dose					
First	440 (99.1)	272 (99.6)	168 (98.2)	77 (92.8)	45 (97.8)
Second	4 (0.9)	1 (0.4)	3 (1.8)	6 (7.2)	1 (2.2)
Time to onset post-AZD1222, days, median	12.0	11.0	13.0	8.0	9.0
(IQR, range)§	(9.0–15.0, 2–45)	(9.0–14.0, 4–32)	(9.0–16.0, 2–45)	(2.0–34.3, 0–71)	(7.0–12.5, 4–25)
Laboratory values post-vaccination					
Platelet count at onset‖					
$<150 \times 10^9$/L	356 (80.2)	228 (83.5)	128 (74.9)	48 (57.8)	19 (41.3)
$>150 \times 10^9$/L or 'normal'	5 (1.1)	1 (0.4)	4 (2.3)	14 (16.9)	1 (2.2)
Unknown	83 (18.7)	44 (16.1)	39 (22.8)	21 (25.3)	26 (56.5)
Median platelet count (IQR), x 10^9/L	42.0 (19.0–73.5)	38.5 (18.0–67.0)	51.0 (27.5–91.0)	113.0 (43.5–139.5)	66.0 (23.0–135.0)
D-dimer level¶					
>4000 ng/mL	209 (47.1)	139 (50.9)	70 (40.9)	19 (22.9)	4 (8.7)
<4000 ng/mL	40 (9.0)	28 (10.3)	12 (7.0)	17 (20.5)	2 (4.3)
Unknown	195 (43.9)	106 (38.8)	89 (52.0)	47 (56.6)	40 (87.0)
Median (IQR), ng/mL	17 000 (5800–35 000)	20 000 (5370–35 666)	12 806.5 (6519.25–23 472.75)	5501.0 (979–13 000)	4400 (3448–12 200)
Presence of anti-PF-4 antibodies‖					
Yes	118 (26.6)	94 (34.4)	24 (14.0)	4 (4.8)	1 (2.2)
No	25 (5.6)	11 (4.0)	14 (8.2)	11 (13.3)	2 (4.3)
Unknown/pending	301 (67.8)	168 (61.5)	133 (77.8)	68 (81.9)	43 (93.5)
Coagulation abnormality					
Disseminated intravascular coagulation	26 (5.9)	17 (6.2)	9 (5.3)	5 (6.0)	1 (2.2)
Yes (not specified)	34 (7.7)	22 (8.1)	12 (7.0)	3 (3.6)	1 (2.2)
No	34 (7.7)	26 (9.5)	8 (4.7)	3 (3.6)	0
Missing	350 (78.8)	208 (76.2)	142 (83.0)	72 (86.7)	44 (95.7)
Fibrinogen level					
High	22 (5.0)	10 (3.7)	12 (7.0)	8 (9.6)	3 (6.5)
Normal	105 (23.6)	73 (26.7)	32 (18.7)	11 (13.3)	1 (2.2)
Low	75 (16.9)	60 (22.0)	15 (8.8)	3 (3.6)	2 (4.3)
Missing/unknown	242 (54.5)	130 (47.6)	112 (65.5)	61 (73.5)	40 (87.0)

Data are n (%) or n, except where indicated.
Abbreviations: CVST: cerebral venous sinus thrombosis; DVT: deep vein thrombosis; IQR: interquartile range; MI: myocardial infarction; PE: pulmonary embolism; PF: platelet factor; TTS: thrombosis with thrombocytopenia syndrome.

* Categories are defined as follows: Typical – case aligned with typical TTS; Possible – available data consistent with TTS, but insufficient for definitive alignment; No – data inconsistent with typical TTS; and Unknown – insufficient data to draw any conclusion. † Median ages of individuals with venous thromboses, arterial thromboses, and multiple-site thromboses were 49.5 (IQR: 38.0–59.75), 50.0 (42.0–59.0), and 49.5 years (41.25–59.75), respectively. Respective median ages of individuals with CVST, splanchnic vein thrombosis, PE, and DVT were 47.0 years (IQR: 32.0–56.0), 47.0 years (37.75–55.0), 53.0 years (46.0–64.0) and 56.0 years (48.0–65.0). Median age of individuals with stroke was 48.0 years [IQR: 35.0–60.0]. ‡ All known sites of both venous and arterial thromboses are listed and are therefore not mutually exclusive.

§ Median time to onset was 12.0 days (IQR: 9.0–15.0) for all cases involving venous thromboses and 10.0 days (8.0–14.0) for cases involving arterial thromboses. For cases involving CVST or splanchnic venous thrombosis, median time to onset was 11.0 (IQR: 8.0–14.0) and 12.0 days (9.5–15.0), respectively, compared to 13.0 days (10.0–18.0) for cases involving DVT/PE. Data were frequently missing in the cases categorised as 'unknown'. ‖ All reported cases were identified as having an adverse event within the 20 preferred terms under the high-level term of 'Thrombocytopenias' or within the standardised MedDRA query of 'Hematopoietic Thrombocytopenia-Narrow'. ¶ Units were frequently unspecified. ‖ Methodology of assessment was frequently unspecified.

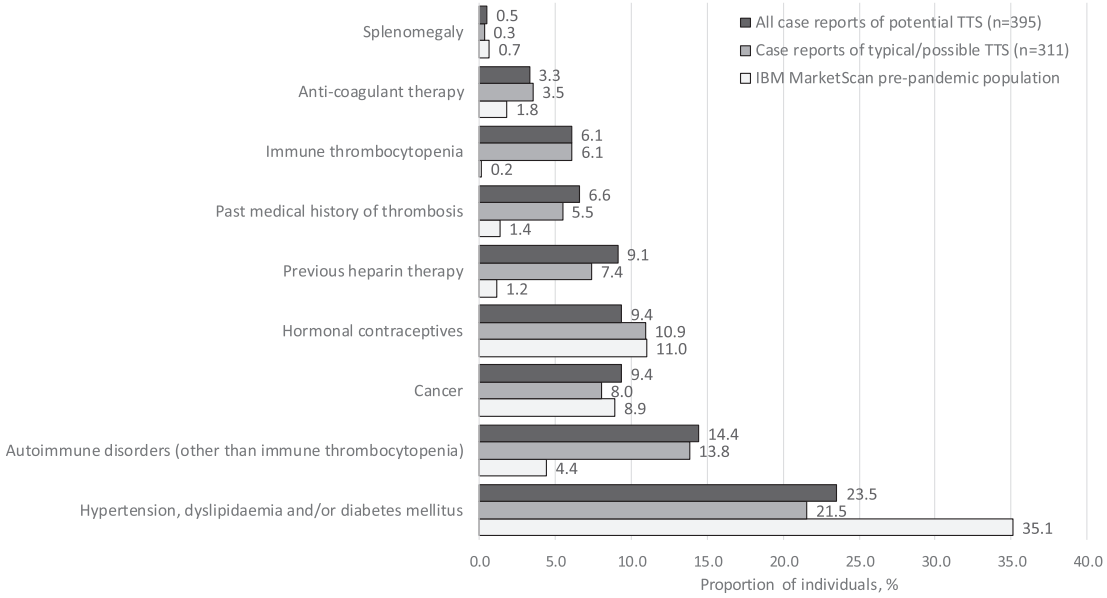

Fig. 1. Medical history and concomitant medications associated with reports of possible cases of TTS (N = 573) and case reports adjudicated as 'typical'/'possible' TTS (n = 444) in the Global Safety Database versus rates in a pre-pandemic reference population. The burgundy and grey bars show percentages based on 395 and 311 case reports, respectively, that contained relevant information for review of medical history and concomitant medications. The orange bars show findings from an analysis of the IBM MarketScan US healthcare insurance claims database using the population available on January 1, 2019; pharmacy or medical claims were identified during 24 or 12 months before index thrombosis claim, respectively. Abbreviations: TTS = thrombosis with thrombocytopenia syndrome.

was 40.0 years (IQR: 20.0–54.0) in the population derived from the IBM MarketScan databases and in the range 60–69 years for known vaccinees through April 2021 (Fig. S2B). Of 395 and 311 cases, 241 (61.0 %) and 196 (63.0 %) were female, compared to 51.6 % in the IBM MarketScan population. Notable rate differences between all 395 and the 311 'typical'/'possible' TTS cases from the AstraZeneca Global Safety Database and the pre-pandemic IBM MarketScan population included 14.4 %, 13.8 % and 4.4 % with autoimmune disorders (other than immune thrombocytopenia), 9.1 %, 7.4 % and 1.2 % with previous heparin therapy, 6.6 %, 5.5 % and 1.4 % with a past medical history of thrombosis, and 6.1 %, 6.1 % and 0.2 % with immune thrombocytopenia, respectively. Rates of splenomegaly, anticoagulant therapy, use of hormonal contraceptives, cancer, and hypertension, dyslipidaemia and/or diabetes mellitus appeared similar between groups or higher in the IBM MarketScan population.

The most common presenting symptom was headache, which was reported as an adverse event associated with AZD1222 in 202/573 (35.3 %) cases, including in 183/444 (41.2 %) 'typical'/'possible' TTS cases (Table 2). Of these cases, 126/202 (62.4 %) and 119/183 (65.0 %), respectively, included CVST (Table 2). In cases with CVST, headache was reported in 126/214 (58.9 %) of all cases and 119/196 (60.7 %) of 'typical'/'possible' cases (Table 2). The median time to onset of headache in 'typical'/'possible' TTS cases was 9.0 days (IQR: 6.0–11.0) and median time to onset of thrombosis with thrombocytopenia was 11.0 days (IQR: 9.0–14.3) (Table 2). A narrative review of case reports of potential TTS with adverse events of headache is included in the Supplementary Appendix (p5–6); it was not feasible to determine further qualitative characteristics of headache events due to lack of specific information in spontaneous reports.

3.6. Outcomes

Overall, 127/573 (22.2 %) cases were fatal (Table S7). Of the 444 cases of 'typical'/'possible' TTS, 105 (23.6 %) died, including 60/154 (39.0 %) in the February/March cohort, and 21/151 (13.9 %) and 24/139 (17.3 %) in the early and late April cohorts, respectively (Table S8). In the May–June cohort the fatality rate was 13.1 % overall and 15.7 % in 'typical'/'possible' cases (Table S4). In October–December cohort the fatality rate was 16.0 % overall and 17.5 % in 'typical'/'possible' cases (Table S5).

Specific sites of thrombosis and occurrence of concomitant bleeding, particularly intracranial bleeding, were associated with fatality (Fig. S4, Fig. S5). Among the 444 'typical'/'possible' TTS cases, 21.8 % with venous thromboses, 30.9 % with arterial thromboses, and 26.9 % with multiple-site thromboses were fatal. Among those with specific venous thromboses, the highest rates of fatal events were in those with splanchnic venous thrombosis and/or abdominal thrombosis (36.0 %), and CVST (30.1 %) (Fig. S5A). Overall, 165 (37.2 %) cases involved bleeding events (Table 1); of these, 69 (41.8 %) resulted in death, including 59/125 (47.2 %) of those with intracerebral bleeding. The fatality rate was 61.1 % and 50.0 % in cases with arterial thrombosis plus intracerebral bleeding or plus other bleeding events, respectively (Fig. S4B). Severity of thrombocytopenia in association with bleeding also affected the fatality rate. Among 94 cases reporting a platelet count $< 50 \times 10^9$/L at onset who had a bleeding event, 50 (53.2 %) were fatal, compared to 9 (12.7 %) fatal events within the remaining 71 cases who had a platelet count recorded and who had a bleeding event.

3.7. Summary of all cases of thrombosis and thrombocytopenia reported to the AstraZeneca Global Safety Database in 2021

A total of 2060 cases of concurrent thrombosis and thrombocytopenia were reported to the database in 2021, with 90 % reported as occurring after the first dose of AZD1222 (Fig. S6A). The number of case reports, according to month of case onset, peaked in April (n = 485) and generally decreased thereafter (Fig. S6A). The number of cases reported monthly by region/country generally mirrored trends in the number of doses administered within those regions/countries, particularly first doses. Brazil was a notable exception, with case report numbers remaining low throughout

Table 2
Frequency of reported headache, and time to onset of headache and thrombosis, in the case reports of thrombosis with thrombocytopenia, overall and in those adjudicated as 'typical'/'possible' TTS.

	All reported cases (n = 573)	Cases adjudicated as 'typical'/'possible' TTS (n = 444)
Case reports with symptom of headache	202 (35.3)	183 (41.2)
Median time to onset of headache post-vaccination, days (IQR)	8.0 (2.0–11.0)	9.0 (6.0–11.0)
Median time to onset of suspected TTS post-vaccination, days (IQR)	11.0 (9.0–14.0)	11.0 (9.0–14.25)
Case reports with symptom of headache and CVST	126/202 (62.4)	119/183 (65.0)
Median time to onset of headache post-vaccination, days (IQR)	8.0 (3.0–11.0)	9.0 (6.0–11.0)
Median time to onset of suspected TTS post-vaccination, days (IQR)	11.0 (9.0–14.0)	11.0 (9.0–14.0)
Case reports with CVST	214 (37.3)	196 (44.1)
Case reports with CVST with symptom of headache	126/214 (58.9)	119/196 (60.7)

Abbreviations: CVST: cerebral venous sinus thrombosis; IQR: interquartile range; TTS: thrombosis with thrombocytopenia syndrome.

2021 (Fig. S6A,B). Overall, fatality rates were generally highest at the start of the year and decreased over time, consistent with the cohorts reported in this analysis (Fig. S6C). The numbers of reported cases in November and December were very low and associated with a fluctuation in the fatality rate (Fig. S6C).

4. Discussion

Multiple large, well-designed clinical trials have been conducted to assess AZD1222 safety and efficacy for preventing COVID-19 [1–3]. However, these study populations are not sufficient for identifying very rare adverse events (defined as a rate of < 1 in 10,000) [23] such as TTS. At data cut-off for the primary dataset analysis (April 26), >58.3 million doses (52.7 million first doses, 5.6 million second doses) of AZD1222 had been administered in the UK, EU, Canada and Australia, providing a much larger, global population from which to investigate reports of rare safety signals.

Up to April 26, we identified 573 reported cases of thrombosis with thrombocytopenia in the AstraZeneca Global Safety Database, the largest international dataset of potential TTS cases to date. Previous pharmacovigilance-based analyses of thrombotic and/or thrombocytopenia events post-vaccination conducted with earlier data cut-offs using EudraVigilance [24] and VigiBase [25] evaluated event frequency but did not formally review cases for alignment to typical TTS. Our adjudication of, and findings from, this comprehensive real-world dataset are an important addition to the literature on TTS as they provide important context for interpreting potential TTS case reports from often incomplete spontaneous reporting and surveillance data. Our methodology and results are thereby complementary to recent regional and smaller clinical haematology case series', for which more complete datasets and follow-up were available [6–9,19,22]. These datasets, which had more definitive diagnosis, also helped inform adjudication of cases in our cohort.

Based on expert adjudication, 77.5 % of cases aligned with the characteristic pattern of TTS reported in other clinical series [6–9,21,22,26], a proportion consistent with that from a recent UK Expert Haematology Panel analysis utilising more detailed clinical data (74.8 %) [19]. Conversely, 22.5 % of cases in our primary dataset were adjudicated as not being TTS or as 'unknown'. This rate increased over time, implying increased attention to thrombotic events following vaccination. The proportion of reported cases with uncommon sites of thrombosis (CVST/splanchnic venous thrombosis) decreased over time, whereas the proportion with DVT/PE (for which background rates are substantially higher [10,27] and thus may not have initially been considered as potential TTS cases) increased. Moreover, reporting dynamics may have been influenced by the elevated risk of serious thrombotic events after SARS-CoV-2 infection [13,28]. Cases classified as 'unknown' could not be definitively adjudicated due to the limitations of post-marketing surveillance data. Nevertheless, there was a reduction in levels of missing data for key parameters such as platelet count, D-dimer level and fibrinogen, which may reflect more follow-up and/or increasing knowledge of their importance in more recent cases. Comprehensive and consistent collection and reporting of these parameters will be important in further characterising TTS.

Our reporting rate of 'typical'/'possible' TTS cases post-first-dose vaccination in this dataset, 7.5 per million vaccinated persons, is somewhat lower than other reported estimates of TTS frequency, including TTS estimates from a UK clinical case review analysis (10 per million vaccinated persons aged $\leq$ 50 years; 20 per million vaccinated persons aged > 50 years) and an EMA analysis (12.8 per million persons post first vaccine dose) [19,29], and the estimated rate of thromboembolic events with low platelets from a UK MHRA analysis (15.7 per million persons post first vaccine dose) [30]. This discrepancy may be due to differences in criteria for case identification, the population/cohort of vaccinees analysed, and/or reporting within surveillance systems. Consequently, the current data on reporting rates cannot be directly translated to an incidence of TTS following AZD1222. Additionally, all estimates of TTS frequency should be considered in the context of recent analyses suggesting that SARS-CoV-2 infection, which is now common in many populations [31], is associated with a substantially increased risk of such events [13,28].

Expert review and adjudication was required in our analysis because these post-marketing safety surveillance reports were frequently incomplete, and data required for definitive diagnosis using published definitions were missing [6–9,19–22,26]. Nonetheless, results from the score-based algorithm incorporating suggested criteria [21,22] (Fig. S3) were consistent with those from expert adjudication (99.0 % agreement for 'typical'/'possible' cases; Table S4). Importantly, this algorithmic approach is suitable for large-scale, pharmacovigilance-based analyses, in which key parameters are often missing and more stringent clinical classification approaches cannot be applied. This will be valuable for ongoing surveillance of vaccination in different populations [13,28].

Characteristics of 'typical'/'possible' TTS cases in our series were broadly consistent with other key datasets and case series [6,8,19,20,24]. Our cases frequently included otherwise uncommon sites of thrombosis, including CVST and splanchnic venous thrombosis, as well as unusual combinations of thromboses at multiple sites. Median time to onset in 'typical'/'possible' TTS cases was 12.0 days (IQR: 9.0–15.0), which is aligned with the typical time-window for onset reported elsewhere [6,8]. Overall, 61.9 % of our cases were reported in women, consistent with other early reports [6,8,13,24], but this proportion was lower in the April, May–June, and October–December cohorts (cases in females/males: 55.9 %/43.8 %, 49.7 %/47.5 %, and 45.4 %/45.4 %, respectively, excluding 'missing' data), consistent with Pavord *et al.* [19]. Furthermore, our data support findings suggesting that TTS risk may be lower in the elderly [6,8,19,24]; the median age of

'typical'/'possible' TTS cases was 50.0 years, whereas the median age of known vaccine recipients in the UK and Europe through the end of April was in the range 60–69 years (Fig. S2).

We had sufficient TTS cases and information to enable evaluation of medical history and concomitant medications in the context of rates in a pre-pandemic reference population. The individuals in our series were more likely to have had prior heparin therapy, prior anticoagulant therapy, prior medical history of thrombosis, immune thrombocytopenia, or other autoimmune disorders, compared with the general population, indicating potential risk factors for TTS post-vaccination. These findings provide initial areas of interest for further investigation of risk factors and mechanisms.

Our dataset included co-reported adverse events following AZD1222, enabling analysis for possible TTS 'alarm symptoms'. The most common co-reported adverse event was headache, which has been previously proposed as a specific presenting symptom and has been associated with CVST in TTS cases [9]. However, only 65.0 % of the 'typical/possible' TTS cases with headache as a symptom had CVST and only 60.7 % of the 'typical/possible' TTS cases with CVST had headache as a symptom, suggesting that headache may serve as a broader warning symptom for TTS, not just CVST, potentially associated with the inflammatory component of TTS pathophysiology.

One challenge to the use of headache as an alarm symptom for TTS is that headache is also commonly reported as a symptom of COVID-19 [32] and after COVID-19 vaccination [9,33]. Furthermore, more than half of our case reports did not co-report headache. Nevertheless, our analysis of the kinetics of headache and thrombosis onset is valuable in this context. Although most cases of headache reported following vaccination occur within 2–4 days and then resolve [9,33], median time to headache onset in our 444 'typical'/'possible' TTS cases was 8.0 days, with limited reports of resolution, similar to findings in TTS cases following Ad26.COV2.S [9]. Median time to onset of thrombosis diagnosis was 2–3 days later. As suggested previously [9], these findings indicate that late-onset headache post-vaccination without resolution should be a flag warranting further investigation in the context of TTS.

The overall fatality rate of 'typical'/'possible' TTS cases was 23.6 %, which is consistent with recent findings [19]. Fatality rate decreased from 39.0 % in February/March to 15.5 % in April, and was 13.1 % and 17.5 % in the May–June and October–December cohorts, potentially indicating improvement in TTS management and/or earlier diagnosis, followed by a stabilisation of fatality rate over time. This stabilisation was also largely reflected in the rate of fatalities reported among total thrombosis with thrombocytopenia cases reported to the database; very low total case reports in November and December likely contributed to the noted fluctuations in the fatality rate for the last months of 2021. The decrease in fatality rate coincides with the issuing of treatment guidelines from professional societies (Table S9, Fig. S6D), highlighting the importance of prompt diagnosis and intervention, as well as utilisation of intravenous immunoglobulin therapy and avoidance of heparin-based anticoagulants [15–18]. Indeed, an Australian study attributed its low TTS case fatality rate (3 % through June 17, 2021) to early diagnosis and treatment [34]. Fatality rates in our series were higher in cases with concomitant bleeding; low platelet count (<50 x10^9/L) appeared to increase the likelihood of bleeding and of that bleed being fatal.

Our data on the numbers of case reports with thrombosis and thrombocytopenia submitted to the AstraZeneca Global Safety Database over time generally coincided with very large populations receiving a first dose of AZD1222 in the countries in this analysis. Very few cases were reported following subsequent doses, including booster doses, in agreement with previous reports [11]. The low number of cases reported from Brazil in 2021 is consistent with previously reported geographic variations in TTS reports [10,35].

Our analysis – and post-marketing safety data in general – has limitations. Challenges include the potential for underreporting, selective reporting, and inflation of case numbers due to media-driven heightened public awareness, as well as possible reporting duplication. In contrast to systematically collected clinical trial data, these are passive surveillance data comprising reports from healthcare professionals and vaccinees; thus, data validation is often not feasible. Information is dependent on what is contained in the reports and thus often incomplete and ambiguous; e.g., severity of thrombocytopenia, anti-PF4 antibody level (PF4 has been implicated as a potential contributor to the mechanism behind TTS [36]), and D-dimer level were often missing, and units and methods of measurement were unclear. These limitations preclude estimation of TTS incidence and are important to consider in the context of future analyses. While follow-up of participants in clinical studies of AZD1222 is ongoing [3], these long-term safety data are not anticipated to provide further information on TTS incidence due to the expected time to onset of cases post-vaccination. Further characterisation of TTS would require ongoing safety surveillance of spontaneously reported cases as well as active surveillance studies in large populations receiving primary series vaccination with AZD1222.

In conclusion, during the COVID-19 pandemic, TTS events reported after AZD1222 vaccination are extremely rare and the overall protective benefits of AZD1222 against COVID-19 greatly outweigh the risks from vaccination [29]. Furthermore, widespread vaccination against COVID-19 reduces the substantially increased risk of SARS-CoV-2-infection-related events of thrombosis with thrombocytopenia [13]. Our understanding of the benefit:risk balance continues to evolve along with data on TTS cases and associated background event rates. Analysis of post-marketing safety surveillance datasets using a consistent algorithmic approach will be important in furthering our knowledge of TTS characteristics and risk factors.

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Availability of data and material

Informed consent was not obtained for this secondary use of existing information. The source data for these analyses are thus not available for sharing. The US population data for these analyses were made available to the authors by third-party license from IBM Watson, a commercial data provider in the United States, and AstraZeneca (who have a license for analysis of these data). The ICD-10 code listings used can be found in Table S10. Visit

https://marketscan.truvenhealth.com/marketscanportal/ for more information on accessing IBM Watson data.

Author's contributions

All authors contributed to manuscript drafts, approved the final draft, and made the decision to submit the manuscript for publication. Conceptualisation of the analyses was done by MAL, SR, LBF, JM, HGdS, PB, and MN; methodology for the analyses was developed by MAL, SR, MY, LBF, NKS, JM, NF, MA, PB, and MN. Data extraction, analysis, and validation was done by MAL, SR, MY, NKS, JM, NF, MA, SK, and MN; all authors had full access to the data from the AstraZeneca global safety database and the IBM MarketScan databases relating to these analyses and vouch for the integrity, accuracy, and completeness of the data and analyses. Supervision of the project and analyses was done by MY, JM, and MN. MAL, SR, PB, and MN wrote the original draft of the article; all authors critically reviewed and revised the manuscript and approved the final draft for submission.

Declaration of Competing Interest

MAL declares consultancy work for AstraZeneca in relation to AZD1222, including for the present analyses.

SR is a previous employee of AstraZeneca (2006–2010) and declares consultancy work for AstraZeneca in relation to the present analyses.

MY, LBF, NKS, JM, NF, MA, HGdS, PB and MN are employees of AstraZeneca and may hold stock and/or stock options.

MN participates on a Data Safety Monitoring Board or Advisory Board at the Karolinska Institute.

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Appendix A. Supplementary data

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