Venous thromboembolism after mechanical restraint in psychiatric hospitals: population based cohort and self-controlled case series study

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ABSTRACT

OBJECTIVE

To examine the short term risk of venous thromboembolism (VTE) after mechanical restraint among inpatients at psychiatric hospitals.

DESIGN

Population based cohort and self-controlled case series study.

SETTING

Psychiatric hospitals in Denmark, from 1 January 2000 to 30 September 2022.

PARTICIPANTS

24 423 inpatients (aged ≥18 years) exposed to mechanical or chemical restraint at psychiatric hospitals. The self-controlled case series included 1285 patients with incident VTE occurring during or shortly after a stay in a psychiatric hospital.

MAIN OUTCOME MEASURES

Cumulative incidence of VTE, weighted by propensity, and risk ratios or differences (including number needed to harm) in the cohort study. Incidence rate ratios in predefined risk periods after restraint were used in the self-controlled case series.

RESULTS

At 30 days after restraint, the cumulative incidence of VTE was 3.5 per 1000 patients (95% confidence interval (CI) 2.5 to 4.7) in the mechanical restraint group and 1.7 per 1000 patients (1.0 to 2.6) in the chemical restraint group, corresponding to a risk ratio of 2.07 (1.25 to 3.71), a risk difference of 1.8 per 1000 patients (0.5 to 3.2), and a number needed to harm of 548 (311 to 1912). In the self-controlled case series, the incidence rate ratio was 4.49 (3.09 to 6.54) in the 14 days after mechanical restraint compared with baseline periods.

CONCLUSIONS

Mechanical restraint was associated with an elevated risk of VTE. Although the absolute risk was low, these findings highlight the importance of preventive strategies to reduce the risk of VTE in patients exposed to mechanical restraint.

Introduction

People with mental illness have an elevated risk of venous thromboembolism (VTE),[1] partly owing to the presence of multiple VTE risk factors (including somatic comorbidities) and lifestyle factors such as smoking and physical inactivity.[2 3] In addition, antipsychotic medication has consistently been associated with increased incidence of VTE.[4 5] The mechanisms underlying this association are probably multifactorial, involving metabolic changes induced by drugs, sedation, and reduced mobility.[4]

Reduced mobility is a well established risk factor for VTE, particularly in hospital inpatients.[6] In psychiatric settings, mobility may be further restricted through coercive intervention (use of non-consensual measures such as mechanical restraint, isolation, and involuntary commitment). Mechanical restraint uses devices (eg, waist belts, wrist straps, ankle straps, or gloves) to physically restrict patient movement and is one of several coercive measures that may be used in psychiatric inpatient settings to prevent patients from harming themselves or others.[7] Although controversial, mechanical restraint remains in use in most countries for which data are available. A recent review,[8] including data from 22 countries (with data from after 2010 from 11 countries), found that the proportion of inpatients at psychiatric hospitals exposed to mechanical restraint ranged from less than 1% to 51%, depending on the country and service context.[8] In Europe, the reported prevalence varies from less than 1% to 26% across countries, and substantial variation within countries has also been reported, suggesting that local hospital practices play a major role.[7-9] Despite the known physical health risks in people with severe mental illness,[3] the potential adverse physical health outcomes of mechanical restraint remain largely unexplored.[10]

VTE and sudden death after mechanical restraint have been suggested in case reports.[10] However, few studies have investigated the link between mechanical restraint and VTE.[10-16] The existing studies are heterogeneous, small, have generated conflicting results,[15 16] have lacked appropriate control groups,[11-13 15 16] and did not provide precise timing of mechanical restraint in relation to VTE outcomes.[11 15] These limitations raise concerns about the causal interpretation of previously reported associations. Further knowledge regarding the potential adverse consequences of mechanical restraint is essential for guiding timely and appropriate care. In this study, we sought to assess the risk of VTE in patients exposed to mechanical restraint in Danish psychiatric hospitals using two complementary approaches: an active comparator (chemical restraint) cohort study with propensity score weighting and a self-controlled case series design.

Methods

Setting

Our study is based on registry data from Denmark. The Danish healthcare system is publicly funded through taxation and ensures universal access to

healthcare services for all residents. This care includes access to hospitals, general practitioners, and specialist practitioners, as well as partial reimbursement for prescription medications.[17] Each resident is assigned a unique identification number at birth or immigration, which enables unambiguous linkage at the individual level across national health registries and administrative registries.[18]

In Denmark, the use of mechanical restraint has been the focus of sustained national initiatives aimed at reducing coercion in psychiatric care over the past decade. After the introduction of national targets and monitoring systems in the mid-2010s, the overall use of mechanical restraint in psychiatric hospitals declined, although the reductions were uneven across regions and were often accompanied by substitution with other coercive measures, such as chemical restraint.[19] Despite policy attention and legislative revisions, mechanical restraint remains in use.

Data sources

We obtained individual data from several nationwide Danish registries, and retrieved exposure information from the Danish National Register of Coercive Measures in Psychiatric Units. This register contains nationwide records of all legally defined coercive measures applied in psychiatric inpatient wards, with complete coverage from 2000 onward.[20] Reporting of coercive measures is mandated by law and must occur within 10 days after initiation. The Danish National Register of Coercive Measures in Psychiatric Units records coercive events according to their legal classification under the Danish Mental Health Act,[21] including mechanical restraint and acute sedation with coercion (chemical restraint), which is recorded separately from both voluntary drug treatment and other forms of coercive drug treatment (aimed at treating the underlying psychiatric illness over time rather than managing acute agitation). For each episode of coercive intervention, the registry captures the type of measure used and its timing; for mechanical restraint, duration is also recorded, whereas for chemical restraint, no information on medication type, dose, or duration of sedative effect is available.[22]

Hospital contacts providing information on VTE outcomes, previous somatic comorbidities, and diagnoses of psychiatric disorders were obtained from the Danish National Patient Registry,[23] which has recorded all inpatient hospital contacts since 1977 in all hospitals in Denmark, as well as outpatient, emergency department, and psychiatric contacts since 1995.

We obtained data on personal characteristics, including sex, date of birth, death, and migration status, from the Danish Civil Registration System,[18] which includes all residents of Denmark. Causes of death were identified through the Danish Register of Causes of Death,[24] with data available up to and including 2020. We obtained information on dispensed prescription medications from the Danish National Prescription Registry,[25] which contains data on all prescriptions filled at Danish pharmacies since 1995. We derived socioeconomic variables, including educational attainment, income, and marital status, from registries maintained by Statistics Denmark. Finally, as a proxy for externalising and high risk behaviour, criminal convictions were identified from the Danish National Crime Register.[26]

Study designs

Firstly, we conducted a cohort study comparing two types of restraint: mechanical and chemical. Secondly, we conducted a self-controlled case series analysis including patients who experienced a VTE and were exposed to mechanical restraint at some point during an inpatient stay at a psychiatric hospital.

Cohort study

Study population

The study population included all Danish residents aged 18 years or older who were admitted to a psychiatric hospital between 1 January 2000 and 30 September 2022 and exposed to mechanical restraint or chemical restraint. We included the first psychiatric admission during the study period in which the first exposure during the admission was either mechanical restraint or chemical restraint. We excluded admissions in which both mechanical restraint and chemical restraint were applied on the same day as the first exposure, to ensure mutually exclusive exposure groups (supplementary fig S1).

Exposures

We defined the exposure as mechanical restraint occurring while an individual was admitted to a Danish psychiatric hospital. Mechanical restraint comprised physical fixation by waist belts, either alone or in combination with wrist straps, ankle straps, or gloves. Under the Danish Mental Health Act,[21] mechanical restraint may be used only temporarily and to the extent necessary to prevent an imminent risk of physical harm to the patient or others, serious harassment of other patients, or substantial damage to property. Prolonged mechanical restraint beyond a few hours is permitted only when required to protect the life, physical integrity, or safety of the patient or others.

Chemical restraint was selected as an active comparator because it is likely to be the closest alternative to mechanical restraint in terms of clinical indication. Specifically, according to the Danish Mental Health Act,[21] chemical restraint may be used when a doctor determines that sedative drugs given by force is important for improving the condition of a very agitated patient and cannot be achieved without the use of force.[21] The choice of sedative depends on the clinical presentation. Benzodiazepines are often preferred in cases of agitation related to intoxication, whereas antipsychotics are favoured in agitation related to psychosis. In cases of multiple mechanical restraint or chemical restraint episodes within the same hospital admission, the type of restraint and the index date were defined by the first occurrence.

Outcomes

The primary outcome of interest was VTE, including both incident and recurrent events. Diagnoses of VTE were identified from somatic hospital departments and included both inpatient and outpatient contacts, according to both primary and secondary diagnostic codes (supplementary table S1). A validation study reported positive predictive values of 88% for VTE coding, 86% for deep vein thrombosis, and 90% for pulmonary embolism, on the basis of Danish hospital registry data.[27] If no hospital contacts with a VTE diagnosis were registered before death, any deaths with pulmonary embolism as the underlying cause were included as a primary outcome. We included two secondary outcomes in the cohort study: all cause mortality and incident VTE (including deaths with pulmonary embolism as the underlying cause). To ensure inclusion of incident cases only, we used data from 1977 onward to identify the first recorded VTE event. Patients with a VTE event before restraint were excluded from the cohort in the analysis of incident VTE (supplementary fig S1).

Covariates

Informed by a directed acyclic graph (supplementary fig S2) based on available literature and data, we included a wide range of potentially confounding variables. These variables included age,

calendar period, sex, country of birth, marital status, educational level, income, main diagnosis leading to admission, coercive antipsychotic treatment during admission (data available since 2004), coercive treatment of a somatic disease, time from admission to mechanical restraint or chemical restraint, preadmission (ie, outside hospital setting) use of an antipsychotic drug, other preadmission medication use, history of somatic disease, recent fracture or physical trauma, earlier psychiatric hospital contacts, and previous criminal convictions. All variables were based on data from the period leading up to admission or restraint. A detailed description of the variables and corresponding windows of assessment is provided in the supplementary file (supplementary tables S1-S3).

Statistical analysis

The primary objective of this study was to assess VTE risk among patients exposed to mechanical restraint. Accordingly, the target estimand was the average treatment effect (of mechanical restraint) among patients exposed to mechanical restraint, to determine the risk of VTE in a population whose distribution of measured risk factors is similar to that of patients exposed to mechanical restraint.

To estimate the average treatment effect among patients exposed to mechanical restraint, we used propensity score weighting. Propensity scores were derived from a logistic regression model estimating the probability of receiving mechanical restraint, conditional on baseline covariates (as previously described). We applied standardised mortality ratio weights[28]: patients in the mechanical restraint group were assigned a weight of 1, whereas those in the chemical restraint group were assigned weights based on the odds of receiving mechanical restraint (calculated as the propensity score divided by one minus the propensity score). We assessed covariate balance between groups with absolute standardised mean differences, with values <0.1 indicating acceptable balance (supplementary table S4, supplementary figs S3-S4).

To estimate the cumulative incidence (risk) of VTE, we used a weighted Aalen-Johansen estimator, treating death as a competing risk.[29] Follow-up began on the date of restraint and ended at the occurrence of VTE, death, or 90 days after restraint, whichever came first. The follow-up period was extended until 31 December 2022 to allow complete follow-up. We plotted the cumulative incidence of VTE for both the mechanical restraint and chemical restraint groups, and estimated risk ratios and risk differences at 15, 30, and 90 days after restraint. The primary time point was 30 days after restraint. We included the 15 day time point to capture any earlier emergence of differences in VTE risk, and included the 90 day time point because it is a commonly used definition of hospital associated VTE.[30] We also calculated the number needed to harm as 1 divided by the risk difference.[31] To evaluate the risk ratio over time, we contrasted the cumulative incidence curves to derive a time varying risk ratio curve. The 95% confidence intervals (CIs) were estimated with 500 nonparametric bootstrap samples.

We conducted five sensitivity analyses. Firstly, to deal with non-adherence (eg, patients who initially received chemical restraint who were later exposed to mechanical restraint within the same admission, or vice versa), we repeated the primary analysis with censoring at the time of such switches. Secondly, to assess the risk of VTE in patients with similar probability of receiving either mechanical restraint or chemical restraint, on the basis of the included variables, we redefined the target estimand as the average treatment effect in the overlap population.[28] Overlap weights were calculated as 1 minus the propensity score for the mechanical restraint group and as the propensity score for the chemical restraint group. Thirdly, to assess the potential effects of unmeasured confounding effects by smoking and obesity, we conducted a probabilistic quantitative bias analysis[32] (supplementary file). Next, to examine the association between mechanical restraint duration and VTE, we estimated the change in VTE rate per additional hour of restraint by using a landmark approach (supplementary file). Finally, to assess the potential effect of differences in legal indications between mechanical restraint and chemical restraint, we repeated the main analysis by using a comparator of physical restraint, which has the same legal indications as mechanical restraint (supplementary file).

Self-controlled case series study

To further investigate the incidence of VTE after mechanical restraint, we used a self-controlled case series design.[33] This method is an epidemiological study design in which individuals act as their own control (ie, comparisons are made within individuals). Hence, only individuals who have experienced an event are included and all time invariant confounding is eliminated. The self-controlled case series design investigates when a person has an elevated risk, rather than who has an elevated risk.[34] This design is well suited for studying transient exposures and outcomes with a well defined onset.

The observation period began on 1 January 2000, the date of immigration, or the patient's 18th birthday, whichever occurred last, and ended on 30 September 2022, emigration, or death, whichever came first. During the observation period, we included patients who experienced an incident VTE either during an inpatient stay at a psychiatric hospital (from admission to 90 days after discharge) or within a risk period after mechanical restraint (supplementary fig S5). In contrast to the cohort analysis, only the first incident VTE was considered, because recurrent events within individuals might not be independent,[34] whereas all mechanical restraint episodes within the observation period were included, both before and after the VTE event. We defined risk periods as the 90 days after each mechanical restraint and subdivided into 0-14 days, 15-29 days, and 30-90 days after mechanical restraint (fig 1). A pre-exposure period of 15 days preceding each mechanical restraint was included to account for potential changes in baseline risk. For overlapping risk periods, we gave precedence to the period associated with the most recent mechanical restraint event (fig 1).

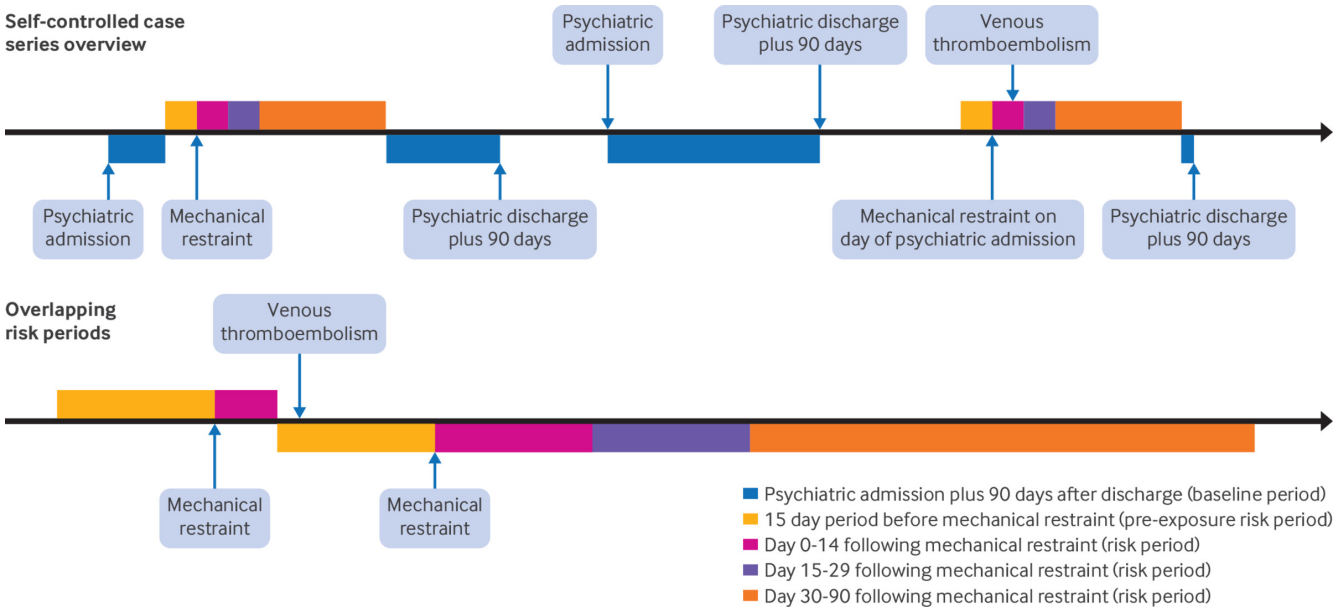

Fig 1 | Overview of the self-controlled case series study. Self-controlled case series overview includes psychiatric admissions and episodes of mechanical restraint during the observation period (1 January 2000 to 30 September 2022) in patients experiencing a venous thromboembolism. Baseline periods start on the day of psychiatric admission and end 90 days after discharge. Pre-exposure risk periods are defined as the 15 days preceding a mechanical restraint episode. Risk periods following mechanical restraint comprise the 90 days after restraint and are subdivided into day 0-14, day 15-29, and day 30-90. Overlapping risk periods after multiple restraint episodes are resolved by prioritising the pre-exposure period and the risk period associated with the most recent restraint. The example shows a venous thromboembolism occurring immediately after one restraint episode allocated to the pre-exposure period of the subsequent episode

We estimated incidence rate ratios and 95% CIs comparing VTE incidence during each risk period versus the baseline period with conditional Poisson regression, with the natural logarithm of the interval length included as an offset. Models were adjusted for age with discrete time intervals based on age percentiles at the time of VTE.

We conducted subgroup analyses stratified by age (<60 years, ≥60 years), sex (male, female), and calendar period (<2011, ≥2011). These cut-off thresholds were selected according to Danish guidelines introduced in 2011 recommending thromboprophylaxis for patients who have been mechanically restrained for at least 24 hours, if at least one of the following criteria is met (earlier VTE, known thrombophilia, or active cancer) or at least two of the following criteria are met (age >60 years, body mass index >30, diagnosis of chronic obstructive pulmonary disease, diagnosis of heart failure, diagnosis of acute or chronic inflammation, and treatment with sex hormones or antipsychotic medication).[35]

We performed three sensitivity analyses. Firstly, to consider potential misclassification of VTE events that occurred shortly after mechanical restraint but were assigned to the pre-exposure interval of a subsequent mechanical restraint episode, because of prioritising the most recent risk period (figure 1), we excluded the pre-exposure period. Secondly, to evaluate the assumption of an event independent observation period (ie, that the occurrence of the outcome did not influence subsequent observation time), we excluded patients who died within 90 days after a VTE event. Thirdly, to assess the incidence of VTE after the first observed mechanical restraint episode, we included only risk periods related to that episode.

All data management and statistical analyses were performed in R statistical software version 4.5.1.

Patient and public involvement

Patients and members of the public were not involved in the development of the research question, study design, data interpretation, or reporting, primarily because the study relied exclusively on pseudonymised registry data, which did not allow identification or contact with individual patients.

Results

Cohort study

In total, 24 423 patients exposed to either mechanical restraint or chemical restraint were included in our study (supplementary fig S1), 10 208 of whom were exposed to mechanical restraint. In the mechanical restraint group, the median age at the time of restraint was 40.5 years (interquartile range (IQR) 27.8-53.7 years), and 6950 patients (68.1%) were men (table 1). Compared with the chemical restraint group, the mechanical restraint group differed most notably in diagnosis leading to hospital admission (2952 patients (28.9%) with schizophrenia and related disorders were exposed to mechanical restraint, 6674 (47.0%) to chemical restraint), sex (6950 (68.1%) of those exposed to mechanical restraint were men, and 6686 (47.0%) men were exposed to chemical restraint), and time from admission to restraint (4928 (48.3%) were mechanically restrained on the day of admission, and 4152 (29.2%) were chemically restrained on the day of admission) (table 1). The median duration of mechanical restraint was 13.4 hours (IQR 5.3-29.2 hours). Earlier exposure to the alternative restraint type within six months was uncommon (4.7% in the mechanical restraint group and 2.5% in the chemical restraint group). After propensity score weighting, covariate balance was achieved across all included variables (absolute standardised mean differences <0.1) (table 1, supplementary fig S3).

Table 1 | Baseline characteristics of the cohort study population before and after propensity score weighting. Data are number (%) unless otherwise stated

Characteristic	Before weighting			After weighting*		
	Chemical restraint group (n=14 215)	Mechanical restraint group (n=10 208)	SMD	Chemical restraint group (n=10 230)	Mechanical restraint group (n=10 208)	SMD
Age						
Median (IQR) age (years)	46.7 (31.3-62.9)	40.5 (27.8-53.7)	0.29	40.4 (27.6-54.2)	40.5 (27.8-53.7)	0.01
Sex						
Men	6686 (47.0)	6950 (68.1)	0.44	6959 (68.0)	6950 (68.1)	<0.01
Calendar period						
Median (IQR) calendar period	2012 (2005-18)	2009 (2005-14)	0.28	2009 (2005-14)	2009 (2005-14)	0.02
Socioeconomic status						
Born in Denmark	11 632 (81.8)	8676 (85.0)	0.09	8689 (84.9)	8676 (85.0)	<0.01
Marital status:			0.18			0.03
Divorced	3708 (26.1)	1939 (19.0)		1839 (18.0)	1939 (19.0)	
Married	2857 (20.1)	1994 (19.5)		2099 (20.5)	1994 (19.5)	
Not married	7650 (53.8)	6275 (61.5)		6291 (61.5)	6275 (61.5)	
Educational level:			0.21			0.02
Low	6663 (46.9)	5633 (55.2)		5678 (55.5)	5633 (55.2)	
Medium	4617 (32.5)	3094 (30.3)		3098 (30.3)	3094 (30.3)	
High	2031 (14.3)	878 (8.6)		894 (8.7)	878 (8.6)	
Unknown	904 (6.4)	603 (5.9)		560 (5.5)	603 (5.9)	
Income:			0.11			0.01
First quartile	3434 (24.2)	2749 (26.9)		2730 (26.7)	2749 (26.9)	
Second quartile	3481 (24.5)	2599 (25.5)		2644 (25.8)	2599 (25.5)	
Third quartile	3498 (24.6)	2582 (25.3)		2613 (25.5)	2582 (25.3)	
Fourth quartile	3802 (26.7)	2278 (22.3)		2242 (21.9)	2278 (22.3)	
Psychiatric admission						
Main admission diagnosis:			0.56			0.07
Organic disorders	2051 (14.4)	1696 (16.6)		1829 (17.9)	1696 (16.6)	
Substance use disorders	1110 (7.8)	2030 (19.9)		1930 (18.9)	2030 (19.9)	
Schizophrenia and related disorders	6674 (47.0)	2952 (28.9)		2919 (28.5)	2952 (28.9)	
Mood disorders	2631 (18.5)	1263 (12.4)		1325 (13.0)	1263 (12.4)	
Neurotic disorders	458 (3.2)	607 (5.9)		557 (5.4)	607 (5.9)	
Eating disorders	65 (0.5)	61 (0.6)		66 (0.6)	61 (0.6)	
Personality disorders	317 (2.2)	607 (5.9)		690 (6.7)	607 (5.9)	
Intellectual disabilities	110 (0.8)	108 (1.1)		100 (1.0)	108 (1.1)	
Developmental disorders	113 (0.8)	101 (1.0)		95 (0.9)	101 (1.0)	
Behavioural disorders	144 (1.0)	148 (1.4)		148 (1.4)	148 (1.4)	
Intentional self-harm	16 (0.1)	104 (1.0)		75 (0.7)	104 (1.0)	
Non-disease health factors	423 (3.0)	480 (4.7)		444 (4.3)	480 (4.7)	
Other	103 (0.7)	51 (0.5)		53 (0.5)	51 (0.5)	
Coercive treatment:						
Antipsychotic	170 (1.2)	45 (0.4)	0.08	50 (0.5)	45 (0.4)	0.01
Somatic disease	70 (0.5)	74 (0.7)	0.03	101 (1.0)	74 (0.7)	0.03
Time from admission to restraint:			0.42			0.05
Same day	4152 (29.2)	4928 (48.3)		4739 (46.3)	4928 (48.3)	
1-6 days	6313 (44.4)	2935 (28.8)		2962 (29.0)	2935 (28.8)	
≥7 days	3750 (26.4)	2345 (23.0)		2529 (24.7)	2345 (23.0)	
Preadmission psychotropic drugs						

Clozapine	380 (2.7)	327 (3.2)	0.03	313 (3.1)	327 (3.2)	0.01
Typical antipsychotics	2827 (19.9)	2684 (26.3)	0.15	2881 (28.2)	2684 (26.3)	0.04
Atypical antipsychotics	5309 (37.3)	3697 (36.2)	0.02	3806 (37.2)	3697 (36.2)	0.02
Antidepressants	4668 (32.8)	4047 (39.6)	0.14	4191 (41.0)	4047 (39.6)	0.03
Lithium	730 (5.1)	528 (5.2)	<0.01	581 (5.7)	528 (5.2)	0.02
Benzodiazepines	3343 (23.5)	2913 (28.5)	0.11	2970 (29.0)	2913 (28.5)	0.01
Somatic comorbidities						
Cardiovascular disease	1212 (8.5)	954 (9.3)	0.03	941 (9.2)	954 (9.3)	0.01
Cancer	473 (3.3)	275 (2.7)	0.04	319 (3.1)	275 (2.7)	0.03
COPD	626 (4.4)	571 (5.6)	0.05	608 (5.9)	571 (5.6)	0.02
Diabetes	600 (4.2)	478 (4.7)	0.02	498 (4.9)	478 (4.7)	0.01
Kidney disease	150 (1.1)	161 (1.6)	0.05	163 (1.6)	161 (1.6)	<0.01
Liver disease	320 (2.3)	499 (4.9)	0.14	556 (5.4)	499 (4.9)	0.02
Obesity	330 (2.3)	242 (2.4)	<0.01	266 (2.6)	242 (2.4)	0.01
Alcoholism	317 (2.2)	673 (6.6)	0.21	634 (6.2)	673 (6.6)	0.02
Fracture or physical trauma	682 (4.8)	844 (8.3)	0.14	828 (8.1)	844 (8.3)	0.01
Venous thromboembolism	399 (2.8)	254 (2.5)	0.02	244 (2.4)	254 (2.5)	0.01
Psychiatric comorbidities						
Organic disorders	1308 (9.2)	987 (9.7)	0.02	1060 (10.4)	987 (9.7)	0.02
Substance use disorders	2958 (20.8)	3576 (35.0)	0.32	3599 (35.2)	3576 (35.0)	<0.01
Schizophrenia and related disorders	5814 (40.9)	3321 (32.5)	0.17	3405 (33.3)	3321 (32.5)	0.02
Mood disorders	3155 (22.2)	2247 (22.0)	<0.01	2307 (22.5)	2247 (22.0)	0.01
Neurotic disorders	2806 (19.7)	2679 (26.2)	0.16	2702 (26.4)	2679 (26.2)	<0.01
Eating disorders	299 (2.1)	310 (3.0)	0.06	372 (3.6)	310 (3.0)	0.03
Personality disorders	1368 (9.6)	1753 (17.2)	0.22	1841 (18.0)	1753 (17.2)	0.02
Intellectual disabilities	396 (2.8)	408 (4.0)	0.07	438 (4.3)	408 (4.0)	0.01
Developmental disorders	345 (2.4)	304 (3.0)	0.03	308 (3.0)	304 (3.0)	<0.01
Behavioural disorders	1649 (11.6)	1560 (15.3)	0.11	1521 (14.9)	1560 (15.3)	0.01
Intentional self-harm	381 (2.7)	642 (6.3)	0.18	634 (6.2)	642 (6.3)	<0.01
Non-disease health factors	4097 (28.8)	3143 (30.8)	0.04	3158 (30.9)	3143 (30.8)	<0.01
Other	1850 (13.0)	1417 (13.9)	0.03	1485 (14.5)	1417 (13.9)	0.02
Other preadmission drugs						
Anticoagulants	376 (2.6)	259 (2.5)	0.01	274 (2.7)	259 (2.5)	0.01
Antihypertensives	2724 (19.2)	1761 (17.3)	0.05	1880 (18.4)	1761 (17.3)	0.03
Aspirin	1219 (8.6)	850 (8.3)	0.01	858 (8.4)	850 (8.3)	<0.01
Glucocorticoids	449 (3.2)	352 (3.4)	0.02	401 (3.9)	352 (3.4)	0.02
Loop diuretics	912 (6.4)	589 (5.8)	0.03	636 (6.2)	589 (5.8)	0.02
Statins	1281 (9.0)	818 (8.0)	0.04	857 (8.4)	818 (8.0)	0.01
Metformin	504 (3.5)	309 (3.0)	0.03	326 (3.2)	309 (3.0)	0.01
Opioids	1820 (12.8)	1789 (17.5)	0.13	1862 (18.2)	1789 (17.5)	0.02
Criminal offences						
Sexual	101 (0.7)	122 (1.2)	0.05	112 (1.1)	122 (1.2)	0.01
Violence	1001 (7.0)	1493 (14.6)	0.25	1493 (14.6)	1493 (14.6)	<0.01
Property	1643 (11.6)	2220 (21.7)	0.28	2241 (21.9)	2220 (21.7)	<0.01
Driving under influence	296 (2.1)	602 (5.9)	0.20	556 (5.4)	602 (5.9)	0.02
Drug related	893 (6.3)	1158 (11.3)	0.18	1153 (11.3)	1158 (11.3)	<0.01
Other	1796 (12.6)	2063 (20.2)	0.21	1992 (19.5)	2063 (20.2)	0.02

SMD=absolute standardised mean difference; IQR=interquartile range; COPD=chronic obstructive pulmonary disease.

* Weighted using standardised mortality ratio weights (weighted numbers are rounded to nearest integer).

At 30 days after restraint, the cumulative incidence of VTE was 3.5 (95% CI 2.5 to 4.7) per 1000 patients in the mechanical restraint group and 1.7 (1.0 to 2.6) per 1000 patients in the chemical restraint group (table 2, fig 2). The corresponding risk ratio was 2.07 (95% CI 1.25 to 3.71), and the risk difference was 1.8 (0.5 to 3.2) per 1000 patients, corresponding to a number needed to harm of 548 (311 to 1912). The risk ratio peaked shortly after restraint and remained stable from day 8 onward (fig 3).

Table 2 | Weighted cumulative incidence of venous thromboembolism on day 15, 30, and 90 after restraint and corresponding risk ratios and risk differences comparing mechanical restraint to chemical restraint

Timepoint	No of events (No at risk)*	Cumulative incidence per 1000 (95% CI)	Risk ratio (95% CI)	Risk difference per 1000 (95% CI)
Day 15				
Chemical restraint exposure group	13 (10 095)	1.2 (0.6 to 2.0)	1	0
Mechanical restraint exposure group	28 (10 046)	2.7 (1.8 to 3.8)	2.20 (1.17 to 4.58)	1.5 (0.3 to 2.7)
Day 30				
Chemical restraint exposure group	17 (10 030)	1.7 (1.0 to 2.6)	1	0
Mechanical restraint exposure group	36 (9961)	3.5 (2.5 to 4.7)	2.07 (1.25 to 3.71)	1.8 (0.5 to 3.2)
Day 90				
Chemical restraint exposure group	30 (9806)	2.9 (1.9 to 4.3)	1	0
Mechanical restraint exposure group	52 (9767)	5.1 (3.9 to 6.5)	1.75 (1.15 to 2.90)	2.2 (0.6 to 4.1)

CI=confidence interval.

* Weighted numbers are rounded to the nearest integer.

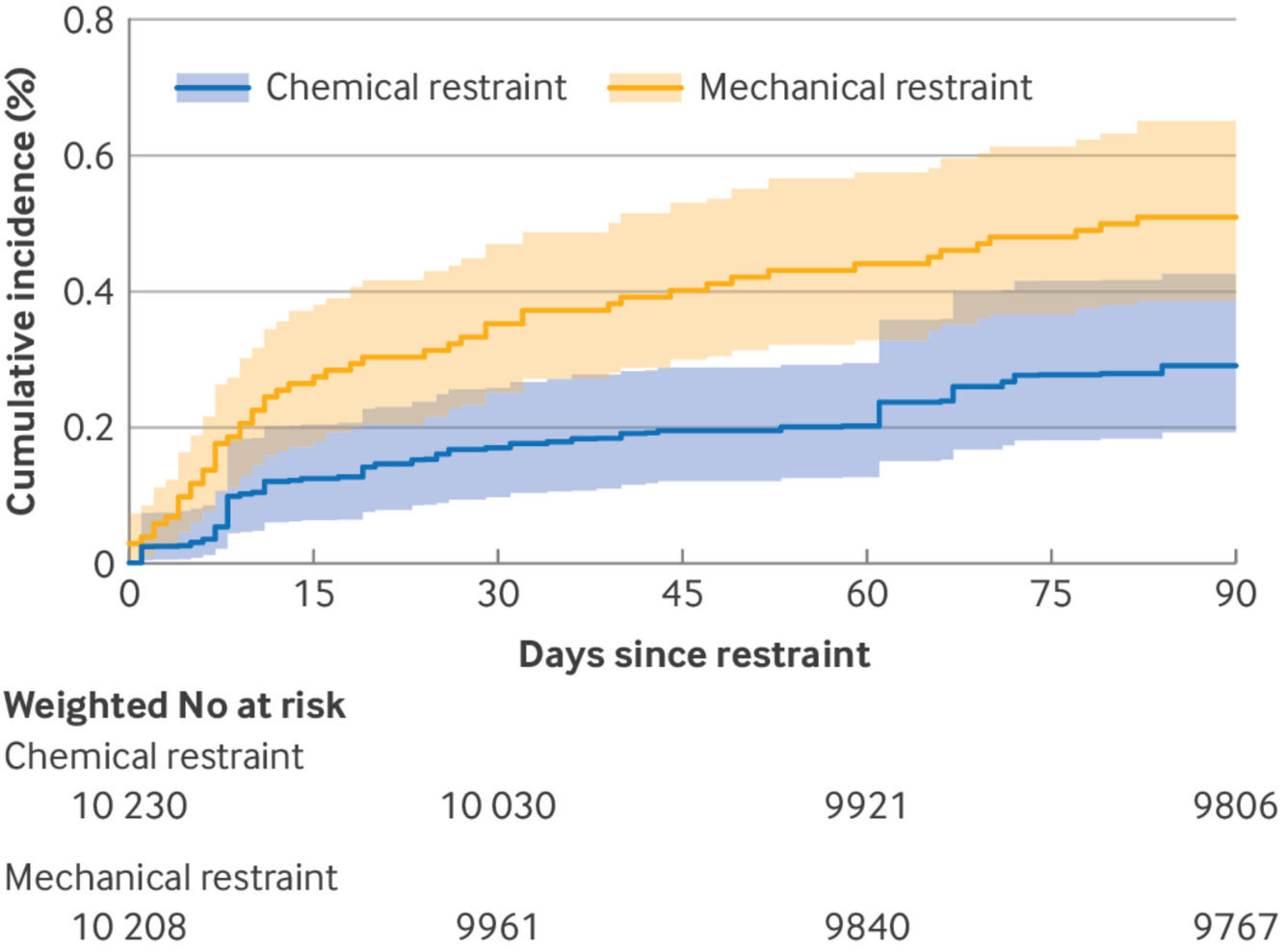

Fig 2 | Weighted cumulative incidence of venous thromboembolism in patients exposed to mechanical or chemical restraint by time since restraint. Shaded areas correspond to 95% confidence intervals

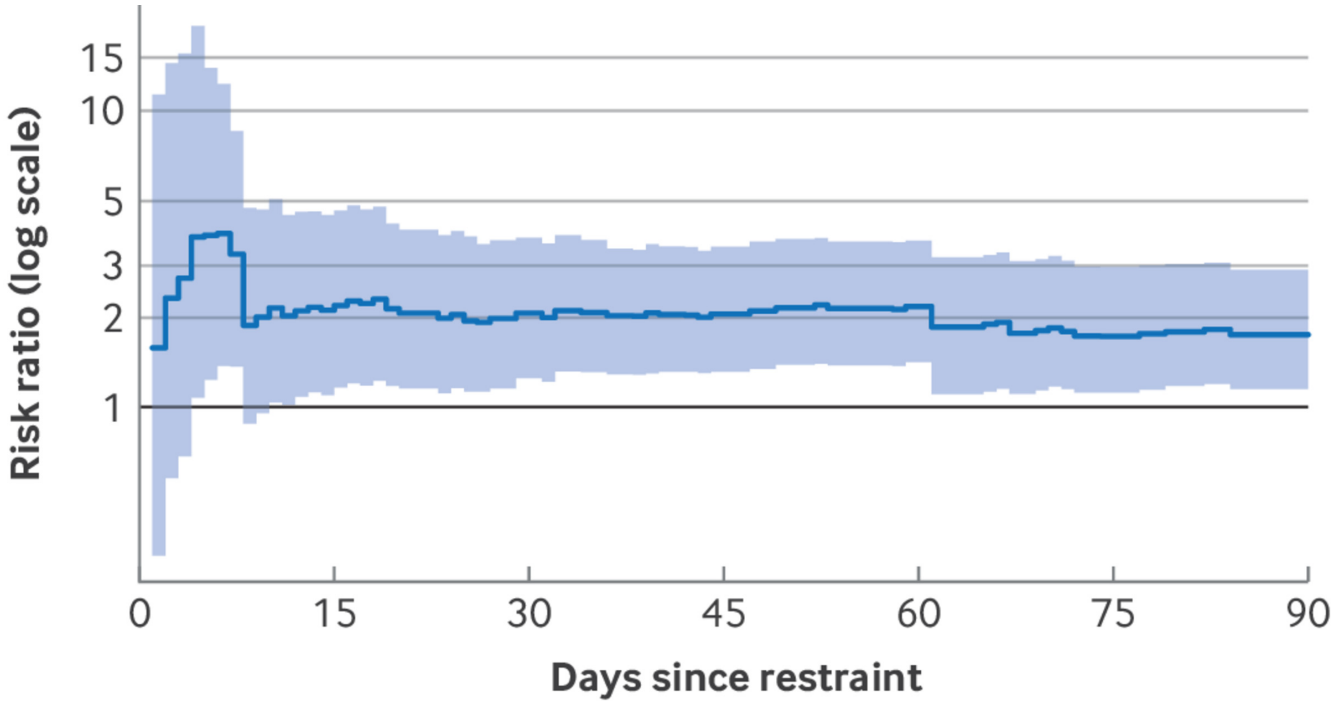

Fig 3 | Weighted risk ratio of venous thromboembolism among patients exposed to mechanical restraint compared to those exposed to chemical restraint by time since restraint. Black horizontal line represents no difference between groups, shaded area corresponds to 95% confidence interval

Within the first 30 days after restraint, 13.0% of patients in the chemical restraint group had been exposed to mechanical restraint, and 13.5% of patients in the mechanical restraint group had been exposed to chemical restraint (supplementary fig S6). When patients were censored at the time of the treatment switch, the risk ratio at 30 days after restraint was similar to the main results (2.13, 95% CI 1.17 to 3.89) (supplementary table S5).

When the overlap population was targeted, all covariates were well balanced (supplementary fig S3). All estimates were attenuated, with a risk ratio at 30 days after restraint of 1.70 (95% CI 1.03 to 2.88) and a risk difference of 1.4 (0.1 to 2.9) per 1000 patients (supplementary table S5).

In patients exposed to mechanical restraint, the risk at 30 days after restraint of all cause mortality was 21.4 (95% CI 18.7 to 24.3) per 1000 patients, and this proportion increased to 39.0 (35.8 to 43.2) per 1000 patients by day 90 (supplementary table S6, supplementary fig S7). Compared to chemical restraint, the all cause mortality risk ratio 30 days after mechanical restraint was 1.16 (95% CI 0.89 to 1.49), and the risk difference was 2.9 per 1000 patients (-2.5 to 7.5) (supplementary table S6). The risk ratio was highest in the initial days after restraint and declined over time (supplementary fig S8). Information on specific causes of death is provided in supplementary file.

For the analysis of incident VTE, we included 23 770 patients without a history of VTE (supplementary fig S1). The risk ratio 30 days after restraint of incident VTE was 1.91 (95% CI 1.03 to 3.56), and the risk difference was 1.3 (0.1 to 2.6) per 1000 patients (supplementary table S6).

Results from a quantitative bias analysis assessing unmeasured confounding by smoking and obesity showed modest attenuation of the risk estimates (supplementary file). In a descriptive analysis, each additional hour of mechanical restraint was associated with an estimated 6% (95% CI 2% to 9%) increase in the rate of VTE (supplementary file).

In a sensitivity analysis comparing mechanical restraint with physical restraint, the baseline characteristics were slightly more imbalanced than observed in the primary mechanical restraint/chemical restraint comparison (supplementary table S8). The risk ratio for VTE 30 days after restraint of 2.70 (95% CI 1.40 to 6.43) was higher than for the primary mechanical restraint/chemical restraint comparison (supplementary table S9).

Self-controlled case series study

During the observation period, we included 1285 patients with incident VTE occurring during either the baseline or risk periods (supplementary fig S5). In this group, 1175 VTE events occurred during baseline periods outside of mechanical restraint risk periods, whereas 85 VTE events occurred within 90 days after mechanical restraint. We observed an additional 25 VTE events in the 15 day pre-exposure window before mechanical restraint. The median age at the time of VTE was 57.5 years (IQR 45.0-71.4 years), and 662 patients were women (51.5%).

The incidence rate ratio of VTE in the 14 days after mechanical restraint was 4.49 (95% CI 3.09 to 6.54), compared to the baseline period. The incidence rate ratio declined in subsequent risk periods: 15-29 days after mechanical restraint the incidence rate ratio was 1.64 (0.93 to 2.89), and 30-90 days after mechanical restraint, the incidence rate ratio was 0.92 (0.60 to 1.40) (table 3).

Table 3 | Self-controlled case series incidence rate ratios comparing the incidence rate of venous thromboembolism in the time following mechanical restraint with that in baseline periods

Risk period	No of person years	No of events	Incidence rate ratio (95% CI)
Baseline*	2969.5	1175	1
Pre-exposure†	72.9	25	2.19 (1.39 to 3.43)
Day 0-14	50.7	42	4.49 (3.09 to 6.54)
Day 15-29	44.4	14	1.64 (0.93 to 2.89)
Day 30-90	151.9	29	0.92 (0.60 to 1.40)

CI=confidence interval.

* Baseline periods start on the day of psychiatric admission and end 90 days after discharge.

† Pre-exposure risk periods are defined as the 15 days preceding a mechanical restraint episode.

Subgroup analyses showed the highest incidence rate ratios in men (5.85 (95% CI 3.70 to 9.26)) and patients who were restrained during 2011-2022 (5.96 (3.73 to 9.52)). We observed no difference in the incidence rate ratio in the 14 days after restraint between patients 18-59 years of age versus ≥60 years of age (supplementary table S10). All sensitivity analyses showed similar results to the main analysis (supplementary table S11).

Discussion

Principal findings

In this nationwide, population based study with two complementary study designs, we observed a twofold greater risk of VTE in the 30 day period after restraint in patients exposed to mechanical restraint than in patients exposed to chemical restraint. Within individual analyses revealed a fourfold increase in VTE incidence in the 14 days after mechanical restraint. Despite the increased relative measures, the absolute risk of VTE after mechanical restraint remains low (risk of 3.5 per 1000 patients 30 days after restraint).

In stratified self-controlled case series analyses before versus after publication of the Danish guidelines on thromboprophylaxis in relation to mechanical restraint in 2011,[35] we found no evidence of lower VTE incidence after 2011 among patients exposed to mechanical restraint during admission to a psychiatric hospital. We could not determine whether this reflects suboptimal implementation of the guidance or whether VTE occurs despite appropriate preventive measures.

Comparison with other studies

A few studies have investigated VTE in relation to mechanical restraint. A Japanese study that examined 1308 hospital admissions in a setting in which patients' D-dimer levels were routinely measured at admission, found that the odds of deep vein thrombosis were elevated in patients who were mechanically restrained compared to those who were not (odds ratio 6.0, 95% CI 2.4 to 13.9).[15] Although confounding by indication might have been introduced as a result of inpatients not exposed to restraint being used as a comparison group, 9.3% of patients being restrained developed deep vein thrombosis at some point during admission. This incidence is much higher than the VTE risk 30 days after restraint of 0.35% observed in our study. D-dimer measurements are not taken routinely for inpatients at Danish psychiatric hospitals; consequently, our study might have underestimated the absolute VTE risk. A recent case-control study from Japan showed a similar association (odds ratio 6.7, 95% CI 3.4 to 13.3).[36] In contrast to the Japanese studies, a Belgian study found no cases of VTE in 296 patients exposed to restraint, most of whom received low molecular weight heparin as a prophylactic measure.[16] A recent Danish study[14] (2007-2019) estimated a within individual risk ratio of VTE of 4.38 in the 30 days after mechanical restraint, higher than our estimates for the same risk period. This discrepancy likely reflects different baseline definitions. Baandrup et al[14] treated all non-restraint time as unexposed, including time outside psychiatric hospital admission, which may challenge exchangeability. In contrast, we restricted baseline time to periods of admission to a psychiatric hospital.

In the secondary outcome analyses, we observed a 2% risk of death 30 days after restraint. Death in the period after restraint has previously been reported.[10] However, given the relatively young age of this patient group, this finding warrants further attention.

Potential biological mechanisms

The most plausible pathophysiological mechanism linking mechanical restraint to VTE is immobilisation, which promotes venous stasis and impairs venous return. Prolonged physical inactivity facilitates thrombus formation and is a well established risk factor for VTE.[6] This risk might be further amplified in people with severe mental illness because of pre-existing risk factors. This proposed mechanism is supported by our finding of a graded increase in the VTE rate as duration of mechanical restraint increases, although this observation should be interpreted as descriptive rather than causal. Vigorous physical exertion during the application of mechanical restraint may contribute to secondary mechanism linking mechanical restraint to VTE. Given that both physical trauma and minor injuries are established VTE risk factors.[6]

Strengths and limitations

This study has several strengths and some limitations. Selection bias and referral bias were unlikely because we included all patients from Danish psychiatric hospitals. By applying appropriate weighting, we preserved the target population of interest. Furthermore, we ensured complete follow-up by linkage to national registry data.

Exposure misclassification was unlikely because Danish law requires reporting of episodes of coercion within psychiatric hospitals. The positive predictive value of VTE coding is 88%,[27] but some cases might potentially be underreported because of the circumstances surrounding mechanical restraint. If such underreporting were differential (eg, patients exposed to mechanical restraint have a diminished likelihood of being diagnosed with VTE), our findings would underestimate the true association between mechanical restraint and VTE.

Our study might have been subject to residual confounding despite adjustment for several measured factors. We lacked data on voluntary antipsychotic treatment during hospital admission and

lifestyle factors such as smoking and body weight. Results from the quantitative bias analysis suggested that unmeasured confounding by smoking or obesity alone was unlikely to fully explain the observed association. To partially account for unmeasured behavioural and health related confounding, we included information on criminal convictions, because individuals with criminal convictions tend to have poorer physical health than those without.[37]

Additionally, we used an active comparator to reduce confounding by indication. Nonetheless, given that mechanical restraint is more often applied in the context of severe aggression or violence, residual confounding related to these indications is likely. By using a self-controlled case series design, we eliminated time invariant confounding by design. However, time varying factors, such as confounding by indication, may still have confounded the observed association (eg, mechanical restraint applied due to acute psychosis, violent behaviour, or substance use). A study has reported elevated D-dimer and soluble P-selectin plasma levels in seemingly healthy people experiencing acute psychosis, with no earlier use of antipsychotic agents. Therefore, psychosis itself might possibly have thrombogenic effects.[38] To reduce this potential confounding, we compared mechanical restraint risk periods with other periods of psychiatric admission during which the underlying VTE risk was likely to be exchangeable.

Conclusions and implications

Mechanical restraint in inpatients at psychiatric hospitals was associated with an elevated short term risk of VTE, although the absolute risk remained low. Our findings add to existing evidence that prolonged mechanical restraint is associated with clinically relevant adverse outcomes, and support ongoing efforts at the policy and service levels to further limit the use and duration of mechanical restraint when less restrictive alternatives are feasible.

From a clinical perspective, our results suggest that systematic consideration of thromboprophylaxis after mechanical restraint may be warranted, balancing potential benefit against the risk of adverse effects such as bleeding. Overall, our findings provide empirical data with potential to inform both clinical decision making and future guideline development regarding the prevention of VTE related to mechanical restraint.

What is already known on this topic

People with severe mental illness have an increased risk of venous thromboembolism (VTE)

Mechanical restraint restricts mobility, but evidence on VTE risk after restraint is limited and has lacked robust comparators and clear timing of risk

What this study adds

Mechanical restraint was associated with a twofold higher risk of VTE 30 days after restraint compared with chemical restraint

Within individual analyses showed a more than fourfold increase in VTE incidence in the 14 days after mechanical restraint

Absolute risk was low, but findings support heightened vigilance and prevention efforts around restraint episodes

Contributors: JHV and HTS presented the initial study idea. All authors participated in designing the study. JHV, LP, and HTS had full access to the underlying data and took responsibility for the data integrity. JHV reviewed the literature, completed the initial draft, and performed the statistical analysis, with input from LP and IP. All authors revised the article for important intellectual content and contributed to the discussion and interpretation of the results. All authors have read and approved the final version of the manuscript. HTS is the study's guarantor. The authors used Microsoft Copilot exclusively to assist with grammar and language refinement during manuscript preparation. The authors reviewed, revised, and approved all content and accept full responsibility for the final manuscript. No AI tools were used for data analysis, interpretation, or generation of scientific content. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Transparency: The lead author (JHV) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: We aim to disseminate our findings to relevant patient organisations and clinical stakeholders through presentations at professional meetings and conferences, summaries shared with national clinical societies, and publicly accessible lay summaries provided via institutional communication channels.

Provenance and peer review: Not commissioned; externally peer reviewed.

Ethical approval: The study was reported to the Danish Data Protection Agency through Aarhus University (serial number 603). According to Danish legislation, ethical approval and informed consent are not required for registry-based studies.

Data sharing: Data sharing: The individual level data used in this study are derived from Danish national health and administrative registries and are stored on secure servers at Statistics Denmark. According to Danish data protection regulations, these data cannot be shared publicly. Statistical code is available in the supplementary material.

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Supplementary file: Restraint and risk of venous thromboembolism