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Tranexamic acid use is not associated with the risk of melanoma in Danish women: A nested case-control study using Danish health registries

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ABSTRACT

Background: Repurposing already approved drugs in a cancer setting has gained increasing interest in recent years. Tranexamic acid is an anti-fibrinolytic drug that has recently been suggested as an anti-cancer drug due to its anti-inflammatory and anti-carcinogenic effects in animal studies. In this study, we aimed to investigate the possible melanoma-preventive role of tranexamic acid in Danish women.

Method: In this nested case-control study, we identified female cases 18–60 years with first-time melanoma during 2000–2015 and age-matched them with 10 female controls. The odds ratio (OR) of melanoma with tranexamic acid ever- or high use (≥ 100,000 mg) was estimated using conditional logistic regression.

Results: A total of 7986 women with incident melanoma were eligible for study inclusion and were matched to 79,860 controls. Most exposed cases and controls were exposed to low cumulative doses of tranexamic acid corresponding to around 5 days of continuous treatment (1000 mg 3 times daily) for the presumed main indication, i.e., menorrhagia.

The crude OR associating tranexamic ever use with melanoma was 1.04 (95% CI 0.98–1.11, p = 0.20), and the adjusted OR was 1.03 (0.97–1.10, p = 0.32). We found no dose-response pattern or effect measure modification by age, histologic type, localization, or clinical stage. However, prolonged use with cumulative doses of tranexamic acid (≥ 100,000 mg) was associated with an increased risk of melanoma (adjusted OR 1.23,95 %, CI 0.96–1.56), compared with non-use.

Conclusion: We found no association between tranexamic acid use and the risk of melanoma in Danish women. This could be explained by underlying dose- or biological factors, and sporadic use patterns. A higher risk of melanoma was seen among prolonged users which could be due to surveillance bias.

1. Introduction

Inflammation is considered a hallmark of cancer, involved in tumor growth and dissemination for several solid tumors [1]. Somatic mutations drive melanoma initiation [2], while a host-generated inflammatory microenvironment is acknowledged as pivotal for melanoma progression [3]. Thus, repurposing anti-inflammatory drugs in a melanoma preventive setting has gained increasing interest in recent years.

Epidemiological studies and meta-analysis have shown an association between long-term use of non-steroidal anti-inflammatory drugs or aspirin and reduced risk of melanoma, although still debated because of the possible influence of gender and dose of treatment [4–6].

Interestingly, a recent study has suggested tranexamic acid as an anti-cancer drug, based on experimental animal models [7]. Tranexamic acid is a well-known drug that inhibits conversion from plasminogen to its active form plasmin, primarily used for its anti-fibrinolytic effects, thus reducing the risk of bleeding [8]. Interestingly, tranexamic acid also affects relevant anti-inflammatory and anti-carcinogenic pathways [9,10], and modulates the immune response, both after surgery and in healthy volunteers [11].

Although the drug has been safely used in Europe since the 1980s for bleeding disorders, menorrhagia, angioedema, and surgical and

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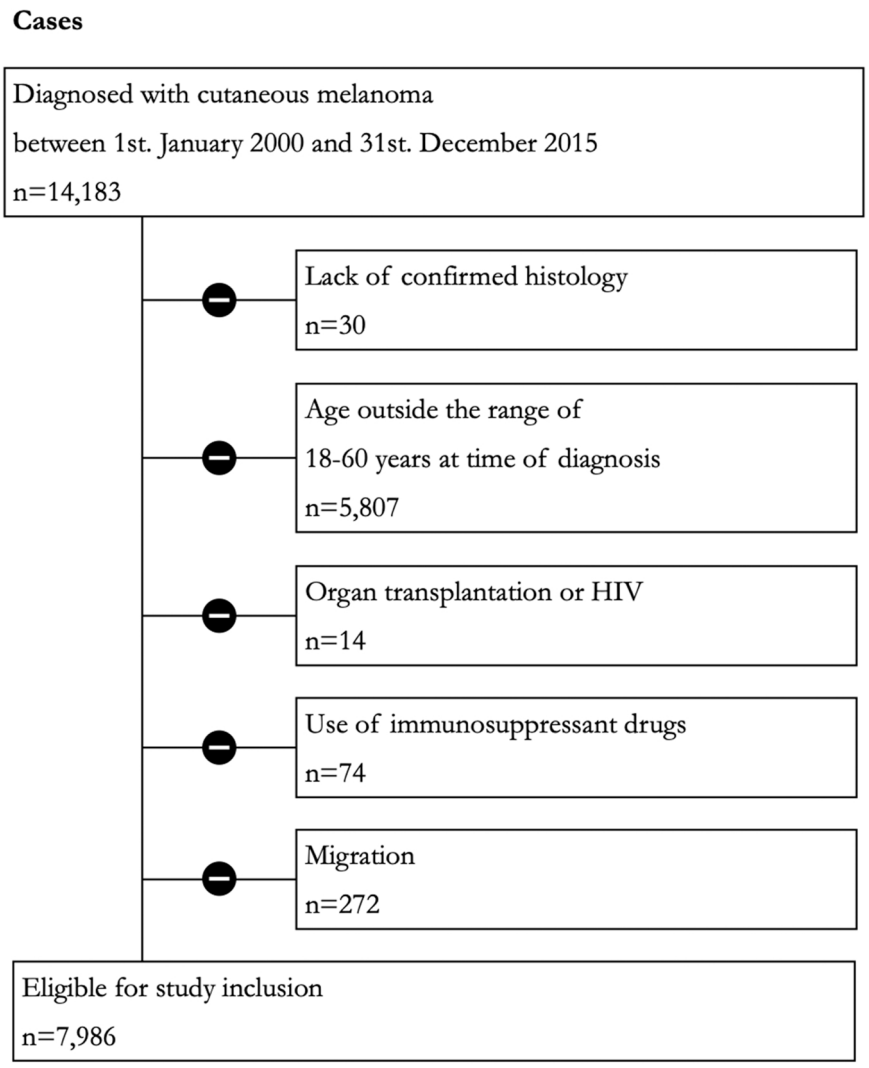

Fig. 1. Flowchart of excluded cases.

traumatic bleeding, no current epidemiological studies have investigated the possible preventive role of tranexamic acid in melanoma [12–14].

The objective of our study is to evaluate the use of tranexamic acid and the risk of melanoma in Danish women.

2. Material and method

2.1. Study design

We used a nested case-control design, identifying cases as women aged 18–60 years with a first-time melanoma diagnosis and matched each case to 10 controls by risk-set sampling.

2.2. Data sources

The Danish health registries were used to obtain individual-level data on the Danish population; The Danish Cancer Registry [15], the Danish Pathology Registry [16], the National Prescription Registry [17], the National Patient Registry [18], Registers in Statistics Denmark on educational level and income [19] and the Civil Registration System [20]. Diagnoses were obtained from the Danish Patient Registry, including both inpatient and outpatient diagnoses.

2.3. Study population

Our source population was the entire Danish female population aged 18–60 years. The female sex is referred to as it is registered in the Danish Central Person Registry. We identified all incident melanoma in Denmark from 1st. January 2000–31st. December 2015. Cases were assigned an index date corresponding to the date of diagnosis. To be eligible as a case or control, we required that the woman resided continuously in Denmark 5 years before the index date, to ensure sufficient baseline data on all individuals included in the study and did not have a history of certain conditions predisposing to malignant melanoma, including organ transplantation, HIV, or use of azathioprine, cyclosporine or mycophenolate mofetil [21–23]. Using risk-set sampling, we matched each case to 10 controls on the year of birth. Controls were assigned an index date corresponding to the date of diagnosis of their matched case. Consistent with the risk-set sampling scheme, cases were eligible to be sampled as controls before being diagnosed with melanoma. The algorithms used to select the study population have been validated [24].

2.4. Exposure

The main indication for oral tranexamic acid in women in the primary care setting is menorrhagia, with a recommended dose of 1000 mg administered three times a day [25]. In Denmark the only strength of

tranexamic acid tablets available since 1995 has been 500 mg per tablet, thus 180,000 mg corresponds to 360 tablets or around 60 days of continuous treatment. We arbitrarily defined the main exposure of interest as a cumulative tranexamic acid (ATC code B02AA02) dose of 100,000 mg corresponding to ≈ 30 days of continuous treatment with the above-mentioned dose or approximately 6 months of intermittent exposure with use only during menstruation. The reference category is never-use of tranexamic acid unless specified otherwise. We disregarded the use of drugs within 1 year before the index date, i.e., applied a 1-year lag time for the exposure definition. We examined dose-response associations by modeling cumulative dose as a categorical variable (1 – 30,000; 30,000–60,000; 60,000–100,000; 100,000–200,000; and 200,000 + mg) and as a continuous variable. We only considered orally administered tranexamic acid, disregarding preparations that were administered parenterally, as these were not recorded in the prescription registry. In the inpatient setting tranexamic acid is mainly administered to reduce bleeding in a surgical or traumatic setting [26].

2.5. Covariates

We controlled for age and calendar time by the matched design and -analysis. Further, the following variables were included as covariates in all regression analyses: use of photosensitizing drugs (oral retinoids, topical retinoids, tetracycline, macrolides, fluoroquinolones, aminoquinolones, methoxypsoralene, amiodarone, and hydrochlorothiazide), use of other drugs that may influence the likelihood of being diagnosed with malignant melanoma (oral contraceptive therapy, estrogen and/or progestogen therapy, acetaminophen, NSAIDs, low-dose aspirin, penicillins, and statins), a history of alcohol-related disorders, chronic obstructive pulmonary disease, diabetes type I, and II, moderate/severe chronic kidney disease, a modified Charlson comorbidity index (0, 1, 2, ≥3) [27] and, lastly, highest achieved education. Use of the above-listed drugs was defined as having filled two or more prescriptions for a given drug while any discharge or outpatient diagnosis was sufficient for a given medical condition. Similarly, as for our exposure metric, we applied a lag time of 12 months in the assessment of covariates.

2.6. Supplementary analyses

We examined whether the association varied by pre-specified subgroups, including age (≤ 50, > 50 years) histological type (superficial spreading, nodular, lentigo, acral, and other), localization (head/neck, trunk, upper limb, lower limb, unspecified) and disease stage (localized, non-localized, unknown).

2.7. Statistical analyses

We estimated odds ratios (OR) for malignant melanoma associated with the use of tranexamic acid using conditional logistic regression. As part of the dose-response evaluation, we included cumulative dose as a continuous, explanatory variable in unconditional logistic regression models. In these analyses, we estimated the OR associated with each doubling in cumulative dose while including age and calendar time as continuous, linear covariates. We evaluated effect measure modification by including interaction terms in the conditional logistic regression model and tested for effect measure modification using a maximum likelihood ratio test of the model without interaction terms nested in the model with interaction terms.

The analytical code to create the tables, figures, and analysis results for this study is available upon request to Anton Pottegård (apottegaard@health.sdu.dk). Deidentified data can be made available for authorized researchers after application to Statistics Denmark.

2.8. Approvals

Purely registry-based research does not require ethical approval in Denmark.

Table 1
Baseline characteristics of cases and controls, based on tranexamic acid use and suggested confounders. Confounding from sex was controlled by restriction while confounding from age and calendar time was controlled by the matched study design.

	Cases (n = 7986) n (%)	Controls (n = 79,860) n (%)
Use of tranexamic acid		
Never use	7317 (91.6 %)	73,964 (92.6 %)
Ever use	669 (8.4 %)	5896 (7.4 %)
Prolonged use (≥ 100,000 mg)	79 (1.0 %)	628 (0.8 %)
Use of photosensitizing drugs		
Topical retinoids	112 (1.4 %)	827 (1.0 %)
Oral retinoids	136 (1.7 %)	1176 (1.5 %)
Tetracycline	292 (3.7 %)	2585 (3.2 %)
Macrolides	2321 (29.1 %)	22,935 (28.7 %)
Aminoquinolines	423 (5.3 %)	3506 (4.4 %)
Amiodarone	-	19 (0.0 %)
Hydroclorothiazide	251 (3.1 %)	2268 (2.8 %)
PUVA treatment	-	24 (0.0 %)
Use of other drugs		
Low-dose aspirin	151 (1.9 %)	1787 (2.2 %)
Acetaminophen	397 (5.0 %)	5474 (6.9 %)
NSAIDs	3668 (45.9 %)	38,118 (47.7 %)
Penicillins	5786 (72.5 %)	57,416 (71.9 %)
Statins	244 (3.1 %)	2960 (3.7 %)
Estrogen therapy, progestogen therapy or combination therapy	1173 (14.7 %)	10,890 (13.6 %)
Oral contraceptives	4441 (55.6 %)	40,551 (50.8 %)
Medical history		
Alcohol related disorders	38 (0.5 %)	754 (0.9 %)
Diabetes	158 (2.0 %)	2135 (2.7 %)
COPD	69 (0.9 %)	855 (1.1 %)
Chronic kidney disease	24 (0.3 %)	261 (0.3 %)
Charlson Comorbidity Index		
0	6972 (87.3 %)	70,373 (88.1 %)
1	590 (7.4 %)	6885 (8.6 %)
2	313 (3.9 %)	1643 (2.1 %)
3 +	111 (1.4 %)	959 (1.2 %)
Education		
Short	1359 (17.0 %)	17,399 (21.8 %)
Medium	3396 (42.5 %)	31,972 (40.0 %)
Long	3100 (38.8 %)	25,555 (32.0 %)
Unknown	131 (1.6%)	4934 (6.2 %)

3. Results

3.1. Cases and controls

In the study period, 14,183 women were diagnosed with malignant melanoma in Denmark. We excluded 30 due to lack of confirmed histology, 5807 due to age outside the range of 18–60 years at diagnosis, 14 due to organ transplantation or HIV, 74 due to use of immunosuppressant drugs, and 272 due to migrations (Fig. 1). Thus, a total of 7986 women were eligible for study inclusion and matched to 79,860 controls, fulfilling the same eligibility criteria. The median age at the time of diagnosis for the study population was 45 years. Characteristics of the cases and controls, based on the use of medication, comorbidity, and education, are presented in Table 1.

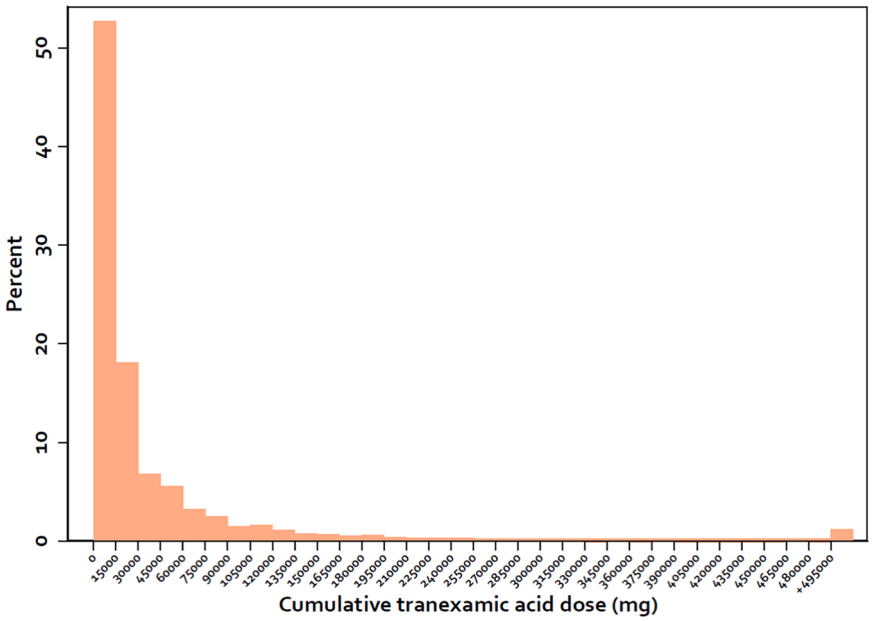

Fig. 2. Percentage distribution of cumulative dose of tranexamic acid among all ever users of tranexamic acid.

Table 2
Crude and adjusted odds ratios (OR, and 95% CI) for the association between exposure to tranexamic acid and melanoma, estimated as continuous cumulative dose and by groups defined as non-use, ever use, and prolonged use (≥ 100,000 mg).

	Cases	Controls	Minimally adjusted OR[a] (95% CI)	Adjusted OR** (95% CI)
Non-use	7317	73,964	1.0 (ref.)	1.0 (ref.)
Ever use	669	5896	1.15 (1.06–1.25)	1.16 (1.06–1.26)
Prolonged use (≥ 100,000 mg)	79	628	1.26 (1.00–1.60)	1.23 (0.96–1.56)
Cumulative dose (mg)				
1 – 30,000	338	3123	1.10 (0.98–1.23)	1.11 (0.98–1.24)
30,000–60,000	170	1550	1.13 (0.96–1.33)	1.14 (0.97–1.35)
60,000 – 100,000	82	595	1.43 (1.13–1.80)	1.39 (1.10–1.77)
100,000 – 200,000	45	377	1.21 (0.89–1.66)	1.18 (0.86–1.62)
200,000 +	34	251	1.34 (0.94–1.93)	1.29 (0.90–1.86)
Continuous†	669	5896	1.04 (0.98–1.11), p 0.20	1.03 (0.97–1.10), p 0.32

* * Adjusted for age and calendar time (by design), photosensitizing drug use, oral contraceptive therapy, estrogen and/or progestogen therapy, acetaminophen, NSAIDs, low-dose aspirin, penicillins, and statins, a history of alcohol related disorders, chronic obstructive pulmonary disease, diabetes type I and II, moderate/severe chronic kidney disease, modified Charlson comorbidity index and highest achieved education.

† ORs for every doubling in cumulative dose estimated in unconditional logistic regression models restricted to ever users with age and index date included as covariates

[a] Adjusted for age and calendar time (by design)

3.2. Exposure and doses

Most exposed cases and controls were exposed to low cumulative doses of tranexamic acid e.g., the median cumulative dose was 15,000 mg (i.e., one package of 30 ×500 mg tablets) and the 95th percentile was 183,000 mg (Fig. 2).

3.3. Association between tranexamic acid use and melanoma

There was no clear dose-response pattern when categorizing cumulative dose or for each doubling of dose assuming a linear relationship with adjusted OR of 1.03 (0.97–1.10, p = 0.32) for each doubling of cumulative dose among users (Table 2).

Prolonged use with cumulative doses of tranexamic acid (≥ 100,000 mg) was associated with a 23 % increased risk of melanoma compared to never use (crude OR of 1.26 (95 % CI 1.00–1.60) and adjusted OR of 1.23 (95 % CI 0.96–1.56)) (Table 2).

3.4. Subgroup analyses

The was no apparent effect measure modification by age, histological type, localization, or clinical stage, however, the confidence intervals were wide reflecting a lack of statistical precision in examining subgroup effects (Table 3).

4. Discussion

To our knowledge, this is the first epidemiological study to address the association between the use of tranexamic acid and the risk of melanoma. Overall, we found no reduced risk of melanoma associated with tranexamic acid use, however, prolonged use of tranexamic acid was associated with an increased risk of melanoma compared with never-users.

4.1. Bias based on behavioral factors seems unlikely

Contradictory to our hypotheses, we found that high users of tranexamic acid had an increased risk of melanoma, however, several factors may impact this finding. Notable differences between tranexamic acid users and non-users may influence the likelihood of developing and/or getting diagnosed with melanoma, thus biasing the results. We lacked data on UV exposure, the only fully established exogenous risk factor for melanoma [28]. It is not known whether tranexamic acid users are more or less likely to be exposed to UV radiation than non-users, thus, the direction of any potential bias from confounding by UV exposure is difficult to quantify. Further, users of tranexamic acid may see their doctor more frequently increasing the likelihood of being diagnosed with melanoma compared to non-users. This has been shown previously for phosphodiesterase inhibitors and melanoma where the positive association likely results from more frequent healthcare contacts in users, i.e., surveillance bias [29,30]. Skin type and family history

Table 3
Crude and adjusted odds ratios (OR, and 95% CI) for the association between high use of tranexamic acid (≥ 100,000 mg) and melanoma, estimated by subgroups.

Subgroup	Cases exposed/ unexposed	Controls exposed/ unexposed	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	P-value†
Age					0.27
≤ 50 years	29 / 5191	266 / 51,972	1.07 (0.73–1.57)	1.04 (0.71–1.53)	
> 50 years	50 / 2126	362 / 21,992	1.42 (1.04–1.96)	1.38 (1.00–1.90)	
Type					0.67
Superficial spreading	58 / 5372	475 / 54,302	1.23 (0.93–1.62)	1.22 (0.92–1.61)	
Nodular	6 / 420	33 / 4273	1.90 (0.78–4.61)	1.75 (0.72–4.29)	
Lentigo	(n < 5)	7 / 457	(-)	(-)	
Acral lentiginous	(n < 5)	8 / 370	(-)	(-)	
Other	14 / 1445	105 / 14,562	1.30 (0.74–2.28)	1.19 (0.67–2.10)	
Localization					0.61
Skin of head and neck	7 / 346	39 / 3532	1.95 (0.86–4.45)	1.99 (0.87–4.56)	
Skin of trunk	33 / 2794	220 / 28,121	1.47 (1.01–2.13)	1.41 (0.97–2.05)	
Skin of upper limb	11 / 1018	100 / 10,360	1.13 (0.60–2.13)	1.10 (0.58–2.09)	
Skin of lower limb	23 / 2594	222 / 26,271	1.05 (0.68–1.62)	1.02 (0.66–1.58)	
Unspecified part of skin	5 / 565	47 / 5680	1.04 (0.41–2.65)	0.99 (0.39–2.53)	
Stage					0.92
Localized	61 / 5215	485 / 52,761	1.26 (0.96–1.65)	1.23 (0.94–1.62)	
Non-localized	6 / 456	39 / 4606	1.53 (0.64–3.65)	1.41 (0.59–3.37)	
Unknown	12 / 1646	104 / 16,597	1.19 (0.65–2.18)	1.13 (0.62–2.08)	

† P-values from a maximum likelihood test of the model without interaction terms nested in the model with interaction terms
[a] Adjusted for age and calendar time (by design), photosensitizing drug use, oral contraceptive therapy, estrogen and/or progestogen therapy, acetaminophen, NSAIDs, low-dose aspirin, penicillin, and statins, a history of alcohol related disorders, chronic obstructive pulmonary disease, diabetes type I and II, moderate/severe chronic kidney disease, modified Charlson comorbidity index and highest achieved education.

are other risk factors for malignant melanoma but these are not likely to be associated with the use of tranexamic acid [31]. Lastly, we can not rule out the impact of unmeasured confounders i.e., smoking and BMI.

4.2. Coagulation drives inflammation and may be a contributing biological factor for the increased risk of melanoma in high-users

This study's main presumable indication for tranexamic acid use is menorrhagia, associated with heavy or prolonged cyclic bleeding. Bleeding, coagulation, and inflammation are complexly interconnected factors, with coagulation being an effective driver of inflammation [32]. It is also known that inflammation plays a role in menorrhagia, either due to prolonged bleeding and wound repair or the underlying causes of menorrhagia i.e., adenomyosis [33]. This increased inflammation level may diminish tranexamic acid's effects if we acknowledge the role of inflammation in melanoma progression [1,3].

4.3. The dose of tranexamic acid may play a role in preventing melanoma

We chose to investigate melanoma due to the suggested responsiveness of melanocytic cells on.

inflammatory signals and the known negative prognostic impact of an inflammatory tumor microenvironment.

in patients with melanoma [34]. Tranexamic acid affects anti-inflammatory and anti-carcinogenic pathways [9,10], and modulates the immune response, both after surgery and in healthy volunteers [11]. However, a clinical study investigating the anti-inflammatory role of perioperative treatment with tranexamic acid found that higher doses of tranexamic acid were more effective in reducing inflammation [35]. Thus, the doses of tranexamic acid, that patients were exposed to in this study, could be too low or given at ineffective time points or for too short a cumulative duration, to plausibly affect the development of melanoma.

4.4. External validity

In this study, we have investigated the melanoma-preventive role of tranexamic acid in Danish women between 18 and 60 years of age. Thus, in regard of external validity, our results cannot be generalized to a broader population and will only reflect the selected group concerning age and biological sex. In addition, the results will only reflect Danish conditions and melanoma incidence, thus in countries with a higher incidence of melanoma a possible association may have been more prominent and associated with higher power of the results in general.

5. Conclusions

We found no association between tranexamic acid use and the risk of melanoma in Danish women. High use was associated with a higher risk of melanoma, presumably due to surveillance bias. In addition, we were unable to evaluate the effects of high cumulative tranexamic doses due to sporadic use patterns.

Author contributions

ML. Bønnelykke-Behrndtz, A. Pottegård, L. Rosenkrantz Hølmich conceived the study. A.Pottegård and KB. Kristensen designed the study and performed the analyses. ML. Bønnelykke-Behrndtz and KB Kristensen drafted the original manuscript. All authors contributed substantially to reviewing the manuscript and approved the final version.

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Conflict of interests

Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier, and LEO Pharma, all regulator-mandated phase IV studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. All other authors declare no financial or personal conflicts of interest.

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