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Article

Steroid-Induced Thrombosis: Comprehensive Analysis Through Use of the FAERS Database

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Abstract

Background/Objectives: Thrombosis, a critical condition that can have severe consequences, such as myocardial infarction and cerebral infarction, can be induced by steroid drugs. Although the mechanisms for inducing thrombosis are known for some types of steroid drugs, much remains unknown about the differences in the tendency and mechanisms for thrombosis. **Methods:** To address this knowledge gap, we analyzed the relationship between thrombosis and steroid use by utilizing the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) database. From the database, we extracted demographic and drug information and information on reported adverse events from 2004 to 2024. We characterized drugs according to physiological function, receptor specificity, and Anatomic Therapeutic Chemical classification and calculated the proportion of steroid drugs that were likely to induce thrombosis. **Results:** Among steroid drugs, sex hormones such as androgens, progestogens, and estrogens appeared to have particularly high potential for causing thrombotic events. Results of principal component analysis and cluster analysis indicated that sex hormone preparations were associated with an increased risk of venous thrombosis. In addition, cardiovascular medications and mineralocorticoids, which are used to treat diseases of major organs, showed a tendency to induce large-vessel occlusions. **Conclusions:** These findings may be useful for selecting steroid drugs for patients who are at risk for similar adverse effects.

Keywords: steroids; FAERS database; venous thromboembolism; arterial thrombosis; sex hormones; pharmacovigilance

1. Introduction

Because of their anti-inflammatory and immunosuppressive effects, steroid drugs are used widely in the treatment of various diseases [1,2]. Pharmaceuticals with a steroid backbone can be categorized into several types, including glucocorticoids, mineralocorticoids, sex hormones, and anabolic steroids [3]. Glucocorticoids have immunosuppressive and anti-inflammatory properties and are used to treat nearly all autoimmune diseases, chronic inflammatory disorders, allergies, and some malignant tumors [4]. Sex hormones are broadly categorized as female and male hormones, and female hormones are subdivided into progestins and estrogens. These are used primarily for contraception and osteoporosis prevention and in the treatment of menstrual disorders, menopausal symptoms, and certain cancers [5–10]. Anabolic steroids generally promote muscle growth and protein synthesis; they are used medicinally to treat muscle weakness caused by various conditions [11,12].

However, Steroids are also known to cause various adverse effects [13]. A cohort study conducted in the United States revealed that short-term use (≤ 30 days) of oral corticosteroids increased the incidence of sepsis (5.30%), venous thromboembolism (3.33%), and fractures (1.87%) [13]. However, the mechanisms underlying these adverse effects, including thrombosis, remain largely unclear. In Japan, the Ministry of Health, Labor and Welfare has issued guidelines addressing thrombosis as a serious adverse effect, which underscores the need for further research [14].

Thrombosis can be broadly classified into arterial and venous thrombosis [15]. A shared underlying mechanism is endothelial dysfunction. Under normal conditions, endothelial cells produce nitric oxide and prostacyclin, which suppress platelet aggregation, promote fibrinolysis via tissue plasminogen activator, and inhibit coagulation via anticoagulant factors. In endothelial dysfunction, these protective functions are lost, which leads to a thrombogenic state. Dysfunctional endothelium increases lipoprotein permeability, causing accumulation in the subendothelial space and triggering local inflammation, macrophage differentiation, and foam cell formation. These processes eventually lead to the development of atherosclerotic plaque and arterial thrombosis. In atherosclerotic regions, the anticoagulant activity of endothelial cells is reduced, which accelerates the development of thrombosis. Conversely, venous thrombosis is mainly caused by blood stasis and hypercoagulability. Factors such as inflammation, hypoxia, and mechanical stress caused by blood pooling may induce endothelial dysfunction, in which tissue factor is expressed and which initiates the coagulation cascade. Hypoxia from venous stasis activates thrombogenic factors such as plasminogen activator inhibitor-1 and von Willebrand factor, while suppressing fibrinolysis, which exacerbates endothelial dysfunction. This vicious cycle characterizes venous thrombosis [16,17]. Although these mechanisms are largely elucidated, the tendency of different types of steroid drugs to induce specific types of thrombosis remains unclear [18]. We hypothesized that the tendency to develop thrombosis (e.g., arterial vs. venous) varies by steroid class.

Therefore The U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) [19] is a collection of numerous reports of adverse event from the United States and abroad, which are useful for analyzing the relationship between thrombosis and steroid drugs. In this study, we used the FAERS database to comprehensively identify steroid drugs that may induce thrombosis and to clarify their associated characteristics and classifications.

2. Results

2.1. Creation of the Data Table

In the analysis, the FAERS drug information (DRUG) table (127,228,343 rows) and the adverse event (REAC) table (54,645,478 rows) were used. We combined the information in these tables to create an informal data table, consisting of 18,328,780 rows, for analysis. Duplicate entries were removed during the creation of the data table (Figure 1).

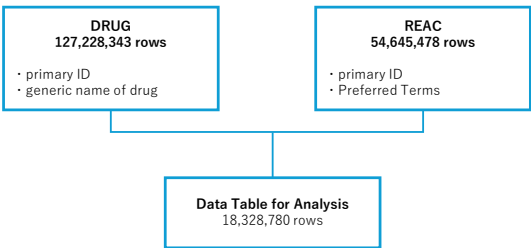


Figure 1. Flowchart of the process for creating the analysis data table. Data in the DRUG (drug information) and REAC (adverse event information) tables from the FDA Adverse Event Reporting System (FAERS) were combined, allowing for duplicates, and were linked by means of the primary ID number.

2.2. Steroid Drugs That Induce Thrombosis

All steroid drugs included in the informal data table are listed in Table 1. Scatter plots were generated for drugs with 1000 or more reported adverse events in the data table. These scatter plots (Figure 2) depict the correlation between steroid drugs and thrombosis. Each plot represents a steroid drug; the greater the natural logarithm of the reporting odds ratio (ROR) and the negative logarithm of the *p* value [$-\log(p \text{ value})$](Supplementary Table S1), the more statistically significant the drug is

estimated to induce thrombosis. Steroid drugs for which the natural logarithm of the ROR > 0 and *p* < 0.05 were documented and analyzed.

Table 1. Drugs that have steroid structure.

2-METHOXYESTRADIOL	DESOXIMETASONE	GANAXOLONE	ORYZANOL
7-KETO-DEHYDROPIANDROSTERONE	DESOXYCORTONE	GESTODENE	OUABAIN
20-HYDROXYECDYSONE	DEXAMETHASONE	GESTONORONE	OXYMESTERONE
ABIRATERONE	DEXBUDESONIDE	GESTRINONE	OXYMETHOLONE
ACETYLDIGITOXIN	DIENOGEST	GINSENSINOSIDE RG3	PANCURONIUM
ACETYLDIGOXIN	DIFLORASONE	GITALOXIN	PARAMETHASONE
ALCLOMETASONE	DIFLUCORTOLONE	GUGGULSTERONE	PENGITOXIN
ALDOSTERONE	DIFLUPREDNATE	HALCINONIDE	PIPECURONIUM
ALFADOLONE	DIGITALIN	HALOMETASONE	PRASTERONE
ALFAXALONE	DIGITOXIN	HALOPREDONE	PREDNAZOLINE
ALGESTONE	DIGOXIN	HYDROCORTISONE	PREDNICARBATE
ALLYLESTRENOL	DIMETHISTERONE	HYDROXYPROGESTERONE	PREDNIMUSTINE
ALORADINE	DROSPIRENONE	HYDROXYCHOLIC ACID	PREDNISOLAMATE
AMCINONIDE	DROSTANOLONE	IODINE (I31 I) NORCHOLESTEROL	PREDNISOLONE
ANDROSTANOLONE	DYDROGESTERONE	LANATOSIDE C	PREDNISONE
ANDROSTENEDIOL	EMERGENCY CONTRACEPTIVES	LANATOSIDES	PREDNYLDENE
ANDROSTENEDIONE	EPICHOLESTANOL	LEVONORGESTREL	PREGNANDIOL
ANECORTAVE	EPIMESTROL	LOTEPREDNOL	PREGNENOLONE
ATAMESTANE	EPLERENONE	LYNESTRENOL	PROCINONIDE
BECLOMETASONE	EPRISTERIDE	MAZIPREDONE	PROGESTERONE
BETA-ACETYLDIGOXIN	EQUILIN	MEDROGESTONE	PROMEGESTONE
BETAMETHASONE	ESTETROL	MEDROXYPROGESTERONE	PROMESTRIENE
BETA-SITOSTEROL	ESTRADIOL	MEDRYSONE	PROSCILLARIDIN
BOLDENONE	ESTRAMUSTINE	MEGESTROL	QUINBOLE
BRASSICASTEROL	ESTRIOL	MEPITIOSTANE	QUINESTRADOL
BREXANOLONE	ESTROGENS	MEPREDNISONE	QUINESTROL
BUDESONIDE	ESTROGENS CONJUGATED	MEPROSCILLARIN	RAPACURONIUM BROMIDE
CAMPESTEROL	ESTRONE	MESTANOLONE	RIMEXOLONE
CANRENOIC ACID	ESTROPIPATE	MESTEROLONE	ROCURIUM
CANRENONE	ETHINYLESTRADIOL	MESTRANOL	RUSCOGENIN
CHENODEOXYCHOLIC ACID	ETHISTERONE	METANDIENONE	SEGESTERONE
CHLORMADINONE	ETHYLESTRENOL	METENOLONE	SELENONORCHOLESTEROL (75 SE)
CHLORODEHYDROMETHYLTESTOSTERONE	ETIPREDNOL DICLOACETATE	METHANDRIOL	SITOSTEROLS
CHOLESTEROL	ETONOGESTREL	METHASTERONE	SODIUM TAUROCHOLATE
CHOLESTERYL BENZOATE	ETYNDIOL	METHYLESTRADIOL	SPIRONOLACTONE
CHOLIC ACID	EXEMESTANE	METHYLPREDNISOLONE	STANZOLOL
CICLESONIDE	FLUCLOROLONE ACETONIDE	METHYLTESTOSTERONE	STEROIDS
CINBUFAGIN	FLUDROCORTISONE	METILDIGOXIN	STIGMASTANOL
CINOBUFOTALIN	FLUDROXYCORTIDE	METIBOLONE	STIGMASTEROL
CIPROCIENONIDE	FLUMEDROXONE	MIFEPRISTONE	STROPHANTHIN-K
CLASCOTERONE	FLUMETASONE	MINAXOLONE	TAUROSELCHOLIC ACID
CLOBETASOL	FLUNISOLIDE	MOMETASONE	TELAPRISTONE
CLOBETASONE	FLUCINOLONE ACETONIDE	MOXESTROL	TESTOSTERONE
CLOCORTOLONE	FLUCINONIDE	NANDROLONE	TIBOLONE
CLOPREDNOL	FLUCORTIN	NOMEGESTROL	TIXOCORTOL
CLOSTEBOL	FLUCORTIN BUTYL	NORCHOLESTENOL IODOMETHYL	TRENBOLONE
COLLAGENASE	FLUCORTOLONE	NORELGESTROMIN	TRIAMCINOLONE
CONVALLATOXIN	FLUOROMETHOLONE	NORETHANDROLONE	TRILOSTANE
CORTISONE	FLUOXYMESTERONE	NORETHISTERONE	TRIMEGESTONE
CORTIVAZOL	FLUPAMESONE	NORETYNODREL	ULIPRISTAL
CYPROTERONE	FLUPREDNIDENE	NORGESTIMATE	ULOBETASOL
DANAZOL	FLUPREDNISOLONE	NORGESTREL	URSODEOXYCHOLIC ACID
DEFLAZACORT	FLUTICASONE	NORGESTRIENONE	URSODOXICOLTAURINE
DEHYDROCHOLIC ACID	FORMESTANE	NORMETHANDRONE	VAMOROLONE
DEOXYCHOLIC ACID	FORMOCORTAL	NORUCHOLIC ACID	VECURONIUM
DEPRODONE	FULVESTRANT	OBETICOLIC ACID	VITAMIN D1
DESLANOSIDE	FUSIDIC ACID	ONAPRISTONE	WITHANIA SOMNIFERA
DESOGESTREL	GALETERONE	ORIC 101	ZURANOLONE
DESONIDE			

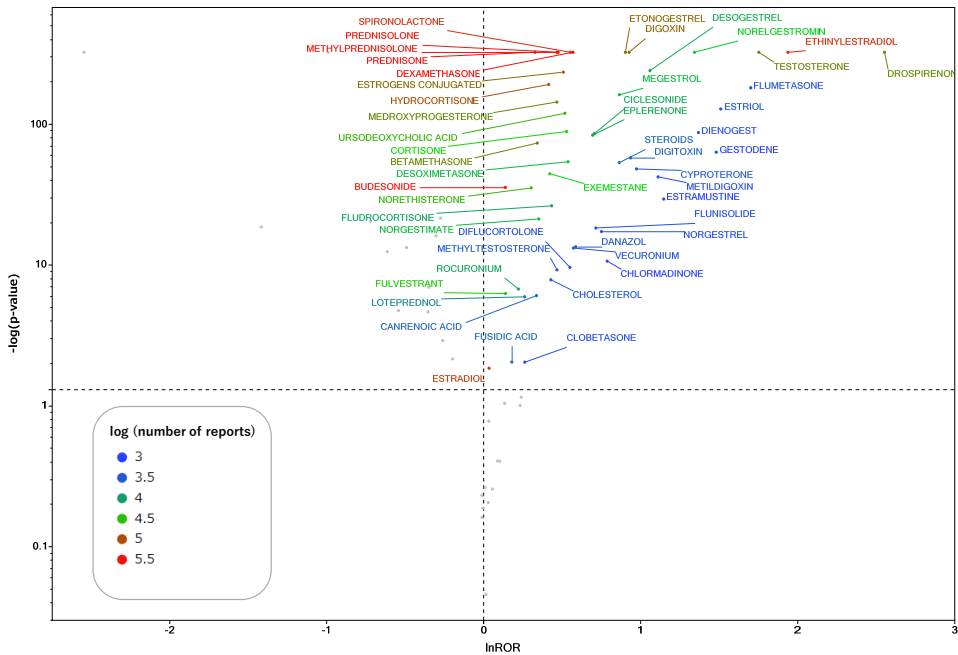


Figure 2. Volcano plot for steroids and thromboses. The vertical axis represents the statistical significance according to Fisher’s exact test, and the horizontal axis represents the risk of inducing thromboses. The steroid names and their leaders are colored according to the number of reports.

2.3. Classification of Steroid Drugs and Their Relationships to Thrombogenesis

Steroids with a high potential to induce thrombosis ($\ln\text{ROR}<0$, $p<0.05$) were categorized according to their physiological functions, receptor specificity, and Anatomical Therapeutic Chemical (ATC) classification. We then calculated the proportions of steroids in each classification (Table 2). According to results of Fisher’s exact test, androgens were significantly increased the risk of thrombosis ($\text{ROR} = 5.305$, $p < 0.05$).

Table 2. Distribution on volcano plots and the p-values and RORs by drug class.

Steroid Classification	Steroids Likely to Induce Thromboses *#	Number of All Steroids by Drug Class *	Steroids Likely to Induce Thromboses/Number of All Steroids by Steroid Class (%)	ROR	95%CI	p-value
Androgen	3	4	75.0	5.305	5.203-5.408	<.0001
Antiandrogen	1	2	50.0	2.651	2.363-2.973	<.0001
Antiestrogen	1	1	100.0	1.151	1.090-1.214	<.0001
Antiprogesterone	0	1	0.0	—	—	—
Bile Acid	1	3	33.3	1.679	1.612-1.748	<.0001
Cardiac Glycoside	3	3	100.0	2.532	2.476-2.589	<.0001
Enzyme	0	1	0.0	—	—	—
Estrogen	5	7	71.4	3.327	3.292-3.360	<.0001
Glucocorticoid	15	27	55.6	1.510	1.500-1.519	<.0001
Mineralocorticoid	1	1	100.0	1.543	1.432-1.661	<.0001
Mineralocorticoid Receptor Antagonist	3	3	100.0	1.746	1.713-1.780	<.0001
Non-steroidal Neuromuscular Blocker	2	2	100.0	1.353	1.261-1.450	<.0001
Phytosteroid	0	1	0.0	—	—	—
Progestogen	12	17	70.6	3.572	3.533-3.610	<.0001
Steroid (General)	1	1	100.0	2.375	2.153-2.618	<.0001
Steroid Antibiotic	1	1	100.0	1.198	1.051-1.365	0.0092
Steroid Aromatase Inhibitor	1	1	100.0	1.525	1.442-1.611	<.0001
Sterol	1	1	100.0	1.536	1.336-1.765	<.0001

2.4. Principal Component Analysis

We performed a principal component analysis (Figure 3). According to the results, the contribution rates of principal components 1, 2, and 3 were 34.0%, 13.7%, and 8.54%, respectively. Component 1 is considered to be associated with the estimated risk of thrombosis onset because all the loading vectors of thrombosis-related terms were in a positive direction. For component 2, pulmonary embolism, deep vein thrombosis, and superficial vein thrombosis had high positive loading vectors. Adverse events whose vectors loaded highly in a negative direction included coronary artery bypass, arterial occlusive disease, and peripheral arterial occlusive disease. Thus, higher values of principal component 2 were associated with a tendency toward venous thrombosis. The relationship between principal component 2 and thrombosis-related terms was analyzed at the Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ) level (Figure 4); SMQs are systematically grouped MedDRA terms related to specific medical areas of interest and are used to comprehensively and efficiently extract and analyze terms for safety evaluations and adverse event analyses. Drugs classified under the SMQ for “arterial embolism and thrombosis” had low values for principal component 2, whereas those under “venous embolism and thrombosis” had high values. With regard to principal component 3, loading vectors in the positive direction included those for transient ischemic attack, stroke, myocardial infarction, hemorrhagic stroke, and coronary artery occlusion. In contrast, loading vectors in the negative direction included those for disseminated intravascular coagulation, thrombotic microangiopathy, and heparin-induced thrombocytopenia.

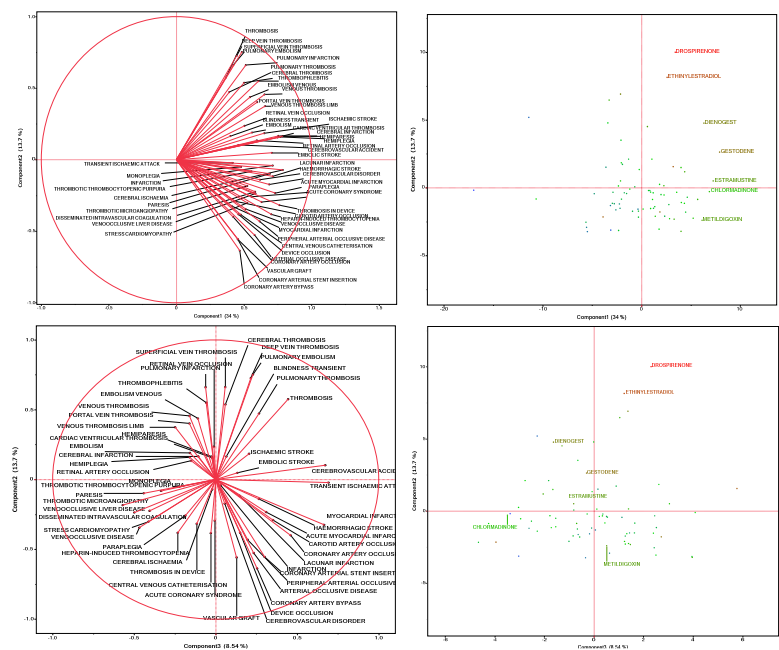


Figure 3. Relationships of thromboses with steroids according to principal components analysis. (a) and (b) Results for components 1 (physiological functions) and 2 (receptor specificity). (c) and (d) Results for components 2 and 3 (Anatomic Therapeutic Chemical classification). Loading plots (a) and (c) represent the association between adverse events related to thromboses and each principal component. Each loading vector represents an adverse effect. Score plots (b) and (d) represent the relationship between steroids and each principal component. Each dot refers to a specific steroid drug.

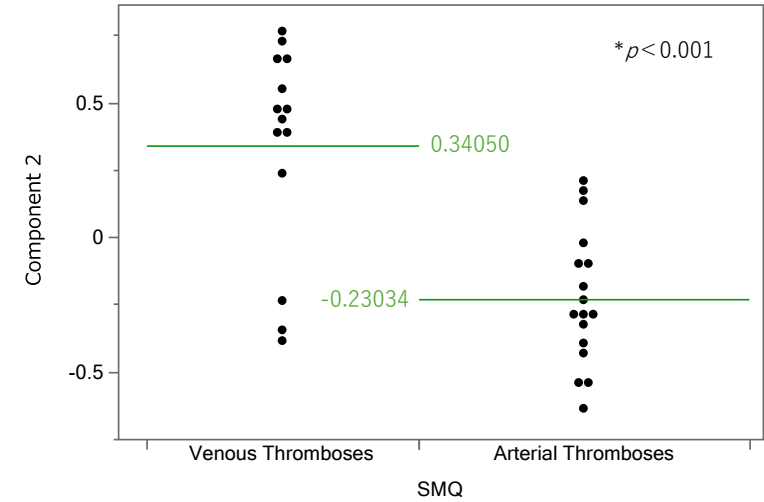


Figure 4. The relationship between component 2 and each steroid at the level of the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ). Cases classified as “Thromboses of unspecified or mixed vessels” were excluded. The average values of principal component 2 for each SMQ were 0.3050 for “Venous embolism and thrombosis” and −0.23034 for “Arterial embolism and thrombosis.” *Welch’s *t* test was performed to assess the statistical significance of the difference.

2.5. Hierarchical Cluster Analysis

Hierarchical cluster analysis performed with principal components 1, 2, and 3 (see section 2.4) resulted in the classification of drugs into four broad clusters (Figure 5). Drugs with high values for principal component 1 included sex hormone preparations found across clusters, as well as digoxin, digitoxin, and methyl digoxin in cluster 4. Cluster 3 was characterized by drugs with high values for

principal component 2, whereas drugs with high values for principal component 3 were included primarily in cluster 4. On the basis of the results of the cluster analysis, we created a constellation dendrogram to visualize the relationship between drugs and adverse events (Figure 6).

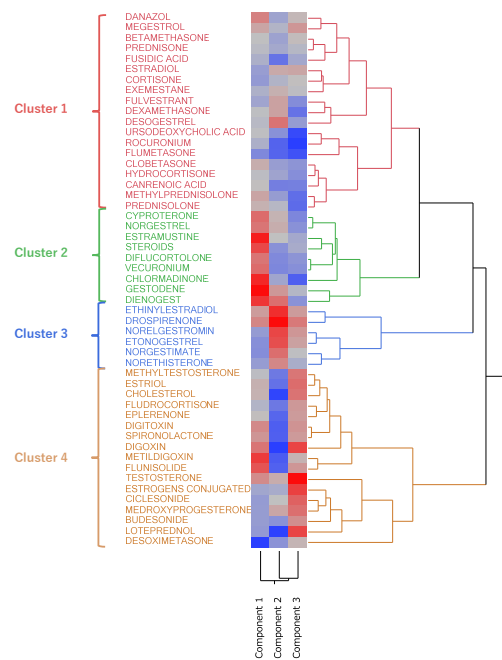


Figure 5. Results of hierarchical cluster analysis, depicting the relationship between 52 side effects related to thromboses and 51 steroids. In the color map, the redder the color, the higher the value of each principal component, and the bluer the color, the lower the value.

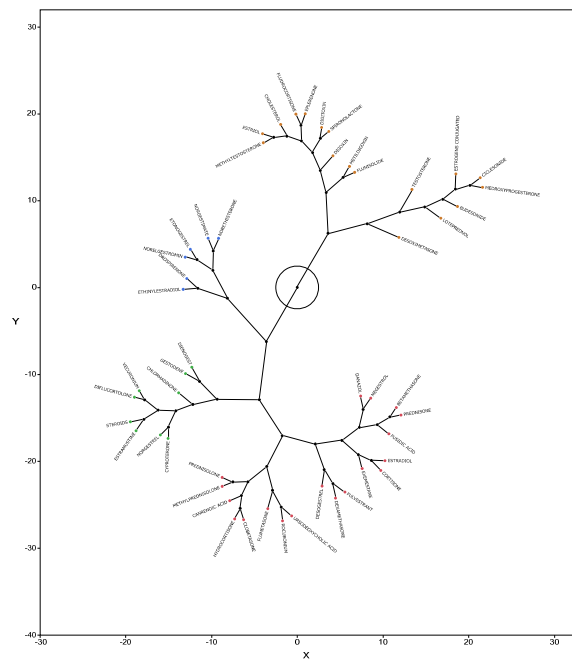


Figure 6. Constellation dendrogram. The figure, enabling a visual understanding of the results of the cluster analysis. Dots indicate individual data lines, and line lengths indicate relative distances to clusters.

3. Discussion

3.1. Classification of Steroid Drugs with High Thrombogenic Potential

In this study, 51 steroid drugs showed statistically significant associations with thrombosis (those for which the natural logarithm of the ROR > 0 and $p < 0.05$). These 51 drugs were categorized into 15 therapeutic groups according to the ATC classification. Of these groups, the androgen class exhibited the highest thrombogenic potential (ROR = 5.305, $p < 0.001$), followed by progestogens (ROR = 3.572) and estrogens (ROR = 3.227). These results suggest that sex hormone preparations, in particular, have a strong tendency to induce thrombosis. Previous studies have also confirmed an increased risk of venous thromboembolism with testosterone therapy, attributed to enhanced thrombogenesis and reduced fibrinolysis [20]. Moreover, results of a meta-analysis of Dutch cohort and case-control studies of the use of oral contraceptives suggest a thrombogenic risk associated with female hormone preparations [21]. Our findings are consistent with this previous evidence; thus, clinicians must carefully consider the risk of thrombosis when administering steroid drugs related to sex hormones, and preventive measures and monitoring must be implemented when necessary. Unlike previous studies that focused on specific steroid drugs, the novelty of our research lies in our use of the large-scale FAERS database, which enabled a comprehensive analysis of the entire spectrum of steroid drugs. This approach allowed us to identify associations between thrombosis and steroid drugs that had not been sufficiently studied before, such as cardiac glycosides (e.g., digoxin) and anabolic steroids.

3.2. Principal Component Analysis

Principal component analysis is a technique used to reduce the dimensionality of a dataset, enhancing interpretability while minimizing information loss [22]. In this study, principal component 1 represented the estimated risk of thrombosis onset; principal component 2 represented the type of thrombosis, with a positive correlation with venous thrombosis and a negative correlation with arterial thrombosis. This finding suggests that the vectors for drugs associated with venous thrombosis are loaded in the positive direction, whereas those associated with arterial thrombosis are loaded in the negative direction. Principal component 3 appears to correspond to occlusive events in major vessels of vital organs in the positive direction and to microvascular-level thrombosis in the negative direction. On the basis of this hypothesis, score plots were examined. Drugs strongly associated with principal component 1, and thus with high potential for inducing thrombosis in general, included gestodene, estramustine, and chlormadinone. Drugs such as drospirenone, ethinylestradiol, and norelgestromin were strongly and positively associated with principal component 2, which indicated a high potential for inducing venous thrombosis. In addition, loteprednol, digoxin, and obeticholic acid were estimated to have high potential for inducing arterial thrombosis. A strong association with principal component 3, which characterized testosterone, conjugated estrogens, and digoxin, suggested a potential to cause occlusion of major vessels in vital organs. Previous studies have also indicated that digoxin and testosterone are associated with cardiac events and an increased risk of arteriosclerosis [23]. Conversely, drugs such as rocuronium, ursodeoxycholic acid, and flumethasone were estimated to be more likely to induce microvascular thrombosis. These findings are expected to be useful in monitoring thrombosis according to the type of steroid drug administered to patients.

3.3. Cluster Analysis

Hierarchical cluster analysis is a method used to group and classify similar data [24]. As a result of our analysis, the drugs were classified into four clusters (Figures 5 and 6), and the drugs included in each cluster are listed in Table 3. Cluster 2 contained drugs with high values for principal component 1. All drugs in cluster 3 and some in other clusters had high values for principal component 2. These drugs included drospirenone, ethinylestradiol, and etonogestrel, most of which were sex hormone preparations, particularly progestogens or estrogens. This suggests that female

hormone preparations have potential for inducing venous thrombosis. Cluster 4 showed a strong correlation with principal component 3 and included drugs such as testosterone, digoxin, and loteprednol. These drugs are used in the treatment of diseases in major organs and include cardiovascular medications and mineralocorticoids.

Table 3. Drug Clusters.

Cluster 1		Cluster 2		Cluster 3		Cluster 4	
DANAZOL	Androgen	CYPROTERONE	Antiandrogen	ETHINYLESTRADIOL	Estrogen	METHYLTESTOSTERONE	Androgen
FULVESTRANT	Anti-estrogen	ESTRAMUSTINE	Estrogen	NORELGESTROMIN		TESTOSTERONE	
URSODEOXYCHOLIC ACID	Bile Acid	DIFLUCORTOLONE	Glucocorticoid	NORGESTIMATE		DIGITOXIN	
ESTRADIOL	Estrogen	VECURONIUM	Non-steroidal Neuromuscular Blocker	DROSPIRENONE	Progestogen	DIGOXIN	Cardiac Glycoside
BETAMETHASONE		GESTODENE		ETONOGESTREL		METILDIGOXIN	
CLOBETASONE		NORGESTREL	Progestogen	NORETHISTERONE		ESTRIOL	Estrogen
DEXAMETHASONE		CHLORMADINONE				ESTROGENS CONJUGATED	
FLUMETASONE		DIENOGEST				BUDESONIDE	
METHYLPREDNISOLONE	Glucocorticoid	STEROIDS	Steroid (General)			DESOXIMETASONE	Glucocorticoid
CORTISONE						CICLESONIDE	
HYDROCORTISONE						FLUNISOLIDE	
PREDNISOLONE						LOTEPREDNOL	
PREDNISONE						FLUDROCORTISONE	Mineralocorticoid
CANRENOIC ACID	Mineralocorticoid Receptor Antagonist					EPLERENONE	Mineralocorticoid Receptor Antagonist
ROCURONIUM	Non-steroidal Neuromuscular Blocker					SPIRONOLACTONE	
DESOGESTREL	Progestogen					MEDROXYPROGESTERONE	Progestogen
MEGESTROL						CHOLESTEROL	Sterol
FUSIDIC ACID	Steroid Antibiotic						
EXEMESTANE	Steroid Aromatase Inhibitor						

3.4. Study Limitations

This study had several limitations. First, the FAERS database contains reports of spontaneous adverse events; it does not provide information about all patients who were administered the drugs, and thus the true incidence of adverse events cannot be calculated, and absolute risk assessments cannot be performed. Furthermore, spontaneous reports of adverse events are subject to reporting bias, including underreporting, overreporting, and misreporting. This bias could have affected our analyses of FAERS data. Second, some values may be missing from the FAERS database, and some included reports may be inaccurate. To address this, we excluded data suspected to be missing or erroneous in the age and gender data tables. Third, the number of drugs analyzed was limited by the number of reported cases. Information not considered in this analysis—such as patients’ underlying diseases, concomitant drug use (presence, type, and number), and methods and duration of drug administration—could have affected the manifestation of adverse events. In particular, when multiple drugs are administered, determining which drug caused the adverse event may be difficult [25]. Further research is expected to yield insights that take these confounding factors into account.

4. Materials and Methods

4.1. FAERS Database

FAERS is a large-scale database consisting of case reports. The FAERS comprises seven data tables: DEMO, which contains patient information such as age, sex, and weight; DRUG, which includes drug information; REAC, which contains information on reported adverse events; OUTC, which contains descriptions of clinical outcomes; RPSR, which provides the information sources; INDI, which contains data on drug indications; and THER, which includes details about therapy dates and treatment progress. In this analysis, the DRUG and REAC tables were integrated on the basis of a unique identifier. This allowed for the creation of a unified dataset (the informal table described in section 2.1) in which each record corresponded to a specific drug and adverse event. To avoid overestimation in case-based aggregation, duplicate cases based on the same unique identifier were excluded. To accurately assess the effects and adverse events of individual drugs, we excluded records of cases involving combination therapies, focusing only on groups in which the target drug was used alone. For this study, we utilized FAERS data from the first quarter of 2004 (January–March) through the third quarter of 2024 (July–September). Because the data were open access and anonymized, this study was exempt from ethical review and informed consent by the Meiji Pharmaceutical University Ethics Committee.

4.2. Selection of Target Drugs and Control of Adverse Events

To obtain Simplified Molecular Input Line Entry System (SMILES) representations of drug names listed in FAERS, we used the Python library PubChem Py [26] to search the PubChem database. Of the 5523 drugs in FAERS that were assigned SMILES representations, 233 drugs containing a steroid backbone were extracted and analyzed (Table 4) 1. The following SMILES Arbitrary Target Specification (SMARTS) expression for the steroid backbone was used in the analysis:

“[#6]~1~[#6]~2~[#6]~3~[#6]~4~[#6]~5~[#6]~6~[#6]~7~[#6]~8~[#6]~9~[#6]~10~11~12~13~14~15~16~17~18~19~20~21~22~23~24~25~26~27~28~29~30~31~32~33~34~35~36~37~38~39~40~41~42~43~44~45~46~47~48~49~50~51~52~53~54~55~56~57~58~59~60~61~62~63~64~65~66~67~68~69~70~71~72~73~74~75~76~77~78~79~80~81~82~83~84~85~86~87~88~89~90~91~92~93~94~95~96~97~98~99~100~101~102~103~104~105~106~107~108~109~110~111~112~113~114~115~116~117~118~119~120~121~122~123~124~125~126~127~128~129~130~131~132~133~134~135~136~137~138~139~140~141~142~143~144~145~146~147~148~149~150~151~152~153~154~155~156~157~158~159~160~161~162~163~164~165~166~167~168~169~170~171~172~173~174~175~176~177~178~179~180~181~182~183~184~185~186~187~188~189~190~191~192~193~194~195~196~197~198~199~200~201~202~203~204~205~206~207~208~209~210~211~212~213~214~215~216~217~218~219~220~221~222~223~224~225~226~227~228~229~230~231~232~233~234~235~236~237~238~239~240~241~242~243~244~245~246~247~248~249~250~251~252~253~254~255~256~257~258~259~260~261~262~263~264~265~266~267~268~269~270~271~272~273~274~275~276~277~278~279~280~281~282~283~284~285~286~287~288~289~290~291~292~293~294~295~296~297~298~299~300~301~302~303~304~305~306~307~308~309~310~311~312~313~314~315~316~317~318~319~320~321~322~323~324~325~326~327~328~329~330~331~332~333~334~335~336~337~338~339~340~341~342~343~344~345~346~347~348~349~350~351~352~353~354~355~356~357~358~359~360~361~362~363~364~365~366~367~368~369~370~371~372~373~374~375~376~377~378~379~380~381~382~383~384~385~386~387~388~389~390~391~392~393~394~395~396~397~398~399~400~401~402~403~404~405~406~407~408~409~410~411~412~413~414~415~416~417~418~419~420~421~422~423~424~425~426~427~428~429~430~431~432~433~434~435~436~437~438~439~440~441~442~443~444~445~446~447~448~449~450~451~452~453~454~455~456~457~458~459~460~461~462~463~464~465~466~467~468~469~470~471~472~473~474~475~476~477~478~479~480~481~482~483~484~485~486~487~488~489~490~491~492~493~494~495~496~497~498~499~500~501~502~503~504~505~506~507~508~509~510~511~512~513~514~515~516~517~518~519~520~521~522~523~524~525~526~527~528~529~530~531~532~533~534~535~536~537~538~539~540~541~542~543~544~545~546~547~548~549~550~551~552~553~554~555~556~557~558~559~560~561~562~563~564~565~566~567~568~569~570~571~572~573~574~575~576~577~578~579~580~581~582~583~584~585~586~587~588~589~590~591~592~593~594~595~596~597~598~599~600~601~602~603~604~605~606~607~608~609~610~611~612~613~614~615~616~617~618~619~620~621~622~623~624~625~626~627~628~629~630~631~632~633~634~635~636~637~638~639~640~641~642~643~644~645~646~647~648~649~650~651~652~653~654~655~656~657~658~659~660~661~662~663~664~665~666~667~668~669~670~671~672~673~674~675~676~677~678~679~680~681~682~683~684~685~686~687~688~689~690~691~692~693~694~695~696~697~698~699~700~701~702~703~704~705~706~707~708~709~710~711~712~713~714~715~716~717~718~719~720~721~722~723~724~725~726~727~728~729~730~731~732~733~734~735~736~737~738~739~740~741~742~743~744~745~746~747~748~749~750~751~752~753~754~755~756~757~758~759~760~761~762~763~764~765~766~767~768~769~770~771~772~773~774~775~776~777~778~779~780~781~782~783~784~785~786~787~788~789~790~791~792~793~794~795~796~797~798~799~800~801~802~803~804~805~806~807~808~809~810~811~812~813~814~815~816~817~818~819~820~821~822~823~824~825~826~827~828~829~830~831~832~833~834~835~836~837~838~839~840~841~842~843~844~845~846~847~848~849~850~851~852~853~854~855~856~857~858~859~860~861~862~863~864~865~866~867~868~869~870~871~872~873~874~875~876~877~878~879~880~881~882~883~884~885~886~887~888~889~890~891~892~893~894~895~896~897~898~899~900~901~902~903~904~905~906~907~908~909~910~911~912~913~914~915~916~917~918~919~920~921~922~923~924~925~926~927~928~929~930~931~932~933~934~935~936~937~938~939~940~941~942~943~944~945~946~947~948~949~950~951~952~953~954~955~956~957~958~959~960~961~962~963~964~965~966~967~968~969~970~971~972~973~974~975~976~977~978~979~980~981~982~983~984~985~986~987~988~989~990~991~992~993~994~995~996~997~998~999~1000~1001~1002~1003~1004~1005~1006~1007~1008~1009~1010~1011~1012~1013~1014~1015~1016~1017~1018~1019~1020~1021~1022~1023~1024~1025~1026~1027~1028~1029~1030~1031~1032~1033~1034~1035~1036~1037~1038~1039~1040~1041~1042~1043~1044~1045~1046~1047~1048~1049~1050~1051~1052~1053~1054~1055~1056~1057~1058~1059~1060~1061~1062~1063~1064~1065~1066~1067~1068~1069~1070~1071~1072~1073~1074~1075~1076~1077~1078~1079~1080~1081~1082~1083~1084~1085~1086~1087~1088~1089~1090~1091~1092~1093~1094~1095~1096~1097~1098~1099~1100~1101~1102~1103~1104~1105~1106~1107~1108~1109~1110~1111~1112~1113~1114~1115~1116~1117~1118~1119~1120~1121~1122~1123~1124~1125~1126~1127~1128~1129~1130~1131~1132~1133~1134~1135~1136~1137~1138~1139~1140~1141~1142~1143~1144~1145~1146~1147~1148~1149~1150~1151~1152~1153~1154~1155~1156~1157~1158~1159~1160~1161~1162~1163~1164~1165~1166~1167~1168~1169~1170~1171~1172~1173~1174~1175~1176~1177~1178~1179~1180~1181~1182~1183~1184~1185~1186~1187~1188~1189~1190~1191~1192~1193~1194~1195~1196~1197~1198~1199~1200~1201~1202~1203~1204~1205~1206~1207~1208~1209~1210~1211~1212~1213~1214~1215~1216~1217~1218~1219~1220~1221~1222~1223~1224~1225~1226~1227~1228~1229~1230~1231~1232~1233~1234~1235~1236~1237~1238~1239~1240~1241~1242~1243~1244~1245~1246~1247~1248~1249~1250~1251~1252~1253~1254~1255~1256~1257~1258~1259~1260~1261~1262~1263~1264~1265~1266~1267~1268~1269~1270~1271~1272~1273~1274~1275~1276~1277~1278~1279~1280~1281~1282~1283~1284~1285~1286~1287~1288~1289~1290~1291~1292~1293~1294~1295~1296~1297~1298~1299~1300~1301~1302~1303~1304~1305~1306~1307~1308~1309~1310~1311~1312~1313~1314~1315~1316~1317~1318~1319~1320~1321~1322~1323~1324~1325~1326~1327~1328~1329~1330~1331~1332~1333~1334~1335~1336~1337~1338~1339~1340~1341~1342~1343~1344~1345~1346~1347~1348~1349~1350~1351~1352~1353~1354~1355~1356~1357~1358~1359~1360~1361~1362~1363~1364~1365~1366~1367~1368~1369~1370~1371~1372~1373~1374~1375~1376~1377~1378~1379~1380~1381~1382~1383~1384~1385~1386~1387~1388~1389~1390~1391~1392~1393~1394~1395~1396~1397~1398~1399~1400~1401~1402~1403~1404~1405~1406~1407~1408~1409~1410~1411~1412~1413~1414~1415~1416~1417~1418~1419~1420~1421~1422~1423~1424~1425~1426~1427~1428~1429~1430~1431~1432~1433~1434~1435~1436~1437~1438~1439~1440~1441~1442~1443~1444~1445~1446~1447~1448~1449~1450~1451~1452~1453~1454~1455~1456~1457~1458~1459~1460~1461~1462~1463~1464~1465~1466~1467~1468~1469~1470~1471~1472~1473~1474~1475~1476~1477~1478~1479~1480~1481~1482~1483~1484~1485~1486~1487~1488~1489~1490~1491~1492~1493~1494~1495~1496~1497~1498~1499~1500~1501~1502~1503~1504~1505~1506~1507~1508~1509~1510~1511~1512~1513~1514~1515~1516~1517~1518~1519~1520~1521~1522~1523~1524~1525~1526~1527~1528~1529~1530~1531~1532~1533~1534~1535~1536~1537~1538~1539~1540~1541~1542~1543~1544~1545~1546~1547~1548~1549~1550~1551~1552~1553~1554~1555~1556~1557~1558~1559~1560~1561~1562~1563~1564~1565~1566~1567~1568~1569~1570~1571~1572~1573~1574~1575~1576~1577~1578~1579~1580~1581~1582~1583~1584~1585~1586~1587~1588~1589~1590~1591~1592~1593~1594~1595~1596~1597~1598~1599~1600~1601~1602~1603~1604~1605~1606~1607~1608~1609~1610~1611~1612~1613~1614~1615~1616~1617~1618~1619~1620~1621~1622~1623~1624~1625~1626~1627~1628~1629~1630~1631~1632~1633~1634~1635~1636~1637~1638~1639~1640~1641~1642~1643~1644~1645~1646~1647~1648~1649~1650~1651~1652~1653~1654~1655~1656~1657~1658~1659~1660~1661~1662~1663~1664~1665~1666~1667~1668~1669~1670~1671~1672~1673~1674~1675~1676~1677~1678~1679~1680~1681~1682~1683~1684~1685~1686~1687~1688~1689~1690~1691~1692~1693~1694~1695~1696~1697~1698~1699~1700~1701~1702~1703~1704~1705~1706~1707~1708~1709~1710~1711~1712~1713~1714~1715~1716~1717~1718~1719~1720~1721~1722~1723~1724~1725~1726~1727~1728~1729~1730~1731~1732~1733~1734~1735~1736~1737~1738~1739~1740~1741~1742~1743~1744~1745~1746~1747~1748~1749~1750~1751~1752~1753~1754~1755~1756~1757~1758~1759~1760~1761~1762~1763~1764~1765~1766~1767~1768~1769~1770~1771~1772~1773~1774~1775~1776~1777~1778~1779~1780~1781~1782~1783~1784~1785~1786~1787~1788~1789~1790~1791~1792~1793~1794~1795~1796~1797~1798~1799~1800~1801~1802~1803~1804~1805~1806~1807~1808~1809~1810~1811~1812~1813~1814~1815~1816~1817~1818~1819~1820~1821~1822~1823~1824~1825~1826~1827~1828~1829~1830~1831~1832~1833~1834~1835~1836~1837~1838~1839~1840~1841~1842~1843~1844~1845~1846~1847~1848~1849~1850~1851~1852~1853~1854~1855~1856~1857~1858~1859~1860~1861~1862~1863~1864~1865~1866~1867~1868~1869~1870~1871~1872~1873~1874~1875~1876~1877~1878~1879~1880~1881~1882~1883~1884~1885~1886~1887~1888~1889~1890~1891~1892~1893~1894~1895~1896~1897~1898~1899~1900~1901~1902~1903~1904~1905~1906~1907~1908~1909~1910~1911~1912~1913~1914~1915~1916~1917~1918~1919~1920~1921~1922~1923~1924~1925~1926~1927~1928~1929~1930~1931~1932~1933~1934~1935~1936~1937~1938~1939~1940~1941~1942~1943~1944~1945~1946~1947~1948~1949~1950~1951~1952~1953~1954~1955~1956~1957~1958~1959~1960~1961~1962~1963~1964~1965~1966~1967~1968~1969~1970~1971~1972~1973~1974~1975~1976~1977~1978~1979~1980~1981~1982~1983~1984~1985~1986~1987~1988~1989~1990~1991~1992~1993~1994~1995~1996~1997~1998~1999~2000~2001~2002~2003~2004~2005~2006~2007~2008~2009~2010~2011~2012~2013~2014~2015~2016~2017~2018~2019~2020~2021~2022~2023~2024~2025~2026~2027~2028~2029~2030~2031~2032~2033~2034~2035~2036~2037~2038~2039~2040~2041~2042~2043~2044~2045~2046~2047~2048~2049~2050~2051~2052~2053~2054~2055~2056~2057~2058~2059~2060~2061~2062~2063~2064~2065~2066~2067~2068~2069~2070~2071~2072~2073~2074~2075~2076~2077~2078~2079~2080~2081~2082~2083~2084~2085~2086~2087~2088~2089~2090~2091~2092~2093~2094~2095~2096~2097~2098~2099~2100~2101~2102~2103~2104~2105~2106~2107~2108~2109~2110~2111~2112~2113~2114~2115~2116~2117~2118~2119~2120~2121~2122~2123~2124~2125~2126~2127~2128~2129~2130~2131~2132~2133~2134~2135~2136~2137~2138~2139~2140~2141~2142~2143~2144~2145~2146~2147~2148~2149~2150~2151~2152~2153~2154~2155~2156~2157~2158~2159~2160~2161~2162~2163~2164~2165~2166~2167~2168~2169~2170~2171~2172~2173~2174~2175~2176~2177~2178~2179~2180~2181~2182~2183~2184~2185~2186~2187~2188~2189~2190~2191~2192~2193~2194~2195~2196~2197~2198~2199~2200~2201~2202~2203~2204~2205~2206~2207~2208~2209~2210~2211~2212~2213~2214~2215~2216~2217~2218~2219~2220~2221~2222~2223~2224~2225~2226~2227~2228~2229~2230~2231~2232~2233~2234~2235~2236~2237~2238~2239~2240~2241~2242~2243~2244~2245~2246~2247~2248~2249~2250~2251~2252~2253~2254~2255~2256~2257~2258~2259~2260~2261~2262~2263~2264~2265~2266~2267~2268~2269~2270~2271~2272~2273~2274~2275~2276~2277~2278~2279~2280~2281~2282~2283~2284~2285~2286~2287~2288~2289~2290~2291~2292~2293~2294~2295~2296~2297~2298~2299~2300~2301~2302~2303~2304~2305~2306~2307~2308~2309~2310~2311~2312~2313~2314~2315~2316~2317~2318~2319~2320~2321~2322~2323~2324~2325~2326~2327~2328~2329~2330~2331~2332~2333~2334~2335~2336~2337~2338~2339~2340~2341~2342~2343~2344~2345~2346~2347~2348~2349~2350~2351~2352~2353~2354~2355~2356~2357~2358~2359~2360~2361~2362~2363~2364~2365~2366~2367~2368~2369~2370~2371~2372~2373~2374~2375~2376~2377~2378~2379~2380~2381~2382~2383~2384~2385~2386~2387~2388~2389~2390~2391~2392~2393~2394~2395~2396~2397~2398~2399~2400~2401~2402~2403~2404~2405~2406~2407~2408~2409~2410~2411~2412~2413~2414~2415~2416~2417~2418~2419~2420~2421~2422~2423~2424~2425~2426~2427~2428~2429~2430~2431~2432~2433~2434~2435~2436~2437~2438~2439~2440~2441~2442~2443~2444~2445~2446~2447~2448~2449~2450~2451~2452~2453~2454~2455~2456~2457~2458~2459~2460~2461~2462~2463~2464~2465~2466~2467~2468~2469~2470~2471~2472~2473~2474~2475~2476~2477~2478~2479~2480~2481~2482~2483~2484~2485~2486~2487~2488~2489~2490~2491~2492~2493~2494~2495~2496~2497~2498~2499~2500~2501~2502~2503~2504~2505~2506~2507~2508~2509~2510~2511~2512~2513~2514~2515~2516~2517~2518~2519~2520~2521~2522~2523~2524~2525~2526~2527~2528~2529~2530~2531~2532~2533~2534~2535~2536~2537~2538~2539~2540~2541~2542~2543~2544~2545~2546~2547~2548~2549~2550~2551~2552~2553~2554~2555~2556~2557~2558~2559~2560~2561~2562~2563~2564~2565~2566~2567~2568~2569~2570~2571~2572~2573~2574~2575~2576~2577~2578~2579~2580~2581~2582~2583~2584~2585~2586~2587~2588~2589~2590~2591~2592~2593~2594~2595~2596~2597~2598~2599~2600~2601~2602~2603~2604~2605~2606~2607~2608~2609~2610~2611~2612~2613~2614~2615~2616~2617~2618~2619~2620~2621~2622~2623~2624

Table 6. Drugs for analysis.

ABIRATERONE	DEXAMETHASONE	FLUMETASONE	MOMETASONE
BECLOMETASONE	DENOGEST	FLUNISOLIDE	NORELGESTROMIN
BETAMETHASONE	DIFLUCORTOLONE	FLUOCINOLONE ACETONIDE	NORETHISTERONE
BUDESONIDE	DIFLUPREDNATE	FLUOCINONIDE	NORGESTIMATE
CANRENOIC ACID	DIGITOXIN	FLUOROMETHOLONE	NORGESTREL
CHLORMADINONE	DIGOXIN	FLUTICASONE	OBETICHOIC ACID
CHOLESTEROL	DROSPIRENONE	FULVESTRANT	PRASTERONE
CICLESONIDE	DYDROGESTERONE	FUSIDIC ACID	PREDNISOLONE
CLOBETASOL	EPLERENONE	GESTODENE	PREDNISONE
CLOBETASONE	ESTRADIOL	HYDROCORTISONE	PROGESTERONE
COLLAGENASE	ESTRAMUSTINE	HYDROXYPROGESTERONE	ROCURNIUM
CORTISONE	ESTRIOL	LEVONORGESTREL	SPIRONOLACTONE
CYPROTERONE	ESTROGENS	LOTEPREDNOL	STEROIDS
DANAZOL	ESTROGENS CONJUGATED	MEDROXYPROGESTERONE	TESTOSTERONE
DEFLAZACORT	ESTROPATE	MEGESTROL	TIBOLONE
DEOXYCHOLIC ACID	ETHINYLESTRADIOL	METHYLPREDNISOLONE	TRIAMCINOLONE
DESOGESTREL	ETONOGESTREL	METHYLTESTOSTERONE	ULOBETASOL
DESONIDE	EXEMESTANE	METILDIGOXIN	URSODEOXYCHOLIC ACID
DESOXIMETASONE	FLUDROCORTISONE	MIFEPRISTONE	VECURONIUM
			WITHANIA SOMNIFERA

Table 7. Preferred terms for analysis.

PT		
ACUTE CORONARY SYNDROME	EMBOLIC STROKE	PULMONARY INFARCTION
ACUTE MYOCARDIAL INFARCTION	EMBOLISM	PULMONARY THROMBOSIS
ARTERIAL OCCLUSIVE DISEASE	EMBOLISM VENOUS	RETINAL ARTERY OCCLUSION
BLINDNESS TRANSIENT	HAEMORRHAGIC STROKE	RETINAL VEIN OCCLUSION
CARDIAC VENTRICULAR THROMBOSIS	HEMIPARESIS	STRESS CARDIOMYOPATHY
CAROTID ARTERY OCCLUSION	HEMIPLEGIA	SUPERFICIAL VEIN THROMBOSIS
CENTRAL VENOUS CATHETERISATION	HEPARIN-INDUCED THROMBOCYTOPENIA	THROMBOPHLEBITIS
CEREBRAL INFARCTION	INFARCTION	THROMBOSIS
CEREBRAL ISCHAEMIA	ISCHAEMIC STROKE	THROMBOSIS IN DEVICE
CEREBRAL THROMBOSIS	LACUNAR INFARCTION	THROMBOTIC MICROANGIOPATHY
CEREBROVASCULAR ACCIDENT	MONOPLÉGIA	THROMBOTIC THROMBOCYTOPENIC PURPURA
CEREBROVASCULAR DISORDER	MYOCARDIAL INFARCTION	TRANSIENT ISCHAEMIC ATTACK
CORONARY ARTERIAL STENT INSERTION	PARAPLEGIA	VASCULAR GRAFT
CORONARY ARTERY BYPASS	PARESIS	VENOOCCLUSIVE DISEASE
CORONARY ARTERY OCCLUSION	PERIPHERAL ARTERIAL OCCLUSIVE DISEASE	VENOOCCLUSIVE LIVER DISEASE
DEEP VEIN THROMBOSIS	PORTAL VEIN THROMBOSIS	VENOUS THROMBOSIS
DEVICE OCCLUSION	PULMONARY EMBOLISM	VENOUS THROMBOSIS LIMB
DISSEMINATED INTRAVASCULAR COAGULATION		

4.5. Classification of Steroid Drugs with High Potential for Inducing Thrombosis

The analyzed drugs were classified into 18 categories based on physiological function, receptor specificity, and ATC classification (Table 8). We calculated the proportion of steroid drugs within each category that were likely to induce thrombosis.

Table 8. The classification of steroids.

Steroid Classification	
Androgen	Mineralocorticoid
Antiandrogen	Mineralocorticoid Receptor Antagonist
Antiestrogen	Non-steroidal Neuromuscular Blocker
Antiprogesterone	Phytosteroid
Bile Acid	Progestogen
Cardiac Glycoside	Steroid (General)
Enzyme	Steroid Antibiotic
Estrogen	Steroid Aromatase Inhibitor
Glucocorticoid	Sterol

4.6. Principal Component Analysis

We performed principal component analysis for the drugs listed in Table 6. (Supplementary Table S2) We then used the results focusing on principal components 1, 2, and 3 to create association diagrams.

4.7. Hierarchical Cluster Analysis

In a method similar to that for the principal component analysis, we used the aggregated table from Section 4.4 and principal components 1, 2, and 3 for the cluster analysis. The Ward method [24,37] was employed as the clustering technique.

4.8. Statistical Analysis

To merge the data tables, we used Python. To perform statistical analyses, we used JMP Pro 18 (SAS Institute Inc., Cary, NC, USA). A *p* value of less than 0.05 was considered statistically significant.

5. Conclusions

According to the results of this study, 51 steroid drugs have a high potential for inducing thrombosis. Furthermore, through principal component analysis and cluster analysis, characteristics related to venous and arterial thrombosis for each steroid drug and the tendency of onset based on their classifications were also estimated. Therefore, we achieved our objective of identifying and characterizing steroid drugs that can induce thrombosis. This research thus provides new evidence for risk assessment of steroid treatment. These findings need to be confirmed by observational studies or randomized controlled trials in the future to provide more detailed data on thrombosis-inducing steroid drugs. These insights could prove useful in selecting appropriate medications and monitoring for adverse effects in patients who receive steroid treatment.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Table S1: List of 77 steroids with Potential Risk of Inducing Thromboses Based on RORs and *p*-values; Table S2: InROR Matrix for Steroids and Thromboses.

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