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ORIGINAL RESEARCH ARTICLE

# Thromboembolic Events in Women Exposed to Hormonal Contraception or Cyproterone Acetate in 2012: A Cross-Sectional Observational Study in 30 French Public Hospitals

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**Abstract**

*Background* In the context of the European reassessment of the benefit–risk balance of hormonal contraceptives, French data about thromboembolic events were requested.

*Objective* The aim of this study was to determine the number of patients exposed to hormonal contraception or cyproterone acetate among hospitalized females diagnosed with a thromboembolic event in 2012, to retrospectively analyze specific risk factors of venous and arterial thromboembolism and to assess the magnitude of the underreporting of such events to the national pharmacovigilance system.

*Methods* This cross-sectional study included 15- to 49-year-old women with pulmonary embolism, venous cerebral thrombosis, ischemic stroke, or myocardial infarction, hospitalized in 2012, and identified within the computerized hospital databases of 30 French teaching hospitals.

**Key Points**

Apart from exposure to hormonal contraception or cyproterone acetate, age and thrombophilia were the main risk factors for venous thromboembolism; age and smoking were the main risk factors for arterial thromboembolism.

Among cases of venous thromboembolism and arterial thromboembolism, the proportion of women with no risk factors taking third- or fourth-generation combined oral contraceptives (COCs) was higher than the proportion of women with no risk factors taking first- and second-generation COCs.

It is essential to assess thromboembolic risk factors at the first prescription and renewal of hormonal contraceptives.

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*Results* Among the 2,966 cases identified, 803 (27.1 %) patients had been exposed to a hormonal contraceptive (747) or to cyproterone acetate (56). Among these, there were 452 venous thromboembolic events (VTEs) and 351 arterial thromboembolic events (ATEs). Age ≥40 years and personal thrombophilia diagnosed after the event were the main VTE risk factors, while current smoking and age ≥40 years were the main ATE risk factors. The mean number of associated risk factors was significantly lower for VTE than for ATE (1.1 vs 2.3). The proportion of cases with no risk factors was higher for third- and fourth-generation than for first- and second-generation combined oral contraceptives. Overall, the under-reporting rate was 92.5 % (95 % CI 70.0–97.3).

*Conclusion* This study highlighted the need to strengthen the knowledge of patients and health professionals about thromboembolic risk factors at the first prescription and renewal of hormonal contraceptives.

## 1 Introduction

Today, women can use different methods of hormonal contraception. Combined estrogen-progestogen and progestogen-only contraceptives are available through oral or non-oral administration routes, and with various doses of progestogen and estrogen (Table 1). In France, cyproterone acetate only (CAO) is restricted to the treatment of hirsutism, and cyproterone acetate combined with ethinylestradiol (CAEE) is restricted to the treatment of acne. In other European countries, however, CAEE is also registered as a contraceptive.

The thromboembolic risk of hormonal contraceptives has been studied since their marketing authorizations in the early 1960s [1]. The Summary of Product Characteristics (SmPCs) of all combined oral contraceptives (COCs) and cyproterone acetate drugs now clearly state the risks of venous and arterial thrombosis in the 'contraindications', 'special warnings and precautions for use' and 'adverse effects' sections. COCs are usually categorized in generations according to their progestogen (Table 1) [2]. During the past 10 years, several studies have shown a higher risk of venous thrombosis with third- and fourth-generation COCs than with first- and second-generation COCs [3–12]. The risk of arterial thromboembolism has also been identified with new progestogens used in COCs as well as with non-oral hormonal contraceptives [13, 14]. According to a recent communication of the European Pharmacovigilance Risk Assessment Committee (PRAC) released in October 2013, the estimated risk of a venous thromboembolic event (VTE) (yearly per 10,000 women) is lower with combined hormonal contraceptives (oral and non-oral) containing the progestogens levonorgestrel, norgestimate, and norethisterone (5–7 cases), higher with the progestogens etonogestrel and norelgestromin (6–12 cases), and highest with the progestogens gestodene, desogestrel, and drospirenone (9–12 cases) [15]. For comparison, in women who are not using combined hormonal contraceptives and who are not pregnant, there are around two cases of VTE yearly per 10,000 women [15]. A recent systematic review and network meta-analysis showed that the absolute risk of venous thrombosis in non-users of hormonal contraceptives reported in two studies was 1.9 and 3.7 per 10,000 women years, respectively [16]. Based on data from 15 studies, the use of COC was found to increase the risk of VTE by a factor of four. This study also showed that the risk of VTE in second-generation progestogen users was similar to that in first-generation users (relative risk 0.9, 95 % CI 0.6–1.4), while third-generation users had a slightly higher risk than second-generation users (1.3, 95 % CI 1.0–1.8) [16].

In December 2012, a French woman who had had a stroke 4 years earlier while being treated with a third-generation COC (gestodene/ethinylestradiol) sued the marketing authorization holder (MAH) and the French drug authority (Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM). This affair, followed by the report of four deaths in women using CAEE (Diane-35®), got a great deal of media attention, and in a short space of time several other women brought a lawsuit against the MAH of third- and fourth-generation COCs and CAEE. In January 2013, at the request of the ANSM, the European Medicine Agency (EMA) initiated the reassessment of the benefit–risk balance (article 31 referral) of third- and fourth-generation COCs and CAEE. In May 2013, marketing authorizations for drugs containing CAEE were suspended in France. At the same time, the French Health Ministry asked for rapidly available additional data about thromboembolic events in women receiving hormonal contraception in France. In this context, the French Network of the 31 Regional Pharmacovigilance Centres (RPVC), supported by the ANSM, devised a study in collaboration with the Medical Records Database units of their home teaching hospitals.

The primary objective of this study was to determine the number of patients exposed to hormonal contraception or cyproterone acetate among hospitalized females diagnosed with a thromboembolic event in 2012. The secondary objectives were to retrospectively analyze the individual risk factors of thromboembolic events in exposed patients and to assess the magnitude of under-reporting of these events to the national pharmacovigilance system.

## 2 Method

A cross-sectional study was conducted by 30 RPCVs (all but one) within the computerized hospital databases,

**Table 1** List of hormonal contraceptives and drugs containing cyproterone acetate available in France, 2012

| Type | Progestogen | Estrogen | Brand names[a] |
|---|---|---|---|
| Combined oral contraceptives (COCs) | | | |
| First generation | Norethisterone | EE | Triella |
| Second generation | Levonorgestrel | EE | Adepal, Amarance, Daily, Evanecia, Leelo Lovavulo, Ludeal, Minidril, Optilova, Pacilia, Trinordiol, Zikiale |
| | Norgestrel | EE | Stediril |
| Third generation | Desogestrel | EE | Cycleane, Mercilon, Desobel, Varnoline, Desogestrel/EE generics |
| | Gestodene | EE | Carlin, Edenelle, Efezial, Felixita, Harmonet, Meliane, Melodia, Minesse, Minulet, Moneva, Optinesse, Perleane, Phaeva, Sylviane, Tri-Minulet, Gestodene/EE generics |
| | Norgestimate | EE | Cilest, Effiprev, Tricilest, Triafemi |
| Fourth generation | Chlormadinone | EE | Belara |
| | Drospirenone | EE | Belanette, Convuline, Drospibel, Jasmine, Jasminelle, Yaz, Rimandia, Drospirenone/EE Generic |
| | Dienogest | Estradiol valerate | Qlaira |
| | Nomegestrol | Estradiol | Zoely |
| Non-oral combined contraceptives | | | |
| | Norelgestromine | EE | Evra (transdermal) |
| | Etonogestrel | EE | Nuvaring (vaginal ring) |
| Progestogens only | | | |
| | Levonorgestrel | | Microval |
| | Desogestrel | | Antigone, Cerazette, desogestrel generics |
| | Etonogestrel | | Implanon, Nexplanon (implants) |
| | Levonorgestrel | | Mirena (intrauterine device) |
| | Medroxy progesterone | | Depo Provera (suspension for injection) |
| Cyproterone acetate-containing drugs | | | |
| | Cyproterone acetate | EE | Cypropharm, Diane35, Evepar, Holgyeme, Lumalia, Minerva, Cyproterone Acetate/EE generics |
| | Cyproterone acetate | | Androcur, Cyproterone Acetate Generics |

*EE* ethinylestradiol

[a] Oral administration route unless otherwise stated

*Programme de Médicalisation des Systèmes d'Information* (PMSI) of their home teaching hospital.

## 2.1 Data Source

The PMSI database contains administrative data (name, gender, date of birth, dates of hospital admission and discharge, ward) and clinical data (diagnostic codes of the *International Statistical Classification of Diseases and Related Health Problems, 10th Edition* (ICD-10), medical acts and procedures). For each hospital admission, an individual discharge abstract is filled in. One principal diagnosis and up to 15 secondary diagnoses are coded. Among ICD-10 codes, the following serious thromboembolic events were selected: pulmonary embolism (ICD-10 code I26 [pulmonary embolism]), cerebral venous thrombosis (codes G08 [intracranial and intraspinal phlebitis and thrombophlebitis] and I67.6 [non-pyogenic thrombosis of the intracranial venous system]), cerebral ischemia (code I63 [cerebral infarction]) and myocardial infarction (code I21 [ST and non-ST elevation myocardial infarction]).

For each selected case, clinical data were further collected from the patients' medical files by the medical staff of the RPVCs.

## 2.2 Case Definition

All women aged 15–49 years discharged from hospital between January 1st and December 31st 2012, with at least one ICD-10 code for a thrombotic event of interest were pre-selected.

All cases of women exposed to a hormonal contraceptive or to a cyproterone-containing drug were included.

**Table 2** Venous and arterial thromboembolic risk factors selected for the study

| VTE risk factors | ATE risk factors |
|---|---|
| **Listed in 'contraindications' section of COC SmPCs** | |
| Personal history of venous thrombosis | Personal history of arterial thrombosis (including transient cerebral ischemia) |
| Personal thrombophilia known before VTE | Migraine with aura |
| | Antiphospholipid syndrome |
| **Listed in 'special warnings and precautions for use' section of COC SmPCs** | |
| Age ≥40 years | Age ≥40 years |
| Obesity (BMI ≥ 30) | Obesity (BMI ≥ 30) |
| Recent thrombogenic condition: surgery <1 month, immobilization more than 3 days | Current smoking |
| Familial history of venous thrombosis in 1st degree parents, aged under 50 years | Familial history of arterial thrombosis in 1st degree parents, aged under 50 years |
| Early post-partum period (4 weeks if normal delivery, 6 weeks if cesarean delivery) | Arterial hypertension |
| | Diabetes mellitus |
| | Dyslipidemia |
| | Lupus |
| **Others, not listed or diagnosed after the occurrence of the event** | |
| Personal thrombophilia diagnosed after the event | Personal hyperhomocysteinemia (over >50 μmol/L) |
| Active neoplasia | Foramen ovale and/or atrial septal aneurysm |
| Long journey >5 hours | Antiphospholipid syndrome diagnosed after the event |
| Concomitant drugs promoting VTE: thalidomide, antineoplastic agents, antipsychotics | Other cardiovascular abnormalities (e.g., valvulopathy, atrial septal defect) |
| | Concomitant medicines promoting ATE (e.g., vasoconstrictors) |
| | Illicit drug intake (cannabis, heroin, cocaine) |

*ATE* arterial thromboembolic event, *BMI* body mass index, *VTE* venous thromboembolic event

### 2.3 Definition of Exposure

Exposure to a hormonal contraceptive or to a drug containing cyproterone acetate was identified by consulting patients' electronic or paper-based hospital medical files. A woman was considered exposed if her hospital medical file mentioned the use of a hormonal contraceptive method or a drug containing cyproterone acetate (Table 1) at the time of or up to 1 month prior to the event. Information on hormonal contraceptives or drugs containing cyproterone acetate was obtained from the patient's hospital medical record and, when necessary, by calling her general practitioner or gynaecologist and/or pharmacist when contact details were available in the patient's file. Physicians were not contacted if no contraception was mentioned in the patient's file.

For cyproterone acetate, the indication was also collected.

### 2.4 Exclusion Criteria

Cases were excluded if the thromboembolic event mentioned in the medical file did not correspond to the inclusion ICD10 codes (i.e., deep venous thrombosis without pulmonary embolism, transient ischemic attack, cerebral trauma), if the thromboembolic event mentioned was part of the medical history of the patient, or if the hormonal treatment mentioned was neither a contraceptive nor cyproterone acetate (i.e., clomiphene, chlormadinone alone, nomegestrol alone). Pregnant women were also excluded.

### 2.5 Identification of Risk Factors

All risk factors were retrospectively identified in the medical files of selected cases.

Risk factors for venous and arterial thrombosis considered in this study are listed in Table 2. This selection was based on established risk factors [16, 17] and was validated by a specialist in thromboembolic diseases. According to the SmPCs of COCs, we classified the risk factors as 'contraindications' and 'special warnings and precautions for use', and we gathered together in a third category entitled 'not listed or diagnosed after the event' the risk factors that could not be assessed before prescription of the drug or that were revealed after the occurrence of the event.

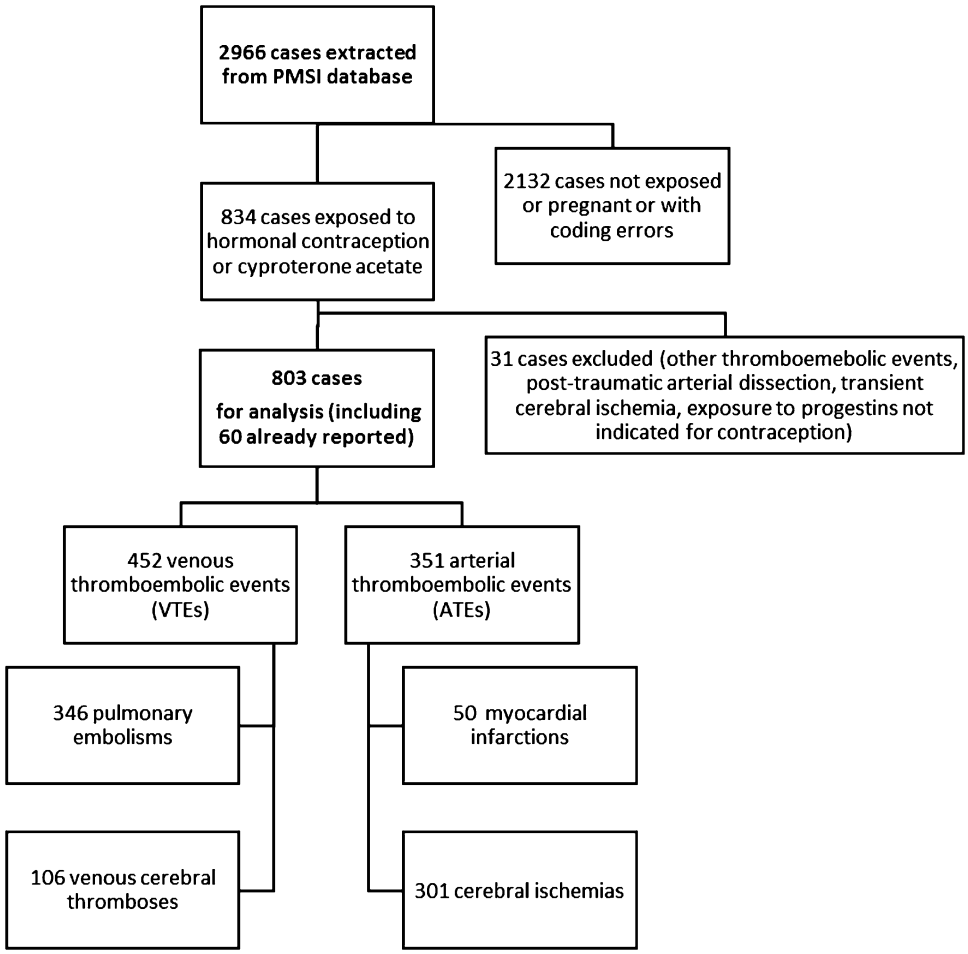


**Fig. 1** Screening, selection and distribution of cases for analysis. *PMSI Programme de Médicalisation des Systèmes d'Information* (computerized hospital databases)

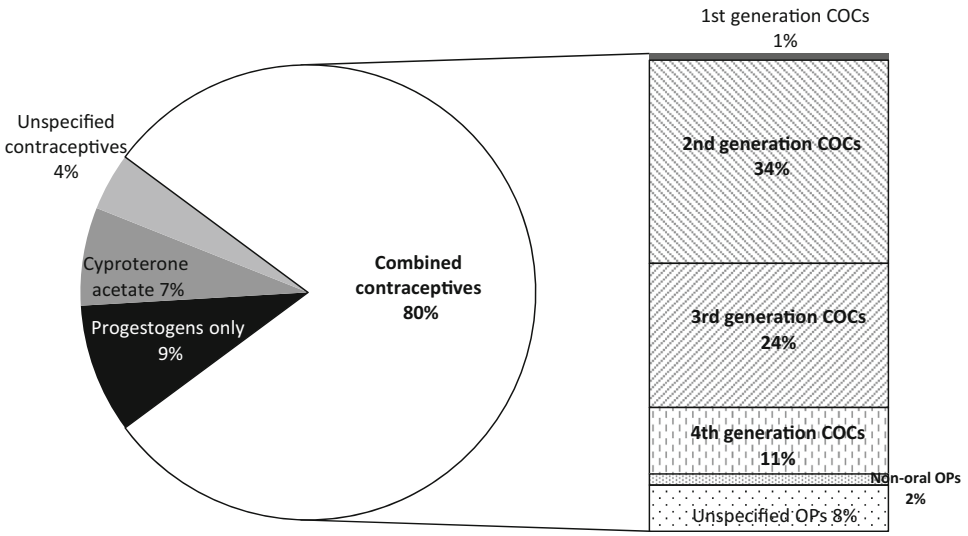


**Fig. 2** Proportion of hormonal contraceptives among the 803 cases of thromboembolic events. Combined contraceptives are split in the *vertical bar*; *COC* combined oral contraceptive, *OP* combined oestrogen and progestogen contraceptive

Smoking was defined as current smoking. This item was collected for all cases although it is not considered a risk factor for VTE and was therefore not included in the global VTE risk factor analysis.

Personal thrombophilia was defined as the presence of one or more of the following blood coagulation disorders: factor V Leiden mutation, prothrombin gene mutation, protein C and/or protein S and/or antithrombin deficiencies (≤50 %), resistance to activated protein C, antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, anti-β2 glycoprotein I).

Dyslipidemia included hypercholesterolemia and/or hypertriglyceridemia.

### 2.6 Data Analysis

All cases were recorded in the French Pharmacovigilance Database. Cases that had been spontaneously reported before the start of the study were considered duplicate cases and were updated if necessary.

Thromboembolic events were classified as venous, including pulmonary embolism and venous cerebral thrombosis, or arterial, including cerebral ischemia and myocardial infarction.

Drugs were classified according to Table 1.

Characteristics of patients (age, risk factors), thromboembolic events and drugs were described using percentages for categorical variables and means and standard deviations for continuous variables. Categorical variables were compared using the Chi-square or Student test, and Microsoft® Office Excel 2007 was used for all analyses.

**Table 3** Distribution of venous and arterial thromboembolic events according to drug exposure

| | VTE | | ATE | | Total |
|---|---|---|---|---|---|
| | PE | CVT | CI | MI | |
| All combined contraceptives | 286 | 94 | 227 | 33 | 640 |
| First- + second-generation COCs | 102 | 41 | 119 | 19 | 281 |
| First-generation COCs | 6 | 1 | 2 | 0 | 9 |
| Second-generation COCs | 96 | 40 | 117 | 19 | 272 |
| Third- + fourth-generation COCs | 153 | 44 | 78 | 7 | 282 |
| Third-generation COCs | 107 | 28 | 54 | 4 | 193 |
| Desogestrel | 66 | 15 | 20 | 0 | 101 |
| Gestodene | 37 | 11 | 29 | 3 | 80 |
| Norgestimate | 2 | 2 | 2 | 0 | 6 |
| Fourth-generation COCs | 46 | 16 | 24 | 3 | 89 |
| Drospirenone | 43 | 15 | 19 | 3 | 80 |
| Dienogest | 1 | 1 | 4 | 0 | 6 |
| Nomegestrol | 2 | 0 | 0 | 0 | 2 |
| Chlormadinone | 0 | 0 | 1 | 0 | 1 |
| Non-oral combined | 9 | 2 | 3 | 1 | 15 |
| Vaginal ring | 6 | 1 | 2 | 1 | 10 |
| Transdermal | 3 | 1 | 1 | 0 | 5 |
| Unspecified combined | 22 | 7 | 27 | 6 | 62 |
| Progestogens only | 29 | 4 | 31 | 10 | 74 |
| Oral | 21 | 3 | 16 | 7 | 47 |
| Intrauterine device | 2 | 0 | 7 | 0 | 9 |
| Implant | 5 | 1 | 5 | 2 | 13 |
| Unspecified | 1 | 0 | 3 | 1 | 5 |
| Unspecified contraceptive | 8 | 1 | 18 | 6 | 33 |
| Cyproterone acetate/EE | 21 | 6 | 23 | 1 | 51 |
| Cyproterone acetate only | 2 | 1 | 2 | 0 | 5 |

*ATE* arterial thromboembolic event, *CI* cerebral ischemia (ischemic stroke), *COC* combined oral contraceptive, *CVT* cerebral venous thrombosis, *EE* ethinylestradiol, *MI* myocardial infarction, *PE* pulmonary embolism, *VTE* venous thromboembolic event

### 2.7 Legal Authorizations

This study was authorized by the management and the medical commissions of all of the hospitals involved. This collaborative study received the support of the ANSM.

## 3 Results

### 3.1 General Description

Among the 2,966 cases of thrombotic events initially identified, 803 (27.1 %) patients were found to have been exposed to a hormonal contraceptive or to cyproterone acetate.

There were 452 VTEs and 351 arterial thromboembolic events (ATEs). Among the VTEs, there were 346 cases of pulmonary embolism (43.1 % of all events) and 106 cases of cerebral venous thrombosis (13.2 % of all events). Among ATEs, there were 301 cases of cerebral ischemia

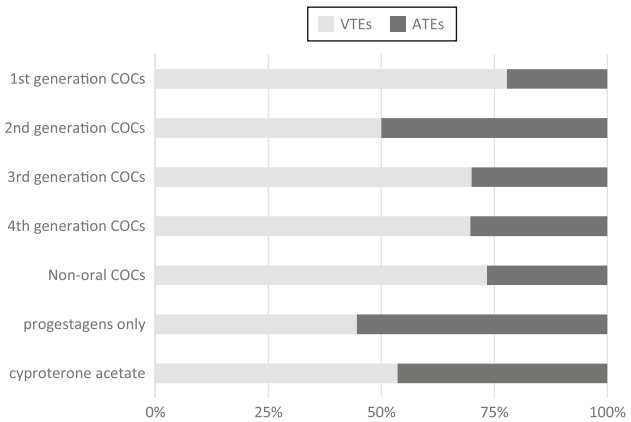


**Fig. 3** Thromboembolic profiles of hormonal contraceptives and pooled cyproterone acetate-containing drugs. *ATEs* arterial thromboembolic events (*dark grey bar*), *COCs* combined oral contraceptives, *VTEs* venous thromboembolic events (*light grey bar*). VTEs do not include deep venous thrombosis without pulmonary embolism

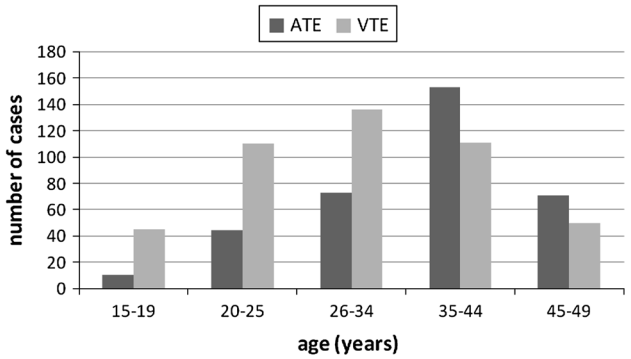


**Fig. 4** Age distribution of women with venous thromboembolic events (*VTEs*) and arterial thromboembolic events (*ATEs*)

(37.5 % of all events) and 50 cases of myocardial infarction (6.2 % of all events) (Fig. 1).

Combined contraceptive (oral and non-oral) accounted for 80 % of the drugs (Fig. 2). Of the 640 cases exposed to combined contraceptives, 563 concerned oral forms (first-generation COCs 1 %, second-generation COCs 34 %, third-generation COCs 24 % and fourth-generation COCs 11 %).

The breakdown of thromboembolic events for each type of drug is detailed in Table 3. A balanced thromboembolic profile, with 50 % of VTE and 50 % of ATE was observed for cases exposed to second-generation COCs. A higher proportion of VTE (70 %) was observed for cases exposed to third- or fourth-generation COCs, whatever the progestogen, except for dienogest (but the number of cases was very low). A higher proportion of VTE was also observed for CAEE and CAO (53 and 60 %, respectively). Conversely, a higher proportion of ATE (56 %) was observed in cases exposed to progestogen-only contraceptives (Fig. 3).

Globally, the mean age of women exposed to the drugs was 33.5 ± 9.5 years; patients were younger in the VTE group (31.1 ± 9.3 years) than in the ATE group (36.7 ± 8.7 years; $p < 0.0001$). The age distribution is presented in Fig. 4.

Cases exposed to third- and fourth-generation COCs were younger than those exposed to second-generation COCs (mean age 32.0 ± 9.0 years, 29.4 ± 8.7 years and 34.7 ± 9.8 years, respectively) ($p = 0.003$ for third-generation COCs; and $p < 0.0001$ for fourth-generation COCs, vs second-generation COCs). Cases exposed to progestogen-only contraceptives were older than those exposed to second-, third- and fourth-generation COCs (mean age 38.5 ± 7.6 years; $p = 0.002$).

Of the 51 cases exposed to CAEE, the indication was specified in 34 cases (66.6 %) and was contraception (26), acne (6), hirsutism and alopecia (1 each). The mean age of these 51 women was 28.1 ± 8.1 years. The mean age of the five women exposed to CAO was 34.2 ± 9.4 years.

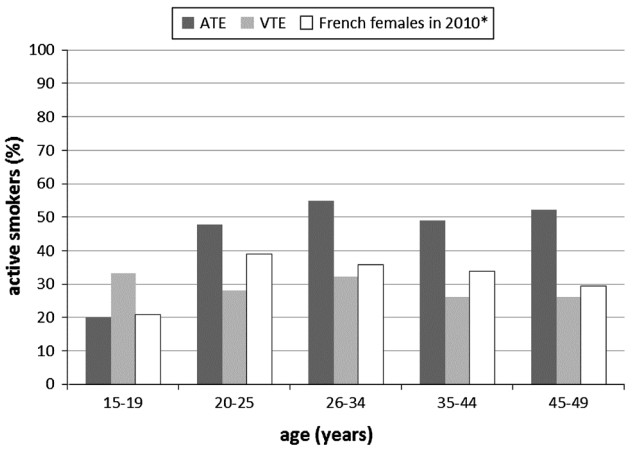


**Fig. 6** Proportion of current smokers among cases of venous thromboembolic events, arterial thromboembolic events and general French female population (data from INPES 2010 [18]). *VTE* venous thromboembolic event (*grey bar*), *ATE* arterial thromboembolic event (*black bar*); general French female population (*white bar*); *Asterisk* 45–49 years corresponds to data for 45–54 years

## 3.2 Global Risk Factor Assessment

Among the 803 cases, 174 (21.7 %) had no identified specific risk factor (148 VTEs and 26 ATEs). The proportions of cases with no risk factor, with one risk factor, and with at least two risk factors according to drug category are shown in Fig. 5. The proportions of cases with no risk factor were highest in those exposed to third- and fourth-generation COCs, non-oral combined contraceptives

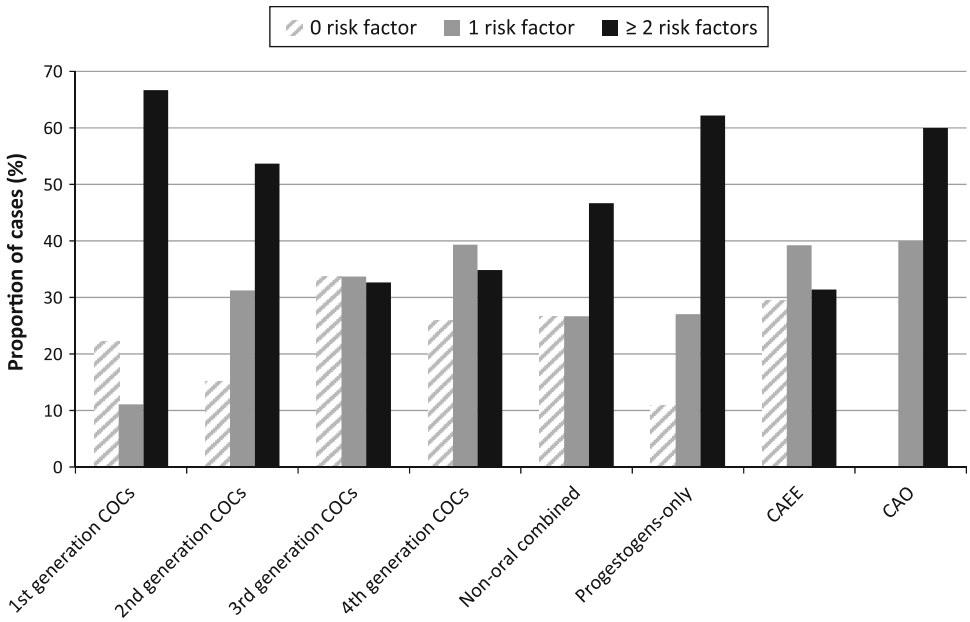


**Fig. 5** Proportion of cases according to number of risk factors and exposure. Cases with no risk factors (*hatched bar*), one risk factor (*grey bar*) and at least two risk factors (*black bar*); *COC* combined oral contraceptive, *CAEE* cyproterone acetate/ethinylestradiol, *CAO* cyproterone acetate only

**Table 4** Venous thromboembolic risk factors (sorted by frequency in COC-exposed cases)

| Risk factor | COCs ($n = 340$) | Non-oral combined ($n = 11$) | PROG ($n = 33$) | CAEE ($n = 27$) |
|---|---|---|---|---|
| Age ≥40 years old | 75 (22.1 %) | 3 (27.3 %) | 12 (36.4 %) | 1 (3.7 %) |
| Personal thrombophilia diagnosed after VTE | 72 (21.2 %) | 3 (27.3 %) | 4 (12.1 %) | 4 (14.8 %) |
| Obesity (BMI ≥ 30) | 51 (15.0 %) | 0 | 11 (33.3 %) | 4 (14.8 %) |
| Familial history of venous thrombosis | 44 (12.9 %) | 2 (18.2 %) | 2 (6.1 %) | 4 (14.8 %) |
| Long journey >5 hours | 31 (9.1 %) | 1 (9.1 %) | 1 (3.0 %) | 5 (18.5 %) |
| Immobilization >3 days | 27 (7.9 %) | 2 (18.2 %) | 2 (6.1 %) | 1 (3.7 %) |
| Surgery <1 month | 15 (4.4 %) | 0 | 4 (12.1 %) | 0 |
| Personal history of venous thrombosis | 10 (2.9 %) | 0 | 9 (27.3 %) | 0 |
| Concomitant medicines promoting VTE | 6 (1.8 %) | 0 | 2 (6.1 %) | 1 (3.7 %) |
| Active neoplasia | 5 (1.5 %) | 1 (9.1 %) | 3 (9.1 %) | 0 |
| Personal thrombophilia known before VTE | 4 (1.2 %) | 0 | 1 (3.0 %) | 0 |
| Early post-partum | 3 (0.9 %) | 0 | 6 (18.2 %) | 0 |

COCs includes all generations, but not unspecified COCs

*BMI* body mass index, *CAEE* cyproterone acetate/ethinylestradiol, *COCs* combined oral contraceptives, *PROG* progestogens only, *VTE* venous thromboembolic event

**Table 5** Arterial thromboembolic risk factors (sorted by frequency in COC-exposed cases)

| Risk factor | COCs ($n = 223$) | Non-oral combined ($n = 4$) | PROG ($n = 41$) | CAEE ($n = 24$) |
|---|---|---|---|---|
| Current smoking | 113 (50.7 %) | 2 (50 %) | 20 (48.8 %) | 9 (37.5 %) |
| Age ≥40 years | 105 (47.1 %) | 2 (50 %) | 26 (63.4 %) | 5 (20.8 %) |
| Dyslipidemia | 71 (31.8 %) | 2 (50 %) | 3 (7.3 %) | 6 (25.0 %) |
| PFO and/or ASA revealed after ATE | 43 (19.2 %) | 2 (50 %) | 6 (14.6 %) | 5 (20.8 %) |
| Migraine with aura | 39 (17.5 %) | 0 | 5 (12.2 %) | 4 (16.7 %) |
| Hypertension | 23 (10.3 %) | 0 | 11 (26.8 %) | 4 (16.7 %) |
| Obesity (BMI ≥ 30) | 23 (10.3 %) | 0 | 6 (14.6 %) | 1 (4.2 %) |
| Familial history of arterial thrombosis | 14 (6.3 %) | 0 | 5 (12.2 %) | 2 (8.3 %) |
| Personal hyperhomocysteinemia diagnosed after ATE | 14 (6.3 %) | 0 | 1 (2.4 %) | 1 (4.2 %) |
| Consumption of illicit drugs | 14 (6.3 %) | 0 | 0 | 3 (12.5 %) |
| Concomitant medicines promoting ATE | 8 (3.6 %) | 0 | 3 (7.3 %) | 0 |
| Other cardiovascular abnormalities diagnosed after ATE | 7 (3.1 %) | 0 | 0 | 0 |
| Personal history of arterial thrombosis | 6 (2.7 %) | 0 | 5 (12.2 %) | 0 |
| Diabetes mellitus | 2 (0.9 %) | 1 (25 %) | 5 (12.2 %) | 0 |
| Antiphospholipid syndrome diagnosed after ATE | 2 (0.9 %) | 0 | 0 | 1 (4.2 %) |
| Antiphospholipid syndrome known before ATE | 1 (0.4 %) | 0 | 1 (2.4 %) | 0 |

COCs includes all generations, but not unspecified COCs

*ASA* atrial septal aneurysm, *ATE* arterial thromboembolic event, *BMI* body mass index, *CAEE* cyproterone acetate/ethinylestradiol, *COCs* combined oral contraceptives, *PFO* patent foramen ovale, *PROG* progestogens only

and CAEE, while most of the cases exposed to second-generation COCs or to progestogen-only contraceptives had two risk factors or more.

The mean number of risk factors in the VTE group was significantly lower than that in the ATE group (1.1 vs 2.3; $p < 0.0001$).

When risk factors in cases exposed to first- and second-generation COCs were compared with those exposed to third- and fourth-generation COCs, only the proportions of patients aged over 40 years old and patients with obesity were significantly different (26.8 vs 18.8 %, $p = 0.005$ and 21.1 vs 10.2 %, $p = 0.004$, respectively).

### 3.3 Age and Smoking

Of the 803 cases, 307 (38.2 %) were identified as smokers. The proportion of smokers in the ATE group, the VTE group, and in the general female population for each age class is shown in Fig. 6. In the ATE group, the proportion of smokers was around 50 % in all age classes, except for those under 20 years, with 20 % of smokers. In the VTE group, the proportion of smokers was around 30 % whatever the age class. The proportion of smokers over 35 years old was 31.9 % in the ATE group and 8.6 % in the VTE group.

### 3.4 Specific Venous Thromboembolic Event Risk Factor Assessment

The most frequent risk factors identified were age ≥40, personal thrombophilia diagnosed after the occurrence of VTE, obesity, a familial history of VTE, and a long journey >5 hours (Table 4).

Thrombophilia was diagnosed after the occurrence of VTE in 84 women, revealing 34 cases of heterozygous factor V Leiden mutations (of these, two were associated with heterozygous prothrombin gene mutations, two with protein S deficiencies and two with antiphospholipid syndrome), 15 cases of isolated heterozygous prothrombin gene mutations, three cases of protein C deficiency, eight cases of isolated protein S deficiency, three cases of combined protein C and S deficiency, two cases of isolated resistance to activated protein C and 19 cases of isolated antiphospholipid syndrome. Of the 84 women, four had a personal and nine had a familial history of venous thrombosis. Women in whom thrombophilia was revealed were exposed at the time of the VTE to a combined (oral and non-oral) contraceptive in 75 cases, to cyproterone acetate in five cases (4 CAEE) and to a progestogen-only contraceptive in four cases.

Personal thrombophilia was already known before the VTE in five cases: three women with heterozygous factor V Leiden mutations, one with resistance to activated protein C and one with protein S deficiency. At the time of the VTE, four women were receiving a COC while one woman was receiving a progestogen-only contraceptive.

### 3.5 Specific Arterial Thromboembolic Event Risk Factor Assessment

Current smoking and age were the main arterial risk factors (Table 5).

Regarding arterial risk factors listed in the 'contraindications' section of COC SmPCs, a personal history of arterial thrombosis and antiphospholipid syndrome was rarely encountered but migraine with aura was frequently identified.

**Table 6** Risk factors in the 48 cases documented for time to onset of the thromboembolic event after first use of hormonal contraceptives

| | Time to onset | |
|---|---|---|
| | Within 1 year | After 1 year |
| Venous thromboembolic events ($n = 35$) | | |
| No risk factor | 7 | 6 |
| 1 risk factor | 10 | 2 |
| ≥2 risk factors | 7 | 3 |
| Personal thrombophilia | 5 | 1 |
| Long journey >5 hours | 4 | 2 |
| Familial history of venous thrombosis | 2 | 2 |
| Obesity | 1 | 2 |
| Age ≥40 years | 1 | 1 |
| Personal history of venous thrombosis | 1 | |
| Immobilization >3 days | 1 | |
| Active neoplasia | 1 | |
| Surgery <1 month | | |
| Arterial thromboembolic events ($n = 13$) | | |
| No risk factor | 0 | 0 |
| 1 risk factor | 2 | 4 |
| ≥2 risk factors | 2 | 5 |
| Current smoking | 2 | 4 |
| Dyslipidemia | 2 | 3 |
| Obesity | 1 | 1 |
| Migraine with aura | 1 | 2 |
| PFO ± ASA | 1 | 2 |
| Age ≥40 years | | 1 |
| Antiphospholipid syndrome | | 1 |
| Other cardiovascular abnormalities | | 1 |

*ASA* atrial septal aneurysm, *PFO* patent foramen ovale

In cases exposed to COCs or CAEE, dyslipidemia and the presence of a patent foramen ovale and/or atrial septal aneurysm were two common risk factors.

The other cardiovascular abnormalities revealed after the occurrence of ATE in seven cases exposed to COCs were as follows: atrial septal defect ($n = 3$), heart valve defects ($n = 2$), emboligenic arrhythmia ($n = 1$) and emboligenic right internal carotid artery defect ($n = 1$).

One woman with ischemic stroke and exposed to progestogen-only contraception had lupus associated with antiphospholipid syndrome already known before the ATE.

### 3.6 Time to Onset

Time to onset of the thromboembolic event after the start of the current contraceptive was documented in 324 cases, but the duration of treatment was possibly biased by unknown previous contraception.

We identified 48 cases for which the event certainly occurred during the first exposure to hormonal contraceptives (35 VTE and 13 ATE). Of these, 24 (68 %) VTEs and four (31 %) ATEs occurred during the first year of treatment. The distribution of the number of risk factors (0, 1, 2 and more) is detailed in Table 6. All ATE cases had at least one risk factor, whatever the time to onset. In VTE, thrombophilia was the most frequent risk factor, especially in cases occurring during the first year of treatment. The only case with both thrombophilia and a time to onset greater than 1 year after the start of treatment was a 45-year-old woman treated with a progestogen-only contraceptive for 19 years, who had undergone surgery less than 1 month before and was diagnosed with a heterozygous prothrombin gene mutation.

### 3.7 Outcome of the Thromboembolic Event

Full recovery was observed in 451 women whereas 248 recovered with sequellae, 37 were recovering according to the last information and 10 had died (outcome not documented in 57 cases). Of the 10 who died, seven cases were VTE (five cases of pulmonary embolism and two of cerebral venous thrombosis) and three were ATE (two cases of cerebral ischemia and one myocardial infarction).

### 3.8 Contraception After the Event

Of the 736 women who completely recovered or recovered with sequellae, 203 were explicitly prescribed another form of contraception: progestogen-only contraceptive: 131, intrauterine device: 58, switch to another COC: 4, condoms: 4, tubal ligation: 3, and not specified: 3.

### 3.9 Cases Already Reported (Duplicates)

Of the 803 cases, 60 had been reported spontaneously to RPVC before the study (7.5 %). This corresponds to a mean under-reporting rate of 92.5 % (95 % CI 70.0–97.3). The main differences between the duplicate series and the non-reported series were a higher proportion of VTEs (77 vs 54 %, $p = 0.001$), a lower age (mean 28.2 vs 33.5 years, $p < 0.0001$), a higher proportion of cases with no risk factors (33.3 vs 19.8 %, $p = 0.013$), a higher proportion of onset occurring during the first year of treatment (46.7 vs 14.5 %, $p < 0.0001$), and a higher proportion of women exposed to third- and fourth-generation COCs or CAEE (50.0 vs 34.2 %, $p = 0.014$ and 16.7 vs 5.6 %, $p = 0.001$, respectively) in the spontaneously reported cases.

## 4 Discussion

This study led to the rapid identification and complete analysis of 803 serious thromboembolic events (452 VTEs and 351 ATEs) that occurred in 2012 in women exposed to hormonal contraceptives or to cyproterone acetate and hospitalized in 30 French teaching hospitals.

First- and second-generation COCs were associated with a balanced number of venous and arterial thromboembolic events, while third and fourth generations as well as non-oral COCS had a greater proportion of VTEs.

Associated thrombosis risk factors were less frequent in women with VTEs than in women with ATEs, and also less frequent in women taking third- and fourth-generation COCs than in those taking first- and second-generation COCs.

The main risk factors for VTE were age and thrombophilia while the main risk factors for ATE were age and smoking.

Only 7.5 % of cases had been reported spontaneously and mostly concerned young women with no risk factors exposed to third- and fourth-generation COCs or CAEE, with a thromboembolic event occurring during the first year of exposure.

We identified more VTE cases than ATE cases, although we did not consider deep venous thrombosis without pulmonary embolism. This is consistent with the reported 4- to 5-fold increase in the risk of VTE [5, 6], and is also expected given the lower overall arterial risk in females under 50 years old and the lower increase in the risk of ATE with COCs [13, 14].

We found that half of ATE cases were current smokers over 35 years of age. When we compared our results with the available data on active smoking among French women according to age category in 2010 [19], ATE cases had a higher proportion of smokers between 20 and 49 years old.

Moreover, although smoking is not established as a risk factor for VTE, we would like to highlight that we found a higher proportion of smokers between 15 and 20 years old in VTE cases than in the general female population. The association between age over 35 and smoking is currently listed in the ‘special warnings and precautions for use’ section of COC SmPCs and is considered a contraindication by the French Society of Endocrinology and the World Health Organization [18, 20, 21].

The risk factor analysis showed a higher proportion of women with no risk factors among VTE and ATE cases exposed to third- and fourth-generation COCs than in those taking first- and second-generation COCs. In particular, age over 40 years and obesity were significantly less frequent in the former. This finding is in keeping with a recent French study conducted by the national healthcare system involving more than 4 million women, which showed that

patients reimbursed for third-generation COCs were younger and had lower cardiovascular risk [22]. This recent study also confirmed higher risks of pulmonary embolism and myocardial infarction for third-generation COCs than for second-generation COCs, as already shown in previous studies [4–11].

Almost all of the women exposed to progestogen-only contraceptives had at least one risk factor for a thromboembolic event and were significantly older than those in all other categories of the study. These findings were expected as they were consistent with medical practice in that one preferentially chooses these molecules for patients with a past medical history or a risk of a thromboembolic event [18].

In our series, the treatment period was probably underestimated, even though we contacted practitioners for additional information about treatment duration and previous contraception. Thus, we analyzed time to onset only for fully documented cases after the first use of contraception. van Hylckama et al. showed a significant 12.6-fold increase in VTE during the first 3 months of treatment, but also a 5-fold increase after 1 year, and a persistent high risk for desogestrel over 2 years [5]. This finding and the frequent missing information about the exact duration of exposure should challenge the widely held view that a thromboembolic event is related to hormonal contraception only if it occurs within the first year of treatment. Improvements are particularly needed to collect this information.

The under-reporting rate of 92.5 % is similar to that in other publications. In a systematic review of 37 studies, Hazell and Shakir [23] found a median under-reporting rate of 94 % (interquartile range 82–98 %), with no significant difference between general practice and hospital-based studies. In their review, three studies that focused on thromboembolic events and oral contraceptives specifically showed under-reporting rates of 85, 96, and even 100 %. Serious adverse drug reactions were preferentially reported and the main reasons for not reporting were expectedness, lack of time, fear of possible involvement in litigation, and lack of understanding of the purpose of reporting systems [23].

This study is the first French study to include all types of contraceptive drugs and to be based on the exhaustive collection of validated clinical data. One strength is the large participation, with 30 of the 31 RPVC and 30 of the 32 French university hospitals contributing to the study. This ensured that the work was representative for continental France. We underline the interest of this joint study, which allowed us to collect cases of thromboembolic events rapidly and thus to compensate for under-reporting.

We considered exposure to any hormonal contraceptive drug, independently of the reimbursement status. Second- and third-generation COCs were the most widely used hormonal contraceptives in our series. Available data about COCs in France show that consumption of the different types of COC in 2012 was similar to that in 2011, with 1.3 % for first-generation COC, 49.5 % for second generation, 33.5 % for third generation and 15.6 % for fourth generation [24]. This distribution is very similar to the distribution of thromboembolic events according to the type of COC (Fig. 3). It underlines the fact that thromboembolic events occur with all generations of COCs.

We also collected exposure to all kinds of hormonal contraception, including progestogen-only and drugs containing cyproterone acetate. Even though the latter are not authorized for contraception in France, their SmPC is very similar to that for contraceptives. Our data show that the main indication in women who experienced a thromboembolic event was contraception.

Our study has some limitations: cases of deep venous thrombosis without pulmonary embolism were not included in order to have data on only serious events that systematically result in hospitalization. Cases with a fatal outcome before hospitalization, or undiagnosed cases are missing here. Hospitalization reports were sometimes poorly informative about past drug history, and exposure to contraception may have been omitted from the patient's file. This may have lowered the number of cases with exposure to such drugs and the proportion of 27.1 % is probably underestimated. The starting date for current contraception and information on previous contraceptives was difficult to obtain, even though practitioners were contacted. The time to onset was therefore difficult to assess. In the same way, risk factors may have been underestimated. The results of investigations performed after the event (i.e., thrombophilia testing) were sometimes missing, incomplete or ambiguous, with, for example, no protein S gene mutation test available. For protein C and S deficiency, only values under 50 % were considered to avoid pseudo deficiencies due to inflammation, or treatment with anticoagulants or hormones [25, 26]. Migraine with aura, the only form of migraine considered an arterial risk factor, was also difficult to assess as 'with' or 'without' aura was rarely specified in the patient's file. Smoking is a known arterial risk factor, but smoking status was not always mentioned in the medical files. In particular, the exact quantification in pack-years was often missing, as was information on the weaning period. This may have led to an overestimation of exposure to cigarette smoke or, conversely, former smokers with persisting arterial risks may have been excluded. The results on smoking status were compared with available data for the general female population in France, but no statistical test could be performed.

Very few cases were found with CAO and therefore no conclusions can be drawn from our results, except that thromboembolism can also occur during treatment with CAO.

Our series underlines the fact that the information sought by practitioners or provided by the patient before the prescription of contraceptives may be inaccurate. If we consider that the prescriber meticulously inquires about personal medical history, in the setting of a trusting doctor–patient relationship, it seems surprising that a combined hormonal contraceptive was prescribed to several women with a personal history of venous thromboembolism, thrombophilia or arterial thrombosis even though this drug should have been contraindicated.

Moreover, besides age, smoking and thrombophilia, other risk factors we encountered were listed in the 'special warnings and precautions for use' section of COC SmPCs. These included obesity, dyslipidemia, and a familial history of venous or arterial thrombosis. One may consider that these factors should have been identified at the time of prescription or renewal, especially in view of the fact that it is currently recommended to reassess the contraceptive method in women aged 35–40 years because of a well known increase in the risk of thromboembolism with age and during the premenopausal period [27].

Our data also provide elements to justify better information for women, especially about risk factors and drug-induced adverse effects, and underline the need to improve communication with hormonal contraceptive prescribers. The wide diffusion of updated and validated data about thrombosis risk factors towards prescribers also appears necessary to ensure the efficient exchange of information.

The occurrence of thromboembolic events, especially ATE, after the first year of hormonal contraception should also be highlighted to encourage practitioners to regularly reassess contraceptive prescription, by taking into account increasing age and dyslipidemia as well as migraine with aura and, of course, smoking habits.

The traceability of successive contraception methods in patients' medical files also needs to be improved to ascertain the patient's precise exposure to contraceptives. Thromboembolic events are typically multifactorial events, and predisposing factors as well as exposure to drugs or toxic substances need to be considered. This should lead to hormonal contraception being considered a 'real drug treatment' without calling into question its social and cultural dimensions.

Improvements are required to ensure (i) better communication between patients and practitioners about risk factors and drug-induced adverse effects, and (ii) better traceability of contraceptives (hormonal or not) in the patient's medical file.

In October 2012, the ANSM recommended to prescribe second-generation COCs containing levonorgestrel as first-line contraceptives, following the literature analyses performed by the EMA showing that the risk of venous thromboembolism was twice as high in women taking a third-generation COC (containing desogestrel or gestodene) or a COC containing drospirenone (called fourth-generation COC) than in women taking a second-generation COC containing levonorgestrel [28]. In November 2013, the EMA reminded healthcare professionals that combined hormonal contraceptives containing the progestogens levonorgestrel, norethisterone or norgestimate had the lowest risk of VTE [29].

The results of our field survey could form the basis for the future assessment of the impact of such recommendations in France, with regard to the risk factor status of women who experience thromboembolism. We therefore plan to conduct a similar study in about 4 years' time with the expectation of finding a decrease in thromboembolic events in women exposed to hormonal contraception, but also with the hope of an improved spontaneous reporting rate to the pharmacovigilance system. Furthermore, a recent increase in spontaneous reporting has been observed. This is probably linked to the wide coverage in the French media of the thromboembolic risks of hormonal contraceptives.

## 5 Conclusion

This study was based on real-life clinical data. It therefore reflects the occurrence of thromboembolic events during contraception and completes existing epidemiological data with an exhaustive assessment of risk factors in medically validated cases.

Although some risk factors encountered in this study were identified after the thromboembolic event, the prior existence of identifiable risk factors underlined the need for clinicians to inform women and involve them in a thorough individual assessment of the benefit–risk balance at the first prescription and at the renewal of their contraception treatment. This seems to be the prerequisite to ensure the best 'benefit–risk ratio' for these particular drugs, and to encourage their proper use. It implies that both the public and health professionals have full knowledge of the thromboembolic factors and requires the wider diffusion of a list of validated risk factors. The latest European recommendations return to the prescription of second-generation COCs containing levonorgestrel at first [29]. The results of this field survey can be an interesting basis for a future assessment of the impact of such recommendations regarding the risk factor status of women who experience thromboembolism. Besides the expectation of a decrease in the number of thromboembolic events, we also hope to improve the spontaneous reporting rate to the pharmacovigilance system.

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*Contributorship statement*

MG designed data collection tools, collected, cleaned and analyzed the data, drafted and revised the draft paper.

AG designed data collection tools, collected, cleaned and analyzed the data, drafted and revised the draft paper.

MNB collected and analyzed the data, drafted and revised the draft paper.

NM collected and analyzed the data, drafted and revised the draft paper.

VG collected and analyzed the data, drafted and revised the draft paper.

AD designed data collection tools.

GMS collected and analyzed the data, drafted and revised the draft paper.

NP initiated the collaborative project, designed data collection tools, collected, cleaned and analyzed the data, drafted and revised the draft paper.

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