



Combined hormonal contraceptive use in Europe before and after the European Commission mandated changes in product information☆☆☆

Deeksha Khialani^{a,*}, Mary Elizabeth Jones^b, Szimonetta Komjáthiné Szépligeti^c, Anne Gulbech Ording^c, Vera Ehrenstein^c, Irene Petersen^b, Astrid van Hylckama Vlieg^a

^a Leiden University Medical Center, Department of Clinical Epidemiology, Albinusdreef 2, PO Box 9600, 2300 RC, Leiden, The Netherlands

^b University College London, Department of Primary Care and Population Health, Gower St, Bloomsbury, WC1E 6BT, London, United Kingdom

^c Aarhus University, Department of Clinical Medicine - Department of Clinical Epidemiology, Olof Palmes Allé 43-45, 8200 Aarhus N, Aarhus, Denmark

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ABSTRACT

Objectives: We investigated combined hormonal contraceptives (CHC) prescribing patterns (focusing on combined oral contraceptives; COC) in three countries (Netherlands, Denmark, United Kingdom) in a time period preceding and in a time period following the European Commission's decision to update product information, and we estimated changes in incidence of venous thromboembolism (VTE) between the two periods.

Study design: We conducted a drug utilization analysis and a cohort study using routinely collected data. We calculated number, proportion and incidence rate of new users, switchers, and stoppers of COC in both time periods. VTE incidence was calculated in new users of COC and in all women aged 18–49 years.

Results: In all countries, the largest proportion (>75%) of new users used COC containing levonorgestrel, norethisterone, or norgestimate, (i.e., indicated by European Medicines Agency (EMA) as the safest preparations) in both time periods. Switching did not demonstrate a clear pattern towards these types of COC and distribution of stoppers was similar in both time periods. While the proportion of new users initiating COC containing levonorgestrel, norethisterone, or norgestimate increased slightly, this did not translate to a decrease in the overall VTE incidence.

Conclusion: All three countries had the greatest proportion of women initiating a COC containing levonorgestrel, norethisterone, or norgestimate, and this proportion increased in the period after the European Commission decision albeit the increase was small due to the high percentage of use before the decision. This did not translate into a measureable change in the incidence of VTE.

Implications: Both before and after the European Commission's decision, the largest proportion of new users started with combined oral contraceptives containing levonorgestrel, norethisterone, or norgestimate. Earlier studies had already indicated an increased risk of VTE associated with COC containing other progestogens compared with these preparations, so it is possible that physicians were already preferentially prescribing COC containing levonorgestrel, norethisterone, or norgestimate to new users.

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1. Introduction

Several large population-based observational studies and meta analyses, including a review by European Medicines Agency (EMA) in 2013, have concluded that the risk of venous thromboembolism (VTE) is higher for recently developed progestogens in combined hormonal contraceptives (CHC), such as desogestrel and drospirenone, compared

with progestogens which were developed much earlier, such as levonorgestrel, norethisterone and norgestimate [1–7]. However, this was not confirmed by all as discussed in a statement by Bitzer et al. [8].

CHC containing the newer type of estrogen, i.e., estradiol, may be associated with a similar or even a lower risk on thrombosis compared with CHC containing levonorgestrel and ethinylestradiol [9–11].

On 16 January 2014, the European Commission adopted a legally binding decision to update the product information of all CHC throughout the European Union. This included: information to patients regarding the risk of VTE associated with contraceptives and other risk factors, and information to health care professionals regarding the types of CHC with the lowest VTE risk. The aims of this study were to investigate the CHC prescribing patterns (specifically focusing on combined oral contraceptives; COC) in three European Union member states (Netherlands,

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* Corresponding author. Tel.: +31 71 526887.

E-mail address: d.khialani@lumc.nl (D. Khialani).

Denmark and United Kingdom (UK)) in a time period including the completion of the 2013 review and in a time period including the implementation of the resulting recommendations, and to estimate any changes in the VTE incidence between the two time periods.

2. Methods

2.1. Data sources and study population

We used routinely collected data from Netherlands, Denmark and UK. In Netherlands, we used data from The Dutch Foundation for Pharmaceutical Statistics (SFK) [12]. In Denmark, data were linked from Danish Civil Registration System, Danish National Patient Registry and the Danish National Prescription Registry. In UK, we used The Health Improvement Network (THIN) primary care database. All analyses were restricted to women aged 18 to 49 years.

Drug utilization and cohort studies were divided into two 25-month time periods: 1 January 2012 to 31 January 2014 and 1 February 2014 to 29 February 2016.

2.2. Statistical analysis of drug utilization

This study focuses on the prescription pattern of COC, containing both an estrogen and a progestogen component. The COC containing the progestogens levonorgestrel, norethisterone and norgestimate were reported to be the safest by the EMA and therefore were grouped. The other COC present in our study were those containing the progestogens desogestrel, gestodene, drospirenone, dienogest, nomegestrol and cyproterone acetate. These were grouped together as the 'other' group.

A drug utilization study investigated COC prescribing patterns. The number, proportion, and incidence rate of new users (starters) of each COC preparation were assessed for both time periods. A starter was defined as a woman who did not use COC in the 2 years prior to start of her first COC prescription in each time period.

Similarly, we assessed the number, proportion, and incidence rate of women who switched to a different COC (switchers) or discontinued COC use (stoppers) in both periods.

COC switchers and stoppers were defined among prevalent users. Prevalent users of COC were defined as women who used at least one cycle of COC during each time period or at least one cycle of COC in the 7 months prior to each time period. Prevalent users were eligible to switch or stop COC in the relevant 25-month time period. A period of 7 months was used to include women with prescriptions lasting 6 months, allowing 1 month of leeway between prescriptions for inclusion as a prevalent user.

A switch was defined as the start of a new COC preparation within 7 months of the last prescription for the initial COC preparation. A COC discontinuation was defined as more than 7 months without a new COC prescription after the last COC prescription.

In all three countries, we calculated the proportion of different progestogens of COC within new users of COC. We assessed the number of switchers in both periods, the proportion of switch, and the incidence rate of switching (per 1000 person years; pys). These were reported as switch from the COC preparations classified as the safest (i.e., containing levonorgestrel, norethisterone, or norgestimate) to COC containing other progestogens and vice versa (further stratification of the group containing other progestogens led to small numbers, nonetheless this is shown in supplementary tables S1–3).

In Denmark and UK, we reported the number of women stopping COC use in both periods and the proportion of stoppers that had been prescribed COC classified as the safest or COC containing other progestogens before discontinuation. The incidence rate of starting and stopping COC use is also reported in Denmark and UK.

In Netherlands, due to the lack of data in the SFK database, we could not report the incidence rate of starting or stopping COC.

2.3. Statistical analysis of the cohort study

The SFK database from Netherlands does not provide a definitive VTE diagnosis, which is why we used treatment as a proxy and performed two analyses. Firstly, a VTE event was assumed in case of at least one prescription of vitamin K antagonist (VKA), with or without heparin, or Direct Oral Anticoagulant (DOAC); the latter according to the first dose which is specific for VTE. Secondly, a VTE event was assumed in case of a prescription of heparin with VKA or DOAC. In Denmark, VTE was defined using discharge diagnoses recorded in Danish National Patient Registry. In UK, VTE was defined using diagnoses obtained from the THIN database.

The VTE incidence among new users was calculated in both time periods using up to 10 months of follow-up after COC initiation. VTE incidence per 10,000 pys in new users was also stratified by the type of preparation used, i.e., COC classified as the safest and COC containing other progestogens. Women with a previous VTE were excluded from VTE analyses. SFK lacked the complete medical history of the women in the database; however, we were able to confirm that none of the VTE cases in our study had a previous VTE since 2000. In Denmark and UK, the VTE incidence in the source population of all women aged 18–49 years was also calculated. As Dutch data contained only women with at least one COC prescription, such an analysis was not possible.

Data were analyzed using R version 3.4.1 in Netherlands, SAS version 9.4 in Denmark, and STATA version 15.1 in the UK.

3. Results

3.1. Participants

Table 1 shows the description of the cohort selection. The number of women 'at risk' of starting is reported. Additionally, the number of new users without VTE history is shown. Further detail on the cohort selection is provided in the supplemental method section.

3.2. Drug utilization study

In all three countries, the largest proportion of new users started with a COC containing the progestogens levonorgestrel, norethisterone or norgestimate (Tables 2a–2c) and this proportion increased from the first to the second time period. For levonorgestrel specifically, this proportion increased from 75.9% in the first to 83.1% in the second time period in the Netherlands (Table 2a), from 61.3% to 74.6% in Denmark (Table 2b), and from 62.9% to 67.7% in the UK (Table 2c). Concurrently, the proportion of new users initiating a COC, containing another progestogen such as desogestrel and cyproterone acetate decreased in all three countries from the first to the second time period (Tables 2a–2c). In Denmark, the incidence rate of new users decreased from 37.0 per 1000 pys (95% confidence interval (CI): 36.7–37.2) in the first to 32.6 per 1000 pys (32.3–32.8) in the second period (Table 2b). In UK, the incidence rate decreased from 57.4 per 1000 pys (56.8–57.9) in the first to 48.5 per 1000 pys (48.0–49.0) in the second period (Table 2c).

Among prevalent users, the overall number of switchers decreased in the second time period compared with the first time period. This trend was observed both for switchers away from COC classified as the safest as for switchers to COC classified as the safest, albeit the latter was not observed in the UK (Tables 2a–2c). Supplementary tables S1–3 to a large extent show similar results, but now stratified for the individual progestogens in the other group. When stratifying on progestogens, not all switches showed a similar trend but numbers were small. The decreasing trend in switching can also be observed by analyzing the overall incidence of switching in all three countries. In Netherlands, the incidence rate decreased from 21.3 per 1000 pys (21.0–21.7) in the first to 17.6 per 1000 pys (17.3–18.0) in the second time period. In Denmark, it decreased from 266.1 per 1000 pys (264.6–267.6) to 120.3 per 1000

Table 1
Description of cohort selection in both time periods in all three countries

Women between 18 and 49 years of age						
	Time Period 1*	Time Period 2*	Time Period 1*	Time Period 2*	Time Period 1*	Time Period 2*
	Netherlands		Denmark		United Kingdom	
N at-risk of becoming a New User = (A)	<i>Not available</i>	<i>Not available</i>	1,025,588	1,035,365	552,422	527,554
(A) without COC prescription in 2 years prior to first prescription in relevant study period = (B)	New Users 534,939	New Users 427,500	New Users 66,526	New Users 59,880	New Users 44,300	New Users 33,712
(B) PY	<i>Not available</i>	<i>Not available</i>	1,800,531	1,839,266	772,287	695,154
(A) without previous VTE = (C)	New Users in VTE analysis (<i>Not feasible</i>)	New Users in VTE analysis (<i>Not feasible</i>)	New Users in VTE analysis 66,402	New Users in VTE analysis 59,762	New Users in VTE analysis 44,152	New Users in VTE analysis 49,239
All in dataset with prescription of COC in study period or within 7 months before study period = (D)	Prevalent Users 1,014,899	Prevalent Users 759,364	Prevalent Users 427,089	Prevalent Users 399,938	Prevalent Users 266,924	Prevalent Users 214,623
N of switchers = (E)	14,724	9982	118,670	57,265	17,284	11,790
N of stoppers = (F)	<i>Not available</i>	<i>Not available</i>	169,168	162,928	63,878	49,326
(E and F) PY	691,073	565,751	445,980	476,207	290,113	218,157

COC, combined oral contraceptives; VTE, venous thromboembolism; PY, person-years.

* Time period 1 (1 January 2012 to 31 January 2014) and Time period 2 (1 February 2014 to 29 February 2016) refers to the periods before and after the European Medicines Agency (EMA) review and recommendation, respectively.

pys (119.3–121.2). In UK, it decreased from 59.6 per 1000 pys (58.7–60.5) to 54.1 per 1000 pys (53.1–55.0).

The incidence rate of COC discontinuation (stoppers) increased in UK (Table 2c), from 220.2 per 1000 pys (218.5–222.0) in the first to 226.2 per 1000 pys (224.2–228.2) in the second time period, but decreased in Denmark, from 379.3 per 1000 pys (377.5–381.1) to 342.1 per 1000 pys (340.5–343.8) (Table 2b). In both countries, the distribution of stoppers was similar in both time periods (Tables 2b–2c).

3.3. Cohort study

There was no measurable change in the VTE incidence within new users in the three countries between the two time periods (Table 3). The slight change that is seen in the VTE incidence is not only observed within the overall new user group, but also within the group of women starting with COC classified as the safest or COC containing other progestogens.

The VTE incidence in all women aged 18–49 years (source population) in Denmark and UK did not change significantly between the two time periods (Table 4).

4. Discussion

Among new users, all three countries had the greatest proportion of women initiating a COC containing levonorgestrel, norethisterone, or norgestimate (i.e., classified by EMA as the safest preparations) in the time periods before and after the European Commission decision of January 2014, and this proportion increased in all three countries in the period after the decision. The proportion of new users initiating a COC containing other progestogens decreased accordingly in all three countries. However, with almost 75% or more of new users already initiating a COC containing levonorgestrel, norethisterone, or norgestimate in all three countries before the decision, there was little room for a large increase in the use of these COC preparations in the period after the decision.

While there was an increase in the proportion of women initiating the preparations containing levonorgestrel, norethisterone, or norgestimate (and a decrease in the number of COC users, i.e. new users and prevalent users) in the second time period, this did not translate into a measurable change in the VTE incidence within new users in the three countries nor in the source population in Denmark and UK.

Table 2a
New users and Switchers of COC before and after EMA recommendations (Netherlands)

	COC users Time Period 1*		COC users Time Period 2*	
New users	534,939		427,500	
Levonorgestrel	405,864 (75.9%)		355,105 (83.1%)	
Norethisterone	3263 (0.6%)		3262 (0.8%)	
Norgestimate	2007 (0.4%)		47 (0.0%)	
Gestodene	12,351 (2.3%)		8162 (1.9%)	
Desogestrel	29,339 (5.5%)		19,173(4.5%)	
Drospirenone	43,197 (8.1%)		28,583 (6.7%)	
Nomegestrol	2879 (0.5%)		2539 (0.6%)	
Dienogest	1923 (0.4%)		1166 (0.3%)	
Cyproterone acetate	34,116 (6.4%)		9463 (2.2%)	
	COC users	Total PY	COC users	Total PY
		Time Period 1*		Time Period 2
Switchers (different type)**	14,724	691,073	9982	565,751
Safest to Other	6062 (41.2%)	527,534.4	4745 (47.5%)	471,731.1
Other to Safest	5486 (37.3%)	163,538.9	2646 (26.5%)	94,019.8
		IR per 1000 PY		IR per 1000 PY
		(95% CI)		(95% CI)
		21.3 (21.0–21.7)		17.6 (17.3–18.0)
		11.5 (11.2–11.8)		10.1 (9.8–10.3)
		33.5 (32.7–34.4)		28.1 (27.1–29.2)

Safest group consists of progestogens levonorgestrel, norethisterone, norgestimate.

Other group consists of progestogens desogestrel, gestodene, drospirenone, cyproterone, nomegestrol, dienogest.

COC, combined oral contraceptives; EMA, European Medicines Agency; PY, person-years; IR, incidence rate; CI, confidence interval.

* Time period 1 (1 January 2012 to 31 January 2014) and Time period 2 (1 February 2014 to 29 February 2016) refers to the periods before and after the European Medicines Agency (EMA) review and recommendation, respectively.

** Switching between different types means between progestogens (not between different doses).

Table 2b
New users, switchers and stoppers of COC before and after EMA recommendations (Denmark)

	COC users	Total PY	IR per 1000 PY (95% CI)	COC users	Total PY	IR per 1000 PY (95% CI)
		Time Period 1*			Time Period 2*	
New users	66,526	1,800,531	37.0 (36.7–37.2)	59,880	1,839,266	32.6 (32.3–32.8)
Levonorgestrel	40,803 (61.3%)	1,800,531	22.7 (22.4–22.9)	44,662 (74.6%)	1,839,266	24.3 (24.1–24.5)
Norethisterone	44 (0.1%)	1,800,531	0.0 (0.0–0.0)	0 (0%)	1,839,266	0.0 (0.0–0.0)
Norgestimate	8010 (12.0%)	1,800,531	4.5 (4.4–4.6)	5087 (8.5%)	1,839,266	2.8 (2.7–2.8)
Gestodene	6604 (9.9%)	1,800,531	3.7 (3.6–3.8)	3369 (5.6%)	1,839,266	1.8 (1.8–1.9)
Desogestrel	4850 (7.3%)	1,800,531	2.7 (2.6–2.8)	2454 (4.1%)	1,839,266	1.3 (1.3–1.4)
Drospirenone	2330 (3.5%)	1,800,531	1.3 (1.2–1.4)	1534 (2.6%)	1,839,266	0.8 (0.8–0.9)
Nomegestrol	107 (0.2%)	1,800,531	0.1 (0.1–0.1)	315 (0.5%)	1,839,266	0.2 (0.2–0.2)
Dienogest	1532 (2.3%)	1,800,531	0.9 (0.8–0.9)	725 (1.2%)	1,839,266	0.4 (0.4–0.4)
Cyproterone acetate	2246 (3.4%)	1,800,531	1.3 (1.2–1.3)	1734 (2.9%)	1,839,266	0.9 (0.9–1.0)
Switchers (different type)**	118,670	445,980	266.1 (264.6–267.6)	57,265	476,207	120.3 (119.3–121.2)
Safest to Other	7539 (6.4%)	114,048.9	66.1 (64.6–67.6)	11,246 (19.6%)	293,416.5	38.3 (37.6–39.0)
Other to Safest	81,605 (68.8%)	331,931.1	245.9 (244.2–247.5)	33,119 (57.8%)	182,790.3	181.2 (179.2–183.1)
Stoppers	169,168	445,980	379.3 (377.5–381.1)	162,928	476,207	342.1 (340.5–343.8)
Safest	45,760 (27.1%)	114,048.9	401.2 (397.6–404.9)	98,648 (60.6%)	293,416.5	336.2 (334.1–338.3)
Other	123,408 (73.0%)	331,931.1	371.8 (369.7–373.9)	64,280 (39.5%)	182,790.3	351.7 (348.9–354.4)

Safest group consists of progestogens levonorgestrel, norethisterone, norgestimate.

Other group consists of progestogens desogestrel, gestodene, drospirenone, cyproterone, nomegestrol, dienogest.

COC, combined oral contraceptives; EMA, European Medicines Agency; PY, person-years; IR, incidence rate; CI, confidence interval.

* Time period 1 (1 January 2012 to 31 January 2014) and Time period 2 (1 February 2014 to 29 February 2016) refers to the periods before and after the European Medicines Agency (EMA) review and recommendation, respectively.

** Switching between different types means between progestogens (not between different doses).

The slight change that is seen in the VTE incidence is not only observed within the overall new user group, but also within the group of women using COC containing levonorgestrel, norethisterone, or norgestimate and the women using COC containing other progestogens. This suggests that COC were prescribed to different risk women in the second time period, i.e. to lower risk women in Netherlands and UK and to higher risk women in Denmark.

Preparations containing the progestogens levonorgestrel, norethisterone, or norgestimate were already preferentially prescribed in all three countries before the EMA review and recommendations. The Dutch GP guidelines in 2011 and the Danish medicinal products agency in 2012 stated that physicians should preferably prescribe COC containing levonorgestrel with 30 micrograms of estrogen [13,14]. Furthermore, in Denmark during the period between 2011 and 2014, the

number of women using a COC containing levonorgestrel, norethisterone, or norgestimate, was increasing to surpass COC containing desogestrel or gestodene as the most commonly dispensed COC, with only about 11% of new users receiving a COC containing desogestrel, gestodene, drospirenone or cyproterone acetate by the end of 2014 [15]. A British study using data from the THIN showed a much larger proportion of new users of COC containing levonorgestrel (70.1%) in the year 2002 compared to drospirenone (9.4%) and cyproterone (42.6%). These proportions increased slightly for all progestogen types (levonorgestrel: 74.3%; drospirenone: 19.2%; cyproterone: 49.8%) in 2010. Then also, the COC containing the progestogen levonorgestrel was the most commonly prescribed COC type [16].

Data on the source population of all women aged 18–49 years was available in Denmark and UK, and showed as mentioned above, a

Table 2c
New users, switchers and stoppers of COC before and after EMA recommendations (United Kingdom)

	COC users	Total PY	IR per 1000 PY (95% CI)	COC users	Total PY	IR per 1000 PY (95% CI)
		Time Period 1*			Time Period 2*	
New users (overall)	44,300	772,287	57.4 (56.8–57.9)	33,712	695,154	48.5 (48.0–49.0)
Levonorgestrel	27,843 (62.9%)	772,290	36.1 (35.6–36.5)	22,836 (67.7%)	695,150	32.9 (32.4–33.3)
Norethisterone	2480 (5.6%)	772,290	3.2 (3.1–3.3)	1779 (5.3%)	695,150	2.6 (2.4–2.7)
Norgestimate	4085 (9.2%)	772,290	5.3 (5.1–5.5)	2500 (7.4%)	695,150	3.6 (3.5–3.7)
Gestodene	1092 (2.5%)	772,290	1.4 (1.3–1.5)	632 (1.9%)	695,150	0.9 (0.8–1)
Desogestrel	3270 (7.4%)	772,290	4.2 (4.1–4.4)	2378 (7.1%)	695,150	3.4 (3.3–3.6)
Drospirenone	3433 (7.7%)	772,290	4.4 (4.3–4.6)	2244 (6.7%)	695,150	3.2 (3.1–3.4)
Nomegestrol	5 (0.0%)	772,290	0 (0–0)	14 (0.0%)	695,150	0 (0–0)
Dienogest	79 (0.2%)	772,290	0.1 (0.1–0.1)	33 (0.1%)	695,150	0 (0–0.1)
Cyproterone acetate	2013 (4.5%)	772,290	2.6 (2.5–2.7)	1296 (3.8%)	695,150	1.9 (1.8–2)
Switchers (different type)**	17,284	290,113	59.6 (58.7–60.5)	11,790	218,157	54.1 (53.1–55.0)
Safest to Other	5255 (30.4%)	211,434	24.8 (24.2–25.5)	3432 (29.1%)	162,422	21.1 (20.4–21.8)
Other to Safest	3697 (21.4%)	78,679	47.0 (45.5–48.5)	2742 (23.3%)	55,735	49.2 (47.4–51.1)
Stoppers	63,878	290,113	220.2 (218.5–222.0)	49,326	218,157	226.2 (224.2–228.2)
Safest	46,168 (72.3%)	211,434	218.4 (216.4–220.4)	36,615 (74.2%)	162,422	225.4 (223.1–227.8)
Other	17,710 (27.7%)	78,679	225.1 (221.8–228.4)	12,711 (25.8%)	55,735	228.1 (224.1–232.1)

Safest group consists of progestogens levonorgestrel, norethisterone, norgestimate.

Other group consists of progestogens desogestrel, gestodene, drospirenone, cyproterone, nomegestrol, dienogest.

COC, combined oral contraceptives; EMA, European Medicines Agency; PY, person-years; IR, incidence rate; CI, confidence interval.

* Time period 1 (1 January 2012 to 31 January 2014) and Time period 2 (1 February 2014 to 29 February 2016) refers to the periods before and after the European Medicines Agency (EMA) review and recommendation, respectively.

** Switching between different types means between progestogens (not between different doses).

Table 3
Change in VTE incidence among all new users and within new users of the safest and other progestogens in the three countries

	Time Period 1*				Time Period 2*				
	COC Users	VTE Events	Total PY	IR per 10,000 PY (95% CI)	COC Users	VTE Events	Total PY	IR per 10,000 PY (95% CI)	IRR of VTE (95% CI)
Netherlands									
VTE Events defined as Heparin + VKA or DOAC									
New users	534,939	225	316,524.0	7.1 (6.2–8.0)	427,500	123	272,115.9	4.5 (3.7–5.3)	0.6(0.5–0.7)
Safest	411,134	166	253,378.6	6.6 (5.6–7.6)	358,414	95	230,272.1	4.1 (3.3–5.0)	0.6 (0.5–0.7)
Other	123,805	59	63,145.4	9.3 (7.0–11.7)	69,086	28	41,843.9	6.7 (4.2–9.2)	0.7 (0.6–0.8)
VTE Events defined as VKA or DOAC									
New users	534,939	318	316,620.7	10.0 (8.9–11.2)	427,500	250	272,173.8	9.2 (8.1–10.3)	0.9 (0.9–0.9)
Safest	411,134	250	253,454.1	9.9 (8.6–11.1)	358,414	202	230,326.4	8.8 (7.6–10.0)	0.9 (0.9–0.9)
Other	123,805	68	63,166.6	10.8 (8.2–13.3)	69,086	48	41,847.4	11.5 (8.2–14.7)	1.1 (1.0–1.1)
Denmark									
New users	66,402	58	52,000.0	11.2 (8.3–14.0)	59,762	68	47,900.0	14.2 (10.8–17.6)	1.3 (0.9–1.8)
Safest	48,774	41	38,400.0	10.7 (7.4–14.0)	49,653	47	40,100.0	11.7 (8.4–15.1)	1.1 (0.7–1.7)
Other	17,628	17	13,600.0	12.5 (6.5–18.4)	10,109	21	7800.0	26.8 (15.3–38.3)	2.2 (1.1–4.1)
United Kingdom									
New users	44,152	40	29,712	13.5 (9.9–18.4)	49,239	33	33,534	9.8 (7.0–13.8)	0.8 (0.5–1.2)
Safest	34,297	26	23,062	11.3(7.7–18.6)	39,227	26	26,832	9.7 (6.6–14.2)	0.9 (0.5–1.5)
Other	9855	14	6648	21.1(12.5–35.6)	10,012	7	6702	10.4(5.0–21.9)	0.5(0.2–1.3)

Safest group consists of progestogens levonorgestrel, norethisterone, norgestimate.

Other group consists of progestogens desogestrel, gestodene, drospirenone, cyproterone, nomegestrol, dienogest.

VTE, venous thromboembolism; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; PY, person-years; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval.

* Time period 1 (1 January 2012 to 31 January 2014) and Time period 2 (1 February 2014 to 29 February 2016) refers to the periods before and after the European Medicines Agency (EMA) review and recommendation, respectively.

decreased incidence rate of women initiating a COC in the period following the Commission's decision compared to the period before. This may be due to more women initiating alternative contraceptive methods, such as progestogen-only pills or intrauterine devices (IUD). The number of women using COC in Denmark decreased by 9% during the period from 2011 to 2014, so the decrease in new users identified in this study may be part of a larger trend away from COC in Denmark [15].

Among prevalent COC users, switching between COC preparations did not demonstrate a clear pattern towards COC containing levonorgestrel, norethisterone, or norgestimate across all three countries, as may have been expected after the Commission's decision. However, in all three countries the overall incidence rate of switching decreased in the second time period. This may be an indication that more women were satisfied with their initial COC preparation or that more women switched to an alternative to the contraceptive pill rather than to a different COC preparation. Previous research has suggested that the number of women stopping COC increased in Netherlands as different forms of contraception were utilized more frequently, such as IUD [17]. Similarly in UK, the usage of long acting reversible contraceptives (LARC), such as injectables, implants and IUD have increased over the last 10 years [18]. The slight increased incidence rate of COC discontinuation observed in UK in the second time period of this study would also support the latter explanation for fewer switches, though these analyses cannot definitively determine the cause for the decreased incidence of switching COC.

This study has a few limitations. Firstly, in all three countries COC are prescribed by general practitioners/gynecologists. This may not be representative of practices and trends in other European countries. In contrast to Netherlands and Denmark, the UK data only reflects a prescription from a GP and not filled prescriptions/dispensings by women at pharmacies, representing "primary compliance". This may potentially lead to an overestimation of the actual intake of COC in UK; however, this is unlikely to affect any trend in prescription that can be observed. Thirdly, the definition of new users indicates that these are not all first time users. This may have led to an underestimation of the VTE incidence, since previous users without a history of VTE are less prone to develop VTE, consistent with the attrition of susceptibles principle. Furthermore, stoppers are defined as women without a subsequent COC prescription in the 7 months after the final prescription. Though uncommon, it is possible that women received prescriptions that lasting more than 6 months, which would overestimate stoppers. For both these limitations, it is important to keep in mind that the aim was to assess trends between two time periods, and all definitions are consistent in both time periods. A limitation of the SFK is the lack of information regarding the definitive diagnosis of VTE; however, we used two proxies for VTE diagnosis to minimize this limitation. Nonetheless, the analysis using prescription of a VKA or DOAC as a proxy may overestimate VTE incidence because the VKA treated group includes women treated for atrial fibrillation. The second analysis using the prescription of heparin with a VKA or DOAC may underestimate VTE incidence because the SFK includes information from community pharmacies, but not hospital

Table 4
Change in VTE incidence in all women aged 18–49 years (i.e., the source population) (Denmark and United Kingdom)

	Time Period 1*			Time Period 2*			
	VTE events	Total PY	IR per 10,000 PY (95% CI)	Denmark			
				VTE events	Total PY	IR per 10,000 PY (95% CI)	IRR of VTE (95% CI)
Overall	1863	2,185,144.0	8.5 (8.1–8.9)	2059	2,136,297.0	9.6 (9.2–10.1)	1.130 (1.128–1.133)
				United Kingdom			
Overall	1129	1,567,700.0	7.2 (6.8–7.6)	890	1,267,700.0	7.0 (6.6–7.5)	0.975 (0.971–0.979)

VTE, venous thromboembolism; PY, person years; IR, incidence rate; IRR, incidence rate ratio; CI, confidence interval.

* Time period 1 (1 January 2012 to 31 January 2014) and Time period 2 (1 February 2014 to 29 February 2016) refers to the periods before and after the European Medicines Agency (EMA) review and recommendation, respectively.

pharmacies. Women who received heparin in hospital are therefore missed. Heparin is also given for prophylaxis during surgeries, dialysis etc. However, these conditions are rare in young women and are unrelated to COC use. In addition, our selection consisted of heparin and VKA and not just heparin. Therefore, an underestimation of VTE events due to this is unlikely.

The SFK also lacked information on the source population and was unable to follow women that switched pharmacies. These limitations did not allow for the calculation of the incidence rate of new users, nor an accurate estimate of the incidence rate of stoppers, so these values were not reported.

A key strength of this study is the use of large national databases, representative of the three participating countries. This study also allowed comparison between three countries to assess the potential effect of the implementation of EMA recommendation in Europe.

In conclusion, all three countries had the greatest proportion of women initiating a COC containing levonorgestrel, norethisterone, or norgestimate, and this proportion increased in the period after the European commission decision albeit the increase was small due to the high percentage of use before the decision. This did not translate into a measureable change in the incidence of VTE.

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A. van Hylckama Vlieg and I. Petersen designed the study. D. Khialani, M. Jones, S. Szépligeti and A. Ording analyzed and interpreted the data. D. Khialani and A. van Hylckama Vlieg drafted the manuscript. M. Jones, I. Petersen, S. Szépligeti, A. Ording, V. Ehrenstein critically revised the manuscript for important intellectual content.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.conx.2020.100018>.

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