Thromboembolic safety of norethisterone vs levonorgestrel in combined oral contraceptive users: a pooled analysis of 4 large prospective cohort studies

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BACKGROUND: Norethisterone (acetate) and levonorgestrel are marketed globally as components of combined oral contraceptives. Although guidelines recommend both as first-line combined oral contraceptives, no direct, comparative safety studies are available.

OBJECTIVE: We directly compared the thromboembolic event risk associated with the use of norethisterone acetate-containing and levonorgestrel-containing combined oral contraceptives.

STUDY DESIGN: Data regarding the cohorts of interest, norethisterone/norethisterone acetate (ethinylestradiol ≤30 μg) and levonorgestrel (ethinylestradiol ≤30 μg), were retrieved from a pooled dataset comprising 4 prospective, noninterventional, active-surveillance cohort studies in 14 European countries, the United States, and Canada, with similar study design but differing medication cohorts. Baseline characteristics and parameters of reproductive, contraceptive, and medical history were summarized using descriptive statistics. Propensity score subclassification was applied to balance baseline parameters between cohorts. Time-to-event analysis of venous thromboembolic events was performed on the basis of the extended Cox model to calculate crude and adjusted hazard ratios, including 95% confidence intervals. The time of venous thromboembolic events was censored at the end of the observation period for women who did not have an event. Women who dropped out or were lost to follow-up without reported venous thromboembolic events were censored at the time they last confirmed that they did not have an event.

RESULTS: The pooled dataset included 235,437 combined oral contraceptive users who were followed up for a total of 571,163 women years. Among these, 40,142 women were users of norethisterone/norethisterone acetate (ethinylestradiol ≤30 μg), and 39,098 women were users of levonorgestrel (ethinylestradiol ≤30 μg), contributing 61,976 and 84,816 women years of observation, respectively. The observed prevalence of prognostic factors at baseline showed typical features of US and European combined oral contraceptive users. Both cohorts showed a similar, low rate of thromboembolic events, and we could exclude a 1.5-fold increased venous thromboembolism risk for norethisterone/norethisterone acetate relative to levonorgestrel (adjusted hazard ratio, 0.73; 95% confidence interval, 0.48–1.11).

CONCLUSION: These data confirm the similar risk profiles of norethisterone/norethisterone acetate and levonorgestrel regarding thromboembolic events in routine combined oral contraceptive use of around 80,000 women from Europe and the United States/Canada. The analysis provides reassurance for both combined oral contraceptive users and clinicians regarding the safety of oral contraceptives and potentially opens discussion on norethisterone acetate as a potential gold standard therapy in clinical and postmarket research alongside levonorgestrel-combined oral contraceptives.

Key words: combined oral contraceptives, hormonal contraception, levonorgestrel, norethisterone acetate, safety profile, thromboembolic event, thromboembolic risk, venous thromboembolic events

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Why was this study conducted?

Norethisterone acetate-combined oral contraceptives (COCs) are widely used in the United States and recommended as first-line hormonal therapy alongside levonorgestrel-COCs. However, there are limited published data directly comparing the safety profiles of the 2 medicines. We undertook a direct comparative analysis of norethisterone acetate-containing COCs and levonorgestrel-containing COCs, assessing their thromboembolic safety profiles.

Key findings

We could exclude a 1.5-fold increased venous thromboembolism risk for norethisterone/norethisterone acetate relative to levonorgestrel.

What does this add to what is known?

The analysis provides reassurance for both COC users and clinicians regarding the safety of oral contraceptives and potentially opens discussion on norethisterone acetate as potential gold standard therapy alongside levonorgestrel in clinical and postmarket research on COCs.

Introduction

Combined oral contraceptives (COCs) containing a combination of estrogen and progestin provide reliable contraception and noncontraceptive benefits, such as bleeding control and pelvic pain reduction. The safety profile of COCs is generally well-established. Age, body mass index (BMI), and family history of thromboembolic events are recognized as significant, independent cofactors that increase a user's risk of experiencing such events while using hormonal therapy. Use of COCs is therefore contraindicated in the presence of specific conditions (eg, a combination of age ≥35 years and smoking ≥15 cigarettes per day[1]). However, in most women, low-dose COCs (containing 10−30 μg of estrogen) are considered a safe and reliable contraceptive choice.[2,3] Although an increased relative thromboembolic risk during hormonal treatment is present, the absolute increase in risk is low and does not outweigh the health benefits, particularly when compared with the thromboembolic risk during pregnancy or the postpartum period.[4]

The estrogenic component of combined hormonal contraceptives is generally believed to drive the increased thromboembolic risk associated with these medications.[5] Consequently, over the last decades a gradual reduction of the estrogen dosage, from 75 to 150 μg down to 10 to 30 μg, improved the safety profile of COCs, while maintaining contraceptive and therapeutic efficacy.[6] There have been ongoing discussions on whether the progestin component additionally influences the thromboembolic risk associated with COCs, and if so, whether this varies between different types of progestins. Starting from the late 1960s, several progestin generations have been developed in a continuous attempt to improve cycle control and tolerability of COCs.[7] However, with the exception of levonorgestrel (LNG), the release of new estrogen-progestin combinations into the market has been earmarked by pill scares based on epidemiologic data suggesting an increased risk of venous thromboembolic events (VTEs) compared with earlier pill generations.[6,8,9]

Norethisterone acetate (NETA) and LNG were 2 of the first progestins introduced for medical use and are classified as first- and second-generation progestins, respectively. From a research perspective, LNG is the first-choice progestin, and it has been accepted by regulators as the gold standard because it has been shown to not increase the thromboembolic risks derived from the estrogen component (most frequently ethinylestradiol [EE]).[10] LNG is currently used in monophasic and triphasic formulations of COCs and at a low dosage (30 μg) in progestogen-only pill formulations. It is further used in emergency birth control pills, combined hormonal menopausal therapy, intrauterine devices, and subcutaneous implants. NETA is a prodrug of norethisterone (NET). NET and NETA are marketed as progestin-only oral contraceptives (available in Europe), progestin-only injectable contraceptives, COCs, and combined hormonal menopausal therapy. They are considered to have almost identical safety profiles and a low risk of venous and arterial thromboembolism. NET/NETA-containing COCs are recommended as first-line therapy alongside LNG-containing COCs.[10]

No data are currently available directly comparing the thromboembolic risk profiles of LNG and NET/NETA. We have conducted several large, prospective cohort studies on the risk of VTEs associated with the use of hormonal contraceptives. All studies were designed as noninferiority trials. In 4 of these studies,[11−14] a substantial number of women using COCs containing NET/NETA or LNG in combination with low-dosage (≤30 μg) EE were included. On the basis of these studies, we performed a pooled analysis to assess whether NETA/EE-containing COCs carry a different thromboembolic risk compared with LNG/EE-containing COCs.

Materials and Methods

Data source

The pooled subject-level data originated from 4 large, prospective, observational, active-surveillance cohort studies that focused on the occurrence of self-reported, medically confirmed VTEs associated with the use of hormonal contraceptives. All included studies followed the European Active Surveillance Study/International Active Surveillance Study (EURAS/INAS) study design.[12,15]

Table 1 shows key characteristics, such as study setting, sample size, and primary endpoints of all included studies. Patient inclusion and exclusion criteria, the method of patient recruitment and follow-up, and obtained data (including prognostic factors for VTEs) were similar among the studies. The recruitment process via gynecologists did not interfere with the usual prescribing behavior or with the individual needs of the participants. The specific COCs were prescribed according to routine clinical practice, and the study

TABLE 1
Study overview

Study name	EURAS-OC/LASS	INAS-OC	INAS-SCORE	INAS-FOCUS
Design	Prospective, noninterventional cohort study	Prospective, noninterventional cohort study	Prospective, noninterventional cohort study	Prospective, noninterventional cohort study
Study period	Nov 2000—Dec 2010	Aug 2005—March 2013	Aug 2009—Feb 2017	Nov 2010—Feb 2019
Cohorts (baseline)[a] Target Comparator	DRSP LNG, Other OCs	DRSP24d, DRSP21d, Other OCs	DNG/E2Val, Other OCs	DRSP/EE+, DRSP-EE-, Other OCs
Sample size	59,510	85,100	50,203	82,882
Number of participants included in analysis	58,020	82,382	38,394	56,641
Max. follow-up	10 y	5 y	7 y	8 y
Setting	EURAS-OC: Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom LASS: Germany and Austria	United States, Austria, Germany, Italy, Poland, and Sweden	United States, Austria, France, Germany, Italy, Poland, Sweden, and the United Kingdom	United States, Canada, Russia, and Ukraine
Primary outcomes	VTE, ATE	VTE, ATE	VTE, ATE	VTE, ATE
Secondary outcomes	Unintended pregnancy, acute renal failure, hepatic diseases, breast cancer (LASS)	Return to fertility, drug utilization	Unintended pregnancy, adolescents	Cancer, unintended pregnancy

ATE, arterial thromboembolism; *DNG*, dienogest; *DRSP*, drospirenone; *E2Val*, estradiol valerate; *EE*, ethinylestradiol; *EURAS-OC*, European Active Surveillance Study for Oral Contraceptives; *INAS-FOCUS*, International Active Surveillance Study — Folate in Oral Contraceptives Utilization Study; *INAS-OC*, International Active Surveillance Study of Women Taking Oral Contraceptives; *INAS-SCORE*, International Active Surveillance Study — Safety of Contraceptives: Role of Estrogens; *LASS*, Long-term Active Surveillance Study; *LNG*, levonorgestrel; *OC*, oral contraceptives; *VTE*, venous thromboembolic event.

[a] Hormonal cohort abbreviations: DRSP=DRSP/EE-containing COCs, DRSP24d (containing 24 "active" DRSP/EE pills and 3 "sugar" pills), DRSP21d (containing 21 active DRSP/EE pills and 7 "sugar" pills), DRSP/EE+ containing DRSP/EE and 451 μg of metafolin (L-5-methyltetrahydrofolate), DRSP/EE- containing DRSP/EE without additional folate, DRSP/E2 containing drospirenone (0.5 or 2 mg) with 1 mg 17beta-estradiol (E2), LNG-containing OCs.

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was discussed with the participants only after a COC was decided. No additional medical inclusion or exclusion criteria were applied. All users of a new COC were eligible for study inclusion. However, women who were not willing to participate in long-term follow-up or had a language barrier were excluded.

Baseline questionnaires used in all studies captured basic demographics in addition to reproductive, contraceptive, and medical history, and specific information on cardiovascular risk factors. During follow-up, participants were actively contacted every 6 to 12 months and received a questionnaire designed to capture relevant patient-reported clinical outcomes, adverse events, and hormonal treatment history. Patient-reported VTEs were validated by the study team via medical source documentation. At study end, all VTEs underwent blinded adjudication via independent subject-matter experts.

Because of a 4-level follow-up process that included reestablishing contact with study participants via next-of-kin, gynecologists, and telephone and address-registry searches, a low loss-to-follow-up rate (mean 6.3%) was achieved in all studies.

Cohorts and outcomes of interest

In the pooled dataset we defined 2 cohorts of interest: users of NET or NETA combined with EE ≤30 μg and users of LNG combined with EE ≤30 μg, referred to as NET/NETA (EE ≤30 μg) and LNG (EE ≤30 μg). The outcome of interest was defined as VTEs (including deep venous thrombosis [DVT] and pulmonary embolism [PE]).

Statistical analysis

We evaluated the noninferiority of thromboembolic safety of NET/NETA compared with the gold standard LNG. For postmarketing studies assessing the thromboembolic risk of COCs, the United States Food and Drug Administration requires a study design capable of detecting a 1.5- to 2-fold increased risk for VTEs. With a sample size of 61,976 and 84,816 women years (WY) of observation in the NET/NETA (EE ≤30 μg) and LNG (EE ≤30 μg) cohorts, respectively, a 1-sided test size (alpha level) of 0.025, and an assumed VTE incidence of 9/10,000 WY, the statistical power was estimated as 98% to exclude a 2-fold increased risk for VTEs.

Baseline characteristics, including reproductive, contraceptive, and medical history, were summarized descriptively. The incidence of VTEs was obtained during follow-up and expressed as incidence rate (IR) based on the occurrence of new cases per 10^4 WY.[16] Time-to-event analysis of VTEs was performed on the basis of the

extended Cox model to calculate crude and adjusted hazard ratios (HR) with 95% confidence intervals (CI). Propensity score (PS) subclassification was applied to balance baseline covariates between cohorts.[17,18] All baseline (time-fixed) population characteristics have been included in the PS model as linear terms, and age and BMI have been additionally included as quadratic terms. The adequacy of the PS model was assessed by comparing exposure cohort subjects within strata based on the absolute standardized difference of continuous and binary covariates. Absolute standardized differences with a value of <0.1 (10%) have been used to indicate adequate balance between exposure groups, and 0.25 served as a threshold for imbalance, as suggested by Imbens and Wooldridge.[19] All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC).[20]

Ethics

Studies were conducted in accordance with the ethical principles of the Declaration of Helsinki; planning and study conduct were subject to the national laws and regulations of the participating countries, including approval from local institutional review boards/independent ethics committees. All studies were registered in the public clinical trials registry of the United States National Library of Medicine. All participants signed an informed consent form at baseline.

Results

Participants

Overall, 235,437 study participants who were followed up for a total of 571,163 WY of exposure were included in the pooled dataset. Among these, 40,142 women were users of NET/NETA (EE ≤30 μg), and 39,098 women were users of LNG (EE ≤30 μg), contributing 61,976 and 84,816 WY of observation, respectively.

Descriptive data

Table 2 depicts the number of study participants with baseline information, region of origin, and descriptive statistics on participant characteristics (age, weight, and BMI), gynecologic history, hormonal

TABLE 2
Population characteristics of study participants

Population characteristics	NET/NETA (EE ≤30 μg)	LNG (EE ≤30 μg)
Number of women	40,142 (100.0)	39,098 (100.0)
Region of origin: European Union	1100 (2.7)	26,664 (68.2)
Patient characteristics		
Age at study entry (y)	26.3±7.71	25.1±8.10
Age <20	7613 (19.0)	11,374 (29.1)
20–<30	21,073 (52.5)	17,711 (45.3)
30–<40	8386 (20.9)	7151 (18.3)
40–<50	2836 (7.1)	2748 (7.0)
≥50	234 (0.6)	114 (0.3)
Missing	0	0
Weight at study entry (kg)	70.2±18.15	65.1±14.64
Height at study entry (cm)	164±7.1	166±6.7
BMI at study entry (kg/m^2)	26.1±6.39	23.7±5.13
<25	21,753 (54.2)	27,934 (71.4)
25–<30	9383 (23.4)	6928 (17.7)
30–<35	4890 (12.2)	2534 (6.5)
35–<40	2232 (5.6)	1001 (2.6)
≥40	1655 (4.1)	590 (1.5)
Missing	229 (0.6)	111 (0.3)
Gynecologic history		
Age at menarche (y)	12.6±1.60	12.8±1.46
Ever been pregnant (gravidity)	21,563 (53.7)	15,310 (39.2)
Ever given live birth (parity)	17,453 (43.5)	13,487 (34.5)
Number of live births	1.8±0.9	1.7±0.9
OC history		
Ever used OC (yes/otherwise)	29,284 (73.0)	29,179 (74.6)
Ever switched OC (yes/otherwise)	19,746 (49.2)	17,957 (45.9)
Duration of OC-use at study entry (y)	5.5±5.50	6.0±6.19
Cardiovascular risk factors		
High blood pressure (yes/otherwise)	1466 (3.7)	1173 (3.0)
High cholesterol (yes/otherwise)	1135 (2.8)	828 (2.1)
Family history of ATE (yes/otherwise)	899 (2.2)	612 (1.6)
Family history of VTE (yes/otherwise)	998 (2.5)	1839 (4.7)
Smoker (yes/otherwise)	5383 (13.4)	11,839 (30.3)
Heavy smoker (>15 cigarettes)	734 (1.8)	1934 (4.9)
Medical history		
Diabetes (yes/otherwise)	464 (1.2)	279 (0.7)
Stroke (yes/otherwise)	32 (0.1)	19 (0.0)
Pulmonary embolism (yes/otherwise)	17 (0.0)	18 (0.0)
Deep venous thrombosis (yes/otherwise)	40 (0.1)	98 (0.3)
Cancer (yes/otherwise)	279 (0.7)	185 (0.5)
Myocardial infarction (yes/otherwise)	19 (0.0)	98 (0.3)
Any surgery (yes/otherwise)	13,398 (33.4)	12,311 (31.5)
Medication		
Regular use of medication (yes/otherwise)	12,329 (30.7)	7681 (19.6)
Education		
Higher-than-university entrance level (yes/otherwise)	27,234 (67.8)	17,011 (43.5)

ATE, arterial thromboembolism; *BMI*, body mass index; *EE*, ethinylestradiol; *LNG*, levonorgestrel; *NET*, norethisterone; *NETA*, norethisterone acetate; *OC*, oral contraceptives; *VTE*, venous thromboembolism.

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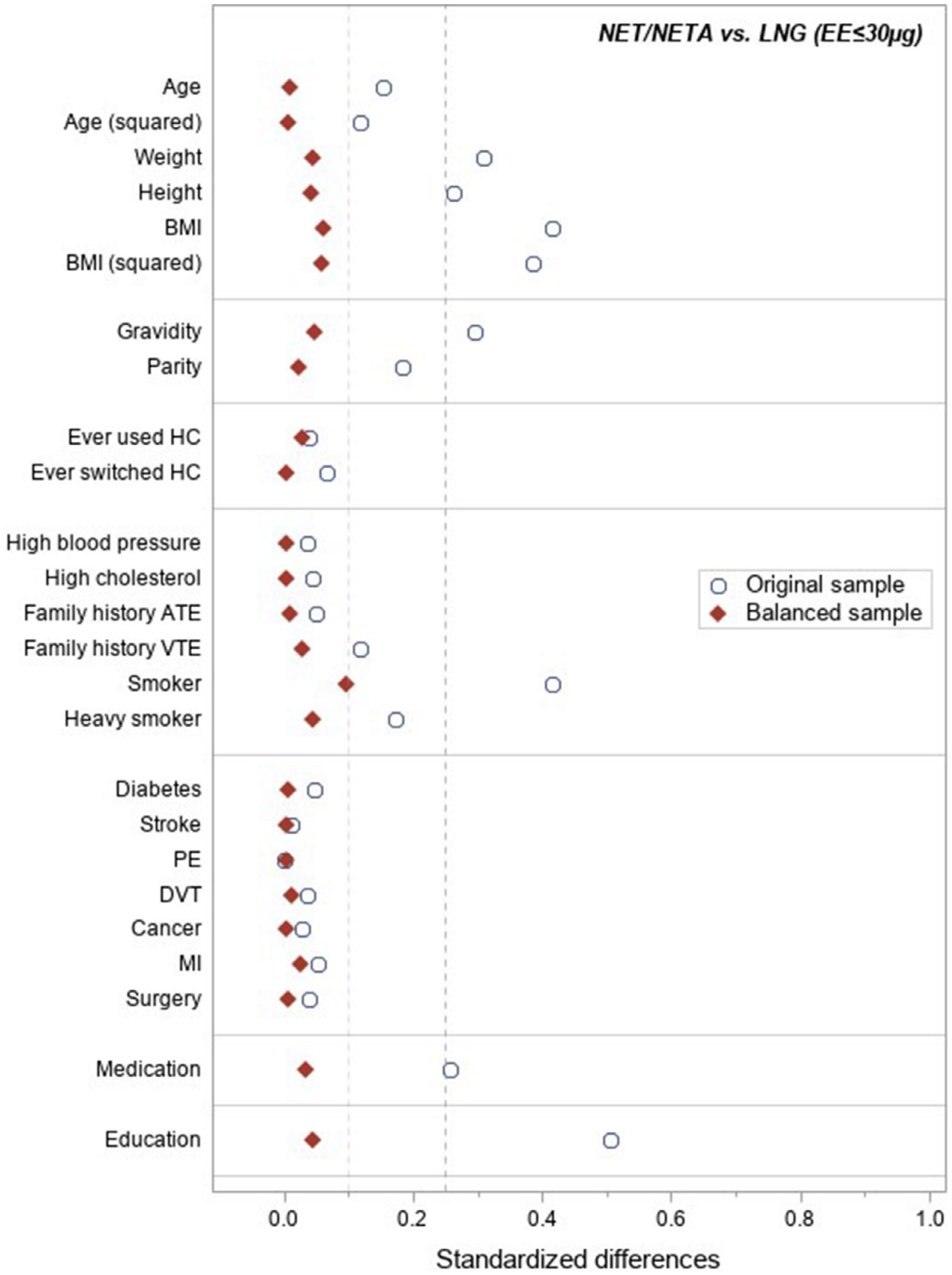
FIGURE 1
Standardized differences in original and propensity score-balanced samples



ATE, arterial thromboembolism; *BMI*, body mass index; *DVT*, deep vein thrombosis; *EE*, ethinylestradiol; *HC*, hormonal contraceptive; *LNG*, levonorgestrel; *MI*, myocardial infarction; *NET/NETA*, norethisterone/norethisterone acetate; *PE*, pulmonary embolism; *VTE*, venous thromboembolism.

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contraceptive history, cardiovascular risk factors, medical history, regular use of medication, and educational background for both cohorts. The greatest part of the NET/NETA (EE ≤30 μg) cohort consisted of study participants from the United States (97.3%), whereas only 31.8% of study participants in the LNG (EE ≤30 μg) cohort originated from the United States.

Overall, baseline characteristics were comparable between the cohorts. Nevertheless, a few differences, which were most likely based on different regional distribution and a slightly uneven age distribution among cohorts, could be observed ("original sample" provided in Figure 1). There were more study participants who had been pregnant at least once before study entry in the NET/NETA (EE ≤30 μg) than in the LNG (EE ≤30 μg) group (53.7% and 39.2%, respectively). This was most likely owing to the age distribution; the NET/NETA (EE ≤30 μg) cohort contained a lower fraction of very young women (aged <20) and a higher fraction of women aged 20−<30, as opposed to the LNG (EE ≤30 μg) cohort. Study participants in the NET/NETA (EE ≤30 μg) group had a significantly higher BMI (mean BMI, 26.1±6.39) than those in the LNG (EE ≤30 μg) cohort (mean BMI, 23.7±5.13). Furthermore, study participants in the NET/NETA (EE ≤30 μg) cohort had a higher propensity (30.7%) for regularly taking medication than study participants in the LNG (EE ≤30 μg) cohort (19.6%). Both a higher mean BMI and increased likelihood to routinely use prescription medication are features often observed in women originating from the United States, as previously described.[13] Overall, both cohorts showed typical characteristics of US and European COC user populations regarding age structure, socioeconomic and lifestyle (ie, smoking) factors and cardiovascular risk factors.[12,14,21]

Main results

In total, 43 validated VTEs in 61,976 WY occurred in the NET/NETA (EE ≤30 μg) user cohort, as opposed to 75 VTEs during an observation time of 84,816 WY in the LNG (EE ≤30 μg) user cohort (Table 3). Thus, study participants taking NET/NETA (EE ≤30 μg) had a similar risk of encountering a VTE (IR, 6.9; 95% CI, 5.0−9.3 per 10,000 WY) to study participants taking LNG (EE ≤30 μg) (IR, 8.8; 95% CI, 7.0−11.1 per 10,000 WY). VTEs were categorized as either DVT and/or PE on the basis of the source documentation. Study participants taking LNG (EE ≤30 μg) showed a higher unadjusted risk of DVT than those taking NET/NETA (EE ≤30 μg), with an overlap of 95% CI. The IRs were 4.5 in 10,000 WY (95% CI, 3.0−6.5) and 7.4 in 10,000 WY (95% CI, 5.7−9.5) in the NET/NETA (EE ≤30 μg) and LNG (EE ≤30 μg) cohorts, respectively. The unadjusted risk of PE was very similar between cohorts; IRs were 2.6 per 10,000 WY (95% CI, 1.5−4.2) and 2.4 per 10,000 WY (95% CI, 1.4−3.6) in the NET/NETA (EE ≤30 μg) and LNG (EE ≤30 μg) cohort, respectively.

A time-to-event analysis was performed on the basis of the extended Cox model considering time-varying exposure to COCs. PS analysis was applied to reduce imbalance of baseline covariates between treatment groups. The validity of the model was demonstrated by the standardized differences summarized over strata as weighted average yielded on PS subclassification, which were consistently <0.25 and mostly <0.1, indicating an adequate balancing of the cohorts on measured baseline covariates (Figure 1).

The crude (unadjusted) HR for NET/NETA (EE ≤30 μg) vs LNG (EE ≤30 μg) regarding VTEs was 0.78 with a 95% CI including unity (95% CI, 0.53−1.16) (Figure 2).

When subclassifying study participants into homogeneous strata based on their PS, an adjusted HR of 0.73 (95% CI, 0.48−1.11) of NET/NETA (EE ≤30 μg) vs LNG (EE ≤30 μg) was measured. Thus, a 1.5-fold increased VTE risk for NET/NETA (EE ≤30 μg) relative to LNG (EE ≤30 μg) could be excluded. As most of the study participants in the NET/NETA (EE ≤30 μg) group came from the United States, an additional US-specific subgroup model was applied and yielded a similar result: HR, 0.76 (95% CI, 0.44−1.32). When considering only DVT or PE events, no major difference in the risk profile could be detected either. Forest plots of crude and adjusted HRs including upper and lower 95% CI highlight the very similar VTE risk profiles of NET/NETA (EE ≤30 μg) and LNG (EE ≤30 μg) users (Figure 2).

TABLE 3
Absolute numbers and incidence rates of venous thromboembolism, deep venous thrombosis, and pulmonary embolism events including 95% confidence intervals

Venous thromboembolism	NET/NETA (EE ≤30 μg)	LNG (EE ≤30 μg)
Women years	61,976	84,816
VTE		
Number of events	43	75
IR (95% CI)[a]	6.9 (5.0−9.3)	8.8 (7.0−11.1)
DVT		
Number of events	28	63
IR (95% CI)[a]	4.5 (3.0−6.5)	7.4 (5.7−9.5)
PE		
Number of events	16	20
IR (95% CI)[a]	2.6 (1.5−4.2)	2.4 (1.4−3.6)

CI, confidence interval; *DVT*, deep venous thrombosis; *EE*, ethinylestradiol; *IR*, incidence rate; *LNG*, levonorgestrel; *NET*, norethisterone; *NETA*, norethisterone acetate; *PE*, pulmonary embolism; *VTE*, venous thromboembolism; *WY*, women years.

[a] IR and CI are presented per 10,000 WYs of exposure.

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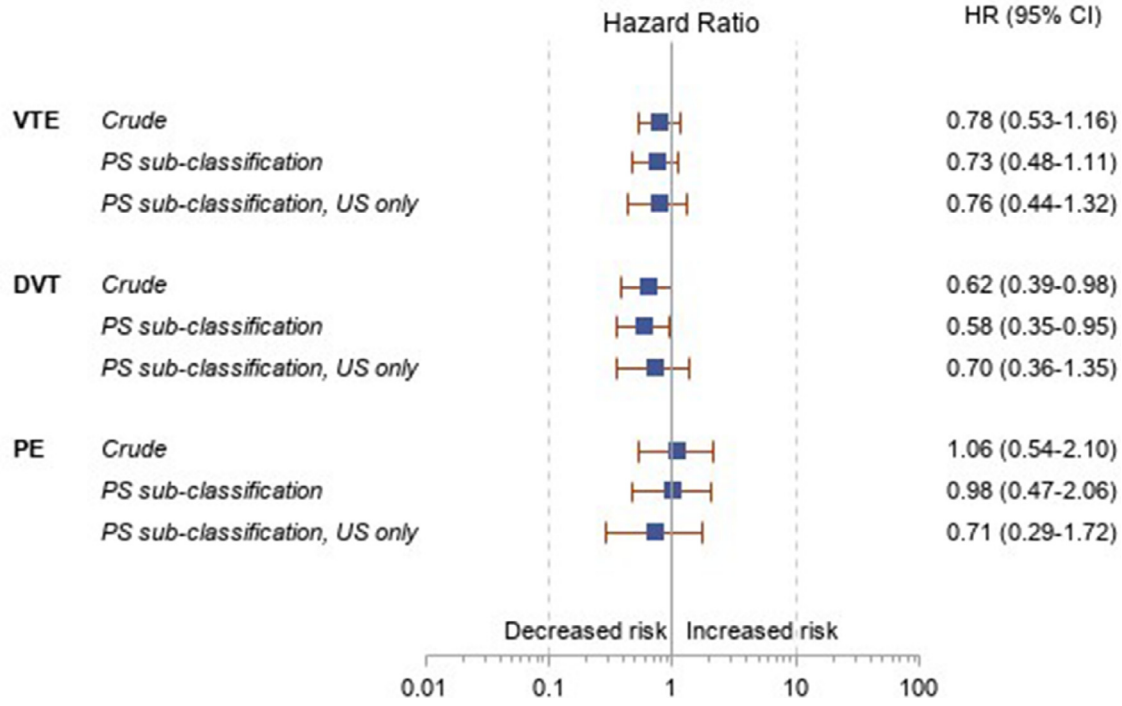
FIGURE 2
Hazard ratios and forest plots for total cohort and US sub-cohorts.



CI, confidence interval; *DVT*, deep vein thrombosis; *HR*, hazard ratio; *PE*, pulmonary embolism; *PS*, propensity score; *VTE*, venous thromboembolism.

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Discussion

Principal findings and implications

LNG and NET/NETA are recommended as first-line hormonal contraceptives[10] because of their relatively low risk of VTEs.[22] There is a small but real increased VTE risk associated with these medications.[23] To date, there are no data that directly compare the risk of VTEs with LNG and NET/NETA.

Thus, this pooled analysis aimed to assess the safety profile of NET/NETA compared with the regulatory gold standard progestin, LNG, in combined hormonal treatments.

The observed prevalence of prognostic factors at baseline was similar to that described in previous studies.[12,24] Overall, cohorts showed typical features of US and European COC users with respect to age, lifestyle, and cardiovascular risk factors. Because of regional differences in prescribing practices, the pooled-analysis cohort compositions varied with respect to region of origin. The NET/NETA cohort comprised almost only study participants from the United States, whereas approximately two-thirds of the LNG cohort came from the United States and one-third from Europe. This distribution might explain the few differences seen in baseline characteristics between cohorts, in particular age distribution, BMI, and frequency of medication use. Our studies consistently observed a trend toward higher BMI at study enrollment and a more pronounced use of concomitant medication in US study participants than in European study participants. These 2 US-specific cohort characteristics are reflected in the baseline data of the NET/NETA (EE $\leq$30 μg) cohort, comprising mostly study participants from the United States.

To reduce the potential for observed differences in the distribution of established risk factors for thromboembolic events, a PS subclassification was carried out, which successfully balanced baseline characteristics between cohorts, as expressed by standardized differences consistently <0.25. This approach equally accounted for confounding variables in both cohorts, rendering them comparable with regard to the occurrence of treatment-related events. An additional US-specific analysis accounted for the uneven geographic distribution of cohorts.

Our results show that the VTE IR is low in both COC cohorts, implying that the absolute risk of VTEs with either formulation is low when compared with several other progestins, as reported previously.[25–27] Moreover, we observed that a 1.5-fold increased VTE risk for NET/NETA-containing COC users relative to LNG-containing COC users could be excluded. These results are in line with previous data showing a similar thromboembolic risk profile of NETA and LNG[28] and with the clinical prescribing guidelines recommending LNG and NETA as first-line oral contraceptives.[10] Currently, LNG is the gold standard active comparator[29] for postauthorization safety studies

of COCs. It is unclear why NET/NETA is not considered a valid active comparator alongside LNG, although absence of direct comparative analysis of LNG and NET/NETA may be a contributing factor.

Strengths and limitations

A comparative analysis of VTEs in women taking different hormonal treatments is generally complicated by the rare occurrence of these events and by the influencing risk factors other than the treatment itself, such as age, smoking, and personal and family history of certain diseases. The nature of observational, noninterventional study design cannot completely account for differences in these variables, nor can they be completely balanced by the use of PSs. Any confounding variable not considered in the PS model (eg, because it is unknown/unmeasured) might lead to a residual risk of hidden bias, which is a methodological limitation of any observational study.[30,31]

A key strength of the EURAS/INAS study design, and therefore the pooled analysis, is that the typical potential distorting factors of observational research were limited. Factors associated with prescription choice were measured at baseline and accounted for through the PS-subclassification analysis. A low loss-to-follow-up could be obtained for all included studies, in part because of the ability to follow-up directly with study participants even if they did not return to the enrolling center. Selection bias was not a major issue because adverse events of in- and out-patients were included in the analyses, and the demographic characteristics of the participants were representative for COC users. Misclassification bias probably had no substantial impact on the results because precise information on the exposure and the outcomes of interest were available. Finally, reliable information on the duration of current use was available.

All included studies possess numerous methodological strengths that are substantial for the validity of our results. First, a prospective, comparative cohort design and the availability of the above-mentioned confounder information. Second, the accurately controlled validation process, a blinded adjudication of outcomes of interest, and a rigorous follow-up procedure. Finally, the sophisticated statistical analyses (eg, stratified analyses by geographic region, sensitivity analyses on the impact of the adjudication process, outcome definition, prognostic factor/covariate selection, and choice of comparator cohort), which were further strengthened by the PS-subclassification applied in this analysis. Furthermore, the study design enabled observing representative populations of oral contraceptive users under routine clinical conditions.

Conclusions

Our pooled analysis, based on 4 prospective, noninterventional cohort studies comprising 79,240 premenopausal women who were followed up for a total of 146,792 WY, showed that NET/NETA and LNG carry a similar low VTE risk when contained in a combined hormonal preparation. Within the general limitations of observational research, we conclude that the pooled analysis and the primary design of the included studies are methodologically sufficient to exclude an increased risk of NET/NETA in premenopausal women. Given that all included studies did not interfere with prescription behavior of treating healthcare practitioners and reflected routine contraceptive use in around 80,000 women of reproductive age in a wide geographic range covering 14 European countries and the United States/Canada, we believe that the generalizability of these results is high. These data provide real-world evidence directly comparing the VTE risk profiles of NET/NETA- and LNG- containing COCs, providing reassurance to clinicians and regulators that their risk profiles are low and comparable. ■

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