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Cardiovascular risks associated with the use of drospirenone-containing combined oral contraceptives ☆

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Abstract

Objectives: The "Long-term Active Surveillance Study for Oral Contraceptives" investigated the risks of long-term use of a 21-day regimen of drospirenone and ethinylestradiol (DRSP) compared to established oral contraceptives (OCs) in a routine clinical setting.

Study design: Prospective, controlled, non-interventional cohort study conducted in seven European countries with three main exposure groups: new users of DRSP, levonorgestrel-containing OCs (LNG), and OCs containing other progestogens (Other OCs). All self-reported clinical outcomes of interest (OoI) were validated via attending physicians and relevant source documents. Main OoI were serious clinical outcomes, in particular cardiovascular events. Comprehensive follow-up procedures were implemented. Statistical analyses were based on Cox regression models.

Results: A total of 1,113 study centers enrolled 59,510 women. Overall 28%, 26% and 45% of these women used DRSP, LNG and Other OCs, respectively. Study participants were followed for up to ten years (mean value, 5.4 years), which generated 318,784 woman-years (WY) of observation. Low loss to follow-up and drop-out rates of 2.9% and 16.8% were achieved. DRSP, LNG, and Other OCs showed similar incidence rates of venous thromboembolism. Corresponding hazard ratios (HRs) were close to unity. For arterial thromboembolic events (ATE) and initiation of antihypertensive treatment statistically significant lower risks were found for DRSP compared to LNG and Other OCs.

Conclusion: DRSP use was associated with similar general health risks and a low risk of ATE compared to OCs containing other progestogens.

Implication statement: The 21-day regimen of drospirenone-containing combined oral contraceptives is associated with similar risk of VTE compared to other combined oral contraceptives as well as potentially with a lower risk of ATE.

Keywords: ATE; VTE; Oral contraceptives; Prospective cohort study; Routine clinical practice

1. Introduction

This article describes the final results of the Long-term Active Surveillance Study for Oral Contraceptives (LASS), the follow-up study to the European Active Surveillance (EURAS) Study [1].

The EURAS study was initiated in November 2000 and completed in December 2005. A total of 59,510 users of oral contraceptives (OCs) was enrolled between November 2000 and June 2004 by 1,113 study centers in 7 European countries. Three OC user groups – users of preparations containing 3 mg of drospirenone (DRSP) and 30 μg of ethinylestradiol (EE), levonorgestrel-containing OCs, and OCs containing other progestogens – were followed throughout the study. The results suggested that the overall risk of adverse outcomes as well as the risk of venous and arterial thromboembolism do not differ materially from the risks associated with the use of levonorgestrel-containing OCs or other OCs.

However, the statistical power of the EURAS study to investigate the risk of rare outcomes – such as arterial thromboembolism – was limited. Therefore, another five-year follow-up study of the EURAS cohort, namely the LASS study, was conducted with the expectation that this extended

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follow-up would yield a substantial increase in statistical power. The presented paper reports the results on cardiovascular outcomes. Other outcomes will be reported elsewhere.

2. Materials and methods

A cohort of 58,674 women starting OC use was actively monitored for up to 10 years for the occurrence of rare or unexpected adverse outcomes possibly related to exposure to OCs. The methodology of the LASS study is identical to that of the EURAS study on oral contraceptives described elsewhere [1], so most methodological details are presented succinctly. Some, however, are described in more detail than in the original paper in order to address subsequent discussions of methodology.

Planning, conduct, and evaluation of the study were supervised by an independent Safety Monitoring and Advisory Council, which endorsed all the conclusions presented in this publication. Primary ethical approval of the study was granted by the physicians' association in Berlin, Germany ("Ethik-Kommission der Ärztekammer Berlin"). The study is registered in the public clinical trials registry of the US National Library of Medicine under the registration number NCT00676065.

2.1. Study objectives

The primary objective of the LASS study was to assess the risks of long-term use of DRSP-containing OCs and of established OCs – in particular levonorgestrel-containing OCs – in a study population that is representative for the actual users of the individual preparations. The main clinical outcomes of interest for the long-term follow-up were cardiovascular events, in particular arterial thromboembolism (ATE) such as acute myocardial infarction and stroke, as well as venous thromboembolism (VTE) such as deep venous thrombosis and pulmonary embolism. Secondary objectives were to ascertain: (1) long-term drug utilization patterns of DRSP-containing OCs and established OCs in a study population that is representative for OC use under routine medical conditions, (2) first-time use of antihypertensive drugs following the start of OC use, and (3) the occurrence of other serious diseases such as gynecological cancers. The results on the first and third secondary objective will be reported elsewhere.

2.2. Study population

The LASS study was based on the existing long-term EURAS cohort of 58,674 OC users from seven European countries – Austria, Belgium, Denmark, France, Germany, The Netherlands and the United Kingdom. A random sample of all OC prescribers in these countries was contacted for participation in the study. The 1113 participating study centers had to enroll all women who were OC starters (first-ever users), OC switchers (switching from one OC to another), or OC restarters (restarting OC use following an intake break of at least 4 weeks) provided that they signed the informed consent and data privacy form. More specific inclusion or exclusion criteria were not applied in keeping with the noninterference approach of the study design. These recruitment procedures for study centers and study participants were suitable for the enrollment of a representative sample of typical OC users. A comparison of age structure, socioeconomic and life-style factors, cardiovascular risk factors, the spectrum of prescribed OCs, and the percentages of urban and rural OC users showed similar characteristics of the study population and the representative consumer panels of TNS Infratest [2–4], one of the leading European institute for opinion, political, social and market research. Therefore it can be assumed that the study population reflects quite well the characteristics of the actual OC users in the participating countries.

The EURAS study had followed the study participants for one to five years. When it concluded, a total of 47,799 women were still in follow-up. The LASS study succeeded the EURAS study and extended the follow-up period for an additional 5 years. Over this extended period, ZEG (Berlin Center for Epidemiology and Health Research, Berlin, Germany) maintained active contact (= *active surveillance*) every twelve months with all cohort members. This yielded a total follow-up time of 6 to 10 years for members of this long-term cohort.

2.3. Data collection and quality control

Baseline data were recorded within the EURAS study [1] via self-administered questionnaires on participants' state of health, medical history including medication history and history of OC use, and potential prognostic factors for serious diseases, particularly cardiovascular disease and cancer. Follow-up assessments for each woman in the EURAS study were scheduled every 6 months. In the LASS study this interval was extended to 12 months. It was assumed at the start of the LASS study that women who had responded regularly to questionnaires for up to 5 years would not stop responding if the intervals were longer. The two studies used identical questionnaires, including for the occurrence of adverse events. They requested detailed reasons for discontinuing hormonal contraception or switching to another preparation if applicable. The questionnaires were reviewed for completeness, plausibility and consistency of the responses. Missing or inconsistent information was clarified directly with the women by phone. A low loss to follow-up rate was essential for the validity of the study. In order to minimize loss to follow-up, a comprehensive follow-up process was established which is described elsewhere [1]. For reported serious adverse events – including ATE and VTE – a group of medical doctors specializing in epidemiology, drug safety and internal medicine (medical reviewer group) contacted the study participants as well as the diagnosing or treating physicians

to clarify and validate the information (including diagnosis, diagnostic procedures, exposure and treatment) received from participants [1]. All serious adverse events were classified as confirmed or not confirmed. Events that were confirmed by a diagnostic measure with high specificity (e.g., phlebography for deep venous thrombosis or cerebral magnetic resonance imaging for cerebrovascular accidents) or by a clinical diagnosis supported by a diagnostic test with low specificity (such as D-dimer for venous thromboembolism) were considered confirmed. Events were considered not confirmed if the diagnosis reported by the participant was excluded by diagnostic measures, if a different medical condition was diagnosed by the attending physician, or if the participant did not contact a health professional to clarify her symptoms and no diagnostic measures were performed [1]. The primary analysis was based on confirmed cases only. Unconfirmed cases were only used for sensitivity analyses.

For the final analysis, classification of VTE was verified by independent blinded adjudication. In order to minimize classification bias, all decisions made by the medical reviewer group were reassessed by three independent medical experts specializing in radiology and nuclear medicine, cardiology, as well as internal medicine and vascular diseases. These specialists reviewed all available information on the reported events. Brand names, doses, regimens and compositions of the hormonal contraceptives used by the study participants were rendered anonymous for this process [1].

2.4. Evaluation

The principles of data evaluation are described elsewhere [1]. The analyses were carried out in accordance with the statistical analysis plan, which was approved by the Safety Monitoring and Advisory Council prior to the first inferential analysis.

Cox regression models were used for inferential statistics. Adjustment for potential confounding was based on an a priori defined expert model (primary model). Standard errors in the regression models were adjusted for clustering due to repeated measurements obtained from single individuals at different time points. For venous thromboembolism this model included age, body mass index (BMI), duration of current hormonal contraceptive use and family history of venous thromboembolism; for arterial thromboembolism it included age, BMI, smoking, treated hypertension and a family history of fatal ATE. All these potential confounders were included as time varying covariates in the statistical model. In addition, a "backward stepwise procedure" was chosen to generate a reduced model (secondary model). This procedure started with all available exposures and relevant covariates (e.g., starter, restarter and switcher status, estrogen dose of the OC preparation, educational level) - like in a saturated model. All covariates that had no relevant impact on the risk estimates were removed from the model in a stepwise procedure. The results of the primary and secondary models were nearly identical. Therefore, only the results of the primary model are reported.

Three exposure groups were compared: users of new OCs containing DRSP, users of OCs containing levonorgestrel (LNG), and users of OCs containing other progestogens. In addition, monophasic DRSP and LNG preparations that contained exactly 30mcg EE were compared in order to eliminate the influences of the EE dose and the regimen. All VTE and ATE were always adjudicated for the hormonal contraceptive used by the respective patient at the time. It did not matter whether the patient was a starter, a switcher or a restarter at the time of the event. If hormonal contraceptive use had been stopped during the three-month period prior to the VTE diagnosis, the event was adjudicated to the last hormonal contraceptive used before the event.

The analyses for VTE analyzed two different datasets: all VTE and what are known as idiopathic VTE. The latter dataset excludes VTE cases with acute risk factors (such as pregnancy, delivery, trauma, immobilization, long-haul travel, surgery, and chemotherapy). The analysis of this dataset allows a comparison of the LASS data with the results from other scientific groups who base their analyses on hypothesized idiopathic VTE.

3. Results

A total of 59,510 women was enrolled by 1,113 active study centers. Overall, 836 of these 59,510 women (1.4%) had to be excluded because they: (1) declined to sign the informed consent form, (2) were enrolled two or more times by one or more study centers, (3) continued to use their old OC (long-term users), or (4) did not use any OC. The remaining 58,674 quality-controlled computerized data sets from the women (one per woman) with baseline information were analyzed. In the combined EURAS and LASS studies these 58,674 study participants were followed up for 318,784 woman-years (WY) of observation. At baseline, 16,534 women were prescribed DRSP-containing OCs, 15,428 women had LNG-containing OCs, 26,341 women had other OCs, and 371 women had non-oral hormonal contraceptives (NOHC) such as patches, injections, vaginal rings and intrauterine systems. Although the EURAS study was aimed primarily at users of OCs, the erroneously enrolled new users of NOHC were also analyzed to acquire some data representing the baseline characteristics of women who switched to non-oral contraceptives after study entry.

During follow-up 18%, 21% and 24% of users of DRSP, LNG and Other OCs switched to another OC or NOHC brand. At the end of the LASS study DRSP, LNG, Other OCs and NOHC had been used for 52,278 WY, 57,539 WY, 106,221 WY and 15,177 WY, respectively. For 87,569 WY of 318,784 WY study participants had not used any hormonal contraceptive. Overall, 13% and 1% of this time can be attributed to intended and unintended pregnancies, respectively.

At the end of the EURAS study 1,401 women, or 2.4%, had been lost to follow-up. This means that it was not possible to make contact with these 1401 women after a certain time point in the EURAS follow-up. During the 5 additional follow-up years of the LASS study an additional 668 women were lost to follow up. However, during this period it was possible to reestablish contact with 368 women who had been classified as lost to follow-up at the end of the EURAS study. In sum, 1701 women, or 2.9%, were lost to follow-up during the 10-year follow-up period (Table 1). Furthermore, 16.6% of the study population informed the investigators at some point in time about their decision to stop study participation. In contrast to women who are lost to follow-up, women who drop out do provide information on adverse events which may have influenced their decision to stop study participation. In addition to these results for the total study population, it is also important to compare the exposures with each other. Substantial differences in loss to follow-up rates would indicate that the results for one exposure group might show a greater degree of bias. A comparison of the exposure groups (Table 1), however, shows that all loss to follow-up rates are low. In particular, differences among the OC groups are very minor (loss to follow-up ratio DRSP/LNG = 0.9 and DRSP/Other OCs = 1.0).

The baseline characteristics of the study population are described in great detail elsewhere [1]. Overall the study population had typical characteristics of a European OC user population regarding age structure, socioeconomic and life-style factors and cardiovascular risk factors. The distribution of risk factors and preexisting diseases was comparable among the user groups. However, four exceptions were found: (1) the prevalence of obesity (BMI ≥ 30.0 kg/m^2), (2) the prevalence of women with a family history of VTE, (3) the percentage of women with preexisting arrhythmia were higher in the DRSP group than in the LNG and Other OCs groups; and (4) the mean age in the NOHC and the no-use groups was higher compared to the OC groups. In the early recruitment phase the differences in the prevalence of obesity were substantial. During the first recruitment year the percentage of obese women in the DRSP group was almost 3 times that of the other groups. At the end of the recruitment phase the risk ratio for the prevalence of obesity was about 1.6 (although for starters it was still 2.4). The corresponding risk ratios for family history of VTE and preexisting arrhythmia were 1.3 and 1.5. Since an elevated BMI and preexisting arrhythmia are well-known risk factors for VTE and recurrent arrhythmia, respectively, the DRSP group had at least a slightly higher baseline risk for VTE and arrhythmia compared to the other two OC groups.

Table 1
Loss to follow-up: Number and percentage per exposure group[#].

	Loss to follow-up at end of EURAS	Contact re-established during LASS follow-up	Loss to follow-up at end of LASS
Total number(% of study population*) *of which*	1401 (2.4)	368 (0.6)	1701 (2.9)
DRSP(%*)	401 (2.4)	117 (0.7)	476 (2.9)
LNG(%*)	419 (2.7)	102 (0.7)	490 (3.2)
Other OCs (%*)	579 (2.2)	149 (0.6)	732 (2.8)
NOHC(%*)	2 (0.5)	0 (0.0)	3 (0.8)

* Study population = 58,674; DRSP = 16,534; LNG = 15,428; Other OCs = 26,341; NOHC = 371.
[#] Number and percentage refer to the exposure group the study participants were in at baseline.

3.1. Venous thromboembolic events

A total of 306 VTE was observed, with a similar incidence in all OC/NOHC groups: the DRSP group had 56 cases and 10.7 VTEs per 10,000 WY, the LNG group 53 cases and 9.2 VTEs per 10,000 WY, the Other OCs group 144 cases and 13.6 VTEs per 10,000 WY, and the NOHC group 14 cases and 9.2 VTEs per 10,000 WY (Table 2). The incidence in the 'no use' group was substantially lower: 39 cases or 4.5 VTE per 10,000 WY (95% CI: 3.2–6.1). The incidence for the sub-groups of non-pregnant and pregnant non-users were 2.8 VTE per 10,000 WY (95% CI: 1.7–4.2) and 20.3 VTE per 10,000 WY (95% CI, 12.0–32.0).

For 61 of the 306 VTE cases (20%), a pulmonary embolism (PE) was observed (DRSP 14 cases, LNG 14 cases, Other OCs 23 cases, NOHC 3 cases, 'no use' 7 cases). The PE incidence rates for the OC/NOHC groups were similar (2.0 to 2.7 events per 10,000 WY). Again the incidence for the 'no use' group was substantially lower (0.8 events per 10,000 WY) compared to that for use of hormonal contraceptives.

Overall, the point estimates of the VTE incidence rates for the OC groups were similar with a broad overlap of 95% confidence intervals. The adjusted hazard ratio for DRSP versus LNG was 1.1 with a 95% confidence interval of 0.8 to 1.7 (Table 3). A comparison of DRSP versus Other OCs yielded an adjusted hazard ratio of 0.7 with a 95% confidence interval of 0.5 to 1.0. Combining the LNG group with the Other OCs group and then comparing them with the DRSP group yielded an adjusted hazard ratio of 0.8 with a confidence interval of 0.6 to 1.1.

In total, the continuous LNG regimens with 30 μg EE represented 56% (32,038 WY) of the LNG exposure. This order of magnitude was sufficient to make a direct comparison of DRSP versus LNG on the basis of 30 μg EE. A total of 35 VTEs were observed in the LNG/30mcg EE group and 56 VTEs in the DRSP group (Table 4). This corresponds to an incidence of 10.9/10,000 WY for the LNG/30mcg EE group and 10.7/10,000 WY for the DRSP group. The Cox regression analysis yielded a crude HR for DRSP versus LNG/30mcg EE of 1.0 (95% CI: 0.7–1.5) and an adjusted HR of 1.0 (95% CI: 0.6–1.5). LNG preparations with less than 30 mcg EE showed a lower incidence rate (7.5 VTE/10.000 WY) compared to the 30 mcg EE preparations

Table 2
Thromboembolic events: Number, incidence and 95% confidence intervals per exposure group.

	DRSP		LNG		Other OCs		NOHC		No use		Total
Category	n	Incidence* (95% CI)	n	Incidence* (95% CI)	n	Incidence* (95% CI)	n	Incidence* (95% CI)	n	Incidence* (95% CI)	n
All VTE	56	10.7 (8.1; 13.9)	53	9.2 (6.9; 12.0)	144	13.6 (11.4; 16.0)	14	9.2 (5.0; 15.5)	39	4.5 (3.2; 6.1)	306
of which											
PE	14	2.7 (1.5; 4.5)	14	2.4 (1.3; 4.1)	23	2.2 (1.4; 3.2)	3	2.0 (0.4; 5.8)	7	0.8 (0.3; 1.6)	61
All ATE	7	1.3 (0.5; 2.8)	22	3.8 (2.4; 5.8)	34	3.2 (2.2; 4.5)	4	2.6 (0.7; 6.7)	17	1.9 (1.1; 3.1)	84
of which											
AMI	1	0.2 (0.0; 1.1)	6	1.0 (0.4; 2.3)	5	0.5 (0.2; 1.1)	0	0.0 (0.0; 2.4)	5	0.6 (0.2; 1.3)	17
Stroke	4	0.8 (0.2; 2.0)	7	1.2 (0.5; 2.5)	22	2.1 (1.3; 3.1)	4	2.6 (0.7; 6.7)	9	1.0 (0.5; 2.0)	46
TIA	1	0.2 (0.0; 1.1)	5	0.9 (0.3; 2.0)	6	0.6 (0.2; 1.2)	0	0.0 (0.0; 6.7)	3	0.3 (0.1; 1.0)	15
Other ATE	1	0.2 (0.0; 1.1)	4	0.7 (0.2; 1.8)	1	0.1 (0.0; 0.5)	0	0.0 (0.0; 6.7)	0	0.0 (0.0; 0.4)	6

* per 10,000 WY; CI = confidence interval; TIA = transient ischemic attack.

with DRSP and LNG. The differences were not statistically significant (Table 4).

For the analysis of so-called idiopathic VTE, 100 VTE cases with acute risk factors (such as pregnancy, delivery, trauma, immobilization, long-haul travel, surgery, chemotherapy) were excluded. The following adjusted HRs were found: 1.0 (95% CI, 0.6–1.2) for DRSP versus LNG and 0.8 (95% CI, 0.6–1.2) for DRSP versus Other OCs.

In the combined analysis of all OC groups, starting OC use for the first time and recurrent OC use after a break of at least four weeks showed an increased risk of VTE risk during the first 6 months, after which the risk remained fairly stable over time. In particular, the highest risk was found during the initial three months of use. OC users who switched preparations without an intake break of at least one treatment cycle did not show a higher VTE risk after starting the new preparation than the risk associated with long-term intake. Restarters and switchers with an intake break had a statistically significant higher risk during the initial three months compared to the following months. The point estimate of the relative risk during the initial three months was even higher for starters. However, the statistical power for inferential statistics was limited in this user group. Details are shown in Table 5.

3.2. Arterial thromboembolic events

A total of 84 ATE was observed in the study (Table 2): 17 AMIs, 46 strokes, 15 TIAs and 6 complete thromboses of peripheral or intestinal arteries. The ATEs break down among the groups as follows: DRSP 7 cases, LNG 22 cases, Other OCs 34 cases, NOHC 4 cases, and 'no use' 17 cases. This corresponds to ATE incidence rates of 1.3 ATE/10,000 WY for DRSP, and of 3.8, 3.2, 2.6, and 1.9 for LNG, Other OCs, NOHC and 'no use' respectively. The adjusted hazard ratios for the comparisons of DRSP versus LNG, versus Other OCs and versus LNG/Other OCs combined were consistently below one, at 0.4, 0.4, and 0.4 respectively (Table 3). All three comparisons showed statistically significant differences between DRSP and the comparator groups. A subanalysis of DRSP versus LNG/30mcg EE yielded an adjusted HR of 0.3 (95% CI: 0.1–0.7).

Seventeen cases of acute myocardial infarction (AMI) were observed (DRSP 1, LNG-containing OCs 6, Other OCs 5, NOHC 0, 'no use' 5; see Table 2). At 0.5 AMI/10,000 WY (95% CI 0.3-0.9), the incidence for all OC/NOHC groups combined is in the same range as the incidence for the 'no use' group (0.6 AMI/10,000 WY; 95% CI, 0.2–1.3). Within the OC groups, incidence varied between 0.2 (DRSP) and

Table 3
Adjusted* hazard ratios (HR), adjusted* rate differences (RD) and corresponding 95% confidence intervals (CI) for venous and arterial thromboembolic events.

	DRSP vs.					
	LNG		Other OCs		LNG & Other OCs	
	HR (95% CI)	RD (95% CI)	HR (95% CI)	RD (95% CI)	HR (95% CI)	RD (95% CI)
VTE	1.1 (0.8; 1.7)	0.8 (−3.0; 4.5)	0.7 (0.5; 1.0)	−3.6 (−7.2; 0.0)	0.8 (0.6; 1.1)	−2.1 (−5.3; 1.2)
ATE	0.4 (0.2; 0.9)	−2.5 (−4.4; −0.6)	0.4 (0.2; 0.9)	−2.0 (−3.4; −0.5)	0.4 (0.2; 0.8)	−2.1 (−3.5; −0.8)
Stroke***	0.5 (0.2; 1.4)	−1.1 (−2.6; 0.3)	0.4 (0.2; 0.9)	−1.7 (−3.0; −0.5)	0.4 (0.1; 1.0**)	−1.5 (−2.7; −0.4)

* prognostic factors used for adjustment: VTE – age, BMI, current duration of contraceptive use, family history of VTE; ATE – age, BMI, smoking, treated hypertension and family history of fatal ATE; Stroke – age, BMI, smoking, treated hypertension, family history of fatal stroke.
** exact value: 0.97.
*** including transient ischemic attacks.

Table 4
Comparison DRSP/30mcg EE versus LNG/30mcg EE and LNG/<30mcg EE: Number of cases, incidence, adjusted hazard ratio (HR) and 95% confidence interval (CI).

	VTE Cases	Incidence*	HR#	95% CI
DRSP vs. LNG/30mcg EE	56 35	10.7 10.9	1.0	0.6–1.5
DRSP vs. LNG/<30mcg EE	56 18	10.7 7.5	1.2	0.7–2.0
LNG/30mcg EE vs. LNG/<30mcg EE	35 18	10.9 7.5	1.3	0.7–2.3

* per 10,000 WY;
# adjusted for age, BMI, duration of current OC use and family history of VTE.

1.0 AMI/10,000 WY (LNG). The low number of AMI cases did not allow for a meaningful Cox regression analysis.

Forty-six cases of stroke occurred during follow-up: DRSP 4 cases, LNG 7 cases, Other OCs 22 cases, NOHC 4 cases, and 'no use' 9 cases (Table 2). This corresponds to incidence rates of 0.8, 1.2, 2.1, 2.6, and 1.0 strokes/10,000 WY, respectively. In addition to these strokes, 1, 5, 6, 0, and 3 TIAs were observed in the DRSP, LNG, Other OCs, NOHC and 'no use' groups, respectively. Cox regression analysis of strokes including TIAs yielded crude and adjusted hazard ratios of 0.5, 0.4 and 0.4 for the comparisons DRSP versus LNG, DRSP versus Other OCs, and DRSP versus LNG/Other OCs combined. The upper 95% confidence limits of these hazard ratios for the latter two comparisons did not include unity (Table 3).

3.3. Initiation of antihypertensive therapy

A total of 2,284 out of 58,674 study participants (3.9%) initiated antihypertensive treatment after study entry: 293 DRSP users, 470 LNG users, 721 users of Other OCs, 133 NOHC users and 667 women who had stopped OC use. This corresponds to the following treatment initiation rates: DRSP 56.0/10,000 WY, LNG 81.7/10,000 WY, Other OCs 67.9/10,000 WY, NOHC 87.6/10,000 WY, and 'no use' 76.2/10,000 WY.

The corresponding hazard ratios adjusted for age, BMI, untreated hypertension at baseline, and smoking were 0.7 (95% CI 0.6-0.8) for each of the three comparisons among OC groups: DRSP versus LNG, DRSP versus Other OCs, and DRSP versus LNG/Other OCs combined. Given the high number of events, these analyses were statistically robust ($p < .001$). In addition, the comparison of DRSP versus 'no use' was also statistically significant (HR 0.7; 95% CI 0.6-0.8).

4. Discussion

No major differences were found between the OC groups for incidence rates of VTE. Crude and adjusted HRs also indicated similar risk levels for these outcomes. By contrast, a statistically significant reduced risk of ATE and initiation of antihypertensive treatment was found for the DRSP group compared to the LNG and Other OCs groups.

The methodological limitations of prospective, non-interventional, active surveillance cohort studies such as LASS have been discussed elsewhere [1,5,6]. Like in other non-experimental studies it is not possible to entirely eliminate potential effects of bias and residual confounding [7–12]. Within these limitations the LASS study combines several methodological strengths that support the validity of its results: (1) a prospective, comparative cohort design; (2) availability of important confounder information (e.g., BMI and family history of cardiovascular outcomes); (3) validation of outcomes of interest and exposure for the relevant cases; (4) comprehensive long-term follow-up and very low loss to follow-up to minimize underreporting; (5) independent, blinded adjudication of critical outcomes; (6) relevant statistical analyses (e.g., stratified analyses by user status and exposure period; comparison of isochronous, new user cohorts; sensitivity analyses on the impact of prognostic factors); (7) study population representative for OC users under routine clinical conditions; (8) reproducibility of the typical time pattern of VTE risk; (9) large study size (318,784 woman-years of active follow-up); and (10) supervision by an independent Safety Monitoring and Advisory Council as well as scientific independence from the study funder.

The results on VTE showed a similar risk for all OC groups. This was also the case for potential or idiopathic

Table 5
Risk of VTE for various user statuses by duration of use categories: Incidence rates by time to event categories and incidence rate ratios with their 95% confidence intervals.

User statuses	0–3 months (VTE per 10,000 WY; point estimates and 95% CI)	4+ months (VTE per 10,000 WY; point estimates and 95% CI)	Incidence rate ratio (point estimates and 95% CI)
Starters	11.1 [2.3–32.4]	3.7 [1.4–8.0]	3.0 [0.8–12.5]
Switchers without intake break	12.5 [7.0–20.6]	12.5 [10.0–15.5]	1.0 [0.6–1.7]
Recurrent users with intake break ≥ 4 weeks	23.9 [16.8–32.9]	11.8 [9.6–14.3]	2.0 [1.4–2.9]
of which Restarters	28.7 [16.4–46.6]	11.9 [8.7–16.0]	2.4 [1.4–4.3]
Switchers with intake break ≥ 4 weeks	21.1 [13.1–32.3]	11.7 [8.9–15.1]	1.8 [1.1–3.0]

* VTE = venous thromboembolism; 95% CI=95% confidence interval.

VTE. Sensitivity analyses that included all other available prognostic factors for VTE confirmed the results of the primary analyses. The high prevalence of obesity among DRSP users during the first year of recruitment was caused by widespread media reports that DRSP-containing OCs "make you slim", a misconception triggered by the fact that DRSP is not only a progestogen but also an aldosterone antagonist. This problem was alleviated by a change in the manufacturer's marketing strategy. Overall, adjustment for the differences in baseline risks had no major impact on the risk estimates (change of approximately 20% - in the case of BMI - or less).

Even though these risk factors had only a slight impact on group comparisons on account of the good group comparability, they did exert a considerable influence on VTE incidence – independently of exposure affiliation. Thus women of age 50 or above had a 10-fold higher VTE incidence compared to teenagers, women with class II obesity (BMI > 35 kg/m^2) had a more than 5-fold higher risk compared to women with a BMI below 20, and a family history of VTE tripled the risk of VTE. The most relevant analysis of the VTE risk associated with the use of DRSP and other progestogen-containing OCs compared users of DRSP with users of LNG products that contained 30 μg EE, because it eliminated the influences of the EE dose and the regimen, and allowed a direct comparison of the progestogens DRSP and LNG. The resulting hazard ratio of 1.0 and the narrow confidence intervals suggest that the two progestogens are associated with a similar VTE risk.

The ATE hazard ratios were lower than unity to a statistically significant extent for the DRSP arm compared to the other two OC arms and LNG/30mcg EE subgroup. The statistical power for the analysis of AMI and stroke was not high enough for reliable conclusions. Nevertheless, the incidence rates for AMI and stroke were consistently lower for the DRSP arm compared to the other two OC arms. Therefore, the results on AMI and stroke endorse the overall ATE results. In view of the antimineralocorticoid activity of DRSP [13] it is conceivable that DRSP has a positive impact on the occurrence of ATE. The substantial aldosterone antagonistic effect of DRSP/estrogen combinations has been demonstrated in several randomized clinical trials that showed clinically relevant reductions in systolic and diastolic blood pressure [14–16]. This antihypertensive effect is also reflected in the low proportion of DRSP users in the LASS study who needed antihypertensive treatment after starting treatment with a DRSP-containing OC. Furthermore, it has been demonstrated that aldosterone antagonists such as DRSP can reduce cardiovascular disease and even cardiovascular mortality beyond their antihypertensive effects [17,18]. Therefore it is plausible that DRSP is associated with a lower risk of ATE compared to OCs containing other progestogens. This is also supported by the INAS-OC study [5] and the EURAS-HRT study which showed even more pronounced effects in a population of HRT users [19].

From a methodological point of view it is unlikely that selection or information bias had a major impact on the ATE results of the LASS study. Here it should be noted that both inpatients and outpatients were documented during follow-up, and that diagnostic bias plays a less important role in connection with ATE than VTE. Moreover, misclassification bias is probably not an issue as precise information on exposure and ATE outcomes was available. In addition, information on the relevant prognostic factors was available.

Currently, only sparse results on the ATE risk associated with DRSP-containing OCs are available from other epidemiological studies [5,20]. Some of these results also lack internal consistency (e.g., showing a higher risk of ATE combined with lower cardiovascular mortality). It will be interesting to see the results of future epidemiological studies on these outcomes. Based on the evidence currently available, we believe that the LASS study's results on ATE are valid and should be considered in risk/benefit assessments of DRSP-containing OCs. Given that (1) the DRSP arm in this study did not show a higher risk for any of the clinical outcomes (including VTE) than the other OC arms, (2) epidemiological studies do not consistently show an increased risk of VTE for DRSP-containing OCs [1,5,20–31], and (3) the risk of ATE is probably lower for DRSP, it seems unjustified to consider DRSP a second-line progestogen. Prescriptions of combined oral contraceptives always require careful risk/benefit assessments for each individual woman. A hormonal contraceptive with antimineralocorticoid activity would appear to be an interesting option for several clinical situations.

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