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Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: final results from the International Active Surveillance Study of Women Taking Oral Contraceptives☆,☆☆

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Abstract

Objectives: The "International Active Surveillance Study of Women Taking Oral Contraceptives" investigated the risks of short- and long-term use of an extended 24-day regimen of drospirenone and ethinylestradiol ($DRSP_{24d}$) compared to established oral contraceptives (OCs) in a routine clinical setting.

Study Design: Prospective, controlled, noninterventional cohort study conducted in the United States and six European countries with three main cohorts: new users of $DRSP_{24d}$, $DRSP_{21d}$ (21-day regimens of DRSP-containing OCs), and non-DRSP (OCs without DRSP). 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 venous thromboembolism (VTE). Comprehensive follow-up procedures were implemented. Statistical analyses were based on Cox regression models. Primary statistical variable was the VTE hazard ratio (HR) for $DRSP_{24d}$ vs. non-DRSP.

Results: A total of 2285 study centers enrolled 85,109 women. Study participants were followed for 2 to 6 years, which generated 206,296 woman-years (WY) of observation. A low loss to follow-up of 3.3% was achieved. $DRSP_{24d}$, $DRSP_{21d}$, non-DRSP and levonorgestrel-containing OCs (LNG) showed similar incidence rates of venous and arterial thromboembolism, fatal outcomes, cancer, severe depression and other serious adverse events. VTE incidence rates for $DRSP_{24d}$, $DRSP_{21d}$, non-DRSP and LNG were 7.2, 9.4, 9.6 and 9.8 VTE/10,000 WY, respectively. Adjusted HRs for $DRSP_{24d}$ vs. non-DRSP and $DRSP_{24d}$ vs. LNG were 0.8 [95% confidence interval (CI), 0.5–1.3] and 0.8 (95% CI, 0.4–1.5).

Conclusion: $DRSP_{24d}$, $DRSP_{21d}$, non-DRSP and LNG use was associated with similar risks of serious adverse events, and particularly VTE, during routine clinical use.

Implication Statement: The 24-day regimen of drospirenone-containing combined OCs is associated with similar risks of venous and arterial thromboembolism, fatal outcomes, cancer, severe depression and other serious adverse events compared to 21-day regimens of drospirenone-containing combined OCs, OCs without drospirenone and LNGs.

Keywords: VTE; ATE; SAE; Prospective cohort study; Routine clinical practice

1. Introduction

The International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC) was a postauthorization safety study requested by the Food and Drug Administration and the European Medicines Agency. It was designed as a large, transatlantic, controlled, prospective, observational, active surveillance study that investigated the cardiovascular and general safety of a 24-day regimen of combined oral contraceptives (COCs), which contain 3

☆ Conflict of interest: The study was funded by a manufacturer of hormonal contraceptives. The study was supervised by an independent Safety Monitoring and Advisory Council with full authority over the study (including study protocol, protocol amendments, data analysis and stopping the study). The funder had no access to the source data and did not participate in designing the study or analyzing the data.

☆☆ Registration number at the clinical trials registry of the US National Library of Medicine: NCT00335257 (Please note: This is not a clinical trial.)

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mg of drospirenone (DRSP) and 20 μg of ethinylestradiol (EE). This cohort study followed new users of the 24-day regimen ($DRSP_{24d}$) and other marketed oral contraceptives (OCs), using a noninterference approach to provide standardized, comprehensive and reliable information on these treatments in routine clinical practice.

When INAS-OC was planned in 2005, clinical experience suggested that serious clinical outcomes associated with $DRSP_{24d}$ use were rare. Results from epidemiological studies on $DRSP_{24d}$ or any other regimen of DRSP and EE were not available at that time. It is not known whether the extension of a 21-day COC regimen to a 24-day regimen has an impact on the cardiovascular risk associated with the use of OCs. It is conceivable that the reduction in so-called hormone swings due to a shorter pill-free period leads to a lower incidence of venous thromboembolism (VTE) compared to 21-day regimens of the same progestin. It is also conceivable, however, that the higher cumulative doses of progestin and estrogen lead to a higher risk. Therefore, a sufficiently large study to investigate the cardiovascular risk associated with $DRSP_{24d}$ was called for. Differentiating between the inherent background population risk and a potential incremental risk for cardiovascular and other safety outcomes of interest due to treatment is often challenging. Active safety surveillance using valid epidemiological study designs has been proved to be a valid method to address this matter [1,2].

This publication presents the main safety outcomes of the INAS-OC study. Other study results (e.g., contraceptive failure, return to fertility, analyses of subpopulations, impact of current duration of use, etc.) will be reported elsewhere.

2. Materials and methods

The methodology of the INAS-OC study is similar to that of the European Active Surveillance study on Oral Contraceptives, which is described elsewhere [3]. Therefore, methodological details regarding questionnaires, follow-up procedures and blinded adjudication are presented succinctly.

2.1. Study objectives

The primary objective of the study was to assess the risks of short- and long-term use of $DRSP_{24d}$ and of established OCs in a study population that is representative of the actual users of the individual preparations. This included an estimate of the absolute risk of rare serious adverse events (SAEs; i.e., adverse events that result in death, a life-threatening experience, inpatient hospitalization, persistent or substantial disability/incapacity, or require medical/surgical intervention to prevent one of said outcomes). The main clinical outcomes of interest for the short- and long-term follow-up were VTE and arterial thromboembolism (ATE) — deep venous thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction (AMI) and cerebrovascular accidents (CVA) — with a particular focus on VTE. Planning, conduct and evaluation of the study were supervised by an independent Safety Monitoring and Advisory Council, which endorsed all conclusions presented in this publication. The primary ethical approvals in the United States and Europe were provided by the Western Institutional Review Board (WIRB) in Olympia, WA, USA, and the ethical committee of 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 NCT00335257.

2.2. Study population

Recruitment of the cohort members was conducted via a network of more than 2200 OC-prescribing study centers in Europe and the United States. The combined cohort was planned to include more than 80,000 women, including about 50,000 women in the United States and 30,000 women in six European countries: Austria, Croatia, Germany, Italy, Poland and Sweden. Recruitment in the United States began in August 2005 and finished in January 2009. Because of the late market introduction of $DRSP_{24d}$ in Europe, recruitment did not commence there until October 2008 and was completed in October 2010. Patients were followed in the United States until July 2011 and in Europe until January 2013. Loss to follow-up activities lasted until the spring of 2013. Participating women could be starters (first-ever users of OCs), switchers (users who switched from one OC to another — without an intake break or an intake break of less than 4 weeks), or restarters (women who restarted OC use after an intake break of at least 4 weeks). More specific inclusion or exclusion criteria were not made because of the noninterference approach of the study design. At the participating centers, all women seeking a prescription for a new OC were asked whether they were willing to participate. The objective was to avoid influencing the prescribing behavior, while at the same time making significant efforts to ensure standardized, comprehensive and reliable documentation of all baseline characteristics and adverse events during the follow-up period.

2.3. Baseline survey and follow-up

Baseline data were recorded on a questionnaire that addressed the participants' state of health and potential prognostic factors for cardiovascular disease. Participants provided their medical history, including medication history and history of hormonal contraceptive use. They also provided their addresses and phone numbers, those of relatives or friends who could serve as back-up contacts and those of their primary care physicians or gynecologists [3]. Baseline questionnaires were completed in the physicians' offices and checked by the physicians or their coworkers. Follow-up assessments for each woman were scheduled every 6 months for up to 72 months after study entry. The

self-administered follow-up questionnaires addressed the occurrence of adverse events. Reasons for discontinuing OC use or switching to another hormonal contraceptive were requested 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 telephone. A low loss to follow-up rate was essential for the validity of the study. To minimize loss to follow-up, a comprehensive follow-up process was established, which is described elsewhere [3]. Study participants received a small compensation for each follow-up on returning the questionnaire. Follow-up questionnaires that contained information about SAEs were immediately passed on to the medical reviewer group at the Berlin Center for Epidemiology and Health Research [3]. All group members were medical doctors specializing in epidemiology, drug safety and internal medicine. In case of unclear or missing information, the women were contacted by telephone, e-mail or other means. For many events, it was necessary to contact the diagnosing or treating physician for clarification and validation of the information received from the patient [3]. These physicians were compensated for the time needed to provide the requested information and medical records. All SAEs were classified as confirmed or not confirmed. Events that were confirmed by diagnostic measures with high specificity (e.g., phlebography for DVT or cerebral magnetic resonance imaging for CVA) or by clinical diagnosis supported by a diagnostic test with low specificity (such as D-dimer for VTE) were considered confirmed. Events were considered not confirmed if the diagnosis reported by the patient was excluded by diagnostic measures, if a different medical condition was diagnosed by the attending physician, or if the reporting woman did not contact a health professional to clarify her symptoms and no diagnostic measures were performed that could have clarified the diagnosis [3].

2.4. Blinded adjudication

For the purpose of continuously monitoring safety data during the study, classification of reported SAEs was performed by the investigators at the Berlin Center for Epidemiology and Health Research. For the final analysis, classification of the primary outcomes of interest — VTE — was verified by independent blinded adjudication. To minimize misclassification bias, the decisions made by the investigators were reassessed by three independent medical experts specializing in cardiology, internal medicine and imaging procedures. These specialists reviewed all available information regarding the reported event. Brand names, dose, regimen and composition of the hormonal contraceptives used by the study participants were rendered anonymous for this process [3].

2.5. Evaluation

The statistical analyses included both an "as treated" (AT) and an "intention to treat" (ITT) analysis. The safety conclusions of the study are based on the AT analyses because the ITT approach potentially dilutes differences between treatments [3]. In this study, however, conclusions based on ITT results did not differ from the conclusions based on AT results. Therefore, only the most important ITT results are reported. Cox regression models were used for inferential statistics. 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.

Based on the rather small number of outcomes, adjustment for potential confounding was based on a priori defined expert models with a limited number of well-established covariates. For VTE the models included age, body mass index (BMI), duration of current hormonal contraceptive use and family history of VTE. In addition, the impact of a high number of actual or potential prognostic factors such as educational level, geographical region, user status (starter, switcher, restarter), smoking, concomitant medication and surgical interventions was evaluated using a backward stepwise approach. This approach was only taken for exploratory analyses. The results were almost identical with the expert model. Therefore, only the results of the expert model are reported.

The analyses focused on comparisons among the two primary cohorts ($DRSP_{24d}$ and non-DRSP) and a subcohort of levonorgestrel-containing OCs (LNG). In addition, users of 21-day regimens of DRSP were grouped in a separate cohort ($DRSP_{21d}$). Furthermore, over the 6 years of follow-up, many women changed their OC, switched to a non-oral hormonal contraceptive (NOHC) or stopped all forms of hormonal contraception either temporarily or permanently. All study participants — including pregnant women — were included in the follow-up until the end of the study, unless they withdrew their informed consent. Overall data on three additional cohorts — users of $DRSP_{21d}$, users of NOHC and nonusers — were also available. Exploratory analyses of these data are also presented if they contribute to better understanding of the results.

The primary outcome of interest was the VTE hazard ratio (HR) between users of $DRSP_{24d}$ and non-DRSP, as well as between $DRSP_{24d}$ and LNG. The null hypothesis to be tested was as follows: $HR_{VTE} \geq 2$ (i.e., the VTE HR for $DRSP_{24d}$ vs. non-DRSP or LNG is 2 or higher). The alternative hypothesis was: $HR_{VTE} < 2$. All analyses were performed with the statistical software packages SAS 9 and StataES8.

Sample size calculations showed that 80,000 women with a total OC exposure of more than 100,000 woman-years (WY) should be sufficient to exclude a twofold risk of VTE for $DRSP_{24d}$ users compared to users of OCs without DRSP (non-DRSP) as well as for $DRSP_{24d}$ users compared to LNG users. These calculations were based on a VTE incidence in the general user population of 9.1 VTE/10,000 WY [3] and a power of 90%. Exposure periods of up to 6 years were analyzed to ensure that the venous thromboembolic risk estimate was representative for routine clinical OC use. In

addition, a subanalysis of the relative risk during different exposure periods (6 months or less, 7–12 months, more than 12 months) was conducted.

3. Results

A total of 91,474 women were enrolled by 2285 study centers. Overall, 6365 of these 91,474 women (7.0%) had to be excluded because they were enrolled two or more times by one or more study centers, continued to use their previous hormonal contraceptive (long-term users), or did not start using their prescribed OC after study entry. The remaining 85,109 quality-controlled computerized data sets from the women with baseline information were analyzed. At study entry, 15,542 women received a prescription for $DRSP_{24d}$, 9377 for $DRSP_{21d}$, and 60,190 for non-DRSP (10,254 of these women used LNG). These data are summarized in Table 1.

3.1. Baseline characteristics of the user cohorts

For each of the main user cohorts (i.e., $DRSP_{24d}$, $DRSP_{21d}$, non-DRSP) and the LNG subcohort, Table 2 shows the number of women with baseline information (*N*), the exposure for the AT and ITT populations, plus the corresponding proportion of exposure for each of these populations, as well as descriptive statistics for age, weight and BMI. At study entry, 18.3% of women were prescribed $DRSP_{24d}$, 11.0% $DRSP_{21d}$, 70.7% non-DRSP and 12.0% LNG. These proportions are reflected in each cohort's contribution to the overall exposure in the ITT populations (18.8%, 11.5%, 69.7% and 12.2 for $DRSP_{24d}$, $DRSP_{21d}$, non-DRSP and LNG, respectively). This indicates that the average follow-up for the (sub)cohorts was similar. This is reassuring given that significant differences in follow-up time could be a source of information bias.

Mean age was almost identical in all four (sub)cohorts. The age distribution — as indicated by the minimum, 5, 25, 50, 75 and 95 percentiles as well as the maximum values — corresponds to the typical age profile of OC users. Mean weight and mean BMI were similar for all (sub)cohorts too. However, a geographical comparison showed substantial differences between Europe and the United States. The mean weight and BMI in the United States were 71.3 kg and 26.8 kg/m^2, respectively; the corresponding values in Europe were 62.5 kg and 22.6 kg/m^2.

Overall, 23.9% of the study population were starters at study entry, 21.4% were switchers, and 54.7% were restarters. No major differences were observed between the four (sub)cohorts.

Regarding gynecological history parameters the four (sub)cohorts were almost identical: for example, a mean age of 12.8 years at menarche for all (sub)cohorts and an average of 1.6 to 1.7 live births at study entry.

The distribution of prognostic factors for cardiovascular outcomes of interest as well as the medical history of selected diseases is shown in Table 3. Major differences among the three cohorts were not found at baseline for most of the risk factors examined. A total of 2.0%, 2.1%, 2.0% and 1.9% of $DRSP_{24d}$, $DRSP_{21d}$, non-DRSP and LNG users, respectively, had a family history of fatal ATE before the age of 50. The proportion of current smokers was slightly lower among $DRSP_{24d}$ users compared to $DRSP_{21d}$, non-DRSP and LNG users (19.6%, 24.1%, 22.2% and 25.2%). However, the differences between the two regions are striking, especially the physicians' observance of contraindications (smokers above the age of 35) for prescribing OCs. Overall, the prevalence of smoking was higher in Europe than in the United States by a factor of nearly 2: 30.5% vs. 16.5%. The corresponding factor for women above the age of 35 was 5.7: 25.8% vs. 4.5%. By contrast, the proportion of women who used regular concomitant medication was substantially higher in the United States compared to Europe (25.8% vs. 11.8%). Psychotropics were the most widely used concomitant medication in the United States: 12.5% vs. 2.1%. Educational levels of the study participants were similar across cohorts. Overall, there were no major differences in baseline risks for the four (sub)cohorts.

Table 1
Number of women enrolled, excluded and analyzed

Women	*n*	(%)[a]	[%][b]
(A) Who agreed to participate	91,474	–	[100.0]
(B) Excluded			
because of protocol violations[c]	6365	–	[7.0]
(C) Analyzed	85,109	(100.0)	[93.0]
Cohorts			
$DRSP_{24d}$	15,542	(18.3)	[17.0]
$DRSP_{21d}$	9377	(11.0)	[10.3]
non-DRSP	60,190	(70.7)	[65.8]
of which LNG	10,254	(12.0)	[11.2]
User status			
Starters	20,370	(23.9)	[22.3]
Switchers	18,211	(21.4)	[19.9]
Restarters	46,528	(54.7)	[50.9]
Regions			
United States	52,169	(61.3)	[57.0]
Europe	32,940	(38.7)	[36.0]
European countries			
Austria	4294	(5.0)	[4.5]
Croatia	948	(1.1)	[1.0]
Germany	13,567	(15.9)	[14.8]
Italy	5728	(6.7)	[6.3]
Poland	6290	(7.4)	[6.9]
Sweden	2113	(2.5)	[2.3]

[a] Percentage of women who agreed to participate.
[b] Percentage of women who were in the final analysis.
[c] Women who (1) were enrolled two or more times by one or more study centers, (2) continued their previous hormonal contraceptive (long-term user), or (3) never started OC use after study entry.

3.2. Loss to follow-up

A total of 85,109 study participants were followed up for 206,296 WY of observation. In total, 2815 of the 85,109

Table 2
User cohorts: number of women, exposure, and descriptive statistics at study entry

	$DRSP_{24d}$	$DRSP_{21d}$	Non-DRSP	LNG	Total
N at baseline (%)	15,542 (18.3)	9377 (11.0)	60,190 (70.7)	10,254 (12.0)	85,109 (100.0)
WY (AT) (%)	26,491 (12.8)	17,112 (8.3)	105,333 (51.1)	19,472 (12.8)	206,296 (100.0)[a]
WY (ITT) (%)	38,772 (18.8)	23,721 (11.5)	143,802 (69.7)	25,066 (12.2)	206,296 (100.0)
Age (y), mean (SD)	26.2 (7.6)	26.1 (7.5)	26.3 (7.7)	26.2 (8.0)	26.3 (7.7)
Age, minimum	12	12	11	12	11
Age, 5th percentile	17	17	17	16	17
Age, 25th percentile	20	20	20	20	20
Age, median	24	24	25	24	25
Age, 75th percentile	31	31	31	31	31
Age, 95 percentile	41	41	42	43	42
Age, maximum	54	65	57	55	65
Weight (kg), mean (SD)	66.9 (16.0)	67.1 (16.7)	68.2 (16.9)	67.3 (16.1)	67.9 (16.8)
Weight, minimum	36	32	32	32	32
Weight, 5th percentile	49	49	49	49	49
Weight, 25th percentile	56	56	57	57	57
Weight, median	63	63	64	64	64
Weight, 75th percentile	73	73	75	74	75
Weight, 95th percentile	99	100	102	100	101
Weight, maximum	172	169	248	191	248
BMI (kg/m^2), mean (SD)	24.6 (5.7)	24.4 (5.8)	25.0 (6.0)	24.6 (5.6)	24.9 (5.9)
BMI, minimum	12.8	13.5	12.0	13.5	12.0
BMI, 5th percentile	18.4	18.3	18.4	18.3	18.4
BMI, 25th percentile	20.7	20.5	20.9	20.8	20.8
BMI, median	23.1	22.8	23.5	23.1	23.4
BMI, 75th percentile	26.8	26.6	27.6	27.0	27.4
BMI, 95th percentile	36.3	36.4	37.1	35.9	36.9
BMI, maximum	63.7	66.2	75.4	64.5	75.4

[a] Includes 57,360 WY for the NOHC and "no use" cohorts.

women, or 3.3% (3.3% for $DRSP_{24d}$, 3.2% for $DRSP_{21d}$, 3.3% for non-DRSP and 3.1% for LNG), were lost to follow-up during the 4- to 6-year follow-up period. The rates of those who were lost to follow-up for the United States and Europe were similar: 3.8% and 2.6%, respectively.

3.3. Serious adverse events

Overall, 5964 SAEs were reported by the participants. The incidence rates for the three main cohorts and the LNG subcohort were similar: $DRSP_{24d}$, 248.4 SAEs/10,000 WY;

Table 3
Prognostic factors for outcomes of interest and medical history of selected diseases per user cohort: total number and percent of enrolled women

Risk factor	$DRSP_{24d}$		$DRSP_{21d}$		Non-DRSP		LNG		Total	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Treated high blood pressure	320	(2.06)	210	(2.24)	1,812	(3.01)	292	(2.85)	2,342	(2.75)
High cholesterol	203	(1.31)	111	(1.18)	752	(1.25)	136	(1.33)	1,066	(1.25)
Family history of ATE	317	(2.04)	193	(2.06)	1,182	(1.96)	190	(1.85)	1,692	(1.99)
Family history of VTE	354	(2.28)	233	(2.48)	1,494	(2.48)	258	(2.52)	2,081	(2.45)
BMI [25–30 kg/m^2)	3,226	(20.8)	1,826	(19.5)	13,183	(21.9)	2,189	(21.3)	18,235	(21.4)
BMI [30–35 kg/m^2)	1,335	(8.59)	767	(8.18)	5,938	(9.87)	889	(8.67)	8,040	(9.45)
BMI $\geq$35 kg/m^2	945	(6.08)	575	(6.13)	4,375	(7.27)	601	(5.86)	5,895	(6.93)
Smoking	3,051	(19.6)	2,257	(24.1)	13,375	(22.2)	2,585	(25.2)	18,683	(22.0)
Heavy smoking[a]	428	(2.75)	352	(3.75)	2,125	(3.53)	412	(4.02)	2,905	(3.41)
Diabetes mellitus	101	(0.65)	63	(0.67)	529	(0.88)	89	(0.87)	693	(0.81)
Myocardial infarction	2	(0.01)	3	(0.03)	17	(0.03)	6	(0.06)	22	(0.03)
Stroke/TIA	3	(0.02)	3	(0.03)	15	(0.02)	4	(0.04)	21	(0.02)
PE	1	(0.01)	0	(0.00)	24	(0.04)	3	(0.03)	25	(0.03)
DVT	9	(0.06)	8	(0.09)	81	(0.13)	6	(0.06)	98	(0.12)
Cancer	87	(0.56)	55	(0.59)	323	(0.54)	48	(0.47)	465	(0.55)
Any surgery	5,322	(34.2)	3,213	(34.3)	21,455	(35.6)	3,828	(37.3)	29,990	(35.2)
Depression or attempted suicide	414	(2.66)	236	(2.52)	1,653	(2.75)	310	(3.02)	2,303	(2.71)

TIA, transient ischemic attack.
[a] >15 cigarettes per day.

$DRSP_{21d}$, 255.2 SAEs/10,000 WY; non-DRSP, 262.3 SAEs/10,000 WY; and LNG, 271.0 SAEs/10,000 WY. The crude HR for $DRSP_{24d}$ vs. non-DRSP was 0.9 with a 95% confidence interval (95% CI) of 0.8 to 1.0. Adjustment for age, BMI and geographical region yielded almost identical results. All other possible comparisons between OC (sub) cohorts showed also HRs close to unity.

The study participants who stopped all uses of hormonal contraceptions reported 2065 SAEs. This corresponds to a reporting rate of 419.2 SAE/10,000 WY and is substantially higher than the reporting rate for the OC cohorts (rate ratio for nonuse vs., e.g., $DRSP_{24d}$: 1.84). Closer analysis, however, showed that these differences were primarily a matter of SAEs in connection with pregnancy, delivery or puerperium (e.g., preeclampsia, placenta previa). Nonpregnant women who had stopped hormonal contraceptive use had similar SAE incidence rates compared to OC users. These results will be published separately.

Fig. 1 shows the SAEs by organ system. Here too, a comparison between the OC cohorts showed no notable differences. The rate ratios for $DRSP_{24d}$/non-DRSP in the individual disease categories vary between 0.6 (95% CI, 0.2–1.3) for benign neoplasms and 1.7 (95% CI, 0.6–5.2) for diseases of the ear. A direct comparison of the 15 disease categories for the three main cohorts showed that the highest individual incidence rates were found in three, five, and seven categories for $DRSP_{24d}$, $DRSP_{21d}$ and non-DRSP, respectively. From a statistical point of view, the actuarial expectation would be five "highest" incidence rates per cohort. The pattern found in this study can therefore easily be explained by chance and — in comparison to non-DRSP — provides no indication of a heightened SAE risk for $DRSP_{24d}$ users in any of the 15 disease categories.

A direct comparison of the OC (sub)cohorts regarding malignant neoplasm showed no relevant difference: 26 cases for $DRSP_{24d}$ (9.8/10,000 WY), 14 cases for $DRSP_{21d}$ (8.2/10,000 WY), 119 cases for non-DRSP (10.7/10,000 WY) and 19 cases for LNG (9.8/10,000 WY). Comparison of the individual cancer categories also did not show any noteworthy differences. The most frequent cancers were breast cancer ($DRSP_{24d}$, 2.8 cases/10,000 WY; $DRSP_{21d}$, 2.5 cases/10,000 WY; non-DRSP 3.7 cases/10,000 WY; LNG, 2.6 cases/10,000WY) and cervical cancer ($DRSP_{24d}$, 1.3 cases/10,000 WY; $DRSP_{21d}$, 1.3 cases/10,000 WY; non-DRSP 2.1 cases/10,000 WY; LNG 3.1 cases/10,000 WY).

In the United States, $DRSP_{24d}$ is also approved for the treatment of premenstrual dysphoric disorder. Therefore, it is conceivable that $DRSP_{24d}$ is preferentially prescribed to women with depression. At study entry, however, there were no relevant differences between the cohorts regarding the history of depressive disorders. After study entry, 9 users of $DRSP_{24d}$ (3.4 events/10,000 WY; 95% CI, 1.6–6.4) and 40 users of non-DRSP (3.8 events/10,000 WY; 95% CI, 2.7–5.2) suffered from severe depression (i.e., associated with hospitalization, attempted suicide or suicide). One $DRSP_{24d}$ user committed suicide (0.4 events/10,000 WY), and three $DRSP_{24d}$ users attempted suicide (1.1 events/10,000 WY). The corresponding numbers for the non-DRSP cohort are 6 suicides (0.6 events/10,000 WY) and 16 suicide attempts (1.5 events/10,000 WY). A direct comparison of $DRSP_{24d}$ with other (sub)cohorts yielded crude and adjusted HRs below 1; the CI always included 1.

Overall, 64 study participants died after study entry; the most recent exposures were a DRSP-containing OC (2.2 cases/10,000 WY; 95% CI, 1.2–3.8) in 14 cases and non-DRSP (3.5 cases/10,000 WY; 95% CI, 2.6–4.6) in 50 cases.

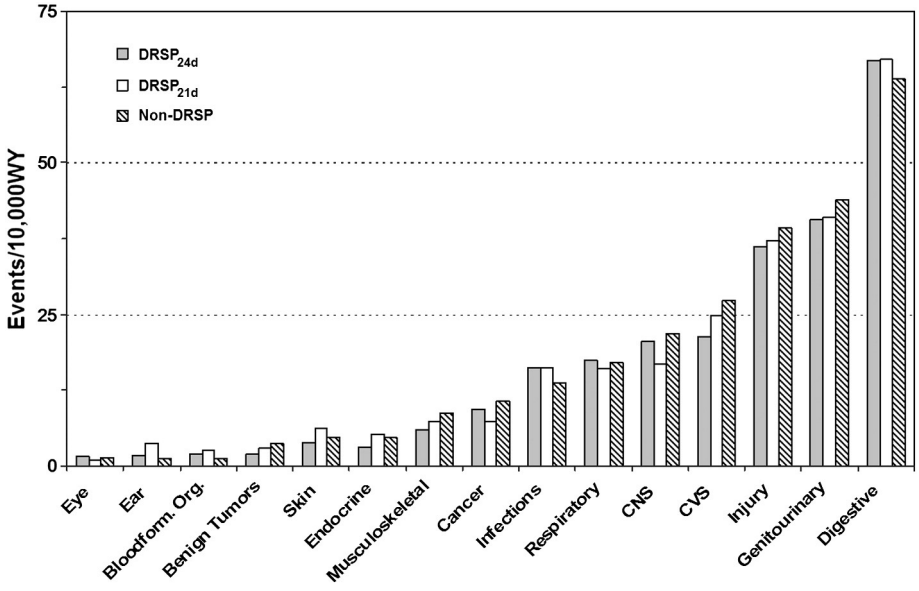

Fig. 1. SAEs by organ system (according to *International Classification of Diseases, 10th Edition*).

The most frequent causes were fatal accidents (34.4%, the majority vehicular), cardiovascular events (17.2%), suicides (14.1%), malignant neoplasms (12.5%), homicides (6.3%) and overdoses of illegal drugs (6.3%). According to the Safety Monitoring and Advisory Council's blinded causality assessment, 6 of the 64 cases were possibly or probably causally related to hormonal contraceptive use: 3 cardiovascular events, 2 cancer cases and 1 case of status asthmaticus. None of the possibly related cases were associated with use of a DRSP-containing OC.

3.4. Venous thromboembolism

A total of 162 VTE cases were observed, with similar incidence rates in the $DRSP_{24d}$, $DRSP_{21d}$, non-DRSP, LNG and NOHC (sub)cohorts: $DRSP_{24d}$ cohort 19 cases and 7.2 VTE per 10,000 WY; $DRSP_{21d}$ cohort 16 cases and 9.4 VTE per 10,000 WY; non-DRSP cohort 101 VTE and 9.6 VTE per 10,000 WY; LNG subcohort 19 VTE and 9.8 VTE per 10,000 WY; NOHC cohort 7 VTE and 8.6 VTE per 10,000 WY; and "no use" cohort 19 cases and 3.9 VTE per 10,000 WY (Table 4). An analysis of the "NOHC" cohort (injections, implants, levonorgestrel-releasing intrauterine devices, vaginal rings or contraceptive patches) was neither meaningful (because of the heterogeneity of the included products) nor intended. Therefore, a detailed analysis of this cohort was not done. Overall, the point estimates of the incidence rates of the main OC (sub)cohorts ($DRSP_{24d}$, $DRSP_{21d}$, non-DRSP, LNG) were similar with a broad overlap of the CIs. A total of 7 of 19 VTE in the "no use" cohort were associated with pregnancy and delivery. Exclusion of these cases resulted in an incidence rate of 2.9 VTE per 10,000 WY. Overall, the VTE risk for OC users was about three times higher than that for nonpregnant nonusers.

For 62 (38%) of the 162 VTE cases, a PE was observed ($DRSP_{24d}$: 9 cases; $DRSP_{21d}$: 7 cases; non-DRSP: 34 cases; LNG: 7 cases; NOHC: 4 cases; "no use" cohort: 8 cases). The PE incidence rates (calculated per 10,000 WY) for the OC cohorts were similar with a broad overlap of CIs: $DRSP_{24d}$, 3.4 (95% CI, 1.6–6.4); $DRSP_{21d}$, 4.1 (95% CI, 1.6–8.4); non-DRSP, 3.2 (95% CI, 2.2–4.5); and LNG, 3.6 (95% CI, 1.4–7.4).

A Cox regression analysis (Table 4) was carried out in accordance with the statistical analysis plan. The crude HR for $DRSP_{24d}$ vs. non-DRSP was 0.7 with a 95% CI of 0.4 to 1.2. The adjusted HR was 0.8 with a 95% CI of 0.5 to 1.3. Therefore, the null hypothesis ($HR_{VTE}>2$) can be rejected, and a twofold higher risk of VTE during $DRSP_{24d}$ use compared to non-DRSP use can be excluded. A comparison of the $DRSP_{24d}$ cohort with the LNG subcohort showed similar results: the crude HR was 0.8 with a 95% CI of 0.4 to 1.4. The adjusted HR was 0.8 (Table 4) with a 95% CI of 0.4 to 1.5. The corresponding ITT analyses for $DRSP_{24d}$ vs. non-DRSP and LNG resulted in adjusted HRs of 0.9 (95% CI, 0.6–1.3) and 0.7 (95% CI, 0.4–1.3).

Alternative analyses using a backwards stepwise procedure for the selection of numerous other prognostic factors (see above) yielded almost identical results [adjusted HRs for $DRSP_{24d}$ vs. non-DRSP and LNG: 0.8 (95% CI, 0.5–1.3) and 0.8 (95% CI, 0.4–1.4), respectively]. In addition, a stratified analysis of the VTE per user status (starters, switchers and restarters) did not indicate a higher VTE risk for $DRSP_{24d}$ users of a particular user status compared to other OC (sub) cohorts. The adjusted HRs for switchers and restarters were always lower than 1.0. The number of events for starters was too low for a robust analysis (2 and 1 VTE for $DRSP_{24d}$ and LNG starters, respectively). The point estimate of the incidence rate for $DRSP_{24d}$ starters (2.8 VTE/10,000 WY) was similar to LNG starters (2.4 VTE/10,000 WY).

The geographical region (United States or Europe) also had no substantial impact on the relative risk estimates. For the United States and Europe, calculation of the adjusted HRs for $DRSP_{24d}$ vs. non-DRSP yielded 1.0 (95% CI, 0.5–1.8) and 0.6 (95% CI, 0.3–1.5), respectively. The corresponding values for $DRSP_{24d}$ vs. LNG were 1.0 (95% CI, 0.4–2.4) and 0.7 (95% CI, 0.2–1.9), respectively.

In the validation process for VTE, 23 reported events were identified that did not represent VTE according to the criteria described above. Because these cases were unanimously classified by the blinded adjudicators as not being VTEs, the risk of misclassification seems low. To assess possible error, an additional evaluation was performed in which potential VTEs were combined with confirmed VTEs.

Table 4
VTE incidence rates, crude and adjusted HRs, and 95% CIs

VTE	(Sub)Cohort	Incidence (events/10,000 WY)		HR ($DRSP_{24d}$ vs. comparators)			
		Point estimate	95% CI	Crude estimate	95% CI	Adjusted[a] estimate	95% CI
Confirmed	$DRSP_{24d}$	7.2	4.3–11.2	–	–	–	–
	Non-DRSP	9.6	7.8–11.6	0.8	0.5–1.3	0.8	0.5–1.3
	LNG	9.8	5.9–15.2	0.8	0.5–1.6	0.8	0.4–1.6
"Idiopathic"	$DRSP_{24d}$	4.9	2.6–8.4	–	–	–	–
	Non-DRSP	7.2	5.7–9.0	0.7	0.3–1.2	0.7	0.4–1.3
	LNG	7.2	3.9–12.1	0.7	0.3–1.6	0.7	0.3–1.6
Confirmed and potential	$DRSP_{24d}$	1.5	0.4–3.9	–	–	–	–
	Non-DRSP	2.8	1.9–4.1	0.8	0.5–1.3	0.8	0.5–1.3
	LNG	3.6	1.4–7.4	0.8	0.4–1.6	0.8	0.4–1.6

[a] Adjusted for age, BMI, current duration of use and family history of VTE.

This subanalysis yielded only slight deviations from the analysis of confirmed VTE: adjusted HR for $DRSP_{24d}$ vs. non-DRSP, 0.8 (95% CI, 0.5–1.3), and adjusted HR for $DRSP_{24d}$ vs. LNG, 0.8 (95% CI, 0.4–1.6).

The advantages and disadvantages of limiting the analysis of VTE to so-called "idiopathic VTE" are the subject of scientific debate [2]. From our point of view, this analytical approach has only limited validity. However, to allow for comparison of our study data with the results from other scientific groups, an exploratory analysis of "idiopathic VTE" was done. For this analysis, VTE cases with acute risk factors (such as pregnancy, delivery, trauma, immobilization, long-haul travel, surgery and chemotherapy) were excluded. The following adjusted HRs were found: adjusted HR for $DRSP_{24d}$ vs. non-DRSP, 0.7 (95% CI, 0.4–1.3), and adjusted HR for $DRSP_{24d}$ vs. LNG, 0.7 (95% CI, 0.3–1.6).

Based on previous discussions with other scientific groups and regulatory authorities, several additional comparisons between DRSP subcohorts and other subcohorts were done. These analyses included a comparison of DRSP- and LNG-containing COCs with 20 μg EE. The point estimates of all crude and adjusted HRs for these comparisons were 1.0 or lower; all CIs included 1.0 (Table 5).

The analyses presented are based on Cox regression models. In the case of VTE, it is conceivable that the proportional hazard assumption used in those models (i.e., that effect parameters multiply hazard) does not hold. Therefore, time-dependent factors were included in the Cox model. The appropriateness of the model was checked by comparing results of this analysis with results of an alternative analysis that stratifies by time of exposure. The well-established high VTE risk during the first months of hormonal contraceptive use was confirmed by the stratified analysis. Overall, the VTE incidence associated with hormonal contraceptive use dropped from about 18 VTE per 10,000 WY in the first 6 months to about 5 VTE after the first year of use. The results of the stratified analysis are shown in Fig. 2. The point estimates of the adjusted HRs for $DRSP_{24d}$ vs. non-DRSP were similar for all three exposure periods (≤6, 7–12, and >12 months). The results do not suggest that the proportional hazard assumption does not hold for the comparison of $DRSP_{24d}$ and other OC (sub)cohorts.

Table 5
Cox regression analysis of the risk of VTE: crude and adjusted HRs for additional comparisons of cohorts of interest.

Comparison groups	Crude		Adjusted	
	HR	95% CI	HR	95% CI
$DRSP_{24d}$ vs. other OCs[a]	0.7	0.5–1.2	0.8	0.5–1.3
$DRSP_{24d}$ vs. OCs_{21d}	0.8	0.5–1.2	0.8	0.5–1.3
$DRSP_{24d}$ vs. non-$DRSP_{24d}$	0.6	0.3–1.2	0.8	0.4–1.6
$DRSP_{20\mu g\ EE}$ vs. $DRSP_{30\mu g\ EE}$	0.8	0.4–1.7	0.9	0.5–1.9
$DRSP_{24d}$ vs. OC_{-3P}	0.7	0.4–1.2	0.8	0.5–1.3
$DRSP_{30\mu g}$ vs. $LNG_{30\mu g}$	1.0	0.4–2.3	0.9	0.4–2.1
$DRSP_{20\mu g}$ vs. $LNG_{20\mu g}$	0.8	0.3–1.8	0.7	0.3–1.8

OC_{21d}, all COCs with a 21-day regimen (including DRSP-containing OCs); non-$DRSP_{24d}$, 24-day regimens of all OCs without DRSP; $DRSP_{20\mu g\ EE}$, DRSP-containing COC with 20μg of EE; $DRSP_{30\mu g\ EE}$, DRSP-containing COC with 30 μg of EE; OC_{-3P}, OC without gestodene, desogestrel and DRSP; $LNG_{30\mu g}$, levonorgestrel-containing COC with 30 μg of EE; $LNG_{20\mu g}$, levonorgestrel-containing COC with 20 μg of EE.

[a] Including OCs with DRSP.

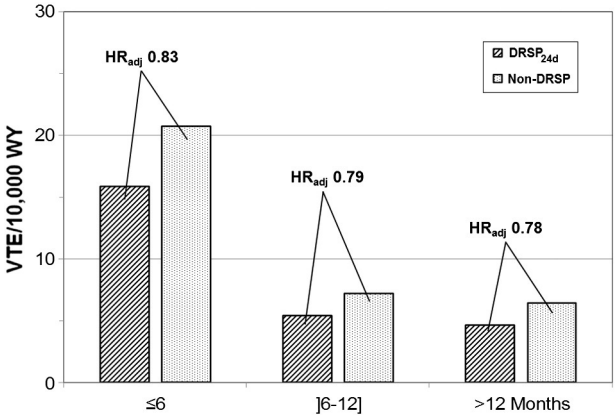

Fig. 2. VTE risk for different exposure periods: incidence rates and adjusted HRs for $DRSP_{24d}$ vs. non-DRSP for each exposure period.

3.5. Arterial thromboembolism

A total of 46 ATEs were observed: 16 AMIs, 21 ischemic strokes, 6 transient ischemic attacks and 3 complete thromboses of a peripheral artery. The ATEs break down among the (sub)cohorts as follows: $DRSP_{24d}$, 4 cases; $DRSP_{21d}$, 3 cases; non-DRSP, 30 cases; LNG, 7 cases; NOHC, 2 cases; and "no use," 7 cases. This corresponds to ATE incidence rates of 1.5 ATE/10,000 WY for the $DRSP_{24d}$ cohort and of 1.8, 2.8, 3.6, 2.5 and 1.4 for the $DRSP_{21d}$, non-DRSP, LNG, NOHC and "no use" cohorts, respectively. The incidence rates were lower for the DRSP cohorts compared to the other HC cohorts, but the 95% CIs overlap widely.

Cox regression analysis was not carried out for the original data set — in accordance with the analysis plan; that is, HRs were only to be calculated if a minimum of five confirmed events were available in each of the comparison groups. This requirement was not fulfilled for the DRSP and NOHC cohorts. However, after artificially increasing the number of events in the $DRSP_{24d}$ cohort to 5, an analysis of $DRSP_{24d}$ vs. non-DRSP and $DRSP_{24d}$ vs. LNG was possible. The artificially high HRs were below 1 and the 95% CI did not include two: $DRSP_{24d}$ vs. non-DRSP, 0.7 (95% CI, 0.2–1.7), and $DRSP_{24d}$ vs. LNG, 0.5 (95% CI, 0.1–1.3). Therefore, a twofold higher risk of ATE for $DRSP_{24d}$ users compared to users of non-DRSP and LNG can be excluded.

4. Discussion

All (sub)cohorts (including LNG) showed similar incidence rates for VTE, ATE, SAE, death, cancer and

depression. Crude and adjusted HRs also indicated similar risk levels for these (sub)cohorts.

In analyzing the results of nonexperimental studies, including INAS-OC, it is not possible to entirely eliminate potential effects of bias or residual confounding. This in turn limits the ability to infer causation [4]. The effects of bias and residual confounding can be reduced by compiling valid information on potential sources of confounding, and by applying sophisticated statistical and epidemiological methodologies [5]. However, the weaker the association that is being studied, the more difficult it is to infer causation conclusively [6,7]. Relative risk estimates that are close to unity may not allow differentiation among causation, bias and confounding [8,9]. In fact, relative risks of two or less are difficult to interpret by means of observational research in general [10,11]. These limitations suggest that risk estimates close to unity — such as those in our study — do not exclude small relative risks.

Regarding different types of bias, we do not consider selection bias to have been a major issue in INAS-OC because the study included both inpatients and outpatients, and because the demographic characteristics of its participants are representative for adult OC users [3]. We also do not consider misclassification bias to have had any substantial impact on the results, given that the study had precise information on both exposure and the outcomes of interest. It also had reliable information on participants' duration of current use. The study was therefore able to reproduce the well-established increase in VTE risk during the initial months of COC use [2,12,13]. Another noteworthy point here is the low loss to follow-up rate of 3.3%. It is theoretically possible that a disproportionately high percentage of SAEs might have occurred in precisely those patients who were lost to follow-up, because the SAEs might have led to a loss of contact with the investigators. However, an advantage of the INAS-OC study design is that it enables the investigator team to retain direct contact with participants. If women changed their gynecologists, for example, due to reasons such as seeking better treatment or moving to another town, contact was not lost.

In contrast, it was not possible to exclude diagnostic bias. Clinical symptoms of VTE cover the spectrum from a nonspecific, slight symptoms or the complete absence thereof to dramatic, acute, life-threatening symptoms [14–16]. A high level of awareness for potential cardiovascular risks of COC use — in particular in association with new products — might have led to more diagnostic procedures and, therefore, to more detected VTE. If that were the case, however, we assume that it would not have influenced the cohorts of interest differently. If anything, it would have led to overestimating the relative risk of the rather new 24-day DRSP regimen. The potential for diagnostic bias in this study, therefore, should not have resulted in underestimating the risk of VTE associated with $DRSP_{24d}$ use.

One strength of this study was the availability of information on many important prognostic factors for the outcomes of interest. It is true that the study's noninterventional character meant that the information that it had on specific gene mutations was only available for the VTE cases, not for the great majority of study participants. Nevertheless, this limitation was mitigated by information on family history of VTE for all study participants, which has a higher predictive value than gene mutations for VTE [17].

The HRs remained close to unity if COCs containing desogestrel and gestodene were excluded from the analysis. This shows that possible differences between the cohorts were not "diluted" by including COCs that are potentially associated with a greater risk of VTE. This inference is also supported by the comparison between $DRSP_{24d}$ and LNG, and particularly by the comparison of the DRSP- and LNG-containing preparations with 20 μg EE.

Unlike for $DRSP_{21d}$, results from large epidemiological studies are not available for $DRSP_{24d}$. Our results on VTE risk associated with $DRSP_{21d}$ are consistent with the results from the Ingenix, EURAS and LASS studies as well as a German case–control study [2,3,18,19]. In contrast, cohort studies from Denmark and the United States as well as several case–control studies [20–24] reported an increase in VTE risk for $DRSP_{21d}$ compared to COCs containing levonorgestrel and other so-called second-generation progestins. In particular, the Danish cohort study is quite often used as the reference for an increased VTE risk of $DRSP_{21d}$ compared to second-generation OCs. This study linked several national registers in Denmark. Advantages and disadvantages of this methodological approach compared to the methodology used in EURAS-like studies (e.g., the INAS-OC study) have been discussed extensively [1,25–30]. The Danish register studies are much larger than field studies like INAS-OC. However, the narrow CIs in large observational studies are misleading because their calculation "only takes into consideration random variation of data. It ignores the systematic errors, the biases and confounders, that will almost invariably overwhelm the statistical variation" [10]. In addition, specific limitations of the Danish register studies — such as sparse information on relevant prognostic factors (e.g., BMI and family history of VTE) and limited validity of information on exposure and clinical outcomes [31] — increase the impact of bias and confounding compared to the INAS-OC study. It should be noted that the cohorts in the Danish register studies — unlike the cohorts in the INAS-OC study — were substantially different with regard to their age structure (and potentially with regard to a number of other important prognostic factors) and that, accordingly, crude and age-adjusted relative risks estimates were substantially different. Our analyses show, however, that the combination of risk factors (e.g., age 45, obesity and family history of VTE) results in overadditive risk increases that cannot be correctly adjusted for if information on one of these risk factors is missing. In addition, the recent findings from the Danish database that the levonorgestrel intrauterine system is associated with statistically significant protection against venous thrombosis

[32] and thrombotic stroke [33] show the limitations of this database. This paradoxical protective effect is unprecedented in contraceptive research and devoid of biological plausibility. Hence, bias in the database is the most likely explanation. Therefore, the Danish register study does not invalidate our results on $DRSP_{24d}$ and $DRSP_{21d}$.

The INAS-OC study combines several methodological strengths that provide substantial support for the validity of its results: (1) prospective, comparative cohort design; (2) availability of important confounder information (e.g., BMI and family history of VTE); (3) validation of outcomes of interest and exposure for the relevant cases; (4) comprehensive follow-up procedure and very low loss to follow-up to minimize underreporting; (5) independent, blinded adjudication of VTE cases; (6) relevant statistical analyses (e.g., stratified analyses by geographical region, user status, and exposure period; comparison of isochronous, new user cohorts; sensitivity analyses on the impact of the adjudication process, outcome definition, prognostic factor/covariate selection, and choice of comparator cohort); (7) study population representative for OC users under routine clinical conditions; (8) reproducibility of the typical time pattern of VTE risk; and (9) supervision by an independent Safety Monitoring and Advisory Council plus scientific independence from the study funder.

In our judgment, the INAS-OC results are valid within the general limitations of observational research. We conclude that $DRSP_{24d}$, $DRSP_{21d}$ and non-DRSP use are associated with similar health risks during routine clinical use. This includes the risk of VTE and ATE.

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