Comparison of the pharmacologic and clinical profiles of new combined oral contraceptives containing estradiol

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Abstract: Three estradiol (E2)-containing oral contraceptives, estradiol valerate/cyproterone acetate (E2V/CPA, Femilar®), estradiol valerate/dienogest (E2V/DNG, Qlaira®/Natazia™), and estradiol/nomegestrol acetate (E2/NOMAC; Zoely®), have received approval for use in general practice. Only Finnish women currently have access to all three E2-based formulations. E2/NOMAC is currently approved only in Europe, while E2V/DNG is approved globally. To assist clinicians counseling women considering use of one of these formulations, we conducted a review of the published information about the current E2-containing oral contraceptives.

A literature search was conducted using the Ovid interface and a combination of free search terms relevant to estradiol and oral contraception to identify suitable articles for inclusion in this review. The available data show that E2V/DNG, E2/NOMAC, and E2V/CPA are all effective oral contraceptives. While direct comparisons are lacking, indirect evidence suggests that E2V/DNG and E2/NOMAC may have better bleeding profiles than E2V/CPA. E2V/DNG is also approved for the treatment of heavy menstrual bleeding. Both E2V/DNG and E2/NOMAC have minimal influence on hemostatic, lipid, and carbohydrate metabolism parameters, or induce less change in these parameters relative to ethinylestradiol-based oral contraceptives.

However, the predictive value of these surrogate parameters is a matter of debate, and whether these differences can be translated into meaningful clinical outcomes needs to be established in large-scale, post-marketing, prospective, Phase IV cohort studies. Future studies are required to determine whether E2-based oral contraceptives confer additional benefits compared with those of ethinylestradiol-based COCs.

Keywords: estradiol valerate, dienogest, nomegestrol acetate, cyproterone acetate

Introduction

Over the last 50 years, refinements in the formulation of combined oral contraceptives (COCs) have focused on improving their tolerability and safety. Primary modifications include a reduced ethinylestradiol (EE) dose and incorporation of new progestins with improved selectivity profiles which are closer in function to natural progesterone.1 Drospirenone (DRSP), dienogest (DNG), and nomegestrol acetate (NOMAC) are the most recent progestins introduced to the market, and products containing nestorone and trimegestone are in development.

Although the contraceptive effects of COCs are mainly achieved through progestin alone, estrogen remains an important component because its inclusion enhances contraceptive efficacy and helps regulate bleeding. While the type of progestin and dosing regimen used may affect overall cycle control,2 COCs with lower EE doses tend to have poorer cycle control (ie, unscheduled bleeding and/
or spotting) relative to formulations with the same progestin and a higher EE dose.²⁻⁴ Very low-dose EE products administered in a 24/4 and 26/2 regimen (15 μg in combination with gestodene 60 μg,³ and 10 μg in combination with norethindrone acetate 1 mg,⁴ respectively) have been approved. Although EE 15 μg/gestodene 60 μg appears to have acceptable cycle control and tolerability,⁷ no data are available for EE 10 μg/norethindrone acetate 1 mg. Although the reduction of the EE dose to less than 50 μg has greatly improved the cardiovascular safety profile of combined pills, the benefit of dose reduction to 20 μg or lower has not been definitively established.⁹ Even with modern “low-dose” EE formulations, factors related to hepatic and carbohydrate metabolism, as well as hemostasis, may be maintained at an upregulated level. Biological potency of estrogens depends on ligand-receptor interactions plus the rate of absorption, distribution, metabolism, and elimination. For EE, both its receptor binding affinity and its biological potency with regard to various clinical and metabolic parameters are usually greater than with estradiol (E₂).¹⁰,¹¹ Reliance on the use of EE in COCs has largely been due to its higher oral bioavailability (38%–48%) compared with other estrogens.¹⁰ Inclusion of a 17α-ethinyl group on estradiol greatly enhances oral activity due to inhibition of hepatic metabolism, in particular, reduced metabolism to weaker estrogens. Oral EE is completely and rapidly absorbed in the gastrointestinal tract, undergoing oxidation to yield free hydroxylated and methylated active metabolites plus sulfate and glucuronide conjugates during first-pass metabolism in the gut and liver.¹² In contrast, oral E₂ is completely absorbed in the gastrointestinal tract and undergoes extensive metabolism to less potent estrone and estrone sulfate during the absorption process and in the liver.¹³ As a result, oral bioavailability of estradiol is typically only about 3%–6%.¹² The higher intrinsic estrogenic activity of EE combined with the reduced degradation and active metabolites results in more pronounced effects on hepatic metabolism and hemostatic changes relative to E₂. More simply put, oral EE activates the liver through both a first-pass effect and recirculation of EE, while hepatic activation of oral E₂ occurs predominantly through first pass. For this reason, even nonoral routes of EE administration result in dose-related effects on hepatic globulins.¹⁴ It has been hypothesized that using oral E₁ might reduce the relative impact on the hepatic and hemostatic effects and adverse events associated with EE, given that activation by recirculation does not occur.¹⁵,¹⁶ Early attempts to develop E₂-containing oral contraceptives as alternatives to EE-based formulations showed that E₂-containing formulations could achieve effective inhibition of ovulation and contraception. However, these early formulations were associated with unacceptable bleeding patterns and, thus, were suspended from further development.¹⁷⁻²¹ The bleeding problems associated with these earlier attempts to incorporate E₂ into an oral contraceptive might be explained, in part, by the activity of 17β-estradiol dehydrogenase. This enzyme rapidly converts E₂ (but not EE) into estrone (E₁),²²,²³ an estrogen with only weak estrogenic activity that is unable to maintain stable endometrial proliferation.²³ The rate of transformation of E₂ to its metabolites may be influenced by some progestins;¹³ consequently, progestins with minimal impact on E₂ metabolism and endometrial stroma stability may improve cycle stability with E₂-based oral contraceptives.²⁴

To date, only three E₂-containing oral contraceptives have received regulatory approval for use in general practice. These include estradiol valerate/cyproterone acetate (E₂/V/CPA; Femilar®, Bayer Oy, Turku, Finland), estradiol valerate/dienogest (E₂/V/DNG; Qlaira®/Natazia™, Bayer HealthCare Pharmaceuticals, Berlin, Germany), and estradiol/nomegestrol acetate (E₂/NOMAC; Zoely®; Theramex Srl, Milan, Italy). Clinicians and other family planning providers need informed guidance when counseling their patients about E₂-containing oral contraceptives, because a number of factors may influence women’s choice. As new data have become available, this comprehensive review seeks to compare and contrast the pharmacologic and clinical profiles of E₂-containing oral contraceptives.

Methods
A systematic literature search was conducted using Ovid to search both MEDLINE and EMBASE simultaneously for clinical studies published up to February 20, 2013 on the three marketed E₂-containing COCs (E₂/V/DNG, E₂/NOMAC, and E₂/V/CPA). The search strategy combined free text terms relevant to oral contraception and estradiol as follows: (beta estradiol OR beta estradiol OR E₂ OR natural estradiol OR natural estradiol) AND contracep* (where* is a wild character). The titles and abstracts from the electronic searches were initially assessed for relevant articles published in English. In addition, the reference lists of pertinent review articles identified were also examined for relevant studies not captured by the electronic search. Studies evaluating the pharmacologic and clinical profiles
of these E₂-containing COCs were chosen for inclusion in this review.

**Approved formulations and regimens**

E₂V/CPA is a biphasic preparation taken in a 21/7 cycle regimen (E₂V 1 mg/CPA 1 mg on days 1–10, E₂V 2 mg/CPA 2 mg on days 11–21, and a 7-day pill-free interval). The rationale for the biphasic E₂V/CPA regimen has not been discussed in the literature, but phasic regimens are generally used in order to optimize control of bleeding.

E₂V/DNG is taken in a 26/2 cycle, with E₂V 3 mg on days 1–2, E₂V 2 mg/DNG 2 mg on days 3–7, E₂V 2 mg/DNG 3 mg on days 8–24, E₂V 1 mg on days 25–26, and placebo on days 27–28. This specific regimen was established as the lowest effective dose of E₂V combined with DNG for efficient ovulation inhibition while maintaining acceptable bleeding control. The regimen for E₂V/DNG was designed to provide phased delivery of hormones with estrogen dominance early in the cycle and progestin dominance from the mid-to-late part of the cycle. Early estrogenic dominance is thought to allow for initial endometrial proliferation and upregulation of progesterone receptors; this enhances sensitivity to mid-cyclic progestin action, leading to endometrial stroma stability at the end of the cycle, thereby resulting in predictable bleeding. The rationale for estradiol alone towards the end of the cycle and the short hormone-free interval is to ensure that overall estradiol levels remain relatively stable throughout each cycle (including the hormone-free interval).

E₂/NOMAC is a monophasic preparation taken over a cycle of 24/4 days (E₂ 1.5 mg/NOMAC 2.5 mg on days 1–24 and placebo on days 25–28). The 2.5 mg dose of NOMAC was established as the optimum dose needed for ovulation inhibition. The 1.5 mg E₂ dose was selected based on the dose used in estrogen replacement therapy established to provide adequate estrogen levels for prevention of osteoporosis in postmenopausal women. The rationale behind the 24/4 regimen for E₂/NOMAC is based, in part, on the greater ovarian suppression achieved relative to the conventional 21/7 regimen, which may result in a greater contraceptive margin and a shorter duration of withdrawal bleeding (compared with traditional 21/7 regimen oral contraceptives), as well as decreased hormonal fluctuations (particularly for E₂) and associated hormone withdrawal symptoms. The bleeding control achieved with E₂/NOMAC has been hypothesized to be due to the ability of NOMAC to maintain endometrial stability through its minimal impact on endometrial E₂ metabolism, which ensures sufficient E₂ levels in the endometrium and thus prevents endometrial breakdown.

The absolute bioavailability of E₂ following oral E₂/NOMAC administration was estimated to range between 1% and 5%, and that following oral E₂V/DNG administration to be about 3%–6%. E₂V is rapidly hydrolyzed and converted to 17β-estradiol (E₂) during absorption in the gastrointestinal tract following oral administration (1 mg of...
E2V contains 0.76 mg of E2. The E2 pharmacokinetic profile following oral micronized E2 (1.5 mg) appears to be similar to that following oral E2V (2 mg, Figure 1).

**Indications and pivotal studies for approved E2-containing COCs**

E2V/CPA is available in Finland only and indicated for women >40 years and for women aged 35–40 years for whom an oral contraceptive containing EE is not appropriate. The pivotal registration study for E2V/CPA was an open-label trial that recruited 288 Finnish women aged 30–49 (mean 39.3 ± 3.4) years and was conducted over thirteen 28-day cycles. E2V/DNG is available globally and is indicated for contraception and for the treatment of heavy menstrual bleeding in “women without organic pathology who desire oral contraception”. The pivotal registration studies for the contraception indication included two open-label, noncomparative efficacy trials, one undertaken in Europe and the other in the US and Canada. The European study enrolled 1,377 women aged 18–50 years and was conducted over twenty 28-day cycles. The US and Canadian study enrolled 499 women aged 18–35 years, and although initially planned for 13 cycles, was later extended to 28 cycles. This latter study, although undertaken to assess contraceptive efficacy, cycle control, and safety of E2V/DNG, was not powered for a separate Pearl Index calculation. The pivotal registration studies for the treatment of heavy menstrual bleeding indication included two similarly designed, randomized placebo-controlled studies, one undertaken in Europe and Australia (n=221) and the other in the US and Canada (n=190).

E2/NOMAC is available in Europe, Australia, and some South American countries, and is indicated for contraception. There were two pivotal registration studies for E2/NOMAC, one conducted in Europe, Asia, and Australia and the other in the US. Both studies were randomized open-label, comparative trials that recruited women aged 18–50 years, of whom 3,323 were randomized to receive E2/NOMAC and 1,110 to EE/DRSP (30 μg/3 mg; Yasmin®, Bayer HealthCare Pharmaceuticals) for 13 cycles.

**Clinical profiles**

**Pharmacodynamic effects**

The pharmacodynamic effects of E2V/CPA, E2V/DNG, and E2/NOMAC, as well as the individual progestin components (CPA, DNG, and NOMAC, respectively), have been well documented.

In essence, the main contraceptive effects of these combined formulations are due to the progestin component; this is also the case with other COCs containing EE.

CPA 1 mg daily appears sufficient to inhibit ovulation. A dose-ranging study of CPA (0.125–1.00 mg daily) in healthy women aged 20–28 years (n=12) showed that CPA 1 mg inhibited ovulation (as determined by daily measurements of luteinizing hormone, follicle-stimulating hormone, E2, and progesterone) in all women assessed (n=5). Concomitant effects of CPA on the endometrium and cervical mucus were not reported in this study.

The ovulation-inhibiting effects of DNG were assessed in a dose-ranging (0.5 mg–3 mg DNG daily) study in healthy women aged 18–35 years (n=102) using the Hoogland score, which determines ovarian activity based on largest follicular size and highest serum hormone levels. Dose-dependent ovulation-inhibiting effects were observed across the doses tested. Ovulation was suppressed in all women taking 2 mg (n=20) or 3 mg (n=23) of DNG daily. In addition, endometrial thickness was reduced compared with pretreatment. DNG also induced moderate suppression of endogenous E2 production.

The contraceptive effects of NOMAC have also been assessed in a dose-ranging (1.25–5 mg NOMAC daily) study in 13 healthy women. In this study, pituitary-ovarian function was determined by measuring E2, follicle-stimulating hormone, and luteinizing hormone levels. Ovulation was inhibited in all women across the doses of NOMAC. In a separate study of 16 normally cycling women assessing the effects of NOMAC (2.5 mg or 5 mg daily) on mid-cycle cervical mucus, the changes observed were similar to those induced by progesterone during the luteal phase. In a more recent study, 2.5 mg of NOMAC was again shown to inhibit ovulation and decrease cervical mucus scores (ie, indicative of increased hostility to sperm penetration) in healthy women aged 18–35 years (n=9). These data support cervical mucus inhibition as a secondary contraceptive mechanism.

The approved formulations of E2V/CPA, E2V/DNG, and E2/NOMAC all consistently inhibit ovulation in ≥95% of women. However, studies with E2V/CPA were performed in small samples of women with a mean age of 39 (range 30–49) years, and as such may overestimate the rate of ovulation inhibition in “more fertile” younger women. In addition, the contraceptive effects of E2V/CPA achieved through alteration in cervical mucus and the endometrium have not, to our knowledge, been reported. E2V/DNG has been shown to have suppressive effects on endometrial growth and cervical mucus as assessed by transvaginal ultrasound in healthy women aged 18–35 years (n=100); mean
maximal endometrial thickness decreased from 10.1 mm at baseline to 6.5 mm during cycle 3. Although treatment was associated with a reduction in the ultrasound appearance of cervical mucus, the quality of mucus was not assessed. \(^{40}\) Similar changes in cervical mucus and the endometrium were observed with \(E_2/NOMAC\) in healthy women aged 18–35 years (n=32); mean maximum endometrial thickness was reduced from 9.9 mm at screening to 4.9 mm in cycle 6. In this study, cervical mucus, assessed using the Insler cervical mucus score, decreased from a mean maximum of 8.9 at screening to 2.3 during the first treatment cycle (with lower scores indicating poor likelihood of sperm penetration). \(^{47}\)

### Contraceptive efficacy

The approved \(E_2/V/CPA\), \(E_2/V/DNG\), and \(E_2/NOMAC\) formulations appear to have similar contraceptive efficacy profiles (Table 1). \(^{30,34–36,39}\) The net pregnancy rate with \(E_2/V/CPA\) was reported to be 0.4% over 12 months in Finnish women (n=288) aged 30–49 years; one pregnancy occurred in 2,800 cycles of exposure, equating to a Pearl Index of 0.46. \(^{34}\) Again this may be an overestimation of the contraceptive efficacy of \(E_2/V/CPA\) in younger more fertile women. In addition, this lone study would be insufficient to meet current recommendations for regulatory approval of a new hormonal contraceptive in Europe (“for any new contraceptive, at least 400 women should have completed one year of treatment”). \(^{49}\)

The contraceptive efficacy of \(E_2/V/DNG\) was established in two open-label, noncomparative studies, one conducted in Europe and the other in North America, in over 1,850 women aged 18–50 years. \(^{35,36}\) In the European study (conducted in Austria, Germany, and Spain), the Pearl Index at 20 cycles of treatment was reported to be 0.73 in women aged 18–50 years and 0.94 in women aged 18–35 years (n=998). \(^{35}\) The second study conducted in North America recruited women aged 18–35 years (n=490) and reported a Pearl Index of 1.64 at one year; however, this study was not sufficiently powered for a stand-alone contraceptive efficacy calculation.

The contraceptive efficacy of \(E_2/NOMAC\) was established in two randomized, open-label, comparative studies (compared with EE 30 \(\mu\)g/DRSP 3 mg [Yasmin]), one conducted in Europe, Asia, and Australia, \(^{40}\) and the other in the US, Canada, Argentina, Brazil, Chile, and Mexico, \(^{39}\) in over 3,250 women aged 18–50 years. The study conducted in Europe, Asia, and Australia reported a Pearl Index of 0.31 in women aged 18–50 years, and a Pearl Index of 0.38 in women aged 18–35 years (n=1,315). The other \(E_2/NOMAC\) efficacy study reported a Pearl Index at one year of 1.13 in women aged 18–50 years, with a corresponding Pearl Index of 1.27 in women aged 18–35 years (n=1,375).

Of note, the Pearl indices reported at one year from the \(E_2/V/DNG\) and \(E_2/NOMAC\) studies that included study centers in the US were slightly higher than for the similar studies conducted elsewhere. This is a well recognized phenomenon in contraceptive research, and may, in part, be due to differences in compliance rates and/or recruitment practices. \(^{50}\)

Indeed, residential poverty level, an indirect measure of individual income, was shown to be the strongest predictor of noncompliance in a US oral contraceptive clinical trial. \(^{51}\) Nonetheless, the one-year Pearl indices for the approved \(E_2\)-containing oral contraceptives are consistent with those reported for recently approved low-dose EE-containing formulations (Pearl indices 0–1.6). \(^{50}\)

### Bleeding profile

A direct comparison of bleeding profile between oral contraceptive formulations, especially by cycle, is difficult due to the lack of uniform definitions and results across studies. \(^{52}\)

<table>
<thead>
<tr>
<th>Table 1 Summary of published studies reporting contraceptive efficacy of estradiol-containing oral contraceptives</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
</tr>
<tr>
<td>(E_2/V/CPA^{34})</td>
</tr>
<tr>
<td>(E_2/V/DNG^{35})</td>
</tr>
<tr>
<td>Germany</td>
</tr>
<tr>
<td>Spain</td>
</tr>
<tr>
<td>(E_2/V/DNG^{36})</td>
</tr>
<tr>
<td>Europe, Asia</td>
</tr>
<tr>
<td>Australia</td>
</tr>
<tr>
<td>&gt;35–50</td>
</tr>
<tr>
<td>(E_2/NOMAC^{30})</td>
</tr>
<tr>
<td>Argentina, Brazil</td>
</tr>
<tr>
<td>Chile, Mexico</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; CPA, cyproterone acetate; \(E_2\), estradiol valerate; DNG, dienogest; NOMAC, nomegestrol acetate; \(E_2\), estradiol.
Although the World Health Organization has made recommendations for the analysis of menstrual patterns, these have not been uniformly adopted. Nonetheless, irrespective of definitions used, studies that assessed bleeding profiles associated with E₂V/CPA, E₂V/DNG, and E₂/NOMAC consistently suggest that these oral contraceptives are associated with shorter, lighter bleeding versus comparator EE-containing pills or baseline.²⁷,³⁰,³⁴,³⁶,³⁹,⁴¹

Table 2 summarizes the number of uterine bleeding days using 90-day and 91-day reference periods observed in the randomized controlled trials with E₂V/DNG and E₂/NOMAC compared with EE/levonorgestrel (EE 20 µg/LNG 100 µg, Miranova®, Bayer HealthCare Pharmaceuticals) and EE/DRSP (Yasmin), respectively.²⁷,³⁰,³⁹ The study with E₂V/DNG and EE/LNG was conducted over seven 28-day cycles in centers across Germany, the Czech Republic, and France, and reported uterine bleeding data from 399 women aged 18–50 years in both treatment groups.²⁷ These studies demonstrated statistically significant and/or clinically meaningful reductions in bleeding/spotting days with E₂V/DNG and E₂/NOMAC compared with the comparator EE-based oral contraceptives.²⁷,³⁰,³⁹ There are no available bleeding data with E₂V/CPA where the data are reported by reference period.

The data reported by cycle with both E₂V/DNG and E₂/NOMAC are also consistent with reduced bleeding (or an absence of bleeding) relative to the comparator EE-based formulations. For example, the rate of absence of withdrawal bleeding (mean over cycles 1–7) was 19.4% (range 16.8%–22.3%) in women treated with E₂V/DNG compared with 7.7% (range 6.2%–10.5%) in women treated with EE/LNG.²⁷ In the open-label North American E₂V/DNG study, the rate of absent withdrawal bleeding occurred in a mean 23.5% of women through cycles 1–12 (range 17% and 32%).³⁶ For E₂/NOMAC, in the study conducted in Europe, Asia, and Australia, 30% of women had at least one absence of withdrawal bleeding during cycles 2–4. Moreover, a progressive increase in the incidence of absent withdrawal bleeding from 22% to 31% occurred in cycles 4–12, indicating a tendency towards absent withdrawal bleeding with continued use.³⁰ In the comparator EE/DRSP formulation group, the incidence of absent withdrawal bleeding was relatively stable, ranging from 3% to 6%. A similar trend towards absent withdrawal bleeding with continued use (approximately 18%–34%) was also observed with E₂/NOMAC, but not with EE/DRSP (approximately 4%–9%), in the study conducted in North and South America.³⁹

<table>
<thead>
<tr>
<th>Study</th>
<th>Formulation</th>
<th>Reference period</th>
<th>Bleeding/spotting days (n)</th>
<th>Spotting days (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahrendt et al.²⁷</td>
<td>E₂V/DNG</td>
<td>R1 R2 R3 R4</td>
<td>17.3* 15.9 15.9 13.4*</td>
<td>2.1 3.0 3.0 2.1</td>
</tr>
<tr>
<td>Mansour et al.³⁰,³⁹</td>
<td>E₂V/DNG</td>
<td>R1 R2 R3 R4</td>
<td>15.0 12.5 11.0 10.5</td>
<td>10.5 15.6 15.6 10.5</td>
</tr>
<tr>
<td>Westhoff et al.³⁹</td>
<td>E₂V/DNG</td>
<td>R1 R2 R3 R4</td>
<td>15.0 12.5 11.0 10.5</td>
<td>10.5 15.6 15.6 10.5</td>
</tr>
</tbody>
</table>

Notes: Data estimated from published graphs; †90-day reference period used; ‡91-day reference period used. EE/DRSP (Yasmin): N=51; N=101; N=102; N=102; N=102; N=102; N=102; N=102; N=102; N=102; N=102; N=102; N=102. EE/LNG (Miranova®): N=100; N=100; N=100; N=100; N=100; N=100; N=100; N=100; N=100; N=100; N=100; N=100; N=100.
Intracyclic bleeding was reported to occur in approximately 14% of women receiving E_2/V/DNG (ranging from 10.5% to 18.6%) over cycles 1–7 compared with approximately 12% of women receiving the comparator EE/LNG formulation (ranging from 9.9% to 17.1%). In the open-label, North American E_2/V/DNG study, intracyclic bleeding ranged from 28.8% to 11.2% during cycles 2–13, with the data generally indicative of a tendency to less intracyclic bleeding with continued use. For E_2/NOMAC, in the study conducted in Europe, Asia, and Australia, intracyclic bleeding progressively decreased with continued E_2/NOMAC use from about 34% to 14% (through cycles 1–13); a similar trend was observed with the comparator EE/DRSP (28% to 13% through cycles 1–13). A similar trend towards progressively decreased intracyclic bleeding with continued E_2/NOMAC use (from about 31% to 16% through cycles 1–13) was also observed in the study conducted in North and South America.

The overall bleeding profile associated with E_2/V/CPA is less well characterized compared with the other two approved E_2-based formulations. In the pivotal, open-label, noncomparative study in Finnish women, intracyclic bleeding occurred in 33% of E_2/V/CPA users (mainly spotting) at 3 months, decreasing to 22% at 6 months and 24% at 12 months. Much lower rates of intracyclic bleeding were reported with E_2/V/CPA (n=26) in a second study (0%–15%), which was a randomized double-blind trial including biphasic E_2/V/norethisterone, but it is not clear from the report whether the incidence of spotting (20%–40%) included intracyclic bleeding. Using the comparator E_2/V/norethisterone (n=24), intracyclic bleeding occurred in 6%–42% of women (highest during the second cycle). Absent bleeding with E_2/V/CPA ranged between 5% and 19% (versus 6%–25% in the comparator group). The mean number of bleeding/spotting days per cycle decreased from 5.0 ± 1 days in the pretreatment cycle to 3.8 ± 3.3 days by cycle 12. In contrast, the number of bleeding/spotting days per cycle remained relatively stable with the comparator E_2/V/norethisterone (between 4.9 ± 1.2 days to 5.2 ± 2.5 days).

**Hemostasis, lipid, and carbohydrate metabolism, and other parameters**

Generally, E_2 and E_2/V at equimolar doses are expected to have similar influences on hemostasis, lipids, and carbohydrate metabolism parameters, but less than those observed with EE. However, surrogate indices of hemostasis, lipids, and carbohydrate metabolism, or any other surrogate marker, cannot be translated into meaningful clinical outcomes, and the risk of cardiovascular events in users of oral contraceptives containing E_2 or E_2/V needs to be established in large-scale, post-marketing, prospective, Phase IV cohort studies. Indeed, two large international active surveillance studies, i.e., the International Active Surveillance Study-Safety of Contraceptives: Role of Estrogens (INAS SCORE) and the Choice of estrogen and long-term investigation of nomegestrol acetate–International Active Surveillance Study (INAS-CELINA) are currently underway to investigate the occurrence of adverse cardiovascular events within a 5-year period in COC users (including E_2/V/DNG and E_2/NOMAC, respectively). To the best of our knowledge, no such active surveillance studies have been undertaken or are planned for the E_2/V/CPA oral contraceptive.

Large prospective cohort studies have the best ability to assess uncommon adverse outcomes like venous thrombosis, because their design allows for collection of baseline information on important confounders, such as obesity and age. Recently published database studies have suggested that oral contraceptives containing CPA, desogestrel, or DRSP in combination with EE are associated with an elevated risk of venous thrombosis compared with LNG pills. However, a large prospective Phase IV study similar in design to the INAS-CELINA and INAS-SRCO studies did not demonstrate an increase in risk for deep vein thrombosis with these progestins.

E_2/V/CPA appears to have minimal influence on hemostatic parameters over three cycles. Both total cholesterol and high-density lipoprotein cholesterol were reported to decrease (by 9% and 5%, respectively) to baseline over 13 cycles in one study, but no significant changes were reported in total cholesterol or high-density lipoprotein cholesterol in the pivotal Finnish study. In the latter study, serum triglyceride levels increased >20% over 13 cycles.

The impact of E_2/V/DNG and E_2/NOMAC on hemostatic and lipid parameters relative to EE-based oral contraceptive comparators is summarized in Table 3; both formulations appear to have less influence on these parameters than the EE-based formulations. However, it is important to keep in mind that none of these potential surrogate markers of venous thromboembolism risk have ever been validated. Estrogens influence both thrombotic and fibrinolytic pathways, and the net effect on hemostasis is difficult to predict. High-density lipoprotein cholesterol and low-density lipoprotein cholesterol were reported to increase and decrease, respectively, with both E_2/V/DNG and E_2/NOMAC during up to seven cycles of treatment. The overall changes relative to baseline in these parameters were <10% for E_2/V/DNG.
and <2% for E₂/NOMAC.\textsuperscript{61,63} Total cholesterol increased with both E₂/V/DNG and E₂/NOMAC, but by ≤5% relative to baseline. Mean increases in endogenous thrombin potential-based activated protein C sensitivity ratios from baseline to cycle 3 were significantly lower with E₂/V/DNG (0.09 versus 0.56, \(P < 0.001\)) and E₂/NOMAC (0.20 versus 0.46, \(P < 0.01\)) than with EE/LNG (EE 30 µg/LNG 150 µg; Microgynon\textsuperscript{8}, Bayer Healthcare Pharmaceuticals) or EE/LNG (EE 20 µg/LNG 100 µg; Miranova) comparators, respectively.\textsuperscript{62,64} Additionally, insulin and glucose remained relatively unaffected by E₂/V/DNG and E₂/NOMAC during oral glucose tolerance tests.\textsuperscript{61,63}

The available data across four separate randomized trials seem to suggest that increases in sex hormone binding globulin (SHBG) with both E₂/V/DNG and E₂/NOMAC are more or less in the same range;\textsuperscript{61-64} however, increases in SHBG with the EE-based comparators in these studies were more inconsistent. In general, it would be expected that EE increases SHBG levels to a greater extent than E\textsubscript{2}.\textsuperscript{10} In COCs, the extent of an EE-induced (or E\textsubscript{2}-induced) SHBG increase may be attenuated by inclusion of a progestin with androgenic activity.\textsuperscript{10} Of note, the progestins used in the three approved E\textsubscript{2}-containing oral contraceptives do not have any androgenic activity,\textsuperscript{66} and as such are not expected to attenuate the limited estrogen-induced SHBG increase with the E\textsubscript{2}-containing oral contraceptives.

### Safety and tolerability

The relevance of nonspecific adverse events with oral contraceptives reported outside randomized placebo-controlled trials has been questioned because the limited level 1 evidence suggests that these nonspecific events may not occur significantly more often with oral contraceptives and that they may simply reflect their background prevalence in the population.\textsuperscript{67} With this in mind, the adverse events reported in E₂/V/CPA, E₂/V/DNG, or E₂/NOMAC studies with ≥250 patients receiving one of the three oral contraceptives that were judged to be treatment-related were in general typical of those reported with EE-based oral contraceptives.\textsuperscript{27-30,35,36,39} Results from the randomized comparator studies of E₂/V/DNG and E₂/NOMAC show a similar distribution of adverse events. In the only placebo-controlled studies, where E₂/V/DNG was used to manage heavy menstrual bleeding in North America and in Europe/Australia, breast pain and irregular bleeding were more common in women receiving E₂/V/DNG, while headache was more commonly reported with placebo (Table 4).\textsuperscript{37,38} For E₂/V/CPA (n=288) in the Finnish study, adverse events reported after 6 months included breast tenderness (9.4%), edema (8.5%),

### Table 3 Changes from baseline in hemostatic, lipid, and carbohydrate metabolism indices

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Junge et al\textsuperscript{61-63} (7 cycles)</th>
<th>Klipping et al\textsuperscript{62-64} (3 cycles)</th>
<th>Agren et al\textsuperscript{61} (6 cycles)</th>
<th>Gaussem et al\textsuperscript{64} (3 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostasis</td>
<td>Prothrombin fragment I + 2</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>D-dimer</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Factor VII activity</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Factor VIII activity</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Protein C activity</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>APC sensitivity</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>APC sensitivity ratio</td>
<td>++</td>
<td>++</td>
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<td>++</td>
</tr>
<tr>
<td>PAI-1 antigen</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>PAI-1 activity</td>
<td>++</td>
<td>++</td>
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<td>++</td>
</tr>
<tr>
<td>Lipid</td>
<td>Total cholesterol</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Notes: *intraindividual change; \#APC-r, Rosing’s activated protein C resistance normalized ratio; ¥factor V Ila or VIIc; m, no change (<10% change); +, ≥10% increase; –, ≥10% decrease; ++, ≥20% increase; —, ≥20% decrease; +++, ≥50% increase; ——, ≥50% decrease.

Abbreviations: APC, activated protein C; aPTT, activated partial thromboplastin time; NR, not reported; PAI-1, plasminogen activator inhibitor type 1; E, estradiol valerate; DNG, dienogest; NOMAC, nomegestrol acetate; EE, ethinylestradiol; LNG, levonorgestrel.
headache (6.6%), and depression (4.2%), decreasing to 7.7%, 5.5%, 4.4%, and 2.7%, respectively, by 12 months.  

Discontinuations due to adverse events during up to 20 cycles of treatment with E₂/V/DNG were reported to be up to 14%, with discontinuations due to bleeding problems ranging up to 5% over the first year of use. Similar discontinuation rates were documented for E₂/NOMAC, with up to 18% discontinuing due to adverse events over one year and up to 5% due to bleeding problems. For E₂/V/CPA, 16% of women discontinued due to adverse events typically related to hormone use (“edema, breast tenderness, headache, weight change, and mood changes”) over one year and 9% due to menstrual problems.  

The effects of E₂/NOMAC (n=56) on bone mineral density were compared with those of EE/LNG (EE 30 µg/LNG 150 µg; Microgynon, n=54) in women aged 20–35 years over 2 years in a randomized controlled trial. No clinically relevant effects on bone mineral density were observed during this time with E₂/NOMAC or with the EE/LNG oral contraceptive comparator. In the absence of data on the effects of E₂/V/DNG or E₂/V/CPA on bone mineral density, it might be postulated that because similar doses of E₂ are used relative to E₂/NOMAC, the effects on bone density would be similar.

**Other indications and benefits**

The choice between the E₂/V/CPA, E₂/V/DNG, and E₂/NOMAC formulations is currently restricted by regional availability; so far, only Finnish women have access to all three E₂-based formulations. Elsewhere, women have either the option of E₂/V/DNG or E₂/NOMAC (eg, Europe) or E₂/V/DNG (eg, the US) alone as the only available E₂-based formulations.

Several studies have been conducted with E₂/V/DNG to assess additional health benefits. No studies assessing additional health benefits associated with the other two E₂-based formulations have been published. E₂/V/DNG has been shown to profoundly reduce menstrual blood loss in women with objectively confirmed heavy menstrual bleeding without organic pathology in two randomized, placebo-controlled, double-blind studies, one conducted in the US and Canada and the other in Europe and Australia. These studies led to the approval of E₂/V/DNG for the treatment of heavy menstrual bleeding, a unique indication for this oral contraceptive formulation. The effect is rapid, with the greatest reduction in menstrual blood loss achieved by the first withdrawal bleed after treatment initiation and maintained with no loss of effect with continued treatment. Moreover, the observed reduction in menstrual blood loss with E₂/V/DNG (median 88% reduction after seven cycles of treatment) appears to approach that achieved with the LNG-releasing intrauterine system. Overall, 64% of women with excessive menstrual blood loss receiving E₂/V/DNG met the study criteria for treatment success (defined as menstrual blood loss <80 mL and a ≥50% reduction from baseline) compared with only 12% with placebo. Secondary endpoints in the two randomized studies included the impact of treatment with E₂/V/DNG on heavy menstrual bleeding-related impairment of work productivity (presenteeism) and activities of daily living. These studies showed that E₂/V/DNG had a consistent positive impact on work productivity and activities of daily living in women with heavy menstrual bleeding, and that these improvements could be translated into a reduction in the monetary burden associated with this condition.

Two more randomized, double-blind, active-controlled studies, one conducted in North America and the other in Western Europe, Thailand, Australia, and Mexico, were undertaken to assess the effect of E₂/V/DNG on hormone withdrawal-associated symptoms (principally headache or pelvic pain) in women (n=414, across both studies) who experienced these symptoms with other COCs taken in the traditional 21/7 regimen. Switching to E₂/V/DNG was shown to reduce the severity of these symptoms to a greater extent than switching to comparator triphasic EE/norgestemate (Ortho Tri-Cyclen® Lo, Ortho-McNeil-Janssen Pharmaceuticals Inc, Raritan, NJ, USA; n=204) or a monophasic EE/LNG (Microgynon; n=218).
A multicenter, double-blind, randomized study was conducted in Europe and Asia/Pacific to determine the effect of \(E_{2}\) V/DNG (n=92) on oral contraceptive-related sexual dysfunction using EE/LNG (Microgynon, n=99) as a comparator. Among women reporting baseline sexual dysfunction while using an oral contraceptive, switching to either \(E_{2}\)V/DNG or EE/LNG resulted in similar improvements in desire and arousal, a reduction in associated distress, and decreased vaginal symptoms. A study from Italy also suggested some benefit on sexual function with \(E_{2}\) V/DNG (n=57), but the open-label noncomparative nature of this study provides no reference for the observed changes, making it impossible to draw conclusions from these results.

Conclusion

In summary, \(E_{2}\) V/DNG, \(E_{2}\)NOMAC, and \(E_{2}\) V/CPA are all effective oral contraceptives. The contraceptive effectiveness of \(E_{2}\) V/CPA was, however, assessed in women with a mean age of 39 years, and as such may not be directly generalizable to younger more fertile women. Although direct comparability between the studies is difficult, the available data suggest that \(E_{2}\) V/DNG and \(E_{2}\)NOMAC may have better bleeding profiles than \(E_{2}\) V/CPA. Currently, \(E_{2}\) V/DNG is the only oral contraceptive approved for the treatment of heavy menstrual bleeding. Emerging data suggest that \(E_{2}\) V/DNG may be a good alternative to other COCs taken in the conventional 21/7 regimen for women susceptible to hormone-associated withdrawal symptoms, but there is insufficient evidence to conclude whether the effect is due to the components of the formulation or the dosing regimen. Both \(E_{2}\) V/DNG and \(E_{2}\)NOMAC generally have minimal influence on hemostatic, lipid, and carbohydrate metabolism parameters, or induce less change in these parameters than EE-based oral contraceptives. Whether these differences can translate into meaningful clinically important outcomes (specifically cardiovascular events) needs to be established in future large-scale prospective studies.

Disclosure

Jeffrey T Jensen has received payments for consulting and giving talks for Bayer HealthCare Pharmaceuticals, a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by Oregon Health and Science University. Jeffrey T Jensen is also a consultant and speaker for Merck Sharp & Dohme, a consultant for HRA Pharma and Agile Pharmaceuticals, and has received research funding from Abbott Pharmaceuticals, Bayer HealthCare, Warner Chilcott, the Population Council, and the National Institutes of Health. Johannes Bitzer has participated in advisory boards for Bayer HealthCare Pharmaceuticals, Merck Sharp & Dohme, Lilly, Solvay Pharma, and Boehringer Ingelheim, and has lectured at meetings supported by Bayer HealthCare Pharmaceuticals, Merck Sharp & Dohme, Lilly, Solvay Pharma, and Boehringer Ingelheim. Marco Serrani is an employee of Bayer HealthCare Pharmaceuticals, the manufacturer of \(E_{2}\) V/DNG. Richard Glover and Latoya M Mitchell of inScience Communications, Springer Healthcare, provided writing assistance during development of this manuscript. This assistance was funded by Bayer HealthCare Pharmaceuticals.

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