EXPERT OPINION

Hormonal contraception, thrombosis and age

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Introduction: This paper reviews the risk of thrombosis with use of different types of hormonal contraception in women of different ages.
Areas covered: Combined hormonal contraceptives with desogestrel, gestodene, drospirenone or cyproterone acetate (high-risk products) confer a sixfold increased risk of venous thromboembolism as compared with nonusers, and about twice the risk as compared with users of products with norethisterone, levonorgestrel or norgestimate (low-risk products). Transdermal patches and vaginal ring belong to high-risk products. The risk of thrombotic stroke and myocardial infarction is increased 50 – 100% with use of combined products, with little difference in risk between different progestins. Progestin-only products do not confer any increased risk of venous or arterial thrombosis, except for progestin depot, which may double the risk of venous thrombosis.
Expert opinion: First choice in women below 35 years should be a combined low-risk pill, that is, with a second-generation progestin, with the lowest compliable dose of estrogen. Young women with risk factors of thrombosis such as age above 35 years, genetic predispositions, adiposity, polycystic ovary syndrome, diabetes, smoking, hypertension or migraine with aura should not use high-risk products, but should primarily consider progestin-only products, and be careful to use low-risk combined products.

Keywords: age, hormonal contraception, oral contraceptives, thrombosis, venous thrombosis

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1. Introduction

Hormonal contraception includes oral contraceptives, contraceptive patches, implants, vaginal ring, levonorgestrel intrauterine system and intramuscular depot. The different routes of administration may be further subdivided into combined hormonal contraception (CHC) with both estrogen and progestin and progestin-only products. The combined products often exist with different doses of hormones, and the time they have been used appears to modify their influence on the risk of venous thrombosis.

Considering thrombotic diseases, these include on the venous side deep venous thrombosis and pulmonary embolism, together venous thromboembolism (VTE). On the arterial side, the important end points are myocardial infarction and thrombotic stroke. Female sex hormones (natural or artificial) have a differential influence on these clinical end points.

Recently, carefully conducted studies on the influence of hormonal contraception on the risks of VTE, myocardial infarction and stroke clarify the risks of also newer products. This review discusses these recently established results, and how age is influencing the risk of different types of thrombosis.

2. Hormonal contraception

To achieve an overview over the many different types of hormonal contraceptive products, it is useful to categorize them according to three axes: i) in combined

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Article highlights.

- New epidemiological studies have provided valid and precise estimates about the risk of thrombotic complications with use of modern hormonal contraception.
- For combined products, the progestin type is the primary determinant for the risk of venous thrombosis. Low-risk products with norethisterone, levonorgestrel or norgestimate confer about half the risk of venous thrombosis as combined high-risk pills with desogestrel, gestodene, drospirenone or cyproterone acetate.
- Combined products with 30 – 40 mcg estrogen confer about 20% higher risk than products with 20 mcg estrogen, with the same dose and type of progestin.
- Progestin-only pills, levonorgestrel intrauterine system, and implants don't confer any increased risk of venous or of arterial thrombosis.
- Transdermal patches and vaginal ring belong to high-risk products.

This box summarizes key points contained in the article.

estrogen–progestin versus progestin-only products; ii) the combined products in high (50 µg ethinylestradiol [EE]), middle (30 – 40 µg EE) and low-dose (15 – 20 µg EE), and in those containing natural estrogen (E2); and iii) according to the progestin type. In **Figure 1**, the available combinations according to these three axes are indicated. Not all existing combinations are available in all countries.

3. Venous thromboembolism in young women

The incidence rate of VTE in non-pregnant women who are not using hormonal contraception increases with increasing age from 1 per 10,000 women-years in 20-year-old women, 3 per 10,000 women-years in women of 30 years and 5 per 10,000 in women of 40 years [1].

Well-established risk factors of VTE include previous venous thrombosis, hormonal contraception, family disposition, coagulation disorders such as APC-resistance or factor V Leiden mutation, immobilization, pregnancy and cancer diseases.

About two-thirds of VTEs are deep venous thromboses, and one-third are pulmonary embolisms (with or without detected deep venous thrombosis) [1].

4. Venous thromboembolism and hormonal contraception

The influence of hormonal contraception on the risk of VTE has been reported and debated since the 1960s. The results of studies assessing the risk with use of specific product types and specifying the applied reference group are listed in **Table 1** [1-22].

In all these 22 studies, an increased risk of VTE was found with use of CHC. The relative risk has only decreased slightly over recent decades, despite the reduction in the dose of estrogen used in the pills (**Table 1**). The relative risk of VTE with use of CHC with levonorgestrel has been found to be about three in newer studies when compared with nonusers.

Of 14 studies specifically assessing the risk in users of CHC with desogestrel or gestodene, 13 found a higher risk with use of these products when compared to the use of CHC with levonorgestrel. The difference was statistically significant in 9 of the 13 studies. Of five studies not demonstrating a significant difference, two were re-analyses [7,10] of primary studies demonstrating a significant difference [6,8], while one study by Dinger *et al.* did not find any difference [13]. The two re-analyses do not appear more statistically robust than the analyses in the primary studies. In the largest recent study with validated end points, the rate ratio between CHC with desogestrel versus levonorgestrel was 2.2 (1.7 – 2.8) [1].

Similarly, of 10 studies specifically assessing the risk of VTE in users of CHC with drospirenone versus users of CHC with levonorgestrel, 6 found significant differences, 3 (all by Dinger *et al.*) showed no difference [13,16,22]. In all seven studies demonstrating a difference, the rate ratio of VTE between users of CHC with drospirenone vs levonorgestrel was 1.5 – 2.8, and the relative risk was 6.3 as compared with nonusers in both the large Dutch [14] and Danish [1] study.

The studies demonstrating risk differences between CHC with different progestins are generally methodologically more transparent and more robust than those demonstrating no difference, especially concerning exclusion of women with predispositions for VTE [23].

All studies except one agree that the risk of VTE in users of CHC with desogestrel or gestodene is the same as in users of CHC with drospirenone [1,13-15,22]. Gronich *et al.* found a 43% (1.2 – 1.8) higher risk of VTE in users of CHC with drospirenone compared with users of CHC with desogestrel, and a rate ratio of 1.7 (1.0 – 2.7) when compared to CHC with levonorgestrel [20].

The reason for the differential influence on the risk of VTE from different CHC seems to be explained by a direct influence on the coagulation process, and is also indicated by a differential influence on sex hormone binding globulin, a surrogate marker of the relative risk of VTE [24-26].

Figure 2 summarizes the results for different specific product groups, stratified according to estrogen dose, progestin type and route of administration. The figures are derived from the studies in **Table 1**, and weighted according to size. The relative risk during the first year is about 50% higher than after the first year. After few years of use, the relative risk is stable and increased with the figures indicated.

4.1 Women at risk of venous thromboembolism

About 10% of women (and men) are genetically predisposed for VTE. The most frequent condition is resistance to the

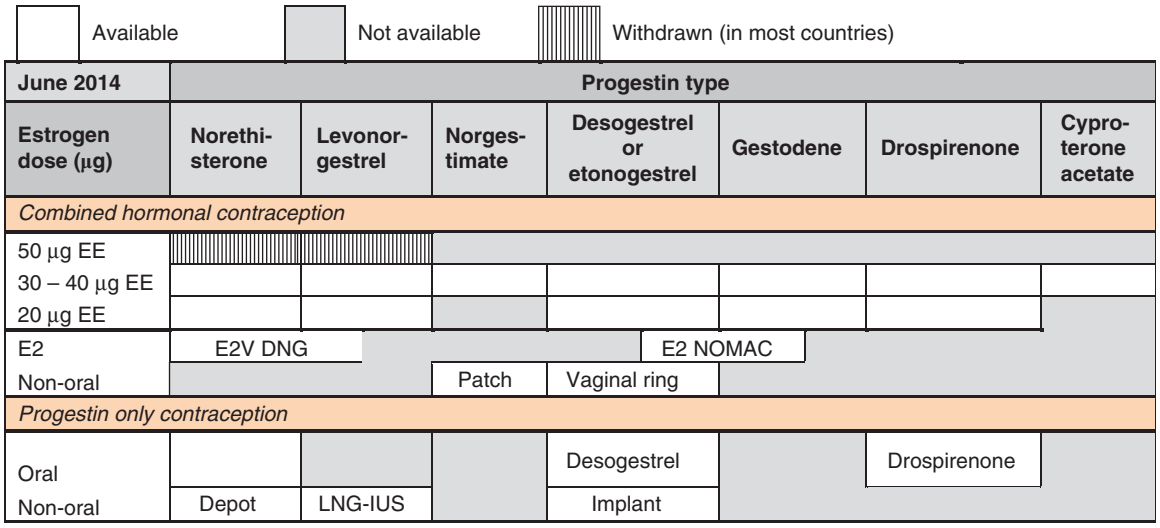

Figure 1. Available combined estrogen–progestin and progestin-only hormonal contraception according to estrogen dose and progestin types.

CHC: Combined hormonal contraceptives; DNG: Dienogest; E2: Estradiol (natural estrogen); E2V: Estradiolvalerate; EE: Ethinylestradiol (synthetic estrogen); LNG-IUS: Levonorgestrel intrauterine system; NOMAC: Nomegestrol acetate.

Table 1. Relative risk of venous thromboembolism in current users of different combined hormonal contraceptives as compared with nonusers unless otherwise specified.

Study First author (ref.)	Data sampling (Period)	Venous thrombosis (Number)	CHCs with levonorgestrel RR (95% CI)	CHCs with desogestrel/gestodene RR (95% CI)	CHCs with drospirenone RR (95% CI)
Blomenkamp [2]	1988 – 1992	126	3.8 (1.7 – 8.4)	8.7 (3.9 – 19.3)	-
WHO [3,4]	1989 – 1993	433	3.6 (2.5 – 5.1)	7.4 (4.2 – 12.9)	-
Jick [5]	1991 – 1994	80	1 (reference)	1.8 (1.0 – 3.2)	-
Spitzer [6]	1991 – 1995	471	3.7 (2.2 – 6.2)	6.7 (3.4 – 13.0)	-
Lewis [7]	1993 – 1995	502	2.9 (1.9 – 4.2)	2.3 (1.5 – 3.5)	-
Farmer [8]	1991 – 1995	85	3.1‡ (2.1 – 4.5)	5.0‡ (3.7 – 6.5)	-
Todd [9]	1992 – 1997	99	1 (reference)	1.4 (0.7 – 2.8)	-
Bloemenkamp [10]	1994 – 1998	185	3.7 (1.9 – 7.2)	5.6 (not given)	-
Parkin [11]	1990 – 1998	26	5.1 (1.2 – 21.4)	14.9 (3.5 – 64.3)	-
Lidegaard [12]	1994 – 1998	987	2.9 (2.2 – 3.8)	4.0 (3.2 – 4.9)	-
Dinger [13]	2000 – 2004	118	1 (reference)	1.3 (NA)	1.0 (0.6 – 1.8)
Vlieg [14]	1999 – 2004	1524	3.6 (2.9 – 4.6)	7.3 (5.3 – 10.0)/5.6 (3.7 – 8.4)	6.3 (2.9 – 13.7)
Lidegaard [15]	1995 – 2005	4213	2.0 (1.8 – 2.3)	3.6 (3.3 – 3.8)	4.0 (3.3 – 4.9)
Dinger [16]	2002 – 2008	680	1 (reference)	NA	1.0 (0.6 – 1.8)
Parkin [17]	2002 – 2009	61	1 (reference)	NA	2.7 (1.5 – 4.7)
Jick [18]	2002 – 2008	186	1 (reference)	NA	2.8 (2.1 – 3.8)
Lidegaard [1]	2001 – 2009	4246	2.2 (1.7 – 2.8)	4.2 (3.6 – 4.9)	4.5 (3.9 – 5.1)
Confirmed only	2001 – 2009	2707	2.9 (2.2 – 3.8)	6.8 (5.7 – 8.1)	6.3 (5.4 – 7.5)
FDA Kaiser [19]	2001 – 2007	625	1 (reference)	NA	1.5 (1.2 – 1.9)
Gronich [20]	2002 – 2008	518	1 (reference)	1.4 (0.9 – 2.1)	1.7 (1.0 – 2.7)
Lidegaard [21]	2001 – 2010	5287	3.2 (2.7 – 3.8)	6.5 (4.7 – 8.9)*	NA
Dinger [22]	2005 – 2010	162	1 (reference)	NA	0.8 (0.5 – 1.6)

*Vaginal ring with the third-generation progestin etonogestrel.

‡Absolute risk per 10,000 years.

CI: Confidence interval; NA: Not available; RR: Relative risk.

anti-clotting effect of activated protein C (APC resistance), which increases the risk of VTE about 6 times. This condition is caused by a mutation, the so-called factor V Leiden mutation.

Most often, the combination of risk factors confers a relative risk of VTE corresponding to a multiplication of the relative risk of each risk factor. Thus, if a low-risk CHC increases the risk of VTE 3 times, and this product is used by a woman

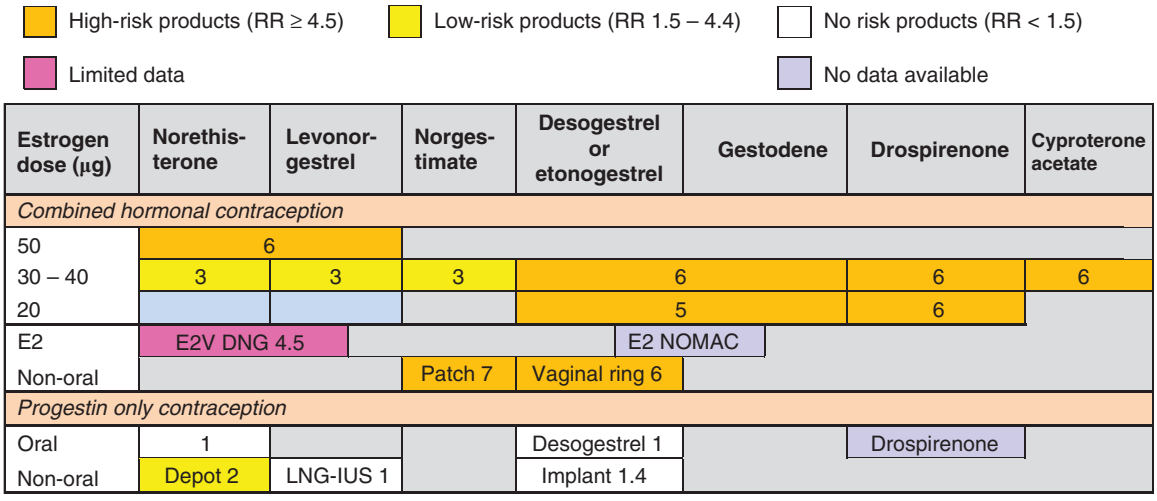

Figure 2. The relative risk of venous thromboembolism in current users of different types of hormonal contraception according to estrogen dose, progestin type and route of administration. Nonusers reference group.
DNG: Dienogest; E2: Estradiol (natural estrogen); E2V: Estradiolvalerate; LNG-IUS: Levonorgestrel intrauterine system; NOMAC: Nomegestrol acetate; RR: Relative risk.

with a genetic APC-resistance, such a woman will have a relative risk of VTE of 3 × 6 = 18, as compared with nonusers without such a genetic predisposition.

A non-pregnant woman at 20 years not using CHC has an incidence rate of VTE of 1 in 10,000 years. If she uses a low-risk CHC product, her absolute risk will be 3 per 10,000 years. If she at the same time has a hereditary APC resistance (mainly factor V Leiden mutation), her absolute risk will be 18 per 10,000 years, and if she uses the product for 10 years, the absolute risk will be not 180, but about 250 per 10,000 years, because the risk increases with each year she gets older. An absolute risk of a VTE of 2.5% will be a too high risk for many women. If she was 30 years instead, her absolute risk after 10 years use would be about 6%. Some studies have demonstrated synergy, which is more than a multiplicative risk when different risk factors are combined, which would bring the estimates even higher up.

Therefore, women with known risk factors of VTE are advised to be reluctant to use CHC. The *relative risk* of VTE with different dispositions is as follows: previous thrombosis: > 50 [27], genetic abnormalities such as factor V Leiden mutation (heterozygous): 6, deficiency of protein C: 10, of protein S: 10, of antithrombin: 25, and of prothrombin 20210A: 3 [28]. Pregnancy with delivery on average: 8, adiposity: 2 – 3 and immobilization 2 – 5 depending on how long time you are immobilized. Family disposition (first-degree relatives with VTE before their 50th year) doubles the risk of VTE. Women with such dispositions are generally recommended to use progestin-only contraception, which does not increase the risk of VTE except perhaps for medroxyprogesterone depots. A genetic screening should until further also be restricted to women with a family disposition.

5. Thrombotic stroke and myocardial infarction in young women

The overall incidence rate of a first thrombotic stroke and a first myocardial infarction in women of reproductive age is 3 and 1 per 10,000 years, respectively. Both arterial end points have a steeply increasing incidence rate with increasing age: Thrombotic stroke thus from 0.3 per 10,000 years in women 15 – 19 years old, to 6.4 per 10,000 years in women 45 – 49 years old, more than a 20-fold increased absolute risk with increasing age [29].

The incidence rate of myocardial infarction increases from 0.04 per 10,000 years in women 15 – 19 years old to 3.8 per 10,000 years in women 45 – 49 years old, a 100-fold exponential increase with increasing age [29].

Thus, in women below 35 years, VTE is more frequent than the arterial end points, whereas among women above 35 years, thrombotic stroke and myocardial infarction are together more frequent than the venous complications [1,29].

The mortality in young women with a first thrombotic stroke is about 1.5%, and after a first myocardial infarction about 10%, but the survivors have more often lasting repercussions after an arterial thrombosis than after a VTE [29].

Risk factors for arterial thrombosis include previous arterial thrombosis, smoking, hypertension, diabetes, hyperlipidemia, heart arrhythmia, CHC and short education [29].

For thrombotic stroke each of the risk factors roughly doubles the risk, while for myocardial infarction smoking implies a relative risk of four, even more with heavy smoking and diabetes a relative risk of five [29].

In case of exposure for several risk factors, one has to multiply the relative risk of each risk factor to achieve the combined effect.

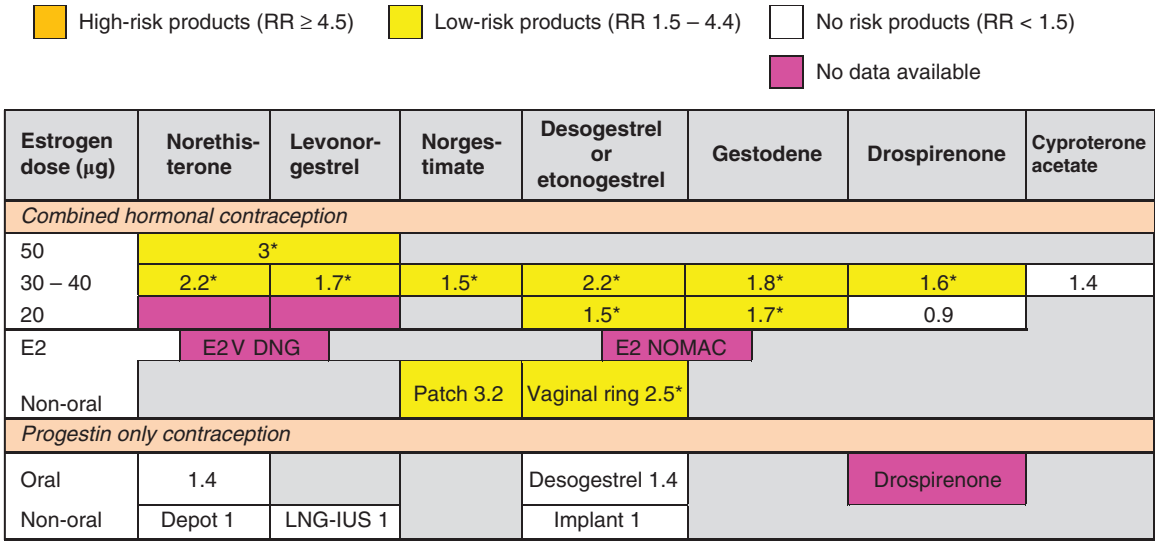

Figure 3. The relative risk of thrombotic stroke in current users of different types of hormonal contraception according to estrogen dose, progestin type and route of administration. Nonusers reference group.

*Indicates a significantly increased risk.

DNG: Dienogest; E2: Estradiol (natural estrogen); E2V: Estradiolvalerate; NOMAC: Nomegestrol acetate; RR: Relative risk.

6. Hormonal contraception, thrombotic stroke and myocardial infarction

Figure 3 has summarized the relative risk of thrombotic stroke in users of different types of hormonal contraception [20,29-33].

It appears that CHC in general confers less relative risk of the arterial complications than of VTE.

The newer studies have found less influence on thrombotic stroke than the earlier studies, perhaps due to a more effective exclusion of predisposed users by time. While middle dose CHC with desogestrel or gestodene may double the risk, the other combinations and all the low-dose combinations (20 μg estrogen) increase the risk about 50%, with no consistent difference according to the progestin type.

For myocardial infarction similar results were demonstrated, with relative risks among current users of CHC of between 1.5 and 2.0 for low- and middle dose products, and again with no consistent difference according to progestin type [34-42].

None of the included progestin-only products conferred a significantly increased risk of thrombotic stroke or of myocardial infarction.

In contrast to the risk of VTE, the relative risk of arterial complications with use of CHC does not decrease by time.

6.1 Women at an increased risk of arterial thrombosis

Age is the most important risk factor of arterial thrombosis. In young women, the baseline frequency of thrombotic stroke and myocardial infarction is so low, that a 1.5 – 2-fold increased risk is not a major concern. In women over 35 years, on the other hand, no other risk factors for arterial thrombosis should be present. Smoking in particular confers a significant contribution to myocardial infarctions in women of reproductive age. Therefore smokers, especially heavy smokers, should not use CHC after 35 years of age. Women with diabetic vascular complications should also avoid CHC.

In young women below 35 years, several risk factors at the same time may also contraindicate use of CHC.

For women at an increased risk of arterial thrombosis, progestin-only contraception may be a good alternative, because these products have not been found to increase the risk of either thrombotic stroke or myocardial infarction [29].

Previous thrombosis of any kind contraindicates CHC and progestin depot, but not other progestin-only products.

7. Expert opinion

Besides its role as an effective contraceptive, CHC offers several important noncontraceptive benefits, such as regular menstruation, diminished dysmenorrhea, less menstrual bleeding, less acne, and a decreased risk of ovarian, endometrial and colorectal cancer. The thrombotic complications are the most important risk aspects. A large majority of women with VTE will survive their thrombosis, but a timely diagnosis and treatment are crucial for the prognosis. Therefore, efforts should be made to ensure that women with contraindications against CHC are not prescribed such products, and that those who use these products are informed about the symptoms of these complications, especially VTE.

Minimizing the thrombotic risk should be primary in deciding which product to use. According to this survey, first choice hormonal contraception in healthy young women could be a low-risk combined pill with norethisterone,

levonorgestrel or norgestimate. Second choice a progestin-only product such as levonorgestrel intrauterine system or progestin only pill, and third choice a high-risk combined product.

For women with risk factors of venous or arterial thrombosis and women past 35 years, first choice should be a progestin-only product. Second choice a low-risk combined pill with norethisterone, levonorgestrel or norgestimate. High-risk products should generally not be taken, although we have to accept that some women are willing to run a risk after appropriate information.

Previously, women with risk factors of thrombosis were told not to use any type of hormonal contraception. With newer large-scale studies, we have now sufficient scientific information to conclude, that progestin-only contraception, such as levonorgestrel intrauterine system, progestin-only pills and implants do not significantly increase the risk of either venous or arterial thrombosis, and that these products therefore are not contraindicated for such women. Levonorgestrel intrauterine system may even protect against VTE [21].

To ensure appropriately informed contraceptive choices among women, several bodies have to act together.

First, the scientists have to reach agreement about the scientific evidence. Except for few industry-associated experts, there is now consensus among independent researchers, that the risk of VTE first of all is influenced by the progestin type in combined hormonal contraceptives.

Second, health authorities (FDA in the USA and EMA in Europe) must address the new scientific evidence and make appropriate label information for the different contraceptive products. This is now accomplished, though not until 8 years after launch of the new products in the case of drospirenone.

Third, the marketing holders should accept rather than deny or question the results of well-conducted new studies. As late as at the international congress of contraception in Lisbon, May 2014, the main talk on this issue by Johannes Bitzer still questioned the scientific evidence of a differential risk of venous thrombosis with CHC with different progestins.

Fourth, clinicians should implement the scientific evidence in their clinical guidelines. As long as international congresses primarily deny or downplay new scientific evidence, appropriate clinical guidelines are delayed, often for years. Interpretation of the scientific evidence often benefits by assistance from epidemiologically skilled clinicians.

Fifth, the clinicians should follow the new clinical guidelines in the counseling of their clients.

And sixth, the media should bring balanced information rather than dramatized documentaries with young women with venous thromboses, which may cause pill scares without imparting knowledge among the users.

The collaboration between these six different bodies leaves much to be desired. For example, open scientific discussions where also people having demonstrated inconvenient results are invited to reply to critique raised on their studies.

Some countries have over the last decade established regional or national prescription registries. Together with regional or national databases of discharge diagnoses, it will be possible to reduce the time for post-marketing studies, with faster and more reliable risk estimates than previously presented. Thereby, we will be able to provide risk assessment of new medical products already few years after their introduction. The experiences from recent years recommend such assessments to be completed without any influence from the marketing holder. Likewise, clinical guidelines should be elaborated by independent boards of clinical experts.

Declaration of interest

The author has been an expert witness in two legal cases on hormonal contraception and venous thrombosis, and has received honoraria for speeches on pharmacoepidemiological issues from Eisai, Effik and Chemo.

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