Summary, discussion and future perspectives
Summary

Chapter 1 presents the history, mechanism of action, and efficacy of combined oral contraceptives (COCs) and the association of its use to the rare but serious adverse event of venous thromboembolism (VTE). As VTE is seen as a multicausal disease, also the contribution of other risk factors to the risk of VTE in COC-users, including thrombophilia and family history, is discussed. Further, a comparison is made with the risk of VTE in women during pregnancy, a condition, which is hormonally comparable. This chapter ends with the outline of this thesis and the rationale for initiating the different studies that are part of this thesis.

Hereditary thrombophilia and the risk of venous thromboembolism during combined hormonal contraceptive use

Severe hereditary thrombophilia (protein S-, protein C-, or antithrombin deficiency)

Information on the risk of VTE in COC-users who have severe thrombophilic defects, i.e. protein S-, protein C- or prothrombin deficiency, is very limited, whereas this risk in women in combination with other thrombophilic defects is hardly considered in any study. In Chapter 2 a retrospective cohort study was described, in which we assessed the effects of COC-use on the absolute risk of VTE in protein S, protein C, or antithrombin-deficient women and the contribution of other known thrombophilic defects. From a large family cohort of protein S-, protein C-, and antithrombin-deficient families, we enrolled female relatives of fertile age and male relatives in the same group who were used as a reference group. In total, 222 women were analyzed, of whom 101 (45%) were deficient. Fifty-six deficient and 79 non-deficient women had ever used COCs.

Absolute risk of VTE in protein S–, protein C–, and antithrombin-deficient women was high in comparison to non-deficient female relatives, as shown by the incidence of VTE of 1.64 versus 0.18 per 100 person years in deficient versus non-deficient women and the adjusted RR was 11.9 (95% confidence interval (CI), 3.9-36.2). COC-use hardly contributed to the overall risk of VTE during fertile lifetime: cumulative event rates at from the age of 15 up to 50 years were similar in women, who ever- or never used COCs, and in men. However, event-free survival
curves showed VTE to occur earlier in deficient ever-users and, although less pronounced, in deficient never-users than in deficient men. We hypothesized that these differences between women and men are related to COC-use in deficient ever-users and pregnancy in deficient never-users. Therefore, both COC-use and pregnancy resulted in the occurrence of VTE in deficient women at a younger age, but did not increase the overall risk of VTE during fertile lifetime.

The absolute risk of VTE in deficient women during COC-use was almost 10-fold higher than in non-deficient COC-users, as demonstrated by an incidence rate of 4.62 versus 0.48 per 100 pill-years of use. This risk is almost 100-fold higher than the most recently published absolute risk noted in the general population of COC-users, in whom the incidence rate according to the latest evidence varies between 0.05-0.09 per 100 pill-years of use.\(^1\)\(^3\)

The 10-fold higher risk observed in non-deficient COC-users in this family cohort is explained by the presence of other thrombophilic defects, such as presence of factor V Leiden or prothrombin 20210A mutation or an increased factor VIII: the incidence rate during actual COC-use increased by concomitant thrombophilic defects, from 3.49 to 12.00 per 100 pill-years in deficient women and from 0 to 3.13 per 100 pill-years in non-deficient women. Based on these results, it is concluded that women with hereditary deficiencies of protein S, protein C, or antithrombin are at high risk of VTE during use of COCs, particularly when other thrombophilic defects are present. Therefore, we recommend that the use of COCs in these women is strongly discouraged.

**Mild hereditary thrombophilia (factor V Leiden or prothrombin 20210A mutation)**

Current contraception guidelines discourage COC-use in women with hereditary thrombophilic defects.\(^4\) However, qualifying all hereditary thrombophilic defects as similarly strong risk factors might be questioned. Several studies indicated the risk of VTE associated with a factor V Leiden and prothrombin 20210A mutation as considerably lower than a deficiency of protein C, protein S, or antithrombin.\(^5\)\(^6\) In view of these differences, withholding COCs in women with these mild hereditary thrombophilic defects might be less favorable, as pregnancy and especially the postpartum period is a stronger risk factor for VTE than is COC-use. Therefore, when discouraging COC use, an increased risk of unintended pregnancy must be taken into account, as alternative contraception may be less reliable.
Hence, to adequately balance the risk and benefits of COCs, reliable estimates of the VTE risk associated with both COC-use and pregnancy are needed for women with mild thrombophilic disorders. In Chapter 3 a retrospective family cohort was presented, in which the VTE risk during COC-use and pregnancy (including postpartum) was assessed in 798 female relatives with or without a heterozygous, double heterozygous, or homozygous factor V Leiden or prothrombin G20210A mutation.

Overall, absolute VTE risk in women with no, single, or combined defect was 0.13 (95% CI: 0.08-0.21), 0.35 (95% CI: 0.22-0.53), and 0.94 (95% CI: 0.47-1.67) per 100 person-years, while these were 0.19 (95% CI: 0.07-0.41), 0.49 (95% CI: 0.18-1.07), and 0.86 (95% CI: 0.10-3.11) during COC-use, and 0.73 (95% CI: 0.30-1.51), 1.97 (95% CI: 0.94-3.63), and 7.65 (95% CI: 3.08-15.76) during pregnancy. COC-use and pregnancy were independent risk factors for VTE, with the highest risk during the postpartum period, as demonstrated by adjusted Hazard Ratios (HR) of 16.0 (95% CI: 8.0-32.2) versus HR of 2.2 (95% CI: 1.1-4.0) during COC use.

Obtained absolute risks were put into perspective in a modelling exercise, in which both the risks of alternative contraceptive-related VTE and the risk of pregnancy-related VTE (resulting from contraceptive failure) were considered. Summarizing these extrapolations, both the levonorgestrel-containing (Mirena) and copper-containing intrauterine device carry a lower overall risk of VTE and have adequate contraceptive efficacy; these contraceptives were therefore considered good alternatives to COCs. Condom use has the lowest contraceptive efficacy, with an up to 60-fold increased risk of unintended pregnancy, which makes this option the least favorable alternative.

Based on these results, rather than strictly contraindicating COC-use, we recommended that detailed counseling is given on all contraceptive options, including COCs, with addressing the associated risks of both VTE and unintended pregnancy, enabling these women to make an informed choice.

Meta-analysis of studies evaluating risk of COC-use in women with thrombophilia

In chapter 4, a systematic review and meta-analysis was presented which took a clinical case presentation “A 29-year-old woman previously tested heterozygote for
Factor V Leiden mutation (in a research setting 6 years ago) asks: what is my risk of thrombosis if I would start using combined oral contraceptives (COCs)?” as a starting point. A meta-analysis was performed to evaluate the risk of VTE in COC-users with thrombophilia. A distinction was made in ‘mild’ (factor V Leiden, prothrombin-G20210A mutation) and ‘severe’ thrombophilia (antithrombin-, protein C-, protein S-deficiency, double heterozygosity or homozygosity of factor V Leiden and prothrombin-G20210A mutation). Twelve case-control- and three cohort studies were identified.7-20

In COC-users, mild thrombophilia increased VTE risk six-fold (relative risk (RR) 5.89, 95% Confidence Interval [CI]: 4.21-8.23), while severe thrombophilia increased VTE risk seven-fold (RR 7.15, 95% CI: 2.93-17.45).

However, to adequately assess the impact of the observed relative increase in risk, information on the absolute risk is needed. One cohort study reported a VTE incidence of 0.49 and 2.0 per 100 pill-years of use in COC-users with mild thrombophilia,20 while two studies18,19 reported incidences of 4.3 and 4.6 per 100 pill-years in COC-users with severe thrombophilia, indicating a far higher risk (Table 3). The incidence of VTE in COC-users with double heterozygosity or homozygosity of factor V Leiden or prothrombin-G20210A mutation was 0.86 per 100 pill-years, suggesting that the absolute risk of this double defect is less serious than a antithrombin-, protein C-, or protein S deficiency.20 All absolute risks are estimated in family members of thrombophilic families, i.e. relatives of thrombophilic patients with VTE, and therefore also have a positive family history, which increases their baseline risk of VTE two- to three-fold.29-32 To put observed risks into perspective, in COC-users with mild thrombophilia and positive family history the absolute VTE risk is increased eight- to 33-fold, and 70-fold in COC-users with severe thrombophilia, when compared to the VTE risk of 0.06 per 100 person-years,1 estimated in the general population of COC-users.

However, it was noted that the risk of mild thrombophilia was largely estimated in a community setting, while risk of severe thrombophilia was exclusively evaluated in thrombophilic family cohorts. This is inherently due to the very low prevalence of severe thrombophilia. Further, absolute risks were all estimated in members of thrombophilic family cohort studies, risks will therefore be more pronounced because of the co-existing family history, than in the general population of COC-users tested positive.
In conclusion, the presence of mild and severe thrombophilia increases the risk of VTE in COC-users six- to seven-fold. However, absolute VTE risk estimates indicate the contribution of severe thrombophilia to the VTE risk in COC-users as considerably higher (4.3 and 4.6 per 100 pill-years) than the additional risk of mild thrombophilia (0.49 and 2.0 per 100 pill-years), but with the caveat that these risks were estimated in thrombophilic COC-users who also had a positive family history. As a co-existing family history increases VTE risk two- to threefold, estimated risks are more pronounced than in a general population of COC-users tested positive for thrombophilia.

In the weighing of above results, we took into account the GRADE quality of evidence grading, that sound epidemiological studies as included in this meta-analysis would be graded as low evidence, but when observed effects are large and there is no obvious bias explaining those effects, the evidence may be rated as moderate or even high, as further research is very unlikely to change our confidence in the estimate of effect (http://gradeworkingroup.org). From this standpoint we propose the strong recommendation is given that based on the high additive risk, to avoid COC-use in women with severe thrombophilia in all cases. The additive VTE risk of mild thrombophilia is modest and when no other risk factors are present, e.g. family history, we recommend that COC-use should not be denied in women who consider alternative adequate contraception not acceptable, as in this situation the increased risk of pregnancy-related VTE and increased risk of pregnancy outweigh the COC-associated risk.

**Family history and risk of venous thromboembolism during combined hormonal contraceptive use**

As demonstrated in the studies described above (Chapter 2, 3 and 4), women from thrombophilic families have an increased risk of VTE, which increases further during COC-use and pregnancy. It is unknown whether this additional risk differs between relatives of male and female patients with VTE, and also whether it matters if the female patient had a hormonally-related VTE (during COC-use or pregnancy). To explore this question, we performed a retrospective family cohort study, which was presented in Chapter 5. In this family cohort of 1005 first-degree female relatives of reproductive age, we compared VTE risk in relatives of female versus male patients, and between relatives of female patients with and without hormonally-related VTE.
In this cohort, VTE risk in relatives of female (0.32, 95%CI:0.23-0.43) versus male patients (0.39, 95%CI:0.28-0.53) was comparable, but young age (<45 years at time of 1st VTE) of the patient, and presence of thrombophilia, COC-use and pregnancy of the relative were factors which significantly increased risk of VTE. In the multivariable analysis, thrombophilia, COC-use and pregnancy of relative, but not patients’ age, remained independent risk factors.

Additionally, the heterogeneity analysis of risk estimates suggested that VTE risk in relatives of female versus male patients differs during pregnancy-postpartum (Hazard Ratio [HR], 11.6 [95%CI:5.9-22.7] versus 6.6 [95%CI:3.2-13.6]) and to a lesser extent during COC-use (HR, 3.6 [95%CI:1.9-6.7] versus 2.7 [95%CI:1.4-5.3]), although not statistically significant.

Taking hormonal exposure in the patient at the time of VTE into account, incidence of VTE was significantly higher, i.e. 0.43 (95%CI:0.31-0.59) per 100 person-years in relatives of patients with hormonally-related VTE, than in relatives of female patients without hormonally-related VTE (0.13 [95%CI:0.05-0.27], HR, 3.1 [95%CI:1.3-7.4], p=0.011).

When considering only relatives of female patients, the noted higher HRs of pregnancy and COC-use are mainly observed in relatives of patients with hormonally-related VTE. The risk estimates in relatives of female patients without hormonally-related VTE were substantially lower.

The observed heightened risks suggest that female relatives of patients with hormonally-related VTE are more susceptible to hormonal exposure.

Several studies have explored the impact of positive family history and it is considered an independent risk factor of VTE with reported odds ratios varying between 2.2 to 2.7.21-23 Of these, two studies have reported the VTE risk of a positive family history as higher in female relatives during fertile age than in male relatives of that age.24,25 To our knowledge, only one study has evaluated sex of patient as one of the potential indicators of VTE risk in their first-degree relatives.26 They reported highest VTE risk in relatives of patients with unprovoked VTE and in relatives of patients who had VTE at younger age (below 45 years), whereas the sex of patient was no significant risk indicator for VTE (OR: 0.96 [95% CI: 0.67-1.38]).
However, in this study those patients with estrogen-associated VTE’s were classified as having unprovoked VTE. It is well possible that the highest risk in relatives of young patients with VTE (age below 45 years) as found in this study, is partly explained by an increased risk in female relatives of patients with hormonally (estrogen)-related VTEs (who are inherently young), as observed in our study.

In our study, we also evaluated the influence of patient’s age at time of first VTE and observed an overall increased risk of VTE in female relatives of younger patients (first VTE below 45 years), but in multivariable analyses, influence of patient’s age was no longer an independent risk indicator. Although the authors of this study indicate that it is possible that inclusion of patients with estrogen-associated VTE among the patients with unprovoked VTE could have diluted the comparison of VTE risk between first-degree relatives of patients with unprovoked versus provoked VTE, they were unable to assess this directly. Thus, no previous studies with a similar objective are available for comparison.

In conclusion, this is the first analysis taking into account a positive family history, based on a hormonally-related VTE. Although further research is needed, our data suggest that a positive family history originating from a female patient, especially when that patient experienced a COC or pregnancy-related VTE may further increase VTE risk in her female relatives. We recommend to consider this information in the counseling women on contraceptive choices.

Clinical profile and recurrence rate in women with venous thromboembolism during combined oral contraceptive use

COCs increase risk of venous thromboembolism (VTE). However, it is yet not fully understood who will develop COC-associated VTE and evidence on recurrence risk varies.

In order to gather more information, we set up a prospective cohort, presented in Chapter 6, of consecutive Dutch women with COC-associated VTE that, according to Dutch General Practitioner (GP) guidelines, was preferentially prescribed levonorgestrel-containing CHCs since 1998. The aim of this study was to describe clinical characteristics and post-VTE contraception choices, and to prospectively assess VTE recurrence.
The cohort included 125 women with COC-associated VTE, of whom the majority had experienced deep vein thrombosis and pulmonary embolism. Their median age was 29 years and 69/125 (55%) used levonorgestrel-containing COCs at time of VTE. In 63%, the women had already used the COC for more than 1 year. Prior to the COC-associated VTE, 68% reported previous periods of uneventful COC-use and/or pregnancies. Many had additional risk factors: thrombophilia (34%), first-degree family history (31%), obesity (24%), and temporary risks (14%, postpartum, trauma, surgery, and immobilization).

Post-VTE, all women had discontinued COC-use and received thromboprophylaxis in subsequent pregnancies (20%). Median follow-up after anticoagulant therapy completion was 37 months (range 7–98 months). VTE recurred in 5 women, with an annual recurrence rate of 1.2% (95% CI: 0.44-2.63), and 1.8% (95% CI: 0.30-5.90) in the first year.

Several comparative studies evaluated the risk of recurrence in women with CHC-associated VTE. However, these studies often included these women as a subgroup, or CHC exposure was combined with exposure to pregnancy and/or hormone replacement, or studies were restricted to women with CHC use as single risk factor. Our cohort study presents an annual recurrence rate of 1.2% and 1.8% in the first year post index-VTE in women without further CHC use. Indirect comparison suggests that this rate compares favorably to that observed in previous studies (1.8–5.6%). Although a comparator group of women of fertile age with idiopathic VTE was considered, this did not appear feasible due to the very low number of women of fertile age presenting with idiopathic VTE, which is also related with the high prevalence of CHC-use in the Netherlands (61% between 18 and 30 years of age). However, studies reporting a recurrence rate after idiopathic VTE indicated a far higher recurrence risk, i.e. 15–17%, than noted after a CHC-associated VTE with subsequent risk management, i.e. discontinuation of CHC.

The design of our study did not enable any prediction up front on who will develop CHC-associated VTE, and we did not see any clear pattern. In this random sample of women with CHC-associated VTE, the majority had already used their present CHC for more than 1 year, had previous uneventful CHC use and/or pregnancies even in the presence of other risk factors and was on the preferred second-generation CHC. The only avoidable risk factor seemed to be a positive family history.
A surprising 31% of women had a first-degree family member with VTE, which currently is not considered a contra-indication to CHC use. Recurrence was low when CHC use was discontinued and thromboprophylaxis was offered in pregnancies, but larger studies are needed to confirm this.

Summarized, our findings did not show any clear pattern in risk factors in this random sample of women with CHC-associated VTE. The only avoidable risk factor seemed to be a positive family history. A surprising 31% of women had a first-degree family member with VTE, which currently is not considered a contra-indication to CHC use. The recurrence was low with subsequent risk management of COC-discontinuation and thromboprophylaxis in subsequent pregnancies.

**Discussion and implications for future research**

The studies described in this thesis show that the risk of VTE in COC-users is increased substantially in women with severe thrombophilia (protein S-, C- or antithrombin-deficiency), leading us to the recommendation that COC-use should be strongly discouraged (*Chapter 2*). However, in women with a factor V Leiden or a prothrombin-G20210A mutation, the absolute risk of VTE during COC use was only modestly increased, and importantly lower than the absolute risk observed during the pregnancy-postpartum period (*Chapter 3*). These data provide evidence that the current WHO guideline (2015) on medical eligibility criteria for contraceptive use, which strictly contraindicates COC use in these women, needs reconsideration. The results of the study do not allow to ‘promote’ COC use in asymptomatic family-carriers of FVL or PT G20210A mutation, but indicate that when COC use is discontinued or avoided, the need for adequate alternative contraception has high priority. Rather than strictly contraindicating COC-use, we recommend that these women should be given detailed counseling on all contraceptive options, including COCs, in which the associated risks of both VTE and unintended pregnancy and additional VTE risk factors present need to be addressed. Based the results of our meta-analysis (*Chapter 4*), which evaluated the VTE risk in COC-users with or without thrombophilia, we proposed recommendations regarding COC-use in women with mild and severe thrombophilia. In this, a woman tested positive for factor V Leiden in the past, who wishes to start combined oral contraception was taken as a starting point, as such situation is often a reason for consulting a hematologist.
The results of the meta-analysis showed that in COC-users mild thrombophilia (factor V Leiden, prothrombin-G20210A mutation) and severe thrombophilia (antithrombin-, protein C- or protein S-deficiency, double heterozygosity and homozygosity of factor V Leiden or prothrombin-G20210A mutation) increased VTE risk six to seven-fold. However, to value the impact of the relative increase in risk, the increase in absolute risk needs to be taken into account. The cohort studies included in this meta-analysis reported a VTE incidence of 0.49 and 0.2 per 100 pill-years of use in COC-users with mild thrombophilia, but incidences of 4.3 and 4.6 per 100 pill-years in COC-users with severe thrombophilia, indicating a considerably higher risk. However, all absolute risks are estimated in family members of thrombophilic families, i.e. relatives of thrombophilic patients with VTE, and therefore also have a positive family history. As a co-existing family history increases VTE risk two- to threefold, the observed absolute risk estimates are more pronounced than in a general population of COC-users tested positive for thrombophilia. Taking into account the GRADE quality of evidence grading, we proposed a strong recommendation that given the high additive risk, COC-use should be avoided in women with severe thrombophilia in all cases. The additive VTE risk of mild thrombophilia is modest and when no other risk factors are present, e.g. no family history, COC-use should not be denied in women who consider alternative adequate contraception not acceptable, as in this situation the increased risk of pregnancy-related VTE and increased risk of pregnancy outweigh the COC-associated risk. The VTE risk during pregnancy in women with mild thrombophilia (heterozygote for factor V Leiden or prothrombin G20210A mutation) was estimated (Chapter 3) to be as high as 1.97 per 100 pill-years. In this study, also absolute risk of VTE in COC-users versus users of alternative contraceptive methods, i.e. LNG-IUD users, copper-IUD users, and users of male condom, were compared. In this analysis both the risks of contraceptive-related VTE and the risk of pregnancy-related VTE (resulting from contraceptive failure) were considered. In these extrapolations, the LNG-IUD and copper-IUD both carried a lower overall risk of VTE and therefore good alternatives to COCs. Condom use had the lowest contraceptive efficacy, with an up to 60-fold increased risk of unintended pregnancy, which makes this option the least favorable alternative contraceptive method.

As shown in these two studies (Chapter 2, 3) and meta-analysis (Chapter 4) discussed above, women from thrombophilic families have increased risk of venous thromboembolism (VTE), which increases further during hormonal exposure.
Our cohort study, which evaluated whether this family-conferred risk is gender- or hormone-specific (Chapter 5), suggested that it does matter when a positive family history is originating from a female patient, especially whether the patient experienced a VTE during COC-use or during pregnancy or the post-partum period. Regarding possible clinical implications, we recommend to consider that women could be at higher VTE risk during COC-use and during pregnancy if they have a mother or sister with VTE, especially if that VTE also occurred during COC-use or in the pregnancy or postpartum period. Therefore, reviewing the family history prior to prescribing COCs should include specific data on who experienced VTE under what circumstances.

Finally, detailed information on clinical characteristics is presented, collected in a cohort of 125 consecutive women who had experienced a VTE while using a COC that we followed to estimate recurrence rate post COC-associated VTE. Detailed information on the clinical characteristics of these women was collected (Chapter 6). In 68% of women additional VTE risk factors besides COC-use were present, of which thrombophilia, family history and obesity reported in a high frequency. The design of this study did not permit any conclusion to predict up front on who will develop COC-associated VTE, and we did not see any clear pattern. However, this is in line with the concept of VTE being a multicausal disease: besides COC-use a variety of additional risk factors in a high frequency were concomitantly present in these women and that it can take years before a combination of these risks at one point in time results in a symptomatic VTE. This is supported by the observation that in this sample of consecutive women with COC-associated VTE, two-third of women already had used their COC for more than 1 year, had used COCs before and also had pregnancies without any complication. As in clinical practice routine screening for thrombophilia is considered not useful prior to start of COC-use, the only ‘avoidable’ risk factor seems to be a positive family history. A surprisingly high percentage of women (31%) had a first-degree family member with VTE. In two-third of cases, the family history originated from the mother or sister and in most cases was related to VTE during COC-use or the pregnancy-postpartum period. In current guidelines a family history of VTE is not a strict contra-indication to COC-use. It is therefore recommended, also in view of the outcome of our study suggesting that a positive family history could also be hormone-specific, to put a detailed first-degree family history in at a prominent place in the counseling on potential risk factors to COC-use.
Based on median follow-up after anticoagulant therapy completion of 37 months (range 7–98 months) a low annual VTE recurrence (1.2%) was observed with post-VTE risk management, which consisted of discontinuation of COC-use and thromboprophylaxis in pregnancies. Therefore, detailed counseling in the choice of adequate alternative contraception post-COC-related VTE is important.

In conclusion, there is “no other medication in the history of medical science that has been studied more extensively than the combined oral contraceptive pill’ (US Food and Drug Administration), which recently had its 50-year anniversary. Although the studies in this thesis and many other studies available gave us further detailed insight in the contribution of VTE risk factors to the VTE risk associated with the use of COCs and pregnancy, as well as new starting points for further research, the risk of COC-associated VTE is still not resolved.

Current developments in contraceptive methods

Combined hormonal contraceptives

Up to today, a combined hormonal contraceptive that has no increased risk of VTE has not been developed, although science does not stand still. As for the currently approved COCs, despite a more than 10-fold decrease in dose, and development of many new progestogens, the risk of VTE, although considerably lower, persisted.

Several options have been developed or are ongoing based on the theory that the risk of VTE may be modified by the type of estrogen, the route of administration, or lowering the estrogen dose.

Some new estrogens are being developed such as the fetal estrogen estretol, but it is as yet unclear whether these will have different effects on the risk of VTE. Further, recently two new COCs (Qlaira©, Zoely©) became available on the market, which contain estradiol instead of ethinylestradiol. However, there is yet no sufficient clinical trial information to conclude that changing ethinylestradiol into estradiol will change the risk of VTE. Published data showed that alterations regarding hemostatic variables, SHBG-levels and thrombin-generation activated protein-C resistance (APC-resistance) were in the range of that noted with levonorgestrel containing COCs, but unfortunately none of these are validated surrogates for the clinical endpoint of VTE.32-34
As to a different route of administration, it is suggested that orally administered estrogen has higher prothrombotic effect that is possibly related to high concentrations of estrogen in the liver due to the “first-pass” effect. However, the combined hormonal contraceptive vaginal ring (ethinylestradiol-desogestrel) and transdermal patch (ethinylestradiol-norelgestromin) were recently shown to have an increased risk of VTE that was comparable to that noted for 3rd and 4th generation COCs.36

On the other hand, a case-control study in postmenopausal women who used either oral or estradiol patches observed no increased risk of VTE in women using patches,37 and hemostatic variables might be less influenced with transdermal administration of estradiol,38 but more robust clinical trial data are lacking. Therefore, the patient leaflet of estradiol-containing patches has not been adapted regarding the risk of VTE. However, gynecological organizations recommend considering the possibly lower risk of VTE with transdermal administration of estradiol.39

Finally, there are some data in postmenopausal women suggesting that statins could potentially attenuate the estrogen-related risk of VTE, but adequate controlled studies are needed to further explore this observation.40

Non-hormonal contraceptives

The development of non-hormonal contraceptives is ongoing,41 but the number of potential candidates in the clinical phase is still limited: several clinical contraception studies with selective progestogen-receptor modulators (SPRMs) like mifepristone, ulipristal,42 have been published, but as yet no product has been put forward as an alternative to a COC. In India, since the early 1990s, a selective estrogen-receptor modulator (SERM) - ormeloxifene – is on the market for contraception, which has to be taken once a week.43 This product is not approved for contraception in the Western world. The documentation on the effectiveness and safety of this product in the public domain is too sparse to draw any meaningful conclusion, but those SERMs that are approved in indications for postmenopausal women indicate that these products induce a 2-fold increased risk of VTE.44 Other potential candidates could be prostaglandin E2 receptor antagonists but research is still in the preclinical development phase.45
Contraception and pregnancy in women at increased risk of VTE

As to the possibilities of reliable alternative contraception for women post-VTE, the progestogen-only preparations are considered a very good alternative. Although traditionally they are seen as contraceptives especially for women who have completed their family, these products can compete with COCs as these have excellent contraceptive efficacy and rapid return of fertility when discontinued.\textsuperscript{46,47} The amount of data supporting the progestogen-only preparations to be non-thrombotic is increasing; the largest amount of data up to now is collected on the levonorgestrel-containing IUD (Mirena®) showing that this levonorgestrel-containing intrauterine device does not increase the risk of VTE.\textsuperscript{36,48} Recently, also a slightly smaller and lowered-dosed levonorgestrel-containing IUD (Jaydess®) has been registered, but this product is not yet available in all EU countries. Also the data now available for an etonogestrel-containing implant (Implanon®), and the oral progestogen-only pill (Cerazette®) containing desogestrel do not show an increased risk of VTE.\textsuperscript{1,36,48} However, limited data indicate that the medroxyprogesterone injectable (Depo-Provera®) increases the risk of VTE.\textsuperscript{17,48} It is difficult to explain why one of the progestogen-only preparations would have an opposite safety pattern regarding risk of VTE. A possible explanation might be that the characteristics of the women who use this contraceptive are different, as this contraceptive may be used only when other contraceptives are unsuitable. The reasons for its restricted indication are the considerable delay in return to fertility after discontinuation of this product and the observed decrease in bone mineral density noted in adolescent women. As to recommending non-hormonal contraception, the copper-IUD is a very good alternative with adequate contraceptive properties. However, above mentioned alternative contraception methods have effects on the menstrual bleeding pattern: progestogen-only contraception, including the levonorgestrel-containing intrauterine device induce unpredictable bleeding pattern and the copper IUD will increase the duration and amount of menstrual blood loss. These adverse events could lead to discontinuation and it is recommended to discuss beforehand that such effects on the menstrual bleeding pattern can be expected and whether such adverse effects would be acceptable to the woman. Guidance on the expected bleeding pattern, which could improve with longer duration, is shown to increase continuation rates.\textsuperscript{49,50} The current options of adequate progestogen-only contraception, especially oral progestagen-only, are still limited, but several new products are currently in the clinical development phase.\textsuperscript{51}
While the hormonal (estrogenic) exposure of a COC is avoidable, this is not the case for a pregnancy. This introduces the difficult dilemma what should be done if the VTE risk pattern of the woman is not straightforward. In case of a previous history of thrombosis, the decision is clear: several guidelines recommend thromboprophylaxis during pregnancy and in the postpartum period. But what if the risk is less clear, i.e. there are known risk factors but these have not resulted in symptomatic VTE? International clinical guidelines still rely heavily on expert opinion, and there are contradictory views in these on initiation, dosing and duration of thromboprophylaxis in pregnancy and postpartum period due to the absence of adequate controlled trials. Thromboprophylaxis in pregnancy in high-risk patients is also poorly discussed in the product information of the low molecular weight heparins (LMWHs), and dose recommendations specifically for use in pregnancy are not given. More pharmacodynamic and pharmacokinetic information is needed to support an adequate dose/per day, taking into account the differences in hemostatic balance that are induced by the pregnant state. Additionally, it might be worthwhile to gather more information on the increasing estrogen levels and hemostatic changes in pregnancy and the post-partum period. More insight in this pattern could be helpful on what would be the most appropriate time point to start and stop thromboprophylaxis. A better documented timing will also improve the balance between coagulation and bleeding in the critical period after the partus.

Improving safe use of combined oral contraceptives

Lastly, in view of the current situation that there is no thrombosis risk-free combined hormonal contraceptive to be expected soon, the focus should be on who can safely use COCs and who should not be prescribed a COC. Recently, the European Medicines Agency has performed an extensive review of available published and unpublished data available on the risk of VTE during use of all combined oral contraceptives and non-oral combined hormonal contraceptives (CHCs) available in the EU. This committee has concluded that “the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks, and that the well-known risk of VTE with all CHCs is small. But the review has reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care.”
EU-wide, this review resulted in the implementation of updated texts in the physicians’ product information and patient leaflet reflecting the VTE risk differences between COCs and contributing risk factors. Additionally, several tools (a VTE physicians’ and patient card) have recently been made available. In this material, also special focus is made on recognition of VTE in young women, as VTE can present itself as atypical, and on the impact of other risk factors for VTE present. An overview of the guidance on VTE risk factors is given in the tables below.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity (body mass index over 30 kg/m²)</td>
<td>Risk increases substantially as BMI rises.</td>
</tr>
<tr>
<td></td>
<td>Particularly important to consider if other risk factors also present.</td>
</tr>
<tr>
<td>Prolonged immobilization, major surgery, any surgery to the legs or pelvis,</td>
<td>In these situations it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilization. Another method of contraception should be used to avoid unintentional pregnancy.</td>
</tr>
<tr>
<td>neurosurgery, or major trauma</td>
<td>Antithrombotic treatment should be considered if COC has not been discontinued in advance.</td>
</tr>
<tr>
<td>Positive family history (venous thromboembolism ever in a sibling or parent</td>
<td>If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use</td>
</tr>
<tr>
<td>especially at a relatively early age e.g. before 50).</td>
<td></td>
</tr>
<tr>
<td>Other medical conditions associated with VTE</td>
<td>Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease and sickle cell disease</td>
</tr>
<tr>
<td>Increasing age</td>
<td>Particularly above 35 years</td>
</tr>
</tbody>
</table>

*Adapted from ‘Assessment report on combined hormonal contraceptives’ of the European Medicines Agency 201452
Table 2. Text on VTE risk factors included in the patient leaflet of a COC*

<table>
<thead>
<tr>
<th>Factors that increase your risk of a blood clot in a vein</th>
</tr>
</thead>
<tbody>
<tr>
<td>The risk of a blood clot with X is small but some conditions will increase the risk. Your risk is higher:</td>
</tr>
<tr>
<td>• if you are very overweight (body mass index or BMI over 30kg/m2);</td>
</tr>
<tr>
<td>• if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (eg. below the age of about 50). In this case you could have a hereditary blood clotting disorder;</td>
</tr>
<tr>
<td>• if you need to have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a cast. The use of X may need to be stopped several weeks before surgery or while you are less mobile. If you need to stop X ask your doctor when you can start using it again.</td>
</tr>
<tr>
<td>• as you get older (particularly above about 35 years);</td>
</tr>
<tr>
<td>• if you gave birth less than a few weeks ago.</td>
</tr>
</tbody>
</table>

The risk of developing a blood clot increases the more conditions you have.

*Adapted from ‘Assessment report on combined hormonal contraceptives’ of the European Medicines Agency 2014

Future perspectives

Up to now, the association between COC-use and risk of VTE has been the topic of many studies, including those presented in this thesis. It is expected that many more will follow, as this risk is still unsolved. Yet, the situation today is that the majority of women in the Western world uses a COC for contraception, and will do so for the upcoming years. Therefore, three lines are proposed: First, continuing further research to increase knowledge of risk factors influencing VTE risk in COC-users that can differentiate between women who can and who cannot safely use a COC. Second, further research may not result in absolute certainty in predicting individual VTE risk in COC-users, therefore uncertainties in VTE risk needs to be taken into account in the counseling in contraceptive choices. Three: alongside, there is a necessity to increase awareness that VTE, although rarely, can occur in healthy (young) COC-users. Indeed, awareness and education of thrombosis is the goal of the initiated World Thrombosis Day, which was first held on October 13th, 2014.
Increasing knowledge of risk factors predicting VTE risk in COC-users

As to predicting individual VTE risk, it was already put forward years ago that, despite increasing knowledge and better prophylaxis in risk situations, the prevalence of VTE was constant since 1979. This was then believed largely due to the inability to recognize those persons at greatest risk.\textsuperscript{54} However, the prevalence in 2015 is actually not much lower, as it is still referred to as about 1 in 1000 persons.\textsuperscript{55} This indicates that identifying persons at greatest risk are still insufficient.

The common theme in this thesis is the contribution of other VTE risk factors to the risk of VTE during COC-use. Of these, the increased risk of VTE in COC-users with a known hereditary thrombophilia is reasonably well established, of which 2 studies in this thesis have further contributed that there are large differences in absolute risk between mild and severe thrombophilias (Chapters 2 and 3). However, in clinical practice, testing for any thrombophilia is not considered contributing in predicting VTE risk prior to start of COC-use, as due to the low prevalence, a very large number of women needs to be tested to prevent one VTE.\textsuperscript{56} Further, withholding COCs in non-symptomatic women tested positive for mild thrombophilia (factor V Leiden or prothrombin G20210A mutation), might be reconsidered when the woman has no adequate alternative contraception, as in this situation the increased risk of pregnancy and pregnancy-related VTE outweigh the COC-associated risk.

Further, there are a number of recognized exogenous or temporary risk factors that add up to the VTE risk of COC-use, e.g. surgery, trauma, immobilization, or obesity. These risk factors are indeed frequently present in COC-users who experienced VTE, as is also reported in one of the studies in this thesis that reported on the clinical profile of these women. However, these daily life risks are also very common in women who do not experience COC-associated VTE. Therefore, the predictive value of these risks for the individual woman is uncertain.

Also a positive family history is an established predictor of VTE risk, and recently the number of studies exploring the association between family history and VTE is increasing. In 2004, a large family-based study, which addressed the heritability of VTE and the potential mode of inheritance, showed that VTE is not solely due to environmental exposures.
The authors found that a multifactorial non-Mendelian inheritance model fitted best as the cause for VTE, and concluded that VTE is probably a result of multigenic action as well as environmental exposures.\textsuperscript{54} This outcome is consistent with the commonly accepted hypothesis that VTE is a multifactorial disease.\textsuperscript{47} Indeed, up to now several family cohort studies have shown VTE to occur more often in first-degree relatives of patients with VTE than in the general population. These studies showed that the increased VTE risk observed in relatives is not fully explained by the presence of known hereditary thrombophilias, as risk of VTE is also increased in relatives without thrombophilia. An increased risk of VTE in non-thrombophilic women was also observed in our family cohort studies. Further to this, emerging data indicate that a family-conferred risk might be of particular importance in young relatives, as pointed out in comments accompanying recent published studies evaluating details of VTE risk of a family history.\textsuperscript{57,58} These studies, one focusing on characteristics of relatives of symptomatic probands\textsuperscript{26} and the other focusing on characteristics of symptomatic probands with or without unprovoked VTE,\textsuperscript{27} showed that VTE is aggregated in families and that “uncovering the sources of this familial aggregation (genetic and non-genetic) may be worthwhile”. It was suggested that for younger relatives, a positive family history is a major risk factor for VTE that trumps known thrombophilic disorders.\textsuperscript{57} This more increased risk was especially observed in younger female relatives. With respect to above studies exploring predictors of risk of VTE, the recommendation to further explore the role of family history is supported, as information on family history is ready to be used within the counseling on VTE risks and contraception. In these studies, no specific attention was given yet to a possible familial susceptibility to hormonal exposure (COC-use and pregnancy). Our study, discussed in Chapter 5, focused on this question and although this is the first study, the results suggested that a hormonally (COC-use or pregnancy)-associated VTE in a female proband could be of additional relevance in predicting the VTE risk in her female relatives.

Options to further expand research on VTE risk factors influencing VTE risk during COC-use (and pregnancy) within families are using currently available data in order to increase the population. Options are to link existing family cohorts. Another approach could be to pool existing studies in women who experienced a COC- or pregnancy-associated VTE and focus on data collected on first-degree family history, although these studies have the drawback that most often a family history is self-reported.
Further, existing registries could be used to evaluate VTE risk patterns in women between generations of families. In this, the multigenetical data collected in the LifeLines cohort study and biobank\textsuperscript{39} would be an excellent source.

**Improvement in counseling on contraceptive options**

Although above discussed focus on further research will bring more differentiation in VTE risks and may find additional risk factors, it needs to be considered that absolute certainty in predicting individual VTE risk may not be reached. We didn’t achieve this in the past 50 years: although there are few definite situations in which COCs should not be prescribed, the majority of the defined risk factors result in a mild increase in VTE for which it remains difficult to draw definite conclusions. Also the results of the studies in this thesis underline that with few exceptions, single VTE risk factors result in a mild increase in risk. From these uncertainties in predicting VTE risk it follows that from the first contraception consult on detailed counseling is recommended on all contraceptive options, including COCs, addressing both existing risk factors of VTE and risk of unintended pregnancy. In the counseling, existing adequate alternatives (levonorgestrel-containing IUD, progestogen-only implant, oral progestogen-only tablet, copper IUD) could be far better promoted as equally good alternatives, as contraceptive adequacy and tolerability pattern can compete with that of a COC. Although, no direct comparison versus COCs is available, as such studies are difficult to perform, several studies compared different progestogen-only products which showed good efficacy, tolerability and acceptance\textsuperscript{47,48} In comparison to COCs, the return of fertility after discontinuation or removal of these products is equally rapidly restored. Prior counseling on the unpredictable bleeding pattern to be expected is shown to reduce discontinuation rates.\textsuperscript{49,50} The one exception is the depot medroxyprogesterone (Depo-Provera©) of which data are disadvantageous with regard to return of fertility and its risk of VTE is yet uncertain.

To improve counseling on contraceptive options, the following lines to take are proposed:

- Training of health care professionals in risks and benefits of all contraceptive options, taking into account relevant risk factors of VTE;
• Developing decision aids, such as information cards, which present all adequate contraceptive options, stating their pro’s and con’s.

• Evaluation of the effectiveness of such training in prescribing practices on contraception in implementation studies; in this evaluation also the patient view can be taken into account.

• Alongside, a well-informed public, i.e. the women in need for contraception, will also a good safeguard to improve safe use of contraceptives. Therefore, ideally all sources of information accessible for the public related to contraceptive choices, need to be updated with adequate objective information that will help women to select the most appropriate method of contraception.

Increasing awareness of VTE in COC-users and health care providers

Apart from continuing research, a further focus on measures to improve physicians and patient’s awareness of VTE during use of COCs is needed. Although this seems obvious, we learned from the recent discussions on Diane 35 in public literature and the media, that a major issue appeared the unawareness that healthy young women could suffer from a VTE during COC-use, as the doctor and patient had not in all cases recognized the presence of a VTE. Therefore, diagnosis and treatment was delayed. Additionally, temporary risk factors that add up to the VTE risk during COC-use, such operation, or immobilization, are not common knowledge.

Recently, the European Medicines Agency has requested to implement a EU-wide update of the official information in physicians’ product information and patient leaflet on differences in risk of VTE between COCs. Additionally, guidance is included regarding the complexity of other risk factors that can increase risk. Although these updated texts present the latest information, these are difficult to read due to the large amount of data presented and the complexity of the VTE risk as many additional risk factors can additionally contribute. Therefore, there is a need for clear and concise information that presents contraceptive effectiveness and risks of all contraceptives currently available. Such an information card could be used as a tool in the counseling on the most suitable contraceptive for the individual woman.
Within this effort, it is also recommended to provide more consistency in the information on risk of VTE during contraceptive use that is available in all information areas, including the many (commercial) websites that are focusing on providing information on contraceptive options for women.

In conclusion, increasing awareness of risk factors for VTE that can be used to better predict who can safely use COCs will improve the balance between preventive interventions to avoid this rare but serious complication of COCs and withholding an adequate contraceptive; increasing knowledge of VTE as a rare adverse event will improve recognition of VTE and will result in a more timely diagnosis and treatment.
References


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