Contraception and Thrombophilia – A statement from the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF e.V.) and the Professional Association of German Gynaecologists (BVF e.V.)

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Venous thromboembolism (VTE) is responsible for more than half a million deaths annually in the European Union, most in older people following surgery, but some in women of reproductive age using various hormonal contraceptives. In some parts of the population inherited defects of the blood coagulation system (factor V Leiden, prothrombin G20210A, protein C, protein S and antithrombin deficiency) are responsible for an increased risk of VTE, which is also influenced by concomitant factors: e.g. long-distance travel, immobilisation, advanced age, cigarette smoking, high BMI, surgery, malignancy, fluid loss, pregnancy, oral contraceptive use and hormone replacement therapy (HRT).

Laboratory testing: General screening for thrombophilia prior to the prescription of oral contraceptives (OC) is not recommended. Laboratory testing for thrombophilia should be limited to women with a positive family and/or personal history of VTE or vascular occlusion.

- Factor V Leiden is by far the most common congenital thrombophilia. Heterozygous factor V Leiden (5-fold increased VTE risk) is present in 3–13%, homozygous factor V Leiden (10-fold increased VTE risk) in up to 0.2–1% of people of European origin.
- Prothrombin mutation G20210A: Autosomal dominant mutation inheritance (2% of people of European origin) leads to a 3-fold increase in VTE risk is substantially increased if one or more additional risk factors are present such as factor V Leiden or protein C, S, or antithrombin deficiency.
- Protein C and protein S: VTE risk increases with protein C or S deficiency (odds-ratio 3–15 and 5–11, respectively).
- Antithrombin deficiency leads to a 4 to 50-fold increase in VTE risk depending on the type of deficiency.

Female hormonal contraceptives containing progestogens with or without combination with a synthetic estrogens (mainly ethinylestradiol [EE]) or a natural estrogen (e.g. estradiol or its derivative estradiol valerate) affect the incidence of VTE in healthy women without known risk factors as follows (VTE cases per 10,000 woman-years):

- **No method-related increased risk (3–4):** Non-hormonal contraceptives (e.g. tubal sterilisation, condoms, spermicides, behavioral methods, copper IUDs)
- **No or only slightly increased risk (3–4):** Levonorgestrel IUS, progestogen-only pill, estrogen-free oral contraceptives
- **Moderately increased risk (3–10):** Combined OCs (COCs) with < 50 µg EE containing norethisterone, norethisterone acetate, levonorgestrel, norgestimate, chlormadinone acetate, dienogest; COCs with estradiol valerate and dienogest; vaginal combined estrogen/progestogen ring, depot injectables
- **Moderately increased risk (6–14):** COCs with < 50 µg EE containing desogestrel, gestodene, cyproterone acetate or drospirenone; combined estrogen/ progestogen contraceptive patch

Detection of women at risk for VTE via family and personal history is absolutely required before any hormonal therapy (e.g. contraception, hormonal replacement). General screening for thrombophilia is not recommended. Additional individual risk factors must be considered. Each patient should be advised about early symptoms of vascular occlusion. For patients with an increased risk of VTE a risk-benefit analysis must be done regarding non-hormonal choices and non-contraceptive benefits of individual hormonal treatment (e.g. for COCs: regular menstrual cycles, less dysmenorrhoea, improvement of acne vulgaris). Shared decision-making and informed consent are strongly recommended. **J Reproduktionsmed Endokrinol 2011; 8 (Special Issue 1): 178–218.**

Key words: thrombophilia, factor V Leiden, prothrombin 20210, protein C, protein S, antithrombin, venous thromboembolism, screening, hormonal contraceptives, risk groups, patient counseling, personal history, family history

Preliminary Remarks

This statement addresses venous thromboembolic complications in women, with and without the use of various types of contraception. Because epidemiological studies have also associated combined oral contraceptives (COCs) with an increased risk of arterial thromboembolism (myocardial infarction, transient ischemic attacks, ischemic strokes), secondary attention is devoted to arterial thromboembolic events.

This statement focuses on the risk associated with thrombophilia – other potential risk constellations such as obesity, heavy smoking, PCO syndrome, diabetes mellitus, insulin resistance etc. have to be considered on an individual basis – including the resulting diagnostic and treatment consequences. These recommendations do not release physicians from their professional duty to attend to each individual case, including the provision of extensive information to the patient about treatment options and their effects and/or side effects.

Disclaimer

Medical knowledge is constantly changing. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy may become necessary or appropriate. Readers are advised to check the most current product information provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and contraindications. It is the

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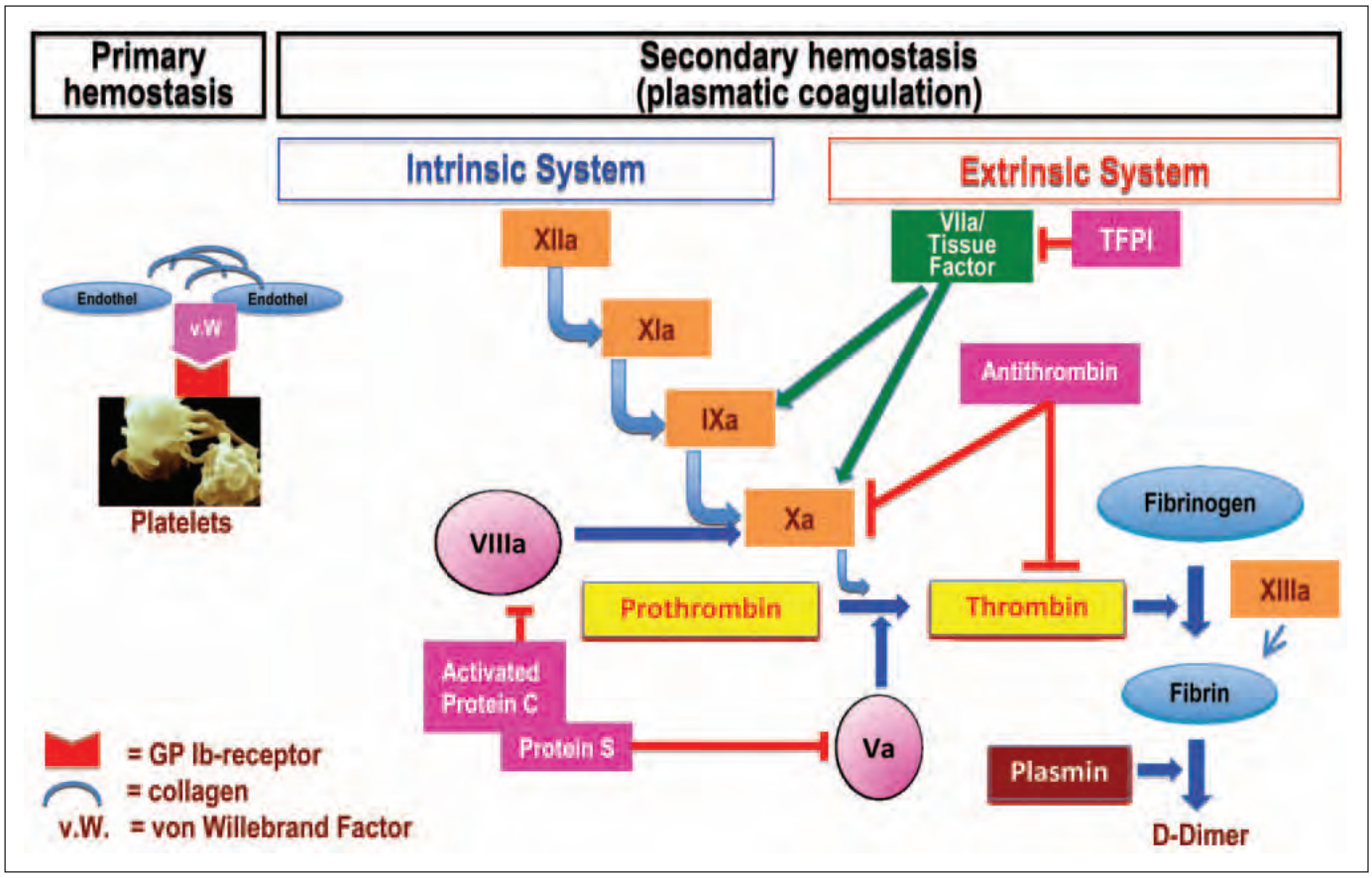

Figure 1a. Schematic representation of primary and secondary hemostasis. Mod. from [1].

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1. What is Hemostasis?

Hemostasis is a crucial physiological reaction which ensures that bleeding stops and blood vessels close following an injury. In addition to the blood vessel's endothelium, platelets and plasmatic coagulation factors play a major role in hemostasis.

A number of reactions are triggered when a blood vessel is damaged:
- the vessel constricts, which reduces blood flow
- platelets are activated to adhere and aggregate, forming a platelet thrombus
- plasmatic coagulation is activated, forming a fibrin mesh that reinforces the initial thrombus.

When a blood vessel is damaged, subendothelial structures are exposed, of which collagen and tissue factor (thromboplastin) play an especially strong procoagulatory role. Platelets bind to exposed collagen within seconds. In the process, the von Willebrand factor forms a "bridge" between the collagen and platelets (Fig. 1a). Tissue factor (TF), an integral-membrane protein which is expressed from e.g. fibroblasts and smooth muscle cells, initiates plasmatic coagulation. The TF/factor VIIa complex activates factor X (FXa), which together with its co-factor Va converts prothrombin into thrombin (Fig. 1a). Thrombin catalyzes the conversion of soluble fibrinogen into insoluble fibrin. Fibrin polymerizes into a fibrin mesh, which is mechanically stabilized via cross-linking by factor XIIIa. In vivo coagulation takes place on cell surfaces, such as TF-expressing cells and activated platelets (Fig. 1b).

For decades a model was taught according to which plasmatic coagulation is initiated by 2 different systems (extrinsic and intrinsic coagulation systems). It is now clear that these two systems are inseparable. For one thing, the TF/FVIIa complex also activates factor IX. For another thing, polyphosphates are released when platelets are activated, which bind directly to factor XII and activate it. Moreover, it has also been shown that ribonucleic acid (RNA), which is released from damaged cells, also induces activation of the classical intrinsic coagulation system.

In physiological terms, the coagulation process is limited by coagulation inhibitors at the site of the vessel lesion. These "naturally produced" anti-coagulants include:
- "tissue factor pathway inhibitor" (TFPI), which inhibits the TF/FVIIa/FXa complex
- antithrombin, which inhibits especially thrombin and factor Xa
- protein C and protein S.

The vessel's endothelium assumes an important role in these anti-coagulatory processes. The effect of antithrombin is strengthened by heparan sulfate on the vessel's surface. The protein C system is activated when thrombin binds to its integral-endothelium receptor thrombomodulin. Via the complex of thrombomodulin and thrombin, protein C is converted into its active form, namely acti-

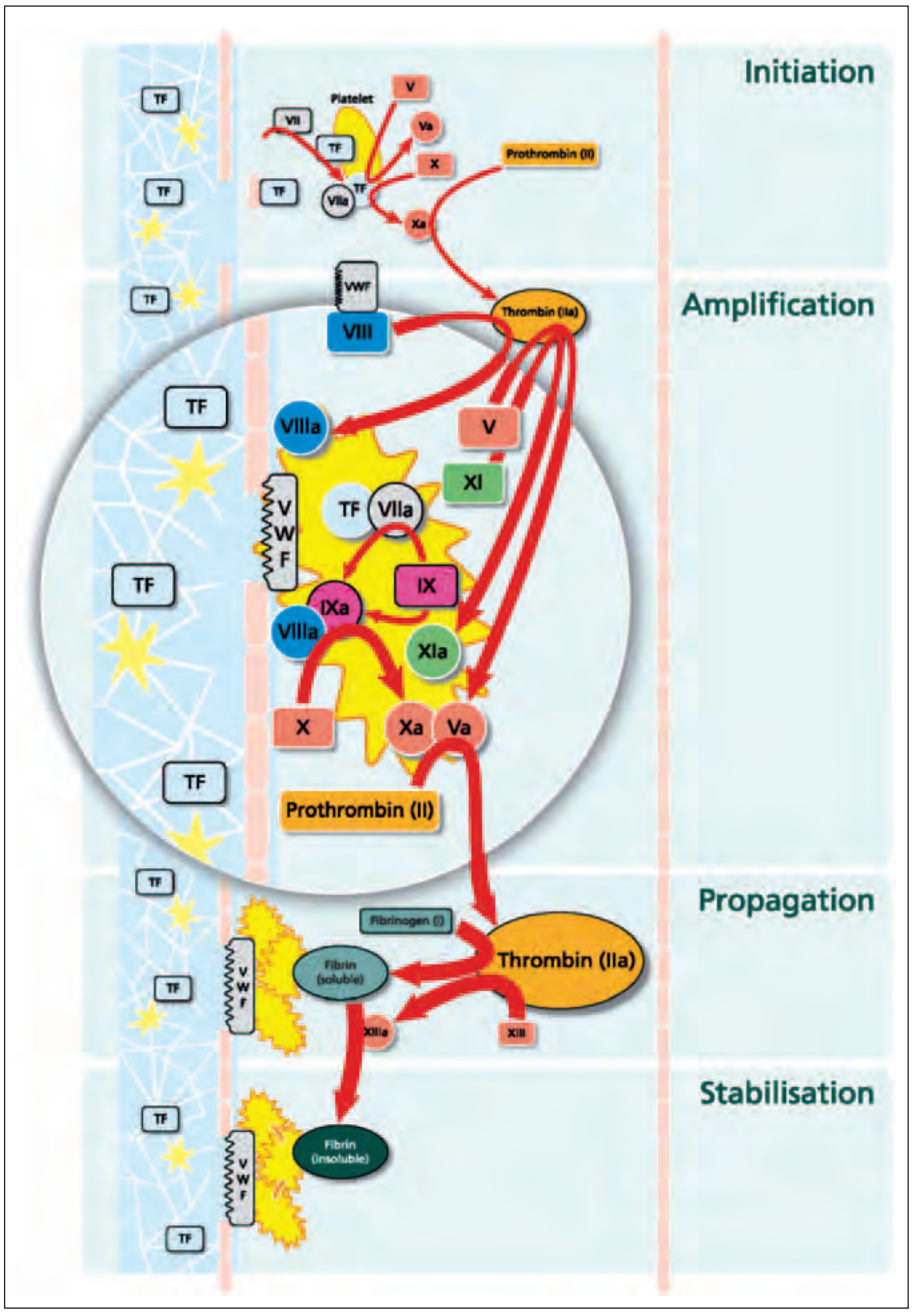

Figure 1b. Coagulation cascade in vivo. (Graphic kindly made available by Novartis Behring, Marburg).

vated protein C (APC). Together with its co-factor protein S, APC inhibits factors Va and VIIIa (Fig. 1a).

At the end of the wound-healing process, the fibrinolytic system ensures that the vessel reopens. The main enzyme in fibrinolysis is plasmin (Fig. 1a). Plasmin dissolves the fibrin clot, producing fibrin degradation products such as D-dimers (Fig. 1a).

Deficient regulation of hemostasis, whether due to an excess of pro-coagulatory factors or to a decline or defective functioning of anticoagulatory mechanisms, induces a tendency to develop thromboses (thrombophilia).

2. Thromboembolism – Etiology, Clinical Relevance and Diagnosis

2.1. Prevalence of Thromboembolic Disease

Approximately 1.1 million cases of venous thromboembolism (VTE) are diagnosed in the European Union every year, including deep venous thrombosis (DVT) and pulmonary embolism, of which 150,000 cases end in death [2]. Also of note is the fact that most thromboembolism cases are asymptomatic and are therefore not diagnosed. Cohen et al. (2007) estimate that around 220,000 deaths across Europe are due to undiagnosed pulmonary embolism. VTE is therefore a serious health problem that claims more victims per year in the EU than do breast cancer, HIV/AIDS and traffic accidents. The incidence in both sexes rises exponentially with age [3–5], with VTE occurring very rarely in young, healthy women. According to Heit et al. 60% of all VTE could be attributed to hospitalization or nursing home residence [6, 7]. These figures clearly indicate that VTE represents an enormous risk for certain population groups, whereas the vast majority of the younger population faces only a slight risk.

Approximately one out of every ten deaths in hospitals (one percent of all patients admitted) is due to pulmonary embolism [8].

Venous thromboses and venous thromboembolism (VTE) occur primarily in the lower extremities and pulmonary vessels. They occur less frequently in the upper extremities, and rarely in other blood vessels (e.g. liver, mesentery, kidney, brain or retinal vessels).

A distinction is made between VTE induced by reversible risk factors (secondary VTE) and that which is not (idiopathic VTE).

Reversible (strong) risk factors include: surgery, hospitalization, immobilization in plaster casts or other fixed bandages in the month before diagnosis, and malignancies. Weaker factors include estrogen treatment, pregnancy, long-distance journeys (e.g. > 8h) and the above-mentioned strong risk factors within a period from 3 months to 1 month prior to diagnosis.

Common to all definitions of non-idiopathic VTE is the identification of acute reasons (e.g. surgical procedures, trauma, immobilization). This distinction is of limited practical relevance, however, because: 1. the proportion of what are termed idiopathic VTE is declining as scientific knowledge advances, and 2. bias presumably plays a role in determining the incidence of idiopathic VTE in connection with COCs, because mention of the COC "risk factor" in clinical practice often suffices to terminate the search for further VTE risk factors.

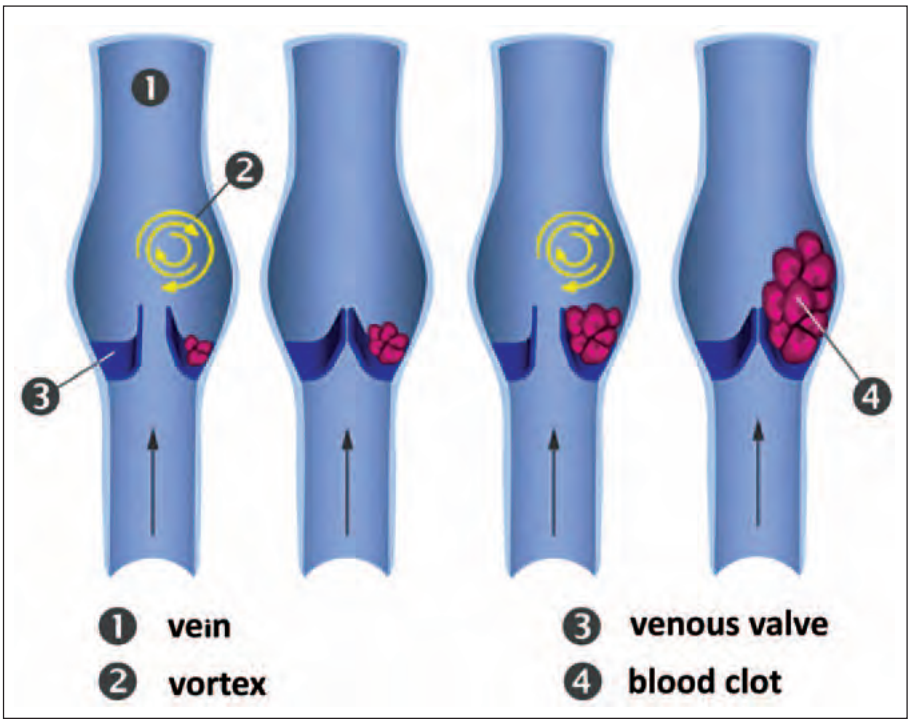

Figure 2. Genesis of venous thrombosis (with kind permission of www.internisten-im-netz.de).

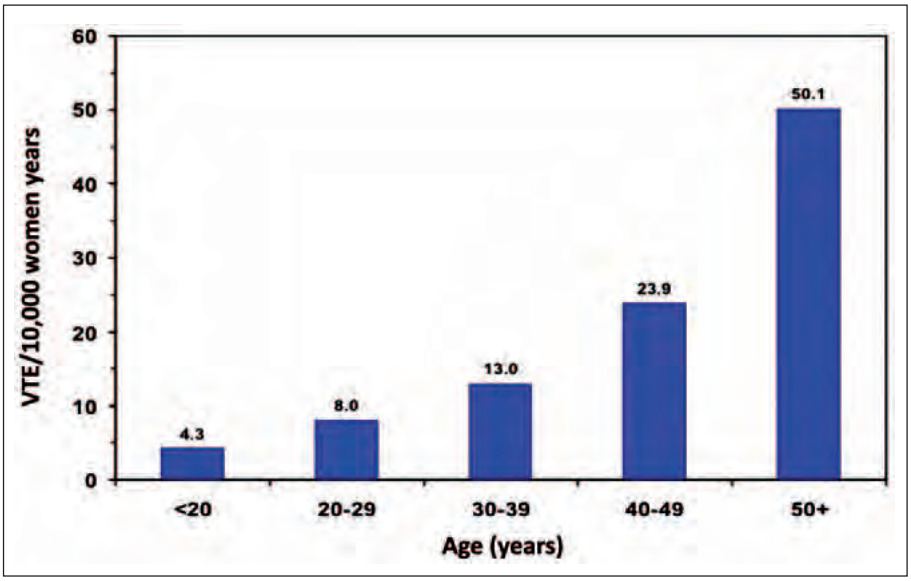

Figure 3. Risk of venous thrombosis by age (per 10,000 women/year) for COC users. Source: LASS study interim report: http://clinicaltrials.gov/ct2/show/NCT00676065; Dinger, 2010 personal communication.

Of special note here is that venous thromboses, and also pulmonary embolism, often remain unrecognized. They frequently cause non-specific, minor symptoms, which are often not properly understood by patients. This means that diagnoses are only made following a targeted search, and this search in turn is frequently triggered by the mention of risk factors. Overall, thromboembolism represents an under-diagnosed condition with a high number of unreported cases.

2.1.1. Incidence of Venous Thrombosis (Fig. 2)

The incidence, or number of new cases, in Germany is 1–1.8 per 1,000 residents per year (higher rate in women than men). The incidence has increased over the past few decades. Both a rise in risk factors (e.g. increased weight) and advances in diagnostics play a role here. Incidence also increases with age (Fig. 3) (see also [5]).

The incidence of arterial occlusion is also low for women of fertile age. A large-scale study of oral contraceptive users showed the incidence of stroke for women under 50 years of age to be 20 out of 100,000 (EURAS, Dinger et al. 2007 [9]).

The risk of venous thrombosis and embolism as well as arterial occlusion depends on sex and age. Venous thromboses and thromboembolism are rare in young women who do not show risk factors.

The incidence of serious complications (e.g. pulmonary embolism) is lower than the incidence of acute DVT in the leg by approximately a factor of 10, and deaths due to thromboembolic complications in COC users are extremely rare – they are observed without other identifiable causes in approximately 1–4 per million women using the Pill. The risk of mortality is due essentially to failure to identify the underlying condition (venous thrombosis or pulmonary embolism).

For VTE only, the following figures apply: incidence ~0.0008, lethality ~0.005, deaths ~4 in one million woman-years [9].

Use of COCs increases the risk by a factor of 2–6 [10].

2.2. Etiology of Thromboembolism

The presence of a thrombophilic genetic mutation (e.g. factor V Leiden, prothrombin G20210A, hereditary deficiencies of antithrombin, protein C, protein S, etc.) increases the underlying risk of thrombosis, which is further increased by the use of COCs; see Table 1 [11, 12].

Thromboembolism is a multi-factor condition, whose risk can increase on a multiplicative basis with the number of risk factors.

2.2.1. Additional Dispositional Risk Factors

In addition to COC type and thrombophilic aspects, various other factors increase the risk of venous thrombosis or arterial occlusion.

In more than half of individuals with hereditary anomalies, venous thrombosis does not occur spontaneously. Various other risk factors function as triggers (Tab. 2), such as:

Table 1. Risk of venous thrombosis with thrombophilia, with and without oral contraception. Because some results are limited, the data for with/without OC use come from different studies. Risk with versus without OC use is therefore not directly comparable; the columns must be considered separately (e.g. for heterozygous prothrombin G20210A mutation, one should not conclude that the risk with OC use doubles from 3–6).

Thrombophilia	DVT risk, OR	DVT risk with OC, OR
Factor V Leiden mutation, heterozygous	5	16
Factor V Leiden mutation, homozygous	10	(Data from a meta-analysis of heterozygous and a few homozygous cases. The VTE risk for homozygote carriers with OC use has thus far not been sufficiently studied, and could lie considerably higher)
Prothrombin G20210A mutation, heterozygous	3	6
Prothrombin G20210A mutation, homozygous	due to rarity, no data	(Data from a meta-analysis of heterozygous and a few homozygous cases. The VTE risk for homozygote carriers with OC use has thus far not been sufficiently studied, and could lie considerably higher)
Prothrombin G20210A mutation heterozygous + factor V Leiden mutation heterozygous	4–15	8–17
Congenital protein S deficiency	5–11	5
Congenital protein C deficiency	3–15	6–24
Congenital antithrombin deficiency type I/II	4–50 depending on type of AT deficiency	13 28% of OC users suffer thrombosis
Factor VIII elevation	5–8	9–13
Antiphospholipid antibodies (lupus anticoagulants, anti-cardiolipin antibodies, anti-β2-glycoprotein I antibodies)	2–16 depending on antibody or combination thereof	insufficient study results
Hyperhomocysteinemia	risk rises by 1.3 for each increase of 5 µmol	insufficient study results
Lipoprotein (a) > 300 mg/l	1.8	no data
MTHFR C677T polymorphism	not elevated	not elevated

– **Age:** The risk of a thromboembolic event increases exponentially with age. Below the age of 40, the risk of such an event is approximately 1 in 10,000 (0.01%), at age 60 it is approximately 1 in 1,000 (0.1%), and above 80 years it is approximately 1 in 100 (1%) per year [13–16].
  The risk of thrombosis increases with age, lack of movement, ageing of the vascular system and other factors. If hereditary susceptibility factors (thrombophilia) are present, thromboses occur earlier, often before the age of 45.
– **Use of oral hormonal contraceptives (OC)**
– **Hormone replacement therapy**
– Cigarette **smoking:** Not all studies, however, confirm an increased risk of VTE for smoking. The EURAS study, for example, did not when adjustment was done for other risk factors [17]
– **Obesity**
– **General lack of movement**, long periods of sitting with bent legs (air and car travel, computer work)
– **Immobilization:** Illnesses requiring long periods of bed rest, injuries from accidents, bone fractures, surgery, plaster casts
– **Other illnesses:** Malignancies and myeloproliferative diseases, cardiac insufficiency, infections, nephrotic syndrome
– **Central venous catheters**
– **Pregnancy**, **puerperium**

The risk of arterial thromboembolic events or cerebrovascular insults increases with:
– Age
– Cigarette smoking
– Positive family history, i.e. occurrence of arterial thromboembolic events in a sibling or parent < 50 years of age. If hereditary predisposition is suspected, a medical specialist should be consulted before a decision to use a COC is made.
– Obesity (BMI > 30 kg/m^2)
– Dyslipoproteinemia
– Arterial hypertension
– Migraines
– Valvular heart disease, atrial fibrillation, cardiac insufficiency
– Postpartum
– Diabetes mellitus
– Other diseases: Malignancies and myeloproliferative diseases, vasculitis, chronic inflammatory diseases such as rheumatoid arthritis

Note: The presence of a major risk factor or multiple risk factors for venous or arterial disorders can also be a contraindication for COC prescriptions.

2.3. Clinical Diagnosis of Thromboembolism

2.3.1. Symptoms

Typical symptoms of deep vein thrombosis in the leg (Fig. 4):
– Swelling
– Spontaneous, strain-dependent pain alleviated by elevation
– Tenderness from pressure on inner foot and along vein with the thrombosis
– Pain in the calf on flexing the foot
– Increased prominence of visible veins

Table 2. Risk factors for venous thromboembolism. Mod. from: [Scottish Intercollegiate Guidelines section 10]

Age Exponential increase in risk with age. In the general population: < 40 years: annual risk 1/10,000 60–69 years: annual risk 1/1,000 > 80 years: annual risk 1/100 (May reflect immobility and coagulation activation)
Weight 3-fold risk if obese (body mass index > 30 kg/m^2) (May reflect immobility and coagulation activation)
Varicose veins 1.5-fold risk after major general/orthopaedic surgery, but low risk after varicose vein surgery
Previous VTE Recurrence rate 5%/year, increased by surgery
Thrombophilia Low coagulation inhibitors (antithrombin, protein C or S) Activated protein C resistance (e.g. factor V Leiden) High coagulation factors (I, II, VIII, IX, XI), prothrombin G20210A Antiphospholipid syndrome High homocysteine
Other risks for thrombotic states Malignancy: 7-fold increased risk compared with the general population Heart failure Recent myocardial infarction/stroke Severe infection Inflammatory bowel disease, nephrotic syndrome Polycythaemia, paraproteinaemia Beheçt's disease, paroxysmal nocturnal haemoglobinuria
Hormone therapy Oral combined contraceptives, HRT, raloxifene, tamoxifen (3-fold risk) High-dose progestogens (6-fold risk)
Pregnancy, puerperium 10-fold risk*
Immobility Bed rest > 3 days, plaster cast, paralysis (10-fold risk) Risk increases with duration
Prolonged travel see text
Hospitalisation Acute trauma, acute illness, surgery (10-fold risk)
Anaesthesia 2-fold greater risk for general (versus spinal/epidural)
* Note: Puerperium risk > pregnancy

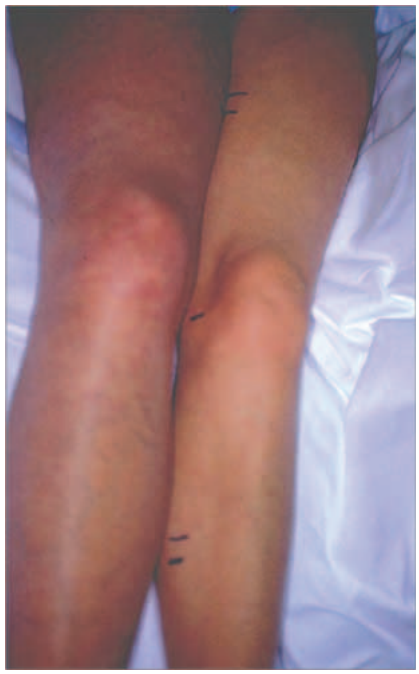

Figure 4. Venous thrombosis in the leg. Source: R. Bauersachs.

Typical symptoms of pulmonary embolism:
- Sudden or gradual dyspnea, during exertion or at rest depending on the stage
- Respiration-related thoracic pain
- Therapy-resistant pneumonia of indeterminate origin
- Coughing, blood traces in sputum
- Tachycardia
- Syncope

Note: The symptoms are extremely variable. All symptoms can occur either individually or in combination. Deep thromboses and pulmonary embolism can also occur without symptoms.

Possible symptoms of a venous (sinus) or arterial thrombosis (insult) in the central nerve system:
- Unusual, strong and/or persistent headache
- Impaired vision: sudden partial or complete loss of sight, double vision
- CNS symptoms, slurred speech or aphasia, vertigo, sudden weakness or pronounced numbness on one side or in one part of the body, impaired co-ordination
- Collapse with or without focal seizures

Thromboses can occur less frequently in other locations, such as venous thromboses in the arm including swelling with or without pain, or in the mesentery (possibly acute abdomen), or myocardial infarction.
- COC users should be strongly urged to consult a physician if they show signs of thrombosis.

2.3.2. Recurrent Venous Thromboembolism

Around 30% of patients with VTE in their histories show a recurrence within 10 years, with the highest risk in the first year following the initial diagnosis [18, 19].

2.3.3. Summary
- Identification of venous thrombosis and resulting pulmonary embolism is crucial for prompt treatment. Unrecognized DVT carries a high risk of pulmonary embolism, and unrecognized pulmonary embolism is linked with high mortality.
- Typical symptoms of DVT such as pain, swelling and/or tautness in the leg should be reported as promptly as possible to a physician in order to initiate diagnostic procedures. The Wells

Table 3. Wells Score for determining clinical probability of venous thrombosis in the leg (following German S2 guideline on diagnosing and treating venous thrombosis and pulmonary embolism, 2010) [20].

Clinical features	Score
Active cancer	1.0
Paralysis, paresis, recent plaster immobilization of lower limb	1.0
Bed rest (> 3 days); major surgery (< 12 weeks)	1.0
Pain/stiffness along deep venous system	1.0
Entire leg swollen	1.0
Calf swelling > 3 cm compared to asymptomatic leg	1.0
Pitting edema	1.0
Collateral superficial veins	1.0
Previous documented DVT	1.0
Alternative diagnosis at least as likely as DVT	–2.0

Score ≥ 2.0: high probability of venous thrombosis in the leg; score < 2.0: probability of venous thrombosis in the leg not high

Table 4. Wells Score for determining clinical probability of pulmonary embolism (following German S2 guideline on diagnosing and treating venous thrombosis and pulmonary embolism, 2010) [21]

Clinical features	Score
Previous venous thrombosis or pulmonary embolism	+1.5
Recent surgery or immobilization	+1.5
Cancer	+1
Hemoptysis	+1
Heart rate > 100 beats/minute	+1.5
Clinical symptoms of venous thrombosis	+3
Alternative diagnosis less likely than pulmonary embolism	+3

Score 0–4: Pulmonary embolism unlikely; score > 4: Pulmonary embolism likely

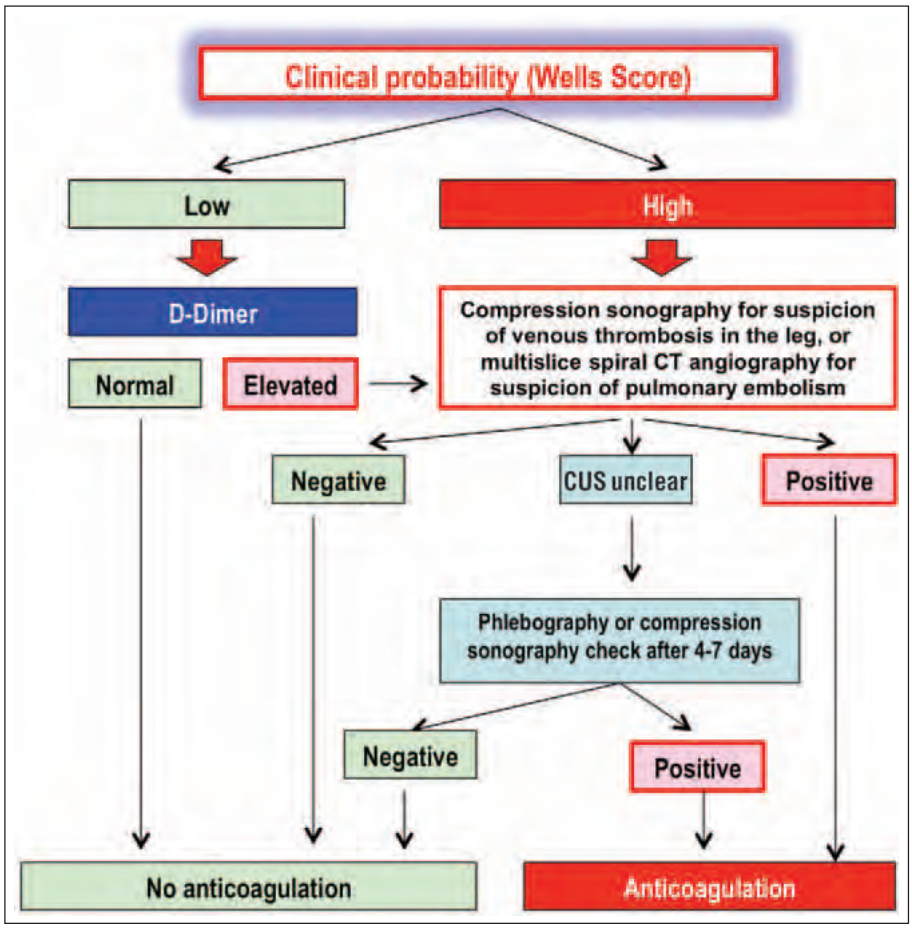

Figure 5. Diagnostic algorithm for venous thrombosis in the leg or pulmonary embolism for patients with stable hemodynamics. Mod. from [German S2 guideline on diagnosing and treating venous thrombosis and pulmonary embolism, 2010]. (CUS = compression sonography)

Table 5. Checklist for typical symptoms of blood clots

ACHES checklist for signs of arterial or venous thrombosis

A = Abdominal pain

C = Chest pain: sudden appearance and spread into left arm; sudden strong coughing without apparent cause
Sudden shortness of breath

H = Headache: New occurrence, long duration, one-sided, worsening of a migraine, crescendo character, scotoma, impaired speech

E = Eye problems: Impaired vision, partial or complete blindness or double vision

S = Swelling of the leg: strong pain and/or swelling of one leg

Additional symptoms: Weakness, numbness in one part of the body, dizziness or faintness

Score can be used to estimate the clinical probability of venous thrombosis in the leg (Tab. 3) or pulmonary embolism (Tab. 4). It combines examination results with VTE risk factors [21]. However, because the Wells Score cannot reliably diagnose or exclude a thrombosis, it may only be used in conjunction with other diagnostic parameters (see the diagnostic algorithm for venous thrombosis in the leg and pulmonary embolism in Figure 5).

– Patients should also be acquainted with the "ACHES" checklist for early warning signs of venous and arterial occlusion (Tab. 5).

2.4. Clinical Factors for Assessing the Risk of Coronary Heart Disease and VTE

2.4.1. Family History

Value of family history of venous thrombosis as a predictive factor for individual risk, also with respect to thrombophilic factors:

A family history of venous thrombosis can indicate the presence of genetic risk factors. Carriers of genetic factors have a higher risk of first-time venous thrombosis, and a higher risk still if environmental factors are also present. For example, factor V Leiden mutation synergistically increases the risk of venous thrombosis for women who take oral contraceptives [22]. Because general laboratory screening for thrombophilic factors is not cost-effective [11, 23], research is focusing on identifying criteria that increase the probability of finding

genetic risk factors in laboratory tests. Family history is one of these criteria. Various studies have examined the value of family histories as surrogate parameters for identifying known genetic risk factors for venous thrombosis [24–28]. These studies suggest that family histories are not very suitable for identifying known genetic risk factors. Some studies, however, have shown a link between family history and the occurrence of venous thrombosis [29, 30]. This also applies to OC users. The **LASS study**[1] showed that COC users with a positive family history for VTE showed a threefold higher VTE risk than COC users with a negative family history [17]. The question also arises of whether family history is of additional value in predicting individual risk of venous thrombosis when genetic risk factors have already been identified. The case control study by Bezemer et al. (2009) [31] addresses this issue.

Case-control study by Bezemer et al. (2009) [31]:

- **Study objective:** The case-control study by Bezemer et al. (2009) [31] examined the value of family history for determining the risk of venous thrombosis in connection with known risk factors.
- **Study population:** A multivariant analysis of environmental and genetic risk factors for venous thrombosis was performed as part of a population-based case-control study that used blood samples and information about family and environmental factors from 1,605 patients with first-time venous thromboses and from 2,150 control persons.
- **Definition of family history:** Patients were asked whether their parents, brothers or sisters had had a venous thrombosis, and if so at what age. Because the patients' partners served as the control persons, children were not included in these histories. A family history was considered positive if at least one of these first-degree relatives had had a venous thrombosis.
- **Results (see Table 6):** A total of 505 patients (31.5%) and 373 control persons (17.3%) reported a venous thrombosis in one or more first-degree relative. A positive family history increased the risk of venous thrombosis by a factor of more than 2 (odds ratio 2.2, 95% confidence interval 1.9–2.6), and a positive family history with more than one relative increased the risk by a factor of up to 4 (3.9, 95% CI: 2.7–5.7). Family history correlated only poorly with known genetic risk factors. Family history correlated with the occurrence of venous thrombosis in patients both with and without genetic or environmental risk factors. The risk of venous thrombosis increased with the number of demonstrated risk factors. For persons with genetic and environmental risk factors and a positive family history, the risk was up to 64 times higher than for those who had a negative family history and no known risk factors.
- **Conclusions:** Family history is a risk indicator for first-time venous thrombosis, regardless of whether other risk factors are identified. In clinical practice, family history could be more useful than laboratory testing for thrombophilia in assessing the risk of venous thrombosis.

Summary:

- Family history of deep venous thrombosis and pulmonary embolism, which is reported by approximately 3% of women of fertile age, is a strong predictor for the risk of VTE.
- Family history of coronary heart disease (CHD): Occurrence in parents before the age of 45 years (some sources use 50): Myocardial infarction in the mother; stroke, thrombosis, thromboembolism in either parent.
  Diseases/conditions in the patients' grandparents and in the siblings of their parents can be added to the assessment.
  For CHD risk above and beyond VTE risk, metabolic conditions including lipid metabolic disorders, diabetes mellitus, hypertension etc. also play a role.
- Family history of fatal myocardial infarction/stroke before the age of 50, which is reported by approximately 2% of women in fertile age, is a strong predictor of cardiovascular risk [9].
- If family history is positive for cardiovascular disease, laboratory testing may be needed for further clarification (e.g. thrombophilia parameters for VTE, lipid status for arterial thromboembolism), possibly also family testing.
- Family history of cardiovascular disease is an accurate predictive parameter for assessing probability of same in the patient and other family members.

2.4.2. Risk Factor: Travel

The following analysis is based on a 2010 Internet publication from the Centers of Disease Control in Atlanta, USA (Barbeau: Deep Vein Thrombosis and Pulmonary Embolism 2010)[2] that takes into account surveys and meta-analyses by Anderson et al. (2003) [32], Goodacre et al. (2005) [33], Kuipers et al. (2007) [34, 35], and Geerts et al. (2008) [36].

It examined known risk factors and different types of travel. A population-based case-control study of adults who were treated for a (first-time) VTE showed that long periods of travel (≥ 4 hours) double the risk of VTE. The risk increased most in the first week after travel, but remained elevated for two months. Air travel did not show a different effect from bus, rail or car travel, which suggests that the increased risk from air travel is due primarily to the length of inactivity. Additional risk factors include factor V Leiden mutation, oral contraceptives for women, BMI > 30 kg/m^2, and height > 190 cm. Some of these effects were most prevalent for air travel. In addition, persons under 160 cm in height only showed a greater VTE risk after longer periods of air travel. These results suggest that additional factors combine with air travel to play a role in elevated VTE risk.

Clinical Studies

Two subsequent retrospective cohort studies examined VTE frequency and air travel.

The first is a cohort study of 2,630 healthy Dutch commercial pilots [37]. The incidence of VTE in this group was 0.3 per 1,000 person-years. When the data were adjusted for age and sex, the rate did not differ from that for the general Dutch population. There was no

[1] http://clinicaltrials.gov/ct2/show/NCT00676065

[2] http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter2/deep-vein-thrombosis-pulmonary embolism.aspx

Table 6. Family history and VTE. Mod. from [31], with permission.

Family History[a]	No. (%)		Odds Ratio (95% CI)	
	Patients with venous thrombosis	Control subjects	Per stratum of type of risk identified	Relative to the group with no known riskfactors and fegative family history
No Known Risk Factors				
All	n = 389	n = 1538	…	…
Negative	261 (67.1)	1286 (83.6)	1 (Reference)	1 (Reference)
Positive				
Any relative	128 (32.9)	252 (16.4)	2.5 (1.9–3.2)	2.5 (1.9–3.2)
Relative < 50 y	53 (13.6)	98 (6.4)	2.7 (1.9–3.8)	2.7 (1.9–3.8)
> 1 Relative	23 (5.9)	27 (1.8)	4.2 (2.4–7.4)	4.2 (2.4–7.4)
Environmental Risk Factors Only[b]				
All	n = 823	n = 378	…	…
Negative	596 (72.4)	310 (82.0)	1 (Reference)	9.5 (7.8–11.5)
Positive				
Any relative	227 (27.6)	68 (18.0)	1.7 (1.3–2.4)	16.4 (12.2–22.2)
Relative < 50 y	107 (13.0)	27 (7.1)	2.1 (1.3–3.2)	19.5 (12.5–30.4)
> 1 Relative	39 (4.7)	4 (1.1)	5.1 (1.8–14.3)	48.0 (17.0–135.6)
Genetic Factors Only[c]				
All	n = 130	n = 196	…	…
Negative	71 (54.6)	150 (76.5)	1 (Reference)	2.3 (1.7–3.2)
Positive				
Any relative	59 (45.4)	46 (23.5)	2.7 (1.7–4.4)	6.3 (4.2–9.5)
Relative < 50 y	33 (25.4)	15 (7.7)	4.6 (2.4–9.1)	10.8 (5.8–20.2)
> 1 Relative	14 (10.8)	6 (3.1)	4.9 (1.8–13.4)	11.5 (4.4–30.2)
Environmental and Genetic Factors				
All	n = 263	n = 47	…	…
Negative	172 (65.4)	40 (85.1)	1 (Reference)	21.2 (14.7–30.6)
Positive				
Any relative	91 (34.6)	7 (14.9)	3.0 (1.3–7.0)	64.1 (29.4–139.8)
Relative < 50 y	47 (17.9)	4 (8.5)	2.7 (0.9–8.0)	57.9 (20.7–162.1)
> 1 Relative	21 (8.0)	3 (6.4)	1.6 (0.5–5.7)	34.5 (10.2–116.5)

CI: confidence interval; [a]: History of venous thrombosis among parents, brothers, and sisters; [b]: Surgery, injury, immobilization, and pregnancy or puerperium within 3 months before the index date, use of oral contraceptives or hormone therapy at the index date, and diagnosis of malignancy within 5 years before or within 6 months after the index date; [c]: Low levels of antithrombin, protein C, or protein S; factor V Leiden mutation; or prothrombin 20210 mutation

association between VTE incidence in the pilots and the number of hours they flew.

The second study examined 8,755 employees of several international organizations [34]. VTE frequency following flights of over 4 hours was 1.4 per 1,000 person-years. The absolute risk for VTE was given as 1 per 4,656 flights. The VTE rate for women was higher, especially for those taking oral hormonal contraceptives. The incidence was also higher for persons with BMI > 25 kg/m^2 and height < 1.65 m or > 1.85 m. VTE risk increased with flight duration and the number of flights during an 8-week period, with a 3-fold risk for persons who took five or more long-distance flights (≥ 4 hours). Each additional flight increased the risk of VTE by a factor of 1.4. The risk was highest in the first two weeks following a long-distance flight, and returned to baseline after 8 weeks.

Both studies examined population groups that were younger (average age 35–40 years) and healthier than the general population, so the results are not transferrable to a population group with heightened risk.

Preventive Measures for Travellers

Several randomized, controlled studies have assessed the effect of preventive measures on the risk of VTE following air travel [38][3].

All the studies examined the risk of asymptomatic DVT in travelers for flights of ≥ 7 hours. All travelers were encouraged to exercise at regular intervals during the flight and to drink only non-alcoholic beverages. Ultrasound tests were done between 90 minutes and 48 hours post-flight to determine the presence of DVT in the leg. The effect of

[3] http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter2/deepvein-thrombosis-pulmonary-embolism.aspx; http://www.who.int/cardiovascular_diseases/wright_project/phase1_report/WRIGHT%20REPORT.pdf

compression stockings, aspirin, low molecular-weight heparin and various natural extracts with anti-coagulatory properties were examined. None of the pharmacological interventions showed a significant effect. Compression stockings (10–20 mmHg and 20–30 mmHg) reduced the risk of asymptomatic DVT. Four travelers in one study, however, developed superficial thrombophlebitis after wearing compression stockings. None of the travelers participating in the studies showed symptomatic DVT or pulmonary embolism.

All travelers are encouraged to ensure sufficient hydration, wear loose-fitting clothing and flex their calves at regular intervals on extended trips. Compression stockings show a favorable effect if other VTE risk factors are present. Currently there are no convincing data showing that pharmacological interventions significantly reduce the risk of VTE from traveling.

Table 7. Risk of venous thromboembolism in surgical patients without prophylaxis (According to Geerts et al. (2001) [41] and Geerts et al. (2004) [42].

Risk category	Deep vein thrombosis (%)		Pulmonary embolism (%)	
	Calf	Proximal	Clinical	Fatal
Low risk – minor surgical operations, age < 40 years, no additional risk factors*)	2.0 %	0.4 %	0.2 %	< 0.01 %
Moderate risk – minor surgical operations with additional risk factors*) **or** surgical operations in patients aged 40–60 without additional risk factors	10–20%	2–4%	1–2%	0.1–0.4%
High risk – surgical operations in patients > 60 years **or** surgical operations in patients aged 40-60 years with additional risk factors*)	20–40%	4–8%	2–4%	0.4–1.0%
Highest risk – surgical operations in patients > 40 years with multiple risk factors **or** hip or knee arthroplasty **or** major trauma or spinal cord injury	40–80%	10–20%	4–10%	0.2–5%

*Additional risk factors include one or more of the following: advanced age, cancer, prior venous thromboembolism, obesity, heart failure, paralysis, or presence of a molecular hypercoagulable state (eg, protein C deficiency, factor V Leiden).

Summary of recommendations to prevent VTE from long-distance travel [36, 39]:

- The following general measures are recommended for travelers spending > 8 hours on an airplane: avoid tight clothing on the lower extremities and around the waist, ensure adequate fluid intake, and exercise (flex) calf muscles on a frequent basis (grade 1C).
- These same general measures are recommended for long-distance travelers with additional VTE risk factors. If active thrombosis prevention is under consideration on account of elevated VTE risk, properly fitted knee-length graduated compression stockings (GCS) that provide pressure of 15–30-mmHg (grade 2C) for the ankle area can be recommended, or a single prophylactic pre-flight shot of low molecular-weight heparin (LMWH) (grade 2C).
- Aspirin is not recommended to long-distance travelers as a preventive measure for venous thrombosis (grade 1B).

Risk groups for travel-related thromboembolism, following the International Consensus Statement by Schobersberger et al. (2008) [40]:

Group 1: Low Risk
Long-distance travelers without risk factors listed for Groups 2 and/or 3

Group 2: Medium Risk
Presence of two or more of the following factors

- Oral contraception
- Hormone replacement therapy
- Pregnancy or puerperium
- Family history of venous thrombosis
- Documented thrombophilia
- Marked varicose veins, chronic venous insufficiency
- Obesity (BMI > 30)
- Age > 60 years

Group 3: High Risk

- Previous VTE
- Manifest malignancy or other serious disease
- Immobilization, e.g. plaster cast
- Major recent surgery

2.4.3. Risk Factor: Surgery
Perioperative Use of Hormonal Contraceptives
The American College of Chest Physicians [36] assigns surgical operations to 3 different categories for thrombosis risk:
Low risk: Minor operations on otherwise healthy, active patients.
Medium risk: Most general surgical, open gynecological and urological operations.
High risk: Hip and knee joint endoprostheses, hip fractures and spinal cord injuries. The thrombosis risks are shown in Table 7 [42].

Every type of combined hormonal contraception increases the risk of thrombosis. However, the current German thrombosis prevention guideline no longer recommends discontinuing COC use before surgery. This is due to the extended period of residual hypercoagulation of approximately 6 weeks following cessation of use and the risk of unplanned pregnancy. Instead, patients should be provided peri-operative with sufficient thromboprophylaxis (in accordance with the current thrombosis prevention guideline).

Citation from the German AWMF (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*) guideline on preventing venous thromboembolism (www.awmf.org/leitlinien/aktuelle-leitlinien/ll-liste/deutsche-gesellschaft-fuer-chirurgie.html): "A special evaluation of the LASS-Study on request of the FDA showed in the first three months after major orthopedic surgery a 7-fold higher risk for VTE when compared to OC use independent of any operation. Compared to non-users of OC the risk had been increased 2-fold [Dinger 2011, personal communication]. Despite a large study population of more than 17,000 women, this is not statistically significant." And "the risk of unplanned pregnancy if OC use is discontinued before surgery should be

weighed in relation to the reduced risk of thrombosis. Discontinuing OC use is not recommended. Users of hormonal contraceptives should receive physical and medication-based thromboprophylaxis before more extensive surgery".

The **LASS study** (http://clinicaltrials.gov/ct2/show/NCT00676065) showed a 7-fold higher VTE risk for OC users in the first three months following major surgery [Dinger, personal communication]. The authors therefore recommend for the (infrequent) cases that fertile women make long-term plans for major surgery (e.g. hip or knee replacement) that they discontinue OC use at least 6 weeks before surgery. In such cases, a 3-month period should also elapse before resuming COC use.

For minor surgery, hormonal contraception can be resumed or started for the first time 14 days after an ambulatory procedure or hospital discharge.

2.4.4. Summary

- Some coagulation factors return to normal only 2–3 months following discontinuation of oral hormonal contraceptives.
- Before every operation, surgeons should ask patients about possible use of combined oral contraceptives, vaginal ring, contraceptive patch or other forms of hormonal contraception.
- Women with oral contraceptives should receive peri-operative thromboprophylaxis according to the current thrombosis prevention guideline.

2.5. Diagnosing Venous Thrombosis in the Leg and Pulmonary Embolism

Correctly diagnosing venous thrombosis in the leg is essential for appropriate treatment and for preventing subsequent pulmonary embolism. To determine or exclude venous thrombosis in the leg and pulmonary embolism, medical associations recommend diagnostic algorithms. If used consistently, VTE lethality can be reduced (interdisciplinary German S2 guideline from the AWMF on diagnosing and treating venous thromboembolism and pulmonary embolism, 2010: **Diagnostik und Therapie der Venenthrombose und der Lungenembolie).** These algorithms cover the following:

- **Clinical diagnostic measures:** The clinical probability of venous thrombosis in the leg or of pulmonary embolism can be estimated using the Wells Score (Tab. 3, 4) and should be documented. The Wells Score covers typical clinical symptoms of VTE, and includes examining and palpating the affected part of the body as well as determining the presence of VTE risk factors. Because a clinical examination alone is not sufficient to determine or exclude VTE, further diagnostic measures should be undertaken (D-dimer test for lower clinical probabilities and imaging procedures for higher probabilities).
- **Laboratory tests:** A blood test to determine the D-dimer concentration is helpful in excluding VTE. This test should only be done after determining the clinical probability of VTE. D-dimers are degradation products of the proteolysis of cross-linked fibrin. They indicate increased fibrin formation with secondary fibrinolysis, as occurs with VTE. If the test is negative, it excludes VTE with a high probability. But the sensitivity of individual D-dimer tests varies, and is usually not 100%. It therefore has to be combined with a score (Wells) for the clinical probability of VTE. If the Wells Score shows a low clinical probability and the D-dimer concentration lies in the normal range, VTE can be excluded. If the clinical probability is low but the D-dimer concentration is elevated, further tests must be done. The same is true for high clinical probability of VTE with a normal D-dimer concentration. If the clinical probability is high, therefore, a D-dimer test can be omitted in favor of proceeding directly to imaging tests.
  Elevated D-dimer values, however, do not always indicate venous thrombosis. These values can be high for other reasons, such as following surgery or injury, during an infection, or in conjunction with a tumor. If the D-dimer test is positive, further diagnostic means must be undertaken to determine or exclude VTE.
- **Imaging procedures:** Actual diagnosis of venous thrombosis in the leg and pulmonary embolism is done by imaging procedures.
  The gold standard for diagnosing leg DVT in routine practice is non-invasive imaging by ultrasound, i.e. compression sonography (Fig. 6). It is considerably less stressful for patients than x-rays with contrast agents (phlebography).
- For diagnosing pulmonary embolism, multi-slice spiral CT pulmonary angiography is generally used for patients with stable hemodynamics. Imaging via ventilation/perfusion scintigraphy is also possible. Scintigraphy, however, yields a high proportion of non-usable diagnostic results. Pulmonary angiography is rarely indicated these days. Echocardiography is used in determining or excluding right ventricular dysfunction.

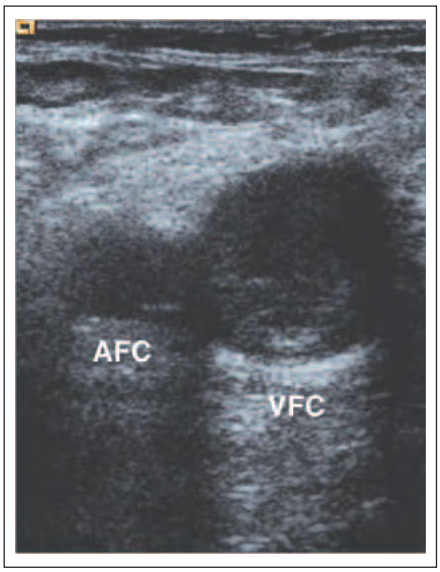

Figure 6. Venous thrombosis in the leg shown by compression sonography (thrombosis in right femoral vein – VFC). The vein is distended, with non-compressible diameter (AFC = common femoral artery). Source: B. Luxembourg.

2.5.1. Summary

- Diagnoses of venous thrombosis in the leg and pulmonary embolism should be based on algorithms that encompass the clinical probability of VTE, laboratory testing of D-dimer concentrations, and imaging procedures.
- **Deep venous thrombosis of the leg:** The gold standard for DVT diagnostics in daily practice is non-invasive ultrasound imaging as compression sonography.
- **Pulmonary embolism:** Multi-slice spiral CT angiography or ventilation/perfusion scintigraphy are non-invasive imaging tests for pulmonary embolism. Echocardiography is used to determine right ventricular dysfunction.

2.6. Summary

Prevalence of VTE: An estimated 1.1 million cases of venous thromboembo-

lism (including DVT and pulmonary embolism) occur every year in the European Union, and are associated with more than 150,000 deaths [2]. VTE is therefore a serious health problem that claims more victims annually in the EU than breast cancer, HIV/AIDS and traffic accidents. However, the risk is associated to a very high degree with age and hospitalization [3–5, 7], which means that VTE represents an enormous risk for certain population groups whereas the majority of the younger population faces only a very slight risk.

Mortality: Pulmonary embolism is the cause of death for approximately one out of every ten patients who die in hospital (1 percent of all patients admitted) [8].

Age dependency in women (per 10,000 women/year): < 20 years: 4.3; 20–29 years: 8; 30–39 years: 13; 40–49 years: 23.9; ≥ 50 years: 50.1) [9].

Symptoms of DVT and pulmonary embolism:
- Venous thromboembolism is underdiagnosed because its symptoms can often be non-specific or even absent at first.
- Typical symptoms of venous thrombosis in the leg are pain, sensitivity to pressure, edema, swelling, cyanotic skin coloring, and/or dilated superficial veins in the affected leg.
- DVT is often asymptomatic for bedridden patients on account of reduced hydrostatic pressure.
- The greatest risk associated with DVT is the possibility that a pulmonary embolism may develop. Typical symptoms of pulmonary embolism include thoracic pain, dyspnea, coughing, hemoptysis, treatment-resistant pneumonia, tachycardia and/or syncope. Pulmonary embolism is often the result of a number of different developments at different points in time, and its symptoms are often initially indistinct or even absent. Death can occur suddenly and unexpectedly.

Risk factors:
- Numerous hereditary and acquired risk factors can contribute to VTE. Typically more than one factor contributes to VTE pathogenesis, i.e. VTE is a multifactorial disease.
- Each patient's risk profile should be determined, and thromboprophylaxis measures should be considered for typical risk situations such as surgery or immobilization.
- Numerous thrombophilic factors elevate individual risk.
- Oral hormonal contraceptives and hormone replacement therapy also increase the risk by a factor of 2–6 for healthy women, and have a multiplicative effect on patients with known thrombophilic factors.

Early determination of risk:
- **Family history:** Family histories of cardiovascular conditions including VTE are an important instrument for determining risk.
- **Travel-related thrombosis:** The risk of VTE is increased by trips of 4 or more hours, regardless of whether they are by plane, car or bus. For trips of more than 8 hours, general measures are always recommended (e.g. exercise, sufficient hydration). Thromboprophylaxis consisting of suitable compression stockings or application of heparin (LMWH) are recommended only for high-risk patients; aspirin is not recommended. Patients taking oral contraceptives but without further DVT risk factors generally only have a low to medium risk of thrombosis from long-distance travel. Before departure, presence of any additional risk factors should be determined which could change the risk category assignment.

Diagnosis:
- Diagnoses of venous thrombosis in the leg and pulmonary embolism should be based on algorithms that encompass the clinical probability of VTE, D-dimer laboratory tests, and imaging procedures.
- **Deep venous thrombosis of the leg:** The gold standard for DVT diagnosis in regular practice is non-invasive ultrasound imaging as compression sonography.
- **Pulmonary embolism:** Multi-slice spiral CT angiography or ventilations/perfusion scintigraphy are non-invasive imaging tests for pulmonary embolism. Echocardiography is used in determining right ventricular dysfunction.

Thrombosis prevention guidelines:
The consensus guidelines from the American College of Chest Physicians (ACCP) [36] are revised every 2–3 years, and are considered the international standard. In Germany, the national guidelines published by the AWMF (*Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften*) need to be given preference. The German S3 thrombosis prevention guideline was issued in 2009 [43]. The German S2 guideline for diagnosing and treating venous thrombosis and pulmonary embolism was published by the AWMF in 2010

2.7. Important Websites: English Associations

Guidelines

Management of venous thromboembolism:
A Clinical Practice Guideline from the American College of Physicians and the American Academy of Family Physicians (2007) [44].

EAST Practice Parameter Workgroup for DVT Prophylaxis (2011) [45]

Prevention of venous thromboembolism:
Guideline from the National Institute for Health and Clinical Excellence (2010): Venous thromboembolism (surgical) [46].

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) (2008): Prevention of venous thromboembolism [36].

Oral contraceptives and the risk of venous thromboembolism:
Guideline from the Royal College of Obstetricians and Gynaecologists (2010): Venous Thromboembolism and Hormonal Contraception [47].

SOGC clinical practice guidelines: Oral contraceptives and the risk of venous thromboembolism: an update (2011) [48, 49].

3. Laboratory Tests and Patient Information/ Counseling

3.1. General Preliminary Remarks

Venous thromboembolism (VTE) is a multi-factor condition with roles played by environmental factors, acquired risk

factors such as age, excess weight and oral contraceptives, and hereditary factors. Numerous studies have investigated genetic factors in VTE, ranging from candidate gene studies to genome-wide association studies. They show that genetic variants lead either to an excess of prothrombotic factors or to a deficiency in anti-thrombotic factors.

Factor V Leiden mutation is the most often and best studied genetic predisposition factor for VTE, followed by the prothrombin G20210A mutation and deficiencies in protein S, protein C and antithrombin [50].

A large number of additional laboratory parameters and genetic variants associated with VTE risk have been studied. These have not been included in routine thrombophilia screening thus far because it is unclear how significant they are for treatment decisions in general practice. For example, there is a known association between blood group and VTE risk, with O and A2 showing a lower risk than other blood groups [51]. This association is based among other things on higher Willebrand factor and factor VIII levels – two known risk factors for VTE – in individuals who do not have blood groups O or A2. How and whether VTE risk changes here with the use of oral contraceptives is unclear. Blood group therefore does not play a role in prescribing oral contraceptives.

Various types of genetic polymorphism are often associated with only a slightly higher risk of thrombosis. For example, an association between VTE risk and polymorphism in the *CYP4V2* region was recently described, although the risk was only slightly elevated (odds ratio: 1.14–1.39) [52]. Moreover, this VTE risk was further weakened on adjustment for other VTE risk factors [52].

These examples show that a range of genetic determinants are involved in the risk of VTE which however play no role in clinical practice because it is entirely unclear what influence they have on VTE risk with the use of oral contraceptives.

Various individual factors increase the risk of VTE in connection with genetic thrombophilic factors. For example, carriers of factor V Leiden or prothrombin G20210A mutation show a multiple increased risk of VTE if they use oral hormonal contraceptives [53, 54], undergo hormone replacement therapy [55], or smoke cigarettes [56]. This suggests that for many individuals, genetic thrombophilic factors alone are not sufficient to trigger VTE. The accumulation of risk factors, which can also occur on a transient basis, can however trigger VTE. It is therefore more important in clinical practice to identify and avoid acquired risk factors than to determine a number of different types of polymorphism.

Table 8. Indications for thrombophilia testing

Thromboembolism at a young age
Recurrent thromboembolism of unclear origin
Thrombosis in atypical location (sinus veins, mesentery veins, etc.)
Suspicion of antiphospholipid antibodies (e.g. patient has systemic lupus erythematosus) or antiphospholipid syndrome
Three or more spontaneous miscarriages (possibly two depending on individual demand and distress)
Stillbirth
Consideration of oral contraception prescription with family history of thrombosis (first-degree or possibly second-degree relatives with thromboembolism before the age of 50)
Pregnancy or planned pregnancy with own history of thromboembolism

3.2. Indications for Thrombophilia Testing

Thrombophilia testing should only be performed if the results are of clinical significance regarding the patient's family, life situation, age, desire for children, etc.

From the perspective of gynecology, thrombophilia testing should be done if one of the symptoms or conditions described in Table 8 is present.

3.3. Laboratory Testing for Thrombophilia

Laboratory testing for thrombophilia should cover the following parameters in Table 9 a, b.

Although not advisable for the general population, thrombophilia screening makes sense for risk groups, e.g. women with a positive family history (multiple occurrence of thromboembolism in first-degree relatives or thromboembolism in first-degree relatives at a young age) before prescribing oral contraceptives.

Table 9a. Clinically relevant thrombophilia markers

APC resistance test for factor V Leiden mutation, or genetic testing right away for factor V Leiden mutation
Prothrombin G20210A mutation
Antithrombin
Protein C
Protein S
Factor VIII
Antiphospholipid antibodies (lupus anticoagulants, anti-cardiolipin antibodies, anti-β2-glycoprotein I antibodies)

Accumulated risk factors can also be a contraindication for prescribing COCs. Special mention should be given here to cardiovascular risk factors linked to a higher risk of arterial thromboembolism (e.g. age > 35 years plus strong nicotine use or presence of multiple cardiovascular risk factors such as obesity, arterial hypertension, or known hyperlipidemia). Additional tests are recommended in individual cases, e.g. blood glucose, HbA1c, lipid status, lipoprotein (a), thyroid hormones, homocysteine, CRP, blood counts, creatinine.

If homocysteine levels are high, it may be necessary to clarify the cause; in the event of low to medium hyperhomocysteinemia, benefits of folic acid, vitamin B6 and B12 regarding vascular occlusion are not confirmed.

3.4. Preliminary Considerations for Thrombophilia Testing

What should be considered when taking blood samples and interpreting the results?

Numerous conditions and medications influence some thrombophilia parameters. These especially include pregnancy and puerperium, ovulation inhibitors, anti-coagulants, and acute-phase reactions. Potential influences are listed in Table 10.

The following parameters are not influenced:

- Molecular genetics (factor V Leiden mutation, prothrombin G20210A mutation)
- antiphospholipid antibodies (anti-cardiolipin antibodies, β2 glycoprotein I antibodies) except lupus anticoagulants

Table 9b. Diagnostic tests for thrombophilia. Mod. from [Seligsohn U, Lubetsky A, Genetic Susceptibility to Venous Thrombosis. N Engl J Med 2001; 344: 1222–31].

Test	Genetic basis for test	Conditions or states that can influence test results	Factors that can distort determination of thrombophilia parameters
High significance			
APC resistance	Factor V Leiden mutation (other polymorphisms/mutations not part of routine testing)	Lupus anticoagulants, antibodies against protein C. Only for certain test procedures: (pregnancy, oral contraceptives, increased factor VIII level, protein S deficiency)	Lupus anticoagulants, thrombin inhibitors, direct factor Xa inhibitors vitamin K antagonists, heparin in high concentrations, coagulation factor deficiencies (in part only for certain test procedures)
Factor V Leiden mutation (heterozygous/homozygous)	G1691A in exon 10 of factor V gene		Genetic testing not suitable following liver or allogeneic stem cell transplants
Prothrombin mutation	G20210A in a non-coding area of prothrombin gene		Genetic testing not suitable following liver or allogeneic stem cell transplants
Elevated factor VIII level		Physical and mental stress, pregnancy, oral contraceptives, increased age, acute-phase response, liver disease, corticoid treatment, Cushing syndrome, hyperthyroidism	Lupus anticoagulants, unfractionated heparin in therapeutical doses, thrombin inhibitors and direct factor Xa inhibitors can distort test procedures for factor VIII activity
Lupus anticoagulants		Infectious diseases	High heparin concentrations, vitamin K antagonists, thrombin inhibitors, direct factor Xa inhibitors
Anticardiolipin and β2-glycoprotein I antibodies		Infectious diseases	
Intermediate significance			
Protein C deficiency	>250 different mutations	Acute thrombosis, treatment with vitamin K antagonists, vitamin K deficiency, liver disease, sepsis, disseminated intravascular coagulation, antibodies against protein C	
Protein S deficiency	>200 different mutations	Acute thrombosis, treatment with vitamin K antagonists, vitamin K deficiency, pregnancy, oral contraceptives, liver disease, malignancies, treatment with asparaginase, sepsis, disseminated intravascular coagulation, chronic inflammatory intestinal disease, HIV, nephrotic syndrome, antibodies against protein S (e.g. with lupus erythematosus)	Lupus anticoagulants, thrombin inhibitors, heparin and factor V Leiden mutation can distort test procedures for protein S activity
Antithrombin deficiency	>200 different mutations	Acute thrombosis, heparin treatment, preclampsia, liver disease, sepsis, disseminated intravascular coagulation, nephrotic syndrome, treatment with asparaginase, exudative enteropathy, major surgery	Thrombin inhibitors and direct factor Xa inhibitors can distort test procedures for AT activity
Low significance			
Elevated homocysteine level	Mutations in genes encoding methyltetrahydrofolate reductase (MTHFR) or cystathionine β-synthase	Deficiencies of folic acid, vitamin B6 or vitamin B12; increased age, renal disease, smoking, hypothyroidism, malignancies, medication (e.g. MTX, phenytoin)	
Dysfibrinogenemia	>200 different mutations	Liver disease, disseminated intravascular coagulation	Thrombin inhibitors

Table 10. Influence of different 2nd and 3rd-generation progestogens, progestogen-only preparations, pregnancy, vitamin K antagonists, and acute phase reaction during thrombosis on different clotting parameters

	Protein S	Protein C	Antithrombin	D-dimer	Lupus anti-coagulants	Factor VIII
2nd-generation OVH	decrease possible	slight increase possible	–	slight increase possible	–	slight increase possible
3rd-generation OVH	decrease	slight increase possible	slight increase possible	slight increase possible	–	increase
Progestogen-only Pill	increase possible	slight decrease possible	–	–	–	–
Pregnancy and puerperium (up to 6 weeks postpartum)	strong decrease possible	– (slight increase possible toward end of pregnancy)	–	marked increase with duration of pregnancy	–	marked increase
Vitamin K antagonists (phenprocoumon, warfarin)	marked decrease	marked decrease	–	increase possible when drug use stopped	false positive results possible, if diagnostic guidelines not followed (confirmation and mixing tests)	–
Heparin treatment	–	–	decrease	possible increase when drug use stopped	false positive results possible, if diagnostic guidelines not followed (confirmation and mixing tests)	Test usually aPTT-dependent, therefore influence possible with unfractioned heparins if no heparin neutralizer used
Acute phase, acute thrombosis	consumption-dependent slight decrease possible	consumption-dependent slight decrease possible	slight decrease possible	elevated	–	often strongly elevated

OVH = Ovulation inhibitor; – = no influence

Table 11. Notes for taking and sending blood samples for thrombophilia tests

Test	Material	Note
Molecular genetic (factor V Leiden mutation, prothrombin G20210A mutation) and possibly other PCR analyses	1–5 ml EDTA blood sample is transportable, can be sent by post	Do not centrifuge or freeze EDTA blood sample!
Clotting tests (protein C, protein S, antithrombin, lupus anticoagulants, APC resistence, factor VIII)	1–3 ml frozen citrate plasma, strongly centrifuge citrate tube 2× and pipette supernatant without cells into neutral tube. Store and transport at –20 °C.	Alternatively the citrate blood can be sent as whole blood to the lab via courier within 4 hours. Citrate **whole** blood should never be frozen or refrigerated!
Homocysteine	1–3 ml EDTA blood. Immediately centrifuge blood tube and store plasma separately because homocysteine can otherwise enter plasma from erythrocytes and lead to false high results! If immediate centrifuging is not possible, store sample on ice. Use of special tubes (acid citrate, fluoride) can increase sample stability.	Fasting blood samples should be taken.

Depending on the test procedure, APC resistance can be influenced by pregnancy and oral contraceptives as well as by high doses of anticoagulants. Other test procedures are available, however, that are not subject to these influences (information can be provided by clinical laboratories).

Care should therefore be taken to exclude the above-mentioned influences on thrombophilia testing. **If this is not possible, always make sure to advise the laboratory of the clinical situation (e.g. pregnancy week, current medication)** and have the results evaluated by an experienced hemostaseologist.

3.4.1. Diagnostic Samples

See the notes in Table 11 on taking and transporting blood samples for thrombophilia testing.

3.5. Counseling Patients about Risk Factors

3.5.1. General

Clear information is key for counseling patients and deciding on the right treatment and/or contraception. In Germany, legislation went into effect on February 1st 2010 that stipulates extensive counseling with patients before and after genetic screening. Counseling must include discussion of the relevant findings

in Table 9a as well as of the following clinical parameters. For acne patients, every elevated risk factor requires consideration of non-hormonal dermatological treatment to minimize individual risk as much as possible.

Clinical parameters that must be considered when counseling patients about hormonal contraception:

Age: The risk of suffering a thromboembolic event increases exponentially with age. The risk is approximately 1 in 10,000 (0.01%) per year in those under 40 years of age, approximately 1 in 1,000 (0.1%) at the age of 60, and approximately 1 in 100 above the age of 80 (1%) [13–16, 57].

However, the VTE incidence rate for women of fertile age who do not take hormonal contraception has been corrected upwards over recent years, to approximately 4 VTE per 10,000 woman-years [9].

Family history: Risk increases with positive history of cardiovascular disease in the parents below the age of 45.

Patient history: History of venous or arterial thromboembolism, localization and degree of seriousness of thromboembolism, causal connection with exogenous events, evaluation in context of family history, bodily status, additional risk factors, and laboratory confirmed thrombophilia.

Contraception duration: VTE develops most frequently during first year of OC intake [9, 57].

The following individual risk factors in patient history (**Caution:** For long-term OC use, the potential for these symptoms/conditions to appear/reappear must be regularly determined, and indications for continued use reevaluated).

Cardiac disease: coronary heart disease, cardiac insufficiency, valvular heart disease, atrial fibrillation (exclude hyperthyroidism).

Thyroid: thyroid dysfunction (hyper/hypothyroidism).

Cigarette smoking: Although several studies have described cigarette smoking as increasing the risk of VTE [4, 58–66] it probably cannot be viewed as a relevant risk overall [67–69]. A greater risk of arterial cardiovascular disease, however, must be considered.

Obesity: Increased risk of VTE and arterial cardiovascular disease.

Also, as body weight increases, contraceptive effectiveness decreases for both Implanon® (should be removed or replaced before three years in overweight women, see summary of product characteristics – SPC) and Evra® (≥ 90 kg, see SPC). This has also been discussed for oral contraceptives: An association was not found in the EURAS study, but the INAS study in the USA, with a high percentage of overweight participants, has shown a decrease in effectiveness for women of BMI > 35 that is statistically significant but of minor clinical relevance [70, 71].

Immobilization: Increased risk with immobilization (e.g. following accidents or surgery with long periods of bed rest), plaster casts, lack of activity due to acute infections or inflammatory diseases. Hormonal contraception need not be interrupted before surgery if the surgeon is notified and appropriate pre- and post-operative heparin treatment is administered (see also section 2.4.3).

Lipid metabolic disorder: Increased risk of arterial cardiovascular disease.

Diabetes mellitus: Increased risk of arterial cardiovascular disease. See also contraception recommendations for patients with diabetes mellitus.

Arterial hypertension: Increased risk of arterial cardiovascular disease.

Malignancies, myeloproliferative diseases: Increased VTE risk, in part also greater risk of arterial thromboembolism.

Nephrotic syndrome: Increased risk of venous and arterial thromboembolism.

Migraines: Increased risk with first occurrence or worsening of migraines, marked hemiplegic and/or crescendo character, scotoma.

Lupus erythematosus: Increased risk with inflammatory reactions, which can affect all parts of the body including skin, joints and organs. Increased risk of venous and arterial thromboembolism especially if antiphospholipid antibodies are present.

Postpartum: Increased VTE risk shortly after giving birth! Risk: 51 per 10,000 births in the first three months postpartum [72].

See also recommendations for women who are nursing!

3.5.2. Patient Counseling about Genetic Screening

As of February 1, 2010, the Genetic Diagnosis Act (*Gendiagnostikgesetz,* or GenDG) in Germany stipulates that patients must receive appropriate counseling and provide written consent before genetic testing is done. Once the results are obtained, patients must receive appropriate counseling again, which must be documented, from a specially qualified physician (e.g. human geneticist or other specialist with relevant additional qualification).

Key information from the GenDG[4] is as follows (see footnote for German/English versions[5]).

The German Genetic Diagnosis Act (*Gendiagnostikgesetz,* GenDG) went into effect on February 1, 2010. The aim of this legislation is "to determine the requirements for genetic examinations … and to prevent any discrimination and disadvantage based on genetic characteristics, especially in regard to the duty of the state to protect human dignity and to ensure the individual right to self-determination via sufficient information" (§1 GenDG). The Act has special consequences for all physicians who perform or initiate genetic analyses. Genetic testing and counseling must be both initiated and performed by physicians. A distinction must be drawn between diagnostic and predictive testing. Predictive analyses require consultation with a physician who specializes in human genetics.

[4] www.gesetze-im-internet.de/bundesrecht/gendg/gesamt.pdf

[5] https://www.eshg.org/fileadmin/www.eshg.org/documents/Europe/LegalWS/Germany_GenDG_Law_German_English.pdf.

Duty to inform (§9): Before every genetic test, the physician in charge must inform the patient about the purpose, type, scope and significance of the test. The GenDG stipulates that all remaining sample material be destroyed immediately after the test is concluded, and the documentation must be destroyed after 10 years. Patients must be informed that they can choose to have the documentation kept for longer periods of time. Patients must also be informed about risks associated with the testing, about their right not to be informed, and about the right to revoke their consent. This information can be provided via suitable reading material, or in person. The informational content must be documented in writing.

Consent (§8): Patients must sign that they have received adequate information and that they agree to have the planned genetic analysis performed. Consent must also clarify whether the results will be provided to further individuals besides the physician. Here too the patients have the right to revoke their consent.

Counseling (§10): When the results are available, the physician is to provide the patient with counseling based on specialist genetic knowledge. If the results yield signs of genetically conditioned illnesses other than the original indication for genetic testing, consultation with a physician specializing in human genetics is to be offered.

Consultation with a specialist in human genetics or medical doctor with certification in genetic examinations is required both before and after a **predictive** genetic test. This consultation should also and especially cover possible medical, psychological and social issues connected with the test and the results. The patient should also be informed of support measures for psychological and physical difficulties. The physician must document the content of the consultation.

3.5.3. Interpreting the Laboratory Results

This section includes basic information about thrombophilic parameters, as well as prevalence, associated VTE risk, and changes thereto with use of hormonal contraception, and also indications for thrombosis prevention. In addition to the medication described here for VTE risk situations (e.g. surgery, inactivity during acute illness, infections, immobilization of extremities via e.g. plaster casts), physical measures should also always be taken (early exercise and/or prevention of inactivity during illness wherever possible, as well as prophylactic stockings).

Hormonal contraceptives increase the risk of VTE, especially for women with thrombophilia. Because side effects and cost make it inadvisable to take thrombosis prevention medication on a continuous basis together with contraceptives in order to reduce the risk of VTE, the choice of contraception is especially important for women with thrombophilia.

3.5.3.1. Factor V Leiden Mutation

Factor Va is normally inactivated by activated protein C (APC). The factor V Leiden mutation is marked by guanine instead of adenine in nucleotide position 1691 in the factor V gene. This in turn destroys a cleavage site for APC in the factor V molecule (FVR506Q). The changed structure in the Leiden variant of factor V impairs the degradation of factor Va by APC (factor V becomes "resistant" to inactivation by APC) and factor Va retains its coagulation-promoting effect. This leads to an imbalance between coagulation-inhibiting and -promoting influences, which in turn increases the tendency for thromboses to develop (thrombophilia).

The APC-resistant phenotype can be determined in plasma samples. Tests for the APC-resistant phenotype show a sensitivity and specificity of 98–100% for factor V Leiden mutation. The genotype (factor V Leiden mutation, hetero- or homozygous) is determined by molecular genetic testing. It is an autosomal dominant hereditary condition.

Heterozygous carriers are found in the general European population with a frequency of 3–13%, homozygous carriers with a frequency of 0.2–1% [73]. In Asians and Africans, by contrast, the mutation occurs rarely (< 1%, [73]). Factor V Leiden mutation is commonly found in European VTE patients (10–50%).

Heterozygous carriers have an approximately 5-fold increased risk of VTE (95% confidence interval 4.4-5.5) [12]. The risk of thrombosis with homozygous factor V Leiden mutation was long overestimated. One study calculated an 80-fold increased VTE risk for homozygous carriers [74]. However, several studies and a meta-analysis by Gohil et al. have shown that the relative VTE risk in homozygous carriers is "only" approximately 10 times increased (95% confidence interval 6.7–13.3) [12, 75]. A meta-analysis by Segal et al. [76] determined a relative risk of 17.8 (7.98–39.89) for VTE occurrence in homozygous family members of patients with known factor V Leiden mutation.

A meta-analysis by **Wu et al.** [77] calculated the VTE risk (odds ratio) for women with factor V Leiden mutation taking oral contraception. Due to the small number of homozygous carriers, this meta-analysis unfortunately could not determine separate risk values for hetero- and homozygous carriers. The pooled analysis of hetero- and homozygous carriers (with a very small number of homozygous cases) taking oral contraception showed a 15.6-fold increased VTE risk (95% confidence interval 8.7–28.2) [77]. The VTE risk for homozygous carriers taking oral contraception has thus far not been sufficiently studied, but is presumably considerably higher than shown by the pooled analyses.

Continuous thrombosis prophylaxis is not necessary for patients who have not had VTE. Thrombosis prophylaxis in VTE risk situations consists of low molecular-weight heparin or fondaparinux. New oral anti-coagulants such as Rivaroxaban or Dabigatran can be used, but thus far are only authorized for VTE prophylactic purposes for major orthopedic surgery. Dosing is done in accordance with the German S3 guideline on preventing venous thrombosis (www.awmf.org). The significance of factor V Leiden mutation for the VTE recurrence risk and the duration of anticoagulation treatment post-VTE is discussed below.

3.5.3.2. Prothrombin G20210A Mutation

Prothrombin is the proenzyme of the serine protease thrombin, which converts fibrinogen to fibrin.

Substitution of adenine for guanine in position 20210 of the prothrombin gene

leads to higher plasmatic prothrombin levels, and is associated with an approximately three-fold higher risk of thrombosis (95% confidence interval 2.2–3.5) for heterozygous carriers [12]. This mutation is determined exclusively by molecular biological methods.

Heterozygous carriers are found in 1.7–3.0% of the general European population. Homozygous carriers are very rare (< 0.1 %, Rosendaal et al. [74]). On account of this low prevalence, the data is thus far not sufficient for estimating the VTE risk for homozygous carriers. A heterozygous prothrombin G20210A mutation is found in 7–16% of patients with VTE.

A meta-analysis by Emmerich et al. [54] showed a relative VTE risk of 7.14 (95% confidence interval 3.4–15.0) for women taking oral contraception; a meta-analysis by Wu et al. [77] showed a relative risk of 6.1 (95% confidence interval 0.8–45.6). These meta-analyses included data from both hetero- and homozygous carriers although with only a small number of homozygous participants. The VTE risk for homozygous carriers taking oral contraceptives is presumably considerably higher, but has thus far been little studied.

The same thrombosis prophylactic measures should be taken here as for factor V Leiden mutation.

3.5.3.3. Compound Heterozygotes for Factor V Leiden and Prothrombin G20210A Mutations

If both prothrombin G20210A and factor V Leiden mutations are present, there is a 4 to 15-fold increased relative risk of VTE (Wu et al. [77]: OR = 4.0 with a 95% confidence interval of 1.0–16.0, Emmerich et al. 2001 [56]: OR 14.7 with a 95% CI of 3.5-62.0; these analyses included hetero- and homozygous carriers but with a small overall number of homozygous cases).

The odds ratio for VTE with oral contraception for individuals carrying both the prothrombin G20210A and factor V Leiden mutations is 8-17 (Wu et al. 2005 [77]: OR = 7.9 with a 95% confidence interval of 1.7–37.4; Emmerich et al. [56]: OR = 17.0 with a 95% CI of 3.6–72.8; these analyses included hetero- and homozygous carriers but with a small overall number of homozygous cases).

The same thromboprophylaxis measures should be taken here as for factor V Leiden mutation.

3.5.3.4. Antithrombin Deficiency

Antithrombin (AT) is the major antagonist of thrombin, although it also inhibits other coagulation factors such as IXa, Xa and XIa. The effect of AT is accelerated multiple times by heparin.

Hereditary AT deficiency can result from reduced AT production. Blood levels show a parallel reduction of AT antigen and AT activity (type I AT deficiency). In type II AT deficiency, AT molecules form that show limited heparin- or thrombin-binding capacity; this type is characterized by lower AT activity while the antigen concentration is largely normal. With rare exception the patients are heterozygous carriers. Thus far only a few homozygous carriers with type II AT deficiency have been described [78]. This is due to embryogenic lethality of serious congenital AT deficiency.

Congenital AT deficiency is found in approximately 0.2% of the general population and in approximately 1–3% of patients with VTE.

AT deficiency is diagnosed by repeated testing of AT activity. This procedure identifies not only type II but also type I AT deficiency.

It may also be necessary to determine the AT antigen concentration and do molecular biological testing to find the type of AT deficiency.

Family screening can be helpful in determining hereditary AT deficiency. Genetic testing is the only way to conclusively demonstrate homozygosity, because homozygous carriers can show AT activity comparable to heterozygous carriers. Thus far more than 270 different mutations of the AT gene (*SERPINC1*) are known that can lead to AT deficiency [78]. Inheritance is generally autosomal dominant.

Before undertaking time-intensive and high-cost diagnostic procedures, however, acquired AT deficiency should be excluded. Antithrombin levels are often reduced with acute thromboembolism. The same is true for heparin treatment, impaired liver synthesis, heightened AT consumption due to surgery or trauma, and protein loss via the kidneys (nephrotic syndrome) or intestines.

VTE risk depends on the type of AT deficiency. Patients with type II HBS (heparin-binding defect) AT deficiency have a lower thrombosis risk than patients with type I or other forms of AT deficiency. The relative risk of thrombosis lies between 4 and 50.

The VTE risk for hereditary AT deficiency and use of oral contraception has thus far been little studied. A meta-analysis by Wu et al. [77], which covered only two studies and did not differentiate among AT deficiencies, yielded an odds ratio of 12.6 (95% CI 1.4–115.8) for women with AT deficiency taking oral contraception.

Continuous thromboprophylaxis is generally not necessary for patients who have not suffered a thromboembolic event. For thrombotic risk situations, however, care must be taken to ensure sufficient prophylactic measures. It is important to note that heparin-based thromboprophylaxis is only of limited effectiveness for AT deficiency, because heparin needs AT to work. It is recommended to determine the type, duration and dose of thromboprophylaxis for e.g. surgery in consultation with an experienced specialist in hemostaseology.

3.5.3.5. Protein C Deficiency

Along with thrombin, protein C binds to the endothelial receptor thrombomodulin and thus becomes activated protein C (APC). Its anti-thrombotic effect derives from cleaving factors Va and VIIIa as well as from activating fibrinolysis. Protein C also inhibits inflammation and apoptosis. Hereditary protein C deficiency is found in 0.2–0.4% of the general population and in 2–5% of VTE patients.

Hereditary protein C deficiency is found by repeated determination of protein C activity combined with the exclusion of acquired causes of protein C deficiency. Acquired protein C deficiency is observed most often in conjunction with acute thromboembolism, impaired liver synthesis, or treatment with vitamin K antagonists. Sepsis, especially meningo-

coccal sepsis, can also lead to severe acquired protein C deficiency.

Molecular biological testing is only seldom needed to show hereditary protein C deficiency. Thus far more than 250 different mutations are known in the protein C gene (*PROC*) that can lead to deficiency. Most individuals with protein C deficiency are heterozygotes and often suffer thromboembolism already as young adults (autosomal dominant inheritance). Homozygous carriers show severe protein C deficiency (protein C activity often < 1%) and usually already develop purpura fulminans, disseminated intravascular coagulation and venous thromboembolism in the neonatal period.

VTE risk estimates for protein C deficiency differ strongly. Odds ratios of 3–15 are given. The thrombosis risk for individuals in affected families (protein C deficiency plus thromboembolism in at least one family member) is generally higher than in unselected patient groups.

VTE risk with oral contraception for hereditary protein C deficiency has thus far been little studied. A meta-analysis which covered only two studies calculated an odds ratio of 6.3 (95% CI 1.7–23.9) [77]. This analysis, however, also places the risk of thromboembolism for protein C deficiency without oral contraception, based on data from a single study, at only 2.5 (95% CI 1.2–5.1). A study of family members of patients with protein C deficiency found use of hormonal contraceptives to be associated with a relative thrombosis risk of 23.6 (3.7–535.6) [79].

VTE prophylaxis for protein C-deficient patients in thrombosis risk situations generally consists of low molecular-weight heparin or fondaparinux.

If a vitamin K antagonist should be used to treat VTE, it must be noted that rapid decline in the already low protein C levels can lead to coumarin necrosis. To prevent this, coumarin must be dosed very low at the beginning and heparin must be administered until the treatment-appropriate INR range is reached.

Protein C concentrate (Ceprotin®) is indicated in the case of severe protein C deficiency with purpura fulminans or coumarin necrosis, as well as short-term prophylaxis for surgery or at the start of coumarin treatment.

3.5.3.6. Protein S Deficiency

Protein S is also a coagulation inhibitor. Protein S is a co-factor in the inactivation of factor Va and VIIIa by activated protein C.

Protein S deficiency occurs considerably more often in acquired than hereditary form. It occurs under oral contraception, in pregnancy, with acute thromboembolism, impaired liver synthesis, treatment with vitamin K antagonists, inflammatory bowel disease and HIV.

Hereditary protein S deficiency is found by repeated determination of free protein S antigen levels or protein S activity in plasma, combined with exclusion of acquired protein S deficiency. Molecular biological testing of the protein S gene (*PROS1*) is only rarely necessary, but it can help differentiate acquired from hereditary protein S deficiency and also show homozygous inheritance. A problematic aspect is that currently available methods only enable a mutation to be determined in approximately 50% of cases. Family testing can therefore be helpful in determining hereditary protein S deficiency. Thus far more than 200 different mutations in the *PROS1* gene are known that can lead to protein S deficiency. Inheritance is generally autosomal dominant, and affected individuals are usually heterozygous mutation carriers. Homozygous or compound heterozygous carriers are very rare and often already suffer purpura fulminans and recurrent VTE in the neonatal period.

Hereditary protein S deficiency is found in 0.2–2% of the general population and in 1–7% of VTE patients. VTE risk estimates for protein S deficiency differ strongly. Odds ratios of 5–11 are given. The thrombosis risk for individuals in affected families (protein S deficiency plus thromboembolism in a family member) is generally higher than for unselected patient groups.

VTE risk with hereditary protein S deficiency with oral contraception has thus far been little studied. A meta-analysis by Wu et al. [77] that covered only two studies calculated a VTE odds ratio for protein S deficiency with oral contraception of 4.9 (95% CI 1.4–17.1).

Continuous thromboprophylaxis is not necessary for patients who have not had VTE. Thromboprophylaxis in VTE risk situations consists of low molecular-weight heparin or fondaparinux. Dosing is done in accordance with the German S3 guideline on preventing venous thrombosis (www.awmf.org).

Protein S deficiency can also lead to coumarin necrosis at the start of coumarin treatment, so as in the case of protein C deficiency, care must be taken to ensure gradual coumarin dosing when treatment starts.

3.5.3.7. High Factor VIII Levels

Factor VIIIa is a co-factor in the activation of factor X by factor IXa. As such, it has a pro-coagulatory effect.

High factor VIII levels are found by repeated determination of factor VIII activity in plasma.

A large number of factors can lead to a temporary rise in factor VIII levels, such as acute phase reactions, especially acute and chronic infections as well as auto-immune diseases, acute thromboembolism, pregnancy, malignancies, liver diseases and medication. Factor VIII is also influenced by blood type, age and weight (increases with age and BMI: [80]). Persistent high levels of factor VIII are associated with a higher risk of thrombosis.

Increased factor VIII activity is found in approximately 5–10% of the general population and in approximately 10–30% of VTE patients. Patients with heightened factor VIII have an approximately 5 to 8-fold greater risk of VTE [77, 81].

The relative VTE risk with oral contraception for higher factor VIII levels is 8.8 (4.1–18.8) to 13.0 (4.9–34.3) [77, 81, 82].

VTE prophylaxis for individuals with higher factor VIII levels in VTE risk situations generally consists of low molecular-weight heparin or fondaparinux. Dosing is done in accordance with the German S3 guideline on preventing venous thrombosis (www.awmf.org).

3.5.3.8. Antiphospholipid Syndrome
Antiphospholipid antibodies are a heterogeneous group of antibodies against phospholipid protein complexes. Based on the current state of research, the relevant antiphospholipid antibodies are lupus anticoagulants, anticardiolipin antibodies and β2-glycoprotein I antibodies. They are associated with antiphospholipid syndrome, or APS for short.

APS is defined by persistent evidence of antiphospholipid antibodies in patients with venous or arterial thromboembolism or pregnancy complications (≥ 3 otherwise inexplicable miscarriages before the 10th week of pregnancy, ≥ 1 miscarriage or stillbirth with no unusual morphological features in the ≥ 10th week of pregnancy, or premature birth before the 34th week due to placental insufficiency or [pre]clampsia).

Lupus anticoagulants were first described in patients with systemic lupus erythematodes (SLE). The term is misleading, because the antibodies occur not only in connection with SLE, and especially because the tendency is not toward bleeding but rather toward thrombosis. There is a propensity for venous and arterial thromboembolism.

Eighty percent of APS patients are women. In the general population, lupus anticoagulants are found at a rate of 0–1.7% [83], anticardiolipin antibodies at 2.7–23.5% [83] and β2-glycoprotein I antibodies at approximately 3% [84]. Antiphospholipid antibodies are found in 2–10% of patients with VTE.

Lupus anticoagulants are found by performing two screening tests followed by two confirmation tests. Anticardiolipin and β2-glycoprotein I antibodies are determined with the help of ELISA test procedures. Anticardiolipin antibodies are only viewed as a criterion for APS if anticardiolipin IgG or IgM antibodies show at least a medium to high titer (> 40 GPL or MPL or titer > 99th percentile).

Antiphospholipid antibodies are present in approximately 50% of cases associated with other diseases (autoimmune diseases, especially systemic lupus erythematodes, malignancies, infections, drug-associated). They can occur on a transient basis in the course of infections. Excluding transient antibodies is the reason for repeating the antibody diagnostic procedure after 12 weeks, as prescribed by international guidelines.

Caution: Lupus anticoagulants extend the aPTT. This is an in-vitro phenomenon, which is typically not associated with a propensity for bleeding. Despite the extended aPTT, there is a propensity for thrombosis!

For patients without an underlying autoimmune condition, the relative risks are as follows:
– for VTE with:
  • lupus anticoagulants: 4.1–16.2 [85]
  • anticardiolipin antibodies (medium to high titer): 0–2.5 [85]
  • β2-glycoprotein I antibodies: 2–4 [84, 86]
– for arterial thrombosis:
  • lupus anticoagulants: 8.7–10.8 [85]
  • anticardiolipin antibodies (medium to high titer): 0–18.0 [85]
  • β2-glycoprotein I antibodies: 0–8 [85].

Patients with positive antiphospholipid antibodies in multiple tests (lupus anticoagulants + anticardiolipin antibodies + β2-glycoprotein I antibodies) have the highest risk of thrombosis [87].

The risk of venous and arterial thromboses from oral contraceptives with the presence of antiphospholipid antibodies has not yet been sufficiently studied. The already existing risk of cerebral ischemia has been found to increase approximately 5-fold, and the risk of myocardial infarction approximately 4-fold [88].

Prevention:
Acetyl salicylic acid should be considered as thromboprophylaxis for patients with systemic lupus erythematodes and persistent demonstrated antiphospholipid antibodies [89].

Modification of classic reversible cardiovascular risk factors such as arterial hypertension and hypercholesterolemia where applicable, in order also to reduce the risk of arterial thrombosis [89].

Because antiphospholipid antibodies occur on a secondary basis in 50% of cases, it can be necessary to clarify their genesis.

Thromboprophylaxis in VTE risk situations for persons who have not had thromboembolism consists of low molecular-weight heparin or fondaparinux. Dosing is done in accordance with the German S3 guideline on preventing venous thrombosis (www.awmf.org).

VTE with antiphospholipid syndrome is an indication for long-term anticoagulation. When treating VTE, it must be considered that lupus anticoagulants usually extend the aPTT and that aPTT is not suitable for monitoring purposes when unfractionated heparin is administered.

3.5.3.9. Mild Hyperhomocysteinemia
Homocysteine is an intermediate product of amino acid metabolism, formed by demethylation of the amino acid methionine. The amino acid cysteine can be formed from homocysteine via the enzyme cystathione β-synthase (CBS). Methionine can be synthesized from homocysteine via the enzyme methyltetrahydrofolate reductase (MTHFR). Folic acid and vitamins B12 and B6 are co-factors in homocysteine metabolism.

Hyperhomocysteinemia is associated with VTE (VTE in the leg, pulmonary embolism) and cardiovascular events such as myocardial infarction and stroke.

Possible causes of hyperhomocysteinemia are: folic acid and/or vitamin B12 or B6 deficiencies, polymorphism/mutation in the genes encoding MTHFR or CBS, renal insufficiency, nicotine abuse, high coffee consumption, medication (e.g. methotrexate, theophylline, anticonvulsives), hypothyroidism, and others.

Mild hyperhomocysteinemia is found in approximately 11% of women in Europe aged 20–40 years [90]. Mild hyperhomocysteinemia is found in 6–30% of patients with VTE.

An increase of 5 µmol/l in the homocysteine level is linked with a venous thrombosis risk of 1.3 (95% CI 1.0–1.6) [91]. The odds ratio is 1.2 (95% CI 1.1–1.3) for coronary heart disease, and 1.8 (95% CI 1.6–2.0) for ischemic stroke [92].

The thromboembolism risk for individuals with hyperhomocysteinemia who are taking oral contraception has not been sufficiently studied. Due to the only

slightly higher risk of venous thrombosis in connection with mild hyperhomocysteinemia and the insufficient data in connection with hormonal contraception, it is generally not recommended to determine homocysteine levels in connection with use of the Pill. One study, however, has shown an increased risk of cerebral ischemia for hyperhomocysteinemia and oral contraception (OR 6.2; 95% CI 1.7–22.0 [93].

Preventive measures in the case of known mild to medium hyperhomocysteinemia:

Homocysteine levels can be lowered by substituting folate, vitamin B12 and vitamin B6, but not the occurrence of VTE or cardiovascular events (myocardial infarction, stroke). The benefit of vitamin intake has not been demonstrated [94–97].

Clarification of hyperhomocysteinemia genesis where applicable to exclude treatable causes. Modification of classic cardiovascular risk factors where applicable. On account of their homocysteine-elevating effects, no consumption of nicotine, no or only low consumption of coffee.

3.5.3.10. Homozygous Methyltetrahydrofolate Reductase (MTHFR) C677T Polymorphism
C677T polymorphism leads to reduced MTHFR enzyme activity. Compared to CC genotype carriers, TT carriers have approximately 25% higher homocysteine concentrations (approx. 2.5 µmol/l) in plasma. The effect on homocysteine level depends on folate intake.

Approximately 10% of Europeans are *MTHFR* 677 TT carriers [98].

VTE risk is not significantly influenced even by *MTHFR*677 polymorphism in homozygous form (odds ratio for Europeans: 1.1 with 95% CI 0.97–1.2, not significant [12]; the relative risk of an ischemic stroke is 1.4 [95% CI 1.1–1.8], TT versus CT and CC genotype carriers among Europeans; [99]). The risk of myocardial infarction is not increased [100].

The influence of *MTHFR* C677T polymorphism on the risk of thrombosis with oral contraception has not been sufficiently studied. Due to insufficient data, molecular genetic testing for *MTHFR* C677T polymorphism is not currently applicable to Pill use in routine cases. Further studies are needed to clarify whether *MTHFR* C677T polymorphism is relevant to prescription decisions for patients with a higher risk of cerebral ischemia. One study calculated a relative risk of ischemic cerebral insult of 5.4 (95% CI 2.4–12.0) for homozygous carriers of *MTHFR* 677 polymorphism with oral contraception [101]; another study showed an odds ratio of 8.9 (95% CI 3.7–21.1 [102].

3.5.3.11. Significance of Thrombophilia Parameters Post-VTE
An increased risk of VTE recurrence could not be clearly demonstrated for the prothrombin G20210A mutation [76, 103]. Carriers of homo- or heterozygous factor V Leiden have a slightly higher risk of VTE recurrence (odds ratio 1.56, 95% confidence interval 1.14–2.12 and 2.65, 95% CI 1.2–6.0) [76]. Individuals with antithrombin, protein C or protein S deficiency show a higher VTE recurrence risk [104]. Thus far, however, there are no studies that show benefits of extended anticoagulation for patients with these thrombophilia parameters. National and international guidelines that specify post-VTE anticoagulation duration therefore currently do not take thrombophilia diagnostics into account. By contrast, long-term anticoagulation is recommended for patients with antiphospholipid syndrome (www.awmf.org/leitlinien/aktuelle-leitlinien/ll-liste/deutsche-gesellschaft-fuer-angiologie-gesellschaft-fuer-gefaessmedizin.html; [105].

3.6. General Recommendations for Apparently Healthy Women

In individual cases, thrombosis can also be triggered in apparently healthy non-risk women (i.e. negative own and family histories, negative lab tests) by the use of hormonal contraceptives, which can lead to pulmonary embolism and in rare cases to death. As with the at-risk population, additional factors play a role, such as exsiccosis due to diarrhea and severe vomiting, immobilization, limited movement, and low-pressure conditions on long flights. Therefore all women (as well as men who face similar risk constellations although not taking the Pill!) should adhere to the following.

3.7. General Recommendations

3.7.1. Immobilization/Inactivity
For surgery and plaster casts, as well as immobilization/inactivity with "internal" conditions such as infections: Prophylactic anticoagulants in accordance with the German S3 guideline on preventing venous thromboembolism (www.awmf.org/leitlinien/aktuelle-leitlinien/ll-liste/deutsche-gesellschaft-fuer-chirurgie.html)!

Air or car travel > 4 hours: Thromboprophylaxis with low molecular-weight heparin only for at-risk individuals! Compression stockings depending on risk constellation. For this see section 2.4.2. Car travel should include regular stops with exercise.

3.7.2. Air Travel
Clinics at the Munich and Frankfurt airports can provide counseling and treatment. For long-distance flights, check in and boarding should be done early enough to place carry-on luggage in the overhead compartment instead of under the seat so as to ensure leg room. An exercise program to promote circulation is recommended, including regular leg movement and occasional walking if possible. Seats at aisles or emergency exits are preferable due to greater leg room. Avoid consumption of alcohol or sleeping tablets on long trips.

In general, sufficient hydration should be ensured during extended periods of confinement (e.g. on trips or during other periods of inactivity/immobilization). See next section. At least 0.25 liter of water should be consumed every 2 hours during air travel [40].

3.7.3. Hydration
The human body consists of up to 70% water. This percentage is slightly lower for women than for men on account of the relatively higher fat content in tissue. To prevent dehydration, at least 1–3 liters (at least 3% of body weight) of water need to be consumed per day. Fluid loss of 2% already leads to a decline in physical performance, concentration and short-term memory.

An adult body loses 200–400 ml of water daily via the skin, 400–600 ml via the lungs, 1500 ml via the urinary system

and 100 ml via the intestinal system. In certain circumstances the body can lose considerably more fluid via the skin (sweat) such as during strenuous exercise or fever.

Daily fluid requirements for adults with normal hydration status is 30–40 ml per kilo of body weight per day. For a body weight of 70 kg, that would be approximately 2.5 liters/day. In the event of fever, daily adult fluid needs rise by approximately 10 ml per kilo of body weight per 1 °C temperature above 37 °C (S3 guideline from the Deutsche Gesellschaft für Ernährungsmedizin: www.awmf.org). Diarrhea and vomiting can also cause major fluid loss, which must be rapidly restored.

If intake is lower than output, there is a danger of exsiccosis: sensation of thirst, dry skin and mucous membranes, diminished skin turgor, decreased urine production, elevated serum and urine molarity, headache, nausea, paresthesia, muscle spasms, tachycardia, hypertension, increased temperature, weight loss, followed by agitation up to and including delirium. The clinical symptoms increase with the extent of fluid loss.

A useful rule of thumb for preventing dehydration in hot environments or during strenuous physical activity is to monitor the frequency and type of urination. Emptying a full bladder containing colorless or lightly colored urine at least every 3–5 hours shows the absence of dehydration.

If input exceeds output volume, there is a danger of edema (legs, lungs), ascites, combined with weight gain and possibly arterial hypertension. It is often necessary to limit the amount of fluid intake for conditions such as cardiac, liver and renal insufficiency, as well as edema.

3.7.4. Risk Factors

Avoid additional risk factors such as smoking, excess weight and malnutrition. Regular exercise is extremely important. If other clotting disorders are identified in addition to factor V Leiden, individual consultation with a hemostaseology specialist is recommended.

3.7.5. Contraception

Use of oral hormonal contraception in particular, but also vaginal rings (Nuva Ring®), hormonal patches (Evra®) or other steroid hormones increases the risk of thrombosis. The appropriate contraception depends on the individual risk profile, and should be determined in consultation with the gynecologist and possibly also with a hemostaseologist.

3.7.6. Pregnancy

Women with a positive own or family history of venous or arterial thromboembolism should consult with their physicians when planning for pregnancy in order to assess the risk of thrombosis, clarify the existence of additional risk factors and discuss prophylactic measures and possible treatment during pregnancy and puerperium. Women who take vitamin K antagonists should be informed of the teratogenic properties of these preparations.

3.7.7. Patient Information

Coagulation defects such as heterozygous factor V Leiden mutation are common, with the latter occurring in 5% of the population. The majority of factor V Leiden mutation carriers do not know that they have a higher individual risk. Multiple factors are generally involved in VTE, which means that it is very important for preventive purposes to identify additional acquired risk factors. Especially women taking hormonal contraception should be informed of additional thromboembolism risk factors so that appropriate prophylactic measures can be taken in situations with a higher risk of thrombosis.

3.8. Summary

3.8.1. Laboratory Screening

- Thrombophilia screening of all women taking hormonal contraception is not justified.
- **Indications for thrombophilia testing:** Thromboembolism at a young age, the need to clarify otherwise unexplained recurrent thromboses/embolism, thromboses in unusual locations, consideration of oral contraception prescription with family history of thrombosis, suspicion of antiphospholipid antibodies, post-thromboembolic patients with planned or current pregnancy, ≥ 3 miscarriages, stillbirth (Tab. 8).
- Thrombophilia testing plays only a secondary role in deciding the duration of anticoagulation post-VTE.
- **Genetic Diagnosis Act (GenDG):** Genetic testing for thrombophilia must comply with the GenDG patient information requirements beforehand as well as counseling and documentation regarding the results.
- **Costs:** Covered by country-specific health insurance policies or on a private basis.

3.8.2 Patient Information/Counseling

- General recommendations for preventing thromboses in healthy individuals have been described in detail.
- VTE is generally a product of multiple factors. Ongoing thromboprophylaxis is not necessary for asymptomatic individuals with thrombophilia. Additional acquired risk factors can trigger VTE. Information should therefore be provided about VTE risk factors and care should be taken to ensure thromboprophylaxis in risk situations.
- Contraception, in particular oral contraceptives, increase the risk of VTE. Because continuous thromboprophylaxis is not an option for individuals taking hormonal contraception, it is crucial to assess individual risk of thromboembolism in deciding for or against the use of hormonal contraception.
- As a basis for counseling patients, this paper compiles VTE risk information for clinically relevant thrombophilia parameters with and without use of contraception.
- Due to the low frequency of some thrombophilia parameters, e.g. homozygous factor V Leiden mutation or homozygous prothrombin G20210A mutation, in some cases sufficient data is not available to precisely assess VTE risk with oral contraception.
- Over and above this, it is crucial to select a contraceptive with the lowest possible cardiovascular risk (see Section 4).
- In all cases, the question of whether or not to take an oral contraceptive is an individual decision for individuals with thrombophilia, and the diagnostic and treatment guidelines presented here are solely for informational purposes.
- Carrying a thrombophilia alert (including family history, patient history, lab test results, risk assessment [like allergy, cortisone, etc. alerts]) is helpful for correctly assessing throm-

bosis risk in situations such as emergency surgery.

4. Contraceptive Selection for Women with Thrombophilia and/or Previous Thromboembolism

4.1. Preliminary Remarks

This statement focuses on venous thromboembolitic complications in women, with and without the use of various types of contraception. Because epidemiological studies have also associated the use of combined oral contraceptives (COCs) with an increased risk of arterial thromboembolism (myocardial infarction, transient ischemic attacks, ischemic strokes), secondary attention is devoted to arterial thromboembolic events.

This statement concentrates on the risk associated with thrombophilia – other potential risk constellations such as obesity, heavy smoking, PCO syndrome, diabetes mellitus, insulin resistance etc. have to be considered on an individual basis – including the resulting diagnostic and treatment consequences. These recommendations do not release physicians from their professional duty to care for each individual case, including providing extensive information to the patient about treatment options and their effects and/or side effects. Neither the authors nor the publishers assume any form of liability for or related to the information contained herein (see disclaimer).

In assessing the VTE risk of different contraceptives it is important to know VTE incidence rates for different age groups in the healthy population as well as for groups with additional risk factors such as obesity and positive family history. The incidence rate for women who do not use hormonal contraceptives has been corrected upwards in recent years [9, 57, 106]. Comparative VTE risks for pregnancy and puerperium have also had to be revised, because incidence rates (20–30 VTE/10,000 woman-years) are evidently higher than previously assumed [72, 107–109].

In its 2004 "Medical Eligibility Criteria for Contraceptive Use" and its 2008, 2009 and 2010 updates, the WHO has analyzed different patient health situations and provided recommendations for selecting the appropriate contraceptive methods. These recommendations fall into categories 1 through 4 (Tab. 12).

Table 12. Medical Eligibility Criteria for Contraceptive use. WHO 2004, 2008, 2009, 2010.

Category		Clarification
1	No restriction for the use of the contraceptive method	Always usable
2	Advantages of using the method generally outweigh the theoretical or proven risks	Broadly usably
3	Theoretical or proven risks usually outweigh the advantages of using the method	Caution/Counseling
4	Unacceptable health risk if the contraceptive method is used	Do not use

The final section of this paper will address the WHO recommendations on deep venous thrombosis, pulmonary embolism, known thrombogenic mutations, superficial venous thromboses, ischemic cardiac diseases, stroke, hyperlipidemia and systemic lupus erythematosus, including antiphospholipid antibodies (Tab. 13).

4.2. Thrombophilia Risk of Different Contraceptives

4.2.1. Combined Oral Hormonal Contraceptives (COC)

Cigarette smoking: VTE risk with the use of oral hormonal contraceptives shows a continuous increase with the number of cigarettes smoked per day [111] (Fig. 7). The odds ratio for > 20 cigarettes is 1.9. However, not all studies have shown similar results, and it is questionable whether smoking in fact represents a risk for VTE (see Section 3.5.1).

Age and BMI: The EURAS study showed VTE incidence rates (VTE/10,000 woman-years) for non-overweight women of 1.7 for women under 25 years of age, 4.9 for women aged 25–39, and 19.9 for women > 40, all with a BMI < 25 (Fig. 8). For all three of these age groups, risk increases additionally for women with higher BMI values. For the age group under 25, for example, risk increases from 1.7 VTE/10,000 woman-years for BMI < 25–7.7 for BMI 25–30, and to 14.9 for BMI > 30 [Dinger 2008, personal communication]. The risk from COC also depends on the following factors of influence.

Duration of use: The maximum risk from COC exists within the first 3 months following the start of use [11, 113–116]. In the first half year there is a 6 to 8-fold increase in thrombosis risk over baseline compared to that for a same-age comparative group [117]. It is important to note that after a break in use (due to planned pregnancy, break-up of partnership, lack of prescription), there is once again an increased risk. This holds regardless of whether the same or a different preparation is taken [114]. Short-term (e.g. 1–2 cycle) breaks in use should therefore be viewed critically. By contrast, changing the preparation without interrupting use is not associated with increased risk [114].

Hemostatic changes caused by COC use reverse approximately 6 weeks after use is stopped [116]. This is confirmed by the LASS study [118], which found no increased risk following two months of non-use.

VTE risk is highest at the start of OC use, and decreases over time. If use is interrupted for 4 weeks, VTE risk is just as high as at the start of the first Pill phase and then again shows a continuous decrease (Fig. 9, 10) [114].

Estrogen dose: Risk depends on the dose of ethinyl estradiol (EE) [111, 119].

– **Dose reduction from 50 to 30–40 µg EE:** A lower risk been shown for a reduction in dose from 50 to 30–40 µg ethinyl estradiol, although the results are partially conflicting [111, 118]. Epidemiological studies have shown that VTE incidence in women without other VTE risk factors who use COCs with low estrogen content (< 50 µg ethinyl estradiol) is 20 to 40 cases per 100,000 woman-years. By contrast, incidence in the typical population of OC users is approximately 90 cases per 100,000 woman-years [9].

Table 13. Summary of classifications for hormonal contraceptive methods and intrauterine devices (categories see Tab. 12). Source: U.S. Medical Eligibility Criteria for Contraceptive Use, 2010. Mod. from [110].

Condition	COC/P/R	POP	DMPA	Implants	LNG-IUD	Cu-IUD
Smoking						
a) Age < 35 yrs	2	1	1	1	1	1
b) Age ≥ 35 yrs						
i) < 15 Cigarettes/day	3	1	1	1	1	1
ii) ≥ 15 Cigarettes/day	4	1	1	1	1	1
Obesity						
a) ≥ 30 kg/m² BMI	2	1	1	1	1	1
b) Menarche to <18 yrs and ≥ 30 kg/m² BMI	2	1	2	1	1	1
Cardiovascular Disease (Multiple risk factors for arterial cardiovascular disease such as older age, smoking, diabetes, and hypertension)	3/4	2	3	2	2	1
Hypertension						
a) Adequately controlled hypertension	3	1	2	1	1	1
b) Elevated blood pressure levels (properly taken measurements)						
i) Systolic 140–159 mmHg or diastolic 90–99 mmHg	3	1	2	1	1	1
ii) Systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg*	4	2	3	2	2	1
c) Vascular disease	4	2	3	2	2	1
History of high blood pressure during pregnancy (current blood pressure measurable and normal)	2	1	1	1	1	1
Deep venous thrombosis (DVT)/ pulmonary embolism (PE)						
a) History of DVT/PE, not on anticoagulant therapy						
i) Higher risk for recurrent DVT/PE (≥ 1 risk factor)	4	2	2	2	2	1
– History of estrogen-associated DVT/PE						
– Pregnancy-associated DVT/PE						
– Idiopathic DVT/PE						
– Known thrombophilia, including antiphospholipid syndrome						
– Active cancer (metastatic, on therapy, or within 6 months after clinical remission), excluding non-melanoma skin cancer						
– History of recurrent DVT/PE						
ii. Lower risk for recurrent DVT/PE (no risk factors)	3	2	2	2	2	1
b) Acute DVT/PE	4	2	2	2	2	2
c) DVT/PE and established on anticoagulant therapy for at least 3 months						
i) Higher risk for recurrent DVT/PE (≥ 1 risk factor)	4	2	2	2	2	2
– Known thrombophilia, including antiphospholipid syndrome						
– Active cancer (metastatic, on therapy, or within 6 months after clinical remission), excluding non-melanoma skin cancer						
– History of recurrent DVT/PE						
ii) Lower risk for recurrent DVT/PE (no risk factors)	3	2	2	2	2	2
d) Family history (first-degree relatives)	2	1	1	1	1	1
e) Major surgery						
i) With prolonged immobilization	4	2	2	2	2	1
ii) Without prolonged immobilization	2	1	1	1	1	1
f) Minor surgery without immobilization	1	1	1	1	1	1
Known thrombogenic mutations* (e.g. factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies)	4	2	2	2	2	1
Superficial venous thrombosis						
a) Varicose veins	1	1	1	1	1	1
b) Superficial thrombophlebitis	2	1	1	1	1	1
Current and history of ischemic heart disease*		**I C**		**I C**	**I C**	
	4	2 3	3	2 3	2 3	1
Stroke* (history of cerebrovascular accidents)		**I C**		**I C**		
	4	2 3	3	2 3	2	1
Known hyperlipidemias	2/3	2	2	2	2	1
Rheumatic Diseases						
Systemic lupus erythematosus*			**I C**			**I C**
a) Positive (or unknown) antiphospholipid antibodies	4	3	3 3	3	3	1 1
b) Severe thrombocytopenia	2	2	3 2	2	2	3 2
c) Immunosuppressive treatment	2	2	2 2	2	2	2 1
d) None of the above	2	2	2 2	2	2	1 1

I =Initiation; C = Continuation; COC = combined oral contraceptive; P = combined hormonal contraceptive patch; R = combined hormonal vaginal ring; POP = progestin-only pill; DMPA = depot medroxyprogesterone acetate; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing IUD; Cu-IUD = copper IUD; BMI = body mass index; DVT = deep venous thrombosis; PE = pulmonary embolism.
* Condition that exposes a woman to increased risk as a result of unintended pregnancy.

– **Dose reduction from 30–40 to 20 µg EE:** Further reduction of the ethinyl estradiol dose to 20 µg EE appears to lead to an additional although only slight reduction in VTE risk [9, 57].
– **Dose reduction from 30–40 µg EE to non-EE COC:** Lidegaard et al. [57] note that progestogen-only preparations are not associated with a higher risk of VTE for women of fertile age. Mini-Pills with levonorgestrel or norethisterone: VTE rate ratio of 0.59 (0.33–1.03) (data based on 65,820 woman-years), or with 75 µg desogestrel: VTE rate ratio of 1.12 (0.36–3.49) (data based on 9,044 woman-years). (Authors' note: Clear indications are not available as to whether these results can be transferred without qualification to women with marked risk factors.)
– **Risk assessment of COC with estradiol or estradiol valerate:** Compared to ethinyl estradiol, estradiol and estradiol valerate lead to less liver enzyme induction and less impact on hemostasis. **It is currently unclear whether this theoretical advantage also actually leads to a lower incidence of VTE.**

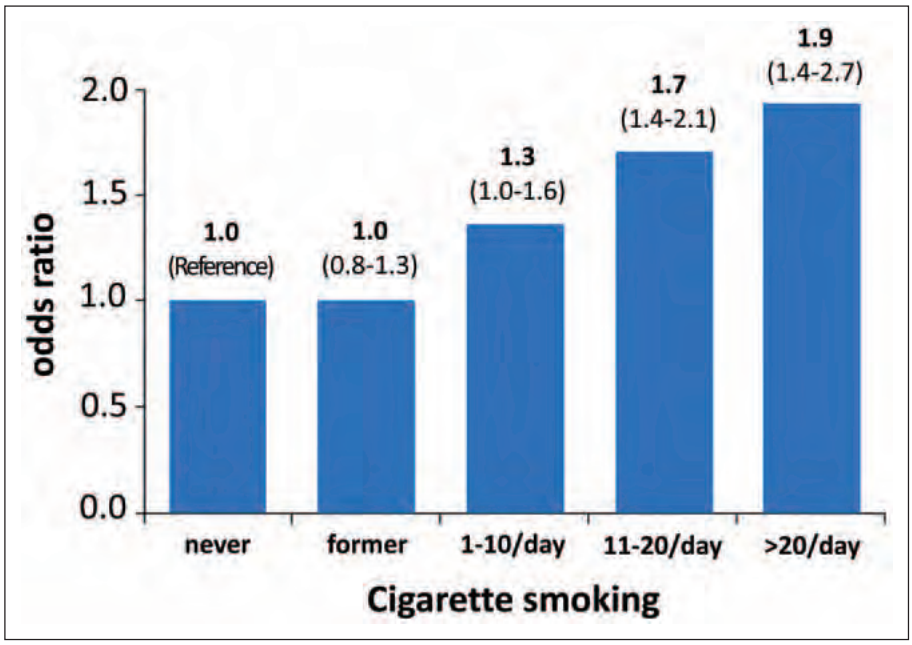

Figure 7. Cigarette smoking as risk factor for VTE with use of OCs. Mod from [112].

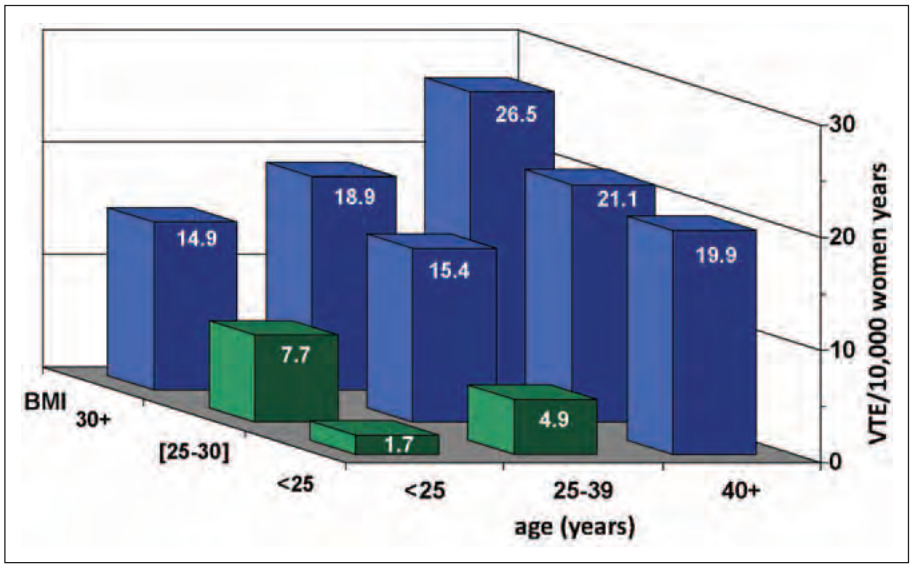

Figure 8. BMI and age as risk factors for VTE with OC use. Weight and age are independent risk factors with additive effect. Mod from [112].

Progestogens and their dosage: The influence of different progestogens on the risk of VTE is disputed. Levonorgestrel is usually taken as the reference for comparisons between different progestogens. According to the best currently available studies [9], VTE incidence for levonorgestrel-containing COCs with less than 50 µg EE lies at approximately 8 VTE per 100,000 woman-years. While it describes the risk for the typical OC user population, this value is of only limited use on account of the strong age-dependency of risk in individual cases. See Figure 8 for age-dependency of risk.

Incidence rates for norethisterone, norethisterone acetate, and norgestimate are similar to that for levonorgestrel [57].

Studies published in the mid-1990s showed a higher risk for **gestoden and desogestrel**, which are known as **third-generation progestogens,** compared to **levonorgestrel** (see meta-analysis by Kemmeren et al. [120]. Studies that adjust for the temporal dependence of risk (higher in the initial months of exposure following first use or resumption of use) and correctly adjust quantitatively for age differences showed no significant differences between the new and established progestogens of the time. However, the methodological shortcomings of all available studies do not allow clear conclusions to be drawn regarding causal connections. Results on cyproterone acetate (CPA) are also conflicting. This applies even to results from the same working group that analyzed the same data source at different points in time with different methodologies. Thus Lidegaard [121] found an incidence of 31 VTE per 100,000 woman-years with a confidence interval of 13–49 using a Danish patient registry, whereas six years later [57] the point estimate for incidence was clearly outside the 2003 confidence interval at 71 VTE per 100,000 woman-years. In the same period of time the relative risk compared to levonorgestrel rose from 0.7–1.9. These differences cannot easily be explained by coincidence, and highlight the considerable methodological difficulties in carrying out and evaluating studies of VTE risk in OC users.

Regarding **chlormadinone acetate (CMA)**, there are no indications of a higher VTE risk **compared to levonorgestrel-containing COCs** [122]. This also applies to ethinyl estradiol-containing COCs with **dienogest** [117].

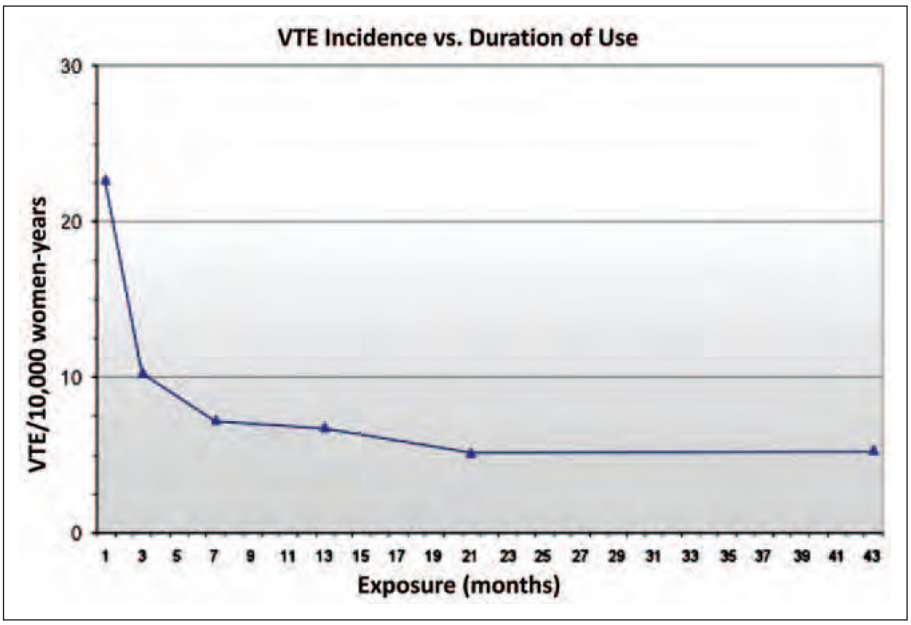

Figure 9. VTE risk over time following start of COC use. Mod. from [114].

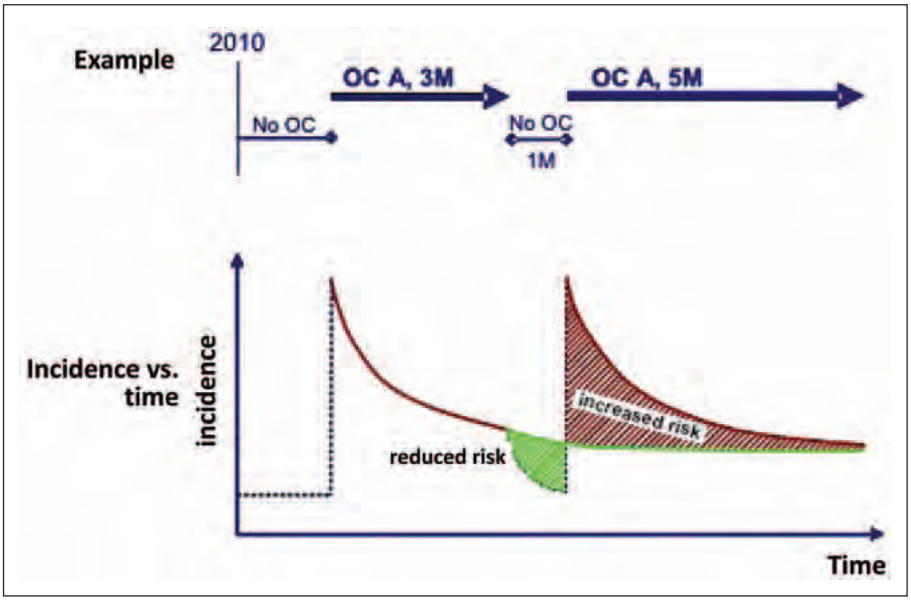

Figure 10. Influence of short breaks in Pill use on VTE risk. Mod. from [114].

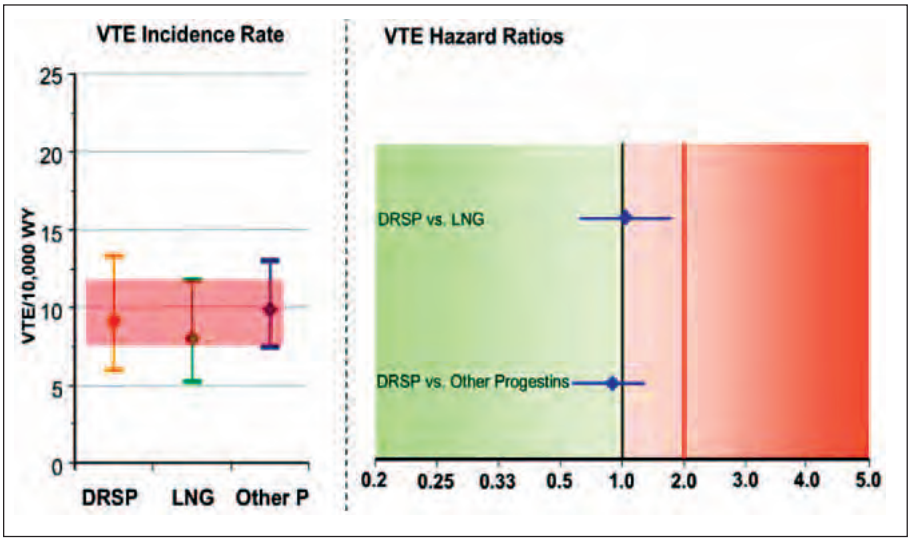

Figure 11. VTE risk factors with OC use: VTE risk of drospirenone-containing OCs. Mod. from [9].

Conflicting results have also been found for **drospirenone**. Two large-scale prospective cohort studies (Fig. 11) [9, 123] and a German case-control study [117] showed no higher risk, while two studies published in 2009 – a retrospective cohort study in Denmark [57] and a Dutch case-control study [113] – showed a slightly higher risk compared to levonorgestrel-containing preparations. The two latter studies, however, exhibit substantial methodological shortcomings [124, 125]. The Dutch study was not statistically significant, and also not representative for either the cases or controls. In the Danish study, short-term and long-term use were misclassified to a considerable degree, and information about important risk factors was not available. In addition, an independent validation study showed that probably around 30% of the diagnoses that the authors took from the Danish patient registry were incorrect [126]. In addition, shortly before this statement went to press, the Boston Collaborative Drug Surveillance Program published the results from two retrospective case-control studies in the USA and England using the PharMetrics [127] and GPRD databases [128]. Both studies yielded higher risk estimates for drospirenone-containing COCs with 30 µg EE. These studies too show considerable shortcomings. The GPRD results, which are based on confirmed VTE, are not statistically significant. The incidence rates, which are too low overall, show that the database compiled only some of the VTE (possible 'ascertainment bias'). In addition, the substantially different risk estimates for pulmonary embolism and deep venous thrombosis (factor 4) indicate the presence of considerable differential diagnostic bias. The PharMetrics study was based on non-confirmed VTE from a database used for calculating benefits, which cannot provide a reliable scientific basis unless the diagnoses are confirmed by health records. The study was not able to reproduce known risks such as the dependence on duration of use (see above), and did not have access to information on major prognostic factors.

In sum, the VTE risk of drospirenone- versus levonorgestrel-containing COCs cannot be conclusively ascertained. The studies with the best methodology do not

Table 14. Classification of contraceptives according to the risk of VTE in healthy women of reproductive age without additional risk factors (such as obesity, immobilization, positive family history of cardiovascular disease, cigarette smoking). [Rabe & Dinger 2011, personal communication]

Risk	Age (Years)	Incidence (VTE/10,000 women years)	Contraceptive method/ Population group	Published Studies	Ongoing Studies
Reference	≤ 19 20–29 30–39 40–49	1–2 2–3 3–4 5–7	Healthy, non-pregnant women of childbearing age not using a contraceptive Non-hormonal contraceptive methods – tubal sterilization – condoms, spermicides – behavioral methods	Lidegaard 2009 [57]: I = 3.0 (2.9–3.2); Ex = 4813 TWY Dinger 2007 [9]: I = 4.4 (2.4–7.3); Ex = 65 TWY Review Article: Heinemann 2007	INAS-OC and INAS-SCORE (EURAS-type studies; end 2013 and 2014, respectively)
	15–49	**3–4**	– copper IUDs		
Unchanged or Slightly increased	**15–49**	**3–4**	Progestin-containing contraceptives (slight increased risk cannot completely be excluded in comparison to non-hormonal contraceptive methods; therefore non-hormonal methods should be preferred for women with a history of thrombophilia) – Levonorgestrel-IUS – Progestin-only pill – Progestin-only ovulation inhibitor – Progestin depot injections	Lidegaard 2009 [57]: Levonorgestrel-IUS I = 3.4 (2.3–4.7); Ex = 101 TWY Progestin-only pill I = 2.0 (1.1–3.3); Ex = 75 TWY	EURAS-IUD (EURAS-type study; ends 2012) LASS (EURAS-type study; ends 2011)
Moderately increased – Level 1	≤ 19 20–29 30–39 40–49	3–4 5–8 8–10 15–22	Combined oral contraceptives with < 50 µg Ethinyl estradiol and – Levonorgestrel (LNG), Norethisteron, Norethisterone acetat or Norgestimate (NGM)	Lidegaard 2009 [57]: I = 5.5 (4.7–6.3); Ex = 367 TWY (underestimation due to misclassification of current duration of use and other reasons)	LASS (EURAS-type study; ends 2011)
	15–49	**6–10**		Dinger 2007 [9]: I = 8.0 (5.2–11.7); Ex = 31 TWY	
			– Chlormadinone acetate (probably no higher risk than with LNG-containing COCs; however, a slightly higher risk cannot be excluded)	Waldmann-Rex 2009 [122]: I = 2.4 (0.9–5.2); Ex = 25 TWY (underestimation due to methodological short-comings)	No EURAS-type study
			– Dienogest (probably no higher risk than with LNG-containing COCs; however a slightly higher risk cannot be excluded)	Dinger 2010 [117]: OR vs LNG: 1.0 (0.6–1.8); 95 Ca/303 Cn	INAS-SCORE (EURAS-type study; ends 2014)
			– MPA depot injection (classification is based on a methodologically limited study with a limited number of cases and controls; overestimation of risk compared to other hormonal contraceptives possible)	van Hylckama, Vlieg et al. 2010 [131]: OR* 3.6 (1.8–7.1); 20 Ca/15 Cn (*vs. non-use of hormonal contraceptives; OR vs. LNG: ~1)	No EURAS-type study
			Combined oral contraceptive pills with Estradiol valerate and Dienogest (less influence on hemostasis compared with Ethinyl estradiol/Dienogest; however, risk assessment should be based on the VTE-incidence of Ethinyl estradiol/Dienogest as long as robust data are not available)		INAS-SCORE (EURAS-type study; ends 2014)
			NuvaRing® (provisional classification based on interim results from the TASC study)		TASC (EURAS-type study; ends 2012)
– Level 2	**15–49**	**6–14**	Combined oral contraceptives with < 50 µg Ethinyl estradiol and – Drospirenone (DRSP) (inconsistent study results; in contrast to retrospective database studies 2 prospective cohort studies and 1 retrospective field study did not show an increased risk compared to LNG-containing COCs; based on currently available data a slightly increased risk is possible)	Lidegaard 2009 [57]: I = 7.8 (6.4–9.5); Ex = 131 TWY (no substantial missclassification of duration of use; potential overestimation of risk compared to LNG [see above]) Dinger 2007 [9]: I = 9.1 (5.9–13.3); Ex = 29 TWY Dinger 2010 [117]: OR vs LNG: 1.0 (0.5–1.8); 85 Ca/281 Cn Jick et al. 2011 [127]: OR 2.2 (1.5–3.4); 166 Ca/550 Cn Parkin et al. 2011 [128]: OR 2.9 (1.1–7.4); 57 Ca/176 Cn	LASS (EURAS-type study; ends 2011) INAS OC (EURAS-type study; ends 2011)
			– Desogestrel (DSG), Gestoden (GSD) or Cyproterone-acetate (CPA) (risk of VTE in comparison with LNG-containing preparations scientifically controversial, however a slightly to moderately higher risk is possible)	Lidegaard 2009 [57]: DSG/GSD I = 6.8 (6.5–7.2); Ex = 2008 TWY CPA I = 7.1 (5.7–8.7); Ex = 127 TWY (less substantial underestimate of the risk compared to LNG [see above]) Case-control studies with and without adjustment for duration of use showed ORs of ~ 2 and ~ 1. Numerous review articles available; the most balanced representation being the decision of the High Court of Justice in 2002 [132]	LASS (EURAS-type study; ends 2011)
			Evra contraceptive patch (VTE risk compared to COCs with LNG or NGM controversial; a slightly to moderately increased risk is possible)	Dore 2010 [133]: OR vs NGM: 2.0 (1.2–3.3); 102 Ca/353 Cn Jick 2010 [134]: ORs vs LNG from 2 sources 46 Ca/207 Cn & 97 Ca/382 Cn: 2.0 (0.9–4.1) & 1.3 (0.8–2.1)	No EURAS-type study
Substantially increased	**15–49**	**20–30**	Pregnancy and the first three months after childbirth; risk after cesarean section significantly higher than after spontaneous delivery	Heit 2005 [72]: I = 29.3 (23.8–35.6); Ex = 50 TWY Lidegaard 2011 [135]: RR vs 'non-pregnant non-users' 10.6 (9.4–12.0); 265 Cases	No EURAS-type study

Ex = Exposure in 1000 woman-years; Ca = Number of relevant cases in a case control study; I = Incidence of VTE/10,000 WY with 95% CI; Cn = Number of relevant controls in a case control study; OR = odds ratio; RR = relative risk; TWY = 1,000 woman-years; * cases/controls

show indications of a higher risk for drospirenone, but these studies too have methodological limitations and cannot exclude a slight increase in risk.

The PhVWP (Pharmacovigilance Working Party) of the European Medicines Agency (EMA) [129] completed in May 26th, 2011, a review of all available data, including some further re-analyses and information on additional analyses regarding the risk of venous thromboembolism (VTE) associated with drospirenone-containing combined oral contraceptives (COC), such as Yasmin and Yasminelle. Altogether seven epidemiological studies [9, 57, 113, 117, 123, 127, 128] have analysed/evaluated an association between drospirenone-containing COC and VTE.

The assessment has not changed the conclusion that the risk of VTE with any COC (including those containing drospirenone) is very small. The PhVWP concluded that the data have shown that drospirenone-containing COCs are associated with a higher VTE risk than levonorgestrel-containing COCs and that the risk may be similar to that for COCs containing desogestrel or gestodene. The PhVWP recommended that the product information for all drospirenone-containing COCs should be updated to reflect these conclusions. There is no reason for women to stop taking drospirenone-containing COCs, such as Yasmin and Yasminelle, or any other COCs. In Germany the BfArM (Bundesinstitut für Arzneimittel und Medizinprodukte) (2011) [130] published a similar statement at their homepage.

What remains is that the use of any combined oral hormonal contraception (COC) is always associated with a higher risk of VTE. The risk depends on the estrogen dose and is possibly modulated by the choice of progestogen. Whether there actually are clinically relevant differences in the thromboembolism risk for different progestogens is still the object of discussion.

Table 14 compares the risk of thrombosis/VTE with different hormonal contraceptives for healthy women of fertile age without additional risk factors compared to the risk for women in pregnancy and puerperium.

Table 15. Estimates (Odds Ratios) of Venous Thromboembolism Risk in Current Users of Ortho Evra Compared to Oral Contraceptive Users (http://www.rxlist.com/ortho-evra-drug.htm) (per 4.5.2011)

Epidemiologic Studies Evra & VTE	Comparator product	Odds Ratio (95 % CI)
i3 Ingenix NGM Study in Ingenix (Cole et al. 2007 [137], Dore et al. 2010 [133], Cole et al. 2008 [138], Dore et al. 2009 [139])	NGM/35 µg EE[a]	2.2* (1.2–4.0)[b]
BCDSP[c] NGM Study in Pharmetrics database (Jick et al. 2006 [140], Jick et al. 2007 [141], Jick et al. 2010 [142])	NGM/35 µg EE	1.2 (0.9–1.8)[d]
BCDSP LNG[e] Study in Pharmetrics database (Jick et al. 2010 [134])	LNG/30 µg EE	2.0 (0.9–4.1)[f]
Pharmetrics database (Jick et al. 2010 [134])	LNG/30 µg EE	1.3 (0.8–2.0)[g]

* Increase in risk of VTE is statistically significant; [a] NGM = norgestimate; EE = ethinylestradiol; [b] Pooled odds ratio from Cole et al. 2007 [137], Dore et al. 2010 [133]. [Initial 33 months of data: Odds Ratio (95 % CI) = 2.5† (1.1–5.5); Separate estimate from 24 months of data on new cases not included in the previous estimate: Odds Ratio (95 % CI) = 1.4 (0.5–3.7)]; [c] BCDSP = Boston Collaborative Drug Surveillance Program; [d] Pooled odds ratio from Jick et al. 2006 [140], Jick et al. 2007 [141], Jick et al. 2010 [142]. [Initial 36 months of data: Odds Ratio (95 % CI) = 0.9 (0.5–1.6); Separate estimate from 17 months of data on new cases not included in the previous estimate: Odds Ratio (95 % CI) = 1.1 (0.6–2.1); Separate estimate from 14 months of data on new cases not included in the previous estimates: Odds Ratio (95% CI) = 2.4* (1.2–5.0)]; [e] LNG = levonorgestrel; [f] 48 months of data; [g] 69 months of data

4.2.1.1. Combined Contraceptive Patch (Evra®)

Product description: A contraceptive patch measuring 20 cm^2 that releases the active agents ethinyl estradiol and norelgestromin, a metabolite of norgestimate. The ethinyl estradiol release was originally given as 20 µg/day, but corrected in the Summary of Product Characteristics (SPC) to 33.9 µg/day [136]. The patch has an effective duration of 1 week; three are used followed by a 1-week break.

Due to FDA recommendations, the first report was presented in the USA in November 2005 on increased estrogen exposure from Evra® compared to oral hormonal contraceptives with 35 µg ethinyl estradiol. Additional information was added to the package leaflet in September 2006 after the results of the first two epidemiological studies on the VTE risk of Evra® were presented. In January 2008 the results of a third epidemiological study were added to the package leaflet.

A possibly higher thrombosis risk with Evra® is based on the following factors (Tab. 15):

For Evra® the area under the curve (AUC) for steady state levels of ethinyl estradiol is approximately 60% higher than for oral preparations. By contrast, peak concentrations of ethinyl estradiol for Evra® are 25% lower. Inter-individual variability of ethinyl estradiol levels is higher for Evra® than for OCs. It is not known whether serious side effects are due to pharmacokinetic differences (American RxList, September 8, 2010).

In fact there is little data in the literature as to whether these qualitative pharmacokinetic differences affect VTE risk.

On the individual study results: The first epidemiological study was done by the Boston Collaborative Drug Surveillance Program (BCDSP). It showed that the risk of non-lethal VTE events in connection with Evra® is comparable to the risks for COCs containing 35 µg ethinyl estradiol and the progestogen norgestimate. New cases were added to those originally published. Point estimates for the later cases are higher than those for the earlier ones (Tab. 16). The total study size comprises 162 cases and 626 controls. The odds ratio for the VTE risk of Evra® versus that of a norgestimate-containing Pill was 1.23 (0.86–1.77).

The second study, which also had access to patient records, was done by i3 Ingenix. Its results showed a nearly twofold higher risk of medically confirmed VTE events for the use of Evra® compared to a 35 µg ethinyl estradiol-containing Pill with the progestogen norgestimate [137]. However, at 1.1 the

lower confidence limit for the odds ratio is only slightly above 1.

A third study also done by BCDSP compared the risk of non-lethal VTE events for Evra® with that for COCs with 30 µg ethinyl estradiol and the progestogen levonorgestrel [133]. It examined idiopathic VTE cases and age-matched controls in the PharMetrics and MarketScan databases. The VTE odds ratios for Evra® compared to levonorgestrel-containing Pills were 2.0 (0.9–4.1) and 1.3 (0.8–2.1) For women > 40 years of age in the PharMetrics database, a statistically significant higher risk was found, although no adjustment was made for multiple testing. The authors reached the conclusion that a higher risk cannot be excluded for this age group.

Based on the study results described, the "Rote Liste" (German pharmaceutical directory) as well as the German and American summaries of product characteristics (SPC) contain an alert for a possibly higher risk of VTE.

"Rote Liste" status on September 9, 2010: "Data from a retrospective cohort study with women aged 15–44 years suggests that VTE incidence in women who have used Evra® is higher than that in users of an oral contraceptive containing levonorgestrel."

German Summary of Product Characteristics (SPC) (003648-C647) (status September 8, 2010): This contains the same text as that on the "Rote Liste" above. It notes that the incidence is 1.4 times higher (95% CI 0.9–2.3) for women with and without other VTE risk factors and 1.5 times higher for women without additional VTE risk factors (95% CI 0.8–2.7).

American Summary of Product Characteristics (SPC): Three case-control studies [133, 134, 137, 140, 141, 143] examined the VTE risk for women aged 15–44 years who had used the Evra® contraceptive patch compared to that for women who had used oral contraceptives with 30–35 µg ethinyl estradiol (EE) and norgestimate or levonorgestrel. Electronic patient data from "healthcare claim" databases were used. Norgestimate is the pro-drug for norelgestromin, the progestogen in Ortho Evra®. These studies (Tab. 15), which differed slightly in design, yielded odds ratios between 0.9 and 2.5. Interpretations of these odds ratios extended from no higher risk to a nearly doubled risk. One study (i3 Ingenix) examined the patient records of VTE cases. In the three major clinical studies (n = 3,330 with 1,704 woman-years following exposure) there was one non-lethal case of pulmonary embolism with Ortho Evra®. A non-lethal post-operative case of pulmonary embolism with Ortho Evra® was also reported (www.rxlist.com/ortho-evra-drug.htm).

Possible bias factors in VTE studies on Evra®:
All three studies are based on databases that do not contain data or valid data for all relevant risk factors (e.g. BMI, family history). Due to Evra®'s different method of administration as well as market positioning, it can be assumed that the user populations differ markedly, and therefore also the risk profiles. It cannot be assumed, however, that the influence of these different risk profiles could be fully considered in evaluating VTE risk. In addition, it is not unlikely that in the USA, media reports as well as intensive advertisements and videos indicating a two-fold higher VTE rate by lawyers seeking clients (e.g. YouTube) have encouraged more frequent diagnostic measures for Evra® patients, which in turn has led to a higher detection rate of VTE (detection bias). On the other hand, it is also likely that this has led to a more careful exclusion of risk patients (healthy user effect). The net result of these opposing effects is difficult to assess.

WHO Medical Eligibility Criteria: For known thrombophilic mutations (e.g. factor V Leiden, prothrombin G20210A mutation, protein S, protein C or antithrombin deficiency):

Classification: grade 4 = contraindication for Evra®.

Summary regarding VTE:
- The data are not definitive, but indicate what might be as much as a two-fold higher risk compared to levonorgestrel-containing OCs. Until sufficient valid information is available, a higher risk should be presumed in the interest of patient safety.
- When Evra® is prescribed, patients must be informed of the potentially higher risk.
- Evra® is contraindicated for patients with a heightened risk of VTE.

4.2.1.2. Combined Vaginal Ring (NuvaRing®)
Product description: Contraceptive vaginal ring that releases 0.120 mg etonogestrel (metabolite of desogestrel) and 15 µg ethinyl estradiol per day for 21 days, and thus inhibits ovulation.

SPC: According to the manufacturer, the thromboembolism risk for NuvaRing® is equivalent to that for COCs. NuvaRing® is a convenient form of contraception that inhibits ovulation without daily Pill intake.

Studies: Unfortunately the results of the Transatlantic Active Surveillance on Cardiovascular Safety of NuvaRing (TASC) are not yet available (http://clinicaltrials.gov/ct2/show/NCT00524771). Interim results on the basis of approximately 30,000 woman-years and 29 VTE show no higher risk for NuvaRing® compared to COC users – also after excluding desogestrel- and gestoden-containing COCs. The relevant Safety Monitoring and Advisory Council came to the conclusion that the data provide no indication of higher risk; however, robust conclusions regarding a slightly higher potential risk cannot yet be drawn at present [Dinger, personal communication].

Due to the known increased risk of thrombosis with combined estrogen-containing preparations, **an "existing or previous venous thrombosis" is therefore also considered a contraindication for NuvaRing®.**

Metabolic studies: The effects of NuvaRing® on hemostatic parameters have been examined in an open comparative study with 87 women [144].The comparison group received a combined oral contraceptive (30 µg ethinyl estradiol and 150 µg levonorgestrel). The data show that NuvaRing® exerts only slight, clinically non-relevant effects on the coagulation parameters, comparable to those of levonorgestrel-containing oral contraceptives.

WHO Medical Eligibility Criteria: NuvaRing® is placed in the same category as combined oral contraceptives. For known thrombophilic mutations (e.g. factor V Leiden, prothrombin G20210A

mutation, protein S, protein C or antithrombin deficiency): **Classification: grade 4 = contraindication.**

Summary regarding VTE:
- There are currently no definitive findings on NuvaRing® that show an increased VTE risk compared to COCs. Interim results from the TASC study suggest the provisional conclusion that VTE risk is comparable to that for combined oral contraceptives (Tab. 15).
- When NuvaRing® is prescribed, patients should be informed of a higher VTE risk as with COCs.
- The SPC lists an existing or previous venous thrombosis as a contraindication.

4.2.2 Progestogen-Only Contraceptives

4.2.2.1. Non-Estrogen Ovulation Inhibitor (Cerazette®)

Product description: desogestrel-only Pill (75 µg desogestrel per pill), whose progestogen level lies slightly above the ovulation-inhibiting dose (60 µg/day for desogestrel) and thus inhibits ovulation. Drawback: irregular menses occur in some patients. In contrast to the classical mini-Pill, this preparation can be taken up to 12 hours delayed.

SPC: No information is provided by the manufacturers about VTE or CHD risks. No definitive studies are available.

Metabolic studies: A randomized, controlled, double-blind study compared the hemostaseological effects of Cerazette® with those of a mini-Pill with 30 µg levonorgestrel. The authors concluded that the two preparations are similar and have favorable – with respect to VTE risk – effects on hemostasis [145]. In general it should be assumed that the higher VTE risk from COCs is due primarily to the estrogen.

Epidemiological studies: Lidegaard et al. [57] indicate that progestogen-only preparations for women of fertile age without pre-existing diseases are not associated with an increased risk of VTE; mini-Pills with levonorgestrel or norethisterone: rate ratio for VTE: 0.59 (0.33–1.03) (study size: 65,820 woman-years) or with 75µg desogestrel rate ratio 1.12 (0.36–3.49) (study size: 9,044 woman-years).

WHO Medical Eligibility Criteria: For known thrombophilic mutations (e.g. factor V Leiden, prothrombin G20210A mutation, protein S, protein C or antithrombin deficiency): **Classification: grade 2 (broadly usable method).**

In general, at-risk women (e.g. carriers for factor V Leiden mutation) should use a non-hormonal means of contraception. If this is not possible, one option under certain circumstances is to use a progestogen-only Pill following individual risk-benefit consideration and extensive information/counseling and documentation. In such cases primary consideration could be given to a levonorgestrel-containing "classical" mini-Pill, because current study results about it are based on the most solid data.

Summary regarding VTE:
- Cerazette® is a progestogen-only preparation, which on account of its relatively high dose of the progestogen desogestrel compared to the "classical" mini-Pill, has an ovulation-inhibiting effect. Like the combined Pill, it can be taken up to 12 hours delayed. In contrast to COCs, it can also be taken during puerperium. Like with OCs, to ensure contraceptive effectiveness a period of 36 hours between two pills may not be exceeded.
- Cerazette® does not have a heightened risk of thrombosis according to the Lidegaard study [57], although the study's relatively small number of Cerazette® users and the large confidence interval mean that a higher risk than for the "classical" progestogen-only Pill cannot be excluded.

4.2.3. "Classical" Progestogen-Only Pill

Without ovulation-inhibiting effect; "classical" progestogen-only pill (POP)

Product description: The "classical" POP is a progestogen-only preparation with norethisterone (dose: 0.35 mg/day) levonorgestrel (dose: 0.03 mg/day), whose progestogen level lies below the ovulation-inhibiting dose and thus does not have an ovulation-inhibiting effect. It must be taken daily within a 3-hour window of time. Frequent intermenstrual bleeding is the major side effect. Only limited use is possible during puerperium because the substances can cross over into breast milk.

SPC: No information from the manufacturers about VTE or CHD risk.

Studies: No definitive studies or postmarketing studies.

Metabolic studies: A randomized, controlled, double-blind study compared the hemostaseological effects of Cerazette® (see above) with those of a POP containing 30 µg levonorgestrel. The authors concluded that the two preparations are similar and have favorable effects – with respect to VTE risk – on hemostasis [145]. In general it should be assumed that the higher VTE risk with COCs is due primarily to the estrogen.

Epidemiological studies: Lidegaard et al. [57] indicate that progestogen-only preparations for women of fertile age without pre-existing diseases are not associated with a heightened risk of VTE; POPs with levonorgestrel or norethisterone: rate ratio for VTE: 0.59 (0.33–1.03) (study size: 65,820 woman-years) or with 75 µg desogestrel: rate ratio 1.12 (0.36–3.49) (study size: 9,044 woman-years).

WHO Medical Eligibility Criteria: For known thrombophilic mutations (e.g. factor V Leiden, prothrombin G20210A mutation, protein S, protein C or antithrombin deficiency): **Classification: grade 2 (broadly usable method).**

Primary consideration could be given here to a "classical" POP, because of the available studies.

If compliance (3-hour window) is not ensured, specialists favor Cerazette® as the next option. Ultimately, however, full decisional and educational responsibility lies with the prescribing gynecologist.

Summary regarding VTE:
According to the **Lidegaard study** [57], the classical POP does not have a higher thrombosis risk for women without previous cardiovascular diseases. The sample size for the two above-mentioned progestogens is considerably higher than for the desogestrel-containing Pill Cerazette®. In theory the favorable study results could be distorted in so far as primarily older women take the POP after previous COC use and be-

cause women with an existing disposition for VTE presumably have a lower chance of receiving a POP prescription ("healthy user effect"). In quantitative terms, however, these effects could only distort the results to a slight degree. Overall it can be assumed that the classical POP does not lead to a higher risk of thrombosis.

4.2.4. Subdermal Contraceptive Implant (Implanon®)

Product description: Implanon® is a progestogen-only preparation (etonogestrel), which is implanted subcutaneously on the inner side of the upper arm, and has a contraceptive effect for three years based on continuous steroid release. The maximum steroid levels in serum after 4 days lie at 814 pg/ml, after 4–6 months in steady state at 200 pg/ml, and are still sufficient to inhibit ovulation after 3 years [146]. A new version of Implanon® is currently coming onto the market, namely Implanon® NTX, which can be localized by soft-tissue x-ray and whose new inserter enables simpler and safer subcutaneous implantation.

SPC: Contains no information from the manufacturer on increased risk of VTE or CHD.

Metabolic studies: A randomized, controlled, double-blind study compared the hemostaseological effect of Implanon® with those of a corresponding levonorgestrel-containing preparation. The authors concluded that the two preparations had similar and overall only slight effects on hemostasis [147].

Epidemiological studies: No epidemiological studies have been done on the CHD or VTE risks for Implanon®.

Attempts have therefore been made to extrapolate from epidemiological data on oral intake of the corresponding progestogen to the use of Implanon®. This assumes that the average serum levels are comparable. Complete comparability is not given, however, because it is unclear whether the constant steady state steroid levels with Implanon® affect the VTE risk in similar ways to the strong daily fluctuations in progestogen level from oral intake.

Lidegaard et al. [57] conclude that progestogen-only preparations for women of fertile age without pre-existing diseases are not associated with a higher risk of venous thromboembolism; mini-Pills with levonorgestrel or norethisterone: VTE rate ratio of 0.59 (0.33–1.03) (study size: 65,820 woman-years), or with 75 µg desogestrel: VTE rate ratio of 1.12 (0.36–3.49) (study size: 9,044 woman-years).

WHO Medical Eligibility Criteria: For known thrombophilic mutations (e.g. factor V Leiden, prothrombin G20210A mutation, protein S, protein C or antithrombin deficiency) (analogous to mini-Pill): **Classification: grade 2 (broadly usable method).**

Summary regarding VTE:
- Implanon® has not been studied with respect to VTE.
  Extrapolation using the VTE data from the Lidegaard study (see comment above) does not yield a higher risk of thrombosis, although there is only limited comparability with oral preparations. In cases of doubt, therefore, preference should be given to oral progestogen-only preparations.
- Compared to the depot progestogens which the WHO classifies as "broadly usable" (grade 2), Implanon® can be immediately removed from the body if complications arise.
- When counseling patients, the greater risk of menstrual disorders should be explained; problems removing Implanon® should be solved by the new inserter for Implanon® NTX.

4.2.5. Levonorgestrel Intrauterine System (Mirena®)

Product description: levonorgestrel-containing intrauterine system with an effectiveness duration of 5 years. The mean release rate of levonorgestrel lies at 20 µg/24 hours the first year, and at approximately 10 µg/24 hours after 5 years. The average release rate of levonorgestrel over a period 5 years is 14 µg/24 hours. Systemic levonorgestrel levels are lower than those for the mini-Pill. Menstrual volume and duration decrease as well as rates of dysmenorrhea and transcervical infections. The amenorrhea rate for first use is 20%, and for multiple use up to 60%.

SPC: Contains no information from the manufacturer on the risk of VTE or CHD.

Metabolic studies: Hemostaseological studies have been done on oral administration of levonorgestrel (see mini-Pill).

Epidemiological studies: Lidegaard et al. [57] found no heightened risk of VTE for Mirena® users in a study based on 101,351 woman-years: rate ratio 0.89 (0.64–1.26). A limiting consideration is that the authors were only able to estimate the average duration of use. Cross-reference with oral levonorgestrel preparations (see mini-Pill) with consideration of the low systemic serum levels for Mirena® users, however, supports the supposition that Mirena® use does not lead to higher VTE risk.

In a case-control study van Hylckama Vlieg et al. [131] assessed the risk factors for venous thrombosis. Premenopausal women aged 18 to 50 years using depot-medroxyprogesterone acetate or levonorgestrel intrauterine devices were compared to nonusers of hormonal contraceptives. No increased risk was associated with levonorgestrel intrauterine devices (odds ratio 0.3; 95% CI 0.1–1.1).

WHO Medical Eligibility Criteria: Classification as grade 2 (broadly usable method).

Special case – patients taking oral anticoagulants: Experts recommend that insertion of an intrauterine system should take place 4 weeks at the earliest after start of anticoagulant intake [148].

Summary regarding VTE:
- The study by Lidegaard et al. [57] shows no increase in VTE risk: rate ratio 0.89 (0.64–1.26) (study size: 101,351 woman-years).
- Specialists consider insertion 4 weeks after start of anticoagulant intake possible (warning: "off-label" use).

4.2.6. Depot Progestogens

Product description:
- Depot progestogens are progestogens that are released over a period of 2–3 months after i.m. or s.c. application. There are currently two older preparations:
- Noristerat® from Bayer-Schering with norethisterone enanthate (200 mg)
- Depo-Clinovir® from Pfizer with 150 mg depot medroxyprogesterone acetate, and the lower dosed and s.c.

administrable preparation Sayana® (104 mg DMPA) introduced in 2009.

SPC: Contains no information from the manufacturer on VTE or CHD risk

Metabolic studies: An Egyptian study with 30 women found no change in hemostatic parameters following 3-month and 15-month treatment with depot-medroxyprogesterone [149].

Epidemiological studies: The World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1998) [150] assessed the cardiovascular risk of oral hormonal contraceptives compared to progestogen-only depot injections and combined contraceptive depot injections. It studied 3,697 women with cardiovascular diseases (59% stroke, 31% VTE and 10% acute myocardial infarction). At the time, 53, 37, and 13 women were taking oral progestogen preparations, injectable progestogen preparations, and combined injectable contraceptives, respectively.

The overall adjusted odds ratios for all cardiovascular diseases for current use of oral progestogen-only preparations, injectable progestogen-only preparations, and combined depot contraceptives, compared to non-users of any type of steroid hormonal contraceptives, were 1.14 (0.79–1.63), 1.02 (0.68–1.54), and 0.95 (0.49–1.86), respectively. No significant differences in the odds ratios for stroke, VTE, or myocardial infarction could be found in connection with any type of contraception. However, a slight, non-significant increase was found in the odds ratios for VTE for current use of oral progestogen-only and for progestogen-only depot preparations. For women with a history of hypertension, the odds ratio for stroke rose for users of all oral progestogens compared to non-users of steroid hormonal contraceptives who had no history of hypertension, from 7.2 (6.1–8.5) to 12.4 (4.1–37.6).

The authors state that although the study has only a small number of disease cases (11 VTE cases and a total of 37 venous and arterial thromboembolic events), the data suggest that there is no or only a slight increase in risk of stroke, VTE or myocardial infarction for use of oral or injectable progestogen-only or combined estrogen/progestogen-containing contraceptives.

By contrast, the sub-analysis of a Dutch case-control study [131] with 20 VTE cases and 15 controls among users of depot-medroxyprogesterone acetate yielded a three-fold VTE risk (95% confidence interval: 1.2–7.5) compared to that for non-users of hormonal contraception (i.e., the study found similar risks for depot-medroxyprogesterone acetate and levonorgestrel-containing COCs). The WHO study and especially the Dutch study, however, have considerable methodological shortcomings (e.g. insufficient information on VTE risk factors to adequately adjust for preferential use of non-estrogen contraceptives by risk patients, limited comparability of cases and controls). A conclusive statement about VTE and CHD risk is therefore not possible on the basis of these studies.

Van Hylckama Vlieg et al. [131] examined the risk of DVT for depot-medroxyprogesterone acetate compared to a levonorgestrel-releasing intrauterine device. Multi-variant analyses considering environmental and genetic factors were performed in the course of a large case-control study on risk factors for venous thrombosis. These analyses took premenopausal women aged 18–50 who were neither pregnant nor within 4 weeks post-partum, and who were not taking oral contraceptives, for a total of 446 cases and 1146 controls. Injectable depot-medroxyprogesterone acetate was associated with a 3.6-fold (1.8–7.1) higher risk of venous thrombosis compared to that for non-users of hormonal contraceptives. No higher risk was found for the levonorgestrel-releasing intrauterine device (odds ratio 0.3; 0.1–1.1). Because too few women used a contraceptive patch or implant, unfortunately no risk estimate could be given here. The risk of venous thrombosis was higher for depot-medroxyprogesterone acetate, whereas a higher risk for the levonorgestrel-releasing intrauterine device could be excluded. This device is considered one of the safest contraceptive options with respect to venous thrombosis.

In addition, attempts can be made to extrapolate from epidemiological data gathered for oral use to depot use of the corresponding progestogen. As already mentioned, Lidegaard et al. (2009) [57] indicate that progestogen-only preparations in women of fertile age without previous cardiovascular disease are not associated with an increased risk of VTE; progestogen-only pills with levonorgestrel or norethisterone: rate ratio for VTE: 0.59 (0.33–1.03) (study size: 65,820 woman-years) or with 75 µg desogestrel rate ratio 1.12 (0.36–3.49) (study size: 9,044 woman-years). Extrapolation assumes that average serum levels correspond. Complete comparability is not given, however, as it is not clear whether the constant steroid levels in the steady state under depot progestogens have effects on VTE risk similar to those of the strongly fluctuating levels with oral progestogens.

Overall, there is no sufficient demonstration of higher VTE or CHD risk for depot progestogens. However, a slightly higher VTE risk cannot be fully excluded.

WHO Medical Eligibility Criteria: For known thrombophilic mutations (e.g. factor V Leiden, prothrombin G20210A mutation, protein S, protein C or antithrombin deficiency) (analogy: mini-Pill): **Classification: grade 2 (broadly usable method).** Due to the possible conversion of norethisterone enanthate to ethinyl estradiol, the author team recommends classifying the norethisterone enanthate-containing depot injection (Noristerat) as grade 3. This statement is based on the study by Chu et al. (2007) [151] showing that norethisterone acetate is converted to ethinyl estradiol following oral intake of 10–40 mg per day at a rate of 0.2–0.33%.

Summary:
- Increased VTE risk has not been sufficiently demonstrated, although it also cannot be fully excluded.
- According to the WHO criteria, these preparations have a grade 2 classification for use by VTE risk patients. The authors of this paper, however, advise against doing so because if unexpected complications arise, the progestogen can remain systemically active for 2–3 months and in some cases for up to 12 months.

4.2.7. Postcoital Pills

Post-coital hormonal methods of shifting or suppressing ovulation following unprotected sexual relations.

Product descriptions:
Yuzpe method (1.0 mg levonorgestrel and 100 µg ethinyl estradiol): Venous and arterial thromboembolism in authorization studies: None published. No VTE cases occurred in a study by Vasilakis et al. [152] of two doses of 100 µg ethinyl estradiol and 0.5 mg levonorgestrel covering 12,416 woman-years.
Metabolic studies: A randomized clinical study by van Rooijen et al. [153] examined the effects of emergency contraception with levonorgestrel alone and in combination with ethinyl estradiol. Both methods led to accelerated thrombin generation in the Hemker test, with a stronger effect shown by the combination with ethinyl estradiol.

Levonorgestrel (0.75 or 1.5 mg): The FDA (www.fda.gov/ohrms/dockets/ac/03/briefing/4015B1_12_FDA-Tab%205-1-Medical%20Officer%20Review.doc) (retrieved 9.9.2011) lists data from 22 studies with approximately 15,000 study participants Good overall tolerability is reported, with no venous or arterial thromboembolism.
Metabolic studies: A randomized clinical study by van Rooijen et al. [153] examined the effects of emergency contraception with levonorgestrel alone and in combination with ethinyl estradiol**.** Both methods led to accelerated thrombin generation in the Hemker test, with a stronger effect shown by the combination with ethinyl estradiol.

ellaOne® (30 mg ulipristal acetate): No venous or arterial thromboembolism was observed in an authorization study (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM215510.pdf) (retrieved 9.9.2011) with 4,636 participants. In clinical studies with several 1000 participants no VTE had been observed. In addition, there was no pharmacovigilance reporting of VTE for the more than 270,000 women who have already taken ellaOne® in the post-marketing phase [Schuller, personal communication based on Periodic Safety Update Report July 2011].
Metabolic studies: Hemostaseological studies have not been done.

4.2.8. Copper IUDs
Product description: Copper-containing intrauterine devices that inhibit sperm ascension and ability to fertilize the egg cell via continuous release of copper in the uterine cavity. Also inhibit implantation.

WHO Medical Eligibility Criteria: Classification as grade 1 (method can always be used).

Restrictions: If there are contraindications for intrauterine devices (see SPC): e.g. inflammatory genital diseases, anomalies in the uterine cavity (e.g. myomas, septation) etc. For nulliparous women, insertion only after careful risk/benefit analysis.

4.2.9. Additional Options
For women: Additional current, non-hormonal alternatives include chemical methods (e.g. spermicides), barrier methods (e.g. cervical caps, diaphragms), and natural family planning methods (see relevant literature). A permanent method consists of uterine tube sterilization.

For men: Feasible methods include condoms, as well as the permanent option of vasectomy.

4.3. Contraception for Specific Patient Groups

4.3.1. Contraception for Women Taking Anticoagulants on a Short- or Long-Term Basis
The WHO Medical Eligibility Criteria recommend the use of progestogen-only preparations for women undergoing anticoagulation treatment (grade 2 classification). In Germany, this recommendation can be viewed in more nuanced form, for the following reasons:
– The INR can be monitored at any time and at short intervals in Germany. If monitoring (at least every 2 weeks) confirms levels in the accepted range, anticoagulation treatment should not prohibit use of an ovulation inhibitor.
– Use of an ovulation inhibitor prevents ovulation or endometrium-related blood discharge.

However, when anticoagulation is stopped, the ovulation inhibitor should be discontinued approximately 6 weeks beforehand because of the residual coagulation-promoting effect.

Hypermenorrhea is a not infrequent problem with ongoing anticoagulation, and should be actively discussed with patients. Signs of anemia and iron deficiency should also be watched for and treated. Ways of treating hypermenorrhea under anticoagulation include:
– Mirena®
– Ovulation inhibitors
– COC intake without interruption ("off label" recommendation)
– If family planning is concluded: e.g. endometrial ablation

COC use should never be restarted without a risk evaluation following cessation of vitamin K antagonists.

Anticoagulation treatment (phenprocoumon, warfarin) carries a higher risk of teratogenesis, especially if taken in the 6–8th weeks of gestation (OR: 3.9). The miscarriage rate is 42%, with higher rates also for premature births (16%) and intrauterine growth retardation. A suitable safe means of contraception is therefore needed, and should be actively discussed with the patient [154].

Ideally, these women should plan pregnancies with care and possibly switch from oral anticoagulants to low molecular-weight heparin about 2 cycles before conception.

4.3.2. Contraception before Surgical Operations
See section 2.4.3.

4.3.3. Contraception During Puerperium
Women should not take combined contraceptives for three weeks post-partum. If they are no longer nursing, they can then use a COC. It should be considered, however, that although VTE risk is highest within the first 3 weeks post-partum, it remains elevated for a period of approximately 3 months (Lidegaard, 2007: www.lidegaard.dk/Slides/OC%20epidem/PP%2007-11-20%20en.pdf; slide 16)

Progestogen-only preparations can be taken before day 21 post-partum, and also while nursing.

4.3.4. Emergency Contraception
For healthy women: No restriction in selecting a preparation.

For women with increased VTE risk: Given the extensive data on levonorgestrel-only preparations, and due to the

thrombogenic potential of estrogens, the authors advise against progestogen/estrogen combinations and in favor of a levonorgestrel-only preparation.

4.3.5. WHO Recommendations for At-Risk Patients

The World Health Organization has published contraception classification criteria for women with specific medical risks. The "WHO Medical Eligibility Criteria" are available on the Internet (Tabs. 12,13).

Table 13 shows contraceptive recommendations for known thrombophilic factors (e.g. factor V Leiden mutation, prothrombin G20210A mutation, protein S/protein C/antithrombin deficiencies), and different risk situations affecting lupus erythematosus.

The authors of this paper, however, hold that depot progestogens should only be recommended to risk patients following the most careful of risk/benefit analyses.

5. Summary and Recommendations for Use

Preamble with liability disclaimer: All recommendations regarding the use of contraceptives by non-healthy individuals are "off-label" recommendations which the author team has compiled in consensus to the best of its knowledge and belief on the basis of the available literature. The physician must make each individual decision on the basis of an individual risk/benefit analysis. The information contained herein should assist in that process, but neither the authors nor the publishers assume any type of liability individually or collectively with respect to the information or its use (see disclaimer).

5.1. Women without Thrombophilia Risk who Desire Contraception

Contraceptive counseling: The following alternatives depend on age, family size, and planned duration of contraception: the Pill (COC), vaginal ring, Mirena®, contraceptive patch, hormonal implant, mini-Pill, depot progestogen. Each case must be decided individually, with consideration of the specific life situation, risk factors, "non-contraceptive benefits", and also "shared decision-making" aspects.

Estrogen dose: The lower the dosage of ethinyl estradiol, the higher the rate of intermenstrual bleeding; whereas the higher the dose, the greater the effect on the coagulation system and the probability of thromboembolitic complications. In the absence of specific VTE risk factors, a preparation with the lowest possible dosage of ethinyl estradiol (≤ 30 µg estradiol) should be selected. If contraindications are present, non-estrogen methods should be used.

Ethinyl estradiol versus estradiol or estradiol ester: The extent to which further risk can be further minimized by the use of estradiol or its ester needs to be shown by epidemiological studies.

Progestogen selection: Progestogens are chosen with consideration of whether signs of androgenization are present (e.g. acne vulgaris, seborrhea, hirsutism). In this case, androgen-antagonist progestogens are prescribed, e.g. cyproterone acetate, chlormadinone acetate, dienogest or drospirenone.

Although a higher VTE risk for the **progestogens** desogestrel, gestoden and cyproterone acetate has not been established beyond doubt, a somewhat higher risk than for other progestogens should be assumed in benefit/risk considerations in the interest of patient protection.

5.2. Women with Heightened Thrombophilia Risk who Desire Contraception

Family history:

- **Family history of CHD:** Conditions/events in parents before the age of 45 (some sources use 50): myocardial infarction in the mother; stroke, thrombosis, thromboembolism in either parent. Diseases in the parents and siblings of the parents, as well as in the siblings of the patient, can be added to the assessment.
  For CHD risk above and beyond VTE risk, metabolic conditions including lipid metabolic disorders, diabetes mellitus, hypertension etc. also play a role.
- In the study by Dinger [9], approximately 2% of women of fertile age have a positive first-degree family history of fatal myocardial infarction/stroke before the age of 50; similarly, first-degree family history of deep venous thrombosis and pulmonary embolism is reported by approximately 3% of women of fertile age.
- For positive family histories of cardiovascular disease, further clarification may be needed by laboratory testing, possibly family screening.
- In clinical practice, family history is often more useful than laboratory tests for thrombophilia in assessing the risk of venous thrombosis [31].

Thrombophilia testing (laboratory):

- Thrombophilia parameters can help in assessing the risk of VTE. However, laboratory tests show thrombophilia in only approximately 50–60% of patients who have had VTE. Negative thrombophilia results, therefore, do not exclude a higher risk of VTE. This is important to note when determining risk, especially if lab results are negative but family history is positive.

5.3. Contraceptive Counseling with Consideration of VTE Risk Factors

Non-hormonal contraceptive methods: Barrier methods, chemical methods, natural family planning, etc. Contraceptive effectiveness is inferior to that of hormonal methods.

Copper IUDs are the only method that the WHO also recommends for women with a higher risk of thrombosis (grade 1 classification), but are not considered acceptable by all women.

Progestogen-only pills or non-estrogen ovulation inhibitors: Epidemiological studies show low risk of VTE [57].

Progestogen-only contraceptives do not appear to be associated with higher risk, and can therefore be used by thrombophilic individuals or post-thromboembolism. The same applies to Mirena®.

The WHO classifies them as possible second-choice methods (grade 2). Consistent intervals (3-hour time window per day) are needed for the classical mini-Pill, the window for the non-estrogen ovulation inhibitor (Cerazette) is up to 12 hours. Higher occurrence of menstrual disorders compared to COCs.

VTE risk data for the desogestrel-only contraceptive Cerazette are less robust than those for levonorgestrel-only contraceptives. It is therefore unclear

whether there are slight differences between these non-estrogen preparations.

Hormonal implants: Implanon®: No epidemiological studies on VTE risk. No available data from authorization studies.

Risk assessment similar to mini-Pill; in contrast to depot progestogens, Implanon can be promptly removed if side effects should occur.

Depot progestogens: No available data from authorization studies.

The WHO classifies them as a possible second-choice method (grade 2); the authors of this paper advise caution, however, because depending on the preparation they can have long-term effects of 3–12 months following the last injection.

Combined oral hormonal contraceptives, vaginal ring, and contraceptive patch:
- **Absolute contraindication:** Previous arterial or venous thromboembolism (without current therapeutic anticoagulation).
- **Relative contraindication** on individual case-by-case basis.

5.4. Limitation of the WHO Contraception Prescription Recommendations

A limitation of the WHO contraception prescription recommendations [110, 155] for women with specific medical risks is that these recommendations do not differentiate for thrombogenic mutations and whether these are homozygous or heterozygous (e.g. factor V Leiden mutation, prothrombin G20210A mutation). They also do not cover polymorphisms or the degree of protein C, protein S and antithrombin deficiency.

The WHO criteria only list the thrombophilia results, without further differentiation:

"Known thrombogenic mutations (e.g., factor V Leiden; prothrombin mutation; protein S, protein C, and antithrombin deficiencies)."

For treating certain types of illnesses, gynecologists depend on hormonal methods, which can include combined oral hormonal contraceptives.

Table 16 differentiates between two groups, of lower and higher VTE risk respectively, for use of estrogen-containing contraceptives. Taking account of these two risk groups, the flow diagram in Figure 12a, b shows treatment recommendations for estrogen-containing COCs in connection with family history, patient history, and thrombophilia diagnoses. Ultimately, only in the case of positive family history, negative patient history, and negative thrombophilia lab results can COCs be used for appropriate indications (see disclaimer).

A relevant thrombosis risk with hereditary thrombophilia very probably only arises when in addition to the actual (genetic) feature, e.g. heterozygous factor V Leiden mutation, other factors are also present which are currently not measurable. They can be seen in anamneses: patient history of thrombosis or embolism, family history, and/or multiple miscarriages. This also applies to the data for counseling pregnant women who show "only" heterozygous factor V Leiden mutation but no clinical prehistory.

Testing for thrombophilia should be prompted by positive patient or family history; otherwise the laboratory results alone are of relatively little use in estimating individual risk.

For all patients with known thrombophilia and who do not show a positive own or family history: if gynecologists prescribe hormonal contraception, they must undertake careful risk/benefit analyses and discuss them with the patient – also regarding psycho-social issues in the event of unwanted pregnancy – in particular for girls/young women – as well as with respect to the considerably higher risk of VTE.

Also with these patients, alternatives to hormonal contraception should always be discussed in detail. In each case an individual decision must be made with careful discussion of the benefits and risks and with "shared decision-making" considerations. The authors can only present selection models here; liability in each individual case is borne entirely by the attending physician.

It remains to note that this information refers to individual case decisions that are not backed by studies and not considered in the WHO recommendations.

Table 16. VTE risk assessment for different thrombophilia constellations with class A lower and class B higher

Risk profile A
Moderately elevated DVT risk
Heterozygous factor V Leiden mutation G1691A without own or family history of DVT, and without additional risk factors
Heterozygous prothrombin G20210A mutation without own or family history of DVT, and without additional risk factors
Heterozygous protein C deficiency without own or family history of DVT, and without additional risk factors
Heterozygous protein S deficiency without own or family history of DVT, and without additional risk factors
Risk profile B
Strongly elevated DVT risk
Previous thrombosis or arterial occlusion
Thrombophilia and positive family history
Thrombophilia and additional risk factors such as – smoking – obesity – varicose veins – regular corticoid intake – chronic intestinal inflammation
Homozygous factor V Leiden mutation G1691A, with or without DVT history
Homozygous prothrombin G20210A mutation with or without DVT history
Combined heterozygous factor V Leiden mutation + prothrombin G20210A mutation with or without DVT history
Demonstrated antiphospholipid syndrome
Antithrombin deficiency
Other thrombophilia combinations
Insufficient study results for lipoprotein (a)
No contraception limitations for MTHFR polymorphism

The following thrombophilia constellations are a contraindication for combined oral hormonal contraceptives, even if the patient's own and family history are negative:
- factor V Leiden homozygous,
- prothrombin G20210A homozygous
- factor V Leiden heterozygous + prothrombin G20210A mutation
- factor V Leiden homozygous + prothrombin G20210A mutation
- antithrombin deficiency[6]
- protein C deficiency[6]
- protein S deficiency[6]

[6] No clear cut-off exists to separate severe cases from non-severe cases of inhibitor deficiencies (Luxembourg 2011, personal communication)

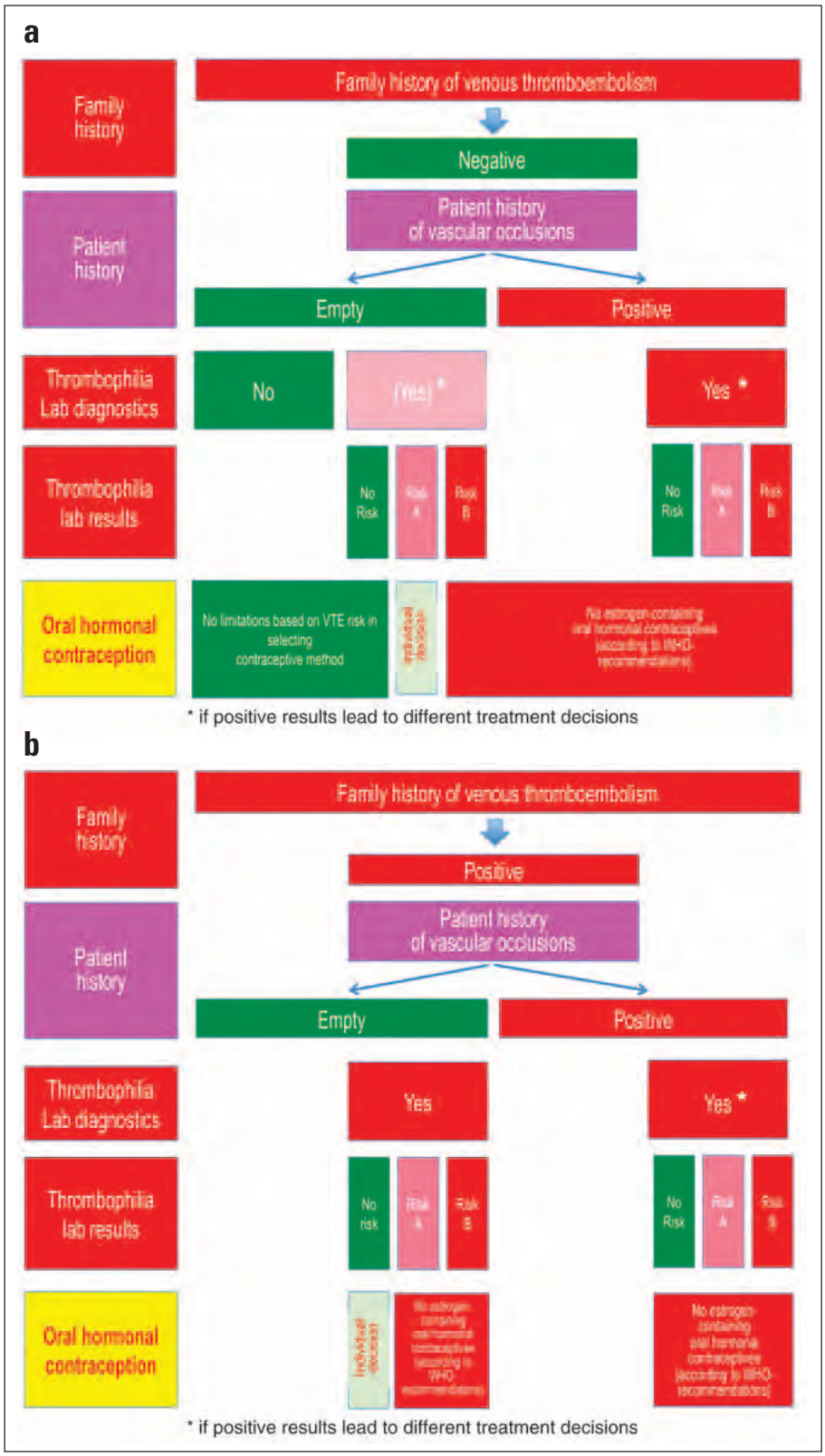

Figure 12 a, b. Flow diagram for assessing VTE risk (based on family/patient history and thrombophilia tests) in choice of contraceptive. Source: T. Rabe.

For the following pathological results, a specialist in internal medicine or a hemostaseologist specializing in thrombophilia should be consulted:

– presence of antiphospholipid antibodies

5.5. Previous thrombosis combined with exogenous event (e.g. accident, immobilization) without laboratory confirmed thrombophilia

No data confirm that COCs are safer for patients with a history of reversible risk-associated thrombosis than for those with a history of idiopathic thrombosis. Decisions as to whether the recurrence risk following risk-associated VTE is low should not be made by the gynecologist.

Instead, decisions should be made with an angiologist and hemostaseologist. In any event, such decisions can only be made on an individual case basis following careful risk/benefit analysis and patient counseling regarding treatment options and associated risks.

Even for women with a negative family history and no laboratory confirmed thrombophilia, who have had a thrombosis in connection with an external non-hormonal dependent event, no estrogen-containing hormonal contraceptives should be prescribed because there are currently no data for this situation showing that estrogen-containing COCs do not increase the risk of recurrent thrombosis. According to the WHO, the first preference should be a copper IUD (or if no more children are planned, sterilisation for either the man or the woman); as a less preferred alternative, consideration could be given to a classical mini-Pill with norethisterone or levonorgestrel or a levonorgestrel-containing IUD. In such cases the possible use of depot progestogen injections or a desogestrel-containing mini-Pill (non-estrogen ovulation inhibitor), categorized by the WHO as grade 2, should be viewed with caution. In relationships with rare sexual intercourse a combination of condoms and spermicides should be discussed, especially if condoms are currently being used for sexually transmissible disease prevention. But with unsure methods the considerably higher risk of VTE and of unplanned pregnancy should also be considered.

However, if serious treatment considerations (e.g. severe menstrual disturbances, acne vulgaris with severe distress following exhaustion of dermatological means of treatment, etc.) require the use of an estrogen-containing COC in individual cases, the patient must be extensively informed and counseled about the risk-benefit analyses and possible consequences of treatment options, and this must be confirmed with a written declaration of informed consent as part of the medical records.

This statement is based on the following observations and studies: The risk of recurrent thrombosis following an initial VTE is approximately 20–30% within 10 years [156–159]. The lifetime risk of recurrent thrombosis is higher for men than for women, with the latter showing a longer interval between first-time and recurrent thromboses. Lijfering et al. (2009) [160] trace this to women having first-time thromboses at a younger age due to hormonal factors. In contrast to this, Douketis et al. (2011) [161] show no difference between men and women in recurrence with or without hormone-associated VTE. Christiansen et al. (2010) [162] indicate that the risk profile for recurrent thrombosis differs considerably from that for first-time thrombosis.

Only one study group (49 women taking OCs, 18 postmenopausal women taking HRT) showed a lower risk of recurrent VTE for women with a non-provoked estrogen-dependent VTE, but the risk is also not significantly lower than for women without estrogen intake [163]. This small study could not be considered in the above-described risk assessment.

Finally, it is unclear whether previous thrombosis/embolism with trigger factors and without estrogen influence increases the risk of recurrent thrombosis with estrogen intake. For this reason as a general principle women who have had a thromboembolic event should not use estrogen-containing contraceptives.

5.6. Approach for Specific Risk Groups

– Women taking oral anticoagulants should be actively offered contraception on account of teratogenesis and a substantially higher rate of pregnancy complications. Every type of contraception is possible here, given stable adjustment of anticoagulation therapy. Ethinyl estradiol-containing contraceptives need to be discontinued 6 weeks before anticoagulation is stopped. Careful INR adjustment and regular INR testing should be done at least every two weeks.
– Regarding the choice of contraception for patients with risk factors, see the 2009 WHO Medical Eligibility Criteria for contraceptive use (2010 update) [110], which analyze different patient health situations and recommend suitable contraceptive methods (Tabs. 12, 13).

Depending on the seriousness of the laboratory results – both separately and in combination – decisions must be made on an individual basis as to whether the woman should have to do without hormonal contraception.

5.7. General Treatment Recommendations

– If combined hormonal oral contraceptives are used, then preparations with lower EE doses – depending on tolerability and menstrual pattern – and progestogens with low VTE risk (Tab. 14).
– Reduce cigarette smoking if applicable, or better yet stop altogether
– Reduce weight if applicable
– Avoid additional risk factors such as exsiccosis, immobilization/inactivity during extended travel.

5.8. Further Notes on Contraception Decisions

Combined oral hormonal contraceptives can be required for "non-contraceptive benefits", namely for conditions that cannot be treated otherwise.

– certain types of **acne vulgaris** (following dermatological consultation and exhaustion of non-hormonal means of treatment). An alternative for severe otherwise treatment-resistent acne as an "off-label" recommendation in individual cases: chlormadinone acetate (e. g. Chlormadinon 2 mg fem Jenapharm®) (day 1–5) plus transdermal estrogen (e.g. Estreva® gel, Gynokadin® gel) then 3-day break (Rott 2011, personal communication).
– **irregular menses:** following unsuccessful treatment with selected phytopharmaceuticals
– **dysmenorrhea:** following unsuccessful treatment with selected phytopharmaceuticals

In the event of positive patient or family history, the decision as to whether to prescribe a hormonal contraceptive in any individual case must follow clinical consideration and individual, well documented counseling.

Non-hormonal contraceptives can be considered as alternatives:

– spermicides, condoms
– copper IUD
– tubal sterilization
– vasectomy

Follow-up exams for oral hormonal contraceptives:
Case history: If VTE risk factors are present, query for early symptoms of cardiovascular disease (non-specific pain [see "ACHES" checklist]), migraines, impaired vision, medication history, leg symptoms.

Clinical testing: Blood pressure/pulse rate at rest.

Laboratory tests:
Only with relevant indication: e.g. HbA1c, lipids, HOMA index, liver values.

D-dimer test: D-dimer concentrations can be helpful in assessing the recurrence risk of venous thrombosis.

Paraclinical testing:
Ultrasound only with relevant indication: Androgenization with suspicion of polycystic ovaries, ovarian cysts, endometriosis, etc.

5.9. Notes on Evaluating Medical Studies on VTE and Contraceptives

For all case-control studies, it is important that the control group is representative of the user population. In addition, cases and controls should be comparable with respect to prevalence of major known prognostic factors. In theory, controls can be matched to cases. In practice, however, it is seldom possible to find controls for each VTE case who match more than 2 or 3 of the prognostic factors. It is therefore necessary to adjust for the differences in "non-matched" prognostic factors. This means that information on the major prognostic factors – sex, age, weight (BMI), duration of exposure, cigarette smoking, family history, and thrombophilia diagnoses – has to be available. Because it is known that approximately one half of VTE cases show pathological thrombophilia test results, information about family history at least should be available for both cases and controls. This is generally only the case with field studies. Without knowledge of thrombophilia diagnostics or family history, as was the case for all studies in the 1990s on comparative VTE risk for second and third-generation progestogens, it is not possible to con-

clusively evaluate VTE risk. Studies should also record duration of Pill use when thromboses occur as well as Pill-free intervals and previous use of other OC preparations.

Reports on VTE and contraceptives in Germany are compiled by the Arzneimittelkommission der deutschen Ärzteschaft or by the Bundesinstitut für Arzneimittel und Medizinprodukte. This type of spontaneous reports, however, cannot provide the basis for comparative risk assessment of different preparations. Such reports are better suited for identifying signs of risk that should then be systematically investigated.

For Europe, data are compiled and evaluated by the European Medicines Agency (EMA) in London, and for the USA by the FDA.

A spontaneous reporting system yields only a low percentage of even serious undesired events. This percentage is strongly influenced by external factors. Spontaneous reporting procedures by healthcare professionals can be negatively influenced by possible liability issues. This is particularly the case in the USA. On the other hand, aggressive advertising by lawyers there can encourage patients to report undesired results and thus establish causal connections between conditions and potential factors. Independently of the individual country, however, the greatest influence is exerted by the respective mass media.

Hasty risk assessments on the basis of individual studies are dangerous – whereas compilation of prospective data by large-scale studies with clear end points (e.g. the EURAS study) provides a more reliable basis for evaluating the VTE risk of hormonal contraceptives. For other questions, it can often be cost-effective and time-saving to use databases. When examining the VTE risk for hormonal contraception, however, it should be noted that the data in these databases is not gathered for the primary purpose of scientific study. Diagnoses and tests for suspected conditions are used to justify therapeutic and diagnostic measures – which means that diagnostic validity is often limited, only a small percentage of risk factors are documented, and exposure data are based on prescriptions which in the case of OCs are not at all equivalent with the actual start of exposure. Not infrequently, this results in erroneous assignment of severe undesired events and exposure.

Conflict of Interest

The author team reserves the right to update this statement in 12 months if new studies lead to changes in relevant material.

T. Rabe has held talks for Jenapharm, Bayer-Schering Pharma, HRA, and MSD, receiving payment and in some cases travel expenses. Some advisory board activity. Chairman of the Deutsche Gesellschaft für Gynäkologische Endokrinologie und Reproduktionsmedizin e.V. (DGGEF).

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M. Ludwig has held events together with Bayer-Schering Pharma, Grünenthal and Jenapharm and received payment for presentation or consulting functions. He is a member of a private laboratory and medical group that provides gynecological-endocrinological and hemostaseological services.

H. Rott receives no funding from the pharmaceutical industry; she is a member of a private medical and laboratory group specializing in hemostaseological services.

J. Dinger directs a private institute (Berlin Center for Epidemiology and Health Research) that performs epidemiological studies financed by unconditional grants from manufacturers of COCs – Bayer-Schering Pharma and MSD. Some of these studies are cited in this statement. No paid presentation or consulting work.

R. Bauersachs does not state any conflict of interest with respect to this statement.

A. O. Mueck has given talks for Bayer-Schering Pharma, MSD, Jenapharm, and HRA, receiving payment and in some cases travel expenses. Advisory board activities for the companies named. President of the Deutsche Gesellschaft für Menopause.

B. Luxembourg works at the Department of Molecular Hemostaseology for the German Red Cross Blood Donation Service (DRK-Blutspendedienst) of Baden Württemberg-Hessen and the University Hospital Frankfurt. No other personal or business sources for conflict of interest.

C. Albring is President of the Berufsverband der Frauenärzte e.V. (German Association of Obstetricians and Gynecologists) and Chairman of the AG Hormone. He has no financial or other connection with any pharmaceutical industry.

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