Endocrine determinants of haemostasis and thrombosis risk: Focus on thyroid hormone
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The Influence of Thyroid Function on the Coagulation System and its Clinical Consequences

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Several studies indicate that low plasma levels of thyroid hormone shift the haemostatic system towards a hypocoagulable and hyperfibrinolytic state while high levels of thyroid hormone lead to more coagulation and less fibrinolysis. Low levels of thyroid hormone thereby seem to lead to an increased bleeding risk while high levels, by contrast, increase the risk of venous thromboembolism. Key players in this interaction are factor VIII and von Willebrand Factor; hypothyroidism causes a higher incidence of acquired von Willebrand’s syndrome and with increasing levels of free thyroxine, levels of factor VIII and von Willebrand Factor increase gradually.

Here, we discuss the literature on the effect of thyroid hormone on the haemostatic system and the associated risk of bleeding and venous thromboembolism. Patients with hypothyroidism are at increased risk of developing bleeding complications, which could be relevant in patients undergoing invasive procedures. Furthermore, physicians should be aware of the possibility of hyperthyroidism as underlying risk factor for venous thromboembolism, especially in unexplained cases. Clinical studies are needed to further investigate the significance for general practice of these findings.
Thyroid hormone is known to affect several cardiovascular parameters. Hypothyroidism is associated with an unfavorable lipid profile because thyroid hormone stimulates the clearance of cholesterol in the liver [1]. Overt and subclinical hypothyroidism increase the risk of cardiovascular disease and mortality [2, 3]. Hyperthyroidism is known to increase the risk of atrial fibrillation [4, 5] and overt as well subclinical hyperthyroidism increases the risk of arterial thrombosis and mortality [6-8]. Although less known, thyroid hormone also influences the coagulation system. Several studies indicate that low levels of thyroid hormone shift the haemostatic system towards a hypocoagulable and hyperfibrinolytic state while high levels of thyroid hormone lead to more coagulation and less fibrinolysis. Low levels of thyroid hormone thereby seem to lead to a higher bleeding risk while high levels, on the other hand, increase the risk of venous thromboembolism. The clinical implications of the effects of thyroid hormone on the haemostatic system, however, have received relatively little attention. Therefore, for this review we set out to evaluate and discuss the effect of plasma thyroid hormone concentrations on the haemostatic system and its associated risk of bleeding and venous thromboembolism.

EFFECTS OF THYROID HORMONE ON MARKERS OF COAGULATION AND FIBRINOLYSIS

As early as 1965, Simone et al. showed significantly reduced levels of factor (F) VIII, FIX and FXI in hypothyroid patients [9]. More recently, increased bleeding time, prothrombin time (PT) and activated partial thromboplastin time (APTT), and decreased FVIII activity as well as von Willebrand Factor (VWF) activity were observed in patients with overt hypothyroidism when compared with controls [10]. These abnormalities were reversed after treatment with levothyroxine. These results were supported by a prospective study showing that severe short-term hypothyroidism in patients following a total thyroidectomy for thyroid cancer was associated with...
significantly lower levels of VWF and FVIII compared with the same patients when they were in euthyroid state [11]. An observational cohort study showed that hypothyroidism resulted in hyperfibrinolysis (shorter clot lysis time) and a reduced activated thrombin-activatable fibrinolysis inhibitor (TAFIa)-dependent prolongation of clot lysis [12]. Other analyses in this study showed lower clot maximum absorbance, shorter clot lysis time, smaller clot lysis area and less compact fibrin clots, all of which abnormalities were resolved upon restoration of euthyroid state [13]. Two studies performed by the same group compared untreated hypothyroid patients to age-matched healthy controls and found that FVII activity, and levels of fibrinogen, antithrombin (AT), plasminogen activator inhibitor-1 (PAI-1) and thrombomodulin (TM) as well as TAFI levels were significantly increased in patients with hypothyroidism, whereas FV, FVIII, FX, VWF, protein C and protein S activities, and tissue factor pathway inhibitor (TFPI) levels were significantly decreased [14, 15]. Since these results seem to result in contradicting effects on the coagulation system (e.g. lower levels of FVIII and vWF suggest a hypocoagulable state whereas decreased levels of protein C and S suggest a hypercoagulable state) these studies are hard to interpret in functional terms.

In subclinical hypothyroidism, there does seem to be a net prothrombotic effect with higher levels of FVII, PAI-1 and tissue plasminogen activator (t-PA), compared with healthy controls, while these levels were reduced after 6 months of therapy with levothyroxine [16]. TAFI levels appeared to be increased in subclinical hypothyroidism [17] and another study showed that global fibrinolytic capacity was significantly lower in patients with subclinical hypothyroidism, compared with a control group [18].

The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors has been described in several studies in the past decades. A recent systematic review and meta-analysis reported the influence of hyperthyroidism on the coagulation and fibrinolytic system in vivo [19]. A total of 29 articles consisting of 51 studies were included. The studies were of varying quality. Five cross-sectional studies (hyperthyroid subjects and euthyroid controls), 4 intervention studies (before and after treatment in hyperthyroid patients), and 4 experimental studies (before and after use of thyroid hormone in euthyroid subjects) of medium/
high quality were used for meta-analysis. In the 4 medium quality observational cross-sectional studies, levels of VWF, fibrinogen and D-dimer were significantly increased in persons with subclinical hyperthyroidism compared with euthyroid controls [20-22]. In patients with overt hyperthyroidism only fibrinogen levels had been measured which were slightly increased [23]. In the 4 medium quality intervention studies, increased levels of plasma fibrinonectin, VWF, thrombomodulin and PAI-1, and decreased levels of (t-PA) were observed during hyperthyroidism when compared to the euthyroid state after anti-thyroid treatment [24-27]. Four experimental studies investigated laboratory parameters in healthy volunteers taking thyroid hormone for a specific period of time and this exogenous thyrotoxicosis led to increased plasma levels of tissue factor, FVIII, FIX, FX, VWF, fibrinogen, D-dimer and PAI-1, and resulted in a prolongation of clot lysis time and shortening of aPTT [28-30]. In the meta-analysis, it was concluded that hyperthyroidism shifts the haemostatic balance towards a hypercoagulable and hypofibrinolytic state, which was observed in both endogenous and exogenous hyperthyroidism, and in both subclinical and overt hyperthyroidism. After publication of this systematic review, another study of experimental hyperthyroidism added that the procoagulant factors XIII subunit B, FII, FV, and FXI also correlated with higher FT4 levels [31]. Also, a positive correlation could be found for FIX. Concomitantly, plasminogen, the main enzyme promoting fibrinolysis, was decreased. Others investigated patients who shifted from severe hypothyroidism to mild hyperthyroidism during thyroid cancer treatment and showed in vitro that during levothyroxine treatment, the activation times of platelet adhesion and aggregation after stimulation with collagen and epinephrine/adenosine-diphosphate were significantly shortened [32]. The previously shown effects of increasing levels of thyroid hormone on VWF and FVIII were confirmed in this study. The effect of exogenous hyperthyroidism on TAFI was studied in healthy volunteers who were randomised to receive levothyroxine or no medication for 14 days in a crossover design [12]. Thyroid hormone excess resulted in a hypofibrinolytic condition and in an enhanced TAFIa-dependent prolongation of clot lysis. In addition, a trend towards decreased plasma TAFI levels was observed. Hooper et al. showed that hyperthyroid subjects displayed higher clot maximum absorbance compared to controls and longer clot lysis time [33], which
correlated with FT$_4$ levels. Plasma levels of fibrinogen and PAI-1 were significantly higher in patients compared to controls.

In Table 1, we summarized the available evidence on the influence of thyroid hormone status on haemostatic balance. These results suggest that hypothyroidism leads to a hypocoagulable and hyperfibrinolytic state which could translate in a higher risk of bleeding. At the other end of the spectrum, hyperthyroidism leads to a hypercoagulable and hypofibrinolytic state which could lead to a higher risk of venous thromboembolism.

Table 1. Available evidence on the influence of thyroid hormone status on haemostatic balance, risk of bleeding and risk of venous thromboembolism

<table>
<thead>
<tr>
<th>Thyroid function</th>
<th>Haemostatic balance</th>
<th>Increased risk</th>
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<tbody>
<tr>
<td></td>
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<td>Possibly abnormal vaginal bleeding [37, 38, 55]</td>
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<tr>
<td>Subclinical hypothyroidism</td>
<td>Possibly hypercoagulable state [16-18]</td>
<td>Possibly abnormal vaginal bleeding [39]</td>
</tr>
<tr>
<td>Lower levels of FT$_4$ within</td>
<td>Possibly hypocoagulable state [41]</td>
<td>Possibly bleeding [40]</td>
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<tr>
<td>reference ranges</td>
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<tr>
<td>Higher levels of FT$_4$ within</td>
<td>Possibly hypercoagulable state [23]</td>
<td>VTE [41-43]</td>
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<tr>
<td>reference ranges</td>
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<tr>
<td>Subclinical hyperthyroidism</td>
<td>Possibly hypercoagulable state [20-22]</td>
<td>Unknown</td>
</tr>
<tr>
<td>Overt hyperthyroidism</td>
<td>Hypercoagulable state [12, 24-33] VTE [47-50]</td>
<td></td>
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</table>

VTE indicates venous thromboembolism; FT$_4$, free thyroxine.

BLEEDING

In Table 1, the available evidence on the influence of thyroid hormone on the risk of bleeding and thrombosis is summarized. In line with the observed effects on the coagulation system in patients with hypothyroidism, a notable prevalence of aVWS has been observed in hypothyroid patients. This association was first addressed by several case reports. In a systematic review on hypothyroidism and aVWS, published in 2008, several epidemiological studies of low to medium quality were identified, and no studies of high quality [34]. Still, the results supported a pivotal role of VWF in the bleeding tendency in patients with overt hypothyroidism. The bleeding episodes
were mainly mucocutaneous, the bleeding tendency was ameliorated by desmopressin administration and laboratory tests showed low levels of VWF and low FVIII levels. In 2012, the first prospective study on aVWS in patients with newly diagnosed overt hypothyroidism was published [35]. In this study consecutive hypothyroid patients were enrolled before or within the first 48 hours of replacement therapy. Patients were divided into severe (VWF:antigen (Ag) and/or VWF:Ristocetin (RCo) ≤10%), moderate (VWF:Ag and/or VWF: RCo between 10 and 30%) or mild aVWS (VWF:Ag and/or VWF:RCo between 30 and 50%). Among 90 hypothyroid patients, a prevalence of aVWS of 33% was found. There were no patients with severe aVWS, 9% had moderate and 23% had mild aVWS. Bleeding score was negatively correlated with both VWF:Ag and VWF:RCo. After restoration of euthyroidism, VWF:Ag had significantly increased by 44%, VWF:RCo by 36%, FVIII by 39%, and endogenous thrombin potential by 10%.

Although it is commonly accepted among clinicians that hypothyroidism leads to an increased risk of abnormal vaginal bleeding [36], the available data is scarce. One study found that menorrhagia was more common in 171 women with hypothyroidism than in 214 healthy controls (7% versus 1%). Another study reported that the prevalence of menstrual disturbances was similar among 586 women with hyperthyroidism (18.3%) and 111 women with hypothyroidism (15.3%) compared with 105 healthy controls (23.8%) [37]. However, patients with severe hypothyroidism had a higher prevalence (34.8%) of menstrual disturbances than mild-moderate cases (10.2%). Others stated that hypothyroidism may be greatly underdiagnosed as a cause of menorrhagia [38], but this was based on a study in IUD-using women suffering from increased menstrual bleeding in whom FT4 and thyroid-stimulating hormone (TSH) levels were all in the normal range while thyrotropin-releasing hormone (TRH) stimulation tests were consistent with occult hypothyroidism in the 10 women having the highest TSH levels [39]. Of note, all had significant improvement in bleeding symptoms within 3 months after treatment with levothyroxine.

Recently, it was suggested that low plasma levels of FT4 within the reference range also influence the risk of bleeding. The FACTORS (Factors in Oral Anticoagulant Safety) study is a case-control study in patients receiving vitamin K antagonist (VKA) treatment, including 110 cases with major haemorrhage and 220 matched controls treated with VKA without major haemorrhage [40]. In this study, the risk
of major haemorrhage was 5-fold increased in patients with an FT$_4$ level below 13 pmol/l, compared with patients with an FT$_4$ level above 13 pmol/l (OR: 5.1, 95% confidence interval (CI): 0.9-28.6). At a cut-off of 14 pmol/l, the risk was 3-fold increased (OR: 2.9, 95% CI: 1.0-8.5).

**VENOUS THROMBOEMBOLISM**

Even within the normal range, higher plasma levels of free thyroxine (FT$_4$) are associated with an increased risk of VTE (i.e. the composite of deep vein thrombosis (DVT) and pulmonary embolism (PE)) in a dose-response manner [41-43] (Figure 1). Interestingly, two studies observed ORs below 1 for low levels of FT$_4$, suggesting that low levels of FT$_4$ could protect against VTE [41, 43]. In a case-control study on leg vein thrombosis (the ACT study), parameters of thyroid function were assessed at time of presentation in 190 cases and 379 sex-matched controls [43]. For several cut-off levels, it was observed that the risk of VTE gradually increased with increasing levels of FT$_4$. FT$_4$ levels above 17 pmol/l yielded a sex- and age-adjusted OR of 2.2 (95% CI, 1.2-4.2) for unprovoked DVT, which further increased up to an OR of 13.0 (95% CI, 1.1-154.1) for FT$_4$ levels above reference range. Likewise, in a prospective case–cohort study performed within the HUNT2 cohort in Norway, where blood was sampled some time before the thrombotic event, the risk of VTE clearly increased gradually with increasing levels of FT$_4$ (OR 2.5 (95% CI 1.3-5.0) for FT$_4$ levels exceeding 17.3 pmol/l relative to levels below this cut-off) [42]. This risk was even higher with shorter time between blood sampling and thrombosis (up to an OR of 9.9 (95% CI 2.9-34.0) when the period between blood sampling and thrombosis was less than 0.5 years. In a third study, a large population-based case–control study (MEGA study) designed to identify risk factors for VTE, the aims were a) to study the effect of thyroid hormone levels on the levels of coagulation proteins, and b) to assess the role of the latter in the association between FT$_4$ and VTE [41]. Blood was donated at a median of 10 months after the event. High levels of FT$_4$ were associated with increased concentrations of procoagulant factors, i.e. FVIII, FIX, fibrinogen, and VWF (see Figures 2-4 for effects of different levels of FT$_4$.
on FVIII and VWF in controls), and also with an increased risk of VTE, up to an OR of 2.2 (95% CI 1.0-4.6) for levels above 24.4 pmol/l relative to FT₄ levels between 15.5 and 18.9 pmol/l. In 11 cases and 1 control, clinical hyperthyroidism was diagnosed shortly before or after the thrombotic event, leading to a 17-fold increased risk of VTE (OR 17.0, 95% CI 2.2-133.0). The ORs approached unity after adjustment for FVIII and VWF, suggesting that the effect was mediated by these factors.

Figure 1. Risk of venous thromboembolism (VTE) according to plasma levels of free thyroxine in the ACT study, the MEGA study and HUNT2 cohort. Risks are expressed as odds ratio (OR) (95% confidence interval). FT₄ indicates free thyroxine. The analyses of the ACT study were adjusted for age and gender. For each cut-off level below the 50th percentile, subjects below the cut-off were compared to subjects above this level with the use of the latter as reference, and vice versa for cut-off levels above the 50th percentile. The analyses of the MEGA study were adjusted for age, sex, body mass index and smoking. Serum FT₄ levels of 15.5–18.9 pM were chosen as the reference group. Analyses in the HUNT2 cohort were adjusted for age and gender and restricted to the cases with VTE within 0.5 years from blood sampling. As cut-off points for FT₄, the 2nd, 5th, 10th, 90th, 95th and 98th percentiles in the control group were used. For the lower percentiles, the numbers of case and control subjects below the cut-off percentile were compared with the numbers above this cut-off percentile. For the higher percentiles, the opposite was done.
Figure 2. Effect of different levels of FT₄ on factor VIII activity (FVIII:C) (IU/mL) in controls of the MEGA study (means with 95% confidence intervals). FT₄ indicates serum free thyroxine (pmol/L).

Figure 3. Effect of different levels of FT₄ on factor VIII antigen (FVIII:ag) (U/dL) in controls of the MEGA study (means with 95% confidence intervals). FT₄ indicates serum free thyroxine (pmol/L).

Figure 4. Effect of different levels of FT₄ on von Willebrand factor (VWF) (U/dL) in controls of the MEGA study (means with 95% confidence intervals). FT₄ indicates serum free thyroxine (pmol/L).
Several studies investigated the risk of VTE in patients with overt hyperthyroidism. These studies are summarized in Table 2. At first, numerous case reports, the first of which was published already in 1927 [44], addressed the possible association between hyperthyroidism and cerebral venous thrombosis (CVT) [45, 46]. One of these case reports pointed out that the incidence reported in the literature of the combination of CVT and thyrotoxicosis was already significantly higher than expected by chance alone (0.1 x 10^-6 per year vs. 0.0032 x 10^-6/year), suggesting that thyrotoxicosis, probably through a factor VIII-mediated hypercoagulability, is a predisposing factor for the development of CVT [45]. From the 7 published papers on this topic, 6 studies have shown an increased risk of VTE in patients with hyperthyroidism [47-52] and one did not find such an association [53]. In a cohort study of 428 hyperthyroid patients, 3 patients (0.7%) had a documented episode of VTE within 6 months of diagnosing hyperthyroidism [48]. In this study without a control population, although it was concluded that the absolute risk of VTE in acute hyperthyroidism was low, the incidence of VTE in this study was much higher than in the general population (0.7% vs. 0.072% in 6 months in the general population [54]). Another cohort study among patients with hyperthyroidism caused by Graves’ disease, multinodular goiter or toxic adenoma investigated the occurrence of VTE between six months before and six months after the diagnosis of hyperthyroidism [47]. Out of 587 patients, five patients experienced a VTE during the study period, resulting in an incidence rate of 8.7 per 1,000 person-years which is also much higher than in the general population. The third study was a large population study in 8,903 patients with hyperthyroidism and a control cohort of 44,515 persons without hyperthyroidism. Here, hyperthyroidism was associated with a 2.3 times greater risk (95% CI 1.20-4.45) for PE compared with controls during a 5-year follow-up period and after adjusting for confounding factors [49]. During this 5-year follow-up period, a substantial part of the patients had probably become euthyroid which may have resulted in an underestimation of the short-term risk. Recently, a nationwide population-based cohort study was performed using data from the Danish Civil Registration System and the Danish National Patient Registry. In this study, data from 85,856 patients diagnosed with hyperthyroidism and 847,057 age- and sex-matched general population comparison cohort members were evaluated [50].
### Table 2. Clinical endpoint studies in hyperthyroidism.

<table>
<thead>
<tr>
<th>Author, Year [ref]</th>
<th>Study design</th>
<th>Cohort; objective</th>
<th>Sample</th>
<th>Clinical endpoints</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danescu, 2009 [53]</td>
<td>Cohort</td>
<td>National Discharge Survey; to study the incidence of VTE in patients discharged from short stay hospitals in the United States between 1979 to 2005 with or without hyperthyroidism.</td>
<td>Exposed: 633 000 patients with hyperthyroidism(^1) Unexposed: 908 172 patients without thyroid dysfunction</td>
<td>PE &amp; DVT</td>
<td>Relative risk: 0.98, 95% CI 0.96-1.01</td>
<td>Hyperthyroidism is not associated with an increased risk of VTE.</td>
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<tr>
<td>Lin, 2010 [49]</td>
<td>Cohort</td>
<td>The Taiwan Longitudinal Health Insurance Database; to estimate the risk of PE among hyperthyroid patients compared with non-hyperthyroid patients.</td>
<td>Exposed: 8 903 patients with hyperthyroidism(^1) Unexposed: 44 515 patients without thyroid dysfunction.</td>
<td>PE</td>
<td>Relative risk 2.31, 95% CI 1.20-4.45</td>
<td>Patients with hyperthyroidism are at increased risk of PE.</td>
</tr>
<tr>
<td>Ramagopalan, 2011 [51]</td>
<td>Cohort</td>
<td>Three databases of linked statistical records of hospital admissions in England; to study the risk of VTE in patients admitted to the hospital with immune-mediated diseases.</td>
<td>Exposed: 101 402 individuals with hyperthyroidism(^1) Unexposed: 313 716 individuals without hyperthyroidism</td>
<td>PE &amp; DVT</td>
<td>Rate ratio 1.56, 95% CI 1.23 to 1.95</td>
<td>Graves’ disease is associated with an increased risk of VTE.</td>
</tr>
<tr>
<td>Kootte, 2012 [47]</td>
<td>Cohort</td>
<td>Hospital records of three hospitals in the Netherlands between 2003 to 2009; to determine the risk of VTE in all patients with overt hyperthyroidism.</td>
<td>Exposed: 587 patients with overt hyperthyroidism(^2)</td>
<td>PE &amp; DVT</td>
<td>5/587 had VTE resulting in an incidence rate of 8.7 per 1,000 person-years, 95% CI 2.8-20.2</td>
<td>The incidence of VTE in patients with hyperthyroidism is higher than expected.</td>
</tr>
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<td>Zöller, 2012 [52]</td>
<td>Cohort</td>
<td>The Swedish Hospital Discharge Register; to study the risk of VTE after hospital admission for autoimmune disorders.</td>
<td>Exposed: 50 954 individuals with Graves’ disease(^3) Unexposed: total population of Sweden.</td>
<td>PE</td>
<td>standardised incidence ratio 6.50, 95% CI (5.84–7.23)</td>
<td>Graves’ disease is associated with a high risk of PE in the first year after hospital admission.</td>
</tr>
<tr>
<td>Author, Year [ref]</td>
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<td>Kim, 2013 [48]</td>
<td>Cohort</td>
<td>Consecutive outpatients presenting to the endocrinology clinic at two district hospitals in New Zealand from 2006 to 2008; to identify all occurrences of objectively proven symptomatic VTE in the 6 months following the diagnosis of hyperthyroidism.</td>
<td>Exposed: 428 patients with acute hyperthyroidism&lt;sup&gt;2&lt;/sup&gt;</td>
<td>PE &amp; DVT &amp; CVT</td>
<td>3/428 (0.7%) had VTE</td>
<td>The absolute risk of VTE in acute hyperthyroidism is low.</td>
</tr>
<tr>
<td>Dekkers, submitted [50]</td>
<td>Cohort</td>
<td>The Danish Civil Registration System and the Danish National Patient Registry; to compare the rate of all-cause mortality as well as first occurrence of VTE, acute myocardial infarction, ischemic and non-ischemic stroke, arterial embolism, atrial fibrillation, and percutaneous coronary intervention in the two cohorts.</td>
<td>Exposed: 85 856 patients diagnosed with hyperthyroidism&lt;sup&gt;1&lt;/sup&gt; Unexposed: 847 057 general population comparison cohort</td>
<td>PE &amp; DVT</td>
<td>Hazard ratio 3.28, 95% CI 2.71-3.97, within 3 months after diagnosis of hyperthyroidism</td>
<td>Patients with hyperthyroidism are at increased risk of VTE.</td>
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</table>

DVT indicates deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; CI, confidence interval.
<sup>1</sup> Based on diagnostic codes
<sup>2</sup> Biochemically confirmed
Patients with hyperthyroidism had a 3-fold increased risk of a first occurrence of VTE within 3 months after diagnosis of hyperthyroidism (hazard ratio 3.28, 95% CI 2.71-3.97). Diagnoses of hyperthyroidism and VTE were retrieved from ICD codes. The fifth and sixth study investigated the risk of VTE in patients with auto-immune disease, one of which was Graves’ disease [51, 52]. One was a large cohort study achieved from three databases of linked statistical records of hospital admissions in England which concluded that Graves’ disease was associated with an increased risk of VTE with a rate ratio of 1.56 (95% CI 1.23 to 1.95) compared with a reference cohort of subjects without auto-immune disease [51]. The Swedish Hospital Discharge Register was used to perform a cohort study with a control group with 50954 individuals with Graves’ disease, again, based on diagnostic codes. It was concluded that Graves’ disease was associated with a high risk of PE in the first year after hospital admission (standardised incidence ratio 6.50, 95% CI 5.84–7.23, compared with the total population of Sweden) [52]. However, the design of these two studies limits allocation as to whether the disease was active (overt hyperthyroidism) or already treated at time of the diagnosis of VTE. The final study that did not find an association between hyperthyroidism and VTE risk aimed to explore a possible role of thyroid dysfunction in VTE using the National Hospital Discharge Survey (NHDS) in the United States. The authors concluded that hyperthyroidism was not associated with an increased risk of VTE but these results are hard to interpret, since the identification of patients with hyperthyroidism was based on diagnostic codes after discharge and it was unknown whether patients were already treated at the time of VTE [53]. Besides, information on thyroid hormone status at the time of VTE was lacking.
DISCUSSION AND CONCLUDING REMARKS

From the available literature it can be concluded that low levels of FT$_4$ lead to a hypocoagulable and hyperfibrinolytic state and to an increased risk of bleeding. Besides, low levels of FT$_4$ may protect against VTE. With increasing levels of thyroid hormone, more coagulation and less fibrinolysis is present and the risk of VTE is increased in a dose-response kind of way, resulting in increased VTE risk in overt hyperthyroidism.

Despite the increase in body weight, hypertension and dyslipidaemia, which are associated with a prothrombotic environment, patients with overt hypothyroidism have an increased bleeding tendency. Observed bleedings were mucocutaneous and related to aVWS. Besides, less compact fibrin networks with enhanced fibrinolysis were observed in hypothyroidism. Low levels of FT$_4$ within the normal range may also lead to a higher risk of bleeding [40] but this has so far only been described in anticoagulated patients. In literature, it is suggested that (subclinical) hypothyroidism could lead to an increased risk of menorrhagia [36] but the available evidence is scarce [37-39, 55]. Considering the effect of thyroid hormone on haemostasis, theoretically, it is likely that hypothyroidism could lead to more vaginal blood loss. Besides, one could speculate that this is also caused by a direct effect of thyroid hormone on muscle contractility and connective tissue. At present, it seems that low levels of FT$_4$ lead to an increased prevalence of menorrhagia. Since this is a clinically relevant problem, this should be investigated in more detail.

With higher levels of FT$_4$, the risk of VTE is increased in a dose response kind of way. The study within the HUNT2 cohort demonstrated a second dose-response relation, i.e. that the relative risk for VTE was higher when the time between VTE and blood sampling became shorter. Such dose-response associations are suggestive for a causal relation. Likewise, in studies investigating the relation between VTE and FT$_4$, a longer time between thyroid function measurement and blood sampling could cause an underestimation of the relation. One could debate whether the observed increased risk of VTE with higher levels of FT$_4$ is influenced by so-called nonthyroidal illness syndrome (NTIS). The most common and earliest change in this syndrome is inhibition of T$_4$-to-T$_3$ conversion, with a resulting decrease in the
circulating T₃ level [56]. The analyses in the study of van Zaane et al. showed that cases had higher T₃ levels compared with controls, while there was a clear association between T₃ and VTE, making it highly unlikely that the findings are a reflection of NTIS [43].

Due to lack of a control group in the majority of the studies investigating patients with overt hyperthyroidism [47-49], it is impossible to calculate relative risks for VTE in these studies. In some studies investigating the risk of VTE in overt hyperthyroidism, it is likely that patients who already achieved euthyroidism were also included, which probably dilutes the observed risk for VTE. Besides, some studies also included recurrent hyperthyroidism which could further dilute the risk for VTE since in general, patients with recurrent hyperthyroidism are diagnosed earlier, and are therefore exposed to high levels of FT₄ to a lesser extent and for a shorter duration of time. Studies that used ICD codes to investigate the risk of VTE in hyperthyroidism may not have provided reliable data on the underlying cause of diagnosed hyperthyroidism and thyroid function at the time of diagnosis of VTE, and may also have underestimated the relation.

Until now, there are no clinical endpoint studies in patients with biochemically confirmed hyperthyroidism that included a control group (Table 2), except for the MEGA-study and the ACT study, but these studies included only a few patients with overt hyperthyroidism [41, 43]. Nevertheless, high relative risks were found in both studies, i.e. of 17 and 13. At present, the limitations of the currently available evidence hamper the formulation of specific recommendations for clinical practice. Thus, a study in a cohort of consecutive patients with newly diagnosed and biochemically confirmed hyperthyroidism, with a control group of patients without hyperthyroidism is warranted. Thyroid function parameters will need to be collected at several timepoints to justify the classification of VTE as provoked by hyperthyroidism. Such a design would allow for the calculation of absolute and relative risks for VTE in hyperthyroidism and would provide information on the time relation between the diagnoses of hyperthyroidism and VTE, as hyperthyroidism may be present some time before it is diagnosed.

Only when such evidence is present we can really determine implications for clinical practice. At the moment it is not clear whether we should just be cautious
for VTE in patients with hyperthyroidism, or should screen for hyperthyroidism in patients with VTE, or both. If hyperthyroidism will be established as a risk factor for VTE, this should imply a shorter duration of treatment with anticoagulants. Recently, two Scientific and Standardization Committees of the ISTH proposed criteria to categorize episodes of VTE as provoked by a transient risk factor [57]. Based on these criteria, hyperthyroidism could be considered as a minor (yet important) transient risk factor during the 2 months before diagnosis of VTE, since it leads to a 3 to 10-fold increase in risk of a first VTE, comparable to risk factors like pregnancy or puerperium. VTE is considered as a multicausal disease in which several determinants combine to cross a so-called ‘thrombotic threshold’ [58] and a high level of FT4 could contribute to develop VTE, mainly by increasing levels of FVIII and VWF. For future research, it would be interesting to investigate the safety and effectiveness of thromboprophylactic treatment in high risk hyperthyroid patients.

Only few studies have been performed trying to elucidate the mechanism by which hyperthyroidism increases the risk of VTE. The effect of thyroid hormone on haemostasis seems to be a direct effect on gene transcription of coagulation proteins [59-61]. Recently, it was discovered that the hypercoagulable state observed in patients with hyperthyroidism is mediated via the thyroid hormone receptor β [62]. In addition to stimulation of coagulation factors mediated via the thyroid hormone receptor β, altered clot structure/lysis may be another mechanism for increased thrombotic risk in hyperthyroidism [33]. However, as exogenous hyperthyroidism in healthy volunteers had no effect on any of the clot structure parameters, additional mechanisms for the effects on haemostasis observed in healthy volunteers using levothyroxine must be present.

Another consequence of the hypercoagulable state induced by hyperthyroidism is the possibility that thyromimetics that are currently investigated may increase the risk for VTE. These compounds specifically stimulate the thyroid hormone receptor β to lower cholesterol levels in dyslipidaemia [63]. It is important that future prospective clinical trials assess the effect of this class of agents on coagulation and fibrinolysis markers, and on the risk of thrombotic events. The same accounts for patients treated with relatively high doses of levothyroxine for several reasons including differentiated thyroid cancer.
Other topics of interest for further research are whether thyroid function can be used as a continuous variable in prediction studies on bleeding and/or VTE risk. Also would it be interesting to investigate whether hyperthyroidism leads to the same increase in risk of DVT as for PE. Risk factors for DVT are shown not to be always the same as for PE. A well-known example is the factor V Leiden (FVL) paradox: the FVL mutation poses a clearly higher risk for DVT than for PE [64]. Since hyperthyroid patients display firmer clots, one could hypothesize that the risk is higher for DVT than for PE.

In summary, low levels of thyroid hormone shift the haemostatic system to a hypocoagulable and hyperfibrinolytic state while high levels of thyroid hormone lead to a more prothrombotic state. Key players in this interaction are FVIII and VWF. Patients with hypothyroidism are at increased risk of developing bleeding complications due to impaired coagulation (higher incidence of aVWS) and fibrinolysis, and this could be relevant in patients undergoing invasive surgical procedures. With increasing levels of free thyroxine (FT$_4$), levels of FVIII and VWF increase gradually. Physicians should be aware of the possibility of hyperthyroidism as underlying risk factor for venous thromboembolism, especially in unexplained cases. Clinical studies are needed to further investigate the consequences for general practice of the influence of thyroid hormone on the haemostatic system.

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