

## Editorial Focus

# Thyroid disease and haemostasis – a relationship with clinical implications?

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The association between thyroid diseases and the haemostatic system has been investigated since the beginning of the past century, but underlying mechanisms and their clinical impact have not been definitely elucidated (1). There are indications that thyroid diseases modify primary and secondary haemostasis and lead to bleeding and thrombosis. The possible pathophysiological mechanisms are thyroid hormone excess or deficiency, autoimmunity or a direct mechanical effect of an enlarged thyroid gland. While some patients with overt hypothyroidism have a bleeding tendency due to an acquired von Willebrand syndrome (2), patients with overt hyperthyroidism do have increased factor VIII and von Willebrand Factor levels. However, an increased thrombotic risk for patients with hyperthyroidism has not been proven.

In addition, an influence of overt thyroid dysfunction on oral vitamin K antagonist sensitivity has been described (3). Although not recognised by several clinicians, the effect of vitamin K antagonists is potentiated in thyrotoxicosis and attenuated in hypothyroidism. This disease-drug interaction has been described in a number of case reports and in animal studies, in particular for overt hyperthyroidism, in which a change in thyroid function was associated with a change in warfarin sensitivity, irrespective of the nature of the underlying thyroid disease (3–4). As the pharmacokinetic parameters – plasma clearance, volume of distribution, plasma protein binding – were unaffected by thyrotoxicosis, warfarin potentiation was thought to reflect an enhanced pharmacodynamic effect (3). This means that hypothyroid patients require higher dosages to obtain the target international normalised ratio (INR) compared to euthyroid anticoagulated patients and, conversely, hyperthyroid patients require a reduced dosage to reach the target INR.

Data on subclinical thyroid dysfunction and anticoagulation are lacking. In this issue of *Thrombosis and Haemostasis*, Bucearius and colleagues present the first published study on the influence of subclinical hyperthyroidism on oral vitamin K antagonist therapy (5). Retrospectively, they studied 178 patients with

subclinical hyperthyroidism undergoing iodine-131 therapy for a benign thyroid disease that were on vitamin K antagonists with an INR target range of 2 to 3. The patients with subclinical hyperthyroidism were compared with two small control groups (overt hyperthyroidism, 15 patients; euthyroidism, 40 patients). The main outcome variable was an INR value within or out of target range during hospital stay for iodine-131. In a subgroup of 40 patients with subclinical hyperthyroidism, in which also INR values during euthyroidism were available, these INR values were compared. Multivariate analysis and intraindividual comparison did not show any effect. This study shows that a strong interaction between subclinical hyperthyroidism on oral vitamin K antagonists is unlikely.

However, some aspects require comment. Sensitivity and stability are the main characteristics of treatment with oral vitamin K antagonist that can be modified by any disease or external factors (drugs, food, seasonal variations, etc.). A different mean dosage of oral vitamin K antagonist required to maintain INR within the target range in the presence or in the absence of any agents is per definition a modified sensitivity of oral vitamin K antagonist. This is relevant for clinical practice because physicians should measure INR more frequently at the occurrence and at the disappearance of any clinical status influencing oral vitamin K antagonist sensitivity, such as in case of overt hyperthyroidism and hypothyroidism. Influence on oral vitamin K antagonist stability is also clinically relevant. Instability is associated with a greater risk of haemorrhage and thrombotic complications. Of the various methods used to assess the stability, the time spent in the therapeutic range is the most commonly used and widely accepted parameter because it is easy to calculate when INR data are available (6). This time span is estimated by linear interpolation between successive INR measurements, calculating the portion of time during each interval that was spent in-range, summing across all intervals, and then dividing by the total duration of therapy.

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Received September 4, 2008  
Accepted September 4, 2008

Prepublished online October 13, 2008  
doi:10.1160/TH-08-09-0576

**Thromb Haemost 2008; 100: 727–728**

Unfortunately, whether subclinical hyperthyroidism influences oral vitamin K antagonist sensitivity has not been analysed by Bucerius and colleagues. Their analysis suggests a lack of effect on oral vitamin K antagonist stability, but the calculation of the time spent in the therapeutic range would have provided more convincing evidence. Regarding sensitivity, no data have been provided on mean oral vitamin K antagonist dosage: the subgroup of 40 patients would have been an optimal population. Finally, the moderate sample size, especially of the control group, for a study of patients with a subclinical disease limits the statistical power and makes it impossible to draw strong conclusions.

In spite of these limitations, the authors' effort is still relevant for its potential clinical and research impact. As they correctly underlined in the manuscript, subclinical hyperthyroidism may cause atrial fibrillation that often requires oral anticoagulation. Therefore, an adequately powered prospective study on the sen-

sitivity and stability of vitamin K antagonists in patients with subclinical hyperthyroidism is warranted. Even if routine thyroid hormone screening in a patient with new atrial fibrillation detects a hormonal cause of atrial fibrillation, patients may be at risk of complications until euthyroidism is reached. Moreover, thyroid blocking agents, such as methimazole, and antiarrhythmic drugs for atrial fibrillation modify oral vitamin K antagonist sensitivity. In particular, amiodarone causes an increased sensitivity to warfarin which causes an increased INR at the beginning of therapy (3). Beyond the predictable pharmacokinetic drug-drug interaction requiring a significant warfarin dose reduction, the iodine-rich amiodarone affects the thyroid gland, causing overt hypothyroidism or thyrotoxicosis in 14%-18% of cases (3). Many physicians are not familiar with these complex drug-drug-disease interactions. More research on this topic will definitely clarify the relationship and may, in the meantime, improve the awareness of this relationship among clinicians.

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