Clinical studies on thyroid diseases
Eskes, Silvia

Citation for published version (APA):
Eskes, S. A. (2014). Clinical studies on thyroid diseases

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 6

Discussion
DISCUSSION

In the present thesis, a number of clinical studies on issues related to thyroid diseases are presented. We focused on some aspects of thyroid disease: prevention of Hashimoto’s thyroiditis, diagnosis of associated autoimmune hypophysitis in Hashimoto’s thyroiditis, and treatment of amiodarone-induced thyrotoxicosis (AIT). In this final chapter, the results of the different studies presented in this thesis are summarized and considerations, implications and suggestions for further research are discussed.

Prevention of progression of Hashimoto’s thyroiditis

Hashimoto’s thyroiditis is the most common cause of spontaneous hypothyroidism in iodine sufficient countries. It is primarily characterized by the presence of antibodies against thyroid peroxidase (TPO-Ab) and thyroglobulin (Tg-Ab). Thyroid antibodies are very prevalent in the general adult population; in the National Health and Nutrition Examination Survey (NHANES III), 14.6% of the females without known thyroid disease had TPO-Ab, and in a UK study among female blood donors without overt thyroid disease TPO-Ab were found in 17.8%. In women with at least one first or second degree relative with autoimmune thyroid disease, the prevalence of TPO-Ab is 27%; in women with a first degree relative it is 43-48%. Recently, Beumer et al. stated that euthyroid females with at least one first or second degree relative with autoimmune thyroid disease show a characteristic pattern of abnormalities in serum levels of tissue remodeling factors, growth factors, chemokines, (vascular) adhesion molecules as well as cytokines and that there is also a difference in levels of some of these proinflammatory cytokines and chemokines between the subjects who converted to TPO-Ab positivity compared to those who did not. This implies that a very early identification of individuals at risk for a thyroid autoimmune disease might be possible. In euthyroid subjects, the presence of TPO-Ab is associated with a slightly higher but still normal serum TSH. In a large community survey, TPO-Ab positive women developed hypothyroidism at an annual rate of 2.1%, compared to the annual incidence of 0.35% in the general female population.

The presence of TPO-Ab thus carries a risk of impending thyroid failure. The relative risk of developing (subclinical) hypothyroidism over 10 years follow up was 36.3 (95% CI 18.8-70.3) in TPO-Ab positive compared to TPO-Ab negative women. After adjustment for the effect of the initial serum TSH and age this figure was 5.3 (1.56-17.7). TPO-Ab > 100 kU/L constitute an independent dose-dependent risk factor for the occurrence of overt thyroid dysfunction in a 5 year-follow up of a cohort of 790 women in Amsterdam. In this same cohort, a nested case-control study showed that the progression in time from euthyroidism via subclinical hypothyroidism to overt autoimmune hypothyroidism is a gradual process taking several years and starting with the occurrence of TPO-Ab. In contrast overt autoimmune hyperthyroidism develops faster in terms of months. Both processes are influenced by environmental factors as smoking and iodine intake (Figure 1).
As shown in figure 1, certain environmental factors provoke the transition from euthyroidism to autoimmune hypo- or hyperthyroidism. Yet, to make use of these factors to prevent thyroid dysfunction is not that straightforward. For example to refrain from smoking and having a high iodine intake will diminish the risk of developing hyperthyroidism, however, cessation of smoking and a higher iodine intake favors the development of hypothyroidism. Alcohol consumption seems to protect against hypothyroidism and hyperthyroidism, but of course has other negative health effects. The risk of developing autoimmune hypothyroidism and Graves’ hyperthyroidism is higher in the postpartum period. However, refraining from getting pregnant to prevent autoimmune thyroid disease (AITD) seems not a reasonable option. The role of oral estrogens in the prevention of AITD is not completely clarified. Estrogen use may protect against the development of TPO-Ab and Hashimoto’s hypothyroidism, whereas smoking, exposure to stress and postpartum are risk factors for Graves’ disease. The postpartum period (but not stress) is also linked to Hashimoto’s hypothyroidism, whereas alcohol intake also lowers the risk of Graves’ hyperthyroidism. (Derived from Effraimidis et al. Eur J Endocrinol 2011; 164 (1): 107-113).

Figure 1. Proposed scheme of the natural history of autoimmune thyroid disease (AITD). AITD is viewed as a multifactorial disease in which thyroid autoimmunity develops in subjects with a particular genetic susceptibility and is provoked by environmental factors. One of the early signs of AITD is the occurrence of thyroid antibodies in serum, where after the disease may progress via subclinical to overt thyroid dysfunction. The transition of euthyroidism into overt autoimmune hypothyroidism (Hashimoto’s hypothyroidism, HH) may take years, but in contrast the transition from euthyroidism into overt autoimmune hyperthyroidism (Graves’ hyperthyroidism, GH) occurs relatively fast in a couple of months. Environmental factors like smoking and alcohol intake protect to a certain extent against TPO-Ab and Hashimoto’s hypothyroidism, whereas smoking, exposure to stress and postpartum are risk factors for Graves’ disease. The postpartum period (but not stress) is also linked to Hashimoto’s hypothyroidism, whereas alcohol intake also lowers the risk of Graves’ hyperthyroidism. (Derived from Effraimidis et al. Eur J Endocrinol 2011; 164 (1): 107-113).
Selenium

Several studies revealed a decrease of TPO-Ab after selenium supplementation in patients with Hashimoto’s thyroiditis under L-T4 treatment\(^{23}\), opening a role for selenium in preventing progression of autoimmune thyroid disease to subclinical and overt hypothyroidism. Selenium is an essential trace element that was discovered in 1817 by Jons Jacob Berzelius who named it after Selene, the Greek goddess of the moon. As selenocysteine, selenium is a component of selenoproteins, some of which have important enzymatic functions, others have roles that have not yet been fully elucidated\(^{24}\). The main selenoproteins families are the glutathione peroxidases, the thioredoxin reductases and the iodothyronine deiodinases. Glutathione peroxidases protect the cell from oxidative stress. Thioredoxin reductases form a cellular redox system, which is essential for cell development and proliferation; iodothyronine deiodinases catalyze the conversion of T4 to T3\(^{25}\). Oxidative stress is believed to contribute to the development of several diseases and to be involved in the control of the immune system as well as in the pathogenesis of autoimmune diseases. Antioxidants may possibly counteract the disease-promoting effects of oxidative stress. There is evidence supporting an ameliorating role of antioxidants on the course of Graves’ disease and Graves’ orbitopathy. Antioxidants administered alone improve some clinical signs and symptoms of hyperthyroidism and, when combined with antithyroid drugs, induce a more rapid control of clinical manifestations and a faster achievement of euthyroidism\(^{26}\). A large randomized clinical trial has shown that antioxidant supplementation (selenium) may as well be beneficial for mild Graves’ orbitopathy, also preventing progression to more severe orbitopathy\(^{27}\).

It is hypothesized that the effect of selenium on TPO-Ab is based on the reduced damage by reactive oxygen species via enhanced expression of the glutathione peroxidases and improvement of redox status in the thyrocyte through increasing activity of thioredoxin reductases\(^{25}\). We investigated whether it would be possible to decrease TPO-Ab in an early stage, when the patient still has a normal TSH. We therefore performed a randomized, double blind, placebo-controlled study in which we gave 61 TPO-Ab positive, euthyroid subjects who did not use any thyroid hormone medication, 200 mcg sodium selenite daily or placebo for six months. Serum TPO-Ab and TSH remained unchanged, in the treated group as well as in the placebo group (chapter 2). Until now seven other prospective studies have been published on this topic. Five found a decrease in TPO-Ab\(^{28-32}\), in two TPO-Ab were unchanged\(^{33,34}\), as in our study. Our study and that of Nacamulli et al.\(^{32}\) were the only two where patients were not treated with L-T4 medication. Demands in L-T4 replacement therapy were found either unaltered or underreported. Three studies reported a greater improvement of well-being in the selenium group than in the placebo group\(^{28,29,33}\). In contrast to these studies, we did not find an effect on quality of life. Karanikas et al. also investigated the immunological influence of selenite in terms of cytokine production patterns; they found no effect\(^{33}\). All these studies were conducted in Europe where selenite supply is marginal; it is therefore not known whether the additional selenium intake corrected a deficit or constituted an add-on effect. A thorough monitoring of the selenium status changes in the patients is often missing. We evaluated the efficiency of selenium supplementation by assessing the selenium status of the patients before, during and after study completion. We also measured selenoprotein P (SePP) concentrations. SePP is a selenoproteins that transports selenium and is considered the best indicator of selenium status and selenium intake\(^{35}\). The baseline serum selenium in our study was 73 μg/L, which is at the lower end of the frequency histogram of selenium concentrations in the UK and below the lower normal limit of serum selenium in the USA NHANES population\(^{36}\). After suppletion with 200 mcg selenite daily, selenium concentrations raised to 96 μg/L at 3 months and 95 μg/L at
6 months; a plateau had been reached within three months, also for SePP. This demonstrates an efficient supplementation and good patient compliance. Studies reporting a decrease in TPO-Ab upon selenium supplementation originate from countries with prevalent iodine deficiency. Studies failing to observe a decrease in TPO-Ab were done in Austria and The Netherlands, countries with sufficient iodine intake. It has been proposed that selenium may play a role as a co-factor to iodine deficiency in thyroid destruction. In iodine-deficient thyroid glands, the generation of free radicals is greatly increased. As selenoproteins are involved in antioxidant defenses, selenium deficiency can exacerbate oxidative stress caused by iodine deficiency. Selenium deficiency combined with iodine deficiency does indeed increase the amount of thyroid cell necrosis. It can be hypothesized that selenium supplementation is more likely to cause a fall in TPO-Ab concentration in iodine-deficient regions than in iodine-sufficient regions. Because of the conflicting results on TPO-Ab, it is too early to recommend selenium supplementation in patients with autoimmune thyroiditis.

The clinical benefit of a decrease in TPO-Ab has not been demonstrated so far, except in pregnancy. Negro et al. demonstrated a greater TPO-reduction and a decreased incidence of postpartum thyroiditis and hypothyroidism in 77 TPO-Ab positive pregnant women who received selenomethionine 200 μg/day during pregnancy and the postpartum period, compared to 74 TPO-Ab positive pregnant women receiving placebo. Interesting subjects that could be investigated in future studies are: a. What is the effect of selenium supplementation in selenium-replete regions like the USA? b. What is the effect of selenium as adjunct to antithyroid drugs on recurrence rate of Graves’ hyperthyroidism? c. Is selenium valuable in more severe Graves’ orbitopathy? d. Does selenium supplementation at treatment with radioactive iodine of Graves’ hyperthyroidism reduce the frequency and severity of Graves’ orbitopathy after treatment?

**Diagnosis of associated autoimmune hypophysitis in Hashimoto’s thyroiditis**

**A. Growth hormone deficiency**

Two studies found growth hormone deficiency (GHD) in 5% of patients with autoimmune hypothyroidism. We hypothesized that, if indeed the prevalence of GHD in these patients was that high, this could be an explanation for the persistent complaints in some of them, despite adequate treatment with thyroxine. Therefore, we wanted to examine the prevalence of GHD in patients with Hashimoto’s thyroiditis.

Serum insulin-like growth factor (IGF-I) is growth hormone (GH-) dependent and can be used as an indicator of GH status. However, IGF-I level is affected by factors as age, nutritional status, thyroid function and lean body mass. A normal IGF-I does not exclude growth hormone deficiency (GHD), but IGF-I can be of some diagnostic assistance if levels are below the age-adjusted normal range. The diagnosis of GHD requires provocative tests of GH secretion. The insulin tolerance test (ITT) is considered the diagnostic test of choice, but is contraindicated in patients with seizure disorders or cardiovascular disease. It is associated with uncomfortable side effects and requires constant monitoring even in healthy adults. An alternative test is the combined administration of arginine and GH-releasing hormone (GHRH), which is safe and provides a strong stimulus to GH secretion. Biller et al. evaluated the relative performance of GHRH-arginine, the ITT, arginine alone, clonidine, levodopa and the combination of arginine and levodopa. The GHRH-arginine test, with 95% sensitivity and 91% specificity at a GH cutoff of 4.1 μg/liter at the central laboratory used, compared well to the ITT, which had an optimal GH cutoff of 5.1 μg/liter (96% sensitivity and 92% specificity). The performance of the other tests was much poorer. The GHRH-arginine test is well tolerated. Biochemical criteria for the diagnosis of GHD are complicated by the lack of normative data that are age-,
sex-, and BMI adjusted. The GH response in the GHRH-arginine test is influenced by BMI and age\(^4^2\). Corneli et al.\(^4^4\) analyzed cut-off points for different BMI levels and Colao et al.\(^4^5\) for different BMI and ages. An alternative provocative test for the diagnosis of GHD is the combined administration of GHRH plus GH-releasing peptide-6 (GHRP-6). GHRP-6 is a synthetic GH secretagogue that is a very potent and reproducible stimulus of GH secretion. It has previously been reported that this test is not confounded by body composition and age\(^4^6\). It produces responses similar to ITT but is free from serious side effects and there are no known contraindications\(^4^2\). However, because GHRH directly stimulates the pituitary, the GHRH/GHRP-6 test, as well as the GHRH-arginine test can give a falsely normal GH response in patients with GHD of hypothalamic origin\(^4^7\). We established reference values for IGF-I, the GH peak in the ITT and in the GHRH/GHRP-6 stimulation test and analyzed the influence of age, gender and BMI (chapter 3a). We studied 296 subjects recruited from the general population, equally distributed according to sex and age between 20 and 70 years. Serum IGF-I level was measured in all subjects, and an ITT (0.15 U/kg Actrapid iv) and GHRH/GHRP-6 test (1 μg GHRP-6/kg) were performed in 49 subjects. We found no sex difference in IGF-I and in the GHRH/GHRP-6 test, but in the ITT males had a higher GH peak. Both IGF-I and the GH response in the ITT were significantly influenced by age, whereas the GH response in the GHRH/GHRP-6 test was significantly affected by BMI. Age-adjusted reference values were established for each test. GHRP-6 is not yet commercially available, current guidelines recommend the use of the ITT or GHRH-arginine test to establish the diagnosis of GHD\(^4^2\). A recent study tested a novel agent for the diagnosis of adult GHD: macimorelin, which is a ghrelin mimetic that stimulates GH secretion. It was safe, can be given orally and the sensitivity and specificity were comparable with GHRH-arginine test. The GH peak after macimorelin was inversely associated with body mass index and the authors suggest separate cut off points for obese and nonobese subjects\(^4^8\).

B. Autoimmune hypophysitis

In chapter 3b we investigated the prevalence of GHD in patients with autoimmune hypothyroidism (AIH). We included 515 patients with spontaneous AIH (TPO-Ab ≥ 100 kU/L) who were adequately treated with T4 (TSH 0.2-5.0 mU/L). Patients with a history of hypothalamic or pituitary disease, or hypothyroidism after thyroid surgery or I\(^1^3^1\), were excluded. If the IGF-I concentration was below the 10\(^{th}\) percentile of age-specific reference values, a GHRH/GHRP-6 test was done. GHD was defined as a GH peak after GHRH/GHRP-6 below the 2.5\(^{th}\) percentile of age-specific reference values. Of the 515 included patients (476 female, 39 male), 49 patients (9.5%) had an IGF-I concentration below the 10\(^{th}\) percentile. These patients underwent a GHRH/GHRP-6 test. Two of them had a GH peak below the 2.5\(^{th}\) percentile. In one patient (male, 49 yrs) the basal GH concentration was undetectable and did not rise after GHRH/GHRP-6, nor in an insulin tolerance test (ITT). The second patient (female, 41 yrs) had a GH peak during the GHRH/GHRP-6 test below the 2.5\(^{th}\) percentile, although GHD could not be confirmed with an additionally performed ITT. The other 47 patients had a GH peak above the 2.5\(^{th}\) percentile. So we found the prevalence of GHD in Dutch patients with AIH is 0.4% (two of 515). Two earlier studies\(^3^9,4^0\) found a much higher prevalence of about 5%. They measured antipituitary antibodies (APA) in patients with AIH and when these were positive, they tested pituitary function because the presence of APA could suggest autoimmune pituitary involvement. However, although other organ-specific antibodies are considered good markers of the respective endocrine diseases, APA, because of several methodological problems, are not considered very specific and sensitive markers of autoimmune pituitary disease\(^4^9\). Clinically, autoimmune hypophysitis or lymfocytic hypophysitis, is suggested by isolated partial or total
hypopituitarism, association with other autoimmune endocrine diseases and enlargement of the pituitary on MRI. APA have been detected not only in some patients with lymphocytic hypophysitis, but also in patients with pituitary adenomas, primary empty sella syndrome and autoimmune endocrine diseases but without pituitary function impairment. In a study of 40 patients with idiopathic isolated GHD and 31 patients with multiple pituitary hormone deficiencies (MPHD), APA in a high titer (>1:8) were found in only 1/40 patients (2.5%) with isolated GHD and 7/31 (23%) with MPHD. Moya Chimenti et al. found a low prevalence of APA positivity in patients with suspected autoimmune hypophysitis. However, in a 5 year-follow up study of patients with autoimmune polyendocrine syndrome, hypopituitarism occurred in 28/149 (18.8%) APA-positive patients but in none of the 50 APA-negative patients. Insufficient sensitivity and specificity of the currently reported methods prevents recommending measurement of APA as standard of care in the diagnosis of hypophysitis. We selected patients for further testing of GHD on the basis of an IGF-I below the 10th percentile. However, the patients with GHD in the other studies had significant lower IGF-I concentrations than the patients without GHD and all adult GHD patients have an IGF-I SD score of -1.50 or less. Until now, there have been no other publications in literature that confirm a high prevalence of GHD in patients with AIH as found by the Italian groups. Therefore, we think it is unlikely that we have missed patients with GHD by limiting further investigation to patients with IGF-I concentrations below the 10th percentile. Based on our study, it seems there is no place for routine tests of GH status in these patients and persisting complaints are unlikely due to missed GHD.

Treatment of amiodarone-induced thyrotoxicosis

In chapter 4 we reviewed the literature on amiodarone and the thyroid. Assessment of TSH and TPO-Ab before starting amiodarone treatment is recommended. Both baseline elevation of TSH as well as the presence of TPO-Ab are risk factors for the development of amiodarone-induced hypothyroidism. The presence of TPO-Ab at baseline indicates a relative risk of 7.3. Amiodarone-induced hypothyroidism occurs rather early (6-18 months) after starting amiodarone, and is best treated with L-T4. Amiodarone-induced thyrotoxicosis (AIT) may occur at any time during amiodarone treatment; its onset is often fast and explosive, due to iodine-induced thyrotoxicosis (type 1) or destructive thyrotoxicosis (type 2). TSH monitoring every 3-6 months during amiodarone treatment is recommended, but its usefulness is limited by the often sudden explosive onset of AIT and the spontaneous return of a suppressed TSH to normal values in about 40% of the cases. Although mixed cases do occur, distinguishing between AIT type 1 and 2 is advised for selecting a treatment modality that is appropriate from a pathophysiological point of view. Many studies report poor efficacy of anti-thyroid drugs. In AIT type 1 thionamides lack efficacy because high intrathyroidal iodine stores antagonize the inhibitory effects of thionamides on thyroidal iodine utilization. The addition of perchlorate can be useful because this is an inhibitor of thyroidal iodine trapping and reduces intrathyroidal iodine stores. Because AIT type II is caused by thyroid destruction and not by increased hormone synthesis, thionamides are not expected to be rapidly effective in the treatment. Based on pathophysiology and retrospective studies, the preferred treatment of AIT type 1 is with the combination of perchlorate and methimazole and AIT type 2 with prednisone, either alone or in combination with thionamides. The addition of thionamides can be effective in mixed cases of AIT. For the same reason, prednisone can be combined with perchlorate. Moreover, a beneficial effect of perchlorate can be supposed in AIT type 2 because it inhibits the cytotoxic effect of amiodarone on thyrocytes in vitro, although to a lesser extent than steroids. Most physicians discontinue amiodarone treatment in AIT type 2. Withdrawal of amiodarone removes the cause of amiodarone induced thyroiditis. But in many cases this is an unattractive option,
because amiodarone is often given to patients who are resistant to other antiarrhythmic drugs and sometimes withdrawal is impossible. In addition, amiodarone and its metabolites have actions that may protect the patients from some of the effects of thyrotoxicosis. Amiodarone has β-adrenoreceptor blocking activity and it might protect the heart from thyroid hormone excess because it has a hypothyroid-like effect on the heart. To be able to continue amiodarone treatment would probably be advantageous in some patients. In fact, when amiodarone is withdrawn, there still is a continuing effect on the thyroid because of the long half-life of the drug and its metabolites. There are some reports that amiodarone can be continued in AIT type 2. We wanted to investigate whether AIT type 2 can be cured without withdrawing amiodarone. Furthermore, we were interested in the efficacy and tolerability of treatment with methimazole with or without prednisone, with or without perchlorate and treatment with triple therapy. Therefore, we performed a randomized multicenter study where patients with AIT type 2 were randomized to receive prednisone 30 mg/d (n=12), sodium perchlorate 500 mg twice daily (n=14) or prednisone plus perchlorate (n=10); all patients continued amiodarone and were also treated with methimazole 30 mg/d. The follow up was two years. Euthyroidism was reached in all patients despite continuation of amiodarone. The initial therapy was efficacious in all patients who were treated with prednisone or with the combination of prednisone and perchlorate. Of the patients who were initially treated with perchlorate, 29% were still thyrotoxic after 3 months. They became euthyroid after addition of prednisone. The time to normalization of FT4 and TSH was not significantly different between the groups; the addition of perchlorate to prednisone gave no better outcome. Thus prednisone remains the preferred treatment modality of AIT type 2. Recurrent thyrotoxicosis occurred in three of the 36 patients (8.3%). Our study is the first prospective and controlled trial indicating that discontinuation of amiodarone in AIT type 2 is not necessary for restoration of euthyroidism. It can be argued that the time to normalize FT4 and TSH is longer when amiodarone is continued, but that was not found in a retrospective study where eight AIT type 2 patients treated with prednisone under continuation of amiodarone, were compared to 32 matched controls with AIT type 2 who were treated with prednisone after discontinuation of amiodarone; the median time to first normalization of thyroid hormone levels did not significantly differ between both groups (24 and 31 days respectively). In this study, recurrences were found in 5/7 (71.4%) patients continuing amiodarone, compared to 3/32 (9.4%) of patients who stopped this medication. This is much higher than the recurrence rate in our study and in a Japanese study, which reported 6% recurrences of AIT type 2 occurring 5-8 years after the first episode while amiodarone was continued. Our management algorithm is depicted in Fig. 2.
Dronedarone is a noniodinated benzofuran derivative that is pharmacologically related to amiodarone, but because it lacks an iodine moiety, it does not have the iodine-related side effects of amiodarone. It also has a shorter half-life and less accumulation in tissues. Dronedarone has demonstrated efficacy in the treatment of arrhythmia in terms of prevention of atrial fibrillation recurrences. However, in a prospective, randomized study of 504 patients dronedarone was less effective than amiodarone in decreasing atrial fibrillation recurrence rate, although it had a better safety profile. Furthermore, there are concerns about the safety of dronedarone in certain patients. There are reports that dronedarone may increase mortality and hospitalization for heart failure in patients with advanced NYHA class and in patients with permanent atrial fibrillation. In addition to gastrointestinal side effects that may lead to discontinuation in 5-10% of patients, dronedarone may induce very rare but severe liver and lung toxicity. Lower efficacy and these safety concerns preclude the use of dronedarone as alternative medication for amiodarone.

---

**Fig. 2.** Amsterdam algorithm for the management of amiodarone-induced thyrotoxicosis (AIT). AM, amiodarone; KClO₄, twice daily 500 mg potassium or sodium perchlorate; MMI, once daily 30 mg; I¹³¹, high therapeutic dose +/- rhTSH; TAPER, gradually tapering of drug dose to zero.
REFERENCE LIST


8. Strieder TGA, Tijssen JGP, Wenzel BE, Endert E, Wiersinga WM. 2008 Prediction of progression to overt hypothyroidism or hyperthyroidism in female relatives of patients with autoimmune thyroid disease using the Thyroid Events Amsterdam (THEA) score. Archives of Internal Medicine168 (15):1657-1663.


