International guidelines in thyroid disease in daily practice
Vienna, Austria - June 8-9, 2012
General information

Venue
The conference takes place at the

Hilton Vienna
Am Stadtpark 1
1030 Vienna, Austria

Language
The official language of this conference is English.

Scientific secretariat
Serono Symposia International Foundation
Salita di San Nicola da Tolentino, 1/b
00187 Rome, Italy

Associate Project Manager: Dorina Monaco
Tel.: +39-06-420 413 314
Fax: +39-06-420 413 677
E-mail: dorina.monaco@seronosymposia.org

Senior Project Manager: Flaminia Masprone
Tel.: +39-06-420 413 206
Fax: +39-06-420 413 677
Email: flaminia.masprone@seronosymposia.org

Specialist Medical Advisor: Davide Mineo
Tel: +39-06-420 413 313
Fax: +39-06-420 413 677
Email: davide.mineo@seronosymposia.org

Serono Symposia International Foundation
is a Swiss Foundation with headquarters
in 14, rue du Rhône, 1204 Geneva, Switzerland.

Organizing secretariat
Vitalis Events SA
PO Box 501 - 1211 Geneva 4 – Switzerland
Conference coordinators: Patrick Mengelt / Rachel Long
Tel: +41 22 800 2322 / Fax +41 22 800 2324
E-mail: ssifvienna@vitalis-events.com
International guidelines in thyroid disease in daily practice

Serono Symposia International Foundation Conference on:

International guidelines in thyroid disease in daily practice
Vienna, Austria - June 8, 9, 2012

Aim of the conference
Thyroid disorders are among the most commons encountered in the endocrinological practice. In the Colorado study (US), 9.4% of subjects had high TSH concentration, with higher frequency found in women than in men. There is no unanimity of opinion among specialists regarding the need for thyroid screening, or in the approach to treatment of hypothyroidism, especially whether or not subclinical hypothyroidism should be treated. Also, there is still controversy if women who desire pregnancy should be screened for thyroid diseases and whether or not they should be treated in borderline situations.

Thyroid nodules are common, with an estimated prevalence ranging from 3% to 7% on the basis of palpation. From 20% to 48% of patients with one palpable thyroid nodule are found to have additional nodules when investigated by ultrasound. The American Cancer Society estimates that thyroid cancer incidence is increasing by approximately 6% per year. Scientific Thyroid Societies over the world have updated their recommendations for the evaluation and management of thyroid disorders, nodules and cancer, and these topics will be addressed.

This Conference, hosted by Serono Symposia International Foundation, will represent a unique opportunity to confront different experiences from several well-recognized experts in Europe. Main objectives of the meeting will be to review recently published international guidelines in thyroid disorders with criticism and to address potential controversies in daily practice.

Learning objectives
After attending this conference, participants will have up-to-date knowledge on thyroid diseases and will be able to:

- Incorporate recent guidelines in the daily management of thyroid disorders
- Apply the most recent evidence in screening and management of thyroid disorders to the general population and in pregnancy
- Assess the short comings of new guidelines in thyroid diseases
- Carefully assess the clinical relevance of subclinical thyroid disease
- Evaluate the role of newer therapies in the management of thyroid cancer

Target Audience
Endocrinologists, internal medicine and geriatrics specialists, gynecologists involved in diagnosis and management of patients with thyroid disorders.

Accreditation
Serono Symposia International Foundation (www.seronosymposia.org) is accredited by the European Accreditation Council for Continuing Medical Education (EACCME) to provide the following CME activity for medical specialists. The EACCME is an institution of the European Union of Medical Specialists (UEMS), www.uems.net

The Conference “International guidelines in thyroid disease in daily practice” (June 8-9, 2012, Vienna - Austria) is designated for a maximum of 9 (nine) hours of European CME credits (ECMEC). Each medical specialist should claim only those credits that he/she actually spent in the educational activity. EACCME credits are recognized by the American Medical Association (AMA) towards the Physician’s Recognition Award (PRA). To convert EACCME credit to AMA PRA category 1 credit, please contact the AMA.
Learning effectiveness project

The world of CME is changing with many different live and online formats, and Serono Symposia International Foundation (SSIF) is continually trying to improve its CME activities.

With your participation in a structured series of evaluations, SSIF can provide cutting-edge learning activities designed to give you the greatest value from the time you invest.

SSIF is running the learning effectiveness project for this meeting.

You will be involved in three main steps:

- **During the conference**: you will be asked to complete a questionnaire, at the beginning and at the end of the conference, to assess the program in various domains.
- **Post-event**: three weeks after the event we will email you a short questionnaire which will give you the opportunity to tell us how much of what you learned has had an affect on your know-how and daily practice.
- **Follow-up**: three-months after the event, we will contact you with the final questionnaire.

We will collate and analyse your responses and use the results to improve and develop our ongoing programs.

Of course, we commit to maintaining the confidentiality of the information you provide and we will inform you about the results of the process regarding the activity that you attended.

Thank you very much for participating in this project!

follow us on twitter

http://twitter.com/SSIF_Endo

All Serono Symposia International Foundation programs are organized solely to promote the exchange and dissemination of scientific and medical information. No forms of promotional activities are permitted. All Serono Symposia International Foundation programs are made possible thanks to educational grants received from: Celgene, Centre d’Esclerosi Multiple de Catalunya, ComtecMed, Congrex Sweden, Congrex Switzerland, Cryo-Save, Dataanalysis, Esaote, European Society of Endocrinology, Fondazione Humanitas, Fundación IVI, ISFP International Society for Fertility Preservation, ISMH International Society of Men’s Health, K.I.T.E., Merck Serono, Sanofi-Aventis, University of Catania, Vall d’Hebron University Hospital.
Scientific organizers

**George J. Kahaly**
Department of Medicine I
Gutenberg University Medical Center
Mainz, Germany

**Jacques Orgiazzi**
Service d’endocrinologie-diabétologie-maladies métaboliques
Hospices Civils de Lyon
Centre hospitalier Lyon-Sud, Université Lyon 1
Pierre-Bénite, France

Scientific committee

**Luigi Bartalena**
Department of Clinical and Experimental Medicine
University of Insubria
Varese, Italy

**George J. Kahaly**
Department of Medicine I
Gutenberg University Medical Center
Mainz, Germany

**Jacques Orgiazzi**
Service d’endocrinologie-diabétologie-maladies métaboliques
Hospices Civils de Lyon
Centre hospitalier Lyon-Sud, Université Lyon 1
Pierre-Bénite, France

**Simon Pearce**
Institute of Genetic Medicine
Newcastle University
Newcastle upon Tyne, UK
<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>City, Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maria Alevizaki</td>
<td>Endocrine Unit, Department of Medical Therapeutics</td>
<td>Athens, Greece</td>
</tr>
<tr>
<td></td>
<td>Athens University School of Medicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alexandra Hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Athens, Greece</td>
<td></td>
</tr>
<tr>
<td>Rebecca S. Bahn</td>
<td>Division of Endocrinology, Diabetes, Metabolism and Nutrition</td>
<td>Rochester, Minnesota, USA</td>
</tr>
<tr>
<td></td>
<td>Mayo Clinic School of Medicine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mayo Clinic School of Medicine</td>
<td></td>
</tr>
<tr>
<td>Luigi Bartalena</td>
<td>Department of Clinical and Experimental Medicine</td>
<td>University of Insubria, Endocrinology Unit</td>
</tr>
<tr>
<td></td>
<td>Ospedale di Circolo, Varese, Italy</td>
<td></td>
</tr>
<tr>
<td>Sabina Baumgartner-Parzer</td>
<td>Department of Medicine III</td>
<td>Vienna, Austria</td>
</tr>
<tr>
<td></td>
<td>Division of Endocrinology and Metabolism</td>
<td></td>
</tr>
<tr>
<td>Bernadette Biondi</td>
<td>Department of Clinical and Molecular Endocrinology and Oncology</td>
<td>University of Naples Federico II</td>
</tr>
<tr>
<td></td>
<td>Naples, Italy</td>
<td></td>
</tr>
<tr>
<td>Tomasz Bednarczuk</td>
<td>Department of Internal Medicine and Endocrinology</td>
<td>Medical University of Warsaw</td>
</tr>
<tr>
<td></td>
<td>Warsaw, Poland</td>
<td></td>
</tr>
<tr>
<td>Henning Drale</td>
<td>Department of General, Visceral and Vascular Surgery</td>
<td>University Hospital</td>
</tr>
<tr>
<td></td>
<td>Medical Faculty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>University of Halle-Wittenberg</td>
<td>Halle, Germany</td>
</tr>
<tr>
<td>Lionel Groussin</td>
<td>Service des maladies endocriniennes et métaboliques</td>
<td>Hôpital Cochin, AP-HP</td>
</tr>
<tr>
<td></td>
<td>Université Paris-Descartes</td>
<td>Paris, France</td>
</tr>
<tr>
<td>Laszlo Hegedüs</td>
<td>Department of Endocrinology and Metabolism</td>
<td>Odense University Hospital and University of Southern Denmark</td>
</tr>
<tr>
<td></td>
<td>Odense, Denmark</td>
<td></td>
</tr>
<tr>
<td>Barbara Jarzab</td>
<td>Department of Nuclear Medicine and Endocrine Oncology</td>
<td>Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology</td>
</tr>
<tr>
<td></td>
<td>Gliwice Branch, Gliwice, Poland</td>
<td></td>
</tr>
<tr>
<td>George J. Kahaly</td>
<td>Department of Medicine I</td>
<td>Gutenberg University Medical Center</td>
</tr>
<tr>
<td></td>
<td>Mainz, Germany</td>
<td></td>
</tr>
<tr>
<td>John H. Lazarus</td>
<td>Centre for Endocrine and Diabetes Sciences</td>
<td>Cardiff University</td>
</tr>
<tr>
<td></td>
<td>Cardiff, Wales, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>Sophie Lebouleux</td>
<td>Service de Médecine Nucléaire et Cancérologie Endocrinienne</td>
<td>Institut Gustave Roussy</td>
</tr>
<tr>
<td></td>
<td>Villejuif, France</td>
<td></td>
</tr>
<tr>
<td>Laurence Leenhardt</td>
<td>Nuclear Medicine / Thyroid and Endocrine Tumors Unit</td>
<td>Pitié-Salpêtrière Hospital</td>
</tr>
<tr>
<td></td>
<td>Paris, France</td>
<td></td>
</tr>
<tr>
<td>Birte Nygaard</td>
<td>Department of Internal Medicine, Endocrine Unit</td>
<td>Herlev Hospital, University of Copenhagen</td>
</tr>
<tr>
<td></td>
<td>Herlev, Denmark</td>
<td></td>
</tr>
<tr>
<td>Paul D. Olivo</td>
<td>Department of Molecular Microbiology, Washington University, St Louis, MO - USA</td>
<td>Guidel Corporation</td>
</tr>
<tr>
<td></td>
<td>San Diego, CA - USA</td>
<td></td>
</tr>
<tr>
<td>Jacques Orgiazzi</td>
<td>Service d’endocrinologie-diabétologie-maladies métaboliques</td>
<td>Hospices Civils de Lyon</td>
</tr>
<tr>
<td></td>
<td>Hospices Civils de Lyon</td>
<td>Centre hospitalier Lyon-Sud, Université Lyon 1</td>
</tr>
<tr>
<td></td>
<td>Pierre-Bénite, France</td>
<td></td>
</tr>
<tr>
<td>Simon Pearce</td>
<td>Institute of Genetic Medicine</td>
<td>Newcastle University</td>
</tr>
<tr>
<td></td>
<td>Newcastle upon Tyne, UK</td>
<td></td>
</tr>
</tbody>
</table>
List of faculty members

Aldo Pinchera  
Department of Endocrinology  
University of Pisa  
Pisa, Italy

Kris Poppe  
Endocrine Unit  
Universitair Ziekenhuis UZ Brussel (VUB)  
Brussels, Belgium

Paolo Vitti  
Department of Endocrinology and Metabolism  
University of Pisa  
Pisa, Italy

Jean-Louis Wémeau  
Clinique Endocrinologique Marc Linquette  
CHU de Lille  
Lille, France
# Scientific program

**Friday - June 8, 2012**

**09.00 - 13.00**  Registration

**14.00**  Welcome to Vienna  
S Baumgartner-Parzer (Austria)

**14.10**  Introduction  
J Orgiazzi (France)

## Session I  Hyperthyroidism / Thyroid autoimmunity

**Session Chairman:** GJ Kahaly (Germany)

**14.30**  L1: Genetics vs. environment in autoimmune thyroid disease  
T Bednarczuk (Poland)

**15.00**  L2: TSH receptor autoantibodies: Differentiation and clinical relevance  
PD Olivo (USA)

**15.30**  L3: Guidelines for the management of Graves’ hyperthyroidism  
R Bahn (USA)

**16.00**  Coffee Break

**16.30**  L4: Consensus management of Graves’ orbitopathy  
L Bartalena (Italy)

**17.00**  L5: Cardiac involvement in Graves’ vs. non-autoimmune hyperthyroidism  
B Biondi (Italy)

**17.30**  L6: Thyroid autoimmunity and pregnancy  
K Poppe (Belgium)

**18.00**  End of the day

## Session II  Hypothyroidism / Thyroid nodules

**Session Chairman:** A Pinchera (Italy)

**09.00**  L7: New guidelines for the management of thyroid dysfunction during pregnancy  
JH Lazarus (United Kingdom)

**09.30**  L8: Cardiovascular risks of subclinical hypothyroidism  
S Pearce (United Kingdom)

**10.00**  L9: New European guidelines for the treatment of hypothyroidism  
B Nygaard (Denmark)

**10.30**  Coffee break

**11.00**  L10: Guidelines for diagnosis of thyroid nodules  
P Vitti (Italy)

**11.30**  L11: Guidelines for the treatment of thyroid nodules  
JL Wemeau (France)

**12.00**  L12: New treatment modalities of thyroid nodules  
L Hegedus (Denmark)

**12.30**  Lunch

## Session III  Thyroid cancer

**Session Chairman:** J Orgiazzi (France)

**14.00**  L13: Surgery for thyroid cancer: State of the Art  
H Dralle (Germany)

**14.30**  L14: Management of differentiated thyroid cancer  
S Leboulleux (France)

**15.00**  L15: Management of medullary thyroid cancer  
B Jarzab (Poland)

**15.30**  Coffee break

**16.00**  L16: Ultrasonography guidelines for the follow-up of thyroid cancer  
L Leenhardt (France)

**16.30**  L17: Management of metastatic / poor prognosis forms of thyroid cancer / new targeted therapies  
L Groussin (France)

**17.00**  L18: Pitfalls: Interesting cases of differentiated thyroid cancer  
M Alevizaki (Greece)

**17.30**  Concluding remarks  
GJ Kahaly (Germany)

**17.40**  End of the conference

**Conference dinner**
Serono Symposia International Foundation adheres to guidelines of the European Accreditation Council for Continuing Medical Education (EACCME) and all other professional organizations, as applicable, which state that programs awarding continuing education credits must be balanced, independent, objective, and scientifically rigorous. Investigative and other uses for pharmaceutical agents, medical devices, and other products (other than those uses indicated in approved product labeling/package insert for the product) may be presented in the program (which may reflect clinical experience, the professional literature or other clinical sources known to the presenter). We ask all presenters to provide participants with information about relationships with pharmaceutical or medical equipment companies that may have relevance to their lectures. This policy is not intended to exclude faculty who have relationships with such companies; it is only intended to inform participants of any potential conflicts so participants may form their own judgments, based on full disclosure of the facts. Further all opinions and recommendations presented during the program and all program-related materials neither imply an endorsement, nor a recommendation, on the part of Serono Symposia International Foundation. All presentations solely represent the independent views of the presenters/authors.

The following faculty provided information regarding significant commercial relationships and/or discussions of investigational or non-EMEA/FDA approved (off-label) uses of drugs:

Maria Alevizaki  Declared no potential conflict of interest
Rebecca S. Bahn  Declared no potential conflict of interest
Luigi Bartalena  Declared his presentation includes discussion of the potential use of rituximab for Graves’ orbitopathy.
Sabina Baumgartner-Parzer  Declared no potential conflict of interest
Bernadette Bioni  Declared no potential conflict of interest
Tomasz Bednarczuk  Declared no potential conflict of interest
Henning Dralle  Declared no potential conflict of interest
Lionel Groussin  Declared no potential conflict of interest
Laszlo Hegedüs  Declared receipt of honoraria from Genzyme, Novo Nordisk and Theraction. Declared to be member of Genzyme, Novo Nordisk and Theraction advisory boards and to be a stakeholder in Theraction
Barbara Jarzab  Declared receipt of consultation fees from Astra Zeneca and to be member of the Astra Zeneca advisory board
George J. Kahaly  Declared no potential conflict of interest
John H. Lazarus  Declared no potential conflict of interest
Sophie Leboulleux  Declared receipt of honoraria from Genzyme
Laurence Leenhardt  Declared no potential conflict of interest
Birte Nygaard  Declared no potential conflict of interest
Paul D. Olivo  Declared to be an employee of Quidel corporation
Jacques Orgiazzi  Declared receipt of honoraria from Merck Serono
Simon H.S. Pearce  Declared to be member of GSK advisory board and of Merck-Serono ETA-2011, Krakow
Aldo Pinchera  Declared no potential conflict of interest
Kris Poppe  Declared receipt of honoraria from Merck-Serono ETA-2011, Krakow
Paolo Vitti  Declared no potential conflict of interest
Jean Luis Wémeau  Declared no potential conflict of interest
Lectures
Abstracts
Autoimmune thyroid disease (AITD) covers a spectrum of phenotypes. From a clinical point of view, patients can be divided into those with Graves’ disease (GD) characterized by hyperthyroidism, those with Hashimoto’s thyroiditis (HT) characterized by hypothyroidism, and into a group of euthyroid subjects with elevated thyroid autoantibodies. Despite evident phenotypic differences, it is likely that they partly share a common aetiology. AITD is postulated to develop as a result of a complex interaction between several genetic and environmental factors. Recently, significant progress has been made in our understanding of the mechanisms leading to AITD. The most convincing evidence for a genetic predisposition to AITD is provided by twin studies, which suggest that ~75% of the predisposition to development of AITD is attributable to genetic factors whereas environmental factors could explain the remaining ~25%. Various techniques have been employed to identify susceptibility genes to AITD, including candidate gene analysis and whole genome screening. Several genes have been convincingly shown to confer susceptibility to AITD; some of these genes are unique to GD. Susceptibility genes can be classified into two groups: (1) immune-regulatory genes (e.g., HLA, CTLA-4, PTPN22 and CD40); (2) thyroid-specific genes (thyroglobulin and TSH receptor genes). Numerous environmental and endogenous factors might play a role in the development of AITD, e.g., iodine excess, selenium deficiency, smoking, low birth weight, fetal microchimerism, stress, drugs, environmental toxicants, viral and bacterial infections. A thorough understanding of genetic and environmental factors is essential to improve the diagnosis, prevention and treatment of AITD.
Autoantibodies to the thyroid-stimulating hormone (TSH) receptor (anti-TSHR) are unique in that they are directly involved in the pathophysiology of certain autoimmune thyroid diseases (AITD). Anti-TSHR antibodies can act as agonists that mimic the action of TSH and stimulate the thyroid gland. These thyroid-stimulating antibodies (TSAb) are the causative agent of autoimmune hyperthyroidism or Graves’ disease. Other types of anti-TSHR antagonize or block the action of TSH and in doing so can cause autoimmune hypothyroidism. Thyroid-blocking antibodies (TBAb) have not been as extensively studied as TSAb and the clinical utility of their detection is less well-established.

Our group has developed both TSAb and TBAb bioassays based on a cell line that expresses a chimeric TSHR and contains a TSH-inducible luciferase gene. We have tested the performance of these bioassays using thyroid-stimulating and thyroid-blocking monoclonal antibodies as well as sera from patients with AITD. Our data demonstrate that these TSAb and TBAb bioassays are useful tools for evaluating patients with different types of anti-TSHR antibodies and may help clinicians characterize the diverse clinical presentations of patients with AITD.
Evidence-based practice guidelines for the management of patients with Graves’ disease or toxic nodular goiter were developed by a task force of expert clinicians jointly appointed by the American Thyroid Association and the American Association of Clinical Endocrinologists. The recommendations center on the patient and her/his individual needs and preferences. This is manifest in the section pertaining to Graves’ disease in that no general recommendation to use one particular treatment option (e.g. radioactive iodine [RAI], thyroidectomy or antithyroid medication) over the others is given. Rather, the treating physician is encouraged to discuss with the patient each of the treatment options, including the logistics, benefits, expected speed of recovery, drawbacks, potential side effects and cost so that the course of action incorporates both the relevant medical considerations and the personal values and preferences of the patient. The guidelines are more prescriptive concerning the particular antithyroid drug to be used. Recent evidence indicates that propylthiouracil (PTU) can cause fulminant hepatic necrosis that may be fatal. Accordingly, the guidelines state that methimazole (MMI, or carbimazole) should be used in virtually every patient who chooses antithyroid drug therapy, except during the first trimester of pregnancy when PTU is preferred. Closely related to this strong recommendation is the suggestion that patients started on PTU during the first trimester be switched to MMI at the beginning of the second trimester, depending upon clinical judgement. Lastly, while the guidelines recommend that MMI be given for only approximately 12-18 months, they also allow for longer-term treatment in patients not in remission who prefer this approach. The guidelines were published simultaneously in Thyroid 21 (6); 593-654, 2011 and Endocrine Practice 17 (3); 456-520, 2011 and are also available on the websites of the 2 associations.
Graves’ orbitopathy (GO), particularly in its moderate-to-severe expressions, is a rare disease and represents a therapeutic dilemma, due to the limited number of randomized clinical trials available in this field. GO goes through a florid inflammatory phase (active disease), then stabilizes, and eventually inactivates (burnt-out disease) within 1–2 years. Medical treatments are effective during the active phase. Residual manifestations after inactivation are corrected surgically (rehabilitative surgery, including orbital decompression, squint surgery, eyelid surgery).

Mild GO usually does not require any specific treatment and can conservatively managed by local measures (artificial tears, ointments, dark glasses, prisms for mild diplopia). Selenium given for 6 months has proven to be effective in improving mild manifestations and preventing progression to more severe forms. Stable control of thyroid dysfunction and smoking withdrawal are important preventive actions. Sight-threatening GO (mostly due to Dysthyroid Optic Neuropathy, DON) must be treated aggressively with intravenous infusions of 1 gram of methylprednisolone for 3 consecutive days, to be repeated the next week. If response is poor in terms of recovery of visual acuity and other signs of DON, the patient must be promptly submitted to urgent orbital decompression. High-dose systemic glucocorticoids represent the first-line treatment also for moderate-to-severe GO. Although oral glucocorticoids are effective, intravenous glucocorticoids are more effective and generally better tolerated. Severe adverse events may, however, occur. Accordingly, treatment should be undertaken in specialized centers under strict medical surveillance. Information on the optimal regimen of intravenous glucocorticoid therapy is presently lacking. The most commonly used regimen is based on 12 weekly infusions of methylprednisolone to a cumulative dose of 4.5 grams. If response to glucocorticoids is suboptimal, the patient can submitted to a second cycle of intravenous glucocorticoids combined with orbital radiotherapy (10-20 Gy per eye in 10 fractionated doses over 2 weeks) or to a combination of oral glucocorticoids and cyclosporine. About 30-40% of GO patients are eventually dissatisfied with treatment outcome. Medical treatments are ineffective if GO is inactive. Novel therapies are currently being investigated, with particular regard to the CD20+ B cell-depleting agent, rituximab. However, evidence is too limited (small open studies, case reports) to draw sound conclusions on its efficacy and safety.
Hyperthyroidism is a common endocrine disorder that has important clinical consequences for the cardiovascular system. However, Graves disease, toxic multi nodular goiter and toxic adenoma differ in their cardiovascular implications. Several clinical differences can help to differentiate these three causes of hyperthyroidism: the patient’s age at presentation, clinical features and severity of symptoms and signs, duration and progression of the disease and associations with other autoimmune conditions are particularly important.

Graves disease is an autoimmune disorder, and is the most common cause of hyperthyroidism in areas of iodine sufficiency. In patients with Graves disease, hyperthyroidism is frequently associated with pulmonary arterial hypertension and other autoimmune cardiovascular effects, such as cardiac valve involvement, dilated cardiomyopathy, pulmonary arterial hypertension and peripartum cardiomyopathy.

Toxic adenoma and toxic multinodular goiter are both characterized by thyroid autonomy; these two conditions account for ~60% of cases of hyperthyroidism in iodine deficient areas and develop in middle aged and elderly people. Both conditions are frequently associated with heart disease. Patients may have subclinical or overt thyrotoxicosis depending on the amount of autonomously hyperfunctioning thyroid tissue. Thyroid hormone excess associated with thyroid autonomy can have serious cardiovascular consequences, even though the symptoms are often mild.

Atrial fibrillation is an important cardiac complication in elderly patients with thyroid autonomy and might not revert when euthyroidism is restored, if it has been present for a long time and is coexistent with heart disease. Patients aged over 65 years with toxic multinodular goiter and atrial fibrillation are also at an increased risk of stroke. Moreover, atrial fibrillation is an independent predictor of congestive heart failure in patients with hyperthyroidism.

Consequently, the etiology of hyperthyroidism must be established to enable correct treatment of the disease and the cardiovascular complications.
Thyroid autoimmunity (TAI) is the most common cause of hypothyroidism before and during pregnancy, and furthermore has 20-30% of euthyroid women with TAI in early gestation tendency to become hypothyroid as gestation progresses. Many studies have shown that the presence of TAI without overt thyroid dysfunction is associated with a significantly increased risk for miscarriage, premature delivery, perinatal death, low motor and IQ in the offspring. This association does not imply a causal relationship and several hypotheses have been proposed (immune disorders, inappropriate TH levels and increased maternal age in women with TAI).

Concerning L-thyroxine (LT4) intervention trials, Negro et al. performed a study in euthyroid pregnant women with TAI, in which the miscarriage rate was reduced to 3.5% among LT4-treated TAI + women compared with 13.8% among untreated TAI + (p<0.05). These data were recently confirmed in an assisted reproductive setting, by Kim et al.

In women who already receive LT4, the recommendation is to adjust the dosage to reach trimester specific serum TSH level during pregnancy (or ≤ 2.5 mIU/L) and when hypothyroidism is diagnosed during pregnancy, LT4 should be initiated immediately [100-150 µg/day]. In a recent study by Yassa et al., it was proposed to increase immediately the LT4 dosage by a two-tablet increase a week at confirmation of pregnancy and in a study by Abalovich et al. it was shown that in hypothyroid women, who are planning to become pregnant, serum TSH levels should be in the lower normal range (~1.2 mIU/L), in order to obtain a serum TSH level ≤ 2.5 mIU/L during the first trimester. For all hypothyroid LT4-treated women, serum TSH levels should be monitored every 6-8 weeks unless an increase in dosage is needed (then after 4 weeks).

Screening for thyroid dysfunction and TAI should be performed as part of the work-up in women with well-defined high-risk conditions and it is proposed to evaluate TSH in euthyroid women with TAI ~ every 4-6 weeks during pregnancy. The current serum TSH level during the first trimester of pregnancy should be ≤ 2.5 mIU/L, but probably future randomized, placebo-controlled trials could change the optimal TSH threshold that should be obtained in order to ameliorate the pregnancy outcome.

References:
There is considerable debate around the diagnosis and management of thyroid dysfunction in pregnancy. The American Endocrine Society (Endo Soc) published guidelines in 2007 (1) but advances in several areas have resulted in recent guidelines from The American Thyroid Association (ATA) (2) and Endo Soc(3).

Care in interpreting FT4 measurements in pregnancy is recommended. Ideally TSH and FT4 reference ranges should be established in each laboratory. Women receiving L-T4 should increase the dose, usually by about 30%, when pregnant to achieve a TSH not → 2.5mIU/L in 1st trimester. Overt and subclinical hypothyroidism (SCH) are common in pregnancy (up to 5%). Whether all SCH women should receive L-T4 during gestation is still unclear. Results of the CATS study (4) did not show benefit in IQ of 3 year old children in a RCT. TPO antibodies are seen in 10% of pregnant women. There is not enough evidence to recommend screening for TPOAb and L-T4 treatment although some studies suggest this may be beneficial. Similarly isolated hypothyroxinaemia is not currently an indication for treatment. Hyperthyroidism (usually due to Graves’ disease) should be actively managed. Propylthiouracil (PTU) is the drug of choice for 1st trimester because Methimazole/Carbimazole (MMI/CBZ) have an increased risk of congenital malformations at this period. Because of potential hepatotoxicity of PTU MMI/ CBZ should be used for the rest of the pregnancy.

Screening for thyroid function in early gestation is controversial although possibly cost effective. All guidelines currently recommend criteria for screening but a significant number of women with thyroid dysfunction may be missed. Further studies are indicated.

References:
1 Abalovich M et al J Clin Endocrinol Metab. 2007;92:S1-47
Mild hypothyroidism was first associated with cardiovascular disease 40 years ago. Since then, numerous large population studies have found an increased risk of vascular events or death in individuals with a single raised TSH, as compared to euthyroid controls. Although the initial analysis of the Whickham survey failed to confirm the above finding, re-analysis using tighter phenotype definitions has confirmed an excess of Ischaemic Heart Disease events and vascular deaths in subjects with subclinical hypothyroidism. Meta-analysis of 15 studies, encompassing more than 2,500 subclinical hypothyroidism patients has confirmed an excess of vascular events and mortality in this group. Interestingly, these effects are most significant in younger individuals, aged 65 years or less.

The mechanism(s) underlying this excess in vascular events in subclinical hypothyroidism remains ill defined. Numerous factors, including adverse lipid profiles, cardiac systolic and diastolic dysfunction, endothelial dysfunction and abnormalities in clotting factors might be responsible. A key question is whether treatment with levothyroxine could improve the prognosis of individuals with subclinical hypothyroidism. The gold-standard of well-powered RCT studies with hard clinical events as endpoints have not been performed. Randomised studies with symptoms or surrogate vascular markers as endpoints have shown benefits in some but not all studies. Our analysis of 4,735 subclinical hypothyroid patients (TSH 5-10 mU/l) from a UK primary care database suggests that levothyroxine therapy is safe, and may be beneficial in younger patients (<70 yrs) who were followed up for 8 years. In contrast, older patients in the same study did not derive any similar improvement in outcome following levothyroxine treatment. Reassuringly, an excess of adverse events such as atrial fibrillation were not observed in levothyroxine treated subjects. At the moment, clinicians have to decide on a case-by-case basis about the potential benefits of levothyroxine treatment, assessing symptoms, underlying vascular risk and age in their decision to treat.
Background. Data suggest that persistent symptoms are present in a group of L-T4 treated hypothyroid patients with normal serum TSH. The use of T4+T3 combination therapy in such patients is controversial. The ETA nominated a taskforce to review the topic and formulate guidelines in this area.

Methods. Taskforce members developed a list of relevant topics. Recommendations on each topic are based on a systematic search, discussions within the task force, and comments from the ETA membership at large.

Results. Suggested explanations for persistent complaints include: awareness to have a chronic disease, presence of associated autoimmune diseases, thyroid autoimmunity per se, and inadequacy of L-T4 treatment to restore physiological T4 and T3 concentrations in serum and tissues. There is insufficient evidence that T4+T3 combination therapy is better than T4 monotherapy, and it is recommended that T4 monotherapy remains the standard treatment of hypothyroidism. T4+T3 combination therapy might be considered as an experimental approach in compliant L-T4 treated hypothyroid patients who have persistent complaints despite normalized TSH values, provided they have previously received support to deal with the chronic nature of their disease, and associated autoimmune diseases have been ruled out. Treatment should be reserved for use by accredited internist/endocrinologists, and discontinued if no improvement is experienced after three months. It is suggested to start combination therapy in a L-T4/L-T3 dose ratio between 13:1 and 20:1 by weight [L-T4 once daily, and the daily L-T3 dose –if possible- in two doses]. Currently available combination preparations all have a L-T4/L-T3 dose ratio of ≤13:1, and are not recommended. Close monitoring is indicated, aiming not only at normal serum TSH and FT4 but also at normal serum FT4/FT3 ratio’s.

Conclusion. T4+T3 combination therapy should be considered as an experimental treatment modality. The present guidelines are offered to enhance its safety and to counter its indiscriminate use.
Thyroid nodules are a common clinical finding, with an estimated prevalence of 3% to 7% at palpation. The prevalence of non-palpable thyroid nodules detected by thyroid ultrasound (US) in the general population is much higher, and it is similar to that reported in autptic series. Furthermore, many patients with palpable thyroid nodule are found to have additional nodules on US. Due to this high frequency, several guidelines (GL) or consensus statements were developed in the last years, for the optimization of nodular thyroid disease management. Some recommendations were upgraded or downgraded in different guidelines on the basis of expert opinion. The GL agree on most of the issues, although some points differ, likely due to differences in Europe vs USA with respect to iodine intake and the availability of US.

US, sensitive thyrotropin (TSH) assay, and fine-needle aspiration (FNA) cytology are widely recognized to be the basis for the management of thyroid nodules. Thyroid scintiscan is not necessary for diagnosis in most cases. However, it may be warranted in patients with a low serum TSH value or a multinodular goiter, to detect functional autonomy, most common in iodine-deficient areas. When an abnormal TSH is found, differences in the GL are present in recommending measurement of FT4, FT3 and TPOAb. Basal calcitonin measurement is always advised in European GL, while it is considered non cost-effective in USA. Some GL suggest US guided FNA in nodules of any size with suspicious US patterns, while others GL rely only on nodule size and not US pattern.

Treatment with L-thyroxine is not advised in ATA GL, while it may be taken into consideration for small nodular goiter in young patients living in iodine deficient areas in other GL. Mini invasive treatments as an alternative to surgery are considered only in few GL.
Unsurprisingly all thyroid guidelines recommend surgery for nodules suspected of malignancy, as suggested by clinical, ultrasonographic, or cytological features. Surgery has also to be considered for benign nodules when cosmetic reasons, excessive growing, local discomforts or special anxiety of the patient are present. In this case lobectomy + isthmectomy (in some places now by axillary route with robotic assistance) can still be preferred, even if total thyroidectomy appears to be a better option as soon as diffuse multinodular dystrophy appears ultrasonographically evident. Radioactive iodine (131I) is also used in some countries in Europe for autonomously functioning nodules to obtain a rapid reduction of its volume and prevent hyperthyroidism.

Most of the apparently benign nodules can be surveyed, considering their usual stability, or even the possibility of spontaneous reduction of size in 10-30% of cases. However there are no consensual recommendations concerning the time interval of ultrasound follow-up: 6-24 months (AAE, ATA, Korean Society, LATA, NCI) or progressively spaced (6 months, then 1, 2, 5, 10 years. French Society of Endocrinology). Similarly there is no consensual agreement concerning the delay to repeat cytological diagnosis: systematically after 6 or 12 months, or only for increasing nodules (specially if size → 20% in a year), or showing clinical or ultrasound secondarily suspicious findings.

Most of the guidelines do not recommend use of levothyroxine, considering results of the main meta-analysis and risks of subclinical thyrotoxicosis. Nevertheless efficacy of levothyroxine or iodine versus placebo has been proved in iodine mild deficiency areas to obtain reduction of size and to prevent further development of the perinodular dystrophy. Suppressive therapy is not indicated in autonomous thyroid nodules, in older patients and in those with potential risks of bone and cardiac disease.
New non-surgical treatment modalities for thyroid nodules are based on the sclerosing properties of various forms of energy. These techniques have been known for long, and increasingly utilized during the last two decades. They have offered interventional possibilities in the management of various benign and malignant lesions. Whether using percutaneous ethanol injection (PEI), interstitial photocoagulation therapy (ILP) radiofrequency ablation (RFA), or the less researched high-frequency ultrasound or microwave therapy, the mechanism is closely related to a direct coagulative necrosis and local partial or complete small vessel thrombosis. Studies started in the early 1990s and the best evidence relates to PEI and ILP.

Although the therapy is generally performed on an out-patient basis, the cost, time-consumption, and necessary personnel vary considerably. Furthermore, there are major limitations before the data can be translated into evidence-based application. These relate to:

- Small study-populations
- Lack of standardization of therapy algorithms (calculation of exposure time, energy delivered and number of treatment sessions)
- Lack of control group(s)
- Insufficient data regarding effect on quality of life (QoL), thyroid function, and induction of thyroid autoimmunity
- To short follow-up periods to allow reporting long-term efficacy and recurrence-rates
- Paucity of data reporting on whether subsequent therapy (such as e.g. surgery) is impeded by any of these non-surgical therapy options

Importantly, the major scientific thyroid societies do not, with the exception of PEI for solitary benign cysts, recommend these modalities on a routine basis. And, if used, this should be in few centres highly skilled in interventional ultrasound-guided therapy. Despite this, much evidence of efficacy has accumulated and this is most convincing for PEI, ILP, and RFA. The techniques have been or can be used in solitary hyperfunctioning thyroid nodules as well as solitary non-functioning thyroid nodules. Generally, with one therapy session, a shrinkage of about 45-50% is the norm. Depending on type and time of exposure, number of sessions, and pretreatment variables this can be increased up to 80-90% shrinkage in some individuals. Most often efficacy is negatively correlated with initial thyroid nodule size. Quality of life is improved but at present only evaluated using a visual analogue scale and not disease specific questionnaires. Side-effects, besides pain, are limited in number but some are serious. In cystic nodules, the remission rate is around 80% and recurrence with long-term follow-up is low. Based on a limited number of studies, in highly selected patients, and lack of control groups, it seems that the majority of lymph nodes with thyroid cancer metastases respond completely to therapy. But whether this affects survival is unclarified.

Conclusions: Based on relatively weak evidence it seems that both solitary functioning and non-functioning thyroid nodules can efficaciously and with limited side-effects be treated with PEI, ILP, and RFA. Best evidence relates to PEI therapy of solitary cysts. Few studies have been adequately designed and compared the techniques head-to-head. The techniques should be offered in institutions with highly skilled personnel in ultrasound-guided interventional therapy. Treating lymph node metastases remains an experimental procedure.
Abstract not in hand at the time of going to press.
Radioiodine (131I) is administered to patients with differentiated thyroid cancer after total thyroidectomy with three aims: first, to eradicate normal-thyroid remnants (ablation) in order to achieve an undetectable serum thyroglobulin level and to facilitate the follow-up modalities; second, to irradiate any persistent neoplastic focus in order to decrease the risk of recurrence; and third, to perform 131I total-body scanning in order to diagnose persistent carcinoma. In patients with low-risk thyroid cancer, it is unclear whether the administration of 131I provides any benefit after complete surgery. Guidelines of the American Thyroid Association conclude that data are too conflicting to support a recommendation for or against the routine use of 131I postoperatively in patients with low-risk thyroid cancer, whereas guidelines of the European Thyroid Cancer Taskforce are more favourable toward its use.

131I ablation should therefore be used with the minimal amount of radioactivity, and with the best-tolerated TSH stimulation methods. Recombinant human thyrotropin and thyroid hormone withdrawal provide similar ablation rates after the administration of 3.7 GBq of 131I. Until recently, discrepant results have been reported with recombinant human thyrotropin when lower activities [1.8 GBq or 1.1 GBq] are administered. Major new prospective data are now available with the results of two large prospective multicentric trials comparing the use of a low activity (1.1 GBq) to a high activity [3.7 GBq] and the use of stimulation with thyroid hormones withdrawal to the use of recombinant human thyrotropin (1, 2). These two studies both were non-inferiority trials, showing that the ablation rates were equivalent between the 131I doses and between the thyrotropin-stimulation methods. According to these results, the use of recombinant human thyrotropin and low-dose [1.1 GBq] postoperative radiiodine ablation may be sufficient for the management of low-risk thyroid cancer.

References:
Medullary thyroid cancer (MTC) is a rare thyroid malignancy and occurs in 5-7% of all cases. Surgery is the most important in the management of MTC. Its extension depends on preoperative disease evaluation and is based on plasma or serum calcitonin and CEA levels as well as on neck ultrasound imaging. Careful evaluation of neck lymph nodes is necessary and, if lymph node metastases or elevated plasma CT (→ 400 pg/ml) are present, preoperative imaging for detection of distant metastases is required, however, FDG-PET is not routinely performed. Adequacy of surgery for MTC is usually judged by the postoperative normalization of calcitonin levels ("biochemical cure") and negative prognosis factors to achieve biochemical remission are very high preoperative in CT level (→ 150000 pg/ml) and the presence of neck lymph node metastases. In the presence of advanced local or distant disease, less aggressive neck surgery may be appropriate to maintain local disease control.

According to ATA Guidelines 2009, the initial evaluation and treatment of postoperative patient is based on basal serum calcitonin and CEA level. Estimation of the doubling time for CT and CEA which is an estimate of disease kinetics is also helpful. Patients with CT and CEA doubling time of less than 1 year have worse prognosis.

Facing progressive disseminated nonoperable MTC disease, the clinician has few options: chemotherapy or targeted therapy. Chemotherapy has not been shown effective and among TKI (tyrosine kinase inhibitors) vandetanib is the first drug registered and it is recommended by NCCN Guidelines. The phase III clinical trial (Wells 2011) has documented the prolongation of time to progression from 19,5 months to 30,1 months. Side effects and their management will be discussed.
Follow-up guidelines for patients with thyroid cancer (TC) were recently published in Europe and the US. Ultrasonography (US) of the neck is now considered as the first line imaging tool for follow up of patients with TC. Neck US enables accurate evaluation of thyroid bed and cervical lymph nodes and has a high diagnostic accuracy for persistent or recurrent disease. The widespread use of US, the variability of procedure, reports and indications have raise questions. Then, there is a need for guidelines focusing on these issues. For low risk patients, tests with a high negative predictive value are required to avoid any unnecessary treatment in cured patients. In contrast, the sensitivity of the diagnostic tools for malignancy must remain accurate in high risk patients.

The aim of the consensus is
• to assist physicians in deciding which patients should undergo ultrasound examination and how frequently;
• to standardize ultrasound procedure and reports;
• to define US findings suspected for recurrence;
• to define the indication and limits of US guided cytology of suspicious lymph nodes and/or thyroid bed recurrences and the indication of thyroglobulin assessment in the needle washout;
• to discuss the place of new ultrasound-guided minimally invasive surgical alternatives in the treatment of selected cases of thyroid cancer.

A French good practice guide for cervical ultrasound scan and echo-guided techniques in treating TC was recently published. It is time to take this good practice guide one step further. On behalf of the ETA Executive Committee, a task force is setting up comprising specialists from different countries. The recommendations will be based on the analysis of the current literature comprising the published guidelines and ultrasound practice experiences of the participants. The opportunity to set up multicentric clinical trials at a European level will be discuss.
Most patients with thyroid cancer can be cured by a proper surgery, eventually followed by radioactive iodine treatment when indicated. The overall prognosis is excellent, with an estimated five-year relative survival rate around 95%. An estimated 56500 new cases of thyroid cancer and 1800 deaths will occur in the United States in 2012. Significant progress has been made during the past years to identify the thyroid cancer with a worrisome prognosis. Disease stage, patient age, histopathologic factors, specific molecular abnormalities affect the prognosis. More aggressive lesions are typically found among tall cell, oncocytic, diffuse sclerosing variants of differentiated tumors, medullary thyroid cancers and among poorly differentiated and anaplastic thyroid cancers. Patients with progressive distant metastasis with or without radioiodine uptake are defined as having a refractory thyroid cancer. Fluorodeoxyglucose positron emission tomography can help recognize which metastatic thyroid cancer will have an aggressive behaviour requiring a targeted therapy. The knowledge of the key molecular abnormalities driving this type of cancer has provided some insight into potential targeted kinases for newly available drugs.

Metastatic disease management should give preference to locoregional approaches or watchful waiting in case of slow progressive disease. A patient with a macroscopic progressive disease, according to the RECIST (Response Evaluation Criteria In Solid Tumors) rules, should be proposed a clinical trial. National networks taking care of patients with refractory cancer may help define which patients should enter an experimental treatment. Several phase II trials have proven the efficacy of targeted therapies in progressive thyroid cancer. Significant but manageable toxicities may be present. Phase III trials are now in progress to determine if there is an impact on the overall survival. This strategy lead to the recent approval in Europe of vandetanib, a RET kinase inhibitor, for patients with advanced medullary thyroid cancer.

Primary or secondary resistance to targeted therapies should be anticipated and investigated to define new therapeutic strategies. Obtaining tumor material may be required to personalize the future of cancer treatment.
After the wide application of neck ultrasound there has been an epidemic of incidental discovery of thyroid nodules. Thyroid nodules, either single or multiple, carry a risk of 10% of being malignant, usually of the papillary subtype. The method with the highest precision to reveal the presence of malignancy in the incidental thyroid nodule is fine needle aspiration (FNA). Ultrasonographic characteristics guiding the decision to perform FNA are hypoechoigenicity, the presence of irregular halo, abnormal vascularity and the presence of microcalcifications. Previously the size of a nodule (i.e. $\geq$1cm) was a major determinant of the decision to perform FNA. However, FNA should be performed in even smaller nodules in the presence of suspect findings in the ultrasound. In case of malignancy total thyroidectomy is usually performed although in the majority of cases the health risk associated with papillary microcarcinomas appears to be very small. It should be remembered that a small percentage of microcarcinomas may present with lymph node metastasis.

The management of differentiated thyroid carcinoma (DTC) has been addressed in the recently published and revised guidelines from both the European and the American Thyroid Association. Radioiodine treatment (RAI) is frequently indicated for remnant ablation; this can be performed either after thyroid hormone withdrawal, or, equally effectively, by exogenous administration of rhTSH. Clinical research is focusing on identifying the low-risk cases, where RAI administration has no benefit for the patient. The follow-up of DTC patients includes thyroid hormone and TSH measurements. Basal and stimulated thyroglobulin levels are used as an index of persistent or recurrent disease and neck ultrasound should be performed to ensure lack of recurrence. Recently it has been suggested that risk for recurrence should be reassessed at time intervals and further follow-up accordingly modified. The TSH suppression with thyroxine is currently milder. DTC cases illustrating these policy changes in management will be discussed.