Treatment of Graves’ disease in 2015: an update

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Outline

- A short note on Graves’ disease
- What do guidelines say?
- What do we do?
- Advantages and disadvantages of treatment strategies
- What to do in special circumstances?
- What will we do in 2025?
A short note on Graves’s disease

- **Auto-immune stimulation of thyrocytes through TSH-receptor activation**
  - Endogenous hyperthyroidism
  - Goiter formation
  - Might be associated with orbitopathy (& dermatopathy)

- **First described in 12\(^{th}\) century (Sayyid Ismail al-Jurjani)**
  - 1835 (dr. Robert Graves) and 1840 (Karl Adoph von Basedow)
  - Aka “exophthalmic goiter” < late 19\(^{th}\) century

- **Epidemiology**
  - Incidence 100-200 / 100,000 per year; female predominance (5:1)
  - Most common in 3\(^{rd}\) and 5\(^{th}\) decades of life

- **Diagnosis based on US/scintigraphy and TRAb seropositivity**
**Thyrotropin receptor stimulating immunoglobulin G (TRAb)**

- Trigger for auto-immunity unknown
- Risk factors: smoking, familial Hx, auto-immune diseases
- Produced by B-cells; mimics TSH-action, leading to enhanced T4 and T3 secretion and escape from feedback loop
HPT-axis

TSH

TRH

TSH-R

T4 + T3

FT4 Reference Range

Hypothyroid

Hyperthyroid

TSH Reference Range

Free T4

<ref>
9 pmol/L

0.7 ng/dL

23 pmol/L

1.8 ng/dL
</ref>
HPT-axis in Graves’ disease

T4 + T3

TSH

TRAb

TSH-R

TRH

Hypothalamus

Infundibulum

Posterior pituitary

Anterior pituitary

Free T4

9

0.7

23 pmol/L

1.8 ng/dL

TSH

> x100

x2

TSH Reference Range

Hypothyroid

FT4 Reference Range

Hyperthyroid

TSH

0.4

1.0

10

100

1,000

TSH miU/L

Undetectable
A short note on Graves’s disease

**Treatment**
- Focus on restoration of euthyroid state
  - As quickly (3-8 weeks) and safely as possible
- Avoidance of short-term complications; minimizing therapeutic side effects
- Avoidance of (immediate & long-term) relapse

**Surgery**

**Radio-iodine treatment (RAI)**

**Medical treatment (antithyroid drugs, ATD)**
- Block & replacement therapy
- Titration therapy
What do guidelines say?

- **NIV Richtlijn Schildklierfunctiestoornissen (2012)**
  - ATD good option for most patients as primary therapy
  - No differentiation between block-replace or titration therapy
  - Duration 12-18 months
  - ATD of choice: thiamazol (30 mg starting dose)
  - Consider RAI or surgery i.c.o. big goiter and/or high Ab titers

- **ATA/AACE Thyrotoxicosis Guidelines (2011)**
  - Pts with GD should be treated with ATD / RAI / Surgery
  - ATD (methimazol is ATD of choice): pts with high likelihood of remission; pts not suited for surgery or RAI
    - More or less advice against B+R < higher rate of ATD side effects
    - Duration: 12-18 months; stop treatment after measuring TSH-R Ab
  - RAI: incipient pregnancy wish; not suited for surgery; ATD contra-indications or intolerance
  - Surgery: pts with large goiters, urgent pregnancy wish (<4-6 months), suspicious thyroid lesions
What do guidelines say?

  - i.c.o. ATD treatment
    - Perform baseline complete blood count, and liver profile before starting
    - During treatment:
      - Differential white blood count i.c.o. febrile illness and pharyngitis
      - Liver function and transaminase measurement only i.c.o. suggestive symptoms
    - Methimazol (MMI) in single dose
What to choose?

<table>
<thead>
<tr>
<th></th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATD</strong></td>
<td>- Chance of permanent remission</td>
<td>- Minor side effects in up to 15% of pts</td>
</tr>
<tr>
<td></td>
<td>- Avoidance of permanent hypothyroidism</td>
<td>- Major side effects: rare</td>
</tr>
<tr>
<td></td>
<td>- Lower initial cost</td>
<td>- Fetal consequences when pregnant</td>
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<tr>
<td></td>
<td></td>
<td>- Requires more frequent monitoring</td>
</tr>
<tr>
<td><strong>RAI</strong></td>
<td>- Permanent(?) resolution of hyperthyroidism</td>
<td>- Permanent hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Radiation exposure→hygienic measures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Postradiation thyroiditis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Development / worsening of orbitopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Oncogenic? (patient concern)</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td>- Rapid, permanent(?) cure of hyperthyroidism</td>
<td>- Permanent hypothyroidism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Risk of surgical complications</td>
</tr>
<tr>
<td></td>
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<td>- High cost</td>
</tr>
</tbody>
</table>

Choice of treatment based on chance of remission & patient characteristics (age, pregnancy wish, co-morbidities, goiter size, orbitopathy, patient’s preference)
Chances of relapse

+/-50% (15-80%) after 1-2 years of ATD therapy

Risk higher in:
- Young pts, men, smokers, big goiters (> 80 g), severe disease activity & persistently high TRAb, high thyroid blood flow (Doppler), associated Graves’ orbitopathy, after excessive iodine intake (high background iodine intake?)

Laurberg, Acta Endocrinol 1986

Nedrebo, EJE 2002
### Chances of relapse

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
<th>Statistical significance (P) of difference between males and females (by χ²/t test)</th>
<th>Odds ratio and 95% confidence interval</th>
<th>Age &lt;40 yr</th>
<th>Age ≥40 yr</th>
<th>Statistical significance (P) of difference between age groups (by χ²/t test)</th>
<th>Odds ratio and 95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successful medical treatment (%)</td>
<td>19.6</td>
<td>40</td>
<td>&lt;0.01</td>
<td>0.37 (0.17–0.79)</td>
<td>32.6</td>
<td>47.8</td>
<td>0.01</td>
<td>0.53 (0.32–0.87)</td>
</tr>
<tr>
<td>Failed medical treatment (%)</td>
<td>80.4</td>
<td>60</td>
<td></td>
<td>2.73 (1.27–5.89)</td>
<td>67.4</td>
<td>52.2</td>
<td>0.6</td>
<td>1.89 (1.15–3.12)</td>
</tr>
<tr>
<td>Mean first dose of radioiodine (MBq)</td>
<td>299</td>
<td>301</td>
<td>0.9</td>
<td>&lt;br&gt;</td>
<td>&lt;br&gt;</td>
<td>&lt;br&gt;</td>
<td>&lt;br&gt;</td>
<td>&lt;br&gt;</td>
</tr>
<tr>
<td>Cure with 1 dose of radioiodine (%)</td>
<td>47</td>
<td>74</td>
<td>&lt;0.0001</td>
<td>0.31 (0.17–0.54)</td>
<td>66.5</td>
<td>71</td>
<td>0.4</td>
<td>0.8 (0.47–1.36)</td>
</tr>
<tr>
<td>Cure with &gt;1 dose of radioiodine (%)</td>
<td>53</td>
<td>26</td>
<td></td>
<td>3.25 (1.84–5.74)</td>
<td>33.5</td>
<td>29</td>
<td>1.24</td>
<td>1.24 (0.73–2.11)</td>
</tr>
</tbody>
</table>

Allahabadi et al., JCEM 2000

<table>
<thead>
<tr>
<th>At initial diagnosis</th>
<th>Smoking</th>
<th>Yes</th>
<th>6.9</th>
<th>1.6–31</th>
<th>0.029</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSHR-Ab</td>
<td>Positive</td>
<td>n.i.</td>
<td>n.i.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>n.i.</td>
<td>n.i.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At the end of ATD</td>
<td>Smoking</td>
<td>Yes</td>
<td>7.0</td>
<td>1.4–36</td>
<td>0.019</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSHR-Ab</td>
<td>Positive</td>
<td>27.7</td>
<td>3.0–256</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After ATD withdrawal</td>
<td>Smoking</td>
<td>Yes</td>
<td>8.1</td>
<td>1.1–59</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSHR-Ab</td>
<td>Positive</td>
<td>38.0</td>
<td>3.4–423</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>1.0</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Glinoer et al., EJE 2001
219 pts after ATD treatment (min. 6 months)
-52% B+R
-48% titration

Maximum FU 10 yrs; 829 pt years

43.5% relapse rate

Goiter size predictive

Previous smoking protective?

No effect of age, sex, disease severity, treatment regimen
What do you do?

First-line treatment of uncomplicated Graves’ disease

- □ = Europe
- ■ = US (2011 data)
What do you do?

Bartalena et al., Clin Endo 2015
‘Full’ block- & replacement therapy as initial therapy in most pts

- Thiamazol 3x10 mg (or temporarily higher starting dose) +/- beta-blockade for symptom control
- Once euthyroid: add levothyroxine to achieve TSH +/- 1 mU/L; keep thiamazol 20-30 mg/day (once daily)
- Duration 12-18 months, withdrawal after 2x TRAb-seronegative

Consider surgery i.c.o.

- Big goiter; suspicious nodule; ATD intolerance; urgent pregnancy wish; persistent TSH-R Ab seropositivity

Consider RAI i.c.o.

- ATD intolerance, high surgical risk, patient’s preference

I.c.o. first relapse: consider ATD / RAI / Surgery

I.c.o. second relapse: consider RAI / Surgery
What do studies suggest?

- **Medical therapy >< surgery >< radio-iodine**
  - Side effects?
    - Risk of GO development
  - Relapse rate?
  - QoL pts?

- **Only 1 RCT comparing these 3 modalities!**
  - n = 179 pts, FU ≥ 48 months
  - Normalisation of hyperthyroidism at 6 weeks = among the 3
  - Relapse rate:
    - ATD (full B+R): 37% (42% in young pts; 34% in older pts)
    - RAI: 21%
    - Surgery: 6% (3% in young; 8% in older pts)
  - Equal pt satisfaction (questionnaire) and sick day leave

Törring et al., JCEM 1996
What do studies suggest?

- 59 pts with relapse; increase in TR Ab in 55% of them
- However: relapse in 23% of pts with negative TR Ab at time of withdrawal!

Törring et al., JCEM 1996
Medical therapy

- Optimal duration?

- Block & replacement vs. titration therapy?
  - Is maintenance dose of ATD important?

- Is type of ATD important?
  - ~ success rate?
  - ~ complication rate?

- Is starting / maintenance dose of ATD important?
  - ~ success rate?
  - ~ complication rate?
Medical therapy – duration; block vs. titration

- **Cochrane Database Review (2010)**
  - 26 RCTs, 3388 pts (83% female)
  - Poor study quality overall

  - **Duration (4 trials)**
    - 12-18 months better than 6 months with respect to relapse rate (25-38% vs. 60-70%)
    - No benefit > 18 months

  - **Block-replace vs. titration-block regimens (12 trials)**
    - Similar relapse rates (51 vs. 54%) at one year after withdrawal
    - Higher AER (rashes: 10 vs. 6%) and withdrawal rate (16 vs. 9%) in block-replace groups

  - No benefit of thyroxine addition post treatment (5 trials)
  - No difference PTU vs. MMI (1 trial)
  - Possible benefit of azathioprine (1 trial)
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Block Replace n/N</th>
<th>Titration n/N</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 12 to 24 month follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edmonds 1994</td>
<td>17/34</td>
<td>24/36</td>
<td>5.9 %</td>
<td>0.51 [0.20, 1.31]</td>
<td></td>
</tr>
<tr>
<td>Grebe 1998</td>
<td>6/9</td>
<td>15/16</td>
<td>1.1 %</td>
<td>0.14 [0.02, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Jordan 1995</td>
<td>11/19</td>
<td>17/22</td>
<td>3.1 %</td>
<td>0.42 [0.11, 1.54]</td>
<td></td>
</tr>
<tr>
<td>Mciver B 1996</td>
<td>8/13</td>
<td>8/17</td>
<td>2.6 %</td>
<td>1.75 [0.42, 7.28]</td>
<td></td>
</tr>
<tr>
<td>Wilson 1996</td>
<td>10/28</td>
<td>20/35</td>
<td>5.4 %</td>
<td>0.43 [0.16, 1.15]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>103</strong></td>
<td><strong>126</strong></td>
<td><strong>18.1 %</strong></td>
<td><strong>0.52 [0.30, 0.89]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 52 (Block Replace), 84 (Titration)
Heterogeneity: Chi² = 4.38, df = 4 (P = 0.36); I² = 9%
Test for overall effect: Z = 2.40 (P = 0.016)

2 Over 24 month follow-up

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Block Replace n/N</th>
<th>Titration n/N</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
<th>Weight</th>
<th>Peto Odds Ratio Peto,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benker 1998</td>
<td>85/147</td>
<td>84/144</td>
<td>24.4 %</td>
<td>0.98 [0.62, 1.56]</td>
<td></td>
</tr>
<tr>
<td>Goni Iriarte 1995</td>
<td>17/28</td>
<td>22/35</td>
<td>5.1 %</td>
<td>0.91 [0.33, 2.52]</td>
<td></td>
</tr>
<tr>
<td>Leclere 1994</td>
<td>39/98</td>
<td>46/98</td>
<td>16.6 %</td>
<td>0.75 [0.43, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Lucas 1997</td>
<td>20/30</td>
<td>18/30</td>
<td>4.9 %</td>
<td>1.33 [0.47, 3.76]</td>
<td></td>
</tr>
<tr>
<td>Nedrebo 2002</td>
<td>47/98</td>
<td>41/91</td>
<td>16.2 %</td>
<td>1.12 [0.63, 1.99]</td>
<td></td>
</tr>
<tr>
<td>Rittmester 1998</td>
<td>57/98</td>
<td>30/51</td>
<td>11.3 %</td>
<td>0.97 [0.49, 1.93]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>499</strong></td>
<td><strong>449</strong></td>
<td><strong>78.4 %</strong></td>
<td><strong>0.96 [0.74, 1.25]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>636</strong></td>
<td><strong>614</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.86 [0.68, 1.08]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 322 (Block Replace), 332 (Titration)
Heterogeneity: Chi² = 10.00, df = 11 (P = 0.53); I² = 0.0%
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Chi² = 4.19, df = 2 (P = 0.12), I² = 52%
More stable thyroid function with block- & replacement therapy?

- Less TSH fluctuation → less auto-antigen presentation?
- Less doctors’ visits & thyroid function tests?

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>B&amp;R (n = 223)</th>
<th>Titration (n = 149)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (SD)/%</td>
<td>mean (SD)/%</td>
<td></td>
</tr>
<tr>
<td>Number of TFTs per year</td>
<td>3.2 (1.2)</td>
<td>3.4 (1.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Number of abnormal TFTs per year</td>
<td>1.8 (1.3)</td>
<td>1.8 (1.4)</td>
<td>0.74</td>
</tr>
<tr>
<td>Patients with at least one abnormal TFT in first 3 months (%)</td>
<td>77.1</td>
<td>67.1</td>
<td>0.23</td>
</tr>
<tr>
<td>Patients with TSH &gt; 20 mIU/l at any time during follow-up (%)</td>
<td><strong>9.9</strong></td>
<td>6.0</td>
<td>0.67</td>
</tr>
<tr>
<td>Patients with FT4 &gt; 48 pmol/l at any time during follow-up (%)</td>
<td>43.9</td>
<td>36.2</td>
<td>0.45</td>
</tr>
<tr>
<td>Number of follow-up visits per year</td>
<td>2.9 (1.0)</td>
<td>3.2 (1.3)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

If you do it, do it good!
Medical therapy – type & dose of ATD

- Retrospective study on 536 consecutive new patients with Graves’ disease (1975-1998) – titration therapy

<table>
<thead>
<tr>
<th></th>
<th>MMI 30 mg/d</th>
<th>MMI 15 mg/d</th>
<th>PTU 300 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal FT4 at 12 weeks</td>
<td>97%</td>
<td>86%</td>
<td>78%</td>
</tr>
<tr>
<td>Side effects</td>
<td>30%</td>
<td>14%</td>
<td>50%</td>
</tr>
</tbody>
</table>

- Faster restoration of euthyroid state i.c.o. high initial FT4 (> 7 ng/dL) with MMI 30 vs. 15 mg/d or PTU 300 mg/d
- Faster normalisation of T3 with MMI (15 or 30 mg/d) vs. PTU

Allahabadia et al., JCEM 2000
Medical therapy – type & dose of ATD

Homsanit et al., clin Endo 2001

No pts with large goiters and/or severe thyrotoxicosis!
Medical therapy – type & dose of ATD

He et al., clin Endo 2004

No pts with large goiters and/or severe thyrotoxicosis!
Once daily dosing?
- Plasma $t_{1/2}$ MMI 4-6 hrs
  - Steady state after 10-20 days
- Thyroid-to-serum ratio = 100:1
  - probably longer intrathyroidal $t_{1/2}$ due to accumulation

Once daily dose suffices
- Not to start with cf. side effects
- Not true for PTU ($t_{1/2}$ 75 minutes)

MMI 15 mg in single dose: 24-hr long inhibition of organification in +/- 75% of pts (Okamura et al., 1987)
- Enough for ‘full’ block?

MMI 30 mg daily as starting dose. As maintenance dose?
Medical therapy – adverse effects

- Up to 15% of pts report side effects
  - Itching, rash, hives, joint pain & swelling, fever, altered taste sensation, nausea, and vomiting
  - Dose dependent
  - MMI = PTU

Sundaresh et al., JCEM 2013
Medical therapy – adverse effects

- **Toxic hepatitis**
  - PTU & severe liver injury: 1/10,000 in adults; 1/3000 in children
  - MMI: cholestatic pattern
  - Episodic check up of liver function advisable?

- **Agranulocytosis (1/600 patients - both PTU and MMI)**
  - Idiosyncratic? Dose dependent? → no active surveillance → STOP treatment and check WBC with fever, pharyngitis

- **Drug-induced SLE, vasculitis (esp. long-term PTU)**

- **Congenital malformations → PTU during 1st trimester pregnancy**
  - 1/30 with MMI vs. 1/40 with PTU (+different pattern; see Laurberg lecture at 46th meeting)
**Medical therapy in recurrent disease**

**Arguments for graded ATD withdrawal?**

- **128 pts with 1\(^{st}\) relapse of Graves’ disease**
  - 1\(^{st}\) treatment with ATD (not specified)
  - 2\(^{nd}\) treatment with MMI titration treatment (30 → 2.5 mg daily); duration +/-10 months
  - Hereafter randomisation:
    - 10 months graded withdrawal: relapse 16% @ 48 months
    - 5 months: relapse rate 33% @ 48 months

Liu *et al.*, EJE 2015
Medical therapy – prolonged low-dose B+R

- 108 pts with GO, partial B+R; median FU 80 months
- Complications: 1 pt rash (<MMI) + development of cutaneous vasculitis after 6 years of PTU

Laurberg et al., Thyroid 2011
After restoration of euthyroid state

ATA/AACE: ATD pre-treatment not absolutely mandatory i.c.o. mild hyperthyroidism

Pre-treatment ATD
- No interference with MMI (stop 3-7 days before)
- PTU might decrease efficacy (even when stopping 15d before)

Post-treatment ATD?

Large experience (<1940s); well tolerated
- Not during pregnancy or breastfeeding
- Postpone pregnancy 6-12 months after treatment
Administered activity: high vs. low

ATA/AACE: 10-15 mCi → to cause hypothyroidism

Fixed dose vs. calculated dose?
- No evidence

High dose (10 mCi) vs. low dose (5 mCi):
- Cure rate: 85% vs. 67%
- Hypothyroidism: 61% vs. 41% (can occur many years later!)

10-20% failures
- new I-131 administration, prolonged ATD or surgery required

Radio-iodine treatment

Allahabadia et al., JCEM 2001

Alexander et al., JCEM 2002
Radio-iodine treatment

**Ophtalmopathy**

- Development or progression of pre-existent GO in +/- 15%
  - Mostly mild & transient
  - Additional treatment required in +/- 5%
- Almost completely avoidable with oral GC (and prevention of post-treatment hypothyroidism)
  - R/ prednisolon 0.2 mg/kg starting dose 2 days before RAI; slowly tapering during subsequent 6 weeks
- No RAI
  - active (severe) GO; hyperthyroid state; still smoking(?); high TRAb levels (> 7.5 IU/L)
After restoration of thyroid function

- Importance of experienced surgeon
  - Definition: 20-50-100 thyroidectomies per year?
  - <2% of permanent hypoparathyroidism
  - <1% permanent RLN injury

Near-total thyroidectomy is procedure of choice (NIV, ATA/AACE)

Iodine loading pre-operatively?

- No evidence, only i.c.o. ATD intolerance or uncontrolled hyperthyroidism
- R/ potassium iodide 5–7 drops (0.25–0.35 mL) Lugol’s solution (8mg iodide/drop) or 1–2 drops (0.05–0.1 mL) SSKI (50mg iodide/drop) three times daily mixed in water or juice for 10 days before surgery
Treatment effects on auto-immunity

Laurberg et al., EJE 2008 (FU on Törring study):

Patients were randomized to receive either
- ‘full’ B+R for 18 months
- radioiodine therapy,
- or near total thyroidectomy.
Treatment effects on relapse rate

Network meta-analysis; 7 observational studies, 1 RCT

Relapse rates:
- 53% for ATD
- 15% for RAI
- 10% for surgery

Sundaresh et al., JCEM 2013
Disease monitoring

- **Initial monitoring every 4-6 weeks until restoration of euthyroid state**
  - Focus on FT4 (and FT3)!
- **ATD**
  - Monitor thyroid function every 12-24 weeks once stable disease
  - After drug withdrawal: monitoring after 6 and 12 weeks; thereafter every 12-24 weeks first year; thereafter yearly
- **After RAI & surgery:**
  - First monitoring after 6-8 weeks; thereafter every 12-24 weeks during first year; thereafter yearly
- **TR Ab**
  - During course of ATD?
  - Before ATD withdrawal
What to do in special circumstances?

- Pregnancy
- Graves’ orbitopathy
- Therapy-refractory disease / thyroid storm
Graves’s disease & pregnancy

- **Graves before / at start of pregnancy**
  - PTU in minimal effective dose (~titration therapy)

- **I.c.o. persisting Graves**
  - Switch to MMI in 2nd trimester (minimal effective dose)

- **When still active disease at delivery**
  - Alarm neonatologist about possible delayed neonatal hyperthyroidism

- **In every women with Hx of Graves’** → measure TRAb by 24-28 weeks of gestation to detect possible neonatal Graves’
Graves’s disease & orbitopathy

- Present in 20-30% of patients at diagnosis
- Believed to be associated with TRAb serum titers
- Pts with GO have more severe form of disease, often more difficult to treat

**EUGOGO Guidelines (2008):**
- Importance of restoration of euthyroidism
- Neither ATD nor surgery affect GO

**Laurberg:**
- Similar decrease TRAb after surgery vs. B+R (EJE 2008)
- Prolonged low dose block +/- replacement therapy (Curr Opin 2014)
Definition / clinical signs therapy refractory disease:
- Persistently high TRAb values
- Increase in goiter size
- Persistent elevated T3/T4 ratio

Choose for (2nd) RAI or surgery

Thyroid storm
- Treat precipitating cause
- ATD:
  - R/ glucocorticoids
  - R/ intravenous thiamazol
  - R/ sodium perchlorate (500 mg bid)
- Urgent thyroidectomy
What will we do in 2025?

- Rituximab & other types of immunotherapy?
- Selenium?
- Intra-thyroid dexamethason injection to prevent relapse?
- Tocilizumab, otelixizumab, doxycyline, azithromycin, lanreotide for GO?
- TSH-R and IGF-1R modulators...?
Conclusions

**Initial treatment**

- +/- 50% chance of definite ‘cure’ (higher in Europe vs. US & Japan?)
  - *why don’t you give medical treatment a try?*

- Patient’s preferences
- Use thiamazol (unless 1st trimester pregnancy)
- CAVE high / persistent antibody titers, severe disease activity, big goiter → RAI or surgery upfront?

**Surgery and RAI are safe and effective alternatives**
Conclusions

- **Block & replacement vs. titration**
  - Higher rate of (mild) side effects with ‘full’ block therapy
  - Avoidance of hypo- / hyperthyroid episodes → more stable disease → less risk for GO? more chance of remission?

- **Ending ATD treatment**
  - Predictive role of TRAb seropositivity for relapse

- **Prolonged low dose treatment in pts with persisting disease activity and/or GO?**
"Why do you call it a thyroid 'problem' when it's giving me an excuse for the 20 pounds I gained this year???