Hypogonadism: Determining the best way forward

Updates in Urology for the Primary Care Practice

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Hypogonadism: Determining the best way forward

- Dilemmas of Testosterone Replacement Therapy
  - Cardiovascular risk - TRAVERSE Clinical Trial
  - Polycythemia
  - Prostate health
  - Infertility

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Cardiovascular risk - TRAVERSE Clinical Trial

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Cardiovascular risk - TRAVERSE Clinical Trial

- Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial - Lincoff, et al N Engl J Med 2023;389:107-17 (6/2023)
  - 2015 the USFDA required testosterone manufacturers to conduct a randomized placebo controlled clinical trial to determine the TRT has on the risk of MACEs
  - Multicenter, randomized, double-blind, placebo-controlled, noninferiority trial to assess the cardiovascular safety of testosterone replacement
    - 5246 men, ages 45 to 80 years
    - High risk or preexisting cardiovascular disease (looking for patients who would have cardiac events)
    - Given testosterone gel or placebo

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Cardiovascular risk - TRAVERSE Clinical Trial

- TRAVERSE Trial continued
  - Target testosterone levels were 350-750 ng/dl
  - Primary end point was any of the following:
    - Death from cardiovascular causes
    - Nonfatal myocardial infarction
    - Nonfatal stroke

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Cardiovascular risk - TRAVERSE Clinical Trial

- Secondary end point was each of the following:
  - Death from cardiovascular causes
  - Nonfatal myocardial infarction
  - Nonfatal stroke
- Noninferiority required an upper limit of less than 1.5 for the 95% confidence interval of the hazard ratio

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Cardiovascular risk - TRAVERSE Clinical Trial

- Results
  - 22 months of treatment
  - 33 months of follow up
  - Primary endpoint of a MACE occurred in 182 (7%) of treated patients versus 190 (7.3%) receiving placebo

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Polycythemia

- Secondary polycythemia due to testosterone replacement therapy
  - Testosterone stimulates erythropoiesis through an initial rise in erythropoietin (EPO)
  - There is an establishment of a new EPO/hemoglobin ‘set point’
  - The master iron regulator protein hepcidin is decreased causing increased availability of iron
- This elevated hematocrit seems associated with an increased risk of both arterial and venous thrombosis

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Polycythemia

- In men using TRT - Polycythemia (Hct > 52%) which develops during the first year of treatment increases the risk of MACE and venous thromboembolism - 5.2% vs 3.9%
  - Men with a higher baseline hematocrit are more likely to develop polycythemia

Ory, J; et al; JUrol; Vol. 207, 1295-1301, June 2022.

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Polycythemia

- Management of erythrocytosis
  - Address co-contributing conditions: Sleep apnea, COPD, vaping or tobacco use
  - Change delivery formulation
    - Most common in injections, then pellets, gel, least likely for intranasal and oral delivery
  - If dosing IM injections:
    - Decrease dose and increase frequency
    - Lower dose
    - Change to SQ

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Polycythemia

- Management of erythrocytosis
  - Therapeutic phlebotomy or donate blood at Hct 51% or 52%
  - Hematocrit > 54% requires TRT withdrawal

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Polycythemia

- Managing erythrocytosis
  - Be careful with frequent donations
    - Depletion of iron stores
    - Symptoms of iron deficiency without anemia
      - Weakness, fatigue, reduced exercise performance, difficulty in concentrating, and poor work productivity
      - Neurocognitive dysfunction including irritability
      - Fibromyalgia syndrome
      - Restless leg syndrome

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Prostate health

- TRAVERSE Clinical Trial - prostate safety
  - No increased incidence of
    - High grade prostate cancer (Gleason 4+3)
    - Any prostate cancer
    - Urinary retention
    - Need for BPH surgery
    - Worsening lower urinary tract symptoms

Bhasin S, et al; JAMA Netw Open; 2023 Dec 1;6(12)

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Prostate health

- PSA increased significantly in men receiving TRT
  - Increase occurred during the first year
  - But the rate of prostate biopsy did not differ between the two groups

Bhasin S, et al; JAMA Netw Open; 2023 Dec 1;6(12)

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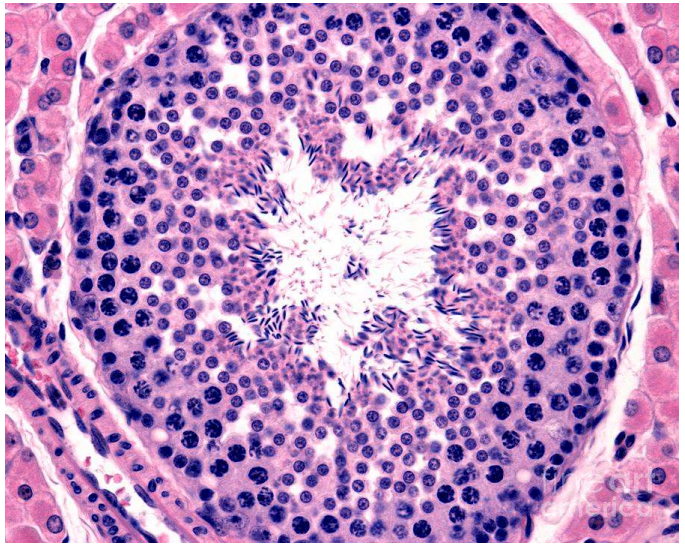
Preserving fertility

- Exogenous testosterone causes feedback inhibition of GnRH, LH and FSH secretion
- Leads to suppression of spermatogenesis



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Preserving fertility

- For men interested in preservation of fertility prior to initiation of testosterone treatment:
  - Clomiphene (Clomid) 25 mg or 50 mg PO every other day
  - hCG 500 - 3000 IU SQ every other day
  - Testosterone and hCG 500 IU SQ every other day

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Preserving fertility

- For men interested in restoring their fertility after they have been using TRT:
  - Stop the TRT
  - Start Clomiphene (Clomid) 50 PO mg every other day
  - Start hCG 2,000-3,000 IU IM or SQ every other day
  - Average time for return of sperm to the ejaculate is 4.6 months

Wenker, EP, et al; J Sex Med, 2015 Jun;12(6):1334-7

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