Cardiovascular Risk and Testosterone  
**Fact vs Fiction**

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Outline

1. Background: organic vs 'late onset' hypogonadism
2. CV risk: current evidence and limitations  
   - Epidemiological studies  
   - Retrospective prescription database studies  
   - Randomised controlled trials  
3. Practical implications

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‘Classic’ Testosterone Deficiency

Defined testicular or hypothalamo-pituitary disease  
Can occur at all ages  
- Testis failure - 95%  
- Pituitary failure - 5%

Testosterone replacement is marvellous  
Restores all the things testosterone does

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Classic Androgen deficiency

Primary (high LH)  
**impaired testis function**

Secondary (low LH)  
**hypothalamo-pituitary**
Classic Androgen deficiency

Primary (high LH)  *impaired testis function*
- Klinefelter’s syndrome
- Infertile men
- Testicular damage  vascular, cancer Rx

Secondary (low LH)  *hypothalamo-pituitary*
- Prolactinoma
- Iron deposition
- Kallmann’s syndrome

Klinefelter’s Syndrome – 47XXY

- **Commonest** chromosomal disorder  1:600 males
- **Commonest cause** of undiagnosed androgen deficiency
- Almost all androgen deficient as adults: benefit from TRT
- Only 25-50% Klinefelter’s are diagnosed in their lifetime

Detection strategies a major challenge

Reject your stereotypical images of KS

Classical KS in textbooks
- gynecomastia
- abdominal obesity
- small testes
- varicose veins

From: Nieschlag and Behre, 2007

*Classical KS in textbooks*
- Profound learning difficulties
- narrow shoulders
- reduced body hair
- horizontal pubic hairline
- small testes
- varicose veins

From Nieschlag and Behre, 2007

~12,000 missed KS males in USA

Failure to systematically examine male genitalia: flaw in education & practice

Klinefelter’s syndrome: The most overlooked cause of androgen deficiency

St John B & McLachlan RI
Endocrinology Today 2015; 4(1): 8-14

The testis is the most accessible endocrine organ

Physical examination is pivotal

Klinefelter’s syndrome

Not always!!
May appear entirely normal and adequately virilised when clothed
Controversy: androgens in health & aging

Low testosterone levels are common

Is this a pathological states in which androgen Rx is effective and safe?

‘Age-related’ ... or ‘Late onset hypogonadism (LOH)’
‘Andropause’
‘Low T’
‘Obesity-related HH’

Massive increase in testosterone prescribing
USA - 9 fold over 2000-2011

WHY?
Recognition of real entity

OF
Wishful thinking + marketing (direct to consumer)
The European Male Aging Study (EMAS) relationship between age and testosterone in 3220 men showed that serum T did not vary with age. Healthy Man Study by Sartorius G et al. Clin Endocrinol 2012;77:755 indicated that serum T did not vary with age.

Successful weight loss combined with optimization of comorbidities can be sufficient to improve symptoms, normalize testosterone levels, and reduce cardiovascular risk in men with “Late Onset Hypogonadism.”
Symptomatic' diabetic with low serum T, normal LH and replete with co-morbidities, CV risk

- Lifestyle
  - Diet
  - Exercise

- Medical
  - diabetes, hypertension, cholesterol

- Psychosexual issues
  - Judicious use of PDE5 inhibitors

Risks and benefits of TRT in middle aged and older men with low T and co-morbidities

Placebo-controlled RCT data is limited...

**Testosterone Trials:** 7 coordinated trials of T treatment in elderly men

- Abd alamira M et al. Coron Artery Dis. 2016; 27:95
- Reaick SM et al. JAMA 2017 ;317:717
- Snyder PJ et al JAMA Intern Med. 2017 ;177:471
- Budoff MJ et al JAMA. 2017;317:708

**T Trial population**

- Men > 65 years
- Serum total T <9.5nM
- One or more symptoms potentially related to low testosterone

| Table 01 - Characteristics at Baseline of Men Enrolled in Testosterone Trials |
|-------------------------------|-----------------|-----------------|
| Characteristics               | Placebo         | Testosterone     |
| N                             | 355             | 355              |
| Demographics                  |                 |                 |
| Age                           | 72 ± 8 ± 5.8    | 72 ± 8 ± 5.7    |
| Smoking                       |                 |                 |
| Alcohol use (no, drinkers)    | 288 (81.1%)     | 285 (80.0%)     |
| Ever smoker (%)               | 266 (75.3%)     | 256 (72.3%)     |
| Diabetes (%)                  | 152 (42.9%)     | 154 (43.4%)     |
| Hypertension (%)              | 259 (72.9%)     | 260 (73.4%)     |
| History of myocardial infarction (%) | 121 (34.0%) | 122 (34.4%) |
| History of stroke (%)         | 17 (4.8%)       | 18 (5.1%)       |
| Sleep apnea (%)               | 76 (21.2%)      | 76 (21.6%)      |

Assessed for eligibility (n=51,085)

<table>
<thead>
<tr>
<th></th>
<th>Excluded</th>
<th>Allocated to Treatment</th>
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<tbody>
<tr>
<td>(n=50,295)</td>
<td>(n=50,295)</td>
<td>(n=790)</td>
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</table>
What to do know about the impacts of testosterone on such men?

- Physical Function Trial
- Sexual Function Trial
- Vitality Trial
- Cognitive Function Trial
- Anemia Trial
- Cardiovascular Trial
- Bone Trial

Testosterone target range: 18-27nM  500-800 ng/dL

Outcomes of T Trial in Aging (co-morbid) Men

- **Sexual Function**: Modest & transient benefits in some aspects. ED: PDE5 inhibitors are more effective.
- **Cognition and memory**: not improved
- **Vitality and fatigue**: in the vitality trial sub study - no benefits
- **Physical function**: some benefits in some testing procedures
- **Bone**: density improved: not compared to established therapies

Medication Adherence to Topical Testosterone Therapy:


15,435 hypogonadal men

Persistence = time to last script OR gap of >30 days OR to at 12 months.

6 months, 34.7%  12 months, 15.4%.

Over time, dose escalation ~ 50% of men resumed therapy

Conclusions. High discontinuation rates irrespective of age, diagnosis, and index dose.

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Testosterone and CV Risk

Current data inconclusive, confusing & contradictory due to inherent limitations of existing studies

Lack of adequately designed and powered randomized controlled clinical trials with cardiovascular events as the primary outcome

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In Men with Type 2 Diabetes Low Testosterone is Common and Associated with an Adverse Cardiovascular Risk Profile

- Diabetic Men with Low Testosterone have Increased:
  - Obesity
  - Insulin Resistance
  - Dyslipidemia
  - Inflammation

Grossmann et al, JCEM 93:1834, 2008

*Relative to reference ranges based on healthy young men

Low Testosterone Independently Predicts Mortality in Men with Type 2 Diabetes

Melbourne Cohort: 572 men with T2D: Age 66 y, BMI 29.2 kg/m², Total T 10.5 nmol/L, HbA1c 7.3%

Observation Time (years)
0                      2                      4                      6                      8
Numbers at risk
126                  126                  126                  126                  126

Free Testosterone (normal range > 230 pmol/L)

- >230 pmol/L
- 160-230 pmol/L
- <160 pmol/L

p<0.001*

Survival (%)
100
80
60
40
20

Meta-Analysis of Epidemiological Studies:
Low serum testosterone predicts increased mortality

16,184 community-dwelling men (US, Europe) mean age 61 years, 9.7 years follow-up

Araujo et al, JCEM 2011

'between study heterogeneity suggests that low testosterone may be a marker of poor health'

Non-causation: low T and poor health share common risk factors
Causation: low T                                    poor health
Reverse causation: poor health                          low T    +   earlier death

Observational studies-by design-can never prove causality

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Inconclusive Cardiac Effects of T Treatment in Retrospective Database Analyses

T treatment associated with increased, decreased or unchanged risk

**Limitations**

- Inadequate outcome validation
- Incomplete covariate ascertainment
- Confounding due to lack of randomisation: e.g. preferential treatment of healthier men
- ? indication for T treatment dose and duration
- ? hypogonadal symptoms
- Baseline and on treatment T levels

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Adverse Events Associated with Testosterone Administration

TOM trial: RCT

- Older men with preexisting cardiovascular disease
- N = 209; age 74 y

Increased Risk of CVS events with Testosterone

- n=23 Testosterone
- n=5 Placebo

Small number and broad array of "cardiovascular-related" events

Inconclusive Cardiac Effects of T Treatment in Meta-Analyses of RCTs in Older Men

<table>
<thead>
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<th>Odds ratio (95% CI)</th>
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<td>Increased Risk in the first 12 months of T treatment</td>
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Labeling change to inform of possible increased risk of heart attacks and strokes with testosterone therapy

No existing RCTs: Underpowered, short-term, CVD events not pre-specified

Need > 10,000 men

Testosterone Treatment: Risks?

- No definitive outcome data regarding long-term CV events
- Non-randomized studies (epidemiologic, prescription database)
  - Subject to confounding, bias and reverse causality
- Existing RCTs: Underpowered, short-term, CVD events not pre-specified
  - Need > 10,000 men

- No evidence for risk if testosterone
  1) for approved indications (organic hypogonadism)
  2) contraindications observed
  3) treatment monitored in line with guideline recommendations

- Possibly increased CVS risk:
  - Older men (>65 years) within the first few months after testosterone initiation, especially if pre-existing cardiovascular disease

Drug Safety Communications

- Labeling change to clarify that testosterone therapy approved only for medical disorders of the HPT* axis
- Benefit and safety not established for the treatment of low testosterone levels due to aging

Perspective

*Yeap et al, MJA 2016*
Testosterone Treatment: Risks?

- No definitive outcome data regarding long-term CV events
- Non-randomized studies (epidemiologic, prescription database)
  - Subject to confounding, bias and reverse causality
- Existing RCTs: Underpowered, short-term, CVD events not pre-specified
  - Need >10,000 men
- No evidence for risk if testosterone
  1) for approved indications (organic hypogonadism)*
  2) contraindications observed*
  3) treatment monitored in line with guideline recommendations*
- Possibly increased CV risk:
  Older men (>65 years) within the first few months after testosterone initiation, especially if pre-existing cardiovascular disease

Testosterone Treatment and Vascular Risk: Clinical Implications

- No evidence that testosterone replacement in men with organic hypogonadism is harmful: testosterone maintain virilisation and optimal health*.
- Vascular risk an important factor in decision making in men without organic hypogonadism*.
  - unless fertility desired
- Vascular risk an important factor in decision making in men with organic hypogonadism*.
  - unless fertility desired

Testosterone Treatment: Benefits in older men with low T

<table>
<thead>
<tr>
<th>Concern</th>
<th>Testosterone effect</th>
<th>1st line therapy</th>
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<tbody>
<tr>
<td>Sexual</td>
<td>Improved overall function, TT&gt;15 -12 nmol/L</td>
<td>PDE5 inhibitor</td>
</tr>
<tr>
<td>Muscle</td>
<td>1.6-2.7 kg increase in muscle</td>
<td>Exercise</td>
</tr>
<tr>
<td>Fat</td>
<td>1.6 to 2.0 kg decrease</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Glucose</td>
<td>Improved insulin resistance, no need HbA1c</td>
<td>Lifestyle, anti-diabetic medications</td>
</tr>
<tr>
<td>Bone</td>
<td>2-7% increase in BMD, lumbar spine</td>
<td>Anti-resorptives</td>
</tr>
<tr>
<td>Mood</td>
<td>No consistent effects</td>
<td>e.g. Counseling, anti-depressants</td>
</tr>
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Not powered for clinically important health outcomes: mortality, quality of life, physical function, falls or fractures

Take Home Messages (1)

**Organic Hypogonadism**
- Underdiagnosed and undertreated
- Benefits of testosterone replacement clearly outweigh cardiovascular (and other) risks
- Think of hypogonadism: e.g. unexplained psychosexual complaints, osteoporosis, anemia, sarcopenia

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Testosterone Treatment: Benefits in older men with low T

**Take Home Messages (2)**

**Older men 'Late Onset Hypogonadism' = Chronic disease-associated low testosterone**

- In older men, low T is often a marker of poor health → bolistic focus on lifestyle and optimization of comorbidities
- Long-term risks of T treatment are unknown: some evidence for increased CV risks, esp. with pre-existing CVD
- Benefits of T treatment are relatively modest: the benefit : risk profile is overall unconvincing
- Current Australian guidelines* recommend against T treatment (more research)

*Yeap et al, MJA 2016
Men with organic hypogonadism should be identified and given testosterone replacement, but further research is needed to clarify whether there is a role for testosterone in other settings (such as ‘late onset hypogonadism’).