Testosterone Deficiency Syndrome –
Time for Proper Personalised Care
**Recommendations – Diagnosis**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restrict the diagnosis of TD to men with persistent symptoms suggesting TD and confirmed low testosterone.</td>
<td>3</td>
</tr>
<tr>
<td>Measure fasting testosterone levels in the morning before 11am, acknowledging that, in normal life, non-fasting levels may be up to 30% lower.</td>
<td>2</td>
</tr>
<tr>
<td>Repeat total testosterone on at least 2 occasions by a reliable method. In addition, measure free testosterone in men with levels close to the lower normal range (8-12nmol/l) or those with suspected or known abnormal SHBG.</td>
<td>1</td>
</tr>
<tr>
<td>Measure LH serum levels to differentiate between primary and secondary TD.</td>
<td>2</td>
</tr>
<tr>
<td>Base decisions on therapy on published action levels rather than laboratory reference ranges.</td>
<td>4</td>
</tr>
</tbody>
</table>
European Male Aging Study

Distribution and Selected Characteristics of Men Ages 40-70 (Tajar et al)

Data derived from over 3000 men

- **Eugonadal**
  - Age: 58.5 (10.7)
  - BMI: 27.3
  - TT: 513.4 ng/dL
  - LH: 5.2 U/L

- **Secondary Hypogonadal**
  - Age: 59.4 (10.4)
  - BMI: 30.8 (4.8)
  - TT: 250.9 ng/dL
  - LH: 4.4 U/L

- **Primary**
  - Age: 70.0 (9.0)
  - BMI: 29.0 (3.9)
  - TT: 216 ng/dL
  - LH: 18.0 U/L

- **Compensated Hypogonadism**
  - Age: 67.3 (9.9)
  - BMI: 26.8 (3.6)
  - TT: 527.8
  - LH: 14.1 U/L
Cheryl suggests Shane attend for age 40 health check

- Diminished energy
- Reduced vitality /well-being
- Increased fatigue
- Depressed mood
- Impaired cognition
- Diminished muscle mass and strength
- Falling asleep in the evening
- BUT NOT MENTIONED AND NOT ASKED
  - DIMINISHED SEXUAL DESIRE
  - ED
  - LOSS OF MORNING ERECTIONS

He works as a lorry driver and pulls over for sleep in the afternoon.

Shane and Cheryl have not had sex since Aston Villa last won away in the premier league - Aug 8th 2015

CONSIDER THE EFFECTIVENESS OF THIS MAN AT WORK and play!
**Established CVD or Familial Hypercholesterolaemia**
**Diabetes age >40 years**
**Chronic Kidney Disease**

**NO**

- Use JBS3 risk calculator
- **10 year CVD risk score**
- **BELOW current NICE threshold***
  - Examine JBS3 ‘lifetime metrics’
  - Heart age
  - Projected CVD risk
  - To inform discussion on risk modification by:
    - Lifestyle changes
    - Drug therapy when indicated

**YES**

- **Lifestyle and drug therapy as recommended in JBS3**
- **ABOVE current NICE threshold***:
  - Lifestyle + Drug therapy

---

*Current NICE Guidance [www.nice.org.uk](http://www.nice.org.uk)*
Shane Visits his GP for a 40 plus check

- Weight 106 Kg, BMI 30. WC 104 cm.
- BP 145/90.
- TC 6.2 LDL 5.1 HDL 0.95 TGs 2.8. IFCC 46. HbA1c 6.3. PSA 0.525. Haematocrit 39%
- Heart age 50. 4.7% 10 year risk.
- He leaves with extensive lifestyle modification advice - most of which he already knew.
Back to Shane

- On arrival home, he delivers the earth shattering news to his wife that “he is obese and unhealthy”.
- Is maximal longevity what he was seeking?
- Was he perhaps wanting to feel less tired at work and be better in the bedroom?
- Does he really want to give up all his pleasures in exchange for a Spartan life?
- Did the consultation address Shane’s agenda or the doctors?
- Is Shane receiving personalised health care?
- Shane DECIDES NOT TO ATTEND FOLLOW-UP
Shane – The impact of a single question!

• “Many men with these health issues have problems getting and maintaining an erection - could this be a problem for you?”
• **A positive response would change the direction of the consultation**
• SHIM 8, AMS 62
• TT 7.2 nmol/l  SHBG 19. LH 2.0
• He therefore has metabolic syndrome, testosterone deficiency and ED, which increases risk by 50%.
• He returns with a prescription for a daily PDE5 inhibitor and testosterone gel. He attends 6 weeks later for follow-up - on his way home from the gym.
CV Risk Factors, Endothelial Dysfunction and ED

Structural Changes
- Atherosclerosis
- Hypertension
- Dyslipidaemia
- Diabetes

Arteries
- Arterial stenosis
- Arterial insufficiency
- Reduced inflow
- Excessive outflow
- Veno-occlusive dysfunction

Trabeculae
- Smooth muscle atrophy and fibrosis
- Impaired relaxation

Functional Changes
- Impaired endothelium-dependent relaxations
- Impairment of neurogenic relaxations
- Impaired vasodilation

We showed that erectile dysfunction is likely to be an independent risk factor for cardiovascular disease and was associated with a 25% increased risk of cardiovascular disease (at the mean age), which is compatible with the findings of a meta-analysis that examined the association between erectile dysfunction and cardiovascular disease risk in 13 studies.  

Except for erectile dysfunction in men, where hazard ratios were highest for men aged around age 45 and then declined gradually with increasing age.
ED in T2DM

Related to Duration, Control and Number of Complications

- Autonomic neuropathy
- Peripheral neuropathy
- Hypertension
- Peripheral vascular disease
- Dyslipidaemia
- Drug side effects
- Cavernosal smooth muscle disorder
- Depression
- Hypogonadism (double risk)
- Psychological Factors
- Plus Ejaculatory disorders. Retrograde / Anejaculation
- Reduced Sensation
Visceral Fat: T2DM and Hypogonadism

European Male Aging Study (EMAS) 
relation between age and testosterone (40-79), n=3174

BMI and BMI are not the same...
the role of visceral fat tissue

189 cm, 93 kg = BMI 26  190 cm, 94 kg = BMI 26

Waist circumference
Testosterone

>  <

Waist circumference
Testosterone
AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS
AND AMERICAN COLLEGE OF ENDOCRINOLOGY
COMPREHENSIVE CLINICAL PRACTICE GUIDELINES FOR
MEDICAL CARE OF PATIENTS WITH OBESITY

W. Timothy Garvey, MD, FACE\textsuperscript{1}; Jeffrey I. Mechanick, MD, FACP, FACE, FACN, ECNU\textsuperscript{2};
Elise M. Brett, MD, FACE, CNSC, ECNU\textsuperscript{3}; Alan J. Garber, MD, PhD, FACE\textsuperscript{4};
Daniel L. Hurley, MD, FACE\textsuperscript{5}; Ania M. Jastreboff, MD, PhD\textsuperscript{6}; Karl Nadolsky, DO\textsuperscript{7};
Rachel Pessah-Pollack, MD\textsuperscript{8}; Raymond Plodkowski, MD\textsuperscript{9}; and
Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines\textsuperscript{*}
Q.3.9. Male hypogonadism

R19. All men who have an increased waist circumference or who have obesity should be assessed for hypogonadism by history and physical examination and be tested for testosterone deficiency if indicated; all male patients with hypogonadism should be evaluated for the presence of overweight or obesity (Grade B; BEL 2).

R20. All male patients with T2DM should be evaluated to exclude testosterone deficiency (Grade B; BEL 2).

R54. Men with true hypogonadism and obesity who are not seeking fertility should be considered for testosterone therapy in addition to lifestyle intervention because testosterone in these patients results in weight loss, decreased waist circumference, and improvements in metabolic parameters (glucose, A1C, lipids, and blood pressure) (Grade A; BEL 1).
Total Testosterone in men with Type 2 Diabetes

Figure 1. Total testosterone in type 2 diabetic men with late onset hypogonadism

Key: \( TT \) = total testosterone

550 men from 5 practices - Hackett et al BJDVD 2009
Testosterone levels and symptoms

434 men (age 50-86 years)

- Loss of libido
- Loss of vigour
- Overweight
- Depression
- Sleeping disorders
- Lacking concentration
- Typ 2-Diabetes mellitus
- Heat flushes
- Erectile Dysfunction

More and more problems

Zitzmann et al. J Clin Endocrinol Metab 2006; 91(11): 4335-4343
How Testosterone Influences Erection

Stimulatory neurotransmitter

- Dopamine, NO, Oxytocin
- Noradrenaline (5HT2c-Rez.)
- Serotonin (partly)
- alpha-MSH (Melanocortin 2 u. 4 Rez.)
- Vasopressin, ACTH

Sexual Stimulation

- Cerebral erection centers
- Spinal erection center S2-S4

Parasympathetic nerves

- Ach
- NANC nerve

Endothel

- O2 + L - Arginine
- eNOS
- NO + Citrulline

G-Protein

- Guanylatecyclase
- Adenylatecyclase

Phosphodiesterase 5 Inh.

- sildenafil, tadalafil, vardenafil, other

Smooth muscle cell

- Testosterone

Testosterone

Stimulatory neurotransmitter

- Sexual Stimulation
- Testosterone

Stimulatory neurotransmitter

- Testosterone

Endothel

- Testosterone

Stimulatory neurotransmitter

- Testosterone

Stimulatory neurotransmitter

- Testosterone

Stimulatory neurotransmitter

- Testosterone

Stimulatory neurotransmitter

- Testosterone
Effects of Testosterone Treatment in Older Men

1. Aim: to show whether TRT works in older men

2. Intervention: Testosterone-Gel vs Placebo-Gel

3. Duration: 1 year

4. Prospective, randomized, placebo-controlled double-blind
# Sexual functions

|                  | Sexual interest and sexual activity | Treatment effect: 0.58  
(95% CI): 0.38–0.78  
P < 0.001 |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>primary</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| secondary        | DISF-M-II interview to score sexual desire. | Treatment effect: 2.93  
(95% CI): 2.13–3.74  
P < 0.001 |
|                  |                                    |                                                  |
|                  | IIEF-5: Erectile Function           | Treatment effect: 2.64  
(95% CI): 1.68–3.61  
P = 0.001 |

*N Engl J Med* 2016 374 611
Sexual activity

Testosterone
n=387

Placebo n=384

N Engl J Med
2016;374:611
Walking distance increased

Increase of ≥50 m in 6-min walk test (%)

Testosterone
n=392
Placebo n=389

P<0.003

Month
0 3 6 9 12

Testosterone
Placebo

N Engl J Med
2016 374 611
## Vitality

<table>
<thead>
<tr>
<th></th>
<th>% of men, whose vitality score increased by at least 4 points</th>
<th>Treatment effect: 1.23 (95% CI): 0.89-1.7</th>
<th>P = 0.22</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>primary</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>secondary</strong></td>
<td>Change in fatigue score</td>
<td>Treatment effect: 1.27 (95% CI): 1.37-2.16</td>
<td>P = 0.006</td>
</tr>
<tr>
<td></td>
<td>SF-36 Vitality-Score</td>
<td>Treatment effect: 2.41 (95% CI): 1.31-4.50</td>
<td>P = 0.03</td>
</tr>
<tr>
<td></td>
<td>PANAS Positive affect score</td>
<td>Treatment effect: 0.47 (95% CI): 0.02-0.92</td>
<td>P = 0.04</td>
</tr>
<tr>
<td></td>
<td>PANAS Negative affect score</td>
<td>Treatment effect: -0.49 (95% CI): -0.79—0.19</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>PHQ-9 Depression-Score</td>
<td>Treatment effect: -0.72 (95% CI): -1.20—0.23</td>
<td>P = 0.004</td>
</tr>
</tbody>
</table>
T Trials part 1: Take home messages

TRT in older men with functional hypogonadism and symptoms is effective

- Significant improvement of all sexual functions
- Good and marked improvement of physical functions
- Increase of good mood and energy
- Decrease of bad mood and depressive mood
- Safe compared to placebo:
  - Prostate-Ca
  - CVD
- Increase of
  - Hematocrit
  - PSA
CONCLUSIONS

In symptomatic men 65 years of age or older, raising testosterone concentrations for 1 year from moderately low to the mid-normal range for men 19 to 40 years of age had a moderate benefit with respect to sexual function, and some benefit with respect to mood and depressive symptoms but no benefit with respect to vitality or walking distance. The number of participants was too small to draw conclusions about the risks of testosterone treatment. (Funded by the National Institutes of Health and others; ClinicalTrials.gov number, NCT00799617.)
Testosterone undecanoate improves sexual function in men with type 2 diabetes and severe hypogonadism: results from a 30-week randomized placebo-controlled study

Geoffrey Hackett*, Nigel Cole*, Atif Saghir†, Peter Jones‡, Richards C. Strange‡ and Sudarshan Ramachandran*§†

*Heart of England Foundation NHS Trust, Sutton Coldfield, †University of Birmingham, Edgbaston, Birmingham, ‡Institute for Science and Technology in Medicine, Keele University Medical School, Keele, §Department of Clinical Biochemistry, University Hospitals of North Midlands, Keele, and §Faculty of Health Sciences, Staffordshire University, Keele, Staffordshire, UK

Conclusions

The present study suggests that benefit in sexual symptoms after TU treatment is evident principally in patients with HG with TT levels ≤8 nmol/L and FT levels ≤0.18 nmol/L. We also suggest that 30 weeks of treatment is necessary before evaluating improvement in erectile function.
BLAST – IIEF -EF Changes from Baseline in Mild (8-12nmol/l) and Severe HG (<8nmol/l)

<table>
<thead>
<tr>
<th></th>
<th>6 weeks</th>
<th>18 weeks</th>
<th>30 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean change in IIEF score / SE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild HG/P</td>
<td>-0.2/0.7</td>
<td>-1.7/1.0</td>
<td>-2.0/0.9</td>
</tr>
<tr>
<td>Mild HG/TU</td>
<td>-0.2/0.8</td>
<td>-0.6/0.5</td>
<td>-0.5/0.8</td>
</tr>
<tr>
<td>Difference between TU and P</td>
<td>0/1.1</td>
<td>1.1/1.1</td>
<td>1.5/1.1</td>
</tr>
<tr>
<td>p</td>
<td>0.94</td>
<td>0.98</td>
<td>0.22</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>6 weeks</th>
<th>18 weeks</th>
<th>30 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean change in IIEF score / SE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe HG/P</td>
<td>-1.5/0.8</td>
<td>-1.1/1.0</td>
<td>-1.9/1.1</td>
</tr>
<tr>
<td>Severe HG/TU</td>
<td>0.8/0.9</td>
<td>2.8/1.5</td>
<td>3.9/1.7</td>
</tr>
<tr>
<td>Difference between TU and P</td>
<td>2.3/1.2</td>
<td>3.9/1.7</td>
<td>5.8/1.9</td>
</tr>
<tr>
<td>p</td>
<td>0.23</td>
<td>0.11</td>
<td>0.0036</td>
</tr>
</tbody>
</table>
BLAST – IIEF – Sexual Desire. Changes from Baseline in Mild (8-12) and Severe HG (<8)

Change in mean sexual desire

Weeks of treatment

Mild HG/P
Mild HG/TU
Difference between TU and P

6 weeks 18 weeks 30 weeks

(Mean change in IIEF score / SE)

-0.5 / 0.2 -0.4 / 0.3 -0.8 / 0.3

0.2 / 0.2 0.4 / 0.2 0.0 / 0.2

0.7 / 0.3 0.8 / 0.3 0.8 / 0.3

p=0.061 p=0.051 p=0.050

Severe HG/P
Severe HG/TU

6 weeks 18 weeks 30 weeks

(Mean change in IIEF score / SE)

-0.5 / 0.2 -0.6 / 0.3 -0.3 / 0.2

1.0 / 0.3 1.6 / 0.4 1.7 / 0.4

1.5 / 0.4 2.2 / 0.5 2.0 / 0.4

p=0.0002 p=0.0001 p<0.0001
## Table: Response to Testosterone Undecanoate in Men with Type 2 Diabetes

<table>
<thead>
<tr>
<th></th>
<th>HbA1c (%)</th>
<th>Weight (kg)</th>
<th>BMI Kg/m²</th>
<th>WC (cm)</th>
<th>TC mmol/l</th>
<th>EF (IIEF)</th>
<th>AMS (pts)</th>
<th>HADS-D</th>
<th>GEQ (%) imp</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.41</td>
<td>-0.7</td>
<td>-0.3</td>
<td>-2.5</td>
<td>-0.25</td>
<td>+3.0</td>
<td>-5.3</td>
<td>-1.01</td>
<td>46</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td><strong>0.007</strong></td>
<td>0.13</td>
<td><strong>0.01</strong></td>
<td><strong>0.012</strong></td>
<td><strong>0.025</strong></td>
<td><strong>0.006</strong></td>
<td>0.095</td>
<td>0.64</td>
<td><strong>&lt;0.001</strong></td>
</tr>
<tr>
<td><strong>82 weeks</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.87</td>
<td>-2.7</td>
<td>-1.00</td>
<td>-4.2</td>
<td>-0.19</td>
<td>+4.31</td>
<td><strong>-9.57</strong></td>
<td>-8.1</td>
<td>-2.18</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td><strong>0.009</strong></td>
<td>0.016</td>
<td><strong>0.019</strong></td>
<td><strong>&lt;0.001</strong></td>
<td>0.035</td>
<td><strong>0.003</strong></td>
<td>0.001</td>
<td>0.001</td>
<td><strong>0.0001</strong></td>
</tr>
</tbody>
</table>
Effects of testosterone treatment on body fat and lean mass in obese men on a hypocaloric diet: a randomised controlled trial

Mark Ng Tang Fui¹ ², Luke A. Prendergast¹ ³, Philippe Dupuis¹ ², Manjri Raval², Boyd J. Strauss⁴, Jeffrey D. Zajac¹ ² and Mathis Grossmann¹ ²*

Methods: We conducted a randomised double-blind, parallel, placebo controlled trial at a tertiary referral centre. A total of 100 obese men (body mass index ≥ 30 kg/m²) with a total testosterone level of or below 12 nmol/L and a median age of 53 years (interquartile range 47–60) receiving 10 weeks of a very low energy diet (VLED) followed by 46 weeks of weight maintenance were randomly assigned at baseline to 56 weeks of 10-weekly intramuscular testosterone undecanoate (n = 49, cases) or matching placebo (n = 51, controls). The main outcome measures were the between-group difference in fat and lean mass by dual-energy X-ray absorptiometry, and visceral fat area (computed tomography).

Conclusions: While dieting men receiving placebo lost both fat and lean mass, the weight loss with testosterone treatment was almost exclusively due to loss of body fat.
Change from Baseline in Body Composition After 10 Weeks of a VLED and Treatment with Intramuscular Testosterone Undecanoate or Placebo

*p<0.05 versus baseline within group; data are mean + 95% confidence interval

NS, not significant; VLED, very low energy diet

Change from Baseline in Body Composition After 56 Weeks of Treatment with Intramuscular Testosterone Undecanoate or Placebo

* p<0.05 versus baseline within group; data are mean + 95% confidence interval

NS, not significant

Symptomatic response to testosterone treatment in dieting obese men with low testosterone levels in a randomized, placebo-controlled clinical trial

M Ng Tang Fui¹,², R Hoermann¹, LA Prendergast¹,³, JD Zajac¹,² and M Grossmann¹,²

In conclusion, among relatively healthy middle-aged obese men with a lowered testosterone level, testosterone treatment over 56 weeks improved symptoms of androgen deficiency above and beyond what was achieved with weight loss alone. In conjunction with the metabolically favorable effects on body composition reported elsewhere, this study identifies a subgroup of men with lowered testosterone levels in whom the long-term benefits and risks of testosterone treatment should, in combination with lifestyle measures, be further assessed in larger longer-term clinical trials.

Figure 2. Three-way interaction between mean adjusted differences between the groups and baseline symptom severity. (a) Interaction between baseline AMS and treatment for AMS. (b) Interaction between baseline IIEF-5 and treatment for IIEF-5.
Testosterone and Cardiovascular Disease

Robert A. Kloner, MD, PhD, Culley Carson III, MD, Adrian Dobs, MD, Stephen Kopecky, MD, Emile R. Mohler III, MD

Testosterone Has Multiple Effects on the Body

THE ROLE OF TESTOSTERONE IN THE BODY

- **Brain**
  - Responsible for sex drive, and aids cognition, memory, and feelings

- **Heart**
  - Increases cardiac output, peripheral & coronary blood flow, shortens QTc interval, decreases reperfusion injury, thrombosis

- **Kidneys**
  - Produces the hormone, erythropoietin, which increases red blood cell production

- **Muscle**
  - Increases mass and strength

- **Sex organs**
  - Responsible for sperm production, prostrate and penis growth, and erectile function

- **Skin**
  - Produces hair and sebum, and supports collagen production

- **Bone**
  - Maintains bone density, bone growth, and bone marrow production of red blood cells

---

**TABLE 1 Testosterone’s Role in Therapy of True Symptomatic Hypogonadism in Young and Older Men**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Young Men</th>
<th>Older Men</th>
<th>Ref. #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Libido</td>
<td>++</td>
<td>++</td>
<td>33-38</td>
</tr>
<tr>
<td>Erectile function</td>
<td>++</td>
<td>++</td>
<td>33-38</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>+</td>
<td>+</td>
<td>69-71</td>
</tr>
<tr>
<td>Mood</td>
<td>+</td>
<td>+</td>
<td>42,43</td>
</tr>
<tr>
<td>Cognition</td>
<td>+</td>
<td>+</td>
<td>47,48</td>
</tr>
<tr>
<td>Energy</td>
<td>+</td>
<td>+</td>
<td>49,50</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>++</td>
<td>++</td>
<td>58-63</td>
</tr>
<tr>
<td>Fat mass</td>
<td>++</td>
<td>+</td>
<td>54</td>
</tr>
<tr>
<td>Hemapoiesis</td>
<td>++</td>
<td>++</td>
<td>69,71</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>++</td>
<td>++</td>
<td>53-55</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>++</td>
<td>++</td>
<td>54-56</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>+</td>
<td>+</td>
<td>67</td>
</tr>
<tr>
<td>Sperm count</td>
<td>--</td>
<td>--</td>
<td>121</td>
</tr>
</tbody>
</table>

**Note:** ++ = strong evidence of positive effect; + = weak evidence of positive effect; -- = strong evidence of negative effect; - = weak evidence of negative effect.

Comparison Tadalafil and Tamsulosin 
Effect on IPSS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Baseline Mean (SD)</th>
<th>12-week Endpoint LS Mean Change (ANCOVA, LOCF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>17.4 (6.0)</td>
<td>-4.2</td>
</tr>
<tr>
<td>Tadalafil 5mg</td>
<td>17.2 (4.9)</td>
<td>-6.3***</td>
</tr>
<tr>
<td>Tamsulosin 0.4mg</td>
<td>16.8 (5.3)</td>
<td>-5.7*</td>
</tr>
</tbody>
</table>

*p<.05, **p<.01, ***p<.001 compared to placebo
*Values for week 1 are based on mIPSS

Please note that tamsulosin is an active control. This study was powered for direct comparisons between tadalafil and placebo and between tamsulosin and placebo.
Comparison Tadalafil and Tamsulosin Effect on IIEF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ED History N (%)</th>
<th>Sexually Active with a Female Partner N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>120 (69.8)</td>
<td>145 (84.3)</td>
</tr>
<tr>
<td>Tadalafil 5mg</td>
<td>121 (70.8)</td>
<td>143 (83.6)</td>
</tr>
<tr>
<td>Tamsulosin 0.4mg</td>
<td>116 (69.0)</td>
<td>139 (82.7)</td>
</tr>
</tbody>
</table>

*<0.001 vs. placebo
ns p=0.699 vs. placebo

IIEF-EF domain baseline to end point LS mean change compared with placebo in men with ED who were also sexually active (60% of patients in the trial).

ns = not significant
Retrospective Cohort Study

Statin, testosterone and phosphodiesterase 5-inhibitor treatments and age related mortality in diabetes

Geoffrey Hackett, Peter W Jones, Richard C Strange, Sudarshan Ramachandran

CONCLUSION

We show that statins, PDE5I and TRT reduce mortality in diabetes. PDE5I, alone and with the other treatments significantly alter age related mortality in diabetic men.
Mortality Data of Men with Type 2 Diabetes mellitus not receiving PDE5 Inhibitors followed for approximately 4 Years (n= 682)

Long Term Mortality Data in Diabetes – The BLAST LONG TERM STUDY (2016) (n=857)
Phosphodiesterase type-5 inhibitor use in type 2 diabetes is associated with a reduction in all-cause mortality

Simon G Anderson, David C Hutchings, Mark Woodward, Kazem Rahimi, Martin K Rutter, Mike Kirby, Geoff Hackett, Andrew W Trafford, Adrian H Heald

What might this study add?
We undertook a retrospective analysis of mortality in a cohort of patients with type 2 diabetes mellitus (T2DM) and therefore high-attendant cardiovascular risk. Our findings demonstrated that, for the first time, PDE5 inhibitor use is associated with significantly reduced mortality in patients with T2DM, an effect which remained after multiple adjustments for known confounding factors.

How might this impact on clinical practice?
Our findings provide strong evidence for PDE5 inhibitors acting to reduce mortality in T2DM. Further evidence is required to elucidate the role of PDE5 inhibitors in cardioprotection.
Multivariate Regression model for risk of mortality (N=7860):
(Anderson, Heald, Hackett, Heart 2016 –press)
Figure 2  Adjusted HRs and 95% CI for the association between treatment for erectile dysfunction, compared with no treatment for erectile dysfunction, and outcomes after a first myocardial infarction in 43 145 men. Number of events are depicted above the point estimate for each outcome. MACE, major adverse cardiac event; CVD, cardiovascular disease.

Conclusions  Treatment for ED after a first MI was associated with a reduced mortality and heart failure hospitalisation. Only men treated with phosphodiesterase-5 inhibitors had a reduced risk, which appeared to be dose-dependent.
PDE5 inhibitors in diabetic peripheral neuropathy

G. HACKETT
Good Hope Hospital, Sutton Coldfield, UK

CONCLUSION

These five cases from clinical practice strongly support the recommendations of other authors that PDE5Is may have an important therapeutic role in peripheral as well as autonomic diabetic neuropathy. Further research is urgently required to investigate this important therapeutic indication. As neuropathy is the commonest complication of diabetes, affecting 50%, and is frequently asymptomatic in the early stages, there may also be a place for early preventive therapy with PDE5Is, especially as 50% of diabetic men will also develop ED.
TADALAFIL - Successful Intercourse in Men With Diabetes (unrestricted medication)

Mean Per-Patient Percentage of “Yes” Responses to SEP Question 3

- Placebo (n=194) 22%
- Tadalafil 10 mg (n=139) 49%
- Tadalafil 20 mg (n=286) 53%

*P<0.001 vs. placebo.

$SEP Question 3: Did your erection last long enough for you to have successful intercourse?
Dashed line within each bar represents baseline SEP3 score (% Yes).

4 ‘High-dose’ (overdosing) PDE 5 inhibitor therapy. High dose PDE 5 inhibitor therapy, i.e. doubling the maximum dose, resulted in a 24% salvage rate of ED patients (n=54) previously unresponsive to 100 mg Sildenafil. According to the personal experience this may also apply for Vardenafil and Tadalafil in individual patients especially in unresponsive diabetics.

5 Shifting patients to another PDE 5 inhibitor. Shifting of real non-responders to Sildenafil to Vardenafil resulted in a rescue-/success rate of 12%. According to the personal experience with more than 8,000 patients on PDE 5 inhibitors only a small minority (5-8%) of real non-responders (vaginal penetration not possible after 4 attempts with the highest dose) on one PDE 5 may be rescued by another one.

6 Daily dosing of PDE 5 inhibitors. Daily dosing of PDE 5 inhibitors for several months in patients previously unresponsive to on demand therapy to either Tadalafil (figure 15.10) or Sildenafil at maximum doses, was able to salvage more than 50% of failures. Although that was proven in preliminary small series for Tadalafil and Sildenafil it can be assumed that this concept holds true also for other PDE 5 inhibitors in particular in patients with severe organic ED.
Testosterone Therapy (5g Testogel®/d/12 wk) Converts Sildenafil 100 mg Non-responders to Responders in Men with Hypogonadism (tT<14nmol/l) and ED

THE COMMON SCENARIO FOR TESTOSTERONE THERAPY.
An obese 50 year old man with metabolic syndrome and ED has failed to respond repeated to Sildenafil 100mg and Tadalafil 20mg. His marriage is severely at risk. His TT is 9.0. LH 2.5 SHBG 32 Haematocrit 40% (AM results repeated)

• OPTION 1
• Rx Alprostadil (injection or intra-urethral)

• Cost £1040@1 per week or £2040@ twice per week funded by patient (NHS if T2DM).
• Training required
• Adverse events: pain, fibrosis, rarely priapism.
• High discontinuation rate.
• UNHAPPY PATIENTS AND PARTNERS
THE COMMON SCENARIO FOR TESTOSTERONE THERAPY.

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- High discontinuation rate.
- UNHAPPY COUPLES

**OPTION 2.**
- Testosterone gel 50mg daily
- Plus DAILY PDE5I
- Annual Cost £414.40@1/week, £428.80.at twice per week
- ALL FUNDED BY THE NHS,
- PATIENT COST = £0
- Adverse events: Improved desire, mood and energy, loss of visceral fat, improved glycaemic control. Raised haematocrit (rare).
- PATIENT TAKES SECONDS to CHOOSE OPTION 2. – A logical Cost Effective Solution to a Real Problem
- THE ISSUE IS NOT MIDDLE AGED MEN SEARCHING FOR THEIR “MOJO” or “ELIXIR OF YOUTH”..
Should PDE5Is be prescribed routinely for all men with newly diagnosed type 2 diabetes?

GEOFFREY HACKETT

Abstract
Diabetes and erectile dysfunction are closely associated. It is good that there is now more awareness of the issue, especially given the strong link to heightened cardiovascular risk. This article challenges current practice and explores the routine use of phosphodiesterase inhibitors.

Br J Diabetes Vasc Dis 2015;15:184-186

Key words: type 2 diabetes, erectile dysfunction, cardiovascular risk, phosphodiesterase type 5 inhibitors, lower urinary tract symptoms

Introduction
I present to my GP as a 53-year-old man with type 2 diabetes (T2DM), HbA1c 6.6 (IFCC 48%), slightly overweight (body mass index 28.5), BP 125/80, total cholesterol 5.1. I am otherwise fit with an excellent marriage. My sex life is OK but not what it used to be and I have noticed that my erections are not as good as they used to be.
TAKE HOME MESSAGES

- Measure TT and FT in men with T2DM and MetS.
- Measure TT in all men with ED
- Men with Low T + co-morbidities need TRT + PDE5I.
- Full response to TRT takes at least 6 months.
- Low T is associated with increased mortality
- TRT reduces mortality in hypogonadal men
- TRT does not increase CV or prostate cancer risk
- Daily PDE5Is salvage 50% of on-demand failures.
- Correcting low T salvages PDE5i failures.
- PDE5Is appear to reduce mortality, heart failure and hospital admissions- THEY ARE NOW GENERIC - SHOULD THEIR USE BE RESTRICTED ANY LONGER.
TESTOSTERONE GEL IN HYPOGONADISM

- BUT
- Can be messy
- around 30% require more than 50mg
- Skin irritation and rashes in 7%
- Partner transfer.
- Greater conversion to DHT by 5AR in skin.
- Patient compliance can be an issue - especially long term
- Monitoring more difficult as daily level assessed rather than long term values
- Effects on insulin resistance may be more convincing with long acting injections
- **MONITORING - TT, SHBG, PSA, FBC, haematocrit** at 3-6 months, then annually. **Bloods 2-4 hours after application. Skin contamination can cause false elevated values**
TESTOSTERONE GEL IN HYPOGONADISM

- Available as 1% and 2% formulations
- Tube, sachet and pump dispenser
- Applied AM after shower or wash
- Needs to be applied long term
- More closely mirrors natural diurnal variation
- Can be stopped abruptly
- Low incidence of raised haematocrit (<5%)
- Higher levels can be achieved / skin contamination
- Generally well tolerated with no interactions with oral drugs
- Active prostate or breast cancer only important contraindications.
TESTOSTERONE INJECTIONS IN HYPOGONADISM

Avoid Cheaper Short Acting preparations as 2-4 weekly unacceptable and not cost effective. Mood swings, variable levels, higher rates of raised haematocrit mean it should be replaced by 1000mg/4ml (12 weekly) formulation.

• Single injection into buttock over 2-3 minutes after WARMING THE AMPOULE

• Loading dose, second dose at 6 weeks then 10-12 weekly.

• Active prostate and breast cancer only clear contra-indication (PSA and DRE At baseline, 6 months then annually)

• Caution with anti-coagulants. Well tolerated

• Rapid withdrawal of T levels not possible

• Greater certainty patient is compliant.
There has never been a better time to offer men “Proper Personalised Care!!”