The Aging Male

and testosteroon

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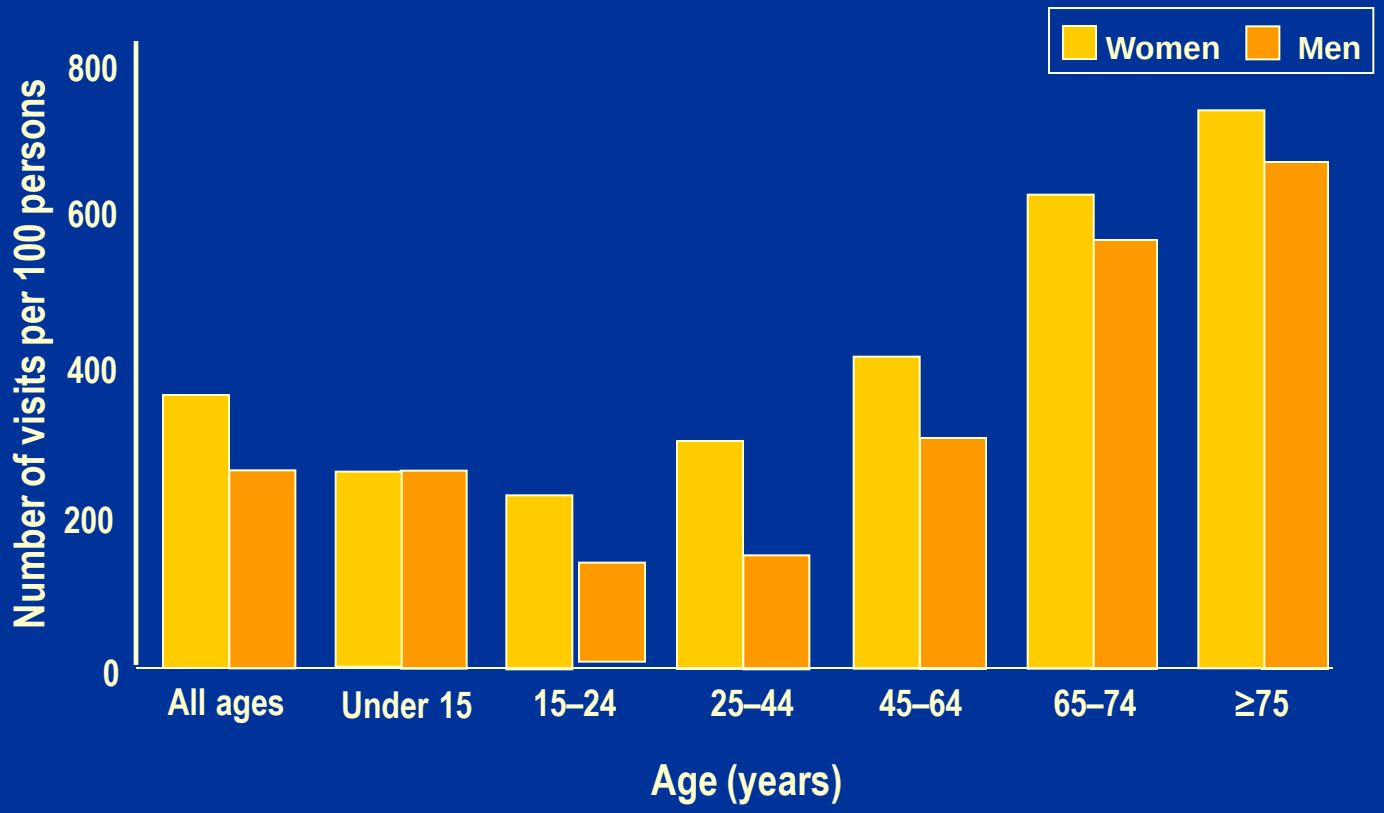
OUTLINE

- Erectile function
- Prostate cancer
- Testosterone deficiency syndrome (TDS)

Mans gebruik nie gesondheidsorg



Center for Disease Control 2003 Statistics

The Aging Male

and testosteroon

WHO cares?

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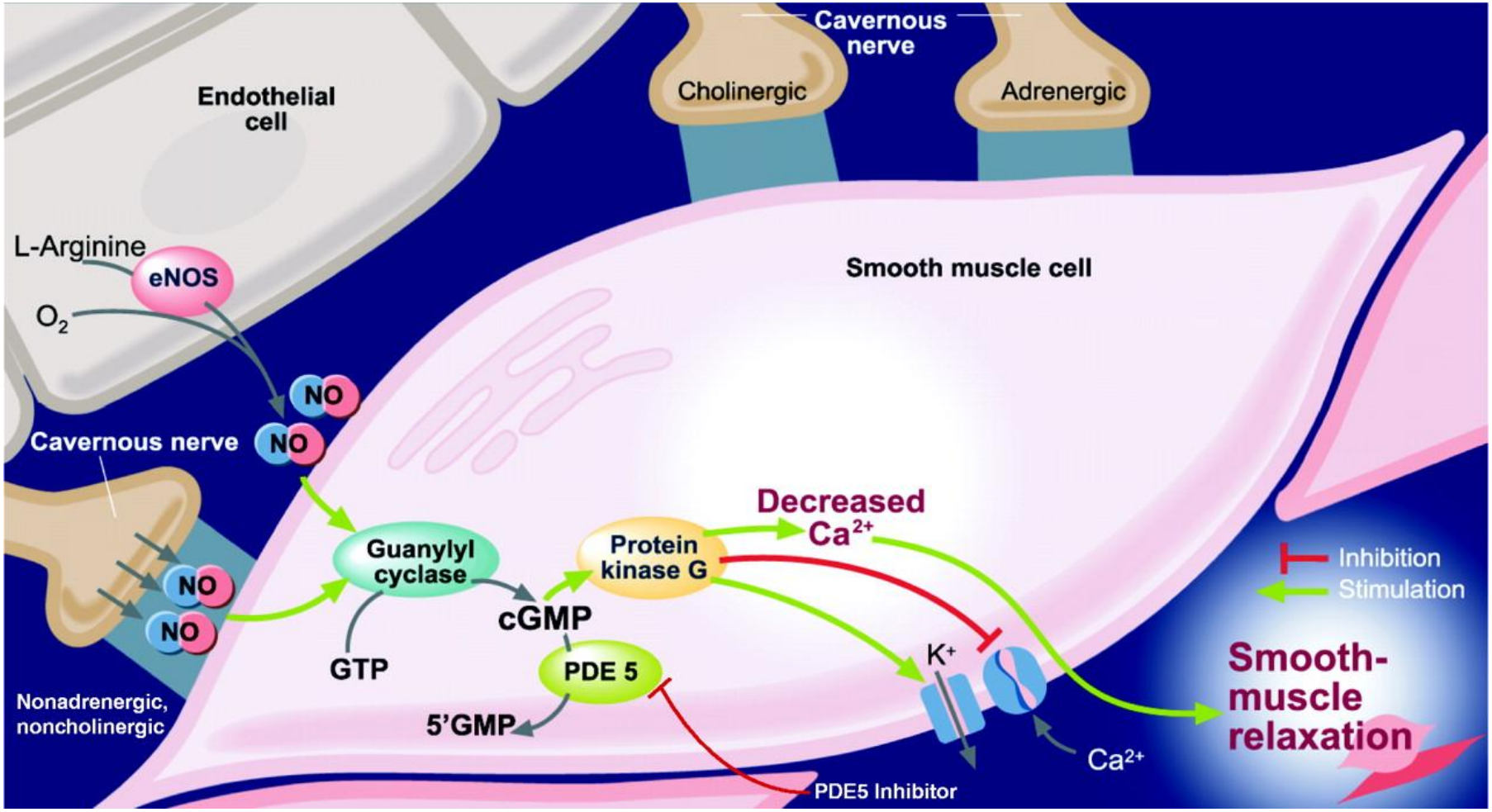
Erectile Dysfunction: Definition

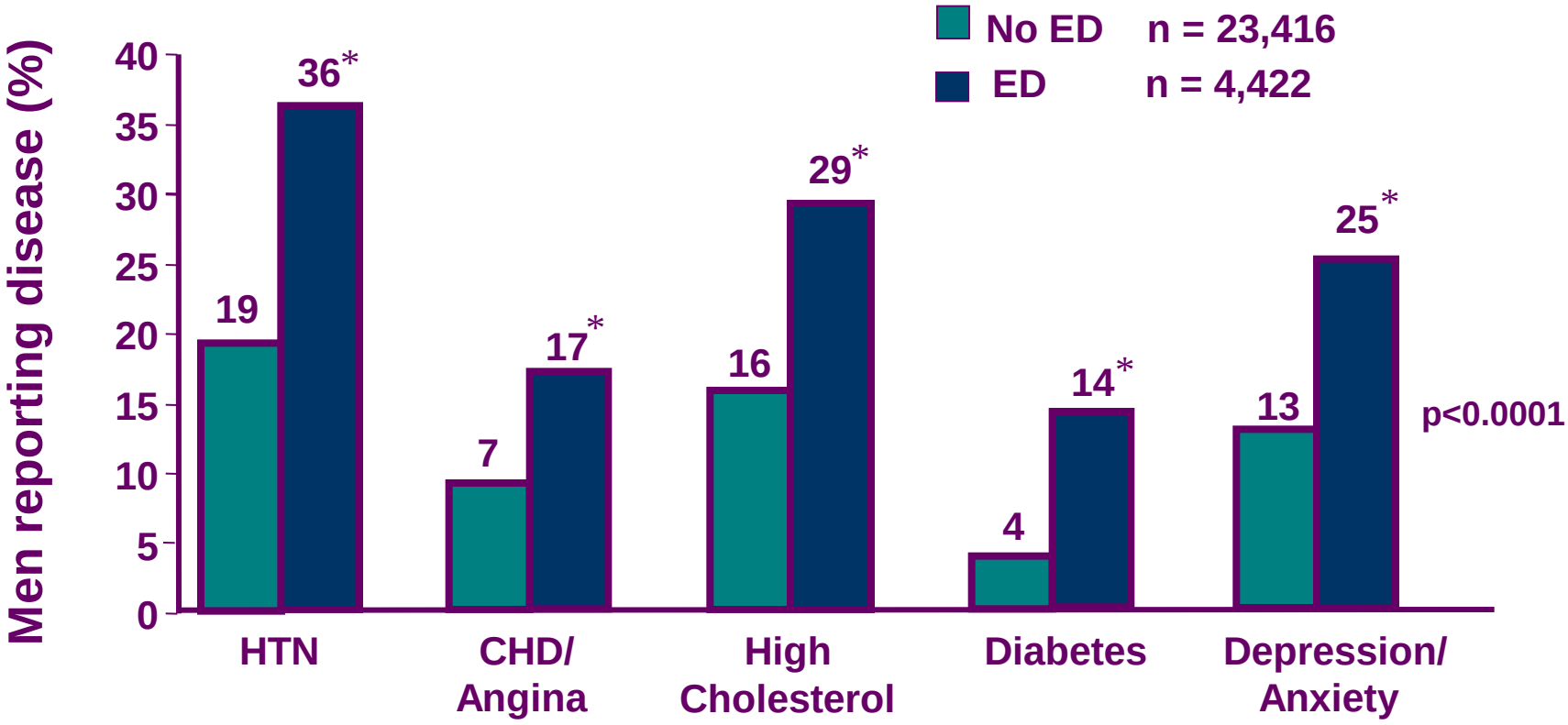
"The inability to achieve and maintain an erection sufficient to permit satisfactory sexual performance"

International Educational Initiative on Erectile Function, 2001


Cavernous nerve
Endothelial cell
Cholinergic
Adrenergic
L-Arginine
eNOS
O_2
Smooth muscle cell
NO
NO
Cavernous nerve
NO
NO
Guanylyl cyclase
GTP
cGMP
Protein kinase G
Decreased Ca^{2+}
PDE 5
5'GMP
K^+
Ca^{2+}
Inhibition
Stimulation
Smooth-muscle relaxation
Nonadrenergic, noncholinergic
PDE5 Inhibitor

ED: Barometer of Men's Health

There is a higher prevalence of comorbid diseases in men with ED (MALES 2001)



NB: 64% of men with ED report at least one or more of these conditions

CVD and ED Share Common Risk Factors

CVD

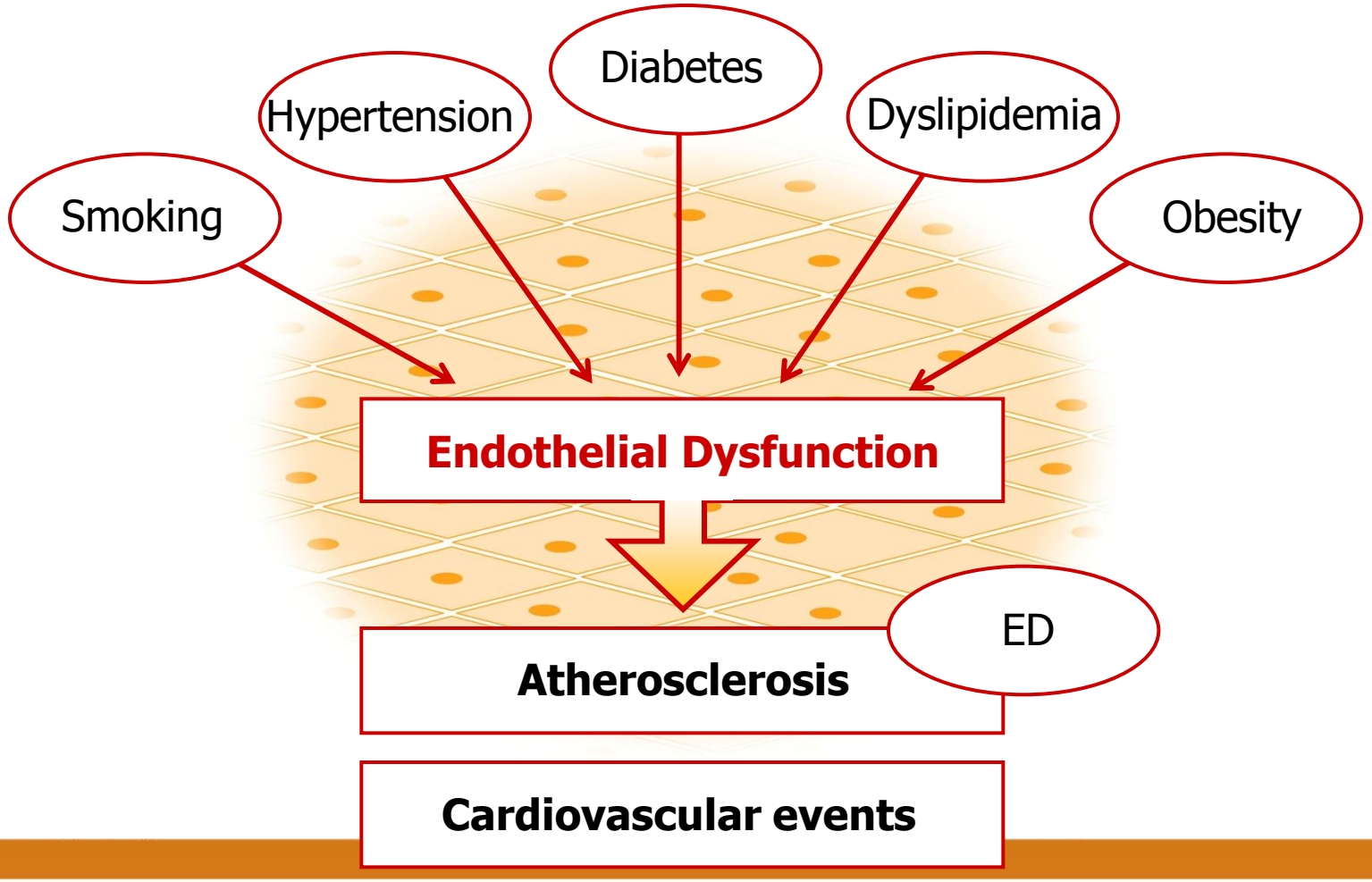
- Age
- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Sedentary lifestyle
- Obesity
- Depression
- Male, post-menopausal female

ED

- Age
- Dyslipidemia
- Hypertension
- Diabetes
- Smoking
- Sedentary lifestyle
- Obesity
- Depression
- Peripheral vascular disease

Kostis, JB 2nd Princeton Consensus, *Am J Cardiol,* 2005:96; 313-321.

Endothelial Dysfunction as a Precursor of Vascular Events



Sasayama et al. Circ J 2003; 6: 656-659

Definition of Endothelial Dysfunction

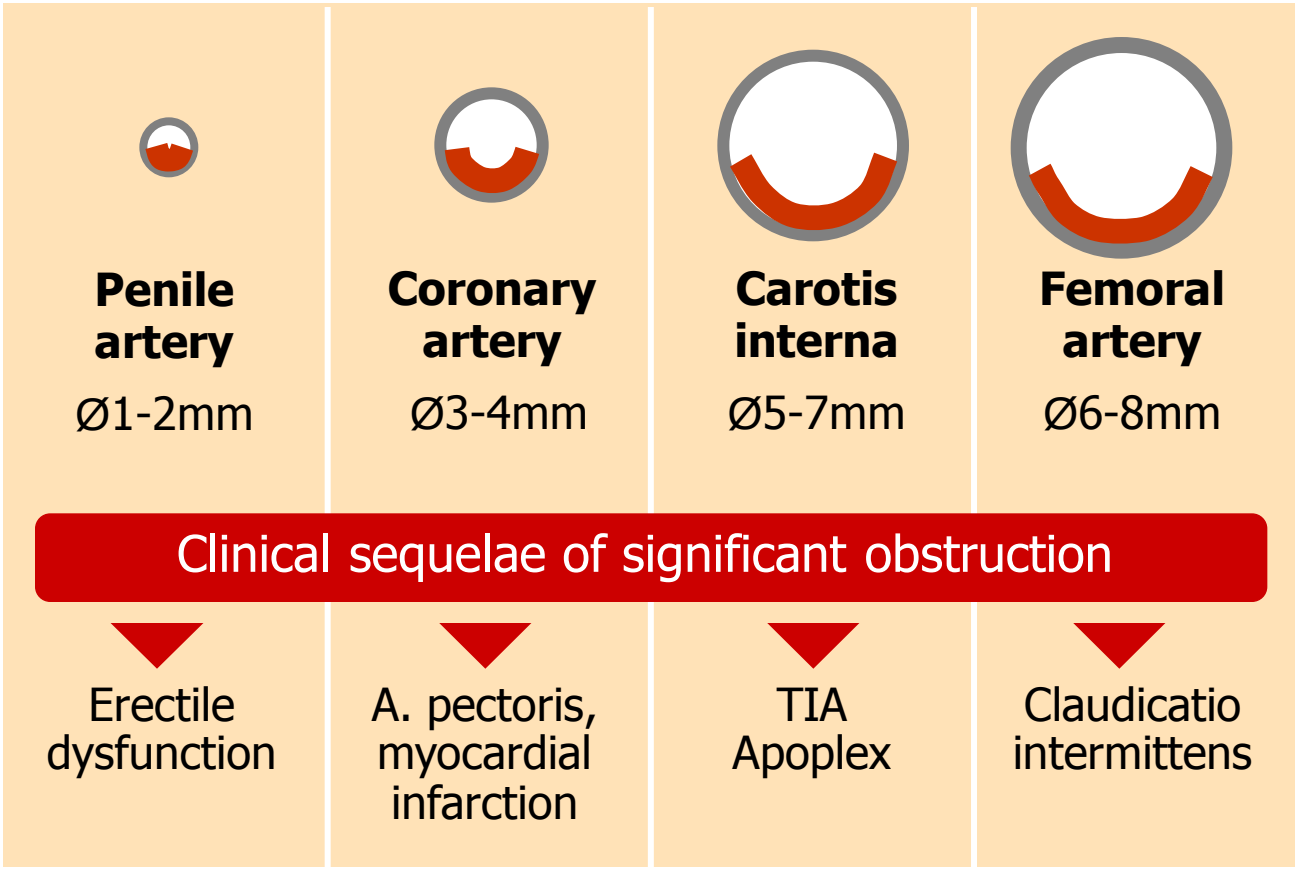
Presence of several or all of the following pathomechanisms:

- Impaired NO-Synthesis and inactivation of NO
- Reduced ability of vasodilatation
- Increased thrombocyte aggregation
- Increased leukocyte adhesion
- Increased proliferation of endothelial smooth muscle
- Decreased number of endothelial progenitor cells (EPCs)

Sasayama et al. Circ J 2003; 6: 656-659

Why does ED Occur before Cardiovascular Diseases?

Hypothesis: Arterial diameter



Modified after Montorsi et al. Am J Cardiol 2005; 96: 19M-23M

ED and CAD

- men with ED exhibit early signs of CAD; may develop more severe CAD
- interval ED symptoms and CAD symptoms and cardiovascular events estimated at 2–3 years and 3–5 years respectively
- ED associated with increased all-cause mortality

ED and CAD

- men with ED thorough medical assessment, including testosterone, fasting lipids, fasting glucose and blood pressure measurement

- evaluated by cardiologist by stress testing with selective use of computed tomography (CT) or coronary angiography

ED and CAD

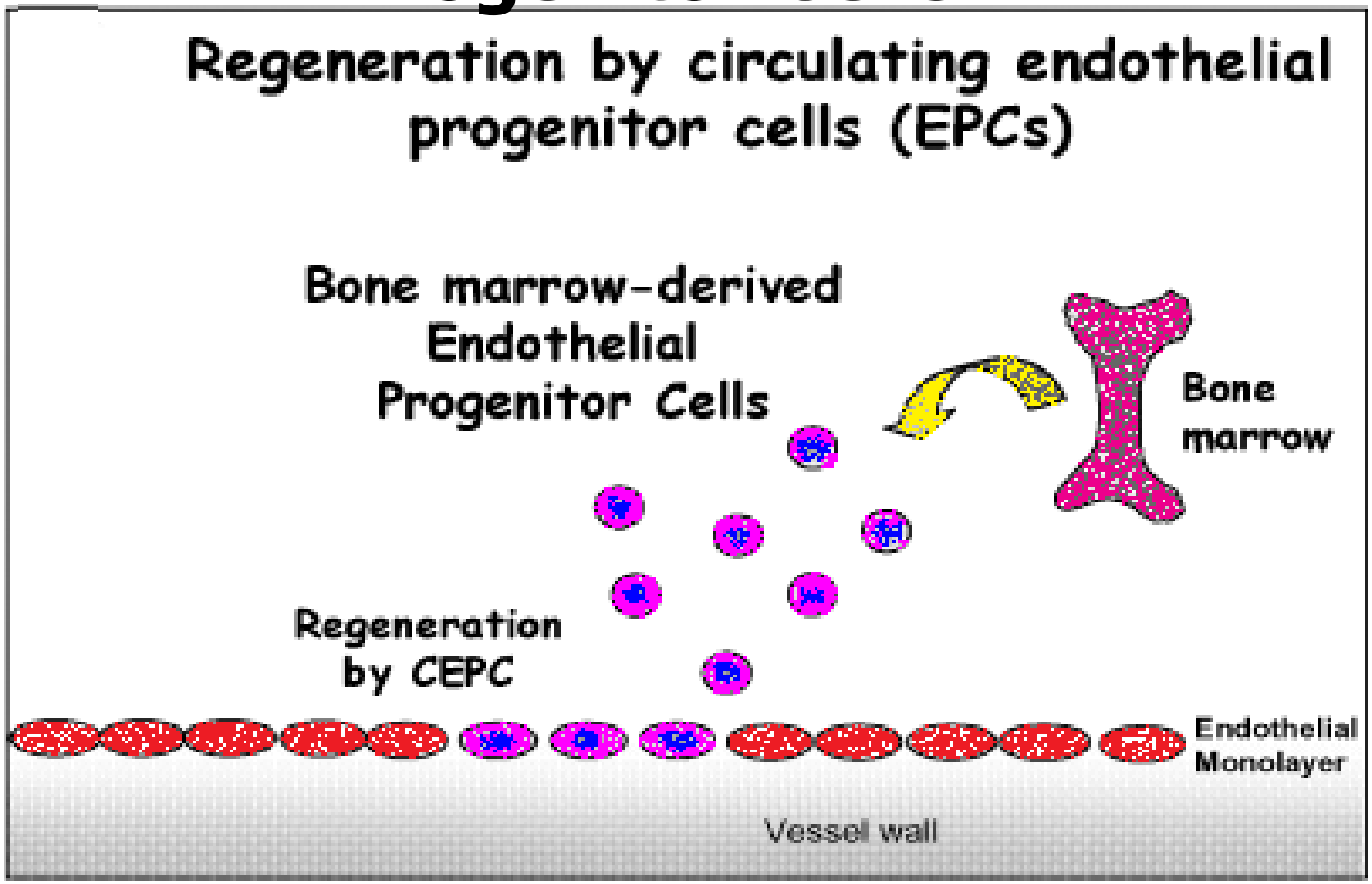
- weight loss and increased physical activity improve erectile function
- phosphodiesterase 5 (PDE5) inhibitors as first-line therapy
- testosterone replacement therapy

ED and Co-morbid diseases: Vardenafil Studies

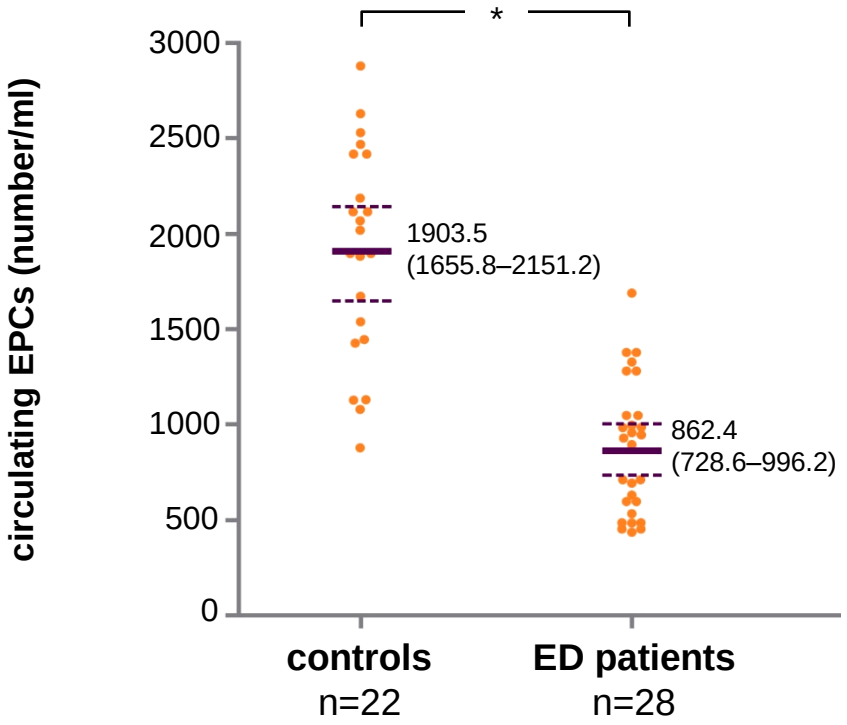
Studies on efficacy of vardenafil in patients with erectile dysfunction and the components of the metabolic syndrome:

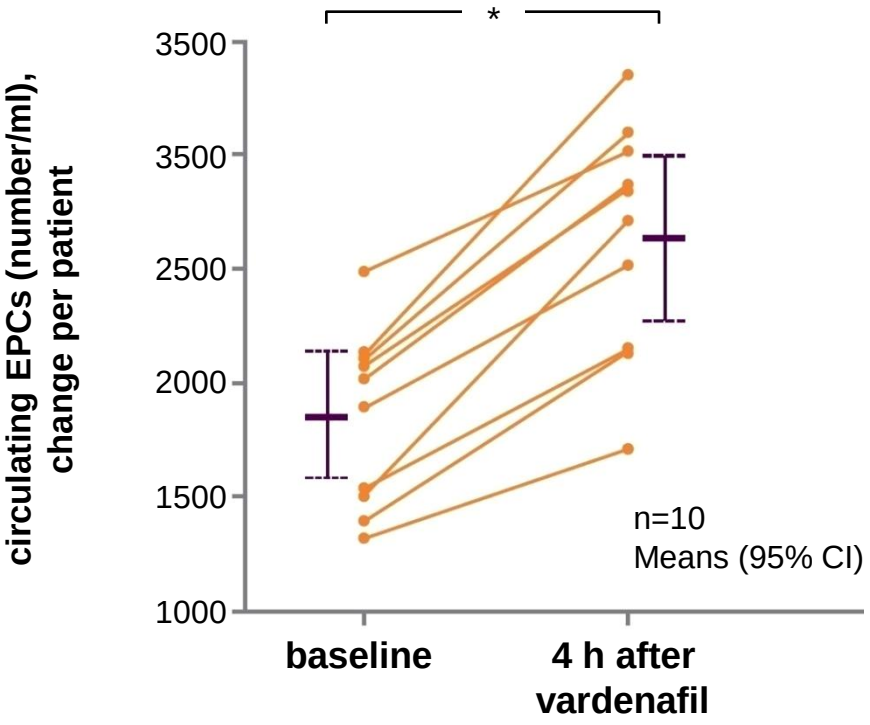
- Type 2 diabetes
- Type 1 diabetes
- Arterial hypertension
- Dyslipidemia

Endothelial Repair by Endothelial Progenitor Cells



Effect of Vardenafil on the Number of Endothelial Progenitor Cells (EPCs)





In men with ED, the number of EPCs is reduced = Indicator of endothelial dysfunction

4 h after intake of vardenafil 20 mg (single dose) significant increase of circulating EPCs

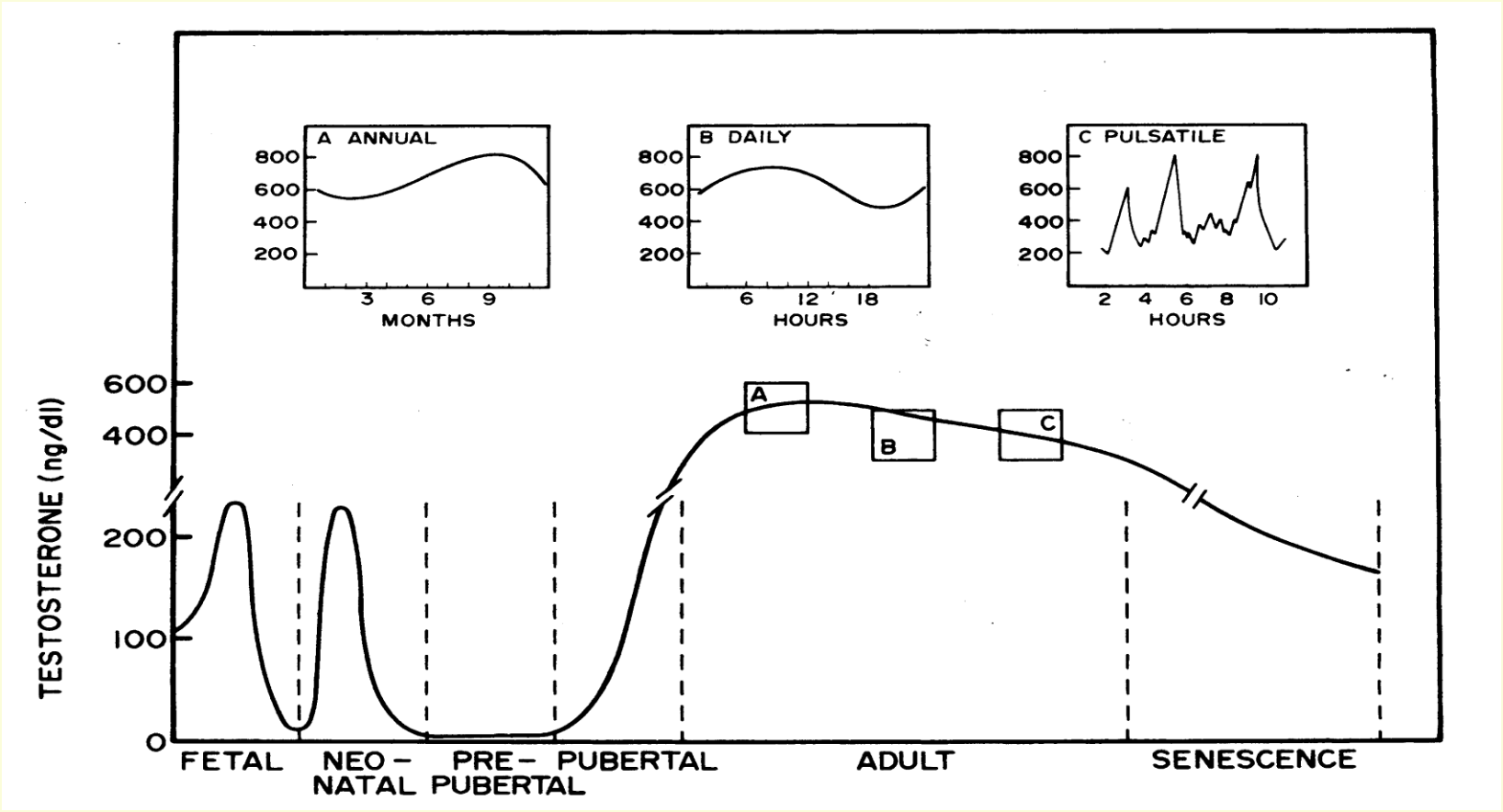
Foresta et al. Int J Impot Res 2005; 17: 377-380

*p<0,001 EPCs = circulating Endothelial Progenitor Cells

MENOPAUSE

- Cessation ovarian function
- Gradual decrease estrogen
- Symptoms
- HRT

s-T CHANGES DURING A LIFETIME



[s-T] IN AGEING MALES

- **total T ⬇ by 30% 25 to 75 years**
- **1/5 men >60 years ⬇**
- **1/3 men >80 years**

Quality of life

- Age associated testosterone decline is one of the major factors that reduce quality of life
  - decreased energy levels
  - impaired sex-life

Moncada I: Testosterone and men's quality of life. The Aging Male, December 2006; 9(4): 189–193

SYMPTOMS

- **changes in**
  - mood, intellectual activity
  - spatial orientation
  - motivation, memory, self-esteem

- **fatigue**
  - sleep disturbances, snoring, sleep apnoea
  - depression, anger
  - sweating, ‘flushes’, palpitations

diminished sexual desire - libido

erection, ejaculation, orgasm

ED and CAD

- men with ED thorough medical assessment, including testosterone, fasting lipids, fasting glucose and blood pressure measurement

- evaluated by cardiologist by stress testing with selective use of computed tomography (CT) or coronary angiography

Laboratory diagnosis

- exclude transient decreases s-T levels
- hypogonadism (primary or secondary) can occur at all ages
- risk factors: chronic illnesses
  - diabetes mellitus
  - COAD
  - arthritic
  - renal, and HIV-related diseases
- obesity
- metabolic syndrome
- hemachromatosis

Laboratory diagnosis

- serum total testosterone between 07-10
- t-T >12 nmol/l
- <8 nmol/l benefits most
- 8-12 nmol/l repeat t-T, also SHBG, calculate free-T

WHO SHOULD BE CONSIDERED FOR TREATMENT?

ONLY IF

- **SYMPTOMS AND SIGNS OF TDS**
- **low s-T (<12 nmol/L)**
- **DRE normal**
- **PSA normal range**

Why to treat

Symptomatic men with TDS

- to induce and maintain secondary sex characteristics
- to improve
  - sexual function
  - sense of well-being
  - muscle mass and strength
  - bone mineral density

J Clin Endocrinol & Metab 91: 1995–2010, 2006 Summary of Evidence-Based Guidelines for Use of Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes

Who definitely not to treat

- breast cancer
- prostate cancer
- palpable prostate nodule or induration
- PSA >2 ng/ml **REFER**
- LUTS >19 International Prostate Symptom Score (IPSS) - **REFER**
- erythrocytosis (hematocrit > 50%) **REFER**
- untreated obstructive sleep apnea **REFER**
- class III or IV heart failure **REFER**

J Clin Endocrinol & Metab 91: 1995–2010, 2006 Summary of Evidence-Based Guidelines for Use of Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes

MANAGEMENT TDS - GP

- Complete history
- Full clinical examination including DRE
- Biochemical work-up
  - Blood sample 08.00 - 10:00
    - t-T and SHBG
    - calculate f-T, b-T
  - PRL, not LH
  - Age related PSA
  - Exclude DM and hypothyroidism

How to treat

- s-T levels during treatment mid-normal range
  - **s-T 19nmol/l**
  - > 24.5 nmol/liter or <12.3 nmol/l adjust dose or frequency
- With any of the approved formulations, chosen on;
  - patient's preference
  - consideration of pharmacokinetics
  - treatment burden
  - cost

J Clin Endocrinol & Metab 91: 1995–2010, 2006 Summary of Evidence-Based Guidelines for Use of Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes

Monitoring strategies and schedule

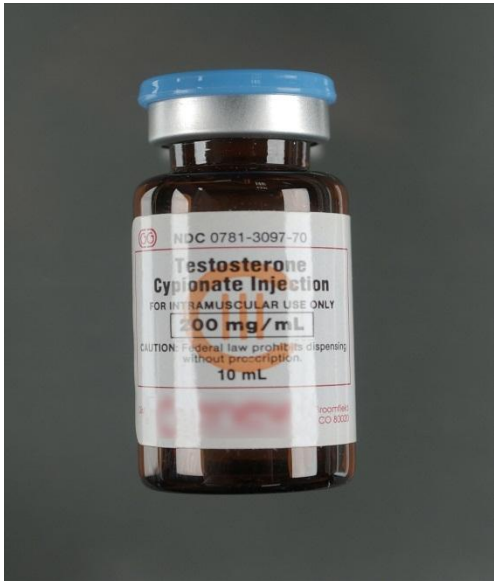
- Evaluate to assess
  - whether symptoms have responded to treatment
  - any adverse effects
  - serum testosterone levels
  - PSA

J Clin Endocrinol & Metab 91: 1995–2010, 2006 Summary of Evidence-Based Guidelines for Use of Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes

OPTIONS T-SUPPLEMENTATION

- oral
- parenteral
- transdermal patches
  - scrotal
  - non-scrotal
- implantable pellets, spheres, microcapsules
- new formulations, SARM

Injectable TRT



testosterone cypionate

Testosterone Enanthate/ cypionate

Advantages

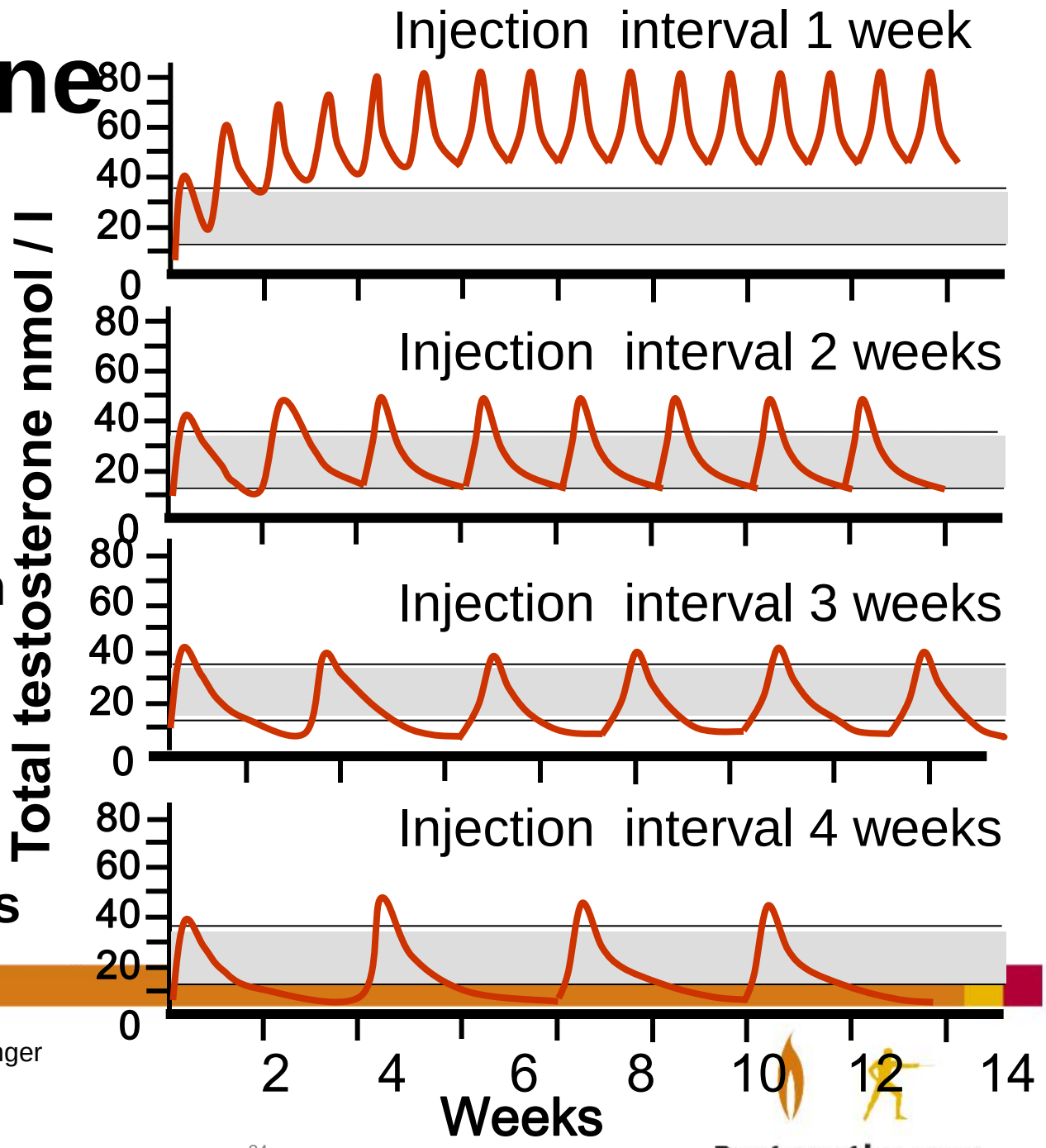
Long experience

Reliable absorption

Disadvantage

Injections

Supraphysiological levels, fluctuations



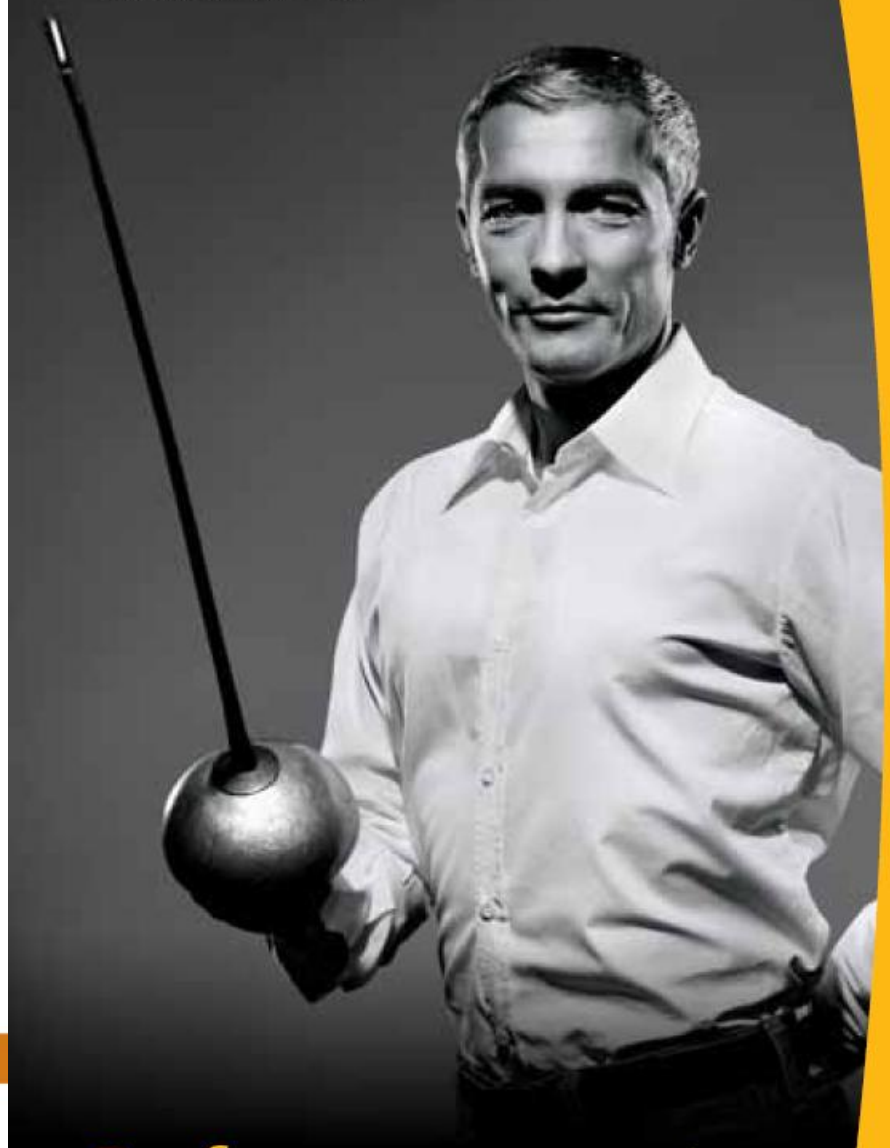
Nieschlag and Behre, Andrology, 2000, Springer

Testosterone undecanoate 1000 mg/4 ml

NEBIDO®

Life keeps getting better[1]

Bayer HealthCare
Bayer Schering Pharma

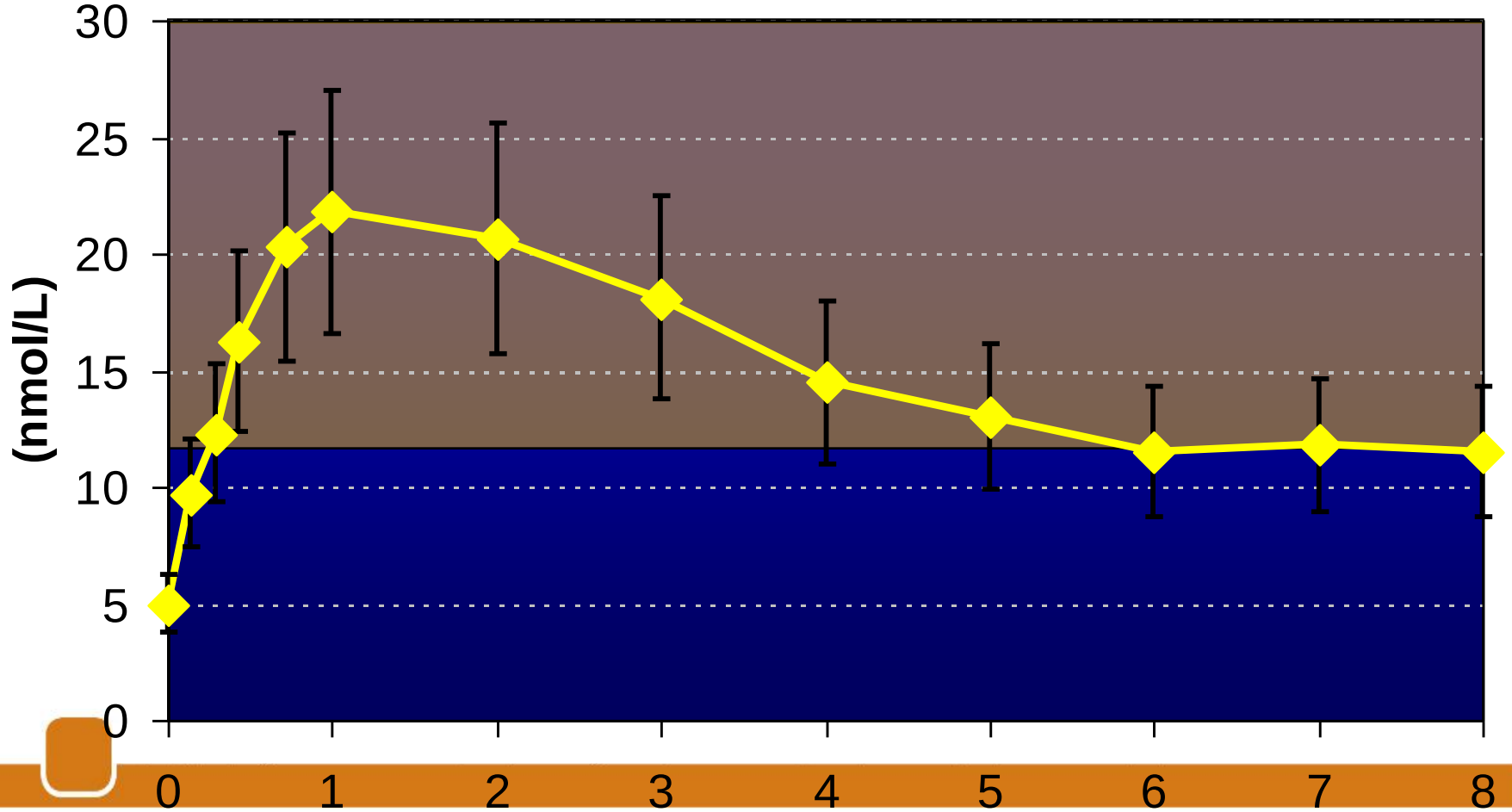


Performance counts, everywhere[2]

4 injections per year to maintain physiological testosterone levels.[4]

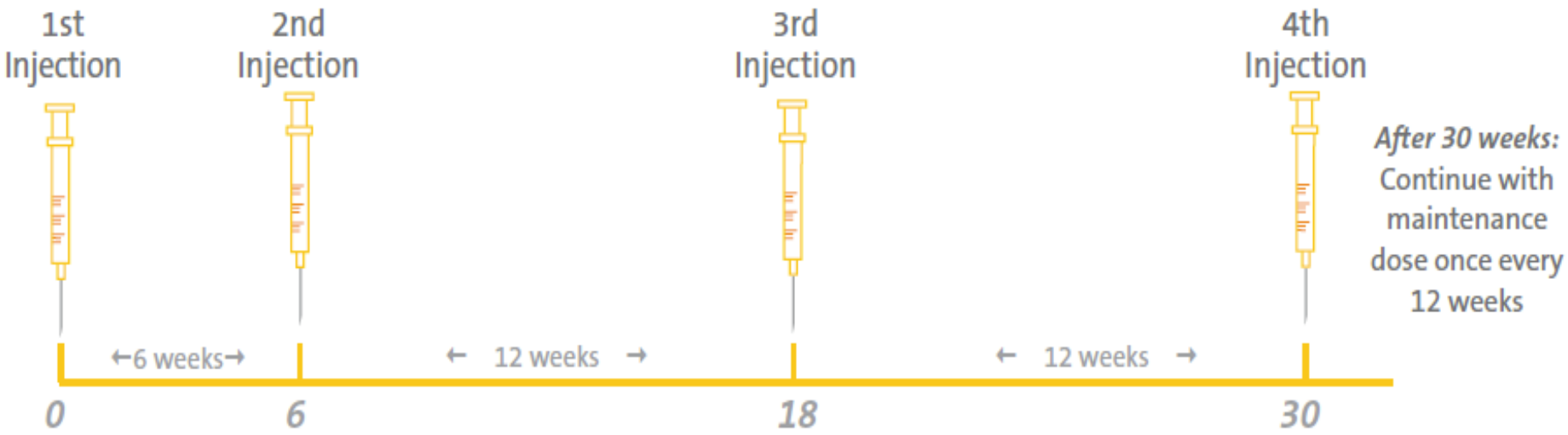
Restore the man.

Testosterone Levels: Single Dose

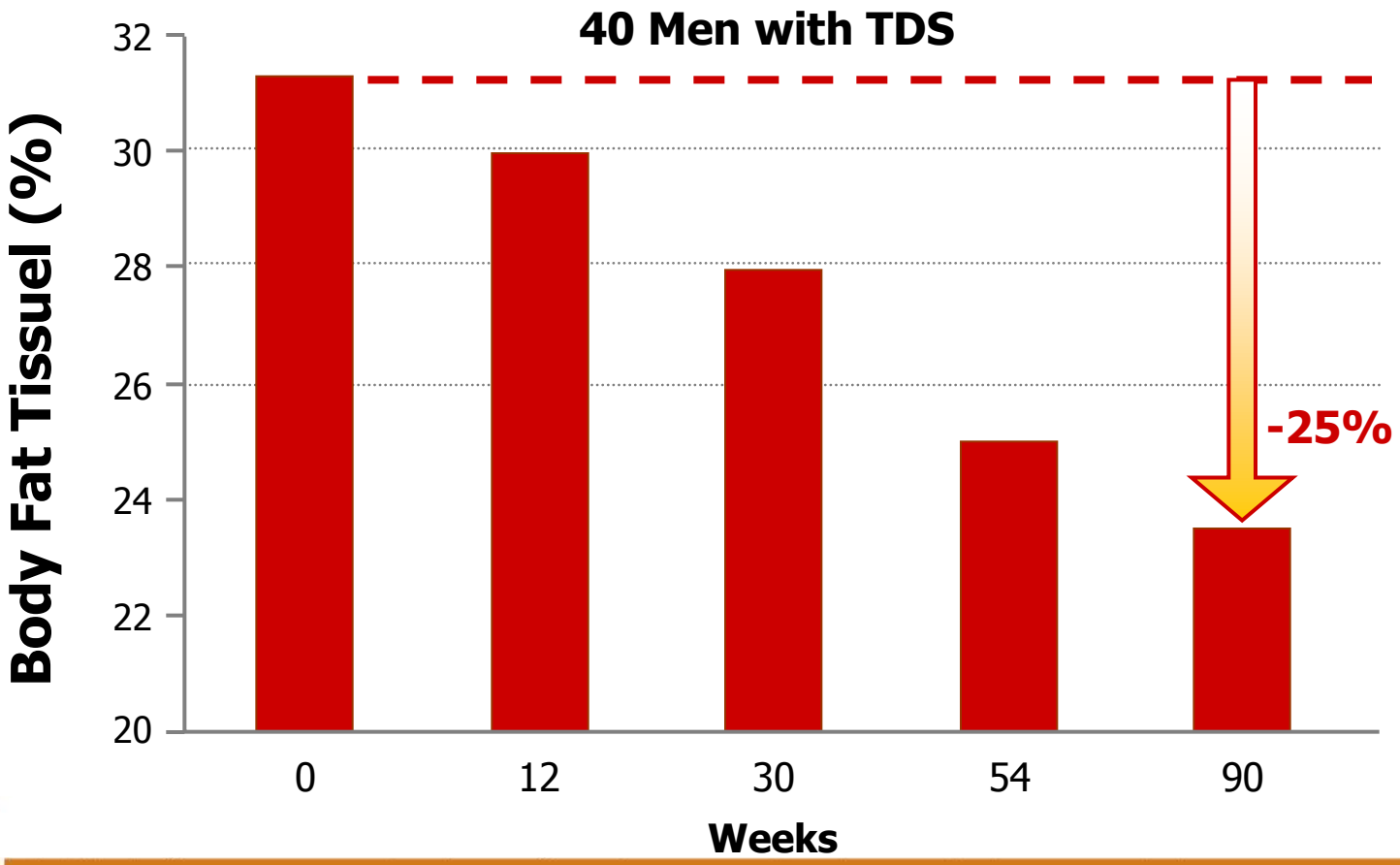


Behre H et al. Eur J Endocrinol 140: 414 – 419 (1999)

Therapy control[5]

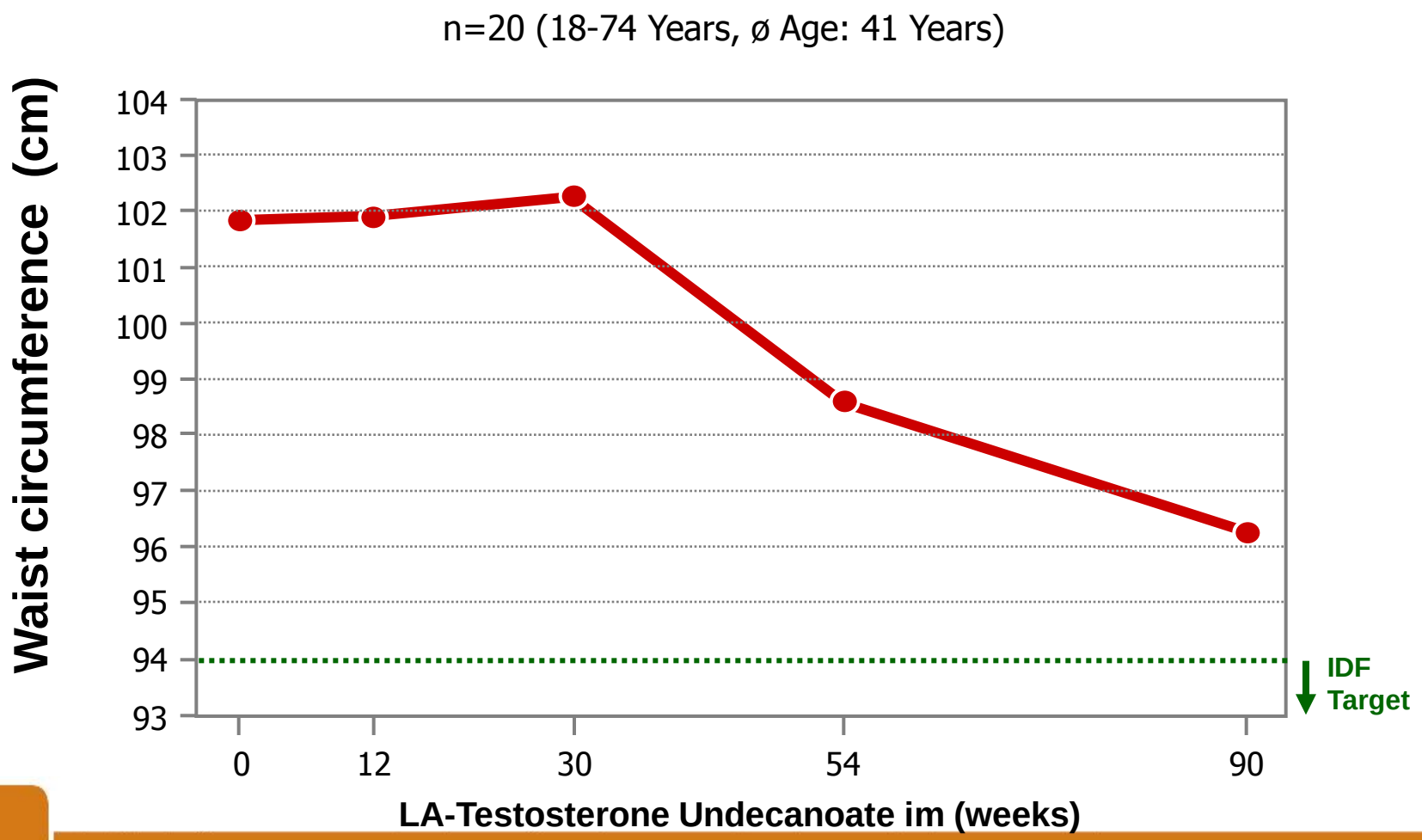


LA-TU and fat tissue



Freude et al. The Aging Male 2006; 9(1):15; DEXA-Messung

LA-TU and waist circumference



Freude et al. Aging Male 2006; 9(1): 15

Testosterone supplementation effects on…

- Visceral Fat, Waist Circumference
- Lipids
- Arterial Blood Pressure
- Insulin Resistance, Glucose Levels

Monitoring strategies and schedule

- DRE, PSA
- repeat FBC, s-T
- NO indication of CA continue,

  FU 6 mo., then annually if improved

CLINICAL RESPONSE MORE NB

The prostate and testosterone therapy (TRT)

- Basics
  - prostate tissue androgen-dependent
  - castration used to treat urinary retention, prostate cancer
- Question
  - will raising testosterone TDS induce an increased risk PCa?
  - medical "lore" - generations physicians “testosterone supplementation is bad for the prostate “ (Morgentaler, 2006).

TRT in hypogonadal men

- mild increases (~15%) prostate volume, PSA
- reach level eugonadal men, but NOT higher (Behre et al., 1994).
- no changes uroflow or postvoid residual urine (Rhoden and Morgentaler, 2004).

TRT in hypogonadal men

- TRT can be initiated in most men
- Men with *severe* obstructive voiding urological assessment crucial before initiating TRT

Prostatic cancer?

- PCa more prevalent when s-T starts to decline (Kirby & Gould, 2005).
- old concept that higher testosterone levels are somehow associated with increased rates of prostate cancer has no scientific support (Morgentaler, 2006)
- higher testosterone levels are not associated with an increased risk of prostate cancer (Carter et al., 1995; Heikkila at al., 1999; Hsing, 2001; Gann et al., 1996)

Prostatic cancer

- LOW testosterone levels are not necessarily protective against prostate cancer
  - men severely reduced testosterone levels had a significantly higher prostate cancer rate of 20%
  - associated with high-grade cancers (Hoffman et al., 2000)
  - a higher stage at diagnosis (Isom-Batz et al., 2005)
  - worse clinical outcomes (Ribiero et al., 1997).

TRT in hypogonadal men

- *Although no large-scale, long-term studies have been performed to evaluate the possibility that there might be a small increased (or decreased) risk of prostate cancer with TRT, current evidence suggests that TRT does not result in any appreciably increased risk of prostate cancer over baseline rates.*

(Morgentaler, 2006).

TRT in hypogonadal men

- With appropriate monitoring, TRT appears to be safe for the prostate
  - men with an elevated PSA level or abnormal DRE should undergo prostate biopsy prior to treatment
  - biopsy should also be performed if prostatic changes occur during the course of treatment
  - TRT in hypogonadal men in the presence of suspected or confirmed prostate cancer is absolutely contraindicated (Nieschlag et al., 2005; Morgental, 2006).

Prostate cancer: epidemiology

- Third most common cause of death from cancer in Western world[1]
- First and second most commonly diagnosed cancer in men in the US and EU, respectively[2-3]
- 237,800 men were newly diagnosed in the EU in 2004 accounting for 15.5% of all male cancers[2]

[1]Parkin DM *et al*. *CA Cancer J Clin* 2005; 55: 108
[2]Boyle P, Ferlay J. *Ann Oncol* 2005; 16: 481–488
[3]Greenlee RT et al. CA Cancer J Clin. 2000, 50, 7-33

Risk factors

- **Age**: Median age at diagnosis ~ 70 years
- **Family history:**
  - one first-line relative with PC: risk x 2
  - 2 or more first-line relatives: risk x 5 to 11
- **Geographical area:**
  - high incidence in USA/Canada & Northern Europe
  - low in South-East Asia
- **Exogenous factors:**
  - diet rich in animal fat, low intakes of selenium, vitamin E, lycopene (carotenoid found primarily in tomatoes and watermelon)

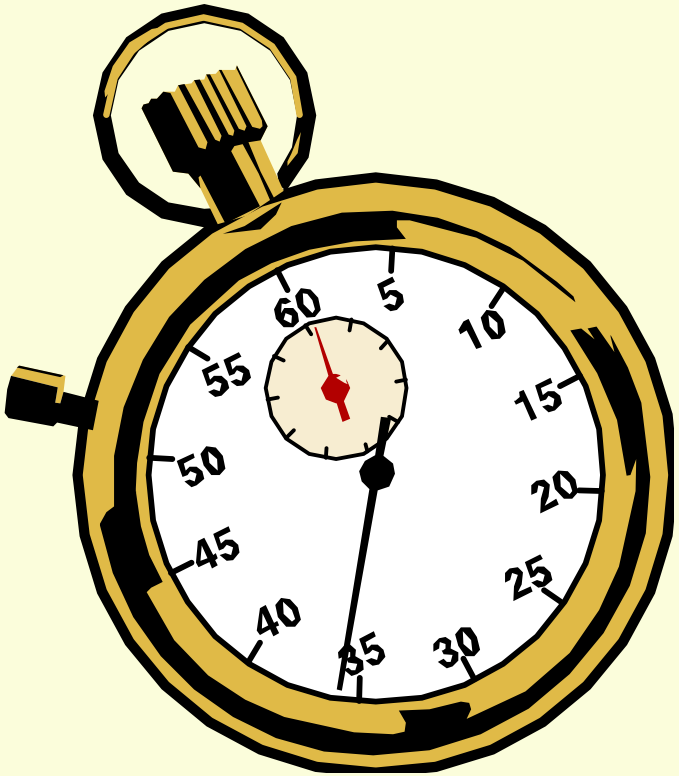
Aus et al. *Eur. Urol.* 2005, 48, 546-551

Symptoms

- PCA often develops asymptomatic
- in 80% of cases during routine medical check ups
- BPH may coexist with prostate cancer
- At an advanced stage:
  - lower back or hip pain, paralysis of lower limbs
  - swollen legs
  - fatigue, loss of weight

How does early detection help?

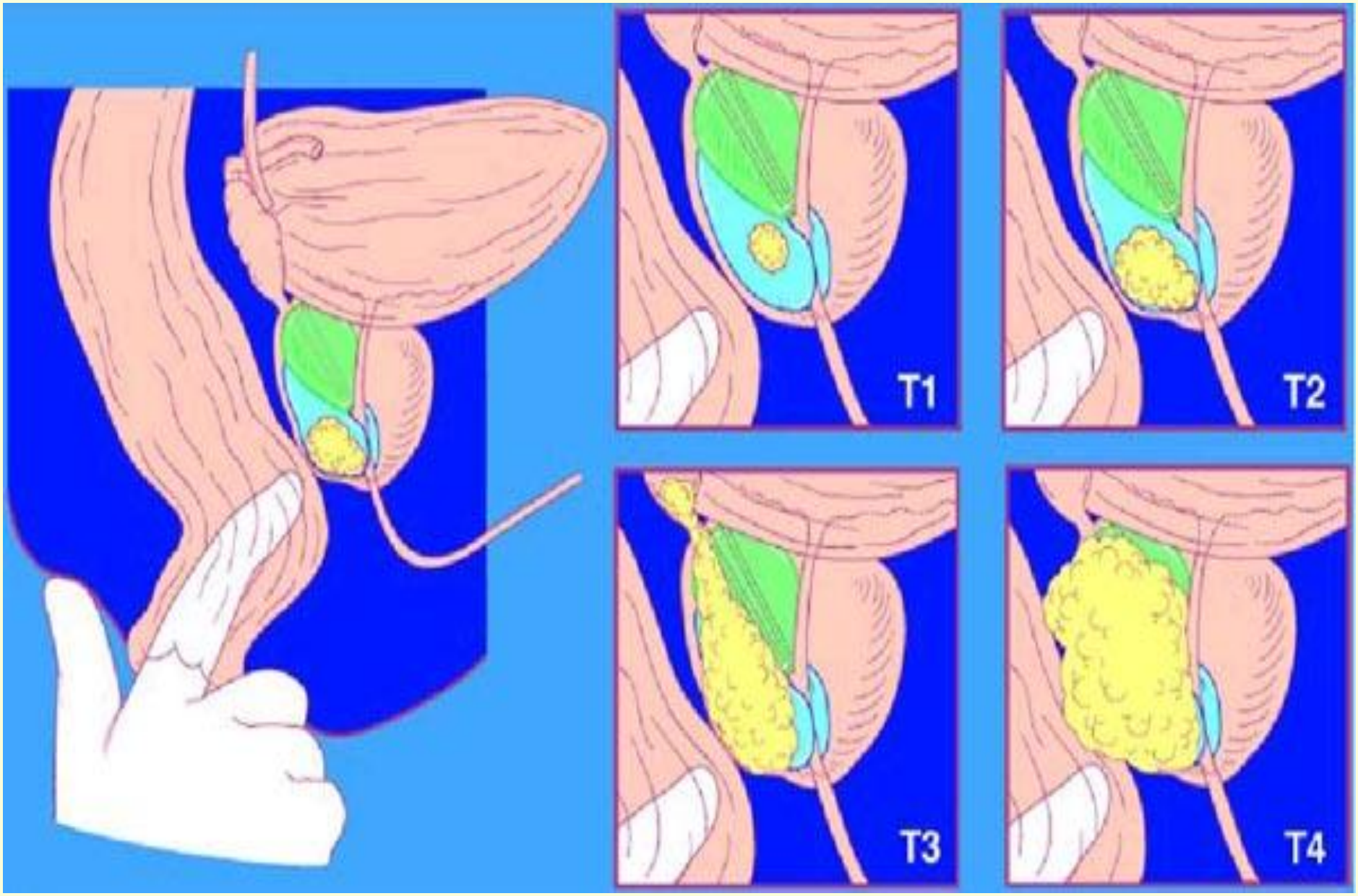
- Survival rate at 5 years **99%** for localized prostate CA
- Survival rate at 5 years CA beyond the gland (late diagnosis) is **only 31%.**



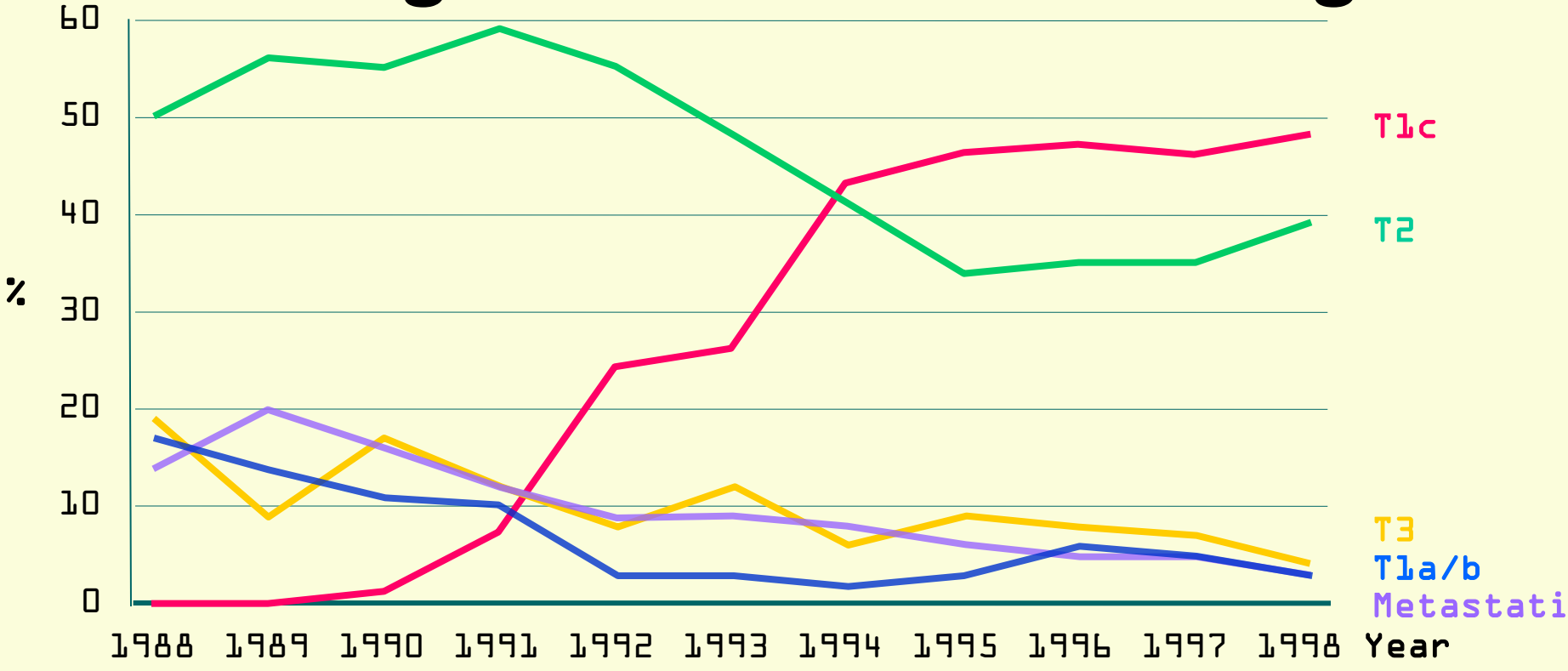
No Warning!

- annual testing is KEY!
- Prostate Specific Antigen (PSA)
- Digital Rectal Examination (DRE)

Basic tools to find Prostate Cancer EARLY!


T1
T2
T3
T4

With early screening, most tumors are now diagnosed at a localized stage



The most common T stage detected today is T1C (impalpable prostate cancer detected by prostate biopsy)

Paquette EL et al. *Urology* 2002; 60: 756–759

What to expect from my doctor

Limit risk: lifestyle factors

- exercise
- overeating
- smoking
- stress
- overworking

Summary

"***We only see what we know***“

--Johann Wolfgang von Goethe [1749-1832]

We only see what we look for