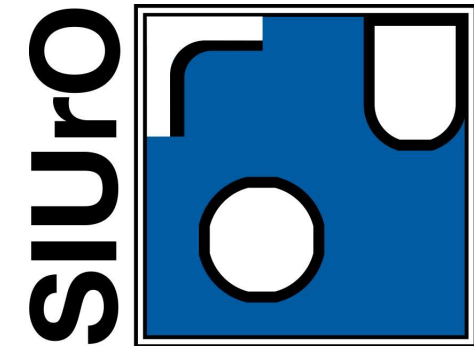
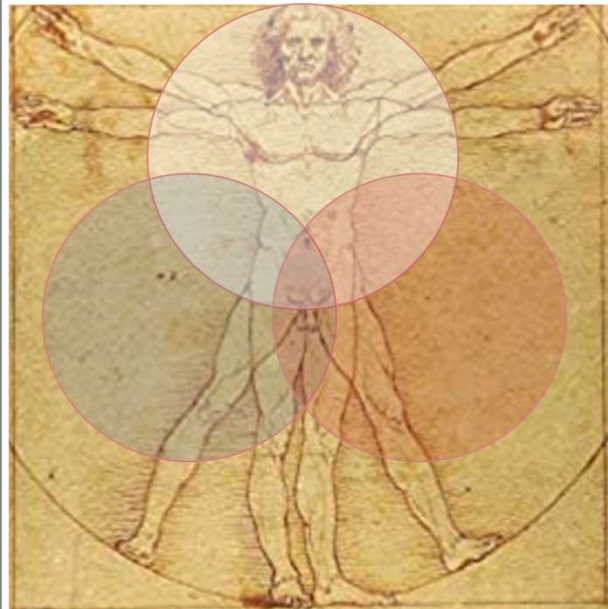


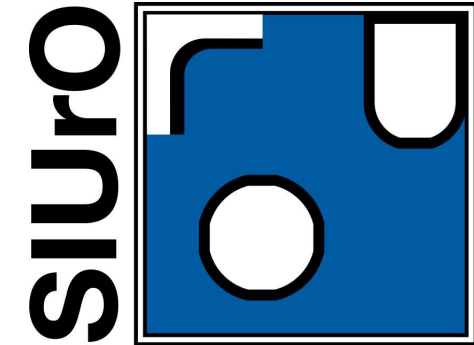
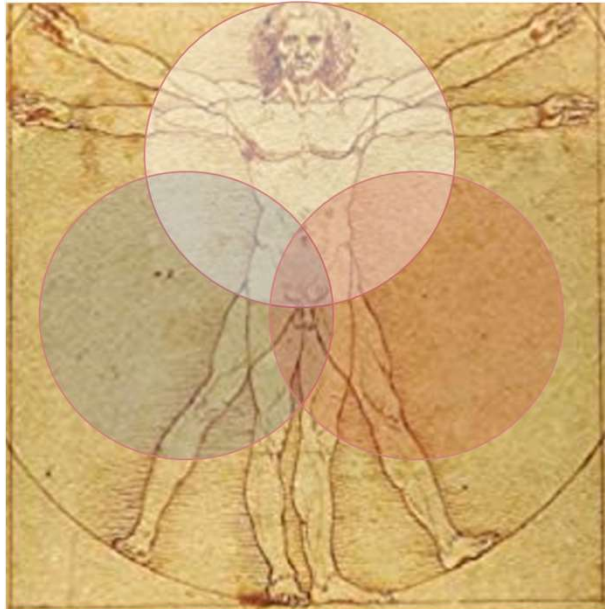
I 3 CERCHI - mHSPC:
LA MEDICINA BASATA SULL'EVIDENZA NELL'APPROCCIO
MULTIDISCIPLINARE AI CASI COMPLESSI



Faculty

Coordinatore:	Giario N. Conti	
Garante metodologico:	Giovanni Pappagallo	
Facilitatore:	Roberta Ceccarelli	
Esperti:		
Nicolò Borsellino	Oncologia Medica	Palermo
Giuseppe F. Colloca	Oncologia Geriatrica	Roma
Marzia Del Re	Farmacologia	Pisa
Alberto Lapini	Urologia	Firenze
Luca Triggiani	Radioterapia Oncologica	Brescia

I 3 CERCHI - mHSPC:
LA MEDICINA BASATA SULL'EVIDENZA NELL'APPROCCIO
MULTIDISCIPLINARE AI CASI COMPLESSI



Il primo cerchio

mHSPC le evidenze disponibili

Il secondo cerchio:

- le comorbidità più comuni e come affrontarle
- le interazioni farmacologiche più comuni e come affrontarle

Il terzo cerchio

- verso una decisione terapeutica condivisa: come proporsi al paziente

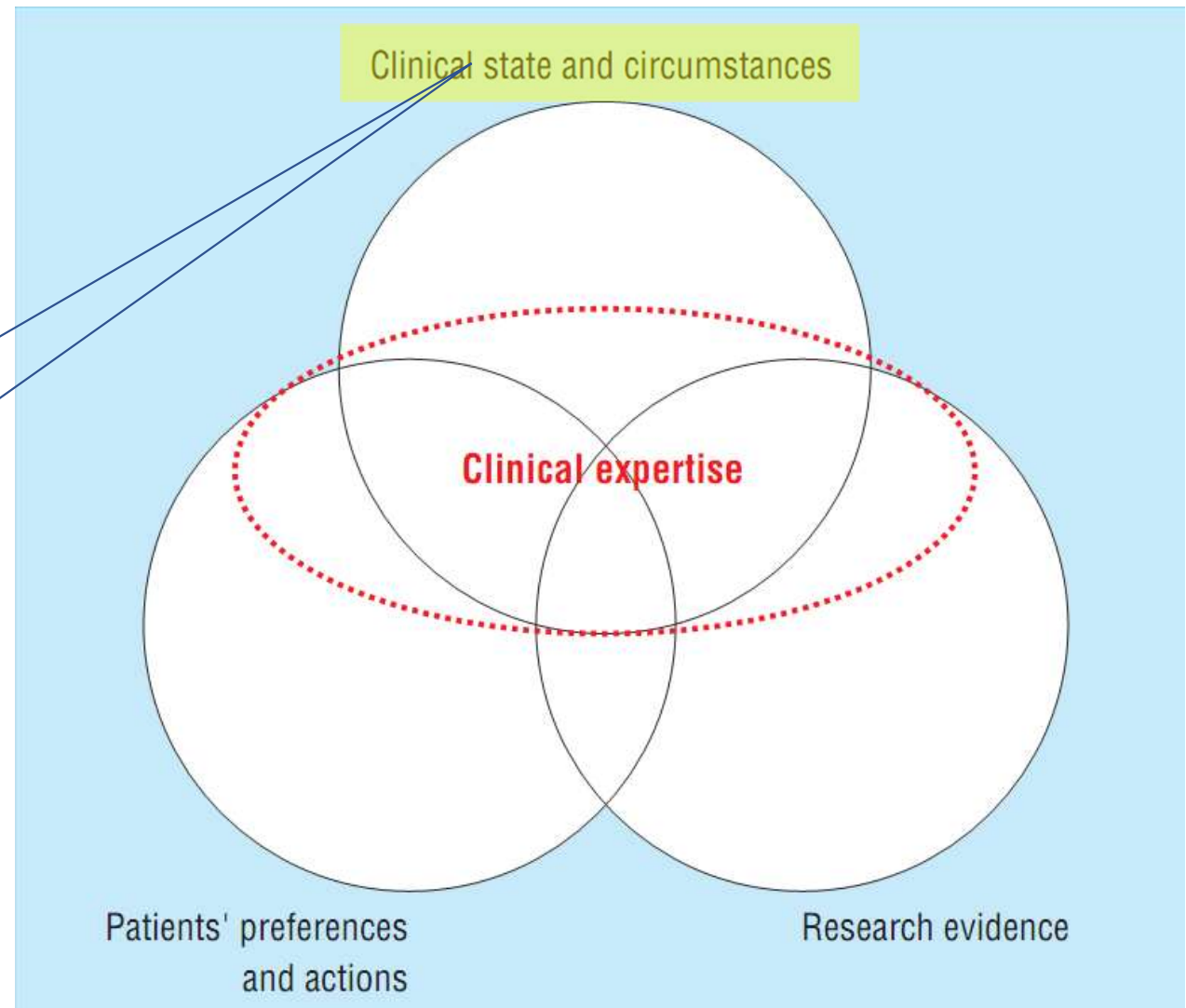
Roberta Ceccarelli, Giario N. Conti, Giovanni Pappagallo

Physicians' and patients' choices in evidence based practice

Evidence does not make decisions, people do

R Brian Haynes *BMJ* 2002;324:1350

La *proposta terapeutica* deve tenere conto delle condizioni cliniche, dei possibili effetti collaterali delle terapie e delle possibili interazioni farmacologiche



Courtesy G.L. Pappagallo

Isn't Androgen Deprivation Enough? Optimal Treatment for Newly Diagnosed Metastatic Prostate Cancer

Alicia K. Morgans, MD, MPH¹; and Himisha Beltran, MD¹

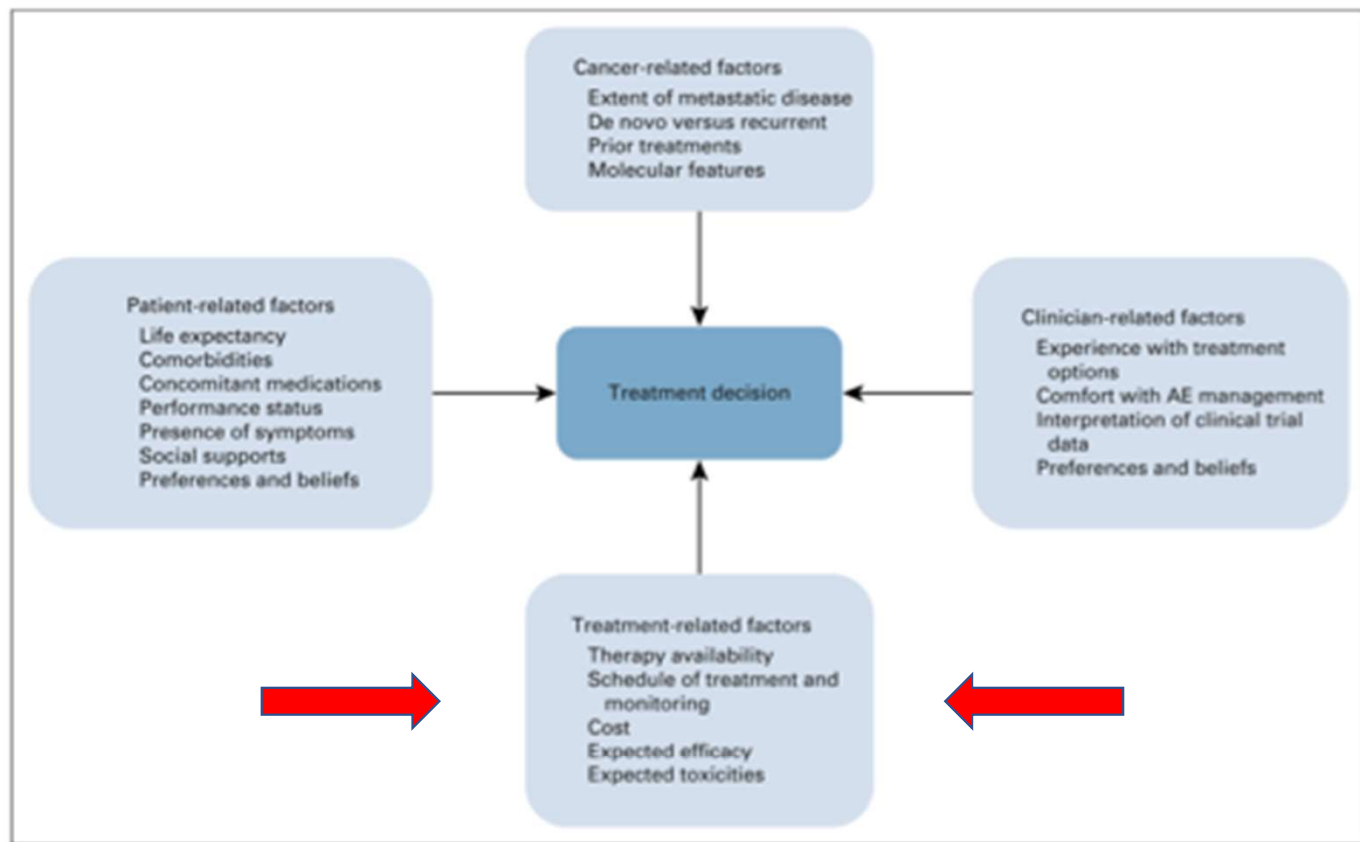
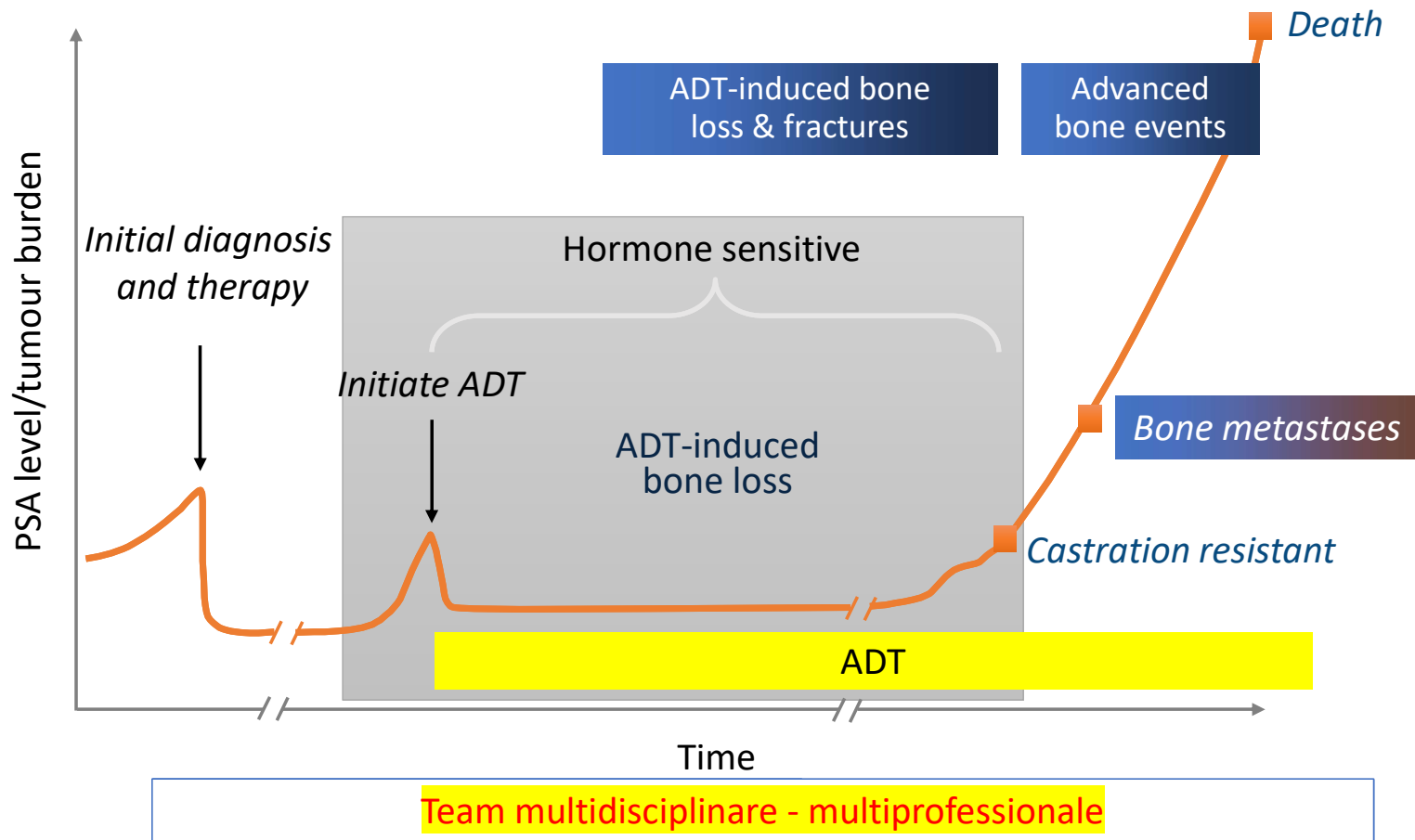


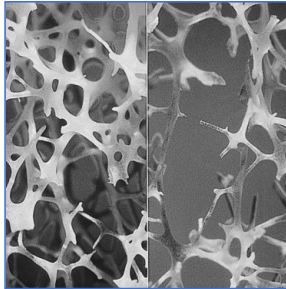



FIG 1. Factors contributing to treatment decisions that should be considered when using shared decision making for patients with metastatic hormone-sensitive prostate cancer. AE, adverse event.

Focus on ADT

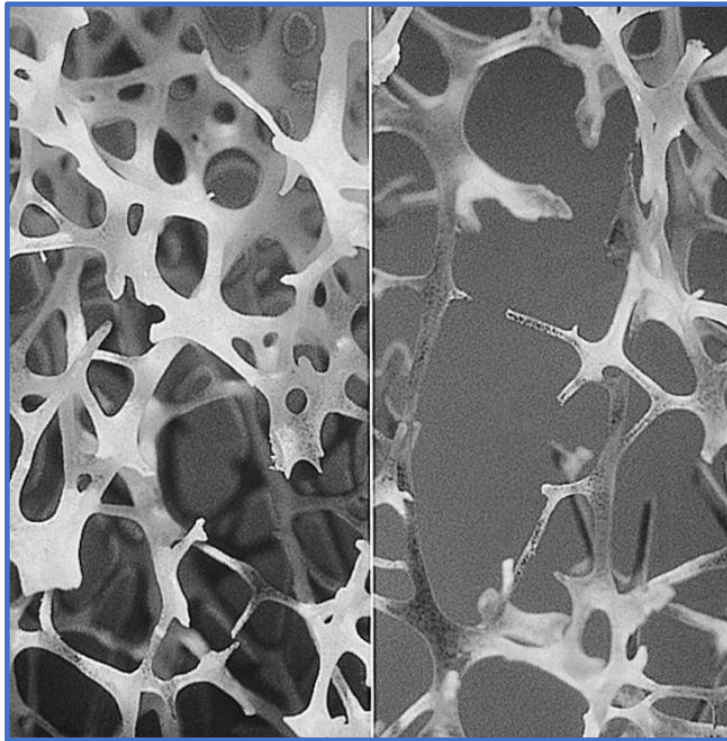


ADT multi eventi avversi differenziati

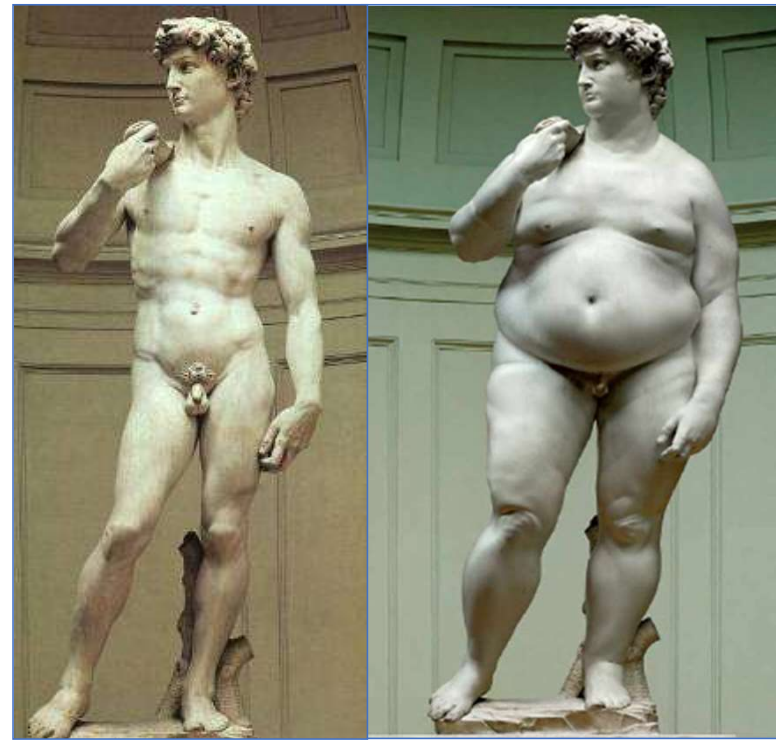
Visible		Non-visible	
Most common	What is seen	What isn't seen	What patients feel
<p>Loss of libido</p> <p>Erectile dysfunction</p>  <p>Hot flashes</p>	<p>Weight gain</p>  <p>Gynaecomastia</p> <p>Loss of muscle mass, strength</p> <p>Hair loss</p> <p>Decreased size of penis and testes</p>	<p>Loss of BMD</p>  <p>Anaemia</p> <p>Onset/worsening of hypertension, diabetes, CV diseases</p> <p>Changes in lipid profile</p>	<p>Fatigue</p> <p>Lack of energy</p> <p>Lack of initiative</p> <p>Depression</p>  <p>Emotional distress</p> <p>Alterations in cognitive function</p>

Bone loss and weight gain are serious long-term adverse effects of ADT

Bone loss



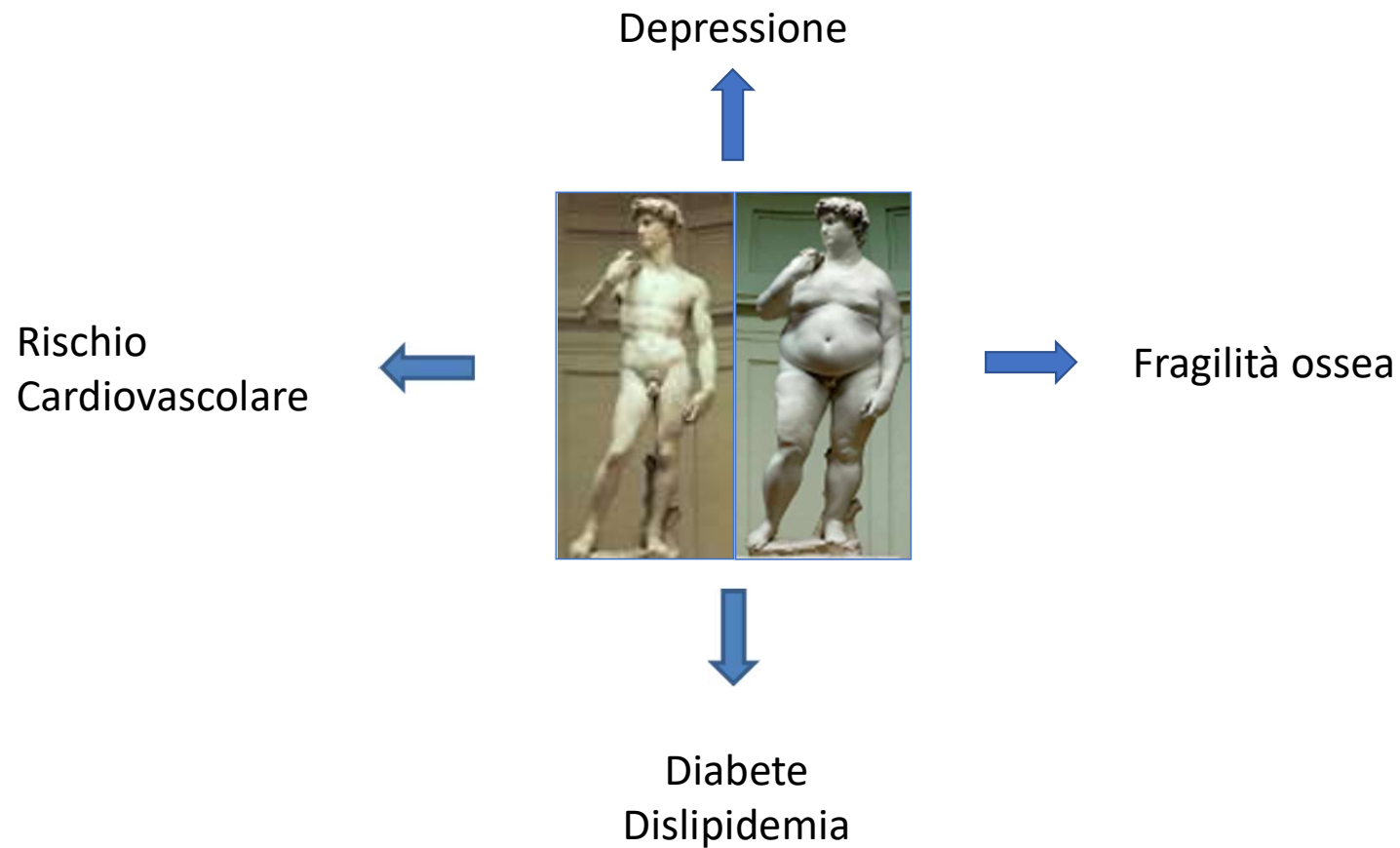
Sarcopenic obesity



Saylor PJ, Smith MR. *J Natl Compr Canc Netw* 2010;8:211–23.

ADT, androgen-deprivation therapy

Terapia ormonale e **qualità della vita**: più facce della stessa medaglia



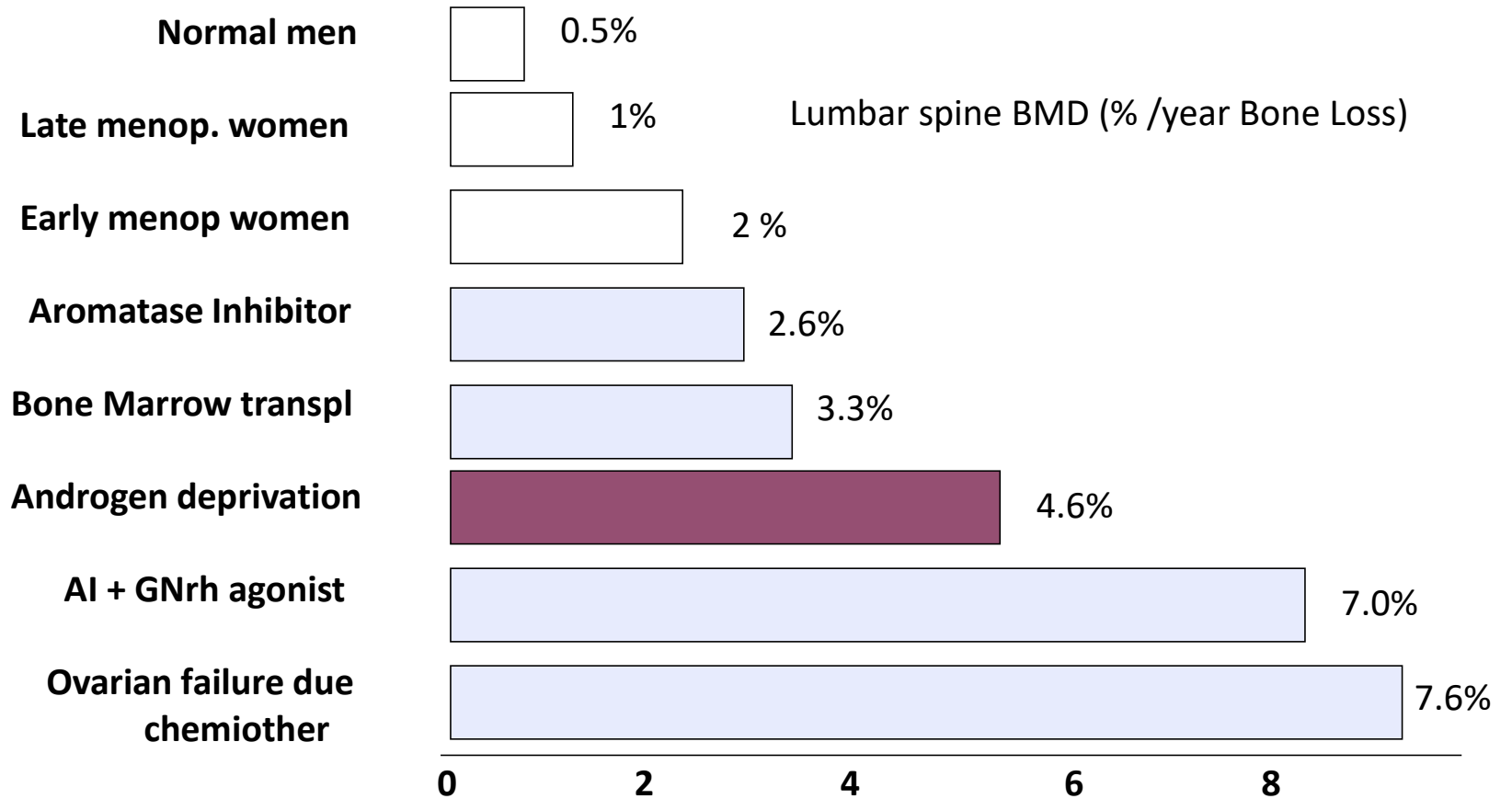
ADT in Men With Prostate Cancer Consistently Produces BMD Decreases

Study	Treatment	BMD Decrease at Mo 12, %
Eriksson ^[1]	Orchiectomy	Hip: 9.6 Radius: 4.5
Maillefert ^[2]	GnRH agonist	Hip: 3.9 Lumbar spine: 4.6
Daniell ^[3]	Orchiectomy or GnRH agonist	Hip: 2.4
Berrutti ^[4]	GnRH agonist	Hip: 0.6 Lumbar spine: 2.3
Higano ^[5]	LHRH agonist + antiandrogen	Hip: 2.7 Lumbar spine: 4.7
Mittan ^[6]	GnRH agonist	Hip: 3.3 Radius: 5.3

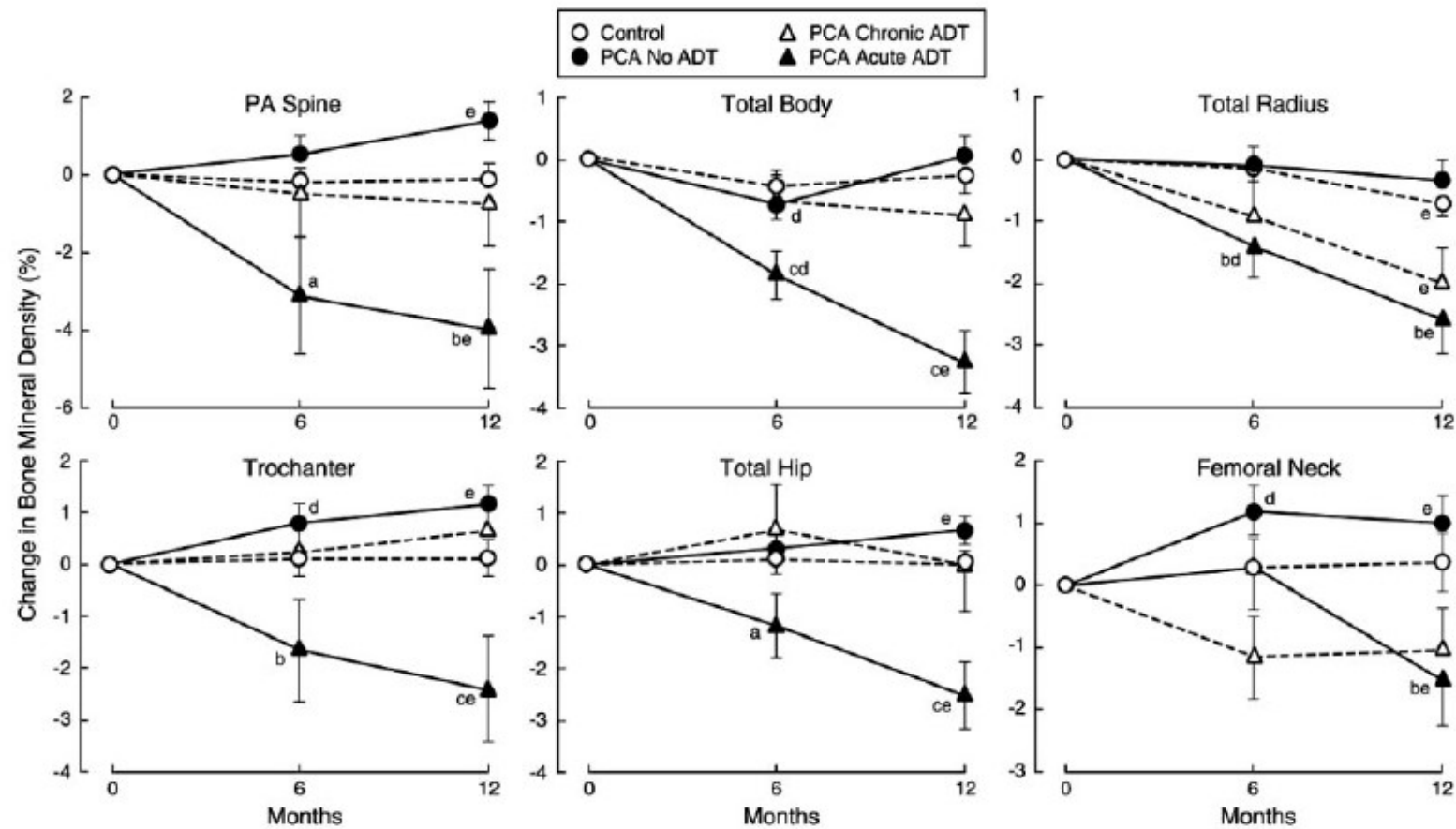
1. Eriksson S, et al. *Calcif Tissue Int.* 1995;57:97-99. 2. Maillefert JF, et al. *J Urol.* 1999;161:1219-1222.

3. Daniell HW, et al. *J Urol.* 2000;163:181-186. 4. Berruti A, et al. *J Urol.* 2002;167:2361-2367. 5. Higano C, et al. *Proc Am Soc Clin Oncol.* 1999;18:314a. 6. Mittan D, et al. *J Clin Endocrinol Metab.* 2002;87:3656-3661

Misura della perdita di massa ossea associata alla terapia mirata contro il cancro¹ (CTIBL)



ADT e perdita precoce di massa ossea





Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion

Daniele Santini ¹, Alfredo Berruti,² Massimo Di Maio ³, Giuseppe Procopio,⁴ Sergio Bracarda,⁵ Toni Ibrahim,⁶ Francesco Bertoldo⁷

Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion

Daniele Santini,¹ Alfredo Berruti,² Massimo Di Maio,³ Giuseppe Procopio,⁴ Sergio Bracarda,⁵ Toni Ibrahim,⁶ Francesco Bertoldo⁷

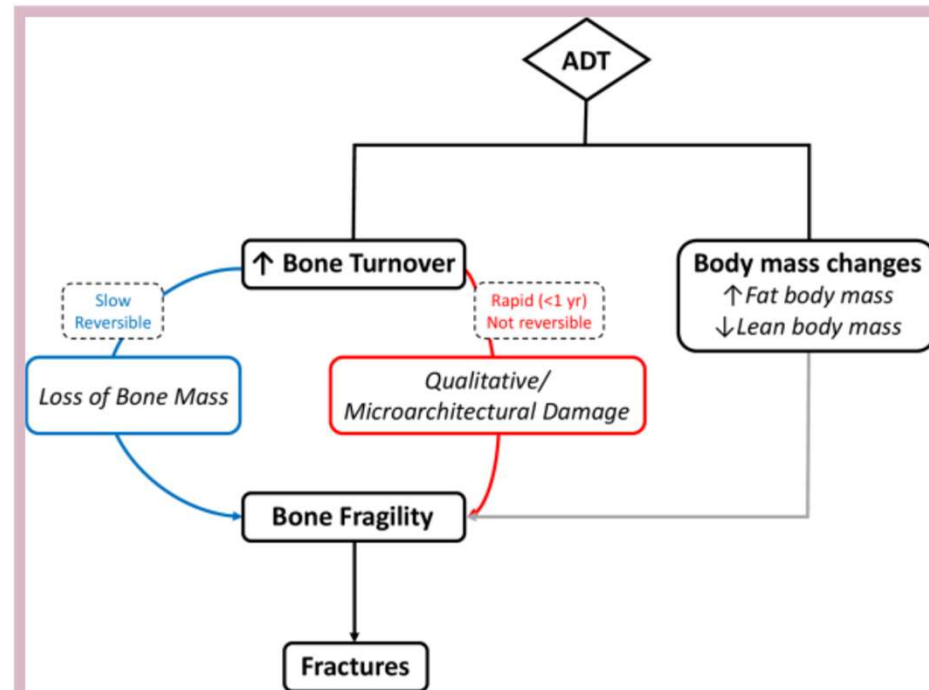
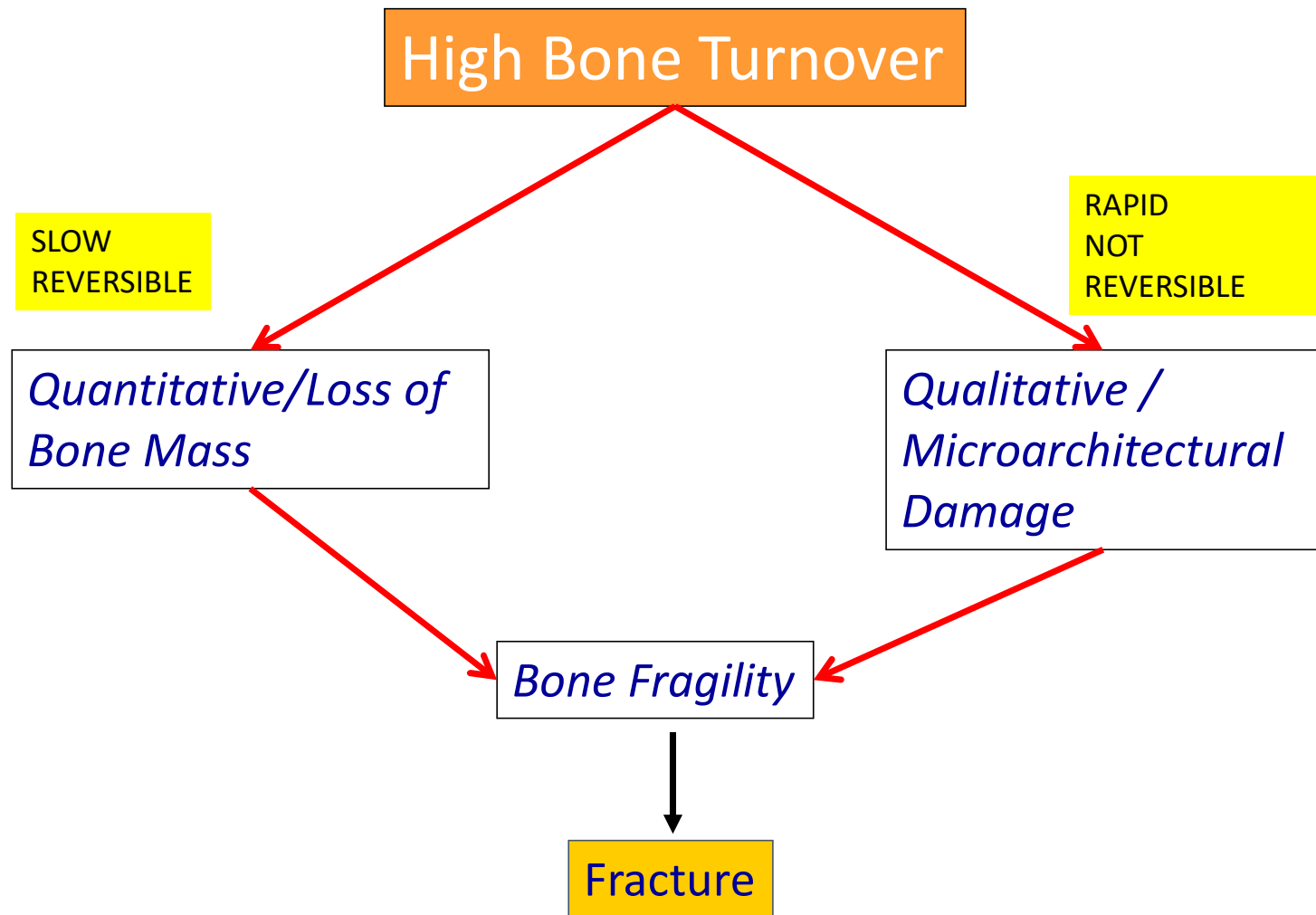


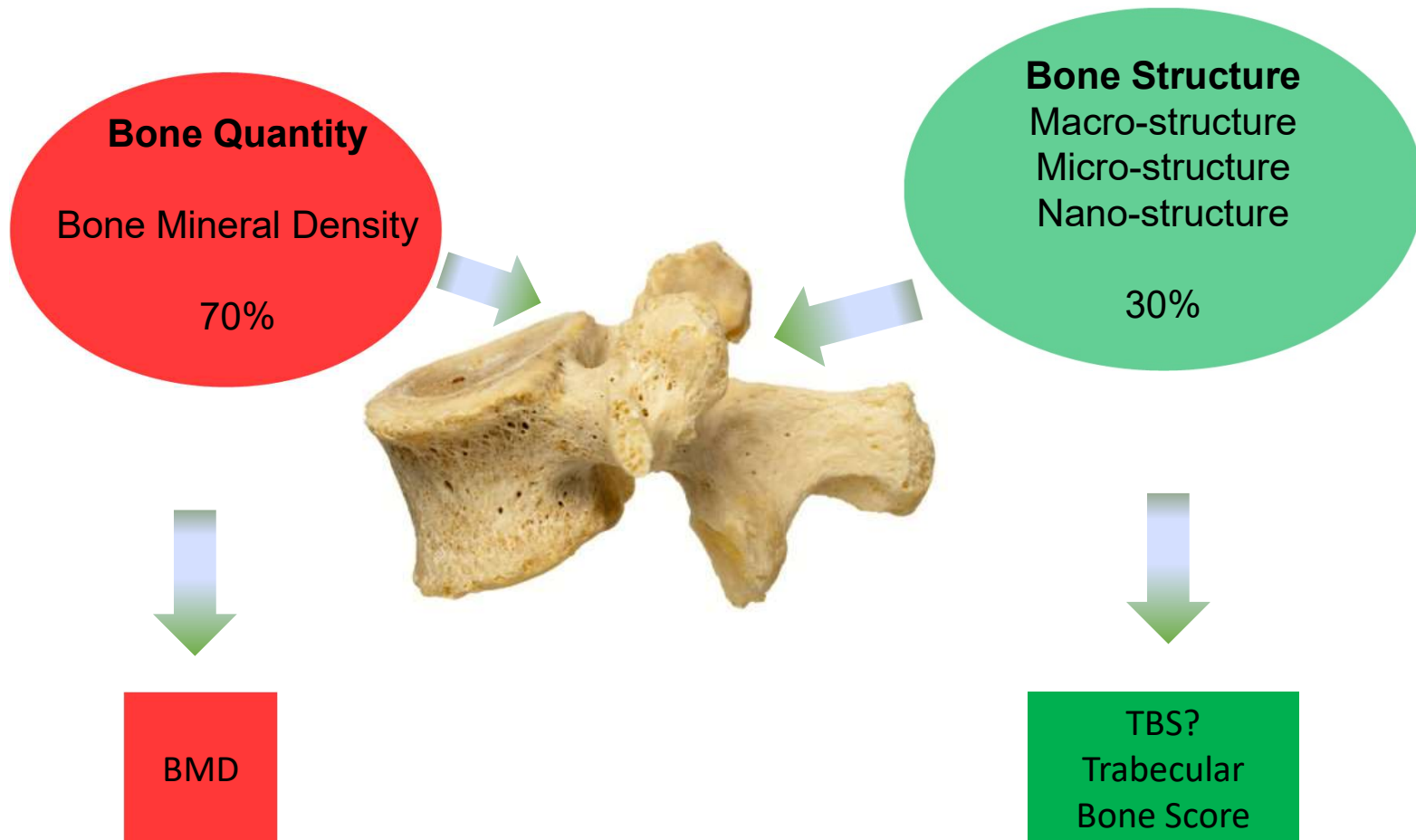
Figure 1 ADT-induced bone impairment. ADT augments bone fragility, and thus the risk of fracture, through two mechanisms: (1) bone turnover increase, which leads to bone mass loss via a slow, reversible process, and to qualitative/microarchitectural alterations via a rapid, non-reversible mechanism; (2) body mass changes, namely increased fat body mass and decreased lean body mass. ADT, androgen-deprivation therapy.



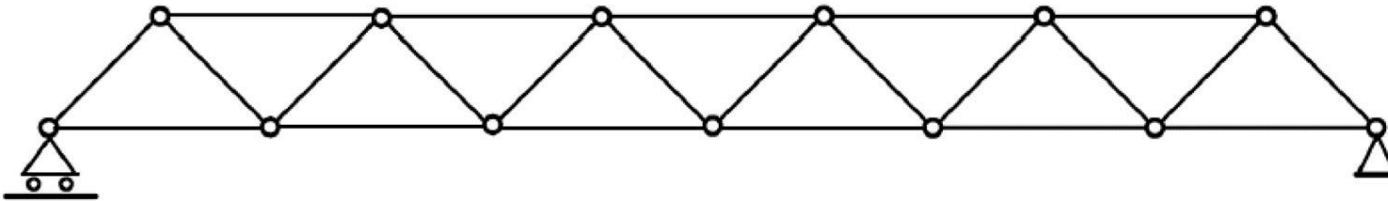
Courtesy of Francesco Bertoldo

Boivin G et al. *Connect Tissue Res.* 2002;43:535-537.

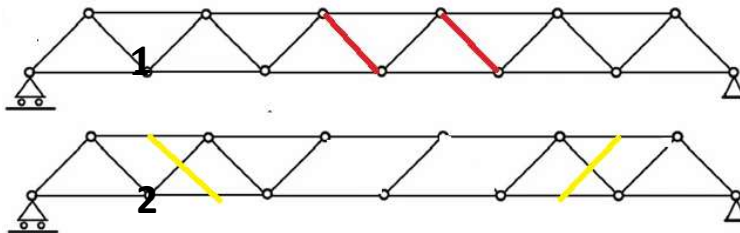
Quantità e qualità dell'osso



Struttura dell'osso – BMD verso TBS



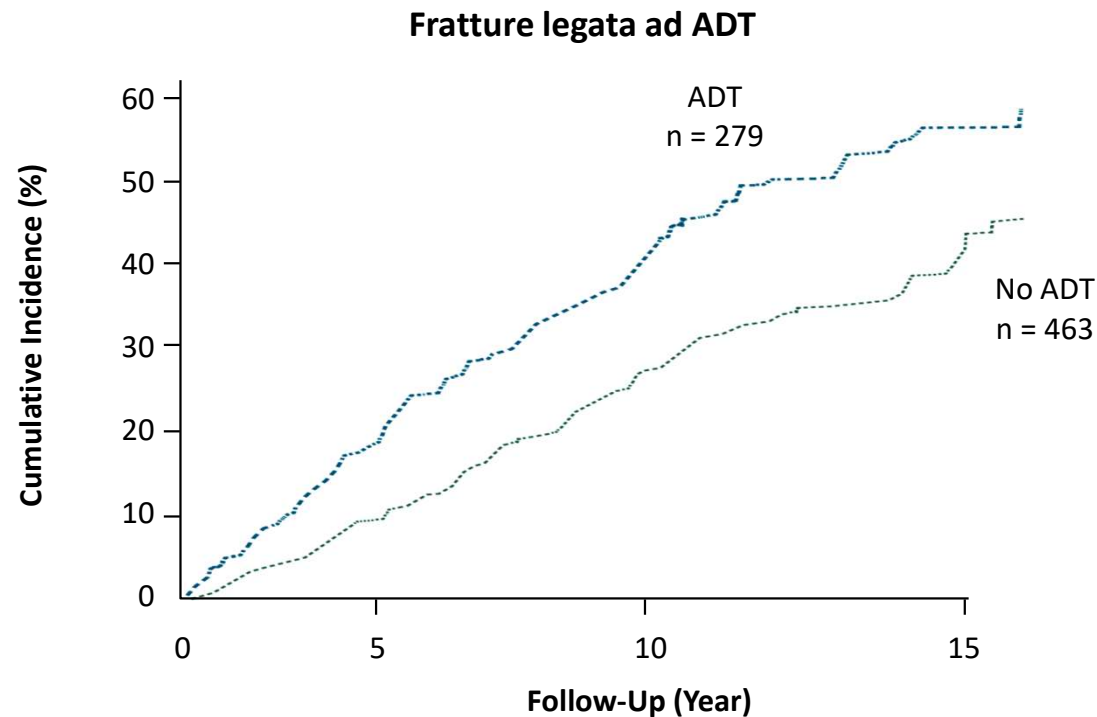
If we would perform a DXA scan of a bridge, we measure the quantity of steel employed (density), but we don't learn anything about the solidity of the reticular structure. TBS provides these informations that BMD ignores.



Same BMD, but different TBS
Bridge 1 is solid
Bridge 2 will collapse



La terapia di deprivazione androgenica **aumenta il rischio** di fratture



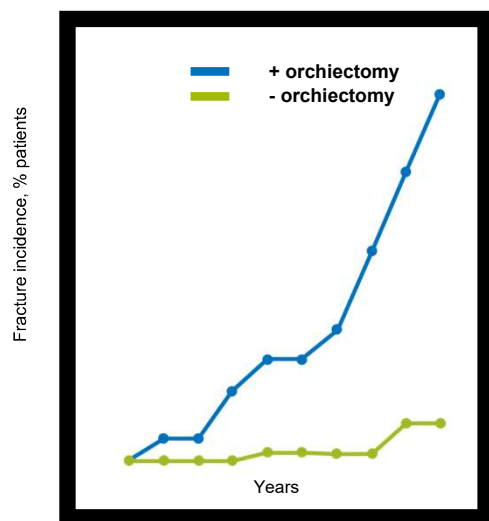
Negli uomini che hanno ricevuto ADT, c'era un aumento del rischio del 70% di una frattura osteoporotica (HR = 1.7; IC 95%: 1.1-2.6)

ADT = terapia di privazione degli androgeni; CI = intervallo di confidenza; HR = hazard ratio.

Dati da uno studio di coorte retrospettivo basato sulla popolazione di 742 Olmsted County, MN, uomini con cancro alla prostata diagnosticato per la prima volta nel 1990-1999 che fu seguito per 6.821 anni-persona.

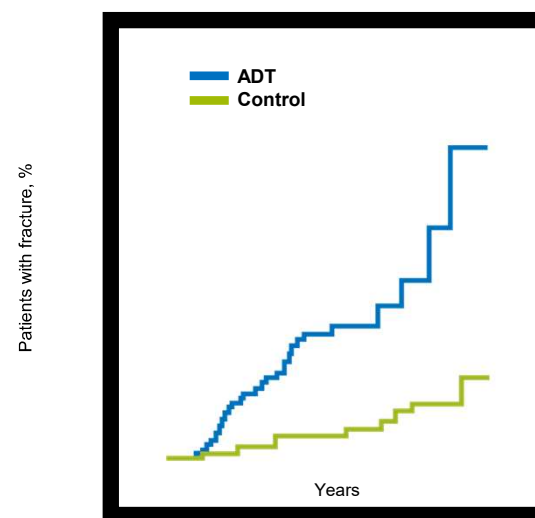
Il rischio fratturativo è particolarmente **precoce** rispetto all'inizio del blocco androgenico

Osteoporosis after orchiectomy



Mod. da [Daniell HW. J Urol 1997; 157: 439-444](#)

Kaplan-Meier plots of patients with fractures after ADT (patient group) or diagnosis (control group)



Mod. da [Lopez AM, et al. Osteoporos Int. 2005; 16: 707-711](#)

Le fratture si verificano molto precocemente rispetto all'inizio della terapia antiandrogenica. Si verificano già nel primo o secondo anno, quindi in un momento in cui spesso non si è ancora verificata un'importante perdita di massa ossea. Ciò ha due conseguenze: la prima è che le fratture non sono attese e la seconda che è necessaria una terapia in prevenzione primaria.

Il rischio di frattura associato a **vari tipi** di ADT

	Adjusted OR (95% CI) any fracture ^a	Adjusted OR (95% CI) accidental fracture ^a	Adjusted OR (95% CI) hip fracture ^a
No ADT	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
GnRH agonists + anti-androgens	3.48 (3.07–3.96)	1.60 (1.36–1.88)	1.82 (1.39–2.38)
GnRH agonist only	1.33 (1.09–1.63)	1.17 (0.93–1.47)	1.70 (1.19–2.42)
Anti-androgen only	2.11 (1.72–2.59)	1.37 (1.07–1.77)	1.81 (1.24–2.63)
Orchiectomy alone	2.54 (1.76–3.66)	2.18 (1.43–3.33)	1.88 (0.96–3.67)
Orchiectomy + pharmacologic ADT	4.32 (3.34–5.58)	1.39 (0.93–2.07)	1.59 (0.86–2.93)

New Zealand Cancer Registry, National Minimal Dataset, Pharmaceutical Collection and Mortality Collection, studiati 25.544 uomini (di età maggiore di 40 anni) con diagnosi di carcinoma della prostata tra il 2004 e il 2012.

L'ADT: ormone gonadotropina (GnRH), anti-androgeni, blocco combinato degli androgeni (agonisti GnRH più anti-androgeni), orchiectomia bilaterale e orchiectomia bilaterale più ADT farmacologico (antiandrogeni e/o agonisti GnRH).

Tra i pazienti che hanno ricevuto ADT, il 10,8% ha avuto una frattura rispetto al 3,2% di quelli che non hanno ricevuto L'ADT ($p < 0,0001$).

L'uso dell'ADT è stato associato a un aumento significativo del rischio di frattura con una OR del 2,83 e di frattura dell'anca, che richiedeva il ricovero in ospedale Odd Ratio del 1,82

Tutte le varie tipologie e combinazioni di ADT determinano un incremento del rischio di frattura.

Coloro che hanno ricevuto il blocco combinato degli androgeni e l'orchiectomia bilaterale con ADT farmacologico hanno avuto il maggior rischio di frattura.

La terapia di deprivazione androgenica (ADT) determina **riduzione** **di sopravvivenza libera da fratture**

ORIGINAL ARTICLE

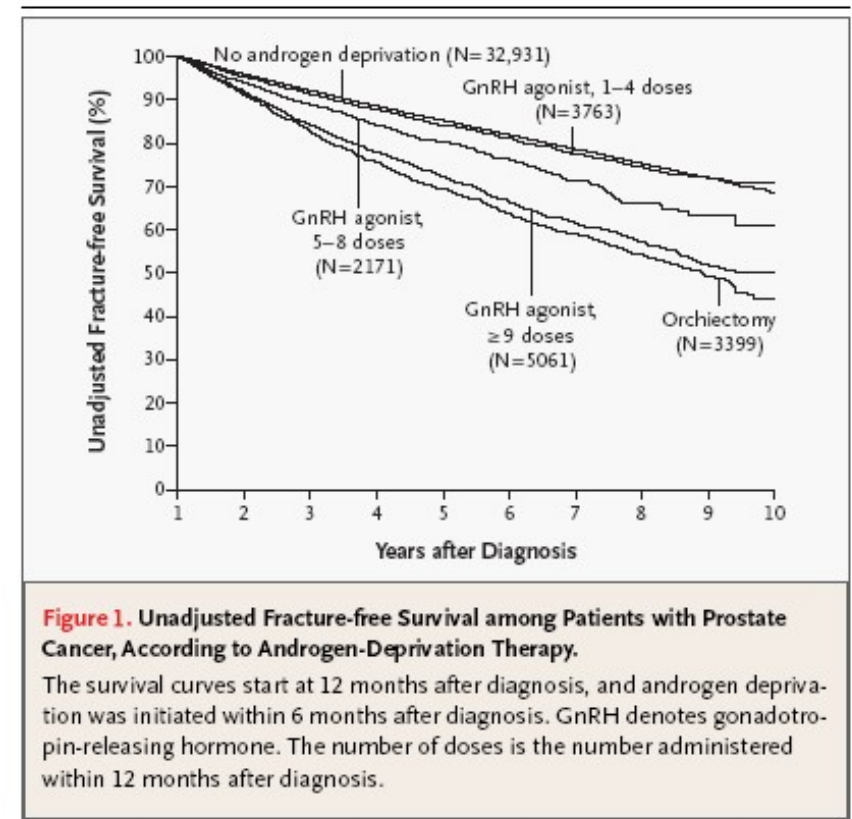
Risk of Fracture after Androgen Deprivation for Prostate Cancer

Vahakn B. Shahinian, M.D., Yong-Fang Kuo, Ph.D., Jean L. Freeman, Ph.D.,
and James S. Goodwin, M.D.

- Negli uomini che sopravvivono almeno 5 anni dopo la diagnosi:
 - Tra quelli che hanno ricevuto ADT, il 19,4% ha riportato una frattura
 - Di quelli che non hanno ricevuto ADT, il 12,6% ha riportato una frattura
 - L'ADT ha comportato un eccesso di rischio di frattura del 45%

Dati da uno studio osservazionale che valuta il rischio di fratture di 50.613 uomini elencati nei database Surveillance, Epidemiology e End (SEER) - Medicare linked database. I pazienti inclusi erano quelli che hanno ricevuto una diagnosi di cancro alla prostata nel periodo dal 1992 al 1997 e sono stati seguiti fino al 2001.

ADT = terapia di privazione degli androgeni; GnRH = ormone rilasciante gonadotropina



Shahinian VB, et al. *N Engl J Med.* 2005;352:154-164.

ESMO Open Bone health management in the continuum of prostate cancer disease: a review of the evidence with an expert panel opinion

Daniele Santini¹, Alfredo Berruti², Massimo Di Majo³, Giuseppe Procopio⁴, Sergio Bracarda⁵, Toni Ibrahim⁶, Francesco Bertoldo⁷

Open access

Table 3 Rate of non-pathological fractures in phase III trials of NHT by setting, grade (all and 3–4) and treatment arm (NHT vs placebo)

Trial	Non-pathological fractures			
	All grade (%)		Grades 3–4 (%)	
	NHT	Placebo	NHT	Placebo
<i>M0 CRPC</i>				
SPARTAN (Apa, n=806; placebo, n=401) ⁴⁹	11.7	6.5	2.7	0.8
PROSPER (Enza, n=933; placebo, n=468) ¹⁰⁵	11.0	4.1	1.3	0.6
<i>M1 CRPC</i>				
Post-CT				
COU-AA-301 (AAP, n=791; placebo, n=394) ¹⁰⁶	5.9	2.3	1.4	0.0
AFFIRM (Enza, n=800; placebo, n=399) ¹⁰⁵	4.0	0.8	1.4	0.3
Pre-CT				
PREVAIL (Enza, n=871; placebo, n=844) ¹⁰⁵	8.8	3.0	2.1	1.1
EORTC 1333/PEACE III (Enza+Rad-223, n=38; Enza, n=38) ⁸²	*12.4			
ERA-223 (AAP+Rad-223, n=401; vs AAP+placebo, n=405) ^{30†}	11			

Only currently approved agents are reported.

*The rate reported refers to the 1-year cumulative incidence of non-pathological fractures in the Enza arm.

†The rate reported refers to the rate of non-pathological fractures in the AAP+placebo arm.

AAP, abiraterone acetate plus prednisone; Apa, apalutamide; M0 CRPC, non-metastatic castration-resistant prostate cancer; M1 CRPC, metastatic castration-resistant prostate cancer; CT, chemotherapy; Enza, enzalutamide; NHT, novel hormone therapy.

Rischio fratturativo in corso di ADT in base all'età e alla durata della deprivazione androgenica

Age, Yrs	Gonadotropin-Releasing Hormone Agonist			Orchiectomy
	1-4 Doses	5-8 Doses	≥ 9 Doses	
	<i>No. Needed to Harm (95% CI)</i>			
66-69	74 (50-146)	42 (29-73)	18 (16-24)	15 (13-18)
70-74	69 (46-146)	39 (27-71)	17 (15-20)	14 (12-17)
75-79	61 (41-125)	34 (24-61)	15 (14-17)	13 (11-15)
≥ 80	46 (32-91)	26 (19-45)	12 (11-13)	10 (9-11)

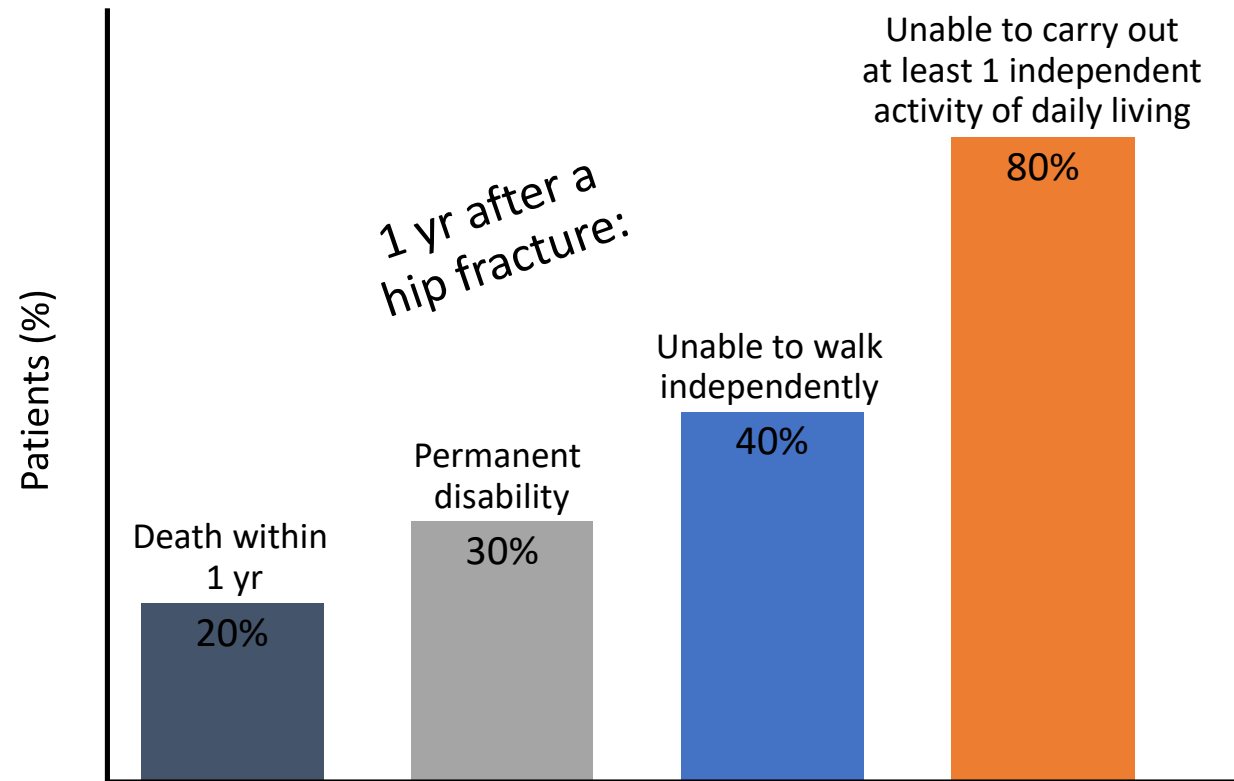
Estimated number needed to harm for the occurrence of any fracture within 12- 60 mos after diagnosis, according to age and extent of androgen deprivation.

Le fratture osteoporotiche sono associate a morbidità

Fratture Vertebrali

- Prevalenza 12-20% (O'Neill et al. J Bone Miner Res. 1996)
- Associate a dolore, disabilità, dipendenza (Matthis et al. Osteoporosis Int. 1998)
- Molte sono asintomatiche anche se clinicamente rilevanti:
 - Predicono nuove fratture (Lau et al. J Bone Joint Surg Am. 2008)
 - Predicono mortalità a 10-anni: HR 2.4

Tutte le fratture sono associate a **morbidity**



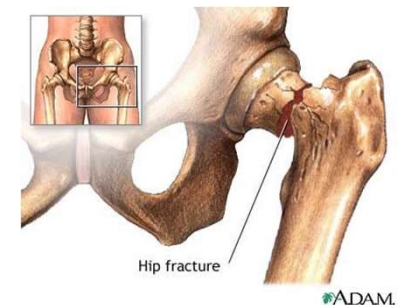
Le fratture osteoporotiche sono associate a mortalità

Hip Fracture

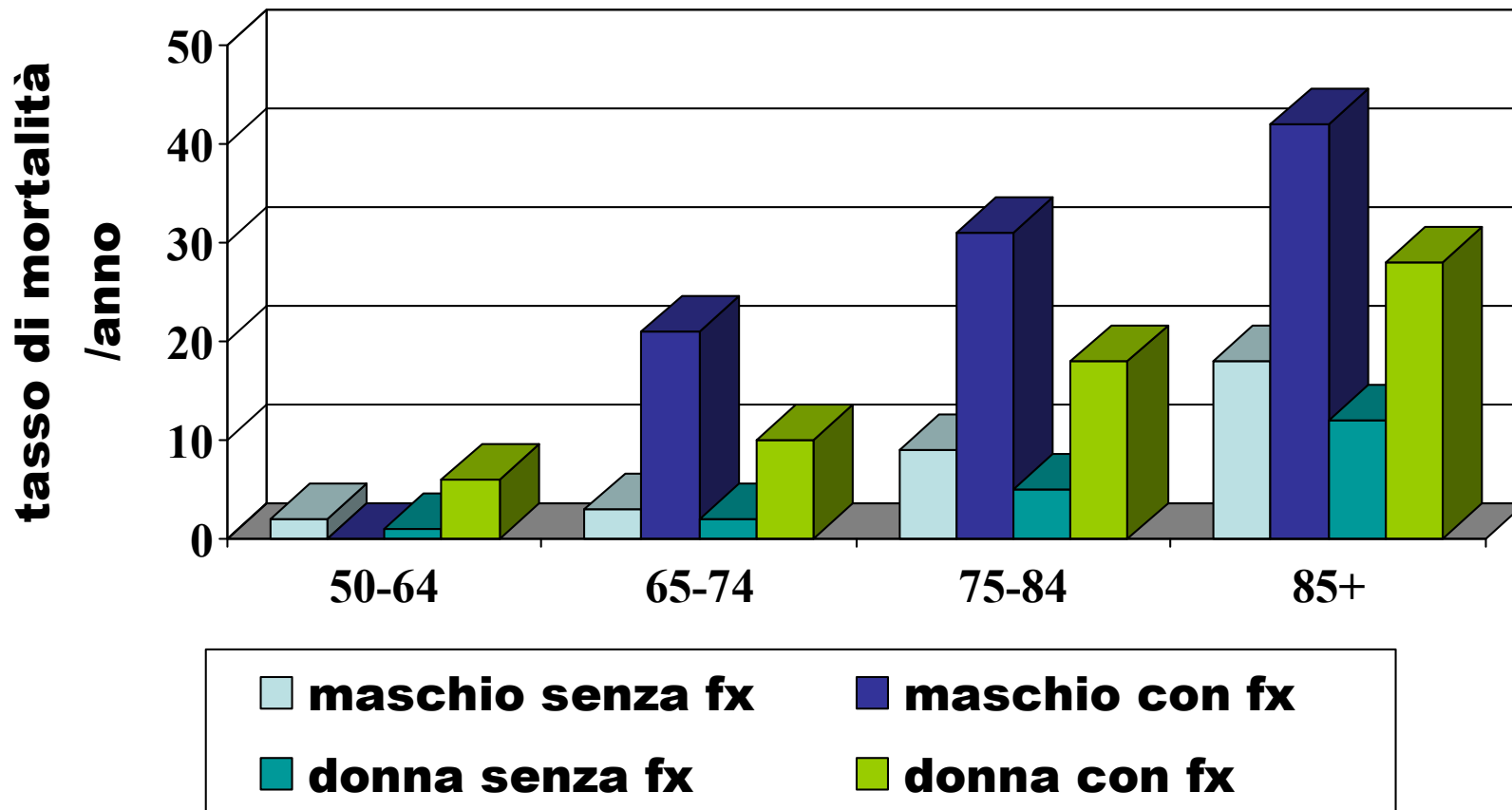
Mortality of hip fracture is greater in men than in women:

1-year mortality for hip fracture in men is 30-35% vs. 17% in women (Campion et al. Am Fam Physician. 2003)

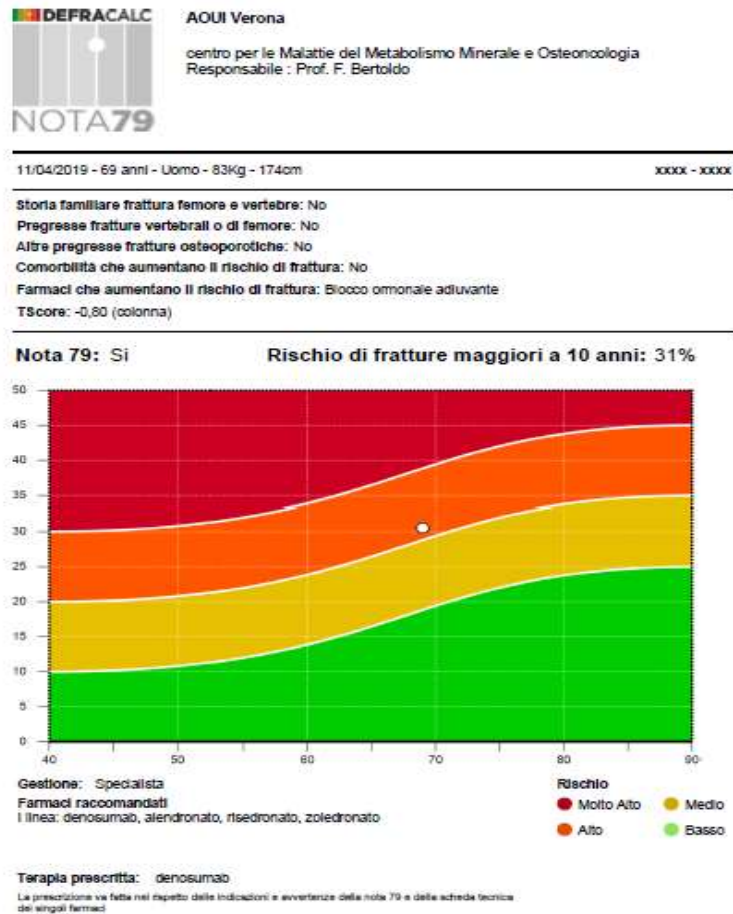
Men are twice as likely to die in hospital after hip fracture (Myers et al. Am J epidemiol. 1991)



Le fratture osteoporotiche sono associate a mortalità

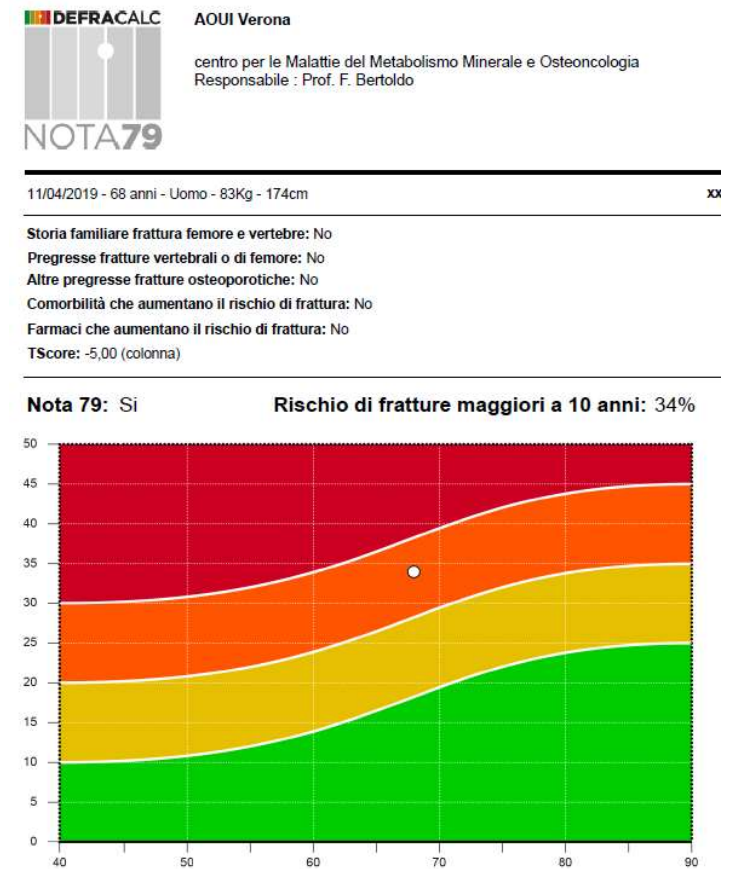


RISCHIO FRATTURA 31%



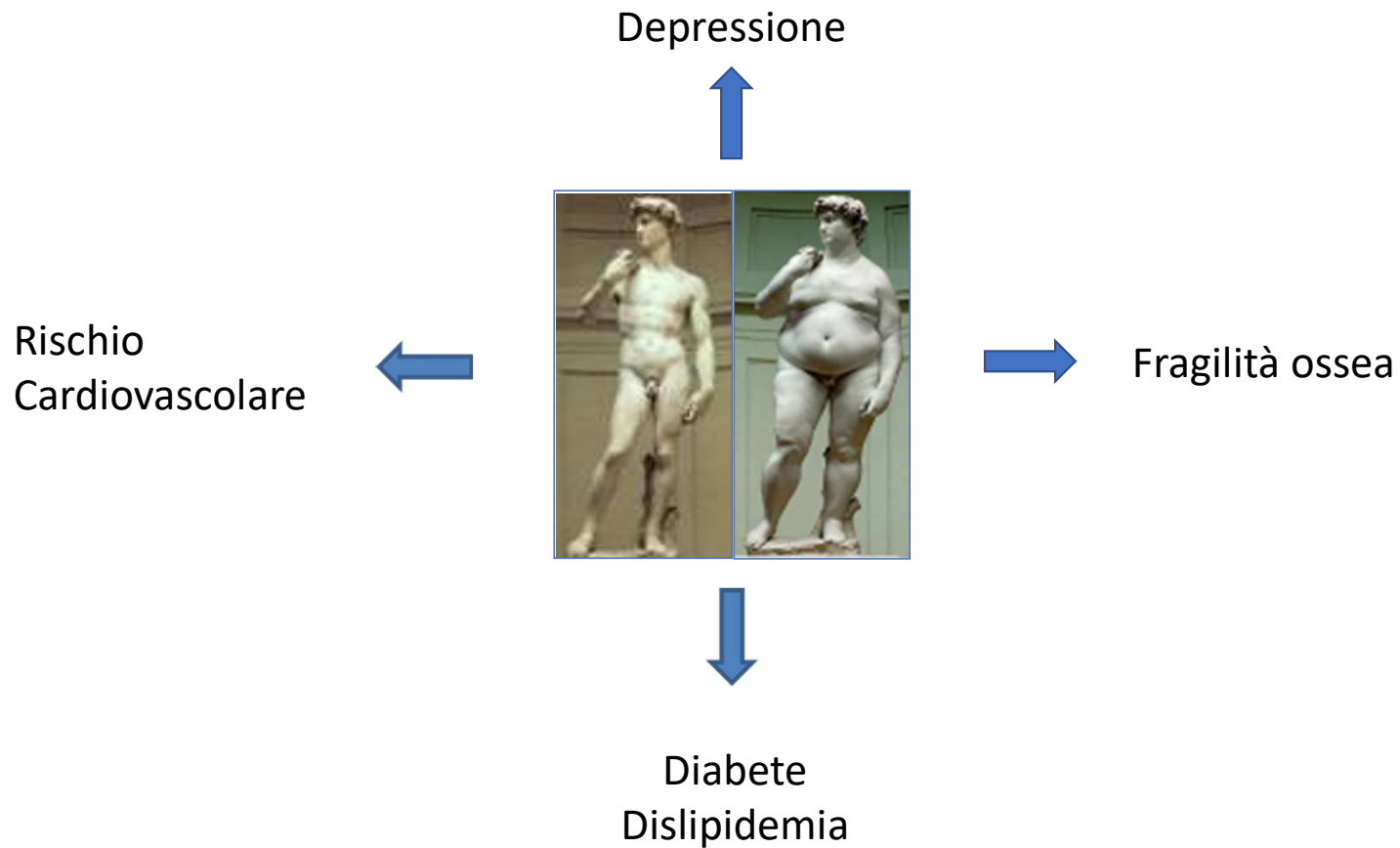
BMD T-score: -0.8

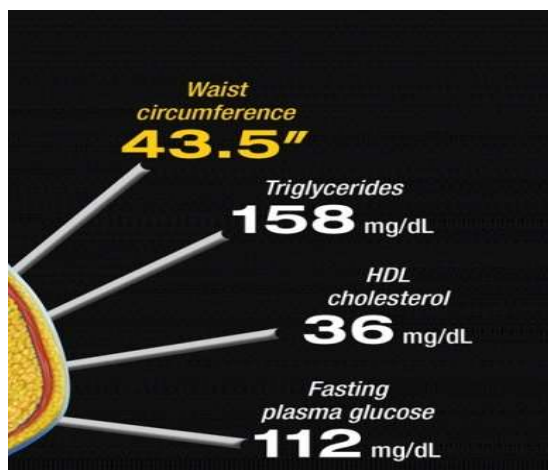
34%



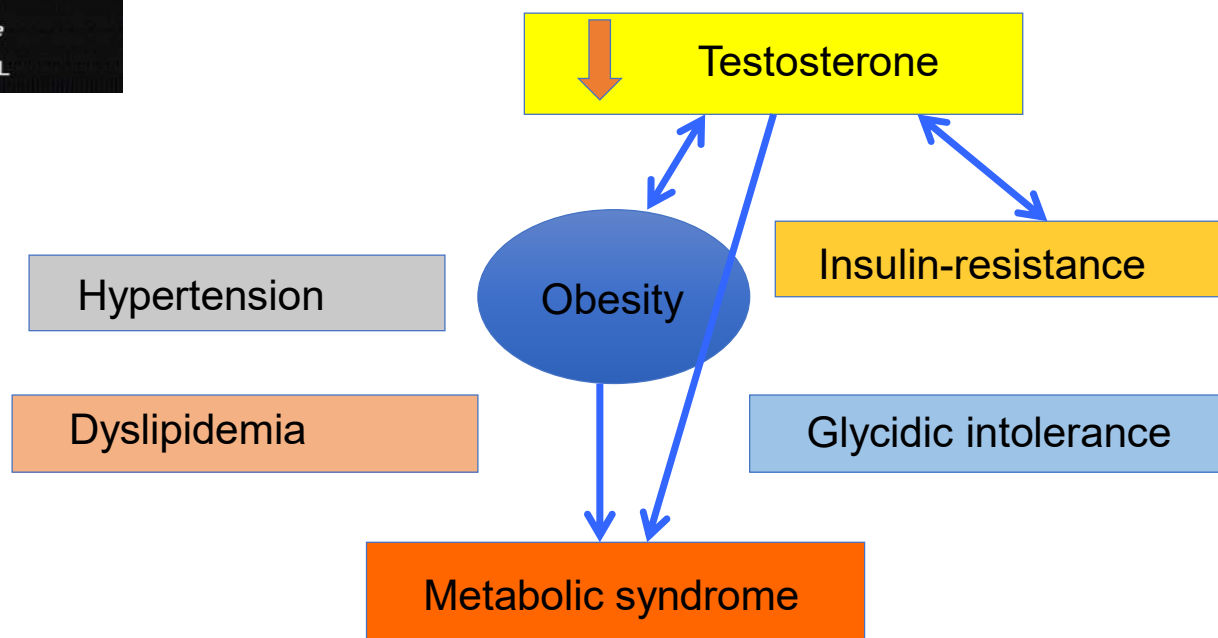
-5

Terapia ormonale e qualità della vita: **più facce** della stessa medaglia

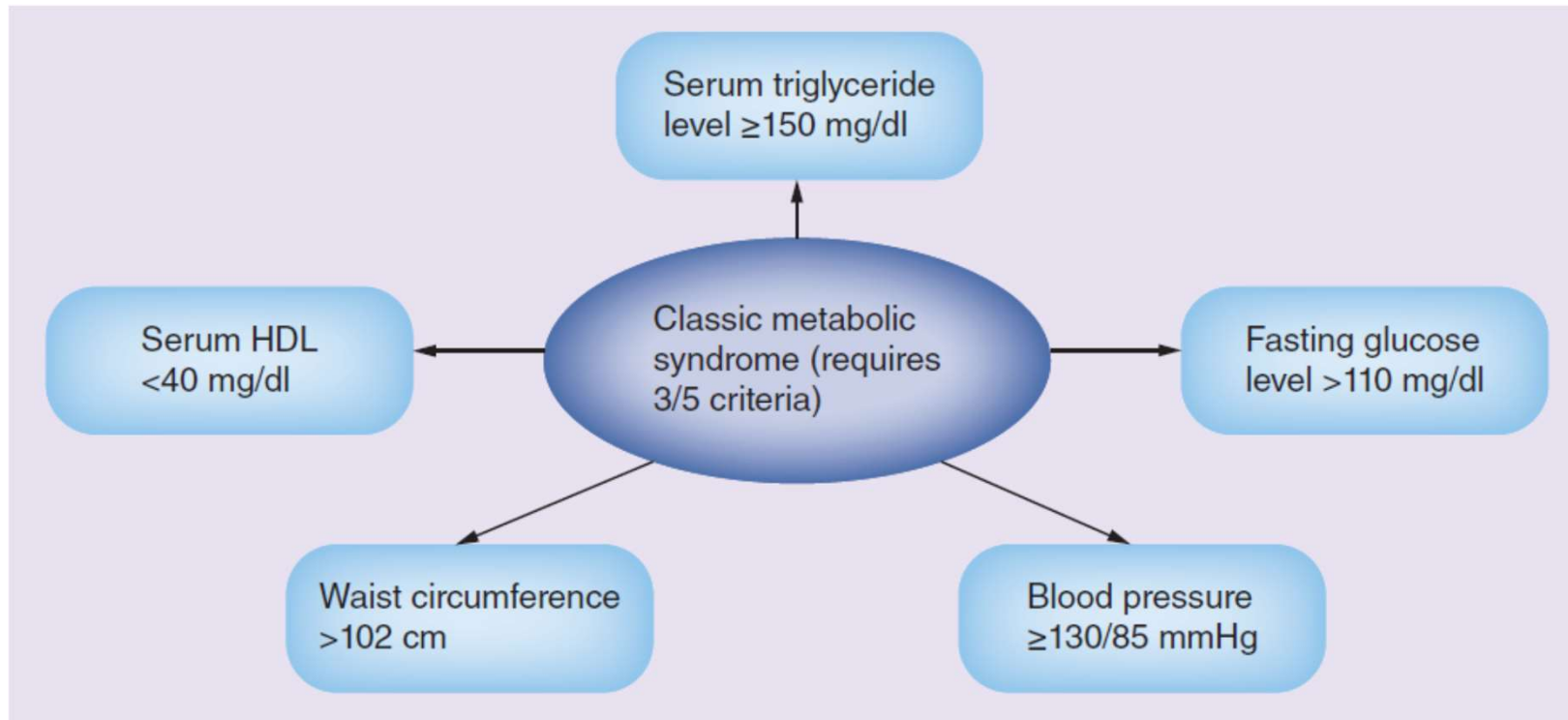




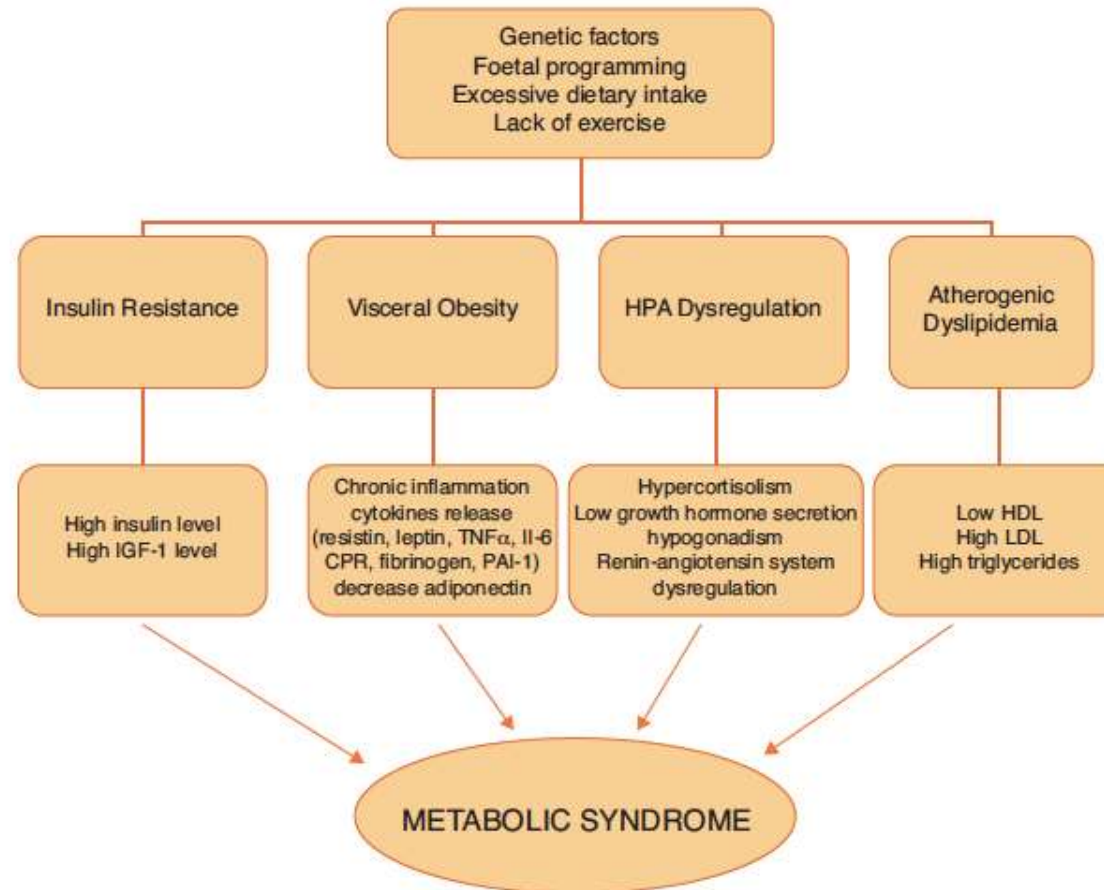
Ipogonadismo e sindrome metabolica



Criteri per definire la sindrome metabolica



Fisiopatologia della sindrome metabolica



Sindrome Metabolica

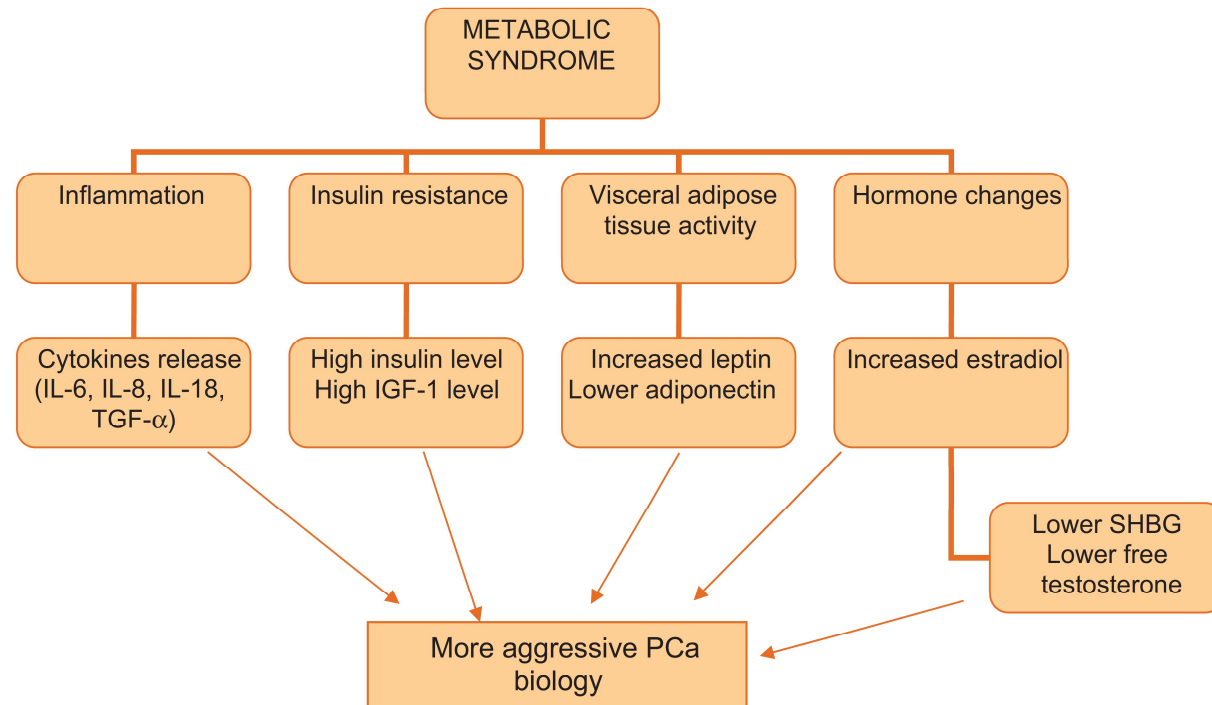
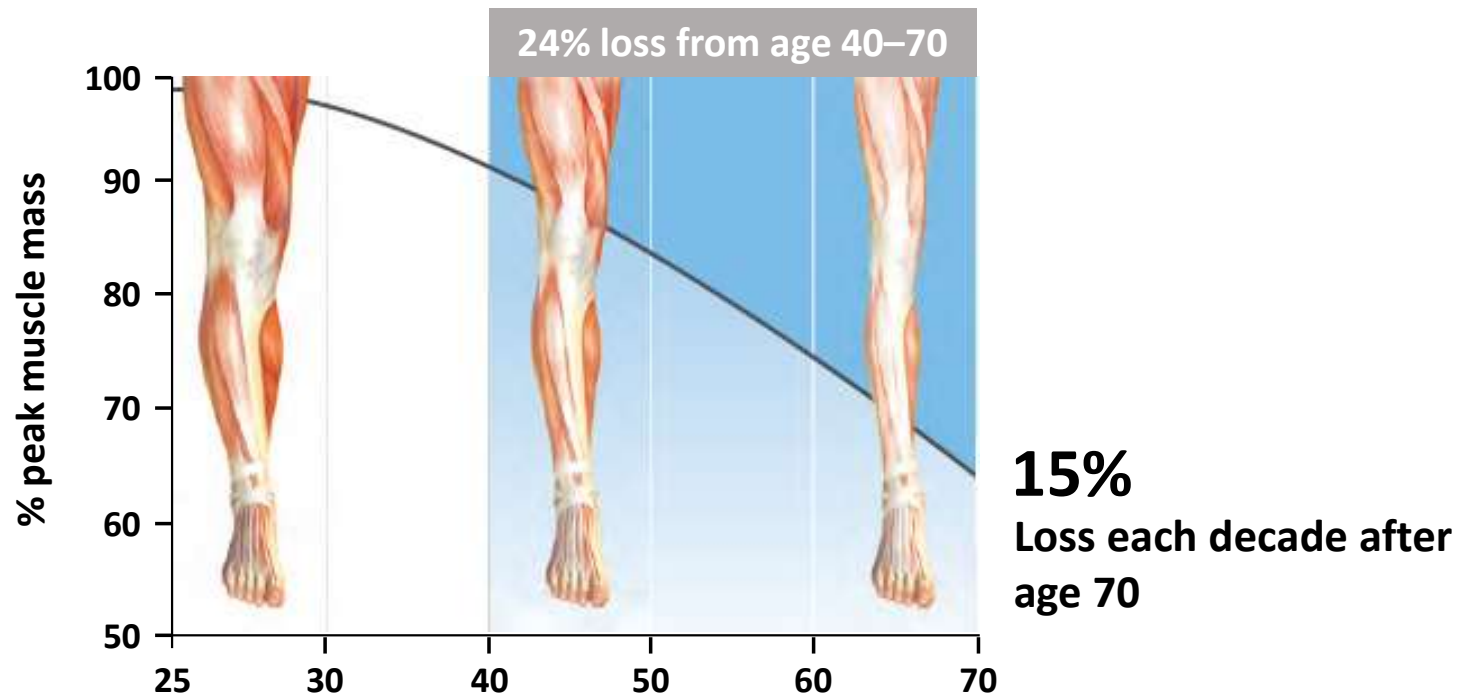


Fig. 4 – Biologic hypothesis for prostate cancer aggressiveness in relation to metabolic syndrome.

IL = interleukin; TGF- α = transforming growth factor- α ; IGF-1 = insulinlike growth factor 1; SHBG = sex hormone-binding globulin; PCa = prostate cancer.

Loss of muscle mass and strength, a natural part of aging

- After age 40, healthy adults can lose 8% of muscle every 10 years
- Between 40 to 70 years old, healthy adults lose an average of 24% of muscle



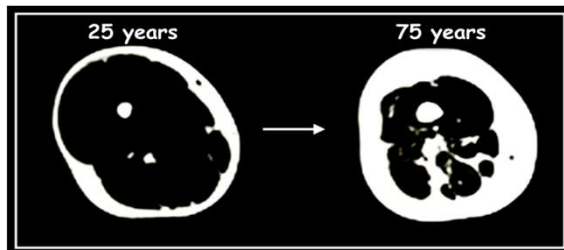
REPORT

Sarcopenia: European consensus on definition and diagnosis

Report of the European Working Group on Sarcopenia in Older People
ALFONSO J. CRUZ-JENTOFT¹, JEAN PIERRE BAEYENS², JÜRGEN M. BAUER³, YVES BOIRIE⁴,
TOMMY CEDERHOLM⁵, FRANCESCO LANDI⁶, FINBARR C. MARTIN⁷, JEAN-PIERRE MICHEL⁸,
YVES ROLLAND⁹, STÉPHANE M. SCHNEIDER¹⁰, EVA TOPINKOVÁ¹¹, MAURITS VANDEWOUDE¹²,
MAURO ZAMBONI¹³

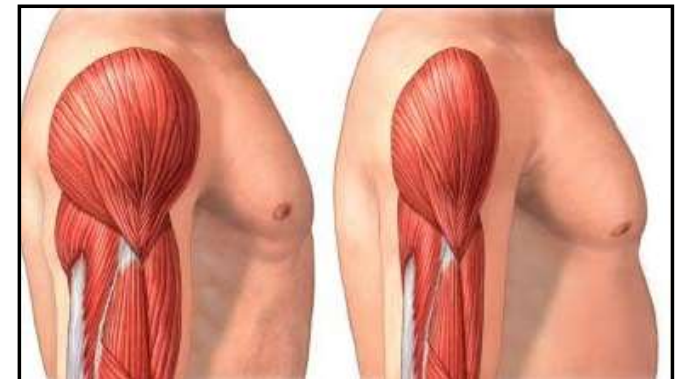


AGING



Sarcopenia

“Sarcopenia is a (geriatric) syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength (and/or function) with a risk of adverse outcomes such as physical disability, poor quality of life and death”



Courtesy of
G. Colloca

ADT induce perdita precoce di massa muscolare, con aumento della fatigue e del rischio di cadute

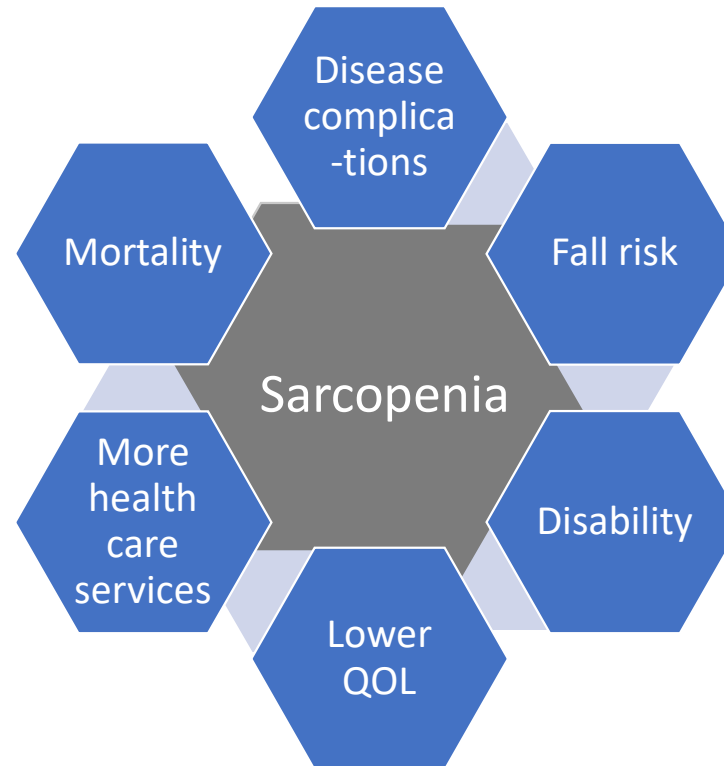
Changes in BMD and Body Composition^a

Outcome	Baseline	Mo 12	Percent change	P value
BMD total hip	0.995 ± 0.136	0.977 ± 0.138	-1.9 ± 2.7%	< 0.001
Percent lean mass	69.7 ± 4.7	68.2 ± 4.8	-2.0 ± 3.3%	< 0.001
Percentage fat mass	27.1 ± 4.9	28.8 ± 5.0	6.6 ± 9.4%	< 0.001

BMD: bone mineral density.

^a Values are shown as the means ± standard deviation.

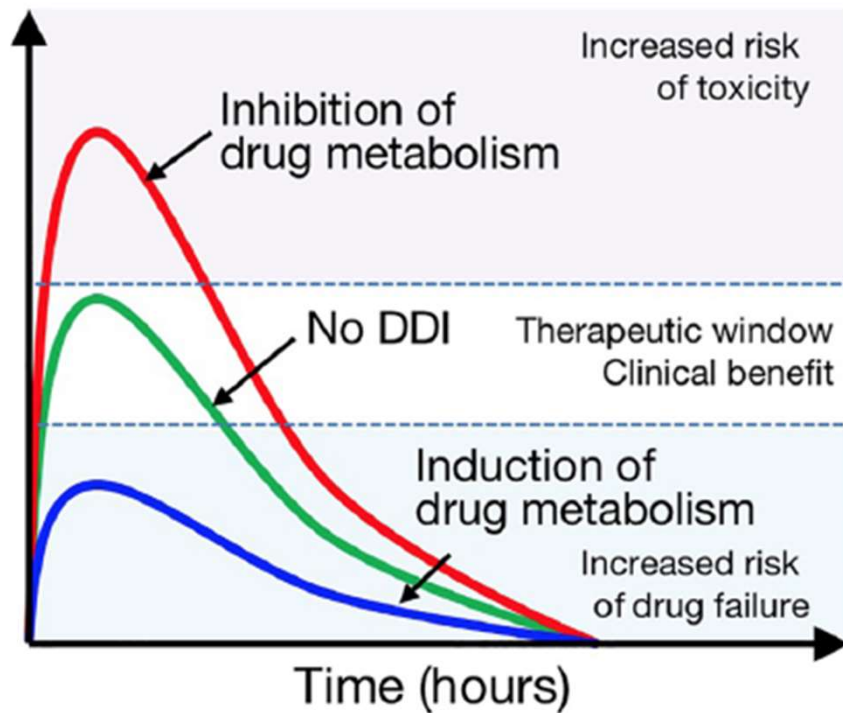
La sarcopenia è associata a numerosi possibili eventi avversi



- 1.Sayer A. In: *Sarcopenia*. John Wiley & Sons, Ltd; 2012.
- 2.Janssen I, et al. *J Am Geriatr Soc*. 2002;50:889-896.







Courtesy of G. Colloca

PK overview of DDIs effect



Drug-drug interactions may further reduce the safety drugs with **narrow therapeutic index** (e.g., anticancer and immunosuppressants, opioid analgesics, selected cardiovascular medications, anticoagulants - warfarin).

Drug-drug interactions - Cardiovascular

ADT	Substrate - metabolism	Induction/ inhibition	DDI effect	Concomitant drug	Substrate - metabolism	DDI effect
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	✓	Dabigatran	CES1, CES2, UGT1A9, 2B7, 2B15, PgP	✓
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	✗ Victim			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	✓			✓
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	Perpetrator 	Apixaban	CYP3A4/5, 1A2, 2C8, 2C9, 2C19, 2J2, PgP, BCRP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	Perpetrator 			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	Perpetrator 			✗ Victim
Apalutamide	CYP2C8, 3A4	Inducer of CYP3A4, 2D6, 2C9, 2C19	Perpetrator 	Rivaroxaban	CYP3A4, 3A5, CYP2J2, PgP, BCRP	✗ Victim
Darolutamide	CYP3A4, UGT1A9, 1A1, 1A3, 2B10	Inhibitor of BCRP, PgP, OATP1B1, OATP1B3	Perpetrator 			✗ Victim
Enzalutamide	CYP2C8	Inducer of 3A4, 2D6, 2C9, 2C19	Perpetrator 			✗ Victim

By Marzia Del Re

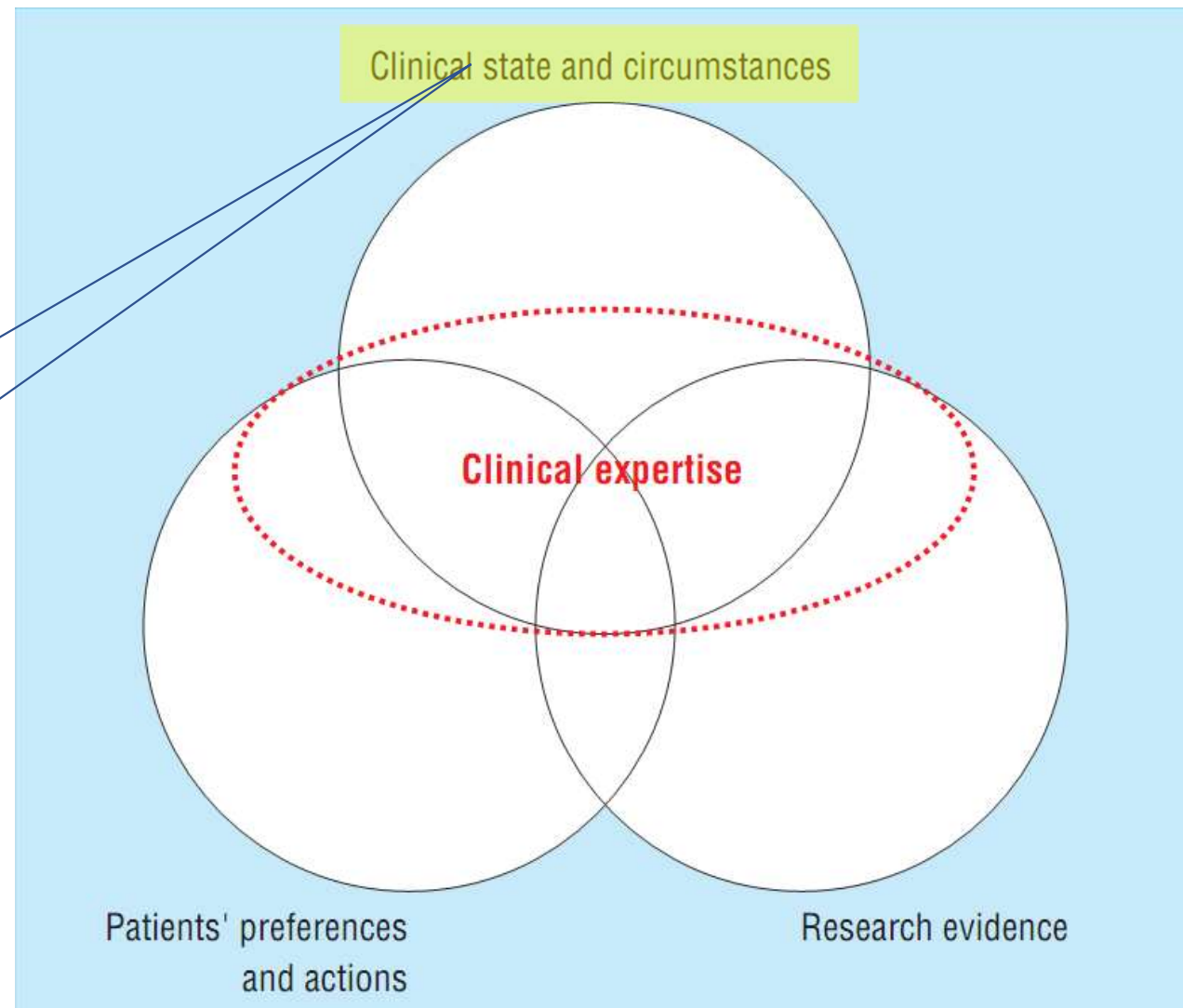
Physicians' and patients' choices in evidence based practice

Evidence does not make decisions, people do

R Brian Haynes *BMJ* 2002;324:1350

Gli esperti che ci affiancano ci aiuteranno a decidere come costruire strategie efficaci: aspettiamo buone notizie

La *proposta terapeutica* deve tenere conto delle condizioni cliniche, dei possibili effetti collaterali delle terapie e delle possibili interazioni farmacologiche



Courtesy G.L. Pappagallo











