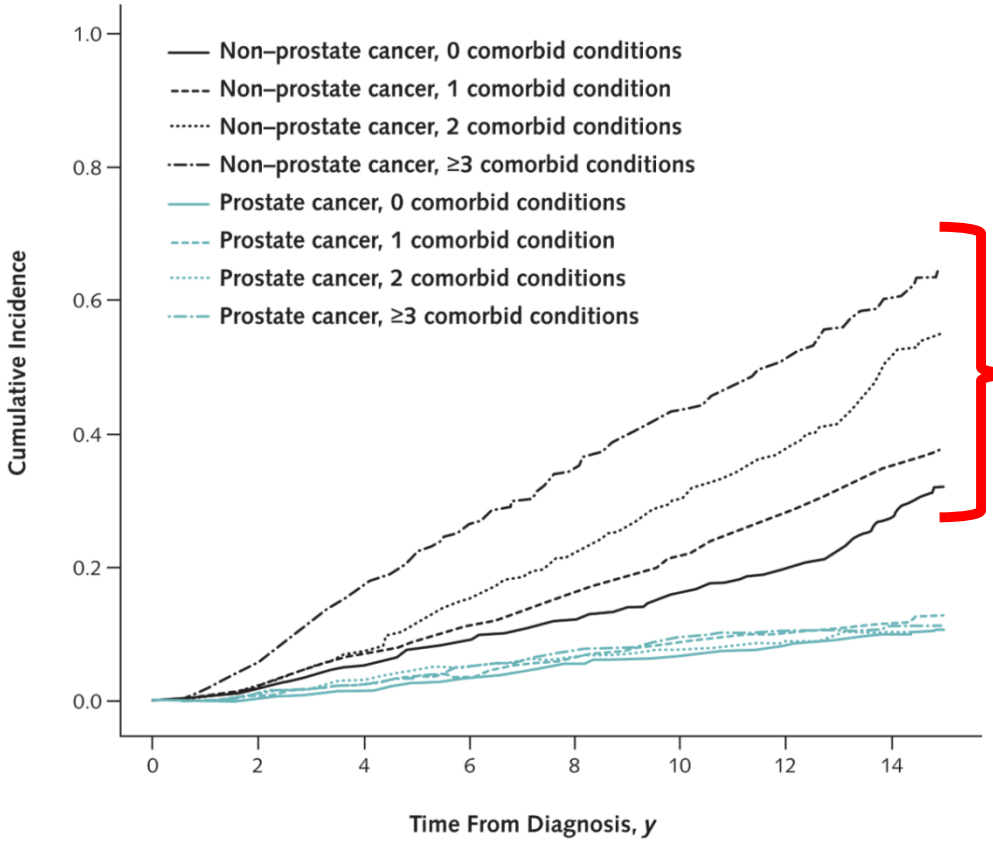
Cardiotossicità da terapia ormonale nel Paziente con Carcinoma della Prostata

Luigi Tarantini – Ospedale “San Martino” Belluno

Perché un Cardiologo ad un Congresso sulla gestione del paziente con Cancro della Prostata ?

Effect of Age, Tumor Risk, and Comorbidity on Competing Risks for Survival in a U.S. Population–Based Cohort of Men With Prostate Cancer



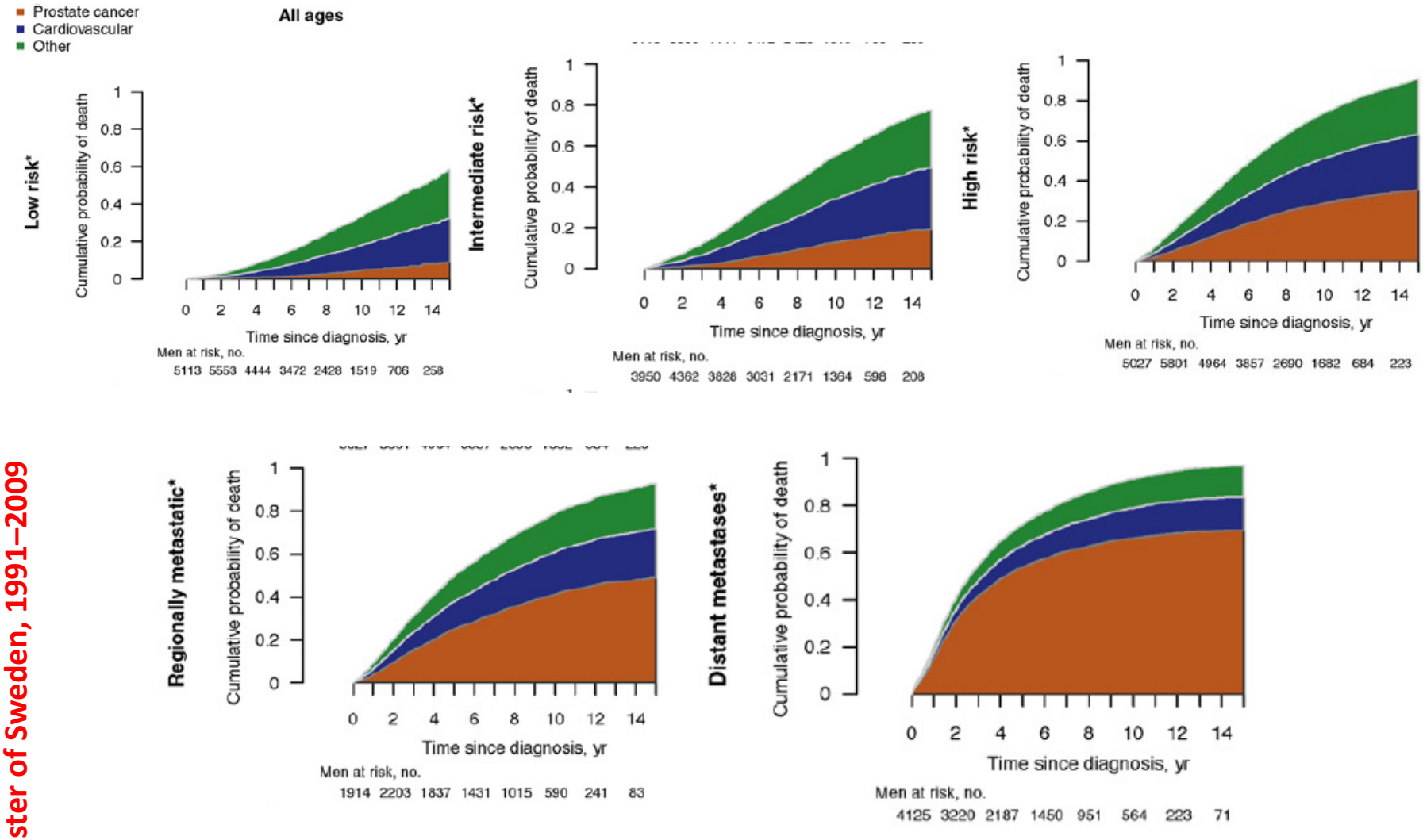
Mortalità non Correlata al tumore

Patients at risk, *n*								
0 comorbid conditions	1221	1192	1136	1057	994	928	855	308
1 comorbid condition	1020	989	922	866	783	703	623	218
2 comorbid conditions	523	511	467	416	373	323	273	84
≥3 comorbid conditions	419	388	335	287	241	194	157	52

Timothy J. Daskivich et Al. Ann Intern Med. 2013 May 21; 158(10): 709–717

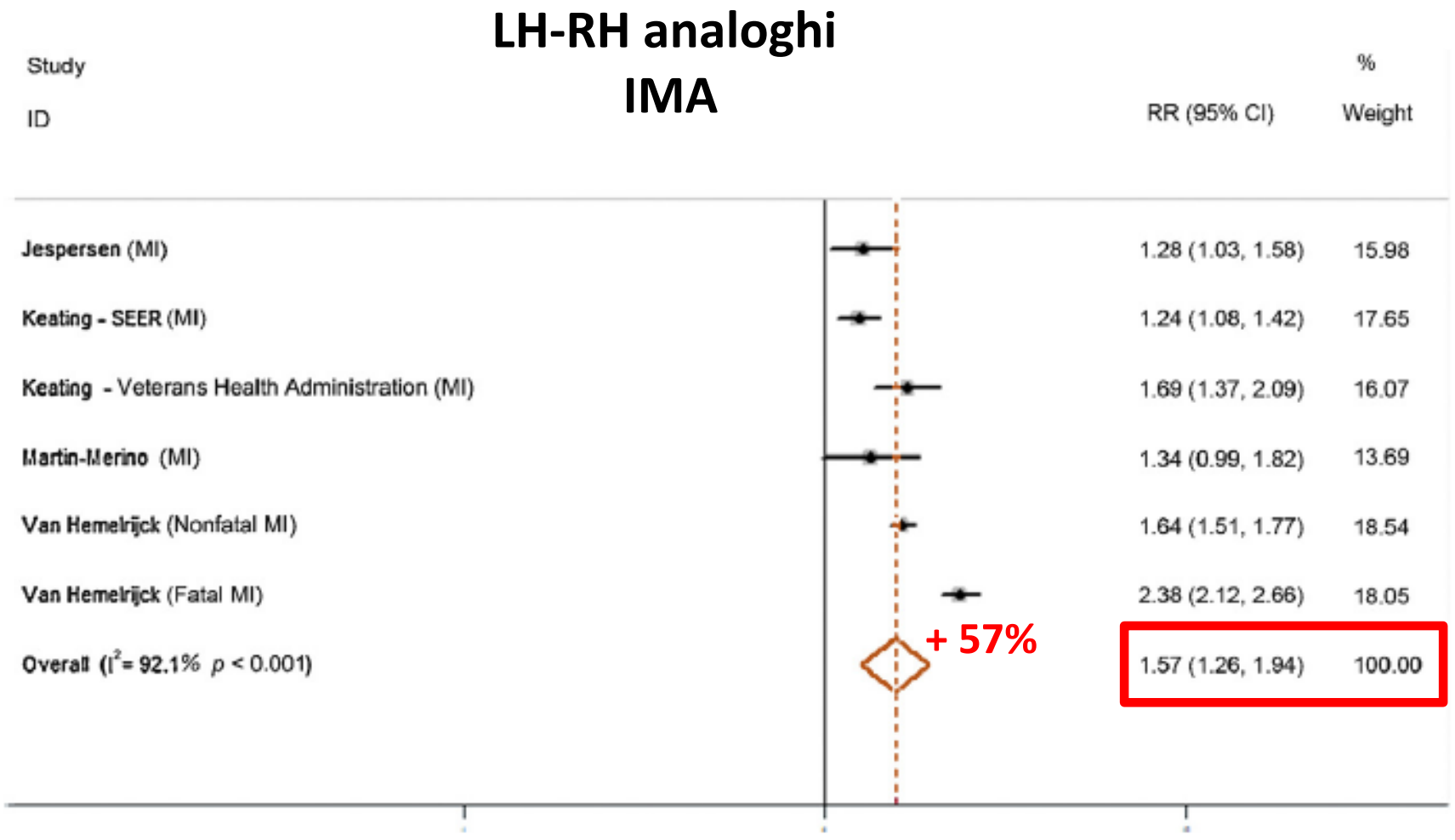
Long-term Outcomes Among Noncuratively Treated Men According to Prostate Cancer Risk Category in a Nationwide, Population-based Study

117 328 patients with prostate cancer in the National Prostate Cancer Register of Sweden, 1991–2009



Jennifer R. Rider et Al. EUROPEAN UROLOGY 6 3 (2 01 3) 8 8 – 9

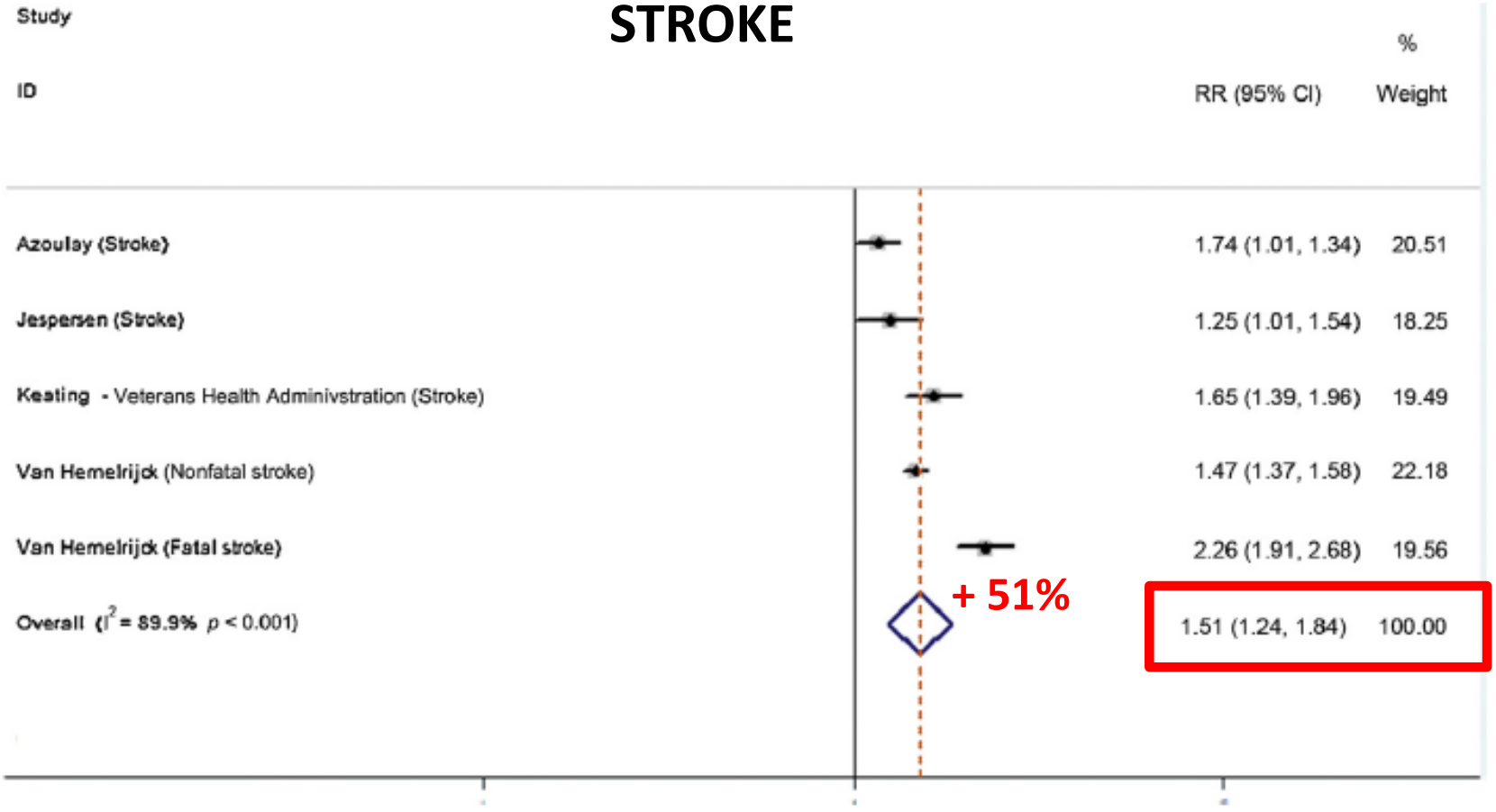
Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta-analysis



Bosco C. Euro Urol 2014

Quantifying Observational Evidence for Risk of Fatal and Nonfatal Cardiovascular Disease Following Androgen Deprivation Therapy for Prostate Cancer: A Meta-analysis

LH-RH analoghi
STROKE



Bosco C. Euro Urol 2014

What Do Prostate Cancer Patients Die Of?

Registro Svedese sui certificati di morte dei MMG: 686500 morti con 62500 paz. Con Ca prostata

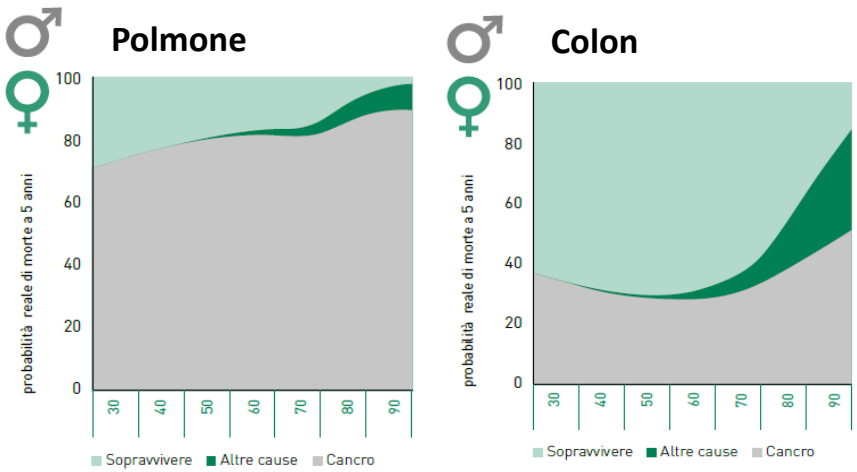
Table 1. HRs for dying from selected conditions when individuals were diagnosed with PC as their first cancer (n = 116,945) compared with all other men (n = 2,152,094)

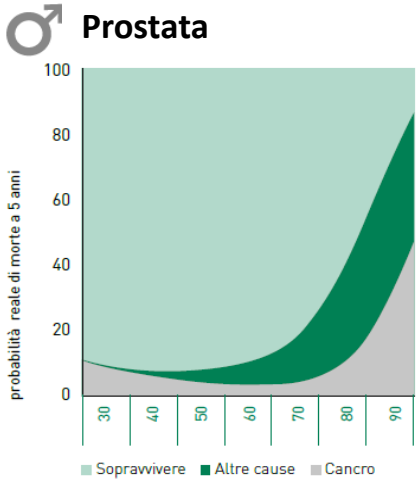
	Underlying cause of death				One of multiple causes of death			
Death cause	Death with PC	Death without PC	HR	95% CI	Death with PC	Death without PC	HR	95% CI
Myocardial infarction	5,693	110,945	1.01	0.98–1.04	6,902	126,381	**1.06**	1.04–1.09
Other coronary heart disease	3,909	65,615	**1.04**	1.01–1.08	9,284	144,697	**1.18**	1.15–1.20
Cerebrovascular accident	3,457	56,340	0.99	0.96–1.03	6,664	93,601	**1.14**	1.11–1.17
Arterial disease	1,453	24,752	0.97	0.92–1.02	5,059	82,634	1.02	0.99–1.05
Heart failure	1,421	15,393	**1.18**	1.11–1.24	10,422	113,598	**1.36**	1.34–1.39

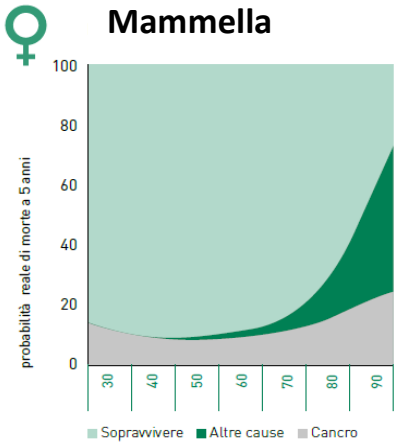
Boldface entries indicate significant HRs.

MATIAS RIIHIMÄKI et Al. The Oncologist 2011

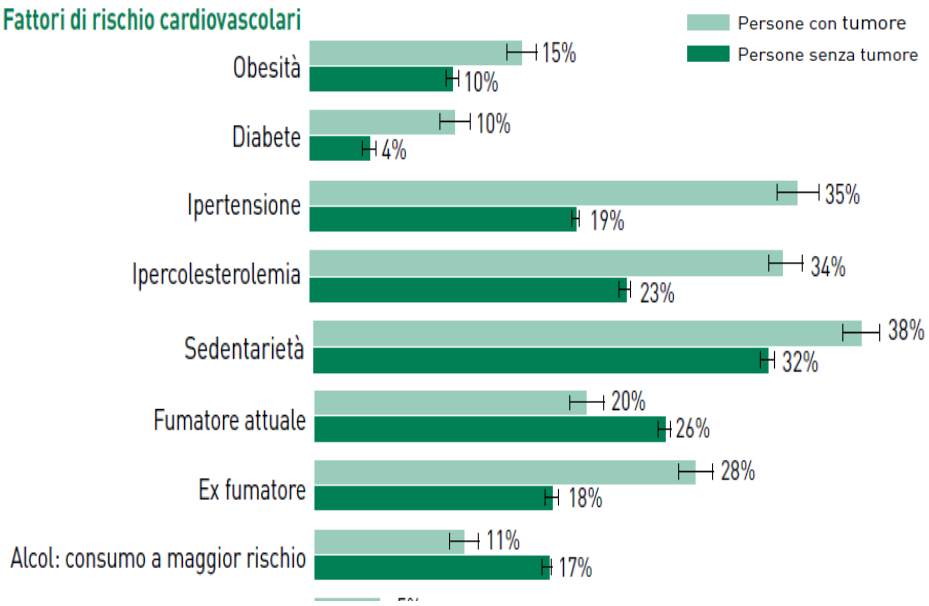
morte per tumore e per altre cause a 5 anni dalla diagnosi per età (stima 2005-2009)

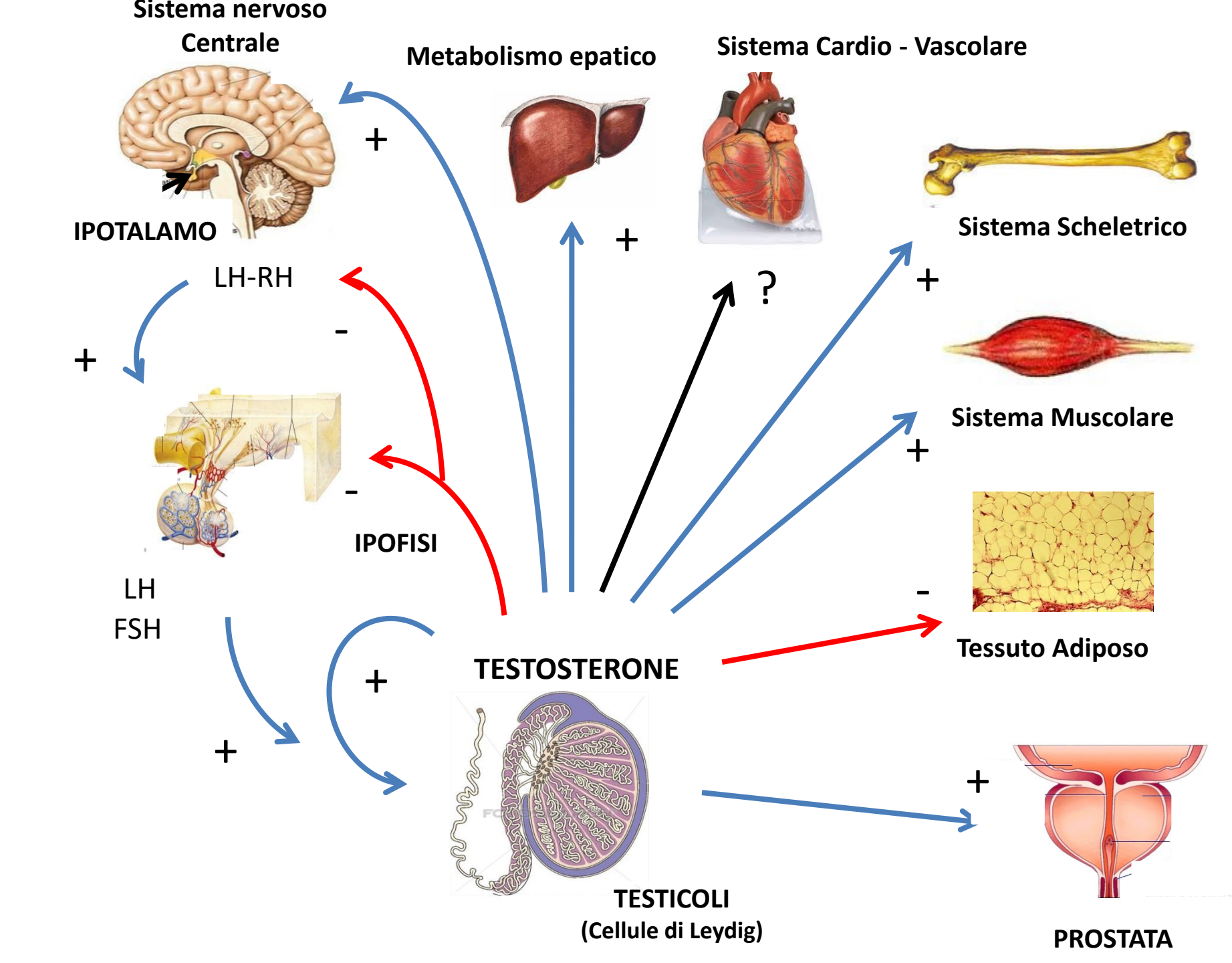






I fattori di rischio CV: confronto fra persone con e senza diagnosi di tumore.



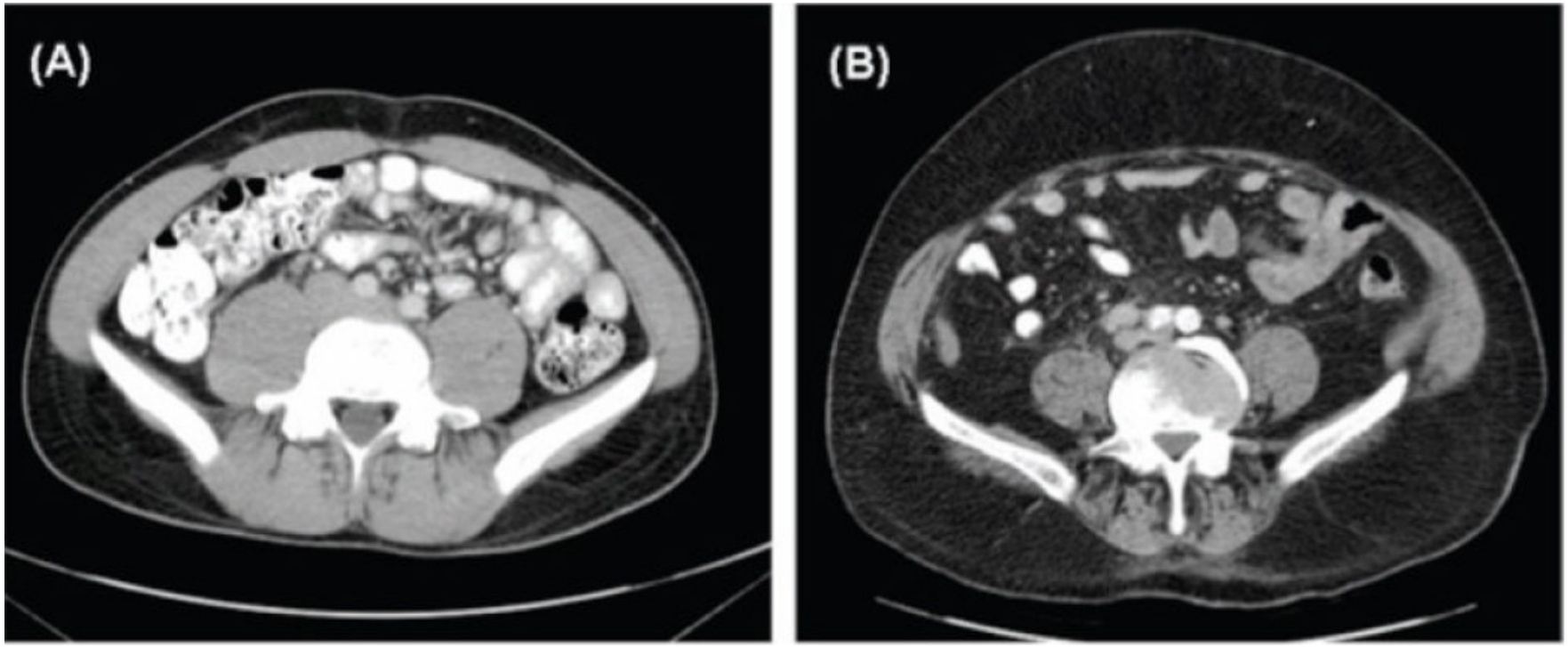

Sistema nervoso Centrale
Metabolismo epatico
Sistema Cardio - Vascolare
IPOTALAMO
LH-RH
+
+
+
?
+
Sistema Scheletrico
-
+
Sistema Muscolare
-
IPOFISI
+
LH
FSH
-
Tessuto Adiposo
TESTOSTERONE
+
+
+
TESTICOLI
(Cellule di Leydig)
PROSTATA

Segni e sintomi della sindrome da deficit di Testosterone

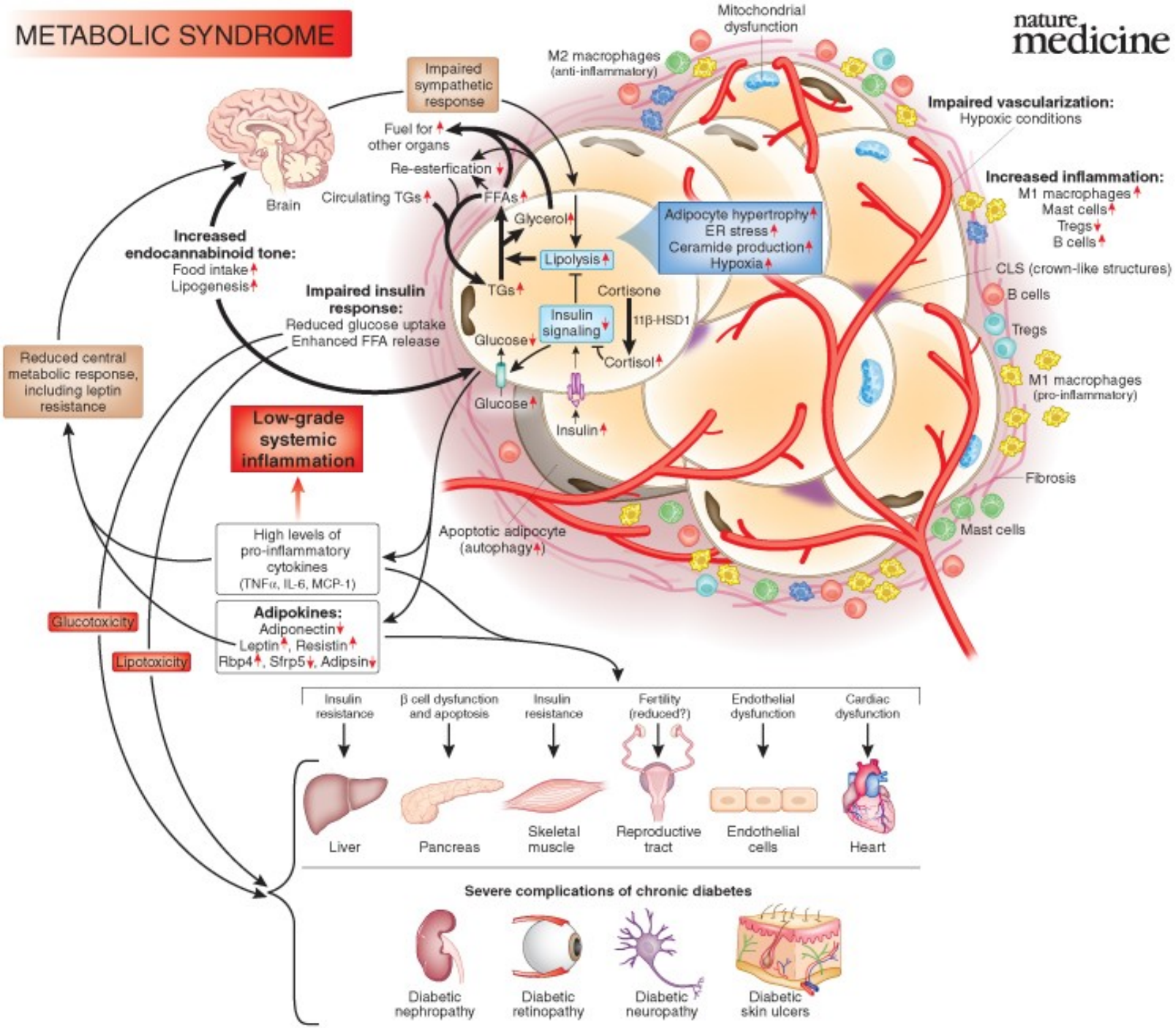
Segni e sintomi più specifici	Segni e sintomi meno specifici
Attività e desiderio sessuale ridotti	Riduzione nell'iniziativa, nella motivazione ed energia vitale
Riduzione delle erezioni spontanee	Umore depresso, Irritabilità
Perdita dei peli pubici, e della necessità di radersi	Scarsa concentrazione, riduzione nella memoria
Ridotte dimensioni dei testicoli	Sonnolenza e disturbi del sonno
Riduzione della densità ossea con tendenza alle fratture	Lieve anemia (normocromica e normocitica)
Riduzione della massa e della forza muscolare	Aumento della massa adiposa e del Body Mass Index
Caldane, sudorazione	Riduzione della capacità fisica e lavorativa

Jackson G et Al. Eur Heart J.2011

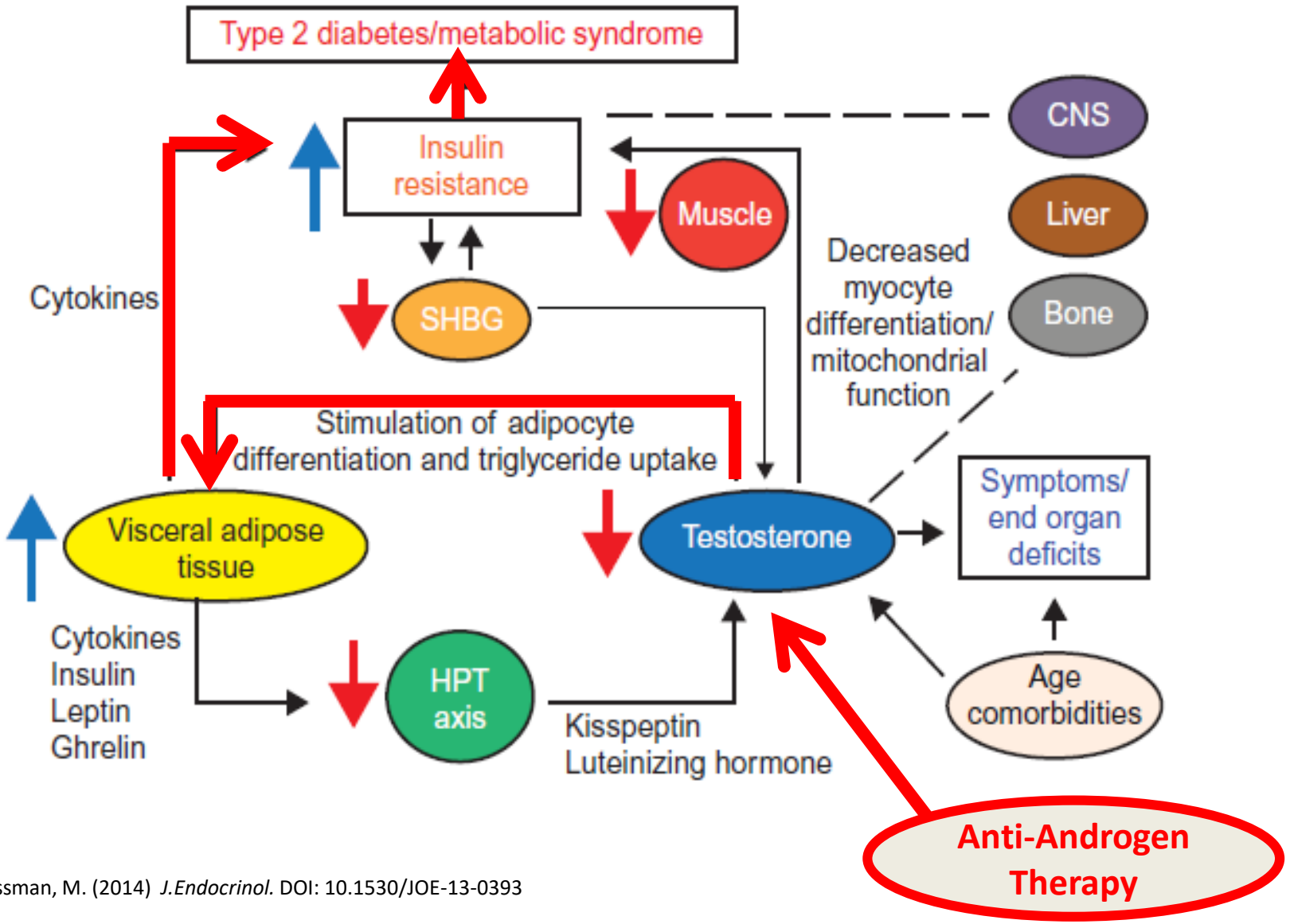
Androgen deprivation therapy (ADT)–related sarcopenic obesity.



Androgen deprivation therapy (ADT)–related sarcopenic obesity. Gonadotropin-releasing hormone (GnRH) agonists cause the accumulation of abdominal subcutaneous fat and loss of lean muscle mass. Cross sectional images of (A) a young healthy man and of (B) a man with ADT-associated sarcopenic obesity caused by long-term GnRH agonist therapy. Panel B is notable for a collection of subcutaneous fat and sparse abdominal and paraspinal musculature. From Saylor PJ, Smith MR. Metabolic complications of androgen deprivation therapy for prostate cancer. J Urol 2009;181:1998–2006; with permission.


METABOLIC SYNDROME
nature medicine
Mitochondrial dysfunction
M2 macrophages (anti-inflammatory)
Impaired sympathetic response
Brain
Fuel for other organs
Re-esterfication
Circulating TGs
FFAs
Glycerol
Lipolysis
TGs
Cortisone
11β-HSD1
Insulin signaling
Cortisol
Glucose
Glucose
Insulin
Adipocyte hypertrophy
ER stress
Ceramide production
Hypoxia
Impaired vascularization:
Hypoxic conditions
Increased inflammation:
M1 macrophages
Mast cells
Tregs
B cells
CLS (crown-like structures)
B cells
Tregs
M1 macrophages (pro-inflammatory)
Fibrosis
Mast cells
Apoptotic adipocyte (autophagy)
Increased endocannabinoid tone:
Food intake
Lipogenesis
Impaired insulin response:
Reduced glucose uptake
Enhanced FFA release
Reduced central metabolic response, including leptin resistance
Low-grade systemic inflammation
High levels of pro-inflammatory cytokines (TNFα, IL-6, MCP-1)
Adipokines:
Adiponectin
Leptin, Resistin
Rbp4, Sfrp5, Adipsin
Glucotoxicity
Lipotoxicity
Insulin resistance
β cell dysfunction and apoptosis
Insulin resistance
Fertility (reduced?)
Endothelial dysfunction
Cardiac dysfunction
Liver
Pancreas
Skeletal muscle
Reproductive tract
Endothelial cells
Heart
Severe complications of chronic diabetes
Diabetic nephropathy
Diabetic retinopathy
Diabetic neuropathy
Diabetic skin ulcers

Links fisiopatologici tra Insulino-Resistenza, Sindrome metabolica, Diabete ed Ipogonadismo



Mod. Grossman, M. (2014) *J.Endocrinol.* DOI: 10.1530/JOE-13-0393

Androgen Deprivation Therapy in Prostate Cancer and Metabolic Risk for Atherosclerosis

Sadeka Shahani, Milena Braga-Basaria, and Shehzad Basaria

Department of Internal Medicine (S.S.), Harbor Hospital of Baltimore, Baltimore, Maryland 21225; Consultant Endocrinologist (M.B.-B.), Baltimore, Maryland 21209; and Division of Endocrinology and Metabolism and Oncology (S.B.), Johns Hopkins University School of Medicine, Baltimore, Maryland 21224

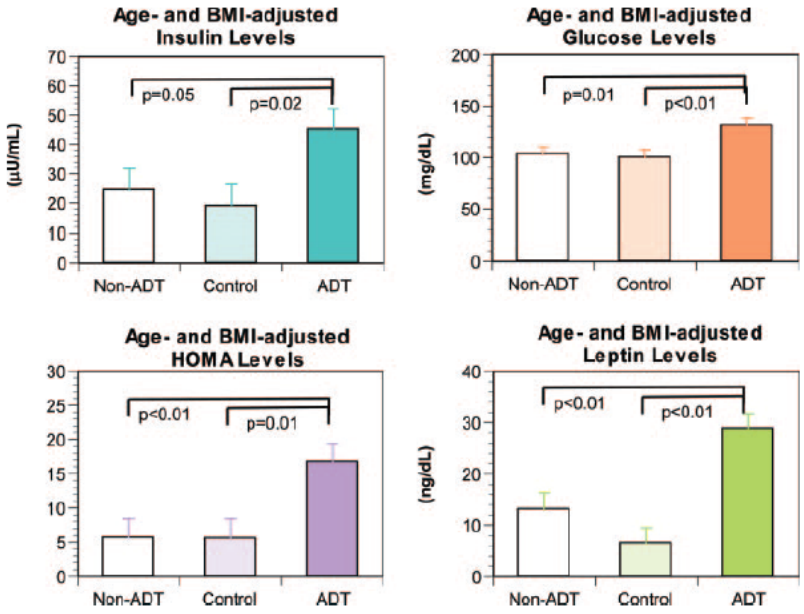


FIG. 2. Higher prevalence of insulin resistance and hyperglycemia in men undergoing long-term ADT compared with age- and disease-matched controls (adapted from Ref. 27).

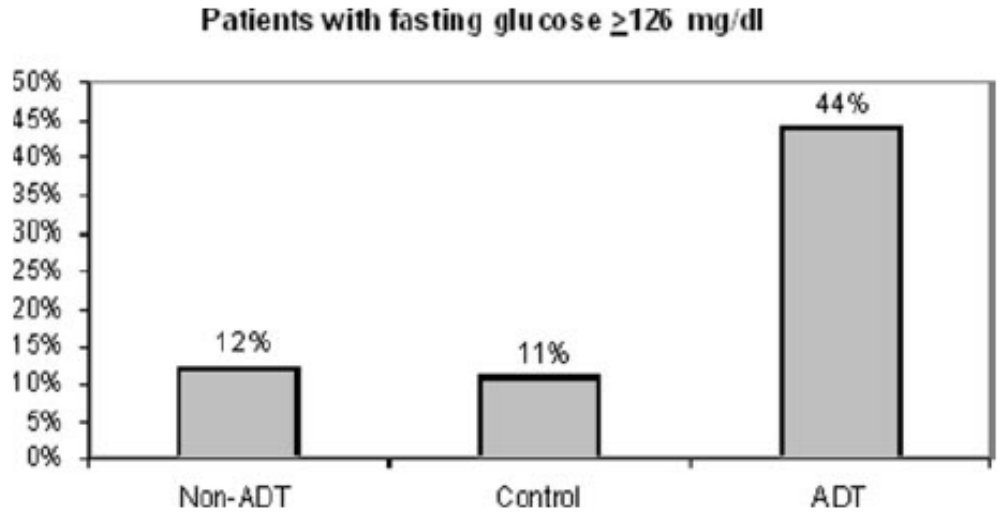
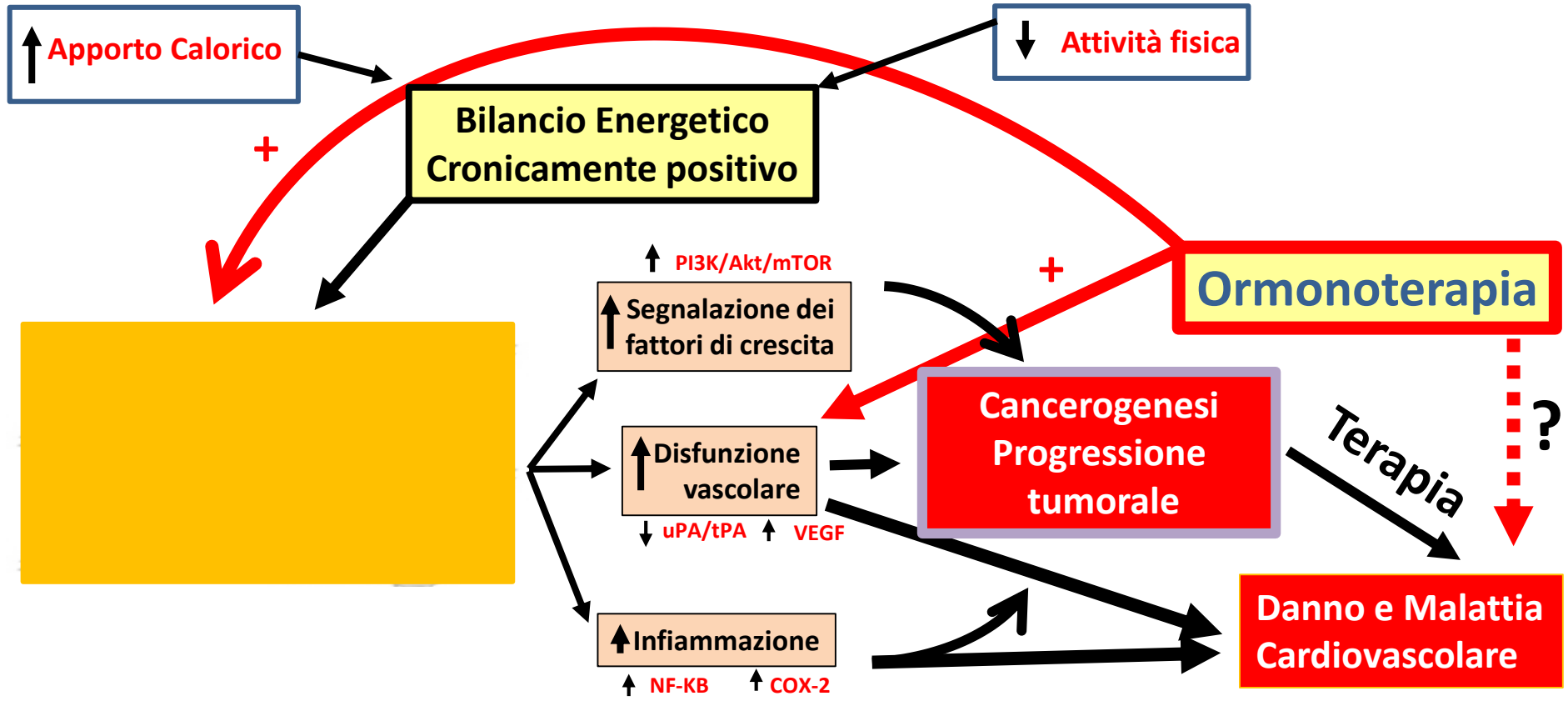
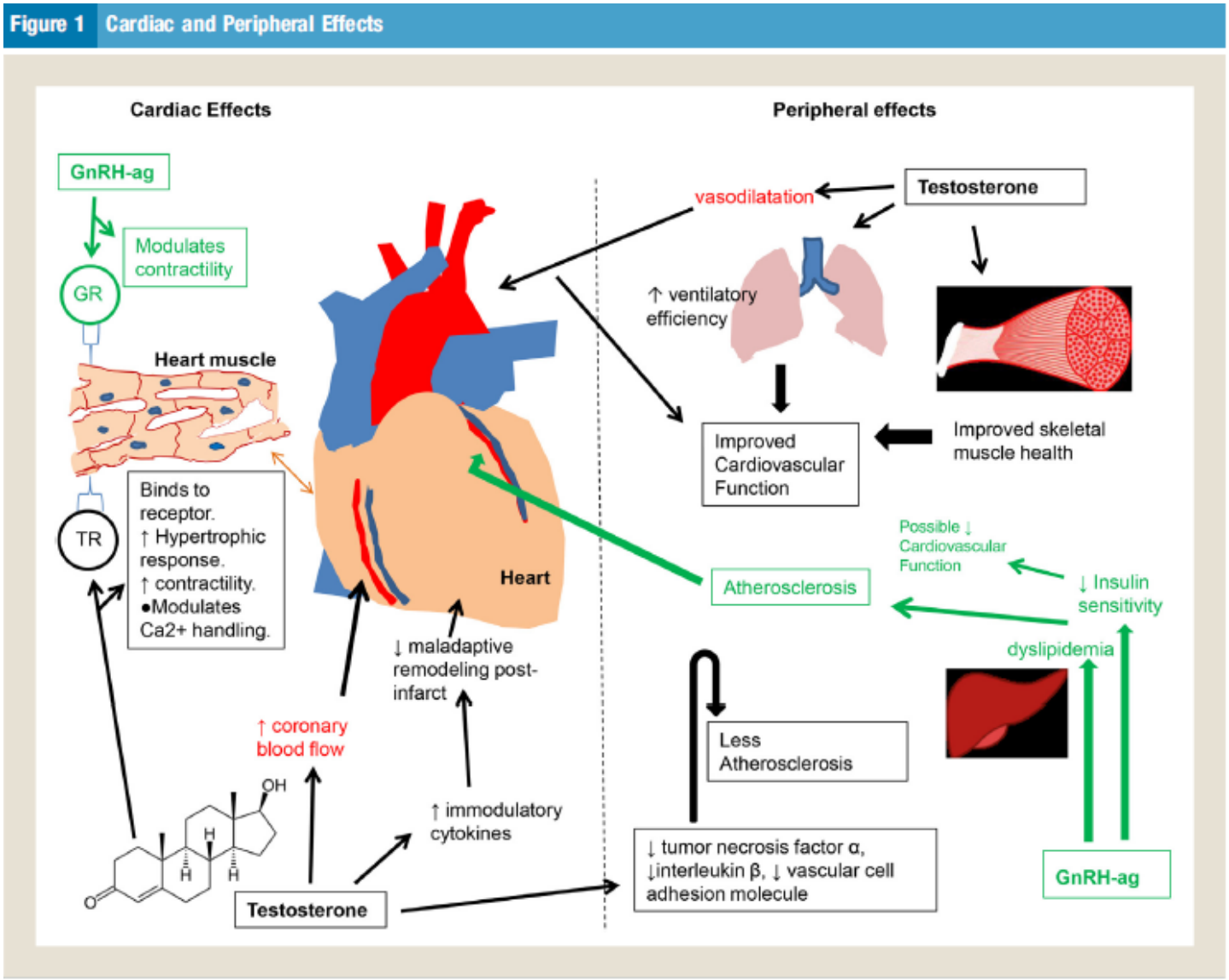


FIG. 3. Prevalence of diabetes in men undergoing prolonged ADT (adapted from Ref. 27).

Modello concettuale sul ruolo dell'ormonoterapia nell'insorgenza della Cardiotossicità

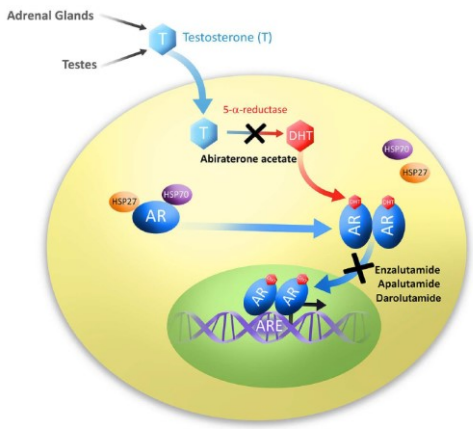


The Effects of Androgen Deprivation Therapy on Cardiac Function and Heart Failure: Implications for Management of Prostate Cancer



Scott Edelman Clinical Genitourinary Cancer, 2014

The Cardiovascular Toxicity of Abiraterone and Enzalutamide in Prostate Cancer



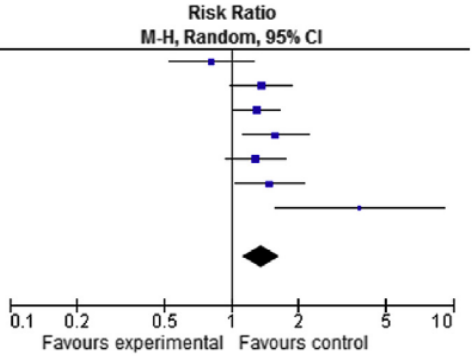
Abiraterone and enzalutamide are standard therapies for treatment
of metastatic PC.

increased the risk of cardiac toxicity by **36%** for all-grade.
In addition, the risk of arterial hypertension was increased by 100%

A

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFFIRM	49	800	30	399	11.6%	0.81 [0.53, 1.26]
COU-AA-301	126	791	46	394	16.6%	1.36 [1.00, 1.87]
COU-AA-302	126	542	96	540	20.9%	1.31 [1.03, 1.66]
LATITUDE	74	597	47	602	15.1%	1.59 [1.12, 2.25]
PREVAIL	88	871	66	844	17.2%	1.29 [0.95, 1.75]
STAMPEDE	69	948	47	960	14.6%	1.49 [1.04, 2.13]
TERRAIN	22	183	6	189	4.0%	3.79 [1.57, 9.13]
Total (95% CI)		**4732**		**3928**	**100.0%**	**1.36 [1.13, 1.64]**
Total events	554		338			

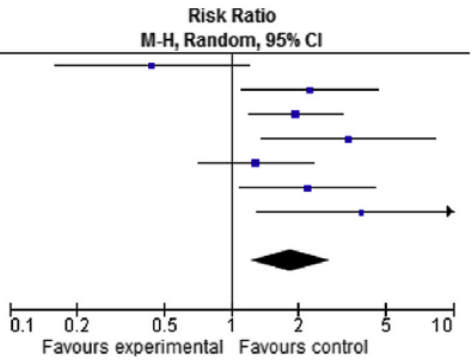
Heterogeneity: Tau² = 0.03; Chi² = 11.67, df = 6 (P = 0.07); I² = 49%
Test for overall effect: Z = 3.21 (P = 0.001)



B

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
AFFIRM	7	800	8	399	10.6%	0.44 [0.16, 1.19]
COU-AA-301	41	791	9	394	15.2%	2.27 [1.11, 4.62]
COU-AA-302	45	542	23	540	19.9%	1.95 [1.20, 3.18]
LATITUDE	20	597	6	602	12.0%	3.36 [1.36, 8.31]
PREVAIL	24	871	18	844	17.4%	1.29 [0.71, 2.36]
STAMPEDE	24	948	11	960	15.3%	2.21 [1.09, 4.48]
TERRAIN	15	183	4	189	9.6%	3.87 [1.31, 11.45]
Total (95% CI)		**4732**		**3928**	**100.0%**	**1.84 [1.21, 2.80]**
Total events	176		79			

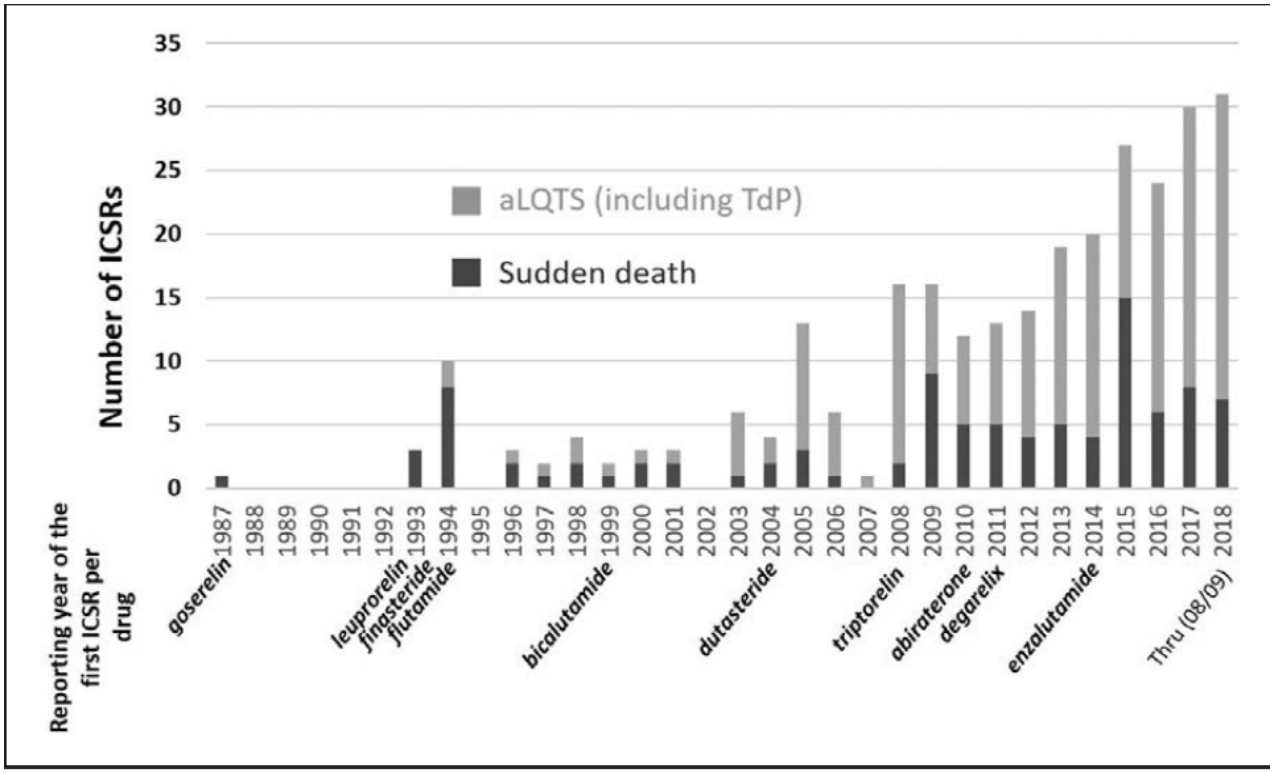
Heterogeneity: Tau² = 0.17; Chi² = 13.34, df = 6 (P = 0.04); I² = 55%
Test for overall effect: Z = 2.86 (P = 0.004)



Iacovelli R. et AL. Clinical Genitourinary Cancer 2017

Androgenic Effects on Ventricular Repolarization

L'ipogonadismo indotto dalla ADT determina **allungamento del QT** e soprattutto in presenza di altri fattori (es. farmaci o disionia) può determinare la comparsa di **torsione di punta o addirittura morte impovvisa** (184 casi associati ad ADT nel database VIGIBASE. Questo è particolarmente rilevante nel caso dell'**Enzalutamide**, un nuovo inbitore della sintesi del Testosteorne (17% dei casi di morte improvvisa)



Joe-Elie Salem et Al Circulation in press

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Hormonal agents					
Abiraterone	Moderate CYP3A4 inhibition, strong P-gp inhibition; CYP3A4/P-gp competition				
Enzalutamide	Strong CYP3A4 induction, strong P-gp inhibition; CYP3A4/P-gp competition				
Bicalutamide	Moderate CYP3A4 inhibition				
Tamoxifen	Strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4 competition				

- Strong CYP3A4 and/or P-gp inducer—should not be used (dark brown).
- Moderate CYP3A4 or P-gp inducer—use with caution or avoid (light brown).
- Moderate CYP3A4 or P-gp inhibitor—use with caution, consider dose reduction or different NOAC (orange).
- Mild CYP3A4 and/or P-gp inducers or inhibitors—caution is needed with polypharmacy or in the presence of ≥2 bleeding risk factors (yellow).

AHA/ACS/AUA Science Advisory

Androgen-Deprivation Therapy in Prostate Cancer and Cardiovascular Risk

A Science Advisory From the American Heart Association, American Cancer Society, and American Urological Association

Endorsed by the American Society for Radiation Oncology

Glenn N. Levine, MD, FAHA, Chair; Anthony V. D'Amico, MD, PhD; Peter Berger, MD, FAHA; Peter E. Clark, MD; Robert H. Eckel, MD, FAHA; Nancy L. Keating, MD, MPH; Richard V. Milani, MD, FAHA; Arthur I. Sagalowsky, MD; Matthew R. Smith, MD, PhD; Neil Zakai, MD; on behalf of the American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association

Circulation 2010, 121:833-840: originally published online February 1, 2010
doi: 10.1161/CIRCULATIONAHA.109.192695
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 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Cardiovascular Effects of Androgen Deprivation Therapy for the Treatment of Prostate Cancer

ABCDE Steps to Reduce Cardiovascular Disease in Patients With Prostate Cancer

Table 3. ABCDE Algorithm for Prostate Cancer Survivors

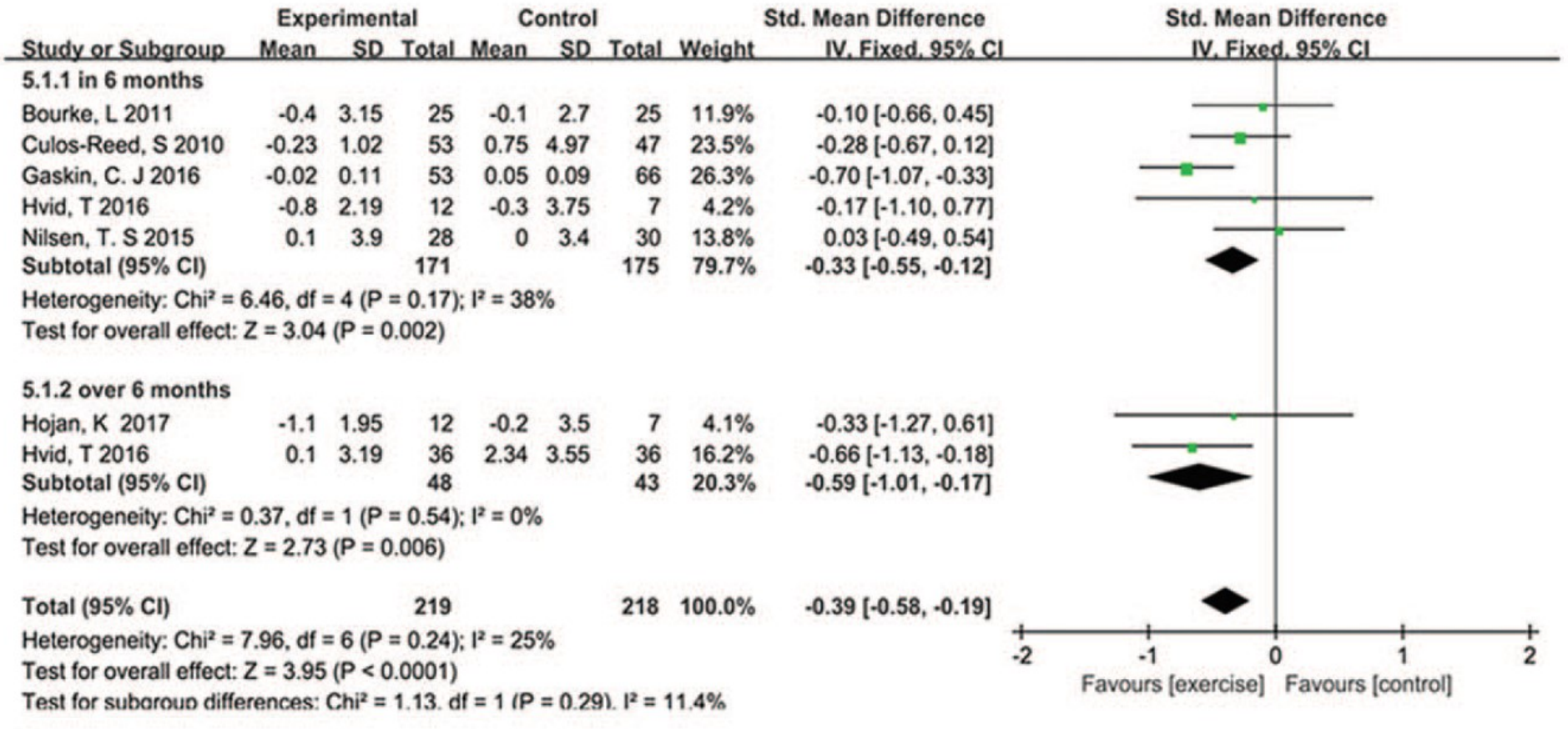
A	Awareness	Increased awareness of patients of cardiovascular signs and symptoms
	Aspirin	Aspirin 81 mg daily for primary or secondary prevention of cardiovascular events
B	Blood pressure	Goal blood pressure <140/90 mm Hg
C	Cholesterol	High-intensity statin therapy for preexisting CVD or hyperlipidemia
	Cigarettes	Smoking cessation counseling, therapy
D	Diabetes mellitus	Frequent blood glucose monitoring
		Metformin for diabetes mellitus if possible
	Diet	Diet rich in fruits, vegetables, and whole grain and low in saturated fat with 600 IU vitamin D daily and adequate calcium (1200 mg/d)
		Avoidance of excessive alcohol
E	Exercise	150 min/wk of moderate-intensity physical activity or 75 min/wk of vigorous exercise

CVD indicates cardiovascular disease.

Bathia N. et Al. Circulation 2016

Exercise overcome adverse effects among prostate cancer patients receiving androgen deprivation therapy. An update meta-analysis

change in body BMI compared to exercise group and control group in 6 months and over 6 months



Medicine (2017) 96:27(e7368)

La piramide dell'Attività fisica: Costruire un programma personalizzato per migliorare l'aderenza !!!

La dieta mediterranea come «stile alimentare» da integrare con lo stile di vita !!!!

Conclusioni

- La cardiotossicità da ormonoterapia è generalmente provocata dal peggioramento del profilo di rischio CV

- I soggetti a maggior rischio di eventi sono ovviamente i pazienti con cardiopatia strutturale o ad alto rischio CV (es. diabetici, multipli FR, etc.etc.)

- La cardiotossicità può manifestarsi con un ampio spettro fenotipico (es., Cardiopatia ischemica, Ipertensione arteriosa, Scompenso cardiaco, aritmie, Ictus)

- E' importante una <u>appropriata gestione integrata</u> (Oncologo- Cardiologo) per valutare lo stato CV nel paziente ad alto rischio finalizzata a:
  1) Valutazione del danno d'organo (entità della cardiopatia strutturale) e del rischio CV;
  2) Trattamento «aggressivo» dei fattori di rischio modificabili;
  3) Monitoraggio delle variazioni dello stato CV e metabolico nel tempo (soprattutto nei primi mesi della terapia nel caso degli antiandrogeni di II generazione);
  4) Avviare il paziente ai programmi di prevenzione/riabilitazione (dieta /esercizio fisico/farmaci)

Grazie per l’Attenzione !!!