Cardiotossicità da Ormonoterapia

REGIONE DEL VENETO
ULSS 1 DOLOMITI

Luigi Tarantini – Cardiologia
Ospedale «San Martino» Belluno

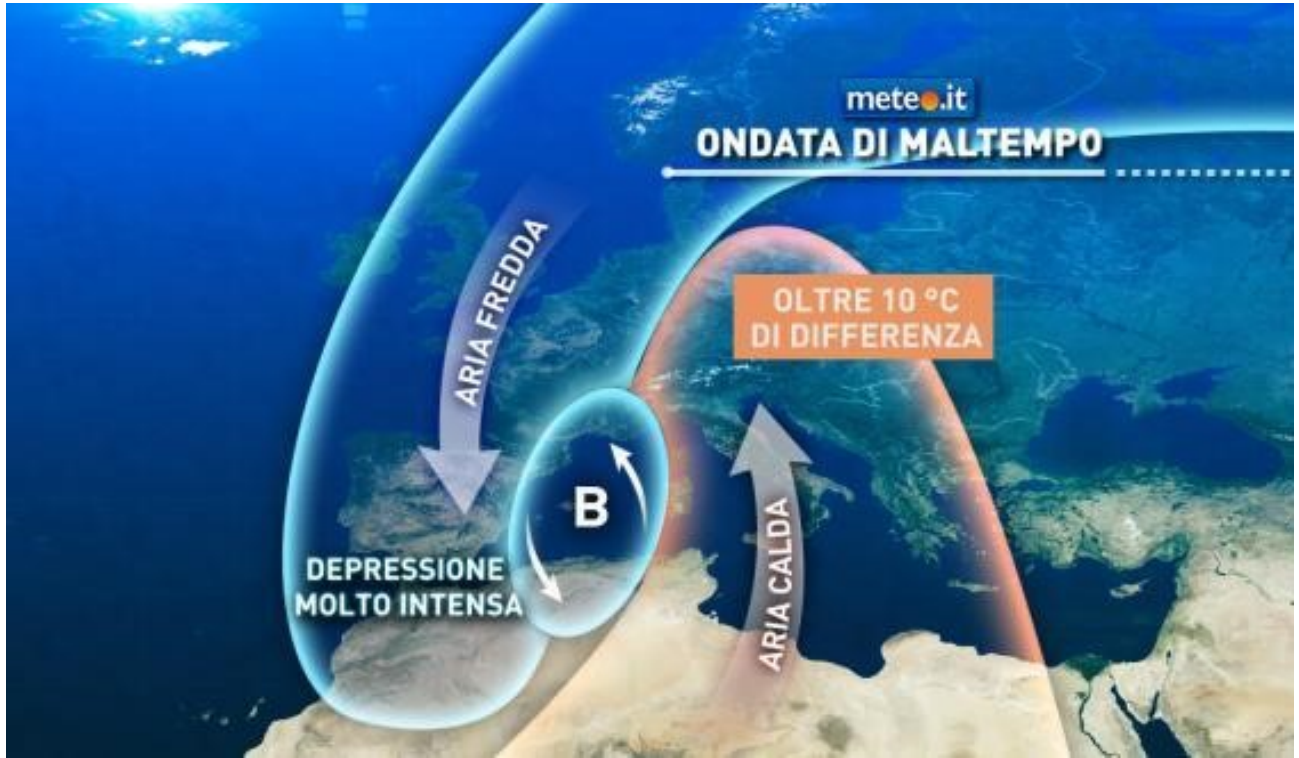
Negrar 26 Gennaio 2019

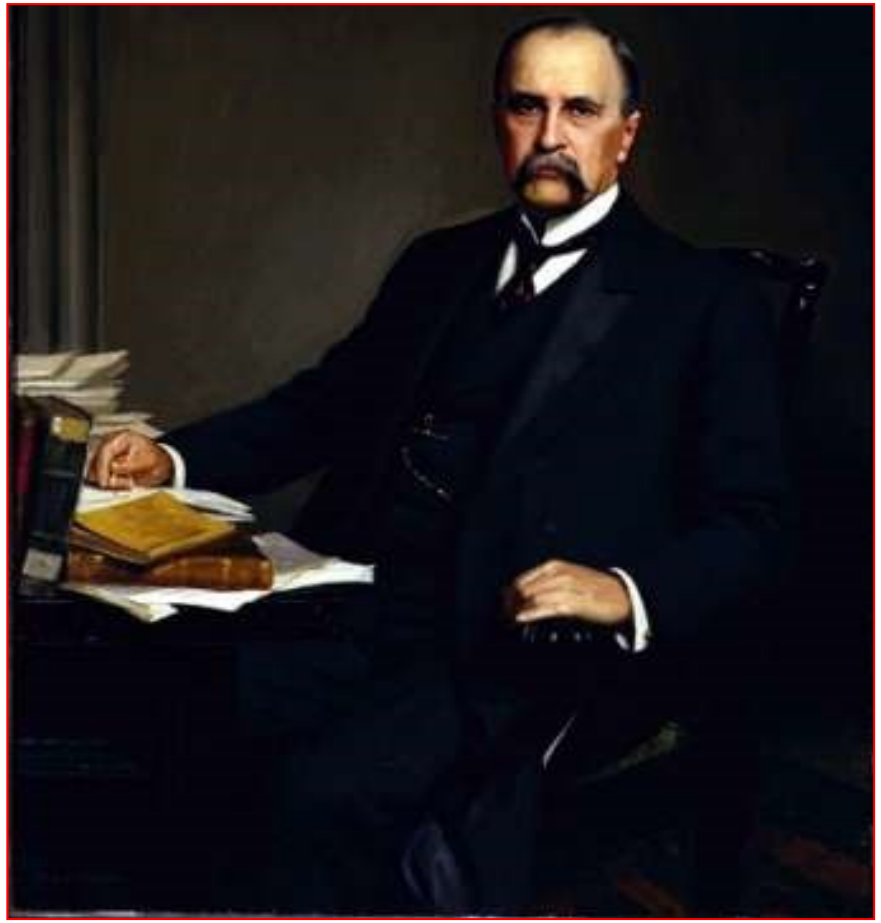
Cardiotossicità da Ormonoterapia ovvero l'effetto «Butterfly»* in Cardio-oncologia

Effetto Butterfly (Principio della Dipendenza sensibile dalle condizioni iniziali)

In un sistema dinamico a variazioni infinitesime delle condizioni iniziali corrispondono variazioni significative del comportamento futuro

«Does the Flap of a Butterfly's wings in Brazil Set Off a Tornado in Texas?» Edward N. Lorenz Sc.D. , MIT





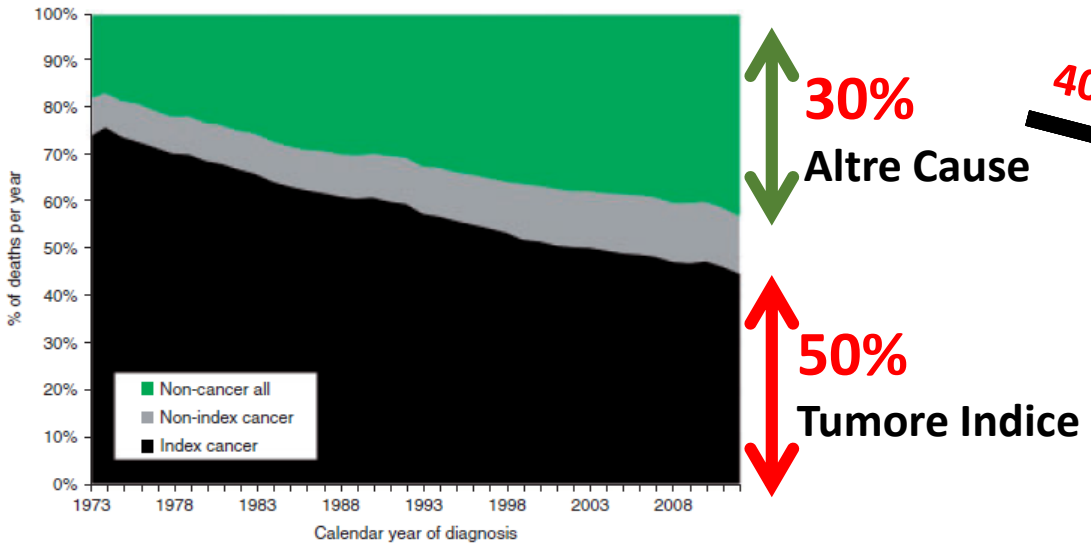
«Forse è più importante conoscere che tipo di paziente ha la malattia, piuttosto che sapere che tipo di malattia ha il paziente»

Sir William Osler

“Perhaps it is more important to know what kind of patient has the disease, than to know what kind of disease has the patient.»

Causes of death among cancer patients

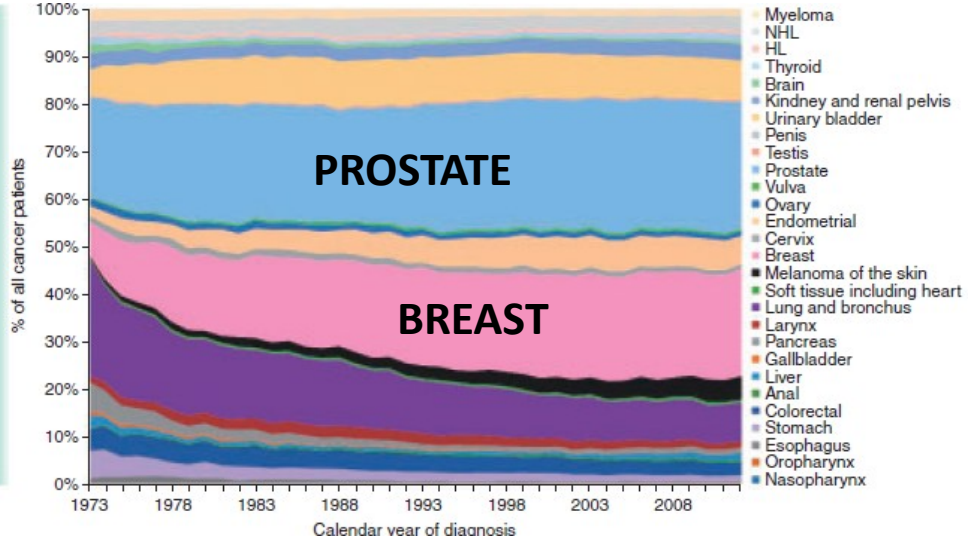
US death certificate data in Surveillance, Epidemiology, and End Results Stat 8.2.1 were used to categorize cancer patient death as being due to **index-cancer,** non index-cancer, and noncancer cause **from 1973 to 2012**



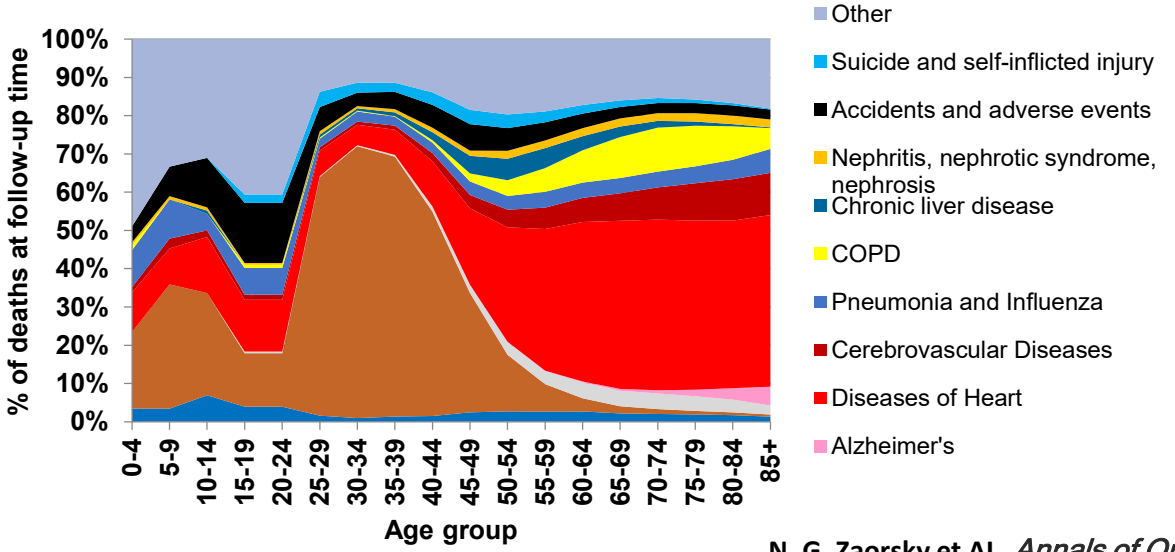
30%
Altre Cause

50%
Tumore Indice

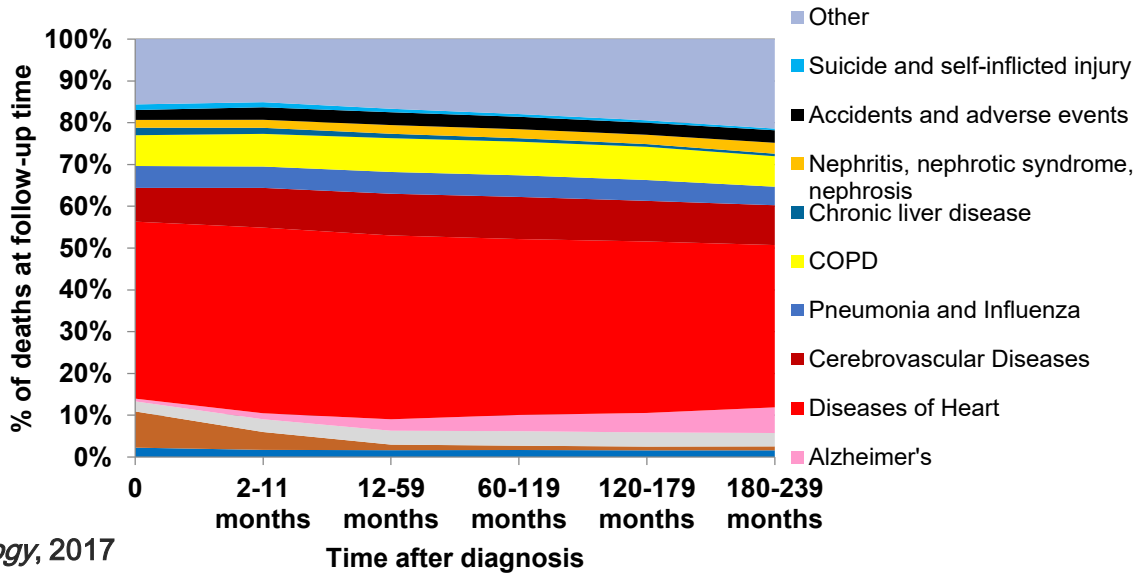
40% CVD



Non-cancer deaths vs. follow-up time



Non-cancer deaths vs. follow-up time



N. G. Zaorsky et AL. *Annals of Oncology*, 2017

Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study

Saro H. Armenian, Lanfang Xu, Bonnie Ky, Canlan Sun, Leonardo T. Farol, Sumanta Kumar Pal, Pamela S. Douglas, Smita Bhatia, and Chun Chao

n = 36,232 ≥ 2-year survivors of adult-onset cancer compared with matched non cancer controls

m. Myeloma IRR, 1.70

Lung/bronchus IRR, 1.58

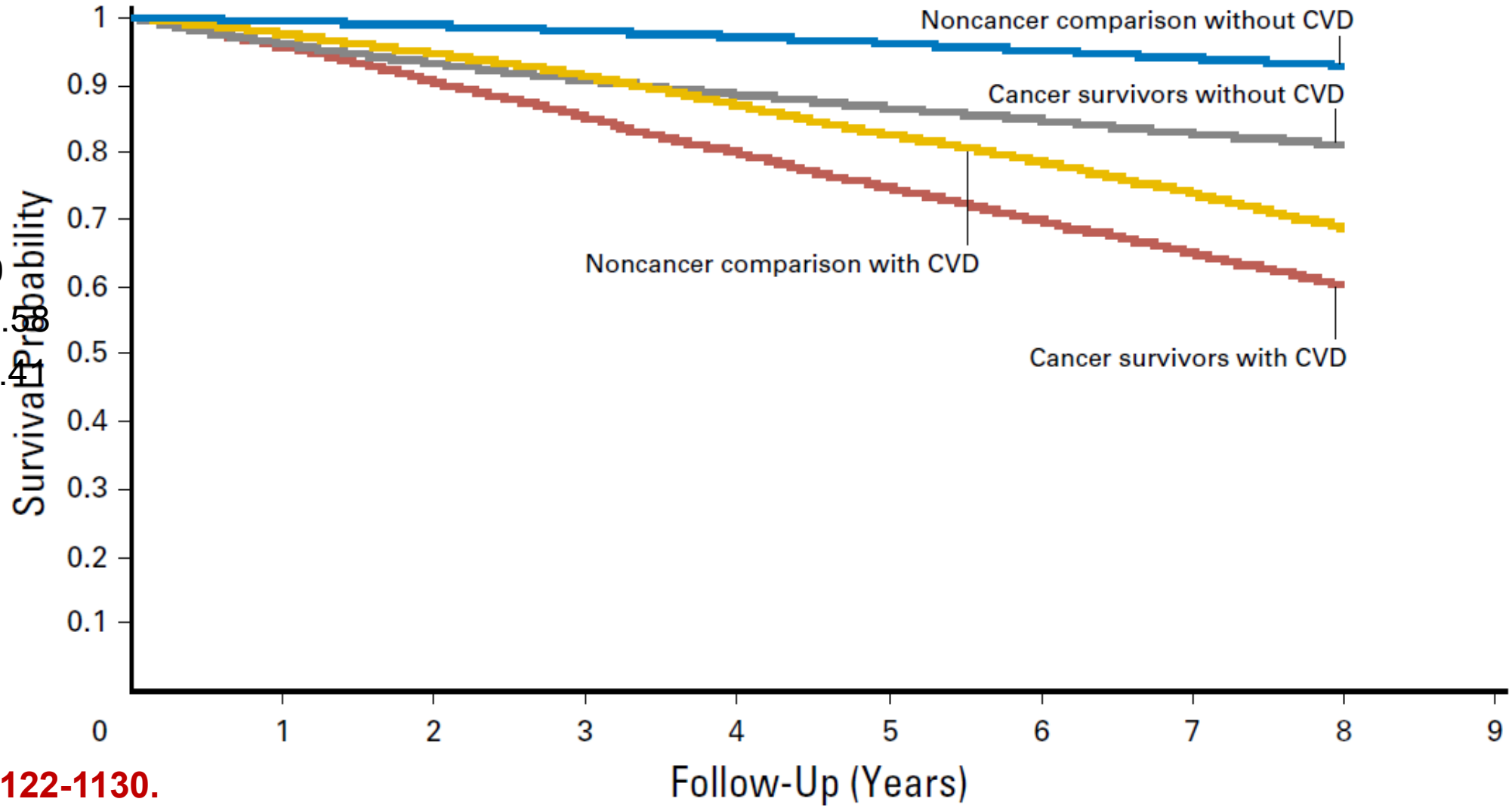
Ovarian cancer IRR, 1.41

LNH IRR, 1.41

Kidney IRR, 1.24

Breast IRR, 1.13

IRR, incidence rate ratio



J Clin Oncol. 2016 34:1122-1130.

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J Clin Oncol. 2016 34:1122-113

Table 1. Study Participant Characteristics

Characteristic	Cancer Survivors* (N = 36,232)	Noncancer Controls* (N = 73,545)	*P*
Age at diagnosis, years			—
Median	60	60	
Range	40.0-96.0	40.0-96.0	
Sex, No. (%)			—
Female	19,055 (52.6)	39,225 (53.3)	
Male	17,177 (47.41)	34,320 (46.7)	
Hypertension, No. (%)†			< .01
No	12,344 (34.1)	29,790 (40.5)	
Yes	23,888 (65.9)	43,755 (59.5)	
Diabetes, No. (%)†			< .01
No	27,745 (76.6)	57,719 (78.5)	
Yes	8,487 (23.4)	15,826 (21.5)	
Dyslipidemia, No. (%)†			< .01
No	15,257 (42.1)	32,408 (44.1)	
Yes	20,975 (57.9)	41,137 (55.9)	
Overweight/obese, No. (%)†			< .01
No	20,502 (56.6)	47,497 (64.6)	
Yes	15,730 (43.4)	26,048 (35.4)	
Smoking, No. (%)†			< .01
Never	24,368 (67.3)	58,045 (78.9)	
Ever	11,864 (32.7)	15,500 (21.1)	

Cardiotossicità e Ormonoterapia : Casi clinici

Caso Clinico 1

- **2014** (72aa) BMI: 33.6 kg/mq, Giro-Vita 113 cm, Iperteso in terapia, Glicemia 96 mg/dl, per ripresa di **Ca prostatico (Gleason VI [3+3])** curato con Rx terapia (2009) ed **Enantone** trimestrale con successiva buona risposta del PSA

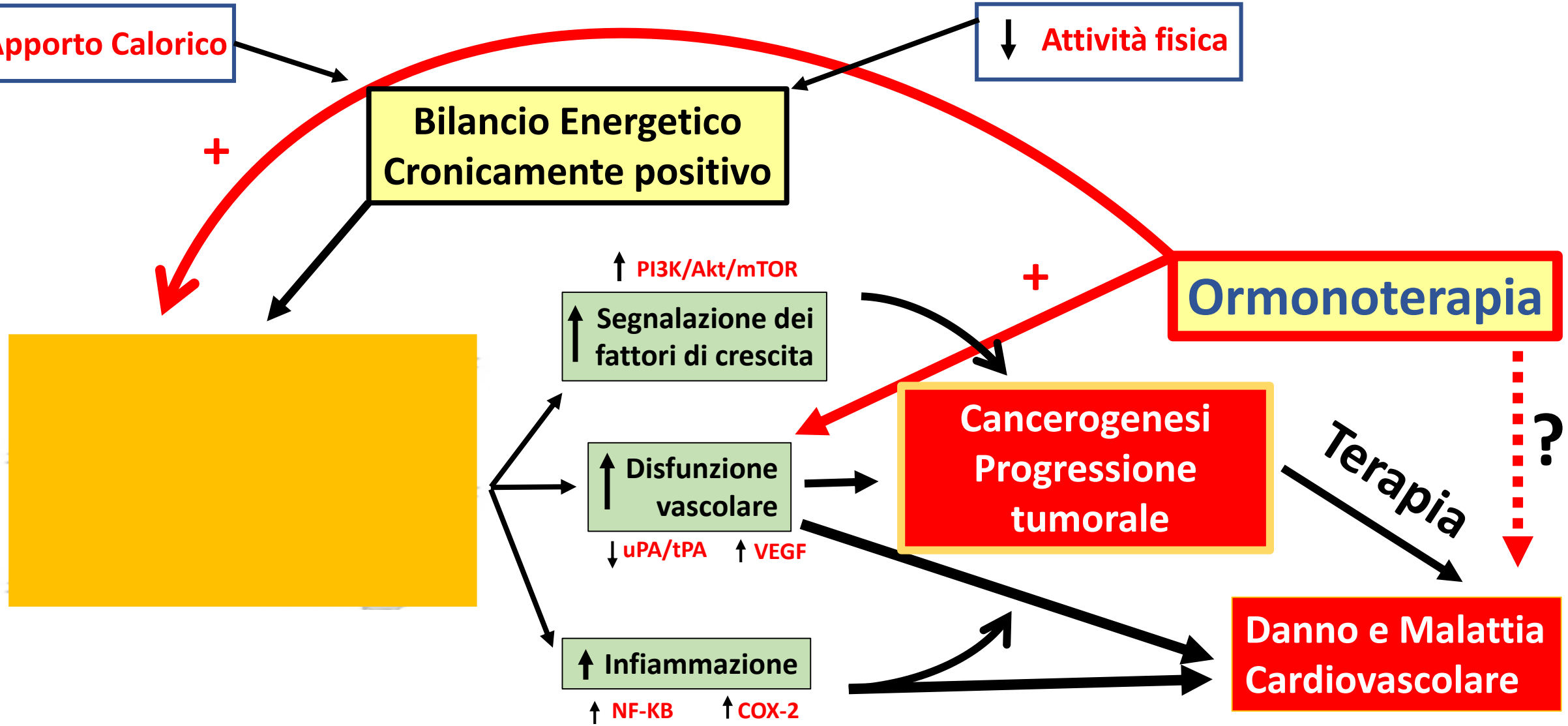
- **Aprile 2016** M.P.G. Uomo (77aa) Obeso (BMI 38.1 Kgr/mq, Giro-vita 128 cm), PA > 160/100 mmHg, Glicemia 131 mg/dl, **inviato per polso aritmico (FA), dispnea (NYHA II) ed edemi**; (Eco IVSn eccentrica, EF 50%, PA polmonare 70 mmHg, TAPSE 12); russamento e sonnolenza diurna → Polisomnografia → in AA tempo sat<90%: 97% → OSAS

Caso Clinico 2

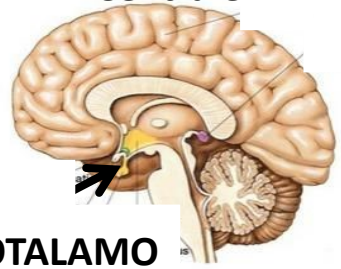
- **2011** (65aa) BMI: 31.4 kg/mq, Giro-Vita 103 cm, Ipertesa + Ipercolesterolemica, Glicemia : 108 mg/dl, **Ca mammario (Dx),** T3N1M0, ER+, HER2-, KI-67:11%: Mastectomia, **AC (DOX. 240 mg/mq)** + Rx terapia + **Letrozolo X 5 anni**

- **Novembre 2016** DA. Donna di 70 aa., Obesa (BMI 32.1 Kgr/mq, Giro-vita 108 cm), Ipertesa, Dislipidemia mista con Glicemia di 126 mg/dl, **Inviata per dispnea (NYHA II) e polso aritmico con singolo episodio di ortopnea e dolore toracico:** ECG: FA; Eco: IVSn Concentrica con disfunzione diastolica III , EF 50%, PA polmonare 49 mmHg. Alla CGF: Malattia Trivasale critica

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



Sistema nervoso Centrale

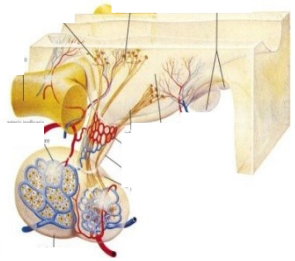


IPOTALAMO

LH-RH

+

-



IPOFISI

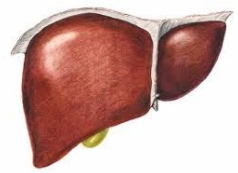
LH

FSH

+

+

Metabolismo epatico



+

Sistema Cardio - Vascolare

?

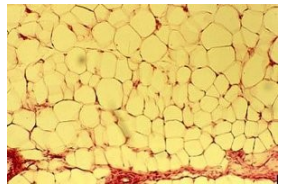
+

Sistema Scheletrico

+

Sistema Muscolare

+



-

Tessuto Adiposo

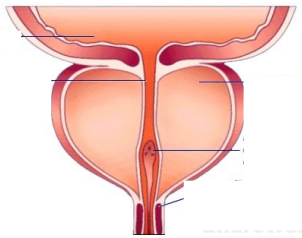
TESTOSTERONE

+

TESTICOLI

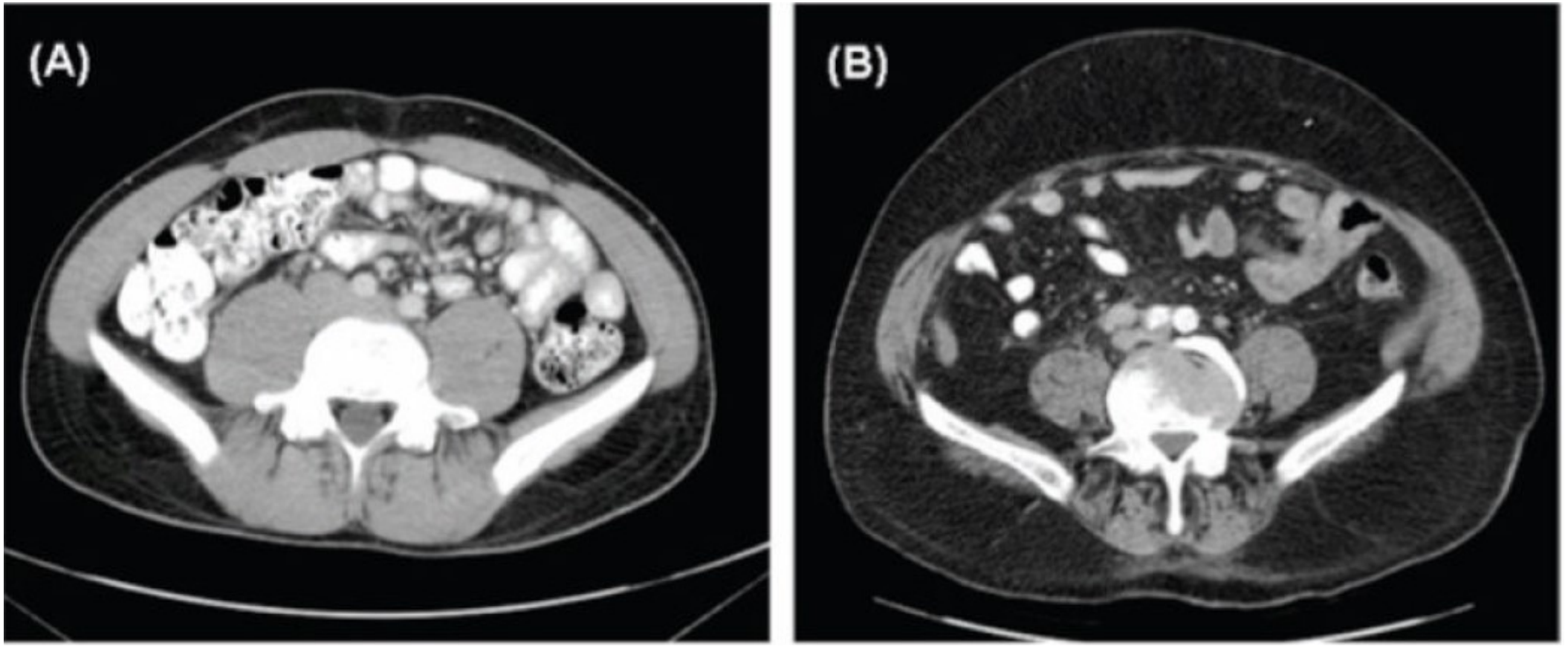
(Cellule di Leydig)

+



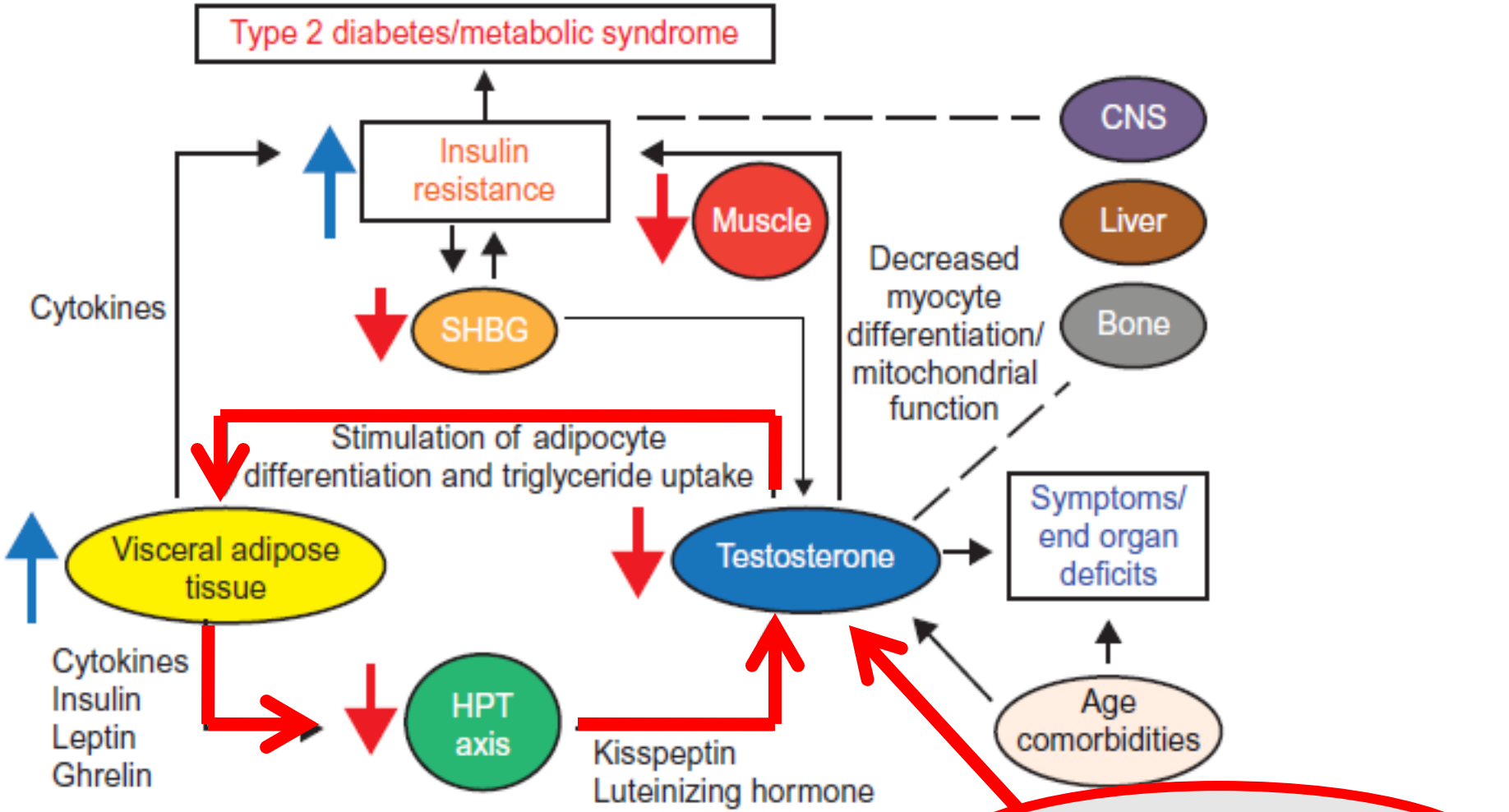
PROSTATA

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.

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



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

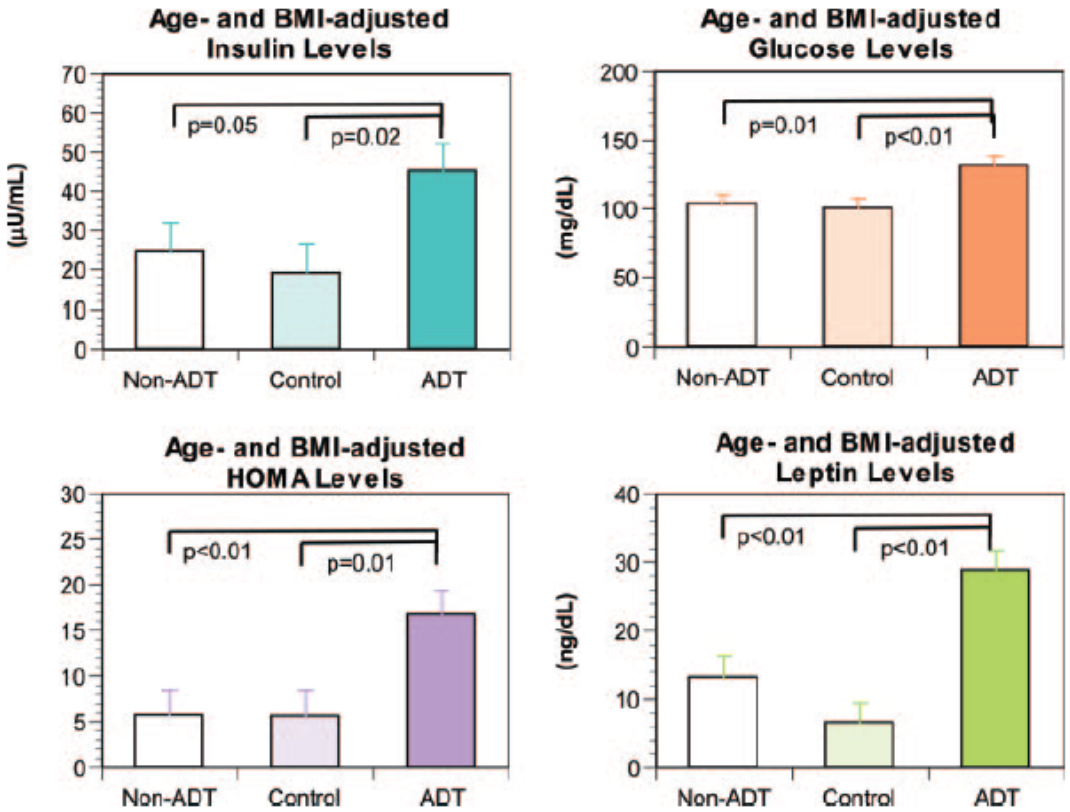


FIG. 2. Higher prevalence of insulin resistance and hyperglycemia in men undergoing long-term ADT compared with age- and disease-matched controls (adapted from Ref. 27).

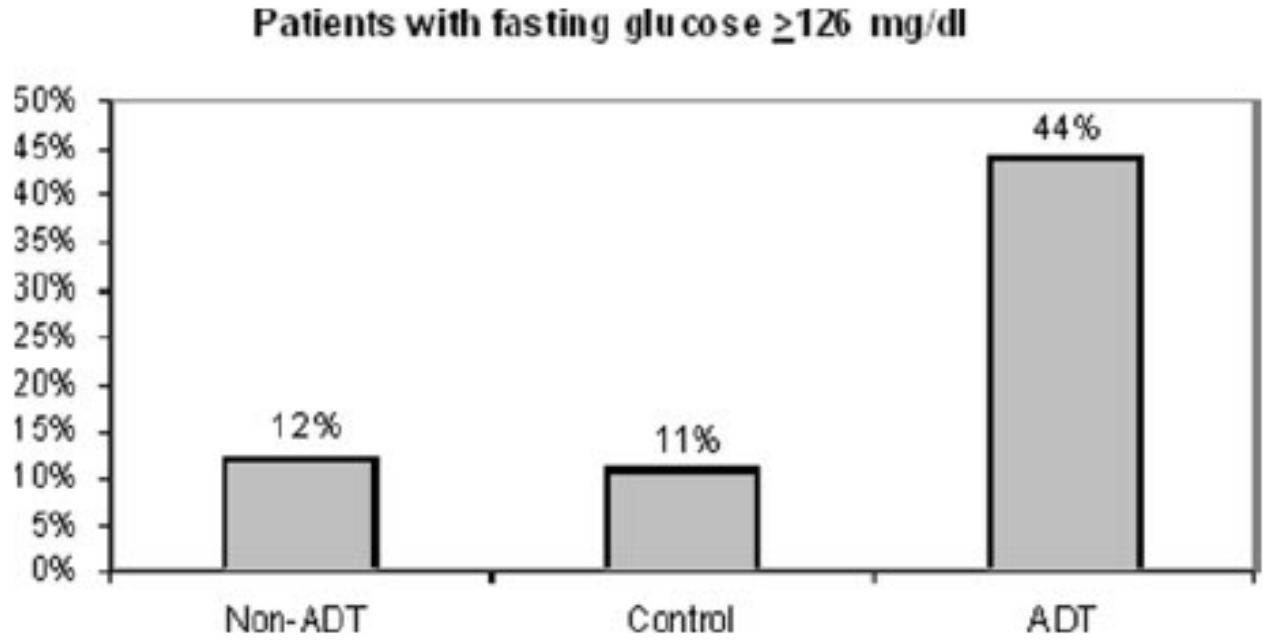
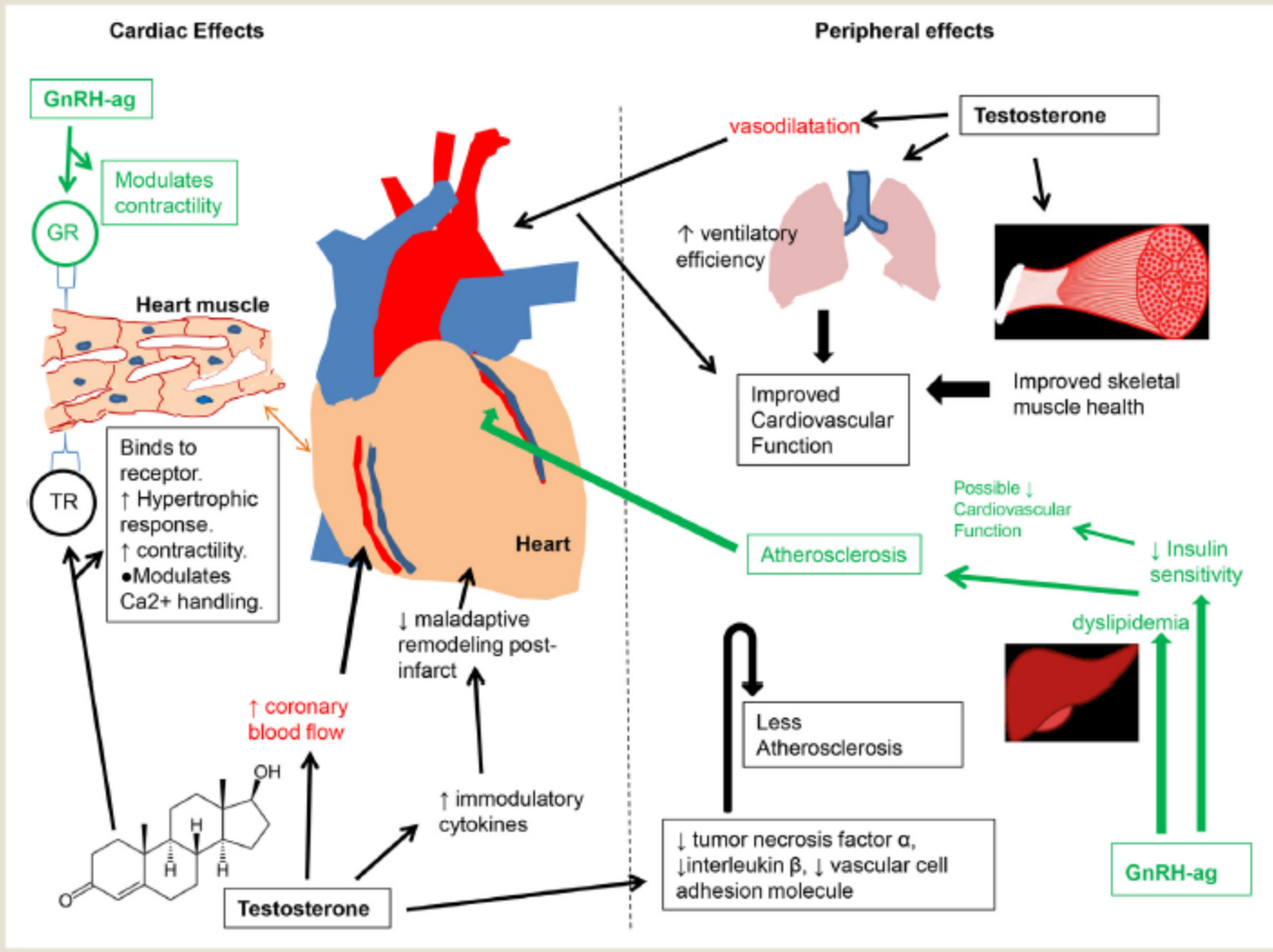


FIG. 3. Prevalence of diabetes in men undergoing prolonged ADT (adapted from Ref. 27).

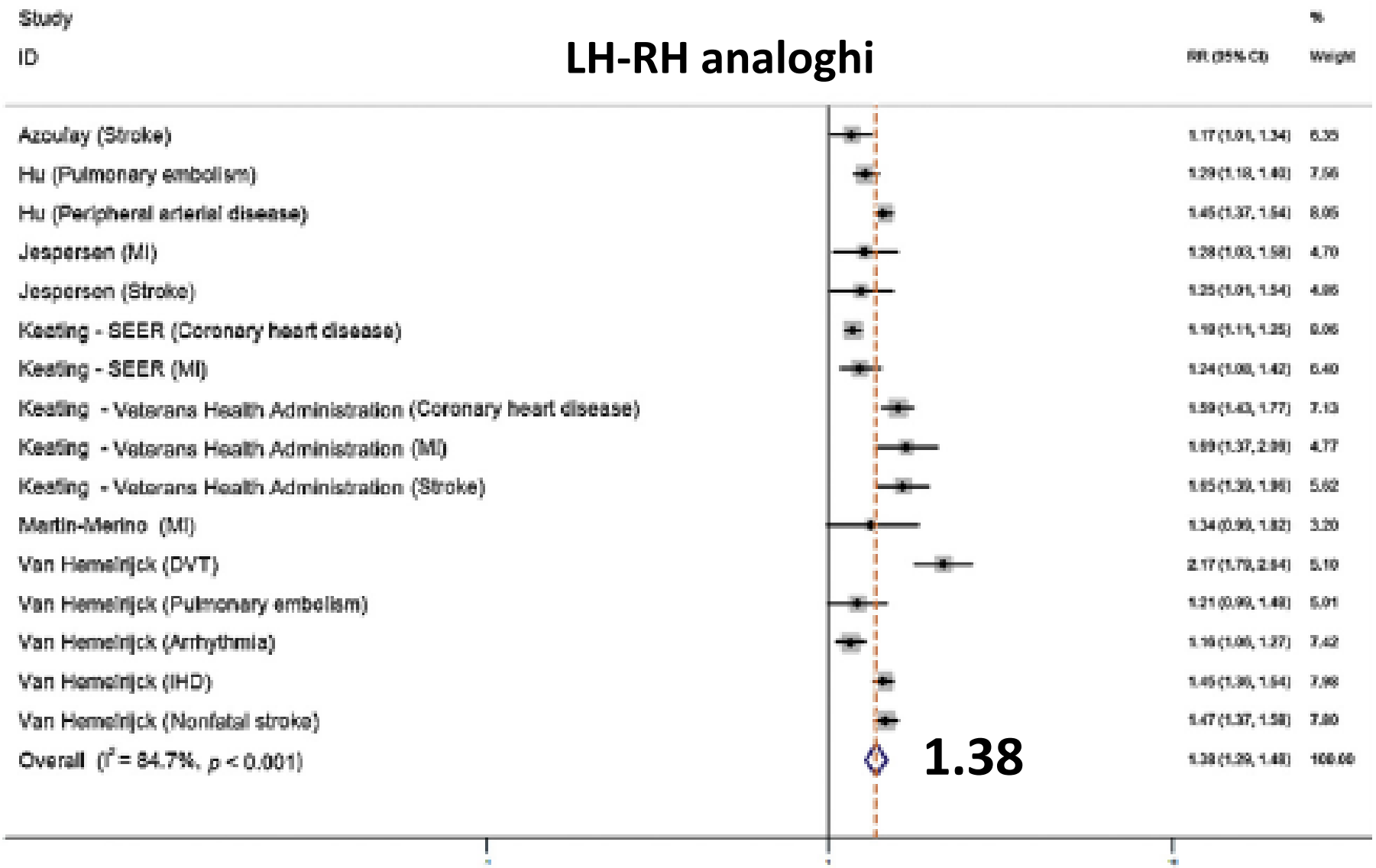
The Effects of Androgen Deprivation Therapy on Cardiac Function and Heart Failure: Implications for Management of Prostate Cancer

Figure 1 Cardiac and Peripheral Effects



Scott Edelman Clinical Genitourinary Cancer, 2014

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

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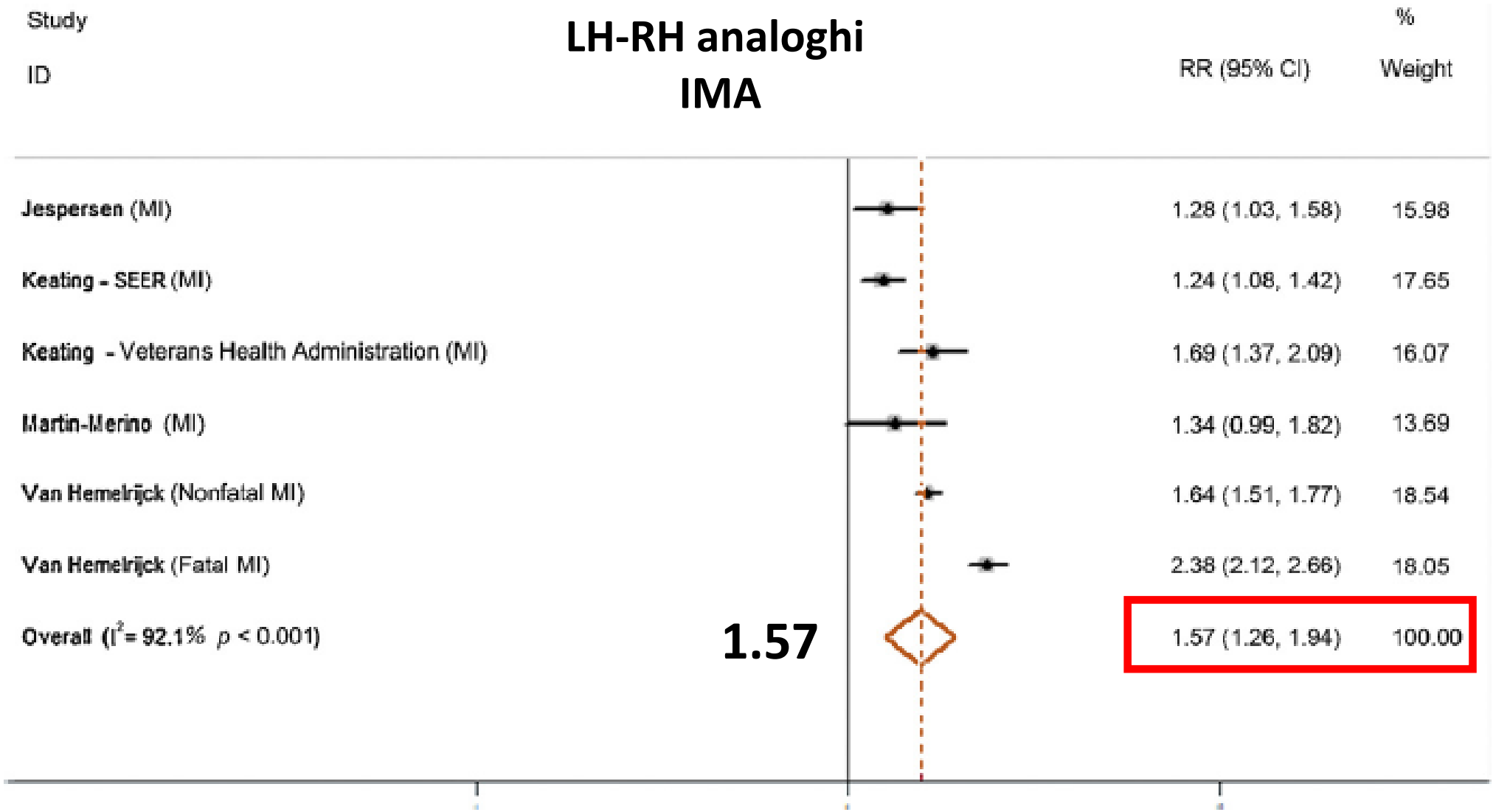

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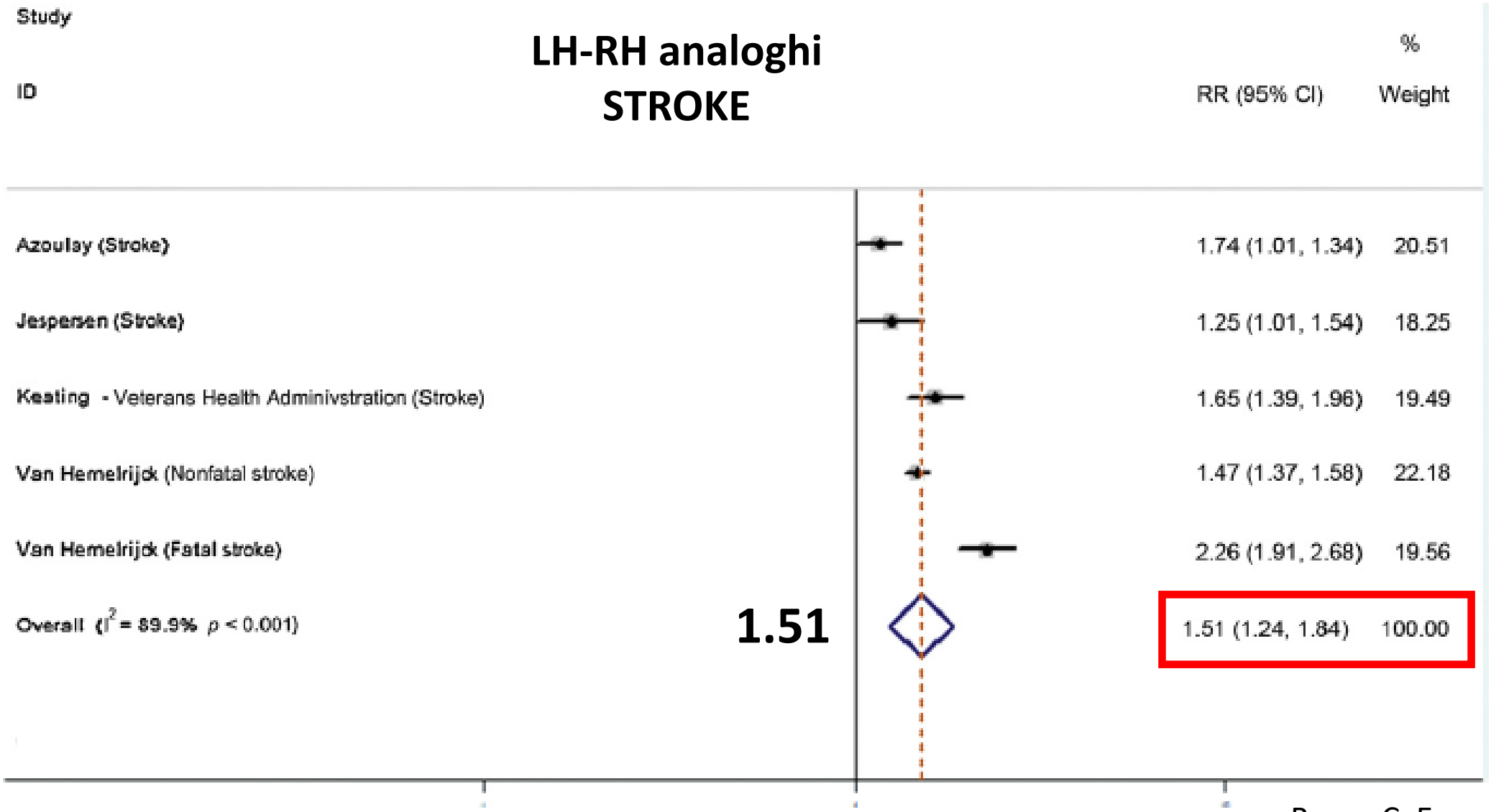


Bosco C. Euro Urol 2014

What Do Prostate Cancer Patients Die Of?

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

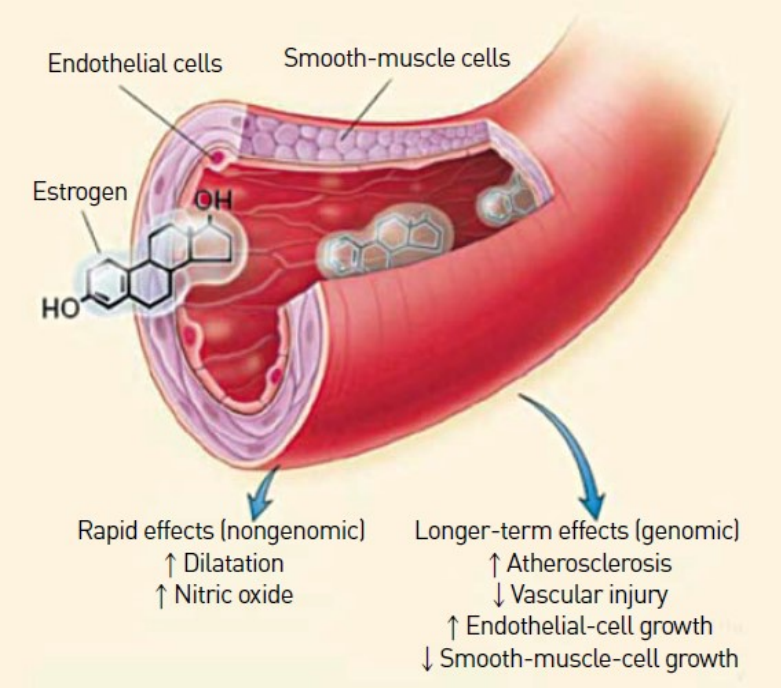
Table 1. HRs for dying from selected conditions when individuals were diagnosed with PC as their first cancer (n = 116,945) compared with all other men (n = 2,152,094)

	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.

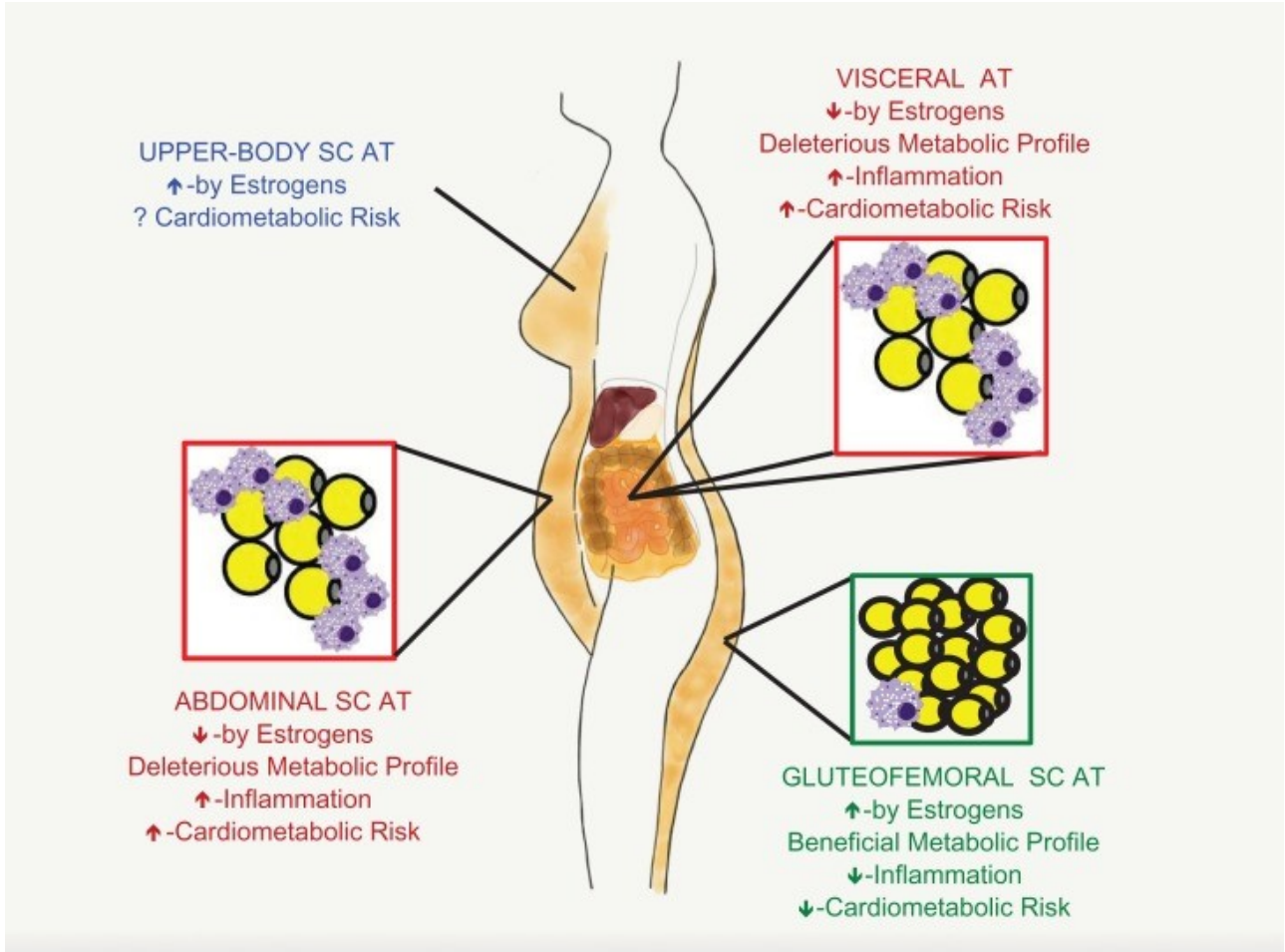
MATIAS RIIHIMÄKI et Al. The Oncologist 2011

The effects of oestrogens on cardiometabolic health

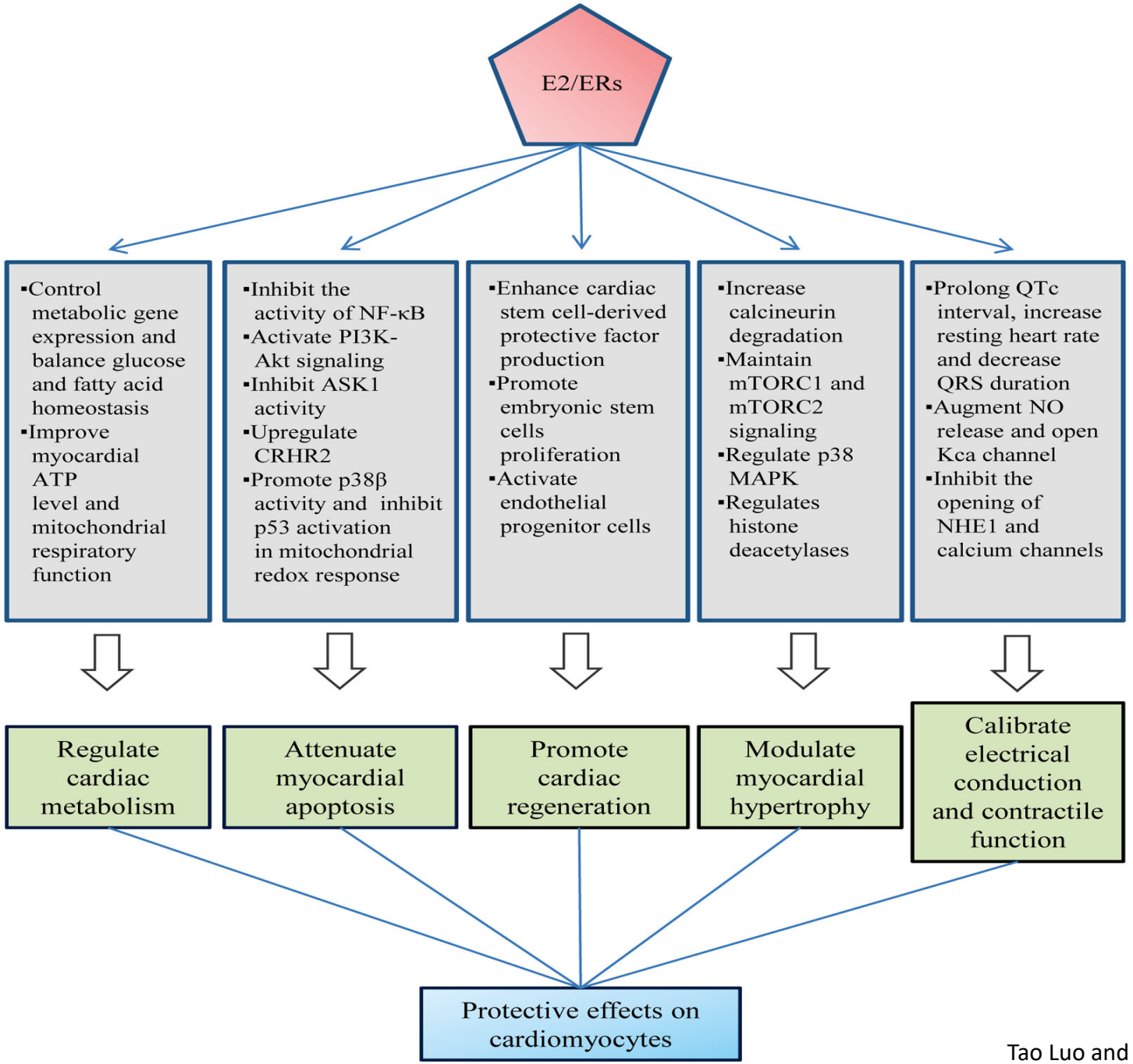


Serum Lipoproteins	Coagulation and Fibrinolytic Systems	Antioxidant System
↓ Total cholesterol	↓ Plasma fibrinogen	↓ Oxidation LDL cholesterol
↓ LDL cholesterol	↓ Antithrombin III	
↑ HDL cholesterol	↓ Protein S	
↑ Triglycerides	↓ Plasminogen activation	
↓ Serum Lp(a) lipoprotein	↑ Fibrinolysis	
	↓ Factor VII	

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.



The Role of Estrogen and Estrogen Receptors on Cardiomyocytes



Tao Luo and Jin Kyung Kim, Can J Cardiol. 2016

Risk of bias assessment overview in Long term adjuvant endocrine therapy Studies

Studi Osservazionali

Paper	Study design	Exposure definition	Outcome/case definition	Control selection	Confounding	Missing data	Censoring
Abdel-Qadir 2016	Cohort	High	High	NA	Low	Unknown	Low
Chen 2014	Cohort	High	Low	NA	High	Unknown	Low
Haque 2016	Cohort	High	Low	NA	Low	Low	Low
Hernandez 2008	Cohort	Unknown	Low	NA	Low	Unknown	Low
Hernandez 2009	Cohort	Unknown	Low	NA	Low	High	Low
Ligibel 2012	Cohort	High	Low	NA	High	Unknown	Low
Yang 2014	Cohort	High	Low	NA	High	Unknown	Unknown
Bradbury 2005	Case-control	High	High	Low	High	Low	NA
Geiger 2004	Case-control	Low	Low	Low	High	High	NA
Geiger 2005	Case-control	Low	Low	Low	High	High	NA
Meier 1998	Case-control	Low	Low	Low	High	High	NA

NA=not applicable

Trial Clinici Randomizzati e controllati

Paper	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias
Bliss 2012	Low	Unknown	Low	Low	Low	Low
Boccardo 2006	Unknown	Unknown	Unknown	Low	Unknown	Low
Coombes 2007	Low	Unknown	Low	Low	Unknown	Low
Fisher 1999	Unknown	Unknown	Unknown	Low	Unknown	Low
Fisher 2001	Low	Unknown	Unknown	Low	Unknown	Low
Forbes 2008	Low	Low	Unknown	Unknown	Unknown	Low
Jakesz 2005	Low	Low	High	Unknown	Unknown	Low
Kaufmann 2007	Low	Low	Unknown	Low	Unknown	Low
McDonald 1995	Unknown	Unknown	Unknown	Unknown	Unknown	Low
Colleoni 2011	Low	Unknown	Low	Low	Unknown	Low
Rutqvist 1993	Unknown	Unknown	Unknown	Low	Unknown	Low
van de Velde 2001	Low	Low	High	Unknown	Unknown	Low
Abo-Touk 2010	Low	Unknown	Unknown	Low	Unknown	Low
Goss 2005	Low	Unknown	Low	Low	Unknown	Low
Pagani 2014	Low	Unknown	High	Low	Unknown	Low

Anthony Matthews et Al. BMJ 2018;363:k3845

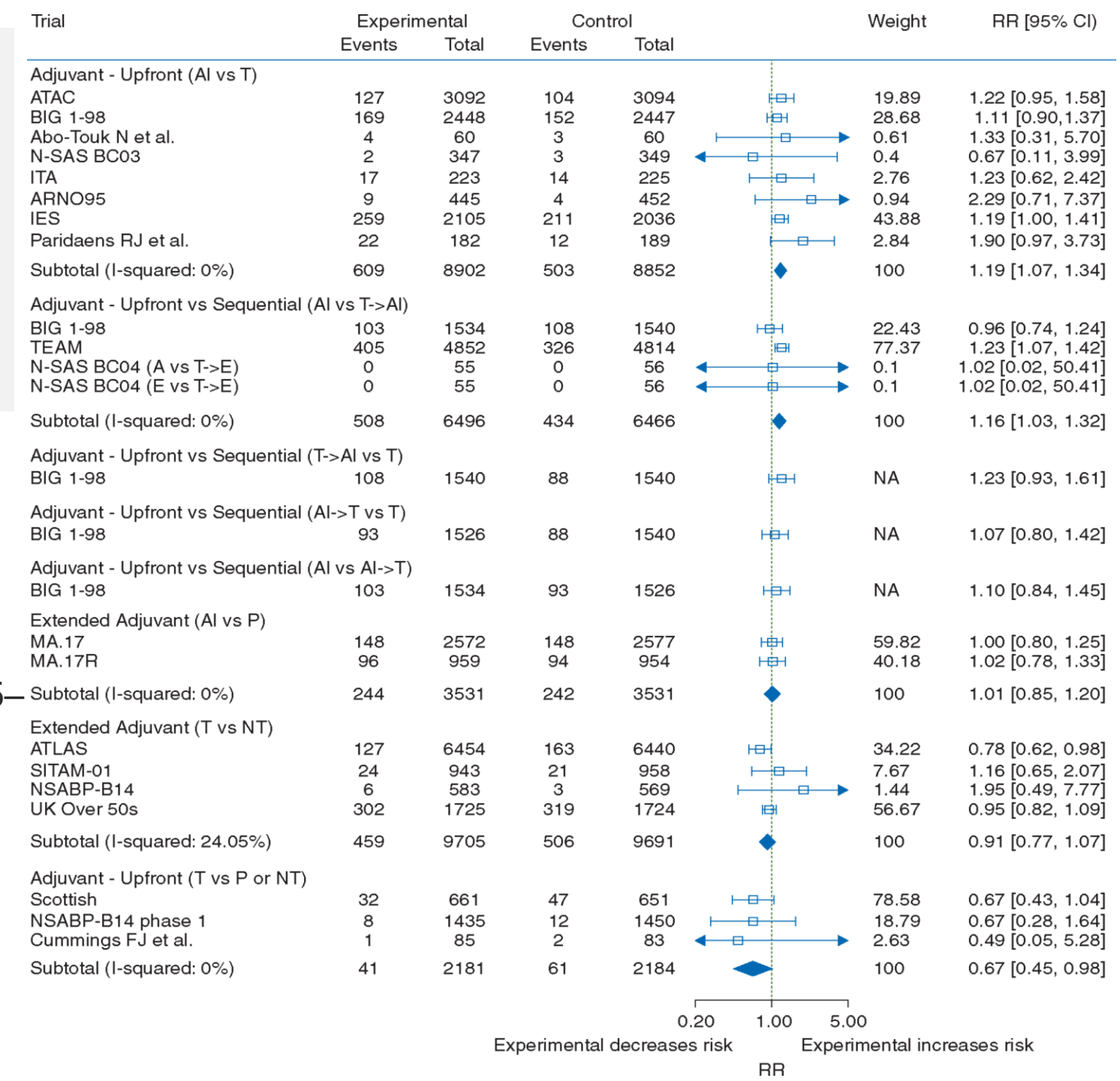
Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials

19 RCTs were included in the meta-analysis (n = 62 345).

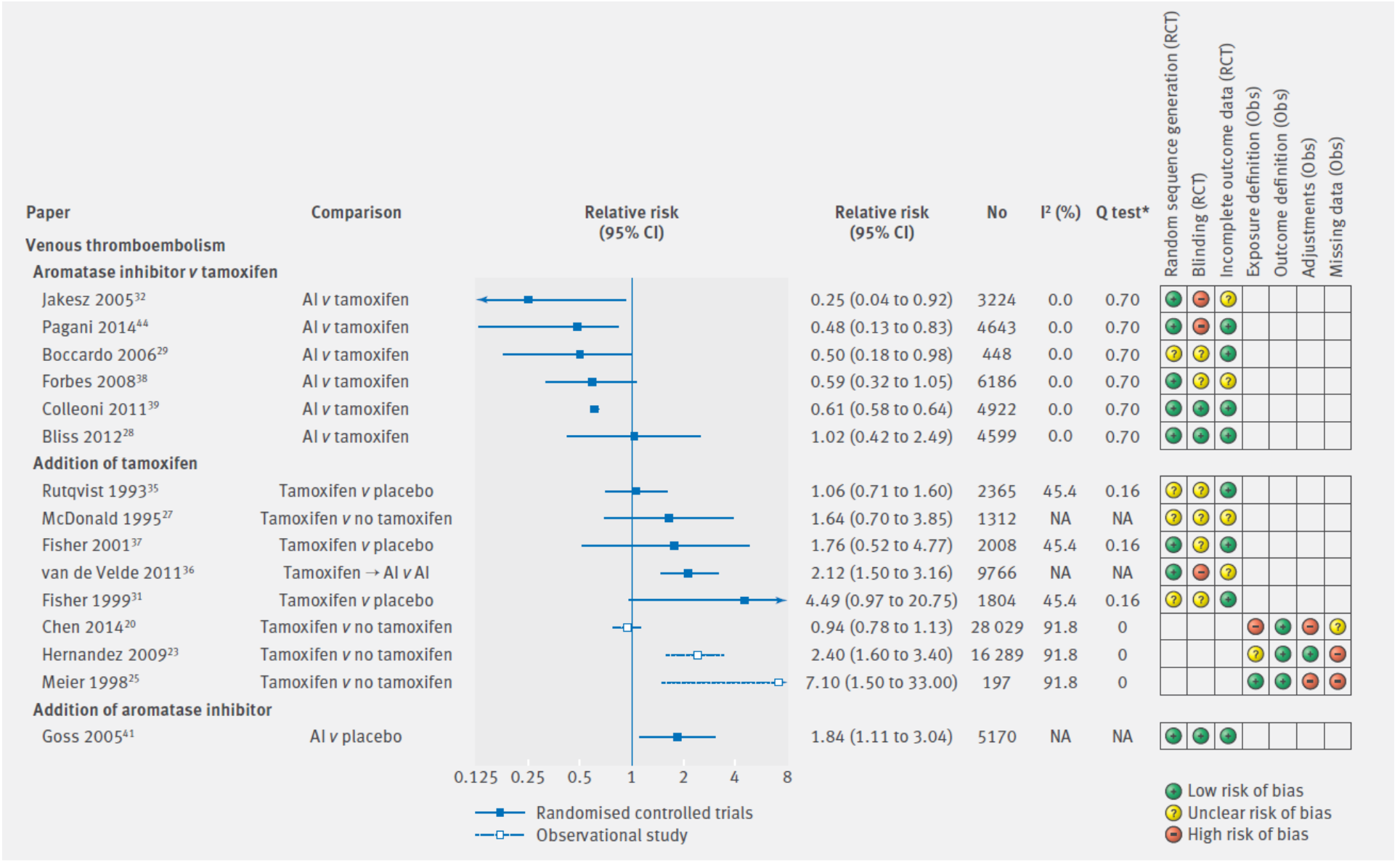
Tamoxifen was associated with a **33% decreased risk** (RR: 0.67, 95% CI: 0.45–0.98) compared with placebo or no-treatment

AIs were associated with a **19% increased risk** (RR: 1.19, 95%CI: 1.07–1.34) compared with tamoxifen.

F. Khosrow-Khavar Ann Oncol. 2016;28(3):487-496

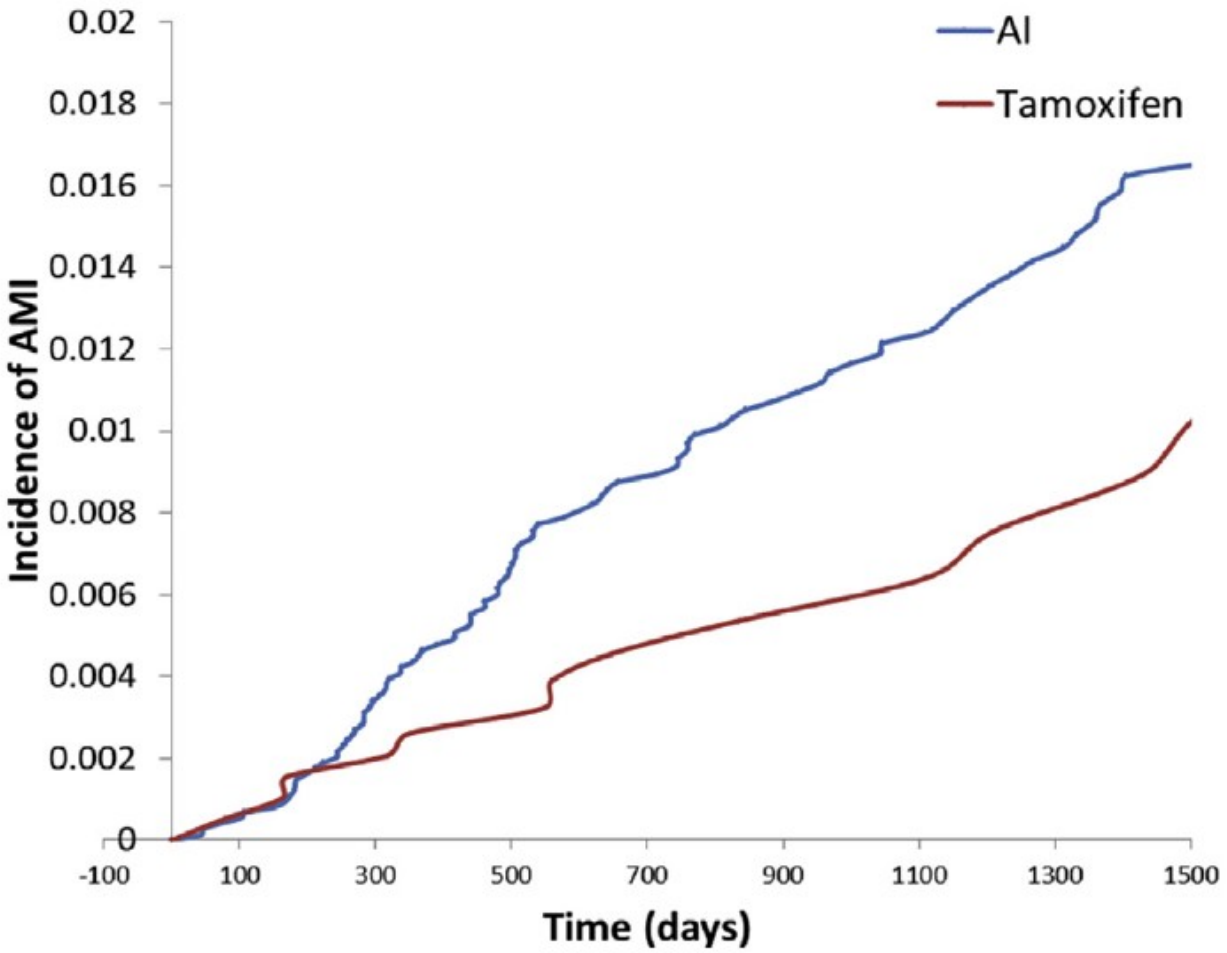


Endocrine therapy and risk of venous thromboembolism

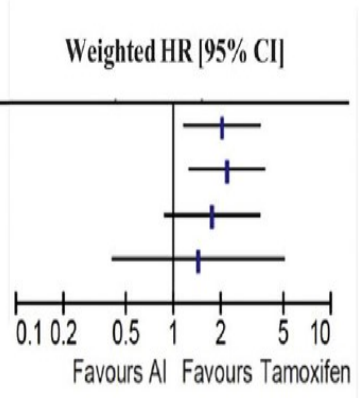


Matthews A. et Al. BMJ 2018

The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer



Study or Subgroup	Aromatase inhibitors Events	Total	Tamoxifen Events	Total
Full cohort	106	7409	17	1941
Aged 66 years and above	98	5869	16	1640
Prior IHD	46	1256	11	328
Lower-risk cohort	21	3426	<6	798



Husam Abdel-Qadir et AL. Eur. J. of Cancer 2016

Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study

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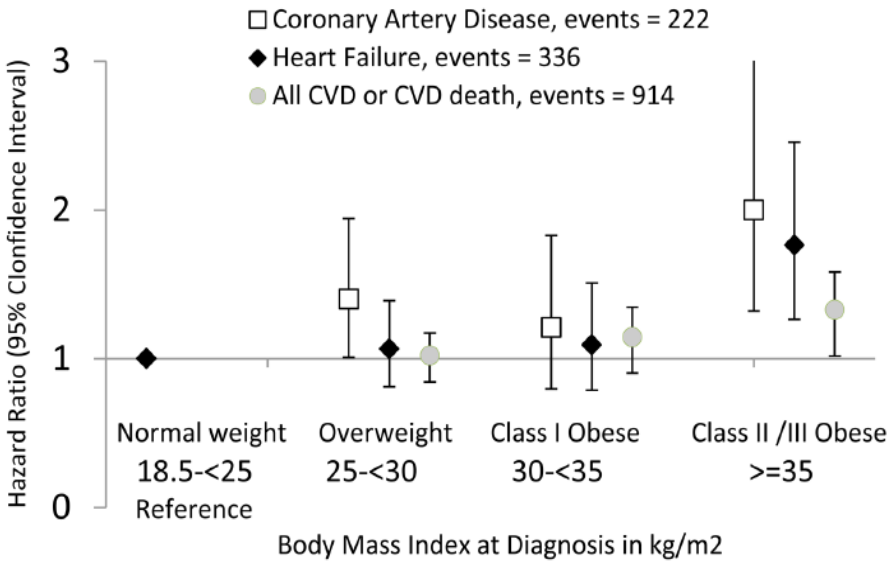
Saro H. Armenian, Lanfang Xu, Bonnie Ky, Canlan Sun, Leonardo T. Farol, Sumanta Kumar Pal, Pamela S. Douglas, Smita Bhatia, and Chun Chao

Table 3. Calculated Crude and Adjusted (Age, Sex, Race/Ethnicity) CVD IRRs by Cancer Type and CVRF (Hypertension, Diabetes, Dyslipidemia) for Cancer Survivors and Comparison Controls

Cancer Type	Crude IRR			Adjusted IRR		
	IRR	95% CI	*P*	IRR	95% CI	*P*
Breast						
Noncancer comparison, < 2 CVRF	1.00 (Ref)	—		1.00 (Ref)	—	
Cancer survivor, < 2 CVRF	2.41	2.22 to 2.62	< .01	1.79	1.64 to 1.95	< .01
Noncancer comparison, ≥ 2 CVRF	1.30	1.19 to 1.43	< .01	1.33	1.21 to 1.46	< .01
Cancer survivor, ≥ 2 CVRF	2.52	2.28 to 2.78	< .01	1.87	1.69 to 2.07	< .01
Kidney						
Noncancer comparison, < 2 CVRF	1.00 (Ref)	—		1.00 (Ref)	—	
Cancer survivor, < 2 CVRF	1.53	1.20 to 1.93	< .01	1.15	0.90 to 1.46	.27
Noncancer comparison, ≥ 2 CVRF	1.01	0.75 to 1.36	.96	1.08	0.80 to 1.46	.61
Cancer survivor, ≥ 2 CVRF	2.19	1.71 to 2.80	< .01	1.83	1.42 to 2.35	< .01
Lung and bronchus						
Noncancer comparison, < 2 CVRF	1.00 (Ref)	—		1.00 (Ref)	—	
Cancer survivor, < 2 CVRF	1.74	1.45 to 2.08	< .01	1.46	1.22 to 1.75	< .01
Noncancer comparison, ≥ 2 CVRF	1.94	1.57 to 2.40	< .01	2.04	1.64 to 2.52	< .01
Cancer survivor, ≥ 2 CVRF	2.49	1.95 to 3.17	< .01	2.29	1.79 to 2.92	< .01
Multiple myeloma						
Noncancer comparison, < 2 CVRF	1.00 (Ref)	—		1.00 (Ref)	—	
Cancer survivor, < 2 CVRF	1.47	1.07 to 2.01	.02	1.28	0.93 to 1.77	.13
Noncancer comparison, ≥ 2 CVRF	1.70	1.17 to 2.47	.01	1.74	1.20 to 2.53	< .01
Cancer survivor, ≥ 2 CVRF	2.74	1.92 to 3.91	< .01	2.59	1.81 to 3.71	< .01
Non-Hodgkin lymphoma						
Noncancer comparison, < 2 CVRF	1.00 (Ref)	—		1.00 (Ref)	—	
Cancer survivor, < 2 CVRF	1.92	1.59 to 2.31	< .01	1.45	1.20 to 1.75	< .01
Noncancer comparison, ≥ 2 CVRF	1.42	1.15 to 1.75	< .01	1.39	1.13 to 1.72	< .01
Cancer survivor, ≥ 2 CVRF	2.62	2.09 to 3.28	< .01	2.12	1.69 to 2.65	< .01
Ovary						
Noncancer comparison, < 2 CVRF	1.00 (Ref)	—		1.00 (Ref)	—	
Cancer survivor, < 2 CVRF	2.11	1.49 to 2.98	< .01	1.47	1.03 to 2.09	.03
Noncancer comparison, ≥ 2 CVRF	1.36	0.94 to 1.96	.11	1.54	1.06 to 2.23	.02
Cancer survivor, ≥ 2 CVRF	2.83	1.90 to 4.22	< .01	2.00	1.33 to 3.00	< .01

Adiposity, Post-Diagnosis Weight Change and Risk of Cardiovascular Events among Early-Stage Breast Cancer Survivors



	80–<90 cm N=480	90–<100 cm N=463	≥100 cm N=417	<80 cm N=535	Per 5 cm N=1,898
Mean (SD) Waist circumference	84.64 (2.71)	94.61 (2.86)	110.66 (10.60)	73.38 (4.67)	89.61 (14.78)
	Hazard Ratio for CVD (95% Confidence Interval)				
CVD Event or Death [a]	154	162	156	124	596
Age & race-adjusted [b]	1.31 (1.02, 1.68)	1.34 (1.04, 1.73)	1.63 (1.26, 2.11)	Ref.	1.06 (1.03, 1.09)
+lifestyle and BMI [c]	1.52 (1.15, 2.00)	1.67 (1.20, 2.32)	2.01 (1.37, 2.94)	Ref.	1.09 (1.05, 1.14)
+tumor & treatment [d]	1.50 (1.14, 1.97)	1.63 (1.17, 2.26)	2.02 (1.37, 2.97)	Ref.	1.09 (1.04, 1.14)
+pre-existing CVD risk factors [e]	1.48 (1.12, 1.95)	1.60 (1.15, 2.22)	1.93 (1.31, 2.84)	Ref.	1.08 (1.03, 1.13)

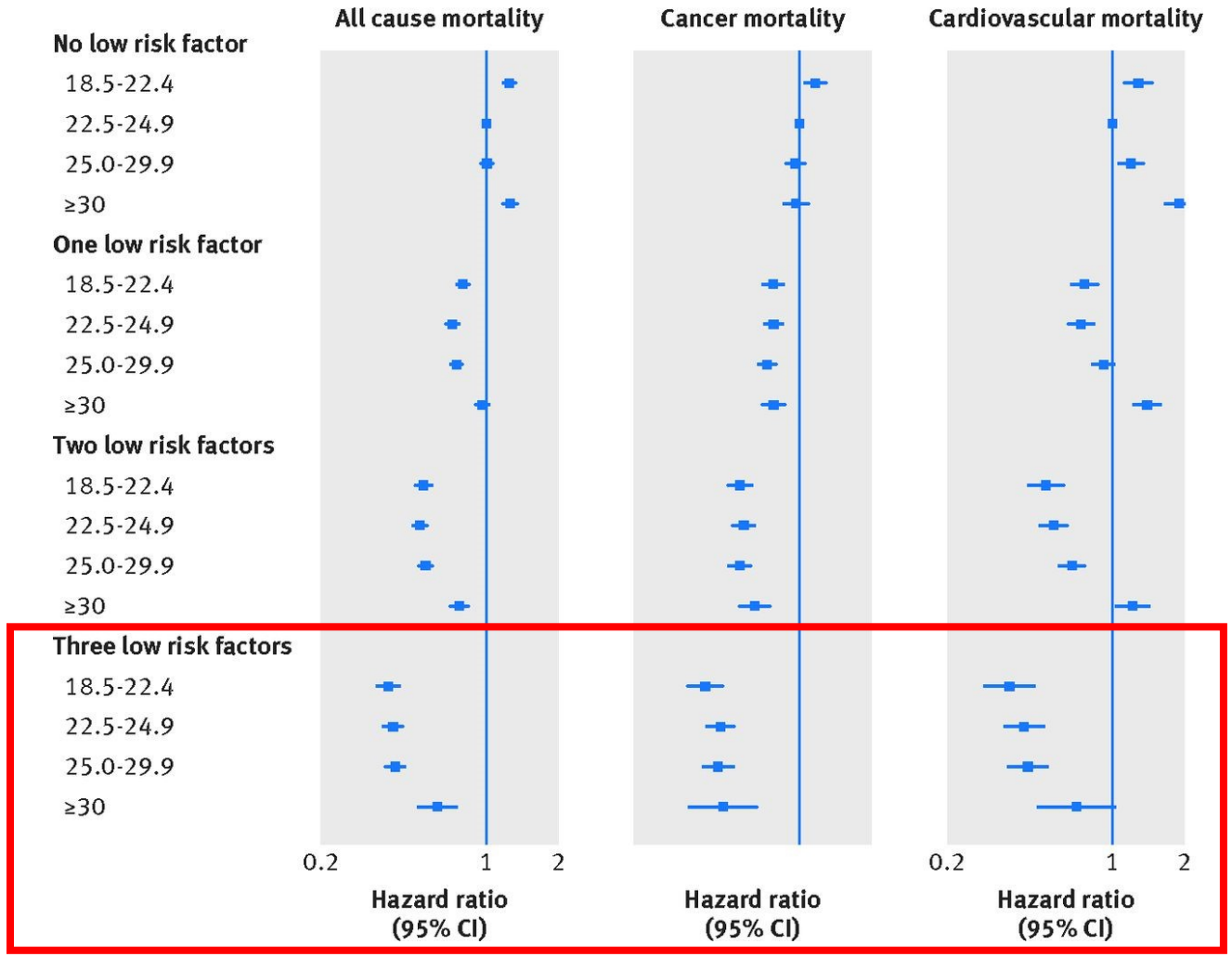
Elizabeth M. Cespedes Feliciano et Al. Breast Cancer Res Treat. 2017

Combined associations of body weight and lifestyle factors with all cause and cause specific mortality in men and women: prospective cohort study

74 582 women from the Nurses' Health Study and **39 284 men** from the Health Professionals Follow-up Study who were free from cardiovascular disease and cancer at baseline

Low risk lifestyles:
- never smoking,
- exercise ≥30 min/day at moderate or vigorous intensity,
- AHEI* score in upper two fifths, and
- moderate alcohol consumption (5-15 g alcohol/day in women, 5-30 g alcohol/day in men).

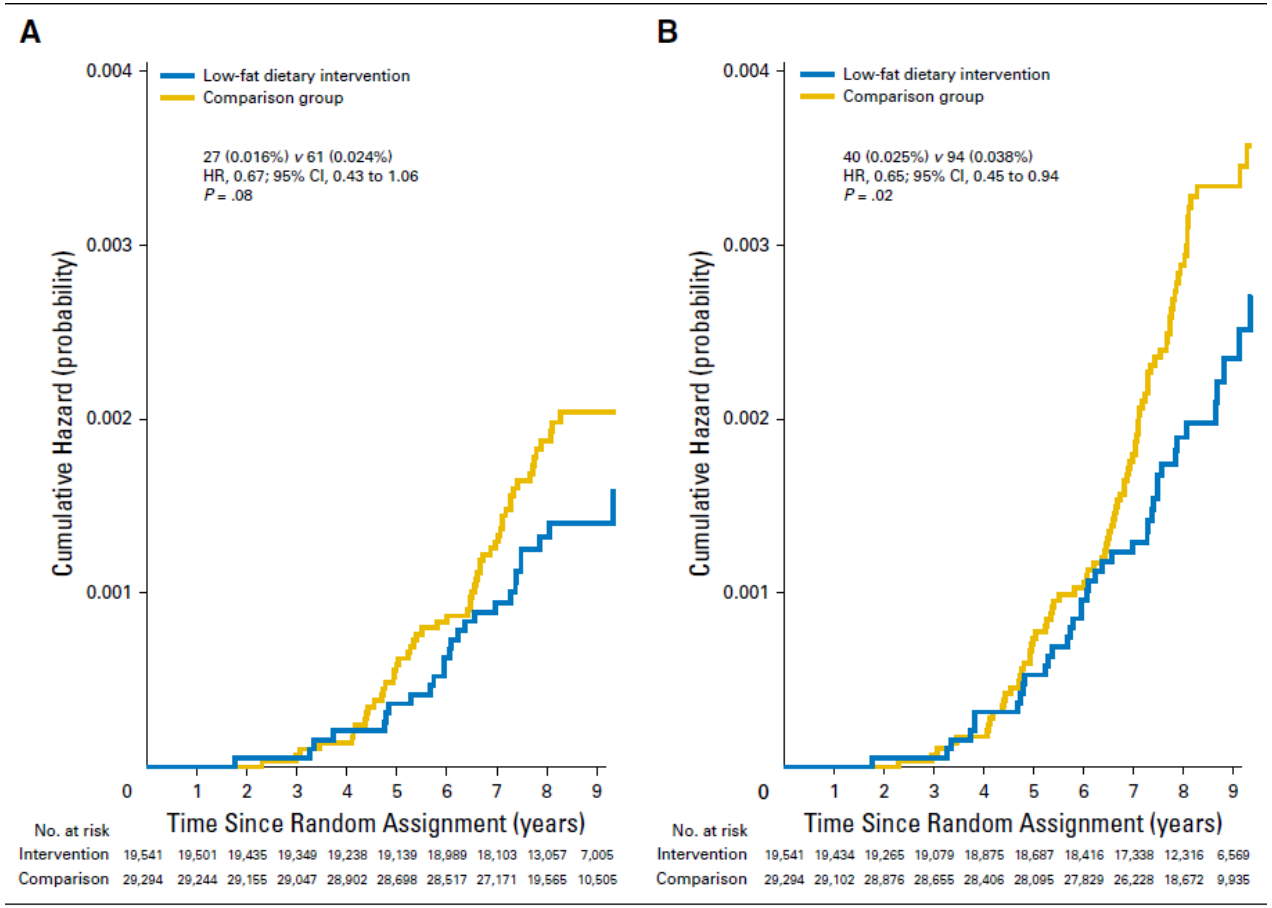
** Alternate Health Eating Score*



Veronese N. et al. BMJ. 2016;355:i5855

L’importanza dello Stile Alimentare

Low-Fat Dietary Pattern and Breast Cancer Mortality in the Women’s Health Initiative Randomized Controlled Trial



Dietary modification influence on deaths as a result of (**A**) and after (**B**) breast cancer during the 8.5-year (median) dietary intervention period.

Rowan T. Chlebowski et Al. JCO 201

VOLUME 34 · NUMBER 7 · MARCH 1, 2016

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial Comparing Telephone Versus In-Person Weight Loss Counseling on Body Composition and Circulating Biomarkers in Women Treated for Breast Cancer: The Lifestyle, Exercise, and Nutrition (LEAN) Study

Maura Harrigan, Brenda Cartmel, Erikka Loftfield, Tara Sanft, Anees B. Chagpar, Yang Zhou, Mary Playdon, Fangyong Li, and Melinda L. Irwin

See accompanying editorial on page 646

VOLUME 32 · NUMBER 21 · JULY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Trial of a Telephone-Based Weight Loss Intervention in Postmenopausal Women With Breast Cancer Receiving Letrozole: The LISA Trial

Pamela J. Goodwin, Roanne J. Segal, Michael Vallis, Jennifer A. Ligibel, Gregory R. Pond, André Robidoux, George L. Blackburn, Brian Findlay, Julie R. Gralow, Som Mukherjee, Mark Levine, and Kathleen I. Pritchard

See accompanying editorial on page 2197

VOLUME 33 · NUMBER 28 · OCTOBER 1 2015

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Results of the Exercise and Nutrition to Enhance Recovery and Good Health for You (ENERGY) Trial: A Behavioral Weight Loss Intervention in Overweight or Obese Breast Cancer Survivors

Cheryl L. Rock, Shirley W. Flatt, Tim E. Byers, Graham A. Colditz, Wendy Demark-Wahnefried, Patricia A. Ganz, Kathleen Y. Wolin, Anthony Elias, Helen Krontiras, Jingxia Liu, Michael Naughton, Bilgé Pakiz, Barbara A. Parker, Rebecca L. Sedjo, and Holly Wyatt

Listen to the podcast by Dr Ligibel at www.jco.org/podcasts

Grazie per l’Attenzione