PROGETTO SPECIALE "CARDIO-ONCOLOGIA" 2013-2015
AIOM – ANMCO – AICO – ICOS

Cardiotossicità nel carcinoma mammario da LHRH-Analoghi

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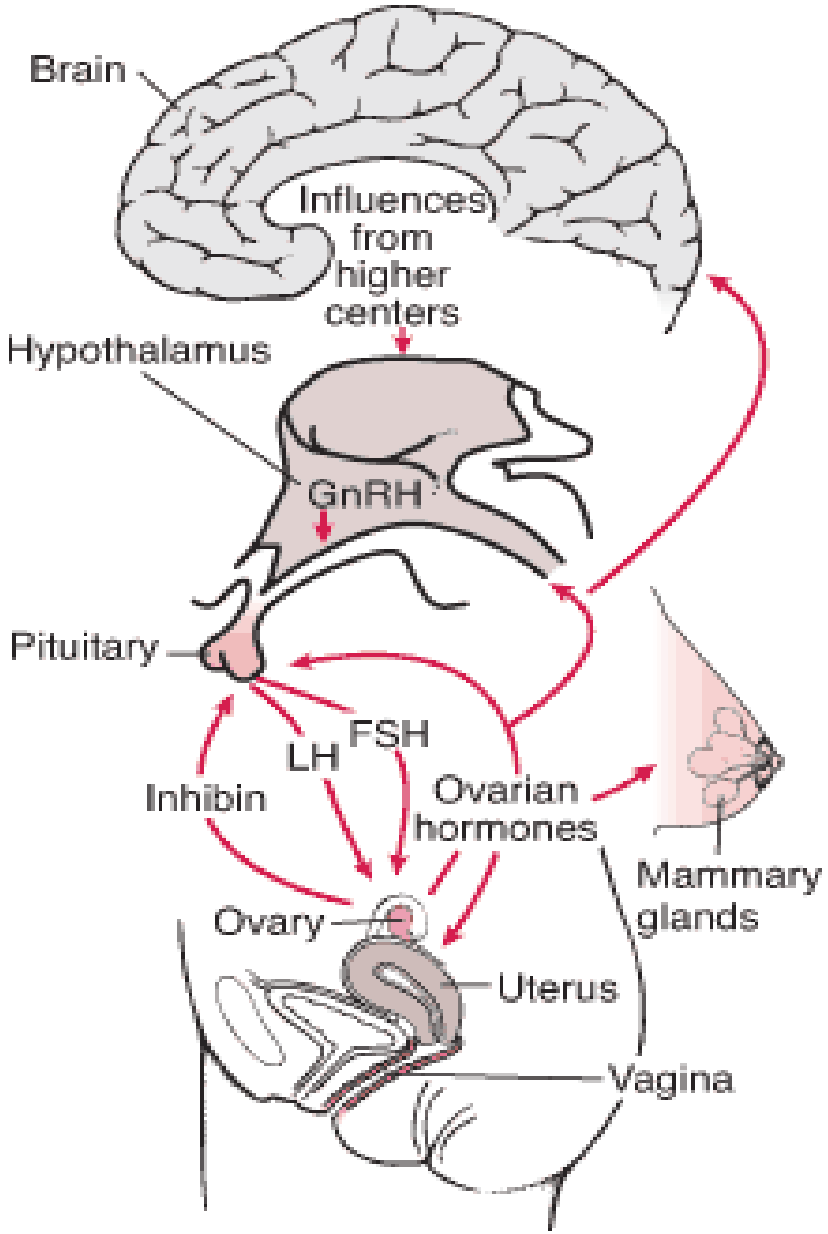
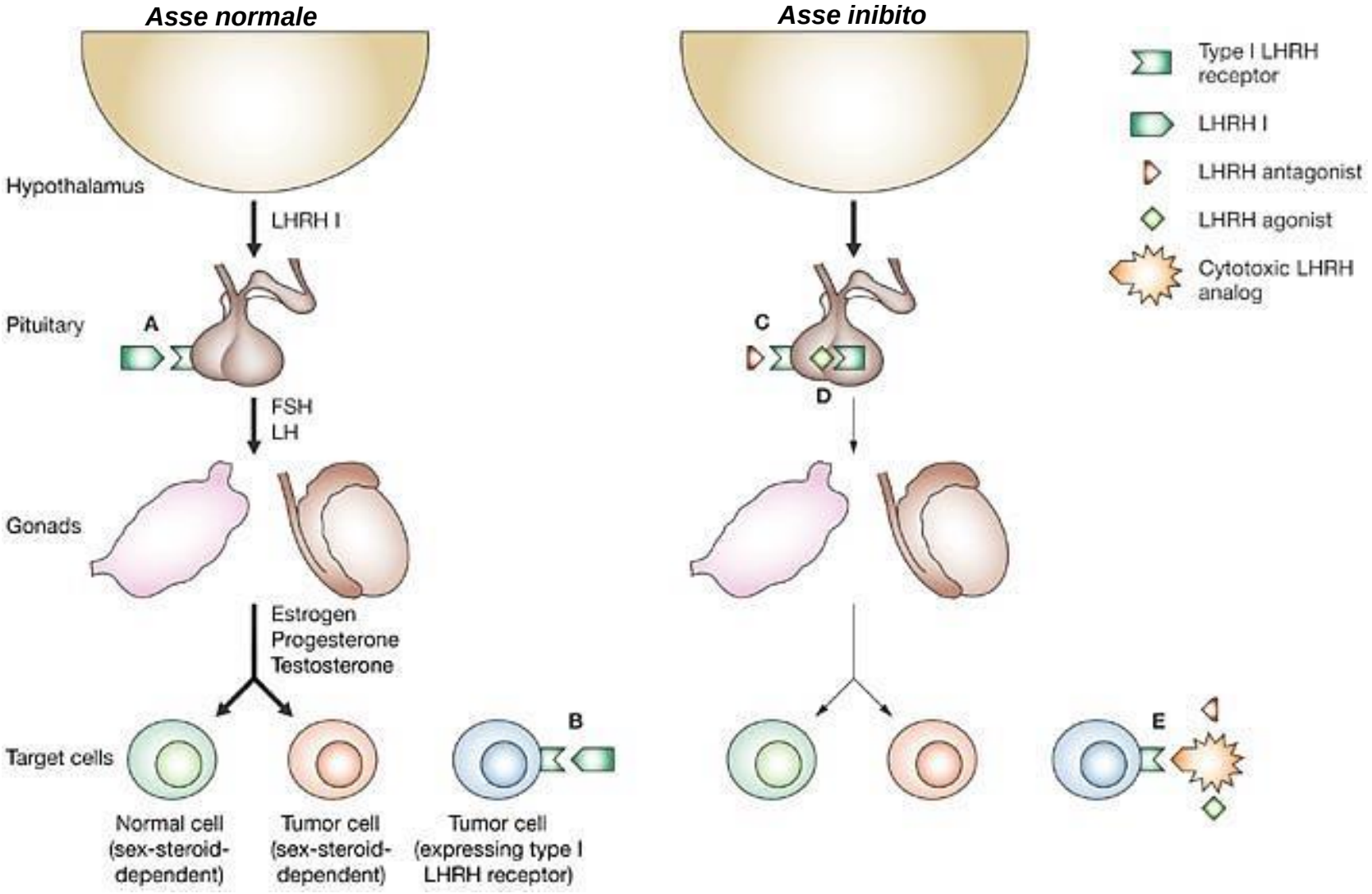
Asse ipotalamo-ipofisi-ovaio



Meccanismo d'azione degli LHRH analoghi



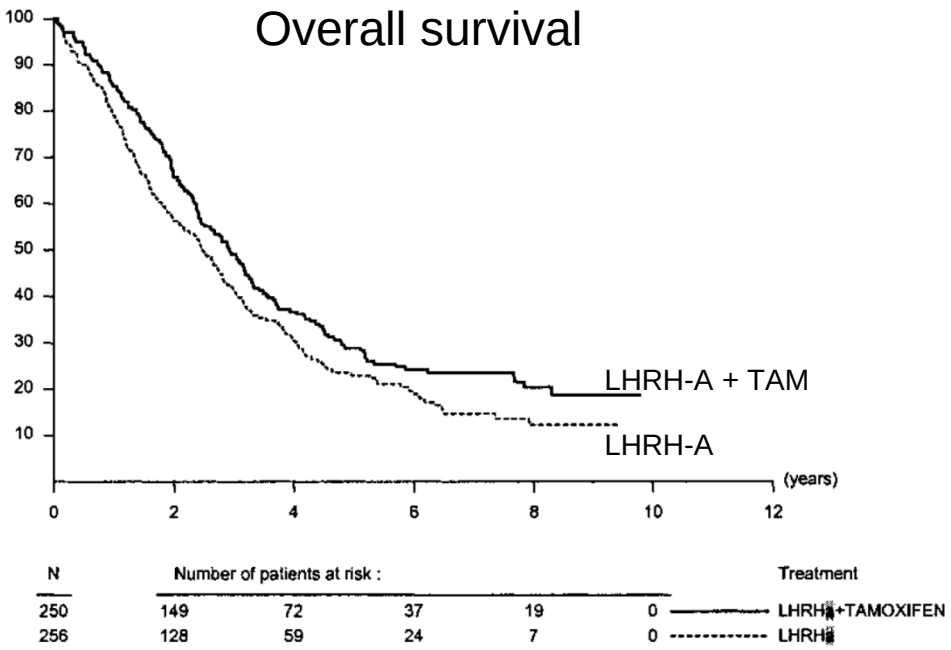
Engel and Andrew, Nat Clin Pract Endocinol Metab 2007

LHRH agonisti

- Legano il recettore per LHRH (cellule gonadotrope ipofisarie)
- Iniziale «flare-up» (per iniziale aumento dei livelli di gonadotropine)
- Dopo somministrazione prolungata: down-regolazione dei recettori con conseguente inibizione della produzione di gonadotropine
- Uso cronico: riduzione dell'estrogeno circolante a livelli simili all'annessiectomia (castrazione biochimica)

LHRH agonisti +/- tamoxifen nel carcinoma mammario metastatico

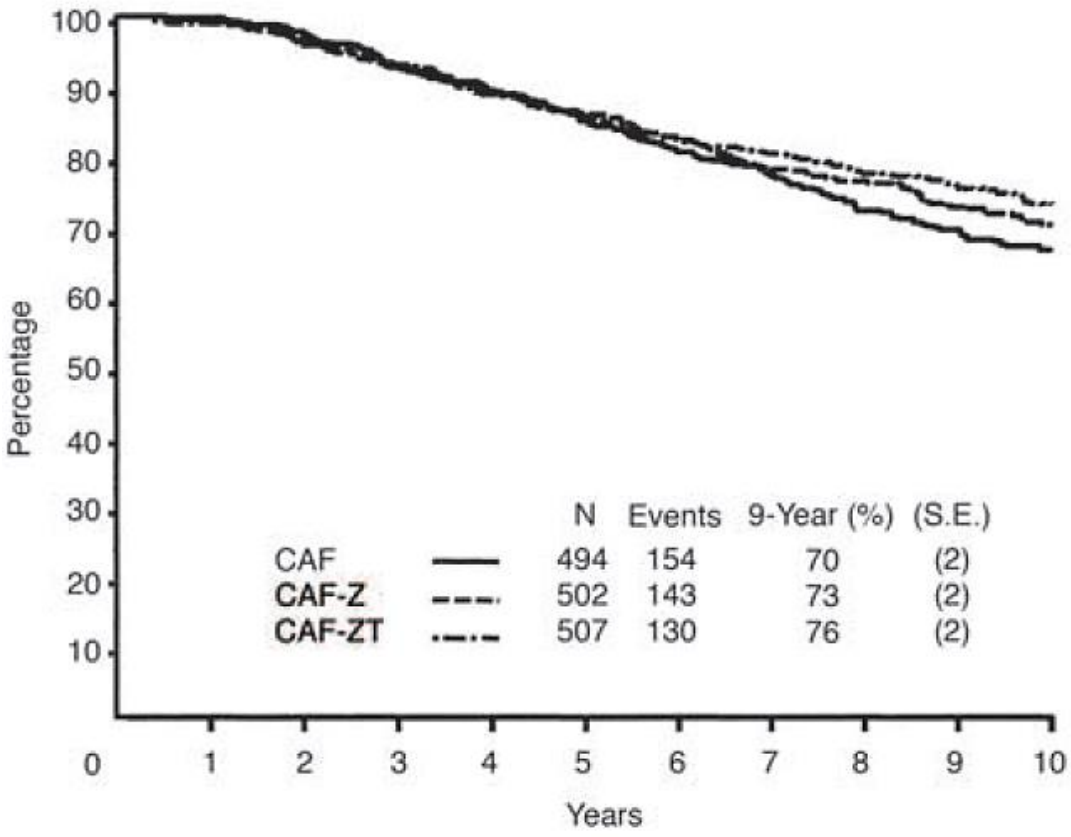
End Point	LHRH agonist alone N=256	LHRH agonist + Tamoxifen N=250	HR	95%CI	p
Median survival, years	2.5	2.9	0.78	0.63-0.96	0.02
Median PFS, months	5.4	8.7	0.70	0.58-0.85	0.0003
Objective response %	29.7	38.8	0.67	0.46-0.96	0.03



Klijn, JCO 2008

Chemoendocrine Therapy for Premenopausal Women With Axillary Lymph Node–Positive, Steroid Hormone Receptor–Positive Breast Cancer: Results From INT 0101 (E5188)

Overall survival

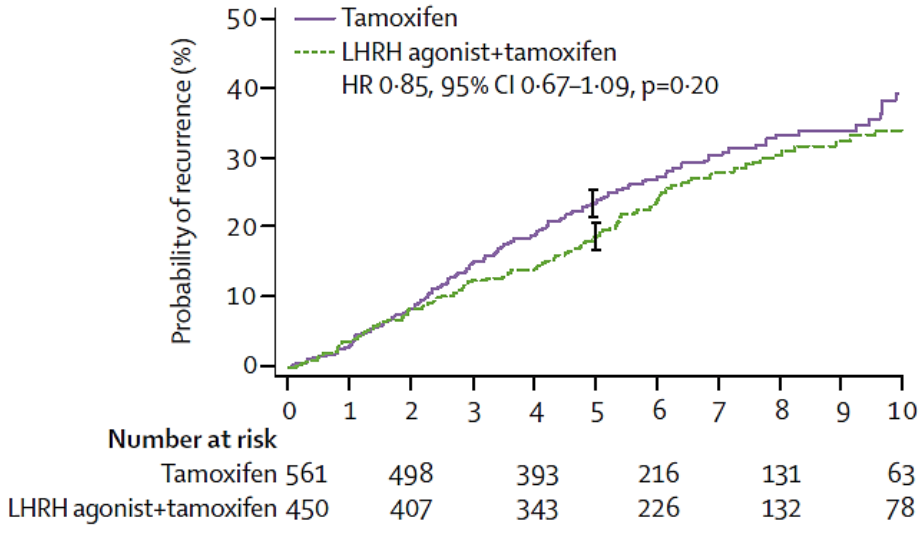


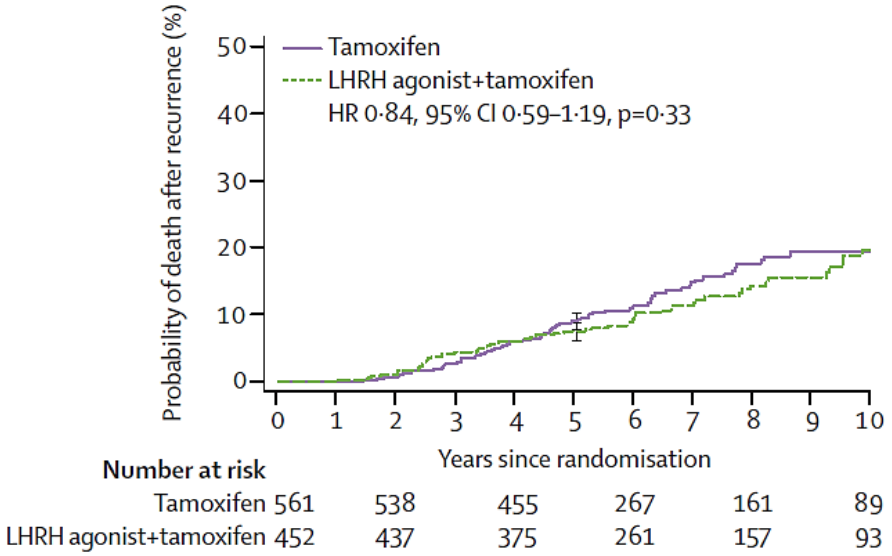
No difference!

Davidson , JCO 2005

Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials

*LHRH-agonists in Early Breast Cancer Overview group**





The addition of an LHRH agonist to tamoxifen **did not significantly reduce** the hazard rates for recurrence (14·5% reduction, 95% CI 32·7% reduction to 8·6% increase, p=0·20), death after recurrence (15·9%, 40·7% reduction to 19·4% increase, p=0·33), or death from any cause (13·7%, 38·1% reduction to 20·3% increase, p=0·39)

Early Breast Cancer Overview Group, Lancet 2007

Studio SOFT

3047 Patients Randomized in ITT, Dec 2003 - Jan 2011

Primary Analysis (n= 2033)
Median follow-up 5.6 years

Two Patient Cohorts (stratified)

No Chemotherapy (47%)
Premenopausal, within 12 weeks of surgery
(Median time since surgery = **1.8 months**)

Prior Chemotherapy (53%)
Premenopausal* after completing chemotherapy;
Randomization within 8 months of completion
(Median time since surgery = **8.0 months**)

RANDOMIZE

→ **Tamoxifen x 5y** (n=1018)

→ **Tamoxifen+OFS x 5y** (n=1015)

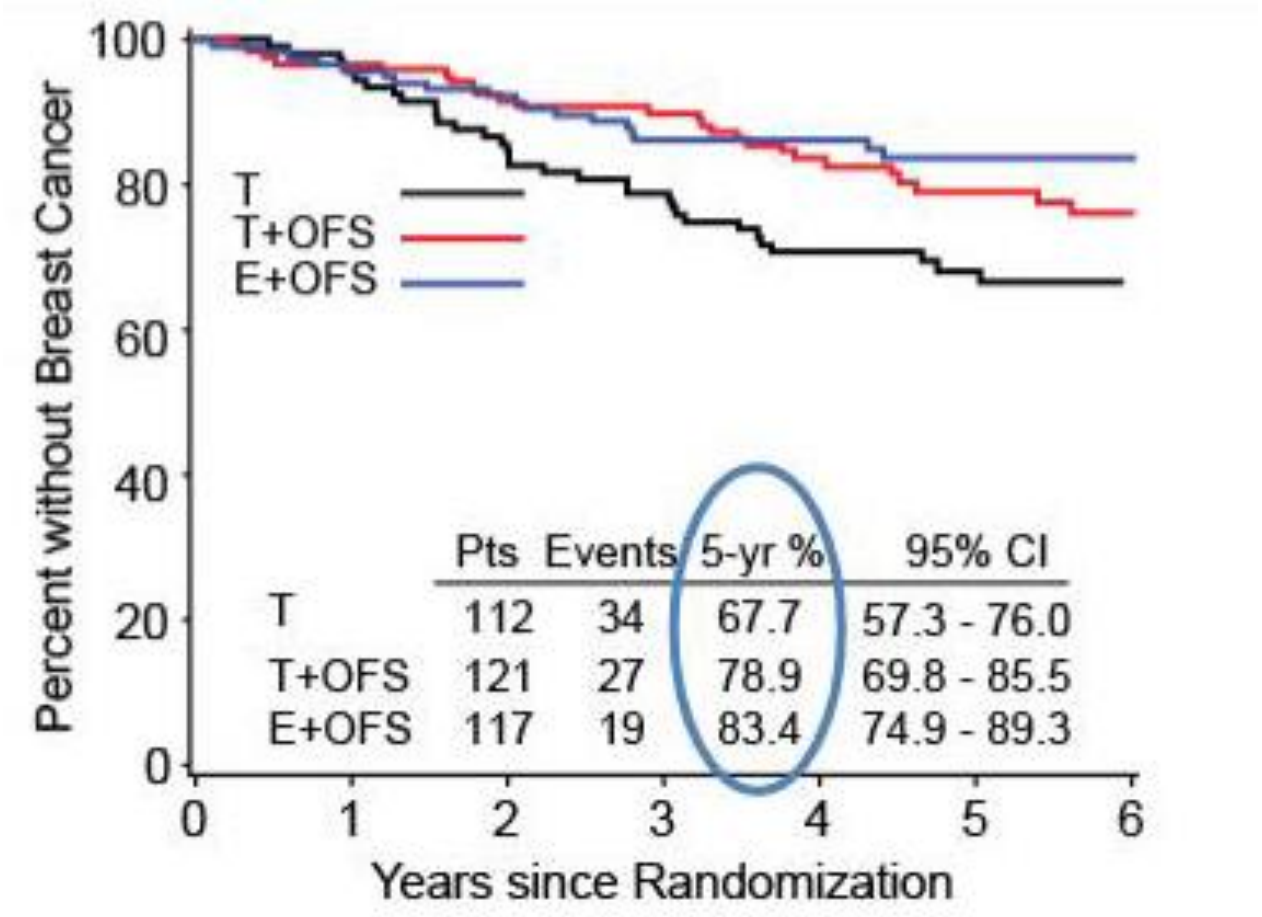
→ **Exemestane+OFS x 5y** (n=1014)

OFS=ovarian function suppression
(GnRH triptorelin, oophorectomy or irradiation)

*According to locally-determined Elevel in premenopausal range

Francis, SABCS 2014; NEJM 2014

Possibile ruolo di LHRH analogo nelle donne giovani



350 pazienti under 35
94% delle pazienti hanno ricevuto ormonoterapia

Francis, SABCS 2014

Potenziale effetto cardiovascolare dei LHRH-agonisti nella donna

Azione metabolica

- Deprivazione estrogenica
- Iperglicemia
- Dislipidemia
- Danno endoteliale

Azione diretta sul cardiomiocita

- Riduzione del calcio intrecellulare -> ridotta funzione contrattile
- Possibile inibizione dei pathway di sopravvivenza cellulare in caso di danno ischemico

Studio SOFT: Eventi avversi

Adverse Event	Tamoxifen (N=1006)								Tamoxifen plus Ovarian Suppression (N=1005)							
	Any Event				Grade 3-5 Event				Any Event				Grade 3-5 Event			
	N	%	95% CI		N	%	95% CI		N	%	95% CI		N	%	95% CI	
Allergic reaction or hypersensitivity	32	3.2	(2.2	4.5)	1	0.1	(0.0	0.6)	44	4.4	(3.2	5.8)	2	0.2	(0.0	0.7)
Injection-site reaction	4	0.4	(0.1	1.0)	0	0.0	.	.	88	8.8	(7.1	10.7)	0	0.0	.	.
Hot flushes	803	79.8	(77.2	82.3)	76	7.6	(6.0	9.4)	939	93.4	(91.7	94.9)	133	13.2	(11.2	15.5)
Depression	469	46.6	(43.5	49.8)	38	3.8	(2.7	5.1)	522	51.9	(48.8	55.1)	44	4.4	(3.2	5.8)
Sweating	486	48.3	(45.2	51.4)	--	--	--	--	621	61.8	(58.7	64.8)	--	--	--	--
Insomnia	466	46.3	(43.2	49.5)	29	2.9	(1.9	4.1)	575	57.2	(54.1	60.3)	46	4.6	(3.4	6.1)
Fatigue	603	59.9	(56.8	63.0)	32	3.2	(2.2	4.5)	631	62.8	(59.7	65.8)	36	3.6	(2.5	4.9)
Hypertension	173	17.2	(14.9	19.7)	54	5.4	(4.1	6.9)	233	23.2	(20.6	25.9)	75	7.5	(5.9	9.3)
Cardiac ischemia or infarction	5	0.5	(0.2	1.2)	4	0.4	(0.1	1.0)	3	0.3	(0.1	0.9)	1	0.1	(0.0	0.6)
Thrombosis or embolism	22	2.2	(1.4	3.3)	17	1.7	(1.0	2.7)	20	2.0	(1.2	3.1)	17	1.7	(1.0	2.7)
Nausea	239	23.8	(21.2	26.5)	0	0.0	.	.	219	21.8	(19.3	24.5)	4	0.4	(0.1	1.0)
Musculoskeletal symptoms	694	69.0	(66.0	71.8)	63	6.3	(4.8	7.9)	755	75.1	(72.3	77.8)	55	5.5	(4.1	7.1)
Osteoporosis	124	12.3	(10.4	14.5)	1	0.1	(0.0	0.6)	201	20.0	(17.6	22.6)	3	0.3	(0.1	0.9)
Fractures	49	4.9	(3.6	6.4)	8	0.8	(0.3	1.6)	54	5.4	(4.1	7.0)	8	0.8	(0.3	1.6)
Vaginal dryness	421	41.8	(38.8	45.0)	--	--	--	--	500	49.8	(46.6	52.9)	--	--	--	--
Libido decrease	427	42.4	(39.4	45.6)	--	--	--	--	477	47.5	(44.3	50.6)	--	--	--	--
Dyspareunia	238	23.7	(21.1	26.4)	14	1.4	(0.8	2.3)	262	26.1	(23.4	28.9)	22	2.2	(1.4	3.3)
Urinary incontinence	162	16.1	(13.9	18.5)	6	0.6	(0.2	1.3)	185	18.4	(16.1	20.9)	5	0.5	(0.2	1.2)
CNS cerebrovascular ischemia	6	0.6	(0.2	1.3)	4	0.4	(0.1	1.0)	2	0.2	(0.0	0.7)	1	0.1	(0.0	0.6)
CNS hemorrhage	14	1.4	(0.8	2.3)	0	0.0	.	.	10	1.0	(0.5	1.8)	1	0.1	(0.0	0.6)
Glucose intolerance†	18	1.8	(1.1	2.8)	3	0.3	(0.1	0.9)	35	3.5	(2.4	4.8)	14	1.4	(0.8	2.3)
Hyperglycemia†	16	1.6	(0.9	2.6)	1	0.1	(0.0	0.6)	46	4.6	(3.4	6.1)	9	0.9	(0.4	1.7)
Any targeted adverse event	959	95.3	(93.8	96.5)	238	23.7	(21.1	26.4)	989	98.4	(97.4	99.1)	315	31.3	(28.5	34.3)

Non significativi aumenti della tossicità cardiovascolare

L'iperglicemia potrebbe essere sottostimata (registrazione iniziata in corso di trial)
Follow up potrebbe non essere adeguato per eventi tardivi (67 mesi)

Francis, NEJM 2014