

Management of Unfavorable-Risk Prostate Cancer

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Disclosure

- I have no conflicts of interest to disclose.

Learning Objectives

- Describe the management of intermediate to very high-risk prostate cancer and the level one evidence on which these recommendations are based.
- Explain the potential interaction of androgen suppression therapy with cardiovascular disease and its impact on mortality.

Pre Test Questions

56 year old man in excellent health

cT3bNxMO, Gleason score 8 and PSA 25

The standard of care is to deliver external beam RT and what duration of androgen suppression therapy?

- A. 4 months**
- B. 6 months**
- C. 12 months**
- D. 28 to 36 months**
- E. 0 months**

A PSA nadir > then what value is a surrogate for prostate cancer-specific mortality following external beam RT and 6 months of androgen suppression therapy?

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- C. 0.05 ng/ml**
- D. 0.10 ng/ml**
- E. None of the Above**

RISK GROUPS

– Low Risk

- PSA \leq 10 and
- Biopsy Gleason \leq 6 and
- T1c or T2a

– Intermediate Risk

- PSA $>$ 10 – 20 or
- Biopsy Gleason 7 or
- T2b

– High Risk – bone scan; CT/MRI pelvis

- PSA $>$ 20 or
- Biopsy Gleason 8 – 10
- T2c or higher

Trials with RT in unfavorable risk Adding Short Course HT

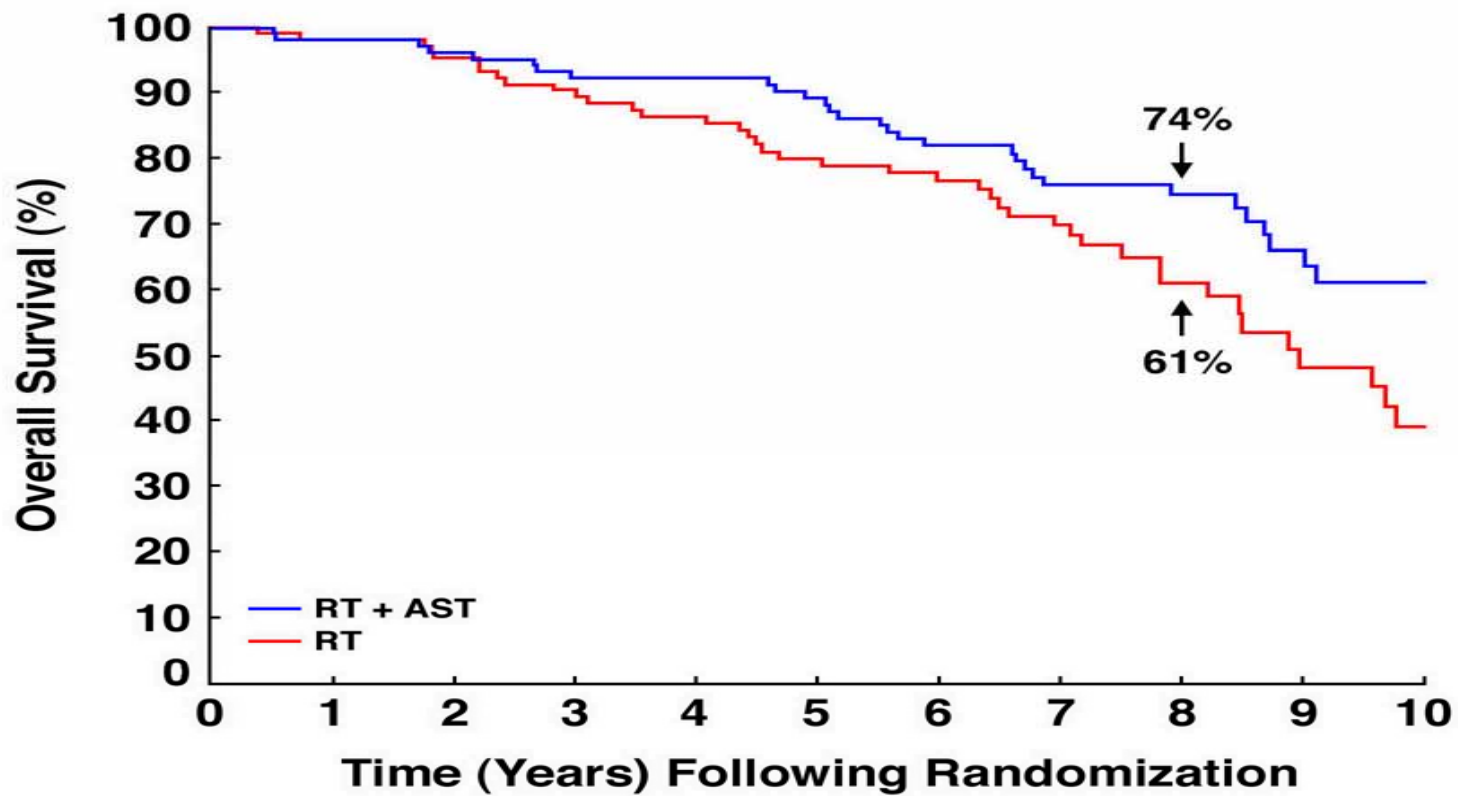
- **70 Gy RT ± 6 mos H Rx – DFCI 95096**
 - 13% overall survival benefit at 8 years
 - T1b to T2b (77% intermediate and 23% high-risk)
 - 58% Gleason score 7
- **66 Gy RT + 0, 3, or 6 mos H Rx – TROG 9601**
 - 13.3% overall survival benefit at 10 years (6 mo arm)
 - 40% T3, 4
 - 38% Gleason score 7
- **3 to 6 mos of H Rx then 64 vs 74 Gy – MRC RT01**
 - 12% PSA benefit at 5 years, no survival benefit
 - 20% T3

Locally Advanced Prostate Ca

- Life long HT \pm RT
 - Hazard Ratio for overall survival
 - SPCG-7 (N = 875, CAB x 3 mos then AA)
 - 0.68 [0.52 to 0.89], p = 0.004 at median f/u 7.6 yrs
 - Intergroup (N = 1205, LHRH/orch)
 - 0.77 [0.61 to 0.98], p = 0.033 at median f/u 6.0 yrs
- RT \pm 3 years of HT
 - EORTC (N = 412, CAB x 1 mo then LHRH)
 - 0.51 [0.37 to 0.73], p < 0.001 at median follow up 5.5 yrs

Synthesis of Trial Data

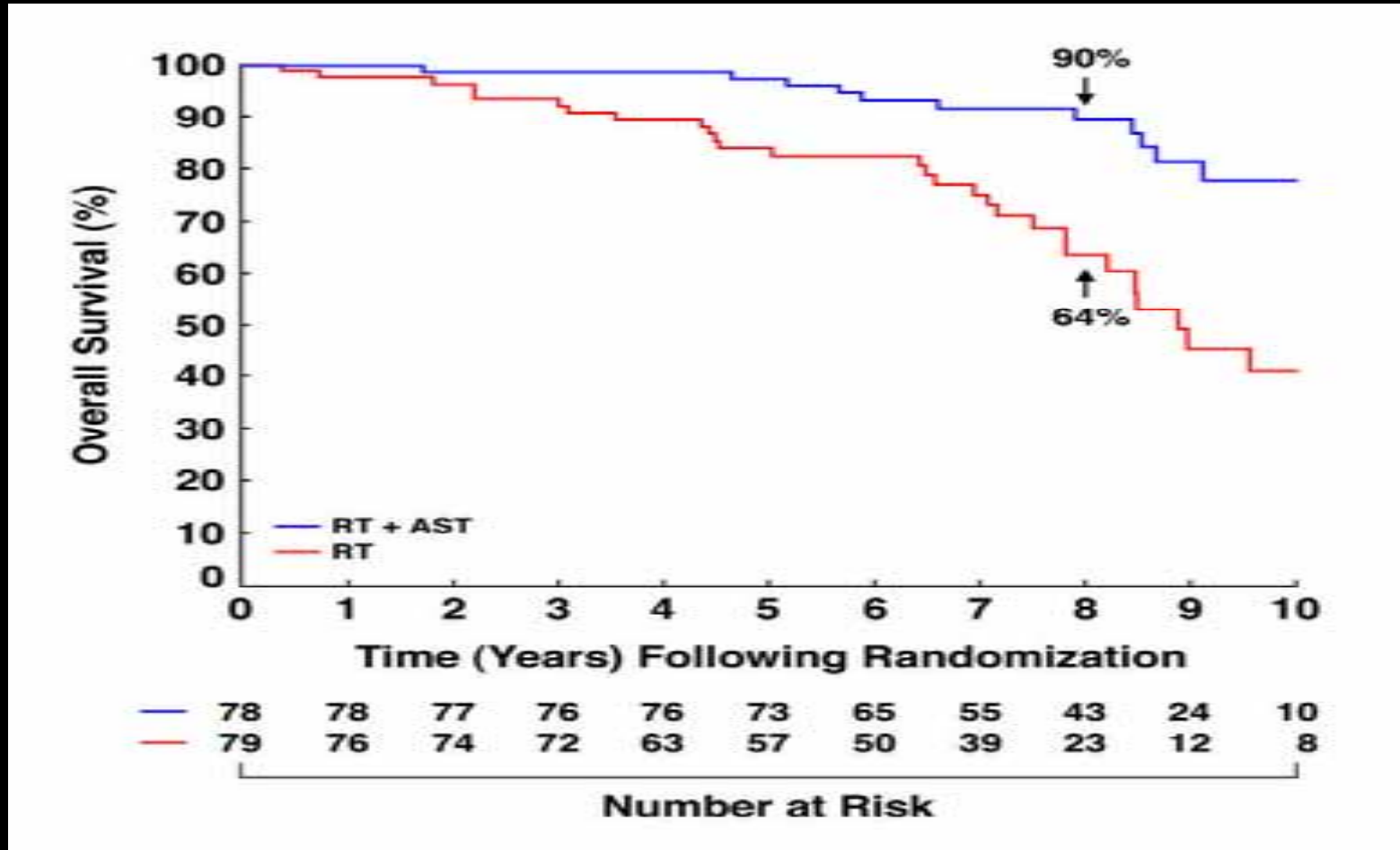
- Overall Survival Benefit
 - EORTC 3 yrs vs 0 (18.3% at 10 years)
 - TROG 6 mos vs 0 (13.3% at 10 years)
 - DFCI 6 mos vs 0 (13% at 8 years)
 - EORTC 3 yrs vs 6 mos (3.8% at 5 yrs)
- 4% benefit for 2.5 more yrs of LHRH agonist



—	102	100	98	93	93	87	75	60	47	27	12
—	104	101	97	92	82	73	62	48	30	18	10

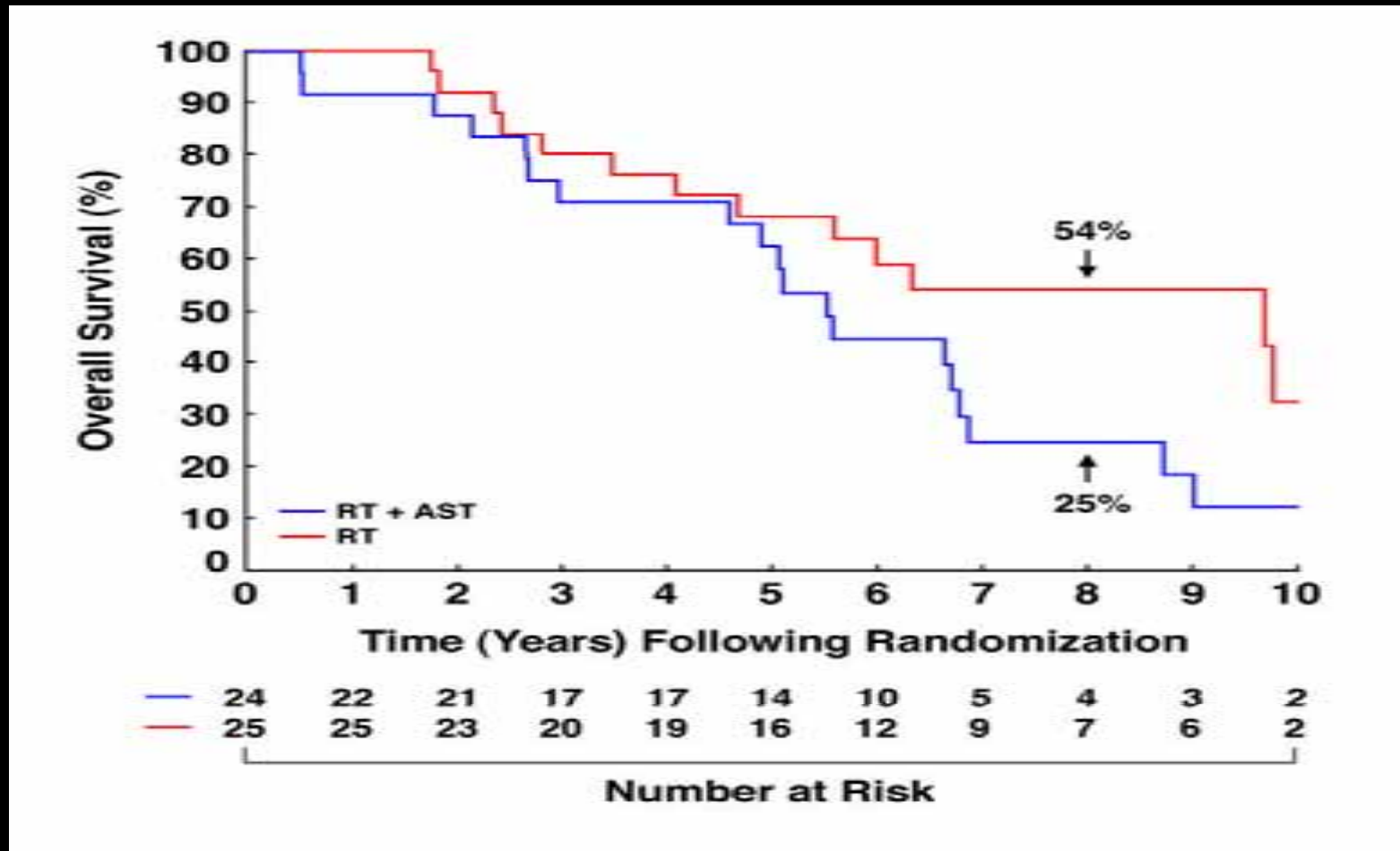
Number at Risk

No or Minimal Comorbidity



Adjusted HR: 4.2 [2.1 to 8.5]; P < 0.001

Moderate to Severe Comorbidity



Adjusted HR: 0.54 [0.27 to 1.1]; P = 0.08

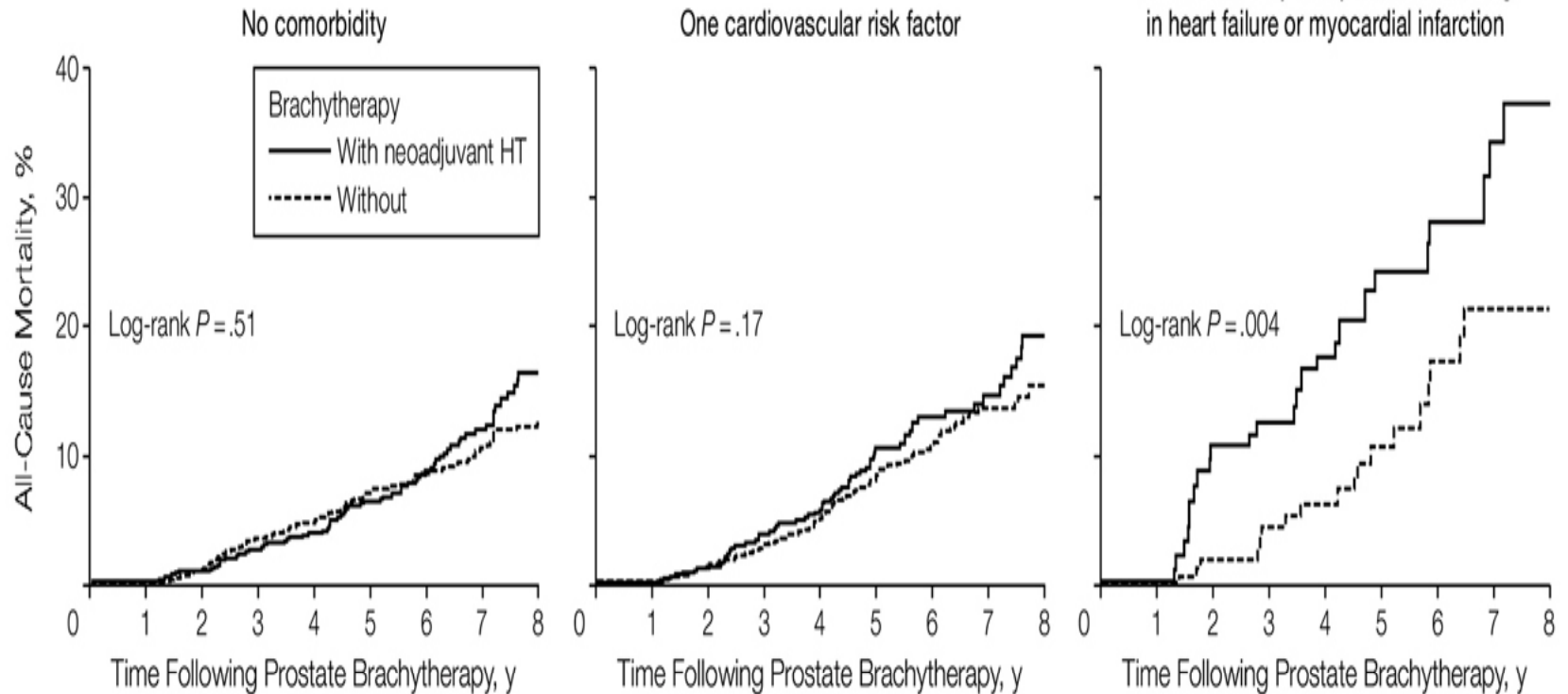
Who makes up the 4%?

1. Healthy

52%

43%

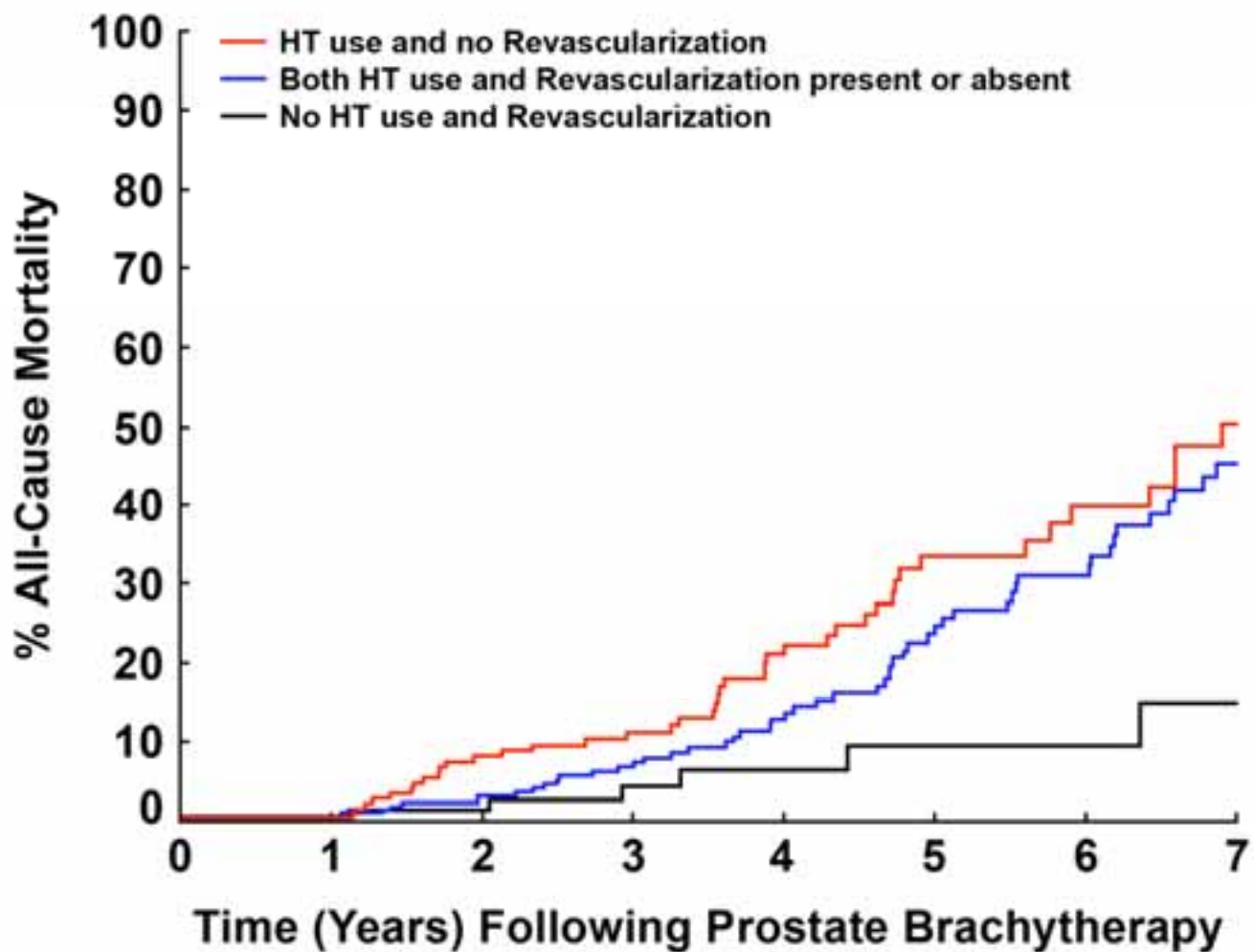
5%



No. at risk

Brachytherapy

With neoadjuvant HT	780	699	532	288	98	646	566	373	176	55	95	79	58	30	8
Without	1873	1582	1073	607	262	1522	1247	765	392	151	161	135	97	46	18



—	157	157	134	105	71	41	25	16
—	246	246	208	161	114	76	55	33
—	92	92	74	50	36	28	19	15

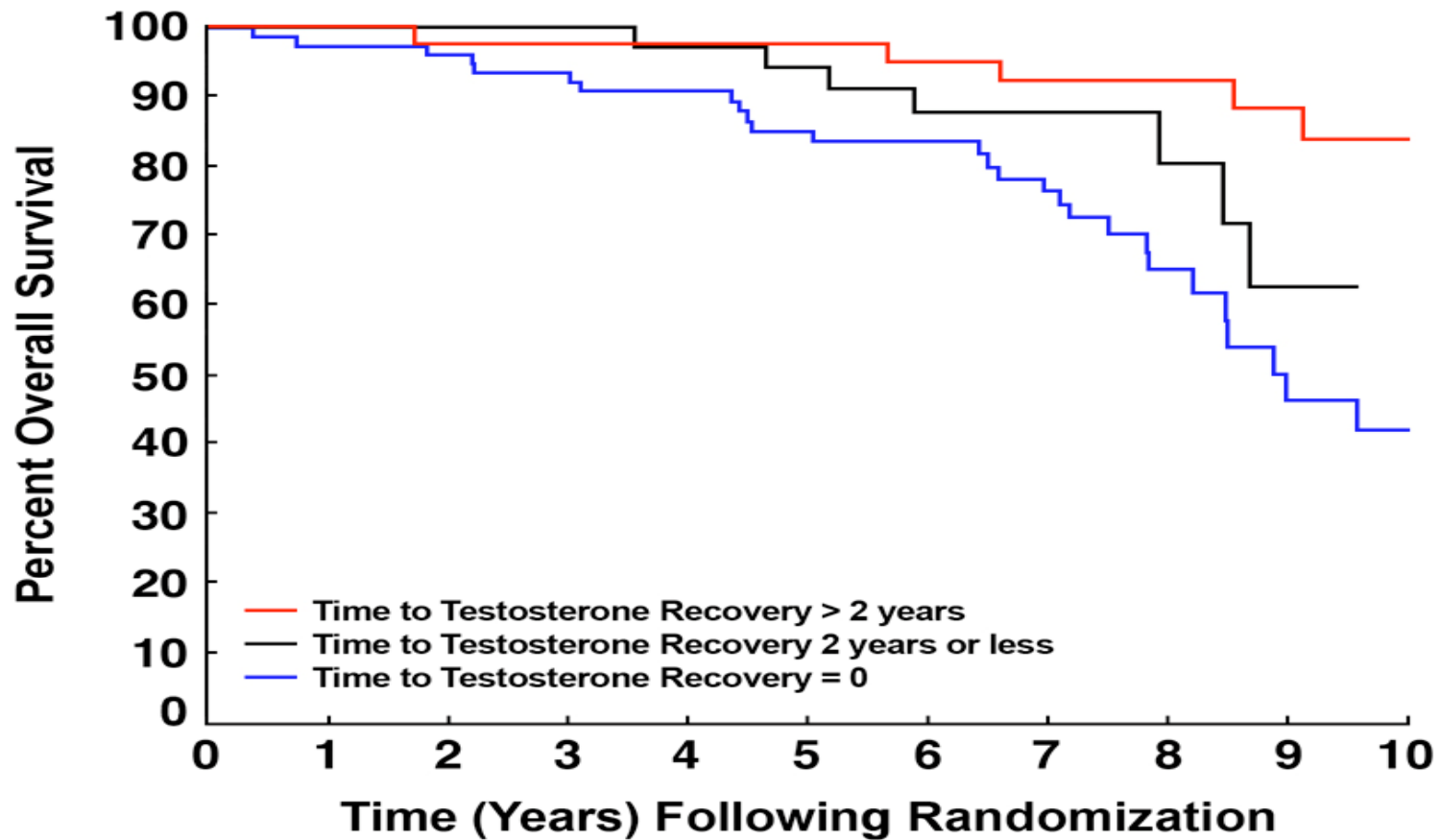
Number at Risk

FDA Warning: GnRH agonists

- **October 20, 2010**
- **Men receiving GnRH agonists were at a small but increased risk for diabetes, heart attack, stroke, and sudden death**

Who makes up the 4%?

1. Healthy (no CAD)



—	79	76	74	72	63	57	50	39	23	12	8
—	34	34	34	34	34	32	26	19	10	4	0
—	43	43	42	42	42	41	39	36	33	20	10
} Number at Risk											

Factors associated with time to testosterone recovery

– More likely to recover sooner

- GS 8-10

- AHR 1.56; 95% CI: 1.04 – 2.34; p=0.03

– Less likely to recover sooner

- Older age*

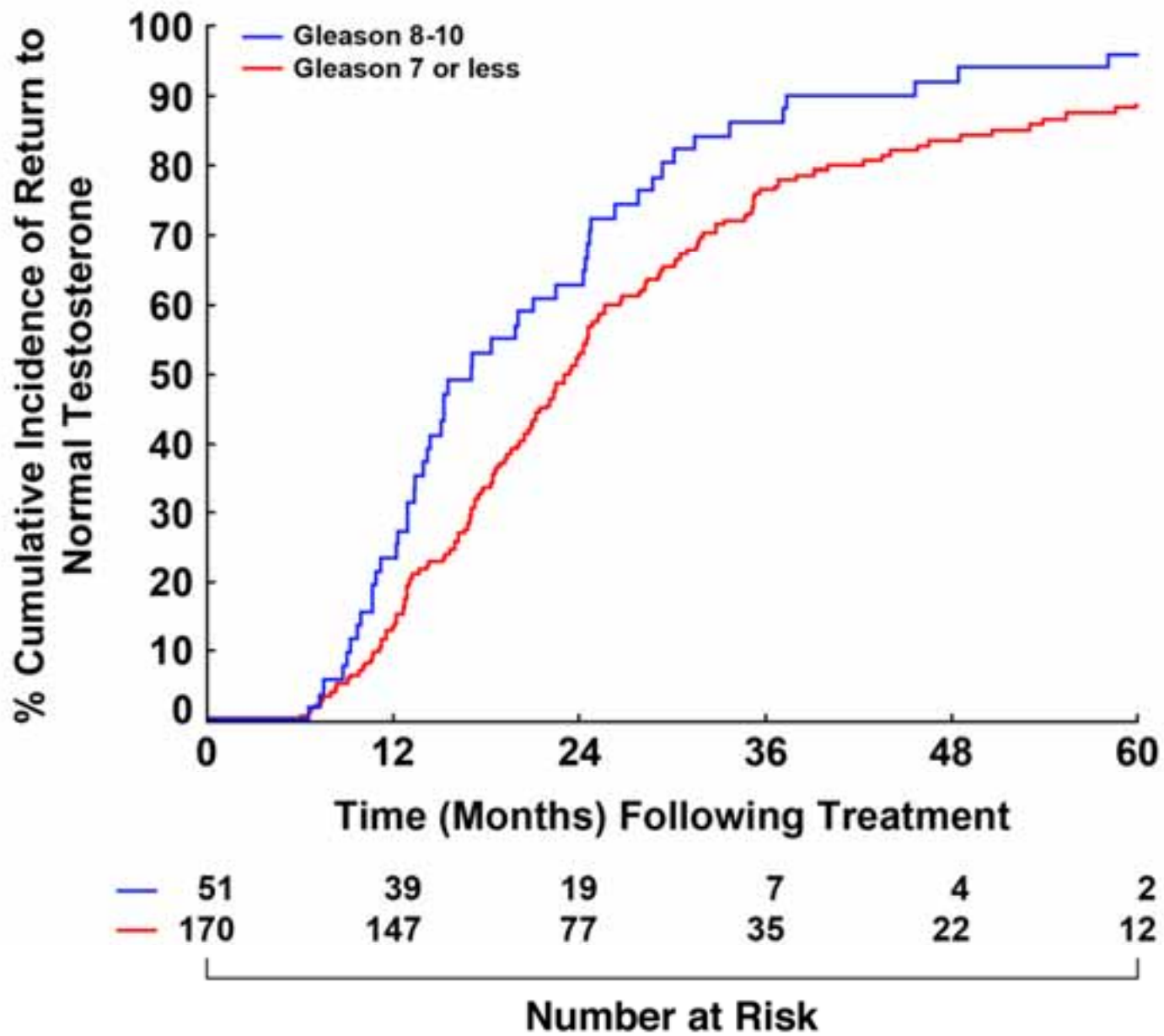
- AHR 0.95; 95% CI: 0.92 – 0.97; p<0.001

- » TTR = (6 + 18) mos or 2 years if in 70's

- » TTR = (6 + 14) mos or 1.67 yrs if in 60's

- » TTR = (6 + 12) mos or 1.5 yrs if age 60 or less

*May explain why HT + RP vs RP studies are negative



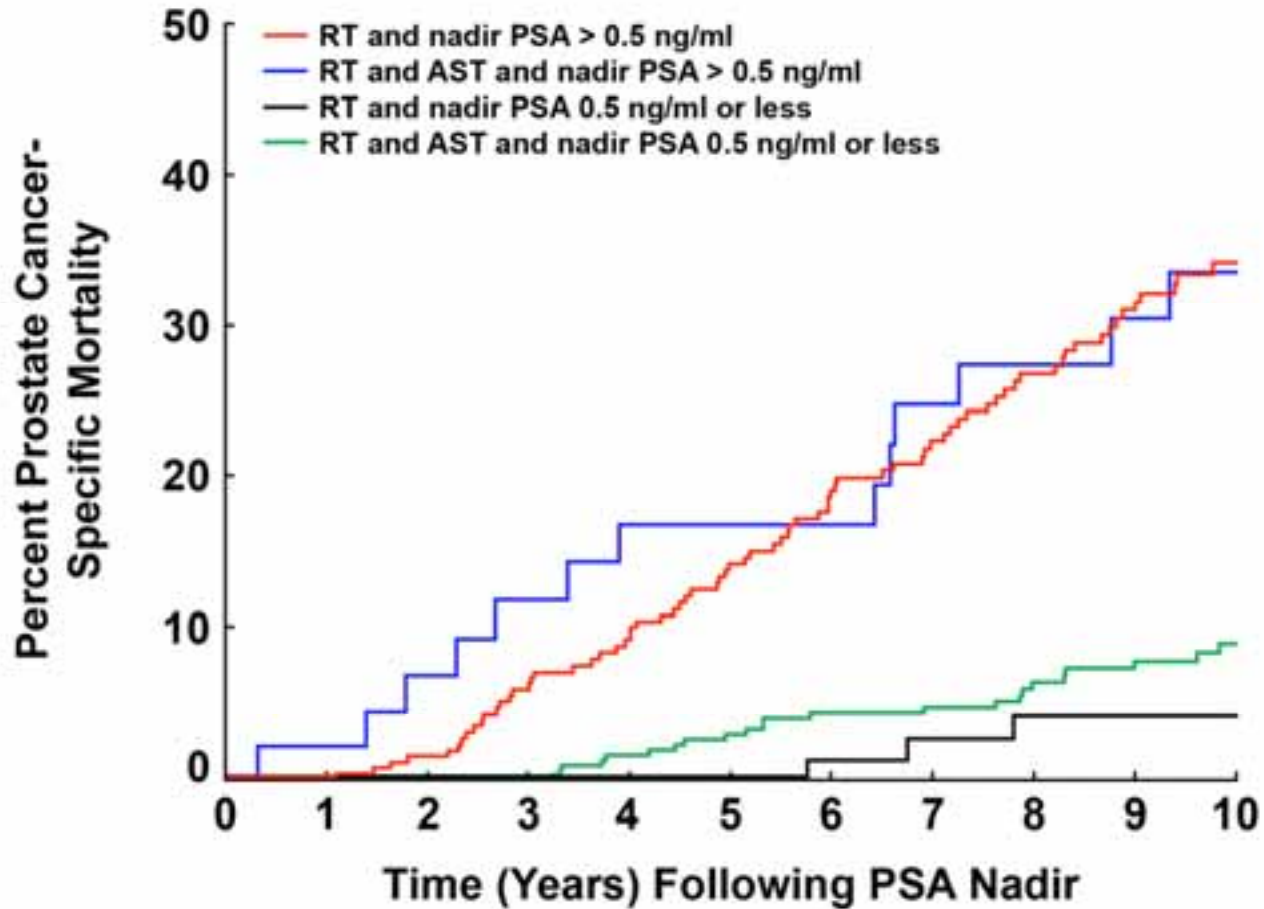
Who makes up the 4%?

1. Healthy (no CAD)
2. Younger (age 60 or less)
3. Gleason score 8 to 10

**PSA and the risk of PC death
in men treated with
RT and AST**

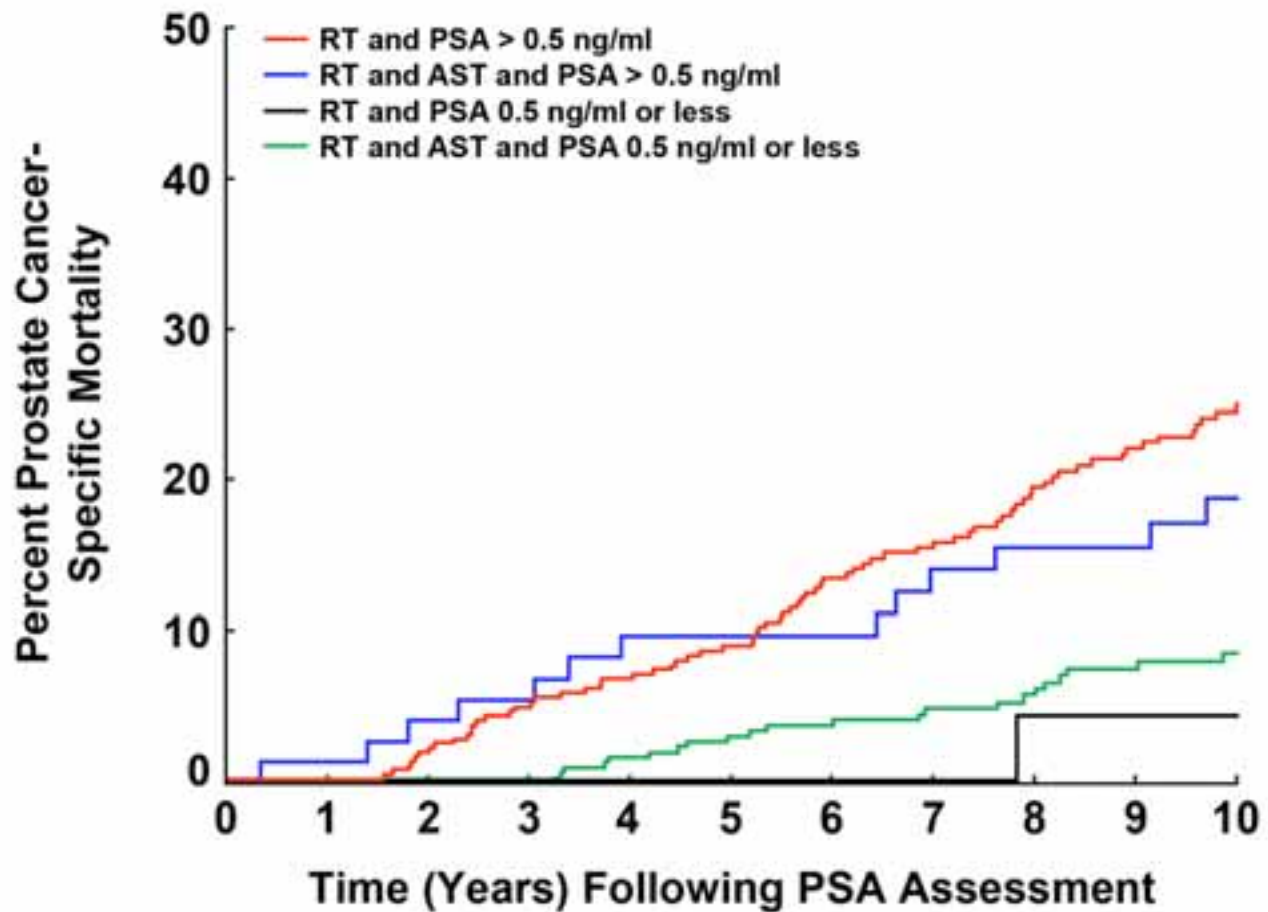
Prentice Criteria for Surrogacy

- Need RCT with a cancer-specific survival benefit
- Surrogate more likely on inferior Rx arm
- Surrogate is a prognostic factor
- Once surrogate achieved, the effect of Rx is lost
 - surrogate occurrence = no survival benefit despite receiving the Rx on the winning arm of the RCT



—	264	252	236	212	194	168	145	121	105	84	47
—	44	42	39	32	30	28	28	25	22	18	10
—	107	96	88	77	66	62	56	45	37	30	20
—	319	307	291	279	265	246	223	195	169	145	96

Number at Risk



—	337	334	317	295	277	256	228	197	166	149	106
—	72	70	68	66	62	60	59	55	50	47	28
—	32	30	30	27	24	23	20	16	15	12	10
—	290	283	276	268	258	239	215	192	172	146	110

Number at Risk

Summary

- **After RT and 6 mos of AST**
 - **PSA > 0.5 ng/ml**
 - **Recommend 2 to 3 years of AST**

Who makes up the 4%?

1. Healthy (no CAD)
2. PSA > 0.5 after RT and 6 mos AST

AST in men with intermediate or high-risk PC receiving high-dose RT

- **GETUG-14**

- RT (80 Gy) ± 4 months AST

- 377 men with T1b to T3a

- Median Age and Follow up: 67.9 and 3.1 years

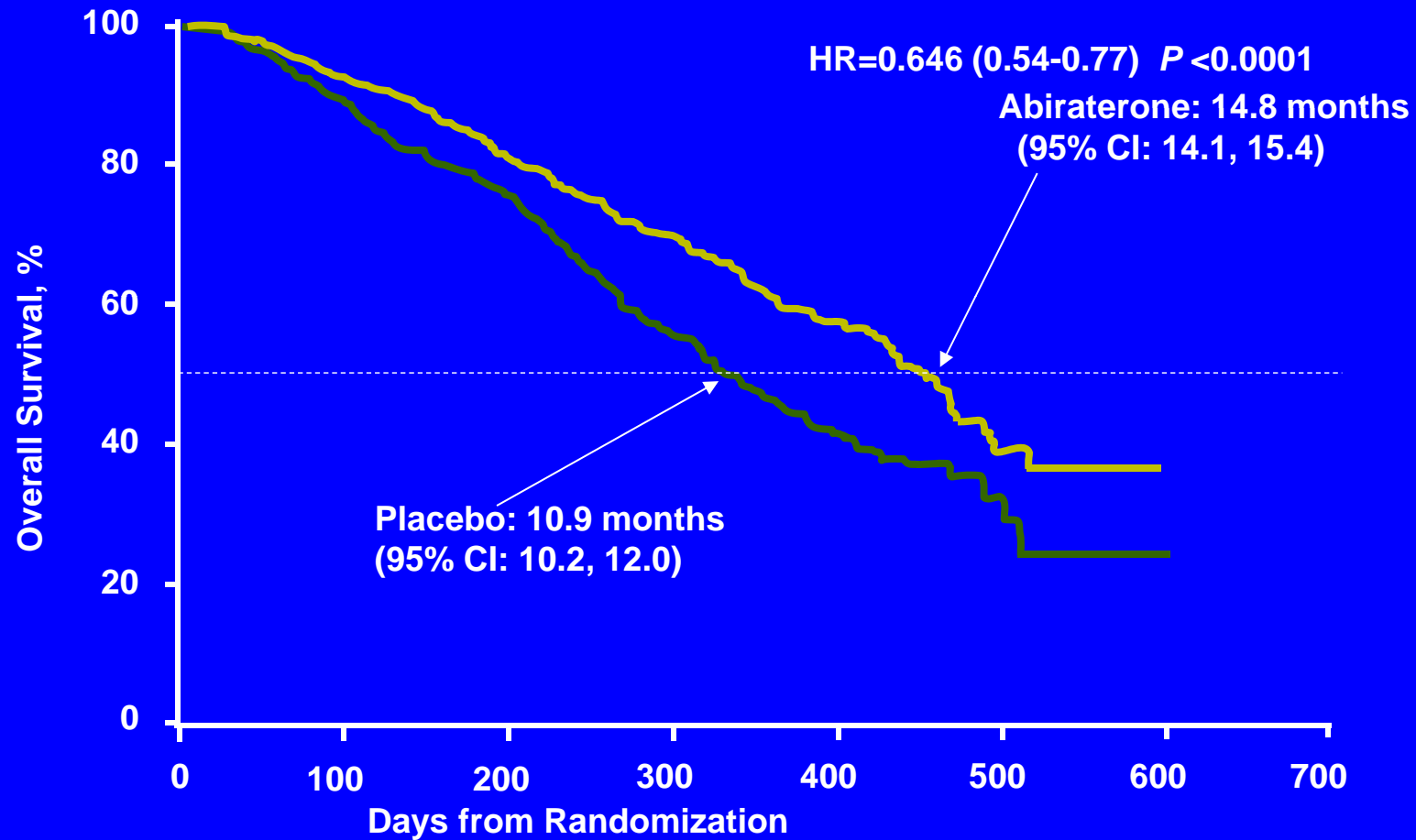
- **At 3 years:**

- Clinical or PSA control (86% vs 92%; p = 0.11)

- Gr 3,4 GU (2.6% vs 6.1%, p = 0.14)

ASCO 2011, Abstract 4521

Abiraterone Acetate Improves OS in M1, post-Taxotere and CRPC



Abiraterone	797	728	631	475	204	25	0
Placebo	398	352	296	180	69	8	1

DeBono et al
ESMO 2011

Risk-Based Mgt: Prostate Cancer

- **High Risk and Locally Advanced**
 - EBRT and HT (6 mos to 3 yrs) – (I)
 - personalize based on PSA response and comorbidity

Post Test Questions

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cT3bNxMO, Gleason score 8 and PSA 25

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