Early Discontinuation of Tamoxifen

T I Barron[1] R M Connolly[2] K Bennett[1]
M J Kennedy[2] J Feely[1]

[1] Dept Pharmacology & Therapeutics,
Trinity College Dublin.
[2] Academic Unit of Clinical & Molecular Oncology
Trinity College Dublin & St. James's Hospital.

Email: barront@tcd.ie

Background

- Adherence & Persistence
  - Definitions
    - » Adherence (Compliance) is the extent to which a patient takes medication in accordance with the prescribed interval and dose.[1]
    - » Persistence is the accumulation of time from initiation to discontinuation of therapy.[1]

[1] ISPOR Medication Compliance & Persistence Special Interest Group. http://www.ispor.org/sigs/MCP_accomplishments.asp#definition

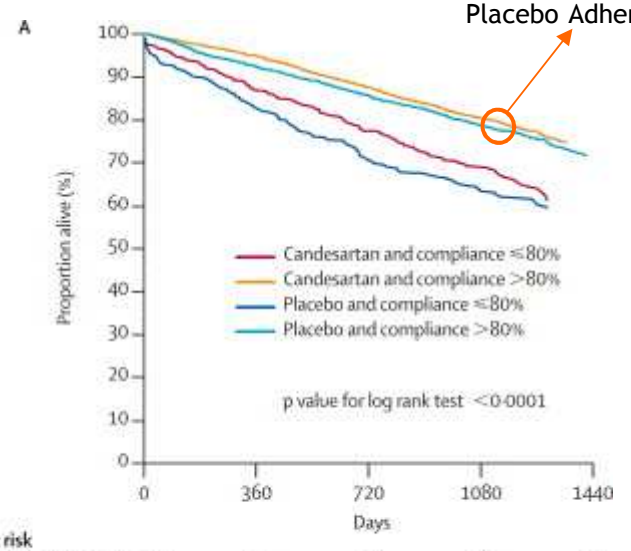
Background

- Significance?
  - Substantial worsening of disease and mortality.
    - McCowen et al - worse survival in poor adherers (HR=1.10, p=0.046)
    - Dezentje et al – lower breast cancer event free time in poor adherers (HR=0.987,p=0.029)
  - Increased healthcare costs.
  - Healthy drug user effect.

Background

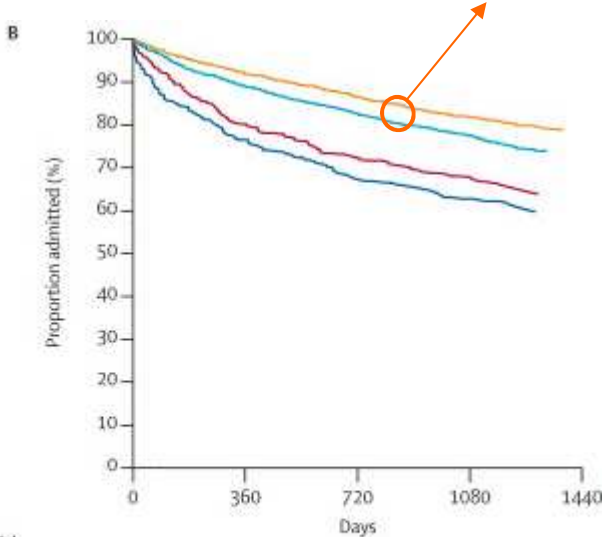
- Charm Study[1]

Mortality:
Candesartan Adherent
Placebo Adherent



Numbers at risk				
Candesartan and compliance ≤80	493	426	380	249
Candesartan and compliance >80	3310	3137	2891	1967
Placebo and compliance ≤80%	435	359	306	209
Placebo and compliance >80%	3361	3106	2864	1951

Hospital Admissions:
Candesartan Adherent
Placebo Adherent



Numbers at risk				
Candesartan and compliance ≤80	493	363	307	199
Candesartan and compliance >80	3310	2923	2588	1724
Placebo and compliance ≤80%	435	295	237	159
Placebo and compliance >80%	3361	2828	2489	1647

[1] Lancet 2005; 366: 2005-11

Background

- Tamoxifen
  - 5 years of treatment reduces the relative breast cancer recurrence risk by 46% and the relative risk of death by 26%.[1]
  - Comparisons of treatment durations indicate that women receiving less than 5 years of treatment have significantly higher breast cancer recurrence rates and mortality.[1,2]

[1] Lancet 1998; 351: 1451-67; [2] Lancet 2005; 365: 1687-717

Background

- Tamoxifen persistence
  - Non-persistence in clinical trials of adjuvant tamoxifen is 16%-32% at 5 years.
  - Non-persistence outside of clinical trials reported as 17% at 2 years to 35% at 5 years.[1-3]
    - » Patient self reported persistence.
    - » Elderly populations (>55 yrs).
    - » Self selection bias (≈50% refused to participate).
  - No objective measurements of tamoxifen persistence outside of the clinical trial setting.

[1] Breast Cancer Res Treat 2006; [2] J Clin Oncol. 2004; 22; 3309-15;
[3] J Clin Oncol. 2001; 19:322-8

Aims

- Aims
  - To evaluate persistence with tamoxifen therapy, in women aged 35 years or older, using prescription refill data from a national prescribing database in Ireland.
    - » Prescription refill data provide accurate and objective estimates of medication use in large populations over long periods of time.

Methods

- Source of data
  - Pharmacy database from the **H**ealth **S**ervices **E**xecutive **P**rimary **C**are **R**eimbursement **S**ervices.
  - National prescribing data for the years 2000 to 2005.

Methods

- Cohort definition
  - All women over the age of 35 years.
  - Commenced on tamoxifen as initial hormonal therapy between January 2001 and January 2004.
    - » Commenced: defined as having no prescription for tamoxifen in the previous 12 months
    - » Initial: defined as having no prescription for any other hormonal therapy (Anastrozole, Exemestane, Letrozole, Toremifene) in the previous 12 months.

Methods

- Measurement of tamoxifen persistence
  - Patients were initially classified as non-persistent if they had a period of 180 consecutive days of no tamoxifen supply.
  - Patients with no prescription for any item in the 12 months following non-persistence were reclassified as lost to follow up.
  - Patients starting alternative hormonal therapy before 180 days of no tamoxifen were reclassified as treatment switchers.

Methods

- Measurement of tamoxifen persistence
  - Patients restarting tamoxifen or starting another hormonal therapy after 180 days of no tamoxifen remained classified as non-persistent.

  - All patients followed for between 1 – 3.5 years (median 2.7) from tamoxifen initiation to identify non-persistence

  and

  for a minimum of 1 year (median 1.7) after non-persistence to identify subsequent hormonal therapy use.

Methods

- Potential determinants of non-persistence
  - Age at initiation of tamoxifen.
  - Co-morbidities.
  - Number of pharmacological agents received.
  - Use of antidepressant, antipsychotic, or anxiolytic/hypnotic agents.
  - Treatment for cognitive or functional impairment (Parkinson's disease or dementia)

Methods

- Statistical analysis
  - Kaplan Meier analysis.
    - Patients were censored at the time of loss to follow up, treatment switch or end of follow up.
  - Cox proportional hazards model.
    - Stepwise selection with criteria for entry of $p < 0.1$.
  - Significance at $p < 0.05$ was assumed.
  - SAS version 9.1 (SAS Institute Inc, Cary, US) was used for all analyses.

Results

- Study Cohort (n=2816)

Table 1: Characteristics of patients starting tamoxifen on the HSE-PCRS database (January 01-January 04)

	n	%
Age (years)*		
35-44	262	9.3
45-54	509	18.1
55-64	592	21.0
65-74	575	20.4
>75	878	31.2
Prescription Drug Use †		
Benzodiazepine anxiolytic/hypnotic	1163	41.3
Antidepressant	534	19.0
Benzodiazepine related hypnotic	390	13.8
Antipsychotic	375	13.3
Co-morbidities †		
Respiratory disease	385	13.7
Cardiovascular disease	599	21.3
Diabetes	117	4.2

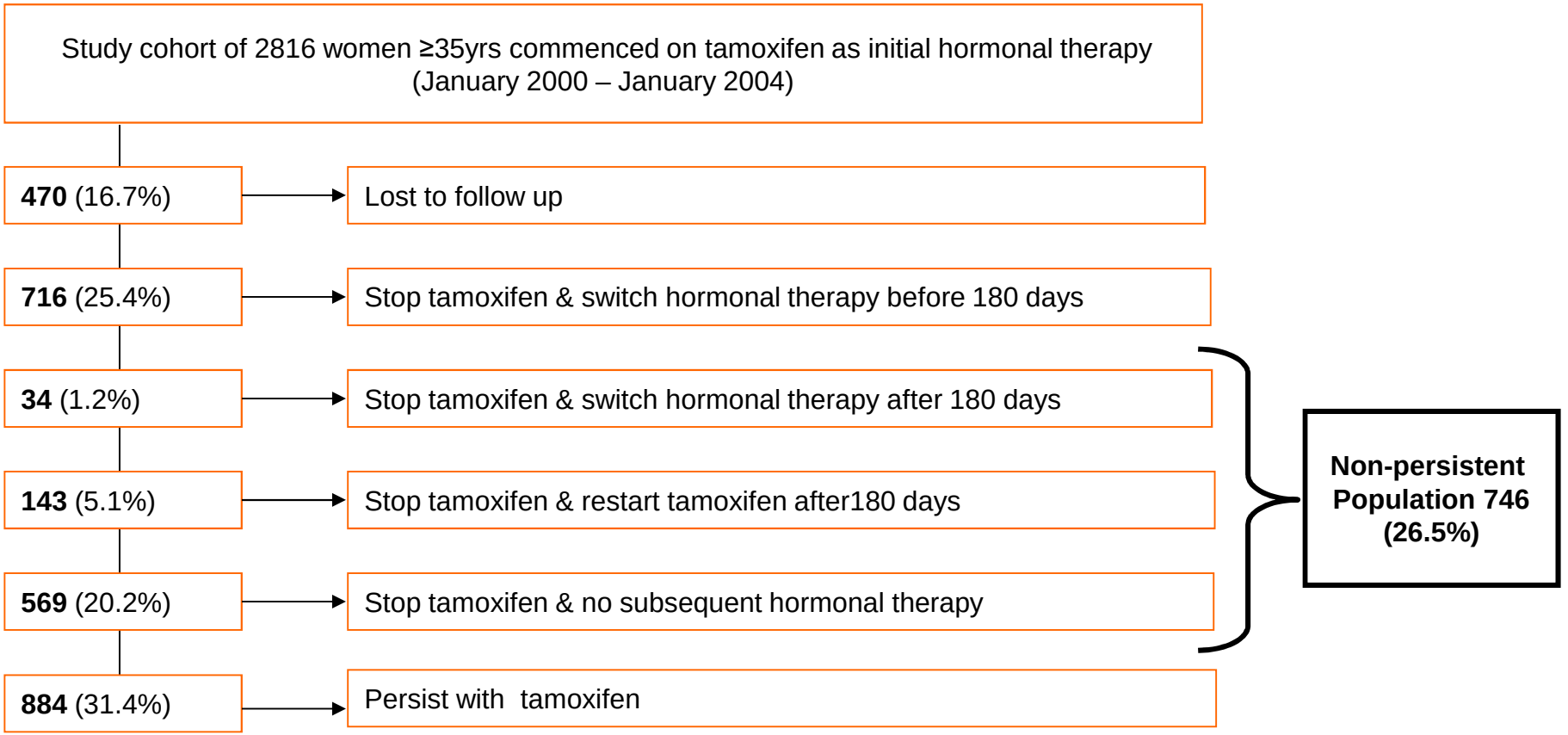
	n	%
Cognitive/functional impairment †		
Parkinson's Disease	81	2.9
Dementia	25	0.9
Number of co-morbidities †		
0	1906	67.7
≥1	910	32.3
Number of cognitive/functional impairments †		
0	2710	96.2
≥1	106	3.8
Mean number of pharmacological agents per month †		
≤1	951	33.8
2-3	920	32.7
4-5	502	17.8
>5	443	15.7

* At tamoxifen initiation; † In 12 months prior to tamoxifen initiation

Results

- Tamoxifen non-persistence

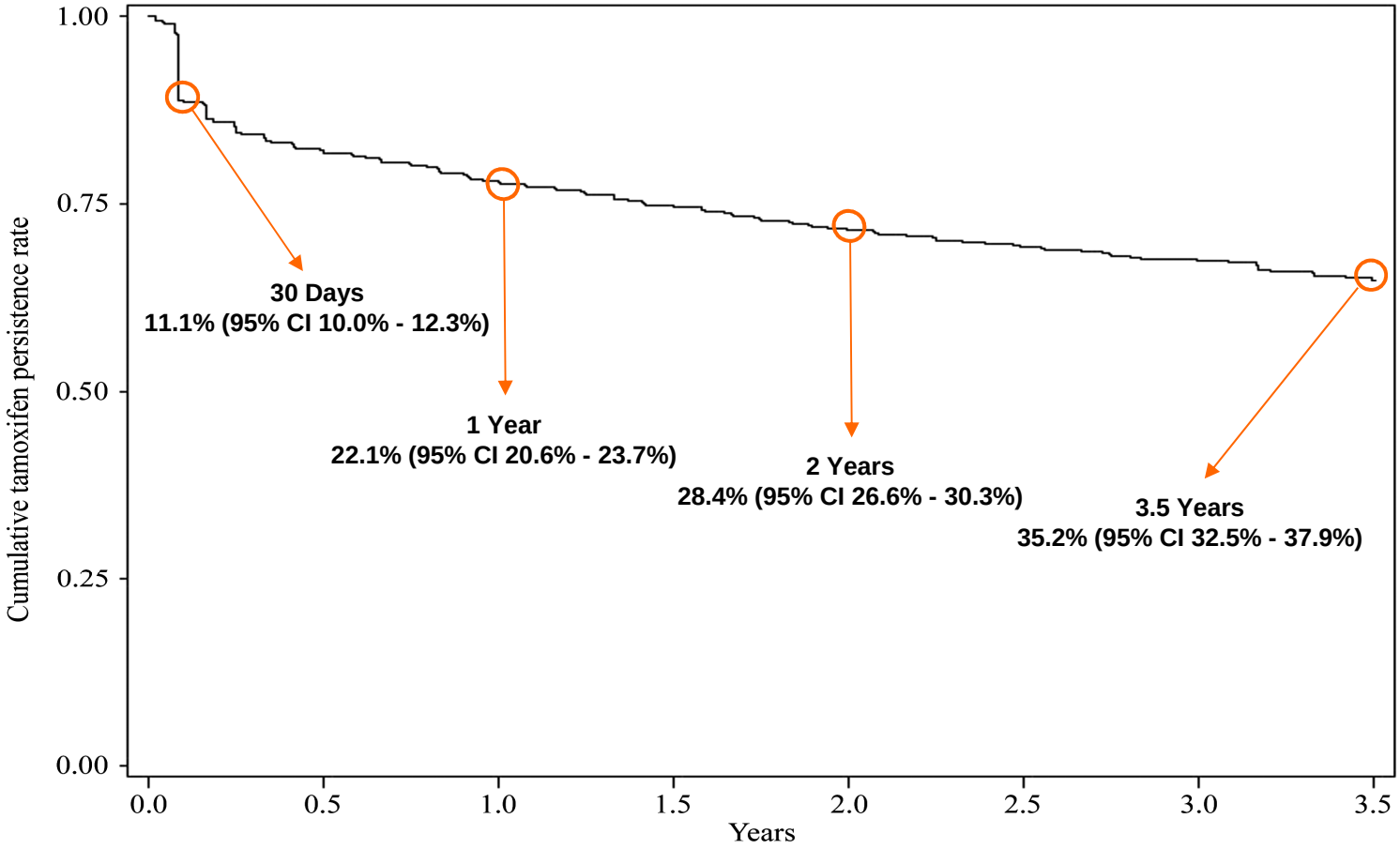
Fig 1: Outcomes for patients starting tamoxifen on the HSE-PCRS database (January 01 - January 04)



Results

- Tamoxifen non-persistence

Fig 2: Kaplan Meier plot of tamoxifen persistence for patients starting tamoxifen (January 01 – January 04)



Results

- Determinants of non-persistence

Table 2: Crude & adjusted hazard ratios (HR) for potential determinants of tamoxifen non-persistence

			Crude HR	95% CI	Adjusted HR	95% CI
Age (years)		35-44	1.36	1.01 to 1.82	**1.36**	1.01 to 1.83
		45-54	Reference	-	-	-
		55-64	1.07	0.84 to 1.37	1.11	0.86 to 1.42
		65-74	1.23	0.96 to 1.57	1.27	0.98 to 1.61
		>75	1.42	1.14 to 1.77	**1.46**	1.16 to 1.83
Prescription Drug Use	Benzodiazepine anxiolytic/hypnotic		0.99	0.86 to 1.15	-	-
	Antidepressant		1.31	1.10 to 1.56	**1.41**	1.18 to 1.70
	Benzodiazepine related hypnotic (ZZZ)		0.81	0.65 to 1.01	-	-
	Antipsychotic		1.16	0.95 to 1.43	-	-
Number of co-morbidities		0	Reference	-	-	-
		≥1	1.04	0.90 to 1.22	-	-
Number of cognitive/functional co-morbidities		0	Reference	-	Reference	-
		≥1	1.78	1.29 to 2.46	**1.72**	1.24 to 2.39
Mean number of pharmacological agents per month		≤1	Reference	-	Reference	-
		2-3	0.89	0.74 to 1.05	0.84	0.71 to 1.00
		4-5	0.87	0.70 to 1.07	**0.76**	0.61 to 0.94
		>5	0.90	0.72 to 1.12	**0.72**	0.58 to 0.92

* At tamoxifen initiation; † In 12 months prior to tamoxifen initiation; ‡ Adjusted for age, antidepressant use, number of cognitive or functional impairments and number of pharmacological agents per month.

Discussion

- Non-persistence with tamoxifen in clinical practice is higher than previously reported.
  - 35.2% of women discontinue tamoxifen by 3.5 years.
  - 22.1% discontinue tamoxifen by 1 year.

Discussion

- The determinants
  - Non-persistence associated with the extremes of age.
  - Treatment with an antidepressant associated with increased non-persistence.
  - Increasing numbers of prescribed medications associated with better tamoxifen persistence.

Discussion

- The limitations
  - No diagnostic or staging information.
  - Unable to assess the influence of patients' beliefs or side effects.
  - Cannot differentiate between discontinuation by the patient or on direction of the prescriber.
  - Non-persistence rates reported may only provide a conservative estimate of non-persistence

Conclusion

- Conclusion
  - Persistence with tamoxifen cannot be assumed
  - Raises concerns about persistence with other oral hormonal therapies and oral anti-neoplastics in general

"Drugs don't work in patients who don't take them"

C. Everett Koop M.D.