Patient Compliance with Drug Regimen and Global Treatment Efficacy

Breast Cancer

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Compliance with breast cancer oral medication regimens is a recognized clinical issue and concern

Present status

More questions than answers

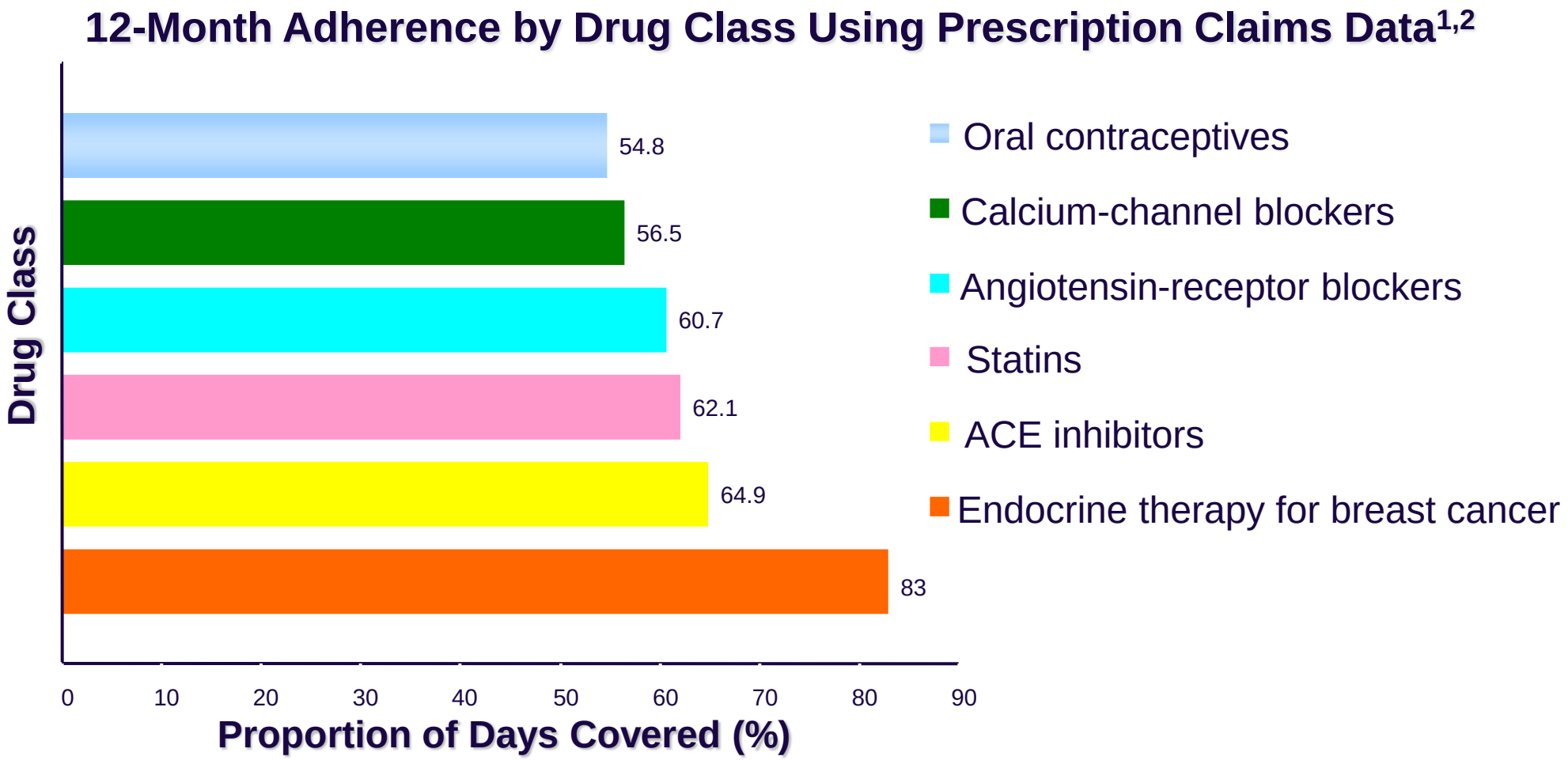
Definitions: Adherence vs Persistence

Adherence: the extent to which patients take therapy as prescribed

Persistence: continuing therapy for the prescribed duration (discontinuation rate)

Related but different: A patient can be persistent but non-adherent, but cannot be adherent but non-persistent.

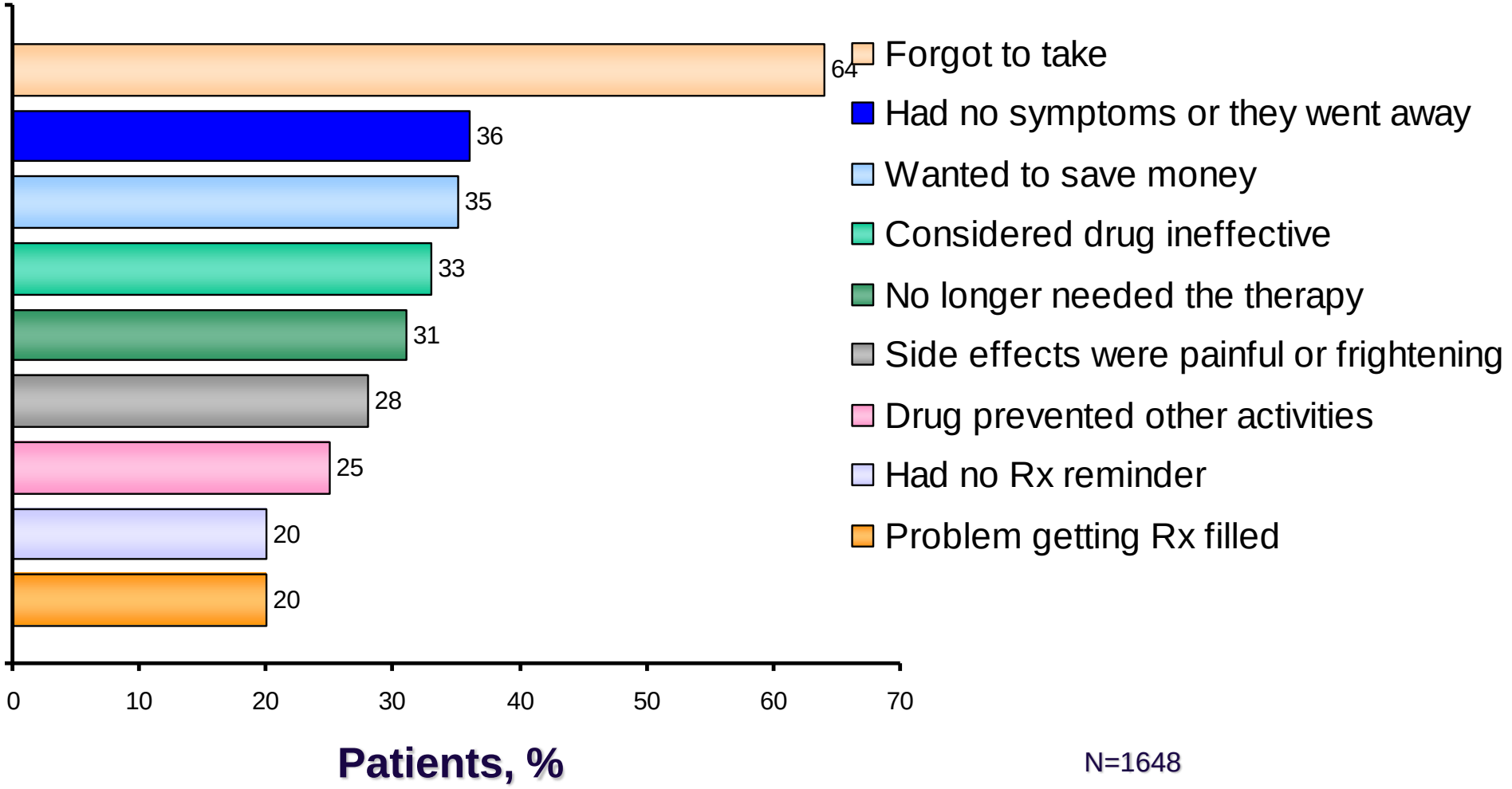
Adherence in Chronic Disease Varies by Drug Class



ACE=angiotensin-converting enzyme.

1. Shrank WH et al. *Arch Intern Med*. 2006;166:332-337. 2. Partridge AH et al. *J Clin Oncol*. 2003;21:602-606.

Patient Component – Reasons for Not Taking Medications

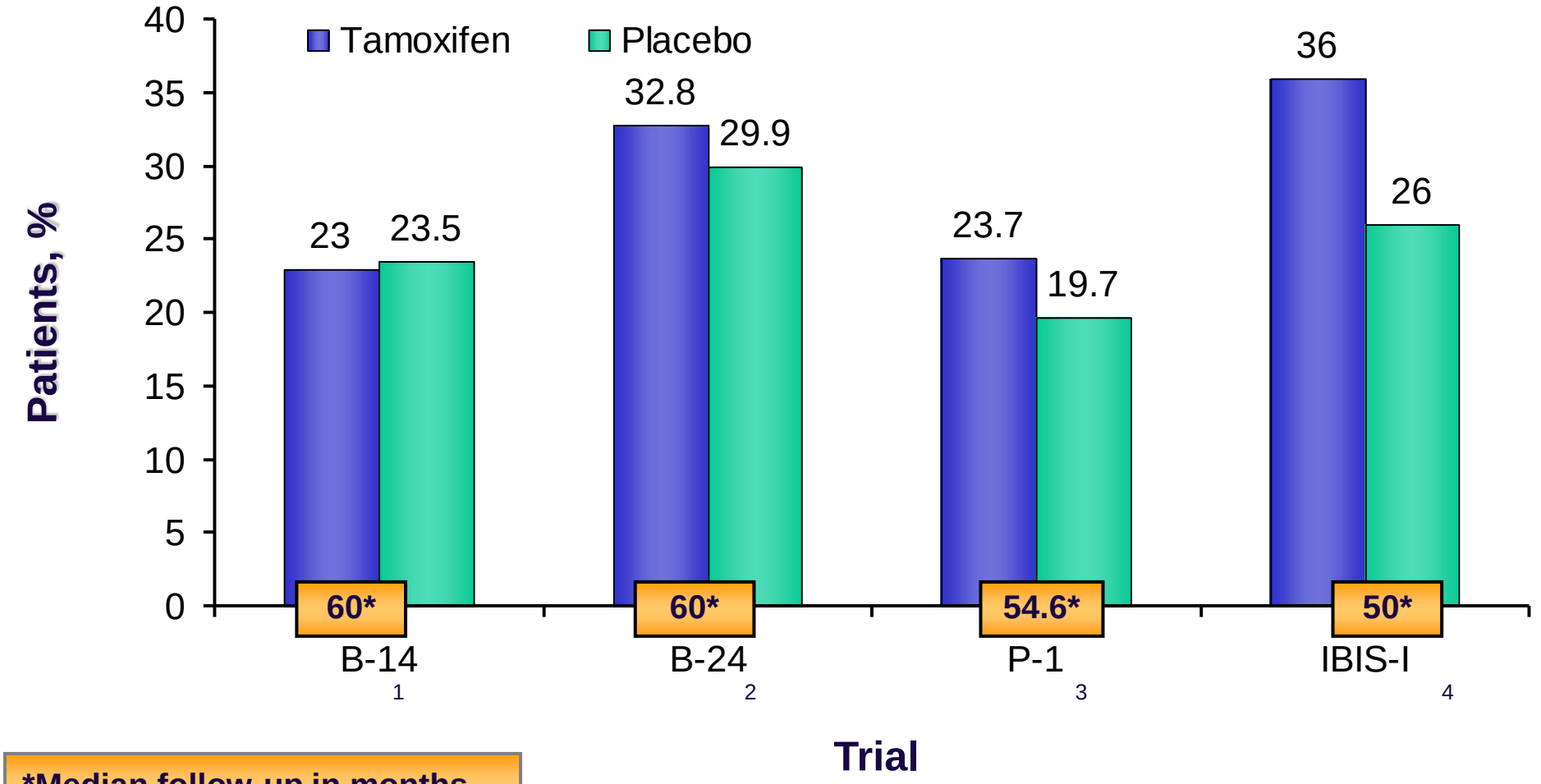


N=1648

Wall Street Journal Online. Harris Interactive. 2005. http://www.harrisinteractive.com/news/printerfriend/index.asp?NewsID=904. Accessed April 29, 2008.

Adherence and Persistence Higher in Clinical Trials Compared to Clinical Practice

Discontinuation Rates in Select Placebo-Controlled Tamoxifen Clinical Trials



***Median follow-up in months.**

IBIS-I=International Breast Cancer Intervention Study.

1. Fisher B et al. *J Natl Cancer Inst*. 1996;88:1529-1542. 2. Fisher B et al. *Lancet*. 1999;353:1993-2000. 3. Fisher B et al. *J Natl Cancer Inst*. 1998;90:1371-1388. 4. Cuzick J et al. *Lancet*. 2002;360:817-824.

Review of Studies Reporting Prevalence of Adherence and/or Persistence to Adjuvant Hormone Therapy in Clinical Practice Settings

Information Source	Reports
Prescription and Medical Claims Database/Registry	15
Medical Record Review of Hospital Database	8
Patient Self-Report	6
Prospective Studies	4

Murphy et al. Breast Cancer Res Treat 2012;134:459-478

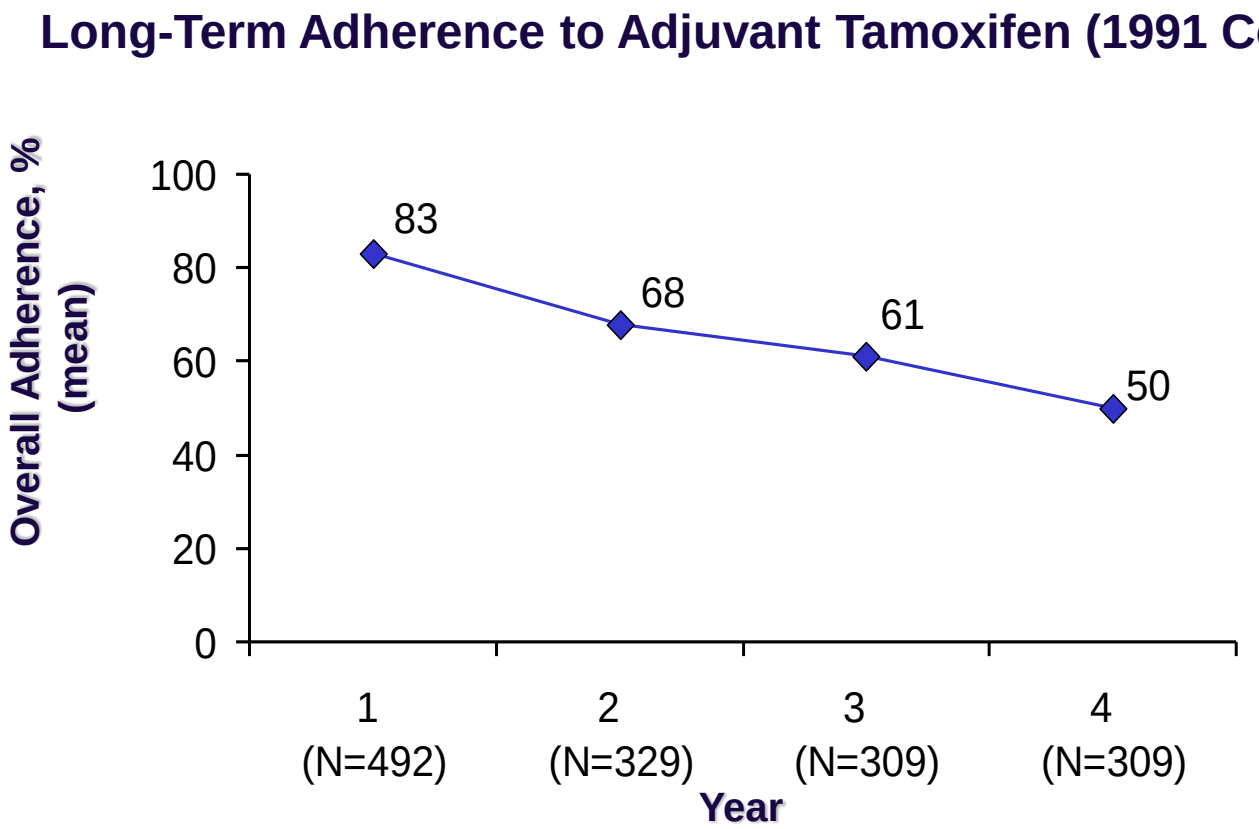
Review
Adherence and Persistence to Adjuvant Breast Cancer Hormonal Therapy in Clinical Practice

- Prevalence of adherence
  - In tamoxifen users (41% to 88%)
  - In aromatase inhibitor users (50% to 91%)
- Prevalence of therapy discontinuation (Persistence)
  - In tamoxifen users (15% to 20% in first year to 31% to 60% at end of year 5)
  - In aromatase inhibitor users (5% to 25% in the first 2 years)

Murphy et al. Breast Cancer Res Treat 2012;134:459-478

Prescription Claims Study of Tamoxifen Adherence in Clinical Practice

- Retrospective analysis of prescription claims database (1990-1996) evaluating rates of days covered by *filled prescriptions*



Partridge AH et al. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. *J Clin Oncol*. 2003;21(4):602-606.
Reprinted with permission from the American Society of Clinical Oncology.

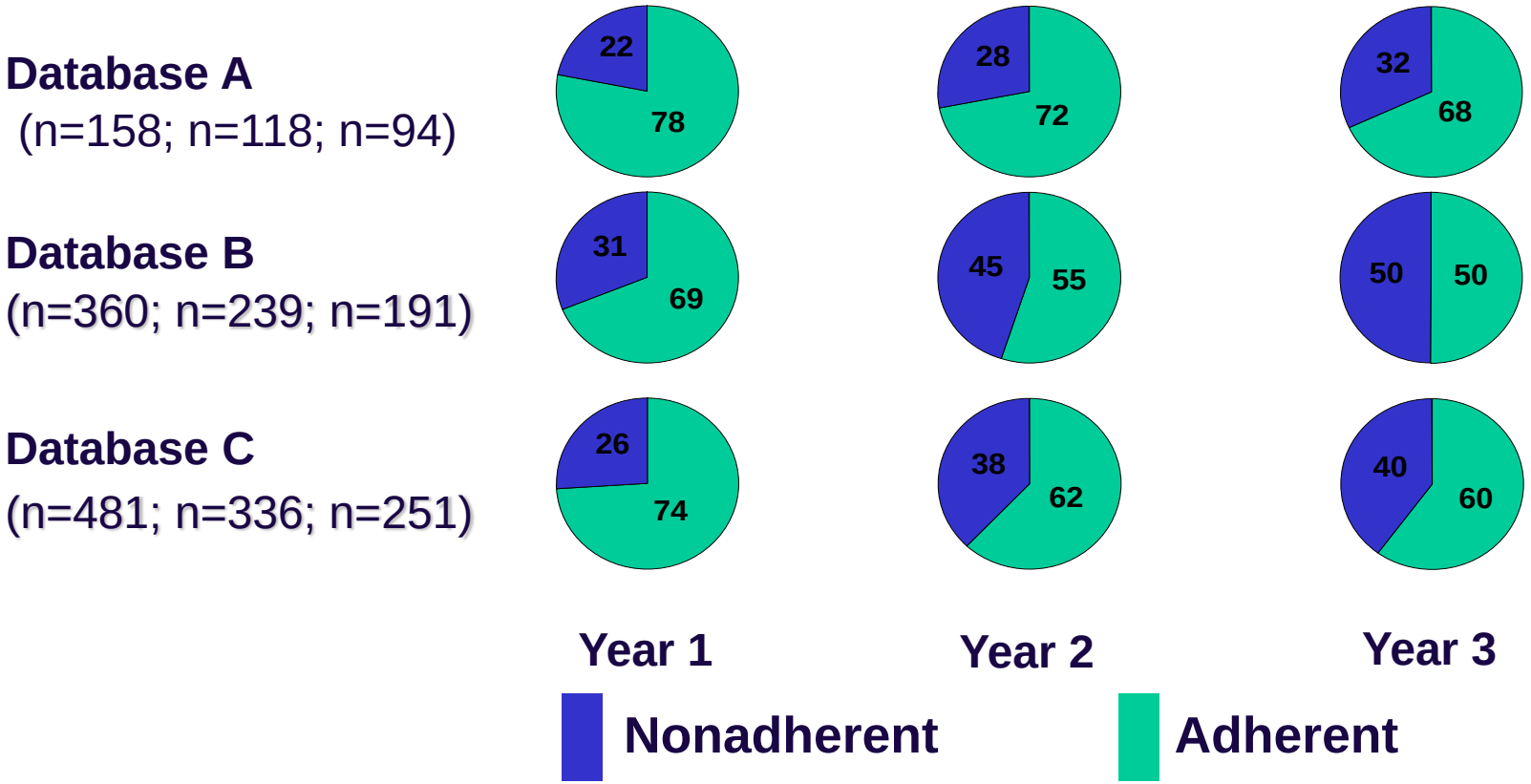
Adjuvant Anastrozole Adherence in Clinical Practice

- 3-year retrospective analysis of claims from 3 prescription claims databases of >12,000 women with breast cancer receiving adjuvant anastrozole
- Adherence defined by a Medication Possession Ratio (MPR)
  - MPR = proportion of days covered/observation period (12-month minimum)
  - For a subset of patients, a full 3-year observation period was available and 3-year adherence rates are shown
  - Patients with MPRs <80% were classified as “nonadherent”

Partridge AH et al. *J Clin Oncol*. 2008;26:556-562.

Proportion of Adherent and Non-adherent Patients Taking Adjuvant Anastrozole

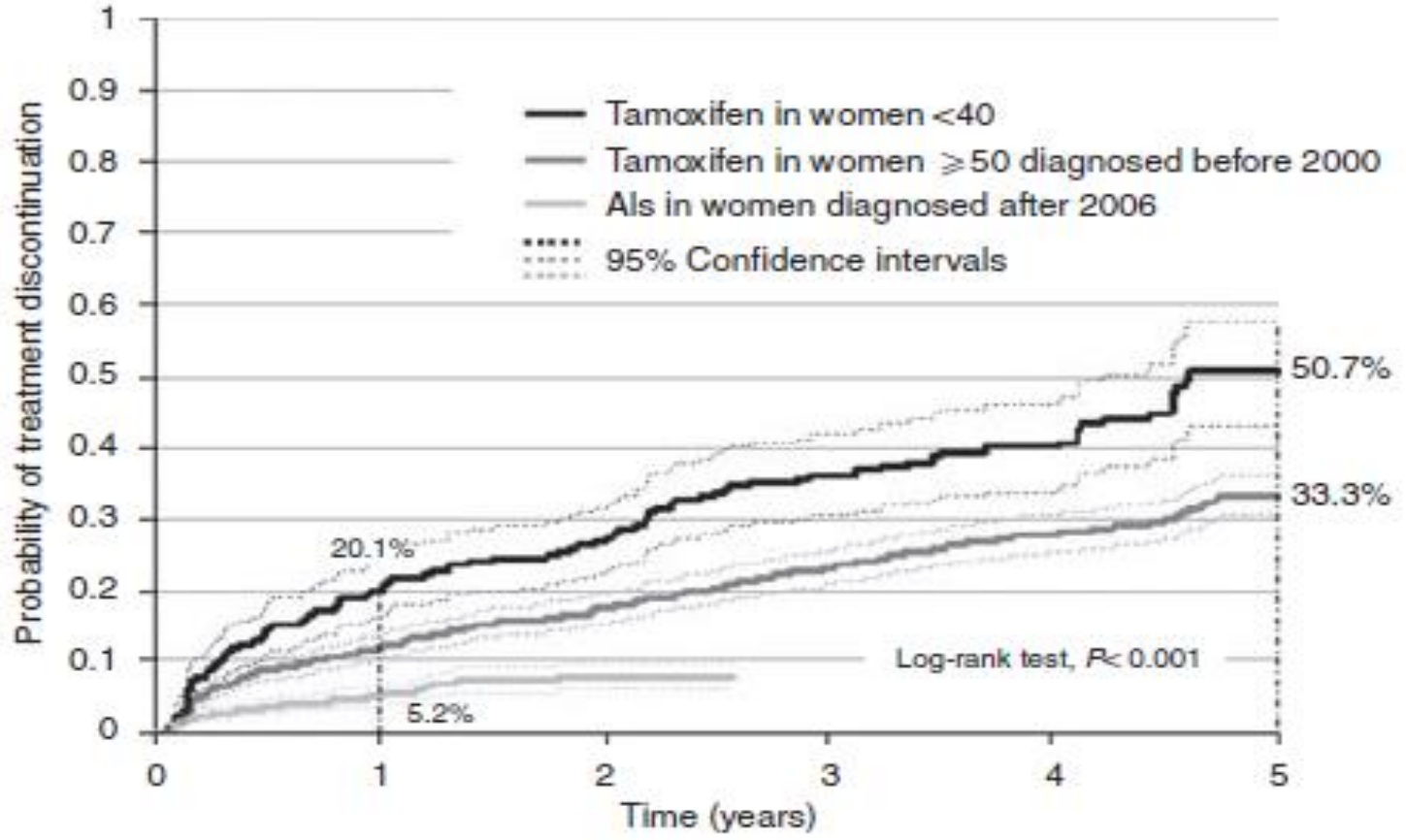
~1 in 4 women with early breast cancer may be suboptimally adherent to adjuvant ARIMIDEX therapy during the first year of treatment.



Note: decline in sample size due to metastatic disease or death.

Partridge AH et al. Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol.* 2008;26(4): 556-562. Reprinted with permission from the American Society of Clinical Oncology.

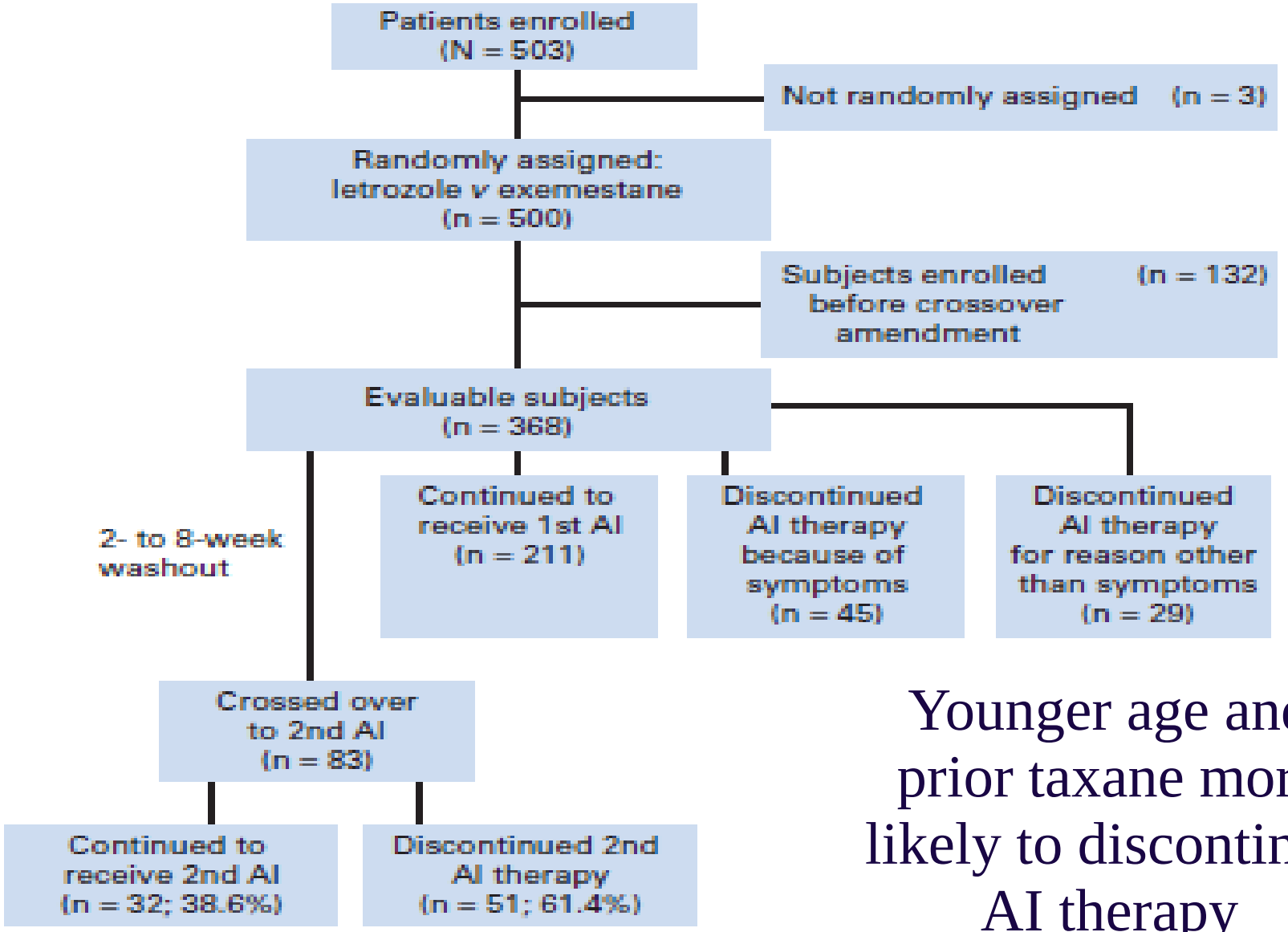
Use of Tamoxifen and Aromatase Inhibitors in the UK General Practice Database (1998-2008)



Adherence/persistence less in younger woman.
Adherence/persistence greater in AI vs tamoxifen users

Huiart et al. Br J Cancer 2011;104:1558-1563

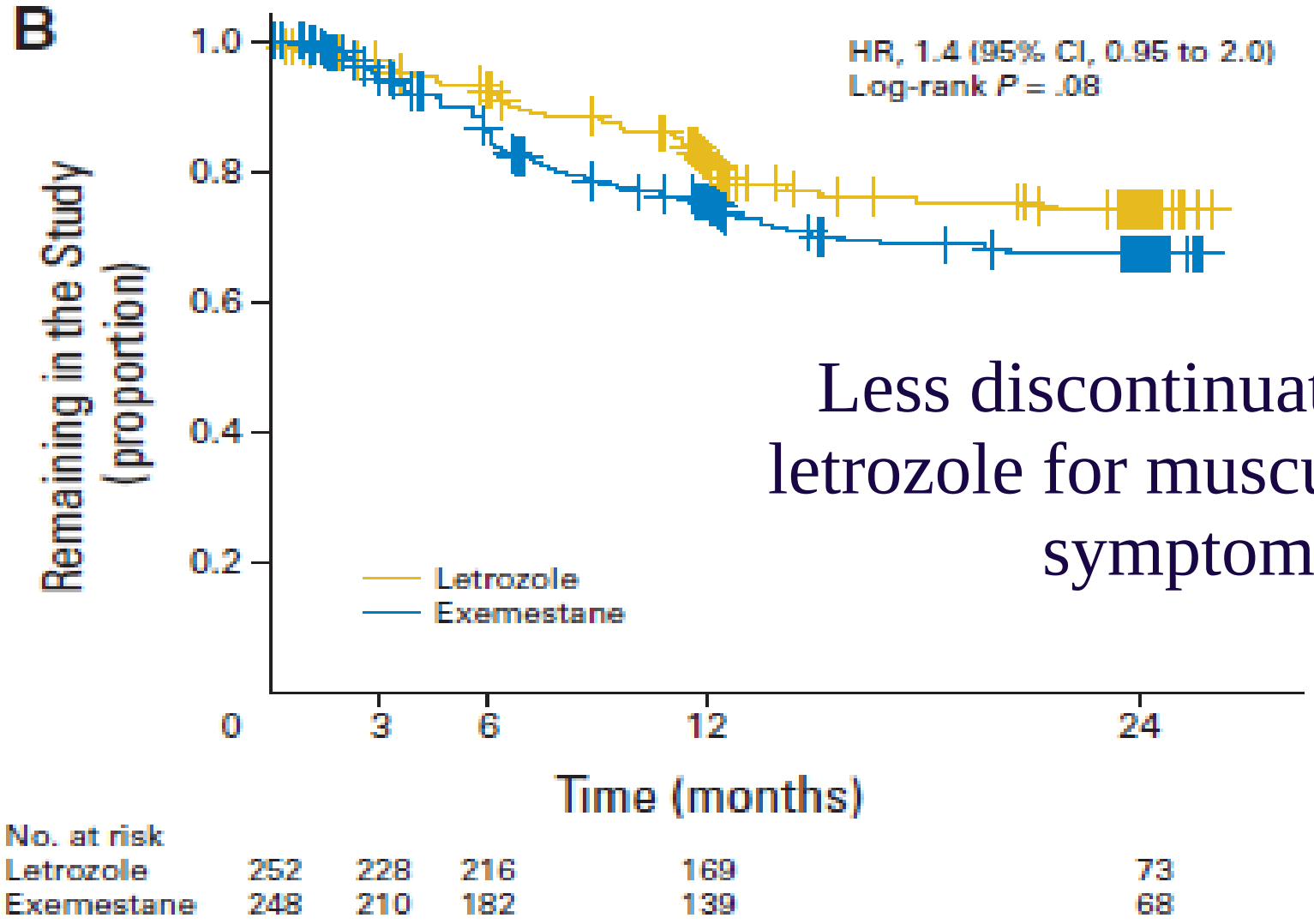
Aromatase Inhibitor Crossover Trial and Discontinuation for Musculoskeletal Symptoms



Younger age and prior taxane more likely to discontinue AI therapy

Huiart et al. Br J Cancer 2011;104:1558-1563

Letrozole vs Exemestane Adjuvant: Time to Discontinuation for Musculoskeletal Symptoms



Less discontinuation with letrozole for musculoskeletal symptoms

Huiart et al. Br J Cancer 2011;104:1558-1563

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Exemestane for Breast-Cancer Prevention in Postmenopausal Women

Paul E. Goss, M.D., Ph.D., James N. Ingle, M.D., José E. Alés-Martínez, M.D., Angela M. Cheung, M.D., Ph.D., Rowan T. Chlebowski, M.D., Ph.D., Jean Wactawski-Wende, Ph.D., Anne McTiernan, M.D., John Robbins, M.D., Karen C. Johnson, M.D., M.P.H., Lisa W. Martin, M.D., Eric Winquist, M.D., Gloria E. Sarto, M.D., Judy E. Garber, M.D., Carol J. Fabian, M.D., Pascal Pujol, M.D., Elizabeth Maunsell, Ph.D., Patricia Farmer, M.D., Karen A. Gelmon, M.D., Dongsheng Tu, Ph.D., and Harriet Richardson, Ph.D., for the NCIC CTG MAP.3 Study Investigators*

MAP.3 Serious Adverse Effects by Severity and Treatment Arm

Serious toxicities	Exemestane n(%)	Placebo n (%)	P-value
Cardiovascular disease	106 (4.7%)	111 (49%)	0.39
Clinical skeletal fractures	149 (6.7%)	143 (6.4%)	0.72
Osteoporosis	37 (1.7%)	30 (1.3%)	0.39
Other malignancies	43 (1.9%)	38 (1.7%)	0.58
Therapy stopped for toxicity	351 (15.4%)	242 (10.8%)	<0.01

Goss, Ingle, Alex-Martinez, Cheung, Chlebowski, et al. N Engl J Med 2001 June 2 [Epub]

Placebo Adherence, Clinical Outcomes, and Mortality in the Women's Health Initiative Randomized Hormone Therapy Trials

Associations between adherence to placebo and risk of fracture, coronary heart disease, cancer, and all-cause mortality where examined in 13,444 postmenopausal women in the WHI trials evaluating estrogen plus progestin or estrogen alone

	Placebo Adherence		
	< 50%	50-80%	≥ 80%
Number	926	2153	10,365

Curtis, Larson, Delzell, Brookhart, Cadarette, Chlebowski, et al. Medical Care 2011;49(5):427-435

Adjusted Variables in the WHI Analyses of Association Between Placebo Adherence and Clinical Outcomes

- Adjusted for age, ethnicity, education, smoking, alcohol, fruit/vegetables intake, red meat intake, BMI, physical activity, physical function, any insurance, mammogram, care provider visit history, colonoscopy ever, family history of fracture or breast cancer, self-reported health, history of diabetes, bilateral oophorectomy, age at first birth, age at menarche, depression, aspirin, corticosteroids, fracture medication, beta blockers, thiazides, loop diuretics, PPIs, NSAIDs, lifetime hormone therapy duration, medication number

Curtis, Larson, Delzell, Brookhart, Cadarette, Chlebowski, et al. Medical Care 2011;49(5):427-435

Relation Between Placebo Adherence (< 80% vs > 80%) and Clinical Events in the WHI Menopausal Hormone Therapy Trials

	Events	Adjusted HR (95% CI)
Death (all cause)	464	0.64 (0.51-0.80)
Hip fracture	127	0.50 (0.33-0.78)
Clinical MI	241	0.69 (0.50-0.95)
Invasive breast cancer	265	0.73 (0.53-1.00)
Cancer death	215	0.60 (0.43-0.82)

Women who adhered to placebo use had substantially more favorable clinical outcomes compared to non-adherence which was not explained by potential confounders

Curtis, Larson, Delzell, Brookhart, Cadarette, Chlebowski, et al. Medical Care 2011;49(5):427-435

Does Adherence/Persistence with Hormone Therapy Influence Breast Cancer Outcomes?

Early Breast Trialist Cooperative Group: Tamoxifen for Early Breast Cancer

30,000 cases with ER positive or unknown tumors and about 10 years follow-up

Trial Duration	Proportional Recurrence Reduction
1 year	21% (SD 3)
2 years	29% (SD 2)
5 years	47% (SD 3)

P trend < 0.00001

EBCTCG Cochrane Database Syst Rev 2001;(1):CD000486

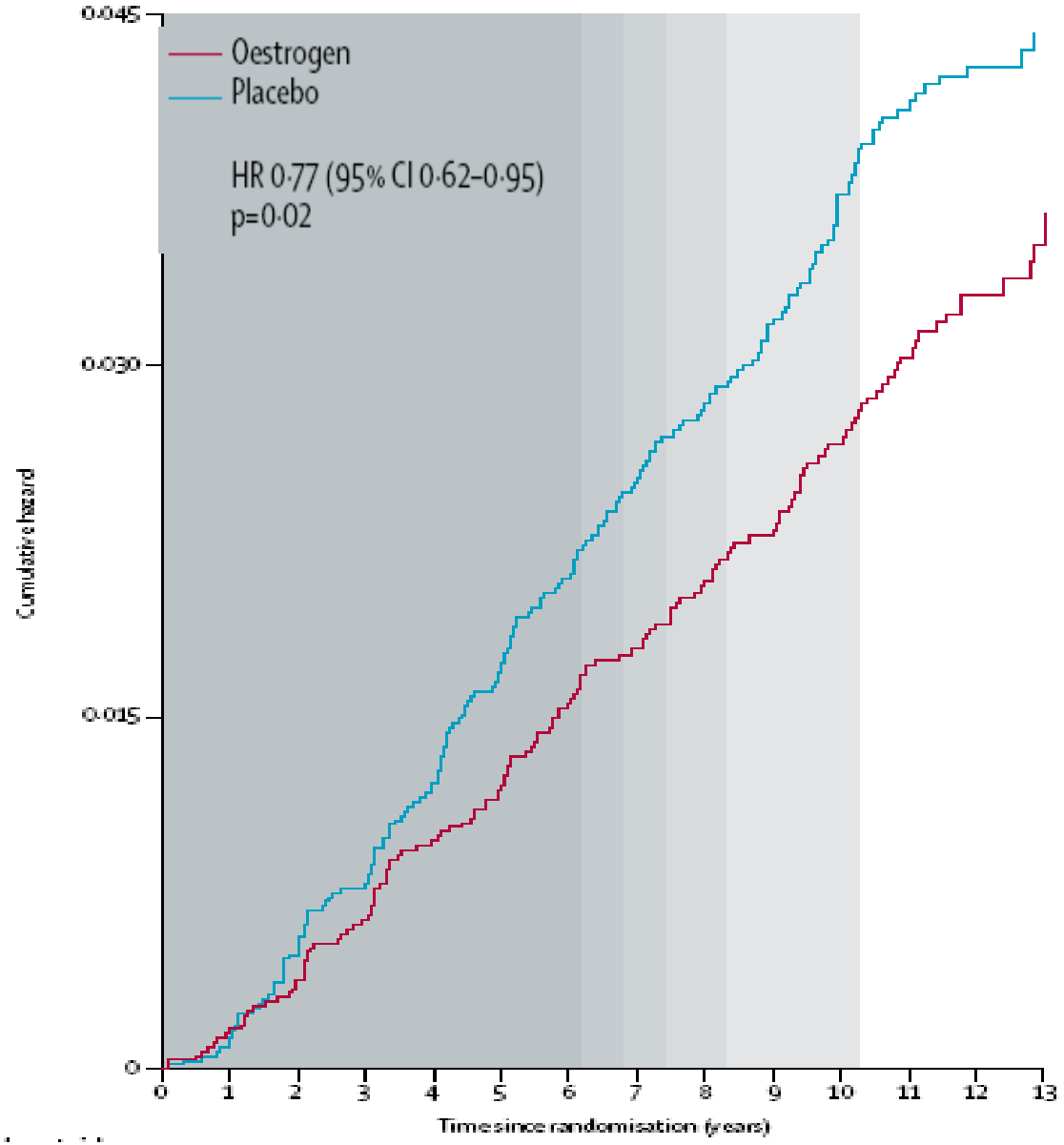
THE LANCET Oncology

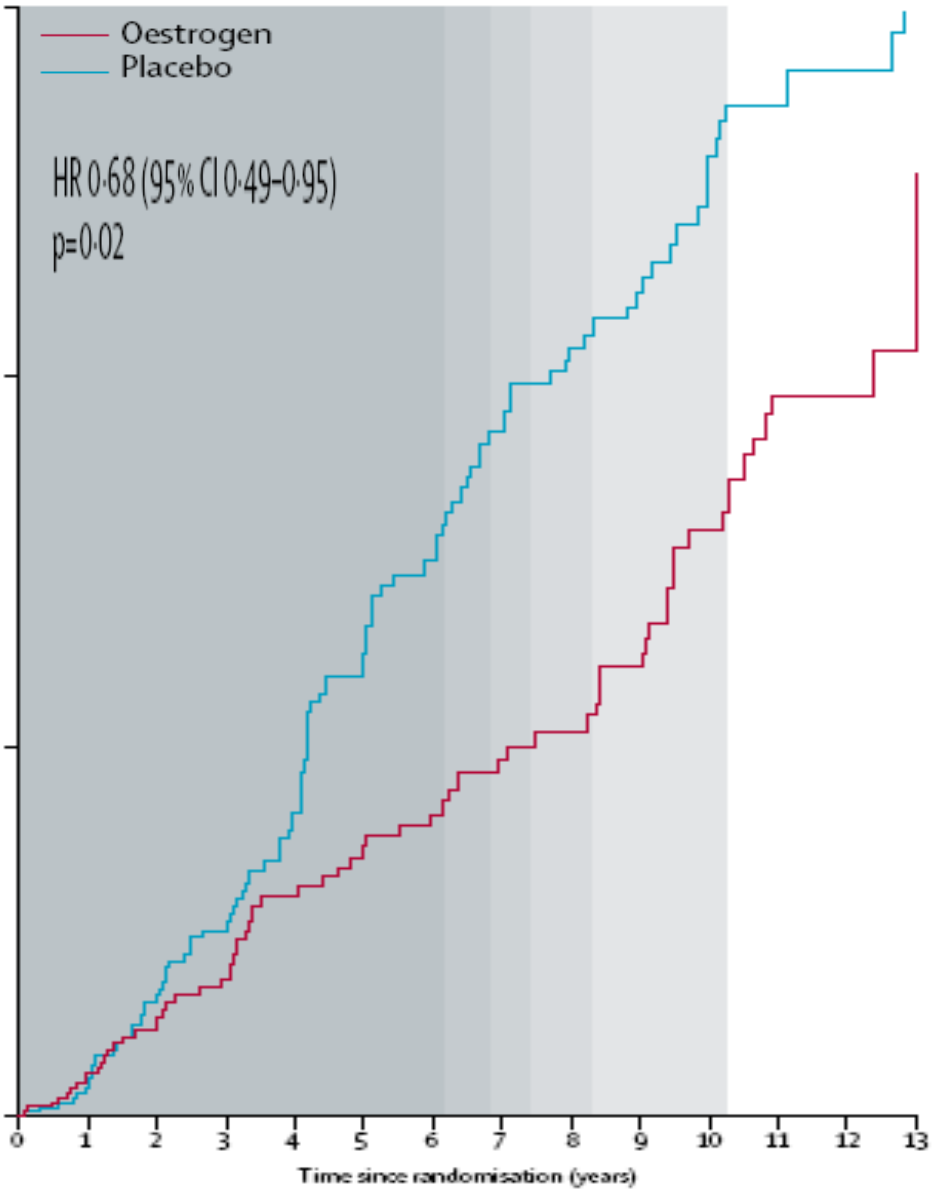
The Lancet Oncology, Early Online Publication, 7 March 2012
doi:10.1016/S1470-2045(12)70075-X

Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial

Prof Garnet L Anderson PhD [a], Prof Rowan T Chlebowski MD [b], Aaron K Aragaki MS [a], Prof Lewis H Kuller MD [c], Prof JoAnn E Manson MD [d], Prof Margery Gass MD [e], Elizabeth Bluhm MD [f], Prof Stephanie Connelly MD [g], Prof F Allan Hubbell MD [h], Prof Dorothy Lane MD [i], Lisa Martin MD [j], Prof Judith Ockene PhD [k], Prof Thomas Rohan MBBS [l], Prof Robert Schenken MD [m], Prof Jean Wactawski-Wende PhD [n]

Estrogen Alone Influence on Breast Cancer Incidence: Intent-to-Treat vs Sensitivity Analysis





Anderson, Chlebowski, Aragaki, et al. Lancet Oncology 2012 March 6 [Epub ahead of print]

Factors Influencing Non-Adherence in Breast Cancer Prevention Trials

Additional prescription medication [1] and not smoking [1, 2] predicted better adherence

Alcohol [2] use and side effects were negative predictors

[1] Maurice, Howell et al. Breast J 2006;12(5):446-50.
[2]Land et al. J Clin Oncol 2010;28:15s

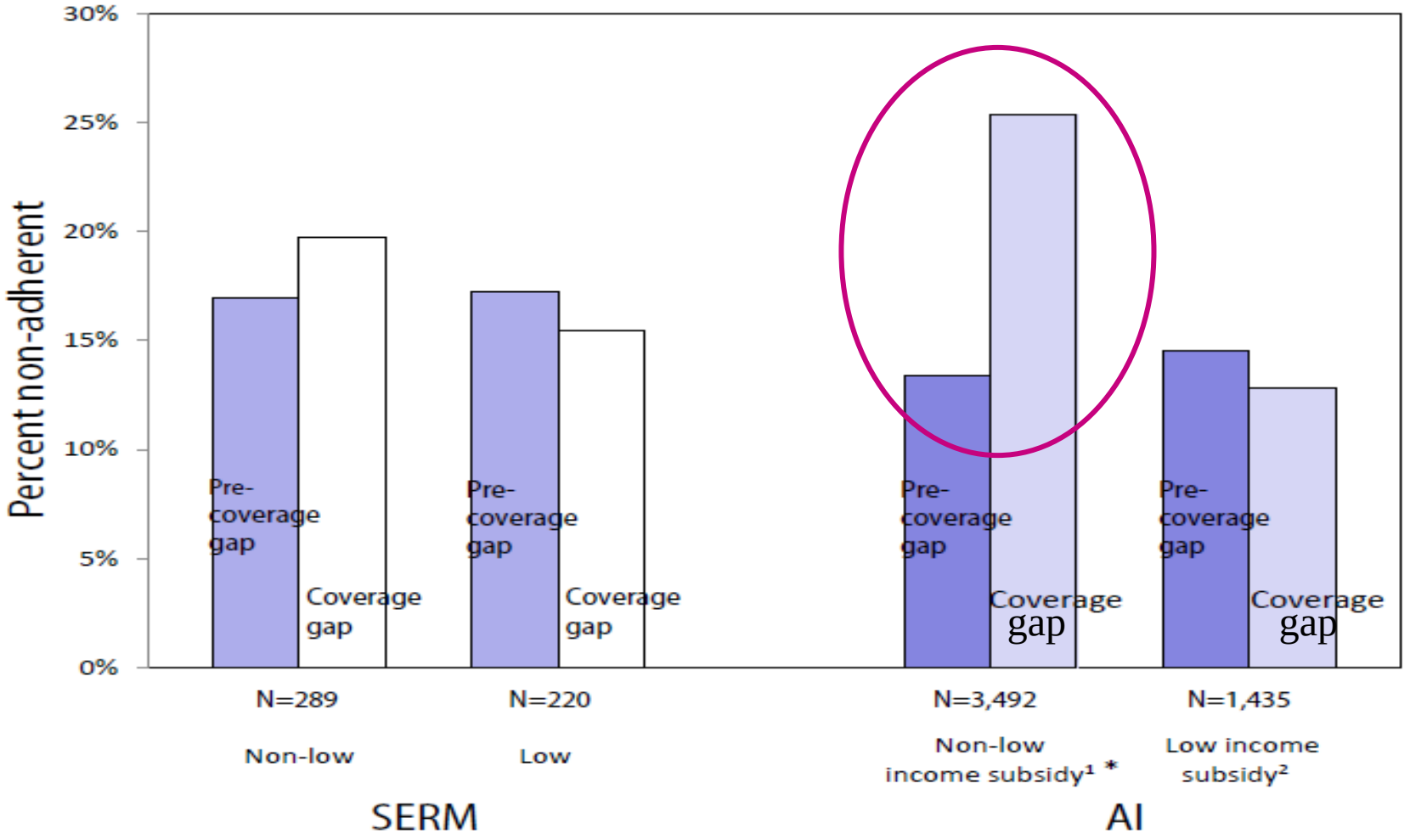
Predictors of Non-Adherence to Aromatase Inhibitors

- Medication possession ratio (MPR) for 1 year of AI therapy in Colorado (USA) breast cancer patients with early stage disease
- 23% of 13,593 were non-adherent (< 80% MPR)
- Associated with non-adherence, younger age, patient cost ≥ 30 $ per prescription

Sedjo, Devine, et al. Breast Cancer Res Treat 2011;125(1):191-200

Cost

Endocrine Therapy Among Hormone Receptor-Positive Breast Cancer Patients Enrolled in Medicare Part D Who Reached Coverage Gap

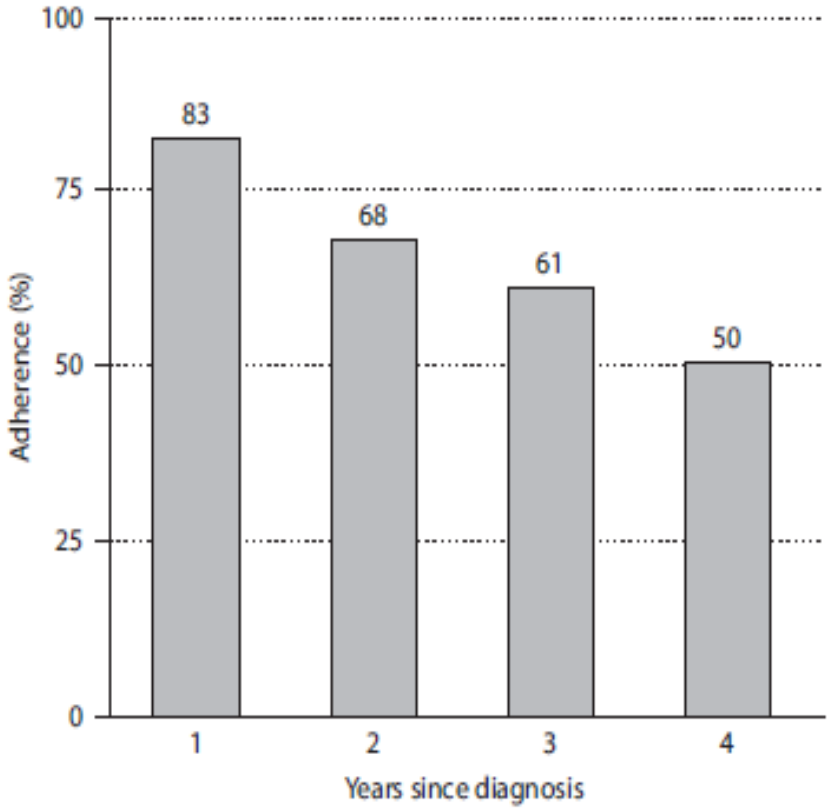


Non-adherence increased for those without low income subsidy for AIs

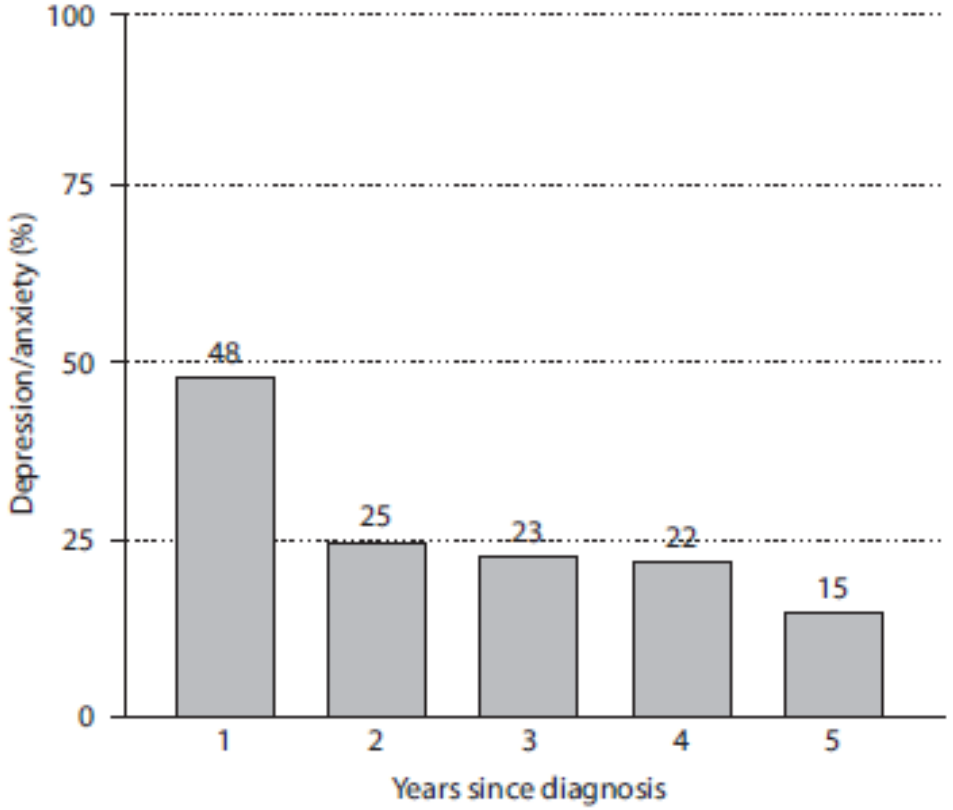
Riley et al. Medicare and Medicaid 2011;1(4):E1-E26

Adherence to Adjuvant Tamoxifen in Clinical Practice and Prevalence of Depression, Anxiety or Both

Adherence



Depression and/or Anxiety



Hypothesis: adherence highest when anxiety regarding disease is highest

Chlebowski, Geller. Oncology 2006;71:1-9, Partridge 2003, Burgers

Physician Component
Outpatient Oncology Linguistic Communication Study

Study of 28 patients on adjuvant hormonal therapy showed:

- Oncologists and patients had good rapport and open communication
- *However, the issue of adherence was poorly addressed*
- Persistence was addressed (12 of 28 visits), but mostly in the context of planned time on therapy
- Discussions of hormonal therapy
  - Focused on medication inventory, side effects, and study/trial findings
- Oncology nurses in these offices were not observed interacting with patients regarding oral therapy (possibly due to practice structure)

Davidson B et al. *J Support Oncol.* 2007;5:139-143.

Adjuvant Hormone Therapy for Receptor Plus Postmenopausal Women with Early Stage Breast Cancer

Link SEER Medicare Part D Data	In Women's Health Initiative Cohort
15,542 in years 2003-2005	3,588 surveyed 2009-2010
Use: SERM 22% , AI 52%	Use: AA 33%, SERM 31%, mix 36%
26% none	17% none
20-30% of users became non-adherent	33% of users became non-adherent
Lack of physician recommendation (12%) most common barrier	
Riley, Warren, Harlan, et al. Medicare Medicaid Res Rev 2011;1(4):E1-26	Toman, LaCroix, Chlebowski (submitted)

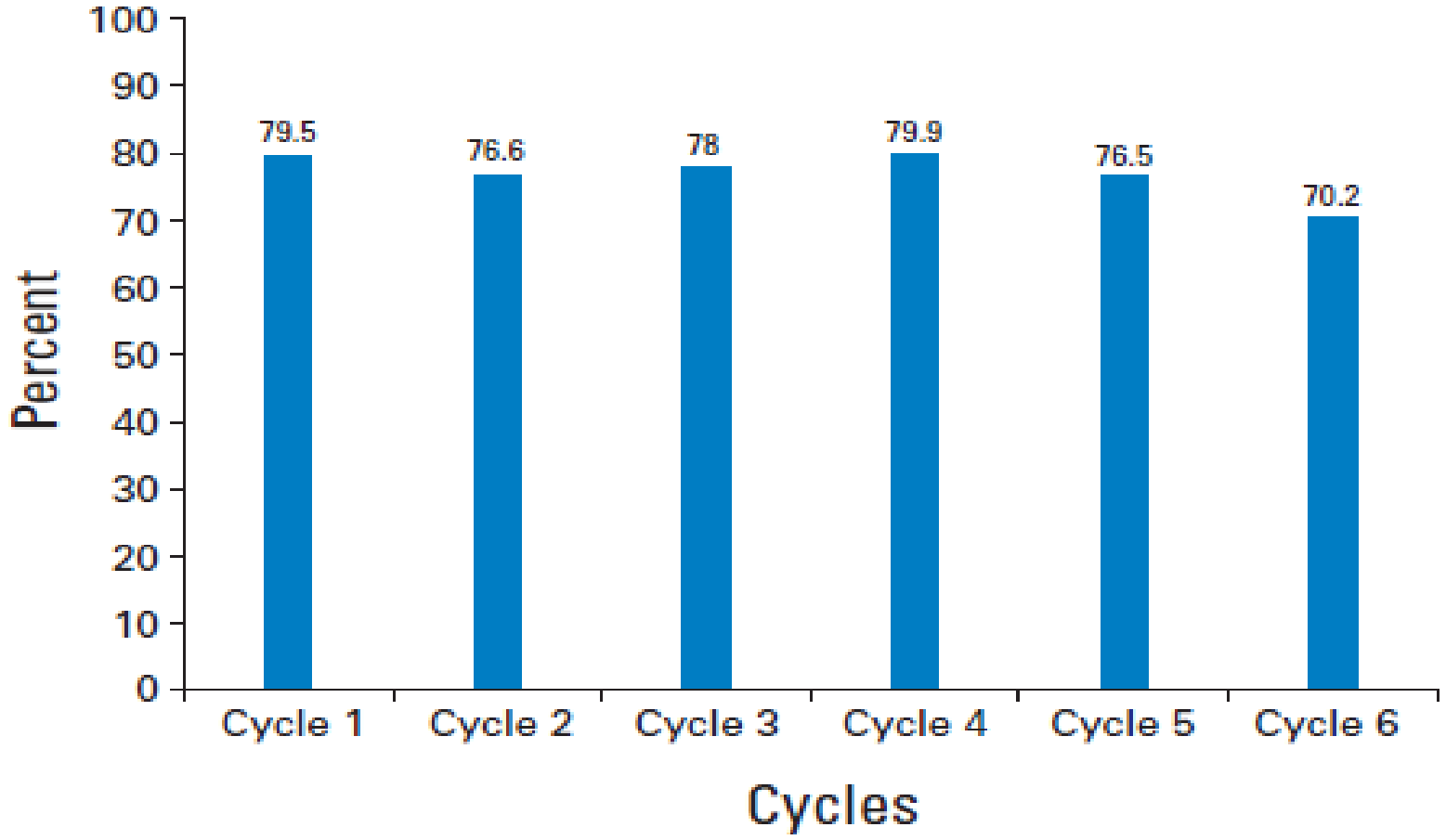
Physician Component
Prescription Refill, Patient Self-Report and Physician Report and Adherence to Hormone Therapy in Early Breast Cancer
A Retrospective Cohort Study

Odds Ratio Associated with Adherence for Each of the Methods Used			
	Physician Report	Telephone Questionnaire	Pharmacy Administrative Database
	N(%)	N(%)	N(%)
Age at diagnosis			
5-74	419 (95.5)	330 (94.2)	409 (79.0)
≥75	90 (94.4)	38 (86.8)	88 (67.0)
P-value	0.075	0.003	0.001

Physicians overestimate adherence

Font, et al. British J Cancer 2012;1-8

Adherence and Persistence with Oral Adjuvant Capecitabine in Older Women in CALGB 49907



Adherence among participants by cycle using the microelectronic monitoring system (MEMS) indicates relatively good adherence to oral chemotherapy

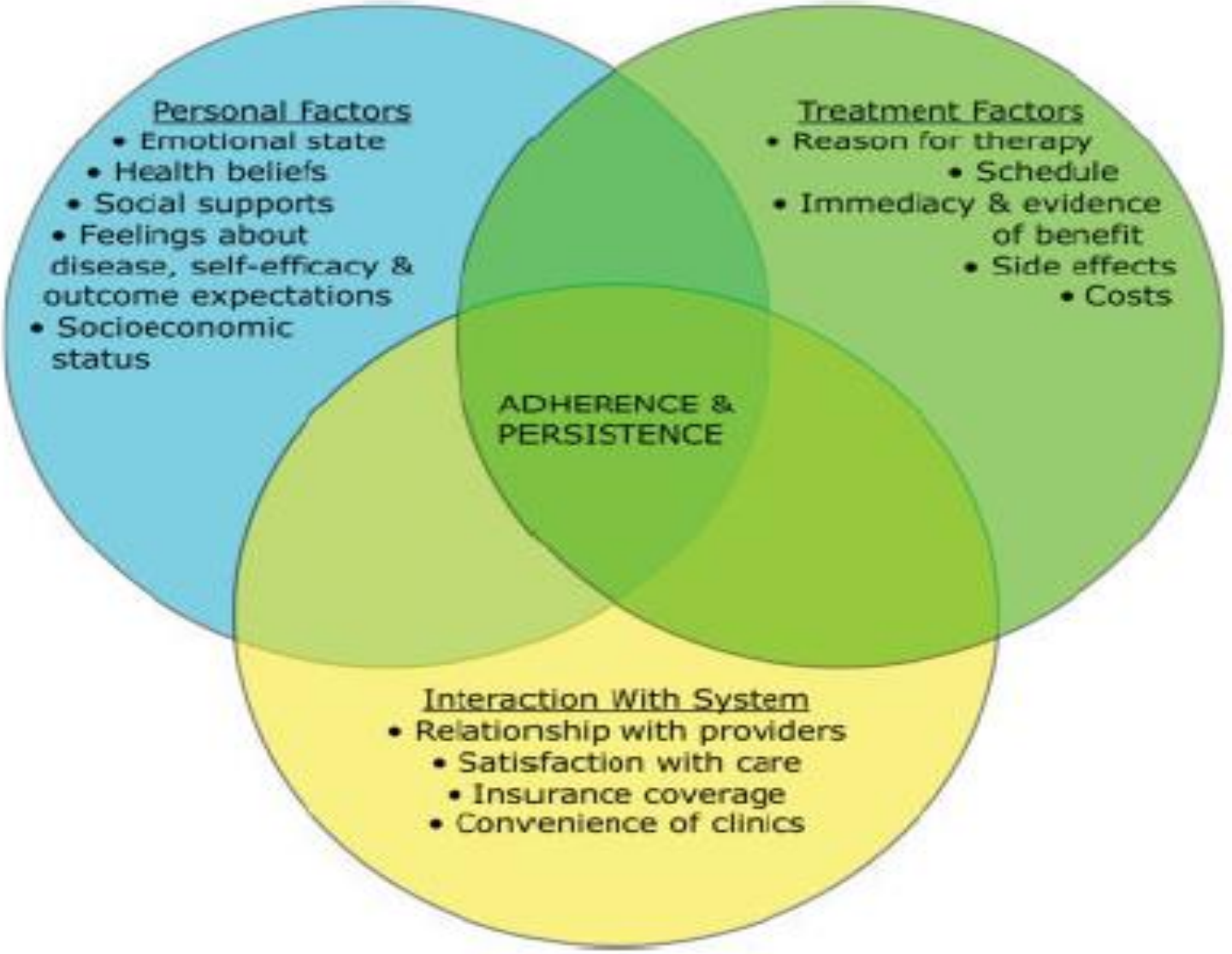
Partridge et al. J Clin Oncol 2010;28:2418-2422

Signs and Predictors of Poor Adherence and Persistence

- Missed appointments, inadequate follow-up
- Poor patient-provide relationship
- Unfilled prescriptions
- Adverse effects from medication, mediation cost
- Lack of belief in treatment
- Psychological problems, particularly depression

Ruddy, Mayer, Partridge. Ca Cancer J Clin 2009;59:56-66.

Model of Adherence and Persistence



Ruddy, Mayer, Partridge. Ca Cancer J Clin 2009;59:56-66.

Interventions for Improving Adherence

- Increased accessibility to healthcare
  - More convenient follow-up appointments
  - Access to pharmacists, behavioral specialists, social workers
- Improved dosing plan
- Educational intervention to increase patient's understanding of:
  - Disease characteristics
  - Risks and benefits of treatment
  - Proper use of medication
- While these are general recommendations, they reflect clinical trial approach

Ruddy, Mayer, Partridge. Ca Cancer J Clin 2009;59:56-66.

Summary and Limitations

Only modest information about factors associated with continued adjuvant hormonal therapy are known.

Few of the correlates identified are easily modifiable

Current medical claim databases, commonly used, contain limited information on healthcare practice patterns or patient characteristics needed to identify modifiable factors

Few proposed remedies have clinical trial efficacy support

Murphy, Bartholomew, Carpentier, et al. Breast Cancer Res Treat 2012;134:459-478.
Ruddy, Mater, Partridge. CA Causes J Clin 2009;59:56-66.