

Adjuvant Therapy In Early Breast Cancer With Zoledronic Acid (AZURE - BIG 01/04): Treatment Effects Are Influenced By Menopausal Status Rather Than Age.

H. Marshall, W. Gregory, R. Bell, D. Cameron, D. Dodwell, M. Keane, M. Gil, C. Davies, & R. Coleman
on behalf of the AZURE Investigators.



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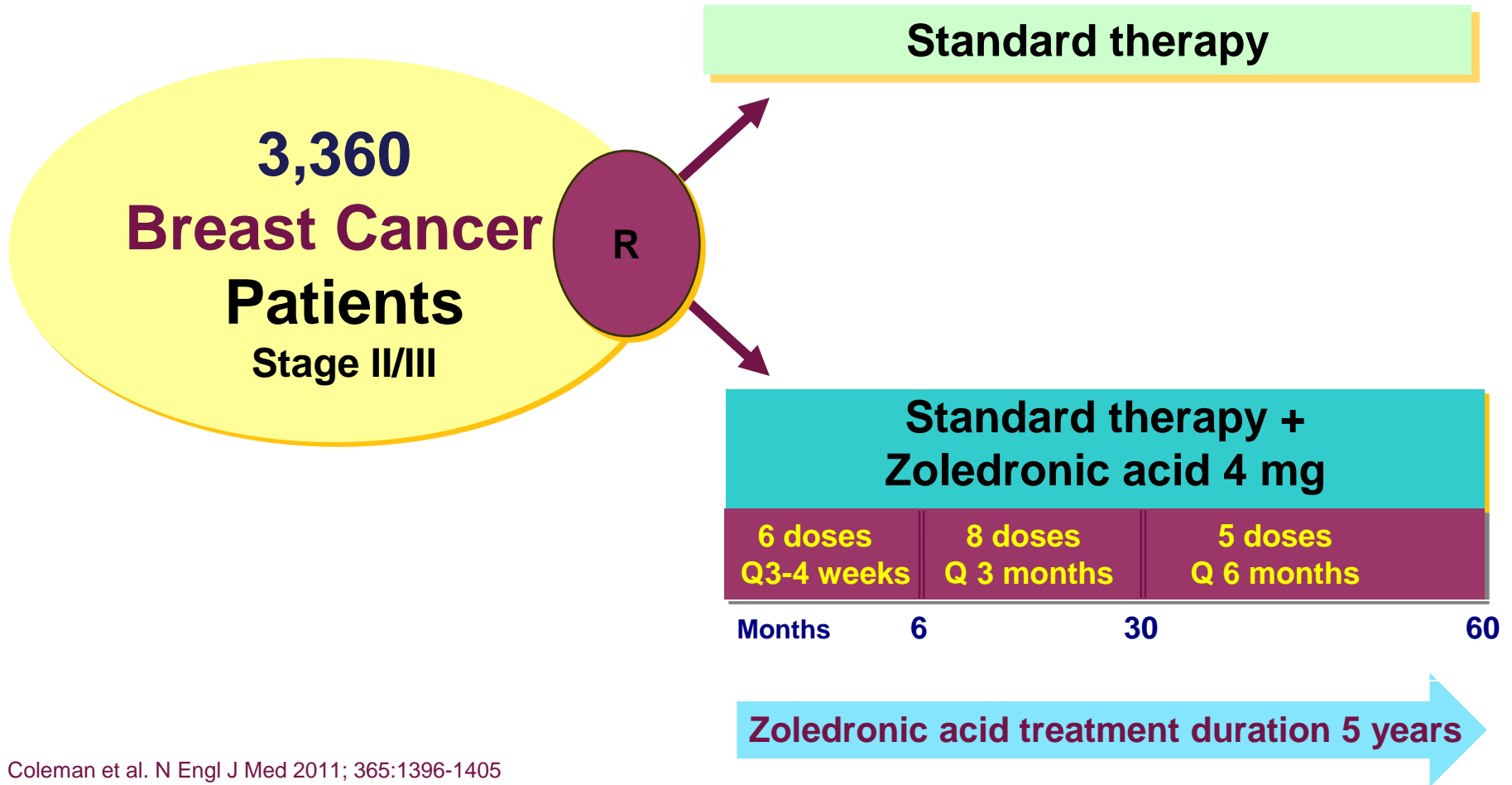
NHS

*National Institute for
Health Research*



AZURE: Study Design

Accrual September 2003 - February 2006



Coleman et al. N Engl J Med 2011; 365:1396-1405

AZURE: Study Endpoints

- **Primary endpoint**
 - Disease Free Survival (DFS)

- **Key secondary endpoints**
 - Invasive DFS (IDFS)
 - Overall survival (OS)
 - Bone metastasis free survival (BMFS)
 - Pre-specified subgroup analyses
 - **Menopausal status**
 - Premenopausal
 - Perimenopausal (< 5 years postmenopause)
 - Established menopause (\geq 5 years postmenopause)
 - Unknown
 - **ER status**
 - Node involvement
 - T stage
 - Chemotherapy type
 - Statin use

AZURE: DFS and IDFS Definitions

	DFS	IDFS
Chest Wall Recurrence	✓	✓
Ipsilateral Breast Recurrence	✗	✓
Regional Recurrence	✓	✓
Distant Recurrence	✓	✓
Death Without Recurrence	✓	✓
Contralateral Breast Cancer	✗	✓
New Primary Cancer	✗	✓
DCIS / LCIS	✗	✗

IDFS is a more robust & appropriate definition for assessing an adjuvant treatment

Dates of recurrence/event = date first suspected

Hudis C. et al. J Clin Oncol 2007;25,2127-32

Menopause Affects Bone Cell Function and Bone Derived Growth Factors

5 – 10 years



PREMENOPAUSAL

Cycling oestradiol

Cycling inhibin

Local activin, BMP

PERI-MENOPAUSAL

↓ Cycling oestradiol

↓ Inhibin B, ↑ FSH

↑ Activin, BMP tone

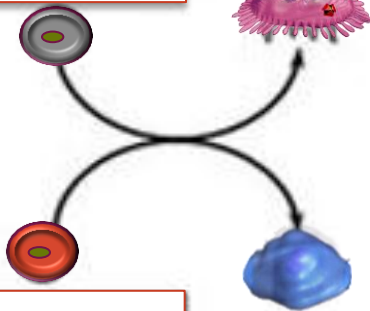
POSTMENOPAUSAL

↓↓ Oestradiol

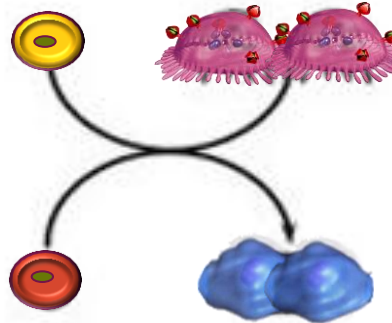
↓ Inhibins A & B ↑ FSH

↑ Activin, ↑ BMP tone

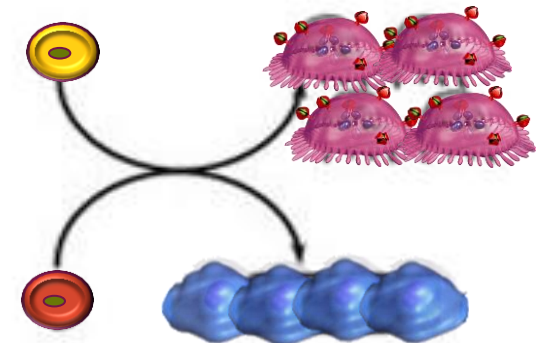
Pre-osteoclast



Normal Turnover



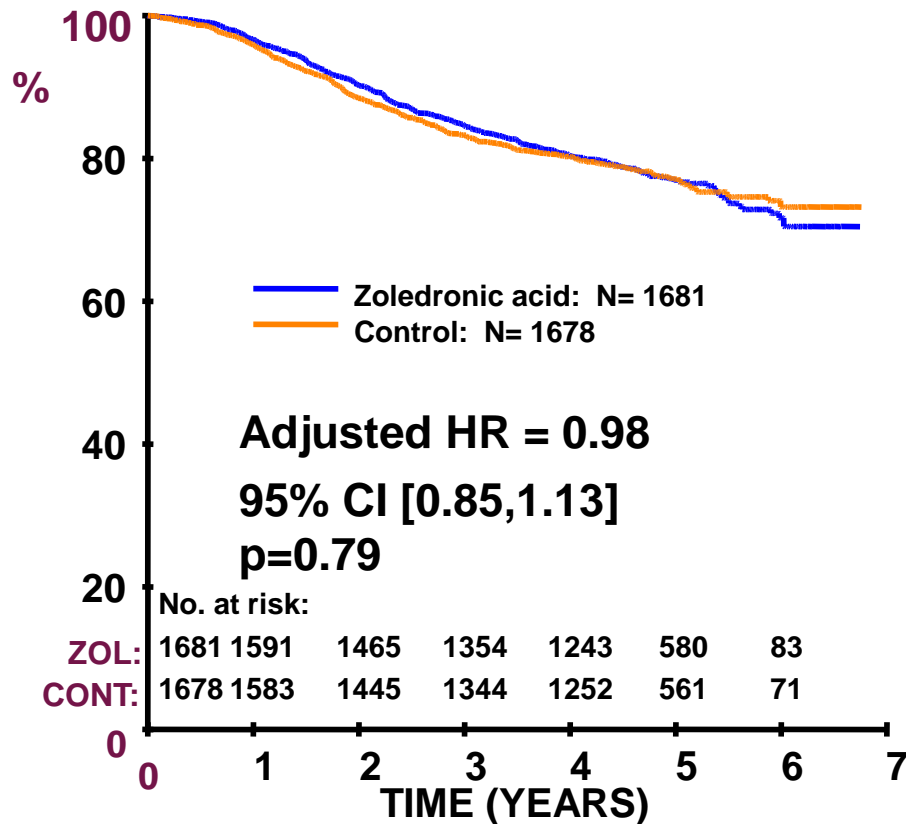
↑ Turnover



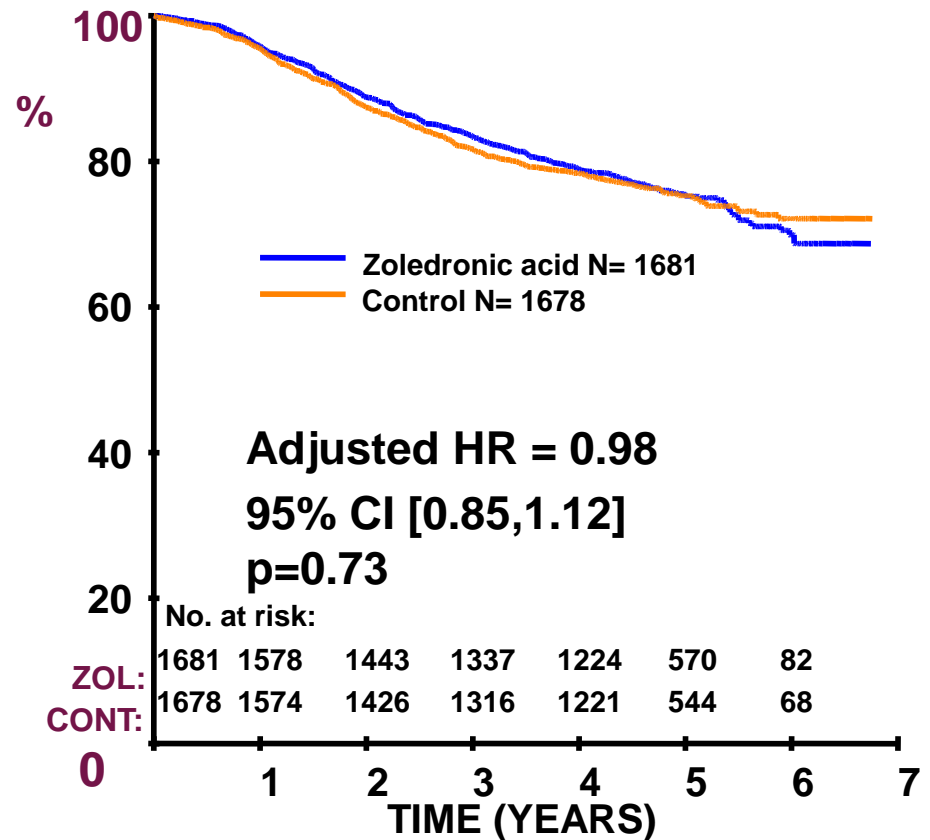
↑↑ Turnover

AZURE: Disease (DFS) and Invasive Disease Free Survival (IDFS)

DFS

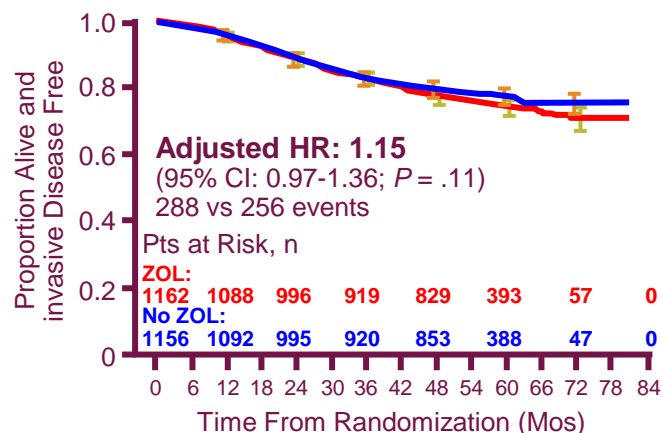


IDFS

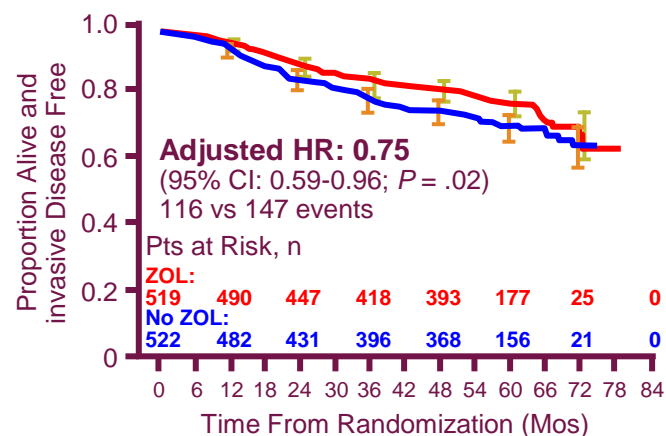


AZURE: Invasive DFS and OS by Menopausal Status

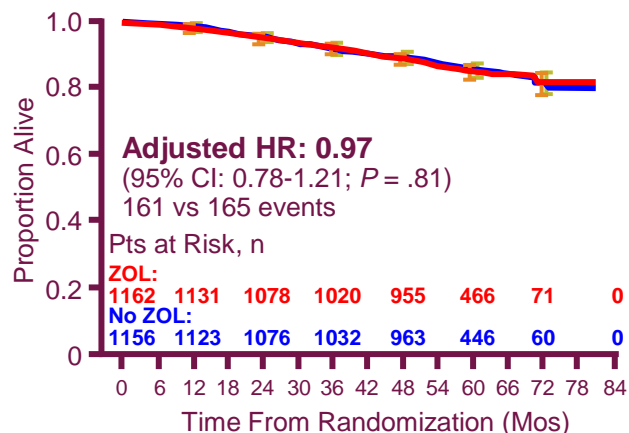
IDFS: Pre, Peri, and Unknown Menopause



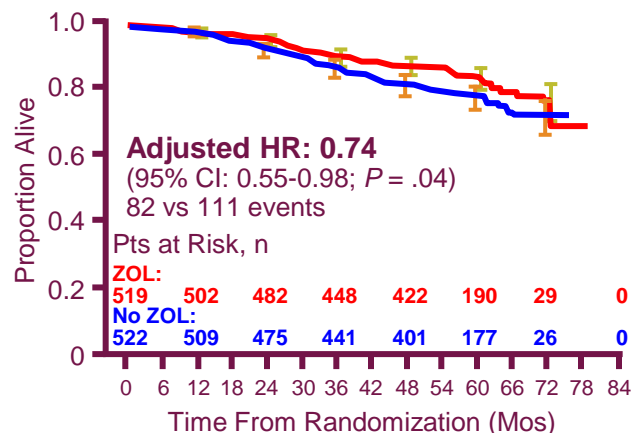
IDFS: > 5 Yrs Postmenopausal



OS: Pre, Peri, and Unknown Menopause

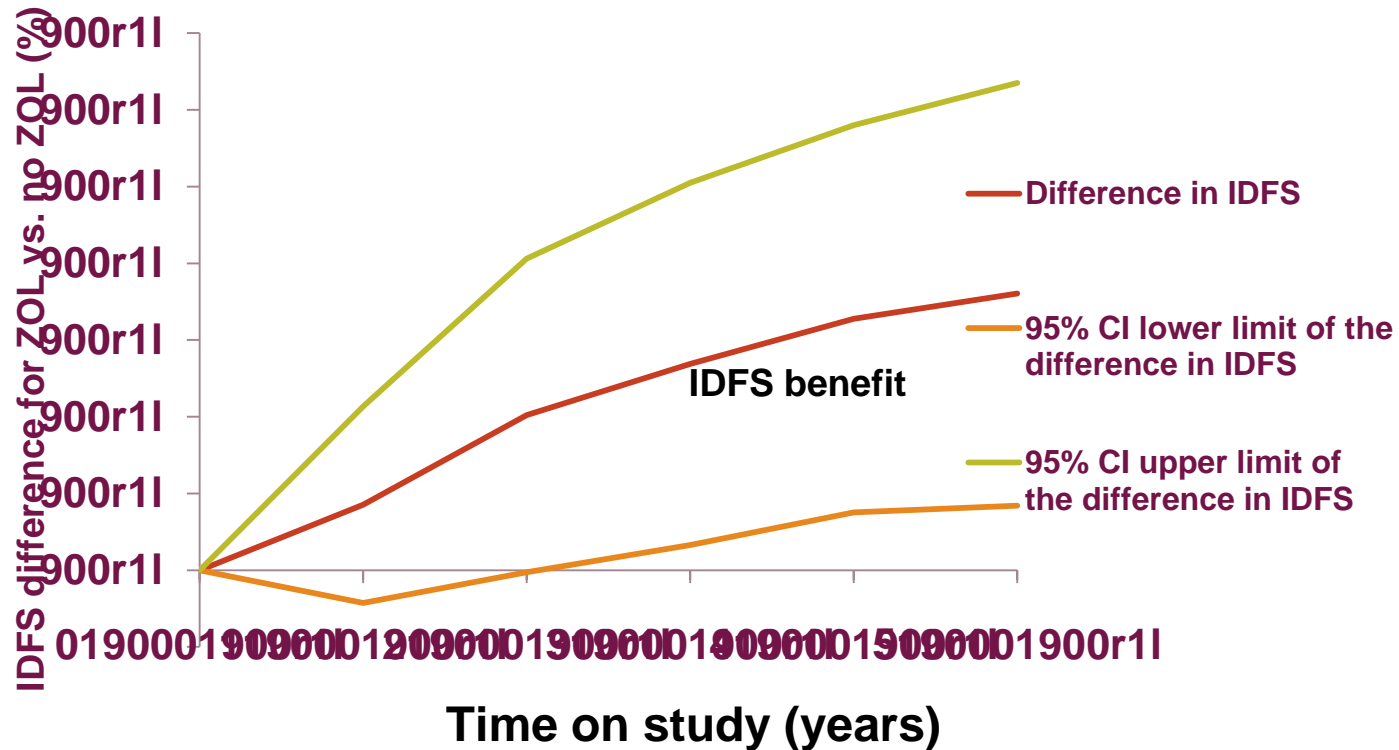


OS: > 5 Yrs Postmenopausal



Coleman RE, et al. N Engl J Med. 2011;365:1396-1405.

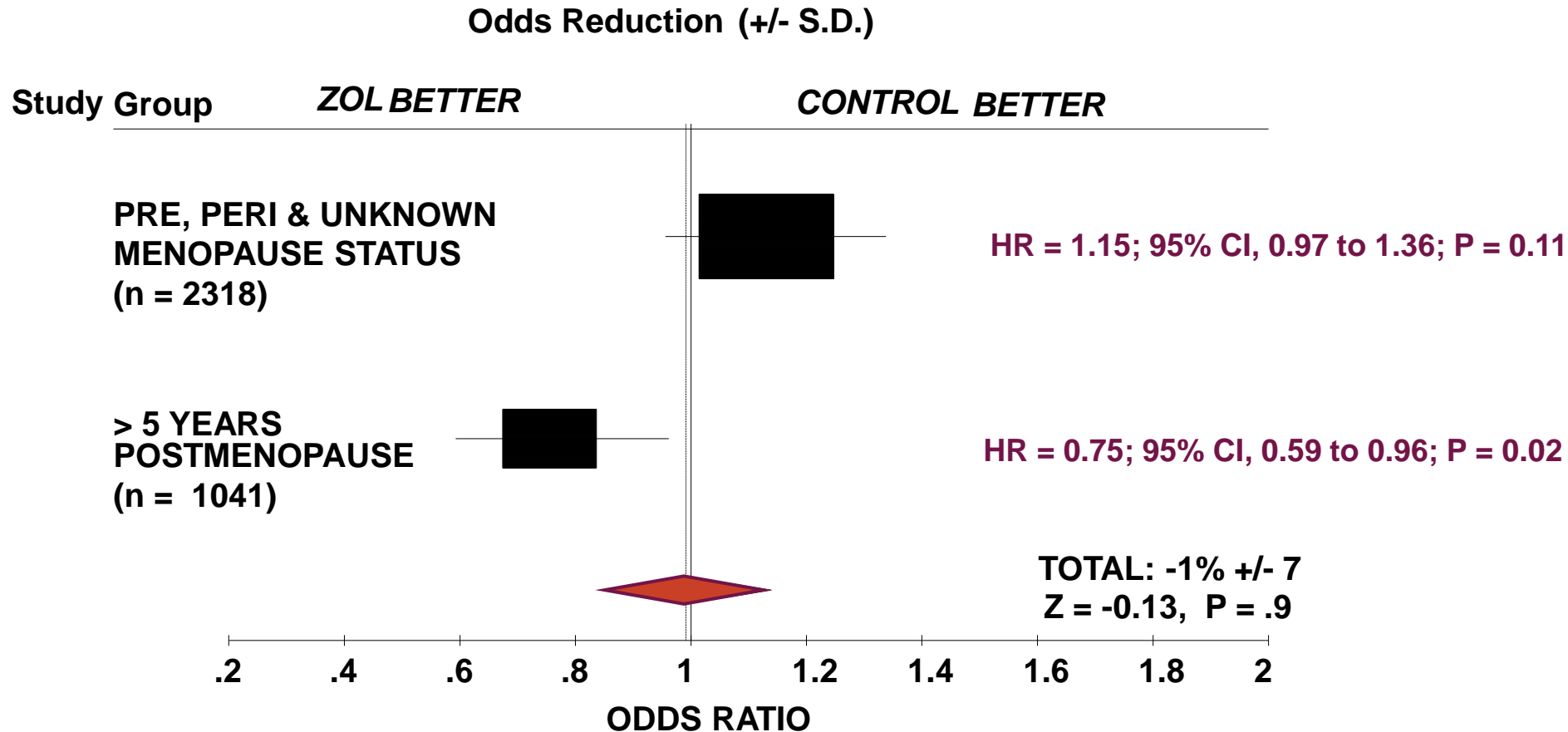
Rapid Emergence of IDFS benefit in >5years Postmenopause Patients



AZURE: Influence of Menopausal Status on Treatment Characteristics

	Pre, peri, unknown menopause (n = 2318)	> 5 years postmenopause (n = 1041)
Planned Systemic Therapy		
• Endocrine alone	2%	10%
• Chemo alone	20%	25%
• Endocrine + Chemo	78%	65%
Planned Chemotherapy type		
• Anthracyclines	97%	85%
Taxanes	27%	16%
Timing of chemotherapy		
• Neoadjuvant	7%	5%
• Postoperative	93%	95%
ER positivity		
• Yes	80%	75%
AI use at any time		
• Yes	48%	63%

Menopausal Status Interaction Effect For IDFS*

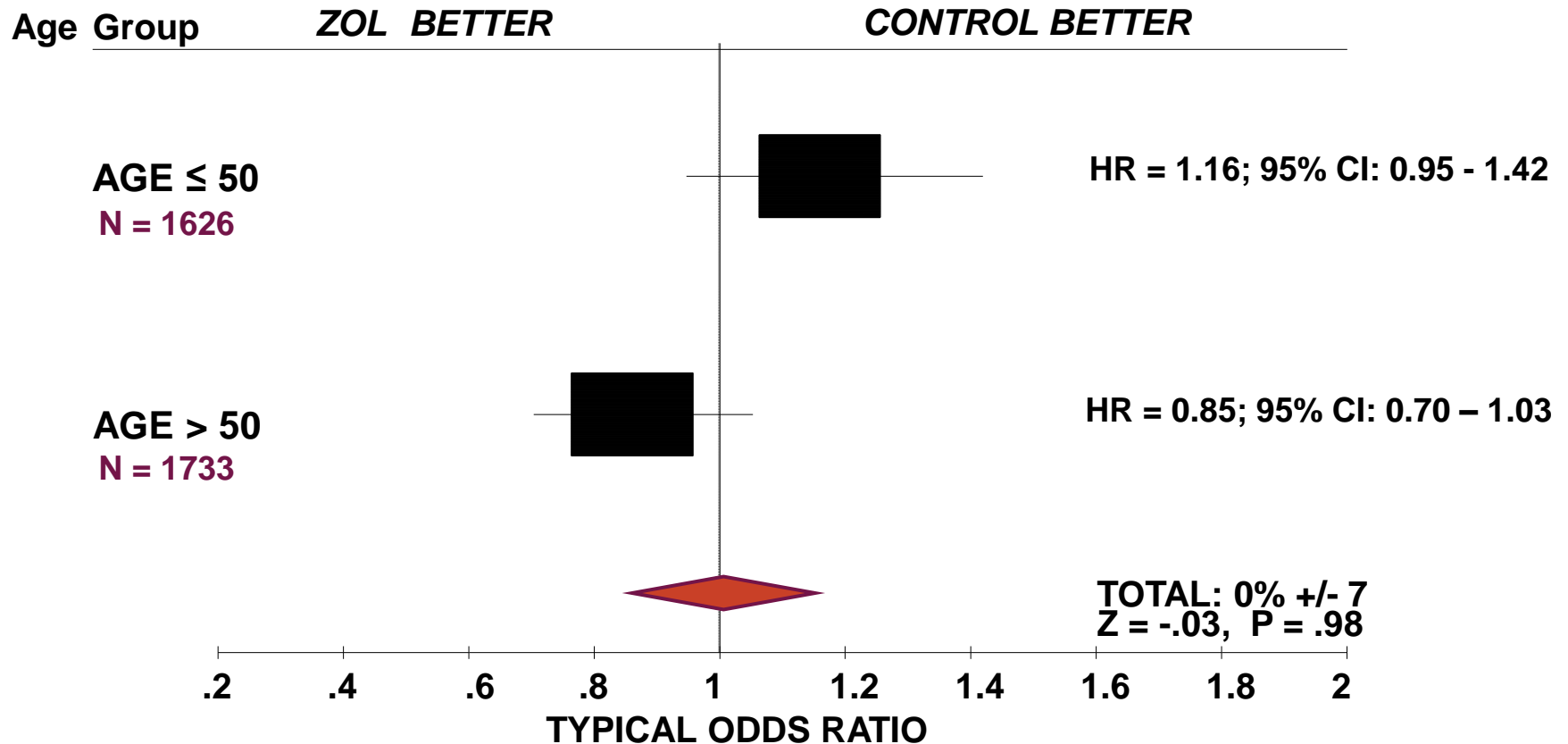


* Planned analysis

χ^2_1 (heterogeneity) = 7.91 P = .005

Age Interaction Effect For IDFS*

Odds Reduction(+/- S.D.)



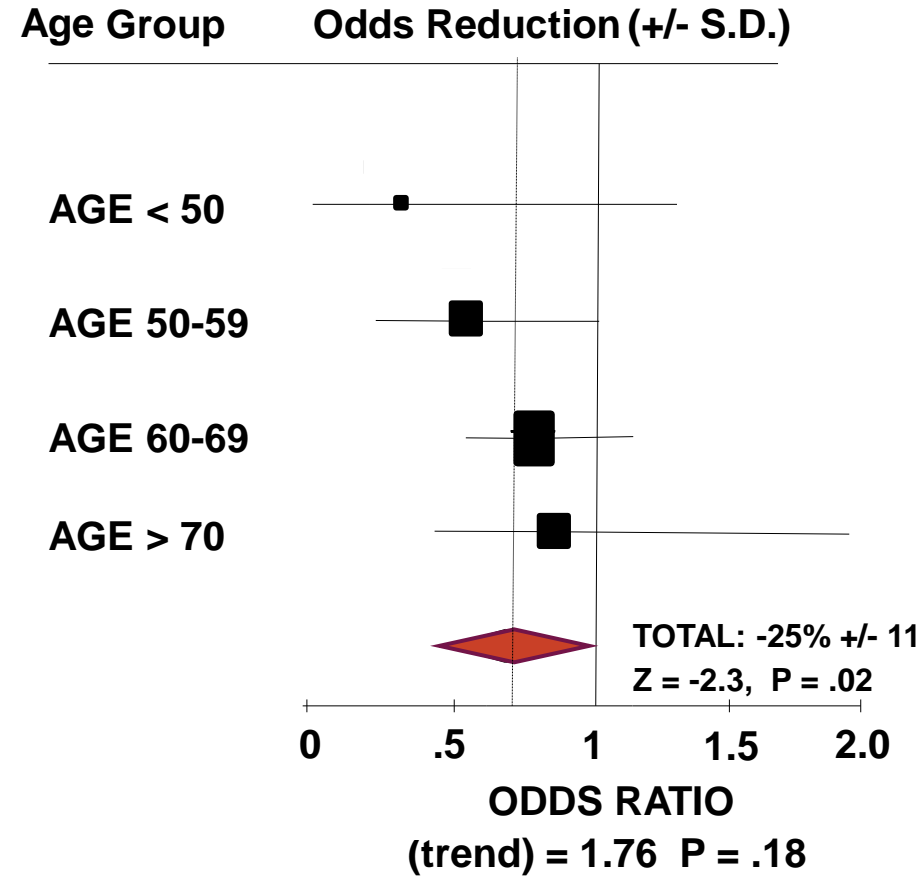
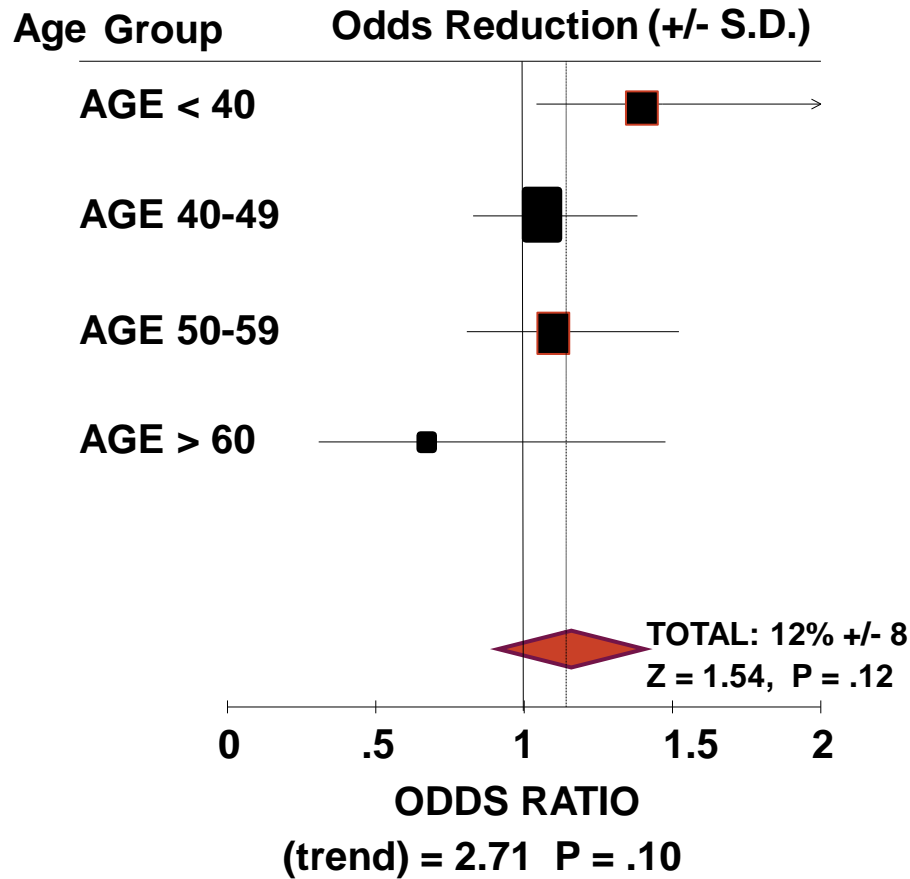
* Post hoc analysis

χ^2_1 (heterogeneity) = 4.18 P = .04

Affect of Menopausal Status on IDFS Outcomes by Age

**IDFS: PRE, PERI AND UNKNOWN MENOPAUSE
- ZOL EFFECT BY AGE**

**IDFS: > 5 YEARS POSTMENOPAUSE
- ZOL EFFECT BY AGE**

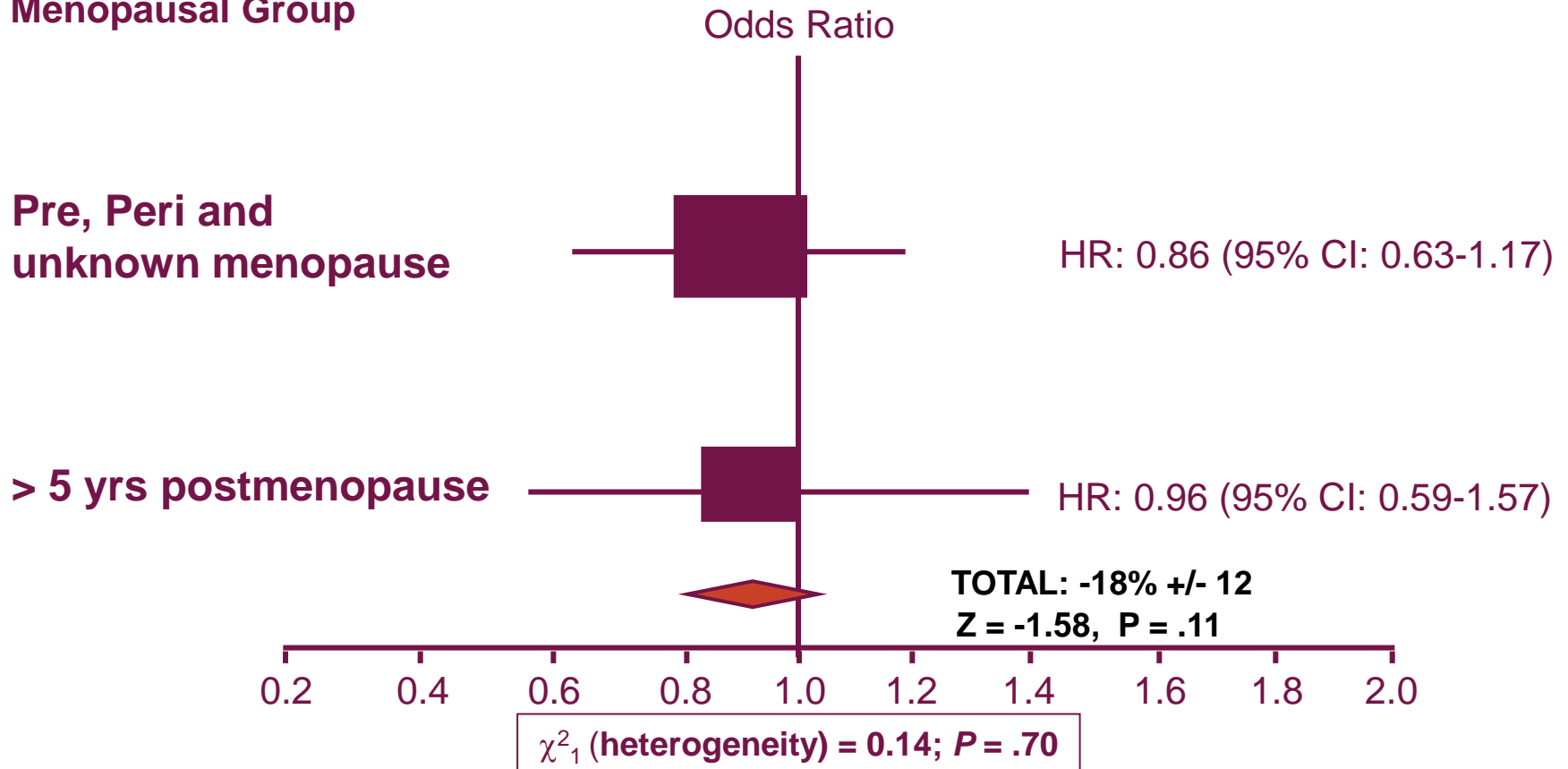


Possibly worse IDFS with ZOL

Significantly better IDFS with ZOL

AZURE: Treatment Effects on First Bone IDFS Recurrence by Menopausal Status

Menopausal Group

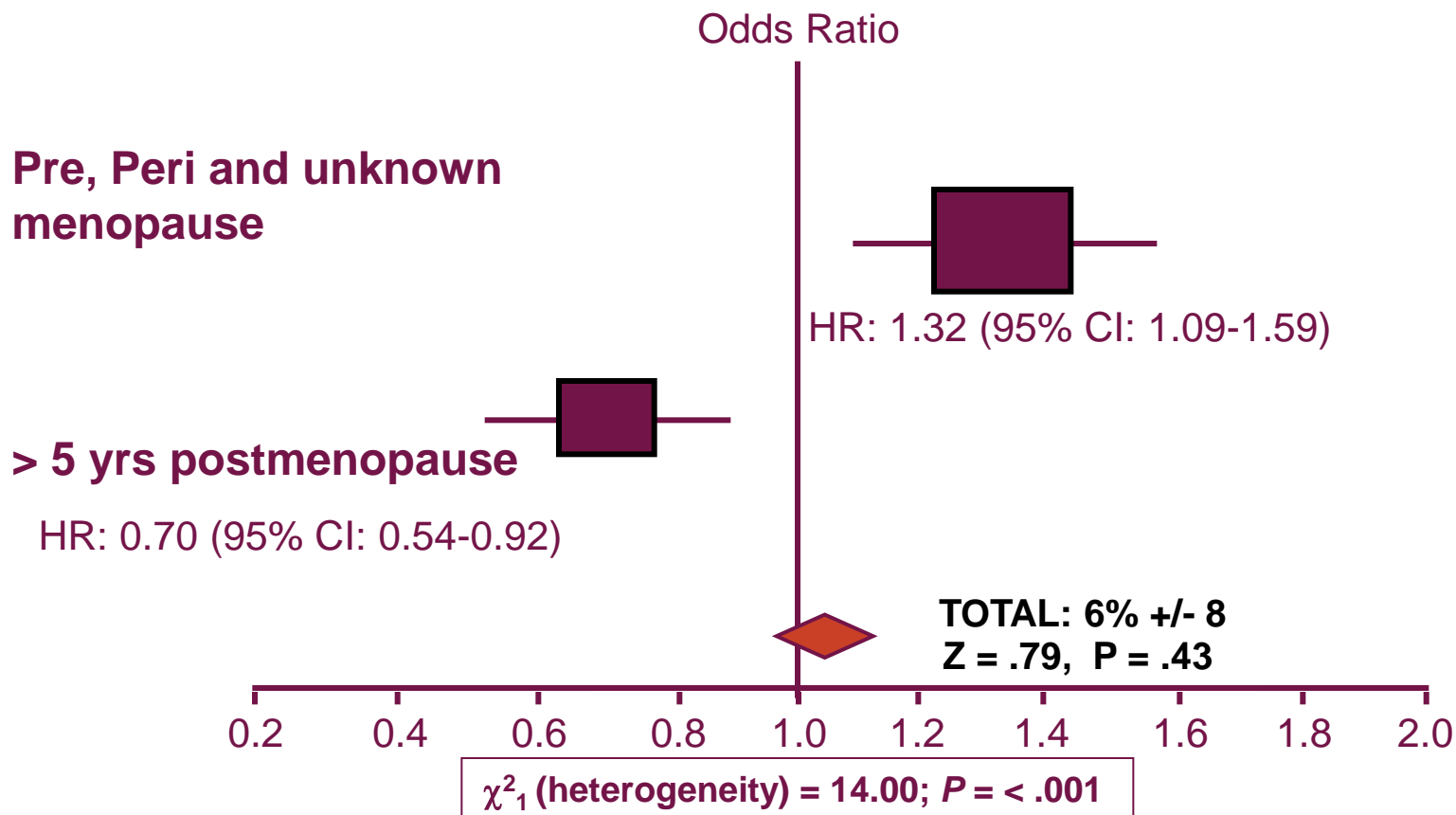


Adjusted for imbalances in ER, lymph node status, and T stage.

No significant differences in bone recurrence by menopausal status or age

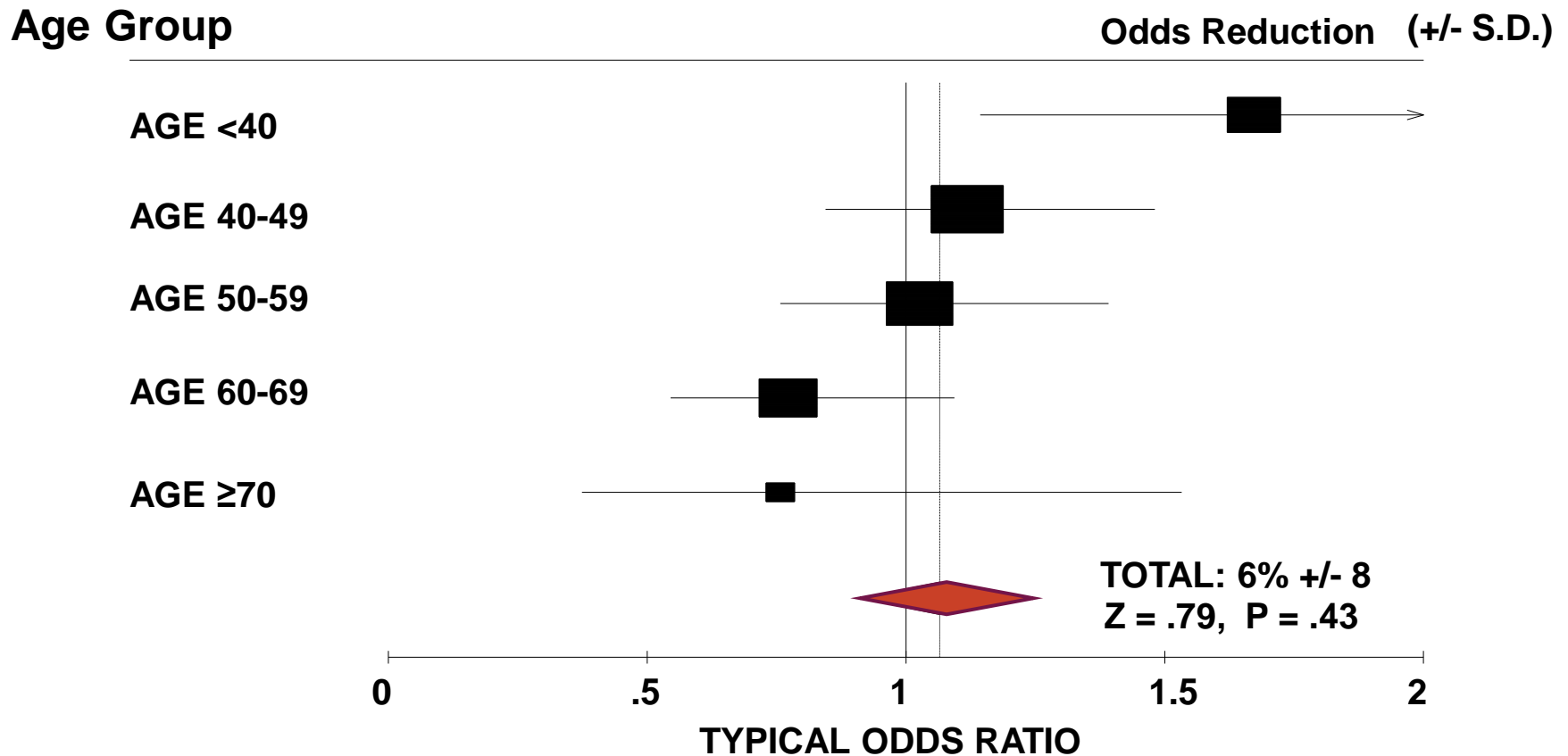
Treatment Effects on First IDFS Recurrence Outside Bone by Menopausal Status

Menopausal Group



Adjusted for imbalances in ER, lymph node status, and T stage.

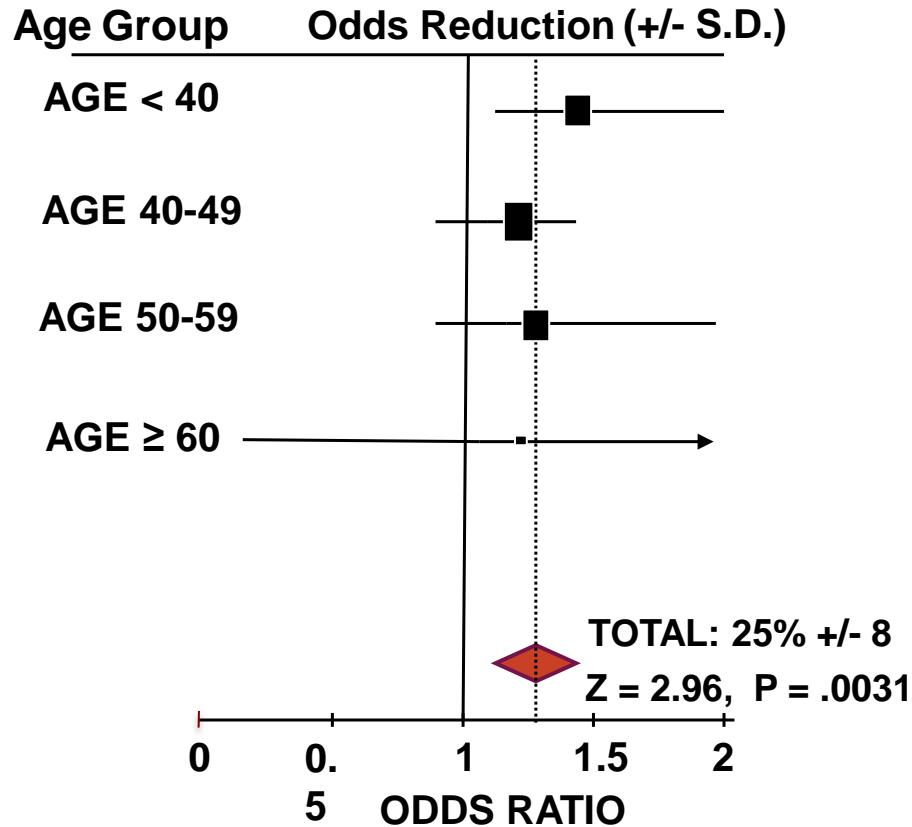
Treatment Effects on First IDFS Recurrence Outside Bone by Age



χ^2_1 (trend) = 8.82 P = .003

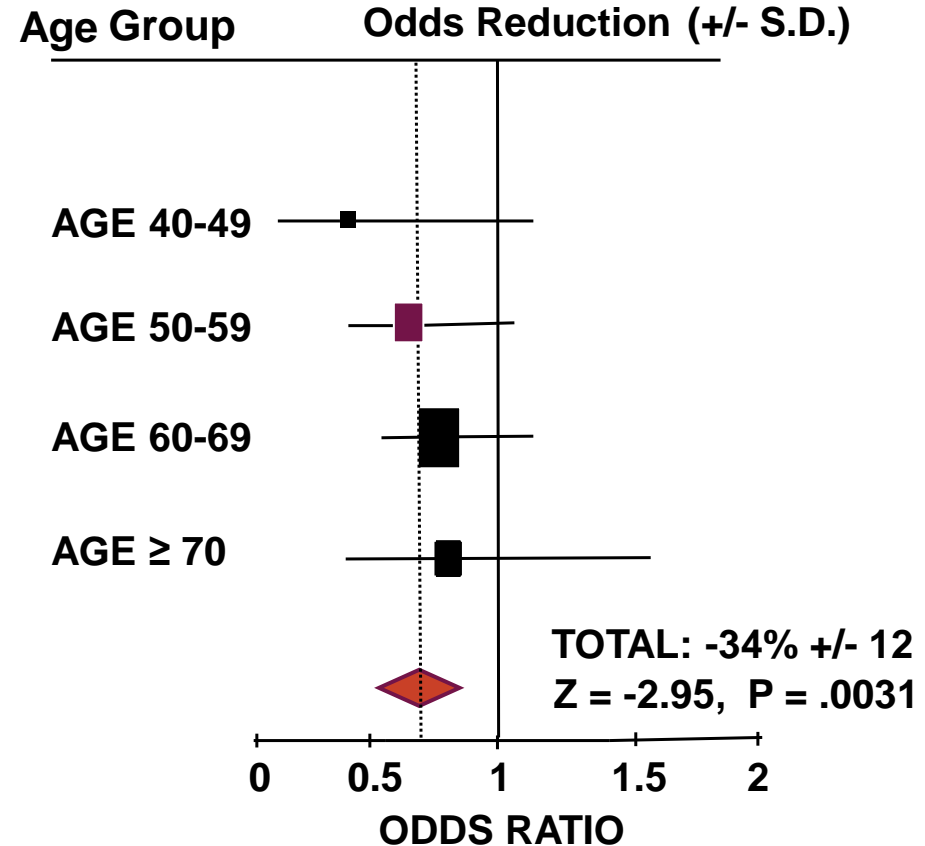
Age Effect on IDFS Excluding Bone by Menopausal Status

PRE, PERI AND UNKNOWN MENOPAUSE - BY AGE



χ^2_1 (trend) = .79 P = .37

> 5 YEARS POSTMENOPAUSE - BY AGE

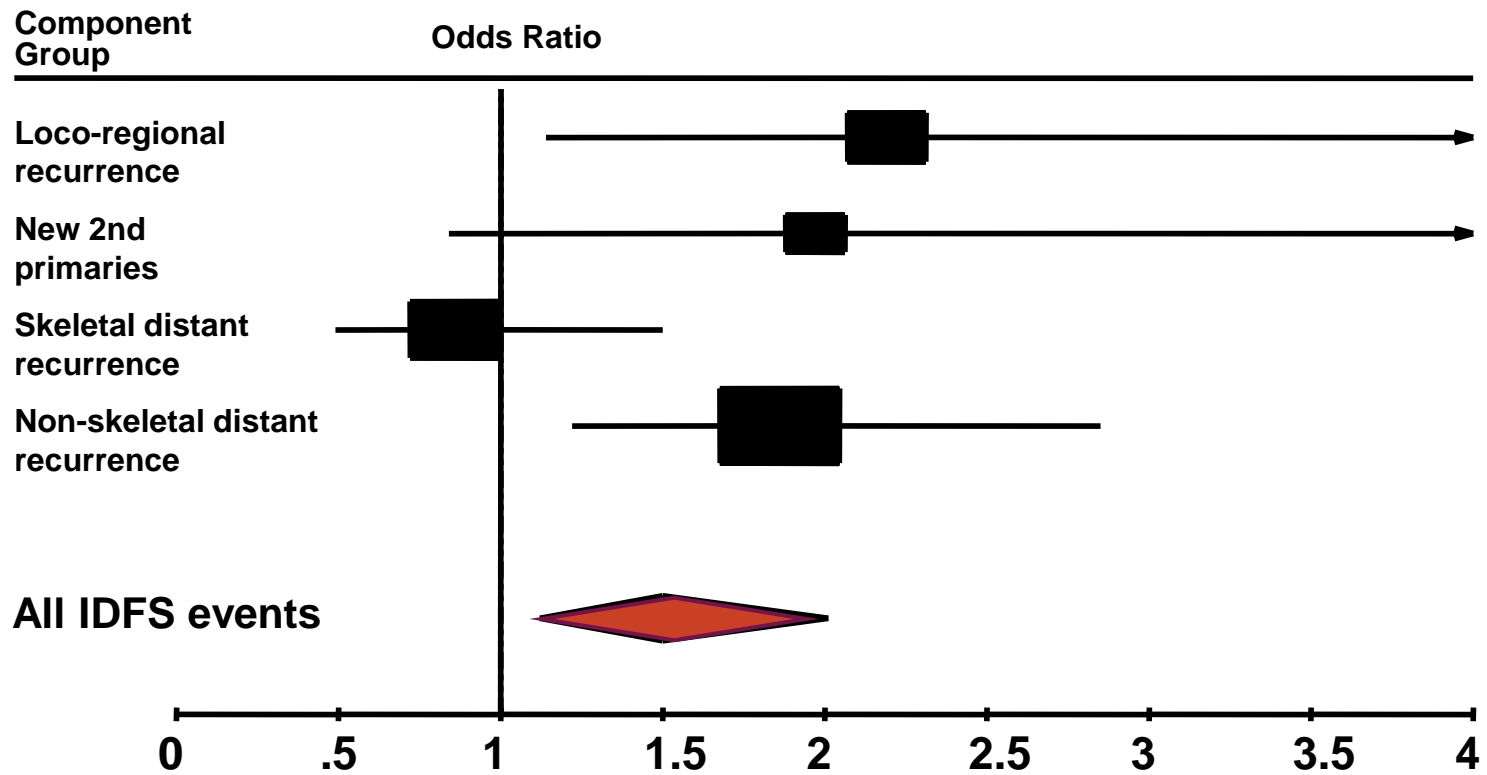


χ^2_1 (trend) = 1.64 P = .20

Significantly worse extra-skeletal IDFS with ZOL

Significantly better extra-skeletal IDFS with ZOL

Impact of Menopausal Status on Site of IDFS Recurrence With Zoledronic Acid



ODDS RATIO: Pre, Peri and unknown menopause / > 5 years postmenopause

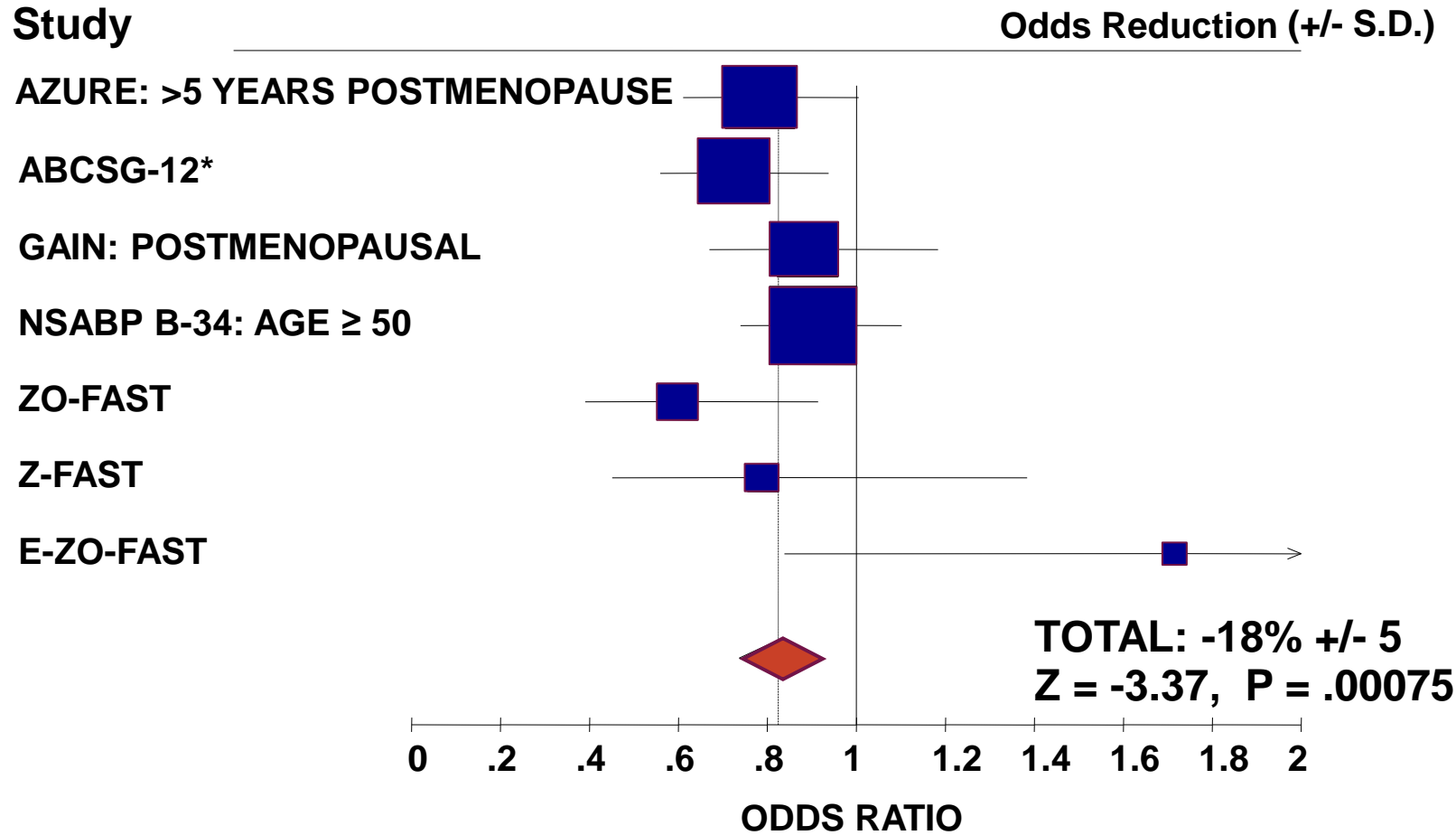
Coleman et al. N Engl J Med 2011; 365:1396-1405 (On line version)

Variable Efficacy in Different Populations (ITT analyses)

	Study Size	Overall DFS result	P value
AZURE	3360	0.98 (0.85, 1.13)	.79
ABCSG XII	1803	0.71 (0.55, 0.92)	.013
ZO-FAST	1065	0.66 (0.44, 0.97)	.04
NSABP-B34	3323	0.91 (0.79, 1.07)	.27
GAIN	2994	0.95 (0.77, 1.16)	.59
Z-FAST	602	0.79 (0.45, 1.39)	.42
E-ZO-FAST	527	1.74 (0.83, 3.67)	.14

Coleman R, et al. *N Engl J Med.* 2011;365:1396-1405.
 Gnant M, et al. *SABCS 2011.* Abstract S1-2.
 De Boer R, et al. *SABCS 2011.* Abstract S1-3.
 Paterson A, et al. *SABCS 2011.* Abstract S2-3
 Mabus V, et al. *SABCS 2011.* Abstract S2-4
 Brufsky A, et. al *Cancer.* 2012 Mar 1;118(5):1192-201
 Llombart A, et al. *Ann Oncol.* 2010; 21:2188-94

Effects of Adjuvant Bisphosphonates on DFS – Postmenopausal Patients Only



χ^2_6 (heterogeneity) = 8.46 P = .21

* Induced menopause

Gregory et al. ASCO 2012, Abs 513.

Conclusions on Role of Adjuvant Zoledronic Acid in Early Breast Cancer

- No overall effect in an unselected population.
- Significant benefit in women with established menopause.
- Apparent harm in pre- and perimenopausal women.
- Differential effects by menopause driven by influences on recurrence rates outside bone.
- Benefits in postmenopausal women now supported by multiple data sets.

Acknowledgements

- The 3360 AZURE patients
- The 174 participating centres
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