WHI

Calcium plus Vitamin D (CaD) Trial

Overview of CaD Session and Introductions

Joan A. McGowan, PhD
Project Officer
WHI Program Office
Director, Musculoskeletal Diseases Branch
National Institute of Arthritis and Musculoskeletal Diseases
National Institutes of Health
Bethesda, Maryland

Overview of Afternoon Sessions on the CaD Trial

- **Background, Hypotheses, and Design**
  Jane A. Cauley, DrPH
- **Special Challenges**
  Barbara B. Cochrane, PhD, RN

Overview of Afternoon Sessions on the CaD Trial

- **Personal Accounts of Participants**

  Facilitator: Linda K. Mickel, RN, CCRN

  Participants: Betty Cintas (Stanford)

  Mary Lou Frost (Buffalo)

  Judy LaCour (Seattle)

  Loretha Young (MedStar)

Overview of Afternoon Sessions on the CaD Trial

The CaD Trial Results

- **Bone Fractures and Bone Mineral Density**
  Rebecca D. Jackson, MD
- **Other Bone Findings**
  Andrea Z. LaCroix, PhD
- **Colon and Rectal Cancer**
  Jean Wactawski-Wende, PhD

Overview of Afternoon Sessions on the CaD Trial

- **Impact on Public Health Recommendations**
  Joan A. McGowan, PhD, NIAMS
- **Audience Questions and Answers**
- ***Closing Remarks for Day One***
  Marcia L. Stefanick, PhD

Background, Hypotheses, and Design

Jane A. Cauley, DrPH
Co-Principal Investigator
Pittsburgh Clinical Center

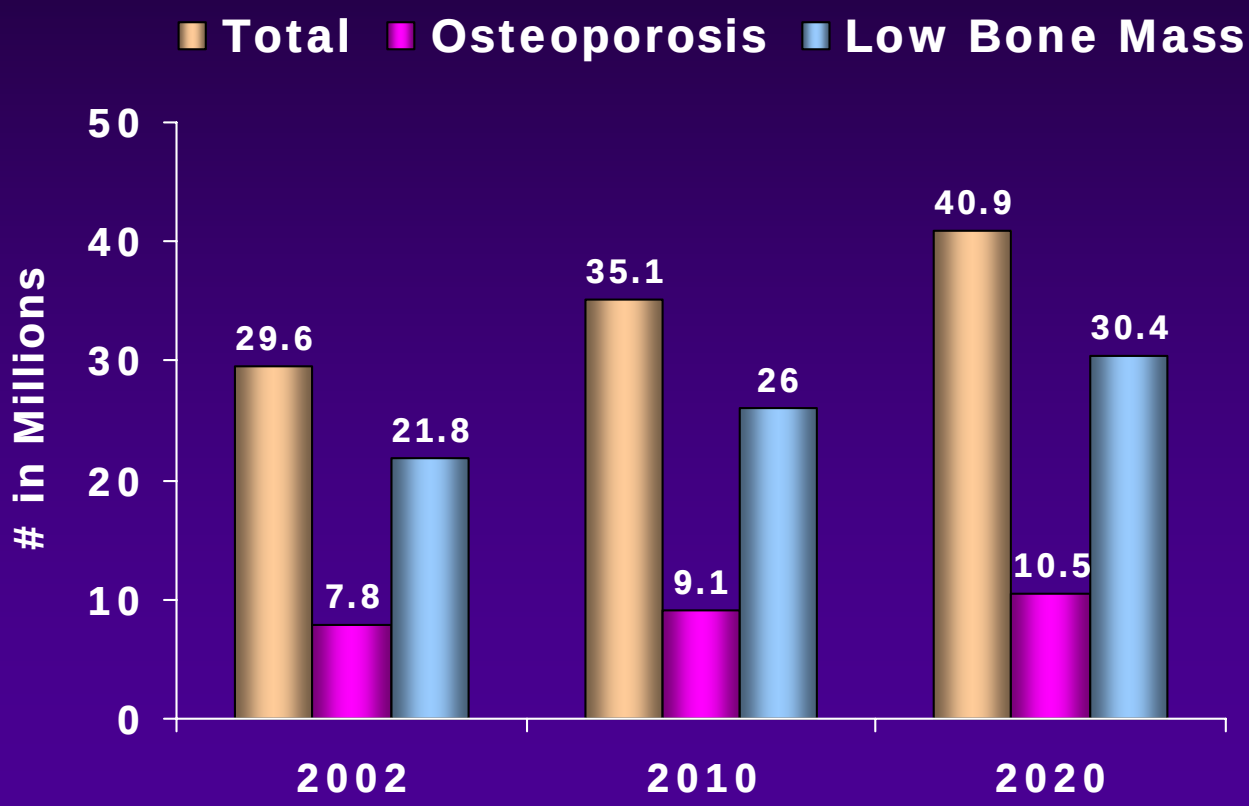
Professor & Vice Chair for Research, Department of Epidemiology
University of Pittsburgh
Pittsburgh, Pennsylvania

Background: Public Health Impact of Osteoporosis and Fractures

- Osteoporosis contributes to:
  - over 300,000 hip fractures annually
  - 1.5 million fractures annually
  - morbidity, loss of independence, and mortality
- Osteoporotic fractures are more common in women than heart attack, stroke, and breast cancer combined
  - 4 of 10 white women age 50+ will experience a hip, wrist or spine fracture

Impact of Osteoporosis will Increase

The number of women with osteoporosis and the number of fractures will increase dramatically due to the aging of the population



America's Bone Health: The State of Osteoporosis and Low Bone Mass in our Nation. **NOF 2002**

Nutrition and Bone Health

- Are calcium and vitamin D critical to bone health?
- Few individuals meet recommended intakes of calcium and vitamin D (CaD)[1]
  - Calcium: 1,200 mg/day
  - Vitamin D: 400 IU, age 50-70
    600 IU, age 70 +
- CaD supplements may slow bone loss and reduce risk of falls
- Limited evidence on CaD supplements and risk of hip and other fractures

[1]Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride, Institute Of Medicine, 1997

Background: Colon and Rectal Cancer

- Second leading cause of cancer death in the U.S.
- Observational studies suggested higher calcium and vitamin D *intakes* may:
  - Lower risk of colorectal cancer
  - Lower risk of polyp recurrence
- Randomized trials found calcium *supplements*:
  - Lowered risk of polyp recurrence
- No large randomized trials on CaD supplementation and prevention of colorectal cancer

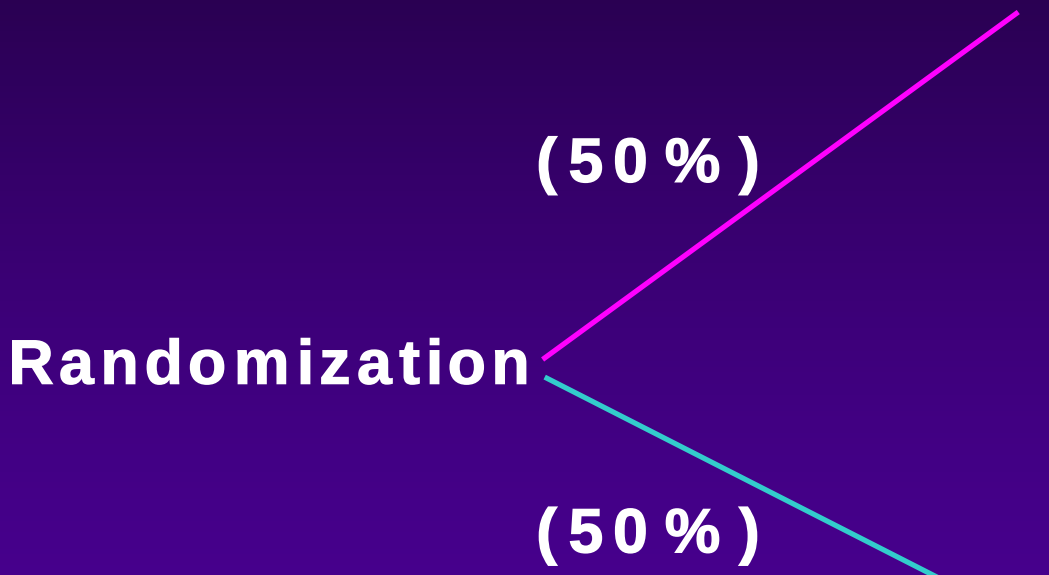
CaD Trial Question

Does calcium and vitamin D supplementation reduce the risk of:

- hip fracture (primary outcome)
- other fractures (secondary outcome)
- colorectal cancer (secondary outcome)

in postmenopausal women?

CaD Trial Design: Double Blind



Intervention
(CaD supplement)

- 1000 mg elemental calcium as calcium carbonate & 400 IU vitamin D_3
- Divided dose; with meals
- Chewable or swallow-able choice beginning Oct, 1997

Control
(Placebo)

Eligibility

- Enrolled in the WHI Diet and/or Hormone Trials
- Exclusions: hypercalcemia, kidney stones, corticosteroid use or calcitriol use
- Allowed to continue personal use of calcium and vitamin D
  - up to 600 IU vitamin D allowed initially
  - later increased to 1000 IU vitamin D

Follow-Up

- 4-week phone call
- Semi-annual contacts to assess:
  - Outcomes
  - Safety and regimen management (pill-taking)
- Annual visits:
  - Outcomes
  - Safety and regimen management
  - Adherence assessed
  - Study pills dispensed
  - Clinical examinations
- Bone mineral density (3 clinics)
  - Baseline, year 3, 6, and 9

Safety Considerations

- Study pills discontinued (no unblinding) for:
  - Kidney stones
  - Hypercalcemia (high blood calcium)
  - Kidney dialysis
  - Calcitriol use
  - Personal use of >600 IU (later, 1000 IU) vitamin D supplements

Close-Out

- Close-out visits between October 1, 2004 and March 31, 2005
- Participants unblinded after final outcomes reported
- Average follow-up was 7 years

Special Challenges

Barbara B. Cochrane, PhD, RN
Co-Investigator
Clinical Coordinating Center

Associate Professor and Director, de Tornyay Center for Healthy Aging - University of Washington School of Nursing
Joint Associate Member - Fred Hutchinson Cancer Research Center
Seattle, Washington

Recruitment Challenges

- Creating enthusiasm for another trial:
  - Staff conducted 1 on 1 discussions
  - Brochure
  - Video
- Explaining the science to participants:
  - What unanswered questions on CaD remained
  - Accounting for personal use of CaD

Intervention Challenges: Study Tablet Formulation

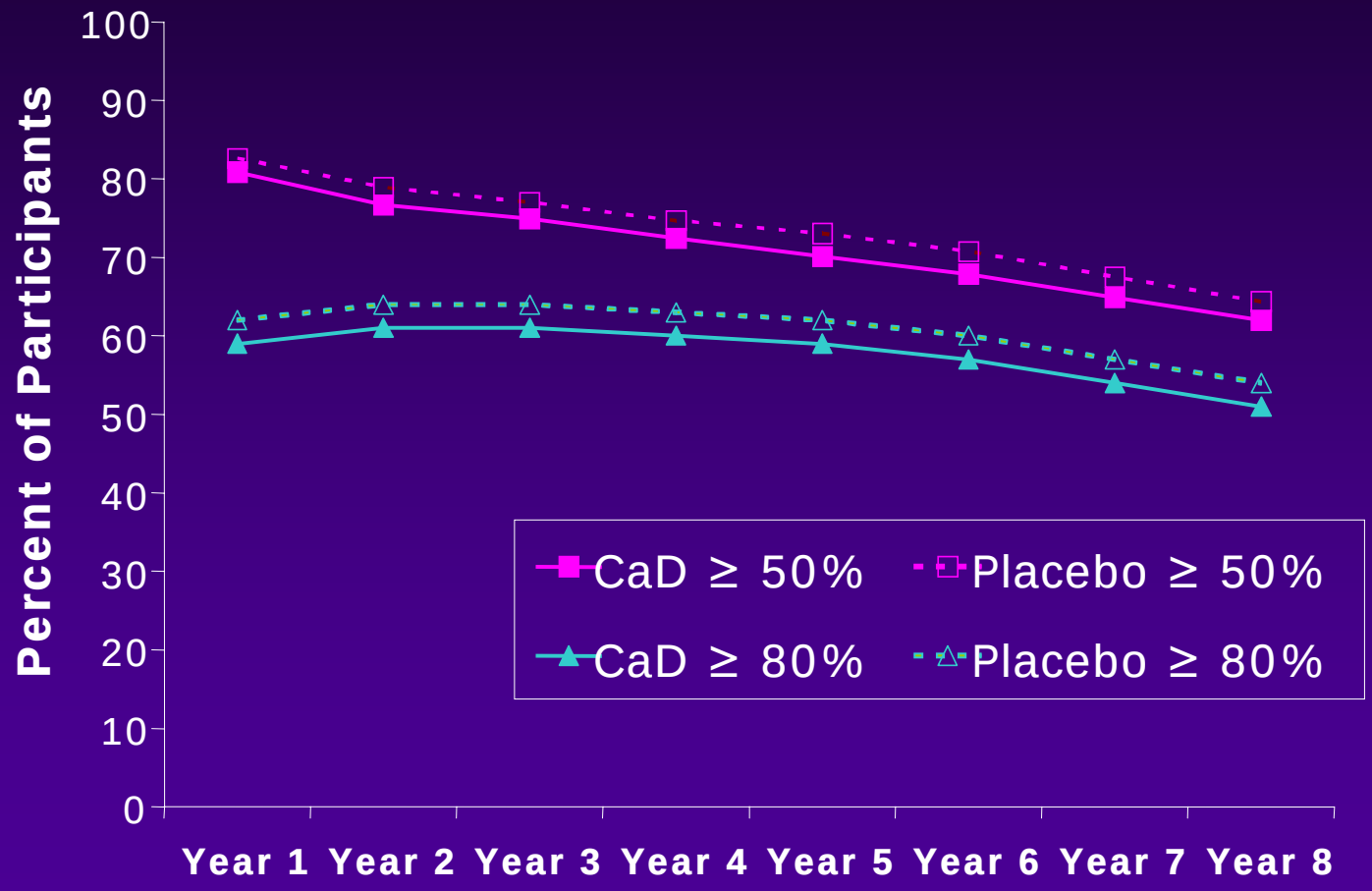
- Initial formulation: Chewable
  - Participants could chew or break tablets
  - Variety of responses to tablet taste and texture
- 1996: Based on a participant survey, began:
  - Taste test
  - 4-week phone call
- 1997: swallow-able formulation introduced - Large, green tablet

Adherence Challenges

- Staying committed to an “easy” trial
  - Informational handouts
  - Switching formulations
  - LARGE pill organizers
  - Regimen modified, if necessary

- Continuing study pills even if intervention stopped in other WHI clinical trial(s)
- Managing symptoms/side effects
  - Self-management strategies
  - Study pill step-down

CaD Adherence Over Time



Personal Accounts of Participants

Linda Kay Mickel, RN, CCRN
Clinic Manager
MedStar Clinical Center

Administrative Director
MedStar Clinical Research Center
Washington, DC

Personal Accounts of Participants

Betty Cintas – Stanford Clinical Center

Mary Lou Frost – Buffalo Clinical Center

Judy LaCour – Seattle Clinical Center

Loretha Young – MedStar Clinical Center

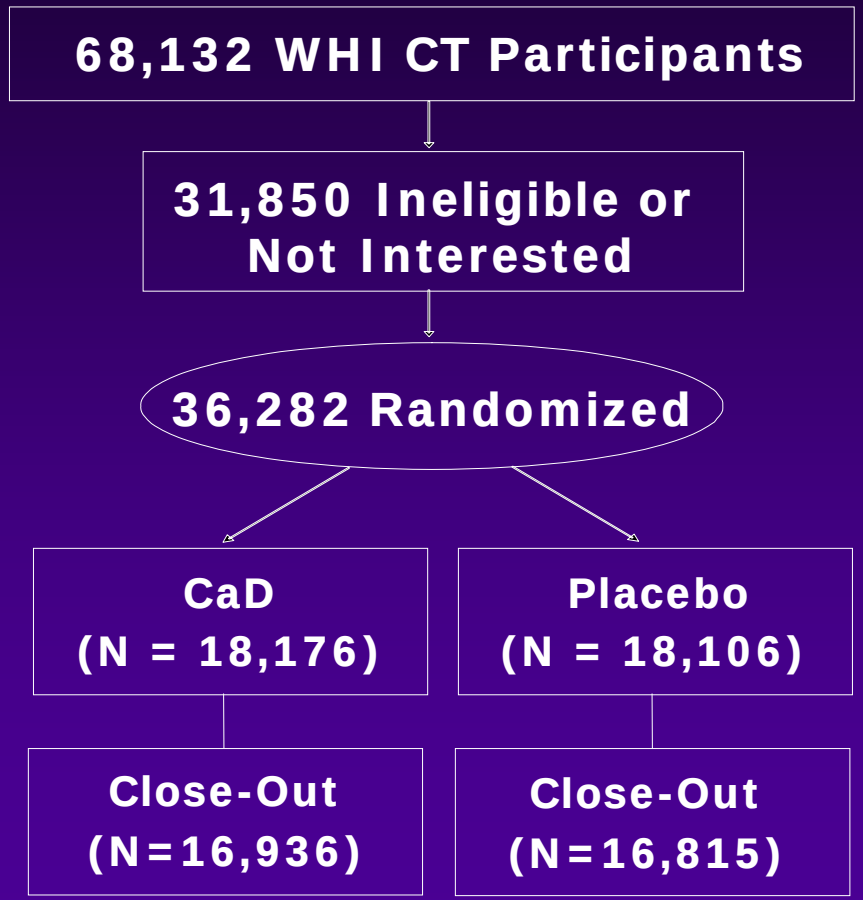
The Calcium plus Vitamin D Trial Results

Bone Fractures and Bone Mineral Density

Rebecca D. Jackson, MD
Principal Investigator
Columbus Clinical Center

Professor of Internal Medicine
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University
Columbus, Ohio

Participant Flow Diagram



NEJM 2006;354:669-83

Baseline Characteristics

	CaD	Placebo
Age at screening		
50-59 years	37.0%	37.0%
60-69 years	45.5%	45.5%
70-79 years	17.5%	17.5%
Race/Ethnicity		
White	82.8%	83.4%
Black	9.3%	9.0%
Hispanic	4.3%	4.0%
American Indian/Native American	0.4%	0.4%
Asian/Pacific Islander	2.0%	1.9%

NEJM 2006;354:669-83

Baseline Characteristics

	CaD	Placebo
Family history of fracture after age 40	37.6%	37.0
History of fracture		
At any age	34.7	34.4
At age >55yr	10.7	10.9
No. of falls in last 12 months		
None	66.6%	67.0%
1	20.4%	20.3%
2	8.7%	8.5%
≥3	4.4%	4.2%

NEJM 2006;354:669-83

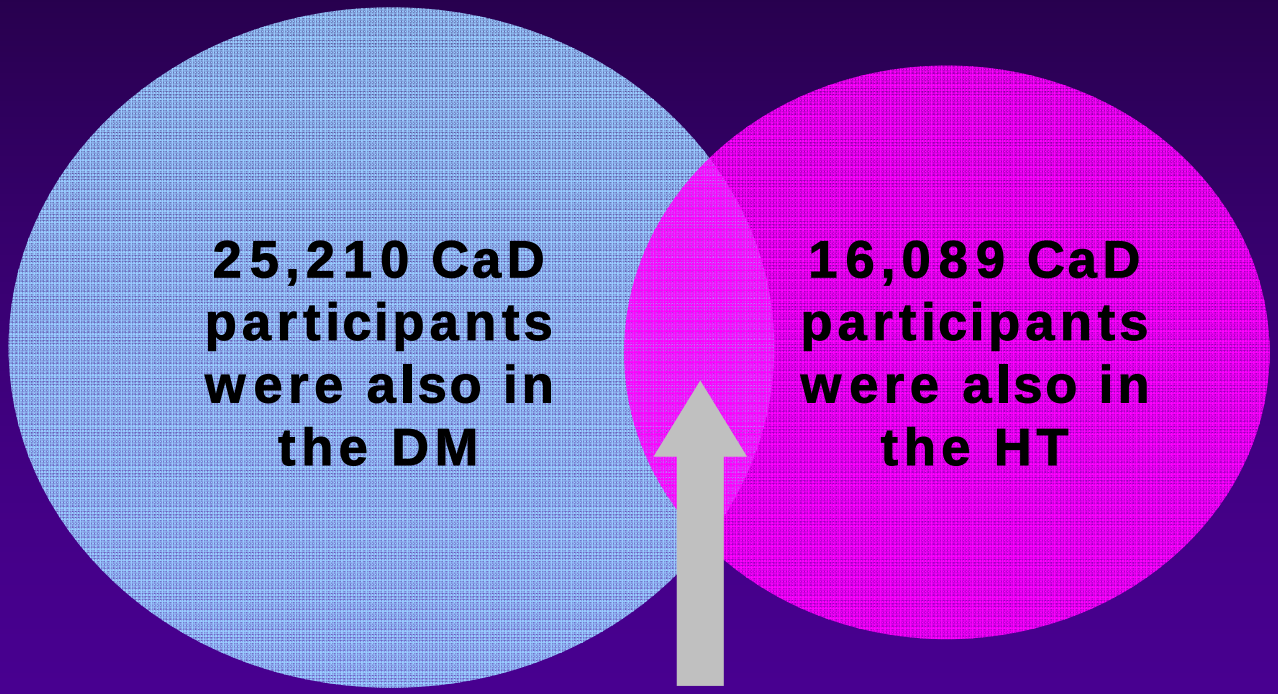
Baseline Characteristics

	CaD	Placebo
Body mass index (mean)	29.1	29.0
Total calcium (mg/day; mean)	1148	1154
Total vitamin D (IU/day; mean)	365	368

NEJM 2006;354:669-83

Design within Other WHI Trials (Overlap)

Of the 36,282 CaD Participants...



5,017 (14%) of CaD participants were in both DM and HT

Fracture Outcomes

- Participants asked every 6 months to report any fractures/hospitalizations:
  - Medical records obtained
  - Physician adjudicators verified fractures
  - Final confirmation of hip fractures performed centrally by blinded adjudicators

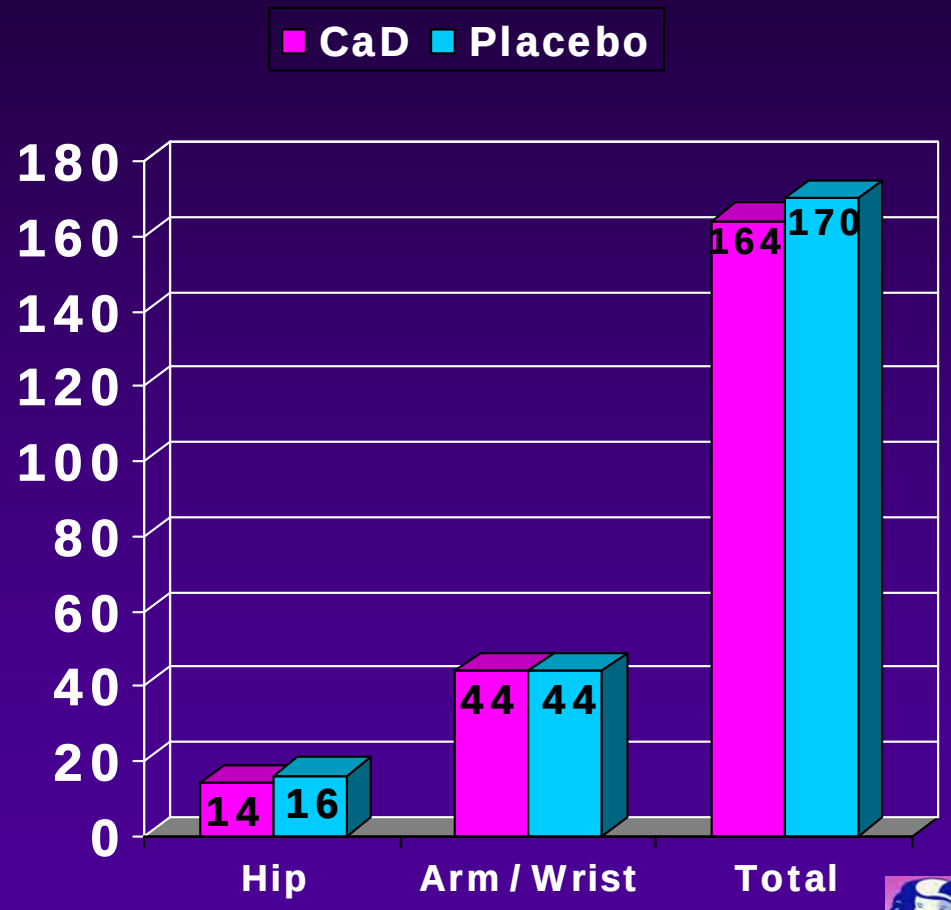
Fracture Results

- 4,260 fractures
  - 2,102 among women assigned to CaD
  - 2,158 among women assigned to placebo
- 374 hip fractures
  - 175 among CaD
  - 199 among placebo

NEJM 2006;354:669-83

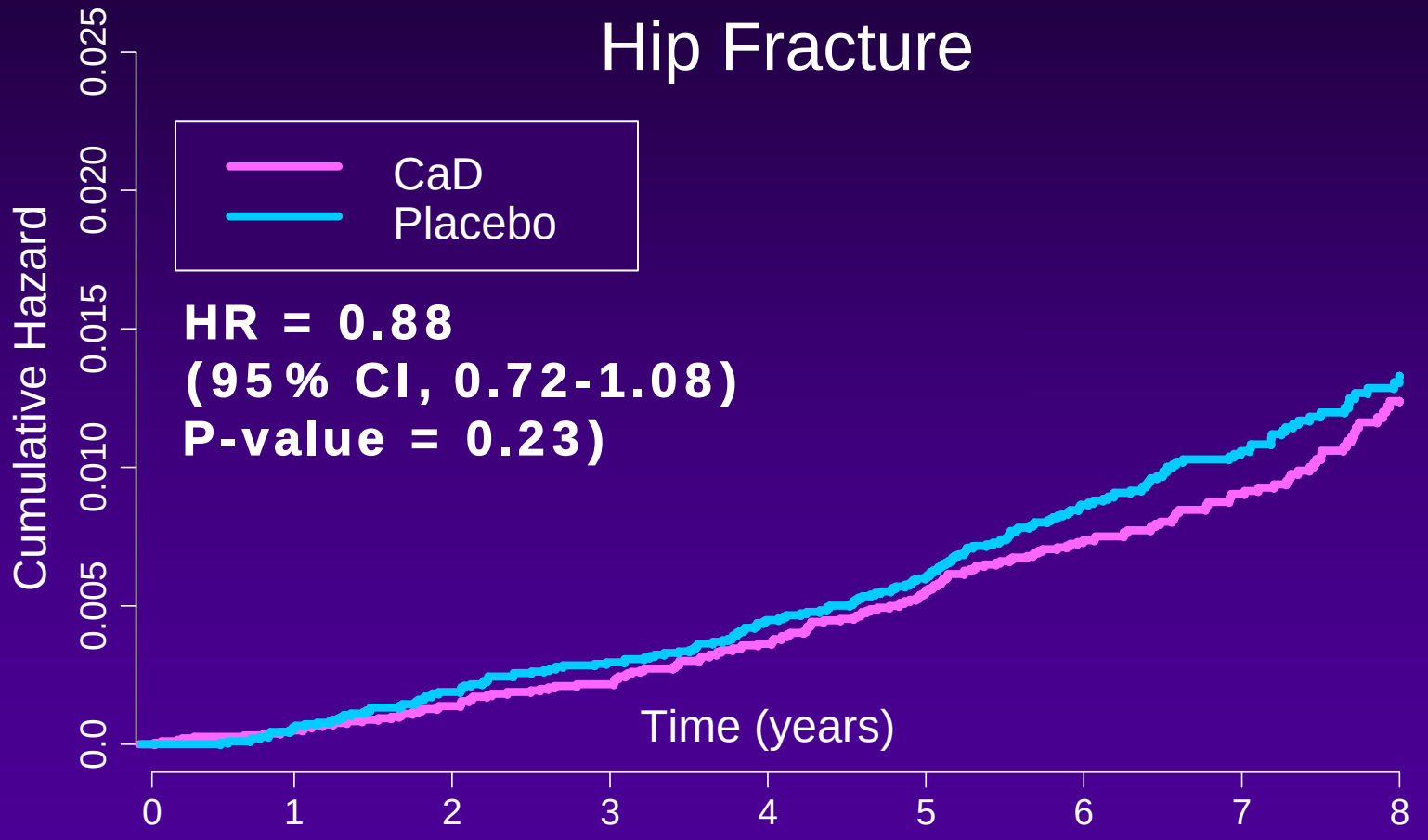
Annualized fracture rates per 10,000 person-years

- Hip fractures
  (HR 0.88; 95% CI 0.72-1.08)
  - 14 CaD
  - 16 placebo
- Lower arm or wrist fractures
  (HR 1.01; 95% CI 0.90-1.14)
  - 44 CaD
  - 44 placebo
- Total fractures
  (HR 0.94; 95% CI 0.87-1.02)
  - 164 CaD
  - 170 placebo



NEJM 2006;354:669-83

Fracture Results



NEJM 2006;354:669-83

Bone Mineral Density Measurement

- Three Clinical Centers: Birmingham, Pittsburgh, Tucson/Phoenix
- Chosen for racial diversity
- Dual energy x-ray absorptiometry (DXA) of lumbar spine, total hip, and total body
- BMD measured at: CaD randomization, annual visits 3, 6 and 9

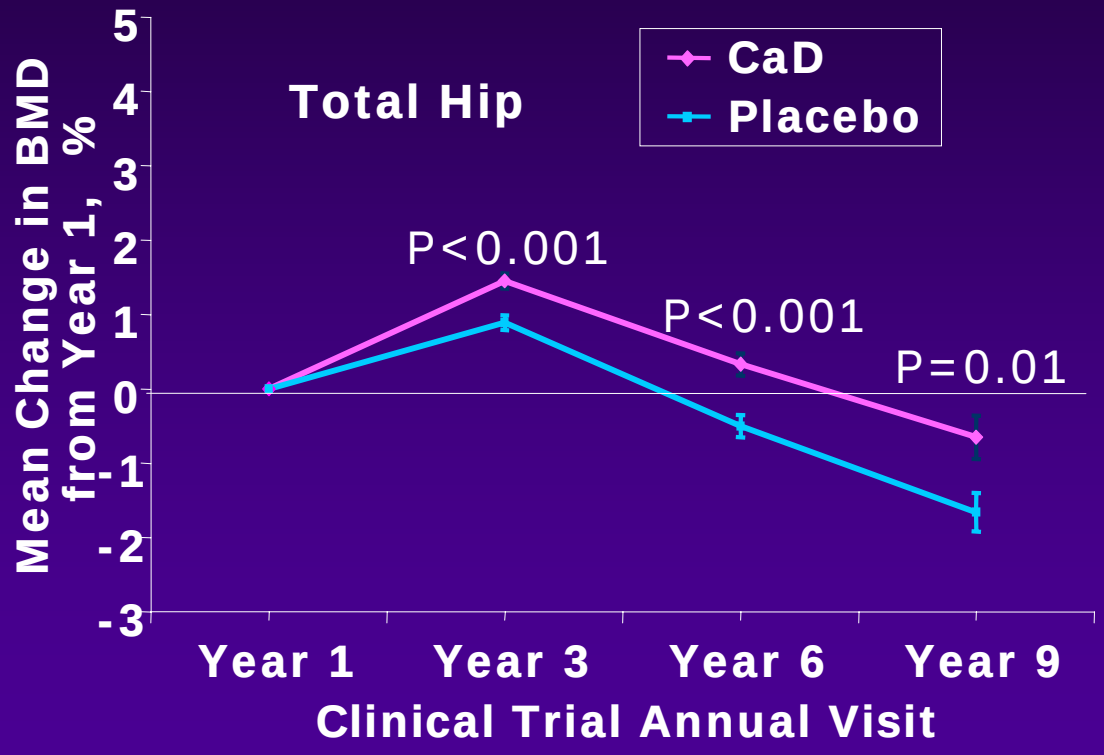
NEJM 2006;354:669-83

Bone Mineral Density Results

Greater preservation in total hip BMD

Average differences between CaD and placebo groups:

- 0.59% at AV3
- 0.86% at AV6
- 1.01% at AV9



NEJM 2006;354:669-83

CaD Safety Monitoring

- Mortality (HR 0.91; 95% CI 0.83 to 1.01; Annualized %: CaD 0.58%, Placebo 0.63%)
  - 744 deaths in CaD group
  - 807 deaths in placebo group
- Kidney stones (HR 1.17; 95% CI 1.02 to 1.34; Annualized %: CaD 0.35%, Placebo 0.30%) reported by:
  - 449 women in CaD group
  - 381 women in placebo group
- Gastrointestinal symptoms were similar

NEJM 2006;354:669-83

Other Bone Findings

Andrea Z. LaCroix, PhD
Co-Principal Investigator
Clinical Coordinating Center

Member – Fred Hutchinson Cancer Research Center

Professor – University of Washington

Scientific Investigator – Center for Health Studies
at Group Health Cooperative

Seattle, Washington

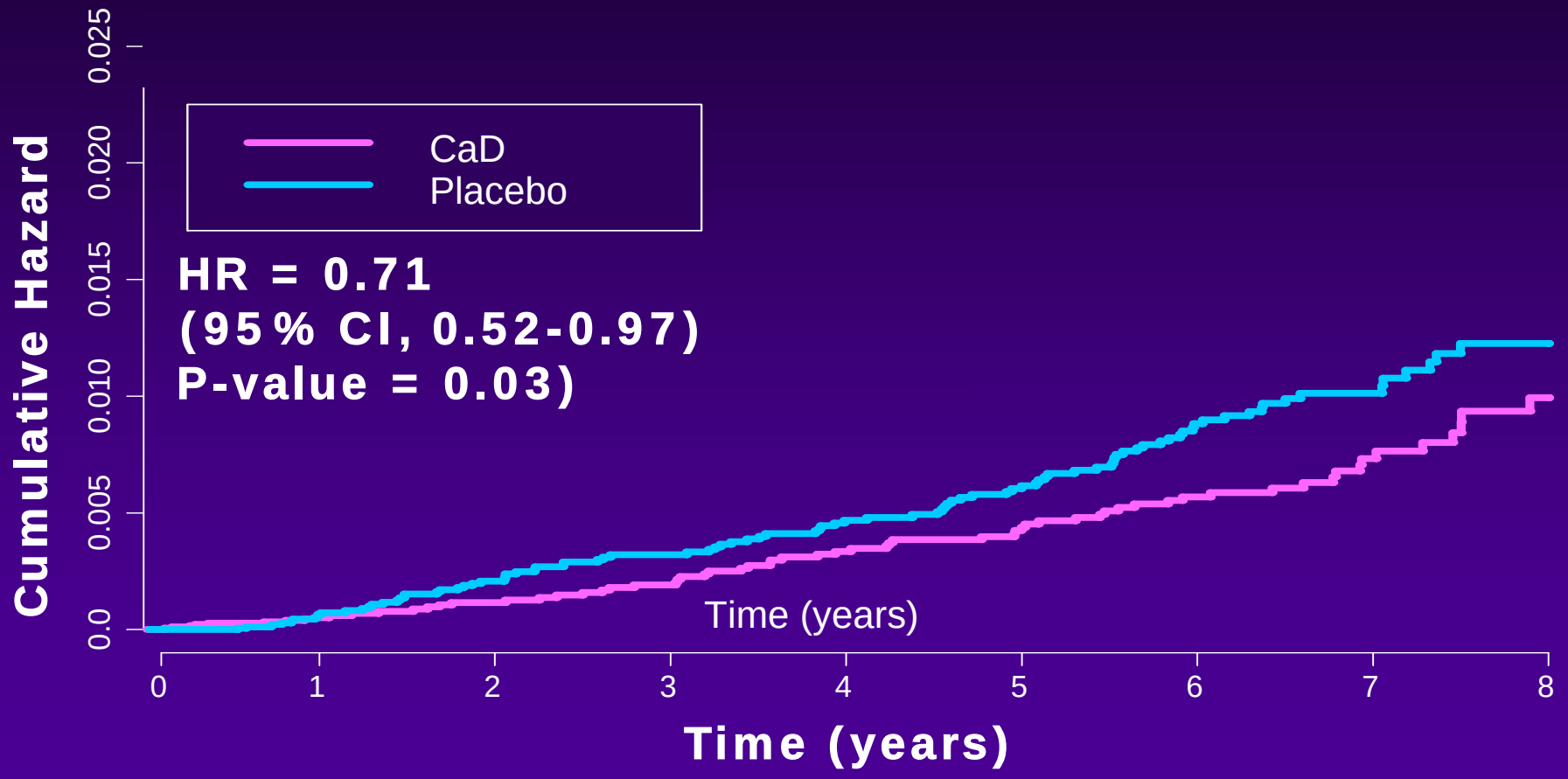
Sensitivity Analyses on Fracture

- Performed to determine impact of stopping study pills early
- Follow-up data included until 6 months after first “non-adherence” (taking <80% of study pills)
- By close-out:
  - 76% still taking study pills
  - 59% taking ≥ 80%

NEJM 2006;354:669-83

Hip Fracture Results while Adherent

(excludes follow-up time 6 months after becoming non-adherent)

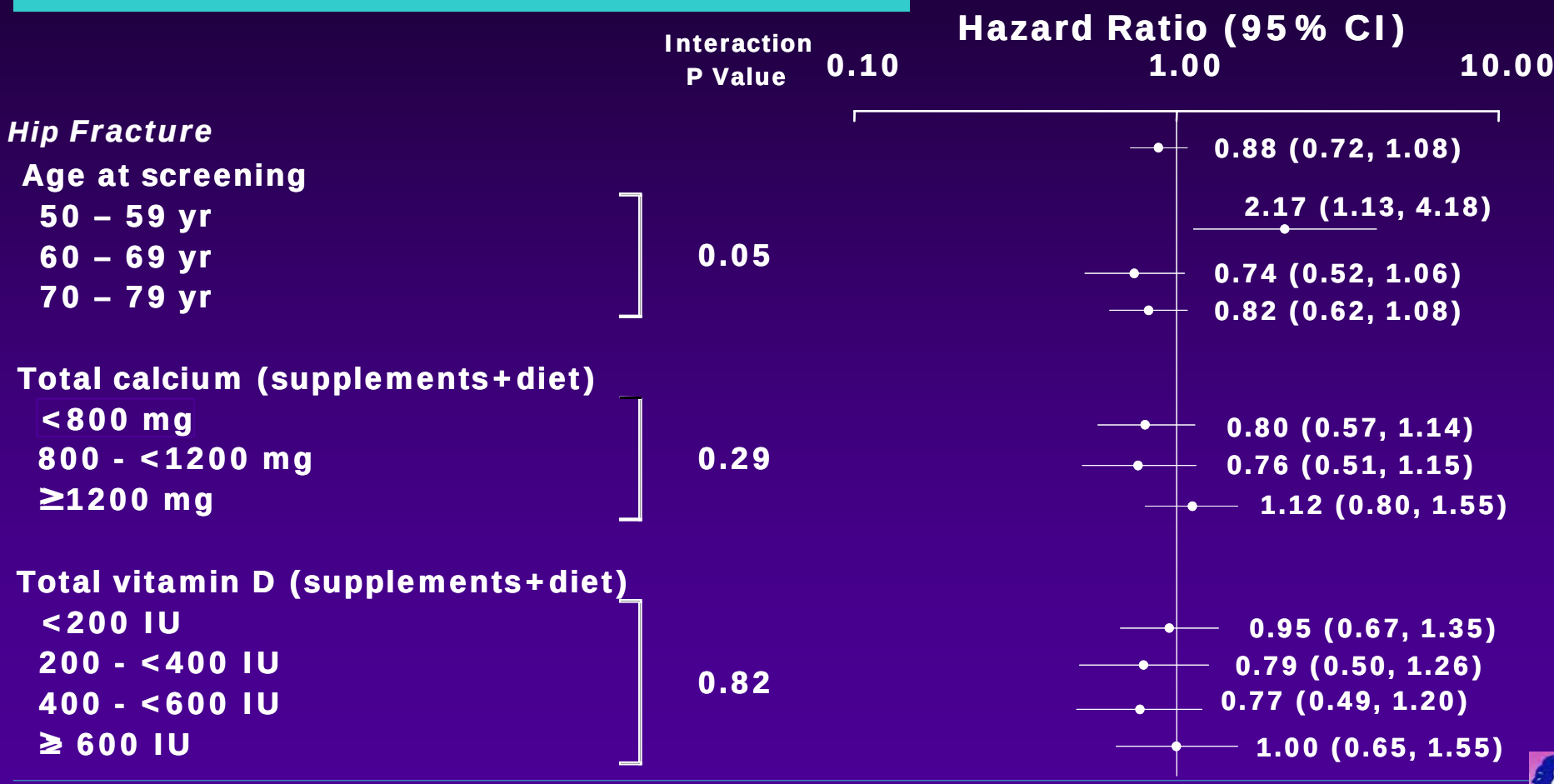


NEJM 2006;354:669-83

CaD Effects on Hip Fracture according to Baseline Participant Characteristics

- To see whether results varied by baseline risk factors for fracture
- 15 participant characteristics examined for hip fracture (as well as other fracture types)
- Analyses adjust for age group, HT and/or DM trial participation and prior fracture
- Up to 3 statistically significant results expected by chance alone

CaD Effects on Hip Fracture according to Participant Characteristics

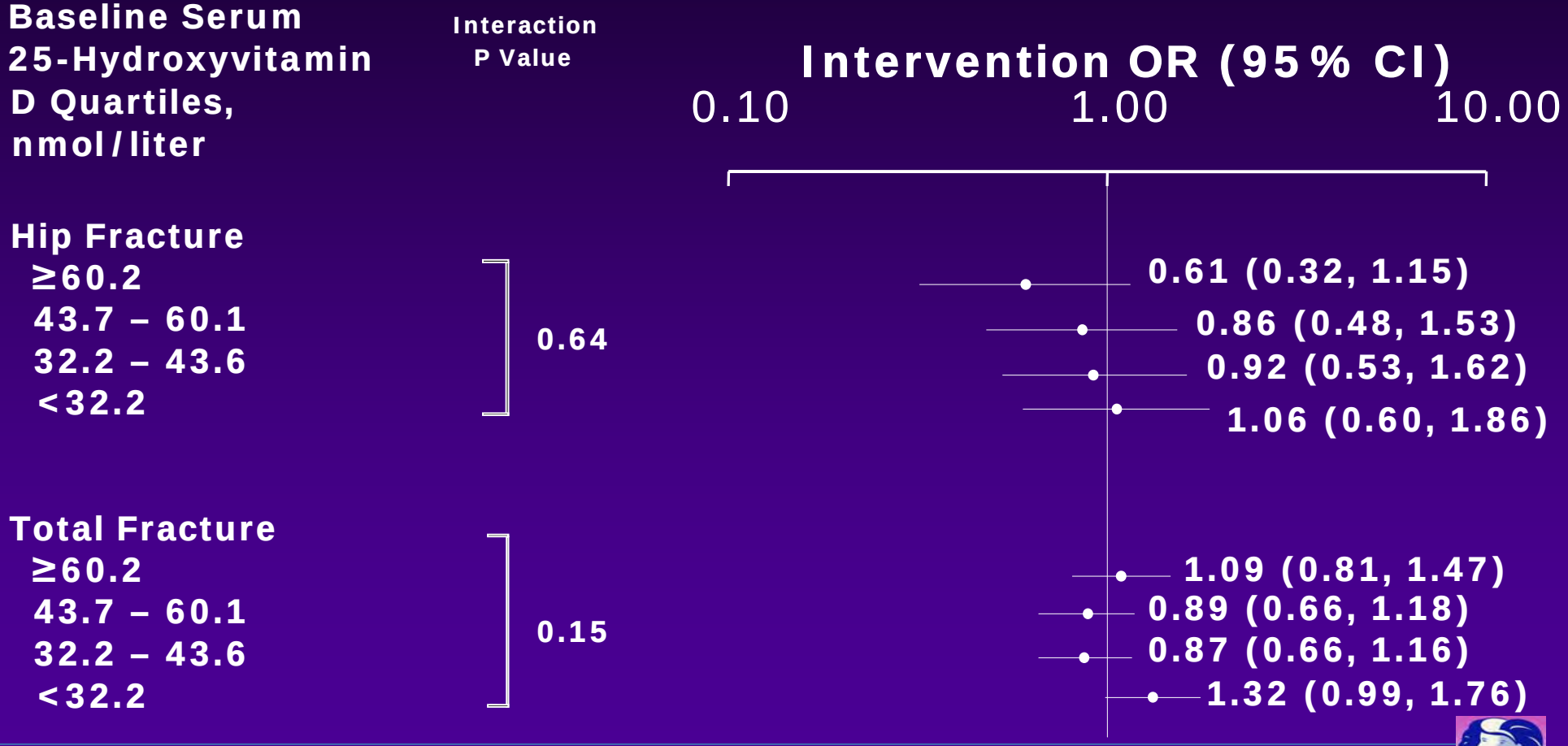


NEJM 2006;354:669-83

Nested Case-Control Study

- Goal: To determine if CaD effects varied by baseline *serum levels* of vitamin D
- Cases: women with hip fracture
- Controls: No fractures during follow-up, matched on age, Clinical Center, ethnicity, baseline blood draw date

CaD Effects on Hip Fracture according to Serum Vitamin D Levels



NEJM 2006;354:669-83

Summary of Fracture Findings

- Main analysis: 12% fewer hip fractures in CaD compared to placebo (p=0.23)
- Sensitivity analysis: 29% fewer hip fractures in CaD compared to placebo (hazard ratio 0.71; 95% confidence interval 0.52-0.97)
- 21% fewer hip fractures among women ≥60 years (HR 0.79; 95% CI 0.64-0.98; p for interaction=0.05)
- Intervention effects did not significantly vary by:
  - Baseline calcium/vitamin D *intake*
  - Baseline *blood levels* of vitamin D

NEJM 2006;354:669-83

Conclusions

- Daily CaD supplementation for an average of 7 yrs:
  - improved hip bone density
  - was associated with modest, non-significant reduction in hip fractures
  - did not significantly reduce clinical vertebral, lower arm/wrist, or total fractures
  - was associated with a decreased risk of hip fracture among adherent women
  - was associated with a decreased risk of hip fracture among women ≥60 years
- Possible role for CaD supplements in hip fracture prevention

NEJM 2006;354:669-83

Colorectal Cancer

Jean Wactawski-Wende, PhD
Principal Investigator
Buffalo Clinical Center

Associate Professor
Departments of Social and Preventive Medicine and Gynecology-Obstetrics
University at Buffalo
Buffalo, New York

Colorectal Cancer and CaD

- Colorectal Cancer was a specified secondary endpoint of the WHI CaD Trial

- Study Question:

  Would daily supplementation with 1000mg of elemental calcium (as calcium carbonate) plus 400IU of vitamin D reduce the risk of colorectal cancer (after an average of 7 years)?

Colorectal Cancer Outcomes

- Colorectal cancer (and other outcomes) were reported every 6 months
- Medical records obtained
  - Colorectal cancers verified by physician adjudicators (local and central)
  - Colorectal cancers coded using the Surveillance, Epidemiology, and End Results (SEER) system
- Colorectal screening was self-reported every 6 months

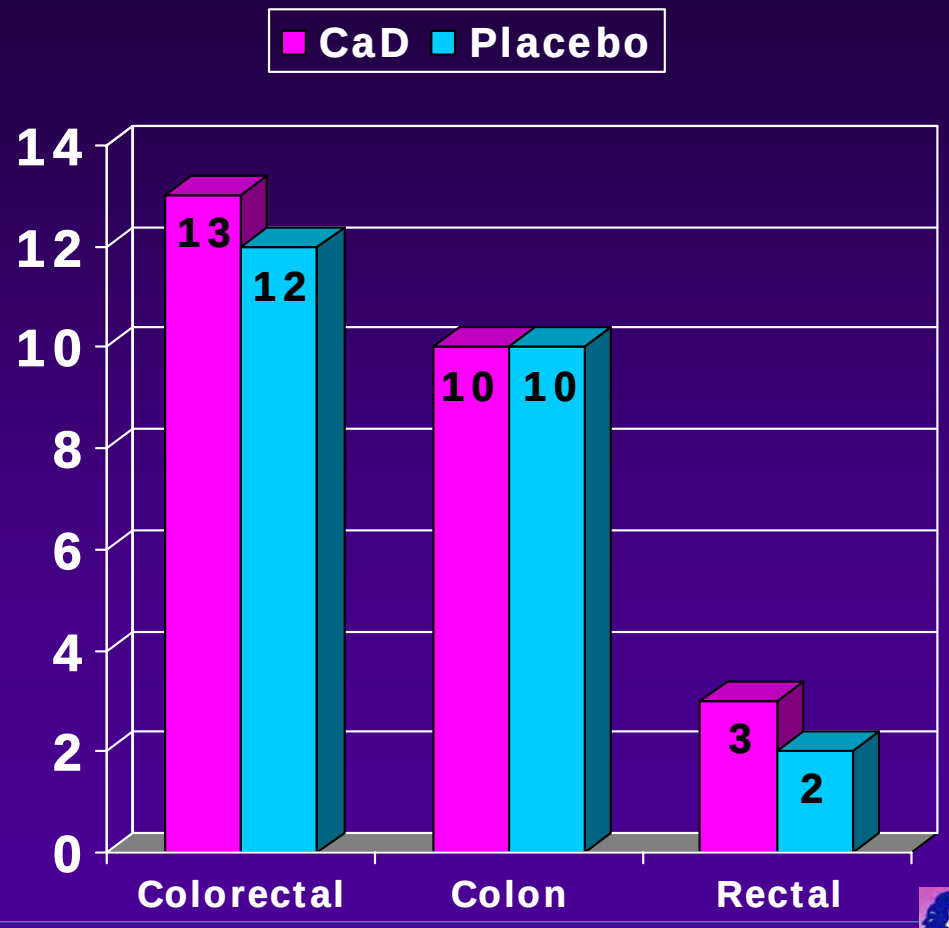
Colorectal Cancer Results

- **322 invasive colorectal** cancers
  - 168 among women assigned to active CaD
  - 154 among women assigned to placebo
    - 254 invasive **colon** cancers
      - 128 CaD
      - 126 placebo
    - 74 invasive **rectal** cancers
      - 44 CaD
      - 30 placebo

NEJM 2006;354:684-96

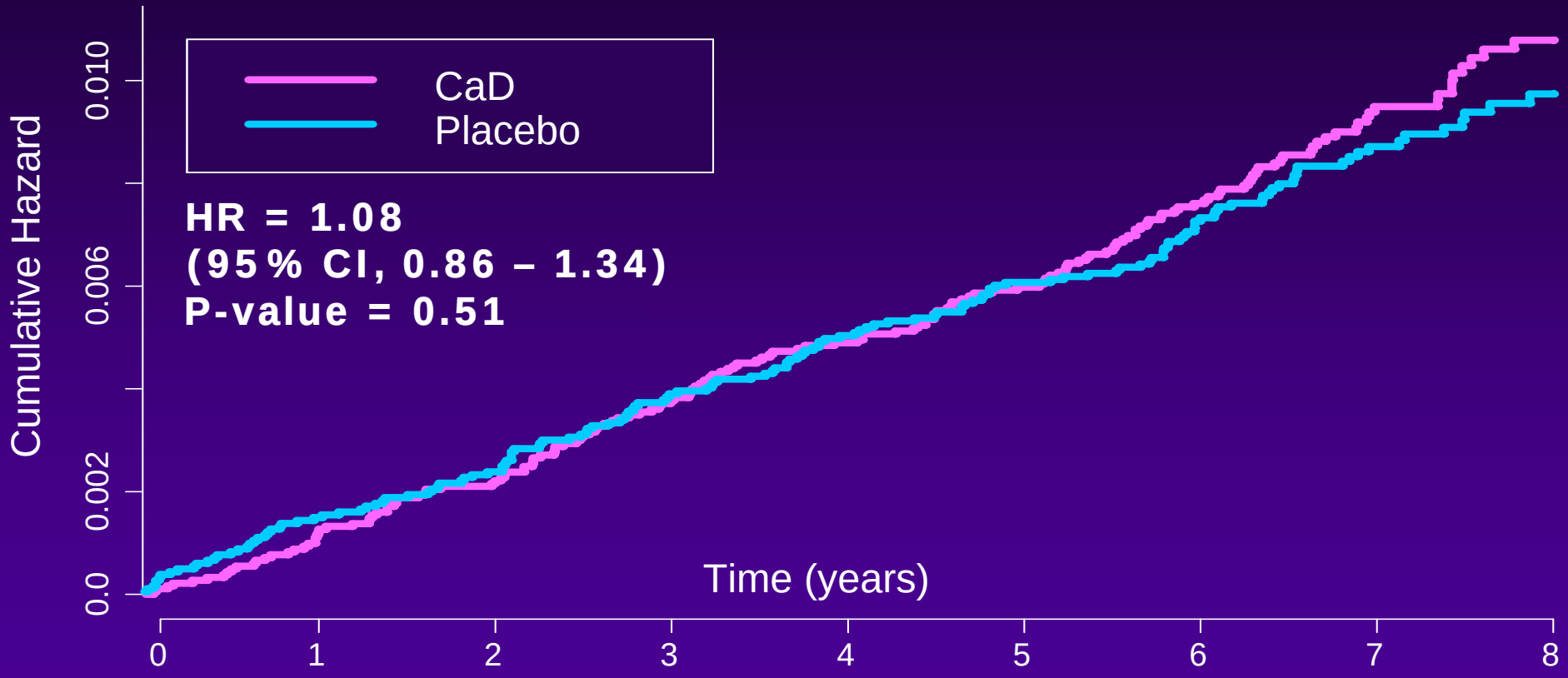
Annualized colorectal rates per 10,000 person-years

- Colorectal cancer
  (HR 1.08; 95% CI 0.86-1.34)
  - 13 CaD
  - 12 placebo
- Colon cancer
  (HR 1.00; 95% CI 0.78-1.28)
  - 10 CaD
  - 10 placebo
- Rectal cancer
  (HR 1.46; 95% CI 0.92-2.32)
  - 3 CaD
  - 2 placebo



NEJM 2006;354:684-96

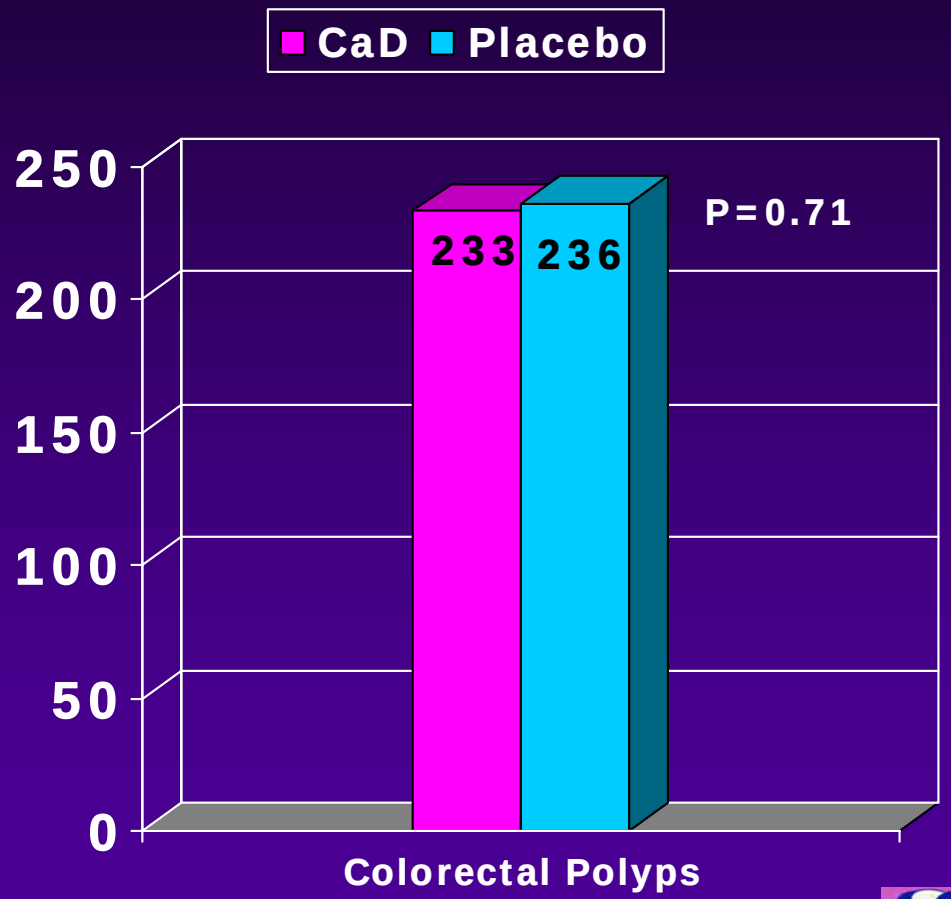
Colorectal Cancer Results



NEJM 2006;354:684-96

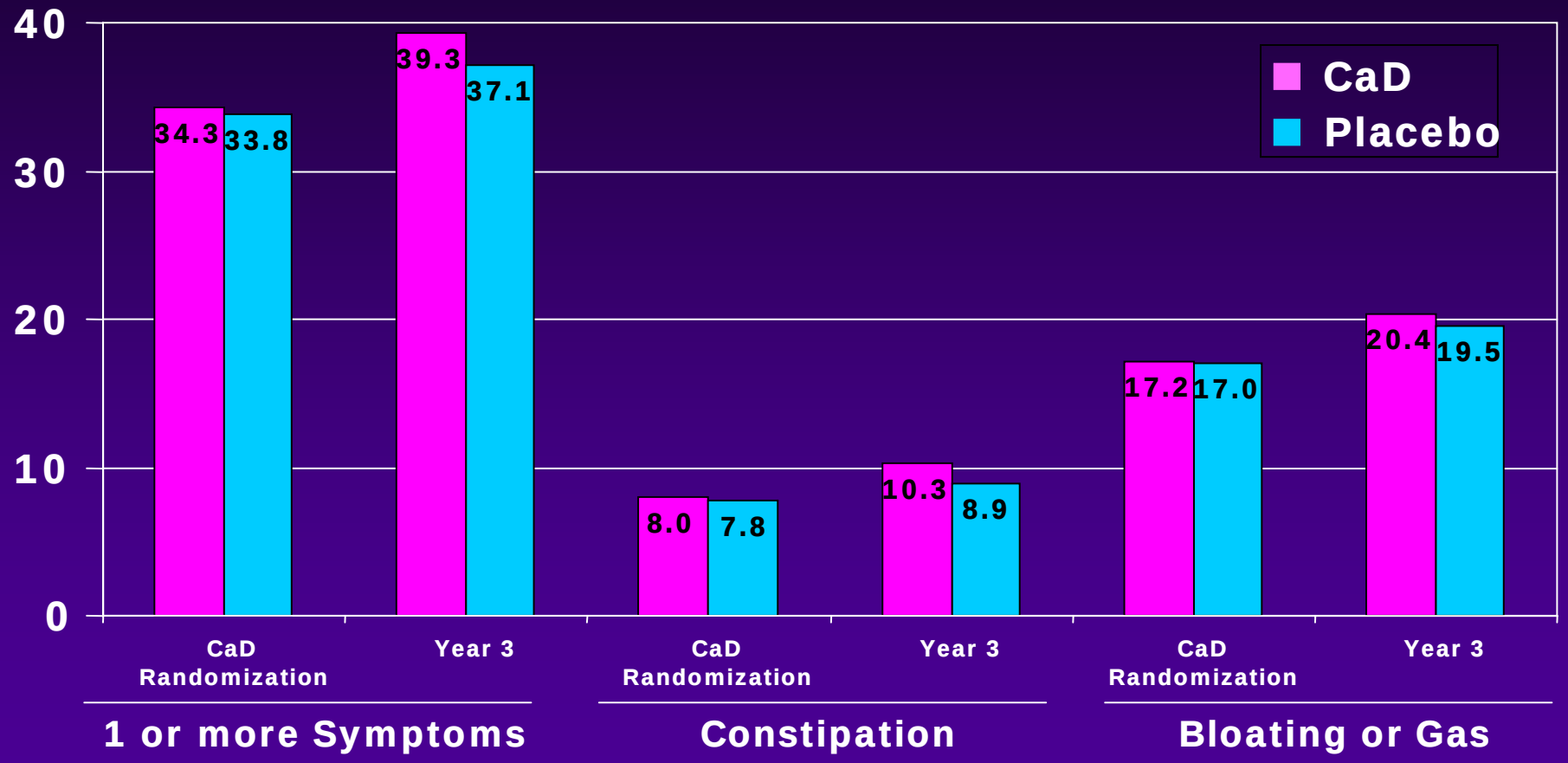
Annualized self-reported colorectal polyp rates per 10,000 person-years

- Colorectal polyps
  (HR 0.99; 95% CI 0.94-1.04)
  - 233 CaD
  - 236 Placebo



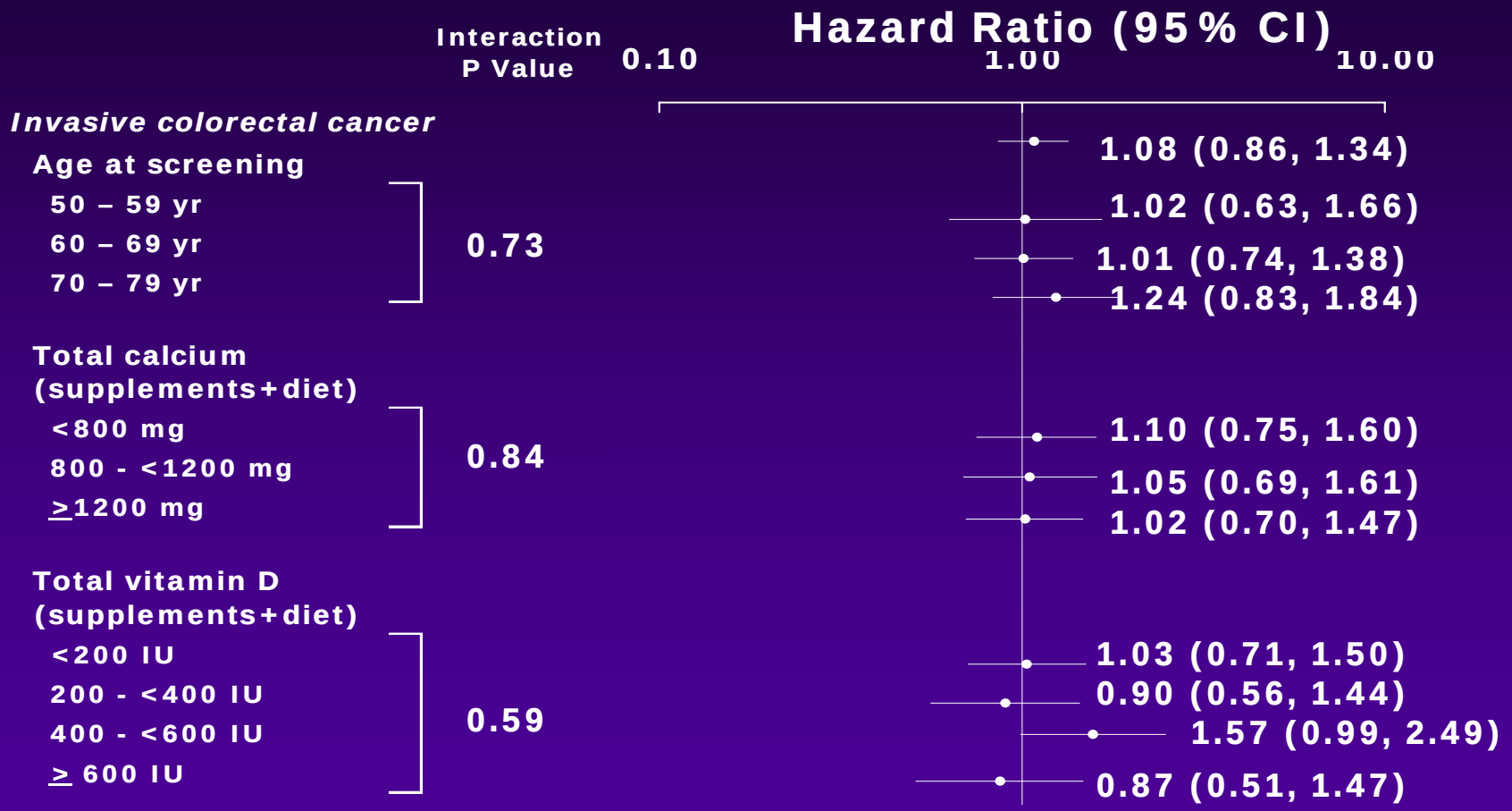
NEJM 2006;354:684-96

Abdominal Symptoms



NEJM 2006;354:669-83; 684-96

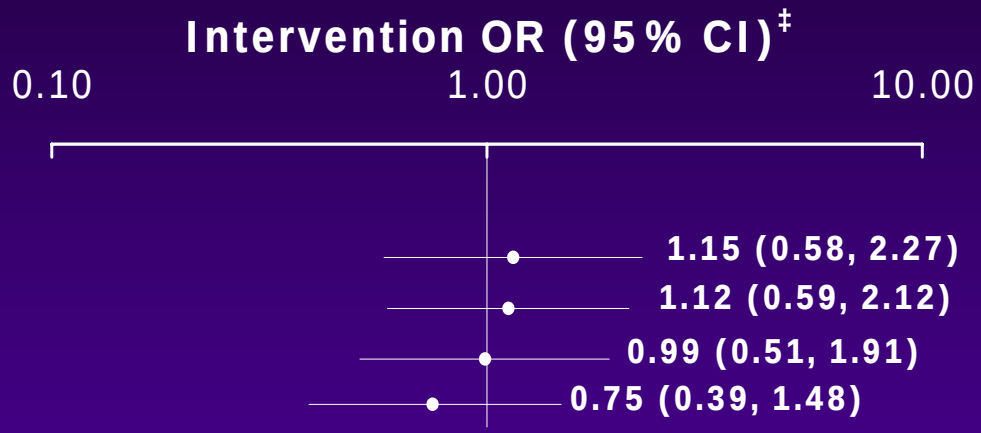
Interactions with Baseline Characteristics



NEJM 2006;354:684-96

Nested Case-Control Study of Serum 25-Hydroxyvitamin D

Baseline Serum 25-Hydroxyvitamin D Quartiles, nmol/liter*	Main Effect OR (95% CI)†
≥58.4	1.00
42.4 - 58.3	1.96 (1.18-3.24)
31.0 - 42.3	1.95 (1.18-3.24)
<31.0	2.53 (1.49-4.32)



P-value for interaction = 0.54

NEJM 2006;354:684-96

Colorectal Cancer Results

- Main analysis: No difference between CaD and Placebo
  (hazard ratio 1.08; 95% confidence interval 0.86-1.34)
- Sensitivity analysis (80% adherence): Results unchanged
  (hazard ratio 0.98; 95% confidence interval 0.73-1.32)
- Intervention effects did not significantly vary by:
  - Baseline personal calcium/vitamin D *intake*
  - Baseline *blood levels* of vitamin D
- Tumor characteristics similar in CaD and placebo groups
- Similar polyp reporting

NEJM 2006;354:684-96

Conclusions

- Daily CaD supplementation for an average of 7 years did not prevent colorectal cancer in postmenopausal women
- Several factors may have limited our ability to detect a difference, including:
  - High personal calcium intakes
  - 7-year study duration
- Although CaD may provide modest protection for hip fracture, this study found no colorectal cancer benefit.
- Findings do not support general use of CaD supplements to prevent colorectal cancer

NEJM 2006;354:684-96

Future Directions

- 5-year WHI Extension study is ongoing and will provide additional follow-up to determine later effects of this intervention
- Additional outcomes will be explored in the CaD trial (kidney stones, mortality, other outcomes)
- Future studies may explore additional questions including other doses, formulations, populations…

Impact on Public Health Recommendations

Joan A. McGowan, PhD

Project Officer

Director, Musculoskeletal Diseases Branch

National Institute of Arthritis and Musculoskeletal Diseases

National Institutes of Health

Bethesda, MD

What Recommendations?

- What are the current dietary calcium and vitamin D recommendations?
- Where do they come from?
- Were participants in the CaD Trial meeting the dietary guidelines for calcium and vitamin D intake?
- Did calcium and vitamin D intakes impact the results of the trial?
- Do the results of the trial impact calcium and vitamin D recommendations?

Dietary Recommendations on Calcium and Vitamin D

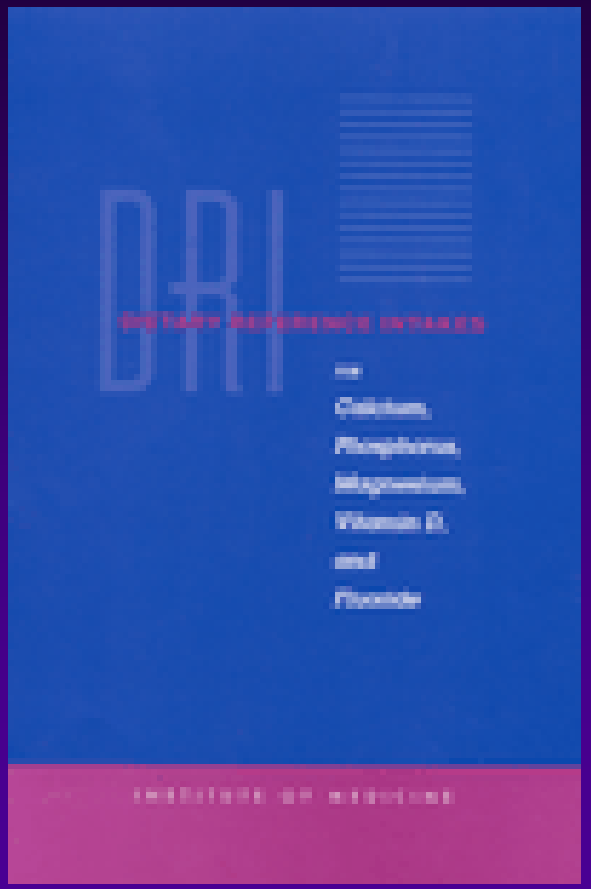
- **DIETARY REFERENCE INTAKES *FOR***

  Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride

  --Food and Nutrition Board

  Institute of Medicine

- An evidence-based process published in 1997



Calcium and Vitamin D Recommendations**

AGE Women and Men	CALCIUM (mg/day)	VITAMIN D (IU/day)
> 50 years	1200	400
> 70 years	1200	600

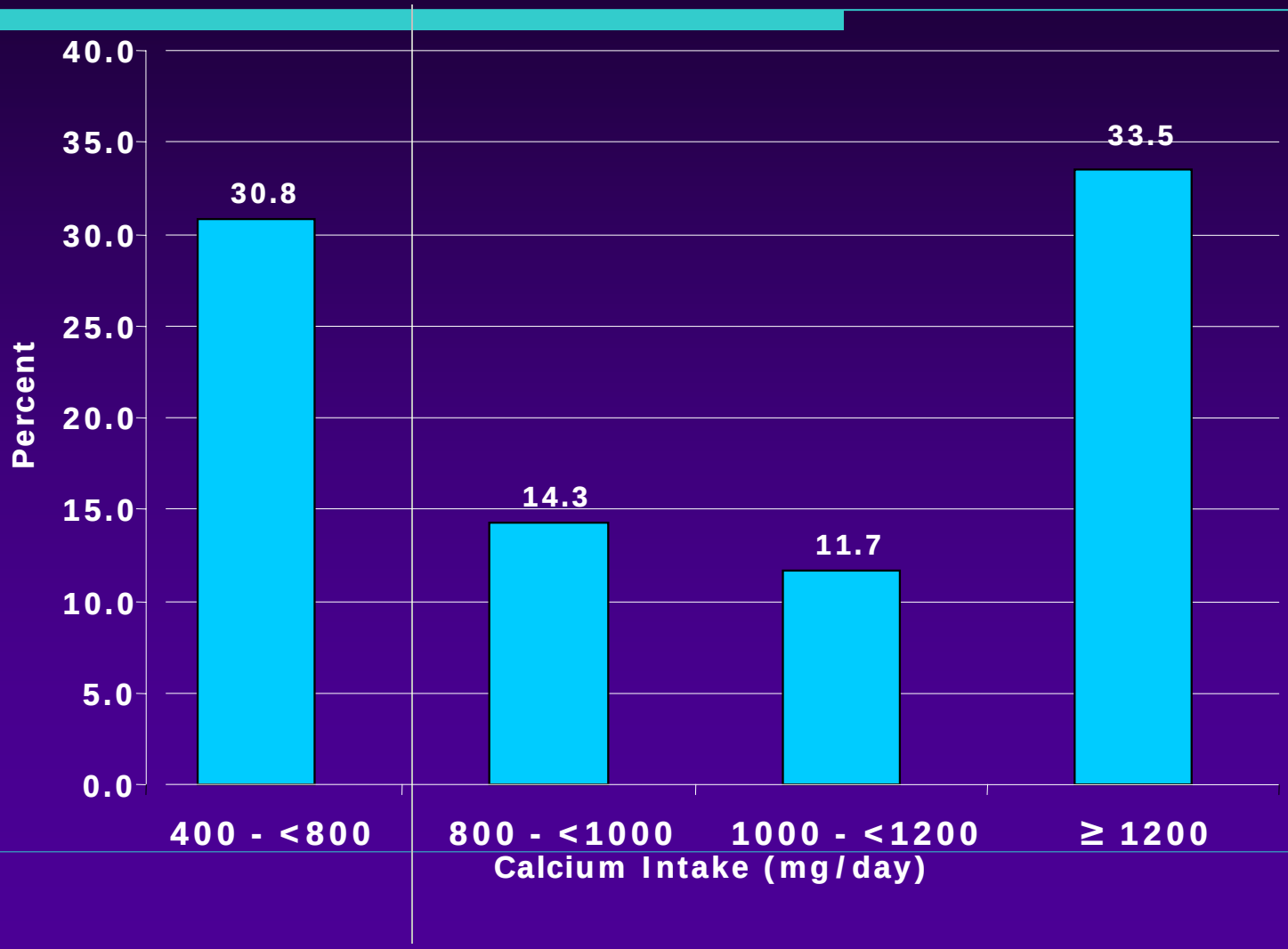
**1997 Institute of Medicine

What We Eat in America: NHANES 2001-2002

- Less than 5% of women over 50 meet or exceed the recommended intake of 1200 mg of calcium a day by dietary intake assessment

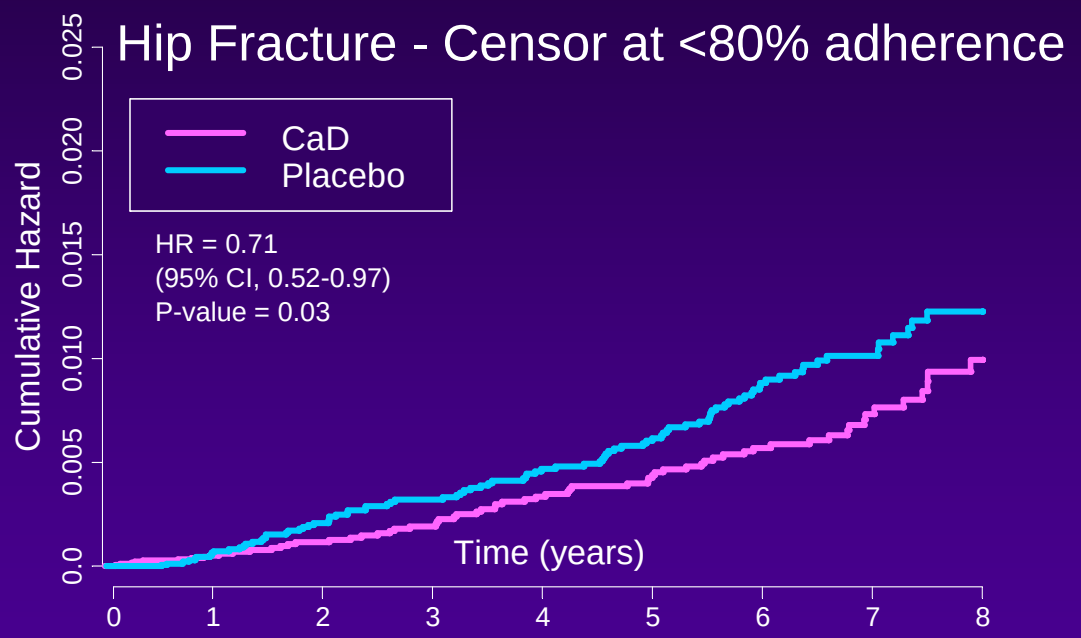
- Median calcium intake per day (from food) for women over 50 is less than 700 mg

Total Calcium Intakes in CaD Trial Participants



Summary of Fracture Findings

- **Main analysis: 12% fewer hip fractures in CaD** compared to placebo (p=0.23)
- **29% fewer hip fractures** in CaD compared to placebo (hazard ratio 0.71; 95% confidence interval 0.52-0.97)
- **21% fewer hip fractures** among women ≥60 years (HR 0.79; 95% CI 0.64-0.98; p for interaction=0.05)



Recommendations for Women (Personal Health Care Providers)

- Scientific findings from the WHI support the current recommendations for calcium and vitamin D for older women
- Calcium and vitamin D are nutrients ***not drugs***
- The calcium recommendations can be met largely from food sources
- Additional analyses and discussion of the total evidence base are needed to incorporate the WHI results into public health recommendations for women

Colorectal Cancer - National Cancer Institute

- Currently there are no recommendations from the NCI on the use of calcium and vitamin D supplements to prevent colorectal cancer.

Recommendations for Women (Personal Health Care Providers)

- Calcium and vitamin D should not be recommended for the prevention of colorectal cancer

Sources of Information

- **Surgeon General's Report: Bone Health and Osteoporosis**

  http://www.surgeongeneral.gov/library/bonehealth/

- **NIH Osteoporosis and Related Bone Diseases – National Resource Center**

  http://www.osteo.org

- **Dietary Guidelines for Americans**
  http://www.health.gov/dietaryguidelines/

- **National Cancer Institute**
  http://www.cancer.gov/cancertopics/types/colon-and-rectal

Audience Q&A

Joan A. McGowan, PhD

Project Officer

Director, Musculoskeletal Diseases Branch

National Institute of Arthritis and Musculoskeletal Diseases

National Institutes of Health

Bethesda, MD

Closing Remarks for Day One

Marcia L. Stefanick, PhD
Principal Investigator
Stanford Clinical Center

Professor of Medicine
Professor of Obstetrics and Gynecology
Stanford University
Stanford, California