

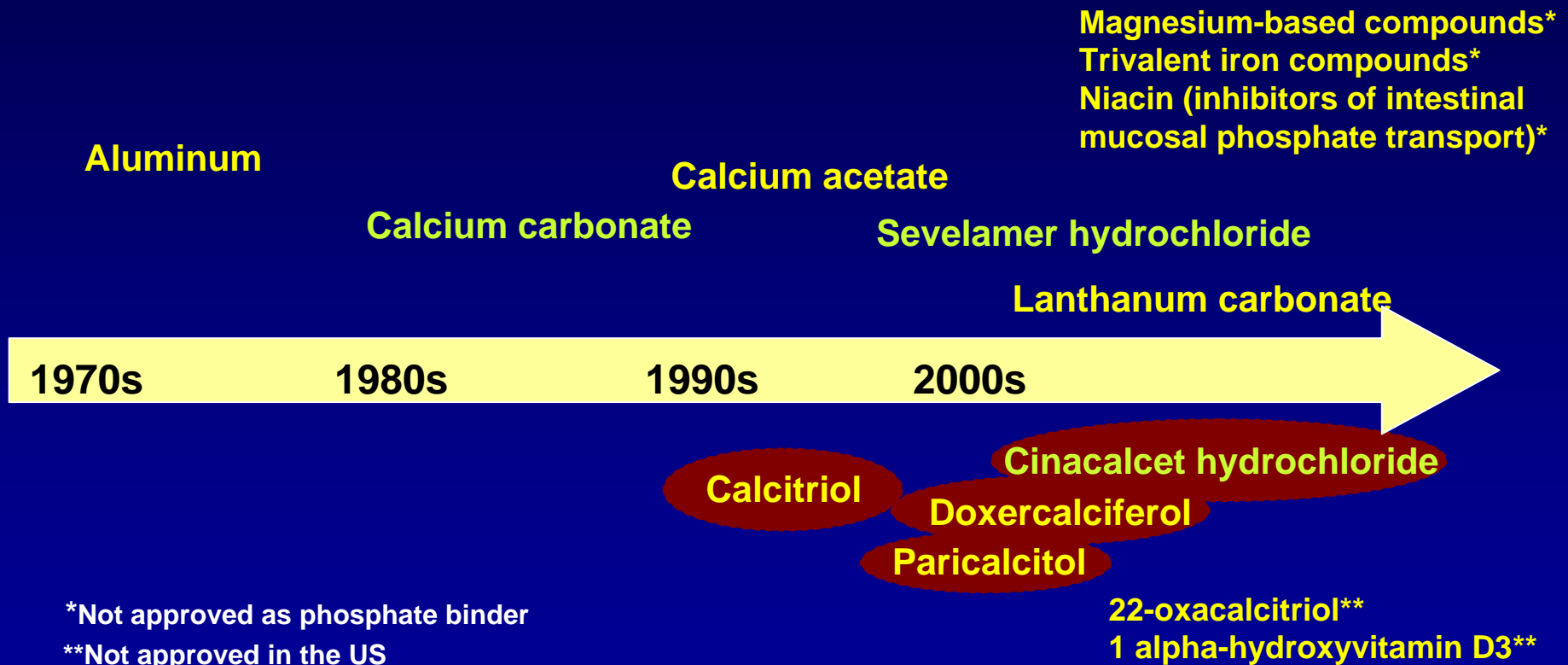
# **SURVIVAL BENEFITS WITH SELECTIVE VDR ACTIVATORS**

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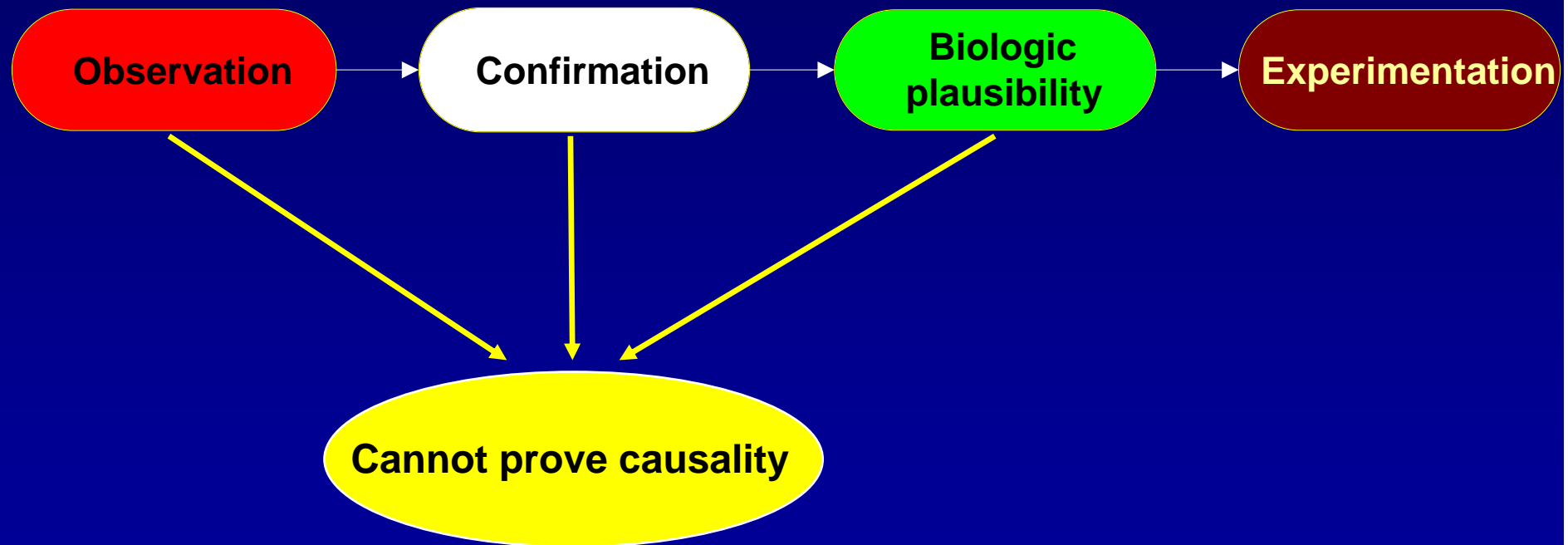
*University of Virginia, Charlottesville, VA*

# Timeline of various treatments for CKD-MBD



Study	Treatment	Comparator	Design	Limitations vis a vis RCT design
<b>Teng 2003</b>	paricalcitol	calcitriol	Baseline Cox models; as-treated analyses.	As treated analysis (not ITT). Selection bias and residual confounding.
<b>Shoji 2004</b>	oral alfacalcidol	no treatment	Baseline Cox models.	Selection bias and residual confounding.
<b>Teng 2005</b>	calcitriol or paricalcitol	no treatment	Time-dependent Cox (primary); MSM, facility-level matching (secondary); ITT.	Residual confounding.
<b>Kalantar-Zadeh 2006</b>	paricalcitol	no treatment	Baseline and time-dependent Cox models.	Selection bias and residual confounding.
<b>Tentori 2006</b>	calcitriol, paricalcitol, doxercalciferol	no treatment; each other	Baseline and time-dependent Cox models. As-treated and ITT.	Selection bias and residual confounding.
<b>Melamed 2006</b>	calcitriol	no treatment	Baseline and time-dependent Cox models.	Selection bias and residual confounding.
<b>Naves-Diaz 2008</b>	oral calcitriol or alfacalcidol	no treatment	Time-dependent Cox models. Used propensity scores.	Selection bias and residual confounding.
<b>Shinaberger 2008</b>	paricalcitol	no treatment	Baseline Cox models.	Selection bias and residual confounding.
<b>Tentori 2009</b>	calcitriol, paricalcitol or doxercalciferol	no treatment; each other	Baseline and time-varying Cox models, MSM, IV.	Appropriateness of IV questionable.

# The Path of Discovery



ORIGINAL ARTICLE

## Survival of Patients Undergoing Hemodialysis with Paricalcitol or Calcitriol Therapy

Ming Teng, M.D., Myles Wolf, M.D., M.M.Sc., Edmund Lowrie, M.D., Norma Ofsthun, Ph.D., J. Michael Lazarus, M.D., and Ravi Thadhani, M.D., M.P.H.

ABSTRACT

From Fresenius Medical Care North America, Lexington, Mass. (M.T., E.L., N.O., J.M.L.); and the Renal Unit, Massachusetts General Hospital, Harvard Medical School, Boston (M.W., R.T.). Address reprint requests to Dr. Thadhani at Bullfinch 127, 55 Fruit St., Massachusetts General Hospital, Boston, MA 02114, or at thadhani.r@mgh.harvard.edu.

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### BACKGROUND

Elevated calcium and phosphorus levels after therapy with injectable vitamin D for secondary hyperparathyroidism may accelerate vascular disease and hasten death in patients undergoing long-term hemodialysis. Paricalcitol, a new vitamin D analogue, appears to lessen the elevations in serum calcium and phosphorus levels, as compared with calcitriol, the standard form of injectable vitamin D.

### METHODS

We conducted a historical cohort study to compare the 36-month survival rate among patients undergoing long-term hemodialysis who started to receive treatment with paricalcitol (29,021 patients) or calcitriol (38,378 patients) between 1999 and 2001. Crude and adjusted survival rates were calculated and stratified analyses were performed. A subgroup of 16,483 patients who switched regimens was also evaluated.

### RESULTS

The mortality rate among patients receiving paricalcitol was 3417 per 19,031 person-years (0.180 per person-year), as compared with 6805 per 30,471 person-years (0.223 per person-year) among those receiving calcitriol ( $P < 0.001$ ). The difference in survival was significant at 12 months and increased with time ( $P < 0.001$ ). In the adjusted analysis, the mortality rate was 16 percent lower (95 percent confidence interval, 10 to 21 percent) among paricalcitol-treated patients than among calcitriol-treated patients. A significant survival benefit was evident in 28 of 42 strata examined, and in no stratum was calcitriol favored. At 12 months, calcium and phosphorus levels had increased by 6.7 and 11.9 percent, respectively, in the paricalcitol group, as compared with 8.2 and 13.9 percent, respectively, in the calcitriol group ( $P < 0.001$ ). The two-year survival rate among patients who switched from calcitriol to paricalcitol was 73 percent, as compared with 64 percent among those who switched from paricalcitol to calcitriol ( $P = 0.04$ ).

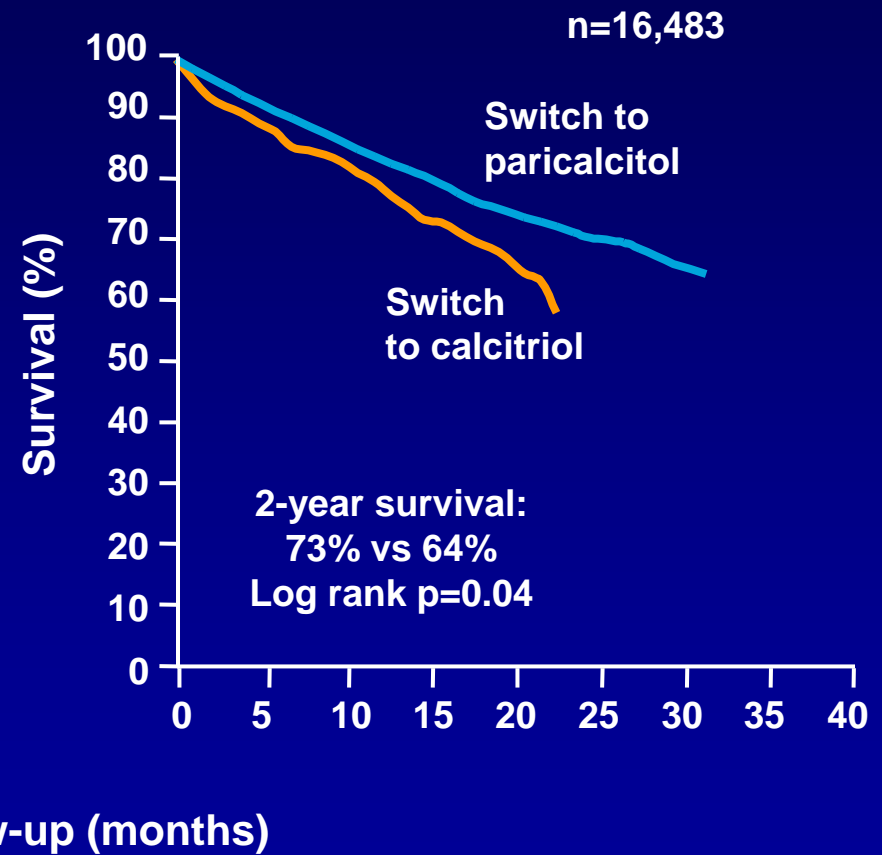
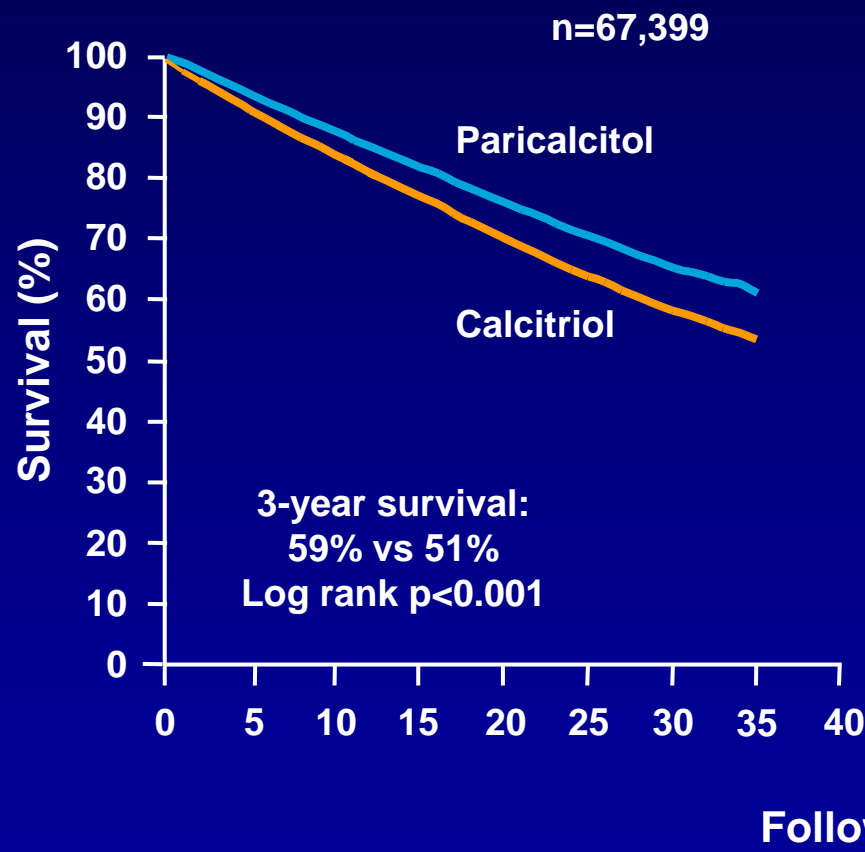
### CONCLUSIONS

Patients who receive paricalcitol while undergoing long-term hemodialysis appear to have a significant survival advantage over those who receive calcitriol. A prospective, randomized study is critical to confirm these findings.

# Paricalcitol vs. Calcitriol in ESRD

- 67,399 prevalent ESRD patients from 1999 to 2001
- Paricalcitol vs. Calcitriol
- Follow-up maximum 36 months
- Outcome: All-cause deaths
- Patients censored when switching treatment (“as-treated analysis”)
- Patients switching treatment analyzed separately
- Baseline Cox models

# Paricalcitol vs. Calcitriol in ESRD



# Paricalcitol vs. Calcitriol in ESRD<sup>1</sup>: Questions It Left Open

- Did not examine vitamin D vs. no vitamin D
- Unclear if observed advantage of paricalcitol present when compared to agents other than calcitriol
- Unclear if findings can be extended to non-ESRD populations
- Baseline Cox models do not account for temporal changes in covariates
- As-treated analysis vs. Intention-to-Treat (ITT)
- No dose-response effect examined
- Potential for selection bias
- Potential for residual confounding



# Vitamin D vs. no Vitamin D in ESRD

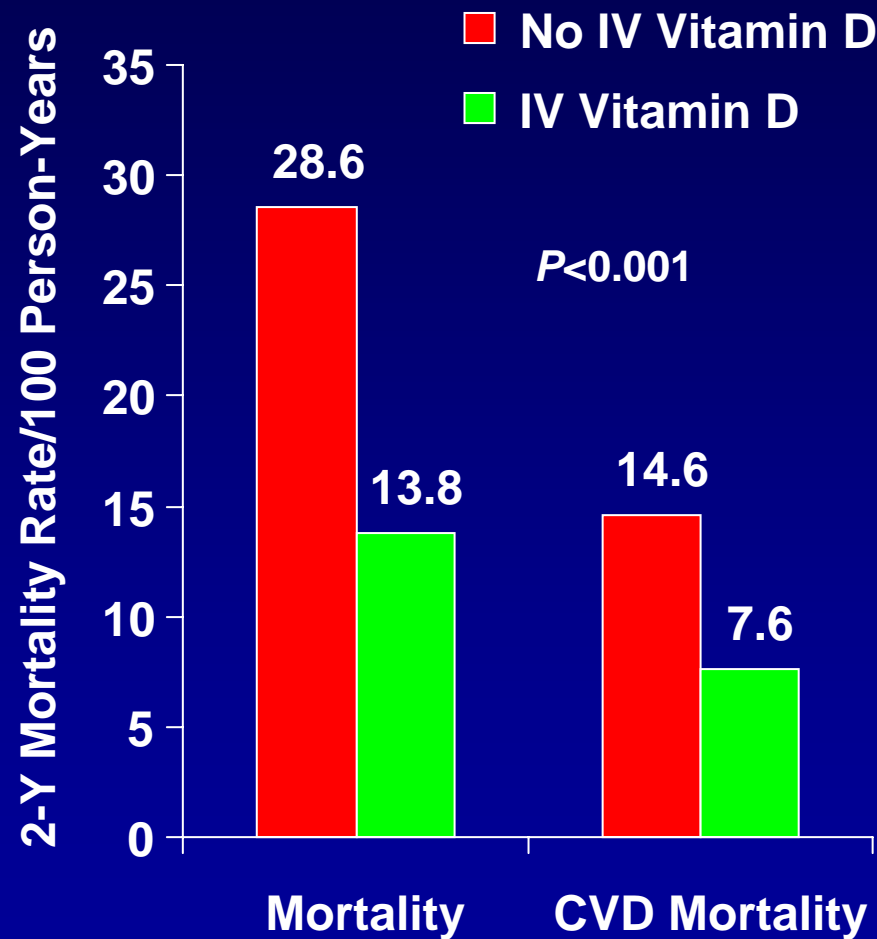
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- Multiple studies: Shoji 2004, Teng 2005, Kalantar-Zadeh 2006, Tentori 2006, Melamed 2006, Naves-Diaz 2008, Tentori 2009

# Vitamin D vs. no Vitamin D in ESRD

- 51,037 prevalent ESRD patients from 1996 to 1999
- Paricalcitol or Calcitriol vs. No treatment
- Follow-up maximum 24 months
- Outcome: All-cause deaths
- Intention-to-Treat analyses
- Time-dependent Cox models (primary)
- Marginal structural models, facility-level matching (secondary)

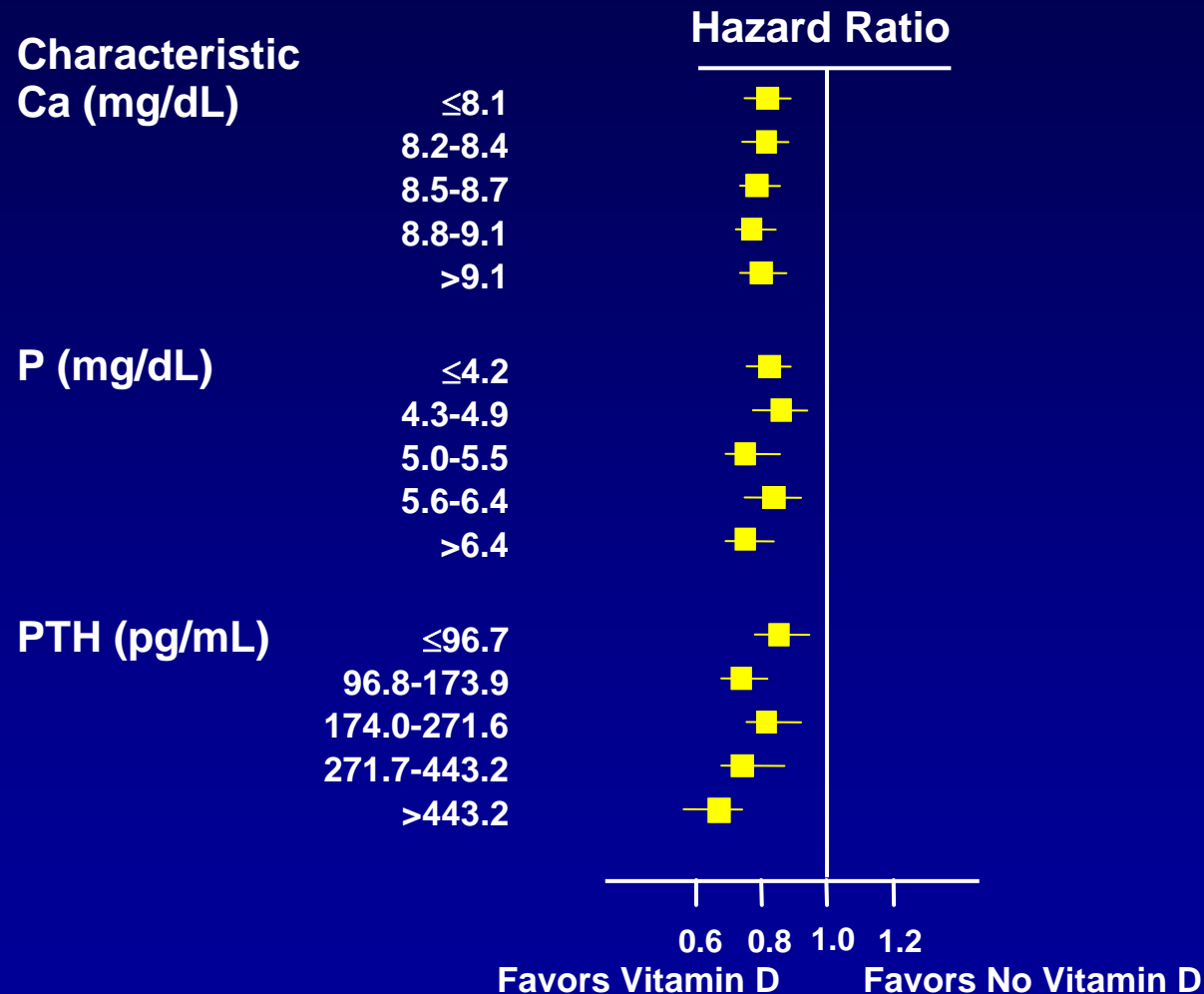
# Vitamin D vs. no Vitamin D in ESRD



## Results

- Adjusted 2-y survival advantage of 20% for IV vitamin D use
- Benefit of IV vitamin D use seen in most strata, even in patients with low iPTH and elevated Ca and P

# Associated Mortality Risk by Level of Serum P, Ca, and PTH in Patients on Hemodialysis With and Without IV Vitamin D Therapy



# Paricalcitol vs. Calcitriol in ESRD<sup>1</sup>: Questions Answered

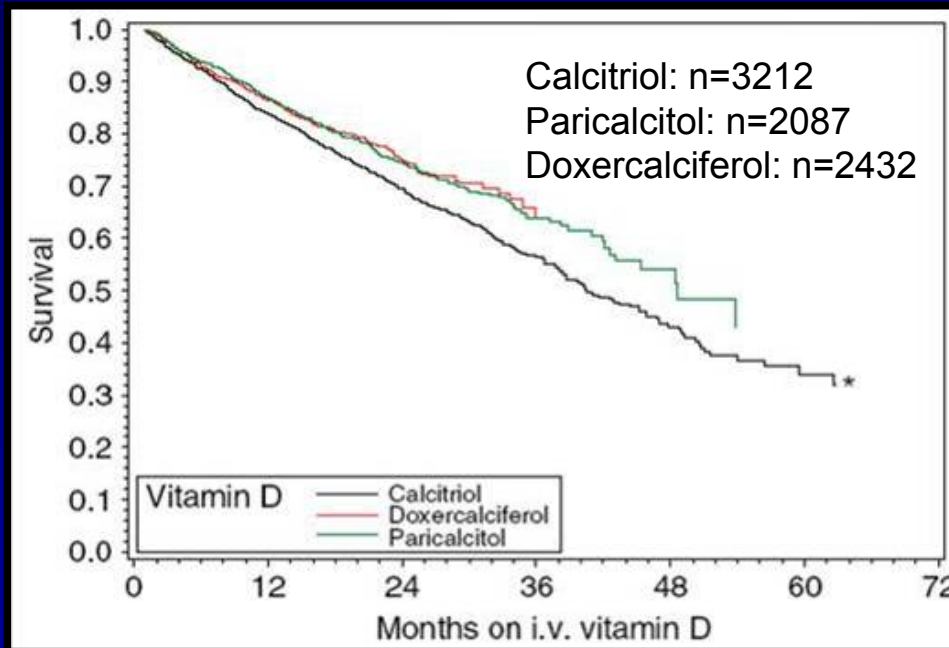
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- Unclear if observed advantage of paricalcitol present when compared to other agents
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- Potential for selection bias
- Potential for residual confounding

<sup>1</sup>Teng et al, NEJM 2003

# Outcomes Associated with Different Types of Active Vitamin D

- 14,586 prevalent ESRD patients from 1999 to 2004
- Paricalcitol vs. Doxercalciferol vs. Calcitriol vs. No treatment
- Outcome: All-cause and cardiovascular deaths
- As Treated and Intention-to-Treat analyses
- Baseline and Time-dependent Cox models

# Outcomes associated with different types of Active Vitamin D



\* $p < 0.001$

- **Unadjusted mortality** was identical in patients on doxercalciferol and paricalcitol and higher in patients on calcitriol
- **Adjusted mortality** was identical in the three vitamin D treated arms
- **Adjusted mortality** was higher for patients who did not receive vitamin D vs. those who did

# Comparing Teng 2003 with Tentori 2006

- Teng 2003
  - Advantages
    - Much larger sample size
  - Disadvantages
    - Used only baseline Cox models
    - Used as-treated analysis
- Tentori 2006
  - Advantages
    - Used time-dependent Cox models
    - Used intention-to-treat analysis
  - Disadvantages
    - Smaller sample size

Differences could also be due to other factors:

- Different population
- Different era



# Paricalcitol vs. Calcitriol in ESRD<sup>1</sup>: Questions Answered

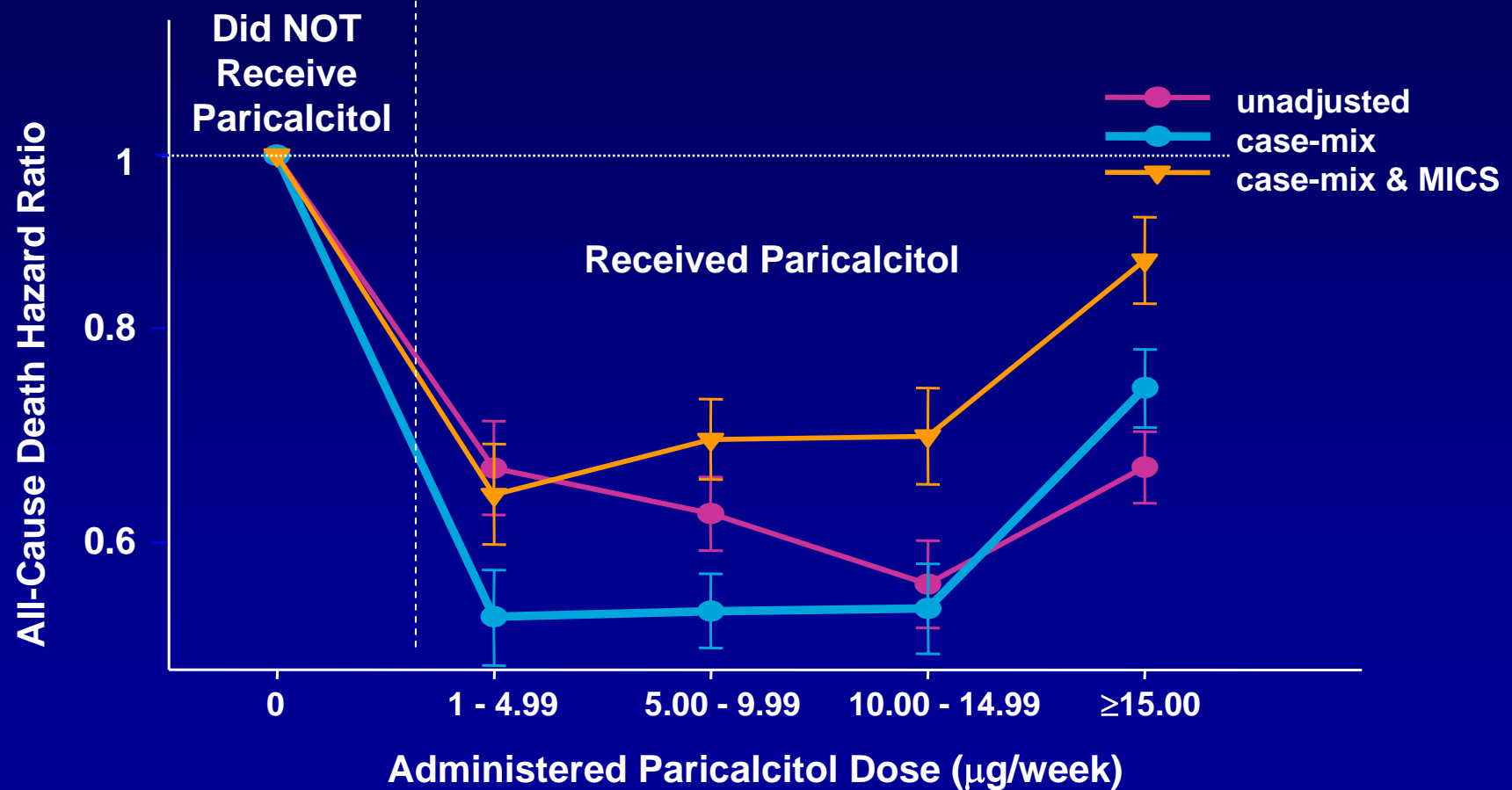
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- Potential for selection bias
- Potential for residual confounding

<sup>1</sup>Teng et al, NEJM 2003

# Vitamin D vs. no Vitamin D: Dose-Response Effect

- 58,058 prevalent ESRD patients from 2001 to 2003
- Paricalcitol (different doses) vs. No treatment
- Follow-up maximum 24 months
- Outcome: All-cause deaths
- As-treated analyses
- Baseline and Time-dependent Cox models

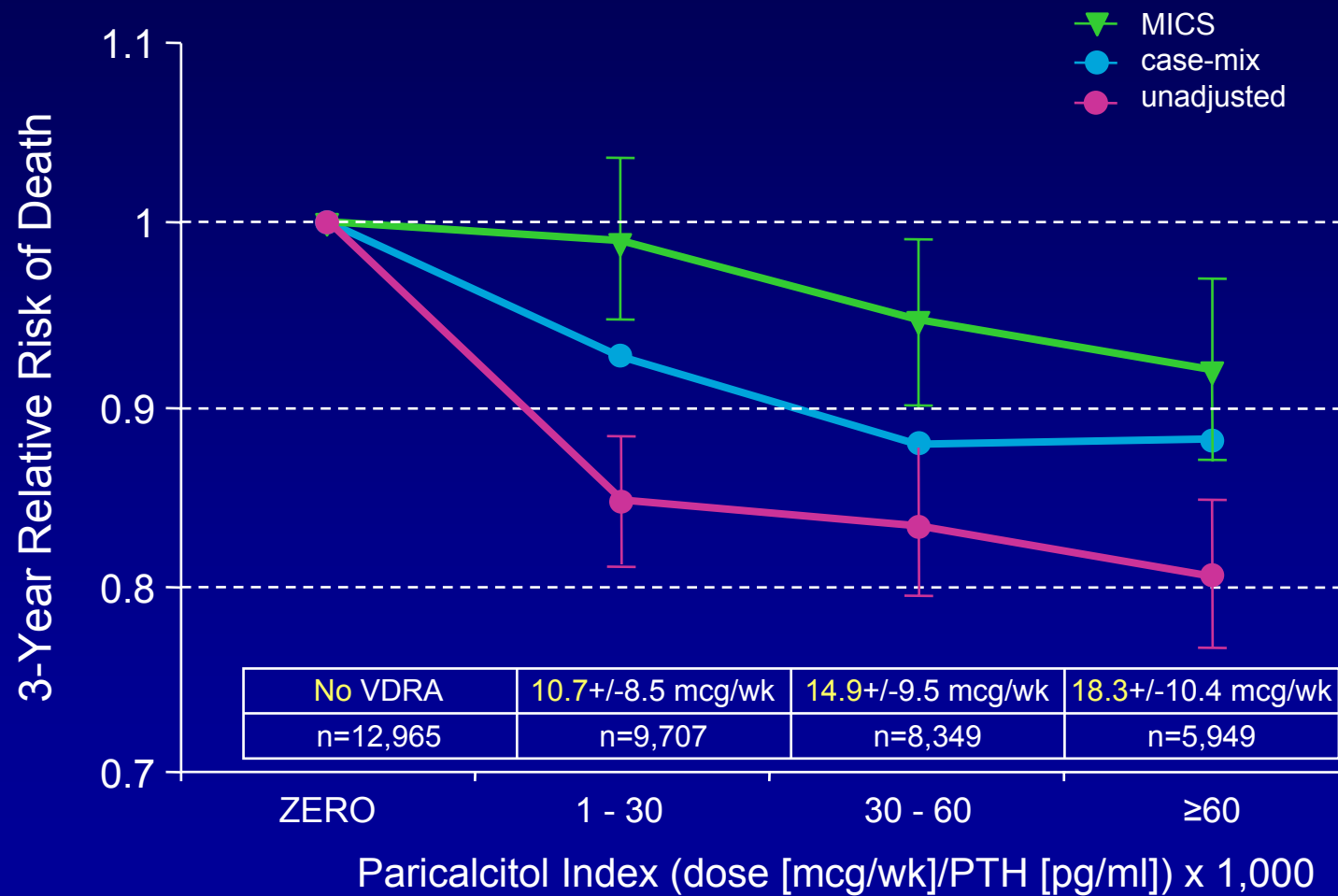
# Vitamin D vs. no Vitamin D: Dose-Effect Relationship



# Vitamin D vs. no Vitamin D: Dose-Effect Relationship

- 34,307 prevalent ESRD patients from 2001
- Paricalcitol index = weekly paricalcitol dose (mcg/week)/PTH (pg/ml) \* 1000
- Follow-up maximum 30 months
- Outcome: All-cause deaths
- As-treated analyses
- Baseline Cox models

# Vitamin D Dose-Effect: The Role of PTH



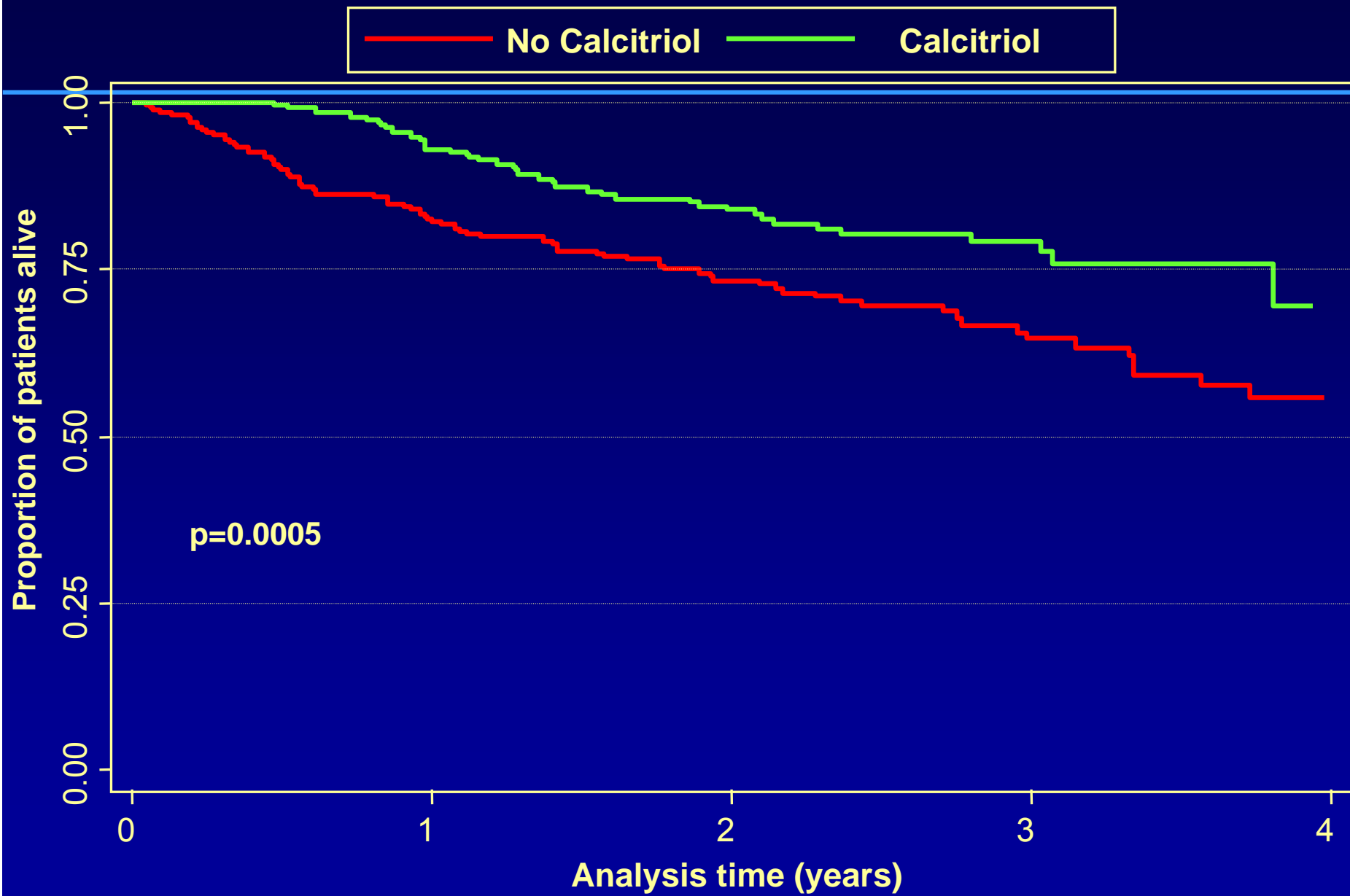
# Paricalcitol vs. Calcitriol in ESRD<sup>1</sup>: Questions Answered

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- Potential for selection bias
- Potential for residual confounding

<sup>1</sup>Teng et al, NEJM 2003

# Outcomes associated with VDRA use in non-ESRD populations

- 520 male US veterans between 1990-2005
- Oral calcitriol vs. no treatment
- Follow-up median 2 years
- Outcomes:
  - All-cause pre-dialysis mortality
  - ESRD incidence
- Fixed-covariate (baseline) Cox models
- Intention-to-treat analyses





# Paricalcitol vs. Calcitriol in ESRD<sup>1</sup>: Questions Answered

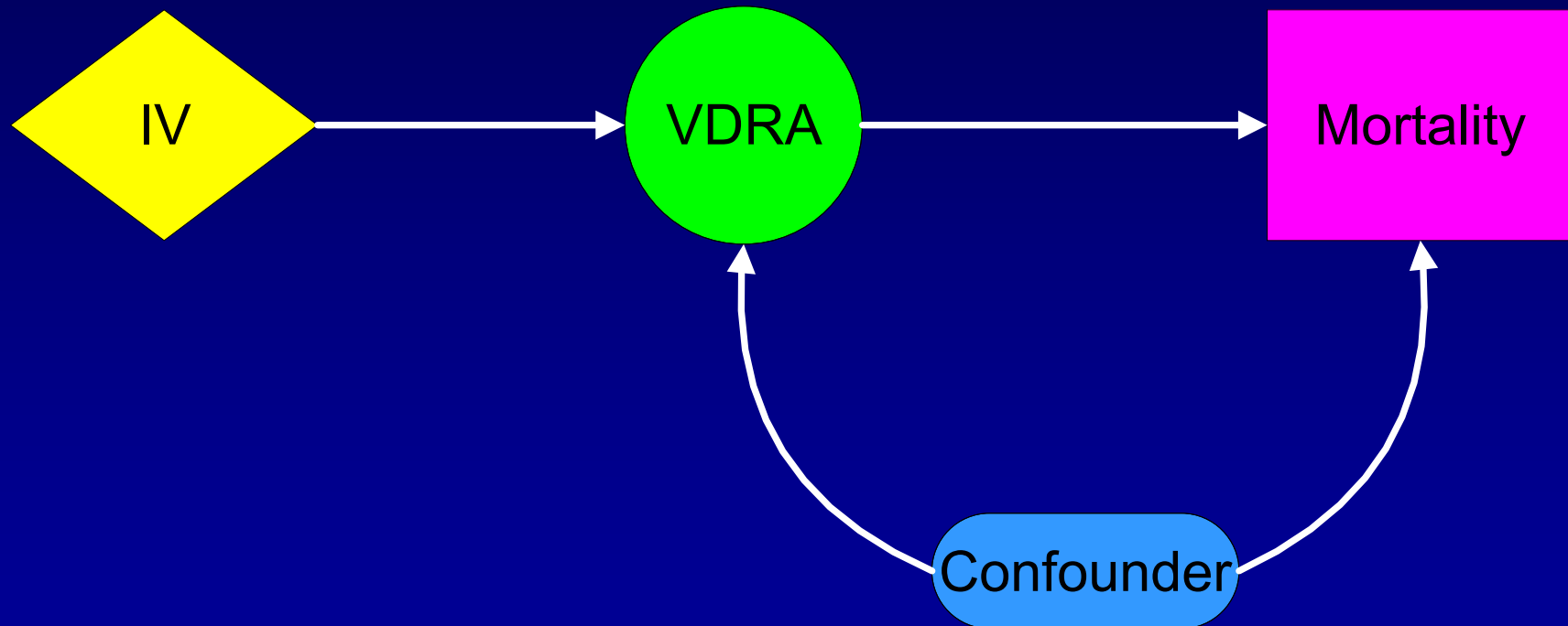
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<sup>1</sup>Teng et al, NEJM 2003

# Vitamin D and Residual Confounding

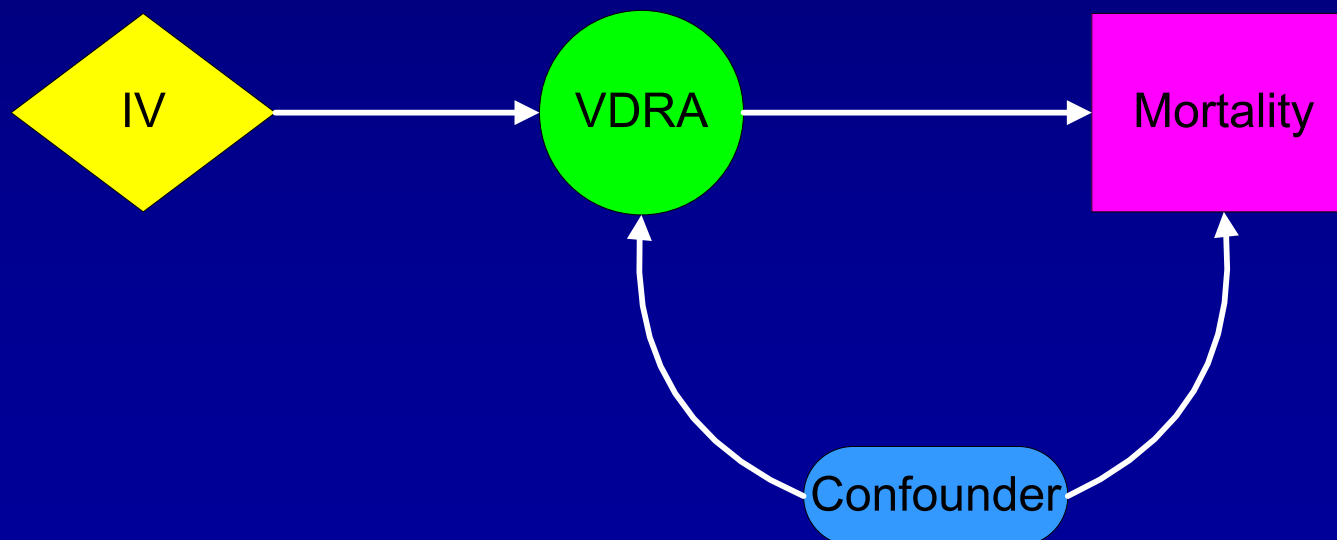
- Methods applied by previous studies cannot address this
- An Instrumental Variable (IV) can be used in observational studies to address residual confounding

# What Is an Instrumental Variable?



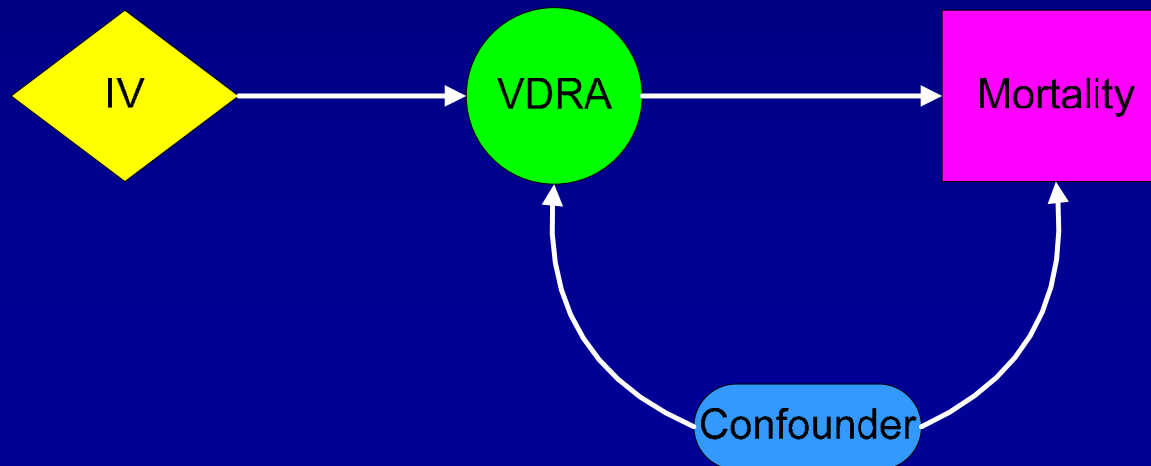
# Conditions for a Valid Instrumental Variable

1. IV affects VDRA
2. IV affects outcome (mortality) only through VDRA
3. IV and outcome (mortality) share no common causes



# Examples of Valid Instrumental Variables

- Randomized treatment assignment
  - Unsuccessful randomization and non-compliance with assigned treatment can render IV invalid
- Mendelian randomization (natural experiments)
- Instruments not assigned by researchers (or by nature)
  - Always open to skepticism regarding their validity



# Vitamin D and mortality in DOPPS

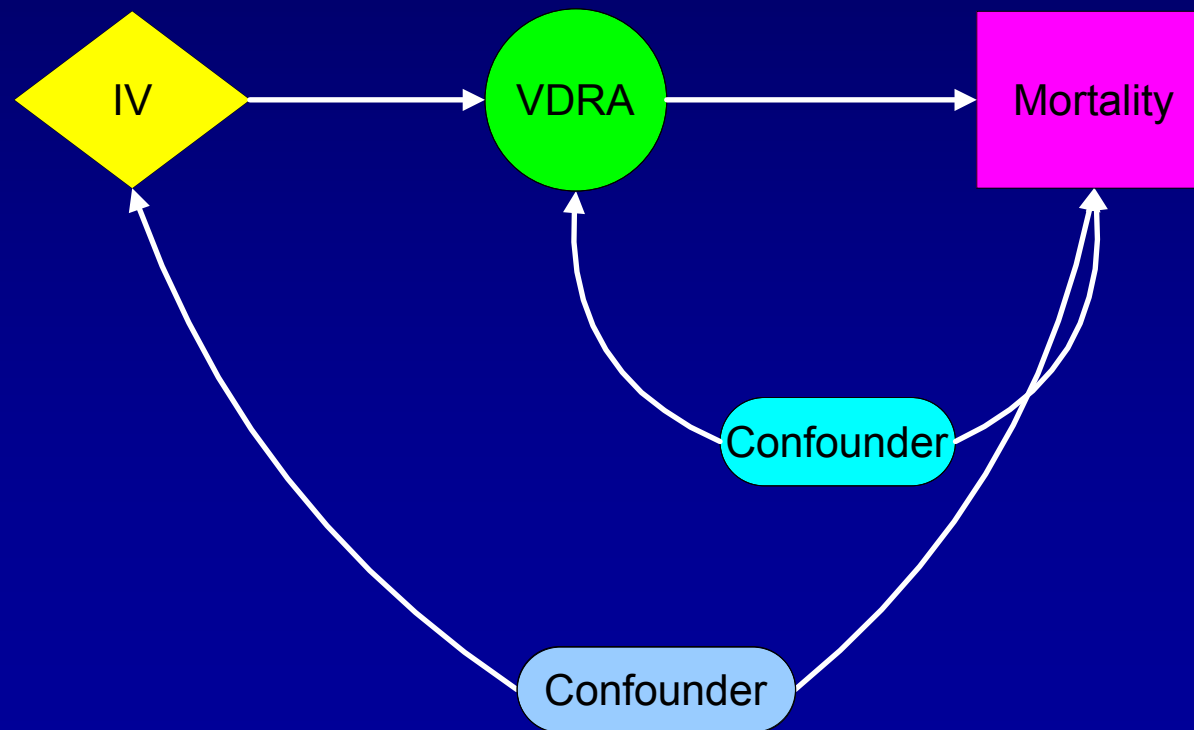
- 38,066 prevalent ESRD patients from 1996 onward (DOPPS I through III)
- Any Vitamin D vs. No treatment; also compared different agents
- Outcome: All-cause deaths
- Follow-up median 1.3 years
- As-treated and ITT analyses
- Baseline and Time-dependent Cox, MSM and IV methods
- IV was the adjusted percentage of Vitamin D administration in any given HD unit

# Vitamin D and mortality in DOPPS

- Vitamin D associated with lower mortality in time-varying Cox [RR = 0.92 (0.87–0.96)], and in baseline [(RR = 0.84 (0.78–0.98)] and time-varying MSM [RR = 0.78 (0.73–0.84)]
- No association in adjusted baseline Cox [RR = 0.98 (0.93–1.02)]
- No association in IV models [RR for facilities in 75th versus 25th percentile of vitamin D prescription: 0.99 (0.94–1.04)]
- No difference in paricalcitol vs. calcitriol or in doxercalciferol vs. calcitriol.

# How an Instrumental Variable Can Be Invalid

- Is it possible that HD units with a higher percentage of VDRA prescriptions provide different care in other ways?

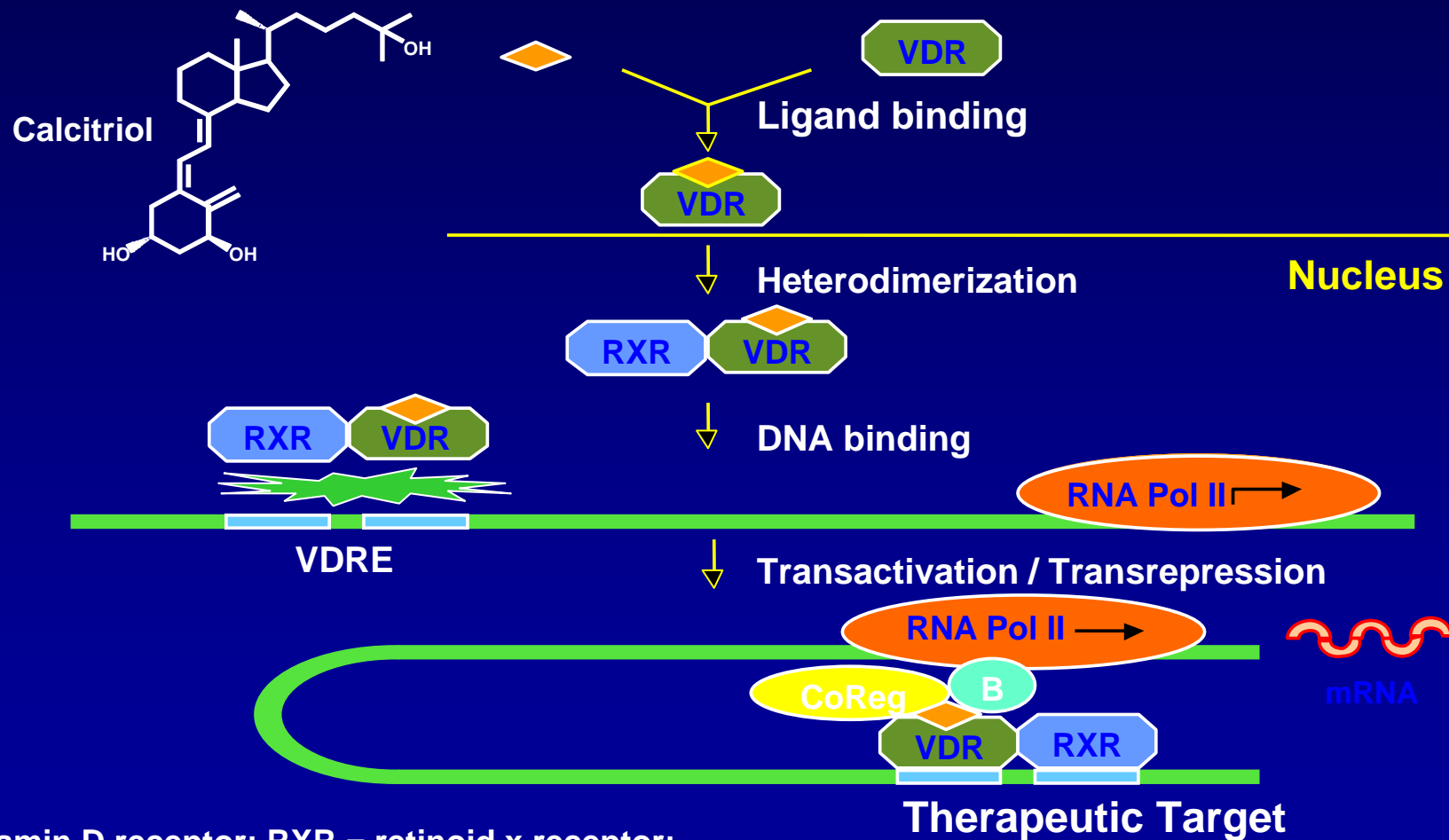




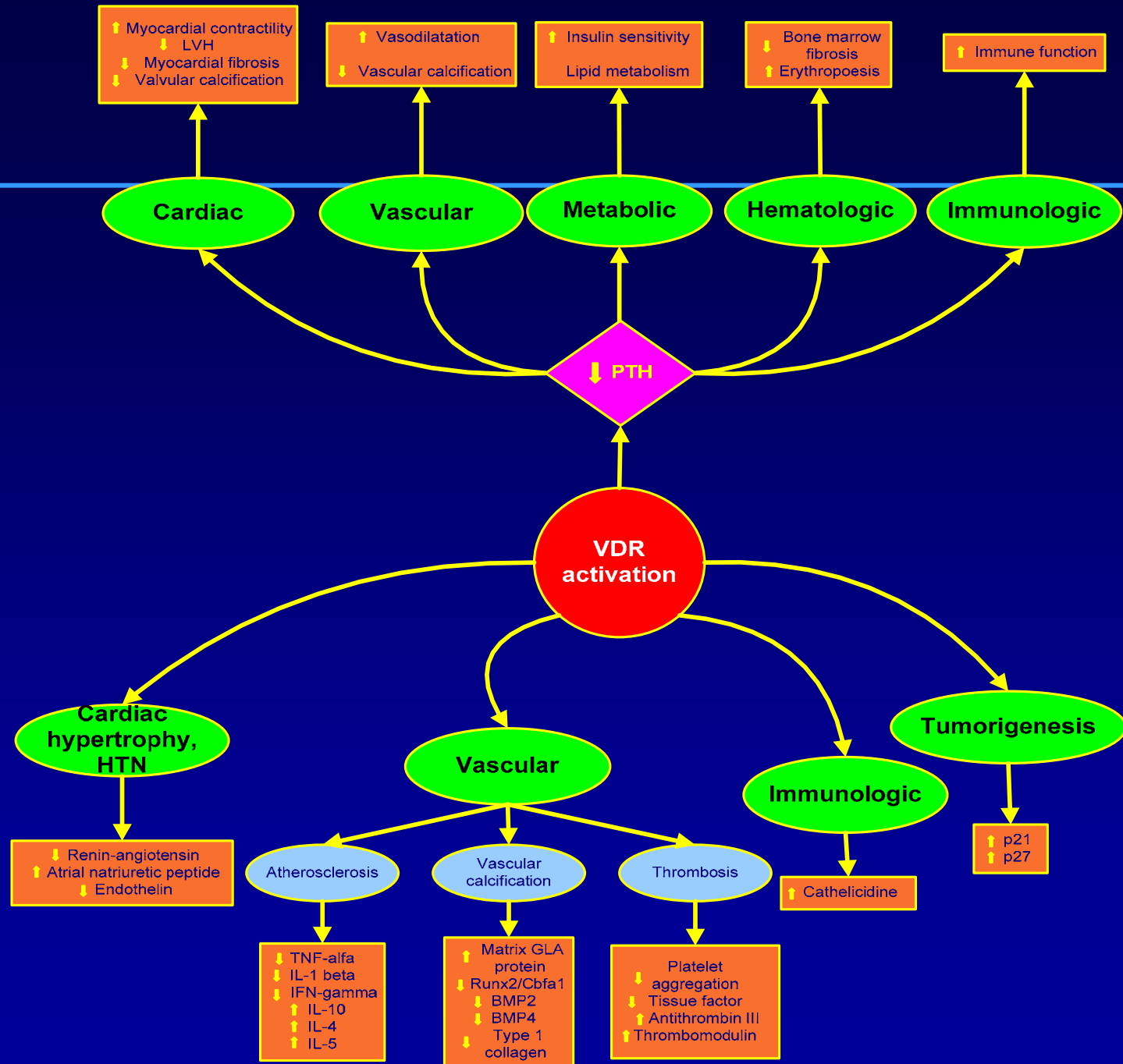
# The Path of Discovery



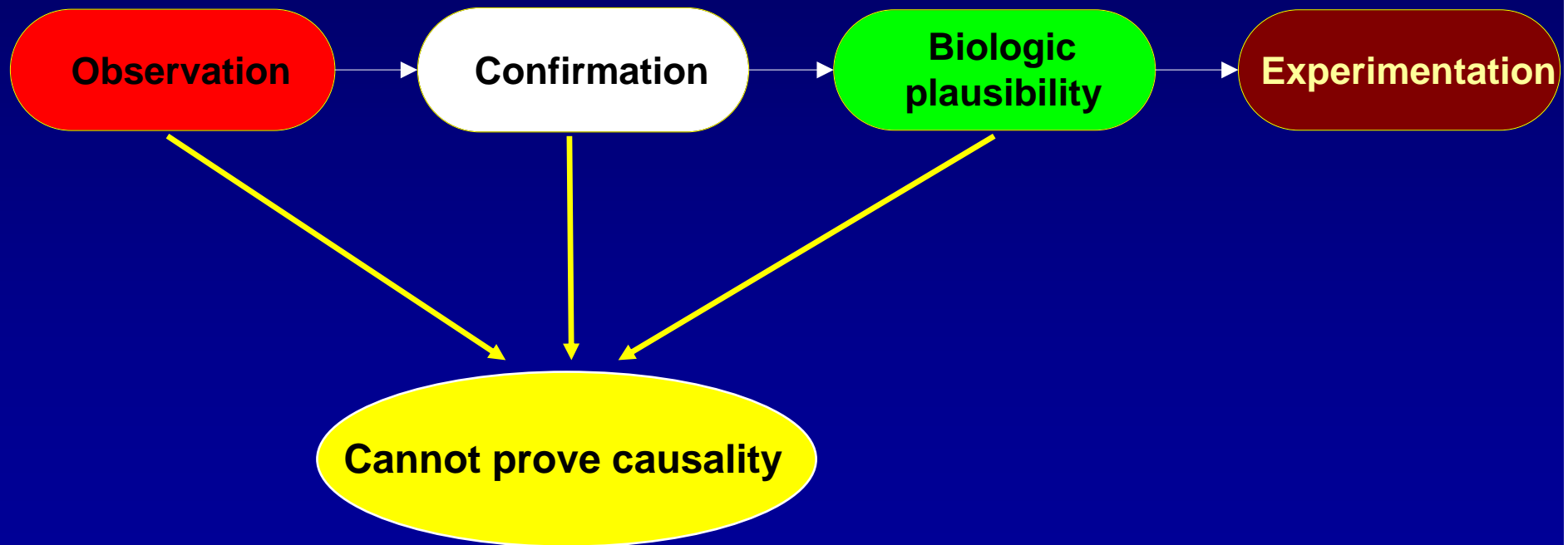
# Cellular Action of Calcitriol and the Vitamin D Receptor



VDR=vitamin D receptor; RXR = retinoid x receptor;  
VDRE = vitamin D response element

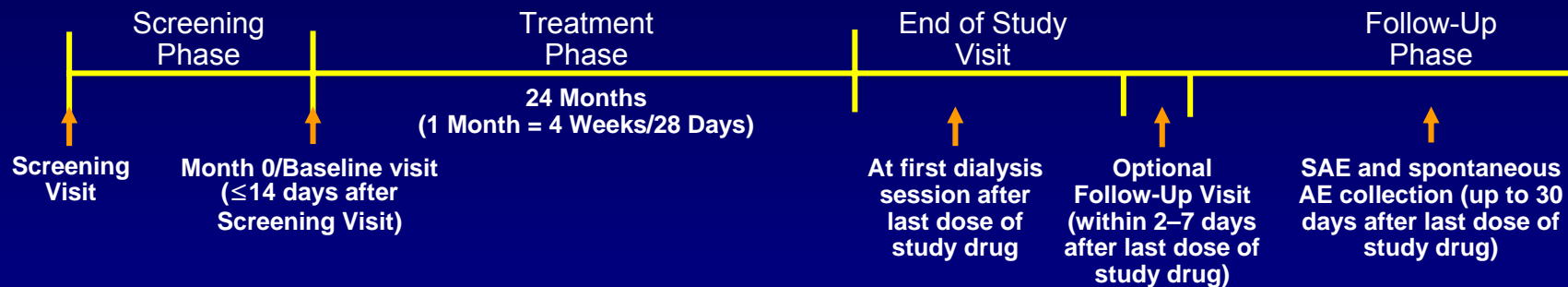


# The Path of Discovery



# Prospective Mortality Trial with Paricalcitol and Calcitriol

- Phase 4, prospective, randomized, active-controlled, double-blind, double-dummy, multicenter study to evaluate the survival benefits of IV paricalcitol compared with IV calcitriol in Stage 5 CKD patients on HD



- 2200 patients to receive paricalcitol or calcitriol (1:1)
- Enrollment initiated July 2003 at 53 US sites. By 2006, only 21 active sites remained and only 220 subjects (10% of target) randomized
- Study terminated in June 2006**

# Outcome Trials with Vitamin D

- No other trial in progress examining mortality as outcome
- Multiple trials examining surrogate outcomes
  - LVH
  - CAC
  - Inflammation
  - Proteinuria
- It is unclear how these trials will impact our clinical practice

# Vitamin D and Mortality: Conclusions

- Multiple observational studies indicate that VDRA use is associated with significantly better survival in ESRD and CKD.
- There is no unanimity in observational studies on whether any VDRA is superior.
- There are plausible biological mechanisms of action to explain the observed associations with better survival.
- The lack of randomized controlled trials prevents us from concluding causality.
- Studies of surrogate end points may provide further impetus to pursue benefits of VDRA beyond treatment of SHPT.