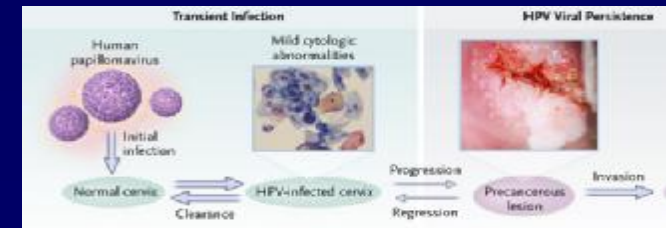
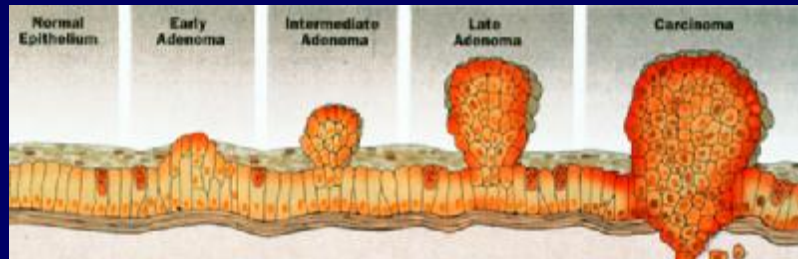


'Validation'/'Qualification' of Surrogate End points: A Cancer Perspective

Arthur Schatzkin, M.D., Dr.P.H.

Division of Cancer Epidemiology and Genetics
National Cancer Institute



2 Different Questions

- Q1: Does exposure-related biomarker predict cancer?
- Q2: Can biomarker be used as surrogate end point in studies of EB vs. cancer?

'Cancer'

- Incidence: primary prevention
- Recurrence, death (prognosis): secondary prevention

Question 1 (Prediction)

Is exposure-related biomarker associated with cancer?

Relative Risk

	Cancer	No Cancer	
Marker +	a	b	a + b
Marker -	c	d	c + d
	a + c	b + d	N

$$RR = [a/(a+b)]/[c/(c+d)]$$

Attributable Proportion/Etiologic Fraction

	Cancer	No Cancer	
Marker +	a	b	a + b
Marker -	c	d	c + d
	a + c	b + d	N

$$RR = [a/(a+b)]/[c/(c+d)] \quad \text{Sens.} = a/(a+c) \quad AP = \text{Sens} [1/(1-RR)]$$

Question 1: (Prediction)

Why is prediction useful?

Helps answer this question: Is the marker on the causal pathway to cancer?

That is, can help elucidate causal pathways for exposure → cancer—i.e., ‘mechanisms’.

2 Different Questions

- Q1: Does exposure-related biomarker predict cancer?
- Q2: Can biomarker be used as surrogate end point in studies of EB vs. cancer?

Surrogate End Points

- **Studies with surrogate end points can be smaller, faster, and cheaper than those with cancer outcomes**
- **Holds for both**
 - **intervention studies (trials)**
 - **observational epidemiologic studies**

What Is 'Validation'/'Qualification' of Intermediate End Point Biomarkers

- Q1: the biomarker is truly on the causal pathway(s) to cancer
- Q2: the study of exposure vs. surrogate end point gives the right answer for exposure vs. cancer (**a tougher requirement!**)

Surrogate and Mediating Endpoints: Current Status and Future Directions

Ross L. Prentice

The identification of surrogate endpoints that can replace "true" endpoints in clinical trials could provide an important advance for the evaluation of therapeutic or preventive interventions. Outcome events that are more frequent in occurrence and more proximate in time, compared with customary disease-specific mortality or incidence outcomes, could give answers that are based on smaller trials of shorter duration. However, reliance on surrogate outcomes is justifiable only if treatment comparisons that are based on a surrogate are a faithful reflection of comparisons that are based on the true endpoint.

I took this perspective, almost 20 years ago (1), in defining a surrogate outcome to be "a response variable for which a test of the null hypothesis of no relationship to the treatment groups under comparison is also a valid test of the corresponding null hypothesis based on the true endpoint," thinking that this was a minimal requirement for a short-term outcome to provide some reliable treatment effect information for the longer term outcome. However, this apparently simple requirement translates to some strong restrictions on the relationship of the treatment to the surrogate and true outcomes: Consider a treatment indicator variable x , a time to response surrogate S , and a time to response true outcome T . A dependence of T on x will imply a dependence of S on x if

1. the hazard rate for T depends on S and
2. the hazard rate for T given S does not depend on x .

The first criterion is typically readily verified empirically, whereas the second, which requires the surrogate to fully mediate the treatment effect on true outcome, is not. Rather, empirical data alone, even if extensive, will not provide certainty concerning criterion 2. Criterion 2 typically entails detailed knowledge of the biological pathways whereby x may affect T and detailed knowledge about the time course of such effects—knowledge that one would not expect to be available if there is uncertainty concerning whether x has any effect on T . For criterion 2 to hold, the surrogate must be comprehensive in being responsive to all pertinent pathways and the implications of the surrogate event occurrence for the true outcome risk must be equivalent in each treatment group being compared.

The article by Ray et al. (2) in this issue considers both the occurrence of distant metastases and general clinical treatment failure as potential surrogate outcomes for prostate cancer-specific death in the context of evaluating the effect of long-term androgen deprivation therapy among prostate cancer patients with locally advanced disease. Among patients who were alive 3 years after randomization, the hazard ratio for prostate cancer-specific death, when long-term androgen deprivation therapy was compared with control treatment, was 0.76 (95% confidence interval [CI]=0.51 to 1.11) among patients without distant metastases and 0.95 (95% CI=0.60 to 1.50) among patients with distant metastases. In the

context of a corresponding unconditional hazard ratio of 0.69 (95% CI=0.52 to 0.93) for prostate cancer-specific mortality, these analyses convey useful information about the importance of a reduction of distant metastasis in mediating the treatment effect on prostate cancer-specific survival, but they do not provide persuasive information concerning the ability of distant metastases to fulfill criterion 2. For example, the estimated prostate cancer-specific mortality rate among men without distant metastases is estimated to be 24% lower in the long-term androgen deprivation group than in the control group. Is this a chance observation or does longer term deprivation have some impact, for example, on local or regional recurrence or on the timing of distant metastasis detection?

Consideration of general clinical treatment failure as a potential surrogate (2) can be viewed as an effort to encompass pathways, in addition to reduction in distant metastases incidence, whereby the treatment may affect prostate cancer-specific death rates. General clinical treatment failure was defined as the time to first occurrence of local prostate recurrence, documented regional or distant metastasis, initiation of androgen deprivation therapy after protocol-directed treatment, or a prostate-specific antigen level of 25 ng/mL or higher after completion of radiation therapy. In spite of the stringency of criteria 1 and 2, a further criterion, as described previously (1), is needed to ensure that a dependence of S on x translates to a dependence of T on x . In this context, one can ask whether some events are included in general clinical treatment failure that help to establish an effect of x on S but have little or no implication concerning an effect of x on T . For example, the initiation of extra-protocol androgen deprivation therapy evidently may differ between treatment groups for purely artifactual reasons (ie, such therapy is unlikely in the first 2 years after randomization for men assigned to the long-term deprivation group). Also, the potential surrogate, general clinical treatment failure, may have a substantial noise component due to issues in defining local recurrence or due to patient concerns leading to unnecessary androgen deprivation therapy. Beyond these issues, the hazard ratio for long-term androgen deprivation vs control treatment was 0.88 (95% CI=0.48 to 1.63) before general clinical treatment failure and 0.81 (95% CI=0.58 to 1.14) after general clinical treatment failure, so that once again these empirical data do not provide convincing

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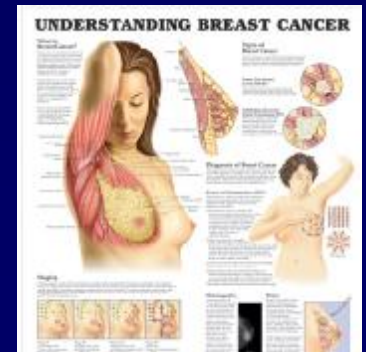
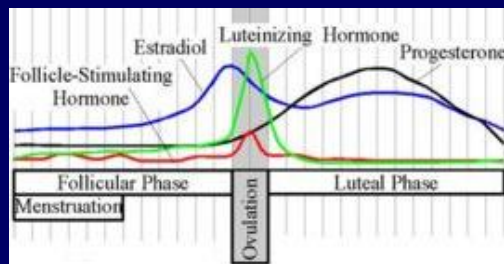
Surrogate Validity

3 conditions needed for validity:

- **Marker associated with cancer**
 - Relative risk
 - Attributable Proportion
- **Exposure/rx associated with marker**
- **Marker mediates association between exposure/rx and cancer**

BMI vs. breast cancer

BMI à estrogens à breast ca



Surrogate Validity

3 conditions needed for validity:

- **Marker associated with cancer**
 - Relative risk
 - **Attributable Proportion**
- Exposure/rx associated with marker
- Marker mediates association between exposure/rx and cancer

Estrogen vs. Breast Cancer (RR's)*

	<u>Estradiol</u>	<u>Free Estradiol</u>
Q1	1.00	1.00
Q2	1.42	1.38
Q3	1.21	1.84
Q4	1.80	2.24
Q5	2.00	2.58

P<.001

P<.001

***JNCI 2002; 94:606-161**

Surrogate Validity

3 conditions needed for validity:

- Marker associated with cancer
- **Exposure associated with marker**
 - RR, % change
- Marker mediates association between exposure/rx and cancer

BMI vs. Estrogen (geom. mean hormone conc.)*

<u>BMI</u>	<u>Estradiol</u> (pmol/L)	<u>Free Estradiol</u> (pmol/L)
<22.5	30.0	0.40
22.5-24.9	34.8	0.51
25.0-27.4	37.3	0.56
27.5-29.9	43.2	0.68
30.0+	54.9	1.00

P<.001

P<.001

*JNCI 2003; 95:1218-26

Surrogate Validity

3 conditions needed for validity:

- **Marker associated with cancer**
 - Relative risk
 - Attributable Proportion = Sensitivity (1-1/RR)
- **Exposure/rx associated with marker**
 - RR, % change
- **Marker mediates association between exposure/rx and cancer**

BMI and Postmenopausal Breast Cancer*

<u>Adjusted for free estradiol</u>	<u>RR (95% CI) for BMI (increase of 5 kg/m²)</u>
No	1.19 (1.05-1.34)**
Yes	1.02 (0.89-1.17)

* JNCI 2003; 95:1218-26

**Prentice criterion 1

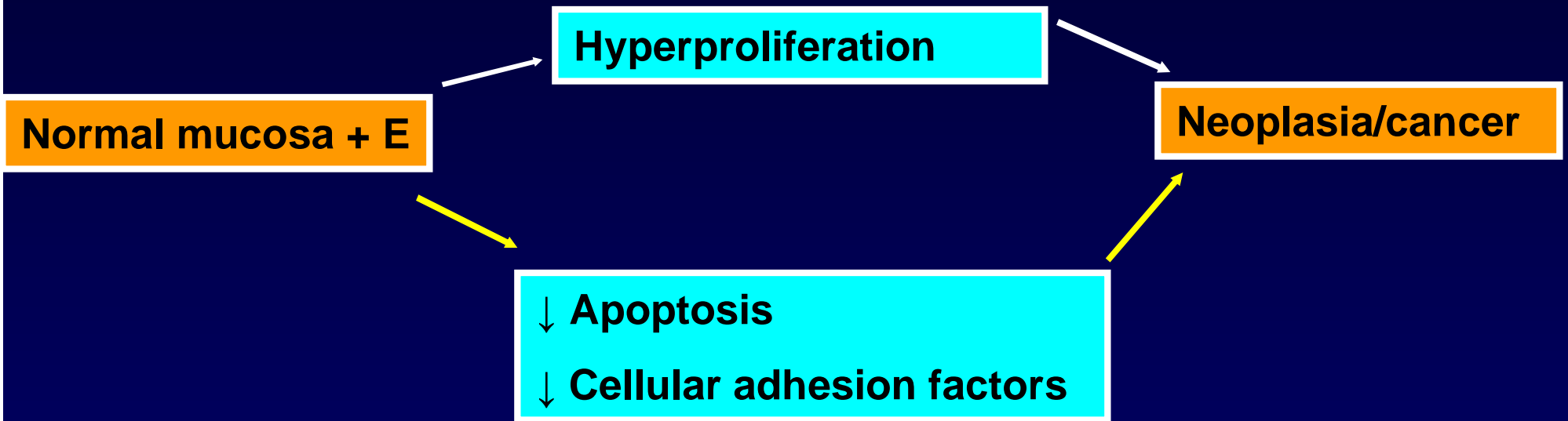
Table 1 | **Number of sexual partners and the risk of cervical dysplasia**

	Number of sexual partners				
	1	2	3–5	6–9	>10
<i>Odds ratio</i>					
Unadjusted	1.0	1.7	3.1*	4.7*	4.4*
Adjusted for HPV status	1.0	1.0	1.1	1.5	1.6

* $p < 0.05$. HPV, human papillomavirus.

‘Validation’ of Surrogate End Point Biomarkers

- **Being on the causal pathway does not guarantee surrogate end point validity**



Alternative pathway is problematic

Proliferation Markers as Surrogate End Points for Colorectal Cancer: Inferences

- Hyperproliferation may give the wrong answer about an intervention agent's effect on CRC
 - Agent reduces proliferation, reduces apoptosis, has no effect on CRC
 - Agent has no effect on proliferation, increases apoptosis, reduces CRC

'Validation' of Surrogate End Point Biomarkers

- **Being on the causal pathway does not guarantee surrogate end point validity**
- **Having a high AP/EF (meaning all or most of cancer goes through biomarker) does not guarantee surrogate end point validity**



Colorectal Adenomas are Pretty Good but not Definitive Surrogates

- **Adenoma heterogeneity:** rx affects only 'innocent' adenomas (à false positive result) or only the few 'bad adenomas' (à false null result)

Colorectal Adenomas are Pretty Good but not Definitive Surrogates

- **Timing:** in polyp trials, no information on early (pre-adenoma) and minimal information on late (small to large adenoma/cancer) events

Hematopoietic Cancer

- Benzene – ↓WBC à leukemia
- Permethrin à MGUS à multiple myeloma

Benzene, ↓WBC, Leukemia

- **Reduced WBC associated with subsequent leukemia among benzene workers**
- **Strong benzene-leukemia evidence**
- **Regulation based on ↓WBC**

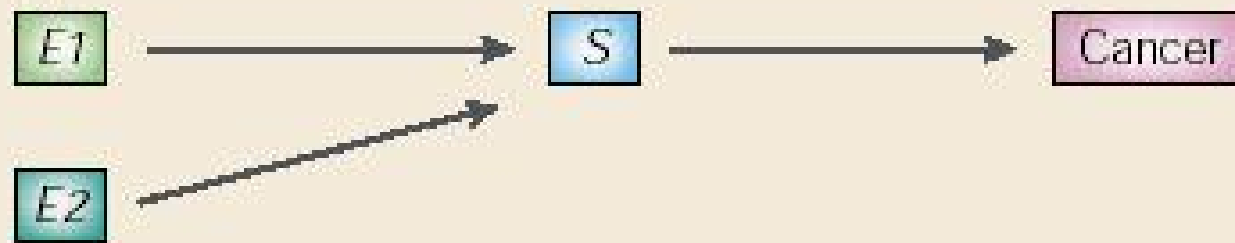
Permethrin, MGUS, Multiple Myeloma

- All MM preceded by MGUS; but not all MGUS goes to MM.
- Permethrin-MM connection: limited data
- How strong can permethrin-MM inferences be based on MGUS?

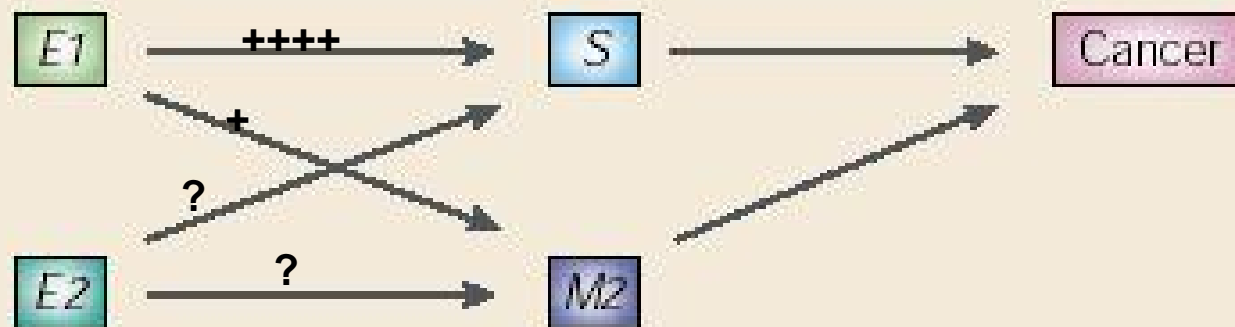
More on Surrogate Validity

- A surrogate end point valid for one exposure or intervention vs. a cancer is not necessarily valid for a 2nd exposure or intervention
- Why? Because an alternative pathway to cancer may exist

a



b



2-Stage Strategy Not a Lock

- **Intervention alters surrogate marker (Stage 1)
AND surrogate marker is associated with cancer (Stage 2)**
- **Counter-example? HRT raises HDL; HDL inversely related to CVD; but HRT does not protect vs. CVD**
 - **Alternative pathway(s)**

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials register maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 26 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 met our inclusion criteria. We treated all occurrences of myocardial infarction and death from cardiovascular causes.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glucose hemoglobin level was approximately 8.3%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.01 to 1.99; $P=0.01$), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; $P=0.06$).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-course analysis. Despite these limitations, patients and providers should consider the potential for an adverse cardiovascular effect of treatment with rosiglitazone in type 2 diabetes.

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Received October 16, 2006; accepted for publication February 21, 2007.

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ORIGINAL CONTRIBUTION

Lowering Homocysteine in Patients With Ischemic Stroke to Prevent Recurrent Stroke, Myocardial Infarction, and Death: The Vitamin Intervention for Stroke Prevention (VISP) Randomized Controlled Trial

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Chin-Hua Wang, PhD

Meir Stampfer, MD, DrPH

Context: In observational studies, elevated plasma total homocysteine levels have been positively associated with ischemic stroke risk. However, the utility of homocysteine-lowering therapy to reduce that risk has not been confirmed by randomized trials.

Objective: To determine whether high doses of folic acid, pyridoxine (vitamin B₆), and cobalamin (vitamin B₁₂), given to lower total homocysteine levels, reduce the risk of recurrent stroke over a 2-year period compared with low doses of these vitamins.

Design: Double-blind randomized controlled trial (September 1996–May 2003).

Setting and Participants: 3680 adults with nondisabling cerebral infarction at 56 university-affiliated hospitals, community hospitals, private neurology practices, and Veterans Affairs medical centers across the United States, Canada, and Scotland.

Interventions: All participants received best medical and surgical care plus a daily multivitamin containing the US Food and Drug Administration's reference daily intakes of other vitamins; patients were randomly assigned to receive once-daily doses of the high-dose formulation ($n=1827$), containing 25 mg of pyridoxine, 0.4 mg of cobalamin, and 2.5 mg of folic acid; or the low-dose formulation ($n=1853$), containing 200 µg of pyridoxine, 6 µg of cobalamin, and 20 µg of folic acid.

Main Outcome Measures: Recurrent cerebral infarction (primary outcome); coronary heart disease (CHD) events and death (secondary outcomes).

Results: Mean reduction of total homocysteine was 2 µmol/L greater in the high-dose group than in the low-dose group, but there was no treatment effect on any end point. The unadjusted risk ratio for any stroke, CHD event, or death was 1.0 (95% confidence interval [CI], 0.8–1.1), with chances of an event within 2 years of 18.0% in the high-dose group and 18.6% in the low-dose group. The risk of ischemic stroke within 2 years was 9.2% for the high-dose and 8.8% for the low-dose groups (risk ratio, 1.0; 95% CI, 0.8–1.3) ($P=.80$ by log-rank test of the primary hypothesis of difference in ischemic stroke between treatment groups). There was a persistent and graded association between baseline total homocysteine level and outcomes: A 2-µmol/L lower total homocysteine level was associated with a 10% lower risk of stroke ($P=.05$), a 26% lower risk of CHD events ($P<.001$), and a 16% lower risk of death ($P=.001$) in the low-dose group and a nonsignificantly lower risk in the high-dose group by 2% for stroke, 7% for CHD events, and 7% for death.

Conclusions: In this trial, moderate reduction of total homocysteine after nondisabling cerebral infarction had no effect on vascular outcomes during the 2 years of follow-up. However, the consistent findings of an association of total homocysteine with vascular risk suggests that further exploration of the hypothesis is warranted and larger trials in different populations with elevated total homocysteine may be necessary.

JAMA. 2004;291:568–575. www.jama.com

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See also pp 576 and 621.

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Effects of Torcetrapib in Patients at High Risk for Coronary Events

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ABSTRACT

BACKGROUND

Inhibition of cholesteryl ester transfer protein (CETP) has been shown to have a substantial effect on plasma lipoprotein levels. We investigated whether torcetrapib, a potent CETP inhibitor, might reduce major cardiovascular events. The trial was terminated prematurely because of an increased risk of death and cardiac events in patients receiving torcetrapib.

METHODS

We conducted a randomized, double-blind study involving 15,067 patients at high cardiovascular risk. The patients received either torcetrapib plus atorvastatin or atorvastatin alone. The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina.

RESULTS

At 12 months in patients who received torcetrapib, there was an increase of 72.2% in high-density lipoprotein cholesterol and a decrease of 24.5% in low-density lipoprotein cholesterol, as compared with baseline ($P<.001$ for both comparisons), in addition to an increase of 5.4 mm Hg in systolic blood pressure, a decrease in serum potassium, and increases in serum sodium, bicarbonate, and aldosterone ($P<.001$ for all comparisons). There was also an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval [CI], 1.09 to 1.44; $P=0.001$) and death from any cause (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; $P=0.006$). Post hoc analyses showed an increased risk of death in patients treated with torcetrapib whose reduction in potassium or increase in bicarbonate was greater than the median change.

CONCLUSIONS

Torcetrapib therapy resulted in an increased risk of mortality and morbidity of unknown mechanism. Although there was evidence of an off-target effect of torcetrapib, we can not rule out adverse effects related to CETP inhibition. (ClinicalTrials.gov number, NCT00134264.)

From the Heart Research Unit (P.J.B.), St. Bartholomew's Hospital, London (M.C.); GlaxoSmithKline, Huddersfield, Stockton-on-Tees, South West Centre, Dallas (S.M.G.), and the University of Amsterdam (J.J.P.K.); Université de Montréal (M.E.); Columbia University (L.M.); Montreal Heart Institute (J.-C.T.); San Francisco General Hospital, San Francisco (D.H.R.); University of Wisconsin, Madison (B.B.); Columbia University, New York (A.R.T.); and Icahn School of Medicine at Mount Sinai, New York (L.M.). Montreal Heart Institute, 3841 Avenue Lacombe, Montreal, QC H3T 1M5, Canada; St. Vincent's Hospital, Sydney, NSW 1570, Australia (B.B.).

*Members of the coronary event working group of the ILLUMINATE trial are listed in the Supplemental Appendix, available with the full text at www.nejm.org.

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3 Sobering Stories (1)

- **Avandia (Rosiglitazone)**
 - Lowered glycated hemoglobin level
 - Increased congestive heart failure and cardiovascular ischemia
- **Folate and B-vitamins**
 - Lowered homocysteine
 - Did not lower cardiovascular events

3 Sobering Stories (2)

- **Torcetrapib***
 - Lowered LDL (72%), raised HDL (25%)
 - Increased cardiovascular events (25%) and all cause mortality (58%)

*torcetrapib plus atorvastatin vs. atorvastatin alone

Surrogates for Prostate Ca Survival (1)

ARTICLE

Potential Surrogate Endpoints for Prostate Cancer Survival: Analysis of a Phase III Randomized Trial

Michael E. Ray, Kyoungwha Bae, Maha H. A. Hussain, Gerald E. Hanks, William U. Shipley, Howard M. Sandler

- Background** The identification of surrogate endpoints for prostate cancer-specific survival may shorten the length of clinical trials for prostate cancer. We evaluated distant metastasis and general clinical treatment failure as potential surrogates for prostate cancer-specific survival by use of data from the Radiation Therapy and Oncology Group 92-02 randomized trial.
- Methods** Patients ($n = 1554$ randomly assigned and 1521 evaluable for this analysis) with locally advanced prostate cancer had been treated with 4 months of neoadjuvant and concurrent androgen deprivation therapy with external beam radiation therapy and then randomly assigned to no additional therapy (control arm) or 24 additional months of androgen deprivation therapy (experimental arm). Data from landmark analyses at 3 and 5 years for general clinical treatment failure (defined as documented local disease progression, regional or distant metastasis, initiation of androgen deprivation therapy, or a prostate-specific antigen level of 25 ng/mL or higher after radiation therapy) and/or distant metastasis were tested as surrogate endpoints for prostate cancer-specific survival at 10 years by use of Prentice's four criteria. All statistical tests were two-sided.
- Results** At 3 years, 1364 patients were alive and contributed data for analysis. Both distant metastasis and general clinical treatment failure at 3 years were consistent with all four of Prentice's criteria for being surrogate endpoints for prostate cancer-specific survival at 10 years. At 5 years, 1178 patients were alive and contributed data for analysis. Although prostate cancer-specific survival was not statistically significantly different between treatment arms at 5 years ($P = .08$), both endpoints were consistent with Prentice's remaining criteria.
- Conclusions** Distant metastasis and general clinical treatment failure at 3 years may be candidate surrogate endpoints for prostate cancer-specific survival at 10 years. These endpoints, however, must be validated in other datasets.

J Natl Cancer Inst 2009;101:228-236

Prostate cancer is a malignancy with a long natural history. Even men who are initially diagnosed with high-grade and locally advanced prostate cancer often survive for many years. Because of the long survival time, clinical trials of prostate cancer that are designed with primary endpoints of overall or prostate cancer-specific survival require long follow-up periods, especially those evaluating treatments for clinically localized disease. The time required for the conception, design, conduct, analysis, and initial reporting of a prostate cancer clinical trial often approaches 10 years (1-4). Identification of surrogate endpoints for prostate cancer cause-specific or overall survival would shorten the time required to conduct prostate cancer clinical trials and thus improve the chances of finding better treatments for prostate cancer. For patients with localized prostate cancer, the ideal surrogate endpoint for survival should use clinical information available as soon as possible after definitive local therapy that will identify patients highly likely to die of their disease. The findings from this study would most directly apply to patients treated with primary external

beam radiation therapy; further research is required to show that the findings could also apply to surgically treated patients.

The Radiation Therapy and Oncology Group (RTOG) 92-02 trial is a phase III, randomized multi-institutional clinical trial that was conducted between June 26, 1992, and April 15, 1995, during the

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Correspondence to: Michael E. Ray, MD, PhD, Radiology Associates of Appleton, 1818 North Meade St, Appleton, WI 54911 (e-mail: michael.ray@theonc.org).

See "Funding" and "Notes" following "References."
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Surrogates for Prostate Ca Survival (2)

- **Potential surrogates:**
 - Distant metastasis
 - ‘General clinical treatment failure’
- **Conclusion: these end points may be candidate surrogates for prostate cancer-specific survival at 10 years**

Surrogates for Prostate Ca Survival (3)

- **BUT—it is possible that a treatment effect on metastasis/rx failure does not have equivalent effect on prostate survival:**
 - Rx improves surrogate end points but not survival (b/o some alternative adverse effect on mortality)
 - Rx has no impact on surrogates but improves survival (b/o some alternative beneficial effect on mortality)

Statistical Considerations: Error in Measurement of Biomarkers

- **Measurement error will attenuate associations**
 - Exposure/rx vs. marker
 - Marker vs. cancer
- **Measurement error can lead to underestimation:**
 - Predictive ability of biomarker
 - Extent to which surrogate mediates the effect of exposure, rx on survival

Surrogate End Point Validity/Qualification: Summary (1)

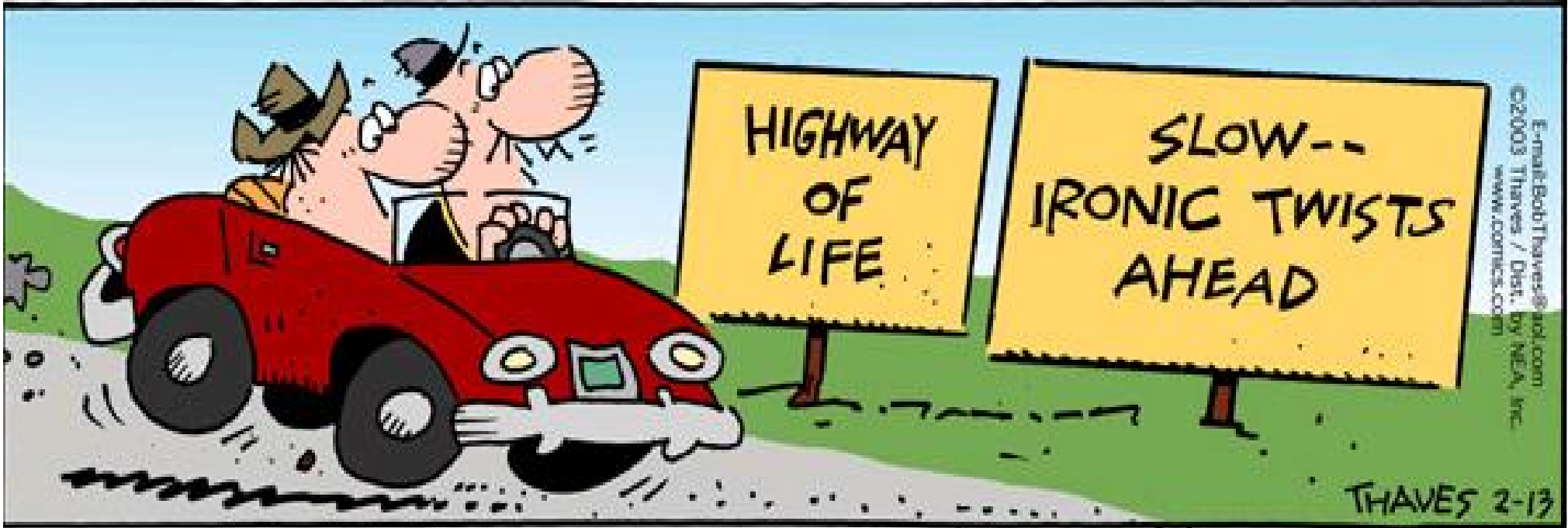
- *Totality* of causal connections is key
- High AP is supportive but not definitive (b/o heterogeneity, timing issues)

Surrogate End Point Validity/Qualification: Summary (2)

- **Mediation of exposure-cancer relation supports validity of surrogacy**
- **Validity is more assured for surrogates both necessary for and relatively close developmentally to cancer (e.g., CIN3)**

Surrogate End Point Validity/Qualification: Summary (3)

- **Advances in validating/qualifying potential surrogate endpoints may come from:**
 - **Meta-analytic approaches (esp. given large sample sizes required for evaluating mediation)**
 - **'Omics' data (transcriptomics, proteomics, metabolomics): potentially comprehensive characterization of multiple pathways**



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THAVES 2-13

Irony of Surrogate Validation

Large, long, costly studies needed for evaluation are precisely the studies surrogates were designed to replace.

Surrogate End Points in Cancer Prevention Research: The 'No Free Lunch' Law*

**Inferential certainty is directly
associated with study cost.**

***or, you get what you pay for**

Intermediate Biomarkers in Cancer Research: Conclusion (1)

- **May be valuable in prediction—can help clarify causal pathways**

Intermediate Biomarkers in Cancer Research: Conclusion (2)

- **As surrogate end points**
 - **May be valuable in Phase II studies (those seeking a biologic effect) or observational ('mechanism') studies**

Biomarkers in Cancer Research: Conclusion (3)

- **The ‘savings’ resulting from use of surrogate end points comes at the cost of inferential certainty-- there’s no free lunch**
- **In conjunction with other studies (polyp trials + cohort studies of CRC), may enhance ‘probability of being right’**

Biomarkers in Cancer Research: Conclusion (5)

- **Replacing explicit cancer end points in Phase III clinical trials and observational studies is risky business**

Biomarkers in Cancer Research: Conclusion (6)

- **As informative as intermediate end point studies can be, we must not lose sight of the critical importance of observational epidemiologic studies and RCTs with incident cancer (or recurrence/mortality) end points.**
 - (And part of that ‘importance’ is evaluating the role of potential surrogate end points.)

YESTERDAY
IN THIS SPACE
I PREDICTED
THAT CANCER
WOULD COME
TO AN END. IT
DID NOT, HOWEVER.
I REGRET ANY
INCONVENIENCE
THIS MAY
HAVE CAUSED.



MSR/1990