Statistics•Collaborative

design and analysis for biomedical research

Post-randomization subgroups: Lessons from the CDP

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Stamler, Canner, the CDP, and adherence

Stamler about analysis of the CDP…

We insisted, "once randomized always counted".
That's a concept not comprehensible at first glance;

A doc asks, "What about those who take the medication?"
We reply, "Compared to whom?"
But the doc is not satisfied,
s

Stamler, Canner, the CDP and adherence

But the doc is not satisfied,

I asked Paul Canner to compare the good adherers to the poor adherers.

One day he brought me two tables.
The first showed good and poor adherers in the clofibrate group.

The rate of coronary disease was 2-3 times higher in the poor adherers.

So it looked as if the drug was effective.

Stamler, Canner, the CDP and adherence

The rate of coronary disease was two to three times higher in the poor adherers.

So it looked as if the drug was effective.

Then he showed me the same table for the placebo group;

it showed exactly the same result.

Poor adherers are different people.

I said, "Paul, this is gold."

Ref: Coronary Drug Project (1980) *NEJM,* p. 1038

Wittes (2016) - A tale of three species – rabbits, chickens and humans: an interview with clinical trials pioneer Jeremiah Stamler. Clinical Trials 3: 320-334

Another CDP lesson – beware time dependent covariate adjustment

- Classic covariate adjustment uses baseline prognostic factors only
  - Adjust for imbalance
  - Gain efficiency

- Epi studies often adjust by time-dependent covariates
- In clinical trials
  - Beware adjustment by time dependent variates
  - (despite Cox time dependent regression model)

Coronary Drug Project
5-Year Mortality

Baseline Cholesterol	Cholesterol Change	% Deaths	
			Placebo
< 250mg%	Fall		21.2
< 250	Rise		18.7
≥ 250 mg%	Fall		20.2
> 250	Rise		21.3

Little change in 5-year mortality in the placebo group.

Thanks to Dave DeMets for this example.

Coronary Drug Project
5-Year Mortality

Example

Baseline Cholesterol	Cholesterol Change	% Deaths	
		Clofibrate	Placebo
< 250mg%*	Fall	16.0	21.2
< 250	Rise	25.5	18.7
≥ 250 mg%	Fall		20.2
> 250 **	Rise		21.3

- In the treatment group
- What if you have "low" cholesterol?
  - Better to go lower.

Coronary Drug Project
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- In the treatment group – good news for ice cream lovers!
- What if you have "low" cholesterol?
  Better to go lower.
- What if you have "high" cholesterol?
  Better to go higher!

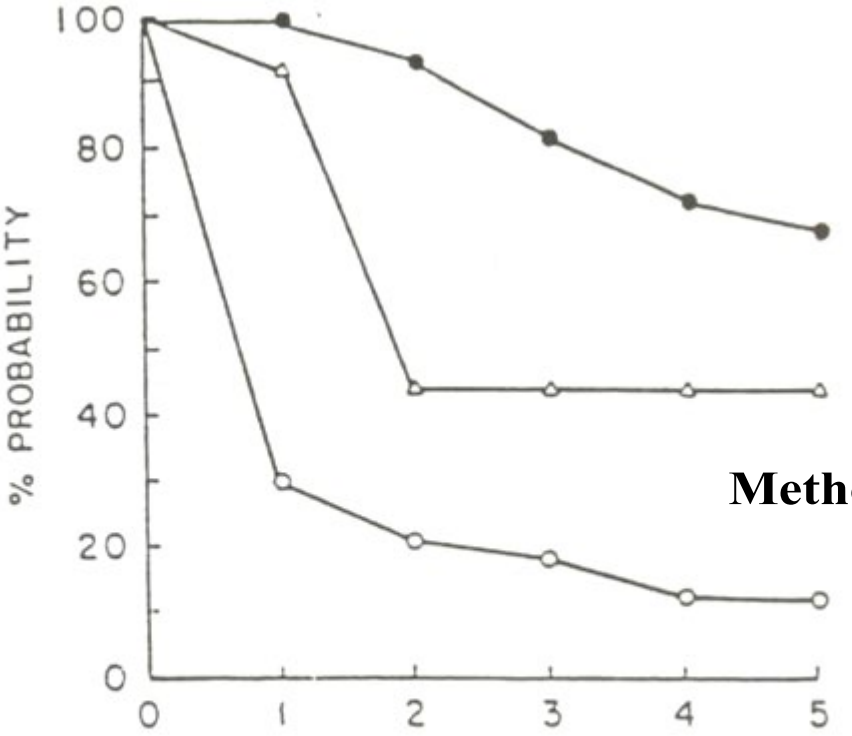
Trialists learned from the CDP…

- Many things, including….
- Not to be seduced by compliance
- Rely on baseline – post-randomization values can be deceptive

Breast Cancer Adjuvant Therapy

Probability of Disease-Free Survival by Years Post Mastectomy (Method I)

Disease Free Survival

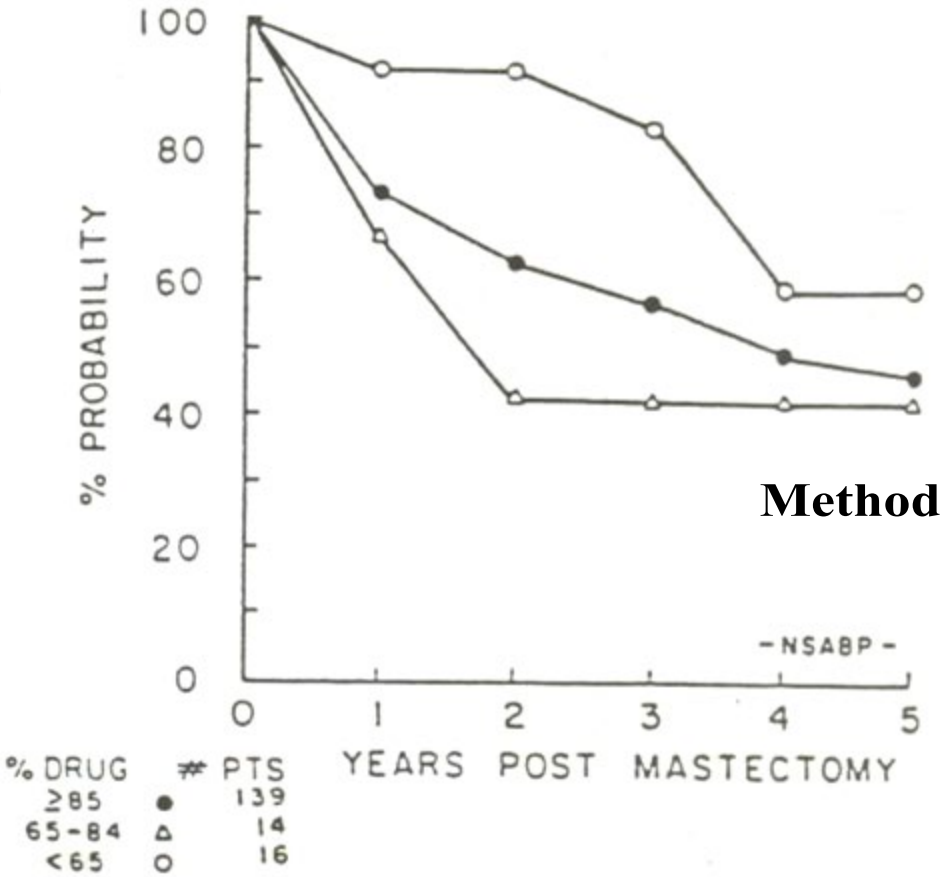


$$\textbf{Method I} = \frac{\textbf{dose received}}{\textbf{total protocol dose}}$$

Breast Cancer Adjuvant Therapy

Probability of Disease-Free Survival for Years Post Mastectomy (Method II)

Disease Free Survival

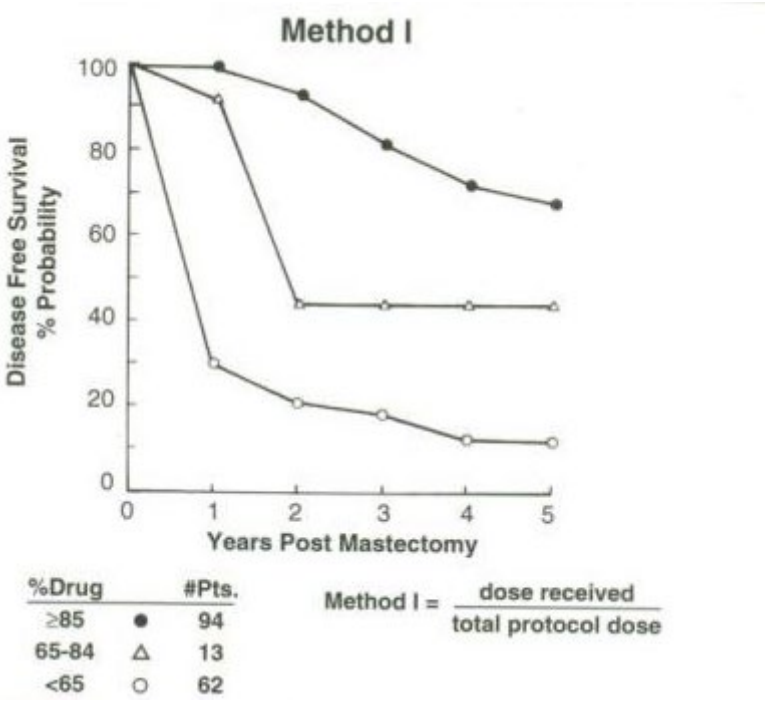


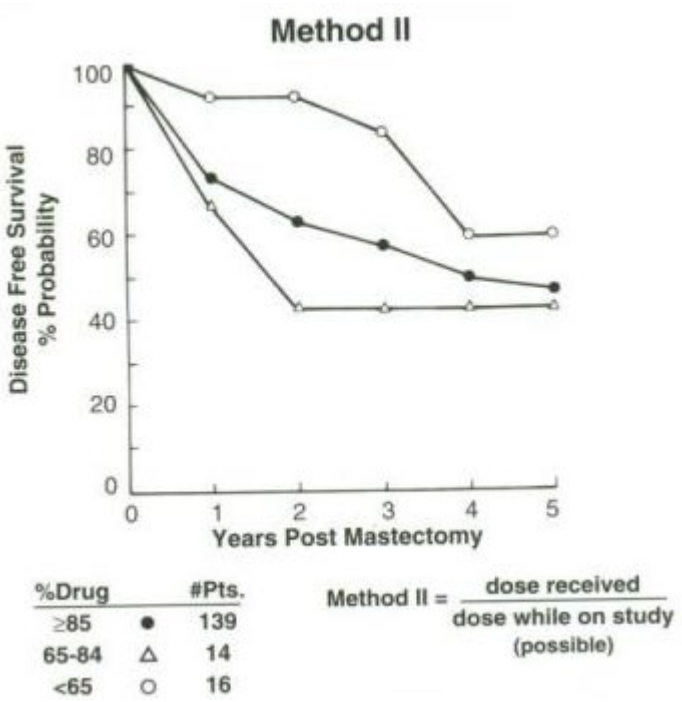
$$\textbf{Method II} = \frac{\textbf{dose received}}{\textbf{dose while on study (possible)}}$$

Breast Cancer Adjuvant Therapy

Probability of Disease-Free Survival by Years Post Mastectomy (N=169)

Not only do the rates change, but so does the order!





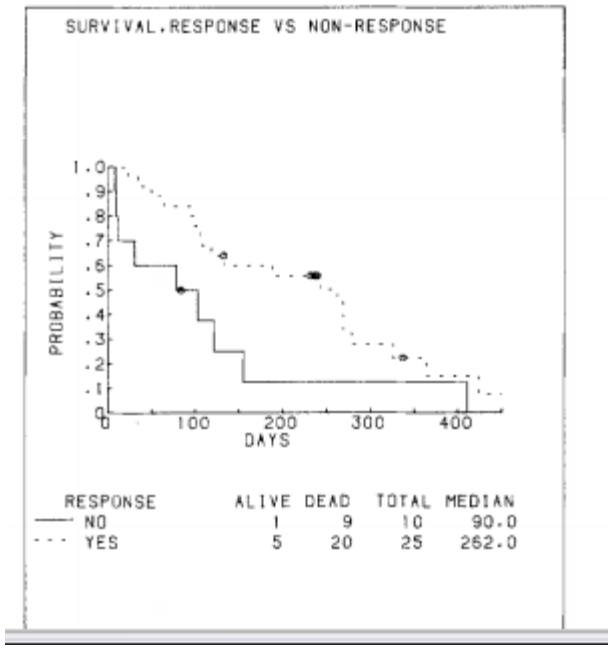
Redmond, Fisher, Wieand (1983) *Cancer Treatment Reports*

Breast Cancer Adjuvant Trial

- **Both previous graphs are for the placebo arm!**
- Lesson
  - Compliance is an outcome
  - Analysis of one outcome, stratified by another, is highly vulnerable to bias

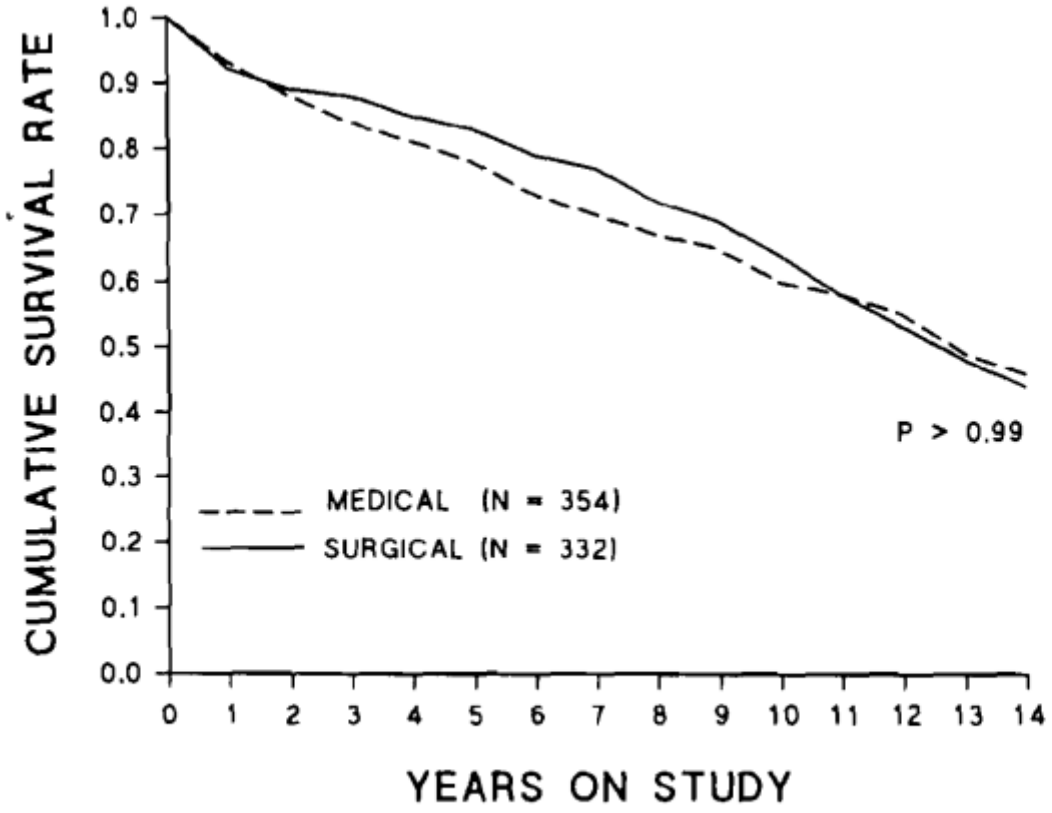
  - (thanks to Dave DeMets for this example)

Examples of non-ITT-responder vs. non-responder



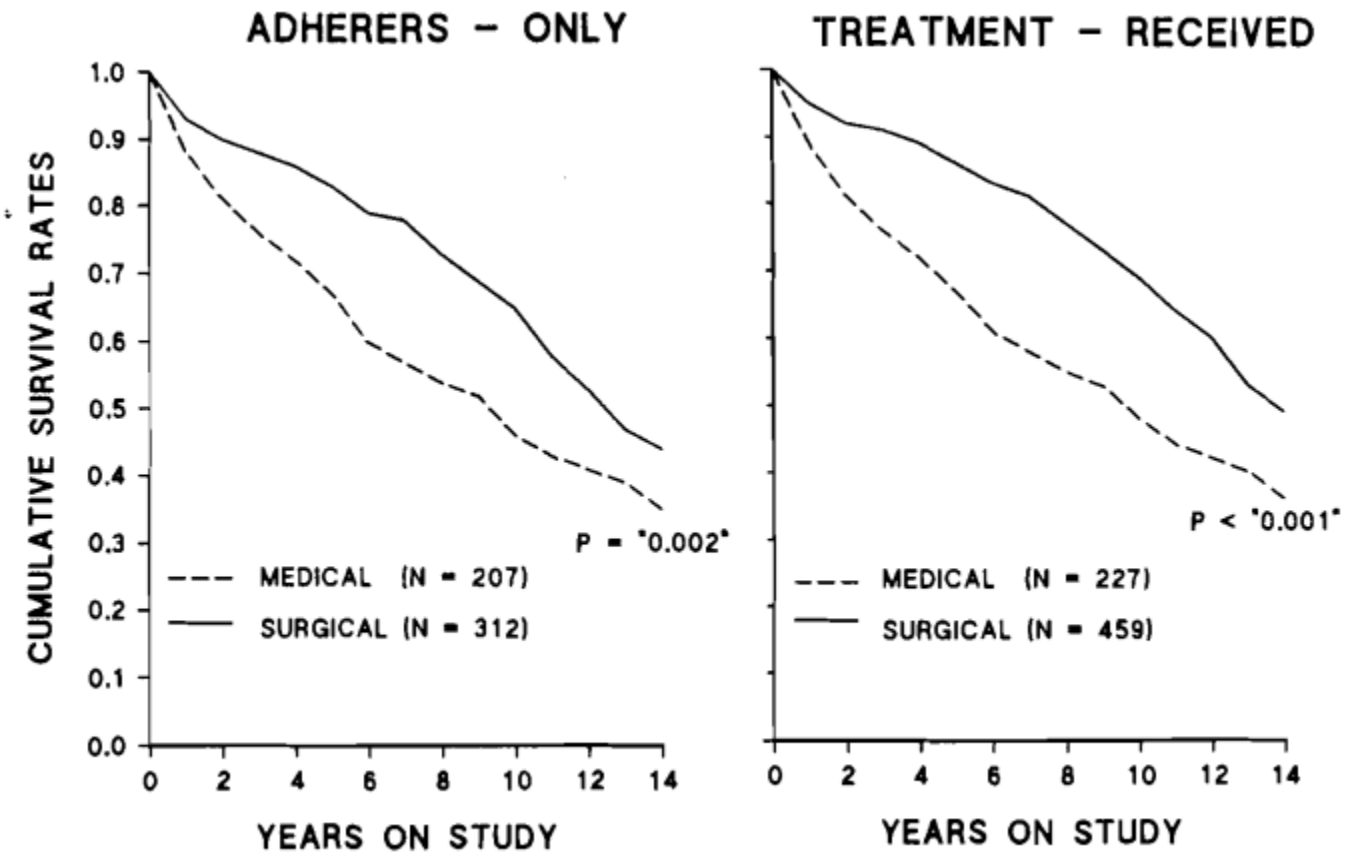
JRAnderson, KC Cain, RD. Gelber (1983). Analysis of Survival by Tumor Response. J Clin Onc 1: 710:719
Simon R, Wittes (1985). Methodologic guidelines for reports of clinical trials. Cancer Treatment Reports 69:1-3

VA trial of bypass surgery: Medical vs. surgical intervention



. Cumulative survival rates from date of randomization by the as-randomized method of analysis

Adherers only and treatment received



'igure 4. Cumulative survival rates from date of randomization by the adherers-only and treatment-received methods of

Peduzzi P, Detre K, Wittes J, Holford T (1991). J Thoracic and Cardiovascular Surgery 101:481-487.
Peduzzi P, Wittes J, Detre K, Holford T (1993). SIM 12:1185-91

Safety analyses

- In analysis of safety, people typically do on-treatment analyses
  - Typical thought – ITT overestimates risk
  - "If I don't take the drug, it can't be causing me harm"

Typical language in protocol or SAP

- "Treatment-emergent adverse events are defined as adverse events that occur after receiving the first dose of study therapy through 30 days after the last dose of study therapy."
- Why don't we count adverse events from time of randomization?
- Why stop at 30 days?

SAVOR-TIMI
Saxagliptin all-cause mortality

FDA briefing book…

Table 22: Sensitivity Analyses for All-cause Mortality Endpoint (mITT-FDA)

	Saxagliptin N=8240	**Placebo** N=8173	**Hazard Ratio*** (95.1% CI)
On-study Deaths	416 (5.1%)	376 (4.6%)	1.10 (0.96, 1.27)

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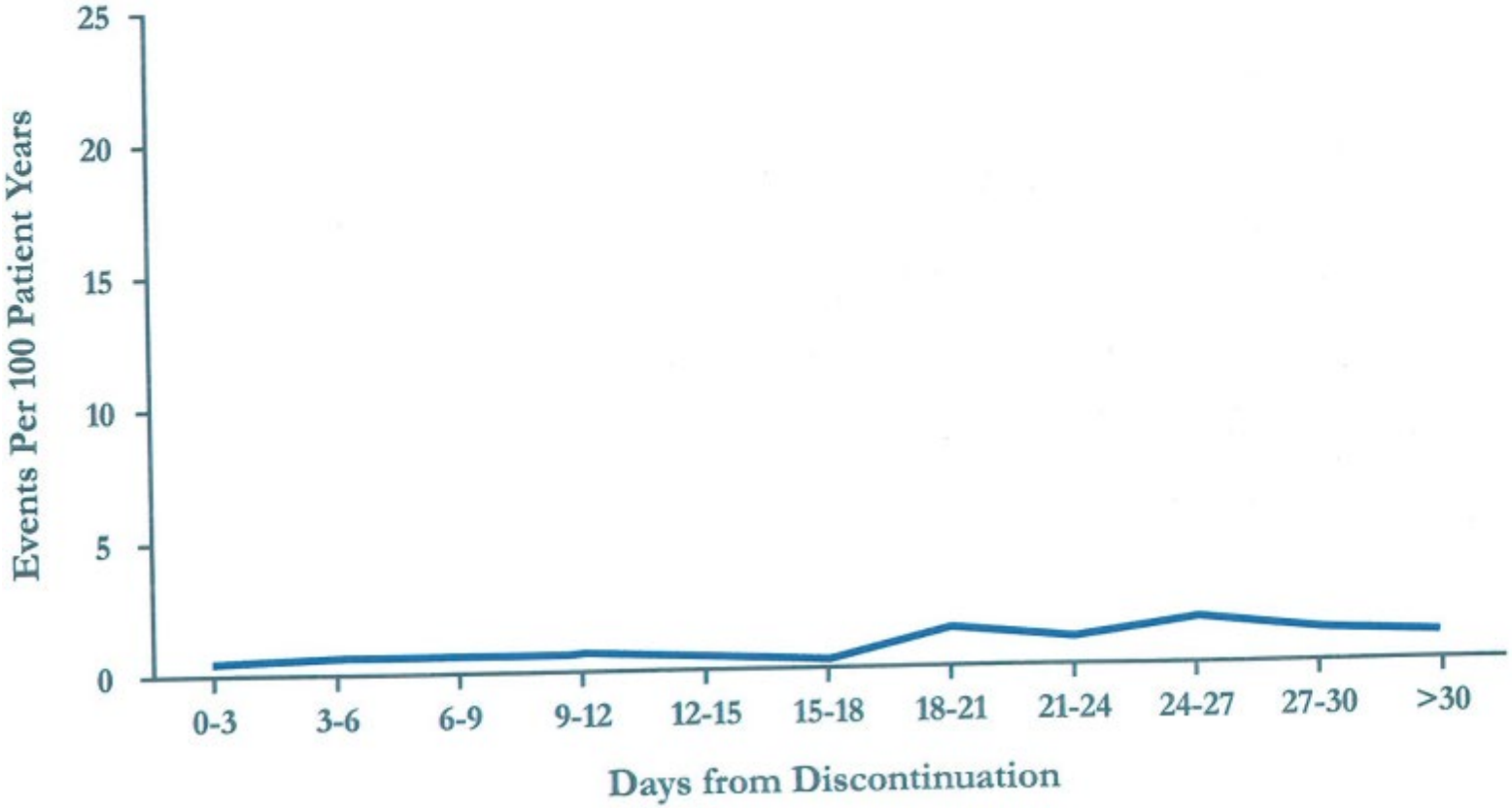
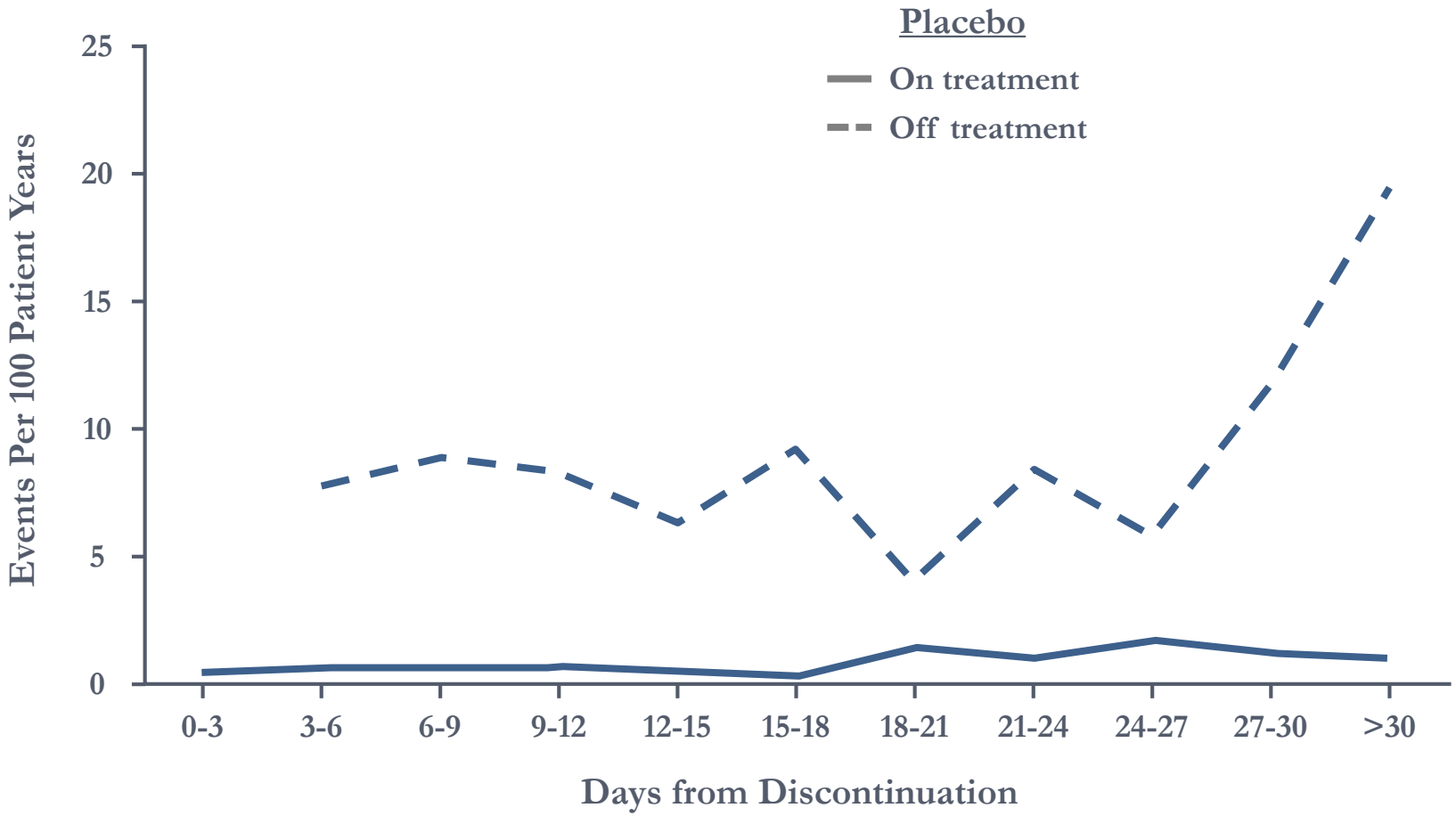
On-treatment† + 30 days Deaths	297 (3.1%)	248 (2.5%)	1.18‡ (0.99, 1.39)
On-treatment† + 7 days Deaths	256 (3.1%)	204 (2.5%)	1.23 (1.02, 1.48)

† Events were censored at last dose + 30/7 days as appropriate.
* All Cox proportional hazards analyses used here to compute hazard ratio are stratified by renal impairment and CV risk categories.

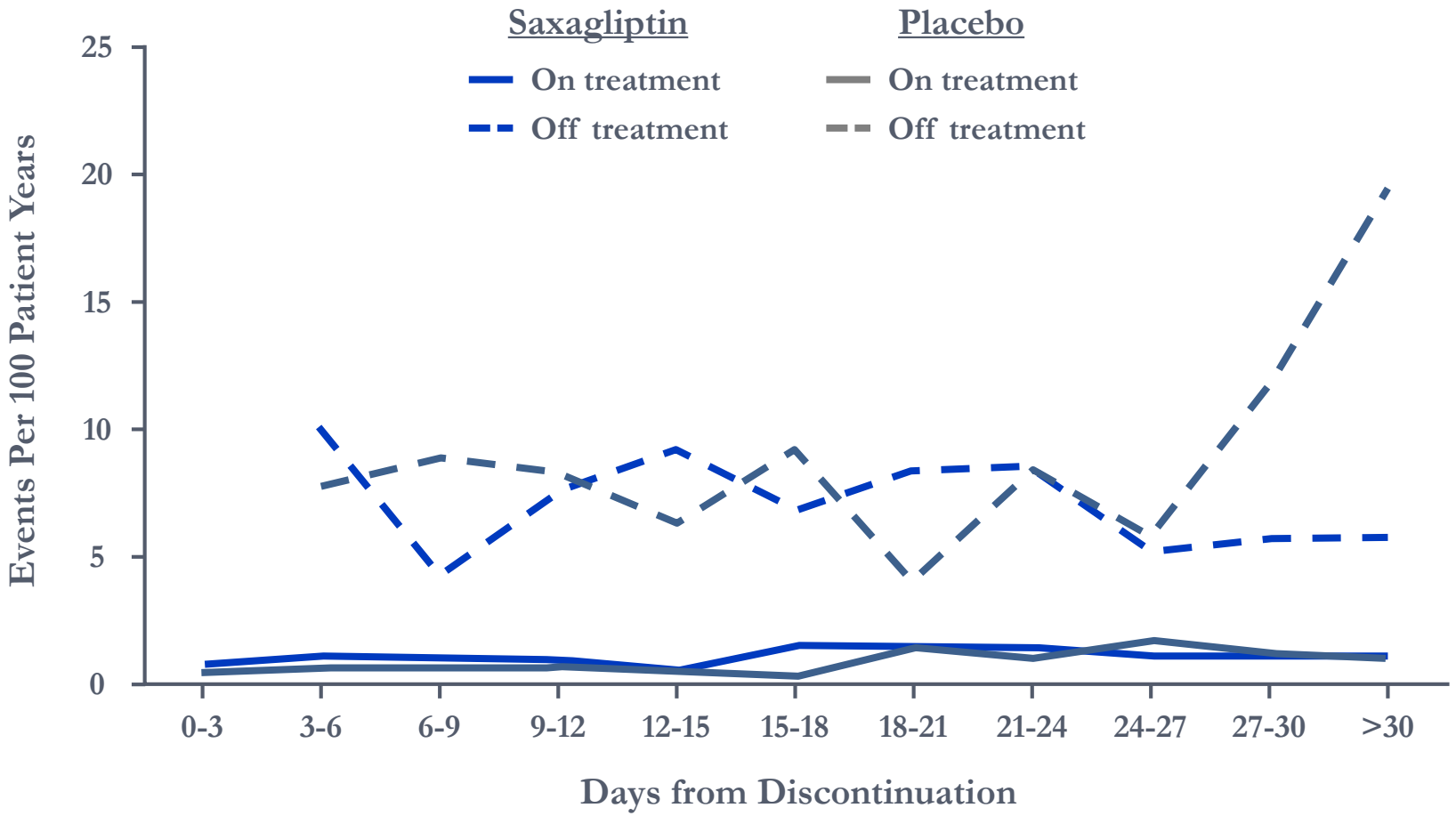
Placebo: Mortality rate on treatment



Placebo: Mortality Higher Rate Off Than On



Saxagliptin: Mortality Higher Rate Off Than On



Suitable moral

- People may be removed from treatment because of illness
- People may have serious event late because of cascade
- So, do intent-to-treat
- But….
  - **In the long run we are all dead – John Maynard Keynes**
  - **Don't do simply binomial events**
  - **Do time-to-event analyses**
  - **Yang Wittes Pitt clinical Trials 2019 16:63-70**

Leftover shadows of biased analyses

- Lesson is not yet truly integrated into many people's thoughts.
- Oncology trials still compare responders to non-responders

And then there is "rescue" therapy

- Many analyses censor at the time of rescue
- But "rescue" is an outcome….
- Remember….
  - "Analysis of one outcome, stratified by another, is highly vulnerable to bias"

Completers and per protocol analyses

- Many still report "completers" analyses as if they are interpretable
- The ICH recommends per protocol analyses (1998)
  - Section 5.2.2 of ICH E9
  - Dealt with in the addendum, but still present
  - If a protocol says, "stop drug if LFT bad," and person stops, that is "per protocol" but often excluded (thanks to Hernan for that insight)
  - Can we think of per protocol using causal analysis?

- Murray EJ, Hernán MA (2016). Getting the most out of randomized clinical trials: A call for better per-protocol effect estimates. Clinical trials 13:372-278
- Murray EJ, Hernán MA (2018). Improved adherence adjustment in the Coronary Drug Project. Trials 19:158

Summary

- Randomization is much more than a "this is the rule" activity
- It forms the fundamental basis for inference
  - For efficacy
  - For safety
  - Don't get seduced by adherence, drop-out, rescue
  - Analyze in a way consistent with the belief that made you randomize!
  - And (if you are thinking of violating that principle, copy Canner and look at the placebo group)

Finally, in case you are not convinced…

- Read Sackett & Gent (1979) *NEJM*, p. 1410
- And think about Dave Sackett's words…

  - '[P]er-protocol' analyses confined to compliant patients are inherently invalid, and I consider them nefarious when carried out by folks who know better." –
    - David Sackett, unfinished manuscript