



Some Other Issues in the Design and Analyses of RCTs

Robert Platt, PhD
Richard Cook, PhD

January 22, 2010

Cluster RCTs - Background

- Clusters (hospitals, schools, regions) are randomized, not individuals.
- Useful when individual randomization not feasible
 - Intervention takes place at group level (e.g. hospital-level intervention)
 - Contamination (treatment of one person affects nearby non-treated subjects)

Intra-Cluster Correlation (ICC)

- The main challenge in cluster RCTs
- Observations within cluster are correlated
 - Patients at the same clinic/hospital may share SES, background treatments, exposures
 - Patients at the same clinic/hospital may undergo similar ancillary treatments/processes.
 - Measurement issues may cluster by site

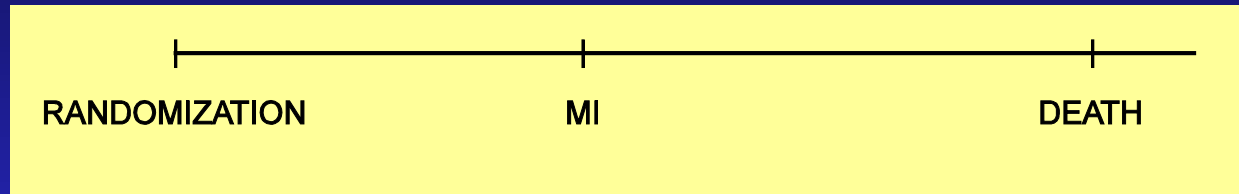
ICC

- What can/should be done?
- ICC affects sample size (higher ICC leads to fewer independent observations)
- If we can estimate ICC before the study, can adjust sample size calculation straightforwardly
- After study is done, can adjust analyses straightforwardly

Time to Event Responses

- With a clear endpoint like death, standard methods of analysis and sample size estimation apply
- Cox regression yields hazard ratio (relative risk) estimate
- Sample size is driven by the number of observed deaths determined by
 - number of patients
 - survival distribution
 - duration of follow-up

Multiple Lifetime Events



- Composite Endpoint: time to first of MI and DEATH
- Interpretation of relative risk?

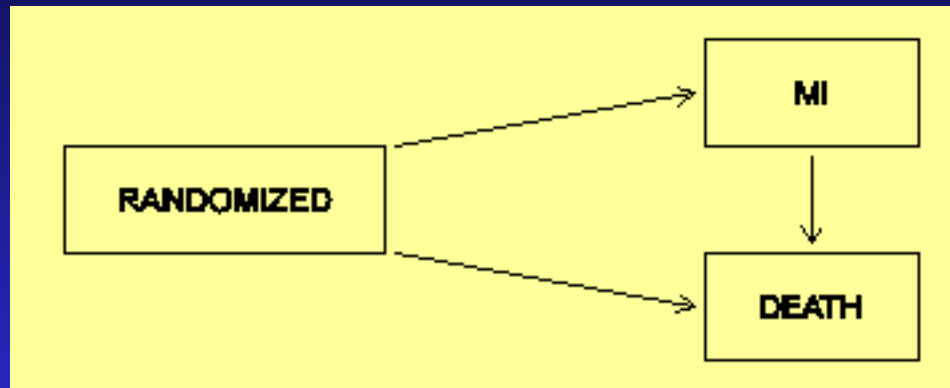
Advantages Attributed to Composite Endpoints (Ferreira-Gonzalez et al., JCE, 2007)

1. Reduces sample size requirement
2. Estimates the net clinical benefit of a therapy
3. Improves understanding the effect of the interventions avoiding competing risks
4. Avoids the need to choose a single primary endpoint when many may be of equal importance
5. Avoids adjustment for multiple comparisons

Disadvantages Attributed to Composite Endpoints (Ferreira-Gonzalez et al., JCE, 2007)

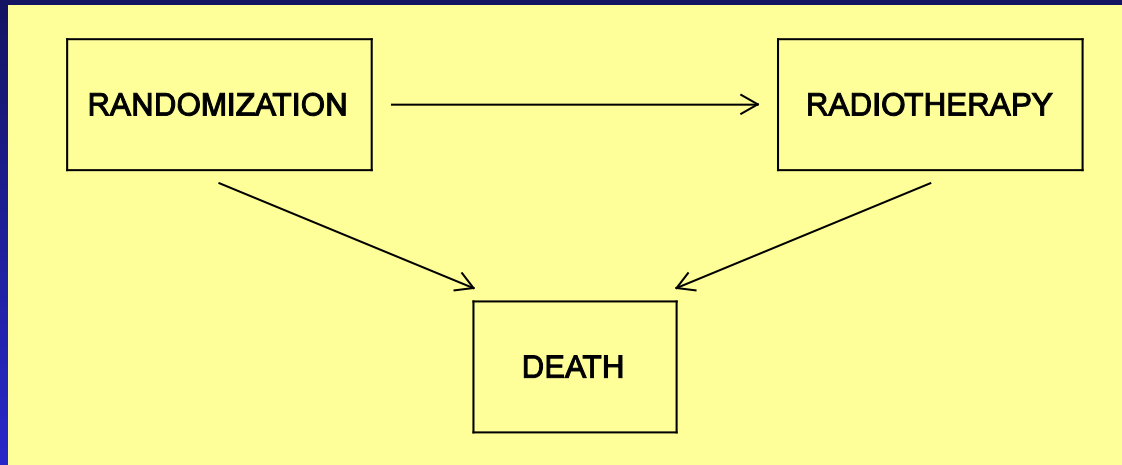
1. Practical interpretation could be problematic when component endpoints are dissimilar in patient importance
2. Interpretation can be problematic if either the event rates or relative risk reduction vary appreciably across components
3. Potential masking of an increase in a harmful effect associated with an experimental intervention
4. Possibility of biases secondary to competing risk
5. The larger the number of components the more the work to accurately ascertain the composite
6. Excessive influence of the more subjective (clinician-driven) component outcomes
7. Alpha error must be adjusted to draw confirmatory conclusions about the components

Competing Risk Analysis



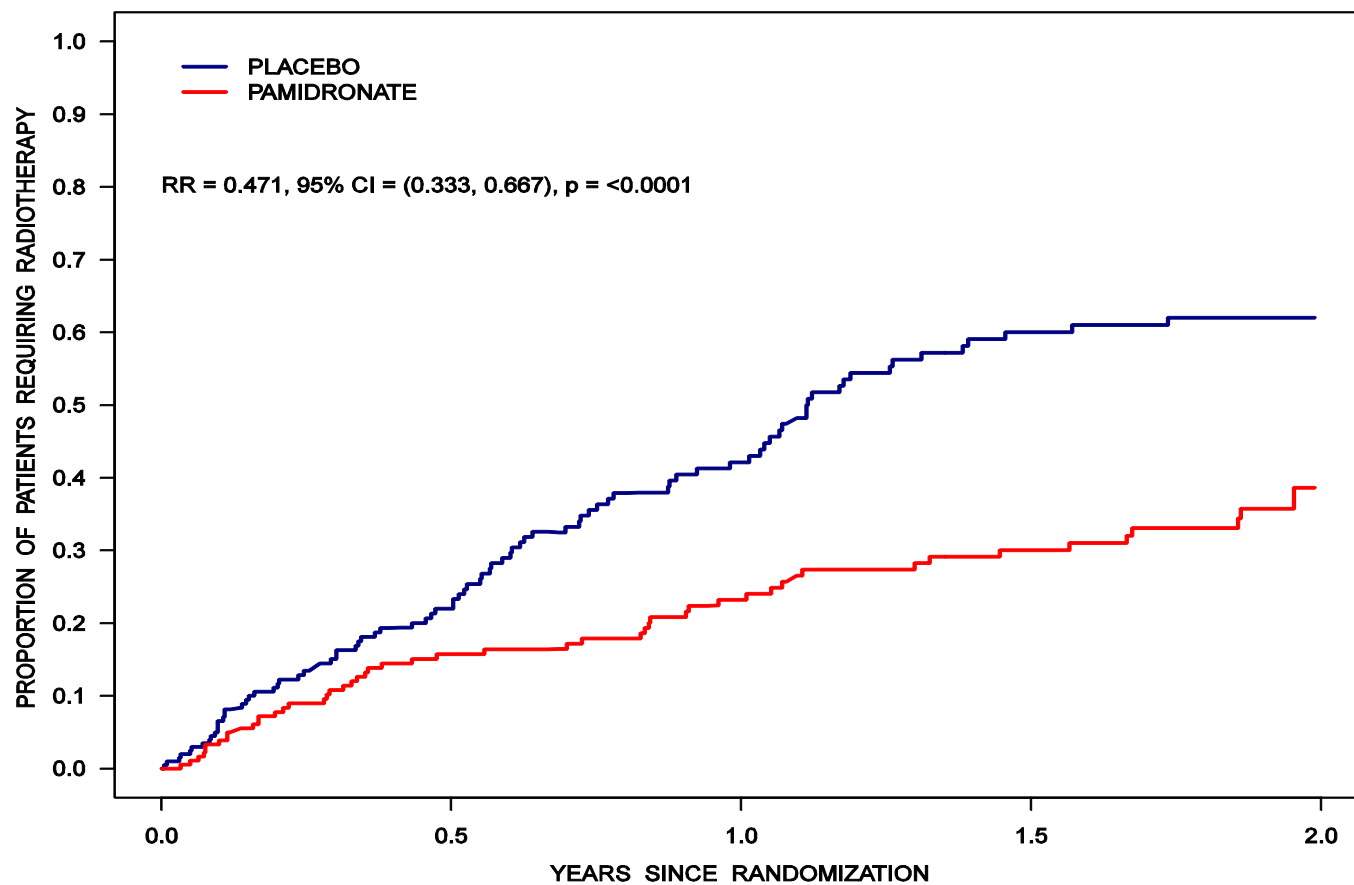
- There is nothing problematic with competing risk analyses!
- For estimation of the cause-specific relative risk of MI we censor people at death
- Alternatives to Kaplan-Meier estimates can be used for incidence

An Example from Oncology

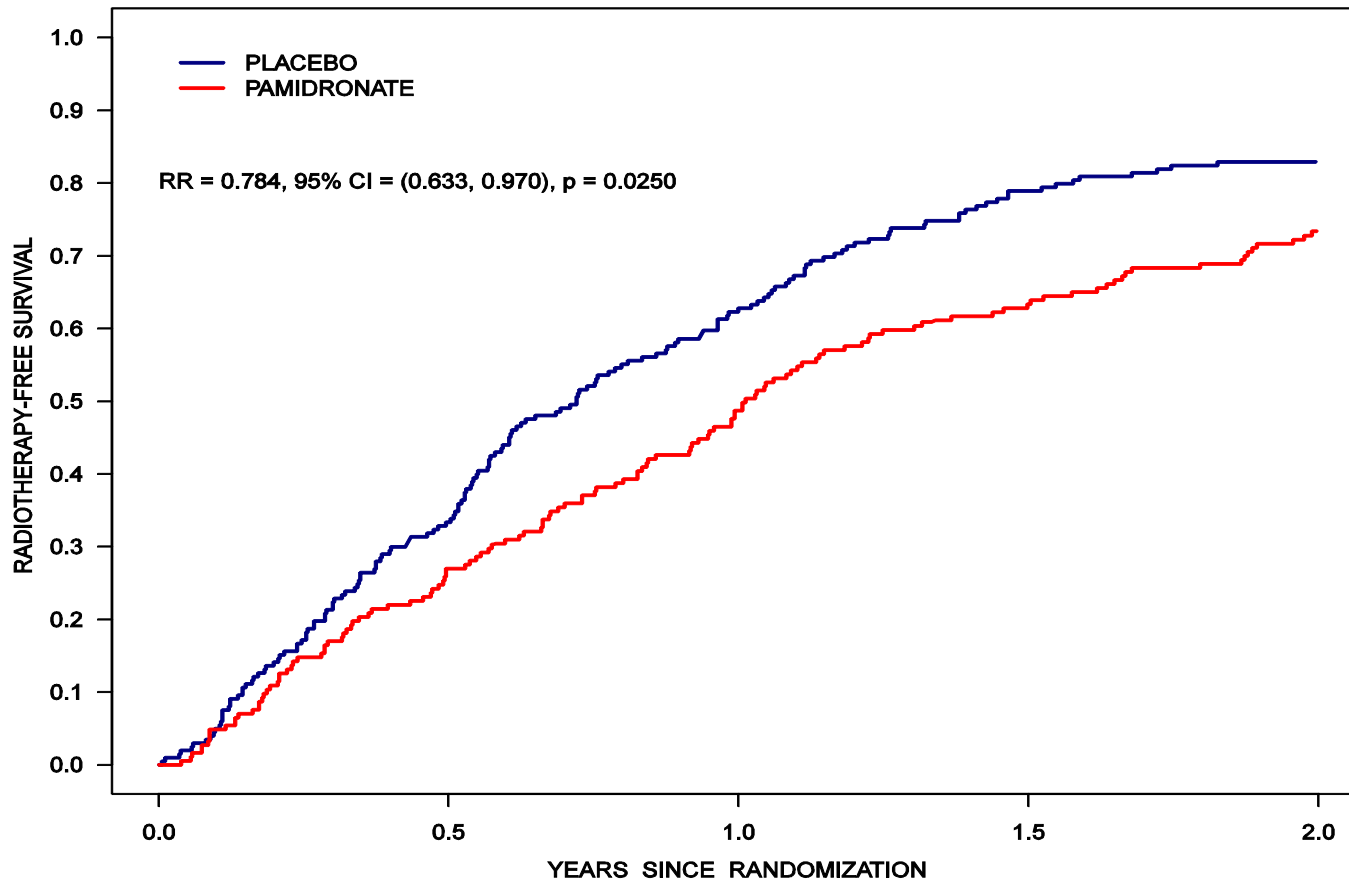


- Patients with cancer metastatic to bone
- Trial of palliative therapy to reduce bone pain requiring radiotherapy
- We do not expect effect of treatment or survival
 - Time to first radiotherapy
 - Radiotherapy-free survival

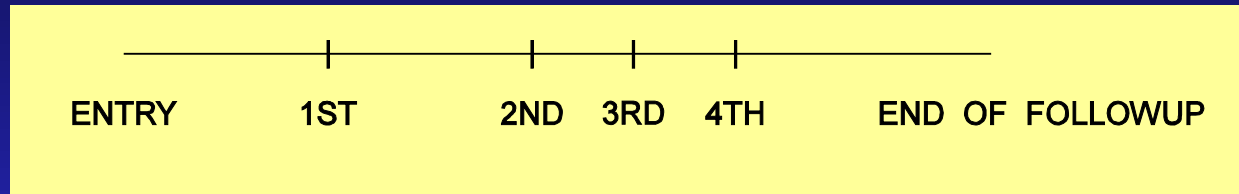
Competing Risk Analysis



Event-Free Survival Analysis



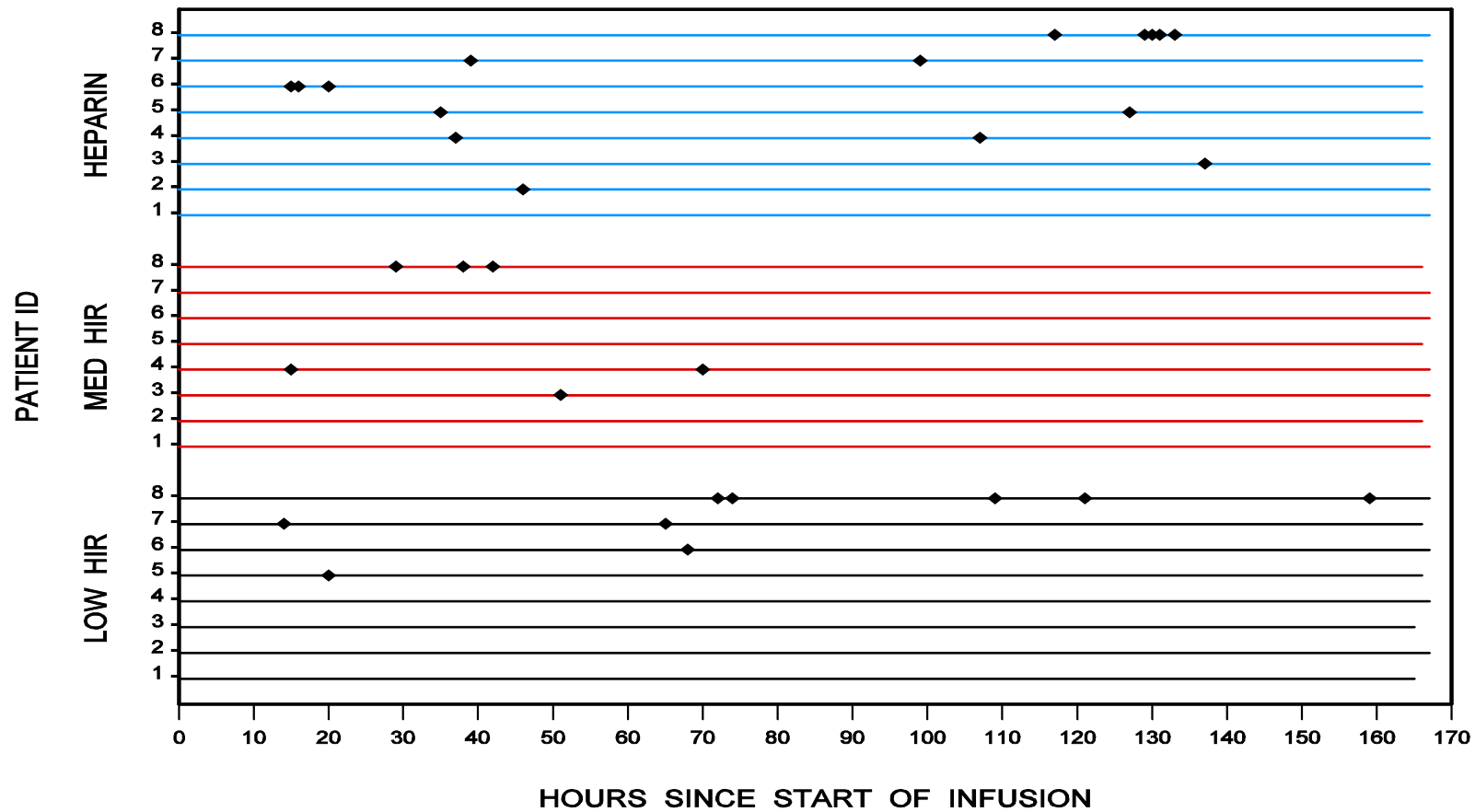
Recurrent Event Analyses



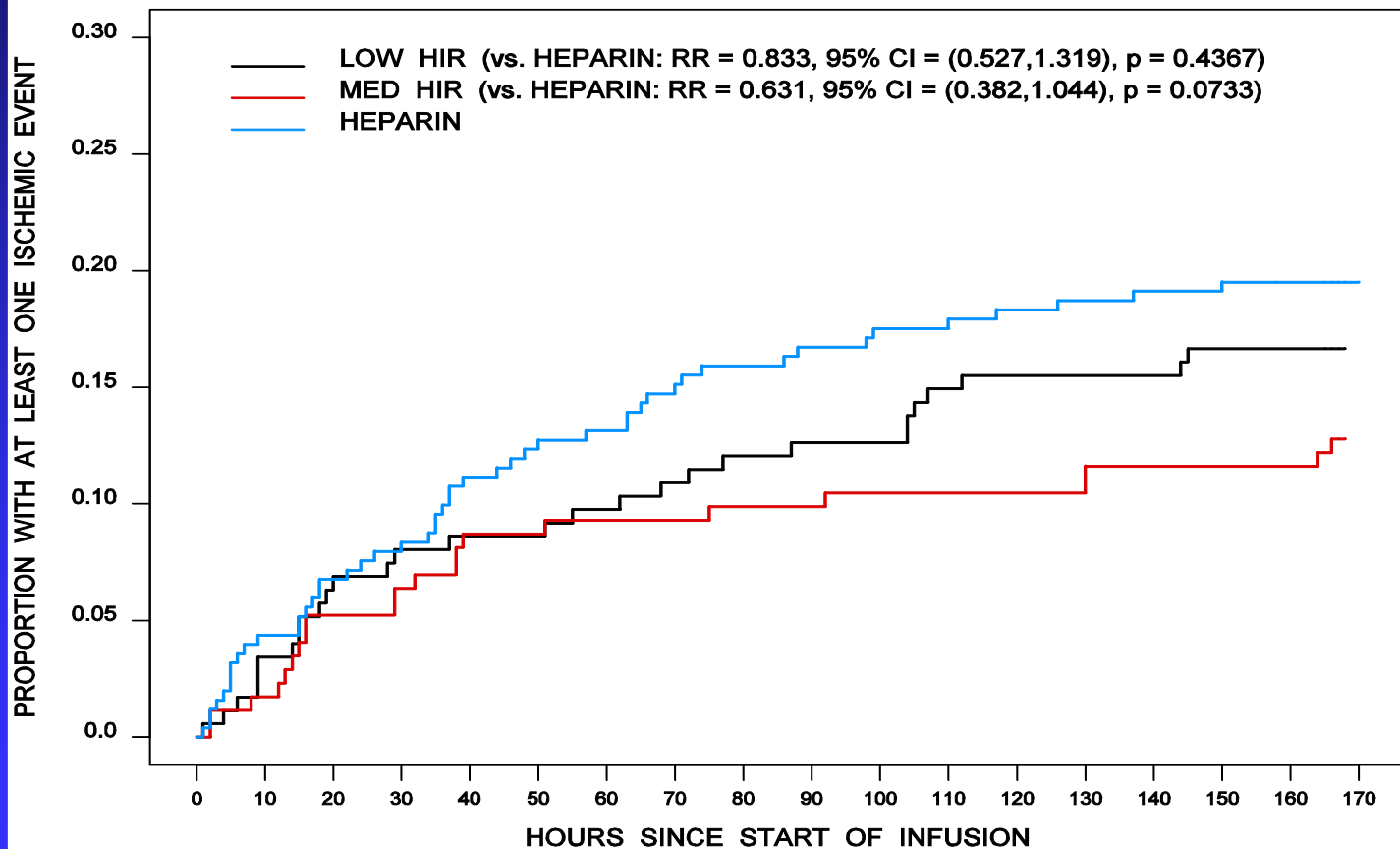
Frequently events are transient and recur over time

- episodes of arrhythmia
- TIAs
- repeated hospitalizations

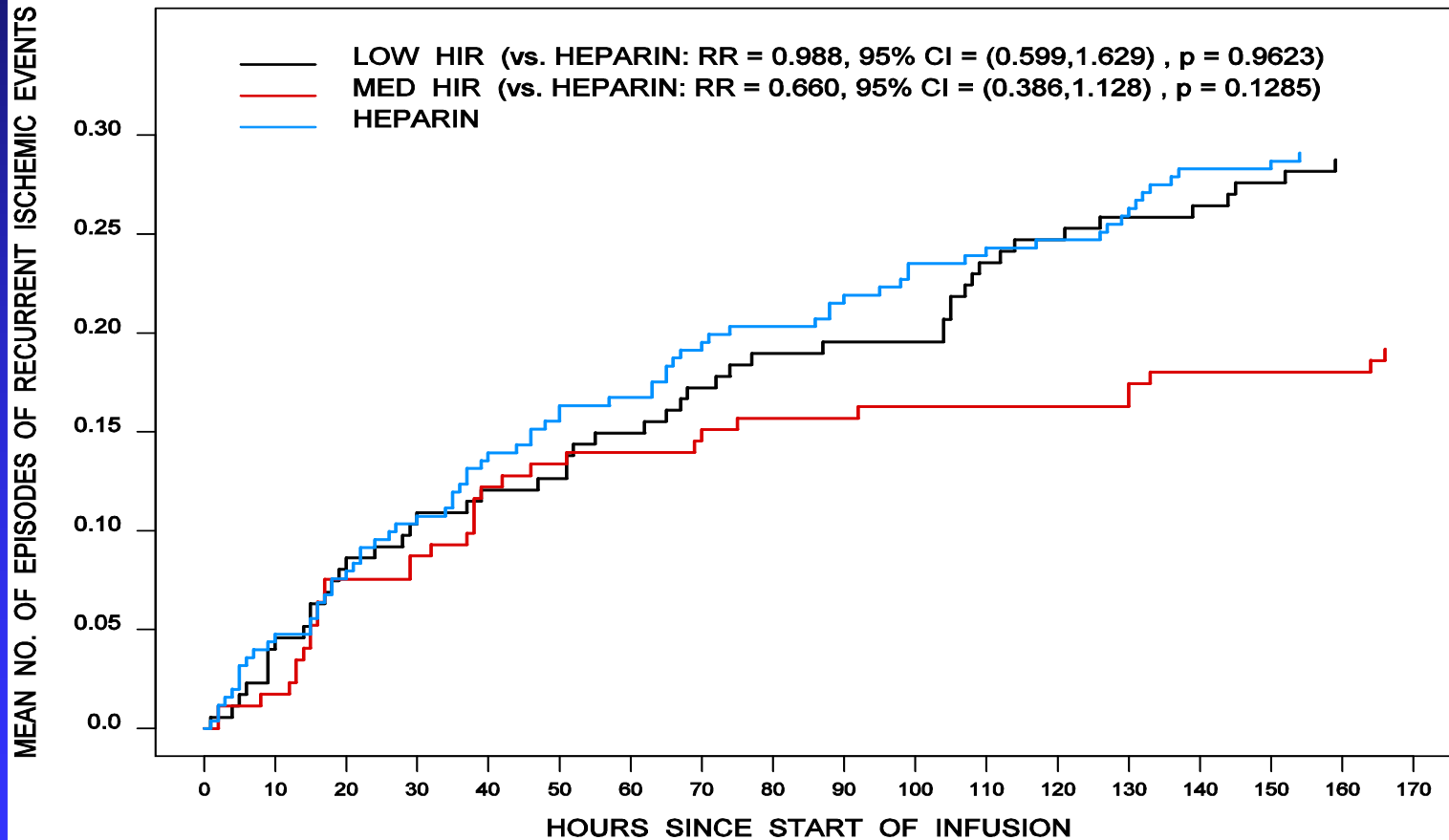
Sample Timeline for OASIS Pilot Study (Circulation, 1997)



Kaplan-Meier for Time to First Event



Recurrent Events Analysis



When should we consider Recurrent Event Analyses

- When interest lies in a measure of overall disease burden or cost
- When counts of events are meaningful
- When cost effectiveness analyses are of interests and events incur costs

Selected References on Composite Endpoints

Bethel MA et al. (2008) Determining the most appropriate components for a composite clinical trial outcome. *American Heart Journal* 156 (4): 633-640

Buzney EA, Kimball AB. (2008) A critical assessment of composite and coprimary endpoints: a complex problem. *J Am Acad Dermatol* 59:890-896.

Braunwald E, Cannon CP, McCabe CH, (1992) An approach to evaluating thrombolytic therapy in acute myocardial infarction. The 'unsatisfactory outcome' end point. *Circulation* 86:683-687.

Cannon CP (1997) Clinical perspectives on the use of composite endpoints. *Controlled clinical trials* 18:517-529.

Chi GYH (2005) Some issues with composite endpoints in clinical trials. *Fundamental & Clinical Pharmacology* 19:609-619.

Ferreira-Gonzalez et al. (2007) Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. *BMJ* doi:10.1136

Ferreira-Gonzalez I, Permanyer-Miralda G, Busse JW, Bryant DM, Montori VM, Alonso-Coello P, et al. (2007) Methodologic discussions for using and interpreting composite endpoints are limited, but still identify major concerns. *J Clin Epidemiol* 60:651e7.

Ferreira-Gonzalez et al. (2007) Composite endpoints in clinical trials: the trees and the forest. *J Clin Epidemiol* 60:660-661.

Ferreira-Gonzalez et al. (2008) Composite endpoints in clinical trials. *Rev Esp Cardiol* 61(3):283-90.

Freemantle N et al. (2003) Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA Vol 289. No.19 2545-2575.t

Freemantle N, Calvert M. (2007) Weighing the pros and cons for composite outcomes in clinical trials. Journal of Clinical Epidemiology 60:658-659

Hallstrom AP, Litwin PE, Weaver WD (1992) A method of assigning scores to the components of composite outcome: an example from the MITI trial. Controlled Clinical Trials 13:148-155.

Lim Eet al. (2008) Composite outcomes in cardiovascular research: a survey of randomized trials. Ann of Intern Med 149:612-617.

Montori VM, et al., (2005) Validity of composite end points in clinical trials. BMJ Vol 330 2005.

Neaton JD, Gray G, Zuckerman BD, Konstam M, (2005) Key issues in end point selection for heart failure trials: composite end points. Journal of Cardiac Failure Vol.11 No. 8 2005.RTG