Analysing recurrent events: a review of statistical methodology and future directions, with application to major trials in heart failure

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Outline

**Motivation**
Conventional analyses
Examples

**Analysis of Recurrent Events**
Standard Methods
Results

**Analysis of Recurrent Events II**
But what about Informative Censoring...
Results
Motivation

Conventional analyses
Composite Endpoints

- Include two or more types of related clinical events
- Increase event rate and avoid multiplicity
- Examples in cardiovascular trials:
  - CV death, MI and stroke in hypertension trials
  - CV death and HF hospitalisation in heart failure trials
What is wrong with Composite Endpoints?

Only first hospitalisation is analysed, repeats are ignored

- Heart failure characterised by repeat hospitalisations
- Distressing for patients and caregivers
- Major driver of enormous cost
- Analysing all hospitalisations evaluates the effect of treatment on true burden of disease
Motivation

Examples
EMPHASIS-HF (Zannad et al NEJM 2011)

- Compared eplerenone vs. placebo in 2737 patients with mild HF
- Primary endpoint composite of HF hospitalisation and CV death

<table>
<thead>
<tr>
<th>HF Hospitalisations</th>
<th>Eplerenone (N=1364)</th>
<th>Placebo (N=1373)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 Admissions</td>
<td>186</td>
<td>277</td>
</tr>
<tr>
<td>≥ 2 Admissions</td>
<td>67</td>
<td>110</td>
</tr>
<tr>
<td>All admissions</td>
<td>312</td>
<td>481</td>
</tr>
<tr>
<td>‘Unused’ admissions</td>
<td>126</td>
<td>204</td>
</tr>
</tbody>
</table>
CHARM-Preserved (Yusuf et al The Lancet 2003)

- Component arm of CHARM, EF ≥ 40% trial
- Compared candesartan vs. placebo in 3021 patients
- Primary endpoint composite of HF hospitalisation and CV death

<table>
<thead>
<tr>
<th>HF Hospitalisations</th>
<th>Candesartan (N=1513)</th>
<th>Placebo (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 Admissions</td>
<td>229</td>
<td>278</td>
</tr>
<tr>
<td>≥ 2 Admissions</td>
<td>94</td>
<td>114</td>
</tr>
<tr>
<td>All admissions</td>
<td>390</td>
<td>547</td>
</tr>
<tr>
<td>‘Unused’ admissions</td>
<td>161</td>
<td>269</td>
</tr>
</tbody>
</table>
Analysis of Recurrent Events

Standard Methods
Poisson

- Commonly used for event rates
- Simple: total number of events divided by total follow-up in each group
- Gives a rate ratio for recurrent events
- Assumes that all events are independent
Andersen-Gill

- Extension of Cox proportional-hazards model
- Analyses gap times
- Each gap time contributes to the likelihood
- Gives a hazard ratio for recurrent events
- Assumes that events are independent
- Robust standard errors accommodates heterogeneity
Negative Binomial

- Events within an individual related - naturally accommodated by NB
- Each individual has their own individual Poisson hospitalisation rate
- Poisson rates vary according to Gamma
- Straightforward to implement
- Does not require complex data files
Analysis of Recurrent Events

Results
<table>
<thead>
<tr>
<th>Model</th>
<th>Estimate</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>0.69</td>
<td>(0.59, 0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poisson</td>
<td>0.63</td>
<td>(0.55, 0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Negative binomial</td>
<td>0.53</td>
<td>(0.42, 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Estimate</td>
<td>95% CI</td>
<td>p-value</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>Adjudicated composite</td>
<td>0.89</td>
<td>(0.77,1.03)</td>
<td>0.118</td>
</tr>
<tr>
<td>Unadjudicated composite</td>
<td>0.86</td>
<td>(0.74,1.00)</td>
<td>0.050</td>
</tr>
<tr>
<td>Poisson</td>
<td>0.71</td>
<td>(0.62,0.81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Negative binomial</td>
<td>0.68</td>
<td>(0.54,0.85)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Andersen-Gill</td>
<td>0.71</td>
<td>(0.57,0.88)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Bootstrap Simulation of Power

Sample Size

Statistical Power

- Negative Binomial for HFH
- Unadjudicated Composite
- Adjudicated Composite
Analysis of Recurrent Events II

But what about Informative Censoring...
Incorporating Time to CV Death

- Increase in HF hospitalisations $\Rightarrow$ increased risk of death
- Censoring due to CV death not independent
- Comparison of hospitalisation rates confounded

Informative censoring must be incorporated into analysis
Composite of Repeat HFHs and CV Death

Treat CV death as an additional event

- CV death treated in same way as a HF hospitalisation
- Andersen-Gill, Poisson, negative binomial
- Rate ratio for composite of HF hospitalisation and CV death
- Death that occurs during HF hospitalisation treated as single event
Joint Frailty Model

Joint modelling strategies simultaneously analyse event rates and death

- Each patient has their own independent frailty term $\nu_i$
- Proportionately affects heart failure hospitalisation rate $Y_i$ and time to death $T_i$
- Integrate out random effects to jointly model $Y$ and $T$

$$f_{Y,T}(y_i, t_i) = \int f_{Y|\nu}(y_i | \nu_i) f_{T|\nu}(t_i | \nu_i) f_{\nu}(\nu_i) d\nu_i$$
Poisson Parameterisation

- Poisson distribution for heart failure hospitalisations, with random effect
- Exponential distribution for time to death, with random effect
- Gamma distribution for random effect, so that:
  - Unconditional distribution for $Y_i$ is Negative Binomial
  - Unconditional distribution for $T_i$ is Lomax

Random effects proportionally affects hospitalisation rate and time to death in same way
Analysis of Recurrent Events II

Results
Composite of Recurrent HFHs and CV Death

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</tr>
</thead>
<tbody>
<tr>
<td>Poisson</td>
<td>0.78</td>
<td>(0.69, 0.87)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Negative binomial</td>
<td>0.75</td>
<td>(0.62, 0.91)</td>
<td>0.003</td>
</tr>
<tr>
<td>Andersen-Gill</td>
<td>0.78</td>
<td>(0.65, 0.93)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Note that there were 170 CV deaths in each group.
Joint Frailty Model

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<th>Estimate</th>
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<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate ratio</td>
<td>0.69</td>
<td>(0.55, 0.85)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.96</td>
<td>(0.73, 1.26)</td>
<td>0.769</td>
</tr>
</tbody>
</table>

Marginal analysis of CV death: 0.99 (95% CI 0.80-1.22, p=0.918)
Summary

- Composite endpoints are frequently used in clinical trials
- Recurrent events within individuals are ignored
- Uncertainty as to how to do this statistically
- LWYY, WLW

- Increase in HF hospitalisations associated with an increased risk of death
- Joint modelling strategies account for competing risk of death
Summary

- **CHAMPION (Wireless Implantable Haemodynamic Monitoring system)**
  - Rate of HF hospitalisations in 6 months - NB
  - Rate of HF hospitalisations - A-G

- **PARAGON-HF (Valsartan)**
  - Cumulative number of HF hospitalisations and CV death

- **COAPT (MitraClip)**
  - HF hospitalisations
References

