Some Approaches for the Estimation of Censored Patient Reported Outcomes: Results Using the Kansas City Cardiomyopathy Questionnaire

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Kráľ P.[1], Ratitch B.[2], O'Kelly M.[3], Niklasson A.[4]
[1]IQVIA, Slovakia, [2]Eli Lilly, Canada, [3]IQVIA, Ireland, [4]AstraZeneca, Sweden

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Introduction

- Patient reported outcomes (PRO) are important in evaluating symptoms and impacts such as health related quality of life (HRQoL)
- It is not straightforward to estimate treatment effects for PROs where an event censors the measure of the effect of interest. The censoring often stems from an event such as death which makes further trial data collection impossible, but may also be related to treatment and/or outcome of interest and needs to be accounted for in the analysis
- There exists a variety of methods to handle this censoring problem quantitatively. In the project we focus on standard repeated measures approach, quantile regression and principal stratum approach
- The objective of this project was to explore, using real trial data obtained from the National Institutes of Health (NIH) with Western Institutional Review Board (WIRB) waiver, how estimates of the treatment effect can vary, depending on how censoring is taken into account, using a selection of the methods available (see Poster by O'Kelly et al. for a fuller review of methods)

Methodology

- We used data from two heart failure studies whose data are available from the NIH: TOPCAT (NCT00094302) and HF-ACTION (NCT00047437) (Table 1)
- In these studies the Kansas City Cardiomyopathy Questionnaire (KCCQ) PRO was collected
- The event of death was accounted for by:
  a) The standard repeated measures approach – standard ANCOVA in observed survivors
  b) A death="worst score" approach analysed via nonparametric ANCOVA and quantile regression
  c) A principal stratum approach, which identifies a "stratum" of subjects who would be expected to survive to the end of the study irrespective of treatment group assigned

Table: 1 Key study attributes of TOPCAT and HF-ACTION

	HF-ACTION	TOPCAT
Countries	United States, Canada, France	United States, Canada, Brazil, Argentina*
Study end year	2007	2012
# subjects	2,331	1,767
Ejection fraction status	HFrEF	HFpEF
KCCQ time points after baseline	Every 3 months for 12 months, and annually thereafter for up to 4 years	At 4 months, 12 months, and then annually until final study visit
Percent deaths at 12 months	Exercise group: 3.9% Standard therapy group: 5.1%	Spironolactone: 4.3% Placebo: 5.3%
Percent deaths at 36 months	Exercise group: 13.6% Standard therapy group: 14.4%	Spironolactone: 13.8% Placebo: 16.6%

*Russia and Georgia excluded (see Pokharel(2017))

Results

For both studies, differences in survival rates between the treatment groups were relatively small; nevertheless, the pattern of results was helpful in understanding the interplay of death vs. health related quality of life in the studies. For TOPCAT (N=1,767), where the estimate of hazard of death was lower for the experimental treatment group in the period analysed, the estimate of effect on change from baseline (CFB) in KCCQ was estimated to be slightly higher in the principal stratum of survivors, than in the equivalent "naïve" observed survivor population (4.3 vs. 3.7). For the HF-ACTION study (N=2,331), the survivors stratum was also estimated to have higher CFB "(1.2 vs. 1.09 at Month 24 and 3.6 vs. 3.5 at Month 36) where the separation of the survival estimates (not shown) was slightly larger.

Table 2: TOPCAT (Change from baseline in KCCQ, KCCQ scores are transformed to a range of 0-100, higher scores reflect better health status)

	Month 4 Survivors: n1=789, n2=769		Month 12 Survivors: n1=705, n2=683		Month 24 Survivors: n1=544, n2=520		Month 36 Survivors: n1=357, n2=334	
Method	**Pvalue**	**Estimate (95% CI)**	**Pvalue**	**Estimate (95% CI)**	**P-value**	**Estimate (95% CI)**	**P-value**	**Estimate (95% CI)**
Nonparametric ANCOVA/Quantile regression	0.0001	2.99 (1.03,4.945)	0.0088	3.28 (0.86,5.707)	0.0795	2.75 (-0.67,6.172)	0.0289	5.35 (0.37,10.325)
Standard repeated measures approach	<.0001	3.98 (2.127, 5.836)	0.0235	2.41 (0.325, 4.495)	0.3149	1.23 (-1.175, 3.644)	0.018	3.71 (0.638, 6.784)
Principal stratum	<.0001	3.96 (2.068,5.85)	0.0204	2.59 (0.402,4.784)	0.2769	1.49 (-1.197,4.18)	0.0201	4.25 (0.665,7.827)

Table 3: HF-ACTION (Change from baseline in KCCQ, KCCQ scores are transformed to a range of 0-100, higher scores reflect better health status)

	Month 3 Survivors: n1=781, n2=748		Month 12 Survivors: n1=681, n2=671		Month 24 Survivors: n1=492, n2=495		Month 36 Survivors: n1=273, n2=285	
Method	**P value**	**Estimate (95% CI)**	**P value**	**Estimate (95% CI)**	**P-value**	**Estimate (95% CI)**	**P-value**	**Estimate (95% CI)**
Quantile regression	0.0006	2.35 (1.02,3.676)	0.0027	2.11 (0.6,3.624)	0.043	1.76 (-0.57,4.089)	0.0698	7.29 (1.93,12.649)
Standard repeated measures approach	0.015	1.78 (0.346, 3.208)	0.0065	2.37 (0.662, 4.069)	0.3126	1.09 (-1.032, 3.221)	0.0212	3.54 (0.53, 6.544)
Principal stratum	0.0188	1.75 (0.289,3.208)	0.01	2.34 (0.56,4.118)	0.3256	1.2 (-1.189,3.582)	0.0502	3.63 (-0.004,7.26)

Discussion

- **It is challenging to obtain a universally acceptable estimate of treatment effect when the primary objective is to assess changes in PROs but censoring occurs**
- **Each method has limitations and advantages regarding their implementation, with regard to the range of hypotheses which could be tested, scale of the estimates, interpretation of the results etc. (see Poster by O'Kelly et al.)**
  - **Quantile regression: Combines treatment effect on HRQoL and survival, may be difficult to interpret**
  - **Principal stratum: Difficult to model stratum membership**
  - **Standard approach: May be misleading if treatment affects survival**
- **The results presented indicate that whatever the approach is chosen, it is helpful a) to provide more than one estimate and thus allow readers of the study report to get a more complete picture regarding the interplay of benefit and risk for subjects; and b) to provide a clear and full definition of the estimand associated with each estimate of treatment effect**

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