Meta-regression to estimate treatment effects in cost-effectiveness models:

aldosterone blockers in recent myocardial infarction complicated by heart failure

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Background

- Aldosterone blockers in conjunction with other neurohormonal modulators are recommended for use in heart failure (HF) and acute myocardial infarction (MI) in patients with left ventricular dysfunction (including heart failure and post-MI).

- A recent synthesis [Ezekowitz and McAlister, 2008] of individual trials confirmed that aldosterone blockade improves patient prognosis, demonstrating a 20% reduction in all-cause mortality.

- This analysis did not address differences between treatments.

Background

- Existing trials are clinically heterogeneous, and typically these include either patients with recent MI complicated by HF (e.g. EPHESUS trial) or a wider population of patients with HF (e.g. RALES trial).

- Although only EPL is licensed for post-MI treatment, SPI could be used in some clinical settings.

  •Inexistence of reference clinical trial of SPI in patients with recent MI complicated by HF

  •Inexistence of H2H clinical trials between EPL and SPI

- Understanding potential differences is important when aiming at informing decision making based on the cost effectiveness of these treatments.

This paper

- The objective of this study is to estimate the expected clinical benefits of individual aldosterone blockers:
  - EPL
  - SPI

  in patients with recent MI complicated by HF.

- The results of this analysis will inform a decision model estimating the value for money of using eplerenone (EPL) when compared to spironolactone (SPI) for this patient population.

Methods

- The evidence for the efficacy of spironolactone, eplerenone, or canrenoate (CAN) compared to placebo or active control was identified in a recent systematic review of randomized controlled trials [Ezekowitz and McAlister, 2008].

- A **meta-regression model** was adopted to aggregate the efficacy results from these trials.

- This methodology allows all existing evidence to be incorporated and, further, allows explicit characterization of clinical heterogeneity among the respective the trial populations.

- The treatment effects of EPL and SPI on all cause mortality for patients with MI complicated by HF were estimated.

Methods

- A **bayesian meta-regression model** was also conducted. Convergence was evaluated using the Gelman-Rubin statistics. 1 million simulations run: the first 10,000 simulations were discarded and inferences were achieved by drawing only 1 in every 100 simulations (thin=100)

- The inclusion of available individual patient data (IPD) instead of aggregate data on the two larger trials (RALES and EPHESUS) was evaluated.

- This was accomplished through Bayesian inference.

- Evidence on CAN was used only to inform differences between populations, although this treatment is not currently licensed across Europe.

Results

- Seventeen randomized controlled trials (evaluating a total of 10448 patients) were included.
- Of these trials, 13 were conducted in patients with HF (3036 patients) and four trials (7412 patients) specifically tested aldosterone blockade after MI.
- SPI was used in 12 trials (2464 patients), CAN in three trials (1200 patients) and EPL in two trials (6784 patients).

Results

- **Meta-regression estimates** of relative risks for distinct treatments in heart failure and myocardial infarction populations

Relative Risk vs. standard care*					
				[95% Conf. Interval]	
	Drug	Estimated	Std. Err.	lower	higher
Myocardial Infarction	Spironolactone	0.963	0.460	0.256	3.624
	Eplerenone	0.860	0.049	0.734	1.009
	Canrenoate	0.667	0.170	0.329	1.351
				[95% Conf. Interval]	
	Drug	Estimated	Std. Err.	lower	higher
Heart Failure	Spironolactone	0.751	0.046	0.635	0.889
	Eplerenone	0.671	0.320	0.178	2.526
	Canrenoate	0.520	0.227	0.155	1.746

* non linear combinations of coefficients derived from the meta regression.

Results

- **Bayesian meta-regression estimates** using IPD and AD data - estimated relative risks for distinct treatments in heart failure and myocardial infarction populations

Relative Risk vs. standard care*					
				[95% Cred. Interval]	
	Drug	**Estimated**	**Std. Err.**	**Lower**	**higher**
Myocardial Infarction	Spironolactone	1.086 +	0.551	0.391	2.504
	Eplerenone	0.858	0.049	0.766	0.960
	Canrenoate	0.691	0.177	0.406	1.089
				[95% Cred. Interval]	
	Drug	**Estimated**	**Std. Err.**	**Lower**	**higher**
Heart Failure	Spironolactone	0.752	0.045	0.667	0.846
	Eplerenone	0.740	0.370	0.258	1.649
	Canrenoate	0.569	0.257	0.217	1.199

* non linear combinations of coefficients derived from the meta regression.
+ the parameter being estimated presents a skewed distribution. For this reason, the mean of the posterior distribution (1.086 as shown in the table) is distinct from the median (median is 0.9664)

Results

- In **myocardial infarction patients**, spironolactone is expected to have a relative risk of 1.1 while eplerenone is expected to have a relative risk of 0.86.
  - Benefits achieved through the use of eplerenone are quite certain, whilst benefits from spironolactone use are very uncertain in this population.
  - As a consequence of the observed uncertainty, this parameter shows a skewed posterior distribution, with the median being different than the mean.

- In **heart failure patients**, spironolactone is expected to have a relative risk of 0.75.
  - Benefits achieved through the use of spironolactone in heart failure patients are quite certain and both point estimate and confidence intervals are in line with the results observed in the RALES trial [Pitt 1999].
  - Eplerenone is estimated to have a relative risk of 0.740, but this result is quite uncertain.

Results

- In both sets of patients canrenoate is expected to have the lower relative risk, although a statistically significant result for being a beneficial treatment was not produced.
- Results were more precise when data from the two larger trials (RALES and EPHESUS) were included as IPD.
- Using both methods the results for SPI and EPL were robust to a sensitivity analysis where evidence on CAN was excluded
- Bayesian posteriori distributions are useful to execute accurate assessment of uncertainty in decision models

Conclusions

- The benefits of EPL in MI patients estimated through the meta-regression model are concordant with the results established in the larger clinical trial (EPHESUS).

- These are estimated to exceed the benefits from SPI use in the same population, but there is great uncertainty concerning the estimates for SPI due to the lack of large clinical trials in this population.

- By complying with the standards for an accurate assessment of uncertainty in decision models, these results are appropriate to inform cost effectiveness of eplerenone and spironolactone in patients with recent MI complicated by HF.

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Thanks!