

SUBPOPULATION TREATMENT EFFECT PATTERN PLOT (STEPP) FOR CATEGORIZATION OF BASELINE CHARACTERISTICS

Andrea Parodi, Valos, Genova, Italy
Dmitri Petratchenko, Valos, Genova, Italy

INTRODUCTION

Interactions between treatment and covariates, such as prognostic factors, in randomized trials are important because they are essential ingredients of individualized treatments rather than assuming that one size fits all. When the covariate is continuous, such interactions are often sought by crude statistical methods, typically involving categorizing the continuous covariate. When treatment effects in subgroups are compared; the results may depend on the cut point chosen. Categorization of the variable of interest is often tricky. To decide what is the right cut-offs for selecting subgroups of subjects we decided to use STEPP method.

We have been asked by the Sponsor to investigate the predictive value of Time from diagnosis (TFD) of the disease to start of treatment, but pre-specified cut-offs could bring to a meaningless result.

Using the STEPP we firstly explored the association between TFD and morbidity/mortality events (MM), then we chosen cut-offs for categorization based on our findings.

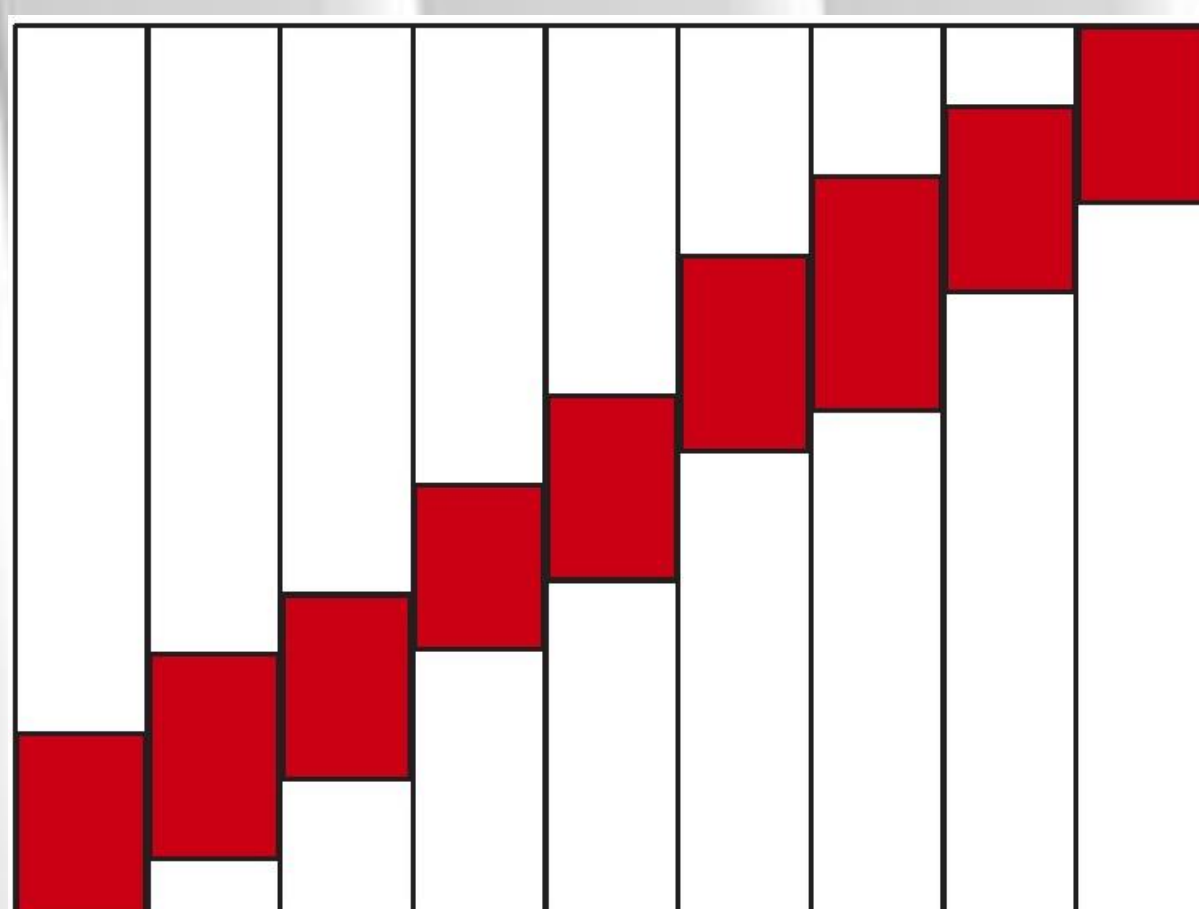
STEPP METHOD

This method is based on constructing overlapping subpopulations of patients with respect to a variable, and in observing the pattern of the treatment effects estimated across the subpopulations.

A Cox model for each subpopulation calculates hazard ratios and confidence intervals. Confidence intervals do not take in account the fact a subject is considered in different subgroups, so inference cannot be done with this technique and its goal is just descriptive, for finding the cut-offs to be used for categorizing the variable of interest.

The theory of sliding window approach has been taken from the paper "Patterns of treatment effects in subsets of patients in clinical trials" (Bonetti, 2004).

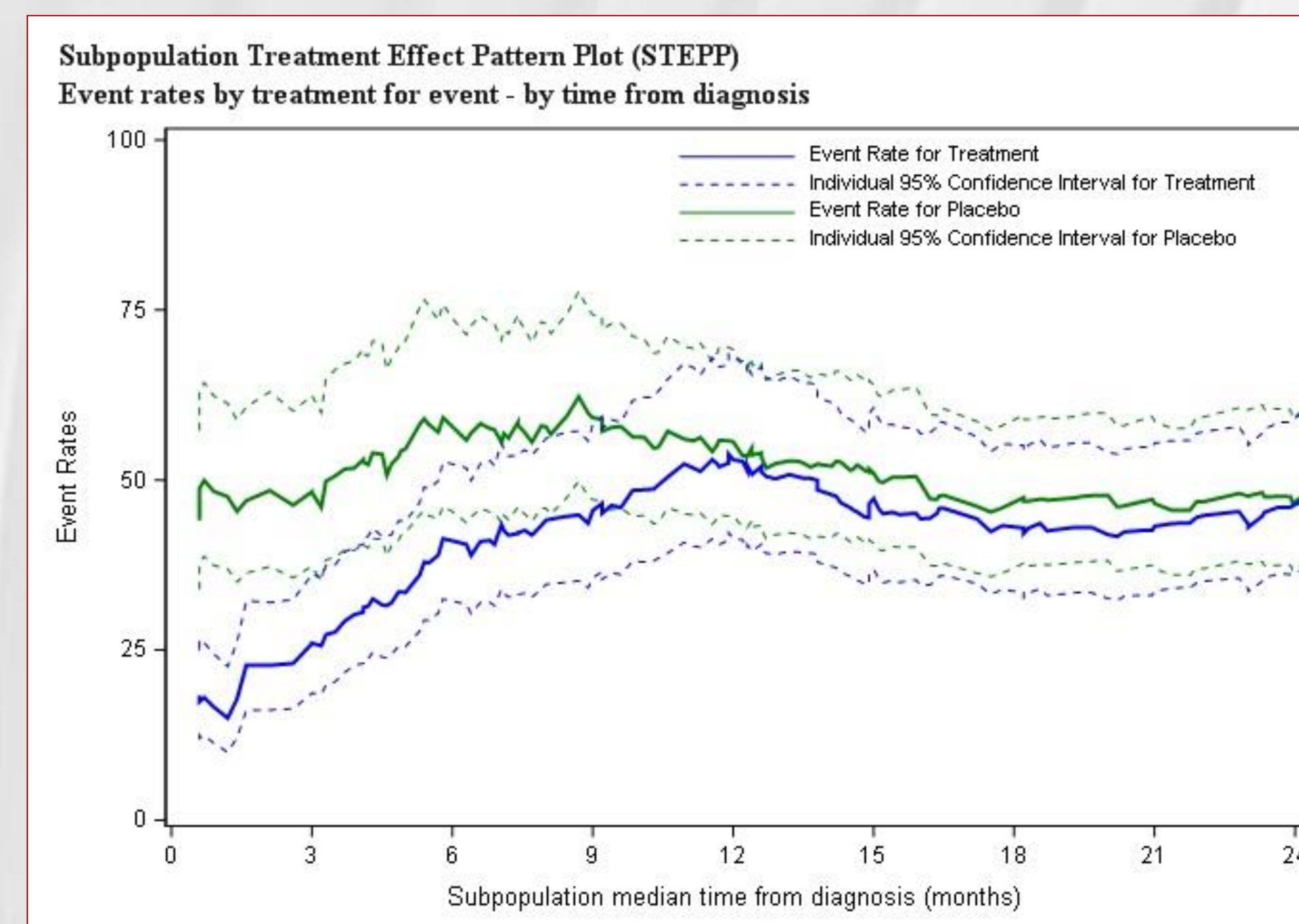
Figure 1 below gives an idea of how subpopulations are created. Each vertical white bar indicates the whole cohort, while each red bar indicates the subpopulation within the cohort.



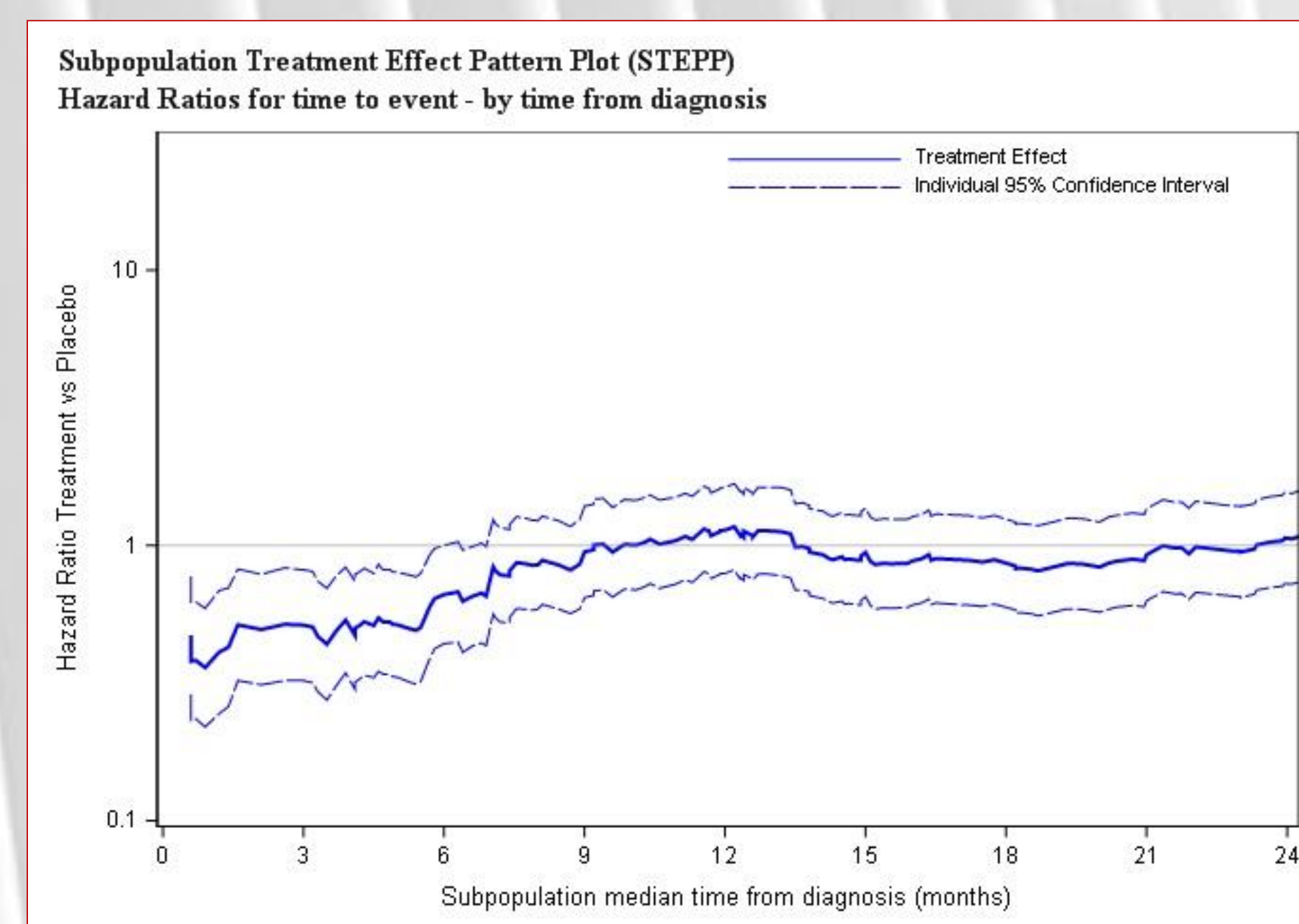
STEPP FOR TIME FROM DIAGNOSIS

The MM rate in each subpopulation was plotted against TFD values for each treatment arm. If a covariate has no effect, MM rates should be similar for all subpopulations, with any differences resulting from chance alone.

The Figure 2 below plot is one way of exploring prognostic effects of TFD nonparametrically, using MM rates.



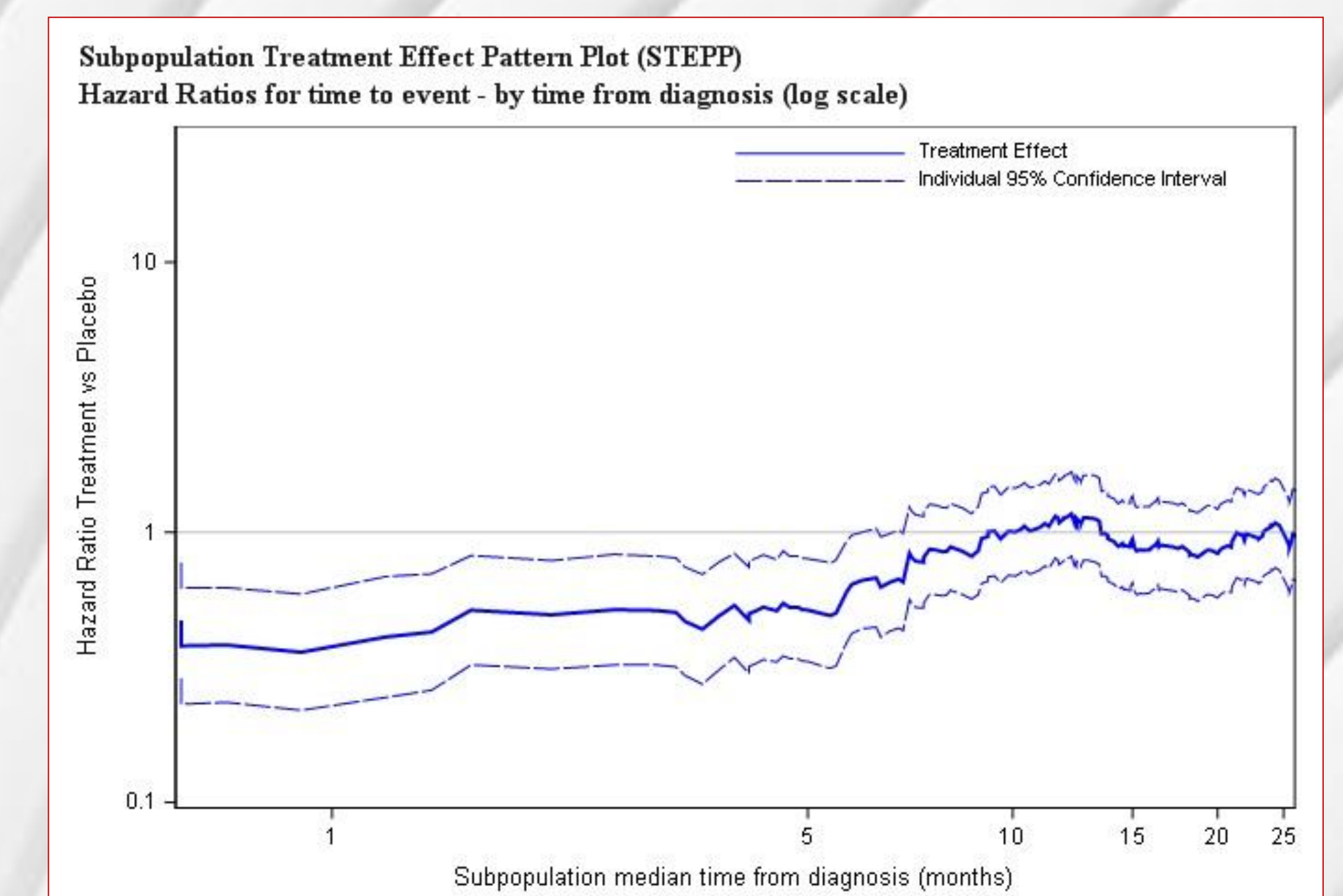
In this situation, the difference in MM rates between treatments varies according to the value of TFD. The MM rate for treatment shows a growth from zero up to 9 months and reach the Placebo's Event Rate around 12 months. The Placebo Event Rate is always worse than the Treatment one. Both Event Rates seem to increase through TFD before month 12 and then they show to have the same trend. The treatment seems to be effective only if taken within 12 months from diagnosis, with a bigger effect if taken as soon as possible. The magnitude of the treatment effect is better observable in the STEPP where hazard ratios (corrected by baseline covariates) and confidence intervals are shown (Figure 3).



The effect of treatment seems to be quite stable for subjects taking treatment within Month 6 from diagnosis, where HR is around 0.5 on average, then slightly decreases for subjects taking treatment between Months 6 and 9 and finally becomes null (HR around 1) for all other subjects with a longer TFD. The overall message we can get from the STEPP is that lower TFD is associated with treatment effect, indicating an as soon as better way for treating subjects. Thus STEPP analysis provides evidence of heterogeneous treatment effects related to TFD.

For a better understanding of the effect pattern behind STEPP, a graph with log scale of TFD is shown (Figure 4), because the distribution of subpopulations in y-axis is not linear: the great majority of subjects assumes treatment within 1 year from diagnosis and log scale let us expand the points in the first months.

The logarithmic graph supports what noticed before.



CATEGORIZATION OF TIME FROM DIAGNOSIS

From the above STEPP we observed that TFD is an important prognostic factor and three categories of subjects can be a good solution for categorization.

- Subjects treated within 6 months from diagnosis: they are those with more benefit from treatment
- Subjects treated within 6 and 9 months from diagnosis: a benefit from treatment is still present, but not as strong as in the first category
- Subjects treated after 9 months from diagnosis: no beneficial effect for treated subjects.

REFERENCES

Bonetti M, Gelber RD (2004) Patterns of treatment effects in subsets of patients in clinical trials. Biostatistics 5: 465–481.