An Unsupervised Machine Learning Approach to assess Heterogeneity of Treatment Effects over Patient Phenotypes

Xinhui Ran[1], Andre Zimerman[1], Robert P. Giugliano[1], David A. Morrow[1], Sabina A. Murphy[1], Andrea Bellavia[1]

[1]TIMI Study Group, Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (US)

INTRODUCTION

- Primary results from randomized clinical trials (RCT)s only inform on the average treatment effect in the studied population, and it is important to understand whether treatment effect varies across patients' phenotypes
- Common approaches for Heterogeneity of Treatment Effect (HTE) assess subgroup analyses one variable at the time and have recognized limitations.[1] Recent approaches for evaluating HTE, such as risk-based and effect-based modeling, are based on supervised algorithms.
- We propose a clustering-based approach for the assessment of HTE over patient phenotypes, thus maintaining the unsupervised nature of classical subgroup analysis while jointly accounting for relevant patient characteristics.

CLUSTERING PROCEDURE FOR HETEROGENITY OF TRT EFFECT

1. Select covariates of interest. Commonly the same characteristics evaluated in subgroups analysis one at the time, selected a-priori
2. Conduct Model-based clustering[2] for patient phenotyping. Model-based approach allows for mixed-type data, soft assignment & variable selection
3. Cluster diagnostics, assessing misclassification rates and AIC/BIC
4. Cluster description and interpretation, assessing discriminative power and population characteristics by clusters
5. Evaluate treatment effects over clusters
6. Validation. Replicate clustering with training/validation split or using bootstrap over several random splits

R code to replicate procedure is available at the QR code link.

ILLUSTRATIVE EXAMPLE

- ENGAGE AF-TIMI 48 compared 2 regimens of edoxaban (Factor Xa inhibitor) vs warfarin in atrial fibrillation. Both edoxaban regimens were noninferior to warfarin to prevent stroke or systemic embolism (primary endpoint).[3]
- Heterogeneity of the high-dose edoxaban vs. warfarin effect was observed over several individual covariate subgroups.
- We used phenotype-based HTE to help elucidate some of these results with respect to what patients would most benefit from the drug, applying our clustering procedure and comparing results to those from an effect-based approach (CATE estimated using Causal Survival Forest).[4]
- Model-based clustering identified 3 subgroups of trial participants (Figures 1-2 Table 1). Treatment effects varied over subgroups (Figure 3)

Figure 1. Probability of misclassification (left panel) and discriminative power of original covariates (right panel)

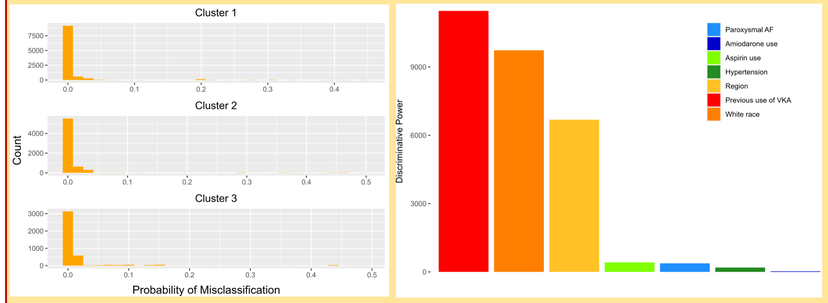
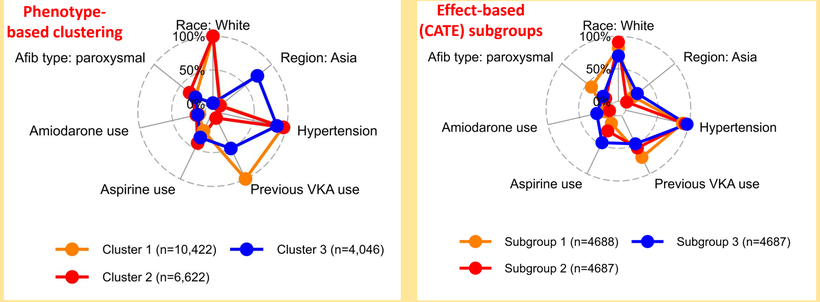


Table 1. Baseline characteristics by clusters

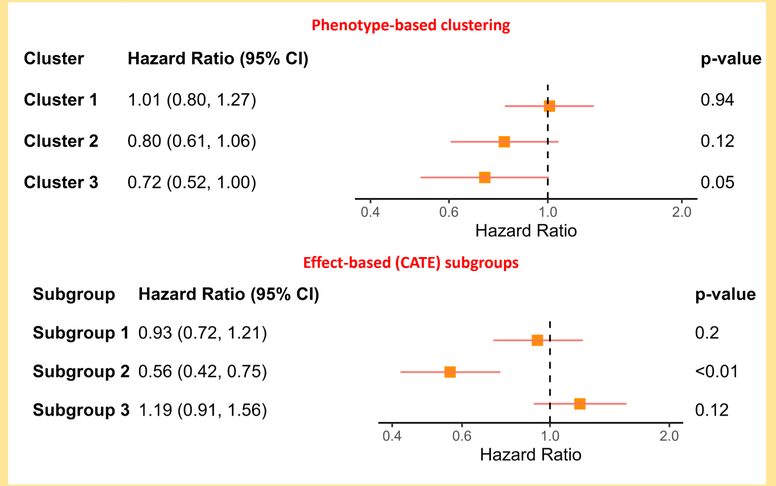
Characteristic	Cluster 1 (N=10422)	Cluster 2 (N=6622)	Cluster 3 (N=4046)
Region			
North America	3357 (32.2%)	**1065 (16.1%)**	251 (6.2%)
Latin America	924 (8.9%)	932 (14.1%)	804 (19.9%)
Western Europe	2039 (19.6%)	1177 (17.8%)	18 (0.4%)
Eastern Europe	3819 (36.6%)	3325 (50.2%)	0 (0%)
Asia–Pacific region and South Africa	283 (2.7%)	123 (1.9%)	2973 (73.5%)
White	10406 (99.8%)	6600 (99.7%)	53 (1.3%)
Atrial Fibrillation type			
paroxysmal	2255 (21.6%)	2200 (33.2%)	907 (22.4%)
persistent	1950 (18.7%)	1896 (28.6%)	1021 (25.2%)
permanent	6217 (59.7%)	2526 (38.1%)	2118 (52.3%)
Hypertension	9873 (94.7%)	6378 (96.3%)	3490 (86.3%)
Previous use of VKA	10422 (100%)	0 (0%)	2014 (49.8%)
Aspirin use	2154 (20.7%)	2739 (41.4%)	1282 (31.7%)
Amiodarone use	1063 (10.2%)	957 (14.5%)	471 (11.6%)

Figure 2. Radar plots for clusters interpretation



Cluster 1: white not-VKA naive; Cluster 2 white VKA naïve; Cluster 3: non-white

Figure 3: Hazard Ratios for the primary endpoint comparing high-dose edoxaban vs. warfarin in identified subgroups



CONCLUSIONS

- Both clustering and CATE indicated the presence of subgroups with higher treatment benefits. Subgroups identified with the clustering approach (phenotypes) provide easier patients characterization: the highest benefit is in patients who are more likely to be non-white, living in Asia, and without previous use of vitamin K antagonist (if white).
- Existing approaches for multivariable HTE stratify over subgroups that depend on the outcome of interest. HTE over clustering provide an unsupervised approach for assessing how the treatment effect varies over patient phenotypes with potential immediate applicability in clinical practice .

References:

1 Kent DM et al. The Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement. Ann Intern Med. 2020 Jan 7;172(1):35-45.

2 Marbac M, Sedki M. Variable selection for model-based clustering using the integrated complete-data likelihood. Stat Comput 27, 1049–1063 (2017).

3 Giugliano RP et.al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 2013; 369:2093-2104.

4 Cui Y et al. Estimating Heterogeneous Treatment Effects with Right-Censored Data via Causal Survival Forests. Journal of the Royal Statistical Society: Series B, 85(2), 2023.

Contact: xran@bwh.harvard.edu timi.org/biostatistics