

# Informative Censoring and Outcome Definition in a Target Trial Emulation Framework using Real-World Data

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## INTRODUCTION

Oral anticoagulants are commonly prescribed for patients with atrial fibrillation (AF) to prevent stroke and systemic thromboembolism. However, anticoagulant treatment, regardless of whether it involves a vitamin K antagonist (VKA) or a direct oral anticoagulant (DOAC), can be associated with the development of kidney events and/or progression of kidney damage [1-2]. When using Electronic Health Records (EHR) in a Target Trial Emulation (TTE) framework [3] to evaluate the impact of a treatment on an outcome defined by a dynamical decline process, some issues arise not only due to the baseline confounding factors, but also for the potential informative censoring caused by treatment discontinuation or switch and related to the definition of the outcome itself. If these aspects are not taken into account, a biased estimate of the treatment effect is highly probable.

## OBJECTIVES

To investigate accelerated renal function decline in patient with AF using anticoagulation therapy, exploring differences among VKA vs DOAC users using EHR of the Observatory of CardioVascular Diseases (OCVD) in the Friuli-Venezia Giulia region (FVG, Italy) in a TTE framework.

## METHODS

To define renal outcomes as kidney failure (KF) and AKI (Acute Kidney Injury), we considered hospital admissions for renal causes identified by ICD9-CM codes but also the worsening in the eGFR biomarker defined in two ways: the date of the first eGFR value that showed a decline  $\geq 30\%$  with respect to the baseline value or was below 15 ml/min/1.73 m<sup>2</sup>. In the alternative approach, for each subject a linear regression

line was fitted through all his/her eGFR measurements. To be considered a sustained decline the linear regression slope needed to be negative, the time to the event was defined as the moment the regression line crossed the 30% decline threshold (or was below the 15 ml/min/1.73 m<sup>2</sup>) [4]. Two approaches were compared to define the follow up: Intention to Treat (ITT), where the censoring date was the first date among the administrative censoring date or death, whatever come first, and Per-Protocol (PP) where the follow-up terminated at the first date among administrative censoring date, drug group switch (from VKA to DOAC or viceversa) or therapy discontinuation date or death. Therapy discontinuation was defined as the date of the last anticoagulant medication purchase, extended by the number of days the purchase was expected to cover based on the quantity dispensed, plus an additional 90 days. In all the analyses, death as a first event was treated as a competing risk for the renal outcomes. To take into account baseline confounders, Inverse Probability of Treatment Weights (IPTW) were estimated using logistic regression to predict the treatment group assignment, according to characteristics of subjects at the index date. Results of the weighting procedure were considered appropriate if the standardized mean difference (SMD) between weighted treatment groups was  $< 0.1$ . Since a differential rate of loss to follow-up between treatment groups (due to switch and discontinuation) was highly expected, in order to take into account simultaneously differences at baseline and informative censoring, adjustments were also performed using "combined" weights. These weights were the product of IPTW and time-dependent Inverse-Probability-of-Censoring Weights (IPCW) [5] taking into account monthly or 6-months' time intervals and different set of baseline covariates for sensitivity analyses. Weighted incidence rates of events and weighted cumulative incidence curves were estimated in the overall population and in treatment groups [6]. Hazard ratios (HRs) for renal outcomes were estimated using cause-specific Cox regression models.

## RESULTS

The study cohort was composed by 6873 subjects, 49% treated with DOAC and 51% with VKA. Significant differences at baseline were present between treatment groups, in particular as expected in the year of enrolment. After IPTW estimation, all the differences were below the 10%SMD (21 subjects were excluded due to the positivity violation). Under the ITT approach, no differences in any of the renal outcomes were observed, on the weighted cohort. Conversely adopting the PP, an increased risk of sustained eGFR decline (with the regression method definition) and KF was detected (respectively HR=1.18, [1.03 – 1.35], HR=1.69, [1.10 – 2.60]) in the IPTW-weighted cohort. No differences in AKI were found. When the renal event was defined using the first eGFR measurement below the decline threshold, a significant impact was observed only for KF but not for eGFR decline and AKI (KF HR: 1.43 [1.09-1.87], eGFR Decline HR: 0.99 [0.90-1.10], AKI HR: 1.16 [0.90-1.50]). When IPTWIPCW weights were adopted, the results were substantially confirmed, with less precision of the estimates (wider 95% CI) across the different time-intervals and set of covariates used.

## CONCLUSIONS

When using observational data in the context of a TTE framework, it is crucial to take into account both the confounders issue due to the non-randomized study design but also the informative censoring induced by therapy discontinuation or switch. Moreover, the methods used to define the outcome when a longitudinal biomarker is involved are also relevant.

## REFERENCES

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