Assessing the Utility of External Control Arms to Increase Precision in Cardiorenal Trials: A Feasibility Study in an RCT Subgroup of Sodium-Glucose Cotransporter 2 Inhibitor Users

RWD38

Alfredo E. Farjat[1*], [2]Chris Bauer, [3]Alexander Hartenstein, [2]Alexandra Zerck, [2]Johannes Schuchhardt, [3]Rachel Knapp, [3#]Robert Edfors, [3]Sascha van Boemmel-Wegmann

[1]Bayer BV, Hoofddorp, Netherlands; [2]MicroDiscovery GmbH, Berlin Germany; [3]Bayer AG, Berlin, Germany

*corresponding author: Alfredo E. Farjat, alfredo.farjat@bayer.com. # affiliation at time of study

Disclosures: AEF is an employee of Bayer BV. CB, AZ and JS are employees of MicroDiscovery GmbH. AH, RK and SvBW are employees of Bayer AG. RE is a former employee of Bayer AG.

Introduction

- Finerenone demonstrated a reduction in risk of kidney and cardiovascular events in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in FIDELIO-DKD and FIGARO-DKD phase III randomized controlled trials (RCTs)[1, 2]
- Sodium-glucose co-transporter-2 inhibitors (SGLT2is) have been established as a treatment option for the management of CKD[3]
- FIDELITY (FIDELIO/FIGARO) pooled subgroup analyses indicated an independent and potentially synergistic effect of the concomitant use of “Finerenone + SGLT2is”[4, 5]
- However, the subgroup analysis provided limited evidence on use of “Finerenone + SGLT2is” vs “SGLT2is alone” due to low sample size and number of events[5]

Motivation / Research question

- Is it possible to complement RCT data from FIDELIO-DKD/FIGARO-DKD with SGLT2is users from RWD to get more precise estimates for the combined therapy “Finerenone+SGLT2i” compared to “SGLT2is alone”?

Objectives

- Evaluate the feasibility of creating an external control arm (ECA) from RWD patients to augment the pooled comparator of SGLT2is users to estimate treatment effects
  - ➢ Build an ECA with matching patients from RWD to those from the pooled SGLT2is subgroup from FIDELIO-DKD/FIGARO-DKD phase III trials
  - ➢ Evaluate different matching/adjusting methods
  - ➢ Increase precision and statistical power of treatment effect estimates

Methods / Rationale and study overview

Selection Process

- Selection criteria from the trials were adapted to identify eligible patients from Optum Electronic Health Records with CKD and T2D

Figure 1: Selection process of the ECA cohort and matching with RCT trials

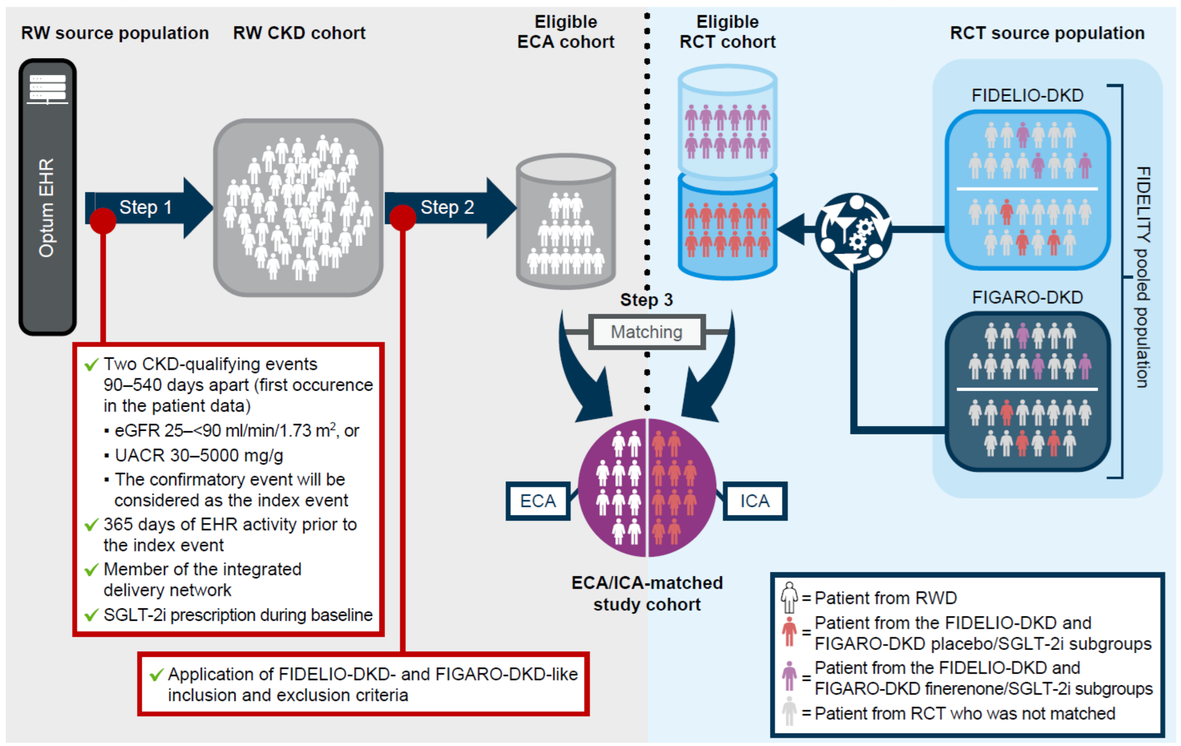
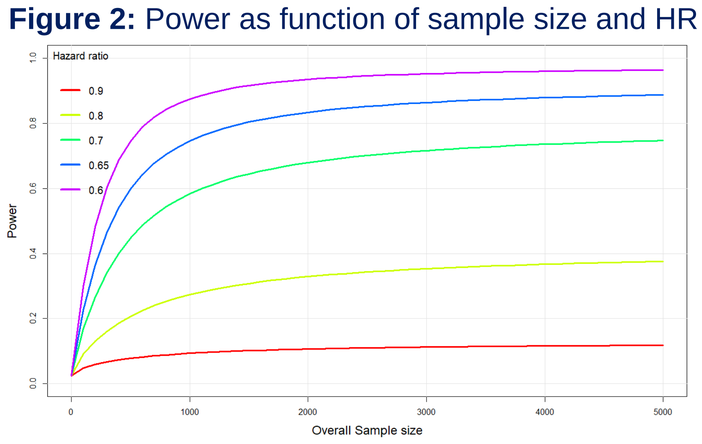


Figure 2: Power as function of sample size and HR



Matching methods

- Propensity score matching[6], Genetic algorithm[7], Linear Integer Programming[7] , Inverse Odds Weighting[6]

External Control Arm

- Matching between ECA cohort to those from the RCT subgroup of SGTL2i users (n=877)
- 43 baseline covariates used for the adjustment
- Metric for assessing quality of matching: Absolute standardized mean difference (ASMD)

Results

- Out of the external pool of **8,272** eligible patients, **877** were successfully matched to the pooled RCT subgroup of SGLT2is users
- **Linear integer programming** algorithm showed best performance with respect to ASMD
- Median (Q1, Q3) ASMD across the **43 matching variables** was 0.000 (0.000, 0.004) (Figure 3)
- Internal (ICA) and external (ECA) controls arms exhibited **similar characteristics and outcomes** (Figures 3 and 4)
- External augmentation of the ICA yielded a 1:3 ratio treatment to controls for the main analyses. Treatment effects were recalculated after augmentation (Figure 5)

Figure 3: ASMD before and after matching between RCT and RWD

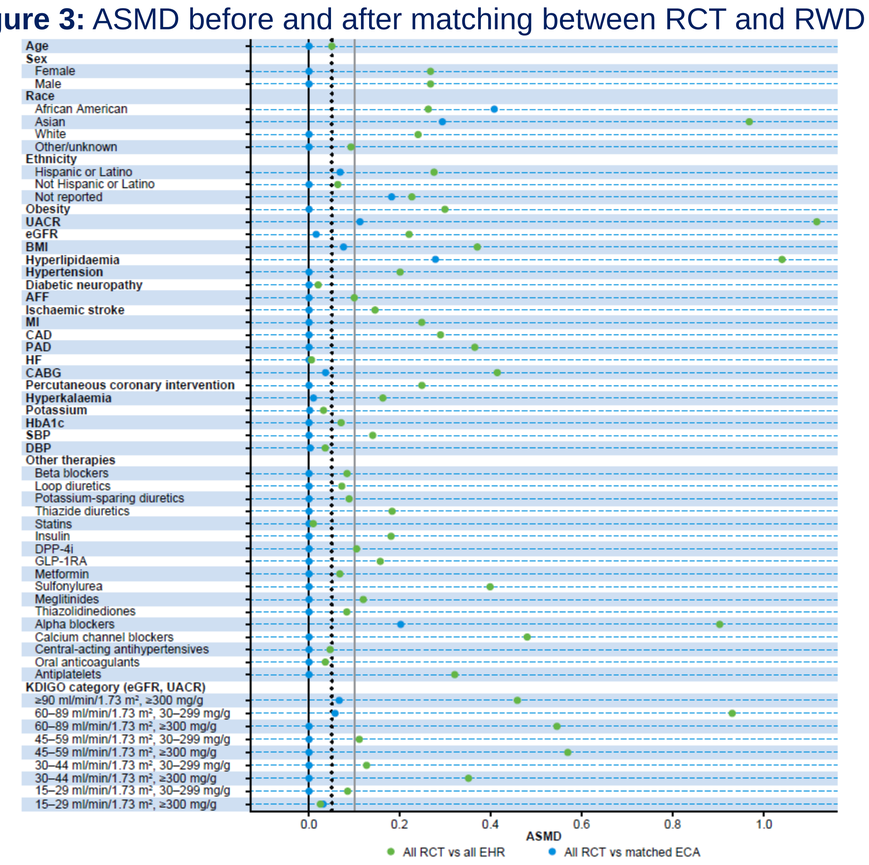


Figure 4: Incidence rates (events per 100 patient-years) of clinical outcomes from ICA and matched ECA patients

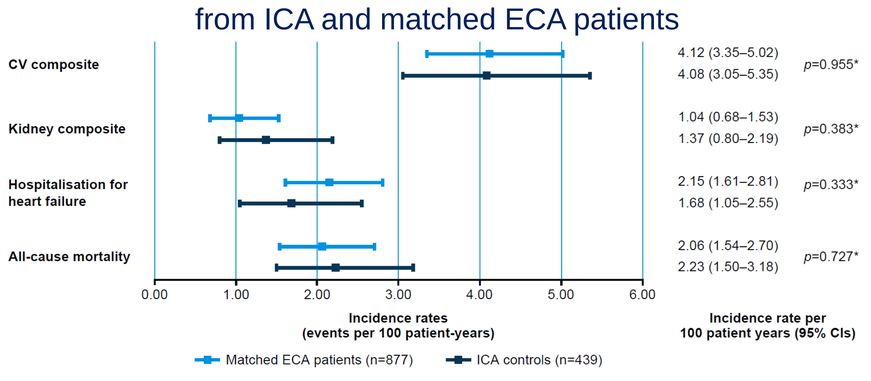
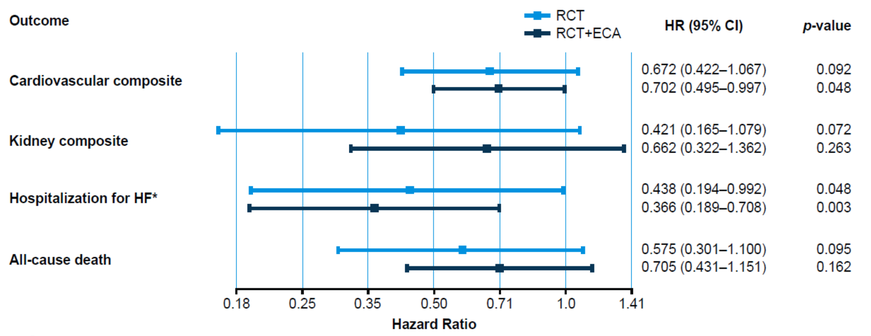


Figure 5: Hazard ratios of clinical outcomes from RCT and RCT+ECA



Conclusions

- High overall agreement in baseline characteristics and clinical outcomes between RCT and ECA patients
- Increased precision of treatment effect estimates achieved through ECA augmentation indicates beneficial effect of Finerenone versus SGLT2is alone
- Our results demonstrate the feasibility of creating an ECA in a large indication such as CKD and T2D

References: 1. Bakris GL, *et al. N Engl J Med* 2020;383:2219–2229; 2. Pitt B, *et al. N Engl J Med* 2021;385:2252–2263; 3. American Diabetes Association. *Clin Diabetes* 2022;40:10–38; 4. Agarwal R, *et al. Eur Heart J* 2022;43:474–484; 5. Rossing P, *et al. Diabetes Care* 2022;45:2991–2998; 6. Li et al. JASA. 2018; 113(521):390-400 7. Privitera S, *et al. Pharm Stat* 2024; 23:288–307.