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Feasibility of constructing an external control arm with real-world data to augment subgroups in cardiorenal trials: A matched cohort study focusing on trial subgroups of sodium-glucose co-transporter-2 inhibitor users at baseline

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

Introduction

- Finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist, demonstrated a reduction in risk of kidney and cardiovascular events in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELIO-DKD and FIGARO-DKD phase III randomised controlled trials (RCTs)[1,2]
- Sodium-glucose co-transporter-2 inhibitors (SGLT-2i) have recently been established as a treatment option for the management of CKD in people with T2D[3]
  - Uptake of SGLT-2i for people with T2D-associated CKD has been slow in clinical practice, with 4.6–11.0% of such patients receiving these agents in 2019/2020.[4] This slow uptake in clinical practice led to low proportions of baseline SGLT-2i use by patients in recent cardiorenal trials
- Pooled subgroup analyses reported consistent cardiorenal benefits of finerenone, independent of concomitant SGLT-2i therapy[5,6]
- However, subgroup analyses in clinical trials often lack an adequate sample size and statistical power to accurately estimate treatment effects, including SGLT-2i subgroup analyses of the pooled FIDELIO-DKD and FIGARO-DKD RCTs[6]

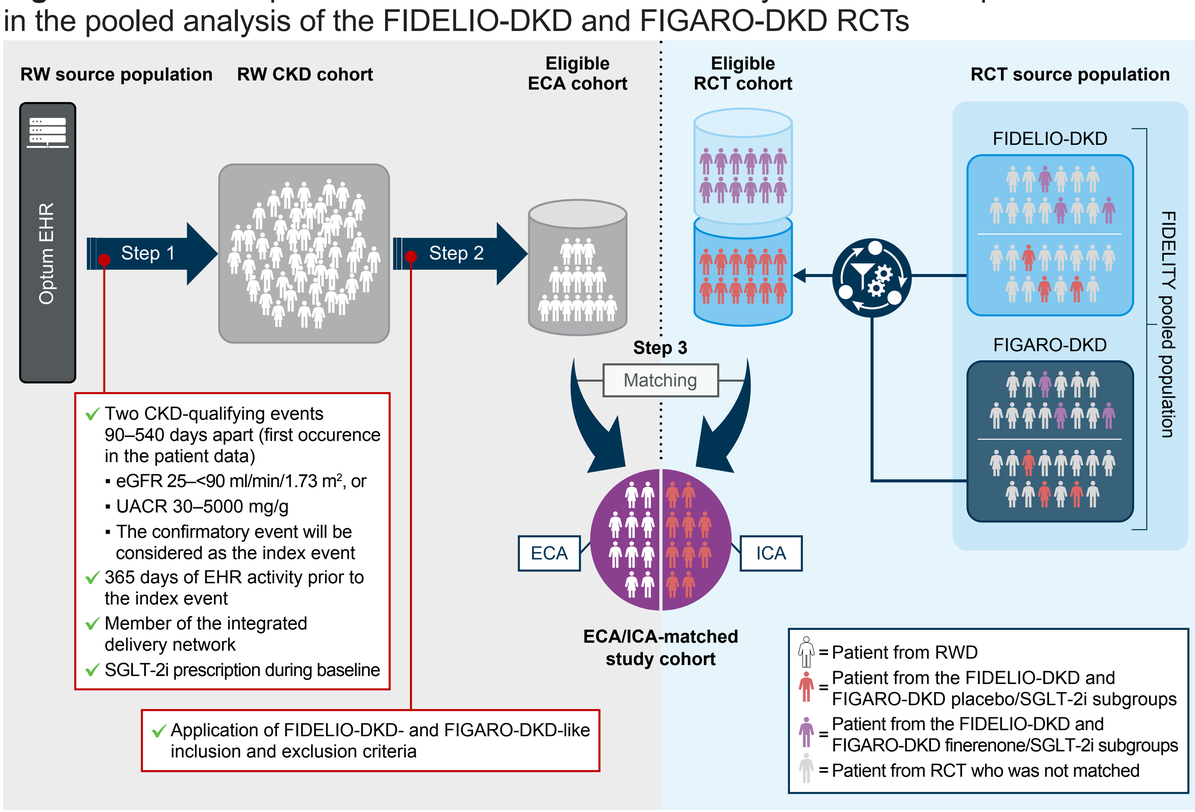
Objective

- The aim of this study was to evaluate the feasibility of building an external control arm (ECA) in order to augment the internal control arm (ICA) to estimate treatment effects
  - The ECA was built by matching patients from real-world data to those from the pooled SGLT-2i subgroups of the phase III RCTs, FIDELIO-DKD and FIGARO-DKD

Methods

- Selection criteria from the RCTs were adapted to identify eligible real-world patients with CKD in US Optum electronic health record (EHR) data from January 2013 to September 2021 (**Figure 1**)
  - Patients were indexed between January 2014 and December 2019

Figure 1. Selection process of the ECA cohort that closely resembles the patients included in the pooled analysis of the FIDELIO-DKD and FIGARO-DKD RCTs



CKD, chronic kidney disease; ECA, external control arm; eGFR, estimated glomerular filtration rate; EHR, electronic health record; ICA, internal control arm; RCT, randomised controlled trial; RW, real-world; RWD, real-world data; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

- Key inclusion criteria for the real-world CKD cohort:
  - Adults aged 18 years and older with T2D diagnosis
  - At least two qualifying measurements of estimated glomerular filtration rate (25–<90 ml/min/1.73 m²) or urine albumin-to-creatinine ratio (30–5000 mg/g), separated by 90 to 540 days (second qualifying value = index date)
  - At least 365 days of EHR activity prior to the index date (baseline period = 365 days) and received care documented in the EHR database from at least one provider in the baseline period
  - SGLT-2i prescription during the 365-day baseline period
  - A member of the integrated delivery network, to ensure data completeness
- To derive the eligible ECA cohort from the real-world CKD cohort, a variety of additional inclusion and exclusion criteria were applied in alignment with those from the FIDELIO-DKD and FIGARO-DKD RCTs, covering baseline medication exposure, the presence of certain comorbidities/acute events and key lab findings, including:
  - Inclusion‡:
    - Prior treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, but not both (in pre-index period of 124 days)
  - Exclusion‡:
    - One inpatient or two outpatient diagnoses of stroke, transient ischaemic attack, acute coronary syndrome or hospitalisation for heart failure (in pre-index period of 44 days)
    - High serum potassium (>4.8 mmol/l), glycated haemoglobin or urine albumin-to-creatinine ratio (in pre-index period of 124 days)
    - Hypertensive crisis, systolic heart failure with left ventricular ejection fraction ≤40% (in pre-index period of 124 days)
    - Dialysis (in pre-index period of 208 days)
    - Use of steroidal mineralocorticoid receptor antagonists or CYP3A4 inhibitors
- Following the identification of the ECA eligible cohort, a mixed linear integer programming approach[7] with a set of 43 medically informed baseline covariates (i.e. demographics, comorbidities, comedications, laboratory results) was used; patients were matched from the eligible ECA cohort to those from the RCT subgroup (finerenone + SGLT-2i and placebo + SGLT-2i, n=877) (**Figure 1**)
- Standardised mean differences assessed matching quality; summary statistics of baseline characteristics and incidence rates of cardiorenal outcomes were compared between the ECA and ICA to determine data homogeneity

‡Varying lookback times were selected for specific characteristics of interest to mirror the baseline, run-in and screening periods used in the RCTs

Results

- From 8272 eligible individuals in the real-world CKD cohort, 877 were successfully matched to the pooled RCT subgroup of SGLT-2i users to form the ECA, leading to a 2:1 ratio of external vs internal controls (n=439) (**Table 1**)

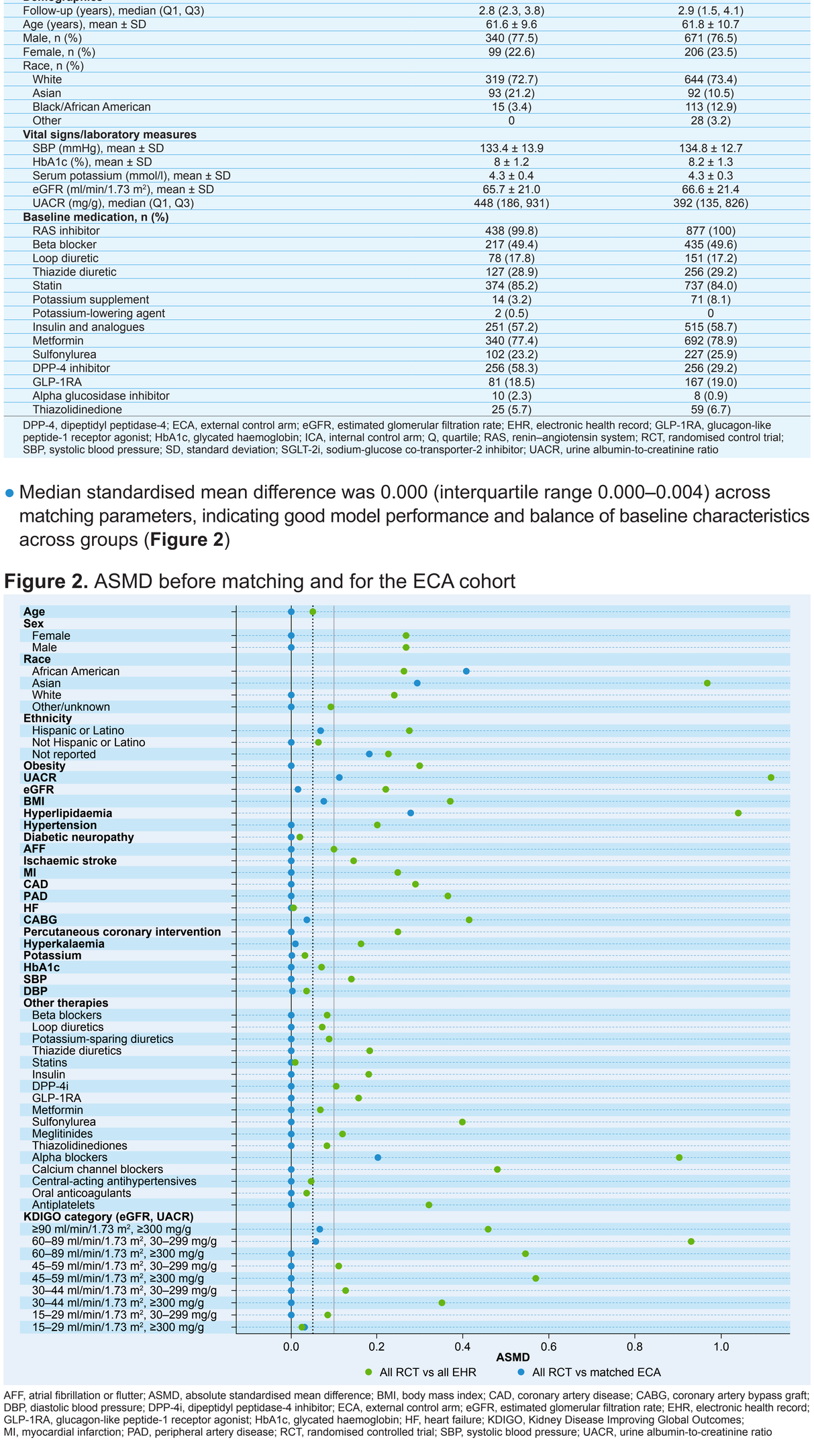
Table 1. Matched patient baseline characteristics in patients with SGLT-2i use at baseline from the pooled analysis and matched EHR

	ICA (Pooled RCTs)	Matched ECA (US Optum EHR)
n	439	877
Demographics		
Follow-up (years), median (Q1, Q3)	2.8 (2.3, 3.8)	2.9 (1.5, 4.1)
Age (years), mean ± SD	61.6 ± 9.6	61.8 ± 10.7
Male, n (%)	340 (77.5)	671 (76.5)
Female, n (%)	99 (22.6)	206 (23.5)
Race, n (%)		
White	319 (72.7)	644 (73.4)
Asian	93 (21.2)	92 (10.5)
Black/African American	15 (3.4)	113 (12.9)
Other	0	28 (3.2)
Vital signs/laboratory measures		
SBP (mmHg), mean ± SD	133.4 ± 13.9	134.8 ± 12.7
HbA1c (%), mean ± SD	8 ± 1.2	8.2 ± 1.3
Serum potassium (mmol/l), mean ± SD	4.3 ± 0.4	4.3 ± 0.3
eGFR (ml/min/1.73 m²), mean ± SD	65.7 ± 21.0	66.6 ± 21.4
UACR (mg/g), median (Q1, Q3)	448 (186, 931)	392 (135, 826)
Baseline medication, n (%)		
RAS inhibitor	438 (99.8)	877 (100)
Beta blocker	217 (49.4)	435 (49.6)
Loop diuretic	78 (17.8)	151 (17.2)
Thiazide diuretic	127 (28.9)	256 (29.2)
Statin	374 (85.2)	737 (84.0)
Potassium supplement	14 (3.2)	71 (8.1)
Potassium-lowering agent	2 (0.5)	0
Insulin and analogues	251 (57.2)	515 (58.7)
Metformin	340 (77.4)	692 (78.9)
Sulfonylurea	102 (23.2)	227 (25.9)
DPP-4 inhibitor	256 (58.3)	256 (29.2)
GLP-1RA	81 (18.5)	167 (19.0)
Alpha glucosidase inhibitor	10 (2.3)	8 (0.9)
Thiazolidinedione	25 (5.7)	59 (6.7)

DPP-4, dipeptidyl peptidase-4; ECA, external control arm; eGFR, estimated glomerular filtration rate; EHR, electronic health record; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; ICA, internal control arm; Q, quartile; RAS, renin–angiotensin system; RCT, randomised control trial; SBP, systolic blood pressure; SD, standard deviation; SGLT-2i, sodium-glucose co-transporter-2 inhibitor; UACR, urine albumin-to-creatinine ratio

- Median standardised mean difference was 0.000 (interquartile range 0.000–0.004) across matching parameters, indicating good model performance and balance of baseline characteristics across groups (**Figure 2**)

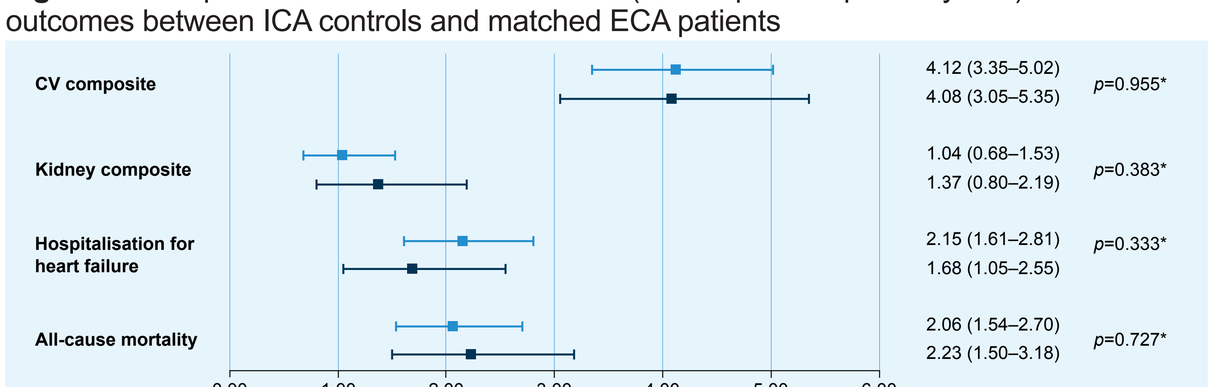
Figure 2. ASMD before matching and for the ECA cohort



AFF, atrial fibrillation or flutter; ASMD, absolute standardised mean difference; BMI, body mass index; CAD, coronary artery disease; CABG, coronary artery bypass graft; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase-4 inhibitor; ECA, external control arm; eGFR, estimated glomerular filtration rate; EHR, electronic health record; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; HF, heart failure; KDIGO, Kidney Disease Improving Global Outcomes; MI, myocardial infarction; PAD, peripheral artery disease; RCT, randomised controlled trial; SBP, systolic blood pressure; UACR, urine albumin-to-creatinine ratio

- Furthermore, crude incidence rates (events per 100 patient-years) of study outcomes were similar between the ECA and ICA (**Figure 3**)

Figure 3. Comparison of crude incidence rates (events per 100 patient-years) of clinical outcomes between ICA controls and matched ECA patients



*Hypothesis test to compare IRs between matched ECA vs ICA controls H_0: IR_ECA=IR_ICA; H_a: IR_ECA≠IR_ICA
CI, confidence interval; CV, cardiovascular; ECA, external control arm; ICA, internal control arm; IR, incidence rate

Conclusions

- High alignment in baseline characteristics and outcome incidence rates indicates adequate homogeneity between the ICA and the matched ECA
- Our results demonstrate the feasibility of creating an ECA in a large indication such as CKD, opening the possibility to evaluate clinical outcomes with an ECA-augmented subgroup in the future

Acknowledgements: The FIDELIO-DKD (NCT02540993) and FIGARO-DKD (NCT02545049) clinical trials were funded by Bayer AG. Medical writing and editorial assistance were provided by Ben Castle, MSc (Healthcare Consultancy Group), with funding from Bayer AG.

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Abstract 956 presented at the International Society for Pharmacoepidemiology (ISPE) 2024; 24–28 August 2024; Berlin, Germany