Randomized clinical trial replication for cardiovascular outcomes of EMPA-REG trial: retrospective cohort study

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BACKGROUNDS

Randomized clinical trial duplication study

- Randomized controlled trials (RCTs) are generally regarded as the gold standard for determining cause-effect relationships between medications and diseases.
- But they have clear limitations: they are expensive, have a limited patient population, and are difficult to follow-up for a long time
- If the results of real-world data (RWD) study can be obtained the same as that of RCT, it will be easier to make regulatory decisions based on the results of future RWD studies.

Study Question

- To what extent findings from existing RCTs can be replicated in the RWD?

METHODS

Target for duplication

- This study used a cohort study design to assess the effect of empagliflozin versus sitagliptin on cardiovascular safety outcomes
- EMPA-REG OUTCOME trial (NCT01131676) was selected to target for duplication.

RCT-RWD agreement assessment

- **Regulatory agreement (RA):** replication of the direction and statistical significance
- **Estimate agreement (EA):** RWD estimate that lies within the RCT 95% confidence interval
- **Standardized difference (SD):** hypothesis tests to evaluate whether there was a difference in findings

Study Design

- **The inclusion/exclusion criteria and follow up** method were applied as same with RCT.
- **Primary outcomes:** major adverse cardiovascular events (MACEs) (all-cause death, myocardial infarction, and stroke)
- **Secondary outcomes:** all-cause death, myocardial infarction, hospitalization for unstable angina, coronary revascularization procedure, stroke, transient ischemic attack, and hospitalization for heart failure
- In order to minimized residual confounding as much as possible, a total of 76 covariates were used and 1:1 propensity score matching was done.

RESULTS

Demographics

- We followed-up (median, 2.7 years) 23,126 matched patients with type 2 diabetes mellitus (11,563 empagliflozin users and 11,563 sitagliptin users).

Characteristics	EMPA-REG Outcome® (RCT)		EMPA-REG Duplicate (RWD)	
	Placebo	Empagliflozin	Sitagliptin	Empagliflozin
Age	63.2 ± 8.8	63.1 ± 8.6	55.5 ± 11.3	55.6 ± 10.9
Male – no. (%)	1680 (72.0)	3336 (71.2)	6799 (58.8)	6829 (59.1)
CV risk factor				
Coronary artery disease	1763 (75.6)	3545 (75.6)	10657 (92.2)	10699 (92.5)
Multi-vessel coronary artery disease	1100 (47.1)	2179 (46.5)	5944 (51.4)	6056 (52.4)
History of myocardial infarction	1083 (46.4)	2190 (46.7)	836 (7.2)	877 (7.6)
Coronary artery bypass graft	563 (24.1)	1175 (25.1)	3195 (27.6)	3264 (28.2)
History of stroke	553 (23.7)	1084 (23.1)	1030 (8.9)	1057 (9.1)
Peripheral artery disease	479 (20.5)	982 (21.0)	687 (5.9)	661 (5.7)
Metformin	1734 (74.3)	3459 (73.8)	8422 (72.8)	8382 (72.5)
Insulin	1135 (48.6)	2252 (48.0)	2098 (18.1)	2074 (17.9)
Sulfonylurea	992 (42.5)	2014 (43.0)	5428 (46.9)	5441 (47.1)
Thiazolidinedione	101 (4.3)	198 (4.2)	1309 (11.3)	1301 (11.3)
GLP-1 agonist	70 (3.0)	126 (2.7)	78 (0.7)	74 (0.6)

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Values are represented as mean ± standard deviation or number (%); CV, cardiovascular; RCT, randomized clinical trial; RWD, real-world data

RCT-RWD agreement

- RA was achieved in 7 out of 8 cardiovascular disease outcomes, and agreement was achieved in all outcome in EA and SD

	HR (95% CI)		Std. diff	Agreement		
	EMPA-REG Outcome® (RCT)	EMPA-REG Duplicate (RWD)		RA	EA	SD
MACEs	0.86 (0.74-0.99)	0.87 (0.79-0.96)	0.1	Y	Y	Y
All-cause death	0.68 (0.57-0.85)	0.78(0.67-0.91)	1.0	Y	Y	Y
Myocardial infarction	0.87 (0.70-1.09)	0.91(0.76-1.08)	0.3	Y	Y	Y
Stroke	1.18 (0.89-1.56)	0.89(0.75-1.05)	-1.7	N	Y	Y
Hospitalization for unstable angina	0.99 (0.74-1.34)	0.94(0.88-1.01)	-0.3	Y	Y	Y
Coronary revascularization	0.86 (0.72-1.04)	0.94(0.87-1.02)	0.8	Y	Y	Y
Transient ischemic attack	0.85 (0.51-1.42)	0.88(0.74-1.04)	0.1	Y	Y	Y
Hospitalization for heart failure	0.65(0.50-0.85)	0.85(0.75-0.95)	1.8	Y	Y	Y

EA, estimate agreement; HR, hazard ratio; MACEs, major adverse cardiovascular events; RA, regulatory agreement, RCT, randomized clinical trial; RWD, real-world data; SD, standardized difference; Stdiff, standardized difference;

CONCLUSION

- Our study results suggest that RWD results can replicate RCT results satisfactorily and have the potential for providing evidence for future regulatory decision-making.
- Further research is needed to determine whether RWD findings can be reliable evidence in various clinical settings or specific patient groups.

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