**Comparison of Adverse Kidney Outcomes with Empagliflozin and Linagliptin Use in Patients with Type 2 Diabetic Patients in a Real-world Setting**

**SUPPLEMENTAL MATERIALS**

SUPPLEMENTAL TABLE 1. Codes for inclusion/exclusion criteria, baseline comorbid conditions and medication use

SUPPLEMENTAL TABLE 2. Diabetes complications severity index

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SUPPLEMENTAL TABLE 4. Linear mixed model for assessing the decline in estimated glomerular filtration rate (eGFR)

SUPPLEMENTAL FIGURE 1. Estimated glomerular filtration rate (eGFR) trajectory of empagliflozin and linagliptin users

**SUPPLEMENTAL TABLE 1. Codes for inclusion/exclusion criteria, baseline comorbid conditions and medication uses.**

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| **Inclusion criteria:** |
| Type 2 diabetes mellitus | ICD-9-CM: 250ICD-10-CM: E11 |
| **Medication** | **Anatomical Therapeutic Chemical (ATC) code** |
| Empagliflozin | A10BK03 |
| Linagliptin | A10BH05  |
| **Exclusion criteria:** |
| Type 1 diabetes mellitus | ICD-9-CM: 250.x1, 250.x3ICD-10-CM: E10 |
| Kidney transplantation | ICD-9-CM: V42.0ICD-10-CM: Z94.0 |
| Dialysis | Hemodialysis: M24-003,M24-010,M24-013F,M24-039,M24-040,M24-041, M24-042 , M24-043, M24-045 , M24-046 , M24-047 , M24-048 , M24-049 , M24-050 , M24-051 ,M24-052,M24-053,M24-054,M24-055,M24-056,M24-057Peritoneal dialysis: 49-444, 58002C, E80-037, M24-001, M24-002, M24-053, M24-054, M24-055,M24-056,M24-057,M24-064,S41-050 |
| Glomerulonephritis | ICD-9-CM: 583.9, 581.3, 582.1, 583.1, 582.2 ICD-10-CM: N02.8, N05.0, N04.1, N03.2, N04.2, N05.2 |
| **Medication** | **Anatomical Therapeutic Chemical (ATC) code** |
| Other SGL2i (dapagliflozin, canagliflozin) | A10BK01, A10BK02 |
| Other DPP4i (sitagliptin,vildagliptin,saxagliptin,alogliptin) | A10BH01, A10BH02, A10BH03, A10BH04 |
| **Baseline Comorbidity** |
| Hypertension | ICD-9-CM: 401-405ICD-10-CM: I10~I13,I15, N26.2 |
| Hyperlipidemia | ICD-9-CM: 272ICD-10-CM: E75.2, E75.3, E75.5, E75.6, E77, E78, E88.1, E88.2, E88.89  |
| Peptic ulcer  | ICD-9-CM: 272ICD-10-CM: K25, K26, K27, K28 |
| Liver diseases | ICD-9-CM: 5712, 5714, 5715, 5716ICD-10-CM: K702, K703, K73, K717, K740, K742, K746, K743, K744, K745 |
| Cancer | ICD-9-CM: 140-208ICD-10-CM: Cxxx, z5112 |
| Severe liver diseases | ICD-9-CM: 5722, 5723, 5724, 5728ICD-10-CM: K729, K766, K767, K721 |
| Metastatic cancer | ICD-9-CM: 196, 197, 198, 1990, 1991ICD-10-CM: C77, C78, C79, C80 |
| **Baseline medications** | **Anatomical Therapeutic Chemical (ATC) code** |
| **Other antidiabetic agents** | 　 |
|  Insulins | A10A |
|  Metformin  | A10BA02, A10BD |
|  Sulfonylureas | A10BB, A10BD02 |
|  Acarbose  | A10BF |
|  Thiazolidinediones (TZD) | A10BG |
|  Glucagon-like peptide-1 (GLP-1)  | A10BJ |
|  Meglitinides | A10BX |
| **Lipid-lowering agents**  | 　 |
|  Statins  | C10AA,C10BA,C10BX  |
|  Fibrates | C10AB, C10BA |
|  Others | C10AC, C10AX |
| **Anti-hypertensive medication** | 　 |
|  ACEI | C09A, C09B |
|  ARB | C09C, C09D |
|  Direct renin inhibitor | C09X |
|  Diuretics | C03 |
|  Thiazide | C03A |
|  Furosemide | C03CA01 |
|  Diuretics-potassium sparing | C03D, C03E |
|  Beta-blockers | C07 |
|  Calcium channel blockers | C08 |
| **NSAIDs** | M01AA, M01AX, M01AB, M01AC, M01AE, M01AG, M01AH |
| **Concomitant medications**  | **Anatomical Therapeutic Chemical (ATC) code** |
| NSAIDs | M01AA, M01AX, M01AB, M01AC, M01AE, M01AG, M01AH |
| Antibacterial agents for system use | J01G, J01CA, J01CE, J01CF, J01CR, J01E, J02AC01, J01XA01, J01XA02, J01AA07 |
| Diuretics | C03 |
|  Thiazide | C03A |
|  Furosemide | C03CA01 |
|  Diuretics-potassium sparing | C03D, C03E |
| ACEIs | C09A, C09B |
| ARBs | C09C, C09D |
| Immunosuppressants  | L04AD, L01BA01  |
| Antiviral agents for system use | J05AB01, J05AB06, J05AB14 |
| Contrast media  | V08A,V08B, V08CA |
| ACEIs: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; DPP4i, dipeptidyl peptidase-4 inhibitor ;NSAID: non steroid anti-inflammatory drug ; SGLT2i, sodium-glucose cotransporter 2 inhibitor |

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| **SUPPLEMENTAL TABLE 2. Diabetes Complications Severity Index. (DCSI)** |
| **Complication** |  | **ICD-9 Code (New DCSI) Revised** | **ICD-10 Code (New DCSI) Revised** | **Score****:1** | **Score****:2** |
| **Retinopathy (0-2)** | Diabetic ophthalmologic disease | x | E08, E09 | • | 　 |
|  | Background retinopathy | 362.01 | E11.3x, excludingE11.34x, E11.35x | • | 　 |
|  | Other retinopathy | 362.1 | H35.0x | • | 　 |
|  | Retinal edema | 362.81-362.83 | H35.6xH35.8xH35.9 | • | 　 |
|  | CSME | 362.53 | H35.35x | • | 　 |
|  | Other retinal disorders | 362.81, 362.82 | H35.6xH35.8xH35.9 | • | 　 |
|  | Proliferative retinopathy | 362.02 | E11.34xE11.35x | 　 | •• |
|  | Retinal detachment | 361.x | H33.x | 　 | •• |
|  | Blindness | 369.x | H54.x | 　 | •• |
|  | Vitreous hemorrhage | 379.23 | H43.1x | 　 | •• |
| **Nephropathy (0-2)** | Diabetic nephropathy | 250.4, 249.4x | E08, E09, E10,E11, E13Relevant SubcodesE\*\*.21, E\*\*.22, E\*\*.29 | • | 　 |
|  | Acute glomerulonephritis | 580 | N00.x | • | 　 |
|  | Nephrotic syndrome, Hypertension, nephrosis | 581.x | N04.x | • | 　 |
|  | Chronic glomerulonephritis | 582 | N03.x | • | 　 |
|  | Nephritis/nephropathy | 583 | N05.x | • | 　 |
|  | CKD, Stage 1-Stage 3, CKD unspecified | 585.1, 585.2, 585.3, 585.9 | N18.1, N18.2,N18.3, N18.9 | • | 　 |
|  | CKD, Stage 4-Stage 5, ESRD | 585.4, 585.5, 585.6 | N18.4, N18.5, N18.6 | 　 | •• |
|  | Renal failure NOS | 586, 593.9 | N19 | 　 | •• |
|  | Urine protein ≥30 mg/g of creatinine, or (+) dipstick protein or serum creatinine ≥1.5 mg/Dl | UACR, SCr | 　 | • | 　 |
|  | Serum creatinine >2.0 mg/dL | SCr | 　 | 　 | •• |
|  | eGFR ≤29 mL/min2 (CKD, Stages 4-5) | eGFR | 　 | 　 | •• |
| **Neuropathy (0-1)** | Diabetic neuropathy | 357.2, 250.6, 249.6 | E08, E09, E10,E11, E13Relevant SubcodesE\*\*.4x | • | 　 |
|  | Cranial nerve palsy | 951.0, 951.1, 951.3 | S04.x | • | 　 |
|  | Mononeuritis of upper limb and mononeuritis multiplex  | 354.x | G56.x | • | 　 |
|  | Mononeuritis of lower limb and unspecified site | 355.x | G57.x | • | 　 |
|  | Unspecified hereditary and idiopathic peripheral neuropathy | 356.9 | G60.9 | • | 　 |
|  | Myasthenic syndromes in diseases classified elsewhere | 358.1 | G73.3 | • | 　 |
|  | Carotid sinus syncope | 　 | G90.01 | • | 　 |
|  | Paralytic strabismus  | 　 | H49.x | • | 　 |
|  | Charcot’s arthropathy | 713.5 | M14.6x | • | 　 |
|  | Neurogenic bladder | 596.54 | N31.9 | • | 　 |
|  | Autonomic neuropathy | 337.0x | G90.09 | • | 　 |
|  | Peripheral autonomic neuropathy in disorders classified elsewhere | 337.1x | G90.8, G90.9, G99.0 | • | 　 |
|  | Gastroparesis/diarrhea | 564.5, 536.3 | K31.84, K59.1 | • | 　 |
|  | Orthostatic hypotension | 458.0 | I95.1 | • | 　 |
| **Cerebrovascular (0-2)** | TIA | 435 | G45.x | • | 　 |
|  | Stroke | 431, 433, 434, 436 | I61.x, I63.x, I65.x,I66.x, I67.81 | 　 | •• |
| **Cardiovascular (0-2)** | Atherosclerosis | 440.x,excluding 440.23 & 440.24 | I70.x,excluding I70.25 & I70.26x | • | 　 |
|  | Other IHD | 411 | I24.x | • | 　 |
|  | Angina pectoris | 413 | I20.x | • | 　 |
|  | Other chronic IHD | 414 | I25.x,excluding I25.2 | • | 　 |
|  | Other ASCVD | 429.2 | I25.10 | • | 　 |
|  | Myocardial infarction | 410 | I21.x, I22.x, I23.x | 　 | •• |
|  | Old myocardial infarction | 412 | I25.2 | 　 | •• |
|  | Ventricular fibrillation, arrest | 427.3 | I48.x | 　 | •• |
|  | Atrial fibrillation, arrest | 427.5 | I46.x | 　 | •• |
|  | Paroxysmal ventricular tachycardia | 427.1 | I47.x | 　 | •• |
|  | Ventricular fibrillation and flutter | 427.4 | I49.x | 　 | •• |
|  | Heart failure | 428 | I50.x | 　 | •• |
|  | Atherosclerosis, severe | 440.23, 440.24 | I70.25170.26x | 　 | •• |
|  | Aortic aneurysm/dissection | 441 | I71.x | 　 | •• |
| **Peripheral vascular disease (0-2)** | Diabetic PVD | 250.7, 249.7 | E08, E09, E10, E11,E13Relevant SubcodesE\*\*.51, E\*\*.59, E\*\*.621 | • | 　 |
|  | Other aneurysm, LE | 442.3 | I72.4 | • | 　 |
|  | PVD | 440.21, 443.81, 443.9 | I70.21xI73.89I73.9 | • | 　 |
|  | Foot wound + complication | 892.1 | S91.3x | • | 　 |
|  | Embolism/thrombosis (LE) | 444.22 | I74.3 | 　 | •• |
|  | Gangrene | 785.4 | E10.52, E11.52I96 | 　 | •• |
|  | Gas gangrene | 040.0 | A48.0 | 　 | •• |
|  | Ulcer of lower limbs | 707.1 | L97.x | 　 | •• |
| **Metabolic (0-2)** | Ketoacidosis | 250.1, 249.1 | E1010, E1011 | 　 | •• |
|  | Hyperosmolar | 250.2, 249.2 | E1101, E1100 | 　 | •• |
|  | Other coma | 250.3, 249.3 | E10641, E11641 | 　 | •• |
| Reference: Glasheen WP, Renda A, Dong Y. Diabetes Complications Severity Index (DCSI)-Update and ICD-10 translation. *J Diabetes Complications*. 2017;31(6):1007-1013 |

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| **SUPPLEMENTAL TABLE 3. Factors associated with acute kidney injury occurrences.** |
| Variables | No. of patients | No. of events | Person-time (years) | AdjustedHR | 95% CI | *p-value* |
| **Study cohort** |  |  |  |  |  |  |  |  |
|  | Linagliptin group | 3521 | 144 | 5238.6  | 1.00  | (Reference) |  |
|  | Empagliflozin group | 3521 | 67 | 4687.3  | 0.60  | (0.45 | - | 0.82) | 0.001  |
| **Age group, years** |  |  |  |  |  |  |  |  |
|  | < 65  | 4727 | 132 | 6729.4  | 1.00  | (Reference) |  |
|  | ≧65  | 2315 | 79 | 3196.5  | 0.87  | (0.64 | - | 1.19) | 0.38  |
| **Sex (Male vs. Female)** | 4154 | 148 | 5838.8  | 1.37  | (1.01 | - | 1.86) | 0.05  |
| **eGFR (mL/min/1.73 m2)** |  |  |  |  |  |  |
|  | 60-89.9 vs. ≧90  | 2895 | 95 | 4093.8  | 1.55  | (1.07 | - | 2.24) | 0.02  |
|  | 45-59.9 vs. ≧90  | 1114 | 63 | 1521.0  | 1.95  | (1.25 | - | 3.06) | 0.003  |
| **HbA1C** |  |  |  |  |  |  |  |  |
|  | >7.0 vs. ≦7.0 | 5834 | 167 | 8250.8  | 1.03  | (0.70 | - | 1.51) | 0.88  |
|  | Missing vs. ≦ 7.0 | 111 | 4 | 134.6  | 0.58  | (0.19 | - | 1.80) | 0.35  |
| **UACR** |  |  |  |  |  |  |  |  |
|  | No proteinuria  | 2267 | 31 | 3288.9  | 1.00  | (Reference) |  |
|  | Microproteinuria  | 1260 | 44 | 1769.7  | 2.22  | (1.36 | - | 3.62) | 0.002  |
|  | Macroproteinuria  | 596 | 45 | 802.8  | 3.13  | (1.87 | - | 5.24) | <.001 |
|  | Missing | 2919 | 91 | 4064.5  | 2.05  | (1.33 | - | 3.17) | 0.001  |
| **Baseline Comorbidity** |  |  |  |  |  |  |  |  |
|  | Retinopathy | 499 | 34 | 664.0  | 1.82  | (1.22 | - | 2.74) | 0.004  |
|  | Nephropathy | 1791 | 77 | 2559.8  | 0.93  | (0.65 | - | 1.34) | 0.71  |
|  | Neuropathy | 659 | 22 | 944.3  | 0.74  | (0.46 | - | 1.18) | 0.21  |
|  | Cerebrovascular | 492 | 22 | 659.9  | 1.42  | (0.88 | - | 2.30) | 0.15  |
|  | Angina pectoris | 533 | 19 | 767.4  | 0.79  | (0.47 | - | 1.32) | 0.36  |
|  | Myocardial infarction | 280 | 18 | 356.7  | 1.16  | (0.65 | - | 2.08) | 0.62 |
|  | Heart failure | 431 | 38 | 554.6  | 1.07  | (0.68 | - | 1.68) | 0.77  |
|  | Peripheral vascular disease | 199 | 9 | 273.2  | 1.08  | (0.53 | - | 2.21) | 0.83  |
|  | Metabolic | 13 | 2 | 18.7  | 1.78  | (0.36 | - | 8.73) | 0.48  |
|  | Hypertension | 4383 | 154 | 6170.8  | 1.29  | (0.88 | - | 1.87) | 0.19  |
|  | Hyperlipidemia | 4422 | 118 | 6368.7  | 0.96  | (0.68 | - | 1.36) | 0.83  |
|  | Peptic ulcer  | 817 | 43 | 1147.5  | 1.67  | (1.16 | - | 2.41) | 0.006  |
|  | Liver diseases | 1085 | 40 | 1602.9  | 1.13  | (0.76 | - | 1.66) | 0.55  |
|  | Cancer | 465 | 43 | 591.6  | 2.24  | (1.51 | - | 3.34) | <.001 |
|  | Severe liver diseases | 18 | 2 | 21.5  | 0.43  | (0.08 | - | 2.29) | 0.33  |
| 　 | Metastatic cancer | 45 | 7 | 46.1  | 2.88  | (1.20 | -　 | 6.91) | 0.018  |

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| **SUPPLEMENTAL TABLE 3. Factors associated with acute kidney injury occurrences (continued).** |
| Variables | No. of patients | No. of events | Person-time (years) | AdjustedHR | 95% CI | *p-value* |
| **Prior medication**  |  |  |  |  |  |  |  |  |
|  | **Other antidiabetic agents** |  |  |  |  |  |  |  |  |
|  |  | Insulins | 813 | 47 | 1128.6  | 1.31  | (0.90 | - | 1.91) | 0.16  |
|  |  | Metformin | 6807 | 196 | 9652.4  | 0.63  | (0.35 | - | 1.12) | 0.12  |
|  |  | Sulfonylureas | 4133 | 133 | 6007.8  | 1.02  | (0.75 | - | 1.39) | 0.91  |
|  |  | Acarbose  | 2265 | 80 | 3343.5  | 1.14  | (0.83 | - | 1.57) | 0.41  |
|  |  | Thiazolidinediones  | 1656 | 35 | 2466.4  | 0.57  | (0.38 | - | 0.85) | 0.006  |
|  |  | Glucagon-like peptide-1  | 386 | 15 | 561.1  | 1.23  | (0.70 | - | 2.17) | 0.47  |
|  |  | Meglitinides  | 670 | 33 | 992.8  | 1.19  | (0.79 | - | 1.79) | 0.40  |
|  | **Lipid-lowering agents**  |  |  |  |  |  |  |  |  |
|  |  | Statins  | 4290 | 119 | 6145.3  | 0.79  | (0.56 | - | 1.11) | 0.17  |
|  |  | Fibrates | 756 | 18 | 1102.3  | 0.76  | (0.45 | - | 1.27) | 0.29  |
|  |  | Others | 197 | 6 | 287.1  | 0.96  | (0.41 | - | 2.23) | 0.92  |
|  | **Anti-hypertensive medication** |  |  |  |  |  |  |  |  |
|  |  | ACEI | 450 | 17 | 666.8  | 0.77  | (0.42 | - | 1.42) | 0.40  |
|  |  | ARB | 3659 | 114 | 5192.2  | 0.85  | (0.59 | - | 1.23) | 0.39  |
|  |  | Direct renin inhibitor | 20 | 2 | 30.2  | 3.91  | (0.93 | - | 16.54) | 0.06  |
|  |  | Thiazide | 154 | 10 | 230.2  | 1.22  | (0.57 | - | 2.65) | 0.61  |
|  |  | Furosemide | 362 | 39 | 461.7  | 0.80  | (0.51 | - | 1.25) | 0.33  |
|  |  | Diuretics-potassium sparing | 276 | 32 | 363.1  | 1.12  | (0.64 | - | 1.98) | 0.69  |
|  |  | Beta-blockers | 2186 | 88 | 3080.2  | 1.09  | (0.79 | - | 1.51) | 0.59  |
|  |  | Calcium channel blockers | 1530 | 66 | 2158.7  | 1.25  | (0.91 | - | 1.74) | 0.18  |
|  | **NSAID** | 612 | 24 | 833.0  | 0.73  | (0.46 | - | 1.16) | 0.19  |
| **Concomitant medications** |  |  |  |  |  |  |  |  |
|  | NSAID | 595 | 60 | 786.3  | 3.56  | (2.52 | - | 5.05) | <.001 |
|  | Antibacterial agents for system use | 214 | 38 | 274.8  | 3.06  | (2.06 | - | 4.55) | <.001 |
|  | **Anti-hypertensive medication** |  |  |  |  |  |  |  |  |
|  |  | Thiazide | 107 | 8 | 162.5  | 1.87  | (0.79 | - | 4.42) | 0.16  |
|  |  | Furosemide | 390 | 79 | 460.5  | 5.22  | (3.50 | - | 7.76) | <.001 |
|  |  | Diuretics-potassium sparing | 265 | 43 | 310.7  | 2.55  | (1.53 | - | 4.23) | <.001  |
|  |  | ACEI | 314 | 21 | 445.2  | 1.10  | (0.61 | - | 2.00) | 0.74  |
|  |  | ARB | 2883 | 85 | 4068.2  | 0.82  | (0.59 | - | 1.15) | 0.26  |
|  | Immunosuppressants  | 44 | 4 | 56.2  | 2.44  | (0.87 | - | 6.80) | 0.09  |
|  | Antiviral agents for system use | 12 | 3 | 15.7  | 5.26  | (1.49 | - | 18.52) | 0.01  |
|  | Contrast media  | 17 | 6 | 21.3  | 6.90  | (2.74 | - | 17.37) | <.001 |

ACEIs: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; eGFR: estimated glomerular

filtration rate; NSAID: non steroid anti-inflammatory drug; UACR: urine albumin-creatinine ratio

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| **SUPPLEMENTAL TABLE 4. Linear mixed model for the decline changes in eGFRs.+**  |
| Variables | Adjusted coefficient (β) | 95% CI | *P* value |
| **Treatment group** |  |  |  |  |  |
|  | Linagliptin  | Reference |  |
|  | Empagliflozin  | 1.51  | (0.30  | - | 2.72) | 0.01  |
| **Follow-up time (in quarter)\*** | -0.72  | (-0.81  | - | -0.64) | <.001 |
| **Study cohort\*Follow-up time**  |  |  |  |  |  |
|  | Linagliptin\*time | Reference |  |
|  | Empagliflozin\*time | 0.27  | (0.15  | - | 0.40) | <.001 |
| **Acute kidney injury during follow-up time** |  |  |  |  |  |
|  | No | Reference |  |
|  | Yes | -11.89  | (-15.36 | - | -8.42) | <.001 |
| **Age group, years** |  |  |  |  |  |
|  | <65  | Reference |  |
|  | ≧65  | -17.31  | (-18.57  | - | -16.05) | <.001 |
| **Sex** |  |  |  |  |  |
|  | Female | Reference |  |
|  | Male | -9.47  |  (-10.67 | - | -8.27) | <.001 |
| **Baseline HbA1C** |  |  |  |  |  |
|  | ≦7.0 | Reference |  |
|  | > 7.0 | 2.88  | (1.25  | - | 4.52) | 0.001  |
|  | Missing | 1.76 | (-3.19 | - | 6.71) | 0.49 |
| + eGFR: estimated glomerular filtration rate\*Follow-up time was the number of eGFR measurement in a 3-month interval over the study period. |

**SUPPLEMENTAL FIGURE 1.** Estimated glomerular filtration rate (eGFR) trajectory between empagliflozin and linagliptin groups**.** A. PSM cohort (N=7042); B. patient with acute kidney injury (N=211); C. patients without acute kidney injury (N=6831).

