Supplemental Material

Comparative Effectiveness of Metformin versus Sulfonylurea on Kidney Function Decline or Death Among Patients with Reduced Kidney Function

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Appendix 1, as supplied by the authors. Appendix to: Hung AM, Hackstadt AJ, Griffin MR, et al. Comparative effectiveness of metformin versus sulfonylureas on kidney function decline or death among patients with reduced kidney function: a retrospective cohort study. *CMAJ Open* 2023. DOI:10.9778/cmajo.20210207.

Supplemental Methods

Study Population: New users were patients who filled a first hypoglycemic prescription without any diabetic drug fill in the 180 days prior. Patients were required to persist on this hypoglycemic medication with medication gaps no larger than 180 days until they reached the index date. The index date was defined as reaching an eGFR of <60 ml/min/1.73m2 (Supplemental Figure 1). The index date was restricted to dates between January 1, 2002 and December 30, 2016 to allow sufficient collection of baseline data and follow-up.

Covariates: Study covariates were measured up to 720 days prior to the index date (or index date + 360 days for the 361 days and beyond analysis) and included: age, sex, race, year, number of months from initial antidiabetic medication start to reaching the reduced kidney function threshold, and Veterans Integrated Service Networks (VISN) of care. Physiologic variables were evaluated as the measure closest to the index date and included: body mass index [BMI], blood pressure, HbA1c, low density lipoprotein levels, hemoglobin, presence of proteinuria, and creatinine (both the historical measure prior to index date and the creatinine on the index date). Healthcare utilization (hospitalization, nursing home and additional insurance use including Medicare or Medicaid) was measured in the year prior to the reduced kidney function threshold (or reduced kidney function threshold + 360 days for the 361 days and beyond analysis). We collected data on smoking, and co-morbidities defined in Supplemental Table 2. Selected medications' fills ascertained through pharmacy claims within 180-days were covariates.

eGFR Decline: Identifying the timing of a *sustained* decline in eGFR is challenging in studies using EHR data. This study opted to use the first confirmed eGFR showing a decline because the decline had to have begun by that time or earlier. However, the necessity of observing a confirmatory eGFR 3-12 months later raises the question of whether the second measurement should be the event date. We note that the use of the second "confirmatory" eGFR may exacerbate the uncertainty in event timing, pushing the time back 3-12 months, and if ascertainment bias driven by more aggressive testing in one arm is a concern, this too would be exaggerated by using the confirmatory measurement. In most cases, using rules that require "looking into the future" are discouraged in pharmacoepidemiology because of the potential for immortal time bias. In this, a death that occurred after the first measurement showing an eGFR decline but before a confirmatory measurement would be observed and treated as a death event. Thus, a minimum of 3 months of survival after the eGFR measurement is required to have a sustained eGFR decline event, but no survival time is required to have the primary composite outcome event.

Cohorts: While the effect on mortality was similar between the first and later years, the effect on eGFR decline was notably different. Reaching a sustained 40% eGFR decline or death within the first year of eGFR <60 ml/min is suggestive of serious renal dysfunction. Thus, the events that occurred within that first year may have been indicative of a unique population with significant multimorbidity. This population, which can ultimately only be identified retrospectively by their outcomes, is important and worth understanding, but it is also distinct from the remainder of the cohort. Thus, we separated the first year from the others to better distinguish this population from the remainder which continues in a more typical renal trajectory. This is akin to analyses of cancer outcomes that will begin one-year after medication initiation in order to account for lag-time bias. We noted that after the first year, the proportional hazards assumption was well met for the remaining timeframe.

Propensity Score Weighting: The propensity score modeled the probability of metformin or sulfonylurea continuation at index date given the observed covariates, VISN, and an indicator for imputed covariates. Missing covariates were handled with multiple imputations (see section on multiple imputation). We used matching weights derived from the propensity score to balance both exposure groups on observed covariates. Matching weights were derived beginning at 361 days for the cohort who remained at risk. Standardized mean differences (SMD) were calculated as the difference between groups in number of standard deviations. Smaller SMD values indicate less difference between groups with 0 indicating perfect balance in mean or proportion.

Multiple Imputation: Multiple imputation is used to address missingness in the baseline covariates in the propensity score model and the covariate adjusted cox proportional hazard models. Data values are imputed using Predictive Mean Matching (PMM) which is a semi-parametric imputation approach that fits a regression model to impute the missing values

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but randomly selects a value to impute among observed values closest to the regression-predicted value. Selecting a value from the observed values ensures that imputed values are plausible. PMM is used to create 20 multiply imputed data sets. A regression model is fit for each of the imputed data sets. Predicted values are obtained from a regression model with parameters found using Rubin's rules to combine the parameter estimates from the regression models on the 20 imputed data sets. The modes (discrete variables) and the medians (continuous variables) of the imputed data sets are used for the missing covariate values when calculating the predicted values.

Though multiple imputation was used in estimating the propensity scores, a single set of predicted propensity scores is used to create the propensity score weights. The objective is to create a single set of weights that balance the observed covariate distributions and the observed missingness patterns. The effectiveness of these weights is judged by the weighted table of patient characteristics. The multiple imputation process was leveraged for the propensity score estimation, but it was not essential for attaining proper variance estimates in the weighted analysis. The correct variance estimates are found by treating the propensity score weights as sampling weights, which are akin to survey weights. In contrast, when the covariates are used in direct covariate adjustment, the multiple imputation is needed to attain proper estimates of uncertainty. For ease of computation, the same 20 imputed data sets are used for each regression model.

Competing Risk Analysis It is important to specify the different objectives of the proportional hazards model used in the primary analysis and the competing risks method used to estimate the cumulative incidence function. The primary analysis estimates a cause-specific hazard ratio using a cox proportional hazard regression model treating competing events as censoring events. This estimator is most useful for understanding the association between the medications and outcomes, sometimes referred to as the etiological effect. However, in the presence of competing risks, this hazard ratio cannot be used to estimate the absolute or realized effect size. There is no longer a straightforward relationship between the hazard rate and risk in this model. In particular, the survival curve created by censoring for competing events is biased and its inverse will likely overestimate risk (Anderson 2012)[1]. Risk is estimated using a multistate model (Putter 2007)[2] where the initial state is reduced kidney function. A patient could transition to the outcome of interest or a competing event and these events are treated as terminal states to allow the estimation of the cumulative incidence rate. Cumulative incidence curves are generated using the Aalen–Johansen estimator (Aalen 1978)[3]. The non-parametric Aalen-Johansen estimator is preferred over the semi-parametric Fine and Gray model (Fine 1999) because it allows more flexibility when modeling the cumulative incidence function[4]. The Fine and Gray model assumes proportional sub-distributional hazards and that those censored for competing risks are still in the risk set, both of which are not appropriate for this study. Presenting both cause-specific hazard and estimates of risk is essential to understanding the etiological and the realized effects, which may differ in magnitude due to the competing risks. Thus, both the cause-specific hazard and the cumulative incidence function was estimated for the weighted cohorts.

1) Per Kragh Andersen, Ronald B Geskus, Theo de Witte and Hein Putter (2012) Competing risks in epidemiology: possibilities and pitfalls. International Journal of Epidemiology 41:861–870.

2) H. Putter, M. Fiocco and R. B. Geskus (2007) Tutorial in biostatistics: Competing risks and multi-state models. Statistics in Medicine 26:2389–2430.

3) Odd O. Aalen and Soren Johansen (1978) An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. Scandinavian Journal of Statistics, 5 (3): 141-150.

4) Jason P. Fine and Robert J. Gray (1999) "A Proportional Hazards Model for the Subdistribution of a Competing Risk." Journal of the American Statistical Association 94 (446) : 496-509.

Supplemental table 1: The definition of the composite outcome (reaching the first of GFR event or ESRD).

Outcome	***Definition***
1. GFR event	***40***% decrease in eGFR noted on the first of 2 outpatient laboratory values. Requires change to be present on 2 outpatient GFR calculations between 3 and 12 months apart
2. ESRD	
a. eGFR <15 ml/min/1.73m2	An outpatient laboratory measurement of eGFR <15 ml/min/1.73 m^2 with confirmatory eGFR <15 or dialysis code at least 3 months and less than 12 months apart
b. dialysis	Either an inpatient and outpatient code or 2 outpatient codes for dialysis as the primary diagnosis (at least 3 months and less than 12 months apart) Codes include 1. ICD-9: 585.6 for ESRD on dialysis 2. Procedure codes 3993 or 5498 indicating dialysis treatment 3. CPT4 codes 90935, 90937, 90945, 90947, 90989, 90993, 90921, 90925, indicating dialysis or dialysis training 4. ICD-9: V56 encounter for dialysis catheter; V56.2 PD adjustment; V56.8 Peritoneal dialysis; V45.1 dialysis status
c. transplant	Either an inpatient and outpatient code for renal transplant as the primary diagnosis Codes include 1. ICD 9 codes: 996.81 Complications of Transplanted kidney; V42.0 Kidney replaced by transplant or 55.6, 55.61, 55.69 transplant of Kidney 2. CPT codes: 50360, 50365, 50380 Renal Auto or Allotransplantation

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Supplemental table 2: Definitions of comorbid conditions based on codes in 720 days before reaching Kidney threshold

Covariate Condition	Inclusive conditions	Definition*
Malignancy	Cancer excluding non melanoma skin cancer	ICD 9- CM diagnosis codes:140.X-208.X (exclude 173) ICD10 diagnosis codes: C00* - C96*; D37* -D48*
Liver failure	End stage liver disease	ICD 9- CM diagnosis codes: 570.X- 573.X ICD10 diagnosis codes: K72*; K70.*; K73.*; K74.*; K76.*
Respiratory Failure	Respiratory failure/ Pulmonary Embolism/Hypertension	ICD 9- CM diagnosis codes: 518.81, 518.83, 518.84, 799.1, 415.X, 416.X ICD10 diagnosis codes: J96.*; R092; I26.9*; I27. *
Congestive Heart Failure	CHF (excluding post procedure-CHF	ICD 9- CM diagnosis codes: 428.X, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93 ICD10 diagnosis codes: I11.0, I13.0, I13.2, I50.9, I50.1,I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43
Cardiovascular disease	1. MI	ICD 9- CM diagnosis codes: 410.X, 412.X, 429.7X ICD10 diagnosis codes: I21*
	2. Obstructive coronary disease	ICD 9- CM diagnosis codes: 411.X, 413.X, 414.X ICD10 diagnosis codes: I24.*; I25.*; I20.* ICD 9- CM procedure codes: 36.01, 36.02, 36.03, 36.05, 36.09, 36.10-36.19 CPT procedure codes: 33533-36, 33510-23, 33530, 92980-82,92984, 92995-6, 92974
	3. Peripheral artery disease or revascularization	ICD 9- CM diagnosis codes: 440.2X, 442.2, 443.1, 443.9, 445.0X ICD10 diagnosis codes: I70.2*; I72.*; I77.*; I73.9; I75.* ICD9-CM procedure codes:38.08-09, 38.18, 38.38,38.39, 38.48, 38.49, 38.88, 38.89, 39.25, 39.29, 39.5, 84.1X CPT procedure codes: 35226,35256, 35286, 35351, 35355, 35371, 35372, 35381, 35454, 35456, 35459, 35473, 35474, 35482, 35483, 35485, 35492, 35493, 35495, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35571, 35583, 35585, 35587, 35646, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 34800, 34802-5
	4. Carotid revascularization	ICD9-CM procedure codes: 38.12, 38.11, 00.61, 00.63, 39.28 CPT procedure codes: 35301, 0005T, 0006T, 0007T, 0075T, 0076T, 37215, 37216 ICD10 procedure code: 031H0AG, 031H0JG, 031H0KG, 031H0ZG, 031J09G, 031J0AG, 031J0JG,031J0KG,031H09G, 031J0ZG, 037H34Z, 037H3DZ, 037H3ZZ, 037H44Z, 037H4DZ, 037H4ZZ, 037J3DZ, 037J3ZZ, 037J44Z, 037J4DZ, 037J4ZZ, 037K34Z, 037K3DZ, 037K3ZZ, 037K4DZ,037K4ZZ, 037L34Z, 037L3DZ, 037L3ZZ, 037L44Z, 037L4DZ, 037L4ZZ, 037M34Z, 037M3DZ, 037M3ZZ, 037M44Z, 037M4DZ, 037M4ZZ, 037N34Z, 037N3DZ, 037N3ZZ, 037N44Z, 037N4DZ, 037N4ZZ, 037P34Z, 037P3DZ, 037P3ZZ, 037P44Z, 037P4DZ, 037P4ZZ, 037Q34Z, 037Q3DZ, 037Q3ZZ, 037Q44Z, 037Q4DZ, 037Q4ZZ, 03CH0ZZ, 03CH3ZZ, 03CH4ZZ, 03CJ0ZZ, 03CJ3ZZ, 03CJ4ZZ, 03CK0ZZ, 03CK3ZZ, 03CK4ZZ, 03CL0ZZ, 03CL3ZZ, 03CL4ZZ, 03CM0ZZ, 03CM3ZZ, 03CM4ZZ, 037J34Z, 03CN0ZZ, 03CN3ZZ, 03CN4ZZ, 03CP0ZZ, 03CP3ZZ, 037K44Z, 03CP4ZZ, 03CQ0ZZ, 03CQ3ZZ, 03CQ4ZZ

		HCPCS procedure code: S2211
TIA		ICD 9- CM diagnosis codes: 435.X ICD10 diagnosis codes: G45.0; G45.1;G45.8; G45.9;I67.848
Stroke		ICD 9- CM diagnosis codes: 430.X, 431.X. 434.X, 436.X ICD10 diagnosis codes: I67.89, I60.9, I61.9, I63.30, I63.40 , I63.50, I66.09, I66.19, I66.29, I66.9, I67.89
Serious Mental illness	1. Dementia	ICD 9- CM diagnosis codes: 290.X, 291.2, 292.82, 294.1X, 331.0-331.1X, 331.82 ICD 10 diagnosis codes: F03.9;F01.5*; F10.27; F19.97; F02.80; F02.81; G30.9; G31.* Medications: Donepezil, Rivastigmine, Galantamine, Tacrine, Memantine Bethanechol, Ambenonium, Atomoxetine, Ergoloid Mesylates, Dihydrogenated Ergot, Neostigmine, Physostigmine, Pyridostigmine, Riluzole, Hydergine
	2. Depression	ICD 9- CM diagnosis codes: 311, 300.4, 296.2, 296.3, V79.0 ICD 10 diagnosis codes: F33.9, F34.1, F32.*
	3. Schizophrenia	ICD 9- CM diagnosis codes: 295.X ICD 10 diagnosis codes: F20.*
	4. Bipolar disorder	ICD 9- CM diagnosis codes: 296.0, 296.4X, 296.5X, 296.6X, 296.7, 296.80, 296.89 ICD 10 diagnosis codes: F30.* F31.*
	5. Post traumatic stress disorder	ICD 9- CM diagnosis codes: 309.81 ICD 10 diagnosis codes: F43.10; F43.12
Cardiac valve disease		ICD 9- CM diagnosis codes: 394.X, 395.X, 396.X, 424.0,424.1 ICD 10 diagnosis codes: I05.*; I06.*; I08.*; I34.*; I35.*;
Arrhythmia	Atrial fibrillation/flutter	ICD 9- CM diagnosis codes: 427.3X ICD 10 diagnosis codes: I48.91, I48.92
Smoking		ICD 9- CM diagnosis codes:305.1, V15.82, 989.84 ICD 10 diagnosis codes: F17.200, Z87.891, T65.211A, T65.212A, T65.213A, T65.214A, T65.221A, T65.222A, T65.223A, T65.224A, T65.292A, T65.293A, T65.294A Medications: Varenicline tartrate, Nicotine Replacement (gum, patch, lozenge)
COPD/ Asthma		ICD 9- CM diagnosis codes:491.X, 492.X, 493.X, 496.X, V17.5, V81.3 ICD 10 diagnosis codes: J41.0, J41.1, J44.9, J44.1, J44.0, J41.8, J42-J43.9, J45.20, J45.22, J45.21, J45.990,J45.991, J45.909, J45.998, J45.902, J45.901, Z13.83
HIV		ICD 9- CM diagnosis codes: 042, 079.53, 795.71, V08 ICD 10 diagnosis codes: B20.*; B97.35; Z21
Parkinson's Disease		ICD 9- CM diagnosis codes: 332 ICD 10 diagnosis codes: G20; G21.* Medications: Apokyn, Apomorphine, Carbidopa/levodopa, Entacapone, Pergolide, Pramipexole, Ropinirole, Rotigotine, Selegiline, Tolcapone, Zelapar, Azilect/Rasagiline, Emsam, Isocarboxazid, Phenelzine, Tranylcypromine, Biperiden/Akineton, Comtan/Entacapone, Safinamide, Trihexyphenidyl
Urinary Tract / Kidney Infection		ICD 9- CM diagnosis codes: 590.*, 599.0*, 595.0 ICD 10 diagnosis codes: N11.*; N39.* N30.*
Osteomyelitis		ICD 9- CM diagnosis codes: 730.* ICD 10 diagnosis codes: M86.1*; M86.2*; M86.6*; M86.9*; A02.24
Sepsis/Bacteremia		ICD 9- CM diagnosis codes: 995.91, 995.92, 038.*, 036.2, 790.7 ICD 10 diagnosis codes: A41.9; R65.20; A41.*; A39.4;R78.81

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Pneumonia		ICD 9- CM diagnosis codes: 480.*-486.*, 487.0 ICD 10 diagnosis codes: J11.*; J12.*; J13.*; J14.*; J15.*; J16.*; J17.*; J18.*
Fractures (any)		ICD 9- CM diagnosis codes: 733.1*, 800.*-829.*, E887 ICD 10 diagnosis codes: M84.*; M80.*; S02; *; S12.*; S22.*; S32.*; S42.*; S52.*; S62.*; S72.*; S82.*; S92.*
Falls		ICD 9- CM diagnosis codes: E880.*, E881.*, E884.*,E885.9 ICD 10 diagnosis codes: Z98.8, W18.30XA, W18.49XA, W01.110A,W01.198A,W19.XXXA
Osteoporosis		ICD 9- CM diagnosis codes: 733.0* ICD 10 diagnosis codes: M81.*
Retinopathy		ICD 9- CM diagnosis codes: 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 362.07 ICD 10 diagnosis codes: E08.311; E08.319; E08.3211; E08.3212; E08.3291; E08.3292; E08.3293; E08.3299; E08.3219; E08.3213; E08.3313; E08.3312; E08.3311; E08.3319; E08.3391; E08.3392; E08.3393; E08.3399; E08.3411; E08.3412; E08.3413; E08.3419; E08.3491; E08.3492; E08.3493; E08.3499; E08.3511; E08.3512; E08.3513; E08.3519; E08.3521; E08.3522; E08.3523; E08.3529; E08.3531; E08.3532; E08.3533; E08.3539; E08.3541; E08.3542; E08.3543; E08.3549; E08.3551; E08.3552; E08.3553; E08.3559; E08.3591; E08.3592; E08.3593; E08.3599; E11.311; E11.3491; E11.3492; E11.3493; E11.3499; E11.3591 ; E11.3592; E11.3593; E11.3599 ; E11.3591; E11.3592; E11.3593; E11.3599; E11.3291; E11.3292; E11.3293; E11.3299; E11.3391; E11.3392; E11.3393; E11.3399; E11.3491; E11.3492; E11.3493; E11.3499; E11.319
Amputations		ICD 9- CM diagnosis codes: V49.75; V49.76; V49.77 ICD 10 diagnosis codes: Z89.519; Z47.81; Z89.6*
Medications		
Antipsychotics	Atypical and typical antipsychotic medications	Lithium, Clozapine, Haloperidol, Loxapine, Lurasidone, Molindone, Olanzapine, Paliperidone, Quetiapine Fumerate; Risperidone, Aripiprazole, Asenapine, Ziprasidone, Chlorpromazine, Fluphenazine, Fluphenazine Deconate, Mesoridazine, Perphenazine, Thioridazine, Thiothixene; Trifluoperazine; Triflupromazine, Asenapine, Chlorprothixene, Iloperidone, Molindone, Promazine, Piperacetazine, Methotrimeprazine, Acetophenazine, Fazaclo/clozapine, Molindone
ACE Inhibitors alone/combination		Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril
ARBs alone/combination		Candesartan, Eprosartan, Irbesartan, Losartan, Azilsartan, Olmesartan, Telmisartan, Valsartan
Beta-blockers		Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol Tartrate, Metoprolol Succinate, Propranolol, Penbutolol, Pindolol, Nadolol, Sotalol, Timolol, Nebivolol
Calcium Channel Blockers		Amlodipine, Isradipine; Felodipine, Nifedipine, Nifedipine ER, Nicardipine; Diltiazem, Verapamil, Nimodipine; Nisoldipine; Bepridil, Amlodipine/Atorvastatin, Clevidipine Butyrate; Mibefradil
Thiazide diuretics/ Potassium sparing diuretics		Chlorothiazide, Chlorthalidone, Hydrochlorothiazide, Methyclothiazide, Trichlormethiazide, Metolazone, Indapamide, Eplerenone; Amiloride, Spironolactone,

		Triamterene, Hydrochlorothiazide/Triamterene, Hydrochlorothiazide/Spironolactone, Bendroflumethiazide, Benzthiazide, Cyclothiazide, Hydroflumethiazide, Polythiazide, Quinethazone
Other Antihypertensives		Doxazosin, Prazosin, Terazosin, Clonidine, Guanabenz, Guanfacine, Hydralazine, Methyldopa, Metyrosine, Reserpine, Minoxidil, Alfuzosin, Silodosin, Alseroxylon, Cryptenamine, Deserpidine, Diazoxide, Guanethidine, Mecamylamine, Pargyline, Rescinnamine, Trimethaphan Camsylate
Anti-arrhythmics Digoxin and other inotropes	1. Digoxin	Digoxin, Digitalis
	2. Anti- Arrythmics	Adenosine, Amiodarone, Lidocaine, Flecainide, Ibutilide, Procainamide, Propafenone, Ropafenone, Quinidine, Disopyramide, Verapamil, Dofetilide, Mexiletine, Moricizine, Tocainide
Anticoagulants		Warfarin, Argatroban, Bivalirudin, Dalteparin, Enoxaprin, Eptifibatide, Fondaparinux, Heparin, Lepirudin, Tirofiban, Tinzaparin, Reviparin, Nadroparin, Ardeparin, Certoparin, Dabigatran
Platelet inhibitors, not aspirin		Clopidogrel, Ticlopidine, Aspirin/Dipyridamole, Dipyridamole alone, Abciximab, Factor IX, Factor VIIa, Factor VIII, Prasugrel, Ticagrelor
Statins		Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, Simvastatin, Rosuvastatin, Cerivastatin Pitavastatin, Lovastatin ER, Ezetimibe/Simvastatin, Lovastatin/Niacin, Amlodipine/Atorvastatin
Non-Statin lipid lowering drugs		Cholestyramine, Colesevelam, Clofibrate, Colestipol, Niacin, Niacinamide, Fish Oil Concentrate, Omega 3 Fatty Acids, Gemfibrozil, Fenofibrate, Fenofibric Acid, Ezetimibe Omacor, Tricor/Fenofibrate,Ezetimibe/Simvastatin
Nitrates		Amyl Nitrate, Isosorbide Dinitrate, Isosorbide Mononitrate, Erythrityl Tetranitrate, Nitroglycerin (all forms--SA, Patch, SL, Ointment; Aerosol spray),Ranolazine
Aspirin		Aspirin, Aspirin/ Dipyridamole
Loop Diuretics		Furosemide, Ethacrynic acid, Bumetanide, Torsemide

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; COPD = chronic obstructive pulmonary disease; CPT = Current Procedural Terminology; ICD-9- CM = International Classification of Diseases, Ninth Revision; ICD 10= International Classification of Diseases, Tenth Revision; MI = myocardial infarction; TIA = transient ischemic attack.

If medications are combinations of 2 drug classes then a patient is recorded as using both medications.

* Each co-morbid condition was defined as present if there was 1 specified inpatient or 2 specified outpatient codes separated by 30 days, or 1 specified procedure code or prescription for a medication defining that comorbid condition before reaching the kidney

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Supplemental Table 3: Full cohort of patient characteristics on index date of kidney function decline and on day 361 after kidney function decline

Characteristics	Full Unweighted Cohort at Index Date			Full Unweighted Cohort at 361 Days		
	Metformin (n = 74096)	Sulfonylurea (n = 28967)	SMD†	Metformin (n = 36038)	Sulfonylurea (n = 15541)	SMD†
Age, years*	67.69 [62.7, 74.4]	71.57 [64.2, 79.0]	0.302	69.10 [64.4, 76.0]	73.36 [65.9, 80.3]	0.312
Male, N (%)	70849 (95.6)	28419 (98.1)	0.143	34484 (95.7)	15296 (98.4)	0.162
Race, N (%)			0.046			0.105
White	62649 (84.6)	24210 (83.6)		31855 (88.4)	13304 (85.6)	
Black or African American	9777 (13.2)	4215 (14.6		3415 (9.5)	1971 (12.7)	
Other‡	1670 (2.3)	542 (1.9)		768 (2.1)	266 (1.7)	
Cohort entry to index date, months*	17.00 [6.77, 36.67]	13.77 [5.97, 29.63]	0.172	31.33 [20.1, 51.2]	27.67 [18.7, 43.5]	0.186
Year of reaching kidney threshold, N (%)			0.796			0.84
2002-03	3051 (4.1)	4703 (16.2)		1710 (4.7)	2870 (18.5)	
2004-05	5572 (7.5)	5507 (19.0)		2904 (8.1)	3143 (20.2)	
2006-07	8755 (11.8)	5833 (20.1)		4823 (13.4)	3309 (21.3)	
2008-09	9619 (13.0)	3926 (13.6)		5157 (14.3)	2127 (13.7)	
2010-11	12019 (16.2)	3255 (11.2)		6449 (17.9)	1726 (11.1)	
2012-13	12653 (17.1)	2575 (8.9)		6827 (18.9)	1280 (8.2)	
2014-15	14484 (19.5)	2186 (7.5)		8125 (22.5)	1082 (7.0)	
2016	7943 (10.7)	982 (3.4)		43 (0.1)	4 (0)	
Laboratory Variables						
HbA1c (median [IQR])	6.5 [6.1, 7.0]	6.6 [6.1, 7.3]	0.144	6.4 [6.0, 6.9]	6.5 [6.1, 7.2]	0.21
HbA1c Missing = TRUE (%)	2980 (4.0)	1129 (3.9)	0.006	1423 (3.9)	583 (3.8)	0.01
Estimated Glomerular filtration rate prior to index date ml/min*	70.3 [65.0,78.3]	69.0 [64.2,76.0	0.142	--	--	
Estimated Glomerular filtration rate on index date ml/min*	55.8 [51.5, 58.0]	55.5 [51.4,58.0]	0.006	56.2 [52.7, 58.3]	55.7 [51.7, 58.1]	0.104
Estimated Glomerular filtration on day 361, ml/min*	--	--		65.0 [57.1, 74.0]	63.1 [55.0, 71.8]	0.177
Estimated Glomerular filtration missing	609 (0.8)	380 (1.3)	0.048	2194 (6.1)	1268 (8.2)	0.081
Hemoglobin, g/dL*	14.0 [12.9,15.0]	14.1 [13.0,15.2]	0.05	13.9 [12.9, 14.8]	14.0 [12.9, 15.1]	0.068
Missing Hemoglobin measure (%)	3823 (5.2)	1700 (5.9)	0.031	1890 (5.2)	989 (6.4)	0.048
Low Density Lipoprotein, mg/dL*	84 [67, 105]	89 [71, 111]	0.133	80 [65, 99]	86 [69, 105]	0.16
Missing Low Density Lipoprotein measure (%)	1381 (1.9)	1092 (3.8)	0.115	591 (1.6)	456 (2.9)	0.087
Microalbumin to creatinine ratio stage N(%)			0.159			0.152
A1 (<30 mg/g- normal)	32759 (44.2)	10719 (37.0)		16934 (47.0)	6259 (40.3)	
A2 (30-300 mg/g-	8365 (11.3)	3149 (10.9)		4433 (12.3)	1808 (11.6)	

microalbuminuria)						
A3 (>300 mg/g macroalbuminuiria)	2000 (2.7)	938 (3.2)		938 (2.6)	505 (3.2)	
Unknown	30972 (41.8)	14161 (48.9)		13733 (38.1)	6969 (44.8)	
Proteinuria by urinalysis N (%)			0.072			0.084
Negative	36063 (48.7)	13513 (46.6)		18401 (51.1)	7439 (47.9)	
Urine Protein Trace or 1+	10635 (14.4)	4107 (14.2)		4667 (13.0)	2092 (13.5)	
Proteinuria present at 2+	2530 (3.4)	1001 (3.5)		967 (2.7)	431 (2.8)	
Proteinuria present at 3+ or 4+	667 (0.9)	455 (1.6)		248 (0.7)	200 (1.3)	
Clinical Variables						
Systolic Blood pressure, mm/Hg*	130 [118, 140]	131 [120, 143]	0.112	131 [120, 140]	132 [121, 143]	0.081
Diastolic Blood pressure,mm/Hg*	73 [65, 80]	71 [64, 80]	0.123	73 [66, 80]	71 [64, 79]	0.172
Missing Diastolic Blood pressure	86 (0.1)	50 (0.2)	0.015	30 (0.1)	12 (0.1)	0.002
Body Mass Index, kg/meter *	31.0 [27.6,35.2]	30.1 [26.9,34.1]	0.159	30.7 [27.5, 34.8]	30.1 [26.9, 33.9]	0.121
Missing BMI measure (%)	12796 (17.3)	5791 (20.0)	0.07	6006 (16.7)	3050 (19.6)	0.077
Baseline Co-morbidities N (%)						
Malignancy	8063 (10.9)	3580 (12.4)	0.046	4146 (11.5)	2095 (13.5)	0.06
Liver disease	1321 (1.8)	825 (2.8)	0.071	573 (1.6)	320 (2.1)	0.035
HIV	242 (0.3)	103 (0.4)	0.005	84 (0.2)	51 (0.3)	0.018
Congestive heart failure	6152 (8.3)	4212 (14.5)	0.197	2990 (8.3)	2455 (15.8)	0.232
Cardiovascular disease	19296 (26.0)	9880 (34.1)	0.177	9364 (26.0)	5338 (34.3)	0.183
Stroke	1961 (2.6)	1024 (3.5)	0.051	897 (2.5)	558 (3.6)	0.064
Transient Ischemic Attack	751 (1.0)	407 (1.4)	0.036	362 (1.0)	209 (1.3)	0.032
Serious Mental Illness	17933 (24.2)	5669 (19.6)	0.112	8310 (23.1)	2906 (18.7)	0.107
Smoking	9464 (12.8)	3483 (12.0)	0.023	3776 (10.5)	1532 (9.9)	0.021
Chronic Obstructive Pulmonary Disease	11328 (15.3)	5311 (18.3)	0.082	5494 (15.2)	2894 (18.6)	0.09
History of Respiratory failure	2277 (3.1)	980 (3.4)	0.018	1288 (3.6)	709 (4.6)	0.05
History of Sepsis	1118 (1.5)	509 (1.8)	0.02	754 (2.1)	385 (2.5)	0.026
History of Pneumonia	2411 (3.3)	1426 (4.9)	0.084	1363 (3.8)	937 (6.0)	0.104
Arrhythmia	10374 (14.0)	5529 (19.1)	0.137	5328 (14.8)	3301 (21.2)	0.169
Cardiac valve disease	2109 (2.8)	1205 (4.2)	0.071	1118 (3.1)	699 (4.5)	0.073
Parkinson	550 (0.7)	316 (1.1)	0.037	387 (1.1)	211 (1.4)	0.026
Urinary tract infection	2512 (3.4)	1379 (4.8)	0.069	1513 (4.2)	894 (5.8)	0.072
Osteomyelitis	344 (0.5)	195 (0.7)	0.028	149 (0.4)	99 (0.6)	0.031
Osteoporosis	515 (0.7)	243 (0.8)	0.016	293 (0.8)	147 (0.9)	0.014
Falls	168 (0.2)	75 (0.3)	0.007	123 (0.3)	74 (0.5)	0.021
Fractures	1371 (1.9)	683 (2.4)	0.035	781 (2.2)	419 (2.7)	0.034
Amputation	253 (0.3)	170 (0.6)	0.036	128 (0.4)	71 (0.5)	0.016
Retinopathy	522 (0.7)	385 (1.3)	0.062	209 (0.6)	189 (1.2)	0.067
Use of Medications N (%)						
Angiotensin II Receptor Blockers	9920 (13.4)	3190 (11.0)	0.073	20947 (58.1)	9533 (61.3)	0.066

Beta Blockers	36525 (49.3)	14880 (51.4)	0.042	5352 (14.9)	1922 (12.4)	0.072
Calcium Channel Blockers	21498 (29.0)	8654 (29.9)	0.019	18082 (50.2)	8151 (52.4)	0.045
Thiazide and potassium sparing diuretics	32308 (43.6)	11459 (39.6)	0.082	10641 (29.5)	4726 (30.4)	0.019
Loop Diuretics	11398 (15.4)	6650 (23.0)	0.193	13572 (37.7)	5523 (35.5)	0.044
Other Antihypertensive medications	20684 (27.9)	7949 (27.4)	0.011	5229 (14.5)	3475 (22.4)	0.203
Statin Lipid Lowering Drugs	54817 (74.0)	18806 (64.9)	0.198	11059 (30.7)	4673 (30.1)	0.013
Non- Statin Lipid Lowering agents	13873 (18.7)	4642 (16.0)	0.071	27723 (76.9)	10776 (69.3)	0.172
Anti-arrhythmics digoxin/ inotropes	4852 (6.5)	3161 (10.9)	0.155	6743 (18.7)	2658 (17.1)	0.042
Anticoagulants, platelet inhibitors	6857 (9.3)	3167 (10.9)	0.056	2295 (6.4)	1578 (10.2)	0.138
Nitrates	8478 (11.4)	4690 (16.2)	0.138	3627 (10.1)	1815 (11.7)	0.052
Aspirin	15593 (21.0)	6457 (22.3)	0.03	4037 (11.2)	2350 (15.1)	0.116
Platelet Inhibitors Not aspirin	6885 (9.3)	3154 (10.9)	0.053	7452 (20.7)	3222 (20.7)	0.001
Antipsychotics	5721 (7.7)	1880 (6.5)	0.048	3318 (9.2)	1734 (11.2)	0.065
Oral Glucocorticoids	5751 (7.8)	2143 (7.4)	0.014	2506 (7.0)	912 (5.9)	0.044
Indicators of health care utilization N(%)						
Hospitalized within year (Veterans Health)	9837 (13.3)	4414 (15.2)	0.056	3997 (11.1)	2050 (13.2)	0.064
Hospitalized in 30 days (Veterans Health)	2732 (3.7)	1164 (4.0)	0.017	474 (1.3)	266 (1.7)	0.032
Hospitalized within year (Medicare/ Medicaid)	6165 (8.3)	3648 (12.6)	0.14	3102 (8.6)	2098 (13.5)	0.156
Hospitalized in 30 days (Medicare/ Medicaid)	1074 (1.4)	585 (2.0)	0.044	355 (1.0)	273 (1.8)	0.066
Medicaid use in last year	622 (0.8)	399 (1.4)	0.051	235 (0.7)	256 (1.6)	0.093
Medicare use in last year	24088 (32.5)	10820 (37.4)	0.102	13150 (36.5)	6555 (42.2)	0.117
Nursing Home encounter in last year	230 (0.3)	135 (0.5)	0.025	149 (0.4)	94 (0.6)	0.027
Medicare Advantage Use	11879 (16.0)	4546 (15.7)	0.009	7224 (20.0)	3010 (19.4)	0.017

*Median and Interquartile Ranges reported

† SMD, standardized mean differences are the absolute difference in means or percentage divided by an evenly weighted pooled standard deviation, or the difference between groups in number of standard deviations.

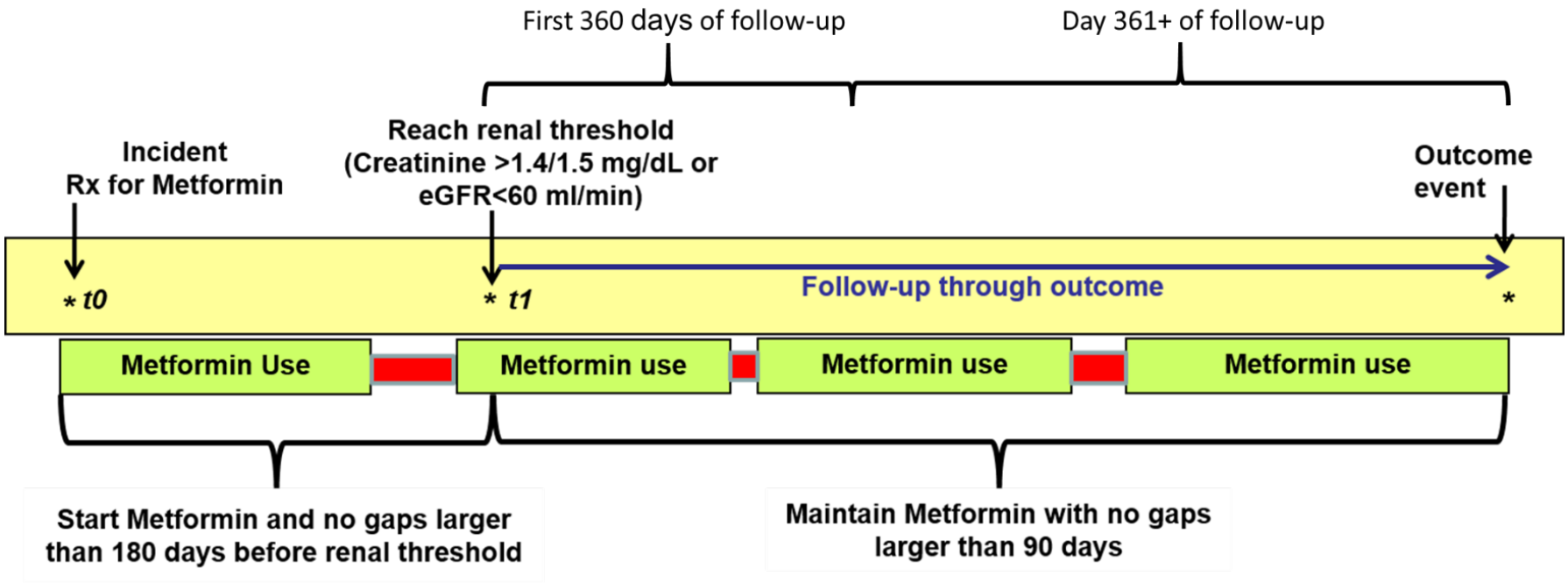
‡Other races include American Indian or Alaska Native, Asian, and Native Hawaiian or Pacific Islander.

Appendix 1, as supplied by the authors. Appendix to: Hung AM, Hackstadt AJ, Griffin MR, et al. Comparative effectiveness of metformin versus sulfonylureas on kidney function decline or death among patients with reduced kidney function: a retrospective cohort study. *CMAJ Open* 2023. DOI:10.9778/cmajo.20210207.

Supplemental Table 4: *Events and N at risk in each Subgroup- *Hazard Ratio reported are from weighted and unadjusted analyses*

	Metformin N= 12,571	**Sulfonylurea N= 12,637**		
Primary Outcome Kidney Event or Death	**Events (N)/ At Risk (N)**	**Events (N)/ At Risk (N)**	**Hazard Ratio* (95% CI)**	**p value for interaction**
Full matched weighted cohort	747/12,571	1033/12,637	0.76 (0.70, 0.83)	
Renin Angiotensin Aldosterone System Inhibitor				
No	295/3482	389/3461	0.65 (0.40, 1.04)	p=0.72
Yes	453/9089	644/9176	0.72 (0.65, 0.80)	
eGFR				
<45 ml/min	60/905	74/880	0.79 (0.59, 1.06)	p=0.01
≥ 45 ml/min	687/11666	958/11757	0.72 (0.66, 0.79)	
Race				
Black	60/1424	89/1429	0.71 (0.53, 0.95)	p=0.84
Nonblack	687/11147	943/11208	0.73 (0.67, 0.79)	
Age, y				
≥ 65	638/9580	873/9612	0.76 (0.69, 0.83)	p=0.80
<65	109/2989	160/3025	0.62 (0.50, 0.76)	
Secondary Outcome Kidney Event				
Full matched weighted cohort	110/12,571	149/12,637	0.89 (0.71, 1.12)	
Renin Angiotensin Aldosterone System Inhibitor				
No	22/3482	31/3461	0.65 (0.40, 1.04)	p=0.87
Yes	88/9089	118/9176	0.76 (0.60, 0.97)	
eGFR				
<45 ml/min	4/905	3/880	1.24 (0.32, 4.78)	p=0.15
≥ 45 ml/min	106/11666	146/11757	0.72 (0.58, 0.90)	
Race				
Black	9/1424	22/1429	0.43 (0.22, 0.84)	p=0.24
Nonblack	101/11147	127/11208	0.78 (0.62, 0.99)	
Age, y				
≥ 65	92/9580	110/9612	0.86 (0.68, 1.10)	p=0.05
<65	18/2989	39/3025	0.38 (0.24, 0.61)	

Supplemental Figure 1: Study Schema



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