ASSESSING POTENTIALLY INAPPROPRIATE MEDICATION USE IN PATIENTS AT RISK FOR ADVERSE DRUG EFFECTS: SPIRONOLACTONE AS A CASE STUDY

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A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
October 2019

Abstract

Background: Polypharmacy and potentially inappropriate medication (PIM) use are common and associated with considerable morbidity, yet they are often modifiable risk factors. However, some PIM use is a result of limited information on medication safety across patient kidney function. One such medication, spironolactone, an aldosterone antagonist indicated for heart failure, has been demonstrated in clinical trials to reduce morbidity and mortality among individuals with normal renal function, but its safety in those with chronic kidney disease (CKD) is unclear.

Methods: We used longitudinal data from the Atherosclerosis Risk in Communities (ARIC) study to quantify PIM use by estimated glomerular filtration rate (eGFR), and to assess the relationship between polypharmacy, PIM use, and subsequent hospitalization and death in older adults. We used commercial claims data from MarketScan and electronic health record data from the Geisinger Health System to identify predictors of spironolactone initiation among patients with heart failure, and used target trial emulation to characterize the risk of hyperkalemia and acute kidney injury (AKI) with spironolactone use among patients using loop diuretics.

Results: Participants in ARIC (N=6,392) with CKD reported more medications than those without CKD ($p<0.001$), and PIM use based on kidney function was prevalent (36%) among those with eGFR <30 ml/min/1.73m^2. More concurrent medications were associated with higher risks of hospitalization and death, but PIM use was not, and there were no differences in the relative risks associated with greater numbers of medications by CKD status. Among patients with incident heart failure in MarketScan (N=22,956) and Geisinger (N=16,547), 7.0% and 9.9% initiated spironolactone within two years, respectively. Patients with eGFR <30 were least likely

to initiate spironolactone compared to patients with eGFR 60-89 (meta-analyzed hazard ratio [HR]: 0.61, 95% confidence interval [CI]: 0.44-0.83). In Geisinger patients with heart failure using loop diuretics (N=17,110), spironolactone initiation was associated with increases in hyperkalemia and AKI risk compared to use of loop diuretics alone (HR 1.69 [CI: 1.35-2.10], and HR 1.12 [CI: 1.00-1.26], respectively), with no observed differences in the relative risk of either outcome associated with spironolactone by eGFR.

Conclusions: Polypharmacy and PIM use were common, with greater numbers of medications associated with greater risk of hospitalization or death. Spironolactone initiation was uncommon within two years of heart failure diagnosis, and least likely among patients with lower kidney function. The addition of spironolactone to loop diuretics increased the risk of hyperkalemia, and more modestly, AKI. Improved data on medication safety in patients with CKD are needed.

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1 Introduction

1.1 Background

1.1.1 Potentially inappropriate medication (PIM) use and polypharmacy

Potentially inappropriate medication (PIM) use as a consequence of unnecessary polypharmacy or using medications that are contraindicated based on kidney function is common, costly, and the cause of substantial morbidity.(1) The impact of PIMs is especially great among patients at an increased risk of adverse drug effects, and those with high medication burdens. For example, vulnerable patients like older adults or those with chronic kidney disease (CKD) are prescribed many medications concurrently including those with safety profiles that become complicated by age-related metabolic factors and renal physiology.(2) In patients with heart failure, where both polypharmacy(3) and CKD[1](4) are prevalent, the adverse effects associated with PIM use can range from minor to severe, but it is often associated with worse patient outcomes. In the context of CKD, this can be further exacerbated by medications that are primarily eliminated by the kidneys, or inherently nephrotoxic, as these patients may not be able to adequately clear the drug or its active and/or toxic metabolites, resulting in exaggerated pharmacologic effects or life-threatening conditions like hyperkalemia.(5) To prevent this, some drugs require a dose adjustment in CKD to accommodate their pharmacokinetics (PK), and other drugs are contraindicated at specific estimated glomerular filtration rate (eGFR) thresholds to mitigate any potential risks. While unnecessary polypharmacy may be preventable with better coordination of care between providers, mitigating the risk for redundant medications, drug-drug interactions, and inappropriate dosing,(6-8) the risks associated with PIM use based on kidney function are not always modifiable. Because of limited therapeutic options for patients with CKD,

[1] Roughly 12-74% of patients with heart failure have CKD; prevalence estimates are highly dependent on study population, heart failure severity, and definition of CKD.

medications are sometimes prescribed in patients where their use may not be necessarily recommended but where any benefits are presumed to outweigh their known risks. Separately, data on the safety and efficacy of certain medications for use in those with reduced kidney function are challenged by insufficient pre-market study and regulatory frameworks.(9-11)

1.1.2 Guidelines for medication use in patients with reduced kidney function

Many approved medications do not have adequate information on appropriate use in patients with CKD.(9, 12-14) The U.S. Food and Drug Administration (FDA) issued an updated "Guidance for Industry" in 2010 recommending sponsors conduct PK studies in patients with CKD for new drug applications (NDA), specifically when the drug is expected to be used in patients with CKD, and when reduced renal function may inhibit adequate clearance of the drug or its metabolites.(15) Although this guidance focuses on drugs that are mainly renally-cleared,[2] FDA does recommend renal studies for drugs that are cleared by non-renal routes, such as those secreted in bile.(15) While the impact of the FDA "Guidance" has been positive in that a greater proportion of NDAs contain renal PK data, there are still many drugs where these studies have not been conducted. In an internal FDA survey, after the first "Guidance" in 1998, 61% of submitted NDAs between 2003 and 2007 for new molecular entities had renal PK studies, as opposed to 44% prior to the guidance.(16) Despite ostensible improvements in collecting pharmacologic data on those with CKD, the safety and efficacy of many medications in this population of patients with multifaceted and evolving medical needs are still relatively unknown, as those with reduced renal function are systematically excluded from clinical trials;(10, 11, 17) this particularly affects legacy medications approved many years ago. Drug manufacturers justify excluding adults with reduced renal function from pre-market testing because of their higher

[2] Those meeting an Agency standard of greater than 30% of the dose excreted unchanged in the urine.

propensity for adverse drug effects compared to adults with preserved kidney function, and the altered PK of a drug when used in these patients;(10, 11, 16, 18) currently, no regulation mandates their inclusion in clinical studies during drug development. All of this creates uncertainly in the clinical application of some medications for use in patients with CKD, and although published guidelines and other resources do exist, conflicting information is often provided on when and how to use certain medications based on kidney function.(9) There are deleterious consequences to this uncertainty in that potentially useful medications may be withheld unnecessarily from CKD patients, and conversely, when some medications are prescribed, it may be in the context of an uncertain risk profile across the spectrum of kidney function.

1.1.3 Spironolactone as a case study for unclear utilization and safety in CKD

1.1.3.1 Spironolactone's indication and pharmacologic properties

Spironolactone (Aldactone®), a potent mineralocorticoid receptor antagonist medication approved in 1960, exemplifies the uncertainty that arises from limited safety data on a medication with known effectiveness. Spironolactone is an aldosterone antagonist indicated for the treatment of heart failure, primarily those with New York Heart Association class III or IV heart failure with severe left ventricular systolic dysfunction, and other conditions including hyperaldosteronism and hypertension.(19) Spironolactone antagonizes aldosterone via competitive binding of receptors in the late distal convoluted tubule responsible for aldosterone-dependent sodium-potassium (Na^+/K^+) exchange, rendering the receptor complex inactive and preventing its translocation into the nucleus of target cells; this inhibits the production of mediator proteins responsible for stimulating Na^+/K^+ exchange.(20-22) By inhibiting Na^+/K^+ exchange, spironolactone acts as a potassium-sparing diuretic allowing more sodium to pass into

the renal collecting duct, and thus promoting diuresis. Spironolactone has ~65% oral bioavailability and a relatively slow onset of action. It is rapidly metabolized by the liver (~1.6 hour half-life) into several active metabolites (primarily sulfur-containing molecules) with relatively long half-lives (13.8 to 16.5 hours), and is mostly excreted in the urine.(19, 23)

1.1.3.2 Spironolactone's cardioprotective and renoprotective effects

Clinical trial data suggest that the addition of spironolactone to standard medication regimens in heart failure, including angiotensin-converting-enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARBs), and β-blockers, is an effective treatment strategy in mitigating morbidity and mortality associated with heart failure. In 1999, the Randomized Aldactone Evaluation Study (RALES) established spironolactone's effectiveness in reducing heart failure re-hospitalization and death in patients with heart failure with reduced ejection fraction (HFrEF) also on loop diuretics. More than a decade later, the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial assessed spironolactone's utility in heart failure with preserved ejection fraction (HFpEF) and found similar reductions with respect to heart failure re-hospitalization, but not mortality. Other randomized studies (24, 25) have corroborated the beneficial effects of spironolactone treatment in various heart failure populations, hypothesizing its pharmacologic effects as an aldosterone antagonist are multifaceted and may benefit patients in various ways, including preserving kidney function.

Aldosterone is critical in heart failure and CKD pathophysiology. In heart failure, aldosterone antagonists can prevent cardiovascular remodeling as a result of heart failure progression, and manage edematous states.(19, 21) Because spironolactone is a pleiotropic hormone, it can bind to mineralocorticoid receptors in various types of tissues including myocardium, endothelium,

and vascular smooth muscles, promoting cardioprotective effects.(20, 26) Edwards et al. found that spironolactone use was associated with reduced left ventricular mass and arterial stiffness in patients with early stage CKD.(27) Studies have also shown that inhibiting the renin-angiotensin-aldosterone system (RAAS) can slow the progression of CKD by reducing systemic arterial and intraglomerular pressure, and by blocking the effects of angiotensin II on the production of mesangial cells, and initiating fibrosis.(28-32) Although ACEi and ARBs act on this system with renoprotective effects, they do not meaningfully suppress aldosterone leading to "aldosterone escape."(29, 31, 33, 34) Evidence suggests that aldosterone contributes to nephropathy,(32, 35) and it is hypothesized that spironolactone's further blockade of the RAAS may be beneficial in mitigating decline in renal function.(30, 31, 33) Prolonged RAAS activation also has adverse cardiovascular effects including increases in myocardial extracellular matrix fibrillar collagen, left ventricular hypertrophy, and myocardial stiffness, and can lead to heart failure.(34)

Since 2000, dozens of clinical trials funded by government and industry sponsors investigating spironolactone's efficacy in treating various cardiomyopathies, liver diseases, and kidney diseases have been completed or are ongoing. The clinical trials in patients with kidney disease have investigated its efficacy among those with varying degrees of kidney dysfunction, from mild or moderate CKD, looking at cardiovascular endpoints like blood pressure and cardiovascular-related mortality, but also renal endpoints like changes in proteinuria and mitigating further decline in kidney function.

1.1.3.3 Spironolactone's safety in reduced kidney function

The single ingredient formulation is not recommended for those with significant impairment of renal function due to their increased risk for primarily hyperkalemia and acute kidney injury

(AKI);(19-21) however, published guidelines have been somewhat inconsistent with respect to what level of kidney function use is contraindicated.(36, 37) Spironolactone was approved without renal safety studies which makes it difficult to adequately establish a risk profile for hyperkalemia and AKI across the spectrum of kidney function. Even in the RALES and TOPCAT clinical trials, patients with reduced renal function were not included because of their increased risk for hyperkalemia and AKI, and therefore, despite a long-marketing history there is a paucity of published data on its potentially variable risks in this group. In several small randomized controlled trials (26, 38-40) looking at the effect of the mineralocorticoid receptor antagonists (including spironolactone) on various cardiovascular endpoints in patients with advanced CKD and those on dialysis, hyperkalemia was infrequent, with similar rates to the placebo groups; however, these studies were conducted in highly-controlled clinical settings, and include patients on eplerenone which is less potent than spironolactone. The spironolactone label does give general recommendations on dosing within ranges of eGFR, but it does not utilize a specific contraindicated eGFR threshold. The label also recommends spironolactone not be used with other potassium-sparing diuretics, or during potassium supplementation, and cautions against use with ACEi, ARBs, and nonsteroidal anti-inflammatory drugs (NSAID), as these may also increase the risk of hyperkalemia and AKI.(19)

While the potential for spironolactone-induced hyperkalemia and AKI is well understood based on the drug's mechanism of action, it is not well quantified, and the specific impact of patient kidney function on these risks remains uncertain. In the landmark RALES trial, not only were patients with eGFR less than 30 ml/min/1.73m^2 excluded, enrolled patients were dose-adjusted or discontinued based on changes in their serum creatinine or potassium.(41) Hyperkalemia and AKI were very rare in RALES, and other studies using similar exclusion criteria and monitoring.

(42, 43) Several clinical trials are currently ongoing and may lead to expanded use in heart failure and non-heart failure populations, including those with advanced CKD; presumably safety data will emerge from these studies. Nevertheless, given its rather convincing cardioprotective effects, and potential utility in mitigating CKD progression, in clinical practice today, patients use spironolactone at various levels of kidney function (44) with comorbidities and concomitantly with medications that put them at risk of hyperkalemia and AKI independent of their kidney function or spironolactone use. For that reason, isolating the direct effects of spironolactone on the subsequent development of hyperkalemia and AKI in the context of real-world use is needed to better inform current clinical practice and labeling.

1.2 Objectives

1) a) To characterize medication use across kidney function in older adults, with a focus on polypharmacy and medications deemed "potentially inappropriate" based on kidney function, or age, using data from the Atherosclerosis Risk in Communities (ARIC) study

   b) To quantify the risk of hospitalization and death among those with polypharmacy and PIM use, looking for differences by CKD status

2) To assess the correlates and likelihood of spironolactone initiation, and discontinuation among initiators, in patients with incident heart failure across the spectrum of kidney function, using data from Truven MarketScan Commercial Claims and Encounters database, and electronic health record (EHR) data from the Geisinger Health System

3) To quantify the risks of hyperkalemia and AKI associated with spironolactone use among patients with heart failure on loop diuretics, and to assess for differential risk by kidney function, using EHR data from the Geisinger Health System

2 Kidney function, polypharmacy, and potentially inappropriate medication use in a community-based cohort of older adults[3]

2.1 Abstract

Background: Chronic kidney disease (CKD) afflicts many older adults, and increases the risk for medication-related adverse events.

Objective: To assess the prevalence and associated morbidity and mortality of polypharmacy (use of several medications concurrently), and potentially inappropriate medication (PIM) use in older adults, looking for differences by CKD status.

Methods: We quantified medication and PIM use (from Beers criteria, the Screening Tool of Older People's Prescriptions, and Micromedex®) by level of estimated glomerular filtration rate (eGFR) for participants 65 years or older attending a baseline study visit in the Atherosclerosis Risk in Communities study (N=6,392). We used zero-inflated negative binomial and Cox proportional hazards regressions to assess the relationship between baseline polypharmacy, PIM use, and subsequent hospitalization and death.

Results: Mean age at baseline was 76 ($\pm$5) years, 59% were female, and 29% had CKD (eGFR <60 ml/min/1.73m^2). Overall, participants reported 6.1 ($\pm$3.5) medications and 2.3 ($\pm$2.2) vitamins/supplements; 16% reported $\geq$10 medications; 31% reported a PIM based on their age. On average, participants with CKD reported more medications. A PIM based on kidney function was used by 36% of those with eGFR <30 ml/min/1.73m^2. Over a median of 2.6 years, more concurrent medications were associated with higher risk of hospitalization and death, but PIM

[3] Secora A, Alexander GC, Ballew SH, Coresh J, Grams ME. Kidney Function, Polypharmacy, and Potentially Inappropriate Medication Use in a Community-Based Cohort of Older Adults. Drugs & Aging. 2018;35:735-750.

use was not. While those with CKD had higher absolute risks, there was no difference in the relative risks associated with greater numbers of medications by CKD status.

Conclusion: Polypharmacy and PIM use were common, with greater numbers of medications associated with higher risk of hospitalization and death; relative risks were similar for those with and without CKD.

2.2 Introduction

Older adults constitute a vulnerable and growing segment of the population with a particularly high burden of comorbid conditions like chronic kidney disease (CKD), which affects up to 40% of older adults in the United States.(45, 46) As a consequence of more comorbidities, medication use in older adults is high, yet drug metabolism and clearance may change with age, especially in the setting of CKD.(2) Common in older adults,(6, 47-52) polypharmacy has been linked to higher risk of adverse drug-drug interactions, (6-8, 47, 48, 50, 51, 53, 54) and morbidity and mortality. (53, 55-63)

Another medication-related risk factor that may be associated with morbidity and mortality in older adults, particularly those with CKD, is potentially inappropriate medication (PIM) use. (53, 62, 64) Pharmacy and published medication references suggest that PIMs be avoided or carefully monitored in the setting of older age or CKD to mitigate preventable adverse effects. Certain drugs and drug metabolites are excreted by the kidney, necessitating dose adjustment or drug avoidance in those with reduced kidney function to prevent potentially toxic exposure levels. (5, 65-67) Studies have suggested that PIM use based on level of kidney function is common, (7, 54, 68-76) but not always recognized, (7, 50, 54) with estimates as high as 62-67% in the inpatient and ambulatory setting. (72, 74) Moreover, medication resources for prescribers

often present conflicting recommendations on appropriate renal-based dosing and contraindication, and have uncertain uptake in clinical practice. (9, 12-14, 77) Evaluating overall and specific medication use as potentially modifiable risk factors that might impact health outcomes in older adults is critical.

Several studies have evaluated the risk of hospitalization (57-60, 78) and death (55, 56, 61, 64, 78-86) associated with polypharmacy and PIM use in older populations, but these studies were limited by homogenous samples, cross-sectional study designs, lack of information on kidney function, or limited information on the use of over-the-counter medications. Therefore, we characterized baseline medication use across stages of kidney function in a community-based cohort of older adults, with a particular focus on medications deemed "potentially inappropriate" based on kidney function or age, by any one of three commonly used drug references: the Beers criteria, the Screening Tool of Older People's Prescriptions (STOPP) criteria, and Micromedex®. We then quantified the subsequent risk of hospitalization and death among those with baseline PIM use and polypharmacy, and assessed for differences by CKD status.

2.3 Methods

2.3.1 Study population

The Atherosclerosis Risk in Communities (ARIC) study is a long-standing, population-based, prospective cohort study of 15,792 adults followed since 1987-1989.(87) In brief, ARIC study investigators recruited participants between 45 and 64 years of age in the United States from Forsyth County, North Carolina; Jackson, Mississippi; suburban Minneapolis, Minnesota; and Washington County, Maryland. For this prospective analysis, we included participants who attended ARIC study visit five (baseline visit), which took place between June, 2011, and

August, 2013 (N=6,544). We excluded participants without a serum creatinine measurement at visit five (n=96), those with end-stage renal disease as defined by registration in the United States Renal Data System (n=38), and non-white/non-black participants (n=18) leaving a total study population of 6,392 participants **(Supplementary Figure S1A).** ARIC had IRB approval at all study sites and participants gave informed consent at each visit.

2.3.2 Measurement of kidney function and other covariates

We defined kidney function by a participant's estimated glomerular filtration rate (eGFR). We calculated eGFR using serum creatinine (measured by the modified kinetic Jaffé method), and the equation developed by the Chronic Kidney Disease Epidemiology Collaboration.(88) We classified CKD into G-stages (G1= ≥90 mL/min/1.73m^2; G2= 60-89 mL/min/1.73m^2; G3a= 45-59 mL/min/1.73m^2; G3b= 30-44 mL/min/1.73m^2; G4= 15-29 mL/min/1.73m^2; G5= <15 mL/min/1.73m^2). (53) We also categorized participants by level of albuminuria using their urine albumin to urine creatinine ratio (<30 mg/g, 30-300 mg/g, >300 mg/g). We defined CKD as eGFR <60 mL/min/1.73m^2 at visit five, without regard to CKD duration or level of albuminuria.

We defined diabetes mellitus as a self-reported diabetes diagnosis, or the use of glucose lowering medications in the previous 30 days, and hypertension as a blood pressure measure of systolic ≥150 mm Hg and diastolic ≥90 mm Hg, or antihypertensive medication use during the previous 30 days. For blood pressure measurement, a certified technician collected three seated measurements using a random-zero sphygmomanometer after 5 minutes of rest, and the mean of the second and third readings was used. We defined heart failure by self-reported or physician-assessed heart failure, or prior physician-adjudicated heart failure. We defined cardiovascular disease as prevalent coronary artery disease or stroke. We ascertained myocardial infraction (MI)

since participants' last ARIC visit using self-report. Similar to other ARIC investigations,(89) we defined frailty based on five criteria including weight loss, exhaustion, low energy expenditure, slowness, and weakness; in this analysis, pre-frail (1-2 criteria) and frail (≥3 criteria) were combined. We calculated the Charlson Comorbidity Index (CCI) (90, 91) based on data from previous hospitalizations using abstracted hospital records that were obtained from data linkages with hospitals in the proximity of ARIC study sites, or record requests from hospitals outside of those areas. To ascertain cognitive functioning, we used the Mini-Mental State Examination (MMSE) questionnaire score. We derived body mass index (BMI) using weight (kilogram) and height (meter) measurements taken during physical examinations. We also captured low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides from fasting blood samples drawn during physical examinations. All other variables, such as sex, race, age, current smoking status, and alcohol consumption (grams per week) were self-reported during a structured interview. All definitions were based on information collected at participants' visit five assessment.

2.3.3 Medication use

ARIC study staff captured prescription and over-the-counter (OTC) medication use, as well as vitamin and dietary supplement use, through structured interviews at visit five. Participants brought all medications and other products they had used in the prior 30 days to their study visit. If the participant did not bring their medications, study staff followed-up over the phone to collect these data. Study staff recorded a maximum of 25 products. Thirty-eight participants (0.6%) brought more than 25 products to their study visit; therefore, some product use on those participants was not collected. For the purpose of the current study, we did not count non-injectable solutions, creams/lotions, and devices as medications, leaving 554 unique medications.

2.3.4 Medication references

We categorized all 554 unique prescription and OTC oral, inhaled, or injectable medications by their drug grouping using the generic product identifier classification system. Since medication use information was obtained without regard to the method of attainment (prescription vs. OTC) or frequency of dosing (regular vs. as needed), we grouped all prescription and OTC nonsteroidal anti-inflammatory drugs (NSAIDs) into a combined NSAID category. We assessed medications in three commonly used drug references for older adults: American Geriatrics Society Beers 2015 criteria,(36) Screening Tool of Older People's Prescriptions (STOPP) version 2 criteria,(92) and Truven Health Analytics online pharmacy reference Micromedex® 1.0 (Healthcare Series; electronic version; Greenwood, Colorado; accessed: August, 2016). We identified and cross-referenced medications that were contraindicated or recommended to avoid based on one's kidney function in any of the three references. We also identified and cross-referenced medications that were contraindicated based on one's age alone in Beers and STOPP only, as Micromedex® generally references Beers or STOPP criteria in its age-based recommendations.

Many medications in the Beers and Micromedex® references are noted as contraindicated according to creatinine clearance or glomerular filtration rate that is not adjusted for body surface area. In these instances, we converted the participant's eGFR to unadjusted units (mL/min) by multiplying the eGFR (mL/min/1.73m^2) by their calculated body surface area divided by 1.73, similar to other investigations. (93, 94) Where an absolute threshold was not explicitly stated but reference was made to avoid in "significant" or "severe" renal impairment, we *a priori* assumed

an eGFR threshold of <30 mL/min/1.73m^2; when only "renal impairment" was noted, <60 mL/min/1.73m^2 was used.

2.3.5 Assessment of polypharmacy and PIM use

We categorized polypharmacy using several categories of total number of prescription or OTC medications in the last 30 days, excluding the use of other products such as vitamins and supplements: 0-3 medications, 4-5 medications, 6-9 medications, and 10 or more medications. We defined kidney-based PIM use as the use of a medication that was contraindicated or recommended to avoid based on the participant's kidney function in any of the medication references. Because dose information was not available, PIM use based on dose was not assessed. We defined age-based PIM use as the use of a medication noted in Beers or STOPP as contraindicated in adults age 65 years or older; all participants included in this study were 65 years or older. We did not include contraindications based on two or more combined criteria such as contraindications based on one's age plus an existing condition, or the use of another medication concomitantly. Where references differed with respect to kidney function (i.e. Micromedex lists eGFR <45 mL/min/1.73 m^2, and STOPP lists eGFR <30 mL/min/1.73m^2 for the same drug), we used the stricter criteria for analyses (i.e. eGFR <45 mL/min/1.73m^2). In addition, given that we did not have start dates or duration of use, the use of a medication (e.g. metformin) was counted as potentially inappropriate in a participant if a drug reference recommended not starting the medication at their level of kidney function.

2.3.6 Assessment of hospitalizations and death

ARIC study staff monitor and abstract hospitalization data for ARIC cohort members through data linkages with local hospitals in proximity to each of the four ARIC sites; hospitalizations

outside of the community area are identified through semi-annual participant reports, and subsequent record requests are made to obtain data from those hospitalizations. In this investigation, we included any hospitalization, regardless of the reason. Vital status was captured through linkages to the National Death Index. Participants' observation time began at their visit five (baseline visit/index date), and both hospitalizations and mortality were assessed through December 31, 2014, or participants' last known contact with study staff.

2.3.7 Statistical analysis

We calculated frequencies, means and proportions of cohort characteristics and medication use, including polypharmacy, kidney-based PIMs, and age-based PIMs, for all participants, stratified by CKD stage. We assessed trends across CKD G-stages in cohort characteristics, polypharmacy category, and mean number of medications and vitamins using logistic and linear regression for binary and continuous variables, respectively, and an ordinal CKD G-stage variable. We also used independent sample t-tests and two-sample tests of proportions to compare medication use between CKD and non-CKD participants. We tested for associations between mean number of medications and CKD stage using univariable and multivariable linear regressions. We also tested for associations between PIM use and demographics, comorbidities, and total number of medications using univariable and multivariable logistic regressions, where only covariates independently associated with PIM use ($p<0.05$) in univariable analyses were included in the multivariable model.

We calculated incidence rates for hospitalization and death per 100 person-years in the full cohort. We used univariable and multivariable zero-inflated negative binomial regression with robust variance estimators to calculate incidence rate ratios for hospitalization comparing

categories of polypharmacy, and comparing those with and without PIM use, assessing for interactions between CKD status and both polypharmacy (categorical) and PIM use. We used a zero-inflated model to account for frequent zero-value observations and over-dispersed data. After assessing proportionality using a global test of Schoenfeld residuals, we performed similar analyses using Cox proportional hazards regression to evaluate associations with all-cause mortality. In addition, to evaluate for non-linear associations between the number of medications (continuous) and each of the outcomes, we modeled total number of medications as a cubic spline using four medications as the reference; we also assessed for interactions by CKD status. For hospitalization and death analyses, we assessed age-based PIM use in the full cohort, and kidney-based or combined kidney- and age-based PIM use among only those with CKD at visit five. In the latter analyses, we did not include the use of aspirin-containing products as a kidney-based PIM, since aspirin use was very common in the cohort.

We adjusted all analyses for age, sex, race, BMI, eGFR, LDL cholesterol, HDL cholesterol, triglycerides, smoking status, alcohol consumption, MMSE score, hypertension, diabetes, heart failure, cardiovascular disease, self-reported MI, CCI, frailty, and total vitamins/supplements. In PIM-based analyses, we additionally adjusted for participants' total number of medications (continuous).

All analyses were done using Stata 14 (StataCorp, 2015; College, Station, TX).

2.4 Results

The study population was 58.7% female, 23.0% African American, and had a mean age of 76.3 years (±5.2) (**Table 1A**). The majority had hypertension (69.8%), and 32.4%, 18.6%, 14.7% had

diabetes mellitus, heart failure, and cardiovascular disease, respectively. The mean Charlson Comorbidity Index (CCI) was 4.2 (±1.8), and mean CCI was greater in higher CKD stages. The presence of CKD was common, with 29.1% (N=1,857) of the cohort having an eGFR <60 mL/min/1.73m^2. Twenty-one percent had an albumin-to-creatinine ratio of 30 mg/g or higher.

Antihypertensive medications were the most commonly-used medication group (N=4,819, 75.4%), with beta-blockers the most common antihypertensive class (N=2,141, 33.5%) (**Figure 1A**). Roughly 60% (N=2,859) of those reporting antihypertensive use took two or more antihypertensive medications, and 25.4% (N=1,225) reported three or more (**Supplementary Figure S2A**). Lipid-lowering agents were also commonly reported (N=3,556, 55.6%), with over 10% (N=373) using two or more lipid-lowering agents in the prior 30 days. The use of diabetes medications was not as common among participants overall (N=1,272, 19.9%), but many of those reporting use of diabetes medicines reported using two or more such treatments (N=532, 41.8%). As for analgesics, opioid medications were used in 10.5% (N=668) of participants, and of those, 8.4% (N=56) reporting using more than one opioid during the prior 30 days; the use of NSAID-containing (27.3%) and aspirin-containing (59.4%) products were much more common overall. The proportion of participants taking at least one medication within a medication class generally increased with decreasing eGFR, except for ACE inhibitors, bisphosphonates, antidepressants, anxiolytic/hypnotic/sedatives, and aspirin-containing and other NSAID-containing products (**Figure 1A**). Among participants who did not attend visit five, self-reported medication use at their last 6-month phone interview was similar to those who did attend visit five (**Supplementary Figure S3A**).

On average, participants reported using 6.1 (±3.5) medications and 2.3 (±2.2) vitamins or supplements. Overall, 24.3% (N=1,553), 23.7% (N=1,518), 36.0% (N=2,302), and 15.9% (N=1,019) of the cohort reported using 0-3, 4-5, 6-9, and 10 or more prescription or OTC medications in the prior 30 days, respectively (**Table 2A**). More than 35% of participants used 10 or more products when the use of medications, vitamins, and supplements were combined. Use of ten or more medications was more common among participants with CKD than without CKD (22.7% versus 13.2%, $p<0.001$). Although participants with CKD reported using more medications than those without CKD (7.0 versus 5.7, $p<0.001$), they used slightly fewer vitamins or supplements (2.1 versus 2.3, $p<0.001$).

The association between higher CKD stage and greater number of medications used persisted in adjusted analyses. For example, participants with stage G4 or G5 took an average of 1.32 (95% confidence intervals [CI]: 0.73-1.90) more medications than those with stage G1 or G2 (**Table 2A).** After adjustment, other correlates of greater numbers of medications included heart failure, cardiovascular disease, diabetes mellitus, hypertension, self-reported previous MI, higher CCI, frailty, female sex, white race (compared to African American), higher BMI, higher total numbers of vitamins/supplements, higher triglycerides, lower LDL cholesterol, and lower MMSE (**Supplementary Table S1A**).

Age-based PIM use based on Beers and STOPP criteria occurred in 31.3% (N=2,001) of the full cohort (**Supplementary Table S2A**), and 32.7% (N=608) of the participants with CKD. The most common age-based PIMs were first-generation antihistamines, benzodiazepines, oral estrogens, and zolpidem. In univariable and multivariable analyses, age-based PIM use was

associated with higher total number of medications, CCI, female sex, and no diabetes mellitus or hypertension (data not shown).

Out of the 554 reported medications, 52 unique medications and 19 NSAID-containing products were identified as potentially inappropriate based on kidney function in at least one of the references. Kidney-based PIM use was common among those in CKD stage G4 or G5 (N=36, 35.6%), and somewhat less common in those with CKD stage G3a or G3b (N=223, 12.7%) (**Table 3A**). The most common kidney-based PIMs were metformin (N=42) and NSAID-containing products (N=632). Some other commonly used kidney-based PIMs included fenofibrate, spironolactone, gabapentin, alendronate, and hydrochlorothiazide-containing products. Among people with CKD, kidney-based PIM use was associated with lower eGFR, higher total number of medications, female sex, and no self-reported MI in univariable and multivariable analyses (data not shown).

Among the 6,379 participants with post-visit 5 follow-up, median follow-up was 2.6 years (interquartile range: 0.8 years). There were 4,178 hospitalizations in 2,197 cohort members (34.4%) over 16,111 person-years of follow-up. Overall, the incidence rate for hospitalization was 26 per 100 person-years (**Table 4A**). Hospitalization incidence increased with greater number of medications (15, 18, 29, and 49 per 100 person-years for 0-3, 4-5, 6-9, and 10 or more medications, respectively). For each category of polypharmacy, participants with CKD had higher absolute risks of hospitalization than those without CKD; however, there were no differences in the relative risks by CKD status (all p for interaction >0.1). In the continuous analysis, there was a non-linear relationship between total number of medications and the risk of hospitalization (**Figure 2A**), with no statistically significant difference by CKD status.

Compared to four medications, the use of five medications was associated with a 15% higher risk of hospitalization (95% CI: 7%-24%), with increasing numbers of medications associated with increasing risk after five medications. With respect to PIM use, although those with age- or kidney-based PIM use had higher hospitalization rates than those without, these risks did not persist in adjusted analyses.

There were 344 deaths during the follow-up period, with an incidence rate of 2 deaths per 100 person-years (**Table 4A**). Similar to hospitalization, incidence of death increased with greater number of medications (1, 1, 3, and 4 per 100 person-years for 0-3, 4-5, 6-9, and 10 or more medications, respectively). For each category of polypharmacy, participants with CKD had higher absolute risks of death than those without CKD; however, like hospitalization, there were no differences in the relative risks by CKD status (all p for interaction >0.1). In continuous analysis, there was a non-linear relationship between total number of medications and the risk of death (**Figure 3A**), with a suggestion of higher risk with less than four medications. There was no statistically significant difference in the association of total number of medications and mortality by CKD status. Compared to four medications, the use of five and six medications were not associated with increases in risk, but seven medications was associated with a 60% increase in the risk of death (95% CI: 12%-128%), with increasing numbers of medications associated with increasing hazard ratios until plateauing after 11 medications. Age- or kidney-based PIM use was not associated with death.

2.5 Discussion

In this community-based cohort of older adults, approximately one in six participants used 10 or more medications, and more than one in three used 10 or more products when the use of

medications, vitamins, and supplements were combined. Higher numbers of medications were more common among those with lower eGFR, and were associated with greater risks of hospitalization and death. Age-based PIM and kidney-based PIM use were also common in the cohort, but were associated with hospitalization only in unadjusted analyses, and not associated with mortality risk. Our findings underscore the value of routine assessments of medication use among older adults, and suggest that minimizing unnecessary medication use may be an approach to reducing morbidity and mortality.

Some have hypothesized that polypharmacy may be a surrogate marker of inappropriate medication use as it can increase the risk of adverse drug effects (ADEs), (6, 48) and adverse drug-drug and drug-disease interactions. (8) A study by Onder et al (58) found that the primary risk factor for ADE-related hospitalization in older adults was polypharmacy. Other studies have assessed the risk of mortality in older adults with polypharmacy, and how various comorbidities differentially affect that risk. (55, 56, 61) A recent study by Schöttker et al (55) observed that those taking 10 or more medications with fewer concurrent comorbidities had a higher relative risk of non-cancer mortality than those with more concurrent comorbidities. We hypothesized that the interaction between polypharmacy and comorbidities might be driven in part by the presence of CKD, where ADEs are particularly common; (14, 95, 96) however, we found similar risk relationships associated in persons with and without CKD.

An interesting finding from this study was the non-linear relationship between total number of medications and mortality. Our results suggested a potentially higher mortality risk among participants with fewer medications. Although not significant, the U-shaped association between total number of medications and mortality could represent medication underuse, but perhaps it is

more likely a result of residual confounding with providers reducing the number of medications in patients with poorer health status. Participants using higher numbers of medications generally had a higher mortality risk, which may reflect a more severe disease phenotype.

Surprisingly, both kidney- and age-based PIM use were not associated with adverse outcomes in our study. While prior studies have been somewhat equivocal with respect to these associations, our results differ from those which showed an increased risk in morbidity and mortality associated with PIM use. (64, 79-82) Our null results suggest that the risks associated with PIM use in older adults may be minimal due to an increase in provider monitoring, or may be specific to certain medications used in specific clinical situations not captured in a community-based cohort. For example, most kidney-based PIM use was due to metformin and NSAIDs, and metformin use at lower eGFRs is now increasingly recognized as acceptable clinical practice. There is also the potential for channeling bias, whereby only healthy or adherent people were prescribed medications deemed contraindicated, and in whom the benefits were considered to outweigh any apparent risks. It is also possible that using a "prevalent user" design selected out participants susceptible to the effects of PIM use, leaving only patients where these medications could be tolerated.(64) The observed reductions in the reported number of vitamins and supplements with decreasing levels of kidney function in this study suggest that patients may heed some provider warnings about PIM use; however, the high proportion of NSAID use seen in those with CKD runs counter to that suggestion. Regardless, coordinated prescribing and an increase in clinical assessments of common physiological changes as a result of aging, including reduced kidney function, could further prevent inappropriate or unnecessary medication use.(3, 53)

One major impediment to preventing age- or kidney-based PIM use is the inconsistency between medication guidelines for older adult patients (77) and those with reduced kidney function. (9, 13, 14) There is no gold standard reference with which to determine contraindication in either group, which can lead to confusion on appropriate prescribing. This can also lead to inconsistent findings between studies with different operationalized definitions of PIM use, and may be a reason why this and some other investigations have observed a null result with respect to PIM use. (61, 78, 83-86) In this analysis, we found that the accessed medication references often varied in which drugs were contraindicated or recommended to avoid based on kidney function, used several different kidney function metrics, and in several instances, provided only qualitative guidelines without a specific level of kidney function noted. This lack of granularity may be a result of expansive exclusion criteria, such as older patients and those with CKD, in pre-market pharmacokinetic and safety studies.(16) In the absence of such data, recommendations may be quite subjective; moreover, medication resources often inconsistently report what data were used to formulate a recommendation.(9, 77)

Our study had several strengths. The ARIC cohort is a well-established cohort of older adults from several geographically diverse communities. Because cohort members have a comprehensive physical exam at study visits, rich clinical data exist on each participant, including labs. Actual medication use was captured, rather than dispensed medications, and OTC medications, vitamins and supplements are also recorded.

Our study also had several limitations. Analyses were limited to participants who attended visit five and may not include participants unable to attend based on their health status; however, for those who did not attend, last reported medication use from phone interviews was similar to

those included in the study cohort. Because medication use was captured as any use in the prior 30 days at a single visit, contraindicated drug-drug interactions and concurrent duplicate medication use could not be assessed. We could not assess PIM use with respect to dosing as dose information was unavailable. Medication use was captured through a patient inventory at their study visit and was therefore dependent on the participant bringing in the medications, or self-reporting use in the prior 30 days. Few patients had eGFR <45 ml/min/1.73m^2, and we had no information on specialist care. If medication management was undertaken by a kidney specialist in those with more advanced CKD, medication-related adverse events may be mitigated, possibly contributing to the lack of effect modification by CKD status. As with any pharmacoepidemiologic investigation, despite controlling for numerous confounders, residual confounding by indication is possible. Finally, this study used a "prevalent user" design rather than assess risk after exposure initiation, therefore the population may lack persons who experienced adverse events early during polypharmacy or PIM use.

2.6 Conclusions

We found that polypharmacy and PIM use were relatively common in older adults, and that higher numbers of medications were associated with higher risk of hospitalization and mortality. Unexpectedly, while age- and kidney-based PIM use were common, they were not associated with hospitalization or mortality after adjustment for other covariates. Although CKD was associated with higher absolute risk of hospitalization and death across all categories of medication use, the relative risk associated with greater number of medications was not different by CKD status. Greater coordination of care across providers may help to reduce the prevalence of polypharmacy and PIM use in populations who are particularly vulnerable to adverse events from medications.

2.7 Tables

Table 1A: Study cohort demographic and baseline characteristics, stratified by level of kidney function

	Overall	Chronic kidney disease G-stage: eGFR (mL/min/1.73m^2)						P for trend
		G1: ≥90	G2: 60-89	G3a: 45-59	G3b: 30-44	G4: 15-29	G5: <15	
Participants	6,392	571 (8.9%)	3,964 (62.0%)	1,275 (19.9%)	481 (7.5%)	91 (1.4%)	10 (0.2%)	
Mean age (SD)	76.3 (5.2)	73.2 (4.2)	75.9 (5.0)	77.8 (5.4)	78.9 (5.5)	79.1 (5.7)	78.6 (4.9)	<0.001
Female	3,755 (58.7%)	362 (63.4%)	2,319 (58.5%)	736 (57.7%)	284 (59.0%)	46 (50.5%)	8 (80.0%)	0.11
Race								
White	4,919 (77.0%)	253 (44.3%)	3,223 (81.3%)	1,016 (79.7%)	366 (76.1%)	59 (64.8%)	2 (20.0%)	<0.001
Black	1,473 (23.0%)	318 (55.7%)	741 (18.7%)	259 (20.3%)	115 (23.9%)	32 (35.2%)	8 (80.0%)	<0.001
Body Mass Index (SD)	28.7 (5.8)	29.7 (7.1)	28.4 (5.5)	28.8 (5.5)	29.6 (6.0)	28.8 (6.1)	30.5 (6.6)	0.18
Current smoker	358 (5.6%)	54 (9.5%)	228 (5.8%)	49 (3.8%)	21 (4.4%)	6 (6.6%)	0 (0.0%)	<0.001
Mean alcohol use (SD)	27.5 (64.1)	32.8 (93.2)	29.9 (64.6)	23.7 (52.9)	15.1 (42.9)	14.1 (43.5)	12.0 (37.9)	<0.001
Mini-Mental State Examination (SD)	27.3 (3.1)	27.0 (3.1)	27.6 (2.9)	27.0 (3.3)	26.5 (3.4)	25.8 (4.8)	25.9 (2.1)	<0.001
LDL cholesterol (SD)	2.7 (0.9)	2.8 (0.9)	2.7 (0.9)	2.7 (0.9)	2.5 (0.9)	2.5 (1.2)	2.2 (0.8)	<0.001
HDL cholesterol (SD)	1.3 (0.4)	1.4 (0.4)	1.4 (0.4)	1.3 (0.4)	1.2 (0.3)	1.2 (0.4)	1.1 (0.3)	<0.001
Triglycerides (SD)	1.4 (0.7)	1.2 (0.5)	1.4 (0.7)	1.5 (0.7)	1.6 (0.9)	1.5 (0.9)	1.4 (0.8)	<0.001
Albuminuria	(n=5,683)	(n=495)	(n=3,480)	(n=1,173)	(n=440)	(n=86)	(n=9)	
<30 mg/g	4,488 (79.0%)	410 (82.8%)	2,913 (83.7%)	884 (75.4%)	253 (57.5%)	28 (32.6%)	0 (0.0%)	<0.001
30-300 mg/g	1,035 (18.2%)	79 (16.0%)	515 (14.8%)	251 (21.4%)	151 (34.3%)	34 (39.5%)	5 (55.6%)	<0.001
>300 mg/g	160 (2.8%)	6 (1.2%)	52 (1.5%)	38 (3.2%)	36 (8.2%)	24 (27.9%)	4 (44.4%)	<0.001
Comorbidities								
Charlson Comorbidity Index (SD)	4.2 (1.8)	3.7 (1.7)	4.0 (1.6)	4.6 (2.0)	5.4 (2.3)	6.1 (2.6)	7.6 (3.7)	<0.001
Hypertension	4,461 (69.8%)	403 (70.6%)	2,579 (65.1%)	978 (76.7%)	410 (85.2%)	81 (89.0%)	10 (100.0%)	<0.001
Diabetes	2,072 (32.4%)	205 (35.9%)	1,153 (29.1%)	436 (34.2%)	224 (46.6%)	49 (53.8%)	5 (50.0%)	<0.001
Hypertension and diabetes	1,706 (26.7%)	171 (29.9%)	912 (23.0%)	371 (29.1%)	201 (41.8%)	46 (50.5%)	5 (50.0%)	<0.001
Heart Failure	1,191 (18.6%)	103 (18.0%)	594 (15.0%)	282 (22.1%)	164 (34.1%)	41 (45.1%)	7 (70.0%)	<0.001
Cardiovascular disease	940 (14.7%)	44 (7.7%)	500 (12.6%)	233 (18.3%)	133 (27.7%)	26 (28.6%)	4 (40.0%)	<0.001
Self-reported myocardial infarction	486 (7.6%)	26 (4.6%)	248 (6.3%)	125 (9.8%)	69 (14.3%)	16 (17.6%)	2 (20.0%)	<0.001
Frailty	3,132 (49.0%)	289 (50.6%)	1,847 (46.6%)	643 (50.4%)	292 (60.7%)	55 (60.4%)	6 (60.0%)	<0.001

Table 1A Key: Standard deviation (SD); estimated glomerular filtration rate (eGFR); high-density lipoproteins (HDL); low-density lipoproteins (LDL); Body Mass Index in kg/m^2; albuminuria (urine albumin to urine creatinine ratio) could not be calculated for all participants

Table 2A: Association between reported number of medications and vitamins/supplements and chronic kidney disease stage

	Overall (n=6,392)	Chronic kidney disease stage: eGFR (mL/min/1.73m^2)				P for trend
		G1/G2: ≥60 (n=4,535)	G3a: 45-59 (n=1,275)	G3b: 30-44 (n=481)	G4/G5: <30 (n=101)	
Number of medications (mean and SD)	6.1 (3.5)	5.7 (3.4)	6.5 (3.5)	7.8 (3.8)	8.9 (4.3)	<0.001
Number of vitamins/ supplements (mean and SD)	2.3 (2.2)	2.3 (2.3)	2.1 (2.1)	2.0 (2.0)	1.7 (1.6)	<0.001
Number of combined medications and vitamins/ supplements (mean and SD)	8.4 (4.3)	8.1 (4.3)	8.7 (4.3)	9.8 (4.5)	10.6 (4.7)	<0.001
Proportion reporting ≥10 combined medications and vitamins/supplements	2,272 (35.5%)	1,488 (32.8%)	495 (38.8%)	227 (47.2%)	62 (61.4%)	<0.001
Proportion reporting ≥10 medications	1,019 (15.9%)	597 (13.2%)	240 (18.8%)	142 (29.4%)	40 (39.6%)	<0.001
Proportion reporting 6-9 medications	2,302 (36.0%)	1,546 (34.1%)	501 (39.3%)	215 (44.7%)	40 (39.6%)	<0.001
Proportion reporting 4-5 medications	1,518 (23.7%)	1,143 (25.2%)	291 (22.8%)	74 (15.4%)	10 (9.9%)	<0.001
Proportion reporting 0-3 medications	1,553 (24.3%)	1,249 (27.5%)	243 (19.1%)	50 (10.4%)	11 (10.9%)	<0.001
Total medications only (Continuous)[a]						
Unadjusted model		ref	0.81 (0.59-1.02)	2.07 (1.75-2.40)	3.16 (2.48-3.84)	
Adjusted model		ref	0.27 (0.08-0.46)	0.69 (0.40-0.98)	1.32 (0.73-1.90)	

[a] linear model: average number of additional medications relative to reference [95% confidence interval (CI)]; constant = 5.72 (CI: 4.09-7.36) medications

Table 2A Key: Standard deviation (SD); estimated glomerular filtration rate (eGFR); Fully adjusted model was adjusted for hypertension, cardiovascular disease, diabetes, heart failure, self-reported MI, CCI, frailty, sex, race, BMI, age, MMSE, HDL, LDL, triglycerides, current alcohol use, and current smoking status

Table 3A: Prevalence of kidney-based potentially inappropriate medication use by chronic kidney disease stage

Potentially inappropriate medication	Chronic kidney disease stage: eGFR				Reference	Criteria	Overall use	PIM use
	G1: ≥90	G2: 60-89	G3a/b: 30-59	G4/5: <30				
Metabolic agents								
Diabetes medication								
Metformin	99 (17.3%)	437 (11.0%)	175 (10.0%)	4 (4.0%)	Micromedex STOPP	eGFR <45 mL/min/1.73m^2 eGFR <30 mL/min/1.73m^2	715 (11.2%)	42 4
Sitagliptin-metformin	3 (0.5%)	10 (0.3%)	2 (0.1%)	0	Micromedex	eGFR <45 mL/min/1.73m^2	15 (0.2%)	0
Glipizide-metformin	0	5 (0.1%)	3 (0.2%)	0	Micromedex	eGFR <45 mL/min/1.73m^2	8 (0.1%)	2
Pioglitazone-metformin	0	6 (0.2%)	6 (0.3%)	0	Micromedex	eGFR <45 mL/min/1.73m^2	12 (0.2%)	1
Acarbose	2 (0.4%)	0	0	1 (1.0%)	Micromedex	SCr >2.0 mg/dL	3 (0.1%)	1
Exenatide	1 (0.2%)	2 (0.1%)	0	0	Micromedex	CrCl <30 mL/min	3 (0.1%)	0
Antihyperlipidemic								
Fenofibrate	5 (0.9%)	58 (1.5%)	73 (4.2%)	6 (5.9%)	Micromedex	Severe renal impairment	142 (2.2%)	6
Gemfibrozil	4 (0.7%)	44 (1.1%)	31 (1.8%)	1 (1.0%)	Micromedex	Severe renal impairment	80 (1.3%)	1
Endocrine-metabolic								
Desmopressin	0	1 (0.0%)	0	0	Micromedex	CrCl <50 mL/min	1 (0.0%)	0
Cardiovascular agents								
Diuretic (loop and thiazide)								
Triamterene-hydrochlorothiazide	13 (2.3%)	162 (4.1%)	127 (7.2%)	3 (3.0%)	Micromedex	Significant renal impairment	305 (4.8%)	3
Lisinopril-hydrochlorothiazide	44 (7.7%)	197 (5.0%)	106 (6.0%)	1 (1.0%)	Micromedex	eGFR <30 mL/min/1.73m^2	348 (5.4%)	1
Amiloride	0	1 (0.0%)	0	0	Micromedex Beers	CrCl <50 mL/min CrCl <30 mL/min	1 (0.0%)	0 0
Triamterene	0	1 (0.0%)	0	0	Micromedex Beers	SCr >2.5 mg/dL CrCl <30 mL/min	1 (0.0%)	0 0
Chlorthalidone	2 (0.4%)	23 (0.6%)	14 (0.8%)	0	Micromedex	SCr >2.5 mg/dL	39 (0.6%)	0
Hydrochlorothiazide	69 (12.0%)	497 (12.5%)	249 (14.2%)	10 (9.9%)	Micromedex	SCr >2.5 mg/dL	825 (12.9%)	2
Ethacrynic acid	0	0	1 (0.1%)	0	Micromedex	GFR <10 mL/min	1 (0.0%)	0
Aldosterone receptor antagonist								
Eplerenone	0	3 (0.1%)	2 (0.1%)	0	Micromedex	CrCl <30 mL/min	5 (0.1%)	0
Spironolactone	11 (1.9%)	60 (1.5%)	58 (3.3%)	8 (7.9%)	Micromedex Beers	GFR <10 mL/min CrCl <30 mL/min	137 (2.1%)	0 6
Angiotensin II receptor antagonist								
Aliskiren-valsartan	0	1 (0.0%)	0	0	Micromedex	GFR <60 mL/min	1 (0.0%)	0
Olmesartan-amlodipine-hydrochlorothiazide	2 (0.4%)	2 (0.1%)	1 (0.1%)	0	Micromedex	CrCl <30 mL/min	5 (0.1%)	0
ACE inhibitor								
Amlodipine-benazepril	9 (1.6%)	57 (1.4%)	29 (1.7%)	0	Micromedex	CrCl <30 mL/min	95 (1.5%)	0
Antihypertensive								
Aliskiren-hydrochlorothiazide	0	1 (0.0%)	0	0	Micromedex	CrCl <30 mL/min	1 (0.0%)	0
Anti-infective agents								
Antiretroviral								
Lamivudine-zidovudine	0	1 (0.0%)	0	0	Micromedex	CrCl <50 mL/min	1 (0.0%)	0

Table 3A: Continued

Potentially inappropriate medication	Chronic kidney disease stage: eGFR				Reference	Criteria	Overall use	PIM use
	G1: ≥90	G2: 60-89	G3a/b: 30-59	G4/5: <30				
Antibiotic								
Nitrofurantoin macrocrystalline	1 (0.2%)	13 (0.3%)	3 (0.2%)	0	Micromedex	CrCl <60 mL/min	17 (0.3%)	2
Amoxicillin-clarithromycin-lansoprazole	0	1 (0.0%)	1 (0.1%)	0	Micromedex	CrCl <30 mL/min	2 (0.0%)	0
Trimethoprim	0	4 (0.1%)	4 (0.2%)	1 (1.0%)	Micromedex	CrCl <15mL/min	9 (0.1%)	0
Sulfamethoxazole-trimethoprim	2 (0.4%)	22 (0.6%)	21 (1.2%)	2 (2.0%)	Micromedex	CrCl <15mL/min	47 (0.7%)	0
Miscellaneous								
Methenamine hippurate	0	2 (0.1%)	0	0	Micromedex	Renal impairment	2 (0.0%)	0
Methenamine-sodium salicylate	2 (0.4%)	2 (0.1%)	1 (0.1%)	0	Micromedex	Severe renal impairment	5 (0.1%)	0
Central nervous system agents								
Analgesic								
Phenazopyridine	3 (0.5%)	6 (0.2%)	3 (0.2%)	0	Micromedex	GFR <50 mL/min	12 (0.2%)	2
Fentanyl	3 (0.5%)	5 (0.1%)	6 (0.3%)	0	Micromedex	Severe renal impairment	14 (0.2%)	0
Anticonvulsant								
Gabapentin	34 (6.0%)	169 (4.3%)	113 (6.4%)	12 (11.9%)	Micromedex	CrCl <30 mL/min	328 (5.1%)	7
Acetazolamide	0	3 (0.1%)	0	0	Micromedex	CrCl <10 mL/min	3 (0.1%)	0
Alzheimer's/dementia								
Galantamine	0	3 (0.1%)	2 (0.1%)	0	Micromedex	CrCl <9 mL/min	5 (0.1%)	0
NSAIDs	402 (70.4%)	2,799 (70.6%)	1,237 (70.4%)	60 (59.4%)	Micromedex	Many depending on product	4,498 (70.4%)	N/A
					STOPP	eGFR <50 mL/min/1.73m^2		632
					Beers	CrCl <30 mL/min		49
NSAIDs (excluding aspirin containing products)	188 (32.9%)	1,127 (28.4%)	417 (23.7%)	11 (10.9%)	Micromedex	Many depending on product	1,743 (27.3%)	N/A
					STOPP	eGFR <50 mL/min/1.73m^2		194
					Beers	CrCl <30 mL/min		8
Antiparkinsonian								
Pramipexole	2 (0.4%)	29 (0.7%)	8 (0.5%)	1 (1.0%)	Micromedex	CrCl <30 mL/min	40 (0.6%)	1
Selegiline	0	0	1 (0.1%)	0	Micromedex	CrCl <30 mL/min	1 (0.0%)	0
Psychotherapeutic agents								
Buspirone	2 (0.4%)	20 (0.5%)	4 (0.2%)	0	Micromedex	Severe renal impairment	26 (0.4%)	0
Duloxetine	4 (0.7%)	35 (0.9%)	19 (1.1%)	4 (4.0%)	Micromedex	CrCl <30 mL/min	62 (1.0%)	2
					Beers	CrCl <30 mL/min		2

Table 3A: Continued

Potentially inappropriate medication	Chronic kidney disease stage: eGFR				Reference	Criteria	Overall use	PIM use
	G1: ≥90	G2: 60-89	G3a/b: 30-59	G4/5: <30				
Antineoplastic agents								
Capecitabine	0	2 (0.05%)	1 (0.06%)	0	Micromedex	CrCl <30 mL/min	3 (0.05%)	0
Methotrexate	9 (1.6%)	30 (0.8%)	29 (1.7%)	1 (1.0%)	Micromedex	CrCl <10 mL/min	69 (1.1%)	0
Calcium regulating agents								
Alendronate	22 (3.9%)	144 (3.6%)	59 (3.4%)	2 (2.0%)	Micromedex	CrCl <35 mL/min	227 (3.5%)	9
Ibandronate	1 (0.2%)	14 (0.4%)	6 (0.3%)	0	Micromedex	CrCl <30 mL/min	21 (0.3%)	0
Risedronate	3 (0.5%)	17 (0.4%)	13 (0.7%)	0	Micromedex	CrCl <30 mL/min	33 (0.5%)	0
Zoledronic acid	0	4 (0.1%)	3 (0.2%)	0	Micromedex	CrCl <35 mL/min	7 (0.1%)	0
Adrenergic blockers								
Silodosin	1 (0.1%)	5 (0.1%)	1 (0.1%)	0	Micromedex	CrCl <30 mL/min	7 (0.1%)	0
Adrenergic agonist & 2nd generation antihistamine								
Desloratadine-pseudoephedrine	0	1 (0.0%)	0	0	Micromedex	Renal impairment	1 (0.0%)	0
Anticoagulants								
Factor Xa inhibitors								
Fondaparinux	0	0	1 (0.1%)	0	Micromedex	CrCl <30 mL/min	1 (0.0%)	0
					Beers	CrCl <30 mL/min		0
					STOPP	eGFR <15 mL/min/1.73m^2		0
Direct thrombin inhibitors								
Dabigatran	2 (0.4%)	23 (0.6%)	14 (0.8%)	0	Beers	CrCl <30 mL/min	39 (0.6%)	0
					STOPP	eGFR <30 mL/min/1.73m^2		0
Anticholinergic agents								
Tolterodine	10 (1.7%)	22 (0.6%)	14 (0.8%)	2 (2.0%)	Micromedex	CrCl <10 mL/min	48 (0.8%)	0
Hyperuricemia agents								
Probenecid	1 (0.2%)	4 (0.1%)	4 (0.2%)	0	Beers	CrCl <30 mL/min	9 (0.1%)	0
Colchicine	6 (1.1%)	21 (0.5%)	44 (2.5%)	5 (5.0%)	STOPP	eGFR <10 mL/min/1.73m^2	76 (1.2%)	1
Hemorrheologic agents								
Pentoxifylline	0	3 (0.1%)	2 (0.1%)	0	Micromedex	CrCl <30 mL/min	5 (0.1%)	0

* Micromedex does note that below an eGFR of 30 mL/min/1.73m^2, the use of metformin is contraindicated, but Micromedex also notes that patients should not be started on metformin if their eGFR is under 45 mL/min/1.73m^2, and that if their eGFR falls below 45 mL/min/1.73m^2 "risks and benefits of continued use should be considered" (Glucophage; metformin HCl; oral tablet; 2017).

Table 3A Key: Potentially inappropriate medication (PIM); creatinine clearance (CrCl); estimated glomerular filtration rate (eGFR); glomerular filtration rate (GFR); Serum creatinine (SCr); Nonsteroidal anti-inflammatory drug (NSAID); Criteria column is the kidney function threshold where medication use is to be avoided; Qualitative criteria such as "significant" or "severe" renal impairment were categorized as eGFR <30 mL/min/1.73m^2, and "renal impairment" was categorized as <60 mL/min/1.73

Table 4A: Incidence rate ratios and hazard ratios for hospitalization and death, respectively, by polypharmacy and PIM use

	Hospitalizations (N=4,178)[a] among 2,197 participants				Death (N=344) among full cohort			
Overall incidence rate	26 per 100 PYs				2 per 100 PYs			
	Hospitalizations	**Incidence rate**	**Unadjusted IRR**	**Adjusted IRR**	**Deaths**	**Incidence rate**	**Unadjusted HR**	**Adjusted HR**
Polypharmacy (overall)								
0-3 medications	607	15 per 100 PYs	0.85 (0.73-0.99)*	0.91 (0.78-1.06)	53	1 per 100 PYs	1.07 (0.72-1.58)	1.17 (0.78-1.76)
4-5 medications	702	18 per 100 PYs	ref	ref	48	1 per 100 PYs	ref	ref
6-9 medications	1,664	29 per 100 PYs	1.67 (1.46-1.91)*	1.37 (1.20-1.55)*	141	3 per 100 PYs	1.99 (1.44-2.77)*	1.65 (1.16-2.35)*
10+ medications	1,205	49 per 100 PYs	2.88 (2.48-3.34)*	1.93 (1.64-2.27)*	102	4 per 100 PYs	3.42 (2.43-4.82)*	2.40 (1.60-3.59)*
Polypharmacy by CKD status[b]								
CKD								
0-3 medications	188	25 per 100 PYs	1.10 (0.80-1.50)	1.13 (0.84-1.52)	20	3 per 100 PYs	1.37 (0.71-2.62)	1.57 (0.81-3.03)
4-5 medications	214	23 per 100 PYs	ref	ref	17	2 per 100 PYs	ref	ref
6-9 medications	705	39 per 100 PYs	1.76 (1.37-2.27)*	1.45 (1.14-1.84)*	73	4 per 100 PYs	2.19 (1.29-3.69)*	1.91 (1.11-3.28)*
10+ medications	558	57 per 100 PYs	2.60 (1.98-3.40)*	1.85 (1.38-2.48)*	55	6 per 100 PYs	3.12 (1.81-5.37)*	2.58 (1.45-4.60)*
No CKD								
0-3 medications	419	13 per 100 PYs	0.80 (0.67-0.95)*	0.85 (0.71-1.01)	33	1 per 100 PYs	0.99 (0.61-1.61)	1.01 (0.61-1.68)
4-5 medications	488	16 per 100 PYs	ref	ref	31	1 per 100 PYs	ref	ref
6-9 medications	959	25 per 100 PYs	1.53 (1.31-1.79)*	1.33 (1.14-1.55)*	68	2 per 100 PYs	1.66 (1.09-2.55)*	1.51 (0.95-2.38)
10+ medications	647	44 per 100 PYs	2.81 (2.35-3.38)*	2.01 (1.68-2.41)*	47	3 per 100 PYs	3.09 (1.97-4.87)*	2.40 (1.43-4.05)*
PIM use								
Age-based PIM								
No	2,663	24 per 100 PYs	ref	ref	223	2 per 100 PYs	ref	ref
Yes	1,515	30 per 100 PYs	1.28 (1.15-1.43)*	0.98 (0.88-1.09)	121	2 per 100 PYs	1.23 (0.99-1.54)	1.13 (0.88-1.46)
Kidney-based PIM[c]								
No	1,576	37 per 100 PYs	ref	ref	162	4 per 100 PYs	ref	ref
Yes	791	49 per 100 PYs	1.46 (1.17-1.81)*	1.15 (0.91-1.45)	80	5 per 100 PYs	1.19 (0.78-1.80)	0.97 (0.59-1.58)
Age- or kidney-based PIM[c]								
No	1,291	38 per 100 PYs	ref	ref	137	4 per 100 PYs	ref	ref
Yes	1,076	43 per 100 PYs	1.32 (1.11-1.56)*	1.05 (0.89-1.24)	105	4 per 100 PYs	1.26 (0.93-1.72)	1.28 (0.91-1.79)

[a] Some participants had multiple hospitalizations during follow-up [b] Polypharmacy (categorical) and CKD status interaction not statistically significant [c] Includes participants with CKD only (eGFR <60 mL/min/1.73m^2) *=p≤0.05

Table 4A Key: Potentially inappropriate medication (PIM); Chronic kidney disease (CKD); Incidence rate ratio (IRR); Hazard ratio (HR); Person years (PYs); estimated glomerular filtration rate (eGFR); Model was adjusted for estimated glomerular filtration rate, hypertension, cardiovascular disease, diabetes, heart failure, self-reported myocardial infarction, Charlson Comorbidity Index, frailty, sex, age, race, Body Mass Index, current smoking status, current alcohol use, Mini-Mental State Evaluation, high-density lipoproteins, low-density lipoproteins, triglycerides, and total vitamins/supplements. PIM use analyses were additionally adjusted by total number of medications (continuous).

Supplementary Table S1A: Mean number of additional medications (confidence interval)

	Unadjusted	Adjusted[a]
Heart failure	2.57 (2.36 - 2.78)*	1.17 (0.97 - 1.38)*
Cardiovascular disease	2.28 (2.04 - 2.52)*	0.75 (0.50 - 0.99)*
Diabetes	2.47 (2.29 - 2.64)*	1.18 (1.01 - 1.35)*
Hypertension	2.39 (2.21 - 2.57)*	1.46 (1.30 - 1.63)*
Self-reported myocardial infarction	2.34 (2.02 - 2.66)*	0.12 (-0.19 - 0.44)
Charlson Comorbidity Index (per point)	0.60 (0.55 - 0.64)*	0.31 (0.26 - 0.36)*
Frailty	0.84 (0.67 - 1.01)*	0.30 (0.16 - 0.45)*
Alcohol use (per gram per week)	0.00 (-0.01 - 0.00)	0.00 (-0.00 - 0.00)
Current smoker	-0.36 (-0.74 - 0.02)	-0.17 (-0.49 - 0.14)
Female	0.43 (0.26 - 0.61)*	0.77 (0.60 - 0.94)*
White	-0.22 (-0.42 - -0.01)*	0.39 (0.19 - 0.58)*
BMI (per 1 kg/m^2)	0.14 (0.12 - 0.15)*	0.06 (0.05 - 0.07)*
Age (per year)	0.04 (0.02 - 0.05)*	-0.04 (-0.06 - -0.03)*
MMSE (per point)	-0.07 (-0.10 - -0.05)*	-0.04 (-0.06 - -0.01)*
Triglycerides (per 0.1 mmol/L)	0.60 (0.48 - 0.72)*	0.32 (0.19 - 0.45)*
HDL cholesterol (per 0.1 mmol/L)	-1.40 (-1.63 - -1.16)*	0.18 (-0.08 - 0.43)
LDL cholesterol (per 0.1 mmol/L)	-1.18 (-1.27 - -1.09)*	-0.79 (-0.87 - -0.70)*
Vitamins/supplements (per additional vitamin)	0.13 (0.09 - 0.17)*	0.18 (0.15 - 0.21)*

* = statistically significant ($p<0.05$)
[a] Constant = 5.72 (4.09-7.36)

Supplementary Table S1A Key: Fully adjusted linear model was identical to linear model in table 2, adjusted for CKD stage, hypertension, cardiovascular disease, diabetes, heart failure, self-reported myocardial infraction, Charlson Comorbidity Index (continuous), frailty, sex, race, Body Mass Index (BMI) (continuous; rounded to nearest whole number), current smoking status, current alcohol use (continuous; rounded to nearest gram), age (continuous; rounded to nearest whole number), Mini-Mental State Examination (MMSE) (continuous), high-density lipoproteins (HDL) (continuous; rounded to the nearest tenth), low-density lipoproteins (LDL) (continuous; rounded to the nearest tenth), triglycerides (continuous; rounded to the nearest tenth), and total number of vitamins/supplements (continuous); race compared white to African American.

Supplementary Table S2A: Prevalence of age-based PIM use

Potentially inappropriate medication	Reference	Overall use
Metabolic agents		
Diabetes medication		
Glyburide	Beers	107 (1.7%)
Endocrine-metabolic		
Megestrol	Beers	8 (0.1%)
Estrogens (oral)	Beers	172 (2.7%)
Desiccated thyroid extract	Beers	2 (0.0%)
Cardiovasuclar agents		
Antiarrhythmic		
Disopyramide	Beers	1 (0.0%)
Alpha adrenergic agonist		
Guanfacine	Beers	12 (0.2%)
Methyldopa	Beers	5 (0.1%)
Anticholinergic		
Hyoscyamine	Beers	14 (0.2%)
Propantheline	Beers	1 (0.0%)
Dicyclomine	Beers	40 (0.6%)
Clidinium/chlordiazepoxide	Beers	14 (0.2%)
Antiemetic		
Dimenhydrinate	Beers	6 (0.1%)
Meclizine	Beers	104 (1.6%)
Scopolamine	Beers	1 (0.0%)
Antibiotic		
Nitrofurantoin macrocrystalline	Beers	17 (0.3%)
Central nervous system agents		
Anxiolytic		
Meprobamate	Beers	2 (0.0%)
Antidepressant		
Paroxetine	Beers	80 (1.2%)
Desipramine	Beers	1 (0.0%)
Doxepin	Beers	14 (0.2%)
Imipramine	Beers	13 (0.2%)
Nortriptyline	Beers	36 (0.6%)
Barbituate		
Butabarbital	Beers	2 (0.0%)
Phenobarbital	Beers	6 (0.1%)
Hypnotic		
Eszopiclone	Beers/STOPP	7 (0.1%)
Zaleplon	Beers/STOPP	4 (0.1%)
Zolpidem	Beers/STOPP	166 (2.6%)
NSAID		
Ketorolac tromethamine	Beers	3 (0.0%)
Antiparkinsonian		
Benztropine mesylate	Beers	3 (0.0%)
Trihexyphenidyl	Beers	3 (0.0%)
Skeletal muscle relaxant		
Carisoprodol	Beers	6 (0.1%)
Chlorzoxazone	Beers	2 (0.0%)
Cyclobenzaprine	Beers	105 (1.6%)
Metaxalone	Beers	14 (0.2%)
Methocarbamol	Beers	17 (0.3%)
Analgesic		
Meperidine	Beers	1 (0.0%)
Anticoagulant		
Dipyridamole	Beers	7 (0.1%)
Containing multiple products		
1st generation antihistamines	Beers/STOPP	779 (12.2%)
Benzodiazepines	Beers/STOPP	545 (8.5%)
Antipsychotics	STOPP	66 (1.0%)
Amitriptyline-containing	Beers	117 (1.8%)
Atropine-containing	Beers	20 (0.3%)

Supplementary Table S2A key: Nonsteroidal anti-inflammatory drug (NSAID); note all criteria were based on medication use after 65 years old. Reference noted above is the reference with the most restrictive criteria (i.e. any use contraindicated), as opposed to contraindication based on comorbid conditions or concurrent use with another medication. Therefore, some medications noted in both references are only labeled with the reference with the most restrictive criteria.

2.8 Figures

Figure 1A: Proportion of participants reporting at least one medication in the prior 30 days, by category of medications

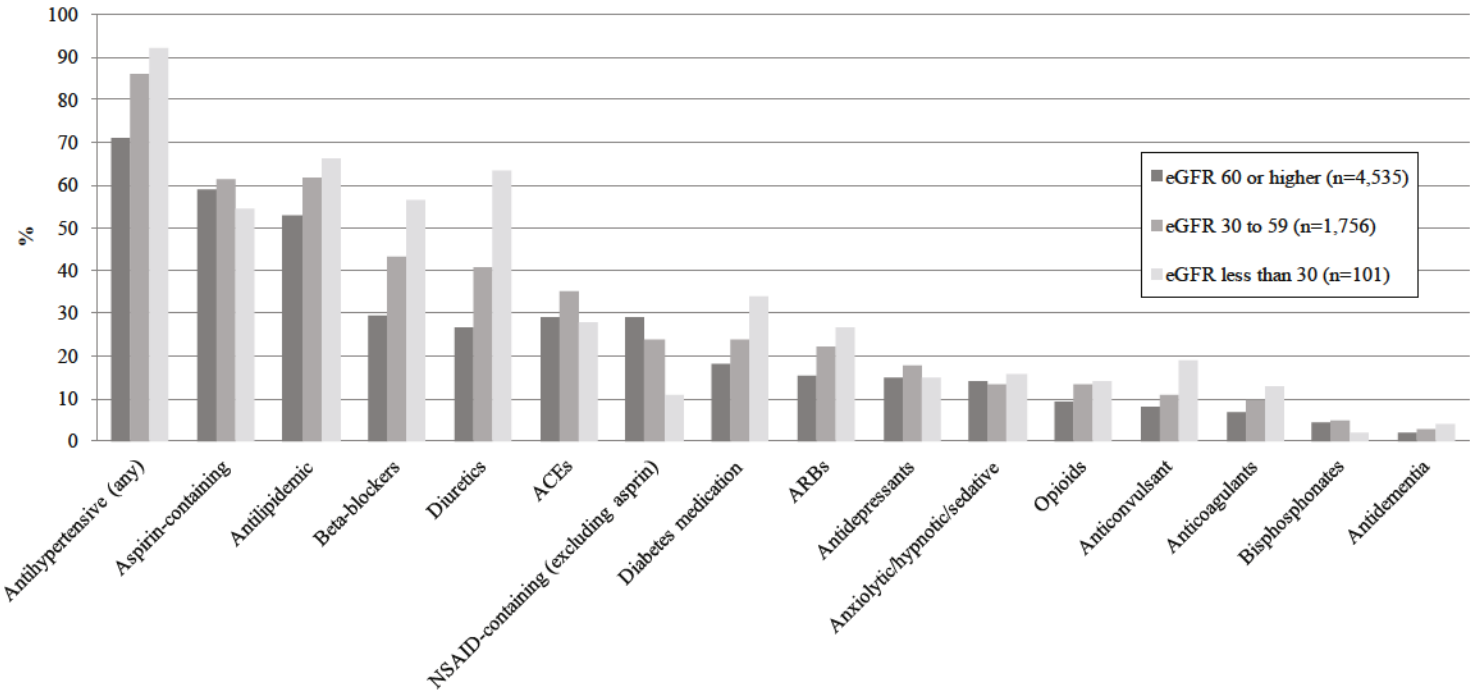


Figure 1A Legend: categorized by estimated glomerular filtration rate (eGFR); units in mL/min/1.73m^2

Figure 1A Key: Nonsteroidal anti-inflammatory drug (NSAID); Angiotensin-converting-enzyme (ACE) inhibitor or ACE combination product; Angiotensin II receptor blockers (ARB) or ARB combination product; Antihypertensive includes diuretics, beta-blockers, calcium channel blockers, ACE/combination, and ARB/combination.

Figure 2A: Risk of hospitalization across total number of medications

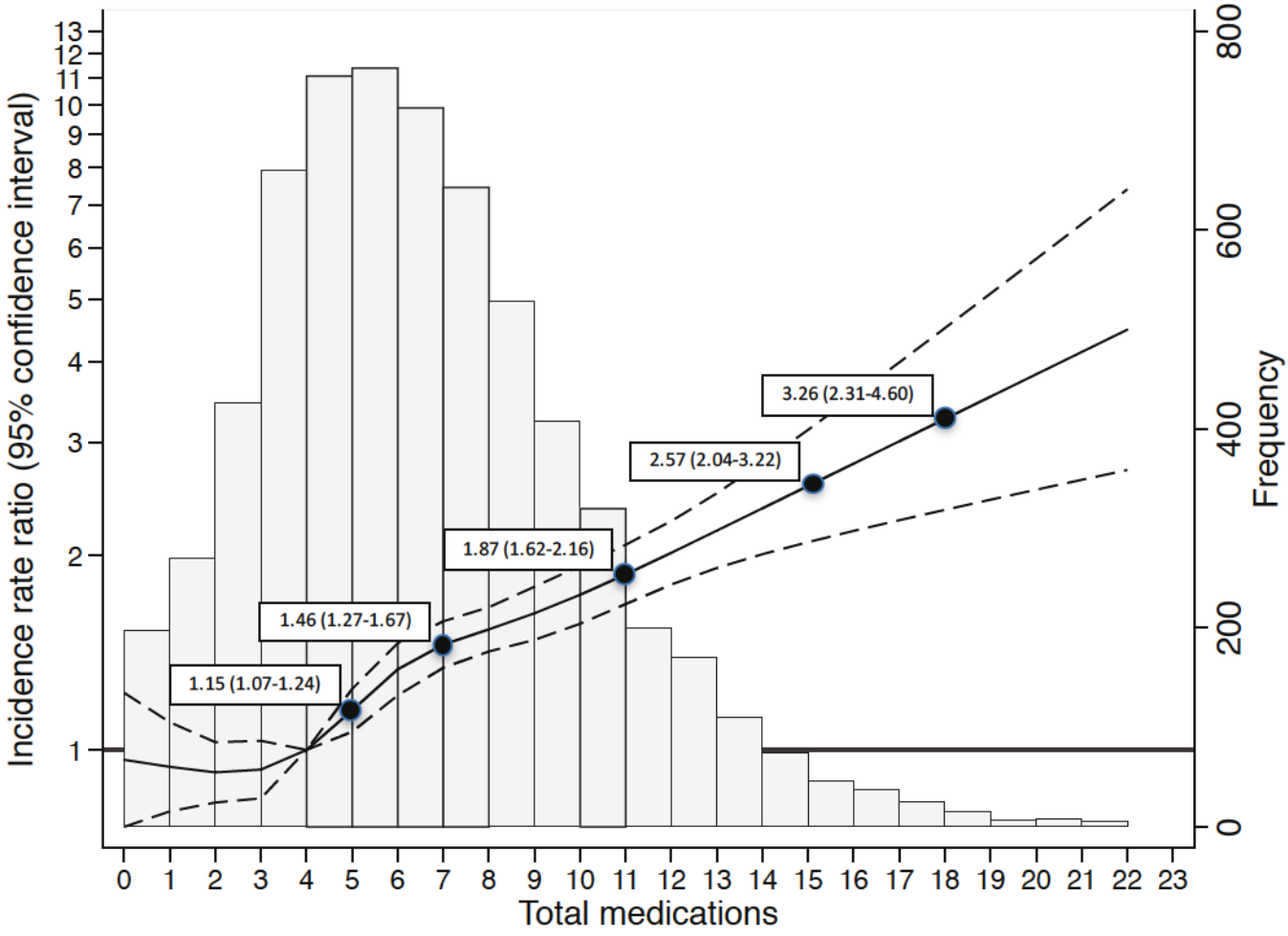


Figure 2A Key: Histogram depicts the distribution of total number of medications in the cohort (right y-axis). The solid black line (black dashed lines are 95% confidence interval) is the adjusted incidence rate ratio, representing the average (covariates were centered at cohort means) participant's risk of hospitalization across total number of medications, relative to the reference (4 medications). Model was adjusted for estimated glomerular filtration rate, hypertension, cardiovascular disease, diabetes, heart failure, self-reported myocardial infarction, Charlson Comorbidity Index, frailty, sex, race, Age, Body Mass Index, current smoking status, current alcohol use, Mini-Mental State Evaluation, high-density lipoproteins, low-density lipoproteins, triglycerides, and total vitamins/supplements.

Figure 3A: Risk of death across total number of medications

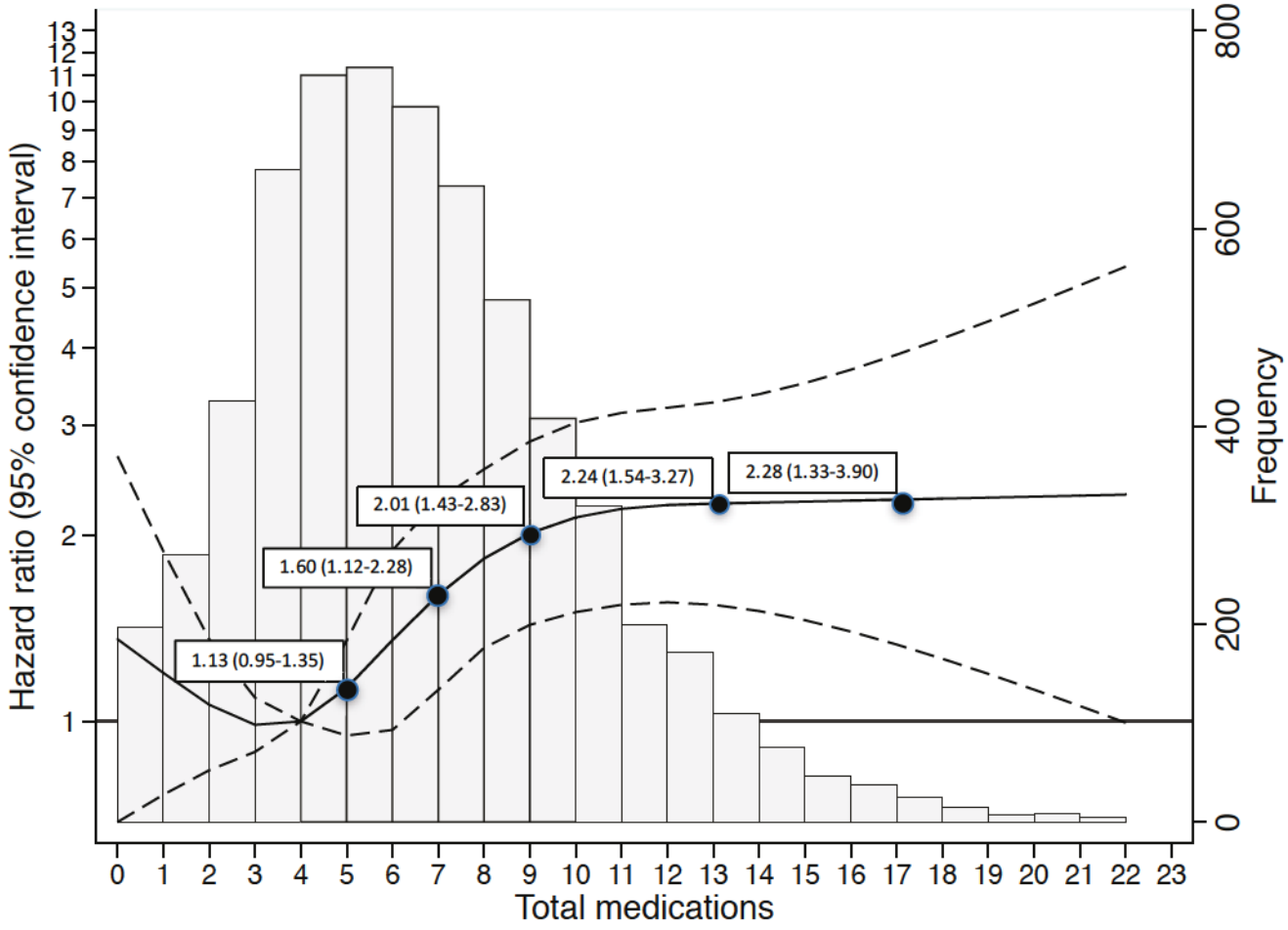
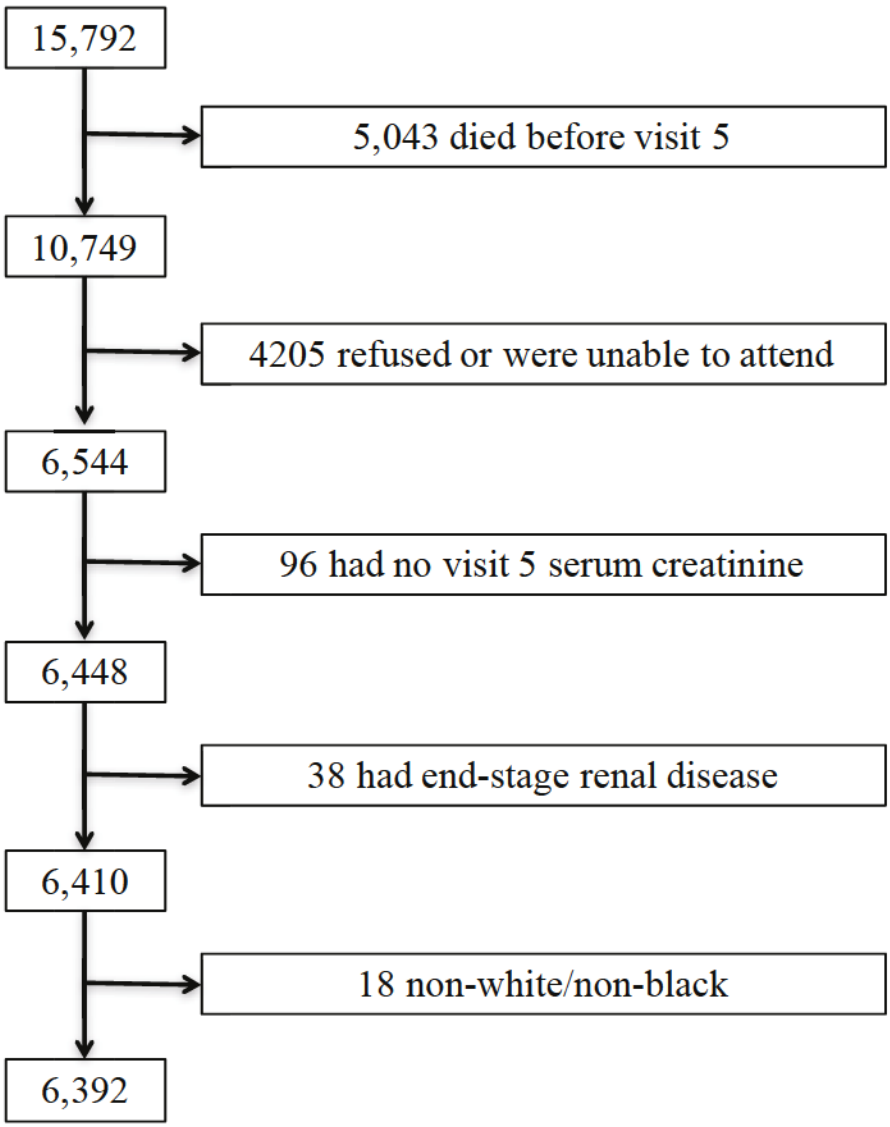
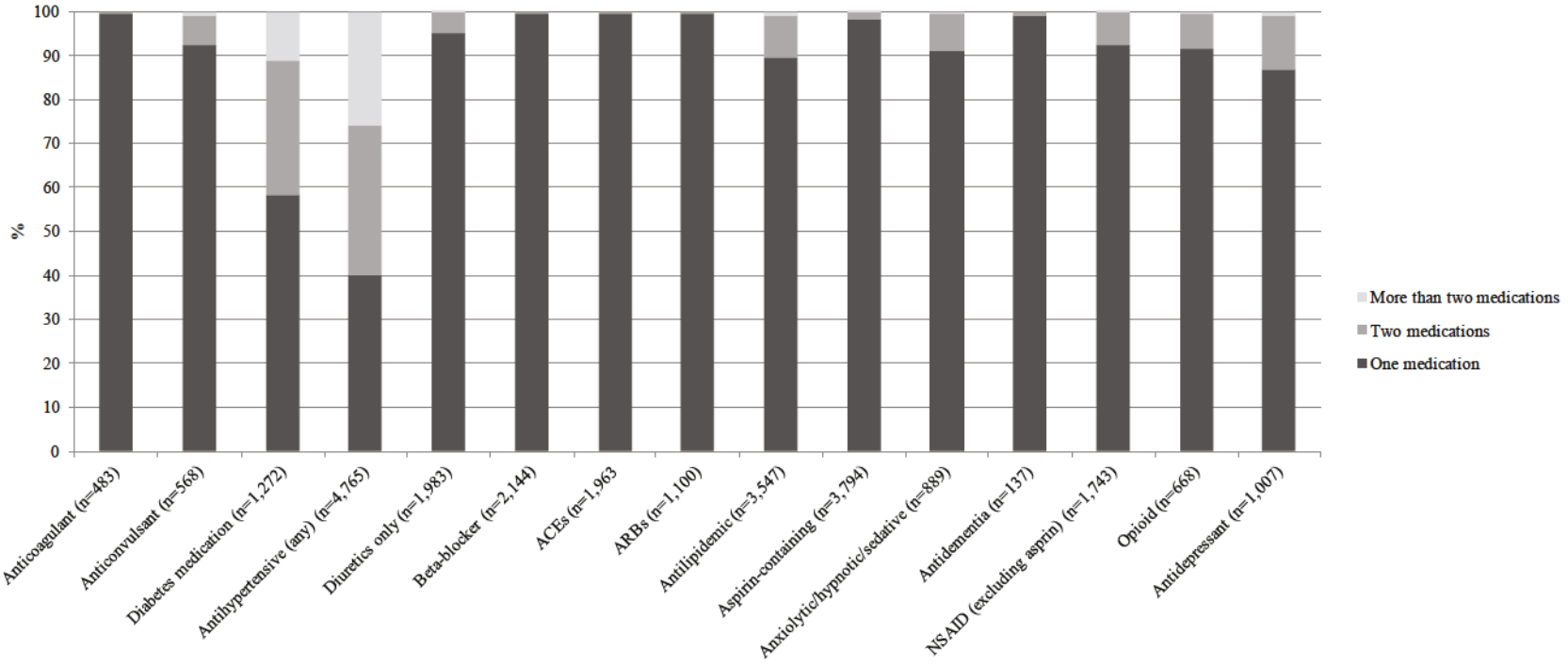


Figure 3A Key: Histogram depicts the distribution of total number of medications in the cohort (right y-axis). The solid black line (black dashed lines are 95% confidence interval) is the adjusted hazard ratio, representing the average (covariates were centered at cohort means) participant's risk of death across total number of medications, relative to the reference (4 medications). Model was adjusted for estimated glomerular filtration rate, hypertension, cardiovascular disease, diabetes, heart failure, self-reported myocardial infarction, Charlson Comorbidity Index, frailty, sex, race, age, Body Mass Index, current smoking status, current alcohol use, Mini-Mental State Evaluation, high-density lipoproteins, low-density lipoproteins, triglycerides, and total vitamins/supplements.

Supplementary Figure S1A: Study cohort flowchart

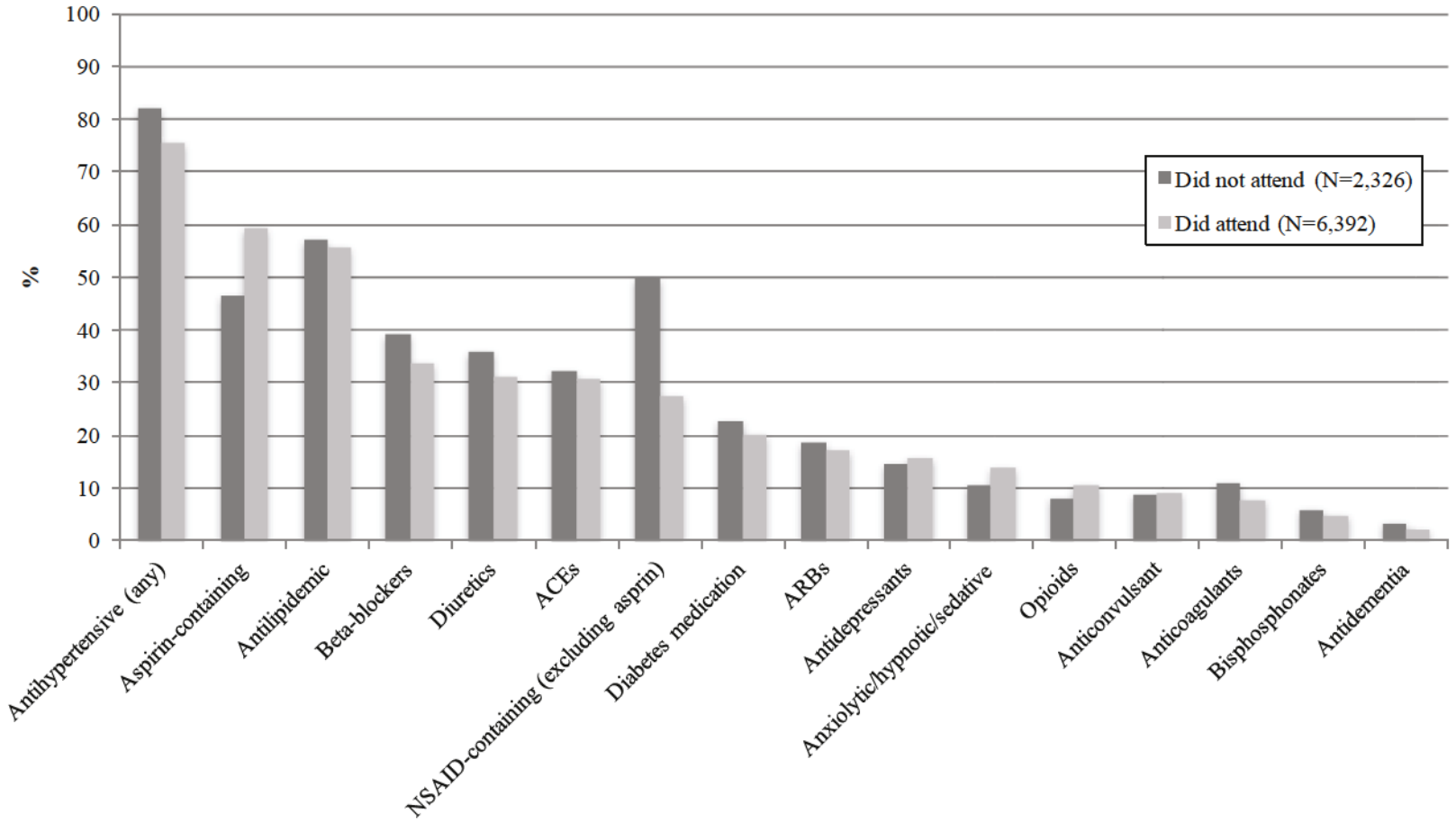


Supplementary Figure S2A: Proportion of participants taking two or more medications within the same drug category



Supplementary Figure S2A Key: Nonsteroidal anti-inflammatory drug (NSAID); Angiotensin-converting-enzyme (ACE) inhibitor or ACE combination product; Angiotensin II receptor blockers (ARB) or ARB combination product; Antihypertensive includes diuretics, beta-blockers, calcium channel blockers, ACE/combination, and ARB/combination

Supplementary Figure S3A: Proportion of participants reporting at least one medication by category of medications comparing those who attended visit five to those who did not attend visit five



Supplementary Figure S3A Key: For those who were alive but did not attend visit five, medication information presented above is from ARIC participants' last 6-month phone interview (conducted between June 2010 - June 2011)

3 Spironolactone use among patients with heart failure across the spectrum of kidney function

3.1 Abstract

Background: Spironolactone, effective in reducing morbidity and mortality in heart failure (HF), is not recommended in those with reduced kidney function. This study characterized spironolactone initiation among patients with HF, and evaluated differential initiation by kidney function.

Methods: We included patients with incident HF and available laboratory data in the MarketScan Commercial Claims database (MS) from 2010-2015, and the Geisinger Health System Integrated Electronic Health Record (GS) from 2004-2016. We assessed spironolactone use through prescription orders and dispensing, and used Cox proportional hazards regression models to identify patient characteristics associated with spironolactone initiation.

Results: Among 22,956 patients in MS, the mean age was 54.3 ($\pm$8.7) years, 47.2% were female, and the mean estimated glomerular filtration rate (eGFR) was 79.2 ($\pm$21.5) ml/min/1.73m^2. The 16,547 patients in GS were older (74.1 years $\pm$12.9), more often female (51.7%), and had a lower mean eGFR (62.4 $\pm$24.3). There were 1,398 initiators of spironolactone (3.5 per 1,000 person-months [PM]) in MS, and 1,747 initiators (3.1 per 1,000 PM) in GS; 7.0% and 9.9% initiated within two years in MS and GS, respectively. In adjusted models, patients with eGFR <30 were less likely to initiate than patients with eGFR 60-89 (meta-analyzed hazard ratio: 0.61, 95% confidence interval: 0.44-0.83); there were no differences between any other eGFR category. Loop diuretic use and lower serum potassium (<3.5, compared to 3.5-4.9) were associated with greater likelihood of initiation.

Conclusion: Fewer than one in ten patients with HF initiated spironolactone over two years. Initiation was least likely among those with the lowest renal function.

3.2 Introduction

Heart failure (HF) is common and causes substantial morbidity, with roughly half of patients dying within five years of their initial diagnosis.(97) Chronic kidney disease (CKD) is prevalent among patients with HF, and can further complicate treatment options for patients with already complex and evolving medical needs. While several treatments, such as aldosterone antagonists, angiotensin-converting enzyme inhibitors (ACEi), and angiotensin II receptor blockers (ARB), may reduce morbidity and mortality among patients with HF, these medications can impact potassium homeostasis, increasing the risk of hyperkalemia.

Spironolactone, an aldosterone antagonist indicated for the treatment of severe heart failure with reduced ejection fraction (HFrEF),(19) has been shown to be effective in reducing repeat hospitalization and mortality.(24, 25, 34, 41, 98) While American Heart Association (AHA) guidelines recommend aldosterone antagonists in these patients (99, 100) as well as "appropriately selected" heart failure patients with preserved ejection fraction (HFpEF), they recommend against use in patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2 due to concerns for hyperkalemia. Nevertheless, several ongoing trials sponsored by mix of government and industry sponsors (101) are evaluating spironolactone in patients with CKD, including those with end-stage kidney disease. Previously published cross-sectional study data suggest that the use of aldosterone antagonists is limited in patients with HF and reduced kidney function, but highly variable across hospital systems; however, this could also be true of patients with normal kidney function. (44, 102)

Patients with HF and CKD may benefit from spironolactone,(29, 103) but little is known about its actual use in this higher-risk population, or the extent to which patients' kidney function impacts the likelihood of spironolactone initiation in the context of other common comorbidities and concomitant medications. Given the uncertainty in its use among patients with lower eGFR, we examined the prevalence and correlates of spironolactone initiation, and discontinuation among initiators, in two large, diverse cohorts of patients with incident HF in the United States.

3.3 Methods

3.3.1 Study design and data sources

We used patient-level data from two large electronic health databases: Truven MarketScan Commercial Claims and Encounters database (MarketScan) and Electronic Health Record (EHR) data from the Geisinger Health System (Geisinger) in Pennsylvania, United States (U.S.). For MarketScan analyses, we used paid health care encounter claims from employer-sponsored insurance providers for patients not eligible for Medicare (<65 years old), including administrative claims related to medication dispensing, and inpatient, outpatient, and laboratory encounters from 2010 through 2015. Of note, MarketScan's laboratory data only includes patients whose insurance providers have contracts with large central labs (e.g. Quest Diagnostics). For Geisinger analyses, we used EHR data from 2004 through 2016, including inpatient, outpatient, and laboratory data for patients receiving primary care at Geisinger; linkage with the United States Renal Data System (USRDS) was used to obtain end-stage renal disease (ESRD) status for exclusion. Medication data at Geisinger were captured from medication orders, and medication reconciliation during health care encounters. Analyses were conducted separately in each database.

3.3.2 Population

We included patients age 18 years or older with incident International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) or ICD-10 diagnosis codes indicating HF (**Supplementary Table S1B**) from inpatient or outpatient records, and at least one available serum creatinine (SCr) and potassium (K) labs, and medication data (N=66,869 from MarketScan; N=32,536 from Geisinger). In most patients (~65%), the incident HF code was for unspecified HF (**Supplementary Table S2B**).

We excluded patients with ESRD, defined by ICD-9/10 diagnosis or procedure codes or USRDS registry, those with less than 90 days of available lookback in the data, those with any spironolactone use prior to their incident HF code date, and patients without an available outpatient SCr or K measured within 180 days before or seven days after their incident HF code date, leaving a total study population of 22,956 in MarketScan, and 16,547 in Geisinger **(Supplementary Figure S1B)**.

3.3.3 Exposure

Using a six-month window (180 days) before the HF index date to up to seven days after, we selected baseline eGFR and K as the closest measurement to the index date **(Supplementary Figure S2B)**. We defined eGFR based on outpatient SCr and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.(88) MarketScan data does not have information on race, an input in the CKD-EPI equation; therefore, all MarketScan participants were considered non-black for estimating eGFR which would bias African-American patients eGFR roughly 15% lower than expected. We classified eGFR using four primary categories (≥90

mL/min/1.73m^2; 89-60 mL/min/1.73m^2; 59-30 mL/min/1.73m^2; <30 mL/min/1.73m^2). We classified potassium levels using three categories (<3.5 mEq/L; 3.5-4.9 mEq/L; >5.0 mEq/L).

3.3.4 Outcomes

Patients were followed from their index date until incident spironolactone use, or administrative censoring, which we defined as an individuals' last recorded health care encounter date (inpatient, outpatient, laboratory, or medication order), death (for Geisinger only) or the end date of the study period (December 31st, 2015 for MarketScan, and December 31st, 2016, for Geisinger), whichever came first. We defined the primary outcome of interest, incident initiation of any spironolactone product (single-ingredient or spironolactone-hydrochlorothiazide combination products), as the first recorded spironolactone product dispensing claim or medication order, among those with no prior claims or orders for spironolactone products in the MarketScan or Geisinger data, respectively. For discontinuation analyses, we defined duration of spironolactone use as continuous use after initiation, allowing for a 60-day gap between the end of one prescription and the start of the next. We defined discontinuation as the last date of continuous spironolactone coverage noted in the prescription claims or medical record among those with at least 30 days of available follow-up after their continuous spironolactone coverage ended.

3.3.5 Covariates

We used administrative files to capture demographic data and, for MarketScan, information on insurance type and region where the patient resides. We defined comorbidities using ICD-9/10 diagnosis codes in the outpatient or inpatient setting prior to the index HF date (**Supplementary Table S1B**). To improve the sensitivity and positive predictive value of hyperlipidemia and

diabetes mellitus, we used diagnosis codes or the prior use of a statin or diabetes medication, respectively. Similarly, we defined coronary and peripheral artery disease using diagnosis codes or through relevant procedure codes such as coronary artery bypass grafting, or vascular shunt or bypass. We defined time-fixed baseline medication use as a dispensing or prescribing that overlapped the index HF date, or within 6 months prior to the index HF date. Diuretic class and ACEi/ARB use were modeled as baseline (time-fixed) and time-varying use, allowing for a 60-day gap in prescriptions. We also calculated patients' Charlson Comorbidity Index (CCI) score. (90, 91)

3.3.6 Statistical analysis

We calculated frequencies, means, and proportions of cohort characteristics, including demographics, comorbidities, and prior medication use. We computed cumulative incidence of spironolactone initiation over three years after incident HF; in Geisinger, we incorporated the competing event of death. Competing risk analyses were not performed in MarketScan as mortality were not available.

We used Cox proportional hazards regression models with robust variance estimators to quantify the association between kidney function and spironolactone initiation. We included eGFR category, serum K category, diuretic class use, and ACEi/ARB use as both baseline (time-fixed), and time-varying exposures, in separate models. Final models were adjusted for age, sex, CCI, year of HF diagnosis, history of liver disease, peptic ulcer disease, chronic obstructive pulmonary disease (COPD), myocardial infarction, hyperlipidemia, hypertension, coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease/stroke, diabetes mellitus, cancer, cirrhosis, ascites, acute kidney injury (AKI), atrial fibrillation, proteinuria,

eGFR, serum potassium, and prior use of anticoagulants, ACE, ARB, antiarrhythmics, cardiac glycosides, beta-blockers, calcium channel blockers, statins, vasodilators, loop diuretics, thiazide diuretics, and potassium-sparing diuretics (excluding spironolactone). MarketScan analyses were additionally adjusted for region of residence, and Geisinger analyses were additionally adjusted for race. We combined hazard ratios (HRs) using random effects meta-analysis. We estimated duration of spironolactone use after initiation using Kaplan-Meier functions, stratified by eGFR category, and assessed the role of time-varying eGFR and K in spironolactone discontinuation using fully-adjusted Cox proportional hazards regression models.

All analyses were conducted using Stata 15.1 (StataCorp; College Station, TX) and SAS 9.4 (SAS Institute Inc; Cary, North Carolina).

3.3.7 Sensitivity analysis

We conducted several sensitivity analyses to assess the robustness of our findings in both the MarketScan and Geisinger cohorts. In separate analyses, we restricted the cohorts to those with at least two outpatient SCr measurements in the years before their HF diagnosis, and to those with incident HF diagnosis codes referencing systolic failure (ICD-9: 428.2x & 428.4x; ICD-10: I50.2x & I50.4x) where it is most often used. In the Geisinger cohort, in separate analyses, we adjusted for time-varying systolic blood pressure (SBP), imputing SBP using multiple imputation by chained estimating equations when necessary, and accounted for the competing risk of death.

3.4 Results

3.4.1 Study population

The MarketScan incident HF cohort (N=22,956), was 47.2% female, and had a mean age of 54.3 years (±8.7), whereas in the Geisinger cohort (N=16,547) 51.7% were female, and the mean age was 74.1 years (±12.9) (**Table 1B**).

Overall, mean eGFR was higher in MarketScan (79.2 [±21.5] mL/min/1.73m^2) than in Geisinger (62.4 [±24.3] mL/min/1.73m^2), with only 17% below <60 mL/min/1.73m^2 in MarketScan compared with 47% in Geisinger. Past history of COPD, hyperlipidemia, hypertension, CAD, and diabetes were common (>30%) in both cohorts. Previous use of ACEi, beta-blockers, and statins were also common (>40% with previous use). The proportion of patients with previous use of loop (N=8,185, 35.7%) and thiazide (N=3,429, 14.9%) diuretics at baseline was lower in the MarketScan cohort compared to Geisinger (N=12,468 [75.3%] and N=5,372 [32.5%], respectively).

3.4.2 Spironolactone initiation

Among the 22,956 patients in MarketScan and 16,547 in Geisinger, median follow-up after incident HF date was 13.3 months (interquartile range [IQR]: 19.9 months) and 22.0 months (IQR: 46.1 months), respectively. Overall, 1,398 of the incident HF patients in MarketScan initiated spironolactone (3.5 per 1,000 person-months), and 1,747 of the incident HF patients in Geisinger (3.1 per 1,000 person-months). Rates of spironolactone initiation were lower with lower eGFR (3.4, 3.1, 3.0, 2.0 per 1,000 person-months for ≥90, 89-60, 59-30, <30 mL/min/1.73m^2, respectively) in Geisinger; however, in MarketScan, this was not observed (3.2, 3.4, 5.1, 3.2 per 1,000 person-months for ≥90, 89-60, 59-30, <30 mL/min/1.73m^2, respectively).

In MarketScan (**Figure 1B)**, cumulative incidence of spironolactone initiation was 5.6%, 7.0%, and 8.5% at 12, 24, and 36 months post-HF diagnosis (log rank p<0.001), respectively, whereas in Geisinger, cumulative incidence of spironolactone initiation was 7.9%, 9.9%, and 12.1% at 12, 24, and 36 months post-HF diagnosis (log rank p<0.001), respectively.

Median dose at spironolactone initiation was 25 milligrams, and this was consistent in both cohorts, across all eGFR categories.

3.4.3 Kidney function as a predictor of spironolactone use

In adjusted analyses modeling kidney function as a time-fixed variable (**Table 2B**), eGFR <30 mL/min/1.73m^2 was associated with a 41% lower likelihood of spironolactone initiation (HR_{meta}: 0.59; 95% confidence interval [CI]: 0.47 to 0.76) compared to an eGFR of 60-89 mL/min/1.73m^2; there was no difference in the likelihood of initiation for eGFR categories ≥90 or 30-59 mL/min/1.73m^2 compared to 60-89 mL/min/1.73m^2.

In adjusted analyses modeling kidney function as a time-varying exposure (**Table 3B**), eGFR <30 mL/min/1.73m^2 remained associated with a decreased likelihood of initiation (HR_{meta}: 0.61; 95% CI: 0.44 to 0.83) compared to eGFR of 60-89 mL/min/1.73m^2; again, there was no difference in the likelihood of initiation for eGFR categories ≥90 or 30-59 mL/min/1.73m^2 compared to 60-89 mL/min/1.73m^2.

Meta-analyzed results were consistent in sensitivity analyses (**Supplementary Table S3B)** restricting to only those with routine labs prior to HF diagnosis, restricting to only those with systolic HF codes, and when the initiation of single-ingredient spironolactone was used as the

outcome (data not shown). In sensitivity analyses conducted in Geisinger alone, results were also consistent when accounting for time-varying systolic blood pressure, and the competing risk of death.

3.4.4 Time-varying serum K and medications as predictors of spironolactone use

Serum potassium <3.5 mEq/L was associated with an increased likelihood of initiation compared to 3.5-4.9 mEq/L (HR_{meta}: 2.40; 95% CI: 1.95 to 2.96). Loop and thiazide use were associated with an increased likelihood of initiation, as well ([HR_{meta}: 2.49; 95% CI: 2.21 to 2.80] and [HR_{meta}: 1.27; 95% CI: 1.03 to 1.57], respectively]. Time-varying ACEi/ARB use was not associated with spironolactone initiation.

3.4.5 Comorbidities and previous medication use

In adjusted analyses, women were less likely to initiate spironolactone compared with men. Past history of cirrhosis and ascites, as well as prior use of cardiac glycosides and beta-blockers, were strongly associated with spironolactone initiation, and a history of acute kidney injury (AKI) and atrial fibrillation were associated with lower likelihood of spironolactone initiation.

3.4.6 Duration and discontinuation of spironolactone use

Median duration of spironolactone use was 6.3 and 10.2 months in MarketScan and Geisinger, respectively. Duration was shorter with lower eGFR in both cohorts (**Figure 2B**).

Among spironolactone initiators, 855 and 1,447 patients discontinued spironolactone after initiation in MarketScan and Geisinger, respectively. In the 30 days prior to discontinuation, 107 patients had at least one hospitalization (13% of individuals discontinuing spironolactone), and

18 had two or more in the MarketScan cohort; AKI was noted as the cause for hospitalization in nine patients. Of the 1,447 patients at Geisinger who discontinued spironolactone, 424 patients (29% of individuals discontinuing spironolactone) had at least one hospitalization in the 30 days prior to their discontinuation, and 62 had two or more; AKI was noted in 49 patients and hyperkalemia was noted in five patients as the cause for hospitalization.

For time-to-event analyses using time-varying lab data, serum K >5.0 mEq/L was a risk factor for discontinuation in both cohorts, compared with 3.5-4.9 mEq/L; in Geisinger, serum K <3.5 mEq/L was also a risk factor for discontinuation, as well as eGFR <30 mL/min/1.73m^2 (compared with ≥90 mL/min/1.73m^2).

3.5 Discussion

In this analysis of two large cohorts of patients with HF, one derived from commercial claims (MarketScan) and one derived from EHR data (Geisinger), use of spironolactone was low, with fewer than one in ten individuals initiating use within two years of a new diagnosis of HF. After controlling for concurrent comorbidities and medication use, those with the lowest level of kidney function were the least likely to initiate spironolactone. Among initiators, the duration of use was short, especially among those with lower kidney function. Our findings are important because data on the use of spironolactone in U.S. patients with HF are limited, and they have potential implications for both prescribers and regulators as spironolactone is being evaluated for use in patients with less severe HF, and across the spectrum of kidney function.(101)

Immediately after the Randomized Aldactone Evaluation Study (RALES)(41) demonstrated spironolactone's effectiveness in reducing cardiovascular hospitalization and death in patients

with HFrEF in 1999, utilization of spironolactone increased by a factor of up to five in several health systems around the world;(104, 105) however, whether this effect has persisted has not been assessed. We found that, overall, spironolactone use is modest in the setting of HF in two U.S.-based cohorts, even lower than what has been observed from cohorts outside of the U.S. where prevalence of use ranged from roughly 15% to 30%. (106-109) Our results support an analysis by Dev et al (102) which found that aldosterone antagonists may be underutilized as a class in the U.S., even among ideal candidates. Dev et al speculate the underutilization is primarily due to provider-based barriers, specifically lack of coordination of care between providers and experience with prescribing aldosterone antagonists. Some other possible barriers that may account for the low rates of use include concern regarding potential adverse effect profile, limited pharmaceutical marketing and promotion, regulatory advisories or label warnings, and coverage and reimbursement policies.

While spironolactone is not explicitly contraindicated in those with lower eGFR in its Food and Drug Administration (FDA) drug label,(19) the AHA guidelines for HFrEF recommend aldosterone antagonists in patients with eGFR >30 mL/min/1.73 m^2 (SCr of $\leq$2.5 mg/dL in men or $\leq$2.0 mg/dL in women), and potassium <5.0 mEq/L.(99, 100) Similarly, the Kidney Disease: Improving Global Outcomes (KDIGO) guideline on the treatment of hypertension in CKD supports the use of diuretics in patients with CKD, but recommends caution with prescribing spironolactone and other aldosterone antagonists.(12) We found that spironolactone initiation among those with eGFR <30 ml/min/1.73 m^2 was consistently low. Across both cohorts, those with eGFR <30 mL/min/1.73m^2 were the least likely to initiate spironolactone, and among those who were prescribed the drug, they also had the shortest duration of use. These findings suggest that kidney function remains an important clinical factor in whether patients are prescribed

spironolactone, and that providers may believe the risks of hyperkalemia outweigh spironolactone's benefits in some higher risk patients.

Patients with serum creatinine >2.5 mg/dL were excluded from RALES. As such, effectiveness was never established in the setting of reduced GFR in that original study. However, since its publication, clinical trial data suggest that patients with lower GFR would benefit from spironolactone's cardiovascular effects.(26, 38-40) Additionally, spironolactone and other aldosterone antagonists with antifibrotic/antiproteinuric properties may also confer renal benefit.(30, 31, 33, 110) As a pleiotropic hormone, spironolactone may be particularly promising in patients with CKD where there are limited therapeutic options, and where refractory hypertension is common.(111) More data are needed on how the benefit-to-risk ratio of these drugs varies across the spectrum kidney function.

Our study has a few notable strengths. We used two large electronic data resources with longitudinal records over extended time periods, including recent years where published data on spironolactone use is particularly limited. Data included laboratory measures of serum creatinine and potassium, and in Geisinger, clinical measurement of blood pressure. There are some limitations that must also be noted. Data used in this study were not collected for research purposes. We used diagnosis codes to define comorbidities, and some may have limited sensitivity and specificity. While we did conduct a sensitivity analyses looking at only systolic failure, we could not differentiate different types of HF using ICD-9/10 diagnosis codes for most patients. Medication data were obtained through prescription claims (MarketScan) and orders (Geisinger), and adherence could not be verified. Finally, compared with the Geisinger data, follow-up in MarketScan was somewhat limited, and we did not observe clear differentiation

between eGFR categories when calculating estimates of cumulative incidence of spironolactone initiation; this may be a function of unreported lab results for MarketScan cohort members.

3.6 Conclusions

We found that spironolactone initiation was uncommon among patients with incident HF in two, large U.S.-based cohorts. Spironolactone initiation was least likely in those with eGFR <30 mL/min/1.73m^2, after accounting for concurrent comorbidities and medication use. Duration of use after initiation was also shortest among those with the lowest levels of kidney function. Overall, these findings suggest that spironolactone is prescribed fairly infrequently to patients with heart failure, particularly among patients with low eGFR. Further research is needed to better establish a benefit-to-risk profile for spironolactone among patients with HF across the spectrum of kidney function, and whether it may be co-prescribed with potassium binders to achieve better safety profiles.

3.7 Tables

Table 1B: Sample characteristics, by cohort

	MarketScan	Geisinger
N (Total)	22,956	16,547
Female	10,830 (47.2%)	8,560 (51.7%)
Age (mean and SD)	54.3 (8.7)	74.1 (12.9)
Race (non-white)	n/a	341 (2.1%)
Kidney function, SCr, and K levels		
serum creatinine (mean and SD)	1.0 (0.5)	1.2 (0.6)
eGFR (mean and SD)	79.2 (21.5)	62.4 (24.3)
eGFR (category)		
≥90 mL/min/1.73m^2	8,590 (37.4%)	2,379 (14.4%)
60-89 mL/min/1.73m^2	10,541 (45.9%)	6,467 (39.1%)
30-59 mL/min/1.73m^2	3,125 (13.6%)	6,218 (37.6%)
<30 mL/min/1.73m^2	700 (3.1%)	1,483 (9.0%)
serum potassium (mean and SD)	4.3 (0.5)	4.3 (0.5)
serum potassium (category)		
<3.5 mEq/L	588 (2.6%)	623 (3.8%)
3.5-4.9 mEq/L	20,555 (89.6%)	14,170 (85.6%)
≥5.3 mEq/L	1,809 (7.9%)	1,754 (10.6%)
CCI (mean and SD)	4.5 (2.6)	7.0 (2.8)
Comorbidities		
liver disease	2,894 (12.6%)	1,041 (6.3%)
peptic ulcer disease	609 (2.7%)	924 (5.6%)
COPD	7,613 (33.2%)	7,946 (48.0%)
myocardial infarction	3,206 (14.0%)	3,415 (20.6%)
hyperlipidemia	15,757 (68.6%)	12,736 (77.0%)
hypertension	18,946 (82.5%)	13,980 (84.5%)
coronary artery disease	9,158 (39.9%)	8,591 (51.9%)
CEVD/stroke	3,994 (17.4%)	4,558 (27.5%)
peripheral artery diseaee	3,083 (13.4%)	3,392 (20.5%)
diabetes	10,078 (43.9%)	7,289 (44.1%)
cancer	3,013 (13.1%)	3,357 (20.3%)
cirrhosis	369 (1.6%)	180 (1.1%)
ascites	646 (2.8%)	218 (1.3%)
acute kidney injury	2,360 (10.3%)	2,830 (17.1%)
atrial fibrilation	3,339 (14.5%)	5,716 (34.5%)
proteinuria	1,116 (4.9%)	974 (5.9%)
Previous medication use		
anticoagulants	5,127 (22.3%)	8,709 (52.7%)
ACEi	9,199 (40.1%)	9,239 (55.8%)
ARB	4,993 (21.8%)	2,973 (18.0%)
antiarrythmic	2,440 (10.6%)	2,940 (17.8%)
cardiac glycoside	1,280 (5.6%)	2,359 (14.3%)
beta blocker	12,980 (56.5%)	12,736 (77.0%)
calcium channel blocker	6,934 (30.2%)	6,397 (38.7%)
statin	10,402 (45.3%)	10,196 (61.6%)
vasodilator	1,837 (8.0%)	1,311 (7.9%)
Previous diuretic use		
loop diuretic	8,185 (35.7%)	12,468 (75.3%)
thiazide diuretic	3,429 (14.9%)	5,372 (32.5%)
K-sparing diuretic	946 (4.1%)	598 (3.6%)

Table 1B Key:
Angiotensin-converting enzyme inhibitors (ACEi); Angiotensin II receptor blockers (ARB); cerebrovascular disease (CEVD); Charlson Comorbidity Index (CCI); chronic obstructive pulmonary disease (COPD); estimated glomerular filtration rate (eGFR); standard deviation (SD); serum creatinine (SCr); serum potassium (K).

Count (percentage) are presented for categorical variables.

Table 2B: Time-fixed predictors of spironolactone initiation, by cohort and meta-analyzed

	MarketScan		Geisinger		Meta-analyzed: HR_{meta} (CI)
	Unadjusted: HR (CI)	Adjusted: HR (CI)	Unadjusted: HR (CI)	Adjusted: HR (CI)	
Female	0.78 (0.70-0.87)*	0.87 (0.78-0.98)*	0.76 (0.69-0.83)*	0.79 (0.72-0.88)*	0.83 (0.75-0.91)*
Age	1.01 (1.00-1.01)	1.00 (0.99-1.00)	0.98 (0.98-0.99)*	0.99 (0.98-0.99)*	0.99 (0.97-1.01)
Race (non-white)	n/a	n/a	1.16 (0.85-1.60)	1.03 (0.75-1.42)	n/a
eGFR (categorical)					
≥90 mL/min/1.73m^2	0.92 (0.82-1.04)	0.97 (0.86-1.10)	1.16 (1.02-1.32)*	0.99 (0.86-1.14)	0.98 (0.89-1.07)
60-89 mL/min/1.73m^2	ref	ref	ref	ref	ref
30-59 mL/min/1.73m^2	1.43 (1.24-1.65)*	1.04 (0.89-1.22)	0.89 (0.80-1.00)*	0.99 (0.88-1.12)	1.00 (0.92-1.11)
<30 mL/min/1.73m^2	0.86 (0.61-1.21)	0.50 (0.34-0.74)*	0.53 (0.42-0.68)*	0.65 (0.50-0.84)*	0.59 (0.47-0.76)*
Serum K (categorical)					
<3.5 mEq/L	2.78 (2.26-3.44)*	2.06 (1.65-2.57)*	1.58 (1.28-1.95)*	1.62 (1.32-1.99)*	1.82 (1.44-2.30)*
3.5-4.9 mEq/L	ref	ref	ref	ref	ref
≥5.0 mEq/L	1.25 (1.04-1.51)*	1.15 (0.95-1.40)	1.08 (0.92-1.26)	1.08 (0.92-1.27)	1.11 (0.98-1.25)
Charlson Comorbidity Index	1.04 (1.02-1.06)*	0.97 (0.93-1.02)	0.95 (0.93-0.97)*	0.98 (0.94-1.02)	0.98 (0.95-1.01)
Comorbidities					
liver disease	1.53 (1.33-1.76)*	1.11 (0.92-1.34)	1.70 (1.43-2.00)*	1.12 (0.91-1.39)	1.11 (0.97-1.28)
peptic ulcer disease	0.80 (0.55-1.16)	0.80 (0.55-1.15)	1.01 (0.82-1.25)	1.10 (0.89-1.36)	0.97 (0.72-1.32)
COPD	1.31 (1.17-1.46)*	1.13 (1.00-1.28)	1.06 (0.97-1.17)	1.06 (0.96-1.18)	1.09 (1.01-1.18)*
myocardial infarction	1.40 (1.22-1.61)*	1.36 (1.15-1.62)*	1.05 (0.93-1.18)	1.07 (0.93-1.23)	1.20 (0.95-1.52)
hyperlipidemia	0.79 (0.71-0.88)*	0.85 (0.75-0.97)*	1.04 (0.93-1.16)	0.95 (0.83-1.09)	0.90 (0.80-1.00)
hypertension	1.03 (0.90-1.19)	0.85 (0.73-0.99)*	0.92 (0.81-1.04)	0.84 (0.73-0.97)*	0.85 (0.76-0.94)*
coronary artery disease	1.17 (1.05-1.30)*	0.89 (0.78-1.02)	1.05 (0.95-1.15)	1.00 (0.89-1.12)	0.95 (0.85-1.06)
CEVD/stroke	0.80 (0.69-0.93)*	0.89 (0.76-1.06)	0.88 (0.79-0.98)*	1.03 (0.91-1.17)	0.97 (0.84-1.12)
peripheral artery disease	1.01 (0.86-1.18)	0.94 (0.79-1.12)	0.92 (0.82-1.04)	0.91 (0.79-1.04)	0.92 (0.83-1.03)
diabetes	1.17 (1.06-1.30)*	1.00 (0.87-1.14)	1.08 (0.98-1.18)	0.99 (0.88-1.11)	0.99 (0.91-1.09)
cancer	1.01 (0.86-1.18)	1.04 (0.84-1.29)	0.82 (0.72-0.94)*	0.92 (0.78-1.09)	0.96 (0.85-1.10)
cirrhosis	5.01 (4.01-6.27)*	3.31 (2.48-4.41)*	4.25 (3.22-5.62)*	3.71 (2.62-5.25)*	3.47 (2.78-4.33)*
ascites	3.59 (2.94-4.40)*	2.35 (1.88-2.94)*	2.66 (1.95-3.63)*	2.30 (1.65-3.20)*	2.33 (1.94-2.81)*
acute kidney injury	1.26 (1.06-1.48)*	0.81 (0.67-0.99)*	0.74 (0.63-0.86)*	0.75 (0.63-0.88)*	0.78 (0.68-0.88)*
atrial fibrilation	1.52 (1.33-1.73)*	0.76 (0.65-0.90)*	1.18 (1.07-1.30)*	0.90 (0.80-1.01)	0.84 (0.71-0.99)*
proteinuria	1.38 (1.11-1.72)*	1.35 (1.08-1.70)*	1.09 (0.89-1.33)	1.00 (0.81-1.24)	1.16 (0.86-1.56)
Previous medication use					
anticoagulants	1.77 (1.58-1.97)*	1.12 (0.99-1.28)	1.49 (1.35-1.65)*	1.02 (0.91-1.13)	1.06 (0.97-1.16)
ACEi	2.22 (2.00-2.48)*	1.50 (1.33-1.68)*	1.68 (1.51-1.87)*	1.26 (1.12-1.41)*	1.37 (1.16-1.63)*
ARB	1.22 (1.08-1.37)*	1.13 (0.99-1.28)	1.41 (1.27-1.57)*	1.25 (1.12-1.40)*	1.20 (1.08-1.32)*
antiarrythmic	1.97 (1.73-2.25)*	1.17 (1.01-1.35)*	1.80 (1.63-2.00)*	1.31 (1.17-1.46)*	1.25 (1.12-1.40)*
cardiac glycoside	4.32 (3.79-4.94)*	2.24 (1.92-2.61)*	2.53 (2.29-2.80)*	2.11 (1.88-2.37)*	2.16 (1.97-2.37)*
beta blocker	3.89 (3.38-4.48)*	2.18 (1.87-2.55)*	2.83 (2.37-3.38)*	1.75 (1.45-2.11)*	1.97 (1.59-2.44)*
calcium channel blocker	1.26 (1.13-1.40)*	0.89 (0.79-1.00)	0.92 (0.84-1.01)	0.76 (0.68-0.84)*	0.82 (0.70-0.96)*
statin	1.07 (0.96-1.19)	0.87 (0.77-0.99)*	1.32 (1.19-1.47)*	0.99 (0.87-1.12)	0.93 (0.82-1.05)
vasodilator	1.96 (1.70-2.27)*	1.11 (0.95-1.31)	1.63 (1.43-1.87)*	1.47 (1.27-1.70)*	1.28 (0.97-1.69)
Previous diuretic use					
loop diuretic	7.08 (6.23-8.05)*	4.82 (4.18-5.56)*	5.96 (4.76-7.47)*	4.85 (3.86-6.10)*	4.83 (2.28-5.45)*
thiazide diuretic	1.71 (1.51-1.93)*	1.36 (1.19-1.54)*	1.69 (1.54-1.85)*	1.50 (1.36-1.67)*	1.44 (1.31-1.58)*
K-sparing diuretic	1.39 (1.11-1.74)*	1.19 (0.95-1.49)	1.60 (1.33-1.93)*	1.51 (1.25-1.81)*	1.35 (1.07-1.71)*
HF diagnosis year					
2004-2005	n/a	n/a	0.96 (0.81-1.15)	0.87 (0.72-1.04)	n/a
2006-2007	n/a	n/a	0.80 (0.67-0.96)*	0.76 (0.63-0.91)*	n/a
2008-2009	n/a	n/a	1.04 (0.88-1.23)	0.97 (0.82-1.16)	n/a
2010-2011	ref	ref	ref	ref	ref
2012-2013	1.03 (0.91-1.16)	1.25 (1.10-1.42)*	1.26 (1.06-1.49)*	1.37 (1.15-1.62)*	1.29 (1.17-1.43)*
2014 and after	0.89 (0.77-1.02)	1.12 (0.96-1.31)	1.01 (0.86-1.19)	1.31 (1.10-1.55)*	1.21 (1.04-1.41)*
Region of United States					
NE region	ref	ref	n/a	n/a	n/a
NC region	1.48 (1.25-1.77)*	1.31 (1.09-1.56)*	n/a	n/a	n/a
S region	1.31 (1.15-1.49)*	1.23 (1.08-1.41)*	n/a	n/a	n/a
W region	1.48 (1.22-1.80)*	1.30 (1.07-1.60)*	n/a	n/a	n/a

Table 2B Key: * p<0.05; angiotensin-converting enzyme inhibitors (ACE); angiotensin II receptor blockers (ARB); cerebrovascular disease (CEVD); chronic obstructive pulmonary disease (COPD); confidence interval (CI); estimated glomerular filtration rate (eGFR); hazard ratio (HR); heart failure (HF); northcentral (NC); northeast (NE); not applicable (n/a); potassium (K); reference (ref); serum creatinine (SCr); south (S); west (W)

Table 3B: Model with time-varying predictors of spironolactone initiation, by cohort and meta-analyzed

	MarketScan	Geisinger	Meta-analyzed: HR_{meta} (CI)
	Adjusted: HR (CI)	Adjusted: HR (CI)	
	Time-varying		
eGFR (categorical)			
≥90 mL/min/1.73m^2	0.92 (0.81-1.04)	0.94 (0.80-1.10)	0.93 (0.84-1.02)
60-89 mL/min/1.73m^2	ref	ref	ref
30-59 mL/min/1.73m^2	1.07 (0.91-1.25)	1.05 (0.94-1.18)	1.06 (0.96-1.16)
<30 mL/min/1.73m^2	0.50 (0.35-0.73)*	0.69 (0.54-0.88)*	0.61 (0.44-0.83)*
Serum K (categorical)			
<3.5 mEq/L	2.13 (1.69-2.69)*	2.64 (2.19-3.17)*	2.40 (1.95-2.96)*
3.5-4.9 mEq/L	ref	ref	ref
≥5.0 mEq/L	1.03 (0.85-1.26)	1.03 (0.87-1.22)	1.03 (0.91-1.17)
Current medication use			
loop diuretic	2.34 (2.07-2.64)*	2.64 (2.36-2.95)*	2.49 (2.21-2.80)*
thiazide diuretic	1.14 (0.98-1.34)	1.41 (1.22-1.62)*	1.27 (1.03-1.57)*
K-sparing diuretic	0.64 (0.41-1.00)*	1.16 (0.77-1.75)	0.87 (0.48-1.55)
ACEi/ARB	1.06 (0.94-1.19)	1.08 (0.98-1.20)	1.07 (0.99-1.16)
	Time-fixed		
Female	0.87 (0.78-0.98)*	0.78 (0.71-0.87)*	0.82 (0.74-0.91)*
Age	1.00 (0.99-1.01)	0.99 (0.98-0.99)*	0.99 (0.98-1.00)
Race (non-white)	n/a	0.96 (0.70-1.32)	n/a
Charlson Comorbidity Index	0.98 (0.93-1.02)	0.97 (0.93-1.01)	0.97 (0.95-1.01)
Comorbidities			
liver disease	1.11 (0.92-1.34)	1.16 (0.94-1.44)	1.13 (0.98-1.30)
peptic ulcer disease	0.78 (0.54-1.13)	1.09 (0.88-1.34)	0.96 (0.69-1.32)
COPD	1.24 (1.09-1.40)*	1.06 (0.95-1.17)	1.14 (0.98-1.33)
myocardial infarction	1.34 (1.13-1.60)*	1.08 (0.93-1.24)	1.20 (0.97-1.48)
hyperlipidemia	0.78 (0.69-0.89)*	0.93 (0.81-1.06)	0.85 (0.72-1.01)
hypertension	0.89 (0.76-1.03)	0.91 (0.80-1.05)	0.90 (0.81-1.00)
coronary artery disease	0.89 (0.77-1.02)	0.97 (0.86-1.09)	0.94 (0.86-1.03)
CEVD/stroke	0.85 (0.72-1.01)	1.05 (0.92-1.19)	0.95 (0.77-1.17)
peripheral artery disease	0.93 (0.78-1.12)	0.91 (0.80-1.04)	0.92 (0.82-1.02)
diabetes	1.11 (0.97-1.26)	1.01 (0.90-1.13)	1.05 (0.96-1.15)
cancer	1.03 (0.83-1.27)	0.92 (0.78-1.09)	0.96 (0.84-1.10)
cirrhosis	3.54 (2.65-4.73)*	3.70 (2.62-5.21)*	3.61 (2.89-4.50)*
ascites	2.54 (2.02-3.20)*	2.25 (1.62-3.12)*	2.44 (2.02-2.95)*
acute kidney injury	0.85 (0.70-1.05)	0.75 (0.63-0.88)*	0.79 (0.69-0.90)*
atrial fibrilation	0.72 (0.61-0.86)*	0.84 (0.75-0.95)*	0.79 (0.68-0.91)*
proteinuria	1.40 (1.11-1.76)*	1.03 (0.83-1.28)	1.20 (0.89-1.62)
Previous medication use			
anticoagulants	1.19 (1.05-1.36)*	1.07 (0.96-1.20)	1.12 (1.01-1.25)*
antiarrythmic	1.34 (1.15-1.56)*	1.41 (1.27-1.58)*	1.39 (1.27-1.52)*
cardiac glycoside	2.71 (2.30-3.19)*	2.28 (2.03-2.57)*	2.46 (2.08-2.91)*
beta blocker	3.00 (2.57-3.50)*	2.00 (1.65-2.41)*	2.46 (1.65-3.66)*
calcium channel blocker	1.00 (0.89-1.12)	0.81 (0.74-0.90)*	0.90 (0.73-1.10)
statin	0.91 (0.80-1.03)	1.06 (0.93-1.20)	0.98 (0.85-1.14)
vasodilator	1.30 (1.10-1.52)*	1.57 (1.36-1.82)*	1.43 (1.19-1.72)*
HF diagnosis year			
2004-2005	n/a	0.97 (0.81-1.17)	n/a
2006-2007	n/a	0.82 (0.68-0.99)*	n/a
2008-2009	n/a	0.97 (0.82-1.16)	n/a
2010-2011	ref	ref	ref
2012-2013	1.22 (1.07-1.39)*	1.31 (1.10-1.55)*	1.25 (1.13-1.39)*
2014 and after	1.08 (0.92-1.26)	1.19 (1.00-1.40)*	1.13 (1.01-1.27)*
Region of United States			
NE region	ref	n/a	n/a
NC region	1.38 (1.16-1.65)*	n/a	n/a
S region	1.31 (1.14-1.49)*	n/a	n/a
W region	1.35 (1.10-1.65)*	n/a	n/a

Table 3B Key:
* p<0.05; Angiotensin-converting enzyme inhibitors (ACEi); angiotensin II receptor blockers (ARB); cerebrovascular disease (CEVD); chronic obstructive pulmonary disease (COPD); confidence interval (CI); estimated glomerular filtration rate (eGFR); hazard ratio (HR); heart failure (HF); northcentral (NC); northeast (NE); not applicable (n/a); potassium (K); reference (ref); serum creatinine (SCr); south (S); west (W);

This model included both time-fixed and time-varying covariates (as noted). ACEi and ARB use was combined in time-varying analyses.

Supplementary Table S1B: Operationalized definitions for patient comorbidities

Condition	Operationalized definitions			
	ICD-9 diagnosis	ICD-10 diagnosis	ICD-9 procedure	Medication class
Heart failure (any)	428.x 402.01 402.11 402.91 404.01 404.03 404.11 404.13 404.91 404.93 398.91	I50.x I11.0 I13.0 I13.2 I09.81	N/A	N/A
Systolic heart failure	428.1x 428.4x	I50.2x I50.4x	N/A	N/A
Liver disease	070.22 070.23 070.32 070.33 070.44 070.54 070.6 070.9 456.0-456.2 570.x 571.x 572.2-572.8 573.3 573.4 573.8 573.9 V42.7	B18.x I85.0 I85.9 I86.4 I98.2 K70.0-K70.4 K70.9 K71.1 K71.3-K71.5 K71.7 K72.1 K72.9 K73.x K74.x K76.0 K76.2-K76.9 K76.8 K76.9 Z94.4	N/A	N/A
Peptic ulcer disease	531.x-534.x	K25.x-K28.x	N/A	N/A
COPD	416.8 416.9, 490.x-505.x 506.4 508.1 508.8	I27.8 I27.9 J40.x-J47.x J60.x-J67.x J68.4 J70.1 J70.3	N/A	N/A
Myocardial infarction	410.x 412.x	I21.x I22.x I25.2x	N/A	N/A
Hyperlipidemia	272.0 272.1 272.4 272.9	E78.0x E78.2 E78.4x E78.5	N/A	Statin drug
Hypertension	401.x - 405.x	I10 I15	N/A	N/A
Coronary artery disease	414.0 410.x 412 414.8 414.9	I25.x I70.0 I24.x	36.1	N/A
CEVD/stroke	362.34 430.x-438.x	G45.x G46.x H34.0 I60.x-I69.x	N/A	N/A
Peripheral artery disease	443.9 440.2x-440.4x 707.1x 785.4	I70.2x I73.x	38.18 39.50 39.25 39.29	N/A
Diabetes	250.x 357.2 362.0x 366.41	E08.x-E11.x E13.x	N/A	Diabetes drug
Cancer	140.x-172.x 174.x-208.x 238.6	C00.x-C26.x C30.x-C34.x C37.x-C41.x C43.x C45.x-C58.x C60.x-C85.x C88.x C90.x-C97.x	N/A	N/A
Cirrhosis	571.2 571.5 571.6	K74.3 - K74.6x	N/A	N/A
Ascites	789.5x	R18.x	N/A	N/A
Acute kidney injury	584.9	N17.9	N/A	N/A
Atrial fibrillation	427.3x	I48.x	N/A	N/A
Proteinuria	791.0	R80.x	N/A	N/A

Supplementary Table S1B Key: Diabetes drugs include, but are not limited to, insulin, biguanides, sulfonylureas, alpha-glucosidase inhibitors, and thiazolidinediones. cerebrovascular disease (CEVD); International Classification of Diseases (ICD); chronic obstructive pulmonary disease (COPD)

Supplementary Table S2B: Incident heart failure codes, by cohort

	MarketScan	Geisinger
N (Total number of patients)	22,956	16,547
Heart failure, unspecified (428.0, I50.9)	15,258 (66%)	10,541 (64%)
Systolic code (428.1x, I50.2x)	1,887 (8%)	2,382 (14%)
Diastolic code (428.3x, I50.3x)	2,647 (12%)	2,569 (16%)
Combined systolic and diastolic code (428.4x, I50.4x)	468 (2%)	191 (1%)
All other codes*	2,696 (12%)	864 (5%)

Supplementary Table S2B Key: * = the vast majority were for code 402.x

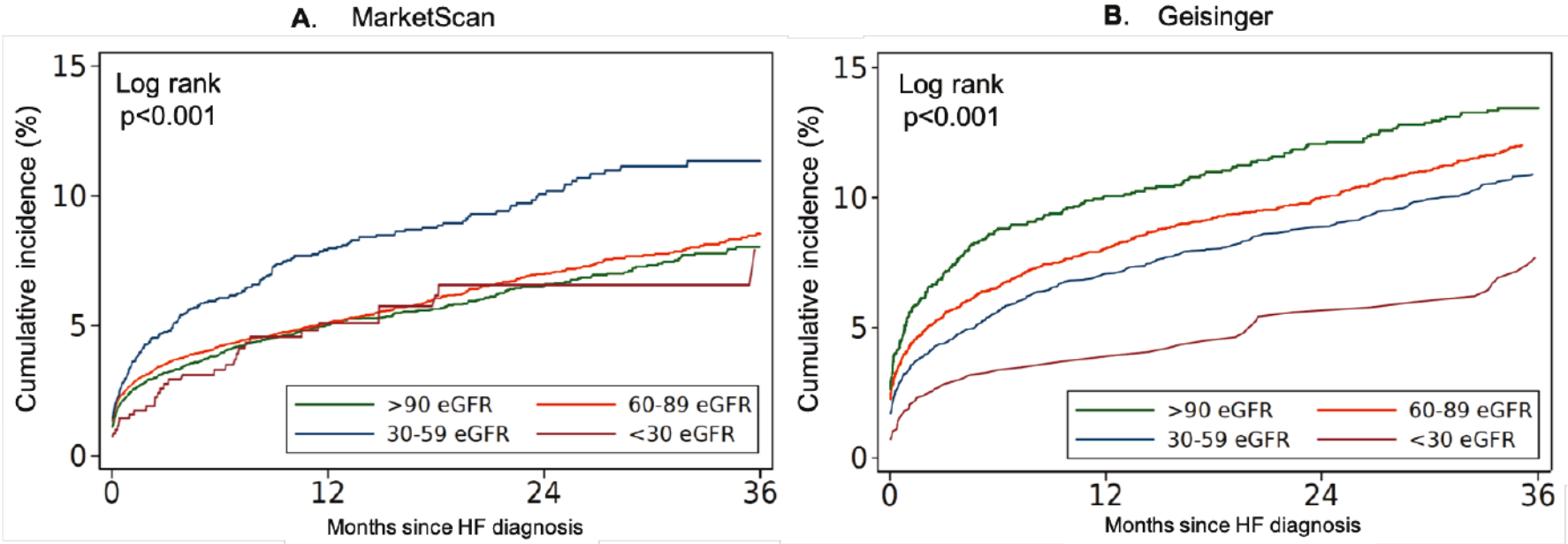
Supplementary Table S3B: Sensitivity analyses with kidney function as predictor spironolactone use

	Sensitivity 1: HR (CI)	Sensitivity 2: HR (CI)	Sensitivity 3: HR (CI)	Sensitivity 4: HR (CI)
MarketScan eGFR category				
≥90 mL/min/1.73m^2	0.89 (0.77-1.03)	0.71 (0.53-0.95)*	n/a	n/a
60-89 mL/min/1.73m^2	ref	ref	n/a	n/a
30-59 mL/min/1.73m^2	0.97 (0.81-1.16)	0.84 (0.58-1.22)	n/a	n/a
<30 mL/min/1.73m^2	0.50 (0.33-0.72)*	0.52 (0.23-1.19)	n/a	n/a
Geisinger eGFR category				
≥90 mL/min/1.73m^2	0.90 (0.76-1.06)	1.01 (0.72-1.41)	0.95 (0.80-1.09)	0.90 (0.77-1.05)
60-89 mL/min/1.73m^2	ref	ref	ref	ref
30-59 mL/min/1.73m^2	1.04 (0.93-1.18)	0.94 (0.72-1.24)	1.04 (0.93-1.17)	1.04 (0.93-1.17)
<30 mL/min/1.73m^2	0.69 (0.54-0.88)*	0.44 (0.22-0.85)*	0.68 (0.54-0.86)*	0.59 (0.47-0.75)*
Meta-analyzed: HR_{meta} (CI)				
≥90 mL/min/1.73m^2	0.89 (0.80-1.00)	0.84 (0.59-1.18)	n/a	n/a
60-89 mL/min/1.73m^2	ref	ref	n/a	n/a
30-59 mL/min/1.73m^2	1.02 (0.92-1.12)	0.90 (0.73-1.13)	n/a	n/a
<30 mL/min/1.73m^2	0.61 (0.45-0.83)*	0.47 (0.28-0.79)*	n/a	n/a

Supplementary Table S3B Key: * = $p<0.05$; Angiotensin-converting enzyme inhibitors (ACEi); angiotensin II receptor blockers (ARB); confidence interval (CI); estimated glomerular filtration rate (eGFR); heart failure (HF); hazard ratio (HR); not applicable (n/a); reference (ref); All sensitivity models used were fully-adjusted and included time-varying eGFR, K, diuretic class use, and ACEi/ARB. *Sensitivity 1* analyses were restricted to patients with at least two lab measurements any year before HF diagnosis (MarketScan N=15,385; Geisinger N=15,504). *Sensitivity 2* analyses were restricted to patients with incident systolic or combined systolic + diastolic HF (MarketScan N=2,355; Geisinger N=2,573). *Sensitivity 3* analyses included time-varying systolic blood pressure (Geisinger N=16,547). *Sensitivity 4* analyses used a competing risk (death) framework (Geisinger N=16,547).

3.8 Figures

Figure 1B: Cumulative incidence of spironolactone initiation by 3 years, overall and stratified by kidney function



Baseline kidney function	12 months	24 months	36 months
Total	5.6%	7.0%	8.5%
>90 eGFR	5.2%	6.7%	8.4%
60-89 eGFR	5.2%	7.2%	8.9%
30-59 eGFR	8.2%	10.6%	12.0%
<30 eGFR	5.2%	6.8%	8.2%

Baseline kidney function	12 months	24 months	36 months
Total	7.9%	9.9%	12.1%
>90 eGFR	10.5%	12.7%	14.3%
60-89 eGFR	8.3%	10.5%	12.7%
30-59 eGFR	7.3%	9.2%	11.5%
<30 eGFR	3.9%	5.8%	8.0%

Figure 1B Key: estimated glomerular filtration rate (eGFR); heart failure (HF); Cumulative incidence plots for the MarketScan (A) and Geisinger (B) cohorts were truncated at three years (36 months) after incident HF diagnosis. Geisinger estimates accounted for competing risk of death.

Figure 2B: Kaplan-Meier plot for discontinuation of spironolactone after initiation, stratified by kidney function

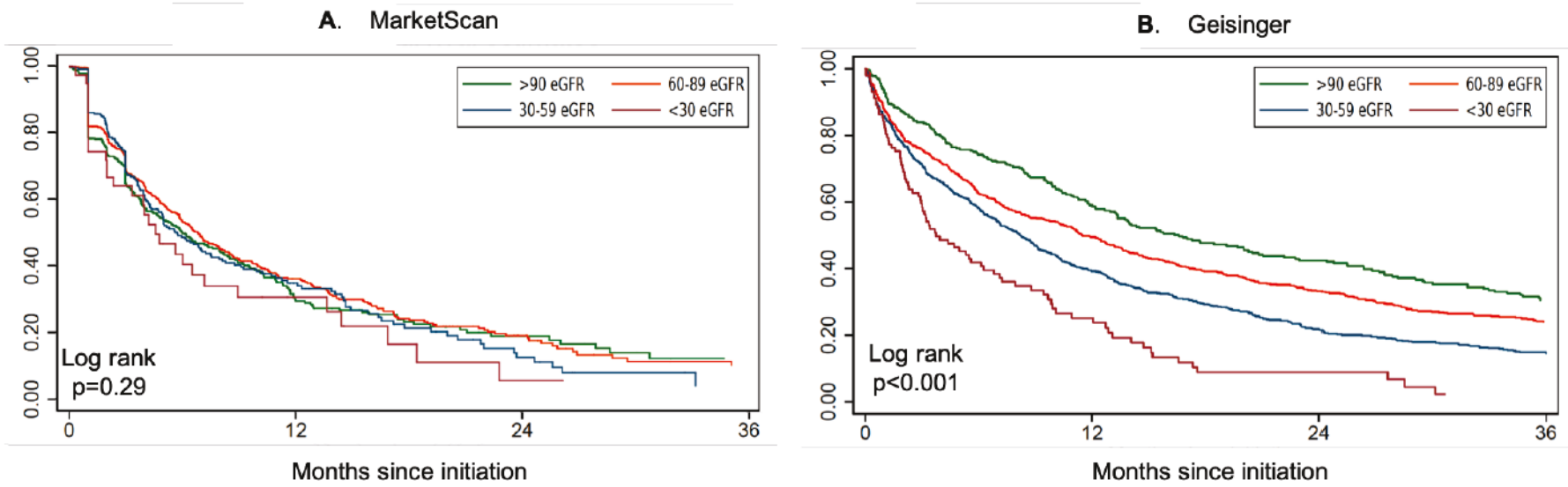
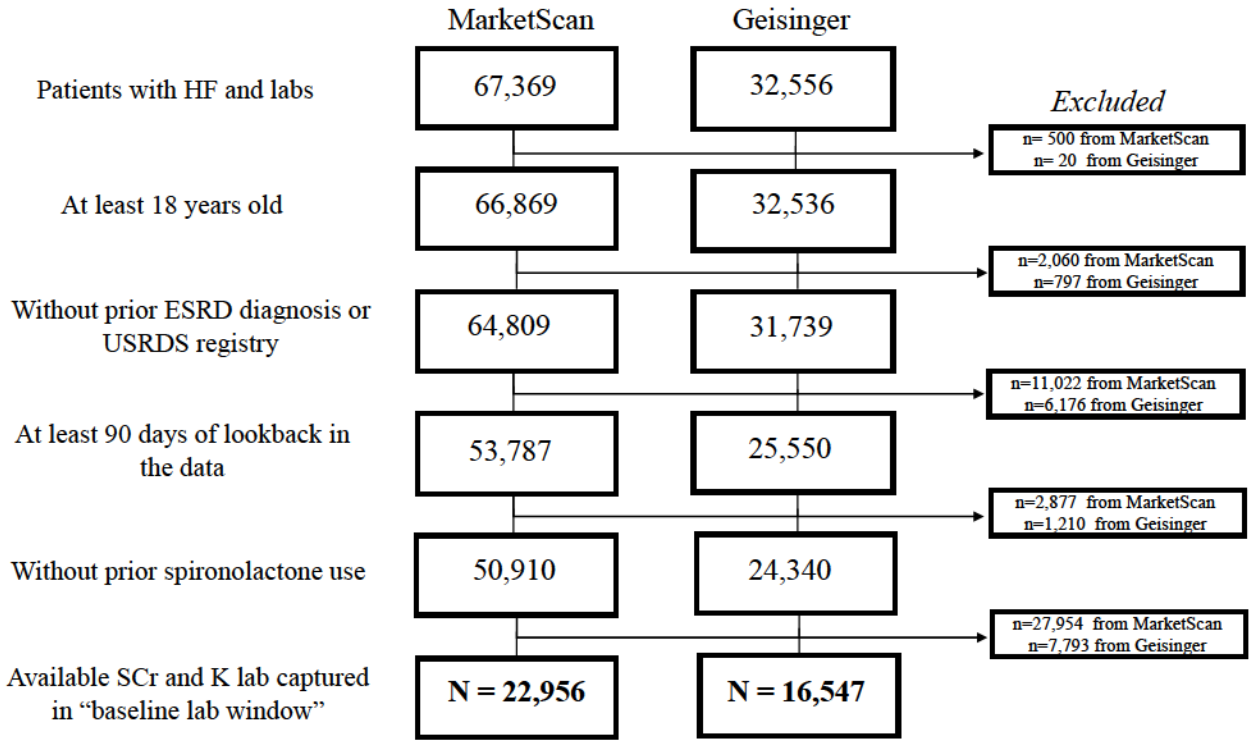


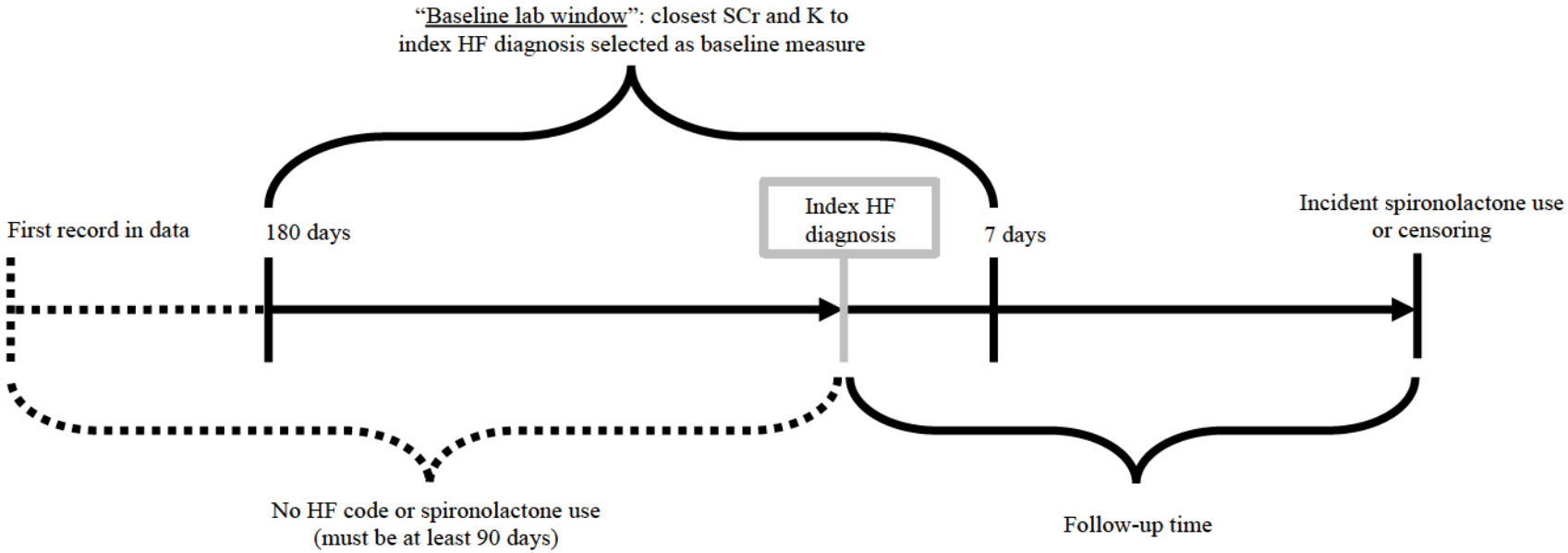
Figure 2B Key: estimated glomerular filtration rate (eGFR); Spironolactone initiators were censored at discontinuation (defined as no spironolactone prescription in 30 days after the last prescriptions days' supply ended), or last record in the data, whichever came first. Data were truncated at three years (36 months) post-initiation for the MarketScan (A) and Geisinger (B) cohorts

Supplementary Figure S1B: Study cohort flow diagram



Supplementary Figure S1B Key: end-stage renal disease (ESRD); heart failure (HF); serum creatinine (SCr); serum potassium (K); United States Renal Data System (USRDS). We defined "baseline lab window" as 180 days before through seven days after index HF diagnosis. For both MarketScan and Geisinger, we defined patients' HF index date as the first HF diagnosis code date; to ensure this was an incident diagnosis, patients were required to have had at least 90 days of available claims (MarketScan) or records in the EHR (Geisinger) to check for prior HF codes. If the incident HF code was from an inpatient record, the hospital discharge date was used as the index date.

Supplementary Figure S2B: Diagram of exposure time allocation and "baseline lab window"



Supplementary Figure S2B Key: Heart failure (HF); serum creatinine (SCr); serum potassium (K); To be included, patients must have had at least 90 days of available claims or records with no HF code noted or spironolactone prescription, and available SCr and K labs in the "baseline lab window". Patients were censored at incident spironolactone use or last record in the data, whichever came first. Geisinger analysis included competing risk of death as sensitivity analysis.

4 Hyperkalemia and acute kidney injury with spironolactone use among patients with heart failure

4.1 Abstract

Background: The risk of hyperkalemia and acute kidney injury (AKI) with spironolactone use among patients with heart failure is unclear, particularly in patients with reduced kidney function.

Methods: We identified 17,110 patients with heart failure treated with loop diuretics between 2004 and 2016 within the Geisinger Health System. We estimated the incidence of hyperkalemia and AKI associated with the addition of spironolactone and used target trial emulation methods to minimize confounding by indication. We report risks associated with the addition of spironolactone compared to loop diuretics alone by level of kidney function.

Results: Over a mean follow-up of 134 months, 18.9% (N=3,229) initiated spironolactone. Patients initiating spironolactone were younger and had a higher mean estimated glomerular filtration rate (eGFR) (p=0.001 for both). In as-treated analyses, incidence rates (IRs) of hyperkalemia were highest when patients were on spironolactone without a loop diuretic (3.3 per 1,000 person-months), followed by both loop diuretics and spironolactone (2.9), loop diuretics alone (1.4), and neither (1.3). The IRs for AKI were highest when patients were on both loop diuretics and spironolactone (10.1), followed by loop alone (7.4), spironolactone alone (5.3), and neither (4.6). In propensity score matched target trial emulation, spironolactone initiation was associated with a moderate increase in hyperkalemia risk and a small increase in AKI risk compared to loop alone [hazard ratio (HR) 1.69 (confidence interval (CI): 1.35-2.10), and HR

1.12 (CI: 1.00-1.26), respectively]. There were no differences in the relative risk of either outcome associated with spironolactone by level of eGFR (all interactions p>0.05).

Conclusion: The addition of spironolactone to loop diuretics in patients with heart failure increases the risk of hyperkalemia, and to a lesser degree, AKI. While the absolute risks were higher for both outcomes among those using spironolactone with reduced kidney, the relative risks associated with spironolactone were not different by level of kidney function. These risks must be weighed against the potential benefits of spironolactone.

4.2 Introduction

Spironolactone is an aldosterone antagonist indicated for the treatment of New York Heart Association Class III-IV heart failure with reduced ejection (HFrEF).(19) Concomitant spironolactone and loop diuretics decreased heart failure hospitalization and mortality among patients with HFrEF in the landmark Randomized Aldactone Evaluation Study (RALES) study.(41) Evidence for spironolactone's effectiveness among patients with heart failure with preserved ejection (HFpEF) is less established,(112) but data from the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial suggest a benefit for spironolactone in HFpEF, with a protective effect for heart failure hospitalization but not mortality.(113) Nevertheless, any benefits associated with spironolactone must be weighed in the context of its known serious risks, specifically hyperkalemia and acute kidney injury (AKI).(19, 32, 43, 104, 114-119)

Most prior clinical trials of spironolactone focused on patient populations with relatively preserved kidney function. In both RALES and TOPCAT, patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2, serum creatinine (SCr) >2.5 mg/dL, and serum

potassium (K) >5.0 mEq/L were excluded.(41, 113) In addition, patients' SCr and K were regularly monitored during study visits, allowing for dose adjustments and discontinuation that may have mitigated the risk of hyperkalemia and AKI. The risks of spironolactone in less controlled, real-world settings are not well understood, particularly among those with reduced kidney function who are already at higher risk for hyperkalemia and AKI.

Despite current clinical guidelines recommending aldosterone antagonists use only at eGFR >30 mL/min/1.73m^2,(99, 100) patients are prescribed spironolactone across all levels of eGFR.(44) Randomized controlled trials are ongoing to better understand whether aldosterone antagonists provide cardiovascular and renal benefit in patients with advanced chronic kidney disease (CKD).(101) Given the existing use, and potential for expanded use in patients with HFpEF and lower kidney function, there are important unanswered questions regarding the real-world safety profile of spironolactone in the context of concurrent comorbidities and medications. Because previous work suggests that spironolactone is most commonly used in addition to loop diuretics, and because the latter may also modify the risks of hyperkalemia and AKI, we quantified the absolute and relative risks of hyperkalemia and AKI associated with spironolactone use among a population of patients with heart failure on loop diuretics, and evaluated for differential risk by level of kidney function.

4.3 Methods

4.3.1 Data source and population

We used integrated electronic health record (EHR) data from the Geisinger Health System (Geisinger) in Pennsylvania, United States. These EHR data include inpatient and outpatient records for patients receiving their primary care at Geisinger, as well as medication orders,

medication reconciliation and laboratory results. We included patients age 18 years or older with a heart failure diagnosis code from inpatient or outpatient records and a subsequent outpatient prescription for a loop diuretic from 2004-2016 (**Supplementary Table S1C**). We excluded patients with end-stage renal disease (ESRD), those with spironolactone use prior to the first loop diuretic order in the data, and patients without an antecedent serum creatinine or potassium.

4.3.2 Study designs and exposure definitions

To determine the incidence of hyperkalemia and AKI during real-world use of spironolactone in heart failure, we performed an as-treated analysis, with patients' time at risk (T_0) starting at the first loop diuretic prescription after their initial heart failure diagnosis. We classified time at risk according to time-varying loop diuretic and spironolactone use (single-ingredient [SI] spironolactone or combination spironolactone with hydrochlorothiazide). In the continuous use periods, we allowed for a 30-day gap between the end of one prescription and the start of the next for the same medication, and included a 15-day "washout" period at the end of a continuous use episode where outcomes could still be observed. Primary exposure groups in the time-varying, as-treated analysis were thus loop diuretic use without spironolactone (loop alone), spironolactone use without a loop diuretic (spironolactone alone), concomitant use of both a loop diuretic and spironolactone, and no use of either drug.

To strengthen evidence for a causal relationship between spironolactone and hyperkalemia and AKI, we performed a target trial emulation with an intention-to-treat (ITT) design.(120-123) This method, particularly when combined with propensity score matching, helps to minimize confounding by indication, allowing for a direct assessment of the risks associated with spironolactone in comparable patients. We utilized the ITT principle (i.e. treatment

assignment/status at baseline is carried forward regardless of subsequent changes to treatment) to analyze a series of "trials" where each "trial" represents a fixed time window when a patient may or may not begin a specific treatment regimen. To mimic a hypothetical "trial" selection process, enrollment criteria in each "trial" (cohort years: [1] 2004-2006, [2] 2007-2009, [3] 2010-2012 and [4] 2013-2016) included heart failure diagnosis, loop diuretic prescription order, no prior spironolactone order, and potassium <5.0 mEq/L. Within each "trial", patients who received an initial spironolactone prescription were compared to eligible patients who did not. Time at risk (T_0) began on the date of the first spironolactone prescription for spironolactone users (treatment), and a random loop prescription during that "trial" period for controls. Control patients were eligible to be treatment or control patients in subsequent "trials", whereas treatment patients were no longer eligible due to their previous spironolactone use. In the final analysis, the "trial" cohorts were pooled to create a combined dataset.

4.3.3 Study outcomes

In both the as-treated and ITT analyses, patients were followed until the outcomes of interest (hyperkalemia and AKI), death, last recorded health care encounter date (including inpatient, outpatient, laboratory, or medication order dates), or the end of the study period (December 31st, 2016), whichever came first. We defined hyperkalemia by inpatient International Classification of Disease, Ninth Revision (ICD-9) or ICD-10 codes 276.7 or E87.5, respectively, and AKI by inpatient ICD-9 or ICD-10 codes 584.9 or N17.9, respectively.

4.3.4 Kidney function, potassium, and other covariates

We defined eGFR based on outpatient serum creatinine (SCr) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.(88) We classified eGFR using four primary

categories (≥90 mL/min/1.73m^2; 60-89 mL/min/1.73m^2; 30-59 mL/min/1.73m^2; <30 mL/min/1.73m^2), and as linear splines with a knot at 60 mL/min/1.73m^2. We classified serum potassium (K) levels using three categories (<3.5 mEq/L; 3.5-4.9 mEq/L; >5.0 mEq/L), and as linear splines with knots at 3.5 mEq/L and 4.9 mEq/L; in the ITT analysis, only one knot was used (3.5 mEq/L). Baseline SCr and K were considered the closest measurements to T_0 within the window of 365 days before to seven days after that date. If there was no available outpatient SCr or K, we used available inpatient SCr or K within the same window.

Other medications were captured as prescriptions that overlapped T_0 and were modeled as time-fixed variables; the exception was angiotensin-converting-enzyme inhibitor (ACEi) or angiotensin II receptor blockers (ARB) use, which was modeled as a time-varying variable in the as-treated analysis. We defined comorbidities using ICD-9/10 diagnosis codes in the EHR (**Supplementary Table S1C**). We also calculated patients' Charlson Comorbidity Index (CCI) score.(90, 91)

4.3.5 Statistical analysis

We calculated frequencies, means, and proportions of the primary analytic cohorts' characteristics at T_0, including demographics, comorbidities, and prior medication use. We also stratified cohort characteristics by ever/never spironolactone initiators (in as-treated analyses), and cohort "trial" years (in ITT analyses), and we assessed for trends using logistic and linear regression for binary and continuous variables, respectively. We calculated incidence rates for hyperkalemia and AKI (per 1,000 person-months) by as-treated exposure groups, both overall and stratified by time-varying eGFR category. We also calculated and plotted cumulative

incidence of hyperkalemia and AKI over three years after T_0 in the ITT analyses, incorporating the competing event of death, and stratifying by eGFR.

We used time-to-event Fine and Gray regression models to estimate subdistributional hazards ratios (sHR) accounting for the competing risk of death.(124) We choose the Fine and Gray method because it does not assume the competing event (death) is non-informative, and censored as such. With respect to the outcomes of interest, hyperkalemia and AKI, this assumption is likely not appropriate. Comparing exposure groups in as-treated analyses, we used unadjusted and fully-adjusted models with time-fixed covariates, as well as adjusted models where eGFR, K, and ACEi/ARB use were included as time-varying covariates. In as-treated analyses, we tested for an interaction between time-varying eGFR (linear spline) and exposure group. In ITT analyses comparing treatment to control groups, we used unadjusted and fully-adjusted models, as well as adjusted models weighted by the inverse probability of treatment (IPTW), and 1:1, "nearest-neighbor" propensity score (PS) matched analyses using calipers of 0.014; after matching, all standardized mean differences were <0.10. In the ITT analyses, we also tested for an interaction between T_0 eGFR (linear spline) and treatment. We used robust variance estimators to account for within-person correlation. To assess for a heterogeneity of effect among cohort "trial" years in the ITT analyses, we tested for an interaction between "trial" and treatment status, and found no statistically significant interaction.

We adjusted final models for age, sex, race (non-white), eGFR (linear spline), K (linear spline), time with heart failure, year of first loop order, CCI, history of hyperkalemia, history of AKI, cardiovascular disease (CVD), peripheral artery disease (PAD), diabetes mellitus, cancer, cirrhosis, ascites, atrial fibrillation, proteinuria, and prior use of anticoagulants, ACEi, ARB,

other antihypertensives (combined: beta-blocker, calcium channel blockers, vasodilators), antiarrhythmics, cardiac glycosides, statins, thiazide diuretics, and potassium-sparing diuretics (excluding spironolactone). ITT analyses were additionally adjusted by time between the first loop order and T_0. We used the same covariates to calculate the propensity scores, and we calculated stabilized weights for IPTW analyses.

All analyses were conducted using Stata 15.1 (StataCorp; College Station, TX) and SAS 9.4 (SAS Institute Inc; Cary, North Carolina).

4.4 Results

4.4.1 Study population

There were 17,110 patients with heart failure who used loop diuretics during the study period; 50.5% were female (N=8,635), 2.4% were non-white (N=414), and the mean (standard deviation [SD]) age was 73.2 (13.0) years (**Table 1C**). Diabetes (46.6%; N=7,977) and CVD (66.3%; N=11,347) were common, as was the use of ACEi/ARB (80.2%; N=13,726), statins (66.2%; N=11,331), anticoagulants (59.8%; N=10,233), and other antihypertensives (89.5%; N=15,308). Roughly 19% (N=3,229) went on to initiate spironolactone over a mean follow-up of 134 months; these patients were younger and had higher mean eGFRs at baseline compared with never initiators (p=0.001 for both).

4.4.2 Real-world incidence of hyperkalemia and AKI

There were 995 hyperkalemia events (7,287 deaths) in 681,944 person-months (PMs) of observation time. Overall, incidence rates (IRs) per 1,000 PMs were highest for those on spironolactone without a loop diuretic (3.3), followed by concomitant loop and spironolactone

(2.9), loop without spironolactone (1.4), and no use of either (1.3) (**Table 2C**). In adjusted models with time-varying eGFR, K, and ACEi/ARB use, both concomitant loop and spironolactone, and spironolactone alone, were associated with a more than two-fold increase in the risk of hyperkalemia (sHR 2.06 [Confidence Interval [CI]: 1.70-2.49] and sHR 2.28 [CI: 1.40-3.69], respectively) compared to loop use without spironolactone (**Table 3C**).

There were 4,212 AKI events (5,387 deaths) in 620,094 PMs of observation time. In contrast to trends in hyperkalemia, IRs per 1,000 PMs for AKI were highest for those on concomitant loop and spironolactone (10.1), followed by loop without spironolactone (7.4), spironolactone without a loop (5.3), and no use of either (4.6). In adjusted models with time-varying covariates, concomitant loop and spironolactone was associated with a 37% increase in the risk of AKI (sHR 1.37 [CI: 1.23-1.53]) compared to loop use without spironolactone, but there was no statistically significant difference in risk with spironolactone alone without the use of a loop diuretic (sHR 0.77 [CI: 0.52-1.13]).

Although the absolute risks of hyperkalemia and AKI increased in lower eGFR categories, there were no differences in the relative risks of these adverse outcomes by eGFR (interaction with exposure groups not statistically significant; $p>0.05$).

4.4.3 Target trial emulation assessing add-on spironolactone therapy

In the pooled target trial emulation, there were 24,127 patients [treatment group (concomitant loop and spironolactone) = 2,000; control group (loop without spironolactone) = 22,127]. More than half (51.8%, N=12,499) were female, and mean (SD) age was 73.8 (12.7) years (**Supplementary Table S2C**).

There were 1,197 hyperkalemia events (163 in the treatment group) (**Table 4C**), with a one-year cumulative incidence of 1.7% and 4.0% in the control and treatment groups, respectively. Cumulative incidence of hyperkalemia at one year was lowest for patients with T_0 eGFR $\geq$60 mL/min/1.73m^2 in the control group (1.2%), followed by those with eGFR $\geq$60 mL/min/1.73m^2 in the treatment group and those with eGFR <60 mL/min/1.73m^2 in the control group (both 2.1%); those with eGFR <60 mL/min/1.73m^2 in the treatment group had the highest cumulative incidence (6.3%) (**Figure 1C**). In the fully-adjusted model (**Figure 2C**), treatment was associated with an increase in the risk of hyperkalemia compared to control (sHR 1.75 [CI: 1.46-2.09]), and this was similar when using IPTW (sHR 1.58 [CI: 1.28-1.94]) and 1:1 PS-matching (N=1,976 in each group; sHR 1.69 [CI: 1.35-2.10]).

There were 5,582 AKI events (560 in the treatment group), with a one-year cumulative incidence of 9.5% and 14.9% in the control and treatment groups, respectively. Similar to hyperkalemia, cumulative incidence of AKI at one year was lowest for patients with T_0 eGFR $\geq$60 mL/min/1.73m^2 in the control group (5.8%), followed by those with eGFR $\geq$60 mL/min/1.73m^2 in the treatment group (10.8%), and those with eGFR <60 mL/min/1.73m^2 in the control group (13.1%); those with eGFR <60 mL/min/1.73m^2 in the treatment group had the highest cumulative incidence (20.2%). In the fully-adjusted model, treatment was associated with an increased risk of AKI compared to control (sHR 1.18 [CI: 1.08-1.30]) and this was similar when using 1:1 PS-matching (N=1,976 in each group; sHR 1.12 [CI: 1.00-1.26]), and IPTW (sHR 1.21 [CI: 1.08-1.36]).

Similar to the as-treated analysis, there were no differences in the relative risks of hyperkalemia or AKI by eGFR (interaction with treatment status not statistically significant; $p>0.05$).

4.5 Discussion

In this large, real-world cohort of patients with heart failure prescribed loop diuretics, approximately one in five were prescribed spironolactone. The cohort was at high risk for hyperkalemia and AKI, with the highest rates among patients with eGFR <60 mL/min/1.73m^2, and those prescribed spironolactone. In a propensity-matched, target trial emulation, we observed a 69% increased risk of hyperkalemia with spironolactone compared to loop diuretics alone, and a 12% increased risk of AKI. The relative risks of hyperkalemia and AKI were not modified by renal function in either analyses. These findings are important because relatively little is known about the real-world safety of spironolactone, particularly among a broader heart failure population (HFrEF and HFpEF) across the spectrum of kidney function.

A more complete understanding of spironolactone-associated hyperkalemia and AKI is critical for utilization to expand to higher risk patients excluded from the clinical trials. In RALES, the pivotal study that established spironolactone's effectiveness in HFrEF, the cumulative incidence of hyperkalemia was very modest (~2% in the spironolactone group vs. ~1% in placebo among randomized patients over the study period),(41) likely due to the selection of a lower risk study population by excluding patients based on their SCr and K, and regular monitoring thereafter. Lee et al (2013)(42) found similar crude rates of both hyperkalemia and AKI when restricting their real-world systolic heart failure study cohort to align with the RALES inclusion. Similar inclusion criteria and monitoring were applied in the TOPCAT trial among patients with HFpEF; however, cumulative incidence of hyperkalemia was higher (~19% in the spironolactone group

vs. ~9% in placebo among randomized patients over the study period) than what was reported in RALES, and drug discontinuation due to "abnormal renal function" was higher for spironolactone patients versus placebo patients (3.9% vs 2.3%, respectively; p=0.006).(113) Our study results were consistent with the TOPCAT trial showing more pronounced risks with spironolactone use, and the findings from other studies, including those in various heart failure sub-populations like in older women and in those after an acute myocardial infarction, except that AKI was more common in our cohort overall.(34, 43, 125)

As expected, the absolute risk of both hyperkalemia and AKI with spironolactone use increased with lower eGFR; however, we observed no difference in *relative* risk for hyperkalemia or AKI associated with spironolactone by level of kidney function (interactions not significant in as-treated or ITT). Differences in risk by kidney function could not be explored in RALES and TOPCAT because those with higher SCr were excluded; however, other studies have observed relatively infrequent and mild spironolactone-associated increases in SCr, and K, among those with reduced kidney function.(26, 30, 38-40, 118, 126) Similar to ACEi and ARB medications, studies have demonstrated an early reduction in eGFR with spironolactone in the setting of CKD and diabetic nephropathy, but this appears to be transient, with little evidence of a persistent reduction in the context of longer-term use.(29, 42, 43, 118, 127, 128) Also, among those with heart failure potentially indicated for spironolactone, there are many other common risk factors which can all contribute to hyperkalemia risk independent of one's kidney function like older age, diabetes mellitus, volume-depleting illness, and use of ACEi, ARB, and other medications, making spironolactone's safety challenging to study in observational study settings.(31, 114-116, 129) Several clinical trials funded by both government and industry sponsors are evaluating

spironolactone's safety and efficacy in patients with CKD, including those with ESRD, evaluating cardiovascular and renal endpoints.

Despite the ongoing trials, more data are needed to better understand whether spironolactone's risks outweigh prospective benefits in patients who are currently exposed. Spironolactone is used among patients with various comorbidities, at different levels of SCr and K, and with exposure to various concomitant medications that can all make hyperkalemia or AKI more likely. In general, aldosterone antagonists are not recommended in heart failure patients with eGFR <30 mL/min/1.73m^2 by the American Heart Association (AHA),(99, 100) yet these patients have limited therapeutic options and may derive benefit from its pleiotropic pharmacologic properties; outside of its cardiovascular benefit,(26, 27, 38-40, 130, 131) some data suggest spironolactone may also slow the progression of CKD.(28, 30, 31, 33, 103, 127, 128, 130, 132, 133) Nevertheless, we observed a marked increase in the incidence of these primary safety outcomes in patients with spironolactone use at lower eGFRs, but it is also clear that routine monitoring of SCr and K is warranted at all levels of kidney function. With a better understanding of spironolactone's safety profile in heart failure, ideal candidates for spironolactone can be chosen with the risks for hyperkalemia and AKI balanced accordingly.

Our study has several notable strengths. We used a large, integrated EHR system with access to all primary care patient records across the health system, including laboratory, inpatient, and outpatient data. Patients in the Geisinger primary care system generally have little attrition, with many years of detailed records. Mortality data were also available. Our study also had some limitations. While many Geisinger patients have extended follow-up, patients are relatively homogenous with respect to race and ethnicity. We used ICD-9/10 diagnosis codes for

comorbidities and outcomes; particularly for hyperkalemia and AKI, these codes are likely to be quite specific, and select for the most severe cases.(134, 135) Because most heart failure diagnosis codes are for unspecified heart failure, we could not differentiate between reduced or preserved ejection fraction.

4.6 Conclusions

Spironolactone use was were relatively uncommon among patients on loop diuretics with heart failure. Concomitant use of spironolactone and a loop diuretic was associated with an increased risk of hyperkalemia and, to a lesser extent, AKI compared to loop diuretic use without spironolactone, with no evidence of risk modification across the spectrum of eGFR. Spironolactone has known benefits and risks in narrower patient populations, and this study offers insight into its safety profile under real-world conditions, specifically among those with heart failure and reduced kidney function where its use has historically been discouraged by clinical guidelines.

4.7 Tables

Table 1C: Study population at T_0, stratified by initiation of spironolactone

	Overall	Never initiators	Ever initiators	P for trend
N (total)	17,110	13,881 (81.1%)	3,229 (18.9%)	
Female	8,635 (50.5%)	7,189 (51.8%)	1,446 (44.8%)	0.00
Non-white	414 (2.4%)	313 (2.3%)	101 (3.1%)	0.00
Age (mean)	73.2 (13.0)	74.2 (12.6)	68.8 (13.6)	0.00
CCI (mean)	7.1 (2.8)	7.2 (2.8)	6.5 (2.8)	0.00
Baseline labs				
K (mean), mg/dL	4.3 (0.5)	4.3 (0.5)	4.3 (0.6)	0.00
SCr (mean), mEq/L	1.2 (0.6)	1.2 (0.6)	1.1 (0.5)	0.00
Kidney function				
eGFR (mean)	61.8 (23.9)	60.9 (23.8)	65.8 (23.8)	0.00
≥90 mL/min/1.73m^2	2,404 (14.1%)	1,821 (13.1%)	583 (18.1%)	0.00
60-89 mL/min/1.73m^2	6,487 (37.9%)	5,185 (37.4%)	1,302 (40.3%)	0.00
30-59 mL/min/1.73m^2	6,728 (39.3%)	5,579 (40.2%)	1,149 (35.6%)	0.00
<30 mL/min/1.73m^2	1,491 (8.7%)	1,296 (9.3%)	195 (6.0%)	0.00
Comorbidities				
Time with HF	177.3 (464.5)	184.3 (476.6)	147.0 (406.9)	0.00
CVD	11,347 (66.3%)	9,256 (66.7%)	2,091 (64.8%)	0.04
Hyperkalemia	1,123 (6.6%)	937 (6.8%)	186 (5.8%)	0.04
PAD	3,755 (21.9%)	3,086 (22.2%)	669 (20.7%)	0.06
Diabetes	7,977 (46.6%)	6,433 (46.3%)	1,544 (47.8%)	0.13
Cancer	3,178 (18.6%)	2,677 (19.3%)	501 (15.5%)	0.00
Cirrhosis	302 (1.8%)	122 (0.9%)	180 (5.6%)	0.00
Ascites	310 (1.8%)	151 (1.1%)	159 (4.9%)	0.00
AKI	3,284 (19.2%)	2,743 (19.8%)	541 (16.8%)	0.00
Atrial fibrillation	6,745 (39.4%)	5,481 (39.5%)	1,264 (39.1%)	0.72
Proteinuria	1,113 (6.5%)	915 (6.6%)	198 (6.1%)	0.34
Medications				
ACEi or ARB	13,726 (80.2%)	10,743 (77.4%)	2,983 (92.4%)	0.00
Other antihypertensive	15,308 (89.5%)	12,270 (88.4%)	3,038 (94.1%)	0.00
Anticoagulants	10,233 (59.8%)	8,126 (58.5%)	2,107 (65.3%)	0.00
Arrhythmic	3,776 (22.1%)	2,821 (20.3%)	955 (29.6%)	0.00
Cardiac glycoside	3,223 (18.8%)	2,223 (16.0%)	1,000 (31.0%)	0.00
Statin	11,331 (66.2%)	9,100 (65.6%)	2,231 (69.1%)	0.00
Thiazide diuretic	5,605 (32.8%)	4,260 (30.7%)	1,345 (41.7%)	0.00
Other k-sparing diuretic	567 (3.3%)	413 (3.0%)	154 (4.8%)	0.00

Table 1C Key: T_0 / baseline is the first loop diuretic order after initial heart failure diagnosis; Charlson Comorbidity Index (CCI); serum potassium (K); serum creatinine (SCr); estimated glomerular filtration rate (eGFR); heart failure (HF); cardiovascular disease (CVD); peripheral artery disease (PAD); acute kidney injury (AKI); angiotensin-converting-enzyme inhibitor (ACEi); angiotensin II receptor blockers (ARB); potassium-sparing (k-sparing); for mean values, parentheses designate standard deviation (SD); CVD is a composite category including cerebrovascular disease/stroke, coronary artery disease, and myocardial infarction; time with HF is the mean time between initial HF diagnosis and first loop prescription after the initial HF diagnosis; proteinuria was defined using diagnosis codes; "ever initiators" include those who ever took spironolactone, even if it did not overlap with a loop diuretic.

Table 2C: Incidence of hyperkalemia and acute kidney injury stratified by primary exposure groups and kidney function (As-treated analysis)

	eGFR category (mL/min/1.73m^2)	Hyperkalemia		Acute Kidney Injury	
		Total person-months (PM)	Incidence rate per 1,000 PMs	Total person-months (PM)	Incidence rate per 1,000 PMs
Loop alone	≥90	49,638	0.6	48,137	2.9
	60-89	153,154	0.7	146,177	4.0
	30-59	189,436	1.3	170,912	8.7
	<30	41,979	4.8	34,601	21.4
	Overall	434,207	1.4	399,826	7.4
None	≥90	26,176	0.5	24,774	2.0
	60-89	73,115	0.6	68,324	2.7
	30-59	72,634	1.2	62,737	6.2
	<30	20,214	4.7	14,384	10.9
	Overall	192,140	1.3	170,220	4.6
Spironolactone alone	≥90	1,161	1.7	1,124	3.6
	60-89	2,701	1.9	2,457	2.9
	30-59	2,743	5.1	2,371	7.2
	<30	376	5.3	243	20.6
	Overall	6,980	3.3	6,196	5.3
Loop and spironolactone	≥90	7,666	1.6	7,335	4.6
	60-89	16,420	1.6	15,289	7.7
	30-59	21,334	3.3	18,695	11.3
	<30	3,196	10.3	2,531	32.0
	Overall	48,617	2.9	43,853	10.1

Table 2C Key: estimated glomerular filtration rate (eGFR); "loop and spironolactone" represents concomitant use of a loop diuretic and spironolactone, "loop alone" represents use of a loop diuretic without spironolactone, "spironolactone alone" represents spironolactone use without a loop diuretic, and "none" is no use of either spironolactone or a loop diuretic.

Table 3C: Risk of hyperkalemia and acute kidney injury comparing primary exposure groups (As-treated analysis)

	Hyperkalemia			Acute Kidney Injury		
	Unadjusted	**Fully-adjusted (time-fixed)**	**Fully-adjusted (time-varying)**	**Unadjusted**	**Fully-adjusted (time-fixed)**	**Fully-adjusted (time-varying)**
Loop alone	ref	ref	ref	ref	ref	ref
None	0.59 (0.50-0.70)*	0.59 (0.49-0.70)*	0.61 (0.51-0.73)*	0.44 (0.40-0.48)*	0.43 (0.39-0.47)*	0.45 (0.41-0.49)*
Spironolactone alone	2.55 (1.66-3.92)*	2.83 (1.82-4.39)*	2.28 (1.40-3.69)*	0.79 (0.55-1.13)	0.81 (0.57-1.17)	0.77 (0.52-1.13)
Loop and spironolactone	2.30 (1.91-2.77)*	2.36 (1.94-2.86)*	2.06 (1.70-2.49)*	1.46 (1.32-1.62)*	1.45 (1.30-1.62)*	1.37 (1.23-1.53)*

* $p<0.05$

Table 3C Key: Data shown are subdistributional hazard ratios (sHR) with loop as the reference; models were adjusted by age, sex, race, eGFR, K, time with HF, year of first loop order, CCI, history of hyperkalemia, AKI, CVD, PAD, diabetes mellitus, cancer, cirrhosis, ascites, atrial fibrillation, proteinuria, and prior use of anticoagulants, ACEi, ARB, other antihypertensives, antiarrhythmics, cardiac glycosides, statins, thiazide diuretics, and potassium-sparing diuretics; time-varying variables in fully-adjusted models were eGFR, K, and combined ACEi or ARB use; "loop and spironolactone" represents concomitant use of a loop diuretic and spironolactone, "loop alone" represents use of a loop diuretic without spironolactone, "spironolactone alone" represents spironolactone use without a loop diuretic, and "none" is no use of either spironolactone or a loop diuretic.

Table 4C: Hyperkalemia and acute kidney injury events for treatment and control groups by cohort "trial" year (Intention-to-treat analysis)

Cohort "trial" year	Loop + S (treatment)	Loop alone (control)	Hyperkalemia		Acute Kidney Injury	
			Total events	Events in treated	Total events	Events in treated
2004-2006	166	1,938	125	18	477	45
2007-2009	376	4,500	301	39	1,274	110
2010-2012	554	6,300	371	40	1,799	163
2013-2016	904	9,389	400	66	2,032	242
Pooled	**2,000**	**22,127**	**1,197**	**163**	**5,582**	**560**

Table 4C Key: Treatment group refers to patients using loop and spironolactone concomitantly; Control group refers to patients using loop without spironolactone; Control group patients can be included in subsequent cohort "trial" years as a treatment or control, but treatment group patients are not eligible for subsequent cohort "trial" years; patients were excluded if T_0 K > 5.0 mEq/L.

Supplementary Table S1C: Coding algorithms for outcomes and comorbidities

Condition	Operationalized definitions			
	ICD-9 diagnosis	ICD-10 diagnosis	ICD-9 procedure	Medication class
Heart failure (any)	428.x 402.01 402.11 402.91 404.01 404.03 404.11 404.13 404.91 404.93 398.91	I50.x I11.0 I13.0 I13.2 I09.81	N/A	N/A
Cardiovascular disease (CEVD/Stroke, CAD, MI)	362.34 430.x-438.x, 414.0 410.x 412 414.8 414.9, 410.x 412.x	G45.x G46.x H34.0 I60.x-I69.x, I25.x I70.0 I24.x, I21.x I22.x I25.2x	36.1	N/A
Hyperkalemia	276.7	E87.5	N/A	N/A
Peripheral Artery Disease	443.9 440.2x-440.4x 707.1x 785.4	I70.2x I73.x	38.18 39.50 39.25 39.29	N/A
Diabetes	250.x 357.2 362.0x 366.41	E08.x-E11.x E13.x	N/A	Diabetes drug
Cancer	140.x-172.x 174.x-208.x 238.6	C00.x-C26.x C30.x-C34.x C37.x-C41.x C43.x C45.x-C58.x C60.x-C85.x C88.x C90.x-C97.x	N/A	N/A
Cirrhosis	571.2 571.5 571.6	K74.3 - K74.6x	N/A	N/A
Ascites	789.5x	R18.x	N/A	N/A
Acute kidney injury	584.9	N17.9	N/A	N/A
Atrial fibrillation	427.3x	I48.x	N/A	N/A
Proteinuria	791.0	R80.x	N/A	N/A

Supplementary Table S1C Key: International Classification of Diseases (ICD); cerebrovascular disease (CEVD); coronary artery disease (CAD); myocardial infarction (MI)

Supplementary Table S2C: Study population used for intention-to-treat analysis, pooled and stratified by cohort "trial" years

	Cohort "trial" years using ITT design					P for trend
	Cohort 2004-2006	Cohort 2007-2009	Cohort 2010-2012	Cohort 2013-2016	Pooled	
N (total)	2,104 (8.7%)	4,876 (20.2%)	6,854 (28.4%)	10,293 (42.7%)	24,127	
Female	1,068 (50.8%)	2,529 (51.9%)	3,531 (51.5%)	5,371 (52.2%)	12,499 (51.8%)	0.30
Non-white	34 (1.6%)	98 (2.0%)	150 (2.2%)	269 (2.6%)	551 (2.3%)	0.00
Age (mean), years	73.7 (12.3)	73.6 (12.4)	73.8 (12.5)	73.9 (13.0)	73.8 (12.7)	0.15
CCI (mean)	6.7 (2.5)	7.2 (2.7)	7.5 (2.8)	7.8 (3.0)	7.5 (2.8)	0.00
Baseline labs						
K (mean), mg/dL	4.3 (0.4)	4.2 (0.4)	4.2 (0.4)	4.2 (0.4)	4.2 (0.4)	0.00
SCr (mean), mEq/L	1.2 (0.5)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)	1.2 (0.6)	0.00
Kidney function						
eGFR (mean)	61.8 (22.9)	61.4 (23.6)	60.4 (23.8)	59.6 (23.7)	60.4 (23.6)	0.00
≥90 mL/min/1.73m^2	275 (13.1%)	646 (13.3%)	907 (13.2%)	1,277 (12.4%	3,105 (12.9%)	0.00
60-89 mL/min/1.73m^2	819 (38.9%)	1,830 (37.5%)	2,472 (36.1%)	3,635 (35.3%)	8,756 (36.3%)	0.15
30-59 mL/min/1.73m^2	839 (39.9%)	1,971 (40.4%)	2,823 (41.2%)	4,368 (42.4%)	10,001 (41.5%)	0.00
<30 mL/min/1.73m^2	171 (8.1%)	429 (8.8%)	652 (9.5%)	1,013 (9.8%)	2,265 (9.4%)	0.00
Comorbidities						
CVD	1,412 (67.1%)	3,388 (69.5%)	4,877 (71.2%)	7,236 (70.3%)	16,913 (70.1%)	0.01
Hyperkalemia	78 (3.7%)	284 (5.8%)	446 (6.5%)	869 (8.4%)	1,677 (7.0%)	0.00
PAD	410 (19.5%)	1,141 (23.4%)	1,665 (24.3%)	2,634 (25.6%)	5,850 (24.2%)	0.00
Diabetes	923 (43.9%)	2,322 (47.6%)	3,423 (49.9%)	4,996 (48.5%)	11,664 (48.3%)	0.00
Cancer	401 (19.1%)	928 (19.0%)	1,318 (19.2%)	2,078 (20.2%)	4,725 (19.6%)	0.07
Cirrhosis	27 (1.3%)	60 (1.2%)	114 (1.7%)	209 (2.0%)	410 (1.7%)	0.00
Ascites	42 (2.0%)	110 (2.3%)	148 (2.2%)	214 (2.1%)	514 (2.1%)	0.79
AKI	170 (8.1%)	694 (14.2%)	1,426 (20.8%)	2,814 (27.3%)	51,04 (21.2%)	0.00
Atrial fibrillation	762 (36.2%)	1,926 (39.5%)	2,947 (43.0%)	4,709 (45.7%)	10,344 (42.9%)	0.00
Proteinuria	109 (5.2%)	292 (6.0%)	479 (7.0%)	772 (7.5%)	1,652 (6.8%)	0.00
Medications						
ACEi or ARB	1,684 (80.0%)	3,984 (80.7%)	5,520 (80.5%)	7,517 (73.0%)	18,705 (77.6%)	0.00
Other antihypertensive	1,815 (86.3%)	4,354 (89.3%)	6,230 (90.9%)	9,150 (88.9%)	21,549 (89.3%)	0.07
Anticoagulants	1,124 (53.4%)	2,888 (59.2%)	4,244 (61.9%)	6,143 (59.7%)	14,399 (59.7%)	0.00
Arrhythmic	399 (19.0%)	1,087 (22.3%)	1,590 (23.2%)	2,083 (20.2%)	5,159 (21.4%)	0.34
Cardiac glycoside	533 (25.3%)	1,130 (23.2%)	1,405 (20.5%)	1,576 (15.3%)	4,644 (19.2%)	0.00
Statin	1,308 (62.2%)	3,286 (67.4%)	4,770 (69.6%)	6,703 (65.1%)	16,067 (66.6%)	0.95
Thiazide diuretic	777 (36.9%)	1,654 (33.9%)	2,142 (31.3%)	2,546 (24.7%)	7,119 (29.5%)	0.00
Other k-sparing diuretic	69 (3.3%)	151 (3.1%)	205 (3.0%)	227 (2.2%)	652 (2.7%)	0.00

Supplementary Table S2C Key: Index date (T_0); Charlson Comorbidity Index (CCI); serum potassium (K); serum creatinine (SCr); estimated glomerular filtration rate (eGFR); heart failure (HF); cardiovascular disease (CVD); peripheral artery disease (PAD); acute kidney injury (AKI); angiotensin-converting-enzyme inhibitor (ACEi); angiotensin II receptor blockers (ARB); potassium-sparing (k-sparing); for mean values, parentheses designate standard deviation; time with HF is the mean time between initial HF diagnosis and first loop prescription after the initial HF diagnosis; proteinuria was defined using diagnosis codes; CVD is a composite category including cerebrovascular disease/stroke, coronary artery disease, and myocardial infarction.

4.8 Figures

Figure 1C: Cumulative incidence of hyperkalemia and acute kidney injury for treatment and control groups in 3 years, stratified by kidney function (Intention-to-treat analysis)

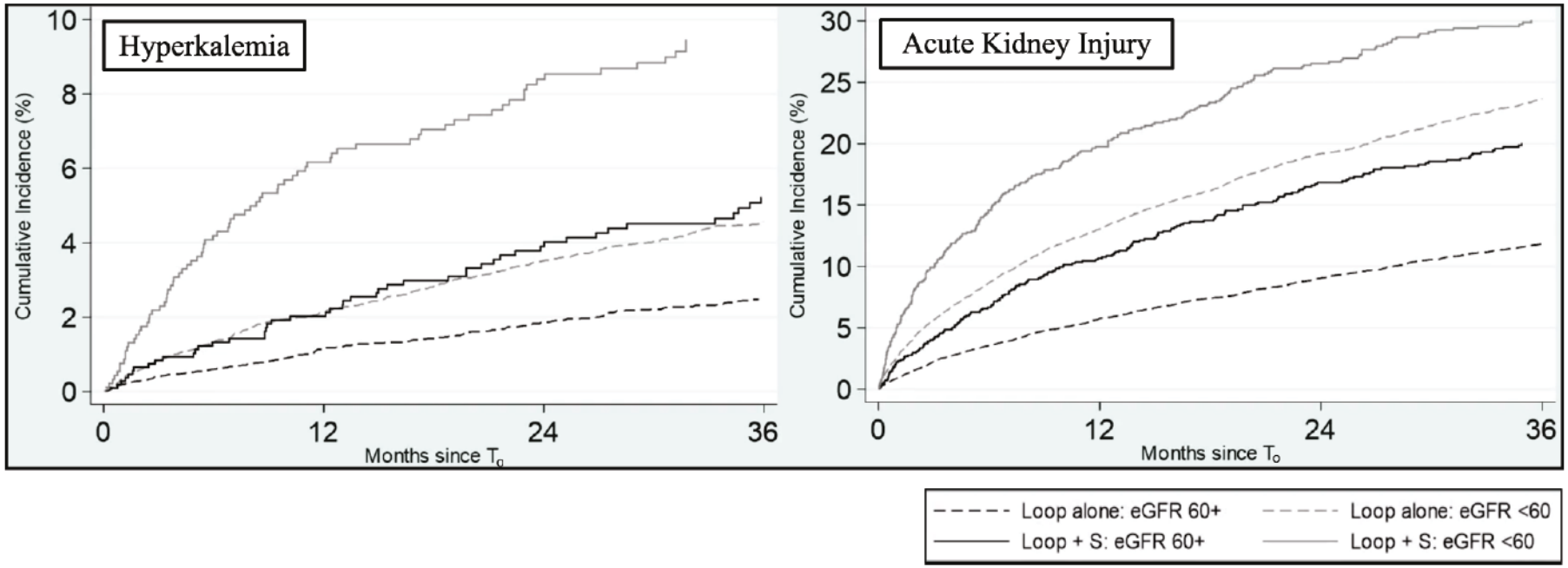
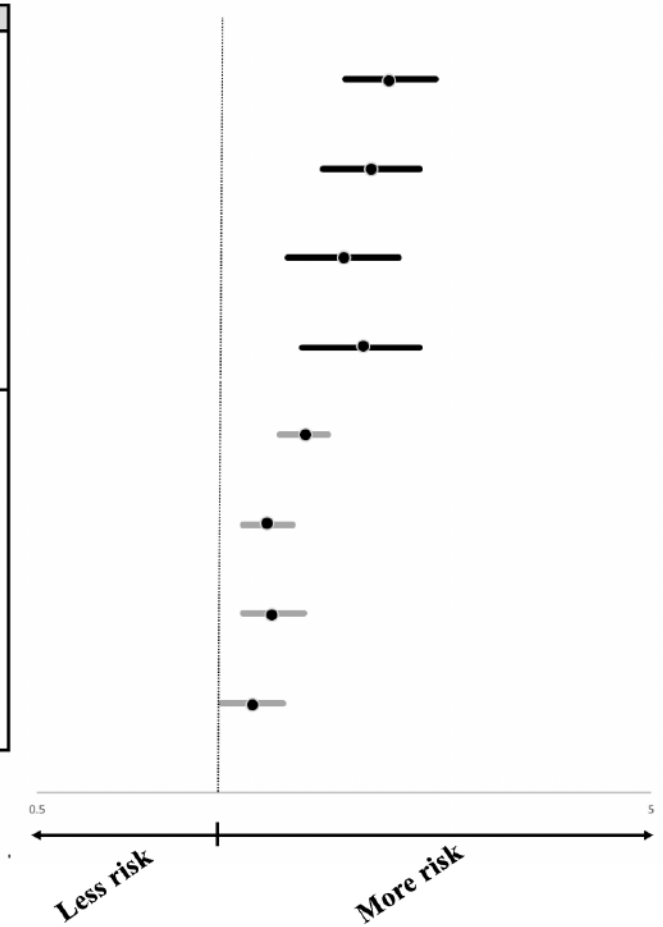


Figure 1C Key: estimated glomerular filtration rate (eGFR); Cumulative incidence estimates account for the competing risk of death; Loop alone refers to the control group; Loop and spironolactone (Loop + S) refers to the treatment group; eGFR units (mL/min/1.73m^2); T_0 for treatment group = initiation of spironolactone; T_0 for treatment group = random loop order date in relevant cohort "trial" years. For hyperkalemia, one-year cumulative incidence was 1.7% and 4.0% in control and treatment group, respectively; for AKI, one-year cumulative incidence was 9.5% and 14.9% in control and treatment group, respectively.

Figure 2C: Risk of hyperkalemia and acute kidney injury comparing treatment to control groups (Intention-to-treat analysis)

Outcome	Model	sHR (CI)
Hyperkalemia	unadjusted	1.88 (1.59-2.23)*
	fully-adjusted	1.75 (1.46-2.09)*
	IPTW	1.58 (1.28-1.94)*
	PS-matched	1.69 (1.35-2.10)*
Acute Kidney Injury	unadjusted	1.36 (1.24-1.49)*
	fully-adjusted	1.18 (1.08-1.30)*
	IPTW	1.21 (1.08-1.36)*
	PS-matched	1.12 (1.00-1.26)*



* $p<0.05$

Figure 2C Key: Inverse probability of treatment weights (IPTW); propensity score (PS); figure plotted on log scale; models were adjusted by age, sex, race, eGFR, K, time with heart failure relative to first loop prescription order, year of first loop order, time since first loop order, CCI, history of hyperkalemia, AKI, CVD, PAD, diabetes mellitus, cancer, cirrhosis, ascites, atrial fibrillation, proteinuria, and prior use of anticoagulants, ACEi, ARB, other antihypertensives, antiarrhythmics, cardiac glycosides, statins, thiazide diuretics, and potassium-sparing diuretics.

5 Conclusions

5.1 Synthesis of primary findings

In a community-based cohort of older adults, we observed prevalent polypharmacy and potentially inappropriate medication (PIM) use, with patients taking more medications and more PIMs at lower estimated glomerular filtration rates (eGFR). Greater numbers of medications were associated with greater risks for hospitalization and death, but PIM use was not. These findings suggest the benefits from routine medication management in older adults including better coordination of care between providers, and increased monitoring of kidney function. An improved accounting of patients' medications may mitigate the risk of adverse drug events in acutely susceptible patients, specifically reducing unnecessary or redundant medications, but without improved pre-market data on medication safety in patients with chronic kidney disease (CKD), prescribing guidelines will continue to be challenged by a lack of empirically-based eGFR thresholds for safe use.

With respect to guidelines on PIM use based on kidney function, there were some noted discrepancies between guidelines on thresholds where specific medications were not recommended. The lack of consistency observed between medication guidelines is likely a function of the limited information on safety in higher risk patients like older adults and those with CKD. This can create subjective prescribing guidelines that are reliant on consensus opinion or qualitative guidance, or use kidney function thresholds for safe use based on limited studies, and using antiquated metrics or data. For example, potassium-sparing diuretics such as amiloride, triamterene, and spironolactone, and anticoagulants such as fondaparinux and dabigatran, appear to be particularly discrepant across the references used in our study.

Interestingly, we did not find an association between PIM use and morbidity and mortality in our study, which may have been due to our prevalent user design (i.e. creating a cohort affected by a "depletion of susceptibles"), and/or our narrow definition of PIM use that did not include medication dose. Nevertheless, the overall lack of information on medication safety in those with CKD, and ostensible ambiguity across clinical guidelines, may be contributing to deleterious consequences with serious effects on patient outcomes. In patients with CKD who already have with limited therapeutic options, the benefits of a medication may outweigh the risks, but providers may get equivocal or confusing information simply from consulting with different published guidelines.(9, 13, 14, 77) Therefore, better understanding the safety of medications across the spectrum of kidney function, and establishing empirically-based kidney function thresholds when risk is outsized relative to any potential benefits should be a public health priority given the prevalence of kidney disease worldwide. Incentivizing industry to conduct these studies in new drug applications submitted for approval moving forward may require increased regulatory authority whereby marketing is contingent on establishing a safety profile in patient populations like those with CKD, where safety can not be inferred and adverse drug events are common.

We used spironolactone as a case-study of a medication with known risks, but conflicting guidelines on its safety across kidney function. Because it was approved in a time when approval was based on limited or no renal pharmacokinetic (PK) information, particularly if drug manufacturers were not seeking a specific label claim, there is uncertainty surrounding its safety profile among those with CKD. Spironolactone has utility in refractory hypertension and severe heart failure, common comorbidities of patients with CKD, yet little is known about what level of kidney function use is safe, and whether any cardiovascular benefits, or even potential renal

benefits, may offset its most serious risks of hyperkalemia and acute kidney injury (AKI). Currently, the American Heart Association (AHA) guidelines (99, 100) recommend no use of aldosterone antagonists in patients with heart failure (reduced or preserved ejection fraction) with eGFR <30 mL/min/1.73m^2, but it is unclear how these guidelines affect clinical practice and which patients are ultimately prescribed spironolactone given its established effectiveness. In order to assess its real-world safety across the spectrum of kidney function, we first needed to understand the incidence and predictors of use in real-world clinical practice; observed differences in who is ultimately exposed must be taken into account when assessing its real-world safety.

In two separate cohorts of patients with heart failure, less than 10% of patients initiated spironolactone within two years of their incident heart failure diagnosis, and patients with eGFR <30 mL/min/1.73m^2 were the least likely to initiate spironolactone compared to other levels of kidney function; these patients also had the shortest duration of use. In addition, those with loop diuretic use and lower serum potassium were more likely to use the spironolactone. Our findings suggest that patients' kidney function influences whether they are prescribed spironolactone, and may partly reflect providers' knowledge of the current guidelines in heart failure; however, decisions on which medications are prescribed in patients are often more complex and multifaceted, and generally based on a multitude of factors including, but not limited to, disease severity and comorbidities. Importantly, even though utilization was lowest at lower eGFRs, these patients were still prescribed the medication in the context of other comorbidities and with concomitant medications that may have increased their risk of hyperkalemia and AKI. With real-world safety data on spironolactone lacking, its necessary that providers have a more

complete understanding of these risks as to appropriately balance them with any benefits, particularly among those where use is not necessarily recommended.

Using integrated electronic health record (EHR) data from primary care patients with heart failure in a Pennsylvania health system, we observed increases in the risk of hyperkalemia, and more modestly AKI, with the use of spironolactone and a loop diuretic compared to the use of a loop diuretic without spironolactone. While the absolute risks were highest among spironolactone users with lower eGFRs, as expected, the relative risks of hyperkalemia and AKI were not modified by renal function. This latter point was a particularly interesting finding given an expected differential risk in lower eGFRs due to the compounding interactions with concurrent heart failure and with the use of a potassium-sparing diuretic drug; however, residual confounding by indication may have biased the interaction effect towards the null. Given the ongoing clinical trials investigating spironolactone's efficacy with respect to cardiovascular and renal endpoints in advanced CKD and diabetic nephropathy, and the potential for expanded use to all heart patients (reduced or preserved ejection fraction), quantifying the real-world risks of hyperkalemia and AKI can better equip providers currently treating patients, specifically patients with limited therapeutic options. As an inexpensive generic medication with known utility in heart failure, spironolactone's risks may be tolerable in some patients despite concurrent comorbidities like CKD.

5.2 Regulatory implications

Our work exposed a fundamental flaw in the drug approval and regulatory process with respect to data on safety in higher risk patients like those with CKD. When a new drug application (NDA) is submitted for approval, the drug has gone through rigorous testing in pre-clinical and

clinical studies, but the medicine often has not been thoroughly tested in those with compromised renal function, and that lack of information brings about ambiguity in how to use the medicine in these patients. In general, patients with reduced kidney function are excluded from clinical trials during drug development because their kidney function impacts the PK of a drug putting them increased risk for adverse events. Without empirical evidence from pre-market testing, limited post-market studies, including observational studies, sometimes fill that void, and recommendations become based on these limited data. This has consequences on patient outcomes in that some patients are channeled into potentially less effective medications based on their kidney function unnecessarily, while others may be prescribed a medication that is potentially less safe than an alternative.

Regulations around studying drugs in those with CKD are inadequate in that presently there is no requirement that they be represented in pre-market clinical trials.(10, 11, 16, 18) Although there have been improvements in the proportion of NDAs summited with renal PK studies since the U.S. Food and Drug Administration (FDA) first issued a "Guidance for Industry" on the topic,(16) many still lack such data, particularly in medicines approved many years ago, like spironolactone. The most effective method of collecting safety data in patients with CKD is to require their inclusion in studies during drug development; this method was utilized in 1993 to ensure women were included in cardiovascular drug trials. One way to more expeditiously instate this fundamental change in regulation is to allow Sponsors to conduct safety and efficacy trials for those with CKD separate from the pivotal trials used as the basis for approval. To incentivize Sponsors even further, patent exclusivity could be granted for marketing in patients with CKD if safety and efficacy could ultimately be established in those studies. However, in the interim, FDA should continue to encourage Sponsors of NDAs to conduct safety studies in

patients with reduced kidney function, and perhaps moving forward consider basing approval of a medicine on the NDA having adequate renal PK data, especially in all drugs that are renally-cleared. Another way FDA could assert their authority and mandate these data are collected are through required studies after the medicine is approved for marketing; however, FDA's regulatory authority is limited with respect to the designing, implementing, and enforcing post-market study.(136) Also, this assumes that there is some basis for inferring the drug's safety in CKD based on other similar drugs or active pharmaceutical ingredients.

One method that has become increasingly more common in drug development is population PK (popPK) analysis, specifically when there are limited data on sub-groups that may be ultimately exposed to the drug.(137, 138) This method utilizes flexible mathematical models to predict PK (and pharmacodynamic [PD]) parameters of a drug using data from patients across several different clinical trial samples, perhaps taking different doses or on different time schedules. These "opportunistic" samples are derived from abstracting patient-level serum drug concentration data and other information, including demographics and comorbidities, from select patients in clinical trials, and pooling data for greater statistical power to estimate dose-concentration relationships, and for the ability to assess sources of variability in drug concentration in patient sub-groups of interest. The data usually come from clinical trials with unbalanced designs, from sub-studies that are not typically used in PK analyses, and from less rich data obtained in later phase trials.(139) This is a cost-effective, post-hoc method to better understand the PK (or PK/PD), and other safety data, in sub-populations of patients where only limited data exist, and can help to establish safe dosing thresholds when studies were not powered adequately to define them. The FDA has issued two "Guidance's" on popPK (1999 and 2019),(139, 140) and encourages its use in the drug development process, where appropriate.

Nevertheless, despite a real need for better safety and efficacy data for drugs used in the setting of CKD, and available regulatory and/or analytical methods to acquire such data, the problem persists. In 2019,(17) the American Society of Nephrology, the International Society of Nephology, and the European Renal Association issued a joint statement pleading for drug manufacturers to enroll patients with CKD in clinical trials during drug development, and for regulators to intervene on this issue if necessary. Newer drugs for the treatment of type II diabetes that can potentially benefit patients with CKD by mitigating further decline in renal function like Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors and Dipeptidyl peptidase 4 (DPP-4) inhibitors were never tested in patients with eGFR <30 mL/min/1.73m^2. This is also true of the vast majority coronary heart disease drugs.(10) Related to spironolactone, while ongoing clinical trials assessing both its cardioprotective and renoprotective properties in patients with CKD will presumably provide more quality data on its safety profile in the setting of reduced kidney function, the current labeling should reflect the lack of data on its safety in this population, particularly in regards to establishing an eGFR threshold for safe use. Until randomized controlled trial data can fill that ostensible void, observational study data, like the data generated from our studies, are critical for quantifying risk across the spectrum of kidney function.

5.3 Summary of public health significance

- Polypharmacy is a common yet modifiable risk factor for morbidity and mortality in older adults; measures should be taken to better coordinate prescribing between providers to reduce unnecessary or inappropriate medications.

- PIM use based on kidney function is prevalent in older adults, and may be a function of medication labels and clinical guidelines lacking critical information on how and when to use medicines in patients with CKD; regulatory agencies and drug manufacturers must make collecting pre-market renal PK/PD data a priority in drug development.
- Spironolactone is an aldosterone antagonist with proven utility in heart failure, yet data on its safety across the spectrum of kidney function is limited as patients at the highest risk of hyperkalemia and AKI, namely those with existing CKD, were excluded from clinical trials.
- Spironolactone initiation among patients with heart failure is relatively rare given the drug's rather convincing cardioprotective effects and its hypothesized benefit in mitigating CKD progression; those with the lowest kidney function were least likely to initiate the drug, and had the shortest duration of use, compared to those with higher eGFRs.
- Spironolactone initiation among loop diuretic users with heart failure was associated with an increase in the risk of hyperkalemia, and more modestly AKI, but these risks were not modified by eGFR; however, those with lower eGFRs had higher absolute risks of both common adverse effects.
- Providers must balance spironolactone's risks with its known benefits, and consider whether it is appropriate given a patient's comorbidities; quantifying these risks in real-world settings will better inform current clinical practice guidelines on spironolactone use in heart failure treatment.
- Current labeling for spironolactone products should more explicitly acknowledge the lack of empirical evidence for an eGFR threshold that determines safe use, while at the same

time cautioning patients and providers on its risks, particularly among those with CKD who are already at an increased risk of hyperkalemia and AKI.

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Vita

Education

Johns Hopkins University, Bloomberg School of Public Health
Doctoral Candidate (Doctor of Philosophy) – Epidemiology; 2015–present

- Other secondary areas of graduate training: biostatistics, clinical pharmacology
- Dissertation: "Assessing potentially inappropriate medication use in patients at risk for adverse drug effects: spironolactone as a case study"

Johns Hopkins University, Bloomberg School of Public Health
Master in Public Health – Epidemiology/Biostatistics; 2012

New York University, College of Arts & Science
Bachelor of Arts – Psychology; 2004

Experience

U.S. Food and Drug Administration (FDA), Center for Drug Evaluation Research (CDER), Office of Pharmacovigilance and Epidemiology (OPE), Division of Epidemiology (DEPI), Silver Spring, MD; 2012 – present

Epidemiologist (2013–present)

Oak Ridge Institute for Science and Education (ORISE) FDA fellow
(2012–2013)

Center on the Continuum of Care in the Addictions, University of Pennsylvania School of Medicine, Philadelphia, PA; 2010–2011

Project manager / research team lead

Substance Treatment and Research Service (STARS), New York State Psychiatric Institute (NYSPI), Columbia University Department of Psychiatry, Columbia-Presbyterian Medical

Center, New York, NY; 2006 –2010

Project manager / site supervisor

National Center on Addiction and Substance Abuse (CASA) at Columbia University, New York, NY; 2004–2006

Research assistant / study coordinator

New York University, School of Social Work, New York, NY; 2003–2004; 2006

Research assistant / interviewer

Publications / Presentations

Publications

Qiao Y, Shin JI, Sang Y, Inker LA, **Secora A,** Luo S, Coresh J, Alexander GC, Jackson JW, Chang AR, Grams ME (2019)
Discontinuation of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in chronic kidney disease
Mayo Clinic Proceedings; in press (2019)

Zonozi R, Wu A, Shin JI, **Secora A,** Coresh, K, Inker, LA, Chang AR, Grams ME (2019)
Elevated vancomycin trough levels in a tertiary health system: frequency, risk factors, and prognosis
Mayo Clinic Proceedings; 94 (1): 17-26. PMID: 30611444

Staffa J, Meyer T, **Secora A,** McAninch J (2019)
Commentary on: "Methodologic limitations of prescription opioid safety research and recommendations for improving the evidence base"
Pharmacoepidemiology and Drug Safety; 28 (1): 13-15. PMID: 30221420

Secora A, Alexander GC, Ballew SH, Corseh, J, Grams ME (2018)
Kidney function, polypharmacy, and potentially inappropriate medication use in a community-based cohort of older adults
Drugs and Aging; 35 (8): 735-750. PMID: 3003934, PMCID: 6093216.

Shin JI, **Secora A**, Alexander GC, Inker LA, Coresh J, Chang, AR, Grams ME (2018)

Risks and benefits of direct oral anticoagulants across the spectrum of GFR among incident and prevalent patients with atrial fibrillation
Clinical Journal of the American Society of Nephrology; 13 (8): 1144-1152. PMID: 30002224

Lazarus B, Wu A, Shin JI, Sang Y, Alexander GC, **Secora A**, Inker LA, Coresh J, Chang, AR, Grams ME (2018)
Association of metformin use with risk of lactic acidosis across the range of kidney function: a community-based cohort study
JAMA Internal Medicine; 178 (7): 903-910. PMID:29868840

Coyle DT, Chen C-Y, Ocran-Appiah J, **Secora A**, Kornegary C, Staffa J (2017)
Opioid analgesic dose and the risk of misuse, overdose, and death: a narrative review
Pharmacoepidemiology and Drug Safety; 27 (5): 463-472. PMID: 29243305

By K, McAninch J, Keeton S, **Secora A**, Kornegay C, Hwang C, Ly T, Levenson M (2017)
Important statistical considerations in the evaluation of post-market studies to assess whether opioids with abuse-deterrent properties result in reduced abuse in the community
Pharmacoepidemiology and Drug Safety; 27 (5): 473-478, PMID: 28833803

Secora AM, Trinidad JP, Zhang R, Gil R, Dal Pan G (2017)
Drug availability adjustments in population-based studies of prescription opioid abuse
Pharmacoepidemiology and Drug Safety; 26 (2): 180-19, PMID: 28000295

Secora AM, Dormitzer CM, Staffa JA, Dal Pan GJ (2014)
Measures to quantify the abuse of prescription opioids: a review of data sources and metrics
Pharmacoepidemiology and Drug Safety; 23 (12): 1227-1237, PMID: 25257660

Secora AM, Eddie D, Wyman BJ, Brooks DJ, Mariani JJ, Levin FR (2010)
A comparison of psychosocial and cognitive functioning between depressed and non-depressed patients with cannabis dependence
Journal of Addictive Diseases; 29 (3), 325-337, PMID: 20635282, PMCID: PMC3065775
Levin FR, Mariani JJ, **Secora A**, Brooks D, Cheng WY, Bisaga A, Nunes E, Aharonovich E, Raby W, Hennessy G (2009)

Atomoxetine treatment for cocaine abuse and adult attention-deficit/hyperactivity disorder (ADHD): a preliminary open trial
Journal of Dual Diagnosis; 5(1), 41-56, PMID: 19430599 PMCID: PMC2679511

Book chapters

Pharmacoepidemiology, Sixth Edition (2020); editors: Strom, Kimmel, Hennessy; publisher: John Wiley & Sons Ltd.
McAninch J, **Secora A**, Staffa J, Kornegay C
Chapter 28: "Pharmacoepidemiologic research on drugs of abuse"

Poster Presentations

International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE); Philadelphia, PA; 2019: "*Hyperkalemia and acute kidney injury risk with spironolactone use among patients with heart failure*"

American Heart Association's Epidemiology, Prevention, Lifestyle, and Cardiometabolic Health Scientific Sessions (AHA-Epi); Houston, Texas; 2019:

1) "*Real-World Spironolactone Use Among Patients with Heart Failure*"

2) "*Discontinuation of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers in Chronic Kidney Disease*"

International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE); Prague, Czech Republic; 2018: "*Opioid Analgesic Utilization, Poisonings, and Deaths: The Impact of Hydrocodone Rescheduling*"

International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conference; Baltimore, MD; 2018: "*Kidney function, Polypharmacy, and Potentially Inappropriate Medication Use in a Community-Based Cohort of Older Adults*"

American Heart Association's Epidemiology, Prevention, Lifestyle, and Cardiometabolic Health Scientific Sessions (AHA-Epi); Portland, OR; 2017: "*Use of Novel Oral Anticoagulants Among Patients with Atrial Fibrillation Increased Even in Those with Severely Impaired Kidney Function*"

American Society of Nephology annual meeting and scientific exposition (ASN); New Orleans, LA; 2017:

1) "*Risks and Benefits of Direct Oral Anticoagulants Across the Spectrum of Glomerular Filtration rate among Patients with Atrial Fibrillation*"

2) "*Risk factors for the occurrence of supratherapeutic vancomycin levels*"

International Conference on Pharmacoepidemiology & Therapeutic Risk Management (ICPE); Montreal, Canada; 2017: "Kidney function, *Polypharmacy, and Potentially Inappropriate Medication Use in a Community-Based Cohort of Older Adults*"

American College of Epidemiology (ACE) Annual Meeting; Silver Spring, MD; 2014: "*Drug Availability Adjustments in Population-Based Studies of Prescription Opioid Abuse*"

College on Problems of Drug Dependence (CPDD) conference; San Diego, CA; 2013: "*Numerators and denominators to quantify the abuse of prescription opioids: A review of data sources and metrics*"

College on Problems of Drug Dependence (CPDD) conference; Quebec City, Canada; 2007:

1) "*Contingency Management for Attendance in a Pharmacotherapy Clinical Trial for Cannabis Dependence*"

2) "*A Comparison of Psychosocial Functioning and Cognitive Functioning Between Depressed and Non-Depressed Patients with Cannabis Dependence*"

Oral Presentations

Drug Safety Oversight Board (DSOB) meeting, FDA, CDER; Silver Spring, MD; 2018: "Gabapentinoid use, abuse, and associated mortality"

Spotlight session presentation at ICPE 2017 conference; Montreal, Canada; 2017: "Kidney function, polypharmacy, and potentially inappropriate medication use in a community-based cohort of older adults"

Symposium by Johns Hopkins Center of Excellence in Regulatory Science and Innovation (CERSI) and FDA Center for Drug Evaluation and Research (CDER); Silver Spring, MD; 2016: "Substitutability of Generic Drugs: Perceptions and Reality"

Grand Rounds, FDA, CDER; Silver Spring, MD; 2013: "Abuse-

deterrent formulations for opioid drug products: epidemiology, science, and case studies"

Columbia University, College of Physicians and Surgeons; New York City, NY; 2008 & 2009: "Substance abuse treatment & Alcoholics Anonymous in New York City: Engagement and Effectiveness"

Fellowships / Scholarships

Center for Drug Safety and Effectiveness (CDSE) scholar;
Johns Hopkins University; 2015–2019

The National Institutes of Health (NIH) Cardiovascular Disease Epidemiology T32 Training Program; National Research Service Award;
Johns Hopkins University; 2015–2019

Oak Ridge Institute for Science and Education (ORISE) Fellowship at Food and Drug Administration (FDA)
Oak Ridge Associated Universities (ORAU) & FDA; 2012–2013

Trainings / Certificates

Pharmacoepidemiology and drug safety certificate;
Johns Hopkins University; 2017

Phoenix® WinNonlin software training: pharmacokinetic/ pharmacodynamic and toxicokinetic modeling;
Johns Hopkins University, graduate pharmacology (course); 2016

Pharmacoepidemiology research and training certificate;
University of Pennsylvania Center for Clinical Epidemiology and Biostatistics (FDA program); 2013–2014

Sentinel distributed database querying tools and modular programs training; FDA, CDER; 2013

Clinical Practice Research Datalink (CPRD) GOLD training; FDA, CDER; 2013

SAS statistical software training, SAS Institute; FDA, CDER; 2012

Quintles IMS Health (now IQVIA) integrated database training;

FDA, CDER; 2012

Memberships / Societies

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 2018–present
- International Society of Pharmacoepidemiology (ISPE), 2016–present