IgA Nephropathy and Risks of Kidney and Cardiovascular Events and Death: The KNIGHT Study

Thida C. Tan, MPH,[1] Rishi V. Parikh, MPH,[1] Ajit Mahapatra, MD,[2] Robert Perkins, MD,[3] Alan S. Go, MD,[1,4,5,6]

[1] Division of Research, Kaiser Permanente Northern California, Oakland, CA
[2] Department of Nephrology, Kaiser Permanente Santa Clara Medical Center
[3] Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA
[4] Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA
[5] Departments of Epidemiology, Biostatistics and Medicine, University of California, San Francisco, San Francisco, CA
[6] Department of Medicine (Nephrology), Stanford University School of Medicine, Palo Alto, CA

Introduction. IgA nephropathy (IgAN) leads to inflammation and kidney fibrosis, is the most common type of glomerulonephritis globally, and contributes significantly to the global burden of chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Yet, few population-based data exist from the U.S. about adults with IgAN and the subsequent risks of kidney, cardiovascular, and mortality outcomes compared with those who have non-IgAN CKD or with those who do not have CKD. IgA nephropathy (IgAN) leads to inflammation and kidney fibrosis, is the most common type of glomerulonephritis globally, and contributes significantly to the global burden of chronic kidney disease (CKD) and end-stage kidney disease (ESKD). Yet, few population-based data exist from the U.S. about adults with IgAN and the subsequent risks of kidney, cardiovascular, and mortality outcomes compared with those who have non-IgAN CKD or with those who do not have CKD.

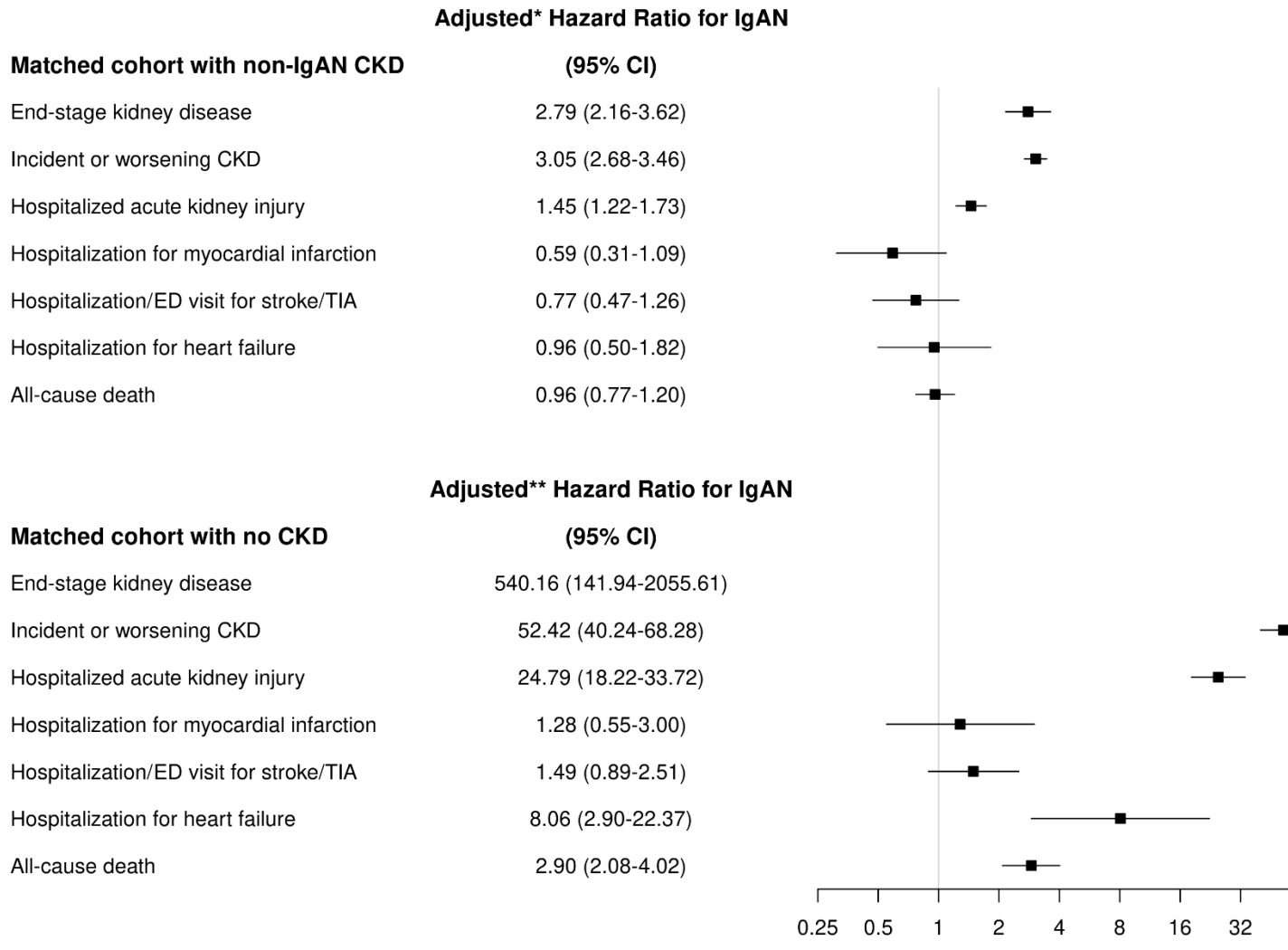
Methods. We conducted a retrospective study within Kaiser Permanente Northern California, a large integrated healthcare delivery system based in California that currently provides comprehensive medical care for >4.5 million members. To enhance ascertainment of IgAN, we used validated natural language processing algorithms applied to electronic health record data to identify adults with biopsy-proven IgAN between 2010-2020. We next identified separate age-and-sex-matched cohorts of adults with non-IgAN CKD (eGFR <60 ml/min/1.73m2 and no evidence of IgAN or other glomerulonephritis) and adults without CKD (eGFR ≥60 ml/min/1.73m2 and no proteinuria or diagnosed kidney disease) up to a 10:1 ratio to IgAN patients. We then compared subsequent rates of ESKD (i.e., receipt of kidney replacement therapy), worsening CKD (50% reduction in eGFR from baseline, reaching an eGFR <15 mL/min/1.73m2, or ESKD), hospitalized acute kidney injury, cardiovascular outcomes (acute myocardial infarction, heart failure, stroke/transient ischemic attack), and death through December 2021 using Cox proportional hazards models adjusted for potential confounders (e.g., demographics, clinical characteristics, laboratory results).

Results. Among 1651 adults with biopsy-confirmed IgAN, we separately matched 1267 IgAN patients with 9863 adults who had non-IgAN CKD and 1651 IgAN patients with 16,510 adults who did not have CKD. Compared with matched adults who had non-IgAN CKD, those with IgAN had higher adjusted rates of ESKD (adjusted hazard ratio [aHR]: 2.79, 95% CI: 2.16-3.62), worsening CKD (aHR: 3.05, 95% CI: 2.68-3.46), and hospitalized acute kidney injury (aHR: 1.45, 95% CI: 1.22-1.73) but no significant adjusted differences in cardiovascular events and death after accounting for potential confounders (**Figure**). Compared with matched adults who did not have CKD, those with IgAN had substantially higher adjusted rates of adverse kidney

outcomes as well as higher adjusted rates of hospitalization for heart failure (aHR: 8.06, 95% CI: 2.90-22.37) and death (aHR: 2.90, 95% CI: 2.08-4.02) but not significantly different adjusted rates of acute myocardial infarction or stroke/transient ischemic attack (**Figure**).

Conclusions. Within a large, diverse community-based population in the U.S., adults with IgAN experienced higher adjusted rates of adverse kidney outcomes compared with non-IgAN CKD, as well as higher rates of heart failure and death compared with adults with no CKD.

Figure. Adjusted hazard ratios for IgAN and clinical outcomes in matched cohorts of adults with non-IgAN CKD and adults with no CKD.



Abbreviations: IgAN, IgA nephropathy; CKD, chronic kidney disease; CI, confidence interval; ED, emergency department; TIA, transient ischemic attack.

*Adjusted for: age, self-reported race, tobacco use, prior myocardial infarction, prior stroke or transient ischemic attack, prior coronary revascularization, heart failure, diabetes mellitus, hypertension, dyslipidemia, chronic lung disease, depression, estimated glomerular filtration rate, proteinuria (estimated

urine albumin-to-creatinine ratio). Missing values for estimated glomerular filtration rate and estimated proteinuria imputed using multiple imputation across 50 datasets.

**Adjusted for: age, self-reported race, tobacco use, prior atrial fibrillation or flutter, heart failure, diabetes mellitus, hypertension, dyslipidemia, chronic liver disease.