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Real-world challenges associated with the use of systemic glucocorticoids in a US IgAN cohort

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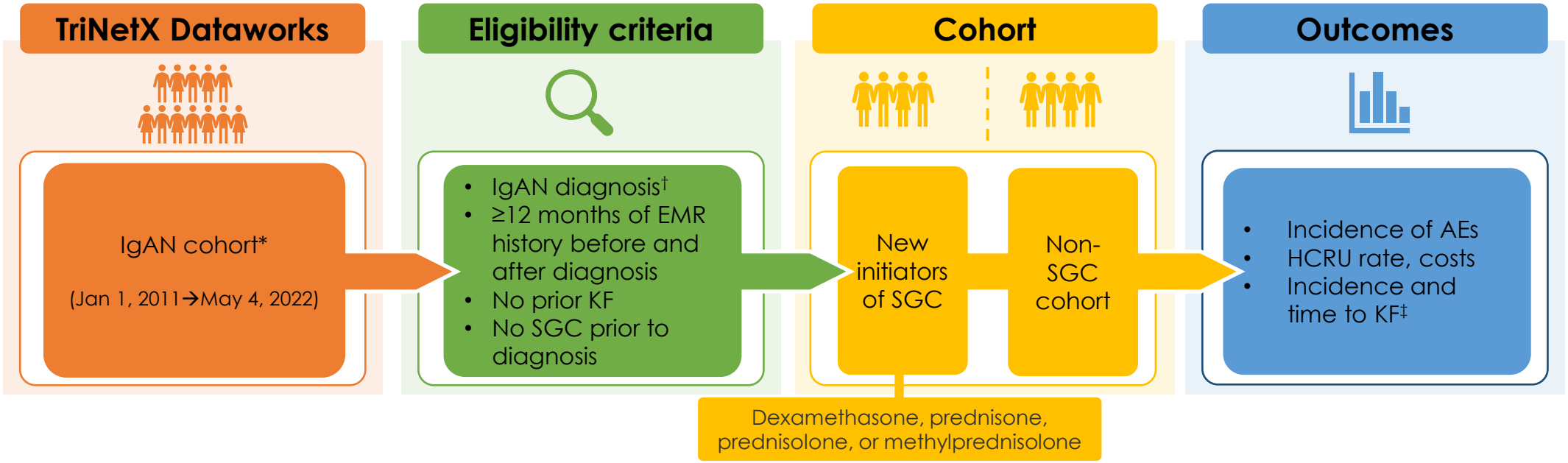
Introduction

- IgAN is the most common primary glomerular disease,[1] with most patients reported to progress to kidney failure within 10 to 15 years of diagnosis[2]
- The KDIGO 2021 guidelines recommend[1]:
  - optimized supportive care (including RAS inhibition) as the first management strategy for IgAN
  - to consider a 6-month SGC treatment regimen if risk of progressive CKD remains high despite optimized supportive care*
- There is limited real-world evidence describing the use of SGC and their impact on safety, HCRU, and kidney failure in patients with IgAN
- We present the incidence of AEs, HCRU rates and costs, and rates of kidney failure in a real-world cohort of patients with IgAN, comparing new initiators of SGC with patients who have never initiated SGC

*The important risk of treatment-emergent toxicity must be discussed with patients, particularly those who have an eGFR <50 mL/min per 1.73 m^2.
AE, adverse event; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HCRU, healthcare resource utilization; IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; RAS, renin–angiotensin system; SGC, systemic glucocorticoids.
1. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. *Kidney Int.* 2021;100(4S):S1-S276. 2. Pitcher D, et al. *Clin J Am Soc Nephrol*. 2023;18(6):727-738.

Method: Non-interventional, retrospective, real-world study using a US IgAN cohort



Analyses

Propensity score matching of patients in both cohorts was based on characteristics at diagnosis

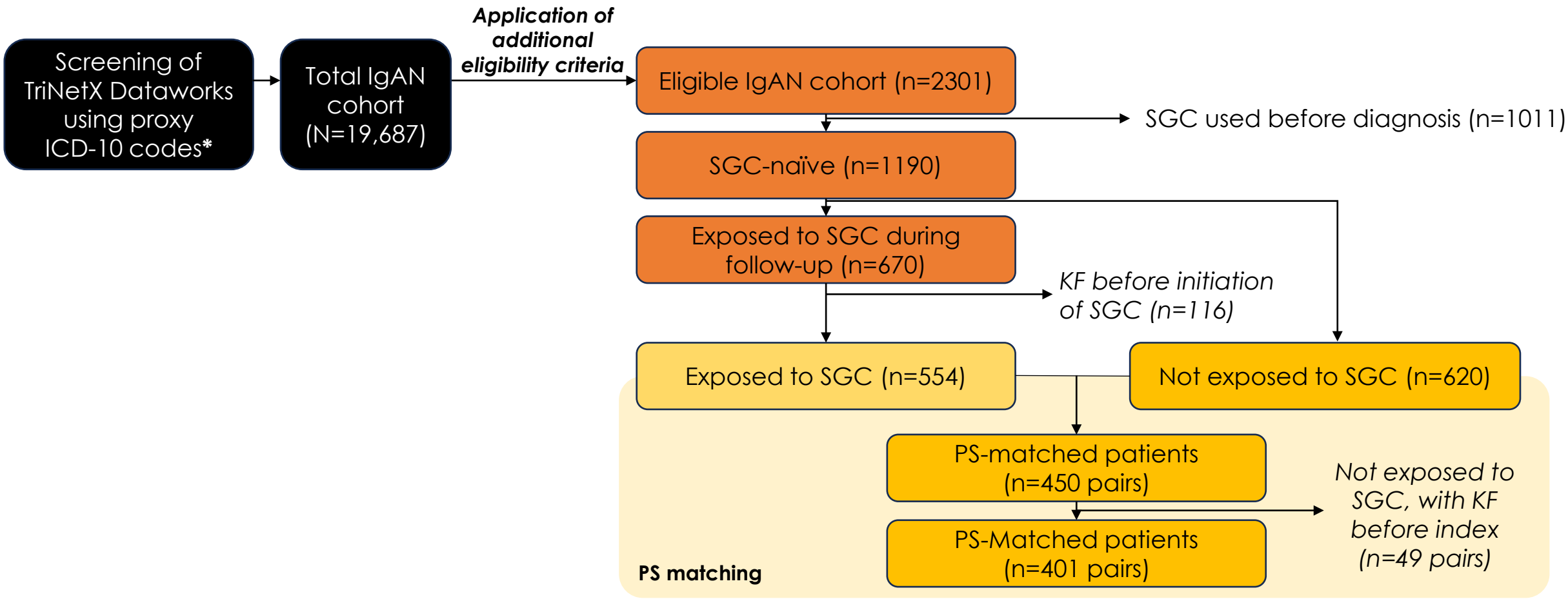
Time of SGC initiation defined the **index date** (non-SGC recipients were given a **pseudo-index date** corresponding to the lag from diagnosis of their matched SGC cohort counterpart)

Statistical analyses

- AEs: Chi-square test or Fisher's exact test
- HCRU rate and costs: Kruskal-Wallis test
- Time to KF: Kaplan-Meier approach and Fine and Gray models
- Risk of KF: Cox proportional hazard models with adjustment for unbalanced variables at index/pseudo-index date

*Identified using proxy ICD-10 codes: N02.8 (recurrent and persistent hematuria with other morphologic changes) or N04.1 (nephrotic syndrome).
†Within 30-180 days of previous diagnosis. ‡Diagnosis of end-stage CKD via ICD-10 code, occurrence of transplant procedures, or eGFR measurements <15 mL/min/1.73 m^2
AE, adverse event; EMR, electronic medical records; HCRU, healthcare resource utilization; ICD, International Classification of Diseases; IgAN, immunoglobulin A nephropathy; KF, kidney failure; SGC, systemic glucocorticoids; US, United States.

Results: Selection of PS-matched cohorts



Median duration of follow-up: *3.5 (SGC cohort) and 3.1 (non-SGC cohort) years*

*N02.8 (recurrent and persistent hematuria with other morphologic changes) or N04.1 (nephrotic syndrome).
ICD, International Classification of Diseases; IgAN, immunoglobulin A nephropathy; KF, kidney failure; PS, propensity score; SGC, systemic glucocorticoids.

Results: Characteristics at index

Baseline characteristics	SGC (n=401)	Non-SGC (n=401)	*p*-value
Age, mean (SD)	41.9 (18.5)	40.8 (17.8)	0.37
Sex (females), n (%)	181 (45.1)	182 (45.4)	0.94
CKD stage, n (%)			0.35
1-2	123 (30.7)	132 (32.9)	
3	93 (23.2)	96 (23.9)	
4	41 (10.2)	27 (6.7)	
Missing	144 (35.9)	146 (36.4)	
CCI			**0.002**
Mean (SD)	1.95 (2.1)	1.56 (1.9)	
CCI category, n (%)			**0.02**
0	129 (32.2)	171 (42.6)	
1	36 (9.0)	32 (8.0)	
2	136 (33.9)	123 (30.7)	
3+	100 (24.9)	75 (18.7)	
Comorbidities, n (%)			
Hypertension	247 (61.6)	216 (53.9)	**0.03**
Asthma	33 (8.2)	17 (4.2)	**0.02**
Congestive heart failure	17 (4.2)	14 (3.5)	0.58
Peripheral vascular disease	17 (4.2)	18 (4.5)	0.86
Cerebrovascular disease	13 (3.2)	6 (1.5)	0.10
Chronic pulmonary disease	48 (12.0)	25 (6.2)	**0.005**
Connective tissue disease	15 (3.7)	14 (3.5)	0.85
Mild liver disease	31 (7.7)	29 (7.2)	0.79
Diabetes without complication	39 (9.7)	46 (11.5)	0.42
Moderate or severe renal diseases	209 (52.1)	179 (44.6)	**0.03**
Diabetes with complication	23 (5.7)	20 (5.0)	0.64
Cancer	21 (5.2)	9 (2.2)	**0.03**
Moderate or severe liver disease	13 (3.2)	5 (1.3)	0.06

- Baseline characteristics were generally well balanced between cohorts
- Significant differences in CCI distribution and certain comorbidities were observed*

*Results for time to kidney failure at 1-5 years were adjusted for unbalanced characteristics at index/pseudo-index date.
CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; SD, standard deviation; SGC, systemic glucocorticoids.

Results: Adverse events

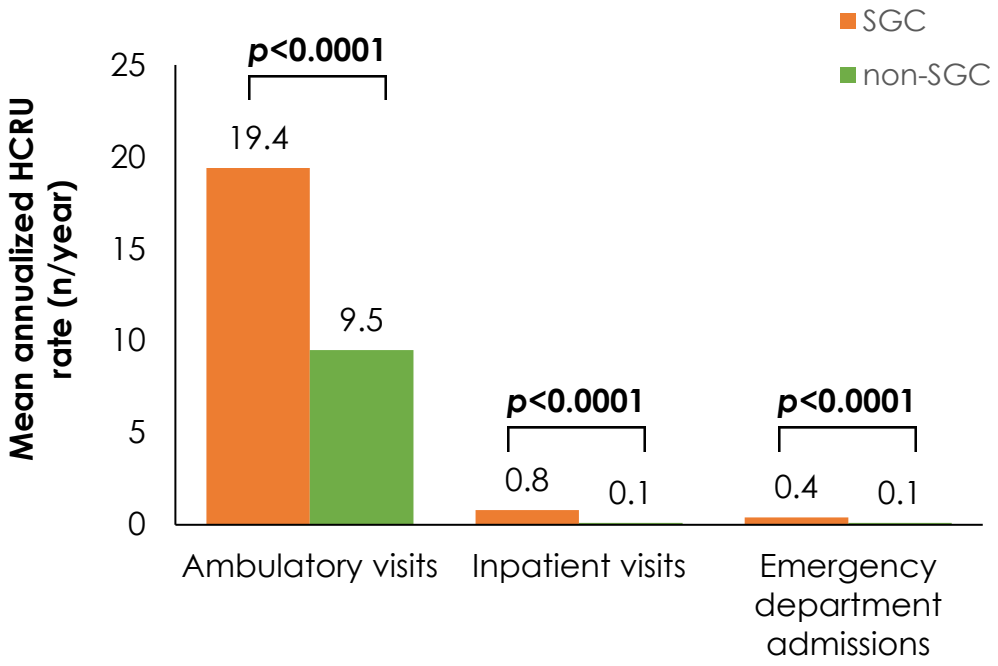
AEs*, n (%)	SGC (n=401)	Non-SGC (n=401)	p-value
Hypertension	294 (73.3)	252 (62.8)	**0.002**
Incident hypertension*	65 (42.2)	53 (28.7)	**0.009**
Arthralgia	131 (32.7)	83 (20.7)	**<0.001**
Dyspnea	109 (27.2)	46 (11.5)	**<0.001**
Fatigue	99 (24.7)	57 (14.2)	**<0.001**
URTI	87 (21.7)	50 (12.5)	**0.001**
New onset of diabetes mellitus	67 (16.7)	57 (14.2)	0.330
Peripheral/face edema	59 (14.7)	17 (4.2)	**<0.001**
Increase in WBC count	36 (9.0)	13 (3.2)	**0.001**
Dermatitis	35 (8.7)	21 (5.2)	0.050
Dyspepsia	31 (7.7)	15 (3.7)	**0.020**
Confirmed fracture	21 (5.2)	24 (6.0)	0.650
Acne	19 (4.7)	8 (2.0)	**0.030**
Weight increased	17 (4.2)	5 (1.3)	**0.010**
Severe infection requiring hospitalization	14 (3.5)	1 (0.3)	**0.001**
GI bleeding requiring hospitalization	9 (2.2)	2 (0.5)	**0.030**
Reported onset of glaucoma	8 (2.0)	10 (2.5)	0.630

AEs ordered from high to low according to SGC treatment group.
*Among patients without hypertension diagnosis before index/pseudo-index date.
AE, adverse event; GI, gastrointestinal; SGC, systemic glucocorticoids; URTI, upper respiratory tract infection; WBC, white blood cell.

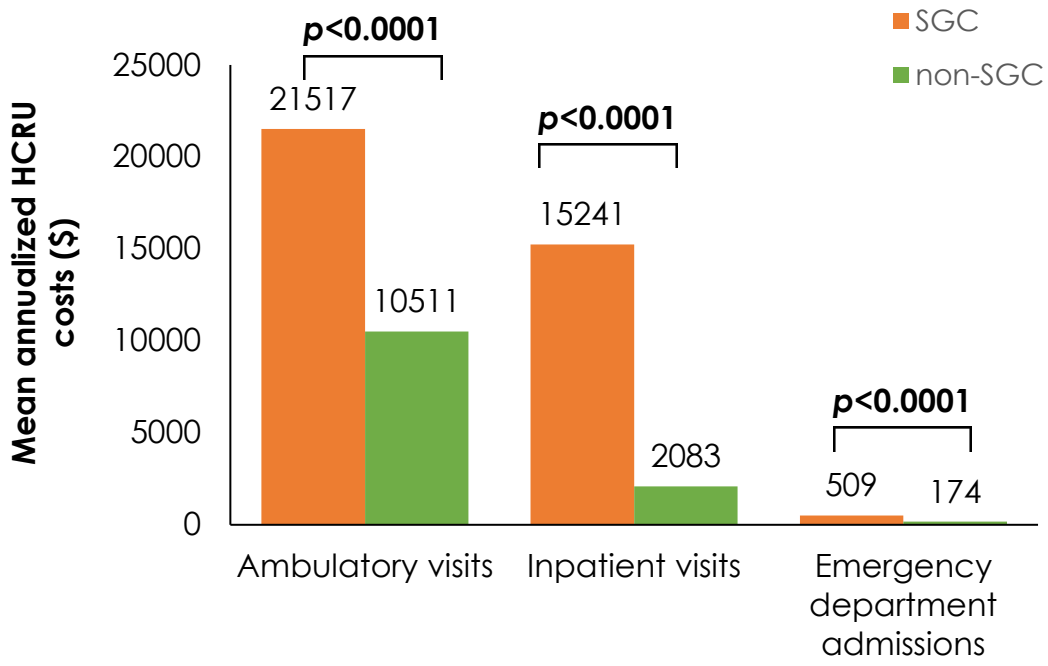
Of AEs that occurred in at least ten of the 802 patients, **those who received SGC experienced a significantly increased incidence of AEs** except for fractures, new onset of diabetes, and reported onset of glaucoma

Results: Healthcare resource utilization and costs

Mean annualized HCRU rate



Mean annualized HCRU costs*



Annualized mean HCRU rates and costs **were significantly greater across all HCRU types for the SGC versus non-SGC cohort**, including an 8-fold increase in inpatient visits, a 4-fold increase in emergency department admissions, and twice as many ambulatory visits

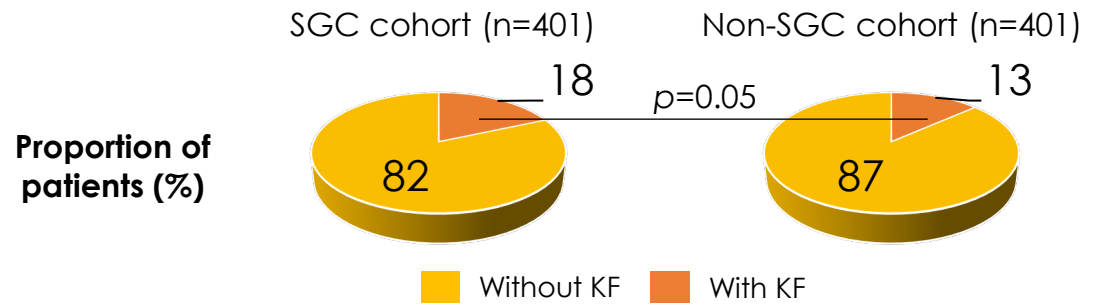
*Cost was estimated by multiplying the number of visits of the category of interest (or number of overnight stays for inpatient hospital cost) by the average cost of the category adjusted to 2022 USD using medical care component of the consumer price index.[1]

HCRU, healthcare resource utilization; SGC, systemic glucocorticoids; USD, United States dollars.

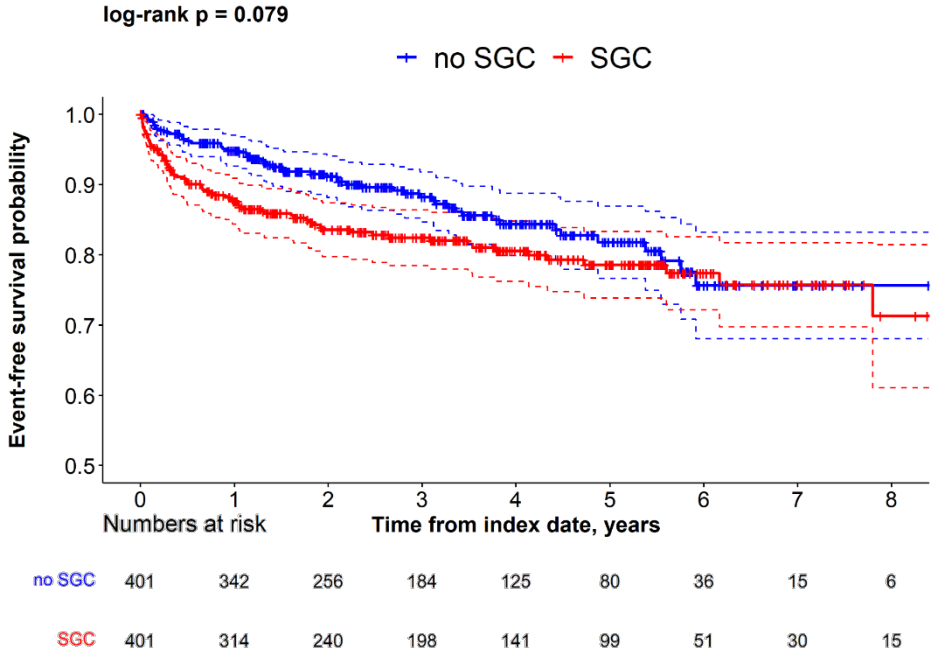
1. MEPS HC-229E: 2021 Emergency Room Visits June 2023, MEPS HC-229D: 2021 Hospital Inpatient Stays May 2023, MEPS HC-229F: 2021 Outpatient Department Visits June 2023.

Results: Incidence and onset of kidney failure

Patients with KF during follow-up



KM survival for time to KF



A higher proportion of the SGC cohort had KF during follow-up than the non-SGC cohort

A faster onset of KF was observed in the SGC cohort, especially in the first year

CI, confidence interval; KM, Kaplan-Meier; KF, kidney failure; SGC, systemic glucocorticoids.

Results: Time to kidney failure at 1-5 years after index/pseudo-index date

The difference in the incidence of KF between cohorts was greatest at 1 year*

Time	Patients with KF		Unadjusted model		Adjusted model†	
	SGC (n=401)	Non-SGC (n-401)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
1 year	48	20	2.5 (1.5-4.2)	**0.0005**	2.3 (1.4-3.9)	**0.0015**
2 years	61	32	2.0 (1.3-3.1)	**0.0014**	1.8 (1.2-2.8)	**0.0053**
3 years	64	39	1.7 (1.2-2.5)	**0.008**	1.6 (1.0-2.3)	**0.028**
4 years	68	46	1.5 (1.0-2.2)	**0.0273**	1.4 (0.9-2.0)	0.0826
5 years	71	49	1.5 (1.0-2.1)	**0.0343**	1.3 (0.9-1.9)	0.1183

Based on the adjusted model, the difference in time to KF between cohorts was not explained by different proportions of comorbid conditions or CKD stage at index

*Results were compared using Fine and Gray model. †Adjusted for unbalanced characteristics at index/pseudo-index date.
CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; KF, kidney failure; SGC, systemic glucocorticoids.

Study limitations

- There was no specific ICD-10 code for IgAN at the time this study was implemented, which may have led to misclassification on diagnosis
  - The study population was defined as patients with a limited set of ICD-10 codes used for glomerular disease (N02.8 and N04.1); sensitivity analyses conducted using only N02.8 yielded similar results
- The real-world EMR database reflects standard of care clinical practice, which impacts the availability of data at timepoints of interest, and patients with more data may differ from patients with less data (e.g. sicker patients may have more frequent clinic visits), thus introducing potential bias in outcomes of interest
  - However, the number of patients with available or missing data at each timepoint per group was similar
- Although unbalanced characteristics at index were adjusted for, potential residual confounding for IgAN disease severity at index is possible

EMR, electronic medical records; ICD, International Classification of Diseases; IgAN, immunoglobulin A nephropathy

Discussion

- This real-world analysis demonstrates significant side effects and costs for patients with IgAN treated with SGC compared with patients not treated with SGC
- Incidence of KF was higher in patients using SGC compared with those who did not receive SGC
- The results support the KDIGO 2021 recommendation that, given the limited evidence base on the effectiveness of SGC, treatment toxicity should be carefully considered before exposing patients with IgAN to SGC treatment

IgAN, immunoglobulin A nephropathy; KDIGO, Kidney Disease: Improving Global Outcomes; KF, kidney failure; SGC, systemic glucocorticoids.

Acknowledgments

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