Canadian Society of Nephrology/ Société canadienne de néphrologie CSN/SCN

CANADIAN JOURNAL OF KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Original Clinical Research

Canadian Journal of Kidney Health and Disease
Volume 6: 1–9

DOI: 10.1177/2054358119892372
journals.sagepub.com/home/cjk
SAGE

The Risk of Stroke and Stroke Type in Patients With Atrial Fibrillation and Chronic Kidney Disease

Trevor Mace-Brickman[1], Anan Bader Eddeen[2], Juan-Jesus Carrero[3], Patrick B. Mark[4], Amber O. Molnar[2,5], Ngan N. Lam[6], Deborah Zimmerman[7], Ziv Harel[8], and Manish M. Sood[2,6,8,9]

Abstract

Background: Atrial fibrillation (AF) and chronic kidney disease (CKD) are known to increase the risk of stroke.
Objectives: We set out to examine the risk of stroke by kidney function and albuminuria in patients with and without AF.
Design: Retrospective cohort study.
Settings: Ontario, Canada.
Participants: A total of 736 666 individuals (>40 years) from 2002 to 2015.
Measurements: New-onset AF, albumin-to-creatinine ratio (ACR), and an estimated glomerular filtration rate (eGFR).
Methods: A total of 39 120 matched patients were examined for the risk of ischemic, hemorrhagic, or any stroke event, accounting for the competing risk of all-cause mortality. Interaction terms for combinations of ACR/eGFR and the outcome of stroke with and without AF were examined.
Results: In a total of 4086 (5.2%) strokes (86% ischemic), the presence of AF was associated with a 2-fold higher risk for any stroke event and its subtypes of ischemic and hemorrhagic stroke. Across eGFR levels, the risk of stroke was 2-fold higher with the presence of AF except for low levels of eGFR (eGFR < 30 mL/min/1.73 m^2, hazard ratio [HR]: 1.38, 95% confidence interval [CI]: 0.99-1.92). Similarly across ACR levels, the risk of stroke was 2-fold higher except for high levels of albuminuria (ACR > 30 mg/g, HR: 1.61, 95% CI: 1.31-1.99). The adjusted risk of stroke with AF differed by combinations of ACR and eGFR categories (interaction *P* value = .04) compared with those without AF. Both stroke types were more common in patients with AF, and ischemic stroke rates differed significantly by eGFR and ACR categories.
Limitations: Medication information was not included.
Conclusions: Patients with CKD and AF are at a high risk of total, ischemic, and hemorrhagic strokes; the risk is highest with lower eGFR and higher ACR and differs based on eGFR and the degree of ACR.

Abrégé

Contexte: La fibrillation auriculaire (FA) et l'insuffisance rénale chronique (IRC) augmentent le risque d'accident vasculaire cérébral (AVC).
Objectif: Nous voulions analyser le risque d'AVC selon la fonction rénale et l'albuminurie chez des patients atteints d'IRC avec ou sans FA.
Type d'étude: Étude de cohorte rétrospective.
Cadre: Ontario, Canada.
Sujets: Un total de 736 666 individus (>40 ans) entre 2002 et 2015.
Mesures: Les nouveaux cas de FA, le rapport albumine/créatinine urinaire (RAC) et le débit de filtration glomérulaire estimé (DFGe).
Méthodologie: Au total, 39 120 patients appariés ont été examinés pour le risque d'AVC ischémique, hémorragique ou autre, en tenant compte du risque concurrent de mortalité toutes causes confondues. Les effets d'interactions des combinaisons RAC/DFGe et de l'issue de l'AVC, avec ou sans FA, ont également été étudiés.
Résultats: Pour un total de 4 086 AVC (5,2 %), dont 86 % d'AVC ischémiques, la présence de FA était associée à un risque deux fois plus élevé de survenue d'un AVC et d'un de ses sous-types (ischémique et hémorragique). Pour l'ensemble des niveaux de DFGe, le risque d'AVC se révélait deux fois plus élevé en présence de FA, sauf pour les faibles valeurs de DFGe

(DFGe <30 mL/min/1,73 m^2; RR: 1,38; IC 95 %: 0,99-1,92). De même, pour l'ensemble des niveaux de RAC, le risque d'AVC s'avérait deux fois plus élevé en présence de FA, à l'exception des patients présentant une albuminurie élevée (RAC >30 mg/g; RR: 1,61; IC 95 %: 1,31-1,99). Le risque ajusté d'AVC avec FA différait selon les catégories de combinaisons RAC/DFGe (valeur de p de l'interaction: 0,04) lorsque comparé aux cas sans FA. Les deux types d'AVC se sont avérés plus fréquents chez les patients atteints de FA, et les taux d'AVC ischémiques différaient significativement selon les catégories de DFGe et de RAC.

Limites: Les renseignements sur la médication n'ont pas été inclus.

Conclusion: Les patients atteints d'IRC et de FA sont plus susceptibles de subir un AVC ischémique, hémorragique ou total. Ce risque s'avère encore plus élevé en présence d'un faible DFGe et d'un RAC élevé, et diffère selon les valeurs de DFGe et de RAC.

Keywords

stroke, atrial fibrillation, eGFR, albuminuria, chronic kidney disease, epidemiology, ischemic

Received July 16, 2019. Accepted for publication October 20, 2019.

What was known before

Atrial fibrillation (AF) is a well-recognized risk factor for stroke in patients with chronic kidney disease (CKD); however, the stroke risk associated with combinations of estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR) both with and without AF is less clear.

What this adds

In this population-based administrative data study, a lower eGFR and a higher ACR were associated with a higher risk of stroke. The presence of AF conferred a roughly 2-fold higher risk of stroke across all eGFR and ACR categories.

Background

Chronic kidney disease (CKD) is defined as a reduction in glomerular filtration rate and/or proteinuria routinely measured by the albumin-to-creatinine ratio (ACR) and has a prevalence of 10% to 15% globally.[1,2] Multiple cardiovascular diseases, including coronary artery disease, peripheral vascular disease, and stroke, are associated with CKD.[3,4] Atrial fibrillation (AF) is associated with an increased risk of stroke and is a common arrhythmia found in patients with CKD (event rate estimates range from 19 to 63 per 1000 person-years).[5-7]

The association of AF and stroke in patients with advanced CKD presents a problematic clinical situation as there is limited evidence regarding the optimal role of anticoagulation for stroke prevention.[8-13] Coupled with a high hemorrhage risk in patients with CKD and a high competing risk of mortality, understanding the true risk of stroke in this population is of increased importance.[14-16]

The complex interactions between CKD, AF, and stroke have made it difficult to establish a clear understanding of how AF increases the risk of stroke in patients with CKD. The 2016 Kidney Disease Improved Global Outcomes (KDIGO) consensus conference on arrhythmias and CKD identified the need for further research characterizing the risk of AF-associated stroke in CKD across the spectrum of estimated glomerular filtration rate (eGFR) and albuminuria.[17] Thus, we assessed the stroke risk by CKD stage in patients with and without AF, accounting for the competing risk of death. We hypothesized that both CKD stage and the presence of AF would significantly alter the risk of stroke.

[1]Department of Medicine, University of Ottawa, ON, Canada
[2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada
[3]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[4]Institute of Cardiovascular & Medical Sciences, University of Glasgow, UK
[5]Department of Medicine, McMaster University, Hamilton, ON, Canada
[6]Division of Nephrology, University of Alberta, Edmonton, Canada
[7]Division of Nephrology, University of Ottawa, ON, Canada
[8]Division of Nephrology, St. Michael's Hospital, University of Toronto, ON, Canada
[9]Ottawa Hospital Research Institute, The Ottawa Hospital, Civic Campus, ON, Canada

Corresponding Author:
Manish M. Sood, Ottawa Hospital Research Institute, The Ottawa Hospital, Civic Campus, 2-014 Administrative Services Building, 1053 Carling Avenue, Box 693, Ottawa, ON K1Y 4E9, Canada.
Email: Msood@toh.on.ca

Methods

Design and Setting

We conducted a retrospective cohort study in Ontario, Canada using health care databases at the Institute for Clinical Evaluative Sciences (ICES). This study was conducted using a prespecified protocol and reporting of the results adheres to the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) guidelines (Supplementary Table 1).[18] The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

Data Sources

We ascertained patient characteristics, laboratory data, and outcome data from linked administrative databases. The Gamma-Dynacare database was used to obtain outpatient serum creatinine and ACR laboratory data. Gamma-Dynacare is a laboratory service provider that contains outpatient lab information for individuals who had blood work drawn at any of their 225 collection sites in Ontario. Demographics and vital status information were obtained from the Ontario Registered Persons Database. Diagnostic and procedural information from all hospitalizations was determined using the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). The CIHI National Ambulatory Care Reporting System (CIHI-NACRS) database contains diagnostic information from all emergency department (ED) visits. Information was also obtained from the Ontario Health Insurance Plan (OHIP) database, which contains all health claims for inpatient and outpatient physician services. We identified patients with a history of kidney transplant or dialysis therapies (exclusion criteria) using the Canadian Organ Replacement Register. These datasets were linked using unique encoded identifiers and analyzed at ICES. Whenever possible, we defined patient characteristics and outcomes using validated codes (Supplementary Table 2).

Study Cohorts

The study cohort was accrued from April 1, 2002 to March 31, 2012 (see Supplementary Figure 1). To be included, patients had to have 1 outpatient measure of urine ACR test and a serum creatinine measurement within 12 months of each other. For each patient, the date of the first eligible incident AF diagnosis was taken as the index date. We excluded patients <40 years of age due to the small sample size of younger individuals and those with a history of kidney transplantation, dialysis, or stroke before their index date.

Exposure and Outcomes

Incident AF was defined by a single International Classification of Diseases (ICD) or billing code on first diagnosis during hospitalization, ED visit, or ambulatory care visit. The diagnosis of AF using ICD, OHIP, and NACRS has been previously validated with specificity and sensitivity $>90\%$.[19] To mimic a randomization process, unexposed individuals without AF were assigned an index date based on the distribution of the index dates in the AF group such that there were no differences between the two. We further examined the effects of ACR and eGFR as continuous and categorical variables (ACR in mg/g: <3, 3-30, >30, and eGFR in mL/min/1.73 m^2: >90, 60-90, 45-59, 30-44, <30). A validation study of outpatient serum creatinine values found that most of the patients with a low eGFR had a similar or lower eGFR on repeat testing at least 30 days later.[20] We used the Chronic Kidney Disease Epidemiology Collaboration equation to calculate eGFR.[21] The study outcomes were any incident stroke or subgroups of stroke type (ischemic or hemorrhagic). Ischemic stroke included transient ischemic events. Hemorrhagic strokes included intracranial or subarachnoid events. Hospitalization encounters with ischemic stroke and hemorrhagic events were identified using validated ICD codes, in CIHI-DAD and NACRS (Supplementary Table 2).[22]

Statistical Analysis

Patients were followed from their index date until the outcome of interest, death, end-stage renal disease (defined as dialysis or kidney transplantation), or end of the study period (March 31, 2015). Known demographics and comorbid risk factors for stroke and stroke type were captured at the index date. We used standardized differences to compare baseline characteristics by AF status. Continuous variables are reported as medians (interquartile ranges [IQRs]) and categorical variables as numbers and percentages. Standardized differences describe differences between group means relative to the pooled standard deviation and are less sensitive to large sample sizes than traditional hypothesis testing.[23] A difference $>$ 10% is considered significant. We calculated the incidence rate using the cumulative incidence function for any stroke and stroke subtypes. We used propensity score matching followed by Fine and Grey subdistribution hazards model to examine the association of AF exposure and our outcomes.[24] The following variables were included in the propensity score model: year of ACR, time from ACR to index date, sex (male referent), income quintile (lowest quintile referent), location (rural vs urban), and comorbidities at baseline (diabetes mellitus, hypertension, myocardial infarction, congestive heart failure, major hemorrhage, coronary artery disease, coronary revascularization, peripheral artery disease, peripheral vascular disease, and chronic obstructive pulmonary disease). Individuals with AF were greedy matched 1:1 without replacement to non-AF individuals on the logit of the propensity score (± 0.05), eGFR and ACR category. Fine and Grey models account for the competing risk of death and are especially useful in CKD studies where death is a common competing event.[25,26] We estimated the

Table 1. Baseline Characteristics of the Study Cohort by Atrial Fibrillation Status Among Propensity Score–Matched Patients.

Characteristics	Total cohort (N = 78 240)	Atrial fibrillation (N = 39 120)	No atrial fibrillation (N = 39 120)
Age (mean, SD)	74.9 (10.6)	74.6 (10.5)	75.1 (10.6)
Men, n (%)	43 322 (55.4)	21 646 (55.3)	21 676 (55.4)
Income quintile, n (%)			
1 (low)	15 725 (20.1)	7802 (19.9)	7923 (20.3)
2	17 149 (21.9)	8578 (21.9)	8571 (21.9)
3	15 988 (20.4)	8016 (20.5)	7972 (20.4)
4	15 068 (19.3)	7570 (19.4)	7498 (19.2)
5 (high)	14 310 (18.3)	7154 (18.3)	7156 (18.3)
Urban residence, n (%)	70 415 (90.0)	35 187 (89.9)	35 228 (90.1)
Albumin-to-creatinine ratio (mg/g), median, (interquartile range)	1 (1-5)	2 (1-5)	2 (1-5)
<3	51 482 (65.8%)	25 741 (65.8%)	25 741 (65.8%)
3-30	21 460 (27.4%)	10 730 (27.4%)	10 730 (27.4%)
>30	5298 (6.8%)	2649 (6.8%)	2649 (6.8%)
Estimated glomerular filtration rate (mL/min/1.73 m^2), mean (SD)	70.8 (20.7)	70.8 (20.8)	70.9 (20.6)
>90	15 180 (19.4%)	7590 (19.4%)	7590 (19.4%)
60-90	39 320 (50.3%)	19 660 (50.3%)	19 660 (50.3%)
45-59	13 658 (17.5%)	6829 (17.5%)	6829 (17.5%)
31-44	7696 (9.8%)	3848 (9.8%)	3848 (9.8%)
≤30	2386 (3.0%)	1193 (3.0%)	1193 (3.0%)
Comorbidities, n (%)			
Congestive heart failure	20 770 (26.5)	10 746 (27.5)	10 024 (25.6)
Major hemorrhage	4738 (6.1)	2403 (6.1)	2335 (6.0)
Myocardial infarction	4241 (5.4)	2123 (5.4)	2118 (5.4)
Coronary artery disease	32 884 (42.0)	16 469 (42.1)	16 415 (42.0)
Peripheral vascular disease	1812 (2.3)	894 (2.3)	918 (2.3)
Coronary artery bypass grafting	1359 (1.7)	665 (1.7)	694 (1.8)
Chronic obstructive pulmonary disease	4311 (5.5)	2186 (5.6)	2125 (5.4)
Diabetes mellitus	48 078 (61.4)	23 726 (60.6)	24 352 (62.2)
Hypertension	64 725 (82.7)	32 112 (82.1)	32 613 (83.4)

Note. All standardized differences were less than 10% between matched pairs (atrial fibrillation vs no atrial fibrillation) for all covariates listed.

subdistribution hazard ratio (sHR) using regression modeling of the cumulative incidence function. To assess whether the stroke risk differed by the presence of AF and kidney function, a multiplicative interaction for AF × eGFR/ACR was examined. In this model, we created categories of all possible combinations (30 in total) of eGFR (>90, 60-90, 45-59, 30-44, <30), ACR (<3, 3-30, >30), and AF (present/absent). We conducted all analyses with SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Two-sided *P* values < .05 were treated as statistically significant.

Results

Baseline Characteristics

From a total cohort of 736 666 eligible patients from Ontario, Canada from 2002 to 2015, we identified 41 049 (5.6%) patients who developed incident AF from which 39 120 (95.3%) were matched 1:1 with individuals without AF.

There were no statistical differences between those with and without AF after matching (Table 1). The average age was 74.9 (±10.6) years and 55.4% were male. The mean eGFR was 70.8 ± 20.7 mL/min/1.73 m^2 and the median (IQR) ACR of 2 mg/g (1-5). Comorbid conditions were common among those with AF, with 27.5% having congestive heart failure, 42.1% having coronary artery disease, 60.6% having diabetes mellitus, and 82.1% having hypertension. This compared to those without AF in whom 25.6% had congestive heart failure, 42.0% had coronary artery disease, 62.2% had diabetes mellitus, and 83.4% had hypertension.

Association of AF With Stroke

A stroke event occurred in 5.2% (4086) of the study cohort (3519 ischemic [86%], 679 hemorrhagic [14%]) (Table 2) with a median (IQR) time to event of 4 (2-6) years from the first AF diagnosis. A stroke event was more common among those with AF (7.0% with AF, crude rate: 13.5, 95%

Table 2. Crude Counts, Event Rates With 95% CIs, and Type of Stroke Events by Atrial Fibrillation Status.

	Atrial fibrillation			No atrial fibrillation		
	n (%)	Cumulative incidence % (95% CI)	sHR (95% CI)	n (%)	Cumulative incidence % (95% CI)	sHR
All stroke events	2665 (6.80)	13.5 (11.27-15.93)	2.12 (1.98-2.26)	1316 (3.36)	8.6 (6.54-10.99)	Ref
Ischemic stroke	2259 (5.77)	11.04 (8.91-13.42)	2.14 (1.99-2.30)	1104 (2.82)	4.38 (4.01-4.78)	Ref
Hemorrhagic stroke	406 (1.04)	2.93 (1.95-4.21)	2.01 (1.70-2.37)	212 (0.54)	1.81 (0.83-3.49)	Ref

Note. CI = confidence interval; sHR = subdistribution hazard ratio.

Table 3. The Hazard Ratio for Stroke by Atrial Fibrillation Status, eGFR and ACR Levels With eGFR > 90/ACR < 3 and Absence of Atrial Fibrillation as Referent.

	ACR < 3		ACR = 3-30		ACR > 30	
eGFR/ACR	No AF	AF	No AF	AF	No AF	AF
>90	Ref	2.23 (1.78-2.79)	1.48 (1.06-2.06)	3.90 (3.02-5.04)	3.80 (2.52-5.72)	3.80 (2.47-5.83)
60-90	1.38 (1.12-1.71)	3.36 (2.76-4.11)	2.18 (1.73-2.74)	4.51 (3.65-5.56)	2.65 (1.88-3.72)	4.93 (3.70-6.58)
45-59	1.94 (1.53-2.49)	3.83 (3.07-4.77)	2.26 (1.71-2.99)	4.77 (3.76-6.05)	2.99 (2.02-4.43)	4.93 (3.52-6.91)
31-44	2.06 (1.55-2.75)	4.10 (3.20-5.24)	2.22 (1.61-3.06)	4.51 (3.45-5.88)	2.53 (1.60-3.99)	5.00 (3.47-7.18)
≤30	2.54 (1.60-4.04)	4.27 (2.91-6.28)	2.68 (1.71-4.21)	3.03 (1.96-4.69)	3.25 (1.83-5.76)	4.40 (2.58-7.51)

Note. The following variables were included in the propensity score model: year of ACR, time from ACR to index date, sex (male referent), income quintile (lowest quintile referent), location (rural vs urban), and comorbidities at baseline (diabetes mellitus, hypertension, myocardial infarction, congestive heart failure, major hemorrhage, coronary artery disease, coronary revascularization, peripheral artery disease, peripheral vascular disease, and chronic obstructive pulmonary disease). Individuals with AF were greedy matched 1:1 without replacement to non-AF individuals on the logit of the propensity score (±0.05), eGFR and ACR category. *P* value for the eGFR/ACR level × AF interaction is .04. eGFR = estimated glomerular filtration rate; ACR = albumin-to-creatinine ratio; AF = atrial fibrillation.

confidence interval [CI]: 11.3-15.9, vs 3.4% without AF, crude rate: 8.6, 95% CI: 6.5-11.0). The median (IQR) time to stroke was 4 (1-6) years in patients with AF compared with 5 (3-7) years in those without AF. During the follow-up period, the total events of death and dialysis were 21 120 (27.0%) (AF—13 676 [35.0%], no AF—7444 [19.0%]) and 2888 (3.7%) (AF—1974 [5.0%], no AF—914 [2.3%]), respectively. Among those with AF, the sHRs for any stroke event, ischemic stroke, and hemorrhagic stroke were similar at 2.12 (95% CI: 1.98-2.26), 2.14 (95% CI: 1.99-2.30), and 2.01 (95% CI: 1.70-2.37), respectively, compared with those without AF.

Association of eGFR, AF, and Stroke

The stroke risk was consistent and approximately 2-fold higher within eGFR categories when comparing patients with and without AF (Supplementary Table 3). The relative risk was highest among those with eGFR of 60 to 90 mL/min/1.73 m^2 (sHR: 2.26, 95% CI: 2.06-2.48) and lowest for eGFR < 30 mL/min/1.73 m^2 (sHR: 1.38, 95% CI: 0.99-1.92). The absolute risk and number of events for stroke with AF were 7% (n = 1367) and 6.3% (n = 75) for eGFR of 60 to 90 mL/min/1.73 m^2 and eGFR < 30 mL/min/1.73 m^2, respectively. For those without AF, the absolute risk and number of events for stroke were 3.2% (n = 623) and 4.8% (n = 57) for the eGFR values of 60 to 90 and <30.

Association of Albuminuria, AF, and Stroke

The stroke risk was consistently higher among those with AF compared with those without AF. The absolute stroke risk was higher at higher ACR levels among patients with and without AF (ACR < 3 mg/g: AF—6.1% and no AF—2.9%; ACR = 3-30 mg/g: AF—8.2% and no AF—4.1%; ACR > 30 mg/g: AF—8.0% and no AF—5.4%). However, the relative stroke risk was higher with lower levels of ACR categories compared with no AF (ACR < 3 mg/g: sHR = 2.23, 95% CI = 2.04-2.43; ACR = 3-30 mg/g: sHR = 2.09, 95% CI = 1.86-2.35; ACR > 30 mg/g: sHR = 1.61, 95% CI = 1.31-1.99) (Supplementary Table 4).

Association of eGFR, Albuminuria, AF, and Stroke

The combined relative risk of stroke by eGFR, ACR, and AF status is presented in Table 3 and Supplementary Table 5. The stroke risk differed significantly by the presence of AF and combined categories of eGFR/ACR (P = .04). Compared with an eGFR > 90 mL/min/1.73 m^2/ACR < 3 mg/g and no AF, there was at least a 2-fold increase in the risk of stroke with AF. The stroke risk was consistently higher in patients with a lower eGFR level with and without AF. Among those with AF, the stroke risk increases in parallel as the ACR increases (except for eGFR > 90 mL/min/1.73 m^2 and eGFR < 30 mL/min/1.73 m^2), whereas in those without AF the stroke risk increases as ACR increases

in all eGFR categories. For high levels of albuminuria and normal kidney function, the stroke risk was similar for those with and without AF (sHR = 3.80 for both). The risk of stroke was 4.4-fold higher for those with a combination of an elevated ACR/lower eGFR with AF and 3-fold higher for those without AF.

Risk of Ischemic and Hemorrhagic Stroke by eGFR and ACR Level

Ischemic and hemorrhagic stroke were more common in patients with AF (event rate: ischemic/AF—11.04 [95% CI: 8.91-13.42], ischemic/no AF—6.93 [95% CI: 5.17-9.04], hemorrhagic/AF—2.93 [95% CI: 1.95-4.21], hemorrhagic/no AF—1.81 [95% CI: 0.83-3.49]) per 1000 person-years of follow-up. The proportion of ischemic strokes was higher with increasing ACR category (3.81% with ACR$<$ 3 mg/g to 5.98% with ACR $>$ 30 mg/g). A similar rise was observed with declining eGFR, albeit with the proportion being relatively similar from an eGFR $\leq$ 60 mL/min/1.73 m^2. There were fewer hemorrhagic stroke events with no discernible difference in the crude risk by ACR or eGFR level among those with AF (AF ACR $<$ 3 mg/g—0.89%, AF ACR $>$ 30 mg/g—0.94%).

Discussion

In this retrospective cohort of 39 120 matched patients, we found that the risk of stroke is associated with AF and that this risk differs significantly based on eGFR and ACR levels. The stroke risk was 4.4-fold higher with the combination of a low level of eGFR, an elevated ACR, and AF compared with those with normal kidney function and no AF. Even in the absence of AF, a low eGFR and a high ACR increased the stroke risk 3.3-fold compared with normal kidney function. We observed a remarkably consistent approximate 2-fold higher stroke risk with the presence of AF across most eGFR and ACR levels. One exception was among those with normal eGFR and high ACR, where the stroke was identical at 3.8-fold higher for those with and without AF. Consistent with previous studies, we observed a higher stroke risk among those without AF with lower eGFR and higher ACR levels.[8-10,15,27] Lastly, the higher stroke risk with AF was largely driven by ischemic stroke events with a little observed difference in hemorrhagic stroke types. Taken together, AF universally increases stroke risk in patients with CKD; however, the risk is modified considerably by eGFR and ACR.

Previous studies have examined the association of stroke, eGFR, and albuminuria with conflicting results. A meta-analysis of 21 studies conducted by Lee et al found that patients with CKD (defined as eGFR $<$ 60 mL/min/1.73 m^2) had a 43% greater risk of stroke than patients with normal baseline eGFR.[27] Subgroup analyses by eGFR level ($>$60, 40-60, $<$40 mL/min/1.73 m^2) demonstrated a dose-response relationship with an increased risk of stroke with worsening eGFR.

A post hoc analysis of ROCKET-AF reported that a reduction in eGFR of 10 mL/min/1.73 m^2 was associated with a 12% increase in the adjusted stroke risk.[15] Fewer studies have compared the relative contributions of both eGFR and proteinuria on stroke risk. Go et al[28] examined 10 908 patients from the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) cohort reporting that both eGFR and proteinuria were independent risk factors for stroke in patients with AF. In contrast, Sandsmark et al[29] reported that proteinuria, but not eGFR, was independently associated with stroke in 3939 patients with CKD from the Chronic Renal Insufficiency Cohort (CRIC). In our study, we found that both eGFR and albuminuria were independently associated with stroke risk in patients with AF, but the risks differed. The adjusted stroke risk by eGFR increased but plateaued once the eGFR was below 60 mL/min/1.73 m^2, whereas it continually increased in a dose-dependent manner with increasing ACR level. This is consistent with and extends the findings reported in CRIC to patients with AF and suggests that albuminuria, as opposed to eGFR, plays a more significant role in determining stroke risk in more advanced CKD. Our study differed from previous studies as our cohort was population based (as opposed to referred and under the care of a nephrologist in CRIC), we had a large number of events (1781 strokes) allowing for detection of risk among eGFR/ACR categories, we accounted for the competing risk of death, and we performed propensity score matching to reduce residual confounding. Our study unifies and advances results from the literature examining the association of eGFR, ACR, and stroke suggesting that CKD increases the risk of stroke; however, this risk is considerably different depending on eGFR and ACR levels.

We found a consistent higher stroke risk across all levels of eGFR and proteinuria, both with and without AF, consistent with previous literature.[27] Across eGFR levels, the stroke risk with AF was 2- to 3.8-fold higher than that without AF. For ACR, the risk was 2- to 3.2-fold higher with AF across the strata of ACR. Interestingly, the difference in relative risk of stroke with AF was attenuated across lower eGFR and higher ACR levels. For example, the presence of AF confers a 3.8-fold increase in stroke risk at eGFR $>$ 90 mL/min/1.73 m^2, whereas it confers a 2-fold increase with eGFR $<$ 30 mL/min/1.73 m^2. This difference in risk is likely attributable to the increase in baseline risk of stroke in the non-AF group and the additional higher competing risk of death among those with low eGFR. For example, the proportion of strokes with no AF increases from 1.01% with eGFR $>$ 90 mL/min/1.73 m^2 to 2.78% with eGFR $<$ 30 mL/min/1.73 m^2. This observation has potentially important clinical consequences as the lower incremental stroke risk attributable to AF at low levels of eGFR may mitigate the benefits of anticoagulation, a question warranting further investigation.

Most of the stroke events were ischemic (85%), as opposed to hemorrhagic strokes, and the crude proportion of ischemic strokes increased in a dose-dependent manner with lower eGFR and higher ACR. Despite creating our matched cohort from a large population (>700 000 individuals), we were unable to determine the adjusted risk of hemorrhagic stroke by eGFR and ACR levels. Previous studies have reported an association between proteinuria and hemorrhagic stroke risk, a finding we were unable to confirm.[29,30]

The role of anticoagulation in advanced CKD and AF for prevention of thromboembolism represents an area of uncertainty. At present, there are no randomized trials demonstrating a reduction in ischemic stroke risk with anticoagulation for CrCl < 25 mL/min.[31-33] We previously reported the stroke risk for 1400 matched pairs of CKD (eGFR < 45) patients with AF with and without warfarin anticoagulation.[8] We found no difference in ischemic stroke risk with baseline and time-varying warfarin use. Similar conflicting results have recently been reported in a primary care population of patients with advanced age in the United Kingdom.[9] Emerging evidence with direct oral anticoagulants (DOACs) seems to suggest a net clinical benefit in patients with lower eGFRs; however, definitive clinical trials remain pending.[34] As such, we did not include anticoagulation in this study.

Our study did have limitations. Certain categories had relatively few events (175 hemorrhagic strokes in total, <80 strokes with eGFR < 30 mL/min/1.73 m^2). As our primary focus was the risk of AF in patients with CKD, we included all patients aged more than 40 in our cohort and did not have information regarding medications. Although we accounted for the competing risk of death in our models, we did not attempt to differentiate death due to stroke from other causes of death. This is due to unreliability in accurately determining the cause of death in administrative database studies.[35] We only used a single measure of eGFR and ACR to categorize kidney function. We excluded individuals with a previous stroke and attempted to capture incident stroke events and as such our stroke risk of 1.3% per year likely represents an underestimate of the true stroke risk. Misclassification of hemorrhagic transformations with ischemic strokes may have occurred.

In this large population-based cohort study, we found that both eGFR and ACR were associated with and modified the stroke risk in patients with CKD. Atrial fibrillation was consistently associated with a higher stroke risk across all eGFR and ACR levels. Furthermore, the risk is largely attributable to ischemic stroke events. Our findings aid in identifying individuals with a high stroke risk with CKD and underscore the importance of AF as an associated risk factor for stroke.

Authors' Note

This work was presented as an oral abstract at the American Society of Nephrology Annual General Meeting on November 2017 in New Orleans, LA, USA. Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions, and statements expressed in the material are those of the authors and not necessarily those of CIHI.

Acknowledgments

The authors thank Gamma-Dynacare for laboratory data and IMS Brogan Inc for use of their Drug Information Database.

Author Contributions

M.M.S., A.B.E., and T.M.-B. contributed to the study design of the manuscript, which was reviewed and developed further by the rest of the authors. A.B.E. conducted the data analysis. T.M.-B. and M.M.S. drafted the first version of the manuscript. The remaining authors contributed to develop the manuscript draft to its final form.

Ethics Approval and Consent to Participate

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a research ethics board.

Consent for Publication

All authors have given their consent for publication of this article.

Availability of Data and Materials

The data and materials are not available for this study.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.M.S. received investigator-initiated grant funding from Otsuka and CME symposium–related speaker fees from Astrazeneca.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: M.M.S. was supported by the Innovation Fund of the Alternative Funding Plan for the Academic Health Sciences Centers of Ontario. This study was supported by the Institute for Clinical Evaluative Sciences (ICES) Western and Ottawa site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). Core funding for ICES Western is provided by the Academic Medical Organization of Southwestern Ontario (AMOSO), the Schulich School of Medicine and Dentistry (SSMD), Western University, and the Lawson Health Research Institute (LHRI). The research was conducted by members of the ICES Kidney, Dialysis and Transplantation team, at the ICES Ottawa and Western facilities, who are supported by a grant from the Canadian Institutes of Health Research (CIHR). The opinions, results, and conclusions are those of the authors and are independent from the funding sources. No endorsement by ICES, AMOSO, SSMD, LHRI, CIHR, or the MOHLTC is intended or should be inferred. Dr Manish M Sood is supported by the Jindal Research Chair for the Prevention of Kidney Disease. Drs N.N.L. and A.O.M. were both supported by KRESCENT New Investigator Awards. Dr J.-J.C. was supported by the Swedish Heart and Lung Foundation.

ORCID iDs

Amber O. Molnar https://orcid.org/0000-0003-4549-0202

Ngan N. Lam https://orcid.org/0000-0002-0129-7091

Manish M. Sood https://orcid.org/0000-0002-9146-2344

Supplemental Material

Supplemental material for this article is available online.

References

1. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *Lancet*. 2013;382(9888):260-272.
2. Carville S, Wonderling D, Stevens P on behalf of the Guideline Development Group. Early identification and management of chronic kidney disease in adults: summary of updated NICE guidance. *BMJ*. 2014;349:g4507.
3. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart Disease and Stroke Statistics—2017 update: a report from the American Heart Association. *Circulation*. 2017;135(10):e146-e603.
4. Sarnak MJ, Levey AS, Schoolwerth AC, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation*. 2003;108(17):2154-2169.
5. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-988. doi:10.1161/01.str.22.8.983.
6. Dad T, Weiner DE. Stroke and chronic kidney disease: epidemiology, pathogenesis, and management across kidney disease stages. *Semin Nephrol*. 2015;35(4):311-322. doi:10.1016/j.semnephrol.2015.06.003.
7. Keskar V, Sood MM. Use of oral anticoagulation in the management of atrial fibrillation in patients with ESRD: con. *Clin J Am Soc Nephrol*. 2016;11(11):2085-2092. doi:10.2215/CJN.03200316.
8. Keskar V, McArthur E, Wald R, et al. The association of anticoagulation, ischemic stroke, and hemorrhage in elderly adults with chronic kidney disease and atrial fibrillation. *Kidney Int*. 2017;91(4):928-936. doi:10.1016/j.kint.2016.10.017.
9. Jun M, James MT, Manns BJ, et al. The association between kidney function and major bleeding in older adults with atrial fibrillation starting warfarin treatment: population based observational study. *BMJ*. 2015;350. doi:10.1136/bmj.h246.
10. Bonde AN, Lip GYH, Kamper A-L, et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. *J Am Coll Cardiol*. 2014;64(23):2471-2482.
11. Skanes AC, Healey JS, Cairns JA, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. *Can J Cardiol*. 2012;28(2):125-136. doi:10.1016/j.cjca.2012.01.021.
12. Verma A, Cairns JA, Mitchell LB, et al. 2014 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. *Can J Cardiol*. 2014;30(10):1114-1130.
13. Kumar S, de Lusignan S, McGovern A, et al. Ischaemic stroke, haemorrhage, and mortality in older patients with chronic kidney disease newly started on anticoagulation for atrial fibrillation: a population based study from UK primary care. *BMJ*. 2018;360. doi:10.1136/bmj.k342.
14. Molnar AO, Bota SE, Garg AX, et al. The risk of major hemorrhage with CKD. *J Am Soc Nephrol*. 2016:27:2828-2832. doi:10.1681/ASN.2015050535.
15. Piccini JP, Stevens SR, Chang Y, et al. Renal dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R(2)CHADS(2) index in the ROCKET AF (Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation) and ATRIA (AnTicoagulation and Risk factors In Atrial fibrillation) study cohorts. *Circulation*. 2013;127(2):224-232.
16. Lutz J, Menke J, Sollinger D, Schinzel H, Thurmel K. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant*. 2014;29(1):29-40. doi:10.1093/ndt/gft209.
17. Turakhia MP, Blankestijn PJ, Carrero J-J, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Eur Heart J*. 2018:2314-2325. doi:10.1093/eurheartj/ehy060.
18. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Med*. 2015;12(10):e1001885.
19. Jensen PN, Johnson K, Floyd J, Heckbert SR, Carnahan R, Dublin S. Identifying atrial fibrillation from electronic medical data: a systematic review. *Pharmacoepidemiol Drug Saf*. 2012;21(1):141-147.
20. Garg AX, Mamdani M, Juurlink DN, van Walraven C. Identifying individuals with a reduced GFR using ambulatory laboratory database surveillance. *J Am Soc Nephrol*. 2005;16(5):1433-1439. doi:10.1681/ASN.2004080697.
21. Matsushita K, Mahmoodi BK, Woodward M, et al. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA*. 2012;307(18):1941-1951. doi:10.1001/jama.2012.3954.
22. Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data. *Pharmacoepidemiology and Drug Safety*. 2012;21(suppl 1):100-128.
23. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Comm Stat Simulat Comput*. 2009;38(6):1228-1234.
24. Dehejia RH, Wahba S. Propensity score-matching methods for nonexperimental causal studies. *Rev Econ Stat*. 2002;84(1):151-161.
25. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509.
26. Hsu JY, Roy JA, Xie D, et al. Statistical methods for cohort studies of CKD: survival analysis in the setting of competing risks. *Clin J Am Soc Nephrol*. 2017. doi:10.2215/CJN.10301016.

27. Lee M, Saver JL, Chang K-H, Liao H-W, Chang S-C, Ovbiagele B. Low glomerular filtration rate and risk of stroke: meta-analysis. *BMJ*. 2010;341. doi:10.1136/bmj.c4249.
28. Go AS, Fang MC, Udaltsova N, et al. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Circulation*. 2009;119(10):1363-1369.
29. Sandsmark DK, Messé SR, Zhang X, et al. Proteinuria, but not eGFR, predicts stroke risk in chronic kidney disease: Chronic Renal Insufficiency Cohort study. *Stroke*. 2015;46(8):2075-2080.
30. Mahmoodi BK, Yatsuya H, Matsushita K, et al. Association of kidney disease measures with ischemic versus hemorrhagic strokes: pooled analyses of 4 prospective community-based cohorts. *Stroke*. 2014;45(7):1925-1931. doi:10.1161/STROKEAHA.114.004900.
31. Rodriguez-Yanez M, Castellanos M, Blanco M, et al. Micro- and macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke. *Neurology*. 2006;67(7):1172-1177. doi:10.1212/01.wnl.0000238353.89194.08.
32. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *New Engl J Med*. 2011;365(10):883-891.
33. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *New Engl J Med*. 2009;361(12):1139-1151.
34. Ha JT, Neuen BL, Cheng LP, et al. Benefits and harms of oral anticoagulant therapy in chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2019;171(3):181-189. doi:10.7326/M19-0087.
35. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *New Engl J Med*. 2011;365(11):981-992.