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Clinical Research

Are Existing Risk Scores for Nonvalvular Atrial Fibrillation Useful for Prediction or Risk Adjustment in Patients With Chronic Kidney Disease?

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See editorial by Hart et al., pages 211–213 of this issue.

ABSTRACT

Background: Comparative effectiveness studies are common in patients with nonvalvular atrial fibrillation (NVAF) and chronic kidney disease (CKD), but the accuracy of current thromboembolic (n = 4) and bleeding (n = 3) prediction scores used for risk adjustment are uncertain in these patients because previous studies have included few CKD patients.

Methods: This was a retrospective cohort study, using Cox models adjusted for time-varying coefficients, of nonanticoagulated adults with incident NVAF and kidney function (defined into **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes [KDIGO] CKD categories) between 2002 and 2013.

Results: Of 58,451 patients (mean age 66 years, 31.3% with CKD) followed for a median of 31 months, 21.3% died, 12.6% had a thromboembolic event (4.2 per 100 patient-years), and 7.8% had a

RÉSUMÉ

Introduction : Les études d'efficacité comparatives incluant des patients atteints de fibrillation auriculaire non valvulaire (FANV) et de néphropathie chronique (NC) sont relativement fréquentes. Cependant, l'exactitude des scores prévisionnels actuels des événements thromboemboliques (n = 4) et des hémorragies (n = 3) utilisés aux fins d'ajustement du risque demeure incertaine du fait que trop peu de patients atteints de NC ont jusqu'ici participé à des études.

Méthodes : Il s'agissait d'une étude de cohorte rétrospective pour la période comprise entre 2002 et 2013 effectuée à l'aide du modèle de régression de Cox, ajusté en fonction de coefficients variables dans le temps, chez des adultes atteints de FANV et de NC ne recevant pas de traitement anticoagulant (degrés d'insuffisance rénale définis selon la classification fournie dans les lignes directrices **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes [KDIGO]).

NVAF and chronic kidney disease (CKD) are common, often coexist, and the presence of either condition increases the risk for the other.[1-5] NVAF is a known risk factor for stroke, transient ischemic attack (TIA), and/or systemic thromboembolism (hereafter referred to as thromboembolic events).[6] Although individuals with CKD are at higher risk for thromboembolic events than those without CKD, they are also at a higher bleeding risk. Although some studies[2,7,8] suggest CKD is an independent risk factor for thromboembolic and bleeding events in NVAF patients, others[9-12] have reported that adding estimates of kidney function to current prediction scores does not improve prognostication. However, the studies on this topic have been limited by small or highly selected samples and/or reliance on administrative data claims codes or a single serum creatinine measurement to identify CKD. Albuminuria, another marker of kidney function, is associated with adverse outcomes independent of estimated glomerular filtration rate (eGFR)[13] and current guidelines (such as the **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes [KDIGO] CKD categorization)[14] advocate classifying kidney function on the basis of eGFR and extent of albuminuria. Indeed, a recent international consensus conference identified risk prediction in NVAF patients with coexistent CKD as a key priority for future research.[15]

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major bleed (2.6 per 100 patient-years). There were graded associations between kidney function and all-cause mortality (adjusted hazard ratio [aHR], 1.88 [95% confidence interval (CI), 1.79-1.98] for very high vs low risk KDIGO category), major bleeding (aHR, 1.61 [95% CI, 1.47-1.76]), and thromboembolic events (aHR, 1.13 [95% CI, 1.04-1.23]). All 7 prediction scores had significantly poorer c statistics in patients with CKD: 0.50-0.59; all $P < 0.0001$ compared with those with normal kidney function (c statistics 0.69-0.70 for the 4 thromboembolic risk scores and 0.60-0.68 for the 3 bleeding risk scores). Inclusion of KDIGO category did not improve calibration or discrimination statistics for current prediction scores.

Conclusions: Existing NVAF risk scores exhibit poor discrimination in patients with CKD, limiting their utility for clinical decision-making or for risk adjustment in comparative effectiveness studies. Although CKD is an independent risk factor for adverse events, adding KDIGO class to current risk scores did not improve their performance.

Résultats : Des 58 451 patients (âge moyen de 66 ans; 31,3 % des patients atteints de NC) suivis pendant une période médiane de 31 mois, 21,3 % sont décédés, 12,6 % ont été victimes d'un événement thromboembolique (4,2 par 100 années-patients) et 7,8 % ont subi une hémorragie grave (2,6 par 100 années-patients). Une gradation du risque a été établie entre la fonction rénale et la mortalité de toutes causes (rapport de risques instantanés ajustés [RRIa] de 1,88 [intervalle de confiance (IC) à 95 % : 1,79 à 1,98] entre les patients à risque très élevé par rapport à ceux à faible risque selon la classification KDIGO), l'hémorragie grave (RRIa de 1,61 [IC à 95 % : 1,47 à 1,76]) et les événements thromboemboliques (RRIa de 1,13 [IC à 95 % : 1,04 à 1,23]). Comparativement aux patients dont la fonction rénale était normale (statistiques c de 0,69 à 0,70 pour les 4 scores de risque d'événement thromboembolique et de 0,60 à 0,68 pour les 3 scores de risque d'hémorragie), les statistiques c étaient significativement inférieures chez les patients atteints de NC pour l'ensemble des 7 scores prévisionnels, soit 0,50 à 0,59; $P < 0,0001$ pour l'ensemble. L'ajout de la classification KDIGO n'a donc pas permis d'améliorer la calibration ni la discrimination statistique des scores prévisionnels actuels.

Conclusions : Les scores de risque actuellement utilisés pour les patients atteints de FANV ne permettent pas une discrimination statistique efficace chez les patients atteints de NC, ce qui limite leur utilité aux fins de prise de décision en clinique et d'ajustement du risque dans le cadre des études d'efficacité comparatives. On sait que la présence d'une NC constitue un facteur de risque indépendant d'événements indésirables, mais l'ajout de la classification KDIGO aux scores de risque actuellement utilisés n'a pas permis d'améliorer leur utilité.

Because of the paucity of randomized trial data that compared antithrombotic treatment options in NVAF patients with CKD, observational studies are being used to inform this treatment decision. Although multiple comparative effectiveness studies have been done, they have reported conflicting results for the risk/benefit ratio for anticoagulation in patients with CKD—perusal of these studies reveals that they often include different covariates in their multivariate adjustments. Thus, determination of the best risk prediction equations in NVAF patients with CKD would help standardize future comparative effectiveness studies. Although the 7 risk prediction models[7,16-21] listed in Table 1 are endorsed in national and international NVAF guidelines, they were derived in relatively small cohorts (often participants in randomized trials with restricted eligibility criteria) and measures of kidney function were not consistently defined or included. Thus, the generalizability of these scores in real-world populations, and particularly in CKD patients, has been called into question.[22-29]

We designed this study to examine (1) the frequency of thromboembolic and bleeding events across kidney function strata in a large population-based sample of nonanticoagulated NVAF patients; (2) the performance of existing NVAF thromboembolic and bleeding risk scores in patients with CKD; and (3) the incremental predictive value of adding KDIGO CKD category to existing risk scores. To avoid the confounding effect of anticoagulants (because their efficacy might differ across KDIGO categories) and to mimic the usual first step in clinical decision-making for these patients, we focused on anticoagulant-naive patients in this study—those who had not yet started warfarin or any of thrombin or factor X inhibitor treatment.

Methods

Data sources

We conducted a retrospective cohort study using deidentified but linked (using unique health number identifiers) Alberta Health administrative databases cross-linked with laboratory data for all adult residents of Alberta (population 4.4 million people). We received approval from Alberta Health and the Health Research Ethics Boards at the University of Alberta and the University of Calgary for performing analyses on these anonymized data sets without individual signed patient consent.

Study sample

The cohort consisted of all adult Albertans (aged 18 years or older) with a diagnosis of atrial fibrillation (AF) (International Classification of Diseases [ICD], ninth revision [-9] Clinical Modification [-CM] code 427.3 and ICD 10th revision [-10] code I48) between May 1, 2002 and March 31, 2013 in any fields of either the discharge abstract database (which captures all acute care hospitalizations with most responsible diagnosis and up to 24 secondary diagnoses), the national ambulatory care reporting system (which captures all visits to emergency rooms or hospital-based specialist clinics in Alberta), or the physician billing claims databases (see Supplemental Table S1 for case definitions for NVAF and all

Table 1. Characteristics of adult Albertans with incident nonvalvular atrial fibrillation and weighting of the variables included in the current risk prediction scores

Variable	Cohort values (N = 58,451), n (%)	Stroke risk scores					Bleeding risk scores		
		$CHADS_2$	CHA_2DS_2-VASc	R_2CHADS_2	ATRIA stroke		HAS-BLED	$HEMORR_2HAGES$	ATRIA bleed
Maximum score		6	9	71*	15		8†	10‡	10
Median score (IQR)		1 (0-2)	3 (1-4)	26 (18-36)	4 (1-8)		2 (1-2)	2 (1-3)	1 (0-3)
High risk§		≥ 2	≥ 3	≥ 27	≥ 5		≥ 3	≥ 2	≥ 5
KDIGO stage									
Low risk	40,148 (68.7)								
Moderate risk	9369 (16)								
High risk	5801 (9.9)								
Very high risk	3133 (5.4)								
eGFR, mL/min/1.73 m^2									
≥ 60	44,217 (75.6)			0-19					
45-59	8046 (13.8)			23-26					
30-44	4264 (7.3)			26-29	1				
< 30	1924 (3.3)			29	1		1	1	3
Albuminuria									
Low	52,132 (89.2)								
Moderate	3354 (5.7)				1				
High	2965 (5.1)				1				
Previous stroke	6287 (10.8)	2	2	18	Without stroke	With stroke	1	1	
Previous bleed	6540 (11.2)						1	2	1
Age, years									
18-64	27,701 (47.4)					8			
65-74	11,431 (19.6)		1	2	3	7	1		
75-84					5	7			
≥ 75	19,319 (33.1)	1	2	3			1	1	2
≥ 85					6	9			
Female sex	27,380 (46.8)		1	5	1	1			
Alcohol misuse	3248 (5.6)						1	1	
Previous myocardial infarction	6618 (11.3)		1‖	6					
Anemia	14,018 (24.0)							1	3
Heart failure	12,751 (21.8)	1	1	−2	1	1			
Diabetes mellitus	12,644 (21.6)	1	1	4	1	1			
Excessive falling	6000 (10.3)							1	
Hepatic disease	409 (0.7)						1	1	
Hypertension	37,485 (64.1)	1	1	5	1	1	1	1	1
Low platelet count	855 (1.5)							1	
Malignancy	6143 (10.5)							1	
Peripheral vascular disease	2021 (3.5)		1‖	6					

AMI, acute myocardial infarction; ATRIA, **Ant**icoagulation and **R**isk Factors **i**n **A**trial Fibrillation; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); eGFR, estimated glomerular filtration rate; HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (>65 Years), **D**rugs/Alcohol Concomitantly; $HEMORR_2HAGES$, **H**epatic or Renal Disease, **E**thanol Abuse, **M**alignancy, **O**lder (Age > 75 Years), **R**educed Platelet Count or Function, **R**ebleeding Risk, **H**ypertension (Uncontrolled), **A**nemia, **G**enetic Factors, **E**xcessive Fall Risk, and **S**troke; INR, international normalized ratio; IQR, interquartile range; KDIGO, **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes; PAD, peripheral artery disease; R_2CHADS_2, **R**enal Dysfunction, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack.

*There are only a total of 71 points rather than 100 because we have no data on diastolic blood pressure and heart rate. Also we only used participants with incident atrial fibrillation in this part of the study.

†Modified score; does not include labile INRs.

‡Modified to exclude genetic testing as per a previous study.[29]

§High risk is defined as greater than the median annual risk for stroke and ≥ 3% annual risk for bleeding as defined in original manuscripts[16-21] (note that for bleeding scores we collapsed categories into high vs low rather than 3 strata).

‖Maximum of 1 point awarded for either PAD and/or AMI.

covariates/outcomes listed in this report) and an outpatient serum creatinine measured at least once in the 3 months after the index AF date. Patients with a history of mitral or aortic valvular disease, valve surgery (see Supplemental Table S1) or end-stage kidney disease (defined as documented chronic dialysis or previous kidney transplant on the basis of linkage to the Alberta kidney program registries) were excluded (Fig. 1). These NVAF case definitions have been evaluated in multiple studies and in those that used inpatient and outpatient data (as we did); sensitivity approached 95% and specificity 99%.[30-32] We focused on incident cases defined as those without any of the relevant diagnostic codes for NVAF in the previous 5 years. We excluded any patients who started anticoagulant therapy in the first 3 months after the index NVAF diagnosis to remove the confounding effect of anticoagulation (using Blue Cross drug data, supplemented by international normalized ratio (INR) measurements, to identify anticoagulated patients, and we censored follow-up for

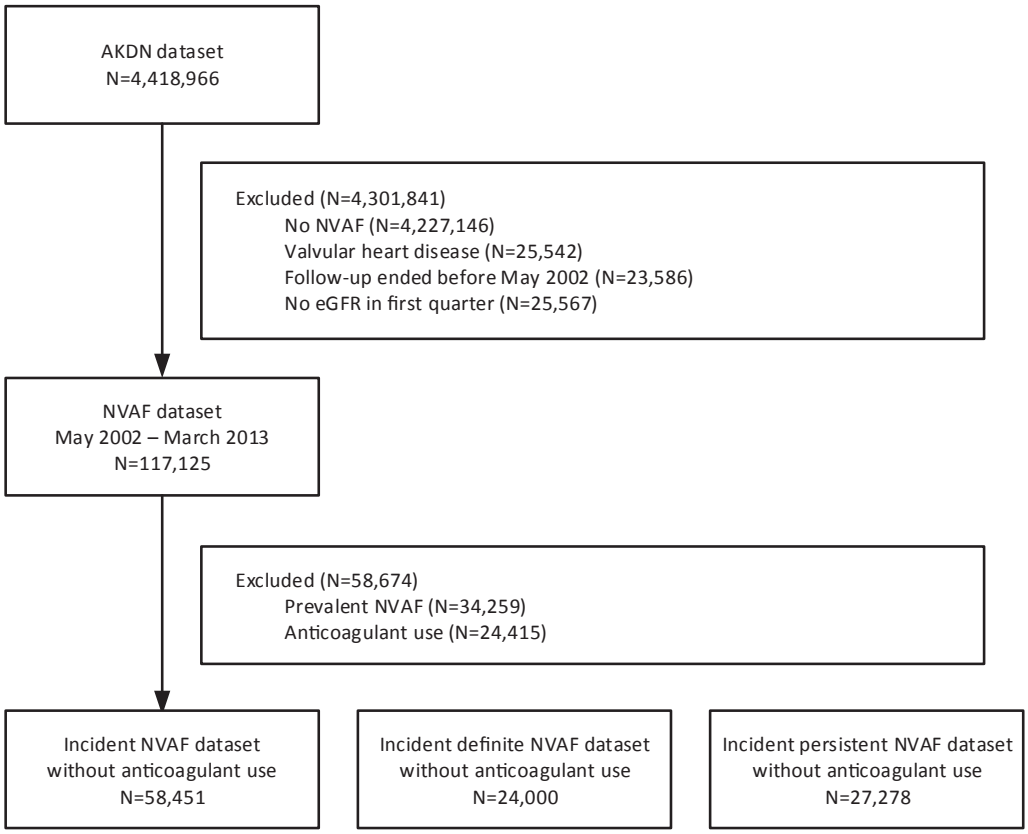

Figure 1. Derivation of study sample. AKDN, Alberta Kidney Disease Network; eGFR, estimated glomerular filtration rate; NVAF, nonvalvular atrial fibrillation.

other patients when they started anticoagulant treatment). As per previous studies,[1,31] we defined a case as being "definite NVAF" if the patient had at least 2 encounters with the health care system within 1 year and at least 30 days apart at which a code of NVAF was recorded. We also evaluated a third literature-based case definition of "persistent NVAF" defined as 2 time-distinct hits in any of the administrative databases at least 7 days apart and within 1 year. For all 3 NVAF case definitions, the index date was defined as the date of the first AF code in the discharge abstract database, national ambulatory care reporting system, or physician billing claims databases.

Kidney function assessments

We used both eGFR (calculated using the CKD-epidemiology equation, as recommended by the international KDIGO guidelines[14]) and albuminuria assessment to categorize patients as being KDIGO low, moderate, high, or very high risk stage for each calendar quarter.[14] eGFR was calculated using the mean outpatient serum creatinine measurement in each quarter and categorized as < 30, 30-44, 45-59, or ≥ 60 mL/min.1.73 m^2. Quarterly median albuminuria was ascertained in participants who had results of dipstick urinalysis, albumin:creatinine ratio (ACR), or protein:creatinine ratio (PCR). We defined albuminuria on the basis of the KDIGO definition as: normal or mild (ACR < 3 mg/mmol, PCR < 15 mg/mmol or negative dipstick), moderate (ACR 3-30 mg/mmol or PCR 15-50 mg/mmol or trace/1+), or severe (ACR > 30 mg/mmol or PCR > 50 mg/mmol or 2+ on dipstick). Patients with absent albuminuria values (25% of our study sample's quarters) were modelled as having no albuminuria (dummy indicator variable) for the main analyses, but in sensitivity analyses we (1) modelled "missing albuminuria" as a category to see if the coefficient differed significantly from no albuminuria before collapsing the groups and (2) imputed 20 values for each missing albuminuria using the predictors eGFR category, sex, heart failure, diabetes mellitus, hypertension, and anemia (variables chosen because they had t statistics > 10 in a simple baseline regression model).

Classification of anticoagulant exposure

We supplemented the Blue Cross medication data (mostly available in participants 65 years of age and older) with INR measurements to improve ascertainment of patients younger than 65 years of age who were taking anticoagulation medication. We used availability of 2 or more outpatient INRs during a single calendar quarter as a marker for probable anticoagulant use.

Covariates and outcomes

As per our previous work, we identified comorbidities using the ICD-9-CM or ICD-10-CA codes validated in administrative databases (see Supplemental Table S1 for details of ICD-9-CM and ICD-10 coding algorithms, previously

Table 2. Overall number of events, rate, and unadjusted hazard ratio (with 95% confidence intervals) for outcomes in adult Albertans with nonvalvular atrial fibrillation who are anticoagulant-naive (N = 58,451)

Variable	All-cause mortality	Thromboembolic event	Stroke	TIA	Systemic embolism	Major bleeding event
Number of events	12,428	7340	5620	2555	611	4625
Rate per 100 person-years	6.57	4.22	3.15	1.40	0.33	2.57
KDIGO stage						
Low risk	1.00	1.00	1.00	1.00	1.00	1.00
Moderate risk	1.99 (1.89-2.09)	1.56 (1.47-1.66)	1.60 (1.49-1.71)	1.69 (1.53-1.86)	1.19 (0.96-1.48)	1.65 (1.52-1.78)
High risk	3.66 (3.49-3.84)	2.02 (1.90-2.16)	2.07 (1.92-2.23)	1.94 (1.74-2.17)	1.58 (1.25-1.99)	2.37 (2.18-2.57)
Very high risk	6.94 (6.62-7.27)	2.64 (2.45-2.85)	2.79 (2.56-3.03)	2.29 (2.01-2.61)	1.93 (1.47-2.54)	3.83 (3.51-4.17)
Albuminuria						
Low	1.00	1.00	1.00	1.00	1.00	1.00
Moderate	1.34 (1.26-1.42)	1.05 (0.97-1.14)	1.03 (0.93-1.13)	1.21 (1.06-1.37)	1.11 (0.85-1.46)	1.31 (1.20-1.45)
High	2.99 (2.85-3.13)	1.52 (1.41-1.64)	1.63 (1.50-1.78)	1.27 (1.10-1.45)	1.46 (1.12-1.91)	2.39 (2.20-2.59)
eGFR, mL/min/1.73 m^2						
$\geq$ 60	1.00	1.00	1.00	1.00	1.00	1.00
45-59	2.23 (2.13-2.34)	1.91 (1.80-2.03)	1.92 (1.80-2.06)	2.04 (1.85-2.25)	1.17 (0.93-1.47)	1.81 (1.68-1.96)
30-44	3.96 (3.77-4.15)	2.37 (2.20-2.54)	2.37 (2.18-2.57)	2.33 (2.06-2.62)	1.80 (1.40-2.32)	2.53 (2.32-2.76)
< 30	8.19 (7.76-8.64)	3.13 (2.84-3.45)	3.37 (3.03-3.75)	2.40 (2.00-2.88)	2.05 (1.41-2.96)	4.03 (3.61-4.50)

eGFR, estimated glomerular filtration rate; KDIGO, **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes; TIA, transient ischemic attack.

validated in other populations, with look-back beginning in April 1994),[32,33] rural/urban residence, and postal code income quintile using the Statistics Canada Postal Code Conversion file. The thromboembolic outcome included any stroke (ischemic or hemorrhagic, and whether hospitalized or not), TIA, and systemic embolism. Our major bleeding outcome included "any bleed requiring emergency department visit or hospitalization, intracranial hemorrhage, or gastrointestinal bleeding" using a standard case definition used by multiple studies in the literature, including a recent Canadian study.[34]

Choice of thromboembolic and bleeding risk scores

We chose the 7 risk prediction models[7,16-21] listed in Table 1 because they are endorsed in national and international NVAF guidelines and are the ones most frequently used in the literature. Details on how to tabulate each of the scores is provided in Table 1.

Follow-up

We followed all study participants from the time they met the NVAF case definition until they started anticoagulant therapy, they left the province, their first clinical event (stroke/TIA/systemic embolism/major bleeding event or death depending on particular objective), they initiated some form of renal replacement therapy, or March 31 2013—whichever came first.

Statistical analysis

In addition to reporting crude rates for the outcomes (all-cause mortality, thromboembolic events, and major bleeding events) in each kidney function stratum, we determined the

Table 3. Number of events, rate, and adjusted hazard ratio for outcomes in adult Albertans with nonvalvular atrial fibrillation who are anticoagulant-naive (N = 58,451)

	All-cause mortality		Thromboembolic events		Major bleeding	
Variable	Events (rate)*	Adjusted HR (95% CI)	Events (rate)*	Adjusted HR (95% CI)	Events (rate)*	Adjusted HR (95% CI)
KDIGO stage						
Low risk	4577 (3.64)	1.00	3854 (3.27)	1.00	2214 (1.83)	1.00
Moderate risk	2333 (7.23)	1.03 (0.98-1.09)	1484 (5.12)	0.99 (0.93-1.05)	916 (3.02)	1.14 (1.06-1.24)
High risk	2678 (13.34)	1.45 (1.37-1.52)	1170 (6.64)	1.09 (1.01-1.17)	800 (4.33)	1.35 (1.24-1.47)
Very high risk	2840 (25.28)	1.88 (1.79-1.98)	832 (8.67)	1.13 (1.04-1.23)	695 (7.01)	1.61 (1.47-1.76)
Albuminuria						
Low risk	8852 (5.59)	1.00	5947 (4.06)	1.00	3471 (2.29)	1.00
Moderate risk	1284 (7.48)	1.04 (0.98-1.10)	655 (4.26)	0.90 (0.83-0.98)	482 (3.01)	1.07 (0.97-1.18)
High risk	2292 (16.71)	1.65 (1.57-1.73)	738 (6.18)	1.06 (0.98-1.15)	672 (5.48)	1.50 (1.38-1.64)
eGFR, mL/min/1.73m^2						
$\geq$ 60	6100 (4.20)	1.00	4531 (3.34)	1.00	2788 (2.00)	1.00
45-59	2389 (9.38)	0.96 (0.91-1.01)	1438 (6.39)	1.05 (0.99-1.12)	864 (3.63)	1.13 (1.04-1.22)
30-44	2214 (16.60)	1.22 (1.15-1.28)	917 (7.92)	1.07 (0.99-1.16)	619 (5.06)	1.25 (1.14-1.37)
< 30	1725 (34.37)	1.94 (1.83-2.05)	454 (10.51)	1.27 (1.15-1.41)	354 (8.07)	1.50 (1.33-1.68)

Adjusted for age (18-64, 65-74, and $\geq$ 75 years), sex, Aboriginal status, social assistance, postal code income quintile, previous thromboembolic event (or previous bleeding event for the outcome bleeding events), and comorbidities. All comorbidities listed in Table 1 were included in the all-cause mortality model. Only the comorbidities included in comparative scores were included in the thromboembolic event and the bleed event models, respectively.

CI, confidence interval; eGFR estimated glomerular filtration rate; HR, hazard ratio; KDIGO, **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes.

*Rate per 100 person-years.

Table 4. Calibration and discrimination statistics for thromboembolic risk scores in nonanticoagulated patients

	$CHADS_2$	CHA_2DS_2-VASc	R_2CHADS_2	ATRIA stroke	$CHADS_2$ KDIGO	$CHADS_2$ Alb	$CHADS_2$ eGFR
Calibration slope	-	-	-	-	1.616 (1.570-1.662)	3.748 (3.684-3.812)	1.455 (1.414-1.496)
Sensitivity	80.3	82.5	80.0	81.1	72.6	82.1	69.3
Specificity	52.4	49.6	51.1	52.4	57.5	48.8	64.0
PPV	10.4	10.1	10.1	10.5	10.5	9.94	11.7
NPV	97.5	97.6	97.4	97.6	96.8	97.5	96.8
C-statistic (95% CI)	0.663	0.661	0.656	0.667	0.650	0.654	0.666
	(0.652-0.675)	(0.649-0.672)	(0.644-0.667)	(0.656-0.679)	(0.638-0.663)	(0.643-0.666)	(0.653-0.680)
NRI (95% CI)	ref	−0.0054	−0.0150	0.0082	−0.0255	−0.0178	0.0062
		(−0.0213 to 0.0105)	(−0.0363 to 0.0063)	(−0.0100 to 0.0264)	(−0.0491 to −0.0019)	(−0.0256 to 0.0282)	(−0.0171 to 0.0295)

The $CHADS_2$ KDIGO score assigned 7 points for very high risk, 5 points for high risk, 3 points for moderate risk, and 0 points for low risk for a maximum of 13 points (high risk is ≥ 3 points). The $CHADS_2$ Alb score assigned 3 points for high risk, 1 points for moderate risk, and 0 points for low risk for a maximum of 9 points (high risk is ≥ 2 points). The $CHADS_2$ eGFR score assigned 7 points for < 30 mL/min/1.73 m^2, 5 points for 30-44 mL/min/1.73 m^2, 4 points for moderate 45-59 mL/min/1.73 m^2, and 0 points for ≥ 60 mL/min/1.73 m^2 for a maximum of 13 points (high risk is ≥ 3 points).

Alb, albuminuria; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); CI, confidence interval; eGFR, estimated glomerular filtration rate; NPV, negative predictive value; NRI, net reclassification index; PPV, positive predictive value.

independent association between kidney function and outcomes during follow-up after controlling for factors that might influence this relation using multivariable Cox regression with time varying covariates (varying each quarter for each variable where relevant: age [18-64, 65-74, 75 years or older], sex, Aboriginal status, social assistance, postal code income quintile, rural/urban status, previous thromboembolic event, or previous bleeding event [as relevant], and any comorbidities included in scores predicting that type of event). All comorbidities were included in the all-cause mortality adjusted model. Unadjusted and adjusted hazard ratios with 95% confidence intervals (CIs) are reported. We determined that the proportional hazard assumption was satisfied by examining plots of the log-negative-log of within-group survivorship probabilities vs log-time.

The data set was evenly divided randomly into a training data set and a validation data set. Using the training data set, we regressed the thromboembolic events against the kidney function categorizations (1 at a time) and constrained the variables from **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) to their preset coefficient values (Table 1).[35] We mapped the coefficients of the kidney categories using their relative sizes to simplified integer score values following the method of Sullivan et al.[36] Using the validation data set, we calculated the scores of $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc), **R**enal Dysfunction, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack (R_2CHADS_2), **An**ticoagulation and **R**isk Factors **i**n **A**trial Fibrillation (ATRIA) Stroke, and the new scores: $CHADS_2$ KDIGO, $CHADS_2$ Albuminuria, and $CHADS_2$ eGFR (we chose the $CHADS_2$ as the baseline model for stroke prediction because it had the highest c statistic in patients without CKD). Calibration was assessed by plotting 1-year observed risk against 1-year predicted risk using a Lowess curve in a figure, and by regressing predicted risk on observed risk. For discrimination and calibration statistics, we used per annum risk categories: 0-2% for low risk and ≥ 3% for high risk in bleeding events—on the basis of consensus in the literature and guidelines for anticoagulant use with the existing risk prediction models.[17-26] For thromboembolic events, we used less than the median for low risk and greater than or equal to the median to define high risk.

For each of the 7 risk prediction scores, we assessed discrimination by calculating sensitivity, specificity, positive predictive value, negative predictive value, and c statistic, and changes from the baseline models after adding KDIGO stage were assessed using the **N**et **R**eclassification **I**mprovement (NRI) index. The incremental value of including kidney function was examined in reclassification tables using 1-year predicted risks; observed risks were included in these tables. Similarly we modified the **H**epatic or Renal Disease, **E**thanol Abuse, **M**alignancy, **O**lder (Age > 75 Years), **R**educed Platelet Count or Function, **R**ebleeding Risk, **H**ypertension (Uncontrolled), **A**nemia, **G**enetic Factors, **E**xcessive Fall Risk, and **S**troke ($HEMORR_2HAGES$) score (which had the best c statistic in patients without CKD) by adding the kidney function categorizations (1 at a time) and compared these new scores using the NRI index.

Table 5. Calibration and discrimination statistics for major bleeding events in nonanticoagulated patients

	HAS-BLED	$HEMORR_2HAGES$	ATRIA bleed	$HEMORR_2HAGES$ KDIGO	$HEMORR_2HAGES$ Alb	$HEMORR_2HAGES$ eGFR
Calibration slope (95% CI)	-	-	-	1.495 (1.468-1.523)	1.473 (1.448-1.499)	1.433 (1.109-1.458)
Sensitivity	40.2	82.0	38.4	55.2	46.9	52.3
Specificity	83.3	49.9	86.3	76.6	81.4	78.6
PPV	7.49	5.22	8.59	7.33	7.81	7.58
NPV	97.6	98.8	97.7	98.1	97.9	98.0
C-statistic (95% CI)	0.618 (0.598-0.637)	0.660 (0.644-0.675)	0.623 (0.604-643)	0.659 (0.639-678)	0.641 (0.622-0.661)	0.654 (0.635-0.674)
NRI (95% CI)	−0.0841 (−0.1226 to −0.0456)	Reference	−0.0724 (−0.1110 to −0.0338)	−0.0017 (−0.0355 to 0.0321)	−0.0363 (−0.0718 to −0.0008)	−0.0106 (−0.0451 to 0.0239)

The $HEMORR_2HAGES$ KDIGO score assigned 2 points for very high risk, 1 point for high or moderate risk, and 0 points for low risk for a maximum of 13 points (high risk is ≥ 4 points). The $HEMORR_2HAGES$ Alb score assigned 2 points for high risk, 1 point for moderate risk, and 0 points for low risk for a maximum of 13 points (high risk is ≥ 4 points). The $HEMORR_2HAGES$ eGFR score assigned 2 points for < 30 mL/min/1.73 m^2, 1 point for 30-44 mL/min/1.73 m^2, or 45-59 mL/min/1.73 m^2, and 0 points for ≥ 60 mL/min/1.73 m^2 for a maximum of 13 points (high risk is ≥ 4 points).

Alb, albuminuria; ATRIA, **A**nticoagulation and **R**isk Factors **i**n **A**trial Fibrillation; eGFR, estimated glomerular filtration rate; CI, confidence interval; HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly; $HEMORR_2HAGES$, **H**epatic or Renal Disease, **E**thanol Abuse, **M**alignancy, **O**lder (Age > 75 Years), **R**educed Platelet Count or Function, **R**ebleeding Risk, **H**ypertension (Uncontrolled), **A**nemia, **G**enetic Factors, **E**xcessive Fall Risk, and **S**troke; KDIGO, **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes; NPV, negative predictive value; PPV, positive predictive value.

Results

The 58,451 anticoagulant-naive patients with incident NVAF in our cohort (mean age 66 years, 47% female) had a high burden of comorbidities (Table 1). During follow-up (median 31 months; interquartile range, 13-59), 7340 patients (12.6%) had a thromboembolic event and 4625 (7.8%) had a major bleed for annualized rates of 4.2 thromboembolic events and 2.6 major bleeds per 100 patient-years.

Frequency of events across kidney function strata

Kidney dysfunction, whether defined on the basis of eGFR alone, the presence of albuminuria alone, or the KDIGO staging system was associated with elevated risk of all-cause mortality, thromboembolic events, or bleeding (Table 2), even after adjustment (Table 3). These hazard ratios were of similar magnitude when we restricted the analysis to the 24,000 individuals who met our definition for definite NVAF or the 27,278 individuals who met our definition for persistent NVAF (data available on request).

Performance of existing scores

Examination of the calibration and discrimination statistics for thromboembolic events (Table 4) and major bleeds (Table 5) revealed that, in our cohort, the thromboembolic risk scores did not perform differently from each other (the NRIs were not significantly different and all c statistics were 0.66) but that $HEMORR_2HAGES$ was the best of the bleeding risk scores (c statistic, 0.66). Analyzing the performance of the 7 established risk prediction scores across the 4 strata of KDIGO categories revealed that all scores performed significantly better for patients with normal kidney function than in patients with CKD (Table 6), and performance significantly worsened as severity of kidney disease increased.

Incremental value of adding KDIGO CKD category to existing scores

The addition of KDIGO class to $CHADS_2$ or replacement of eGFR in the $HEMORR_2HAGES$ score with KDIGO class did not improve either model's discrimination or calibration (none of the NRI were statistically significant). None of these enhanced scores were overfit; all calibration slopes were > 1 (data not shown)—we do not show reclassification tables because the new scores did not improve the prediction. When we modelled missing albuminuria as a separate variable, rather than classifying patients without albumin measurements as low risk, and when we used multiple imputation for the missing albuminuria measures, our findings did not change (data not shown).

Discussion

In this large, population-based study of newly diagnosed anticoagulant-naive NVAF patients, we found that kidney dysfunction is an independent risk factor for thromboembolic and bleeding events with graded risk across KDIGO categories. We also found that the current risk scores perform substantially less well in patients with more advanced kidney disease, but adding KDIGO class to established NVAF risk scores did not improve their predictive value in our cohort.

Table 6. Area under the curve (and 95% confidence intervals) for each established risk stratification scheme according to degree of chronic kidney disease

Risk score	KDIGO low risk	KDIGO moderate risk	KDIGO high risk	KDIGO very high risk	*P* Value for trend	KDIGO moderate to very high risk	*P* value compared with KDIGO low risk
Thromboembolic events							
$CHADS_2$	0.699 (0.682-0.716)	0.578 (0.552-0.604)	0.563 (0.543-0.584)	0.527 (0.502-0.552)	< 0.0001	0.567 (0.553-0.582)	< 0.0001
CHA_2DS_2-VASc	0.694 (0.678-0.710)	0.582 (0.560-0.605)	0.562 (0.540-0.583)	0.536 (0.517-0.555)	< 0.0001	0.569 (0.556-0.582)	< 0.0001
R_2CHADS_2	0.690 (0.673-0.708)	0.566 (0.548-0.584)	0.549 (0.528-0.571)	0.501 (0.500-0.503)	< 0.0001	0.549 (0.538-0.560)	< 0.0001
ATRIA Stroke	0.698 (0.681-0.715)	0.588 (0.565-0.611)	0.575 (0.555-0.595)	0.532 (0.515-0.548)	< 0.0001	0.576 (0.563-0.589)	< 0.0001
Bleeding events							
HAS-BLED	0.605 (0.579-0.630)	0.566 (0.522-0.610)	0.587 (0.533-0.641)	0.566 (0.522-0.611)	0.32	0.602 (0.573-0.631)	0.90
$HEMORR_2HAGES$	0.678 (0.653-0.702)	0.619 (0.590-0.649)	0.557 (0.521-0.593)	0.514 (0.492-0.536)	< 0.0001	0.584 (0.567-0.601)	< 0.0001
ATRIA Bleed	0.601 (0.577-0.625)	0.563 (0.521-0.606)	0.592 (0.538-0.646)	0.585 (0.544-0.625)	0.51	0.614 (0.585-0.643)	0.49

ATRIA, **A**nticoagulation and **R**isk Factors **i**n **A**trial Fibrillation; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); KDIGO, **K**idney **D**isease: **I**mproving **G**lobal **O**utcomes; R_2CHADS_2, **R**enal Dysfunction, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack.

These findings suggest that current NVAF risk scores are inadequate for use in people with CKD, either for bedside clinical decision-making or in comparative effectiveness studies.

Our finding that kidney dysfunction increases the risk of thromboembolic and bleeding events is not surprising because CKD is known to be associated with increased arterial stiffness and activation of various prothrombotic and inflammatory pathways including increased levels of C-reactive protein, interleukin-6 plasminogen activator inhibitor-1, and von Willebrand factor, and abnormal levels of fibrinogen, fibrinopeptide A, thromboplastin, and factors VII-XII. Moreover, individuals with CKD often have comorbid conditions (such as hypertension, diabetes, or heart failure) that are also known to increase these risks.

Our findings that all 4 thromboembolic risk scores had similar performance metrics in patients with normal kidney function (with c statistics between 0.69 and 0.70) but significantly poorer metrics in patients with CKD helps explain the differences in c statistics for the scores in NVAF cohort studies in which underlying proportions of patients with CKD vary. For example, a recent report from the United Kingdom primary care database[37] of 60,594 non-anticoagulated patients with NVAF (only 2.9% of the United Kingdom patients had proteinuria whereas 10.8% of our cohort did) reported higher c statistics of 0.70 (95% CI, 0.69-0.71) for the ATRIA Stroke score and 0.68 (95% CI, 0.67-0.69) for $CHADS_2$ than the results in our cohort. However, the cohort[21] used to derive the ATRIA Stroke score had a higher proportion of patients with CKD than ours (35.8% had an eGFR < 60 and 15.2% had proteinuria) and reported a c statistic of only 0.58 (95% CI, 0.57-0.59) for the CHA_2DS_2-VASc score (ours was 0.66; 95% CI, 0.65-0.67). Although we found that $HEMORR_2HAGES$ provided the best discrimination for predicting risk of major bleeding in our cohort, it was only slightly better than the less complicated scoring systems and all 3 bleeding risk scores showed only modest performance. Although the c statistics for bleeding scores range widely in the literature, our results are very similar to those reported from the Swedish Atrial Fibrillation cohort,[29] which is demographically similar to our study population.

A distinct strength of our study is that we were able to link inpatient and outpatient administrative data, prescribing data, and laboratory data to examine outcomes for anticoagulant-naive NVAF patients whether they were treated in hospital, in emergency rooms, or in outpatient physician clinics. We have previously shown that comorbidity profiles, risk assessments, and treatment patterns differ greatly for NVAF patients in each of these settings,[1] and previous studies on this topic have either focused solely on patients with NVAF detected in hospital or in outpatient clinics. Although there are ongoing patient registries for NVAF, these are subject to substantial selection bias: for example, the **O**utcomes **R**egistry for **B**etter **I**nformed **T**reatment of **A**trial **F**ibrillation (ORBIT-AF) registry in the United States recruits largely from specialized cardiology and electrophysiology clinics (< 20% of participants are from primary care) and preliminary results[38] reveal demographic and treatment patterns substantially different from those seen in population-based studies in NVAF. Moreover, all previous studies (with the exception of

the ATRIA Bleeding score derivation study) have only examined kidney function at baseline whereas we conducted time-varying analyses to incorporate changes in renal function over time. The major issue with our study is the lack of data on over the counter acetylsalicylic acid or nonsteroidal anti-inflammatory drug (NSAID) use by study participants, a common flaw in this literature. However, NSAID use is uncommon among CKD patients because nephrologists actively discontinue these medications. Furthermore, a recent observational study using primary care medical records with full access to information about over the counter medication use showed that there was no association between the use of acetylsalicylic acid or NSAIDs and stroke outcomes (adjusted hazard ratio, 0.97; 95% CI, 0.90-1.04).[37] It should also be acknowledged that our *a priori* decision to focus on anticoagulant-naive patients (reflecting our interest in the point of initial clinical decision-making) resulted in lower rates of bleeding than would be seen in anticoagulated patients. Because the HEMORR$_2$HAGES and ATRIA Bleed scores were developed in anticoagulated patients, and the **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED) derivation cohort had a mix of anticoagulated and nonanticoagulated patients, we conducted a post hoc analysis of the 24,451 patients we excluded from this analysis because they were already receiving anticoagulants; this revealed higher bleeding rates (5.5 per 100 person-years) than in our anticoagulant-naive patients (2.6 bleeds per 100 person-years), but the c statistics for all 3 scores were lower (between 0.562 and 0.591) in anticoagulated patients than we observed (0.618-0.660) in anticoagulant-naive patients.

In conclusion, our findings have clarified the interplay between CKD and outcomes in NVAF and help inform future comparative effectiveness studies. KDIGO identified risk prediction in NVAF patients with coexistent CKD as a key priority for future research[15] and a recent editorial[39] highlighted the omission of renal function from most current NVAF risk scores and the need to address the paucity of research on this topic. Indeed, our data show that current widely used prediction scores for thromboembolic and bleeding events perform poorly in patients with any degree of CKD (KDIGO categories above low risk), highlighting the need for better risk prediction scores in NVAF patients with CKD. In the meantime, our study emphasizes the importance of conducting comparative effectiveness studies in NVAF strata defined according to KDIGO CKD categories.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2016.08.018.