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Renal Impairment and Ischemic Stroke Risk Assessment in Patients With Atrial Fibrillation

The Loire Valley Atrial Fibrillation Project

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Objectives This study sought to determine the risk of ischemic stroke (IS)/thromboembolism (TE) associated with renal impairment and its incremental predictive value over established risk stratification scores (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke [$CHADS_2$] and congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74 years, sex category (female) [CHA_2DS_2-VASc]) in patients with atrial fibrillation (AF).

Background Risk stratification schemes for prediction of IS/TE in patients with AF are validated but do not include renal impairment.

Methods Patients diagnosed with nonvalvular AF and available estimated glomerular filtration rate (eGFR) data in a 4-hospital institution between 2000 and 2010 were identified. The study population was stratified by renal impairment defined by serum creatinine level and by eGFR measured at time of diagnosis of AF. Independent risk factors of IS/TE (including renal impairment) were investigated in Cox regression models. The incremental predictive value of renal impairment over $CHADS_2$ and CHA_2DS_2-VASc were assessed with the c-statistic, net reclassification improvement, and integrated discrimination improvement. We focused on the 1-year outcomes in our analyses.

Results Of 8,962 eligible individuals, 5,912 (66%) had nonvalvular AF and available eGFR data. Renal impairment by both creatinine and eGFR definitions was associated with higher rates of IS/TE at 1 year, compared with normal renal function. After adjustment for $CHADS_2$ risk factors, renal impairment did not significantly increase the risk of IS/TE at 1 year (hazard ratio: 1.06; 95% confidence interval [CI]: 0.75 to 1.49 for renal impairment; and hazard ratio: 1.09; 95% CI: 0.84 to 1.41 for eGFR). When renal impairment was added to existing risk scoring systems for stroke/TE ($CHADS_2$ and CHA_2DS_2-VASc), it did not independently add to the predictive value of the scores, whether defined by serum creatinine level or eGFR. This was evident even when the analysis was confined to only those patients with at least 1 year of follow-up.

Conclusions Renal impairment was not an independent predictor of IS/TE in patients with AF and did not significantly improve the predictive ability of the $CHADS_2$ or CHA_2DS_2-VASc scores. (J Am Coll Cardiol 2013;61:2079–87)
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Both atrial fibrillation (AF) and chronic kidney disease (CKD) are increasingly recognized as significant burdens of morbidity and mortality of global proportions (1–11). Even mild renal impairment has long-term consequences for cardiovascular health outcomes (5–7). Individuals with CKD are more likely to develop AF (12,13) and ischemic stroke (IS)/thromboembolism (TE) (14) than patients with normal renal function. In a recent Danish prospective study

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Abbreviations and Acronyms

AF = atrial fibrillation

$CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke

CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74 years, sex category (female)

CI = confidence interval

CKD = chronic kidney disease

eGFR = estimated glomerular filtration rate

HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitantly

HR = hazard ratio

IDI = integrated discrimination improvement

IS = ischemic stroke

NRI = net reclassification improvement

OAC = oral anticoagulation

TE = thromboembolism

VKA = vitamin K antagonist

of 132,372 individuals with AF, 3,587 individuals had CKD, which was associated with increased risk of IS/TE and bleeding (15), confirming observations of previous smaller studies (14,16,17). This study also showed the benefit of vitamin K antagonist (VKA) therapy on IS/TE outcomes in the setting of CKD, although both VKA and aspirin were associated with an increased risk of bleeding (15).

Renal function is quantified by urinary creatinine clearance or by the estimated glomerular filtration rate (eGFR) (18–20), but few studies have considered the association between eGFR and long-term outcomes in individuals with AF, and existing studies have tended to consider renal function as a dichotomous variable (2–4,14). Also, patients with renal failure have been excluded from randomized trials of IS prevention in AF.

The importance of risk prediction tools for IS/TE (congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke [$CHADS_2$] [21]; and congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65 to 74 years, sex category (females) [CHA_2DS_2-VASc] [22]) in prognosis and treatment planning in AF patients is recognized by their inclusion in major international guidelines (23,24). Renal failure is included as a dichotomous variable in risk prediction tools for bleeding but not included in risk prediction tools for IS/TE (25–27), although the possibility of adding renal impairment (as the little "c") to the CHA_2DS_2-VASc score has been previously proposed (28,29). In a small study of selected AF patients post-catheter ablation, renal dysfunction—defined by eGFR <60 ml/min/1.73 m^2—independently increased the risk of TE (hazard ratio [HR]: 6.8; 95% confidence interval [CI]: 4.2 to 12.1) (30). Therefore, better understanding of the impact of renal function on IS/TE outcomes in a more representative "real-world" population of AF patients is required.

The present study represents the first analysis to consider the association between renal function, as measured by serum creatinine level or eGFR, and the risk of IS/TE events in a "real-world" population of individuals with AF, unrestricted by age or comorbidity. We also investigated the incremental predictive value of adding renal function to established IS risk scores in AF ($CHADS_2$ and CHA_2DS_2-VASc).

Methods

Study population. The methods of the Loire Valley Atrial Fibrillation Project have been previously reported (31). Patients were followed from the first record of AF after January 1, 2000 (i.e., index date) up to the latest data collection at the time of study (December 2010) (see the Methods section in the Online Appendix). Treatment at discharge was obtained by screening hospital stay reports, and information on comorbidities was obtained from the computerized coding system. Patients were excluded from the study if there were no available data with regard to the baseline serum creatinine level at the time of first diagnosis of AF (Fig. 1). For each patient, the $CHADS_2$ (21); CHA_2DS_2-VASc (22); and hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs/alcohol concomitantly (HAS-BLED) (25) scores were calculated (Table 1).

Assessment of renal function. Serum creatinine levels were taken at baseline, which was at first diagnosis of AF. Index date was the time of the first record of AF and thus the serum creatinine (and hence eGFR) measurement was from that index date.

Renal impairment was defined as reported history of renal failure or baseline serum creatinine level of >133 μmol/l in men and >115 μmol/l in women (32). To convert serum creatinine from μmol/l to mg/dl, the former was multiplied by a conversion factor of 88.4. Current consensus guidelines state that prediction equations have greater consistency and accuracy than serum creatinine in the assessment of GFR (18–20,33–35). In addition, prediction equations are equivalent or better than 24-h urine creatinine clearance in all but 1 study (19,20,36). The eGFR (ml/min/1.73 m^2) was calculated (see the Methods section in the Online Appendix).

Outcomes. During follow-up, information on outcomes of TE (including peripheral artery embolism and transient ischemic attack), stroke (ischemic or hemorrhagic), bleeding, and all-cause mortality were recorded. In this study, the outcome of interest was IS/TE. Hemorrhagic strokes were excluded in our analyses.

Statistical analysis. The study population was stratified into 3 categories according to eGFR (in ml/min/1.73 m^2), corresponding to the stages of CKD: ≥60, 30 to 59, and <30 (Fig. 1) (18–20). Because data with regard to proteinuria were not available, stage of renal impairment could not be defined. Baseline characteristics were determined separately for the 3 eGFR strata, and differences were investigated with the chi-square test for categorical covariates and the Kruskal-Wallis test for continuous covariates. Baseline characteristics were also determined by the presence or absence of renal impairment and then further stratification by eGFR.

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