



Does CHA2DS2-VASc score predict mortality in chronic kidney disease?

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Abstract

Chronic kidney disease (CKD) is a leading cause of morbidity and mortality worldwide. Assessment of cardiovascular (CV) and all-cause mortality in CKD patients is of particular importance. CHA2DS2-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke, vascular disease, age 65–74 years, and sex) score was originally formulated to predict the annual thromboembolic risk in patients with nonvalvular atrial fibrillation (AF). The calculation of R2CHADS2 and R2CHA2DS2VASc scores awarded an additional 2 points for CrCl < 60 mL/min and GFR < 60 mL/min/1.73 m². Recent studies have investigated whether CHA2DS2-VASc and R2CHADS2 \pm VASc scores could be used to predict CV or all-cause mortality in patients with CKD. CHA2DS2-VASc score was proven to be a significant predictor of CV and all-cause mortality in CKD patients, and a higher CHA2DS2-VASc score was associated with increased mortality. These findings are quite promising, and they may help physicians to identify high-risk groups in this population.

Keywords CHA2DS2-VASc · Chronic kidney disease · Mortality

Introduction

Chronic kidney disease: epidemiology and definition

Chronic kidney disease (CKD) has been recognized as a leading cause of morbidity and mortality worldwide [1]. The global estimated prevalence of CKD is 13.4% [2] and has been almost doubled over the last three decades due to the decrease in mortality from cardiovascular (CV) and infectious diseases, as well as the population's progressive aging [1]. According to international guidelines, CKD is diagnosed if one or both of the following two criteria are met for at least 3 months: (a) glomerular filtration rate (GFR) < 60 mL/min per 1.73 m² (b) markers of kidney damage (1 or more): (i)

albuminuria [albumin to creatinine ratio (ACR) ≥ 30 mg/g] (ii) urinary sediment abnormality (iii) electrolyte or other abnormality due to tubular disorder (iv) abnormalities on histology (v) structural abnormalities detected by imaging (vi) history of kidney transplantation [3].

Chronic kidney disease and mortality

In 2016, CKD caused 1.19 million deaths globally, which has increased by 28.8% from 2006 [4]. According to World Health Organization estimates, CKD will rank 13th in 2030 among the most common causes of death [5]. The kidney early evaluation program (KEEP) enrolled patients at high risk for developing CKD and contributed to our understanding on CV risk stratification, prognosis and treatment in this setting [6]. CKD was proved to be a significant predictor (OR: 1.44; 95% CI 1.27–1.63) of premature CV death, defined as the occurrence of myocardial infarction or stroke before 55 years in males and 65 years in females [6]. In a longitudinal analysis restricted to a subgroup of KEEP cohort with CKD, lower eGFR, increased albuminuria and diabetes mellitus (DM) have been found as significant predictors of mortality [7]. Both proteinuria and reduction in GFR can predict the development of fatal and non-fatal CV events, regardless of traditional CV risk factors, namely

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hypertension, smoking, hyperlipidemia, age and gender [8]. Therefore, assessing the risk of adverse outcomes and especially mortality associated with CKD is of particular importance for both physicians and patients [9]. At the moment, only one risk model has been developed to predict the occurrence of non-fatal CV events, renal failure requiring transplantation and death, in patients with $eGFR < 30$ mL/min/1.73 m² based on parameters that are readily available in routine clinical practice (age, sex, race, $eGFR$, systolic blood pressure, history of CV disease, DM, urine ACR and smoking) [10].

CHADS2, CHA2DS2-VASc, R2CHADS2 and R2CHA2DS2VASc scores

CHADS2 is a simple score and was initially used for stroke risk stratification in AF. It was derived by the combination of stroke risk factors established in AFI and SPAF studies [11]. CHADS2 was formed by assigning 1 point each for the presence of congestive heart failure, hypertension, age ≥ 75 years, DM and 2 points for history of stroke or transient ischemic attack [11]. CHADS2 manages well in identifying high-risk patients but provides ambiguous results in those at low or moderate stroke risk [12]. As a result, it was subjected to criticism for: (i) low discrimination ability for patients at low risk of stroke (ii) absence of important independent stroke and thromboembolic risk factors (iii) discrepancy between the original validation and further applications in guidelines and real-world cohorts [13, 14].

CHA2DS2-VASc [congestive heart failure, hypertension, age ≥ 75 years, diabetes, prior stroke, vascular disease, age 65–74 years and sex (female) category] score was originally formulated to predict the annual thromboembolic risk in patients with nonvalvular AF [15, 16]. CHA2DS2-VASc is a simple, effective and easy-to-use tool for truly low-risk and truly high-risk patients, but it has difficulties in tailoring anticoagulant treatment in AF patients at intermediate risk of stroke [17]. In individuals with AF and a CHA2DS2-VASc score of 1, therapeutic decisions should be based on the individual balance between thromboembolic and bleeding risk [18].

R2CHADS2 score incorporates the components of CHADS2 score and awards 2 points for renal dysfunction ($CrCl < 60$ mL/min and $GFR < 60$ mL/min/1.73 m²) [19]. It was derived from study subjects enrolled in ROCKET-AF trial. The post hoc analysis of outcomes in ROCKET AF found that impaired renal function is independently associated with the occurrence of stroke or systemic embolism during follow-up of patients with a relatively high risk of stroke (mean CHADS2 score 3.5) receiving warfarin or rivaroxaban. R2CHADS2 score enhanced stroke risk assessment based on the net reclassification index by 8.2%

compared with CHADS2 score and by 6.2% compared with CHA2DS2-VASc score [19]. Piccini et al. applied this model to the ATRIA cohort of > 13 000 patients with nonvalvular AF to validate R2CHADS2 score in an independent population of patients with AF across a broader range of inherent risk [19]. R2CHADS2 risk score exhibited similar power to CHADS2 score regarding stroke occurrence (C statistics 0.672 and 0.673, respectively), however, net stroke risk reclassification was improved 17.4% (95% CI 12.1–22.5%) with R2CHADS2 score. The findings were similar when applied to patients not receiving warfarin (C statistics 0.696 versus 0.704 for R2CHADS2 and CHADS2 scores, respectively). Net reclassification index improved with R2CHADS2 by 22.6% (95% CI 14.5–30.7%) [19].

In the same way, R2CHA2DS2VASc score awards an additional 2 points for $CrCl < 60$ mL/min and $GFR < 60$ mL/min/1.73 m² and has already been used to predict long-term outcomes for patients with coronary artery disease (CAD)20 and acute coronary syndromes (ACS) [20–22].

CHA2DS2-VASc score predicts mortality in several diseases

The validity of CHA2DS2-VASc score in predicting ischemic stroke and thromboembolism has been extended beyond the originally proposed AF field. High CHA2DS2-VASc scores have been associated with increased mortality in patients with several diseases, irrespective of the presence or absence of AF. CHADS2, CHA2DS2-VASc and R2CHADS2 scores have been associated with higher incidence of mortality in patients with stable CAD and ACS [23]. Compared to CHADS2, CHA2DS2-VASc and R2CHADS2 scores provide better discrimination and reclassification for mortality. In addition, CHA2DS2-VASc and R2CHADS2 scores have comparable predictive ability of mortality to GRACE score [23]. CHA2DS2-VASc score was proven to be useful in predicting mortality in HF patients, irrespective of the presence or absence of AF, ischemic or non-ischemic etiology, and reduced or preserved EF [24]. In the same line, Chen et al. also reported that CHADS2, CHA2DS2-VASc and R2CHADS2 scores are moderately accurate predictors of all-cause mortality in systolic HF patients with or without AF. However, only CKD and R2CHADS2 scores seem to be independent predictors of 1 year all-cause mortality in this setting. In terms of predicting all-cause mortality in systolic HF patients, R2CHADS2 seems to be the best of the three scoring systems, especially in systolic HF patients without AF [25]. Moreover, CHA2DS2-VASc score highly predicts all-cause mortality in patients' acute ischemic stroke [26], ICD [27], and acute pulmonary embolism [28]. CHADS2, CHA2DS2-VASc and CHA2DS2-VASc-M (modified version of the CHA2DS2-VASc scoring system in which 1 point was assigned to male

instead of female sex) have also been significantly associated with all-cause mortality in COVID-19 patients [29]. The purpose of this paper is to present the latest knowledge and to describe recent studies investigating whether CHA2DS2-VASc score could be used to predict CV or all-cause mortality in CKD patients, with or without AF.

CHA2DS2VASc and R2CHADS₂ ± VASc score in atrial fibrillation patients with chronic kidney disease

In AF patients with end-stage renal disease (ESRD) on dialysis, Wang et al. reported that CHA2DS2-VASc score predicts mortality during follow-up [30]. Shih et al. also reported mortality in patients with new onset AF undergoing hemodialysis. An increase in CHA2DS2-VASc score was associated with increased mortality in this setting. The annual risk of all-cause death for patients with a CHA2DS2-VASc score of 0 was 10.03% and for those with a CHA2DS2-VASc score of 9 was 63.10%, respectively [31]. Fu et al. refined the CHADS₂ and CHA2DS2-VASc scores by combining creatinine clearance (CrCl) and GFR, and evaluated the performance of CrCl-based and GFR-based schemes in death risk stratification of Chinese patients > 60 years old with AF. Renal function was evaluated with CrCl formula and different GFR formulas, as well. Five different kinds of R2CHADS₂ and R2CHA2DS2VASc schemes were generated by combining CrCl and GFR with CHADS₂ and CHA2DS2VASc scores [32]. Results provided evidence for the significantly better performance of GFR-based schemes—R2(GFR)CHADS₂ and R2(GFR)CHA2DS2VASc—and the moderately better performance of CrCl-based schemes—R2(CrCl)CHADS₂ and R2(CrCl)CHA2DS2VASc—in death risk stratification compared with CHADS₂ and CHA2DS2VASc scores [32]. These findings, however, were not confirmed in a recent study by Premuzic et al. The investigators sought to determine the association of eGFR with CV mortality in AF patients after 24 months of follow-up [33]. They concluded that CV mortality was independently associated with eGFR ($b = 0.169$, $P = 0.04$), male gender ($b = 0.156$, $P = 0.03$), CHA2DS2-VASc ($b = 0.467$, $P = 0.02$) and R2CHA2DS2VASc scores ($b = 0.391$, $P = 0.04$) but not with R2CHADS₂ score. In addition, R2CHA2DS2VASc was not associated with CV mortality more than CHA2DS2VASc [33].

CHA2DS2VASc score in non-atrial fibrillation patients with chronic kidney disease

Recent studies have also shown that CHA2DS2-VASc score can predict mortality in CKD patients. Pravda et al. investigated the association of CHA2DS2-VASc with mortality

and major adverse CV outcomes in patients with ESRD on chronic hemodialysis [34]. A higher CHA2DS2-VASc score was associated with an increased risk for the composite endpoint of all-cause mortality, myocardial infarction, and stroke within the first year of hemodialysis in the low (CHA2DS2-VASc 0–3), intermediate (CHA2DS2-VASc 4–5) and high (CHA2DS2-VASc ≥ 6) CHA2DS2-VASc groups, respectively ($P < 0.01$). A multivariate analysis using the CHA2DS2-VASc score group of 0–3 as the reference group yielded adjusted ORs for the composite endpoint at 1 year that increased as the CHA2DS2-VASc score was higher (OR = 2.6 95% CI 1.6–4.2 and OR = 4.2, 95% CI 3.3–7.5 for patients with the CHA2DS2-VASc score of 4–5 and ≥ 6 , respectively, $P < 0.01$) [34]. CHA2DS2-VASc score was also used as a continuous variable to assess the risk, and was shown that CHA2DS2-VASc score is associated with a 38% increased risk for the composite endpoint [34]. Hsu et al. evaluated the usefulness of CHADS₂ and CHA2DS2-VASc scores for the prediction of CV and all-cause mortality in CKD [35]. Age, male gender, hypertension, heart failure and CHA2DS2-VASc score (HR 1.600; 95% CI 1.254–2.040; $P < 0.001$) were proven to be significant predictors of CV mortality. Similarly, age, male gender, heart failure, CHA2DS2-VASc score (HR 1.503; 95% CI 1.300–1.739; $P < 0.001$) and angiotensin II receptor blockers use were significant predictors of all-cause mortality. Higher stage of CKD was also associated with increased all-cause mortality in CKD [35]. Recently, Vodošek Hojs et al. performed a prospective study in non-dialysis CKD patients and assessed the role of CHA2DS2-VASc score in predicting CV and all-cause mortality in CKD. Kaplan–Meier survival analysis showed that CV ($P = 0.001$) and all-cause ($P = 0.001$) mortality were higher in patients with CHA2DS2-VASc score > 2 . CHA2DS2-VASc score was an independent predictor of CV (HR: 2.04, CI 1.20–3.45, $P = 0.008$) and all-cause mortality (HR: 2.06, CI 1.43–2.97, $P = 0.001$) [36]. The summarized studies investigating the ability of CHA2DS2-VASc score to predict CV and all-cause mortality in CKD are listed in Table 1.

Conclusion

CHA2DS2-VASc score has been widely used to evaluate the risk of stroke in AF patients [37], but has been shown to predict CV and all-cause mortality in CKD patients as well. Indeed, higher CHA2DS2-VASc scores have been associated with increased mortality. These findings are of particular importance because CKD is very common in clinical practice and utilization of CHA2DS2-VASc score may help physicians to identify high-risk groups in this setting. Intensive care along with modification of risk factors and treatment of coexisting diseases may improve prognosis in these patients.

Table 1 Studies investigating the ability of CHA2DS2-VASc score to predict CV and all-cause mortality in chronic kidney disease

Study (Reference)	AF cases /number of Pts	Age (years)	Follow-up, years	Database/type of study	Key findings
Wang et al. [30]	141/774	61.2 ± 11.3 years	3.4 ± 2.5 years	Retrospective observational	CHA2DS2-VASc detects mortality during follow-up ($c=0.638$)
Shih et al. [31]	6.772/77.397	68.8 ± 11.3 years	3.2 years	Retrospective cohort	The annual risk of all-cause mortality for patients with a CHA2DS2-VASc score of 0 was 10.03% and for those with a CHA2DS2-VASc score of 9 was 63.10%, respectively
Premužić et al. [33]	301 AF patients	70.6 years	2 years	Retrospective observational-longitudinal	CV mortality was independently associated with CHA2DS2VASc ($b=0.467$, $P=0.02$) and R2CHA2DS2VASc scores ($b=0.391$, $P=0.04$) but not with R2CHADS2 score
Pravda et al. [34]	105/457	66 ± 13 years	955 ± 765 days	Retrospective observational	CHA2DS2-VASc score predicted the primary composite endpoint (all-cause mortality, myocardial infarction, and stroke) with an AUC of 0.72 (95% CI 0.69–0.75)
Hsu et al. [35]	437 CKD patients	68 ± 12 years	91 months (25th–75th percentile: 59–101)	Retrospective longitudinal	CHADS2 and CHA2DS2-VASc scores (both P value < 0.001) were significant predictors of CVr and all-cause mortality in the multivariate analysis
Fu et al. [32]	219 AF patients	86 years	1.11 years	Retrospective observational	C-statistics of GFR-based schemes—R2(GFR)CHADS2 and R2(GFR)CHA2DS2 VASc—significantly exceeded that of CHADS2 and CHA2DS2VASc scores ($P < 0.05$ for all)
Vodosek Hojs et al. [36]	87 CKD patients	60.3 ± 12.8 years	1696.5 ± 564.6 days	Prospective	CHA2DS2-VASc score was an independent predictor of all-cause (HR: 2.06, CI 1.43–2.97, $P=0.001$) and CV mortality (HR: 2.04, CI 1.20–3.45, $P=0.008$)

AF atrial fibrillation, CKD chronic kidney disease

More studies are needed to further confirm these promising findings so that CHA2DS2-VASc score can be widely used in clinical setting.

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Declarations

Conflict of interest The author(s) declare that they have no conflict of interest.

Human and animal rights statement There is no research involving human participants and/or animals.

Informed consent There is no informed consent because there weren't any human participants.

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