Original Article

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Albuminuria, estimated glomerular filtration rate, and traditional predictors for composite cardiovascular and kidney outcome: a population-based cohort study in Korea

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Background: Certain pharmacotherapies have shown to be effective for both cardiac and kidney outcomes. Although risk prediction is important in treatment decision-making, few studies have evaluated prediction models for composite cardiovascular and kidney outcomes.

Methods: This study included 2,195,341 Korean adults from a nationwide cohort for chronic kidney disease and a representative sample of the general population, with a 9-year follow-up. This study evaluated prediction models for a composite of major cardiovascular events or kidney disease progression that included albuminuria and estimated glomerular filtration rate (eGFR) and/or traditional cardiovascular disease predictors.

Results: The addition of albuminuria and eGFR to a model for the composite outcome that included age, sex, and traditional predictors increased a C statistic by 0.0459, while the addition of traditional predictors to age, sex, albuminuria, and eGFR increased a C statistic by 0.0157. When age and sex-adjusted incidence rates were calculated across the combined Pooled-Cohort-Equations (PCEs) and Kidney Disease: Improving Global Outcomes (KDIGO) risk categories in diabetic or hypertensive participants, the incidence of ≥10 per 1,000 person-years was observed among all categories with high or very high KDIGO risk and among categories with moderate (or low) KDIGO risk and a PCEs 10-year risk of ≥10% (or ≥20%), accounting for 36% of diabetic and 18% of hypertensive populations.

Conclusion: This study strongly supports the utility of the KDIGO risk matrix combined with a conventional cardiovascular risk score for the prediction of composite cardiovascular and kidney outcome and provides epidemiologic data relevant to the development of efficient treatment strategies.

Keywords: Albuminuria, Cardiovascular diseases, Glomerular filtration rate, Kidney diseases, Primary prevention

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Introduction

Precise estimates of the absolute risks of adverse events are important in the development of effective and safe strategies for preventive therapy. Guidelines for the primary prevention of cardiovascular events recommend that clinicians predict individual risks and consider statin, aspirin, and intensive antihypertensive treatments in individuals at high-predicted risk [1–3]. The commonly used risk prediction models such as the Framingham algorithm and the Pooled-Cohort-Equations (PCEs) were developed primarily for atherosclerotic cardiovascular disease (ASCVD) [4,5], which can be prevented by statin or aspirin treatment [6,7]. However, certain treatments such as sodium-glucose cotransporter-2 (SGLT2) inhibitors [8–10], angiotensin-neprilysin inhibitor [11], and finerenone [12,13] as well as antihypertensive treatment have recently shown benefits for reducing heart failure and kidney disease events beyond ASCVD. Conventional models that included traditional cardiovascular disease predictors may not be suitable for the clinical decision of such treatments. The measures of albuminuria and estimated glomerular filtration rate (eGFR) can alternatively or additionally be considered as predictors on the basis of incremental absolute benefits of the treatments at higher albuminuria and lower eGFR levels [10,14]. Nevertheless, few studies have evaluated prediction models for a composite risk of cardiac and kidney events.

To obtain population-representative data about risk prediction of composite cardiovascular and kidney outcome, this study evaluated prediction models for a composite of major cardiovascular events or kidney disease progression that included albuminuria and eGFR levels and/or traditional predictors in a nationwide Korean cohort of patients with chronic kidney disease (CKD) and a representative cohort of the general population.

Methods

Participants

This retrospective cohort study used data from the National Health Information Database of the National Health Insurance Service (NHIS). This public database covers data for the entire population of Korea from 2002 onwards [15]. All data were anonymized prior to being provided for analysis. The Institutional Review Board of Kangwon National University Hospital approved the study protocol and waived informed consent (No. KNUH-2021-04-019).

Adults with CKD were identified from 40- to 79-year-old participants of the nationwide health screening survey in 2009 or 2010 from when serum creatinine and high-density lipoprotein (HDL) cholesterol were measured (Fig. 1). From 12.6 million survey participants, a total of 1,357,054 adults were identified with an eGFR of <60 mL/min/1.73 m^2 at a medical health examination in 2009 or 2010 or dipstick albuminuria ≥1+ once or ≥trace twice during examinations between 2007 and 2010. Health screening and NHIS reimbursement records were collected from January 1, 2005 to December 31, 2019. From the 1,357,054 adults with CKD, 71,052 with missing or outlier data, 144,500 with an eGFR of <15 mL/min/1.73 m^2, and 22,415 who died or developed end-stage kidney disease (ESKD), hospitalized heart failure, or critical ASCVD before the baseline (January 1, 2011) were excluded. The remaining 1,119,087 adults with CKD were included in the final analysis.

To obtain a representative sample of the general population, one-tenth of the nationwide health screening survey participants were randomly selected without reference to a specific condition. From the selected 1,258,655 adults, 47,114 with missing or outlier data, 14,466 with an eGFR of <15 mL/min/1.73 m^2, and 8,385 who died or developed ESKD, hospitalized heart failure, or critical ASCVD before baseline were also excluded. Thus, 1,188,690 adults of the general population were included in the final analysis.

Predictors and risk categories

Using biennial health screening records from 2005 to 2010, the continuous variables of age, systolic blood pressure (SBP), total cholesterol, and HDL cholesterol and the categorical variables of sex (male or female), diabetes status (yes or no), antihypertensive use (yes or no), active smoking (yes or no), albuminuria, and eGFR were determined. Antihypertensive use was identified as the prescription of antihypertensive agents for ≥90 days per year (Supplementary Table 1, available online). Diabetes was defined as the prescription of antidiabetic agents for ≥90 days per year or a fasting blood glucose of ≥126 mg/dL. eGFR was calculated from serum creatinine in 2009 or 2010 using the Chron-

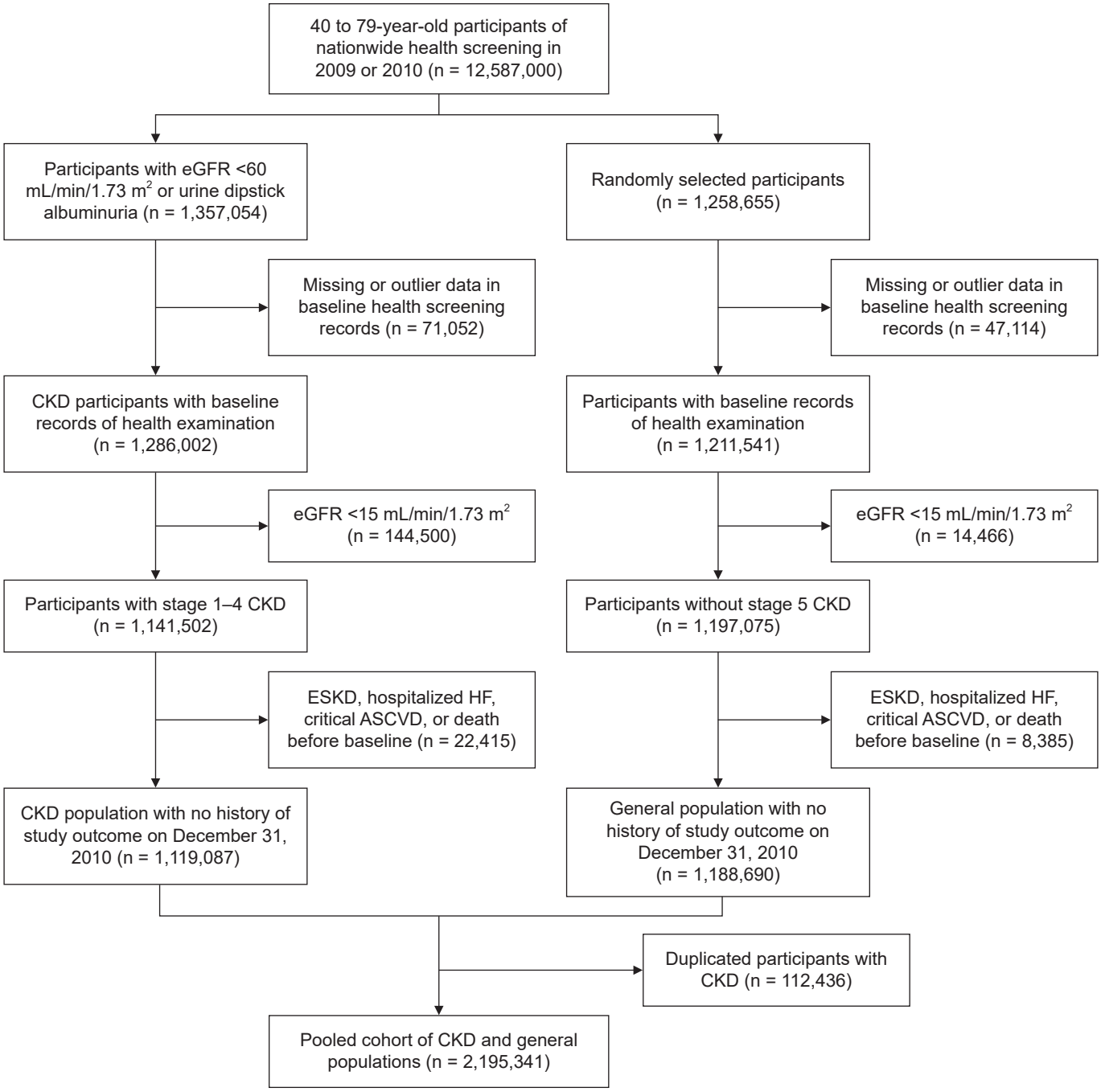

Figure 1. Flow chart of participant selection.
ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure.

ic Kidney Disease Epidemiology Collaboration creatinine equation [16] and categorized into six groups (G0, ≥120; G1, 90 to <120; G2, 60 to <90; G3a, 45 to <60; G3b, 30 to <45; or G4, 15 to <30 mL/min/1.73 m^2). Dipstick albuminuria was categorized into three groups (A1, negative; A2, trace to1+; or A3, ≥2+).

The 10-year cardiovascular risk was calculated using the 2018 revised PCEs [6] and categorized into four groups (<5%, 5% to <10%, 10% to <20%, or ≥20%). Participants were categorized into four risk groups (low, moderate,

high, or very high risk) using the KDIGO risk matrix [17]. Using a combination of the PCEs and KDIGO risk categories, participants were further categorized into 16 groups (i.e., a four-by-four matrix).

Outcomes

The primary outcome was a composite of major cardiovascular events or kidney disease progression. Secondary outcomes included each component of the primary outcome and a composite outcome of major cardiovascular events or kidney failure. Major cardiovascular events consisted of critical ASCVD, hospitalized heart failure, and cardiovascular death. Kidney disease progression was defined as serum creatinine doubling, ESKD, or death from CKD, while kidney failure was defined as ESKD or death from CKD. Critical ASCVD was determined as critical care unit admission or revascularization for acute coronary syndrome or acute ischemic stroke (Supplementary Table 1, available online). Hospitalized heart failure was determined as hospitalization with the primary diagnosis of heart failure. Doubling of serum creatinine from baseline was identified using biennial health screening records. ESKD was determined as dialysis for ≥90 days per year or kidney transplantation. Causes of death were confirmed by the primary cause of death on death certificates from Statistics Korea. The first event of the outcomes was identified from the baseline (January 1, 2011) to the end of the study (December 31, 2019).

Statistical analysis

To predict risks of study outcomes, Cox proportional hazard models were developed with covariates of kidney measures (albuminuria and eGFR) and/or traditional predictors (diabetes status, antihypertensive use, SBP, total cholesterol, HDL cholesterol, and active smoking) in addition to age and sex. The models were evaluated using measures of discrimination and reclassification. Discrimination was quantified using the Uno's C statistic [18], and the change in C statistic was calculated after adding covariates of interest to a prediction model. A reclassification table was constructed to assess the number of participants who moved among the predicted 5-year risk categories of <5%, 5% to <10%, and ≥10% after adding covariates of interest to a model.

To evaluate published models, C statistics were calculated among a model with a single covariate of the PCEs 10-year risk score, a three-variable model that included age, sex, and the KDIGO risk category, and a model that included both the PCEs 10-year risk score and the KDIGO risk category. Furthermore, incidence rates were estimated across the combined PCEs and KDIGO risk categories. Age- and sex-adjusted incidence rates were calculated by multiplying the adjusted hazard ratios and the 95% confidence intervals (CIs) by a constant to make the sum of the products of incidence rates and person-years in risk categories equal to the total number of observed events. To explore the influence of the proportion of renal outcomes in composite cardiovascular and kidney outcome, analyses were repeated for the secondary composite outcome that excluded serum creatinine doubling, which was less serious than kidney failure, from the primary outcome.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Data are presented as numbers and percentages, means and standard deviations, C statistics and 95% CIs, or incidence rates and 95% CIs.

Results

This study included 2,195,341 participants, including 1,119,087 participants with CKD and 1,076,254 without CKD. Compared with non-CKD participants, CKD participants were older and had higher PCEs 10-year risk scores and SBP levels; this group also contained higher proportions of diabetes and antihypertensive users. The baseline characteristics of the general population representing the entire population in Korea are shown in Table 1.

During 9 years of follow-up, the primary composite outcome was noted in 94,405 participants (8.4%) with CKD, in 40,619 participants (3.4%) of the general population, and in 125,650 participants (5.7%) of the pooled cohort. The cumulative incidence of secondary outcomes is provided in Supplementary Table 2 (available online).

Risk discrimination and reclassification by albuminuria and estimated glomerular filtration rate and/or traditional predictors

The C statistic in a full model for the primary composite outcome that included all covariates of age, sex, kidney

Table 1. Baseline characteristics of the study participants

Characteristic	Pooled cohort		General population[a]
	CKD	No CKD	
No. of participants	1,119,087	1,076,254	1,188,690
Age (yr)	60.9 ± 10.9	54.2 ± 9.9	54.8 ± 10.2
Male sex	537,579 (48.0)	515,263 (47.9)	568,967 (47.9)
Albuminuria			
No albuminuria	619,150 (55.3)	1,076,254 (100)	1,138,741 (95.8)
Dipstick albumin 1+ or trace	336,234 (30.0)	0 (0)	33,683 (2.8)
Dipstick albumin ≥2+	163,703 (14.6)	0 (0)	16,266 (1.4)
eGFR (mL/min/1.73 m^2)			
≥120	2,314 (0.2)	7,078 (0.7)	7,301 (0.6)
≥90, <120	163,450 (14.6)	461,014 (42.8)	477,437 (40.2)
≥60, <90	264,274 (23.6)	608,162 (56.5)	634,514 (53.4)
≥45, <60	580,901 (51.9)	0 (0)	58,638 (4.9)
≥30, <45	95,297 (8.5)	0 (0)	9,582 (0.8)
≥15, <30	12,851 (1.1)	0 (0)	1,218 (0.1)
Diabetes	266,702 (23.8)	111,608 (10.4)	138,374 (11.6)
Antihypertensive use	546,882 (48.9)	255,836 (23.8)	310,761 (26.1)
Active smoking	38,831 (3.5)	52,516 (4.9)	40,183 (3.4)
Systolic blood pressure (mmHg)	128.6 ± 14.2	123.7 ± 13.4	124.2 ± 13.6
Total cholesterol (mg/dL)	201.6 ± 32.0	198.4 ± 30.7	198.7 ± 30.9
HDL cholesterol (mg/dL)	52.8 ± 13.0	54.5 ± 12.7	54.4 ± 12.8
10-Yr cardiovascular risk (%)[b]	9.8 ± 10.1	5.1 ± 6.6	5.6 ± 7.2
KDIGO risk category			
Low risk	0 (0)	1,076,254 (100)	1,076,254 (90.5)
Moderate risk	833,017 (74.4)	0 (0)	83,906 (7.1)
High risk	236,783 (21.2)	0 (0)	23,673 (2.0)
Very high risk	49,287 (4.4)	0 (0)	4,857 (0.4)
Cardiovascular risk category (%)			
<5	472,830 (42.3)	730,115 (67.8)	777,663 (65.4)
≥5, <10	253,956 (22.7)	188,474 (17.5)	214,012 (18.0)
≥10, <20	236,994 (21.2)	112,657 (10.5)	136,476 (11.5)
≥20	155,307 (13.9)	45,008 (4.2)	60,539 (5.1)

Data are expressed as number only, mean ± standard deviation, or number (%).
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; KDIGO, Kidney Disease: Improving Global Outcomes.
[a]The participants of the general population were randomly selected from the nationwide health screening survey participants regardless of the presence or absence of CKD. [b]The 10-year risk of cardiovascular disease was calculated using the 2018 revised Pooled-Cohort-Equations.

measures, and traditional predictors was 0.7958 (95% CI, 0.7946–0.7970). We omitted one predictor at a time from the full model, and the C statistic change by omitting albuminuria or eGFR was substantially greater than that by omitting each of the traditional predictors (Fig. 2). For the primary composite outcome, the C statistics in the conventional model that included age, sex, and the traditional predictors and the four-variable model that included age, sex, albuminuria, and eGFR were 0.7499 (95% CI, 0.7485–0.7513) and 0.7800 (95% CI, 0.7786–0.7814), respectively. The addition of kidney measures to the conventional model increased C statistic by 0.0459 (95% CI, 0.0449–0.0469), while the addition of the traditional predictors to the four-variable model increased C statistic by 0.0157 (95% CI, 0.0153–0.0161) (Supplementary Fig. 1, available online). For the secondary composite outcome, the C statistics in the conventional and four-variable models were 0.7992 (95% CI, 0.7978–0.8006) and 0.8162 (95%

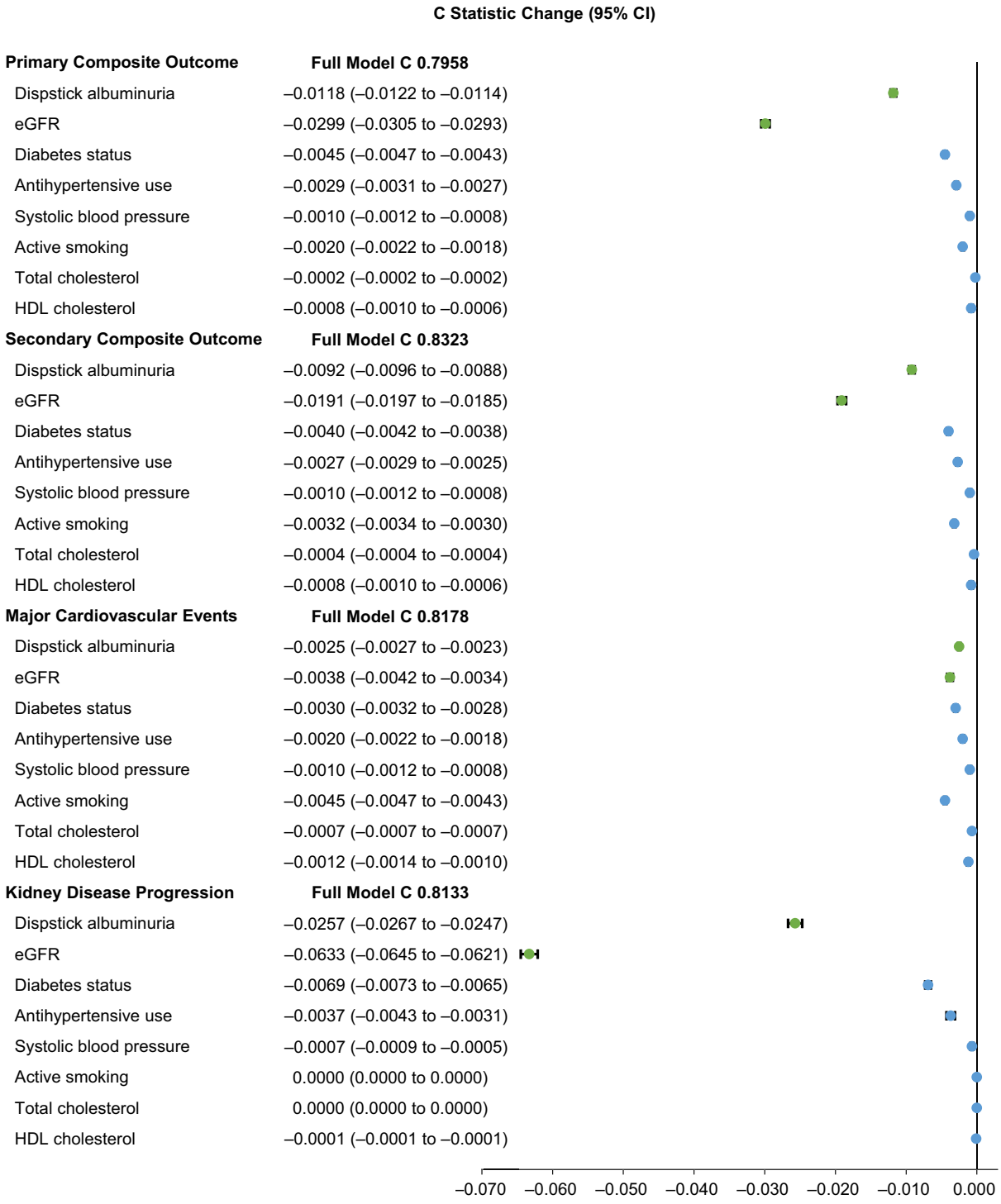

Figure 2. Changes in C statistics with the omission of each predictor from full models for study outcomes in the pooled cohort. Plots show differences in C statistics for four clinical outcomes with omission of kidney measures and traditional predictors from a full model including all predictors. The primary composite outcome was major cardiovascular events or kidney disease progression. The secondary composite outcome was major cardiovascular events or kidney failure. Major cardiovascular events were critical atherosclerotic cardiovascular disease, hospitalized heart failure, and cardiovascular death. Kidney disease progression was defined as serum creatinine doubling or kidney failure.

CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

CI, 0.8152–0.8172), respectively. The C statistic increments by adding kidney measures to a conventional model and by adding traditional predictors to a four-variable model were 0.0331 (95% CI, 0.0323–0.0339) and 0.0161 (95% CI, 0.0157–0.0165), respectively.

Reclassification tables for the predicted 5-year risk categories of <5%, 5% to <10%, and ≥10% were constructed separately in CKD and general populations (Supplementary Table 3, 4, available online) to obtain population-representative data. For the primary composite outcome, the addition of albuminuria and eGFR levels to conventional models yielded net reclassification improvements (NRIs) of 13.8% and 13.4% in CKD and general populations, respectively, while adding traditional predictors to four-variable models yielded NRIs of 5.9% and 3.4%, respectively.

Risk discrimination and incidence rate by the Kidney Disease: Improving Global Outcomes risk and Pooled-Cohort-Equations 10-year risk categories

For the primary composite outcome, the C statistics in a model including a single predictor of the PCEs 10-year risk score and a three-variable model including age, sex, and the KDIGO risk category were 0.7362 (95% CI, 0.7350–0.7374) and 0.7612 (95% CI, 0.7596–0.7628), respectively. The addition of the KDIGO risk category to the PCEs 10-year risk score increased C statistic by 0.0356 (95% CI, 0.0346–0.0366), while the addition of the PCEs risk category to the three-variable model increased C statistic by 0.0106 (95% CI, 0.0096–0.0116) (Supplementary Fig. 2, available online).

When age- and sex-adjusted incidence rates were calculated across the combined PCEs and KDIGO risk categories (Fig. 3), an incidence of ≥20 per 1,000 person-years for the primary composite outcome was observed among all categories with a very high KDIGO risk and among a category with high KDIGO risk and a PCEs 10-year risk of ≥20%. Given the distribution of the participants across the PCEs and KDIGO risk categories, the categories with an incidence of ≥20 per 1,000 person-years accounted for 8.0% of the CKD population and 0.73% of the general population. An incidence of ≥10 per 1,000 person-years was observed among all categories with very high KDIGO risk and those with a PCEs 10-year risk of ≥20% and among categories with high (or moderate) KDIGO risk and a PCEs 10-year risk of ≥5% (or ≥10%), accounting for 49.8% of the CKD population and 7.7% of the general population.

The adjusted incidence rates were also calculated in diabetic or hypertensive participants to obtain clinically relevant data for the treatment of diabetes and hypertension (Fig. 4). For the primary composite outcome, an incidence of ≥10 per 1,000 person-years was observed among all categories with high or very high KDIGO risk and among categories with moderate (or low) KDIGO risk and a PCEs 10-year risk of ≥10% (or ≥20%), accounting for 82.7% of diabetic and 63.1% of hypertensive adults of the CKD population and 35.6% of diabetic and 18.2% of hypertensive adults of the general population. By comparison, the categories with an incidence of ≥10 per 1,000 person-years accounted for 11.9% of nondiabetic and 7.2% of normotensive adults of the CKD population and 4.3% of nondiabetic and 2.3% of normotensive adults of the general population (Supplementary Fig. 3, available online).

For the secondary composite outcome (Fig. 3), an adjusted incidence rate of ≥10 per 1,000 person-years was observed among all categories with a very high KDIGO risk and among categories with high (or moderate) KDIGO risk and a PCEs 10-year risk of ≥10% (or ≥20%), accounting for 21.7% of the CKD population and 2.0% of the general population. In diabetic or hypertensive adults, the incidence of ≥10 per 1,000 person-years was observed among most categories with high or very high KDIGO risk and among categories with moderate KDIGO risk and a PCEs 10-year risk of ≥20% (Supplementary Fig. 4, available online), accounting for 60.3% of diabetic and 37.3% hypertensive adults of the CKD population and 11.6% of diabetic and 5.7% hypertensive adults of the general population.

Discussion

This population-based cohort study in Korea evaluated prediction models for a composite of cardiovascular and kidney outcomes that included albuminuria and eGFR levels and/or traditional predictors. For a composite of major cardiovascular events or kidney disease progression, the C statistic increments by adding albuminuria and eGFR to a conventional model and by adding traditional predictors to a four-variable model were 0.0459 and 0.0157, respectively. When age- and sex-adjusted incidence rates were calculated across the PCEs and KDIGO risk categories, an incidence of ≥10 per 1,000 person-years was observed among

Outcome	KDIGO risk categories			
PCEs 10-yr risk	**Low risk**	**Moderate risk**	**High risk**	**Very High risk**
Primary composite outcome				
	Incidence (95% CI), events per 1,000 person-years			
<5%	2.4	3.0 (3.0–3.1)	6.6 (6.4–6.8)	51.1 (49.2–53.0)
5% to <10%	4.9 (4.7–5.0)	6.5 (6.3–6.7)	12.2 (11.8–12.7)	49.4 (47.5–51.4)
10% to <20%	7.3 (7.1–7.6)	10.0 (9.8–10.3)	18.3 (17.7–18.8)	54.6 (52.7–56.5)
≥20%	11.7 (11.3–12.1)	15.3 (14.8–15.8)	26.7 (25.9–27.6)	67.6 (65.2–70.0)
	Number of participants (%) in CKD population			
<5%	0 (0.0%)	367,603 (32.85%)	94,043 (8.40%)	11,184 (1.00%)
5% to <10%	0 (0.0%)	93,807 (17.32%)	50,356 (4.50%)	9,793 (0.88%)
10% to <20%	0 (0.0%)	170,567 (15.24%)	52,750 (4.71%)	13,677 (1.22%)
≥20%	0 (0.0%)	101,040 (9.03%)	39,634 (3.54%)	14,633 (1.31%)
	Number of participants (%) in the general population			
<5%	730,115 (61.42%)	37,116 (3.12%)	9,335 (0.79%)	1,097 (0.09%)
5% to <10%	188,474 (15.86%)	19,394 (1.63%)	5,160 (0.43%)	984 (0.08%)
10% to <20%	112,657 (9.48%)	17,256 (1.45%)	5,236 (0.44%)	1,327 (0.11%)
≥20%	45,008 (3.79%)	10,140 (0.85%)	3,942 (0.33%)	1,449 (0.12%)
Secondary composite outcome				
	Incidence (95% CI), events per 1,000 person-years			
<5%	1.0	2.1 (2.0–2.1)	4.8 (4.5–5.0)	50.7 (48.4–53.2)
5% to <10%	3.4 (3.3–3.6)	5.4 (5.2–5.6)	9.8 (9.3–10.2)	46.6 (44.4–48.9)
10% to <20%	5.4 (5.2–5.7)	8.4 (8.1–8.7)	14.8 (14.2–15.5)	50.0 (47.8–52.2)
≥20%	8.8 (8.4–9.2)	12.5 (12.0–13.1)	21.7 (20.8–22.7)	60.8 (58.1–63.5)
Major cardiovascular events				
	Incidence (95% CI), events per 1,000 person-years			
<5%	1.4	2.2 (2.1–2.3)	3.1 (2.9–3.3)	6.7 (6.0–7.5)
5% to <10%	3.6 (3.5–3.8)	4.9 (4.7–5.1)	7.0 (6.6–7.3)	11.5 (10.7–12.4)
10% to <20%	5.1 (4.8–5.3)	6.9 (6.6–7.2)	9.9 (9.5–10.4)	15.4 (14.5–16.3)
≥20%	7.6 (7.2–7.9)	9.6 (9.2–10.0)	13.6 (13.0–14.2)	20.4 (19.3–21.5)
Kidney disease progression				
	Incidence (95% CI), events per 1,000 person-years			
<5%	0.9	1.1 (1.0–1.1)	2.9 (2.8–3.1)	31.7 (30.4–33.0)
5% to <10%	1.6 (1.5–1.7)	1.9 (1.8–2.0)	5.9 (5.7–6.2)	40.2 (38.5–42.1)
10% to <20%	2.4 (2.3–2.5)	3.0 (2.8–3.1)	9.5 (9.1–10.0)	49.2 (47.1–51.4)
≥20%	4.0 (3.7–4.2)	5.2 (4.9–5.5)	15.6 (14.9–16.4)	65.8 (62.9–68.8)

Figure 3. Age- and sex-adjusted incidence rates of the primary and secondary outcomes across the PCEs and KDIGO risk categories in the pooled cohort. The incidence rates and 95% CIs were calculated by multiplying age- and sex-adjusted hazard ratios and the 95% CIs by a constant to make the sum of the products of incidence rates and person-years in risk categories equal the total number of observed events. The participants of the general population represent the entire population in Korea.
CI, confidence interval; CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; PCEs, Pooled-Cohort-Equations.

Outcome/population	KDIGO risk categories			
PCEs 10-yr risk	Low risk	Moderate risk	High risk	Very High risk
Primary composite outcome in diabetic adults				
	Incidence (95% CI), events per 1,000 person-years			
<5%	3.9	6.2 (5.6–6.9)	16.4 (14.8–18.3)	89.5 (79.4–100.8)
5% to <10%	4.8 (4.3–5.3)	8.0 (7.3–8.8)	18.2 (16.6–20.0)	81.8 (74.1–90.3)
10% to <20%	7.3 (6.6–8.0)	10.7 (9.8–11.7)	21.8 (20.0–23.8)	71.1 (64.9–77.9)
≥20%	12.0 (11.0–13.2)	16.4 (15.0–18.0)	29.4 (26.8–32.1)	75.9 (69.3–83.2)
	Number of diabetic participants (%) in CKD population			
<5%	0 (0.0%)	16,507 (6.19%)	6,953 (2.61%)	1,034 (0.39%)
5% to <10%	0 (0.0%)	29,764 (11.16%)	12,015 (4.51%)	2,526 (0.95%)
10% to <20%	0 (0.0%)	59,792 (22.42%)	23,492 (8.81%)	6,473 (2.43%)
≥20%	0 (0.0%)	66,223 (24.83%)	30,277 (11.35%)	11,646 (4.37%)
	Number of diabetic participants (%) in the general population			
<5%	21,844 (15.79%)	1,708 (1.23%)	681 (0.49%)	107 (0.08%)
5% to <10%	26,584 (19.21%)	3,051 (2.20%)	1,247 (0.90%)	246 (0.18%)
10% to <20%	35,883 (25.93%)	5,969 (4.31%)	2,287 (1.65%)	662 (0.48%)
≥20%	27,297 (19.73%)	6,648 (4.80%)	3,006 (2.17%)	1,154 (0.83%)
Primary composite outcome in hypertensive adults				
	Incidence (95% CI), events per 1,000 person-years			
<5%	3.2	4.6 (4.4–4.8)	11.0 (10.5–11.6)	69.2 (65.9–72.6)
5% to <10%	5.5 (5.3–5.8)	7.5 (7.2–7.8)	14.5 (13.8–15.2)	58.1 (55.3–61.0)
10% to <20%	8.1 (7.7–8.5)	11.2 (10.8–11.7)	20.3 (19.4–21.2)	60.9 (58.2–63.8)
≥20%	12.7 (12.1–13.3)	16.7 (16.0–17.5)	29.3 (28.0–30.6)	74.5 (71.2–78.0)
	Number of hypertensive participants (%) in CKD populationIncidence			
<5%	0 (0.0%)	116,670 (17.94%)	35,605 (5.47%)	7,723 (1.19%)
5% to <10%	0 (0.0%)	123,179 (18.94%)	33,867 (5.21%)	8,202 (1.26%)
10% to <20%	0 (0.0%)	132,062 (20.31%)	43,083 (6.62%)	12,444 (1.91%)
≥20%	0 (0.0%)	87,565 (13.46%)	35,998 (5.54%)	13,970 (2.15%)
	Number of hypertensive participants (%) in the general population			
<5%	152,173 (35.95%)	11,804 (2.79%)	3,585 (0.85%)	722 (0.17%)
5% to <10%	94,904 (22.42%)	12,334 (2.91%)	3,388 (0.80%)	822 (0.19%)
10% to <20%	75,063 (17.73%)	13,348 (3.15%)	4,302 (1.02%)	1,214 (0.29%)
≥20%	35,838 (8.47%)	8,840 (2.09%)	3,573 (0.84%)	1,377 (0.33%)

Figure 4. Age- and sex-adjusted incidence rates of the primary composite outcome across the PCEs and KDIGO risk categories in diabetic or hypertensive adults. The incidence rates and 95% CIs were calculated by multiplying age- and sex-adjusted hazard ratios and their 95% CIs by a constant to make the sum of the products of incidence rates and person-years in risk categories equal the total number of observed events. The participants of the general population represent the entire population in Korea.
CI, confidence interval; CKD, chronic kidney disease; KDIGO, Kidney Disease: Improving Global Outcomes; PCEs, Pooled-Cohort-Equations.

all categories with very high KDIGO risk and those with a PCEs 10-year risk of ≥20% and among categories with high (or moderate) KDIGO risk and a PCEs 10-year risk of ≥5% (or ≥10%). This study demonstrated first that albuminuria and eGFR allowed more improvement in risk prediction models for composite cardiovascular and kidney outcome compared with traditional predictors. One of its strengths was that composite risk was quantified to compare risk across combined PCEs and KDIGO risk categories.

The categories with an incidence of ≥10% for the primary composite outcome accounted for 7.7% of the general population (Fig. 3). The composite risk in patients with a PCEs 10-year risk of 5% to <10% and high or very high KDIGO risk (0.51% of the general population) was higher than the risk in patients with a PCEs 10-year risk of 10% to <20% and low KDIGO risk (9.48% of the general population). Conversely, the composite risk in patients with low KDIGO risk and a PCEs 10-year risk of ≥20% (3.79% of the general population) was higher than the risk in patients with moderate KDIGO risk and a PCEs 10-year risk of <10% (4.75% of the general population). Such information may be valid in decision-making for preventive therapy as the benefits of treatment are expected to outweigh the potential harms in patients at higher risk, and the present study data are relevant to the development of efficient treatment strategies.

In this study, the categories with an incidence of ≥10 per 1,000 person-years for the primary composite outcome accounted for 35.6% of diabetic adults and 18.2% of hypertensive adults of the general population (Fig. 4). In randomized controlled trials, certain medications showed both cardiac and kidney benefits. For example, SGLT2 inhibitors substantially reduced heart failure and kidney disease events [8–10], and the absolute risk reduction was proportional to the baseline risk [10], while the relative risk reduction was similar among various subgroups [8,9]. Further, a SGLT2 inhibitor improved outcomes independently of diabetes status or baseline glucose levels [19,20]. These benefits are comparable to those of statins: i.e. the relative risk reduction for ASCVD is consistent in subgroups, and the benefit persists independently of baseline cholesterol levels [21,22]. As statins are recommended in individuals at high risk for ASCVD [1,3], SGLT2 inhibitors could also be recommended for adults at high risk for composite cardiovascular and kidney outcome. The KDIGO and American Diabetes Association currently recommend SGLT2 inhibitors for patients with type 2 diabetes and established CKD [23,24]. However, there are no concrete or detailed recommendations for nondiabetic CKD patients, although the U.S. Food and Drug Administration [25] has approved dapagliflozin, an SGLT2 inhibitor, to reduce the risks of cardiac and kidney events in CKD. Given the present data, practitioners should consider SGLT2 inhibitor for diabetic or hypertensive patients with very high KDIGO risk and those with high KDIGO risk and a PCEs 10-year risk of ≥10%. In addition, SGLT2 inhibitor may be considered for those with high or very high KDIGO risk and those with moderate (or low) KDIGO risk and a PCEs 10-year risk of ≥10% (or ≥20%). Besides the SGLT2 inhibitor, an angiotensin-neprilysin inhibitor reduced both cardiac and kidney events in trials for patients with heart failure [11,26], and finerenone showed the same effects in patients with diabetes and CKD [12,27]. These treatments could also be considered in patients at high risk for composite cardiovascular and kidney outcome.

In the present study, the addition of albuminuria and eGFR to a conventional model for major cardiovascular events improved discrimination with a C statistic of 0.0059, and the addition of the kidney measures to the models for ASCVD, heart failure, and cardiovascular death increased C statistics by 0.0029, 0.0085, and 0.0066, respectively (Supplementary Fig. 1, available online). The addition of traditional predictors to a four-variable model for kidney disease progression increased the C statistic by 0.0180. The findings are comparable to those in previous studies. In a previous meta-analysis, the addition of eGFR and urine albumin-creatinine ratio or dipstick albuminuria to the models for coronary artery disease, heart failure, and cardiovascular death increased C statistics by 0.0073, 0.0258, and 0.0167, respectively, while the addition of eGFR and dipstick albuminuria to the models for coronary artery disease and cardiovascular death increased C statistics by 0.0072 and 0.0048, respectively [28]. In both previous and present studies, albuminuria and eGFR improved risk discrimination more evidently in models for heart failure than in those for ASCVD, although dipstick albuminuria used in the present study might improve discrimination to a lesser degree than that by urine albumin-to-creatinine ratio. A four-variable model for ESKD was previously developed in Canadian cohorts of patients with an eGFR of 15 to <60 mL/min/1.73 m^2 [29], and the model adequately predicted

the 2-year and 5-year risk of ESKD in multinational cohorts [30]. Recently, a risk prediction model for ESKD, cardiovascular events, and death that included diabetes, SBP, smoking, and history of cardiovascular disease in addition to the four variables was developed in patients with an eGFR of <30 mL/min/1.73 m^2 [31]. The model showed better discrimination and calibration for longer-term predictions in a validation study [32]. The present 9-year follow-up study in CKD and general populations also showed that the addition of diabetes and hypertension to a four-variable model for kidney disease progression modestly improved discrimination (Fig. 2).

This study has several limitations. First, urine dipstick and serum creatinine were used for kidney measures. Dipstick albuminuria is less sensitive than urine albumin-to-creatinine ratio [33], and creatinine-based eGFR is less accurate for the prediction of adverse events than cystatin C-based eGFR [34]. Further studies are needed to explore the possibility of better performance of prediction models through the use of more accurate kidney measures. Next, the critical ASCVD did not include stable angina, mild stroke, or peripheral arterial disease. As the proportion of the critical ASCVD in the composite

outcome would be lower than that of the whole ASCVD, the contribution of traditional predictors to the improvement in risk discrimination could be underestimated. However, SGLT2 inhibitors and finerenone showed robust benefits for heart failure and kidney disease outcomes but modest or uncertain benefits for ASCVD [8,27]. The inclusion of critical rather than whole ASCVD as a component of the composite outcome might be sufficient in prediction models for decision of such treatments. Finally, the study included 40- to 79-year-old residents in Korea and excluded those with a history of hospitalized heart failure or critical ASCVD, and therefore caution is required when generalizing the results.

In conclusion, in this population-based study in Korea, albuminuria and eGFR, compared with traditional predictors, allowed better discrimination and larger NRIs in risk prediction models for composite cardiovascular and kidney outcome. The high incidence of ≥10 per 1,000 person-years for the composite outcome was observed in diabetic or hypertensive adults with high or very high KDIGO risk and in those with moderate (or low) KDIGO risk and a PCEs 10-year risk of ≥10% (or ≥20%). This study strongly supports the utility of the KDIGO risk matrix combined with cardiovascular risk score category to identify candidates who will most likely benefit from treatment effective for both cardiac and kidney outcomes.

Conflicts of interest

The author has no conflicts of interest to declare.

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Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the data provision review committee of the National Health Insurance Sharing Service (http://nhiss.nhis.or.kr).

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