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The Impact of Treating Metabolic Acidosis in CKD: Consideration of time-varying confounding among treatment, renal function, and acidosis through G-formula

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Objectives : The debate on whether treating metabolic acidosis decelerates chronic kidney disease (CKD) progression persists despite extensive research. Bicarbonate therapy mitigates metabolic acidosis, yet CKD exacerbates it, highlighting the necessity to examine these interactions comprehensively. This study employs G-formula to assess the impact of metabolic acidosis treatment in CKD, considering those intricate interactions.
Methods : A retrospective cohort study was conducted on patients whose eGFR of less than 60 was confirmed at 3-month intervals in two tertiary referral centers. Time-varying Cox analysis and G-formula were used to consider the time-varying effect of metabolic acidosis. In particular, the G-formula was adopted to account for the time-varying confounding between bicarbonate medication, serum total CO2, and creatinine level [Figure 1].
Results : The study included 19,627 participants. Over the median follow-up of 12 (IQR 6.5, 16.5) years. 4,127 patients advanced to end-stage kidney disease (ESKD) and 6,273 patients died. Consistent with expectations, previous serum TCO2 levels (Coefficient 0.163, 95% CI 0.140–0.186, p-value<0.001) and bicarbonate treatment (0.898,0.897–0.899, <0.001) positively influenced the following visit's serum TCO2, whereas previous serum creatinine (-0.398, -0.406– -0.391, <0.001) showed a negative correlation. Initial time-varying Cox analysis suggested metabolic acidosis treatment heightened risks of ESKD progression (aHR 4.28, 95% CI 3.950–4.637, p<0.001) and mortality (aHR 1.22, 95% CI 1.096–1.353, p<0.001). However, implementing the G-formula revealed treatment significantly reduced ESKD progression (aHR 0.90, 95% CI 0.874–0.927) and mortality rates (aHR 0.94, 95% CI 0.934–0.950). Determining the optimal TCO2 levels for bicarbonate administration (<18, <20, <22), we found that <22 offered the most considerable risk reduction (Table 1).
Conclusions : Properly addressing the time-varying confounding among bicarbonate treatment, metabolic acidosis, and renal function suggests the potential benefit of metabolic acidosis treatment in lowering the rates of ESKD progression and mortality among CKD patients.

Figure1_수정.png

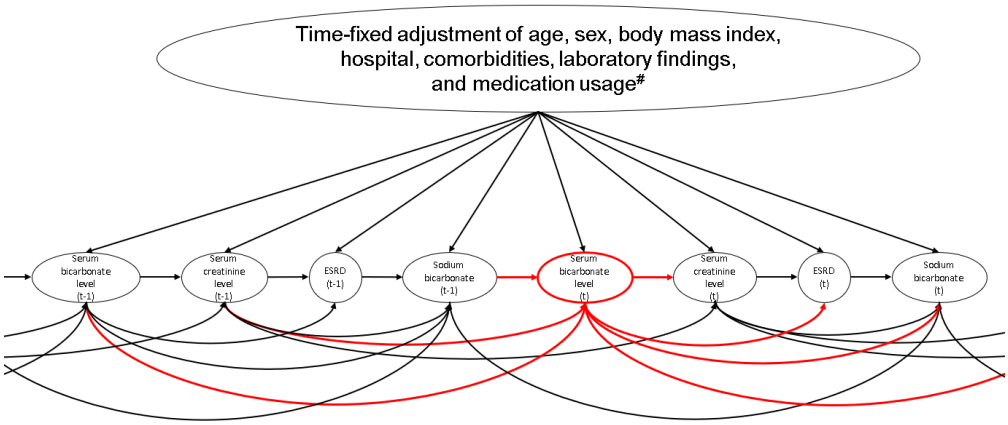

Figure1_수정.png

Table 1. Impact of metabolic acidosis treatment assessed through G-formula: sensitivity analysis based on initial TCO2 levels

Treatment	ESRD		All-cause mortality	
	Risk ratio	95% CI	Risk ratio	95% CI
Always	0.90	0.874–0.915	0.94	0.934–0.950
TCO2 <18	0.99	0.990–0.993	0.998	0.998–0.998
TCO2 <20	0.98	0.977–0.985	0.994	0.994–0.995
TCO2 <22	0.97	0.959–0.973	0.985	0.985–0.988

Time-fixed covariates: Age, Sex, Comorbidities (diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, stroke, myocardial infarction, cerebral hemorrhage, cerebral infarction), hospital, body mass index, medication usage (metformin, sulfonylurea, dipeptidyl peptidase inhibitor, sodium-glucose cotransporter2 inhibitor, insulin, meglitinide, thiazolidinedione, a-glucosidase inhibitor, angiotensin 2 receptor blockers, angiotensin-converting enzyme inhibitor, calcium channel blocker, diuretics, beta blocker, statin, ezetimibe, fenofibrate, omega-3, aspirin, clopidogrel, and direct oral anticoagulants) and laboratory findings (white blood cell count, hemoglobin, albumin, total cholesterol, glucose, aspartate aminotransferase).
Time-varying covariate: Serum total CO2 and creatinine level.