

# Metabolic Acidosis is an Independent Predictor of Adverse Renal Outcomes and Higher Costs in Patients with Chronic Kidney Disease

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## BACKGROUND

Metabolic acidosis is a risk factor for chronic kidney disease (CKD) progression<sup>1</sup>, but less is known about its effect on health care costs and resource utilization. We describe the association between metabolic acidosis and adverse renal outcomes and costs in non-dialysis patients with CKD stages 3-5.

## OBJECTIVE

To investigate the impact of metabolic acidosis on healthcare outcomes and direct costs in the non-dialysis CKD population.

## METHODS

- From electronic medical records data (Optum® EMR) spanning the years 2007 to 2017, we identified non-dialysis-dependent CKD patients (N= 51,558) with ≥ 2 serum bicarbonate tests 28–365 days apart, ≥ 3 eGFR values < 60 mL/min/1.73 m<sup>2</sup> and who either had ≥ 2 years of follow-up data or died during this interval.
  - The Optum® Database contained HIPAA-compliant, de-identified data from a cumulative population of 81 million patients in the United States, including those with all insurance types and those who were uninsured.
- Cohorts were established of patients with two serum bicarbonate values 28–365 days apart in the same range: metabolic acidosis cohort (12 to < 22 mEq/L) and normal serum bicarbonate cohort (22 to 29 mEq/L). The index date was established as the date of the first serum bicarbonate test meeting the inclusion criteria. Serum bicarbonate and eGFR values from hospital inpatient or emergency care involving acute kidney injury weren't used. Patients without a qualifying pair of serum bicarbonate tests were excluded. Patients with metabolic acidosis were over-sampled by preferential selection to ensure adequate sample size.
- Patients were followed for 2 years for the composite adverse outcome, DD40, defined as death, chronic dialysis, kidney transplant, or eGFR decline ≥ 40%, excluding such declines during an episode of acute kidney injury.
- We established predicted all-cause costs in a subset of patients with linked medical claims with general linear regression models using the covariates age, sex, CKD stage, diabetes, hypertension, metabolic acidosis and whether the patient experienced a DD40 outcome. Predicted costs were then applied to the larger EMR population based on each EMR patient's characteristics and summed over the two-year outcome period.
- The incidence of DD40 events and all-cause predicted costs per patient per year (PPPY) were compared between patients in the metabolic acidosis and normal serum bicarbonate cohorts within CKD stage and in total for a 2-year post-index outcome period.
- We assessed the independent effect of serum bicarbonate on death, adverse kidney outcomes (DD40) and healthcare costs in the linked claims subset, controlling for potential confounders [age, sex, race, eGFR, serum bicarbonate, pre-existing diabetes, hypertension, heart failure, Charlson comorbidity score (an index of comorbidity burden), and log albumin-to-creatinine ratio] with logistic and linear regression models.

**Table 1. Demographic and Baseline Characteristics**

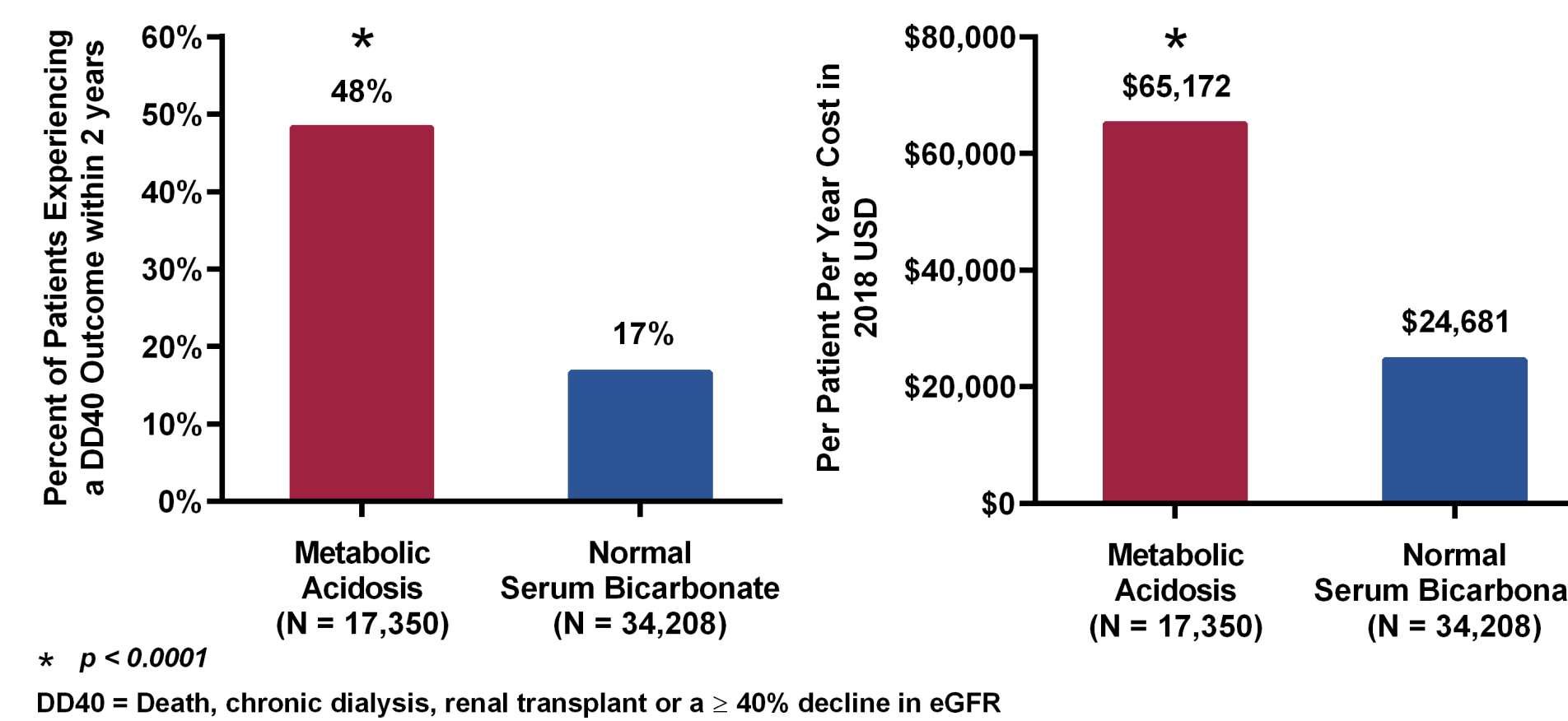
	Total Study Population (N = 51,558)	Metabolic Acidosis Cohort (N = 17,350)	Normal Serum Bicarbonate Cohort (N = 34,208)	P Value
Age (y), mean (SD)	72.9 (11.5)	70.3 (13.3)	74.3 (10.3)	<0.0001
Sex (F) (%)	53	52	53	0.0468
Race (%)				
African American	10	15	7	<0.0001
Asian	2	2	2	<0.0001
Caucasian	82	74	85	<0.0001
Other / Unknown	7	9	5	<0.0001
Comorbidities / Conditions (%)				
Hypertension	62	74	55	<0.0001
Diabetes	31	43	26	<0.0001
Coronary Artery Disease	28	36	24	<0.0001
Edema	25	40	18	<0.0001
Peripheral Vascular Disease	19	29	15	<0.0001
Heart Failure	19	30	14	<0.0001
Charlson Comorbidity Index (CCI) Weighted, mean (SD)	2.3 (2.7)	3.5 (3.1)	1.7 (2.3)	<0.0001
ACE Inhibitors and ARBs Prescription (%)	23	29	20	<0.0001
Alkali Treatment (%)	2	3	1	<0.0001
Serum Bicarbonate (mEq/L), mean (SD)	24.0 (3.6)	19.7 (1.1)	26.1 (2.0)	<0.0001
eGFR (mL/min/1.73 m <sup>2</sup> ), mean (SD)	41.2 (12.1)	37.2 (13.3)	43.2 (10.9)	<0.0001
Hemoglobin (g/dL), mean (SD)	12.2 (2)	11.3 (2.1)	12.6 (1.8)	<0.0001
Serum Albumin (g/dL), mean (SD)	3.7 (0.6)	3.5 (0.7)	3.9 (0.5)	<0.0001
Urinary ACR (mg/g), mean (SD)	190 (554)	277 (692)	127 (414)	<0.0001

P-values are for the comparison of the metabolic acidosis cohort with the normal serum bicarbonate cohort

## RESULTS

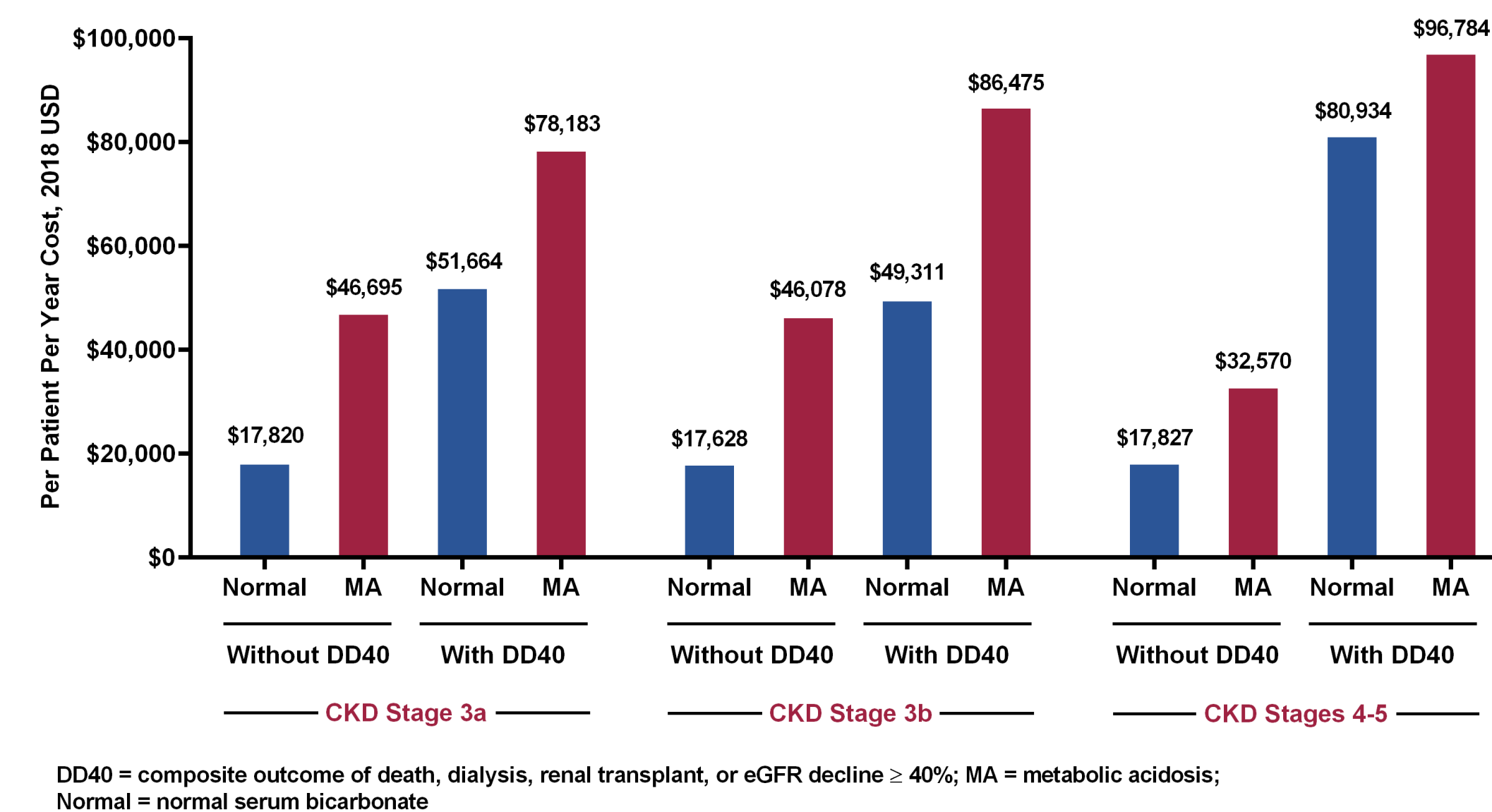
- 51,558 patients with CKD were included in the analysis (Table 1).
- Patients with metabolic acidosis at baseline were younger, had more advanced kidney disease, a higher comorbidity burden, and were more likely to be prescribed angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

**Figure 1. 2-year Incidence Rates of DD40 and Per Patient Per Year Cost, Metabolic Acidosis vs. Normal Serum Bicarbonate**



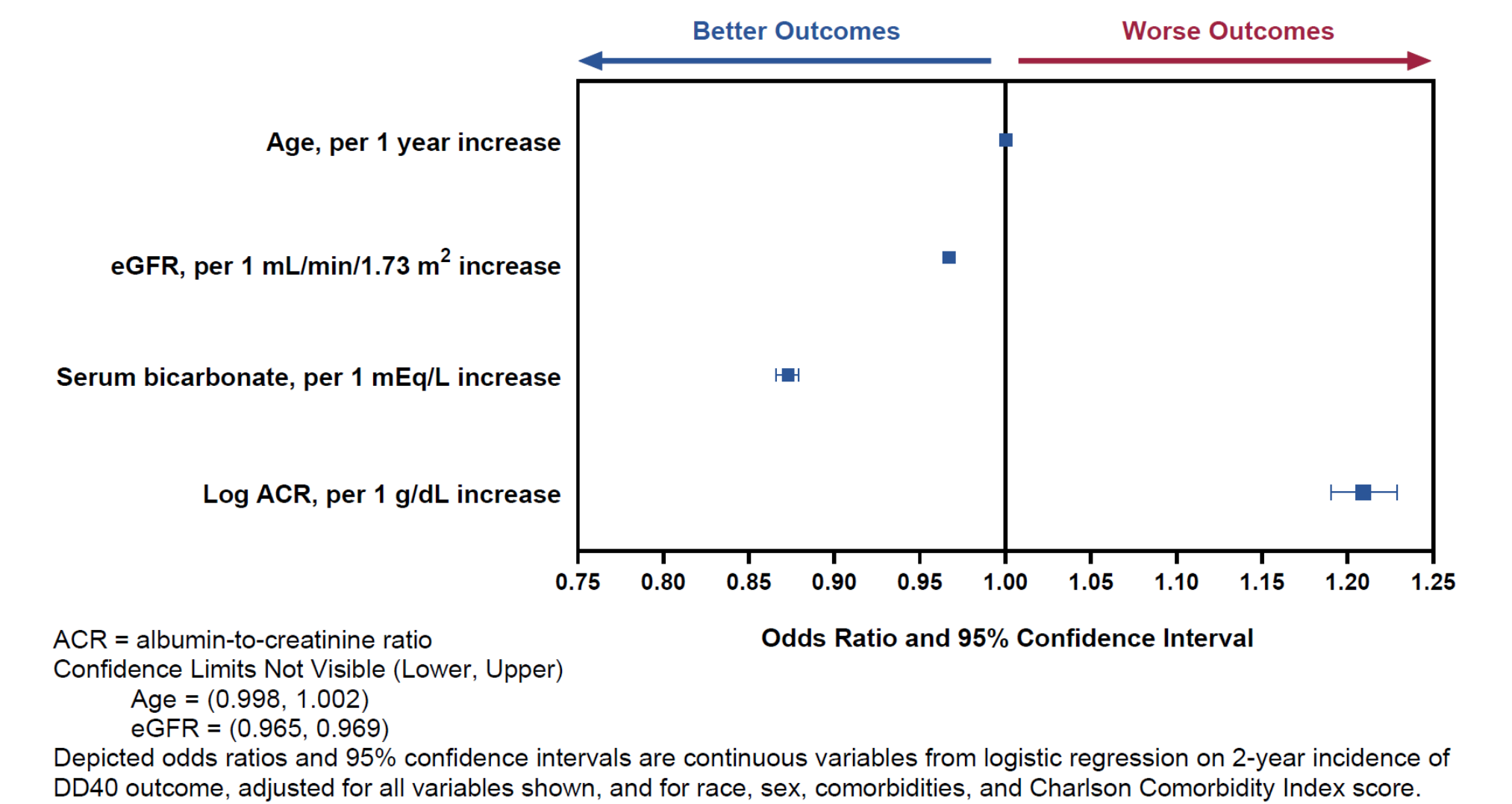
- Unadjusted 2-year incidence rates of composite outcome DD40 (death, dialysis or ≥ 40% decline in eGFR) were significantly higher in patients with metabolic acidosis compared to patients with normal serum bicarbonate at baseline (p< 0.0001) (Figure 1).
- Patients with advanced CKD and metabolic acidosis had significantly higher per patient per year costs compared to patients with normal serum bicarbonate at baseline, \$65,172 vs. \$24,681, respectively (p< 0.0001).

**Figure 2. All-Cause Costs Per Patient Per Year (PPPY), Metabolic Acidosis vs. Normal Serum Bicarbonate, with and without DD40 Outcome (Unadjusted)**



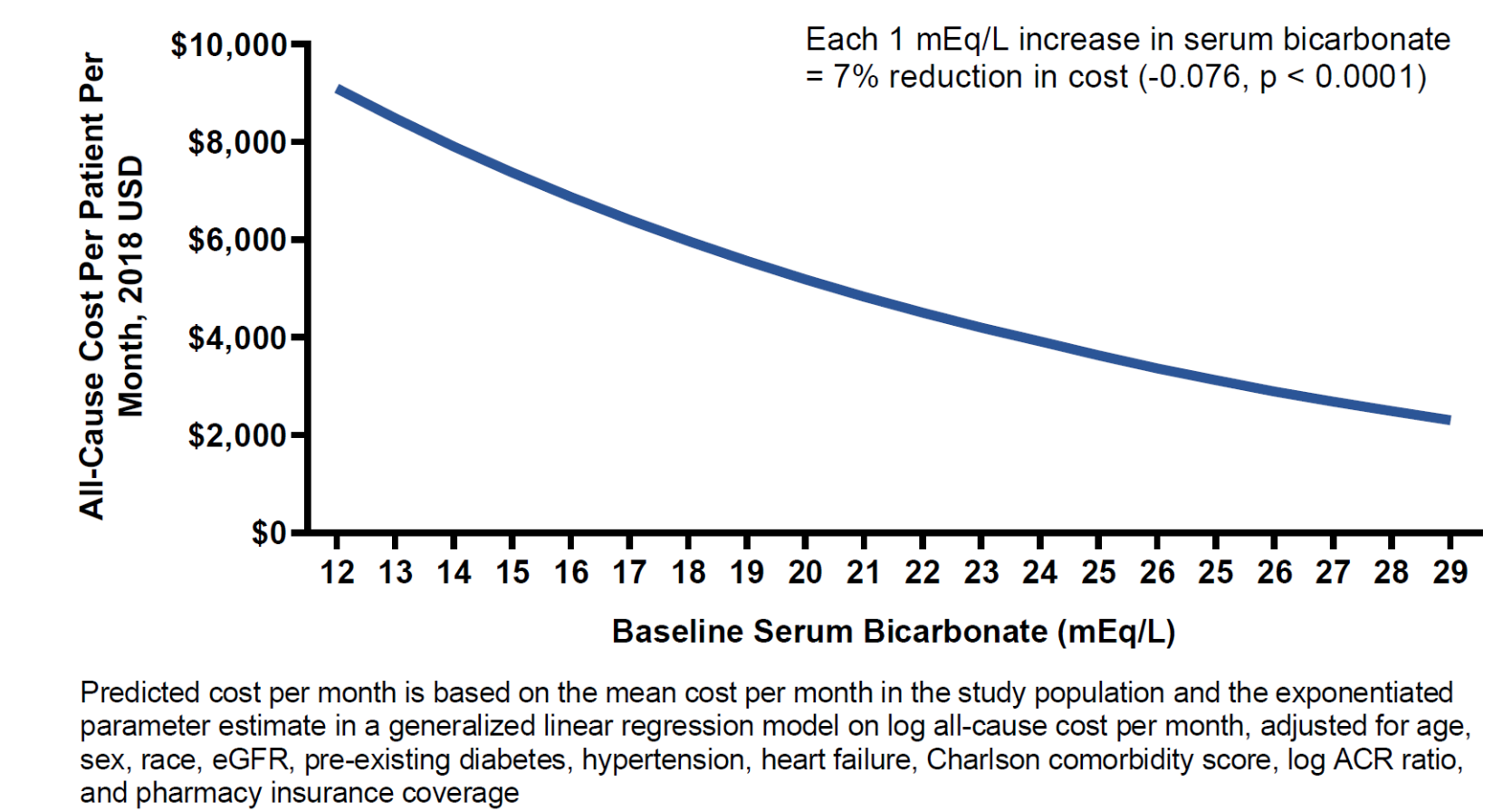
- At each stage of CKD, among patients with and without a DD40 outcome, patients with metabolic acidosis had higher per patient per year costs compared to patients with normal serum bicarbonate at baseline (Figure 2).

**Figure 3. Odds Ratios for 2-Year Incidence of DD40 Outcome**



- Serum bicarbonate was a strong independent predictor of a DD40 outcome after controlling for age, sex, race, eGFR, pre-existing diabetes, hypertension, heart failure, Charlson comorbidity score, and log ACR (p<0.0001) (Figure 3).
- Each 1 mEq/L increase in serum bicarbonate was associated with a 13% decrease in the 2-year risk of experiencing a DD40 event. The odds ratio of DD40 for each 1 mEq/L increase in serum bicarbonate was 0.87 (CI 0.866, 0.879) (Figure 3).

**Figure 4. Predicted Cost Per Month per 1 mEq/L Increment in Serum Bicarbonate**



- Serum bicarbonate was a significant predictor of monthly healthcare cost after controlling for potential confounders (Figure 4).

## CONCLUSION

In this analysis of > 51,000 non-dialysis CKD patients followed for two years, patients with metabolic acidosis had higher rates of death and adverse kidney outcomes (DD40) and higher costs compared to those with normal serum bicarbonate. Each 1 mEq/L increase in serum bicarbonate was associated with a 13% decrease in the 2-year composite endpoint of death, dialysis, kidney transplant or a ≥40% eGFR decline and a 7% decrease in monthly costs.

### Reference

- Kraut JA and Madias NE. *Adv Chronic Kidney Dis.* 24(5): 289-24(5): 289-297, 2017.

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