Cohort Study of Serious Angioedema in Association with Sacubitril/Valsartan Use in Black Patients with Heart Failure

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BACKGROUND

- In the United States, sacubitril/valsartan (sac/val) is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure (HF) in adult patients. Benefits are most clearly evident in patients with left ventricular ejection (LVEF) fraction below normal.*
- Limited data from the approval trial suggested a potential increased risk of serious angioedema among Black patients treated with sac/val relative to angiotensin converting enzyme inhibitors (ACEI).

OBJECTIVE

- To provide real-world estimates of serious angioedema risk among Black patients with HF initiating sac/val relative to ACEI.

METHODS

- We performed a retrospective cohort study implementing a common protocol across 3 nationally representative United States electronic health record and claims data sources: Cardiovascular Research Network (CVRN), Innovation in Medical Evidence and Surveillance (IMEDS), Centers for Medicare and Medicare Services Medicare Fee-for-Service (Medicare).
- We identified eligible new users of sac/val or ACEI between July 7, 2015 (United States sac/val approval date) and December 31, 2019.
- Eligible patients met the following criteria: recorded Black race, continuous medical and drug coverage for ≥1 year prior to the index date (date for first eligible dispensing), known race and sex, age ≥18 years at index date, no prior angioedema diagnoses, HF diagnosis within year prior to index date, no use of sac/val in year prior to index (sac/val initiators only), no use of sac/val or ACEI in year prior to index (ACEI initiators only).
- We calculated incidence rates (IR) of serious angioedema (defined as an inpatient diagnosis) within 1 year of treatment initiation in both exposure groups.
- We estimated hazard ratios (HR) comparing serious angioedema risk between sac/val vs. ACEI initiators using inverse probability of treatment weighting to adjust for measured confounding.
- We repeated all analyses among non-Black patients and using an outcome of any angioedema (defined as a diagnosis in any care setting) within 1 year of initiation.

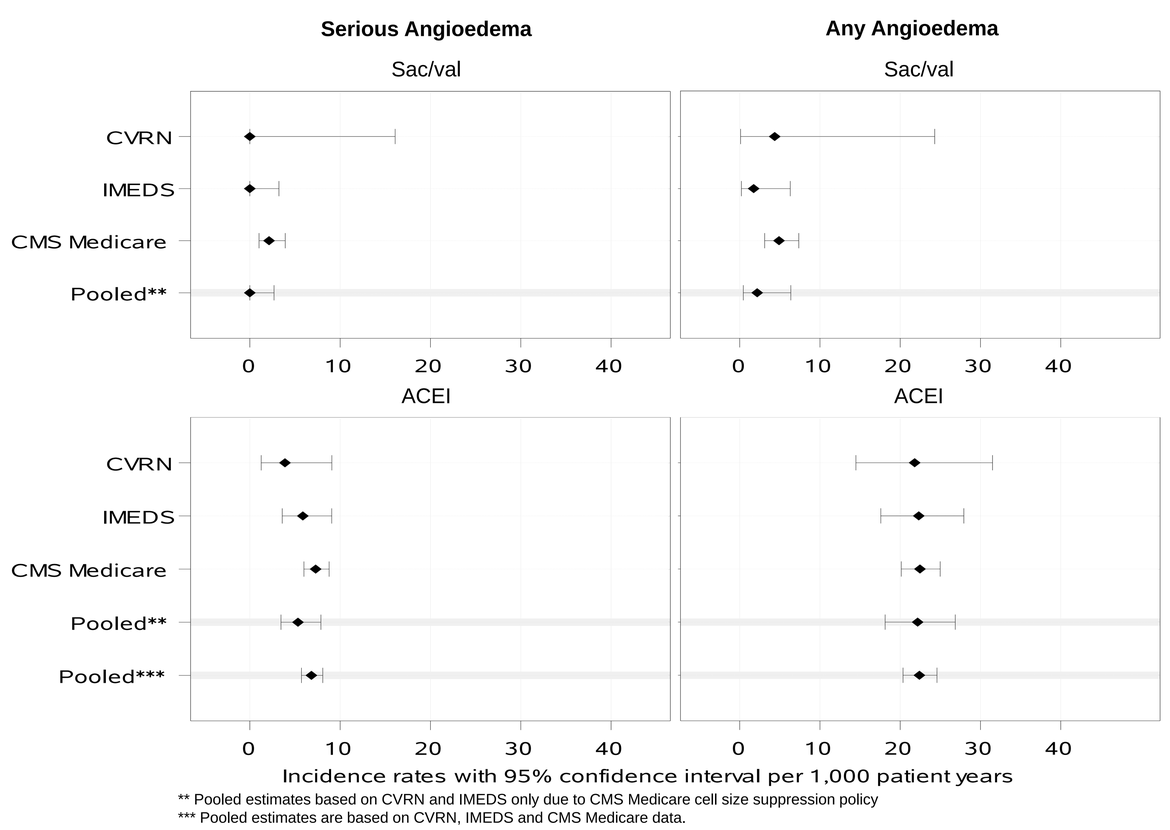
RESULTS

- We identified 118,358 sac/val initiators (19,018 were Black) and 344,355 ACEI initiators (56,626 were Black) across all 3 data sources (**Table 1**).
- Relative to ACEI initiators, sac/val initiators were more likely to be male, younger, have higher cardiovascular comorbidity, and have severe HF regardless of race. Covariate differences between exposure groups were similar in Black and non-Black patients.
- There were <11 serious angioedema events among Black sac/val patients across the 3 data sources, which precluded pooling of Medicare results due to small-cell redaction policies.
- The IR of serious angioedema among Black sac/val patients in Medicare was 2.13 per 1,000 person-years (PY) (95%CI: 1.02-3.92). The pooled IR from CVRN/IMEDS was 0.00 per 1,000 PY (95%CI: 0.00-4.82). The pooled IR of serious angioedema among Black ACEI patients across all 3 data sources was 6.82 per 1,000 PY (95%CI: 5.72-8.08) (**Figure 1**).
- The HR for serious angioedema among Black sac/val patients compared to Black ACEI patients in Medicare was 0.30 (95%CI: 0.14-0.66). There were no serious events among sac/val users within CVRN or IMEDS.
- The meta-analyzed HR for any angioedema among Black sac/val patients compared to Black ACEI patients across all 3 data sources was 0.21 (95%CI: 0.09-0.48) (**Figure 2**).
- IRs were higher among Black patients compared to non-Black patients regardless of exposure or outcome. HRs comparing exposure groups were similar in non-Black patients.

Table 1. Selected Patient Characteristics by Race

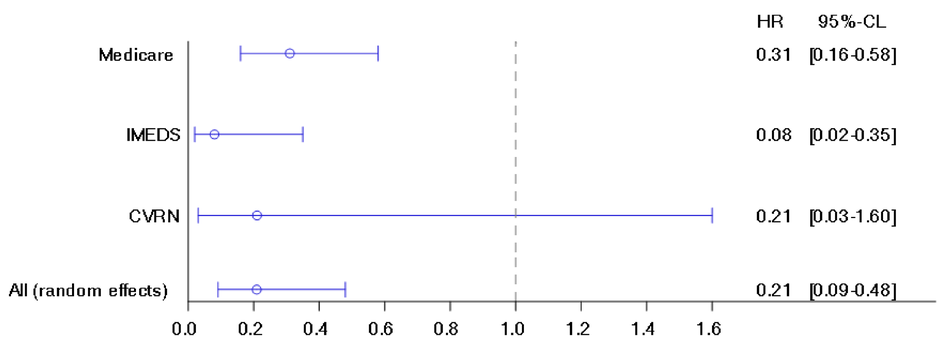
	Black Patients		Non-Black Patients	
	Sac/val N=19,018	ACEI N=52,626	Sac/val N=99,340	ACEI N=291,729
Female, n (%)	8,889 (46.7)	29,090 (55.3)	33,486 (33.7)	153,155 (52.5)
Age, mean (SD)	66.57 (12.49)	69.20 (13.40)	74.36 (9.98)	76.47 (11.31)
2+ HF hospitalizations, n (%)	2,738 (14.4)	4,271 (8.1)	7,814 (7.9)	14,218 (4.9)
Ventricular fibrillation, n (%)	5,126 (27.0)	5,932 (11.3)	25,340 (25.5)	30,454 (10.4)
Angiotensin receptor blockers, n (%)	6,936 (36.5)	9,532 (18.1)	33,730 (34.0)	42,857 (14.7)
Defibrillator, n (%)	8,136 (42.8)	5,475 (10.4)	45,966 (46.3)	39,093 (13.4)

Figure 1. Angioedema Incidence Rates Among Black Patients



** Pooled estimates based on CVRN and IMEDS only due to CMS Medicare cell size suppression policy
*** Pooled estimates are based on CVRN, IMEDS and CMS Medicare data.

Figure 2. Hazard Ratios for Any Angioedema comparing Black Initiators of Sac/val vs. ACEI



LIMITATIONS

- All analyses were potentially impacted by measurement error. Treatment effects may additionally be impacted by channeling bias, selection bias, and unmeasured confounding.

CONCLUSION

- Our study did not observe an increased risk of serious or any angioedema among Black or non-Black HF patients initiating sac/val compared to ACEI in real-world settings.

ACKNOWLEDGEMENTS/DISCLOSURES/FOOTNOTES

- Many thanks are due to data partners who provided data used in the analysis
- The study was sponsored by Novartis Pharma AG. JL and SB are Novartis employees and own Novartis shares.
- *Also registered for an expanded adult HF indication i.e., Heart Failure with Preserved Ejection Fraction, for use in pediatric HF patients and for the treatment of essential hypertension. Approved indications may vary depending upon the individual country.