SUPPLEMENTARY MATERIAL

Real-World Analysis of the Association Between Systemic Inflammation, Cardiovascular Events, and Economic Burden Among Patients with Atherosclerotic Cardiovascular Disease and Chronic Kidney Disease

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Supplementary Material List:

Table S1. Representativeness of the study population

	Patients with ASCVD who are not tested for hsCRP N=10,195,265	Patients with ASCVD who are tested for hsCRP (CPT code) N=1,074,143	P-value	Study population N=74,884
Patient age, years			<0.001	
Mean (SD)	63.5 (13.1)	60.4 (12.3)		60.5 (11.2)
Sex			<0.001	
Women	4,885,860 (47.9%)	530,884 (49.4%)		34,294 (45.8%)
Men	5,152,079 (50.5%)	520,911 (48.5%)		38,637 (51.6%)
Unknown	157,326 (1.5%)	22,337 (2.1%)		1,953 (2.6%)
Patient race and ethnicity			<0.001	
White	5,652,229 (55.4%)	566,909 (52.8%)		42,572 (61.7%)
Hispanic or Latino	1,215,755 (11.9%)	159,132 (14.8%)		9,602 (13.9%)
Black or African American	1,322,412 (13.0%)	130,707 (12.2%)		5,637 (8.2%)
Asian or Pacific Islander	395,575 (3.9%)	43,817 (4.1%)		3,357 (4.9%)
Other	316,312 (3.1%)	39,020 (3.6%)		3,331 (4.8%)

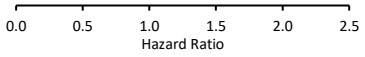
Unknown/missing	1,292,982 (12.7%)	134,547 (12.5%)		10,385 (13.8%)
Patient region			<0.001	
Midwest	2,093,302 (20.5%)	154,142 (14.4%)		7,770 (10.4%)
Northeast	2,496,236 (24.5%)	317,995 (29.6%)		19,168 (25.6%)
South	3,749,698 (36.8%)	349,810 (32.6%)		30,218 (40.4%)
Unknown	36,503 (0.4%)	1,373 (0.1%)		4 (0.0%)
West	1,819,526 (17.8%)	250,812 (23.4%)		17,724 (23.7%)
Patient insurance provider			<0.001	
Commercial	3,579,634 (35.3%)	487,148 (45.5%)		45,703 (61.1%)
Medicaid	1,860,932 (18.3%)	209,082 (19.5%)		6,832 (9.1%)
Medicare Advantage / Medicare FFS	4,701,245 (46.4%)	375,261 (35.0%)		22,317 (29.8%)
Unknown	53,454	2,641		32
Quan-Charleson Comorbidity Index (QCI)				
0	5,551,615 (54.7%)	590,263 (55.1%)	<0.001	55,301 (73.8%)
1	1,710,583 (16.8%)	188,838 (17.6%)		10,784 (14.4%)
2	1,396,740 (13.8%)	144,247 (13.5%)		5,978 (8.0%)
3+	1,495,276 (14.7%)	147,636 (13.8%)		2,821 (3.8%)
Unknown	41,051	3,148		
Mean (SD)	1.1 (1.8)	1.1 (1.7)	<0.001	0.4 (0.9)
Other comorbidities, n, %				
Hypertension	5,916,562 (58.0%)	616,207 (57.4%)	<0.001	36,423 (48.6%)
Heart failure	771,884 (7.6%)	70,047 (6.5%)	<0.001	2,029 (2.7%)
Atrial fibrillation	804,245 (7.9%)	68,949 (6.4%)	<0.001	3,449 (4.6%)
Dyslipidemia	4,806,501 (47.1%)	565,686 (52.7%)	<0.001	42,145 (56.3%)
Autoimmune disease	448,092 (4.4%)	84,458 (7.9%)	<0.001	3,462 (4.6%)
Obesity	1,603,154 (15.7%)	200,895 (18.7%)	<0.001	11,187 (14.9%)
Smoking	1,982,776 (19.4%)	192,399 (17.9%)	<0.001	7,323 (9.8%)
Type 2 diabetes	3,009,876 (29.5%)	321,725 (30.0%)	<0.001	16,106 (21.5%)
Baseline medication use				
Antihypertensive drugs	6,588,255 (64.6%)	669,999 (62.4%)	<0.001	41,150 (55.0%)
Lipid-lowering drugs	4,646,642 (45.6%)	488,206 (45.5%)	0.013	33,762 (45.1%)
Statin	4,396,258 (43.1%)	454,616 (42.3%)	<0.001	31,224 (41.7%)
Other lipid-lowering medications	659,120 (6.5%)	91,278 (8.5%)	<0.001	7,063 (9.4%)
Cardiovascular drugs	1,168,766 (11.5%)	110,356 (10.3%)	<0.001	5,706 (7.6%)
Antiplatelet	1,197,800 (11.7%)	131,301 (12.2%)	<0.001	6,702 (8.9%)
Anticoagulants	787,495 (7.7%)	73,436 (6.8%)	<0.001	3,769 (5.0%)
Vasodilation drugs	432,124 (4.2%)	41,371 (3.9%)	<0.001	1,957 (2.6%)
Other cardiovascular drugs	1,162,457 (11.4%)	109,353 (10.2%)	<0.001	1,046 (1.4%)
Immunosuppressants	1,831,414 (18.0%)	241,103 (22.4%)	<0.001	11,856 (15.8%)

Nonsteroidal anti-inflammatory (NSAIDs)	2,573,660 (25.2%)	319,582 (29.8%)	<0.001	17,535 (23.4%)

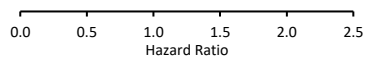
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CPT, Common Procedural Terminology; FFS, fee-for-service; hsCRP, high-sensitivity C-reactive protein; QCI, Quan-Charleson Comorbidity Index; SI, systemic inflammation.

Table S2. Association of systemic inflammation with the occurrence of cardiovascular events

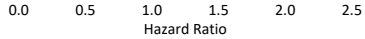
	Revised MACE†			
Patient group	**Patients with event, n (%)**	**Incidence rate per 1,000 PY (95% CI)**	**Adjusted HR (95% CI) p value**	**Forest plot of hazard ratios**
ASCVD without CKD or SI*	1,304 (3.9)	18.31 (17.74, 18.89)	Reference	-
ASCVD without CKD + SI	1,548 (4.9)	13.49 (12.77, 14.24)	1.24 (1.15, 1.34) p<0.001	
ASCVD + CKD all stages without SI	434 (9.9)	33.32 (30.26, 36.61)	1.35 (1.20, 1.52) p<0.001	
ASCVD + CKD all stages + SI	662 (12.1)	40.38 (37.36, 43.57)	1.65 (1.48, 1.82) p<0.001	



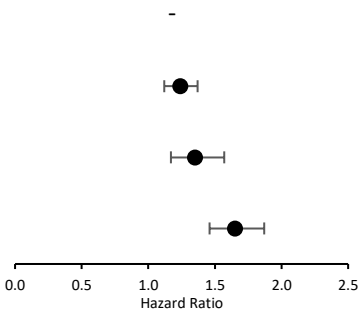
	Non-fatal MI			
Patient group	**Patients with event, n (%)**	**Incidence rate per 1,000 PY (95% CI)**	**Adjusted HR (95% CI), p value**	**Forest plot of hazard ratios**
ASCVD without CKD or SI*	574 (1.7)	7.94 (7.57, 8.33)	Reference	-
ASCVD without CKD + SI	719 (2.3)	5.87 (5.40, 6.38)	1.25 (1.12, 1.40) p<0.001	
ASCVD + CKD all stages without SI	164 (3.8)	12.40 (10.57, 14.44)	1.20 (1.00, 1.44) p=0.051	
ASCVD + CKD all stages + SI	278 (5.1)	16.64 (14.74, 18.71)	1.59 (1.36, 1.86) p<0.001	



	Non-fatal stroke			
Patient group	**Patients with event, n (%)**	**Incidence rate per 1,000 PY (95% CI)**	**Adjusted HR (95% CI), p value**	**Forest plot of hazard ratios**
ASCVD without CKD or SI*	527 (1.6)	6.88 (6.53, 7.23)	Reference	-
ASCVD without CKD + SI	601 (1.9)	5.40 (4.94, 5.88)	1.22 (1.08, 1.38) p=0.001	
ASCVD + CKD all stages without SI	151 (3.5)	11.35 (9.61, 13.31)	1.45 (1.19, 1.75) p<0.001	
ASCVD + CKD all stages + SI	225 (4.1)	13.34 (11.65, 15.20)	1.76 (1.48, 2.09) p<0.001	



Patient group	Patients with event, n (%)	Incidence rate per 1,000 PY (95% CI)	All-cause mortality Adjusted HR (95% CI), p value	Forest plot of hazard ratios
ASCVD without CKD or SI*	706 (2.1)	10.41 (9.99, 10.84)	Reference	
ASCVD without CKD + SI	807 (2.6)	7.08 (6.57, 7.62)	1.21 (1.09, 1.34) p<0.001	
ASCVD + CKD all stages without SI	335 (7.7)	24.05 (21.55, 26.77)	1.34 (1.16, 1.56) p<0.001	
ASCVD + CKD all stages + SI	490 (8.9)	27.59 (25.20, 30.14)	1.49 (1.30, 1.71) p<0.001	



*Reference group

Hazard ratios were estimated from Cox proportional hazards models with time to the first MACE (or its components) as dependent variables, and SI and CKD as independent variables. Models were adjusted for baseline characteristics (patient race/ethnicity, gender, age group, region, insurance group, QCI index category, comorbidities (hypertension, dyslipidemia, obesity, smoking, atrial fibrillation), and medication use (antiplatelet drugs, statins, other lipids [excluding statins], hypertensive drugs, immunosuppressants, cardiovascular drugs [excluding anticoagulants], anticoagulants, CKD medications)

[†]Revised MACE includes nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality

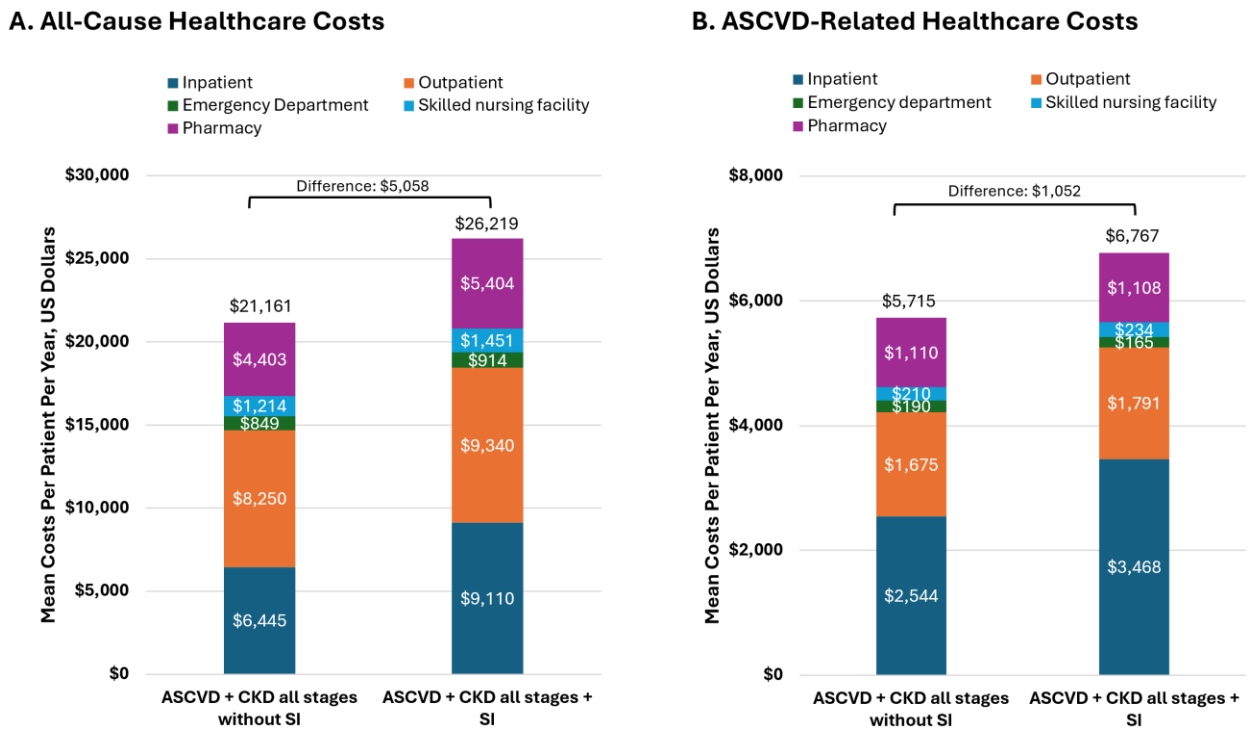
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; SI, systemic inflammation; PY, person-years.

Supplemental Table S3. All-cause and ASCVD-related healthcare resource utilization in patients with ASCVD and CKD all stages

	All-cause		ASCVD-related	
Healthcare resource utilization	**ASCVD + CKD all stages without SI n=4,365**	**ASCVD + CKD all stages + SI n=5,492**	**ASCVD + CKD all stages without SI n=4,365**	**ASCVD + CKD all stages + SI n=5,492**
Inpatient visits, PPPY	0.19 (0.19, 0.20)	0.24 (0.24, 0.25)	0.10 (0.09, 0.10)	0.13 (0.13, 0.14)
Outpatient visits, PPPY	16.83 (16.76, 16.9)	18.05 (17.99, 18.11)	2.56 (2.53, 2.59)	2.71 (2.68, 2.73)
Emergency visits, PPPY	0.40 (0.39, 0.41)	0.43 (0.42, 0.44)	0.08 (0.07, 0.08)	0.07 (0.07, 0.08)
Pharmacy fills, PPPY	25.80 (25.71, 25.88)	28.53 (28.45, 28.61)	11.38 (11.33, 11.44)	12.32 (12.27, 12.37)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; PPPY, per patient per year; SI, systemic inflammation.

Supplemental Figure S1. Healthcare costs in patients with ASCVD and CKD



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; SI, systemic inflammation.

STROBE Checklist

STROBE —Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-9
Bias	9	Describe any efforts to address potential sources of bias	7-9
Study size	10	Explain how the study size was arrived at	6-9, fig1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	6-9
		(*d*) If applicable, explain how loss to follow-up was addressed	6-9
		(*e*) Describe any sensitivity analyses	6-9

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig1
		(b) Give reasons for non-participation at each stage	Fig1
		(c) Consider use of a flow diagram	Fig1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	10, T1
		(c) Summarise follow-up time (eg, average and total amount)	11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	T1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11-13
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13, T2, T3, T4, Fig2, Fig3, Supplement
Discussion			
Key results	18	Summarise key results with reference to study objectives	13-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20