High-sensitivity C-reactive protein and the risk of chronic kidney disease progression or acute kidney injury in post–myocardial infarction patients

Edouard L. Fu, BS,[a,b] Mikael Andersson Franko, PhD,[b] Achim Obergfell, MD, PhD,[c] Friedo W. Dekker, PhD,[a] Anders Gabrielsen, MD PhD,[d] Tomas Jernberg, MD PhD,[e] and Juan Jesús Carrero, PharmD, PhD[b] *Leiden, the Netherlands; Stockholm, Sweden;* [c]*Novartis Pharma AG, Basel, Switzerland*

Abstract Background Persistent, low-grade inflammation likely participates in the pathophysiology of both atherosclerosis and kidney disease. Although high-sensitivity C-reactive protein (hsCRP) predicts future cardiovascular risk in patients with chronic kidney disease (CKD), it is unknown whether hsCRP levels predict adverse renal outcomes in patients with cardiovascular disease.

Methods We studied all myocardial infarction (MI) survivors undergoing hsCRP testing >30 days after their MI during routine health care in Stockholm, Sweden (2006-2011), with available information on estimated glomerular filtration rate (eGFR). HsCRP tests measured during hospitalization/emergency room visits, followed by antibiotics or indicative of acute illness, were excluded, together with patients with ongoing/recent cancer, chronic infections, or immunosuppression. Inflammation was defined over a 3-month baseline window. Study outcomes were CKD progression (composite of doubling plasma creatinine, renal replacement therapy, or renal death) and acute kidney injury (AKI, acute creatinine peaks according to Kidney Disease: Improving Global Outcomes criteria). Multivariable Cox regression was used to adjust for age, sex, eGFR, hemoglobin, time since MI, comorbidities, undertaken procedures, and medications.

Results A total of 12,905 patients (62% men, mean age 73 years and 3 years since MI) were included, of whom 35% had an eGFR<60 mL/min/1.73 m^2. The mean (SD) hsCRP was 3.0 (4.4) mg/L. Baseline hsCRP levels were increasingly higher across lower eGFR categories. During a median follow-up of 3.2 years, 1,019 CKD progressions and 1,481 AKI events were recorded. Patients with hsCRP ≥2 mg/L were at higher risk of both CKD progression (adjusted hazard ratio 1.42; 95% CI 1.21-1.66) and AKI (1.29; 1.13-1.47) compared to those with hsCRP <2 mg/L. This association persisted across single CKD severity stages and after further hsCRP categorization into 4 groups (≤1, 1-3, 3-10, >10 mg/L). Results were robust across subgroups of patients and after exclusion of events occurring during the first 6-12 months.

Conclusions In post-MI patients undergoing routine health care, elevated hsCRP was associated with subsequent risk of AKI and progression of CKD, irrespective of baseline kidney function. (Am Heart J 2019;216:20-29.)

Introduction

There is broad recognition on the existence of a bidirectional relationship between cardiovascular disease (CVD) and chronic kidney disease (CKD), often described with the term *cardiorenal syndrome*.[1] Patients with CKD have accelerated atherosclerosis and increased risk of CVD events,[2-4] and patients with CVD seem to have a higher risk of CKD and more rapid kidney function decline compared to those without.[5-7]

The mechanisms underlying this heart-kidney cross talk are not fully elucidated. Inflammation has been proposed to participate in the pathophysiology of both cardiovascular[8] and kidney damage.[9] Persistent inflammation is

From the [a]*Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands,* [b]*Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden,* [c]*Novartis Pharma AG, Basel, Switzerland,* [d]*Cardiovascular Medicine Unit, Department of Medicine Solna, Karolinska University hospital Solna, Karolinska Institutet, Stockholm, Sweden, and* [e]*Department of Clinical Sciences, Danderyd University Hospital, Karolinska Institutet, Stockholm, Sweden.*

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Reprint requests: Juan Jesús Carrero, Department of Medical Epidemiology and Biostatistics (MEB), Karolinska Institutet, Nobels väg 12A, Box 281, 171 77 Stockholm. E-mail: juan.jesus.carrero@ki.se

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present in a large proportion of patients following a myocardial infarction (MI),[10,11] and such residual inflammatory risk may, in part, contribute to the high recurrence of cardiovascular events and death.[12-14] Persistent inflammation is also highly prevalent in individuals with CKD[15,16] and predicts subsequent cardiovascular risk.[17] However, there are no studies examining whether the residual inflammatory risk of patients with MI is associated with the risk of adverse renal outcomes.

In this health care–based study, we used high-sensitivity C-reactive protein (hsCRP) as a reflection of residual inflammatory risk. We hypothesized that hsCRP in post-MI patients would be associated with subsequent CKD progression and acute kidney injury (AKI) risk, irrespective of baseline kidney function.

Methods

Data sources

We used data from the Stockholm CREAtinine Measurements (SCREAM) health care utilization cohort,[18] which includes all Stockholm residents (Sweden) accessing health care with at least 1 plasma creatinine measured during 2006 and 2011. Given the commonness and indications of plasma creatinine testing, SCREAM captured 68% of the complete adult population census of the region and 99% of all CVD cases.[18] Laboratory data were linked with regional and national administrative databases for complete information on health care utilization, both in outpatient and inpatient care, including diagnoses, procedures, dispensed drugs, and death, with no missingness (if not ordered as part of a health care encounter) or loss to follow-up. The study used only deidentified data and thus was deemed not to require informed consent. It was approved by regional institutional review boards and the Swedish National Board of Welfare and adheres to the Declaration of Helsinki.

Patient selection, study design, and exposure

We included all adult (>18 years old) MI patients accessing health care and undertaking hsCRP and plasma creatinine testing during January 2007 to December 2011. MI patients were identified by relevant *International Classification of Diseases 10th Revision* (*ICD-10*) codes (I21, I22, and I252) registered in outpatient or inpatient care since 1997. All consecutive hsCRP measurements performed in Stockholm health care during the SCREAM data collection period were then extracted. The study exposure is hsCRP as measured in health care. In analyses from the JUPITER trial, hsCRP levels were found stable over time as long as they are not measured during acute infection.[19] Nonetheless, real–world health care differs from controlled settings, with hsCRP testing performed by judgment of the attending physician. Given the multiple indications of hsCRP tests, a number of patient- and test-specific exclusion criteria were applied to avoid, as much as possible, health care use related biases. To minimize confounding by indication bias, we excluded hsCRPs occurring within the 30 days after the (most recent) MI event, hsCRPs tests taken during an inpatient stay or emergency room visit (±1 day, but allowed hsCRPs taken at admission of an elective surgery), and very elevated hsCRPs (>20 mg/L), presumably indicative of acute illness. We also excluded hsCRPs tests followed by the prescription of antibiotics, antivirals, or antimycotics within 7 days on the assumption that infection was the reason for hsCRP testing. Likewise, we excluded hsCRPs during the following 3 months as they may relate to the monitoring and/or resolution of the infection event (definitions in Supplemental Table I). After applying these hsCRP exclusion criteria, we selected the first eligible hsCRP per patient to define a 3-month baseline window. At this point, we excluded patients with comorbidities and/or long-term medications that modify systemic inflammatory levels. These included ongoing/recent cancer (diagnosed within the previous 3 years), chronic infections (hepatitis, tuberculosis, or HIV) and undertaking corticosteroids or immunosuppressive drugs, and undergoing renal replacement therapy (RRT; chronic dialysis or kidney transplantation). Finally, to minimize the possibility of reverse causality, we required patients to survive a minimum of 3 months from the first eligible hsCRP, and we defined the background/residual inflammation of each patient as the geometric mean of all eligible hsCRP tests during a 3-month baseline window. The end of this 3-month window was considered as the index date of the study and the date from which study covariates were derived and follow-up for clinical outcomes was initiated.

As a next step, we excluded patients undergoing RRT (chronic dialysis or kidney transplantation) and lacking recent plasma creatinine measurements to estimate baseline kidney function. Information on RRT was obtained by linkage with the Swedish Renal Register, which contains complete collection of all dialysis and kidney transplant cases in the country. Eligible plasma creatinine measurements were those performed in connection with an outpatient consultation at time of or within the 12 months preceding index date. Baseline plasma creatinine was defined by the geometric mean of all available tests within this period. Plasma creatinine was measured with either enzymatic or corrected Jaffe method (alkaline picrate reaction) and used to estimate glomerular filtration rate (eGFR) with the CKD-Epidemiology Collaboration equation.[20] We defined CKD as eGFR below 60 mL/min/1.73 m^2 and categorized patients according to Kidney Disease: Improving Global Outcomes criteria: category G3a ($45 \leq$ eGFR <60 mL/min/1.73 m^2), G3b ($30 \leq$ eGFR <45 mL/min/1.73 m^2), and

G4/5 (eGFR <30 mL/min/1.73 m^2).[21] Information on race is not available in Sweden by law, and we assumed that all patients were of Caucasian origin.

Study covariates

Study covariates were calculated at index date and included age, sex, comorbidities and undertaken surgical procedures, medication use, and laboratory values. Comorbid conditions are listed in Supplemental Table I and were assessed through *ICD-10* codes issued at time of or before the index date. Information on comorbidities comes from the Regional Healthcare register. Comorbidities identified in this study used established algorithms with an 85%-95% validity.[22] We collected information on coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) by identification of issued Nordic Medico-Statistical Committee surgical procedure codes (Supplemental Table I).

Medications are also listed in Supplemental Table I and were assumed to be used if there was a pharmacy dispensation at the time of or within the previous 3 months from index date or after 15 days. Information on drug dispensations was obtained from the Dispensed Drug Registry, a nationwide register with complete information on all prescribed drugs dispensed at Swedish pharmacies. The coverage of this register is considered virtually complete, as outpatient drug prescriptions and dispensations in Sweden are performed via each citizen's unique personal identification number.

In Stockholm health care, laboratory tests are measured by 3 different laboratories (Aleris, Unilabs, and Karolinska), which are frequently audited to ensure reproducibility and consistency of determinations across the region. HsCRP was measured in plasma by either immunochemistry or turbidimetry, both with a minimum level of detection of 1 mg/L. Baseline hemoglobin was defined as the geometric mean of all available laboratory tests performed in connection with an outpatient consultation at time of or within the 12 months preceding index date. Missing values (ie, the laboratory test was not ordered during the defined window) were coded as "missing."

Study outcomes

The study outcomes were time to CKD progression and AKI. *CKD progression* was defined as the composite of doubling of plasma creatinine (relative to baseline values), RRT, or renal death (primary cause of death with *ICD-10* code N18). RRT events were identified by linkage with the Swedish Renal Register. Deaths (and causes of death) were retrieved from the Swedish patient register, which is ran by the Swedish Government, is updated monthly, and has complete national coverage. AKI was identified by subsequently detected acute elevations in plasma creatinine. An *AKI event* was defined according to Kidney Disease: Improving Global Outcomes criteria[23] as an increase in plasma creatinine by more than 26.5 μmol/L (=0.3 mg/dL) within 48 hours or an increase of 50% or greater relative to baseline known or presumed to have occurred within the prior 7 days. Patients were followed from index date until occurrence of event, migration from the region of Stockholm, or end of follow-up (December 31, 2012), whichever occurred first.

Statistical analysis

We present descriptive values as median and interquartile range, mean and SD, or counts with proportions. Baseline demographics and clinical characteristics are reported for all MI cases and stratified according to CKD stage. Because the optimal definition of inflammation in post-MI patients is not established, we chose the cutoff hsCRP ≥2 mg/L because this was the cutoff used in post-MI randomized controlled trials.[24] As a sensitivity analysis, we further subcategorized hsCRP according to low, middle, and high cardiovascular risk in the general population (hsCRP ≤1, 1-3, >3-10, and >10 mg/L).

Multivariable adjusted hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazard models to determine the association between serum hsCRP and study outcomes. We graphically assessed and found satisfying the proportional hazards assumption by plotting Schoenfeld residuals against ranks of time. Interaction terms in a priori specified strata were used to evaluate the consistency of observed associations and explore effect modifications. To assess the impact of reverse causation, we repeated the main analyses excluding events occurring within the first 6 or 12 months of follow-up. In sensitivity analyses, we redefined CKD progression as a composite of sustained doubling of creatinine, RRT, and renal death. *Sustained doubling of creatinine* was defined as the presence of 2 creatinine measurements which were twice the value of the baseline creatinine measurement and that were distanced in time between 3 months and up to 2 years from each other. All analyses were performed using R version 3.4.1.

Results

The patient flowchart is shown in Supplemental Figure 1. Among 50,931 patients with an MI, 34,057 patients had at least 1 hsCRP test more than 30 days post-MI during 2007 and 2011. After applying patient- and test-specific exclusion criteria, a total of 12,905 adult MI survivors were identified who had eligible creatinine and hsCRP tests available.

Baseline characteristics

Baseline characteristics are shown in Table I, overall and stratified by eGFR categories. Participants had a mean age of 72.6 (SD 12.4) years, 62.2% were men, and the mean time since MI was 3.0 (SD 2.9) years. Hypertension (69.3%), heart failure (44.6%), and atrial fibrillation

Table I. Baseline characteristics of adult post-MI patients in Stockholm 2007-2011, overall and by eGFR category

	Overall (n = 12,905)	eGFR ≥60 mL/min/1.73 m^2 (n = 8358)	45 ≤ eGFR <60 mL/min/1.73 m^2 (n = 2263)	30 ≤ eGFR <45 mL/min/1.73 m^2 (n = 1550)	eGFR <30 mL/min/1.73 m^2 (n = 734)
Mean age (SD), y	72.6 (12.4)	69.1 (11.8)	79.9 (9.3)	82.3 (8.8)	81.2 (9.7)
Male, n (%)	8027 (62.2)	5683 (68.0)	1222 (54.0)	763 (49.2)	358 (48.8)
Mean time since MI (SD), y	3.0 (2.9)	2.9 (3.0)	3.2 (3.0)	3.2 (2.9)	2.9 (2.8)
Laboratory measurements					
Hb, g/dL*	135.4 (16.2)	139.3 (14.7)	131.7 (15.9)	127.0 (16.2)	119.7 (15.3)
hsCRP, mg/L†	2.97 (4.4)	2.63 (4.1)	3.33 (4.6)	3.89 (4.9)	4.70 (5.1)
hsCRP ≤1, n (%)	3755 (29.1)	2792 (33.4)	557 (24.6)	288 (18.6)	116 (15.8)
hsCRP 1-3	3562 (27.6)	2432 (29.1)	595 (26.3)	389 (25.1)	137 (18.7)
hsCRP 3-10	4052 (31.4)	2365 (28.3)	785 (34.7)	594 (38.3)	309 (42.1)
hsCRP >10	1536 (11.9)	769 (9.2)	326 (14.4)	279 (18.0)	172 (23.4)
hsCRP <2	4078 (31.6)	3001 (35.9)	618 (27.3)	324 (20.9)	129 (17.6)
hsCRP ≥2	8827 (68.4)	5357 (64.1)	1645 (72.7)	1226 (79.1)	605 (82.4)
Comorbidities, n (%)					
Diabetes	3755 (29.1)	3407 (26.4)	697 (30.8)	536 (34.6)	319 (43.4)
Hypertension	8943 (69.3)	8388 (65.0)	1700 (75.1)	1201 (77.5)	603 (82.2)
COPD	2155 (16.7)	1949 (15.1)	421 (18.6)	304 (19.6)	161 (21.9)
Cancer >3 y	1071 (8.3)	878 (6.8)	244 (10.8)	171 (11.0)	82 (11.2)
Dementia	323 (2.5)	159 (1.9)	84 (3.7)	60 (3.9)	21 (2.9)
Heart failure	5756 (44.6)	4375 (33.9)	1286 (56.8)	1073 (69.2)	563 (76.7)
Peripheral vascular disease	1858 (14.4)	1497 (11.6)	373 (16.5)	332 (21.4)	186 (25.3)
Stroke	2155 (16.7)	1794 (13.9)	466 (20.6)	332 (21.4)	193 (26.3)
Atrial fibrillation	3794 (29.4)	2994 (23.2)	894 (39.5)	654 (42.2)	313 (42.6)
Inflammatory bowel disease	181 (1.4)	168 (1.3)	41 (1.8)	22 (1.4)	12 (1.6)
Rheumatoid diseases	1639 (12.7)	1278 (9.9)	344 (15.2)	288 (18.6)	181 (24.7)
AKI	323 (2.5)	90 (0.7)	57 (2.5)	85 (5.5)	122 (16.6)
Procedures, n (%)					
CABG	2245 (17.4)	2310 (17.9)	380 (16.8)	260 (16.8)	108 (14.7)
PCI	4943 (38.3)	5756 (44.6)	672 (29.7)	380 (24.5)	168 (22.9)
Medication, n (%)					
Aspirin	8543 (66.2)	8827 (68.4)	1446 (63.9)	944 (60.9)	433 (59.0)
NSAIDs	1278 (9.9)	928 (11.1)	206 (9.1)	118 (7.6)	33 (4.5)
ACEi/ARBs	7149 (55.4)	4513 (54.0)	1308 (57.8)	910 (58.7)	416 (56.7)
MRA	1071 (8.3)	476 (5.7)	256 (11.3)	234 (15.1)	111 (15.1)
β-Blocker	9034 (70.0)	5901 (70.6)	1571 (69.4)	1042 (67.2)	521 (71.0)
Diuretics	4878 (37.8)	2232 (26.7)	1129 (49.9)	983 (63.4)	539 (73.4)
Calcium channel blocker	2555 (19.8)	1580 (18.9)	473 (20.9)	318 (20.5)	189 (25.7)
Digoxin	581 (4.5)	276 (3.3)	163 (7.2)	101 (6.5)	41 (5.6)
Statins	7575 (58.7)	5316 (63.6)	1197 (52.9)	738 (47.6)	327 (44.6)
Ezetimibe	219 (1.7)	167 (2.0)	20 (0.9)	16 (1.0)	9 (1.2)
Fibrates, resins, nicotinic acid	155 (1.2)	100 (1.2)	27 (1.2)	19 (1.2)	10 (1.4)
Other blood pressure	103 (0.8)	59 (0.7)	18 (0.8)	8 (0.5)	21 (2.9)

Hb, hemoglobin; *COPD*, chronic obstructive pulmonary disease; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *ACEi/ARBs*, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; *MRA*, mineralocorticoid-receptor antagonists.

*Hemoglobin was available in 12,521 patients.

†Geometric mean.

(29.4%) were the most common comorbidities. The most common medications used were β-blockers (70.0%), aspirin (66.2%), statins (58.7%), and renin-angiotensin system inhibitors (55.4%). In total, 17.4% of the population had undergone CABG; and 38.3%, PCI. The mean hsCRP for the overall cohort was 2.97 mg/L, and hsCRP level ≥ 2 mg/L was present in 68.4% of patients.

In total, 35.2% of patients were classified with CKD based on their eGFR, with disease severity as follows: 2,263 (17.5%) patients had an eGFR between 45 and 59, 1,550 (12.0%) had eGFR 30-44, and 734 (5.7%) patients had eGFR <30 mL/min/1.73 m^2. Individuals with lower eGFR categories were on average older, had more comorbidities, and had higher mean baseline levels of hsCRP. The proportion of patients with hsCRP ≥2 mg/L increased for each subsequent lower eGFR stratum (Supplemental Figure 2) so that 82.4% of patients with an eGFR <30 mL/min/1.73 m^2 had hsCRP ≥2 mg/L. To investigate whether the progressive increase in hsCRP across eGFR strata was explained by the characteristics of these patients, we performed multivariable logistic regression analyses (Supplemental Table II). After adjustment for patient demographics, comorbidities, and medications, the higher odds of hsCRP ≥2 mg/L remained for patients with more severe CKD.

Association between hsCRP levels, CKD progression, and AKI

During a median follow-up of 3.2 (1.8-4.7) years, 1,019 CKD progressions (annual incidence rate 2.7%) and 1481 AKI events (incidence rate 3.95%) were recorded. Of the 1,019 CKD progression events, 947 events were attributed to doubling creatinine, 21 events to RRT, and 51 events to renal death. In crude analyses, hsCRP levels ≥2 mg/L were associated with a more than 2-fold increased risk for CKD progression and AKI compared to hsCRP <2 mg/L (Table II, Figure 1). After multivariable adjustment, patients with hsCRP levels ≥2 mg/L had a 1.42 (1.21-1.66) times higher risk of CKD progression and 1.29 (1.13-1.47) higher risk of AKI. Categorizing hsCRP into 4 strata (≤1, 1-3, 3-10, and> 10 mg/L) showed a graded relation for both outcomes (both *P* values for trend <0.01). Compared to hsCRP ≤1 mg/L, the adjusted CKD progression HRs for patients with 1-3, 3-10, and >10 mg/L were 1.26 (1.03-1.53), 1.55 (1.29-1.86), and 1.62 (1.31-2.01), respectively. Likewise, compared to hsCRP ≤1 mg/L, the adjusted AKI HRs for patients with 1-3, 3-10, and >10 mg/L were 1.22 (1.04-1.43), 1.43 (1.22-1.66), and 1.51 (1.27-1.81), respectively (Supplemental Table III, Figure 1). The association between hsCRP and the risk of adverse renal outcomes was generally observed within each eGFR stratum at baseline, although CIs widened at the worse CKD severity stages (Table II, Supplemental Table IV). The association between hsCRP and AKI was diminished in sub-analysis of patients with eGFR 30-44 mL/min/1.73 m^2 and eGFR ≤30 mL/min/1.73 m^2.

To test the robustness of our findings, we performed stratified analyses in subgroups of patients. Multiplicative interaction terms were tested to explore the presence of effect measure modification. Patients with hsCRP ≥2 mg/L had a higher risk of CKD progression and AKI across all

Table II. Number of events, incidence rate, and HRs for the association between hsCRP ≥2 mg/L and renal outcomes, overall and across eGFR strata

	No. of events	Annual incidence rate	Crude HR (95% CI)	Adjusted HR (95% CI)*
A. CKD progression				
Overall	1019	2.7%		
hsCRP <2 mg/L	198	1.5%	1.00	1.00
hsCRP ≥2 mg/L	821	3.3%	2.12 (1.82-2.48)	1.42 (1.21-1.66)
B. AKI				
Overall	1481	3.95%		
hsCRP <2 mg/L	293	2.27%	1.00	1.00
hsCRP ≥2 mg/L	1188	4.82%	2.07 (1.82-2.35)	1.29 (1.13-1.47)
	eGFR ≥ 60 mL/min/1.73 m^2	eGFR 45-60 mL/min/1.73 m^2	eGFR 30-44 mL/min/1.73 m^2	eGFR ≤30 mL/min/1.73 m^2
A. CKD progression*				
hsCRP <2 mg/L	1.00	1.00	1.00	1.00
hsCRP ≥2 mg/L	1.33 (1.07-1.65)	1.72 (1.17-2.51)	1.69 (1.09-2.63)	1.11 (0.71-1.72)
B. AKI*				
hsCRP <2 mg/L	1.00	1.00	1.00	1.00
hsCRP ≥2 mg/L	1.53 (1.25-1.88)	1.37 (1.02-1.84)	1.01 (0.76-1.34)	0.99 (0.71-1.38)

HR = hazard ratio; CI = confidence interval; CKD = chronic kidney disease; AKI = acute kidney injury; eGFR = estimated glomerular filtration rate.
* Models were adjusted for age, sex, time since MI, hemoglobin, eGFR, comorbidities (diabetes mellitus, hypertension, COPD, cancer, dementia, heart failure, peripheral vascular disease, stroke, atrial fibrillation, inflammatory bowel diseases, rheumatoid diseases), undertaken procedures (CABG, PCI), and medications (aspirin, NSAIDs, ACEi/ARBs, MRAs, β-blocker, other diuretics, calcium channel blockers, other blood pressure drugs, digoxin, statins, ezetimibe, fibrates, resins, and nicotinic acid).

subgroups compared to those with hsCRP levels <2 mg/L (Figures 2 and 3). Some multiplicative interactions were present, but differences in risk magnitude between substrata were small. For example, the association between hsCRP and renal outcomes was slightly stronger in the absence of heart failure and hypertension rather than presence of these comorbidities.

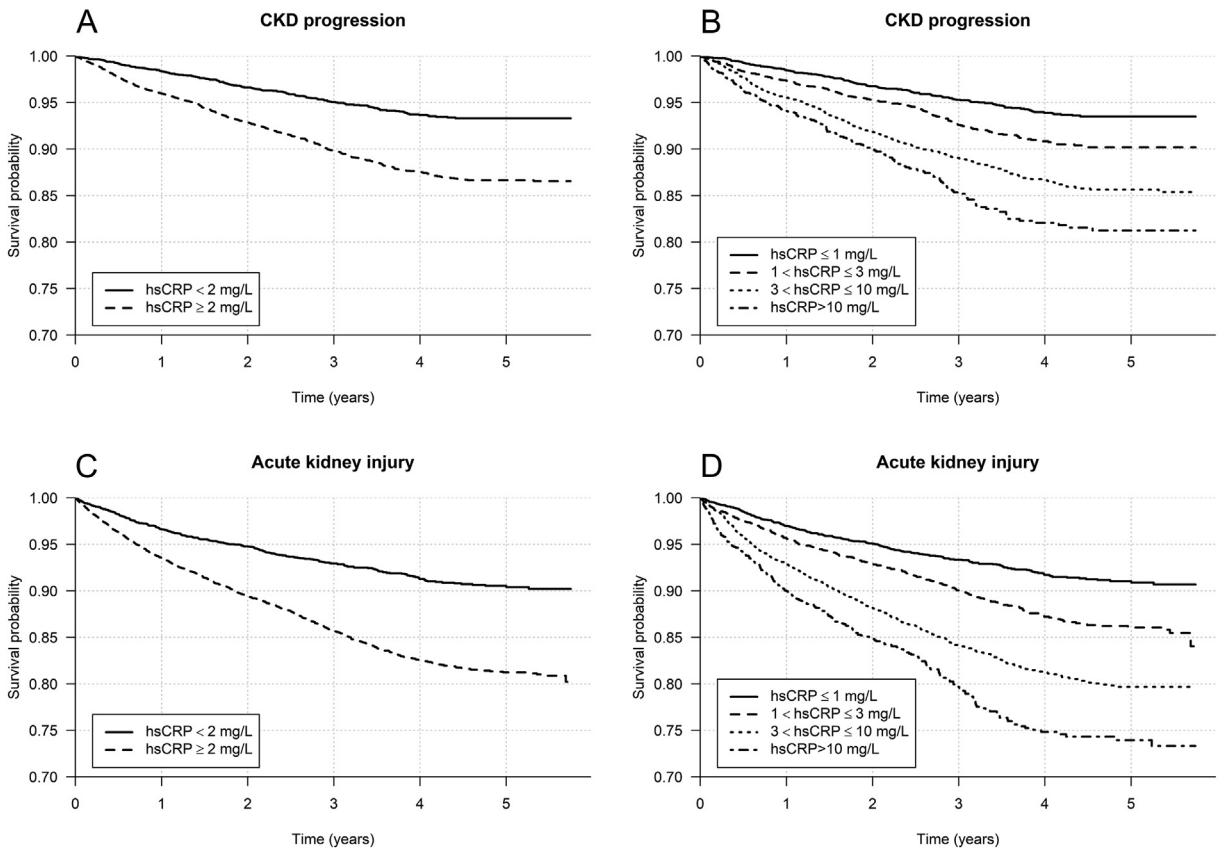
Exclusion of events occurring during the first 6 or 12 months of follow-up did not meaningfully change the magnitude of the estimates (Supplemental Table V), suggesting reverse causation bias to be low. Accounting for death as a competing risk did also not change our main findings (Supplemental Table VI). When redefining the CKD progression definition with sustained doubling of creatinine, results were of similar magnitude to those of our main analyses (Supplemental Table VII).

Discussion

In this large health care–based study of post-MI patients, we present the novel finding that levels of hsCRP were associated with the subsequent risk of CKD progression and AKI. These results were robust and consistent in stratified analyses as well as in analyses addressing reverse causation bias or accounting for the competing risk of death. Whereas a number of studies suggest that inflammation predicts cardiovascular risk in patients with MI,[25,26] our study provides observational evidence of a bidirectional association, improving our understanding of this risk marker in the cardiorenal syndrome.

Although the renal implications of hsCRP levels in post-MI patients have not been previously appreciated, our results agree with observations from the general population[15,27,28] linking inflammation surrogates with the rate of kidney function decline. Also, in a post hoc analysis of the Cholesterol and Recurrent Events (CARE) trial, increased CRP levels were associated with a faster rate of kidney function loss over time among 687 MI patients with eGFR<60 mL/min/1.73 m^2.[29] We extend this observation with the finding that hsCRP is similarly associated with CKD progression risk in MI patients both with normal kidney function and with different severity stages of CKD. A strength in our analysis is the definition of CKD progression with relative plasma creatinine

Figure 1



Kaplan-Meier plots showing the cumulative incidence of CKD progression (**A** and **B**) and AKI (**C** and **D**) for different hsCRP categories at baseline.

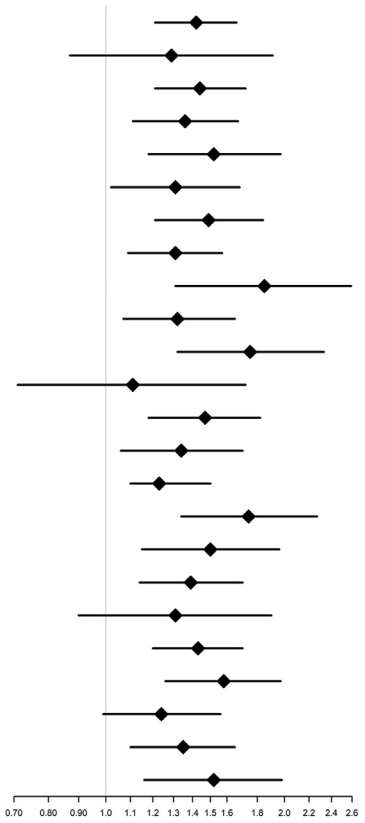
changes using all outpatient measurements performed in our region. This is important given that CKD is generally affected by poor awareness and underutilization of *ICD* diagnoses in health care.[30,31]

There have been no studies exploring the long-term association between inflammation and AKI risk in post-MI patients. AKI is, nevertheless, a frequent acute complication in these patients (with a 5%-30% incidence depending on definitions used) that leads to high morbidity and mortality.[32] In acute MI[33] or in patients undergoing CABG surgery,[34] preoperative hsCRP improved the prediction of AKI during the index hospitalization. Our results suggest that such associations are also observed for the long-term AKI risk.

Observational studies cannot infer causality in the associations reported, and hsCRP in our study may be a marker or a risk factor for kidney disease. However, there are convincing animal studies demonstrating that a proinflammatory environment induces acute changes in the expression of reactive oxygen/nitrogen species in the kidney, promotes the synthesis of adhesion molecules,[35-37] and leads to excessive deposition of extracellular matrix proteins in the glomerulus and renal tubulointerstitium.[38-40] There is also animal evidence that inflammation may provoke long-term kidney damage and that blocking the inflammatory pathway ameliorates several kidney disorders including diabetic nephropathy progression, renal ischemic reperfusion injury, or glomerulonephritis.[41-44] In contrast, interventional evidence in humans is scarce; recently, the Canakinumab Anti-inflammatory Thrombosis Outcome study (CANTOS) reported that IL-1B inhibition did not result in clinically meaningful improvements in eGFR or albuminuria during a median of 3.7 years of follow-up.[24] Although

Figure 2

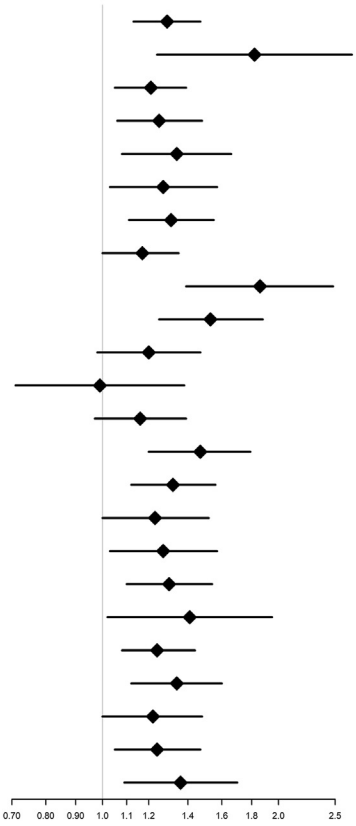
Subgroup	N	Events	Hazard ratio (95% CI)	p-value
Overall	12905	1019	1.42 (1.21 - 1.66)	
Age < 65	3434	143	1.29 (0.87 - 1.91)	0.85
Age ≥ 65	9471	876	1.44 (1.21 - 1.72)	
Male	8022	611	1.36 (1.11 - 1.67)	0.57
Female	4883	408	1.52 (1.18 - 1.97)	
Diabetics	3755	443	1.31 (1.02 - 1.68)	0.23
Non-diabetics	9150	576	1.49 (1.21 - 1.84)	
Hypertensive	8939	769	1.31 (1.09 - 1.57)	0.019
Non-hypertensive	3966	250	1.85 (1.31 - 2.59)	
eGFR ≥ 60	8358	466	1.32 (1.07 - 1.65)	0.16
30 ≤ eGFR < 60	3813	402	1.75 (1.32 - 2.33)	
eGFR < 30	734	151	1.11 (0.71 - 1.72)	
Time since MI < 2 years	6780	558	1.47 (1.18 - 1.82)	0.49
Time since MI ≥ 2 years	6125	461	1.34 (1.06 - 1.70)	
Heart failure	5753	692	1.23 (1.10 - 1.50)	0.007
No heart failure	7152	327	1.74 (1.34 - 2.27)	
Atrial fibrillation	3799	432	1.50 (1.15 - 1.96)	0.91
No atrial fibrillation	9106	587	1.39 (1.14 - 1.70)	
IBD or RD	1795	222	1.31 (0.90 - 1.90)	0.56
No IBD or RD	11110	797	1.43 (1.20 - 1.70)	
Statins	7575	498	1.58 (1.26 - 1.97)	0.030
No statins	5330	521	1.24 (0.99 - 1.56)	
ACE/ARB	7147	619	1.35 (1.10 - 1.65)	0.47
No ACE/ARB	5758	400	1.52 (1.16 - 1.98)	



Forest plot of the association between hsCRP ≥2 mg/L and CKD progression, overall and in subgroups. Models were adjusted for age, sex, time since MI, hemoglobin, eGFR, comorbidities (diabetes mellitus, hypertension, COPD, cancer, dementia, heart failure, peripheral vascular disease, stroke, atrial fibrillation, inflammatory bowel diseases, rheumatoid diseases), undertaken procedures (CABG, PCI), and medications (aspirin, NSAIDs, ACEi/ARBs, MRAs, β-blocker, other diuretics, calcium channel blockers, other blood pressure drugs, digoxin, statins, ezetimibe, fibrates, resins, and nicotinic acid).

Figure 3

Subgroup	N	Events	Hazard ratio (95% CI)	p-value
Overall	12905	1481	1.29 (1.13 - 1.47)	
Age < 65	3434	187	1.82 (1.24 - 2.67)	0.002
Age ≥ 65	9471	1294	1.21 (1.05 - 1.39)	
Male	8022	925	1.25 (1.06 - 1.48)	0.93
Female	4883	556	1.34 (1.08 - 1.66)	
Diabetics	3755	645	1.27 (1.03 - 1.57)	0.62
Non-diabetics	9150	836	1.31 (1.11 - 1.55)	
Hypertensive	8939	1138	1.17 (1.00 - 1.35)	0.001
Non-hypertensive	3966	343	1.86 (1.39 - 2.48)	
eGFR ≥ 60	8358	568	1.53 (1.25 - 1.88)	0.001
30 ≤ eGFR < 60	3813	648	1.20 (0.98 - 1.47)	
eGFR < 30	734	265	0.99 (0.71 - 1.38)	
Time since MI < 2 years	6780	779	1.16 (0.97 - 1.39)	0.17
Time since MI ≥ 2 years	6125	702	1.47 (1.20 - 1.79)	
Heart failure	5753	1038	1.32 (1.12 - 1.56)	0.93
No heart failure	7152	443	1.23 (1.00 - 1.52)	
Atrial fibrillation	3799	640	1.27 (1.03 - 1.57)	0.42
No atrial fibrillation	9106	841	1.30 (1.10 - 1.54)	
IBD or RD	1795	335	1.41 (1.02 - 1.95)	0.52
No IBD or RD	11110	1146	1.24 (1.08 - 1.44)	
Statins	7575	741	1.34 (1.12 - 1.60)	0.17
No statins	5330	740	1.22 (1.00 - 1.48)	
ACE/ARB	7147	907	1.24 (1.05 - 1.47)	0.54
No ACE/ARB	5758	574	1.36 (1.09 - 1.70)	



Forest plot of the association between hsCRP ≥2 mg/L and AKI, overall and in subgroups.Models were adjusted for age, sex, time since MI, hemoglobin, eGFR, comorbidities (diabetes mellitus, hypertension, COPD, cancer, dementia, heart failure, peripheral vascular disease, stroke, atrial fibrillation, inflammatory bowel diseases, rheumatoid diseases), undertaken procedures (CABG, PCI), and medications (aspirin, NSAIDs, ACEi/ARBs, MRAs, β-blocker, other diuretics, calcium channel blockers, other blood pressure drugs, digoxin, statins, ezetimibe, fibrates, resins, and nicotinic acid).

discouraging, these results should be interpreted in view of their post hoc nature and the specificity of the treatment given (IL-1B antagonist). Whether blocking inflammation by this or other pathways could prevent CKD still remains unknown and warrants further investigation.

Even if inflammation would be a mere marker of underlying disease severity, results from this study may help to further improve risk stratification and allow the implementation of measures to attenuate this renal risk. This is relevant given the poor prognosis, worsening of quality of life, and elevated health care costs of both acute and chronic kidney disease in these patients.[2-4] Although screening for inflammation in secondary cardiovascular prevention has remained infrequent,[45] knowledge of these risks can motivate the need for stricter monitoring of kidney function and the implementation of antiproteinuric strategies such as renin-angiotensin system inhibition to retard CKD progression. Furthermore, it can help patient discussions conveying risk and encourage lifestyle changes related to diet (such as reduction of body weight as well as salt and protein intake), exercise, and smoking cessation. Importantly, the progression of CKD in post-MI patients puts them at greater risk for additional cardiovascular events and mortality. Most patients (68.4%) in our cohort had hsCRP ≥2 mg/L. Conversely, only 30% of patients were at low inflammatory risk and hence at a low CKD/AKI risk. In our previous work, we showed that patients with low inflammatory risk tended to be younger, were more often men, and had higher eGFR and lower comorbidity burden compared to those individuals with elevated hsCRP levels.[46] These are also factors associated with slower kidney function decline, but adjustment for these in multivariable analysis did not importantly impact on the relationship between hsCRP and renal outcomes.

Strengths of our study include its large sample size, richness of information on risk factors and confounders, solid outcome definitions, and virtually no losses to follow-up. Our study also has limitations; the studied population was representative of the MI patients with available eGFR from Stockholm, Sweden, during 2007-2011. Extrapolation of our findings to other regions, ethnicities, or periods should be done with caution. Because hsCRP tests were taken in connection to a health care encounter, factors that are associated with blood testing may predict detected inflammation. These factors may also limit the generalizability of our findings. Despite our careful study design to avoid misclassification bias and attempts to address reverse causation, residual and unknown confounding remains intrinsic to observational analyses. In this sense, we acknowledge the lack of information on body mass index or smoking habits that may influence both inflammation and the risk for renal outcomes.

To conclude, higher hsCRP levels among post-MI patients were associated with the subsequent risk of AKI and CKD progression. These results support the hypothesis that inflammation may be one of the pathways connecting cardiac and kidney dysfunction, and awareness of this association may inform clinical decisions as to implementation of preventive therapies and lifestyle changes.

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Declaration of interest

J. J. C. reports grant funding from AstraZeneca, ViforPharma, Merck-Sharp and Dome, and Astellas and consulting from Astellas, AstraZeneca, and Baxter Healthcare. E. L. F. and M. A. F. report no relationships that could be construed as a conflict of interest. A. G. was previously employed by Novartis and currently by AstraZeneca. T. J. reports grant funding from MSD and Novartis and fees for lecturing and consulting for AstraZeneca, MSD, Aspen, and Bayer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.06.019.

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