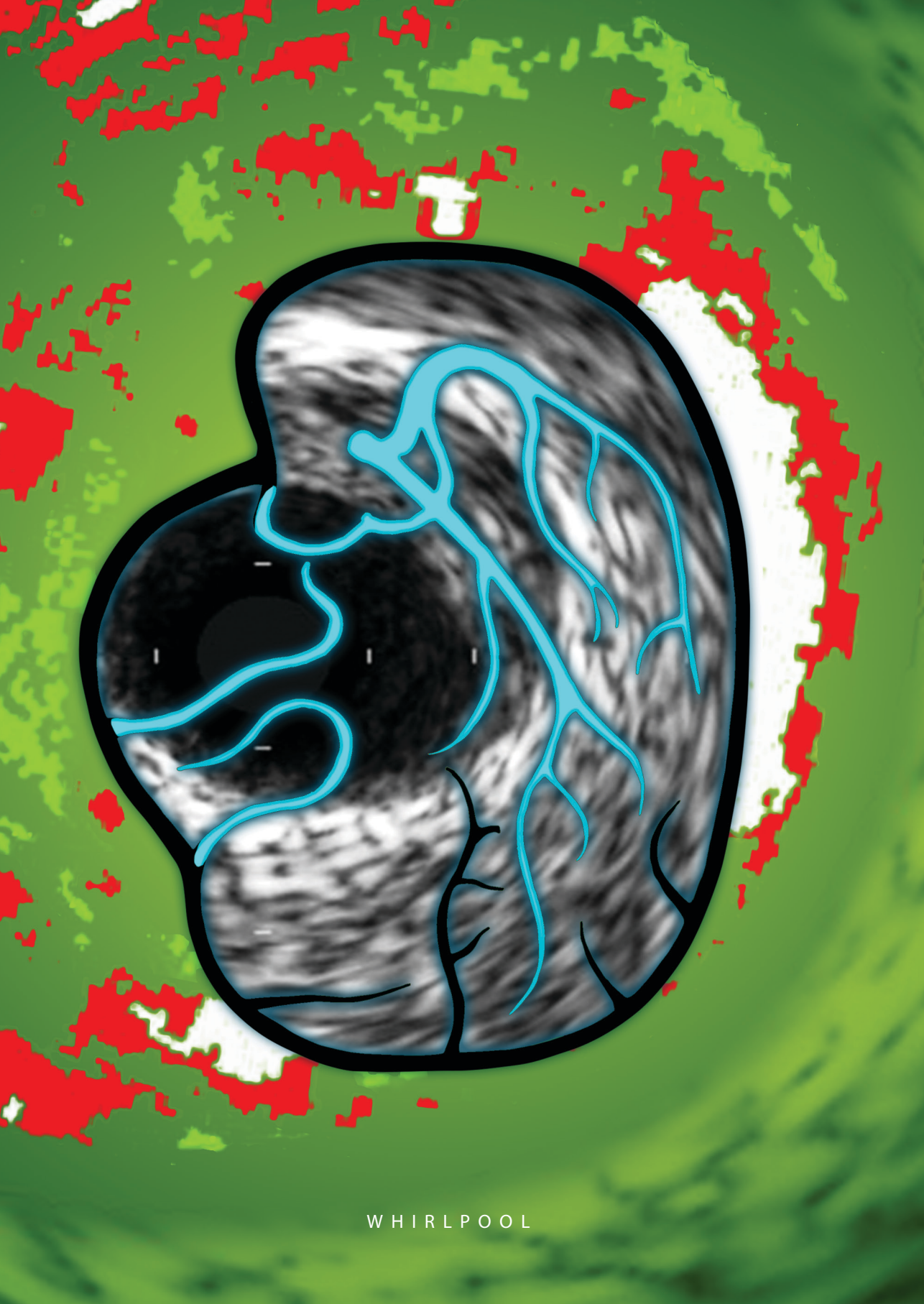
WHIRLPOOL

Part III

IMPLICATIONS OF RENAL FUNCTION FOR ISCHEMIC HEART DISEASE

CHAPTER 9

Evolution of Renal Function and Predictive Value of Serial Renal Assessments among Patients with Acute Coronary Syndrome - The BIOMArCS study

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Submitted

ABSTRACT

Background

Renal dysfunction predicts mortality in acute coronary syndrome (ACS), but its evolution following and preceding ACS has never been described in detail. We aimed to describe this evolution, quantified by creatinine, estimated glomerular filtration rate ($eGFR_{Cr}$), and cystatin C (CysC), from its initial change during ACS until stabilization; and to investigate the predictive value of serial assessments of these renal markers in patients with ACS.

Methods

From 844 ACS patients included in the BIOMArCS study, we analysed a case-cohort consisting of 187 (random sample of 150 patients, plus all those who reached the endpoint) to determine the risk of the composite endpoint (cardiovascular death or hospitalization for non-fatal ACS) in relation to marker levels and their rates of change during 1-year follow-up. In each patient, the marker trajectories were estimated using repeated measurements (mean 8 per patient). Survival analyses were adjusted for GRACE risk score, and based on all available data >30 days after the index ACS to ensure stabilization of renal markers.

Results

Mean age was 63 years, 79% were men, 43% had STEMI, and 67% were in CKD stages 2-3. During hospitalization (median[IQR] duration: 5 [3-7] days), CysC levels indicated deterioration of renal function earlier than creatinine did (CysC peaked on day 3, versus day 6 for creatinine), and stabilized after two weeks. Higher CysC levels predicted the endpoint independently of the GRACE score (per 1SD increase: adjusted HR [95%CI]: 1.68 [1.03–2.74]). However, the rates of CysC change were not significant predictors.

Conclusions

CysC levels are the earliest indicators of deterioration of renal function, which usually does not stabilize during hospitalization, but on average two weeks after index ACS. In ACS patients with normal to moderately impaired renal function, after stabilization of renal function, CysC levels predict adverse events within the first year.

INTRODUCTION

Renal dysfunction, including mild renal impairment ($eGFR_{Cr}$ 60-89 ml/min/1.73m^2),[1,2] is strongly associated both with short- and long-term mortality in patients with ST elevation myocardial infarction (STEMI) and in those with non-STEMI.[3-5] Patients with chronic kidney disease (CKD) are often treated less aggressively for acute coronary syndrome (ACS) than those without CKD.[3,4,6] However, even if they are on optimal therapy they will still have poorer prognosis.[7] Renal dysfunction is associated both with coronary atherosclerosis, including higher coronary plaque burden, plaques containing greater necrotic core and more dense calcium, as well as with abnormalities of cardiac muscle, including left ventricular hypertrophy, dilated cardiomyopathy, and systolic dysfunction.[8-10] Several studies have shown that specific comorbidities such as hypertension, diabetes, and dyslipidemia, contribute both to cardiovascular and renal damage.[11,12] Neuro-hormonal activation is also affected after ACS,[13-15] and angiotensin II may influence deterioration of both cardiovascular and renal functioning.[13,16,17]

In spite of these overlapping pathophysiological aspects, the detailed temporal evolution of renal function immediately following ACS, and preceding a recurrent ACS, has not yet been described. Existing studies have mostly assessed renal function only at a single time point to investigate its prognostic value, and have used for example time of admission, a moment during in-hospital stay or time of discharge as 'study baseline'. However, it is unclear whether a patient's renal function examined at these time points during hospitalization reflects "true" renal functioning or whether it is temporarily disturbed by the index ACS. Moreover, it remains unknown at which moment after ACS renal function stabilizes. Knowing these temporal patterns may help us in expanding our understanding of renal dysfunction in patients with ACS, and thereby aid in identifying high-risk subgroups.

The aim of our study was two-fold: (1) to describe the evolution of renal function from its initial change during ACS until stabilization, according to the kinetics of several renal function parameters (plasma creatinine, estimated glomerular filtration rate [eGFR], and cystatin C [CysC]), (2) to investigate the predictive value of serial renal assessments within the first year after index ACS. For the latter purpose, we also examined whether rates of change of these renal markers are relevant for clinical risk prediction.

METHODS

BIOMArCS is a multi-centre prospective study conducted in 18 Dutch hospitals. Details on the BIOMArCS design are reported elsewhere.[18] Briefly, we included patients who were hospitalized for ACS including STEMI, non-STEMI, and unstable angina pectoris (UAP), with ≥1 cardiovascular risk factor (Table S1). $eGFR_{Cr}$ <30 ml/min/1.73m^2 was an exclusion criterion because of the potential influence of renal clearance on certain biomarkers investigated in the BIOMArCS cohort. Of 844 enrolled patients, 45 reached the study endpoint during a median (IQR) follow-up of 11.5 (2.7–12.1) months.

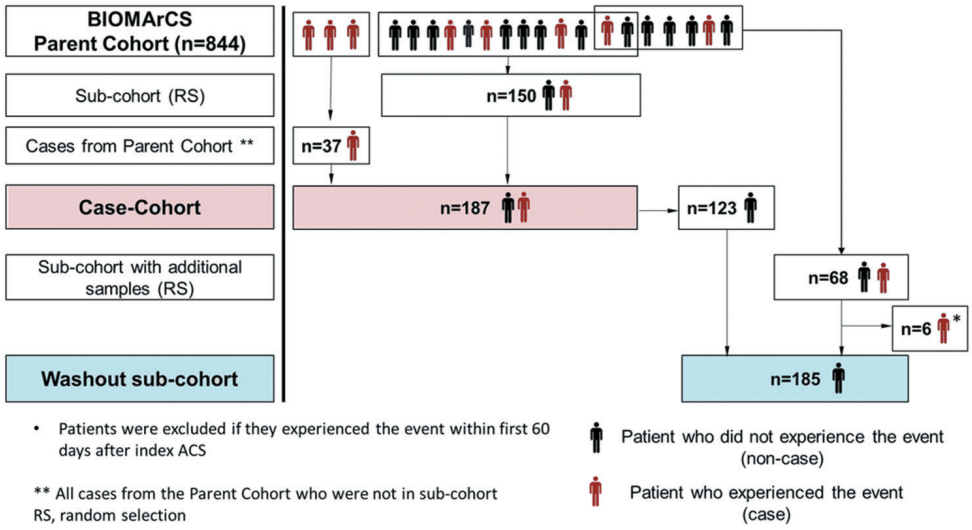
All patients were treated according to prevailing guidelines and at the discretion of the treating physician. The study protocol has been approved by the Institutional Review Board of all participating hospitals and written informed consent was obtained from all patients.

Selection of patients to analyse the relation between renal markers and repeat ACS

For the analysis of the relation between (renal) biomarkers and repeat ACS during 1-year follow-up, we applied a case-cohort design, which allowed a comparison of all study endpoint cases to a limited random sample of non-cases (instead of all non-cases), thereby increasing the study's efficiency.[19] For this purpose, after study completion (i.e., inclusion, follow-up, and study endpoint adjudication) a sub-cohort of 150 patients was randomly sampled from the parent cohort (n=844), using a computer generated random sampling procedure. Subsequently, all patients who experienced the endpoint, but who were not a part of the random sub-cohort were added (37 cases), so that the case-cohort comprised 187 patients (Figure 1). Thus, we analysed all cases, but analyzed only those non-cases (non-endpoint patients) who were present in the random sub-cohort.

Selection of patients to analyse the washout of renal markers after ACS admission

To enable a precise description of early washout biomarker patterns, a total of 68 (8%) BIOMArCS patients underwent additional blood sampling at 24, 48, 72 and 96 hours after the index ACS. We excluded the 6 patients who experienced the study endpoint, and we added the endpoint-free patients from the random sub-cohort. Thus, a total of 185 patients were available for the analysis of washout patterns of renal biomarkers (Figure 1).



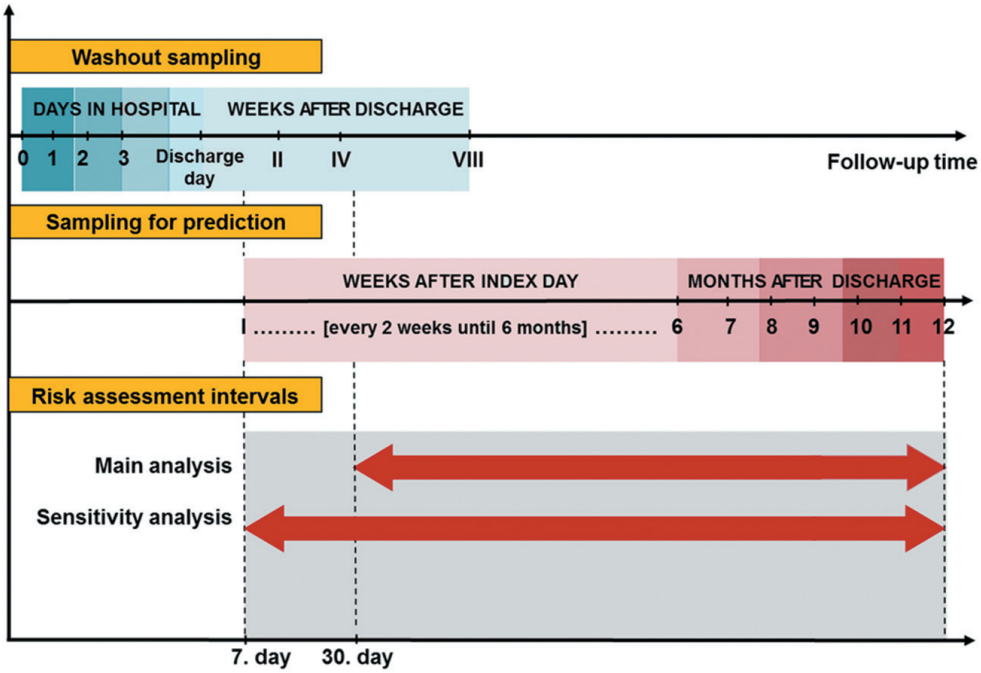


FIGURE 1 **Participants flow chart, study design, and sampling schema.**

Follow-up visits and blood sample collection

Blood samples were collected at admission, hospital discharge, and every two weeks after index ACS during the first six months, followed by monthly collection until one year (Figure 1). A visit window of ±1 week was allowed, and a maximum of two consecutive visits were allowed to be skipped (for personal reasons). If logistic reasons hindered inclusion during hospitalisation, patients could be included on the first outpatient visit within six weeks after discharge; the sampling schedule was then adapted accordingly. A trained research nurse interviewed the patients at each visit and obtained data on anginal status (Canadian Cardiovascular Society classification), heart failure symptomatology (New York Heart Association classification), and factors that might influence biomarker levels, e.g. smoking, occurrence of infections, inflammatory or allergic responses, alterations in medication, interventional or operative procedures and hospital admission. Blood samples were processed on-site and transported batch-wise under controlled conditions (at -80^{0}C) to the department of Clinical Chemistry of the Erasmus MC, Rotterdam where they were stored until analysis was performed.

Glomerular filtration rate (GFR) was determined by the Modification of Diet in Renal Disease (MDRD) Study equation.[20] Patients were categorized using the modified eGFR definition from the National Kidney Foundation – Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines.[21]

Analysis of renal markers

In the 187 case-cohort patients and in the 185 patients that comprise the washout analysis set, renal biomarkers (creatinine and CysC) were measured batch-wise at the laboratory of the department of Clinical Chemistry and Hematology of the University Medical Center Utrecht. Creatinine was measured on clinical routine equipment (AU5800, Beckman Coulter, Brea, CA, USA). Cystatin C was measured by ELISA following manufacturer's instructions (mouse-anti human DuoSet DY1196, R&D Systems, Oxon, UK). Importantly, laboratory personnel were blinded to any patient data and scope of the study, whereas biomarker measurements did not interfere with treatment.

Study endpoints

The study endpoint was a composite of cardiac mortality or a diagnosis of a non-fatal myocardial infarction or unplanned coronary revascularization due to progressive angina pectoris during 1-year follow-up. Any death was considered cardiac unless documented otherwise. Incident non-fatal myocardial infarction was defined as the combination of typical ischemic chest complaints and objective evidence of myocardial ischemia or myocardial necrosis as demonstrated by the ECG and/or elevated cardiac markers. The criteria for non-fatal myocardial infarction during follow-up were the same as those for the index event (Table S1, points 1 and 2 of the inclusion criteria). The Clinical Event Committee, blinded for the renal biomarker results, reviewed hospital records and discharge letters and adjudicated the study endpoints.

Statistical analysis

Case-Cohort – prediction of events

Categorical baseline data are summarized by percentages, and continuous data by medians and 25^{th}–75^{th} percentiles. Differences between cases and non-cases were evaluated by classical statistical tests, as specified in the caption of Table 1.

To obtain valid inferences for the relation between the temporal evolvement of a biomarker and the incidence of the study endpoint, the longitudinal- and event-processes must be jointly modelled. We applied Bayesian semiparametric joint models for this purpose, which combine linear regression and Cox proportional hazard regression. Linear mixed-effects (LME) models were used to describe patient-specific longitudinal biomarker trajectories B(t) as a function of time (t). Non-linear trajectories were modelled by cubic splines. ^{2}Log-transformations of biomarker values were used to assure normal distributions of regression residuals. More specifically, the unit of analysis was the Z-score (i.e., the standardized form) of the ^{2}log-biomarker, which allows a direct comparison of the effects of separate markers. Results are presented as hazard ratios (HR) and corresponding 95% confidence intervals (CI) for a 1SD difference of the biomarker on the log-scale.

The LME models not only provide unbiased estimates B(t) of the biomarker level at timepoint t, but also of its instantaneous rate of change (or: slope) B'(t) at t, that corresponds to the first derivative of B(t). Since we also aimed to study rate of change, we also provided HRs for the instantaneous slope of the marker's trajectory. Results are presented as HRs (95% CIs) for a 0.1SD difference of the marker's rate of change on the log-scale.

Analyses were first performed univariably, and subsequently multivariable adjustment was performed. For this purpose, the GRACE risk score for assessment of post-discharge death and myocardial infraction, as recommended by international guidelines,[22-24] was used. This specific GRACE risk model consists of age, troponin (or CKMB) elevation at admission, history of MI, congestive heart failure and whether CABG was performed at the index hospitalization.[25] The survival model was adjusted for the GRACE risk score, and the LME model was adjusted for GRACE risk score, sex, diabetes, history of coronary artery bypass surgery, history of valvular heart disease, history of stroke, history of peripheral arterial disease.

To describe the average evolution of renal function during the year preceding death or the recurrence of ACS, we analyzed all available data >30 days after the index ACS until the endpoint or last sample moment.

To investigate the predictive value of repeatedly measured markers, we analysed all available data >30 days after the index ACS event, to ensure that all biomarkers were then stabilized. Additionally, a sensitivity analysis was performed on all repeated measurements >7 days after the index ACS. Measurements that were obtained within 7 days after index ACS were excluded to avoid biased estimates due to elevated biomarkers induced by the index ACS.

Analysis of evolution of renal function during the washout phase

LME models were applied to investigate at which time point the renal markers reach their highest point (creatinine, CysC) or lowest point ($eGFR_{Cr}$) and at which time point they return to stable levels. All renal biomarkers were ^{2}log transformed, and non-linear evolutions (for the fixed- and random-effects parts) were modelled by restricted cubic splines. We optimized the position of the spline knots by using Akaike information criteria (AIC) and Bayesian information criteria (BIC). After obtaining optimal evolution curves representing the washout patterns of the renal markers, we calculated the maximum or minimum of these curves to determine the time point of the peak or nadir. To determine the moment of marker stabilization, we also numerically compared the deltas of biomarkers between every two consecutive blood samples (a difference <1% signified a stabilization).

R statistical software (version 2.15.0) was used for advanced statistical analyses, in particular the package JMbayes.[14] All statistical tests were two-tailed and p-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics, Follow-up, and Study endpoints

Baseline characteristics of all patients in the BIOMArCS study and in the case-cohort set are shown in Table 1. In the case-cohort, on admission mean (±SD) age was 63 (±11) years, 79% were men, 43% had STEMI, 42% had non-STEMI, and 15% had UAP. The median (IQR) eGFR was 81 (70–98) mL/min/1.73m^2, and 33% of patients were in CKD stage 1 (GFR ≥90), 56% in CKD stage 2 (GFR 60–89), and 11% in CKD stage 3 (GFR 30–59).

Average evolutions of renal markers during the washout phase

A total of 687 samples were drawn from the 185 non-endpoint patients that comprise the washout analysis set, with a mean of 4 samples per patient. Average washout evolutions of plasma creatinine, eGFRCr and CysC are shown in Figure 2. The figure shows that CysC levels reached a peak on the 3rd day after index ACS. This was followed by a nadir of eGFRCr on the 4th day, and a peak of creatinine levels on the 6th day. We also found different time intervals from the highest or lowest point to stabilization for these markers: CysC – 11 days (stabilized on day 13) , eGFRCr – 10 days (stabilized on day 13) and creatinine – 8 days (stabilized on day 14). Nevertheless, the stabilization of the markers after index ACS appeared to be temporary. Thereafter, levels continued to steadily change during follow-up (Figure 2 and 3).

Average evolutions of renal markers during the year preceding death or the recurrence of ACS

In the time-period >30 days after index ACS, a total of 1117 blood samples were collected from 158 of the 185 patients that comprise the case-cohort, with a mean of 7 samples per patient – the remaining 27 patients (17 study endpoint cases) only had samples in the 0–30 day time window. Although plasma creatinine levels increased slightly prior to the incident event in patients who ultimately reached the study endpoint, substantial overlap was present between average evolutions of these patients and those who remained endpoint-free (Figure 3). $eGFR_{Cr}$ displayed similar dynamics, but with a smaller overlap. Notably, plasma CysC showed substantially higher levels during follow-up in patients ultimately reaching the study endpoint.

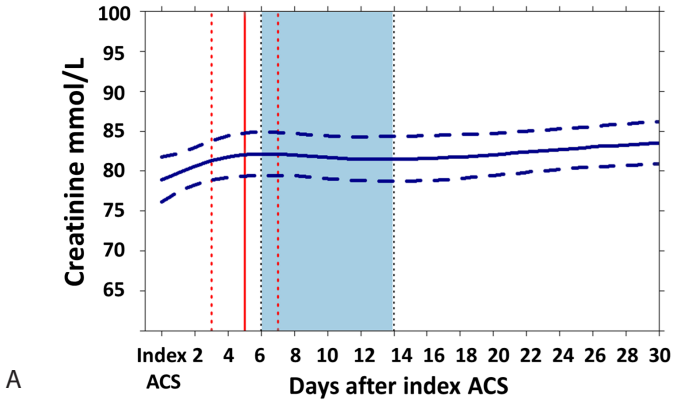
TABLE 1 **Baseline characteristics of the parent cohort and case-cohort set.**

Characteristics	All patients	Case-cohort		
		Non-cases	Cases	p-value
Number of patients	844	142	45	
Presentation and initial treatment				
Age, years *	62.5 (54.3, 70.2)	62.6 (55.0, 70.9)	67.4 (57.1, 76.5)	0.07
Male sex, %	77.9	78.2	80.0	0.79
Admission diagnosis, %				0.46
STEMI	51.7	45.8	35.6	
NSTEMI	37.7	39.4	48.9	
UAP	10.6	14.8	15.6	
Culprit artery, %				
RCA	33.1	34.5	26.7	0.33
LM	2.5	3.5	2.2	1.00
LAD	31.9	33.8	31.1	0.74
LCX	16.5	12.0	20.0	0.17
CABG performed, %	94.4	93.7	89.0	0.33
PCI performed, %	86.3	82.6	87.2	0.49
CKmax, U/L *	513 (200, 1370)	449 (190, 1197)	389 (194, 1122)	0.78
Killip class, %				0.012
Class I		94	82	
Class II		4	16	
Class III		2	0	
Class IV		0	2	
Renal function on admission:				
Urea, mmol/L *		5.9 (5.0, 7.0)	6.8 (4.7, 7.9)	0.19
Creatinine, umol/L *		82 (69, 95)	87 (73, 93)	0.22
eGFRCr, mL/min/1.73m^2 *		83 (69, 98)	78 (71, 92)	0.21
KDOQI classificationa, %				0.16
eGFRCr ≥90		35	24	
eGFRCr 60–89		55	60	
eGFRCr 30–59		10	16	

continued

Characteristics	All patients	Case-cohort		
		Non-cases	Cases	p-value
Medical history, %				
Diabetes mellitus	24	17	38	0.003
Hypertension	56	54	49	0.53
Dyslipidemia	49	51	44	0.46
Prior PCI	26	27	31	0.59
Prior CABG	10	9	24	0.004
Prior MI	27	30	31	0.92
Heart failure	2	3	9	0.097
Valvular heart disease	2	1	9	0.031
Prior CVA/TIA	9	11	20	0.13
PAD	9	6	22	0.004
Medication at first blood sampling moment from 7th day after index ACS, %				
Aspirin	95	93	100	0.20
P2Y12 inhibitor	95	90	97	0.46
Vitamin K antagonist	7	8	9.7	0.72
Statins	96	96	97	1.00
Beta-blocker	90	85	94	0.37
ACE inhibitor or ARB	84	84	90	0.57

ACE: angiotensin converting enzyme; ARB: angiotensin II receptor blocker; CABG: coronary artery bypass grafting; CKmax: maximum creatine kinase during the index admission; LAD: left anterior descending artery; LCX: left circumflex artery; LM: left main coronary artery; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction; SD: standard deviation; Troponinmax: maximum troponin value during the index admission; UAP: unstable angina pectoris. * median (IQR)



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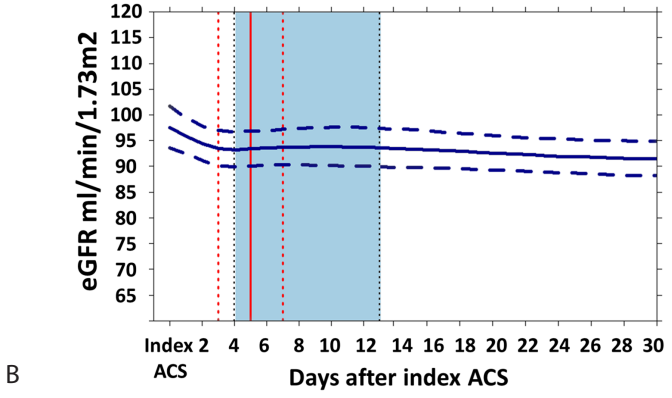

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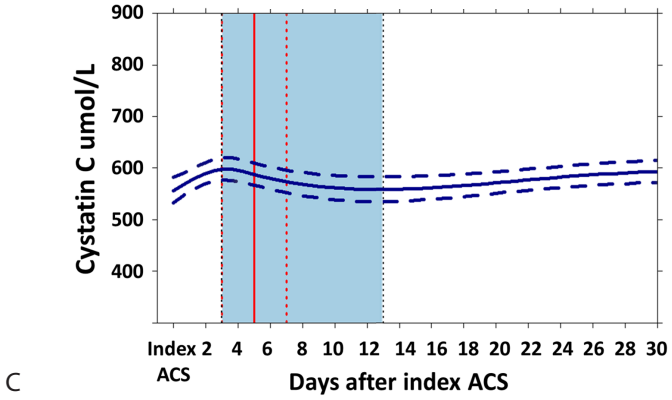

C

FIGURE 2 Average evolutions of renal markers during washout phase. Follow-up time starting from admission is displayed on the x-axis. Biomarker levels are displayed on the y-axis. The solid red line depicts the median discharge day from hospital with corresponding interquartile range (dashed red lines). The left black dashed line displays time of the highest peak of plasma creatinine and CysC and the lowest peak of $eGFR_{Cr}$, and the right black dashed line displays the time moments of biomarker stabilization. The light blue area (between the two black dashed lines) represents the time period from the peaks/nadirs to stabilization. **A**. plasma creatinine (umol/L); **B**. $eGFR_{Cr}$ (ml/min/1.73m^2); **C**. plasma CysC (μg/ml).

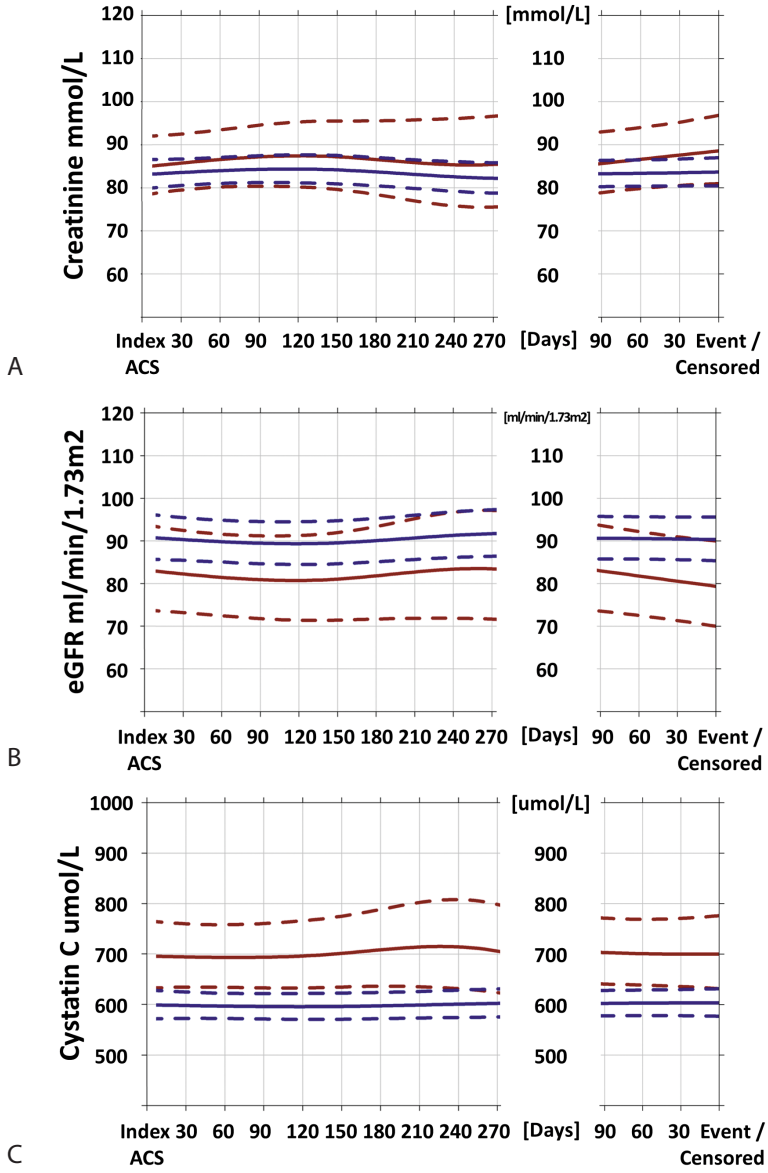

FIGURE 3 Average evolutions of renal markers during the year preceding death or recurrence of ACS in patients who reached the study endpoint (study endpoint cases) and last sample moment in patients who remained endpoint-free (non-endpoint patients). The solid red line depicts the average evolutions of renal function parameters in cases, and the solid blue line depicts the average evolutions in non-cases. The dashed lines represent the 95% confidence interval. Biomarker levels are displayed on the y-axis. X-axis: days from discharge or day 7 after index ACS until event (in study endpoint cases) or last sample moment (in non-endpoint patients). **A**. plasma creatinine (umol/L); **B**. eGFRCr (ml/min/1.73m^2); **C**. plasma CysC (µg/ml).

Predictive value of serially assessed renal markers during the year preceding death or the recurrence of ACS

No clear associations were found between serially assessed plasma creatinine or $eGFR_{Cr}$ and the study endpoints (Table 2). Conversely, serially measured CysC levels were positively associated with the endpoint (HR [95%CI]: per 1SD increase of ^{2}logCysC: 1.79 [1.21–2.63], p=0.006). After controlling for the GRACE risk score, CysC level remained a significant predictor (adjusted HR [95%CI]: 1.63 [1.01–2.66], p=0.043).

In the sensitivity analysis, CysC level measured serially >7 days after the index ACS was slightly weaker, but also a significant predictor (1.68 [1.13–2.46], p=0.009). After adjustment for the GRACE risk score, the risk estimates remained materially the same (adjusted HR [95%CI]: 1.63 [1.01–2.57], p=0.045) (Table S2). None of the rates of change of the renal biomarkers was associated with the endpoint (Table 2, and Table S2).

TABLE 2 Hazard ratios for the primary endpoint in relation to serially assessed marker levels >30 days after index ACS.

	Geometric mean**			Levels[a]		Instantaneous Slope[b]	
	Mean - 1SD	Mean	Mean + 1SD	HR (95%CI)	p-value	HR (95%CI)	p-value
Creatinine	67	84	105				
crude model				1.28 (0.84–1.97)	0.28	1.00 (0.53–1.85)	0.98
+ GRACE risk score [#,*]				1.12 (0.73–1.76)	0.61	1.00 (0.53–1.89)	0.99
eGFR	64	88	120				
crude model				1.52 (0.97–2.37)	0.06	1.00 (0.53–1.86)	1.00
+ GRACE risk score [#,*]				1.32 (0.85–2.10)	0.20	1.02 (0.56–1.87)	0.93
CysC	473.1	613.1	794.6				
crude model				1.79 (1.21–2.63)	0.006	0.99 (0.53–1.90)	0.98
+ GRACE risk score[#,*]				1.63 (1.01–2.66)	0.043	0.99 (0.53–1.83)	0.99

[a] Hazard ratios (HRs) and 95% confidence interval (CI) are given per 1SD increase (creatinine and cystatin C), and 1SD decrease (eGFR) on the 2-log scale at any time point after 30 days after index ACS.
[b] HRs (95%CI) are given per 0.1SD increase in the slope (creatinine and cysC), and 0.1SD decrease ($eGFR_{Cr}$) on the 2-log scale at any time point after 30 days after index ACS.
[#] longitudinal model adjusted for GRACE risk score, sex, diabetes, history of coronary artery bypass surgery, history of valvular heart disease, history of stroke, history of peripheral arterial disease.
* survival model adjusted for GRACE risk score.
** Geometric mean ± 1 standard deviation (SD) of the patient-specific biomarker values after 30 days (presented on the linear scale).

DISCUSSION

In this prospective multicenter study, we sought to describe the trajectories of renal function, and their impact on 1-year cardiac outcome in patients with ACS. We found that plasma CysC levels predict mortality or recurrence of ACS within the first year independently of the GRACE risk score. We also found that CysC levels are the earliest indicators of deterioration of renal function during index ACS. Importantly, we saw that renal function usually does not stabilize during hospitalization, but on average two weeks after index ACS. Altogether, these findings underscore the importance and complexity of renal dysfunction in ACS, and carry implications for the monitoring of renal function in these patients.

The majority of studies in patients with ACS have focused on prognostic value of creatinine levels or estimated GFR assessed at one point in time. However, the prognostic value of serial renal assessments, including CysC levels, is less clear and has mainly been investigated in patients with heart failure.[26] Although some authors[27] have speculated that assessment of renal function should be repeated after hospital discharge in patients with ACS, no study has examined evolution of renal function both during the washout phase early after ACS and during 1-year follow-up. It is here that our study further extends existing evidence.

Our findings support the incremental value of CysC levels for risk assessment by means of the GRACE score. Based on our findings, it seems reasonable to measure CysC levels in the time period after hospital discharge in patients for whom a more complete risk assessment is required. Comparable studies on repeated measurements are scarce. Akerblom et al. assessed whether repeatedly measured CysC levels (at baseline, discharge, and the mean value of both measurements) carry predictive value in 4295 patients with ACS and similar baseline creatinine levels as those in our study.[28] They reported that serial CysC assessment did not improve risk prediction. However, our results were obtained using a different approach. Contrary to Akerblom et al., we examined long-term temporal evolution of renal markers, specifically by using repeated measurements up to 1 year after hospital discharge to estimate the CysC trajectories in each patient. We then jointly modeled these renal trajectories with time-to-event analysis. This joint modeling approach carries several advantages. It enabled us to investigate the association with adverse events in a less biased way.[29] It also allowed us to examine the associations between the rates of change of different renal function parameters and adverse events. The latter analyses suggested that although CysC levels contribute to a patient's clinical risk, their rates of change do not. This is supported by Shlipak et al., who also could not demonstrate a significant association between change in creatinine (delta-creatinine ≥0.3 mg/dl) and outcomes in patients with stable coronary artery disease (CAD) in the Heart and Estrogen/Progestin Replacement Study

(HERS).[30] Thus, it appears that rate of change of renal function is only relevant for clinical risk in patients with CAD and systolic dysfunction, or with heart failure.[26,27,31]

Although we observed a slight deterioration of creatinine-based estimates prior to the incident endpoint, we could not confirm their predictive value as found previously.[1,2] This may be explained by the relatively low prevalence of patients with more severe renal dysfunction in our study. In fact, only 11% of our patients had moderate renal impairment ($eGFR_{Cr}$ 30–59) and there were no patients with $eGFR_{Cr}$ <30 due to the exclusion criteria. However, it appears that CysC levels were still able to detect these subtle differences, which may be of particular interest for patients with mild eGFR reduction ($eGFR_{Cr}$ 60–89), as was the case in 56% of patients included in the study. Although such mild renal dysfunction usually does not require medical attention, accurate monitoring of these subtle differences by cysC may carry potential for improving risk stratification of these patients.

Study limitations

Several aspects of our study warrant consideration. First, the MDRD equation, although validated in patients with ACS, has limitations due to the non-renal factors that influence creatinine measures. Nevertheless, we chose MDRD because it is the most widely utilized $eGFR_{Cr}$ equation, and thus enables comparisons with existing studies. Second, patients were excluded in case of $eGFR_{Cr}$ <30, which limits generalizability of our results to the ACS population at large. Yet we were able to demonstrate, even in this ACS population with a lesser degree of renal impairment, that renal dysfunction quantified by plasma CysC is associated with cardiovascular events. Third, despite controlling analyses for GRACE risk score – a risk model recommended in international guidelines - residual confounding may still be present.

CONCLUSION

During hospitalization for ACS, plasma CysC levels indicate deterioration of renal function earlier than creatinine or $eGFR_{Cr}$. Renal function usually does not stabilize during hospitalization, but on average two weeks after ACS. In patients with normal to moderately-impaired renal function, CysC levels predict mortality or recurrence of ACS within the first year independently of GRACE risk score.

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SUPPLEMENTARY INFORMATION

TABLE S1. Inclusion and exclusion criteria

Inclusion: a patient must meet all criteria	
1	Age ≥40 years
2	Complaints of typical ischemic chest pain, lasting 10 minutes or more within the preceding 24 hours prior to presentation
3a	ECG: (non-)persistent ST segment elevation >1.0 mm in two or more contiguous leads, or dynamic ST segment depression >1.0 mm in two or more contiguous leads, *OR*
3b	Biochemical evidence of myocardial injury: CK-MB or (high-sensitivity) Troponin I or (high-sensitivity) Troponin T elevation according to the applicable ESC guidelines of non ST-elevation acute coronary syndromes
4	Presence of at least 1 of the following risk factors: age ≥75 years, diabetes, prior cardiovascular disease, prior cerebrovascular disease and prior peripheral arterial disease. In addition, other risk factors mentioned below can be considered as well, but each only counts as half a risk factor, i.e., two of these are required for inclusion: age ≥65 years in men, age ≥70 years in females, hypertension, hypercholesterolemia, current smoking, or microalbuminuria†, positive family history of coronary artery disease‡
5	Written informed consent

continued

Exclusion: a patient cannot be included in case of any of the criteria below

1	Myocardial ischemia precipitated by a condition other than atherosclerotic coronary artery disease
2	Left ventricular ejection fraction <30%, or end-stage congestive heart failure (NYHA class III or IV)
3	Renal dialysis, or severe chronic kidney disease with measured or calculated GFR_{Cr} (Cockroft-Gault or MDRD formula) of <30 ml/min/1.73 m^2
4	Co-existent condition with life-expectancy <1 year or otherwise not expected to complete follow-up

GFR_{Cr}: glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; NYHA: New York Heart Association classification
† defined as >2.5-25 mg albumin/mmol creatinine for men and >3.5-35 mg for women, or >20-200 mg/l urinary albumin concentration in a single urine sample
‡ angina pectoris, myocardial infarction, or sudden abrupt death without obvious cause, before the age of 55 in a first-degree blood relative

TABLE S2 Hazard ratios for the primary endpoint in relation to biomarker levels >7 after ACS.

	Geometric mean**			Levels[a]		Instantaneous slope[b]	
	Mean - 1SD	**Mean**	**Mean + 1SD**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Creatinine	67	84	105				
crude model				1.40 (0.94–1.98)	0.09	1.00 (0.53–1.85)	0.98
+ GRACE risk score[#,*]				1.29 (0.86–1.94)	0.61	1.01 (0.54–1.90)	0.98
$eGFR_{Cr}$	64	89	122				
crude model				1.42 (0.97–2.06)	0.08	1.01 (0.54–1.87)	0.93
+ GRACE risk score[#,*]				1.25 (0.82–1.89)	0.30	1.01 (0.53–1.91)	0.97
CysC	466.9	608.9	794.0				
crude model				1.68 (1.13–2.46)	0.009	1.00 (0.54–1.78)	0.98
+ GRACE risk score[#,*]				1.63 (1.01–2.57)	0.045	0.99 (0.53–1.82)	0.95

[a] Hazard ratios (HRs) and 95% confidence interval (CI) are given per 1SD increase (creatinine and cystatin C), and 1SD decrease ($eGFR_{Cr}$) on the 2-log scale at any time point after 7 days after index ACS.
[b] HRs (95%) CI are given per 0.1SD increase in the slope (creatinine and CysC), and 0.1SD decrease ($eGFR_{Cr}$) on the 2-log scale at any time point after 7 days after index ACS.
[#] longitudinal model adjusted for GRACE risk score, sex, diabetes, history of coronary artery bypass surgery, history of valvular heart disease, history of stroke, history of peripheral arterial disease.
* survival model adjusted for GRACE risk score.
** Geometric mean ± 1 standard deviation (SD) of the patient-specific biomarker values after 30 days (presented on the linear scale).