Prognostic value of circulating chromogranin A levels in acute coronary syndromes

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Aims	To determine whether circulating levels of chromogranin A (CgA) provide prognostic information independently of conventional risk markers in acute coronary syndromes (ACSs).
Methods and results	We measured circulating CgA levels on day 1 in 1268 patients (median age 67 years, 70% male) with ACS admitted to a single coronary care unit of a Scandinavian teaching hospital. The merit of CgA as a biomarker was evaluated after adjusting for conventional cardiovascular risk factors. During a median follow-up of 92 months, 389 patients (31%) died. The baseline CgA concentration was strongly associated with increased long-term mortality [hazard ratio per 1 standard deviation increase in logarithmically transformed CgA level: 1.57 (1.44–1.70), $P < 0.001$], heart failure hospitalizations [1.54 (1.35–1.76), $P < 0.001$], and recurrent myocardial infarction (MI) [1.27 (1.10–1.47), $P < 0.001$], but not stroke. After adjustment for conventional cardiovascular risk markers, the association remained significant for mortality [hazard ratio 1.28 (1.15–1.42), $P < 0.001$] and heart failure hospitalization [hazard ratio 1.24 (1.04–1.47), $P = 0.02$], but not recurrent MI.
Conclusion	CgA is an independent predictor of long-term mortality and heart failure hospitalizations across the spectrum of ACSs and provides incremental prognostic information to conventional cardiovascular risk markers.
Keywords	Acute coronary syndromes • Chromogranin A • Troponin T • Echocardiography • Prognosis

During the past decade, major progress has been made in the management of patients with acute coronary syndromes (ACSs). In parallel with advances in medical therapy and increasing use of an early invasive strategy, there has been focus on early risk stratification of patients, and in particular, the potential prognostic utility of circulating biomarkers.[1] Currently, cardiac-specific troponins and B-type natriuretic peptide are the major routinely measured circulating biomarkers in patients with ACSs.[2,3]

Chromogranin A (CgA) is a 439 amino acid, 49 kDa polypeptide, which has been identified throughout the endocrine and nervous systems.[4] Markedly elevated plasma levels have been observed in patients with neuroendocrine tumours,[5] such as pheochromocytoma[6] and carcinoid,[7] and the clinical application of CgA measurements has so far been limited to diagnosis and follow-up of patients with such tumours. However, circulating CgA levels also correlate closely with increased sympathetic activity both in the adrenal medulla and the peripheral nerve endings,[8–10] suggesting that circulating CgA may integrate neuroendocrine signals from various sources and thus represent an index of overall neuroendocrine activity. Moreover, myocardial production of CgA in humans with dilated and hypertrophic cardiomyopathy has recently been demonstrated,[11] and CgA has been shown to increase in

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proportion to clinical severity and to be associated with prognosis in patients with both chronic and post-infarction heart failure.[12,13] In a small population with predominantly ST-elevation myocardial infarction (MI), we have previously reported a univariable association between CgA levels and long-term survival,[14] but because of modest study power, it remains unclear whether CgA is an independent predictor of survival. In patients with unstable angina and non-ST-elevation MI, no prognostic data are currently available. Because increased neuroendocrine activity may be related to potentially harmful pathophysiological processes in patients with both ST-elevation and non-ST-elevation ACS, including endothelial dysfunction and activation of pro-inflammatory cytokines, we hypothesized that circulating CgA levels would be predictive of the incidence of death and non-fatal cardiovascular events across the spectrum of ACS and would provide prognostic information independently of conventional risk markers, including objective measures of left ventricular dysfunction and contemporary cardiac biomarkers.

Methods

Study design

Patients with ACS, defined as a diagnosis of unstable angina, non-ST-elevation MI, or ST-elevation MI, admitted to the coronary care unit (CCU) of the Sahlgrenska University Hospital, Gothenburg, Sweden during the period mid-September 1995 to mid-March 2001, were eligible for participation in a prospective risk stratification programme, PRACSIS (Prognosis and Risk in Acute Coronary Syndromes in Sweden),[15] in which the main study exclusion criteria were age <18 or ≥80 years, non-coronary artery disease associated with a life expectancy <1 year, residence outside the city of Gothenburg, unwillingness to participate, and prior admission resulting in inclusion in the study.

During this 5.5-year period, a total of 2335 patients were included in the PRACSIS programme. Until November 1995, only clinical information was collected in PRACSIS and we did not perform consecutive serum sampling, resulting in only six random morning pilot serum samples being drawn in this period. Thereafter, serum for later analysis was obtained the first morning after admission to the CCU in the patients who, at this stage, were assigned a diagnosis of ACS. Thus, a number of patients were not eligible for blood sampling despite later being considered as having ACS and noted as such. Another portion of patients (*n* = 612) in PRACSIS were transferred to the CCU from an internal medicine ward where they had been admitted owing to an initially uncertain ACS, or from the intensive care unit where they were admitted owing to the need of mechanical ventilation. We lack serum from a majority of these patients. Yet another portion of patients did not survive until the first morning in hospital or were at this time undergoing angiography, and during some holidays serum sampling was not attempted. These patients were included in the PRACSIS programme, but not in the biomarker substudy. Users of proton pump inhibitors on admission (*n* = 38) were also excluded from this study, as proton pump inhibitors are known to increase circulating CgA levels.[16] Thus, the final study group comprised 1268 patients.

The primary outcome measure was mortality from all causes. The median follow-up for this primary endpoint was 92 (interquartile range 71–110) months (until 1 January 2007). Survival confirmation and date of death were obtained from the Swedish National Population Registry. Eleven patients, who emigrated from Sweden, were lost to follow-up and censored at the day of emigration.

Pre-specified secondary outcome measures were the incidence of the following separate morbidity endpoints: heart failure [International Statistical Classification of Disease, Ninth Revision (ICD-9) code 428 or ICD-10 code I50], acute MI (ICD-9 code 410 or ICD-10 code I21 or I22), and stroke (ICD-9 codes 431, 432, 433, or 436 or ICD-10 codes I61, I62, I63, or I64). These data were obtained from the Swedish Hospital Discharge Register. Because of a slower confirmation process than for mortality data, morbidity data were not available after 31 December 2002. Accordingly, the median follow-up period for morbidity data was 50 (interquartile range 32–65) months. For quality control purposes, morbidity data from the Registry were checked against information in the patients' medical records by a cardiologist (M.H.) blinded to biomarker results. No patient was excluded owing to missing data for outcome.

Patients were prospectively classified according to Killip class on admission and during the index hospitalization. Electrocardiographic findings on admission were classified according to the presence or absence of ST-segment elevation and ST-segment depression. On the basis of hospital records and personal interview, patients were classified as having or not having a history of MI, angina pectoris, chronic heart failure, diabetes mellitus, or hypertension. The study protocol was approved by the Regional Ethics Committee before the initiation of the study. Informed consent was obtained from all participating patients.

Blood sampling procedures and echocardiography

Peripheral venous blood was obtained within 24 h of admission by direct venipuncture of an antecubital vein after the patients had been supine for >30 min. Blood samples for CgA determination were drawn into serum tubes and centrifuged within 1 h. Blood samples for the determination of pro-B-type natriuretic peptide (proBNP) were drawn into pyrogen-free tubes with EDTA as anticoagulant, immediately immersed in ice water, and centrifuged within 1 h.

All serum samples were stored at −70°C pending analysis. Plasma and serum samples had been thawed twice prior to CgA analysis. However, CgA is considered to be stable *in vitro* at room temperature and plasma levels are not influenced by repeated thawing–refreezing cycles.[17] Echocardiographic investigation was performed by an experienced investigator within 5 days of hospital admission, as described previously.[18,19]

Biochemical analyses

CgA in serum was measured by a commercially available ELISA assay (code K0025, DakoCytomation, Glostrup, Denmark). The detection limit of the assay was 7.0 U/L, and the intra- and interassay coefficients of variance were <5 and 10%, respectively. According to the manufacturer, the upper reference limit is 18 U/L. Troponin T and creatine kinase MB fraction in serum were measured on a modular platform (Roche Diagnostics, Mannheim, Germany). Troponin T levels were unavailable in 225 subjects, as troponin T measurement was not part of the clinical routine during the first inclusion period. ProBNP$_{3-108}$ was measured using immunofluorescent assays calibrated with spiked plasma (Biosite Inc., San Diego, CA, USA).[20] The minimal detectable concentration was 400 ng/L and the upper range 30 000 ng/L. All samples were run in duplicate in a blinded fashion. Creatinine and total cholesterol concentrations in serum were determined by routine laboratory methods. Creatinine clearance rate (mL/min) was estimated (estimated glomerular filtration rate, eGFR) using the Cockcroft–Gault formula,[21] as [(140 − age) × weight (kg)/serum creatinine (μmol/L)] multiplied by a constant of 1.23 in men and 1.04 in women.

Statistical methods

Categorical variables were reported as proportions and continuous variables as median or mean values. The association between CgA and baseline demographic variables and cardiovascular risk factors was assessed by the Mann–Whitney U test and Spearman rank correlation (r_s) for categorical and continuous variables, respectively. To visualize the relationship between CgA quartiles and mortality, Kaplan–Meier plots were generated. Cox proportional hazards regression analyses were used to calculate crude and adjusted risk estimates associated with a 1 standard deviation (SD) increase in logarithmically transformed CgA levels for the primary endpoint: mortality from all causes, as well as for the following individual secondary endpoints: hospitalizations for heart failure, recurrent MI, and stroke. Adjustments were made for the following confounders: age (continuous), gender, index diagnosis, smoking status, prior MI, angina pectoris, diabetes, hypertension, heart failure, Killip class (dichotomous, i.e. cutoff Killip class >1), eGFR (continuous, logarithmically transformed), heart rate (continuous, logarithmically transformed), and peak creatine kinase-MB (continuous, logarithmically transformed). In addition, adjustments were also made for troponin T, left ventricular ejection fraction, and proBNP (all continuous and logarithmically transformed) in the cohorts where such measurements were available.

The assumption of proportional hazards was assessed by studying whether interaction terms between the logarithm of time and covariates significantly improved the -2 log-likelihood of the model. The assumption was met for all variables in all models, except for the endpoint rehospitalization owing to heart failure, where previous MI and creatine kinase-MB showed a slight non-proportionality in the total cohort, and index diagnosis and creatine kinase-MB in the cohort with troponin T measurements available. Inclusion of the time-dependent covariates into the corresponding models above resulted in only minor changes of the hazard ratios for CgA. We therefore decided to use the original models in order to cohere with our published reports on other markers from the same cohorts and to adjust for the same covariates in the different endpoint analyses.

Similarly, the assumption of linearity for continuous variables was checked by entering the squared transformations of the variables into the models. A significant change in the -2 log-likelihood for any model was considered a sign of non-linearity. All variables met the assumption of linearity in all models, except for age, regarding the endpoint rehospitalization owing to MI in the total cohort and regarding rehospitalization owing to stroke in the three other cohorts. Also, eGFR showed sign of non-linearity regarding heart failure in the cohort where troponin T, ejection fraction, and proBNP were available. For these models, we analysed the hazard ratios for CgA when the corresponding transformations were entered into the model, which resulted in only small changes from the original models, and, for the same reasons as for non-proportionality, we decided to use the models without squared transformation of these covariates.

Our primary objective variable CgA did not show any sign of non-proportionality or non-linearity.

Hazard ratios are given with 95% confidence intervals. All P-values are two-tailed and considered significant if <0.05.

Results

Baseline characteristics

A total of 1268 patients (median age 67 years, 70% male) had blood samples for CgA determination obtained within 24 h of admission and were not users of proton pump inhibitors at the time of admission. The baseline characteristics of patients according to CgA quartiles are presented in *Table 1*, where also data on the entire PRACSIS population are given for comparison. Patients with higher CgA values were more likely to be older, to have lower body mass index, to have clinical evidence of heart failure, a history of MI, angina, congestive heart failure, or diabetes mellitus; to be diuretic users, angiotensin-converting enzyme-inhibitor or angiotensin receptor blocker users, statin users, or aspirin users (data not shown); and to have a low ejection fraction or low eGFR. There was no relation between CgA and troponin T or creatine kinase MB fraction in serum. A significant correlation ($r_s = -0.43$, $P < 0.001$) between eGFR and CgA indicated that renal function influenced the CgA level. On the other hand, the lack of correlation between CgA and troponin T values ($r_s = 0.03$, $P = 0.18$) indicated that myocardial necrosis was not a major explanation for increased CgA levels. There were no significant differences in CgA levels between female and male patients. There was no significant interaction between index diagnosis and CgA regarding outcome. Accordingly, we decided not to analyse these groups separately.

Chromogranin A and long-term mortality

During a median follow-up of 92 months (interquartile range 71–110 months), 389 patients died. CgA serum levels at baseline were closely associated with long-term, all-cause mortality [hazard ratio per 1 SD increase in logarithmically transformed CgA levels: 1.57 (1.44–1.70), $P < 0.001$]. The Kaplan–Meier survival curves by CgA quartiles are depicted in *Figure 1*. After adjustment for conventional risk factors, CgA remained independently associated with mortality [hazard ratio per 1 SD increase in logarithmically transformed CgA levels: 1.28 (1.15–1.42), $P < 0.001$] (*Table 2*). CgA levels were also an independent predictor of mortality in the subgroup of patients in whom troponin T levels were available and adjusted for in addition to the covariates in the first model [$n = 1043$; HR 1.27 (1.13–1.42), $P < 0.001$]. In the group where left ventricular ejection fraction was determined ($n = 824$), CgA was as an independent predictor of all-cause mortality after adjustment for conventional cardiovascular risk factors, troponin T levels, and echocardiographically assessed left ventricular ejection fraction [HR 1.26 (1.10–1.44), $P < 0.001$]. In the group where also data on proBNP were available and additionally adjusted for ($n = 709$), a significant predictive value of CgA was also noted [HR 1.18 (1.01–1.37), $P = 0.04$]. Patients with both CgA and proBNP in the highest quartiles had an especially poor prognosis (*Figure 2*).

Chromogranin A and non-fatal cardiovascular events

By univariable analyses, the baseline CgA concentration was strongly associated with the incidence of heart failure hospitalizations [hazard ratio 1.54 (1.35–1.76), $P < 0.001$] and recurrent MI [hazard ratio 1.27 (1.10–1.47), $P < 0.001$], but not stroke [hazard ratio 1.16 (0.93–1.46), $P = 0.19$] (*Table 2*). After adjustment for conventional risk factors, CgA remained independently associated with the incidence of heart failure hospitalizations [hazard ratio 1.24

Table 1 Patient characteristics according to chromogranin A (U/L) quartile

	CgA ≤14.7 (n = 320)	CgA 14.8–20.9 (n = 315)	CgA 21.0–33.7 (n = 318)	CgA >33.7 (n = 315)	P-value[a]	Entire population[b] (n = 2258)
Age (years)	60 ± 11	65 ± 10	67 ± 9	68 ± 9	<0.001	66 ± 10
Female	89 (28)	98 (31)	90 (28)	102 (32)	0.31	688 (30)
Previous MI	57 (18)	65 (21)	68 (21)	84 (27)	0.002	558 (25)
Previous angina	125 (39)	149 (47)	143 (45)	152 (48)	0.02	1173 (52)
Previous heart failure	14 (4)	26 (8)	19 (6)	43 (14)	<0.001	233 (10)
Previous diabetes	50 (16)	46 (15)	42 (13)	75 (24)	0.01	435 (19)
Previous hypertension (1)[c]	134 (42)	118 (38)	109 (34)	138 (44)	0.83	938 (42)
Previous hypercholesterolaemia (1)[c]	91 (29)	96 (30)	81 (25)	87 (28)	0.41	665 (30)
Current smoker (20)[c]	112 (35)	95 (31)	96 (30)	97 (32)	0.24	648 (30)
ST-elevation MI	137 (43)	121 (38)	134 (42)	139 (44)	0.64	840 (37)
Non-ST-elevation MI	108 (34)	111 (35)	116 (36)	112 (36)	0.54	766 (34)
Unstable angina	75 (23)	83 (26)	68 (21)	64 (20)	0.21	652 (29)
ST-elevation on admission (2)[c]	128 (40)	109 (35)	119 (37)	121 (39)	0.77	744 (33)
ST-depression (no elevation) on admission (2)[c]	32 (10)	35 (11)	33 (10)	43 (14)	0.11	253 (11)
Q-wave on admission (2)[c]	39 (12)	19 (6)	38 (12)	53 (17)	0.01	236 (10)
SBP <100 mmHg on admission (1)[c]	6 (2)	13 (4)	9 (3)	13 (4)	0.23	95 (4)
Heart rate on admission (b.p.m.) (2)[c]	76 ± 19	76 ± 22	75 ± 20	77 ± 21	0.94	77 ± 22
CK-MB max (µg/L)	56 (8, 211)	49 (7, 148)	60 (11, 78)	62 (10, 203)	0.36	38 (5, 150)
Troponin T max (µg/L) (225)[c,d]	0.8 (0.1, 3.9)	0.8 (0.0, 3.4)	1.2 (0.1, 4.3)	0.8 (0.1, 4.1)	0.18	0.6 (0.0, 3.4)
eGFR (mL/min) (19)[c]	82 ± 23	70 ± 20	65 ± 20	56 ± 21	<0.001	67 ± 24
proBNP (ng/L) (265)[c]	1327 (400, 2517)	1551 (572, 3007)	1982 (929, 3572)	2258 (1018, 4307)	<0.001	1772 (702, 3238)
Body mass index (kg/m²) (32)[c]	27.2 ± 4.0	26.3 ± 3.8	25.8 ± 3.7	25.5 ± 4.0	<0.001	26.3 ± 3.9
Killip class II–IV on admission (2)[c]	11 (3)	18 (6)	18 (6)	37 (12)	<0.001	193 (9)
Max Killip class II–IV(2)[c]	33 (10)	47 (15)	65 (20)	85 (27)	<0.001	463 (21)
Thrombolysis/primary PCI	109 (34)	99 (31)	100 (31)	107 (34)	0.98	600 (27)
Other PCI or CABG during hospitalization	88 (28)	92 (29)	90 (28)	71 (23)	0.12	669 (30)
LV ejection fraction (%) (278)[c]	54 ± 11	54 ± 12	51 ± 12	50 ± 13	<0.001	52 ± 13

Data expressed as n (%), mean ± SD, or median (25th, 75th percentile).
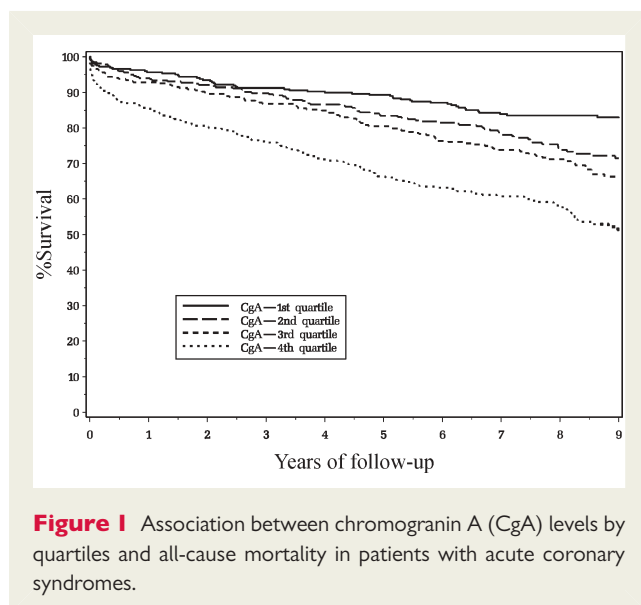CABG, coronary artery bypass grafting; CK-MB, creatine kinase MB fraction; LV, left ventricular; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
[a]Actual CgA value used in P-value calculations.
[b]All ACS patients admitted without proton pump inhibitors during inclusion period.
[c]Number of CgA patients where information was missing.
[d]The troponin T level was below detection in 22% of patients (n = 64, 64, 53, 53 in the CgA quartiles given above).

Figure 1 Association between chromogranin A (CgA) levels by quartiles and all-cause mortality in patients with acute coronary syndromes.

(1.04–1.47), $P = 0.02$], whereas the association with recurrent MI was attenuated [hazard ratio 1.15 (0.96–1.36), $P = 0.12$] (*Table 2*). In the subgroup where troponin T was available and adjusted for, CgA was significantly associated with both the incidence of heart failure ($P = 0.04$) and MI ($P = 0.04$). However, in the subsample of patients with echocardiographic data ($n = 824$), these associations were attenuated and no longer significant after adjustment for left ventricular ejection fraction (*Table 2*).

Discussion

The new information obtained from the present study is that plasma levels of CgA in the acute phase proved to be an independent predictor of all-cause mortality in patients with ACSs after adjustment for conventional risk factors, troponin T levels, echocardiographically assessed left ventricular ejection fraction, and proBNP. CgA levels were also associated with heart failure hospitalizations during follow-up independently of conventional risk factors, including troponin T. However, in the subsample of

Table 2 Associations between chromogranin A concentrations and events during follow-up in patients with acute coronary syndrome

Endpoint	Unadjusted		Adjusted	
	HR[a] (95% CI)	*P*-value	HR[a] (95% CI)	*P*-value
Total cohort ($n = 1268$)				
Mortality	1.57 (1.44, 1.70)	<0.001	1.28 (1.15, 1.42)[b]	<0.001[b]
Heart failure	1.54 (1.35, 1.76)	<0.001	1.24 (1.04, 1.47)[b]	0.02[b]
Recurrent MI	1.27 (1.10, 1.47)	<0.001	1.15 (0.96, 1.36)[b]	0.12[b]
Stroke	1.16 (0.93, 1.46)	0.19	0.96 (0.73, 1.26)[b]	0.76[b]
With troponin T ($n = 1043$)				
Mortality	1.56 (1.43, 1.71)	<0.001	1.27 (1.13, 1.42)[c]	<0.001[c]
Heart failure	1.46 (1.26, 1.71)	<0.001	1.23 (1.01, 1.49)[c]	0.04[c]
Recurrent MI	1.31 (1.12, 1.52)	<0.001	1.21 (1.00, 1.47)[c]	0.04[c]
Stroke	1.18 (0.92, 1.51)	0.19	0.96 (0.71, 1.29)[c]	0.77[c]
With troponin T and LV ejection fraction ($n = 824$)				
Mortality	1.56 (1.41, 1.74)	<0.001	1.26 (1.10, 1.44)[d]	<0.001[d]
Heart failure	1.33 (1.10, 1.61)	0.004	1.12 (0.88, 1.42)[d]	0.36[d]
Recurrent MI	1.31 (1.10, 1.57)	0.003	1.17 (0.95, 1.45)[d]	0.14[d]
Stroke	1.16 (0.86, 1.57)	0.34	0.91 (0.62, 1.33)[d]	0.62[d]
With troponin T, LV ejection fraction, and proBNP ($n = 709$)				
Mortality	1.53 (1.36, 1.72)	<0.001	1.18 (1.01, 1.37)[e]	0.04[e]
Heart failure	1.34 (1.07, 1.36)	0.009	1.11 (0.85, 1.45)[e]	0.45[e]
Recurrent MI	1.22 (1.00, 1.49)	0.052	1.10 (0.86, 1.39)[e]	0.45[e]
Stroke	1.30 (0.95, 1.78)	0.10	1.01 (0.68, 1.48)[e]	0.97[e]

[a]HR, hazard ratio per 1 SD pg/mL increase in the natural logarithm of CgA.
[b]Adjusted for age, gender, index diagnosis, smoking status, prior MI, angina pectoris, diabetes, hypertension, congestive heart failure, heart rate, Killip class (>I) on admission, eGFR, and peak creatine kinase MB fraction.
[c]Adjusted for all variables listed in footnote b and troponin T.
[d]Adjusted for all variables listed in footnote b and troponin T and LV ejection fraction.
[e]Adjusted for all variables listed in footnote b and troponin T and LV ejection fraction and proBNP.
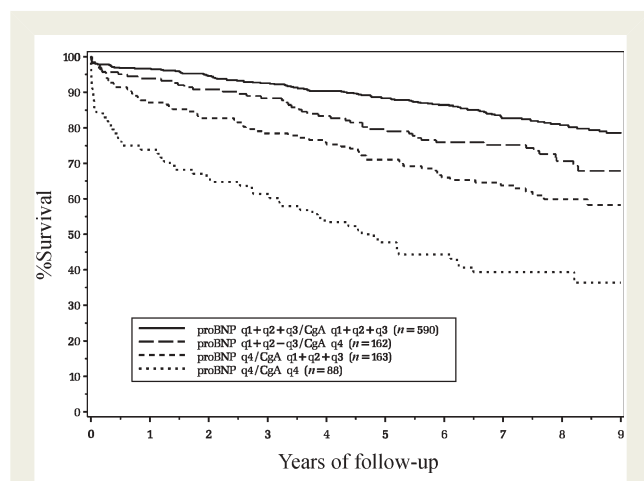
Figure 2 Association between chromogranin A (CgA) and pro-B-type natriuretic peptide (proBNP) levels by combined quartiles (*q*) and all-cause mortality in patients with acute coronary syndromes.

patients with echocardiographic data, the association was attenuated and no longer significant after adjustment for left ventricular ejection fraction. Potential reasons for the lack of a statistically significant independent association with heart failure in this subsample include the relative lack of statistical power and the fact that systolic dysfunction is a very strong predictor of heart failure. The association between CgA and recurrent MI was also attenuated after adjustment for conventional risk factors, but was borderline significant in patients in whom troponin T values were available.

In addition to its strong prognostic merit, several practical features make CgA a promising biomarker for clinical use, e.g. that its long *in vivo* half-life results in relatively high circulating concentrations. This feature simplifies blood collection and pre-analytic handling and makes CgA less prone to rapid fluctuations in circulating concentrations (low signal-to-noise ratio) than many other neurohormones.[17] Moreover, biochemical analysis of CgA can be readily performed using standardized and well-validated, commercially available assays.[22]

The two main causes of death in patients with ACSs are (i) recurrent ischaemic events, manifested as an ACS or sudden death, and (ii) heart failure, which may cause pulmonary congestion, inadequate tissue perfusion, or malignant arrhythmias. Although the univariable association between CgA and heart failure was closer than the associations between CgA and MI in the total cohort, in adjusted models the associations were of similar strength, permitting no clear conclusion to be drawn as to whether the prognostic value of CgA is mediated predominantly via prediction of heart failure or ischaemic events.

A potential link between the CgA and a propensity to heart failure development remains to be documented. However, theoretical considerations suggest that CgA is not only a marker of neuroendocrine activity, but may in itself exert harmful actions on the myocardium. CgA is a pro-hormone with multiple proteolytic cleavage sites,[4] allowing the generation of several peptides with different actions such as vasodilation,[23,24] negative inotropic actions,[25] inhibition of catecholamine secretion,[26] and induction

of apoptosis.[27,28] Accordingly, some of the CgA-derived fragments could have effects of importance for cardiovascular homeostasis and the heart failure development, including catestatin, a potent non-competitive inhibitor of catecholamine release.[29] In a knock-out mouse model, obliteration of CgA gene expression resulted in decreased size and number of chromaffin granules as well as arterial hypertension and ventricular hypertrophy, whereas transgenic expression of human CgA and exogenous injection of human catestatin restored blood pressure.[30] These findings suggest that CgA and catestatin may play a significant role in cardiovascular homeostasis.

The stimulus for CgA production and the pathophysiological role CgA plays in ACSs remain to be accurately defined. Acute ischaemia and subsequent left ventricular dysfunction are both characterized by complex neuroendocrine and immune activation, and may both represent potential correlates of CgA production. Accordingly, the magnitude of the CgA response in ACSs may be related to the initial extent of myocardial injury and subsequent degree of ventricular dysfunction. It is also conceivable that CgA production is a compensatory response to the immune activation associated with ischaemia and heart failure development. Accordingly, in a mouse model, it has recently been demonstrated that CgA and its amino terminal fragments inhibit tumour necrosis factor α-induced increase in vascular permeability by preventing re-arrangement of the cytoskeleton,[31,32] suggesting that CgA could contribute to the regulation of endothelial barrier function.

The source of increased circulating levels of CgA in ACSs is not clear. CgA has been detected in the atrial secretory granules containing atrial natriuretic peptide,[33] and recently myocardial production of CgA in humans with dilated and hypertrophic cardiomyopathy has been demonstrated,[11] suggesting that CgA may be released from the myocardium in conditions characterized by pressure or volume overload. However, this does not rule out the possibility that other organs, including the adrenals, may be contributing sources to increased levels of CgA. Reduced clearance of CgA may also result in higher circulating levels.[34] Arterial and venous blood sampling across vascular beds will be required to determine organ-specific production and clearance of CgA.

Strengths and limitations

The prospective, observational design, long duration of follow-up, and, in a considerable proportion of patients, echocardiographic information concerning left ventricular systolic function and proBNP are all important strengths of the current single-centre study. In particular, objective measures of left ventricular systolic function are not commonly obtained or adjusted for in biomarker substudies of major pharmaceutical multi-centre trials in patients with ACSs. Limitations include the lack of troponin T, echocardiographic data, and/or proBNP in part of the patients, mainly because blood sampling was not performed systematically in the early phase of the study, and because echocardiography was not always feasible in patients who were discharged early. As data may not be missing completely at random, we cannot rule out the possibility of some extent of selection bias. However, given that the hazard ratio estimates do not vary widely between models, we believe that the bias is likely to be minor. Moreover, direct comparison of the hazard ratios of the different multivariate models in *Table 2*

should be avoided. There was relatively modest power to detect associations between CgA and specific morbidity endpoints. However, we believe that these limitations will tend to underestimate, rather than overestimate, the prognostic value of CgA.

Conclusions

This study shows that plasma CgA levels obtained within the first 24 h of admission are independently associated with the incidence of death in patients with ACS. Clinical use of CgA measurements for risk stratification purposes in patients with ACS must, however, await confirmatory evidence from other studies.

Author contributions

A.M.J. interpreted the data and drafted the manuscript. H.R. contributed knowledge on chromogranin and drafted the manuscript in collaboration with A.M.J. T.O. participated in the design of the study and critically revised the paper. T.K. conducted the statistical analyses and critically revised the paper. M.H. conceived and designed the study and critically revised the paper. A.F. performed the CgA analyses and critically revised the paper. K.C. conceived and designed the study and critically revised the paper. K.C. and T.K. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CARDIOVASCULAR FLASHLIGHTS

Aortoesophageal fistula, a catastrophic complication soon after successful repair of an aortic dissection type A

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A 66-year-old man with a history of arterial hypertension underwent emergency cardiac surgery for aortic dissection type A, diagnosed by a computed tomographic scan (*Panel A*) after abdominal pain and syncope. The lesion was repaired with a Dacron tubular prosthesis. In the postoperative period, he improved his condition slowly under mechanical ventilation and inotropic support. At postoperative day 12, he was awake with minimum inotropic support and in weaning from mechanical ventilation.

Suddenly, he presented massive haematemesis. Under the suspicion of an aorto-oesophageal fistula, an urgent upper gastrointestinal endoscopy was performed, showing active bleeding at 36 cm from the dental arcade.

Resuscitation required transfusion of 13 packed red blood cells, four units of fresh frozen plasma, and seven units of platelets.

A Sengstaken–Blackmore tube was inserted in order to contain the bleeding, which was successful for a while.

After stabilization, an aortogram was performed (*Panels B–D*), which revealed contrast leak with active bleeding in the descending thoracic aorta from the true lumen to the oesophagus, at the level of the gastric balloon of the Sengstaken tube which was placed at the oesophagus (*Panel C*).

The placement of an endovascular stent graft was impossible because of the extensive lesions in the aortic wall.

The patient died 15 h after the initial bleeding, in a situation of refractory shock and persistent bleeding.

Aortoesophageal fistula is an uncommon complication in the early postoperative period of aortic dissection type A, usually fatal as a result of exsanguinating haemorrhage before assessment and any treatment can be undertaken.