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High-sensitivity C-reactive protein: potential adjunct for risk stratification in patients with stable congestive heart failure

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Aims To determine the potential adjunct of high-sensitivity (hs) C-reactive protein for risk stratification in patients with stable congestive heart failure (CHF).

Methods and results We studied 546 consecutive patients clinically stable with an ejection fraction <45% who were referred to our centre for evaluation of left ventricular dysfunction. hs C-reactive protein levels were determined on blood samples obtained on entry into the study. Clinical follow-up (median 972 days) was obtained for 545 patients.

Cardiovascular mortality was significantly increased ($P = 0.001$) in patients with hs C-reactive protein >3 mg/L. By multivariable analysis, including clinical, biological, and echocardiographic variables, hs C-reactive protein >3 mg/L was an independent predictor of cardiovascular mortality [HR = 1.78 (1.17–2.72); $P = 0.008$]; the strongest predictive parameter in this model was B-type natriuretic peptide (BNP) ($P = 0.005$). When peak VO_2 was included into the model, hs C-reactive protein >3 mg/L remained an independent predictor of cardiovascular mortality [HR = 1.55 (1.02–2.38); $P = 0.04$]; the strongest predictive parameter in this model was peak VO_2 ($P < 0.0001$). In patients with ischaemic CHF, cardiovascular mortality was significantly increased in patients with hs C-reactive protein >3 mg/L ($P = 0.001$), whereas in patients with non-ischaemic CHF, hs C-reactive protein >3 mg/L was not associated with cardiovascular mortality ($P = 0.098$). By multivariable analysis, hs C-reactive protein >3 mg/L was an independent predictor of cardiovascular mortality in ischaemic patients [HR = 2.16 (1.23–3.78)] but not in non-ischaemic patients [HR = 1.05 (0.52–2.11)].

Conclusion Cardiovascular mortality is increased in CHF patients with hs C-reactive protein >3 mg/L. The impact of hs C-reactive protein is independent of usual prognostic parameters, in particular BNP and peak VO_2. The interest of hs C-reactive protein determination appears to be especially marked in patients with ischaemic cardiomyopathy.

Introduction

Despite significant improvement in medical treatment, congestive heart failure (CHF) remains a major clinical problem with high morbidity and mortality. Risk stratification is therefore an important step for the selection of patients that may benefit from pronounced follow-up, intensive educative programs, and also from alternative therapeutic approaches such as cardiac transplantation or left ventricular (LV) assist devices. Many variables are useful for the identification of high risk CHF patients; these include clinical variables such as New York Heart Association (NYHA) classification, measurement of left and right ventricular function, exercise test variables such as peak oxygen consumption (VO_2), and biological markers of neurohormonal activation such as B-type natriuretic peptide (BNP).[1–3] Although these two latter prognostic markers are powerful when they are combined,[3] cardiopulmonary testing is a time-consuming method that is not systematically used for risk stratification of CHF patients.

The concept that biological markers may accurately predict the outcome of CHF patients is an attractive one. Several reports have indicated that elevated blood levels of inflammatory markers are associated with an adverse prognosis in CHF patients.[4–6] Importantly, proinflammatory cytokine levels do not correlate with neurohormonal markers[7] and it has been suggested that high BNP and interleukin-6 (IL-6) may independently predict mortality in patients with severe CHF.[5]

C-reactive protein is a sensitive marker of inflammation. When compared with other more sophisticated measures

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of cytokine activity, C-reactive protein determination may be more appropriate for routine clinical use. High-sensitivity (hs) assays for C-reactive protein have been standardized across many commercial platforms; moreover, C-reactive protein is highly stable, allowing measures to be made accurately in both fresh and frozen plasma without requirements for special collection procedures.[8] hs C-reactive protein levels have been shown in multiple prospective epidemiological studies to predict vascular risk (myocardial infarction, stroke, or peripheral arterial disease)[9,10] but few data are available regarding the prognostic impact of hs C-reactive protein levels in patients with CHF.

Accordingly, our aim was to determine the potential adjunct of hs C-reactive protein for risk stratification in a series of CHF patients treated with a combination of angiotensin-converting enzyme-inhibitors (ACE) and beta-blockers, who underwent prognostic evaluation in our institution with a systematic determination of a large set of prognostic variables.

Methods

Study population

All patients referred to our centre between January 1998 and January 2003 for evaluation of LV systolic dysfunction were considered for inclusion. Patients were included if they were ambulatory, stable for at least 2 months and had a left ventricular ejection fraction (LVEF) $<45\%$. Patients were excluded if they had a recent (<3 months) myocardial infarction, unstable angina, or coronary revascularization; patients who had experienced a serious infection were also excluded. A total of 546 consecutive patients were included into the study. As part of the prognostic evaluation, patients underwent echocardiography ($n=546$), radionuclide angiography ($n=528$), cardiopulmonary exercise testing ($n=521$), and BNP determination ($n=500$), as previously described.[3] BNP concentrations were measured with use of radioimmunoassay (RIA) (Shionoria BNP kit; Shionogi & Co. Ltd, Osaka, Japan) in 411 patients and with use of a fluorescence immunoassay kit (Triage®, Biosite Diagnostics, San Diego, CA) in 89 patients; for the purpose of the present study, only patients with RIA determination of BNP were included into the multivariable models. The etiology of CHF was determined using routine coronary angiography; patients were classified as having an ischaemic etiology if they had experienced a previous myocardial infarction and/or had significant ($>50\%$) coronary artery disease at angiography. Patients were classified as diabetic if they were treated by oral hypoglycaemic drugs or insulin or if they had a previous history, documented on their medical chart, of elevated (>126 mg/dL) fasting blood glucose on at least two separate occasions in conjunction with adhering to ongoing dietary measures to control their glucose level.

The study was approved by the ethical committee of our institution and written informed consent was obtained from all patients.

hs C-reactive protein level determination

At the time of entry into the study, peripheral blood was collected in tubes containing EDTA and plasma samples were stored at -80°C until analysis. hs C-reactive protein levels were measured on plasma samples using a sensitive latex-enhanced immunonephelometric method with the BN II nephelometer automate from Dade-Behring (Dade™) as previously described.[11]

Follow-up

Clinical follow-up was performed at outpatient visits or by contacting the general practitioner or the cardiologist. All causes of death were adjudicated by two investigators (N.L. and P.d.G.). The primary endpoint of the study was cardiovascular mortality defined as cardiovascular death or urgent cardiac transplantation (UNOS 1).[12] All unexpected sudden deaths were counted as cardiovascular deaths. The cause of cardiovascular death was determined after a detailed review of the circumstances of death and classified as: (i) pump failure death; (ii) sudden death; (iii) vascular death (i.e. death related to myocardial infarction, stroke, or peripheral artery disease). Pump failure death was defined as death owing to shock or low output syndrome and not having an acute ischaemic etiology. Death due to myocardial infarction was defined as death within 1 month of the onset of myocardial infarction. Sudden death was defined as sudden cardiac death without any other obvious cause or symptoms.

Statistical analysis

Continuous variables are expressed as mean $\pm$ SD except for levels of BNP and hs C-reactive protein. These two variables did not follow a normal distribution and were expressed as medians with interquartile range. Baseline and follow-up variables were compared according to preset cutoff values of hs C-reactive protein as recommended by a consensus conference from the American Heart Association for the use of hs C-reactive protein in clinical practice:[13] <1, 1–3, >3 mg/L. Differences between groups were compared by trend test using the general linear model or non-parametric tests, as appropriate. Discrete variables were presented as frequencies and percentages, and were compared using χ^2 analysis and trends were tested using the Mantel–Haenzel test for heterogeneity. The unadjusted association (hazard ratio) between hs C-reactive protein and cardiovascular death was assessed by simple Cox regression analysis. The cumulative survival rates of the different groups according to the cutoff values was estimated using the Kaplan–Meier method, and the differences in survival curves were compared with a log rank test. Multivariable Cox proportional hazards analyses were performed to determine independent predictors of cardiovascular mortality. As cardiopulmonary exercise testing is not systematically available in routine clinical practice, we performed two pre-specified multivariable Cox regression analyses with and without peak VO_2 entered in the model. BNP was dichotomized using the median value of 38 pmol/L and peak VO_2 using the pre-established limit of 50%.[14] Hazard ratios (HR) are presented with 95% confidence interval (95%CI). For each variable, the proportional hazards assumption was tested visually using Kaplan–Meier curves and by examining a plot of $-\ln(-\ln(\text{survival time}))$ against the ln(time). In addition, the proportional hazard was assessed and satisfied by including an interaction time-dependent term in the multivariable Cox regression analysis. For continuous variables, the linearity assumption was assessed by plotting residuals against independent variables. All hypothesis were two-tailed with a 0.05 type I error rate. Analyses were performed with SAS software (release 8.2, SAS Institute Inc., Cary, North Carolina, USA).

Results

The median concentration of hs C-reactive protein was 1.96 mg/L (0.77–4.74). *Table 1* shows the baseline characteristics of the study population. Patients with higher levels of hs C-reactive protein were older, had a higher body mass index, and were more likely to have a history of hypertension and diabetes mellitus. The proportion of patients with ischaemic cardiomyopathy did not differ significantly among hs C-reactive protein subgroups. LVEF and end-diastolic diameter did not differ among hs C-reactive protein subgroups; in contrast, patients with higher levels of hs C-reactive protein had lower right ventricular ejection fraction, peak VO_2, and had higher levels of BNP. Most of the patients received an ACE-inhibitor or an angiotensin

Table 1 Baseline characteristics of the study population according to hs C-reactive protein

hs C-reactive protein	<1 mg/L ($n = 169$)	1–3 mg/L ($n = 175$)	>3 mg/L ($n = 202$)	*P* for trend
Age (years)	54 ± 13	56 ± 12	58 ± 12	0.0006
Male gender (*n*, %)	131 (78)	153 (87)	165 (82)	0.35
Cardiovascular risk factors (*n*, %)				
Hypertension	48 (28)	75 (43)	96 (48)	0.0002
Hypercholesterolaemia	88 (52)	107 (61)	113 (56)	0.46
Diabetes mellitus	36 (21)	49 (28)	64 (32)	0.03
Current or past smokers	114 (67)	132 (75)	142 (71)	0.54
Body mass index (kg/m^2)	25.6 ± 4.1	27.7 + 6.0	27.4 ± 5.6	0.0008
Etiology (*n*, %)				
Ischaemic	65 (39)	72 (41)	90 (45)	
Non-ischaemic	102 (60)	98 (56)	106 (52)	0.18
Undetermined	2 (1)	5 (3)	6 (3)	
Heart failure parameters				
NYHA class III (*n*, %)	33 (20)	44 (25)	53 (26)	0.14
LVEF (%)	33.8 ± 12.4	33.1 ± 12.6	33.5 ± 12.5	0.82
RVEF (%)	41.0 ± 12.7	38.2 ± 14.1	36.2 ± 12.6	0.0006
LVEDD (mm)	63.6 ± 9.7	64.7 ± 9.8	63.7 ± 10.2	0.91
Peak VO_2 (mL/min/kg)	17.6 ± 5.8	15.0 ± 4.2	13.9 ± 4.0	<0.0001
VO_2 (%)	64.4 + 17.9	58.4 ± 15.6	56.6 ± 16.7	<0.0001
Sodium (mEq/L)	138.8 ± 3.3	138.3 ± 3.1	137.7 ± 4.1	0.004
Creatinine (mg/L)	11.0 ± 5.3	11.1 ± 2.7	11.7 ± 3.8	0.13
Haemoglobin (g/dL)	13.9 ± 1.6	13.9 ± 1.5	13.6 ± 1.6	0.08
BNP (pmol/L) (RIA method)	33 (11–89)	38 (11–94)	54 (18–136)	0.020
Medications (n, %)				
ACE-inhibitors or ARB	167 (99)	173 (99)	200 (99)	0.86
Beta-blockers	163 (96)	170 (97)	189 (94)	0.16
Statins	64 (38)	71 (41)	82 (41)	0.60

RVEF, right-ventricular ejection fraction; LVEDD, left-ventricular end-diastolic diameter; %VO2, % of maximal predicted oxygen consumption; ARB, angiotensin 2 receptor blockers.

2-receptor blocker (99%) and a beta-blocker (96%). Forty percent of the patients received a statin but this medication was strongly associated with the etiology of CHF (23% in non-ischaemic CHF vs. 64% in ischaemic CHF, $P < 0.0001$).

Clinical follow-up [median 972 days (598–1574)] was obtained for 545 patients; 113 patients reached the end-point of cardiovascular death ($n = 109$) or urgent transplantation ($n = 4$), 24 patients died from non-cardiovascular causes. Cardiovascular survival rates at 1, 2, and 3 years were 91, 88, and 80%, respectively. When hs C-reactive protein was assessed as a continuous variable, a high hs C-reactive protein was significantly associated with cardiovascular mortality [HR = 1.10 (1.04–1.16); $P = 0.001$]. Kaplan–Meier curves for cardiovascular mortality according to baseline hs C-reactive protein concentrations are shown in *Figure 1*. Clinical outcome was similar for patients in the first or second subgroups of hs C-reactive protein; in contrast, cardiovascular mortality was significantly increased in patients with hs C-reactive protein >3 mg/L (logrank, $P = 0.001$). Multivariable analysis was then performed to select independent predictors of cardiovascular mortality (*Table 2*). In a first model including usual clinical, biological, and echocardiographic variables, a hs C-reactive protein >3 mg/L was selected as an independent prognostic parameter and associated with a HR of 1.78 [1.17–2.72; ($P = 0.008$)]; other variables retained into the model were

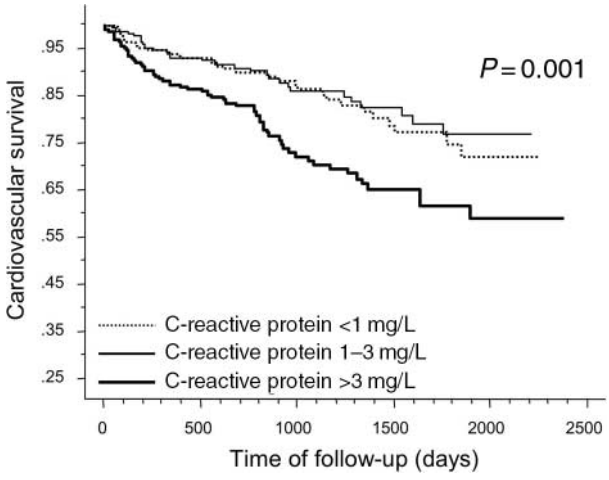

Figure 1 Kaplan–Meier curves for cardiovascular survival as a function of hs C-reactive protein levels at baseline.

BNP ($P = 0.005$), age (0.008), NYHA class 3 ($P = 0.009$), and male gender ($P = 0.019$). *Figure 2* illustrates the potential interest of dual determination of the two biological markers BNP and hs C-reactive protein for risk stratification of CHF patients. When peak VO_2 was included into the

Table 2 Predictors of cardiovascular mortality: multivariable analysis

Variable	Wald χ^{-2}	HR (95%CI)	*P*
Model 1			
BNP >38 pmol/L	7.84	2.25 (1.28–3.97)	0.005
hs C-reactive protein >3 mg/L	7.16	1.78 (1.17–2.72)	0.008
Age	6.94	1.03 (1.007–1.05)	0.008
NYHA class 3	6.78	1.79 (1.16–2.78)	0.009
Male gender	5.52	2.54 (1.17–5.52)	0.019
Ischaemic etiology	3.38	1.52 (0.97–2.37)	0.066
Hypertension	1.17	0.78 (0.50–1.22)	0.28
LVEF	1.05	0.99 (0.97–1.01)	0.31
BMI	0.48	0.98 (0.94–1.03)	0.49
RVEF	0.05	0.99 (0.98–1.02)	0.82
Diabetes mellitus	0.002	1.01 (0.64–1.59)	0.96
Model 2			
Peak VO_2 <50%	34.49	4.30 (2.64–7.00)	<0.0001
Age	13.8	1.04 (1.02–1.06)	0.0002
BNP >38 pmol/L	5.44	1.98 (1.12–3.51)	0.020
hs C-reactive protein >3 mg/L	4.15	1.55 (1.02–2.38)	0.042
Male gender	3.98	2.38 (1.02–5.58)	0.046
Hypertension	2.36	0.70 (0.45–1.10)	0.12
RVEF	1.94	1.01 (0.99–1.03)	0.16
Ischaemic etiology	1.83	1.36 (0.87–2.21)	0.18
NYHA class 3	1.22	1.29 (0.82–2.03)	0.27
LVEF	1.04	0.99 (0.97–1.01)	0.31
BMI	0.34	0.99 (0.94–1.04)	0.56
Diabetes mellitus	0.09	0.93 (0.59–1.48)	0.77

Model 1: BMI, body mass index. Model 2 includes the same variables as model 1 with peak VO_2.

model, a hs C-reactive protein >3 mg/L remained an independent predictor of cardiovascular mortality [HR = 1.55 (1.02–2.38), $P = 0.042$]; other variables retained into the model were peak VO_2 ($P < 0.0001$), age ($P = 0.0002$), BNP ($P = 0.02$), and male gender ($P = 0.046$).

As high concentrations of hs C-reactive protein are predictors of clinical outcome in patients with coronary artery disease,[15] subgroup analyses were then carried out in patients according to CHF etiology. When assessed as a continuous variable, a high hs C-reactive protein was significantly associated with cardiovascular mortality in patients with ischaemic cardiomyopathy [HR = 1.12 (1.04–1.20); $P = 0.001$] but not in patients with non-ischaemic cardiomyopathy [HR = 1.06 (0.97–1.17); $P = 0.16$]. Kaplan–Meier curves for cardiovascular mortality according to baseline hs C-reactive protein concentrations and CHF etiology are shown in *Figure 3*. In patients with ischaemic cardiomyopathy, cardiovascular mortality was significantly increased in patients with hs C-reactive protein >3 mg/L (*Figure 3A*; logrank, $P = 0.001$), whereas in patients with non-ischaemic cardiomyopathy, there was only a non-significant trend for an increased mortality in patients with hs C-reactive protein >3 mg/L (*Figure 3B*; logrank, $P = 0.098$). *Table 3* shows the independent prognostic parameters according to the etiology of LV dysfunction. In patients with ischaemic cardiomyopathy, a hs C-reactive protein >3 mg/L was independently associated with cardiovascular mortality in the two models studied. In contrast, hs C-reactive protein

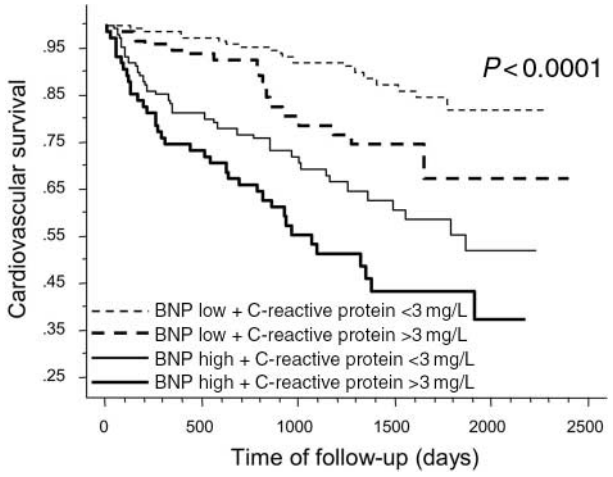

Figure 2 Kaplan–Meier curves for cardiovascular survival as a function of BNP and hs C-reactive protein levels at baseline. Cutoff value for BNP = 38 pmol/L.

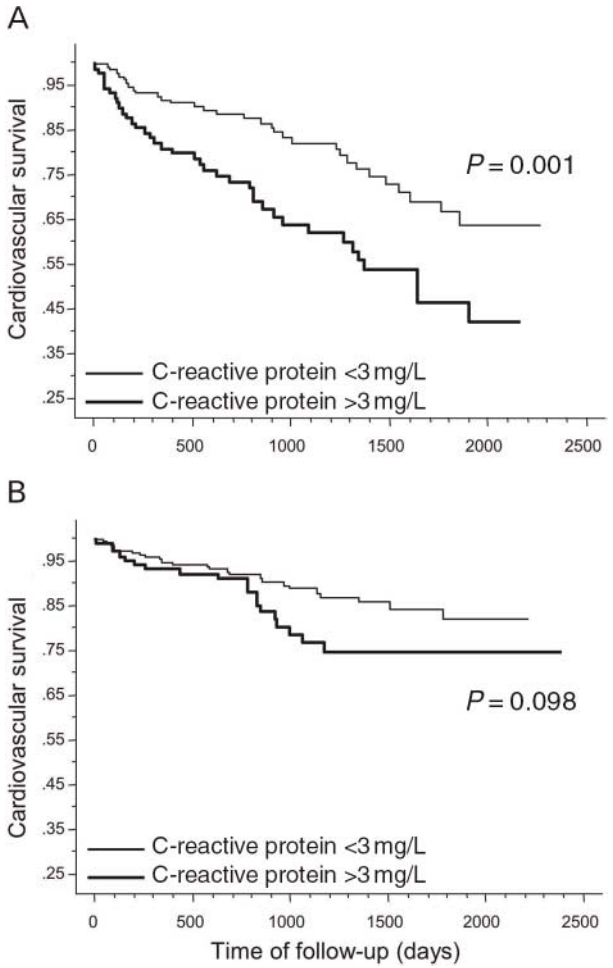

Figure 3 Kaplan–Meier curves for cardiovascular survival as a function of hs C-reactive protein levels at baseline according to CHF etiology: (*A*) ischaemic cardiomyopathy; (*B*) non-ischaemic cardiomyopathy.

was not a predictor of cardiovascular mortality in patients with non-ischaemic cardiomyopathy. Finally, the impact of hs C-reactive protein levels on the cause of death is shown in *Table 4*. Patients with hs C-reactive protein >3 mg/L

Table 3 Predictors of cardiovascular mortality according to etiology of LV dysfunction: multivariable analysis

	Ischaemic ($n = 227$)			Non-ischaemic ($n = 306$)		
Variable	Wald χ^{-2}	HR (95%CI)	*P*	Wald χ^{-2}	HR (95%CI)	*p*
Model 1						
hs C-reactive protein >3 mg/L	7.2	2.16 (1.23–3.78)	0.007	0.02	1.05 (0.52–2.11)	0.89
BNP >38 pmol/L	3.9	2.03 (1.01–4.10)	0.049	5.2	3.26 (1.19–8.98)	0.022
Model 2						
Peak VO_2 < 50%	25.1	5.40 (2.79–10.5)	<0.0001	10.6	3.94 (1.73–9.00)	0.001
hs C-reactive protein >3 mg/L	5.2	1.92 (1.10–3.37)	0.023	0.08	0.90 (0.45–1.82)	0.77
BNP >38 pmol/L	3.2	1.92 (0.94–3.91)	0.072	3.3	2.59 (0.93–7.25)	0.069

Model 1 includes same variables as Table 2. Model 2 includes variables of model 1 and peak VO_2.

Table 4 Impact of hs C-reactive protein >3 mg/L on the cause of cardiovascular death

hs C-reactive protein	<3 mg/L ($n = 344$) (%)	>3 mg/L ($n = 202$) (%)	HR (95%CI)	*P*
Pump failure death	23 (6.7)	21 (10.4)	1.55 (0.88–2.74)	0.12
Sudden death	25 (7.3)	26 (12.9)	1.77 (1.05–2.98)	0.030
Vascular death[a]	8 (2.3)	10 (5.0)	2.13 (0.85–5.31)	0.098

[a]Vascular death includes myocardial infarction, stroke, and death from peripheral artery disease.

had a significantly higher risk of sudden death ($P = 0.03$); pump failure death, and vascular death also tended to be higher in patients with hs C-reactive protein >3 mg/L (non-significant).

Discussion

The present study shows an increased cardiovascular mortality in CHF patients with higher levels of hs C-reactive protein. The impact of hs C-reactive protein is independent of usual prognostic parameters, in particular BNP and peak VO_2. The interest of hs C-reactive protein determination appears to be especially marked in patients with ischaemic cardiomyopathy.

Inflammation in CHF

Different studies have documented an elevation of inflammatory markers in patients with advanced CHF. Increased levels of cytokines such as tumor necrosis factor-alpha (TNF-alpha), soluble TNF receptor 1 and 2, or IL-6 have been reported in various populations of CHF patients and have been associated with CHF severity and with an increased cardiovascular mortality during follow-up.[4–6] However, in spite of these interesting results, cytokines levels are not routinely determined for risk stratification of CHF patients. As stated earlier, the use of hs C-reactive protein as an inflammatory marker may offer several advantages over direct measurement of cytokines activity[8] and therefore could be more appropriate for routine clinical use.

Few studies have reported on hs C-reactive protein levels in CHF patients. Alonso-Martinez *et al.*[16] measured hs C-reactive protein levels in 76 patients with clinical heart failure and found that higher levels were associated with an increased risk of re-hospitalization during follow-up. Yin *et al.*[17] reported on a series of 108 patients with a LVEF <50% and observed that hs C-reactive protein levels were significantly increased with the severity of CHF and that higher levels were associated with an increased risk of a composite endpoint of cardiac death or hospitalization for worsening CHF during follow-up. The higher number of patients included in the present study ($n = 546$) allowed us to demonstrate an impact of hs C-reactive protein levels not only on cardiovascular morbidity but also on cardiovascular mortality. Moreover, our results demonstrate that this association persists in the context of an extensive prognostic evaluation.

Ischaemic vs. non-ischaemic CHF

Previous epidemiological studies have shown that the determination of hs C-reactive protein may help to predict vascular risk.[9,10] We therefore speculated that the prognostic impact of hs C-reactive protein in CHF may differ according to the etiology of LV dysfunction. Indeed, in patients with ischaemic CHF, higher levels of hs C-reactive protein may reflect cytokine activation in the context of severe CHF but may also indicate an increased vascular risk. In the present study, the deleterious impact of an elevated hs C-reactive protein was restricted to patients with ischaemic cardiomyopathy; this was apparent in univariable and multivariable analyses (*Figure 3* and *Table 3*). Interestingly, the increased mortality in our study is very similar to the increased risk for coronary events documented in population-based studies without pre-existing CHF.[18] Although this result was obtained from a subgroup analysis and as such should be taken with caution, the etiology of heart failure was defined prospectively using routine coronary angiography. Patients with hs C-reactive protein >3 mg/L had a significant increase in sudden death and only non-significant trends for an increase in pump failure death and vascular death. However, this does not rule out the hypothesis that part of the deaths encountered in patients with ischaemic CHF and high hs C-reactive protein may be related to acute coronary events. Indeed, in the ATLAS trial, the prevalence of acute coronary findings at

autopsy in patients with ischaemic heart failure was 54% in case of sudden death and 32% in case of myocardial failure.[19]

Study limitations

Our conclusions cannot be extended to all CHF patients; we studied ambulatory patients with relatively well-compensated CHF and after optimization of their treatment including maximal tolerated doses of both ACE-inhibitors and beta-blockers. In addition, our results on the causes of cardiovascular death, which were not adjudicated by an independent Event Committee should be interpreted with caution.

Clinical implications

Risk stratification is an important step before defining the optimal treatment strategy for CHF patients. In the present study, we demonstrate that hs C-reactive protein determination provides prognostic information independent of usual prognostic markers including BNP and peak VO_2. As cardiopulmonary testing is a time-consuming method that is not systematically used for risk stratification of CHF patients, we also analysed the prognostic value of hs C-reactive protein in a model which did not take into account peak VO_2 and found that two biological variables BNP and hs C-reactive protein were the stronger predictors of cardiovascular mortality. If these results were confirmed in independent cohorts, dual determination of the two biological markers as illustrated in *Figure 2* would be a non-invasive, widely available, non-operator-dependent, and relatively inexpensive method for risk stratification. Patients with high levels of both markers could be selected for more sophisticated prognostic evaluation to determine if alternative therapeutic strategies such as cardiac transplantation or LV assist devices are needed. Moreover, our results suggest that the parameters that should be used for risk stratification of CHF patients may differ according to the etiology of LV dysfunction.

Conflict of interest: No conflict of interest exists for this paper.

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