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## Interleukin-1Beta and Risk of Premature Death in Patients with Myocardial Infarction

**Brief title:** IL-1 $\beta$  and mortality in myocardial infarction

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**Data Sharing:** Data sharing including for biological analyses require specific authorizations of the Hospital and Ethics committee on the basis of any new study proposal and will therefore not be made available to others without these approvals.

## **Abstract**

**Background:** Inhibition of the interleukin-1 $\beta$  (IL-1 $\beta$ ) innate immunity pathway is associated with anti-inflammatory effects and a reduced risk of recurrent cardiovascular events in stable patients with previous myocardial infarction (MI) and elevated high sensitivity C-reactive protein (hs-CRP).

**Objectives:** to assess the association between IL-1 $\beta$  level with all-cause mortality in patients with acute ST segment elevation myocardial infarction (MI) undergoing primary percutaneous coronary intervention and the interplay between IL-1 $\beta$  and hs-CRP concentrations on the risk of premature death.

**Methods:** IL-1 $\beta$  concentration was measured among 1398 ST segment elevation MI patients enrolled in a prospective cohort. Crude and hazard ratios for all-cause and cardiovascular mortality were analyzed at 90-days and one-year using a multivariate-cox proportional regression analysis. Major cardiovascular events (MACE) were analyzed.

**Results:** IL-1 $\beta$  concentration measured at admission was associated with all-cause mortality at 90 days (adjusted hazard ratio [adjHR], 1.47 per 1SD increase; 95% CI, 1.16 to 1.87;  $p < 0.002$ ). The relation was nonlinear, and highest tertile of IL-1 $\beta$  was associated with higher mortality rates at 90 days (adjHR: 2.78; 95%CI: 1.61-4.79,  $p = 0.0002$ ) and one-year (adjHR: 1.93; 95%CI: 1.21-3.06,  $p = 0.005$ ), regardless of the hs-CRP concentration. Significant relationships were equally observed when considering cardiovascular mortality and MACE at 90 days (adjHR: 2.42; 95% CI: 1.36-4.28,  $p = 0.002$  and 2.29; 95% CI: 1.31-4.01,  $p = 0.004$ , respectively) and at one year (adjHR: 2.32; 95% CI: 1.36-3.97,  $p = 0.002$  and 2.35; 95% CI: 1.39-3.96,  $p = 0.001$ , respectively).

**Conclusion:** IL-1 $\beta$  measured at admission in acute MI patients is independently associated with the risk of mortality and recurrent MACE.

**Condensed Abstract:** In this observational prospective cohort study that included 1398 patients with ST segment elevation myocardial infarction, IL-1 $\beta$  concentration measured at admission was independently associated with all-cause mortality (adjusted hazard ratio [adjHR], 1.47 per 1SD increase; 95% CI, 1.16 to 1.87;  $p < 0.002$ ) and major cardiovascular event at 90 days and one year. The relation was nonlinear, and highest tertile of IL-1 $\beta$  was markedly associated with higher mortality rates at 90 days (adjHR: 2.78; 95%CI: 1.61-4.79,  $p = 0.0002$ ) and one-year (adjHR: 1.93; 95%CI: 1.21-3.06,  $p = 0.005$ ), regardless of the hs-CRP concentration.

**Keywords:** Interleukin-1 $\beta$ , myocardial infarction, inflammation, C-reactive protein, mortality

## **Abbreviations**

IL-1 $\beta$ : Interleukin-1 $\beta$

IL-6: Interleukin-6

HR: Hazard Ratio

hs-CRP: High sensitivity C-reactive protein

MACE: Major cardiovascular events

MI: Myocardial Infarction

PCI: Percutaneous Coronary Intervention

## **Introduction**

High-sensitivity C-reactive protein (hs-CRP) and Interleukin-6 were identified as biomarkers of cardiovascular risk stratification in acute myocardial infarction (MI) patients (1,2) as they were associated with the size of myocardial infarction and the risk of recurrent events (3). Based on large studies, hs-CRP testing is also recommended in American guidelines to stratify the risk of events among individuals at intermediate risk of atherosclerotic cardiovascular disease. (4) The interleukin 1- $\beta$  (IL-1 $\beta$ ) immune innate pathway has generated growing interest as prior studies demonstrated the pivotal role of the proinflammatory cytokine IL-1 $\beta$  in the atherothrombosis process (5,6). This includes the promotion of monocyte and leukocyte adhesion to endothelial cells, induction of a procoagulant activity, and the growth of vascular smooth-muscle cells (7-9). Recently, inhibition of IL-1  $\beta$  with the human monoclonal antibody, canakinumab, led to a reduction of cardiovascular events in stable coronary artery disease patients with both, previous myocardial infarction (MI) and elevated hs-CRP, establishing the proof of concept of the so-called 'inflammatory hypothesis of atherosclerosis'(10). In addition, high IL-1 $\beta$  concentrations were recently found to be associated with an increased risk of death in patients with acute heart failure (11,12). In acute MI patients, there is no information on IL-1 $\beta$  as a risk marker of mortality and no evidence to suggest that targeting IL-1 $\beta$  during the acute phase may impact clinical outcome. In this context, we sought to evaluate whether IL-1  $\beta$  level, measured during the acute phase of MI, is associated with short- and long-term all-cause mortality and major cardiovascular events in patients hospitalized for mechanical reperfusion of an acute ST-elevation MI.

## **Methods**

*Study population and data collection*

A total of 1398 consecutive patients treated for an acute MI were enrolled in the ongoing ePARIS registry, a prospective registry with extensive clinical and biological data collection. Patients were included if they had an acute ST segment elevation MI treated by primary percutaneous coronary intervention (PCI). Biological sampling was obtained at admission in the catheterization laboratory, following sheath insertion. Patients with other final diagnosis were excluded as well as the patients who did not consent to participate. Following revascularization, patients received anti-ischemic, lipid-lowering and antithrombotic drugs according to the current guidelines. Clinical outcomes were obtained from medical reports or by telephone call. In case of loss to follow-up, the survival status was checked in the birth city hall registry.

#### *Study endpoint and objectives*

The primary objective was to evaluate the association between IL-1 $\beta$  with all-cause mortality at 90 days. The primary endpoint of the study was all-cause mortality at 90 days. Follow-up was continued until the last patient included reached one year of follow-up. Secondary objectives evaluated the association of IL-1 $\beta$  with i) all-cause mortality at one-year follow-up; ii) cardiovascular mortality up to 1 year; iii) major cardiovascular events defined by the association of cardiovascular death, recurrent MI or stroke, up to 1 year.

In an exploratory analysis, we assessed the interplay of IL-1 $\beta$  with hs-CRP on mortality at 90 days.

#### *Blood samples and biochemical measurements*

Blood collected was placed into gel-containing vacutainer tubes, centrifuged within 1 hour, and serum was stored at -80°C until used. Serum concentrations of IL-1 $\beta$  were quantified with ELISA Kit (ThermoFisher Scientific) according to the manufacturer's instructions. The limit of detection of human IL-1 $\beta$  is 0.3 pg/ml. For individuals below the level of detection

(n=150) values have been fixed at 0.3 pg/ml. The calculated overall intra-assay and inter-assay coefficient of variation for IL-1 $\beta$  were 3.8% and 5.3%, respectively. Lipids and hs-CRP levels were analyzed on an autoanalyser Konelab 20 (ThermoFisher Diagnostics) and by using commercial kits from Roche Diagnosis for total cholesterol and from ThermoFisher Diagnostics for triglycerides and direct high-density lipoprotein cholesterol (HDL-C) and from Diasys for hs-CRP. The coefficient of variation of hs-CRP for blinded split samples was 4.4%. The level of detection for the CRP was 0.05 mg/L, the intra- and interassay coefficients of variation were 1.7% and 2.5%, respectively. Low density lipoprotein-cholesterol (LDL-C) was calculated using Friedewald formula when triglyceride levels were below 340 mg/dl or by using commercial kit from ThermoFisher Diagnostics for direct LDL-C when triglyceride levels were above 340 mg/dl. Cardiac Troponin I (cTnI; Dade Behring) measurements were performed by immunoassay using an AXSYM analyser (Abbott, Rungis, France).

#### *Study Oversight*

The first and last authors (JS and MG) designed the study, gathered and analyzed the data and drafted the manuscript. All the authors vouch for the data and analyses reported. The study conforms to the principles outlined in the declaration of Helsinki. The ePARIS registry was declared to the French ministry of Health and Data Protection Authority (CNIL 1542887v0). Written informed consent was obtained from each patient participating to the registry.

#### *Statistical analyses*

Based on an alpha risk of 0.05, a power of 80% and an mean all-cause mortality rate of 8.4% reported previously in a recent analysis of the ePARIS registry(13), we estimated that 1056 patients would be necessary to detect to difference of at least 5% of all-cause mortality between patients with low and high level of IL-1 $\beta$  at 90 days.

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as mean  $\pm$  standard deviation (SD), whereas continuous variables with skewed distribution (IL-1 $\beta$ , hs-CRP, CPK, cTnI and triglycerides) are given as median and interquartile (Q1-Q3) and were logarithmically transformed prior to analysis. Comparisons between 2 groups of subjects were performed using unpaired Student's t-test or Mann-Whitney test as appropriate. The qualitative variables presented as proportions were compared using the chi-square test. IL-1 $\beta$  and hsCRP levels were analyzed either as continuous variables or as tertiles. Since the 3 pg/ml cut-off point was previously identified as the minimum concentration of IL-1 $\beta$  that can be reliably measured, patients with circulating IL-1 $\beta$  levels < 3 pg/ml served as a reference group (14). Patients with IL-1 $\beta$  levels > 3 pg/ml were divided into tertiles. Patients with circulating hs-CRP levels below 2mg/l served as the reference group (15). Patients with hsCRP levels > 2 mg/l were divided into tertiles. Comparisons across subgroups of circulating IL-1  $\beta$  levels were analyzed using the Jonckheere-Terpstra trend test. Circulating levels of IL-1 $\beta$  and hsCRP were equally modelled as a binary variable dichotomized below and above the 3rd tertile. A categorical variable was created using all possible combinations of elevated levels of IL-1 $\beta$  and hs-CRP as follows: IL-1 $\beta$  < 3rd tertile and hs-CRP < 3rd tertile (Low-Low); IL-1 $\beta$  > 3rd tertile and hs-CRP < 3rd tertile (High-Low); IL-1 $\beta$  < 3rd tertile and hs-CRP > 3rd tertile (Low-High); IL-1 $\beta$  > 3rd tertile and hs-CRP > 3rd tertile (High-High). The association between variables and all-cause mortality at 90 days and one year were assessed by Cox regression analysis. The variables identified as potential risk markers of all-cause mortality in univariate analysis ( $p < 0.1$ ) were included in the multivariate cox regression model. Co-variables used in multivariable analysis included: age, gender, creatinine levels, left ventricular ejection fraction <45%, Killip class  $\geq 2$ , out-hospital



cardiac arrest, cardiac-troponin I levels, hsCRP and IL-1 $\beta$  levels, low density lipoprotein-cholesterol levels, high density lipoprotein-cholesterol levels, current smoking, status with regard to use of statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker and beta blockers. Statistical analyses were performed using the R statistical software computer program. Results were considered to be statistically significant at  $p < 0.05$ .

## **Results**

### *Study population*

The flow chart of the study is presented in **Figure 1**. A total of 1398 ST segment elevation MI patients treated with primary PCI had an available measurement for IL-1 $\beta$  and were, therefore, included in the analysis. The median time from symptoms onset to blood sampling (sheet insertion) was 300 minutes (IQR: 160- 750). The follow-up of the cohort was complete for all patients at 90 days and at one-year, with a median follow-up of 5.5 years (interquartile range: 1.2 to 8.2 years). During the first 90 days, 117 patients died (8.4%). At one-year, 153 deaths were recorded (10.9%). Baseline characteristics are displayed in **Table 1**, according to the survival status.

### **Association between IL-1 $\beta$ with all-cause mortality and cardiovascular events**

Concentration of IL-1 $\beta$  analyzed as a continuous variable was associated with all-cause mortality at 90 days (adjusted hazard ratio [HR] 1.47 per one SD increase; 95% CI, 1.16 to 1.87;  $p < 0.002$ ). The results of the univariate and multivariate analysis for all-cause mortality at 90 days are presented in **Table 2**. After adjustment for all factors associated with mortality including cardiovascular risk factors and established prognostic factors including LDL cholesterol, troponin and hs-CRP level, the Cox proportional hazards regression analysis identified that elevated IL-1 $\beta$  levels were significantly associated with a higher risk of death

(**Figure 2**). According to tertiles of IL-1 $\beta$  concentrations, the mortality rate at 90 days was higher among patients at the highest tertile compared with the reference group (adjHR: 2.77; 95% CI: 1.49-5.16, p=0.0013, **Central Illustration A, Supplemental Table 1**).

Kaplan-Meier survival curves for 90 days and one-year mortality (all cause and cardiovascular) showed that patients with elevated IL-1 $\beta$  levels (> Tertile 3) at admission had a marked increased risk of mortality at 90 days and one year compared to those with lower IL-1 $\beta$  levels (< Tertile 3) (**Figure 3**). The analysis of major cardiovascular events showed that the majority of all-cause deaths were cardiovascular deaths (80%) and that cardiovascular mortality and MACE at 90 days were associated with IL-1 $\beta$  concentration (adjHR: 2.42; 95% CI: 1.36-4.28, p=0.002 and 2.29; 95% CI: 1.31-4.01, p=0.004, respectively for patients with IL-1 $\beta$  concentration higher than the third tertile). Results were consistent and even stronger at one-year follow-up (**Figure 4**). Results for non-fatal cardiovascular events showed a similar trend (NS, **Figure 4**).

#### *Interplay between hs-CRP levels, IL-1 $\beta$ and 90 days mortality*

Median hs-CRP level at admission was 5.8 mg/l (2.3-26.8). A marked increased risk of all-cause mortality at 90 days was observed in patients with elevated hs-CRP levels (highest tertile) as compared to the reference group (adjHR: 2.44; 95% CI: 1.15-5.18, p<0.02, **Central Illustration B**). In the study population, 58.7% (n=821) of patients displayed low levels (<3<sup>rd</sup> tertile) of both hs-CRP and IL-1 $\beta$ . In contrast, 4.9% (n= 68) of the population had elevated levels (>3<sup>rd</sup> tertile) of both IL-1 $\beta$  and hs-CRP. Kaplan-Meier survival curves for 90 days according to combination categories of risk based on both IL-1 $\beta$  and hs-CRP levels (below or above the 3<sup>rd</sup> tertile) show the association between all-cause mortality and inflammatory profile (**Central Illustration C**). Patients with elevated IL-1 $\beta$  levels (>3<sup>rd</sup> tertile), with or without concomitant

elevated hs-CRP, had a higher risk of mortality at 90 days than those with low concentrations (<3<sup>rd</sup> tertile) of both IL-1 $\beta$  and hs-CRP.

## **Discussion**

In this prospective cohort study of homogeneous and well characterized acute MI patients, we demonstrate that IL-1  $\beta$  concentration at admission is independently associated with all-cause mortality. We demonstrate that this relationship is not linear and is driven by the markedly increased risk of premature death during the first 90 days among patients with the highest level of IL-1  $\beta$ . Finally, both cardiovascular death and MACE were associated with high level of IL-1 $\beta$  and our results suggest that IL-1  $\beta$  concentration can risk stratify acute MI patients in a synergic fashion with hs-CRP.

Although our findings do not provide mechanistic explanations for the link between IL-1 $\beta$  and mortality, the data on the association of inflammation and myocardial damage are accumulating. Indeed, at the early phase of MI, IL-1 $\beta$  plays an important role during myocardial ischemia-reperfusion injury (16), that may impact short term outcomes of patients undergoing revascularization by primary PCI. Inhibition of IL-1 $\beta$  resulted in attenuated inflammatory injury and, in-vitro, protected cells from IL-1 $\beta$  -induced apoptosis, suggesting an effect on myocardial preservation (17). Prior study has also demonstrated that targeting IL-1 $\beta$  following coronary artery ligation decreased the leukocyte production, inflammation and finally reduced the risk of post-MI heart failure in ApoE (-/-) mice with atherosclerosis (18). Additionally, IL-1  $\beta$  was associated with an increased risk of death in a recent cohort of patients with acutely decompensated heart failure (11).

Three drugs, canakinumab, anakinra and riloncept, are now approved by the United States Food and Drug Administration to inhibit the IL-1 pathway making IL-1 $\beta$  a prognostic and

therapeutic target in coronary patients (19). Indeed, canakinumab, a monoclonal antibody neutralizing IL-1 $\beta$  was shown to reduce hs-CRP and the risk of recurrent ischemic events in stable patients with prior MI (10). The discrepancy between levels of IL-1 $\beta$  and CRP observed in our study may be explained by different kinetics in the release of these biomarkers that is unknown in acute myocardial infarction patients and would have required serial measurement of biomarkers of the inflammatory response to fully explore this hypothesis. However, from a physiologic and clinical perspective, IL-1 $\beta$ , and CRP should be interpreted as parts of the same the central NLRP3 to IL-1 to IL-6 to CRP signaling pathway of innate immunity, that have, at the end, the same pro-atherothrombotic effect. Further, in the CANTOS trial, the impact of IL-1 $\beta$  inhibition on the reduction of clinical events was directly related to the magnitude of both IL-6 and CRP reduction achieved (20,21). Anakinra, an IL-1 receptor inhibitor, can also effectively reduce inflammation and possibly the incidence of heart failure in patients with myocardial infarction, with or without CRP elevation (22,23). This effect would be consistent with the results of the prespecified analysis of the CANTOS trial that demonstrated a signal toward a dose-dependent reduction in heart failure outcomes (24). More importantly, these findings should be put in perspective with the recent results of the randomized, placebo controlled, COLCOT trial, that demonstrated a reduction of ischemic cardiovascular events in acute MI patients treated with colchicine, a drug that target nonspecific inflammation through NLRP3 inflammasome and IL-1 $\beta$  axis (25). These results are promising for the potential use of these anti-inflammatory drugs in MI patients, although none of these interventions were biomarker-guided using CRP or the level of IL-1 $\beta$ .

The present study has limitations and biases inherent to registries. First, despite adjustment for variables known to be associated with all-cause mortality, we may have

unmeasured confounding variables in this analysis. Second, clinical outcomes were not adjudicated, but obtain from medical records, telephone follow-up or national vital statistics system when necessary. Third, IL-1 $\beta$  measurement varies widely across assay platforms and our findings need to be validated in an external cohort. Fourth, IL-6 was not measured and may be superior to CRP or IL-1 $\beta$  to predict the risk of outcomes among patients with ST segment elevation MI (26). However, all these biomarkers provide information on the central NLRP3 to IL-1 to IL-6 to CRP signaling pathway of innate immunity and this analysis highlight the key role of IL-1 in the inflammatory process involved during acute myocardial infarction.

### **Conclusion**

Our study demonstrates that high IL-1 $\beta$  at admission is associated with all-cause mortality, cardiovascular mortality and, MACE in an unselected acute MI population undergoing primary PCI. Elevated IL-1 $\beta$  levels identifies patients at higher risk of mortality at 90 days. This study reinforces the need to further evaluate the benefit of IL-1 $\beta$  inhibitors in patients with acute MI possibly with a selective IL-1 $\beta$  guided approach for treatment.

**Clinical Perspectives:**

Competency in Medical Knowledge: Elevated level of Interleukin 1 $\beta$ , a proinflammatory cytokine, is associated with an increased risk of all cause and cardiovascular mortality among patients with acute myocardial infarction treated by primary PCI.

Translational Outlook: Prospective trials are needed to further evaluate the benefit of IL-1 $\beta$  inhibitors in patients with acute myocardial infarction possibly with a selective IL-1 $\beta$  guided approach.

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## Figure Legends

**Figure 1. Flow chart of the study.** Between January 2003 and April 2014, 1,398 patients treated for an acute myocardial infarction had a measurement of IL-1 $\beta$  and were included in our analysis.

**Figure 2. Adjusted Cox proportional Hazards regression analysis of all-cause mortality at 90 days according to IL-1 $\beta$  levels.** The Blue line indicated the adjusted Hazard Ratio (HR) and the dotted line the 95% confidence interval (CI).

**Figure 3 : Kaplan-Meier cumulative survival curve for All-cause mortality (A) and Cardiovascular Mortality (B) at 90 days and one year according to elevated concentration of IL-1  $\beta$  (> 3<sup>rd</sup> tertile 3).** Crude (log rank) and adjusted (Cox) Hazard Ratio (HR) are provided with 95% confidence intervals (CI).

**Figure 4: Hazard Ratios at 1 year according to elevated concentration of IL-1  $\beta$  (> 3<sup>rd</sup> tertile 3).** Patients with circulating IL-1 $\beta$  levels < 3<sup>rd</sup> tertile served as a reference group. Crude (log rank) and adjusted (Cox) Hazard Ratio (HR) are provided with 95% confidence intervals (CI).

**Central Illustration:** Kaplan-Meier cumulative survival curve for all-cause mortality at 90 days according to IL-1  $\beta$  tertiles (A), hs-CRP tertiles (B) and according to combination categories of risk (high and/or low) based on elevated IL-1 $\beta$  (>3<sup>rd</sup> tertile) and elevated hs-CRP (> 3<sup>rd</sup> tertile) levels (C). Adjusted (Cox) Hazard ratio (HR) are provided with 95% confidence intervals (CI).

**Table 1: Baseline characteristics of the study population according to mortality status at 90 days.** Values are mean±SD or median and interquartile (Q1-Q3). P value indicates significant difference between patients who died or survived at 90 days

	Alive at 90 days (n=1281)	Dead at 90 days (n=117)	P value
<b>Cardiovascular Risk Factor</b>			
Age, year	62.7±13.9	71.6±14.3	<0.0001*
N, (Men/Women)	975/306	71/46	0.0002*
Body Mass Index, (kg/m <sup>2</sup> )	26.0±4.3	25.5 ±4.5	0.32
Dyslipidemia	43.4%	29.9%	0.0047*
Diabetes	18.3%	18.8%	0.88
Hypertension	47.1%	51.3%	0.38
Smoker	41.9%	19.7%	<0.0001*
Family history of coronary artery disease	21.5%	8.5%	0.0009*
Previous cardiovascular events	19.4%	24.8%	0.16
<b>Cardiac Risk Factor on arrival</b>			
Heart rate (beats per min)	75.6±16.7	86.8±24.1	0.0001*
Systolic Blood Pressure (mmHg)	131.0±25.3	122.0±32.5	0.0010*
Left ventricular ejection fraction	50.6±10.9	36.0±15.3	<0.0001*
Left ventricular ejection fraction <45%	23.2%	66.3%	<0.0001*
Out-of-hospital cardiac arrest	4.0%	47.0%	<0.0001*
Killip class ≥2	12.3%	45.2%	<0.001*
Late Presenter (STB>360 min)	39.1%	37.8%	0.79
<b>Biomarkers</b>			
IL-1β, pg/ml	4.40 (1.59-8.67)	5.19 (2.00-12.21)	0.0482*
hs-CRP, mg/l	5.4 (2.2-23.6)	27.3 (4.7-60.0)	<0.0001*
Creatinine Clearance (ml/min)	85 (60-112)	48 (25-77)	<0.0001*
Creatinine Clearance <60 ml/min	24.7%	63.2%	<0.0001*
CPK, U/L	1195 (400-2543)	1107 (488-3161)	0.46
Cardiac Troponin I, pg/ml	37.1 (10.7-91.7)	48.0 (10.5-139.0)	0.070
Triglycerides, (mmol/l)	0.92 (0.66-1.33)	0.93 (0.69-1.40)	0.42
Total Cholesterol, (mmol/l)	4.35±1.12	3.80±1.34	<0.0001*
LDL Cholesterol (mmol/l)	2.93±1.01	2.45±1.22	<0.0001*
HDL cholesterol (mmol/l)	0.90±0.31	0.84±0.31	0.0337*
<b>Discharge Therapy</b>			
Statins	91.5%	43.6%	<0.0001*
Beta-Blockers	84.2%	26.5%	<0.0001*
ACEI/ARB	85.5%	36.8%	<0.0001*

**Table 2:** Association between variables and of all-cause mortality at 90 days in univariate and multivariate Cox regression analyses

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Interleukin-1 $\beta$ , pg/ml	1.20 (1.06 – 1.35)	0.0039	1.47 (1.16 – 1.87)	0.0015*
hs-C-Reactive Protein, mg/l	1.85 (1.48 – 2.31)	<0.0001	1.50 (1.06 – 2.11)	0.0205*
Male Gender	0.50 (0.34 – 0.72)	0.0002	0.92 (0.50 – 1.67)	0.78
Age	1.88 (1.55 – 2.28)	<0.0001	1.75 (1.22 – 2.50)	0.0021*
Creatinine	1.56 (1.40 – 1.75)	<0.0001	1.38 (1.12 – 1.71)	0.0023*
CPK, U/L	1.05 (0.85 – 1.30)	0.67	-	-
Left ventricular ejection fraction <45%	6.03 (3.80 – 9.59)	<0.0001	2.20 (1.24 – 3.90)	0.0073*
Killip class $\geq 2$	5.28 (3.59 – 7.77)	<0.0001	1.15 (0.66 – 2.02)	0.61
Late Presenters STB time >360 min	0.95 (0.65 – 1.39)	0.79	-	-
Out-Hospital cardiac arrest	14.6 (10.2 – 21.1)	<0.0001	12.1 (6.24 – 23.6)	<0.0001*
Previous Cardiovascular Events Previous MACE	1.40 (0.92 – 2.14)	0.11	-	-
Cardiac Troponin I, pg/ml	1.27 (1.00 – 1.60)	0.0461	1.34 (1.00 – 1.80)	0.0468*
Triglycerides	1.05 (0.88 – 1.26)	0.57	-	-
LDL-Cholesterol	0.60 (0.49 – 0.73)	<0.0001	1.09 (0.85 – 1.40)	0.48
HDL-Cholesterol	0.81 (0.66 – 0.98)	0.0357	1.00 (0.75 – 1.34)	0.97
Diabetes	1.02 (0.65 – 1.63)	0.92	-	-
Hypertension	1.18 (0.82 – 1.69)	0.37	-	-
Obesity	1.10 (0.66 – 1.84)	0.71	-	-
Smoking	0.35 (0.22 – 0.55)	<0.0001	1.14 (0.56 – 2.31)	0.72
Statins	0.09 (0.06 – 0.13)	<0.0001	0.44 (0.22 – 0.91)	0.0272*
Beta-blockers	0.08 (0.05 – 0.12)	<0.0001	0.20 (0.10 – 0.40)	<0.0001*
ACEI/ARB	0.11 (0.08 – 0.16)	<0.0001	1.11 (0.51 – 2.42)	0.78

IL-1 $\beta$  and mortality in myocardial infarction.

**January 2003 – April 2014**

**n= 2944** patients admitted for a suspicion an acute ST segment elevation

**n = 467 excluded** because of the following reasons

- 207 = ST segment elevation not confirmed or other diagnosis (TakoTsubo Syndrome, Myocarditis ...)
- 260 = no reperfusion therapy by primary PCI

**n= 2477** patients with

- Confirmed Myocardial Infarction (occluded coronary artery)
- treated by primary PCI

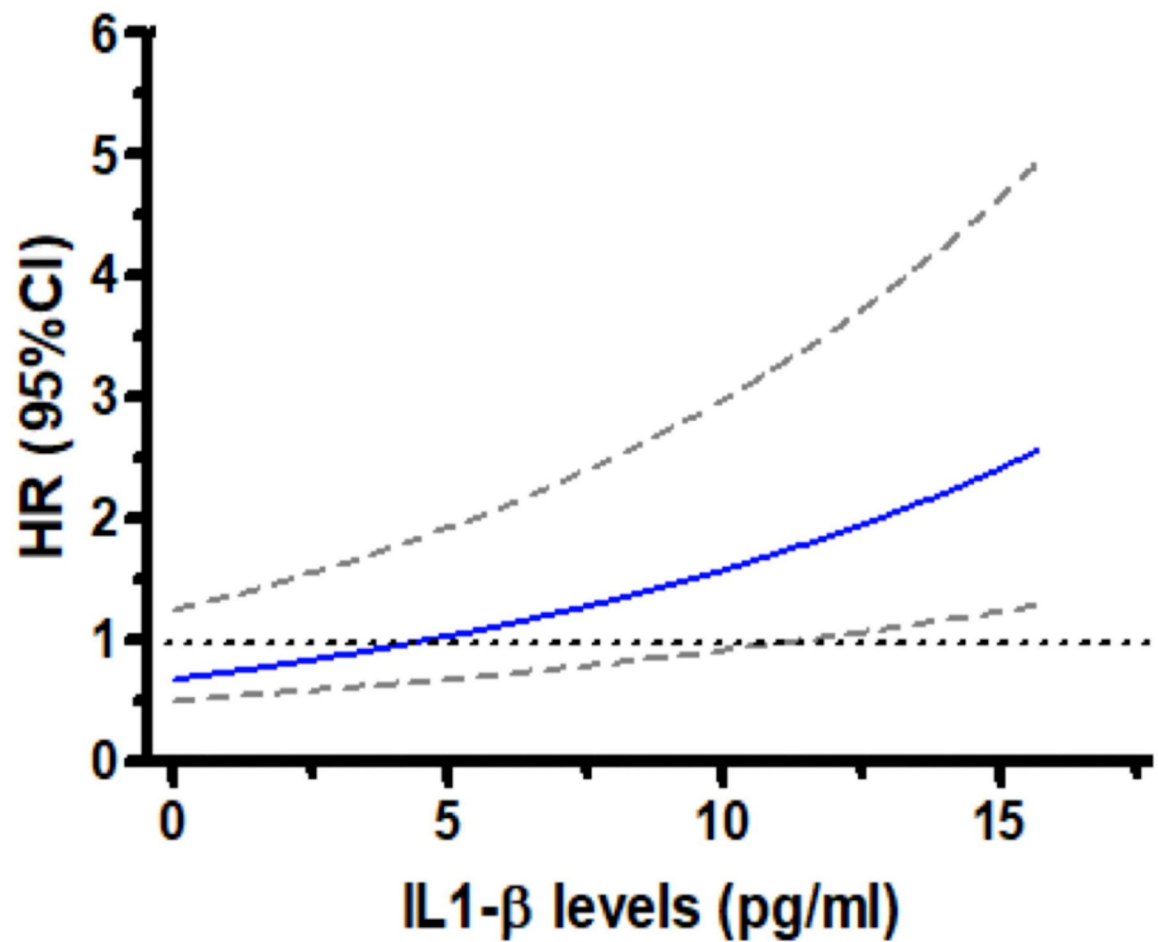
**n = 868 excluded** because the blood sampling for the biobank not performed (off hours mostly)

**n= 1609** patients within the biobank

**n = 211 excluded** because of the absence of enough blood material for the measurement of hs CRP (n=2) and Interleukin 1-Beta (n=209)

**n= 1398** patients with Interleukin 1-Beta measurement

**100% Follow-up for all cause mortality at 90 days**



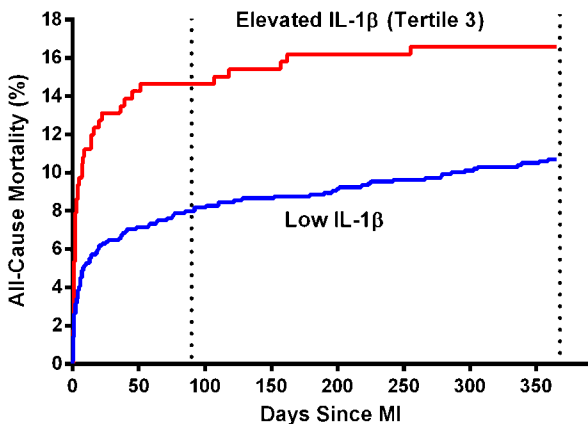


HR 2.11 ; p= 0.0001  
95%CI, 1.44 to 3.10

HR 1.65 ; p= 0.004  
95%CI, 1.17 to 2.33

adjusted HR 2.78 ; p= 0.0002  
95%CI, 1.61 to 4.79

adjusted HR 1.93 ; p= 0.005  
95%CI, 1.21 to 3.06

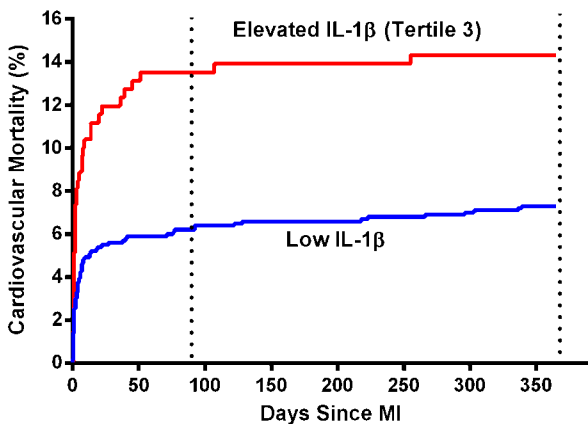


HR 2.19 ; p= 0.0001  
95%CI, 1.46 to 3.28

HR 2.06 ; p= 0.0003  
95%CI, 1.39 to 3.04

adjusted HR 2.42 ; p= 0.002  
95%CI, 1.36 to 4.28

adjusted HR 2.32 ; p= 0.002  
95%CI, 1.36 to 3.97



**All Cause Mortality**

Unadjusted

1.65 (1.17- 2.33) p= 0.004

Adjusted

1.93 (1.21- 3.06) p= 0.005

**Major Cardiovascular Events**

Unadjusted

1.99 (1.36-2.92) p= 0.0004

Adjusted

2.35 (1.39-3.96) p= 0.001

**Cardiovascular Mortality**

Unadjusted

2.06 (1.39-3.04) p= 0.0003

Adjusted

2.32 (1.36-3.97) p= 0.002

**Non Fatal Cardiovascular Events**

Unadjusted

1.89 (0.58-6.15) p= 0.29

Adjusted

2.38 (0.46-12.4) p= 0.30

0.1 1 10 100

