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Impact of C-Reactive Protein Levels and Role of Anakinra in Patients with ST-Elevation Myocardial Infarction

Francesco Moroni, MD[a,b,c,1], **Giuliana Corna, MD**[b,d,1], **Marco Giuseppe Del Buono, MD**[b,e], **Michele Golino, MD**[b,f], **Azita H. Talasaz, PharmD**[b], **Santiago Decotto, MD**[b,g], **Roshanak Markley, MD**[b], **Cory Trankle, MD**[b], **Giuseppe Biondi-Zoccai, MD, MStat**[h,i], **Salvatore Carbone, PhD**[b], **Carla R. Agatiello, MD**[d], **Benjamin Van Tassell, PharmD**[b], **Antonio Abbate, MD, PhD**[a,*]

[a]Robert M. Berne Cardiovascular Research Center, and Division of Cardiology, University of Virginia, Charlottesville, Virginia, United States

[b]Pauley Heart Center, Virginia Commonwealth University, Richmond, VA

[c]Cardiovascular Division, Medicine Department, Università Milano-Bicocca, Milan, Italy

[d]Interventional Cardiology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[e]Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

[f]Department of Medicine and Surgery, University of Insubria, Varese, Italy

[g]Cardiology Department, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

[h]Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Roma, Italy

[i]Mediterranea Cardiocentro, Via Orazio, 2, 80122 Napoli, NA, Italy.

Abstract

BACKGROUND: Interleukin-1 blockade with anakinra reduces C-reactive protein (CRP) levels and prevents heart failure (HF) events after ST-segment myocardial infarction (STEMI). The effectiveness of anakinra according to the degree of systemic inflammation in STEMI has not been addressed.

Correspondence to: Antonio Abbate, MD, PhD, Ruth C. Heede Professor of Cardiology, Robert M. Berne Cardiovascular Research Center, Department of Medicine, Division of Cardiovascular Medicine, University of Virginia – School of Medicine, 415 Lane Rd (MR5); PO Box 801394, Charlottesville, VA 22908-1394, antonio.abbate@virginia.edu; **Benjamin Van Tassell, PharmD**, Professor and Vice Chair for Research, Department of Pharmacotherapy and Outcome Sciences, School of Pharmacy, Virginia Commonwealth University, 1200 E. Broad street, Richmond, VA 23298, bvantassell@vcu.ed.

[1]Both authors have equally contributed to the manuscript.

[*]All authors take responsibility for all aspects of the reliability and freedom from bias of the presented and their discussed interpretation.

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METHODS: We analyzed 139 patients from three Virginia Commonwealth University Anakinra Response Trial randomized clinical trials to assess whether CRP levels predicted HF hospitalization or death in patients with STEMI, and if CRP levels influenced the effects of treatment with anakinra.

RESULTS: CRP cut-off levels for prediction of the composite of death or HF hospitalization for CRP at admission, 3 and 14 days were, respectively 6.45 mg/L (100% of sensitivity and 66.1% specificity), 26 mg/L (100% of sensitivity and 78% specificity) and 9.56 mg/L (100% of sensitivity and 80% specificity. More patients with elevated CRP levels died or had a HF hospitalization (5/47 [11%] vs 0/82 [0%], p=0.004 for CRP at admission; 5/32 [15.6%] vs 0/92 [0%], p<0.001 for day 3 and 5/26 [19%] vs 0/89 [0%], p<0.001 for day 14). A greater number of patients treated with anakinra had low CRP levels at 3 and 14 days compared to placebo (Odds Ratio 0.11 [95% IC 0.04–0.28], p<0.0001 and OR 0.35 [95% CI 0.14–0.86], p=0.02, respectively). Anakinra significantly prevented death or HF hospitalization in patients with high inflammatory burden (p=0.04 for admission, p=0.24 for day 3, and p=0.05 for day 14).

CONCLUSION: Patients with elevated CRP had higher incidence of HF hospitalization or death. Anakinra reduced the number of patients with elevated CRP levels and prevented death or HF hospitalization in patients with elevated CRP levels.

Keywords

ST elevation myocardial infarction; heart failure; C-reactive protein; Interleukin 1 receptor antagonist protein

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) is a major cause of morbidity and mortality worldwide. Despite significant improvement in STEMI management, the incidence of heart failure (HF) remains unacceptably high. Up to 1 in 3 patients develops HF after a first episode of STEMI, and 10% are hospitalized with HF within one year.[1–3] Therefore, there is an unmet need for understanding and targeting the mechanisms that promote HF progression after STEMI.

A close interplay exists between inflammation, myocardial healing, and development of HF after STEMI. Acute myocardial infarction initiates an intense inflammatory response. The pattern and degree of inflammation on presentation of STEMI were shown to reliably predict the development of systolic dysfunction and mortality at 6 months.[4,5,6] Interleukin-1 (IL-1) has been identified as a key pro-inflammatory mediator, as well as a therapeutic target.[7] C-reactive protein (CRP) is a measure of systemic inflammation and a surrogate for IL-1 activity, which increases during STEMI and peaks approximately 72 hours after reperfusion. CRP has become the preferred inflammatory biomarker to assess global inflammatory burden in the setting of cardio-immunology due to the standardized determination assays, relatively long half-life, and large amount of prognostic data available.[5]

Modulation of the inflammatory response appears to be a promising strategy to address residual risk. In particular, IL-1 inhibition with anakinra, recombinant IL-1 receptor antagonist, has shown in pre-clinical and clinical settings to effectively dampen the

inflammatory response after STEMI, as measured by CRP levels, and to reduce the incidence of HF.[8–14] Yet, the effectiveness of anakinra according to the degree of systemic inflammation in STEMI has not been addressed.

In this pooled analysis we sought to determine whether CRP levels predicted HF hospitalization or death in patients with STEMI, and if the acute treatment with anakinra was differentially effective in preventing HF events or death according to CRP levels.

METHODS

We conducted a pooled patient-level analysis of three pilot randomized clinical trials, Virginia Commonwealth University Anakinra Response Trial (VCUART) clinical trials (NCT00789724, NCT00175018, and NCT01950299), previously published separately.[10,11,14] Informed consent was obtained from each patient and the studies protocols conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Briefly, patients (>18 years old) with first episode of STEMI, who had no known pre-existing left ventricular systolic dysfunction or HF were included and randomized to receive either anakinra (Kineret; Swedish Orphan Biovitrum, Stockholm, Sweden) at the dose of 100 mg subcutaneously, once or twice daily, or placebo starting within 12 hours from reperfusion and for up to 14 days after the acute event. For current analysis, anakinra once or twice daily arms were pooled in a single "active treatment arm", as prior work did not demonstrate any difference in outcomes between the two arms.[13] The clinical endpoint of interest was a composite of hospitalization for HF or death, within one year follow-up.

The high sensitivity CRP level was measured at baseline, 3 and 14 days after STEMI in all three studies. The area under curve of the CRP (CRP AUC) concentration was calculated incorporating the above-mentioned determinations as a measure of total inflammatory burden.[10,11] The determination of the CRP levels was performed by LabCorp (Burlington, North Carolina) using high-sensitivity rate nephelometry.

The aim of this analysis was to address the predictive value of CRP levels at baseline, 3 and 14 days after STEMI for HF hospitalization or death during 1 year follow-up by defining the optimal cut-offs values that better predicted the outcome of interest. We then aimed to define whether the acute treatment with anakinra was associated with a larger number of patients with CRP below the cut-off values and its effectiveness in preventing HF events or death according to inflammatory levels. Finally, we planned to test the cut-off value separately in the placebo and anakinra groups.

The endpoint of hospitalization for HF was defined as a hospitalization with HF being the primary diagnosis and meeting the criteria established by a consensus document on the definition of HF after MI as previously described.[15]

We expressed data as number (%) or median [IQR], as appropriate, and we compared groups using Chi-Square and Mann-Whitney, respectively. We chose the cut-off for CRP levels at each time frame using receiver operating characteristics (ROC) curves analysis. Correlation between baseline CRP and time from symptoms onset to PCI was determined

by Spearman's correlation coefficient. Kaplan-Meier curves for event-free survival were constructed for the time-dependent composite endpoint and compared using the log-rank (Mantel-Cox) test. All analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL).

RESULTS

The study population included 139 patients with STEMI. Median age at presentation was 55 [49–61] years, 25 (19%) were women and 47 (36%) self-identified as Black Americans. Median time from chest pain onset to reperfusion was 180 [109–350] minutes, and from reperfusion to investigational treatment was 271 [182–391] minutes.

CRP at admission was available in 129 patients. Median admission CRP was 4.8 [2.3–8.9] mg/L. There was no significant correlation between baseline CRP levels and time from symptom onset to PCI (Rho=0.107, p=0.231). The area under the ROC curve for admission CRP for the composite endpoint of HF hospitalization or death was 0.829 [95% confidence interval (CI) 0.698–0.960] (p<0.001) (Figure 1A). The optimal CRP cut-off point for prediction of the composite outcome of interest was 6.45 mg/L, which had a sensitivity of 100% and a specificity of 66.1%.

Forty-seven (36%) patients presented admission CRP levels ≥ 6.45 mg/L; they were more likely to be female (34% vs 11%, p=0.001) and to have a higher BMI (33 [28–37] vs 28 [25–33] kg/m^2, p=0.034) (Table 1). Significantly more patients with elevated CRP had a HF hospitalization or died (5/47 [11%] vs 0/82 [0%], LogRank p=0.004). Treatment with anakinra was associated with a significant reduction in the rate of HF hospitalizations or death in the group with high levels of CRP (5/19 [26%] in the placebo group vs 0/28 in the anakinra group, LogRank p=0.004) (Figure 2A).

CRP levels at 3 days after STEMI were available in 124 patients, median CRP was 11.9 [4.6–27.0] mg/L. The area under the ROC curve for CRP at 3 days after STEMI for the composite endpoint of HF hospitalization or death was 0.906 [95% CI 0.815–0.997] (p<0.001) (Figure 1B). The optimal CRP cut-off point for prediction of the composite outcome of interest was 26 mg/L, showing a sensitivity of 100% and 78% specificity. CRP levels were ≥ 26 mg/L in 32 (26%) patients. We found no statistically significant differences in clinical characteristics between groups with high or low CRP levels (Table 1).

A significantly greater number of patients treated with anakinra had low CRP levels at 3 days when compared to placebo (66/73 [90%] vs 26/51 [51%], p<0.001; OR 0.11 (95% CI 0.04–0.28), p<0.0001). Significantly more patients with elevated CRP had a HF hospitalization or died (5/32 [15.6%] vs 0/92 [0%], LogRank p<0.001). Treatment with anakinra was associated with a reduction in the rate of the composite endpoint of interest in the high CRP group, with all the events occurring in patients treated with placebo (5/25 [20%] vs 0/7 [0%], LogRank p=0.24) (Figure 2B).

When analyzing the placebo and anakinra groups separately, CRP levels ≥ 26 mg/L at 3 days in patients receiving placebo also predicted HF hospitalization or death (5/25 [20%] vs 0/26

[0%], LogRank p=0.036). No HF hospitalizations or deaths occurred in the anakinra group, independently of the CRP levels.

CRP levels at 14 days were available in 115 patients, median CRP was 4 [1.1–9.0] mg/L. The area under the ROC curve for the CRP levels at 14 days for the HF hospitalization or death was 0.930 [95% CI 0.859–1.001] (<0.0001) (Figure 1C). The optimal CRP cut-off point for prediction of the composite outcome of interest was 9.56 mg/L, showing a 100% sensitivity and 80% specificity. CRP levels were ≥ 9.56 mg/L in 26 (23%) patients; they were more likely to have higher BMI (33.0 [28.3–41.0] vs 28.7 [25.1–34.2] kg/m2, p=0.02), admission CRP (9.3 [6.5–14.6] vs 3.9 [2.1–6.4] mg/L, p<0.001) and 3 days CRP (27.9 [13.0–61.4] vs 9.1 [3.4–17.3] mg/L, p<0.001) compared to those with low CRP levels (Table 1).

A significantly greater number of patients treated with anakinra had low CRP levels at 14 days when compared to placebo (57/67 [85%] vs 32/48 [67%], p=0.02; OR 0.35 (95% IC 0.14–0.86), p=0.02). Significantly more patients with elevated CRP had a HF hospitalization or died (5/26 [19%] vs 0/89 [0%], LogRank p<0.001). Treatment with anakinra was associated with a reduction in the rate of the composite endpoint of interest in the high CRP group, with all the events occurring in patients treated with placebo (5/16 [31%] vs 0/10 [0%], LogRank p=0.05) (Figure 2C).

When analyzing the placebo and anakinra groups separately, CRP levels ≥ 9.56 mg/L at 14 days in patients receiving placebo also predicted HF hospitalization and death (5/16 [31%] vs 0/32 [0%], LogRank p=0.002). No HF hospitalizations or deaths occurred in the anakinra group, independently of the CRP levels.

CRP AUC was available in 115/139 subjects. The area under the ROC curve for CRP AUC was 0.945 [95% CI 0.878 – 1.000]. The optimal cutoff point was 311.5 mg/l, which yielded a Sensitivity of 100% and a Specificity of 83%. Twenty-four patients (17%) had a CRP AUC above the optimal cutoff. Patients with elevated AUC CRP had a higher incidence of the primary endpoint with respect to patients with AUC CRP below the cut off (5/24 vs 0/91, logrank p-value<0.0001). All the events occurred in patients with elevated CRP AUC who were treated with placebo (5/16 vs 0/8, log-rank p-value = 0.099).

During the STEMI admission, 47 (36%) patients presented high CRP levels (≥ 6.45 mg/L). Patients with elevated inflammation at admission that received treatment with placebo, were more likely to have high levels of inflammation at 3 and 14 days after STEMI than those with low CRP levels at admission (Figure 3). All the events of HF hospitalization or death occurred in patients with high levels of CRP at the three different time points (baseline, 3 and 14 days) and received treatment with placebo.

Treatment with anakinra significantly reduced CRP levels at 3 and 14 days after STEMI among those with high levels of inflammation at admission (Figure 3). None of the patients treated with anakinra died or had a HF hospitalization.

DISCUSSION

This pooled patient-level analysis shows that systemic inflammation, measured by CRP levels at admission, 3 and 14 days after STEMI predict HF hospitalization or death. It also shows that patients with high CRP levels at admission are also more likely to have sustained elevated CRP levels during STEMI and worse outcomes. Treatment with anakinra, an IL-1 blocker, significantly reduces the number of patients with elevated CRP levels and prevents HF hospitalization or death in those with high CRP levels.

Myocardial injury following an ischemic event is a source for a local and systemic inflammatory response.[5,16] Reperfusion strategies improve outcomes by reducing the myocardium loss but does not interrupt the inflammatory response. During acute myocardial infarction (AMI), the initial injury caused by ischemia is then exacerbated by an intense inflammatory response during reperfusion (ischemia-reperfusion injury).[9,16] The inflammasome, a macromolecular protein complex activated in response to tissue injury, regulates the secretion of powerful pro-inflammatory cytokines, such as IL-1β and IL-18.[16] IL-6 is produced by monocytes and macrophages in response to IL-1β. [9] CRP is an acute phase reactant synthetized and released from hepatocytes in response to IL-6, that acts as a surrogate of IL-1 activity, the prototypical proinflammatory cytokine.[5,17]

Inflammation is essential for healing; however, an exaggerated inflammatory response is deleterious.[16] CRP levels are increased during STEMI and peak 2–3 days after reperfusion. The intensity of the systemic response is a predictor of adverse events: elevated CRP levels on admission, peak levels and area-under-the-curve (AUC) during hospitalization have been associated with poor prognosis after STEMI.[5,18] CRP levels correlates to post-STEMI complications, such as ventricular remodeling, reduced ejection fraction, HF events, cardiac rupture, and death.[19,20] The determinants of the inflammatory response after the STEMI is unclear and may entail STEMI and pre-existing factors (i.e. obesity).

The VCUART clinical trials showed that targeting IL-1 pathways with anakinra leads to a significant reduction in the acute inflammatory response measured as AUC for CRP after 14 days from STEMI.[8] Yet, it has not been established whether CRP levels at admission or changes of CRP during STEMI predict outcomes in patients treated with IL-1 blockers.

The current analysis shows that those with CRP levels above 6.45 mg/L at admission, above 26 mg/L after 3 days and above 9.56 mg/L after 14 days are more likely to experience HF hospitalization or die. All the HF events and deaths occurred among patients with elevated CRP levels at all three timepoints. Of note, anakinra reduced the number of patients with elevated CRP at each timepoint and it prevented HF hospitalizations or death.

There is a close relationship between CRP and IL-6 levels, two of the most recognized inflammatory markers of cardiovascular events.[5,17] Patients with STEMI have high levels of CRP and IL-6, and this is associated with an increased mortality.[22,23,24] Ammirati et al. analyzed the predictive value of IL-6 levels, among other cytokines, in patients with STEMI before reperfusion and within 6 hours from symptoms onset.[25] They compared patients in the top IL-6 levels versus those in the bottom IL-6 levels and matched controls. Patients with elevated levels of IL-6 were at higher risk of systolic dysfunction at discharge and of dying

within 6 months of follow up, compared to those with low IL-6 levels. Patients in the top IL-6 levels also had significantly higher CRP levels, highlighting the close interplay between both biomarkers, and identifying a high-risk population. These results are consistent with our analysis where patients with high CRP levels had worse outcomes. IL-1 stimulates the production of IL-6 that in turn stimulates liver production of CRP. Although in our trials we did not measure IL-6 levels, one may predict IL-1 inhibition with anakinra would also decrease IL-6 levels with beneficial results.

This analysis is not without limitations. First, this is a pooled analysis of three randomized clinical trials that enrolled a small number of patients with limited power for detecting differences in clinical outcomes. Second, not all patients had CRP measurement at all the three timepoints of interest. Third, we only measured CRP at three timepoints, and we did not measure the levels of IL-1, IL-6 or other cytokines. Measuring additional inflammatory biomarkers and/or using more or different timepoints may provide additional information.

CONCLUSION

This pooled analysis of three VCUART randomized trials shows that patients with elevated CRP levels at admission (≥6.45 mg/L) are likely to have persistently elevated CRP on day 3 (≥26 mg/L) and on day 14 (≥9.56 mg/L), and these values identify patients with STEMI at highest risk of HF hospitalization or death. Treatment with anakinra for up to 14 days after STEMI reduced the number of patients with elevated CRP levels at day 3 and 14, and it prevented HF hospitalization or death in patients with elevated CRP levels.

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Abbreviations:

CRP	C-reactive protein
HF	heart failure
STEMI	ST-segment elevation myocardial infarction
OR	odds ratio
CI	confidence interval
IL-1	interleukin 1
VCUART	Virginia Commonwealth University Anakinra Response Trial
ROC	receiver operating characteristics
AMI	acute myocardial infarction

AUC	area-under-the-curve

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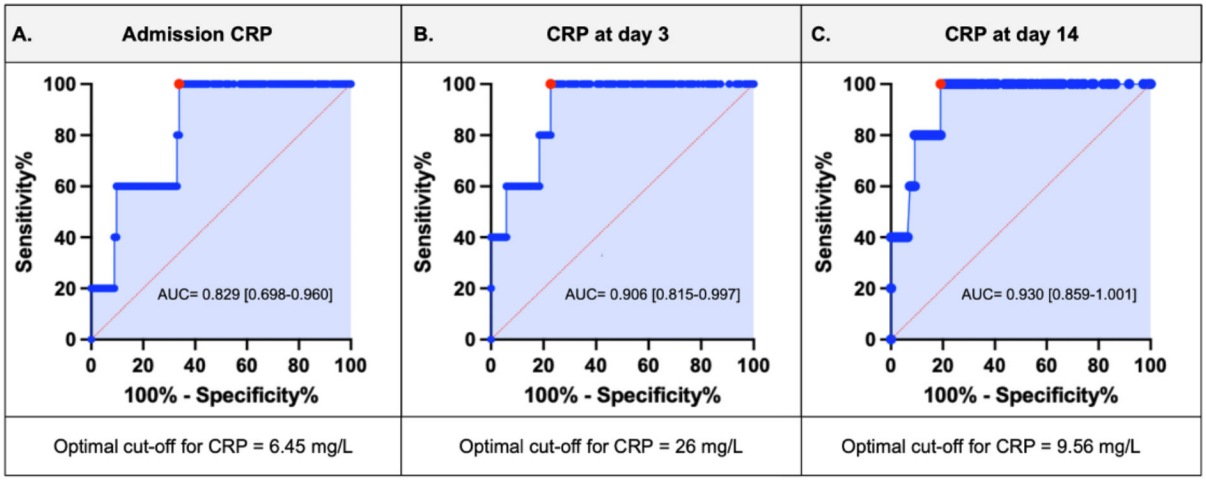

FIGURE 1.

Receiver operating curve for CRP at: **A)** admission, **B)** day 3 and, **C)** day 14. The red dot represents the optimal cut-off level at different time points. *CRP=C-reactive protein. AUC=area under the curve.*

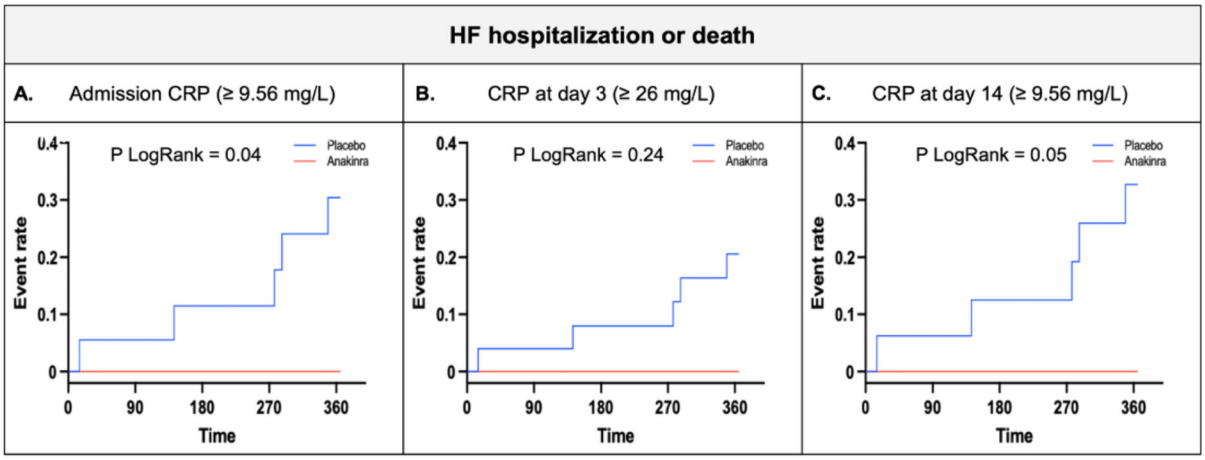

FIGURE 2.

Kaplan-Meier curve for HF hospitalization or death at one year follow up in patients with CRP levels above the cut-off (**A**, admission; **B**, day 3 and; **C**, day 14). *CRP=C-reactive protein.*

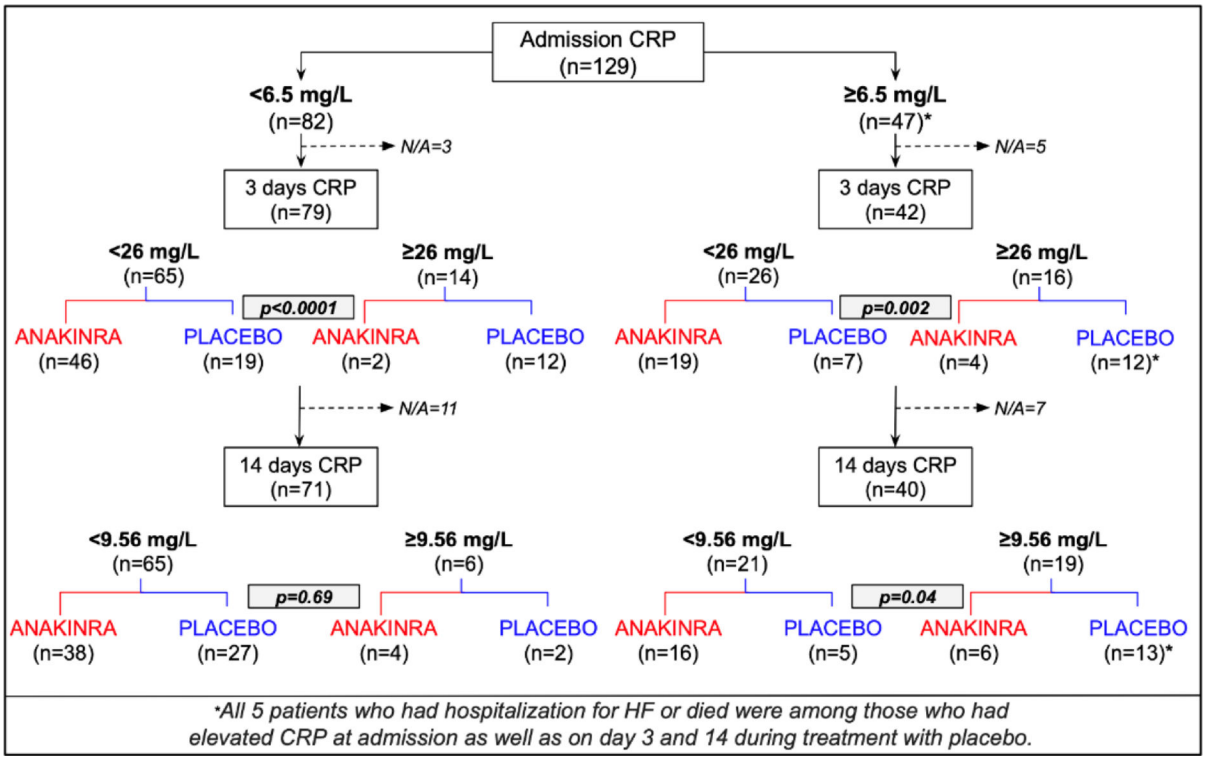

FIGURE 3.

Flow-chart of CRP levels according to admission CRP levels. *CRP=C-reactive protein; HF=heart failure.*

TABLE 1.

Baseline characteristics according to CRP levels at admission, day 3 and 14 after STEMI, divided according to the cut-off at the different time points.

	Admission CRP (mg/L) ***(n=129)***			**CRP at day 3 (mg/L)** ***(n=124)***			**CRP at day 14 (mg/L)** ***(n=115)***		
	≥ 6.45 ***(n=47)***	**< 6.45** ***(n=82)***	**P Value**	**≥ 26** ***(n=32)***	**< 26** ***(n=92)***	**P Value**	**≥ 9.56** ***(n=26)***	**< 9.56** ***(n=89)***	**p Value**
Age, years (Median, IQR)	54 [46–59]	56 [54–63]	0.12	55 [48–61]	55 [49–63]	0.91	56 [43–62]	56 [49–63]	0.64
Women (%)	16	9	**0.001**	26	75	0.97	20	73	0.56
Black Americans (%)	22	25	0.06	11	32	0.97	11	29	0.36
Diabetes mellitus (%)	16	22	0.39	9	27	0.89	7	25	0.91
Hypertension (%)	29	49	0.83	21	56	0.63	16	56	0.94
Dyslipidemia (%)	27	42	0.49	17	48	0.93	11	51	0.18
Smoker (%)	28	45	0.60	18	52	0.98	14	50	0.83
BMI, kg/m^2 (Median, IQR)	33.5 [28.6–36.8]	28.3 [24.9–33.5]	**0.003**	28.9 [27.2–34.2]	30.2 [25.6–34.9]	0.84	33.0 [28.3–41.0]	28.7 [25.1–34.2]	**0.02**
Symptoms onset to PCI, min (Median, IQR)	165 [124–360]	157 [97–307]	0.43	177 [107–330]	161 [105–356]	0.91	184 [127–381]	154 [107–356]	0.47
Admission CRP, mg/L (Median, IQR)	11.1 [8.4–16.6]	3.3 [1.5–4.6]	**0.0001**	6.6 [3.1–12.6]	4.4 [2.3–7.5]	0.05	9.3 [6.5–14.6]	3.9 [2.1–6.4]	**<0.001**

CRP=C-reactive protein; STEMI=ST-segment elevation myocardial infarction; BMI=body mass index; PCI= percutaneous coronary intervention; IQR=interquartile range.