Impact of PCSK9 inhibition on clinical outcomes during the inflammatory stage of SARS-COV-2 infection: the IMPACT-SIRIO 5 randomized trial

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TWITTER: First randomized trial showing significantly reduced death or need for intubation at 30 days and reduced circulating IL-6 levels by a PCSK9 inhibitor compared to placebo in patients with severe COVID-19. Patients with more intense inflammation at baseline had better survival with PCSK9 inhibition versus placebo.

Abbreviations and acronyms

ANOVA = analysis of variance

COVID-19 = 2019 coronavirus disease

Hg = mercury

IL-6 = interleukin-6

LDL-C = low density lipoprotein-cholesterol

LDLR = LDL receptor

PCSK9 = proprotein convertase subtilisin/kexin type 9

HFNC = high flow nasal cannula

HR = hazard ratio

C = cholesterol

CI = confidence interval

CONSORT = CONsolidated Standards of Reporting Trials

ICU = intensive care unit

IQR = interquartile range

LOX-1 = lectin-like oxidized LDL receptor-1

LPS = lipopolysaccharide

NIV = noninvasive ventilation

ox-LDL = oxidized LDL

PO2/FiO2 = arterial partial oxygen pressure to fraction of inspired oxygen ratio

SARS-CoV-2 = severe acute respiratory distress syndrome coronavirus 2

SD = standard deviation

Abstract
Background: The intensity of inflammation during 2019 coronavirus disease (COVID-19) is related to adverse outcomes. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an endogenous enzyme involved in low-density lipoprotein receptor (LDLR) homeostasis and vascular inflammation. PCSK-9 may thus contribute to COVID-19 inflammatory response.
Objectives: To investigate the impact of PCSK9 inhibition versus placebo on clinical and laboratory outcomes in patients with severe COVID-19.
Methods: In this multicenter, double-blind trial, 60 patients hospitalized for severe COVID-19 were randomized 1:1 to receive a single 140mg subcutaneous injection of evolocumab or placebo (NCT04941105). The primary endpoint was death or need for intubation at 30 days. The main secondary endpoint was changes in circulating interleukin-6 (IL-6) at 7 and 30 days from baseline.
Results: Patients randomized to PCSK9 inhibitor had lower rates of death or need for intubation at 30 days vs placebo (23.3% vs 53.3%, HR [95% CI] 0.40 [0.15-0.90], P = 0.02). IL-6 in both arms was reduced at 30 days vs baseline (P = 0.02) but not at 7 days (P = 0.73). IL-6 across time was lower with PCSK9 inhibitor than with placebo (30-day decline: -56% vs -21%; between-group P = 0.02). Among patients with baseline IL-6 above the median, mortality was lower with PCSK9 inhibition vs placebo (13.3% vs 50%, P = 0.03). The PCSK9 inhibitor vs placebo arm had shorter hospital stay (P = 0.03) and oxygen therapy (P = 0.01).
Conclusions: PCSK9 inhibition compared to placebo significantly reduced the primary endpoint of 30-day death or need for intubation as well as IL-6 levels in patients with severe COVID-19. Patients with more intense inflammation at randomization had better survival with PCSK9 inhibition vs placebo, indicating that inflammatory intensity may drive the therapeutic benefits of these agents.

Keywords: COVID-19, randomized controlled trial, PCSK9 inhibition, death, intubation, interleukin-6

Condensed abstract: In a double-blind trial, 60 patients hospitalized for severe COVID-19 were randomized 1:1 to receive a single 140 mg subcutaneous injection of the PCSK9 inhibitor evolocumab or placebo. Patients randomized to PCSK9 inhibitor had lower rates of 30-day death or need for intubation (primary endpoint: 23.3% vs 53.3%, HR [95% CI] 0.40 [0.15-0.90], P = 0.02), lower IL-6 concentrations across time (secondary endpoint, P=0.02), and improved 30-day survival among those with IL-6 at randomization above the median value (13.3% vs 50%, P = 0.03). These preliminary data indicate that PCSK9 inhibition compared to placebo reduces 30-day death or need for intubation and circulating IL-6 levels in patients with severe COVID-19. Improved survival was observed with PCSK9 inhibition vs placebo in those with higher IL-6 at baseline, indicating that inflammatory intensity may drive the therapeutic benefits of these agents.

Introduction

Severe coronavirus disease 2019 (COVID-19) can cause acute respiratory distress syndrome and systemic inflammation which may develop into a cytokine storm (1). The degree of immune dysregulation portends worse prognoses and increased mortality (2-6). Targeting crucial aspects of the inflammatory response during COVID-19 may represent an effective treatment strategy, particularly in critically ill patients (7). Interleukin-6 (IL-6) is a major driver of the inflammatory response in patients with COVID-19. Increased IL-6 levels has been shown to predict a more severe course of COVID-19 disease (8).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme involved in the homeostasis of low-density lipoprotein (LDL) receptors and vascular inflammation (9). During acute inflammation, LDL and apolipoprotein B are oxidized and the accumulation of these oxidized particles promotes the generation of cholesterol crystals in macrophages that in turn activates the inflammasome complex and the release of inflammatory cytokines (8). PCSK9 can directly activate proinflammatory signaling pathways inducing cytokine production (10). In patients with septic shock, lower PCSK9 function implied a decreased inflammatory response and overall improved outcomes (11). Subjects with PCSK9 loss-of-function genotype were characterized by lower levels of PCSK9 and enhanced resolution of infections (12). PCSK9 inhibitors are powerful lipid-lowering agents that might blunt the inflammatory response in patients with COVID-19 through reduction of LDL-cholesterol (LDL-C) and inhibition of PCSK9. Both experimental and clinical data suggest that PCSK9 inhibitors may exert further anti-inflammatory effects that is related to the direct interference with the IL-6 mediated inflammatory pathway and inhibition of PCSK9 (9,11-17).

We sought to determine the impact of PCSK9 inhibition vs placebo on clinical and laboratory outcomes in patients with severe COVID-19 characterized by pneumonia associated with lung involvement and heightened inflammatory response.

Methods

Trial design and patient population

IMPACT-SIRIO 5 (ClinicalTrials.gov number NCT04941105) is a multicenter, double-blind, placebo-controlled, randomized, investigator-initiated clinical trial evaluating the impact of a PCSK9 inhibitor on clinical and laboratory outcomes in patients with severe COVID-19.

Eligible patients were randomly assigned in a 1:1 ratio to receive either PCSK9 inhibitor or placebo, and followed for 30 days. The study was approved by an independent Ethics Committee of the Nicolaus Copernicus University of Poland. Written informed consent was obtained from all patients. The full study rationale is reported in the **Supplement** (18).

Briefly, patients hospitalized for COVID-19 in the participating clinical sites underwent screening for eligibility. Eligible patients were required to have severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by real-time reverse transcription polymerase chain reaction. Further inclusion criteria were age $\geq$18 years and COVID-19 associated pneumonia with typical radiological changes, including ground-glass opacities and consolidations with bilateral and peripheral distribution (19). Additionally, patients had to present with an arterial partial oxygen pressure in mmHg to fraction of inspired oxygen (PO2/FiO2) ratio < 300, and serum levels of interleukin-6 (IL-6) above the upper reference limit. Key exclusion criteria were other known active infections, clinical conditions contraindicating PCSK9 inhibitors, survival expectance of less than 48 hours, estimated glomerular filtration rate <30 ml/min/1.73 m2, absolute neutrophil count (ANC) <2000/mm3, platelet count <50000/mm3, and pregnancy. Full details regarding the inclusion and exclusion criteria are listed in the trial protocol (**Supplement**). Cytokine concentrations were measured with the enzyme-linked immunosorbent assay (ELISA). Patients were treated according to the latest management recommendations for patients with SARS-CoV-2 infection (20). The trial

conduction followed the Declaration of Helsinki, the guideline for Good Clinical Practice by the International Council for Harmonization Committee for Medicinal Products for Human Use [GCP CHMP/ICH/135/95] and local regulations.

Endpoints

Clinical and laboratory outcomes

The primary clinical study endpoint was death or need for intubation by 30 days. The main secondary endpoint was the change in IL-6 concentrations from baseline to 7 and 30 days in the PCSK9 inhibitor versus the placebo arm.

Other secondary endpoints

Other secondary endpoints included the individual components of the primary endpoint, and the durations of oxygen therapy, hospital stay, intubation, noninvasive ventilation (NIV) or high-flow nasal cannula (HFNC).

Randomized interventions

After patient enrollment, allocation to PCSK9 inhibitor or placebo was performed by investigator connection to a prespecified web-link. The random allocation sequence was generated by computer software. The patient lists and their code numbers were kept locked until the end of the trial. Both patients and doctors were unaware of the allocated treatments until after the study was concluded.

Patients randomized to the PCSK9 inhibitor arm received a single 1 ml subcutaneous injection containing 140 mg of evolocumab. Patients randomized to the placebo arm received a single 1 ml subcutaneous injection of 0.9% saline solution.

Statistical analyses

The primary efficacy analysis was on an intention-to-treat basis. Hazard point estimates with two-sided 95% confidence interval (CI) measured by the hazard ratio (HR) were calculated

based on the Cox proportional hazards model. Proportional-hazards assumption was statistically checked. Probability of a clinical event is presented using Kaplan–Meier curves. Data distribution was checked by Kolmogorov-Smirnov's test with data presented as median with interquartile range (IQR) or mean ± standard deviation (SD) as appropriateBaseline characteristics were compared by chi-square or Fisher's exact test for categorical variables, Mann Whitney or t-test for continuous variables. Logarithmic transformation was applied to non-normally distributed biomarkers prior to analysis. To compare changes of IL-6 at 7 and 30 days to baseline in the PCSK9 inhibitor and placebo groups, a two-way repeated measures ANOVA was performed, with multiple comparisons analyzed by the Bonferroni test. The overall F-value of the ANOVA and the corresponding between-group P-value across time points at baseline, 7 and 30 days is reported. A prespecified analysis was performed stratifying the rates of death with PCSK-9 inhibitor or placebo groups by baseline IL-6 concentrations below or above the median value. The correlation between IL-6 (and other biomarkers) and LDL-C was tested with the Spearman coefficient. To examine the 'best' individual decrease of IL-6 concentrations across the explored time frames in comparison to baseline, waterfall plots were constructed dysplaying the greatest percent reductions across time of IL-6 levels in the individual patients. A two-tailed P-value <0.05 was considered statistically significant.

Results

Patient enrollment and characteristics

Enrollment period was June 2021 to May 2022. The CONSORT flow diagram of patient disposition is illustrated in **Figure 1**: 30 patients were assigned to receive PCSK9 inhibitor

(93% or 28 actually received the drug), 30 to placebo (96% or 29 actually received placebo). All patients were admitted to an intensive care unit at the time of enrollment.

Baseline characteristics (**Table 1**) were balanced between the PCSK9 inhibitor and placebo groups in terms of age (66.07 ± 12.09 vs 66.23 ± 11.85 yrs, P = 0.91), sex (37% vs 40% female, P=1.0) and body mass index (BMI) (29.94 ± 5.4 and 29.8 ± 5.21, P = 0.90). Underlying cardiovascular disease was present in 20% vs 27% (P = 0.76), and diabetes mellitus in 27% vs 30% (P = 1.0). Mean days from symptom onset to randomization were 7.8 ± 2.6 vs 8.8 ± 4.2, respectively (P = 0.27). At enrollment, no significant intergroup differences were noted in other demographic or laboratory characteristics (**Table 1**). During the trial, therapeutic measures against COVID-19 and its sequelae (including steroids, remdesivir, antibiotics, heparin and aspirin) were administered in a balanced way to the two treatment groups (**Table 1**).

Primary clinical and laboratory endpoints

Primary clinical outcomes

The rate of the primary clinical endpoint - 30-day death or need for intubation - was significantly lower in patients allocated to PCSK9 inhibitor than in those allocated to placebo (23.3% vs 53.3%, P = 0.02) (**Figure 2A**).

The Kaplan-Meier estimates of the effect of PCSK9 inhibitor vs placebo at 30 days are presented in **Figure 2B**. At 30 days, the HR (95% CI) for death/need for intubation with PCSK9 inhibitor vs placebo was 0.40 (0.15-0.90), P = 0.02.

A sensitivity per protocol analysis of the primary endpoint yielded results consistent with the intention-to-treat analysis: HR (95% CI) 0.37 (0.15-0.91), P = 0.02 (**Supplemental Figure 1**).

Secondary clinical endpoints

Secondary clinical outcomes are presented in **Table 2**. The median duration of oxygen therapy was significantly shorter in the PCSK9 inhibitor compared to the placebo-treated group: 13 (9-21) vs 20 (11-23) days, P = 0.01. Similarly, patients allocated to PCSK-9 inhibitor had a shorter hospital stay: 16 (13-23) vs 22 (15-27) days, P = 0.03. A numerical but non-significant lower mortality was observed in the PCSK9 inhibitor vs placebo group (16.7% vs 33.3 %, P = 0.25) (**Supplemental Figure 2**).

Serum interleukin-6 and LDL-cholesterol concentrations

Median IL-6 concentration at baseline was 51.29 [24.7-86.9] pg/ml. Patients presenting IL-6 concentrations above the median baseline value attained a significant reduction of mortality with PCSK-9 inhibitor vs placebo (**Figure 3**).

In both arms, temporal analysis of IL-6 concentrations showed significantly reduced values at 30 days vs baseline in both arms (P = 0.02) but not at 7 days (P = 0.73). The PCSK9 inhibitor reduced the levels of serum IL-6 significantly more than placebo across the explored time points (F-value = 6.43, between-group P = 0.02). The magnitude of IL-6 reduction at 30 days was more pronounced with PCSK9 inhibitor (delta = -56%) than with placebo (delta = -21%) (**Figure 4A**). The greatest reduction of IL-6 across 7 and 30 days vs baseline in the individual patients is displayed in **Figure 4C**. Sixty percent of patients allocated to PCSK9 inhibitor had > 90% decrease of IL-6 levels vs baseline, while this reduction was noted in 27% of patients allocated to placebo (**Figure 4C**).

Temporal analysis of LDL-C levels showed a progressive decrease in the PCSK9 inhibitor arm vs placebo, whereas the opposite pattern emerged in the placebo arm (F-value = 10.27, P = 0.003) (**Figure 4B**). A moderate direct significant correlation was found between IL-6 and LDL-C concentrations at baseline (r = 0.50, P < 0.001) (**Figure 4D**). Other explored

cytokines and inflammatory markers, including IL-10 and IL-18, also showed significant correlations with LDL-C at baseline (**Supplemental Table 1**).

Safety

At day 30 no adverse events or side effects were reported in relation to PCSK9 inhibitor or placebo administration.

Discussion

In this investigator-initiated, multicenter, double-blind, randomized trial, PCSK-9 inhibitor was superior to placebo with respect to the primary endpoint of death or need for intubation at 30 days in symptomatic hospitalized patients with severe COVID-19. In this study, the pattern of IL-6 changes was affected by the administration of PCSK9 inhibitor, as the magnitude of IL-6 reduction was more pronounced at 30 days with PCSK9 inhibitor vs placebo.

To our knowledge, this is the first study to address the role of PCSK9 monoclonal antibodies in severe COVID-19 through a prospective, randomized, controlled trial.

PCSK9 inhibitors might exert a dual action against SARS-CoV2, one mediated by lowering of LDL-cholesterol particles, which are proinflammatory, and the second through a direct effect on PCSK9. The inflammatory response to SARS-CoV2, with cytokine release, is an immune dysregulation which, if extreme, can lead to multiorgan failure and death. Increased IL-6 levels were shown to be a good predictor of disease severity, risk of intubation and mortality in patient with COVID-19 (21,22). The physiological role of PCSK9 is to mediate LDL-receptor degradation and thus regulate LDL-cholesterol (LDL-C) homeostasis (9). PCSK9 causes increased expression of lectin-like oxidized LDL receptor-1 (LOX-1) that in turn enhances oxidized LDL (ox-LDL) uptake and amplifyes the inflammatory response (9,23).

A direct mechanistic link between PCSK9 and inflammatory cytokines has been investigated. PCSK9 increases the expression of toll-like receptor 4 (TLR4) that plays an important role in the inflammatory signaling responses to various stimuli. TLR4 stimulates the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB) transcription factor that leads to the expression of proinflammatory cytokines such as IL-6 (10,24). The NF-KB pathway has been extensively associated with the pathogenesis and degree of lung injury in common lung diseases associated with a significant inflammatory component such as sepsis(25).

The effect of PCSK9 on TLR4/NF-KB-mediated inflammation has been tested in response to lipopolysaccharide (LPS), by inducing PCSK9 expression (26). In a mouse model of LPS-induced sepsis, PCSK9 was found to induce a systemic release of IL-6 and exacerbate lung and liver inflammation, while PCSK9 deficiency decreased circulating levels of IL-6 and improved organ inflammation (15).

Additionally, experimental data have shown that heightened inflammation mediated by IL-6 during viral coinfection with HIV/HCV may elevate PCSK9 levels (27). Thus, the relation between PCSK9 and IL-6 may be bidirectional. Induction of IL-6 by PCSK9 is supported by data from individuals with PCSK9 loss-of-function mutations with lower IL-6 levels in response to lipopolysaccharide (LPS)-induced inflammation (11).

The major findings of this randomized trial are the reduced mortality or need for intubation at 30 days with PCSK-9 inhibitor treatment compared to placebo, and the reduced 30-day mortality in isolation in the subset of patients with greatest degree of inflammation at randomization (i.e., with baseline IL-6 values above the median of 51.29 pg/mL) in patients receiving PCSK9 inhibitor vs placebo. Although our study was not powered to address mortality, the significant mortality reduction with PCSK9 inhibitor in patients presenting with higher baseline IL-6 levels suggests that immunomodulatory therapies may be particularly

effective during the inflammatory stage if administered to patients with higher IL-6 further improving outcomes. The correlation among reduced inflammation, improved prognosis and PCSK9 inhibition found in this study may be worth investigating in other viral diseases or states such as sepsis or rheumatic disorders characterized by heightened inflammation.

In the present study, the anti-inflammatory effect of PCSK9 inhibitor administration was paralleled by a reduction in LDL-C concentrations at 30 days, whereas an increase in LDL-C levels was noted in the placebo arm, as may occur during inflammatory states (28). It can be speculated that LDL-C particles might contribute to the increased production of inflammatory cytokines. This hypothesis was confirmed by the direct association found between circulating levels of IL-6 and LDL-C at baseline in our trial. Thus, PCSK9 inhibition might exert its action against SARS-CoV2, not only by direct action on PCSK9, blunting the proinflammatory effects of PCSK9, but also by lowering of LDL-C particles, which are proinflammatory.

Limitations

This is the first randomized pilot study to test the hypothesis that PCSK9 inhibition can improve outcomes and reduce inflammation in severe COVID-19. Therefore, a formal sample size analysis was not possible a priori. By a post hoc-analysis of the statistical power on the basis of the enrolled subjects (n = 60) and on the event rates observed in the placebo (53.3%) and PCSK9 inhibitor (23.3%) arms, assuming a two-sided alpha error of 5%, the trial would have reached at least 80% of the power to address the effect of PCSK9 inhibition on the primary endpoint.

Summary and conclusions

In summary, in this randomized trial conducted in patients with severe COVID-19, a single 140mg dose administration of PCSK9 inhibitor yielded a reduction in the need for intubation or death at 30 days, without raising safety concerns, compared to placebo. The decrease in IL-

6 levels at 30 days was also significantly greater with PCSK9 inhibitor than placebo. Mortality was reduced in patients with the highest degree of baseline inflammation (as assessed by IL-6 levels), indicating that the inflammatory risk profile may drive therapeutic benefits. PCSK9 inhibition may represent a novel therapeutic pathway on top of currently recommended therapeutic approaches for severe COVID-19 such as steroids (29). The relevant findings of this pilot trial justify a larger study in patients with COVID-19 and other inflammatory conditions, in view of the potential implications.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In this randomized trial of severe COVID-19 patients, PCSK9 inhibition compared to placebo significantly reduced 30-day death or need for intubation and serum interleukin-6 levels in patients with severe COVID-19. In patients with high intensity inflammation at randomization, PCSK9 inhibition significantly reduced mortality.

TRANSLATIONAL OUTLOOK: Future large-scale trials should confirm the clinical benefits of PCSK9 inhibition in severe COVID-19 as well as in other inflammatory diseases. If the findings are confirmed, these agents could exert a significant impact on public health.

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Table 1. Baseline characteristics of the enrolled study population

Variable	PCSK9 inhibitor group (n = 30)	Placebo group (n = 30)	p-value
Age (yrs), mean ±SD	66.07±12.09	66.23±11.85	0.91
Female, n (%)	11 (37)	12 (40)	1
BMI, mean ± SD	29.94 ± 5.4	29.8 ± 5.21	0.921
Cardiovascular disease, n (%)	6 (20)	8 (27)	0.76
Diabetes, n (%)	8 (27)	9 (30)	1
COPD, n (%)	3 (10)	1 (3)	0.612
Chronic kidney disease, n (%)	1 (3)	2 (7)	1
LDL-cholesterol (mg/dL), mean± SD	78.43 ± 26.1	77.23 ± 30.9	0.877

Acetyl salicylic acid, n (%)	8 (27)	8 (27)	1
$P2Y_{12}$ inhibitor, n (%)	1 (3)	0 (0)	1
Angiotensin Converting Enzyme Inhibitor, n (%)	10 (33)	12 (40)	0.789
Beta-blockers, n (%)	15 (50)	13 (43)	0.796
Days from illness onset to randomization(days), mean ± SD	7.8 ± 2.55	8.8 ± 4.17	0.268
Oxygenation index, median (IQR)	101.22 (83.52, 157.82)	107.75 (75.52, 160.31)	0.828
Unfractionated heparin, n (%)	30 (100)	28 (93)	0.492
Remdesivir, n (%)	8 (27)	10 (33)	0.778
Steroids, n (%)	25 (83)	26 (87)	1
Antibiotics, n (%)	27 (90)	28 (93.3)	0.64

Leukocytes (x10^3/uL), median (IQR)	6.6 (5.29, 9.41)	7.85 (5.86, 10.7)	0.277
Neutrophils (x10^3/uL), median (IQR)	5.01 (4.21, 7.73)	6.85 (4.7, 8.46)	0.329
Platelets (x10^3/uL), mean ± SD	248.07 ± 104.23	258.93 ± 89.27	0.666
Hemoglobin (g/dL), mean ± SD	12.59 ± 1.43	12.96 ± 1.94	0.413
D-dimers (ng/ml), median (IQR)	1093.47 (643.01, 1675.25)	1233 (910, 2429.25)	0.128
Fibrinogen (mg/dL), median (IQR)	541 (484, 709)	606 (508, 761)	0.647

Table 2. Secondary clinical endpoints.

	PCSK9 inhibitor (n=30)	**Placebo (n=30)**	**P value**
Need for intubation, n (%)	6 (31.5)	13 (68.4)	0.05
Death, n (%)	5 (16.7)	10 (33.3)	0.25
Duration of oxygen therapy, days (range)	13 (9-21)	20 (11-23)	0.01
Duration of hospital stay, days(range)	16 (13-23)	22 (15-27)	0.03
Intubation duration, days (range)	10 (3-24)	19 (10-25)	0.27
Time with non-invasive mechanical ventilation or high-flow nasal cannula, days (range)	0 (0-1)	0 (0-1)	0.49

Figure legends

Figure 1. Randomization and treatment assignment. PCSK9= Proprotein convertase subtilisin/kexin type 9 (PCSK9).

Figure 2. Need for intubation or death at 30 days among patients treated with PCSK9 inhibitor or placebo. Figure **2A**: Rates of the primary endpoint in the PCSK9 inhibitor and placebo. Figure **2B**: Kaplan Meier curves of 30-day death or need for intubation in the intention-to-treat population. HR= hazard ratio. CI= confidence interval.

Figure 3A. IL-6 concentrations at baseline, 7 and 30 days after randomization in the PCSK9 inhibitor and placebo arms. **Figure 3B**. LDL-cholesterol levels at baseline, 7 and 30 days after randomization in the PCSK9 inhibitor and placebo arms. **Figure 3C.** Waterfall plot for greatest percentage reductions from baseline in IL-6 levels with PCSK9 inhibitor orbplacebo across 7 and 30 days in comparison to baseline. Inh= inhibitor. **Figure 3D:** Association between IL-6 and LDL-cholesterol concentrations at baseline. IL-6 = interleukin-6. LDL = low density lipoprotein. PCSK9 = proprotein convertase subtilisin/kexin type 9.

Figure 4. 30-day rates of mortality in patients with baseline IL-6 ≤ and > the median value (51.30 pg/mL).

Figure 5. Central illustration.

Figure 1

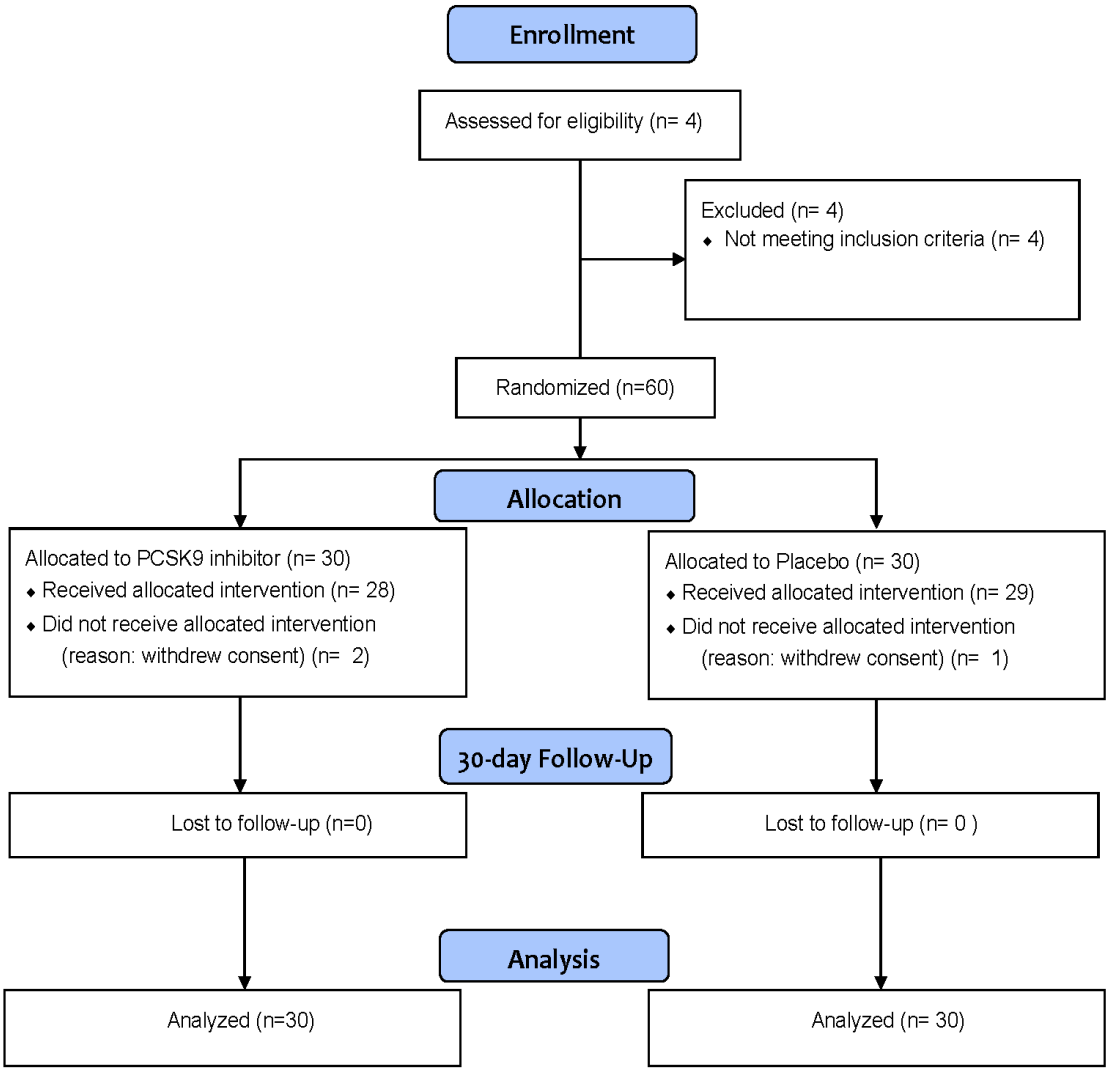
Enrollment
Assessed for eligibility (n= 4)
Excluded (n= 4)
Not meeting inclusion criteria (n= 4)
Randomized (n=60)
Allocation
Allocated to PCSK9 inhibitor (n= 30)
Received allocated intervention (n= 28)
Did not receive allocated intervention (reason: withdrew consent) (n= 2)
Allocated to Placebo (n= 30)
Received allocated intervention (n= 29)
Did not receive allocated intervention (reason: withdrew consent) (n= 1)
30-day Follow-Up
Lost to follow-up (n=0)
Lost to follow-up (n= 0)
Analysis
Analyzed (n=30)
Analyzed (n= 30)

Figure 2

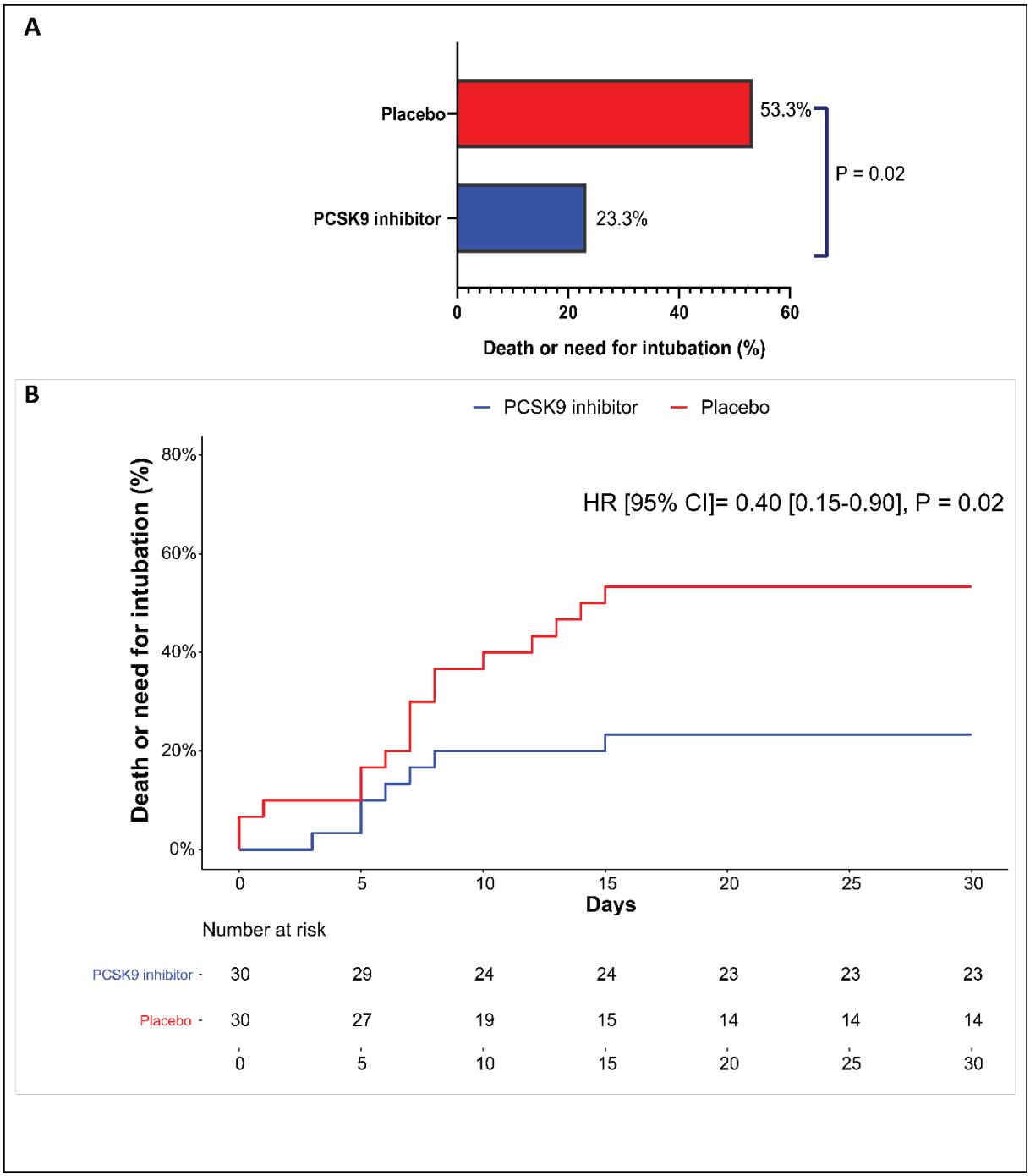
A
Placebo
PCSK9 inhibitor
53.3%
23.3%
P = 0.02
0
20
40
60
Death or need for intubation (%)
B
PCSK9 inhibitor
Placebo
HR [95% CI]= 0.40 [0.15-0.90], P = 0.02
Death or need for intubation (%)
80%
60%
40%
20%
0%
0
5
10
15
20
25
30
Days
Number at risk
PCSK9 inhibitor 30 29 24 24 23 23 23
Placebo 30 27 19 15 14 14 14

Figure 3

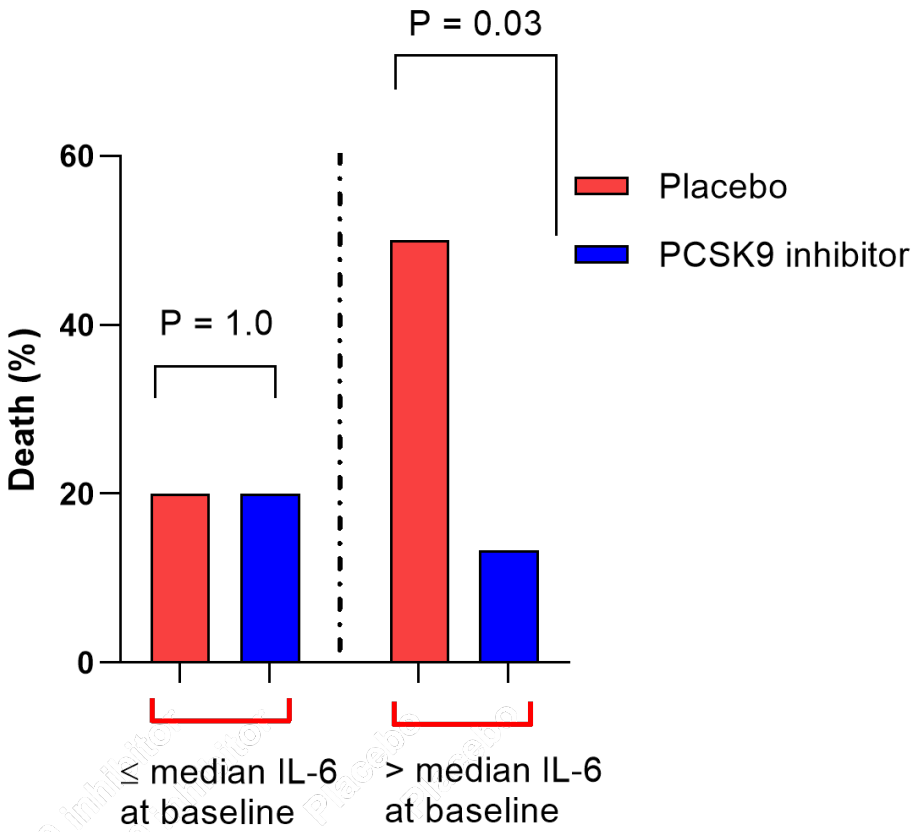
P = 0.03
60
40
20
0
Death (%)
P = 1.0
Placebo
PCSK9 inhibitor
≤ median IL-6
at baseline
> median IL-6
at baseline

Figure 4

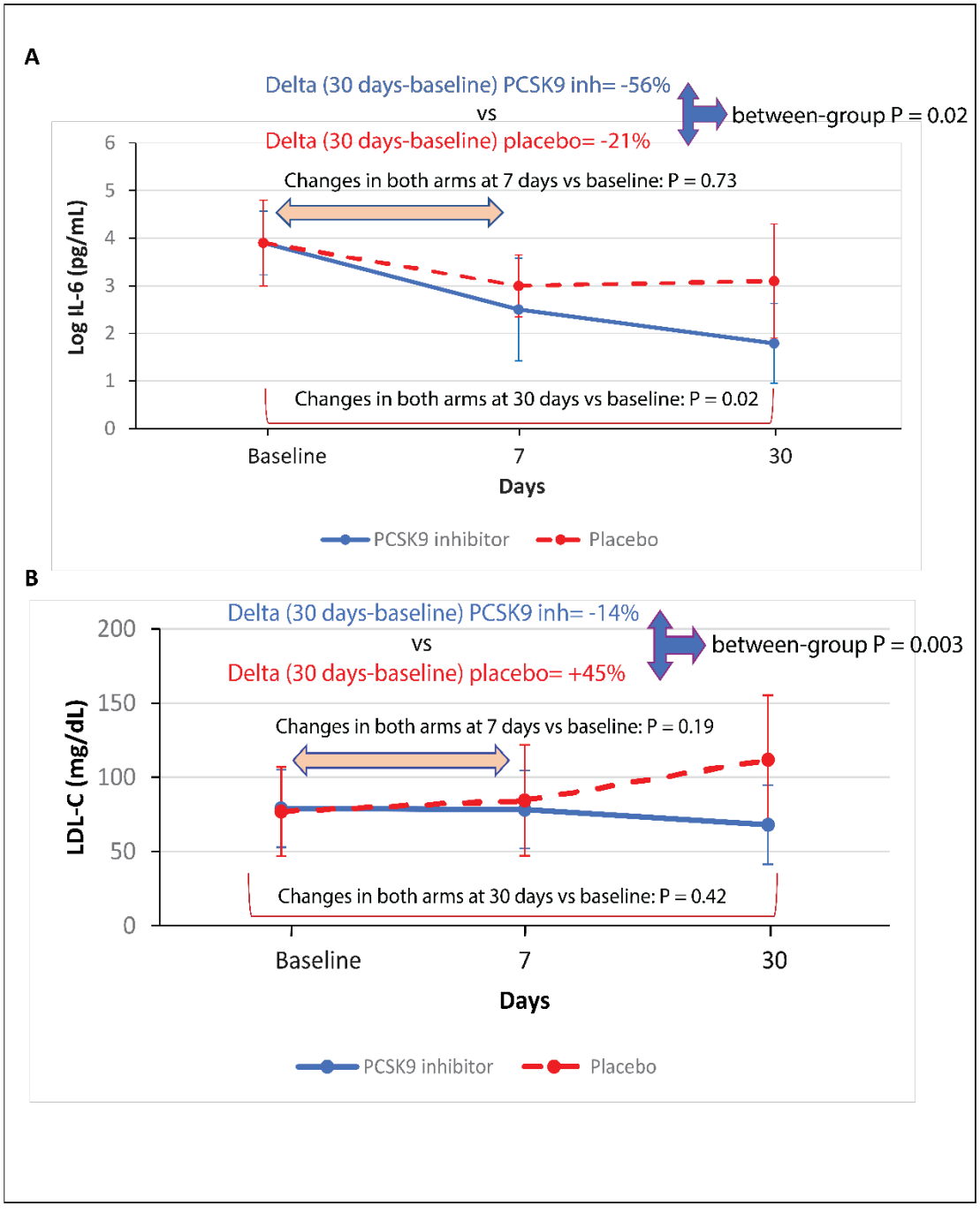
A
Delta (30 days-baseline) PCSK9 inh= -56%
vs
Delta (30 days-baseline) placebo= -21%
between-group P = 0.02
Changes in both arms at 7 days vs baseline: P = 0.73
Changes in both arms at 30 days vs baseline: P = 0.02
Log IL-6 (pg/mL)
0
1
2
3
4
5
6
Baseline
7
30
Days
PCSK9 inhibitor
Placebo
B
Delta (30 days-baseline) PCSK9 inh= -14%
vs
Delta (30 days-baseline) placebo= +45%
between-group P = 0.003
Changes in both arms at 7 days vs baseline: P = 0.19
Changes in both arms at 30 days vs baseline: P = 0.42
LDL-C (mg/dL)
0
50
100
150
200
Baseline
7
30
Days
PCSK9 inhibitor
Placebo

Figure 4C

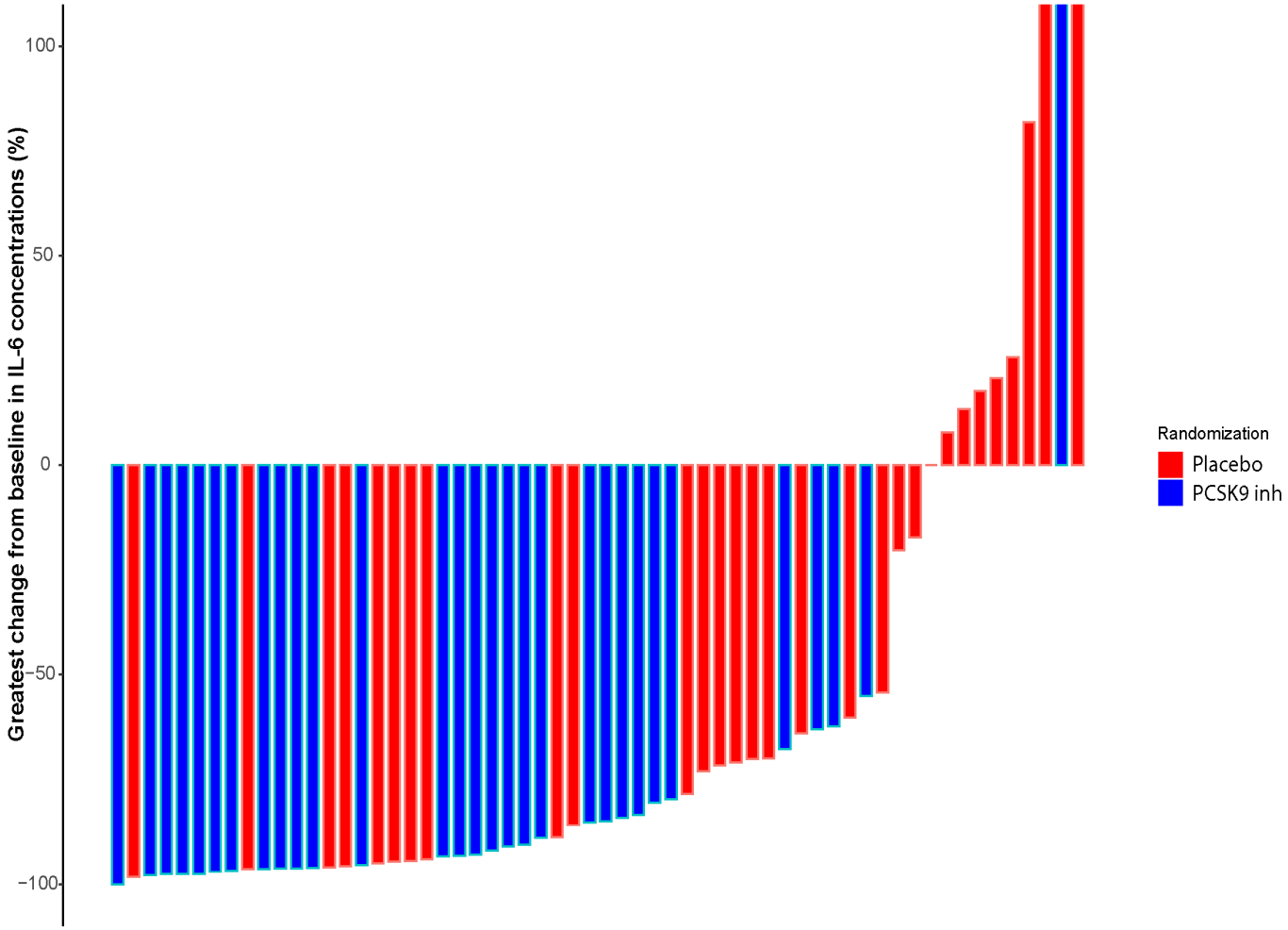
Greatest change from baseline in IL-6 concentrations (%)
100
50
0
−50
−100
Randomization
Placebo
PCSK9 inh

Figure 4D

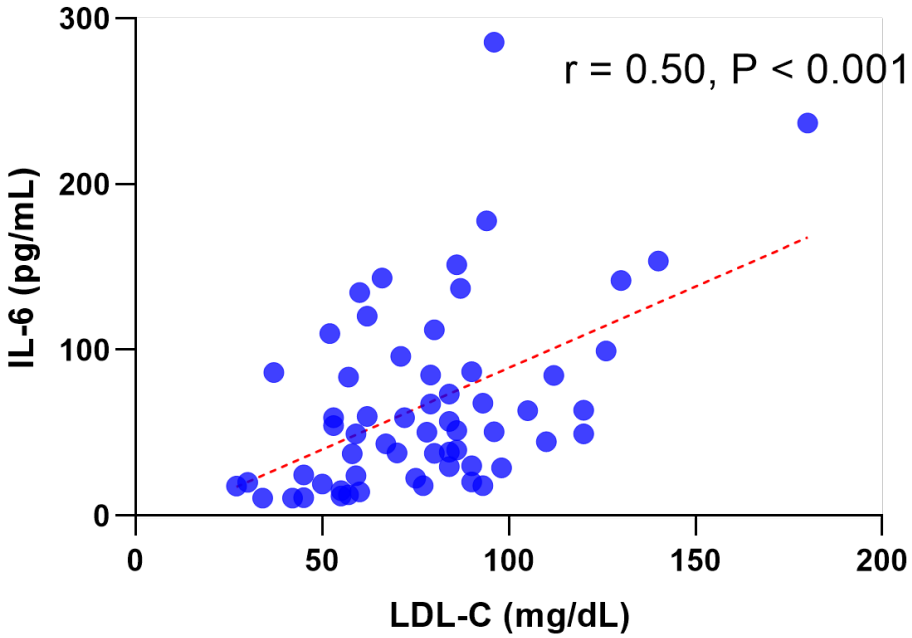

Figure 5. Central Illustration