مجلة الدراسات التربوية والعلمية - كلية التربية - الجامعة العراقية
العدد الخامس والعشرون - المجلد الثاني عشر - علوم الحياة - آب 2025 م
doi.org/10.52866/esj.2023.12.25.16

Clopidogrel Impact in Iraqi patients with Coronary Heart Disease: Effects on Lipids and Inflammation

Yasir Majid Kamil [1*] · Suha Abdul-Khaliq Abdul-Sattar Al-Jowari [2*]
Haitham Ali Abdullah [3*]
[1*,2*] Department of biology, College of Science, University of Baghdad, Baghdad, Iraq.
[3*] CABMS FICMS (cardio.), Ibn Al-Bitar Center for Cardiac Surgery, Baghdad, Iraq.
Fellowship of Iraqi Certificate for Medical Specialties (FICMS) and Certificate of Arabic Board in Medicine (CABM)

Abstract:

This study investigated the effect of clopidogrel on lipid profile-linked parameters in Iraqi patients with coronary heart disease (CHD). The research involved 56 CHD patients and 28 healthy controls, examining demographic, immunological, and biochemical parameters. Key findings revealed significant differences in gender distribution and age across the groups, with males predominant in the clopidogrel non-treated group and females in the control and clopidogrel-treated groups. The mean age was highest in the clopidogrel-treated group. Lipid profile analysis showed that clopidogrel-treated and non-treated groups had significantly higher levels of total cholesterol and triglycerides, and lower levels of high-density lipoprotein compared to the control group. However, there were no significant differences in these lipid parameters between the clopidogrel-treated and non-treated groups. Interleukin-18 levels were significantly different among the groups, but pairwise comparisons did not show significant differences. C-reactive protein levels did not differ significantly across the groups. A significant inverse correlation was found between IL-18 and HDL levels, indicating that higher inflammation may be associated with lower protective cholesterol levels. The study concluded that while clopidogrel effectively prevents thrombotic events, it does not significantly influence lipid metabolism or systemic inflammation.

Key Words: Coronary heart disease, Clopidogrel, Lipid profile, IL-18, C-Reactive Protein .

تأثير الكلوبيدوجريل في مرضى القلب التاجي العراقيين: التأثيرات على الدهون والالتهابات

ياسر ماجد كامل[1*] ، أ.د. سهى عبد الخالق الجواري[2*] ، هيثم علي عبد الله[3*]
[1*,2*] قسم علوم الحياة، كلية العلوم، جامعة بغداد، بغداد، العراق
[3*] زميل المجلس العراقية للاختصاصات الطبية/بورد عربي في الطب

مستخلص:

هذه الدراسة بحثت في تأثير الكلوبيدوجريل على معايير مرتبطة بمستويات الدهون في المرضى العراقيين المصابين بمرض الشريان التاجي (CHD). شملت الدراسة 56 مريضًا يعانون من مرض الشريان التاجي و28 شخصًا من الأصحاء كمجموعة ضابطة، حيث تم فحص المعايير الديموغرافية والمناعية والكيميائية الحيوية. كشفت النتائج الرئيسية عن فروق ذات دلالة إحصائية في توزيع الجنس والعمر بين المجموعات، حيث كان الذكور أكثر شيوعًا في مجموعة المرضى غير المعالجين بالكلوبيدوجريل، بينما كانت الإناث أكثر تواجدًا في المجموعة الضابطة والمجموعة المعالجة بالكلوبيدوجريل. وكان متوسط العمر أعلى في المجموعة المعالجة بالكلوبيدوجريل. أظهر تحليل الدهون أن مجموعتي المرضى المعالجين وغير المعالجين بالكلوبيدوجريل لديهما مستويات أعلى بشكل ملحوظ من الكوليسترول الكلي والدهون الثلاثية، ومستويات أقل من البروتين الدهني عالي الكثافة (HDL) مقارنة بالمجموعة الضابطة. ومع ذلك، لم تكن هناك فروق ذات دلالة إحصائية في هذه المعايير بين مجموعتي المرضى المعالجين وغير المعالجين بالكلوبيدوجريل. كانت مستويات الإنترلوكين-18 (IL-18) مختلفة بشكل ملحوظ بين المجموعات، لكن المقارنات الثنائية لم تُظهر فروقًا ذات دلالة إحصائية. من ناحية أخرى، لم تختلف مستويات بروتين سي التفاعلي - (CRP) بشكل كبير بين المجموعات. كما وُجد ارتباط عكسي ذو دلالة إحصائية بين IL-18 ومستويات HDL، مما يشير إلى أن زيادة الالتهاب قد تكون مرتبطة بانخفاض مستويات الكوليسترول الواقي. خلصت الدراسة إلى أن الكلوبيدوجريل، رغم فعاليته في الوقاية من احداث التخثر، لا يؤثر بشكل كبير على أيض الدهون أو الالتهاب الجهازي.

كلمات مفتاحية: مرض القلب التاجي، كلوبيدوجريل، صورة الدهون، انترلوكين 18، بروتين سي التفاعلي .

Introduction:

Coronary heart disease (CHD), a leading cause of global mortality, is primarily driven by atherosclerosis (Sanchis-Gomar *et al*., 2016). This process involves lipid-rich plaque accumulation in coronary arteries, leading to complications like myocardial infarction. Modifiable risk factors, including dyslipidemia and inflammation, play critical roles (Jinnouchi *et al*., 2020). Dyslipidemia, characterized by imbalanced lipid profiles, promotes plaque formation (Zhao *et al*., 2021), while inflammatory markers like IL-18 and CRP exacerbate vascular dysfunction and thrombotic risk (Landy *et al*., 2024; Strang and Schunkert, 2014). Understanding the interplay between these factors is essential for effective CHD management.

Aim of Study:

To investigate the influence of clopidogrel on lipid profile parameters (total cholesterol, triglycerides, and high-density lipoprotein cholesterol) and inflammatory markers (IL-18 and CRP) in Iraqi patients with coronary heart disease (CHD).

Methodology:

This study highlights significant variations across demographic, immunological and biochemical parameters in coronary heart disease (CHD) patients, particularly among clopidogrel-takers, non-takers, and control groups. A patient and control study were performed on 56 CHD patients with an age range between (40-72) years, and 28 healthy controls with an age range between (34-72) years. Patients were admitted from March to July 2023. The diagnosis was made by the consultant medical staff. It was based on clinical examinations, ECG results, and laboratory tests.

To measure the lipid profile, the serum samples were analyzed for the following biochemical markers: cholesterol (CHOL), high-density lipoprotein (HDL), and triglycerides (TG). These parameters were assayed enzymatically on a fully automated Monarch 240 analyzer using Biorex Instruments, United Kingdom.

Interleukin-18 levels were evaluated depending on sandwich ELISA principles. In brief, Elisa is a quantitative analytical method that shows antigen-an-

tibody reactions via the color change obtained by using an enzyme-linked conjugate and enzyme substrate and that serves to identify the presence and concentration of molecules in biological fluids are generally called enzyme-linked immunosorbent assay (ELISA). Sandwich ELISA principles which use two antibodies, capture antibody and HRP-linked secondary antibody. The sample with an unknown number of antigens is immobilized on wells of the plate by binding with capture antibody. The antigen-antibody complex is linked to an enzyme bound secondary antibody. In the final step a substrate is added that the enzyme can convert to some detectable signal like color (Aydin, 2015).

C-Reactive Protein has been done using a quick manual method of Latex Serology, by taking 1 drop of serum (~50uL) and mixing it with C-Reactive Protein solution on a contrast fiber. Positive result when the reaction agglutinates, and negative when no agglutination seen (Biorex Diagnostics, 2024).

Results and Discussion:

Table 1 represents demographic and clinical characteristics of 84 participants categorized into three groups: Control (N=28), Clopidogrel-treated (N=28), and Clopidogrel non-treated (N=28). It includes gender distribution, mean age, and mean weight, along with statistical comparisons. Gender distribution shows that males were predominant in the clopidogrel non-treated group (48.7%), whereas females were more frequent in the control (42.2%) and clopidogrel-treated (37.8%) groups, with a statistically significant difference (P = 0.03). The mean age was lowest in the control group (47.11 ± 10.0 years) and highest in the clopidogrel-treated group (58.79 ± 6.93 years), showing a highly significant difference (P = 0.0001). Regarding weight, the clopidogrel non-treated group had the highest mean (88.35 ± 10.65 kg), while the control group had the lowest (82.64 ± 7.7 kg), though the difference was not statistically significant (P = 0.074). The mean ± SD values for male and female counts are also presented. Overall, the table highlights significant differences in gender distribution and age across groups, but not in weight.

Table (1): The studied groups assorted by Gender (Mean±SD).

Group	Male No., (%)	Female No., (%)	P-value	Age (Years) Mean ± SD	Weight (KG) Mean ± SD
Control N=28	9 (23.1%)	19 (42.2%)	0.059	47.11±10.0	82.64±7.7
Clopidogrel-treated N=28	11 (28.2%)	17 (37.8%)	0.17	58.79±6.93	86.5±10.31
Clopidogrel non-treated N=28	19 (48.7%)	9 (20%)	0.04	52.25±9.93	88.35±10.65
Mean ± SD	2.26 ± 0.81	1.78 ± 0.76	-	-	-
Total N=84	39	45	-	-	-
P-value	0.03	N. S=0.19	-	0.0001	N. S=0.074
P<0.05, N. S= Not Significant					

For Interleukin-18 (IL-18), the mean levels were 22.0 ± 0.04 ng/L in the control group, 24.83 ± 2.92 ng/L in the clopidogrel-takers, and 28.04 ± 1.66 ng/L in the clopidogrel non-takers. The differences among the groups were statistically significant, with a p-value of 0.05 (Kruskal-Wallis's test), suggesting a relationship between group status and IL-18 levels. The post-hoc pairwise comparisons using the Mann-Whitney U test reveal the specific differences among the study groups for the measured parameters. No statistically significant differences are observed in pairwise comparisons, with p-values of 0.5 (C vs. A), 0.08 (C vs. B), and 0.17 (A vs. B), table 2.

Table (2): Interleukin-18 levels of the studied groups (Mean±SD).

Groups	IL-18 ng/L (mean± SD)	Group Comparisons	P-value
Control (C)	22.0±8.04	C vs. A	0.5
Clopidogrel-takers (A)	24.83±2.92	C vs. B	0.08
Clopidogrel non-takers (B)	28.04±1.66	A vs B	0.17
P-value	0.045	-	
* Kruskal-Wallis's test		**Mann-Whitney U test	

For IL-18 (Interleukin-18), the mean levels were 22.0 ± 8.04 pg/mL in the control group, 24.83 ± 2.92 pg/mL in the clopidogrel-treated, and 28.04 ± 1.66 pg/mL in the clopidogrel non-treated. The difference between the treated group and the non-treated reflects a small effect of clopidogrel on lowering the IL-18 levels, but these differences among the groups were statistically not significant, with a p-value of 0.052 (Kruskal-Wallis's test). The post-hoc pairwise comparisons using the Mann-Whitney U test reveal no specific differences among the study groups for the measured parameters.

The pro-inflammatory cytokine IL-18 was identified as an IFN-γ inducing factor in Kupffer cells and macrophages. Macrophage- and smooth muscle cell-produced IL-18 expressions increase in unstable human atherosclerotic plaques and the increase of IL-18 expression is responsible for strokes (Kuszynski and Lauver, 2022). The beneficial effects of clopidogrel in hypertension are likely due to reduced infiltration of macrophages in the aorta, since macrophages are the main source of ROS in vessels, as well as decreased platelet-monocyte binding (Mittal *et al*., 2014;An *et al*., 2018), which explain the decrease in the IL-18 levels in the treated group, although it was not significant.

Opstad *et al*., (2019) reported that genetic polymorphisms significantly influenced IL-18 levels, suggesting that factors other than clopidogrel primarily govern its regulation. Similarly, a comparative study on ticagrelor and clopidogrel reported no significant differences in IL-18 levels between the two therapies, implying that clopidogrel's effect on IL-18 may be minimal or indirect (Gao *et al*., 2018).

On the other hand, some studies suggest that clopidogrel could modulate IL-18 levels in certain contexts. Ishimatsu *et al*., (2020) observed that clopidogrel reduced IL-18 levels in patients with metabolic syndrome (non-EM), indicating its potential anti-inflammatory effect in specific populations. Saw *et al*., (2008) also suggested that P2Y12 receptor antagonists, including clopidogrel, could influence IL-18 pathways, potentially contributing to its anti-inflammatory profile.

The results of lipid profile show significant differences among the study groups in all lipid profile parameters—Cholesterol (CHOL), Triglycerides (TG), and High-Density Lipoprotein (HDL) as revealed by the Kruskal-Wallis's test ($p<0.01$ for all). The control group had the lowest CHOL (166.96 ± 14.6 mg/dL), TG (119.5 ± 43.88 mg/dL), and the highest HDL levels (52.67 ± 8.73 mg/dL). Clopidogrel-treated exhibited increased CHOL (228.5 ± 28.5 mg/dL) and TG (249.53 ± 29.36 mg/dL), alongside reduced HDL (32.57 ± 4.75 mg/dL). Similarly, clopidogrel non-treated had the highest CHOL (237.39 ± 21.15 mg/dL) and TG (263.85 ± 29.88 mg/dL), with slightly higher HDL (35.57 ± 5.15 mg/dL) compared to clopidogrel-treated but still lower than the control group.

The Mann-Whitney U test further clarified pairwise group differences. For Cholesterol, Triglycerides, and HDL, the control group differed significantly from both clopidogrel-treated (<0.01) and clopidogrel non-treated (p <0.01), while there was no significant difference between clopidogrel-treated and clopidogrel non-treated for CHOL ($p = 0.706$), TG ($p=0.915$), and HDL ($p=0.198$), table 3.

Table (3): Lipid profile values and CRP of the studied groups (Mean±SD).

	Parameters mg/dL (mean± SD)		
Groups	CHOL	TG	HDL
Control (C)	166.96±14.6	119.5±43.88	52.67±8.73
Clopidogrel-treated (A)	228.5±28.5	249.53±29.36	32.57±4.75
Clopidogrel non-treated (B)	237.39±21.15	263.85±29.88	35.57±5.15
P-value	<0.01	<0.01	<0.01
* Kruskal-Wallis's test			
Group Comparisons	CHOL	TG	HDL
C vs. A	<0.01	<0.01	<0.01
C vs. B	<0.01	<0.01	<0.01
A vs B	0.706	0.915	0.198
**Mann-Whitney U test			

The correlation between lipid biomarkers and coronary artery disease has become the focus of cardiovascular research in recent years (Dai *et al*., 2024). These Fats are moved through the bloodstream as lipoproteins. High levels of non-HDL lipoproteins are strongly associated with increased CHD risk. Furthermore, imbalances in blood fat levels, particularly high triglycerides and low HDL cholesterol, are linked to conditions like obesity, diabetes, and cardiovascular problems. While the role of triglycerides alone is debated, their presence alongside low HDL cholesterol clearly elevates CHD risk, leading to higher rates of serious heart events (Shabana *et al*., 2020).

Several studies discussed the elevated cholesterol levels in patients treated with clopidogrel, particularly reflecting underlying cardiovascular disease. A study by Ma, (2024) highlighted that clopidogrel, when combined with atorvastatin, exerts anti-inflammatory effects, which reduce plaque inflammation and improve cardiac function without directly lowering cholesterol levels. This underscores the importance of lipid regulation through adjunct therapies like statins in cardiovascular management. Preclinical studies using ApoE-deficient mice, predisposed to atherosclerosis, revealed that clopidogrel significantly stabilized plaque formation and slowed atherosclerosis progression despite high cholesterol levels, indicating that its benefits occur independent of direct lipid-lowering effects (Heim *et al*., 2016a). Similarly, studies in acute myocardial infarction (AMI) models demonstrated that clopidogrel, alone or combined with aspirin, reduced inflammation and myocardial necrosis markers but did not directly reduce cholesterol levels (Mohamed *et al*., 2014).

In accordance with these findings, some studies reported no significant differences in cholesterol levels between clopidogrel users and non-users. For instance, a study comparing Group A (clopidogrel-treated) and Group B (non-treated) showed no significant difference in cholesterol levels $P = 0.368$ (Tetik *et al*., 2010a).

Similarly, another study reported that hyperlipidemia prevalence was not significantly different in clopidogrel groups receiving 300 mg and 600 mg

doses (*P = 0.62*) (Dangas *et al*., 2009). In opposition to these findings, some studies have emphasized that while clopidogrel is cardioprotective through its antiplatelet and anti-inflammatory effects, it does not independently alter cholesterol metabolism. For example, clopidogrel and aspirin groups showed no significant differences in cholesterol levels (*P = 0.75*) (Wang *et al*., 2015).

This study's significant findings for cholesterol levels between the control group and clopidogrel-treated groups align with the notion that elevated CHOL may reflect underlying cardiovascular disease or metabolic alterations rather than a direct effect of clopidogrel.

HDL-C acts as a protective agent against atherosclerosis and inflammation through multiple mechanisms (antioxidant, anti-inflammatory, anti-apoptotic, anti-thrombotic), promoting cholesterol efflux, vascular protection, plaque stabilization, and LDL oxidation inhibition, resulting in an inverse correlation with cardiovascular diseases (CAD, MI, stroke) and preventative effects against coronary artery disease (Dai *et al*., 2024).

Elevated triglyceride levels are consistently linked to an increased risk of cardiovascular problems. Studies, including the PESA investigation, have demonstrated that even in individuals with seemingly healthy cholesterol levels, triglyceride levels exceeding 150 mg/dL correlate with the presence of subclinical atherosclerosis and inflammation. This connection between high triglycerides and cardiovascular risk is observed even though triglycerides often occur alongside other metabolic issues like insulin resistance, type 2 diabetes, obesity, low HDL cholesterol, and high blood pressure. Therefore, while observational data strongly suggests a link between high triglycerides and atherosclerotic events, it remains unclear whether triglycerides themselves directly cause major adverse cardiovascular events (MACE) independently of these other related metabolic conditions (Zahger *et al*., 2024). While taking Clopidogrel, high TG is considered an independent predictor of high on treatment platelet reactivity in ischemic stroke patients(Chen *et al*., 2022).

In a study of Guo *et al*., (2021) who studied the effect of triglycerides along with insulin in Clopidogrel-takers, he demonstrated that high triglycerides and insulin resistance cannot influence the clopidogrel significantly. Insulin resistance could cause not only chronic inflammation but also endothelial dysfunction, which contributes to the increase of platelet adhesion and aggregation. Relative to aspirin, clopidogrel resistance is more easily affected by con-founding factors such as genes polymorphisms, which made it difficult to correlate insulin resistance with clopidogrel resistance.

A study conducted a meta-analysis focusing on the combined use of statins and clopidogrel in patients with coronary artery disease. While primarily assessing mortality and platelet function, the study observed that this coadministration did not adversely affect lipid parameters such as TG and HDL cholesterol, suggesting a neutral effect on lipid metabolism (K. An *et al*., 2019). Similarly, Tetik *et al*., (2010b) investigated the interaction between statins and clopidogrel in ischemic heart disease, noting improved platelet inhibition without significant changes in lipid profiles, further supporting the idea of clopidogrel having no detrimental impact on TG and HDL levels.

Furthermore, Ensminger *et al*. (2015), in an experimental study on mice, reported significant reductions in atherosclerotic lesions due to clopidogrel. However, serum lipid levels, including TG and HDL, remained unaffected, indicating that clopidogrel's benefits in atherosclerosis are likely independent of its influence on lipid metabolism (Heim *et al*., 2016b). On the other side, to study the clinical significance of clopidogrel's effects on lipid profiles, Deng *et al*., (2023) performed a network meta-analysis evaluating lipid-lowering therapies in patients undergoing percutaneous coronary intervention. While the study highlighted the efficacy of combinations such as Eicosapentaenoic Acid (EPA) with statins, it found limited evidence to attribute substantial changes in TG or HDL levels to clopidogrel, suggesting its effect on lipid profiles may be negligible.

In summary, these results could imply that factors other than clopido-

grel use, such as comorbidities or other medications, may contribute to the observed differences in lipid levels between treated and control groups.

The results for CRP (C-Reactive Protein) show that the mean ± SD is 0.31±0.11 for the Control group, 0.41±0.21 for Clopidogrel-treated, and 0.47±0.23 for Clopidogrel non-treated. The Kruskal-Wallis's test yielded a p-value of 0.152, which indicates no statistically significant difference in CRP levels among the three groups ($p > 0.05$). Pairwise comparisons using the Mann-Whitney U test further confirm this, as the p-values for C vs A (0.28), C vs B (0.053), and A vs B (0.37) all fail to reach statistical significance. Although CRP levels appear higher in Clopidogrel non-treated compared to the other groups, the differences are not statistically significant, suggesting no clear association between CRP levels and group classification, table 4.

Table (4): Lipid profile values and CRP of the studied groups (Mean±SD).

	Parameter (mean± SD)	Frequency		Group Comparisons	
Groups	CRP (+/-)	Positive	Negative	Groups	P values
Control (C)	0.31±0.11	3	25	C vs. A	0.28
Clopidogrel-treated (A)	0.41±0.21	6	22	C vs. B	0.053
Clopidogrel non-treated (B)	0.47±0.23	9	19	A vs B	0.37
P-value	0.152	-	-	-	-
* Kruskal-Wallis's test				**Mann-Whitney U test	

C- Reactive Protein, an inflammatory marker, is a strong predictor of CHD risk and poor cardiovascular prognosis. CRP assays are valuable tools in clinical settings, demonstrating a robust association between elevated CRP levels and increased CHD risk across diverse populations, including both primary and secondary prevention, and even in asymptomatic individuals. CRP levels correlate with metabolic syndrome components (obesity, dyslipidemia, hypertension, hyperglycemia), enhancing cardiovascular risk prediction.

Mechanistically, CRP is implicated in atherogenesis through several pathways. It presents within atherosclerotic lesions, co-localizing with monocytes, macrophages, and lipoproteins, suggesting a direct contribution to the atherosclerotic process (Shrivastava *et al*., 2015). Moreover, CRP directly influences complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation, and thrombosis, highlighting its multifaceted role in vascular inflammation and coronary atherosclerosis (Luo *et al*., 2021). However, the causal relationship between CRP and CHD remains a subject of debate. While substantial data demonstrates an association between elevated CRP levels and CHD, Mendelian randomization studies suggest that CRP may act as a bystander rather than a direct causative factor in atherosclerosis progression. This perspective is supported by experimental data indicating potential contamination artifacts in studies reporting pro-inflammatory and pro-thrombotic effects. Additionally, the tissue damage observed post-myocardial infarction, possibly mediated by CRP's interaction with apoptotic cells and subsequent monomeric CRP formation, requires further investigation (Strang and Schunkert, 2014).

In this study, there was no statistically significant difference in hs-CRP levels between Group A (clopidogrel-treated) and Group B (clopidogrel non-treated). Similar studies found there was no evidence that decreases in inflammatory markers between baseline and 1 month were influenced by treatment type; clopidogrel, when compared to aspirin, did not affect the resolution of acute-phase responses (Woodward *et al*., 2004). In one study, hs-CRP levels showed no significant difference between group A and group B (P = 0.29) (Dash *et al*., 2013).

Clopidogrel was without effect on inflammatory markers, and no beneficial effect was observed in patients with high levels of hs-CRP. The favorable clinical outcomes were attributed to reductions in stroke rates, with no change in cardiovascular mortality (Weber *et al*., 2011). No significant differences in CRP levels were found between group A and group B (*P = 0.214*) (Doğan *et al*., 2019). Opposite to these

findings after therapy, the median serum level of hs-CRP significantly decreased at baseline at the 12th week ($P < 0.001$), with female patients showing significantly higher reductions in hs-CRP levels compared to male patients (*P = 0.006*) (Hajsadeghi *et al*., 2016). Although baseline hs-CRP values were similar (*P = 0.67*), hs-CRP levels were significantly higher in group B compared to group A at the 48th hour (*P = 0.0001*) (Akbulut *et al*., 2009). Levels of hs-CRP significantly decreased in normo-responsive patients compared to nonresponsive patients ($P < 0.001$) (Uzel *et al*., 2014), while hs-CRP levels significantly decreased after treatment ($P < 0.0001$) between groups, showing that treatment suppressed inflammatory markers effectively (Xie *et al*., 2024).

This study suggests that clopidogrel treatment, in this context, did not significantly impact CRP levels, and if there were any, it was a little without significance.

For the correlation coefficient among the parameters, the spearman's correlation coefficient for the parameters studied shows only a significant negative correlation between Interleukin-18, an inflammatory cytokine, and the HDL (high-density lipoprotein), table 5. This finding indicates that increased inflammation may be associated with lower protective cholesterol levels, potentially reflecting cardiovascular risk.

Table (5): spearman's correlation coefficient.

	Correlation Coefficient (r)	P-value
IL-18 and HDL	-0.371	0.005

The inverse correlation between IL-18 and HDL (r = -0.371, *p = 0.005*) indicates that higher IL-18 levels are associated with lower HDL cholesterol. IL-18 is a pro-inflammatory cytokine implicated in atherosclerosis. These correlations underscore the interconnected nature of inflammation, lipid metabolism, and the associations between inflammatory markers (IL-18), highlighting the impact of inflammation on lipid metabolism and cardio-

vascular risk.

Increased body weight causes cellular injury, leading to the production of the inflammatory cytokine IL-18. IL-18 then directly promotes the synthesis of triglycerides (TG) from free fatty acids within adipocytes, resulting in greater fat accumulation and further weight gain (Olusi *et al*., 2003). A study involving patients with psoriatic arthritis and ischemic heart disease demonstrated that IL-18 serum levels negatively correlated with HDL levels (rho = -0.608), suggesting a role in cardiovascular risk (Przepiera-Będzak, *et al*., 2016). Moreover, Viana *et al*. (2023) investigated the relationship between COVID-19 prognosis and cardiovascular risk, noting that alterations in lipoprotein metabolism may play a role. They specifically examined the single nucleotide polymorphism (SNP) rs187238 of the Interleukin-18 (IL-18) gene, which is widely recognized for its association with increased inflammation and cardiovascular disease (CVD) severity. Their findings revealed a negative correlation between IL-18 levels and high-density lipoprotein cholesterol (HDL-c).

Conclusions

In summary, clopidogrel did not significantly alter lipid profiles or inflammatory markers in this study population. The observed differences in lipid levels between CHD patients and controls likely reflect underlying cardiovascular disease or metabolic alterations rather than a direct effect of clopidogrel. The significant inverse correlation between IL-18 and HDL underscores the complex interplay between inflammation and lipid metabolism in CHD. Further research with larger sample sizes and longitudinal designs is warranted to elucidate the long-term effects of clopidogrel on lipid profiles and inflammatory markers in CHD patients.

Reference:

1. Akbulut, M., Kutlu, M., Ozbay, Y., Polat, V., Bilen, M. N., Baydas, A., & Altas, Y. (2009). Efficacy of Clopidrogel on Reperfusion and High-Sensitivity C-Reactive Protein in Patients with Acute Myocardial Infarction. *Mediators of Inflammation*, *2009*, 1–5. https://doi.org/10.1155/2009/932515

2. An, K., Huang, R., Tian, S., Guo, D., Wang, J., Lin, H., & Wang, S. (2019). Statins significantly reduce mortality in patients receiving clopidogrel without affecting platelet activation and aggregation: a systematic review and meta-analysis. *Lipids in Health and Disease*, *18*(1), 121. https://doi.org/10.1186/s12944-019-1053-0

3. An, X., Jiang, G., Cheng, C., Lv, Z., Liu, Y., & Wang, F. (2018). Inhibition of Platelets by Clopidogrel Suppressed Ang II-Induced Vascular Inflammation, Oxidative Stress, and Remodeling. *Journal of the American Heart Association*, *7*(21). https://doi.org/10.1161/JAHA.118.009600

4. Aydin, S. (2015). A short history, principles, and types of ELISA, and our laboratory experience with peptide/protein analyses using ELISA. *Peptides*, *72*, 4–15. https://doi.org/10.1016/j.peptides.2015.04.012

5.BiorexDiagnostics.(2024).*PRODUCT CATALOGUE*. PRODUCT CATALOGUE. https://biorexdiagnostics.com/wp-content/uploads/2024/10/BR001BIO-OCT24-Product-Catalogue.pdf

6. Chen, H., Zhan, Y., Lou, Z., Mao, H., Zhang, C., Li, X., Chen, G., Ouyang, H., Huang, Z., Wen, L., Xu, H., Zheng, Z., Zhao, Y., & Zhao, M. (2022). High triglyceride is an independent predictor of high on-treatment platelet reactivity in ischemic stroke patients. *Journal of Stroke and Cerebrovascular Diseases*, *31*(6), 106448. https://doi.org/10.1016/j.jstrokecerebrovasdis.2022.106448

7. Dai, X., Xue, Z., Wang, X., Chen, K., Hu, S., Tse, G., Rha, S., & Liu, T. (2024). High-sensitivity C-reactive protein to high-density lipoprotein cholesterol ratio predicts long-term adverse outcomes in patients who underwent percutaneous coronary intervention: A prospective cohort study. *Clinical and Experimental Pharmacology and Physiology*, *51*(11). https://

doi.org/10.1111/1440-1681.13919

8. Dangas, G., Mehran, R., Guagliumi, G., Caixeta, A., Witzenbichler, B., Aoki, J., Peruga, J. Z., Brodie, B. R., Dudek, D., Kornowski, R., Rabbani, L. E., Parise, H., & Stone, G. W. (2009). Role of Clopidogrel Loading Dose in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary Angioplasty. *Journal of the American College of Cardiology*, *54*(15), 1438–1446. https://doi.org/10.1016/j.jacc.2009.06.021

9. Dash, A., Maiti, R., Bandakkanavar, T. K. A., Bhaskar, A., Prakash, J., & Pandey, B. L. (2013). Prophylactic Add-on Antiplatelet Therapy in Chronic Kidney Disease With Type 2 Diabetes Mellitus: Comparison Between Clopidogrel and Low-dose Aspirin. *International Journal of Preventive Medicine*, *4*(8), 902–910.

10. Deng, C.-J., Yan, J., Zheng, Y.-Y., Wu, T.-T., Pan, Y., Hou, X.-G., Wang, S.-F., Sirajidin, S., Aimaitijiang, M., & Xie, X. (2023). Effectiveness of lipid-lowering therapy on mortality and major adverse cardiovascular event outcomes in patients undergoing percutaneous coronary intervention: a network meta-analysis of randomised controlled trials. *BMJ Open*, *13*(11), e070827. https://doi.org/10.1136/bmjopen-2022-070827

11. Doğan, T., Kalçık, M., Yetim, M., Yalçınbayır, Ö., BEKAR, L., ÇELİK, O., & SERDAR, O. A. (2019). Evaluation of Fundoscopic Abnormalities in Patients with Coronary Artery Disease. *Middle Black Sea Journal of Health Science*, *5*(1), 26–32. https://doi.org/10.19127/mbsjohs.543978

12. Gao, C.-Z., Ma, Q.-Q., Wu, J., Liu, R., Wang, F., Bai, J., Yang, X.-J., Fu, Q., & Wei, P. (2018). Comparison of the Effects of Ticagrelor and Clopidogrel on Inflammatory Factors, Vascular Endothelium Functions and Short-Term Prognosis in Patients with Acute ST-Segment Elevation Myocardial Infarction Undergoing Emergency Percutaneous Coronary Intervention: a Pilot Study. *Cellular Physiology and Biochemistry*, *48*(1), 385–396. https://doi.org/10.1159/000491768

13. Guo, Y., Zhao, J., Zhang, Y., Wu, L., Yu, Z., He, D., Huang, H., Qu, W., & Luo, X. (2021). Triglyceride glucose index influences platelet reactivity in acute ischemic stroke patients.

BMC Neurology, *21*(1), 409. https://doi.org/10.1186/s12883-021-02443-x

14. Hajsadeghi, S., Chitsazan, M., Chitsazan, M., Salehi, N., Amin, A., Maleki, M., Babaali, N., Abdi, S., & Mohsenian, M. (2016). Changes of high sensitivity C-reactive protein during clopidogrel therapy in patients undergoing percutaneous coronary intervention. *Research in Cardiovascular Medicine*, *5*(1), 3. https://doi.org/10.5812/cardiovascmed.30091

15. Heim, C., Gebhardt, J., Ramsperger-Gleixner, M., Jacobi, J., Weyand, M., & Ensminger, S. M. (2016a). Clopidogrel significantly lowers the development of atherosclerosis in ApoE-deficient mice in vivo. *Heart and Vessels*, *31*(5), 783–794. https://doi.org/10.1007/s00380-015-0696-7

16. Heim, C., Gebhardt, J., Ramsperger-Gleixner, M., Jacobi, J., Weyand, M., & Ensminger, S. M. (2016b). Clopidogrel significantly lowers the development of atherosclerosis in ApoE-deficient mice in vivo. *Heart and Vessels*, *31*(5), 783–794. https://doi.org/10.1007/s00380-015-0696-7

17. Ishimatsu, T., Sasaki, K., Kakuma, T., Harada, A., Hirakawa, Y., Fukumoto, Y., & Ueno, T. (2020). Serum interleukin-18 levels as a predictor for patients with genetic dysfunction of cytochrome P450 2C19 in dual antiplatelet therapy with clopidogrel. *Journal of Cardiology*, *76*(5), 479–486. https://doi.org/10.1016/j.jjcc.2020.06.008

18. Kuszynski, D. S., & Lauver, D. A. (2022). Pleiotropic effects of clopidogrel. *Purinergic Signalling*, *18*(3), 253–265. https://doi.org/10.1007/s11302-022-09876-0

19. Luo, H., Kou, T., & Yin, L. (2021). High-Sensitivity C-Reactive Protein to HDL-C Ratio. *International Heart Journal*, *62*(6), 21–246. https://doi.org/10.1536/ihj.21-246

20. Ma, J. (2024). Effect of Clopidogrel Combined with Atorvastatin on Serum Lipids, Inflammatory Factors and Cardiac Function Parameters in Patients with Angina Pectoris and Coronary Heart Disease. *Pakistan Journal of Zoology*. https://doi.org/10.17582/journal.pjz/20230816081639

21. Mittal, M., Siddiqui, M. R., Tran, K., Reddy, S. P., & Malik, A. B. (2014). Reactive Oxygen Species in Inflammation and Tissue Injury. *Antioxidants & Redox Signaling*, *20*(7), 1126–1167.

https://doi.org/10.1089/ars.2012.5149

22. Mohamed, A. R., El-Hadidy, W. F., & Mannaa, H. F. (2014). Assessment of the Prophylactic Role of Aspirin and/or Clopidogrel on Experimentally Induced Acute Myocardial Infarction in Hypercholesterolemic Rats. *Drugs in R&D*, *14*(4), 233–239. https://doi.org/10.1007/s40268-014-0059-3

23. Olusi, S. O., Al-Awadhi, A., & Abraham, M. (2003). Relations of Serum Interleukin 18 Levels to Serum Lipid and Glucose Concentrations in an Apparently Healthy Adult Population. *Hormone Research in Paediatrics*, *60*(1), 29–33. https://doi.org/10.1159/000070824

24. Opstad, T. B., Kalstad, A. A., Pettersen, A. Å., Arnesen, H., & Seljeflot, I. (2019). Novel biomolecules of ageing, sex differences and potential underlying mechanisms of telomere shortening in coronary artery disease. *Experimental Gerontology*, *119*, 53–60. https://doi.org/10.1016/j.exger.2019.01.020

25. Przepiera-Będzak, H., Fischer, K., & Brzosko, M. (2016). Serum Interleukin-18, Fetuin-A, Soluble Intercellular Adhesion Molecule-1, and Endothelin-1 in Ankylosing Spondylitis, Psoriatic Arthritis, and SAPHO Syndrome. *International Journal of Molecular Sciences*, *17*(8), 1255. https://doi.org/10.3390/ijms17081255

26. Saw, J., Madsen, E. H., Chan, S., & Maurer-Spurej, E. (2008). The ELAPSE (Evaluation of Long-Term Clopidogrel Antiplatelet and Systemic Anti-Inflammatory Effects) Study. *Journal of the American College of Cardiology*, *52*(23), 1826–1833. https://doi.org/10.1016/j.jacc.2008.08.047

27. Shabana, Shahid, S. U., & Sarwar, S. (2020). The abnormal lipid profile in obesity and coronary heart disease (CHD) in Pakistani subjects. *Lipids in Health and Disease*, *19*(1), 73. https://doi.org/10.1186/s12944-020-01248-0

28. Shrivastava, A. K., Singh, H. V., Raizada, A., & Singh, S. K. (2015). C-reactive protein, inflammation and coronary heart disease. *The Egyptian Heart Journal*, *67*(2), 89–97. https://doi.org/10.1016/j.ehj.2014.11.005

29. Strang, F., & Schunkert, H. (2014). C-Reactive Protein and Coronary Heart Disease: All Said—Is Not It? *Mediators of Inflammation*, *2014*, 1–7.

https://doi.org/10.1155/2014/757123

30. Tetik, S., Ak, K., Isbir, S., Eksioglu-Demiralp, E., Arsan, S., Iqbal, O., & Yardimci, T. (2010a). Clopidogrel Provides Significantly Greater Inhibition of Platelet Activity Than Aspirin When Combined With Atorvastatin After Coronary Artery Bypass Grafting: A Prospective Randomized Study. *Clinical and Applied Thrombosis/Hemostasis*, *16*(2), 189–198. https://doi.org/10.1177/1076029609344980

31. Tetik, S., Ak, K., Isbir, S., Eksioglu-Demiralp, E., Arsan, S., Iqbal, O., & Yardimci, T. (2010b). Clopidogrel Provides Significantly Greater Inhibition of Platelet Activity Than Aspirin When Combined With Atorvastatin After Coronary Artery Bypass Grafting: A Prospective Randomized Study. *Clinical and Applied Thrombosis/Hemostasis*, *16*(2), 189–198. https://doi.org/10.1177/1076029609344980

32. Uzel, H., Ozpelit, E., Badak, O., Akdeniz, B., Bariş, N., Aytemiz, F., & Goldeli, O. (2014). Diagnostic accuracy of mean platelet volume in prediction of clopidogrel resistance in patients with acute coronary syndrome. *Anadolu Kardiyoloji Dergisi/The Anatolian Journal of Cardiology*, *14*(2), 134–139. https://doi.org/10.5152/akd.2014.4433

33. Wang, Y., Pan, Y., Zhao, X., Li, H., Wang, D., Johnston, S. C., Liu, L., Meng, X., Wang, A., Wang, C., & Wang, Y. (2015). Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) Trial. *Circulation*, *132*(1), 40–46. https://doi.org/10.1161/CIRCULATIONAHA.114.014791

34. Weber, M., Bhatt, D. L., Brennan, D. M., Hankey, G. J., Steinhubl, S. R., Johnston, S. C., Montalescot, G., Mak, K.-H., Fox, K. A. A., Easton, D. J., Topol, E. J., & Hamm, C. W. (2011). High-sensitivity C-reactive protein and clopidogrel treatment in patients at high risk of cardiovascular events: a substudy from the CHARISMA trial. *Heart*, *97*(8), 626–631. https://doi.org/10.1136/hrt.2010.210419

35. Woodward, M., Lowe, G. D. O., Francis, L. M. A., Rumley, A., & Cobbe, S. M. (2004). A randomized comparison of the effects of aspirin and clopidogrel on thrombotic risk factors and C-reactive protein following myocardial infarction: the CADET trial. *Journal*

of Thrombosis and Haemostasis, *2*(11), 1934–1940. https://doi.org/10.1111/j.1538-7836.2004.01017.x

36. Xie, R., Xu, S., Ao, D., Wang, Y., & Huang, J. (2024). Effect of aspirin combination/clopidogrel combination on high-sensitivity C-reactive protein and P-selectin levels in patients with acute coronary syndrome. *Tropical Journal of Pharmaceutical Research*, *23*(4), 723–730. https://doi.org/10.4314/tjpr.v23i4.7

37. Zahger, D., Schwartz, G. G., Du, W., Szarek, M., Bhatt, D. L., Bittner, V. A., Budaj, A. J., Diaz, R., Goodman, S. G., Jukema, J. W., Kiss, R. G., Harrington, R. A., Moriarty, P. M., Scemama, M., Manvelian, G., Pordy, R., White, H. D., Zeiher, A. M., Fazio, S., … Steg, P. G. (2024). Triglyceride Levels, Alirocumab Treatment, and Cardiovascular Outcomes After an Acute Coronary Syndrome. *Journal of the American College of Cardiology*, *84*(11), 994–1006. https://doi.org/10.1016/j.jacc.2024.06.035