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COMPARATIVE ANALYSIS ON MULTIPLE CORRELATIONS BETWEEN DIFFERENT CHOLESTEROL REDUCING DRUGS

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Abstract*: In this research, multiple correlation analyses of different cholesterol-reducing drugs were examined. There have been several arguments by physicians as to which anti-cholesterol drugs are the best to administer. To solve this problem, four cholesterol-reducing drugs-statin, proprotein convertase subtilisin/kexin (PCSK) inhibitors, fibrates, and nicotinic acid were experimented. The result shows that the drugs are statistically significant and that combining statin and PCSK qlutubitor is the best combination to be administered to the patient. They do improve glycemic control in patients with diabetes, which is an additional benefit. PCSK9 inhibitors, either monoclonal antibodies or small interfering RNA, lower LDL-C by 50-60% by decreasing PCSK9, which decreases the degradation of LDL receptors. PCSK9 inhibitors also decrease Lp (a) levels. PCSK9 inhibitors are very useful when maximally tolerated statin therapy do not reduce LDL sufficiently and in statin intolerant patients. PCSK9 inhibitors have very few side effects.*

Keyword: *Correlations, Cholesterol, Drugs, Physicians, Patients.*

INTRODUCTION

Cholesterol is a growing issue because of its impact on human health (Khera *etal*, 2011). Cigarette smoking, high blood pressure, and high blood cholesterol are the most clearly established risk factors that have been identified as being strongly associated with coronary heart disease (CHD) (Rohatgi *etal*, 2014). Total serum cholesterol level (SCL) is a major risk factor for CHD. Cholesterol is present in every cell of the body and has important natural functions when it comes to digesting foods, producing hormones, and generating vitamin D. A better understanding of lipoprotein production and removal, lipoprotein receptors, and apolipoproteins is needed because they are considered the most important factors in cholesterol (Layoun *etal*, 2017). Cholesterol is classified into two types: low-density lipoproteins (LDL) and high-density lipoproteins (HDL). Lipids are circulating as lipoproteins, consisting of unesterified cholesterol, triglycerides, phospholipids, and protein. The major lipoproteins in blood are: chylomicrons, very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Each of these classes of lipoproteins transports cholesterol and triglyceride to its designated destinations. The level of cholesterol plays a vital role in cardiovascular diseases process. A high level of lipids, including cholesterol and triglycerides in the serum, which also termed as hyperlipidemia, leads to a higher risk of developing

atherosclerotic cardiovascular disease (CVD). Cholesterol level measurement is from serum. Clinically, obtaining a lipid profile assists in the screening, diagnosing, and managing diseases. A non-fasting lipid test can be done anytime without fasting; a fasting lipid test requires a 12-hour fast except for water. Total and HDL cholesterol are measured directly from serum. Fasting LDL-C is still the standard for initiating lipid-lowering therapy, there has been a heated debate over fasting or non-fasting lipid profile among specialists. The rationale behind the discussion of fasting or non-fasting is because the triglycerides level can be affected by the last intake and the limitations of the Friedewald equation (Kolovou *etal*, 2005). Many current guidelines propose that no fasting LDL-C holds similar significance to that of fasting LDL-C (Nordestgaard *etal*, 2007). A fasting lipid panel is a strong recommendation for patients with type 2 diabetes, obesity, medications that may affect lipid levels, such as thiazides and beta blockers and excessive intake of alcohol (Herink and Ito, 2018). Cholesterol and triglycerides desirable levels are; Total cholesterol (below 200 mg/dl), LDL cholesterol (below 100 mg/dl), HDL cholesterol (at or above 60 mg/dl) and Triglycerides (below 150 mg/dl) (Duerden, O'Flynn and Qureshi, 2015). A recommendation has been made that total SCL for adults should be below 200mg/dl and individuals with values between 200mg/dl to 239 mg/dl should be considered as borderline high risk; those with values more than 240 mg/dl should be regarded as high risk for CHD 3, 9. Therefore, the recommended level for children is170mg/dl.

This research aimed at examining several anti-cholesterol drugs with the following objectives:

Testing the significance effects of the drugs, examining whether the drugs are influenced by zero and first partial correlation. Then finally test whether the drugs are influenced by second partial correlation.

This research will help physicians to know the right prescription of cholesterol-reducing drugs to be prescribed to people with this health challenge. It is also significant in terms of the interaction effect of the combined drugs. This will save many lives from the risk of side effects of taking drugs for the treatment of high cholesterol in humans.

METHODOLOGY

The materials for this research work includes medical tools used to diagnose patients with high level of cholesterol. The method adopted is by administering the drugs to the affected patient where data was obtained from Gen. Sani Abacha Specialist Hospital Damauru, Yobe State and the Yobe State University Teaching Hospital Damaturu, Yobe State. The source of data is secondary and the experiment was carried out for twenty (20) days with assume population of 200 clients of three categories (Men, Women and Children).

Data Collection

In this research, secondary method of data collection was adopted. This method is more reliable due to its limitation of biasness in responses.

Instrument of Data Collection

"Patient Intake Report of Anti-Cholesterol Drugs (PIRAD)" was developed as an instrument for this study. It was divided into two sections A and B. Section A elicits information of the patient respondents. Section B, measure the items for independent variables and three dependent variables.

Data Analysis

The methods employed to analyze this research study are Analysis of Variance and Correlation Analysis techniques. The breakdown of the methods is shown below

One – way classification technique

This design is appropriate for experiments having homogeneous experimental materials and units where effects are easy to control. In this design, treatments (drugs) are assigned entirely at random to experimental unit such that each unit has an equal chance of receiving any one drug.

Table 1: Cholesterol level in randomly selected person

Treatments (Drugs)				
1	2	3. . .		k
y_{11}	y_{12}	y_{13} . . .		y_{1k}
y_{21}	y_{22}	y_{23} . . .		y_{2k}
-	-	-	-	-
-	-	-	-	-
-	-	-		-
y_{n1}	y_{n2}	y_{n3}		y_{nk}

The linear statistical model for the experiment is given by;

$$y_{ij} = \mu + \tau_j + \varepsilon_{ij} \begin{cases} j = 1,2, ..., k \\ i = 1,2, \ldots, n \end{cases} \quad (1)$$

Where ; y_{ij} is the i^{th} observation receiving j^{th} drug, μ is the grand mean of the drugs, τ_j is the j^{th} drugs effect and ε_{ij} is a random error that is normally distributed with mean zero (0) and variance (σ^2) . Two sources of variation are considered; variation between groups (drugs) and variation within groups (error). Here, the interest is to test the equality of k – drug effects. That is;

$H_0 : \tau_1 = \tau_2 = \ldots = \tau_k = 0$ And $H_1 : \tau_j \neq 0$ for at least one j .

The analysis of variance (ANOVA) consists of partitioning the total variability into its components parts as follows;

$$SS_{Total} = SS_{Drug} + SS_{Error} \quad (2)$$

The test procedure is summarized in Table 2 below:

Table 2: Analysis of variance for different drugs in reducing cholesterol level

Source of variation	Df	Sum of Squares	mean Square	F - ratio
Drugs	$k-1$	SS_{Drug}	MS_{Drug}	$\frac{MS_{Drug}}{MS_{Error}}$
Error	$N-k$	SS_{Error}	MS_{Error}	
Total	$N-1$	SS_{Total}		

Partial correlation

Simple correlation for zero order between X_i and X_j. The simple correlation of zero order between combinations of two variables is given below;

$$r_{ij} = \frac{\sum X_i X_j}{\sqrt{\sum X_i^2 X_j^2}}, \quad i \neq j \quad ij = 1,2,3,\ldots,n \tag{3}$$

Simple correlation between Statin and PCSK 9 Inhibitors

$$r_{12} = \frac{\sum x_1 x_2}{\sqrt{\sum x_1^2 \sum x_2^2}} \equiv r_{21} \tag{4}$$

Simple correlation between Statin and Fibrates

$$r_{13} = \frac{\sum x_1 x_3}{\sqrt{\sum x_1^2 \sum x_3^2}} \equiv r_{31} \tag{5}$$

Simple correlation between Statin and Nicotinic acid

$$r_{14} = \frac{\sum x_1 x_4}{\sqrt{\sum x_1^2 \sum x_4^2}} \equiv r_{41} \tag{6}$$

Simple correlation between PCSK 9 Inhibitors and Fibrates

$$r_{23} = \frac{\sum x_2 x_3}{\sqrt{\sum x_2^2 \sum x_3^2}} \equiv r_{32} \tag{7}$$

Simple correlation between PCSK 9 Inhibitors and Nicotinic acid

$$r_{24} = \frac{\sum x_2 x_4}{\sqrt{\sum x_2^2 \sum x_4^2}} \equiv r_{42} \tag{8}$$

Simple correlation between Fibrates and Nicotinic acid

$$r_{34} = \frac{\sum x_3 x_4}{\sqrt{\sum x_3^2 \sum x_4^2}} \equiv r_{43} \tag{9}$$

First order partial correlation between the variables

This is a partial correlation between two variables keeping the third variable constant. The following are the partial correlation of three variables for this research:

1. Partial correlation between Statin and PCSK 9 Inhibitors keeping Fibrates constant

$$r_{12.3} = \frac{r_{12} - r_{13} r_{23}}{\sqrt{1 - r_{13}^2}\sqrt{1 - r_{23}^2}} \equiv r_{21.3} \tag{10}$$

2. Partial correlation between Statin and PCSK 9 Inhibitors keeping Nicotinic acid constant

$$r_{12.4} = \frac{r_{12} - r_{14} r_{24}}{\sqrt{1 - r_{14}^2}\sqrt{1 - r_{24}^2}} \tag{11}$$

3. Partial correlation between Statin and Fibrates keeping Nicotinic acid constant

$$r_{13.4} = \frac{r_{13} - r_{14} r_{34}}{\sqrt{1 - r_{14}^2}\sqrt{1 - r_{34}^2}} \tag{12}$$

4. Partial correlation between Statin and Nicotinic acid keeping PCSK 9 Inhibitors constant

$$r_{14.2} = \frac{r_{14} - r_{12} r_{24}}{\sqrt{1 - r_{12}^2}\sqrt{1 - r_{24}^2}} \tag{13}$$

5. Partial correlation between Statin and Nicotinic acid keeping Fibrates constant

$$r_{14.3} = \frac{r_{14} - r_{13} r_{34}}{\sqrt{1 - r_{13}^2}\sqrt{1 - r_{34}^2}} \tag{14}$$

6. Partial correlation between PCSK 9 Inhibitors and Statin keeping Nicotinic acid constant

$$r_{21.4} = \frac{r_{21} - r_{24}r_{14}}{\sqrt{1-r_{24}^2}\sqrt{1-r_{14}^2}} \quad (15)$$

7. Partial correlation between PCSK 9 Inhibitors and Fibrates keeping Nicotinic acid constant

$$r_{23.4} = \frac{r_{23} - r_{24}r_{34}}{\sqrt{1-r_{24}^2}\sqrt{1-r_{34}^2}} \quad (16)$$

8. Partial correlation between PCSK 9 Inhibitors and Nicotinic acid keeping Fibrates constant

$$r_{24.3} = \frac{r_{24} - r_{23}r_{34}}{\sqrt{1-r_{23}^2}\sqrt{1-r_{34}^2}} \quad (17)$$

9. Partial correlation between Fibrates and Statin keeping PCSK 9 Inhibitors constant

$$r_{31.2} = \frac{r_{31} - r_{32}r_{12}}{\sqrt{1-r_{32}^2}\sqrt{1-r_{12}^2}} \quad (18)$$

10. Partial correlation between Fibrates and Nicotinic acid keeping PCSK 9 Inhibitors constant

$$r_{34.2} = \frac{r_{34} - r_{32}r_{42}}{\sqrt{1-r_{32}^2}\sqrt{1-r_{42}^2}} \quad (19)$$

Second order partial correlation coefficient in four variables

If x_1, x_2, x_3 and x_4 are four variables, then the second order partial correlation coefficients kept two variables constant. For partial correlation in four variables, six partial correlation coefficients of second order are; $r_{12.34}$, $r_{13.24}$, $r_{14.23}$, $r_{23.14}$, $r_{24.13}$ and $r_{34.12}$. The formula and the interpretation in harmony with this research are shown below;

1. Partial correlation of Statin and PCSK 9 Inhibitors keeping Fibrates and Nicotinic acid constant.

$$r_{12.34} = \frac{r_{12.4} - r_{13.4}r_{23.4}}{\sqrt{1-r_{13.4}^2}\sqrt{1-r_{23.4}^2}} \quad (20)$$

2. Partial correlation of Statin and Fibrates keeping PCSK 9 Inhibitors and Nicotinic acid constant.

$$r_{13.24} = \frac{r_{13.4} - r_{12.4}r_{23.4}}{\sqrt{1-r_{12.4}^2}\sqrt{1-r_{23.4}^2}} \quad (21)$$

3. Partial correlation of Statin and Nicotinic acid keeping PCSK 9 Inhibitors and Fibrates constant.

$$r_{14.23} = \frac{r_{14.3} - r_{12.3}r_{24.3}}{\sqrt{1-r_{12.3}^2}\sqrt{1-r_{24.3}^2}} \quad (22)$$

4. Partial correlation of PCSK 9 Inhibitors and Fibrates keeping Statin and Nicotinic acid constant.

$$r_{23.14} = \frac{r_{23.4} - r_{12.4}r_{13.4}}{\sqrt{1-r_{12.4}^2}\sqrt{1-r_{13.4}^2}} \quad (23)$$

5. Partial correlation of PCSK 9 Inhibitors and Nicotinic acid keeping Statin and Fibrates constant.

$$r_{24.13} = \frac{r_{24.3} - r_{12.3}r_{14.3}}{\sqrt{1-r_{12.3}^2}\sqrt{1-r_{14.3}^2}} \quad (24)$$

6. Partial correlation of Fibrates and Nicotinic acid keeping Statin and PCSK 9 Inhibitors constant.

$$r_{34.12} = \frac{r_{34.2} - r_{13.2}r_{14.2}}{\sqrt{1-r_{13.2}^2}\sqrt{1-r_{14.2}^2}} \quad (25)$$

Dissemination of Results

The results shall be analyzed and disseminated in each of the table and shall be made in harmony with the stated objectives, research questions and research hypotheses of the study

Multiple correlations analysis of different cholesterol-reducing drugs

Results

The data collected for different cholesterol-reducing drugs for the people taking the drugs are displayed in Table 1 below. The drugs are X_1 = Statin, X_2 = PCSK 9 Inhibitors, X_3 = Fibrates and X_4 = Nicotinic acid.

Table 1: Shows the data and its Computations

x_1	x_2	x_3	x_4	x_1^2	x_2^2	x_3^2	x_4^2	x_1x_2	x_1x_3	x_1x_4	x_2x_3	x_2x_4	x_3x_4
18	16	19	20	324	256	361	400	288	342	360	304	320	380
19	14	14	17	361	196	196	289	266	266	323	196	238	238
15	15	17	14	225	225	289	196	225	255	210	255	210	238
18	13	15	18	324	169	225	324	234	270	324	195	234	270
17	14	18	13	289	169	256	169	221	272	221	208	169	208
19	16	16	11	361	196	324	121	266	342	209	252	154	198
16	16	18	14	256	256	256	196	256	256	224	256	224	224
15	16	18	19	225	256	324	361	240	270	285	288	304	342
18	15	17	18	324	225	324	324	270	324	324	270	270	324
19	15	16	16	361	225	289	256	285	323	304	255	240	272
14	17	16	15	196	289	256	225	238	224	210	272	255	240
15	13	15	14	225	169	225	196	195	225	210	195	182	210
16	12	15	15	256	144	324	225	192	240	240	180	180	225
15	19	18	16	225	361	289	256	285	270	240	342	304	288
13	18	17	20	169	324	225	400	234	221	260	306	360	340
18	16	15	18	324	256	361	324	288	270	324	240	288	270
19	15	19	17	361	225	324	289	285	361	323	285	255	323
17	15	18	14	289	225	256	196	255	306	238	270	210	252
20	16	16	13	400	256	289	169	320	320	260	256	208	208
14	14	17	16	196	196	561	256	196	238	224	238	224	272
335	**302**	**334**	**318**	**5691**	**4618**	**5618**	**5172**	**5039**	**5595**	**5313**	**5063**	**4829**	**5322**

The results obtained for equation (4) – (9), (10) – (19) and (20) – (25) are shown in Table 2, Table 3 and Table 4 below;

Table 2: Simple correlation of zero order between combinations of two variables

Y_{12}	Y_{13}	Y_{14}	Y_{23}	Y_{24}	Y_{25}
0.0145	0.0132	0.0136	0.0133	0.0137	0.0135
1.45%	1.32%	1.36%	1.33%	1.37%	1.35%

Table 3: First-order partial correlation coefficients keeping one variable constant

$Y_{3.12}$	$Y_{4.12}$	$Y_{4.13}$	$Y_{2.14}$	$Y_{3.14}$	$Y_{4.23}$	$Y_{3.24}$	$Y_{2.31}$	$Y_{2.34}$
0.0144	0.0143	0.0130	0.0134	0.0134	0.0131	0.0135	0.0130	0.0133
1.44%	1.43%	1.30%	1.34%	1.34%	1.31%	1.35%	1.30%	1.33%

Table 4: Second-order partial correlation coefficients keeping two variables constant

Y32.12	Y24 .13	Y23 .14	Y14 .23	Y13 .24	Y12 .34
0.0141	0.0128	0.0132	0.0129	0.0133	0.0131
1.41%	1.28%	1.32%	1.29%	1.33%	1.31%

Table 5: ANOVA for different drugs

Model		Sum of Squares	Df	Mean Square	F	Sig.
1	Regression	238.862	4	59.715	4.355	.016b
	Residual	205.688	15	13.713		
	Total	444.550	19			

Discussion

Based on the analysis of the result above in Table 2, it shows that the drugs are positively correlated Discussion Based on the analysis of the result above in Table 2, it shows that the drugs are positively correlated. The effect of combining x_1 and x_2 is higher than every other combination of the drug intake, the result also revealed that the side effect of taking x_1 and x_3 is minimal compared to others. Table 3 indicates that taking x_1 and x_3 relaxing x_4 and taking x_3 and x_1 relaxing x_2 produces the same function in the body which is adequate in lowering cholesterol level in patients given the correlation between the activities of the drugs (Peters *et al*., 2007). In comparing table 2 and table 3, it shows that taking x_2 and x_3 gives the same result as taking x_3 and x_4, relaxing x_2. Also taking x_3 and x_4 is more or less like taking x_2 and x_4 relaxing x_3. The same result is replicated in Table 4 for the patient that takes x_2 and x_4, relaxing x_1 and x_3 at the same time. However, the partial correlation of x_1 and x_3 with others gives a better result, followed by x_2 and x_3, x_3 x_4, and x_2 x_4, and x_1 x_4 and x_1 x_2. Suggesting the presence of other etiological factors, significance changes was observed in patient's cholesterol level accordingly. (De-Cavalto *et al.,* 2008).

Conclusion

In consonance with the results, it shows that combining statin and PCSK inhibitor is the best cholesterol reducing drug, followed by PCSK inhibitor and nicotinic acid, statin and nicotinic acid, fibrates and nicotinic acid, PCSK inhibitor and fibrates, and statin. Although, these drugs are statistically significant, necessary caution needs to be taken. The intake of these drugs should also be guided by the physician for optimum results. Further experimental designed is recommended for PCSK9 inhibitors, satin, fibrate and nicotinic acid to correlate their effect in reducing cholesterol level.

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