# Impact of Gene Polymorphism of Lipoprotein Lipase on Atorvastatin Treatment Outcome in Ischemic Stroke Patient in Najaf Governorate

**Sarah Ali Abbas[1], Ahmed M. AlMudhafar[2], Thekra A. Al-Kashwan[3], Hayder K Hasson[4], Adhwaa Hameed Jaber[5], Najah R Hadi[6*]**


## ABSTRACT

**Background:** Stroke was commonly identified as a neurologically impairment that occur in central nervous system on vascular basis as Acute focal injury. Statin (HMG-CoA reductase Inhibitor), clinical trials in many large scaled shown that in primary and secondary CVD the used of statin was declined rates of (CV). Human Lipoprotein Lipase (LPL) gene coding was place in short arm of chromosome in the p22 region of the same Chromosome and has nine introns and ten axons. **Aim:** The aim of the study is to find out effect of LPL gene polymorphism of response to atorvastatin treatment in patients with ischemic stroke. **Patients and methods:** Samples was Picking up from patients' admission to at Middle Euphrates Center for Neurological Sciences in the main hospital for measurement of the lipid profile, molecular analysis study of genotyping and measurement of human lipoprotein lipase by ELISA technique. **Result:** There is good response to treatment and the response consider statistically significant, the best group response to treatment was homozygous mutation then Heterozygous mutation and the less group response was Homozygous normal, wild. **Conclusion:** The effect of drug on serum biomarker not affected by age except HDL (best result in age<60yr), and not affected by gender and weight state, while in consider to smoking and Hypertension TG (best response in non-smoker, hypertensive) and VLDL (best response in smoker, hypertensive) affected and in diabetic state the Cholesterol and TG affected on response (the best result in non-diabetic). Heterozygous mutation most distributed then homozygous normal and the less distributed was homozygous mutation.


**Key Words:** atorvastatin, gene polymorphism, LPL

**Sarah Ali Abbas[1], Ahmed M. AlMudhafar[2], Thekra A. Al-Kashwan[3], Hayder K Hasson[4], Adhwaa Hameed Jaber[5], Najah R Hadi[6*]**

*[1]Department of Pharmacology and Therapeutics, College of Medicine, University of Kufa, Iraq*
*[2]Department of Pharmacology and Therapeutics, College of Medicine, University of Kufa, Iraq*
*[3]Department of Biochemistry, College of Medicine, University of Kufa, Iraq*
*[4]Department of neurology, College of Medicine, University of Kufa, Iraq*
*[5]Department of Pharmacology and Therapeutics, College of Medicine, University of Kufa, Iraq*
*[6]Department of Pharmacology and Therapeutics, College of Medicine, University of Kufa, Iraq*

**Correspondence**

**Najah R Hadi**

Department of Pharmacology and Therapeutics, College of Medicine, University of Kufa, Iraq

E-mail: drnajahhadi@yahoo.com

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## INTRODUCTION

Stroke was commonly identified as a neurologically impairment that occur in central nervous system on vascular basis as Acute focal injury. Stroke subtype involves subarachnoid hemorrhage, ischemic stroke and cerebral infarction. Intra cerebral Hemorrhage **(Sacco et al. 2013)**. Stroke was major cause of death globally. The percentage of strokes generated by ischemia is 68%, whereas the Percentage of hemorrhagic strokes is 32% **(Krishnamurthi RV et al. 2010)**. A complete history is more helpful for identification the probable sources of Episode of neurological deficiency that looks associated with the transient ischemic attack. The history of patient may help in find the source and spread of focal cerebral ischemia but the accuracy of history is limited **(Bamford J et al. 2001)**. Statin (HMG-CoA reductase Inhibitor) clinical trials in many large scaled shown that in primary and secondary CVD the used of statin was declined rates of (CV) **(Brugts JJ et al. 2009, Mills EJ et al. 2008, and Baigent C et al. 2010)**. There are different response to treatment with approximately half not reach to objective of lipid decreasing **(Gitt et al. 2012)**. Patient Response to statin and relation to genotype is now poor known **(Schachter 2005)**. The databases of personal genetic will be development that Have advantages of taking drug, related to economic advantages in worldwide that decreasing mortality and morbidity from CVD **(NICE 2014)**. Human Lipoprotein Lipase gene coding was place in short arm of chromosome in the p22 region of the same Chromosome and has nine introns and ten axons **(Kobayashi J et al. 2015, Wang G et al. 2007)**. Lipoprotein Lipase in many tissues like skeletal, macrophage was secreted, manufactured in to interstitial space and was consider as glycoprotein **(Kobayashi J et al. 2015, Wang G et al. 2007, Goulbourne CN et al. 2014, and Gadek KE et al. 2018)**. Triglyceride hydrolysis and very low density

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Lipoprotein induced by lipoprotein lipase from chylomicron in blood will yield high density lipoprotein and cholesterol rich Lipoprotein residues. LPL gene located in 8p22 region around 30 kilo bases spanning and the gene contain 10 exon and 9 will code for 475 amino acids. The gene study discovers approximately 100 mutation and. SNP in the gene2 of lipoprotein Lipase that appear change in protein will influence growth of plaque of atherosclerosis and increase risk of stroke. Polymorphism of lipoprotein lipase can be dangerous or protective in stroke starting. Transition of thymine to guanine in Introns 8 in rs320 (8:19961566), and transition of cytosine to thymine in introns 6 in rs285 (8:19957678) will related to high Triglyceride and high density lipoprotein 3, 4 while transverse of cytosine to guanine in exon 9 is rs328 (8:19962213).will Consider as protective factor for stroke by increase proteolytic activity of protein decreasing triglyceride., and improving high Density lipoprotein **(Sepetiba RJ et al. 2007)**.

## PATIENTS AND METHODS

### Patients

Samples were picking up from patients' admission to at East Euphrates Center for Neurological Sciences in the main hospital (Al Sader Teaching Hospital-Najaf- Iraq) from December 2018 to September 2019. The research was involved 142 patient's admission at East Euphrates Center for Neurological Sciences in the main hospital. Every patient has complete history (name, age, sex, region, weight, date, telephone, number, other diseases, treatments blood pressure, and date of follow up.

### Methods

**A. Collection and processing of fresh blood specimens**

**B. Tests**

- **Measurement of the lipid profile**
  1. Measurement of complete fasting cholesterol (TC) concentrations
  2. Detection of fasting triglycerides (TG) levels
  3. Estimation of high-density lipoprotein cholesterol (HDL-C) levels
  4. Determination of LDL-cholesterol
  5. Determination of VLDL-cholesterol
- A Molecular Analysis Study of Genotyping
  1. Extraction of genomic DNA from whole blood.
  2. Measurement of DNA concentration, purifying and integrity
  3. Polymerase chain reaction–Restriction fragment length polymorphism
- Human Lipoprotein Lipase ELISA Kit

as death due to MI, heart failure or cardiac arrhythmia. We collected

## RESULT AND DISCUSSION

**Distribution of stoke case according to:**

A. Age: The age =>60yr consider most distribution
B. Gender: approximately equal
C. Weight state: BMI <25 consider most distribution among stroke patients
D. Smoking: non- smoker considers most distribution.
E. Diabetic Mellitus: non-diabetic most distribution.
F. Hypertension: hypertensive patients most distribution.

**Significance of serum biomarker after Atorvastatin treatment**

There are good response to treatment and the response consider statically significant Due to p-value of Cholesterol, TG, LDL, HDL and VLDL = 0.001 that consider highly significant.

**Significant to groups (20mg, 40mg) in serum biomarker after Atorvastatin treatment**

The different in response between two doses consider statically non-significant due to p-value of Cholesterol, TG, LDL, HDL and VLDL in two doses more than 0.05.

**Association between studied variables and group of the study and effect of Atorvastatin on Serum biomarkers according to Age, Gender, Weight status, smoking, D.M., HTN in two Groups (20mg, 40 mg) using ANCOVA test**

**Age:**

The effect of Atorvastatin on Cholesterol, Triglyceride, LDL and VLDL according to age consider neglected because p-value more than 0.05, except HDL due to p-value less than 0.05.

**Figure 1: Distribution of studied cases (68) case according to essential characteristics**

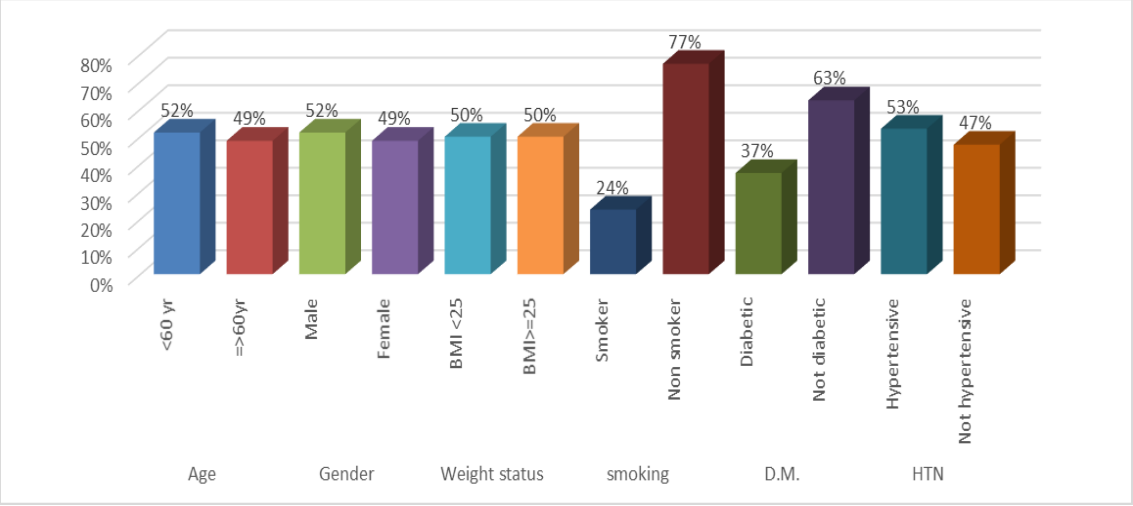

**Table 1: Significance of differences between Serum biomarkers following Atorvastatin (regardless the dose) using paired sample t-test**

| | | Mean | Std. Dev. | p-value |
|---|---|---|---|---|
| Cholesterol | Base line n=68 | 163.44 | 48.08 | 0.001 |
| | End line n=68 | 144.82 | 46.379 | |
| TG | Base line n=68 | 176.25 | 46.082 | 0.001 |
| | End line n=68 | 158.78 | 46.808 | |
| LDL | Base line n=68 | 93.98 | 41.846 | 0.001 |
| | End line n=68 | 81.4 | 36.005 | |
| HDL | Base line n=68 | 34.67 | 11.228 | 0.001 |
| | End line n=68 | 40.36 | 12.249 | |
| VLDL | Base line n=68 | 35.1 | 9.533 | 0.001 |
| | End line n=68 | 31.64 | 9.387 | |
| Concentration | Base line n=68 | 64.38 | 17.308 | 0.001 |
| | End line n=68 | 75.77 | 24.551 | |
| Optic density | Base line n=68 | 0.075 | 0.007 | 0.157 |
| | End line n=68 | 0.092 | 0.0999 | |

**Gender, Weight state:**
The effect of Atorvastatin on Cholesterol, Triglyceride, LDL, HDL and VLDL According to gender and weight state not affected due to P-value more than 0.05.

**Smoking, Hypertension:**
The effect of Atorvastatin on Cholesterol and LDL according to smoking and Hypertension not effected on result because p-value more than 0.05 except TG and VLDL p-value less than 0.05.

**Glycemic state:**
The effect of Atorvastatin on VLDL and LDL according to Glycemic state do not effect on response because p-value more than 0.05 except TG and Cholesterol p-value less than 0.05.

**Distribution of studied cases according to SNP**
Heterozygous mutation most distributed then homozygous normal and the less distributed was homozygous mutation.

**Association between SNP and some essential characteristics and effect of Atorvastatin dose on Serum biomarkers according to SNP using ANCOVA test**
Association between Heterozygous mutation, Homozygous mutation and Homozygous normal, wild and Gender, Weight Status, HTN, D.M. was non-statically significant due to p. value more than 0.05 and the effect of Atorvastatin on cholesterol, TG, LDL, HDL, and VLDL according to Heterozygous mutation, Homozygous mutation and Homozygous normal, wild was consider statically significant due to p value = 0.001. And the best group response to treatment was homozygous mutation then heterozygous mutation and the less group response was homozygous normal, wild.

**Table 3: Distribution of studied cases according to SNP**

| | Count | Column N % |
|---|---|---|
| Heterozygous mutation | 44 | 64.70% |
| Homozygous mutation | 9 | 13.20% |
| Homozygous normal, wild | 15 | 22.10% |

**Table 2: Significant in two groups (20mg, 40mg) in serum biomarker after Atorvastatin treatment**

| | | Estimated baseline | End line | | 95% CI | | 0.126 |
|---|---|---|---|---|---|---|---|
| | | | Mean | Std. Error | LB | UB | |
| Cholesterol | 20mg | 163.44 | 152.008 | 4.859 | 142.304 | 161.712 | 0.079 |
| | 40mg | | 137.639 | 4.859 | 127.935 | 147.343 | |
| Triglyceride | 20mg | 176.26 | 161.892 | 4.414 | 153.075 | 170.708 | 0.328 |
| | 40mg | | 155.682 | 4.414 | 146.866 | 164.498 | |
| LDL | 20mg | 83.99 | 78.871 | 3.031 | 72.816 | 84.925 | 0.308 |
| | 40mg | | 83.947 | 3.031 | 77.893 | 90.001 | |
| HDL | 20mg | 34.68 | 38.714 | 1.425 | 35.869 | 41.56 | 0.106 |
| | 40mg | | 42.021 | 1.425 | 39.175 | 44.866 | |
| VLDL | 20mg | 35.1 | 32.27 | 0.892 | 30.488 | 34.051 | 0.33 |
| | 40mg | | 31.019 | 0.892 | 29.237 | 32.8 | |
| Concentration | 20mg | 35.103 | 67.339 | 3.828 | 59.693 | 74.984 | 0.003 |
| | 40mg | | 84.212 | 3.828 | 76.566 | 91.858 | |
| Optic density | 20mg | 0.076 | 0.08 | 0.017 | 0.047 | 0.114 | 0.29 |
| | 40mg | | 0.106 | 0.017 | 0.072 | 0.139 | |

**Table 4: Association between SNP and some essential characteristics**

| | | SNP | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Heterozygous mutation | | Homozygous mutation | | Homozygous normal, wild | | |
| | | Count | Column N % | Count | Column N % | Count | Column N % | |
| Gender | Male | 22 | 50.0% | 5 | 55.6% | 8 | 53.3% | 0.942 |
| | Female | 22 | 50.0% | 4 | 44.4% | 7 | 46.7% | |
| Weight status | BMI <25 | 21 | 47.7% | 6 | 66.7% | 7 | 46.7% | 0.561 |
| | BMI>=25 | 23 | 52.3% | 3 | 33.3% | 8 | 53.3% | |
| HTN | Hypertensive | 22 | 50.0% | 7 | 77.8% | 7 | 46.7% | 0.270 |
| | Not hypertensive | 22 | 50.0% | 2 | 22.2% | 8 | 53.3% | |
| D.M. | Diabetic | 15 | 34.1% | 6 | 66.7% | 4 | 26.7% | 0.119 |
| | Not diabetic | 29 | 65.9% | 3 | 33.3% | 11 | 73.3% | |

## CONCLUSION

In our research,

- The stroke was most distributed in age more than 60 year, no-smoker, both genders, hypertensive and non-diabetic.
- There is good response to treatment and there are non-statically different in response between two doses (20mg, 40mg), so, prefer less dose to decrease side effect.
- The effect of drug on serum biomarker not affected by age except HDL (best result in age<60yr), and not affected by gender and weight state, while in consider to smoking and Hypertension TG (best response in non-smoker, hypertensive) and VLDL (best response in smoker, hypertensive) affected and in diabetic state the Cholesterol and TG affected on response (the best result in non-diabetic).
- Heterozygous mutation most distributed then homozygous normal and the less distributed was homozygous mutation.
- The best group response to treatment was homozygous mutation then heterozygous mutation and the less group response was homozygous normal, wild.

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