AUCTORES
Globalize your Research

Journal of Women Health Care and Issues
William E. Feeman *

Open Access

Research Article

Angiographic Changes Associated with Dyslipidemia Therapy

William E. Feeman Jr *

The Bowling Green Study Center, Bowling Green, Ohio, USA.

***Corresponding Author:** William E. Feeman Jr., The Bowling Green Study Center, Bowling Green, Ohio, USA.

Received date: April 21, 2023; Accepted date: May 10, 2023; Published date: May 17, 2023

Citation: William E. Feeman, (2023), Angiographic Changes Associated with Dyslipidemia Therapy, J. *Women Health Care and Issues.* 6(3); DOI:10.31579/2642-9756/150

Abstract

Background

Every pregnant woman faces risk of complications during pregnancy, birth, not only due to pregnancy, birth related problems but preexisting disorders which get exaggerated during pregnancy. Prepregnancy awareness of various prepregnancy, peripregnancy factors for safe maternity is essential.

Objective:

Community based study was to know awareness about prepregnancy issues for safe maternity.

Material methods

Study was conducted in tribal communities of remote forestry hilly region. Randomly from each village 20 married women of 15-40 yr in whom pregnancy was possible, 2400 became study subjects in 100 villages around village with health facility.

Results

Of 2400 study subjects, 1396 (58.2%) had scatchy awareness, 30.3% right age for pregnancy, 34.2% possibility of diseases running in family, 35.5% essentiality of knowing last menstruation date (LMD), 935 (35.10%) necessity of good health, 45.6% stress free life, 24.4% avoidance of heavy work and 30% need of care for good health during pregnancy. Only 1247 (52%) were aware of prepregnancy anaemia, (27% said it was due to lack of food, 73% lack of supplements), 51.7% knew about need of extra micronutrients, (41.7% by blood improving tablets, 58.3% extra energy providing diet), 1039 (43.3%) were aware of need of prepregnancy prevention / treatment, of anaemia for preventing complications, (34.6% giddiness, 29.4% legs swelling, nausea, 36.0% dangers of bleeding), 1164 (48.5%) were aware of genital hygiene, (38.0% said prevented genital infection, 62.0% urinary infection, retention).

Conclusion

Many women lacked awareness of appropriate interval, preexisting medical disorders, medication, environment, health care before / during pregnancy hygiene. Age, economic status, education, occupation opportunities of meeting others affected awareness.

Key words: prepregnancy awareness disorders; anaemia; micronutrients; hygiene; effects

Introduction

It is common parlance that it does not make a difference how one lowers low-density lipoprotein cholesterol (LDL-c), so long as LDL-c is brought down low enough. The purpose of this paper is to explore the relationship between LDL-c lowering and changes in angiograms in eight published angiographic regression trials.

Methods:

This author has in his physical possession the databases of eight published angiographic regression trials: the Program on the Surgical Control of the Hyperlipidemias (POSCH) (1), National Heart Lung and Blood Institute Type II Coronary Intervention Study (NHLBI) (2), Saint Thomas Atherosclerosis Regression Study (STARS) (3), Familial Athrosclerosis Treatment Study (FATS) (4), Lipoprotein and Coronary Atherosclerosis Study (LCAS) (5), Pravastatin to Limit Atherosclerosis in the Coronary Arteries (PLAC-I) (6), the Regular Physical Exercise and Low Fat Diet study (Heidelberg study) (7), and the Lopid Coronary Angiography Trial (LOPID) (8).With the exception of STARS, all trials have associated lipid and systolic blood pressure data. (In the case of STARS, full lipid data is not available because this author did not request such data.) End-of-trial (EOT) lipid data was examined in terms of the final angiographic changes, and such findings are the subject of this manuscript.

Results:

First, a caveat. All of these studies were performed prior to the beginning of the 21st century, when the standard methodology for measuring high-density lipoprotein cholesterol (HDL-c) was the precipitation method. At least in Wood County, Ohio, in May of 1999, the methodology was changed to the enzymatic method. These differing methodologies do not give the same

values for HDL-c, the newer (enzymatic) methodology giving a result on the order of 10 mg/dl (0.25 mmoles/L) higher than the result that would have been obtained, had the precipitation method been used. This is important because LDL-c is not generally measured, but rather calculated by the Friedewald formula: LDL-c= CT---HDL-c – TG/5, where CT means total cholesterol and TG means triglycerides. (9) Since the HDL-c values are on the order of 10 mg/dl (0.25 mmoles/L) when the enzymatic method is used, the calculated LDL-c levels will be appropriately on the order of 10 mg/dl (0.25 mmoles/L) lower. This needs to be considered in interpreting the data reported here. This finding is not trivial. The author has reported the case of a patient who suffered an acute myocardial infarction in the absence of any risk factors for atherothrombotic disease—albeit his lipid had not been measured. The patients myocardial infarction occurred while he was in another town and lipids measured at the time of the event were mildly abnormal when measured by the enzymatic method, but much more abnormal when converted to their precipitation method equivalent. When the lipids were converted to their precipitation method equivalent, the prediction was that his event would occur in the sixth decade of life, and he was 53 at the time of his event. [10]

Table I show the distributions of EOT LDL-c in seven angiographic regression trials. (STARS data is not included due the fact that the author only requested a ratio between LDL-c and HDL-c, as explained earlier.) In most of the trials, LDL-c and angiographic plaque progression fall in tandem. This is best seen in POSCH, NHLBI, FATS, and to a lesser extent in LCAS and LOCAT. POSCH utilized the partial ileal bypass surgery as its treatment moiety; NHLBI utilized cholestyramine; FATS utilized a basic treatment of colestipol, combined with either a niacin arm or a lovastatin arm; LCAS utilized fluvastatin, with addition of cholestyramine if the baseline LDL-c exceeded 160 mg/dl after initial dietary therapy; and LOCAT utilized gemfibrozil. PLAC-1, on the other hand, utilized pragvastatin, while Heidelberg was a diet/exercise study.

Trial	Angiographic Outcome	≥ 200	175-199	150-174	125-149	100-124	≤ 99
POSCH	Progression	26	45	51	27	12	2
	Non Progression	15	27	82	83	94	267
	Σ	41	72	133	110	106	269
	% Progression	63%	63%	38%	25%	11%	1%
NHLBI	Progression	16	1	4	0	0	0
	Non Progression	37	10	9	4	7	2
	Σ	53	11	13	4	7	2
	% Progression	30%	9%	31%	0%	0%	0%
FATS	Progression	5	5	7	7	9	5
	Non Progression	7	10	8	12	18	27
	Σ	12	15	15	19	27	32
	% Progression	42%	33%	47%	37%	33%	16%
LCAS	Progression	1	6	14	32	39	21
	Non Progression	2	12	25	54	72	55
	Σ	3	18	39	86	111	76
	% Progression	33%	33%	36%	37%	35%	27%
PLAC-1	Progression	7	21	38	29	31	13
	Non Progression	9	15	32	55	53	17
	Σ	16	36	70	84	84	30
	% Progression	44%	58%	54%	35%	37%	43%
Heidelburg	Progression	6	7	8	6	2	2
	Non Progression	6	16	16	10	9	1
	Σ	12	23	24	16	11	3
	% Progression	50%	30%	33%	38%	18%	67%
LOCAT	Progression	10	22	63	77	38	17
	Non Progression	1	8	29	50	35	21
	Σ	11	30	92	127	73	38
	% Progression	91%	73%	68%	61%	52%	45%

Table I: End of Trial LDL-C

POSCH Means Program on the Surgical Control of the Hyperlipidemias

NHLBI Means National Heart Lung and Blood Institute

FATS Means Familial atherosclerosis Treatment Study

LCAS Means Lipoprotein and Coronary Atherosclerosis Study

PLAC-1 Means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries

Heidelburg Means Study on The Effects of Regular Physical Exercise and Low-Fat Diet on the Progression of Coronary Artery Disease

LOCAT Means Lopid Coronary Angiography Trial

Table II shows the proportion of trials with EOT LDL-c of 99 mg/dl (2.5 mmoles/L) or less. There is clearly an imbalance in the trials, with POSCH achieving the most patients at this goal, followed by FATS and LCAS. NHLBI does not have many patients at this level, but then start of trial LDL-c levels were very high and with only cholestyramine as the treatment moiety, very low levels of LDL-c were very hard to achieve. LOCAT

utilized gemfibrozil, which is not indicated in pure hypercholesterolemia but finds its best use in patients with low HDL-c and high TG. [11]

It is clear from **Table I** that at any given level of EOT LDL-c, the rate of plaque progression differs in the various studies. Thjs implies that since the EOT LDL-c levels are the same, then the difference if plaque progression levels may be due to the means by which LDL-c was lowered.

Trial	No Patients with LDL-C < 99	Total Patients	% Of Total
POSCH	269	731	37%
NHLBI	2	90	2%
FATS	32	120	27%
LCAS	76	333	23%
PLAC-1	30	320	9%
Heidelburg	3	89	3%
LOCAT	37	371	10%

Table II: End of Trial LDL-C

POSCH Means Program on the Surgical Control of the Hyperlipidemias

NHLBI Means National Heart Lung and Blood Institute

FATS Means Familial atherosclerosis Treatment Study

LCAS Means Lipoprotein and Coronary Atherosclerosis Study

PLAC-1 Means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries

Heidelburg Means Study on The Effects of Regular Physical Exercise and Low-Fat Diet on the Progression of Coronary Artery Disease

LOCAT Means Lopid Coronary Angiography Trial

Table III does a similar analysis, but this time examining only those trials with LDL-c of 99 mg/dl (2.5 mmoles/L). Again, as LDL-c decreases, the rate of plaque progression decreases and even at very low levels of EOT LDL-c, there is a difference in plaque progression rates in the various trials. Unfortunately, the plaque progression rates with so few patients makes analysis difficult. However, one can analyze the Table III data in terms of cumulative decline in LDL-c and plaque progression rates. This is done in Table IV. In Table IV, POSCH has a low overall plaque progression rate and this does not improve as LDL-c levels continue to decline and NHLBI has no plaque progression, though patient numbers in this group are very small. In FATS, the plaque progression rate is low below the 80 mg/dl level and is null below the 70 mg/dl level, though again numbers are small. In LCAS and LOCAT plaque progression rated do not reach the null level until LDL-c levels drop below the 60 mg/dl level. In pLAC-1 null rates of plaque progression are never achieved.

Trial	Angiographic Outcome	90-99	80-89	70-79	60-69	50-59	40-49	< 39
POSCH	**Progression**	0	0	0	0	1	0	1
	Non Progression	73	69	60	31	16	4	14
	∑	73	69	60	31	17	4	15
	% Progression	0%	0%	0%	0%	6%	0%	7%
NHLBI	**Progression**	0			0			
	Non Progression	1			1			
	∑	1			1			
	% Progression	0%			0%			
FATS	**Progression**	1	3	1	0	0		
	Non Progression	8	9	6	2	2		
	∑	9	12	7	2	2		
	% Progression	11%	25%	14%	0%	0%		
LCAS	**Progression**	9	9	1	2	0		
	Non Progression	20	20	10	4	1		
	∑	29	29	11	6	1		
	% Progression	31%	31%	9%	33%	0%		
PLAC-1	**Progression**	8	2	2	0	1		
	Non Progression	10	5	1	1	0		
	∑	18	7	3	1	1		
	% Progression	44%	29%	67%	0%	100%		
Heidelburg	**Progression**	2						
	Non Progression	1						
	∑	3						
	% Progression	67%						
LOCAT	**Progression**	9	5	2	1	0		
	Non Progression	7	6	3	2	3		
	∑	16	11	5	3	3		
	% Progression	56%	45%	40%	33%	0%		

Table III: End of Trial LDL-C

POSCH Means Program on the Surgical Control of the Hyperlipidemias
NHLBI Means National Heart Lung and Blood Institute
FATS Means Familial atherosclerosis Treatment Study
LCAS Means Lipoprotein and Coronary Atherosclerosis Study
PLAC-1 Means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries
Heidelburg Means Study on The Effects of Regular Physical Exercise and Low-Fat Diet on the Progression of Coronary Artery Disease
LOCAT Means Lopid Coronary Angiography Trial

Discussion

There can be no doubt about the link between dyslipidemai and ATD. The author has shown that, at least in primary prevention, the population at risk of ATD can be predicted by analysis of the risk factor milieu. (12) Unfortunately, studies in secondary prevention tend to treat ATD risk factors as independent agents. The author has previously shown that there appears to be a lower limit of LDL-c, below which plaque progression rates to not improve. [13] This paper builds on that analysis.

In the 1980's and 1990's, serial angiograms were the method mainly used in randomized controlled clinical trials to assess the outcomes of lipid lowering therapy on ATD. Such trials were easier to do and did not take as much time as clinical event outcomes trials and were less subject to interpretation. The angiographic trials described in this paper are examples of those trials. Angiographic non-progression was associated with fewer future ATD events. (14-16)

The current mantra is "Lower is better." However, as William E.Conner,MD, pointed out, one does not treat a factor, such as cholesterol, to achieve a given number, but rather to prevent disease. (Medical World News, mid-1970's) The purpose of this paper is to show the level of LDL-c lowering that achieves that goal.

Table IV shows that at LDL-c levels below 80 mg/dl (precipitation method of HDL-c measurement, but 70 mg/dl if the enzymatic method is utilized), plaque progression rates are virtually constant at 7%. However, this is an overall rate and the individual studies have different individual rates. There is no level of LDL-c in the overall analysis that guarantees a null rate of plaque progression. On the other hand, not all plaque progression is due to the atherosclerotic process. Specifically, plaques can appear to progress if there is an intra-plaque hemorrhage or plaque erosion with thrombus formation and can appear to regress as the intra-plaque hemorrhage resolves or the thrombus lyses. Given this qualifier, the question becomes a consensus of what level of plaque progression one is willing to accept--given that some plaque progression may be a false positive result.

Trial	≤ 99	≤ 89	≤ 79	≤ 69	≤ 59	≤ 49	≤ 39
POSCH	2 269 2%	2 196 1%	2 127 2%	2 67 3%	2 36 6%	1 19 5%	1 15 7%
NHLBI	0 2 0%	0 1 0%	0 1 0%	0 1 0%			
FATS	5 32 16%	4 23 17%	1 11 9%	0 4 0%	0 2 0%		
LCAS	21 76 27%	12 47 26%	3 18 17%	2 7 29%	0 1 0%		
PLAC-1	13 30 43%	5 12 42%	3 5 60%	1 2 50%	1 1 100%		
Heidelburg	2 3 67%						
LOCAT	17 38 45%	8 22 36%	3 11 27%	1 6 17%	0 3 0%		
∑	60 450 13%	31 301 10%	12 173 7%	6 87 7%	3 43 7%	1 19 5%	1 15 7%

Table IV: Plaque Progression with Respect to End of Trial LDL-c

POSCH Means Program on the Surgical Control of the Hyperlipidemias
NHLBI Means National Heart Lung and Blood Institute
FATS Means Familial atherosclerosis Treatment Study
LCAS Means Lipoprotein and Coronary Atherosclerosis Study
PLAC-1 Means Pravastatin Limitation of Atherosclerosis in the Coronary Arteries
Heidelburg Means Study on The Effects of Regular Physical Exercise and Low-Fat Diet on the Progression of Coronary Artery Disease
LOCAT Means Lopid Coronary Angiography Trial

Furthermore, plaque progression rates in POSCH and NHLBI are lower than in FATS and considerably lower than in LCAS, PLAC-1, Heidelberg, and LOCAT. (See Table IV.) This is true even when the LDL-c levels in each trial are in the same cohort. This in turn suggests that it may make a difference how one lowers LDL-c. Or it could suggest that the method of lowering LDL-c may affect the great modifier of LDL-c atherogenicity--i.e., HDL-c. The best angiographic results are obtained with treatments that affect the metabolism of cholesterol in the gut. POSCH utilized the partial ileal bypass technique to limit cholesterol absorption from the gut, thus limiting the amount of cholesterol absorbed, but perhaps also limiting the metabolism of cholesterol in the gut. In a similar manner, NHLBI used cholestyramine to bind gut cholesterol, thus not making cholesterol available for microbial metabolism. FATS had the next best results and utilized colestipol (another resin), with a lovastatin and a niacin arm. Following FATS with respect to angiographic plaque progression was LCAS, which utilized fluvastatin, though 25% of LCAS patients were also taking cholestyramine. PLAC-1, Heidelberg, and LOCAT did not use any treatments that would affect gut microbial function.

Hazen has shown that when choline and/or carnitine is metabolized by the gut microbiome, multiple metabolites are generated, one of which is trimethylalanine (TMA) which is taken into the body and transported to the liver, where it is oxidized by flavin monooxygenase 3 (FMO3) to form trimethylalanine-N-oxide (TMAO). (13) TMAO in turn blunts reverse cholesterol transport but without significant change to LDL-c or HDL-c. (14) This is associated with increased amounts of large particle HDL-c. (15) None of this is possible without an intact gut microbiome. (15) The precise mechanism by which TMAO enhances atherogenesis is speculative but is consistent with the following scenario: Dietary cholesterol, accompanied by phosphatidylcholine and carnitine, enters the gut where it is absorbed in the distal ileum. Cholesterol is absorbed into the body in the distal ileum, as are presumably phosphatidylcholine and carnitine, but before these latter two compounds are absorbed, they are metabolized to TMA by the gut microbiome. Cholesterol is carried to the liver and metabolized in the well known manner. TMA is also carried to the liver, where FMO3 converts phosphatidylcholine (now reduced to just choline) and carnitine to TAMO. TAMO then blocks reverse cholesterol mediated by HDL particles, perhaps by preventing their off-loading lipid to the hepatocytes via the sterol regulatory element binding protein mechanism. This could result in large cholesterol particles, though not large enough to raise HDL-c levels, but large enough to distort the apo A-1 lipoprotein moiety, making it less effective in removing cholesterol from arterial wall cells, thus allowing plaques to increase in size (plaque progression).

If this scenario is correct, the partial ileal bypass procedure works because it prevents absorption of cholesterol in the distal ileum and this leads to lower LDL-c levels in the blood. No data is available as to the eff3ect of a partial ileal bypass on the absorption of TMA, but if phosphatidylcholine and carnitine are diverted away form the gut microbiome of the distal ileum, production of TMA should be decreased and hence production of TMAO should be decreased. This would allow the HDL particle to participate fully in reverse cholesterol transport. Thus POSCH could support the Lipid Regulatory Hypothesis of Esko Nikkila, MD, (cited in the Helsinki Heart Study(16), which states that plaque regression is best achieved by raising HDL-c while simultaneously lowering LDL-c. This could explain why the Cholesterol Retention Fraction (CRF, defined as [LDL-c minus HDL-c]/LDL-c) perfectly predicted plaque outcome in 731 patients in POSCH. Specifically, if the CRF rose, even minutely at one year, then the angiogram at three years always showed plaque progression and if the CRF fell, even minutely, at one year, the angiogram always showed plaque non-progression. Moreover, in the author's experience, HDL-c is able to compensate for LDL-c until LDL-c levels exceed 170 mg/dl (4.4 mmoles/L) and in POSCH, the rate of plaque progression began to fall once EOT LDL-c levels of 174 mg/dl (4.4 mmoles/L) were achieved**. (See Table I.)**

NHLBI, and to a lesser extent FATS and LCAS, utilize bile acid sequestrants, which bind cholesterol and could conceivably bind phosphatidylcholeine and carnitine, thus making these compounds less available to the gut microbiome, with less TMA being produced in the gut. This would lead to less TMAO being generated in the liver via FMO 3. The other trials did not use agents that interfered with the access of the gut microbiome and showed more plaque progression, possibly because of increased levels of TMAO. This in turn could explain the "failure" of other trials that raised HDL-c but failed to lower subsequent ATD results. Finally, a recent study by Sakuma showed that, at least in the REAL-CAD data, there appeared to be an optimal target goal of LDL-c lowering achieved at 70 mg/dl (enzymatic method, but 80 mg/dl precipitation method equivalent). (20) This finding supports the current paper and its earlier results. (13)

Conclusions

Analysis of the seven angiographic regression trials reveals that the method by which one lowers LDL-c may make a difference in terms of plaque progression. One must account for the gut microbiota to achieve optimal results. There does not appear to be an LDL-c level achieved that guarantees no plaque progression.

References:

1. Buchwald H., Varco RL., Matts JP., et aI (1990). Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. Report of the Program on the Surgical Control of the Hyperlipidemias (POSCH). N Engl J Med;323:946-955.
2. Brensike JF., Levy RJ., Kelsey SF., Passamani ER., Richardson JM, Loh IK., et al (1984). Effects of Therapy with Cholestyramine on Progression of Coronary Arteriosclerosis: Results of the NHLBI Type II Coronary Intervention Study. Circulation.; 69: 313-324.
3. Brown G., Albers JJ., Fisher L., Schaefer SM., Lin JT., Kaplan C., et al (1990). Regression of Coronary Artery Disease as a Result of Intensive Lipid Lowering Therapy in Men With High Levels of Apolipoprotein B. N Engl J Med.323: 1289-1298.
4. Herd JA., Ballantyne CM., Farmer JA., Ferguson JJ., Hones PH., West S., et al. (1997) Effects of Fluvastatin on Coronary Atherosclerosis in Patients With Mid to Moderate Cholesterol Elevations (Lipoprotein and Coronary Atherosclerosis Study {LCAS}). Am J Cardiol. ; 80: 278-286.
5. Pitt B., Mancini GB., Ellis SG., Rosman HS., Park JS., McGovern ME., et al. (1995) Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I): Reduction in Atherosclerosis Progression and clinical Events. J Am Coll Cardiol. 26: 1133-1139.
6. Schuler G., Hambrecht R., Schlierf G., Niebauer J., Hauer K, Neumann J., et al. (1992) Regular Physical Exercise and Low-Fat Diet. Effects on Progression of Coronary Artery Disease. Circulation.86: 1-11.
7. Frick M., Syvanne M., Nieminen MS., (1997) Prevention of the angiographic progression of coronary and vein-graft atherosclerosis by Gemfibrozil after coronary bypass surgery in men with low levels of HDL cholesterol. Circulation ;96:2137-2143.
8. Watts GF., Lewis B., Brunt JNH., Lewis ES., Coltari DJ., Smith LDR.,(1992) et al. Effects on Coronary Artery Disease of Lipid Lowering Diet, or Diet Plus Cholestyramine in the St. Thomas Atherosclerosis Regression Study (STARS). Lancet; 339:563-569.
9. Friedewald WT., Levy RI., Fredrickson DS. (1972). Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. Clinical Chemistry. 18(6): 499-502.

10. Feeman Jr WE., (2008) .,Effect of HDL Measurement Technique on Prediction of Atherothrombotic Disease.. Journal of Clinical Lipidology.2;(5); 401-402.
11. Manninen V., Tenkanen L., Koshinen P., Huttunen JK., Manttari M., Heinonen OP., Frick MN. Joint Effects of Serum Triglyceride and LDL Cholesterol and HDL Cholesterol Concentrations on Coronary Heart Disease Risk in the Helsinki Heart Study. Implications for Treatment. Circulation. 1992; 85:37-45.
12. Feeman Jr WE.,(2020)Enhanced Prediction of the Population at Risk of Atherothrombotic Disease: Back to Framingham.EC Cardiology 7.3: 01-19.
13. Feeman Jr WE., (2013).LDL lowering: Evidence for a Plaque Non-Progression Threshold. Int J Cardiovasc Res.; 2: 5.
14. Buchwald H., Matts JP., Fitch LL., Campos CT., Sanmarcos ME., Amplatz K., et al. (1992).Changes in Sequential Coronary Arteriograms and Subsequent Coronary Event. JAMA.; 268: 1429-1433.
15. Gotto AM., (1995).Lipid Lowering, Regression, and Coronary Events. A Review of the Interdisciplinary Council on Lipids and Cardiovascular Risk Intervention, Seventh Council Meeting. Circulation. 92: 646-656.
16. Rossouw JE., (1995) Lipid-Lowering Interventions in Angiographic Trials. Am J Cardiol.; 76: 86C-92C.
17. Koeth RA., Wang Z., Levison BS., Buffa JA, Org E., Sheehy BT., et al. (2013) Intestinal Microbiota Metabolism of L-Catnitine, a Nutrient in Red Meat, Promotes Atherosclerosis. Nature Medicine. 19: 1-40. (published online)
18. Tang WHW., Wang Z., Levison BS., Koeth RA., Britt EB., Fu Xiaming., Wu Y., Hazen SL.,(2013) Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk. N Eng J Med. 368: 1575-1584.
19. Warrier M., Shih DM., Ferguson D., Gromovsky AD., Brown AL., et al. (2015) The TMAO-Generating Enzyme Flavin Monooxygenase 3 Is a Central Regulator of Cholesterol Balance. Cell Reports. 10: 1-13.
20. Helsinki: Frick MH., Elo O., Haapa K, Heinonen OP., Heinsalmi ,et al. (1987) Helsinki Heart Study: Primary-Prevention Trial with Gemfibrozil in Middle-Aged Men With Dyslipidemia. N Engl J Med.317: 1237-1245.
21. Sakuma M., Iimuro S., Shinozaki T., Kimura T., Nagawa Y., Ozaki Y., et al. (2022) Optimal Target of LDL Cholesterol Level for Statin Treatment: Challenges to Monotonic Relationship with Cardiovascular Events. BMC Medicine.20: 441-454

DOI:10.31579/2642-9756/150