Venipuncture Rate of Liver Function Tests for Patients being Treatment with Statin in Clinical Practice: A Therapeutic Dilemma

Teetouch Ananwattanasuk MD*,**, Chirawat Chiewchalermsri MD**,
Pattama Tongdee MD***, Porntip Nimkuntod MD****

** Department of Internal Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand*
*** Department of Internal Medicine, Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University, Nonthaburi, Thailand*
**** School of Obstetrics and Gynecology, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima, Thailand*
***** School of Internal Medicine, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima, Thailand*

Background: *Statin or 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors are hypolipidemic agent. Its main functionality is to reduce cholesterol. The low-density lipoprotein cholesterol is the major cause of myocardial infarction. The adverse effect of this medication is hepatotoxicity. Doctors always request patient on statin treatment to obtain blood by venipuncture for liver function tests (LFTs) frequently. There are no researches studying the rate and expenditure of venipuncture for LFTs in patients being treated with statin.*
Objective: *To study unnecessary rate on venipuncture for LFTs in patients being treatment with statin at an outpatient clinic.*
Material and Method: *Retrospective cohort study. Data are collected from medical records that being treatment with statin at an outpatient clinic, Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University between March 1, 2012 and March 1, 2014. The 441 patients are divided into two groups. The first group is treated with the appropriate venipuncture for LFTs and the second group is treated with unnecessary venipuncture for LFTs. The expenditure for both groups are used to calculate and compare costs.*
Results: *The number of unnecessary venipuncture in the LFTs group is 308 samples (69.84%). The sample proportions are 85.06% come from staff (262 samples) and 14.94% come from interns (46 samples). The number of appropriate venipuncture for LFTs is 133 samples (30.16%). The sample proportions are 77.44% come from staff (103 samples) and 22.56% come from interns (30 samples). The expenditure of the unnecessary venipuncture for LFTs had a statistically significant difference from the appropriate venipuncture for LFTs [75,500 vs. 4,400 baht (THB)] ($p<0.05$).*
Conclusion: *The expenditure for the unnecessary venipuncture LFTs in patient being treated with statin at the outpatient clinic is statistically higher than the appropriate venipuncture ($p<0.05$).*

Keywords*: Statins, Liver function test, United States Food and Drug Administration*

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Coronary heart disease (CHD), the result of coronary atherosclerosis is the leading cause of morbidity and mortality worldwide[1, 2]. Lowering low-density lipoprotein cholesterol (LDL-C) levels has been shown unequivocally to reduce cardiovascular events and prevent the development of atherosclerosis[3-10]. The beneficial role of statins and lowering LDL-C in primary and secondary prevention of coronary heart disease has resulted in their frequent use in clinical practice. The patient safety concerns, especially regarding hepatotoxicity, have driven multiple trials in difference criteria in statin use[11-14], which have demonstrated a low incidence of statin-related hepatic adverse effects. The most commonly reported hepatic adverse effect is liver toxicity as transaminitis, in the absence of proven hepatotoxicity by liver biopsy. This class effect is usually asymptomatic, reversible, and dose-related. High cardiovascular risk patients whose elevated aminotransferase levels after statin use have no clinical relevance or known stable chronic liver conditions in previous history[15].

Criterion defines the incidence of drug-related

Correspondence to:
Nimkuntod P, 111 School of Internal Medicine, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima 30000, Thailand.
Phone: +66-81-7906061
E-mail: porntipnimk@sut.ac.th

liver test abnormalities with an elevation of the alanine aminotransferase (ALT) level of more than three times the upper limit of normal in combination with elevated total bilirubin levels (>2 times the upper limit of normal) at any time after starting a new drug. In 2008, The National Institute for Health and Care Excellence (NICE)[6] suggested venipuncture for liver function test (LFT) before starting statins and then 3 and 12 months after starting statins. Recently, the United States Food and Drug Administration (USFDA) in 2012[16] suggested work-up LFTs before starting statins and in patients using statins with anorexia, unknown causes of weakness, fatigue, upper abdomen abdominal pain, jaundice, and dark urine color symptoms. For other conditions, venipuncture for LFTs are unnecessary and an inappropriate expenditure. There is no research that studied the suitable rate of venipuncture for LFTs in participants that being treated with statins and no research that studied the expenditure of venipuncture for LFTs in participants that being treated with statins before.

We decided to study the unnecessary venipuncture rate on LFTs in patients being treated with statins at the outpatient clinic. It will be beneficial to decrease any unnecessary venipuncture for LFTs in patients being treated with statins as well as decrease inappropriate expenditures. The study will serve as reference for other Thailand hospitals in the future.

Material and Method

Study population

The study design is retrospective cohort study. Samples are from the medicine outpatient clinic of Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University. Data are collected from dyslipidemia patient files that are being treatment with statin at the medicine outpatient clinic, Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University between March 1, 2012 and March 1, 2014. All participants treated with statin ages equal to or greater than 18 years old underwent a complete cardiovascular evaluation. The study also excluded patients with 1) prior liver diseases such as hepatitis, cirrhosis, hepatocellular carcinoma 2) abnormal liver enzymes before treatment with statin and 3) chronic diseases such as cancers, end-stage renal disease. The sample size is 441.

Study protocol

Data are collected from medical records of patients being treated with statin at the medicine outpatient clinic, Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University between March 1, 2012 and March 1, 2014. The 441 samples are divided into two groups, the first group is treated with appropriate venipuncture for LFTs (before treatment and when patient has fatigue, anorexia, abdominal pain, dark urine, or jaundice) and the second group is treated with unnecessary venipuncture on LFTs as referenced from USFDA. A protocol for discontinuing/continuing/changing statins based on the severity of signs and symptoms.

Definition of terms

Appropriate monitor LFT is defined as venipuncture for LFTs in patient using statins is first, before using statins, and secondly, when patient is fatigue, anorexia, abdominal pain, dark urine, or jaundice according to USFDA recommendation.

Overuse is defined as an unsuitable monitor and work-up venipuncture for LFTs according to USFDA recommendation.

Staff is defined as the physicians who are members of the Panyananthaphikkhu Chonprathan Medical Center staff and are regularly attending their patients at this medical center.

Interns are defined as the physicians who have recently graduated from medical school and are learning the medical practice under supervision at the Panyananthaphikkhu Chonprathan Medical Center.

Statistical analysis

Statistical analyses were performed and continuous variables of the subjects at baseline were expressed as mean and standard deviation (SD) or median. Both suitable and unsuitable venipuncture for LFT group expenditures are also calculated and compared by independent t-test. All reported *p*-values were 2-tailed, and $p<0.05$ was considered statistically significant.

Results

There were 441 samples in the study, separated into 272 females (61.7%) and 169 males (38.3%). The average age is 62.8$\pm$12.6 years old. The range of age is 18 to 91 years old. The average body weight is 63.5$\pm$12.8 kilograms. The average duration of statin treatment is 52.4$\pm$37.4 months. Types of statin are Simvastatin 346 (78.5%), Atorvastatin 89 (20.2%), and Rosuvastatin 6 (1.4%). The underlying diseases of the study population are hypertension 375 (85%), diabetes mellitus 213 (48.3%), coronary artery

Table 1. Baseline characteristics of the study population (n = 441)

Baseline characteristics (n = 441)	Mean ± SD or %
Age (years)	62.8±12.6 (18-91)
Male/female (%)	169 (38.3%)/272 (61.7%)
Body weight	63.5±12.8 (33-103)
Duration of statin use (months)	52.4±37.4 (1-216)
Study groups	
Staff use	365 (82.8%)
Intern use	76 (17.2%)
Types of statins	
Simvastatin	346 (78.5%)
Atorvastatin	89 (20.2%)
Rosuvastatin	6 (1.4%)
Underlying diseases	
Diabetes mellitus	213 (48.3%)
Hypertention	375 (85%)
Coronary artery disease	51 (11.6%)
Chronic kidney disease	40 (9.1%)
Cerebrovascular disease	38 (8.6%)

disease 51 (11.6%), chronic kidney disease 40 (9.1%), and cerebrovascular disease 38 (8.6%). The study populations (group) of 362 staff (82.8%) and 76 interns (17.2%) are examined in Table 1.

The number of unnecessary venipuncture in the LFT group is 308 samples (69.84%). The sample proportions are 85.06% from the staff (262 samples) and 14.94% from the interns (46 samples). The number of suitable venipuncture in the LFT group is 133 samples (30.16%). The sample proportions are 77.44% from the staff (103 samples) and 22.56% from the interns (30 samples). The expenditure for unnecessary venipuncture on LFT is around 75,500 baht (THB) compared with 4,400 baht (THB) for the suitable venipuncture on LFTs. They are statistically significant ($p < 0.05$).

Furthermore, we analyzed the data in the unnecessary venipuncture for LFT group. We found that the percentage of unnecessary venipuncture for LFTs among the staff is 71.77% and among the interns is 60.53% with no statistical significant difference ($p = 0.54$) as shown in Fig. 1. We also analyzed the data in the suitable venipuncture for LFT group. We found that percentage of suitable venipuncture for LFTs among the staff is 28.22% and among the interns is 39.47% with no statistical significant difference ($p = 0.98$) as shown in Fig. 2.

The expenditure for LFTs [ALT, aspartate aminotransferase (AST), and alkaline phosphatase (ALP)] is 50 THB per one examinee. All unsuitable

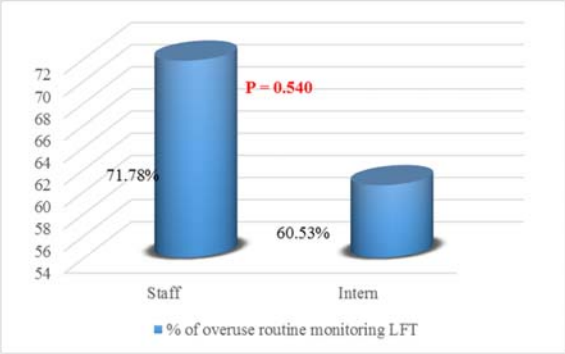

Fig. 1 Percentage of overuse routine monitoring LFT.

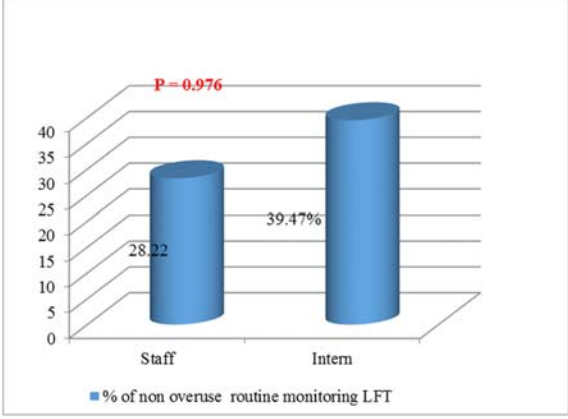

Fig. 2 Percentage of non-overuse routine monitoring LFT.

Table 2. Comparison between overuse of LFT group and non-overuse of LFT group

Data	Overuse of LFT (n = 308)	Non-overuse of LFT (n = 133)	*p*-value
Over rate of LFT	275.89±222.63	31.20±31.20	<0.05*

expenses of venipuncture for LFTs in patients being treated with statin is 75,500 THB. Unsuitable expenses of venipuncture for LFTs in patient being treated with statin are divided into ALT, AST, and ALP. These are 37,750 THB, 28,550 THB, and 9,200 THB, respectively. All suitable expenses of venipuncture for the LFT group in patients being treated with statin is 4,400 THB. Suitable expenses of venipuncture for the LFT group in patients being treated with statin are divided into ALT, AST, and ALP. These are 1,800 THB, 2,050 THB, and 550 THB, respectively. From statistical analysis, we found that the unsuitable expenses of venipuncture for LFTs in patients being treated with statin is more than the suitable expenses of venipuncture for the LFT group in patients being treated with statin with a statistically significant difference (p<0.05) (Table 2 and Fig. 3).

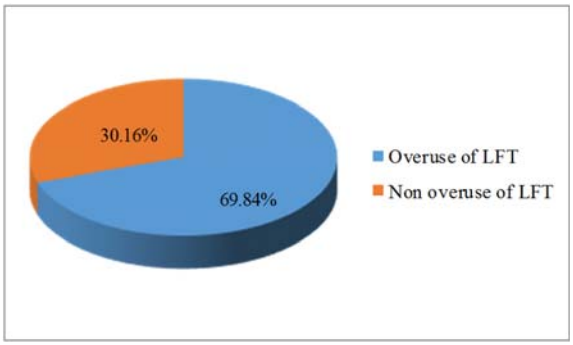

Fig. 3 Routine monitoring of LFT

Discussion

Despite the compelling indication of statin therapy, the physician faces daily challenges when prescribing statins because of associated illnesses, baseline laboratory abnormalities, and possible adverse effects ascribed to by their use. From the results of this study, we found that the unnecessary venipuncture for LFTs in patients being treated with statins at the outpatient clinic of Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University is up to 69.84%. The expenditure for unnecessary venipuncture groups is around 75,500 THB compared with 4,400 THB in the appropriate venipuncture groups. They are statistically significant (p<0.05). These facts question the usefulness and cost-effectiveness of this routine monitoring, given the infrequency of statin-related liver failure cases, the proven safety of most of the statins, and the lack of evidence that routine liver biochemistry assessment[17-24] would prevent idiosyncratic or serious liver disease[18,25,26]. From the author's opinion, causes of unnecessary venipuncture for LFTs in patients being treated with statins are habituation, out of date information, and inaccurate patient history from doctors. Faced with the dilemma of managing the care of patients who have multiple comorbid conditions and who are receiving multidrug therapy, the physician must customize the cost effectiveness of treatment. We hope that information from this study will remind doctors to send only suitable patients that are being treated with statins to venipuncture for LFT. This will reduce unnecessary hospital expense and unnecessary national expense.

There are limitations of this study. Firstly, this study design is a retrospective cohort. The information may be biased or incomplete. Secondly this study collected data from only the Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University. It could not represent all hospitals in the country. Thirdly, this study collected only ALT, AST, and ALP in LFTs. It could not represent all LFTs. Therefore, prospective research should collect study populations in various hospitals and should collect more LFTs such as bilirubin, albumin, and globulin.

Conclusion

The expenditure for the unnecessary venipuncture rate for LFTs in patient being treated with statin at the outpatient clinic, Panyananthaphikkhu Chonprathan Medical Center, Srinakharinwirot University is statistically higher than appropriate venipuncture (p<0.05).

What is already known on this topic?

The present study is not the first report of LFT monitoring after statin use but previous studies cannot be directly applied to the Thai population

because of differences in socioeconomic, ethnic groups and environmental factors that may affect the side effects after statin use.

What this study adds?

LFT monitoring after statin use is supported by increasing evidence that attests not only to the safety but also to the additional management for suitable monitor of statin therapy for these population groups. However, it is important to observe cost and effectiveness after statin use, which is of great significance in reducing the incidence of cardiovascular disease.

Acknowledgements

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Potential conflicts of interest

None.

References

1. Centers for Disease Control and Prevention (CDC). Leading causes of death. FastStats Homepage [Internet]. 2015[cited 2010 Feb 2]. Available from: http://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm
2. Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007; 370: 1829-39.
3. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004; 110: 227-39.
4. Executive summary of the third report of the National Cholesterol Education Program (NCEP). Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-97.
5. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9.
6. National Institute for Health and Clinical Excellence. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. London: National Institute for Health and Care Excellence (UK); 2010.
7. Taylor F, Ward K, Moore TH, Burke M, Davey SG, Casas JP, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database Syst Rev 2011; (1): CD004816.
8. Charles EC, Olson KL, Sandhoff BG, McClure DL, Merenich JA. Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. Am J Med 2005; 118: 618-24.
9. Weismantel D, Danis P. Clinical inquiries. What laboratory monitoring is appropriate to detect adverse drug reactions in patients on cholesterol-lowering agents? J Fam Pract 2001; 50: 927-8.
10. Nimkuntod P, Tongdee P. Plasma low-density lipoprotein cholesterol/high-density lipoprotein cholesterol concentration ratio and early marker of carotid artery atherosclerosis. J Med Assoc Thai 2015; 98 (Suppl 4): S58-63.
11. Chalasani N. Statins and hepatotoxicity: focus on patients with fatty liver. Hepatology 2005; 41: 690-5.
12. Sniderman AD. Is there value in liver function test and creatine phosphokinase monitoring with statin use? Am J Cardiol 2004; 94: 30F-4F.
13. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. Am J Med Sci 2005; 329: 62-5.
14. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004; 126: 1287-92.
15. Calderon RM, Cubeddu LX, Goldberg RB, Schiff ER. Statins in the treatment of dyslipidemia in the presence of elevated liver aminotransferase levels: a therapeutic dilemma. Mayo Clin Proc 2010; 85: 349-56.
16. US Food and Drug Administration. FDA Drug safety communication: important safety label changes to cholesterol-lowering statin drugs [Internet]. 2012 [cited 2012 Feb 28]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm
17. Pfeffer MA, Keech A, Sacks FM, Cobbe SM, Tonkin A, Byington RP, et al. Safety and tolerability

of pravastatin in long-term clinical trials: prospective Pravastatin Pooling (PPP) Project. Circulation 2002; 105: 2341-6.
18. Russo MW, Hoofnagle JH, Gu J, Fontana RJ, Barnhart H, Kleiner DE, et al. Spectrum of statin hepatotoxicity: experience of the drug-induced liver injury network. Hepatology 2014; 60: 679-86.
19. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, et al. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 2002; 137: 581-5.
20. Pasternak RC, Smith SC, Jr., Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol 2002; 40: 567-72.
21. Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. Am J Cardiol 2006; 97: 77C-81C.
22. Bays H. Statin safety: an overview and assessment of the data—2005. Am J Cardiol 2006; 97: 6C-26C.
23. Jacobson TA. Statin safety: lessons from new drug applications for marketed statins. Am J Cardiol 2006; 97: 44C-51C.
24. Smith CC, Bernstein LI, Davis RB, Rind DM, Shmerling RH. Screening for statin-related toxicity: the yield of transaminase and creatine kinase measurements in a primary care setting. Arch Intern Med 2003; 163: 688-92.
25. Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
26. de Denus S, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity: a meta-analysis. Pharmacotherapy 2004; 24: 584-91.

อัตราการเจาะเลือดเพื่อตรวจการทำงานของตับสำหรับผู้ป่วยที่ได้รับยาลดไขมันในเลือดกลุ่มสแตตินในการปฏิบัติทางคลินิก: ความลำบากของการรักษา

ธีธัช อนันต์วัฒนสุข, จิรวัฒน์ เชี่ยวเฉลิมศรี, ปัทมา ทองดี, พรทิพย์ นิ่มขุนทด

ภูมิหลัง: *ยาลดไขมันกลุ่มสแตตินหรือยากลุ่มเอชเอ็มจีโคเอรีดักเทสอินฮิบิเตอร์เป็นกลุ่มของยาลดไขมัน ใช้เป็นเภสัชภัณฑ์เพื่อลดระดับคอเลสเตอรอลโดยเฉพาะไขมันแอลดีแอล ซึ่งเป็นสาเหตุสำคัญในการเกิดโรคหลอดเลือดหัวใจอุดตัน ผลข้างเคียงหรือผลเสียของยากลุ่มนี้ คือ เป็นพิษต่อตับ แพทย์มักสั่งเจาะเลือดเพื่อตรวจการทำงานของตับบ่อยในผู้ป่วยที่ได้รับยากลุ่มสแตติน ไม่พบว่ามีการศึกษาที่เกี่ยวกับอัตราและค่าใช้จ่ายในการเจาะเลือดเพื่อดูการทำงานของตับในกลุ่มผู้ป่วยที่ได้รับยาลดไขมันในเลือดกลุ่มสแตตินเพื่อการรักษาที่เหมาะสมและไม่แพง ในการตรวจรักษาทางการแพทย์*

วัตถุประสงค์: *เพื่อศึกษาอัตราการเจาะเลือดเพื่อตรวจการทำงานของตับเกินความจำเป็นในผู้ป่วยที่ได้รับยาลดไขมันในเลือดกลุ่มสแตตินในแผนกผู้ป่วยนอก*

วัสดุและวิธีการ: *เป็นการศึกษาแบบย้อนหลัง โดยเก็บข้อมูลจากแฟ้มประวัติผู้ป่วยที่ได้รับยาลดไขมันกลุ่มสแตตินจากคลินิกผู้ป่วยนอกโรงพยาบาลชลประทาน ตั้งแต่วันที่ 1 มีนาคม พ.ศ. 2555 ถึง 1 มีนาคม พ.ศ. 2557 รวมเป็นเวลา 2 ปี ได้กลุ่มตัวอย่าง 441 คน โดยแบ่งเป็นกลุ่มที่มีการเจาะเลือดเพื่อตรวจการทำงานของตับอย่างเหมาะสม กับกลุ่มที่มีการเจาะเลือดเพื่อตรวจการทำงานของตับเกินความจำเป็น จากนั้นนำมาคำนวณหาค่าใช้จ่ายที่เสียไป รวมทั้งนำมาเปรียบเทียบกันโดยใช้วิธีการทางสถิติ*

ผลการศึกษา: *กลุ่มที่มีการเจาะเลือดเพื่อตรวจการทำงานของตับเกินความจำเป็นมีจำนวน 308 คน คิดเป็นร้อยละ 69.84 โดยแบ่งเป็นการรักษาจากแพทย์ประจำจำนวน 262 คน คิดเป็นร้อยละ 85.06 และจากแพทย์ใช้ทุนจำนวน 46 คน คิดเป็นร้อยละ 14.94 กลุ่มที่มีการเจาะเลือดเพื่อตรวจการทำงานของตับอย่างเหมาะสมมีจำนวน 133 คน คิดเป็นร้อยละ 30.16 โดยแบ่งเป็นการรักษาจากแพทย์ประจำจำนวน 103 คนคิดเป็นร้อยละ 77.44 และจากแพทย์ใช้ทุนจำนวน 30 คน คิดเป็นร้อยละ 22.56 พบว่าค่าใช้จ่ายที่เสียไปกับการเจาะเลือดเพื่อตรวจการทำงานของตับเกินความจำเป็นเป็นเงิน 75,500 บาท ส่วนในกลุ่มที่มีการเจาะเลือดเพื่อตรวจการทำงานของตับอย่างเหมาะสมมีค่าใช้จ่าย 4,400 บาท พบว่ามีความแตกต่าง อย่างมีนัยสำคัญทางสถิติ ($p<0.05$)*

สรุป: *พบว่าอัตราการเจาะเลือดเพื่อตรวจการทำงานของตับเกินความจำเป็นในผู้ป่วยที่ได้รับยาลดไขมันในเลือดกลุ่มสแตตินในแผนกผู้ป่วยนอก มีมากกว่ากลุ่มที่มีการเจาะเลือดเพื่อตรวจการทำงานของตับอย่างเหมาะสมอย่างมีนัยสำคัญทางสถิติ*