

Comparison of Statins Dose Intensity on HbA1c Control in Outpatients with Type 2 Diabetes: A Prospective Cohort Study

Mohamed A. Hammad, Dzul Azri Mohamed Noor, Syed Azhar Syed Sulaiman, Ahmed A. Khamis, Abeer Kharshid, Nor Azizah Aziz

Abstract—The effect of statins dose intensity (SDI) on glycemic control in patients with existing diabetes is unclear. Also, there are many contradictory findings were reported in the literature; thus, it is limiting the possibility to draw conclusions. This project was designed to compare the effect of SDI on glycated hemoglobin (HbA1c%) control in outpatients with Type 2 diabetes in the endocrine clinic at Hospital Pulau Pinang, Malaysia, between July 2015 and August 2016. A prospective cohort study was conducted, where records of 345 patients with Type 2 diabetes (Moderate-SDI group 289 patients and high-SDI cohort 56 patients) were reviewed to identify demographics and laboratory tests. The target of glycemic control (HbA1c < 7% for patient < 65 years, and < 8% for patient ≥ 65 years) was estimated, and the results were presented as descriptive statistics. From 289 moderate-SDI cohorts with a mean age of 57.3 ± 12.4 years, only 86 (29.8%) cases were shown to have controlled glycemia, while there were 203 (70.2%) cases with uncontrolled glycemia with confidence interval (CI) of 95% (6.2–10.8). On the other hand, the high-SDI group of 56 patients with Type 2 diabetes with a mean age 57.7±12.4 years is distributed among 11 (19.6%) patients with controlled diabetes, and 45 (80.4%) of them had uncontrolled glycemia, CI: 95% (7.1–11.9). The study has demonstrated that the relative risk (RR) of uncontrolled glycemia in patients with Type 2 diabetes that used high-SDI is 1.15, and the excessive relative risk (ERR) is 15%. The absolute risk (AR) is 10.2%, and the number needed to harm (NNH) is 10. Outpatients with Type 2 diabetes who use high-SDI of statin have a higher risk of uncontrolled glycemia than outpatients who had been treated with a moderate-SDI.

Keywords—Cohort study, diabetes control, dose intensity, HbA1c, Malaysia, statin, Type 2 diabetes mellitus, uncontrolled glycemia.

M. A. H. is with the Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia (corresponding author, phone: 00601123561802, e-mail: m_anwaaar@hotmail.com).

D. A. M. N. is with the Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia (phone: 006018-312-4811, e-mail: dzulazri@usm.my).

S. A. S. S. is with the Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia (phone: 006-0164483616, e-mail: sazhar@usm.my).

A. A. K. is with the Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia (e-mail: ahmed.khamis.777@gmail.com).

A. K. is with the Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia (phone: 006010-700-3226, e-mail: abeerkharshid2015@gmail.com).

N. A. A. is with the Endocrinology Clinics, Penang General Hospital, Penang, Malaysia (e-mail: dr_norazizah@yahoo.com).

I. INTRODUCTION

STATINS are a class of drugs used to lower cholesterol levels by inhibiting the enzyme 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase, which plays a central role in the production of cholesterol in the liver, where 70% of the total cholesterol in the body is produced in the liver. High cholesterol levels have been associated with cardiovascular disease (CVD) [1]. Statins are the most widely used category of drugs in the United States, and their benefits regarding reducing low-density lipoprotein cholesterol (LDL-C) and lessening the risk for coronary heart disease (CHD) are well known. Statins have been the primary treatment for the management of dyslipidemia once they developed [2]. It was found that statins can prevent CVD and mortality in those who are at high risk as they have a pleiotropic effect. Moreover, statins are useful for treating CVD in the early stages of a disease (secondary prevention) and those at elevated risk but without CVD (primary prevention) [3].

Diabetes mellitus Type 2 (formerly Noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic disorder that leads to high blood glucose (hyperglycemia) regarding insulin resistance and relative lack of insulin [4]. The main symptoms are constant hunger, excess thirst, and frequent urination. Type 2 diabetes represents about 90% of cases of diabetes, while the other 10% are primarily due to diabetes mellitus Type 1 and gestational diabetes. Nearly 382 million people worldwide, or 8.3% of adults, are estimated to have diabetes. If the same increasing trends continue, by 2035, about 592 million people, or one out of every ten adults, will have diabetes. The increase in new diabetes cases equals nearly three new cases every 10 seconds or almost 10 million per year [5].

HbA1c: A blood test can measure the amount of glycosylated hemoglobin in the blood. The glycosylated hemoglobin test indicates the mean blood glucose level for a person for two- to three-month period before the test. It can help in examining how well a person's diabetes is being controlled over time. Red blood cells contain hemoglobin that provides oxygen to the body cells. Glucose molecules in the blood become adhere to hemoglobin molecules. The combination of glucose molecules and hemoglobin is expressed as that the hemoglobin is glycosylated (also referred to as HbA1c or hemoglobin A1c).

The person's hemoglobin becomes more glycosylated as the individual's blood glucose becomes much higher. The glucose remains jammed to the hemoglobin for the lifespan of the red blood corpuscles, or for a period about 8 to 12 weeks. If people with Type 2 diabetes mellitus drop their glycated hemoglobin (HbA1c) level by 1%, there is a 16% decline in heart failure, 19% lessening in cataract extractions, and 43% reduction in the amputation or death result from peripheral vascular disease [6]. Hyperglycemia is a condition in which an extra amount of glucose circulates in the blood plasma. Hyperglycemia indicates that a glucose level is more than 180 mg/dl (10 mmol/L), but symptoms may not begin to become noticeable until even higher values such as 270-360 mg/dl (15-20 mmol/l). However, chronic levels greater than 125 mg/dl (7 mmol/L) can produce organ impairment [7]. The most recent glycemic goal recommended by the American Diabetes Association, selected by practicality and according to the projected decrease in complications over time, is the HbA1c level of <7% [8], while 50% of the patients with Type 2 diabetes had uncontrolled glycemia [9].

Drugs safety is always important, but especially more important with the statins therapy, for many causes. The crucial one is the fact that statins are frequently prescribed. They are the single most prescribed category of medicines, in the financial term, in the United States. The second reason, they are given for prolonged periods of time. Over several years that typical patients were given a statin, there are many probabilities for adverse events, including abrupt variations in the patient's health condition. A third critical factor is that statins are usually used in above 40 years patients. It tends to be recommended with numerous other drugs for other illnesses such as end-stage renal disease and chronic liver cirrhosis [10]-[12]. This polypharmacy increases the importance of safety problems because the utilization of a high number of medicines in these age categories can significantly raise the risk of drug-drug interactions. Many of the diseases are common in old age, which contributes to drug safety concerns such as anemia [13], [14] and hypertension [15], [16]. Finally, because of the advanced age itself even with excellent health, it probably increases the risk of drug toxicity [17], [18].

A. Aim of Study

This project aims to compare the effects of high and moderate statins dose intensity on HbA1c% controlling in outpatients with Type 2 diabetes mellitus in the endocrine clinic at Hospital Pulau Pinang, Malaysia, between July 2015 and August 2016.

B. Ethical Consideration

From the ethical perspective, this study follows the procedures of the registration in Clinical Research Centre (CRC) in Penang General Hospital and the registration in National Medical Research Register (NMRR ID: NMRR-15-1068-25700) [19]. Also, patients have signed an informed consent form, and all of the study steps were done under experts' supervision. All aspects of the project protocol,

including access to and the use of demographic and clinical information of the patients were authorized by the institutional medical ethics committee and the local health authorities before the initiation of this study. Information on individuals was strictly protected and used for clinical research only. The dignity and privacy of the subjects are protected in the future research and publication.

II. METHODS AND STUDY DESIGN

An observational prospective cohort study design was conducted. Patients with Type 2 diabetes using statins were checked prospectively to determine the effect of statins usage on HbA1c% control. Also, the clinical data were collected from the patients' medical records and the corresponding medical team. Patients with Type 2 diabetes with age 18 years and above having HbA1c test were included in the study. The target of glycemic control (HbA1c < 7% for patient < 65 years, and < 8% for patient ≥ 65 years) was estimated. The results were presented as descriptive statistics [20]. The exclusion criteria included patients with HIV, pregnancy, patients below 18 years old, and patients with Type 1 diabetes.

The categorization of daily statin dose presented in this study was guided by dyslipidemia guidelines which are used to estimate the effects of statins on serum low-density lipoprotein (LDL) cholesterol concentration. High-intensity statin therapy (daily dose, on average, lowers LDL-C by approximately ≥50%) is defined as atorvastatin dose 40-80 mg, rosuvastatin dose 20-40 mg and simvastatin 60-80 mg [21]. While moderate-intensity therapy (daily dose, on average, lowers LDL-C by nearly 30% to <50%) is categorized as atorvastatin 10-20 mg, fluvastatin XL 80 mg, fluvastatin 40 mg twice a day. In addition to lovastatin 40 mg, pravastatin dose 40-80 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg are also classified as moderate-SDI [22], [23].

A. Recruitment

The principal investigator did recruitment. All of those patients with Type 2 diabetes, and who use statins, are getting treatment at the endocrine clinic, Penang General Hospital, Malaysia, and willing to participate in the study for one year by giving a written consent after reading the patient information sheet. Participates are allowed to be withdrawn from the study at any time without any penalty or change in his benefits or treatment in the hospital. Withdrawal also can be due to mental disease, moving to another hospital, incapability, or death. The compensation of subjects would be from the patients with Type 2 diabetes. Fig. 1 provides the flow chart of the study presented in this paper.

B. Data Collection

The principal investigator collected data. A developed, validated data collection form was used for collecting patients' demographics, clinical and laboratory data. Demographic characteristics include age, weight, height, gender, and ethnicity. The related clinical variables involve HbA1c, comorbidities, statins medications, drugs dosage, and their

duration. Data were collected from patients, patients' medical records, and medical team.

C. Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 21.0 (Chicago, Illinois, USA). Parametric data were presented as mean \pm Standard Deviation (SD). Categorical variables were demonstrated as relative frequencies (percentage) and absolute (number). Comparison of continuous factors was made by independent t-test, while Pearson's χ^2 test was used for comparison of categorical variables. All variables that contributed to the level of diabetes control or were significantly associated with statin usage in the bivariate analysis were entered into a logistic regression model; Mantel-Haenszel and ANCOVA were used to monitor the influence of confounders. A CI: 95% and/ or p-value of <0.05 was considered statistically significant.

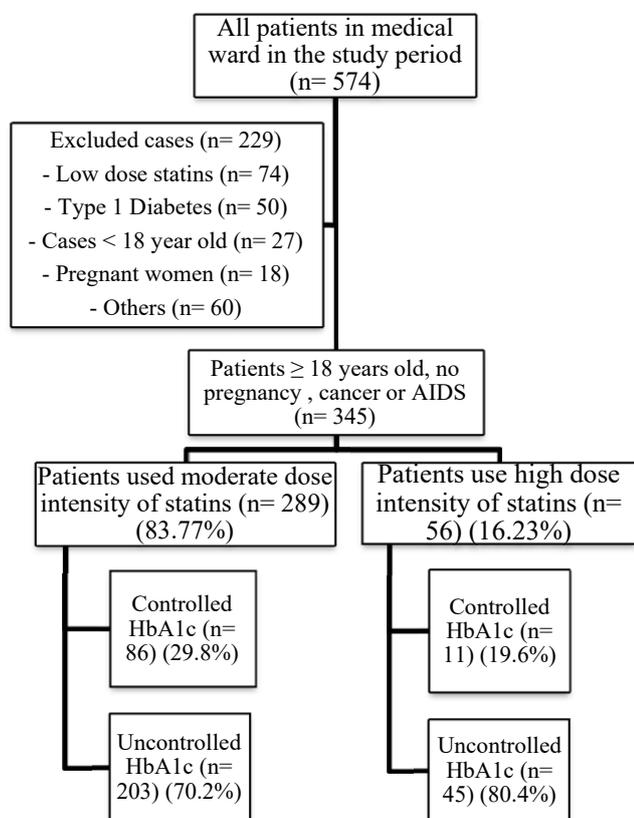


Fig. 1 The flow chart of the study, AIDS: acquired immune deficiency syndrome

III. RESULTS

The study involved 345 patients with Type 2 diabetes (Moderate-SDI group of 289 patients and high-SDI cohort of 56 patients). From the 289 moderate-dose intensity group that had an average age of 57.3 ± 12.4 years, about 86 (29.8%) subjects had controlled glycemia, on the other hand, there were 203 (70.2%) patients with uncontrolled diabetes, CI: 95% (6.2–10.8). While, the high-dose intensity cohort of 56

cases with age 57.7 ± 12.4 years, is distributed among 11 (19.6%) subjects with controlled HbA1c%, and 45 (80.4%) cases had uncontrolled glycemia, CI: 95% (7.1–11.9). The findings indicated that the relative risk (RR) of uncontrolled HbA1c% in diabetic outpatients who used high-SDI is 1.15, also the excessive relative risk (ERR) is 15%. While the absolute risk (AR) is 10.2%, in addition the number needed to harm (NNH) is 10. Table I presents the effect of SDI on HbA1c control, while a comparison of baseline characteristics of HbA1c% with High-SDI and Moderate-SDI is given in Table II.

TABLE I
CONTINGENCY TABLE OF EFFECT OF STATIN DOSE INTENSITY ON HBA1C CONTROL

	Uncontrolled HbA1c	Controlled HbA1c	Total	Risk %
Moderate-SDI	203	86	289	0.702
High-SDI	45	11	56	0.804

TABLE II
COMPARISON OF BASELINE CHARACTERISTICS OF HBA1C% WITH HIGH-SDI AND MODERATE-SDI

Variable	No. of participants		P value
	High-SDI (n = 56)	Moderate-SDI (n = 289)	
Age, (mean \pm SD), year	57.7 \pm 12.4	57.3 \pm 12.4	0.339
Gender			
Male	25 (44.6%)	145 (50.2%)	0.674
Female	31 (55.4%)	144 (49.8%)	0.864
Ethnicity			
Malaysian	26 (46.4%)	112 (38.8%)	0.327
Chinese	14 (25%)	103 (35.6%)	0.425
Indian	15 (26.8%)	72 (24.9%)	0.538
Others	1 (1.8%)	2 (0.7%)	0.635
BMI (mean \pm SD) kg/m ²	29.4 \pm 5.4	28.74 \pm 5.4	0.456
HbA1c%	9.1 \pm 1.98	8.6 \pm 1.98	0.012
Comorbidity	3.7 \pm 1.99	3.6 \pm 1.99	0.131

Atorvastatin was the highest dose intensity statin used (53.6%) as shown in Fig. 2, and Simvastatin was the most moderate-SDI used (92.4%) as presented in Fig. 3.

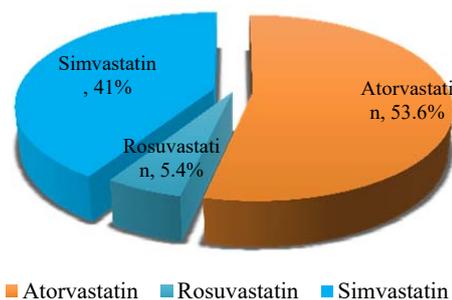


Fig. 2 High-dose intensity statins prevalence among 56 patients with Type 2 diabetes

IV. DISCUSSION

Currently, labels on statin drugs in the United States write information concerning glycemic effects, including diabetes mellitus and elevating in HbA1c or fasting plasma glucose. The US Food and Drug Administration approved these

labeling changes in February 2012 [24]. Most of the available literature discussed the effect of statins in the development of only new cases of Type 2 diabetes mellitus among nondiabetic persons. There is a limited discussion on the effects of statins on the HbA1c control in patients who already had diabetes [25].

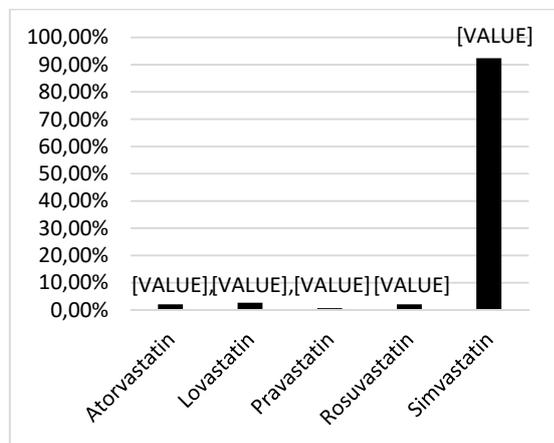


Fig. 3 Moderate-dose intensity statins prevalence among 289 patients with Type 2 diabetes

Preiss et al. [26] collected data from five trials with 32,752 persons who were free of diabetes mellitus at the beginning of statin usage. Then, Preiss et al. investigated the association between the use of statin in different dose intensities and the risk of new-onset diabetes development. They compare the risk of new-onset diabetes development with the use of intensive-dose statin therapy (IDST) as atorvastatin 80 mg and simvastatin 80 mg against moderate-dose statin therapy (MDST) as atorvastatin 10 mg or 20 mg, pravastatin 40 mg, and simvastatin; 20 or 40 mg. About 1449 (8.8%) subjects have developed new-onset diabetes among individuals classified to receive IDST compared with 1300 (8.0%) who were allocated to MDST. Their study had demonstrated that, with no substantial heterogeneity between trials ($I^2 = 0\%$), while the evaluated odds ratio (OR) was 1.12, confidence interval (CI) was 95% (1.04–1.22), [27]. The number needed to treat with IDST along one year period to result in one extra case of diabetes mellitus in comparison with MDST was 498 [28].

The findings of the study presented in this paper were supported by a retrospective study conducted in Malaysia by Liew et al. in 2014, where 1060 medical records of hypertensive patients at a primary care clinic were reviewed. These subjects were selected using systematic random sampling (1:4). Patients' socio-demographics, clinical profile, investigation results, and prescribed medications were collected. 810 (76.4%) hypertensive patients were on statins, out of which 792 (97.8%) were prescribed with simvastatin 10 mg or 20 mg once daily. Analysis of the whole group regardless of diabetes status shows that the statin user cohort had fasting blood glucose and higher HbA1c values. After adjustment for fasting blood glucose, diabetes, and diabetic medication, the difference in HbA1c levels is still significant

(adjusted OR = 1.290, $p = 0.044$, 95% CI 1.006, 1.654). In this study, patients with Type 2 diabetes, no-statin users again, had significantly lower HbA1c level compared to statin users. There is still a significant difference after adjustment for diabetic medications and age (adjusted odd ratio: 1.208, $p = 0.037$, CI: 95% (1.012 - 1.441)). The used statins were associated with higher HbA1c levels among hypertensive patients and patients with Type 2 diabetes with hypertension. Clinicians treating hypertensive patients on statins should consider monitoring the HbA1c level and ensure that those with diabetes have their hyperglycemia under control. The limitation of the study by Liew et al. is that it is retrospective and the affected patients with Type 2 diabetes are with hypertension only [29].

Atorvastatin, a high-potency statin, has a particularly significant effect on glycosylated hemoglobin. A multicenter randomized double-blinded controlled non-inferiority trial of patients with Type 2 diabetes had been conducted in Taiwan [30], and it was found that HbA1c is significantly increased after three months in patients receiving atorvastatin (6.5 % versus 6.6 %), which tallies with the findings of this study.

An increase in HbA1c with high-SDI patients with Type 2 diabetes has been observed. The results of a meta-analysis and several other studies on statins and glycemic control [31] in patients with diabetes [32]-[34] suggest that statin therapy is associated with a modest increase in HbA1c. The results of the study which were demonstrated in this paper with regards to patients with diabetes are consistent with these studies.

In this study, the results showed that atorvastatin is the most high-dose intensity statin used (53.6%) as shown in (Fig. 2), and simvastatin is the most moderate-SDI used (92.4%) as demonstrated in (Fig. 3). While in Australia, atorvastatin is ranked the 1st, and simvastatin is the 2nd in the medicine used [35], while in Norway, simvastatin is ranked the 1st and atorvastatin is ranked the 3rd [36]. Using the multi-attribute scoring tool (MAST), Ramli et al. [37] have found that the Total Utility Score (TUS) of atorvastatin is the highest (84.48) then followed by simvastatin (83.11).

V. CONCLUSION

The risk of uncontrolled glycemia among outpatients with Type 2 diabetes using high-dose intensity of statin group is higher than the risk among outpatients with Type 2 diabetes group who were treated with a moderate dose.

VI. STUDY LIMITATION

This study has been conducted in a single center, where the time was limited, and the study was constrained by information availability in Penang General Hospital.

ACKNOWLEDGEMENT

The authors are grateful to all of the staff at the department of endocrine, department of pharmacy and laboratory teams in Penang General Hospital for their kind support and help in facilitating this study. Special thanks to Universiti Sains Malaysia for providing the USM research fellowship.

Funding: USM Fellowship
Conflicts of Interest: None

REFERENCES

- [1] S. Lewington, G. Whitlock, R. Clarke, P. Sherliker, J. Emberson, J. Halsey, 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*, 370 (9602): 1829–39, Dec. 2007.
- [2] Cholesterol Treatment Trialists (CTT) Collaboration, C. Baigent, L. Blackwell, J. Emberson, et al. "Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomized trials," *Lancet* 2010;376: 1670–1681.
- [3] F. Taylor, Huffman, A. F. Macedo, T. H. Moore, M. Burke, G. S. Davey, K. Ward, Ebrahim S. "Statins for the primary prevention of cardiovascular disease," *Cochrane Database Syst Rev* 1: CD004816, 2013.
- [4] V. Kumar, N. Fausto, A. K.Abbas, R. S. Cotran, S. L. Robbins. "Robbins and Cotran Pathologic Basis of Disease," (7th ed.). Philadelphia, Pa.: Saunders. 2005; 1194–1195, ISBN 0-7216-0187-1.
- [5] (5) D. G. Gardner, "Shoback Dolores. Greenspan's basic & clinical endocrinology," (9th ed.). New York: McGraw-Hill Medical. 2011. Chapter 17. ISBN 0-07-162243-8.
- [6] The global diabetes community "Guide to HbA1c", available at <http://www.diabetes.co.uk/what-is-hba1c.html>, (accessed at 16 -Jul -2015).
- [7] Total Health Institute. Total Health Life (2005)."High Blood Sugar". Retrieved May 4, 2011.
- [8] American Diabetes Association "Glycemic Targets, Standards of medical care in diabetes—2016," *Diabetes Care* 2016;39(1): S39–S46 | DOI: 10.2337/dc16-S008.
- [9] M. A. Hammad, D. A. Mohamed Noor, S. A. Syed Sulaiman, N. A. Aziz, Y. Elsobky, "A prospective study of prevalence of uncontrolled glycaemia in Type 2 diabetes mellitus outpatients," American College of Clinical Pharmacy 2016, ACCP Virtual Poster Symposium, *Pharmacotherapy*, May 18–19, 2016.
- [10] M. A. Hammad, A. A. Khamis, K. M. Al- Akhali, T. M. Ali, A. M. Alasmri, E. M. Al-Ahmari, et al. "Evaluation of Drug Dosing in Renal Failure. IOSR Journal of Pharmacy and Biological Sciences," *IOSR-JPBS* 2016;11(5): PP 39-50.
- [11] S. A. Syed Sulaiman, D. A. Mohamed Noor, M. A. Hammad, K. M. Al-Akhali, A. M. Alasmri, E. M. Al-Ahmari, et al. "Prospective Study of Evaluation of Antibiotics Dosage Adjustment in Patients with Chronic Renal Failure at Aseer Hospital," The 7th Asian Association of Schools of Pharmacy Conference, Taipei, Taiwan, *JAASP* 2015;1: 142.
- [12] M. A. Hammad, K. M. Al Akhali, A. M. Alasmri, E. M. Al-Ahmari, E. M. Mossa, N. M. Algahtani, et al., "Prospective Study of Evaluation of Drug Dosage Adjustment in Patient with Chronic Renal Failure at Aseer Hospital," The 10th Annual Scientific Research Day for Medical, Applied and Basic Sciences, *King Khalid University*, 5.05.2014, P92.
- [13] K. Al Akhali, M. A. Hammad Ali, M. A. Ansari. "Evaluation of Prevalence and Pattern of Anemia – A Hospital Based Study in Aseer Province," Kingdom of Saudi Arabia. *Journal of Experimental Medical & Surgical Research*. Nr. 2 / 2013; 32 -35.
- [14] K. M. Alakhali, M. Selim, M. A. Hammad. "Evaluation of therapeutic drug monitoring of cyclosporine and tacrolimus in kidney transplant patients," *JPCS*.2014;3(8).
- [15] M. A. Khaled, M. Asif Ansari, M. A Hammad Ali. "Analysis of Prevalence Risk Factor and Pharmacotherapy of Hypertension in Outpatients," *Indian Journal of Pharmacy Practice*. 6(4), 2013, p: 64-66. Available at: https://www.researchgate.net/publication/270337790_Analysis_of_Prevalence_Risk_Factor_and_Pharmacotherapy_of_Hypertension_in_Outpatients?ev=prf_pub.
- [16] K. M. Alakhali, A. Ansari, A. HA, "Analysis of Prevalence, Risk Factor and Pharmacotherapy of Hypertension in Outpatients," The 10th Annual Scientific Research Day for Medical, Applied and Basic Sciences, *King Khalid University*, 5.05.2014, P68.
- [17] M. A. Hammad, B. Tangiisuran, N. Abd El Aziz, Y. Hassan. "A prospective study of uncontrolled glycemia secondary to drug-drug interactions in Type 2 diabetes mellitus patients at Penang General Hospital in Malaysia," *Pharmacotherapy*, 2013; 33(5): E50-E50.
- [18] E. A. Brinton, Statin Therapy: Risks vs. Benefit: *Medscape Cardiology*. 2004;8(1).
- [19] National Medical Research Register, National Institute of Health NIH guideline. (updated 11-Nov-2014) Available at: https://www.nmrr.gov.my/fwbLoginPage.jsp?fwbPageId=NMRR_Home (Accessed: 7- Mar -2016).
- [20] American Diabetes Association: "Older Adults, Standards of medical care in diabetes—2016," *Diabetes Care* 2016;39(1): S81–S85. DOI: 10.2337/dc16-S013.
- [21] N. J. Stone, J. G. Robinson, A. H. Lichtenstein, C. N. B. Merz, C. B. Blum, R. H. Eckel, et al. "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines," *J Am Coll Cardiol*. 2014;63(25 PA): 2889-2934. doi: 10.1016/j.jacc.2013.11.002.
- [22] M. R. Law, N. J. Wald, A. R. Rudnicka. "Quantifying effect of statins on low-density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis," *BMJ* 2003;326: 1423.
- [23] N. J. Stone, J. G. Robinson, A. H. Lichtenstein, C. N. B. Merz, C. B. Blum, R. H. Eckel, et al. "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults," *Circulation*. 2014;129: S1-S45. Doi: <http://dx.doi.org/10.1161/01.cir.0000437738.63853.7a>.
- [24] Food and Drug Administration. FDA drug safety communication: Important safety label changes to cholesterol-lowering statin drugs. 2012
- [25] N. Sattar, D. Preiss, H. M. Murray, P. Welsh, B. M. Buckley, A. J. de Craen, et al. Statins and risk of diabetes: a collaborative meta-analysis of randomized statin trials. *Lancet* 2010; 375: 735-42.
- [26] D. Preiss, S. R. Seshasai, P. Welsh, S. A. Murphy, J. E. Ho, D. D. Waters, et al. "Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a metaanalysis," *JAMA*. 2011;305: 2556–2564.
- [27] H. Cederberg, A. Stančáková, N. Yaluri, S. Modi, J. Kuusisto, M. Laakso. "Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6-year follow-up study of the METSIM cohort," 2015.
- [28] K. C. Maki, P. M. Ridker, W. V. Brown, S. M. Grundy, N. Sattar. "An assessment by the Statin Diabetes Safety Task Force: 2014 update," *Journal of Clinical Lipidology* 2014;8(3): S17–S29. DOI: <http://dx.doi.org/10.1016/j.jacl.2014.02.012>.
- [29] S. M. Liew, et al. "Statins use is associated with poorer glycaemic control in a cohort of hypertensive patients with diabetes and without diabetes," *Diabetology & Metabolic Syndrome* 2014, 6:53.
- [30] P. Y. Liu, L. Y. Lin, H. J. Lin, C. H. Hsia, Y. R. Hung, H. I. Yeh, et al. "Pitavastatin and atorvastatin double-blind randomized comparative study among high-risk patients, including those with Type 2 diabetes mellitus in Taiwan (PAPAGO-T study)," *PLoS One*. 2013;8:e76298. doi: 10.1371/journal.pone.0076298. (PMC free article) (PubMed) (Cross Ref).
- [31] S. Erqou, C. C. Lee, A. I. Adler. "Statins and glycaemic control in individuals with diabetes: a systematic review and meta-analysis," *Diabetologia*. 2014;57: 444–52. doi: 10.1007/s00125-014-3374-x. (PubMed) (Cross Ref).
- [32] S. Simsek, C. G. Schalkwijk, B. H. Wolfenbuttel." Effects of rosuvastatin and atorvastatin on glycaemic control in Type 2 diabetes – the CORALL study," *Diabet Med*. 2012;29: 628–31. doi: 10.1111/j.1464-5491.2011.03553.x. (PubMed) (Cross Ref).
- [33] J. Sasaki, Y. Ikeda, T. Kuribayashi, K. Kajiwara, S. Biro, K. Yamamoto, et al. "A 52-week, randomized, open-label, parallel-group comparison of the tolerability and effects of pitavastatin and atorvastatin on high-density lipoprotein cholesterol levels and glucose metabolism in Japanese patients with elevated levels of low-density lipoprotein cholesterol and glucose intolerance," *Clin Ther*. 2008;30: 1089–101. doi: 10.1016/j.clinthera.2008.05.017. (PubMed) (Cross Ref).
- [34] H. Ogawa, K. Matsui, Y. Saito, S. Sugiyama, H. Jinnouchi, M. Sugawara, et al. "Differences between rosuvastatin and atorvastatin in lipid-lowering action and effect on glucose metabolism in Japanese hypercholesterolemic patients with concurrent diabetes. Lipid-lowering with highly potent statins in hyperlipidemia with Type 2 diabetes patients (LISTEN) study," *Circ J*. 2014;78: 2512–5. doi: 10.1253/circj.CJ-14-0810. (PubMed) (Cross Ref).
- [35] Australian Government Department of Health and Ageing. "Australian Statistics on Medicines 2007," (13th ed). Commonwealth of Australia 2009.

- [36] Norwegian Institute of Public Health. “*Drug Consumption in Norway 2003 – 2007*,” Oslo 2008.
- [37] A. Ramli, S. M. Aljunid, S. Sulong, M. F. A. Yusof. “National Drug Formulary review of statin therapeutic group using the multiattribute scoring tool,” *Therapeutics and Clinical Risk Management*. 2013;9: 491-504.