Tropical Journal of Pharmaceutical Research December 2017; 16 (12): 3005-3011
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v16i12.27

Original Research Article

Patterns of statin therapy prescribing among hospitalized patients with Type 2 diabetes mellitus in two Malaysian tertiary hospitals

MH Elnaem[1]*, MH Nik Mohamed[1], HZ Huri[2], SM Azarisman[3]
[1]Department of Pharmacy Practice, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, [2]Department of Pharmacy, Faculty of Medicine, University of Malaya, Kuala Lumpur, [3]Department of Internal Medicine, Faculty of Medicine, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

For correspondence: **Email: drmelnaem@gmail.com; **Tel:** 0060-193944726*

Sent for review: 27 August 2017 *Revised accepted: 28 November 2017*

Abstract

Purpose: *To assess the patterns of statin therapy prescribing among hospitalized patients with type 2 diabetes mellitus (T2DM) in two Malaysian tertiary healthcare institutions and to determine compliance with Malaysian treatment guidelines.*
Methods: *A cross-sectional study was conducted from September to December 2016. The study involved hospitalized T2DM patients aged between 40 to 75 years recruited from the medical wards of two tertiary hospitals in the state of Pahang, Malaysia. Evaluation of statin prescribing was classified as appropriate (statin therapy was prescribed with no concurrent drug interactions) or inappropriate (not receiving any statins, although no contraindications), or potentially inappropriate (drug interactions detected or renal dose adjustment needed).*
Results: *Among the 393 medical records screened, 65 % had a statin therapy prescription. The evaluation of statins prescribing showed that approximately 35 % of patients were not prescribed statins, contrary to national treatment guidelines. Twenty-six percent of the study cases were given drugs that interacted with statins. Renal dose adjustment of the given statin was needed in 5 % of patients. Finally, only one-third of the patients were prescribed appropriate statin doses.*
Conclusion: *A significant portion of T2DM hospitalized patients did not receive their recommended statin therapy for cardiovascular disease prophylaxis. Closer monitoring and further dose adjustments are warranted to optimize statin therapy prescribing. Further interventions to improve statin prescribing should be considered.*

Keywords: *Statin therapy, Prescribing patterns, Cardiovascular diseases, Type 2 diabetes*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Cardiovascular disease (CVD) is recognized as a major contributor to morbidity and mortality among patients with type 2 diabetes mellitus [1]. Statin therapy has been proven to have a principal role in decreasing the CVD risk through their favorable impact on low-density lipoprotein cholesterol (LDL-C) [2]. The reduction in LDL-C levels by the use of statin therapy is expected to

proportionally reduce the risk of the main vascular events in patients at risk, irrespective of their baseline cholesterol levels [3].

The majority of clinical practice guidelines (CPG) recommend statin therapy to patients with T2DM [4,5]. The Malaysian CPG is no exception. According to the Malaysian CPG, patients with T2DM over the age of 40, even without any CVD history should be prescribed with statins regardless of their presenting LDL-C values [6]. Despite the guidelines' clear recommendations, the statin therapy is regarded to be underutilized in the Malaysian healthcare setting [7].

The suboptimal utilization of statin therapy can be attributed to many different factors [8]. Some factors are patient-related such as the commonly reported non-adherence and abrupt discontinuation of statin treatment [9]. The nonadherence to statin therapy is related to adverse treatment effects, e.g., statin-associated muscle symptoms (SAMS), that may occasionally lead to statin intolerance [10]. In these instances, management strategies based on statin rechallenge or intermittent dosing have been discussed [11].

Other reasons for the suboptimal utilization of statin therap are related to the prescribers. It has been reported that not all statin-eligible patients are prescribed with a statin in the real practice [12,13]. Moreover, the mass media coverage of statin-related safety issues has been reported to affect the degree of statin persistence negatively and in some cases lead to discontinuation rate of up to 10% among patients receiving statin treatment [14]. To our knowledge, there–has been no study assessing the appropriateness of statin prescribing among hospitalized Malaysian patients with T2DM.

The objective of this study was to determine the patterns of statin prescribing among hospitalized patients with T2DM and to ascretain if they comply with Malaysian clinical practice guidelines.

METHODS

Study design

This is a cross-sectional study conducted from September to December 2016, examining the medical records from wards in two tertiary referral hospitals in the state of Pahang, Malaysia. The inclusion criteria were hospitalized T2DM patients aged between 40 to 75 years without any contraindications to receiving statin therapy, who have been admitted to the medical ward for not less than 48 hours, with or without overt CVD. These are eligible candidates for statin therapy regardless of baseline LDL cholesterol levels according to the latest Malaysian CPG. Conversely, patients are excluded from the study if they are > 75 years of age, admitted to emergency or critical care units, or known to have active liver disease.

The data collection form was designed to capture patient's demographics, relevant laboratory values, underlying diseases, concurrent medications and history of lipid-lowering therapy use patterns. Specifically, data collected included patient characteristics (age, gender, race, and the onset of DM), clinical indication for receiving statin therapy (primary or secondary CVD prophylaxis), glycemic and lipid laboratory profile (fasting/random blood glucose, HBA1c, LDL-C), concomitant diseases (hypertension, coronary heart disease, chronic kidney disease), prescribed medications, and the duration of previous statin therapy use before hospitalization.

Outcome measures

The primary outcome was the prevalence of statin therapy under-prescribing among hospitalized T2DM patients. The assessment of statin therapy prescribing was principally referring to the recommendations of the Malaysian CPG that endorses statin therapy for all T2DM patients between 40 and 75 years [6]. The output of the evaluation process was categorized as appropriate, inappropriate, or potentially inappropriate. Appropriate statin prescribing refers to those patients who received their recommended statin therapy without significant drug interactions with the concurrent medications. Inappropriate prescribing refers to those patients who did not receive statin therapy or received non-statin lipid-lowering treatment while there was no contraindication to being prescribed with statin therapy. Potentially inappropriate prescribing applies to patients receiving concomitant drugs that significantly interact with statin therapy or patients who had end-stage renal failure and was prescribed with a statin that needed renal dose adjustment. Potentially inappropriate prescribing is also referring to those patients with the very high-risk profile of recent-diagnosis of CVD but prescribed with a low-intensity statin, in contrast to present guidelines on the use of high-dose statins.

The secondary outcome was the identification of the pattern changes in the statin therapy before and after hospitalization (e.g., discontinuation, initiation, switching between different lipid-

lowering therapies). Comparing the received treatment before and during admission was performed to evaluate the potential role of the hospital caregivers in optimizing statin therapy prescribing among patients with T2DM.

Ethics approval

This study protocol received ethical approval from National Medical Research Register (no. NMRR-16-713-29691 IIR) and followed the principles and guidelines of Declaration of Helsinki [15].

Statistical analysis

A descriptive analysis of the patients' characteristics (e.g., indication, comorbidities), their prescribed statin therapy and of the co-prescribed medications was performed. Categorical variables were expressed as counts and percentage frequencies. Data were analyzed using SPSS v.22 software. (IBM SPSS Statistics, NC, USA).

RESULTS

Key features of study population

The total number of patients' records investigated was 401. Eight data collection forms were excluded due to incomplete data or not fulfilling the inclusion criteria. 393 cases were included for analysis. An overview of the main characteristics of the study sample regarding the indication for statin prescription, the intensity of the prescribed statin, and co-morbidities are shown in Table 1.

Characteristics of statin therapy prescriptions

The most commonly prescribed statin therapy was simvastatin 40 mg (n=137, 34.9 %), followed by simvastatin 20 mg (n=62, 16 %). About 32 (8.1 %) of study cases were prescribed with atorvastatin 40 mg. A total of 138 study cases (35.1 %) were not receiving statin therapy, of these two cases were receiving gemfibrozil 300 mg monotherapy as the main lipid-lowering treatment. Other lipid-lowering therapies (LLT) were prescribed together with statins in nine cases only. The complete description of prescribed LLT regimens is shown in Table 2.

Statin-drug interactions

Following the screening of statin therapy prescriptions (n = 255) for potential drug interactions with the concurrently administered medications, the incidence of drug interactions was 40 % (n = 102). The most common drug interaction was involving amlodipine in patients receiving simvastatin 40 mg (n = 30, 11.8 %). Other drug interactions were also noted in patients receiving colchicine, verapamil, warfarin,

Table 1: Overview of the key features of statin therapy prescribing among the study population

Characteristic	Frequency (N)	Percentage (%)
Statin indication		
Primary prophylaxis	255	64.9
Secondary Prophylaxis	138	35.1
Total	393	100
Statin intensity during hospitalization		
No statin therapy	136	34.6
Low intensity	4	1
Moderate intensity	210	53.4
High intensity	41	10.4
Non-statin LLT*	2	0.5
Total	393	100
Hypertension		
Yes	331	84.2
No	62	15.8
Total	393	100
Chronic kidney disease		
Yes	134	34.1
No	259	65.9
Total	393	100

LLT - lipid-lowering therapy

Table 2: Overview of the prescribed lipid-lowering therapies (LLT) among hospitalized T2DM patients

Prescribed LLT	Frequency (N)	Percentage (%)
No statin therapy	136	34.6
Lovastatin 20 mg	1	0.3
Simvastatin 10 mg	2	0.5
Simvastatin 20 mg	62	15.8
Simvastatin 40 mg	137	34.9
Atorvastatin 10 mg	1	0.3
Atorvastatin 20 mg	7	1.8
Atorvastatin 40 mg	32	8.1
Gemfibrozil 300 mg	2	0.5
Atorvastatin 20 mg + Gemfibrozil 300	2	0.5
Atorvastatin 80 mg	2	0.5
Rosuvastatin 10 mg	1	0.3
Atorvastatin 40 mg + Gemfibrozil 300 mg	2	0.5
Atorvastatin 80 mg + Ezetimibe 10 mg	1	0.3
Atorvastatin 80 mg + Fenofibrate 145 mg	2	0.5
Atorvastatin 80 mg + Gemfibrozil 300 mg	1	0.3
Rosuvastatin 20 mg + Ezetimibe 10 mg	1	0.3
Pravastatin 20 mg	1	0.3
Total	393	100

Table 3: Change in pattern of prescribed lipid-lowering therapy (LLT) after hospitalization

Probable change of the prescribed LLT	Frequency	Percentage (%)
No LLT changes	174	44.3
Dose intensification (Continuation of the prescribed statin with increasing dose of ≥25%)	11	2.8
Dose reduction (Continuation of the prescribed statin with decreasing dose of ≥25%)	7	1.8
Discontinuation (Cessation of all types of LLT for three months or more)	44	11.2
Accretion (Continuation of the prescribed LLT with addition of a new non-statin or statin)	2	0.5
Subtraction (Change LLT from combination therapy to monotherapy)	3	0.8
Switch from/to statin (Convert one statin to another statin or non-statin or Convert non-statin to statin)	10	2.5
Initiation (initiate statins for those were not receiving any LLT)	49	12.5
No LLT	93	23.7
Total	393	100

Table 4: Evaluation of lipid-lowering therapy prescribing during hospitalization

Evaluation of lipid-lowering therapy (LLT) regimen	Frequency (N)	Percentage (%)
Appropriate (proper intensity statin regimen and no DDI)	131	33.3
Inappropriate (no statins or non-statin use in eligible patients)	138	35.1
Potentially inappropriate (drug interactions)	102	26
Potentially inappropriate (renal dosing adjustment)	20	5.1
Potentially inappropriate (statin Intensity)	2	0.5
Total	393	100

prednisolone, azole antifungals and macrolide antibiotics.

Change in prescribing pattern of lipid-lowering therapy after hospitalization

We have documented the given LLT before and after hospitalization. The aim was to examine the effect of hospital admission on the prescribing pattern of LLT. It has been found that nearly 44.3 % of the study cases did not exhibit any change in their prescribed LLT upon admission to the two hospitals. About 12.5% had statins initiated in-hospital. Conversely, 11.2 % of patients who were receiving LLT before hospital admission, had them stopped during their hospitalization for unclear reasons. The description and frequency of LLT pattern changes are displayed in Table 3.

Prescribing practice of LLT during hospitalization

We have classified the overall assessment of the prescribed LLT into three broad categories. Appropriate, inappropriate, and potentially inappropriate. We have divided the "potentially inappropriate" category further according to the proposed adjustment needed to be done regarding drug-drug interactions (DDI), renal impairment and intensity of the given statin. The least frequent proposed change was related to the concentration of the given statin. Only 2 cases have been given low-intensity statin although they had a history of CVD for which at least moderate-intensity one may better achieve a higher LDL-C reduction. A complete definition and frequency of each evaluation category are displayed in Table 4.

DISCUSSION

This study outlines real clinical practice-based assessment of statin prescribing.

It also provides insights on how the CPG recommendations affect prescribers' behavior. The percentage of cases eligible to receive statin therapy because of T2DM was twice than those being offered treatment because of previous CVD. It is clear that statin prescribing for primary prevention of CVD is not at the required level among our study cases despite many guideline recommendations. This could be due to the debate surrounding the net benefit of statin treatment [16]. Furthermore, we have found that simvastatin by its available concentrations, is the most commonly prescribed statin. This finding is not consistent with the latest national drug formulary review of statins that recommends atorvastatin as the first-line statin therapy for dyslipidemia [17]. More than half of the study population received a prescription with moderate-intensity statin therapy. The frequent prescribing of moderate intensity statins complies to most clinical guidelines regarding statins for primary prevention of CVD among T2DM patients [5].

A significant portion of patients on statin therapy has at least one potential drug interaction. The

overall percentage of drug interaction incidence is considered to be high. This warrants the need for more intensive screening of statin prescriptions to prevent potential interactions with concurrent medications. A list of common drug interactions with statins has been highlighted in the literature [18]. Five patients were given gemfibrozil as a combination therapy with a statin, which is not recommended as it does not confer any additional CVD protection benefit [5]. Therefore, there is a need for revising the current practice on the appropriate non-statin therapy to be offered as a combination therapy. On the other hand, only two patients were prescribed with ezetimibe although it is endorsed as a recognized and effective add-on therapy to statin treatment if a combination therapy is needed to enhance CVD risk reduction [18].

We have identified a list of pattern changes to the statin therapy before, and after hospitalization in the light of the definitions proposed earlier in a study conducted by Quek *et al* [19]. About half of the patients exhibit no changes in their prescribed lipid-lowering therapy after admission. Initiation of statin therapy to patients who did not previously receive any LLT was noted in 50 cases, which highlights the role and importance of the hospital team in optimizing diabetes care. However, a relatively significant portion (11.2 %) of our sample has had their statins discontinued upon admission for no valid reasons. This discontinuation percentage is larger than what has been previously highlighted in the Picker report in which 5 % of patients were stopped from taking statins [20].

Interestingly, claims of statin-related adverse effects were given as the reason for the high discontinuation percentage [14]. The unexplained LLT discontinuation upon admission underpins the need for healthcare practitioners to emphasize evidence-based practice regarding discontinuation of previous medications for patients with chronic diseases. Although our study has only documented the interruption imposed by prescribers, it is also recognized that the patient's non-adherence is one of the most critical challenges towards enhancing clinical outcomes following statin treatment. In this regard, the development of promising implements such as tailored medicine inventory tool could improve patient's adherence behavior towards their prescribed medications [21].

Concerning the overall evaluation of the prescribed statin therapy, this study showed that only 65% of prime candidates for statins were prescribed with them. Of these patients, about 40 % were receiving statin that interacts with at least one of their co-administered medications. Furthermore, about 20 patients required a renal dose adjustment to their prescribed statin. Less than 40 % of our study sample received statin treatment without any risk of drug interactions which we termed as "appropriate" prescribing. The overall percentage of 65 % is certainly laudable when compared against the findings of a prior US study that found only 52 % of patients with diabetes were receiving a statin therapy [13]. Moreover, our study's prescribing percentage is similar to what has been reported previously by Yusuf *et al.* which looked at the percentage of statin users in high-income countries, and higher than the percentage of statin receivers in middle and low-income countries reported in the same study [22].

Approximately one-third of our study patients (35 %) did not receive any statin therapy either alone or in the form of a combination therapy at the time of data collection. This portion of eligible patients who were not offered statin therapy is relatively smaller than what has been revealed previously by Fu, *et al.* wherein more than one-third of diabetic patients were not on statin treatment [23]. The primary finding of this study in which statins were under-prescribed contradicts the results of previous research that reported the overprescribing of lipid-lowering agents [24]. UK researchers have highlighted the impact of not offering statin therapy to patients at risk. They have estimated that statin under-prescribing may result in a high number of possibly avoidable CVD-related events [25].

Although there is an ongoing debate in the literature about the extent of statin efficacy particularly for primary prevention [26], our study highlights that not all eligible patients have been prescribed with a statin. Therefore, it will be hard to draw clinical practice-based recommendations on statin's efficacy when a significant proportion of eligible candidates are not even receiving their suggested statin treatment.

Limitations of the study

The study has several limitations. First, it was performed in only two tertiary hospitals in the state of Pahang. Therefore, it may not reflect the practice of statin therapy prescribing in other tertiary hospitals in Malaysia. Second, following a cross-sectional design and due to time constrains, no follow-up was planned to track changes in the pattern of statin therapy utilization following discharge of the patients from the hospitals.

CONCLUSION

The findings of this study indicate suboptimal management of diabetic dyslipidemia in a Malaysian hospital setting where a considerable portion of T2DM hospitalized patients did not receive a statin as part of the recommended medications for CVD prophylaxis. Closer monitoring and further dose adjustments are also warranted to ensure optimal statin therapy prescribing without significant drug interactions. Therefore, efforts to further improve statin prescribing should be considered. Prescribing interventions should focus on hospital healthcare professionals who are in a position to optimize medications for CVD prophylaxis among patients with T2DM.

DECLARATIONS

Acknowledgement

The study was supported by an internal grant (no. RIGS16-120-0284) from the Research Management Centre of International Islamic University Malaysia.

Conflicts of interest

No conflict of interest is associated with this study.

Contribution of authors

The authors declare that this work was done by the authors named in this article and all liabilities about claims relating to the content of this article will be borne by the authors.

REFERENCES

1. *Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 2013; 34(39): 3035–3087.*
2. *Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW, García FA, Gillman MW, Kemper AR, Krist AH, Kurth AE, et al. Statin Use for the Primary Prevention of Cardiovascular Disease in Adults US Preventive Services Task Force Recommendation Statement. JAMA 2016; 316(19): 1997-2007.*
3. *Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016; 388(10059): 2532-2561.*
4. *Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2016; 37(29): 2315–2381.*
5. *American Diabetes Association. Standards of medical care in diabetes—2016 abridged for primary care providers. Clin Diabetes 2016; 34(1): 3–21.*
6. *Malaysian Clinical Practice Guideline. Management of Type 2 Diabetes Mellitus; 2015: 1–129.*
7. *Faridah Aryani MY, Fatimah AR, Sivasampu S, Rosliza L, Rosaida MS, Kiew KK, Tee HP, Ooi BP, Ooi ET, Ghan SL, et al. Malaysian Statistics on Medicines 2009, 2010 and 2014: pp 1–206.*
8. *Elnaem MH, Nik Mohamed MH, Huri HZ, Azarisman SM, Elkalmi RM. Statin therapy prescribing for patients with type 2 diabetes mellitus: A review of current evidence and challenges. J Pharm Bioallied Sci 2017; 9(2): 80–87.*
9. *Casula M, Tragni E, Catapano AL. Adherence to lipid-lowering treatment: The patient perspective. Patient Prefer Adherence 2012; 6: 805–814.*
10. *Banach M, Rizzo M, Toth PP, Farnier M, Davidson MH, Al-Rasadi K, Aronow WS, Athyros V, Djuric DM, Ezhov MV, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Arch Med Sci 2015; 11(1): 1–23.*
11. *Mancini GJ, Baker S, Bergeron J, Fitchett D, Frohlich J, Genest J, Gupta M, Hegele RA, Ng D, Pearson GJ, et al. Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Canadian Consensus Working Group Update (2016). Can J Cardiol 2016; 32(7): S35–S65.*
12. *Banks E, Crouch SR, Korda RJ, Stavreski B, Page K, Thurber KA, Grenfell R. Absolute risk of cardiovascular disease events, and blood pressure-and lipid-lowering therapy in Australia. Med J Aust 2016; 204(8): 320e1–320e8.*
13. *Johansen ME, Green LA, Sen A, Kircher S, Richardson CR. Cardiovascular risk and statin use in the United States. Ann Fam Med 2014; 12(3): 215–223.*
14. *Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: A nationwide prospective cohort study. Eur Heart J 2016; 37(11): 908–916.*
15. *Czarkowski M. Helsinki Declaration--next version. Pol Merkur Lekarski 2014; 36(215): 295-297*
16. *Greenland P, Bonow RO. Interpretation and Use of Another Statin Guideline. JAMA Cardiol 2016; 316(19): 1977–1979.*
17. *Ramli A, Aljunid SM, Sulong S, Yusof FA. National Drug Formulary review of statin therapeutic group using the multiattribute scoring tool. Ther Clin Risk Manag 2013; 9: 491–504.*
18. *Grundy SM. Primary prevention of cardiovascular disease with statins: Assessing the evidence base behind clinical guidance. Clin Pharm 2016; 8(2): 1–19.*

19. Quek RG, Fox KM, Wang L, Li L, Gandra SR, Wong ND. Lipid-lowering treatment patterns among patients with type 2 diabetes mellitus with high cardiovascular disease risk. BMJ Open Diabetes Res Care 2015; 3(1): e000132.
20. Yusuf S. Why do people not take life-saving medications? The case of statins. Lancet 2016; 388(10048): 943–945.
21. Wouters H, Van Dijk L, Geers HC, Winters NA, Van Geffen EC, Stiggelbout AM, Bouvy ML. Understanding statin non-adherence: knowing which perceptions and experiences matter to different patients. PLoS One 2016; 11(1): e0146272.
22. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, Gupta R, Kelishadi R, Iqbal R, Avezum A, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. Lancet 2011; 378(9798): 1231–1243.
23. Fu AZ, Zhang Q, Davies MJ, Pentakota S-R, Radican L, Seck T. Underutilization of statins in patients with type 2 diabetes in US clinical practice: a retrospective cohort study. Curr Med Res Opin 2011; 27(5): 1035–1040.
24. Smith MA, Cox ED, Bartell JM. Overprescribing of lipid lowering agents. Qual Saf Health Care 2006; 15(4): 251–257.
25. Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, Bhaskaran K. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ 2016; 353: i3283.
26. Horton R. Off line : Lessons from the controversy over statins. Lancet 2016; 388(10049): 1040.