



**EVALUATION OF EDUCATIONAL INTERVENTION  
IMPACT ON LIPID-LOWERING THERAPY  
PRESCRIBING FOR PATIENTS WITH TYPE 2  
DIABETES IN PAHANG, MALAYSIA**

**BY**

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## ABSTRACT

Hyperlipidemia is a major contributor to the evolution of cardiovascular disease (CVD) among patients with type 2 diabetes mellitus (T2DM). This study aimed to describe the lipid-lowering therapy (LLT) prescribing pattern among patients with T2DM, evaluate the appropriateness of LLT prescribing, assess the attainment of the primary target (LDL-C) for diabetic dyslipidemia treatment and evaluate the impact of academic detailing program on enhancing healthcare providers' knowledge and the overall appropriate LLT prescribing among Malaysian patients with T2DM. The study followed a quasi-experimental design with a control group and pre-tests to assess the impact of educational intervention on the rational statin therapy prescribing among the inpatient and outpatients with T2DM. The impact of educational intervention on knowledge of health care providers concerning statin therapy prescribing was assessed by comparing the achieved knowledge scores before and after the intervention using the same study questionnaire. The evaluation of the appropriateness of statin therapy prescribing was mainly based on the 2015 Malaysian CPG for treatment of patients with T2DM that recommended statin therapy for all patients between 40 and 75 years. The output of the evaluation process was classified into three main classifications, which were appropriate, inappropriate, or potentially inappropriate. A total of 782 hospital records and 816 primary care records were reviewed. Majority of patients were of Malay ethnicity. The prevalence of statins prescribing was about 69% (n=537) and 87% (n=715) in the hospital and primary care setting, respectively. The most commonly prescribed LLT in all settings was moderate intensity simvastatin-based regimens. Prevalence of potential drug interactions were 33% in hospital and 17% in primary care setting. Approximately, 63% of the study subjects were not able to achieve target LDL-C values in primary care. Only 37.5% (hospital) and 71.5% (primary care) of study subjects were receiving appropriate LLT. Regarding the knowledge assessment, healthcare providers' mean score after the educational session was ( $6.73 \pm 1.37$  points) as opposed to the pre-session scores ( $5.28 \pm 1.71$  points). The educational outreach program elicited a statistically significant difference in providers' knowledge scores of 1.450 point (95% CI, 0.918 to 1.982),  $p < .0005$ ,  $d = 0.87$ . The prescribing assessment of educational intervention impact showed a statistically significant difference  $X^2 (2) = 18.390$ ,  $p < 0.001$ . In the post-intervention phase, the proportion of appropriate LLT prescribing was (n = 246, 61.7%) compared to pre-intervention phase (n = 188, 47.1%),  $p < 0.0166$ . Moreover, there was a statistically significant difference in the proportion of inappropriate LLT prescribing between the post-intervention phases compared to pre-intervention phase (n = 81, 20.3% versus n = 125, 31.3%),  $p < 0.0166$ . By contrast, there was no statistically significant difference between the two proportions of LLT prescribing in the control group  $X^2 (2) = 3.031$ ,  $p = 0.220$ . There was a need to improve the management of diabetic dyslipidemia in different practice settings. Still, a significant portion of T2DM subjects was not able to attain LDL-C treatment targets. Prescribing-improvements interventions focused on healthcare providers could potentially have a positive impact on the providers' knowledge and their prescribing of CVD prophylaxis medications among patients with T2DM.

## خلاصة البحث

ارتفاع دهون الدم هو أحد العوامل الرئيسية في حدوث أمراض القلب بين المرضى الذين يعانون من داء السكري من النمط الثاني . وكانت أهداف الدراسة هي تقييم وصف وفعالية العلاج بخفض الدهون بين المرضى الذين يعانون من داء السكري من النمط الثاني . وكذلك تقييم تأثير برنامج تعليمي أكاديمي على تعزيز معرفة مقدمي الرعاية الصحية بعلاجات خفض الدهون مع التركيز بشكل رئيسي على أدوية الستاتين و تحسين وصفها . استند تقييم مدى ملاءمة وصف أدوية الستاتين بشكل رئيسي على الإرشادات الموصى باتباعها والتي أوصت بوصف علاج الستاتين لجميع مرضى داء السكري من النمط الثاني بين 40 و 75 سنة . تم تصنيف ناتج عملية التقييم إلى ثلاثة تصنيفات رئيسية ، وهي ملائمة أو غير ملائمة أو غير مناسبة . تمت مراجعة ما مجموعه 782 سجلاً لمرضى في المستشفيات و 816 سجل لمرضى يترددون على مراكز الرعاية الأولية . كان انتشار وصفات العلاجات المنخفضة لدهون الدم بنسبة حوالي 69 % و 87 % في المستشفيات و مراكز الرعاية الأولية ، على التوالي . كان علاجات خفض الدهون الأكثر وصفا هي القائمة على جرعات متوسطة من عقار سيمفاستاتين . تم تحديد نسب التفاعلات المحتملة مع العقاقير الأخرى 33 % في المستشفيات و 17 % في مراكز الرعاية الأولية . ما يقرب من 63 % من أفراد الدراسة لم يتمكنوا من تحقيق قيم دهون الدم منخفضة الكثافة المستهدفة في الرعاية الأولية . فقط 37.5 % من أفراد الدراسة في المستشفيات و 71.5 % في مراكز الرعاية الأولية كانوا يتلقون علاجات خفض الدهون الملائمة لهم . فيما يتعلق بتقييم المعرفة ، فقد أثار البرنامج التعليمي الأكاديمي فرقا يعتمد به إحصائياً في درجات المعرفة بمقدار 1.450 نقطة . أظهر تقييم أثر التدخل التعليمي وجود فرق ذو دلالة إحصائية في مرحلة ما بعد التدخل ، كانت نسبة الوصف الملائم لعلاجات خفض الدهون (61.7 %) مقارنة مع (47.1%) في مرحلة ما قبل التدخل . على النقيض من ذلك ، لم يكن هناك فروق ذات دلالة إحصائية بين نسب الوصف الملائم لعلاجات خفض الدهون في المستشفيات والمراكز التي لم تستهدف بالتدخل التعليمي . كشفت الدراسة أن هناك علاج دون المستوى الأمثل لارتفاع دهون الدم وان جزء كبير من أفراد الدراسة لم يتمكن من تحقيق أهداف العلاج . يمكن للتدخلات التعليمية التي تركز على مقدمي الرعاية الصحية أن يكون لها تأثير إيجابي على معرفة مقدمي الرعاية و تحسين وصف الأدوية الموصى بها للوقاية من الأمراض القلبية بين المرضى الذين يعانون من داء السكري من النمط الثاني .

## **APPROVAL PAGE**

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## DECLARATION

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## LIST OF ABBREVIATIONS

LLT	Lipid-lowering therapy
CVD	Cardiovascular disease
T2DM	Type 2 diabetes mellitus
ASCVD	Atherosclerotic cardiovascular disease
CPG	Clinical practice guidelines
HC	Health care
NAFLD	Non-alcoholic fatty liver disease
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
TG	Triglycerides
DDI	Drug-drug interaction
PCC	Primary care clinic

# **CHAPTER ONE**

## **INTRODUCTION**

### **1.1 BACKGROUND OF THE STUDY**

#### **1.1.1 Cardiovascular Diseases and Type 2 Diabetes Mellitus**

Cardiovascular disease (CVD) is recognised as the principal cause of mortality among adult Malaysians for over a decade (Ministry of Health Malaysia, 2017). Type 2 diabetes mellitus (T2DM) and hypercholesterolemia are well-established CVD risk factors, and its prevalence is increasing over the years in an alarming trend (Institute for Public Health, 2015).

According to the latest National Health and Morbidity Survey (NHMS) 2015 report, there is a relative increase of 15% in the prevalence of T2DM with overall prevalence percentage of 17.5%. The same increasing pattern has been observed for the prevalence of hypercholesterolemia that exhibits a relative increase of 46% with overall prevalence percentage of 47.7%. The incidence of cardiovascular diseases among patients with T2DM was linked to the abnormal level of low-density lipoprotein cholesterol (LDL-c), and the reduction of LDL-c levels was associated with numerous evidence of decreasing the incidence of CVD event (Pedersen, 2016). The use of lipid-lowering therapy particularly statin therapy was associated with decreasing the CVD risk by 40 to 50% compared with non-statin therapy users (Ting et al., 2010).

It is well-established that T2DM patients are at high risk for major adverse cardiovascular events (MACE), in addition, MACE risk is even greater with longer disease duration and presence of carotid artery stenosis (Noh et al., 2017). According to a 5-year Chinese cohort study aimed to understand the real clinical benefit of offering

statin therapy for T2DM patients, it has been shown that statin therapy was related to a significant decrease in the CVD incidence and all-cause mortality (Fung, Wan, Chan, & Lam, 2017).

### **1.1.2 Dyslipidemia in T2DM Patients**

Dyslipidemia in T2DM patients results from the increased lipolysis occur in the visceral adipocytes lead to further increase of the free fatty acids in liver and plasma. Either insulin deficiency or resistance are the causes of the increased lipolysis that is frequently associated with decreased activity of lipoprotein lipase (D. R. Pokharel et al., 2017).

The common patterns of lipid abnormalities observed in diabetic dyslipidemia are elevated fasting, postprandial triglycerides, elevated LDL-cholesterol, and low HDL-cholesterol. The observed changes in the lipid profile parameters are regarded as significant indicators for the increased CVD risk observed in T2DM patients (Wu & Parhofer, 2014).

It is well known that the management of T2DM is directed towards improving patient's quality of life by reducing the acute and chronic complications (Malaysian Clinical Practice Guideline, 2015). Therefore, optimal management of diabetic dyslipidemia is paramount in preventing or delaying the incidence of diabetes-related cardiovascular complications. Lipid-lowering therapy mainly statins in addition to lifestyle modifications is the recommended approach to manage diabetic dyslipidemia and achieve target lipid levels in most of the T2DM patients (Bell, Al Badarin, & O'Keefe, 2011).

For diabetic dyslipidemia, numerous studies have shown the clinical benefit of statin therapy prescribing in patients with T2DM. In a Taiwanese study aimed to evaluate the effect of statin therapy in patients with T2DM, statin therapy was linked to

a significant decrease in all-cause mortality risk at all correspondent LDL-c levels with the exception of very low LDL-c < 1.6 mmol/l (Chen et al., 2018). Moreover, previous research focusing on reducing the CVD risk among patients with T2DM has demonstrated that the achievement of LDL-c level of less than 2.6 mmol/l was associated with a substantial decrease in the overall CVD risk (Fung et al., 2017; Stone et al., 2014). The finding complies with the recommended reduction in LDL-c level for primary CVD prevention as per the statements of the clinical practice guidelines (Catapano et al., 2016).

### **1.1.3 Statin Therapy Indications**

Statin therapy has relatively broad therapeutic indications for primary or secondary CVD prevention in patients with hypercholesterolemia, atherosclerotic cardiovascular disease (ASCVD) and T2DM (Stone et al., 2014). Therefore, the appropriate statins prescribing and utilisation will result in decreasing the CVD risks and complications.

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) had released updated recommendations for blood cholesterol the treatment as a substantial modality to reduce atherosclerotic cardiovascular risk in adults. The main feature of these updated guidelines is decreasing the threshold of CVD risk that makes more patients eligible to receive statin therapy. These guidelines were the basis for a series of updates that relatively broaden the scope of using lipid-lowering therapy in the clinical practice (Nayor & Vasan, 2016).

Following the application of these updated blood cholesterol management guidelines to the clinical practice, one U.S population-based study showed an increase by 12.8 million out of 115.4 million in the number of adults who would be eligible for

statins therapy especially older adults without cardiovascular disease (Pencina et al., 2014).

Statin medications have been endorsed as first-line therapeutic options for hyperlipidemia, with several studies reported limited differences between them (Godman et al., 2015). Statin therapy is indicated to treat patients with ASCVD as secondary prevention and to reduce the risk of ASCVD in patients with diabetes and hypercholesterolemia as primary prevention. Patients with T2DM aged 40–75 years having their LDL-c between 1.8-4.9 mmol/L and without ASCVD are considered among the four (4) major statins benefit groups in whom all efforts should be directed to reduce the overall incidence of ASCVD events.

Regarding their relative extent of decreasing LDL-c, statin therapy could be classified as high, moderate and low-intensity statins (Stone et al., 2014). Table 1.1 represents all statin therapy by their estimated LDL-c reduction intensity.

Table 1.1 Classification of statin therapy according to their relative LDL-C reduction

<b>Low intensity</b>	<b>Moderate intensity</b>	<b>High intensity</b>
<b>When taken daily, will lower LDL-c in average of 20-25%</b>	<b>When taken daily, will lower LDL-c in average of 30% to &lt; 45%</b>	<b>When taken daily, will lower LDL-C in average of ≥ 45%</b>
<b>Atorvastatin 5 mg</b>	<b>Atorvastatin 10-20 mg</b>	<b>Atorvastatin 40-80 mg</b>
<b>---</b>	<b>Rosuvastatin 5-10 mg</b>	<b>Rosuvastatin 20 mg</b>
<b>Lovastatin 20 mg</b>	<b>Lovastatin 40-80 mg</b>	<b>---</b>
<b>Pravastatin 10-20 mg</b>	<b>Pravastatin 40-80 mg</b>	<b>---</b>
<b>Simvastatin 10 mg</b>	<b>Simvastatin 20-40 mg Or Simvastatin 10 mg (or any low intensity statin) in addition to ezetimibe 10 mg</b>	<b>Simvastatin 40 mg (or other moderate intensity statins) plus ezetimibe 10 mg</b>

Statins eligibility assessment according to these updated guidelines has been investigated in a Korean study involves 19, 920 participants in a health screening program. The results support increasing the number of persons who are qualified to get a benefit from statins therapy (Rhee et al., 2015). Similarly, in a large European population study investigated the impact of guidelines updates on the statin therapy-eligibility, a significant increase in the number of patients eligible to benefit from statin therapy was reported particularly among patients aged 55 years or older (Kavousi et al., 2014). From the previous studies, it is noticeable that there is a change in the statin therapy-eligibility where relatively more patients could attain clinical benefit while there is no risk of overestimation of statins use. Therefore, it is proposed that this study could describe and estimate the change in prescribing patterns of statin therapy and assess the extent of the compliance with CPG recommendations in the daily clinical practice.

In the real clinical practice, prescribing of statin therapy for primary and secondary CVD prophylaxis has frequently been reported to do not comply with the CPG recommendations. The undertreatment of patients at high CVD risk was revealed in one study by Finnikin et al., in which statin therapy was not initiated in many eligible candidates in the general practice (Finnikin, Ryan, & Marshall, 2017). Moreover, it has been highlighted in one study conducted in the US that only one-quarter of the statin-eligible population has been offered the treatment in the daily clinical practice, in addition, those untreated patients are more prone to develop potentially chronic CVD (Navar et al., 2017). Also, it has been shown that failure to reduce LDL-c with recommended lipid-lowering therapy has been related to increased risk of cardiac events (Yeh, Yin, Tseng, Lin, & Yeh, 2017). The enhancement of prescribing efficiency of statin therapy and use of high strength statins have been associated with improvements

in clinical outcomes as shown in a Scottish study that audits the utilisation of statin therapy over ten years (Bennie, Godman, Bishop, & Campbell, 2012).

## **1.2 STATEMENT OF THE PROBLEM**

The recent edition of the national clinical practice guidelines (CPG) for the management of patients with T2DM has recommended statin therapy for all T2DM patients in the age between 40 to 75 years regardless baseline LDL cholesterol levels (Malaysian Clinical Practice Guideline, 2015). However, the underutilization of lipid-lowering therapy among Asian patients with T2DM has been reported in the literature (Wang et al., 2014). The report of the Malaysian diabetes registry has highlighted the suboptimal medical management of dyslipidemia and the importance of improving the utilisation of pharmacological treatment choices (Chew et al., 2012).

According to the report on medicines use in Malaysia, statin therapy underutilization in the Malaysian healthcare facilities has been highlighted (Siti Fauziah et al., 2014). There is a need to optimise the use of the statin treatment in clinical practice. This report recommends that efforts should be directed to improve medical treatment of dyslipidemia for both primary and secondary CVD prevention. Moreover, there is a need to intensify lipid-modifying treatment to reduce national cardiovascular health burden and health care cost in the future.

While planning to enhance the statin therapy rational prescribing, it is worthy to note that there are gaps in knowledge of Malaysian medical practitioners and their practice of the rational prescribing of LLT in compliance with the latest issue of the national dyslipidemia guidelines (Said & Chia, 2017). Therefore, educational intervention and further promotion of the CPG recommendations are considered as an integral part of any prescribing enhancement initiative.

The main objectives of this project were to describe and assess the current prescribing practice of lipid-lowering therapy among T2DM patients and then evaluate the effect of an educational intervention targeting health care providers on enhancing their knowledge and practice of rational statin therapy prescribing. Up to the best of our knowledge, there is no recent assessment of statin therapy prescribing in Malaysian healthcare settings focusing on T2DM patients after the release of 2015 CPG for management of T2DM. In addition, there is no previous study investigating the effect of educational intervention on healthcare providers' knowledge and practice of prescribing statin therapy as a part of T2DM medical management. Therefore, this study was aimed to fill this gap and provide:

1. Current insight into the prevalence of prescribing the first-line statin treatment among Malaysian T2DM patients.
2. Description of common pattern changes in the prescribing of lipid-lowering therapy in hospital and primary care setting.
3. Real practice-based assessment of the quality of the current prescribing practice of statin therapy in different Malaysian healthcare facilities in Pahang.
4. Assessment of the effect of an interactive educational outreach intervention on enhancing knowledge and practice of healthcare providers regarding their prescribing of statin therapy in the daily clinical practice.

### **1.3 THEORETICAL FRAMEWORK**

Primary or secondary CVD prophylaxis as a clinical outcome is affected mainly by the appropriate prescribing of lipid-lowering therapy (LLT) as well as it is also affected by the extent of patient's adherence to the prescribed LLT. In this work, the focus of the study was directed to the appropriate LLT prescribing. The appropriateness of LLT