

Original Research Article

Ischemic heart disease: effectiveness and safety of statin treatment in a Malaysian tertiary healthcare facility

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Abstract

Purpose: To determine the effectiveness and safety of statins in ischemic heart disease (IHD) patients in a Malaysian tertiary hospital.

Methods: This cross-sectional observational study was conducted at Universiti Kebangsaan Malaysia (UKM) Medical Center, Kuala Lumpur, Malaysia and patients were included if they were diagnosed with IHD and treated on statins for three months, or had IHD with no statins prescribed.

Results: A total of 72 patients admitted to the medical ward due to IHD were enrolled in this study. Fifty three of them were statin users and 19 patients had no history of statin treatment. The most commonly used statin was lovastatin ($n = 42, 79.2\%$), atorvastatin ($n = 5, 9.4\%$), simvastatin ($n = 3, 5.7\%$) and rosuvastatin ($n = 3, 5.7\%$). Risk factors found in the study population were dyslipidaemia ($n = 52, 72\%$), hypertension ($n = 58, 80.1\%$), diabetes ($n = 36, 50\%$), advanced age ($n = 63, 87.5\%$), smoking ($n = 19, 26.4\%$) and family history ($n = 16, 22.2\%$). Patients that were on statin were more likely to achieve targeted LDL-C levels compared to those that did not achieve LDL-C levels ($\chi^2 = 7.25, p = 0.007$). There were also no difference in liver enzyme values between statin users and non-statin users.

Conclusion: This study provides information regarding safety and efficacy of statins in the local population and the need for a more stringent approach in achieving targeted lipid levels in IHD patients.

Keywords: Effectiveness of statins, Safety of statin, Ischemic heart disease, Cardiovascular, Liver enzymes, Hypertension, Diabetes

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INTRODUCTION

Ischemic heart disease (IHD) is a rapidly increasing problem around the world [1]. It is also the leading cause of death in Malaysia, accounting for 2,556 deaths in 2002 [2]. Several risk factors have been identified that increases the likelihood of IHD. The established risk factors based on the Wilson study results include current smoking, hypertension, dyslipidemia, diabetes, male sex and advanced age [3]. The presence of these risk factors contributes to the basic pathogenesis of atherosclerosis. Therefore, reducing the risk factors decreases the likelihood

of disease progression and coronary morbidity as well as mortality.

Pharmacological intervention for primary and secondary prevention of IHD is by lowering cholesterol level. This is to prevent atherosclerosis that may lead to incidence of cardiovascular events. In order to achieve the targeted goal, HMG-CoA reductase inhibitor (statins) have been indicated as the first line drug of choice in various guidelines [1]. The available statins include atorvastatin, fluvastatin, lovastatin, rosuvastatin, pravastatin, pitavastatin and simvastatin. The mechanism of action of

statins is inhibition of the rate-limiting enzyme in cholesterol synthesis, HMG-CoA reductase. Nevertheless, each statin is different in terms of chemical structure and efficacy in lipid reduction. The differences in absorption, plasma protein binding, excretion and solubility therefore exhibit variable dose-related efficacy in reducing LDL-C [4].

The primary effect of statin therapy is LDL-C reduction [5]. Reduction in LDL-C level will reduce the progression of atherosclerotic plaque, reduce mortality and promote revascularization in patients with IHD [6]. The response to statin therapy also varies between each individual. However, despite the difference in effect and response to different statins, LDL-C reduction can be expected to range from 20 to 63 % [7]. Recommended therapeutic doses, which typically reduce LDL-C by 30 to 45 %, are atorvastatin 10 to 20 mg, fluvastatin 40 to 80 mg, lovastatin 40 mg, pitavastatin 1 to 4 mg, pravastatin 40 mg, rosuvastatin 10 mg, and simvastatin 20-40 mg [7]. Apart from LDL-C reduction, statin has also been reported to elevate HDL-C levels [5]. The elevations in HDL-C are typically more moderate, with an approximate 5 to 15 % increase. On the other hand, triglyceride levels can be reduced by 10 to 37 % with statins [7].

In view of the variety in effectiveness of the statins, inter-individual response should be considered when initiating the drug. Therefore, this study aims to look at the effectiveness of different statins in reducing lipid levels in IHD patients in the local population.

METHODS

Study design

This study was conducted as a prospective cross-sectional, observational study in UKM Medical Center. Patients included in this study were patients admitted to the medical ward due to incidence of IHD. Samples were selected from the ward admission record. Patients were included in the study if they were 18 years and above and diagnosed with IHD and were either on statins for the past three months prior to admission, or have not been on statins at all. Patients with incomplete data were excluded from the study. The study was approved by UKM Research Ethics Committee, The National University of Malaysia (no. UKM 1.5.3.5/244/NF-013-14/Dr Endang) and was carried out in accordance with International Conference on

Harmonisation of Good Clinical Practice Guidelines [8].

Data collection

Patients with IHD were divided into statin and non-statin groups. In this study, the use of statin is defined as patients taking statins three months prior to hospitalization. Information on type, dose and duration of statin treatment were collected. Lipid profile (LDL-C, HDL-C, triglyceride and total cholesterol) and liver enzymes (ALT and ALP) were also collected. Other data collected were age, gender, height, weight, race, medical history, medication history, social history and family history.

Data analysis

All data collected were analyzed using SPSS version 21.0 software package. Descriptive analysis was conducted to observe for frequency in selected variables. Categorical variables were presented as absolute (n) and relative frequencies (percentages) while numerical data were presented as mean values and standard deviations. The differences in categorical variables were compared using Pearson Chi Square (χ^2) and Fisher's Exact Test. The differences in continuous variables were examined by independent student t-test for two independent variables and a one way analysis of variance (ANOVA) for more than three independent variables. All statistical values were considered significant at $p < 0.05$.

RESULTS

Demographic data

Out of 72 patients with IHD, 53 (73.6 %) patients were on statins 3 months prior to admission while 19 (26.4 %) patients were not on any statin treatment prior to admission (Table 1). The age of patients ranged from 35 to 87 years old with a mean age of 61.76 ± 11.49 years. Patients with IHD that were not on statin prior to admission was significantly younger than those that were on statins ($t(20) = 2.576$, $p = 0.012$). There were more males on statin use compared to females ($\chi^2 = 4.95$, $p = 0.026$). More patients were on statins if they were noted to have a history of IHD compared to those that did not have a history of IHD ($\chi^2 = 14.17$, $p = 0.0001$). The most commonly used statin was lovastatin (n = 42, 79.2 %), atorvastatin (n = 5, 9.4 %), simvastatin (n = 3, 5.7 %) and rosuvastatin (n = 3, 5.7 %). Doses of the statins used in the study population were observed to be low to moderate doses [5].

Risk factors present in the study population were dyslipidaemia (n = 52, 72 %), hypertension (n = 58, 80.1 %), diabetes (n = 36, 50 %), advanced age (n = 63, 87.5 %), smoking (n = 19, 26.4 %) and family history (n = 16, 22.2 %).

Effectiveness of statins

During the study period, 52 (72.2 %) patients had dyslipidemia; with high LDL-C, high TG, high total cholesterol, low HDL-C or a combination of 2 to 3 lipid abnormalities. From a total of 53 patients on statin, 33 (62 %) patients achieved target LDL-C goal, 34 (64.2 %) patients achieved target triglyceride goal and 39 patients (73.6 %) achieved the target HDL-C goal as recommended by NCEP ATP III. Patients that

were on statin were more likely to achieve targeted LDL-C levels compared to those that did not achieve LDL-C levels ($\chi^2 = 7.25, p = 0.007$). There was no difference in achieved target lipid levels between race and gender. There was also no correlation between age and weight with levels of lipids achieved.

Safety of statins

No adverse reactions were reported during the use of statins in this study population. However, liver function tests were examined in patients included in the study. It was found that the levels of aminotransferase (ALT) and alkaline phosphatase (ALP) were not-significant different between the statin and non-statin users.

Table 1: Demographic data of the study population (N=72)

Variable	Statin users		Total (N = 72)
	Yes (n = 53)	No (n = 19)	
Age, years (mean ± SD)	63.77 ± 10.81	56.16 ± 11.73	61.76 ± 11.49
Weight, kg (mean ± SD)	69.23 ± 11.57	63.42 ± 10.95	67.71 ± 1.6
Gender, n (%)			
Male	35 (83)	7 (17)	42 (58)
Female	18 (60)	12 (40)	30 (42)
Ethnicity, n (%)			
Malay	26 (79)	7 (21)	33 (46)
Chinese	19 (73)	7 (27)	26 (36)
Indian	8 (62)	5 (38)	13 (18)
Previous history of IHD, n (%)			
Yes	35(92)	3(8)	38(53)
No	18(53)	16(47)	34(47)

Table 2: Lipid levels of the study population on admission (N = 72)

Lipid levels	Statin users		^a P-value
	Yes (n = 53)	No (n = 19)	
Total cholesterol			
(> 5.18 mmol/L)	24 (45%)	13 (68%)	0.083
(≤ 5.18 mmol/L)	29 (55%)	6 (32%)	
LDL-C			
(> 3.4 mmol/L)	20 (38%)	14 (74%)	0.007*
(≤ 3.4 mmol/L)	33 (62%)	5 (26%)	
Triglyceride			
(> 1.7 mmol/L)	19 (36%)	9 (47%)	0.371
(≤ 1.7 mmol/L)	34 (64%)	10 (53%)	
HDL-C			
(≤ 1 mmol/L)	14 (26%)	8 (42%)	0.203
(> 1 mmol/L)	39 (74%)	11 (58%)	

* P < 0.05 considered significant; ^a Chi-squared test

Table 3: Liver enzymes of the study population on admission (N=67)

Lipid level	Statin users n(%)		^a P-value
	Yes (n = 48)	No (n = 19)	
ALT			
(≤ 44 U/L)	40 (83%)	17 (89%)	0.525
(> 44 U/L)	8 (17%)	2 (11%)	
ALP			
(≤104 U/L)	39 (81%)	16 (84%)	0.776
(>104 U/L)	9 (19%)	3 (16%)	

* $P < 0.05$ considered significant; ^a Chi-squared test

DISCUSSION

Statins are the most widely used drugs around the world. The use of statins, in particular is highly recommended in IHD patients. This is especially true in view of the effectiveness in reducing lipid levels in this group of patients [9]. There have been numerous studies demonstrating the lipid lowering effects of statin in various patient populations [2,4]. However, its effects have been notably varied with inter-individual differences [2]. The aim of this present work is to evaluate the effectiveness of statins in IHD patients in the local population was successful. In general, the number of male IHD patients was higher than female, which was similarly observed in previous studies [2,3].

Several major risk factors were also identified in the present study population such as smoking, hypertension, dyslipidemia, diabetes and advanced age [10]. Early identification of these risk factors in high risk patients as well as patients with known IHD is beneficial. Early and vigorous approach in risk-factor reduction should be performed in order to reduce IHD complications. Interventions include non-pharmacological approach with therapeutic lifestyle modification such as smoking cessation, dietary modification and physical activity as well as drug therapy to treat hypertension, diabetes and dyslipidemia [10].

Dyslipidemia is common amongst patients admitted due to IHD [5]. Early screening of lipid levels in high risk groups is essential in order to detect lipid abnormalities. The NCEP-ATP III recommends beginning screening of all adults at age 20, regardless of cardiovascular risk profile [11]. Early screening promotes healthy behavior and increases public awareness of cholesterol levels [12]. The most prevalent lipid abnormalities in this current work were high total cholesterol followed by high LDL-C levels. The lack in achieving LDL-C levels is a common risk

factor in incidences of IHD complications. As structural homologues of 3-hydroxy 3-methylglutaric acid, statins competitively inhibit HMG-CoA reductase, the last regulated step in the synthesis of cholesterol. These drugs lower serum LDL cholesterol concentrations by up-regulating LDL-receptor activity as well as reducing the entry of LDL into the circulation [13]. Elevated LDL-C has been demonstrated to correlate with recurrent incidence of cardiac events [1]. Indeed, it is important to note that in the present study, there was a strong association between statin use and levels of LDL-C. It was noted that those that were not on statins were more likely to have higher levels of LDL-C compared to patients with normal LDL-C levels. Thus, statin treatment in the local population is significantly associated with a better LDL-C level. Despite the use of statin, it was noted that some patients failed to achieve target lipid goal. Many factors and conditions may contribute to this failure. Despite the low to moderate doses of statin used [5], it has been reported that low HDL cholesterol persisted in more than 50 % of high-risk patients despite statin usage [14]. In this study several factors may have contributed to the failure of treatment. The effect of smoking in increasing triglyceride level has been reported. This is due to secretion of catecholamines which cause lipolysis. Effect of smoking in altering lipid level differs between ethnic groups with higher lipid levels observed in Asian smokers compared to African smokers [15].

Plasma levels of HDL-C have also been shown to have a strong genetic basis with heritability estimates of 40-60 % [16]. Therefore, it can be suggested that in patients with a family history of premature CAD, combination therapy of statins with other agents such as fibrates and niacins can be used [17]. Fibrates mainly affect HDL-cholesterol level by stimulating lipoprotein-lipase activity and thereby facilitates the clearance of chylomicrons and very low density lipoproteins from the plasma. This makes fibrates particularly

suitable for the subgroup of patients who have low HDL-cholesterol levels [18].

Besides this, non-pharmacological strategies for the treatment of dyslipidemia should also be included. Inadequate counseling about proper diet and exercise can also contribute to the failure in reaching target goals. Combination therapies of diet and exercise interventions are efficacious [19]. Combination lifestyle treatments are particularly advantageous because diet and exercise elicit complementary effects on lipid profiles.

The use of statins is relatively safe with adverse reactions being relatively mild and often transient. The most common adverse effects of statins are gastrointestinal upset, muscle aches, and hepatitis [5]. Rarer problems associated with statins are myopathy [13]. However, one of the most important adverse effects associated with statins as a class of drugs is the asymptomatic increase in liver transaminases as well as myopathy [5]. The likelihood of elevated ALT and ALP levels that can cause serious adverse effects to the liver system however is not common. Indeed this is similarly observed in the present work. Previous studies have also reported very minimal incidence (about 1 %) of elevated liver enzymes with the majority occurring during three months of treatment.

The incidence of elevated liver enzymes have also been shown to be dose related [5,20]. The lack of serious liver abnormalities in the current work can be attributed to the low dose of statin use in the present population. Furthermore, statin therapy at low to moderate doses has been previously found to not be associated with a significant risk of liver function abnormalities [21]. It is suggested that marked elevation of liver enzymes are rare and are most likely to occur when potential drug interactions or comorbidities are present (including preexisting liver disease) or the highest dose of statin is used [5,22].

Limitations of the study

In this study, other factors that may also contribute to the outcomes observed, such as diet intake, patient's lifestyle and compliance level, were not measured. A small sample size and unequal distribution of samples in every category may also be one of the drawbacks in the quality of data.

CONCLUSION

The study was able to identify the effectiveness and safety of statins in IHD patients of the local

population. However, it should be noted that there were a number of patients that were not prescribed statins despite being diagnosed with IHD. Further work should be performed to identify reasons statins were not prescribed to these patients. Healthcare professionals should also perform a much more stringent approach in monitoring statin use and stress the need to adhere to both pharmacological and non-pharmacological treatments to ensure the effectiveness of achieving the required lipid levels recommended by NCEP-ATP III.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

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

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