Comparison of the efficacy and level of adherence for morning versus evening versus before bedtime administration of simvastatin in hypercholesterolemic patients

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ABSTRACT

Background: Simvastatin is usually taken in the evening due to the circadian rhythm of hepatic cholesterol biosynthesis. The degree of reduction of low-density lipoprotein cholesterol (LDL-C) and the level of adherence to different administration time remained unknown in the Malaysian population. This study aims to investigate the effect of simvastatin on the percentage changes of lipid profile and the level of adherence to when simvastatin was instructed to be taken at different timing.

Methods: Nine primary care health clinics across Malaysia participated in this study. 147 statin-naive subjects were selected through convenient sampling and randomised into one of the three arms (after breakfast, after dinner or before bedtime). Differences on percentage reduction of LDL-C from baseline and level of adherence among the three groups at week-16 were compared. The main outcomes measured in this study were the percentage change of lipid parameters and the percentage of high-adherence (MMAS=8) at week-16.

Results: 59.2% of the patients were male. The mean age of the study population was 53.93± 10.85 years. Most of the patients were Malays (69.4%); followed by Indians (22.4%) and Chinese (8.2%). LDL-C decreased from 4.26 (Standard Deviation, SD1.01) to 2.36 (SD0.69)mmol/L at week-16 for patients taking simvastatin before bedtime; an absolute reduction of 44.95%.The differences of LDL-C percentage reduction between three arms were significantly different (p<0.001). The greatest LDL-C reduction was observed when simvastatin was taken before bedtime and revealed 56.2% patients with high-adherence at week-16.

Conclusion: Simvastatin showed superior LDL-reduction and higher level of adherence when being instructed to be taken before bedtime.

KEY WORDS:
Simvastatin, LDL-C, Administration Time, Adherence, Malaysia

INTRODUCTION

Hypercholesterolemia has been widely recognised as an important modifiable cardiovascular risk factor due to its involvement in the early process of arteriosclerosis.[1,2] Statins, potent 3-hyroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, are able to effectively modify serum cholesterol profile and remained as the mainstream of current pharmacotherapy management for hypercholesterolemia.[3]

Meta-analyses from Cholesterol Treatment Trialists' (CTT) Collaboration had shown that cardiovascular risk was reduced in proportion to the magnitude of serum low-density lipoprotein cholesterol (LDL-C) reduction.[4,5] Risk of cardiovascular morbidity and mortality are expected to be reduced by approximately one fifth per 1mmol reduction of serum LDL-C level from pre-treatment value, in both high and low risk patients.[5,6] Hence, maximal reduction of LDL-C is desire in order to achieve maximal cardiovascular benefit of statin.

Statins are normally recommended to be taken in the evening or at bedtime due to the peak hepatic cholesterol biosynthesis that occurs during midnight (12.00 am to 3.00 am).[7] Most statin users have other comorbid in which they require to take multiple medications concomitantly and having a complex medication regime. It is well understood that complicated daily regime with multiple daily dosing frequency at different time points may greatly reduce medication adherence.[8] Consequently, patient may not receive maximal therapeutic benefit of statins in reducing cardiovascular burden due to statins' non-compliance or discontinuation. Empowering patients to choose their statin's dosing times according to their conveniences will greatly

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improve the long-term adherence to taking statin. The main objective of the present study was to investigate the differences in degree of percentage LDL-C reduction by simvastatin and its level of adherence when the subjects are instructed to take the statin either after breakfast, after dinner or before bedtime (according to randomisation).

MATERIALS AND METHODS

This was a prospective, open-labelled, multicentre, randomised and active comparator study to compare the efficacy and compliance profile of the simvastatin taken at different times of the day (i.e., after breakfast, after dinner and before bedtime). A total of nine health clinics throughout Malaysia participated in this study.

Statin-naïve adults, who were diagnosed with hypercholesterolemia and were selected as candidates for statin therapy indicated for primary prevention of coronary heart disease (CHD), were recruited into the study. Exclusion criteria included having previous cardiovascular diseases or having elective coronary revascularisation procedure, taking any statin within six months prior to the pre-randomisation screening, taking other concomitant anti-hyperlipidaemia medication which include gemfibrozil, fenofibrate, ezetimide, cholestyramine, etc., documented end-stage renal failure or active liver disease, allergy to any component of statin, employed as night shift workers, autoimmune or cancer patients, pregnant women or child-bearing age women. Potential subjects who were taking daily supplements or any products that might influence blood cholesterol level such as fish oil,[9] oats,[10] plant sterols[11] and red yeast rice[12] were also excluded from this study. All subjects who fulfilled the enrolment criteria were sought for consent to participate in this study based on convenient sampling method.

This study assessed a continuous response variable from independent control and experimental subjects with two controls per experimental subject. The sample size calculation was based on statistical power of 80% and the α-value was defined at 0.05. Previous study showed the response within each subject group was normally distributed with standard deviation of 12.[13] Assuming a 6% difference in LDL-C level was clinically significant,[14] we need 48 experimental subjects in each arm to detect a significant difference. Hence, a minimum of 144 subjects were required in this study.

A total of 147 qualified subjects were randomised into one of three arms (after breakfast, after dinner and before bedtime respectively) in a ratio of 1:1:1 using deck cards in sealed envelopes. The randomisation process was carried out in each health clinic. Sealed envelopes were prepared by the principal investigator and delivered to each health clinic. Three deck cards were concealed in each envelop. The principal site investigators will open the sealed envelope according to sequence arranged by the principal investigator when a subject was recruited into the study. Subsequently, the recruited subject was assigned to one of the three treatment arms in randomised manner.

Every subject is then counselled by trained pharmacists, in order to take statin within the time frame as according to randomized arm. The defined time frames for after breakfast is between 6:00 am to 10:00 am; after dinner between 5:00 pm to 9.00 pm; and at bedtime accordingly. All subjects were requested to maintain their existing diet (unchanged) and lifestyle status throughout the study.

After randomisation (baseline, week-0), all subjects were requested to attend the follow up visit at 8th weeks (first follow up) and 16th weeks (second follow up) post-randomisation. In each visit throughout the study, full lipid profile and liver function test were done according to the pre-designed study protocol. Meanwhile, creatine kinase test was ordered by the physician in-charge if any statin-associated muscle syndrome (SAMS) is suspected has happened. Adherence to simvastatin was assessed using the 8-items Morisky Medication Adherence Scale (MMAS-8) by a trained pharmacist during first and second follow up visits.

The primary end point of this study was the magnitude of differences in percentage of LDL-C reduction from the baseline among the three groups of subjects. The secondary end points was the percentage changes of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) from baseline level and the medication adherence rate that assessed by MMAS-8 (with permission from the author).

Categorical data was reported as numbers (frequency percentage), n (%). Chi-square ($\chi 2$) was used to analyse the difference in frequency of categorical data. The normality of continuous data was assessed by Shapiro-Wilk test. All normally distributed data was reported as mean and standard deviation (SD) while non-normally distributed data was reported as median (interquartile range, IQR). Parametric test was used for those normally distributed data with other assumption preserved. Paired t-test was used to assess the difference of follow up value and baseline value within each arm and analysis of variance (ANOVA) test was conducted to investigate the differences among three arms. Wilcoxon signed rank test and Kruskal-Wallis test were used to assess the differences of follow up value and baseline value within each arm and the difference between three arms, if parametric assumptions were violated. Analyses were performed in accordance to intention to treat principle and $p<0.05$ (two-tailed) was considered as statistically significant.

RESULTS

Baseline characteristic of the population was presented in Table I. All demographic data and other baseline lipid profiles were similar among the three groups ($p>0.05$).

Lipid parameters and their corresponding percentage changes from baseline at week-16 is presented in Table II and Figure 1. With the exception of HDL-C for after dinner and after bedtime groups, all lipid parameters were significantly reduced from baseline when assessed at week-16 (at the end of study).

LDL-C was reduced significantly from baseline at both follow ups in all arms. Median percentage reduction of LDL-C from baseline was 33.12% (after breakfast); 38.02% (after dinner) and 44.95% (before bedtime) respectively at the end of the

Table I: Baseline Characteristic of the Intention-to-treat Population in the Study

Group of Randomization	After Breakfast (n=49)	After Dinner (n=50)	Before Bed (n=48)	p-value
Age (year) (SD)	52.22 (12.04)	54.14 (8.95)	55.44 (9.80)	0.308
Gender, N (%)				
Male	29 (59.2%)	32 (64.0%)	26 (54.2%)	0.61
Female	20 (40.8%)	18 (36.0%)	22 (45.8%)	
Height (cm) (SD)	158.75 (3.95)	160.01 (8.88)	159.89 (5.81)	0.577
Weight (kg) (SD)	67.74 (12.49)	65.39 (12.52)	70.27 (12.82)	0.164
Ethnicity, N (%)				
Malay	34 (69.4%)	35 (70.0%)	33 (68.8%)	0.95
Chinese	4 (8.2%)	5 (10.0%)	3 (6.2%)	
Indian	11 (22.4%)	10 (20.0%)	12 (25.0%)	
Marital Status, N (%)				
Married	44 (89.8%)	45 (90.0%)	41 (85.4%)	0.63
Widowed	3 (6.1%)	1 (2.0%)	4 (8.3%)	
Divorced	2 (4.1%)	4 (8.0%)	3 (6.2%)	
Education Status, N (%)				
Primary	7 (14.3%)	6 (12.0%)	7 (14.6%)	0.92
Secondary	26 (53.1%)	28 (56.0%)	29 (60.4%)	
Tertiary	16 (32.7%)	16 (32.0%)	12 (25.0%)	
Statin and Dose, N (%)				
Simvastatin 10mg	12 (24.5%)	13 (26.0%)	13 (27.1%)	0.67
Simvastatin 20mg	31 (63.3%)	28 (56.0%)	24 (50.0%)	
Simvastatin 40mg	6 (12.2%)	9 (18.0%)	11 (22.9%)	
Baseline Lipid Profile				
TC (mmol/L) (SD)	6.31 (0.95)	6.32 (0.74)	6.58 (1.03)	0.26
TG (mmol/L) (IQR)*	2.14 (1.21)	1.94 (1.49)	2.20 (1.22)	0.22
LDL-C (mmol/L) (SD)	4.15 (0.64)	4.26 (0.78)	4.26 (1.01)	0.749
HDL-C (mmol/L) (SD)	1.20 (0.34)	1.27 (0.25)	1.33 (0.23)	0.061

All categorical data were presented in number (percentage), n (%) and normally distributed data were presented in mean and standard deviation (SD).
* TG was presented as median (IQR) due to follow up data were not normally distributed and non-parametric test would be used for all analysis involving TG.
TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

Table II: Lipid Parameter on 2nd Follow Up (at Week 16) and Percentage Changes From Baseline Among Three Arms

Lipid Parameter	After Breakfast			After Dinner			Before Bedtime			p-value (Between Arms)
TC (mmol/L)*(SD)	6.31 (0.95)	4.88 (1.12)	<0.001	6.32 (0.74)	4.70 (1.21)	<0.001	6.58 (1.03)	4.62 (0.59)	<0.001	0.44
Percent Change (%)†		-21.9 (4.17)			-26.79 (12.16)			-29.33 (6.33)		<0.001
LDL-C (mmol/L)*(SD)	4.15 (0.64)	2.76 (0.77)	<0.001	4.26 (0.78)	2.69 (1.12)	<0.001	4.26 (1.01)	2.36 (0.69)	<0.001	0.06
Percent Change (%)†		-33.12 (6.89)			-38.0.2 (17.3)			-44.95 (3.04)		<0.001
TG (mmol/L)†(IQR)	2.14 (1.21)	1.55 (0.60)	<0.001	1.94 (1.49)	1.47 (1.08)	<0.001	2.20 (1.22)	1.90 (1.38)	<0.001	0.02
Percent Change (%)†		-26.14 (12.04)			-10.37 (19.70)			-11.42 (19.44)		<0.001
HDL-C (mmol/L)*(SD)	1.20 (0.34)	1.42 (0.36)	<0.001	1.27 (0.25)	1.27 (0.15)	0.95	1.33 (0.23)	1.34 (0.31)	0.61	0.04
Percent Change (%)†		+17.32 (13.07)			+2.33 (9.04)			-0.36 (8.36)		<0.001

Parametric data are presented as mean ± standard deviation (SD) and non-parametric data were presented as median (IQR).
* Paired t-test was used to assess the differences between lipid parameter at week 16 versus baseline (within arm) and ANOVA was used to assess the differences of lipid parameter at week 16 months post statin treatment among three arms (between arms) whenever parametric assumption was preserved.
† Wilcoxon signed-rank test was used for within arm analysis and Kruskal-Wallis test was used for between arms analysis whenever parametric assumption is violated.
TC: Total cholesterol; TG: Triglycerides; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

Table III: Post-hoc Pairwise Comparison of Difference in Percentage Changes of Lipid Parameter Following Simvastatin Administration in Two Difference Timing At Week 16 As Compared to Baseline

Lipid Parameter	Percentage Changes (%)	Absolute Difference Between Two Timing (%)	p-value
Total Cholesterol (TC)*			
After Breakfast vs After Dinner	–21.90 vs. –26.79	–4.89	0.024
After Breakfast vs At Bedtime	–21.90 vs. –29.33	–7.43	<0.001†
After Dinner vs At Bedtime	–26.79 vs. –29.33	–2.54	0.032
LDL-Choletserol*			
After Breakfast vs After Dinner	–33.12 vs. –38.02	–4.09	0.099
After Breakfast vs At Bedtime	–33.12 vs. –44.95	–11.83	<0.001†
After Dinner vs At Bedtime	–38.02 vs. –44.95	–6.93	<0.001†
Triglyceride (TG) *			
After Breakfast vs After Dinner	–26.14 vs. –10.37	+15.37	<0.001†
After Breakfast vs At Bedtime	– 26.14 vs. –11.42	+14.72	<0.001†
After Dinner vs At Bedtime	–10.37 vs. –11.42	–1.05	0.929
HDL-Cholesterol*			
After Breakfast vs After Dinner	+17.32 vs. +2.33	+14.99	<0.001†
After Breakfast vs At Bedtime	+17.32 vs. –0.36	+17.68	<0.001†
After Dinner vs At Bedtime	+2.33 vs. –0.36	+2.69	0.384

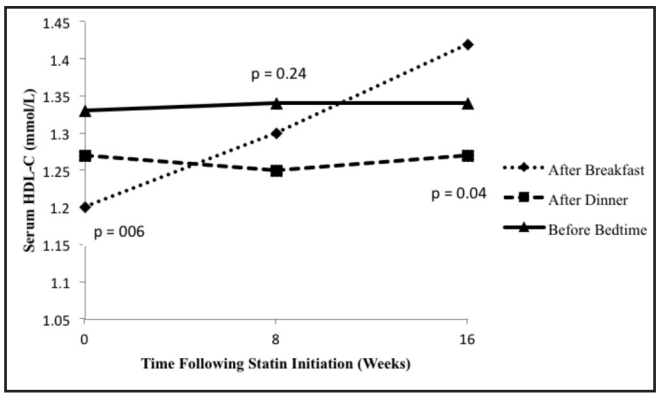

Fig. 1: Mean Serum HDL-C Level from Baseline to Week 16 After Initiation of Statin Therapy Administered at Different Timing.

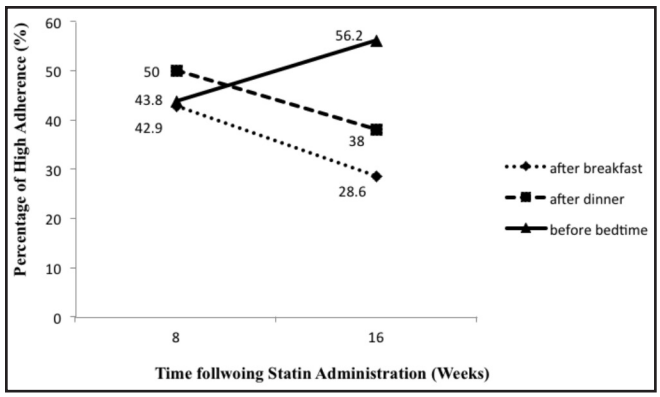

Fig. 2: Percentage of Subjects Remained Highly Adherence throughout the Study When Statin Was Instructed to be Taken at Different Timing.

study (week-16). The differences of LDL-C percentage reduction among three arms were statistically significant different (p<0.001). Post-hoc analyses using Mann-Whitney test revealed that true significant differences lied between "after breakfast" and "before bedtime", as well as between "after dinner" and "before bedtime", indicating a greater efficacy in reducing LDL-C when simvastatin was administered before bedtime.

Similar to LDL-C, all arms demonstrated a significant decline of TC level from their baseline which revealed a median reduction of 21.9% (after breakfast), 26.79% (after dinner) and 29.33% (before bedtime) after 16 weeks of simvastatin therapy. Differences in percentage reduction of TC among three groups were statistically significant (p<0.001).

Statistically significant reductions of TG from baseline were seen in all arms, with a median percentage reduction of 26.14% (after breakfast), 10.37% (after dinner) and 11.42% (before bedtime), p<0.001. This study showed the effect of TG reduction by simvastatin was superior when it was taken after breakfast as compared to the other two arms (p<0.001) (Table III).

At week-16, HDL-C showed a plateau trend (Figure 2) with no further significant changes observed throughout the study when simvastatin was administered after dinner (median change: + 2.33%) or before bedtime (median change: -0.36%). However, it was found that if simvastatin was administered in the morning, HDL-C increased steadily throughout the study and recorded an increase of 17.32% at week-16. These differences in median percent changes among three arms were statistically significant different (p<0.001).

Validated MMAS-8 was used to assess patients' adherence rate to simvastatin, with a score of 8 was defined as high adherence. As illustrated in Figure 2, this study showed only 40-50% of the patients remained high adherence at week 8. The percentage of high-adherence subjects dropped further to 28.6% and 38%, in after breakfast and after dinner arm respectively as study progressed to week-16. Paradoxically, high-adherence rate had shown to increase from 43.8% in week 8 to 56.2% in week-16, when simvastatin was instructed to be taken just before bedtime.

DISCUSSION

Lipid Parameter

Simvastatin is usually advised to be taken in the evening (between 6.00 pm to bedtime), due to the occurrence of peak cholesterol synthesis activity at the midnight (approximately 12.00am to 3.00am) and its short half -life. Hence, mostly patients are given different instructions of administration from time to time. Patients may be instructed to take simvastatin immediately after dinner at one point of time and before bedtime at another point of time. Some studies suggested that newer statins such as atorvastatin and rosuvastatin could be taken at any time of the day, due to their longer elimination half-lives and pharmacokinetic factors.[15-17] However, most of these studies involve only minimal representative of Asian populations by which genetic differences might influence the efficacy and safety of statin through different pharmacokinetics profiles.[18,19]

To the best of our knowledge a study by Saito et al., was the only one that investigated the effect of simvastatin taken at different timing in an Asian (Japanese) population.[20] Our result was similar to results of Saito et al., where LDL-C and TC was reduced in greater magnitude when statin was taken at a time-point closer to midnight, although statistical significance was not achieved between after breakfast and after dinner groups in our study. Other studies involving simvastatin also show a significant greater reduction on TC and LDL-C when taken during the evening compared to morning doses.[21,22]

HDL-C is also known as "good" cholesterol and it was inversely correlated to cardiovascular risk.[1] Recent research had shown that HDL-C level increased modestly among statin usesr, in the range of approximately 4% to 10%.[23] In this study we observed that, when simvastatin was taken in the morning, HDL-C was increased consistently throughout the study and such increment was highly statistically significant different when compared to the other two arms, which remained plateau throughout the study (Table III). In a study assessing the efficacy of morning administration of control release simvastatin and evening administration of immediate release simvastatin, HDL-C was increased in a greater magnitude in the morning arm (mean: 10.2%, SD 20.7) compared to evening arm (mean: 4.5%, SD 11.4).[24] Hence, our study reinforces the potential relation of administration time of statin and the percentage increment of HDL-C. However, the mechanisms that lead to higher HDL-C increment with morning administration of statin still remained unknown.

A significantly greater reduction of TG when simvastatin was taken after breakfast (median: -26.14%) compared with after dinner and before bedtime counterparts (median: -10.37% and -11.42% respectively) (Table III). Remarkably, Barter et al., suggest that there was a significant correlation between the percentage increment of HDL-C and percentage reduction of TG.[25] This is in line with our results (Table II), evidenced with morning administration of simvastatin lead to a greater increment in HDL-C which simultaneously leading to a greater reduction on TG from baseline. Both percentage changes of TG and HDL-C were not significantly different between after dinner and before bedtime arm. Therefore, our study supported the correlation between percentage changes of HDL-C and TG (Table III).

Medication Adherence

In term of adherence, present study found approximately 50% of all subjects had high adherence after 8 weeks. This is in accordance to the WHO report on 2013 that suggested an estimate adherence rate of 50% for chronic preventive treatment in developed country and potentially even lower in developing country.[26] Glader et al., showed a trend of progressive decline in adherence to chronic medication, which reflected in after breakfast and after dinner group of current study.[27] Both groups showed a reduction in adherence rates as time progressed to week-16. Unexpectedly, adherence rate showed an increment as time progressed when simvastatin was instructed to be taken before bedtime, as opposed to Galder et al.[27]

This study has a few limitations. First, we only recruited Malaysian into the study and the result may not be generalized to other Asian countries. Second, we were using LDL-C reduction and effect on other lipid parameters as surrogate marker for cardiovascular risk. The true clinical benefits on cardiovascular morbidity and mortality was not assessed in this study. The third limitation of this study was that it was an opened labelled study by which no blinding procedure was done. The strength of this study was it was a prospective and multicentre study with data from local population.

CONCLUSION

Simvastatin produces a significantly greater reduction in LDL-C and TC when it is instructed to be taken just before bedtime. Nevertheless, the difference in percentage changes of LDL-C between after breakfast and after dinner groups was not statistically significant. Level of adherence also appears to better if simvastatin is taken just before sleep. However, those who will not comply to before bedtime dosing and has low HDL-C with high TG level by which aggressive LDL-C reduction may not necessary may potentially benefit from morning administration of simvastatin.

ETHICS APPROVAL

The study protocol was approved by Medical Research Ethic Committee (MREC) from Ministry of Health, Malaysia (NMRR-14-1106-22887-IIR) approved on June 2016 and in accordance with Good Clinical Practice Guideline and the principles of the Declaration of Helsinki, as revised in Washington in 2013. All participating subjects had provided written consent prior to commencement of any study related activities. The principal investigator and teams visited each study site on a monthly basis to assure the study adhered to the pre-designed protocol and also for quality data assurance.

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